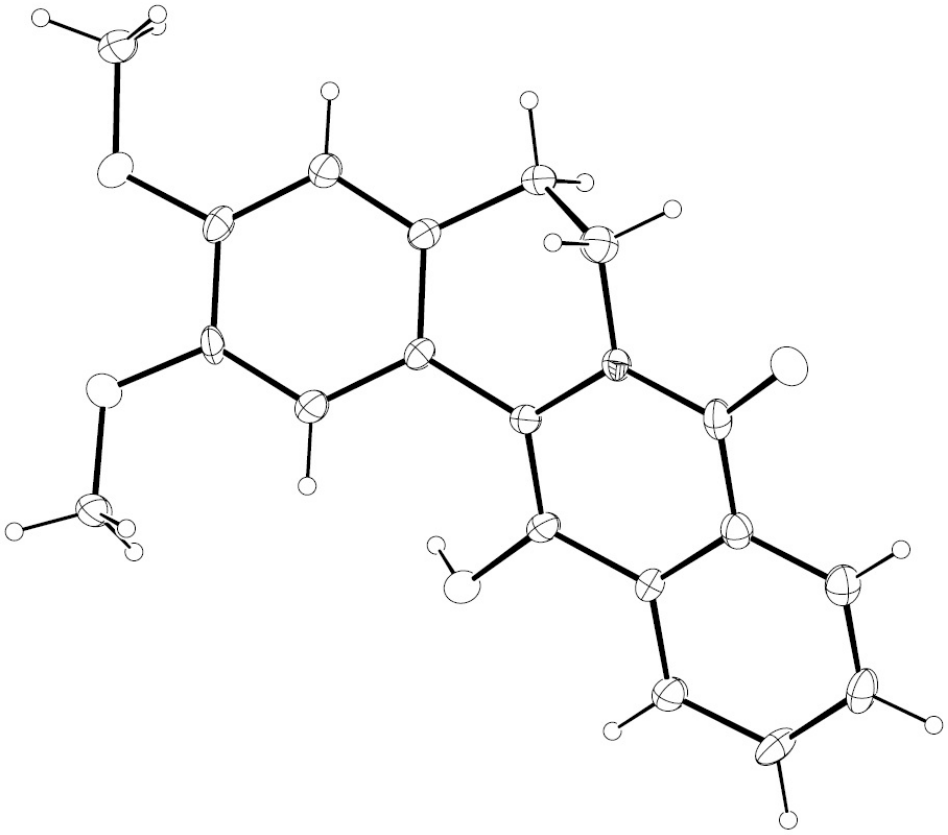
Solutions Manual for Organic Chemistry

Second Edition



Michael S. Leonard

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Solutions to Problems for Chapter 1: Introduction to Organic Chemistry

1. The key information for this problem is that both protons and neutrons have relative masses of 1 atomic mass unit (amu). By comparison, the mass of electrons is negligible, so we need not account for them.

(a) Since this carbon has six protons and six neutrons and they all weigh 1 amu, the atom's total mass is 12 amu.

(b) The seven protons and seven neutrons of this nitrogen atom give it a mass of 14 amu.

(c) This oxygen atom is charged because it has more electrons than protons, so the negative charges outweigh the positive charges. However, since the mass of electrons is negligible, this has no bearing on the question at hand. The eight protons and eight neutrons give this oxygen atom a mass of 16 amu.

(d) Once again, the charge of this fluorine atom does not affect the solution to this question. There are nine protons and ten neutrons, which gives this fluorine atom a mass of 19 amu.

(e) The sum of the protons and neutrons gives a mass of 23 amu for this charged sodium atom.

2. The atomic symbol is provided in the format ${}^{A}_{Z}X$, where X is the element's abbreviation, Z is the atomic number (i.e. the number of protons), and A is the mass number (i.e. the number of protons and neutrons). If there is a charge, it is a superscripted notation on the right side of the element's abbreviation.

(b) ${}^{14}_{7}N$

(c) Since there are two more electrons than protons, the negative charges outweigh the positive charges by two. The negative-two charge is denoted in the superscript on the right: ${}^{16}_{8}O^{2-}$.

(d) This atom is also charged, but it has a negative-one charge because the number of electrons exceeds the number of protons by only one: ${}^{19}_{9}F^{-}$.

(e) This time the number of protons exceeds the number of electrons by one, so there is a positive charge: ${}^{23}_{11}Na^{+}$

3. Since the mass number is the sum of the protons and neutrons, these isotopes of sulfur will have mass numbers of 32, 33, 34, and 36. The atomic symbols are therefore: ${}^{32}_{16}S$, ${}^{33}_{16}S$, ${}^{34}_{16}S$, ${}^{36}_{16}S$.

4. To calculate the average atomic mass, the mass of each isotope is multiplied by its abundance, and these values are totaled.

$$Ave.\,atomic\ mass\ of\ S = (31.9721\ amu)(0.9502) + (32.9715\ amu)(0.0075) + (33.9679\ amu)(0.0421) + (35.9671\ amu)(0.0002) = 32.0644\ amu$$

5. We begin with the given quantity: 1.00 mole of ^{14}N. We can use Avogadro's number to convert that quantity to the number of atoms of ^{14}N. Each atom of ^{14}N weighs 14 amu, and there are 1.66 x 10^{-24} g/amu. These conversions lead us to the conclusion that a mole of ^{14}N weighs 14.0 g.

$$(1.00\ mole\ ^{14}N)\left(\frac{6.02\ \times\ 10^{23}\ atoms\ ^{14}N}{1\ mole\ ^{14}N}\right)\left(\frac{14\ amu}{1\ atom\ ^{14}N}\right)\left(\frac{1.66\ \times\ 10^{-24} g}{1\ amu}\right) = 14.0\ g$$

6. For these problems, we simply use a detailed periodic table (e.g., http://www.nist.gov/pml/data/periodic.cfm) to locate the average atomic masses of the constituent elements. Multiply these masses by the number of atoms of each element in the formula, and the sum is the molecular or molar mass. The units are $^{amu}/_{molecule}$ for the molecular weight, and they are $^{g}/_{mole}$ for the molar mass.

(a) Hydrogen has an average atomic mass of 1.01, while that of oxygen is 16.00.

$$2\ \times\ 1.01 + 16.00 = 18.02$$

Therefore, the molecular weight of water is 18.02 $^{amu}/_{molecule}$. The molar mass of water is 18.02 $^{g}/_{mole}$.

(b) We have the average atomic masses of hydrogen and oxygen from part (a), so we just need the mass of carbon, which is 12.01.

$$2\ \times\ 12.01 +\ 6\ \times\ 1.01 + 16.00 = 46.08$$

The molecular weight of ethanol is 46.08 $^{amu}/_{molecule}$, and its molar mass is 46.08 $^{g}/_{mole}$.

(c) We have all of the atomic masses that we need for the calculation from part (b).

$$13\ \times\ 12.01 +\ 18\ \times\ 1.01 + 2\ \times\ 16.00 = 206.31$$

The molecular weight of ibuprofen is 206.31 $^{amu}/_{molecule}$, and its molar mass is 206.31 $^{g}/_{mole}$.

(d) We need one additional atomic mass for this question. Chlorine has an average atomic mass of 35.45.

$$6 \times 12.01 + 8 \times 1.01 + 2 \times 35.45 + 2 \times 16.00 = 183.04$$

Adipoyl chloride has a molecular weight of 183.04 $^{amu}/_{molecule}$ and a molar mass of 183.04 $^{g}/_{mole}$.

7. We need the molar mass of naloxone ($C_{19}H_{21}NO_4$) for these calculations:

$$Molar\ mass\ of\ naloxone:$$
$$19 \times 12.01\ g/mole + 21 \times 1.01\ g/mole + 14.01\ g/mole + 4 \times 16.00\ g/mole$$
$$= 327.41\ g/mole$$

Now, we can use the molar mass to determine the number of moles present in a 10.0 mg dosage of naloxone, but we must first convert mg to g.

$$(10.0\ mg\ naloxone)\left(\frac{1\ g}{1000\ mg}\right)\left(\frac{1\ mole\ naloxone}{327.41\ g\ naloxone}\right)$$
$$= 3.05 \times 10^{-5}\ moles\ naloxone$$

The molecular formula tells us how many moles of each element are present in a mole of naloxone. Together with Avogadro's number, this information enables us to calculate the number of carbon, hydrogen, nitrogen, and oxygen atoms present in the sample.

$$(3.05 \times 10^{-5}\ moles\ naloxone)\left(\frac{19\ moles\ C}{1\ mole\ naloxone}\right)\left(\frac{6.02 \times 10^{23}\ C\ atoms}{1\ mole\ C}\right)$$
$$= 3.49 \times 10^{20}\ C\ atoms$$

$$(3.05 \times 10^{-5}\ moles\ naloxone)\left(\frac{21\ moles\ H}{1\ mole\ naloxone}\right)\left(\frac{6.02 \times 10^{23}\ H\ atoms}{1\ mole\ H}\right)$$
$$= 3.86 \times 10^{20}\ H\ atoms$$

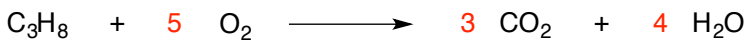
$$(3.05 \times 10^{-5}\ moles\ naloxone)\left(\frac{1\ mole\ N}{1\ mole\ naloxone}\right)\left(\frac{6.02 \times 10^{23}\ N\ atoms}{1\ mole\ N}\right)$$
$$= 1.84 \times 10^{19}\ N\ atoms$$

$$(3.05 \times 10^{-5}\ moles\ naloxone)\left(\frac{4\ moles\ O}{1\ mole\ naloxone}\right)\left(\frac{6.02 \times 10^{23}\ O\ atoms}{1\ mole\ O}\right)$$
$$= 7.34 \times 10^{19}\ O\ atoms$$

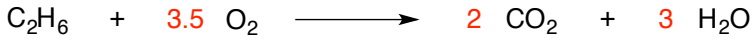
The take home message from this problem is that even very small samples contain exceedingly large numbers of atoms. There are a total of 8.27×10^{20} atoms in a 10.0 mg sample of naloxone.

8. Although reactions are balanced by inspection, it is nevertheless helpful to have a method in mind as you approach each problem. For combustion reactions, begin by placing a coefficient in front of carbon dioxide to balance the number of carbon atoms. Then, place a coefficient in front of water to balance the number of hydrogen atoms present. Finally, put a coefficient in front of oxygen to balance the number of oxygen atoms.

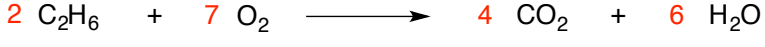
(a) There are three carbons in propane, so we start by putting a 3 in front of carbon dioxide. Since propane contains eight hydrogens, we then put a 4 in front of water. This gives a total of ten oxygen atoms in the products, so a coefficient of 5 is needed in front of oxygen.



(b) In the final step of balancing the equation for the combustion of ethane, a coefficient of 3.5 is necessary in front of oxygen.

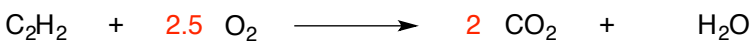


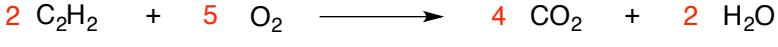
By convention, we use whole number coefficients because we can only have whole numbers of molecules. To obtain whole numbers, we need only multiply each stoichiometric coefficient by two.



(c) In parts (c) through (g), we encounter a similar issue. Fractional coefficients are converted to whole numbers by applying an appropriate multiplication factor, which is two in all of these cases.

(d)





(e)

$$C_6H_6 + 7.5\ O_2 \longrightarrow 6\ CO_2 + 3\ H_2O$$

$$2\ C_6H_6 + 15\ O_2 \longrightarrow 12\ CO_2 + 6\ H_2O$$

(f)

$$C_{14}H_{10} + 16.5\ O_2 \longrightarrow 14\ CO_2 + 5\ H_2O$$

$$2\ C_{14}H_{10} + 33\ O_2 \longrightarrow 28\ CO_2 + 10\ H_2O$$

(g)

$$C_{16}H_{10} + 18.5\ O_2 \longrightarrow 16\ CO_2 + 5\ H_2O$$

$$2\ C_{16}H_{10} + 37\ O_2 \longrightarrow 32\ CO_2 + 10\ H_2O$$

9.

(a) "The combustion of heptane (C_7H_{16}) requires 11 equivalents of oxygen and produces 7 equivalents of carbon dioxide along with 8 equivalents of water."

We are combusting heptane, so it is a reactant. The fact that the reaction "requires" oxygen reminds us that oxygen is a reactant. The needs for 11 equivalents means that the stoichiometric coefficient is 11. The reaction "produces" carbon dioxide and water, so these are products. Their stoichiometric coefficients are given by the number of equivalents stated.

$$C_7H_{16} + 11\ O_2 \longrightarrow 7\ CO_2 + 8\ H_2O$$

(b) "The exhaustive bromination of 1,3-butadiene (C_4H_6) necessitates two equivalents of bromine (Br_2) and yields one equivalent of 1,2,3,4-tetrabromobutane ($C_4H_6Br_4$)."

We are told that a process known as "exhaustive bromination" is happening to 1,3-butadiene. We don't need to know exactly what exhaustive bromination is in order to deduce that 1,3-butadiene is being acted upon and is therefore a reactant. We are told that this process "necessitates" bromine, which is therefore another reactant. Furthermore, two molar equivalents are needed, so we know that the stoichiometric coefficient for bromine is 2. Finally, we are told that the process "yields" 1,2,3,4-tetrabromobutane, so this compound is the product. Only a single equivalent of the product is formed.

$$C_4H_6 + 2\ Br_2 \longrightarrow C_4H_6Br_4$$

10. We are considering the following reaction from Problem 9(b).

We'll need the molar mass of each species for this problem.

$$Molar\ mass\ of\ 1{,}3-butadiene\ (C_4H_6):$$
$$4\ \times\ 12.01\ g/mole + 6\ \times\ 1.01\ g/mole =\ 54.10\ g/mole$$

$$Molar\ mass\ of\ bromine\ (Br_2):$$
$$2\ \times\ 79.90\ g/mole =\ 159.80\ g/mole$$

$$Molar\ mass\ of\ 1{,}2{,}3{,}4-tetrabromobutane\ (C_4H_6Br_4):$$
$$4\ \times\ 12.01\ g/mole + 6\ \times\ 1.01\ g/mole\ +\ 4\ \times\ 79.90\ g/mole =\ 373.70\ g/mole$$

With these conversion factors in hand, we can begin the calculations. To determine how much product can be made from 1.75 g of 1,3-butadiene, we first use the molar mass to convert to moles of 1,3-butadiene. The balanced chemical equation enables us to convert moles of 1,3-butadiene to moles of product. Finally, the product's molar mass is used to convert moles of product into grams of product.

$$(1.75\ g\ butadiene)\left(\frac{1\ mole\ butadiene}{54.10\ g\ butadiene}\right)\left(\frac{1\ mole\ product}{1\ mole\ butadiene}\right)\left(\frac{373.70\ g\ product}{1\ mole\ product}\right)$$
$$= 12.1\ g\ product$$

A similar series of conversions is needed to deduce the amount of product that could be made from 9.50 g of bromine.

$$(9.50\ g\ bromine)\left(\frac{1\ mole\ bromine}{159.80\ g\ bromine}\right)\left(\frac{1\ mole\ product}{2\ mole\ bromine}\right)\left(\frac{373.70\ g\ product}{1\ mole\ product}\right)$$
$$= 11.1\ g\ product$$

The smaller quantity is the 11.1 g of product that can be made from the available bromine. Therefore, 11.1 g is the theoretical yield of product. In other words, it is the maximum amount of product that we can make during this reaction. Bromine is the limiting reactant (a.k.a. the limiting reagent) in this case because it is consumed first and therefore limits how much product can be generated.

11. The percent yield compares the amount of product actually obtained to the amount of product that it is theoretically possible to produce. In this case, we made 77.3% of the maximum possible quantity of product.

$$\%\ yield = \frac{8.58\ g}{11.1\ g}\ \times\ 100 = 77.3\%$$

12. The orbitals have been designated by a number and a letter. The number is the principal quantum number (n), which denotes the shell occupied by the electron. The letter denotes the type of orbital, which comes from the angular momentum quantum number, ℓ. The orbitals s, p, d, and f are denoted by ℓ values of 0, 1, 2, and 3, respectively.

For the remaining two quantum numbers, we may have some choices. The magnetic quantum number, m_ℓ, has values ranging from $-\ell$ to ℓ. If there are multiple values, then any one will suffice. The spin quantum number, m_s, can have a value of $\pm 1/2$, and either value is acceptable.

(a) An electron in a 4s orbital must have a principal quantum number (n) of 4. The s orbital denotes a ℓ value of 0. When ℓ is 0, m_ℓ must also be 0. The single value for m_ℓ shows that there is only one type of s orbital in this shell. The m_s value can be $+1/2$ or $-1/2$.

(b) When an electron resides in a 3p orbital, n must be 3 to designate the shell, and ℓ must be 1 to assign the orbital as p. When ℓ is 1, there are three acceptable values for m_ℓ (–1, 0, or 1), and any of these is acceptable because the three p orbitals within a shell are equal in energy. Once again, the m_s value can be $+1/2$ or $-1/2$.

(c) If an electron is in a 3d orbital, n has to be 3 because the shell has been specified. Similarly, ℓ must be 2 to designate the orbital as d, but when ℓ is 2, there are five values for m_ℓ (–2, –1, 0, 1, or 2). You may choose any one of these because the d orbitals within the same shell are degenerate. As before, the m_s value can be $+1/2$ or $-1/2$.

(d) An electron in a 2p orbital has an n value of 2 and a ℓ value of 1. The former states that the electron is in the second shell, and the latter says that the electron occupies a p orbital. When ℓ is 1, m_ℓ can be –1, 0, or 1. Any one of these values is fine because the three p orbitals in a single shell are equal in energy. The m_s value can be $+1/2$ or $-1/2$.

13.

(a) Mg: $1s^2 2s^2 2p^6 3s^2$ or Mg: $[Ne]3s^2$

(b) Al: $1s^2 2s^2 2p^6 3s^2 3p^1$ or Al: $[Ne]3s^2 3p^1$

(c) Si: $1s^2 2s^2 2p^6 3s^2 3p^2$ or Si: $[Ne]3s^2 3p^2$

(d) S: $1s^2 2s^2 2p^6 3s^2 3p^4$ or S: $[Ne]3s^2 3p^4$

(e) K: $1s^2 2s^2 2p^6 3s^2 3p^6 4s^1$ or K: $[Ar]4s^1$

(f) As: $1s^2 2s^2 2p^6 3s^2 3p^6 4s^2 3d^{10} 4p^3$ or $[Ar] 4s^2 3d^{10} 4p^3$

14. By referring to the periodic table, we can see that only two of these elements (Ge and Sn) are in the same column:

H, Be, Ge, S, Cl, Kr, P, Al, Sn

These are the two that will have the same valence-shell configuration. Their electronic configurations are as follows:

Ge: $1s^2 2s^2 2p^6 3s^2 3p^6 4s^2 3d^{10} 4p^2$
Sn: $1s^2 2s^2 2p^6 3s^2 3p^6 4s^2 3d^{10} 4p^6 5s^2 4d^{10} 5p^2$

Notice that both have the valence-shell configuration $s^2 p^2$.

15. The key guideline is that, when elements form ions, they tend to gain or lose electrons so as to attain the same configuration as the nearest noble gas.

(a) For strontium, this would entail the loss of the two electrons in its valence shell, leaving it with an electronic configuration that matches that of krypton.

Sr^{2+}: $1s^2 2s^2 2p^6 3s^2 3p^6 4s^2 3d^{10} 4p^6$

(b) Aluminum can attain neon's electronic configuration if it loses the three electrons in its valence shell.

Al^{3+}: $1s^2 2s^2 2p^6$

(c) Sulfur acquires argon's electronic configuration if it gains two electrons to fill its valence shell.

S^{2-}: $1s^2 2s^2 2p^6 3s^2 3p^6$

(d) Potassium need only lose a single electron from its valence shell to empty that shell and arrive at the same electronic configuration as argon.

K^+: $1s^2 2s^2 2p^6 3s^2 3p^6$

(e) If bromine were to gain a single electron, its valence shell would be filled, and it would have the same electronic configuration as krypton.

Br^-: $1s^2 2s^2 2p^6 3s^2 3p^6 4s^2 3d^{10} 4p^6$

(f) Phosphorus will acquire three electrons to obtain the same configuration as argon.

P^{3-}: $1s^2 2s^2 2p^6 3s^2 3p^6$

16.

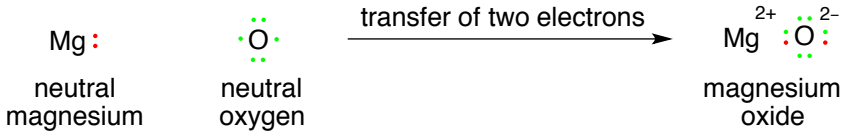
(a) These elements all share the same column of the periodic table (Group IVA), and atomic radius increases as we moved down a column. Lead (Pb) is the furthest down this column, so it is the largest atom.

(b) These elements reside in the same row of the periodic table (Period 3). Atomic radius decreases as we move from left to right across a row, so sodium (Na) is the largest element.

(c) This is an isoelectronic series in which all of the ions have the electronic configuration of argon. Within an isoelectronic series, the species with the greatest number of protons will have the smallest radius. Phosphorus has the fewest protons, so it is the largest of the group.

17. Of the elements list, sulfur is the closest to fluorine on the periodic table, so it is the most electronegative.

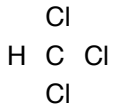
18. Magnesium has two electrons in its valence shell, and oxygen has six. Knowing that atoms form ions by losing or gaining enough electrons to attain the nearest noble gas's electronic configuration, we expect magnesium to lose two electrons and oxygen to gain two. This will give them both the same electronic configuration as neon. The transfer of two electrons from magnesium to oxygen results in Mg^{2+} and O^{2-} ions. The resultant ionic substance is known as magnesium oxide.



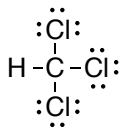
19.

(a) We begin by tallying the available valence electrons. Carbon contributes four. Hydrogen contributes one, and each chlorine contributes seven. This gives a total of 26 electrons.

The next step is to arrange the atoms in a way that maximizes the chance of satisfying their normal valences. Since carbon is the only element in the formula that makes more than one bond, it must go in the center of the molecule with the hydrogen and halogens surrounding it. It is irrelevant where the hydrogen is located (i.e., top, bottom, left, or right). We'll learn why that is the case in Section 15 when we discuss hybridization.

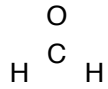


After filling in single bonds between carbon and each of the atoms surrounding it, there are 18 electrons remaining. This provides enough electrons to fill each chlorine's octet using lone pairs.

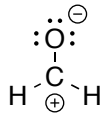


Since each atom has its normal valence, there are no formal charges. This molecule happens to be known as chloroform.

(b) Carbon has four valence electrons, and each hydrogen has one. Oxygen contributes six valence electrons for a total of 12. We position the atoms according to their normal valence. Since carbon makes the most bonds, it is likely to be in the middle of the molecule. Both carbon and oxygen make more than one bond, so there is a question of whether the hydrogen atoms should be placed around carbon or oxygen. Since carbon makes more bonds than oxygen, the hydrogens should surround it.

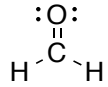


After filling in the bonds between the elements, there are six electrons remaining. This turns out to be an insufficient number to complete the octet for both carbon and oxygen. Additionally, as drawn, both carbon and oxygen would have formal charges.



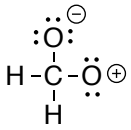
insufficient electrons to complete octet for carbon

When we run out of electrons before filling each atom's octet, a multiple bond may solve the problem. If we insert a double bond between carbon and oxygen, then there are enough remaining electrons to fill oxygen's octet.



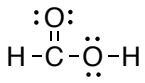
There are no formal charges present. This molecule is called formaldehyde.

(c) This molecule has one additional oxygen that contributes six more valence electrons for a total of 18. If we place the carbon in the center of the molecule and put all of the remaining atoms around it, we run out of electrons before filling all of the octets.



insufficient electrons to complete one oxygen's octet

To resolve this issue, we need to insert a multiple bond, but to do so, one atom must be removed from carbon so that it does not exceed the octet. Consequently, one hydrogen is transferred from carbon to oxygen. This allows us to insert a carbon-oxygen double bond, and now all of the octets may be filled with the available electrons.

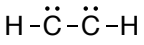


There are no formal charges because all atoms have their typical valence. This molecule happens to be called formic acid.

(d) Each carbon contributes four valence electrons, and each hydrogen adds one. This gives a total of 10 valence electrons that can be used to build the molecule. The two tetravalent carbon atoms are placed at the molecule's core, and the hydrogens are distributed evenly.

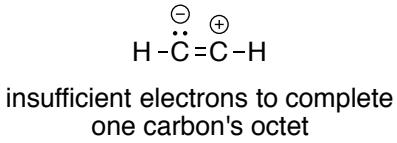
H C C H

After filling in the bonds, only four electrons remain. This is not enough to fill each carbon's octet.

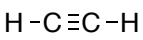


insufficient electrons to complete octets on carbon atoms

Consequently, we consider a multiple bond. However, if a double bond is placed between the carbons, there are still not enough electrons to fill the octet for one of the carbons.



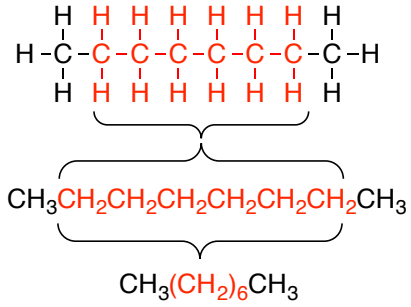
If we add a triple bond between the two carbons, then we are able to fill each carbon's valence shell. Furthermore, we do so while maintaining carbon's usual valence, so there are no formal charges.



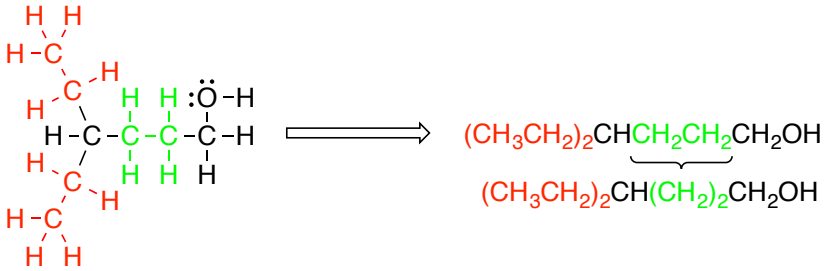
This molecule is called acetylene.

20.

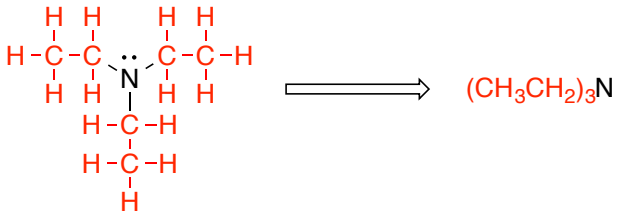
(a) This Lewis structure can be condensed to varying degrees. The molecule has two CH_3 groups, one on each terminus. In between are six CH_2 groups. They can be written individually or condensed into parentheses.



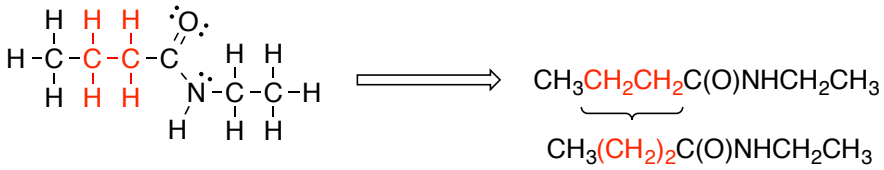
(b) This molecule has two CH_2CH_3 groups attached to the same carbon. These are grouped in parentheses. Additionally, there are two sequential CH_2 groups that can also be grouped in parentheses if desired. The CH_2 connected to the OH group would typically be drawn separately because, as we'll learn shortly, this is an important part of the molecule.



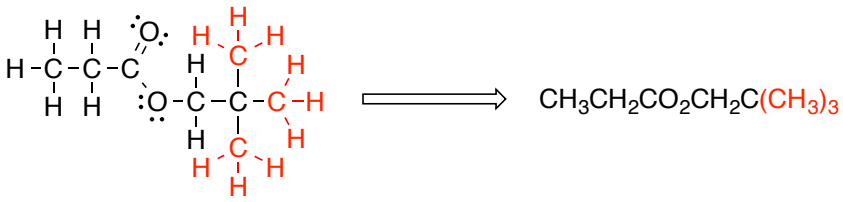
(c) This Lewis structure has three identical groups (CH_2CH_3) bonded to nitrogen. These are all grouped in parentheses to give the condensed formula.



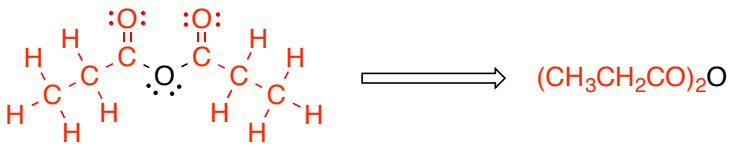
(d) The carbon-oxygen double bond need not be drawn in the condensed formula. Its presence can be implied because we know how many bonds these atoms make when they are uncharged. However, it is common to place the oxygen atom in parentheses. This highlights for the reader that it branches from the preceding carbon and does *not* fall between carbon and nitrogen. Additionally, the two sequential CH_2 groups can be further condensed if desired.



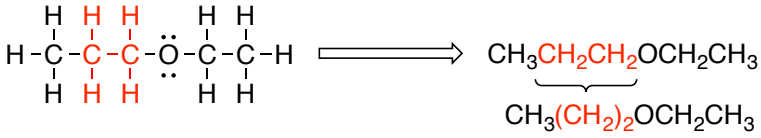
(e) Once again, when condensing this molecule's Lewis structure, the presence of the carbon-oxygen double bond can be implied by the normal valence of the atoms and the fact that there are no formal charges indicated. The three CH_3 groups branching from the same carbon are grouped in parentheses.



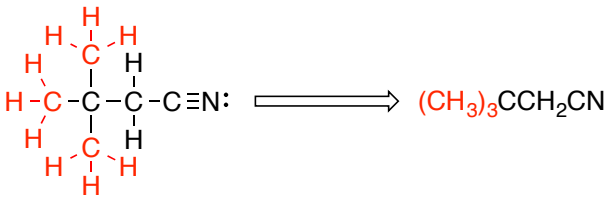
(f) The two groups connected to the central oxygen atom are identical, so they are grouped in parentheses when condensing this Lewis structure. The presence of the carbon-oxygen double bonds is simply implied.



(g) When condensing this Lewis structure, you have the choice of grouping the sequential CH_2 groups if desired.

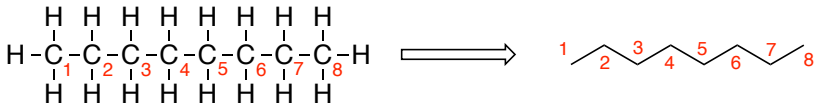


(h) The three CH_3 groups stemming from the same carbon are grouped in parentheses when condensing this Lewis structure. The carbon-nitrogen triple bond need not be drawn. Its presence can simply be implied because we know how many bonds these atoms make when they have no charges.

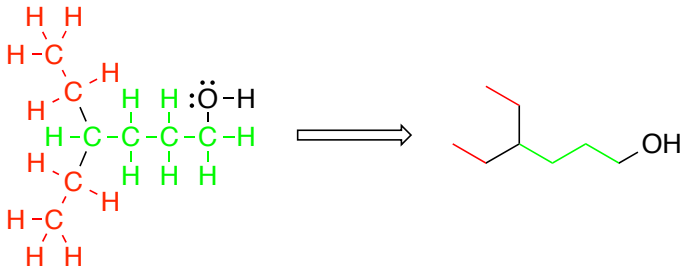


21. Remember that, when drawing skeletal structures, every vertex between bonds and every end of a bond signify a carbon atom. The carbon is understood to have enough hydrogen atoms to give it a total of four bonds, unless a charge or an unpaired electron is shown. Heteroatoms must be drawn, and once we draw an atom's symbol, any hydrogens it possesses must also be shown.

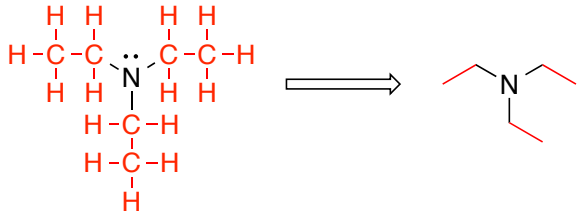
(a) There are eight carbons in this compound, and we can match them to the eight carbons in the skeletal structure.



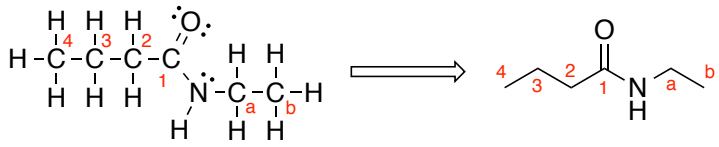
(b) The two CH_2CH_3 groups stemming from the same carbon are highlighted in red. The remaining four carbons in the molecule are shown in green. Note that we must draw the symbol for oxygen, and we must also show the hydrogen bonded to oxygen.



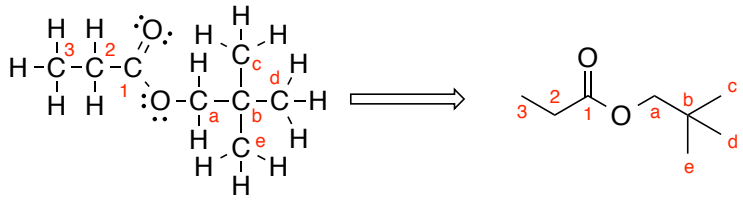
(c) The three CH_2CH_3 groups bonded to the nitrogen are highlighted in red.



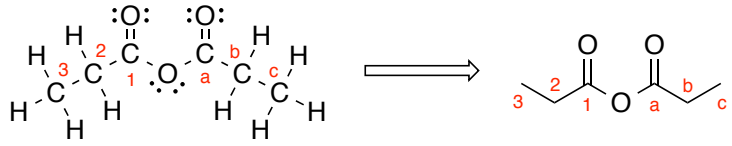
(d) Labeling the carbons with numbers and letters helps to ensure that we have the four carbons in the left-hand portion of the molecule and the two attached to nitrogen as well. Notice that, since we had to draw nitrogen's symbol, the nitrogen's hydrogen was also shown.



(e) Once again, labeling the carbons is quite useful. It ensures that you have the proper number of carbon atoms in the skeletal structure.

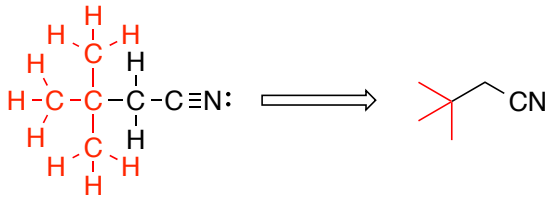


(f) There are three carbons on each side of this molecule.

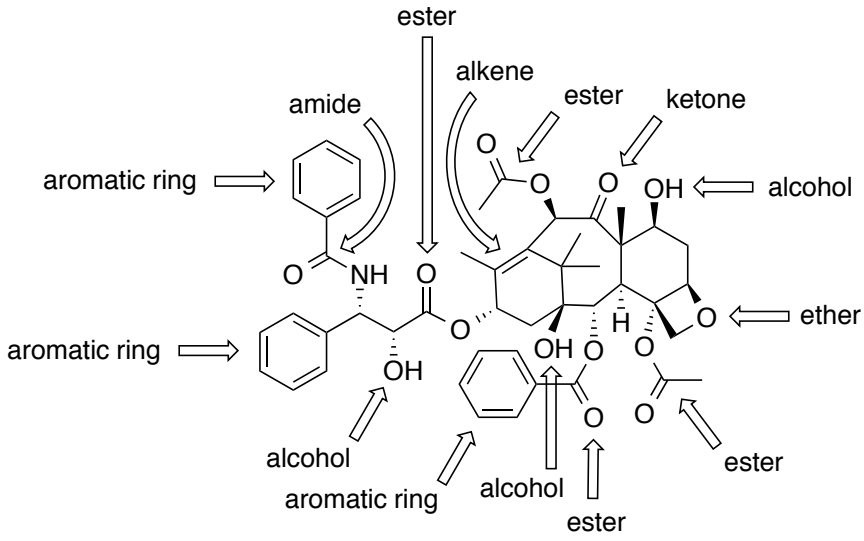


(g) The left-hand side of this compound has three carbons, while there are only two on the right-hand side.

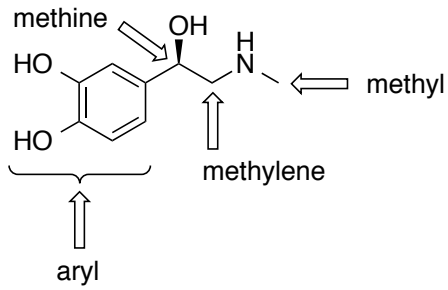
(h) The $C(CH_3)_3$ group is highlighted in red. There is one additional carbon between it and the CN group.



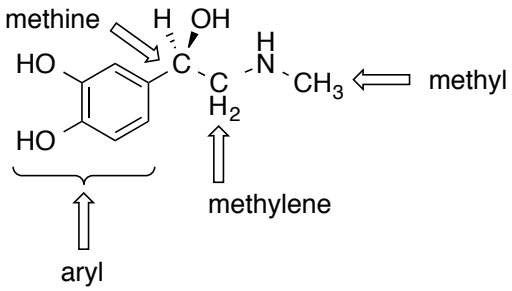
22.



23. The indicated groups include aryl, methine, methylene, and methyl.



If you found this difficult to see, it may help to draw all of the implied hydrogens on the carbons under consideration. This helps to differentiate CH, CH_2, and CH_3 groups.



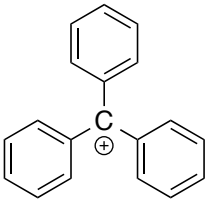
24.

(a) The central carbon has only three bonds and no lone pairs. As a result, it lacks a complete octet and is also charged.

$$Formal\ charge = Valence\ electrons - [unshared + {}^{1}/_{2}\ shared\ electrons]$$

$$Formal\ charge = 4 - \left[0 + {}^{1}/_{2}\ (6)\right] = +1$$

The formal charge of +1 is placed on the central carbon to complete the structure.



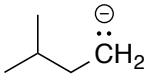
This molecule contains a carbocation.

(b) The terminal carbon has three bonds and a lone pair. It does have a complete octet, but this particular deviation from carbon's normal valence results in a charge.

$$Formal\ charge = Valence\ electrons - \left[unshared + {}^{1}/_{2}\ shared\ electrons\right]$$

$$Formal\ charge = 4 - \left[2 + {}^{1}/_{2}\ (6)\right] = -1$$

The negative charge is placed on carbon to complete the structure.



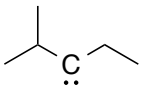
This molecule contains a carbanion.

(c) Although the indicated carbon lacks a complete octet, it does not have a formal charge.

$$Formal\ charge = Valence\ electrons - [unshared + {}^{1}/_{2}\ shared\ electrons]$$

$$Formal\ charge = 4 - [2 + {}^{1}/_{2}\ (4)] = 0$$

Therefore, this structure is fine as is. It contains a carbene.

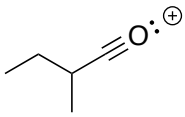


(d) All of the carbons in this compound have their normal valence and are therefore uncharged. However, the oxygen atom deviates from its typical valence and is charged.

$$Formal\ charge = Valence\ electrons - [unshared + {}^{1}/_{2}\ shared\ electrons]$$

$$Formal\ charge = 6 - [2 + {}^{1}/_{2}\ (6)] = +1$$

The +1 charge is placed on the oxygen atom to complete the structure.



25. It is important to be systematic when drawing a series of constitutional isomers. We can start with the four carbons in an unbranched chain. There are two unique places to put oxygen on this chain, and that gives two isomeric alcohols.

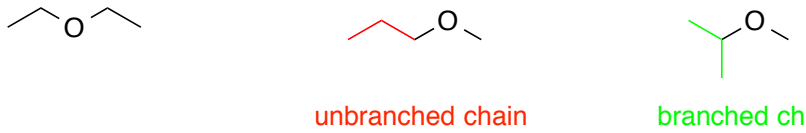
unbranched chain

We could also begin with a branched carbon chain. Once again, there are two unique places for oxygen, which leads to two additional isomeric alcohols.

branched chain

It would also be possible to have an ether as the oxygen-containing functional group. The oxygen can have two carbons on each side, or three carbons on one side

and one on the other. In the latter case, the three-carbon fragment can be unbranched or branched.

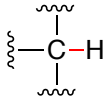


There are a total of seven constitutional isomers of $C_4H_{10}O$.

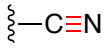
26.

(a) In each case, hydrogen is bonded to an element in Period 3. Within a row, atomic radius decreases as we move from left to right because there are more protons exerting an attractive force on the electrons in the same shell. Chlorine is the furthest to the right and is therefore the smallest element in this grouping. As a result, the chlorine-hydrogen bond is the shortest.

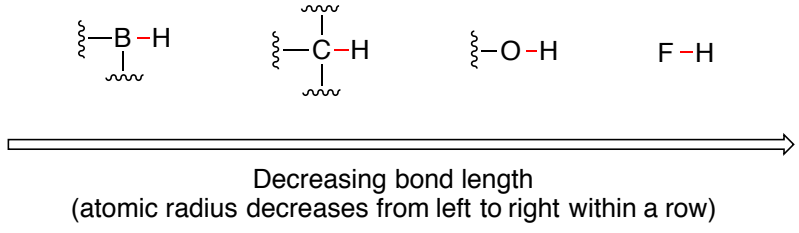
(b) These bonds are all between hydrogen and a Group IVA element. Within a column, the smallest element resides at the top because it has the valence shell with the smallest radius. Carbon is therefore the smallest element in this series, and the carbon-hydrogen bond is the shortest.



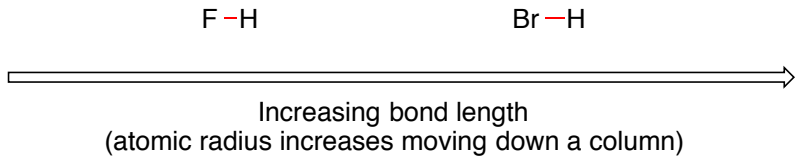
(c) This group consists of two double bonds and two triple bonds. Triple bonds are shorter than comparable double bonds. Additional bonds link the atoms more closely. Of the two triple bonds, the carbon-nitrogen triple bond is expected to be shorter because nitrogen has a smaller radius than carbon.



(d) This group contains atoms in different rows and columns. We can begin by comparing those elements in the same row. Of these, fluorine is the smallest, so the fluorine-hydrogen bond is the shortest.



We can then compare fluorine to bromine since they reside in the same column. Once again, fluorine is smaller, so the fluorine-hydrogen bond is shorter.

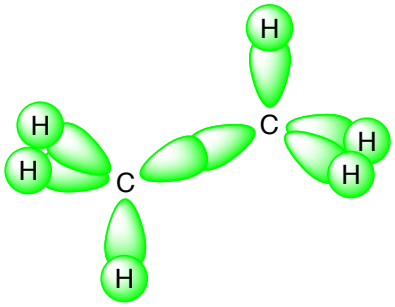


The fluorine-hydrogen bond is therefore the overall shortest bond of the group.

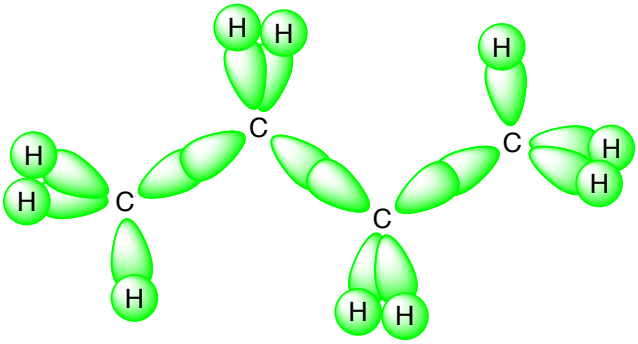
F–H

27.

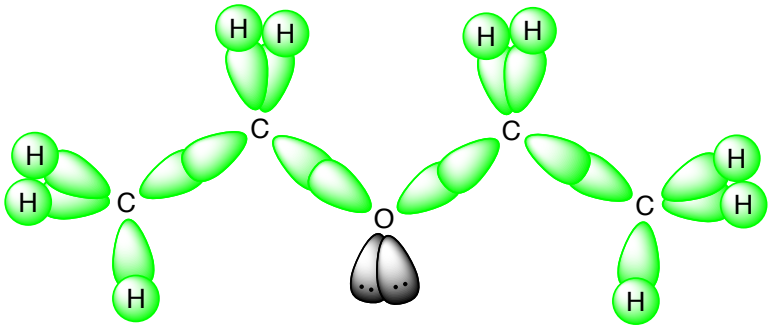
(a) The two carbons are each sp^3 hybridized. Two of their hybrid orbitals are overlapped to form the carbon-carbon bond. The rest of the sp^3 orbitals overlap with hydrogen s orbitals to create the C-H bonds. All of the bonds in the molecule are σ bonds, and all of the bond angles are 109.5°.



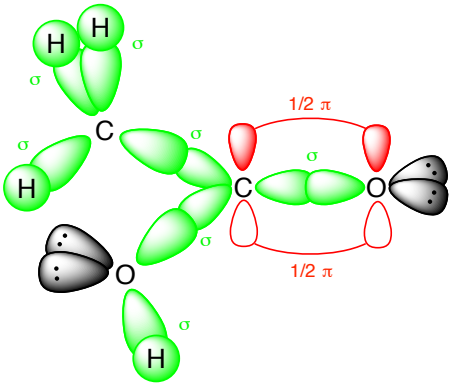
(b) This molecule builds on the structural motif of the preceding example. Two methylene (CH_2) groups are inserted between the terminal methyl (CH_3) groups. Both of the methylene carbons are sp^3 hybridized, just like their methyl counterparts. All of the bonds are σ, and all of the bond angles are 109.5°.



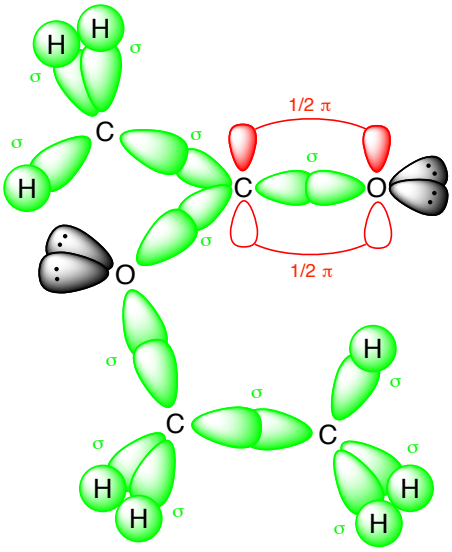
(c) Once again, we expand upon the previous structure by inserting a new group. The central oxygen falls between the two CH_2CH_3 groups, which have the same architecture as in part (b). The oxygen atom is surrounded by two atoms and two lone pairs, so it too is sp^3 hybridized. Two of its hybrid orbitals are used to make σ bonds with the neighboring carbons, while the other two house lone pairs. The orbitals that solely contain lone pairs and do not participate in a bond are gray. All of the bonds are σ bonds, and all of the bond angles are about 109.5°. While the lone pairs on oxygen are diffuse, there is a resistance to compressing the C-O-C bond angle because the CH_2CH_3 groups are large.



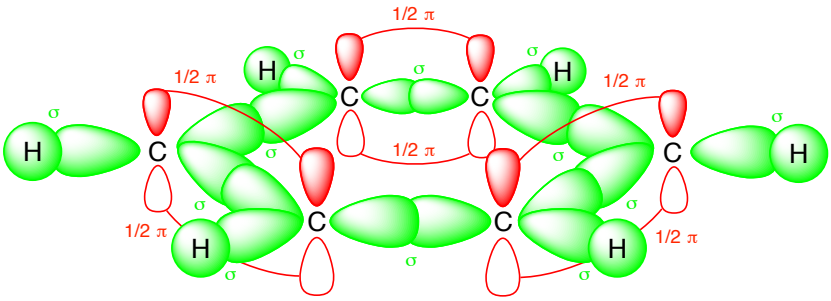
(d) The carbonyl (C=O) consists of sp^2 hybridized carbon and oxygen atoms. Its carbon is surrounded by three atoms, and its oxygen is surrounded by one atom and two lone pairs. The carbonyl carbon uses all of its sp^2 hybrid orbitals to make σ bonds. The carbonyl oxygen uses one for a σ bond and two to house lone pairs. Each atom has an unhybridized p orbital that is used for the π bond. The carbon of the methyl (CH_3) group is sp^3 hybridized, and so is the oxygen of the hydroxyl (OH) group. The molecule's σ bonds are highlighted in green. The orbitals that solely contain lone pairs and do not participate in a bond are gray. The bond angles around sp^3 hybridized atoms are approximately 109.5°, while those around the sp^2 hybridized carbonyl carbon are 120°.



(e) This molecule builds on the structure of the compound in part (d). The difference is that a CH_2CH_3 group is bonded to the carboxyl oxygen to make an ester. The carbons within the CH_2CH_3 group are sp^3 hybridized.

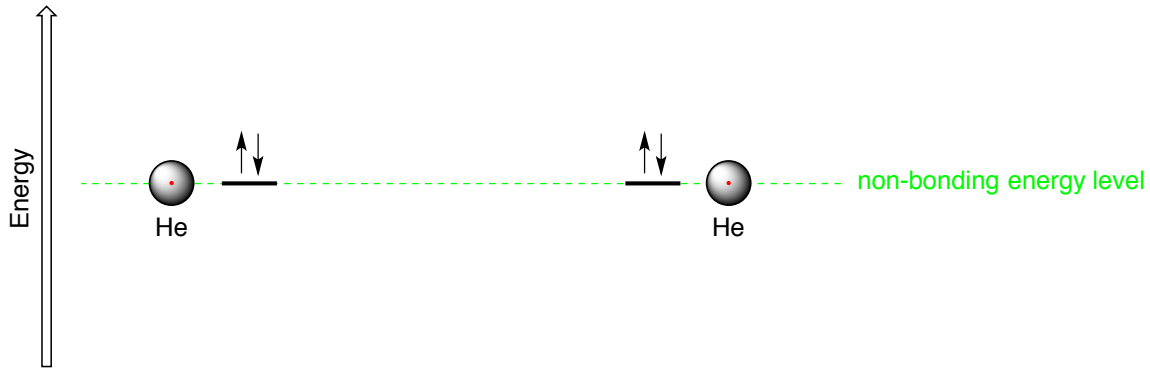


(f) The benzene ring consists of six sp^2 hybridized carbon atoms. Each of these makes two σ bonds with adjacent carbons and one σ bond with its hydrogen. Additionally, each carbon has one unhybridized p orbital that is used to make the molecule's π bonds. All of the bond angles are 120°.

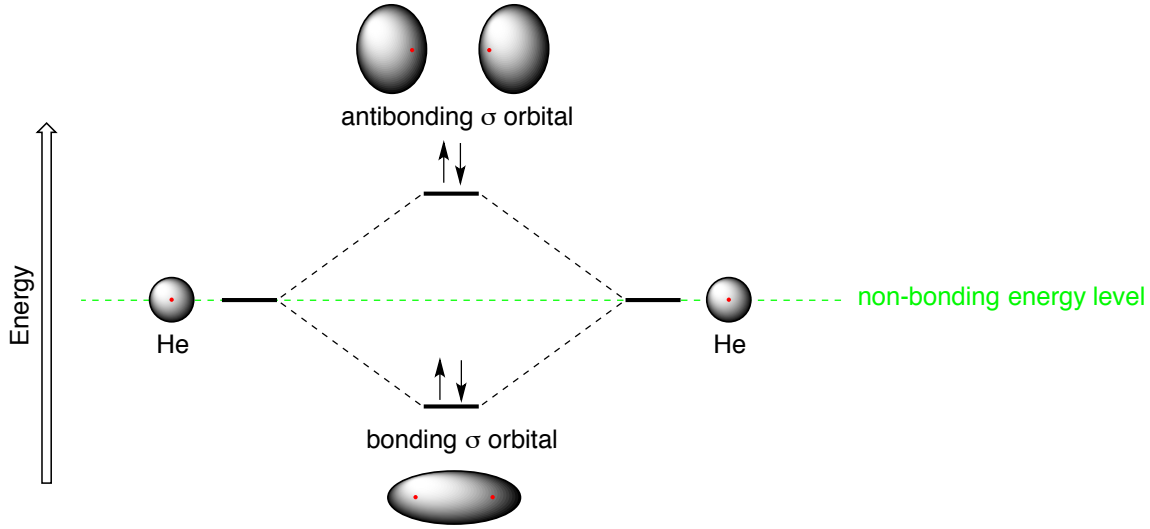


Note that the differing orbital sizes are merely meant to convey a sense of perspective. The larger orbitals at the bottom of the structure denote that this part of the molecule is extending out of the page, closer to the viewer.

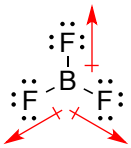
28. As shown in the following diagram, each helium atom has two electrons in its 1s orbital.



As these atoms approach bonding distance, bonding and antibonding σ orbitals would both be populated. Two of the electrons are stabilized, and two are destabilized relative to the non-bonding energy level. The energetic benefit is essentially cancelled by the energetic cost, and there is not a distinct advantage over two helium atoms in the non-bonding state.



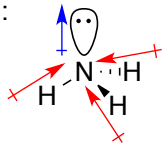
29. Remember that it is critical to consider shape before drawing conclusions about a molecule's polarity. The central atom of BF_3 is surrounded by three atoms and *no* lone pairs. The 24 valence electrons in BF_3 are used in forming the σ bonds and in placing lone pairs on the more electronegative fluorines. Consequently, boron has an incomplete octet. With only three atoms around it, boron is sp^2 hybridized. While there are dipoles pointing toward the fluorine atoms, they are evenly distributed in space and cancel each other, giving this molecule a net dipole of zero.



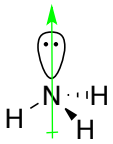
dipoles cancel;
net dipole = 0

It is also important not to make assumptions about polarity based on molecular formula alone. Some students will jump to the conclusion that NH_3 should have the same outcome as BF_3 because their formulas are similar: a central element with three identical atoms around it. However, NH_3 yields a totally different answer when its shape is considered. The molecule has eight valence electrons. This is enough to give nitrogen a lone pair to complete its octet. Since nitrogen is surrounded by three atoms and one lone pair, it is sp^3 hybridized and has a trigonal pyramidal shape. Its individual dipoles have a cumulative component that leads to a net dipole.

Individual dipoles:

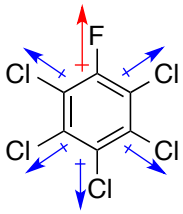


Net molecular dipole:

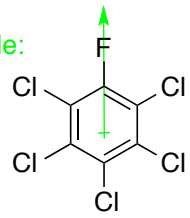


This highly halogenated aromatic ring has a net dipole due to its lack of symmetry. All of the carbons of the ring are sp^2 hybridized and therefore trigonal planar. Thus, the ring is drawn in a geometrically accurate fashion. There is a dipole toward each of the halogens, but since fluorine is more electronegative than chlorine, the dipole it causes is larger. As a result, there is a net molecular dipole.

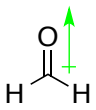
Individual dipoles:



Net molecular dipole:

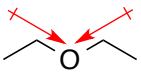


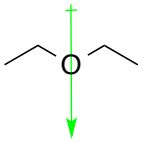
This small aldehyde has an sp^2 hybridized carbon at its core. As a result, this drawing is geometrically accurate. There is a dipole toward the oxygen atom. Since this dipole is unopposed, there is a net molecular dipole. Note that we can also consider the dipoles toward each of oxygen's lone pairs. This does not alter our conclusion though because the net dipole they cause reinforces the dipole of the carbon-oxygen bond.



Similarly, this alkyl halide has a polar carbon-chlorine bond that results in a net molecular dipole. Once again, considering the heteroatom's lone pairs would not alter the conclusion.

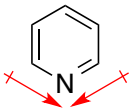
The carbon-oxygen bonds of this ether are polarized toward oxygen. While the horizontal components of these dipole cancel, the vertical components are additive and result in a net molecular dipole.

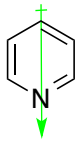
Individual dipoles: 

Net molecular dipole: 

CH_3CH_3 does not contain any bonds that are considered polar. The carbon-carbon bond is non-polar, and the electronegativities of carbon and hydrogen are close enough that the C-H bonds are also considered non-polar. Consequently, this molecule has zero net molecular dipole.

This compound has carbon-nitrogen bonds that are polarized toward nitrogen. Their horizontal components cancel, but their vertical components are additive and result in a net molecular dipole. Yet again, considering the dipole of nitrogen's lone pair does not alter our conclusion.

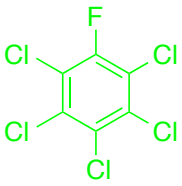
Individual dipoles: 

Net molecular dipole: 

The answers are summarized below. Those molecules with a net molecular dipole are highlighted in green. The non-polar molecules are in black.

BF_3

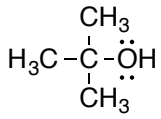
NH_3



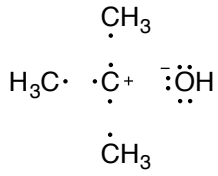
CH_3CH_3

30. In each part, it is helpful to begin by drawing the molecule's structure more fully.

(a) This alcohol's structure is:

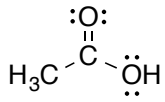


The carbon-carbon bonds are broken evenly, giving one electron to each atom. However, when the carbon-oxygen is broken, both electrons go to the more electronegative oxygen atom.

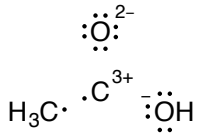


The net charge on the central carbon atom is +1, so this is its oxidation state.

(b) This molecule is a carboxylic acid.

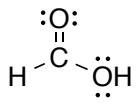


The carbon-carbon bond is broken evenly, but each of the carbon-oxygen bonds are broken so as to give the electrons to oxygen.

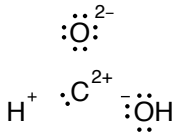


The net charge on the central carbon is +3, so this is its oxidation state.

(c) This is another carboxylic acid.

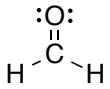


When the carbon-oxygen bonds are broken, the electrons are given to oxygen. However, when the carbon-hydrogen bond is broken, the electrons go to carbon.

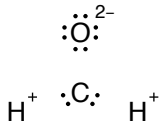


This reveals the oxidation state of +2 for the central carbon.

(d) This molecule is an aldehyde.

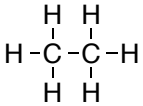


When breaking carbon's bonds, it receives the electrons from hydrogen, but it gives the electrons to oxygen.

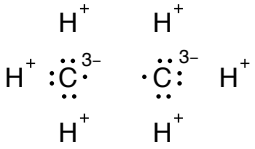


This shows an oxidation state of zero for carbon.

(e) This compound is a two-carbon alkane.

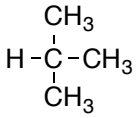


The carbon-carbon bond is broken evenly, but the carbon-hydrogen bonds are broken so as to give carbon the electrons.

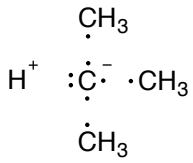


This shows that each carbon has an oxidation state of –3.

(f) This is a branched alkane.

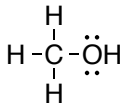


The C-C bonds are broken evenly, but the electrons from the C-H bond go to carbon.

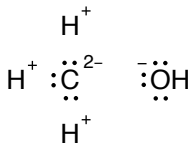


The central carbon is at an oxidation state of –1.

(g) This is an alcohol.

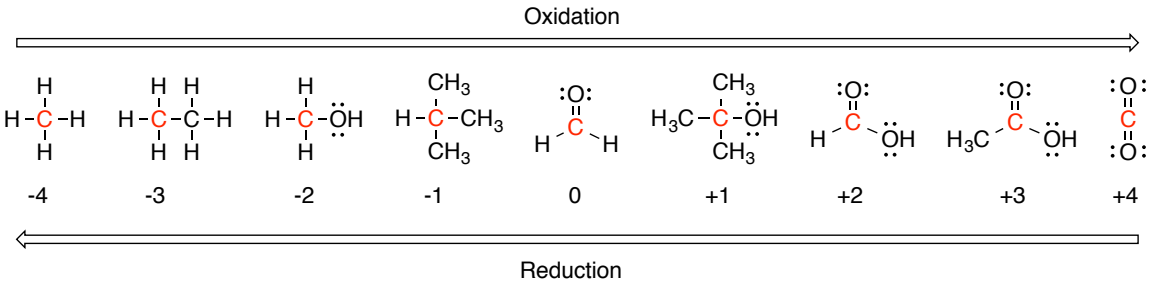


The electrons in the C-O bond go to oxygen, but those in the C-H bonds go to carbon.

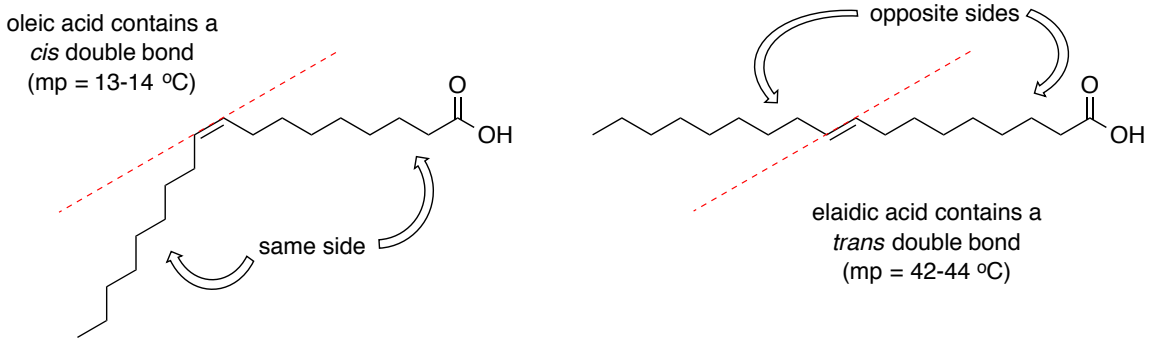


Carbon's oxidation state is –2 in this case.

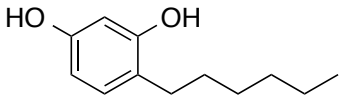
Note: These examples, along with the two given in the text of this Section, represent the spectrum of carbon's oxidation states. They are presented in order below.



31. The sole difference between these compounds is in their alkenes. Oleic acid contains a *cis* alkene, which means that the two groups attached to it are on the same side of the double bond. In contrast, elaidic acid contains a *trans* alkene, meaning that the two groups attached to the alkene are on opposite sides of the double bond. The bend in the backbone of oleic acid makes it more difficult to pack molecules closely in an orderly fashion. As a result, its crystal lattice is weak, and oleic acid melts at a lower temperature. Elaidic acid packs more effectively in the solid state leading to a higher melting point.



32. To be able to move through a hydrophobic medium, a molecule should have some hydrophobic character. Hydrocarbon portions of a molecule (i.e., those parts containing only carbon and hydrogen) are hydrophobic, so a molecule with a larger hydrocarbon segment stands a better chance of moving through the microbial membrane. The last compound in the list meets this criterion. It happens to be known as 4-hexylresorcinol and is used topically for minor infections.



33.

(a) The number of protons for a given element is invariable. The 53 protons allow us to identify this element as iodine by comparison to a periodic table. Since the number of protons is the atomic number, that portion of the symbol is accounted for. The mass number is the sum of the protons and neutrons, which is 127 in this case (53 + 74). The fact that there is one more electron than the total number of protons reveals the negative charge of this ion.

$$^{127}_{53}I^{-}$$

(b) Once again, we are given the atomic number (i.e., the number of protons). This allows us to identify the element as barium. The mass number is 138 (the sum of the 56 protons and 82 neutrons). Since there are two fewer electrons than protons, this ion has a +2 charge.

$$^{138}_{56}Ba^{2+}$$

(c) In this case, we don't have the atomic number, but we can infer it. If the element has 86 electrons and a +1 charge, we know that it must have one less electron than its number of protons. This ion therefore has 87 protons, which means that it is francium.

$$^{223}_{87}Fr^{+}$$

This isotope of francium possesses 136 neutrons, which is determined by taking the difference of the mass number and atomic number.

(d) Since the atomic number (13) was given, we can easily identify this element as aluminum. We total the protons and neutrons to obtain the mass number, and the charge is written as part of the symbol as well.

$$^{27}_{13}Al^{3+}$$

To have a +3 charge, the ion's protons must exceed its electrons by three, so there are 10 electrons.

(e) We haven't been given the atomic number in this symbol, but it doesn't matter because we know that the element is phosphorus. The periodic table shows us that phosphorus has an atomic number of 15, so phosphorus always has 15 protons. The isotope with a mass number of 31 has 16 neutrons. In order to have a –3 charge, this ion must have 18 electrons.

(f) The alkali earth metals fall in Group IIA on the periodic table. Calcium has 20 electrons when neutral but would easily lose two to become a cation with a +2 charge that has argon's electronic configuration (i.e., 18 electrons).

(g) This would be the element in the fourth row of the periodic table that has two electrons fewer than the closest noble gas. If selenium gains two electrons, not only will it have a –2 charge but it will also have the stable electronic configuration of krypton.

(h) Since the element is a noble gas, we are limited to Group VIIIA. The number of neutrons is determined by taking the difference between the mass number and the atomic number. Only xenon has values that would yield 77 neutrons.

34.

(a) The average atomic mass is a weighted average of the masses of the isotopes. The weighting factors are the abundances of each isotope.

$$Ave.\,atomic\ mass = (Isotope\ mass)(Abundance) + (Isotope\ mass)(Abundance)$$

In this problem, we know the average atomic mass and the masses of each isotope, but we don't know the abundance of either isotope.

$$35.453\ amu = (34.9689\ \text{amu})(Abundance) + (36.9659\ \text{amu})(Abundance)$$

Fortunately, we can easily resolve the problem posed by having two unknowns and only a single equation. A second equation presents itself because we know that the sum of the abundances must be 1 (or 100% after multiplying by 100).

$$Abundance\ of\ ^{35}Cl + Abundance\ of\ ^{37}Cl = 1$$

We can rearrange the equation to put the abundance of one isotope in terms of the other.

$$Abundance\ of\ ^{37}Cl\ = 1 -\ Abundance\ of\ ^{35}Cl$$

Plugging this into our original equation gives us a single unknown, the abundance of chlorine-35.

$$35.453\ amu = (34.9689\ \text{amu})\left(Abun.\ ^{35}Cl\right) + (36.9659\ \text{amu})\left(1 -\ Abun.\ ^{35}Cl\right)$$

Distributing within the second term yields this form of the equation.

$$35.453\ amu = (34.9689\ \text{amu})\left(Abun.\ ^{35}Cl\right) + 36.9659\ \text{amu} - (36.9659\ \text{amu})\left(Abun.\ ^{35}Cl\right)$$

We then group terms with the variable on one side of the equation and those without the variable on the other side.

$$(1.997\ amu)\left(Abun.\ ^{35}Cl\right) = 1.5129\ amu$$

Finally, the equation yields the abundance of chlorine-35.

$$Abun.\ ^{35}Cl = 0.7576$$

Using our second equation, we can derive the abundance of chlorine-37.

$$Abundance\ of\ ^{37}Cl\ = 1 -\ Abundance\ of\ ^{35}Cl$$

$$Abundance\ of\ ^{37}Cl\ = 1 -\ 0.7576 = 0.2424$$

These values can be put in a percentage form if we prefer. The abundance of chlorine-35 is 75.76%, while that of chlorine-37 is 24.24%.

(b) Once again, average atomic weight is the weighted average of the masses of the individual isotopes.

$$79.904\ amu = (78.9183\ \text{amu})(Abundance) + (80.9163\ \text{amu})(Abundance)$$

Since we know neither abundance, we must express one in terms of the other.

$$Abundance\ of\ ^{79}Br + Abundance\ of\ ^{81}Br = 1$$

$$Abundance\ of\ ^{81}Br = 1 - Abundance\ of\ ^{79}Br$$

This allows us to develop an equation with a single unknown.

$$79.904\ amu = (78.9183\ \text{amu})\left(Abun.\ ^{79}Br\right) + (80.9163\ \text{amu})\left(1 - Abun.\ ^{79}Br\right)$$

Solving the equation yields the abundance of bromine-79.

$$79.904\ amu = (78.9183\ \text{amu})\left(Abun.\ ^{79}Br\right) + 80.9163\ \text{amu} - (80.9163\ \text{amu})\left(Abun.\ ^{79}Br\right)$$

$$(1.998\ \text{amu})\left(Abun.\ ^{79}Br\right) = 1.0123$$

$$Abun.\ ^{79}Br = 0.5067$$

We can now use our second equation to determine the abundance of bromine-81.

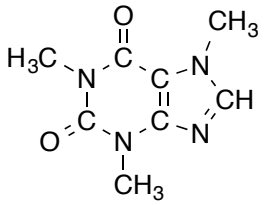
$$Abundance\ of\ ^{81}Br = 1 - Abundance\ of\ ^{79}Br$$

$$Abundance\ of\ ^{81}Br = 1 - 0.5067 = 0.4933$$

These abundances can also be expressed as percentages if desired. A sample of bromine contains 50.67% bromine-79 and 49.33% bromine 81.

The abundances of chlorine and bromine determined in parts (a) and (b) of this problem will be important in our chapter on Mass Spectrometry (Chapter 8).

35. In order to perform calculations involving caffeine, we'll need its molecular formula and weight. The molecular formula is obtained simply by counting the atoms in the molecule. It may help to draw out all of the atoms whose presence was merely implied.



This shows the formula of caffeine to be $C_8H_{10}N_4O_2$. The molecular weight is obtained by tallying the masses of the atoms present.

$$8 \times 12.01\ g/mole + 10 \times 1.01\ g/mole + 4 \times 14.01\ g/mole + 2 \times 16.00\ g/mole = 194.22\ g/mole$$

(a) We are provided with the number of carbon atoms in a sample of caffeine, and we are asked to determine the mass of this sample. To do so, we begin by converting atoms of carbon to moles of carbon because we can only compare different substances on a mole-to-mole basis. The moles of carbon can then be converted to moles of caffeine because the molecular formula tells us that there are 8 moles of carbon in every mole of caffeine. Finally, caffeine's molecular weight enables us to convert from moles of caffeine to grams of caffeine.

$$(3.10 \times 10^{21}\ atoms\ C)\left(\frac{1\ mole\ C}{6.02 \times 10^{23}\ atoms\ C}\right)\left(\frac{1\ mole\ caffeine}{8\ mole\ C}\right)\left(\frac{194.22\ g\ caffeine}{1\ mole\ caffeine}\right) = 0.125\ g\ caffeine$$

Notice how chemists often use the terms molecular weight and molar mass interchangeably. Formally, we used the molar mass of caffeine above, but since the molecular weight and molar mass are numerically identical and differ only in their units, the distinction is often ignored.

(b) Now that we know the mass of this sample of caffeine, which incidentally is about how much you would find in a cup of coffee, we can perform some calculations involving the other constituent atoms. To determine the moles of oxygen in this sample, convert the mass of caffeine to moles using its molecular weight. Then, relate the moles of caffeine to moles of oxygen. The molecular formula tells us that there are two moles of oxygen in every mole of caffeine.

$$(0.125\ g\ caffeine)\left(\frac{1\ mole\ caffeine}{194.22\ g\ caffeine}\right)\left(\frac{2\ moles\ O}{1\ mole\ caffeine}\right) = 0.00129\ moles\ O$$

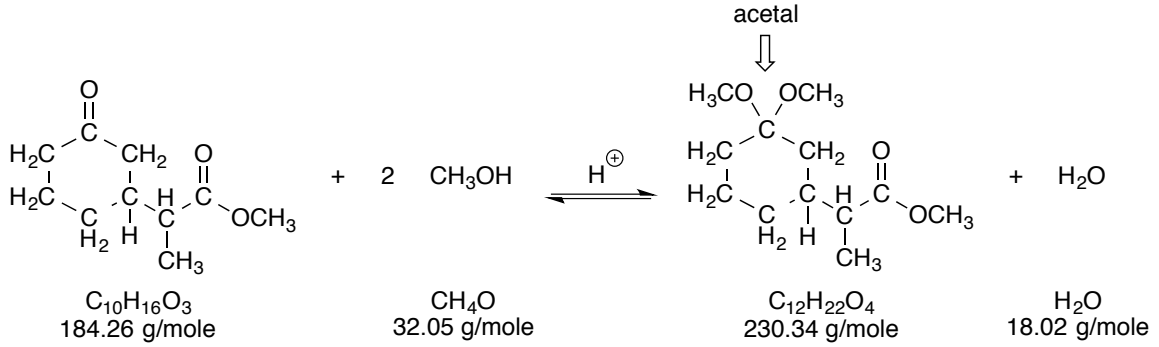
(c) To determine how many hydrogen atoms are in this sample, convert the mass of caffeine to moles of caffeine using the molecular weight. Then, using the information in caffeine's molecular formula ($C_8H_{10}N_4O_2$), convert moles of caffeine to moles of hydrogen. Finally, use Avogadro's number to convert moles of hydrogen to atoms of hydrogen.

$$(0.125\ g\ caffeine)\left(\frac{1\ mole\ caffeine}{194.22\ g\ caffeine}\right)\left(\frac{10\ moles\ H}{1\ mole\ caffeine}\right)\left(\frac{6.02 \times 10^{23}\ atoms\ H}{1\ mole\ H}\right) = 3.87 \times 10^{21}\ atoms\ H$$

(d) To determine how much of this sample's mass is due to nitrogen, convert the mass of caffeine to moles of caffeine. Use the information provided in the molecular formula to relate moles of caffeine to moles of nitrogen. Finally, use nitrogen's molar mass to convert the moles of nitrogen to grams of nitrogen.

$$(0.125\ g\ caffeine)\left(\frac{1\ mole\ caffeine}{194.22\ g\ caffeine}\right)\left(\frac{4\ moles\ N}{1\ mole\ caffeine}\right)\left(\frac{14.01\ g\ N}{1\ mole\ N}\right) = 0.0361\ g\ N$$

36. Before performing calculations, we'll need some information about the reactants and products. To obtain the molecular weights, we first need to find the molecular formulas. It is easier to count the atoms without making errors if you draw out those atoms whose presence was merely implied. To determine the molecular weights, just tally the masses of the atoms in the formula.



(a) To determine the theoretical yield of the acetal, calculate how much can be made from each of the reactants. The smaller value is the theoretical yield, or the maximum amount of product that it is possible to prepare in this reaction.

The mass of the ketone can be converted to moles of ketone using its molecular weight. The moles of ketone are converted to moles of acetal using the 1 : 1 ratio of these substances in the balanced reaction equation. Finally, the molecular weight of the acetal is used to convert moles of acetal into mass of acetal.

$$(5.00\ g\ ketone)\left(\frac{1\ mole\ ketone}{184.26\ g\ ketone}\right)\left(\frac{1\ mole\ acetal}{1\ mole\ ketone}\right)\left(\frac{230.34\ g\ acetal}{1\ mole\ acetal}\right) = 6.25\ g\ acetal$$

We are given the quantity of methanol (CH_3OH) as a volume (mL) rather than a mass (g). However, we were also given the density of methanol, which relates its mass to its volume. This allows for the conversion of milliliters of methanol into grams of methanol. Methanol's molecular weight is used to convert the mass (g) into moles. The balanced chemical equation shows that two moles of methanol are needed to make one mole of acetal. Finally, the moles of acetal are converted into mass using its molecular weight.

$$(2.00\ mL\ CH_3OH)\left(\frac{0.792\ g\ CH_3OH}{1\ mL\ CH_3OH}\right)\left(\frac{1\ mole\ CH_3OH}{32.05\ g\ CH_3OH}\right)\left(\frac{1\ mole\ acetal}{2\ moles\ CH_3OH}\right)\left(\frac{230.34\ g\ acetal}{1\ mole\ acetal}\right)$$
$$= 5.69\ g\ acetal$$

The investigator has enough ketone to make 6.25 g acetal, but that doesn't matter because there is only enough methanol to make 5.69 g acetal. The amount of methanol available limits the amount of acetal that can be prepared, so methanol is the limiting reagent. The theoretical yield of acetal is 5.69 g.

(b) The percent yield is the amount of product obtained divided by the amount of product it was possible to obtain. This quotient is multiplied by 100 to put it in percent form.

$$\%\ yield = \frac{amount\ of\ product\ obtained}{theoretical\ yield\ of\ product} \times 100$$

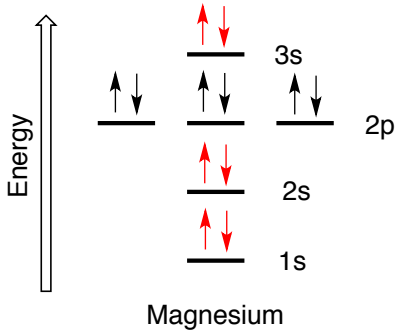
$$\%\ yield = \frac{5.25\ g\ acetal}{5.69\ g\ acetal} \times 100 = 92.3\ \%$$

(c) Since we know that methanol is the limiting reagent, we can begin with the 2.00 mL of methanol used in the reaction. Once again, we must use its density to convert milliliters to grams. Then, the molecular weight of methanol allows for the conversion of mass to moles. The balanced reaction equation shows that two moles of methanol are needed to produce one mole of water. Moles of water can be converted to grams of water using its molecular weight. Finally, the density of water is used to convert mass to volume.

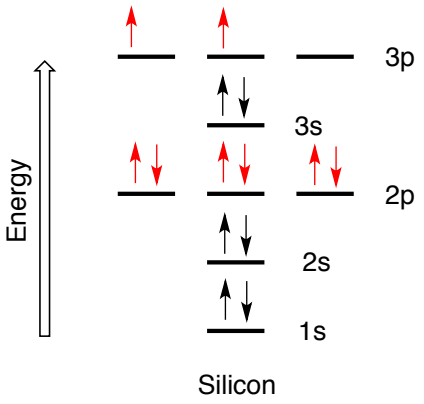
$$(2.00\ mL\ CH_3OH)\left(\frac{0.792\ g\ CH_3OH}{1\ mL\ CH_3OH}\right)\left(\frac{1\ mole\ CH_3OH}{32.05\ g\ CH_3OH}\right)\left(\frac{1\ mole\ H_2O}{2\ moles\ CH_3OH}\right)\left(\frac{18.02\ g\ H_2O}{1\ mole\ H_2O}\right)\left(\frac{1\ mL\ H_2O}{1\ g\ H_2O}\right)$$
$$= 0.445\ mL\ water$$

37.

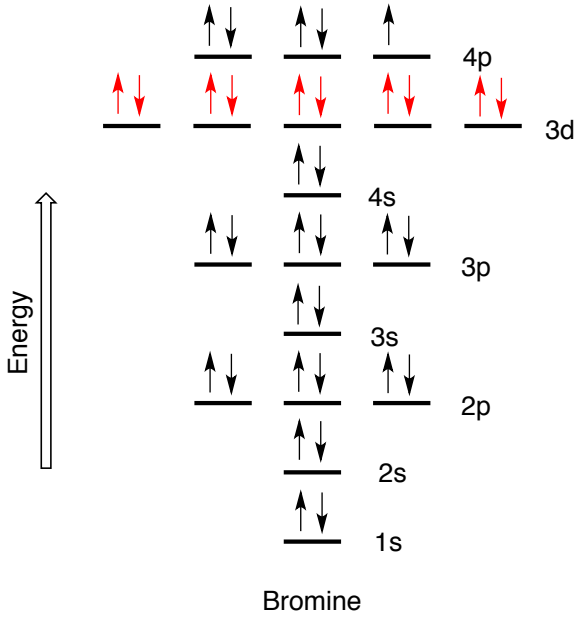
(a) When ℓ = 0, the orbital in question is s. Magnesium has filled 1s, 2s, and 3s orbitals, so it has a total of six s electrons. Note that no value was specified for the principal quantum number, n, so the correct answer includes all s electrons with any n value.



(b) When ℓ = 1, the orbital under consideration is p. Silicon has filled 2p orbitals and only two electrons in the 3p orbitals. This makes for a total of eight p electrons. Again, no n value was specified, so the answer includes all p electrons with any principal quantum number.



(c) When ℓ = 2, the orbital under consideration is d. Bromine has filled 3d orbitals, so it has a total of ten d electrons.



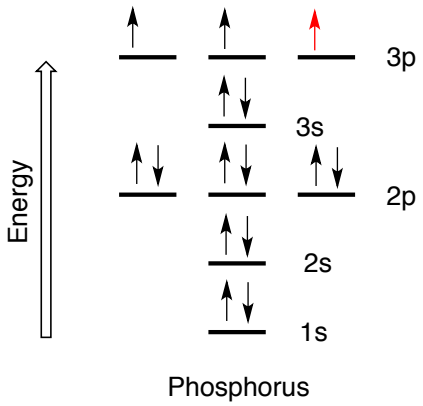
(d) The acceptable values for ℓ include 0 through (n–1). When n = 1, ℓ may only be 0; it cannot have a value of 1 in this instance.

(e) These quantum numbers (n = 2 and ℓ = 1) refer to the 2p electrons. There are three p orbitals in any shell, and each orbital can hold two electrons. So, six electrons can have quantum numbers n = 2 and ℓ = 1.

(f) These two quantum numbers (n = 4 and ℓ = 2) refer to the 4d electrons. There are five d orbitals in a shell, and each holds two electrons. So, ten electrons can have quantum numbers n = 4 and ℓ = 2.

(g) The values for m_ℓ range from $-\ell$ to ℓ. The m_ℓ value given is outside of that range, so it is unacceptable. For the ℓ value given (1), m_ℓ can be –1, 0, or 1. Additionally, m_s can only be $^1/_2$ or $-^1/_2$. The quantum number m_s *cannot* have a value of 1.

(h) Phosphorus' fifteenth electron resides in a 3p orbital, so n = 3 and ℓ = 1. The value for m_ℓ could be –1, 0, or 1 because which value denotes p_x, p_y, and p_z is arbitrary. However, if we simply go in order, m_ℓ = 1 is a logical choice. The m_s value is $^1/_2$ because the spin is up, although this is also arbitrary because all three 3p electrons could have their spins down.



38.

(a) Xe: $1s^2 2s^2 2p^6 3s^2 3p^6 4s^2 3d^{10} 4p^6 5s^2 4d^{10} 5p^6$

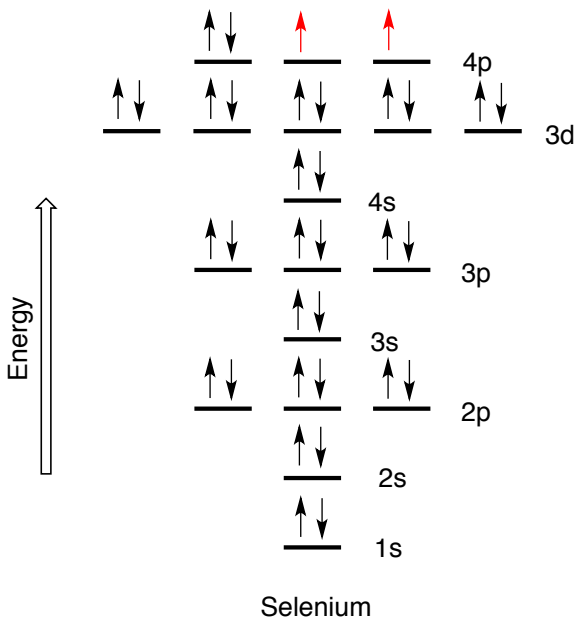
(b) In forming cations, elements lose electrons from their valence shell to attain the preceding noble gas's configuration. Neutral indium has three electrons in its valence shell.

In: $1s^2 2s^2 2p^6 3s^2 3p^6 4s^2 3d^{10} 4p^6 5s^2 4d^{10} 5p^1$

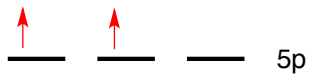
These are lost to form the In^{3+} cation.

In^{3+}: $1s^2 2s^2 2p^6 3s^2 3p^6 4s^2 3d^{10} 4p^6 4d^{10}$

(c) All of the electrons in selenium's filled orbitals are paired. However, the 4p orbitals are not completely filled. It is important to remember how degenerate orbitals fill. Hund's rule states that the most stable electronic configuration has the greatest number of parallel spins. Therefore, the first three electrons in the 4p orbitals have parallel spins. The fourth electron in the 4p orbitals must be paired with another. This leaves two unpaired electrons.



(d) The discussion in part (c) allows us to answer this question more succinctly. It is not necessary to draw the full diagram showing where all of the electrons reside. We know that, if there are any unpaired electrons, they will be in the highest-energy orbitals if they are not completely filled. Tin has only two electrons in the 5p orbitals. According to Hund's rule, these should have parallel spins. As a result, there are two unpaired electrons.



(e) Given that the element is neutral, the number of electrons must be equal to the number of protons. The element whose last electron would appear at $5p^4$ is tellurium. It has 52 protons, which is also the sum of the electrons in the given configuration.

(f) The element must have two more electrons than protons to explain its –2 charge. The given configuration contains a total of 18 electrons. The element with 16 protons is sulfur, so this configuration is for S^{2-}.

(g) The given configuration ($1s^22s^22p^3$) is for *neutral* nitrogen. However, the symbol used was N^{3-}, which has a configuration of $1s^22s^22p^6$.

(h) According to the aufbau principle, electrons should be placed into the lowest energy orbitals available. Consequently, we cannot move to a higher energy orbital until the lower energy orbitals are completely filled. While sulfur does have six valence electrons, there must be two in the 3s orbital to fill it. Therefore, there can only be four in the 3p orbital. Its configuration should be $1s^22s^22p^63s^23p^4$.

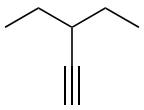
39.

(a) These elements are all in the same column of the periodic table. Each has lost one electron to attain the preceding noble gas's electronic configuration. This, though, does not alter the fact that elements get larger as we move down a column because they are using bigger valence shells. It is merely that the valence shells are one smaller than when the elements were neutral. Regardless, cesium (Cs^+) is the furthest down Group IA, so it is the largest of the group.

(b) The smaller the atoms involved, the shorter the bond will be. Each bond involves a carbon atom. Carbon is paired with an atom in Period 2, 3, or 4. In general, the atoms in Period 2 will be smaller. Furthermore, we know that atomic radius decreases as we move from left to right along a row. Fluorine is the smallest atom of the group since it is at the right end of a row and the top of a column. It makes the shortest bond with carbon.

(c) Potassium (K) is the furthest from fluorine, so it is the least electronegative element of the group.

(d) For comparable types of covalent linkages, single bonds are longer than double bonds, which are in turn longer than triple bonds. There is only one molecule with a carbon-carbon triple bond, which is the shortest bond in this collection of compounds.



(e) The ions Si^{4-}, Cl^-, P^{3-}, and S^{2-} all have eighteen electrons, just like argon. The ions Al^{3+}, Na^+, and Mg^{2+} all have ten electrons, like neon. The smallest ion must be among those with only ten electrons because these ions have valence electrons in the second shell; whereas, the others utilize the third shell. Of the ions with neon's electronic configuration, aluminum (Al^{3+}) has the most protons, so it will pull the electrons closest to the nucleus, making it the smallest ion.

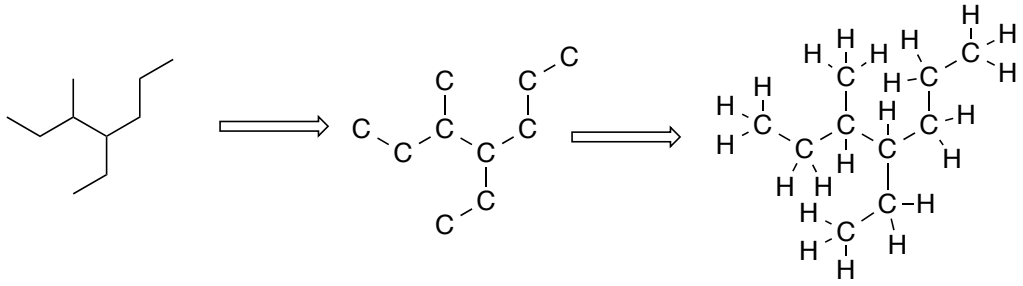
(f) All of these species have krypton's electronic configuration. They all have filled 4s and 4p orbitals. Arsenic (As^{3-}) has the fewest protons to pull the electrons in the valence shell closer to the nucleus. It is therefore the biggest of this isoelectronic series.

(g) A greater disparity in electronegativity makes for a larger dipole. Each bond has a carbon atom. In this series, there are no elements that lie very far to the left of carbon on the periodic table. Considering those elements on the right side of carbon on the periodic table, we find fluorine, which is the most electronegative element. Therefore, the C-F bond has the largest dipole. We could also say that it is the most polar bond.

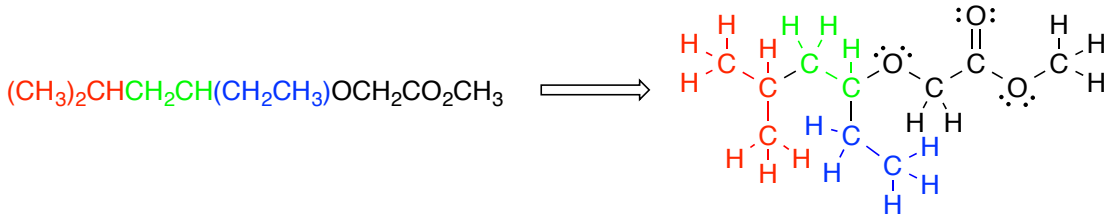
(h) Both H^- and He have the same configuration: $1s^2$. Since helium has more protons to pull these two electrons closer to the nucleus, it is the smaller of the two.

40.

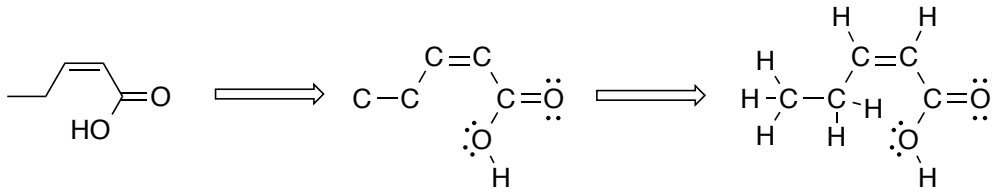
(a) When converting a skeletal structure to a Lewis structure, you can begin by drawing a carbon at the end of every bond where no other element's symbol is shown. Then, you can add enough hydrogens to each carbon to give it a full octet. If a charge or unpaired electron had been shown, we would have to adjust the number of hydrogens to account for that.



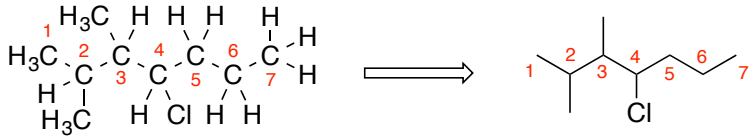
In the branched portion of the molecule, colors are used to show how fragments of the condensed formula match with the corresponding pieces of the Lewis structure.



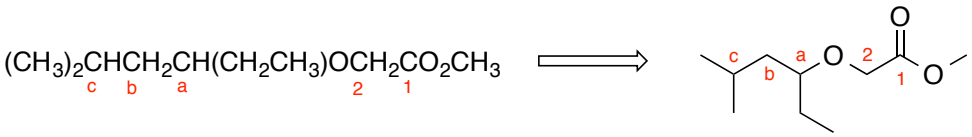
Once again, start by drawing a carbon atom at the end of each bond where no other element's symbol is shown. Then, add enough hydrogens to give each carbon four bonds.



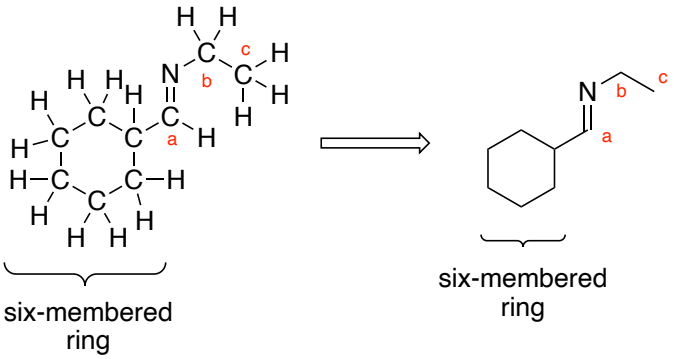
(b) Numbering the atoms can be useful to ensure that none are added or deleted during the conversion.



Label the segments of the molecule in whatever way you see fit to help you make the conversion accurately.

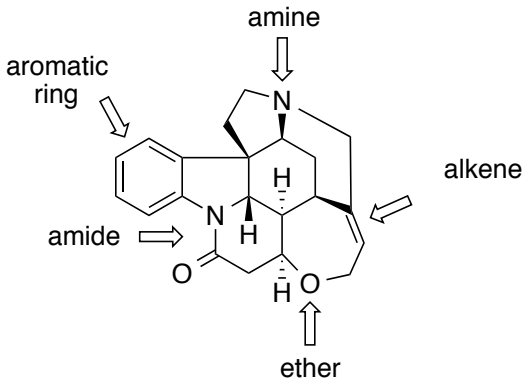


Any labeling you choose to do is solely for the purpose of helping you make the conversion. Sometimes you may find that a molecule has a feature, like the six-membered ring below, that is clear enough that you need not label it.

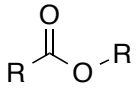


41.

(a) The functional groups in strychnine include an aromatic ring, an amine, an alkene, an ether, and an amide.

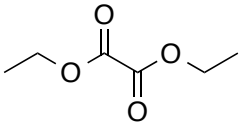


(b) Esters have the following generic structure.

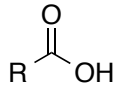


ester

One example of an isomer of $C_6H_{10}O_4$ containing only esters is shown below.

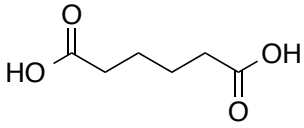


Carboxylic acids contain a carboxyl (CO_2H) group.

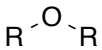


carboxylic acid

An isomer of $C_6H_{10}O_4$ containing only carboxylic acids is shown below.

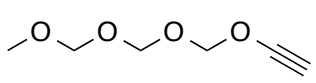


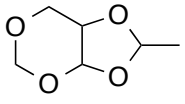
Ethers contain an oxygen atom bonded to two R groups.

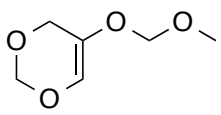


ether

The preceding functional groups had π bonds in them, but an ether does not. A π bond has the effect of removing two hydrogen atoms from the structure. An isomer of $C_6H_{10}O_4$ containing only ethers must either have two π bonds, two rings (a ring also removes a pair of hydrogens from the structure), or one of each. An example of each is shown below.



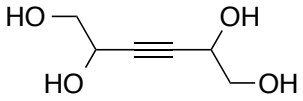


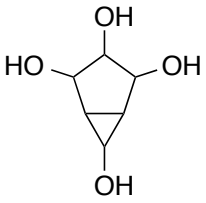


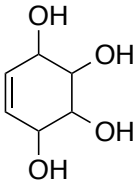
An alcohol contains a hydroxyl group.

alcohol

Since this functional group has no π bonds or rings, the R group must have two π bonds, two rings, or one of each. An example of each follows.

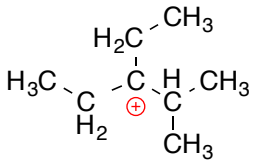






42.

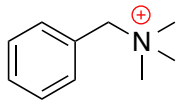
(a) The central carbon of the first molecule has only three bonds and no lone pair. Therefore, it should have a positive charge.



$$Formal\ charge = Valence\ electrons - \left[unshared\ +\ {}^{1}/_{2}\ shared\ electrons\right]$$

$$Formal\ charge = 4 - \left[0 + {}^{1}/_{2}\ (6)\right] = 4 - 3 = +1$$

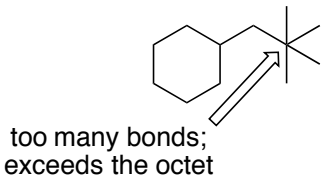
The nitrogen atom in the second molecule deviates from its normal valence. When we do a formal charge calculation, it becomes apparent that this nitrogen should have a positive charge.



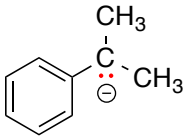
$$Formal\ charge = Valence\ electrons - \left[unshared\ +\ {}^{1}/_{2}\ shared\ electrons\right]$$

$$Formal\ charge = 5 - \left[0 + {}^{1}/_{2}\ (8)\right] = 5 - 4 = +1$$

There is a carbon atom in the final compound that has five bonds. Carbon can never have more than four bonds. It cannot exceed the octet because atoms with n = 2 can house a maximum of eight electrons in their valence shell.



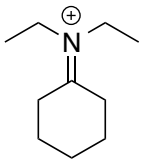
(b) When carbon has a negative charge, it has three bonds and one lone pair.



$$Formal\ charge = Valence\ electrons - \left[unshared\ +\ {}^{1}/_{2}\ shared\ electrons\right]$$

$$Formal\ charge = 4 - \left[2 +\ {}^{1}/_{2}\ (6)\right] = 4 - 5 =\ -1$$

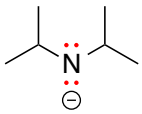
When nitrogen has a positive charge, it has four bonds and no lone pairs, so nothing needs to be added to this structure.



$$Formal\ charge = Valence\ electrons - \left[unshared\ +\ {}^{1}/_{2}\ shared\ electrons\right]$$

$$Formal\ charge = 5 - \left[0\ +\ {}^{1}/_{2}\ (8)\right] = 5 - 4 =\ +1$$

If nitrogen has two bonds and a negative charge, then it must also have two lone pairs.



$$Formal\ charge = Valence\ electrons - \left[unshared\ +\ {}^{1}/_{2}\ shared\ electrons\right]$$

$$Formal\ charge = 5 - \left[4\ +\ {}^{1}/_{2}\ (4)\right] = 5 - 6 =\ -1$$

When oxygen has three bonds and a positive charge, it also has one lone pair.

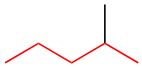
$$Formal\ charge = Valence\ electrons - [unshared\ +\ {}^{1}/_{2}\ shared\ electrons]$$

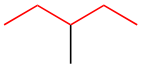
$$Formal\ charge = 6 - [2\ +\ {}^{1}/_{2}\ (6)] = 6 - 5 = +1$$

43.

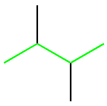
(a) When drawing an exhaustive set of isomers it is critical to be systematic. Begin with an unbranched six-carbon chain. There is only one isomer of this type.

Then, draw a five-carbon chain. The remaining carbon can be placed at two unique locations on this chain, giving two more isomers. Note that placing the remaining carbon on a terminus of the chain would generate the original unbranched isomer that we already drew.



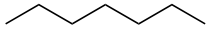


Next, draw a four-carbon chain. The remaining two carbons can be placed in only two unique ways on this chain. We can place one on each central carbon, or we can place both on one of the central carbons. Notice that placing both on one carbon as a CH_2CH_3 group would generate one of the isomers already drawn.

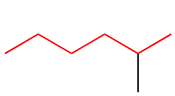


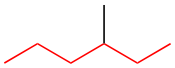
There is no way to shorten the chain further and create new isomers, so C_6H_{14} has a total of five constitutional isomers.

(b) Let's use the same method described above. Start with the longest possible carbon chain to generate the only unbranched isomer.

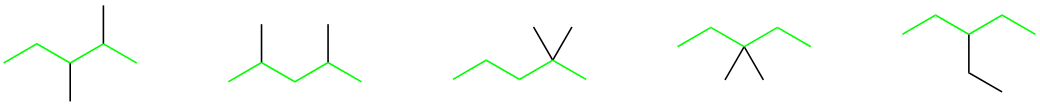


Then, shorten the chain by one. There are two unique ways to place the remaining carbon on this six-carbon chain. We cannot put the last carbon on a terminus because doing so would generate the isomer we already drew above.

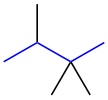




Shorten the chain by one more carbon to make a five-carbon chain. The two remaining carbons can be placed on adjacent interior carbons or non-adjacent interior carbons. They can also both be placed on the same interior carbon in two different locations. Lastly, they can be placed on the central carbon as a CH_2CH_3 group. If this CH_2CH_3 group were placed anywhere else, it would produce a previously drawn isomer.



Lastly, we can shorten the central chain to four carbons. The final three carbons can be distributed across in the interior positions in only one way to make a new isomer.

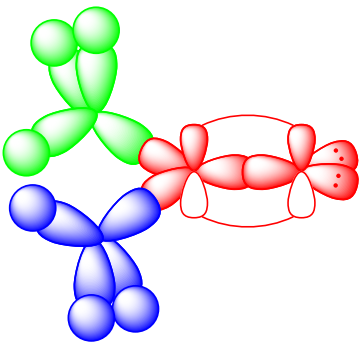


There are a total of nine isomers of C_7H_{16}.

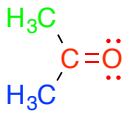
44. In these questions, we have to decide which element is consistent with the bonding pattern shown at each location. Remember that carbon tends to make four bonds. Nitrogen prefers to make three bonds and have one lone pair, while oxygen tends toward two bonds and two lone pairs. Hydrogens are easy to identify because of their spherical s orbitals.

Portions of each molecule have been colored to facilitate matching with the corresponding segments of the simplified structures.

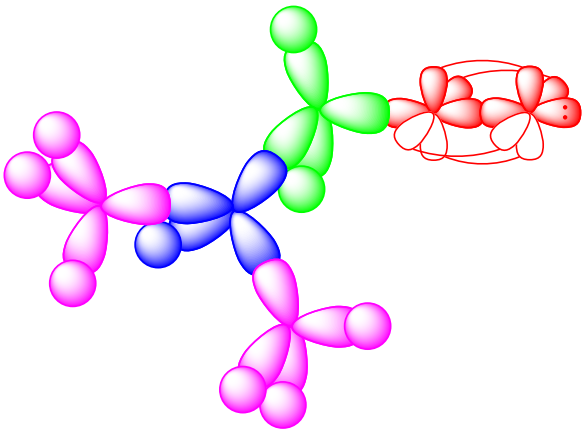
(a)



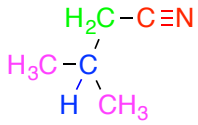
can also be drawn as:



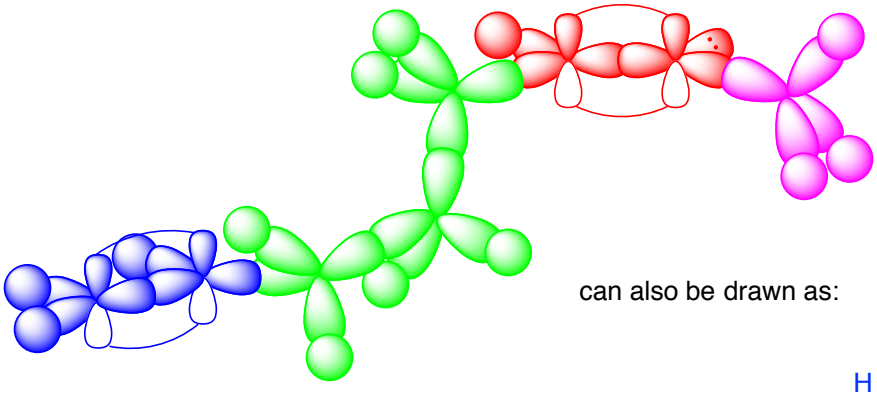
(b)



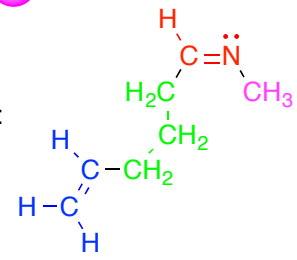
can also be drawn as:



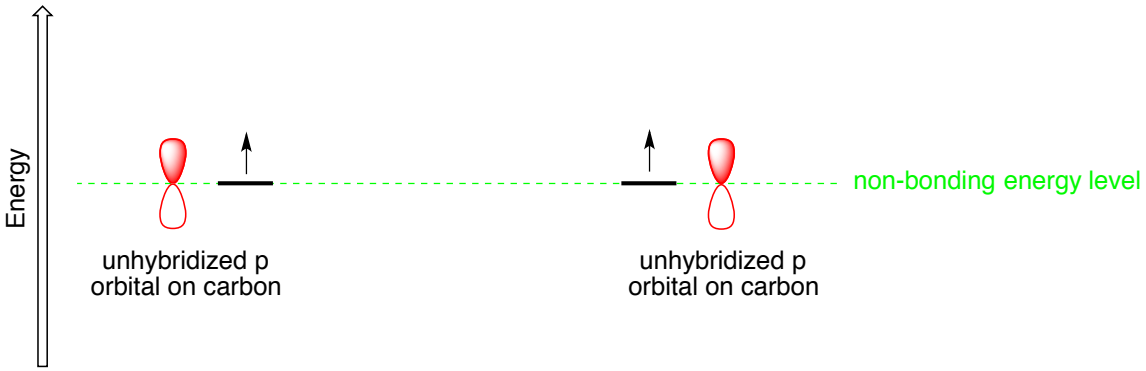
(c)



can also be drawn as:

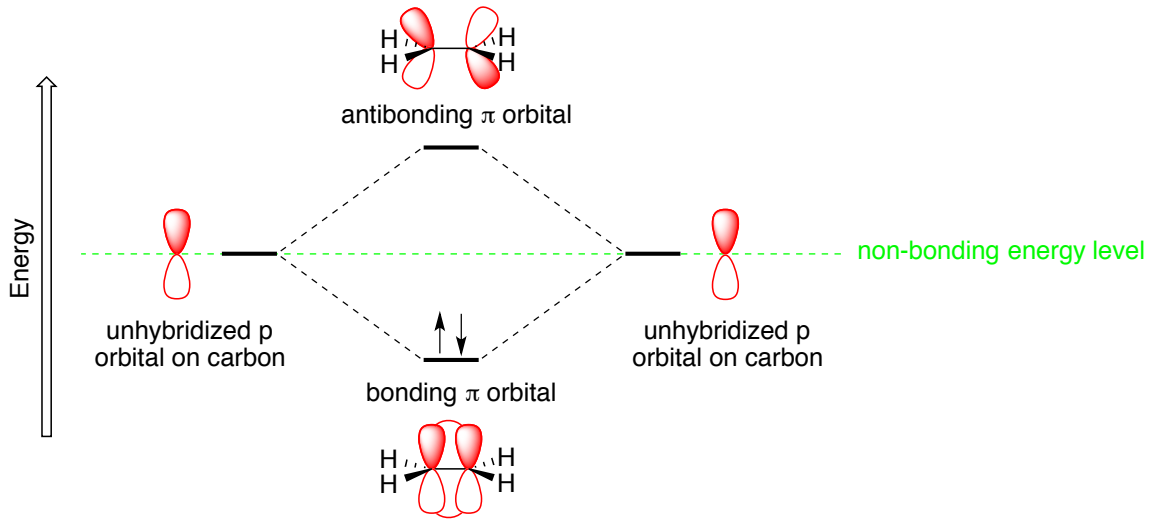


45. Each carbon has an unhybridized p orbital containing one electron.



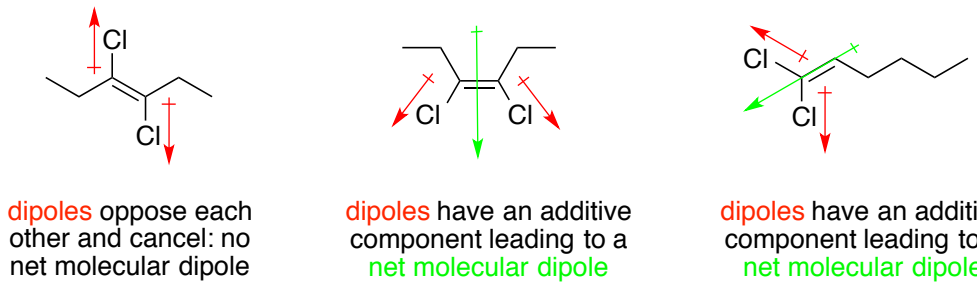
As these are brought into bonding distance, both bonding and antibonding molecular orbitals are produced. The two electrons are paired in the lower-energy

bonding orbital. These electrons are stabilized relative to the non-bonding level as a result. The antibonding π molecular orbital is unoccupied.



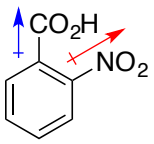
46.

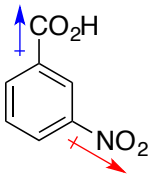
(a) There is no free rotation around a double bond. Rotating about a double bond would break the π bond as the p orbitals twisted out of parallel alignment. As a result, the dipoles directly oppose one another in the first molecule. They cancel, and there is no net molecular dipole. In the second and third molecules, the dipoles have an additive component that leads to a net molecular dipole. Since it has no net molecular dipole, the first molecule is the least polar of the group.

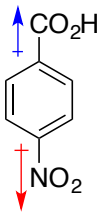


(b) These molecules have dipoles toward the groups attached to the ring. Both groups contain multiple electronegative elements that cause these dipoles. Since the groups differ, the magnitude of the dipoles differs as well. In the first compound, the two dipoles are as close as possible to pointing in the same direction. They will be largely additive, so this molecule has the greatest net molecular dipole. In the second compound, the dipoles have turned in slightly opposite directions. While there will still be a net molecular dipole due to their additive components, the slight opposition diminishes it. In the third structure, the two dipoles directly oppose one another. They will not cancel completely because they differ in magnitude, but this

compound will have the smallest net molecular dipole of the group and is therefore the least polar compound.

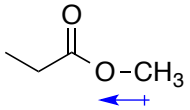




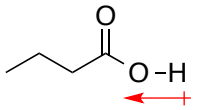


dipoles directly oppose one another leading to the smallest net molecular dipole

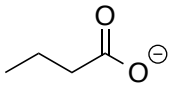
(c) The ester contains an O-C bond. The carboxylic acid contains an O-H bond, and the third compound has a charge. Charge is the epitome of polarity, so the last compound is quite polar. The choice comes down to whether the O-C or O-H bond is more polar. Although carbon and hydrogen have similar electronegativities, hydrogen is slightly less electronegative (refer to the periodic table in Section 9). As a result, the O-H bond has a more significant dipole than the O-C bond. The ester is therefore the least polar of the three.



smaller O-C dipole: least polar molecule



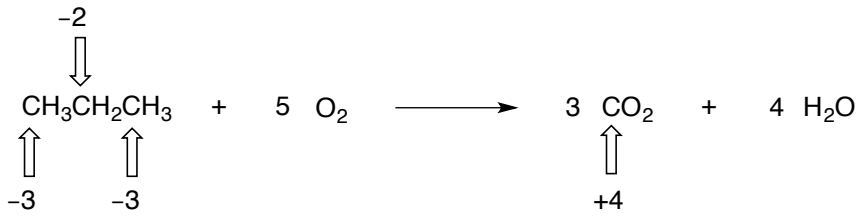
hydrogen is less electronegative than carbon leading to a larger dipole



charge = high polarity

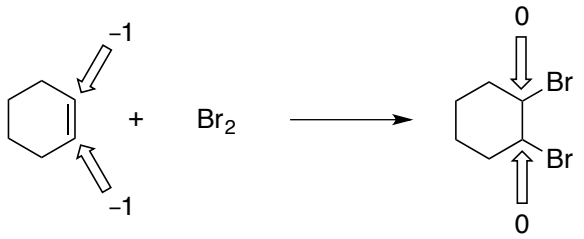
47.

(a) The oxidation state of each carbon is shown in the reaction equation below. Each carbon is oxidized by a significant amount during this combustion reaction. As a result, combustion can also be described as an oxidation reaction, and oxygen (O_2), the reagent that causes this oxidation, can be called an oxidizing agent.

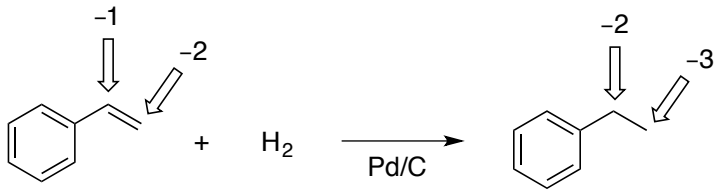


(b) Only some of the carbon atoms undergo a change in this reaction. We can ignore those carbons that are unchanged because their oxidation states will also be unchanged. The two carbons that are affected by the reaction are both oxidized from

the –1 to 0 oxidation state. As a result, this bromination is an oxidation reaction, and bromine (Br_2) is an oxidizing agent.



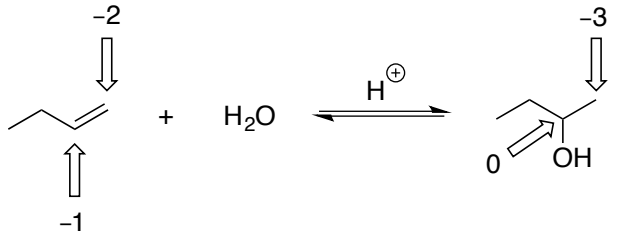
(c) In this reaction, both of the carbons undergoing a transformation are reduced by 1 because they each gain one more hydrogen atom than they had before. As a result, this reaction is a reduction, and hydrogen (H_2) is a reducing agent.



The palladium on carbon (Pd/C) shown below the arrow is merely a catalyst that is used in this reaction. We'll learn more about its role in Chapter 10.

(d) The crucial issue in this problem is noticing that two carbons are undergoing a change. Sometimes students focus only on the carbon that acquires the hydroxyl (OH) group because that is a glaring alteration. However, the terminal alkene carbon is also affected by the reaction, so we must account for its change in oxidation state as well.

The interior carbon is oxidized from –1 to 0, but the terminal carbon is reduced from –2 to –3. The net oxidation state of the two critical carbons is –3 in both the reactant and the product. Therefore, this reaction is neither and oxidation nor a reduction, and water is neither an oxidizing nor a reducing agent.

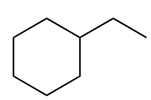


The acid (H^+) shown above the arrow is a catalyst used in this transformation. We'll learn more about the role of this catalyst in Chapter 10.

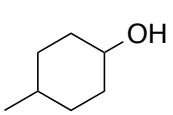
48. These questions focus on intermolecular forces.

(a) The first substance, an alkane, has only van der Waals attractions. The last compound, an ether, can experience stronger dipole-dipole forces, as well as van der Waals attractions. The two middle compounds, an alcohol and an amine, experience hydrogen bonding, dipole-dipole attraction, and van der Waals forces. Since these compounds have the strongest intermolecular forces, one of them will have the highest boiling point.

In deciding between the two, electronegativity makes the difference. Oxygen is more electronegative than nitrogen. This leads to more polar bonds in the alcohol, which will increase the intensity of hydrogen bonding and dipole-dipole attractions. As a result, the alcohol has the highest boiling point.

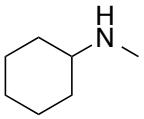


van der Waals

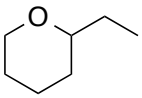


hydrogen bonding
dipole-dipole
van der Waals

more polar bonds



hydrogen bonding
dipole-dipole
van der Waals

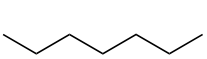


dipole-dipole
van der Waals

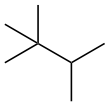
(b) Melting point is affected by the same factors that influence boiling point. Symmetry is also an important consideration for melting point though. Recall that more symmetrical molecules pack more efficiently in the solid state, leading to higher melting points.

The first two compounds are alkanes. They experience only van der Waals attractions and are therefore expected to have lower melting points. Of the two, the second one is more symmetrical, so it has a higher melting point.

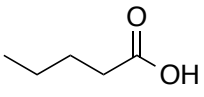
The latter two compounds are carboxylic acids. They experience the full complement of intermolecular forces available to covalent substances, so we expect them to have higher melting points than the alkanes. The second carboxylic acid is the more symmetrical of the two, so it should have the highest melting point of all four compounds in this group.



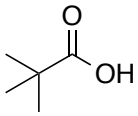
van der Waals



van der Waals
greater symmetry

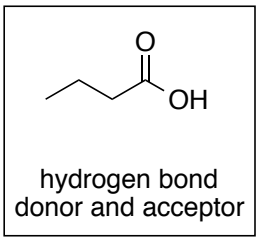


hydrogen bonding
dipole-dipole
van der Waals



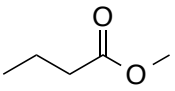
hydrogen bonding
dipole-dipole
van der Waals
greater symmetry

(c) To have high water solubility, a molecule must be capable of extensive interactions with water. It must be a very polar molecule. The first molecule fits this criterion. It is a carboxylic acid, so it can serve as both a hydrogen bond donor and acceptor. The second compound, an alkane, is very hydrophobic. It lacks the ability to hydrogen bond with water, and it contains no polar bonds. The last two molecules, an ester and an ether, can only act as hydrogen bond acceptors. Although they contain polar bonds, their opportunity for interaction with water is less than that of the carboxylic acid. Therefore, we anticipate that the carboxylic acid will be the most water soluble of these four compounds.



hydrogen bond donor and acceptor


no hydrogen bonding possible

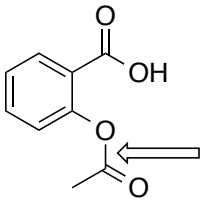


hydrogen bond acceptor

hydrogen bond acceptor

49.

Aspirin is shown below. It is made from three elements: carbon, hydrogen, and oxygen. Specifically, it contains nine carbon, eight hydrogen, and four oxygen atoms. Since it consists of multiple atoms held together by bonds, it can be called a molecule. Alternatively, it may also be called a compound because it contains atoms of more than one element combined in a fixed, precise ratio.

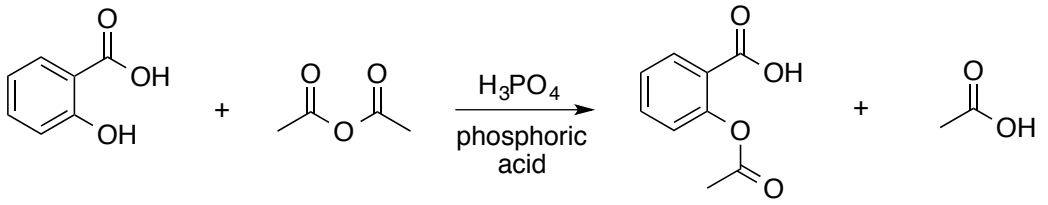


Since the bonds in aspirin result from the sharing of electrons, they are covalent. Aspirin contains twenty-one σ and five π bonds, along with eight lone pairs. The functional groups in aspirin include an aromatic ring, a carboxylic acid, and an ester. Three of its atoms are sp^3 hybridized, while ten are sp^2 hybridized and eight are unhybridized. The bond indicated by the arrow is formed from the overlap of carbon's sp^2 orbital with oxygen's sp^3 orbital.

The conversion factors and calculations explaining the answers in the next paragraph are given in the reaction equation and below it. Note that abbreviations used in the calculations appear underneath the substances' names in the reaction equation.

Based on the following reaction equation, aspirin can be prepared by the treatment of salicylic acid with one equivalent of acetic anhydride. The reaction yields one equivalent of aspirin and one equivalent of acetic acid as a byproduct. A minimum of 5.47 mL of acetic anhydride would be needed to react completely with 8.00 g of salicylic acid to yield up to 10.4 g of aspirin and 3.32 mL of acetic acid. Phosphoric acid, the only substance not included in the calculations, is a catalyst and is therefore neither created not destroyed in the reaction. If an experimenter actually obtains 8.53 g of aspirin from this reaction, the percent yield is 82.0%.

Reaction equation with molecular formulas and molar masses:



salicylic acid (S.A.) $C_7H_6O_3$ molecular weight: 138.13 g/mole

acetic anhydride (A.An.) $C_4H_6O_3$ molecular weight: 102.10 g/mole density: 1.082 g/mL

aspirin $C_9H_8O_4$ molecular weight: 180.17 g/mole

acetic acid (A.Ac.) $C_2H_4O_2$ molecular weight: 60.06 g/mole density: 1.049 g/mL

Calculation of the minimum amount of acetic anhydride needed to react completely with 8.00 g of salicylic acid:

$$(8.00\ g\ S.A.)\left(\frac{1\ mole\ S.A.}{138.13\ g\ S.A.}\right)\left(\frac{1\ mole\ A.An.}{1\ mole\ S.A.}\right)\left(\frac{102.10\ g\ A.An.}{1\ mole\ A.An.}\right)\left(\frac{1\ mL\ A.An.}{1.082\ g\ A.An.}\right)$$
$$= 5.47\ mL\ acetic\ anhydride$$

Calculation of the theoretical yield of aspirin:

$$(8.00\ g\ S.A.)\left(\frac{1\ mole\ S.A.}{138.13\ g\ S.A.}\right)\left(\frac{1\ mole\ aspirin}{1\ mole\ S.A.}\right)\left(\frac{180.17\ g\ aspirin}{1\ mole\ aspirin}\right)$$
$$= 10.4\ g\ aspirin$$

Calculation of the amount of acetic acid formed as a byproduct:

$$(8.00\ g\ S.A.)\left(\frac{1\ mole\ S.A.}{138.13\ g\ S.A.}\right)\left(\frac{1\ mole\ A.Ac.}{1\ mole\ S.A.}\right)\left(\frac{60.06\ g\ A.Ac.}{1\ mole\ A.Ac.}\right)\left(\frac{1\ mL\ A.Ac.}{1.049\ g\ A.Ac.}\right)$$
$$= 3.32\ mL\ acetic\ acid$$

Calculation of the amount of product actually obtained based on an 82.0% yield:

$$\% \; yield = \frac{amount \; of \; product \; obtained}{theoretical \; yield \; of \; product} \times 100$$

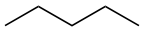
$$82.0\% = \frac{amount \; of \; product \; obtained}{10.4 \; g \; aspirin} \times 100$$

$$\frac{(82.0\%) \; (10.4 \; g \; aspirin)}{(100)} = amount \; of \; product \; obtained = 8.53 \; g \; aspirin$$

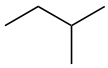
50. Our first step should be to illustrate the information we've been given. The following reaction equation shows the combustion of a hydrocarbon with eight equivalents of oxygen (O_2) to yield five equivalents of carbon dioxide (CO_2) and six equivalents of water (H_2O).

To balance this equation, the hydrocarbon reactant must contain five carbons and twelve hydrogens. We have now deduced the molecular formula of the hydrocarbon fuel in this reaction.

However, we were asked to draw the hydrocarbon's structure, and that is more specific than the molecular formula. There are three constitutional isomers that have the formula C_5H_{12}. One has an unbranched five-carbon chain.



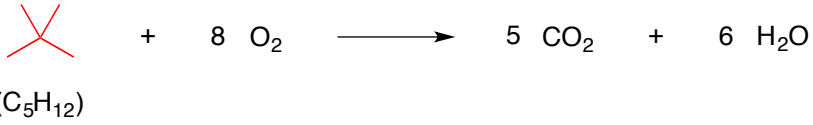
Another has a four-carbon chain with the remaining carbon attached to an interior location.



The last has a three-carbon chain with the two remaining carbons bonded to the central atom of the chain.

We are told that the actual hydrocarbon used has a higher melting point than its isomers. These three isomers all have similar intermolecular forces. Since they are all alkanes, they can only engage in van der Waals attractions. However, the last isomer has the greatest symmetry. As such, it will pack most efficiently in the solid

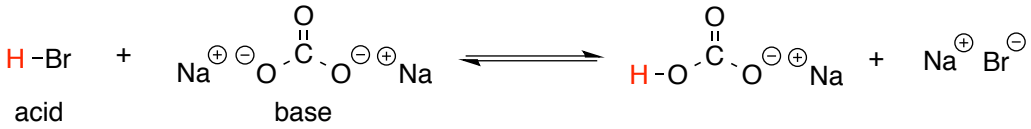
state and therefore has the highest melting point. So, the hydrocarbon used in the combustion reaction was the highly branched alkane:



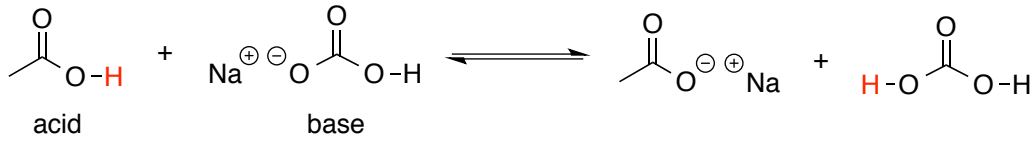
Solutions to Problems for Chapter 2: Acid-Base Chemistry

1. The essence of this problem is deciding which substance is donating the proton (i.e., H^+) and which molecule is accepting it. Recall that a Brønsted-Lowry acid is a proton donor, while a Brønsted-Lowry base is a proton acceptor.

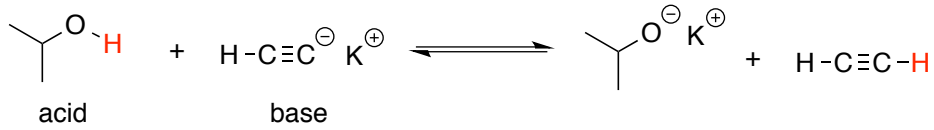
(a) In this reaction, a proton is transferred from hydrobromic acid (HBr), which is the acid, to sodium carbonate (Na_2CO_3), which plays the role of the base.



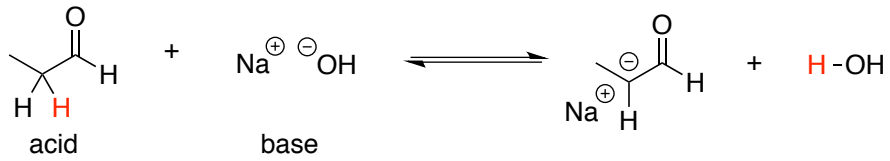
(b) This reaction entails the transfer of a proton from acetic acid (CH_3CO_2H) to sodium bicarbonate ($NaHCO_3$). Acetic acid is the Brønsted-Lowry acid, and sodium bicarbonate is the Brønsted-Lowry base.



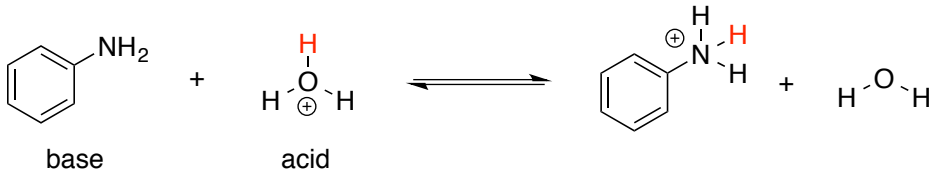
(c) Here, the alcohol donates a proton to the carbanion. The alcohol, as the proton donor, is the acid. The carbanion functions as a proton acceptor, so it is the base.



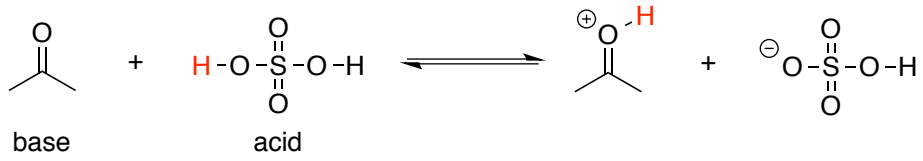
(d) In this problem, it may be helpful to draw out the hydrogens that are implied at the site of reaction. The aldehyde has two protons on the carbon adjacent to the carbonyl. One of these is donated to hydroxide as the reaction moves forward. The aldehyde is therefore the acid, while hydroxide functions as the base.



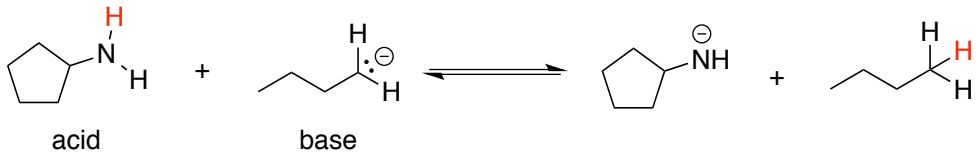
(e) In this transformation, the amine accepts a proton from the hydronium ion (H_3O^+). The amine is the base in this reaction, and hydronium ion is the acid.



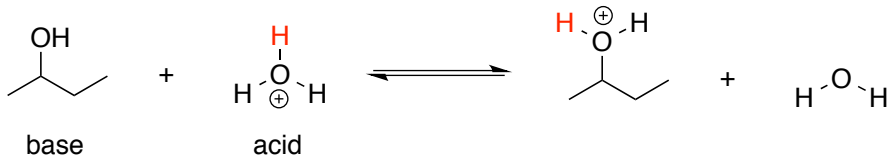
(f) Here, acetone (CH_3COCH_3) is accepting a proton from sulfuric acid. So, acetone is the base, and sulfuric acid is the acid.



(g) This reaction involves the transfer of a proton from the amine to the carbanion. The amine is acting as an acid, while the carbanion is the base.



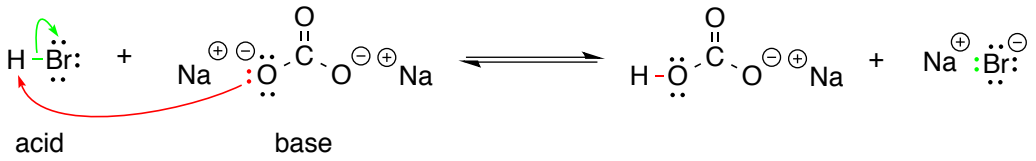
(h) In this acid-base reaction, the hydronium ion (H_3O^+) donates a proton to the alcohol. The alcohol is therefore the base, and the hydronium ion is the acid.



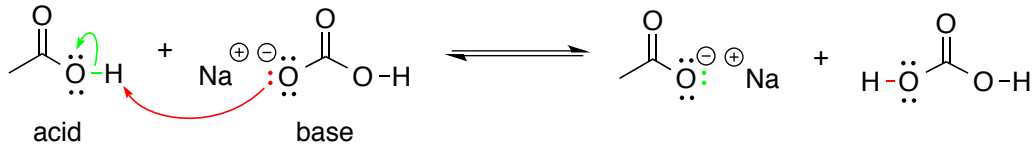
Looking back on this problem, it is worth noting that we saw an amine function as a base (in part e) and as an acid (in part g). Similarly, we saw an alcohol function as an acid (in part c) and as a base (in part h). Compounds that can act as acids or bases depending on the situation are call amphoteric, and we'll revisit them later in this chapter.

2. In each part of this question, identify the electron-rich site on the base. Then, draw an arrow from this site to the proton that is to be transferred from the acid. This arrow illustrates the formation of a new bond between the base and the proton. As the proton acquires this new bond, it must relinquish its preexisting bond, so a second arrow is needed to describe the cleavage of that σ bond. The arrow should begin on the σ bond between the proton and the atom to which it is connected. The electrons flow onto the atom other than hydrogen.

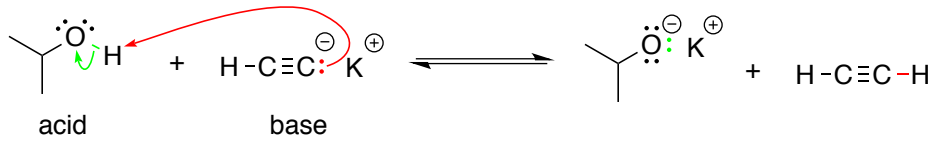
(a) Two oxygens of sodium carbonate (Na_2CO_3) bear formal negative charges. Either of these oxygen atoms uses a lone pair of electrons to form a new bond to the proton of hydrobromic acid (HBr). The proton's bond to bromine is severed as the electrons of that σ bond flow onto bromine, becoming a lone pair.



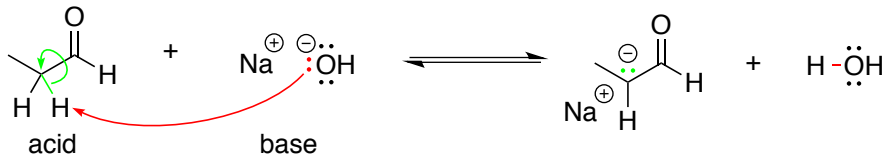
(b) Sodium bicarbonate ($NaHCO_3$) has one oxygen atom with a formal negative charge. This oxygen shares a lone pair with the proton of acetic acid (CH_3CO_2H) to form a new O-H bond. The proton is cleaved from acetic acid when the σ-bonding electrons are deposited onto the oxygen.



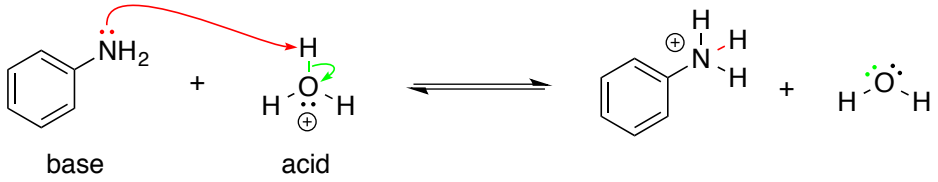
(c) The carbanion is electron rich, as evidenced by its negative charge. The lone pair of electrons responsible for this charge is extended to the alcohol's proton to generate a new C-H bond. The alcohol's O-H bond is cleaved as a result, and the electrons are given to the oxygen atom.



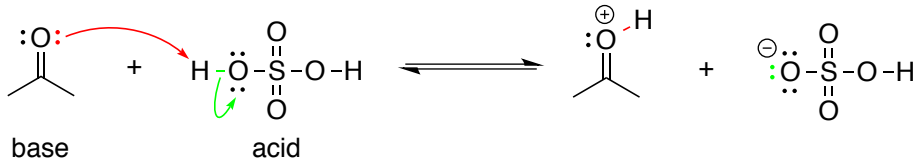
(d) Hydroxide (HO^-) uses a lone pair of electrons to deprotonate (i.e., remove the proton from) the aldehyde. The C-H bond is cleaved as a result, and these electrons flow onto carbon.



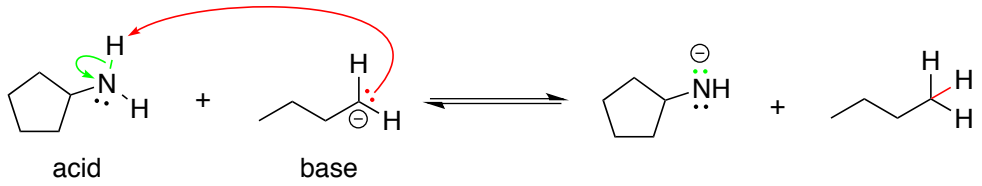
(e) The amine possesses a lone pair of electrons. These are used to create a new bond to one of the protons of the hydronium ion (H_3O^+). As this happens, the electrons in the O-H bond flow onto oxygen to release the proton from the hydronium ion.



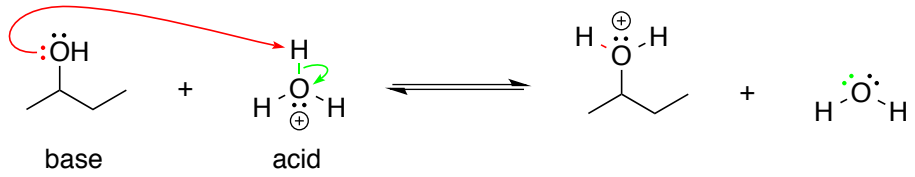
(f) The oxygen of acetone (CH_3COCH_3) has two lone pairs of electrons, one of which is extended to a proton of sulfuric acid to produce a new O-H bond. As this occurs, the proton is freed from sulfuric acid by the flow of σ-bonding electrons onto the neighboring oxygen.



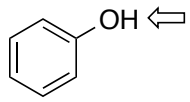
(g) The carbanion has a lone pair of electrons, and this lone pair is used to remove a proton from the amine. The N-H bond of the amine is broken when the electrons of the σ bond are placed on nitrogen as an unshared pair.



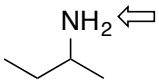
(h) The hydroxyl group of the alcohol has two lone pairs of electrons, and one of them makes the new bond to the proton donated by the hydronium ion. This proton is released from the hydronium ion when the σ bond breaks and the electrons fall onto oxygen as an unshared pair.



3. A Brønsted-Lowry acid must possess a reasonably acidic proton that it can donate to a base. All of these compounds except bromine contain protons. The most acidic protons in each compound are indicated by arrows. Later in this chapter, we'll learn how to identify the most acidic proton(s) in a molecule. Bromine, having no protons whatsoever, cannot possibly function as a proton donor, so it cannot be a Brønsted-Lowry acid.



phenol



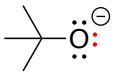
an amine

Br—Br

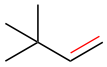
bromine

an alkyne

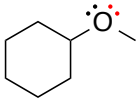
4. A Brønsted-Lowry base must be able to accept a proton. In order to do so, it has to have a pair of electrons that can be used to form a bond to the new proton. A lone pair of electrons or a π-bonding pair of electrons can be used for this purpose. Ordinarily, σ-bonding electrons cannot be used to accept a proton. The alkoxide and the ether possess lone pair electrons, while the alkene has a π-bonding pair, so these compounds can be bases. However, the alkane contains no lone pairs or π bonds, so it is incapable of acting as a base.



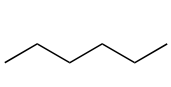
an alkoxide



an alkene



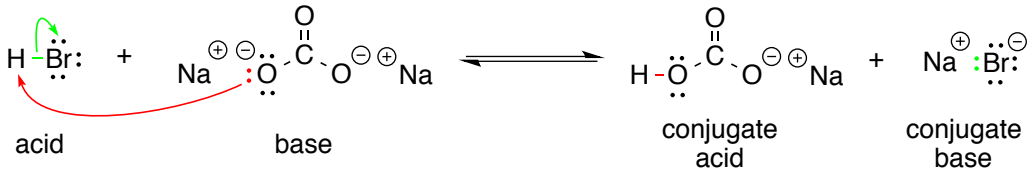
an ether



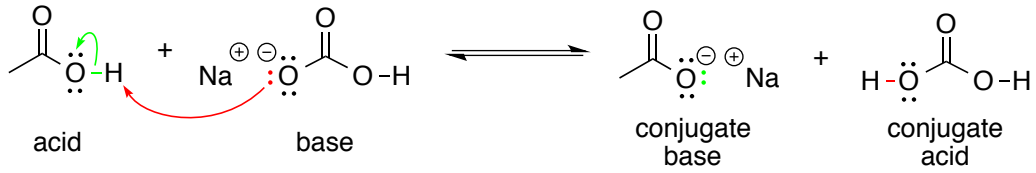
an alkane

5. Once you've identified the acid and base, which you did in Problem 1, it is straightforward to assign the conjugate acid and base. The acid becomes the conjugate base, and the base becomes the conjugate acid.

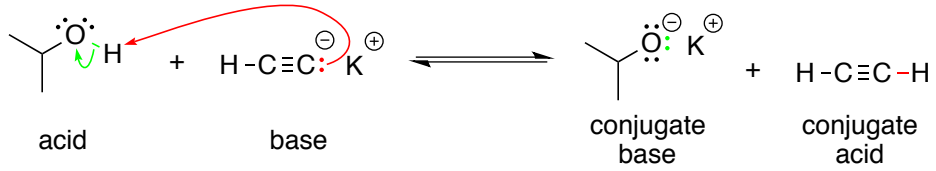
(a)



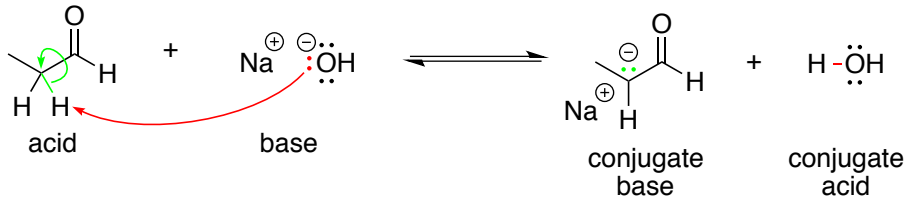
(b)



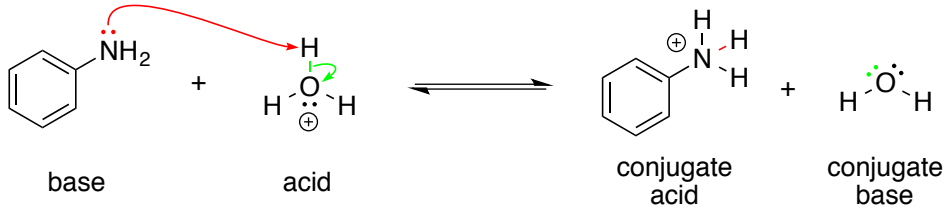
(c)


acid
base
conjugate base
conjugate acid

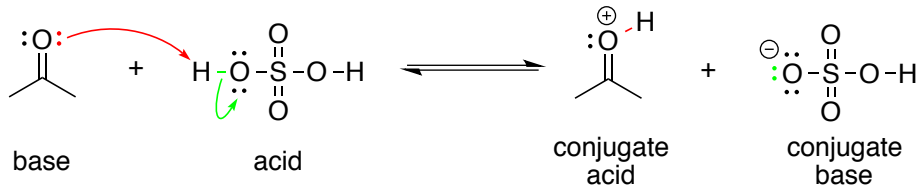
(d)


acid
base
conjugate base
conjugate acid

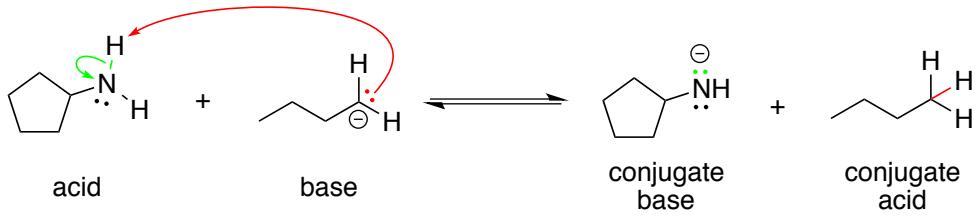
(e)


base
acid
conjugate acid
conjugate base

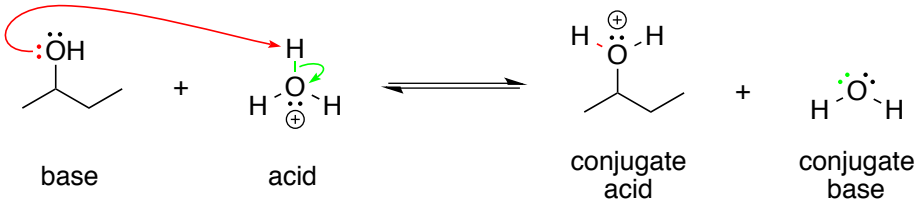
(f)


base
acid
conjugate acid
conjugate base

(g)


acid
base
conjugate base
conjugate acid

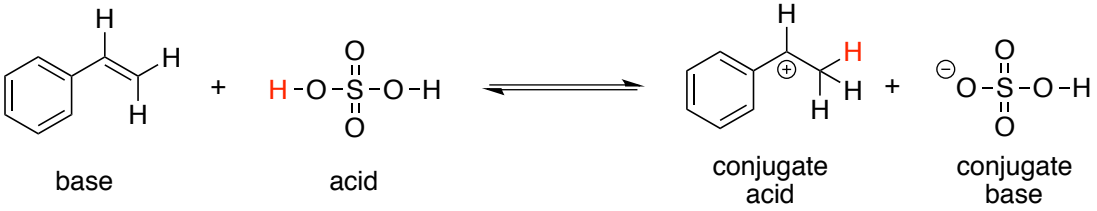
(h)



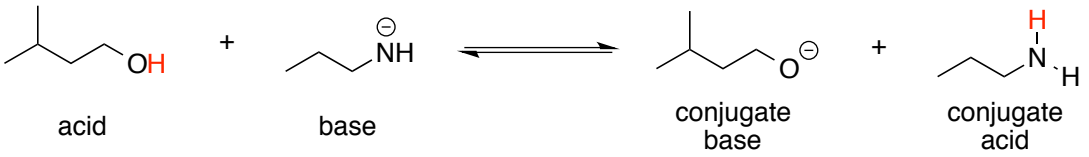
6. The first step is to identify the acid (the proton donor) and the base (the proton acceptor). The proton that has been transferred is implied in some of these problems, so you may find it useful to draw all the hydrogens on the centers undergoing changes during the reaction. This will help to highlight the substance that has received a proton.

Once the acid and base have been identified, the conjugate acid and base can be assigned. The acid becomes the conjugate base, and the base becomes the conjugate acid.

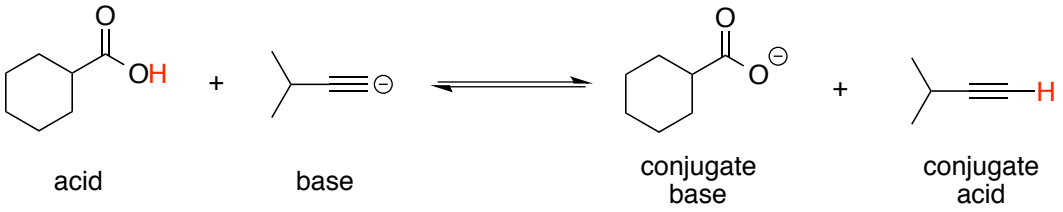
(a) In this problem, the alkene is accepting a proton from sulfuric acid.



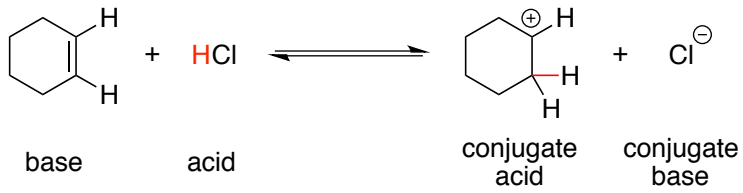
(b) In this reaction, the nitrogen anion is removing a proton from the alcohol.



(c) The reaction entails the transfer of a proton from the carboxylic acid to the carbanion.

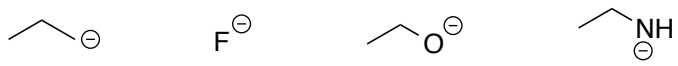


(d) This transformation involves protonation of (i.e., addition of a proton to) the alkene by hydrochloric acid.

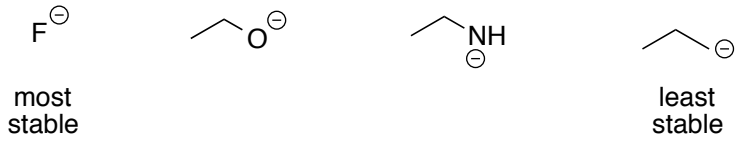


7.

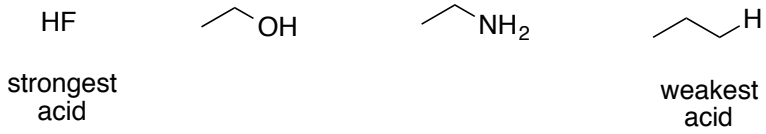
(a) The conjugate bases of each acid are shown below. The negative charge resides on a different element in each, and these elements reside in the same row of the periodic table.



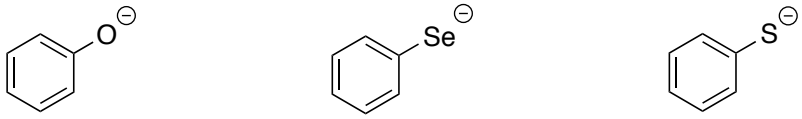
Therefore, the most significant difference between them is electronegativity. The more electronegative the element, the more stable the corresponding anion is.



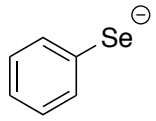
Knowing that a more stable conjugate base results from a stronger acid, we are able to rank the acidity as follows.



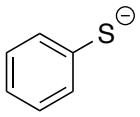
(b) The conjugate bases are shown below.

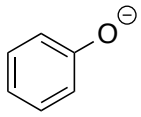


In each, the negative charge resides on a different element, and these elements occupy the same column of the periodic table. Therefore, the most pronounced difference between them is size. The larger the anion, the more diffuse and stable its charge is.



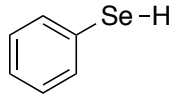
most stable



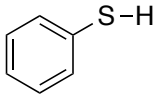


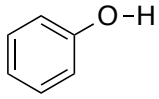
least stable

Since a more stable conjugate base results from a stronger acid, we can now rank the acid strength.



strongest acid

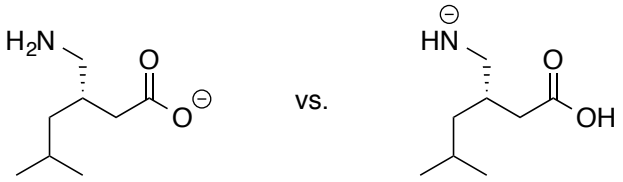




weakest acid

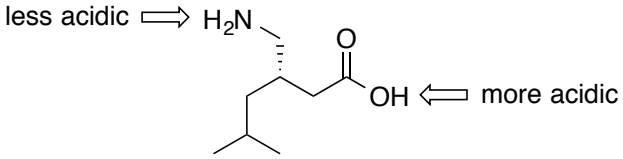
8.

(a) Here, we are choosing between placing a negative charge on oxygen or nitrogen. Since these atoms are in the same row of the periodic table, the most important factor to consider is their electronegativity. Since oxygen is more electronegative, it will be more stable as an anion.



more stable

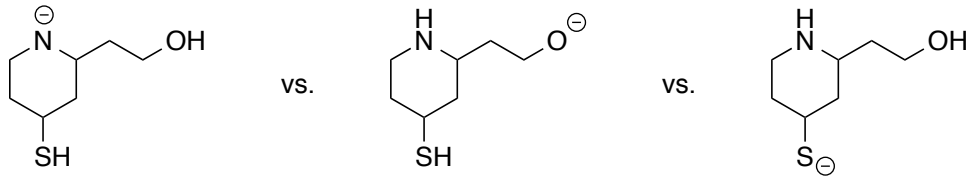
Therefore, the carboxylic acid is more acidic than the amine.



All of the other protons in the molecule reside on carbon. Since carbon also occupies the same row of the periodic table and is less electronegative than nitrogen, these protons are even less acidic.

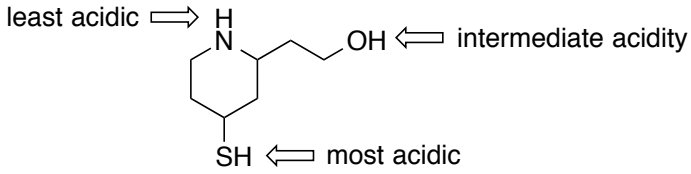
(b) In this molecule, we are comparing the acidity of an amine (N-H), an alcohol (O-H), and a thiol (S-H). These elements do not all occupy the same row or the same column of the periodic table. Nevertheless, we can determine the relative stability of the conjugate bases if we make stepwise comparisons.

Nitrogen and oxygen are in the same row of the periodic table, so the most important difference between them is electronegativity. Since oxygen is more electronegative, it is more stable as an anion. Oxygen and sulfur are in the same column of the periodic table, so their most significant difference is size. Since sulfur is larger than oxygen, it can better disperse and stabilize a negative charge. These comparisons reveal that the sulfur anion is more stable than the oxygen anion, which in turn is more stable than the nitrogen anion.



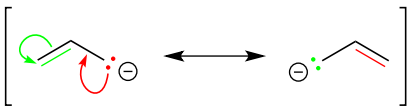
least stable most stable

Remembering that the most stable conjugate base comes from the strongest acid, we can rank the acidity of these protons.

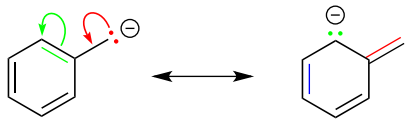


9.

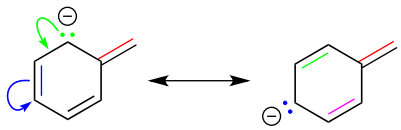
(a) This carbanion has one additional resonance form. It is derived by starting at the site of greatest electron density (the anion itself) and pushing electrons into the adjacent bond. As a double bond is formed to the neighboring carbon, this atom must relinquish one of its bonds so as not to exceed the octet. As a result, the π-bonding electrons are pushed onto the adjacent carbon. This effectively relocates the charge from one side of the molecule to the other.



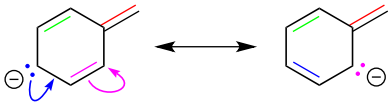
(b) This carbanion has four additional resonance forms. To generate them, we begin at the site of maximum electron density (the anion itself) and push electrons into the neighboring bond. As a double bond is formed to the adjacent carbon, this carbon loses its preexisting π bond so that it does not exceed the octet. The π electrons are pushed onto the next carbon atom.



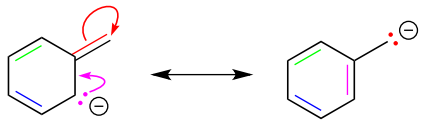
The next resonance form is produced in an analogous fashion. The lone pair of the carbanion is pushed into the adjacent bond to form a new π bond. As this occurs, the neighboring carbon loses its prior π bond as those electrons flow onto the subsequent carbon as a lone pair.



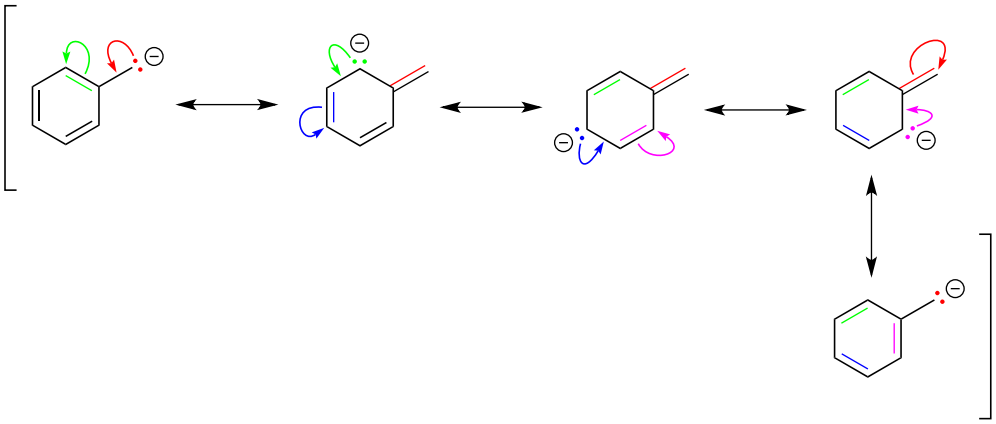
A similar process yields another resonance form. The lone pair of the carbanion flows toward the next π bond, producing a new π bond and pushing the old one onto a distal carbon as a lone pair.



The last resonance structure is derived in the same way.

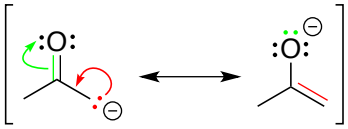


Putting all of these drawings together, we obtain the following diagram that includes all of the resonance structures. At first glance, the initial and final resonance forms may appear to be the same, but note that the π bonds are actually at different locations within the ring. So, they are indeed unique resonance forms.



10.

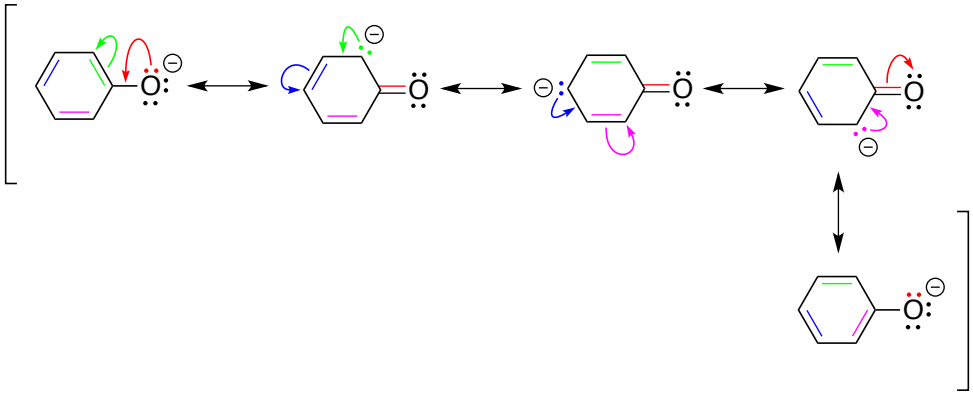
(a) By pushing the lone pair of the carbanion toward the carbonyl, we can derive a resonance structure for this molecule. The carbonyl π bond is displaced onto oxygen, making it the anion.



The two resonance forms differ in the element bearing the negative charge. Carbon and oxygen are in the same row of the periodic table, so electronegativity is the principal consideration. The negative charge is more stable on the more electronegative oxygen atom.

more stable
resonance form

(b) This problem is very similar to Problem 9(b) with the sole exception that the atom residing outside the ring is oxygen rather than carbon. So, the four additional resonance forms are reminiscent of those in Problem 9(b).



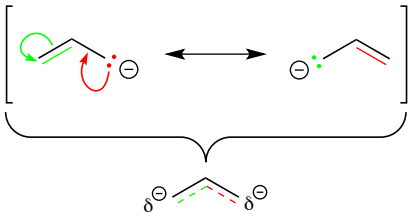
Two of these resonance structures place the negative charge on oxygen, while three place it on carbon. Since carbon and oxygen occupy the same row of the periodic table, the most pronounced difference between them is electronegativity. The anion is more stable when it resides on the more electronegative oxygen atom, so there are two equally stable resonance forms that are more stable than the other three.

more stable resonance forms

There is another factor at play here, and that is the special stability of an aromatic ring. When a six-membered ring contains alternating double and single bonds, it is aromatic and particularly stable. Chapter 13 discusses the origin of this stability. For the time being, suffice it to say that it is best to keep the aromatic ring intact if possible. The two most stable resonance forms also happen to have an undisrupted aromatic ring.

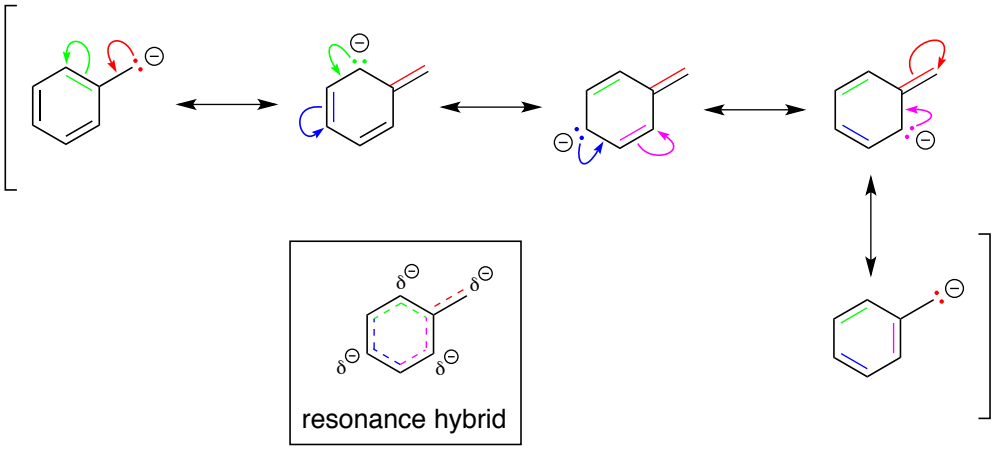
11.

(a) There is partial double bond character in each of the molecule's bonds, and dashed lines are used to represent this in the resonance hybrid. The negative charge is dispersed over the two terminal carbons, each of which bears a partial negative charge.



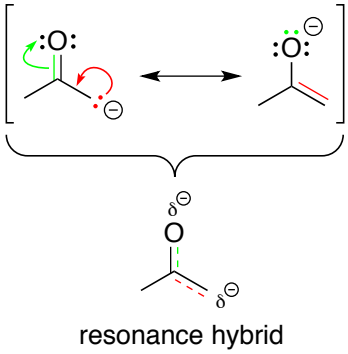
resonance hybrid

(b) Each of the molecule's bonds has partial double bond character, which is represented by the dashed lines. There are four carbons that bear the charge in different resonance forms, so each of these carbons has a partial negative charge in the hybrid.

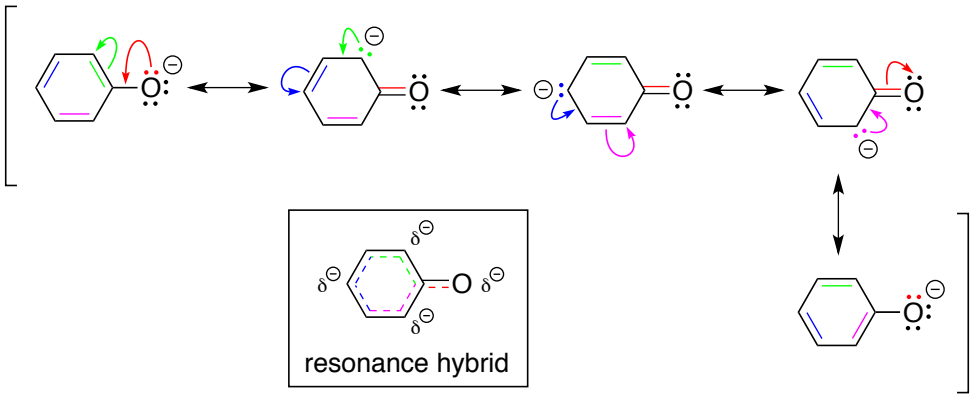


resonance hybrid

(c) The carbon-oxygen bond and one of the carbon-carbon bonds have partial double bond character. The negative charge is spread over one carbon and the oxygen, so these atoms have partial negative charges in the resonance hybrid.

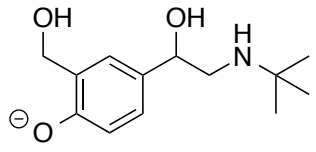


(d) The resonance hybrid reflects the partial double bond character throughout the molecule, as well as the fact that the negative charge is shared by three carbons and the oxygen atom.



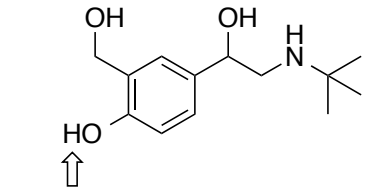
12. In this molecule, there are protons on carbon, nitrogen, and oxygen. Based on element effects, we expect the protons on oxygen to be the most acidic. Since carbon, nitrogen, and oxygen are all in the same row of the periodic table, their electronegativity differences are the most pronounced. A negative charge on oxygen is more stable than a negative charge on nitrogen or carbon since oxygen is the most electronegative of the three.

Now, we have to decide which of the three hydroxyl (OH) groups is the most acidic. Only one yields a conjugate base with resonance stabilization.



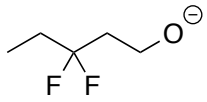
resonance-stabilized
conjugate base

This is the most stable conjugate base of salbutamol, which means that the phenolic proton is the most acidic one in the molecule.



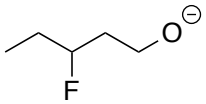
most acidic

13. The negative charge resides on an oxygen without resonance stabilization in each of these bases. There are, however, inductive differences between them. One of the bases has two very electronegative fluorine atoms that are only four bonds from the anion. This provides the largest inductive stabilization of the four compounds shown. The most stable base will be the least reactive (i.e., the weakest).



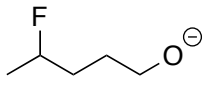
two fluorines
close to anion

One of the bases has a single fluorine atom at this same distance of four bonds from the anion. This results in the second largest inductive electron withdrawal stabilizing the anion. This base is slightly stronger than the previous one because it has less inductive stabilization.



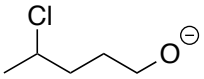
one fluorine
close to anion

There is a base with a single fluorine atom at a distance of five bonds from the anion. The increased distance reduces the electron withdrawal. Since it has less stabilization through induction, it is a stronger base than the two preceding examples.



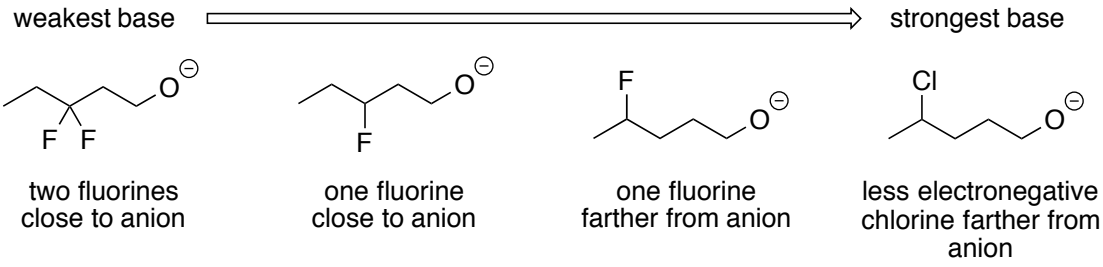
one fluorine
farther from anion

There is also a base with a chlorine atom five bonds from the anion. The increased separation relative to the first two bases and the reduced electronegativity of chlorine both serve to lessen the inductive effect. This compound has the least inductive stabilization and is therefore the strongest base.

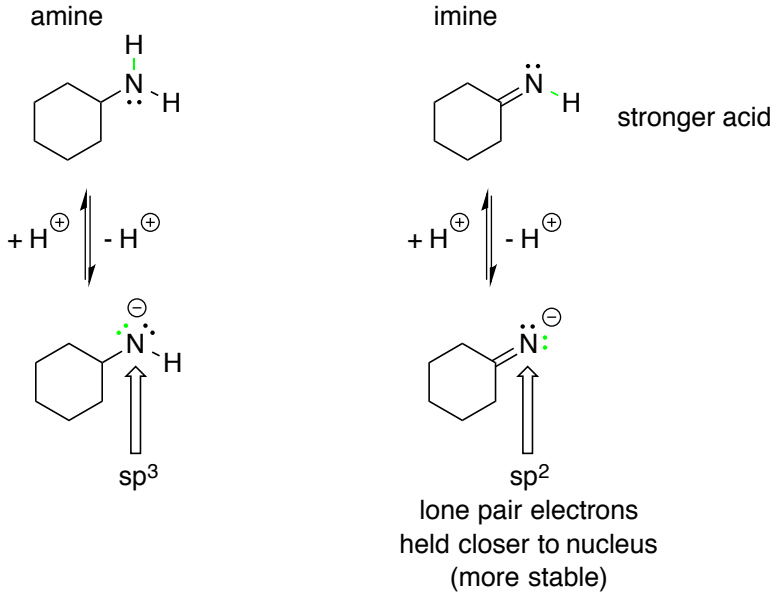


less electronegative
chlorine farther from
anion

The trend is summarized below.

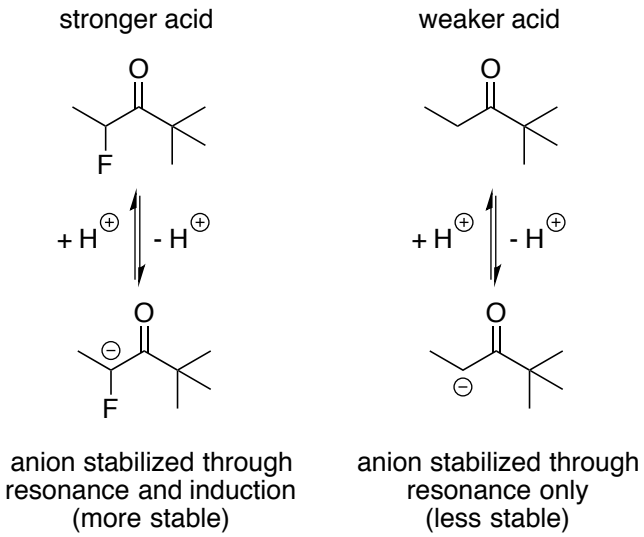


14. When the amine loses a proton, it yields an sp^3 hybridized conjugate base. On the other hand, loss of a proton from the imine provides an sp^2 hybridized conjugate base. The imine's conjugate base has the lone pair electrons in hybrid orbitals that are closer to the nucleus. This is more stable than the alternative. Consequently, the imine is more acidic.

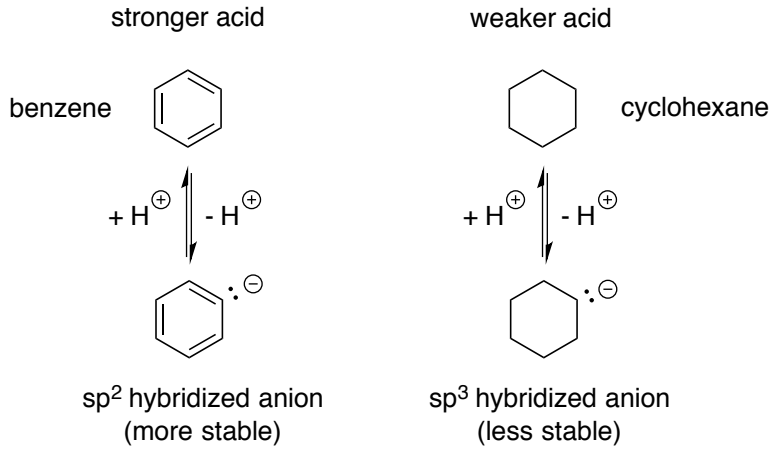


15.

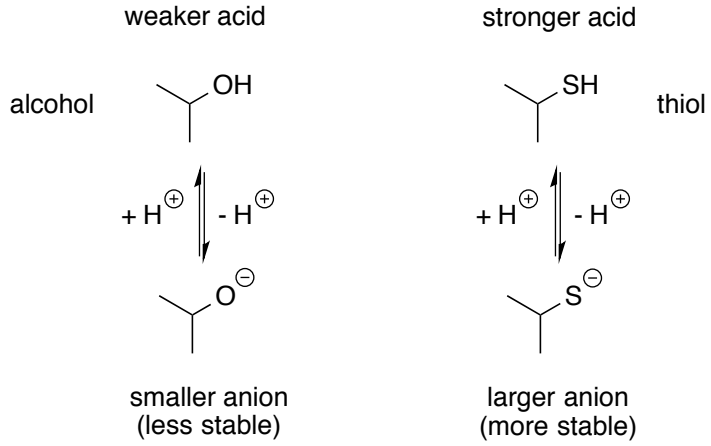
(a) The protons adjacent to the carbonyl are the most acidic in these molecules because the resultant conjugate bases have resonance stabilization. However, the conjugate base of the fluorinated ketone also has inductive stabilization. The unfluorinated ketone's conjugate base lacks this additional layer of stabilization. It is therefore the stronger base, and a stronger conjugate base results from a weaker acid.



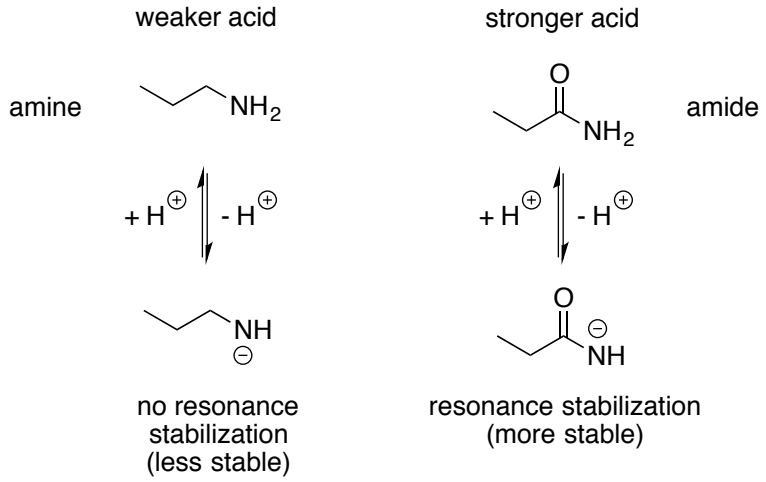
(b) If benzene loses a proton, the resulting conjugate base has an sp^2 hybridized anion. When cyclohexane loses a proton, the conjugate base is sp^3 hybridized. These lone pair electrons are held further from the nucleus and are therefore less stable. The less stable (or stronger) conjugate base comes from the weaker acid.



(c) When the alcohol loses a proton, the anion resides on oxygen. However, when the thiol loses a proton, the anion rests on sulfur. Since these atoms are in the same column of the periodic table, size is their most significant difference. The smaller anion is less stable. Given that the alcohol's conjugate base is therefore stronger, the alcohol can be said to be the weaker acid.

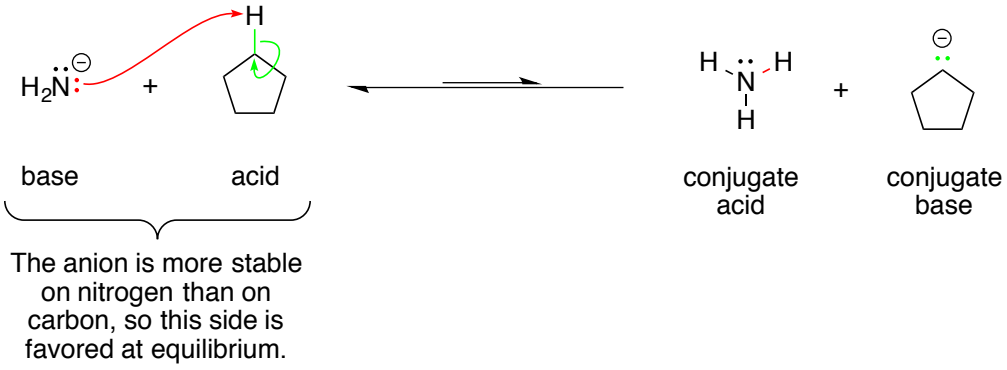


(d) When the amide loses a proton, its conjugate base enjoys resonance stabilization. On the other hand, if the amine were to lose a proton, its conjugate base would have no resonance stabilization. Since it is less stable, the amine's conjugate base is stronger, making the amine with weaker acid.

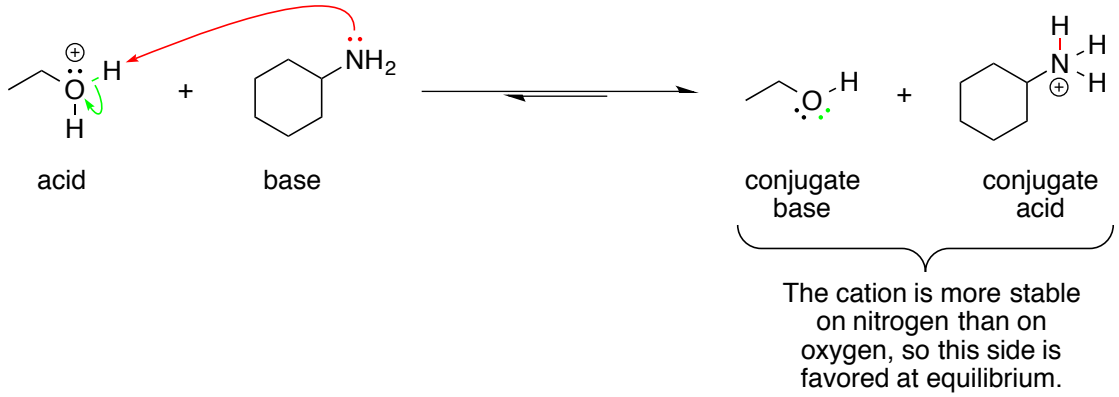


16.

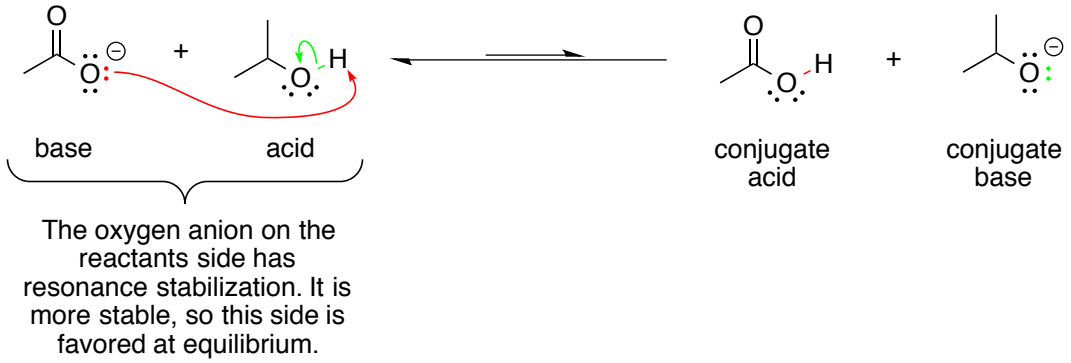
(a) The amide ion (H_2N^-) acts as a base and removes a proton from the cyclic alkane. This yields ammonia (NH_3) and a carbanion as products. There is an anion on each side of the equation, and the anion is more stable on nitrogen than on carbon because nitrogen is more electronegative. Consequently, the reactants are favored at equilibrium.



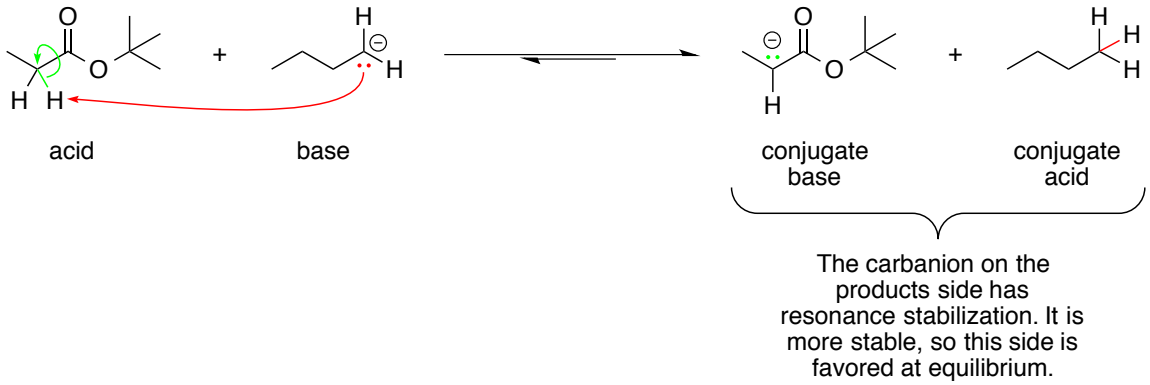
(b) The amine uses its lone pair of electrons to form a bond to a proton from the oxonium ion (i.e., positively charged oxygen). As this occurs, the σ-bonding electrons in the O-H bond fall onto oxygen as an unshared pair. There is a cation on each side of the equation. Since nitrogen is less electronegative than oxygen, it is preferable to have the positive charge on nitrogen. As a result, the products are favored at equilibrium.



(c) A proton is transferred from one oxygen atom to another in this acid-base reaction. There is an oxygen anion on each side of the equation, but the one on the reactants side has resonance stabilization, making it the more stable anion. Consequently, the reactants are favored at equilibrium.



(d) The most acidic protons of the ester reside on the carbon adjacent to the carbonyl. Removal of one of these protons yields a carbanion with resonance stabilization provided by the carbonyl. This carbanion is more stable than the original one, so the products are favored at equilibrium.



17. The guideline that is relevant for this problem is that a strong acid has a large K_a but a small pK_a value.

(a) Sulfuric acid has a much larger K_a value, so it is the stronger acid.

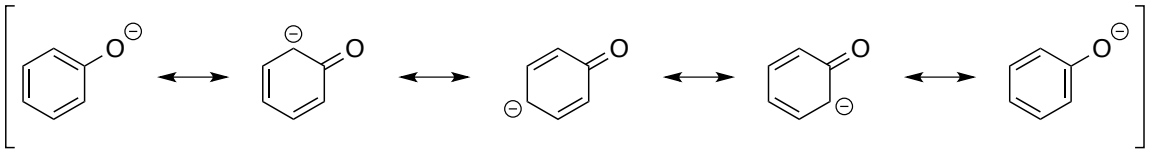
(b) The carboxylic acid has a smaller pK_a value, making it the stronger acid.

(c) The amine has the larger K_a value and is therefore the stronger acid.

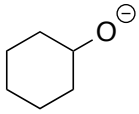
(d) The ammonium ion (i.e., positively charged nitrogen) has the smaller pK_a value, so it is the stronger acid.

18.

(a) The conjugate base of phenol has resonance stabilization.

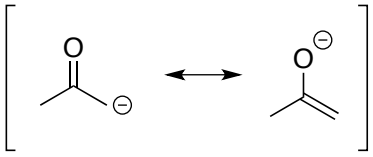


The conjugate base of an alcohol does not have resonance stabilization though.

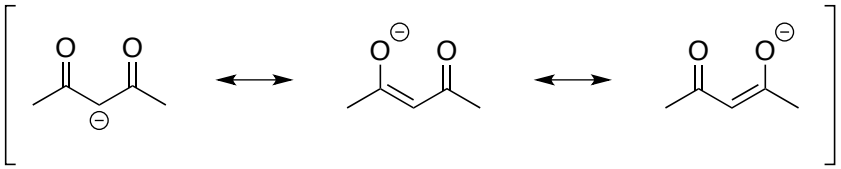


Since phenol's conjugate base is more stable, phenol is a stronger acid.

(b) The conjugate base of a ketone has resonance stabilization. This resonance is particularly helpful because the negative charge is delocalized onto a more electronegative element (i.e., oxygen).

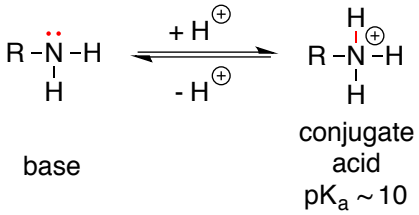


If the central carbon of a β-diketone is deprotonated, the resultant conjugate base has even more resonance stabilization. The negative charge can be delocalized into both carbonyls, thereby placing the electron density on not just one but two electronegative oxygen atoms.

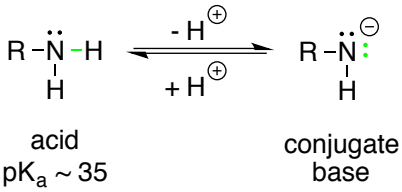


Since this conjugate base is more stable, the β-diketone is the stronger acid.

19. Amines are also amphoteric. An amine can act as a base, yielding an ammonium ion, which has a pK_a of about 10.

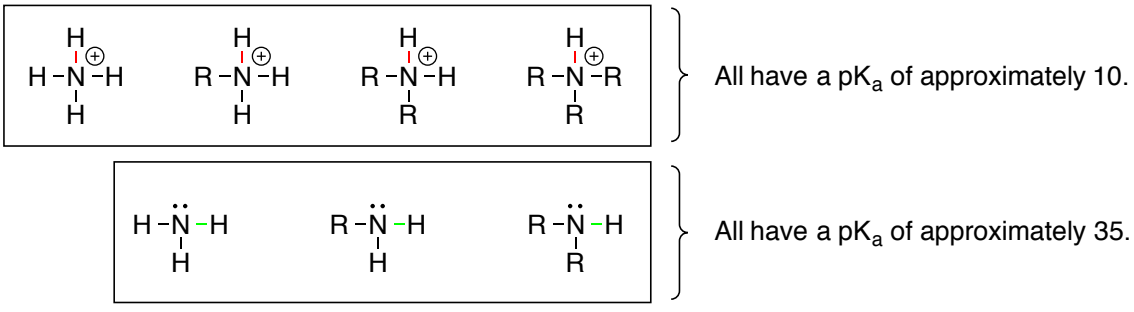


On the other hand, an amine can also act as an acid. There is a pK_a of about 35 when an amine donates a proton.



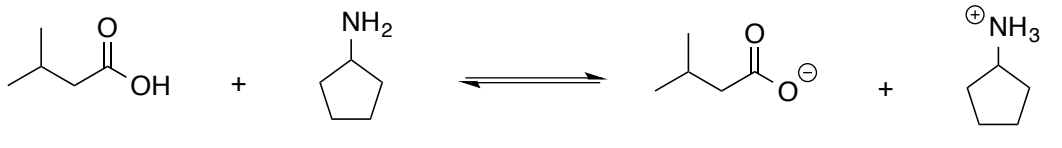
Notice that the pK_a value is always associated with the acid, regardless of which side of the equation it appears on.

It's also worth noting that these pK_a values don't change very much if nitrogen has a different combination of R groups and hydrogens.



20. For each of these problems, draw the expected products. Then, label the acid, base, conjugate acid, and conjugate base. Finally, assign the correct pK_a values to the acid and the conjugate acid. Be careful with amphoteric species to ensure that you have chosen the pK_a value relevant to the reaction taking place.

(a) A proton is transferred from the carboxylic acid to the amine in this acid-base reaction. The carboxylic acid has a pK_a of about 5. The conjugate acid of the amine has a pK_a of approximately 10.



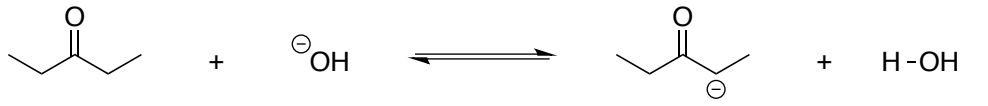
acid
$pK_a \sim 5$

base

conjugate base

conjugate acid
$pK_a \sim 10$

(b) The ketone donates a proton to hydroxide. The ketone's pK_a is around 20. The conjugate acid of hydroxide is water, which has a pK_a of 15.7.



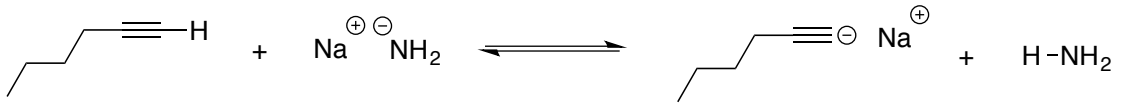
acid
$pK_a \sim 20$

base

conjugate base

conjugate acid
$pK_a = 15.7$

(c) In this reaction, sodamide ($NaNH_2$) removes a proton from the alkyne. The alkyne is the acid and has a pK_a of roughly 25. The conjugate acid of the amide ion ($^-NH_2$) is ammonia (NH_3), which has a pK_a of about 35.



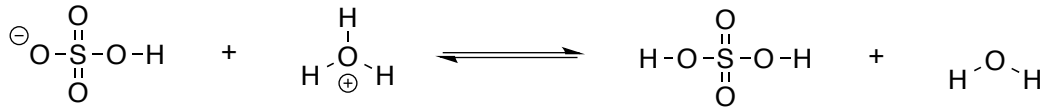
acid
$pK_a \sim 25$

base

conjugate base

conjugate acid
$pK_a \sim 35$

(d) In this transformation, bisulfate (HSO_4^-) removes a proton from the hydronium ion (H_3O^+). The hydronium ion has a pK_a of –1.7, while bisulfate's conjugate acid (sulfuric acid) has a pK_a of –10.



base

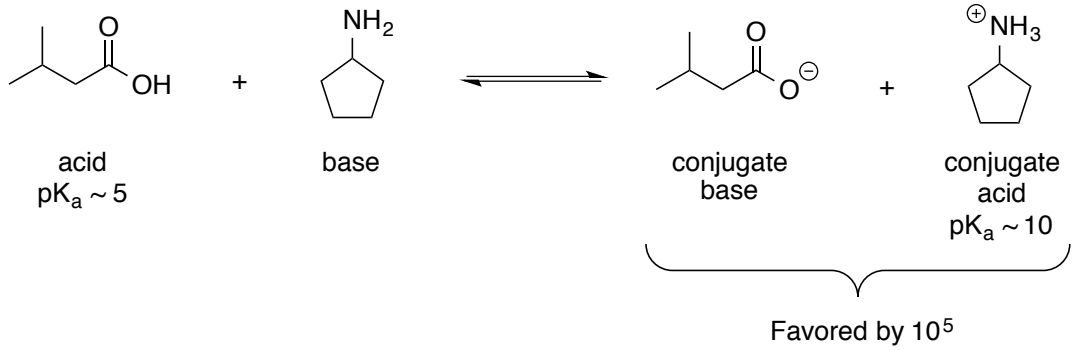
acid
$pK_a = -1.7$

conjugate acid
$pK_a = -10$

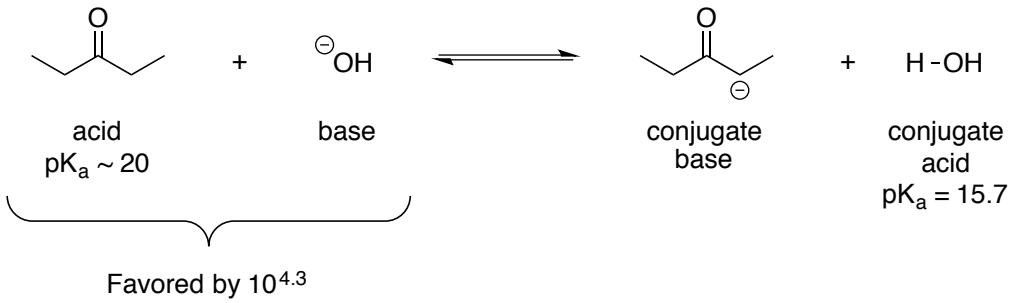
conjugate base

21. The relevant guideline for this problem is that equilibrium favors the side with the weaker acid, which has the higher pK_a value. This side is favored by 10 to the difference in the pK_a values.

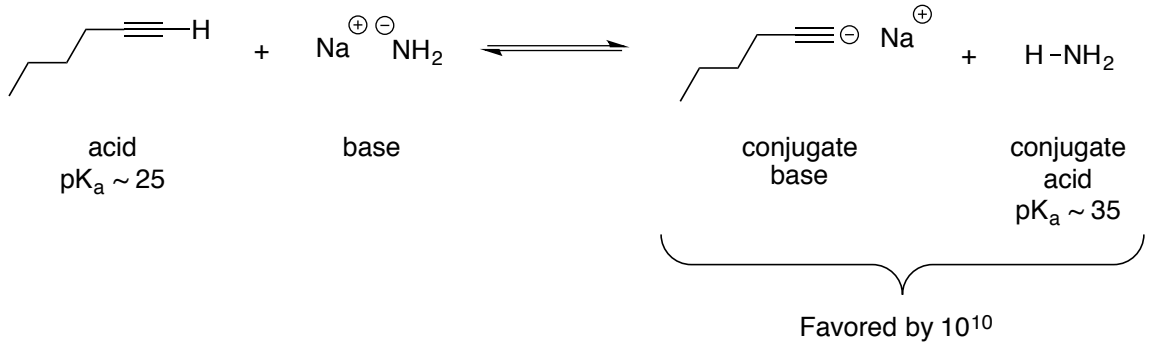
(a) This reaction is virtually the same as the example used in this section. The weaker acid lies on the products side, and this side is favored by 10^5 (or 100,000).



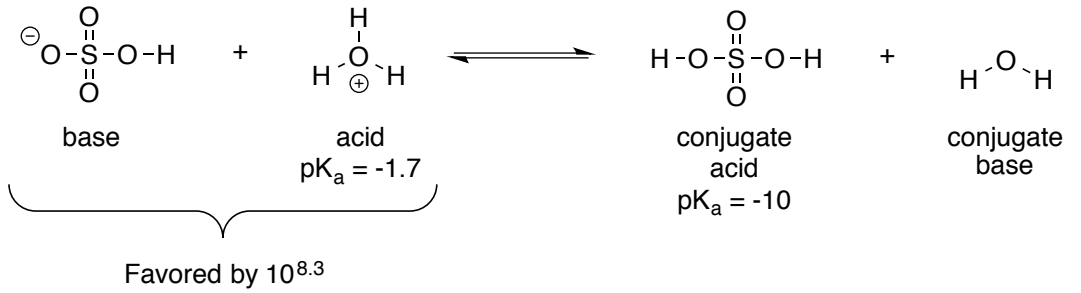
(b) A ketone is a weaker acid than water, so the reactants are favored. They are favored by $10^{4.3}$ (or about 20,000).



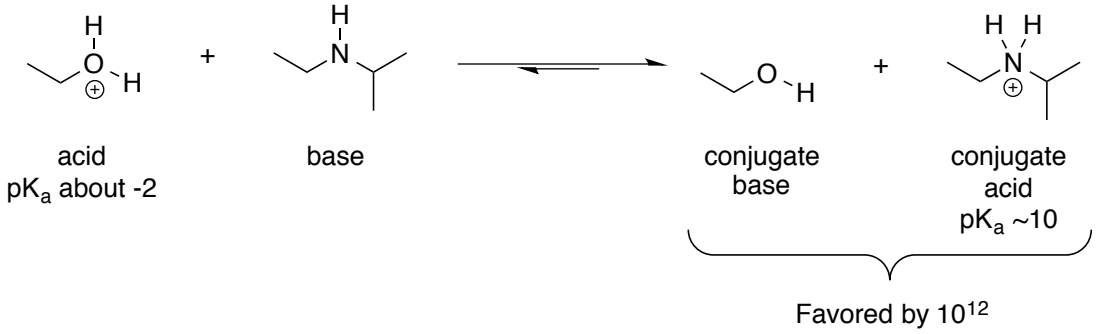
(c) The acids in this reaction are an alkyne and ammonia (NH_3). Ammonia is the weaker acid, so the products are favored by 10^{10} (or 10,000,000,000).



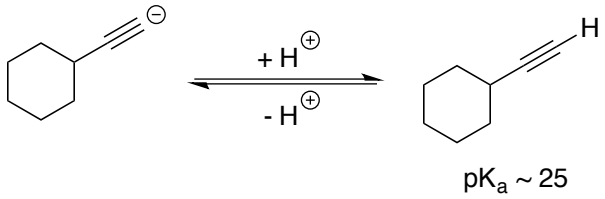
(d) The hydronium ion (H_3O^+) is a weaker acid than sulfuric acid (H_2SO_4). As a result, the reactants are favored, and they are favored by $10^{8.3}$ (or about 200,000,000).



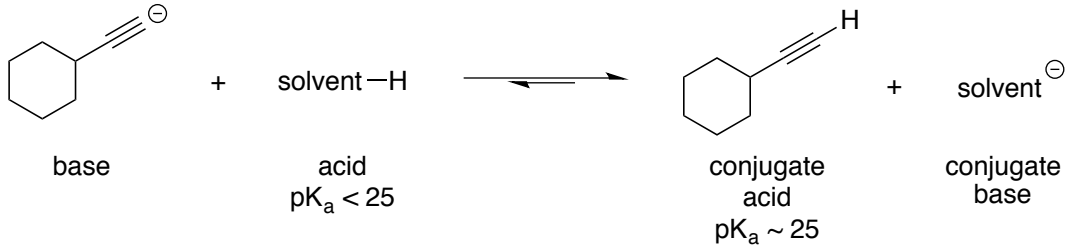
22. In this reaction, a proton is transferred from the oxonium ion (i.e., positively charged oxygen) to the amine. The conjugate acid is a protonated amine. It does appear in our table and has a pK_a of about 10. The protonated alcohol does not appear in our pK_a table; however, it is quite similar in structure to the hydronium ion (H_3O^+), which has a pK_a of -1.7. We can therefore estimate the protonated alcohol's pK_a to be around -2. Since the conjugate acid is the weaker acid in this reaction, the products are favored. They are favored by 10^{12}.



23. Although this is not an acid-base reaction, it still employs a compound that can act as a base. This carbanion's conjugate acid is an alkyne, which has a pK_a of approximately 25.

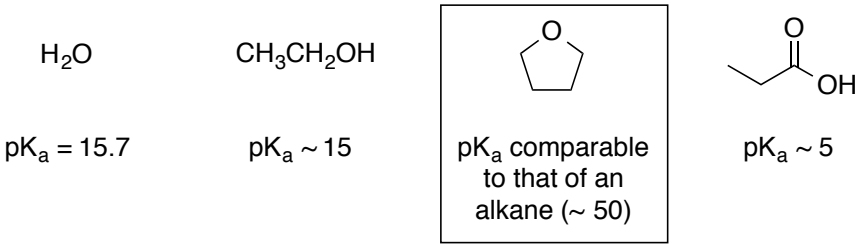


If this carbanion were combined with a solvent having a pK_a of less than 25, an acid-base reaction would ensue. This would quench (i.e., destroy) the carbanion, making it unavailable for the desired S_N2 reaction.

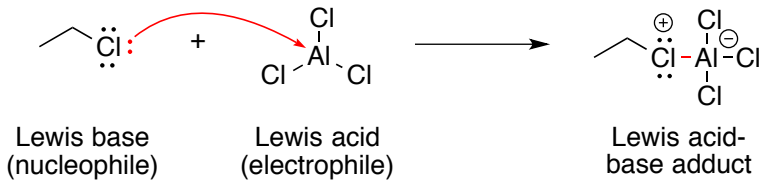


Therefore, we must be careful to choose a solvent with a pK_a value greater than 25. Three of the four proposed solvents have pK_a values listed in our table. Water has a pK_a of 15.7. An alcohol has a pK_a of about 15, and a carboxylic acid has a pK_a of approximately 5. All of these are unsuitable because they would quench the carbanion.

The pK_a table doesn't list a value for an ether; however, we can surmise that the pK_a would be close to that of an alkane (~50). The induction provided by the oxygen atom might increase the acidity a bit relative to an alkane, but this compound will nevertheless be quite reluctant to donate a proton. As a result, this cyclic ether (known as tetrahydrofuran, or THF) would be suitable for the proposed S_N2 reaction.



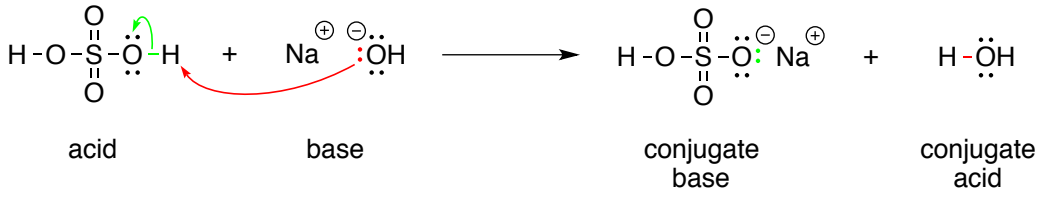
24. Aluminum is much like the boron used in the example in the text in that they both reside in the same column of the periodic table and, as a result, they both lack an octet when they are neutral. Since aluminum lacks an octet, it is electron deficient. This makes it an electron-pair acceptor, or a Lewis acid. The alkyl chloride has three unshared pairs of electrons on chlorine. These enable it to serve as a Lewis base, or an electron pair donor. One of the alkyl chloride's lone pairs is shared with aluminum in this Lewis acid-base reaction. This results in the new chlorine-to-aluminum bond found in the Lewis acid-base adduct.



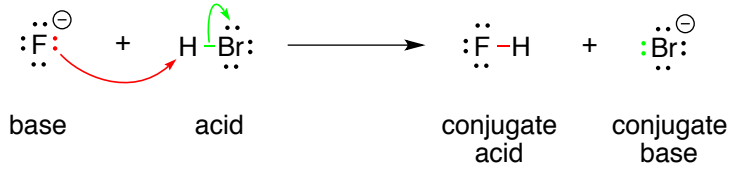
The alkyl chloride is the electron-rich reagent, so it could also be called a nucleophile. The aluminum trichloride is electron-poor on aluminum, so it can be called an electrophile.

25.

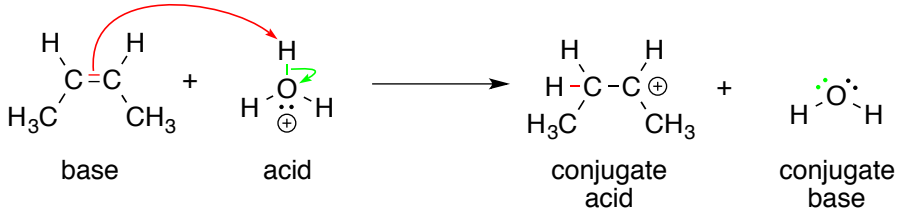
(a) Here, sulfuric acid serves as the proton donor, while hydroxide is the proton acceptor. The spectator ion (Na^+) associates with the anion on each side of the equation.



(b) In this acid-base reaction, fluoride is the proton acceptor, and hydrobromic acid (HBr) is the proton donor.

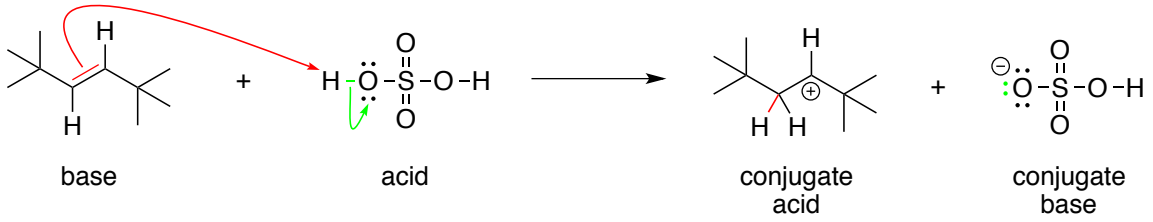


(c) In this instance, the alkene's π bond serves as the proton acceptor. The hydronium ion donates a proton to the alkene to yield a carbocation. Since the alkene is symmetrical, it does not matter which of the two alkene carbons acquires the new proton; the same carbocation will be generated either way.



This is the first step of the acid-catalyzed hydration of an alkene, which we will cover in Chapter 10.

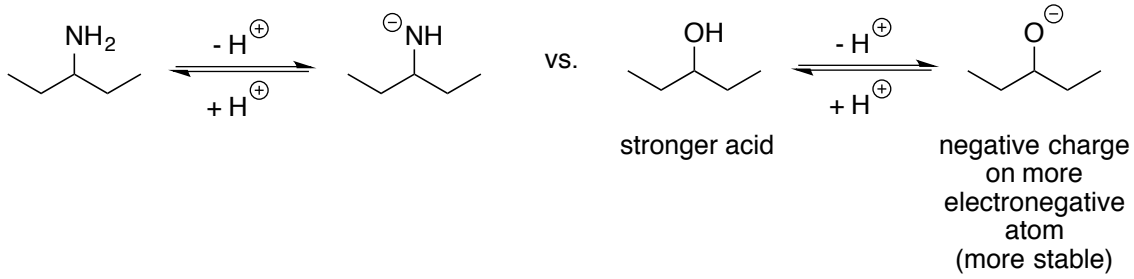
(d) Once again, an alkene's π bond acts as the proton acceptor, but this time it is sulfuric acid that provides the proton needed to generate the carbocation. This is also a symmetrical alkene, so either carbon involved in the double bond can be protonated to yield the same product.



This is an alternative representation of the first step of the acid-catalyzed hydration of an alkene, which we will discuss in Chapter 10 [see part (c) for a different representation].

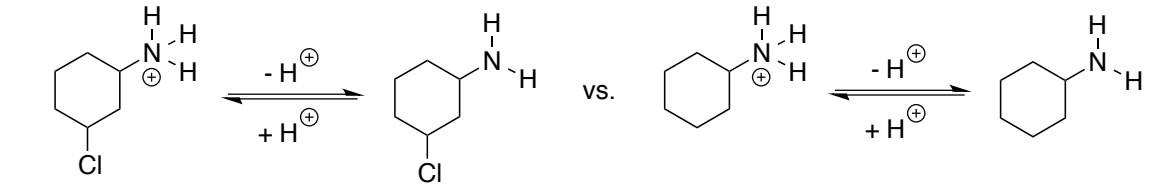
26. The stronger acid has the more stable conjugate base. In instances where the acids are neutral, it is often easiest to compare the stability of the anionic conjugate bases. However, when the acids themselves are charged, it may be simplest to compare them directly.

(a) The loss of a proton from the amine or alcohol provides a negatively charged conjugate base. The element bearing the charge differs in this case. Since nitrogen and oxygen reside in the same row of the periodic table, the most important difference between them is their electronegativity. Since oxygen is more electronegative, it is more stable to have the anion on oxygen, and this in turn makes the alcohol the stronger acid.



We could also use a pK_a-based argument. Amines have pK_a values of about 35; whereas, alcohols have pK_a values of approximately 15. The lower the pK_a, the stronger the acid is.

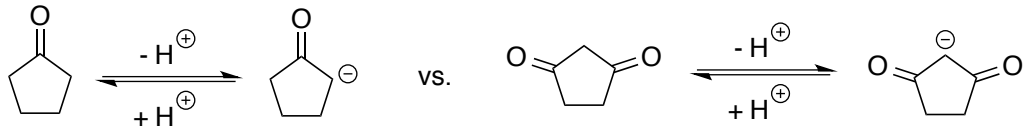
(b) In this case, the two acids are charged and may be compared directly. The electron withdrawal by the halogen actually intensifies the positive charge. As a result, that ammonium ion is less stable and more willing to lose a proton. Consequently, it is the stronger acid.



induction by halogen intensifies the positive charge and destabilizes this cation (stronger acid)

If you prefer to compare the conjugate bases, you make the argument that the chlorinated amine has a lone pair on nitrogen that is stabilized by the delocalization of some electron density through induction. Since this conjugate base is more stable, it results from the stronger acid.

(c) Both of these acids yield conjugate bases with resonance stabilization. However, the diketone's conjugate base has an anion that is resonance stabilized by not just one but two carbonyls. This additional stabilization of the conjugate base makes the diketone the stronger acid.

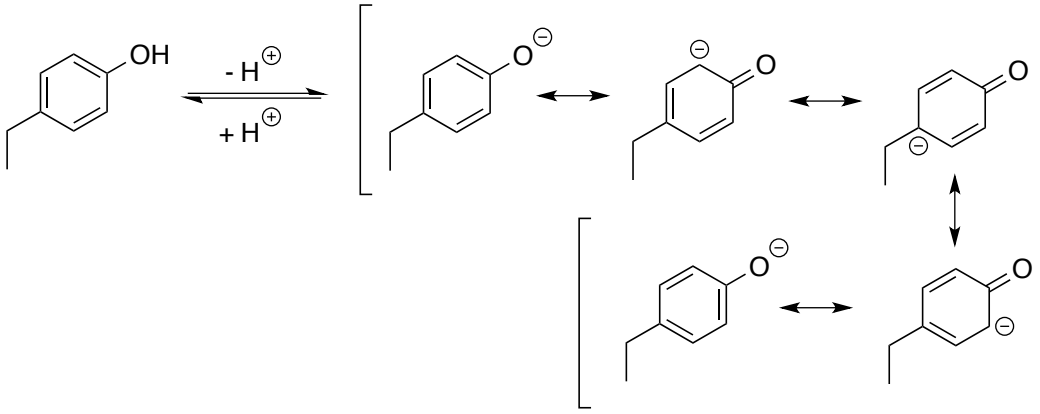


stronger acid

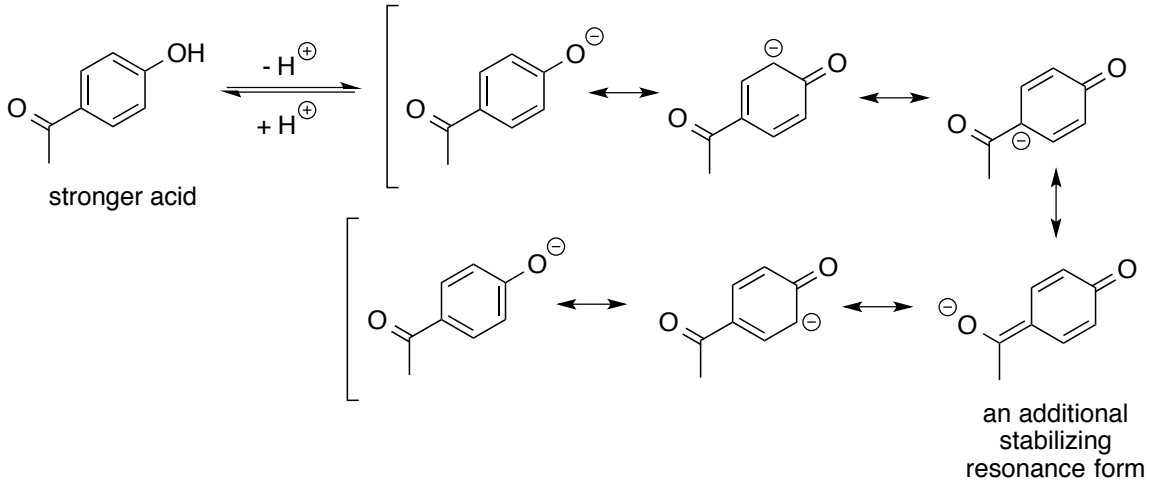
resonance stabilization by two carbonyls (more stable)

We could also use pK_a values to make the case. A ketone has a pK_a of about 20, and as we learned in Problem 18(b) a β-diketone has a pK_a around 9. The lower pK_a represents the stronger acid.

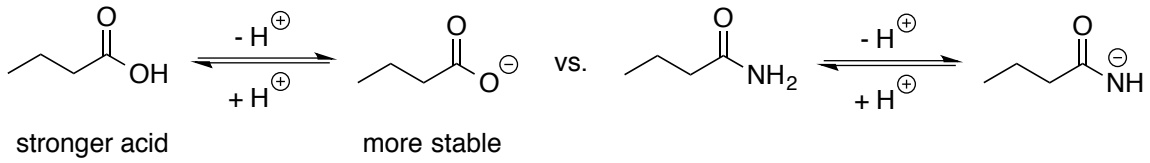
(d) Both of these phenols yield resonance-stabilized conjugate bases. The first one has a total of five resonance structures.



The second phenol has a total of six resonance forms. Not only is there an additional resonance form that further delocalizes the charge, but this additional resonance structure is also especially stabilizing because it places the negative charge on a second electronegative oxygen atom. Since this conjugate base is more stable, it results from the stronger acid.



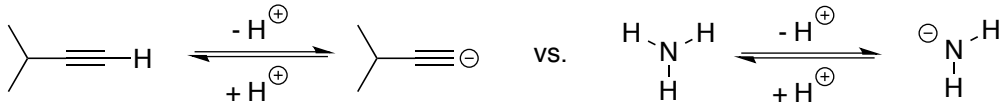
(e) Both the carboxylic acid and the amide produce resonance-stabilized conjugate bases when they lose a proton. The carboxylic acid's conjugate base spreads the negative charge over two electronegative oxygen atoms. On the other hand, the amide's conjugate base spreads the anion over a nitrogen and an oxygen atom. Since nitrogen is less electronegative than oxygen, this is less stabilizing.



The carboxylic acid's conjugate base is more stable, so the carboxylic acid is the stronger acid. This is reinforced by pK_a values. A carboxylic has a pK_a in the vicinity of 5. We have not yet encountered it, but an amide has a pK_a of about 15.

(f) This problem contains a tricky comparison. The conjugate bases differ in two ways: (1) the negative charge resides on different elements and (2) these elements have different hybridizations. In most cases, element effects are more significant than other factors. However, in this case, the hybridizations are so different (sp vs. sp^3) that their importance outweighs that of the elements' electronegativities.

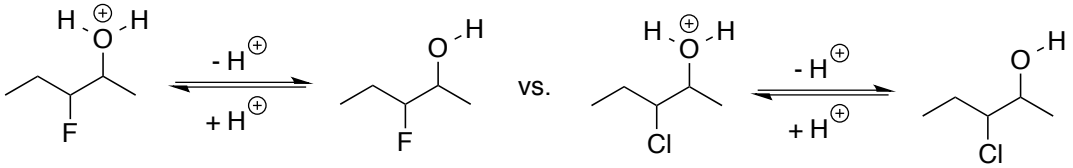
This is revealed by the pK_a values that we encountered in the table in Section 6. An alkyne has a pK_a of about 25, while that of an ammonia is around 35. The alkyne has the lower pK_a value and is therefore the stronger acid, which shows that hybridization effects are more significant than element effects in this particular comparison. This is a rare exception to the order of importance for structural factors that was laid out in Section 4.



$pK_a \sim 25$
(stronger acid)

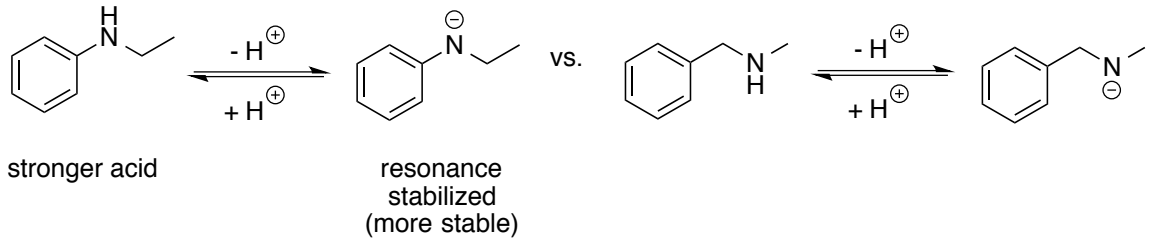
$pK_a \sim 35$

(g) Since the acids are charged, we can compare the stability of these charges directly. In both cases, the positive charge is intensified by the electron withdrawal of the halogen. Due to fluorine's greater electronegativity, it pulls more electron density from the cation, and destabilizes it to a greater extent. As a result, the fluorinated oxonium ion is more willing to donate a proton so as to eliminate the positive charge on oxygen.



greater induction caused by fluorine destabilizes this acid to a greater extent, making it the stronger acid

(h) The first amine produces a conjugate base with a resonance-stabilized anion. The second amine has a conjugate base without resonance stabilization of the charge. The first amine has the more stable conjugate base and is therefore the stronger acid.

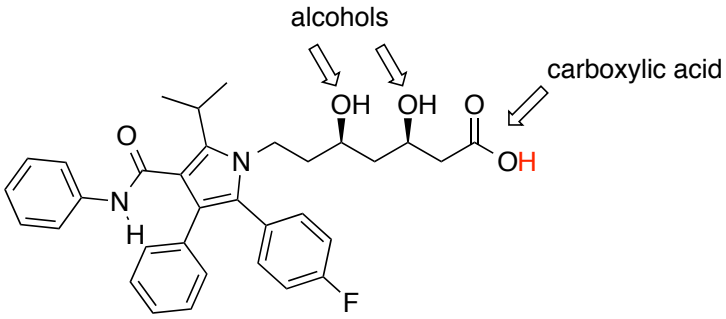


stronger acid

resonance stabilized (more stable)

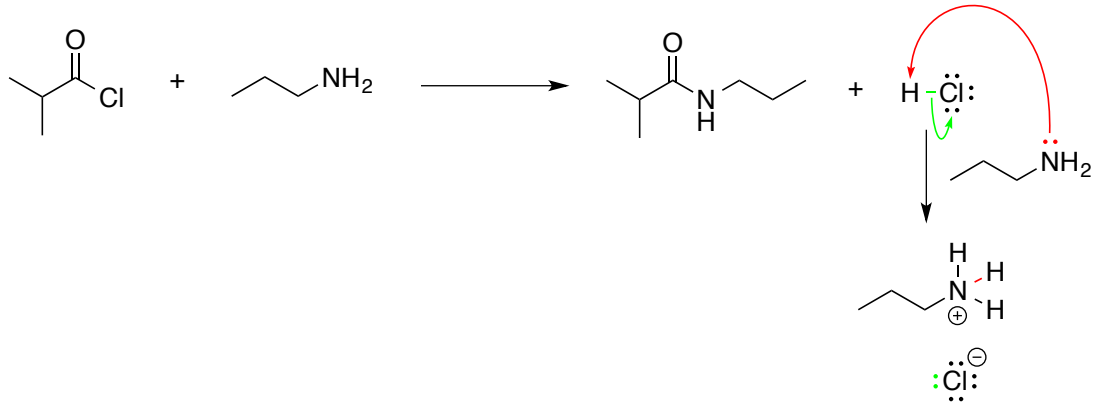
27. There are many protons in Lipitor, some of which have been drawn explicitly and some of which are implied. All of the implied hydrogens reside on carbon atoms. There is also a proton on nitrogen, and protons on oxygens. Element effects tell us that, in general, protons on oxygen will be more acidic than those on nitrogen and carbon due to oxygen's greater electronegativity.

This narrows the choice to one of the two alcohols or the carboxylic acid. The conjugate base of a carboxylic acid has resonance stabilization; whereas, the conjugate base of an alcohol does not. Consequently, the carboxylic acid possesses the most acidic proton in the molecule.

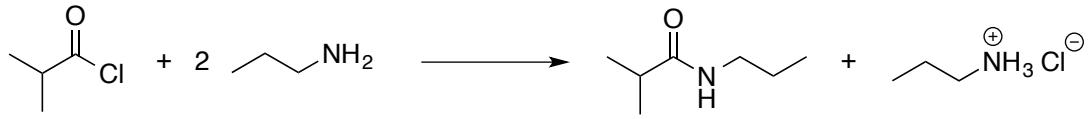


After narrowing the choice down to the alcohols or the carboxylic acid, citing pK_a values is an alternative way to make the choice. The carboxylic acid's pK_a of around 5 is lower than the alcohols' pK_a of about 15. This also reveals that the carboxylic acid is the stronger acid.

28. The second equivalent of the amine accepts the proton from HCl. As this occurs, the σ-bonding electrons between hydrogen and chlorine collapse onto chlorine.

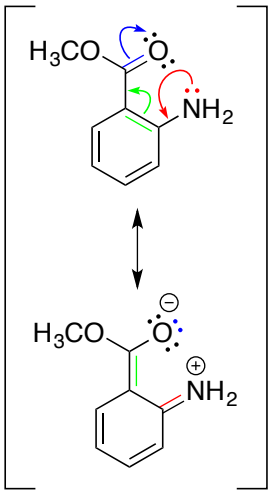


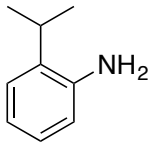
Therefore, the balanced reaction uses one mole of acid chloride for every two moles of amine and produces a mole of amide and a mole of protonated amine.



29. You have to be careful in answering questions of this sort. Some students have a tendency to memorize a certain factor and its effect. For example, a student may memorize that "resonance increases strength." The flaw in this approach is that it does not specify the strength of what. While resonance may increase the strength of an acid, it decreases the strength of that acid's conjugate base. The impact of a factor like resonance, induction, etc. depends on the context. Rather than memorizing, reason your way through an argument, and you will be much more likely to answer the questions correctly.

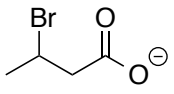
(a) Both of these amines have resonance; however, the first amine experiences resonance involving the ester on the ring. This delocalizes the amine's lone pair to an even greater extent. The second amine has no such resonance involving the other group on the ring. Since this amine's lone pair is more localized on nitrogen, it is the stronger base.

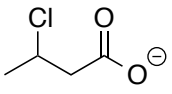




more localized
lone pair
(stronger base)

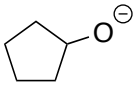
(b) Both of these conjugate bases of carboxylic acids have inductive stabilization provided by the halogens. Induction depends on electronegativity, and bromine is less electronegative than chlorine. Consequently, the brominated compound has less inductive stabilization and is therefore the stronger base.

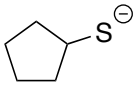




weaker induction
(stronger base)

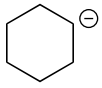
(c) There is a difference in the element bearing the negative charge in these two bases. Oxygen and sulfur reside in the same column of the periodic table, so the most important difference between them is their size. Since oxygen is the smaller atom, it has a more concentrated charge, making it the stronger base.

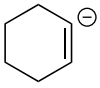




smaller atom
(stronger base)

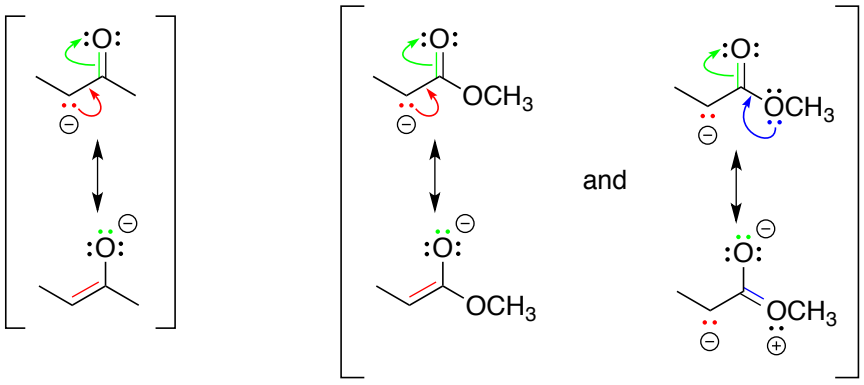
(d) These carbanions have different hybridizations. The first is sp^3 hybridized, while the second is sp^2 hybridized. The sp^3 hybridized carbanion holds its lone pair of electrons further from the positive nucleus, so this is a higher-energy carbanion. Since it is higher in energy, it is less stable and therefore the stronger base.





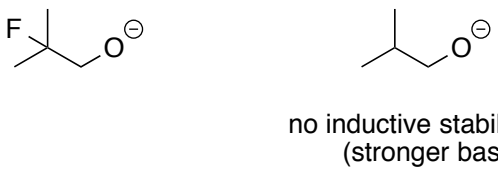
sp^3 hybridized
(stronger base)

(e) Both of these carbanions enjoy resonance stabilization. The conjugate base of the ketone has only one additional resonance form, in which the negative charge is delocalized onto the carbonyl oxygen. The conjugate base of the ester has a similar resonance structure, but the carbonyl can also be used to delocalize the carboxyl oxygen's electrons. In a sense, the carbanion and the carboxyl oxygen are competing for resonance with the carbonyl. As a result, the carbanion is less effectively stabilized than it was in the conjugate base of the ketone. This makes the ester's conjugate base the stronger base.



This outcome is also reflected in the pK_a values. A ketone has a pK_a of about 20, while that of an ester is around 25. The ester's higher pK_a value indicates that it is a weaker acid and therefore has a stronger conjugate base.

(f) These are both conjugate bases of alcohols. The first has inductive stabilization provided by the electronegative fluorine, but the second does not. As a result, the latter base is the stronger one.



(g) The first carbanion is the conjugate base of a ketone, and it has resonance stabilization provided by the carbonyl. The second base has no such resonance stabilization, and it is therefore the stronger base.

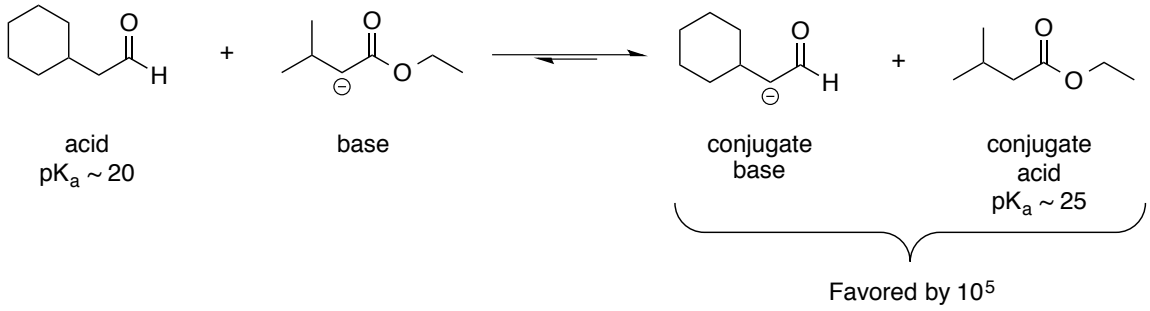
no resonance stabilization
(stronger base)

(h) The negative charge in the first compound is delocalized through resonance. This is not the case with the second compound, which is the stronger base as a result.

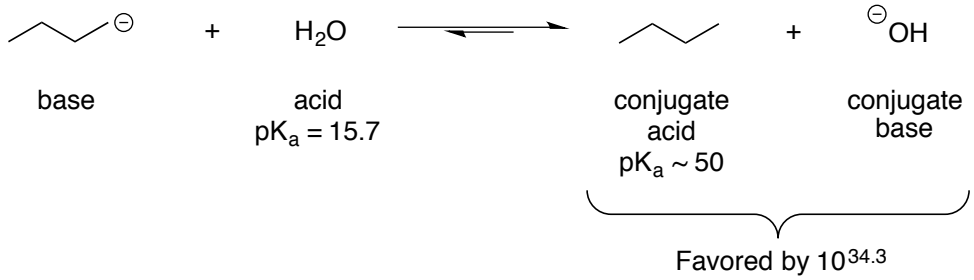
no resonance stabilization
(stronger base)

30. Throughout this problem, be on the lookout for amphoteric species. These compounds can act as both acids and bases, and therefore appear twice in the pK_a table. You'll have to be careful to choose the correct pK_a value.

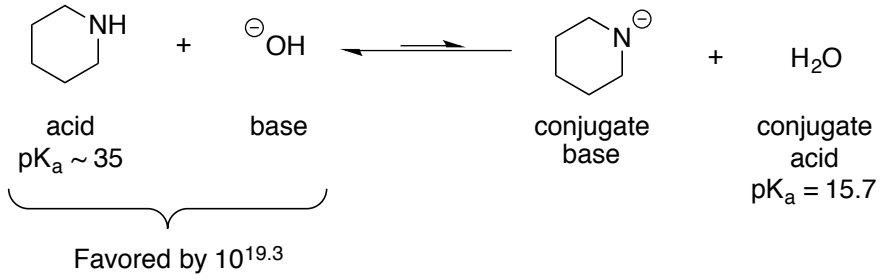
(a) In this reaction, an aldehyde is deprotonated to yield an ester. Aldehydes have pK_a values of about 20. The conjugate acid, an ester, has a pK_a value of approximately 25, so the products are favored by 10^5.



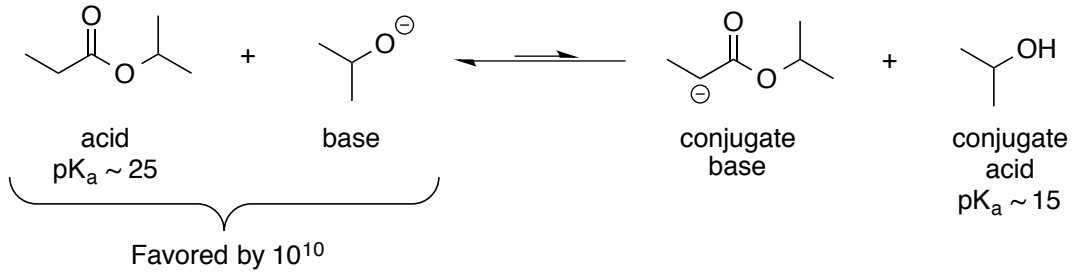
(b) Here, a carbanion is removing a proton from water. The alkane is a much weaker acid than water, so the products are favored at equilibrium by a tremendous amount ($10^{34.3}$).



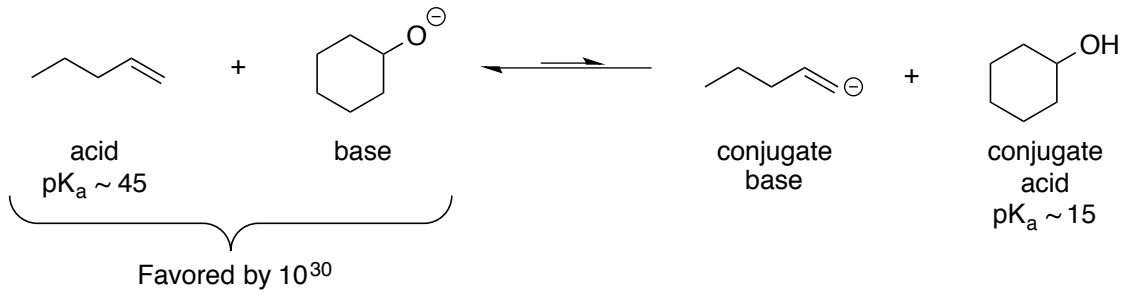
(c) In this reaction, hydroxide is deprotonating an amine, which has a pK_a of 35 or so. Since the amine is a far weaker acid than water, the reactants are favored by a wide margin ($10^{19.3}$).



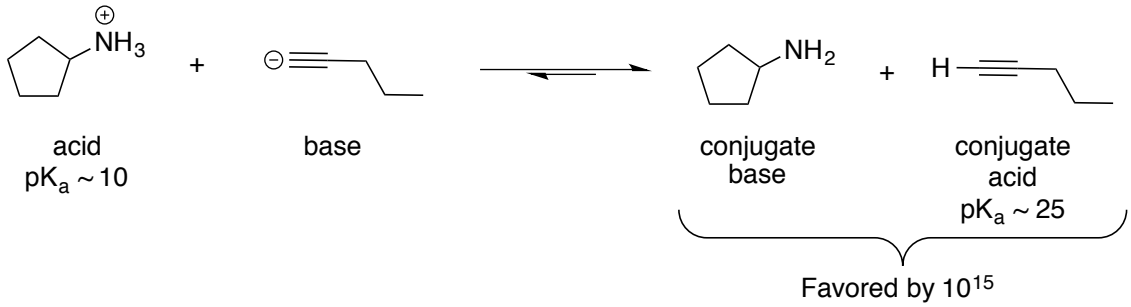
(d) This reaction depicts the deprotonation of an ester to produce an alcohol. An ester is a weaker base than an alcohol though, so the reactants are favored at equilibrium.



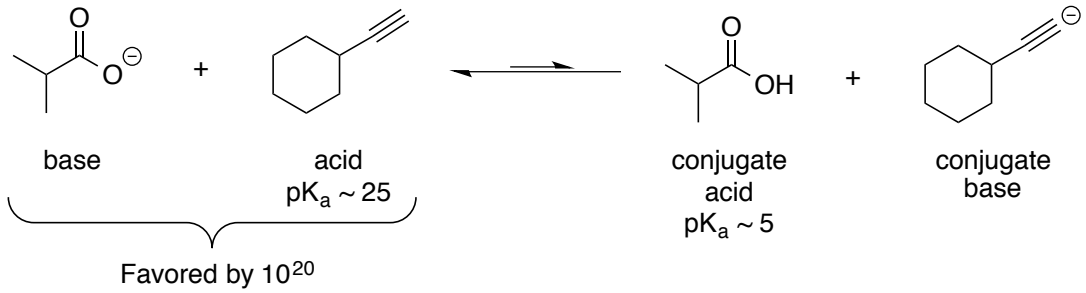
(e) In this example, an alkene is deprotonated to yield an alcohol, but since alkenes are very weakly acidic, the reactants are highly favored.



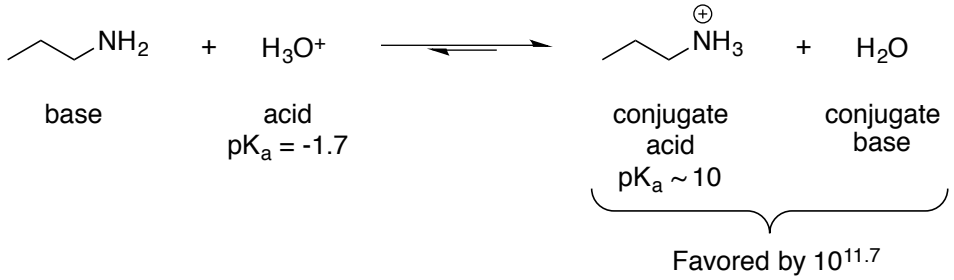
(f) This Brønsted-Lowry acid-base reaction involves the transfer of a proton from a protonated amine to an sp hybridized carbanion. A protonated amine has a pK_a of 10 or so, while an alkyne has a pK_a of about 25. The products are therefore favored by 10^{15}.



(g) Here, an alkyne is deprotonated to generate a carboxylic acid. However, this deprotonation will not be very successful. The alkyne is a much weaker acid than the carboxylic acid, so the reactants are favored in this case by 10^{20}.



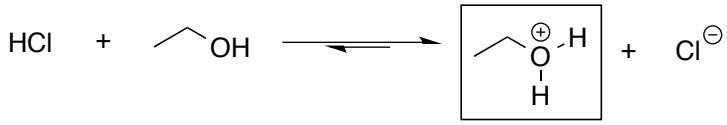
(h) In this reaction, an amine is combined with the hydronium ion. A proton is transferred to the amine as a result. The protonated amine is the weaker acid, so the products are favored at equilibrium.



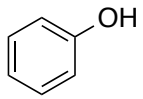
31. As we learned in Section 8, the strongest acid that can exist in a solution is the solvent's conjugate acid. If a stronger acid is introduced, it merely protonates the solvent.

(a) Sulfuric acid is a stronger acid than the solvent's conjugate acid, which is the hydronium ion (H_3O^+). As a result, sulfuric acid protonates water (the solvent), and the effective acid present in the medium is the hydronium ion.

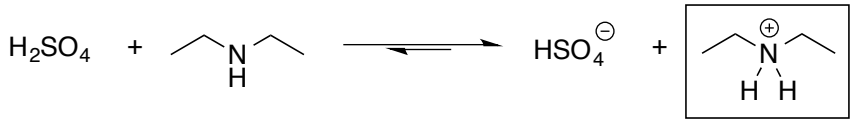
(b) An alcohol is comparable to water, so an alcohol's conjugate acid is comparable to the hydronium ion (pK_a of about –2). Hydrochloric acid is stronger than this solvent's conjugate acid, so HCl protonates the alcohol to produce the effective acid present in the mixture.



(c) In Problem 18(a), we learned that phenol has a pK_a of around 10. The solvent's conjugate acid, the hydronium ion, has a pK_a of –1.7. Phenol is *not* a stronger acid than the hydronium ion, so phenol itself is the effective acid present in this solution.



(d) Sulfuric acid is a very strong acid. It is much stronger than the conjugate acid of an amine, which has a pK_a around 10. Consequently, sulfuric acid protonates the amine, and the resultant ammonium ion is the effective acid present in this medium.



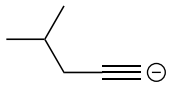
32. Interpreting the phrasing of acid-base questions is an important skill because there are a number of ways to ask what is essentially the same question. You can be asked which of a series is the strongest acid. Asking which of a series has the weakest conjugate base is the same question, simply phrased differently. You could also be asked which compound is the weakest acid, which is the same as asking which has the strongest conjugate base.

Alternatively, you can be given a series of bases and asked which is the strongest. This would be identical to asking which has the weakest conjugate acid. Conversely, you could be asked which base is the weakest, which is the same as asking which has the strongest conjugate acid.

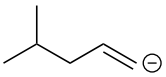
The last version is what we encounter in this question. We have been asked which compound has the strongest conjugate acid. We can certainly draw the conjugate acids and make this comparison, but we can also simply translate the question into "identify the weakest base," which then allows us to compare the given molecules directly to one another.

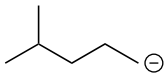
(a) The conjugate bases of an alkyne, alkene, and alkane have sp, sp^2, and sp^3 hybridizations, respectively. The sp hybridized anion is the most stable because its

lone pair is held in an orbital with a high percentage of s character and is therefore close to the nucleus. Since the anion derived from an alkyne is the most stable, it is the weakest base and has the strongest conjugate acid.



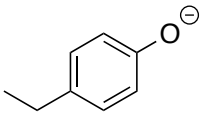
sp hybridized
(weakest base)

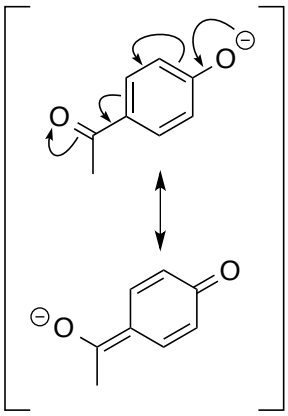




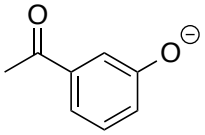
(b) All three of these compounds have resonance stabilization. In the first and last molecules, resonance only allows for delocalization of the charge onto carbons of the aromatic ring. However, in the second structure, the negative charge can be delocalized onto the oxygen of the ketone as well. Notice that, once you become comfortable with drawing resonance structures, you need not necessarily draw out all of the lone pairs as we have done previously. The arrow pushing shown here is analogous to that used in the answer to Problem 29(a) if you need to refer to an example where the lone pair electrons are shown.

Since the middle anion has the most effective resonance stabilization in which the charge is passed to a second electronegative oxygen atom, this is the most stable compound and therefore the weakest base. It will have the strongest conjugate acid.

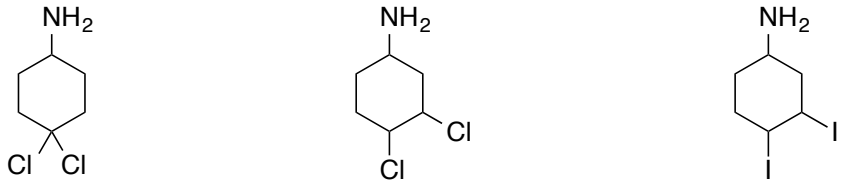




most stabilizing resonance
(weakest base)

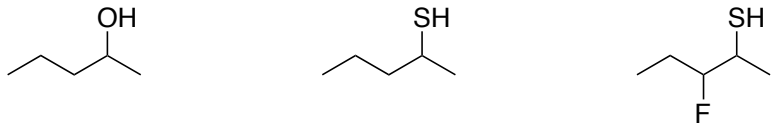


(c) All three of these amines experience induction that delocalizes the lone pair through σ bonds. Induction depends upon electronegativity, so chlorine will yield a larger inductive effect. Of the two chlorinated compounds, one has a chlorine in closer proximity to the amine. This will lead to a greater inductive effect. As a result, the amine's lone pair is most delocalized in the middle compound. This is the weakest base and has the strongest conjugate acid.



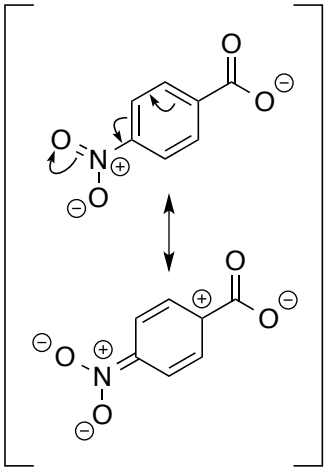
more electronegative halogens
and closest proximity
(weakest base)

(d) There are two factors at play in this question: element effects and induction. Sulfur is a larger atom than oxygen, and as a result, its electron density is more diffuse. This makes sulfur less basic than a comparable oxygen. The fluorinated compound also experiences delocalization of the lone pairs on sulfur through σ bonds due to the inductive effect. This makes it the weakest base, which must have the strongest conjugate acid.

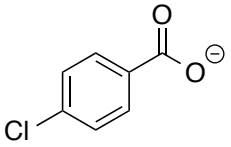


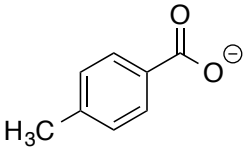
more diffuse electron
density on larger atom and
inductive delocalization
(weakest base)

(e) The most electron-withdrawing group on the ring will provide the most stabilization for the anion. The nitro (NO_2) group can withdraw electron density by resonance. This results in δ^+ character on the carbon adjacent to the basic site. The presence of opposite charges in close proximity is stabilizing. While chlorine also withdraws electron density, it does so only through induction, which is typically a weaker effect than resonance. The methyl group does not withdraw electron density at all. The first base is the most stable and therefore the weakest. It will have the strongest conjugate acid.

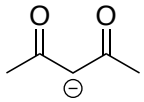


most stabilizing resonance
(weakest base)

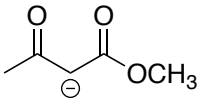


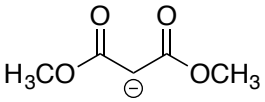


(f) Problem 29(e) showed that a ketone provides better resonance stabilization than an ester. Therefore, the anion that is adjacent to two ketones is the most stable. It is the weakest base and has the strongest conjugate acid.

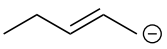


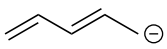
most effective
resonance stabilization
(weakest base)



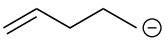


(g) The first carbanion is resonance stabilized by the nearby alkene. The second carbanion benefits from resonance that involves both π bonds in the molecule. The third carbanion is too far from the alkene to be resonance stabilized by it. The middle compound is therefore the most stable, making it the weakest base. It will have the strongest conjugate acid.

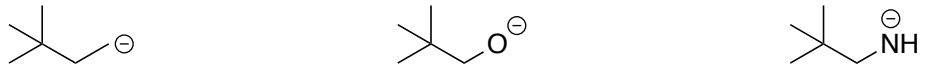




most extensive
resonance stabilization
(weakest base)



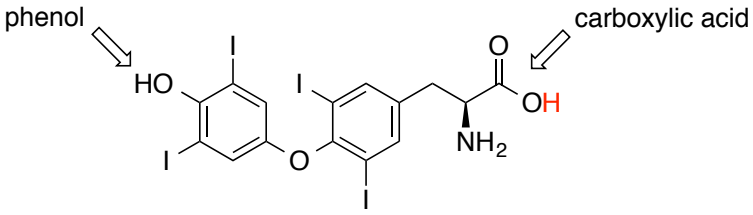
(h) In this comparison, the anion resides on three different elements, all of which occupy the same row of the periodic table. The most significant difference between these elements is electronegativity, and oxygen is the most electronegative of the three. It is therefore the most stable as an anion, so it is the weakest base and has the strongest conjugate acid.



most electronegative atom
(weakest base)

33. Synthroid contains protons bonded to carbon, nitrogen, and oxygen. Due to element effects, protons on oxygen are typically expected to be more acidic than those on nitrogen, which are in turn more acidic than those on carbon. This is because of the fact that, all other things being equal, an anion is more stable on a more electronegative element.

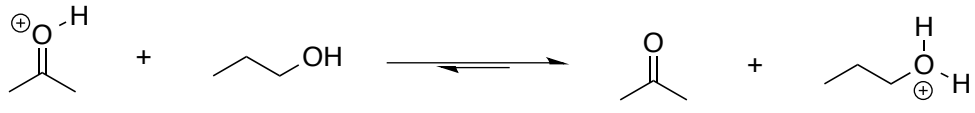
This narrows the choice down to the carboxylic acid proton or the phenolic proton. Both conjugate bases have resonance stabilization. However, the carboxylic acid's conjugate base spreads the negative charge over two electronegative oxygen atoms. This is much more stabilizing than the resonance available to the phenol's conjugate base, which spreads the negative charge over one oxygen and three less electronegative carbon atoms. Consequently, the carboxylic acid proton is the most acidic one in the compound.



Upon narrowing the choice down to the phenol and carboxylic acid, we could also have cited the pK_a values of these acids, 10 and 5 respectively, to justify our choice. The lower pK_a of the carboxylic acid shows it to be the stronger acid. We encountered the pK_a value for a phenol in Problem 18(a).

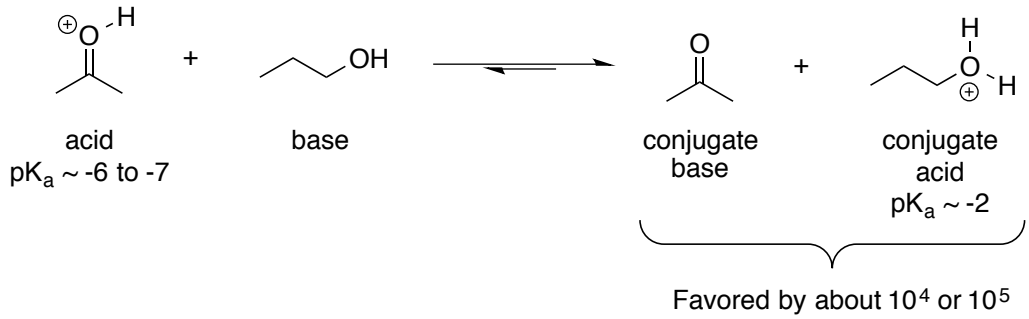
34.

(a) The oxygen atoms of the base and the conjugate base differ in hybridization. The alcohol contains an sp^3 hybridized oxygen, while the ketone has an sp^2 hybridized oxygen. The lone pairs in sp^3 hybrid orbitals are held further from the nucleus, making them higher energy and more available for reaction. As a result, the alcohol is expected to be the stronger base. It will remove the proton from the protonated ketone, and the products are favored at equilibrium.

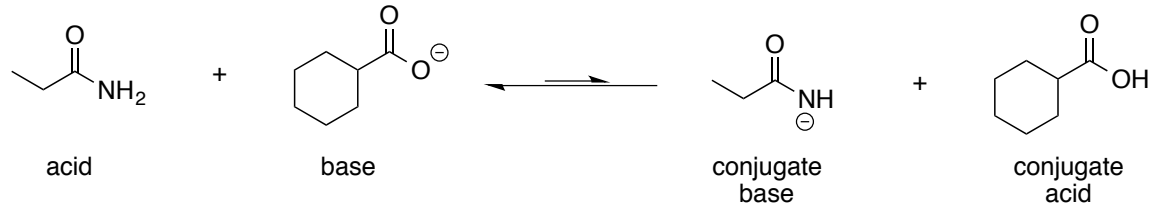


acid base conjugate base conjugate acid

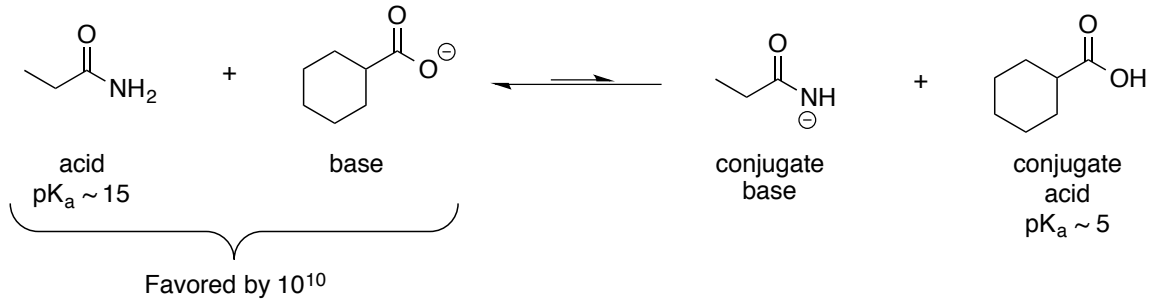
We have not yet encountered the pK_a value of a protonated ketone. It turns out that is around –6 to –7. Given this additional information, we can provide another explanation. The protonated alcohol is a weaker acid, since it has a higher pK_a value, and equilibrium favors the side with the weaker acid.



(b) The anions of the base and the conjugate base both have resonance stabilization. In the conjugate base, the anion is spread over oxygen and a less electronegative nitrogen atom. In the base, the negative charge is spread over two electronegative oxygen atoms. The base has more effective resonance stabilization, and equilibrium favors the side with the more stable species. Consequently, the reactants are favored at equilibrium.

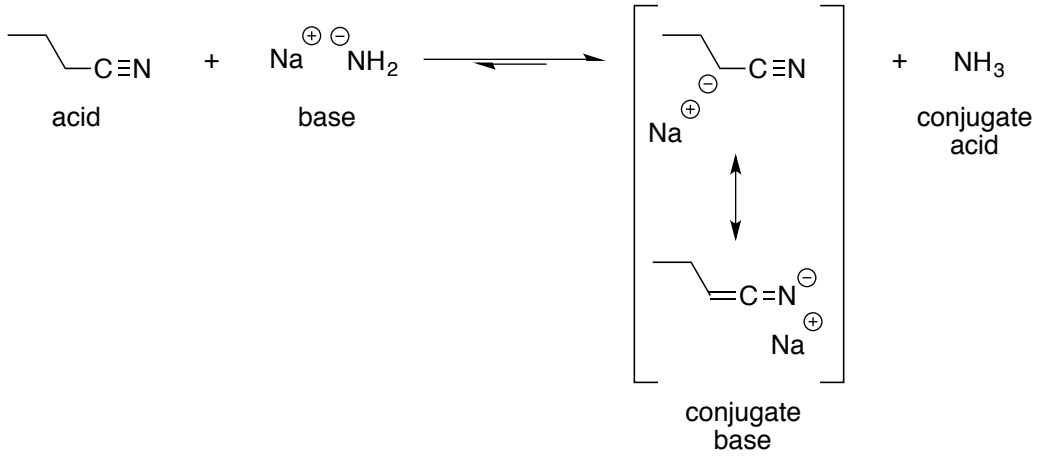


We have not yet seen the pK_a value of an amide. It is approximately 15. Knowing this, we can now arrive at the same conclusion in a different way. The reactant acid is the weaker acid, and equilibrium favors the side with the weaker acid.

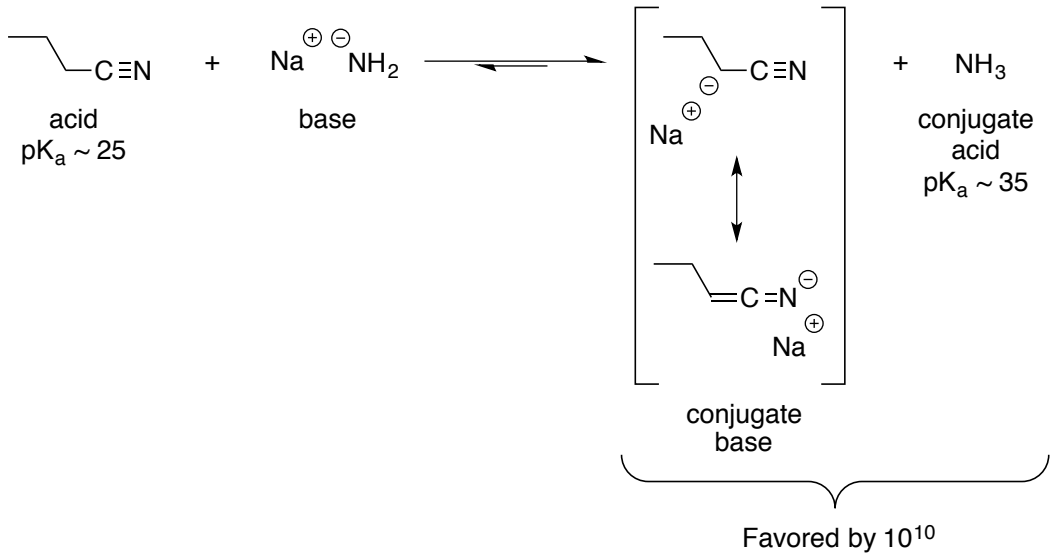


(c) In this reaction, sodamide removes a proton adjacent to a nitrile (C≡N). This is the most acidic site in the nitrile because the conjugate base has resonance stabilization. The charge is spread over a carbon and nitrogen atom, and this anion

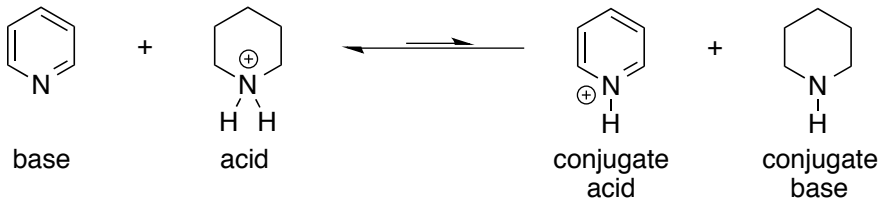
is therefore more stable than the localized charge of $^{-}NH_2$. As a result, the products are favored at equilibrium.



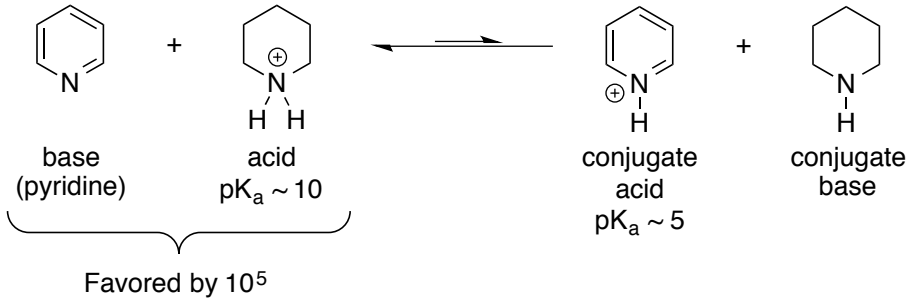
We have not yet encountered the pK_a of a nitrile, but it is approximately 25. Given this additional piece of information, we could now arrive at the same conclusion in a different way. Ammonia (NH_3) is a weaker acid than the nitrile, so the products are favored by 10^{10}.



(d) The hybridization of the nitrogen atom differs in the base and the conjugate base. The nitrogen in the base is sp^2 hybridized. Its lone pair is held close to the nucleus. On the other hand, the nitrogen in the conjugate base is sp^3 hybridized. Its lone pair is held further from the nucleus, so this lone pair is higher in energy and more accessible for reaction. The conjugate base is the stronger base. Since equilibrium favors the side with more stable (i.e., less reactive) species, the reactants are favored at equilibrium.



The base in this particular reaction is known as pyridine. We have not learned the pK_a value of protonated pyridine until now. It is about 5. Knowing this, we can make a different argument to arrive at the same conclusion. The weaker acid is on the reactants side, so this side is favored by about 10^5.



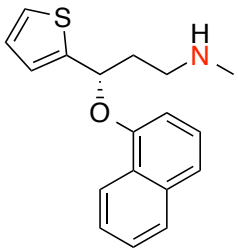
35. Cymbalta contains π bonds, as well as three atoms with lone pairs of electrons (sulfur, oxygen, and nitrogen). All of these are potentially basic sites.

Usually, π bonds are weakly basic. When a carbon-carbon π bond acts as a base, one of the two carbons becomes a carbocation. Since carbocations lack a complete octet, they are highly electron deficient and therefore unstable.

The three atoms that remain occupy different rows and columns of the periodic table, but a stepwise comparison will allow us to evaluate them all. The key is to use oxygen as the linchpin in this comparison because it shares a row or column with the other elements.

Let's begin by comparing oxygen to sulfur. Both have lone pairs of electrons. However, sulfur is a larger atom, so its electron density is more diffuse. This makes it less basic than oxygen, where the electron density is more concentrated.

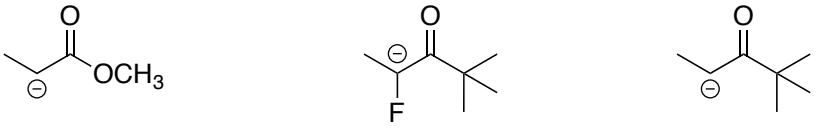
Now, we can compare oxygen to nitrogen. Since it is less electronegative, nitrogen will be more basic. When it acquires a proton, the resultant cation is more stable than it would be on oxygen. Nitrogen is more basic than oxygen, and oxygen is more basic than sulfur. So, the nitrogen of the amine is the most basic site in the molecule.



Additionally, note that the electron density on both oxygen and sulfur is spread out through resonance. This diffusion of electron density also argues for these sites being less basic than the amine, which has a localized lone pair.

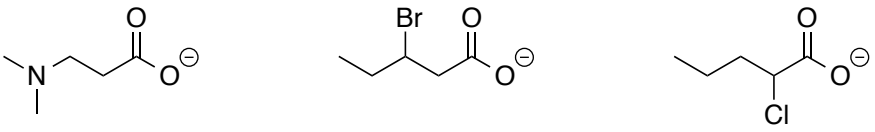
36. Much as we discussed at the beginning of the answer to Problem 32, decoding the question is extremely important. We are being asked which compound in each group has the weakest conjugate base. That is identical to asking which compound is the strongest acid. Therefore, we may compare these compounds directly based on their acidity, or we can draw the conjugate bases and analyze their basicity.

(a) The conjugate bases all benefit from resonance stabilization, but as we saw in Problem 29(e), a ketone provides more effective resonance delocalization than an ester. Of the two ketones, one also has inductive stabilization due to the presence of the halogen. This is the most stable (i.e., weakest) conjugate base.



conjugate base with the most effective resonance stabilization and inductive stabilization (weakest conjugate base)

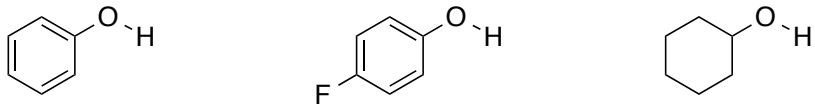
(b) The three conjugate bases have equivalent resonance stabilization, and all experience some induction caused by the electronegative elements present in their structures. However, the most electronegative element among them is chlorine, and it is also closest to the anion, giving the best inductive stabilization.



best inductive stabilization (weakest conjugate base)

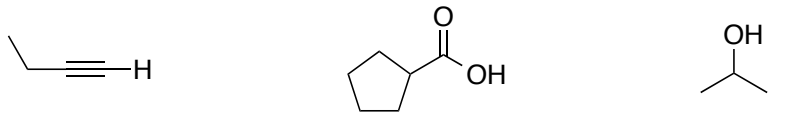
(c) When a proton is lost from each of the acids, the conjugate bases have two lone pairs on their oxygen atoms. In the first conjugate base, the lone pairs are delocalized through resonance. This is also true for the second conjugate base,

which benefits from inductive delocalization as well. The final conjugate base experiences neither resonance nor induction. The middle conjugate base is therefore the most stable (i.e., weakest) base.



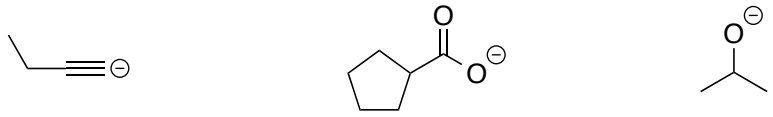
most delocalization through resonance and induction (weakest conjugate base)

(d) Since these acids contain different functional groups altogether, we can approach the problem in multiple ways. We could simply compare the pK_a values for these acids. The pK_a of the carboxylic acid is the lowest, so it is the strongest acid and has the weakest conjugate base.



$pK_a \sim 25$ $pK_a \sim 5$ $pK_a \sim 15$

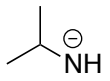
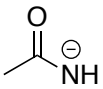
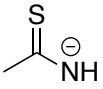
Alternatively, we could have compared the structural features of the conjugate bases. Doing so would suggest that having the anion on oxygen is preferable to placing it on carbon. Additionally, having resonance is preferable to its absence. So, we arrive at the same conclusion in a different way.



anion on electronegative element and also resonance stabilized (weakest conjugate base)

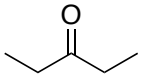
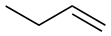
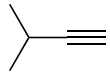
The only concern with the latter approach is that hybridization differences can occasionally trump element effects, as we saw in Problem 26(f). In this case though, hybridization does not outweigh the element effect.

(e) The conjugate bases of these acids differ in multiple ways. Although the anion is on nitrogen in all three, the first has no resonance, while the others do. Of the two resonance-stabilized anions, one spreads the charge over nitrogen and oxygen, while the other delocalizes it over nitrogen and sulfur. Sulfur is a larger element, and its charge will be more diffuse (and therefore more stable), so the last conjugate base is the weakest.

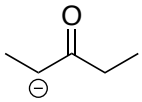
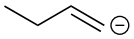
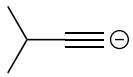
resonance delocalization of
anion onto larger atom
(weakest conjugate base)

(f) Since these acids all contain different functional groups for which we know pK_a values, they can be compared directly. The ketone has the lowest pK_a, so it is the strongest acid and has the weakest conjugate base.

$pK_a \sim 20$ $pK_a \sim 45$ $pK_a \sim 25$

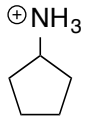
We could also have chosen to compare the conjugate bases. The negative charge resides on carbon in each. However, the ketone's conjugate base has resonance delocalization of the anion. Notably, the anion can be placed on the carbonyl oxygen, which is especially stabilizing because oxygen is a fairly electronegative element. The conjugate bases of the alkene and alkyne have no such resonance stabilization. We therefore expect the ketone's conjugate base to be the most stable (i.e., the weakest).

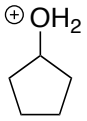
resonance delocalization onto
electronegative element
(weakest conjugate base)

Once again, the only concern with the latter approach is that hybridization differences occasionally trump other effects, as we saw in Problem 26(f). In this case though, hybridization does not outweigh the element and resonance effects.

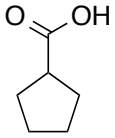
(g) Since the functional groups in these acids all differ, we may compare them directly using pK_a values. For the protonated amine and carboxylic acid, the numbers come directly from our pK_a table. In Problem 22, we learned that we can estimate the pK_a of a protonated alcohol because of its similarity to the hydronium ion (H_3O^+), which is on the table. The protonated alcohol has the lowest pK_a, so it is the strongest acid.



$pK_a \sim 10$

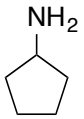


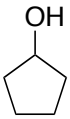
$pK_a \sim -2$

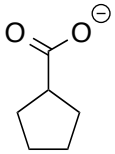


$pK_a \sim 5$

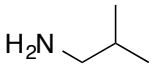
In this case, it is a bit more challenging to compare the conjugate bases because the comparison involves two neutral and one charged species.



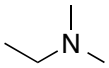




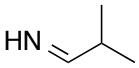
(h) The first acid can lose a proton from nitrogen to yield a conjugate base with an anion that is sp^3 hybridized. The second compound has no proton on nitrogen. It is much harder to remove a proton from carbon, so this molecule does not readily act as an acid. The last molecule can lose a proton from nitrogen to yield a conjugate base with the anion on an sp^2 hybridized atom. Having the lone pair responsible for the charge in a hybrid orbital with more s character is stabilizing. This last conjugate base is therefore the weakest.



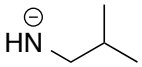
sp^3 hybridized conjugate base:

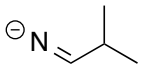


does not readily lose a proton

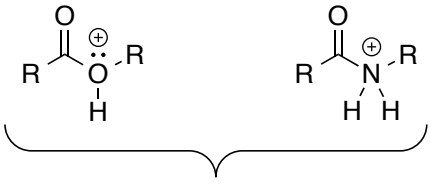


sp^2 hybridized and has the weakest conjugate base:



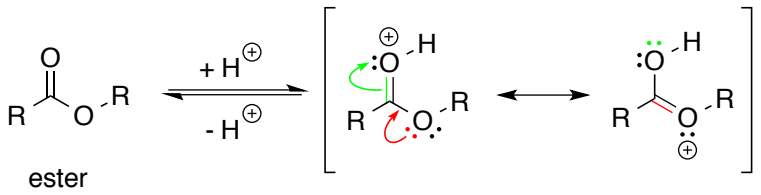


37. Protonation of an ester or amide on the sp^3 hybridized oxygen/nitrogen is undesirable because it yields a cation without resonance stabilization.

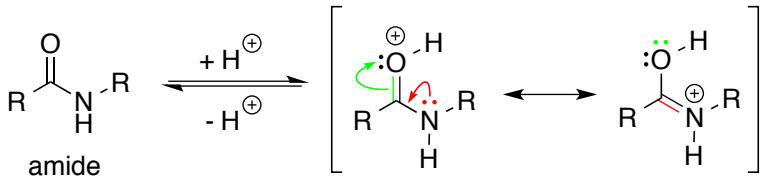


no resonance stabilization

On the other hand, if an ester is protonated on the carbonyl oxygen, the resulting cation has resonance stabilization. The burden of charge can be shared between the two oxygen atoms, making this the preferred mode of protonation.

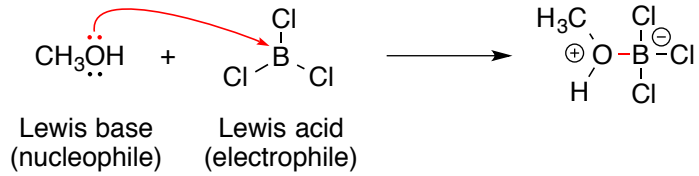


Similarly, protonation of an amide on the carbonyl oxygen results in a resonance-stabilized conjugate acid. The stabilization afforded by delocalization of charge makes this the preferred mode of protonation.

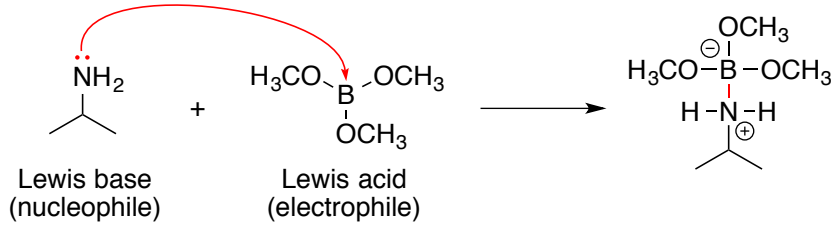


38.

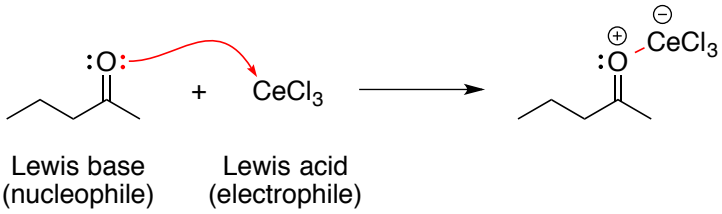
(a) The Lewis base was the missing component in this reaction. The alcohol donates a pair of electrons to boron trichloride, the Lewis acid, to form the Lewis acid-base adduct. The Lewis base is always the nucleophile, and the Lewis acid is always the electrophile.



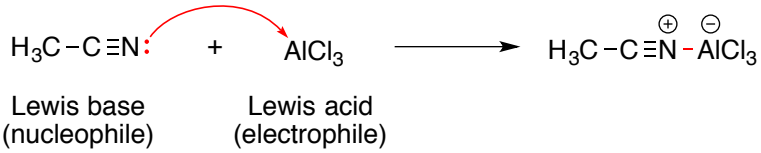
(b) The Lewis acid-base adduct was the missing species in this transformation. It is formed when the amine donates a pair of electrons to boron. Since it functions as the electron-pair donor, the amine is both the Lewis base and the nucleophile. The boron is the electron-pair acceptor, and as such, it is the Lewis acid and the electrophile.



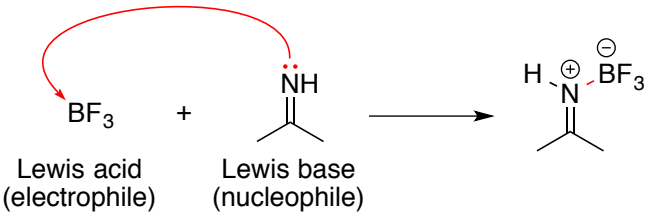
(c) The Lewis acid ($CeCl_3$) was the missing piece of this reaction. The carbonyl oxygen of the Lewis base donates a pair of electrons to cerium trichloride to yield the Lewis acid-base adduct.



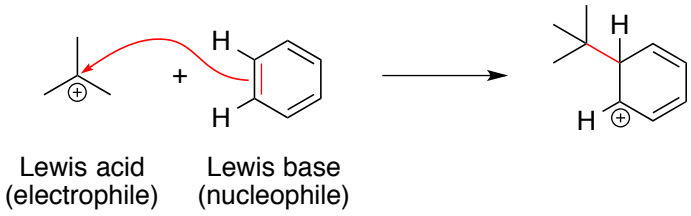
(d) Both the Lewis acid and the Lewis base were missing in this reaction. If we imagine breaking the bond between nitrogen and aluminum and giving those electrons to the more electronegative element (nitrogen), we can infer the structures of the Lewis acid and base.



(e) The Lewis acid and base were also omitted from this reaction. To produce their structures, imagine breaking the bond between the cation and anion and giving those electrons to the more electronegative element, which is nitrogen.



(f) In this reaction, we need to draw the Lewis acid-base adduct. Benzene is clearly more electron rich than the carbocation, which has a positive charge. Any of the three equivalent π bonds of benzene can be donated to the carbocation, making benzene the Lewis base. The protons on the double bond undergoing reaction have been highlighted to facilitate drawing the product correctly. One of the carbons of the double bond acquires the new bond to the Lewis acid; the other has only three bonds and therefore becomes positively charged.



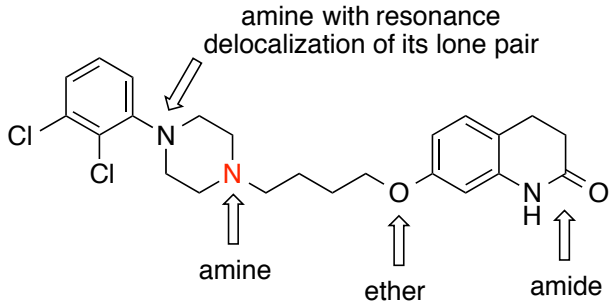
39. This compound contains π bonds, as well as lone pairs on chlorine, oxygen, and nitrogen. Any of these could potentially serve as a base. In general, π bonds are

relatively weakly basic. If a carbon-carbon π bond is used as a base, one of the two carbons becomes a carbocation, which lacks a complete octet and is therefore highly electron deficient. Also, the carbon-carbon π bonds in this molecule happen to be part of aromatic rings, and as we learned in the answer to Problem 10(b), aromatic rings are especially stable. It is therefore undesirable to disrupt the pattern of alternating double and single bonds within these rings.

The remaining functionality includes the halides, an ether, an amide, and two amines. We know that chloride (Cl^-) is an extremely weak base; this is the reason that HCl is such a strong acid. Since chloride, which has a negative charge, is such a weak base, we can expect a neutral chlorine atom (that has less electron density) to be an even weaker base.

The ether is also expected to be a weak base, since the conjugate acid would have a positive charge on oxygen, which is a fairly electronegative element. Protonation of the amide on the carbonyl oxygen would yield a resonance-stabilized cation. However, this would still place a positive charge on a reasonably electronegative element.

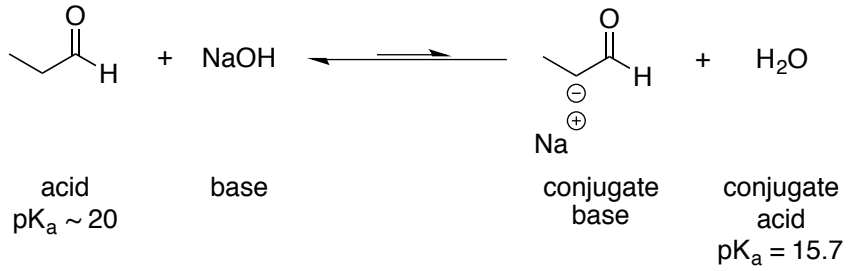
Of the three nitrogen atoms, two have lone pairs that are resonance delocalized. The lone pair of the amide nitrogen is delocalized into the carbonyl, and the amine bonded to the aromatic ring experiences delocalization of its lone pair throughout the ring. When the electron density of a lone pair is spread out and therefore less concentrated, the atom bearing the lone pair is less basic. On the other hand, the amine with no resonance delocalization has its lone pair centralized and concentrated on the nitrogen atom. This site of high electron density is basic. Furthermore, the conjugate acid has a positive charge on nitrogen, which is less electronegative than oxygen and chlorine. Thus, this amine is the most basic site in the molecule.



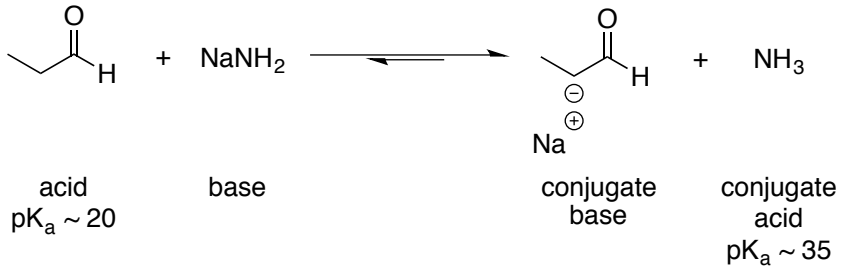
40.

(a) When an aldehyde is treated with hydroxide, the reactants are favored at equilibrium by $10^{4.3}$. That's a factor of roughly 20,000. Remember that Avogadro's number tells us that there are 6.02×10^{23} molecules in a mole, so even a tiny sample contains a huge number of molecules. As a result, this factor of about 20,000

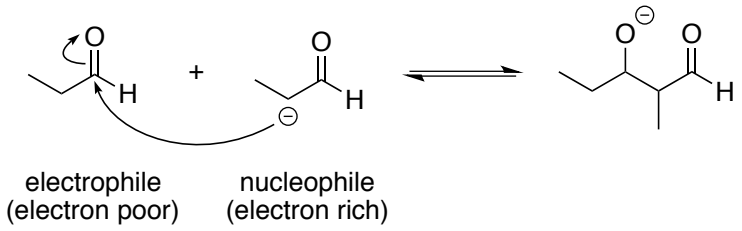
: 1 means that some of the aldehyde's conjugate base does, in fact, coexist with the aldehyde itself.



On the other hand, had we used sodamide for the reaction, the products would be favored by 10^{15}. That's a ratio of 1 : 1,000,000,000,000,000, and effectively represents complete deprotonation of the aldehyde. There is essentially no aldehyde remaining at equilibrium. Since the aldol reaction relies upon aldehyde *coexisting* with its conjugate base, sodamide is not a suitable choice of base.



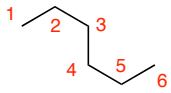
(b) The aldehyde's conjugate base is electron rich, as evidenced by its negative charge. Consequently, it is the nucleophile. The aldehyde's carbonyl carbon is electron poor. It has a δ^+ that results from resonance and induction. It is therefore the electrophile.

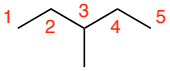


Solutions to Problems for Chapter 3: Alkanes

1.

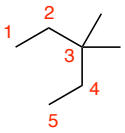
(a) The first molecule in this pairing is a linear alkane with a six-carbon chain. The second molecule, on the other hand, is a branched alkane. It has a five-carbon chain with a one-carbon group attached to C3.





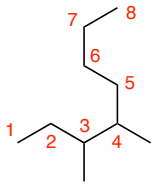
These molecules are isomers because they possess the same formula but different connectivity, and we encountered them in this section.

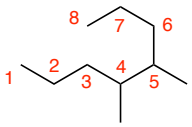
(b) Both of these molecules are branched alkanes. The longest chain in both molecules is five-carbons in length, and they both have two one-carbon groups at C3.



These structures therefore represent the same molecule.

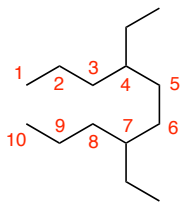
(c) Both of these molecules are branches alkanes, and the longest chain in each is eight-carbons. However, if we number from the terminus closest to the first branch point, the first molecule has two one-carbon groups at C3 and C4, while the second molecule has them at C4 and C5.

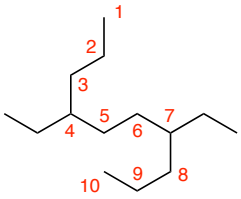




These molecules differ in connectivity and are therefore constitutional isomers.

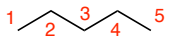
(d) These molecules are both branched alkanes, and they both contain a ten-carbon chain. Regardless of the direction of numbering, they also both contain two two-carbon groups at C4 and C7.



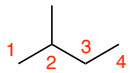


Consequently, these are different representations of the same molecule.

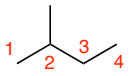
2. A systematic approach is needed when you are attempting to draw all of the isomers for a given molecular formula. The first isomer may simply contain all five of the carbons in a linear chain.



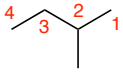
To derive the next isomer, shorten the longest chain by one carbon and consider where that carbon can be placed to produce a branch point. If the longest chain is to be four carbons, then the one-carbon group cannot be attached to C1 or C4 (otherwise we would simply recreate the linear alkane shown above). The one-carbon group could form a branch point a C2 though.



Notice that placing the one-carbon group on C3 would *not* yield a different isomer.



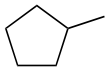
is the same as



if you number from the opposite terminus

Finally, the longest, linear chain can be shortened by one additional carbon, and the remaining two one-carbon groups can both generate branch points. The only new isomer that can be produced in this fashion results from placing both groups on C2.

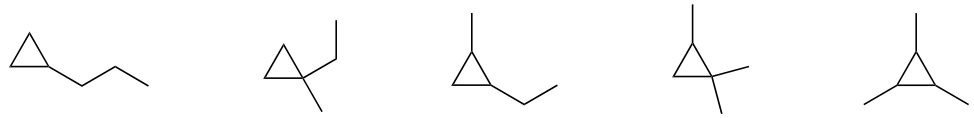
3. To derive isomers with a ring, we must consider rings containing fewer than six members. There is one isomer with a five-membered ring. Since all of the ring carbons are equivalent, the one-carbon group can be placed on any of them.



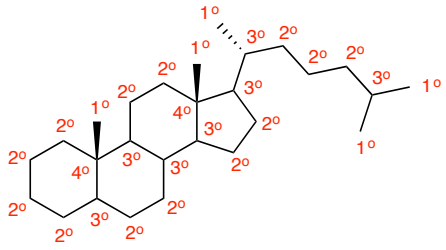
There are four isomers with a four-membered ring. The remaining two carbons can be a single group on the ring, or they can be two one-carbon groups. These two one-

carbon groups can reside on the same carbon, adjacent carbons, or carbons opposite each other on the ring.

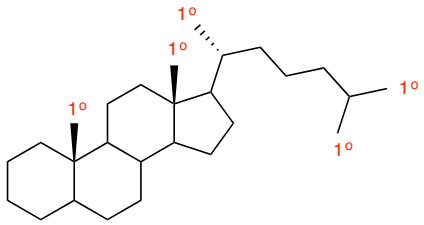
There are five isomers containing a three-carbon ring. The remaining three carbons could be a single group on the ring. Alternatively, there could be a two-carbon group and a one-carbon group on the same position or one adjacent carbons. Finally, there could be three one-carbon groups on the ring. Two of them could be on the same carbon with the last on an adjacent carbon, or they could all reside on different carbons.



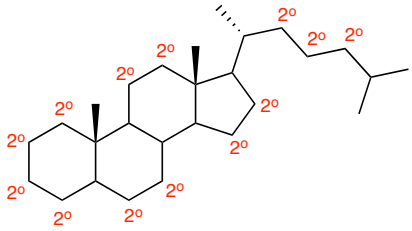
4. Cholestane is shown below. The hydrogens have been deleted to make space for the labels.



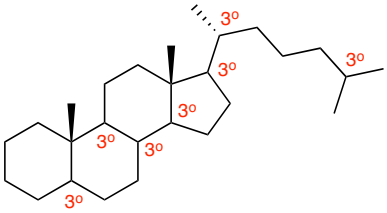
The primary carbons (1˚) are those that are bonded to only one other carbon.



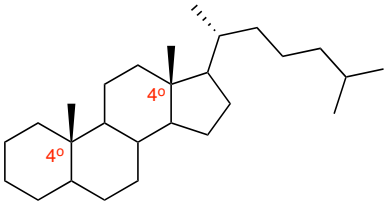
The secondary carbons (2˚) are those that are bonded to two other carbons.



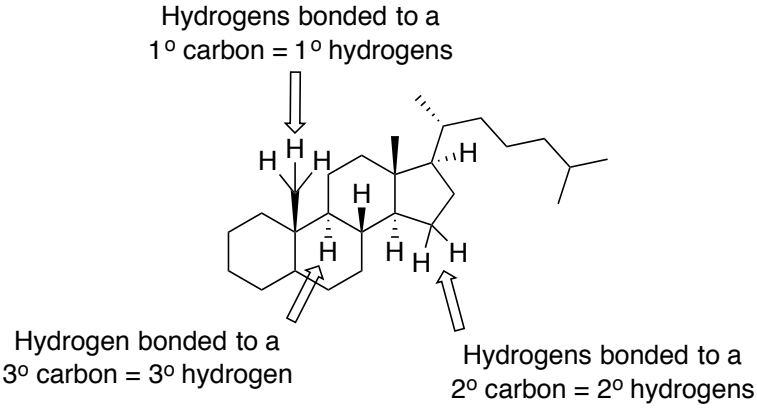
The tertiary carbons (3°) are those that are bonded to three other carbons.



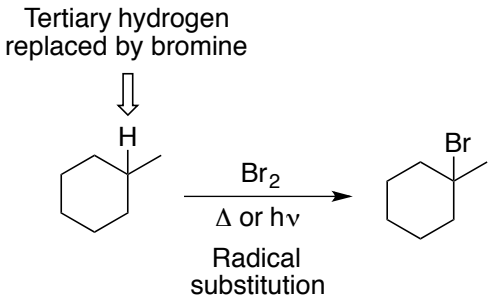
The quaternary carbons (4°) are those that are bonded to four other carbons.



5. The classification of a hydrogen atom depends upon the carbon to which it is bonded. Primary hydrogens are bonded to primary carbons. Secondary hydrogens are bonded to secondary carbons, and tertiary hydrogens are bonded to tertiary carbons.

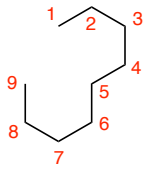


6. The text of the question indicates that a tertiary hydrogen is replaced by bromine in a radical substitution reaction. There is only one tertiary hydrogen in this molecule, so it must be the one that is exchanged for a bromine atom.

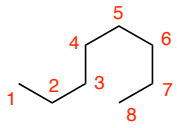


7.

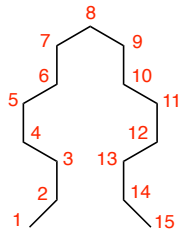
(a) This is a nine-carbon chain, making it nonane.



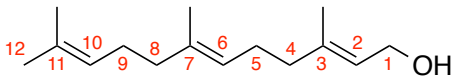
(b) There are eight carbons in this linear alkane, so it is octane.



(c) This fifteen-carbon linear alkane is pentadecane.



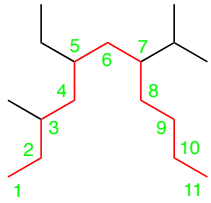
(d) The longest, continuous carbon chain in farnesol includes twelve carbons. The corresponding alkane is dodecane.



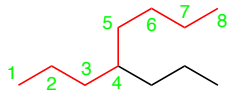
8.

(a) The longest, continuous chain in this molecule is five-carbons in length, so the parent is pentane.

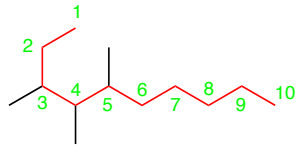
(b) The longest, continuous chain in this structure consists of eleven carbons, so the parent is undecane.



(c) It may be tempting to simply select a parent chain in a horizontal plane, but that might not necessarily be the longest chain. Sometimes following a branch down another path will lead to a longer chain and therefore the correct parent. Such is the case in this example. Following the branch up at C4 allows us to identify octane as the parent. Had we continued numbering horizontally the parent would have been *misidentified* as heptane.



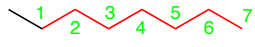
(d) This is another case in which following a branch leads to a longer parent chain than we might have initially expected. There is a nine-carbon chain drawn horizontally, but if the branch on the left side of the molecule is incorporated, a ten-carbon parent (decane) can be identified.



9.

(a) We can begin by drawing the structure implied by the name. Heptane is a seven-carbon chain.

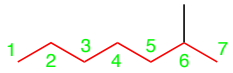
Methyl is a one-carbon group, and the numbering indicates that it is attached to C1.



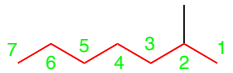
The problem is that the longest, continuous carbon chain is actually eight carbons, not seven. This molecule is simply octane.

(b) Once again, we can begin by drawing the structure implied by the name. Heptane is a seven-carbon chain.

The one-carbon methyl group is bonded to C6.

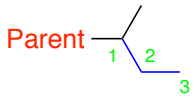


The problem here is that the parent has not been numbered so as to give the substituent the lowest possible number. It should have been numbered from the other terminus to make this 2-methylheptane.

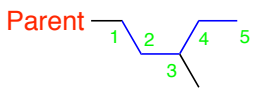


10.

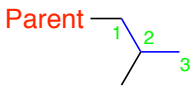
(a) The longest, continuous carbon chain within the *sec*-butyl group is three-carbons in length, so the parent alkyl group is propyl. The propyl group is numbered so that C1 is closest to the parent alkane. There is a methyl group on C1 of the substituent, so the systematic name for the *sec*-butyl group is (1-methylpropyl).



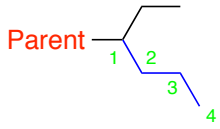
(b) The longest, continuous carbon chain within this substituent is five-carbons long. The parent alkyl group is therefore pentyl. It is numbered so that C1 is adjacent to the parent. There is a methyl group at C3 of the substituent, making the name of this group (3-methylpentyl).



(c) The isobutyl substituent contains a three-carbon parent alkyl group. It is numbered so that C1 is attached to the parent. There is also a methyl group at C2, so the complete name of this substituent is (2-methylpropyl).

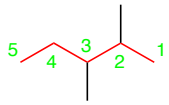


(d) The longest, continuous carbon chain within this substituent is four-carbons in length, so butyl is the parent alkyl group. It must be numbered so that C1 is adjacent to the parent, and there is an ethyl group at C1. The complete name is therefore (1-ethylbutyl).

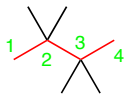


11.

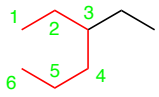
(a) The longest, continuous carbon chain in this molecule is five-carbons in length, so the parent is pentane. It is numbered from right to left so as to give the lowest possible number (2) to the first substituent. There are two methyl groups, and each needs a locant. The complete name is therefore 2,3-dimethylpentane.



(b) The longest chain in this structure is four carbons, making the parent butane. It can be numbered in either direction with no difference in the result. Remember that each of the four methyl groups will need a number, so the IUPAC name is 2,2,3,3-tetramethylbutane.

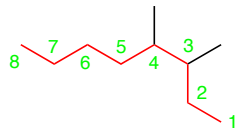


(c) It is important to remember that the parent chain is not necessarily drawn horizontally. In this example, the parent is hexane, not pentane as we would have gotten had we merely selected the horizontal chain. It is numbered so as to give the ethyl substituent the lowest possible number. The systematic name is 3-ethylhexane.



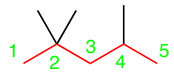
(d) Once again, the longest chain is not merely the one drawn horizontally. It is possible to locate a longer parent: octane. It is numbered from right to left so that

the first substituent receives the lowest possible number, and each methyl group must have a locant. The full systematic name is 3,4-dimethyloctane.

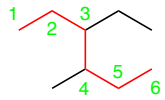


12.

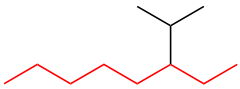
(a) The parent chain in this molecule is pentane. Numbering from either terminus gives the same locant (2) to the first substituent. Therefore, we number so as to give the second substituent the lowest possible number. There are three methyl groups, each of which requires a locant, so the complete name is 2,2,4-trimethylpentane.



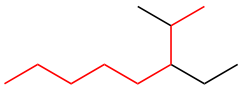
(b) Hexane is the parent chain in this structure. Either direction of numbering will result in locants of 3 and 4 for the two substituents. Since the numbers are the same either way, the tie is broken by giving the alphabetically first substituent (ethyl) the lower number (3). The systematic name is therefore 3-ethyl-4-methylhexane.



(c) There are two possible eight-carbon parents in this molecule. The correct one is the one that has more substituents.

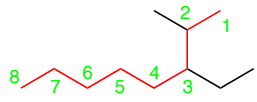


one substituent

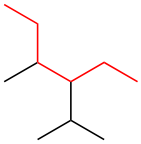


two substituents

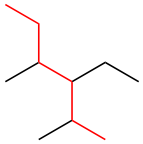
The octane parent is numbered so as to give the lowest possible number to the first substituent, and the complete name is therefore 3-ethyl-2-methyloctane.



(d) This molecule has two contenders for the parent. There is a six-carbon chain with two substituents, as well as a six-carbon chain with three substituents. The latter is the correct parent.

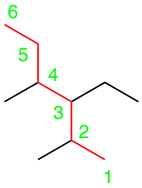


two substituents



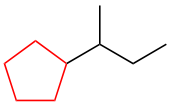
three substituents

This hexane is numbered so that the first substituent gets the lowest possible number, making the complete systematic name 3-ethyl-2,4-dimethylhexane. Remember that the prefix "di" does not count for alphabetization.

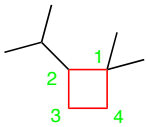


13.

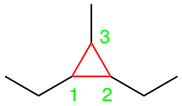
(a) The ring has five carbons, while the attached chain contains only four carbons. Therefore, cyclopentane is the parent. The single substituent is assumed to be at C1 of the ring, so no number is needed. The complete name is *sec*-butylcyclopentane.



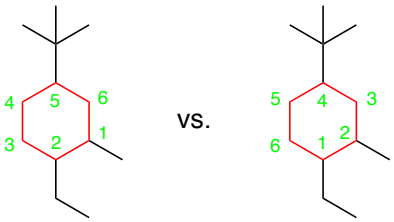
(b) The ring contains more carbons than any single substituent, so cyclobutane is the parent. One of the substituents will receive the locant 1. The correct numbering is decided by giving the lowest possible number to the second substituent. This is achieved by numbering the carbon bearing the methyl groups as C1. Both the first and the second substituent receive the number 1 as a result. The molecule's systematic name is 2-isopropyl-1,1-dimethylcyclobutane. Remember that the "iso" prefix is counted for alphabetization, but the prefix "di" is not.



(c) Cyclopropane is the parent. The substituents will receive the numbers 1, 2, and 3 regardless of how the ring is numbered. Consequently, the tiebreaker of last resort is used, and the ring is numbered so as to give the alphabetically first substituents (ethyl) the lowest possible numbers. As a result, the name is 1,2-diethyl-3-methylcyclopropane.



(d) The parent is cyclohexane. We know that one of the substituents will receive the number 1. There are two ways to number the ring so as to give the second substituent the number 2. The correct option assigns the lower number to the third substituent.

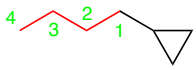


Incorrect Correct

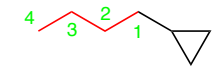
The systematic name is 4-*tert*-butyl-1-ethyl-2-methylcyclohexane.

14.

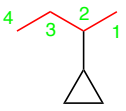
(a) In this instance, the four-carbon chain is larger than the three-carbon ring, so the ring is treated as a substituent on the butane parent. The butane chain must be numbered so that the location of the ring can be communicated. Substituents on acyclic parents nearly always require a locant. The name of this alkane is therefore 1-cyclopropylbutane.



The locant is needed to differentiate 1-cyclopropylbutane from its constitutional isomer 2-cyclopropylbutane.

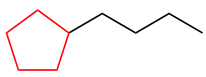


1-cyclopropylbutane

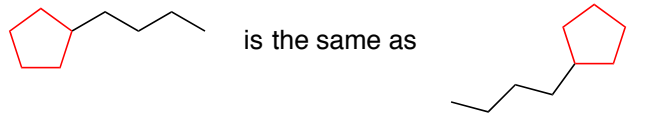


2-cyclopropylbutane

(b) In this molecule, the ring is larger than the four-carbon chain, so it is the parent. When a cycloalkane bears a single substituent, a locant is not necessary. Consequently, the name is butylcyclopentane.

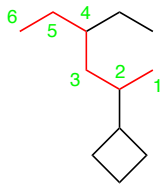


No locant is necessary in this case because placing a butyl group on any carbon of cyclopentane gives the same molecule.



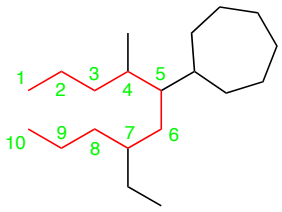
butylcyclopentane butylcyclopentane

(c) The longest, continuous carbon chain in this molecule consists of six carbons. This is larger than the ring, so hexane is the parent. It is numbered so as to give the first substituent the lowest possible number. The complete name is therefore 2-cyclobutyl-4-ethylhexane.



Recall that the prefix "cyclo" is counted for the purpose of alphabetization.

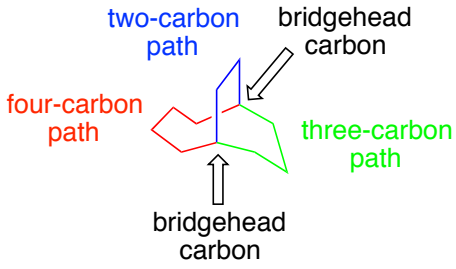
(d) The longest chain in this molecule is ten-carbons in size. It is larger than the seven-carbon ring, so decane is the parent. Numbering from either terminus will give the first substituent the number 4, so we number so as to provide the second substituent with the lowest possible number. Doing so yields the name 5-cycloheptyl-7-ethyl-4-methyldecane.



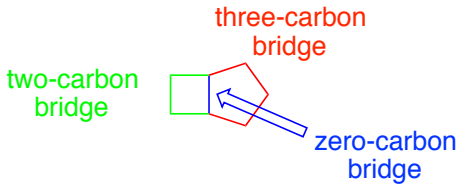
Again, note that the prefix "cyclo" counts in alphabetization.

15.

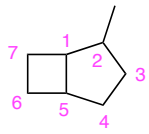
(a) This bicyclic alkane contains eleven carbons, so it is a bicycloundecane. We must also include descriptions of the bridge lengths in the name. There are four-carbon, three-carbon, and two-carbon bridges in this structure, and this leads to the name bicyclo[4.3.2]undecane.



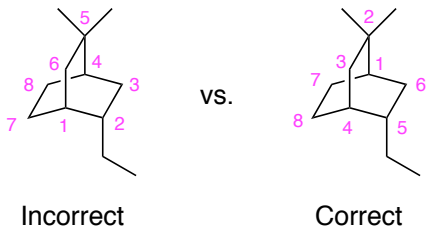
(b) The core of this substituted bicycle is shown below. It is a bicycloheptane because it contains a total of seven carbons in the ring system. We also need to include designations of the bridge lengths, making the name of the ring system bicyclo[3.2.0]heptane.



The complete molecule also has a methyl substituent. We must therefore number the parent in order to relay its location. Numbering begins at a bridgehead carbon and continues along the longest bridge, followed by the second longest bridge. With this information, we can write the complete name of the molecule: 2-methylbicyclo[3.2.0]heptane.

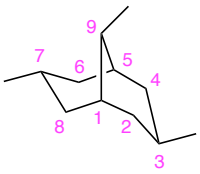


(c) The bicyclic ring system itself, excluding substituents, contains eight carbons, making this a bicyclooctane. All of the bridges are two-carbons in length, so it is a bicyclo[2.2.2]octane. Numbering begins at a bridgehead carbon, but since all of the bridges are of the same length, we can continue down whichever path gives the lowest number to the first substituent. We can break the tie by giving the lowest number to the second substituent.

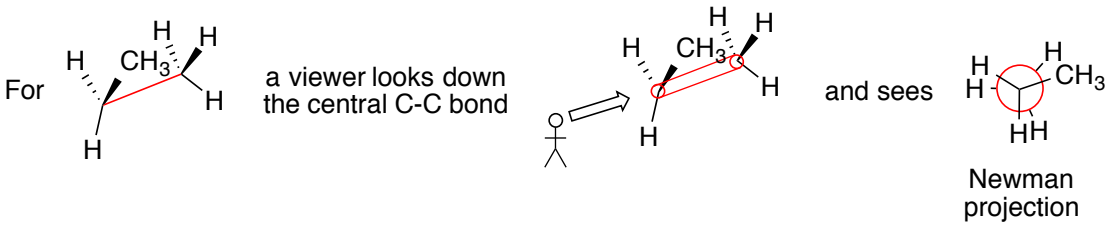


The complete name is therefore 5-ethyl-2,2-dimethylbicyclo[2.2.2]octane.

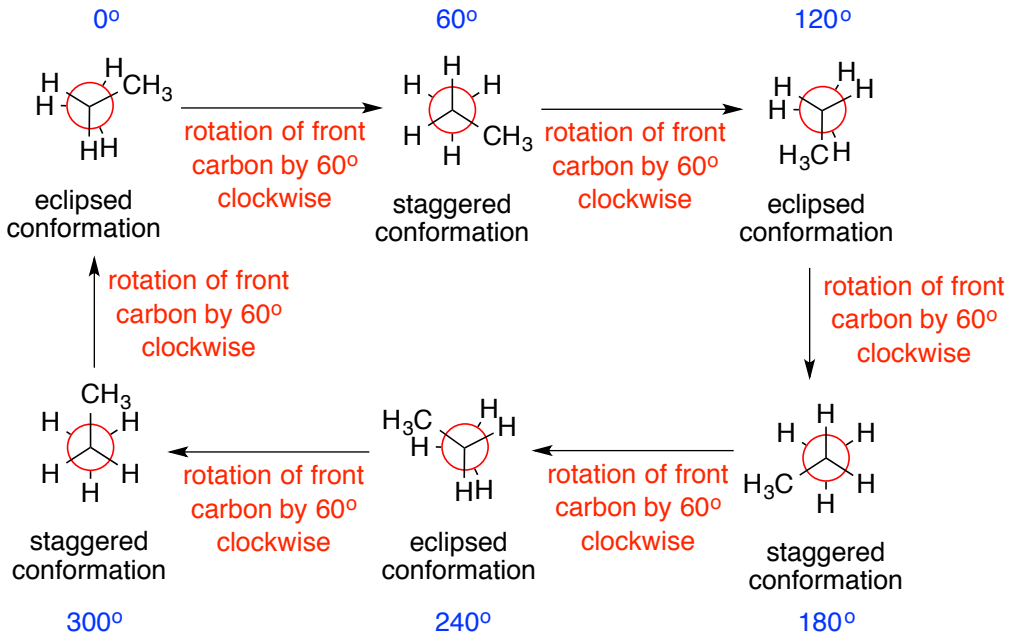
(d) The ring system in this molecule is a bicyclo[3.3.1]nonane. Numbering begins at a bridgehead position and continues along either of the three-carbon bridges, followed by the other, and finally by the one-carbon bridge. The choice of which bridgehead carbon to designate as C1 and which three-carbon bridge to number first does not affect the outcome. The molecule is 3,7,9-trimethylbicyclo[3.3.1]nonane.



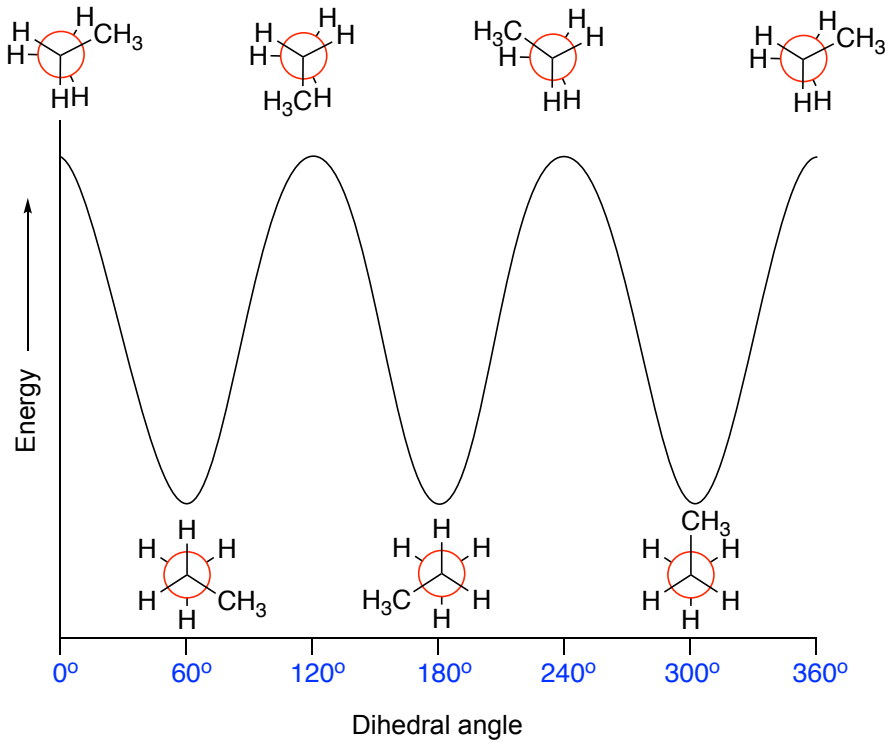
16. Looking down either carbon-carbon bond of propane, we'll see the same thing, so it does not matter which one we choose. The instructions indicated that we should begin with an eclipsed conformation.



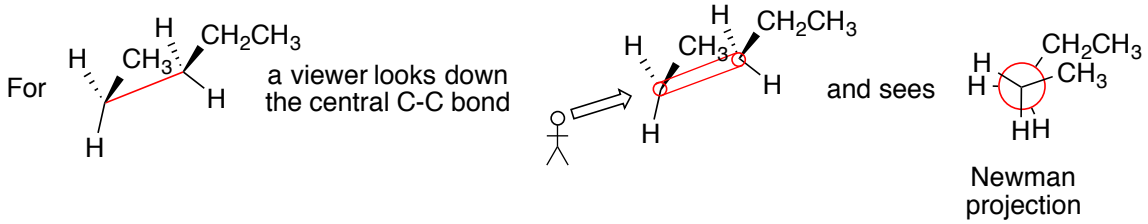
It is easiest to rotate the carbon bearing the methyl group because the methyl group is a distinctive substituent and we can readily follow its progress around the ring. In the diagram below, the front carbon is rotated 60° at a time, generating the expected array of conformations that alternate between eclipsed and staggered.



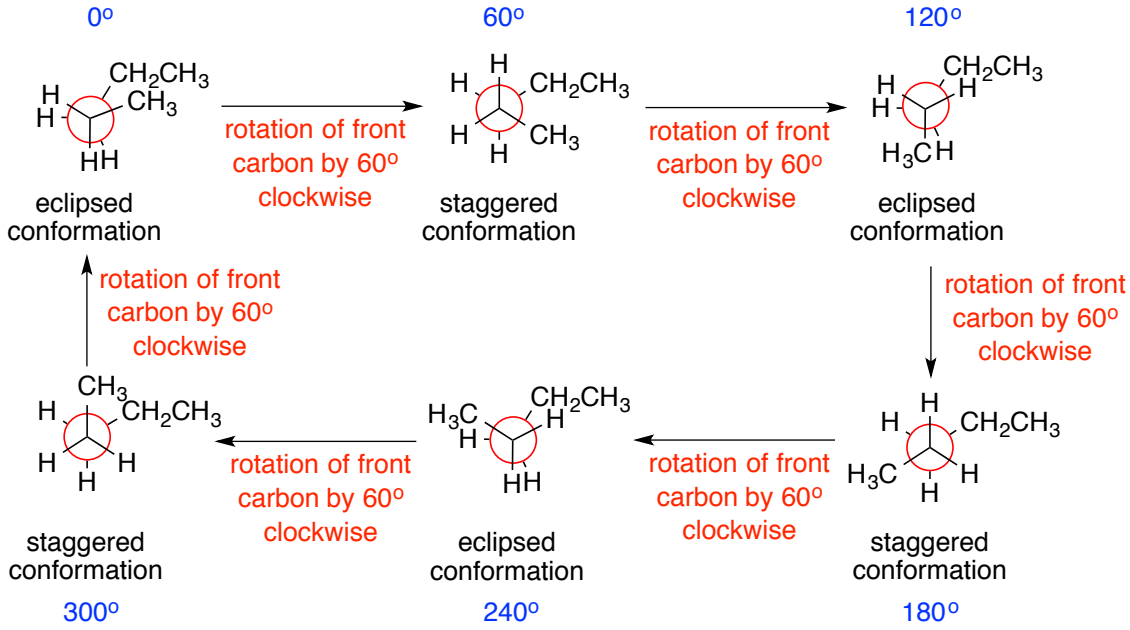
Much as with ethane, all of the eclipsed conformations are equal in energy. All of the staggered conformations are also equal in energy. The eclipsed conformers are higher in energy than the staggered ones. The energy difference will be larger in this case for reasons that we'll discuss when considering the conformational analysis of butane, which appears next in the text.



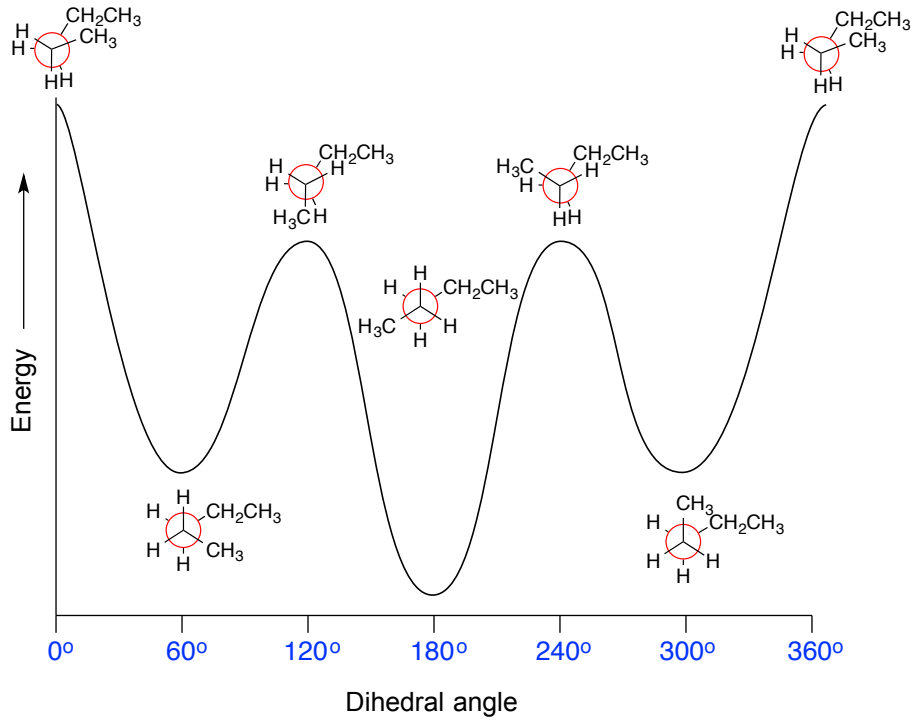
17. Looking down the C2-C3 bond of pentane, we see a methyl group bonded to the front carbon of the Newman "barrel" and an ethyl group bonded to the back carbon.



Beginning with the conformer in which the methyl eclipses the ethyl group, we can rotate the front (or back) carbon in 60° increments to generate the expected alternating pattern of staggered and eclipsed conformations.

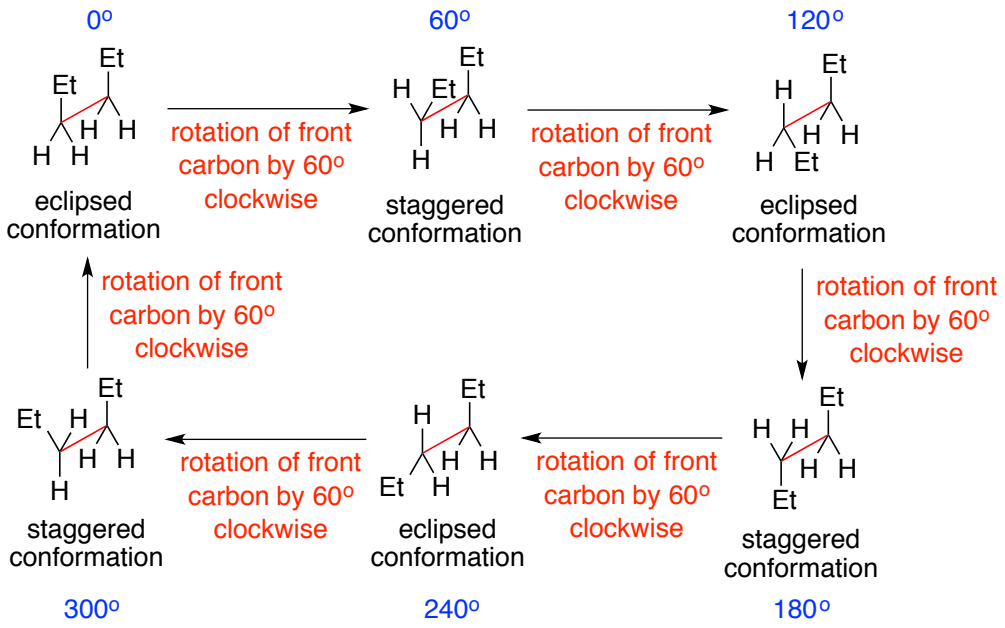


The eclipsed conformation in which methyl eclipses ethyl (0°/360°) is the highest in energy because of its torsional and steric strain. Immediately below it in energy are the two other eclipsed conformers (120° and 240°). The next lowest energy conformations include the two staggered conformers with a gauche interaction (60° and 300°). Finally, the staggered conformation in which the methyl and ethyl are anti (180°) is the lowest in energy.

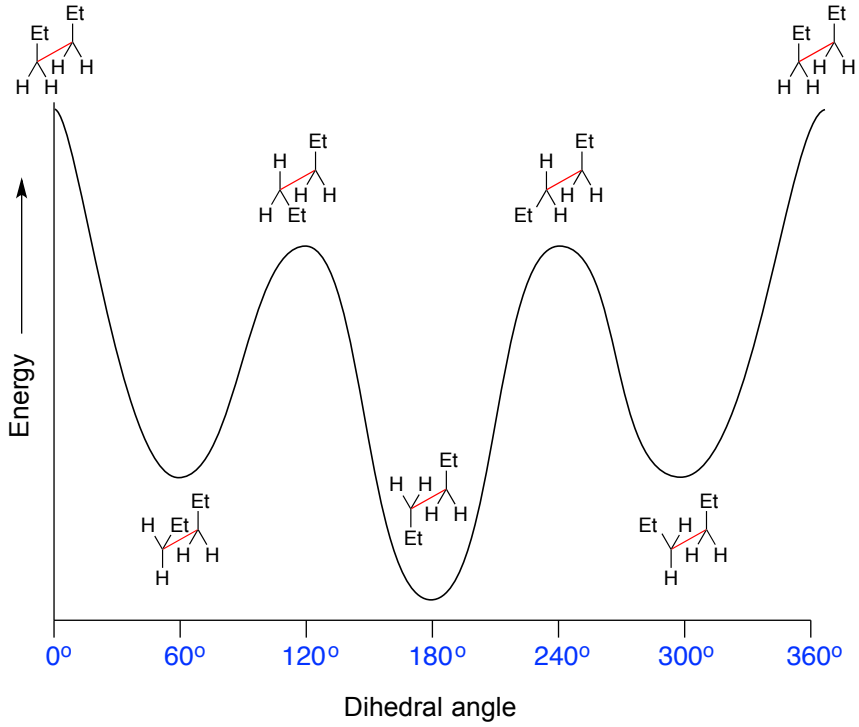


The magnitude of the energy differences between conformations will not be exactly the same as for butane because a methyl group has been replaced by an ethyl group, which will lead to enhanced steric strain.

18. If we focus on the C3-C4 bond of hexane, both the front and back carbons bear ethyl (Et) groups. Rotating 60° at a time, the familiar alternating pattern of staggered and eclipsed conformations is obtained.

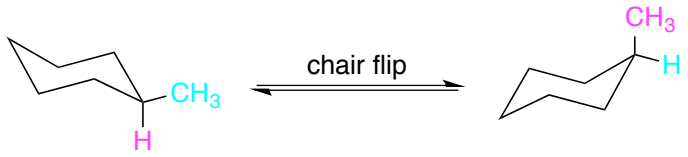


The highest energy conformer (0°/360°) has eclipsing ethyl groups. The other two eclipsed conformations (120° and 240°) are lower in energy than when the ethyl groups are eclipsing but higher in energy than any of the staggered conformers. The two gauche staggered conformations (60° and 300°) are lower in energy than the eclipsed conformers but higher in energy than the anti staggered conformation (180°).



The magnitude of the energy differences between conformers will vary from the values we've seen previously because the two ethyl groups will exhibit greater steric strain than two methyl groups.

19. The process that we are considering is the interconversion of the two chair forms through a conformational change. The A value tells us that the conformer with the axial methyl group is 1.8 kcal/mole higher in energy.



equatorial methyl

axial methyl
(1.8 kcal/mole
higher in energy)

We can plug that value in for ΔG° (note that $\Delta G^\circ = G^\circ_{products} - G^\circ_{reactants}$). Solving for K_{eq} gives a value of approximately 0.05.

$\Delta G^\circ = -RT \ln K_{eq}$

$1.8 \text{ kcal/mol} = -(1.987 \times 10^{-3} \text{ kcal/K mol})(298 \text{ K}) \ln K_{eq}$

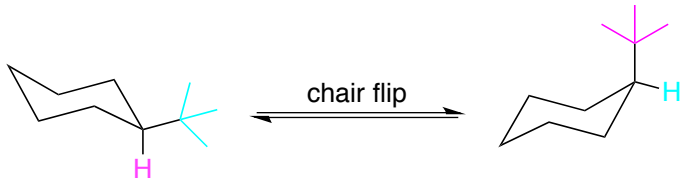
$K_{eq} \approx 0.05$

Since K_{eq} is the ratio of the concentration of products to the concentration of reactants, a value of 0.05 tells us that for every one molecule in the axial conformation there are twenty in the equatorial conformation.

$$K_{eq} = \frac{[products]}{[reactants]} \approx 0.05$$

$$\frac{[products]}{[reactants]} \approx \frac{1}{20}$$

20. The conformational change under consideration is the chair flip that converts the equatorial conformer of *tert*-butylcyclohexane to the axial conformer. The A value tells us that the axial conformation is 4.9 kcal/mole higher in energy.



equatorial *tert*-butyl

axial *tert*-butyl
(4.9 kcal/mole
higher in energy)

We can then use this value along with the R and T values from Problem 19 to solve for the K_{eq}.

$\Delta G^\circ = -RT \ln K_{eq}$

$4.9 \text{ kcal/mol} = -(1.987 \times 10^{-3} \text{ kcal/K mol})(298 \text{ K}) \ln K_{eq}$

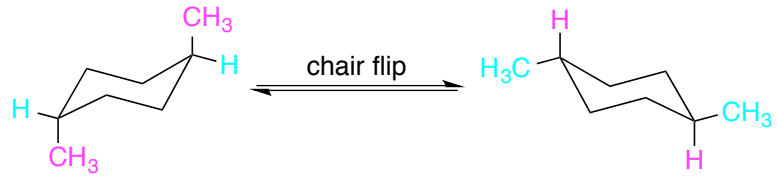
$K_{eq} \approx 0.00025$

This small K_{eq} value shows that for every 10,000 molecules only 2.5 would exist in the axial conformation. Since a half of a molecule isn't a realistic option, we could also say that for every 20,000 molecules only 5 exist in the axial conformation.

$$K_{eq} = \frac{[products]}{[reactants]} \approx 0.00025 = \frac{2.5}{10{,}000} = \frac{5}{20{,}000}$$

21.

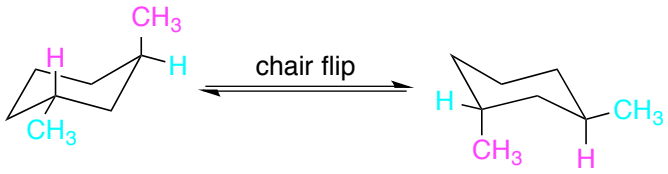
(a) In this pair of chair conformations, one conformer has both methyl groups in the axial position. The energetic cost of placing a methyl group axial is 1.8 kcal/mole, so this conformation is destabilized by twice that amount (3.6 kcal/mole).



Two axial methyls
(2 x 1.8 kcal/mol = 3.6 kcal/mol)

Two equatorial methyls

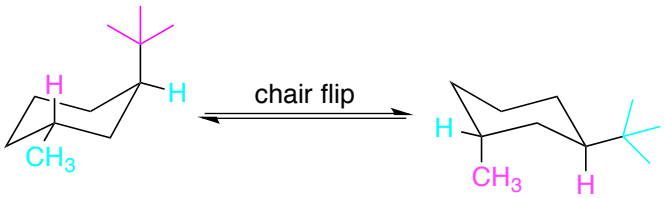
(b) In this pairing, one methyl group is axial in each conformation. Therefore, each conformer is destabilized by 1.8 kcal/mole. Another way of phrasing this is that the two conformations are equal in energy.



One axial methyl
(1.8 kcal/mol)

One axial methyl
(1.8 kcal/mol)

(c) The first conformer in this pairing has an axial *tert*-butyl group. This destabilizes the conformation by 4.9 kcal/mole. The latter conformation has an axial methyl group, which destabilizes the conformer by 1.8 kcal/mole. The conformation with the axial *tert*-butyl group is therefore 3.1 kcal/mole higher in energy than its counterpart.

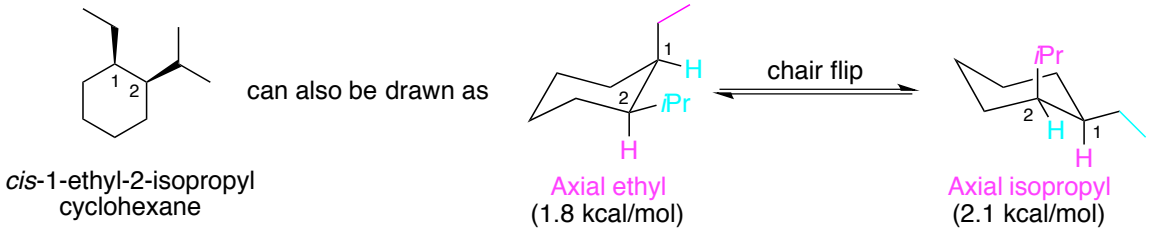


Axial *tert*-butyl
(4.9 kcal/mol)

Axial methyl
(1.8 kcal/mol)

22. We begin by converting the skeletal structure into a chair conformation. One chair conformer has the ethyl group in the axial position. After undergoing a

conformational change to produce the second chair conformation, it is the isopropyl group (*i*Pr) that is axial.



Placement of the ethyl group axial destabilizes the conformation by 1.8 kcal/mole, while the axial placement of the isopropyl group costs 2.1 kcal/mole. The chair flip therefore requires 0.3 kcal/mole.

$\Delta G^\circ = -RT \ln K_{eq}$

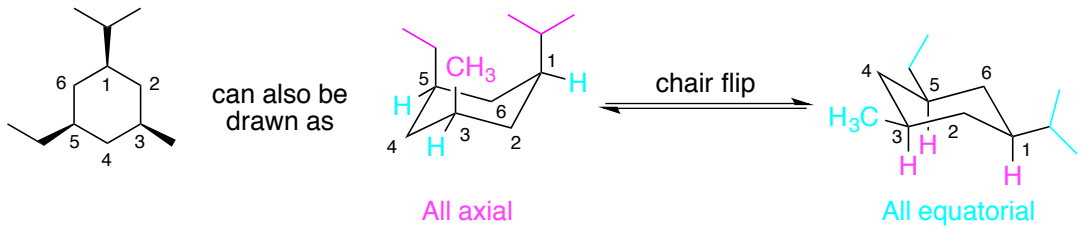
$0.3 \text{ kcal/mol} = -(1.987 \times 10^{-3} \text{ kcal/K mol})(298 \text{ K}) \ln K_{eq}$

$K_{eq} \approx 0.6$

The reactants are favored at equilibrium. For every 10 molecules in the conformation with an axial ethyl group, there are only 6 in the conformation with the larger isopropyl group axial.

$$K_{eq} = \frac{[products]}{[reactants]} \approx 0.6 \approx \frac{6}{10}$$

23. When drawn in a chair conformation, the substituents of this 1,3,5-trisubstituted cyclohexane can all be axial, or they can all be equatorial.



The all-equatorial conformer is naturally favored at equilibrium.

The cost of having all three groups axial is the sum of their A values: 1.8 kcal/mole (methyl) + 1.8 kcal/mole (ethyl) + 2.1 kcal/mole (isopropyl) = 5.7 kcal/mole. As the conformation changes from all axial to all equatorial, this amount of energy is released, so the ΔG° value of -5.7 kcal/mole allows us to calculate the K_{eq}. We'll assume room temperature.

$\Delta G^\circ = -RT \ln K_{eq}$

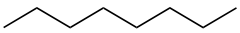
$-5.7 \text{ kcal/mol} = -(1.987 \times 10^{-3} \text{ kcal/K mol})(298 \text{ K}) \ln K_{eq}$

$K_{eq} \approx 15{,}000$

This means that for every 15,000 molecules in the all-equatorial conformer there is only one in the all-axial conformer.

$$K_{eq} = \frac{[products]}{[reactants]} \approx 15{,}000 \approx \frac{15{,}000}{1}$$

24. Octane has the molecular formula C_8H_{18}, which is emblematic of a saturated eight-carbon alkane.

 $= C_8H_{18}$

The combustion of octane necessitates oxygen and produces carbon dioxide and water, as shown in the following *unbalanced* equation.

$$C_8H_{18} + O_2 \longrightarrow CO_2 + H_2O$$

A stoichiometric coefficient of 8 is required for carbon dioxide to balance the eight carbons in the reactant. Similarly, a stoichiometric coefficient of 9 is needed for water to balance the 18 hydrogens in the reactant. Finally, the 25 oxygen atoms on the products side must be balanced with a coefficient of 12.5 for O_2.

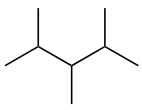
$$C_8H_{18} + 12.5\ O_2 \longrightarrow 8\ CO_2 + 9\ H_2O$$

Since it is customary to use whole-number coefficients, we can multiply all of the stoichiometric coefficients by two to obtain the balanced equation.

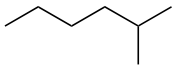
$$2\ C_8H_{18} + 25\ O_2 \longrightarrow 16\ CO_2 + 18\ H_2O$$

25.

(a) In this pairing, the first molecule has eight carbons, while the second has only seven. These molecules simply have different molecular formulas and are therefore unrelated to one another.

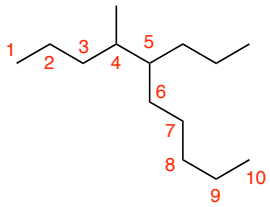


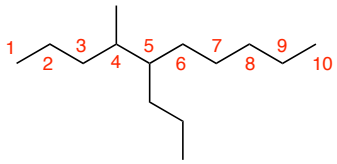
C_8H_{18}



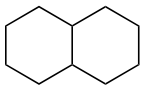
C_7H_{16}

(b) Both of these structures contain ten-carbon chains with a methyl group at C4 and a propyl group at C5. They are therefore identical.

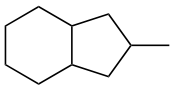




(c) Both of these compounds have ten carbons and eighteen hydrogens. They clearly differ in connectivity though. The first compound has two six-membered rings, while the second has a six- and a five-membered ring. Due to the difference in connectivity, they are constitutional isomers.

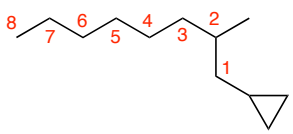


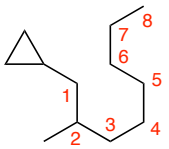
$C_{10}H_{18}$



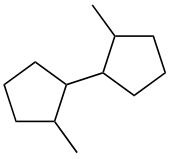
$C_{10}H_{18}$

(d) Both of these structures contain an eight-carbon chain bearing a cyclopropyl group at C1 and a methyl group at C2. They are therefore identical.

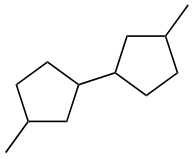




(e) These molecules have the same formula. However, they differ in connectivity. In the first compound, the carbons bearing the methyl groups are adjacent to the bond that joins the rings, but in the second compound, they are not. These molecules are constitutional isomers as a result.

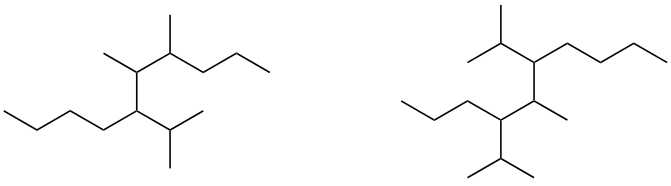


$C_{12}H_{22}$



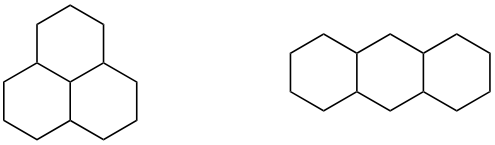
$C_{12}H_{22}$

(f) These molecules differ in formula, so they are unrelated to one another.



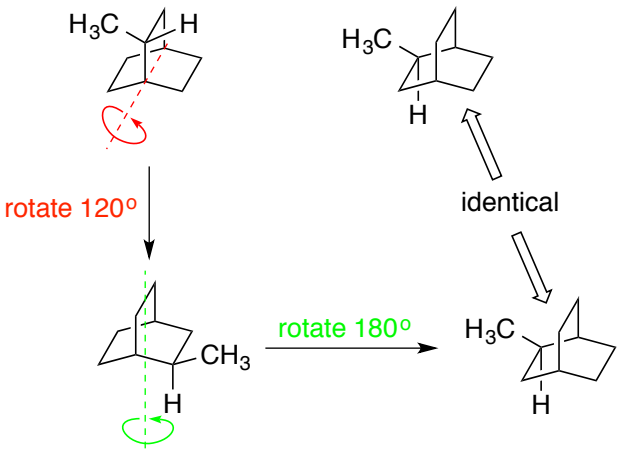
$C_{15}H_{32}$ $C_{17}H_{36}$

(g) At first glance, these compounds may appear to be isomers because they each contain three six-membered rings, which are simply fused differently. However, upon closer inspection, these molecules actually do differ in formula, so they are unrelated.



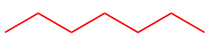
$C_{13}H_{22}$ $C_{14}H_{24}$

(h) These structures have the same formula, so the question becomes: are they identical or are they isomers? We can attempt to align the molecules to answer this question. If the first structure is rotated 120° about an axis through the two bridgehead carbons and then rotated 180° about an axis cutting through the molecule vertically, the two compounds can be aligned. They are therefore identical.

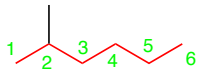


26. When drawing isomers, it is crucial to be systematic in order to avoid confusion. First, we can ascertain that the formula corresponds to a saturated hydrocarbon since it is of the type C_nH_{2n+2}. We therefore know that the isomers must include linear and branched alkanes. Cycloalkanes would have fewer hydrogens.

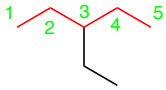
Begin with the linear alkane, which is heptane.



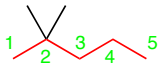
Then, we can shorten the longest, continuous carbon chain by one, making the parent hexane. The remaining carbon can be placed on C2 or C3 to give 2-methylhexane and 3-methylhexane, respectively. Note that placing the methyl group at C4 does not generate a new compound; it would merely be 3-methylhexane again because we would need to number from the opposite terminus so as to give the substituent the lowest possible number.

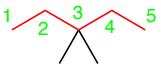


Now that we have exhausted the isomers containing a hexane parent, we can consider those having a pentane parent. If the two residual carbons form a single substituent, it must be placed at C3; otherwise, pentane would no longer be the parent. This gives 3-ethylpentane.

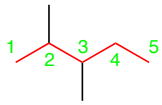


However, the two additional carbons could also be separate substituents. If they reside at the same location, we would have 2,2-dimethylpentane and 3,3-dimethylpentane.

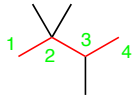




Alternatively, the methyl groups could be placed on different carbons, giving 2,3-dimethylpentane and 2,4-dimethylpentane.



Finally, if we shorten the parent to butane, the three residual carbons must all be methyl groups; otherwise, the parent would no longer be butane. This gives one final isomer: 2,2,3-trimethylbutane.

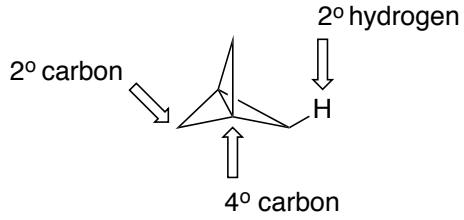


It is not possible to create a smaller parent chain with this formula.

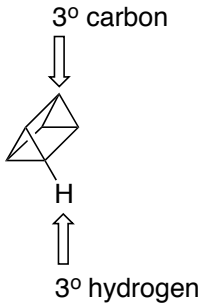
27. Recall that primary (1°) carbons are bonded to one other carbon. Secondary (2°) carbons are bonded to two other carbons. Tertiary (3°) carbons are bonded to three

other carbons, and quaternary (4°) carbons have all four bonds to other carbon atoms. Hydrogens are classified by the type of carbon to which they are bonded.

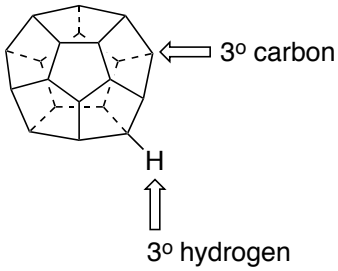
(a)



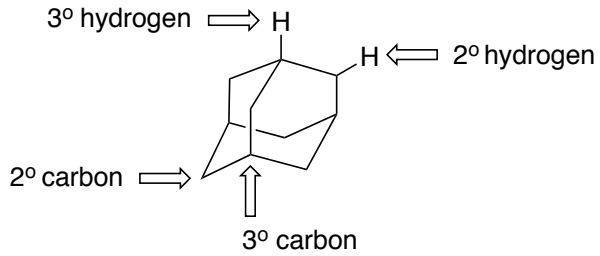
(b)



(c)

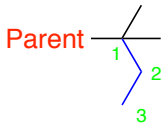


(d)

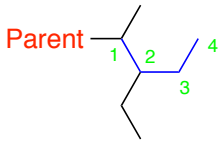


28.

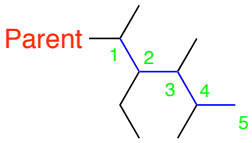
(a) The longest chain within the substituent is propyl. It is numbered so that C1 is bonded to the parent. There are two methyl groups on C1, so the full name of the substituent is (1,1-dimethylpropyl).



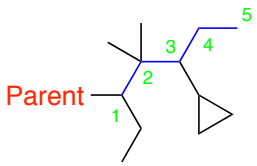
(b) The longest chain emanating from the parent is butyl. Again, it is numbered so that C1 is bonded to the parent. There is a methyl group at C1 and an ethyl group at C2. The full name of this substituent is therefore (2-ethyl-1-methylbutyl).



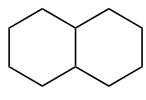
(c) This substituent contains a pentyl group bearing methyls at C1, C3, and C4. There is also an ethyl at C2. The substituent's name is (2-ethyl-1,3,4-trimethylpentyl).



(d) The parent within this substituent is pentyl. It bears an ethyl group at C1, two methyl groups at C2, and a cyclopropyl group at C3. Its name is therefore (3-cyclopropyl-1-ethyl-2,2-dimethylpentyl). Recall that the "cyclo" prefix counts in alphabetization, but the "di" prefix does not.

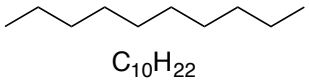


29. We can solve this problem by considering an example of a bicyclic alkane. The following molecule (bicyclo[4.4.0]decane) is just such a species. It has the formula $C_{10}H_{18}$.



$C_{10}H_{18}$

Let's compare that to an acyclic alkane having a comparable number of carbon atoms, such as decane.



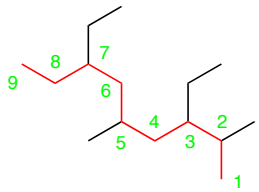
$C_{10}H_{22}$

Decane has the formula that we expect for a saturated alkane: C_nH_{2n+2}. A cycloalkane with a single ring has a formula of the type C_nH_{2n}. However, the bicycle shown above has even fewer hydrogens because it contains a second ring. Its formula takes the form C_nH_{2n-2}.

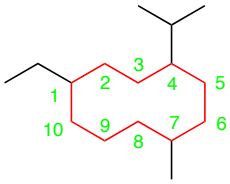
Remember that a ring is a degree of unsaturation. Notice that each degree of unsaturation results in the reduction of the molecule's hydrogen count by 2. This will become especially important in Chapter 5 when we start to deduce structures from experimental evidence.

30.

(a) The longest, continuous carbon chain in this molecule is nonane. It bears two ethyl groups at C3 and C7, as well as two methyl groups at C2 and C5. The complete name of the molecule is 3,7-diethyl-2,5-dimethylnonane.

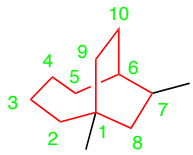


(b) The ring contains more carbons than any single substituent, so it is the parent. The cyclodecane ring can be numbered in two ways that will give the substituents the same set of locants: 1, 4, and 7. To break the tie, the substituent that appears first in alphabetical order (ethyl) is given the lower number. The full name is therefore 1-ethyl-4-isopropyl-7-methylcyclodecane.

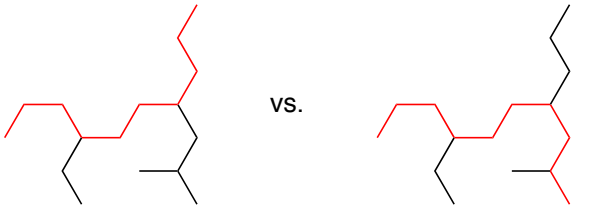


(c) This bicyclodecane bears two methyl groups. To obtain their locants, we number starting at a bridgehead carbon. The numbering proceeds along the longest bridge first. Then, the remaining two bridges are of equal length, so we number along the one that contains a substituent, thereby giving it the lowest number possible. This

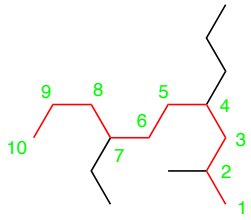
results in the name 1,7-dimethylbicyclo[4.2.2]decane. Remember that the numbers in brackets indicate the length of the bridges in descending order.



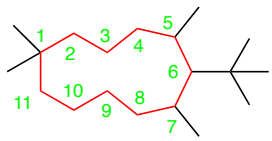
(d) This branched alkane has two possible decane parents. The correct one possesses the greater number of substituents.



When numbered so as to give the first substituent the lowest possible number, the name 7-ethyl-2-methyl-4-propyldecane is obtained.

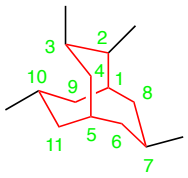


(e) This substituted cycloundecane is numbered so as to give the second substituent the lowest possible number (recall that the first substituent on a cycloalkane will always have the number 1). This results in the name 6-*tert*-butyl-1,1,5,7-tetramethylcycloundecane. Note that neither "*tert*" nor "tetra" is counted when determining alphabetical order.



(f) This bicycloundecane has three three-carbon bridges, making it a substituted bicyclo[3.3.3]undecane. The parent is numbered beginning with a bridgehead carbon as C1. To give the lowest possible number to the first substituent, we start at the bridgehead carbon in the back. Since all three bridges are of the same length, we can number along any of them first, so we choose the one that will result in the

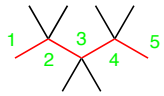
lowest locant for the first substituent. That is the top bridge. Then, the order in which the remaining two bridges are numbered is irrelevant because the same substituent numbers result either way. The complete name of this molecule is 2,3,7,10-tetramethylbicyclo[3.3.3]undecane.



31.

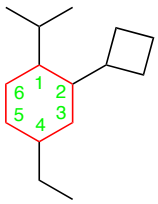
(a) It is easiest to begin by drawing the parent and numbering it.

Then, the substituents can be easily placed according to their locants.



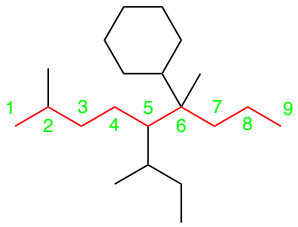
(b) Again, start by drawing the parent and numbering it. With cycloalkanes, any carbon can be chosen as C1.

Then, the substituents are placed according to their numbers.



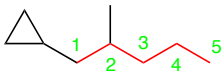
(c) The nonane parent can be drawn first and numbered from either terminus.

Then, the substituents can be placed to complete the structure.



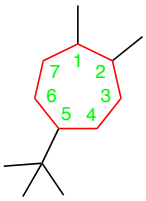
(d) The pentane parent can be first drawn and numbered.

Then, the cycloalkyl and alkyl substituents are placed at the proper locations.



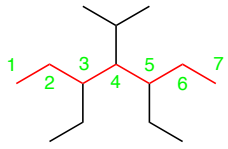
(e) The cycloheptane parent is drawn first. It can be numbered starting with any carbon as C1.

The substituents are then placed on the ring.



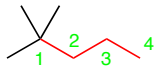
(f) The heptane parent is drawn first. It can be numbered from either terminus.

Then, the two ethyl groups and the isopropyl group are added at the appropriate sites.



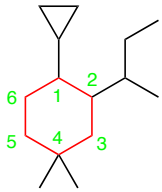
32.

(a) The name suggests a butane parent bearing three methyl groups at C1.

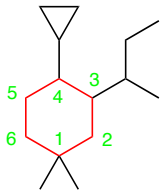


However, adding methyl groups to C1 lengthens the parent chain, which should be pentane instead. The correct name is therefore 2,2-dimethylpentane.

(b) The name suggests a cyclohexane ring bearing cyclopropyl, *sec*-butyl, and two methyl substituents.



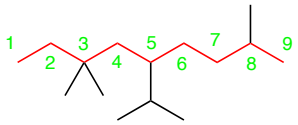
One error is in numbering. With substituted cycloalkanes, the first substituent always receives the locant 1. When multiple substituents are present, the ring is numbered to give the second substituent the lowest possible number. This can be achieved by giving the second methyl group the number 1.



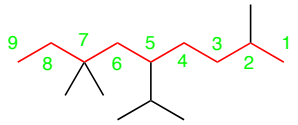
A second error is in alphabetization. The only prefixes that count for alphabetization are cyclo, iso, and neo. So, while the "cyclo" prefix should be used in determining alphabetical order, the "di" and "*sec*" prefixes should not. The proper name will therefore be alphabetized by the "b" of *sec*-butyl, the "c" of cyclopropyl, and the "m" of dimethyl.

Combining the correct numbering and alphabetization, the name becomes 3-*sec*-butyl-4-cyclopropyl-1,1-dimethylcyclohexane.

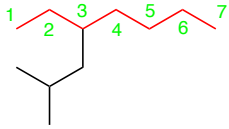
(c) This name suggests a nine-membered linear alkane as the parent. It has three methyl groups, two at C3 and one at C8. It also bears an isopropyl at C5.



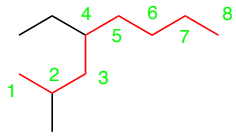
Had the numbering begun at the other terminus, the parent could have been numbered so as to give a lower number to the first substituent. Also, "isopropyl" appears before "trimethyl" in alphabetical order. The proper name is therefore 5-isopropyl-2,7,7-trimethylnonane.



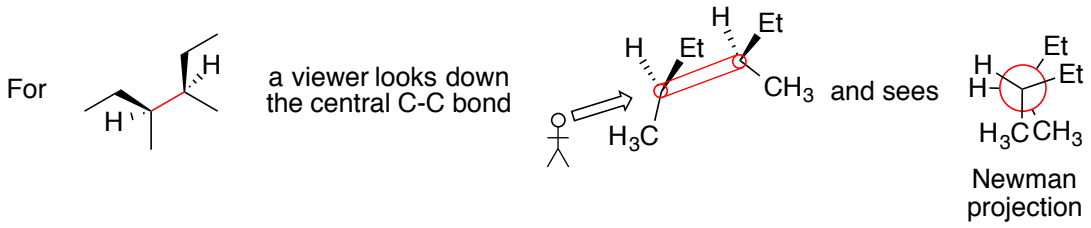
(d) This name tells us that the parent is seven-carbons in length and that it has an isobutyl group on C3.



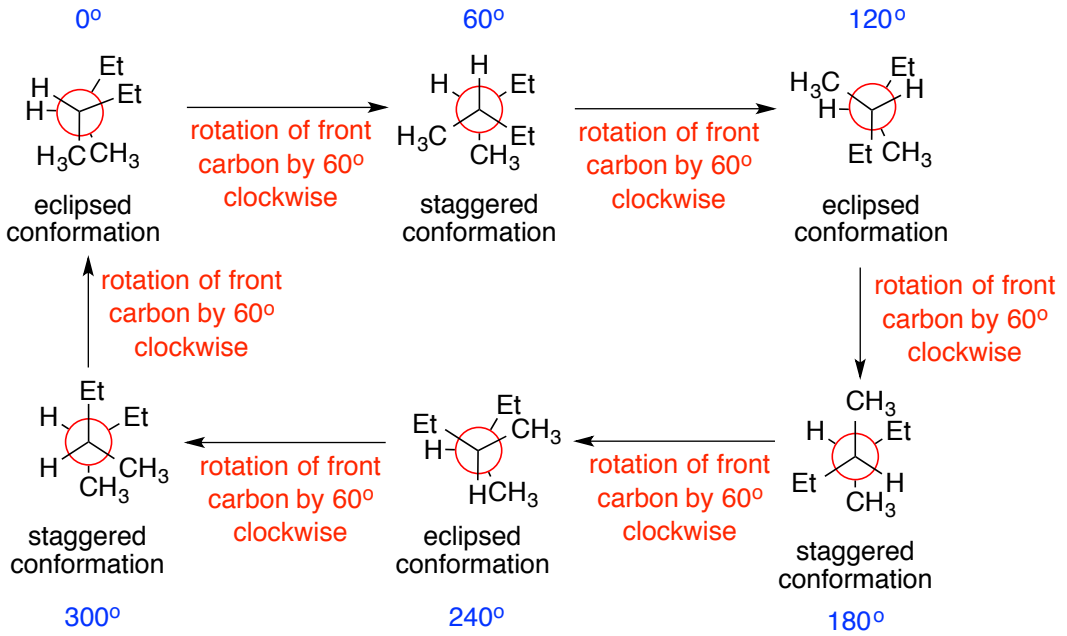
However, a longer parent chain exists within this molecule. It is actually a substituted octane. The correct name is 4-ethyl-2-methyloctane.



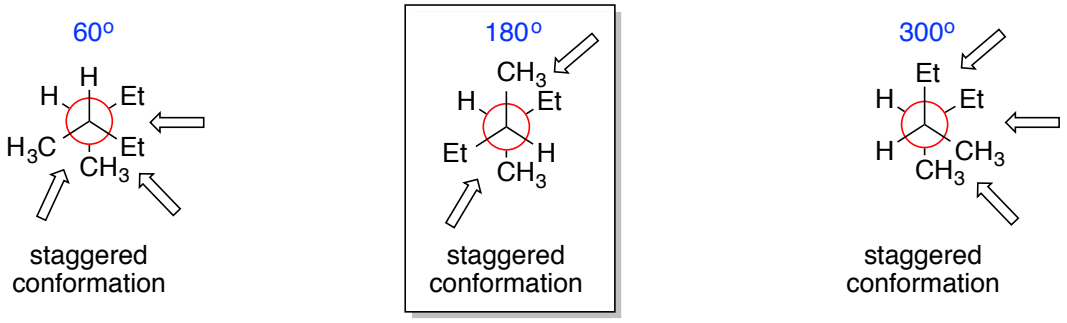
33. To approach the problem systematically, we can first rotate a full 360° in 60° increments about the C3-C4 bond. We can start with any conformation. In the diagram below, the molecule is represented in a conformation where the ethyls and the methyls eclipse each other.



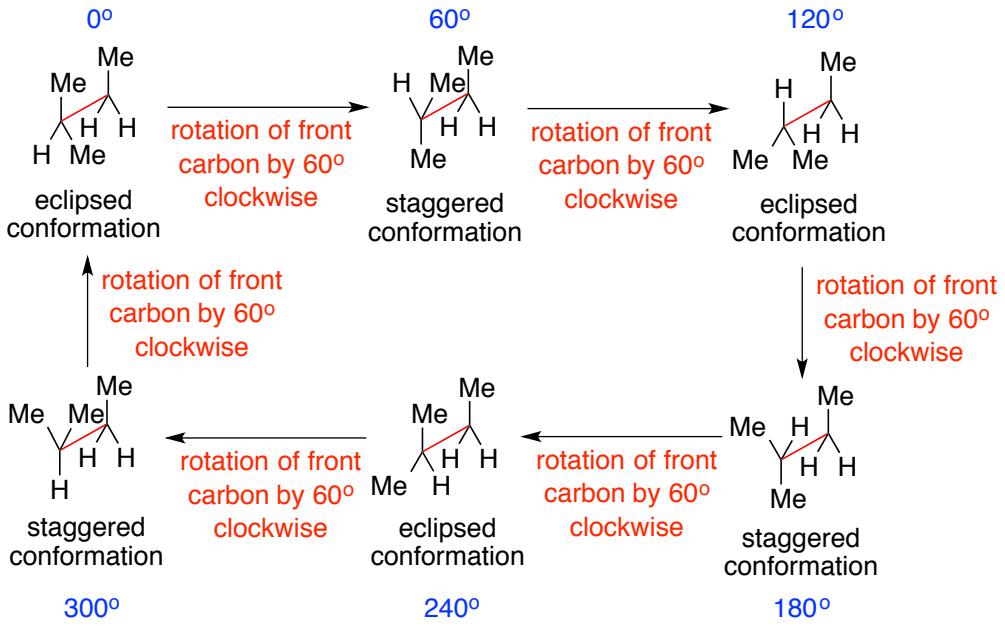
Incremental 60° rotations yield the expected array of staggered and eclipsed conformers.



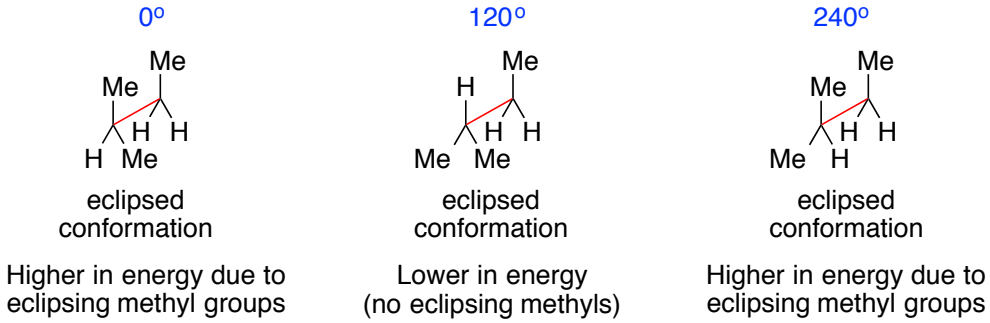
We know that the lowest energy conformation will be one of the staggered conformers. Among those three, the 180° conformer has the smallest number of gauche interactions (as indicated by arrows in the diagram below). It is therefore the most stable conformation.



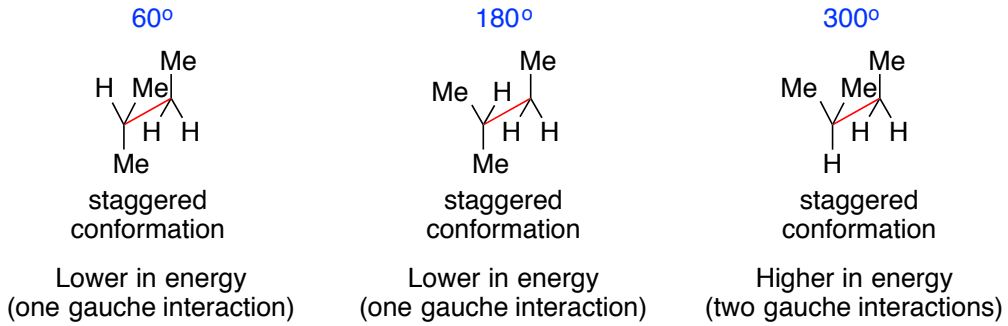
34. Starting with a conformation that has eclipsing methyls, rotation through 60° increments gives the expected alternating pattern of staggered and eclipsed conformers.



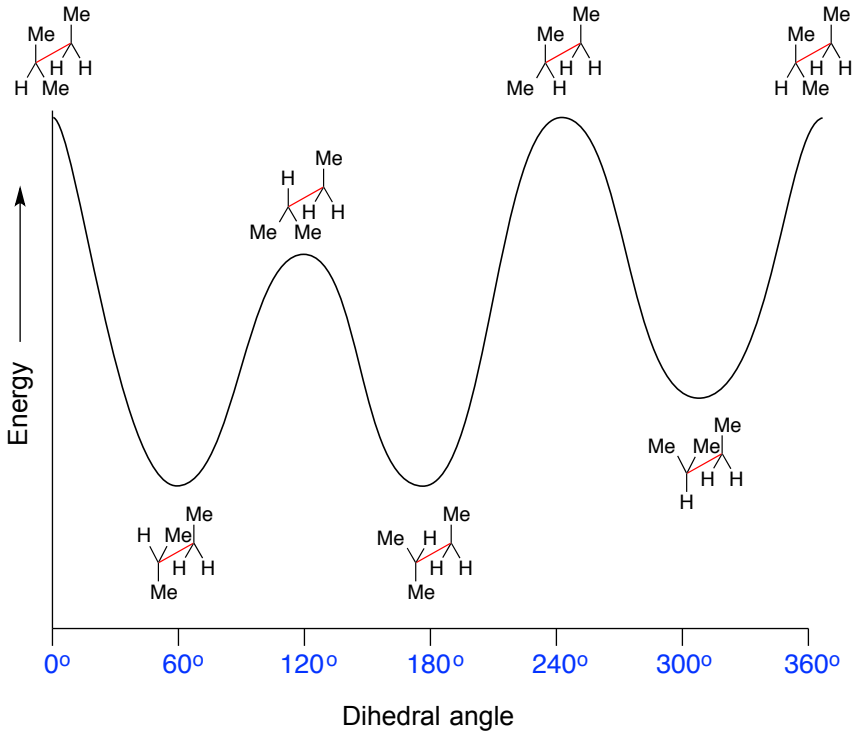
However, when we compare their relative energies, it becomes clear that two eclipsed conformations are higher in energy than the other. The 0°/360° and 240° conformations both have eclipsing methyl groups, which raises their energy relative to the 120° conformation because of steric strain.



All of the staggered conformations exhibit gauche interactions, but the 300° conformer has two gauche interactions, which makes it higher in energy than the other two.



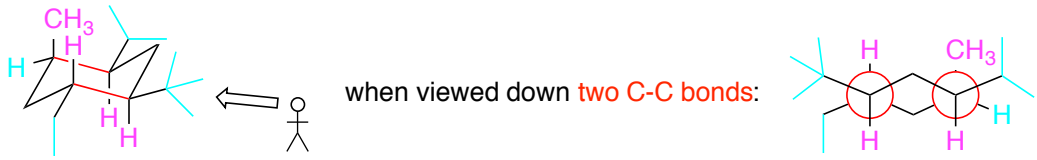
All of this information can be summarized in an energy profile. Note that the staggered conformations are all lower in energy than the eclipsed conformers. However, among the eclipsed conformations, the 120˚ conformer is lower in energy. Also, among the staggered conformations, the 300˚ conformer is higher in energy.



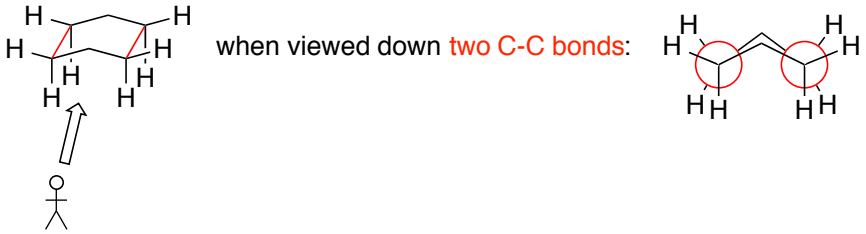
35. This tetrasubstituted cyclohexane ring can be drawn in a chair conformation that places three of the four substituents in equatorial positions. Importantly, the large *tert*-butyl and isopropyl groups, which have bigger A values, are equatorial in this favored conformation. Note that the numbering used is merely for following the atoms and does not correspond to IUPAC numbering.

A viewer can look down the red C-C bonds from the left or right side. The view from the left-hand side is shown in this diagram.

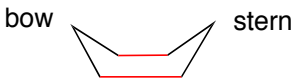
The view from the right-hand side is shown in this diagram.



36. When this conformation of cyclohexane is viewed down two parallel C-C bonds, it becomes apparent that all of its hydrogens are eclipsing. This conformation is therefore higher in energy than the chair conformation due to torsional strain.

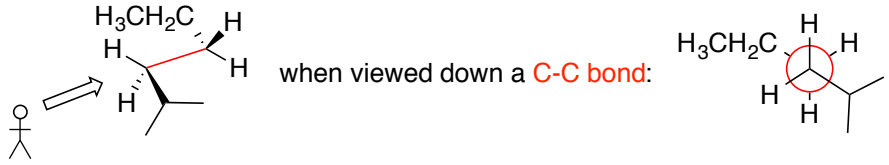


This conformer is known as the boat conformation because it is somewhat reminiscent of the shape of a boat.

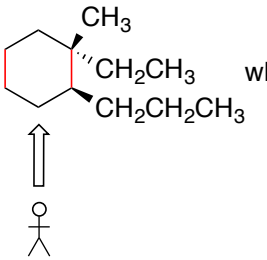


37.

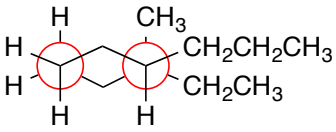
(a) From the viewer's perspective in front of the Newman projection, there is an isopropyl group on the right-hand side of the front carbon angled downward. There is also an ethyl group on the left-hand side of the back carbon angled upward.



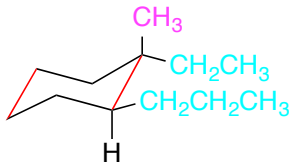
(b) From the viewer's perspective in front of the Newman projection, the right-hand bond holds all three substituents. The propyl group is on the front carbon angled upward. On the back carbon, the methyl group points upward, while the ethyl group points downward.



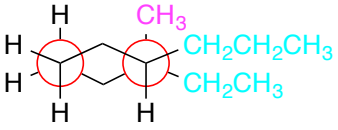
when viewed down two C-C bonds:



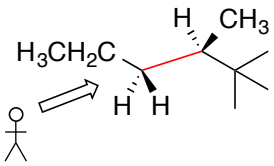
The Newman projection also shows the methyl group to be axial, while the propyl and ethyl groups are equatorial.



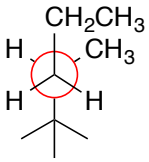
when viewed down two C-C bonds:



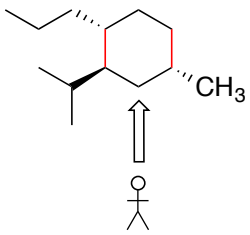
(c) The viewer is in front of the Newman projection and sees an ethyl group on the front carbon pointing straight up. On the back carbon, the viewer sees two substituents: a *tert*-butyl group pointing straight down and a methyl group on the right-hand side angled upward.



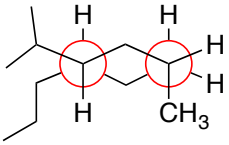
when viewed down a C-C bond:



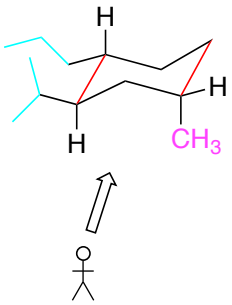
(d) The viewer sees an isopropyl group on the front carbon of the left-hand bond directed upward. On the back carbon of that same bond, there is a propyl group pointing downward. On the front carbon of the right-hand bond, there is a methyl group directed downward.



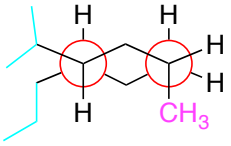
when viewed down two C-C bonds:



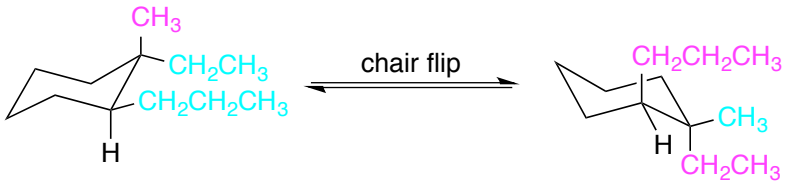
The Newman projection also reveals that the isopropyl and propyl groups are equatorial, while the methyl is axial.



when viewed down two C-C bonds:



38. For the cyclohexane derivative shown in Problem 37(b), one chair conformation has only a methyl group axial. This raises the energy of the conformer by 1.8 kcal/mole. The other chair conformation has both a propyl and an ethyl group axial. The propyl group was not included in our table of A values, but we can surmise that its A value is approximately 1.8 kcal/mole since it is similar in structure to the ethyl group. Therefore, this conformation is elevated in energy by about 3.6 kcal/mole.



Axial methyl
(1.8 kcal/mol)

Axial propyl and ethyl
(~1.8 kcal/mol + 1.8 kcal/mol = 3.6 kcal)

As the conformational change proceeds, an input of 1.8 kcal/mole is needed. As a result, the K_{eq} is approximately 0.05.

$\Delta G^{\circ} = -RT \ln K_{eq}$

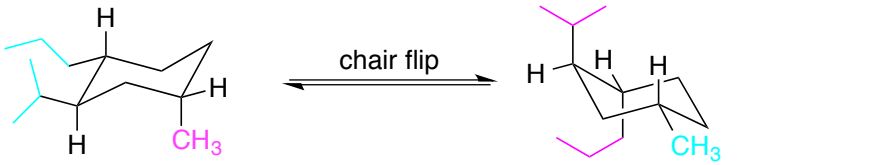
$1.8 \text{ kcal/mol} = -(1.987 \times 10^{-3} \text{ kcal/K mol})(298 \text{ K}) \ln K_{eq}$

$K_{eq} \approx 0.05$

The ratio of products to reactants is therefore about 1 : 20.

$$K_{eq} = \frac{[products]}{[reactants]} \approx 0.05 \approx \frac{1}{20}$$

For the cyclohexane derivative shown in Problem 37(d), the first conformer has only a methyl group axial (A value = 1.8 kcal/mole). The other conformer has both a propyl and an isopropyl group axial. The propyl group's A value is ~1.8 kcal/mole since it is similar in structure to an ethyl group. The isopropyl group's A value is 2.1 kcal/mole. The second conformer therefore has a relative energy of 3.9 kcal/mole.



Axial methyl
(1.8 kcal/mol)

Axial propyl and isopropyl
(~1.8 kcal/mol + 2.1 kcal/mol = 3.9 kcal)

An input of 2.1 kcal/mole is necessary for the conformational change to occur, which makes the K_{eq} about 0.03.

$\Delta G^\circ = -RT \ln K_{eq}$

$2.1 \text{ kcal/mol} = -(1.987 \times 10^{-3} \text{ kcal/K mol})(298 \text{ K}) \ln K_{eq}$

$K_{eq} \approx 0.03$

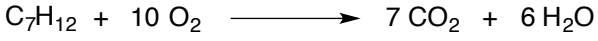
The ratio of products to reactants is therefore approximately 1 : 33.

$$K_{eq} = \frac{[products]}{[reactants]} \approx 0.03 \approx \frac{1}{33}$$

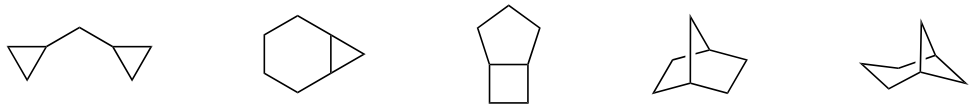
39. We've been given stoichiometric information about a combustion reaction.

The number of moles of carbon dioxide produced allows us to ascertain the number of carbons in the alkane: 7. Similarly, the number of moles of water produced shows the number of hydrogens that the alkane contains: 12.

The balanced equation is therefore:

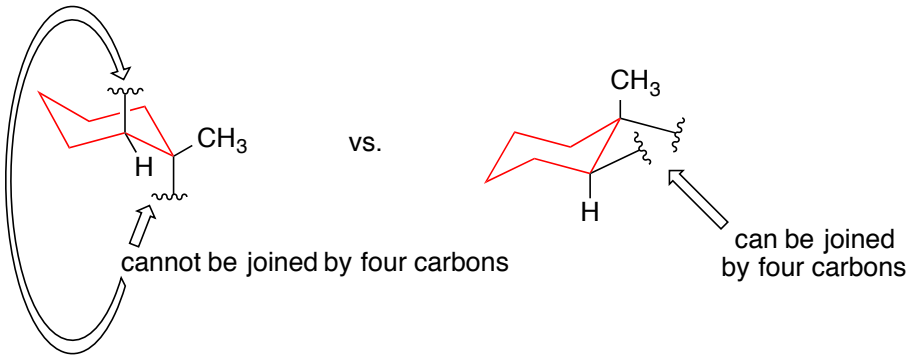


A saturated alkane has a formula of the type C_nH_{2n+2}. That would necessitate 16 hydrogens. This molecule contains four fewer hydrogens, indicating that it contains two degrees of unsaturation. Since it has been specified that the molecule is an alkane (so pi bonds are not an option), it must contain two rings. There are a variety of structures that would meet this criterion. A selection are shown below.

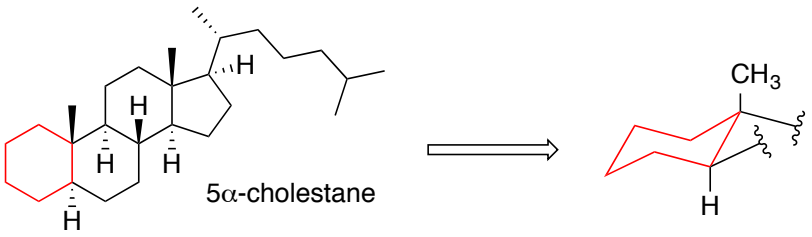


40. We can begin by drawing the left-hand ring in the corresponding chair conformation. At the site of fusion, there is a methyl group directed upward and a

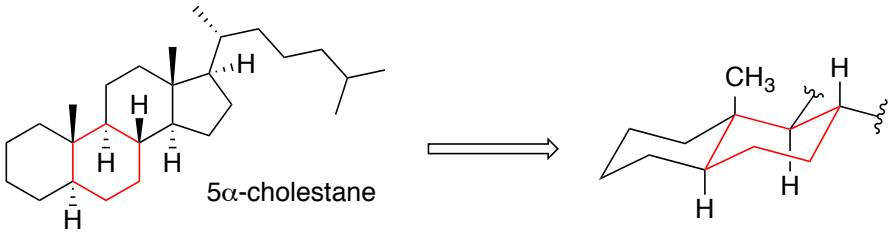
hydrogen pointing down. If the methyl and the hydrogen are equatorial, a six-membered ring cannot successfully be fused. This would entail adding four additional carbons, which is too short of a tether to join the two axial bonds facing opposite directions. On the other hand, if the methyl and hydrogen are axial, the two equatorial bonds can be linked through the insertion of four more carbon atoms.



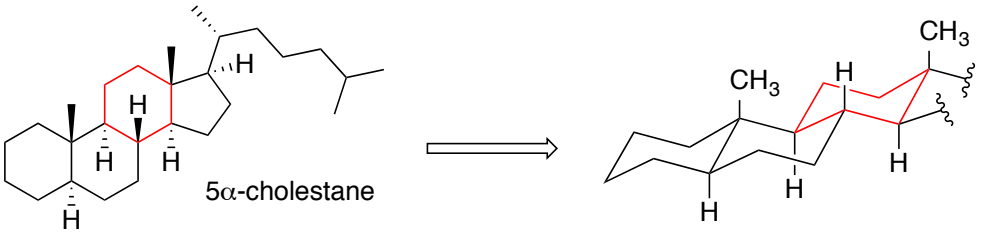
The left-hand ring of 5α-cholestane must therefore be in the latter conformation.



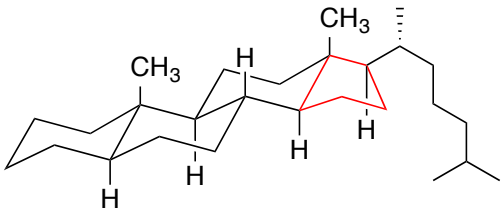
The second six-membered ring can now be added in a chair conformation. The site for the next ring fusion is determined by the connectivity illustrated in the skeletal structure. One hydrogen at this ring-fusion site faces down and the other faces up, but both occupy axial bonds.



The open equatorial valences are used for the third six-membered ring, which can also be drawn in a chair conformation. The site of the final ring fusion has a methyl up and a hydrogen down, and both reside on axial bonds.



Lastly, we can add the five-membered ring and its alkyl group to complete the diagram of 5α-cholestane.



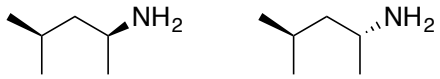
Notice that, as stated in the problem, all three of the six-membered rings exist in chair conformations.

Solutions to Problems for Chapter 4: Stereochemistry

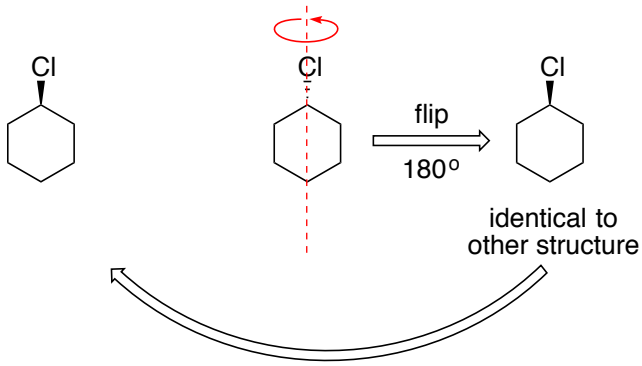
1.

(a) These molecules are constitutional isomers. They both have the formula C_6H_{12}, but there is an obvious difference in connectivity. One molecule contains a five-membered ring, while the other contains a six-membered ring.

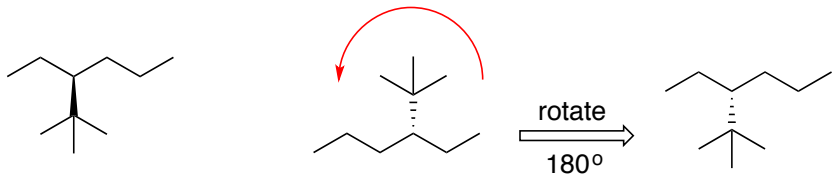
(b) This pairing includes two stereoisomers. These compounds have the same molecular formula and the same connectivity. However, there is a difference in configuration at the center bearing the amino group.



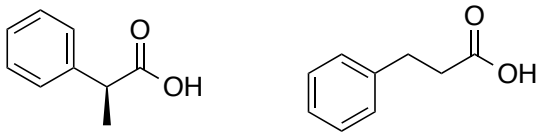
(c) These molecules might appear to be stereoisomers at first glance. However, if we simply flip one of the structures over, we find that it is, in fact, identical to the other.



(d) In this instance, the molecules are stereoisomers. When we attempt to align them, it becomes clear that the configuration differs at the center bearing the *tert*-butyl group.

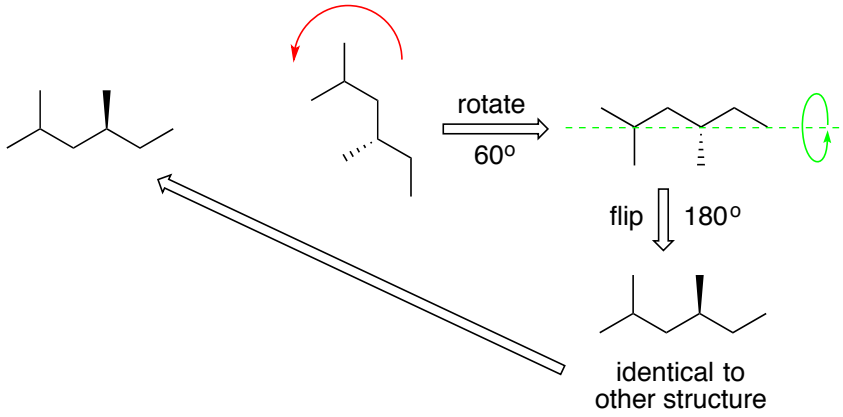


(e) These molecules have the same molecular formula ($C_9H_{10}O_2$), but they exhibit a difference in connectivity, which makes them constitutional isomers.



(f) These are unrelated compounds because they differ in molecular formula. The first structure has six carbons, while the latter has only five carbons.

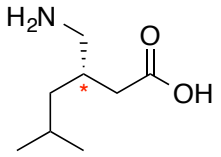
(g) These molecules are identical, but that is not obvious because of how they are drawn. We must attempt to align them in order to determine whether they are the same or different. If the latter structure is rotate 60˚ in the plane of the page and then flipped over, we can see that it is, in fact, identical to the other structure.



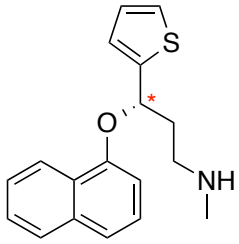
(h) These molecules are stereoisomers. They differ only in the configuration of the center bearing the fluorine.

2. In each of the following answers, the actual chirality of the stereocenters is shown. There is no way that you could have predicted these configurations from the information given in the problem. The actual configuration is shown merely for the sake of interest.

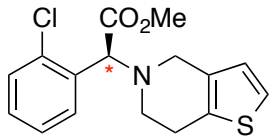
(a) There is one chiral center (*) in Lyrica. It is the only carbon in the molecule bonded to four different groups.



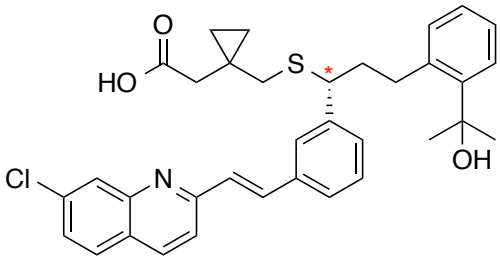
(b) Cymbalta also has a single chirality center (*). It is the carbon in the molecule that is bonded to four different groups.



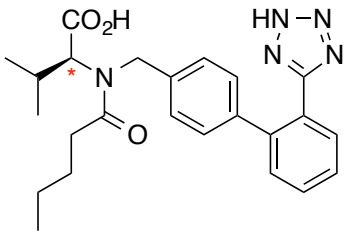
(c) Plavix contains one stereocenter (*) as well. The one carbon in the molecule bonded to four different groups is the chiral center.



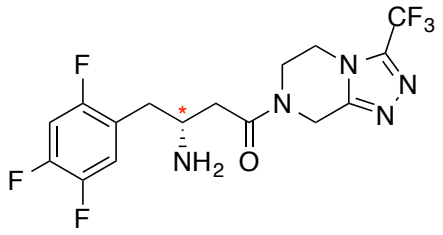
(d) Singulair has its sole stereogenic center (*) at the carbon bonded to four different groups.



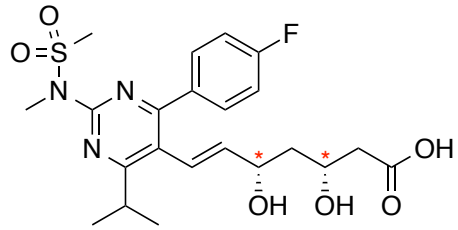
(e) Novartis has one chiral center (*). It is the only carbon in the molecule bonded to four different groups.



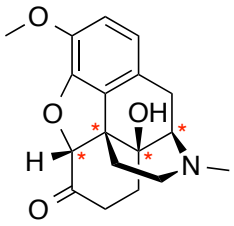
(f) Januvia has one chirality center (*) in its structure too. It is the carbon bearing four unique groups.



(g) Crestor contains two chiral carbons (*). Both of the carbons bearing hydroxyl groups happen to be bonded to four unique groups.

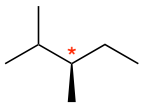


(h) Oxycodone has a total of four stereocenters (*) in its structure. At each of these sites, we find a carbon bonded to four different groups.

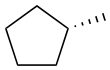


3.

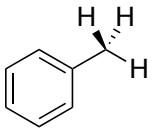
(a) There is a chiral center (*) in 2,3-dimethylpentane, so we do expect the molecule to have an enantiomer.



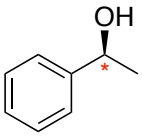
(b) Methylcyclopentane does not contain any chiral centers. The three-dimensionality of the carbon bearing the methyl group has been expressed using a dash; however, this carbon is not bonded to four different groups because the two sides of the ring are identical. As such, we do not expect it to have an enantiomer.



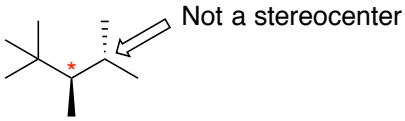
(c) This compound (known as toluene) does not possess any chiral centers. Although the three-dimensionality of the methyl group is illustrated using wedges and dashes, that alone does not make it a chiral center. The carbon of the methyl group does not have four different groups attached to it, nor does any other carbon in the molecule. Since it has no chirality centers, we do not expect toluene to have an enantiomer.



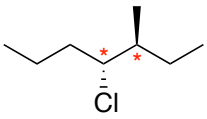
(d) This alcohol does contain a single chiral center (*), so we expect it to have an enantiomer.



(e) This alkane (2,2,3,4-tetramethylpentane) contains a single stereocenter (*). At first glance, it might appear to have two, but the carbon bearing two methyl groups is not a stereocenter because it does not have four different groups. Since the compound does have a single stereocenter, we do expect it to have an enantiomer.

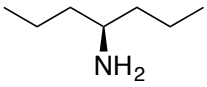


(f) This alkyl chloride contains two chiral centers (*). In Section 6, we'll learn that some molecules containing multiple stereocenters can be achiral if they have internal symmetry. However, there is no internal symmetry in this compound, so we do expect it to have an enantiomer.



(g) At first glance, this molecule may appear to contain a stereocenter. However, remember that the use of wedges and/or dashes in a structural drawing does not necessarily mean that chirality is present. In this case, the carbon bearing the amino group is also bonded to two propyl groups. Therefore, it is not bonded to four

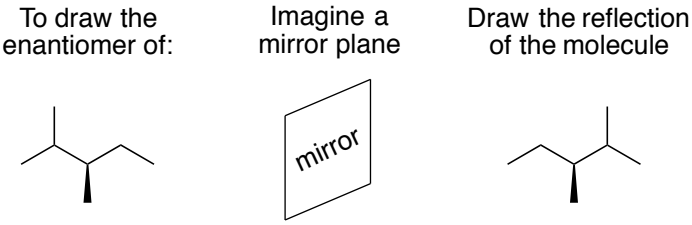
different groups and is not a stereocenter. Consequently, we do not expect this compound to have an enantiomer.



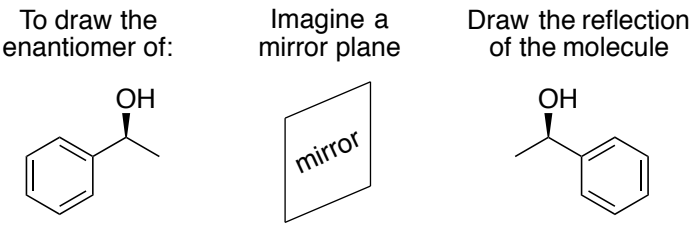
(h) This alkyl bromide contains two chiral centers (*). As mentioned earlier, we will learn in Section 6 that, if internal symmetry is present, a compound with multiple stereocenters may not actually have an enantiomer. Nevertheless, there is no internal symmetry in this instance, so the molecule would be expected to have an enantiomer.

4. In each instance that follows, we imagine a mirror plane and simply draw the reflection of that molecule on the other side of the mirror plane. Groups that are close to the mirror on one side are also close to the mirror on the other side. Groups that are far from the mirror on one side continue to be far from the mirror on the other side. A group coming out of the plane on one side (i.e., a wedge) will still be coming out of the plane on the other side (i.e., it will still be a wedge). Similarly, a group behind the plane (i.e., a dash) will remain behind the plane on the other side (i.e., it will still be a dash).

(a)

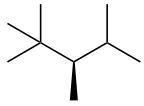


(b)



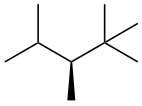
(c)

To draw the enantiomer of:



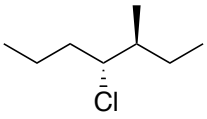
Imagine a mirror plane

Draw the reflection of the molecule



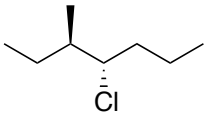
(d)

To draw the enantiomer of:



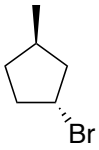
Imagine a mirror plane

Draw the reflection of the molecule



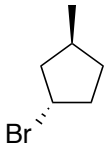
(e)

To draw the enantiomer of:



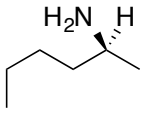
Imagine a mirror plane

Draw the reflection of the molecule



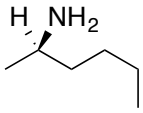
(f)

To draw the enantiomer of:



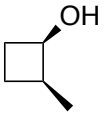
Imagine a mirror plane

Draw the reflection of the molecule



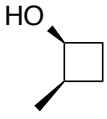
(g)

To draw the enantiomer of:

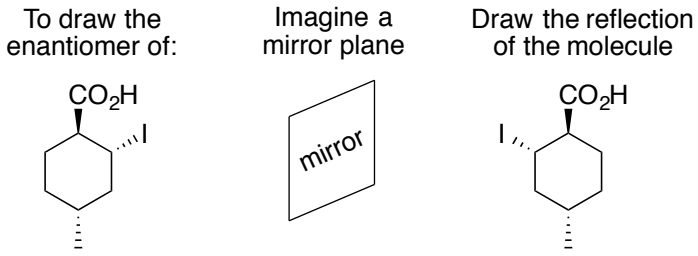


Imagine a mirror plane

Draw the reflection of the molecule

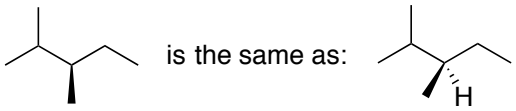


(h)

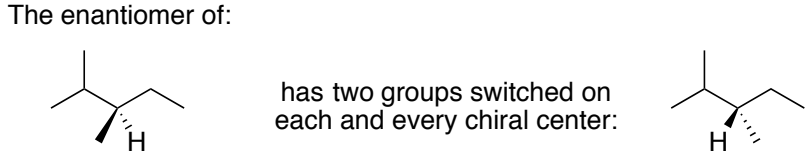


5. In each of the following examples, the exchange of two groups on each and every chiral center generates the enantiomer.

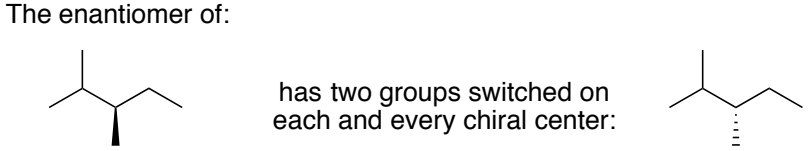
(a) Often when a hydrogen resides on a chiral carbon, its presence will simply be implied. In this example, the chiral center has one implied hydrogen. Since each sp^3 hybridized carbon has two in-plane bonds, a wedge, and a dash and the dash is the only bond missing, the hydrogen must reside on the dash.



We can use this representation with the hydrogen's presence and location specified. Swapping any two groups, such as the methyl group and the hydrogen, generates the enantiomer.

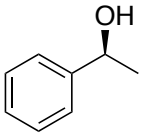


Once you become accustomed to this, you will find that it is not necessary to draw the hydrogen. Notice that, in the diagram above, the methyl is moved from a wedge to a dash. We can do that without explicitly drawing the hydrogen.

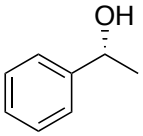


(b) In this problem (and most of those that follow), the enantiomer is drawn without drawing the hydrogen when one is implied on the chirality center. Refer to part (a) of this problem if you need to review how two groups are swapped without taking the time to draw in the implied hydrogen.

The enantiomer of:

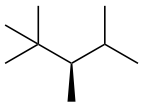


has two groups switched on each and every chiral center:

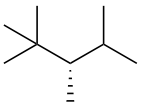


(c)

The enantiomer of:

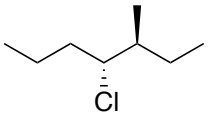


has two groups switched on each and every chiral center:

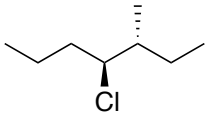


(d) This is the first example that contains two stereocenters. Remember that it is imperative to swap two groups on *all* of the chirality centers in order to produce the enantiomer. Swapping two groups on a subset of the stereogenic centers will result in a different type of stereoisomer that we will learn about in Section 5.

The enantiomer of:

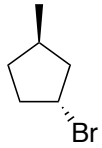


has two groups switched on each and every chiral center:

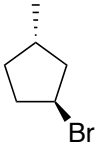


(e) As in part (d) above, be sure to switch two groups on *all* of the chirality centers to generate the enantiomer.

The enantiomer of:

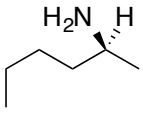


has two groups switched on each and every chiral center:

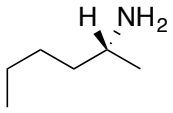


(f) In this instance, the hydrogen on the chiral center happens to be drawn. Note that there are two ways to draw the enantiomer when swapping two groups. One option is to leave the wedge and the dash where they are and switch the groups that reside at the ends of those bonds.

The enantiomer of:

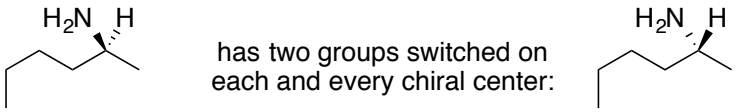


has two groups switched on each and every chiral center:

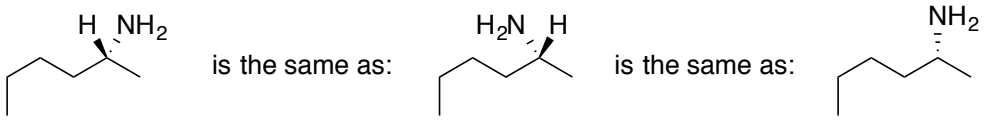


The other option is to leave the groups where they are and simply change the wedge to a dash and vice versa.

The enantiomer of:

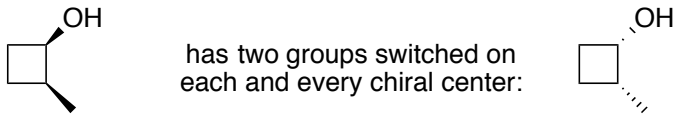


Both methods yield the same enantiomer. It merely looks slightly different.



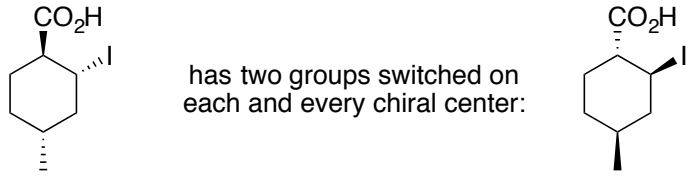
(g) Again, when multiple chirality centers are present, be sure to switch two groups on *all* stereocenters.

The enantiomer of:



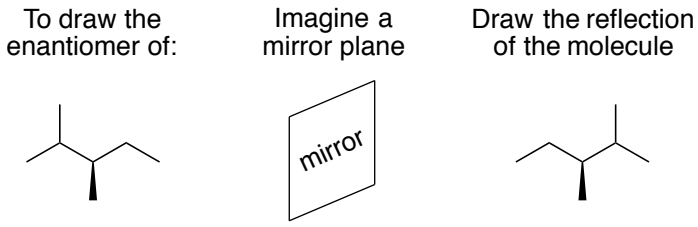
(h) In this example, which contains three chiral centers, we must be mindful of the requirement to interchange two groups on *all* of the stereogenic centers.

The enantiomer of:



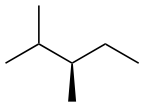
6.

(a) The enantiomer of this chiral molecule can be derived by sketching the mirror image.

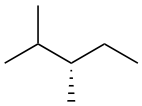


Alternatively, the enantiomer can be drawn be switching two groups on the only chiral center in the molecule.

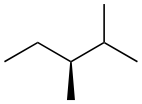
The enantiomer of:



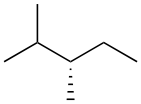
has two groups switched on each and every chiral center:

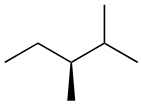


The two drawings differ in orientation but are, in fact, the same molecule.



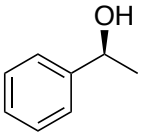
is the same as:





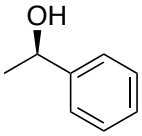
(b) The enantiomer of this chiral compound can be drawn as the mirror image.

To draw the enantiomer of:



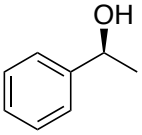
Imagine a mirror plane

Draw the reflection of the molecule

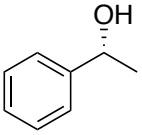


The other method is to switch two groups on the molecule's only chiral center.

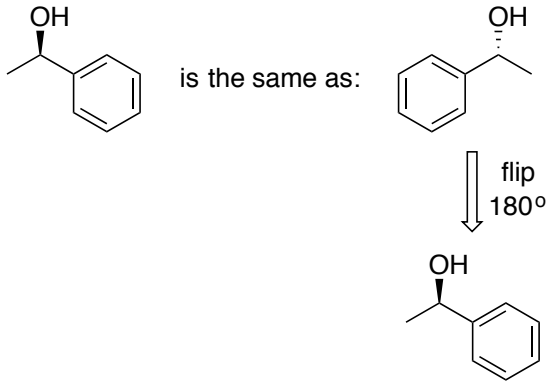
The enantiomer of:



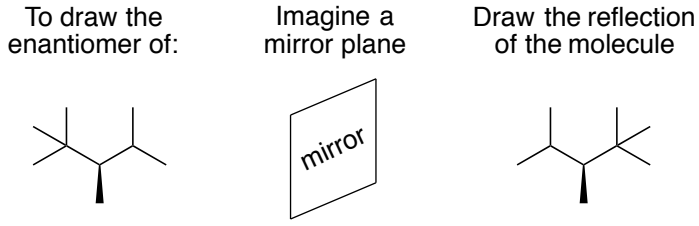
has two groups switched on each and every chiral center:



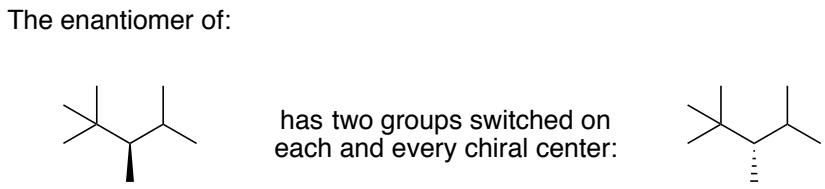
The two methods provide the same answer.



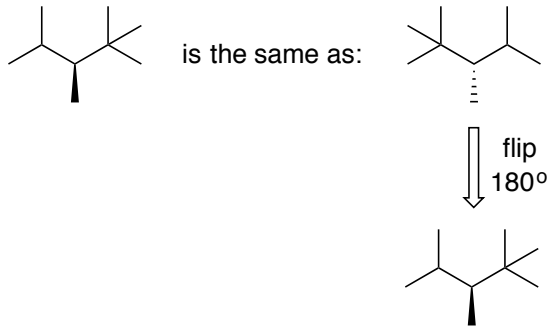
(c) The enantiomer of this molecule can be represented as the mirror image.



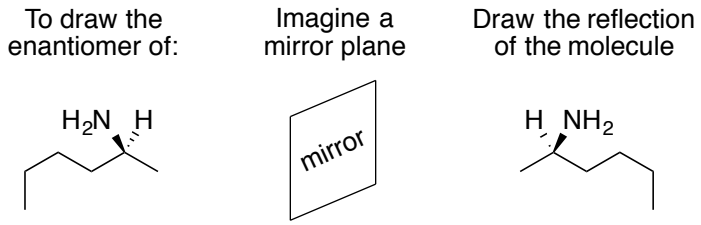
Another option is to switch two groups on the compound's sole chiral center.



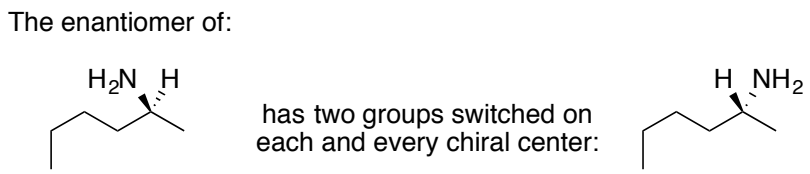
The two methods yield the same answer.



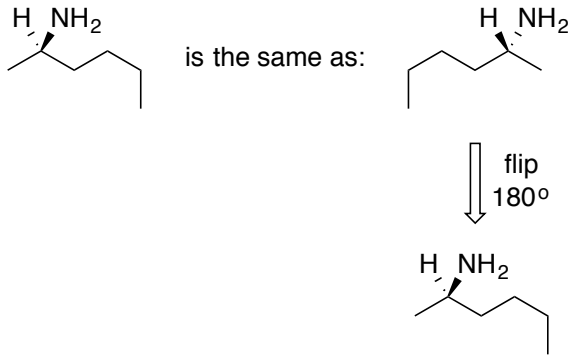
(f) The enantiomer can be drawn by reflection through a mirror plane.



Or, it can be drawn by switching two groups on the chirality center.

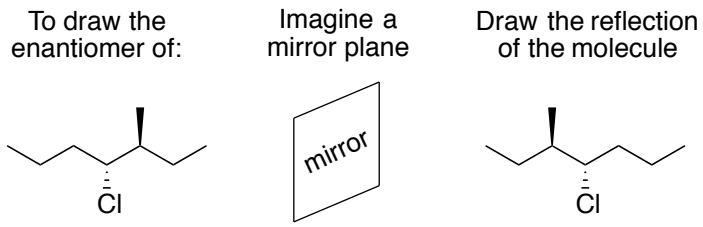


In either case, the answer is the same.

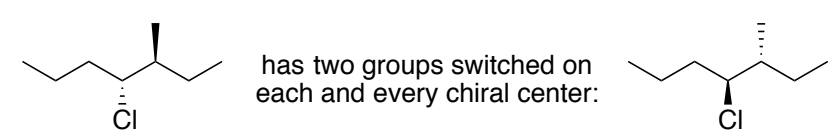


7.

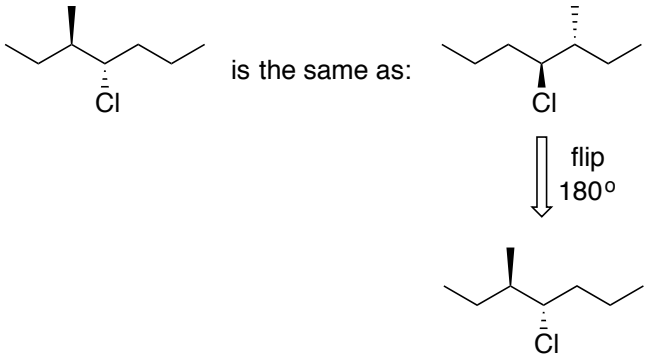
(d) The enantiomer can be drawn as the mirror image.



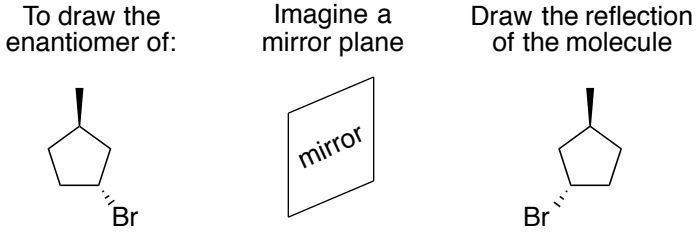
Or, it may be drawn by switching two groups on each of the two chiral centers.



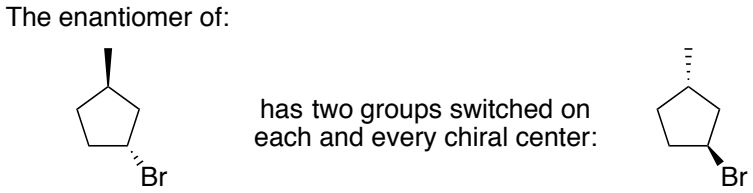
The two methods produce the same answer.



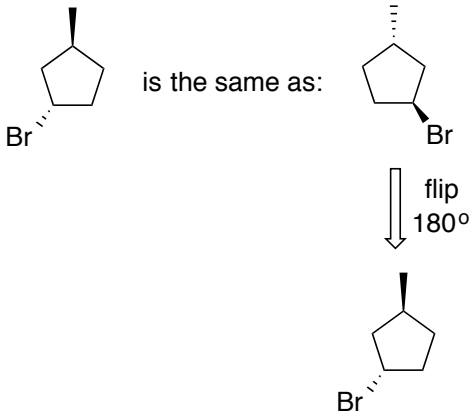
(e) The enantiomer can be drawn as the mirror image.



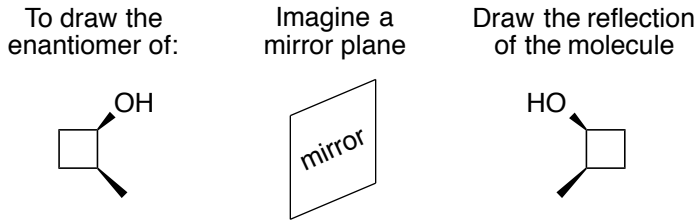
Alternatively, it can be drawn by switching two groups on each of the chiral centers.



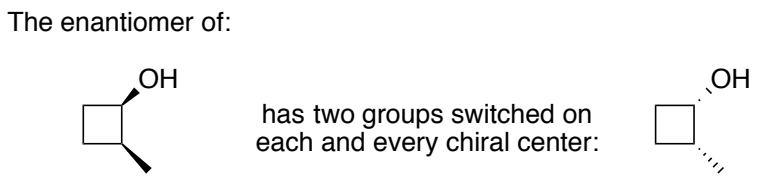
The two approaches yield the same result though.



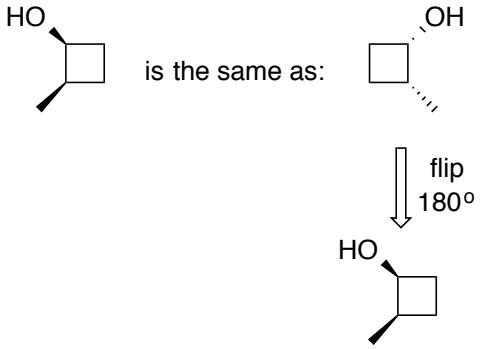
(g) The enantiomer can be drawn as the reflection of the original molecule.



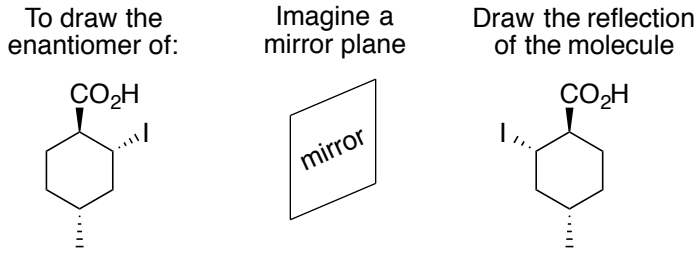
Alternatively, it can be generated by swapping two groups on both of the stereogenic centers.



Either way, the answer is the same.

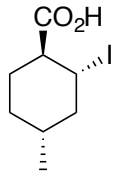


(h) The enantiomer can be represented as the molecule's reflection.

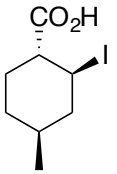


Another choice is to switch two groups on each and every chirality center.

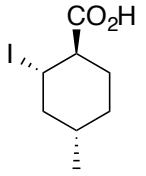
The enantiomer of:



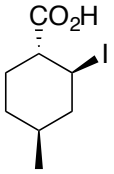
has two groups switched on each and every chiral center:



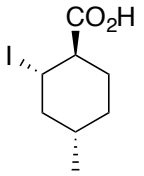
The answer is the same in either case.



is the same as:



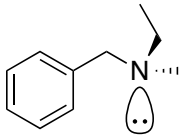
flip 180°



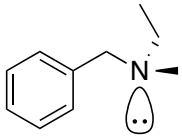
8.

(a) This amine is chiral, so we can draw its enantiomer. However, the two enantiomers readily interconvert through pyramidal inversion due to the presence of a lone pair of electrons on nitrogen.

The enantiomer of:

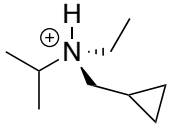


has two groups switched on each and every chiral center:

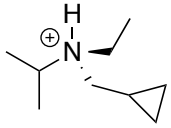


(b) This amine is also chiral and has an enantiomer. These enantiomers do *not* interconvert though. Pyramidal inversion cannot take place since there is no lone pair on the nitrogen atom.

The enantiomer of:

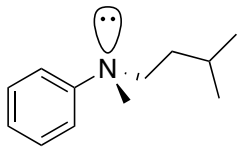


has two groups switched on each and every chiral center:

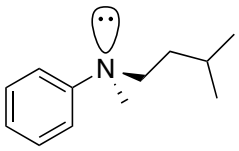


(c) This amine is chiral as well, so it has an enantiomer. These stereoisomers interconvert through pyramidal inversion because there is a lone pair of electrons on nitrogen.

The enantiomer of:

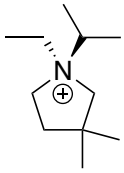


has two groups switched on each and every chiral center:

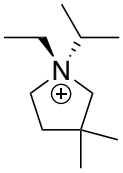


(d) This final amine is chiral too. The nitrogen atom is connected to four different groups because the two sides of the ring differ. Therefore, this amine has an enantiomer, but these enantiomers do *not* interconvert. Pyramidal inversion is not possible because nitrogen does not have a lone pair of electrons.

The enantiomer of:

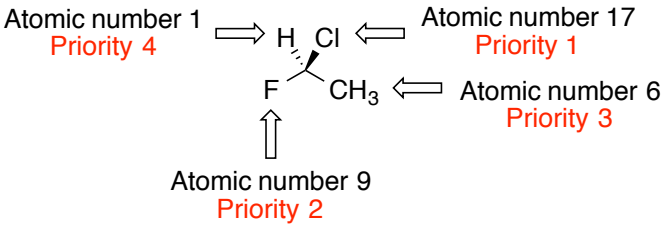


has two groups switched on each and every chiral center:

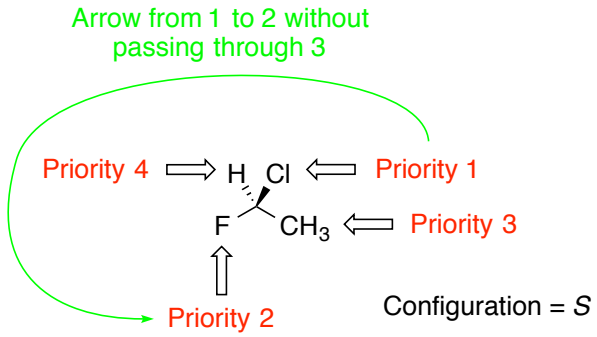


9.

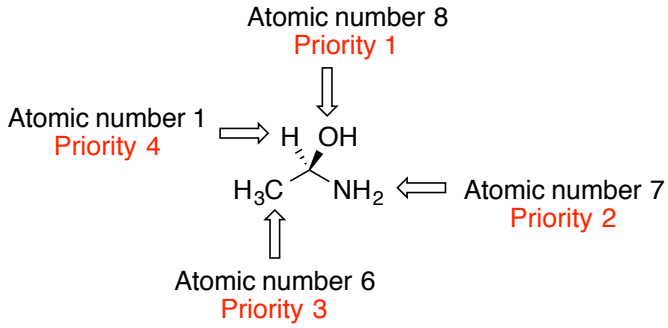
(a) The four atoms directly bonded to the chiral center are Cl, F, C, and H. These are assigned priorities 1, 2, 3, and 4, respectively, on the basis of decreasing atomic number.



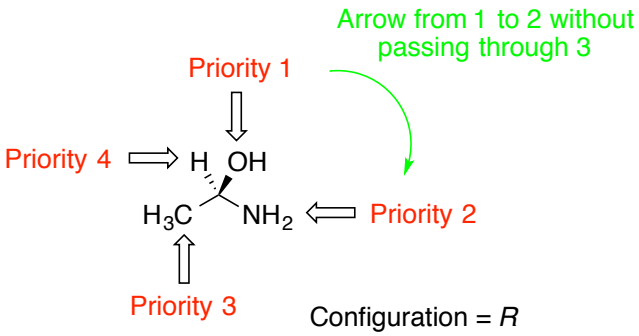
The low-priority group faces backward, and the arrow from priority 1 to 2 without passing through 3 goes in the counterclockwise direction, making the configuration *S*.



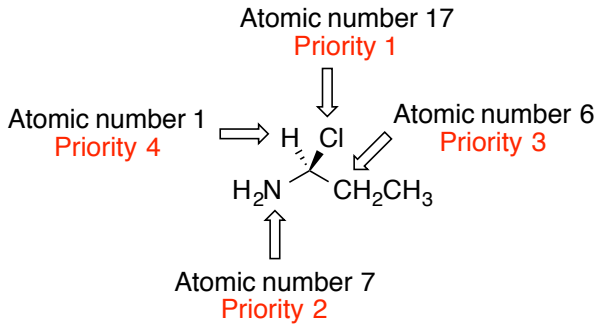
(b) The four atoms bonded directly to the stereogenic center are O, N, C, and H. The priorities are assigned according to decreasing atomic number.



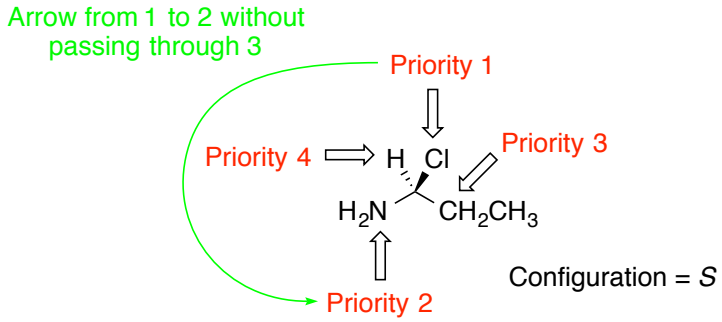
The low-priority group already faces backward. The arrow from priority 1 to 2 without passing through 3 goes clockwise, so the configuration is *R*.



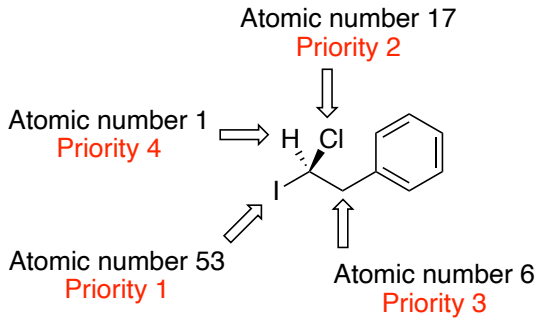
(c) Although the carbon-containing group on the stereocenter has gotten larger, nothing about the analysis changes. The four atoms directly connected to the chirality center are Cl, N, C, and H. The higher the atomic number, the greater the priority is.



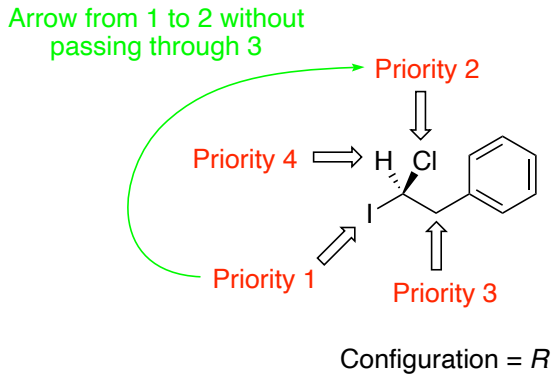
The low-priority group conveniently faces backward, and the arrow from priority 1 to 2 without passing through 3 goes in the counterclockwise direction. The configuration is therefore *S*.



(d) The carbon-containing group on the stereocenter is even larger in this problem, but it makes no difference. The four atoms directly connected to the stereogenic center are I, Cl, C, and H. Higher priorities go to atoms with bigger atomic numbers.



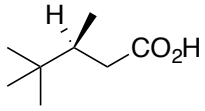
The low-priority group is in the proper position, facing backward. The arrow from priority 1 to 2 without passing through 3 goes in the clockwise direction, rendering the configuration *R*.



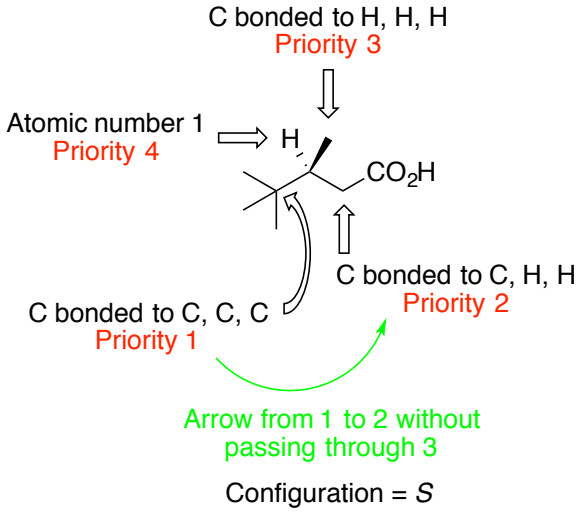
Configuration = *R*

10.

(a) This molecule was drawn with an implied hydrogen on the chirality center. It is best to begin by adding that hydrogen on the proper type of bond. Both the hydrogen and the dash were missing on the stereocenter, so the hydrogen must reside on the dash.



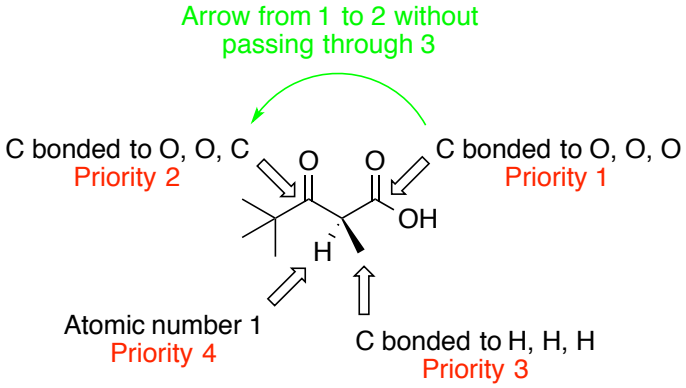
Now that we can clearly see all of the groups on the stereogenic center, we can make priority assignments. Hydrogen (when present) is always priority 4 because there is no atomic number lower than 1. But, in this case, there is a three-way tie for the remaining priorities. In other words, the chiral carbon is bonded to three other carbon atoms. To break the tie, we consider the atoms to which the tied carbons are bonded. The carbon bonded to three other carbons earns priority 1. It is followed by the carbon bonded to only one other carbon, and the methyl group receives priority 3.



Configuration = *S*

The lowest-priority group is facing backward as it should, and the arrow from priority 1 to 2 without passing through 3 shows the configuration to be *S*.

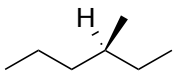
(b) In this question, we have another three-way tie for priorities 1–3. The tie is also broken by considering the atoms to which the tied carbons are bonded. Also, remember that multiple bonds count as individual single bonds to the atom in question. Therefore, the carbon of the carboxylic acid gets credit for all three of its bonds to oxygen. This makes it priority 1. The ketone receives priority 2, and the methyl group has priority 3. The hydrogen, as always, is the lowest priority.



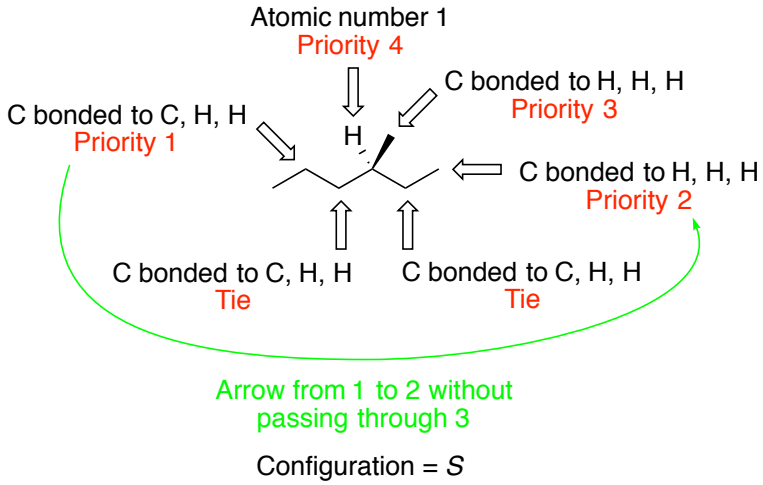
Configuration = *S*

The lowest-priority group faces backward as needed. The arrow from priority 1 to 2 without passing through 3 reveals the configuration to be *S*.

(c) It is best to begin this problem by filling in the implied hydrogen, which resides on a dash.



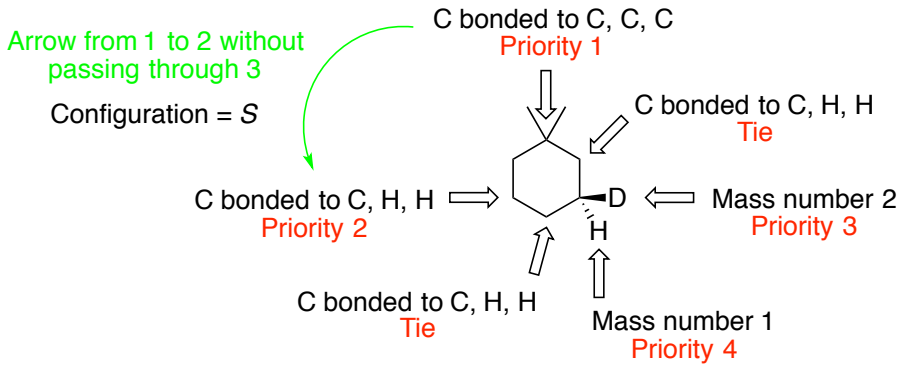
For this molecule, it takes us a bit longer to break the tie. Hydrogen immediately receives priority 4. Of the three tied groups, the methyl has the lowest priority because its carbon is bonded only to hydrogens. However, the ethyl and propyl groups each have a carbon with bonds to C, H, and H. To differentiate these groups, we must move one step further from the chirality center. When we do so, the propyl group wins the highest priority, and the ethyl group comes in second.



The lowest-priority group faces backward as is necessary, and the arrow from priority 1 to 2 without passing through 3 goes in the counterclockwise direction. So, the configuration is *S*.

(d) For this compound, we can quickly ascertain that hydrogen has the lowest priority and deuterium has the second-lowest priority. The both have an atomic number of 1, but their differing mass numbers break the tie.

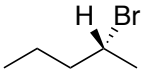
The two carbons attached to the chirality center are utterly tied since they are both bonded to C, H, and H. To differentiate these groups, we move one atom further from the chiral center. Upon doing so, the tie is broken, and all priorities have been assigned.



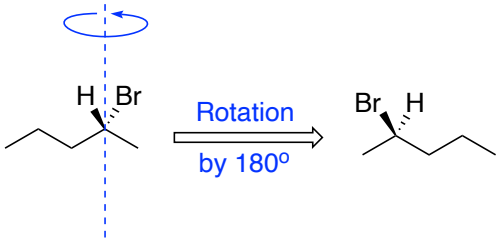
The lowest-priority group already faces backward. The arrow from priority 1 to 2 without passing through 3 goes in the counterclockwise direction. Therefore, the configuration is *S*.

11.

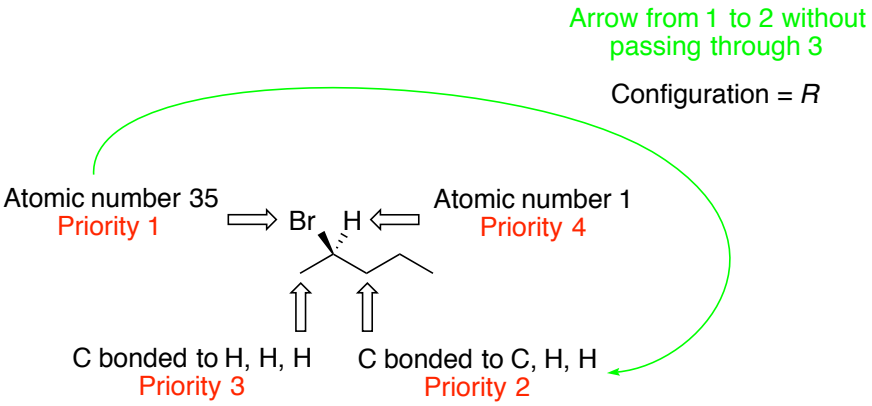
(a) It is best to begin by drawing the implied hydrogen on the chiral center, which in this case happens to reside on a wedge.



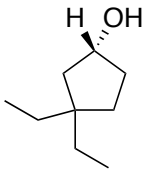
Whenever a hydrogen atom is one of the groups on a chirality center, it must be the lowest-priority group. Since it faces forward, a 180° rotation is necessary to put it in the proper position for assigning a configuration.



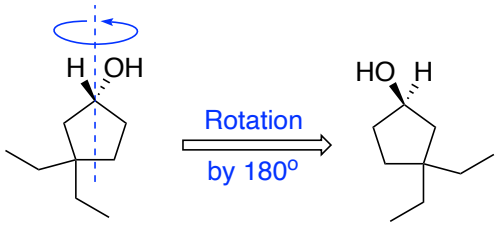
With the hydrogen now facing backward, we can assign the priorities and determine the configuration to be *R*.



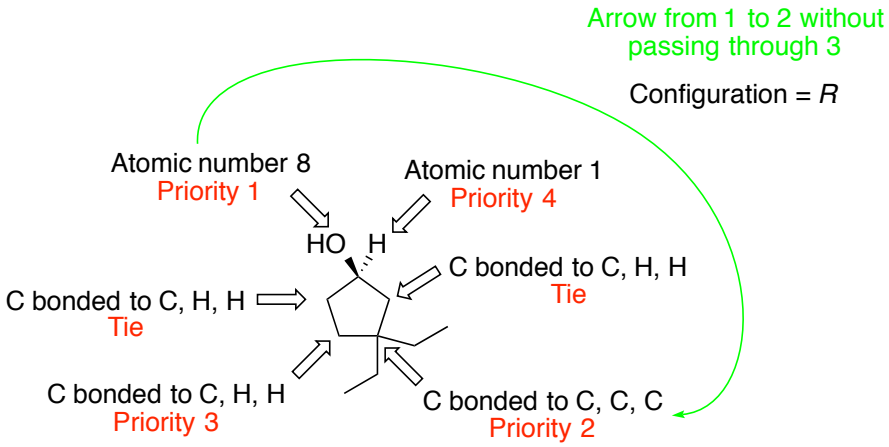
(b) Again, it is wise to begin by adding the implied hydrogen on the stereocenter.



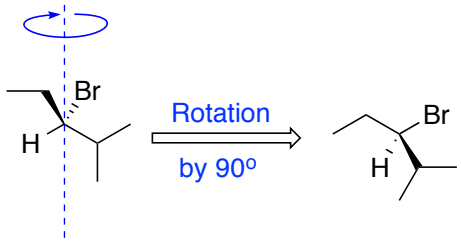
Since the hydrogen faces forward, we must flip the molecule over in order to put it in the correct location for assignment of configuration.



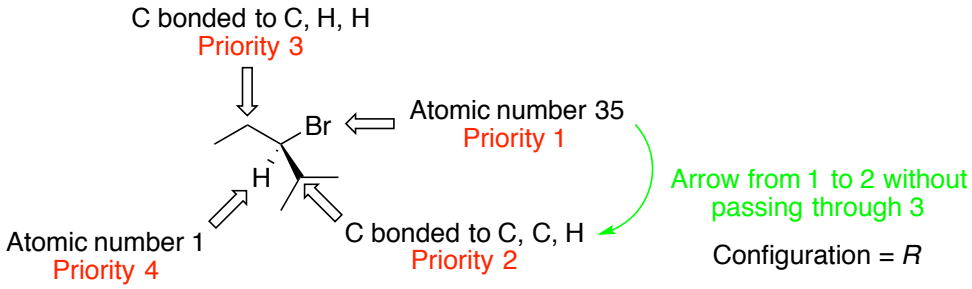
With the hydrogen now in its proper place, we can assign priorities and assign a stereochemical designation. The configuration of this molecule is *R*.



(c) In this case, the hydrogen resides on an in-plane bond rather than a wedge or a dash. If the molecule is rotated by 90˚, then the hydrogen will be in the proper location for assignment of configuration. If you find this difficult to visualize, build a model of the molecule, and the 90˚ rotation will become much more clear.

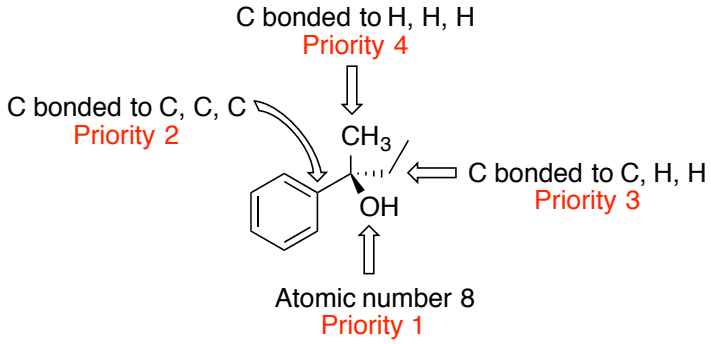


Once the priorities are assigned, the configuration is revealed to be *R*.

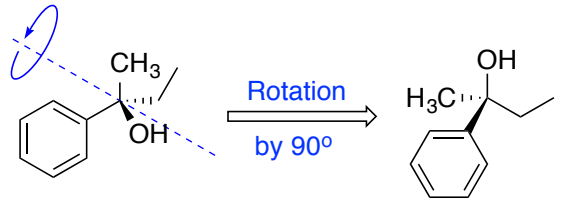


At this point, it is worth mentioning a shortcut that some students attempt to use but which does *not* always work. Some students notice that, in certain examples [such as parts (a) and (b) above], you can simply determine the configuration with the hydrogen improperly placed and then switch your answer from *R* to *S* or vice versa. This shortcut will work reliably only when the hydrogen is on the wedge and is therefore exactly opposite from the location it should occupy. When the hydrogen is on an in-plane bond (as in this question), the shortcut is *not* reliable. In fact, in this question it would have led you to the incorrect answer.

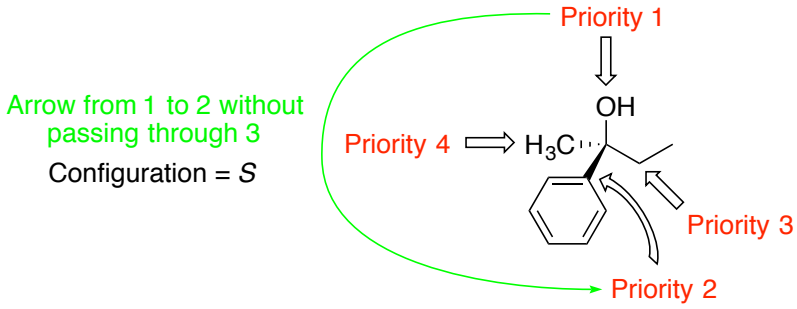
(d) In this question, there is no hydrogen on the chirality center. We should therefore assign priorities first in order to determine which group is the lowest-priority group. Once we have done so, it is apparent that the methyl group is the lowest-priority group and should therefore face backward.



Consequently, we must rotate the molecule so as to put the methyl group on a dash. Again, build a model to help yourself see the rotation.

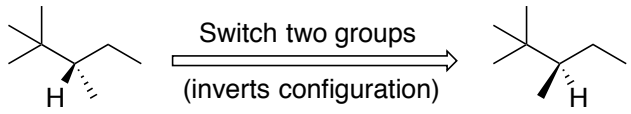


Now, with the lowest-priority group properly placed, the configuration can be determined. It is *S*.

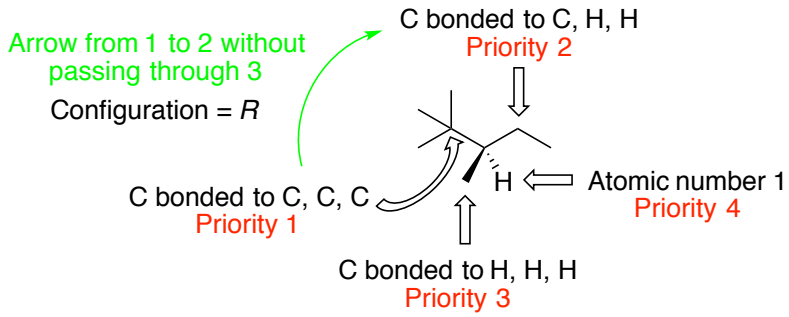


12.

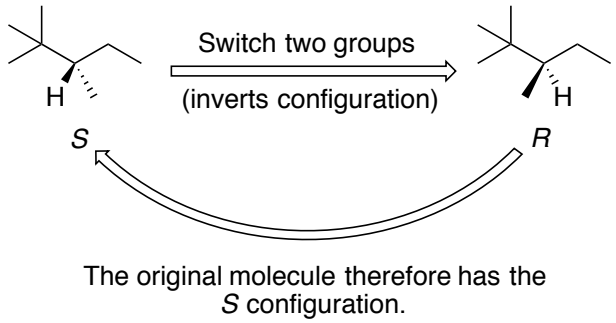
(a) This chiral alkane has been drawn so that the hydrogen faces forward. However, we can switch the hydrogen and the methyl group to place the hydrogen in the proper location for determining configuration. However, it is imperative to remember that the change inverts the configuration of the molecule. We'll have to account for that fact at the end of the problem.



With the hydrogen in the correct location, we can assign priorities to each of the groups. This process shows that the configuration of the molecule currently under consideration is *R*.



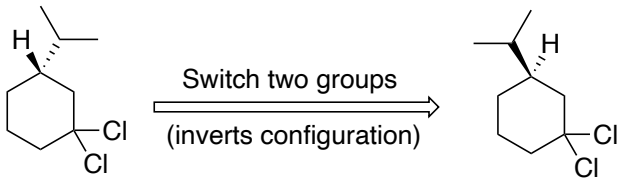
This, however, is not the molecule about which we were originally asked. When we switched two groups on the original molecule, we inverted its configuration and created the enantiomer. The original molecule therefore has the *S* configuration.



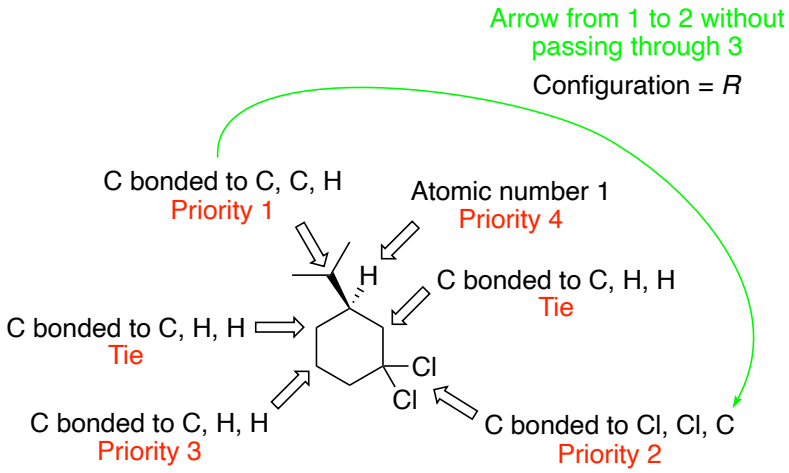
We can therefore name this alkane as (*S*)-2,2,3-trimethylpentane.

(b) This compound has the hydrogen on its chirality center facing forward. However, we can switch it and the isopropyl group to place the hydrogen in the

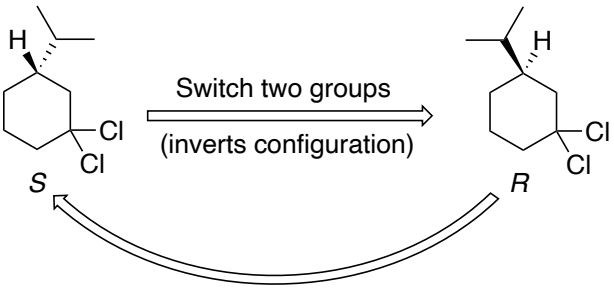
proper location for determination of configuration. We must remember though that this operation has inverted the molecule's configuration.



With the hydrogen now in the proper location, we can assign priorities, as well as the *R* configuration.

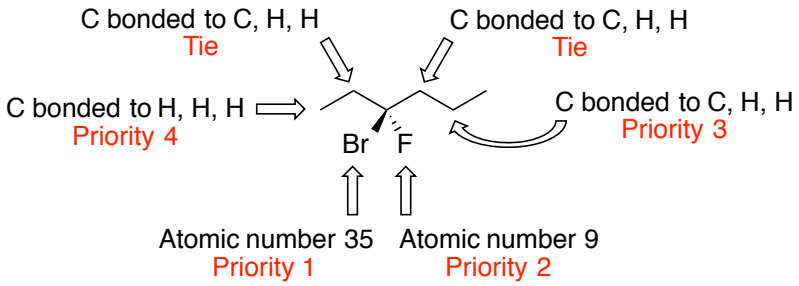


However, this configuration does not apply to the original molecule about which we were asked. When we switched two groups on the stereogenic center, we inverted the configuration, so the original molecule has the *S* configuration.

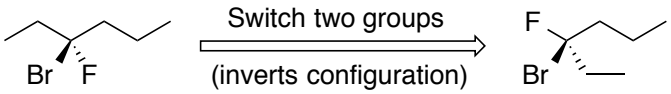


The original molecule therefore has the *S* configuration.

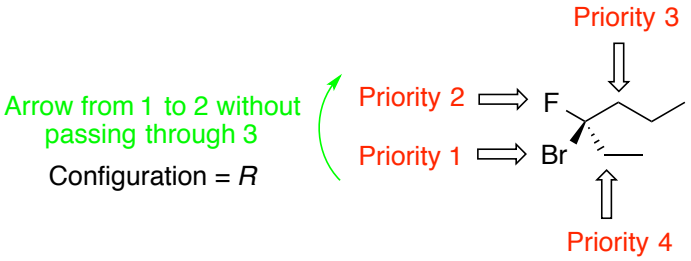
(c) In this problem, there is no hydrogen on the chirality center, so the lowest-priority group is not immediately obvious. Therefore, we should first assign the priorities.



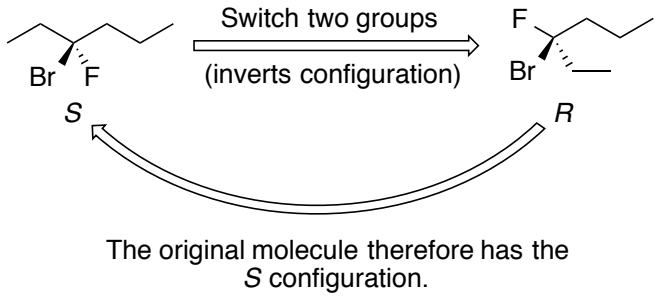
The ethyl group is the lowest-priority group, and it is not on the dash, so we can switch two groups to place it there. However, we must be sure to remember that this has inverted the original molecule's configuration.



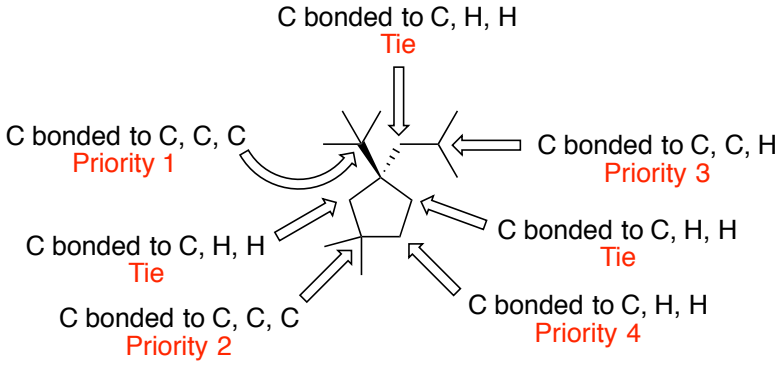
With the lowest-priority group properly placed, we can now assign the configuration, which is *R*.



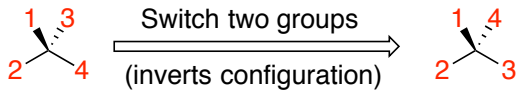
The original molecule therefore has the *S* configuration.



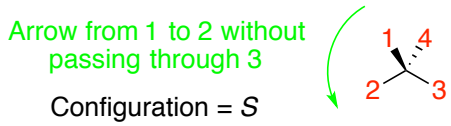
(d) This molecule also has no hydrogen on the chirality center, so it is not obvious which group has the lowest priority. Therefore, we should begin by assigning priorities.



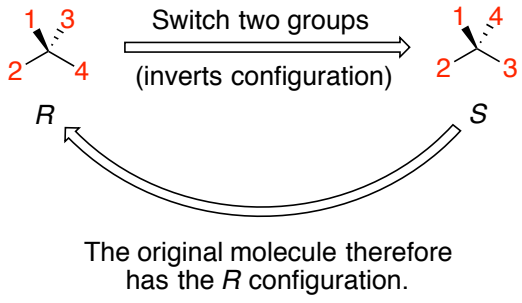
This reveals that the lowest-priority group is not on the dash, and we must switch two groups to put it on the dash. Since this involves moving one side of the ring, you might be concerned about how to draw the molecule after switching the groups. It is important to realize that, once the priorities have been assigned, the identities of the groups don't actually matter any longer. Therefore, we can save ourselves some time and simplify the drawing by replacing the structures of the groups with their priorities. This makes it trivial to switch two groups.



With priority 4 facing backward, we can now determine the configuration, which is *S*.



Therefore, the original cycloalkane had the *R* configuration.



Its complete name is (*R*)-1-*tert*-butyl-1-isobutyl-3,3-dimethylcyclopentane.

13.

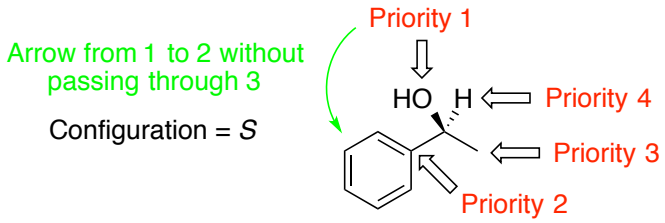
(a) The observed rotation is -2.25°. The concentration is reported in g solute/mL solvent, and the path length is in decimeters (note that 10 cm = 1 dm). The superscript following specific rotation signifies the temperature, and the subscript denotes the wavelength of light used (D = D line of sodium, or 589 nm).

$$[\alpha]_D^{20} = \frac{-2.25^\circ}{\left(\frac{0.25\ g}{5\ mL}\right) 1\ dm} = -45$$

Although the units do not cancel, specific rotation is treated as unitless by convention.

(b) The molecule is levorotary (*l*) since the rotation was negative (i.e., in the counterclockwise direction).

(c) To give the complete name, we must also assign a configuration. Remember that we cannot predict the configuration from the sign of the specific rotation.

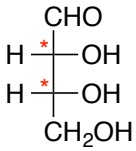


Since the configuration is *S*, the molecule's complete name is (*S*)-(-)-1-phenylethanol.

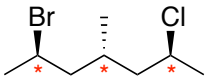
(d) The enantiomer has the opposite configuration and rotates light in the opposite direction, making its complete name (*R*)-(+)-1-phenylethanol. Its specific rotation has the same magnitude but the opposite sign, so it is +45.

14.

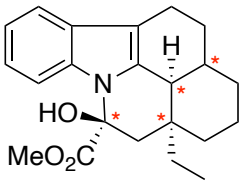
(a) D-Erythrose has two stereocenters (*). There are a maximum of 2^2, or 4, stereoisomers of which D-erythrose itself is one. Therefore, this compound can have up to three additional stereoisomers.



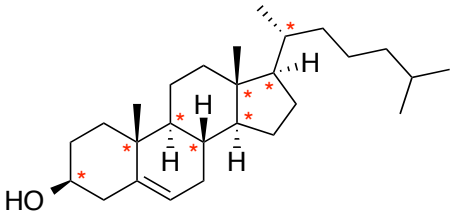
(b) This dihalide has three stereocenters (*), so there are a maximum of 2^3, or 8, stereoisomers. The one shown here is one of the eight, so there can be at most seven additional stereoisomers.



(c) Vincamine has four stereocenters, so there are a maximum of 2^4, or 16, stereoisomers. Since vincamine is one of these, there can be at most 15 additional stereoisomers.

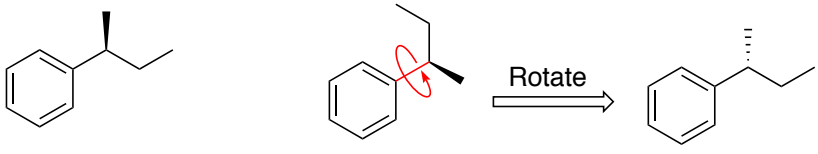


(d) Cholesterol contains eight chirality centers, so there are a maximum of 2^8, or 256, stereoisomers. Cholesterol is one of these, so it can have up to 255 stereoisomers.



15.

(a) Since these molecules are drawn in different conformations, we must rotate around a carbon-carbon bond to put them in comparable conformations. Upon doing so, it becomes clear that these compounds are enantiomers. They each have a single stereocenter and differ in configuration at that center.



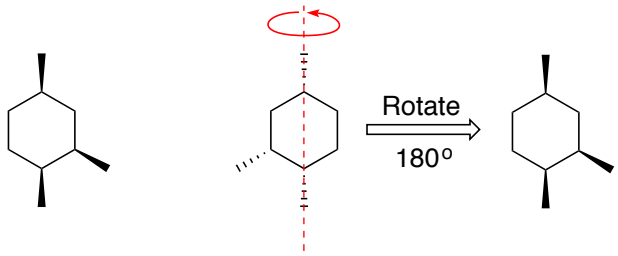
(b) These compounds are diastereomers because they are stereoisomers that are not mirror images.

Another way of conceptualizing this is that *diastereomers will have at least one chiral center with the same configuration and at least one chiral center with a different configuration*. If all of the configurations were the same, the molecules would be identical. If all of the configurations different, the molecules would be enantiomers. In between these two extremes, we encounter diastereomers.

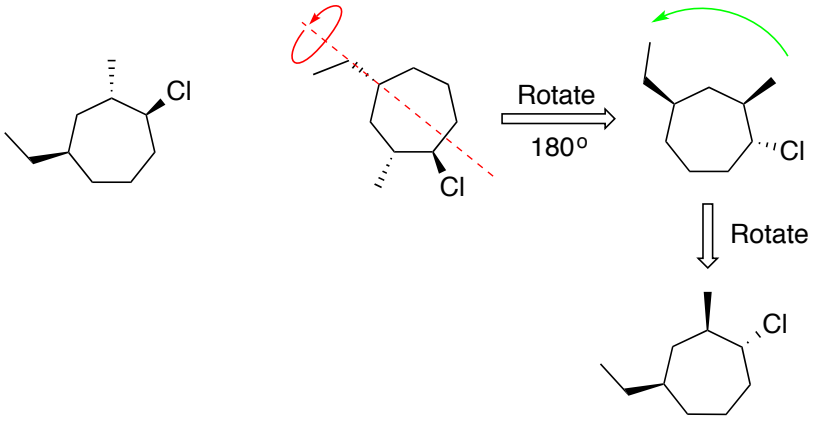
(c) These compounds are constitutional isomers. In the first one, the methyl groups are on adjacent ring atoms (C1 and C2). In the second compound, they are on C1 and C3. This difference in connectivity makes them constitutional isomers.

(d) These compounds are unrelated. They have different molecular formulas. Notice that the first structure contains a chirality center bearing methyl, ethyl, and propyl groups. The second compound has no stereocenter because the tertiary carbon is bonded to a methyl group and two propyl groups.

(e) These compounds are identical. If one of the two is flipped over, it becomes apparent that all of the configurations are the same.



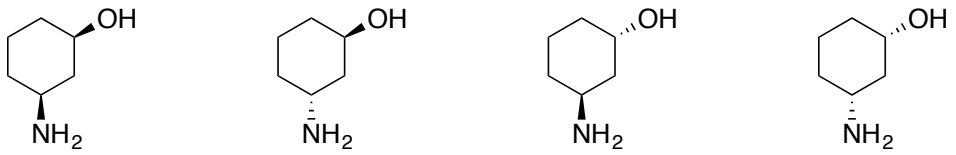
(f) First, we must draw the structures in comparable ways. The latter molecule can be flipped over and rotated ($\frac{1}{7}th$ of a complete turn) to achieve this goal.



When they are drawn comparably, we can see that these compounds have one chirality center with the same configuration and two stereocenters with the opposite configuration. Recall from part (b) that, when at least one chiral center has the same configuration and at least one chiral center has a different configuration, the molecules are diastereomers.

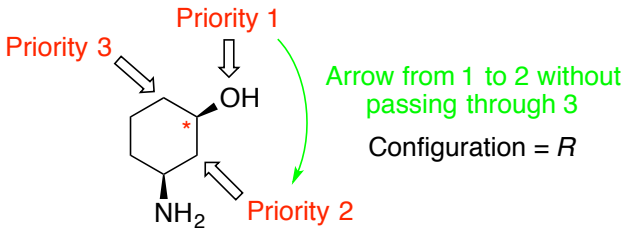
Another way of reaching this same conclusion is to say that the compounds are stereoisomers that are not mirror images.

16. Since this molecule contains two chiral centers, there are a maximum of four stereoisomers. Both substituents on the ring can up. There are two ways that one substituent can face up while the other points downward. Also, both groups can face down.

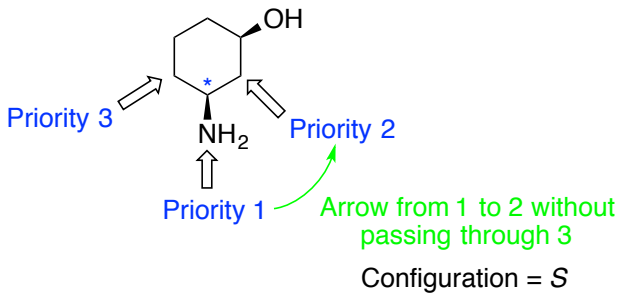


To quickly determine the configurations for all four stereoisomers, we should choose a single one and assign the configurations for its chirality centers. The rest can then be rapidly assigned by comparison. We should also choose the easiest of the stereoisomers to work with, and that would be the one in which the lowest-priority groups on both stereogenic centers (in this case, hydrogens) are already facing backward.

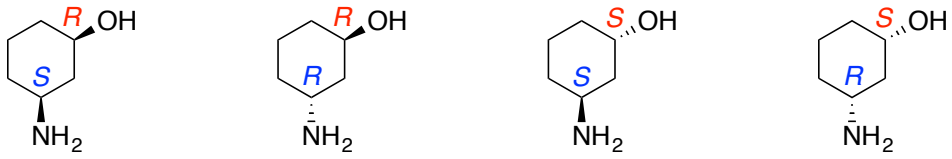
Draw the molecule once for the determination of each configuration in order to avoid confusion. The configuration of the center bearing the hydroxyl group is assigned below. To keep the drawing as simple as possible, the hydrogen (priority 4) has not been filled in because we have already established that it faces backward in this stereoisomer.



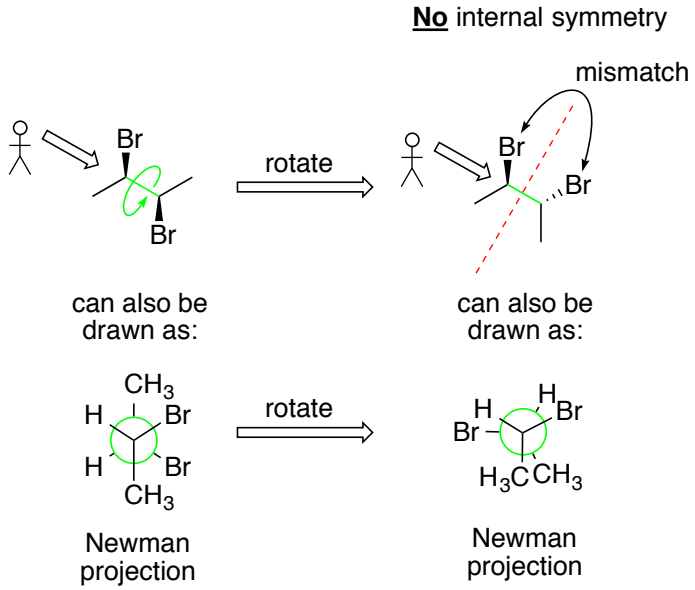
In the next diagram, the configuration of the center bearing the amino group is assigned. Once again, the hydrogen (priority 4) has been omitted since we have already established that it faces backward.



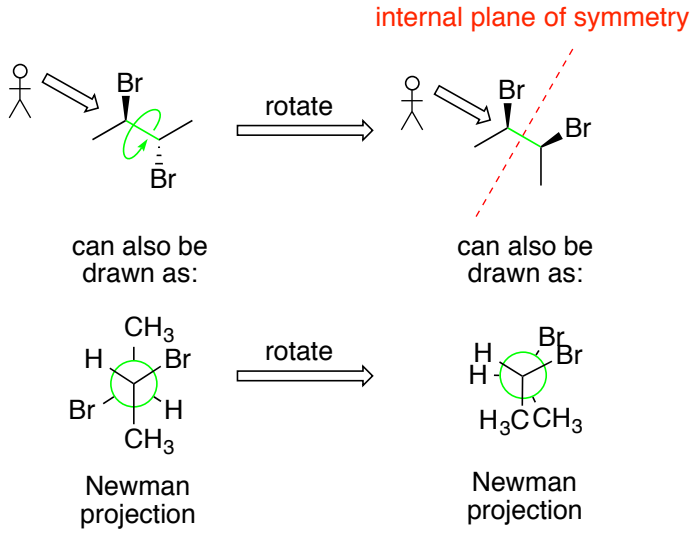
The configurations determined above are also shown on the first structure below. For the three remaining stereoisomers, we need only compare the configuration at each center. If it is the same, the designation is identical to that in the first stereoisomer. If it differs, the designation is the opposite of the one found in the first stereoisomer.



17. When both of the structures are drawn in Newman projections, it becomes even more clear that the first is staggered and therefore provides little opportunity to observe internal symmetry because the carbon backbone is not aligned. It also becomes more apparent that the second structure is an eclipsed conformation that provides a better opportunity to observe internal symmetry because the carbon backbone is now aligned. However, in this case, the bromine atoms are on different sides of the molecule, so it does *not* possess an internal plane of symmetry.

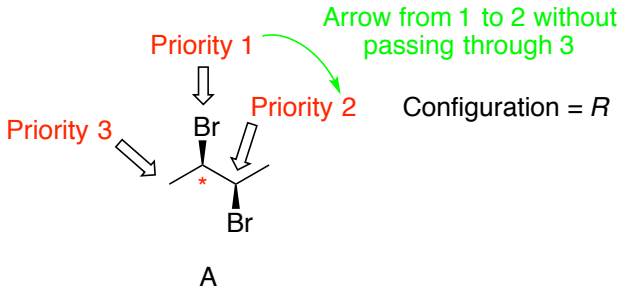


18. When both of the structures are drawn in Newman projections, we can even more clearly see that the first is a staggered conformation, which gives us little opportunity to find an internal plane of symmetry because the carbon backbone is not aligned. However, the second structure is in an eclipsed conformation. Since the carbon backbone is now aligned, we can easily identify its internal plane of symmetry.

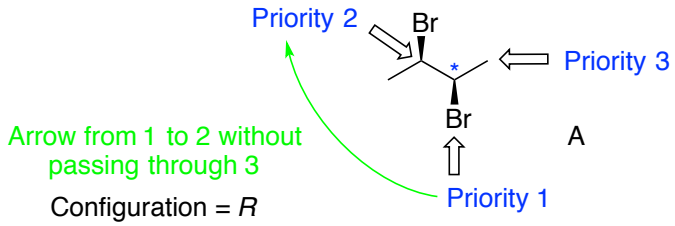


19. It is easiest to carefully assign the configurations of one stereoisomer and then make comparisons to the other stereoisomers to determine the remaining configurations. Always choose the easiest stereoisomer to work with. This is the one in which the lowest-priority groups (hydrogens in this case) are already facing backward: compound A in this case.

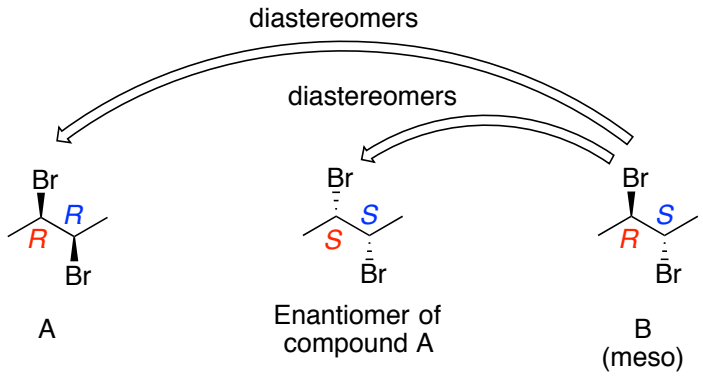
In the diagram below, the configuration of one stereocenter (*) is assigned. For clarity, the hydrogen (priority 4) is omitted because we have already established that it faces backward.



In the next diagram, the configuration of the other stereocenter (*) is assigned. Once again, the hydrogen (priority 4) has been omitted for clarity because we have already established that it faces back.

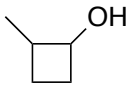


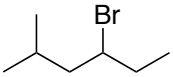
The *R* configurations of compound A are also shown in the first structure of the diagram below. By inspection, we can quickly assign configurations to its stereoisomers based on whether they are the same as those in compound A or different.

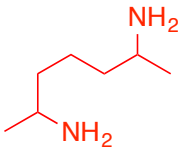


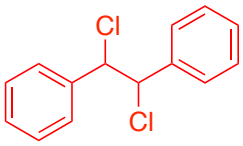
With all of the configurations determined, we can now name each compound. Compound A is (2*R*,3*R*)-2,3-dibromobutane. Its enantiomer is (2*S*,3*S*)-2,3-dibromobutane. Compound B, the meso form, is (2*R*,3*S*)-2,3-dibromobutane.

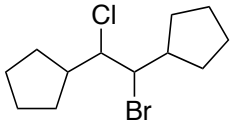
20. The molecules in red below have an internal plane of symmetry in at least one stereoisomer.

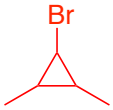


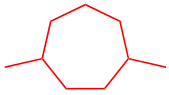


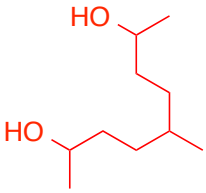




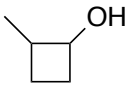




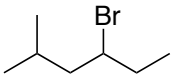




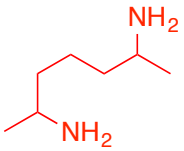
Let's examine each molecule in turn. The first one does not have the potential for any internal symmetry because of the dissimilarity of its substituents.



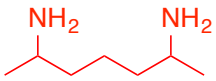
The same is true of the alkyl halide that follows.



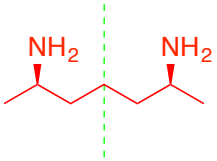
The diamine can have internal symmetry, but it is not immediately obvious due to the way in which the molecule was drawn. If we extend the carbon backbone linearly, the possibility of internal symmetry becomes apparent.



can also be drawn as:

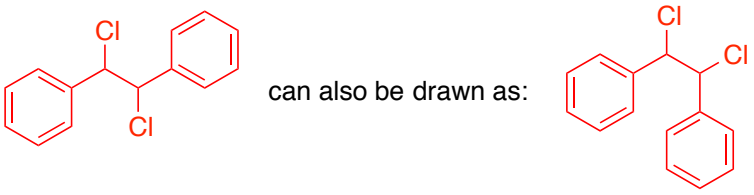


A stereoisomer with both amino groups on the same side of the carbon chain (as drawn below) will have internal symmetry.

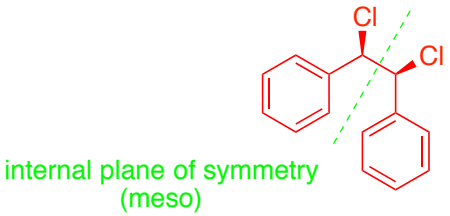


internal plane of symmetry
(meso)

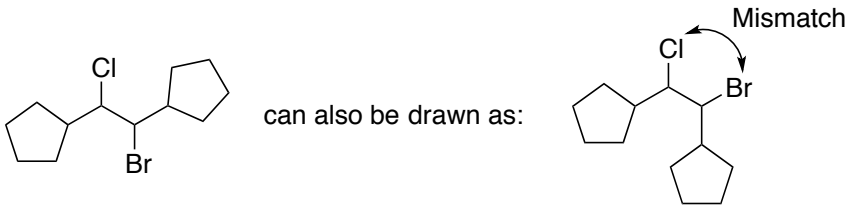
This dichloride also has the potential for internal symmetry. Recall that the molecule must be drawn in its most highly symmetrical conformation in order to highlight internal symmetry. When the phenyl groups align, the potential for symmetry is clear.



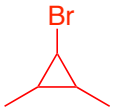
A stereoisomer with the chlorine atoms on the same side of the carbon backbone (as drawn below) will be meso.



The next dihalide cannot have internal symmetry. Even if the rings are aligned, there cannot be internal symmetry because the halides differ.

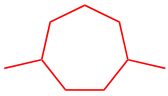


This cyclopropane derivative has the potential for an internal plane of symmetry passing right through the C-Br bond.

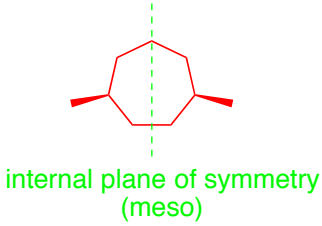


When the methyl groups on either side of this plane are on the same side of the ring, there will be internal symmetry. Consequently, this compound has two meso forms.

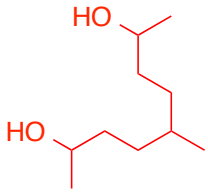
1,4-Dimethylcycloheptane has the potential for internal symmetry.



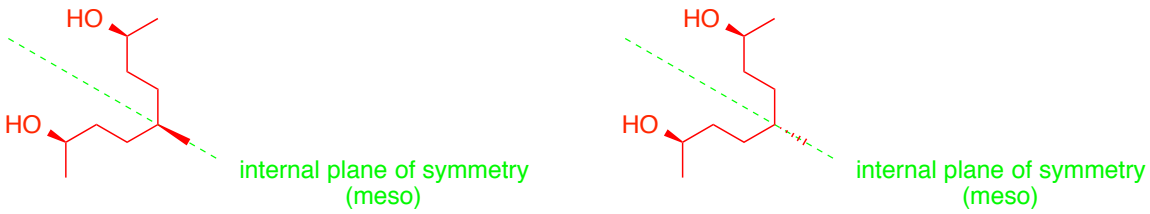
When the methyl groups are on the same side of the ring, a meso form is produced.



This diol (i.e., molecule containing two alcohols) has the potential for internal symmetry.

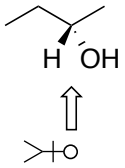


When the hydroxyl groups are on the same side of the carbon backbone (as drawn below), meso forms are produced. This molecule therefore has two meso forms.

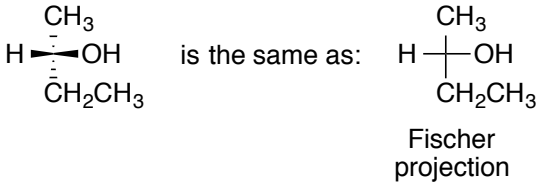


21. In each of these questions, the goal is to view the molecule such that two bonds emanating from the chiral center are on the horizontal axis and are extending toward the viewer, while the other two bonds are on the vertical axis and are receding, as shown generically below.

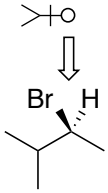
(a) In this part, that perspective can be achieved by viewing the molecule from underneath.



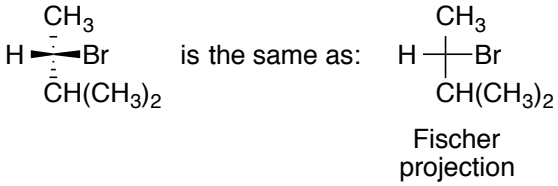
Upon doing so, the viewer sees the molecule as shown below. This is the perspective that is implied by a Fischer projection, in which the bonds are drawn simply as solid lines.



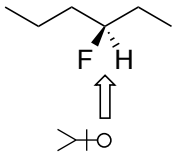
(b) To achieve the perspective necessary for a Fischer projection, this molecule must be viewed from above.



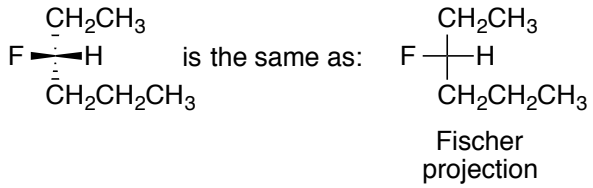
Doing so places it in the proper orientation for the stereochemistry to be implied by a Fischer projection.



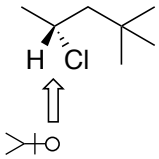
(c) When this molecule is viewed from underneath, the necessary perspective is obtained.



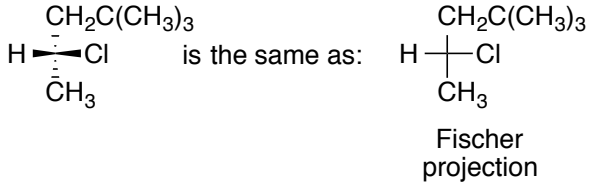
The stereochemistry can then be implied using a Fischer projection.



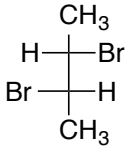
(d) When it is observed from underneath, this molecule appears in the perspective necessary for a Fischer projection.



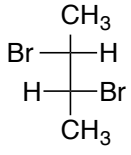
Then, the stereochemistry can be implied using the convention inherent in a Fischer projection.



22. 2,3-Dibromobutane has two chirality centers. Consequently, it can have a maximum of four stereoisomers. (2*S*,3*S*)-2,3-Dibromobutane is one, and we saw its Fischer projection in the preceding text. It is chiral and therefore has an enantiomer, which is (2*R*,3*R*)-2,3-dibromobutane.

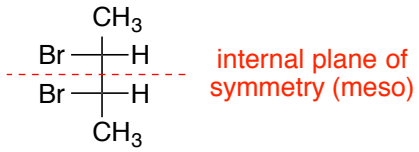


(2*S*,3*S*)-2,3-dibromobutane



(2*R*,3*R*)-2,3-dibromobutane

However, when both bromine atoms are on the same side of the carbon backbone (as portrayed in a Fischer projection), there is an internal plane of symmetry. (2*R*,3*S*)-2,3-Dibromobutane is therefore a meso compound. It is achiral and does not have an enantiomer.

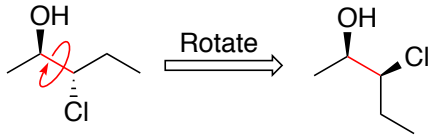


(2*R*,3*S*)-2,3-dibromobutane

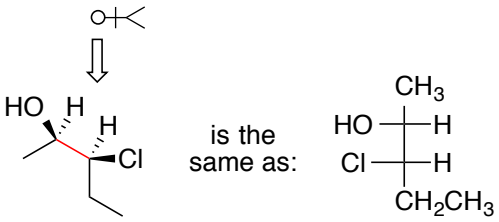
While the maximum number of stereoisomers possible for 2,3-dibromobutane was four, we now see that in actuality there are only three stereoisomers since one is meso.

23.

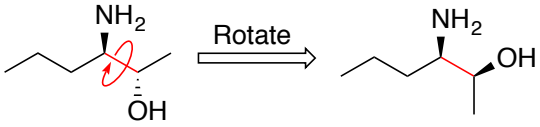
(a) The molecule needs to be in an eclipsed conformation in order to represent it using a Fischer projection. Rotation about the C2-C3 bond provides the necessary conformation.



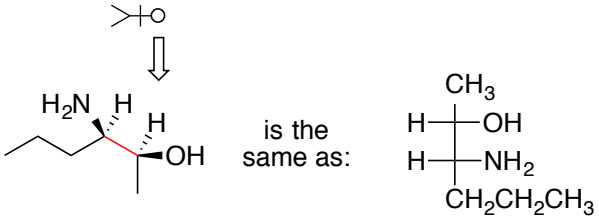
When viewed from above, the molecule is seen in a Fischer projection.



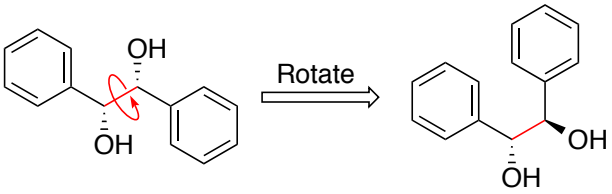
(b) To put the molecule into an eclipsed conformation, we can rotate about the C2-C3 bond.



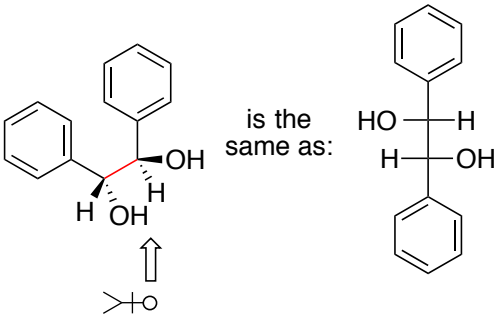
Now, when viewed from above, this amino alcohol can be represented in a Fischer projection.



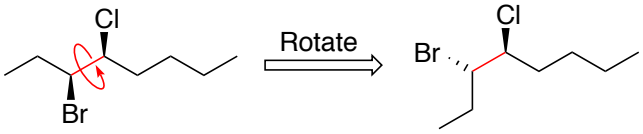
(c) To obtain an eclipsed conformation, the molecule can be rotated about the central carbon-carbon bond.



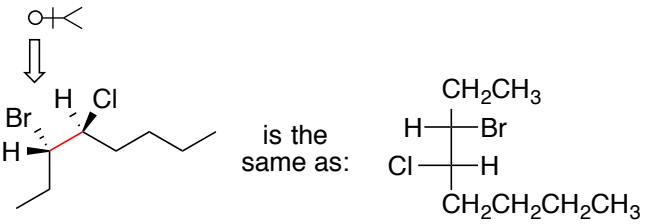
Now, when viewed from underneath, this diol can be portrayed in a Fischer projection.



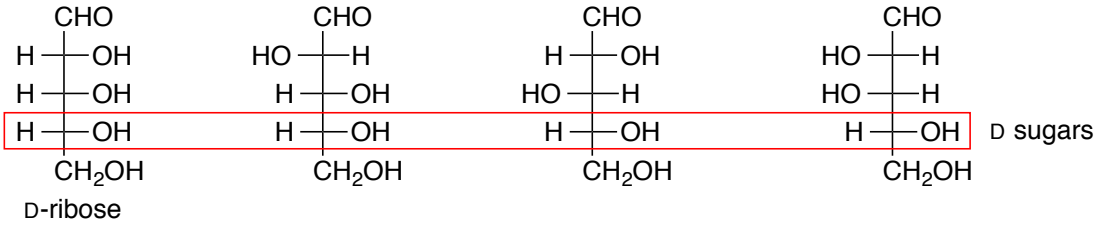
(d) Rotation about the C3-C4 bond gives the needed eclipsed conformation.



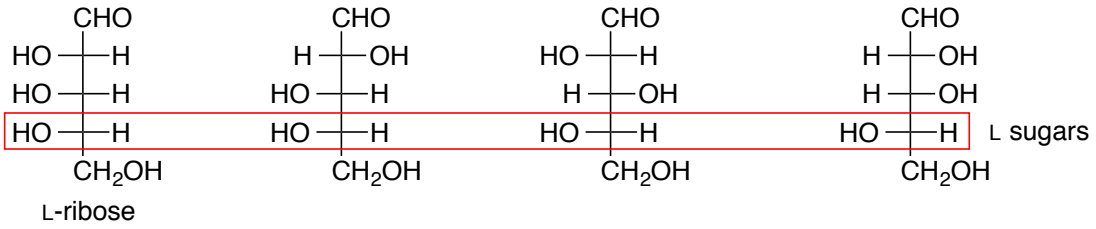
Then, when viewed from above, the dihalide can be drawn in a Fischer projection.



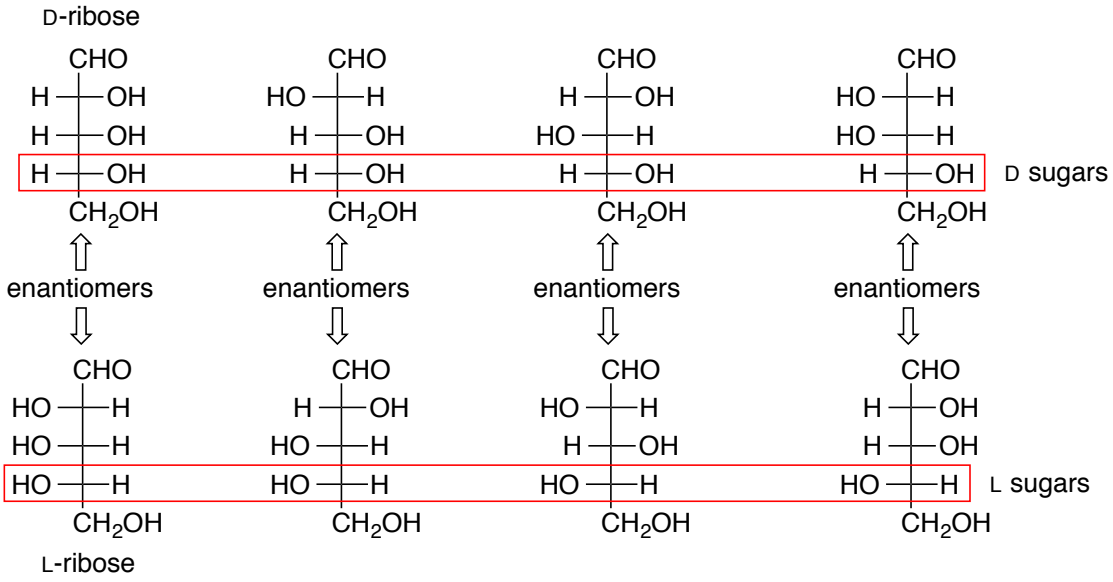
24. D-Ribose has three stereoisomers that are also D sugars. In each, the hydroxyl group on the penultimate carbon faces to the right. These stereoisomers are derived by systematically varying the configurations at C2 and C3.



L-Ribose is the enantiomer of D-ribose. It also has three stereoisomers with the L configuration. In each of these, the hydroxyl group on the penultimate carbon faces to the left.

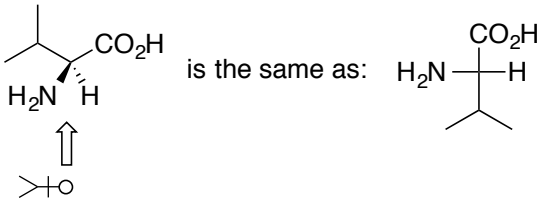


Each of the L-sugars in this series is the enantiomer of a D sugar.

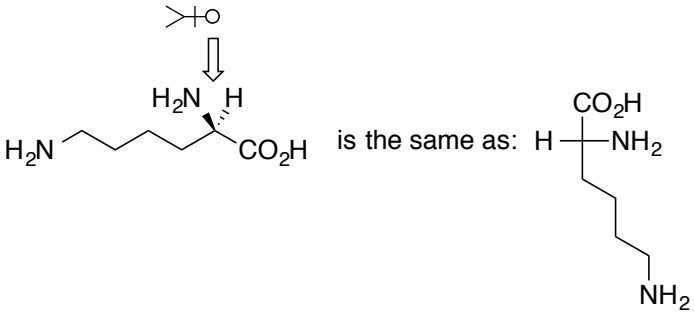


25.

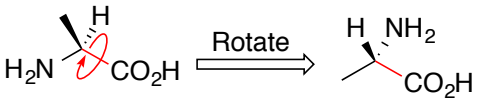
(a) When this enantiomer of valine is viewed in a Fischer projection, the amino group points to the left, so it is L-valine.



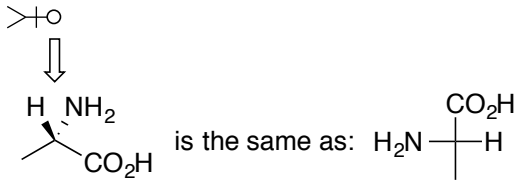
(b) When viewed from above, this enantiomer of lysine appears in a Fischer projection with the amino group on the right, making it D-lysine.



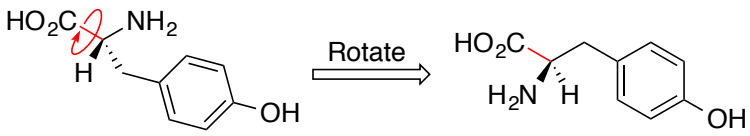
(c) To view alanine in a Fischer projection, we must first rotate about the C1-C2 bond so that the carbon backbone resides in the plane of the page.



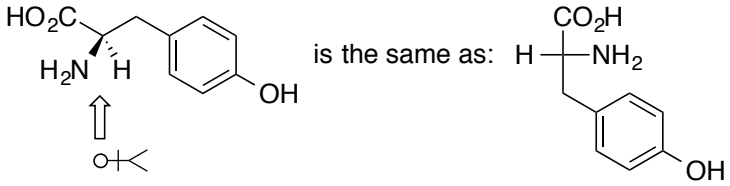
Then, when viewed from above, a Fischer projection with the amino group on the left-hand side results. This means that the molecule is L-alanine.



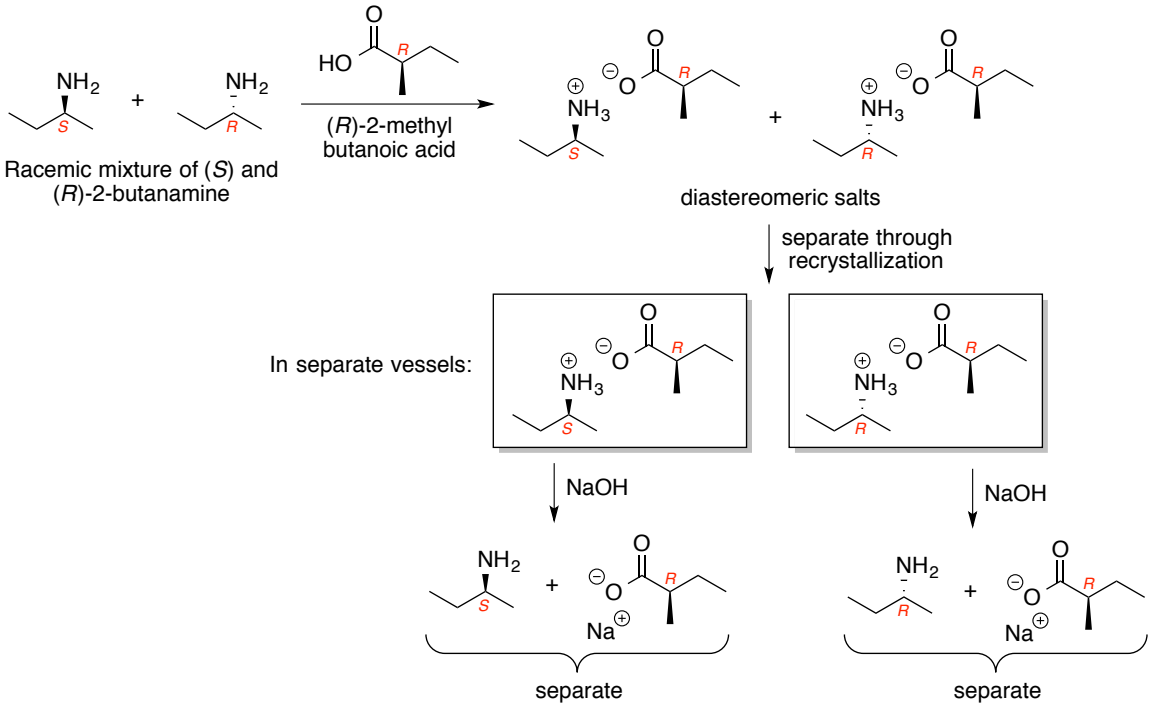
(d) To convert this skeletal structure into a Fischer projection, we must first rotate about the C1-C2 bond so as to place the carbon backbone in the plane of the page.



Then, when it is viewed from underneath, we see tyrosine in a Fischer projection. The amino group is on the right side of the carbon backbone, making this D-tyrosine specifically.



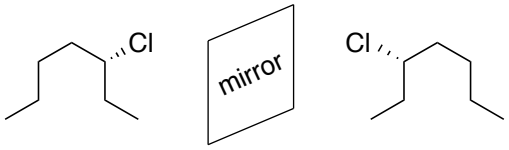
26. The racemic mixture of amines [(*S*) and (*R*)-2-butanamine] can be treated with any chiral, non-racemic carboxylic acid to form diastereomeric salts. In the example below, (*R*)-2-methylbutanoic acid was chosen as the resolving agent. The diastereomeric salts have different properties and can therefore be separated through recrystallization. After the separation is complete, each of the salts may be treated with base to regenerate the amine in its original form. The carboxylate is then easily removed due to its higher water solubility.



27. In this case, the analyte was said to be racemic. A racemic mixture is, by definition, an equal mixture of enantiomers. When this 50/50 mixture is separated, the individual enantiomers, which are present in equal amounts, lead to peaks of equal size in the chromatogram.

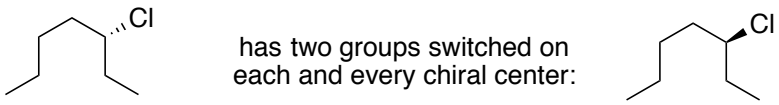
28. A chiral molecule has one and only one enantiomer. However, as we discussed in this Chapter, there are two convenient ways to draw the enantiomer. For each of the following problems, both methods are shown. They produce the same enantiomer; it is simply drawn differently.

(a) The enantiomer can be drawn by reflection through a mirror plane.

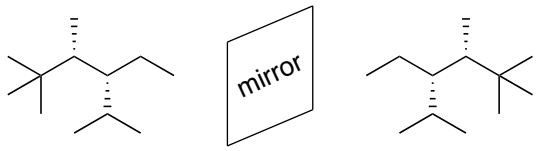


Or, the enantiomer can be drawn by switching two groups on the chiral center. In this case, that could be achieved by switching the chlorine with the implied hydrogen.

The enantiomer of:

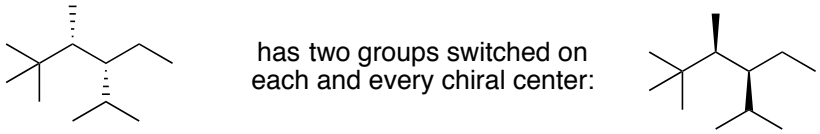


(b) The enantiomer can be drawn as the reflection of the original compound.

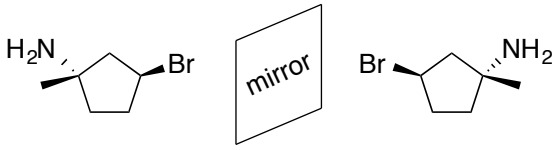


Another option is to switch two groups on each and every chiral center. In this case, that could be achieved by swapping the methyl and isopropyl groups with the implied hydrogens on those centers.

The enantiomer of:

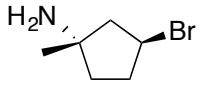


(c) The enantiomer can be portrayed as the reflection of the original molecule.

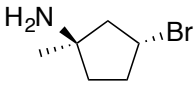


Alternatively, we can switch two groups on each of the chiral centers to obtain the enantiomer.

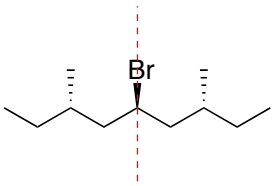
The enantiomer of:



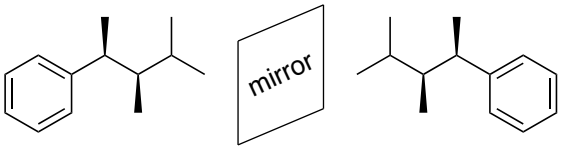
has two groups switched on each and every chiral center:



(d) This molecule is achiral because it possesses an internal plane of symmetry. Therefore, it has no enantiomer.

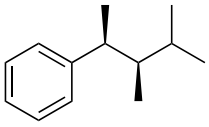


(e) The enantiomer of this molecule can be portrayed as the reflection of the original structure.

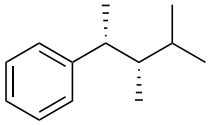


Another choice is to switch two groups on each of the chiral centers. This can be easily achieved by switching the methyl groups on each chiral center with the implied hydrogens on these same centers.

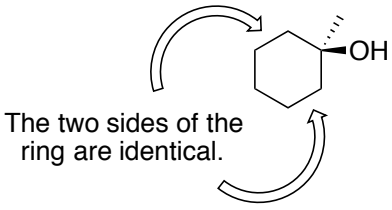
The enantiomer of:



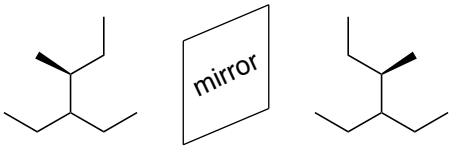
has two groups switched on each and every chiral center:



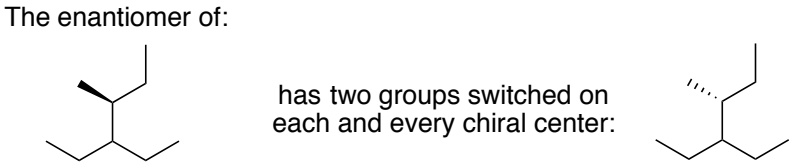
(f) This molecule does not actually contain a chiral center. As such, it is achiral and has no enantiomer.



(g) The enantiomer can be visualized as the reflection of the original molecule.

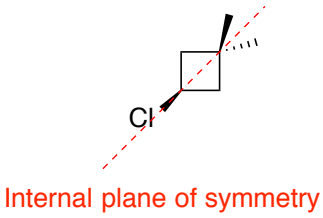


Alternatively, two groups can be switched on the chiral center. In this case, the methyl group and the implied hydrogen on the chiral center have been swapped.



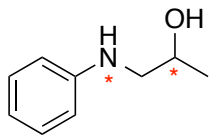
(h) This molecule does not contain chiral centers. The center bearing two methyl groups is not a stereocenter because four different groups are needed for a chirality center. The center bearing the chlorine is also not a chiral center because the two sides of the ring are identical.

The achirality of this molecule is also revealed by the presence of an internal plane of symmetry.

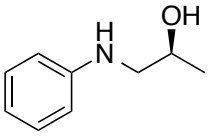


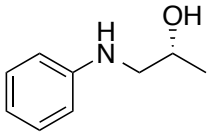
Since the compound is achiral, it has no enantiomer.

29. The compound does, in fact, have two chirality centers (*). One is the carbon bearing a hydroxyl group, methyl group, hydrogen, and larger R group. The other is nitrogen, which bears a lone pair, a hydrogen, and two different R groups.



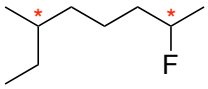
However, the nitrogen undergoes pyramidal inversion at room temperature. Therefore, the configuration at that center is rapidly interconverting. As a result, the only observable difference in configuration occurs at the chiral carbon. The enantiomers having opposite configurations at this center are the only two stereoisomers found at room temperature.



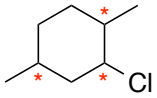


30. The maximum possible number of stereoisomers is 2^n, where n is the number of chirality centers.

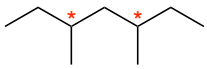
(a) This compound has two stereocenters (*) and therefore a maximum of four stereoisomers.



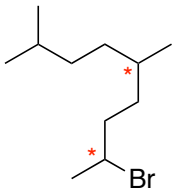
(b) This molecule has three stereocenters (*), giving it a maximum of eight stereoisomers.



(c) This compound has two stereocenters (*) and therefore a maximum of four stereoisomers.

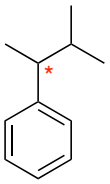


(d) This molecule has two stereogenic centers (*) and a maximum of four stereoisomers.

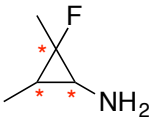


(e) This alcohol has two stereocenters (*), resulting in a maximum of four stereoisomers.

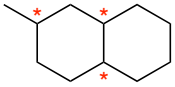
(f) This benzene derivative has a single stereocenter (*), so it has only two stereoisomers.



(g) This amine has three stereocenters (*), resulting in a maximum of eight stereoisomers.

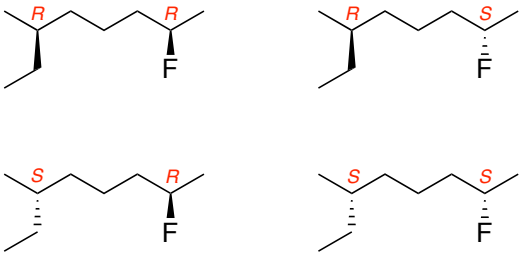


(h) This cycloalkane has three chirality centers (*), so it has a maximum of eight stereoisomers.

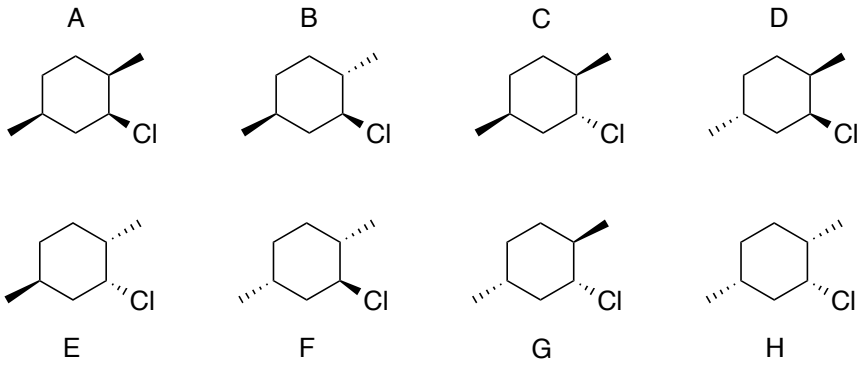


31.

(a) This compound has four stereoisomers. The *R*,*R* and *S*,*S* compounds are a pair of enantiomers, as are the *R*,*S* and *S*,*R* compounds. Any other comparison is between diastereomers.

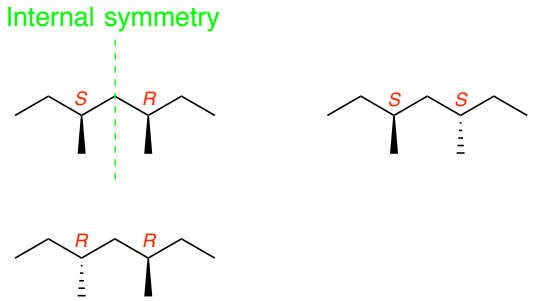


(b) When generating a large number of stereoisomers, it is important to be systematic in your approach. Notice how the list below begins with three wedges (A). Then, the next three stereoisomers (B – D) have one dash in all three possible locations. The following three stereoisomers (E – G) have two dashes and only one wedge, while the final stereoisomer (H) has all dashes.



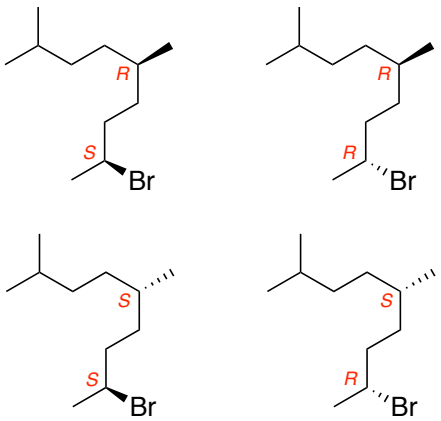
There are four pairs of enantiomers: A & H, B & G, C & F, and D & E. Any other comparison is between diastereomers.

(c) While this molecule has a maximum of four possible stereoisomers, there are in actuality only three. One of the stereoisomers has internal symmetry, so it is meso and has no enantiomer. This reduces the number of stereoisomers by one.



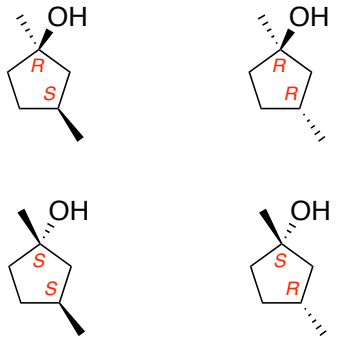
The *S*,*S* and *R*,*R* compounds are a pair of enantiomers. The meso compound is a diastereomer of either of these.

(d) This alkyl halide has four stereoisomers.



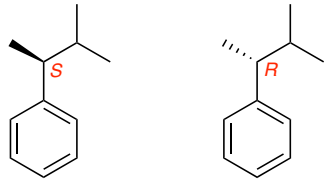
The *S*,*R* and *R*,*S* compounds are a pair of enantiomers, as are the *R*,*R* and *S*,*S* compounds. Any other comparison is diastereomeric.

(e) There are four stereoisomers of this molecule.

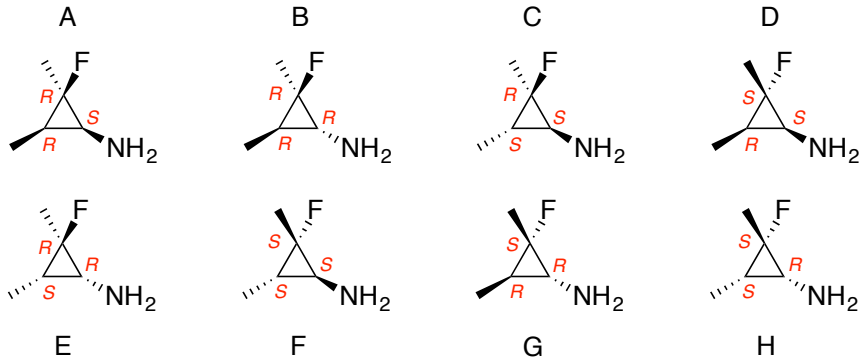


The *R*,*S* and *S*,*R* forms are a pair of enantiomers. So are the *R*,*R* and *S*,*S* forms. All other comparisons are between diastereomers.

(f) Since there is only one stereocenter in this molecule, the only two stereoisomers that exist are a pair of enantiomers.

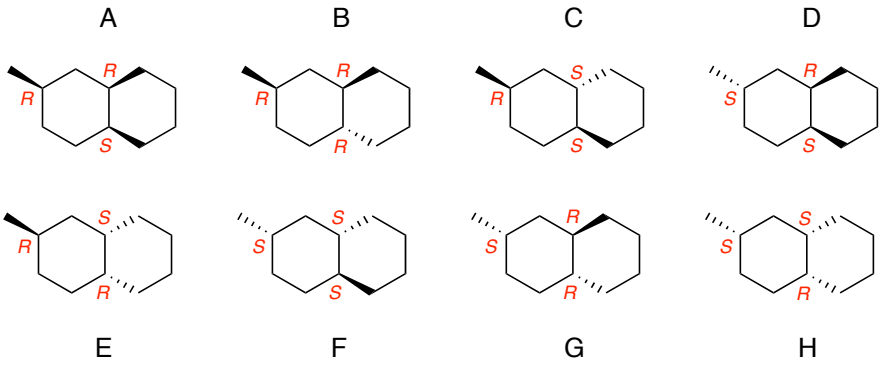


(g) This amine has a total of eight stereoisomers. Remember that systematically varying the stereochemistry is the most methodical way to proceed. Begin with one stereoisomer (A). In the next three stereoisomers (B – D), the configuration has been altered at one chirality center. In the following three stereoisomers (E – G), the configuration has been changed at two out of three stereocenters. Lastly, the final stereoisomer (H) has all three configurations inverted.



There are four pairs of enantiomers: A & H, B & F, C & G, and D & E. Any other comparison is diastereomeric.

(h) This compound has eight stereoisomers that can be systematically generated as follows. Begin with a particular set of configurations (e.g., all wedges in A). The next three stereoisomers (B – D) have one dash in each possible location. The following three stereoisomers (E – G) have two dashes and only one wedge in each possible location. The final stereoisomer (H) has all three dashes.

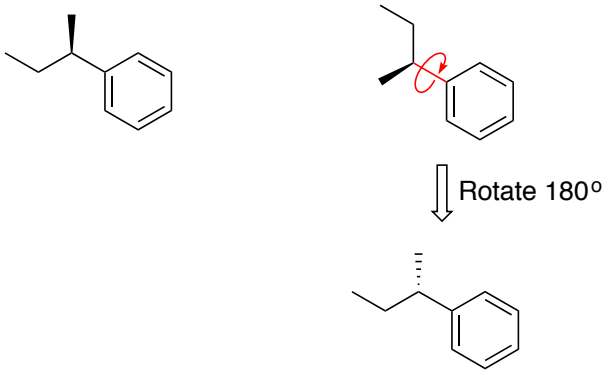


There are four pairs of enantiomers: A & H, B & F, C & G, and D & E. Any other comparison is diastereomeric in nature.

32.

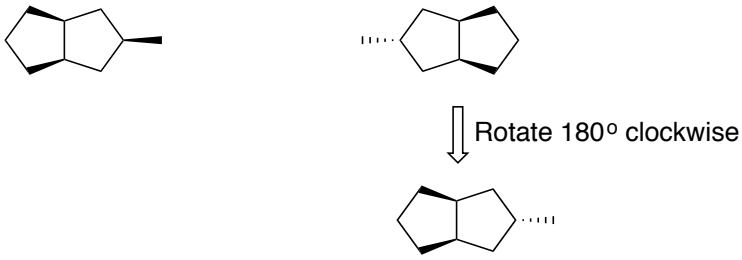
(a) These molecules have the same configuration at one chiral center and a different configuration at the other stereocenter. They are therefore stereoisomers that are not mirror images, which are known as diastereomers.

(b) In order to compare these structures directly, we must rotate about the bond between the stereocenter and the phenyl group. Doing so shows that these molecules differ in the configuration of their one and only chirality center, which makes them enantiomers.

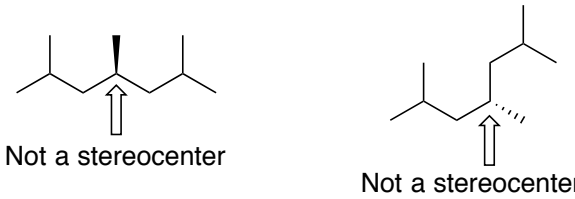


(c) Both of these molecules have an internal plane of symmetry. They are therefore meso compounds, and as such, they do not have enantiomers.

Meso compounds can still have diastereomers though, so we must check their relationship carefully. Upon rotating one of the molecules 180˚, it becomes apparent that these are in fact diastereomers because they are stereoisomers that are not mirror images.

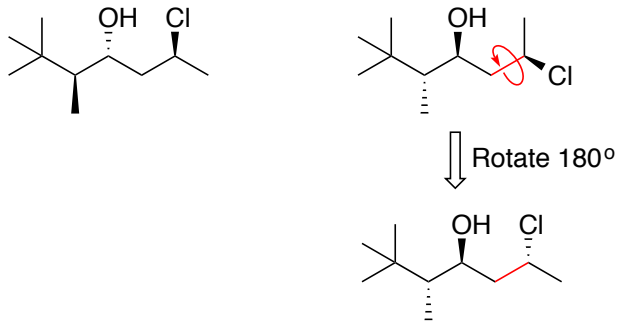


(d) While it may be tempting to begin rotating these molecules in order to make a direct comparison, it is not necessary to do so. The central carbon is not actually a stereocenter because it is bonded to two isobutyl groups. Therefore, these molecules are identical.

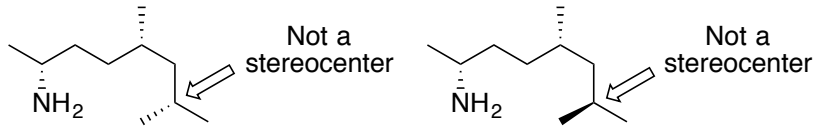


(e) To make a direct comparison between these molecules, it is necessary to make a conformational change to one of them. By rotating 180˚ about the indicated carbon-carbon bond, the molecules adopt comparable conformations. Since they have the

opposite configuration at each and every one of their chirality centers, they are enantiomers.

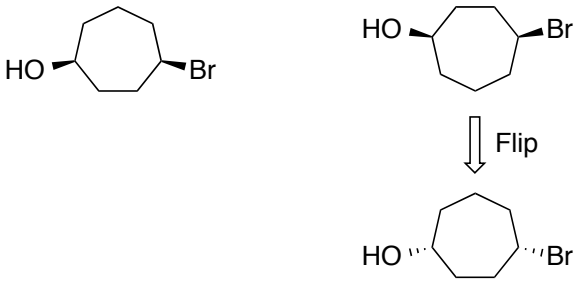


(f) It may be tempting to hastily classify these as diastereomers because they appear to differ in configuration at only one chirality center. But, be sure to take note of the fact that the center bearing two methyl groups is not, in fact, a stereocenter.



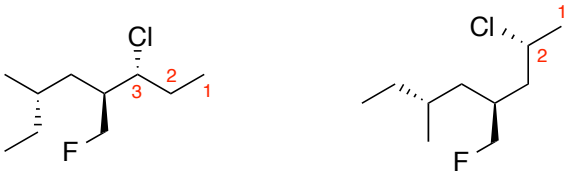
Consequently, we can ignore the wedge and dash notation at that center. Then, it becomes clear that these molecules are in fact identical.

(g) To make a direct comparison between these structures, it is helpful to flip one of them over. Doing so reveals that they are enantiomers since they differ in configuration at both of their stereogenic centers.



(h) It may be tempting to begin to make conformational changes in order to compare the configurations of these molecules directly. However, that is unnecessary in this case. Notice that there is actually a difference in connectivity between the two. The first structure has the chlorine at C3, while the second

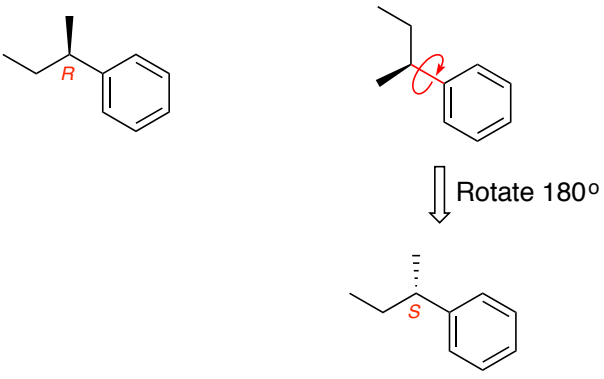
molecule has the chlorine at C2. Therefore, these are constitutional isomers, and we need not compare their configurations.



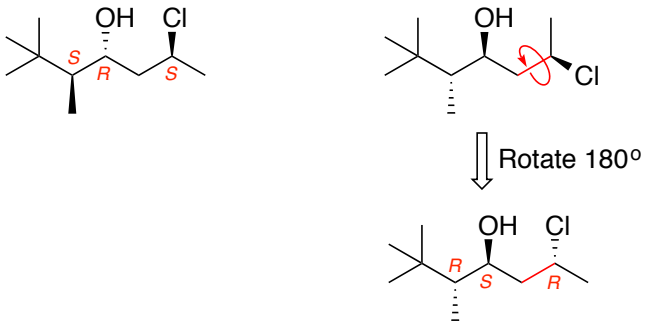
33. While this problem may initially seem daunting, remember that, after determining the configurations for one stereoisomer, you can assign the configurations within other *stereoisomers* by inspection.

(a) The first stereoisomer has *S* and *R* configurations. The second stereoisomer is the same at one center and differs at the other, underscoring the fact that these are diastereomers.

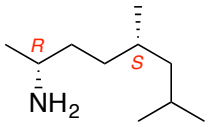
(b) In Problem 32, we made a conformational change to the second stereoisomer in order to directly compare the two. This also facilitates the assignment of configuration. After determining that the first compound has the *R* configuration, we can see that the second molecule must be *S*. This reinforces the conclusion that the two compounds are enantiomers.



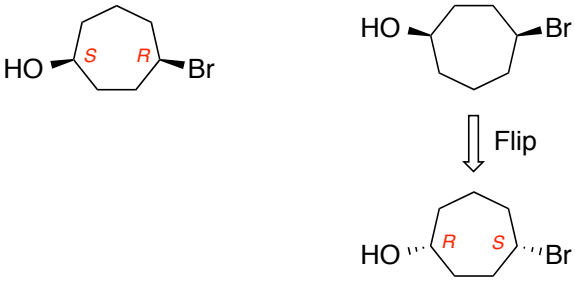
(e) After assigning the configurations within the first molecule, those in the second structure can be rapidly designated by inspection. The fact that the configuration differs at each and every chirality center reinforces the conclusion that these are enantiomers.



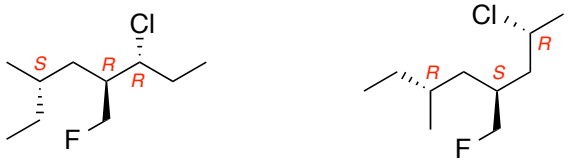
(f) As we determined in Problem 32, the two molecules in this part are identical. The center bearing the amino group has the *R* configuration, while the other stereocenter has the *S* configuration.



(g) Once we assign the configurations in the first molecule, we can tell by inspection that the second molecule simply has the opposite configuration at each of its stereogenic centers. This reinforces the conclusion that these molecules are enantiomers.

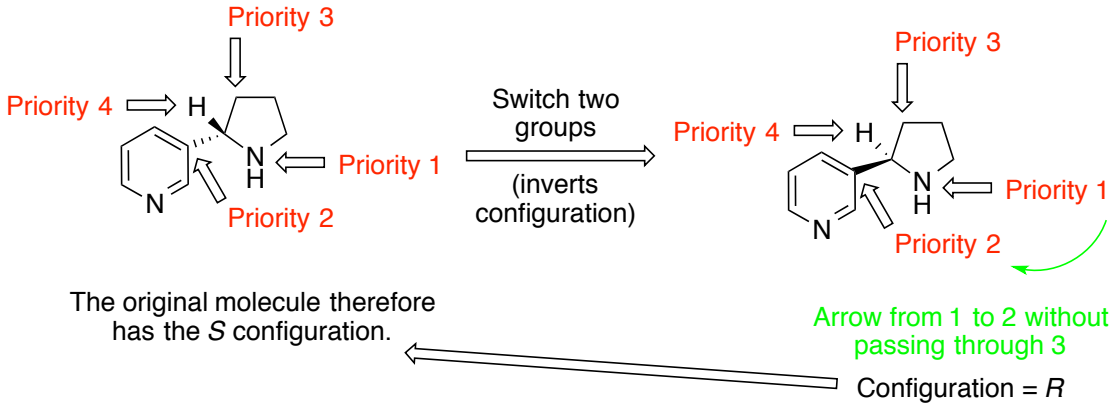


(h) It is important to remember that these molecules are constitutional isomers. Therefore, it would be risky to make direct comparisons between their stereocenters. So, in this last example, it is safest to determine the configuration of each stereocenter in each compound independently.



34.

(a) Nicotine has the *S* configuration.



(b) In solving this equation, it is important to remember that concentration (c) is defined to be in g solute / mL solvent and path length (l) is in decimeters (1 dm = 10 cm).

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{c\ l}$$

$$[\alpha]_{D}^{20} = -169 = \frac{-21^{\circ}}{c\ (0.5\ dm)}$$

$$c = \frac{-21^{\circ}}{(-169)\ (0.5\ dm)} \cong 0.25\ g/mL$$

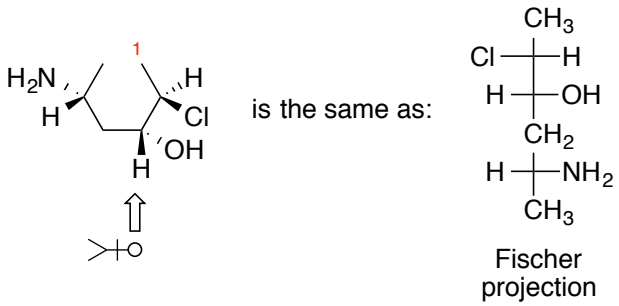
(c) The complete name for nicotine would therefore be (*S*)-(-)-nicotine.

(d) Nicotine's enantiomer would have the opposite configuration and optical activity, making it (*R*)-(+)-nicotine.

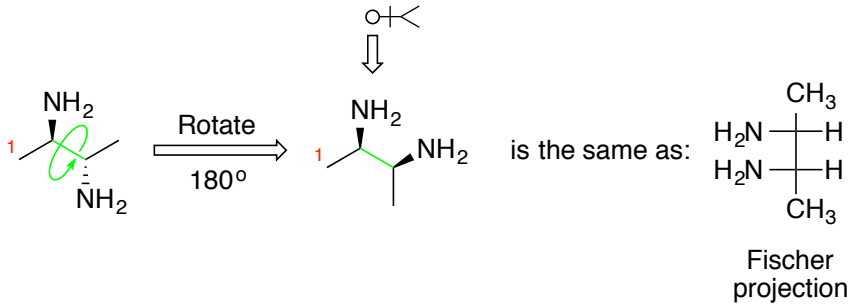
(e) The specific rotation of (*R*)-(+)-nicotine under the same conditions described in part (b) would be +169.

35.

(a) This molecule is already drawn in the proper conformation for a Fischer projection. We need only view it from the appropriate direction, which happens to be from underneath in this case. Remember that C1 must be at the top of the Fischer projection, so the viewer's head must be closer to C1 than their feet.

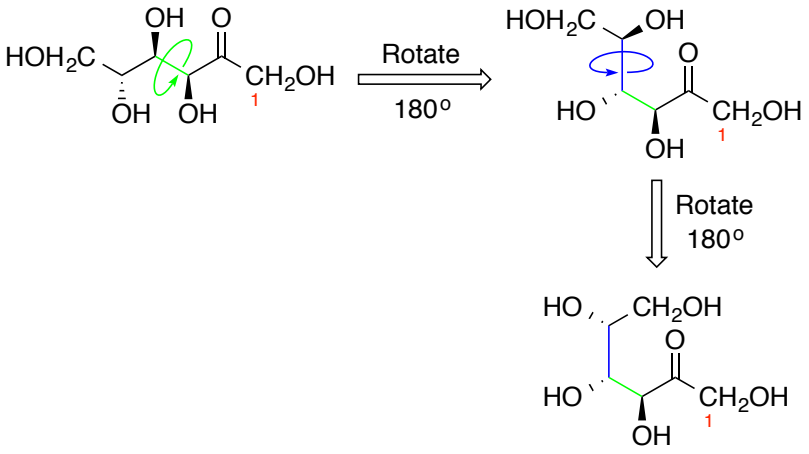


(b) This molecule is not yet properly situated for a Fischer projection. However, a 180° rotation about the central carbon-carbon bond places the compound in the necessary eclipsed conformation. Then, when viewed from above with the viewer's head close to C1, we can observe the structure in a Fischer projection.

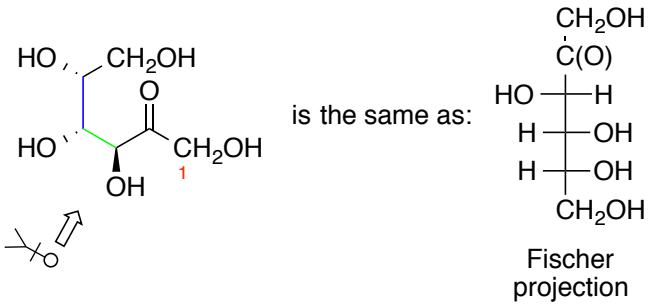


Notice the internal plane of symmetry that makes this compound meso.

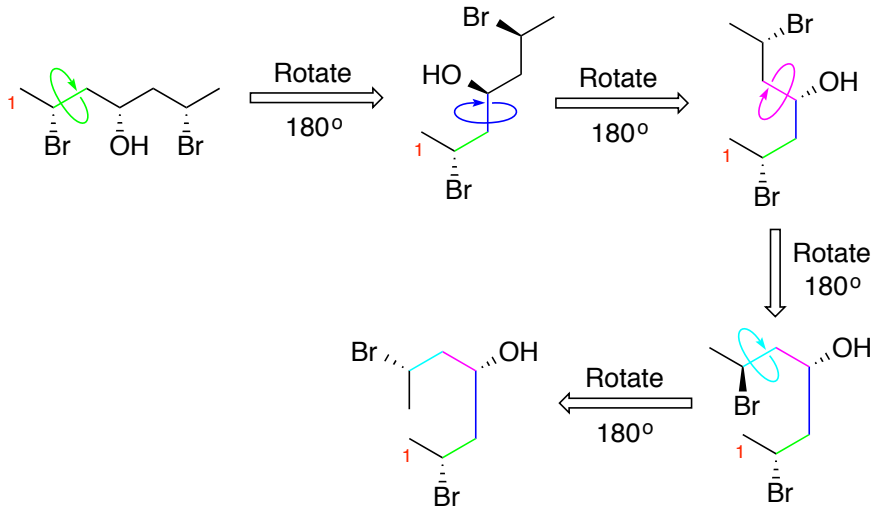
(c) As drawn, fructose also requires conformational changes in order to be viewed as a Fischer projection. Successive rotations about two carbon-carbon bonds yield a conformation suitable for drawing a Fischer projection.



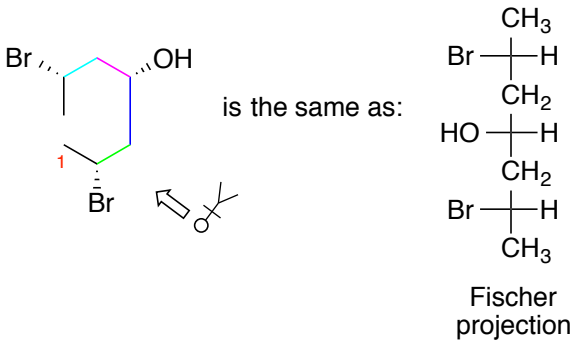
The viewer must approach the molecule from underneath, with his/her head near C1.



(d) This molecule requires several rotations about carbon-carbon bonds in order for it to adopt the conformation necessary for a Fischer projection. Remember that the carbon backbone must continually curl away from the view, and the substituents emanating from the backbone must extend toward the viewer.

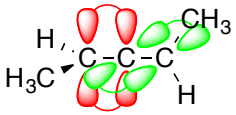


Once it is in the appropriate conformation, the molecule can be viewed from underneath with the viewer's head close to C1. This yields a Fischer projection.

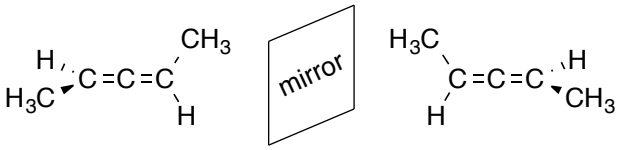


36.

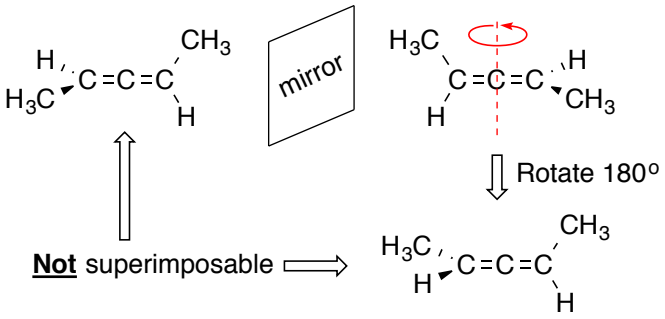
(a) Since the central carbon atom is involved in two π bonds, it is using two orthogonal p orbitals. The red π bond is in the plane of the page, so the sigma bonds on the left-hand allene carbon are perpendicular to that plane. Conversely, the green π bond is perpendicular to the plane of the page, which allows the sigma bonds to reside in the plane of the page.



(b) We can easily draw the mirror image by imagining reflection of the allene through a mirror plane.

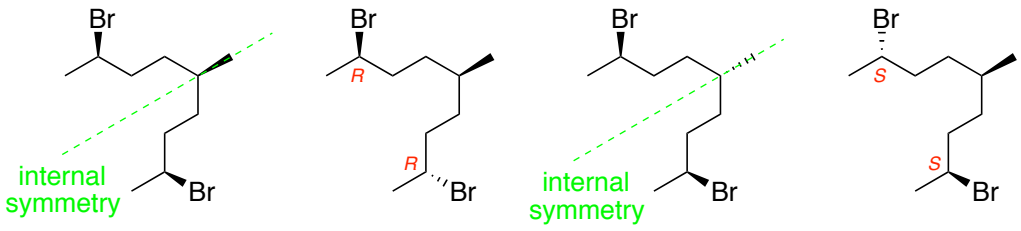


(c) When one of the mirror images is flipped over, we can attempt to align the structures, but the methyl groups on one terminus of the allene are not superimposable.



Since these structures are non-superimposable mirror images, they are enantiomers, despite the fact that the molecule does not contain any chiral carbons.

37. The four stereoisomers of 2,8-dibromo-5-methylnonane are shown below.

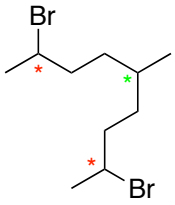


You may have been expecting a maximum of eight stereoisomers for this compound if you counted up to three chirality centers. Two of the four stereoisomers are meso

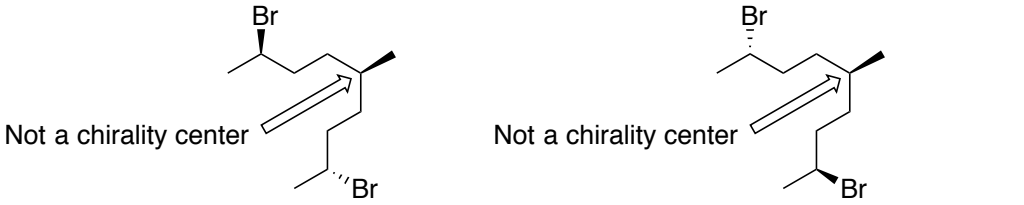
compounds because they have internal symmetry. These meso compounds do not have enantiomers, so this reduces our expectation from eight to six stereoisomers. In the other two stereoisomers (*R*,*R* and *S*,*S*), the central carbon (C5) is *not* a stereocenter because it is attached to two identical alkyl groups. Consequently, placing the methyl group at C5 on the other side of either structure would not actually generate a new stereoisomer. As a result, we can further reduce our expectation from six to four stereoisomers.

The information that follows is not necessary to solve this problem. It is merely provided for your edification.

This is a tricky problem. The compound in question has two stereocenters (*). It also has one additional center that is either not chiral or is a "pseudoasymmetric center" (*).



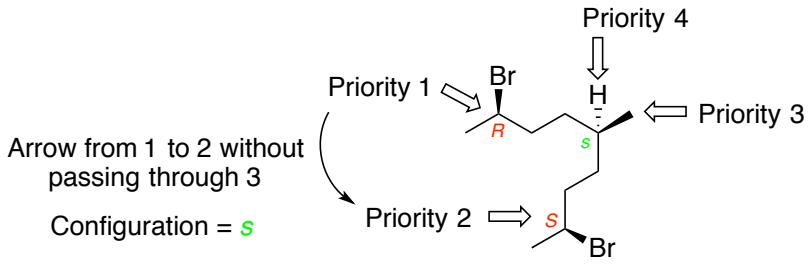
This middle center deserves further comment. When the configurations at C2 and C8 are the same, then the middle center is *not* a stereocenter because it has two identical groups attached to it.



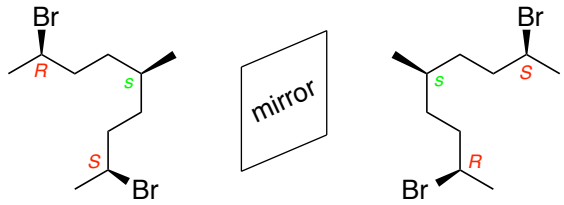
(2*R*,8*R*)-2,8-dibromo-5-methylnonane (2*S*,8*S*)-2,8-dibromo-5-methylnonane

However, if the configurations at C2 and C8 differ, then the middle center is called a "pseudoasymmetric center." It has four different groups attached to it: a hydrogen atom, a methyl group, and two alkyl groups differing in configuration. However, unlike traditional chirality centers, its configuration is not altered by reflection through a mirror plane. It is therefore given a different name to distinguish it from a traditional chirality center, and its configuration is indicated with a lowercase *r* or *s*.

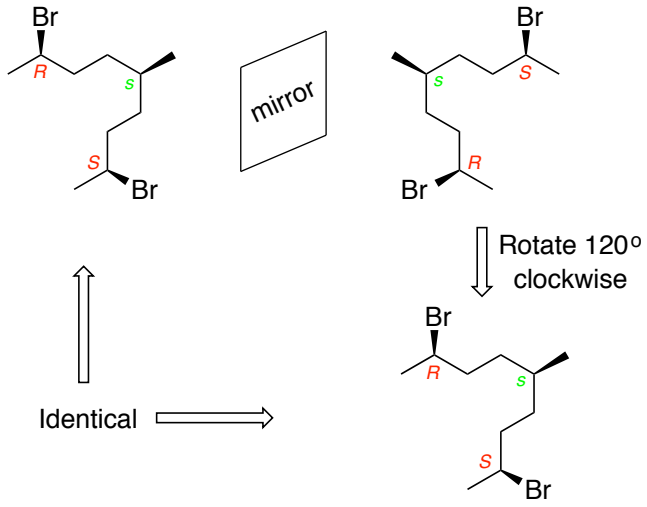
Consider the following stereoisomer. To determine its configuration, you need to know that, when the only difference between two groups is in their configuration, *R* gets a higher priority that *S*. Knowing this, we are able to assign priorities to all four groups and determine that the pseudoasymmetric center has the *s* configuration.



Upon reflection, the configurations of the terminal stereocenters are inverted (*R* to *S* and vice versa). However, the middle center retains the same configuration. This highlights why the middle center is given a different name. It needs to be differentiated from the terminal centers because it has the *s* configuration in both structures, while the traditional stereocenters have different configurations in these molecules.



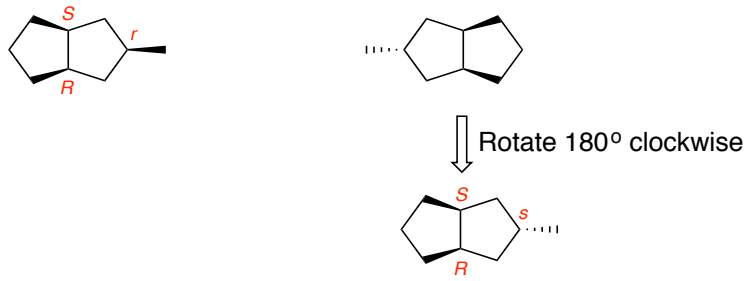
All of this discussion does not change the fact that the stereoisomer in question is meso. Its mirror image is therefore identical to it.



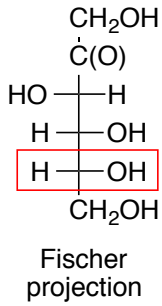
38.

(a) In the first molecule, we can assign the configuration of two centers (*S* and *R*) without a problem. However, we need the extra information from the answer to Problem 37 to determine the configuration of the pseudoasymmetric center. Specifically, we need to know that, when two groups differ only in their

configuration, it is the group with the *R* configuration that receives the higher priority. After having assigned the configurations within the first molecule, we can quickly assign those in the second structure by inspection.



(b) To assign the D or L configuration to a carbohydrate, we examine the penultimate carbon. If its hydroxyl group faces to the right, it is a D sugar. If its hydroxyl group faces to the left, it is an L sugar. Our Fischer projection of fructose from Problem 35(c) reveals that it is a D sugar.



Fischer projection

39.

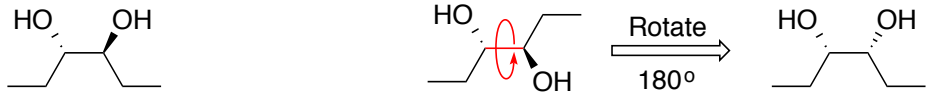
(a) Enantiomers have all the same physical properties, with the exception of specific rotation. They have specific rotations of equal magnitude but opposite sign. On the other hand, diastereomers have completely different and unrelated physical properties.

(1) This first pair of compounds is a pair of enantiomers because they differ in the configuration of each and every chiral center.

As a result, we can say that they will have identical physical properties, with the sole exception being specific rotations of equal magnitude but opposite sign.

(2) To determine the relationship between these compounds, it is wise to begin by putting them in directly comparable conformations. A 180° rotation about the

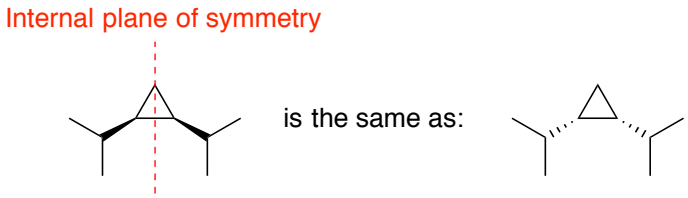
central carbon-carbon bond of the latter compound makes it clear that it is a diastereomer of the first compound.



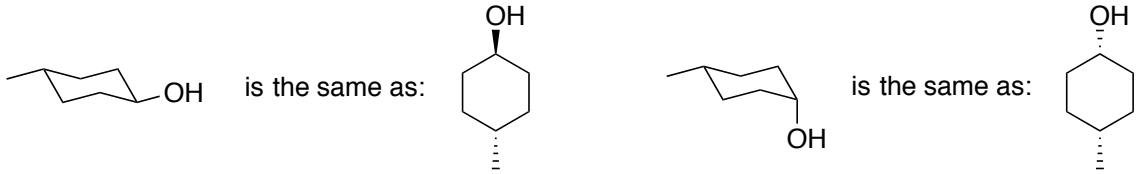
Although the latter compound has internal symmetry (and is therefore meso), this only precludes it from having an enantiomer. It can still possess diastereomers, and the first compound is an example of one.

Insofar as these compounds are diastereomers, we can predict that they will have different and entirely unrelated physical properties. We can also say that the meso compound will have a specific rotation of zero since it is achiral.

(3) These molecules are superimposable mirror images, due to the internal plane of symmetry present in each. As a result, they are identical and will therefore have completely identical properties.



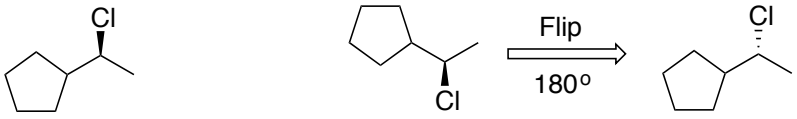
(4) These compounds are diastereomers. This may be more apparent if they are drawn with the ring in the plane of the page. Doing so highlights the fact that they are *trans*/*cis* geometric isomers.



As diastereomers, these molecules are expected to have different and unrelated physical properties.

(b) Enantiomers react identically with achiral reagents but differently with chiral reagents. Diastereomers, on the other hand, react differently with all reagents (achiral or chiral).

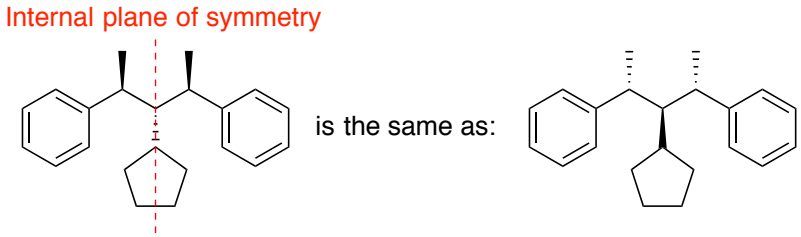
(1) These compounds are enantiomers, a fact that is clearer when one of the two is flipped over.



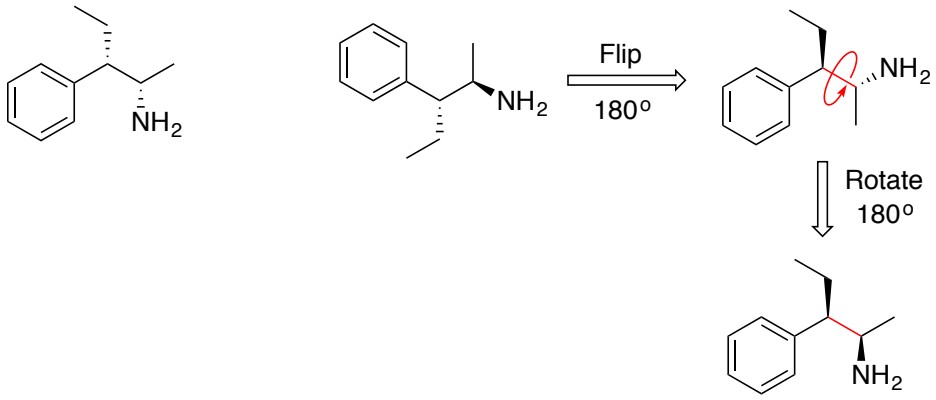
As enantiomers, they will react identically with achiral reagents but differently with chiral reagents.

(2) These molecules differ in the configuration of one out of two stereocenters. Consequently, they are diastereomers and are expected to react differently with all reagents.

(3) Due to the internal plane of symmetry, these mirror images are superimposable. The molecules are therefore identical and will react identically with any reagents (achiral or chiral).



(4) These molecules are enantiomers, but that is not obvious until they are arranged in a comparable fashion. This can be accomplished by flipping the latter structure and then rotating 180° about the carbon-carbon bond that unites the stereocenters.



As enantiomers, we can expect these compounds to react identically with achiral reagents. They will, however, react differently with chiral reagents.

40. Enantiomeric excess is calculated as follows. In the denominator, we should use the specific rotation of the pure enantiomer that has the same sign as that of the mixture [i.e., the specific rotation of (*S*)-carvone, which is +61].

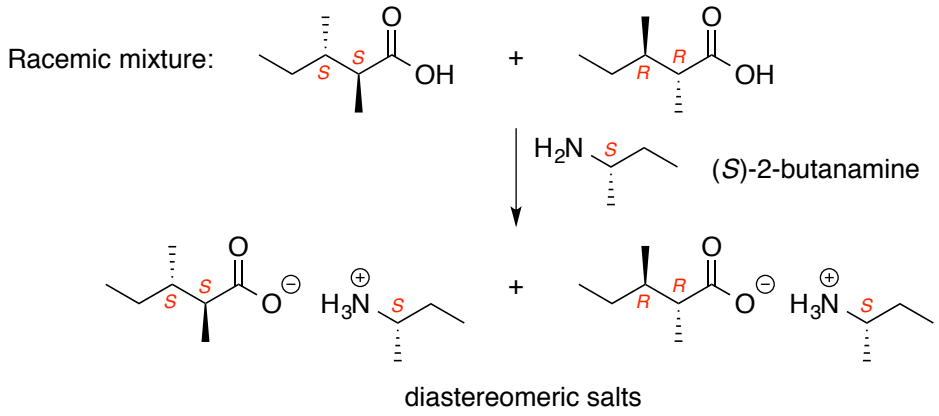
$$ee = \frac{+45}{+61} \times 100 = 74\%$$

We know that (*S*)-carvone is the major enantiomer because it has the same sign for specific rotation as the mixture does. To figure out how much of the mixture is (*S*)-carvone, we add the following two equations.

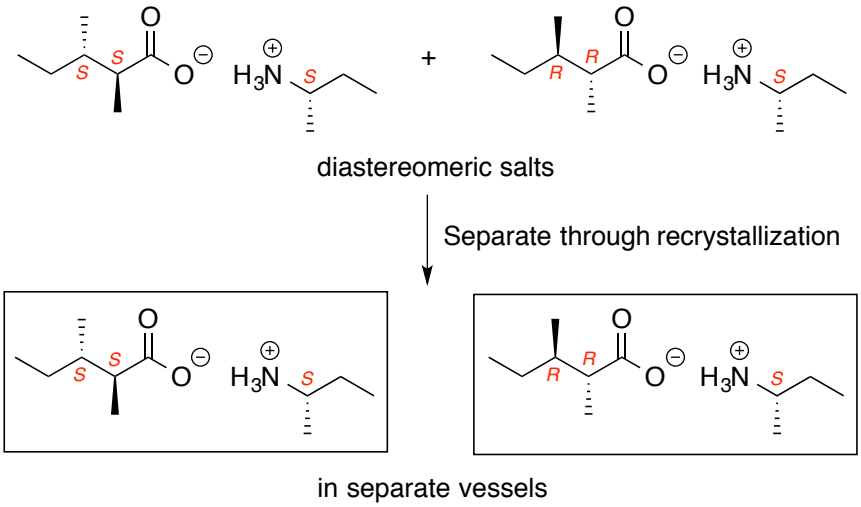
$$\%\ major\ enantiomer + \%\ minor\ enantiomer = 100\%$$
$$\underline{\%\ major\ enantiomer - \%\ minor\ enantiomer = 74\%}$$
$$2\ (\%\ \text{major enantiomer}) = 174\%$$
$$\%\ \text{major enantiomer} = 87\%$$

Thus, (*S*)-carvone accounts for 87% of the mixture, and (*R*)-carvone is the remaining 13% of the mixture.

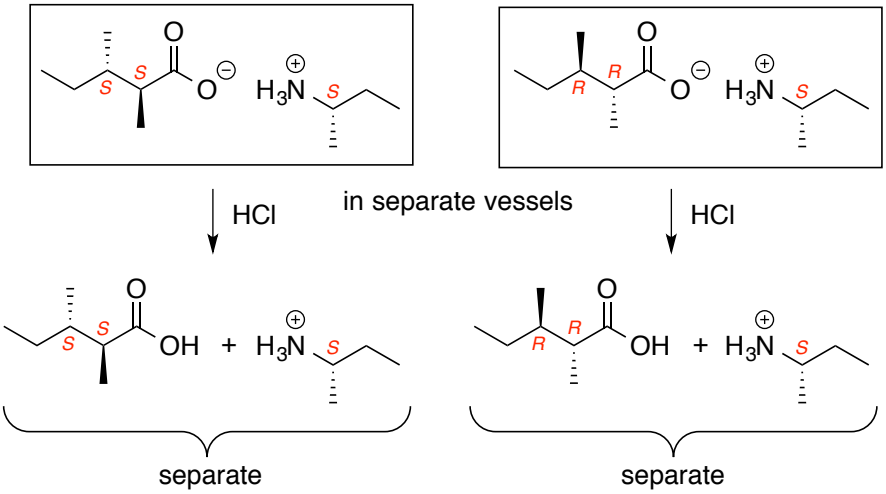
41. Although the enantiomeric carboxylic acids each contain two stereocenters, this changes nothing about the process of resolution. The racemic mixture can be treated with a chiral, non-racemic amine, such as (*S*)-2-butanamine (shown below). This results in the formation of diastereomeric salts.



The diastereomeric salts can be separated through recrystallization because they have different properties, including solubility.



Once they have been separated and are in different vessels, treatment with acid will regenerate the neutral carboxylic acid mixed with the ammonium ion formed from the resolving agent. These compounds are quite different and can be readily separated, through an aqueous wash for instance.



Solutions to Problems for Chapter 5: Infrared Spectroscopy and Nuclear Magnetic Resonance Spectroscopy

1.

(a) Radio waves have the lowest frequency. They are followed by microwaves, infrared, visible, ultraviolet, and X rays. Finally, gamma rays have the highest frequency.

radio waves < microwaves < infrared < visible < ultraviolet < X rays < gamma rays

(b) Since wavelength is inversely proportional to frequency, the order is reversed. Gamma rays have the smallest wavelength. They are followed by X rays, ultraviolet, visible, infrared, and microwaves. Finally, radio waves have the largest wavelength.

gamma rays < X rays < ultraviolet < visible < infrared < microwaves < radio waves

(c) Energy is directly proportional to frequency (and inversely proportional to wavelength). Therefore, the order is the same as in part (a). Radio waves are the lowest energy form of light. They are followed by microwaves, infrared, visible, ultraviolet, and X rays. Finally, gamma rays have the highest energy.

radio waves < microwaves < infrared < visible < ultraviolet < X rays < gamma rays

2. The two important trends to consider are: (1) stronger bonds have higher vibrational frequencies, and (2) lighter atoms yield higher vibrational frequencies.

(a) A double bond is stronger than a single bond, so the carbonyl (C=O) is expected to have the higher vibrational frequency.

(b) Since fluorine is lighter than chlorine, the C-F bond will have the higher vibrational frequency.

(c) A triple bond is stronger than a double bond, so the nitrile (C≡N) will have the higher vibrational frequency.

(d) Hydrogen is lighter than carbon, so the C-H bond will have the higher vibrational frequency.

3. The wavenumber is simply the frequency divided by the speed of light, so wavenumber is directly proportional to frequency.

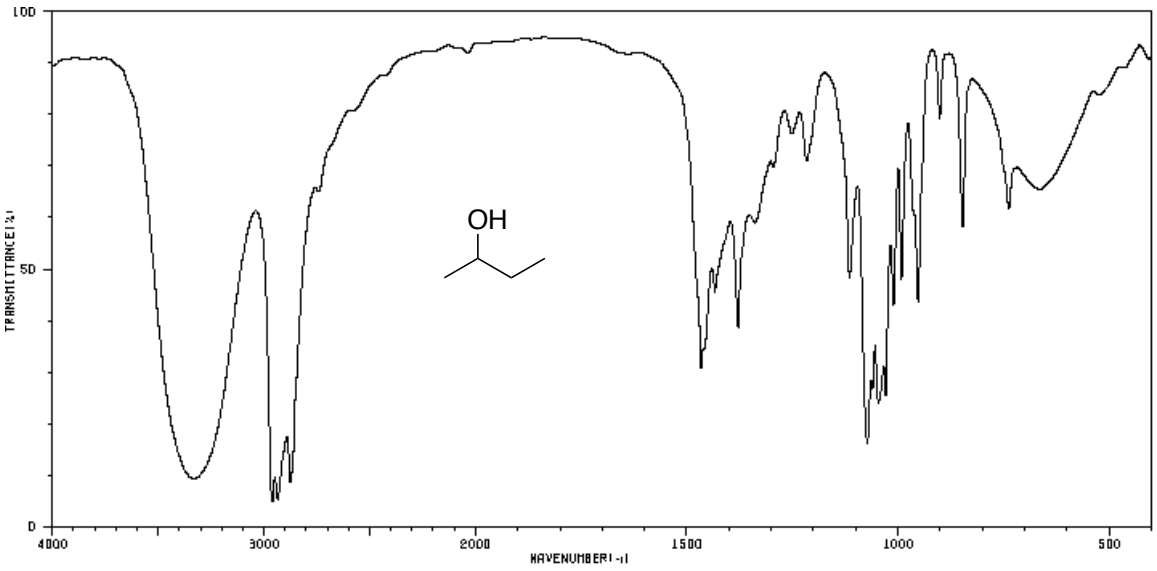
(a) Since the carbonyl (C=O) has the higher vibrational frequency, it also exhibits a signal at a higher wavenumber.

(b) Since the C-F bond has the higher vibrational frequency, it also resonates at a higher wavenumber.

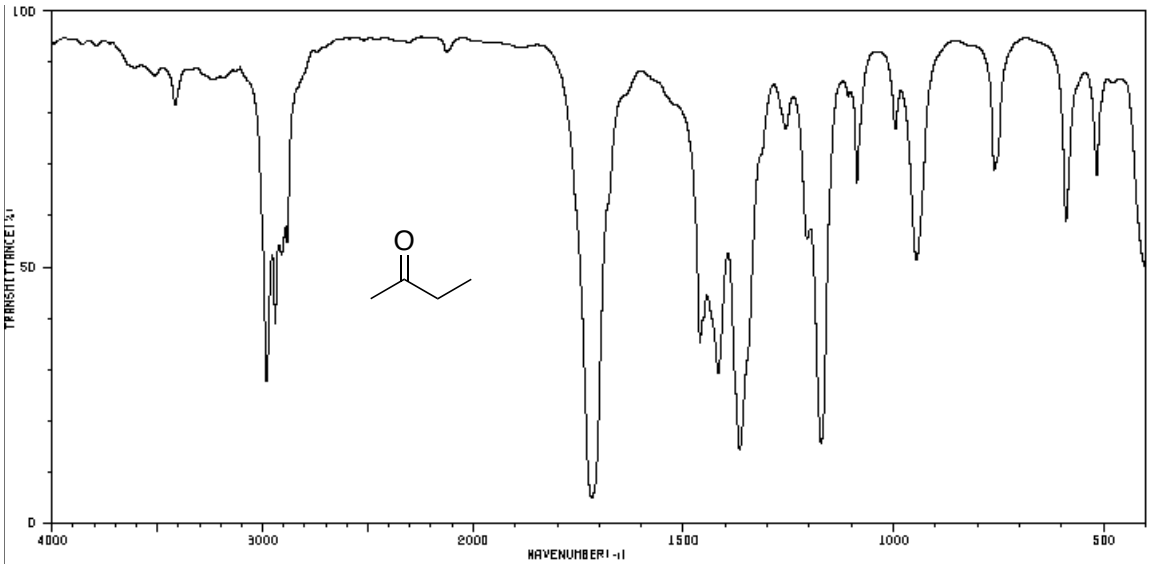
(c) Since the nitrile (C≡N) has the higher vibrational frequency, it also has a signal at a higher wavenumber.

(d) Since the C-H bond has the higher vibrational frequency, its signal appears at a higher wavenumber.

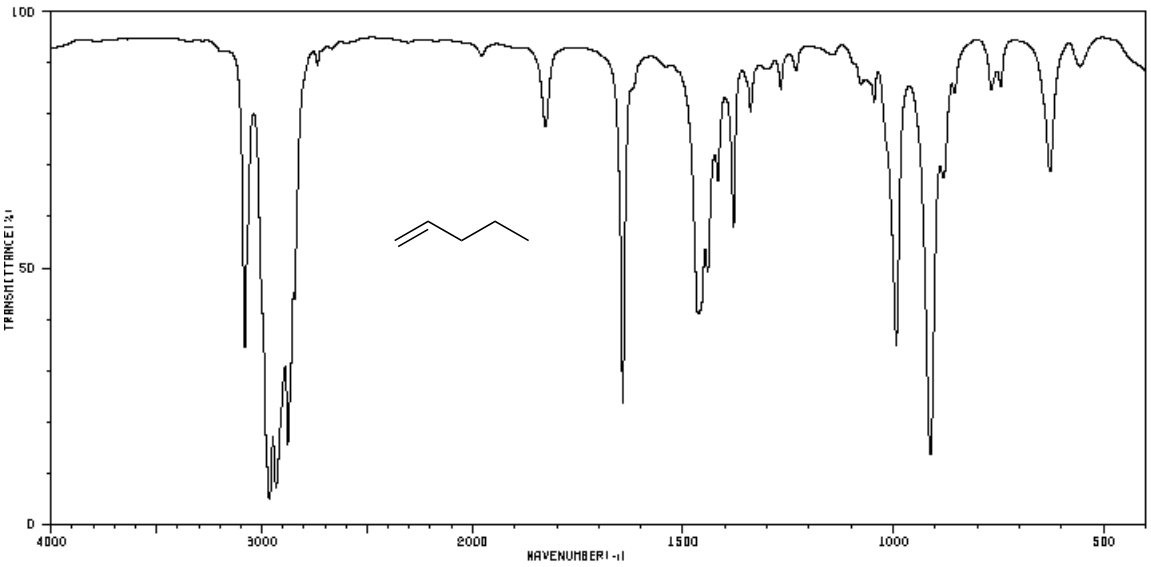
4. The first IR spectrum has a large signal centered around 3350 cm^{-1}. This is indicative of heteroatom-to-hydrogen (i.e., alcohol O-H or N-H) stretching. It also has signals appearing below 3000 cm^{-1}, indicating sp^3 C-H stretching. These signals are consistent with the alcohol.



The second IR spectrum has a prominent signal at ~1700 cm^{-1}, which reveals the presence of a carbonyl. It also displays signals below 3000 cm^{-1} for sp^3 C-H stretching. These features are compatible with the ketone.

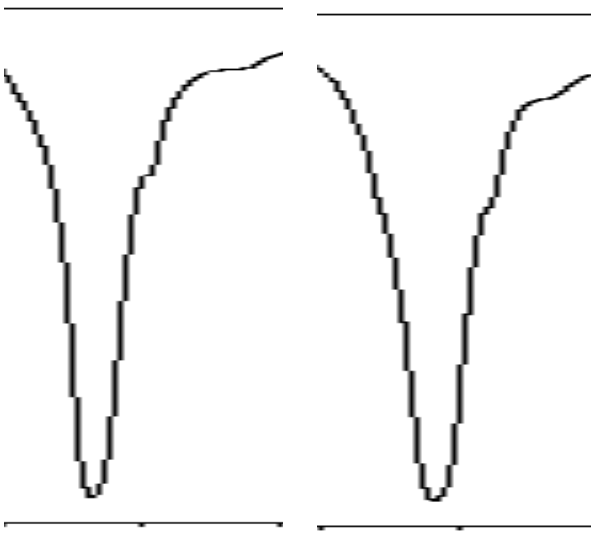


The final IR spectrum has a signal just above 3000 cm^{-1}, as well as signals just below 3000 cm^{-1}. These indicate sp^2 and sp^3 C-H stretching, respectively. The alkene has both types of C-H bonds.



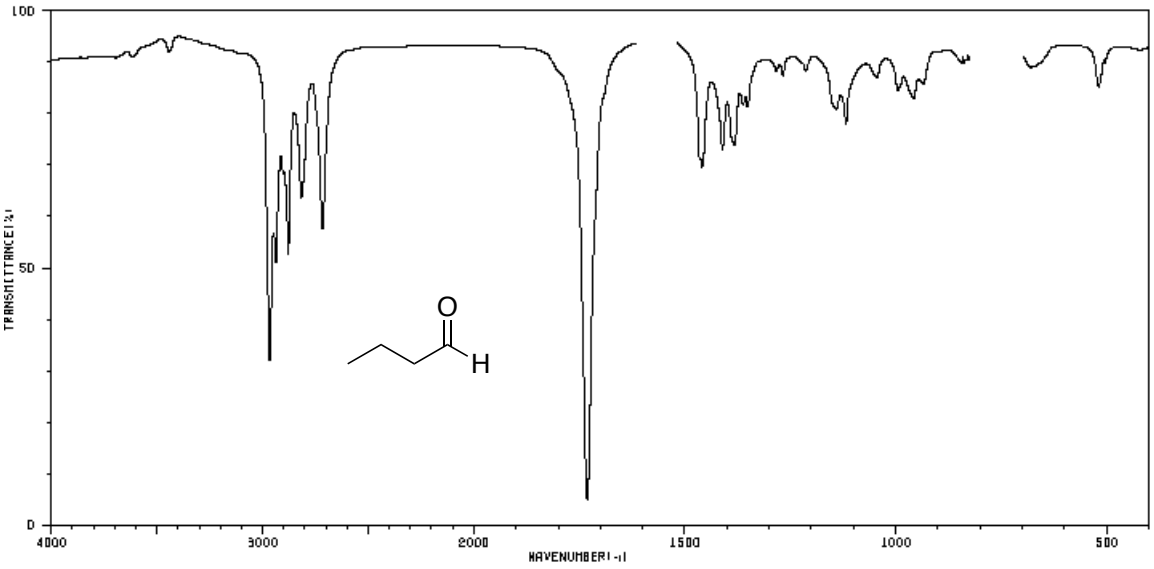
5. The alkene's IR spectrum also displays C=C stretching at ~1650 cm^{-1}.

6. Although the two spectra are quite similar, the first one has a carbonyl resonance appearing at a higher frequency. This is more apparent in the diagrams below, which zoom in on solely the carbonyl signal in each spectrum.

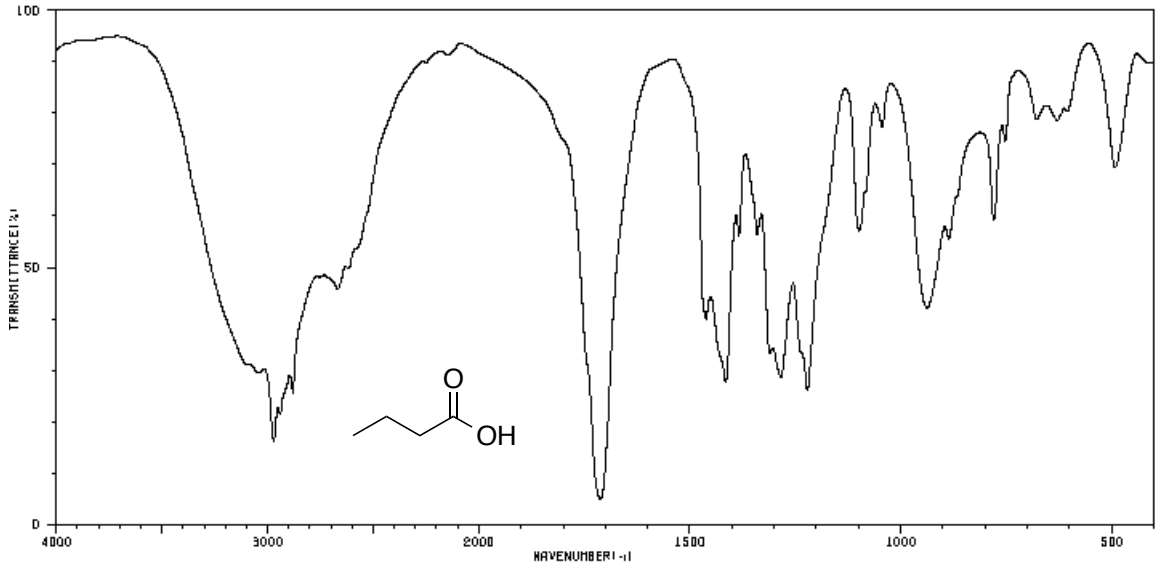


The first spectrum—with the higher-frequency carbonyl signal—is the ester.

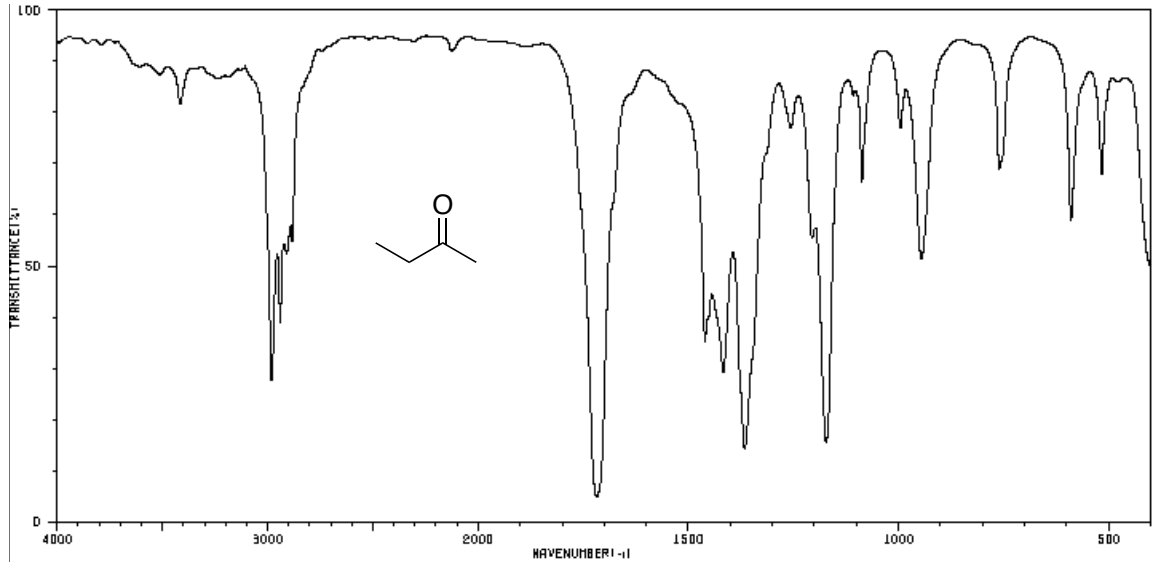
7. The first IR spectrum has a carbonyl resonance in the low 1700 cm^{-1} range. Given the absence of any heteroatom-to-hydrogen stretching, this could be consistent with the ketone or aldehyde. The correlation table presented earlier in this section allows us to differentiate the two because aldehydes also exhibit a special sp^2 C-H stretch at 2700 – 2800 cm^{-1}. This spectrum has that feature, so it can be matched with the aldehyde.



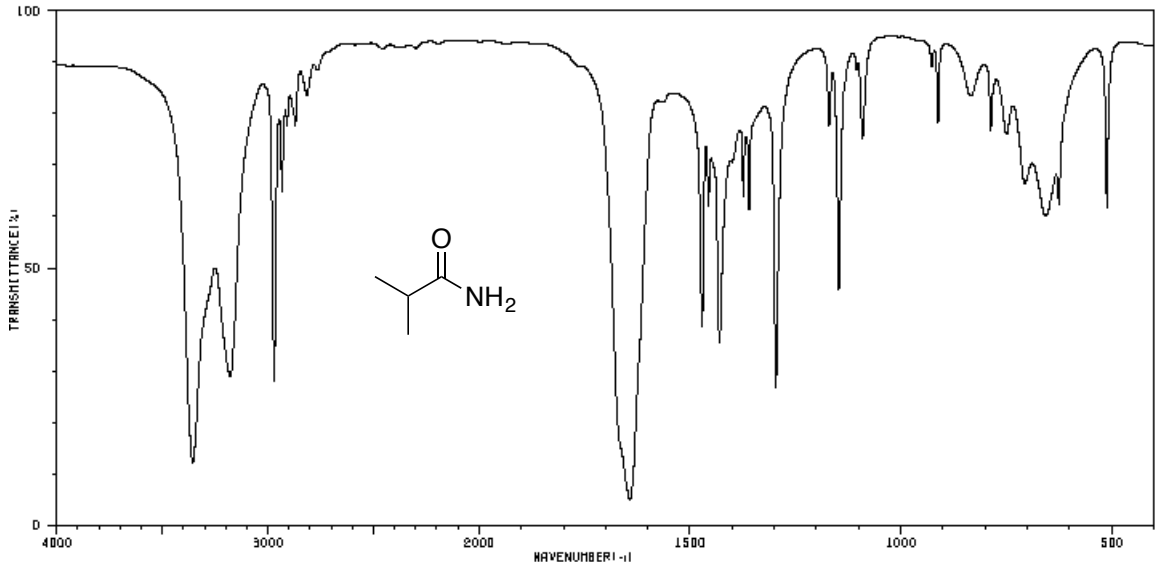
The second spectrum has, in addition to the carbonyl resonance, a broad signal from 2500 – 3500 cm^{-1}. The correlation table shows that this is the O-H stretch of a carboxylic acid.



The third spectrum has a carbonyl resonance in the low 1700 cm^{-1} range, no heteroatom-to-hydrogen stretching, and no aldehyde (sp^2) C-H stretch. It therefore matches the structural features of the ketone.

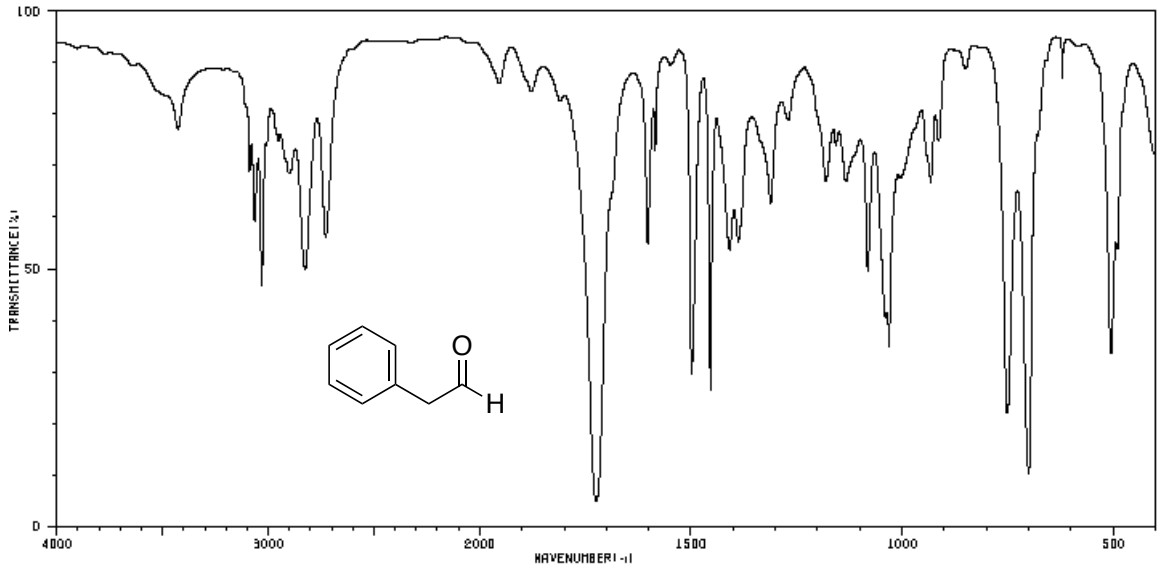


The final spectrum has a low carbonyl resonance appearing at ~1650 cm^{-1}. It also has clear heteroatom-to-hydrogen stretching consistent with N-H bonds. This is the amide.



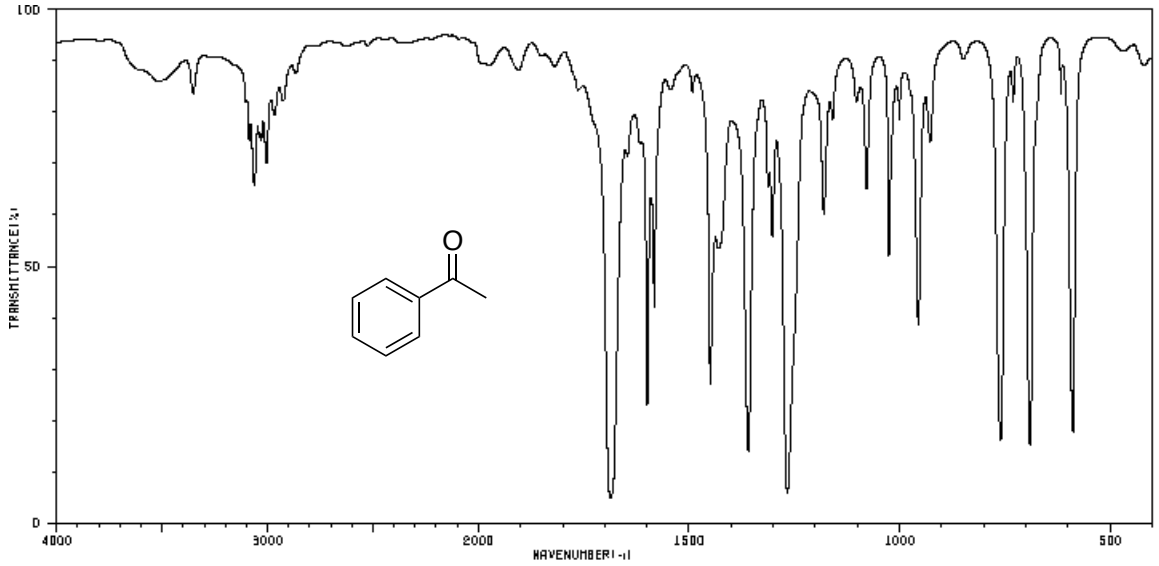
We will address the unique shape of the signals in the heteroatom-to-hydrogen stretching region very soon.

8. The first IR spectrum has a carbonyl resonance slightly above 1700 cm^{-1}. This is consistent with an unconjugated ketone or aldehyde with no ring strain. It therefore matches best with the aldehyde.

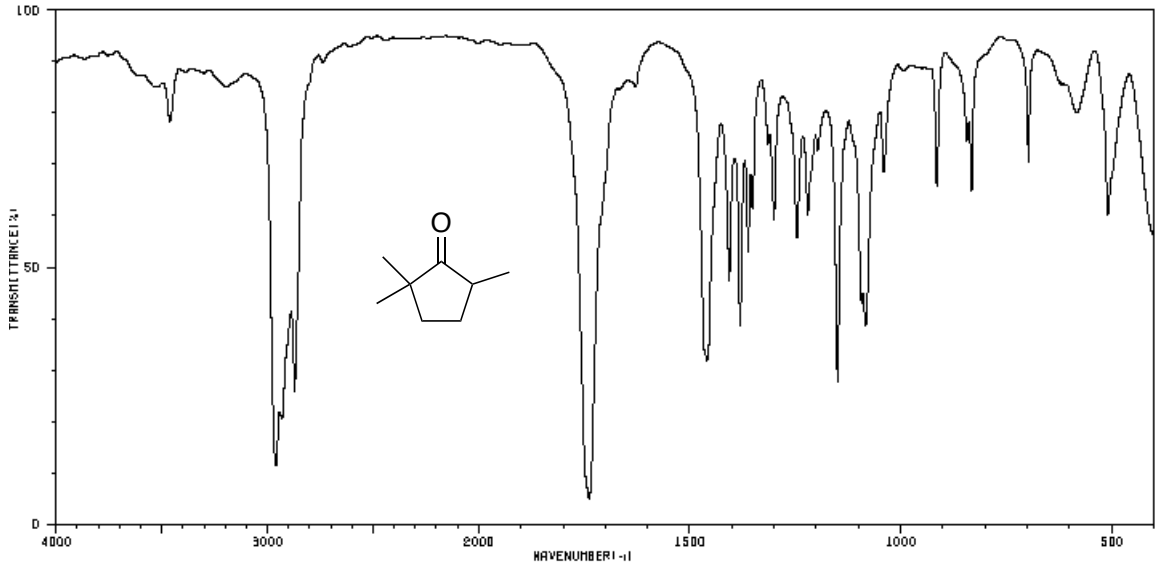


Notice that this spectrum also has the characteristic aldehyde (sp^2) C-H stretch between 2700 and 2800 cm^{-1}.

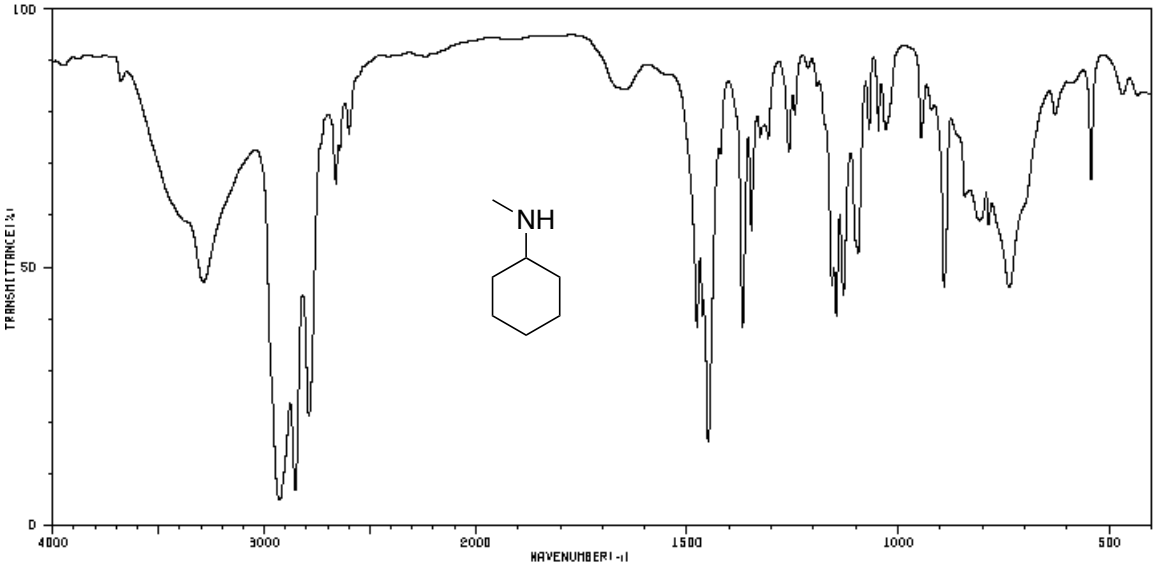
The second IR spectrum has a carbonyl signal that is below 1700 cm^{-1}. This indicates a conjugated ketone or aldehyde, and as a result matches the conjugated ketone.



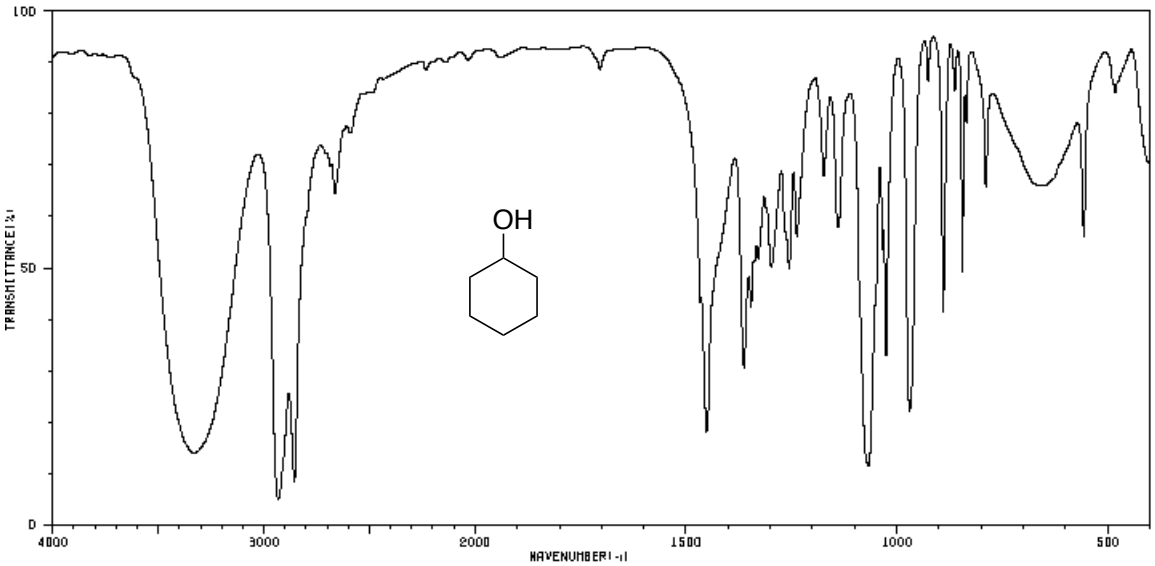
The final IR spectrum has a carbonyl resonance at about 1750 cm^{-1}. Recall that ketones in rings smaller than six atoms have elevated stretching frequencies. This spectrum therefore matches the five-membered cyclic ketone.



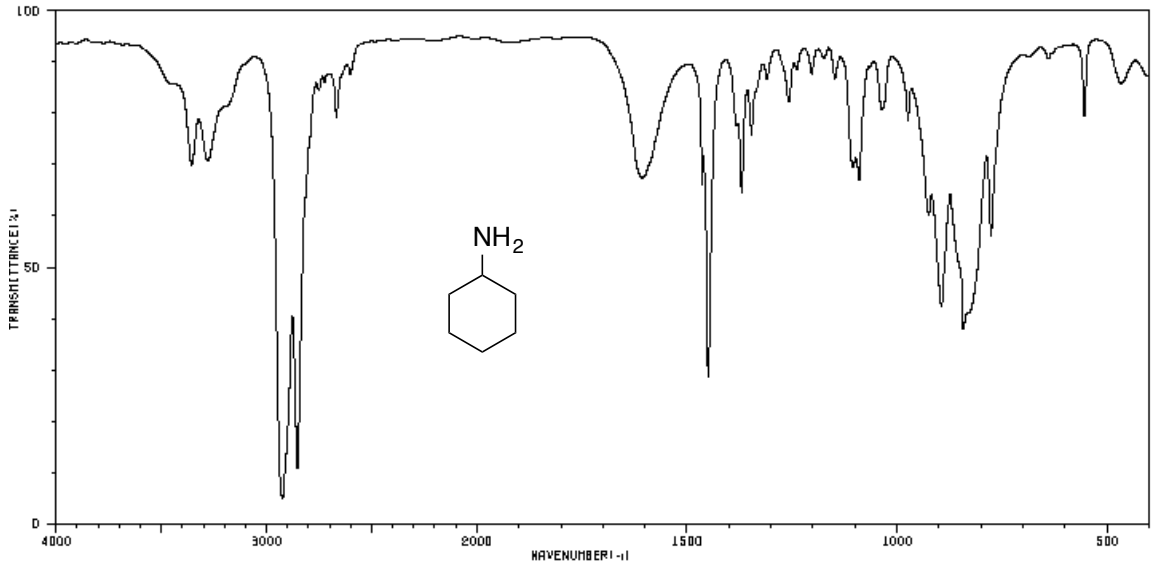
9. The first spectrum has a moderately intense signal in the heteroatom-to-hydrogen stretching region. It is a single signal and is somewhat sharp. These features are indicative of N-H stretching.



The second spectrum has a much more intense, broad signal in the heteroatom-to-hydrogen stretching region. This is consistent with alcohol O-H stretching.



The final spectrum has modest signals in the heteroatom-to-hydrogen stretching region. Additionally, there are two of these sharper signals, which imply the N-H stretching of an NH_2 group.



10.

(a)

$$DOU = \frac{[2n+2] - hydrogens\ in\ formula}{2}$$

$$DOU = \frac{[2(3)+2] - 4}{2} = 2$$

This molecule has two degrees of unsaturation, so it could contain two π bonds, two rings, or one of each. However, it is not feasible to have two rings when there are only three carbons. Three structures consistent with this formula are:

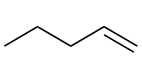
$H_2C{=}C{=}CH_2$ $H_3C{-}C{\equiv}CH$ 

(b)

$$DOU = \frac{[2n+2] - hydrogens\ in\ formula}{2}$$

$$DOU = \frac{[2(5)+2] - 10}{2} = 1$$

This molecule has one degree of unsaturation, so it contains either a π bond or a ring. While there are many structures with this formula, three examples are shown below.

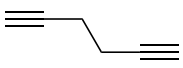
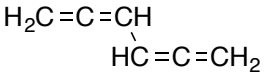


(c)

$$DOU = \frac{[2n+2] - hydrogens\ in\ formula}{2}$$

$$DOU = \frac{[2(6)+2] - 6}{2} = 4$$

This molecule must have some combination of π bonds and rings totaling four degrees of unsaturation. Three structures having this molecular formula are shown below.

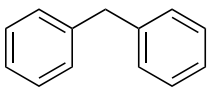
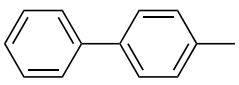
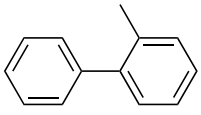
Notice that the benzene ring (the last entry) accounts for four degrees of unsaturation because of its three π bonds and one ring. This is a commonly occurring structural feature, so it is useful to take note of the degrees of unsaturation it contributes to a molecule.

(d)

$$DOU = \frac{[2n+2] - hydrogens\ in\ formula}{2}$$

$$DOU = \frac{[2(13)+2] - 12}{2} = 8$$

This molecule has a large number of degrees of unsaturation. In such situations, it helps to think of larger structural fragments that account for a block of DOUs. Recall from part (c) above that the benzene ring accounts for four degrees of unsaturation. Therefore, we could imagine structures containing two benzene rings, such as:

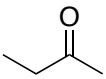
11.

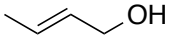
(a) Recall that the presence of oxygen in the formula does not alter the DOU calculation. The oxygen atoms are simply ignored in the calculation.

$$DOU = \frac{[2n+2] - hydrogens\ in\ formula}{2}$$

$$DOU = \frac{[2(4)+2] - 8}{2} = 1$$

The molecule must have one ring or one π bond, such as it does in the following examples.



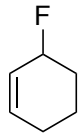


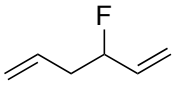
(b) Halogens are monovalent, like hydrogens. Since they effectively take the place of hydrogen atoms in a structure, they are counted as "hydrogen equivalents" in the DOU calculation.

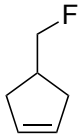
$$DOU = \frac{[2n+2] - hydrogens\ and\ hydrogen\ equivalents\ in\ formula}{2}$$

$$DOU = \frac{[2(6)+2] - 10}{2} = 2$$

This molecule must have two π bonds, two rings, or one of each. Some examples follow.





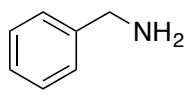


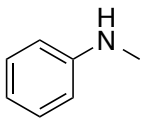
(c) The nitrogen atom counts as half of a carbon atom in the DOU calculation.

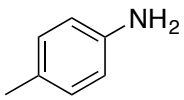
$$DOU = \frac{[2n+2] - hydrogens\ in\ formula}{2}$$

$$DOU = \frac{[2(7.5)+2] - 9}{2} = 4$$

With four degrees of unsaturation, a benzene ring could be a fragment of the molecule. Three sample structures are shown below.





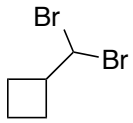


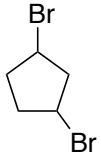
(d) The halogens must be counted as "hydrogen equivalents" in the DOU calculation.

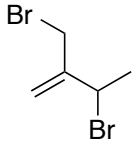
$$DOU = \frac{[2n+2] - hydrogens\ and\ hydrogen\ equivalents\ in\ formula}{2}$$

$$DOU = \frac{[2(5)+2] - 10}{2} = 1$$

The structure must contain one ring or one π bond. A few examples follow.





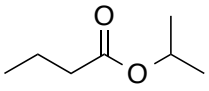


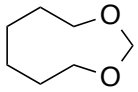
(e) Oxygens do not affect the DOU calculation, so they are simply ignored.

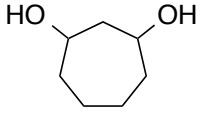
$$DOU = \frac{[2n+2] - hydrogens\ in\ formula}{2}$$

$$DOU = \frac{[2(7)+2] - 14}{2} = 1$$

The molecule must have a ring or a π bond, as in the following examples.





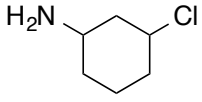


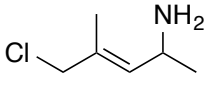
(f) The nitrogen atom counts as half of a carbon atom for the purpose of the calculation, and the halogen must be counted as a "hydrogen equivalent."

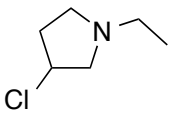
$$DOU = \frac{[2n+2] - hydrogens\ and\ hydrogen\ equivalents\ in\ formula}{2}$$

$$DOU = \frac{[2(6.5)+2] - 13}{2} = 1$$

This structure must therefore contain a ring or a π bond. Three examples are shown below.







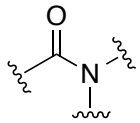
12. Our algorithm for structure solving begins with the calculation of degrees of unsaturation. Remember that, while oxygen atoms do not affect the calculation, the nitrogen atom must be counted as half a carbon.

$$DOU = \frac{[2n + 2] - hydrogens\ in\ formula}{2}$$

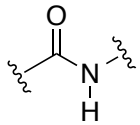
$$DOU = \frac{[2(8.5) + 2] - 9}{2} = 5$$

With a large number of degrees of unsaturation, we usually consider the presence of a benzene ring in the molecule. This will account for four of the five degrees of unsaturation, leaving only one more DOU to explain. We now have one fragment:

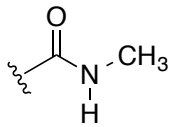
The next step in the algorithm is to spot-check the IR spectrum in three key regions. The carbonyl region contains a signal just below 1650 cm^{-1}. A carbonyl with a resonance this low can easily be confused with C=C stretching, which appears around 1650 cm^{-1}. One feature that helps to distinguish the two types of peaks is that carbonyl signals tend to be more intense, as the one in this spectrum is. A carbonyl resonance this low is indicative of an amide, giving us a second fragment.



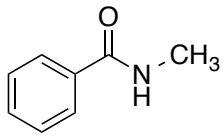
We see signals both above and below 3000 cm^{-1}, which reveal the presence of sp^2 and sp^3 C-H stretching, respectively. Additionally, there is a sharp signal in the heteroatom-to-hydrogen stretching region that suggests an N-H bond. This allows us to revise our amide fragment to:



At this point, it is helpful to compare the molecular formula to the fragments that we've accumulated. There are six carbons in the benzene ring and one in the amide. This leaves us with one additional carbon to incorporate into the structure. Given that the amide can only have one N-H bond (because we don't see two peaks in the heteroatom-to-hydrogen stretching region), the remaining carbon must be bonded to the amide nitrogen. We therefore revise the amide fragment once again:



There is only one way to piece together the two large fragments we've developed. This gives the structure of the unknown.



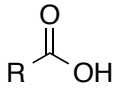
13. Structure solving should always begin with a DOU calculation when a molecular formula is provided. Oxygen atoms may be ignored because they do not affect this calculation.

$$DOU = \frac{[2n + 2] - hydrogens\ in\ formula}{2}$$

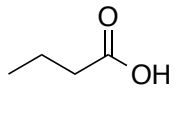
$$DOU = \frac{[2(4) + 2] - 8}{2} = 1$$

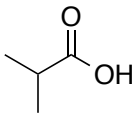
The molecule contains a ring or a π bond, but we must reserve judgment on which one until we consult the spectral data.

The next step in our algorithm is to spot-check three critical regions of the IR spectrum. The carbonyl region does indeed contain a signal at ~1700 cm^{-1}. The C-H stretching region is obscured by a massive signal extending from 2500 – 3500 cm^{-1}. This very broad resonance is the O-H stretch of a carboxylic acid. Of course, carboxylic acids also contain carbonyls, which explains the signal at 1700 cm^{-1}. The carbonyl π bond accounts for the one degree of unsaturation in the molecule.



There are three carbons remaining in the structure. These can be placed on the carbonyl carbon in one of two ways, yielding two reasonable structures for this unknown.





14. Remember to begin by calculating DOUs. Oxygen does not affect the calculation, so it can be ignored.

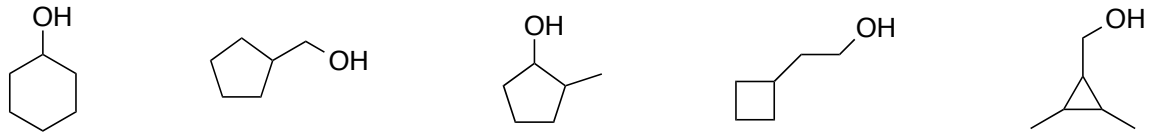
$$DOU = \frac{[2n+2] - hydrogens\ in\ formula}{2}$$

$$DOU = \frac{[2(6)+2] - 12}{2} = 1$$

This compound must have a ring or a π bond. Be sure to reserve judgment on which one to include in the structure until we examine the spectrum.

We can now proceed to spot-check the IR spectrum. This molecule has no carbonyl resonance. It has sp^3 C-H stretching below 3000 cm^{-1} but no sp^2 stretching above 3000 cm^{-1}. It also has a broad stretch centered around 3350 cm^{-1} that suggests the O-H stretch of an alcohol.

There is no evidence for a π bond in this molecule because there is no carbonyl signal and no sp^2 C-H stretching (or C=C stretching for that matter). Therefore, the DOU should be a ring. The ring could be 3, 4, 5, or 6 atoms in size. Combining this observation with the presence of an alcohol in the structure, we can propose many possible structures for this molecule, a few of which are shown below.



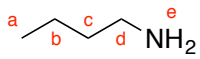
15.

(a) Cyclopropane will exhibit only one signal in the proton NMR. All of its protons are equivalent due to the molecule's symmetry.

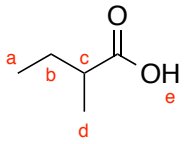
(b) This alcohol, known as isopropyl alcohol, will have three signals in the proton NMR spectrum. The two methyl groups (a) are equivalent to one another because they branch from the same carbon. The methine (i.e., CH) group (b) is unique because it is the only CH in the molecule. The proton of the hydroxyl group (c) is also unique.

(c) This amine will display five proton NMR signals. The methyl group (a) is unique in that it is the only CH_3 group in the molecule. While there are three methylenes

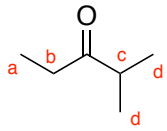
(i.e., CH2 groups), each is located at a different distance from the amino group. This places each methylene (b, c, and d) in a unique chemical environment and causes it to display its own proton NMR signal. Finally, the protons of the amino group (e) are one last type of chemically unique hydrogen and will therefore cause their own signal.



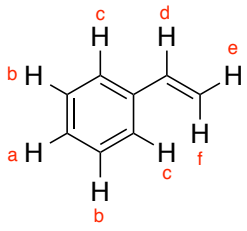
(d) This carboxylic acid will also yield five signals in the proton NMR spectrum. While there are two methyl groups in the molecule (a and d), they are at different locations relative to the acid and are therefore in unique chemical environments. As such, they produce distinct signals. The methylene (b) and the methine (c) each generate a signal. Finally, the carboxylic acid proton itself (e) causes a separate signal as well.



(e) This ketone will give a proton NMR spectrum with four signals. There are three methyl groups in the molecule. Two (d) stem from the same carbon and are therefore identical, while the third (a) is in a different chemical environment. The methylene (b) and the methine (c) each produce a separate signal as well.

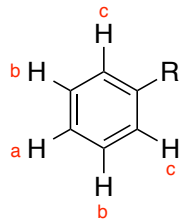


(f) This molecule is known as styrene. It will produce a proton NMR spectrum having six signals. Here, we must carefully consider the issue of symmetry.

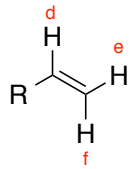


The ring has a single substituent on it. It is easy to be confused by the direction that the substituent is pointing in this drawing, but that is irrelevant because there is free rotation about the carbon-carbon single bond connecting the substituent to the ring. We can highlight the fact that the substituent's directionality is unimportant by temporarily abbreviating it simply as R. This very clearly shows that there are three

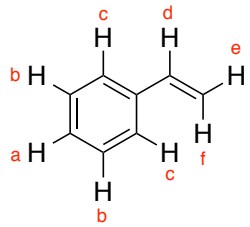
distinct locations on the ring: directly adjacent to the substituent (c), one carbon removed from the site bearing the substituent (b), and opposite the site of substitution (a). These result in three signals. The symmetry of the ring has resulted in only three signals for a total of five protons.



Within the substituent itself, it is important to recognize an element of *asymmetry*. This is best highlighted by temporarily abbreviating the ring as R. The alkene proton next to the R group (d) is one unique type of proton. Protons e and f stem from the same carbon, but they differ from one another because there is *no* free rotation about the carbon-carbon double bond. As such, proton f is *cis* to the R group (i.e., it is on the same side of the double bond), while proton e is *trans* to the R group (i.e., it is on the opposite side of the double bond). Consequently, protons d, e, and f all produce separate NMR signals.



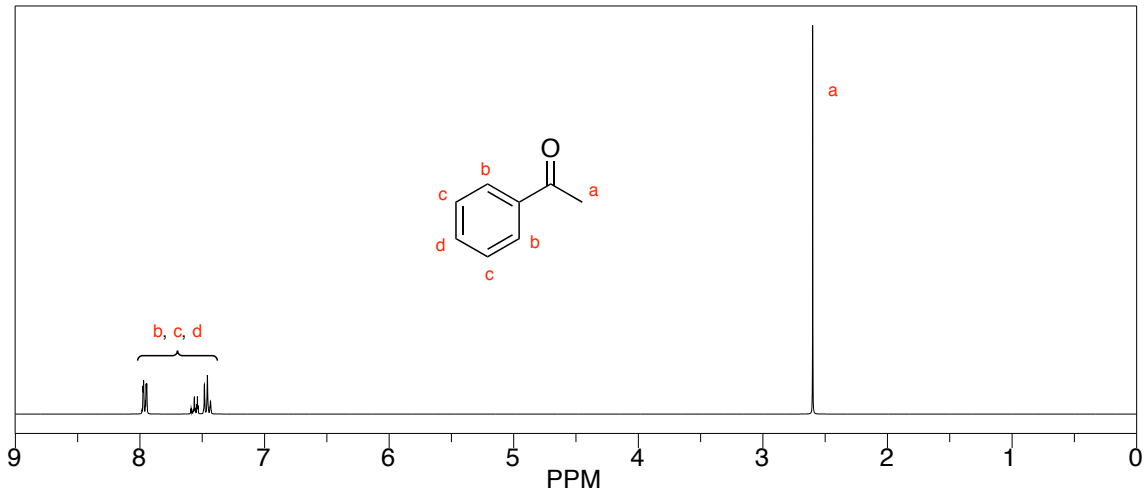
Putting the fragments together, we can see that there are a total of six signals in the proton NMR spectrum of styrene.



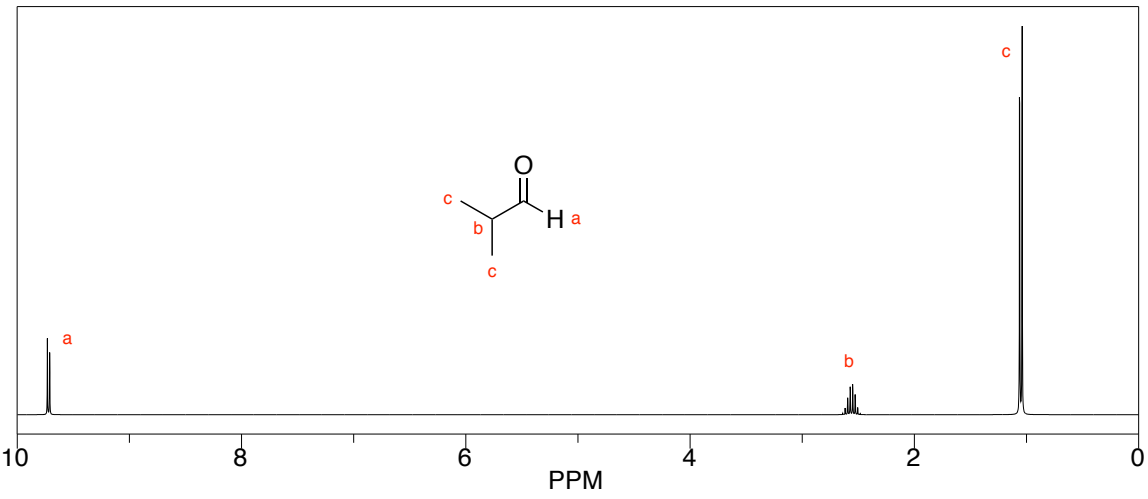
16. When analyzing NMR spectra, it is often most productive to consider the signals from left to right. Those protons on the left-hand side of the spectrum are the most unique and can quickly reveal important structural clues.

The first spectrum has signals between 7 and 8 ppm, which is the region where aromatic protons resonate. There is only one compound with aromatic protons, and that is the ketone. The ketone also has protons on a carbon adjacent to the carbonyl that appear just slightly above 2.5 ppm (a), but this type of proton appears in the other compounds as well and is therefore less diagnostic. There are four types of

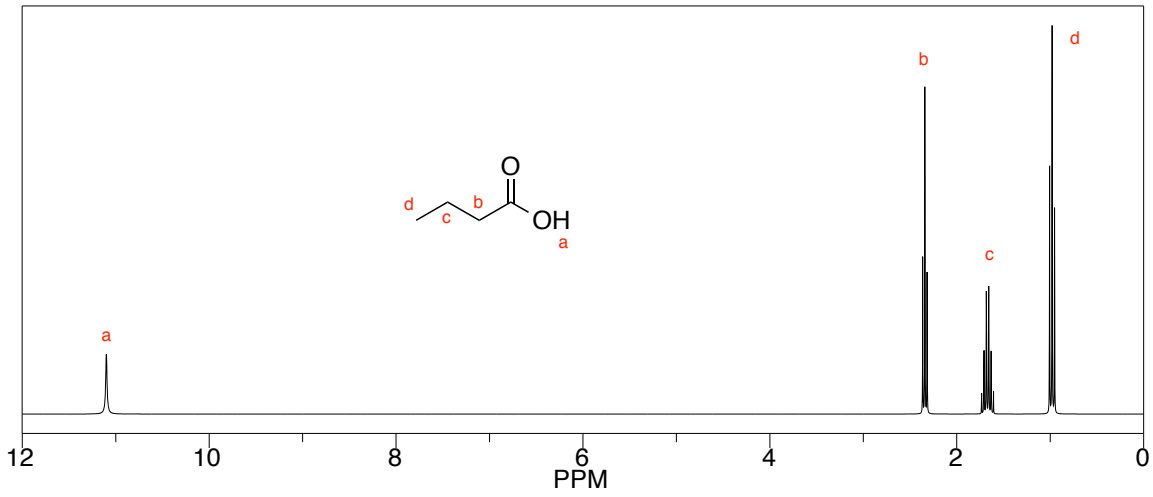
protons in this molecule and four signals in the spectrum, which serves as further confirmation.



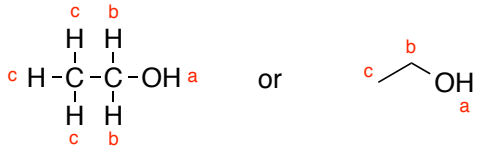
The second spectrum contains a signal between 9 and 10 ppm. Aldehyde protons (a) resonate in this region, which allows us to make the assignment. This compound also contains a proton on a carbon adjacent to the carbonyl at about 2.5 ppm (b) and alkyl protons at about 1 ppm (c), but these are less diagnostic because they also appear in the carboxylic acid. The appearance of three signals in this spectrum also matches the three types of protons in the structure.



The third and final spectrum contains a signal at ~11 ppm, which correlates with a carboxylic acid proton (a). This is sufficient information to match the spectrum to a compound. This structure also has protons on a carbon adjacent to the carbonyl at ~2.3 ppm (b) and two types of alkyl protons between 1 and 2 ppm (c and d). The four signals in this spectrum also correlate with the four types of protons in the structure.



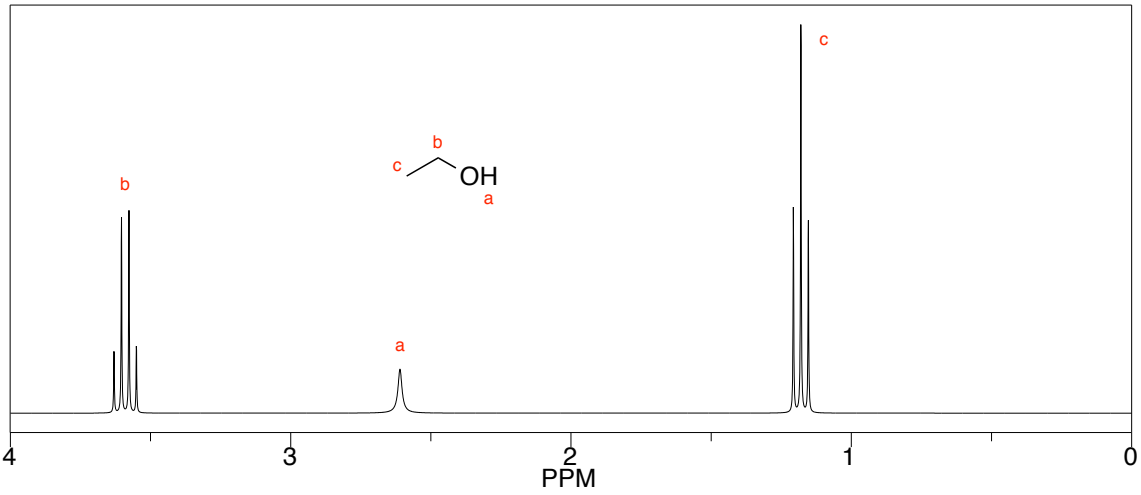
17. Ethanol contains three unique types of protons. The proton of the hydroxyl group is the only one of its type (a). The protons of the methylene (i.e., CH_2) group constitute a second type (b) and the protons of the methyl group are a third type (c).



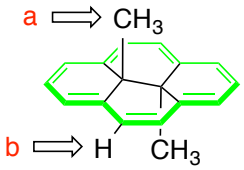
or

These three types of protons now have to be matched to the three signals in the proton NMR spectrum. The proton of the hydroxyl group (a) can undergo hydrogen bonding. Although alcohol protons have variable chemical shifts, they are distinctive in that they are broadened due to their hydrogen bonding. It is therefore straightforward to assign the alcohol proton to the broad signal at ~2.6 ppm.

The protons on the carbon adjacent to oxygen (b) are expected to fall in the range of 2.5 – 4.5 ppm. They can therefore be assigned to the signal at ~3.6 ppm. The protons of the methyl group (c) are protons on a carbon that is adjacent only to another carbon atom. These alkyl protons are expected to appear between 0 and 1.5 ppm, so we can assign them to the signal at ~1.2 ppm.



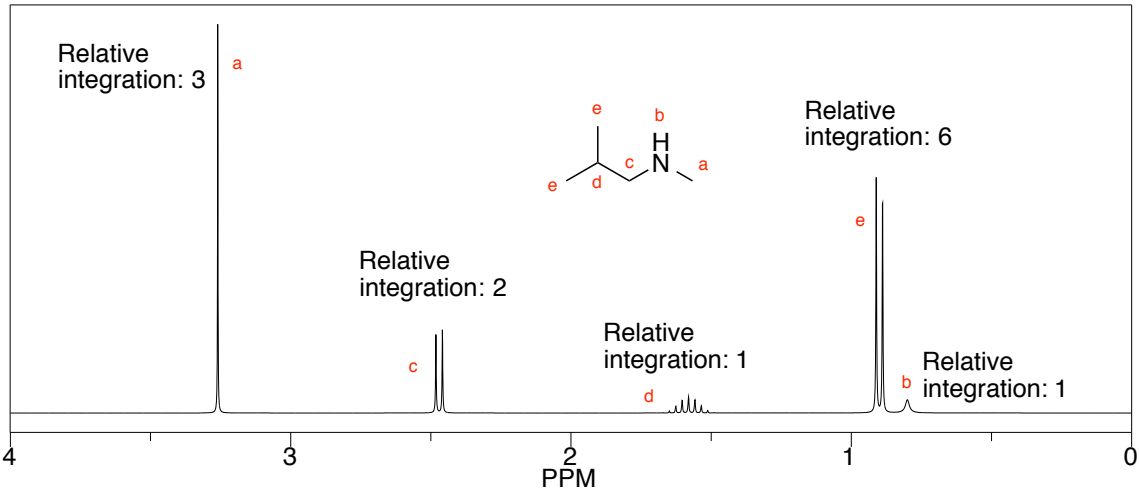
18. We can draw the molecule differently to better highlight the spatial orientation of the methyl groups. These substituents are located above and below the π system extending around the periphery of the molecule.



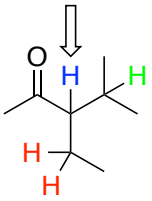
Consequently, the protons of type a are located above and inside the π system and are therefore be shielded by it. On the other hand, proton b is situated outside the π system and is deshielded as a result. Thus, the chemical shift of a is less than that of b.

19. Many of the integration values in this spectrum differ, which makes most of the assignments quite easy. The methyl group labeled a gives rise to the only signal integrating for three hydrogens. The methylene (i.e., CH_2) labeled c causes the only signal that integrates for two hydrogens. The two equivalent methyl groups labeled e cause the only signal integrating for six hydrogens.

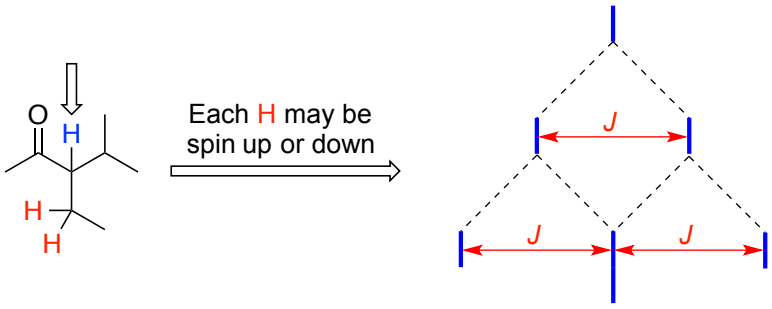
However, the protons labeled b and d each give signals integrating for a single hydrogen. Despite this similarity, they can be differentiated because proton b can hydrogen bond, and its signal is therefore broadened.



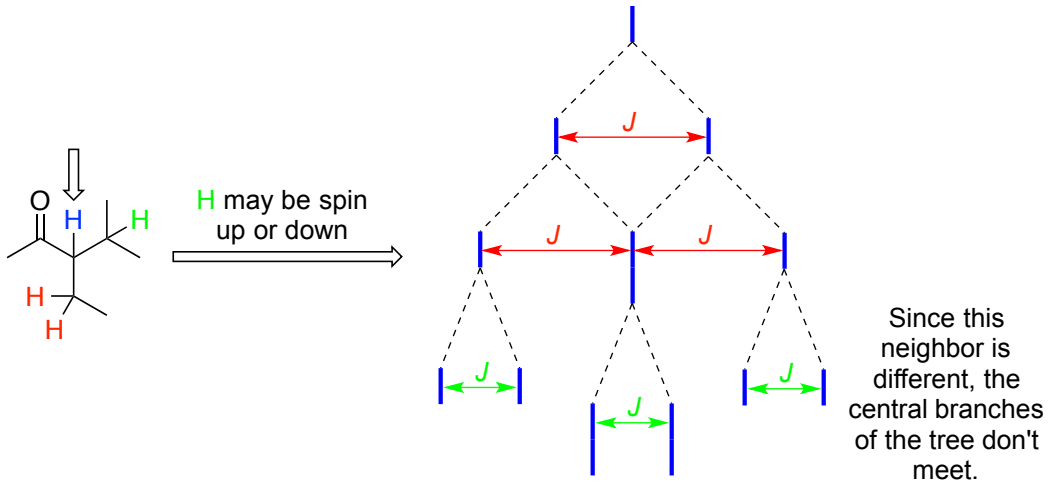
20. The indicated proton has a total of three neighbors. The two neighbors in the methylene (i.e., CH_2) group are equivalent, but the neighbor of the methine (i.e., CH) group differs.



We can consider the splitting by each type of neighbor in either order. Let's begin by considering the splitting due to the protons of the methylene group. Since these two neighboring protons are equivalent, they split the signal with identical coupling constants (or *J* values). This results in a triplet.



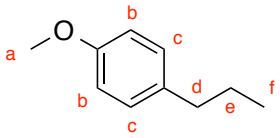
Now, let's turn our attention to the splitting caused by the proton of the methine group. Since this neighbor is different from the others, it splits the signal with a different coupling constant. As such, the central branches of the tree do not meet.



The resulting splitting pattern could be called a triplet of doublets (i.e., three doublets) or a doublet of triplets (i.e., two triplets). In any event, it consists of six peaks, where the middle two are twice as high in intensity.

Nota bene: We'll learn later in this chapter that the methylene protons are actually diastereotopic and are not, therefore, truly equivalent to one another. Depending on how different their *J* values are, this could result in an even more complex splitting pattern.

21. Let's begin by identifying the number of signals in the proton NMR spectrum. There six types of hydrogens in this molecule, so six signals are expected.



Methyl group a has no neighbors. By the n+ 1 rule, it is expected to be a singlet (0 + 1 = 1 peak).

The aromatic protons b each have one neighbor (c). By the n + 1 rule, we therefore expect the signal for b to be a doublet (1 + 1 = 2). This situation can be confusing because it might be tempting to say that there are two neighbors since there are two protons labeled c. However, the correct approach is to focus on a single b proton. It has only one neighbor, so b will be a doublet. It is irrelevant for the coupling that there is another identical b proton in the same situation.

Similarly, the aromatic protons c each have one neighbor (b), so we expect the signal for c to be a doublet as well.

The methylene protons d have two neighbors (e). By the n + 1 rule, we expect d's signal to be a triplet (2 + 1 = 3).

The methylene protons e are a bit trickier because they have two different types of neighbors (d and f). The signal for e will be split into a quartet by the three neighbors f (3 + 1 = 4). Then, each of the four peaks of the quartet will be split into a triplet by the two neighbors d (2 + 1 = 3). As a result, the signal will be a quartet of triplets (or a triplet of quartets). With so many peaks, we could simply call this signal a multiplet. In practice, if the *J* values for the neighbors d and f aren't all that different, they may be able to be treated as though they are equivalent, and the signal would then appear as a sextet (5 + 1 = 6).

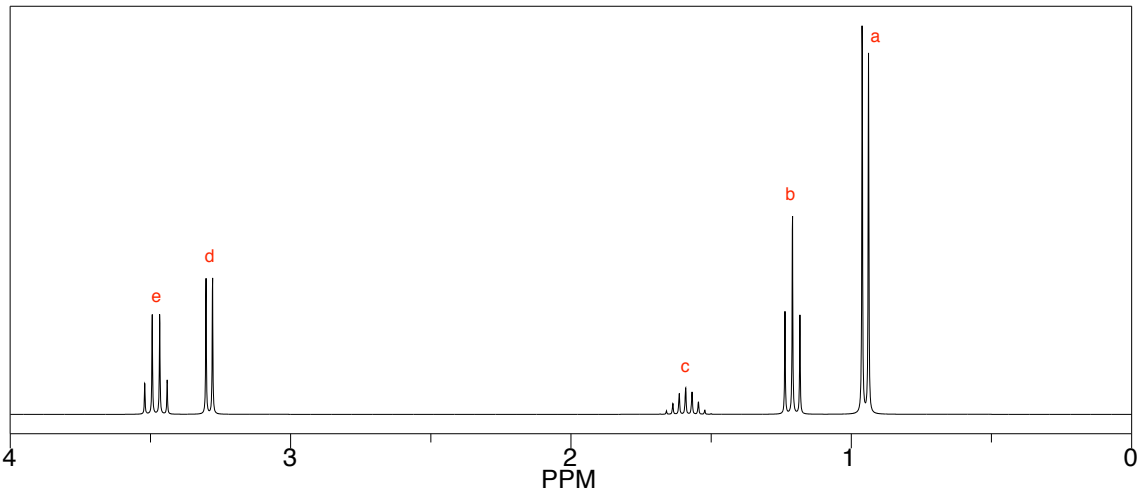
The methyl protons f have two neighbors (e). The signal for f is split into a triplet as a result (2 + 1 = 3).

22. To determine the number of neighbors, we need only rearrange the n + 1 rule as follows:

Splitting = # neighbors + 1

Splitting – 1 = # neighbors

The peaks are labeled in the spectrum below. We'll examine them one at a time.



Signal a is a doublet, and therefore protons a have one neighbor (2 – 1 = 1).

Signal b is a triplet, so protons b have two neighbors (3 – 1 = 2).

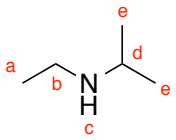
Signal c has many peaks. Often such signals are merely called multiplets and are said to have "many" neighbors, where the exact number is left unspecified.

Signal d is a doublet. Therefore, protons d have one neighbor (2 – 1 = 1).

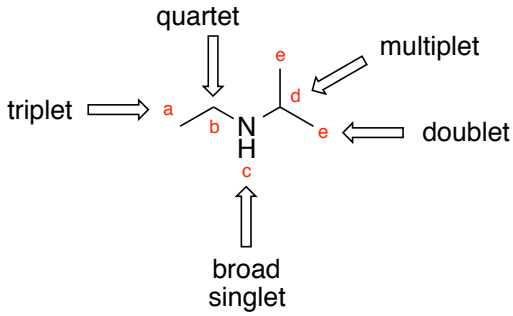
Signal e is a quartet, meaning that protons e have three neighbors (4 – 1 = 3).

23. It is probably most efficient to predict the number of signals and their multiplicity. These predictions can then be compared with the spectra provided.

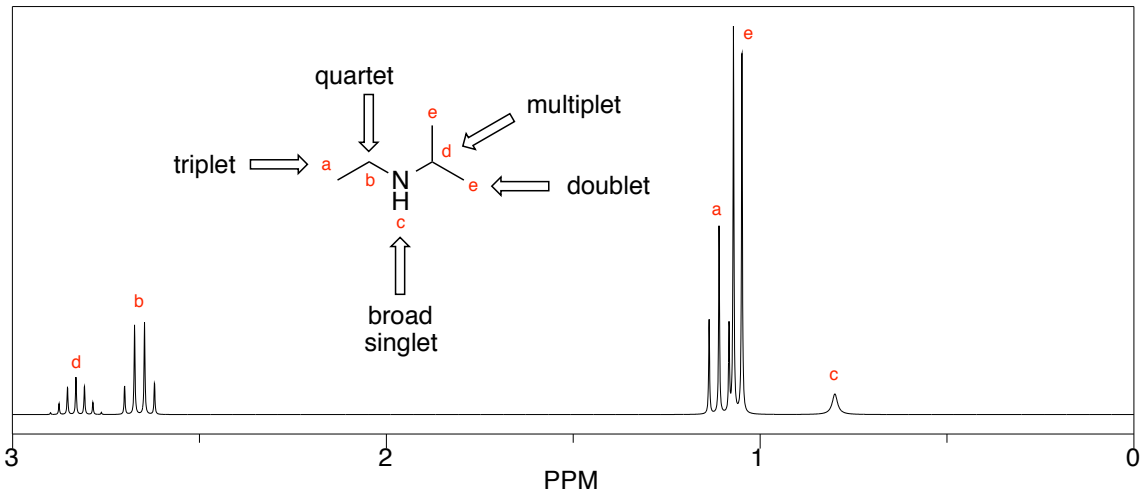
This amine will exhibit five signals in its proton NMR spectrum.



Methyl protons a have two neighbors (b), so the signal for a will be a triplet. Methylene protons b have three neighbors (a), so b's signal will be a quartet. Remember that hydrogen-bonding protons like c do not typically participate in splitting. As such, c does not count as a neighbor to b. Furthermore, we simply expect c to be a broad singlet. Methine proton d has six neighbors (e), so we expect it to be a septet (or simply a multiplet). Methyl protons e have one neighbor (d), making their signal a doublet.

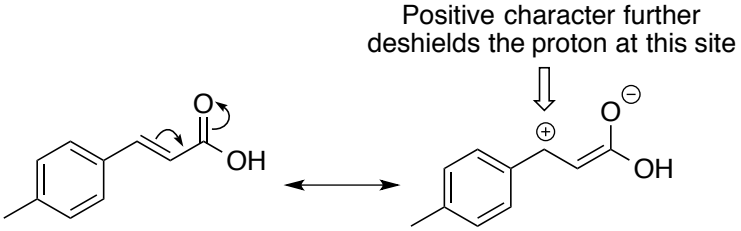


Only one of the three NMR spectra contains this pattern. It is the first one.

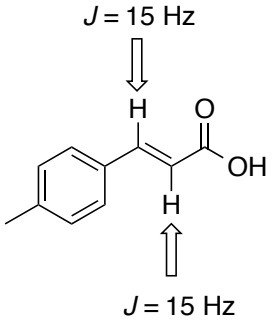


The second NMR spectrum contains no quartet, while the third has no quartet and no doublet.

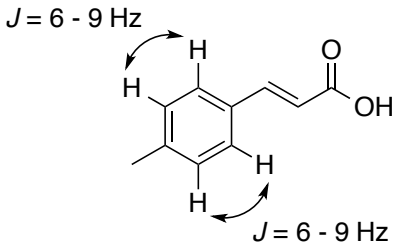
24. The first part of the question asks about the given coupling constants. These *J* values of 15 Hz are given for signals appearing at ~6.3 and 7.5 ppm. The proton at 6.3 ppm is clearly within the range for a vinyl proton. The signal at 7.5 ppm is also for a vinyl proton, but it falls outside the typical vinyl range of 4.5 – 6.5 ppm. This is due to resonance with the carbonyl, which places a significant δ^+ on one of the vinyl carbons, causing its hydrogen to be more deshielded than normal.



The problem stated the *J* values for each of these vinyl protons, which confirm that they are in fact *trans* to each other. Coupling constants for *trans* vinyl protons fall in the range of 14 – 17 Hz; whereas, *cis* vinyl protons would show a coupling constant of only 8 – 12 Hz.

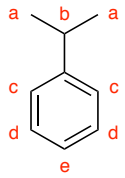


The second part of the question asks about the expected coupling constants for signals a and b. These signals are for the aromatic protons, which are ortho to each other. Consequently, we expect the *J* values to be in the range of 6 – 9 Hz.



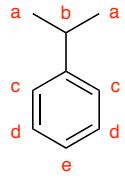
25.

(a) The indicated methyl protons are both chemically and magnetically equivalent. They exist in identical chemical environments, so they cause a single signal (a). This makes them chemically equivalent.

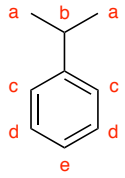


Furthermore, they are equidistant from any other type of chemically equivalent hydrogen in the molecule and therefore couple identically to it. Two examples are shown below. The methyl protons are therefore magnetically equivalent as well.

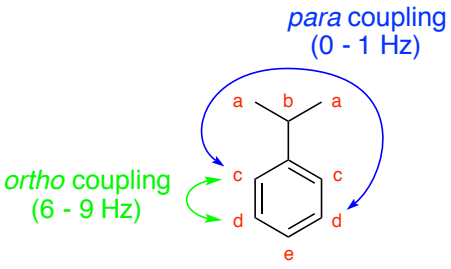
(b) The indicated protons here are chemically inequivalent. They are in different chemical environments and therefore contribute to separate signals (c and d).



(c) These aromatic protons are chemically equivalent because they exist in identical chemical environments and therefore cause a single signal (c).

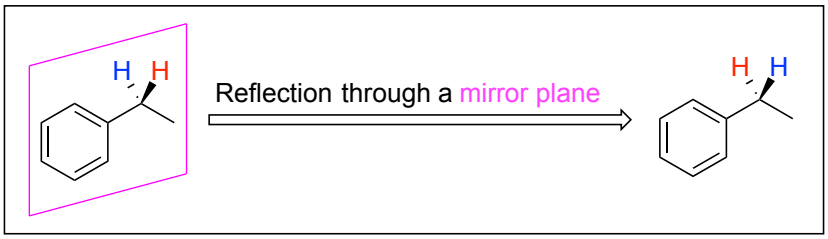


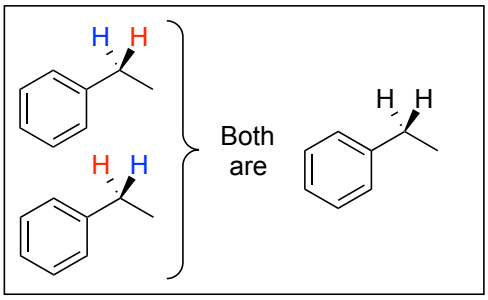
However, these protons are magnetically inequivalent because they couple differently with other chemically equivalent protons (d). A single c proton will split the neighboring d proton with an *ortho* coupling constant. However, that same c proton splits the distal d proton with a *para* coupling constant.



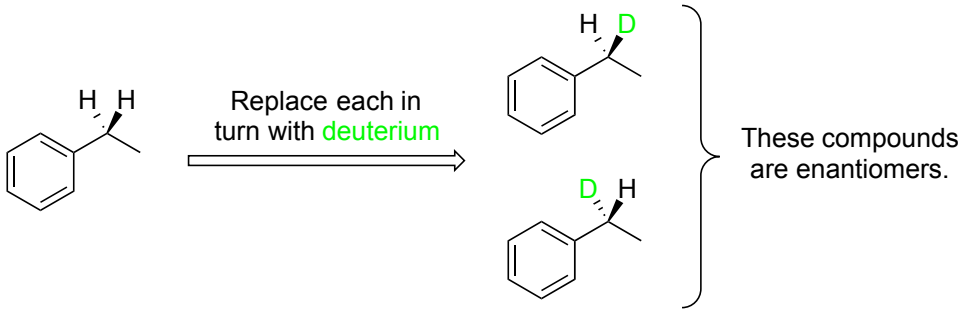
26.

(a) These methylene hydrogens are enantiotopic, and there are two different ways to illustrate the fact. One option is to highlight the internal plane of symmetry in the molecule. While there is no rotational symmetry, reflection through a mirror in the plane of the page interconverts the two protons without any changes to the molecule.



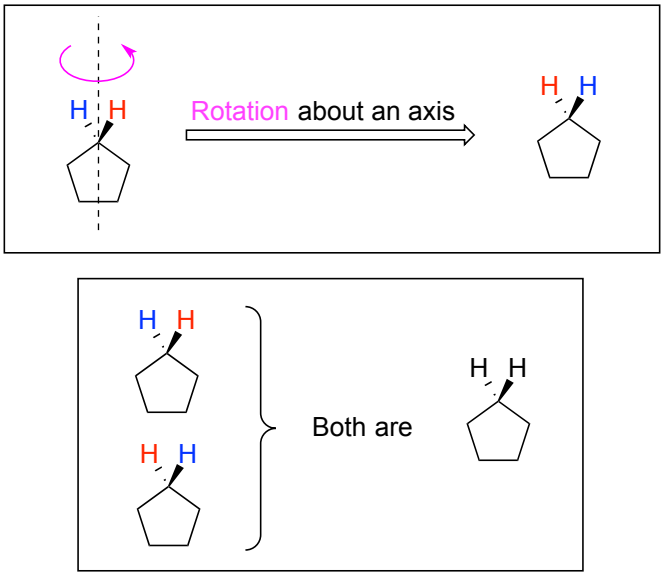


Alternatively, sequential isotopic substitution of the methylene protons provides a pair of enantiomers, which also shows that these hydrogens are enantiotopic.

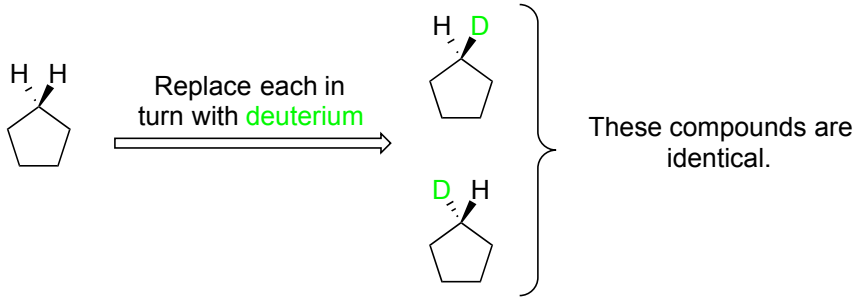


Enantiotopic protons will cause a single proton NMR signal in an achiral environment.

(b) These methylene protons are homotopic. One way to illustrate this focuses on the rotational symmetry of the molecule. Rotation about the axis shown below interconverts these two hydrogens without making any changes to the molecule.

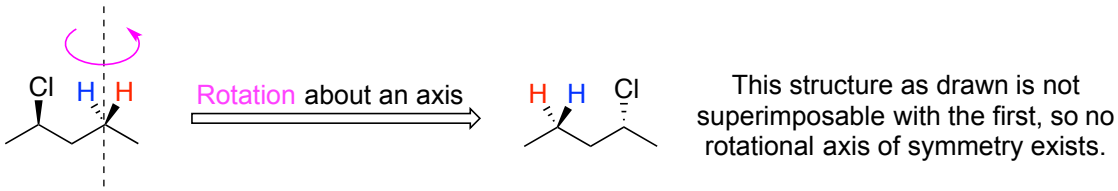


Another option is sequential isotopic substitution. In this case, it produces identical compounds, showing that these methylene hydrogens are homotopic.

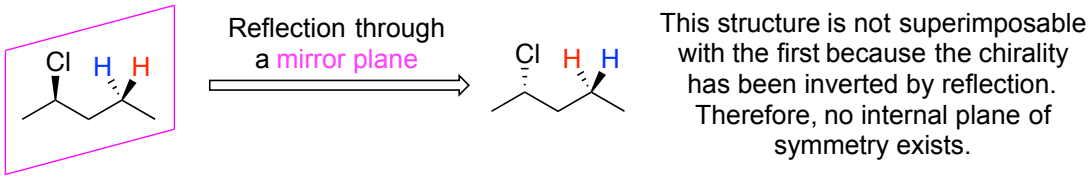


Homotopic protons cause a single signal in the proton NMR.

(c) These methylene hydrogens are diastereotopic. The lack of internal symmetry is one way to illustrate this fact. Rotation of the molecule does not produce an image that is directly superimposable with the first, so there is no rotational symmetry.

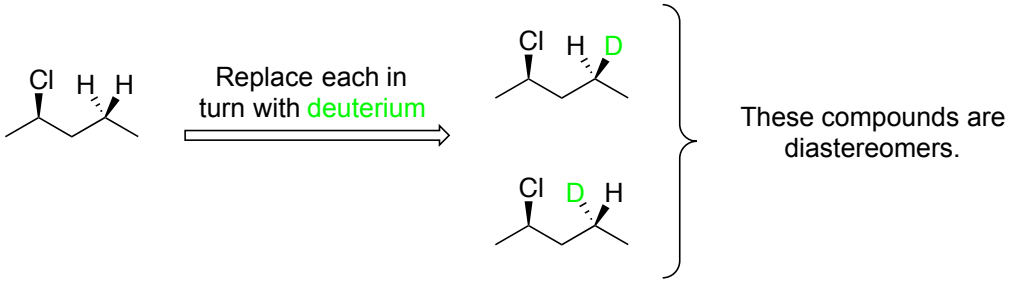


Additionally, there is no internal plane of symmetry. While reflection through a mirror in the plane of the page would interconvert the methylene protons, it would also invert the stereochemistry of the chiral center.



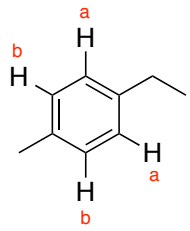
The lack of symmetry through rotation and reflection reveals these methylene protons to be diastereotopic.

Alternatively, sequential isotopic substitution produces a pair of diastereomers. This also shows that the methylene protons in question are diastereotopic.



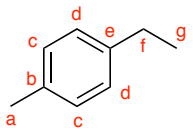
Diastereotopic protons cause different signals in the NMR spectrum.

27. The signal at 7 ppm is the only signal in the aromatic region of the spectrum, so it must account for all of the aromatic hydrogens. There are two types of aromatic protons (a and b). They exist in different chemical environments because protons a are adjacent to an ethyl group, while protons b are adjacent to a methyl group. As a result, they cause separate NMR signals. However, we don't expect these signals to differ significantly in chemical shift because residing next to an ethyl group is not that different from being adjacent to a methyl group.



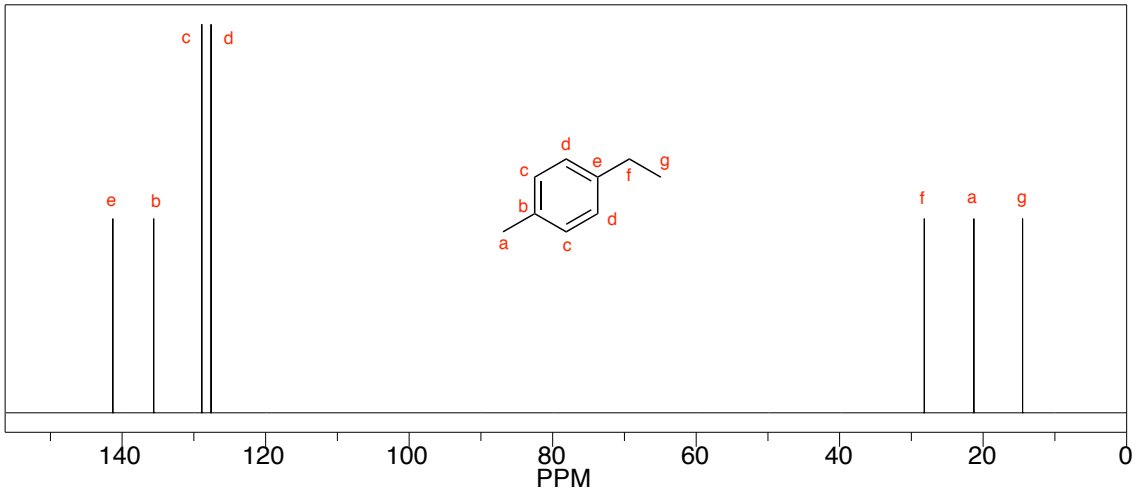
The signal for protons a will be a doublet. The signal for protons b is also a doublet. These two doublets, which are close in chemical shift, experience second-order coupling that causes the interior peaks to rise in intensity and the exterior peaks to fall in intensity. This explains the AB quartet observed at 7 ppm.

28. This compound contains seven unique types of carbons.



Three of these (a, f, and g) are alkyl carbons that are expected to appear in the range 0 – 100 ppm. These carbons are closer to 0 ppm than to 100 ppm because there are no intensely deshielding groups in the molecule. The exact ordering of the three signals is not especially important at this point.

The remaining four signals (b, c, d, and e) are due to atoms participating in carbon-carbon double bonds and are therefore expected to fall between 100 and 150 ppm. Again, the exact ordering of these four signals is not particularly important at this point. However, you would expect the signals for c and d to be larger than the others because they are each due to two identical carbons.



29. Our algorithm for structure solving always begins with a DOU calculation.

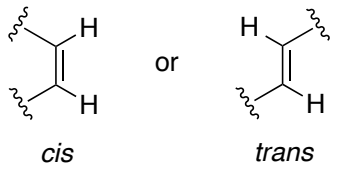
$$DOU = \frac{[2n+2] - hydrogens\ and\ hydrogen\ equivalents\ in\ formula}{2}$$

$$DOU = \frac{[2(5)+2]-6}{2} = 3$$

The compound must have some combination of rings and π bonds adding up to three degrees of unsaturation, but we should reserve judgment on that combination until we analyze the spectra.

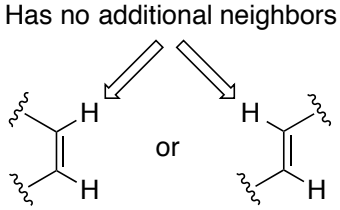
The next step in the algorithm is analysis of the IR. The IR data indicates a carbonyl (1710 cm^{-1}), as well as sp^3 and sp^2 C-H stretching (2920 and 3080 cm^{-1}, respectively). The signal at 1650 cm^{-1} is not in one of our three spot-check regions, but comparison with the correlation table shows this to be C=C stretching. We have now accounted for two of the three degrees of unsaturation. One is the π bond of the carbonyl, and the other is the π bond of the alkene.

Next, we can proceed to the NMR. As usual, let's begin with the most deshielded signals, which are often the most revealing. There is a signal between 4.5 and 6.5 ppm, which is the vinyl-proton range. There is another signal at ~6.6 ppm. While this formally falls in the aromatic region, it cannot be an aromatic proton. We do not have enough carbons or degrees of unsaturation for a benzene ring. Since this signal is not very far above 6.5 ppm, it is quite possible that it too is a vinyl proton that just happens to be especially deshielded. Since both of these signals integrate for one hydrogen, we can begin to develop a fragment.

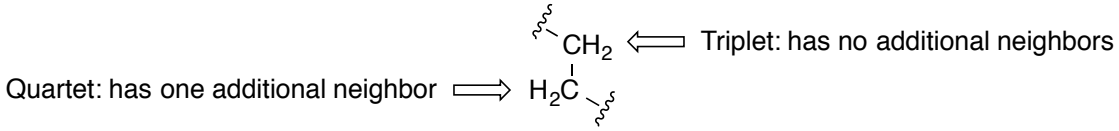


We can surmise that the two vinyl protons are on different alkene carbons because they have very different splitting patterns. The alkene could be *cis* or *trans* since we have not been given *J* values.

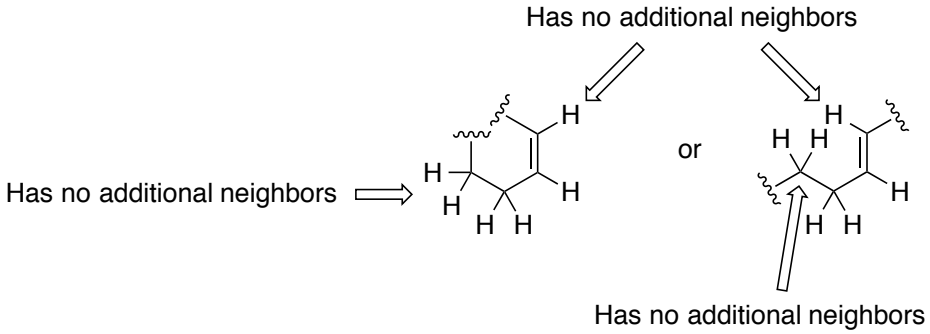
Importantly one of the vinyl protons is a doublet, meaning that it can have no neighbors beyond the one already shown.



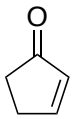
The two remaining NMR signals both integrate for two hydrogens, making them both methylene groups. To achieve the necessary splitting, these methylene groups must be adjacent to each other. One has no additional neighbors, while the other has one additional neighbor.



The additional neighbor can be attained by linking it to the alkene fragment.



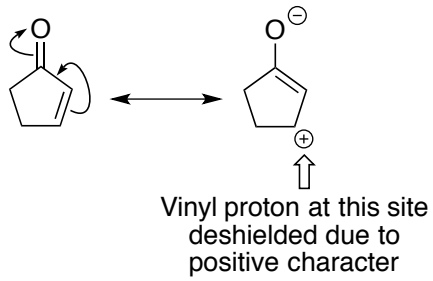
At this point, it is useful to take stock of what remains to be accounted for. The formula shows that one carbon and one oxygen atom have yet to be placed. The IR told us that these must be present in the form of a carbonyl. Additionally, there must be one more DOU. Since there is no evidence for any additional π bonds, it is likely a ring. If we join the two open termini using a carbonyl, everything is accounted for.



Only the *cis* alkene is compatible with a ring size this small. The conjugation of the alkene with the carbonyl explains two issues:

(1) The carbonyl resonance at 1710 cm^{-1} can be rationalized because the increase in wavenumber caused by the five-membered ring is roughly canceled by the decrease in wavenumber resulting from conjugation.

(2) One vinyl proton is especially deshielded due to resonance.



30. As usual, we begin with the calculation of degrees of unsaturation.

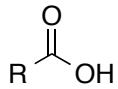
$$DOU = \frac{[2n+2] - hydrogens\ and\ hydrogen\ equivalents\ in\ formula}{2}$$

$$DOU = \frac{[2(5)+2] - 10}{2} = 1$$

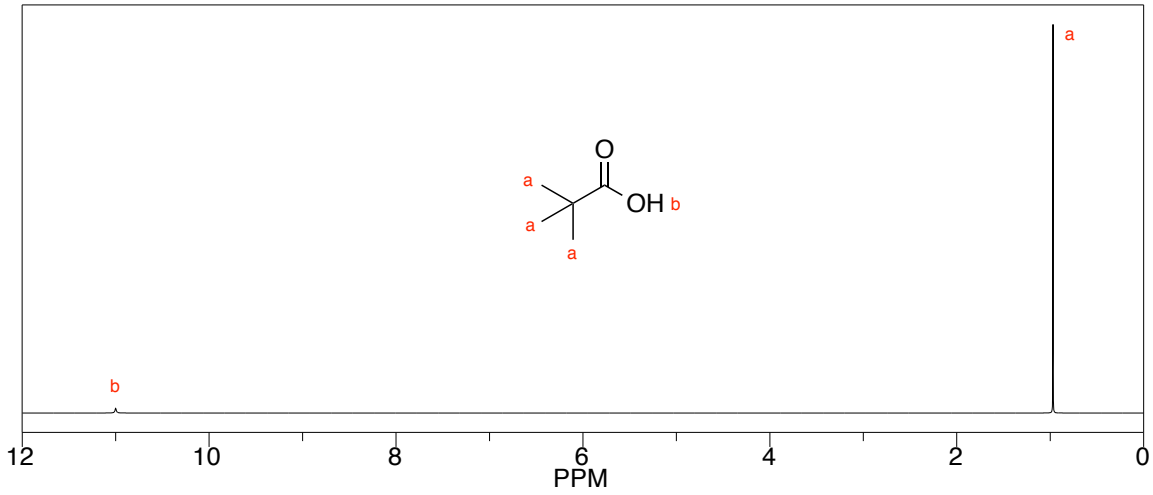
This molecule must therefore contain a ring or a π bond.

The next step in the algorithm is to analyze the IR spectrum. The peak at 1700 cm^{-1} reveals the presence of a carbonyl. We have simultaneously identified the one DOU as the π bond of this carbonyl.

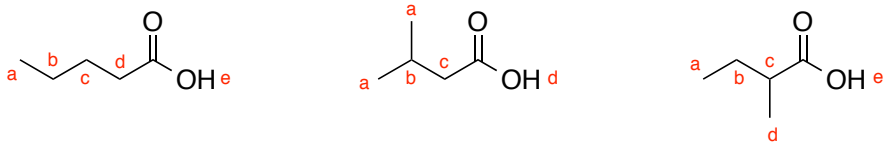
There is also a very broad signal from 2500 – 3500 cm^{-1} that suggests the O-H stretch of a carboxylic acid. Since the carboxylic acid contains the previously identified carbonyl, we can consolidate everything we've learned thus far into a single fragment.



This leaves us with four carbons and nine hydrogens to place. The conundrum is that the proton NMR displays only two signals, and one of these must be due to the carboxylic acid proton. Only one signal remains to explain the presence of all nine hydrogens! Whenever there are relatively few signals to explain a large number of atoms, symmetry is the reason. The most symmetrical way to organize four carbons is into a *tert*-butyl group. By doing this, all three methyl groups stem from the same carbon and are equivalent to one another, so there are indeed only two signals in the proton NMR spectrum.



Any isomer of this compound would be expected to have more NMR signals.



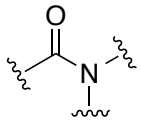
31. As always, it is best to begin by computing the number of DOUs. Remember that nitrogen counts as half of a carbon in this calculation.

$$DOU = \frac{[2n + 2] - hydrogens\ and\ hydrogen\ equivalents\ in\ formula}{2}$$

$$DOU = \frac{[2(10.5) + 2] - 13}{2} = 5$$

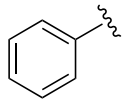
With large numbers of degrees of unsaturation, it is often the case that a benzene ring is a fragment of the structure. This would account for four of the five degrees of unsaturation, leaving one additional ring or π bond.

The IR spectrum shows a carbonyl with a resonance of ~1650 cm^{-1}, which is suggestive of an amide.

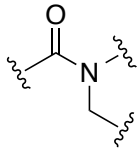


There is also sp^3 C-H stretching below 3000 cm^{-1} and sp^2 C-H stretching above 3000 cm^{-1}, the latter being consistent with the presence of a benzene ring.

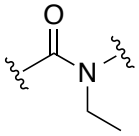
The NMR spectrum shows a total of five hydrogens spread over two signals in the aromatic region (6.5 – 8 ppm). This implies a monosubstituted benzene ring and is consistent with our supposition based on the degrees of unsaturation.



There is a signal just below 4.5 ppm that integrates for two hydrogens. This methylene group is expected to be next to a heteroatom since it falls in the range of 2.5 – 4.5 ppm. We can therefore expand the amide fragment.

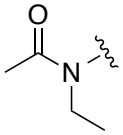


Additionally, since this methylene's signal is a quartet, it must have three neighbors. This allows us to expand the fragment once again into an ethyl group.

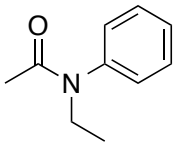


The methyl group that we've just added will be a triplet, so it causes the signal just under 1.5 ppm.

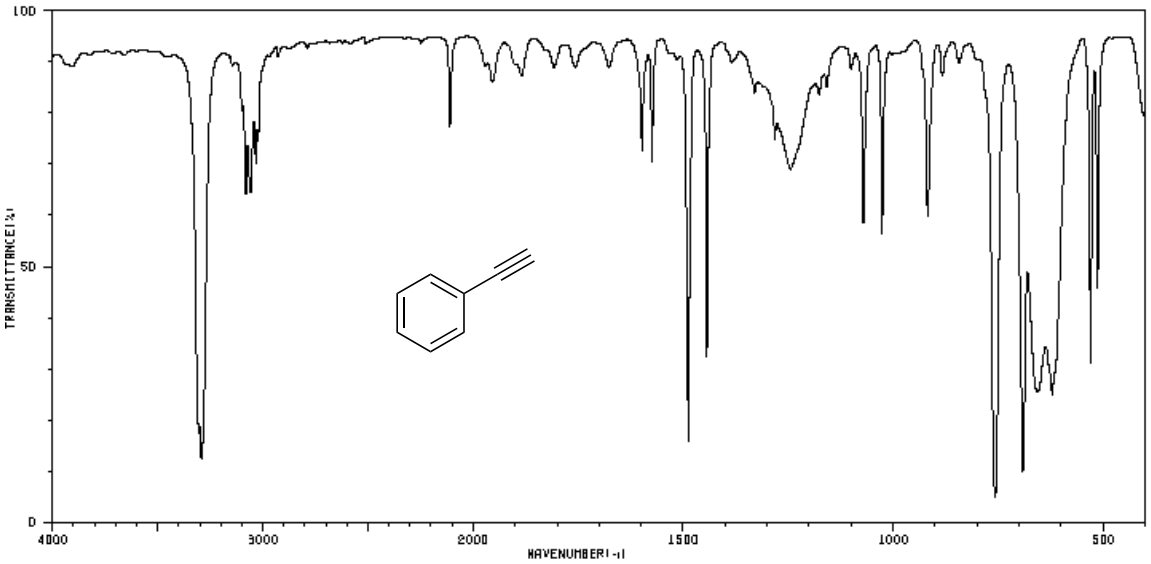
There is only one remaining signal to interpret: the singlet at ~2 ppm. Since it integrates for three hydrogens, it is a methyl group. It falls in the range of 1.5 – 2.5 ppm, so we expect it to be adjacent to a π bond of some type. As such, it must be connected to the carbonyl carbon.



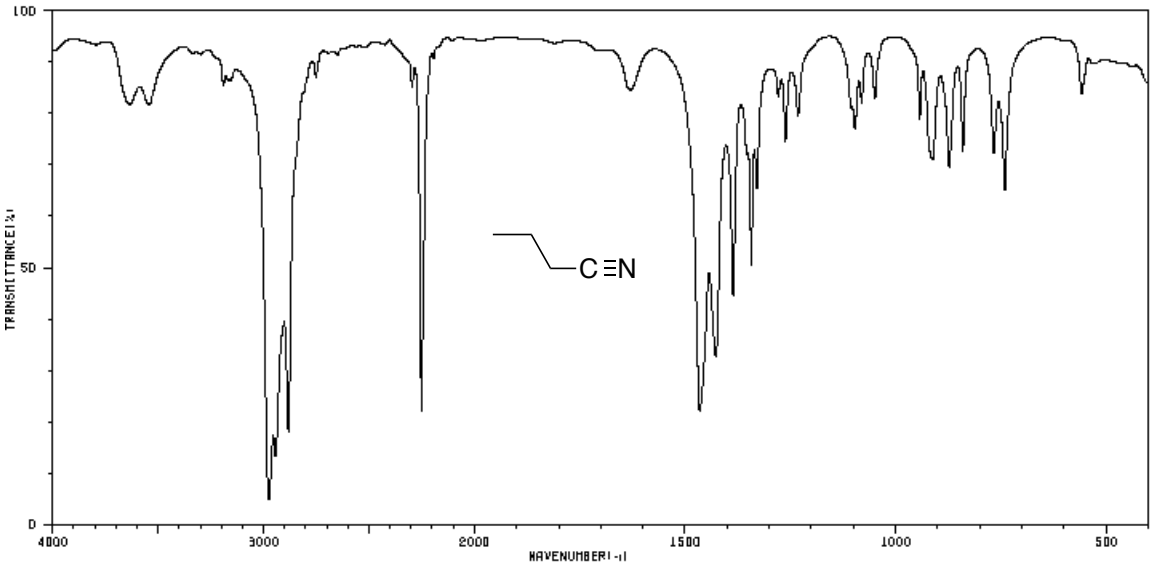
The only remaining site on the amide must hold the phenyl group.



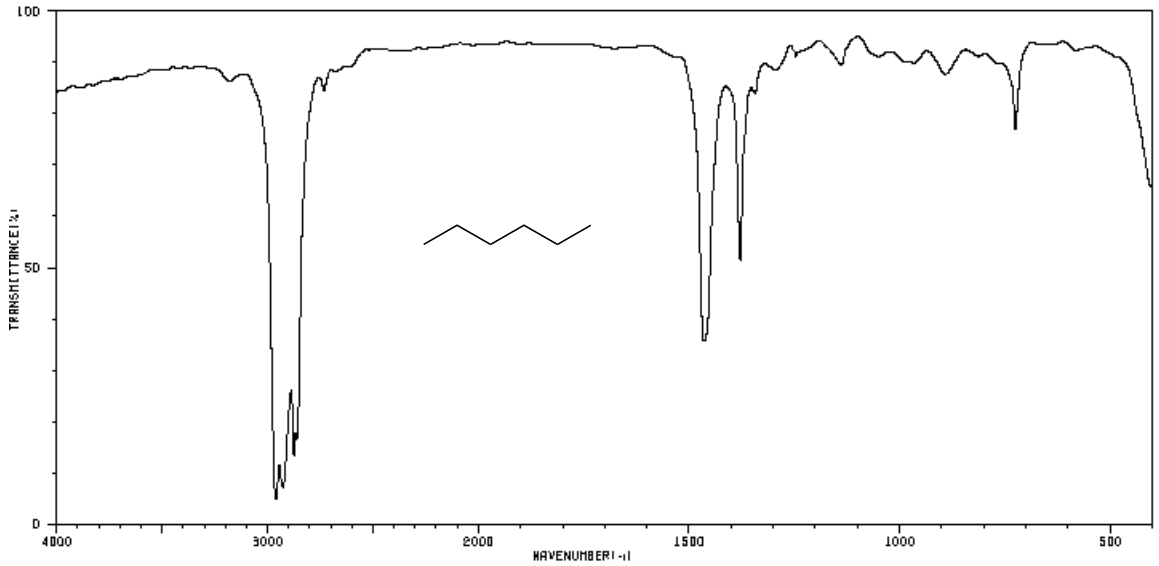
32. Some of these compounds have unusual structural features, and we should check the correlation table to see where these bonds resonate. For instance, we haven't discussed alkynes very much in this chapter. The IR correlation table indicates that the alkyne C-H stretch appears around 3300 cm^{-1}. Also, the C≡C stretch appears at 2100 – 2200 cm^{-1}. The second IR spectrum has both of these features. The alkyne C-H stretch is much more prominent than the stretching of the carbon-carbon triple bond.



The nitrile is also an unusual structural feature. The IR correlation table shows that it resonates at 2200 – 2300 cm^{-1}. The third spectrum contains this signal.

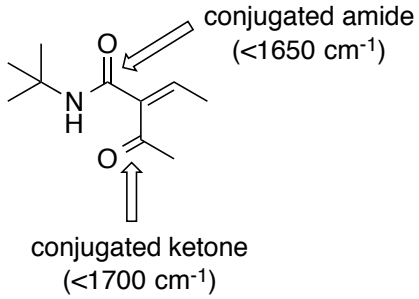


Lastly, the alkane would not be expected to exhibit much beyond the sp^3 C-H stretching below 3000 cm^{-1}. This matches the first spectrum.

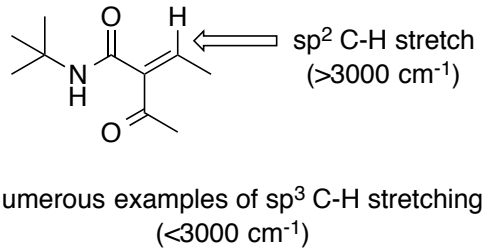


33. For a problem like this, it is best to list the expected resonances. Once these are identified and organized, the IR spectrum can be drawn easily.

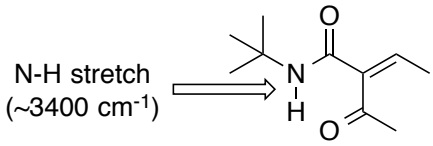
This compound contains two carbonyls. One is a conjugated amide and should therefore appear a bit below 1650 cm^{-1}. The other is a conjugated ketone and should appear a bit below 1700 cm^{-1}.



The compound also contains both sp^2 and sp^3 C-H stretching, which will appear above and below 3000 cm^{-1}, respectively.



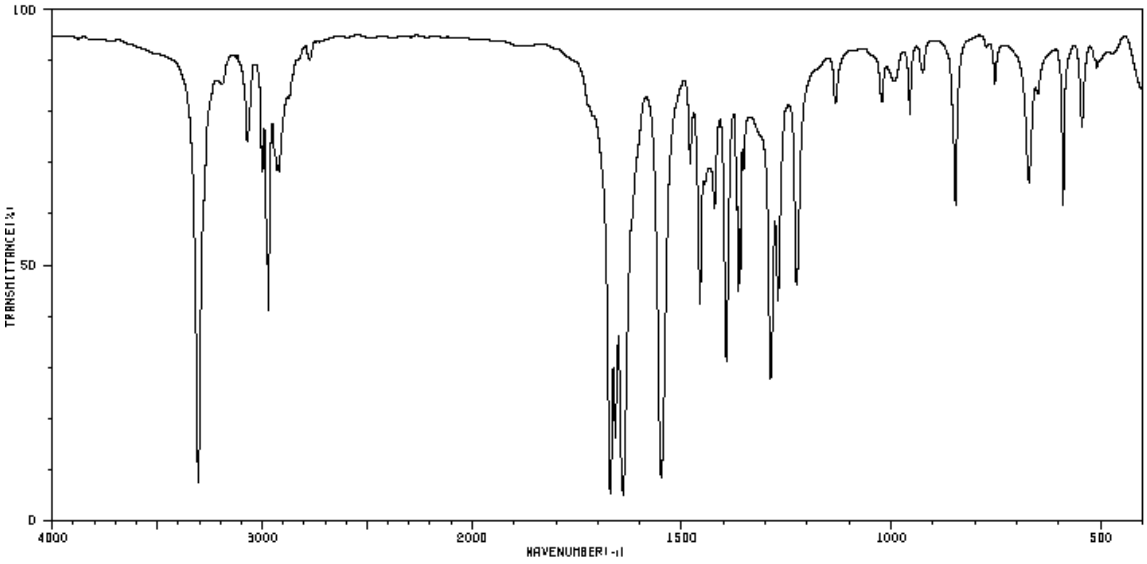
Additionally, there is an N-H stretch that will be expected to appear in the vicinity of 3400 cm^{-1}.



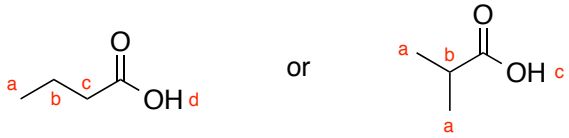
These are the most important signals to include in the IR spectrum. Organize them from highest to lowest wavenumber:

- N-H stretch at ~3400 cm^{-1}
- sp^2 C-H stretch above 3000 cm^{-1}
- sp^3 C-H stretch below 3000 cm^{-1}
- conjugated ketone below 1700 cm^{-1}
- conjugated amide below 1650 cm^{-1}

Then, simply draw peaks at each of these locations. The actual IR spectrum is shown below. Notice that the C=C stretch also appears at about 1650 cm^{-1}.

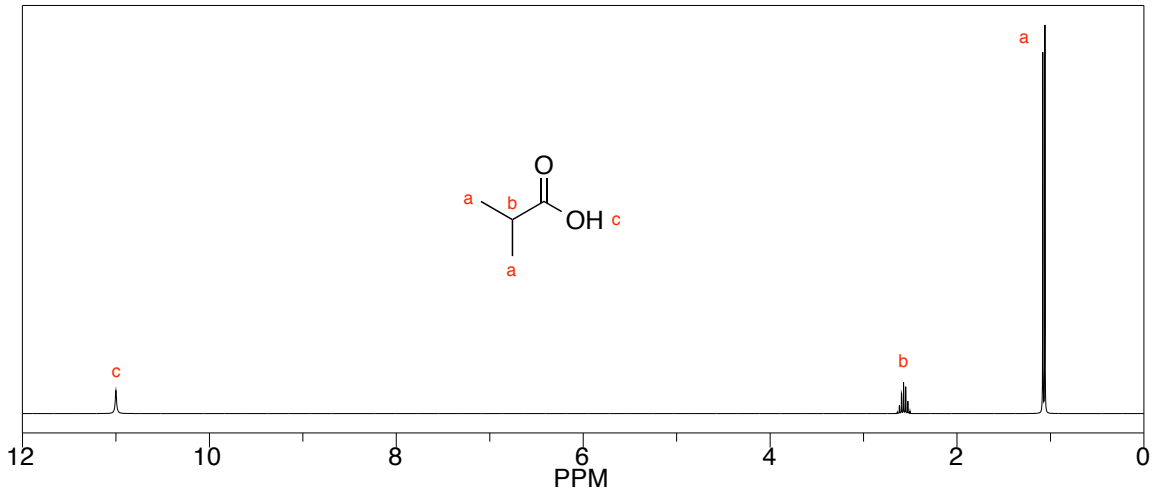


34. The given proton NMR spectrum contains only three signals. This alone allows us to make the determination. Of the two possible carboxylic acids, the first would have four signals, while the second would have three. Therefore, the second structure must be the correct one.

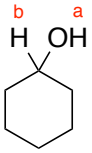


We can go one step further by assigning the peaks. The two methyl groups are the most shielded signal (a). This signal is split into a doublet by its one neighbor (b).

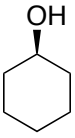
The methine is a multiplet (b) because it has six neighbors (a). The carboxylic acid proton (c) appears at ~11 ppm.



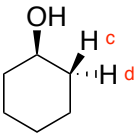
35. The alcohol proton (a) and the methine proton (b) are easy to identify as unique types of hydrogens.



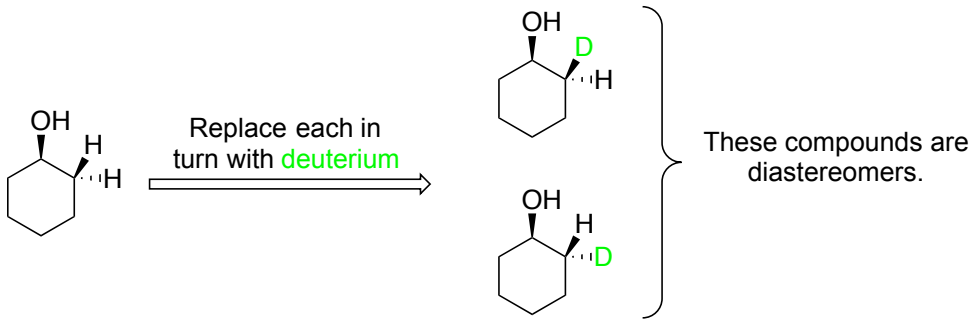
Things get more complicated when we turn our attention to the methylene hydrogens. Although the carbon bearing the hydroxyl group is not a stereocenter, the fact remains that the hydroxyl group must occupy one side of the ring. The molecule is drawn below with the hydroxyl group on the top side of the ring.



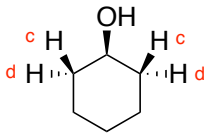
Now, consider the protons of a neighboring methylene. These two hydrogen atoms (c and d) are in different chemical environments because one is closer to the hydroxyl group than the other. Consequently, they cause different signals.



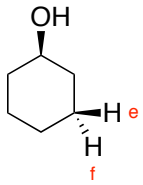
Another way of phrasing this same concept is that these protons are diastereotopic. This can be highlighted through sequential isotopic substitution, which gives diastereomers. Diastereotopic protons are chemically different and are expected to cause different signals.



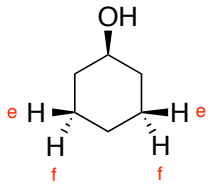
When we consider the other methylene neighboring the alcohol, a second proton of type c is found, and a second proton of type d is found.



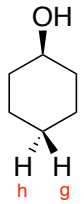
As we move further from the alcohol, another set of diastereotopic protons is found (e and f). These are different from c and d because they are further removed from the alcohol.



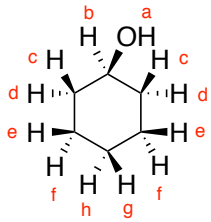
Once again, there is a second proton of each type on the other side of the ring.



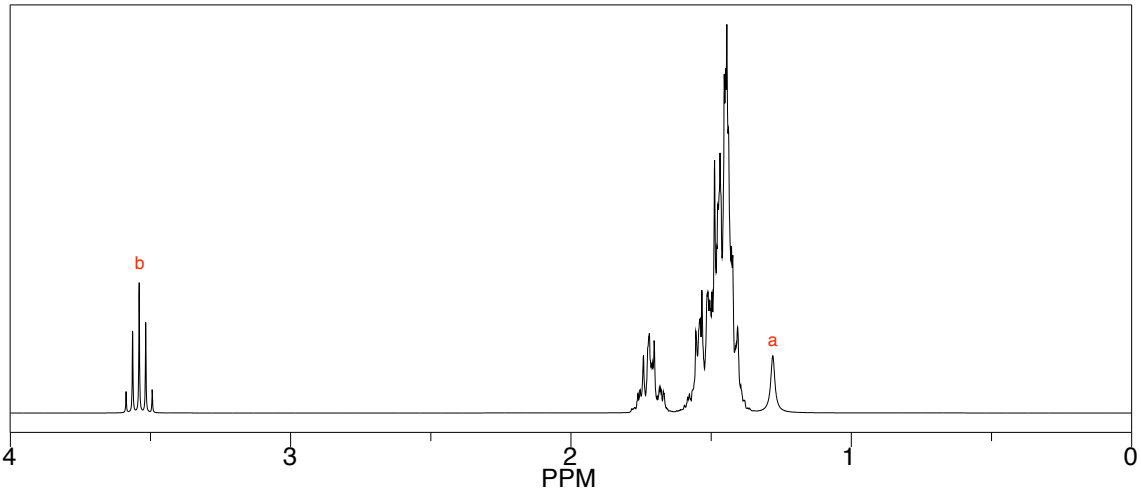
Finally, the methylene most distant from the alcohol consists of another set of diastereotopic protons (g and h).



Taken together, we can see that there are eight types of protons in the molecule (a – h).



The proton NMR spectrum is messy because many of these protons, while formally different, do not have significantly different chemical shifts. As a result, a number of the signals overlap. The ^{1}H NMR spectrum follows. Only protons a and b can be readily distinguished. The rest of the signals overlap in two multiplets.



36. The molecular formula reveals a single degree of unsaturation.

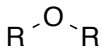
$$DOU = \frac{[2n+2] - hydrogens\ and\ hydrogen\ equivalents\ in\ formula}{2}$$

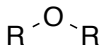
$$DOU = \frac{[2(4)+2] - 8}{2} = 1$$

This molecule therefore contains a ring or a π bond.

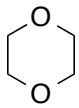
The IR spectrum shows no carbonyl resonance, no sp^2 C-H stretching, and no heteroatom-to-hydrogen stretching. The only notable signal in the functional group region is sp^3 C-H stretching just below 3000 cm^{-1}.

One of the most pressing questions is how to incorporate the two oxygen atoms into the structure. There is no carbonyl stretch in the IR, so they cannot be present as carbonyl oxygens. Similarly, since there is no heteroatom-to-hydrogen stretching, they cannot be added to the structure as alcohols. The only common oxygen-containing functional group that does not require a carbonyl or an O-H stretch is the ether, so there must be two ethers in the compound.





We also know that there is one degree of unsaturation in the molecule. Since there is no evidence for a π bond, it is reasonable to surmise that a ring is present instead. Since the proton NMR contains only one signal, we must make this ring as symmetrical as possible. This entails connecting the two ethers with two carbons on each side.



This molecule contains only one type of proton. All of the protons are on a carbon adjacent to oxygen, so we expect the signal to appear between 2.5 and 4.5 ppm, which is consistent with the data given.

37. As usual, it is best to begin with a calculation of the degrees of unsaturation.

$$DOU = \frac{[2n+2] - hydrogens\ and\ hydrogen\ equivalents\ in\ formula}{2}$$

$$DOU = \frac{[2(8)+2] - 16}{2} = 1$$

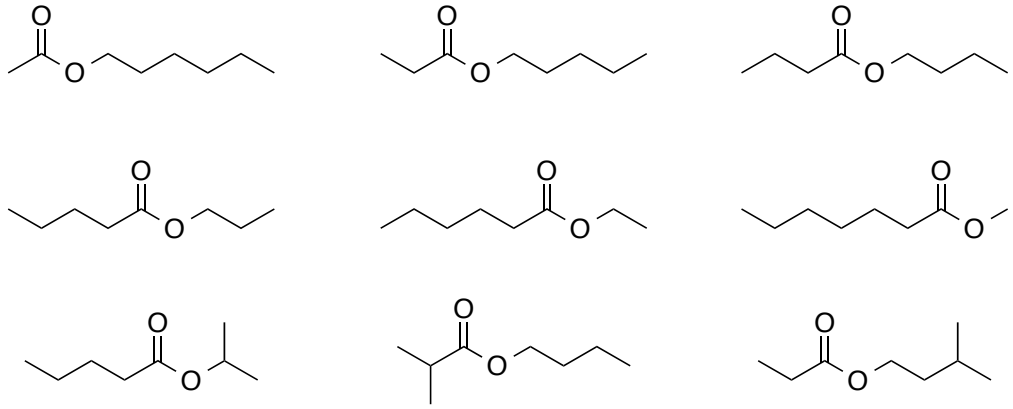
There is one DOU in the molecule, so we can expect there to be one ring or one π bond. But, we must reserve judgment on which one is present until we examine the spectrum.

The IR spectrum contains a carbonyl stretch well above 1700 cm^{-1}. This signal is nearly halfway between 1700 and 1800 cm^{-1}, so it most likely indicates an ester, which would have a resonance at ~1740 cm^{-1}. This accounts for the two oxygen

atoms in the formula as well as the degree of unsaturation, which is the π bond of the carbonyl.

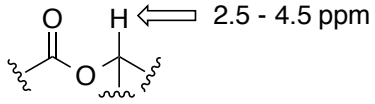
The only other notable signal in the functional group region is the sp^3 C-H stretching just below 3000 cm^{-1}.

There are a wide variety of isomeric esters that are consistent with this information. Several of the many examples are given below, but only three were needed to answer the question.

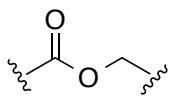


The plethora of possible structures highlights one of the limitations of IR spectroscopy. While it is a very useful tool for quickly identifying the functionality in a molecule, it does not provide much guidance regarding the specific structure of the carbon-hydrogen backbone of the molecule.

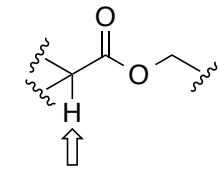
Problem 38. We've already identified the functional group as an ester in Problem 37. We can now build outward from that core as we determine the specific carbon-hydrogen backbone. The most deshielded type of proton near an ester resides on the carbon bonded to the sp^3 oxygen atom.



There are two signals in this region, but the more deshielded one must account for this type of hydrogen because no proton in the molecule can be expected to be more deshielded. The signal at ~3.8 ppm integrates for two hydrogens, so we now know that a methylene group is connected to the ester's sp^3 oxygen.

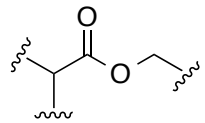


The second most deshielded type of proton in this ester will reside on the carbon adjacent to the carbonyl.

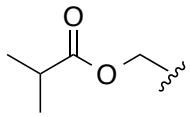


1.5 - 2.5 ppm

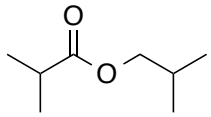
Again, there are two signals in this region of the spectrum, but the more deshielded one must correlate with protons at this location because none of the remaining hydrogens in the molecule are expected to be more deshielded. This signal at ~2.5 ppm integrates for one hydrogen, so a methine group resides at this location.



This methine is split into a multiplet by many neighbors. Among the remaining signals, there are two doublets, each integrating for six hydrogens. These signals suggest two pairs of equivalent methyl groups, each having a single neighbor. One of those pairs should be placed next to the methine to explain the multiplicity of these signals.



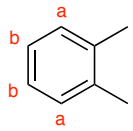
There are only two signals left in the spectrum. The signal at ~2.0 ppm integrates for one hydrogen, so it indicates a methine group. The other pair of equivalent methyl groups must be placed next to this methine to account for the splitting. This leads us to the structure of the unknown.



Notice that, while IR did not allow us to identify the carbon-hydrogen backbone of the unknown, NMR did.

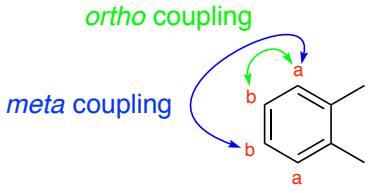
39. The signals for the methyl groups will *not* be particularly useful. In each compound's ^{1}H NMR spectrum, the methyl groups would be expected to cause one singlet in the range of 1.5 – 2.5 ppm.

We must use the signals for the aromatic protons to differentiate the compounds. *Ortho*-xylene has two types of aromatic protons (a and b). We will therefore see two signals, each integrating for two hydrogens, in the range of 6.5 – 8 ppm.



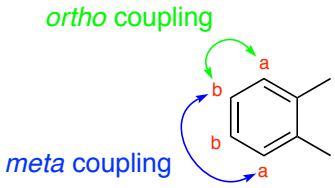
ortho-xylene

Furthermore, each of these signals may appear as a doublet of doublets. The protons in question will experience strong *ortho* coupling and weaker *meta* coupling, which results in this splitting pattern. The couplings are shown in the two diagrams below.



ortho-xylene

a is split into a doublet of doublets

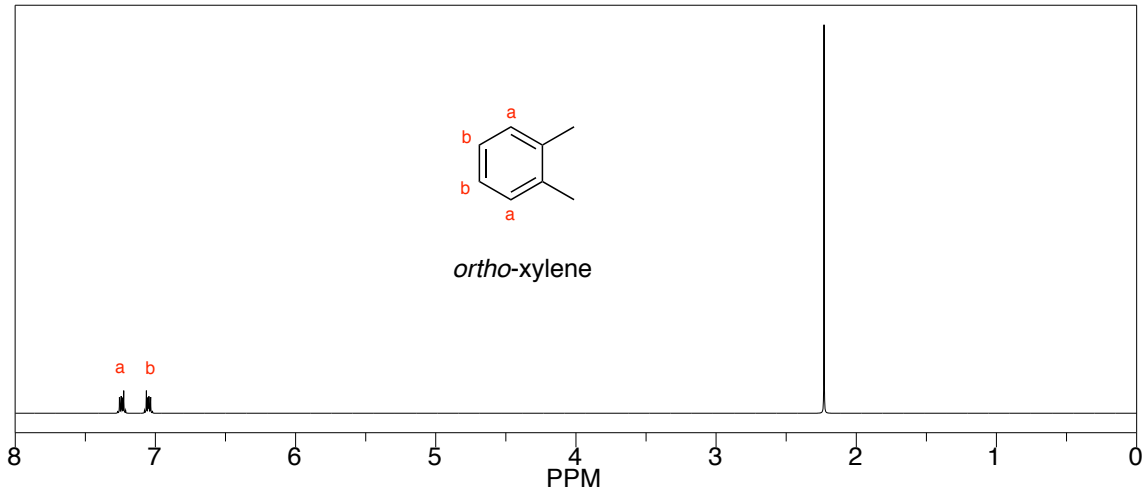


ortho-xylene

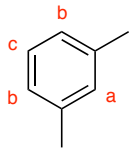
b is split into a doublet of doublets

If you are wondering why b was not split by the neighboring b proton in the second diagram, remember that coupling only occurs between protons that are in different chemical environments. Chemically equivalent protons causing the same signal do not split each other.

The proton NMR spectrum of *ortho*-xylene is shown below.



The aromatic region of *meta*-xylene's proton NMR spectrum is expected to be quite different. First of all, there are three types of aromatic protons (a, b, and c), so we expect three signals in this region. Two of these signals will integrate for only one hydrogen, while the other will integrate for two hydrogens.



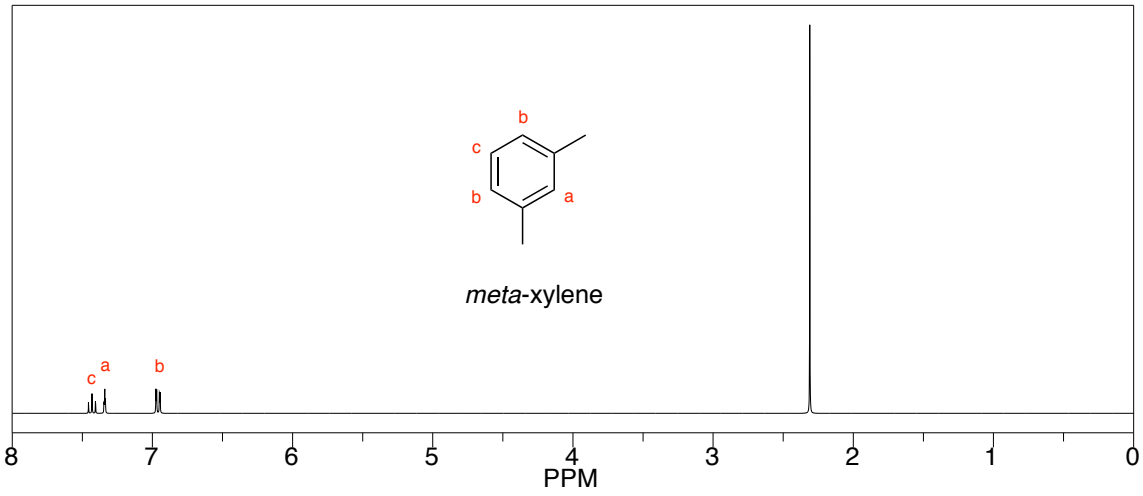
meta-xylene

The splitting patterns are also worth contemplating. Proton a may experience weak *meta* coupling to the two b protons. This would make its signal a triplet. However, since *meta* splitting is weak, the three peaks of the triplet will be quite close, and this signal may even appear as a singlet if the *J* value is quite small. Note that *para* splitting is so small in magnitude that it is very unlikely to be observed.

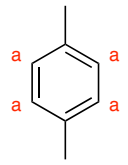
Protons b will be split with strong *ortho* coupling by c and with weak *meta* coupling by proton a. As a result, the signal for b could be a doublet of doublets. Once again though, if the magnitude of the *meta* coupling is small, the second splitting may not be that apparent, and the signal for b might look like a doublet.

Finally, proton c will be split with strong *ortho* coupling by its two neighbors b. *Para* splitting is so small that it would not likely be observed. As such, the signal for c should appear as a triplet.

The ^{1}H NMR spectrum for *meta*-xylene is shown below.

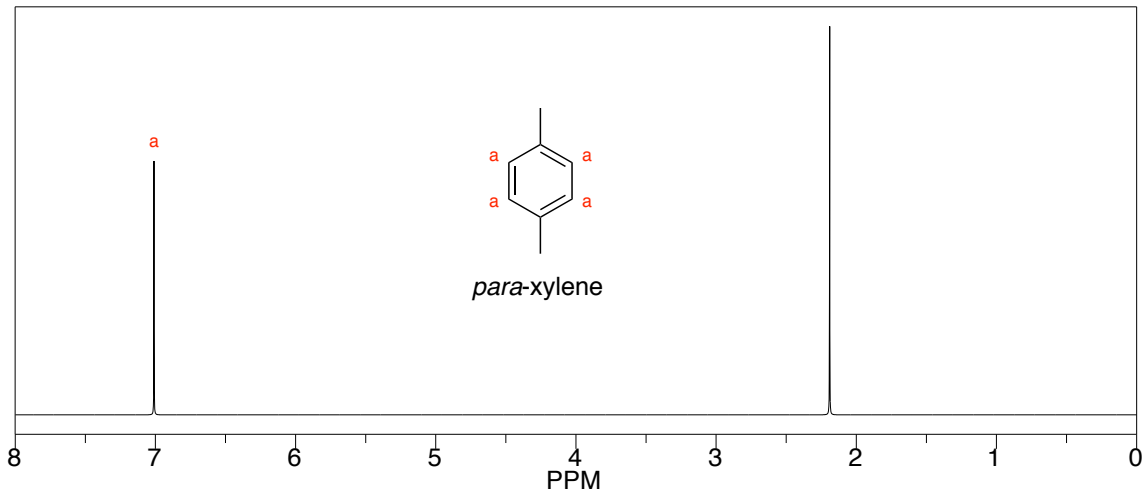


Para-xylene has a much simpler aromatic region. It has only one type of aromatic proton.



para-xylene

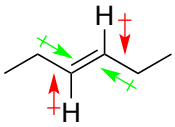
As a result, we expect only a singlet (with a relative integration of four) in the region of 6.5 – 8 ppm.



If you are wondering why the neighboring a protons don't split each other, remember that chemically equivalent hydrogens do not couple.

40. The hint told us to focus on the C=C stretch. The information in the question noted the significance of a bond's polarity in IR spectroscopy. Totally non-polar bonds will not resonate in the IR. So, we should evaluate the polarity of each alkene's double bond.

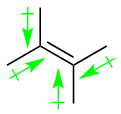
Trans-3-hexene contains a completely non-polar double bond. The dipoles of the C-H bonds point in exactly opposite directions and therefore cancel. Similarly, the dipoles of the $C_{sp^2} - C_{sp^3}$ bonds face exactly opposite directions and cancel each other as well.



trans-3-hexene

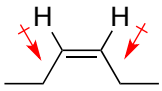
Since *trans*-3-hexene has a totally non-polar C=C bond, it will not resonate in the IR, and there will be no C=C stretch at 1650 cm^{-1}.

Similarly, 2,3-dimethyl-2-butene contains a completely non-polar carbon-carbon double bond. The dipoles of the four $C_{sp^2} - C_{sp^3}$ bonds are symmetrically situated and therefore cancel each other. Consequently, this compound will not exhibit a C=C stretch at 1650 cm^{-1} either.



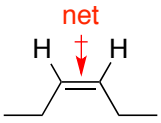
2,3-dimethyl-2-butene

However, *cis*-3-hexene does have a polar carbon-carbon double bond. The two alkene C-H bonds have dipoles that do not cancel completely.



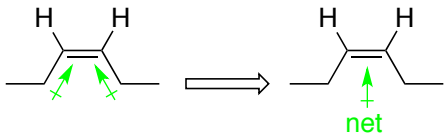
cis-3-hexene

Their horizontal components cancel, but there is an additive vertical component.



cis-3-hexene

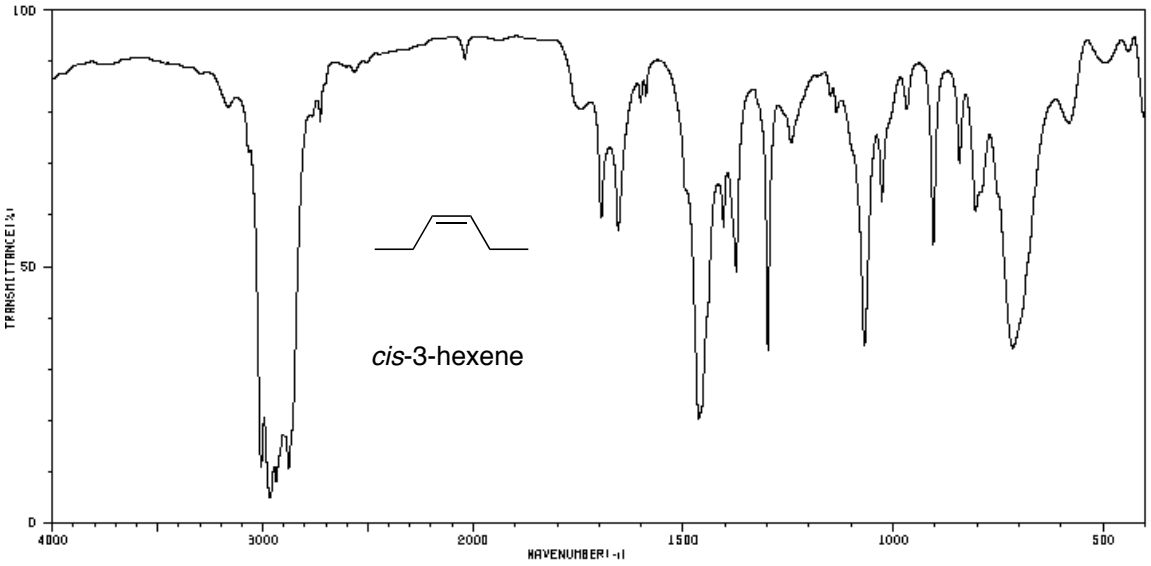
Similarly, the dipoles of the two $C_{sp^2} - C_{sp^3}$ bonds have horizontal components that cancel but vertical components that are additive.



cis-3-hexene *cis*-3-hexene

The net C-H dipole opposes the net $C_{sp^2} - C_{sp^3}$ dipole, but the magnitude of these dipoles is not identical. Therefore, there will be a net dipole for the bond. We need

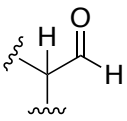
not calculate its each magnitude to know that a C=C stretch at about 1650 cm^{-1} will result. Therefore, it is the third IR spectrum that belongs to *cis*-3-hexene. This is the only one with a signal at ~1650 cm^{-1}.



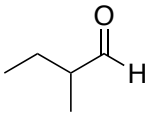
41. In this problem, we have not been provided with a molecular formula, so we cannot perform a degrees of unsaturation calculation, and we may proceed directly to analysis of the IR spectrum. The IR reveals a carbonyl, as well as sp^3 C-H stretching.

The most deshielded signal in the proton NMR appears at ~9.7 ppm and indicates than an aldehyde is present. This is consistent with the observation of a carbonyl in the IR spectrum. Furthermore, if we were to return to the IR spectrum and examine it carefully, we would also see the aldehyde (sp^2) C-H stretch in the range of 2700 – 2800 cm^{-1}.

The aldehyde signal is a doublet, so the aldehyde proton must have one neighbor. This neighbor must be the proton causing the signal at ~2.4 ppm because that is the only other methine (CH) suggested by the spectrum. Furthermore, the chemical shift for this signal is consistent with a proton on a carbon adjacent to a double bond.



There are three remaining signals in the proton NMR. Their integrations tell us that they are a methylene and two methyl groups. There is only one way to add these fragments to our growing molecule.

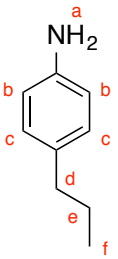


The methine and methylene cause multiplets because they both have many neighbors. One methyl group is a doublet because it has only one neighbor, while the other methyl group is a triplet because of its two neighbors.

The ^{13}C NMR supports our structure because the carbonyl carbon appears above 160 ppm and the four carbons of the alkyl group all reside below 100 ppm.

42. When you are asked to predict a spectrum, the best strategy is to develop a list of the expected signals first. Once you have this list in hand, the spectrum can be easily drawn.

To develop this list, we should begin by determining how many signals will appear. There are six types of protons in this compound (a – f), so we anticipate six signals.



The amine protons (a) will be a broad singlet due to their hydrogen-bonding capability. The chemical shift of amine protons is variable, but should appear somewhere between 1 and 5 ppm. Since there are two protons causing this signal, the relative integration will be two. We can concisely summarize all of this information as follows.

a: δ 1 – 5 ppm (br s, 2H)

The aromatic protons b will appear in the range of 6.5 – 8 ppm. The signal will integrate for two hydrogens, and it will be split into a doublet by the neighbor c.

b: δ 6.5 – 8 ppm (d, 2H)

The same attributes are expected for the signal result from aromatic protons c.

c: δ 6.5 – 8 ppm (d, 2H)

Methylene protons d are on a carbon adjacent to a double bond and will therefore appear between 1.5 and 2.5 ppm. The signal will integrate for two hydrogens. It will be split into a triplet by the two neighbors e.

d: δ 1.5 – 2.5 ppm (t, 2H)

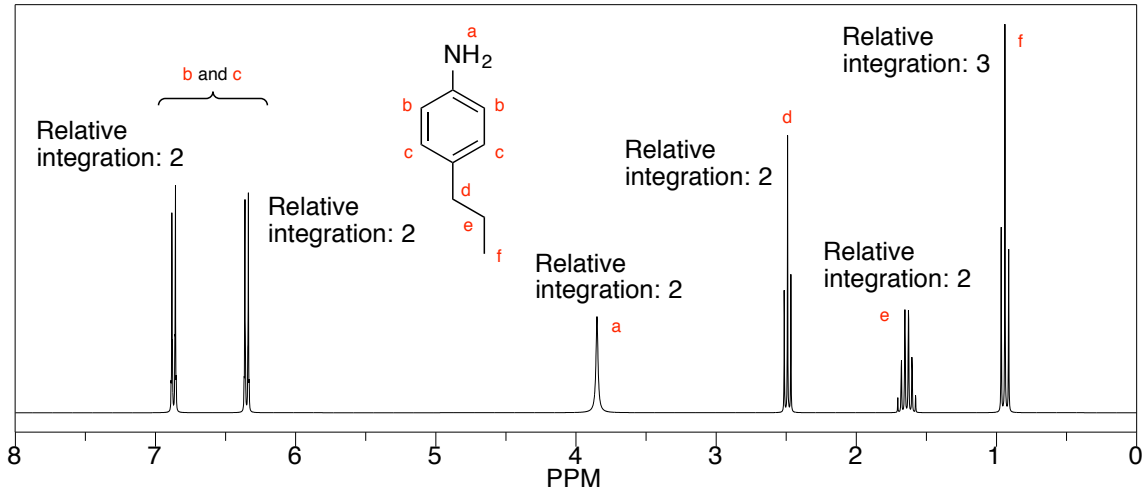
Methylene protons e are alkyl in nature and are expected to appear from 0 – 1.5 ppm. They will likely be at the higher end of this range because they are still relatively close to the aromatic ring. The signal will integrate for two hydrogens, and it will be split into a multiplet by its many neighbors (d and f).

e: δ ~1.5 ppm (m, 2H)

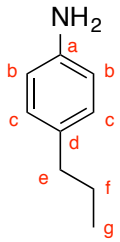
Methyl protons f are part of an alkyl group and will therefore appear between 0 and 1.5 ppm. The signal will integrate for three, and it will be split into a triplet by the two neighbors e.

f: δ 0 – 1.5 ppm (t, 3H)

These signals are now placed onto the spectrum.



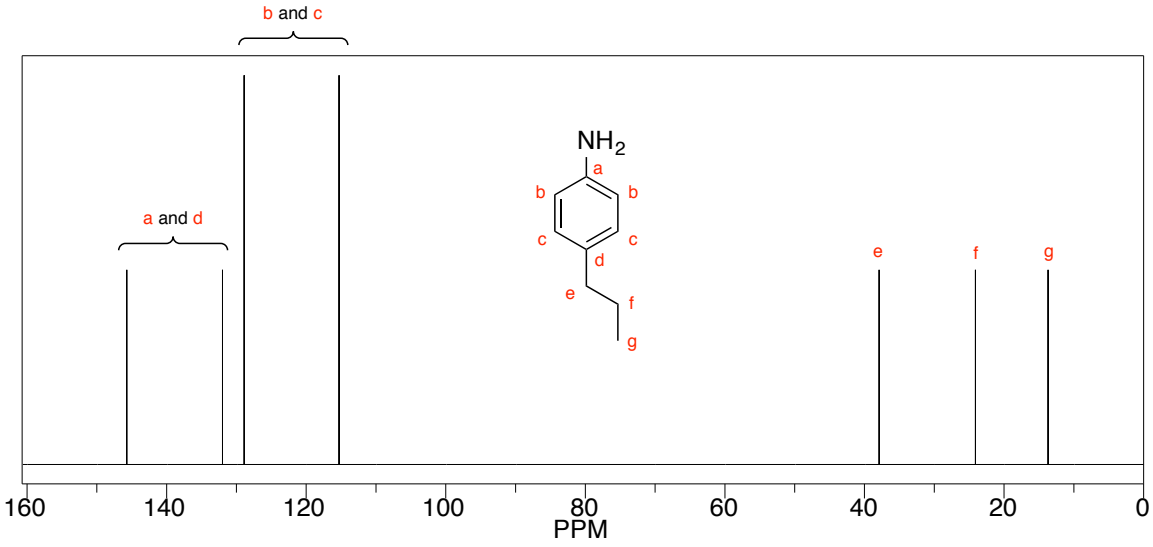
43. There are seven types of carbons in this compound (a – g), so we expect seven signals in the carbon-13 NMR spectrum.



Carbons a – d are all aromatic and will therefore appear between 100 and 150 ppm. The signals for b and c will be larger than the other signals because they account for two carbons rather than just one.

Carbons e, f, and g are all alkyl in nature, so they will appear from 0 – 100 ppm. We can expect e to be the most deshielded because it is closest to the aromatic ring. Carbon f will be a bit more shielded, and carbon g will be the most shielded since it is furthest from functionality.

The complete predicted ^{13}C NMR is shown below.



44. The degrees of unsaturation calculation shows that there are six DOU in this compound.

$$DOU = \frac{[2n+2] - hydrogens\ and\ hydrogen\ equivalents\ in\ formula}{2}$$

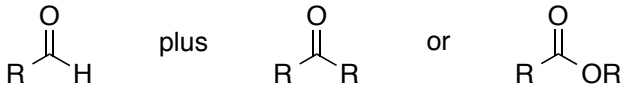
$$DOU = \frac{[2(9)+2] - 8}{2} = 6$$

It is likely that four of these degrees of unsaturation stem from an aromatic ring. Sure enough, there is a signal between 6.5 and 8 ppm in the proton NMR spectrum

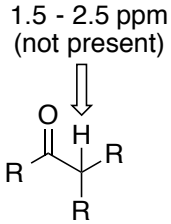
that implies aromatic protons. Also, there are four signals between 100 and 150 ppm in the carbon-13 NMR spectrum. Two of these are larger, which suggests that they may be due to two carbons apiece. Thus, the six carbons of an aromatic ring are also accounted for.

The proton NMR has a signal at ~10 ppm that suggests an aldehyde. The aldehyde's carbonyl π bond would be the fifth degree of unsaturation. The carbon-13 NMR has not just one but two signals above 160 ppm, so there are two carbonyls in the molecule. The aldehyde is one, but we also have a second carbonyl to explain. Its π bond would be the sixth and final degree of unsaturation.

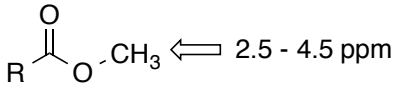
The second carbonyl isn't an aldehyde because there is only one aldehyde proton. Similarly, it cannot be a carboxylic acid because there is no carboxylic acid proton in the ^{1}H NMR spectrum. This leaves a ketone or an ester as the last reasonable possibilities.



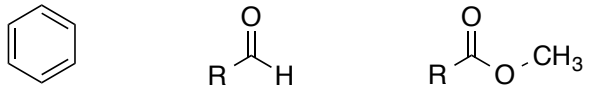
Protons adjacent to ketones appear between 1.5 and 2.5 ppm in the proton NMR spectrum. Given that there aren't any signals in this range, a ketone seems unlikely, especially since there aren't enough remaining carbons in the formula to occupy all of the sites on the carbons adjacent to the ketone.



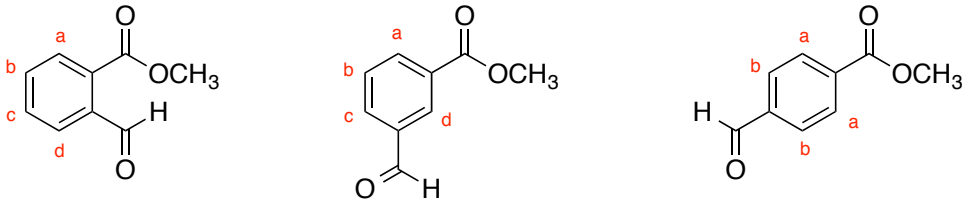
On the other hand, the protons adjacent to an ester's sp^3 oxygen appear between 2.5 and 4.5 ppm. The signal at 3.9 ppm is in this range. It integrates for three, showing that a methyl group occupies this position.



We now have three fragments: an aromatic ring, an aldehyde, and a methyl ester.

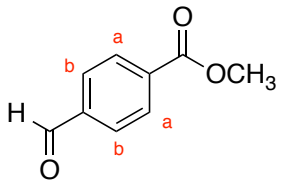


These account for all nine carbons and three oxygens in the molecular formula. All that remains is to properly assemble these fragments. The signal at ~8 ppm integrates for four. Since the aromatic ring has only four hydrogens, both the aldehyde and the ester must be bonded to it. There are three ways to do this, but only one is consistent with the appearance of the signal at ~8 ppm.



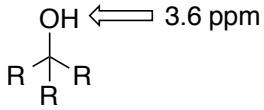
If the ester and aldehyde are adjacent to each other (the first structure in the diagram above), four aromatic signals are expected in the proton NMR. If there is one intervening methine between them (the second structure in the diagram above), we also expect to see four aromatic signals in the ^{1}H NMR. However, if they are opposite each other on the ring (the last structure in the diagram above), then only two aromatic signals are expected.

The signal at ~8ppm has four peaks. This not consistent with either of the first two structures. While they would both yield four signals, these signals would exhibit splitting, so we would expect more peaks. The last structure, however, would yield two doublets (for a total of four peaks). If those doublets have similar chemical shifts, we would observe an AB quartet due to second-order coupling. Since protons a and b are in similar (but still different) chemical environments, the AB quartet is reasonable.

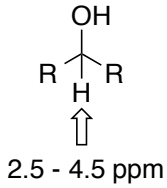


45. We have no formula, so a degrees of unsaturation calculation is not possible. The IR spectrum reveals sp^3 C-H stretching (just below 3000 cm^{-1}) and what is most likely an alcohol O-H stretch (broad signal at ~3350 cm^{-1}).

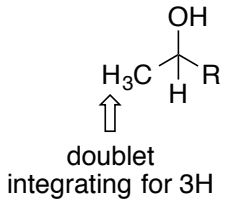
An alcohol proton is expected to appear as a broad singlet between 1 and 5 ppm in the ^{1}H NMR spectrum. Indeed, there is just such a signal at ~3.6 ppm.



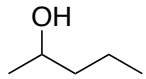
Now that we have an alcohol fragment, we can build outward from it. If there were protons on the carbon bearing the hydroxyl group, these would be expected to appear in the range 2.5 – 4.5 ppm. There is a signal at ~4.0 ppm, and it integrates for one hydrogen, telling us that a methine group resides at this location.



There are three remaining signals in the proton NMR spectrum. One is a multiplet integrating for four. One is a doublet integrating for three, and the last is a triplet integrating for three. The doublet integrating for three is relevant because it suggests a methyl group with one neighbor, and the methine that we just placed could serve as this single neighbor.

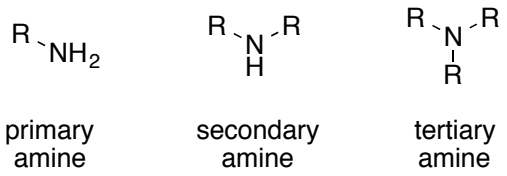


We now have only one site on the alcohol fragment to which we can attach the remaining pieces of the molecule. The multiplet integrating for four must be due to two methylene groups. The triplet integrating for three is a methyl group. Placing them onto our growing fragment gives the unknown's structure.

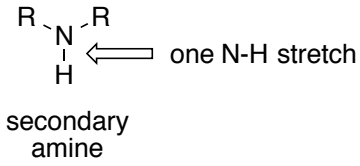


This is consistent with the five carbons below 100 ppm in the carbon-13 spectrum. Additionally, the formula of this molecule ($C_5H_{12}O$) gives a molecular weight of 88 g/mole as stated in the problem.

46. The word "amine" is an important clue in the text of the problem. This tells us the functionality in the molecule. However, amines can be primary, secondary, or tertiary as shown below.

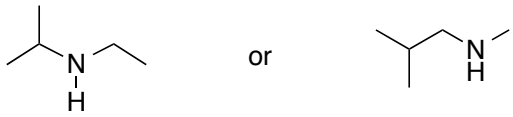


The IR spectrum shows a single, sharp peak in the heteroatom-to-hydrogen stretching region, indicating the presence of *one* N-H stretch. This is consistent only with the structure of a secondary amine. A primary amine would give two peaks in this region because of symmetric and asymmetric stretching, while a tertiary amine would exhibit no signal in this area.

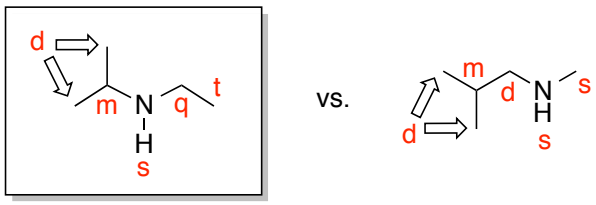


There are no other significant IR signals in the functional group region, except for sp^3 C-H stretching just below 3000 cm^{-1}.

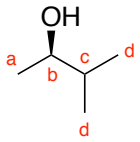
The carbon-13 spectrum has four signals below 100 ppm. One of these is much larger than the others, suggesting that it results from two equivalent carbons. Therefore, the molecule seems to contain a total of five carbons. There are two ways to place five carbons into this structure so that two of them are equivalent. Both of these have molecular weights of 87 g/mole.



These compounds display different splitting patterns in the proton NMR spectrum. The first structure is consistent with the signals report in the problem: a singlet (s), a doublet (d), a triplet (t), a quartet (q), and a multiplet (m).

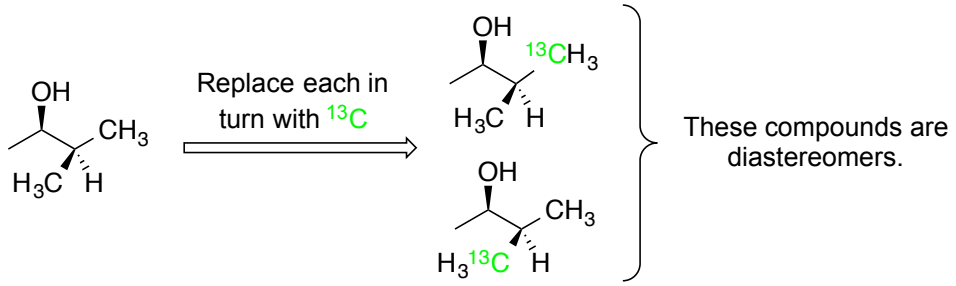


47. The presence of five signals in this alcohol's carbon-13 NMR spectrum is initially surprising because we might have anticipated only four. Two of the methyl groups stem from the same carbon and therefore appear to be equivalent.

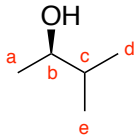


However, we have seen that protons stemming from the same carbon need not necessarily be equivalent. When they are diastereotopic, they give rise to separate signals. If protons can be diastereotopic, it stands to reason that other atoms (like carbon) could be diastereotopic as well.

One test for diastereotopic atoms is sequential isotopic substitution. If we use a pair of isotopes relevant for this situation (e.g., ^{12}C and ^{13}C), sequential isotopic substitution yields diastereomers. This shows that these two carbons are, in fact, diastereotopic.



As such, they are in chemically distinct environments, explaining why five carbon-13 signals are observed.

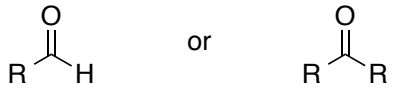


48. The degrees of unsaturation calculation shows that this molecule contains one ring or one π bond.

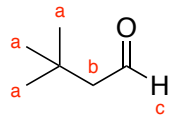
$$DOU = \frac{[2n+2] - hydrogens\ and\ hydrogen\ equivalents\ in\ formula}{2}$$

$$DOU = \frac{[2(6)+2] - 12}{2} = 1$$

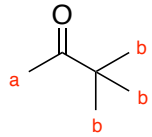
The IR spectrum has a signal at ~1700 cm^{-1}, showing that the DOU is the π bond of a carbonyl. Given the presence of only one oxygen in the molecular formula, this carbonyl could be a ketone or an aldehyde.



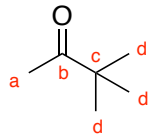
We are left with five carbons to place. There must be some element of symmetry to the molecule because there are only two signals in the proton NMR. It quickly becomes apparent that we cannot generate an aldehyde with this formula that will give only two ^{1}H NMR signals. The most symmetrical aldehyde possible has three signals.



We therefore turn our attention to a ketone. If it contains a *tert*-butyl group, a ketone with this formula can yield only two proton NMR signals.



This ketone would yield four signals in the carbon-13 NMR, which is consistent with the data given.



49. The degrees of unsaturation calculation shows that there are two rings, two π bonds, or one of each in this molecule's structure.

$$DOU = \frac{[2n+2] - hydrogens\ and\ hydrogen\ equivalents\ in\ formula}{2}$$

$$DOU = \frac{[2(5)+2]-8}{2} = 2$$

The IR spectrum has three prominent signals in the functional group region, two of which do not fall in our usual spot-check regions. The signal just below 3000 cm^{-1} is due to sp^3 C-H stretching.

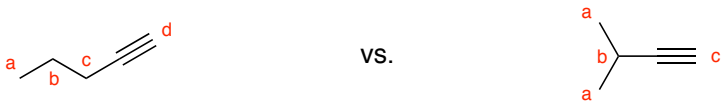
The signals at ~3300 cm^{-1} and between 2100 and 2200 cm^{-1} both point to the same functionality: an alkyne. Alkyne (sp) C-H stretching appears at 3300 cm^{-1}, while C≡C

stretching appears between 2100 and 2200 cm^{-1}. An alkyne includes two π bonds, so it accounts for both DOUs in the molecule.

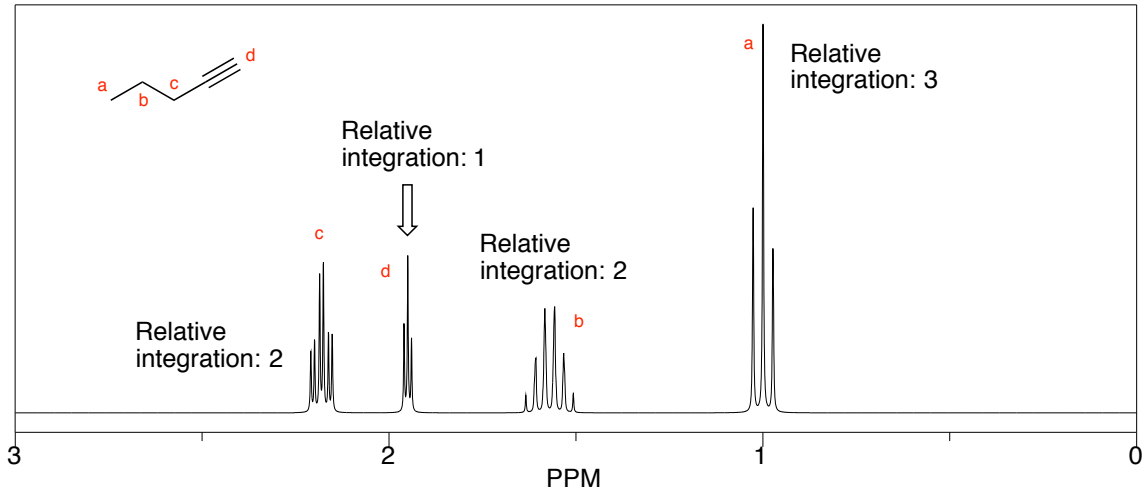
In order for the alkyne to bear a proton, it must be at the terminus of the molecule.

R–C≡C–H

We need only decide how to attach the three remaining carbons so that the structure is consistent with the proton NMR spectrum. There are two choices. We can add these three carbons to the alkyne as a propyl or an isopropyl group. The first compound has the correct number of proton NMR signals.



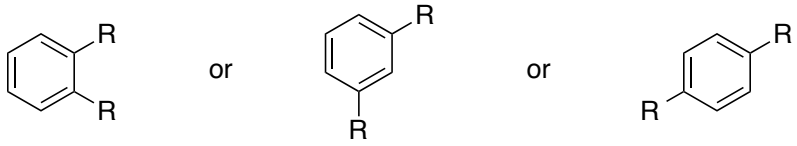
This alkyne has a methyl group (a) that gives a triplet integrating for three. It has a methylene (b) that yields a multiplet integrating for two. It has a second methylene (c) that generates a doublet of triplets due to long-range splitting by the alkyne proton. Similarly, the alkyne proton (d) is a triplet due to long-range coupling with methylene c.



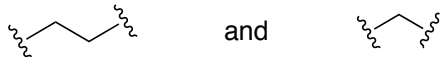
50. Without a molecular formula, we cannot perform a degrees of unsaturation calculation. However, the IR spectrum suggests that some DOUs are present in the molecule. There is a carbonyl resonance just above 1700 cm^{-1}.

There is also both sp^2 and sp^3 C-H stretching (above and below 3000 cm^{-1}, respectively).

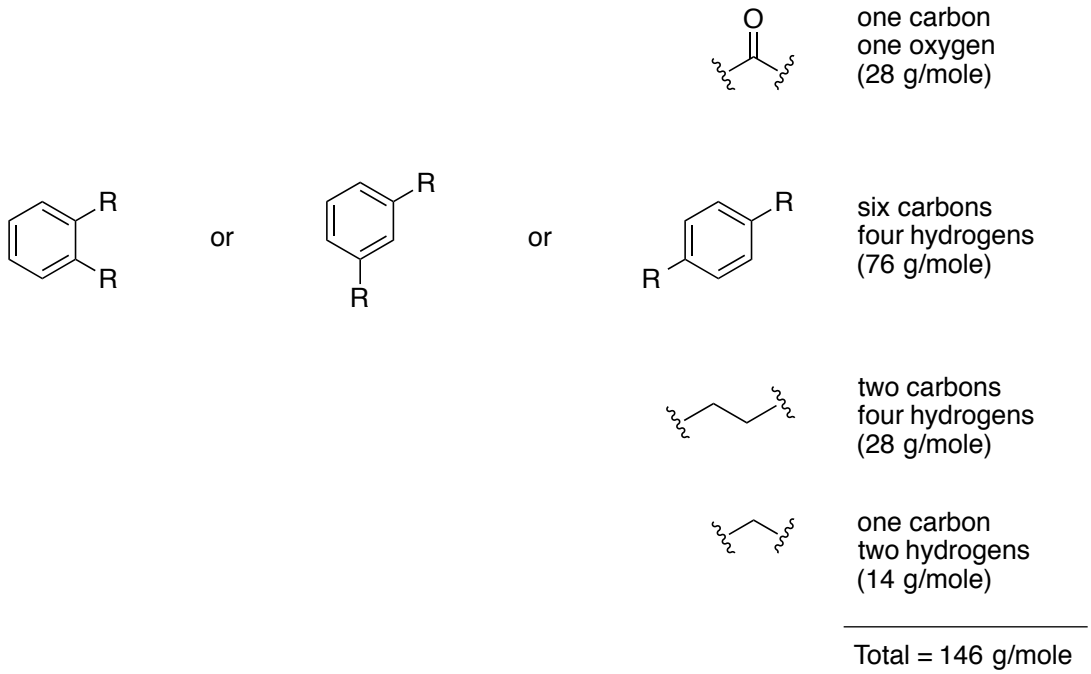
The proton NMR spectrum has a signal between 6.5 and 8 ppm that integrates for four hydrogens. This implies a disubstituted aromatic ring.



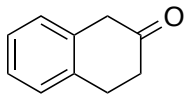
The proton NMR also shows three methylene groups, two of which are adjacent (splitting each other into triplets) and one of which is isolated (yielding a singlet).



If we compare the fragments that we've amassed thus far to the molecular weight, it becomes apparent that we have identified all of the atoms.



Given that there are no methyl groups or other entities that can serve to terminate a chain, there must be another ring present. To draw a reasonable structure with another ring, we should use the disubstituted benzene with the R groups adjacent to each other. For the structure's splitting pattern to be consistent with the proton NMR spectrum, the carbonyl must separate the isolated methylene from the two adjacent methylenes. This yields the compound's structure.



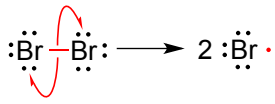
This structure is consistent with the carbon-13 spectrum, which includes one carbonyl above 160 ppm, six aromatic carbons between 100 and 150 ppm, and three sp^3 hybridized carbons below 100 ppm.

Solutions to Problems for Chapter 6: Radical Reactions

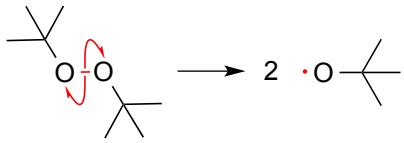
1.

(a) If bromine is homolytically cleaved, one of the shared electrons falls to each of the bromine atoms as the σ bond between them is fragmented.

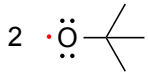
Lone pairs need not necessarily be drawn, but it is nevertheless important to recognize that they are present.



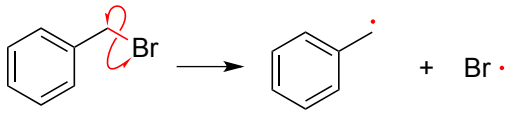
(b) If the oxygen-oxygen bond of di-*tert*-butyl peroxide cleaves homolytically, each of the oxygen atoms acquires one of the σ-bonding electrons.



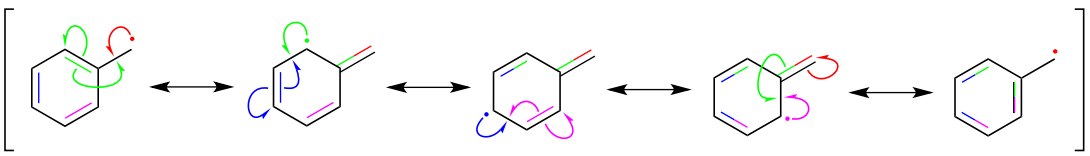
Again, while the drawing of lone pairs is optional, it is important to be cognizant of their presence.



(c) When benzyl bromide cleaves homolytically, both the carbon and the bromine atoms acquire an electron.

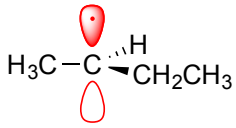


The carbon-centered radical may be delocalized around the ring via resonance.

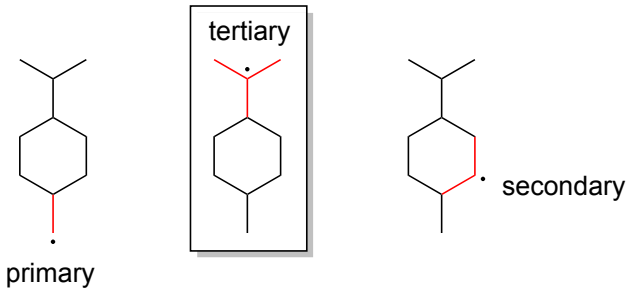


(d) If the carbon-chlorine bond of this chiral molecule homolyzes, both carbon and chlorine receive a single σ-bonding electron.

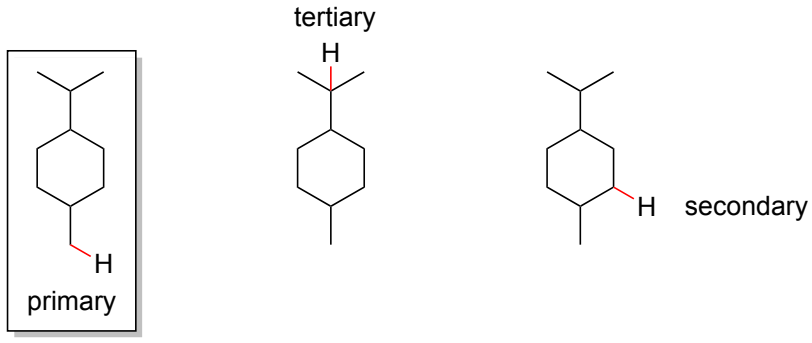
The resultant carbon-centered radical is, however, achiral. When the carbon-chlorine bond was broken, the stereochemistry was erased. The radical is trigonal planar.



2. These three radicals differ in their substitution. The first is on a carbon that is bonded to only one other carbon, making it primary. The second radical has bonds to three additional carbons, so it is tertiary. Finally, the last radical is joined to two neighboring carbons, rendering it secondary. The most substituted radical, which is tertiary in this case, is the most stable.

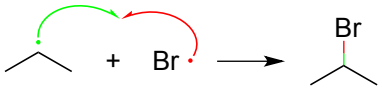


3. The indicated hydrogens are primary, tertiary, and secondary, respectively, and their loss through homolysis would lead to the radicals that we saw in Problem 2. Since the primary radical is the least stable of the three, the primary hydrogen is the most difficult to remove through homolysis. Another way of expressing that same idea is to say that the primary carbon-hydrogen bond has the greatest bond dissociation energy.

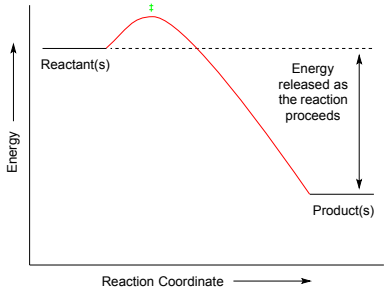


4.

(a) In the first process, a bond is being made from two radicals. Bond formation releases energy.



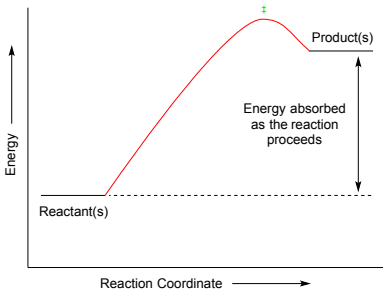
Therefore, this reaction matches energy diagram (ii).



Another way of viewing this is that the product is more stable than the reactants. The reactants are radicals and are therefore electron deficient because they lack a complete octet. On the other hand, the product possesses a filled outer shell for each of its atoms, making it more stable.

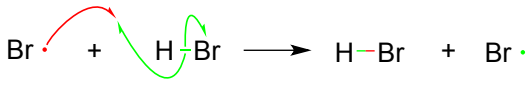
(b) In this reaction, bromine is homolyzed. A bond is cleaved, which necessitates an input of energy.

As a result, this reaction best matches energy diagram (iii).

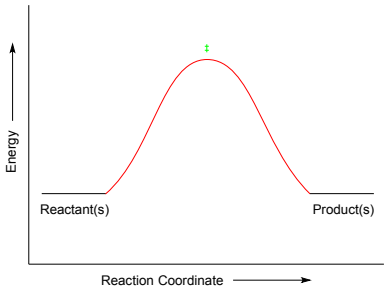


A complementary approach to this problem would be recognizing that the cleavage of a molecule in which all atoms possess complete octets to produce products in which atoms lack the octet will be an energetically uphill process.

(c) In this reaction, a bromine radical abstracts a hydrogen atom from HBr. Although a hydrogen atom is transferred from one bromine atom to another in the process, the products are identical to the reactants.

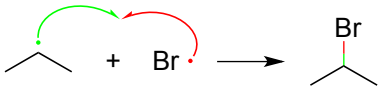


Given that the reactants and the products are completely identical, they must have the same energy. Therefore, this reaction best matches energy profile (i).



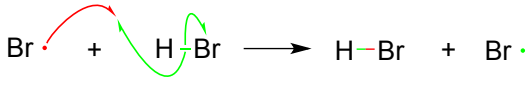
5.

(a) In this step, two radicals combine to yield a product without radicals. This is therefore a termination step.



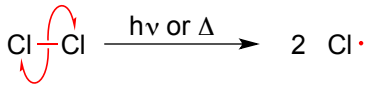
(b) In this instance, radicals are formed. It is therefore an initiation step.

(c) This could be considered a propagation step because there are radicals on both sides of the equation. However, it is worth noting that this step leads to no observable change since the reactants and products are identical.



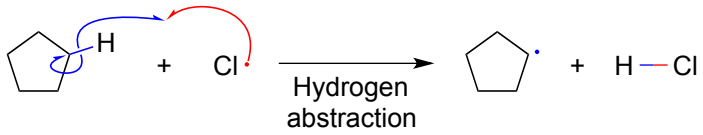
6. The reaction begins with homolysis of a few molecules of chlorine in the presence of light or heat.

Initiation:



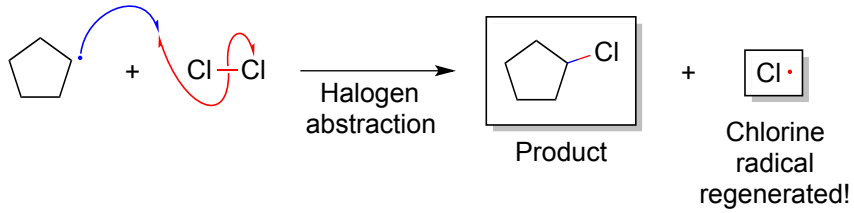
The chlorine radical then abstracts a hydrogen atom from any of the equivalent carbons of cyclopentane. This first propagation step yields one of the products (HCl) along with a carbon-centered radical.

Propagation step 1:



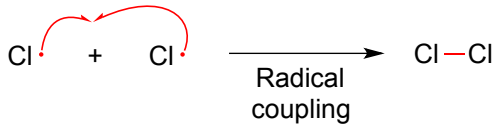
In the second propagation step, the cyclopentyl radical abstracts a chlorine atom from an unreacted molecule of Cl_2. This affords the second reaction product (chlorocyclopentane), and it also regenerates the chlorine radical, which continues the propagation cycle.

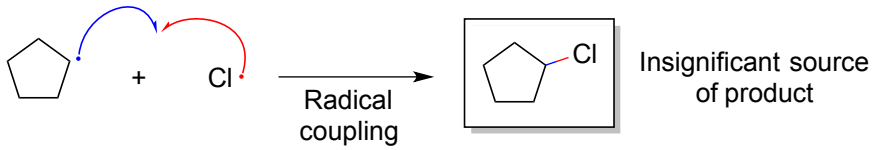
Propagation step 2:



Once the reactants have been consumed, termination steps explain the fate of the few remaining radicals. Any two radicals observed in the steps above can combine in the termination steps. This yields a miniscule amount of additional reaction products.

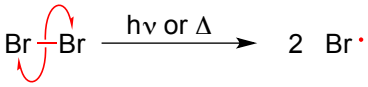
Termination:





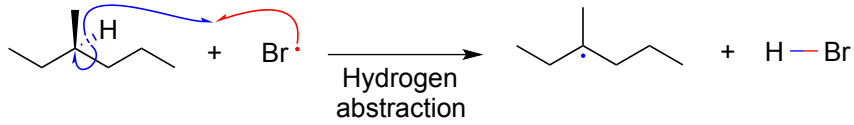
7. This reaction begins with the homolysis of a small number of bromine molecules upon exposure to light or heat.

Initiation:



In this section, we saw that bromine selectively abstracts the hydrogen atom from the most substituted position in the substrate to yield the most stable radical possible. In this example, it is the sole tertiary hydrogen that is removed to afford a tertiary radical along with HBr.

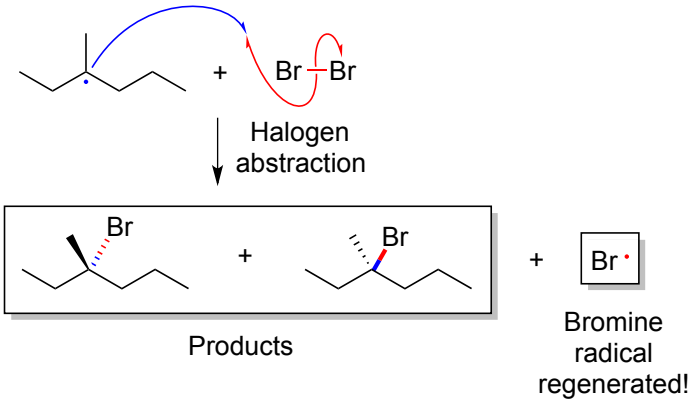
Propagation step 1:



Notice that the tertiary carbon is no longer a stereocenter. When it lost the hydrogen, it underwent rehybridization and became sp^2 or trigonal planar. Therefore, the methyl group is now in the same plane as the ethyl and propyl groups emanating from the radical.

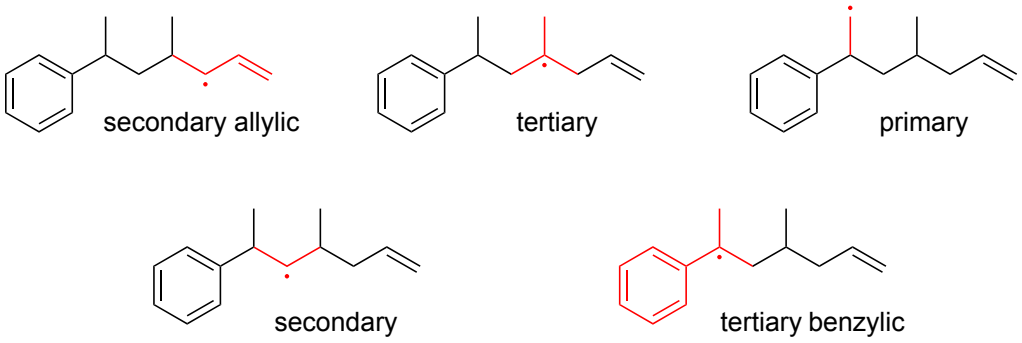
In the second propagation step, the tertiary radical abstracts a bromine atom from an unreacted molecule of Br_2. This leads to the formation of a tertiary alkyl bromide and the regeneration of the bromine radical needed to continue the propagation cycle.

Propagation step 2:

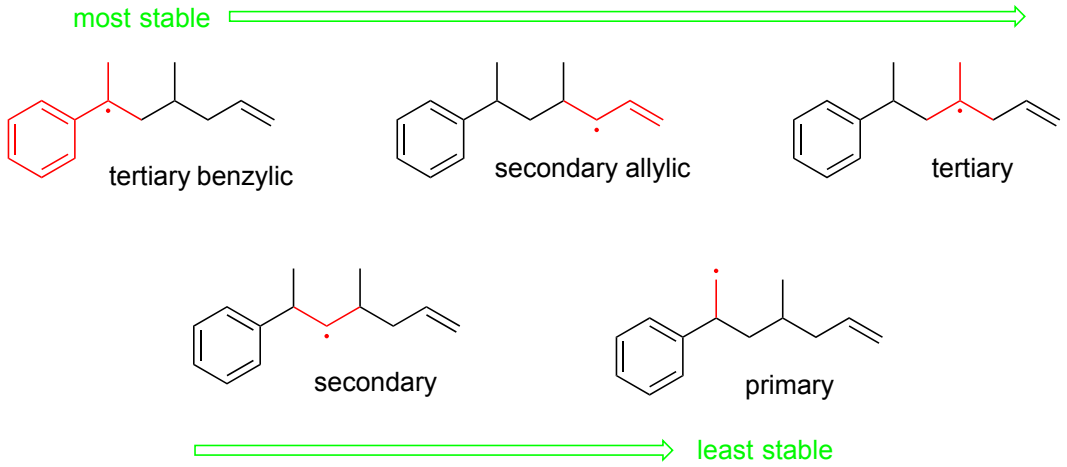


As bromine is added to the radical, stereochemistry reemerges at this center. Since the radical was trigonal planar (i.e., flat), there is no preference for the addition of the bromine atom from one side of the molecule or the other. As a consequence, both configurations are created, leading to a racemic mixture of enantiomers.

8. The first step in solving a problem like this is classifying each radical. Now, we must look for two features in our categorizations: substitution (primary, secondary, tertiary) and resonance (allylic, benzylic). These descriptions are applied to the radicals below.

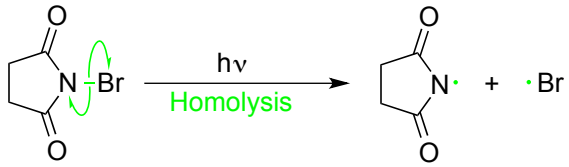


Increased substitution stabilizes a radical, as does resonance delocalization. As we saw from bond dissociation energies, resonance is a more powerful stabilizing factor than increased substitution. Therefore, the benzylic and allylic radicals are the most stable. The benzylic radical has the most conjugation, making it even more stable than the allylic radical. The allylic radical is then followed in stability by the tertiary, secondary, and primary radicals.



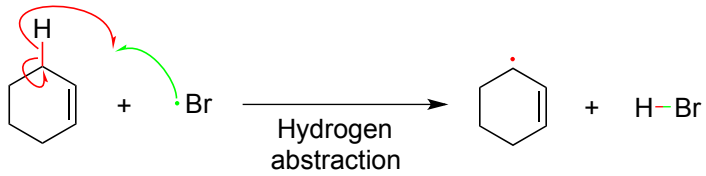
9. The reaction begins with the photochemically induced homolysis of some molecules of NBS.

Initiation:

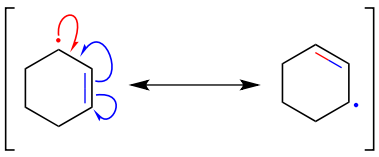


The bromine radical thus created abstracts a hydrogen from the substrate to form the most stable radical possible. In this case, abstraction of a hydrogen atom from either of the two equivalent allylic positions generates an allylic radical.

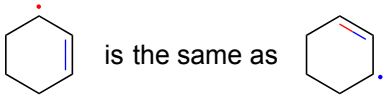
Propagation step 1:



The allylic radical enjoys resonance stabilization.

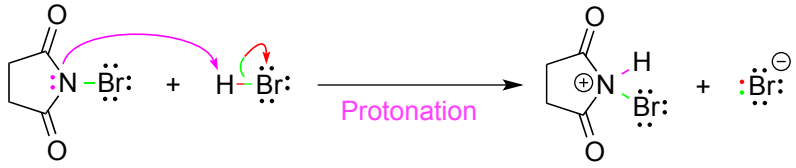


However, in this highly symmetrical substrate, the resonance forms are indistinguishable, so we need only use one moving forward.

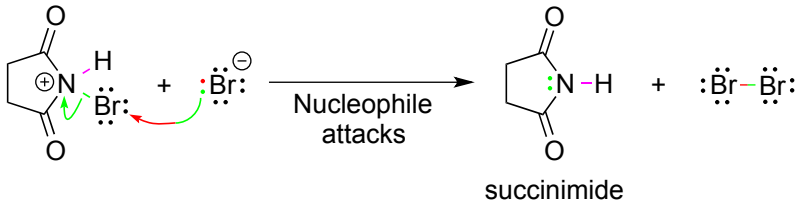


What follows next is a series of two ionic steps that consume the HBr generated during propagation step 1 and produce Br_2 in its place. First, NBS is protonated by the newly formed HBr.

Ionic interlude:

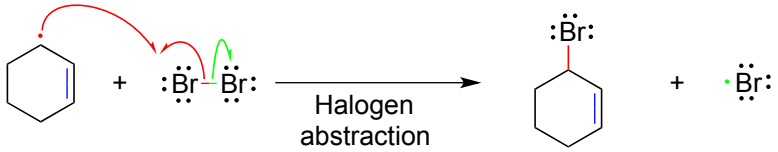


Then, bromide attacks the bromine atom of the conjugate acid of NBS. This yields Br_2 and expels succinimide.

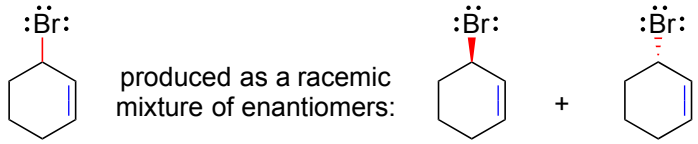


The nascent bromine molecule then reacts with the allylic radical in propagation step 2. A bromine atom is abstracted, leading to the formation of an allylic bromide as the product. Bromine radical is also regenerated, which allows for the continuation of the propagation cycle.

Propagation step 2:

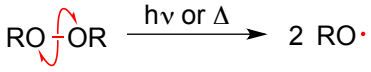


Notice that this reaction leads to the formation of a new stereocenter in the molecule. Since the radical that preceded this stereocenter was trigonal planar (i.e., flat) bromine is added from either side with no preference for one over the other. This results in the formation of a racemic mixture of enantiomers.



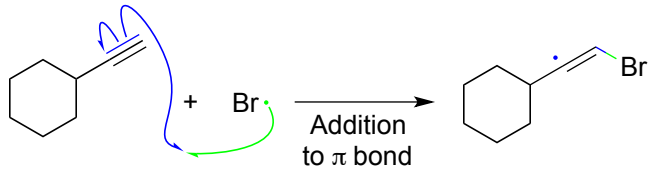
10. The reaction begins with the homolysis of the peroxide upon exposure to light or heat. The alkoxy radical thus formed subsequently abstracts a hydrogen atom from HBr. This yields an alcohol as an insignificant byproduct, along with the bromine radical that can begin the propagation cycle.

Initiation:



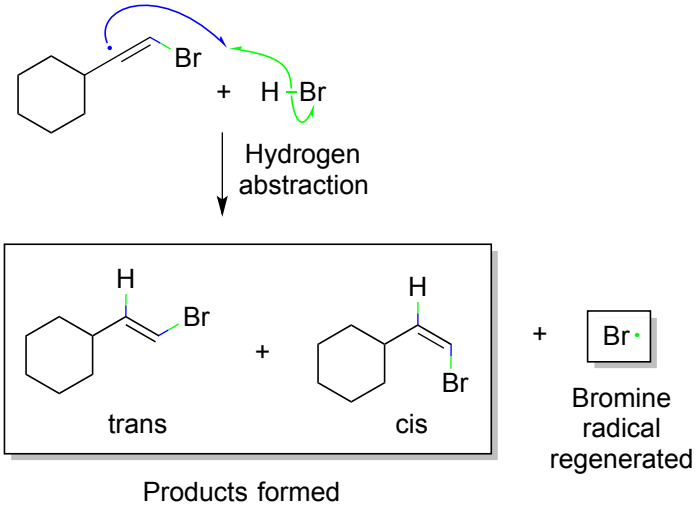
The first propagation step entails the addition of bromine to the alkyne. Bromine radical adds to the terminal carbon to form the more highly substituted carbon-centered radical.

Propagation step 1:

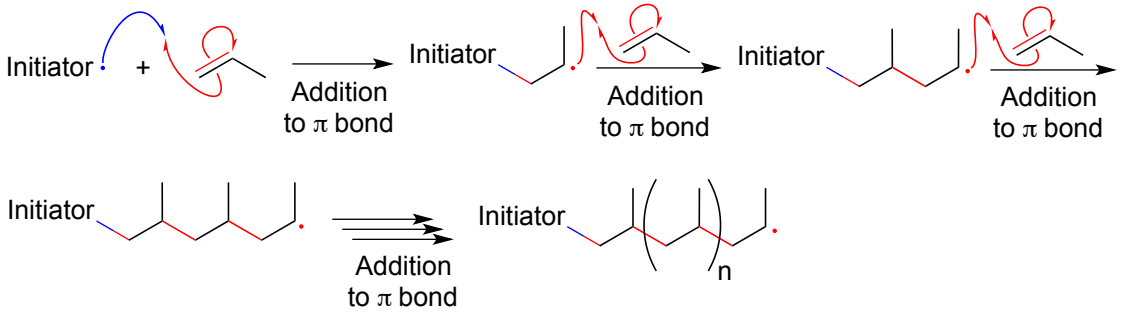


In the second propagation step, that carbon-centered radical abstracts a hydrogen atom from an unreacted molecule of HBr. As this occurs, the interior carbon adopts sp^2 hybridization, and both the *trans* and *cis* configurations of the resultant alkene are formed. Bromine radical is also regenerated and continues the propagation cycle.

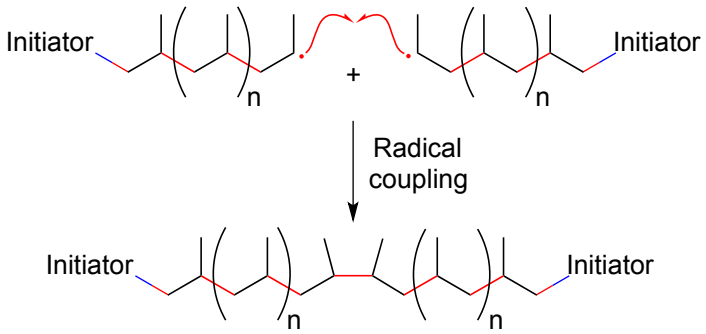
Propagation step 2:



11. The free-radical polymerization of propylene begins when a radical initiator adds to the alkene π bond. More specifically, it adds to the terminal carbon so as to generate the more stable secondary radical intermediate. This radical then adds to the π bond of a new propylene monomer, again producing the more stable secondary radical. This process continues until the chain becomes quite long.



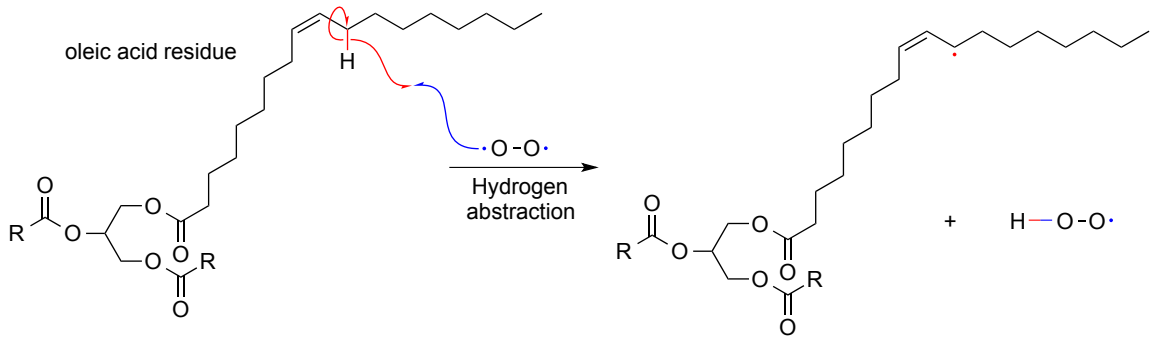
The polymerization could terminate through the union of two chains. The polymer product is known as polypropylene.



12. In this problem, we want to focus on the oleic acid residue because it contains the more reactive allylic hydrogens. The alkyl chains of the two palmitic acid

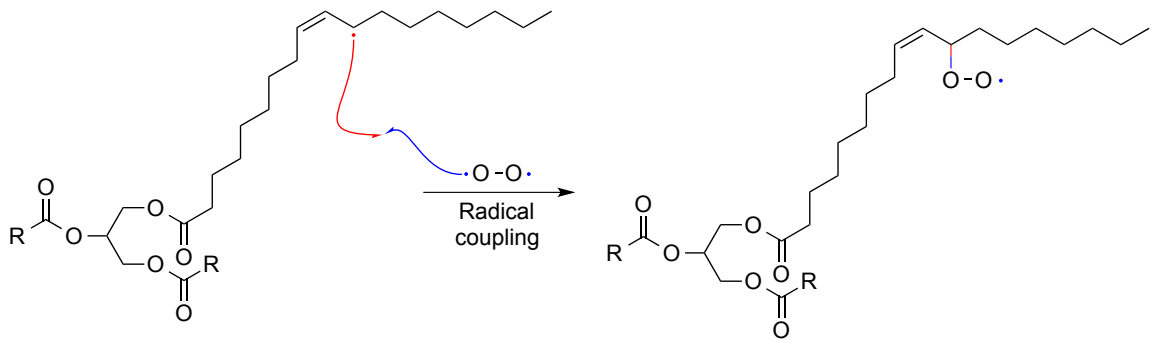
residues have been abbreviated as R groups below. The reaction begins with the abstraction of an allylic hydrogen by oxygen.

Initiation:



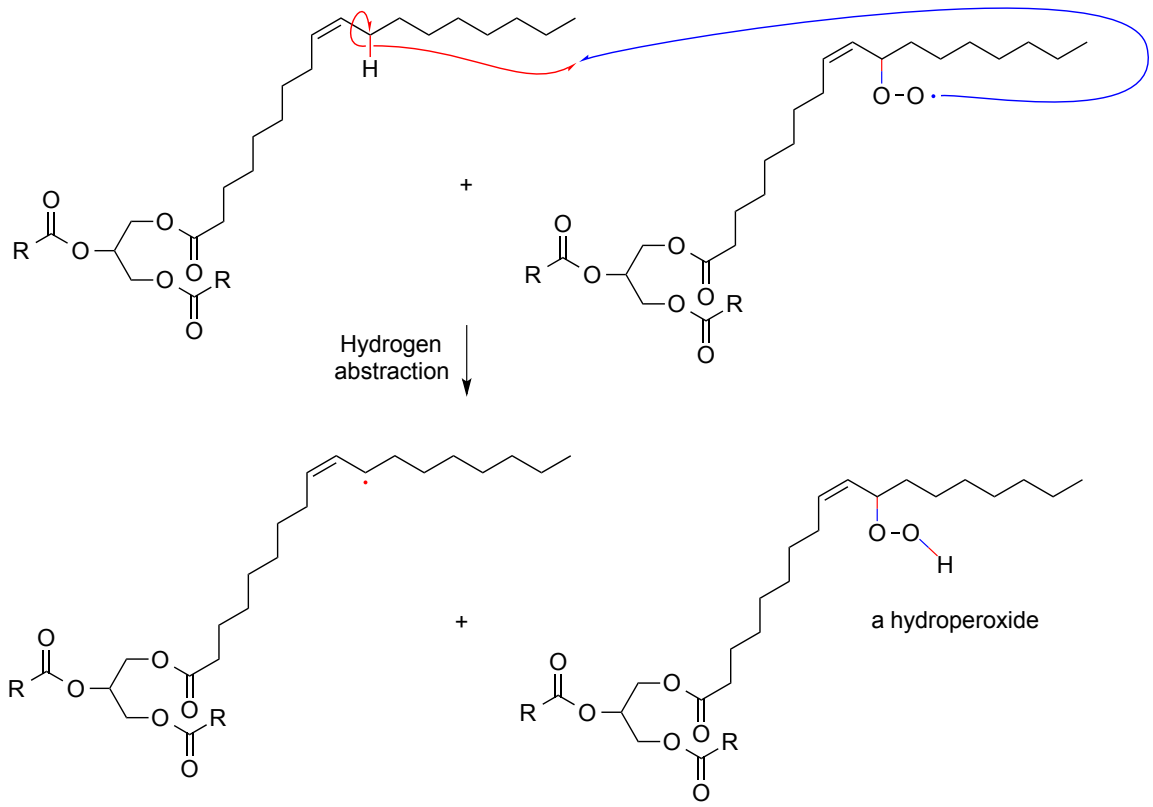
The allylic radical thus generated can combine with another molecule of oxygen.

Propagation step 1:

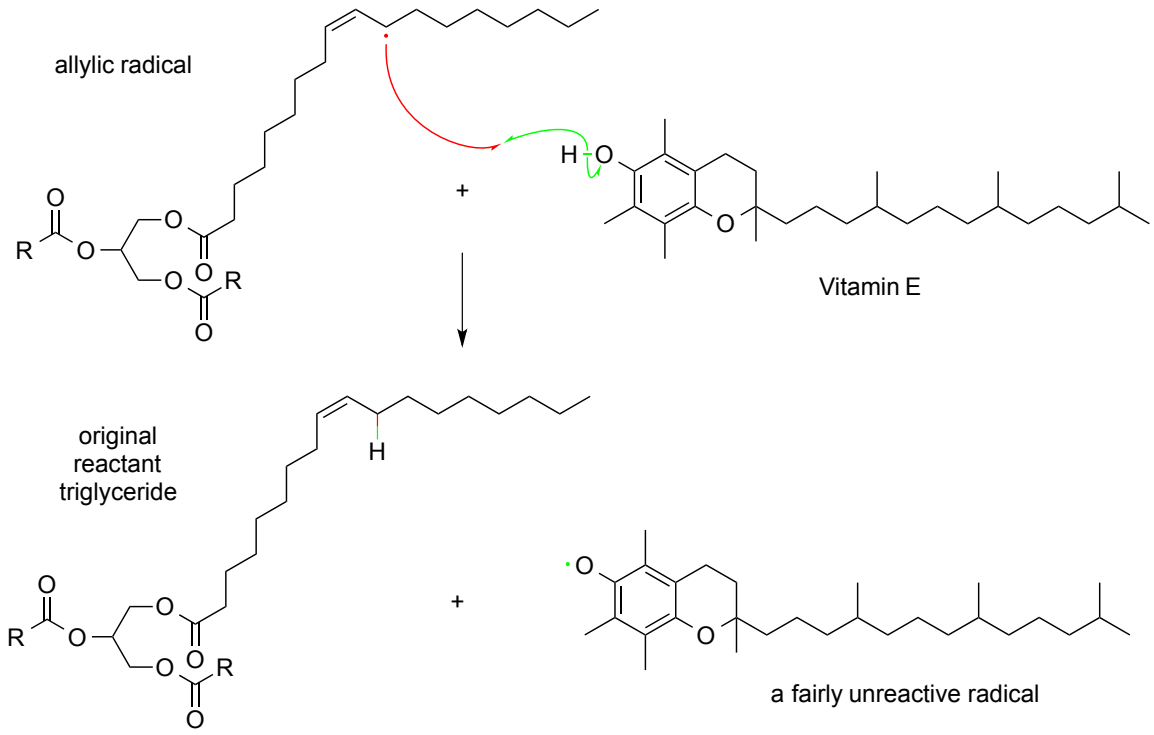


Finally, the hydroperoxy radical abstracts an allylic hydrogen from an unreacted triglyceride to yield a new allylic radical that will continue the propagation cycle as well as the hydroperoxide product.

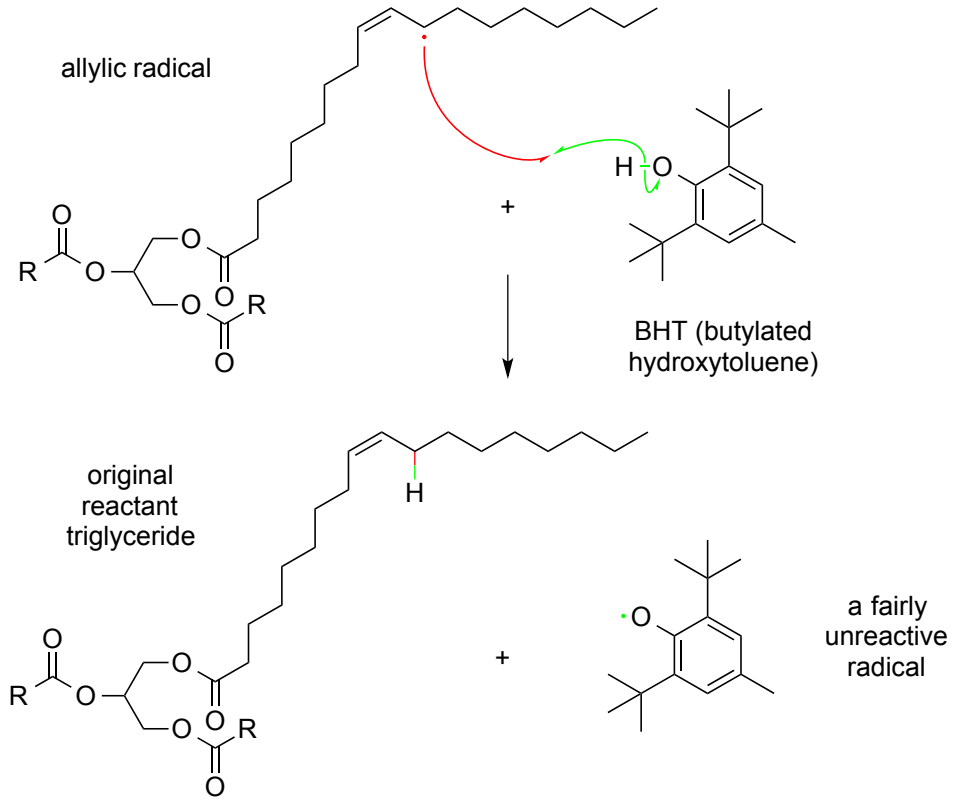
Propagation step 2:



13. The allylic radical formed in the oleic acid residue can abstract the hydrogen atom from the phenol in vitamin E. This quenches the reactivity of the allylic radical by re-forming the reactant triglyceride. Additionally, the radical is now sequestered on vitamin E, where it is resonance stabilized by the aromatic ring and sterically shielded from reaction by the adjacent methyl groups.



14. BHT has a phenol in its structure much like vitamin E does. Consequently, BHT is also capable of donating a hydrogen to the allylic radical formed from the triglyceride. In this way, the original triglyceride is once again re-formed.



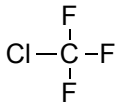
The radical produced from BHT is fairly unreactive because it has both resonance stabilization and steric shielding. The radical can be delocalized into the aromatic ring, much as it could be in vitamin E. Additionally, the large flanking *tert*-butyl groups provide a significant steric barrier to the approach of other molecules. This reduces the likelihood of the phenoxy radical reacting further.

15.

(a) The name Freon 13 has only two digits, so we can infer that the first digit is a zero and was therefore omitted. The first digit is the number of carbons in the molecule minus 1. The first digit being zero shows that there is a single carbon atom in the molecule.

The second digit is a 1, and it is the number of hydrogens in the molecule plus 1. This reveals that the structure has no hydrogens.

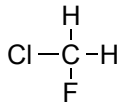
The last digit is the number of fluorines. After placing the three fluorine atoms onto carbon, a single valence remains to be filled. The number of chlorine atoms in the structure is simply inferred. One chlorine is needed to fill carbon's remaining open valence.



(b) Freon 31 also has only two digits in the name. The first digit was therefore a zero that was omitted. This first digit (#C – 1) shows that there is a single carbon atom in the molecule.

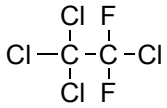
The second digit (#Hs + 1) is a 3, showing that the structure holds two hydrogen atoms.

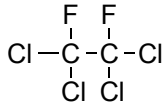
Finally, the third digit (#Fs) reveals the presence of a single fluorine atom. Again, the presence of chlorine is inferred from the number of remaining valences that need to be filled. Since carbon has one bond yet to be explained, a single chlorine atom is placed on the structure.



(c) The name Freon 112 contains all three digits. The first 1 (#C – 1) denotes the presence of two carbon atoms in the structure. The following 1 (#H + 1) shows that there are no hydrogen atoms. The last digit (#Fs) reveals the presence of just two fluorine atoms. These could be placed on the same carbon or on adjacent carbons,

leading to two possible isomers. In either case, four valences need to be filled, and this is accomplished by placing chlorine atoms as needed.

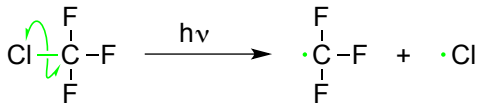




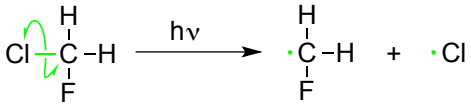
These isomers are known as Freon 112a and Freon 112, respectively.

16. In each instance, the carbon-chlorine bond is the weakest. Chlorine is a fairly large atom, so it makes a longer and therefore weaker bond to carbon. Consequently, this is the bond that homolyzes upon exposure to high-energy radiation. In each case, a chlorine radical is released, and this radical can degrade ozone via the mechanism that we learned in this section.

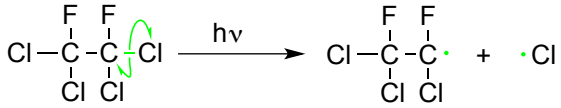
Freon 13:



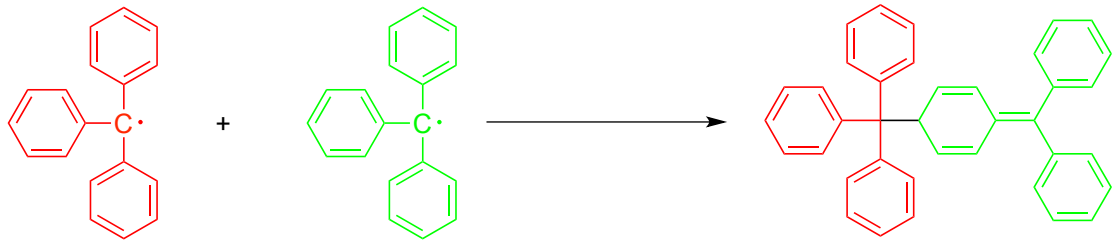
Freon 31:



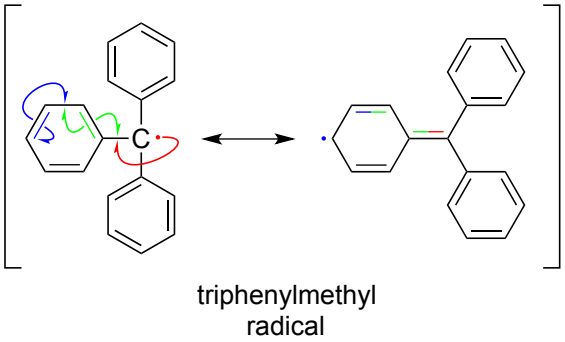
Freon 112:



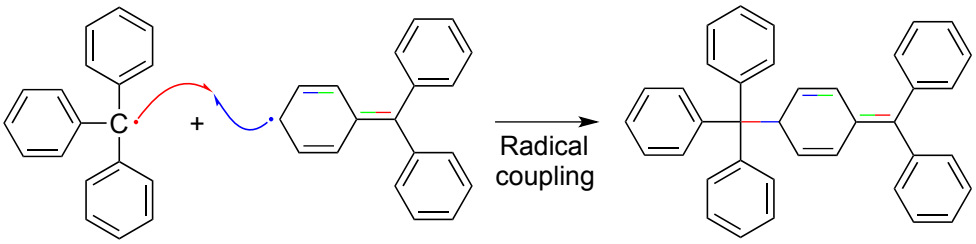
17. If we compare the structure of the triphenylmethyl radical to that of the dimer, it quickly becomes clear how the two triphenylmethyl radicals match the two halves of the dimer. The three rings of each subunit are readily apparent.



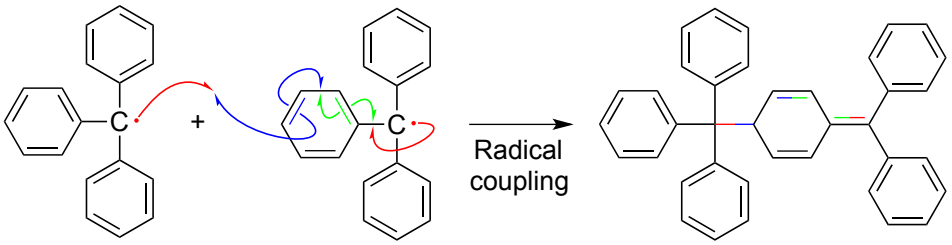
What is less obvious is how the phenyl group (i.e., benzene ring) of one radical is linked to the central carbon of the other. To accomplish this, there must be reactivity on the phenyl groups, and this reactivity is illustrated through resonance forms. While the triphenylmethyl radical has many resonance forms, we focus solely on the one that shows radical character at the site where it is needed for the reaction.



If we then use this resonance form when drawing the reaction mechanism, the desired outcome is easily achieved.

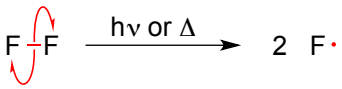


An alternative way to approach this problem entails drawing all of the arrows needed to shift the radical to the appropriate carbon on the phenyl group. However, instead of depositing the radical on a ring carbon and then using that resonance form to illustrate the reaction mechanism, we can simply push that final electron out to the other triphenylmethyl radical to make the new bond linking the halves of the dimer.



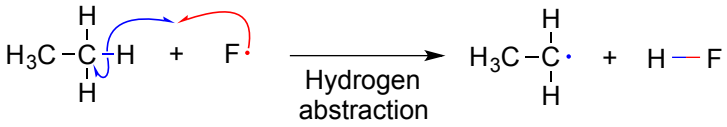
18. Free-radical fluorination of ethane would begin with the homolysis of some fluorine molecules.

Initiation:



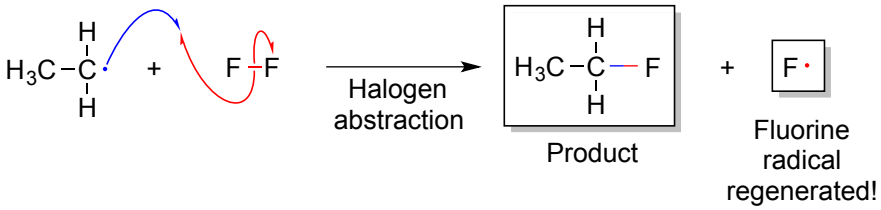
In the first step of the propagation cycle, fluorine radical abstracts a hydrogen atom from ethane. This yields one of the products, HF, as well as ethyl radical.

Propagation step 1:



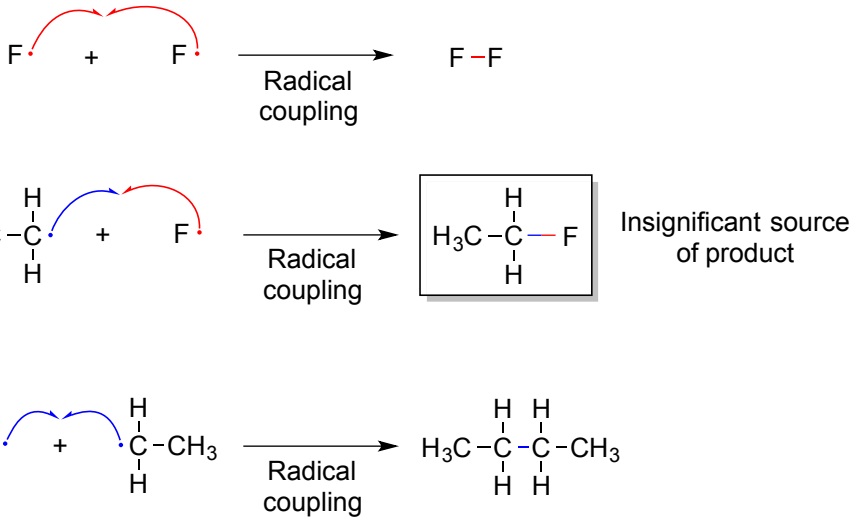
In the second step of the propagation cycle, the ethyl radical abstracts a fluorine atom from an unreacted molecule of fluorine. This affords the other reaction product, fluoroethane, and a fluorine radical that is capable of reentering propagation step 1.

Propagation step 2:



When all of the reactants have been consumed, the few remaining radicals can combine in any conceivable fashion via the termination steps.

Termination:



The overall reaction is:

$$CH_3CH_3 \quad + \quad F_2 \xrightarrow{h\nu \text{ or } \Delta} CH_3CH_2F \quad + \quad HF$$

To calculate the change in enthalpy for the reaction, the energy of the bonds formed is subtracted from the energy of the bonds broken.

$$\Delta H^\circ = \sum [H^\circ \, bonds \, broken] - \sum [H^\circ \, bonds \, formed]$$

$$\Delta H^\circ = [(C-H) + (F-F)] - [(C-F) + (H-F)]$$

$$\Delta H^\circ = [(98) + (36.8)] - [(116) + (135)] = -116.2 \text{ kcal/mole}$$

To draw the reaction energy profile though we'll need to know the change in enthalpy for each of the propagation steps. Recall that, in propagation step 1, the C-H bond is broken and the H-F bond is formed.

$$\Delta H^\circ = \sum [H^\circ \, bonds \, broken] - \sum [H^\circ \, bonds \, formed]$$

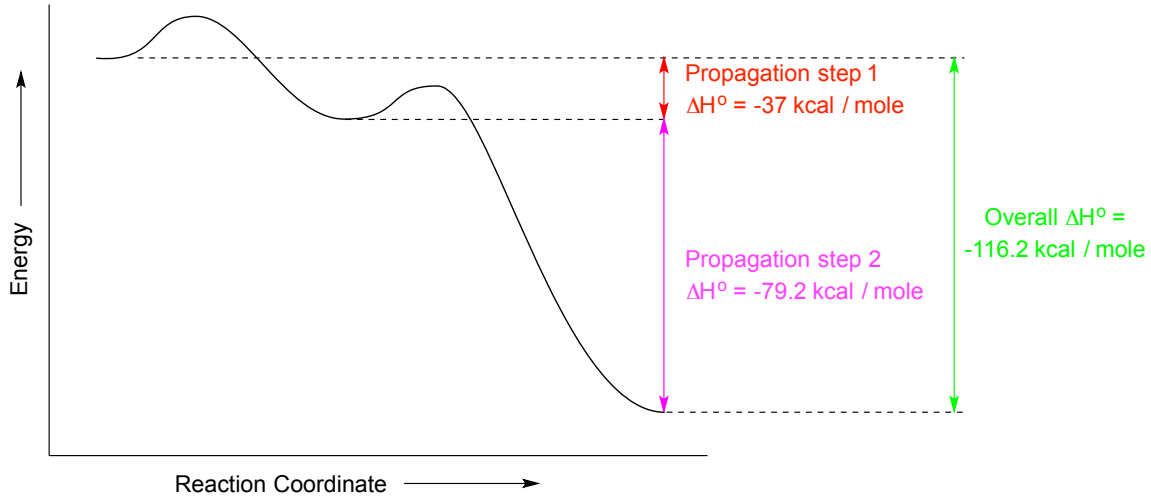
$$\Delta H^\circ = (C-H) - (H-F) = 98 - 135 = -37 \, kcal/mole$$

In propagation step 2, the F-F bond is broken and the C-F bond is created.

$$\Delta H^\circ = \sum [H^\circ \, bonds \, broken] - \sum [H^\circ \, bonds \, formed]$$

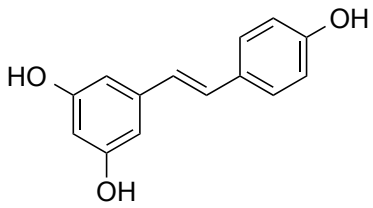
$$\Delta H^\circ = (F-F) - (C-F) = 36.8 - 116 = -79.2 \, kcal/mole$$

With these values in hand, we can draw the reaction energy profile.



While the products are certainly favored at equilibrium, the reaction is *so* exothermic that it tends to be dangerous. This is why it is not commonly used.

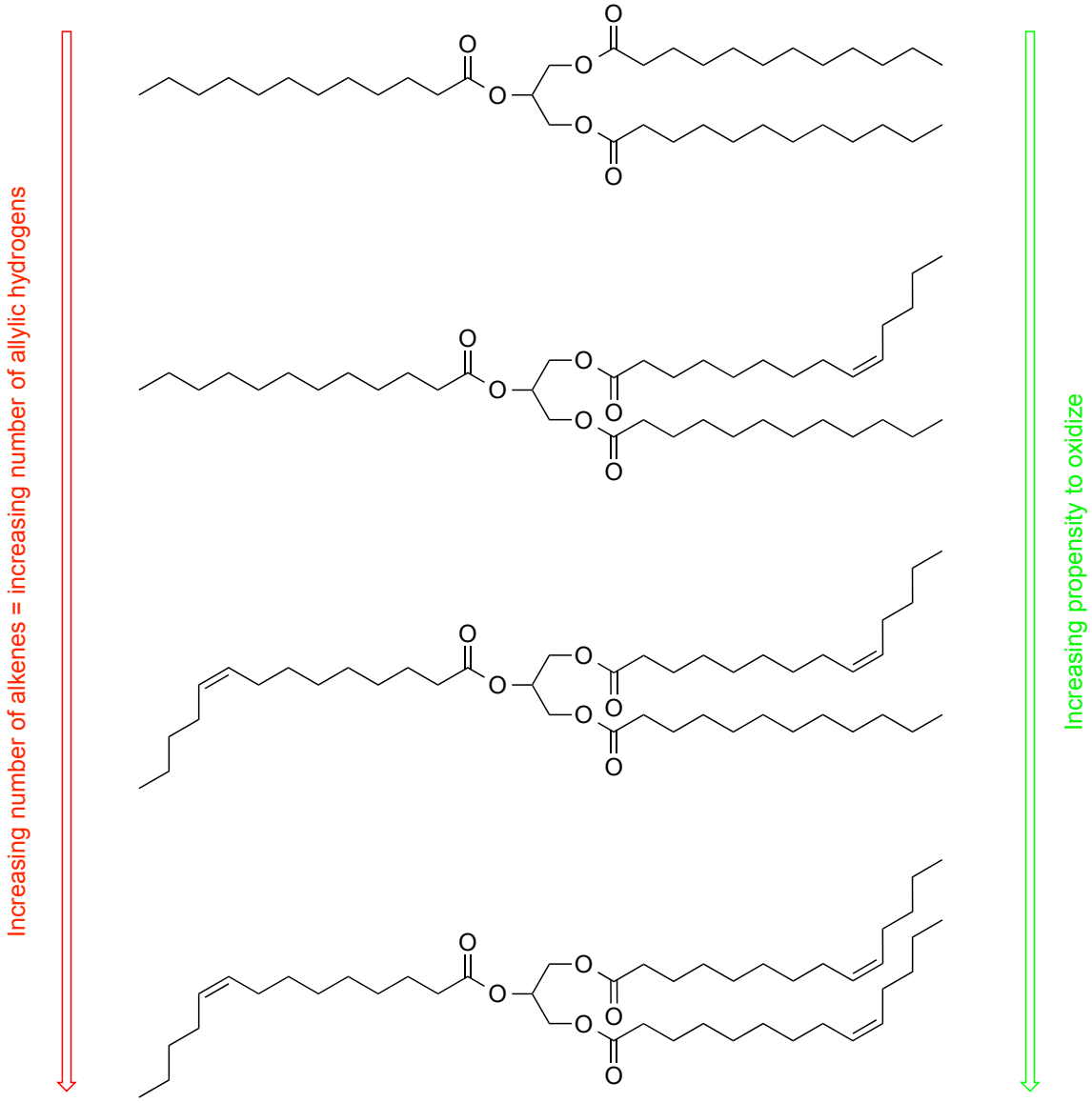
19. The antioxidants that we encountered in this chapter all contained phenols, so the following compound would be the top candidate for a structure with antioxidant activity.



This compound is known as resveratrol, and it is a naturally occurring antioxidant found in grapes and certain berries, like blueberries and raspberries.

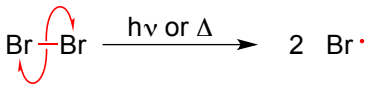
As an aside, it is worth noting that there are antioxidants that do not contain a phenol. However, the ones we saw in this chapter (vitamin E, BHT, and BHA) happened to have that structural fragment, which was key to their activity.

20. A triglyceride with more alkenes has more allylic hydrogens. Since it is the allylic hydrogens that are most easily abstracted during the oxidation of fats and oils, a triglyceride with more allylic hydrogens will have a greater propensity to oxidize.



21. This radical substitution begins with the homolysis of a few molecules of Br_2.

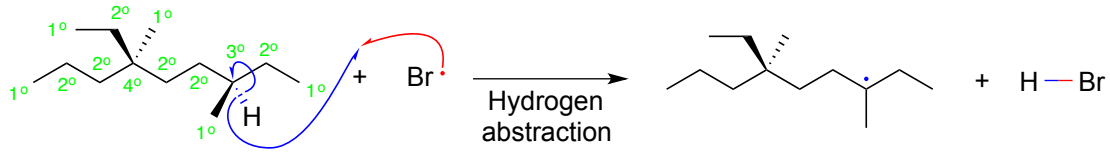
Initiation:



In the first propagation step, the bromine radical abstracts a hydrogen so as to generate the most stable radical intermediate possible. The substrate contains many primary and secondary centers, but only one tertiary center. Removal of the tertiary hydrogen produces a reasonably stable tertiary radical, along with HBr. Notice that the substrate also contains a quaternary center. However, quaternary carbons bear no hydrogens, so hydrogen abstraction from that site is impossible. Also notice that

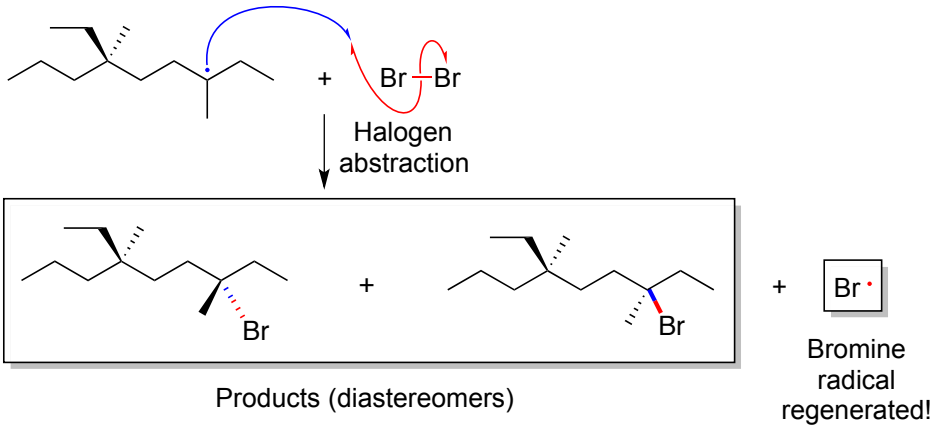
the stereochemistry of the tertiary carbon was lost during this step when that carbon rehybridized from sp^3 to sp^2.

Propagation step 1:



In the second propagation step, the tertiary radical abstracts a bromine atom from an unreacted molecule of Br_2. This yields the product and a new bromine radical to continue the propagation cycle.

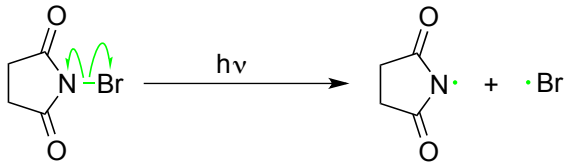
Propagation step 2:



The product contains a new stereocenter, which is formed in both configurations. The other stereocenter is unaffected by this transformation though. As a result, the products are *diastereomers*.

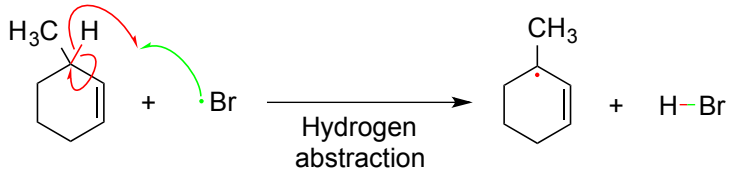
22. Allylic bromination begins with the homolysis of a few molecules of NBS upon exposure to light.

Initiation:

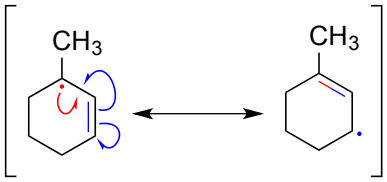


In the first step of the propagation cycle, bromine radical abstracts the tertiary allylic hydrogen, which has the smallest bond dissociation energy since its cleavage makes the most stable radical. HBr is also formed during this step.

Propagation step 1:

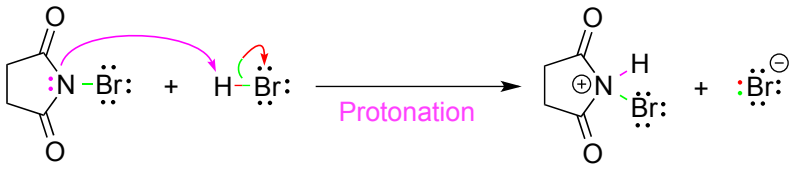


There are two distinct resonance forms of this radical.

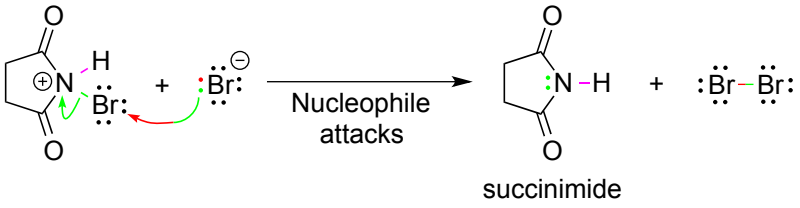


The first propagation step is followed by a two-step ionic interlude in which the HBr that was just produced is consumed and Br_2 is generated. First, NBS is protonated by HBr.

Ionic interlude:

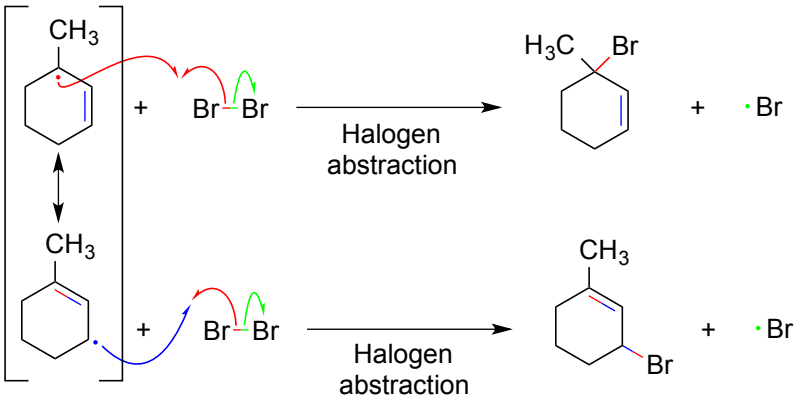


Then, bromide attacks the electrophilic bromine atom. Succinimide is released while Br_2 is formed.

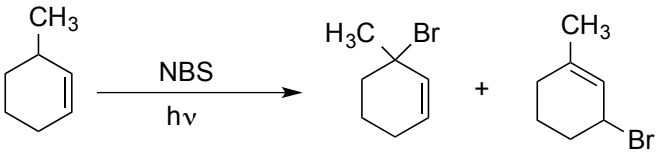


The newly created Br_2 is critical for propagation step 2, in which the allylic radical abstracts a bromine atom. Since there are two resonance forms of the allylic radical, either center that has radical character can abstract a bromine atom, thereby yielding two allylic bromides.

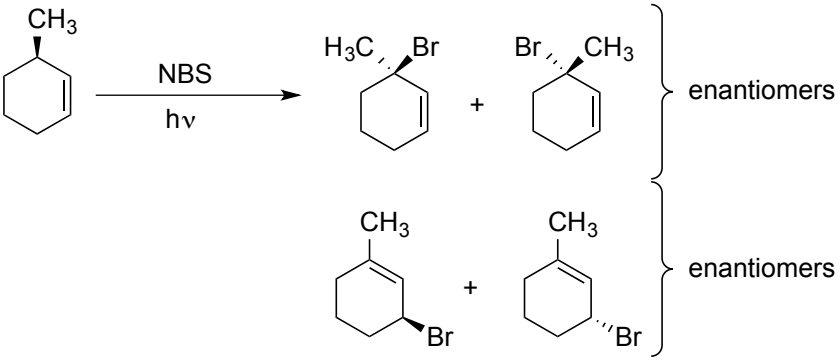
Propagation step 2:



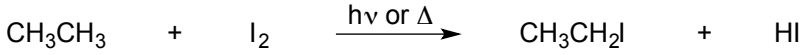
Overall, this reaction has produced two regioisomers.



Furthermore, each regioisomer contains a stereocenter, which is produced in both configurations. Consequently, there are a total of four products of this reaction: two pairs of enantiomers.



23. The overall reaction for the free-radical iodination of ethane uses ethane and iodine as reactants to produce iodoethane and HI as products.



The overall change in enthalpy for the reaction is the energy of the bonds broken minus the energy of the bonds formed.

$$\Delta H^{\circ} = \sum [H^{\circ}\ bonds\ broken] - \sum [H^{\circ}\ bonds\ formed]$$

The C-H and I-I bonds are broken during the course of the reaction, and the C-I and H-I bonds are made.

$$\Delta H^\circ = [(C-H)+(I-I)] - [(C-I)+(H-I)]$$

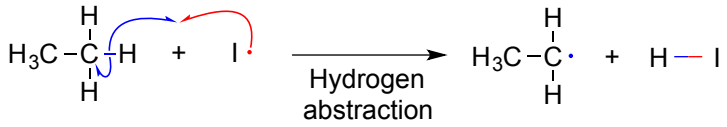
This results in an endothermic reaction with a ΔH° of +5.6 kcal/mole.

$$\Delta H^\circ = [(98)+(35.6)] - [(57)+(71)] = +5.6 \text{ kcal/mole}$$

At this point, we can see why the reaction is not especially useful. Since $\Delta G^\circ \approx \Delta H^\circ$ for this process, we can say that the reaction is endergonic, and the *reactants* are therefore favored at equilibrium. Such a reaction is not synthetically useful.

To draw the reaction energy profile, we must calculate the change in enthalpy for each of the propagation steps. In propagation step 1, the C-H bond is broken while the H-I bond is formed.

Propagation step 1:

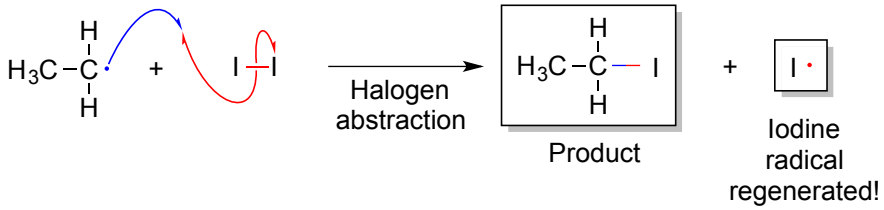


The change in enthalpy for this step is therefore +27 kcal/mole. This is a highly endothermic step.

$$\Delta H^\circ = \sum [H^\circ \text{ bonds broken}] - \sum [H^\circ \text{ bonds formed}]$$

$$\Delta H^\circ = (C-H) - (H-I) = 98 - 71 = +27 \text{ kcal/mole}$$

In the second propagation step, the I-I bond is broken and the C-I bond is made.

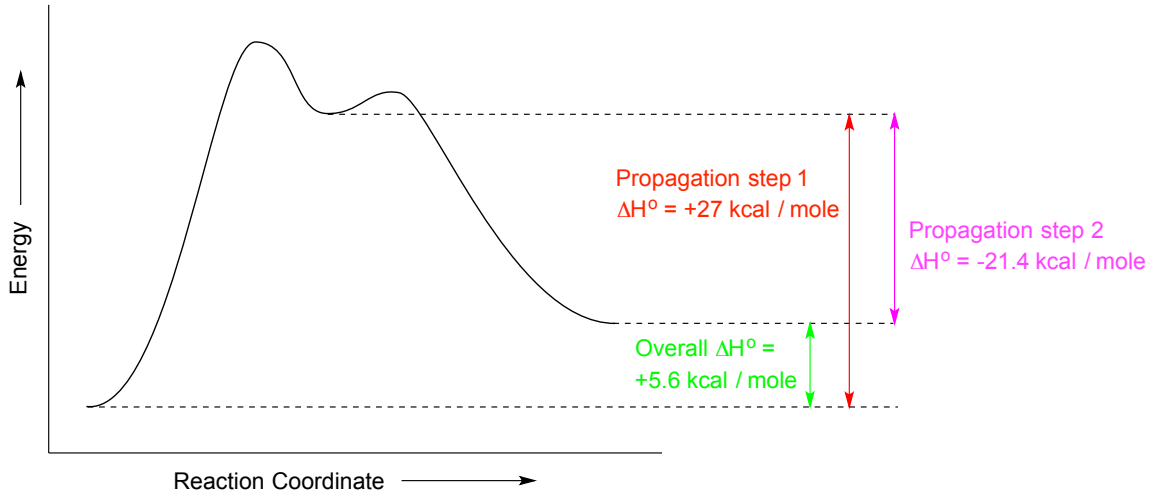


This step is exothermic, releasing 21.4 kcal/mole of energy.

$$\Delta H^\circ = \sum [H^\circ \text{ bonds broken}] - \sum [H^\circ \text{ bonds formed}]$$

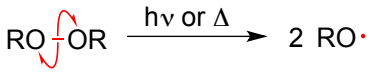
$$\Delta H^{\circ} = (I - I) - (C - I) = 35.6 - 57 = -21.4\ kcal/mole$$

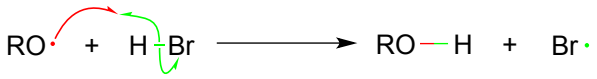
This information can be represented graphically in a reaction energy profile. This energy diagram highlights the fact that, while the second propagation step is exothermic, it is not sufficiently exothermic to overcome the endothermicity of the first propagation step. For this reason, the reaction is overall endothermic.



24. The addition of HBr to an alkene begins with two initiation steps that serve to generate the bromine radical that is instrumental in the propagation cycle. First, the peroxide homolyzes. Then the resulting alkoxy radical abstracts a hydrogen atom from HBr. This produces the critical bromine radical.

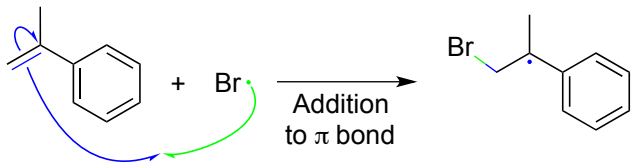
Initiation:





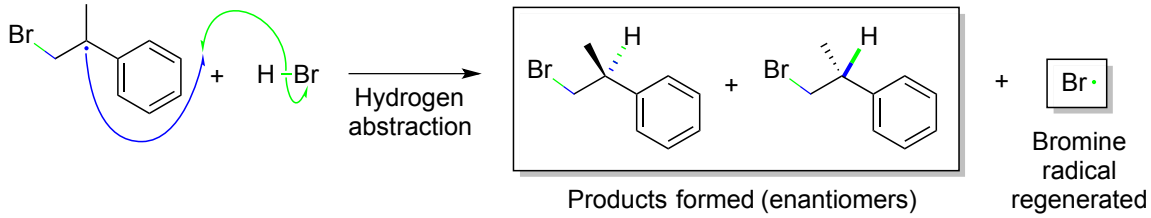
In the first step of the propagation cycle, that bromine radical adds to the alkene's π bond. The addition occurs so as to produce the most stable radical possible. In this case, bromine adds to the terminal alkene carbon because doing so leads to the formation of a tertiary, resonance-stabilized radical.

Propagation step 1:



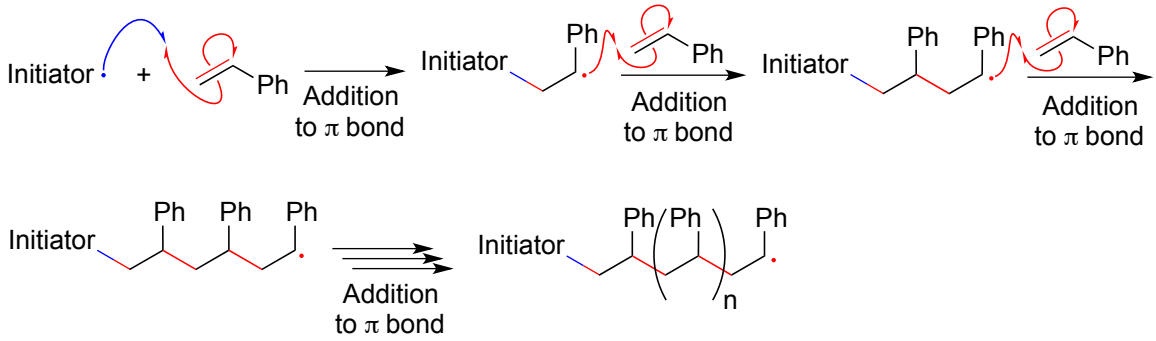
In the second step of the propagation cycle, the carbon-centered radical abstracts a hydrogen atom from HBr to afford the product. However, in so doing, a stereocenter is created. Since the radical is trigonal planar (i.e., flat), there is no preference for addition of the hydrogen atom from one side or the other, so both occur with equal frequency to yield a racemic mixture of enantiomers.

Propagation step 2:

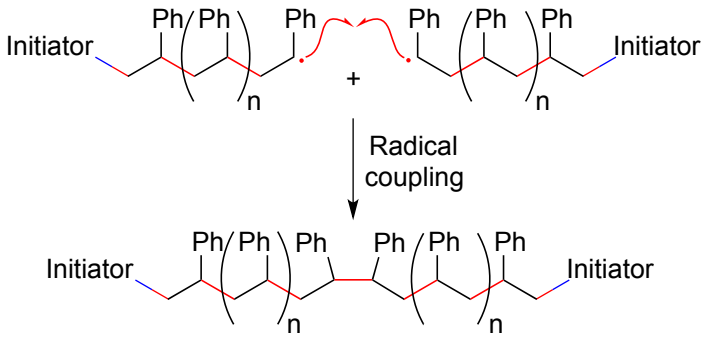


Notice that a bromine radical is also produced in this step, and it allows the propagation cycle to continue.

25. The radical initiator adds the π bond of the alkene of styrene. Furthermore, it adds to the terminal carbon to produce the radical that is not only more highly substituted but also resonance stabilized. This resonance-stabilized radical adds to the terminal carbon of a new styrene monomer, and the process continues, lengthening the chain one monomer at a time.



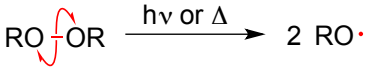
Eventually, the polymerization terminates. This could occur through the union of two radicals.

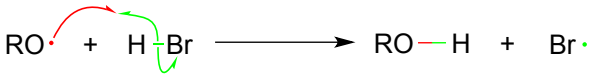


Termination is also possible through disproportionation.

26. This reaction begins with the homolysis of the peroxide. The resulting alkoxy radical then abstracts a hydrogen atom from HBr to yield bromine radical.

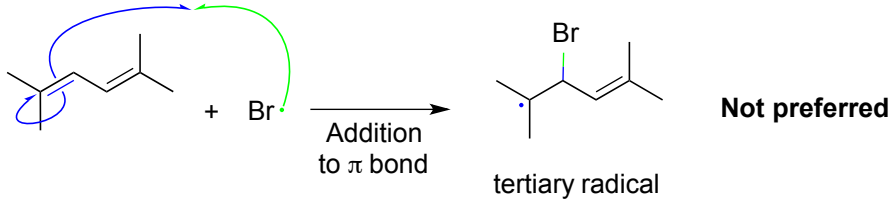
Initiation:

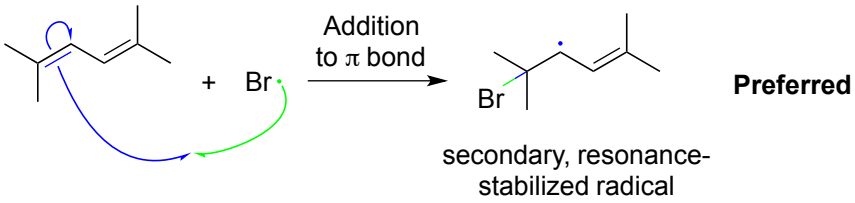




In the first propagation step, bromine radical will add to a π bond of the diene, but we must decide on the proper regiochemistry for the addition. Since the two alkenes of the diene are equivalent (due to the molecule's symmetry), we need not concern ourselves with which alkene undergoes the addition. However, we do need to decide whether the bromine radical adds to the secondary or tertiary alkene carbon. If bromine adds to the secondary alkene carbon, a tertiary radical is formed, and this initially appears to be quite appealing. Alternatively, if bromine adds to the tertiary alkene carbon, a secondary, allylic radical is produced. The resonance stabilization that this latter radical possesses makes it superior to the tertiary radical.

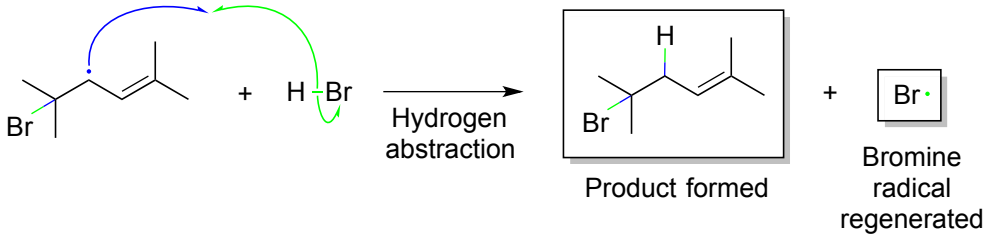
Propagation step 1:



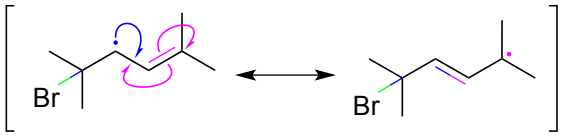


In the second propagation step, the carbon-centered radical abstracts a hydrogen atom from HBr to yield product and a bromine radical capable of continuing the propagation cycle.

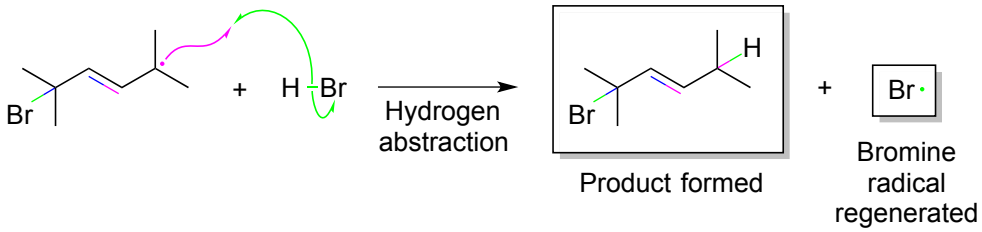
Propagation step 2:



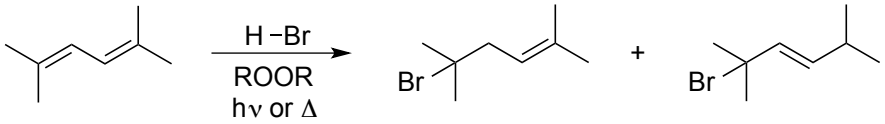
We cannot forget, though, that the radical is resonance stabilized. This means that more than one carbon has radical character.



Consequently, there is an alternative second propagation step in which the other carbon bearing radical character abstracts a hydrogen from HBr to yield an isomeric product.

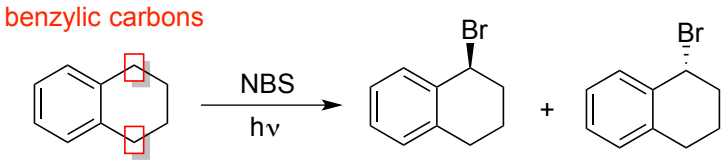


To summarize, the overall reaction is shown below. The transformation results in the formation of two products, which are constitutional isomers.

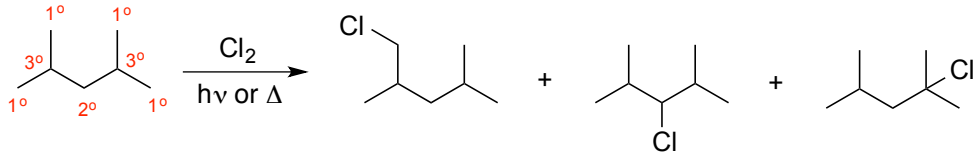


27.

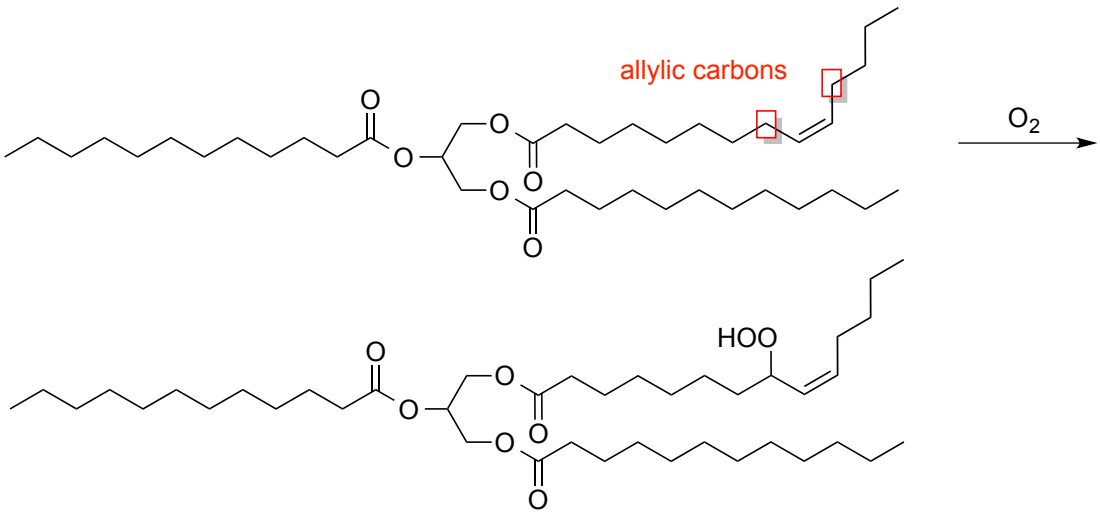
(a) This substrate has two equivalent benzylic carbons. Treatment with NBS and light leads to bromination at either of these sites. The allylic bromination produces a stereocenter. Both configurations are obtained in equal amounts, resulting in the acquisition of the product as a racemic mixture of enantiomers.



(b) Free-radical chlorination has much lower selectivity than free-radical bromination. Consequently, we can expect a mixture of all of the possible chloroalkanes. The substrate contains four equivalent primary carbons, one secondary carbon, and two equivalent tertiary carbons. Chlorination at each of these sites leads to the three expected products of the reaction.

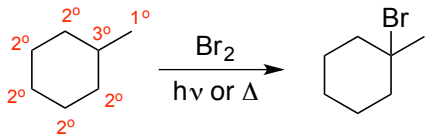


(c) This triglyceride contains two distinct allylic carbons. Oxidation at either of these sites produces hydroperoxide products. Only one of the two possible hydroperoxides is shown below.



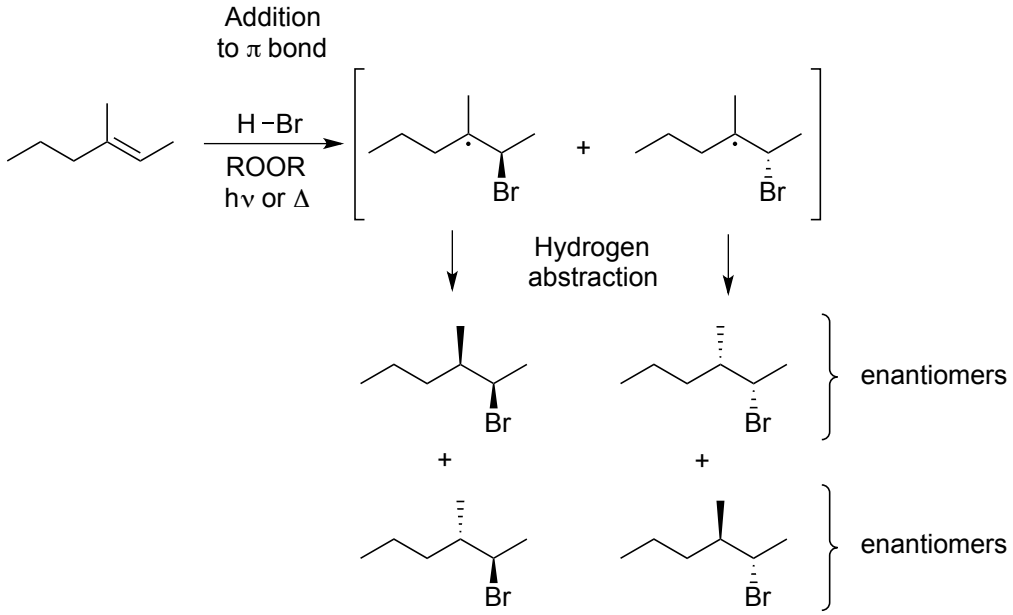
(d) Free-radical bromination is a highly selective process. It proceeds almost exclusively at the most highly substituted carbon of the substrate. This substrate has

a primary carbon, five secondary carbons, and a tertiary carbon. Bromination occurs at the tertiary center to yield the predominant product.

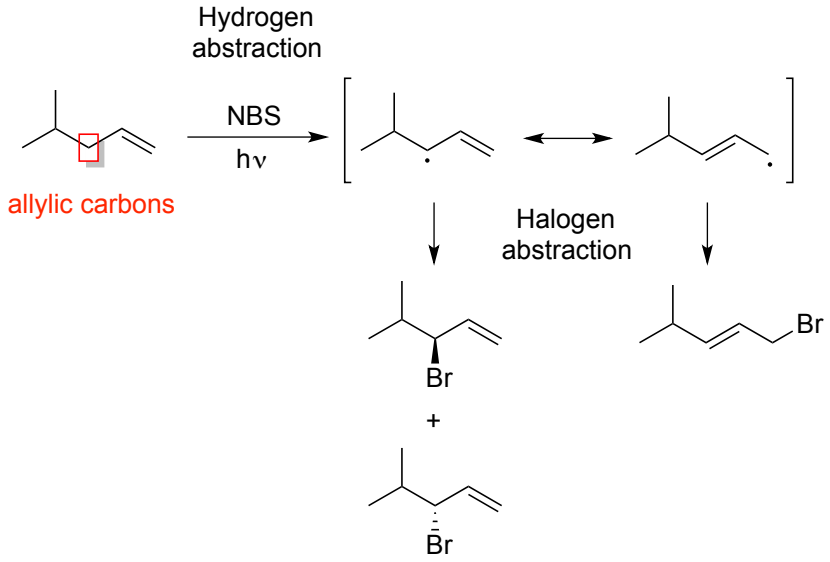


(e) This reaction entails the addition of HBr across the alkene's π bond. Bromine radical formed during initiation first adds to the alkene so as to generate the more stable tertiary radical. A new stereocenter is created in the process and both configurations are obtained.

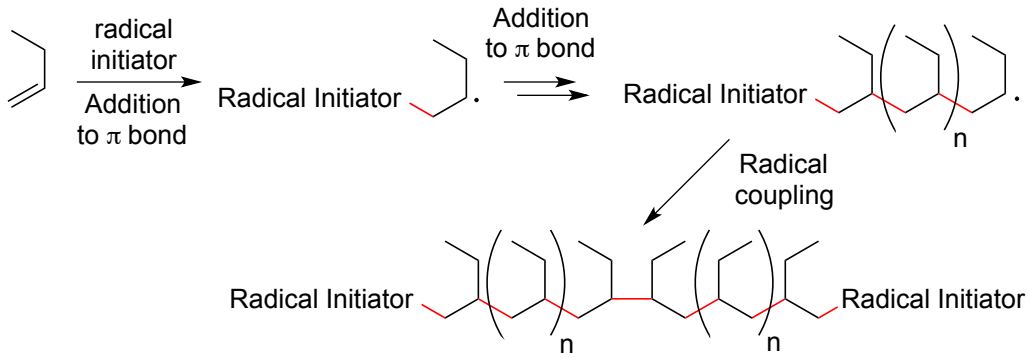
Then, the carbon-centered radical abstracts a hydrogen atom from HBr in the second propagation step. This too generates a new stereocenter with both possible configurations, so the product is a mixture of all four possible stereoisomers (two pairs of enantiomers).



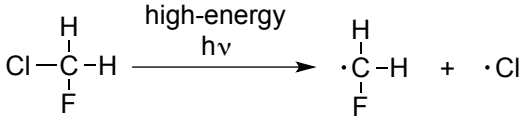
(f) This allylic bromination begins with abstraction of a hydrogen atom from the only allylic center in the molecule. The allylic radical thus formed has two resonance structures, which place radical character at two distinct carbon atoms. Either of these carbons can abstract a bromine atom in the second propagation step to yield product. The secondary, allylic bromide contains a new stereocenter, which is formed with both configurations.



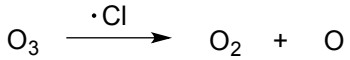
(g) This polymerization starts when the radical initiator adds to the monomer's π bond so as to produce the more stable secondary radical. This radical adds to another monomer, and the process continues to lengthen the chain one monomer at a time. Finally, one way that the polymerization can terminate is through the union of two chains. The new bonds between monomer subunits are highlighted in red below.



(h) We first saw Freon 31 in Problem 15. Upon exposure to high-energy light, the carbon-chlorine bond homolyzes to release a chlorine radical (see Problem 16). This initiates the reaction.



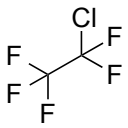
The chlorine radical then degrades ozone into molecular oxygen (O_2) and atomic oxygen (O) via the propagation cycle. Chlorine radical is continually regenerated in the process.



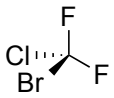
28. For all of these questions it is useful to remember the way in which numbers are assigned to CFCs and related compounds:

- The first digit is the number of carbons minus 1 (omit if 0).
- The second digit is the number of hydrogens plus 1.
- The third digit is the number of fluorines.
- If bromine is present, add "B#" to the name (where # = the number of bromines).

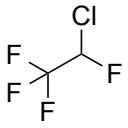
(a) This CFC has two carbons, so the first digit in the name is 1. There are no hydrogens, so the second digit is also 1. There are five fluorine atoms, so the final digit is 5. The name is therefore CFC 115 or Freon 115.



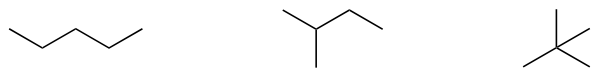
(b) This compound has a single carbon, so the first digit is a zero and is omitted. There are no hydrogen atoms, so the second digit is 1. The third digit is 2, which reflects the presence of two fluorines. Since one bromine atom is also present in this molecule, we add "B1" to the end of the name, making this Freon 12B1. We would not typically refer to this as a CFC since it contains more than just chlorine, fluorine, and carbon.



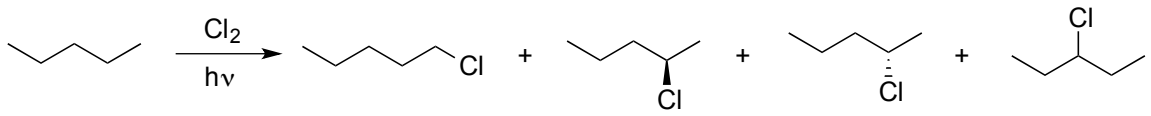
(c) In this structure, there are two carbons, so the first digit is 1. There is one hydrogen, so the second digit is 2. Finally, the four fluorine atoms are indicated by the final digit, 4. The name is therefore CFC 124, or more properly HCFC (hydrochlorofluorocarbon) 124 since it contains hydrogen as well.



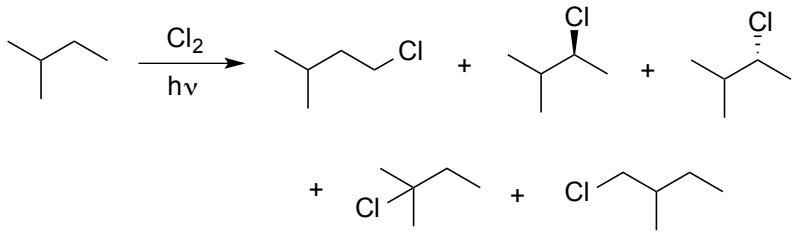
29. There are three isomers having the formula C_5H_{12}:



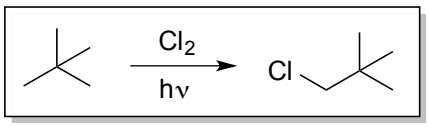
We know that free-radical chlorination is not particularly selective. Therefore, we expect the chlorination of pentane to yield four products. C1, C2, and C3 can all be halogenated to yield unique products. Furthermore, chlorination at C2 yields two enantiomers. This result is not consistent with the information given in the problem.



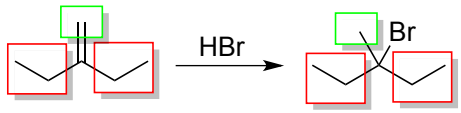
The chlorination of 2-methylbutane yields a total of five products. Halogenation at C1, C2, C3, and C4 all produce unique chloroalkanes. Additionally, reaction at C3 generates a stereocenter in both configurations. This result is also not consistent with the information given in the problem.



Only the chlorination of 2,2-dimethylpropane yields a single chloroalkane. All of the methyl groups of 2,2-dimethylpropane are equivalent, so chlorination at any site yields the same product. The central carbon of 2,2-dimethylpropane has no hydrogens, so no reaction can take place there.

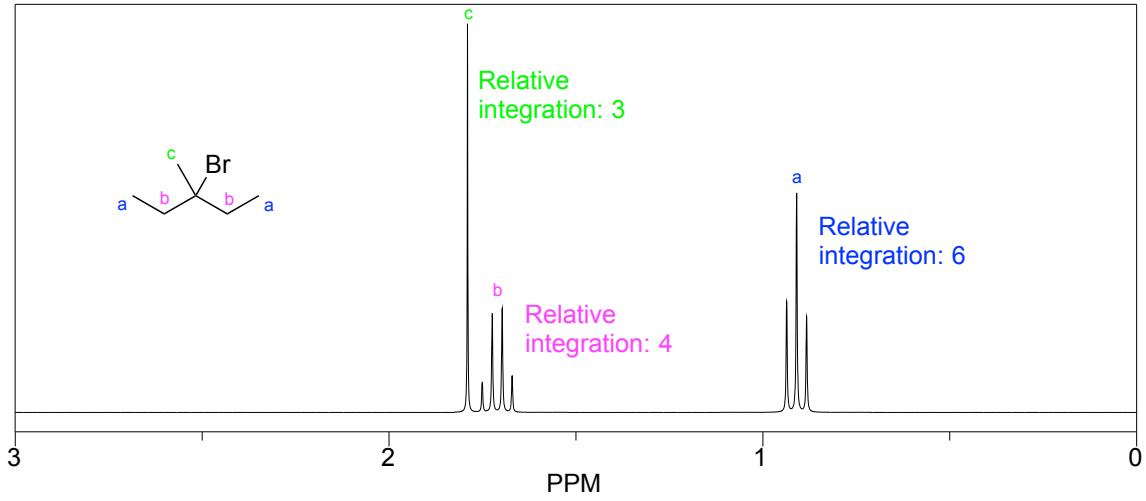


30. The proton NMR signals integrating for 6 and 4 hydrogens suggest that the ethyl groups have been retained unaltered in the product. The remaining signal that integrates for 3 hydrogens implies that the methylene (CH_2) present in the reactant has been converted to a methyl group. The tertiary carbon must bear the bromine atom because there are no additional hydrogens in the NMR spectrum.



In the absence of a peroxide, the regiochemistry of the addition was reversed. This reaction was mentioned briefly at the end of Section 5, and it will be covered in greater depth in Chapter 10.

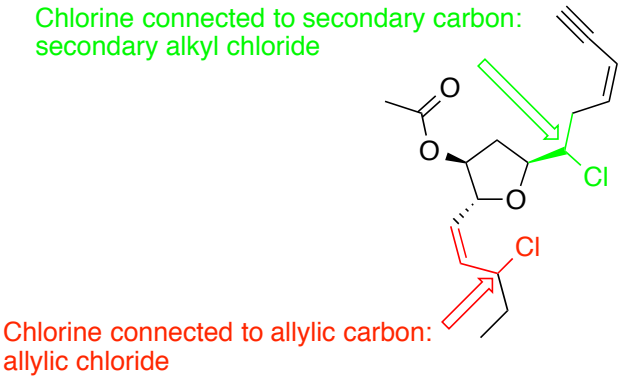
To be thorough, all of the peaks are assigned in the spectrum below.



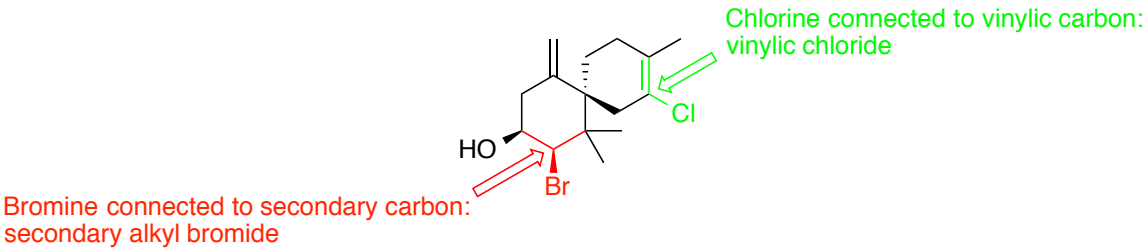
Solutions to Problems for Chapter 7: Substitution and Elimination—Reactions of Alkyl Halides and Alcohols

1. For this problem, it is important to remember that halogens will only ever be bonded to a single carbon when they have their normal valence because halogens are monovalent. They make only one bond, so they can be bonded to only one carbon. Therefore, we do not count the number of carbons bonded to the halogen when classifying halides. Instead, we base the classification on the carbon bearing the halogen.

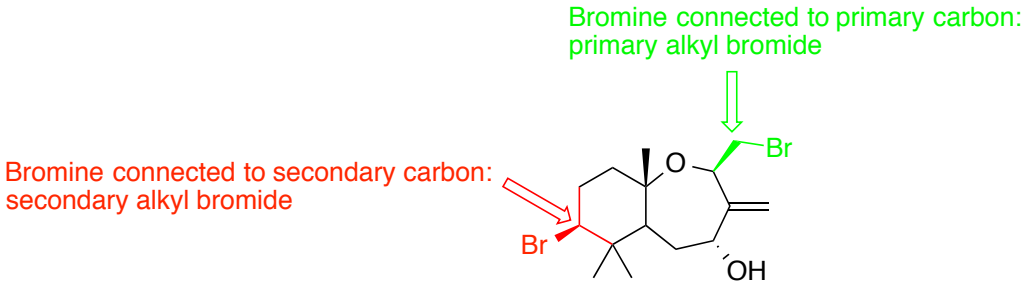
(a)



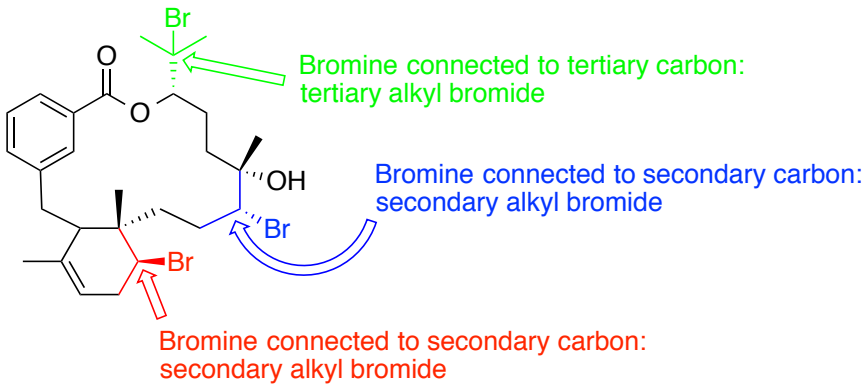
(b)



(c)



(d)



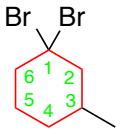
2.

(a) The longest continuous carbon chain is six-carbons in length, leading to a hexane parent. The halogen substituents are chloro and fluoro. They, as well as both methyl groups, require a locant. Remember that the "di" prefix does not count in alphabetization.

1-chloro-2-fluoro-2,4-dimethylhexane

- Six carbon parent = hexane
- Number so as to give the first substituent the lowest possible number
- Add substituent names and numbers

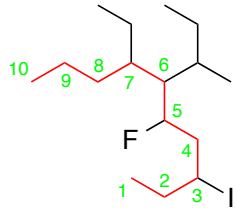
(b) Here the parent is a cyclohexane ring. The first substituent always gets the number 1 in a cyclic compound, so we decide on the proper numbering by considering the locant given to the second substituent. If the carbon bearing two bromines gets the number 1, then both the first and second substituent receive a locant of 1. Remember that each bromine needs its own locant, so we must say "1,1-dibromo" rather than "1-dibromo."



1,1-dibromo-3-methylcyclohexane

- Six carbon, cyclic parent = cyclohexane
- Number so as to give the first substituent the lowest possible number = tie
- Number so as to give the second substituent the lowest possible number
- Add substituent names and numbers

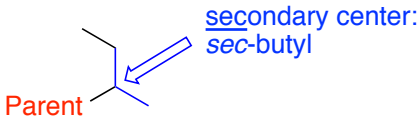
(c) The longest continuous carbon chain in this molecule is decane. Proper numbering gives the first substituent on the molecule the number 3.



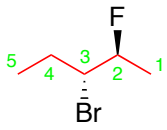
6-*sec*-butyl-7-ethyl-5-fluoro-3-iododecane

- Ten carbon parent = decane
- Number so as to give the first substituent the lowest possible number
- Add substituent names and numbers

Remember that the sec-butyl group is bonded to the parent through a secondary carbon. When determining the substitution within a substituent, the parent is ignored.



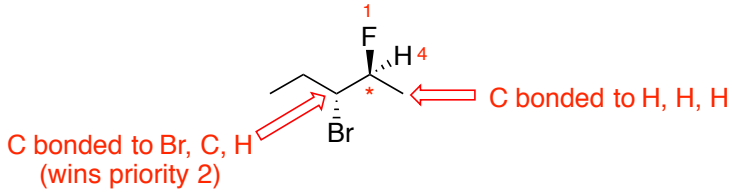
3. Deriving the core name of this molecule is fairly straightforward, but it also has stereochemistry.



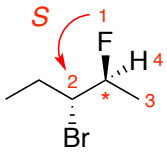
3-bromo-2-fluoropentane

- Five carbon parent = pentane
- Number so as to give the first substituent the lowest possible number
- Add substituent names and numbers

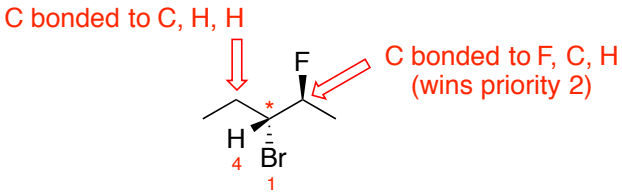
To determine the stereochemical designations, we'll deal with the stereocenters one at a time. The C2 stereocenter is bonded to fluorine (priority 1), hydrogen (priority 4), and two carbons that are tied for priority 2 and 3. The methyl group loses the tiebreaker because it is bonded to three hydrogens.



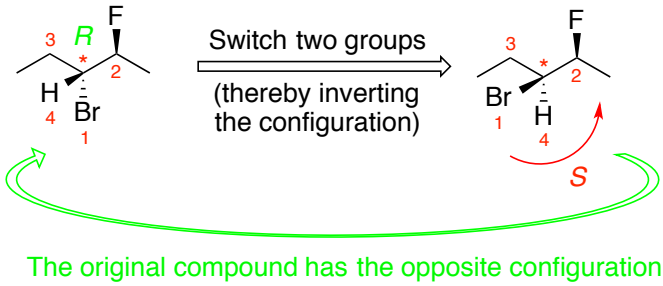
The group bearing priority 4 is on the dash as it should be, so we need only draw an arrow from priority 1 to 2 without passing through 3. This reveals the *S* configuration at C2.



The C3 stereocenter is slightly trickier because the low priority group is not on the dash. C3 is bonded to bromine (priority 1), hydrogen (priority 4), and two carbons that are tied for priority 2 and 3. Of the tied carbons, the one bonded to F, C, and H beats the one bonded to C, H, and H.



Then, we have to switch two groups to place the hydrogen on the dash, recognizing that doing so causes an inversion of configuration. On the new structure with the low priority group appropriately positioned, we can draw an arrow from priority 1 to 2 without passing through 3. This reveals the *S* configuration; however, the original compound has the opposite configuration: *R*.



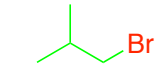
Adding the stereochemical designations to the front of the name, we now have a complete IUPAC name: (2*S*,3*R*)-3-bromo-2-fluoropentane.

4. In each case, the name of the alkyl group precedes the name of the halide.

(a)

tert-butyl iodide

(b)



isobutyl bromide

(c)

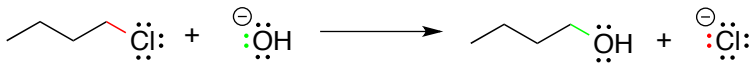
butyl chloride

(d)

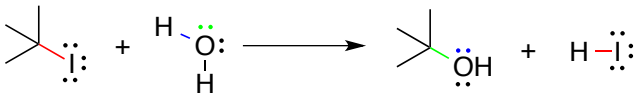
propyl fluoride

5.

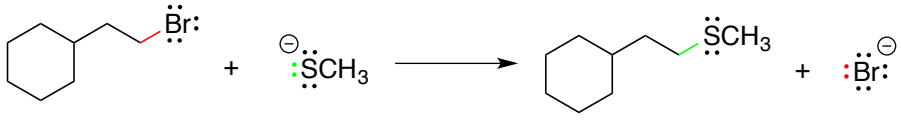
(a) In this instance, a lone pair of electrons on hydroxide is used to make the new carbon-to-oxygen bond. Chloride is lost, and it retains the σ bonding electrons from the carbon-to-chlorine bond of the substrate.



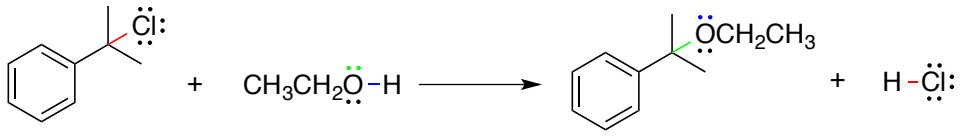
(b) This reaction involves a neutral nucleophile. A lone pair of electrons from water is responsible for forming the new C-O bond. Iodide is lost and retains the σ bonding electrons, using them to form a bond to a proton lost from the oxygen atom. The oxygen atom acquires the O-H σ bonding electrons as a lone pair.



(c) The anionic sulfur uses a lone pair of electrons to make a new C-S σ bond. Bromide is expelled and retains the σ bonding electrons as a lone pair.

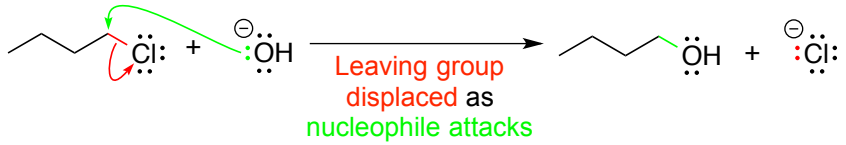


(d) The alcohol is a neutral nucleophile. It employs one of its lone pairs to make the new carbon-to-oxygen σ bond. Chloride is lost and retains its electrons, which are ultimately used to make a bond to the proton lost from oxygen. Oxygen retains the σ bonding electrons as a lone pair.

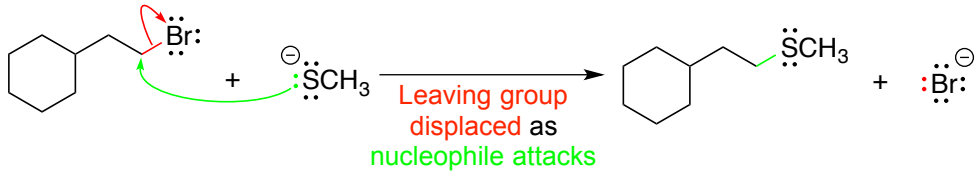


6. In a concerted substitution reaction, all of the bond making and breaking occurs simultaneously, so the nucleophile attacks concurrently with the loss of the leaving group.

(a) Hydroxide uses a lone pair of electrons to attack the carbon bearing the leaving group. This forms a new oxygen-to-carbon bond as chloride is ejected.

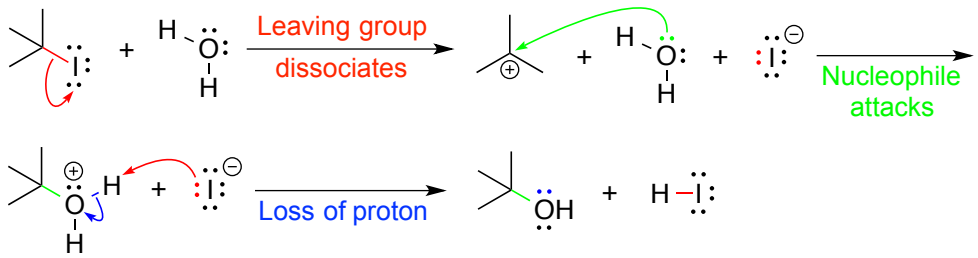


(b) The sulfur anion (also known as a thiolate) uses a lone pair of electrons to form a bond between sulfur and the electrophilic carbon of the substrate. Bromide dissociates simultaneously.

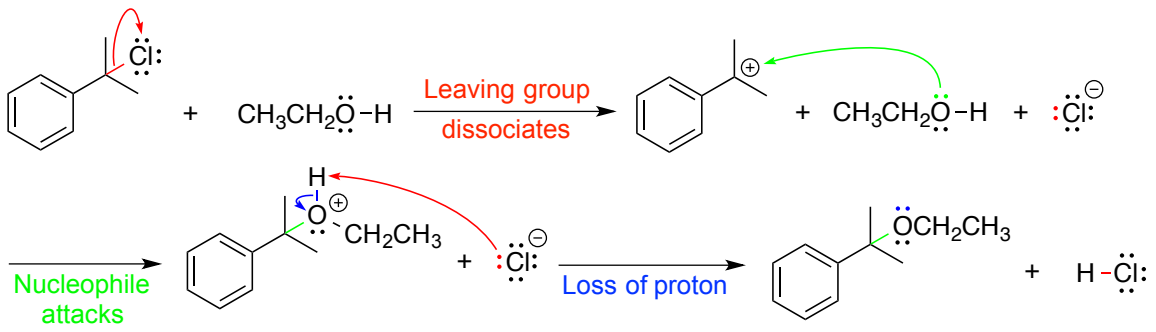


7. In a stepwise substitution reaction, the leaving group dissociates prior to the attacks of the nucleophile. This results in a carbocation intermediate.

(a) This reaction begins with the dissociation of iodide to form a carbocation. Water then uses a lone pair of electrons to attack this carbocation, forming a new oxygen-to-carbon bond. During the attack, all that happens is that a new oxygen-to-carbon bond is formed. Therefore, the oxygen atom of water brings both of its protons with it into the new intermediate, which is an oxonium ion (i.e., positively charged oxygen). Consequently, one mechanistic step remains during which the oxonium ion sheds a proton to yield a neutral alcohol as the product of the reaction. Iodide could serve as the base to remove that proton.



(b) The transformation begins with the dissociation of chloride. The resultant carbocation is attacked by the alcohol (ethanol), which uses a lone pair of electrons to form the new oxygen-to-carbon bond. Much as with the previous reaction, the oxygen of ethanol carries both of its substituents with it into the new intermediate. The oxonium ion then sheds a proton to yield the product as a neutral ether. Chloride could serve as the base that removes the proton.



8.

(a) The rate of the reaction = k [alkyl chloride] [hydroxide]. Therefore, with the changes in concentration described, we can expect the rate of the reaction to increase six-fold.

Rate = k (2 * [alkyl chloride]) (3 * [hydroxide])
Rate = 6 * (k [alkyl chloride] [hydroxide])
Rate = 6 * (rate of the original reaction)

(b) Similarly, the rate of this second-order reaction = k [alkyl bromide] [thiolate]. If the concentration of both species is tripled, we can expect the rate to increase by nine-fold.

Rate = k (3 * [alkyl bromide]) (3 * [thiolate])
Rate = 9 * (k [alkyl bromide] [thiolate])
Rate = 9 * (rate of the original reaction)

9.

(a) The rate of this first-order reaction = k [alkyl iodide]. If no change is made to the concentration of the alkyl iodide, then we expect no change in rate. The alteration to the concentration of water is irrelevant since water does not appear in the rate law.

(b) The rate of this reaction = k [benzylic chloride]. If the concentration of the benzylic chloride is tripled, then we expect a tripling of the reaction rate.

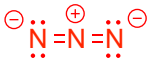
Rate = k (3 * [benzylic chloride])

Rate = 3 * (k [benzylic chloride])
Rate = 3 * (rate of the original reaction)

The change in the concentration of ethanol is immaterial because ethanol does appear in the rate law.

10. Most anions (other than fluoride) are strong nucleophiles, so we can quickly put several of the entries into this category. Don't be fooled by species that are overall neutral but contain ions due to an ionic bond. The presence of metals reveals that these nucleophiles are, in fact, charged.

Strong nucleophiles (anions):


NaOH

CH_3CH_2SH

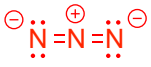
$KOCH_2CH_2CH_3$

$NaNH_2$
NH_3

H_2O
CH_3CH_2OH
CH_3OH
$(CH_3)_2NH$

We also know that polarizable species, even when neutral, make for strong nucleophiles.

Strong nucleophiles (anions, polarizable):


NaOH

CH_3CH_2SH

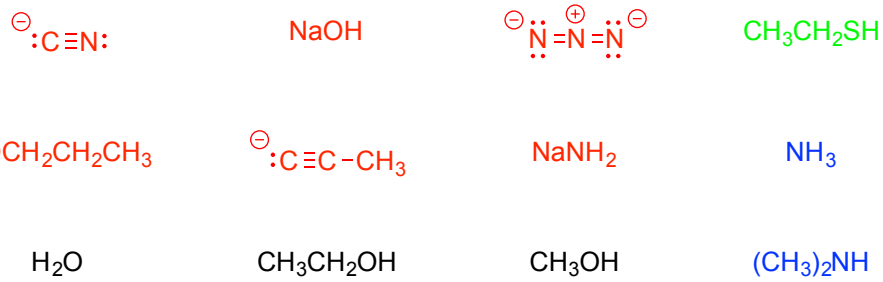
$KOCH_2CH_2CH_3$

$NaNH_2$
NH_3

H_2O
CH_3CH_2OH
CH_3OH
$(CH_3)_2NH$

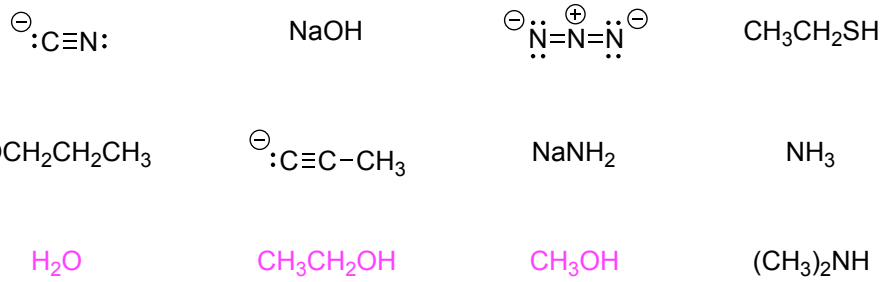
Additionally, electron-releasing elements, even when neutral, can make for strong nucleophiles.

Strong nucleophiles (anions, polarizable, electron-releasing):



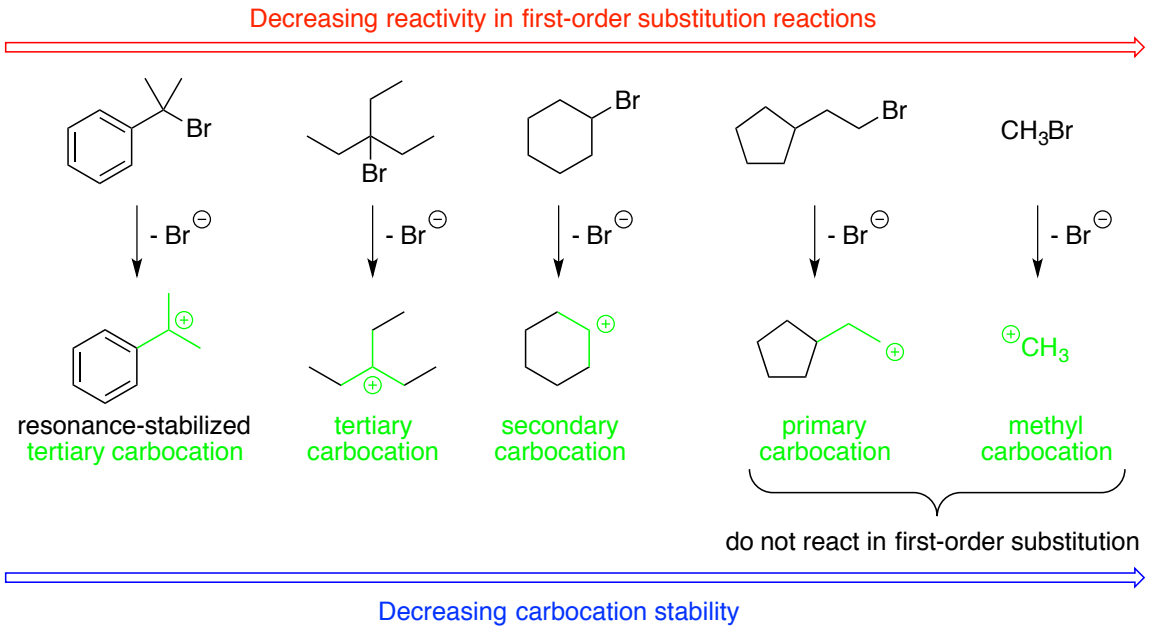
Finally, water and alcohols are weak nucleophiles.

Weak nucleophiles:

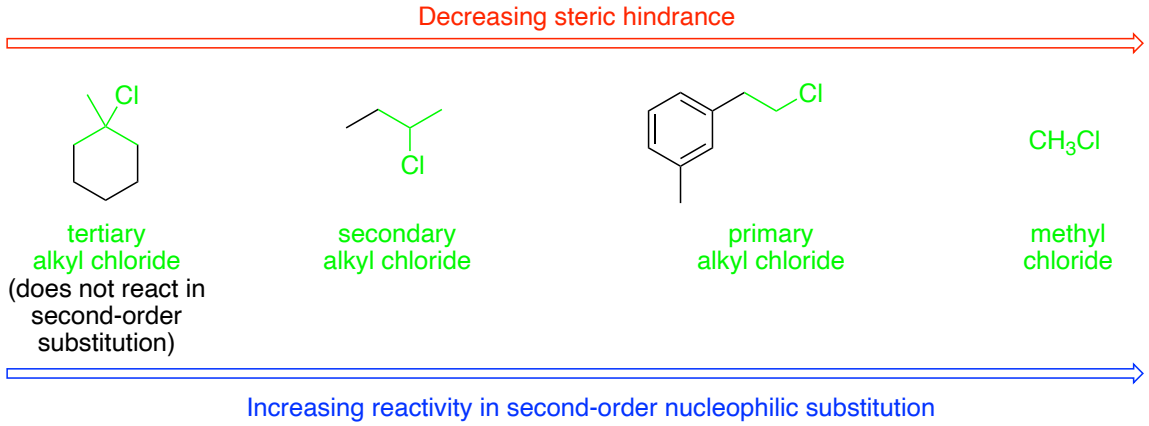


11. First-order substitution reactions entail a carbocation intermediate. A more stable carbocation intermediate makes for a lower energy pathway from reactants to products. Therefore, a substrate that yields a more stable carbocation upon dissociation of the leaving group will have greater reactivity in first-order substitution reactions.

There are two tertiary substrates, both of which lead to tertiary carbocations. However, one of the two tertiary carbocations is also resonance stabilized, making it the more stable of the two and the most stable of the entire series. The secondary, primary, and methyl substrates yield increasingly unstable carbocations. They are therefore increasingly unreactive in first-order substitution.



12. The critical factor for substrates in second-order nucleophilic substitution reactions is steric hindrance. Unhindered substrates react quickly. As steric hindrance increases, the reactivity drops.



13.

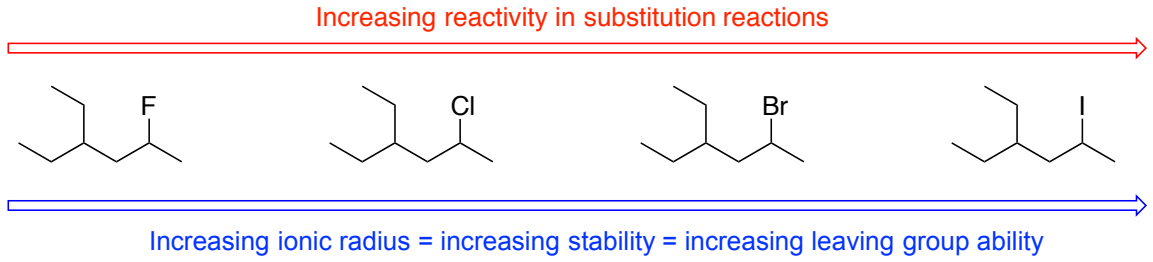
(a) As we identified in Problem 6 when we drew the mechanism for this reaction, it is a concerted process. This means that both the alkyl chloride and the nucleophile are *mechanistically* involved in the rate-determining step. A second-order process like this benefits from a polar aprotic solvent, which can strip away whatever cation may have been present with the nucleophile (e.g., the Na^+ of NaOH). This will leave the hydroxide bare and consequently more reactive than it was previously. Therefore, we would want to select one of the polar aprotic solvents for this reaction, such as DMSO.

(b) We drew the mechanism for this stepwise reaction in Problem 7. In a stepwise substitution reaction, only the substrate is *mechanistically* involved in the rate-determining step, so the process is first order. A first-order reaction benefits from a polar protic solvent that is able to stabilize both the carbocation and the anion (in this case, iodide) formed during dissociation at the outset of the mechanism. Common polar protic solvents are water or alcohols. Since water is a reagent, we would simply use it in a large excess, thereby allowing it to function as the reaction's solvent as well.

(c) We drew a mechanism for this concerted reaction in Problem 6. Concerted substitutions are second-order reactions because both the substrate and the nucleophile are *mechanistically* involved in the rate-determining step. A polar aprotic solvent would accelerate the reaction by stripping away the nucleophile's cation (e.g., the Li^+ of $LiSCH_3$). This leaves the thiolate bare and more reactive. So, we can choose a polar aprotic solvent, such as DMF, for this transformation.

(d) We drew a mechanism for this stepwise reaction in Problem 7. In the first step of this first-order reaction, chloride dissociates from the substrate to form a carbocation. The reaction's rate would be accelerated by a polar protic solvent capable of stabilizing both chloride and the carbocation. Common polar protic solvents include water or alcohols. Since an alcohol (ethanol) is already a reactant, we would simply use it in a large excess so that it can also serve as the solvent for the reaction too.

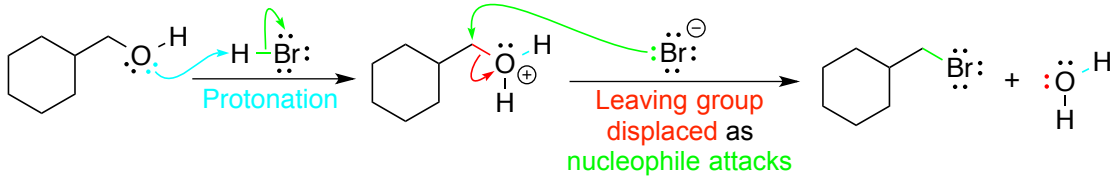
14. All of these substrates are secondary alkyl halides. The only difference is in the nature of the halide leaving group. As the halogen's size increases, so does the ionic radius of the prospective halide leaving group. A larger ion is able to disperse the same -1 charge over a larger area, which has a stabilizing effect. Therefore, the larger the halogen, the more stable the halide leaving group will be. A good leaving group is required for any substitution reaction, and a better leaving group leads to a faster substitution reaction.



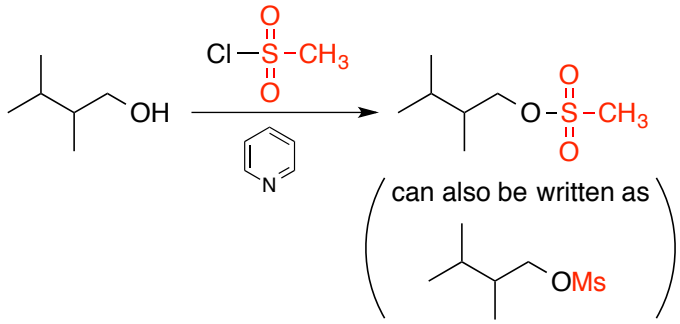
Notice that the question did not stipulate first-order or second-order substitution. Both substitution reactions require a good leaving group, so the kinetics of the process don't affect our answer.

15. Since HBr is a strong acid, it protonates the hydroxyl group in a Brønsted-Lowry acid-base reaction at the outset of this transformation. This step has converted the

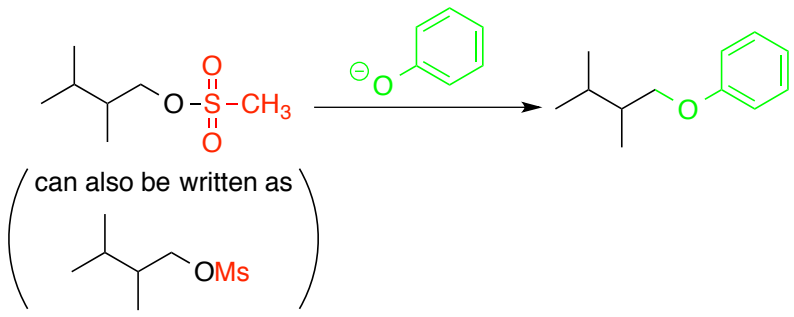
poor leaving group (hydroxide) into a good leaving group (water). However, water cannot simply dissociate from the substrate because this substrate is primary, and primary carbocations are too unstable. Instead, the substitution can follow a concerted mechanism in which it is the attack of the nucleophile that displaces the leaving group. The product is an alkyl bromide.



16. The alcohol is first converted to the corresponding mesylate by treatment with methanesulfonyl chloride (also known as mesyl chloride) and pyridine.

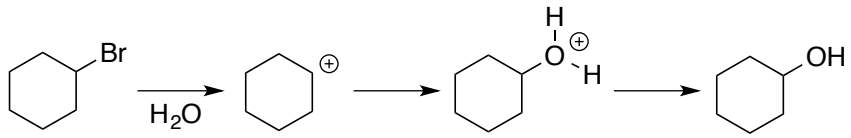


We then need to convert the mesylate into the designated substitution product by choosing the correct reagent. It is important to consider the substrate as we make our decision. This substrate is primary, which means that it is not suitable for a first-order reaction but will readily engage in second-order reaction. Second-order reactions require strong nucleophiles, so we have to choose accordingly. The portion of the product shown in green comes from the nucleophile. We want this nucleophile to be negatively charged so that it will be strong. Had we chosen the neutral version of the nucleophile (PhOH), it would not be potent enough to attack the substrate and incite a concerted reaction.

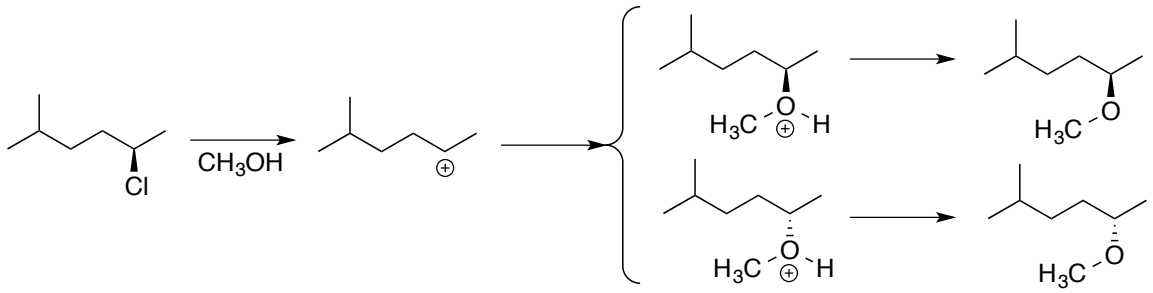


17.

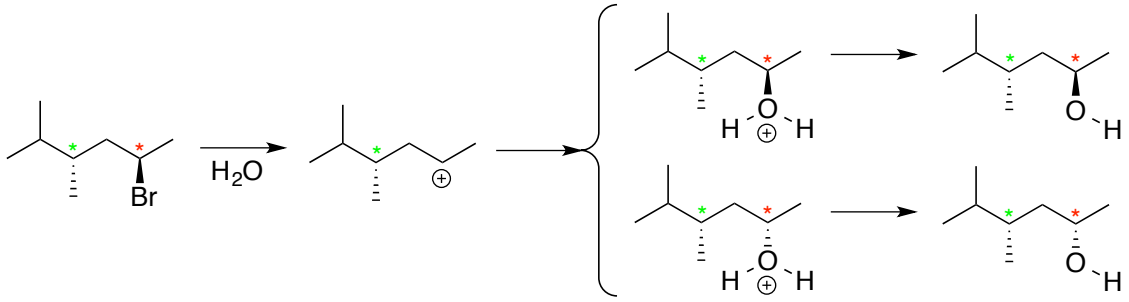
(a) The reaction begins with the dissociation of bromide to generate a secondary carbocation. Water then adds to this electrophilic center to produce an oxonium ion that finally sheds a proton, giving an alcohol as the final product.



(b) The dissociation of chloride initiates the reaction. The stereochemical information is lost when the leaving group dissociates because the carbocation is sp^2 hybridized (i.e., trigonal planar, or flat). The nucleophile (methanol) adds to the carbocation from the front and from the back to yield a racemic mixture of oxonium ions. Loss of a proton completes the reaction, affording enantiomeric ethers.

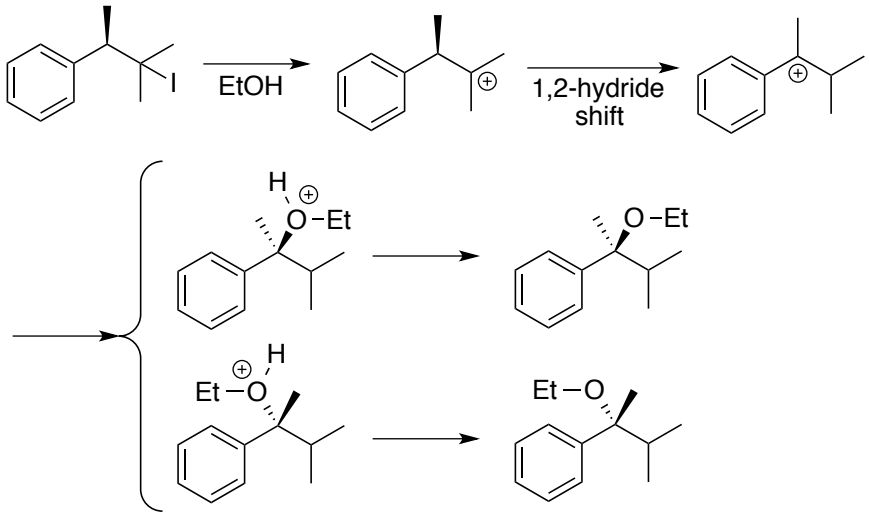


(c) Bromide dissociates in the first step of the mechanism. The stereochemical information is lost at that center when this occurs. Water then adds from both sides of the carbocation to yield two oxonium ions. Loss of a proton completes the mechanism. Notice that the alcohol products are diastereomeric in this case. This is due to the presence of a second stereocenter that is unaffected by the reaction. *If a stereocenter is uninvolved in the transformation, then it cannot be altered.*



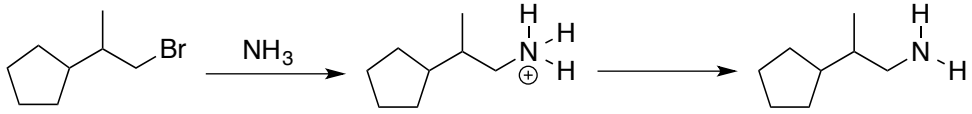
Take note of the fact that there was no carbocation rearrangement during this reaction. Although the carbocation was secondary and the molecule contains tertiary centers, the tertiary centers are not directly adjacent to the carbocation. Carbocation rearrangement necessitates an immediate improvement in stability.

(d) The dissociation of iodide begins the reaction. This loss of leaving group results in a tertiary carbocation. The adjacent center is not only tertiary but also provides an opportunity for resonance stabilization. Consequently, a 1,2-hydride shift occurs to generate the resonance-stabilized, tertiary carbocation. The stereochemical information is lost during this step because the carbocation is sp^2 hybridized (i.e., trigonal planar, or flat). The nucleophile (ethanol) then adds to this center from both sides, and the resultant oxonium ions each lose a proton. The product is a racemic mixture of enantiomeric ethers.



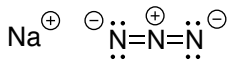
18.

(a) The strong nucleophile, ammonia (NH_3), displaces bromide, leading to an ammonium ion. The ammonium ion subsequently loses a proton to yield the product, which is an amine.

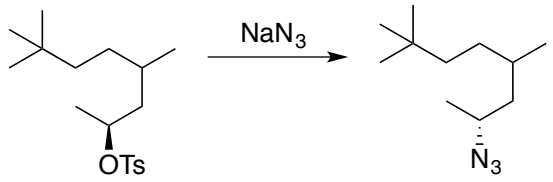


Note that the amine formed above can actually react further. This issue is discussed in greater depth in Chapter 18.

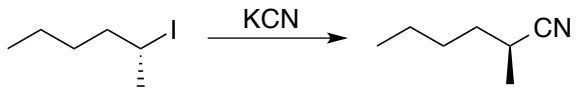
(b) In Problem 10, we saw the importance of looking closely at nucleophiles that appear to be neutral. The presence of a metal in the formula reveals that the nucleophile is actually negatively charged. Sodium azide (NaN_3) has the following structure. Since azide (N_3) has a net charge of -1, it is a strong nucleophile.



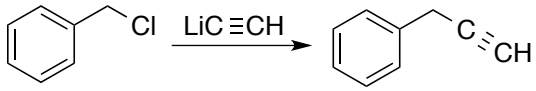
As such, azide displaces the tosylate from the secondary carbon, inverting the stereochemistry of that center in the process.



(c) Again, in this problem, we see a nucleophile that is not, in fact, neutral even though it appears to be at first glance. Potassium has a +1 charge, so cyanide ($^{-}$CN) has a -1 charge. This makes it a strong nucleophile, and it displaces iodide in S_N2 fashion. As it does so, a Walden inversion takes place.

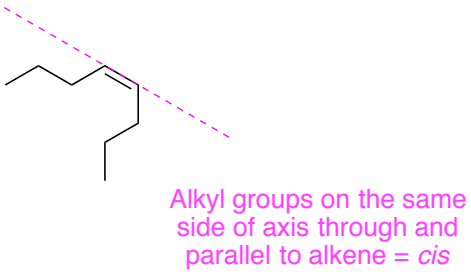


(d) This is yet one more example of the presence of a counterion (Li^{+}) masking the charge on the nucleophile. The acetylide ion ($^{-}$:C≡CH) is negatively charged and is therefore a potent nucleophile. It attacks the benzylic carbon and displaces chloride to yield the product as an alkyne with an extended carbon backbone.



19. In each instance, we should begin by drawing an axis through and parallel to the alkene. If the alkyl groups are on the same side of that axis, the olefin has the *cis* configuration. If the alkyl groups reside on opposite sides of that axis, then the alkene has the *trans* configuration. If either alkene carbon has two identical substituents, it will not exhibit geometric isomerism.

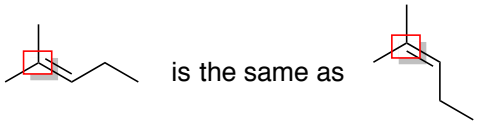
(a)



(b)

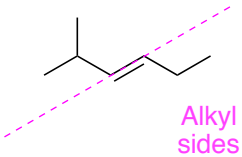
Alkyl groups on the same side of axis through and parallel to alkene = *cis*

(c)



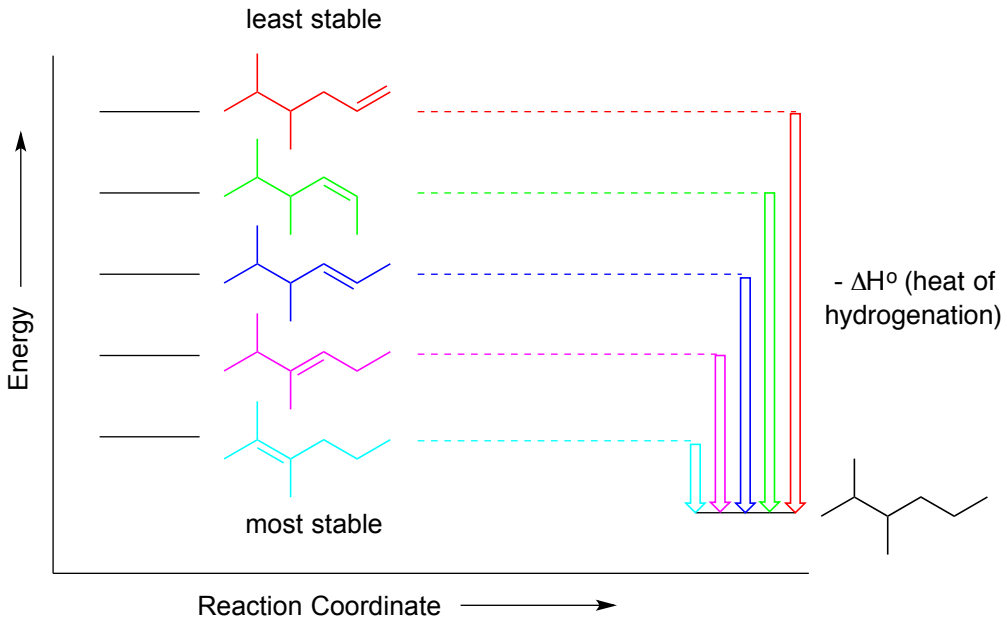
One carbon has two identical substituents. Therefore, no geometric isomerism

(d)

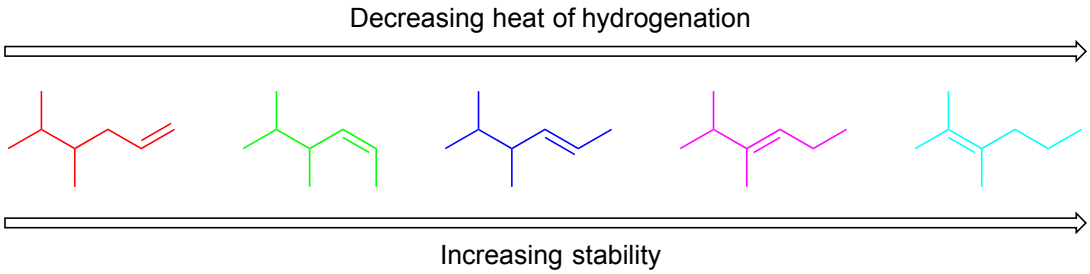


Alkyl groups on opposite sides of axis through and parallel to alkene = *trans*

20. The hydrogenation of any of these alkenes makes the same exact alkane product. Since the energy of the product is a constant, varying heats of hydrogenation can only be explained by the reactant alkenes having different energies. We've learned that alkene stability depends on substitution. The least stable (i.e., highest energy) alkene is monosubstituted. The most stable (i.e., lowest energy) alkene is tetrasubstituted. Of the two disubstituted alkenes, *trans* is more stable than *cis*. When we put all of the rankings into graphical format, it becomes apparent that the least stable alkene will have the greatest heat of hydrogenation.

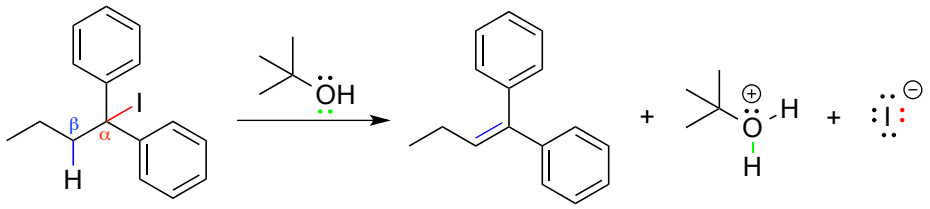


The overall trend then is that the heat of hydrogenation decreases as the alkene's stability increases.

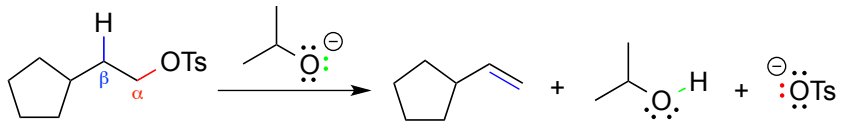


21.

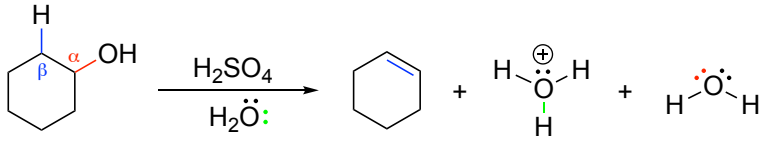
(a) In this reaction, iodide is lost from the α-carbon. Additionally, a lone pair of electrons on the alcohol is used to remove a proton from the only β-carbon that has protons. The C-H σ bonding electrons are used to form the π bond of the alkene.



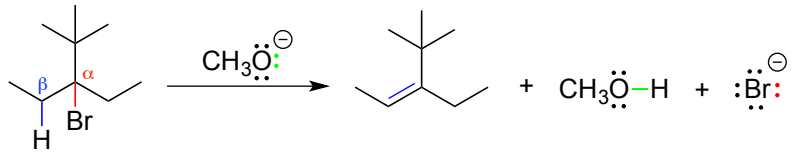
(b) In this elimination, the alkoxide uses a lone pair of electrons to remove a β-proton. The C-H σ bonding electrons form the alkene's π bond, and tosylate is lost in the process.



(c) In this elimination, the poor leaving group (hydroxide) is converted to a good leaving group (water) by protonation using sulfuric acid. This good leaving group is then lost, and water removes a proton from the β position, enabling the formation of the alkene π bond.



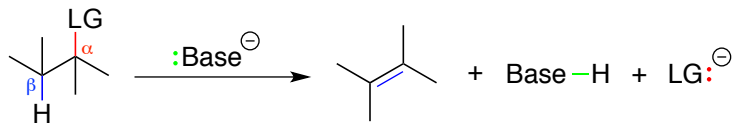
(d) In this example, a lone pair of electrons on the alkoxide is used to remove a β-proton. The π bond is formed using the electrons from the breaking C-H σ bond, and bromide is lost.



22. We know the change in free energy is critical for determining whether or not a reaction is favored at equilibrium.

$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$

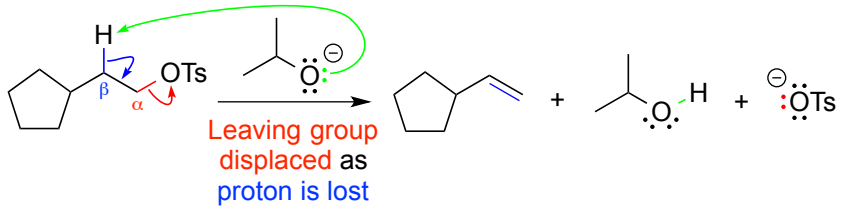
Temperature is a factor in the entropy term of this equation. Notice that the entropy increases in an elimination reaction because two molecules (substrate and base) become three (alkene, protonated base, and leaving group).



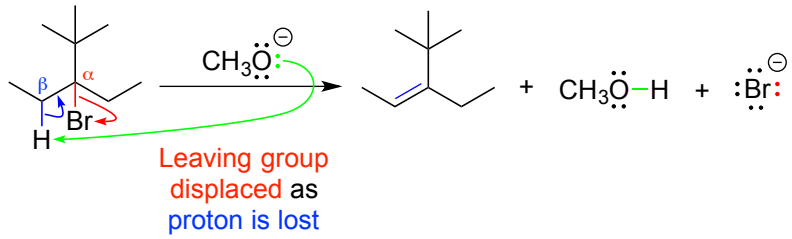
At higher temperatures, the change in entropy affects ΔG° even more significantly because ΔS° is multiplied by a large number when the temperature is higher. This makes the entropy term larger and enhances the likelihood that the overall ΔG° will be negative. When that is the case, the reaction is exergonic, and its products are favored at equilibrium.

23.

(a) In this concerted reaction, the alkoxide removes the β-proton, causing the C-H σ bond to break and the π bond to form. This, in turn, results in the expulsion of tosylate as a leaving group.

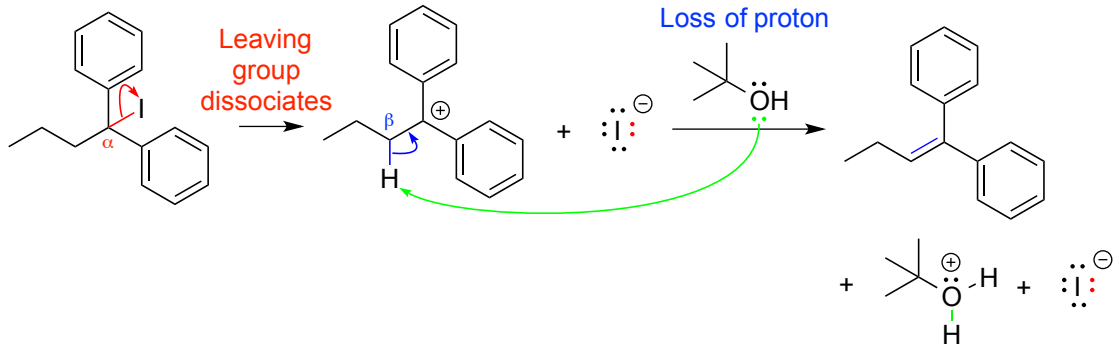


(b) This concerted reaction begins when the alkoxide removes a proton from the β-carbon. As the C-H bond breaks, the π bond is formed, and this in turn expels bromide as a leaving group.

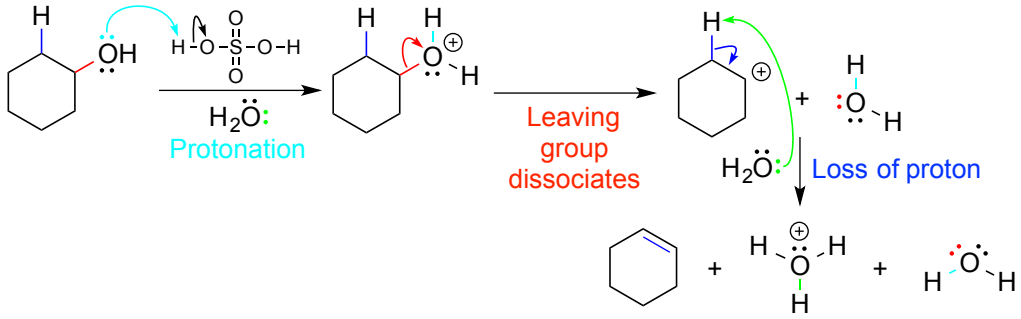


24.

(a) This stepwise elimination begins with the dissociation of iodide from the tertiary carbon. A tertiary carbocation intermediate results. Then, a proton is lost from the only β-carbon that has protons. The alcohol, acting as a weak base, removes the proton, and this allows the alkene's π bond to be produced.



(b) This stepwise elimination must begin with protonation of the hydroxyl group. Hydroxide would be a poor leaving group, and all substitution and elimination reactions require a good leaving group. Protonation converts the leaving group from hydroxide to water, which can then dissociate to yield a secondary carbocation intermediate. Finally, a proton is lost to water, enabling the formation of the π bond.



25.

(a) This is a comparison of hydroxide (^{-}OH) to amide ($^{-}NH_2$). Since the atoms bearing the charge reside in the same row of the periodic table (i.e., same period), the most significant difference between them is electronegativity. Oxygen is more electronegative than nitrogen, meaning that hydroxide is more stable because oxygen has a greater desire for enhanced electron density. Being less stable, amide is more reactive as both a nucleophile and a base. In this example, nucleophilicity does parallel basicity.

NaOH vs. $\boxed{NaNH_2}$

stronger base

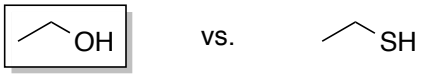
Another approach to this problem entails comparison of the pK_a values of the conjugate acids. Water has a pK_a of 15.7, while ammonia has a pK_a of 32.5. This reveals that ammonia is the weaker acid and therefore has the stronger conjugate base.

(b) This is an instance in which nucleophilicity does not parallel basicity. The conjugate base of phosphine (PH_3) has the anion on phosphorus, which is a larger atom than nitrogen. Recall that, when the atoms bearing the charge reside in the same column of the periodic table (i.e., same family), the most significant difference between them is size. The larger ion is more polarizable, making it a better nucleophile. However, the larger size of the phosphorus anion also allows charge to be distributed over a greater area, which stabilizes this base relative to amide.

$\boxed{^{\ominus}NH_2}$ vs. $^{\ominus}PH_2$

stronger base

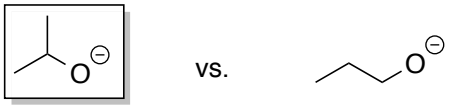
(c) Both ethanol (CH_3CH_2OH) and ethanethiol (CH_3CH_2SH) are weak bases due to their neutrality. Nevertheless, ethanol is the stronger of the two. Sulfur is a larger atom than oxygen, so its electron density is distributed over a larger area, weakening its basicity.



stronger base

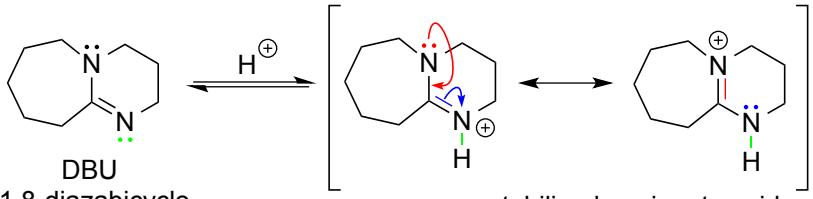
Note that, in this instance, nucleophilicity does not parallel basicity. The size of the sulfur atom (the very thing that rendered it less basic) makes it *more* nucleophilic. A larger atom has a more polarizable electron could, which enables it to form a partial bond to an electrophile from a greater distance. This capability makes for a powerful nucleophile.

(d) This is yet another situation in which nucleophilicity does not parallel basicity. Propoxide ($CH_3CH_2CH_2O^-$) is the better nucleophile of the two because of its relative lack of steric hindrance. The branching present in isopropoxide [$(CH_3)_2CHO^-$] increases its steric hindrance, making it more difficult for isopropoxide to act as a nucleophile. However, it is still able to act effectively as a base. In fact, its reduced solvation, which is also due to its branching, makes it even more reactive in this capacity.



stronger base

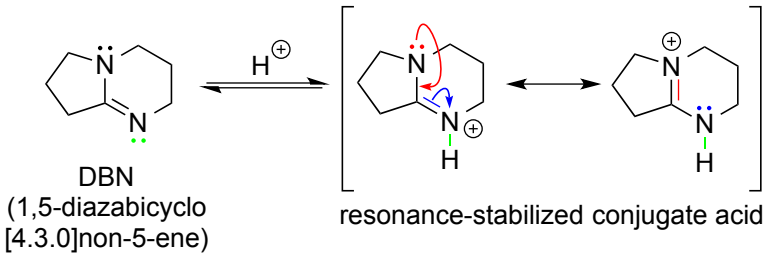
26. Both DBU and DBN contain two nitrogen atoms with lone pair electrons, so there are two locations where we could consider protonation. However, only protonation of the sp^2 hybridized nitrogen allows for resonance-stabilization of the conjugate acid. This resonance stabilization lends great stability to the conjugate acid, which in turn explains the strength of the base.



DBU
(1,8-diazabicyclo
[5.4.0]undec-7-ene)

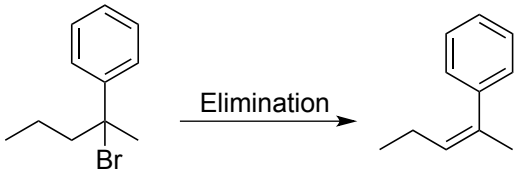
resonance-stabilized conjugate acid

DBN has very similar resonance stabilization of its conjugate acid.

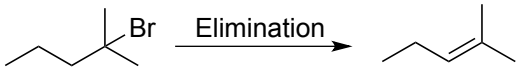


27. Unlike substitution, the order of reactivity of substrates toward first- and second-order elimination reactions is the same. Reactivity in first-order eliminations depends on the stability of the carbocation intermediate, so the more substituted the substrate, the more reactive it will be. Reactivity toward second-order eliminations is determined by the relative stability of the alkene formed. A more highly substituted substrate will give a more highly substituted alkene and therefore reacts more rapidly (due to a lower activation energy barrier). *Although it is for different reasons, both first- and second-order eliminations proceed more readily with more highly substituted substrates.*

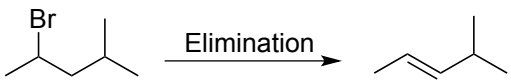
The benzylic bromide is the most reactive of the alkenes listed. In first-order elimination, it will be converted to a resonance-stabilized, tertiary carbocation. In second-order elimination, the stability of the conjugated, trisubstituted alkene product results in a low activation energy barrier to its reaction.



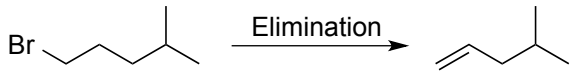
The tertiary bromide is slightly less reactive. The tertiary carbocation that results from a first-order elimination is stable, but not as stable as the resonance-stabilized, tertiary carbocation that resulted from the previous compound. Additionally, in second-order elimination the stability of the trisubstituted alkene that can be formed from this substrate results in a fairly low activation energy barrier.



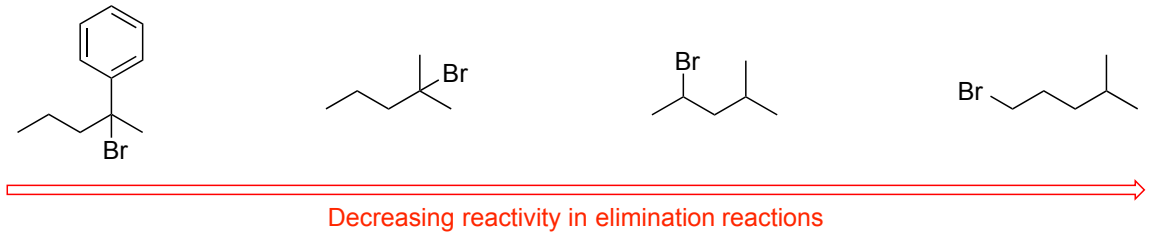
The secondary bromide is less reactive because first-order elimination would proceed through a less stable, secondary carbocation. Second-order elimination is slowed by the fact that the resulting disubstituted alkene is less stable than the previous alkene products, which has the effect of raising the activation energy barrier for the reaction.



Finally, the primary bromide is the least reactive. It will not engage in first-order reaction because of the unstable primary carbocation that would result. The monosubstituted alkene that could result from second-order elimination is the least stable of the alkene products. As a result, this reaction has a higher activation energy barrier than the others.



To summarize, the reactivity of the substrates toward elimination is as follows:



28.

(a) Given that this reaction uses an alcohol (*tert*-butyl alcohol) as the base, we expect it to be a first-order elimination. First-order reactions are favored by polar protic solvents, such as water or alcohols. Since an alcohol is the reagent, we would likely use it in large excess, allowing *tert*-butyl alcohol to serve as both the reagent and the solvent.

(b) This elimination uses an alkoxide, which is a strong base. It is therefore expected to proceed through a second-order pathway. Second-order reactions are favored by polar aprotic solvents, so we could choose a solvent such as DMSO for this reaction.

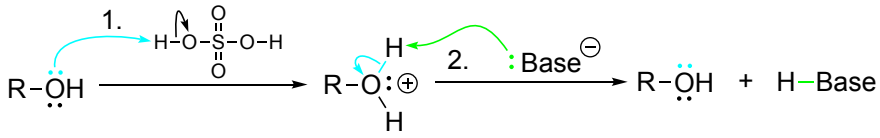
It is worth noting though that sometimes, when an alkoxide is a reagent, the solvent may simply be its conjugate acid (the alcohol). In such cases, the solvent would not be optimal for a second-order process, but the solvent is not the primary factor that impacts the reaction mechanism. Therefore, some deviation in choice of solvent is allowable.

(c) Given the presence of a weak base (water), we expect a first-order pathway, which would be facilitated by using water or an alcohol as the solvent. Since water is a reagent, we would merely use it in a large excess, thereby allowing it to function as the solvent as well.

(d) The presence of the alkoxide, which will act as a strong base, suggests a second-order reaction. A polar aprotic solvent, such as DMF, would facilitate this process.

As noted in part (b) above though, you will sometimes see the conjugate acid of the alkoxide (i.e., the corresponding alcohol) used as the solvent. This is done for convenience even though the alcohol may not be the optimal reaction solvent.

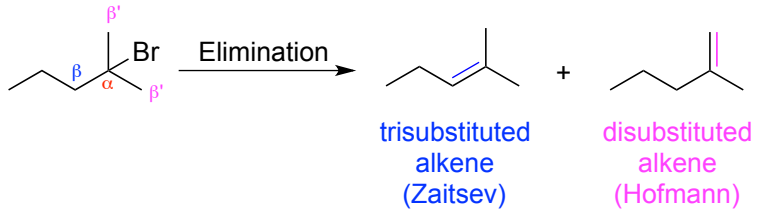
29. The diagram below outlines the situation we are considering. First, an oxonium ion is generated from an alcohol. This can be accomplished by protonation using a strong acid, such as sulfuric acid. Then, we treat with a strong base in an attempt to incite an elimination. However, we cannot forget that the oxonium ion is an acid. Protonated alcohols have low pK_a values (~0), so what transpires is merely a Brønsted-Lowry acid-base reaction. Once the oxonium ion is deprotonated, the leaving group (hydroxide) is once again poor, so no elimination is possible.



We refer to the oxonium ion and a strong base as being "incompatible" because, when mixed, an unintended reaction occurs (i.e., acid-base reaction rather than elimination).

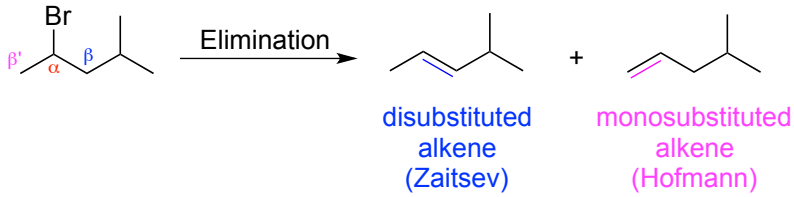
30.

(a) Loss of a proton from β yields a trisubstituted alkene; whereas, the loss of a proton from either of the two equivalent β' positions generates a geminally disubstituted olefin. The more highly substituted alkene, which in this case happens to be trisubstituted, is the Zaitsev product. The disubstituted alkene is the Hofmann product.

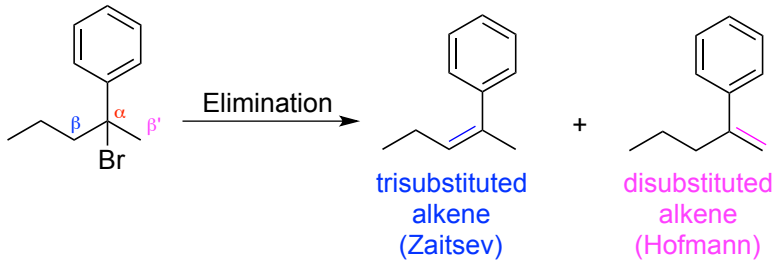


Notice that the loss of a proton from the more substituted β position (secondary, as opposed to primary for β') leads to the more substituted alkene product.

(b) There are two β positions: β is secondary and β' is primary. The loss of a proton from the more substituted β position yields the more substituted (Zaitsev) alkene, which happens to be *trans* disubstituted in this problem. Conversely, the loss of a proton from the less substituted β' position results in the less substituted (Hofmann) alkene, which happens to be monosubstituted.

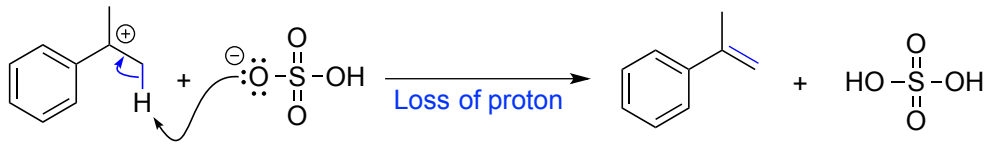


(c) This substrate also has two β-carbons bearing protons. Formally, there is a third β-carbon on the phenyl group; however, it has no protons and therefore cannot participate in elimination. Of the two β-carbons bearing protons, β is secondary, while β' is primary. Loss of a proton from the more substituted β position affords the more substituted (Zaitsev) alkene, which is trisubstituted. On the other hand, the loss of a proton from the less substituted β' position yields the less substituted (Hofmann) product, which contains a geminally disubstituted alkene.

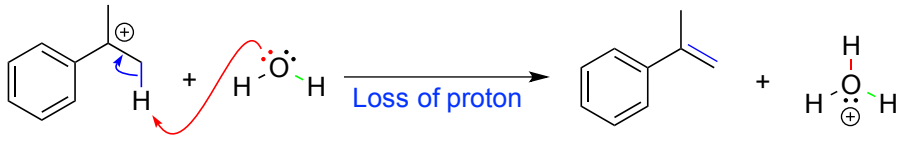


31. At first, it appears as though all three of these approaches give slightly different results. When the proton is lost to bisulfate (a), the byproduct is sulfuric acid (H_2SO_4). When the proton is lost to water (b), the byproduct is the hydronium ion (H_3O^+). And, when the proton is simply lost to an unspecified base (c), the byproduct is a free proton (H^+).

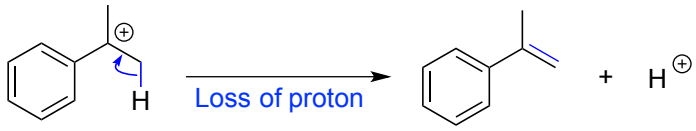
(a)



(b)



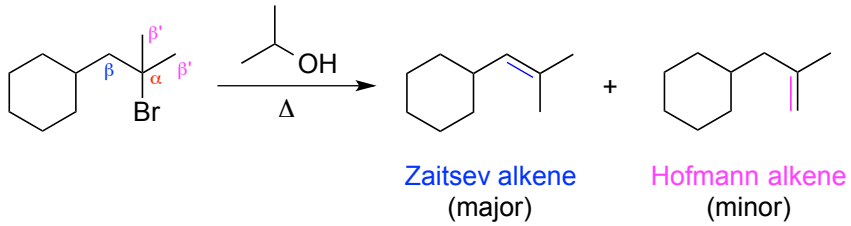
(c)



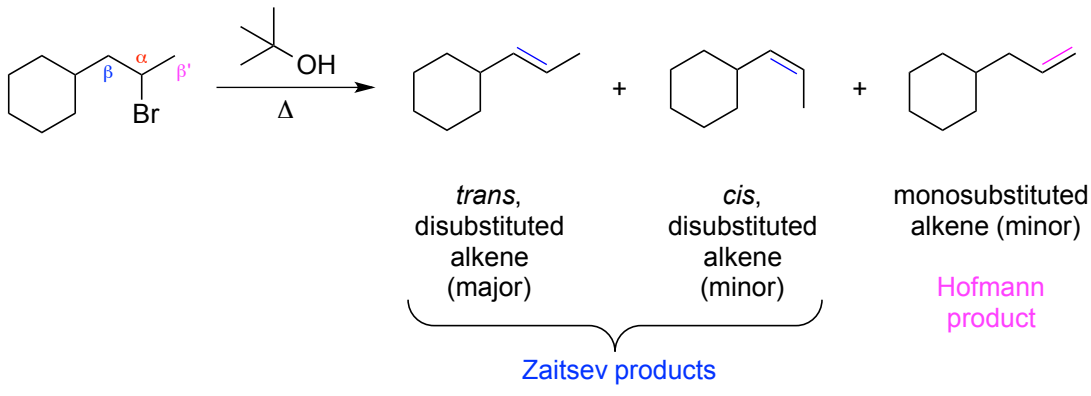
However, if we remember our acid-base chemistry, we'll see that all three of these approaches are mechanistically semantic. Sulfuric acid is such a strong acid that, in an aqueous medium, it protonates water leading to the formation of the hydronium ion. So, the ultimate byproduct of (a) is actually the hydronium ion. This is the same byproduct that we see in (b). In path (c), we know that a proton cannot simply be lost. There must be some base that removes it, even if that base is unspecified. The base is either bisulfate (a) or water (b), and (c) is merely an abbreviated form of those pathways, both of which ultimately produce the hydronium ion as a byproduct.

32.

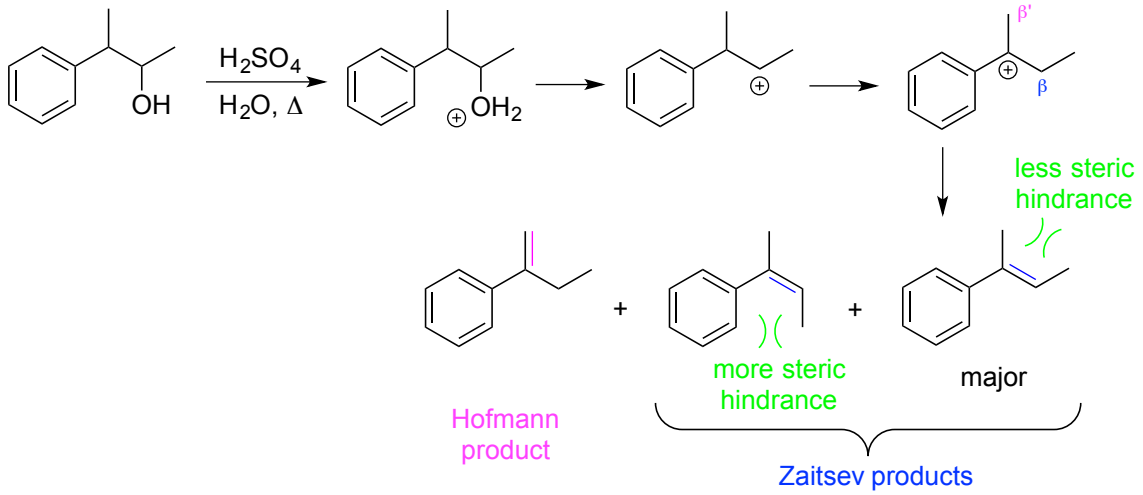
(a) In this elimination reaction, bromide dissociates from the tertiary carbon (α), and then a proton is lost from either β or one of the two identical β' positions. Loss of a proton from β results in a trisubstituted alkene, which is the major product, and the loss of proton from β' yields a geminally disubstituted alkene, which is the minor product.



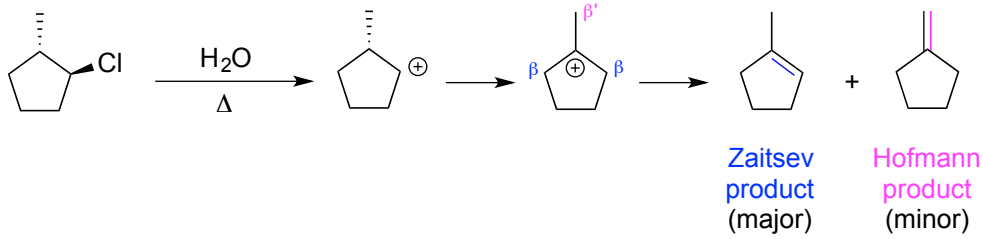
(b) In this reaction, bromide dissociates from the secondary carbon (α), and this is followed by the removal of a proton from β or β'. The loss of a proton from β generates both a *trans* and a *cis* disubstituted alkene; whereas, the loss of a proton from β' results in the formation of a monosubstituted alkene. The *trans*, disubstituted alkene is the most stable of the three, so it is the major product.



(c) In this dehydration (a specific type of elimination in which water is lost), the alcohol is first protonated to form a good leaving group. Water then dissociates, generating a secondary carbocation. This secondary carbocation is adjacent to a benzylic, tertiary carbon, so a 1,2-hydride shift follows to yield a preferable resonance-stabilized, tertiary carbocation. There are two centers adjacent to the carbocation that bear protons: β and β'. Loss of a proton from β yields two geometric isomers of a trisubstituted alkene; whereas, the loss of a proton from β' results in a geminally disubstituted alkene. The trisubstituted alkene that has less steric encumbrance is the major product.



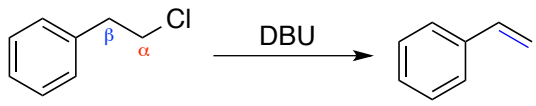
(d) In this elimination, chloride dissociates from the secondary carbon to which it is bonded. The resultant secondary carbocation is adjacent to a tertiary center, so a 1,2-hydride shift ensues. This affords a more stable tertiary carbocation, which then loses a proton from either of the two identical β-carbons or from β'. The loss of a proton from β yields a trisubstituted alkene (the major product), while the loss of a proton from β' generates a geminally disubstituted alkene (the minor product).



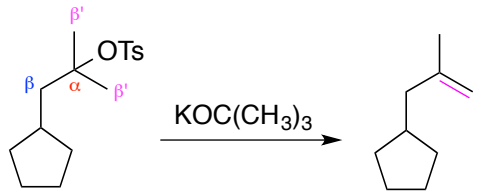
Note that none of the bonds are drawn using wedges or dashes in the products. The stereochemistry is lost at the carbon bearing chlorine once chloride dissociates. Then, when the carbocation rearrangement occurs, the stereochemistry is lost at the center bearing the methyl group. So, stereochemistry is no longer present or relevant in the products.

33.

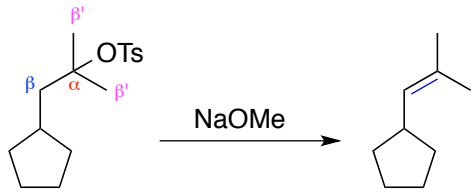
(a) DBU is a strong base that removes a proton from the only β position, leading to the formation of a conjugated alkene product that is known as styrene.



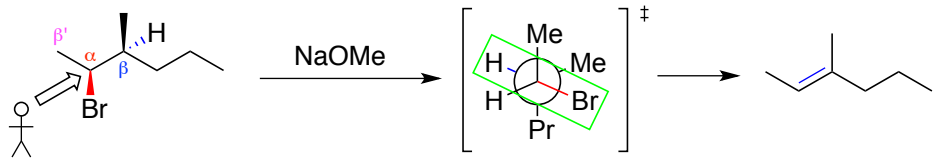
(b) This substrate has two types of β-carbons. The β position is secondary, while the β' position is primary. Since *tert*-butoxide is a bulky base, it removes a proton from the less sterically hindered β' position, which results in the formation of the Hofmann product.



(c) This is the same substrate as in part (b) above; however, it is now treated with methoxide, which is a much smaller strong base. This small, nimble base is able to approach the more substituted β position, removing a proton from this site to yield the Zaitsev alkene.



(d) This alkyl bromide has two β-carbons. The β position is tertiary, while the β' location is primary. As we saw in part (c) above, a small base like methoxide is able to approach the more substituted β-carbon so as to produce the Zaitsev alkene. However, in this problem, the stereochemistry of the product is an issue. Since β has only one hydrogen, we must consider the conformation in which that β-proton is anti-periplanar to the leaving group. In this conformation, the two methyl groups are *cis* to one another. In other words, they are on the same side of the anti-periplanar proton and leaving group. As a result, these methyl groups are *cis* to one another in the product.



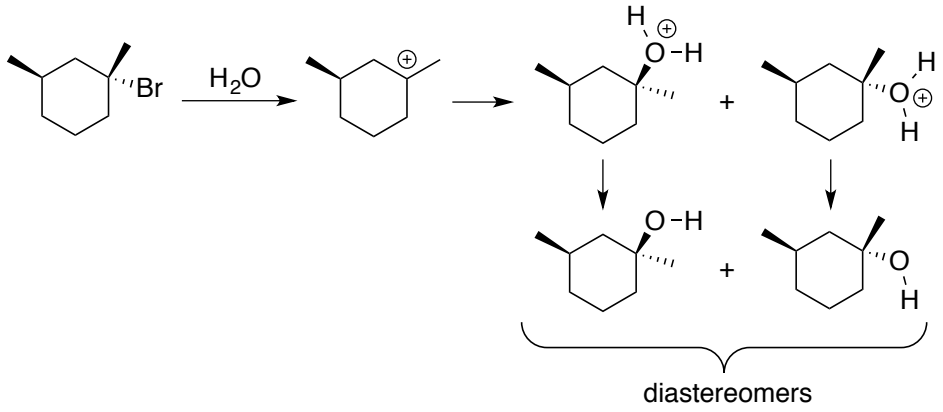
34.

(a) In this reaction, the reagent is a weak nucleophile/base. Consequently, we can quickly narrow down the possibilities to the first-order reactions: S_N1 and E1. The absence of heat (which favors elimination) suggests substitution. An S_N1 pathway is further supported by the size of the reagent. Since it is a small, unhindered molecule, it can be an effective nucleophile.

The substrate is tertiary, which is ideal for first-order pathways. Since the reagent is water, it is likely that it has been used in excess so that it can also serve as the solvent. As such, the reaction has a polar protic solvent, which also facilitates first-order reaction.

Taken together, all of the variables point toward a first-order process, and the small reagent along with the absence of heat suggests that S_N1 is preferable to E1.

The S_N1 reaction begins with the dissociation of bromide. A tertiary carbocation results, and this cation is trigonal planar (i.e., flat). As a result, water will attack the carbocation from both above and below, yielding a mixture of oxonium ions. Both of these shed a proton to form a pair of diastereomeric alcohols.

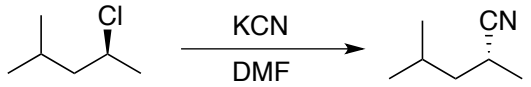


Notice that the configuration of the stereocenter that is uninvolved in the reaction is unaltered.

(b) In this example, it is important to discern that cyanide ($^-$:C≡N:) is actually a negatively charged reagent. We know this because potassium must be a cation (K^+) if it is part of a molecule. As a negatively charged reagent, cyanide is quite reactive. It is a better nucleophile than base. Hydrogen cyanide (the conjugate acid of cyanide) has a pK_a of about 9. Given the fairly high acidity of hydrogen cyanide, we know that its conjugate base (cyanide) is not especially potent. Since the reagent is a strong nucleophile, we suspect S_N2 as the predominant pathway.

The substrate is secondary, which is acceptable for S_N2 reaction. Furthermore, the solvent (DMF) is polar aprotic. Such a solvent will help to accelerate second-order processes by stripping away the potassium cation, thereby leaving cyanide bare and more reactive.

All of the factors we've considered point toward an S_N2 reaction. As cyanide displaces chloride, the configuration of the stereocenter is inverted to yield the product, which is a nitrile.

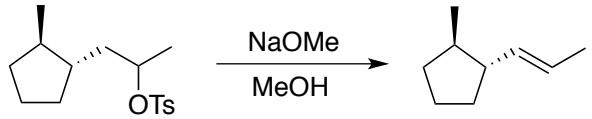


(c) This is another example of a reaction with a negatively charged reagent whose charge is masked by the presence of the counterion. However, we know that sodium must be a cation (Na^+) if it is part of a molecule, which reveals the negative charge on methoxide (^-OMe). Methoxide is a strong nucleophile/base, so we have narrowed the choices down to the second-order reactions: S_N2 and E2.

The substrate is secondary, which is suitable for S_N2 or E2. Given that steric hindrance decreases the rate of substitution and that the reagent is a potent base, the increasing (but not prohibitive) hindrance of the secondary center will reduce the rate of S_N2 reaction enough that E2 becomes the predominant pathway.

The solvent is an alcohol. Polar protic solvents are not optimal for second-order processes, but we've learned (in Problem 28) that when alkoxides are used as reagents it is common to use the conjugate acid (the alcohol) as the solvent merely for the sake of convenience in the laboratory. Although the solvent may not be optimal for the favored pathway, it is not a sufficiently powerful factor for us to alter our decision.

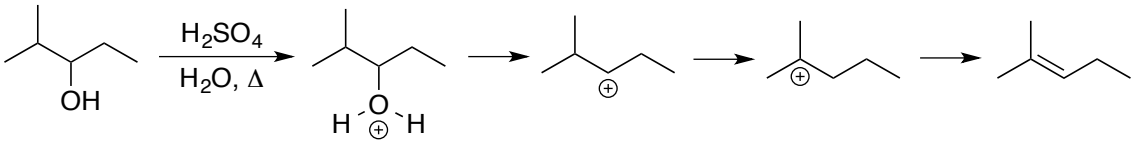
Since the base is small, the proton is removed from the more substituted β center to yield the Zaitsev alkene (with the *trans* configuration) as the major product.



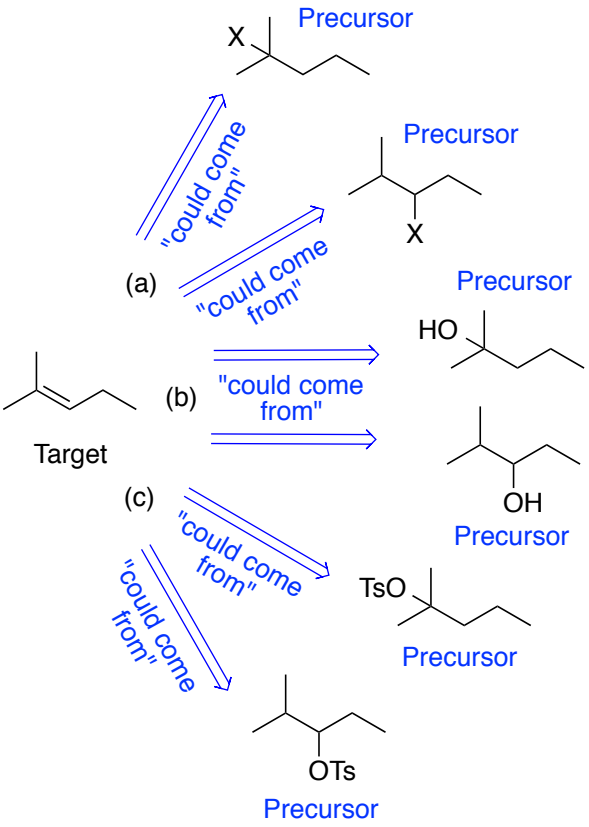
(d) The reagents include sulfuric acid and water, which likely serves as the solvent for the reaction as well. Neither reagent is a strong base or nucleophile, so we can narrow our choices down to first-order processes: S_N1 and E1. The presence of heat suggests that E1 will be favored.

The secondary substrate is suitable for E1, and the polar protic solvent also facilitates a first-order reaction.

The first-order elimination begins with the protonation of the alcohol to convert a poor leaving group into a good one. Water then dissociates to yield a secondary carbocation. Since this carbocation is adjacent to a tertiary center, a 1,2-hydride shift follows to yield a more stable tertiary carbocation. Finally, a proton is lost from the most substituted β-carbon to afford the Zaitsev product.



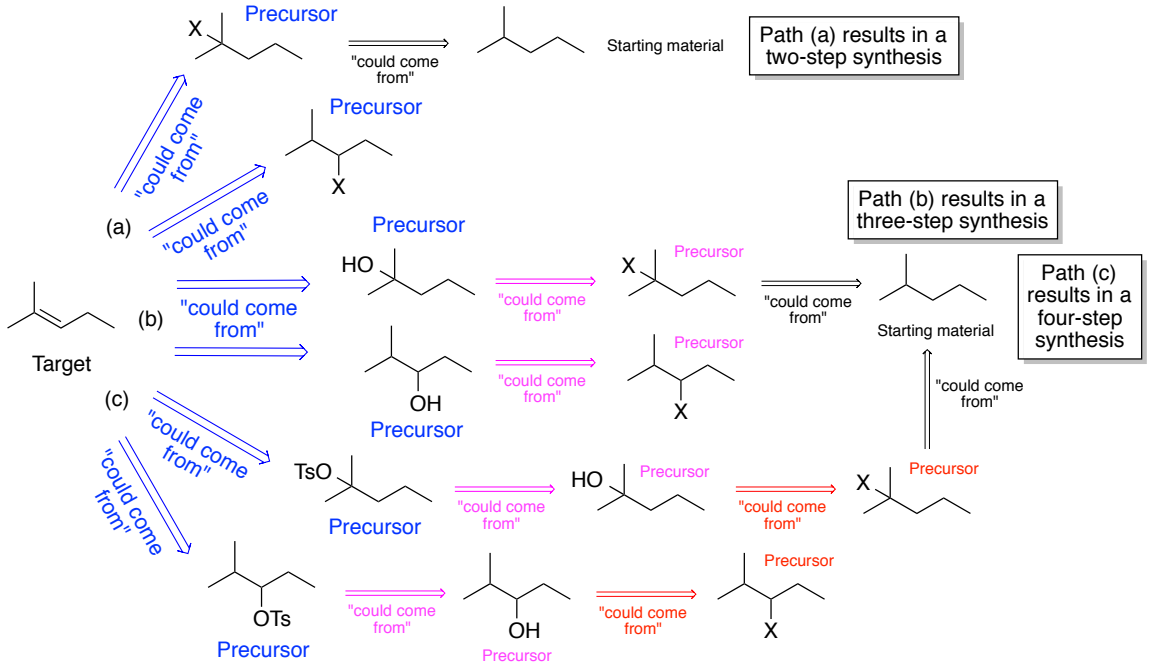
35. The target alkene can be made directly through the elimination of three classes of molecules: (a) alkyl halides; (b) alcohols; or (c) sulfonates. In each case, there are two precursors that could yield the target alkene. In other words, there are two alkyl halides that could undergo elimination to yield the desired alkene, assuming that the conditions are chosen carefully. The same is true for the alcohols and sulfonates.



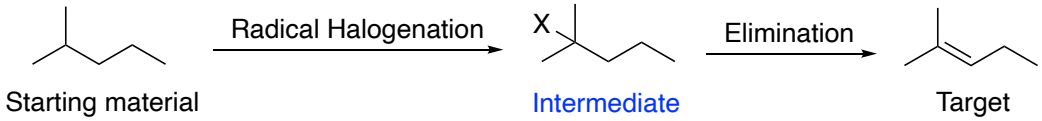
(a) One of the two alkyl halides can be prepared through radical halogenation of an alkane, which happens to be the allowed starting material. This "second generation" of retrosynthesis leads to the allowed starting material in this one instance only. This route will therefore provide the shortest option for a synthesis: two steps.

(b) Each of the alcohols could be made by an appropriate substitution of the corresponding alkyl halide, and one of those alkyl halides can be made through radical substitution of an alkane. This route suggests a three-step synthesis of the target molecule, which is less desirable than the two-step approach identified above.

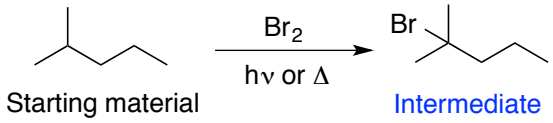
(c) Each of the two tosylates could be made from the corresponding alcohol. The alcohols can, in turn, be prepared from appropriate alkyl halides. One of these alkyl halides can be traced back to an alkane. This path would necessitate four steps, making it the least desirable of all of our options.



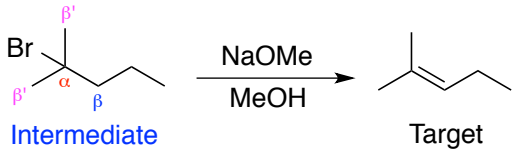
The shortest synthesis is derived from path (a). It necessitates only two steps: radical halogenation followed by elimination. At this stage, we should draw the starting material, intermediate, and target in the usual order that reflects the flow of a synthesis in the laboratory. This highlights the fact that the remaining task is the identification of suitable reagents for each transformation.



We know that radical bromination is more selective than radical chlorination, making it a better choice for the first step. The radical bromination of 2-methylpentane yields almost exclusively the desired intermediate: 2-bromo-2-methylpentane.

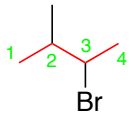


The second and final step of the sequence is the elimination. We want the Zaitsev alkene, so a small, nimble base that can freely approach the more substituted β-carbon is needed. Sodium methoxide, for instance, could accomplish this task. As a strong base/nucleophile, we expect a second-order reaction; however, S_N2 is forbidden with this tertiary alkyl bromide. Consequently, methoxide acts as a strong base, removing a proton from the more substituted β position to yield the target. We've seen previously (Problem 28) that alcohols are common solvents when alkoxides are used as reagents, even if the polar protic alcohol is not the optimal solvent for the reaction.

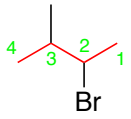


36.

(a) Let's begin by drawing the compound suggested by the name 3-bromo-2-methylbutane.

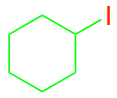


Notice that, for this compound, we'd get the same substituent numbers regardless of the direction of numbering. If we numbered in the opposite direction, the name would be 2-bromo-3-methylbutane.



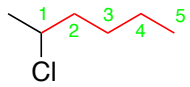
When the exact same substituent numbers are obtained regardless of the direction of numbering, the last resort tiebreaker is to give the lowest number to the substituent that appears first in alphabetical order. The correct IUPAC name would therefore be 2-bromo-3-methylbutane.

(b) In this common name, the alkyl group has been misidentified as a hexyl group. While the alkyl group is six carbons in length, it is also cyclic, so the prefix "cyclo" is necessary. The correct common name is therefore cyclohexyl iodide.

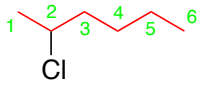


cyclohexyl iodide

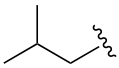
(c) Let's begin this problem by drawing the structure that is implied by the name 1-chloro-1-methylpentane.



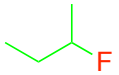
The problem is that the parent has been misidentified. The methyl group should have been included as part of the parent instead of as a substituent. This makes the parent hexane, and the full systematic compound name is 2-chlorohexane.



(d) In this common name, the alkyl group has been misidentified. While it is a four-carbon group, it is not isobutyl, which has the following structure:



Instead, the alkyl group in this molecule is the *sec*-butyl group. The proper common name is therefore *sec*-butyl fluoride.



sec-butyl fluoride

37. The rate law is dependent upon the number of species *mechanistically* involved in the rate-determining step of the reaction. This reaction has only one mechanistic step, so it is easy to identify it as the rate-determining step since there is no other choice.

In this step, there are three molecules that are *mechanistically* involved. In other words, there are three molecules with mechanistic arrows originating from them and/or going to them. All three must be represented in the rate law.

Rate = k [HBr] [alkyne] [HBr]

This can, of course, be simplified as:

Rate = k [alkyne] $[HBr]^2$

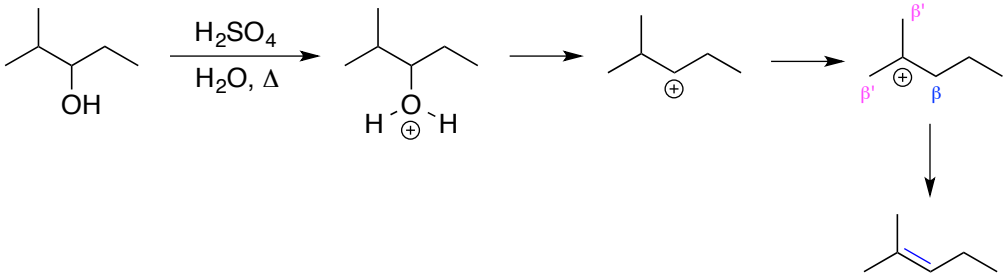
Now that we have written the rate law, we can determine the order of the reaction. The order is the sum of the powers to which each concentration term is raised. Remember that the alkyne term has an implied power of 1.

Rate = k [alkyne]^1 [HBr]^2

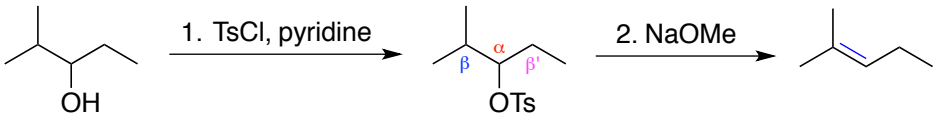
The sum of these powers is 3, so this is a third-order reaction. It may also be called a ternary reaction.

38.

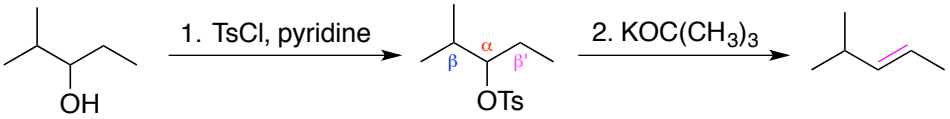
(a) When treated with sulfuric acid, the alcohol is initially protonated. The oxonium ion is now a much-improved leaving group, so it dissociates from the secondary center to afford a secondary cation. Being adjacent to a tertiary center, a 1,2-hydride shift follows to yield the more stable tertiary carbocation. Finally, a proton is lost from the more substituted β position to generate the Zaitsev alkene.



(b) In this sequence, the alcohol is first converted to the tosylate through treatment with tosyl chloride and pyridine. Sodium methoxide is subsequently added, and being a small and nimble base, it is able to remove a proton from the more substituted β-carbon to provide the more substituted (Zaitsev) alkene.



(c) This sequence begins with the same sulfonate formation. The tosylate is then treated with a large and bulky base. Since *tert*-butoxide is so sizable, it is only able to approach the less hindered β' position. Removal of a proton from this center yields the Hofmann product.



When comparing the methods for converting the hydroxyl group into a good leaving group, it is important to notice that protonation leads to only one product. The

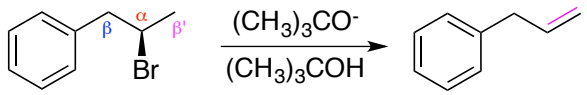
Zaitsev alkene predominates in that reaction. However, in the alternative method, the tosylate can be treated with a small base to yield the Zaitsev product or a large base to generate the Hofmann product. This provides us with greater control. We may produce whichever alkene is desired through careful base selection.

39.

(a) The reagent provides the first clue to the mechanism of this transformation. Since *tert*-butoxide is negatively charged, it is a strong reagent that is likely to participate in a second-order reaction. However, being rather bulky, it is more likely to behave as a base than a nucleophile because plucking a proton from the periphery of the molecule is not very sterically demanding. As a result, we suspect an E2 mechanism.

The secondary substrate is suitable for E2 reaction, and the alcohol solvent, although not optimal for a second-order process, is commonly used with an alkoxide reagent.

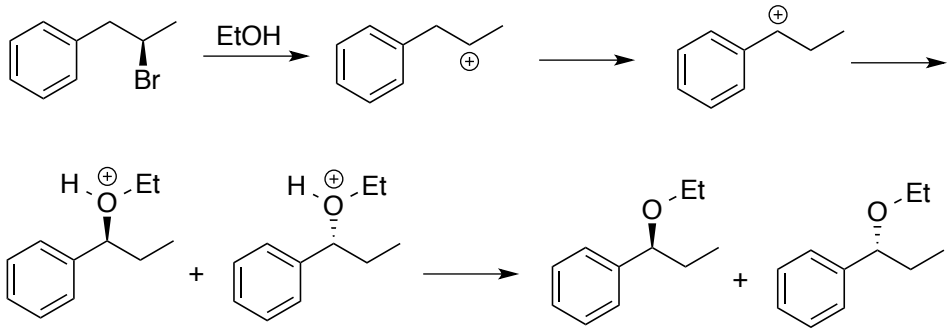
The bulky base removes a proton from the less hindered β' position to yield the Hofmann alkene.



(b) In this reaction, the reagent (ethanol) is weakly reactive since it is an alcohol. This leads us to suspect a first-order pathway. Furthermore, ethanol is a relatively sleek reagent (i.e., not bulky). Given its small size and the lack of heat (which favors elimination), S_N1 is the most probable pathway.

The secondary substrate would make a reasonably stable carbocation, so it is suitable for S_N1. Since the reagent is an alcohol, it is likely used in a large excess, which enables it to also serve as the reaction's solvent. A polar protic solvent like this does, in fact, facilitate a first-order process.

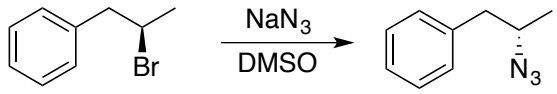
The S_N1 reaction begins with the dissociation of bromide. The secondary carbocation is adjacent to a center that is both secondary and benzylic. Consequently, a carbocation rearrangement (a 1,2-hydride shift) occurs to yield the resonance-stabilized carbocation intermediate. Ethanol adds to this electrophilic carbon from both sides, yielding a racemic mixture of enantiomeric oxonium ions. Each sheds a proton to afford the final products: enantiomeric ethers.



(c) The reagent in this problem carries a net negative charge, although that may not be obvious at first glance. Recall that the presence of a metal in the formula is suggestive of an ionic bond. Sodium forms a +1 cation (Na^+), which shows that azide has a net charge of -1 (N_3^-). As such, it is highly reactive and will engage in a second-order reaction. Azide is very <u>un</u>hindered because its central nitrogen is sp hybridized, making it a linear molecule. Additionally, its conjugate acid (HN_3, hydrazoic acid) has a pK_a of ~4.6, making it about as acidic as a carboxylic acid. This means that azide, the conjugate base, is not particularly basic. Being unhindered and weakly basic, azide is far more likely to behave as a nucleophile. Given that the reagent is a strong nucleophile, S_N2 reaction appears probable.

A secondary substrate is suitable for S_N2, and the polar aprotic solvent DMSO will strip away the Na^+ counterion, leaving azide bare and more reactive as a result. This facilitates the second-order process.

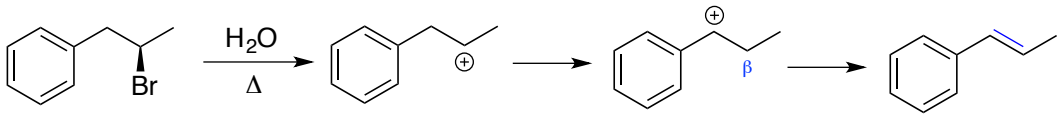
Since all of the factors point toward S_N2, we expect bromide to be displaced by azide in a concerted fashion, which results in an inversion of configuration



(d) In this reaction, the reagent (water) is weakly reactive. This makes the first-order pathways the most probable. The use of heat will help to favor E1 over S_N1.

The secondary substrate is suitable for E1. Since water is the reagent, it is likely used in a large excess, allowing it to function as the solvent as well. This polar protic solvent will facilitate the first-order reaction.

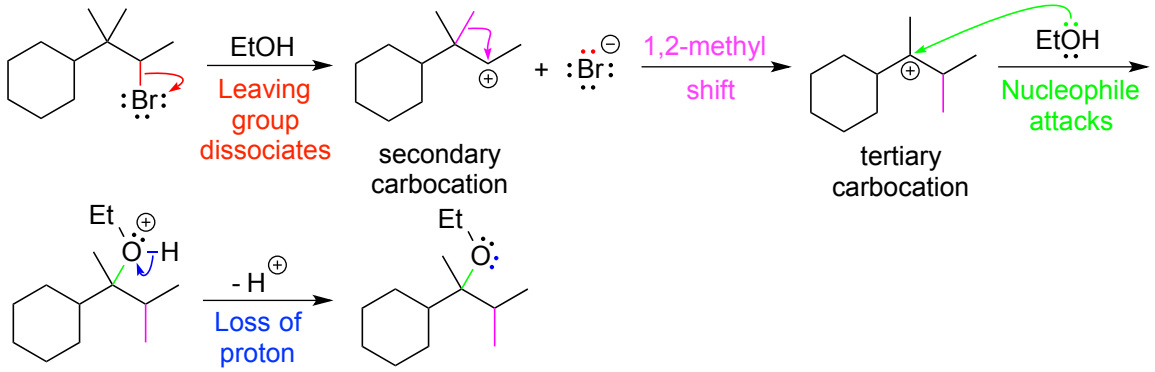
The E1 transformation begins with dissociation of bromide from the secondary center to which it is attached. The resulting secondary carbocation undergoes carbocation rearrangement (a 1,2-hydride shift) to generate a more stable secondary, benzylic carbocation that has resonance. Finally, a proton is lost from the only β-carbon bearing protons to yield a conjugated alkene as the product.



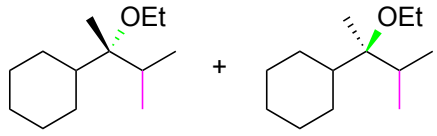
40. The reagent for this transformation is an alcohol, which is weakly reactive. This leads us to first-order pathways. In deciding between S_N1 and E1, we can consider (a) the size of the reagent and (b) the absence of heat. This alcohol (ethanol) is unbranched and therefore fairly small. Given its fairly sleek profile, it can serve as a nucleophile. The absence of heat (which would favor elimination) also persuades us that S_N1 is the predominant pathway.

The substrate is secondary, which is suitable for S_N1 reaction. Additionally, since the reagent is an alcohol, it is likely used in great excess and therefore serves as the solvent as well. A polar protic solvent like this facilitates the first-order process.

This S_N1 reaction begins with the dissociation of bromide from its secondary carbon. This yields a secondary carbocation, which resides next to a more substituted (quaternary) center. As a result, carbocation rearrangement ensues so as to provide a more stable carbocation intermediate. The quaternary carbon has no hydrogens, so a 1,2-hydride shift is impossible. Instead, the next largest group (a methyl group) migrates in a 1,2-methyl shift. This affords a more stable tertiary carbocation. Ethanol then attacks the carbocation to form an oxonium ion as the subsequent intermediate. Finally, this oxonium ion sheds a proton to yield the product, which is an ether.

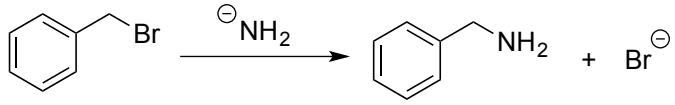


A stereocenter is produced during this transformation when ethanol adds to the carbocation. Since addition to the trigonal planar (or flat) carbocation can occur from either side, a racemic mixture of enantiomers is ultimately produced.

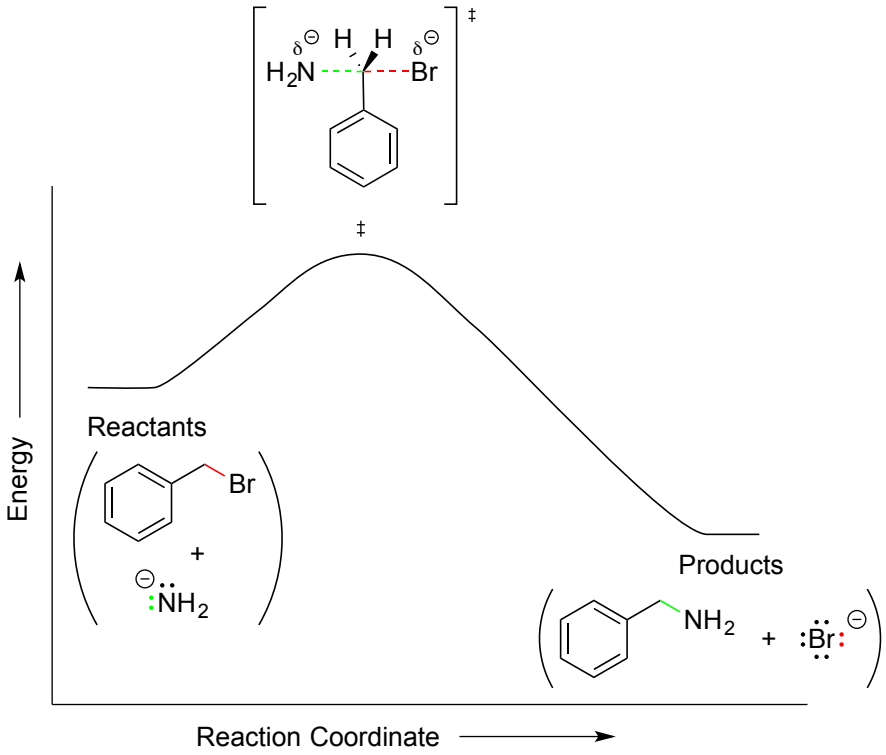


41.

(a) This reaction follows the S_N2 mechanism. Amide ($^-NH_2$) is a strong nucleophile and a strong base; however, this substrate has no β-carbons bearing hydrogens, which makes elimination impossible. As a result, the strong nucleophile engages in a second-order substitution reaction. The primary, benzylic bromide is suitable for S_N2, which occurs in a concerted fashion.

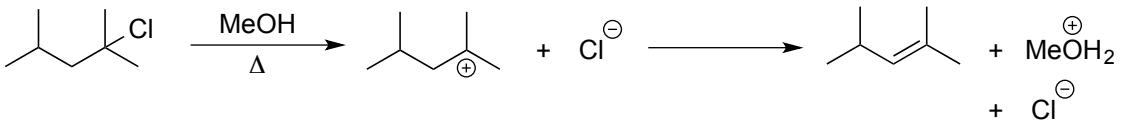


Given that this is a concerted reaction, all the bond making and breaking occurs in a single step. The C-Br bond is cleaved as the C-N bond is formed. The transition state includes a partially formed carbon-nitrogen bond, as well as a partially broken carbon-bromine bond. Both bromine and nitrogen possess δ^- charges in the transition state. Nitrogen is an anion as a reactant and neutral as part of the product, so at the transition state it has an electron density intermediate between the two. Bromine is neutral as part of the reactant and an anion when it is expelled as a leaving group. At the transition state, it has a charge intermediate between the two.



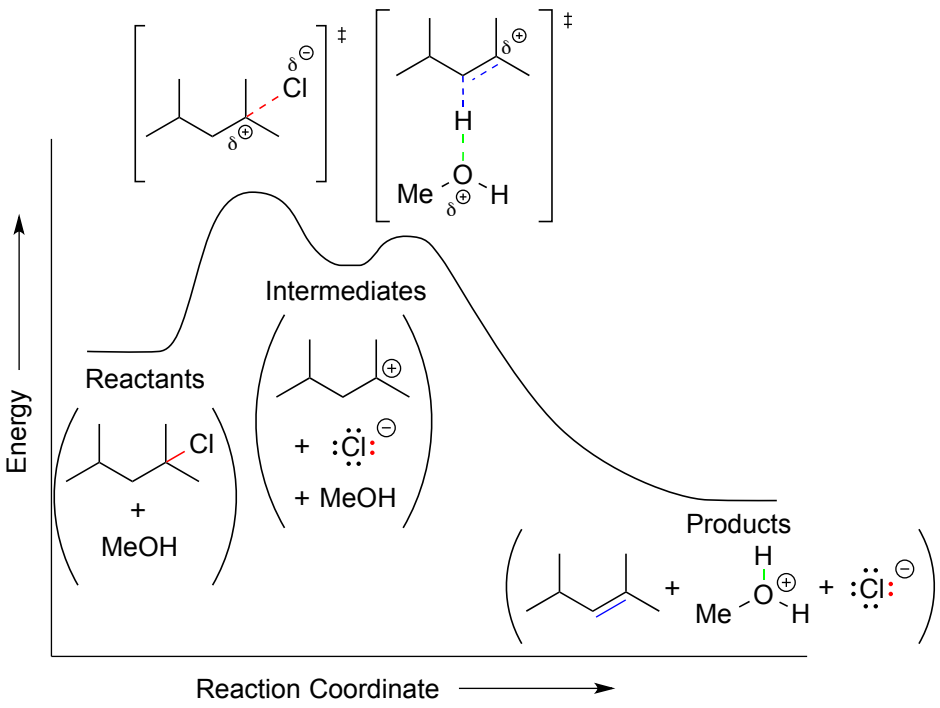
(b) In this transformation, the reagent is weakly reactive, implying a first-order process. The use of heat favors elimination over substitution, so E1 becomes the most likely pathway. Tertiary substrates are perfectly suited to first-order processes, so E1 is in fact the mechanism.

Chloride dissociates from the reactant to yield a tertiary carbocation intermediate. Then, a proton is lost from the more substituted β position to yield the Zaitsev alkene as the product.



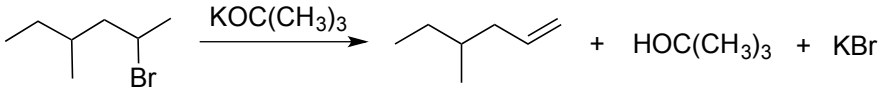
This reaction has two mechanistic steps, so there are two transition states. There is a transition state between the reactants and intermediates, as well as one between the intermediates and products.

In the first transition state, the carbon-chlorine bond is partially broken. This results in a δ^+ on carbon and a δ^- on chlorine. In the second transition state, the weak base begins to pull a proton from the β-carbon. This results in the partial cleavage of the β-carbon–hydrogen bond. The π bond begins to form as well. The carbocation is starting to lose its positive charge, so it has only a δ^+ in the transition state. Methanol begins to acquire a positive charge, making it δ^+ in the transition state as well.

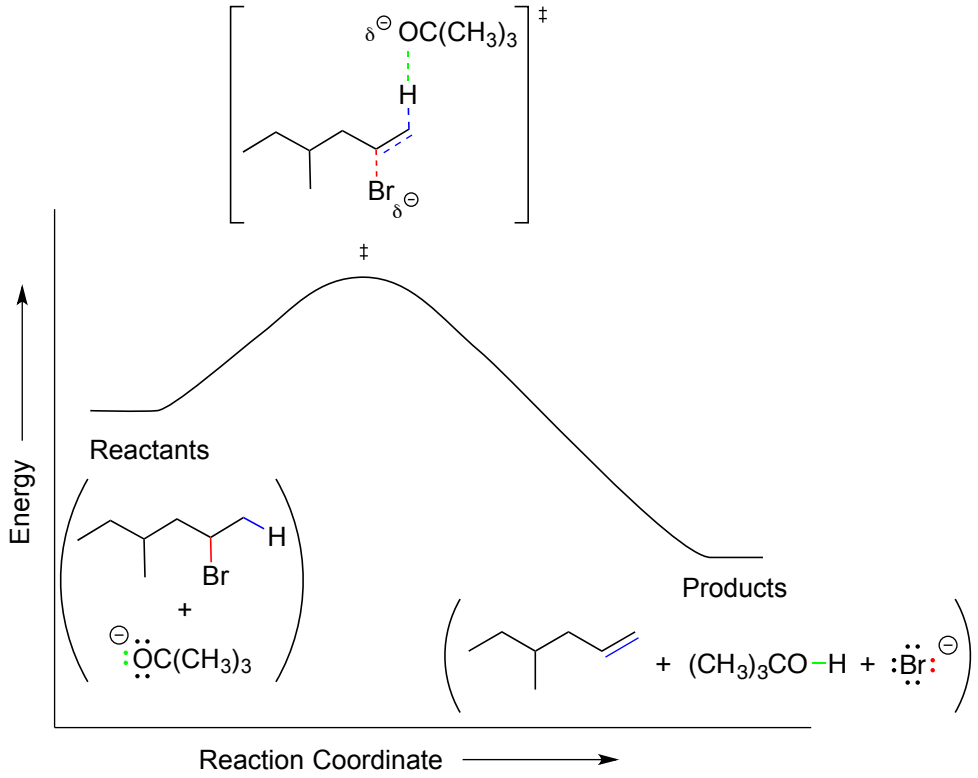


(c) This reaction employs a negatively charged, and therefore highly reactive, reagent. The branching of the alkoxide (*tert*-butoxide) makes it sufficiently bulky that it acts primarily as a base and not a nucleophile. With a strong base present, E2 is likely, and the secondary alkyl bromide allows it. The proton from the less

hindered β position is removed by the bulky base as the π bond is formed and the leaving group is lost. In other words, the process is concerted.

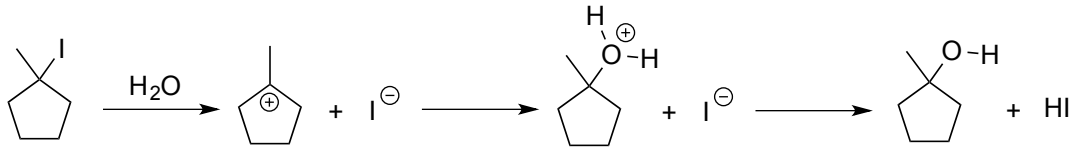


Since all the bond making and breaking occurs concurrently, there is a single mechanistic step with a single transition state between the reactants and products. In the transition state, the base begins to remove the β-proton. As the C-H bond starts to cleave, the π bond starts to form. The carbon-bromide bond also begins to cleave. The base has a negative charge initially but loses that charge when it is converted to a product, so it has a δ^- at the transition state. Bromine is neutral when it is part of the reactant; however, it acquires a negative charge when it dissociates. Consequently, it too has a δ^- at the transition state.

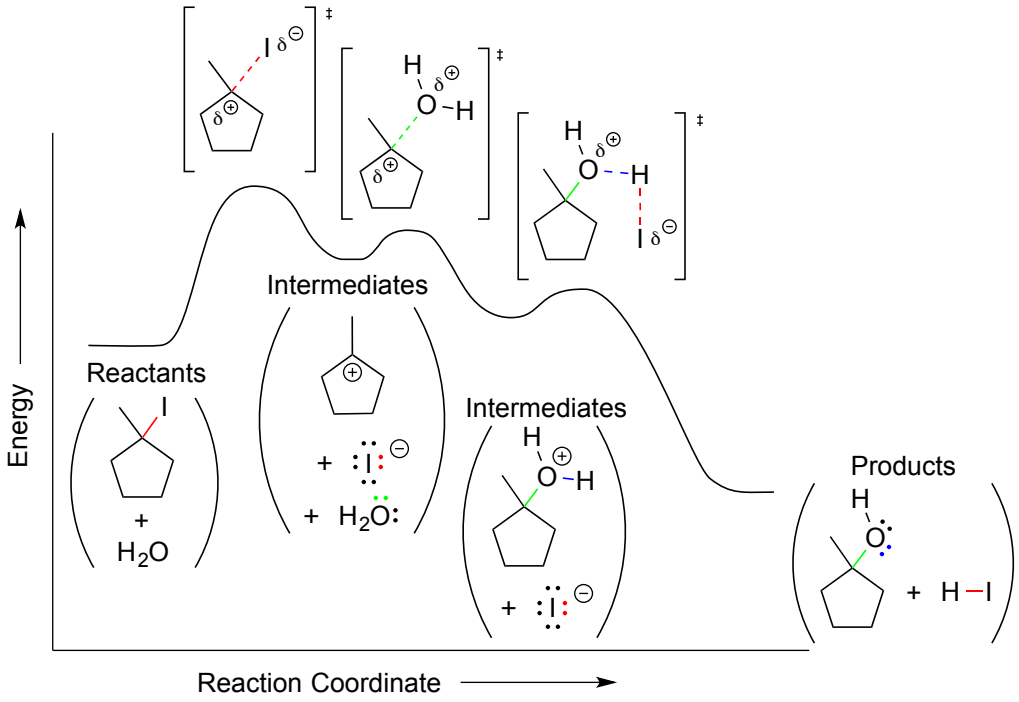


(d) The presence of a weakly reactive reagent (water) leads us to focus on first-order pathways. Water is small, so it can certainly serve as a nucleophile. Due to the absence of heat (which favors elimination), S_N1 is likely the predominant pathway. The tertiary alkyl iodide validates this choice since tertiary substrates lead to stable carbocations, which are ideal for first-order pathways.

The reaction begins with the dissociation of iodide. A tertiary carbocation results, and water adds to it. The resulting oxonium ion sheds a proton to yield the alcohol product.



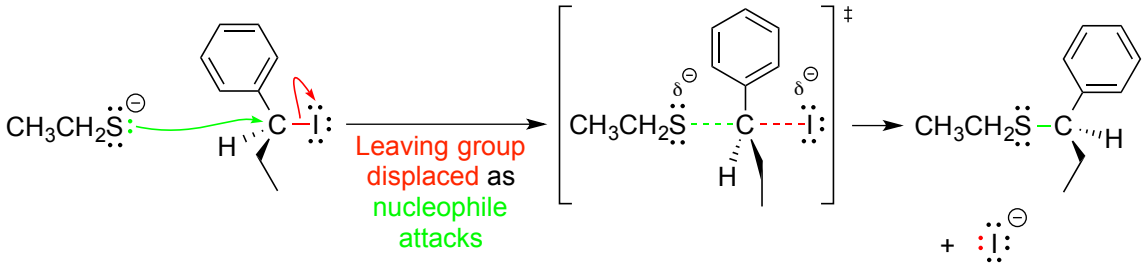
This reaction has three distinct mechanistic steps, each of which will have its own transition state. In the first step, iodide dissociates to yield the carbocation. In its transition state, the C-I bond is partially broken, leading to a δ^+ on carbon and a δ^- on iodine. In the second step, water adds to the carbocation. The second transition state has a partially formed C-O bond. The carbon is losing its positive charge, so it has only a δ^+. The oxygen is acquiring a positive charge, so it has a δ^+ as well. In the third and final step, the oxonium ion loses a proton to yield the product. The transition state for this step has a partially formed H-I bond and a partially broken O-H bond. The iodide is losing its negative charge, so it has only a δ^-; whereas, the oxygen is losing its positive charge, so it has only a δ^+.



42. This reaction utilizes a negatively charged reagent, which is expected to be highly reactive. This leads us to consider second-order processes. Since sulfur is a large atom, it is highly polarizable and therefore a potent nucleophile. Conversely, the thiolate (i.e., sulfur anion) is weakly basic because thiols have pK_a values around 10. Since the reagent is a strong nucleophile, S_N2 emerges as a probable reaction pathway.

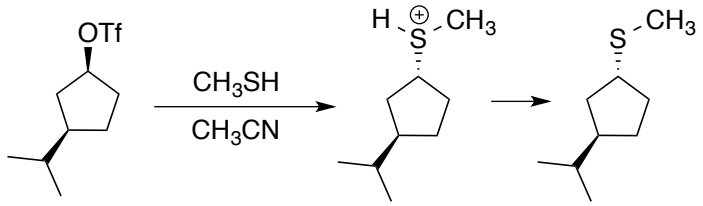
The secondary alkyl iodide is suitable for S_N2. Additionally, the solvent (CH_3CN, acetonitrile) is a polar aprotic solvent, which does facilitate a second-order process. All of the variables point toward S_N2 reaction as the predominant pathway.

Being a concerted process, the S_N2 reaction has a single mechanistic step with only one transition state. The powerful nucleophile attacks the electrophilic carbon bearing the leaving group, concurrently displacing iodide. This results in an inversion of configuration. Although you need not necessarily draw the transition state, it helps us to visualize the Walden inversion. As the nucleophile approaches directly opposite the leaving group, the "umbrella" of substituents on the electrophilic carbon begins to flatten out. The transition state has sp^2 (trigonal planar) character on the electrophilic carbon. As the leaving group dissociates, the inversion of the "umbrella" of substituents is complete, and the configuration is inverted as a result.



43.

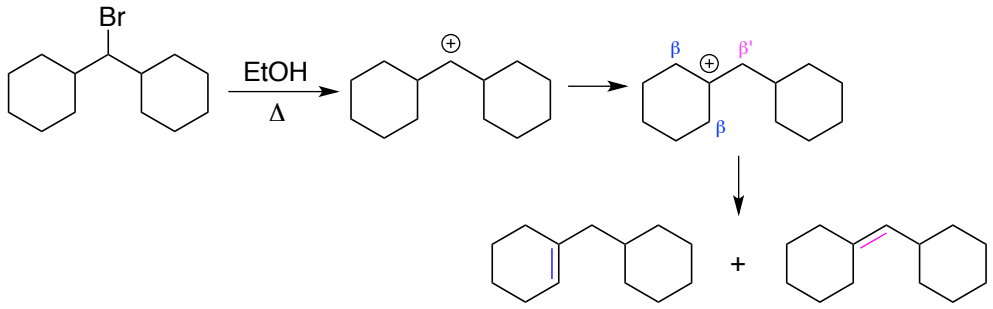
(a) This reaction utilizes a strong nucleophile (the thiol). Although thiols are strong nucleophiles due to their highly polarizable electron cloud, they are weak bases. With a strong nucleophile present in a polar aprotic solvent (acetonitrile), we expect S_N2 reaction to take place. The secondary triflate does allow S_N2 reaction, so the thiol attacks opposite the leaving group. This leads to an inversion of configuration. The resultant sulfonium ion then sheds a proton to yield the thioether product.



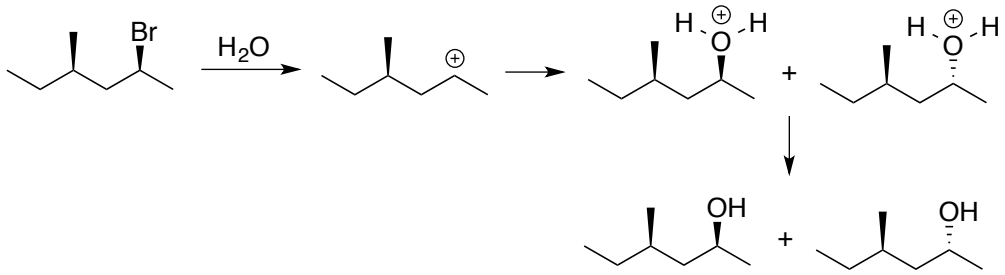
Note that the configuration is only inverted for the stereocenter involved in the transformation. The other stereocenter is unaffected.

(b) In this transformation, heat favors elimination, and the presence of a weak base (ethanol) suggests that the mechanism will be E1. Bromide dissociates, and the secondary carbocation that is formed undergoes a 1,2-hydride shift to yield a more

stable tertiary carbocation. Finally, loss of a proton from either of the two types of β positions yields a trisubstituted alkene, so a mixture of alkene products is obtained.

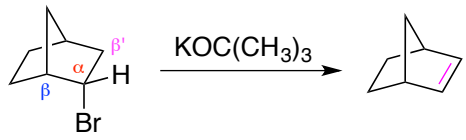


(c) The presence of a weak nucleophile/base suggests a first-order mechanism. Since the reagent is unhindered, it can act as a nucleophile, and the absence of heat (which would favor elimination) points us in the direction of S_N1 reaction. The secondary alkyl bromide is a suitable substrate for S_N1, so it is the dissociation of bromide that starts the reaction. The secondary carbocation is then attacked by water from either side to yield a mixture of diastereomeric oxonium ions. Each of these loses a proton to generate the diastereomeric alcohol products.

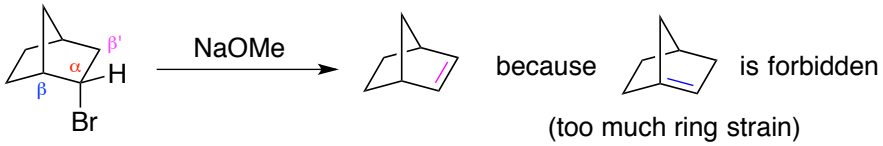


Notice that there is no change in the stereochemistry of the chiral center that is uninvolved in the reaction.

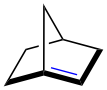
(d) The presence of a strong, bulky base favors E2 reaction, and the secondary substrate is suitable for E2. The bulky base pulls a proton from the less hindered β' position to afford the Hofmann alkene.



Even if a small base were used in this reaction, the product would be the same. The reason is Bredt's rule, which states that a double bond cannot involve the bridgehead carbon of a bicyclic system unless the rings are large enough to avoid massive ring strain. This usually means that a ring must be at least eight-carbons in size to allow a bridgehead alkene.



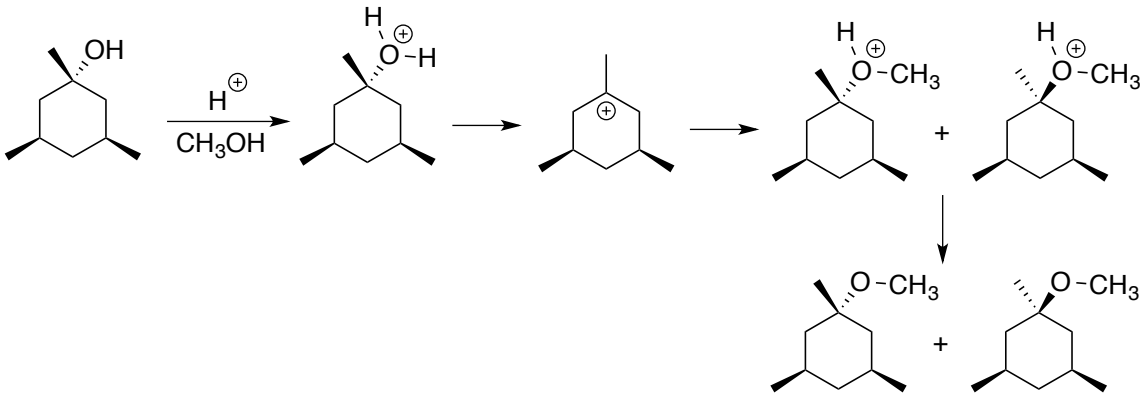
The large amount of ring strain stems from the fact that the "anti-Bredt" alkene has a *trans*-like double bond in a ring smaller than eight carbons.



trans-like double bond in ring smaller than eight carbons

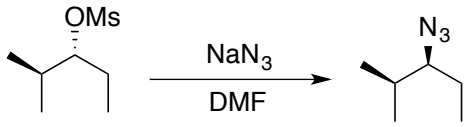
(e) The presence of a weak nucleophile/base suggests a first-order reaction. Since methanol is small and unhindered (allowing it to act as a nucleophile) and there is no heat to favor elimination, S_N1 is the preferred mechanism.

Acid converts the hydroxyl group into a good leaving group through protonation. Water then dissociates to yield a tertiary carbocation. Next, methanol adds to this carbocation from either side, yielding a mixture of diastereomeric oxonium ions. Each of these loses a proton to yield the diastereomeric ethers as the products.



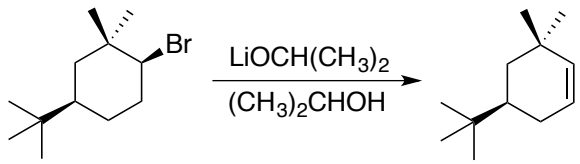
Note that the stereochemistry of the two stereocenters uninvolved in the reaction is unaltered.

(f) The presence of a strong nucleophile (azide, N_3^-) in a polar aprotic solvent (DMF) suggests S_N2 reaction. Since the secondary mesylate allows S_N2, this is in fact what transpires. Azide attacks the electrophilic carbon from the side opposite the leaving group. This results in an inversion of configuration in the product.

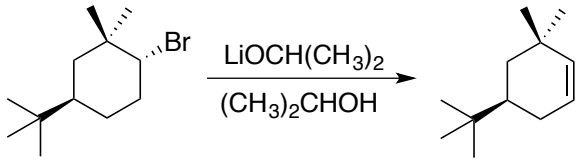


Note that only the configuration of the stereocenter involved in the reaction is inverted.

(g) The presence of a branched (and therefore bulky) strong base suggests E2 reaction. Primary, secondary, and tertiary substrates are all suitable for E2, so that is the mechanism that occurs. Only one β position actually bears protons, so that is the site that reacts with the base, leading to the formation of the alkene product.

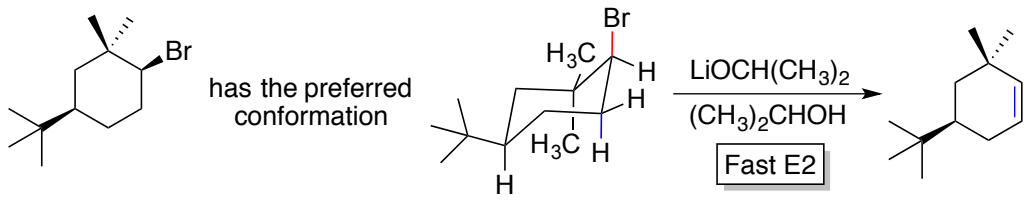


(h) This reaction is quite similar to the one in part (g). It too yields the same alkene product.



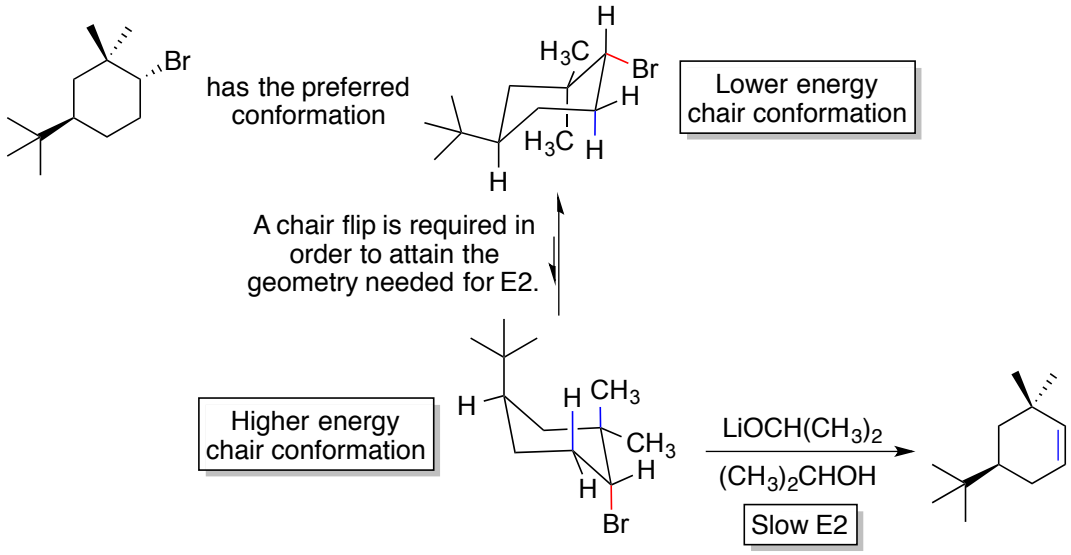
(i) An E2 reaction works best when the substrate can attain an *anti-periplanar* arrangement of the leaving group and the β-proton that is lost. In a cyclohexane ring, the anti-periplanar geometry manifests itself in a 1,2-diaxial arrangement of the β-proton and leaving group.

This geometry is easily attained in the substrate from part (g). The preferred chair conformation places the bulky *tert*-butyl group in the equatorial position. This means that the bromine will be on an axial bond. The β position has an axial proton. This results in a fast E2 reaction.



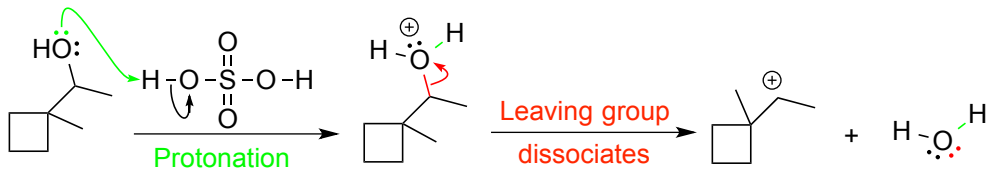
The substrate from part (h) also has a preferred chair conformation that places the bulky *tert*-butyl group in the equatorial position. However, this means that the bromine is equatorial as well. In order to undergo E2, the chair must flip to the less

stable chair conformation that places the bulky *tert*-butyl group in the axial position. Only in this chair conformation is the bromine axial, and when that is the case, it can be eliminated along with its neighboring axial β-proton. Since this E2 reaction proceeds through a higher-energy chair conformation, it is a slower process.



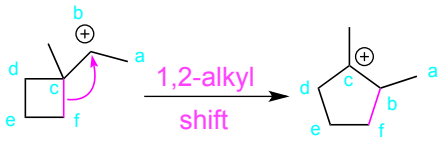
44. In this reaction, the substrate is treated with sulfuric acid and water, which is a weak nucleophile/base. Given the presence of a weak nucleophile/base, we suspect that a first-order reaction will take place. The use of heat will favor elimination over substitution, so E1 is expected to be the predominant pathway. The substrate is a secondary alcohol, which is suitable for E1. Additionally, if water serves as the solvent for the reaction (as well as a reagent), this polar protic solvent will indeed facilitate a first-order process.

The presence of sulfuric acid suggests that the E1 reaction begins with the protonation of the hydroxyl group. The resulting oxonium ion is a good leaving group that dissociates from the secondary center because doing so leaves behind a reasonable carbocation.



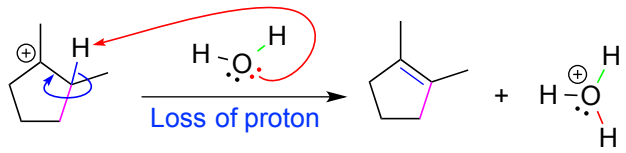
The carbon skeleton of the product is clearly different from that of the substrate. As a result, we know that a carbocation rearrangement must take place because this is the only process that we have learned that can alter the carbon backbone of a molecule. There is no available 1,2-hydride shift that would lead to an enhancement in stability. A 1,2-methyl shift would not yield the carbon skeleton found in the product. This leaves a 1,2-alkyl shift as the only viable choice.

Labeling the carbons will assist us in visualizing the transformation. Carbon c has two equivalent alkyl groups (other than methyl) connected to it, so either the c-f or the c-d bond can migrate. Migration of the c-f bond leads to the inclusion of one additional atom (b) in the ring. This expands the ring from four to five members in size. As b acquires a new bond to f, c loses a bond, which results in a positive charge at that center.

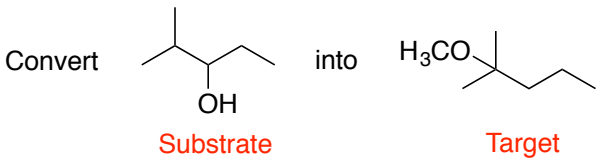


Notice that the 1,2-alkyl shift converted the secondary carbocation into a tertiary carbocation. It also expanded the cyclobutane ring to a cyclopentane ring, which alleviates a significant amount of ring strain. Therefore, the stability enhancement that results from this carbocation rearrangement is quite large.

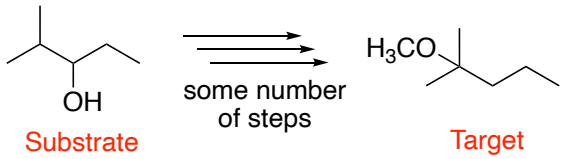
The 1,2-alkyl shift has created the carbon skeleton found in the product. All that remains is to lose a proton from the most substituted carbon adjacent to the carbocation. This yields the Zaitsev alkene as the product of the reaction.



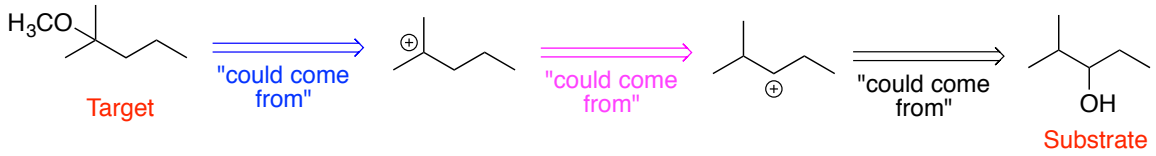
45. In a synthesis problem, it is a good idea to begin by labeling the substrate and the target based on how the question is worded. In this case, the substrate happens to appear first.



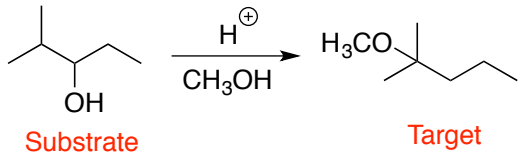
We can then rewrite the problem in a familiar fashion that illustrates the goal very clearly. A powerful clue arises from the fact that the functional group in the target is on a different carbon than the functional group in the substrate. The only process we've seen that leads to the migration of functionality—through rearrangement—is a first-order reaction. This synthesis must therefore involve an S_N1 reaction. We know that it is not E1 because there is no alkene in the product.



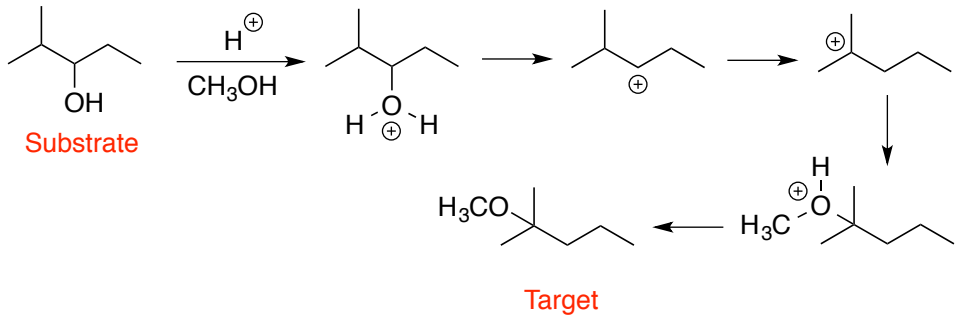
A bit of retrosynthetic analysis clarifies our thoughts. The target could come from a tertiary carbocation to which a nucleophile adds. The tertiary carbocation could, in turn, result from a secondary carbocation that undergoes a 1,2-hydride shift. This secondary carbocation would be produced by the treatment of the corresponding alcohol with acid, which would convert the hydroxyl group into a good leaving group.



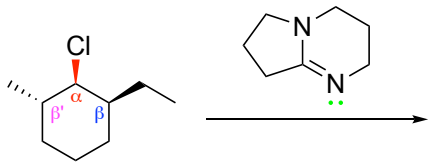
We've identified the need for acid to make the hydroxyl group into a good leaving group. All that remains is to select the proper nucleophile. Since we want an S_N1 reaction because we are relying upon a carbocation rearrangement, we must avoid strong nucleophiles that would go through S_N2 pathways instead. This suggests that the proper nucleophile would be methanol (CH_3OH) rather than methoxide (CH_3O^-), which is too reactive for this application and incompatible with acid.



The synthesis as written above is sufficient to address the question. However, a bit more information is provided below for clarity. The alcohol is first protonated by the acid. The oxonium ion thus formed next dissociates to leave behind a secondary carbocation. The secondary carbocation happens to reside next to a tertiary center, so a 1,2-hydride shift follows. Methanol then adds to the tertiary carbocation, and the resulting oxonium ion sheds a proton to yield the product, which is an ether.

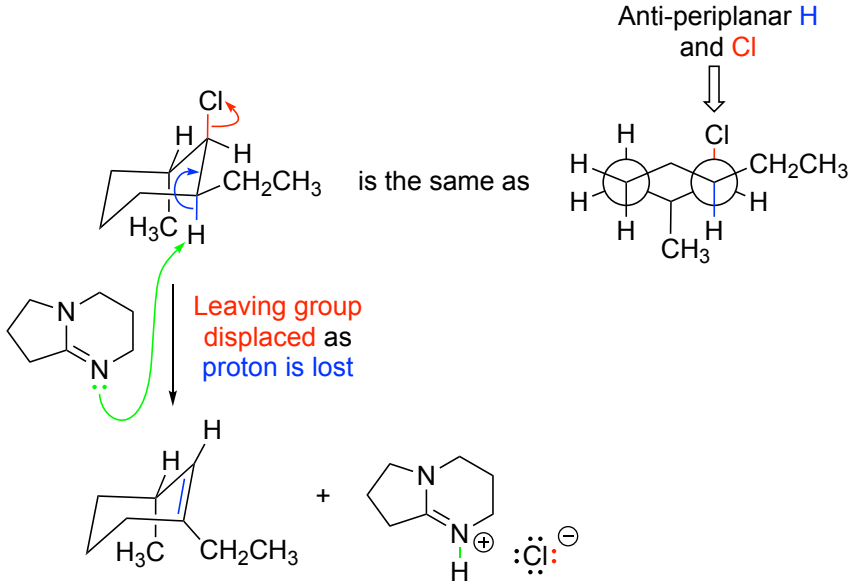


46. DBN is a strong non-nucleophilic base, so we immediately suspect an E2 reaction. The substrate is a secondary alkyl chloride, which is suitable for E2. The complication comes from the presence of two β positions: β and β'. Removal of a proton from either one would lead to alkene products of equivalent substitution; however, there is a difference in stereochemistry between the two locations.

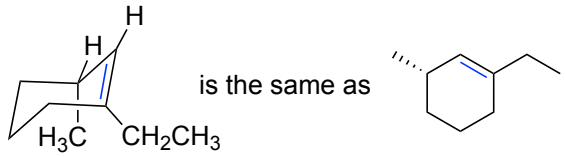


Remember that E2 requires an *anti-periplanar* orientation of the leaving group and the β-proton that is removed. When they are attached to a cyclohexane ring, the proton and the leaving group must both be axial and on adjacent carbons in order to fulfill this requirement. This orientation is sometimes referred to as 1,2-*trans* diaxial. In the chair conformation that places the chlorine in the axial position, only one of the β-hydrogens is also axial. It is only this β-hydrogen that will be reactive in E2. Notice that the Newman projection emphasizes the anti-periplanar orientation of the chlorine and the adjacent axial β-hydrogen.

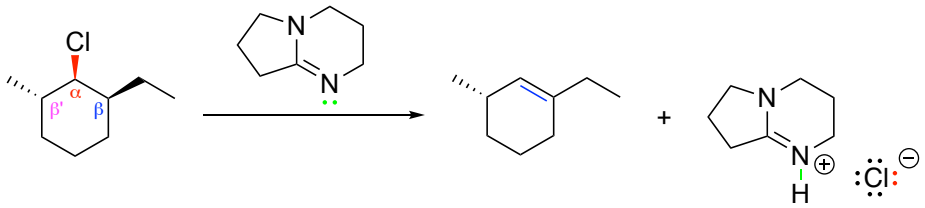
DBN removes the β-hydrogen with the appropriate geometry. As the β-proton is lost, an alkene is formed, and the leaving group is displaced in a concerted fashion.



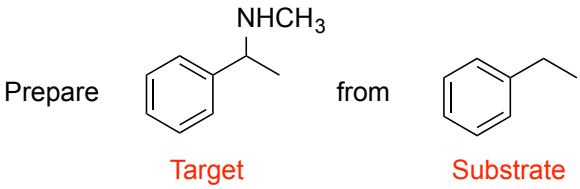
The product may be represented using a traditional skeletal structure as well.



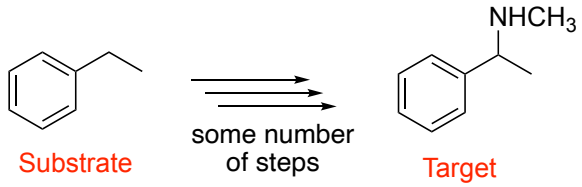
Overall, the elimination of chloride and its neighboring axial β-proton appears as follows.



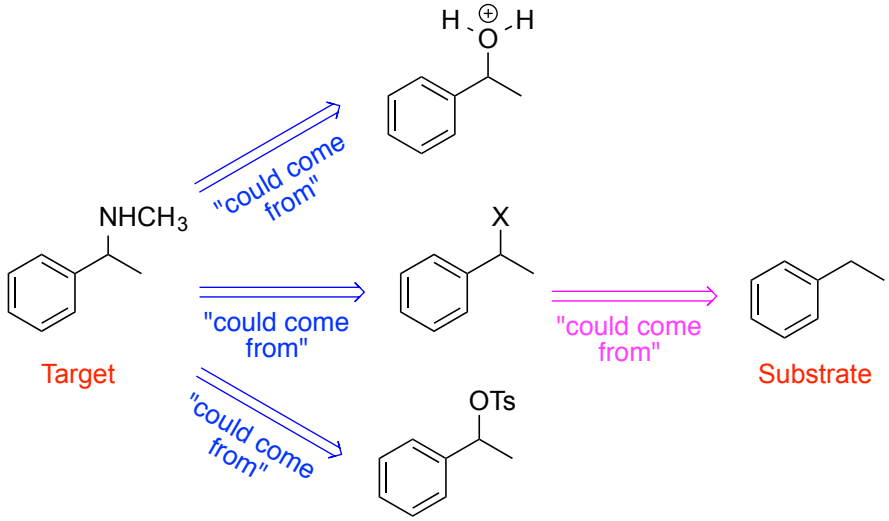
47. It is wise to begin any synthesis problem by labeling the target and the substrate based on the phrasing of the question. The compound that we seek to prepare is the target.



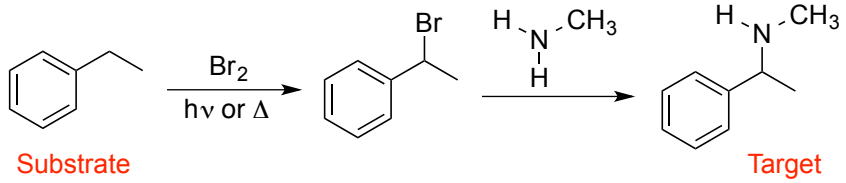
Then, we can rewrite the problem in a more familiar direction. We have to convert the substrate into the target through some number of steps. The number of arrows is not meant to suggest any particular number of steps.



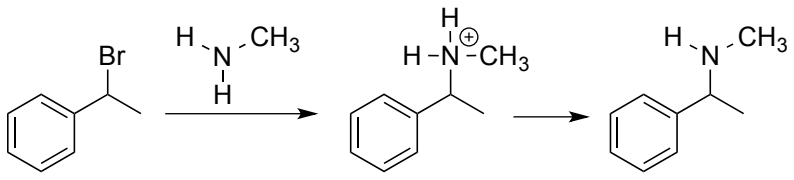
Retrosynthesis provides a useful format for brainstorming. The target could be prepared in one step from a precursor bearing a leaving group. We've learned about three principal categories of leaving groups: water, a halide, or a tosylate. Of the three, only the benzylic halide can be prepared *directly* from the allowed starting material. Having identified the shortest possible synthetic route, we can begin to plan the synthesis.



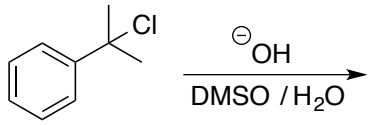
The substrate can be halogenated at the benzylic center using radical bromination. Then, a substitution reaction is required to convert the benzylic bromide into the target amine. Two potential nucleophiles should come to mind for this transformation. We could use the amine (H_2NCH_3) or the corresponding anion ($^-NHCH_3$). However, the anion is quite basic, and if we use it, we are likely to see S_N2 as well as E2 products. Since we only want the substitution product, we are better served by using the neutral amine, which is still a potent nucleophile but is far less basic.



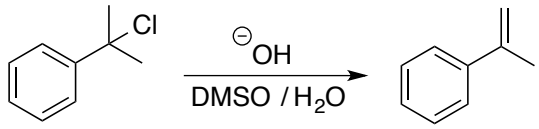
The second step of the synthesis is an S_N2 reaction, in which the amine displaces bromide. This is followed by the loss of a proton from the resulting ammonium ion to afford the neutral product.



48. The IR spectrum is not consistent with the formation of the intended product. There is no broad alcohol O-H stretch between 3200 and 3600 cm^{-1}. We see only sp^2 C-H stretching just above 3000 cm^{-1} and sp^3 C-H stretching below just below 3000 cm^{-1}. This causes us to reevaluate the reaction under consideration.



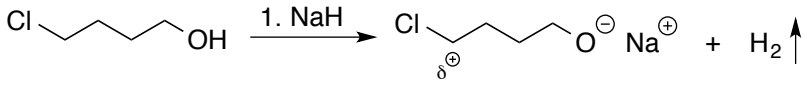
The reagent (hydroxide) is negatively charged and therefore highly reactive, so we suspect a second-order process. Furthermore, hydroxide is small and sterically unencumbered, so an S_N2 reaction is certainly possible. However, the substrate is tertiary, and tertiary centers are too hindered to undergo S_N2. Since the reagent is highly reactive, E2 will occur if S_N2 is forbidden. Consequently, hydroxide removes a proton from one of the two equivalent β centers bearing protons. This yields a conjugated alkene as the actual product of the reaction.



Actual product

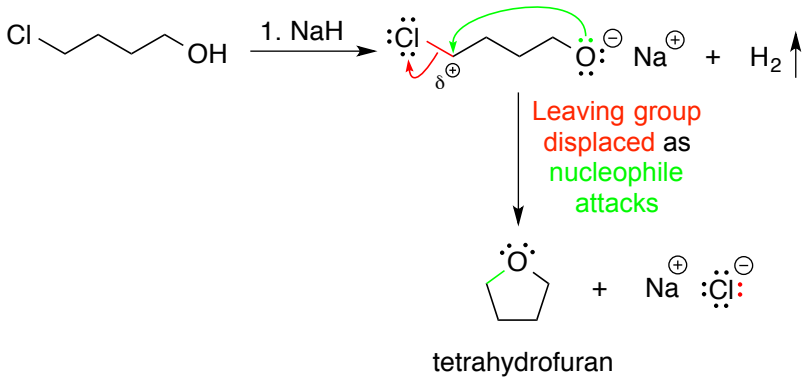
This product is consistent with the IR data. We would expect to see sp^2 C-H stretching just above 3000 cm^{-1} and sp^3 C-H stretching just below 3000 cm^{-1}, but not O-H stretching. Notice that there is also a signal at ~1650 cm^{-1} for the C=C stretching of the alkene.

49. Given the unexpectedly small number of proton NMR signals, we can surmise that an unanticipated reaction took place. Therefore, let's reexamine each of the steps. The initial acid-base reaction is straightforward, and there is nothing that would lead us to predict a surprising result of that step.

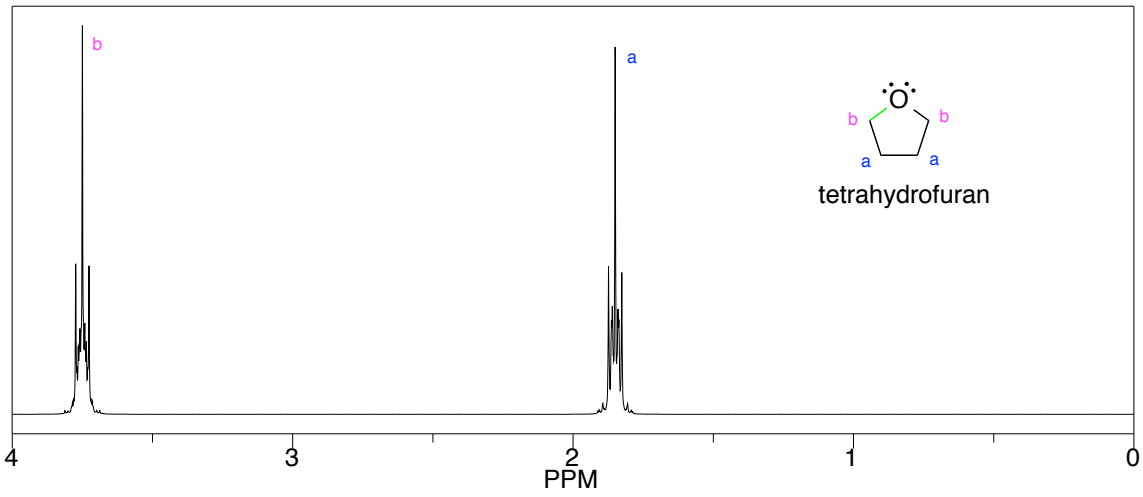


However, the alkoxide product is a bit unusual in that it also contains a halogen. This electronegative halogen renders the adjacent carbon partially positive (δ^+). This means that the alkoxide contains both a nucleophile (the oxygen anion) and an electrophile (the carbon bearing a δ^+). As a result, an *intramolecular* reaction is possible.

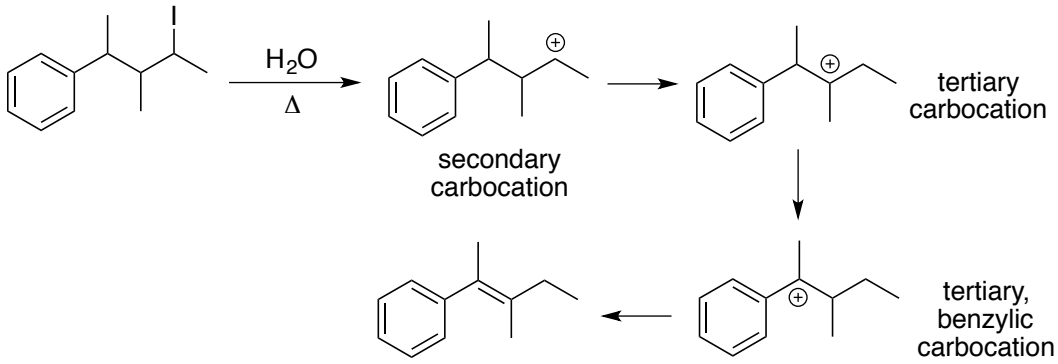
In an intramolecular reaction, the two species that are typically separate reactants happen to reside within a single molecule. This allows the transformation to take place within that single molecule (i.e., intramolecularly). In this case, the strong nucleophile attacks the carbon bearing the leaving group and displaces chloride in an *intramolecular* S_N2 reaction. The result is a five-membered ring containing oxygen. This cyclic ether happens to be known as tetrahydrofuran.



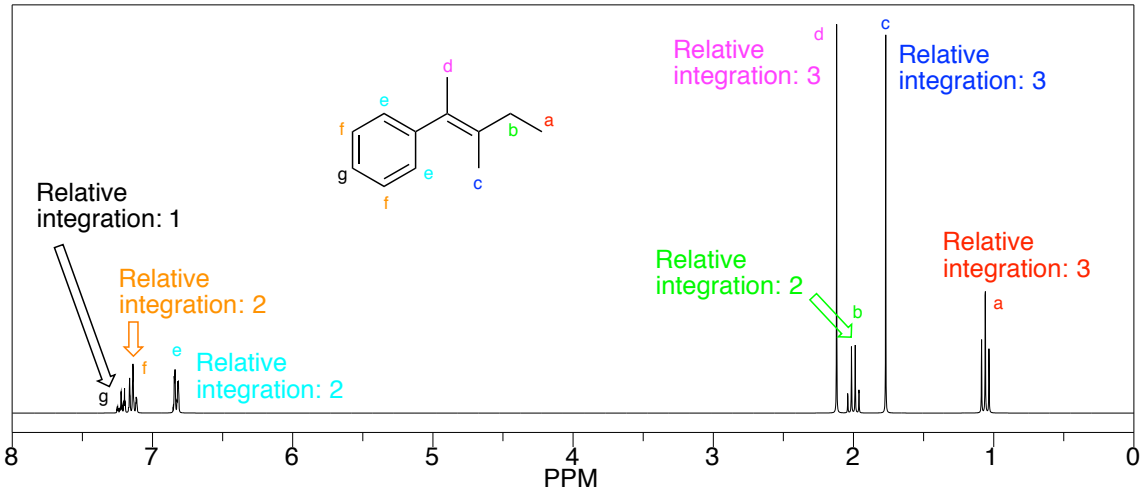
Due to its internal symmetry, tetrahydrofuran only exhibits two signals in the ^{1}H NMR spectrum. The protons labeled a are further from oxygen and therefore more shielded (i.e., closer to 0 ppm); whereas, the protons labeled b are closer to oxygen and more deshielded as a result.



50. Heat is used to favor elimination, so the anticipated mechanism for this reaction is E1 since the base is weak. A closer look at the intermediates may resolve the mystery. Dissociation of iodide yields a secondary carbocation. It will undergo a 1,2-hydride shift to yield a more stable tertiary carbocation. This tertiary carbocation actually undergoes a second 1,2-hydride shift to afford an even more stable tertiary, benzylic carbocation, which has resonance stabilization. Finally, the loss of a proton from the more highly substituted β-carbon bearing protons yields a tetrasubstituted alkene product.



The formation of a tetrasubstituted alkene explains why the product's NMR contains no vinyl protons from 4.5–6.5 ppm. To be thorough, we can assign all of the peaks in the NMR spectrum as follows to ensure that the spectral data are consistent with the proposed product.



Solutions to Problems for Chapter 8: Mass Spectrometry

1. The only possible explanation is that deuterium's abundance must be too low to impact the calculation in any significant way. In fact, the natural abundance of deuterium is 0.0115%. That's a mere 1% of the natural abundance of ^{13}C. Therefore, the probability of having deuterium in a molecule is exceedingly low. As a result, it does not contribute in any meaningful way to the M+1 peak.

2. The maximum number of carbons that this molecule can contain is 10.

$$\frac{128\ amu}{12\ amu\ per\ C} > 10\ C$$

However, $C_{10}H_8$ is an unsaturated substance.

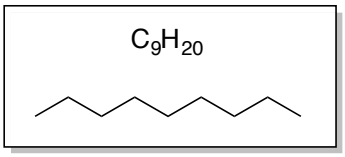
$$Degrees\ of\ Unsaturation = \frac{[2(10)+2]-8}{2} = 7$$

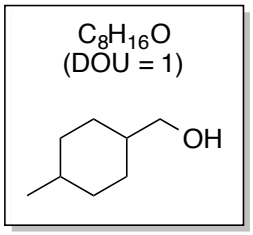
The question asked for the formula of a *saturated* hydrocarbon, so we must remove a carbon from the formula and replace it with 12 hydrogens giving C_9H_{20}. This substance is saturated.

$$Degrees\ of\ Unsaturation = \frac{[2(9)+2]-20}{2} = 0$$

We can now use this formula to derive one containing oxygen. We need only remove a CH_4 unit and replace it with oxygen: $C_9H_{20} - CH_4 + O = C_8H_{16}O$.

While each of these two formulas can correspond to several structures, two possibilities are shown below. For C_9H_{20}, plausible structures cannot have any degrees of unsaturation; however, isomers of nonane that contain branching are possible. For $C_8H_{16}O$, viable structures would need to contain one degree of unsaturation (i.e., one ring or one π bond).





3. The maximum number of carbons that this molecule can contain is 6.

$$\frac{72.0575\ amu}{12\ amu\ per\ C} \approx 6\ C$$

However, a six-carbon molecule without hydrogens is unlikely, so we must remove a carbon and replace it with 12 hydrogens: C_5H_{12}. This substance is saturated; it already contains the maximum number of hydrogens possible. As such, no further replacement of carbons with hydrogens is feasible.

On the other hand, we can incorporate an oxygen into the formula by replacing a CH_4 unit: C_4H_8O. It is also possible to repeat this process to insert a second oxygen into the formula: $C_3H_4O_2$. If an additional oxygen were added, there would be no hydrogen atoms in the molecule, which is improbable.

Therefore, we are left with three formula candidates, and we can now calculate their masses to a larger number of decimal places. Only one matches the HRMS results given in the problem.

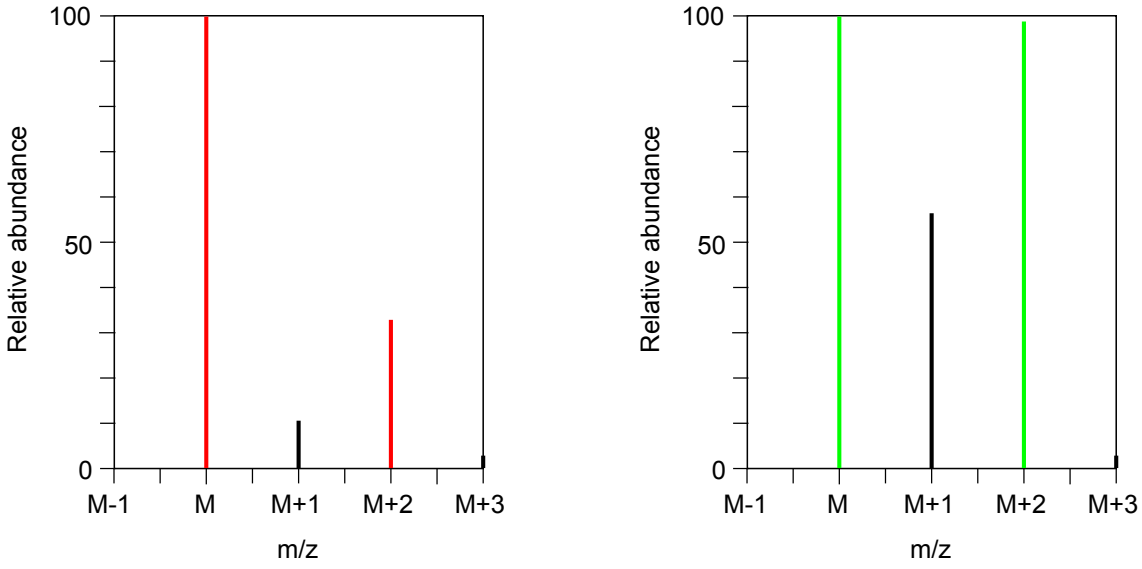
Mass of C_5H_{12}	Mass of C_4H_8O	Mass of $C_3H_4O_2$
5 C = 5 (12.0000 amu)	4 C = 4 (12.0000 amu)	3 C = 3 (12.0000 amu)
+ 12 H = 12 (1.00783 amu)	8 H = 8 (1.00783 amu)	4 H = 4 (1.00783 amu)
	+ O = 15.9949 amu	+ 2 O = 2 (15.9949 amu)
72.09396 amu	72.05754 amu	72.02112 amu

There are multiple structures that correspond to the correct formula. Any plausible structure must have one degree of unsaturation (i.e., one ring or one π bond). Such a structure is shown below.

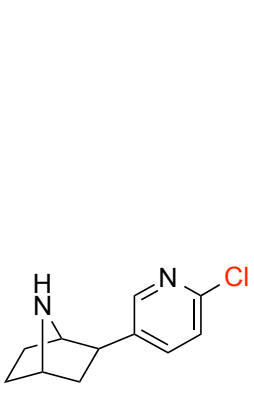
(tetrahydrofuran)

4.

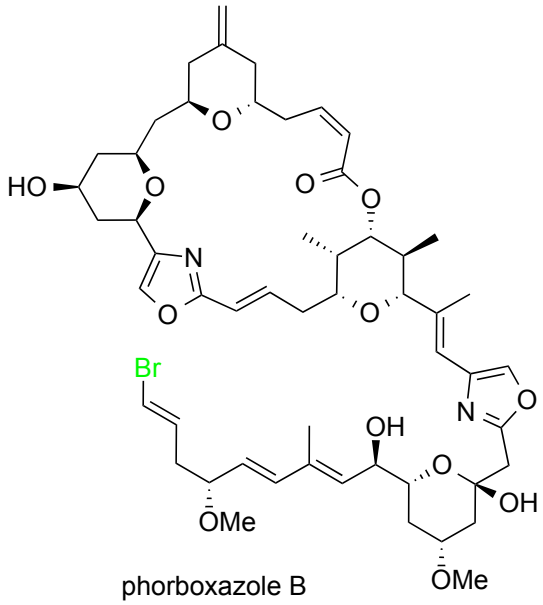
(a) The specific masses are not provided on the x-axis, so we cannot make the assignment based on molecular weights alone. Instead, we must consider the halogens and their effect on the mass spectra. Both compounds possess either chlorine or bromine, so both exhibit M and M+2 peaks due to the isotopes of these halogens. It is the intensity of the M+2 signals that differentiates the mass spectra. The first spectrum displays M and M+2 peaks in a ratio of approximately 3:1, while the second spectrum contains M and M+2 signals in roughly a 1:1 ratio.



Therefore, the first spectrum belongs to epibatidine, whose chlorine causes the 3:1 signal intensity. The second spectrum is that of phorboxazole B, whose Br causes the 1:1 ratio.

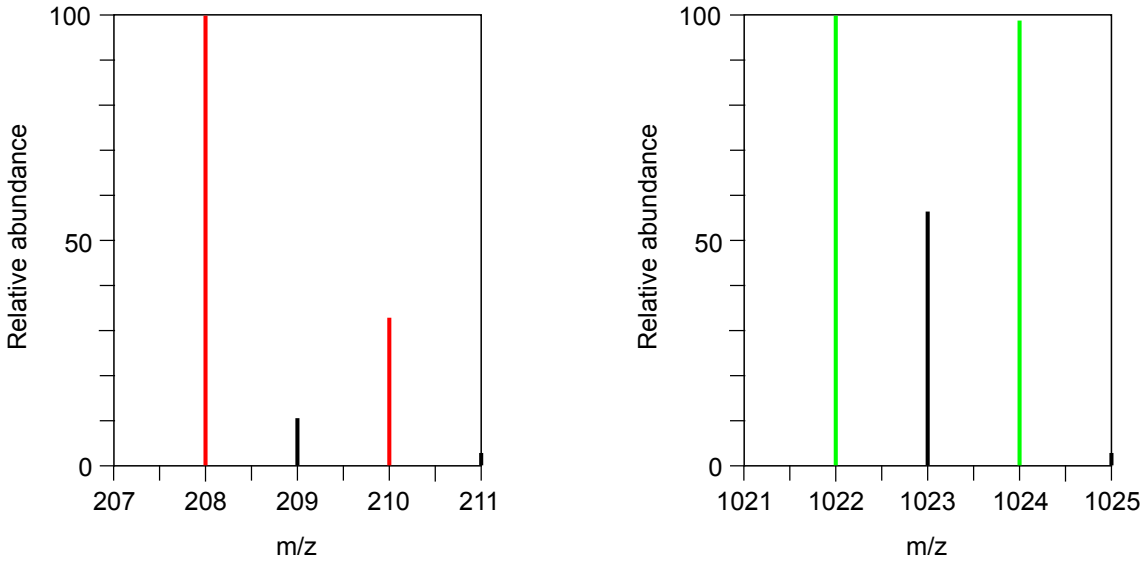


epibatidine



phorboxazole B

Now that the assignments have been made, the mass spectra with specific masses are displayed below.



(b) Both compounds exhibit an M+1 signal because both contain not only carbon but also nitrogen, each of which has a modestly abundant isotope that is one mass unit heavier. In the case of the phorboxazole B spectrum, the M+1 signal is quite abundant. This is merely a consequence of the number of carbons in phorboxazole B. As the number of carbons (n) in a molecule grows, so does the possibility of having ^{13}C. This leads to an enhancement in the intensity of the M+1 signal.

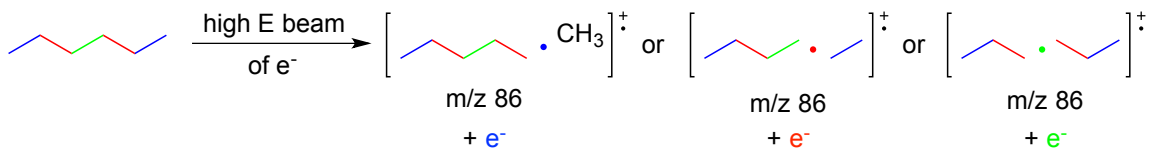
$$(Relative\ abundance\ of\ M+1) = n\ (0.011)\ (Relative\ abundance\ of\ M)$$

Phorboxazole happens to contain 53 carbons. This results in an M+1 peak of approximately 58% relative abundance.

$$(Relative\ abundance\ of\ M+1) = 53\ (0.011)\ (100) = 58.3\%$$

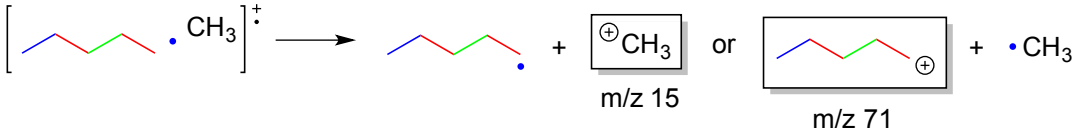
Note that the two nitrogen atoms in phorboxazole also contribute a little bit to the intensity of the M+1 peak.

5. Hexane contains three distinct types of C-C bonds. During the formation of the radical cation, an electron may be ejected from any of these three carbon-carbon bonds. All of the resulting radical cations give rise to a single signal in the mass spectrum at m/z 86.

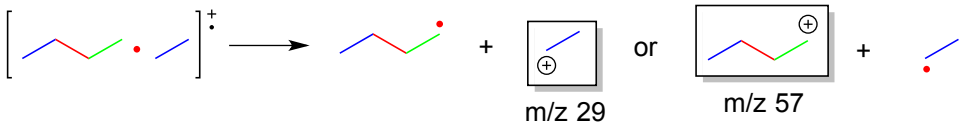


However, each of these radical cations can fragment differently. When an electron is lost from a terminal C-C bond, the radical cation may fragment to yield a pentyl

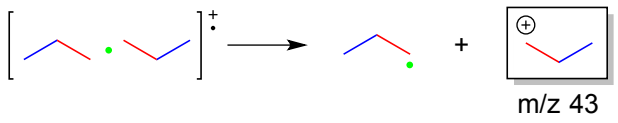
radical and a methyl cation or a pentyl cation and a methyl radical. Only the cations are directly observed in mass spectrometry.



When an electron is lost from an interior C-C bond, the radical cation can split into a butyl radical and an ethyl cation or a butyl cation and an ethyl radical. Again, the cations are detected.

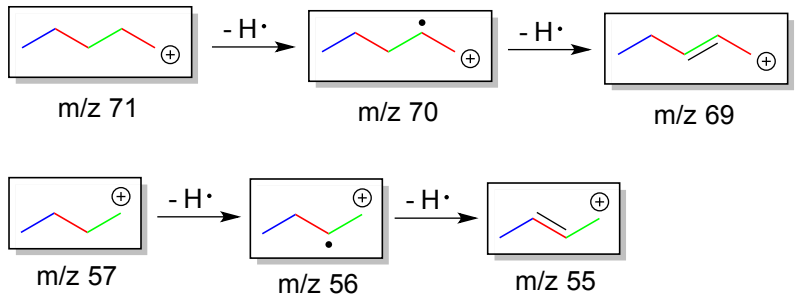


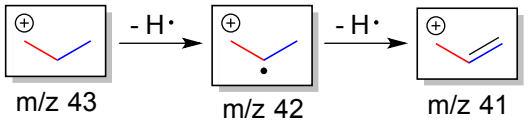
Finally, when an electron is lost from the central C-C bond, the molecular ion can fragment in only one way. Since the two halves of the molecule are equivalent, a propyl radical and a propyl cation are the sole fragments obtained.



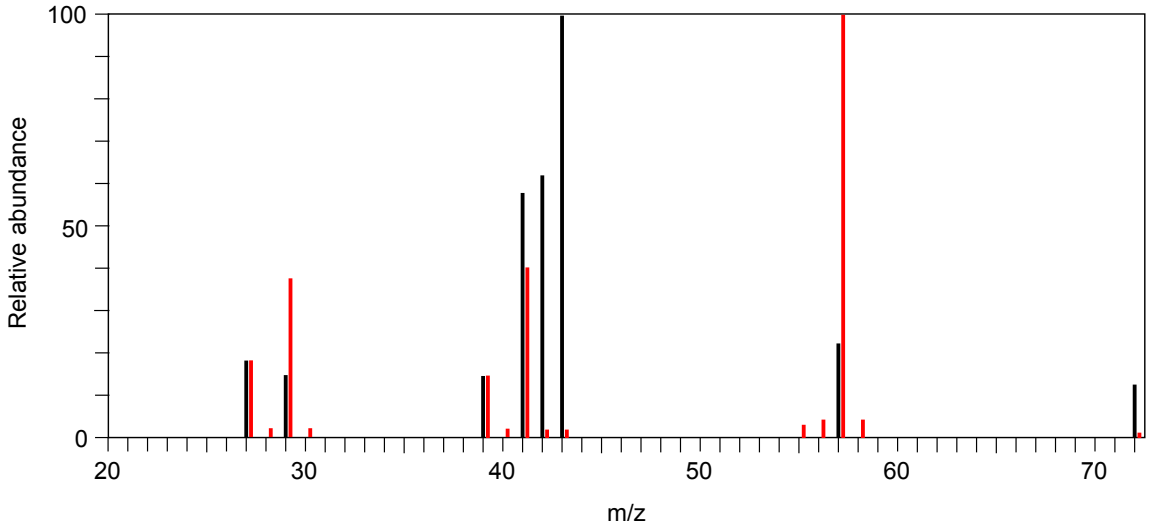
Therefore, we can expect to see signals in the mass spectrum at m/z 86, 71, 57, 43, 29, and 15. Since the methyl cation is less stable than any of the other cations (all of which are primary), it may be fairly low in intensity. Similarly, the pentyl cation (m/z 71) results from a pathway that yields an especially unstable methyl radical, so it too may be quite low in intensity.

We can also expect to see some successive fragmentation of the primary cations to yield their resonance-stabilized counterparts.



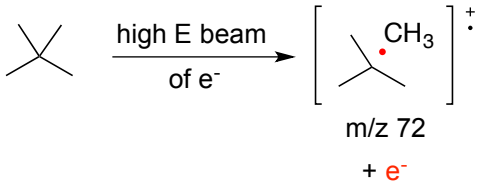


6. The two spectra are overlaid in the following diagram for comparison. There are two especially prominent differences: (1) the red spectrum has a much larger peak at m/z 57 and (2) the red spectrum does not have a significant signal at m/z 43.

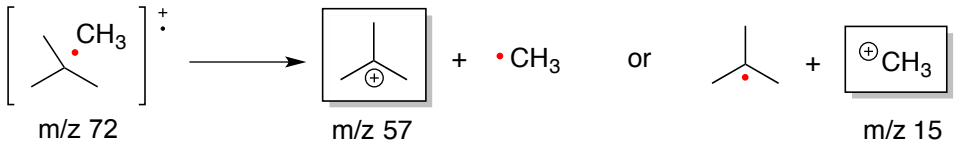


We've already analyzed the fragmentation of pentane in the preceding section, and we do expect it to have a significant propyl cation peak at m/z 43. This allows us to easily assign the black spectrum as that of pentane and the red spectrum as that of neopentane.

Let's consider the fragmentation of neopentane to explain the differences between the spectra. Neopentane has only one type of carbon-carbon bond, so the electron will be expelled from that location alone during ionization.



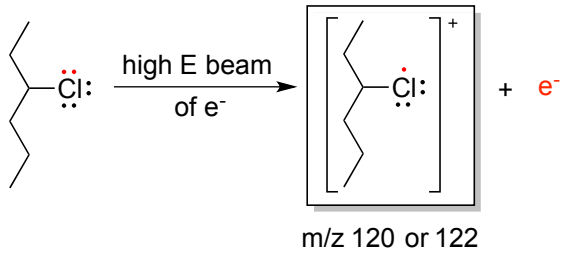
This leads, in theory, to two possible fragmentations. However, a methyl carbocation is quite high in energy, so we expect the *tert*-butyl carbocation at m/z 57 to be the predominant signal.



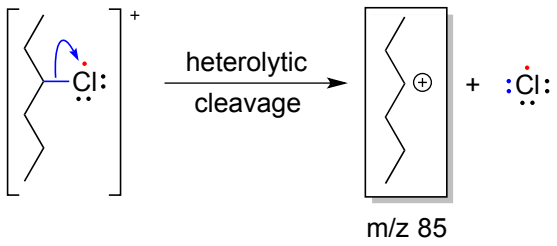
We can also see that there is no clear way to lose a propyl cation from neopentane, hence the absence of the peak at m/z 43.

7.

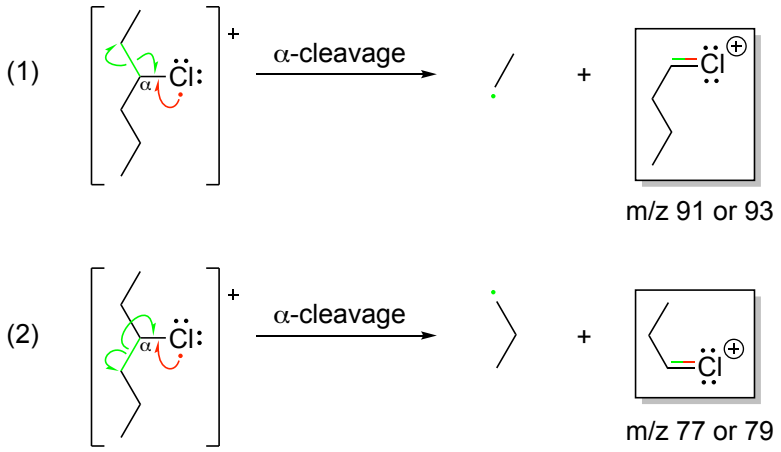
(a) The alkyl chloride is first ionized to give the molecular ion, which appears at m/z 120 or 122 depending upon which isotope of chlorine is present in the molecule.



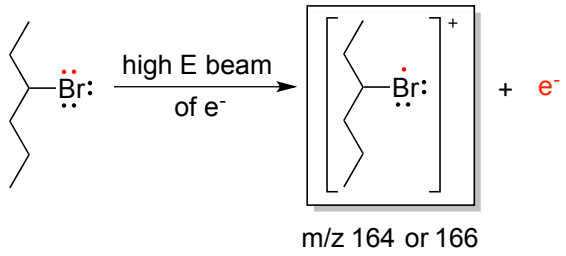
This molecular ion can fragment through two distinct mechanistic pathways: (a) heterolytic cleavage or (b) homolytic cleavage. In heterolytic cleavage, the carbon-to-chlorine bond breaks and both σ-electrons flow onto the more electronegative chlorine atom. The loss of chlorine radical results in a secondary hexyl cation with a m/z ratio of 85.



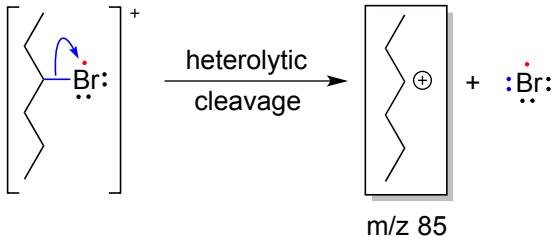
The specific type of homolytic fragmentation that occurs is known as α-cleavage. The chlorine donates its unpaired electron to the adjacent carbon, which reciprocates with an electron from an adjacent carbon-carbon bond. This leads to the scission of the α,β-bond, and since the molecule is unsymmetrical, it can result in the loss of an ethyl or a propyl radical (paths 1 and 2 below, respectively). Since each charged fragment still contains chlorine, we'll see the isotope pattern of M and M+2 for both of the possible cations.



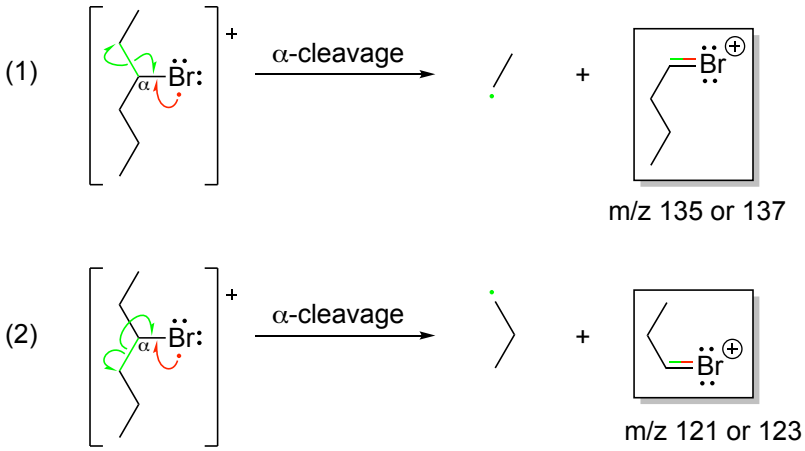
(b) The alkyl bromide can ionize in an analogous fashion, yielding a radical cation with a mass-to-charge ratio of 164 or 166 depending upon the isotope of bromine present.



This radical cation can also fragment through heterolytic or homolytic mechanisms. In the heterolytic cleavage, a bromine radical is lost, and the same secondary hexyl cation that we saw in part (a) is obtained.



The α-cleavage is also analogous to that of the alkyl chloride in part (a). The asymmetry of the molecule results in two parallel homolytic fragmentations, shedding either an ethyl or propyl radical to yield the cations that appear in the mass spectrum. Isotope patterns of M and M+2 are expected for both.

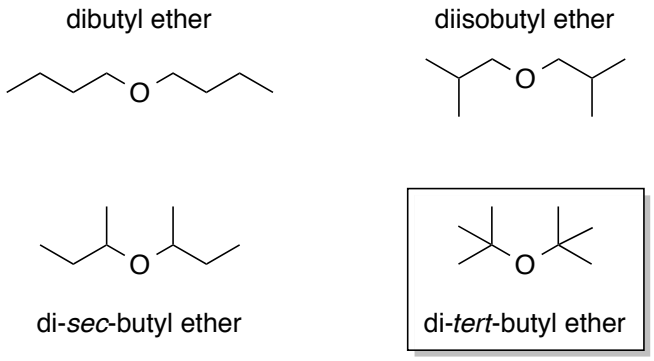


(c) There are two main differences (aside from the masses themselves) that differentiate the mass spectra of the alkyl chloride and the alkyl bromide. One is the relative abundance of the isotope patterns M and M+2. For the alkyl chloride and its fragments that still contain chlorine, these peaks appear in a 3:1 ratio. For the alkyl bromide and its bromine-containing fragments, the M and M+2 peaks appear in a 1:1 ratio.

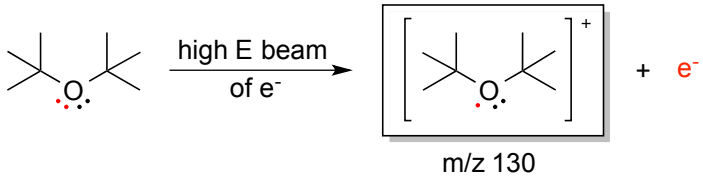
The other major difference is that fragments resulting from α-cleavage are much lower in intensity in the spectrum of the alkyl bromide. Since the C-Br bond is a good deal weaker than a C-C bond, heterolytic cleavage is far more common for this analyte.

It is also worth noting that the actual mass spectra of these compounds will show additional fragments that result from ionization caused by loss of an electron from a C-C bond. The initial ionization will often occur through displacement of a lone pair electron on the halogen. This does not, however, preclude the possibility of other molecules ionizing as we discussed for alkanes: through the loss of an electron from a carbon-carbon bond. Such ionization results in the formation of additional fragments that appear in the mass spectra as well.

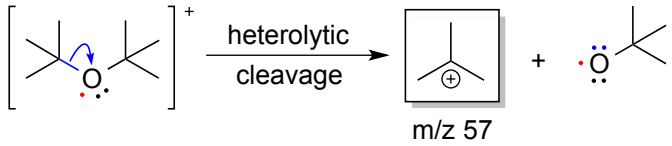
8. The ether that best matches this spectrum is di-*tert*-butyl ether.



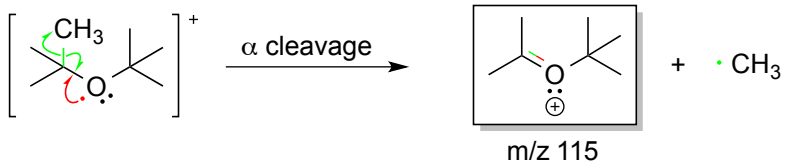
Two of the signals (those at m/z 130 and 57) do not help to differentiate the four ethers. All four compounds have a mass of 130, so their molecular ion peaks are all at m/z 130.



Also, all four ethers can release a four-carbon cation (butyl, isobutyl, *sec*-butyl, or *tert*-butyl) through heterolytic cleavage. We would expect the relative abundance of these signals to differ depending on the carbocation's stability; however, that information was not supplied in the question.

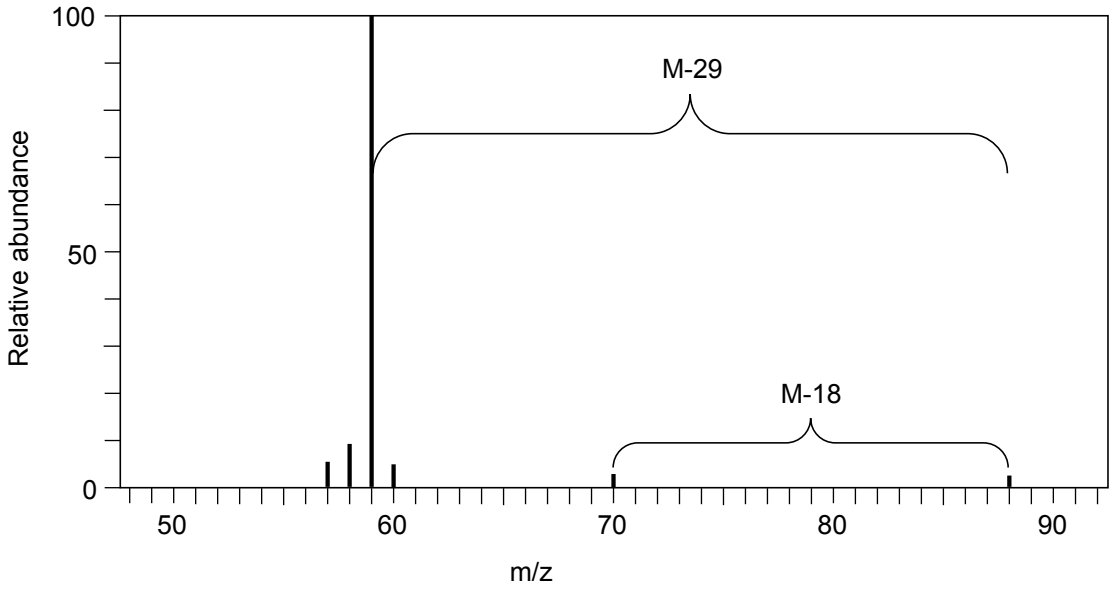


It is the only remaining signal at m/z 115 that sheds light on the structure of the ether. This signal could be classified as an M-15 peak. Two of the ethers (dibutyl and diisobutyl ether) would give rise to M-43 peaks as they release propyl or isopropyl radicals, respectively, through α-cleavage. Di-*sec*-butyl ether could release a methyl radical to produce an M-15 peak, but it would also fragment to lose an ethyl radical, causing an M-29 signal that was not listed among the peaks in the mass spectrum. It is only di-*tert*-butyl ether whose α-cleavage releases methyl radical exclusively, giving rise to only an M-15 peak.

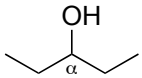


9. This alcohol exhibits a molecular ion peak (albeit a small one) at m/z 88. We know that it contains an oxygen atom since it is an alcohol. This means that we must reserve 16 amu for the oxygen atom. The remaining 72 amu can accommodate five carbons and 12 hydrogens, so the molecular formula is $C_5H_{12}O$. This is a saturated molecule, so we know that there are no rings or π bonds. Nevertheless, there are still several isomeric alcohols with this formula.

Note that the mass spectrum has only two fragments though. One is M-18, which corresponds to the dehydration fragment. The other is M-29, which means that an ethyl radical has been lost.

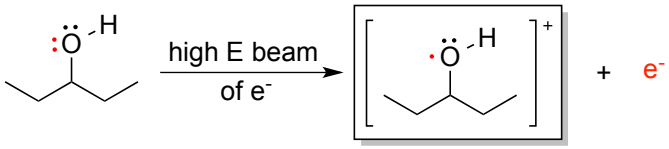


In order for α-cleavage to result in the loss of an ethyl radical only, the alcohol must be symmetrical. In other words, it must have two ethyl groups attached to the α-carbon. The structure must therefore be 3-pentanol.



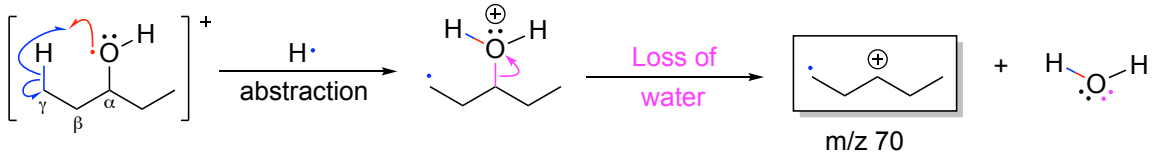
3-pentanol

This molecule exhibits a radical cation at m/z 88.



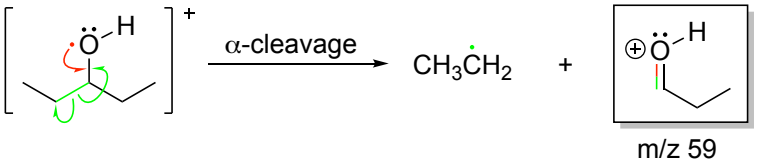
m/z 88
(very small
abundance expected)

When it dehydrates, an M-18 fragment is produced and appears at m/z 70.

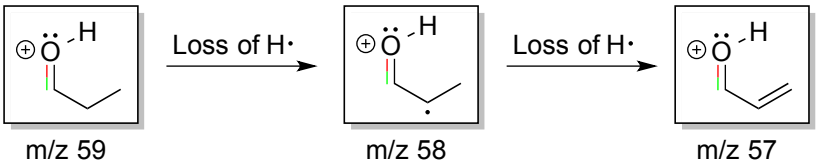


m/z 70
(M-18)

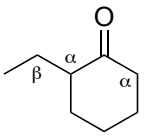
Due to the molecule's symmetry, only a single α-cleavage is possible. It releases ethyl radical to give the M-29 signal at m/z 59.



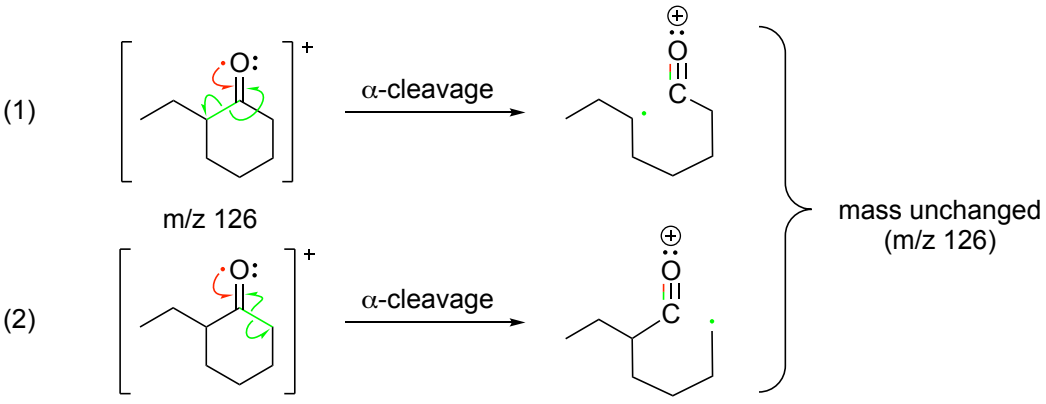
There are a few small signals around m/z 59. The one at m/z 60 is due to the presence of ^{13}C in a small percentage of molecules. The peaks at m/z 58 and 57 are due to the successive loss of hydrogen atoms to extend the conjugation in the molecule.



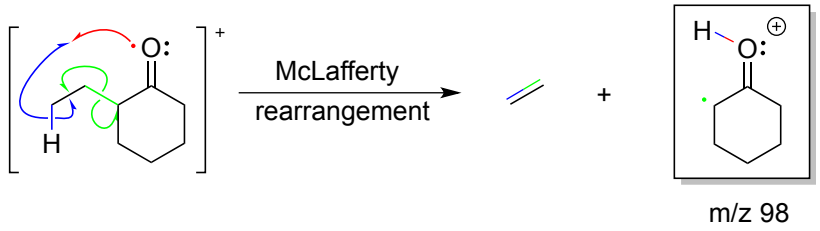
10. The two main fragmentation pathways for ketones include α-cleavage and McLafferty rearrangement. When α-cleavage occurs, the carbonyl carbon to α-carbon bond is broken. In this cyclic molecule, such a reaction will not actually result in a change in mass.



This is further illustrated by the mechanisms of the two α-cleavage pathways shown below. In both, the product has the same formula as the molecular ion and therefore contributes to the same signal at m/z 126.

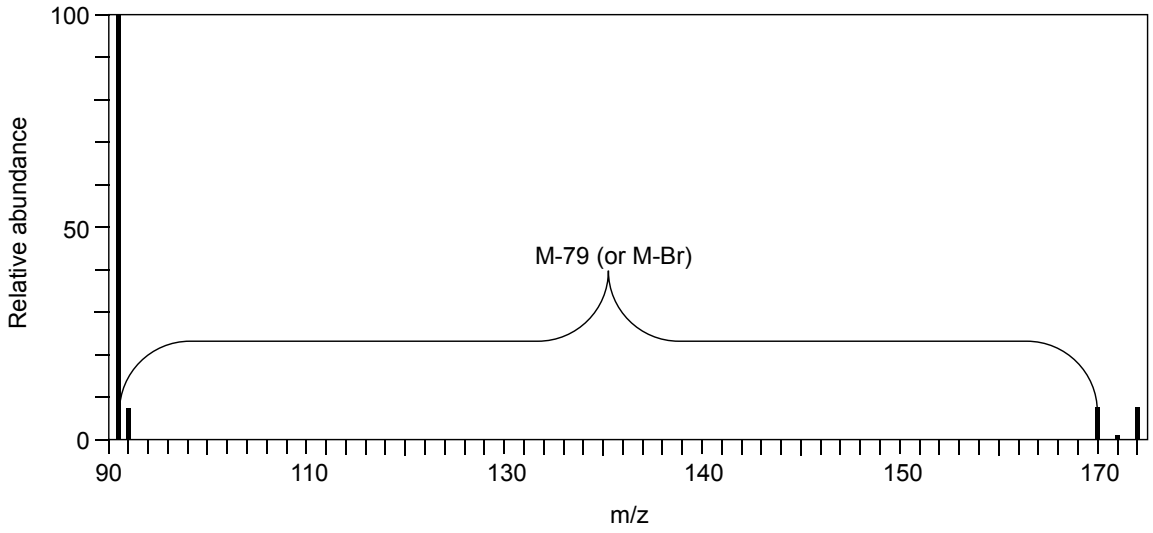


On the other hand, McLafferty rearrangement cleaves the α,β-bond, which will generate a fragment in this case. The loss of ethylene ($H_2C=CH_2$) results in an M-28 signal at m/z 98.



The question suggests that it is a fragment (not the molecular ion) that is the base peak. Since we've only identified a single fragment at m/z 98, this is expected to be the base peak.

11. Initially, it may seem that we have been given too few clues to make an identification. However, if we look closely at the mass spectrum, there is sufficient information to proceed. First, notice that there are M and M+2 peaks of approximately equal height. This suggests the presence of bromine in the molecule. Secondly, this hypothesis is supported by the mass difference between the molecular ion peak (170 amu) and the base peak (91 amu). The difference is 79 amu, which is the mass of bromine.



Knowing that the molecule contains bromine, we reserve 79 amu for it, and the remaining 91 amu could support up to 7 carbons. This gives a possible molecular formula of C_7H_7Br. If we experiment with reducing the carbon count, the formula becomes impossible: $C_6H_{19}Br$. A fully saturated six-carbon molecule containing bromine could only support 13 hydrogens. Therefore, the formula must be C_7H_7Br. This molecule has four degrees of unsaturation.

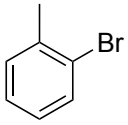
$$Degrees\ of\ Unsaturation = \frac{[2n+2] - Hydrogens\ and\ H\ equivalents\ present}{2}$$

$$Degrees\ of\ Unsaturation = \frac{[2(7)+2]-8}{2} = 4$$

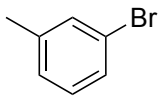
We know that a benzene ring will immediately explain all four degrees of unsaturation, so it is a likely structural component.

1 ring + 3 π bonds = 4 degrees of unsaturation

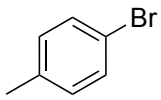
This leaves one remaining carbon, as well as the bromine atom. These fragments may be assembled in four ways. The first three involve the attachment of the carbon and bromine to the ring separately. The final structure places both remaining atoms on one ring carbon.



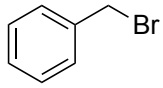
2-bromotoluene



3-bromotoluene

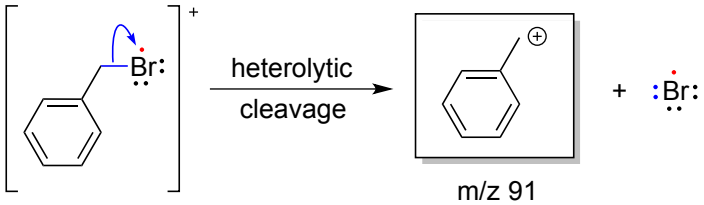


4-bromotoluene



benzyl bromide

We know that alkyl bromides undergo predominantly heterolytic cleavage. Given how massive the base peak is relative to the molecular ion peak, we can surmise that heterolytic cleavage gives rise to a fairly stable carbocation. Only one of the four possible structures gives a resonance-stabilized carbocation when heterolytic cleavage occurs, and that is benzyl bromide.

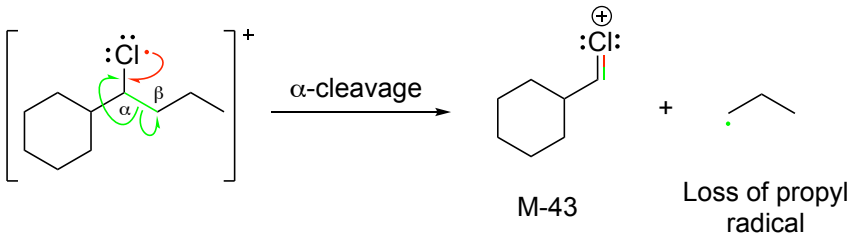


radical cation generated from benzyl bromide

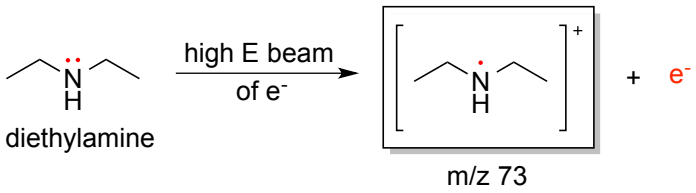
m/z 91
(resonance stabilized)

Therefore, benzyl bromide is most likely to be the unknown substance.

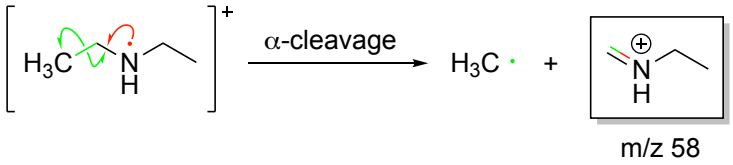
12. An M-43 signal results from the loss of a propyl radical. Both molecules could lose a propyl radical through α-cleavage; however, the alkyl chloride is far more likely to do so. Since a C-Cl bond is relatively close in energy to a C-C bond, both heterolytic cleavage (which breaks the C-Cl bond) and α-cleavage (which breaks a C-C bond) are observed for alkyl chlorides. However, C-Br bonds are much weaker than C-C bonds, so alkyl bromides fragment far more frequently through the heterolytic process, which breaks the weaker C-Br bond. Since α-cleavage occurs infrequently with alkyl bromides, it is the alkyl chloride that should give the more prominent M-43 peak.



13. Heteroatom-containing functional groups have lone-pair electrons, and we expect ionization to occur frequently through the loss of an electron from the lone pair. This results in the radical cation that yields the molecular ion peak at m/z 73.



A mode of fragmentation shared by nearly all of the heteroatom-containing functional groups is α-cleavage. In this symmetrical molecule, a single α-cleavage is possible, and it results in the loss of a methyl radical. This yields the fragment responsible for the base peak at m/z 58 (or M-15).

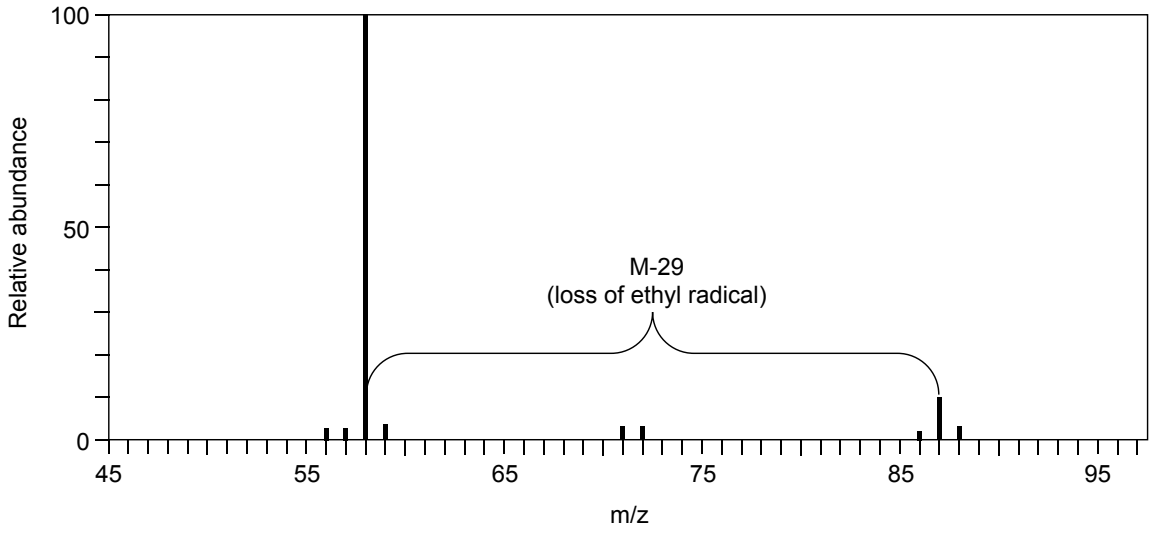


14. The odd mass of the molecular ion peak at m/z 87 suggests that the compound is an amine. This means that we must reserve 14 amu for the nitrogen atom. The remaining 73 amu can support up to 6 carbons; however, C_6HN has too few hydrogens to be a viable formula. Reducing the carbon count allows for a more reasonable number of hydrogen atoms: $C_5H_{13}N$. Remember that nitrogen can be counted as one half of a carbon atom for the purpose of calculating degrees of unsaturation. Therefore, this molecule is completely saturated.

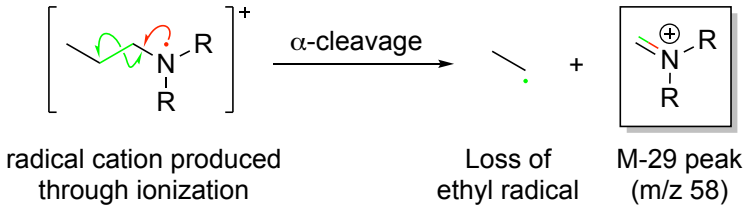
$$Degrees\ of\ Unsaturation = \frac{[2n+2] - Hydrogens\ present}{2}$$

$$Degrees\ of\ Unsaturation = \frac{[2(5.5)+2] - 13}{2} = 0$$

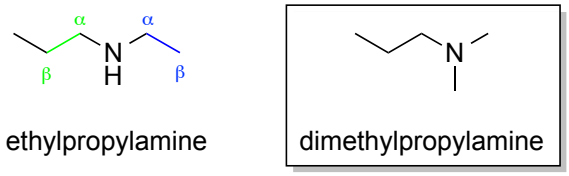
In the mass spectrum, the base peak (58 amu) could also be considered as an M-29 peak, meaning that it results from the loss of ethyl radical.



As we saw in the previous problem, this loss of ethyl radical is likely due to α-cleavage, which is a common mode of fragmentation for amines.



The ammonium ion produced by this fragmentation has a mass of 58 amu. The methylene (CH_2) group and nitrogen atom account for 28 amu. The remaining 30 amu must be explained by the two R groups on nitrogen. This leaves only two choices for the structure: ethylpropylamine and dimethylpropylamine. However, ethylpropylamine possesses a second α,β-bond, whose fragmentation through α-cleavage would be expected to yield a prominent M-15 peak. Since the signals in this region (m/z 72) are miniscule, it is more likely that the structure is dimethylpropylamine, which can undergo only one α-cleavage.



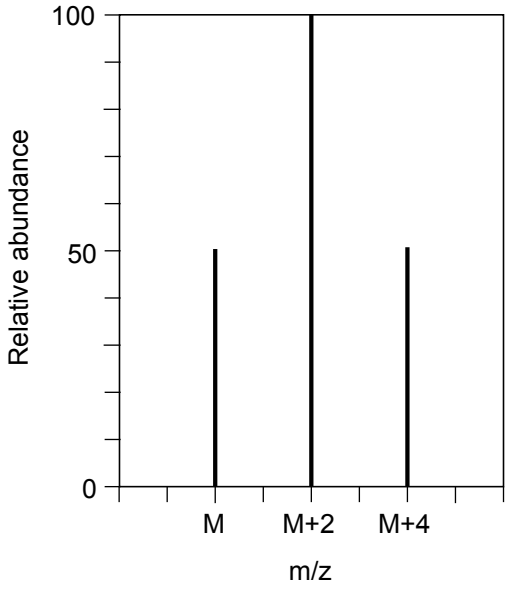
15.

(a) When two bromine atoms are present in a molecule, there are four possible combinations of isotopes, two of which lead to the same mass.

^{79}Br and ^{79}Br = M

^{79}Br and ^{81}Br <u>or</u> ^{81}Br and ^{79}Br = M+2
^{81}Br and ^{81}Br = M+4

Since the isotopes are present in roughly a 1:1 ratio, we expect the intensities of the signals to be 1:2:1 because there are two ways to achieve the mass of M+2, which doubles its probability.

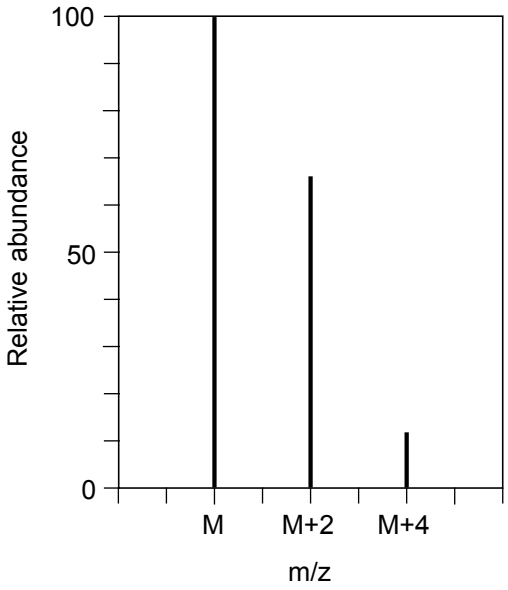


(b) With two chlorines in the structure, there are four possible isotope combinations much like we saw in part (a). Again, two of these lead to the same mass.

^{35}Cl and ^{35}Cl = M
^{35}Cl and ^{37}Cl <u>or</u> ^{37}Cl and ^{35}Cl = M+2
^{37}Cl and ^{37}Cl = M+4

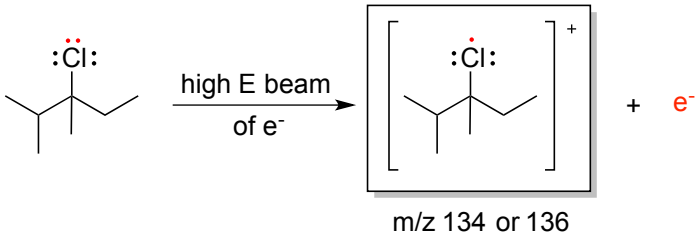
What differs from part (a) is the relative abundance of the M, M+2, and M+4 signals. The natural abundance of ^{35}Cl is about 76%; whereas, that of ^{37}Cl is approximately 24%. Since ^{35}Cl is the more abundant isotope, we can scale its signal to 100% relative abundance, meaning that ^{37}Cl will have a relative abundance roughly one-third as large (~33%).

It will be most likely to have two ^{35}Cl isotopes in the molecule, so the molecular ion peak (M) will have an abundance of 100% relative to its counterparts. The probability of having one ^{37}Cl in the molecule is about 66%: There are two chlorine atoms, and there is a 33% chance of finding ^{37}Cl at either location. Finally, the probability of having two ^{37}Cl isotopes is ~11% (0.33 x 0.33).

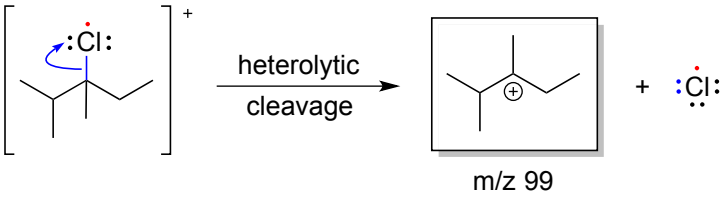


Note that these values will be altered somewhat by the presence of so many carbons and several nitrogens, each of which has the potential to contain an isotope that is one mass unit heavier.

16. This alkyl chloride will frequently be ionized through the loss of an electron from a lone pair. The radical cation that results gives rise to the molecular ion peak.

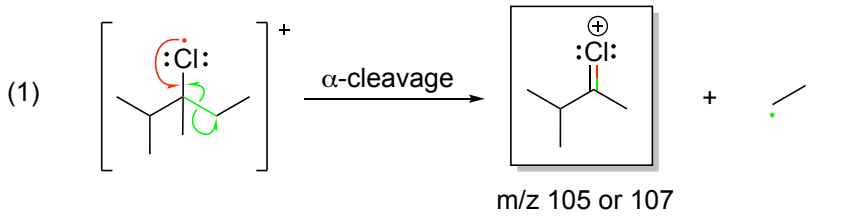


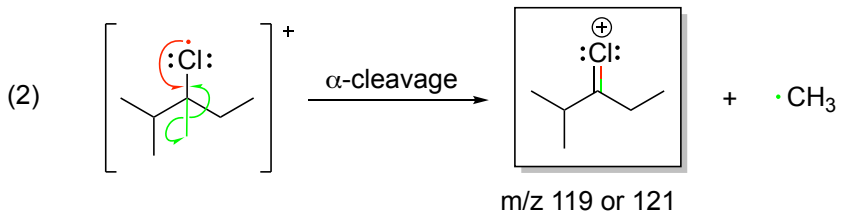
One possible mode of fragmentation is heterolytic cleavage, in which chlorine radical dissociates from the analyte. This leaves behind a tertiary carbocation that causes a signal at m/z 99.

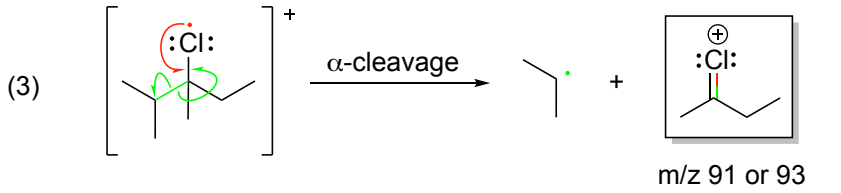


An alternate mode of fragmentation is homolytic (or α) cleavage. In this pathway, chlorine contributes its unpaired electron to the formation of a π bond between itself and the adjacent carbon. The carbon reciprocates by pulling an electron from an α,β-bond, and this results in the loss of a carbon radical. Since there are three

unique α,β-bonds in this molecule, there are three possible α-cleavage events. We can reasonably surmise that the one that releases the secondary isopropyl radical (path 3) will occur with greater frequency than the other two (paths 1 and 2), which release less stable primary or methyl radicals.







17. Recall that the abundance of the M+1 signal is determined by three factors: the number of carbons in the molecule (n); the natural abundance of ^{13}C (1.1%); and the relative abundance of the molecular ion peak (M).

$$(Relative\ abundance\ of\ M+1) = n\ (0.011)\ (Relative\ abundance\ of\ M)$$

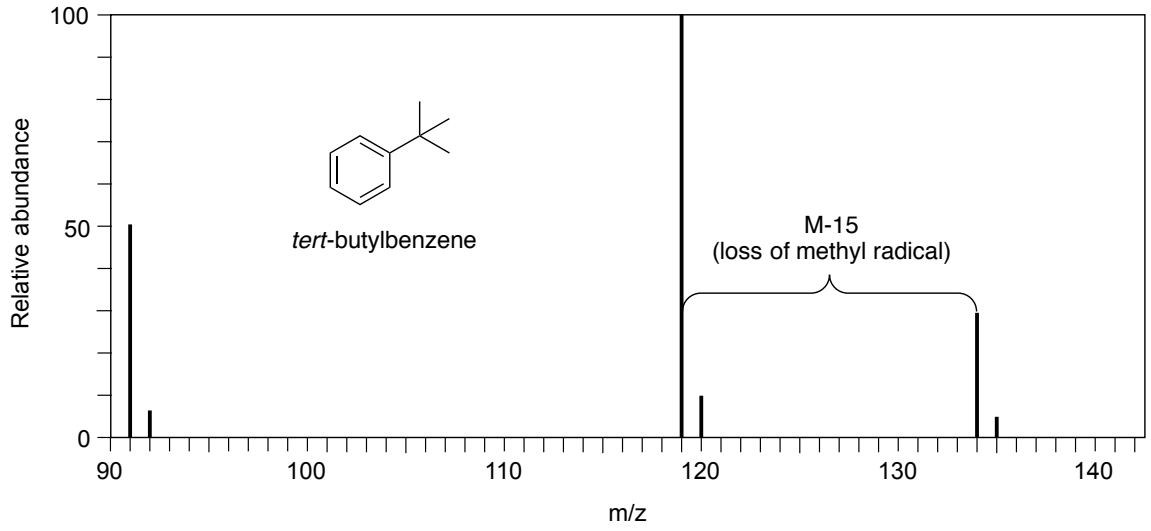
If the relative abundances are known, then the equation can be rearranged to solve for the number of carbons in the molecule.

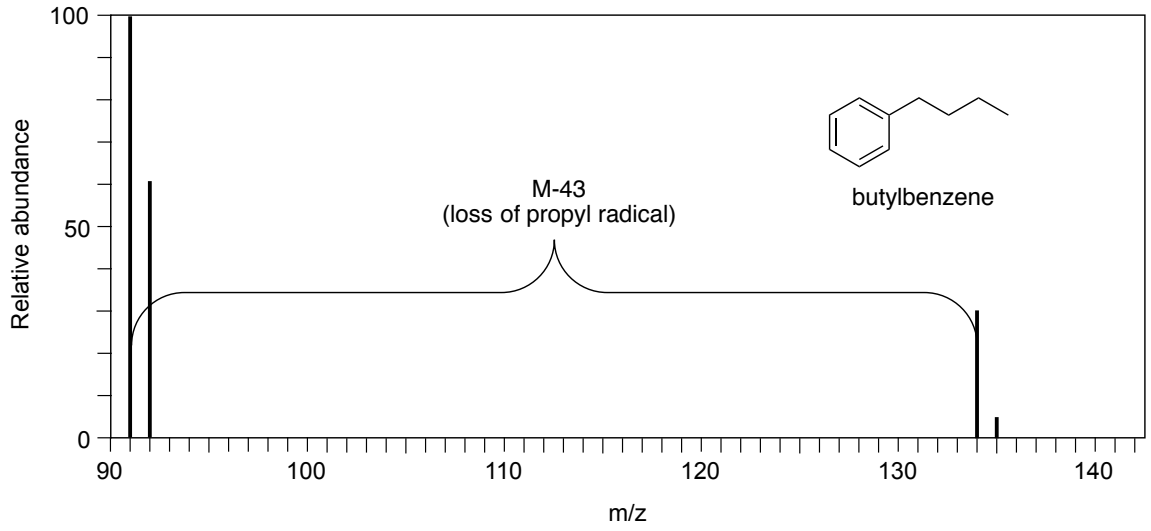
$$n = \frac{(Relative\ abundance\ of\ M+1)}{(0.011)\ (Relative\ abundance\ of\ M)} = \frac{24.4\%}{(0.011)(37\%)} = 59.95\ \cong\ 60$$

This shows that buckminsterfullerene contains 60 carbons. In fact, it is especially unusual because its entire formula is simply C_{60}. It contains no hydrogen atoms or atoms of any type other than carbon.

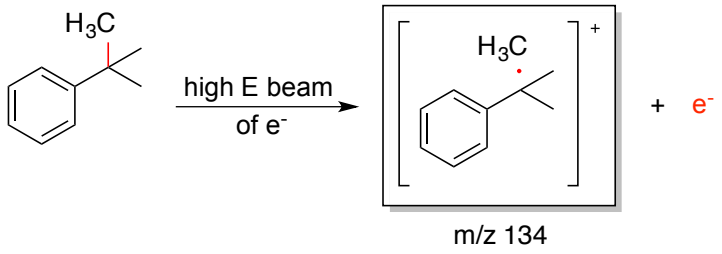
18. The isomers are matched with their mass spectra below. The key comparison in each case is between the molecular ion peak (134 amu) and the base peak. The mass spectrum of *tert*-butylbenzene has a base peak (119 amu) resulting from the loss of

a methyl radical; whereas, the mass spectrum of butylbenzene has a base peak (91 amu) resulting from the loss of a propyl radical.

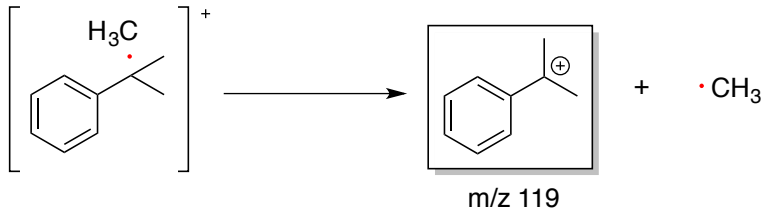




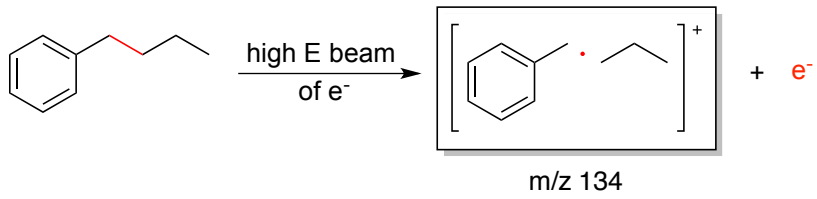
In each case, we expect the bond between the benzylic carbon (i.e., the carbon adjacent to the benzene ring) and its neighbors to be the weakest. This is because a carbocation or radical at the benzylic position will be resonance stabilized. In the case of *tert*-butylbenzene, there is only one type of bond stemming from the benzylic position, and that is a bond to a methyl group. Ionization at this position yields the molecular ion peak at m/z 134.



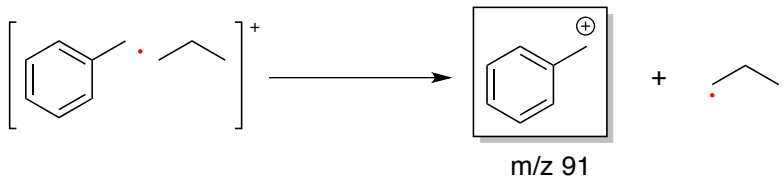
This radical cation can fragment in one of two ways; however, it is more likely that the severe electron deficiency of the carbocation will be placed on the benzylic carbon, which is not only tertiary but also resonance stabilized. This yields the base peak at m/z 119.



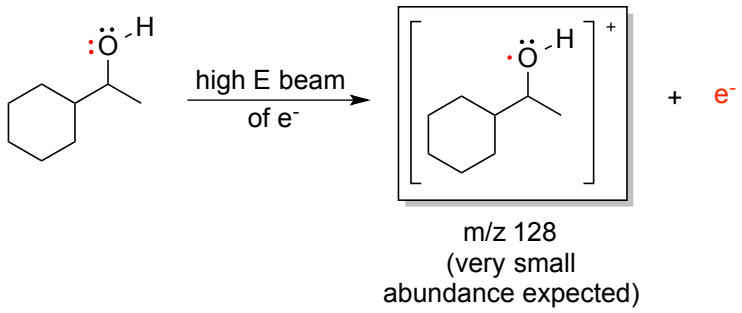
Butylbenzene will also tend to ionize through loss of an electron from the bond between the benzylic carbon and its neighbor. This yields the same molecular ion peak.



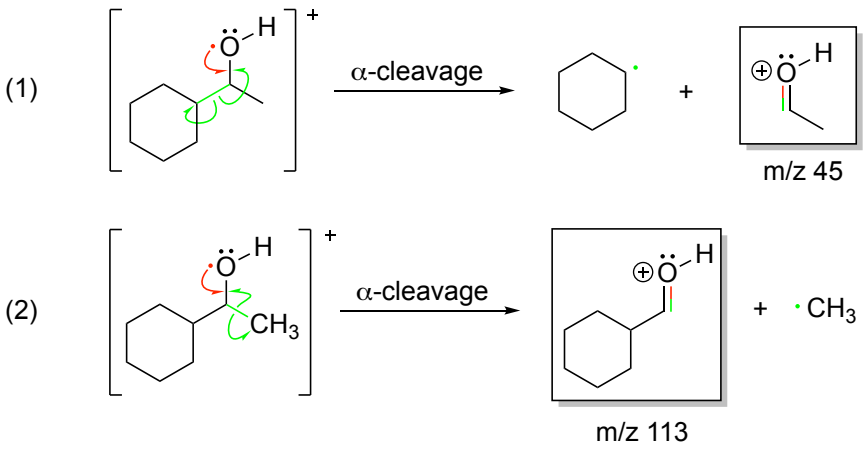
Although this radical cation can also fragment in one of two ways, the most probable places the severely electron-deficient carbocation on the benzylic center where it can be resonance stabilized. This affords the base peak at m/z 91.



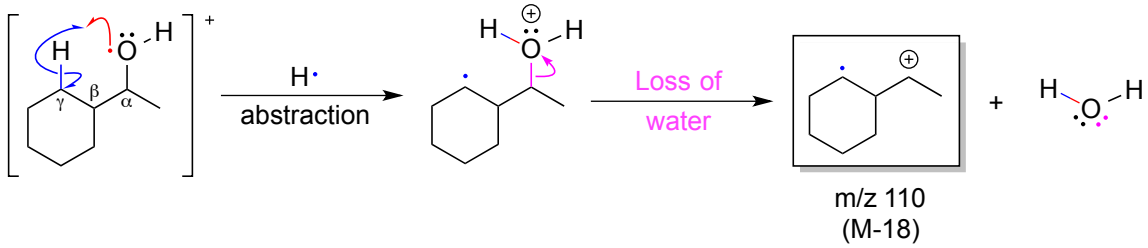
19. A principal method of ionization is through the loss of a lone pair electron. This produces the radical cation that causes the molecular ion peak at m/z 128. As with most other alcohols, the molecular ion peak is expected to be exceedingly small.



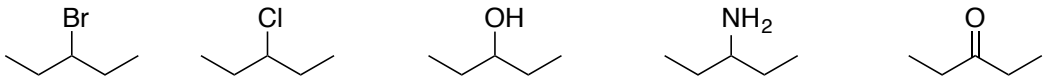
We do not see the heterolytic cleavage of the hydroxyl radical because this radical is high in energy due to the absence of electron-donating substituents. However, α-cleavage is possible. Since there are two different α,β-bonds in this analyte, two α-cleavage events are possible. Each occurs when the oxygen atom donates its unpaired electron to form half of a π bond with the adjacent carbon. The carbon atom reciprocates with an electron pulled from the α,β-bond, and a carbon radical is released as a result. The homolytic cleavage pathways yield signals at m/z 45 and 113.



Additionally, dehydration is a common fragmentation pathway for alcohols. It begins with abstraction of a γ-hydrogen by oxygen. As the C-H bond is homolytically cleaved, the radical is transferred to the γ-carbon. This process yields a good leaving group (water) that subsequently dissociates to afford a new radical cation that is 18 amu lighter than the molecular ion.

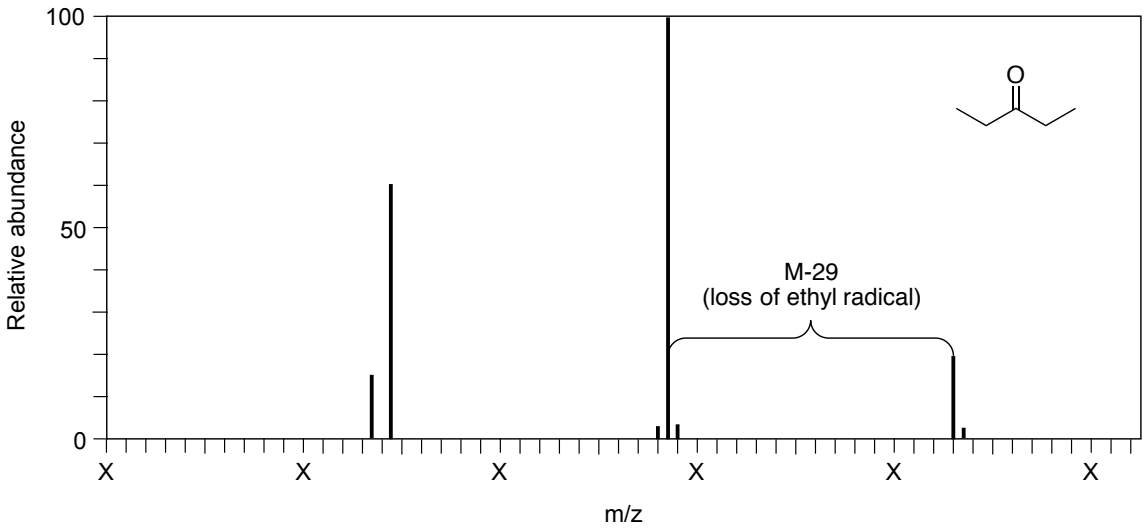


20. It is easiest to begin by identifying a distinguishing feature of each of the molecules. The two alkyl halides will give M and M+2 peaks but in differing ratios. The alcohol will have a small molecular ion peak, but will also show an M-18 signal for dehydration. The amine will have a molecular ion peak with an odd mass. The ketone will lack the preceding features but will show an M-29 signal because its α-cleavage releases an ethyl radical.

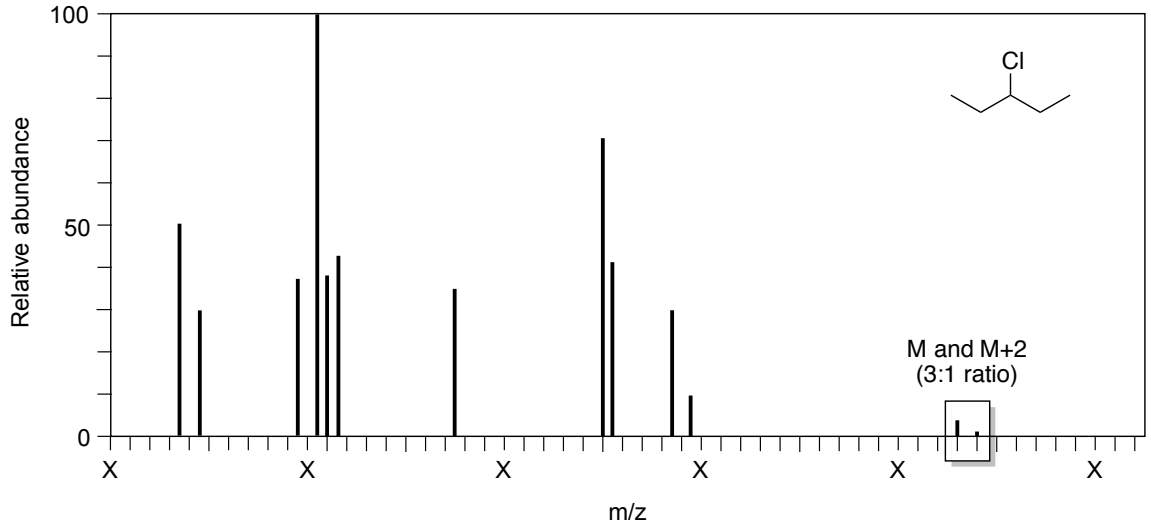


M and M+2 (1:1 ratio)	M and M+2 (3:1 ratio)	Small M and M-18 (dehyration)	Odd M	M-29 (loss of ethyl radical)

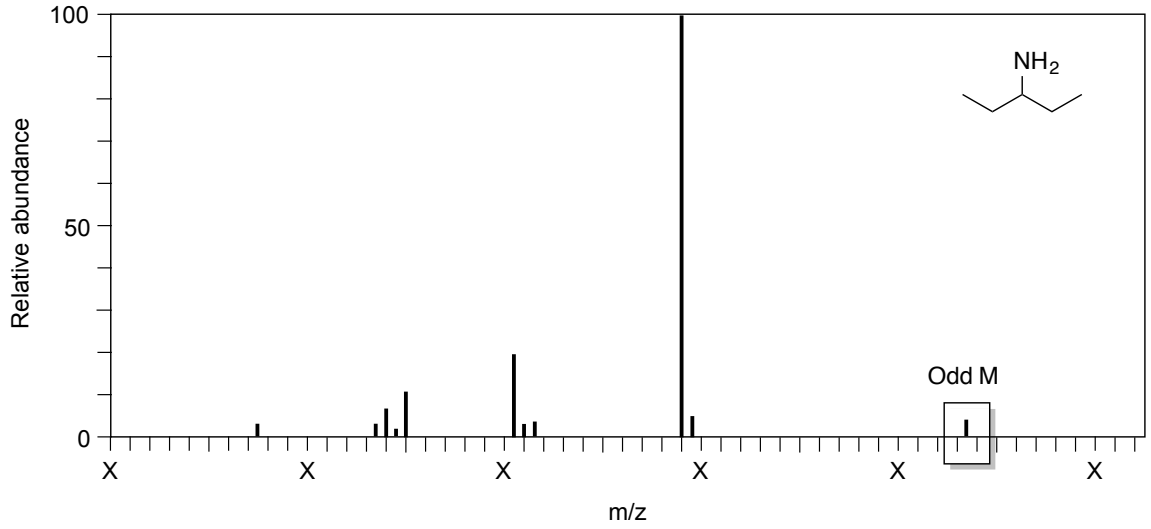
The first spectrum does not have M and M+2 peaks, an odd M value, or an M-18 signal, but it does contain the M-29 signal expected to be among the few notable features of the ketone.



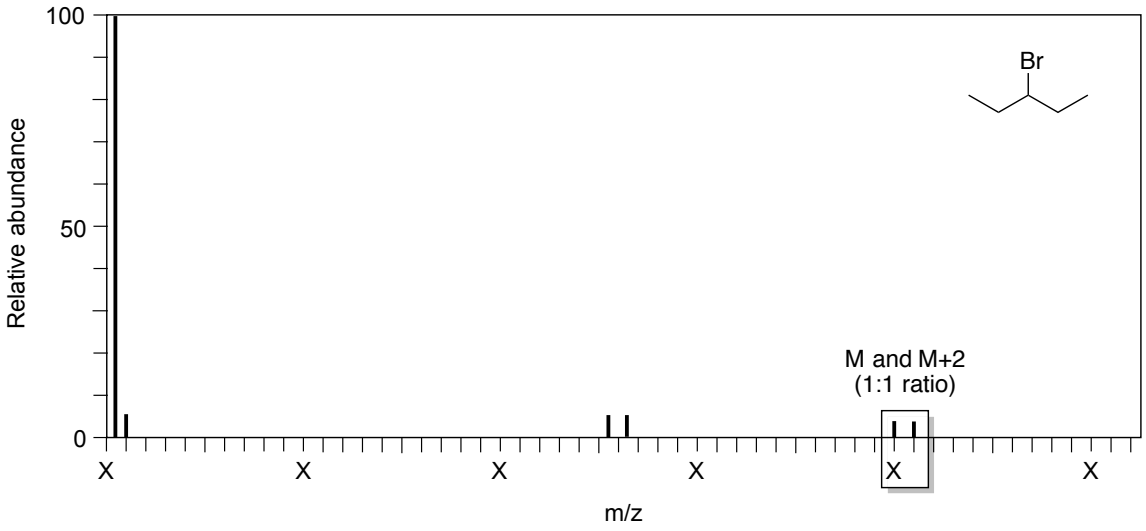
The second mass spectrum exhibits M and M+2 signals in roughly a 3:1 ratio, making it the alkyl chloride.



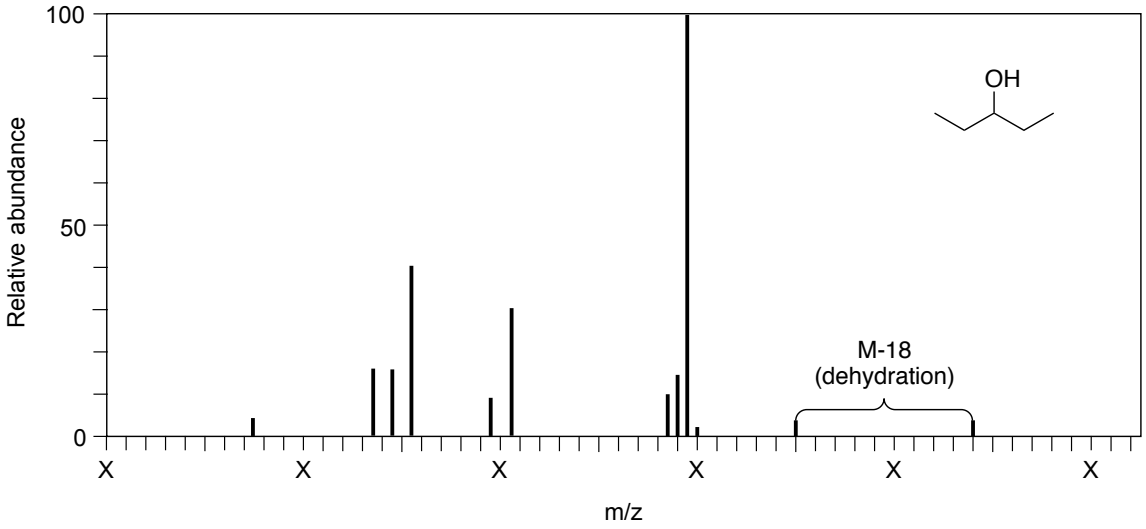
The third spectrum has a molecular ion peak with an odd mass, so it is the amine.



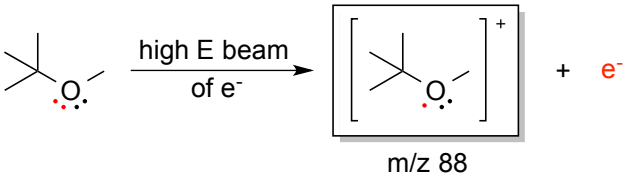
The fourth mass spectrum has M and M+2 peaks in approximately a 1:1 ratio. This must therefore be the alkyl bromide.



Finally, the last spectrum has a small molecular ion peak and an M-18 signal correlating with dehydration, so it represents the alcohol.

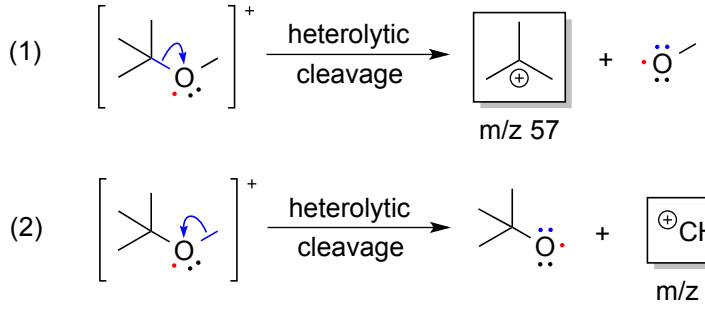


21. Ionization will often occur through the ejection of a lone-pair electron to yield the molecular ion.

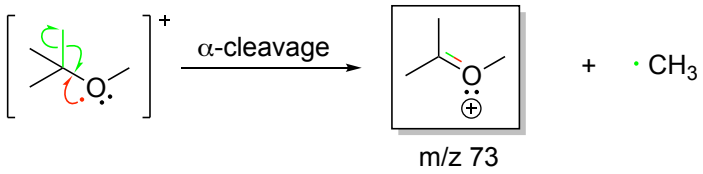


This radical cation can undergo two distinct heterolytic cleavages. In each, the oxygen radical dissociates from a neighboring carbon. This yields signals at m/z 57

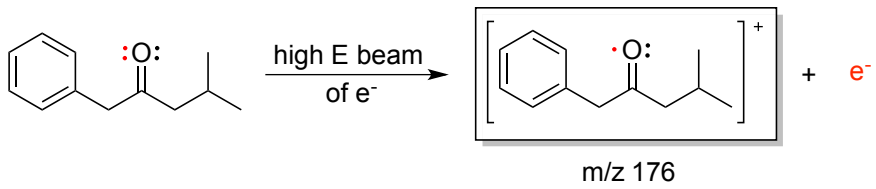
and 15; however, we would certainly expect the signal at m/z 57 to be a good deal higher in intensity due to the enhanced stability of the tertiary carbocation.



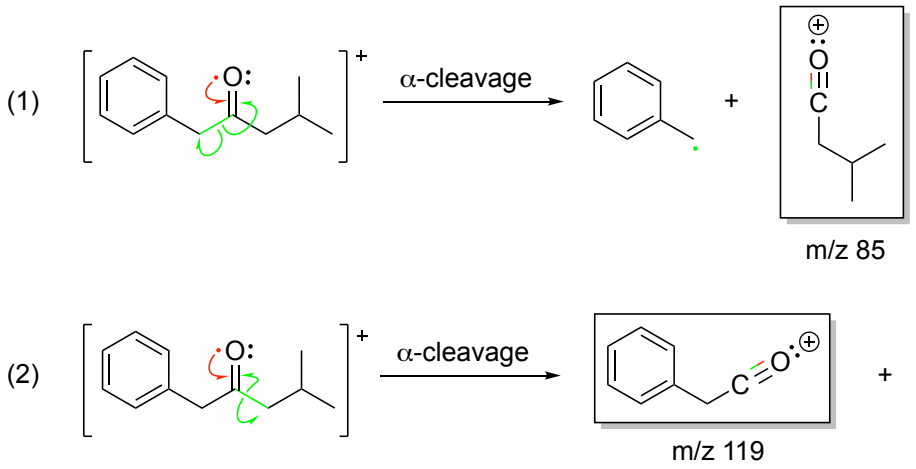
Alternatively, there is a single α-cleavage that is possible for this analyte. Oxygen contributes its unpaired electron to an incipient π bond. The adjacent carbon also contributes a single electron, although this results in the cleavage of an α,β-bond and the release of a methyl radical.



22. Mass spectrometry of benzyl isobutyl ketone begins with ionization, which frequently occurs via the loss of an unshared electron. This generates the molecular ion, which appears at m/z 176.



There are two distinct α-cleavage pathways. In each, oxygen contributes its unpaired electron to a forming π bond. The carbonyl carbon also donates an electron to the forming π bond, but this electron is taken from an adjacent carbon-carbon bond. It results in the fragmentation of that bond and the release of a carbon-centered radical. Peaks at m/z 85 and 119 result from α-cleavage.



Finally, McLafferty rearrangement can occur through the abstraction of a γ-hydrogen by oxygen. Remember that, due to differences between the Greek lettering of alcohols and ketones, the γ-hydrogen is six atoms from the oxygen radical in this case. As the C-H bond fragments, a carbon-carbon π bond begins to form. The β-carbon supplies the other electron needed to complete the π bond by taking it from the α,β-bond. This leads to the scission of that bond. A three-carbon alkene (propylene) is lost, and a peak at m/z 134 is produced.

23. We can begin this problem with an analysis of the molecular formula. This molecule has a large number of degrees of unsaturation.

$$Degrees\ of\ Unsaturation = \frac{[2n+2] - Hydrogens\ present}{2}$$

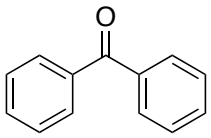
$$Degrees\ of\ Unsaturation = \frac{[2(13)+2] - 10}{2} = 9$$

Recall that a benzene ring accounts for four degrees of unsaturation due to its three π bonds and one ring. Therefore, it seems probable that this molecule contains two benzene rings and one additional degree of unsaturation.

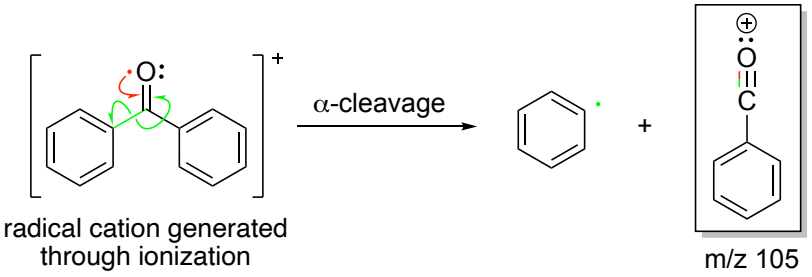
The IR spectrum clarifies the nature of the remaining degree of unsaturation. The signals at 3075 and 1600 cm^{-1} are not surprising because we have inferred the presence of aromatic rings, which would yield sp^2 C-H stretching and aromatic C=C stretching, respectively. The signal at 1665 cm^{-1} is low for a carbonyl. This reveals

that the last degree of unsaturation is a carbon-oxygen π bond and that the carbonyl is highly conjugated.

With two phenyl groups and a carbonyl as fragments, we have accounted for all of the atoms in the formula. Simply stitching them together produces a structure.



We know that ketones fragment through α-cleavage. In this case, that would result only in loss of a phenyl radical, explaining the peak in the mass spectrum at m/z 105.

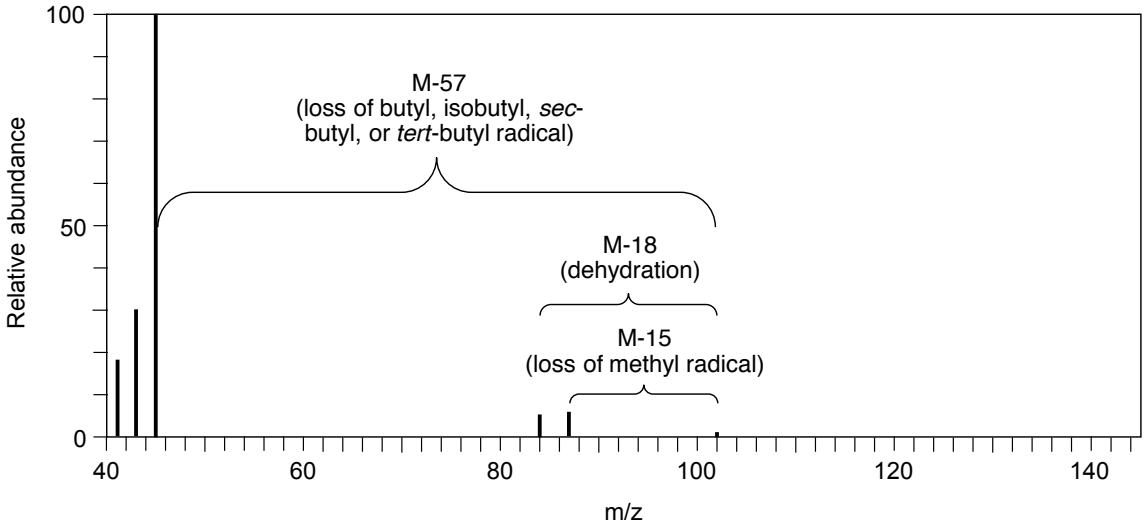


As an aside, this compound (known as benzophenone) absorbs UV light due to its conjugation. This leads to a wide variety of applications, including UV curing and shielding components of mixtures from UV damage.

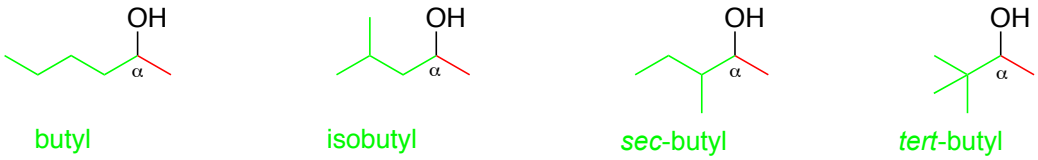
24. We have not been given a molecular formula, so our first endeavor must be to derive one. The molecular ion, although small, appears at m/z 102. Additionally, the NMR spectrum reveals one broad signal integrating for one hydrogen. This suggests a single hydrogen-bonding proton is present in the molecule. Since the molecular mass is even, we can say that the molecule does *not* contain one amine. It could however contain one alcohol.

We should therefore reserve 16 amu for oxygen. The remaining 86 amu can accommodate up to 7 carbons; however, the formula C_7H_2O seems unlikely due to the paucity of hydrogens. If we reduce the carbon count by one, we get a more reasonable number of hydrogen atoms: $C_6H_{14}O$. This molecule is completely saturated.

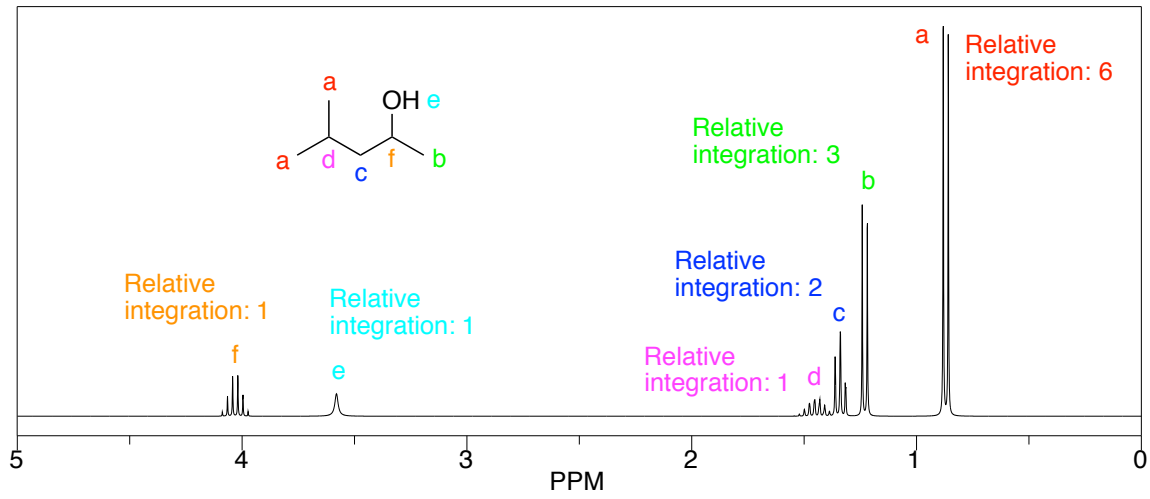
The mass spectrum shows the loss of methyl radical, the loss of water, and the loss of butyl radical (or one of its isomers).



We know that the α-cleavage of alcohols will expel alkyl radicals, so we can reattach the methyl and butyl (or isomeric) radicals to the α-carbon to form four candidates for the unknown compound.



The NMR quickly distinguishes between these four possibilities. The signal with a relative integration of 6 provides the simplest clue. Only one of the four structures has two (and only two) identical methyl groups that would cause such a signal. For clarity all of the signals are assigned below.



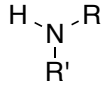
25. In this case, we are not provided with a molecular formula, so let's begin by attempting to ascertain the formula. The molecular ion peak in the mass spectrum appears at m/z 87. This is a significant clue because it shows an odd mass, which is consistent with an amine.

If we reserve 14 amu for the nitrogen atom, the remaining 73 amu can accommodate up to six carbons, but the formula C_6HN is problematic because there is only one hydrogen atom, which is clearly inconsistent with the NMR data. If we reduce the carbon count by one, then we obtain the formula $C_5H_{13}N$. Remember that nitrogen atoms can be counted as one half of a carbon for the purpose of calculating degrees of unsaturation. This molecule is therefore saturated.

$$Degrees\ of\ Unsaturation = \frac{[2n+2] - Hydrogens\ present}{2}$$

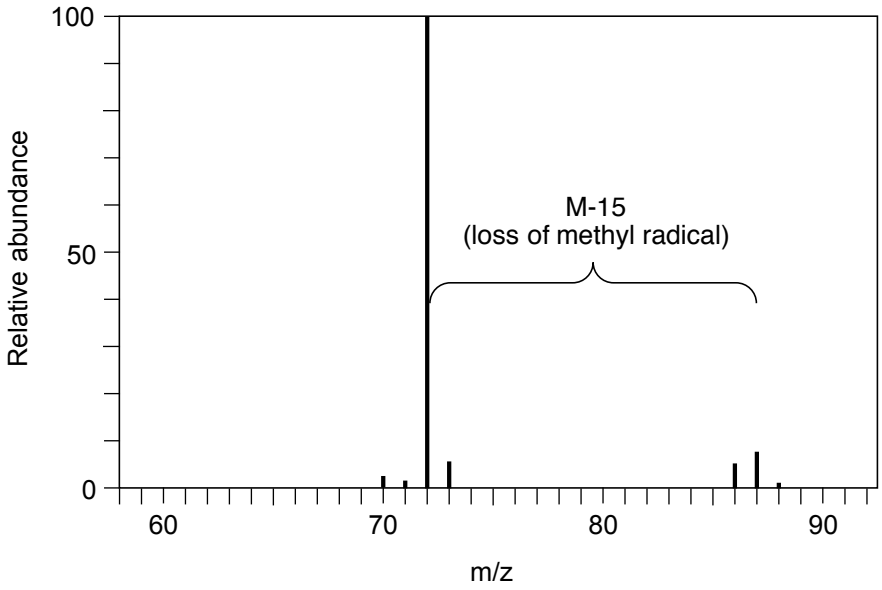
$$Degrees\ of\ Unsaturation = \frac{[2(5.5)+2] - 13}{2} = 0$$

The IR spectrum's single peak near 3400 cm^{-1} confirms the presence of a single N-H bond. Recall that an NH_2 group would yield two signals in this region due to symmetric and asymmetric stretching.

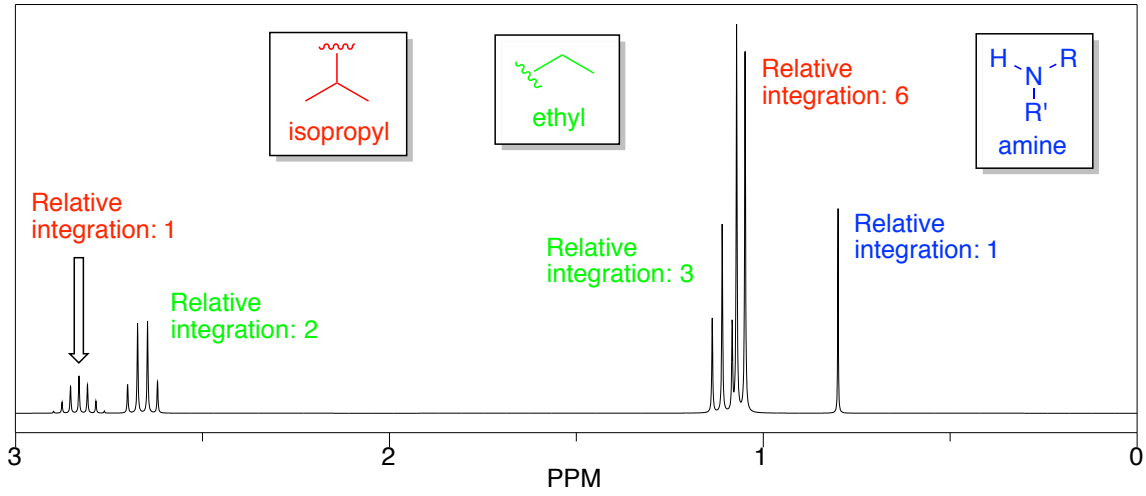


The IR signals just below 3000 cm^{-1} correspond with sp^3 C-H stretching, which is not a surprise since alkyl groups will produce this signal.

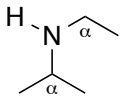
The mass spectrum shows that the unknown amine readily fragments so as to lose a methyl radical. This means that there must be at least one α,β-bond connecting the α-carbon to a methyl group.



The NMR spectrum provides additional helpful clues. The two deshielded signals (above 2.5 ppm) correspond to the protons on carbon atoms adjacent to nitrogen. The methine (CH) can be paired with the two equivalent methyl groups to produce an isopropyl group. The methylene (CH_2) can be paired with the remaining methyl group to generate an ethyl fragment. Finally, the remaining proton must be the amino group's hydrogen.



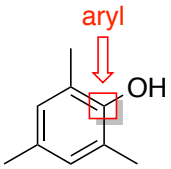
Connecting all the structural fragments produces the following compound, which is known as ethylisopropylamine. Notice that it possesses three methyl groups connected to α-carbons. This explains why the loss of methyl radical through α-cleavage is so prevalent in the mass spectrum.


H
N
α
α

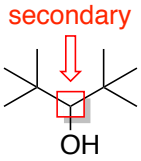
Solutions to Problems for Chapter 9: Alcohols, Ethers, and Epoxides

1.

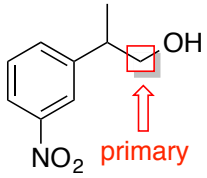
(a) In this structure, the hydroxyl group is bonded to an sp^2 hybridized carbon that is part of an aryl group. Consequently, this is a phenol.



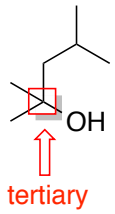
(b) The carbon bearing the hydroxyl group in this molecule is secondary. Therefore, this is a secondary alcohol.



(c) Although there is an aromatic ring in this compound, it is not bonded directly to the hydroxyl group, so this is *not* a phenol. The alcohol is primary because it is bonded to a primary carbon.

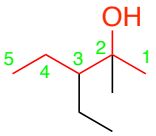


(d) A tertiary carbon bears the hydroxyl group, so this is a tertiary alcohol.



2.

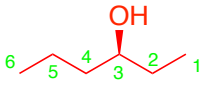
(a) The five-carbon parent alcohol is a 2-pentanol. The substituent names and numbers are then added to give the complete name: 3-ethyl-2-methyl-2-pentanol.



3-ethyl-2-methyl-2-pentanol

- Five carbon parent = pentane
- Replace "e" of suffix with "ol"
- Number so as to give the alcohol the lowest possible number
- Add substituent names and numbers

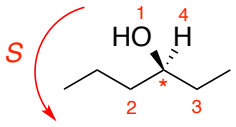
(b) This 3-hexanol has stereochemistry, so we must include the configuration in the name.



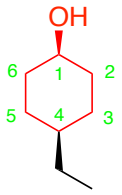
(*S*)-3-hexanol

- Six carbon parent = hexane
- Replace "e" of suffix with "ol"
- Number so as to give the alcohol the lowest possible number
- Assign configuration

When determining the configuration, priorities are assigned to each group on the chiral center (*) using the Cahn-Ingold-Prelog rules. The lowest priority group is already on the dash as required when making the determination. An arrow from priority 1 to 2 without passing through 3 goes in the counterclockwise direction, making the configuration *S*.



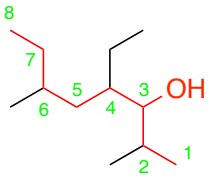
(c) The parent alcohol is cyclohexanol. While no number is needed to assign the location of the alcohol (it is implied to be at C1), we do need a number to designate the ethyl group's position relative to that of the alcohol. Additionally, we must indicate that the hydroxyl and ethyl groups are *cis* to each other.



cis-4-ethylcyclohexanol

- Six carbon, cyclic parent = cyclohexane
- Replace "e" of suffix with "ol"
- Alcohol is numbered 1; number so as to give the substituent the lowest possible number
- Add substituent name and number
- Assign *cis* / *trans* designation

(d) Here we have to be careful to scan closely for the correct parent, which is eight carbons in length.

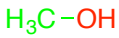


4-ethyl-2,6-dimethyl-3-octanol

- Eight carbon parent = octane
- Replace "e" of suffix with "ol"
- Number so as to give the alcohol the lowest possible number
- Add substituent names and numbers

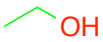
3.

(a) This simplest alcohol has a methyl group attached to the hydroxyl group.



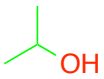
methyl alcohol

(b) Ethanol can also be called by its common name: ethyl alcohol.



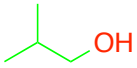
ethyl alcohol

(c) Be careful to note that the alkyl group in this molecule is the isopropyl group (rather than propyl).



isopropyl alcohol

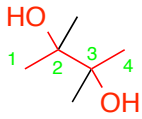
(d) This alcohol contains an isobutyl group.



isobutyl alcohol

4.

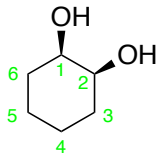
(a) This compound is a butanediol. We must add numbers to the name to indicate the location of the two hydroxyl groups and the substituents.



2,3-dimethyl-2,3-butanediol

- Four carbon parent = butane
- Add "diol" suffix to indicate two alcohols
- Number so as to give the alcohols the lowest possible numbers
- Add substituent names and numbers

(b) This is a cyclohexanediol. Numbers are needed to indicate that the two hydroxyl groups reside on adjacent carbons. We also need to specify the *cis* arrangement of the two hydroxyl groups.



cis-1,2-cyclohexanediol

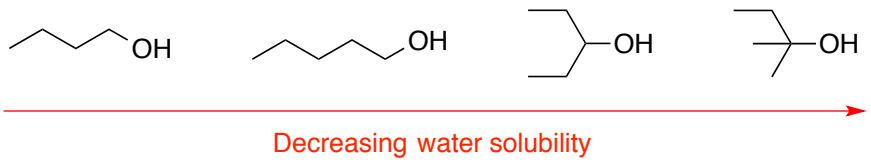
- Six carbon, cyclic parent = cyclohexane
- Add "diol" suffix to indicate two alcohols
- Number so as to give the alcohols the lowest possible numbers

5. Three of these alcohols have five-carbon chains, while the fourth has only four carbons in its chain. The R group is the hydrophobic portion of an alcohol. Since 1-butanol has the smallest hydrophobic portion, it is likely to have higher water solubility. Additionally, the fact that it is an unhindered primary alcohol allows for extensive hydrogen bonding, which also increases water solubility. Therefore, it is expected to be the most water-soluble alcohol.

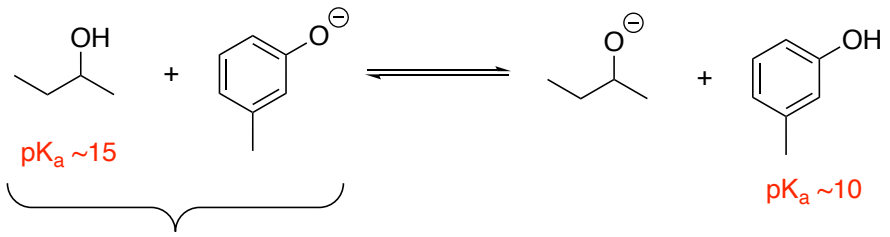
1-Pentanol has a larger hydrophobic R group, but it is also primary and therefore enjoys extensive hydrogen bonding, which increases its water solubility. Consequently, 1-pentanol is expected to be the second most water-soluble compound in the list.

3-Pentanol is a secondary alcohol. Since the carbon bearing the hydroxyl group has two alkyl groups, there is an increase in the steric bulk around this center. This reduces the alcohol's ability to hydrogen bond, thereby reducing its water solubility.

2-Methyl-2-butanol is a tertiary alcohol. The carbon bearing the hydroxyl group has three alkyl groups around it in this case, which further diminishes the alcohol's ability to get close enough to other molecules to hydrogen bond. As a result, this is expected to be the least water-soluble alcohol of the group.



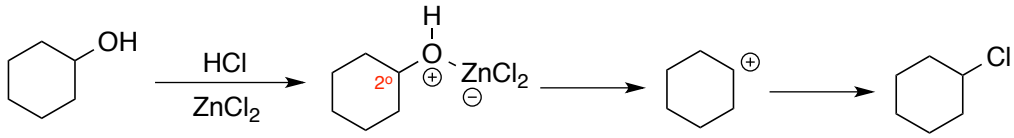
6. In this Brønsted-Lowry acid-base reaction, an alcohol reacts with a phenoxide (or phenolate). The proton transfer would yield an alkoxide and a phenol. However, given the pK_a values of the two acidic species (i.e., the alcohol and the phenol), equilibrium will favor the reactants by 10^5.



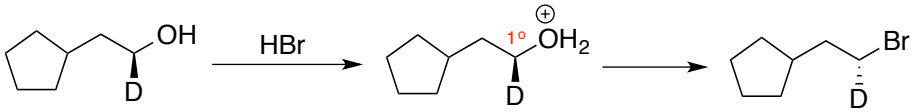
Equilibrium favors the side with the weaker acid (i.e., higher pK_a value)

7.

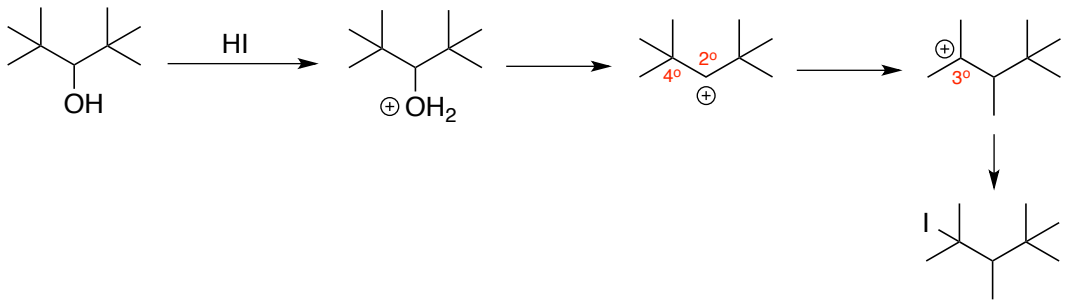
(a) In this question, the Lucas reagent is used to convert cyclohexanol to cyclohexyl chloride. The Lewis acid initially forms a complex with the Lewis basic hydroxyl group. The resultant oxonium ion then dissociates to yield a secondary carbocation. Chloride adds to this carbocation, giving the product.



(b) This primary alcohol is protonated by HBr to yield an oxonium ion. The leaving group does not dissociate because the formation of a primary carbocation is energetically unfavorable. Instead, bromide directly displaces water in S_N2 fashion, which results in a concomitant inversion of configuration.

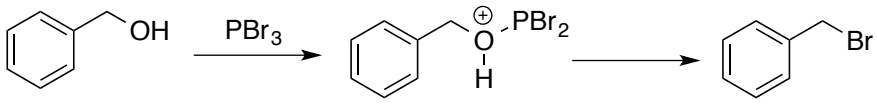


(c) In this reaction, the secondary alcohol is protonated by HI, and the resulting oxonium ion dissociates to leave behind a secondary carbocation. The secondary carbocation is flanked by quaternary centers, so a 1,2-methyl shift follows to afford a more stable tertiary carbocation. It is to this tertiary carbocation that iodide adds to yield the major product.

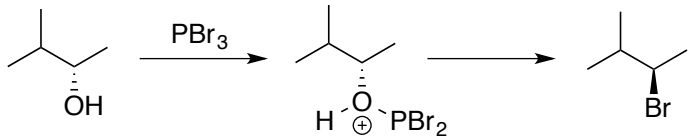


8.

(a) Benzyl alcohol first attacks PBr_3, displacing bromide. The oxonium ion thus formed is displaced by bromide in S_N2 fashion to yield benzyl bromide.



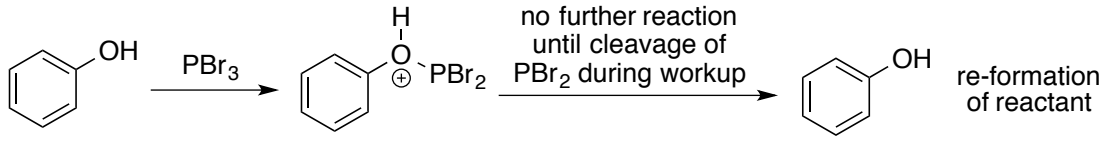
(b) This secondary alcohol similarly attacks PBr_3, displacing bromide. When bromide displaces the oxonium ion via S_N2 reaction, there is an accompanying inversion of configuration.



Note that there is no carbocation rearrangement during this reaction because no carbocation intermediate is formed.

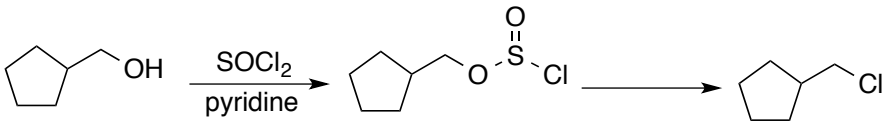
(c) This reaction does not convert phenol into the corresponding aryl bromide. The reason is that the carbon bearing the hydroxyl group is sp^2 hybridized, and sp^2 centers do not undergo S_N2 (or S_N1) reaction.

Phenol can attack PBr_3 and displace a bromide. However, the resulting oxonium ion is unreactive in S_N2 pathways. Therefore, when the reaction mixture is worked up in the laboratory, the oxonium ion will revert to the phenol.



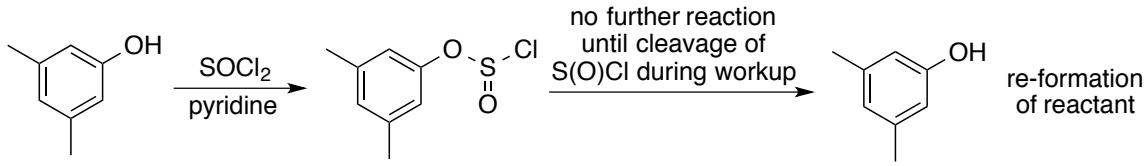
9.

(a) The primary alcohol is first converted to a good leaving group by thionyl chloride. Then, the chloride released in the process acts as a nucleophile and displaces the leaving group to yield the primary alkyl chloride.

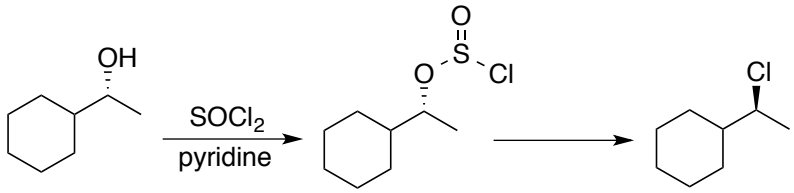


(b) As we saw in Problem 8(c), phenols contain a hydroxyl group on an sp^2 hybridized carbon. Since sp^2 centers are unreactive in S_N2 reactions, a phenol cannot be converted to the corresponding chloride using this method.

The hydroxyl group can attack thionyl chloride; however, the intermediate thus formed is unreactive and simply hydrolyzes upon workup in the laboratory.

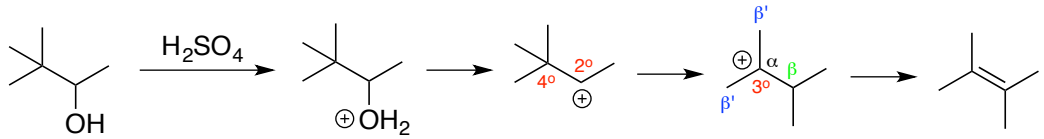


(c) The secondary alcohol is converted to a good leaving group by thionyl chloride. The good leaving group is subsequently displaced to afford the secondary alkyl chloride. During the displacement, an inversion of configuration is observed because the mechanism is S_N2.

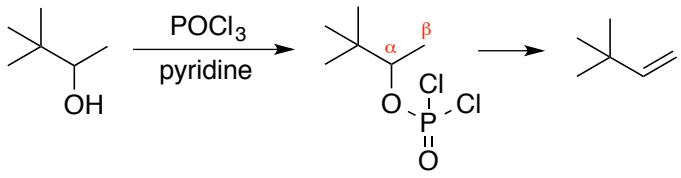


10.

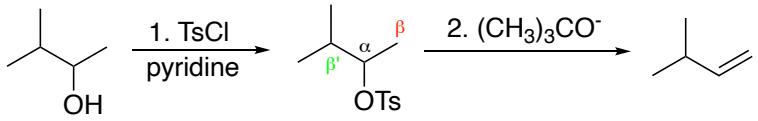
(a) In this reaction, sulfuric acid first protonates the hydroxyl group. Then, water dissociates to form a secondary carbocation. Since this carbocation is adjacent to a quaternary center, a 1,2-methyl shift occurs to yield a more stable tertiary carbocation. Finally, a proton is lost from the most substituted β carbon to afford the Zaitsev product.



(b) In this reaction, phosphorus oxychloride converts the hydroxyl group into a good leaving group. Then, an E2 reaction ensues in which pyridine removes a proton from the only β carbon bearing hydrogens.

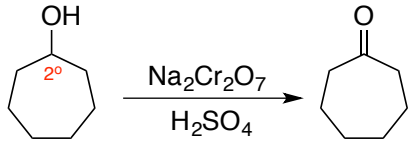


(c) In this sequence, the alcohol is first converted to the tosylate. Then, the bulky base *tert*-butoxide removes a proton from the less hindered β position to generate the Hofmann product.

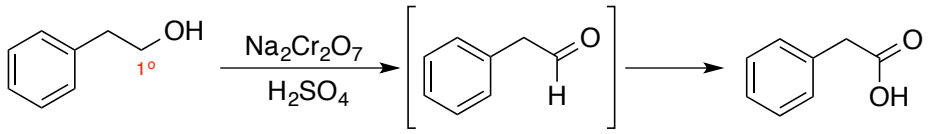


11.

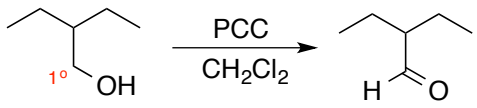
(a) This secondary alcohol is oxidized by chromic acid to the corresponding ketone.



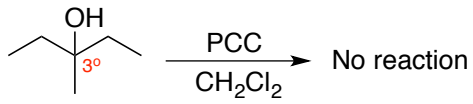
(b) A primary alcohol is oxidized by chromic acid first to the aldehyde and then to the carboxylic acid. The aldehyde cannot be isolated under these conditions.



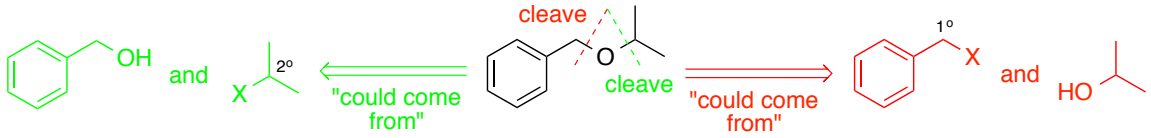
(c) When pyridinium chlorochromate (PCC) is used to oxidize a primary alcohol, the oxidation stops at the aldehyde.



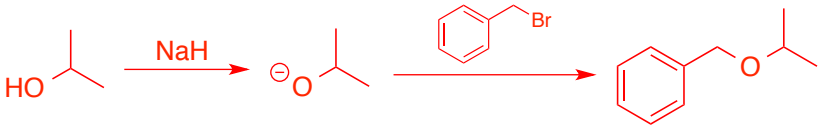
(d) Tertiary alcohols cannot be oxidized without breaking a carbon-carbon bond. These conditions are not strong enough to do that, so there is no reaction.



12. Any Williamson ether synthesis could be approached in one of two ways. However, it is often the case that one method will be more suitable than the other. Either C-O bond of the ether can be disconnected to lead to two possible sets of reactants. Using the green cleavage, the alkyl halide reactant would be secondary. Using the red cleavage, the alkyl halide would be primary. Given that the Williamson ether synthesis involves an S_N2 reaction and that the S_N2 reaction is sensitive to sterics, it is preferable to use the approach (red) that entails the less hindered alkyl halide.

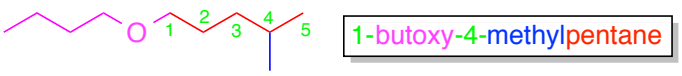


In this approach, isopropyl alcohol is fully deprotonated using a strong base, such as sodium hydride. Then, benzyl bromide is added to the alkoxide. Bromide is displaced in S_N2 fashion, and the desired ether results.



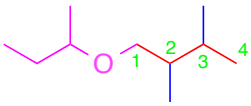
13.

(a) The longest continuous carbon chain is five-carbons in length. Numbering this pentane parent from left to right allows the first substituent to receive the number 1. It is a butoxy group that resides on C1, and methyl group is found at C4.



- Five carbon parent = pentane
- Number so as to give the first substituent the lowest possible number
- Add substituent names and numbers

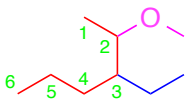
(b) There are two possible four-carbon parents in this molecule, so we choose the one that has more substituents. Numbering from left to right allows the first substituent (*sec*-butoxy) to receive the number 1. There are also methyl groups at C2 and C3.



1-*sec*-butoxy-2,3-dimethylbutane

- Four carbon parent = butane
- Number so as to give the first substituent the lowest possible number
- Add substituent names and numbers

(c) Again, there are two possible six-carbon parents. The one with more substituents is preferred. Numbering from right to left allows us to give the number 2 to the first substituent, which is a methoxy group. There is also an ethyl group at C3.

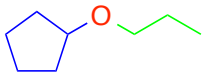


3-ethyl-2-methoxyhexane

- Six carbon parent = hexane
- Number so as to give the first substituent the lowest possible number
- Add substituent names and numbers

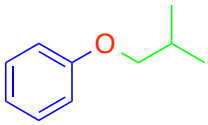
14.

(a) This ether bears a cyclopentyl and a propyl group.



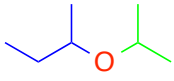
cyclopentyl propyl ether

(b) This ether has a phenyl and an isobutyl group. These names are alphabetized before the word "ether".



isobutyl phenyl ether

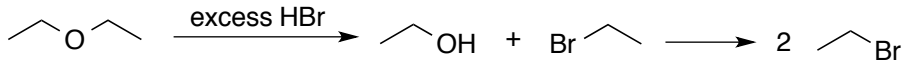
(c) This ether is composed of *sec*-butyl and isopropyl groups. The "*sec*" prefix is not counted toward alphabetization but the "iso" prefix is.



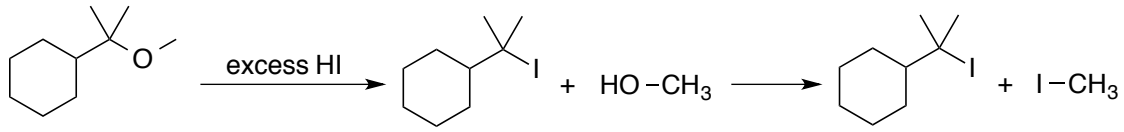
sec-butyl isopropyl ether

15.

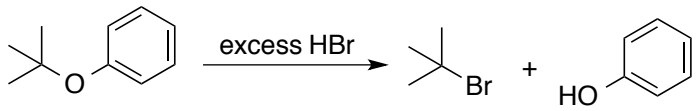
(a) Diethyl ether is first protonated, and then the nucleophilic attack of bromide cleaves off an ethyl group in S_N2 fashion. Ethanol and ethyl bromide result. The molecule of ethanol is then protonated and converted to ethyl bromide via S_N2 reaction as well. Therefore, the final product of the reaction is two equivalents of ethyl bromide. Water is a byproduct.



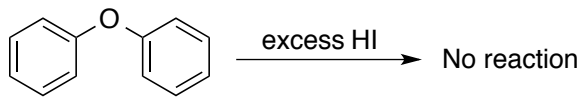
(b) This ether dissociates upon protonation. Methanol departs, leaving behind a tertiary carbocation that is attacked by iodide. This part of the reaction amounts to an S_N1 reaction. The molecule of methanol that was released during the first phase of the reaction is subsequently converted to methyl iodide via protonation and S_N2 reaction. Water is a byproduct here as well.



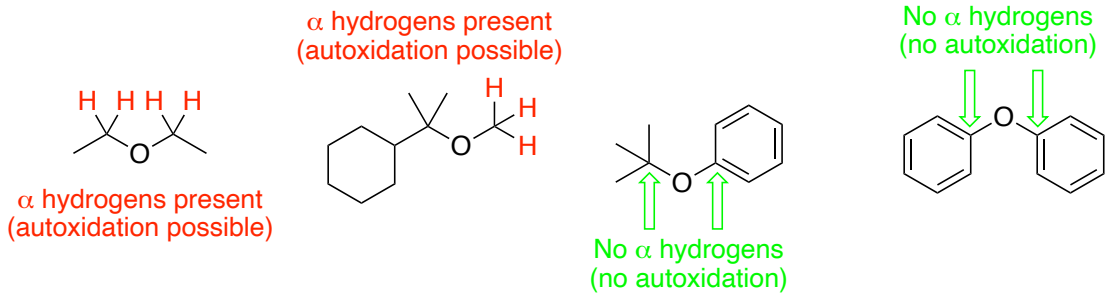
(c) When this ether is protonated, phenol dissociates and leaves behind a tertiary carbocation that is subsequently attacked by bromide. Phenol and the tertiary alkyl bromide are the final reaction products because phenol is unreactive under these conditions. The sp^2 hybridization of the carbon bearing the hydroxyl group prevents it from undergoing S_N1 or S_N2 reaction.



(d) Diphenyl ether is entirely unreactive under these conditions because both of the carbons connected to oxygen are sp^2 hybridized, which makes them ineligible for S_N1 or S_N2 reaction.



16. Autoxidation relies upon abstraction of a hydrogen from the α carbon. Therefore, in order to be susceptible to autoxidation, an ether must have hydrogens in that location.

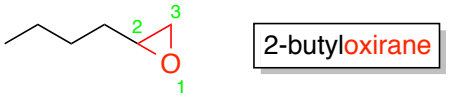


17. Each epoxide can be named as an epoxyalkane or as an oxirane.

(a) For this compound, hexane is the parent. The epoxy group spans carbons 1 and 2.

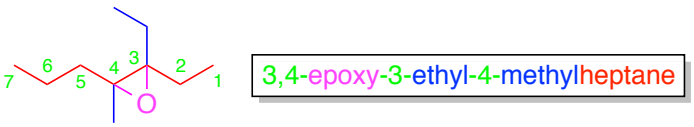
- Six carbon parent = hexane
- Number so as to give the first substituent the lowest possible number
- Add substituent names and numbers

When named as an oxirane, the ring is numbered so as to give the substituent the lower number, making this 2-butyloxirane.



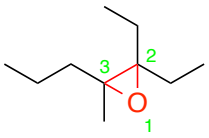
- Parent = oxirane
- Number so as to give the first substituent the lower number
- Add substituent names and numbers

(b) The parent for this compound is heptane. The epoxy group spans carbons 3 and 4, and there are ethyl and methyl substituents as well.



- Seven carbon parent = heptane
- Number so as to give the first substituent the lowest possible number
- Add substituent names and numbers

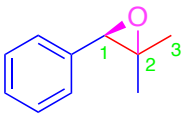
When naming this compound as an oxirane, the substituents will be given the numbers 2, 2, 3, 3 regardless of which direction the numbering goes. Therefore, the tie breaker of last resort is to provide the alphabetically first substituent with the lower number.



2,2-diethyl-3-methyl-3-propyloxirane

- Parent = oxirane
- Since the same substituent numbers are obtained either way, number so that the alphabetically first substituent gets the lower number
- Add substituent names and numbers

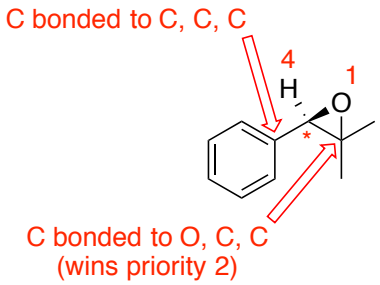
(c) This molecule is a substituted epoxypropane. The propane parent is numbered from left to right so as to give the lowest number to the first substituent.



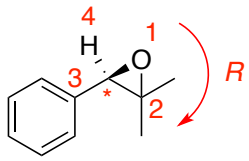
(*R*)-1,2-epoxy-2-methyl-1-phenylpropane

- Three carbon parent = propane
- Number so as to give the first substituent the lowest possible number
- Add substituent names and numbers
- Add stereochemical designation

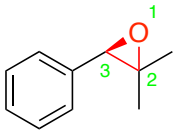
The determination of configuration is probably the most difficult part of the problem. The stereocenter (*) is bonded to oxygen, two carbons, and hydrogen. We can immediately determine that oxygen is priority 1 and hydrogen is priority 4. The two carbons are tied, and that tie must be broken. To do so, we consider the elements to which they are bonded. The carbon of the phenyl group is bonded to C, C, and C; whereas, the right-hand carbon of the epoxide is bonded to O, C, and C, making it the higher priority group of the two.



The lowest priority group faces back, as it should. The arrow from group 1 to group 2 (without passing through group 3) reveals the *R* configuration.



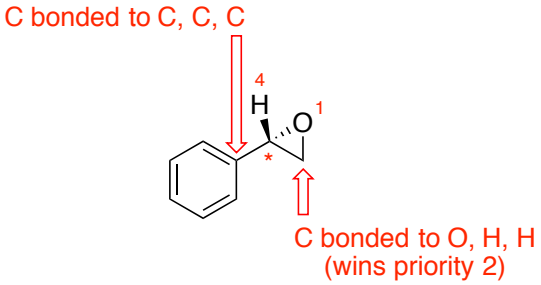
When naming this molecule as a substituted oxirane, the numbering will give the locant 2 to the first substituent regardless of whether it is done clockwise or counterclockwise. To break the tie, we number so as to give the second substituent the lower number.



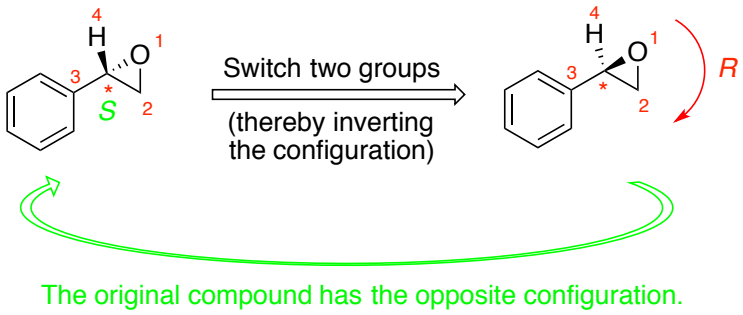
(*R*)-2,2-dimethyl-3-phenyloxirane

- Parent = oxirane
- Number so as to give the first substituent the lower number = tie
- Number so as to give the second substituent the lower number
- Add substituent names and numbers
- Add stereochemical designation

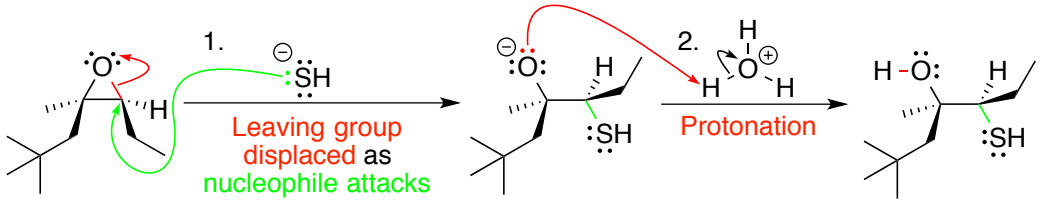
18. Using the common parlance, this compound will be known as styrene oxide; however, we also need to add a stereochemical designation. The stereocenter (*) is bonded to oxygen (priority 1), two carbons (tied for priorities 2 and 3), and hydrogen (priority 4). To break the tie between the two carbons, we note that the carbon of the aromatic ring is bonded to C, C, and C, while the right-hand epoxide carbon is bonded to O, H, and H. The right-hand epoxide carbon has the higher priority substituent, so it wins priority number 2.



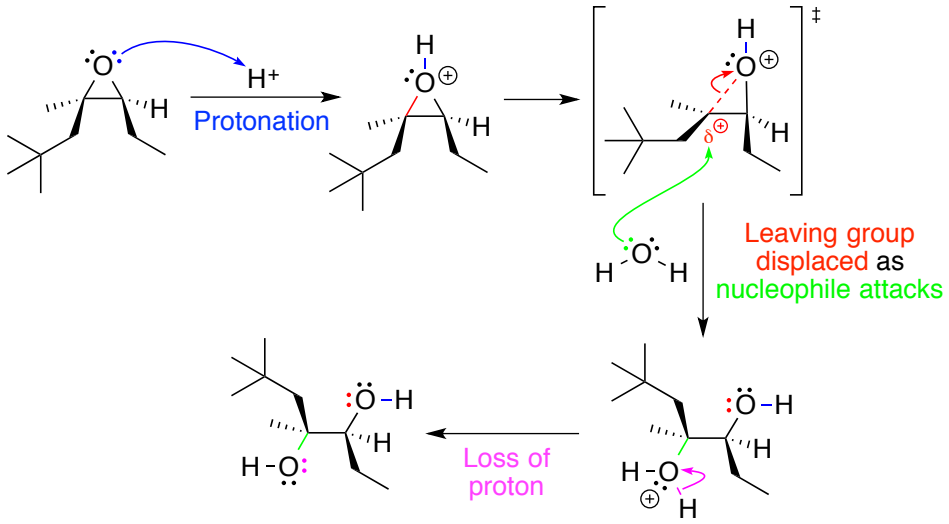
In this case though, the lowest priority group is not facing back as required. We must therefore switch two groups so as to place the hydrogen on the dash. Doing so inverts the configuration of the chiral center. Now, we can assign a configuration of *R*; however, the original compound's configuration was the opposite of this: (*S*). This makes the compound's full common name (*S*)-styrene oxide.



19. This is an opening of an epoxide under basic conditions. In step 1, the strong nucleophile bisulfide ($^-$SH) attacks one of the two epoxide carbons. Since this is an S_N2-style attack, the principal consideration is steric hindrance. The transition state for attack at the less hindered center is lower in energy. The center that undergoes the nucleophilic attack experiences an inversion of configuration; however, the other stereocenter is unaffected by this transformation. In step 2 of the reaction, the alkoxide is simply protonated to yield the final product.

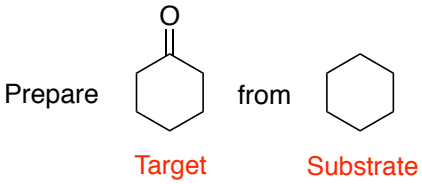


20. This acidic epoxide opening begins with protonation of the epoxide oxygen. The resultant oxonium ion is now more electrophilic than the original epoxide was. This helps to draw in the weak nucleophile. As the alcohol begins to dissociate, a significant δ^+ builds on the more substituted center where it is more stable. Consequently, water is drawn to that site specifically. The mechanism concludes with the loss of a proton from the oxonium ion to yield the neutral vicinal (i.e., neighboring) diol.

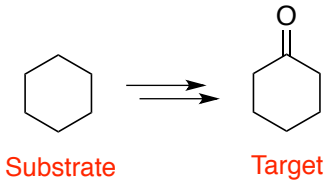


21. For any synthesis problem, it is useful to label the target and the substrate so that we can be clear about what it is exactly that we are trying to make. Students sometimes waste a lot of time on tests attempting to complete a synthesis problem in the wrong direction. In other words, by failing to realize which compound is the target, they may attempt to do the problem in reverse (i.e., trying to make the substrate). This can be a costly error, so it is worth the time to label based on how

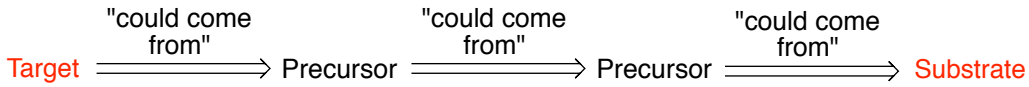
the problem is worded. Since we are asked to prepare the first compound, that is the target.



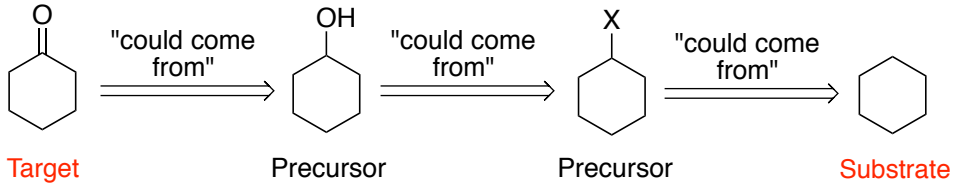
With the target and the substrate accurately labeled, we can now rewrite the problem in a more familiar way, showing how the substrate will be converted to the target through some (as of yet undetermined) number of steps.



In Chapter 7, we learned about retrosynthetic analysis, in which we start with the target and ask ourselves what it could be made from in a single step. We then ask what that compound could be made from in a single step, and this process is repeated until we work our way backwards to an allowable substrate.

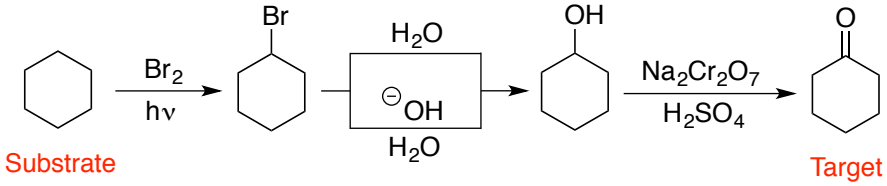


We know that a ketone can be made through the oxidation of the corresponding alcohol. Cyclohexanol, in turn, could be prepared from an alkyl halide via a substitution reaction. Lastly, the cyclohexyl halide can be prepared by the radical halogenation of cyclohexane. Notice that we don't need to work out all of the details (i.e., specific reaction conditions) at this point. We are merely deciding upon a general strategy for preparing the target. This breaks the problem into smaller pieces. Once we have the approach in place, we can turn our attention to choosing the appropriate reagents for the desired conversions.

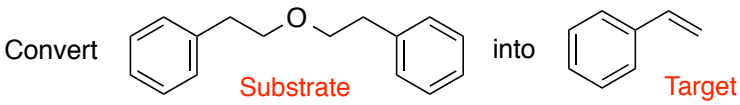


Remember that a retrosynthetic analysis is not a complete answer to the problem. We are not finished until we have written the sequence in the forward direction, specifying all of the conditions to be used. The synthesis begins with the free-radical

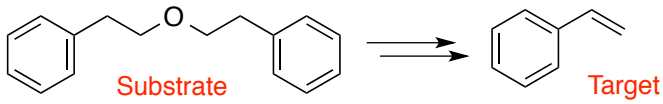
bromination of cyclohexane. This yields cyclohexyl bromide. Cyclohexyl bromide can be converted to cyclohexanol by S_N1 or S_N2 reaction. For S_N1 reaction, we simply add water. For S_N2 reaction, aqueous hydroxide is used. We expect elimination to be a competing reaction when strong base is used, especially since this substrate is secondary, so the S_N1 conditions may be preferable. Finally, cyclohexanol can be oxidized to the target ketone (known as cyclohexanone) using chromic acid prepared from sodium dichromate (or chromium trioxide) and sulfuric acid. Alternatively, PCC oxidation would yield the same product.



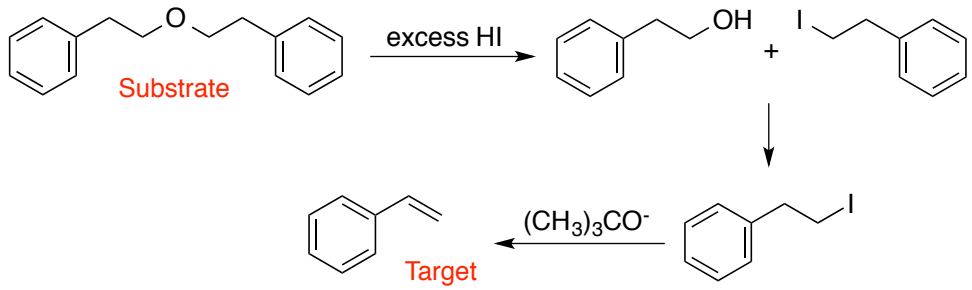
22. Again, it is always wise to begin by labeling the target and the substrate based on the wording of the question. In this case, the problem is worded such that the substrate is shown first.



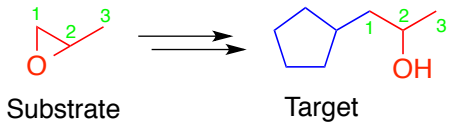
We can rewrite the problem in a more familiar fashion to prevent any confusion.



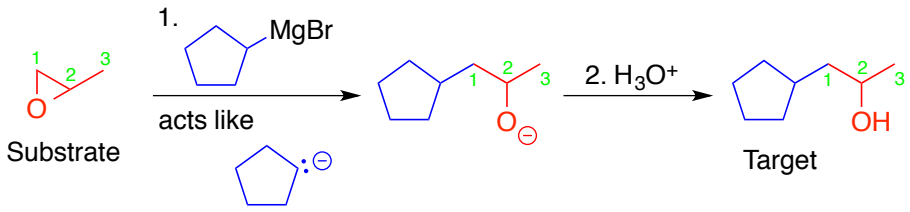
Retrosynthetic analysis is always a useful endeavor in synthesis problems; however, it may not always be strictly necessary. Sometimes the path forward may be clear because the synthesis is brief and/or there are few available reactions of the substrate or an intermediate. In this case, we begin with an ether. We've covered only a limited number of reactions of ethers, and it is pretty clear that we need to cleave the ether into two pieces, which would best be accomplished through acidic cleavage using excess HBr or HI. Two S_N2 reactions ensue since both carbons bonded to oxygen are primary. The first S_N2 reaction cleaves the ether, yielding one equivalent of the alkyl iodide. The second S_N2 reaction converts the alcohol into a second equivalent of the same alkyl halide. Finally, the alkyl halide can be subjected to elimination to afford the alkene. Since there is only one possible elimination product (i.e., there is no choice of regiochemistry between Zaitsev and Hofmann products), we can use a hindered base to minimize any competing and undesired substitution reaction.



23. In this question, we are asked to convert propylene oxide into the target alcohol. The three carbons of propylene oxide can be fairly readily traced to three specific carbons in the target. It is also clear that the epoxide has been opened in the course of the synthesis. The remainder of the target must be introduced as a nucleophile that can open the epoxide. This helps us to determine the structure of the appropriate Grignard reagent.

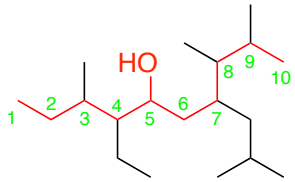


The Grignard reagent acts like a carbanion, which is a strong nucleophile. It therefore attacks the less hindered epoxide carbon (C1) in S_N2 fashion, breaking the C1-O bond and installing the cyclopentyl group on C1. In step 2 of any basic epoxide opening, aqueous acid (or water) is added to protonate the alkoxide. This yields the target alcohol.



24.

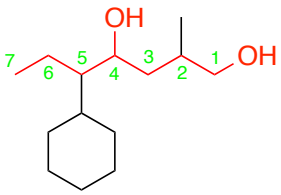
(a) Of the two possible ten-carbon parents, the one shown in red below has more substituents and is therefore the preferred parent. The parent is numbered so as to give the functional group the lowest possible number, regardless of the numbers that the substituents receive. When compiling the final name, remember that iso is one of the few prefixes (cyclo, iso, and neo) that is used in alphabetization.



4-ethyl-7-isobutyl-3,8,9-trimethyl-5-decanol

- Ten carbon parent = decane
- Replace "e" of suffix with "ol"
- Number so as to give the alcohol the lowest possible number
- Add substituent names and numbers

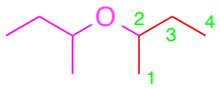
(b) This compound is a diol; however, it is not a vicinal (i.e., neighboring) diol like we saw in several examples when diols were first introduced earlier in this chapter. Nevertheless, the systematic approach to nomenclature is unchanged, and the locants assigned to the two hydroxyl groups reveal that they are not adjacent.



5-cyclohexyl-2-methyl-1,4-heptanediol

- Seven carbon parent = heptane
- Add "diol" suffix to indicate two alcohols
- Number so as to give the first alcohol the lowest possible number
- Add substituent names and numbers

(c) This symmetrical ether would often be termed di-*sec*-butyl ether (or simply *sec*-butyl ether). However, its systematic name is derived by selecting one of the two equivalent alkyl groups as the parent chain. The *sec*-butoxy group is treated as a substituent on C2 of the butane parent.



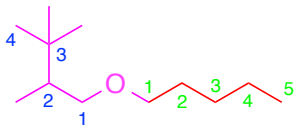
2-*sec*-butoxybutane

- Four carbon parent = butane
- Number so as to give the substituent the lowest possible number
- Add substituent names and numbers

(d) The longest continuous carbon chain is the parent. Even though the left-hand alkyl group has more carbons total, it has only a four-carbon continuous chain. Therefore, it is the right-hand alkyl group with a continuous five-carbon chain that is selected as the parent. This pentane parent is numbered so as to give the only substituent, which in this case is a complex alkoxy substituent, the lowest possible number.

The substituent on C1 of the parent must be given a name according to our rules for complex substituents. The carbons of the substituent are numbered with C1 being the carbon closest to the parent. The longest continuous chain within the

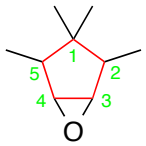
substituent is four-carbons in length. Since the substituent is an alkoxy group, it is termed butoxy specifically. On this butoxy group, there are three methyl groups at locations 2, 3, and 3. This makes the entire complex substituent a 2,3,3-trimethylbutoxy group. This group resides at C1 of the parent, allowing us to finalize the name.



1-(2,3,3-trimethylbutoxy)pentane

- Five carbon parent = pentane
- Number so as to give the substituent the lowest possible number
- Add substituent names and numbers

(e) In this case, it is much more straightforward to name the epoxide as an epoxycycloalkane, rather than as a substituted oxirane. No matter how we number the parent, the first substituent gets the locant 1. Therefore, we break the tie by selecting the numbering method that gives the lowest number to the second substituent. This identifies the carbon bearing two methyl groups as C1. Numbering clockwise or counterclockwise yields the same result. There are four methyl groups, and each one needs a locant. Additionally, the epoxy group spans carbons 3 and 4.

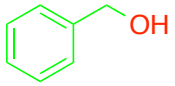


3,4-epoxy-1,1,2,5-tetramethylcyclopentane

- Five carbon, cyclic parent = cyclopentane
- Number so as to give the first substituent the lowest possible number = tie
- Number so as to give the second substituent the lowest possible number
- Add substituent names and numbers

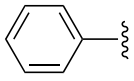
25.

(a) The common name for an alcohol places the name of the alkyl group (benzyl) before the word alcohol.

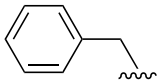


benzyl alcohol

It's important to remember the difference between benzyl and phenyl groups, which are often confused. The phenyl group entails benzene as a substituent, while the benzyl group includes the benzene ring and one additional carbon.

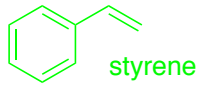


phenyl

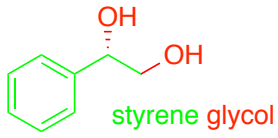


benzyl

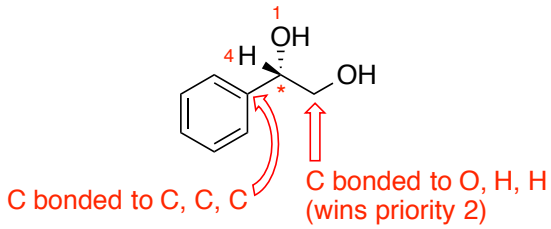
(b) In Problem 18, we learned the name of the alkene known as styrene.



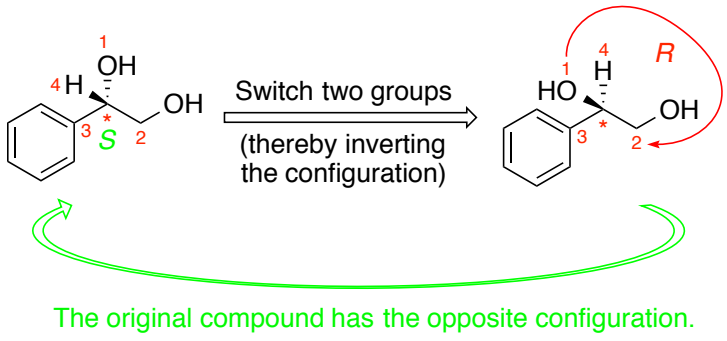
This diol is a glycol (i.e., a vicinal or neighboring diol) derived from styrene, so it can be called styrene glycol.



However, that is not sufficient to name this compound because a stereochemical designation is necessary. The stereocenter (*) is bonded to oxygen (priority 1), two carbons (tied for priority 2 and 3), and hydrogen (priority 4). The carbon bonded to oxygen wins the higher priority of 2.

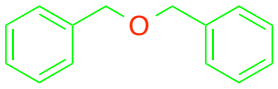


In this instance, the lowest priority group is not positioned on the dash as it needs to be when assigning configuration. Therefore, we must switch two groups in order to place it on the dash. Remember that this inverts the configuration, and that must be taken into account when we determine our final answer. After having switched two groups to put the hydrogen on the dash, the arrow from 1 to 2 without passing through 3 shows the *R* configuration. However, the original compound had the opposite configuration: *S*.



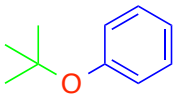
Therefore, the complete common name of this molecule is (*S*)-styrene glycol.

(c) This symmetrical ether has two benzyl groups bonded to the oxygen atom, so it can be called dibenzyl ether. It may also sometimes be termed benzyl ether, although this is somewhat less proper.



dibenzyl ether

(d) This unsymmetrical ether possesses both a *tert*-butyl and a phenyl group. Remember that the prefix *tert* is not one of the prefixes used in alphabetization (cyclo, iso, and neo), so the common name places *tert*-butyl before phenyl.



tert-butyl phenyl ether

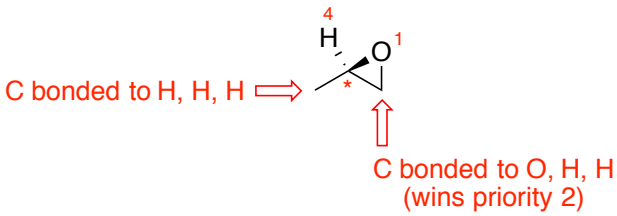
(e) In the section on diol nomenclature, we were introduced to the common names of two small alkenes, one of which was propylene.

propylene

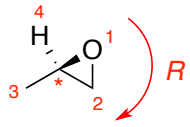
The common name of an epoxide places the name of the alkene from which the epoxide can be made before the word "oxide," making this propylene oxide.

propylene oxide

However, we also need a stereochemical designation to complete the name. The stereocenter (*) is bonded to oxygen (priority 1), two carbons (tied for priority 2 and 3), and hydrogen (priority 4). The carbon bonded to oxygen wins the higher priority of 2.



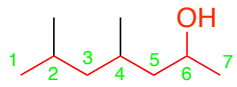
The hydrogen atom is positioned on the dash as it needs to be in order to assign the configuration correctly. The arrow from priority 1 to 2 without passing through 3 reveals the configuration to be *R*.



Therefore, the complete name of this substance is (*R*)-propylene oxide.

26.

(a) We can begin by drawing the structure suggested by this name. Draw a seven-carbon chain first. Then, number it, and place the substituents and the hydroxyl group at the locations indicated.

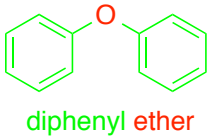


Having done so, we realize that the parent was numbered so as to give the first substituent the lowest possible number. This is incorrect. The parent should be numbered so as to give the functional group the lowest possible number, making this compound 4,6-dimethyl-2-heptanol.

(b) Glycols are vicinal (or neighboring) diols; however, the hydroxyl groups are not on adjacent carbons in this structure. Consequently, it should not be termed a glycol. Instead, we can use a systematic name: 1,3-propanediol.

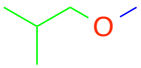
- Three carbon parent = propane
- Add "diol" suffix to indicate two alcohols
- Number so as to give the first alcohol the lowest possible number: same result either way

(c) As we discussed in the answer to Problem 25(a), the benzyl group includes the benzene ring and one additional carbon. Therefore, the phenyl groups of this ether have been misidentified as benzyl groups. The correct name is diphenyl ether.



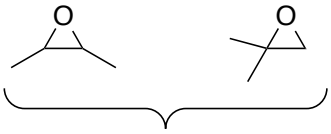
(d) There are two errors in this name. The isobutyl group has been misidentified as *sec*-butyl. Additionally, the alphabetization was done incorrectly because the prefix *sec* is not counted; therefore, *sec*-butyl should appear before methyl. This, however,

becomes irrelevant when the four-carbon alkyl group is correctly identified. This unsymmetrical ether is named isobutyl methyl ether.



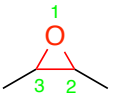
isobutyl methyl ether

(e) Without locants, we cannot distinguish the following two compounds.



Both are dimethyloxiranes

We must therefore provide numbers to identify the locations of the two methyl groups.

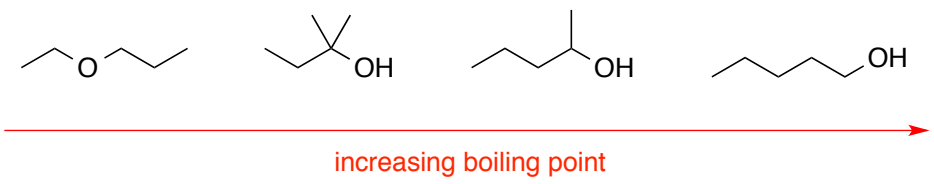


2,3-dimethyloxirane

- Parent = oxirane
- Oxygen is position 1
- Number so as to give the first substituent the lower number: same result either way
- Add substituent names and numbers

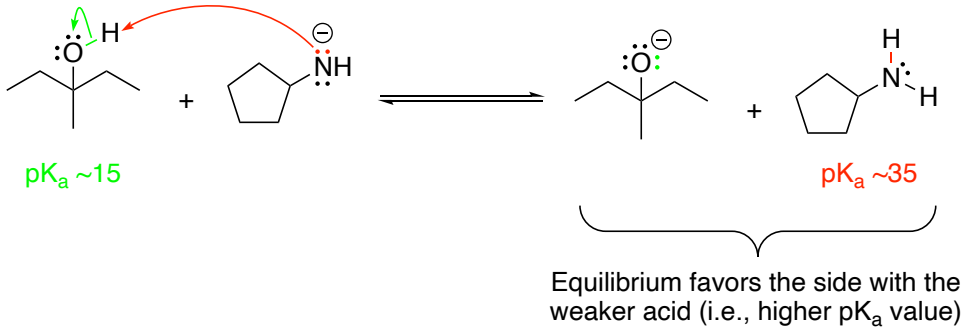
27. Since these molecules are isomers, they all have the same molecular formula. Any differences in boiling point will stem from differences in intermolecular forces. The ether can only serve as a hydrogen bond acceptor. Therefore, in a neat (i.e., pure) sample no hydrogen bonding will take place. The absence of this strong intermolecular force leads to the lowest boiling point of the four isomers.

All of the alcohols possess hydrogen bonding. However, as the steric hindrance around the hydroxyl group increases, we expect to see a decrease in hydrogen bonding take place. Therefore, the tertiary alcohol exhibits the least hydrogen bonding and has the second lowest boiling point. The secondary and primary alcohols have progressively higher boiling points due to the reduced hindrance around the site where hydrogen bonding occurs.



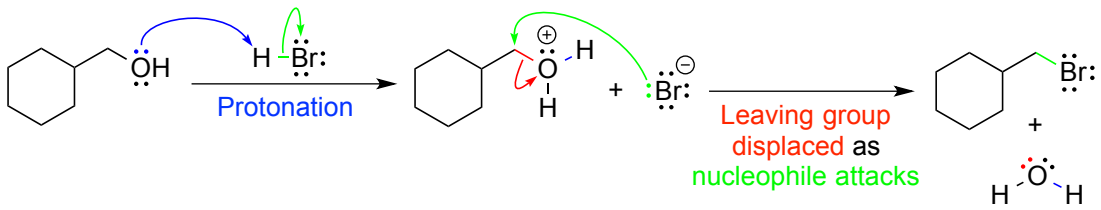
28. This Brønsted-Lowry acid-base reaction entails the transfer of a proton from the hydroxyl group to the nitrogen anion. The products that result are an alkoxide and an amine.

Equilibrium favors the side with the weaker acid, which possesses the higher pK_a value. So, the products are favored at equilibrium. Furthermore, the products are favored by 10 to the difference in the pK_a values, or 10^{20}.

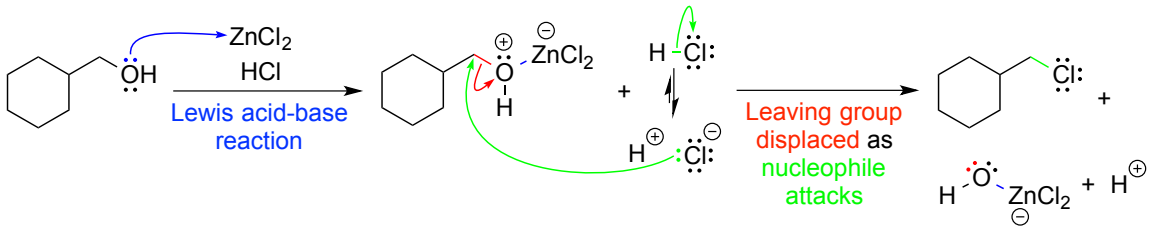


29.

(a) The reaction with HBr begins with the protonation of the alcohol, which transforms it into a good leaving group. Bromide subsequently attacks the carbon bearing the good leaving group because this center is primary and therefore unhindered. This S_N2 reaction expels water and establishes the C-Br bond found in the product.

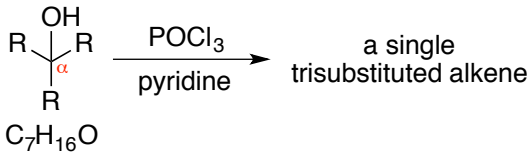


(b) When the Lucas reagent is added to this primary alcohol, the hydroxyl group attacks the Lewis acid, $ZnCl_2$. The resulting Lewis acid-base complex represents a very good leaving group. The unhindered primary carbon is attacked by chloride, and this S_N2 reaction displaces the leaving group while simultaneously installing the C-Cl bond found in the product.

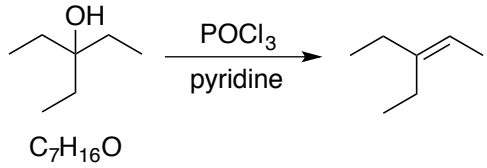


Both of the above mechanisms follow the same pattern of: (1) conversion of the alcohol into a good leaving group followed by (2) S_N2 reaction with a halide. The difference stems from the weaker nucleophilicity of chloride. It is a smaller, less polarizable anion, and as a result, it is a weaker nucleophile than bromide. To compensate for the weaker nucleophilicity of chloride the electrophile must be stronger. The addition of the Lewis acid, $ZnCl_2$, leads to the formation of a more potent electrophile, which allows for successful reaction even when the halide nucleophile is weaker.

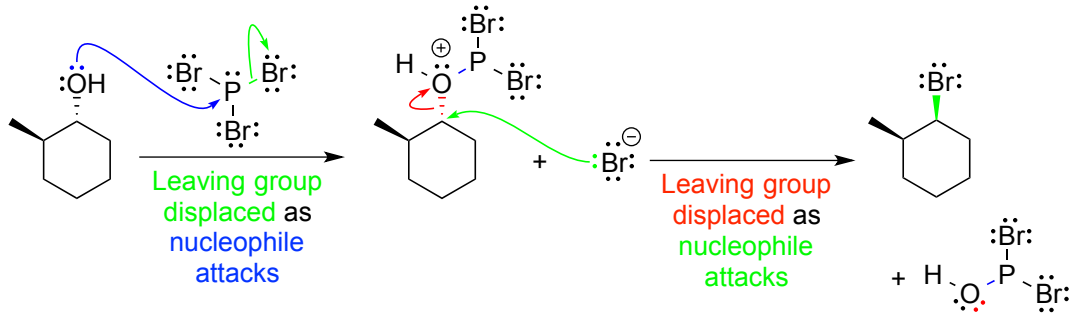
30. Let's begin by sketching out the information that we've been given. We are told that the alcohol reactant is tertiary. Additionally, we know that dehydration of this alcohol yields a single trisubstituted alkene.



Given that there are three alkyl groups surrounding the α carbon, the easiest way to ensure that a single alkene is formed upon dehydration is to make the alcohol symmetrical.

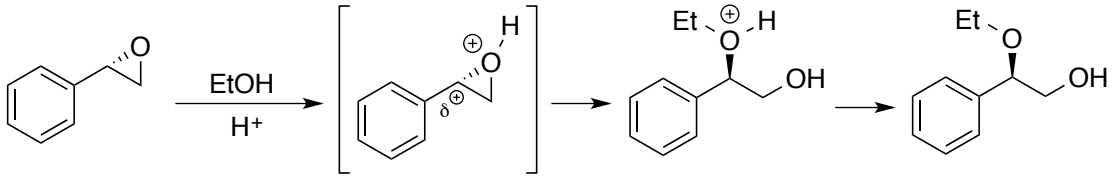


31. The reaction begins with the attack of the hydroxyl group on the electrophilic phosphorus of PBr_3. Phosphorus is rendered electron deficient by the electron-withdrawing effect of the bromine atoms, one of which is displaced as bromide during the attack. With the alcohol now activated as a good leaving group, the attack of bromide on the substrate expels this leaving group in S_N2 fashion. The configuration of the reactive center is inverted during the process, but notice that the configuration of the other chiral center in the molecule is unaltered because that center was uninvolved in the transformation.

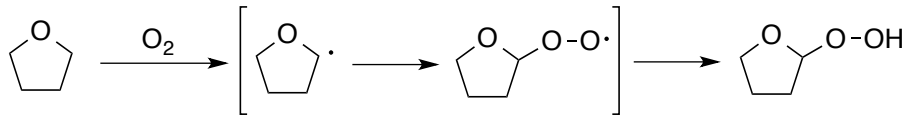


32.

(a) In this acidic epoxide opening, the epoxide oxygen is first protonated. The more substituted epoxide carbon bears a larger partial positive charge (δ^+) and therefore draws in the weak nucleophile, ethanol, from the side opposite the leaving group. Finally, the loss of a proton affords the hydroxyether product.

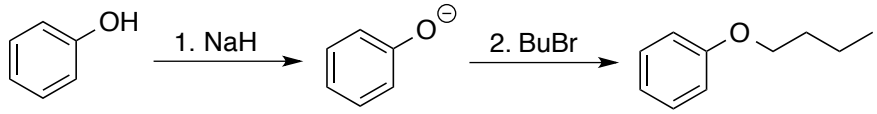


(b) In this autoxidation, a cyclic ether known as tetrahydrofuran (or THF) is converted to a radical at the α carbon. Addition of oxygen to this radical yields a peroxy radical, which abstracts a hydrogen from another molecule of ether to yield the hydroperoxide.



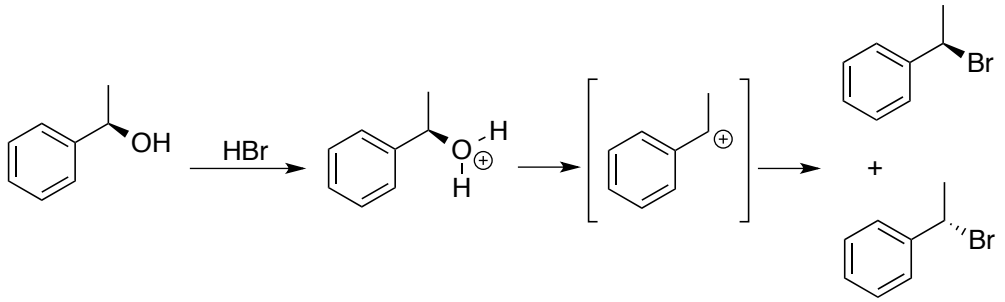
Remember that hydroperoxide formation can lead to laboratory explosions. THF is a common laboratory solvent, so bottles of THF should be checked for peroxides prior to use, especially if they are old.

(c) In this Williamson ether synthesis, phenol is first deprotonated totally by the strong base sodium hydride (NaH). Then, the phenolate attacks the electrophilic carbon of butyl bromide. This S_N2 reaction results in the formation of an ether.

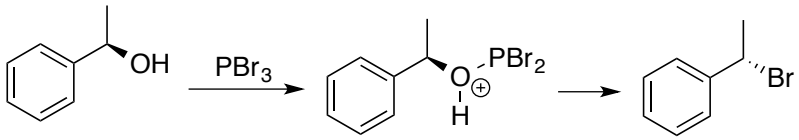


Alternatively, we could have used a weaker base, such as hydroxide, in step 1 because phenols ($pK_a \sim 10$) are much more acidic than alcohols ($pK_a \sim 16$).

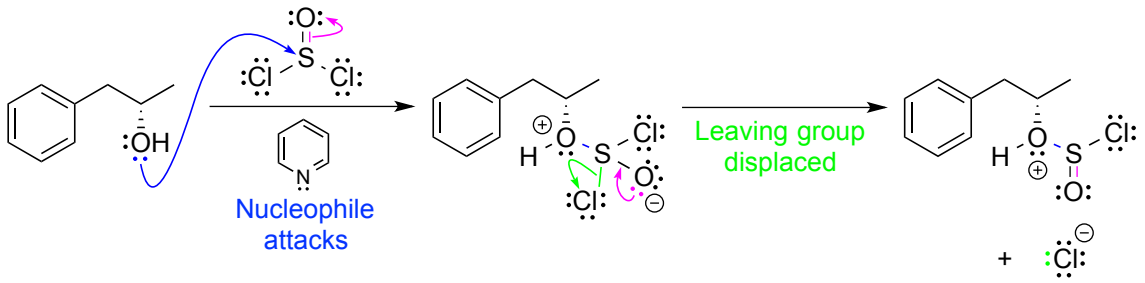
(d) The alcohol is protonated by the strong acid. Since this is a secondary alcohol, the dissociation of water follows. A secondary, benzylic carbocation is generated in the process. Bromide can add to this carbocation from either side to generate a racemic mixture of enantiomeric products.



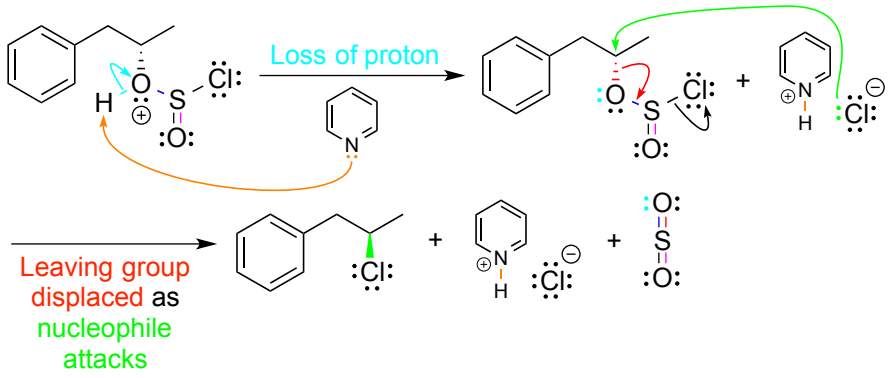
(e) When the same substrate is subjected to PBr_3, the outcome differs. The hydroxyl group attacks PBr_3, displacing a bromide. Then, bromide attacks the carbon bearing the leaving group to yield the product. Since this is an S_N2 process, the configuration is inverted, and only a single enantiomer is produced.



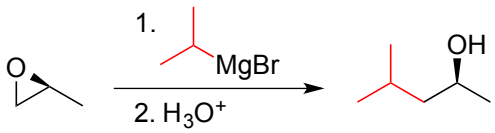
33. This reaction begins with the attack of the hydroxyl group on the electrophilic sulfur of thionyl chloride. This sulfur atom is electrophilic due to the electron-withdrawing effect of the atoms to which it is bonded. During the attack, the π bonding electrons between sulfur and oxygen are displaced onto oxygen. The intermediate thus formed then "collapses" to expel chloride while the sulfur-oxygen π bond is re-formed.



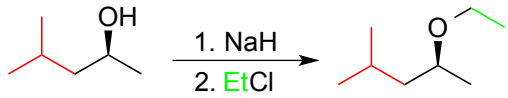
Pyridine, acting as a non-nucleophilic base, then removes a proton from the oxonium ion. The net effect of the mechanistic steps to this point has been the conversion of the hydroxyl group from a poor leaving group into a good one. Consequently, chloride is now able to attack and displace this leaving group via an S_N2 reaction. The electrons of the breaking C-O bond fall between sulfur and oxygen to form the second π bond of sulfur dioxide as chloride is displaced from within the leaving group. Notice that the configuration of the stereocenter was inverted during this final step since it was an S_N2 process.



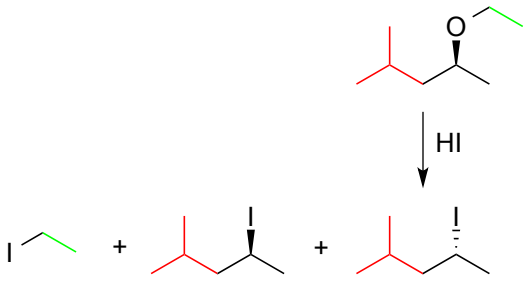
34. The sequence begins with the preparation of an alcohol using a Grignard reagent. In Problem 23, we learned that these reagents act essentially as carbanions and that they can be used to open epoxides under basic conditions. Attack of a Grignard reagent on (*S*)-propylene oxide would occur at the less hindered terminal carbon. The chirality of the stereocenter would be unaffected by the ring-opening reaction since the chiral center itself is not mechanistically involved in the transformation.



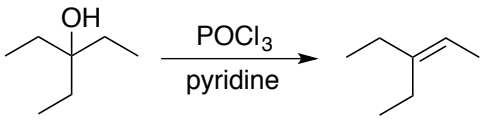
In the next step, a Williamson ether synthesis converts the alcohol into the corresponding ethyl ether.



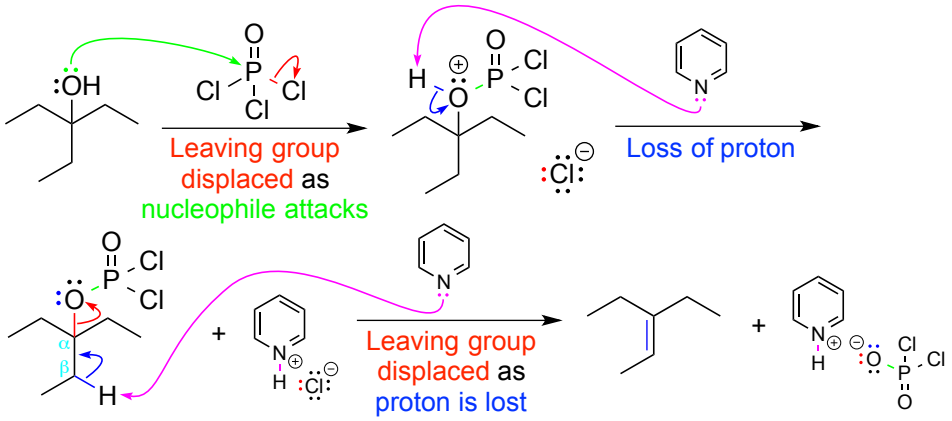
Lastly, acidic cleavage of this ether results in three products: both enantiomers of the secondary alkyl iodide, as well as ethyl iodide. The secondary center undergoes an S_N1 reaction during the ether cleavage. This leads to carbocation formation and, as a result, racemization.



35. The dehydration conducted in Problem 30 is as follows.

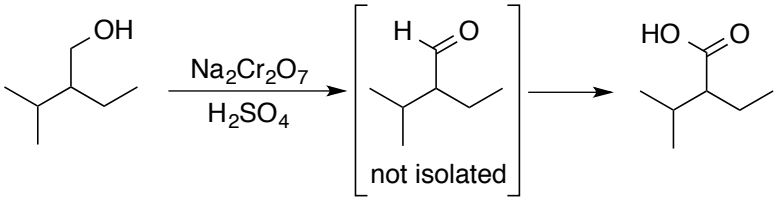


This reaction begins with the attack of the hydroxyl group on the electrophilic phosphorus of $POCl_3$. A chloride is expelled in the process. Pyridine subsequently removes a proton from the oxonium ion. Then, a second molecule of pyridine removes a proton from any one of the three equivalent β positions. The alkene π bond is formed as a result, and the leaving group is displaced from the α carbon.

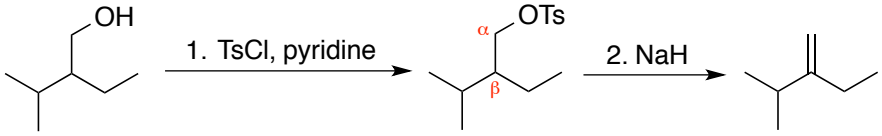


36.

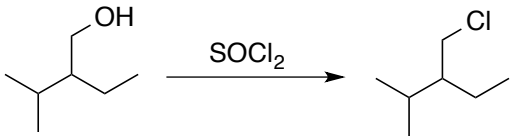
(a) This primary alcohol is oxidized by chromic acid, first to the aldehyde and then to the carboxylic acid.



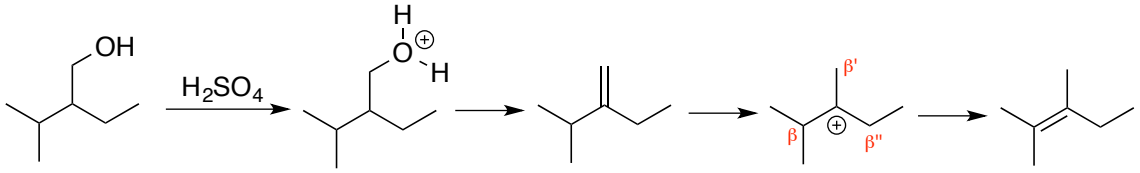
(b) In this reaction, the alcohol is first converted to the tosylate, which is a good leaving group. Then, sodium hydride is added. This non-nucleophilic base removes a proton from the only β position to afford the alkene product.



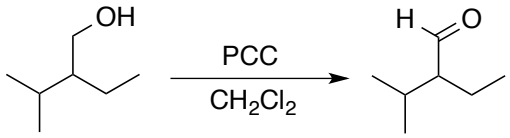
(c) Thionyl chloride effects the conversion of the alcohol into an alkyl chloride.



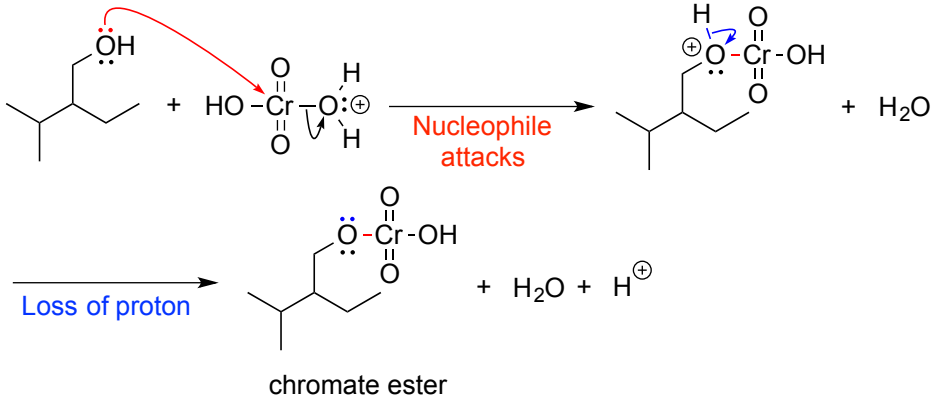
(d) In this dehydration, the alcohol is protonated, and the good leaving group (water) is then lost concurrently with a β proton in an E2 elimination. This initially yields the same alkene as in part (b). However, π bonds can act as bases. The π bond is protonated by the strong acid present in this reaction. The alkene could be protonated in one of two ways, but the protonation leading to the more stable tertiary carbocation prevails. This tertiary carbocation then loses a proton from the most substituted β position to yield the Zaitsev alkene.



(e) When treated with pyridinium chlorochromate (PCC), this primary alcohol is oxidized to the aldehyde. Oxidation stops at this stage due to the absence of water in this reaction. Compare the outcome of this reaction to that of part (a).

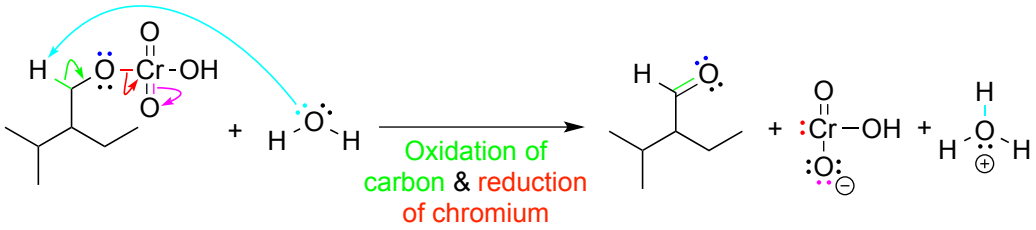


37. The first phase of the mechanism entails the formation of a chromate ester. This occurs when the alcohol attacks a protonated molecule of chromic acid and subsequently loses a proton.

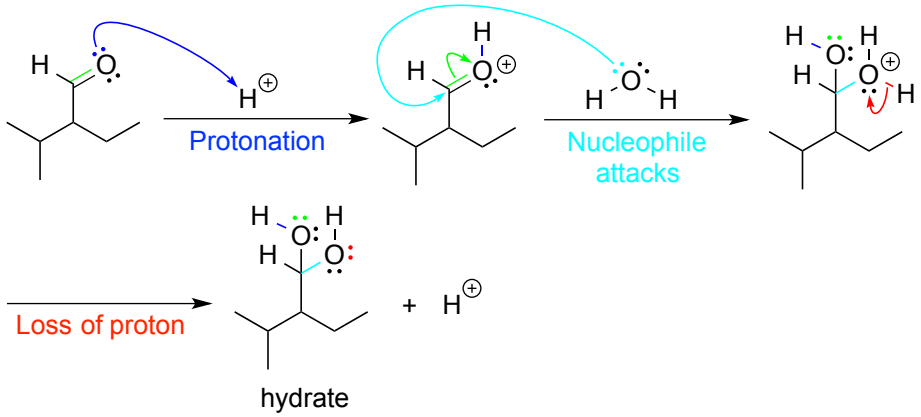


The redox process then occurs when the chromate ester loses a proton from the α carbon. The electrons from the breaking C-H σ bond form the π bond of the

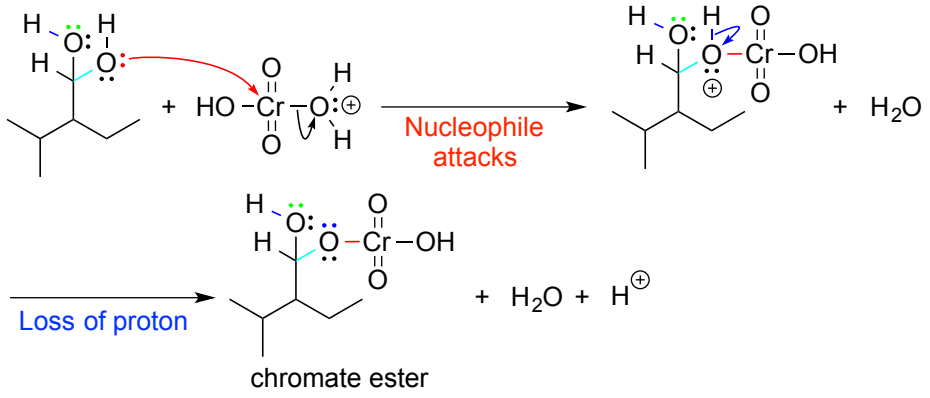
carbonyl. The O-Cr σ bond breaks as a result, and those electrons flow onto chromium, thereby reducing it. To place the formal negative charge on an electronegative element, a chromium-oxygen π bond is pushed onto oxygen.



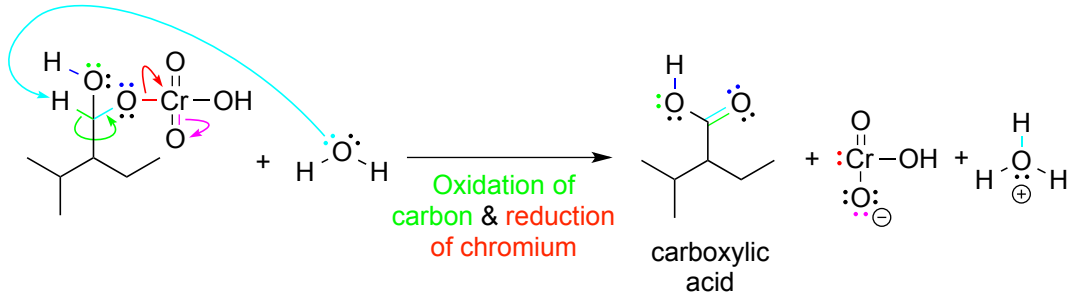
Although this step yielded an aldehyde, it is not the end of the reaction. The aldehyde is susceptible to hydrate formation in aqueous acid, and the hydrate may then be further oxidized to the carboxylic acid. Therefore, the next phase of the mechanism is hydrate formation. It begins with protonation of the carbonyl oxygen. With the electrophilicity of the carbonyl thus enhanced, water attacks the carbonyl carbon and subsequently sheds a proton. The hydrate results.



In the last major segment of the mechanism, the hydrate is oxidized to the carboxylic acid. This process begins with the formation of a new chromate ester. One of the two equivalent geminal hydroxyl groups attacks a protonated molecule of chromic acid. A proton is then lost from the oxonium ion to yield the chromate ester.

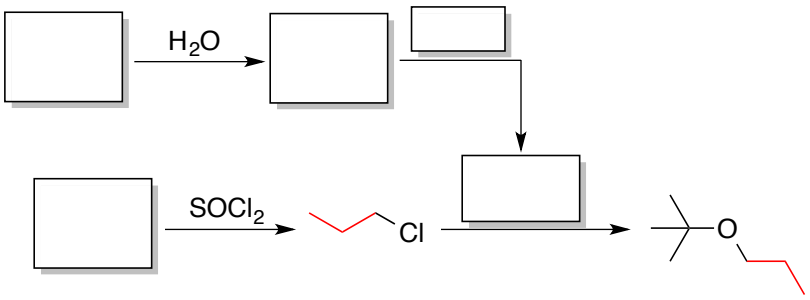


Finally, the second redox process occurs to yield the acid. The sequence of arrows is highly analogous to that found in the first redox. A proton is lost from the α carbon. The electrons from the breaking C-H σ bond become the new carbonyl π bond. As this occurs, the O-Cr σ bond breaks. Those electrons flow onto chromium and reduce it. The electrons from a chromium-oxygen π bond then move onto oxygen to place the formal negative charge on the electronegative oxygen atom.

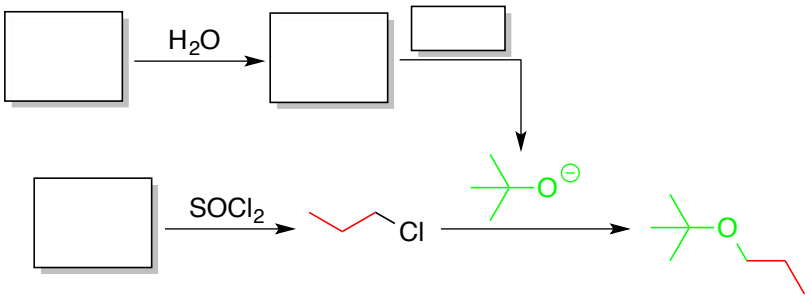


With a long mechanism such as this, it is often helpful to reflect on the sequence of mechanistic phases. This condenses the narrative of the mechanism in a way that makes it much easier to remember and recreate. For this reaction, that sequence was: chromate ester formation, redox, hydrate formation, chromate ester formation, redox.

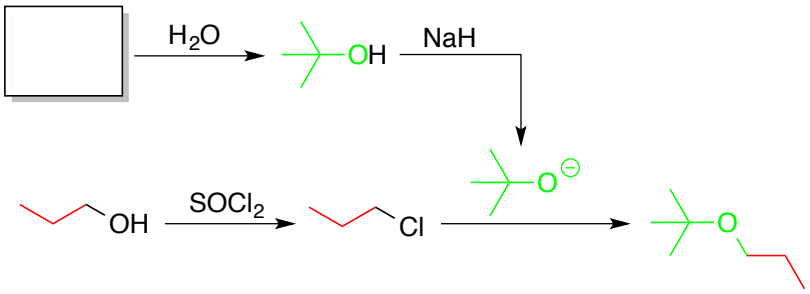
38. We are given relatively little information in this problem, but it is more than enough to fill in the blanks. We may be best served by working backwards from the final product, which is an ether. We've learned that ethers may be synthesized using the Williamson ether synthesis, in which an alkyl halide is attacked in S_N2 fashion by an alkoxide derived from an alcohol. Since this is an S_N2 reaction, it is sensitive to sterics, and the alkyl halide should therefore be unhindered. This allows us to deduce that a propyl halide is one of the precursors to the product. It is easy to see how propyl chloride could be the product of a reaction using thionyl chloride, so we know where to place this structure in the scheme.



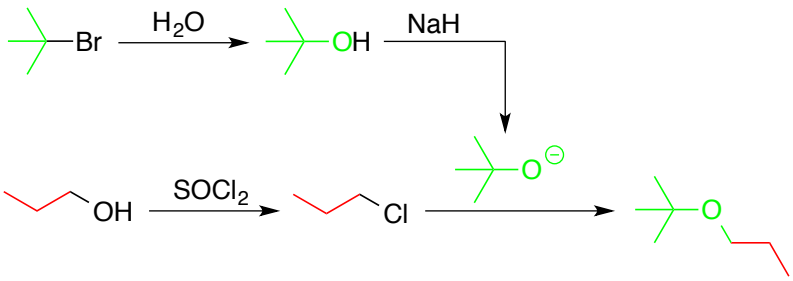
The alkoxide needed to make this ether is *tert*-butoxide, so we can place it as well.



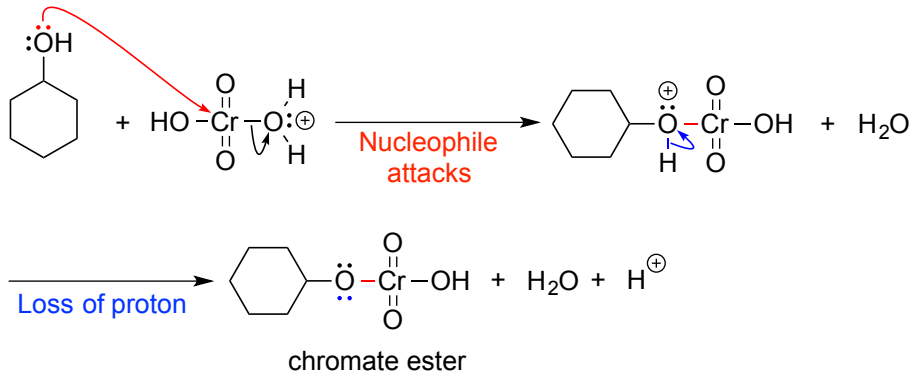
Now, we can start to work backwards toward the original reactants. Propyl chloride would be prepared from propyl alcohol using thionyl chloride. Additionally, *tert*-butoxide can be generated from *tert*-butyl alcohol using a strong base, such as sodium hydride.



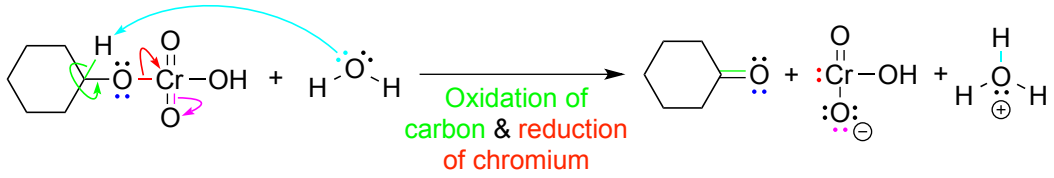
Finally, *tert*-butyl alcohol could be prepared from a *tert*-butyl halide via S_N1 reaction when treated with water.



39. The chromic acid oxidation of a secondary alcohol, like cyclohexanol has only two stages: chromate ester formation and redox. The chromate ester is formed when the alcohol attacks a protonated molecule of chromic acid and then sheds a proton.

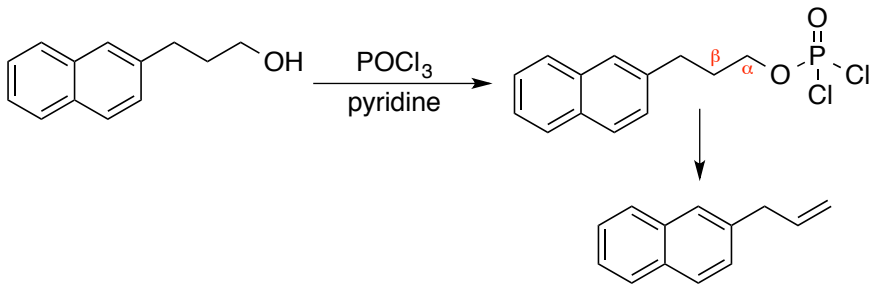


The redox process follows when a proton is lost from the α position. The electrons in the breaking C-H σ bond become the π bonding electrons of the carbonyl. The O-Cr σ bond cleaves, and these electrons flow onto chromium, thereby reducing it. To place the formal negative charge on an electronegative element, the electrons of a chromium-oxygen π bond are pushed onto oxygen.



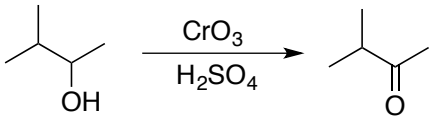
40.

(a) In this dehydration, the hydroxyl group is first activated as a good leaving group by reaction with phosphorus oxychloride. An E2 reaction follows, in which pyridine removes a proton from the only β position, yielding a monosubstituted alkene product.



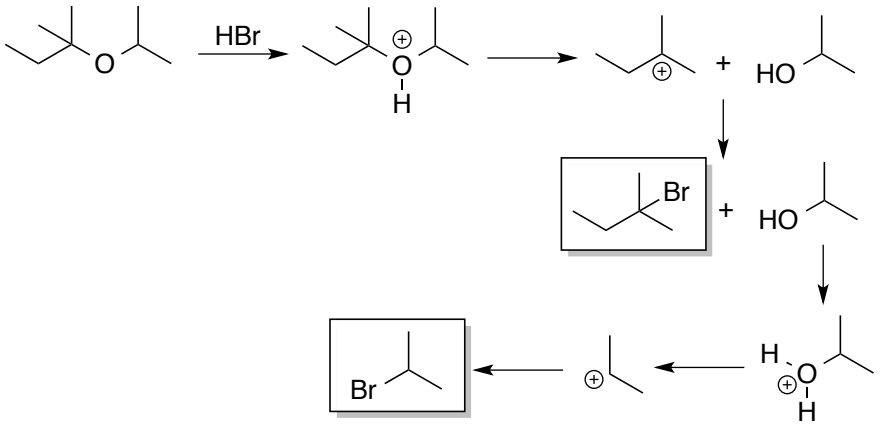
(b) Chromium trioxide and sulfuric acid are used to prepare chromic acid *in situ*. Chromic acid oxidizes this secondary alcohol to the ketone, and no further oxidation

is possible because it would necessitate cleaving carbon-carbon bonds, which is difficult to do.

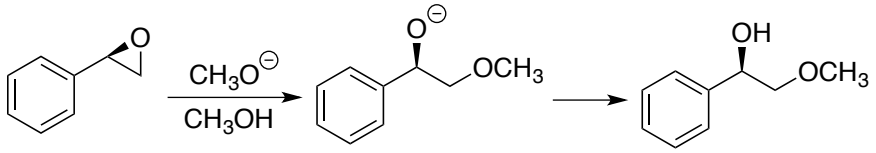


(c) This acidic ether cleavage begins with protonation of the ether oxygen. Isopropyl alcohol then dissociates from the tertiary center to generate a carbocation, which is subsequently attacked by bromide to yield one of the products: 2-bromo-2-methylbutane.

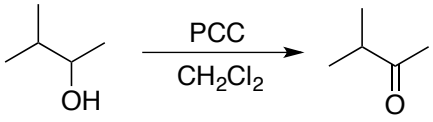
Isopropyl alcohol is subject to further reaction. It is protonated, and the dissociation of water forms a secondary carbocation, which is attacked by bromide to form the other product: isopropyl bromide.



(d) In this basic epoxide opening, methoxide attacks the less hindered, terminal epoxide carbon, opening the ring and generating an alkoxide. The alkoxide then removes a proton from methanol (the solvent) to afford the neutral hydroxyether product.

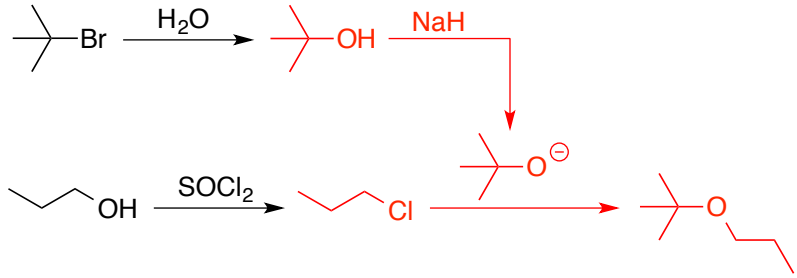


(e) The gentle oxidizing agent PCC oxidizes this secondary alcohol to the ketone.

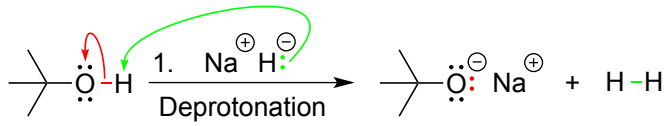


Compare this answer to that for part (b) above. Chromic acid and PCC give different products when primary alcohols are oxidized. However, in the case of secondary alcohols, they yield the same oxidation product.

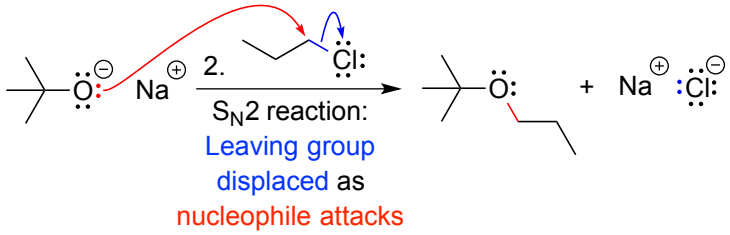
41. The synthetic sequence used in Problem 38 is shown below with the Williamson ether synthesis highlighted in red.



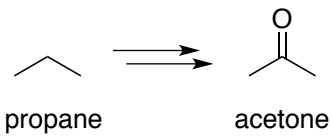
The reaction begins with the deprotonation of *tert*-butoxide using sodium hydride. Hydride (H:$^-$) removes the proton from the alcohol, and the O-H σ bonding electrons fall onto oxygen as a lone pair. Hydrogen gas (H_2) is evolved as a byproduct, and the sodium alkoxide is generated.



When the alkoxide is mixed with propyl chloride, it attacks the electrophilic carbon and displaces chloride.

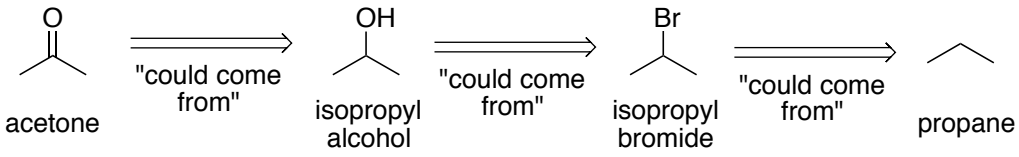


42. In this problem, we are asked to convert propane into acetone.



A retrosynthetic analysis can be a useful way of brainstorming. Right now, we know only one method for the preparation of ketones: oxidation of a secondary alcohol. This suggests that acetone could be prepared from isopropyl alcohol. While isopropyl alcohol cannot be made directly from propane, it could be made from an

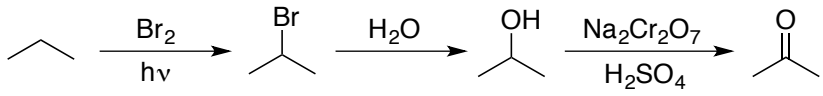
isopropyl halide via a substitution reaction. Isopropyl bromide, in turn, can be made from propane by free radical halogenation.



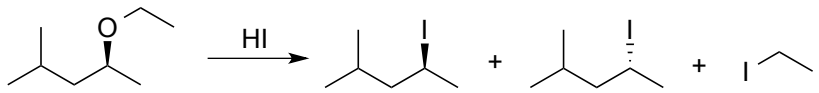
The synthesis begins with the free radical halogenation of propane. As we learned in Chapter 6, bromination is more selective than chlorination, so it is a better choice for this transformation and will yield almost exclusively the secondary alkyl bromide.

Then, isopropyl bromide can be converted into isopropyl alcohol via S_N1 or S_N2 reaction. Either method would be acceptable. To minimize the side products associated with competing elimination when strong base is used, we could select S_N1 conditions (H_2O).

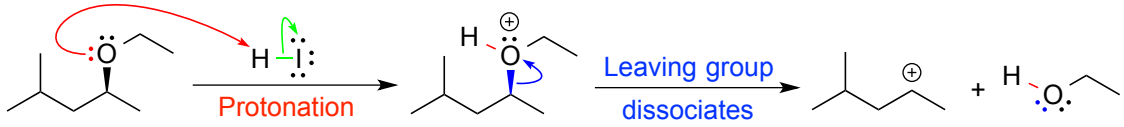
Finally, oxidation yields the target product. This oxidation can use chromic acid (prepared from sodium dichromate or chromium trioxide and sulfuric acid) or PCC. Either will give the same result since the alcohol is secondary and can therefore be oxidized no further than the ketone.



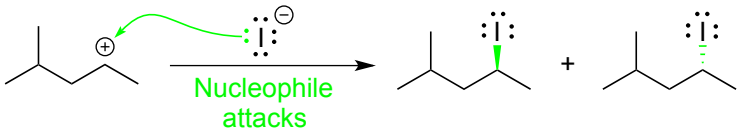
43. The last step of the sequence in Problem 34 is the acidic cleavage of the following ether, which yields three products.



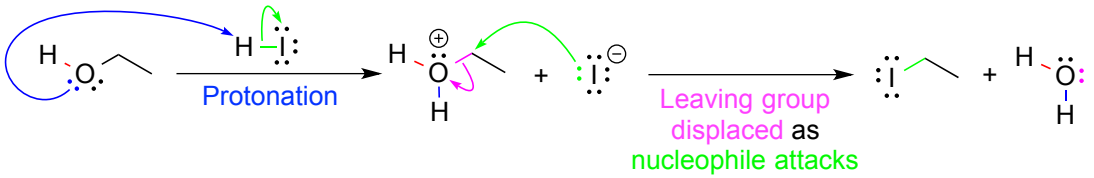
The mechanism begins with protonation of the ether oxygen. Ethanol then dissociates from the secondary carbon to afford a secondary carbocation.



Iodide adds to this carbocation from either side to yield a racemic mixture of enantiomeric alkyl iodides.

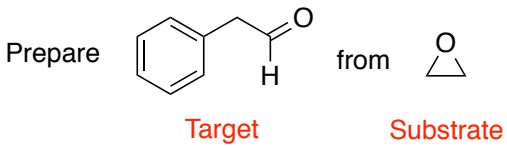


Ethanol reacts further under these conditions. The hydroxyl group is protonated by another molecule of HI. Iodide then attacks the primary carbon of the ethyl group and displaces water. This yields ethyl iodide, the third product of the reaction.

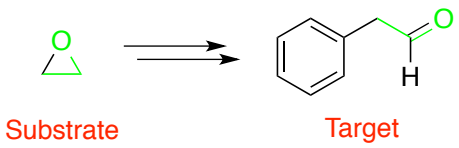


Notice that there are two mechanisms at play in this acidic ether cleavage. The first C-O bond cleavage was an S_N1 reaction because the center bearing the leaving group was secondary and therefore led to a reasonable carbocation. The second C-O bond cleavage was an S_N2 reaction because the primary center is unhindered and would have led to an unstable carbocation.

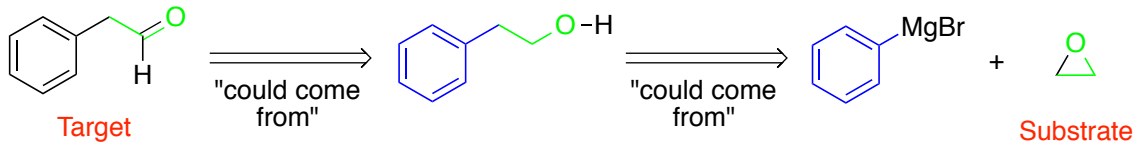
44. It is always wise to begin a synthesis problem by assigning the labels "Target" and "Substrate" to the structures based on the phrasing of the question.



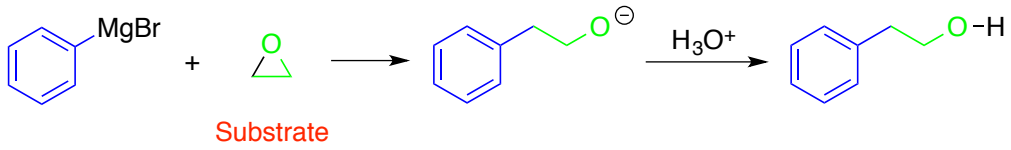
Then, we can rewrite the question in a more familiar manner. This allows us to propose that the two carbons and the oxygen pendent to the ring in the target come from ethylene oxide (the substrate).



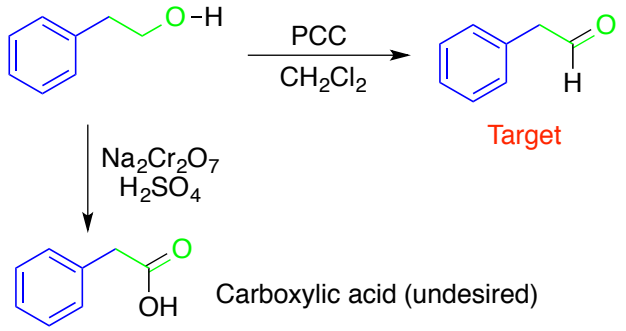
Retrosynthetically, we can say that, based on the reactions we've learned thus far, aldehydes can only be made from the corresponding alcohols. The alcohol could, in turn, be made from ethylene oxide and a Grignard reagent. As we saw in Problems 23 and 34, Grignard reagents effectively act as carbanions and can therefore perform basic opening of epoxides.



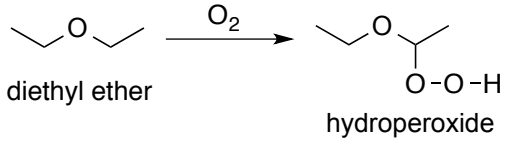
The sequence begins with this basic epoxide opening. The initial reaction yields an alkoxide, and the subsequent addition of acid (or simply water) will allow protonation to generate the alcohol.



This alcohol must be oxidized with the gentle oxidant PCC in order to obtain the desired product, which is an aldehyde. If chromic acid oxidation were used, the product would be the carboxylic acid instead.

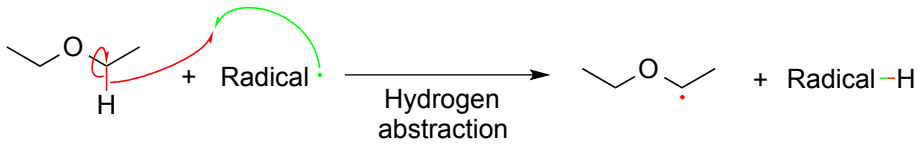


45. Diethyl ether can undergo autoxidation in the presence of oxygen to yield a corresponding hydroperoxide.



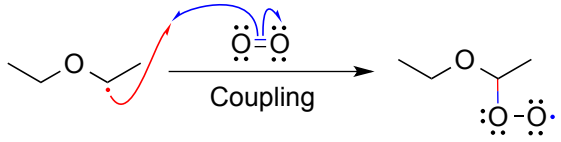
This radical chain reaction begins with initiation in which a trace of some radical abstracts a hydrogen atom from the α carbon of diethyl ether.

Initiation:



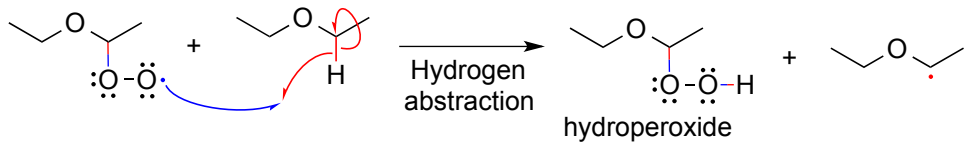
During the first propagation step, the ether radical combines with oxygen to yield a peroxy radical.

Propagation step 1:



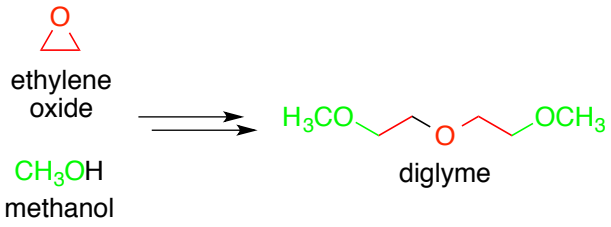
In the second propagation step, this peroxy radical abstracts a hydrogen atom from another molecule of diethyl ether. This results in the formation of the hydroperoxide product, as well as a new ether radical that can reenter propagation step 1.

Propagation step 2:



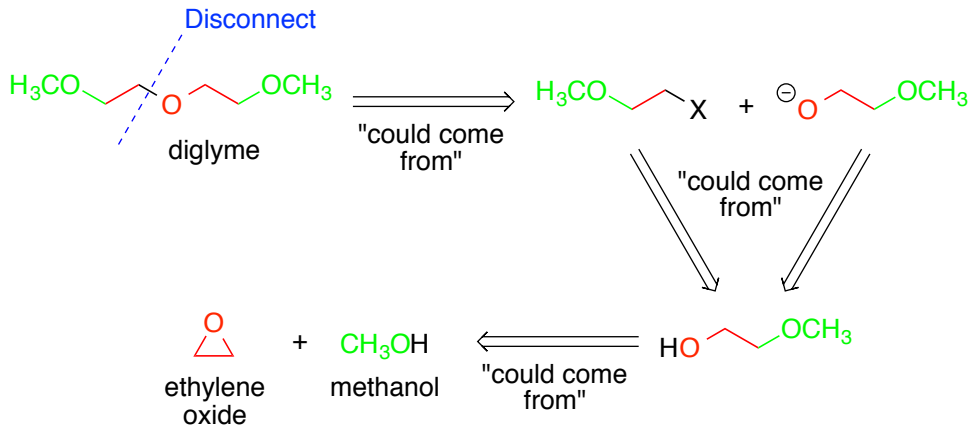
Diethyl ether is a very common laboratory solvent. Given the hazards associated with hydroperoxide formation, bottles of diethyl ether should be tested for peroxides prior to usage, especially if they are old.

46. In this question, we are asked to prepare diglyme, using only ethylene oxide and methanol to obtain all of the carbon atoms in the target molecule. It is useful to begin by sketching out the structures. This allows us to readily identify two methoxy groups that likely derive from methanol molecules, as well as two two-carbon fragments that probably come from ethylene oxide molecules.



As we begin our retrosynthesis, a helpful strategy, especially with symmetrical targets, is to identify a disconnection that divides the molecule into significantly smaller fragments. This is often more productive than slowly chipping away at the molecule from one terminus or another. This approach also tends to lead to more efficient syntheses. If we can build two halves of the molecule and then stitch them together, it will be more efficient than a longer, linear sequence in which we slowly add pieces to a growing molecule, losing yield at each step.

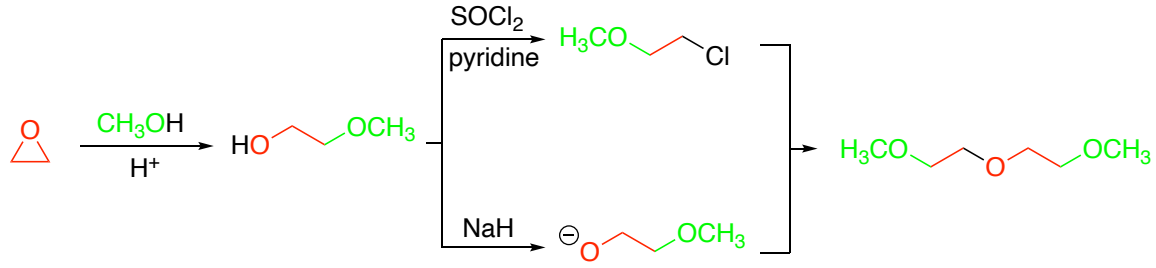
We can implement this strategy by dividing diglyme into two equally sized fragments following the motif of the Williamson ether synthesis. Both the needed alkyl halide and alkoxide are derived from the same hydroxyether precursor. This hydroxyether can, in turn, be prepared by opening ethylene oxide with methanol.



The synthesis begins with the opening of ethylene oxide. Given the symmetry of the epoxide, acidic or basic conditions would lead to the same product. Basic conditions would require the conversion of methanol into methoxide (an extra step) prior to opening the ring. Acidic opening can be performed in a single step.

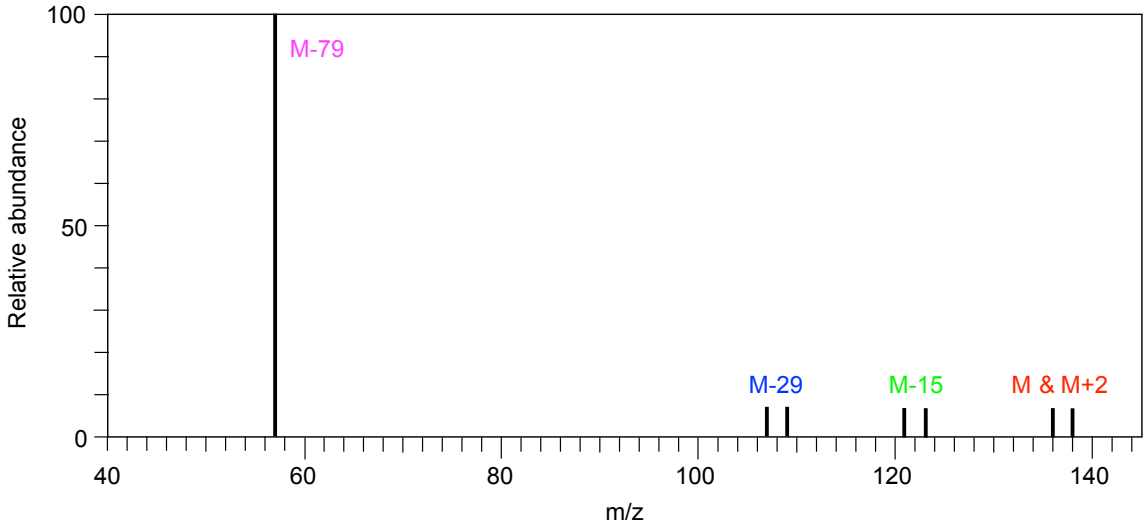
The hydroxyether thus obtained can then be divided into two portions, one of which is converted to the alkyl halide. This could be accomplished using thionyl chloride and pyridine or phosphorus tribromide; however, it would be wise to avoid using HX, which can cleave ethers.

The other portion of the hydroxyether is deprotonated using a strong base, such as sodium hydride. The alkoxide and the alkyl chloride are then combined to yield diglyme via the Williamson ether synthesis.

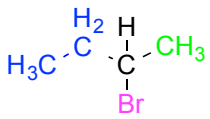


47. The first clue provided by the mass spectrum is that the heights of the M and M+2 peaks are approximately equivalent. This suggests that bromine is present in the alkyl halide.

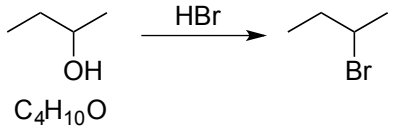
Next, we can identify M-15, M-29, and M-79 peaks. The M-15 peak corresponds to the loss of a methyl group. The M-29 peaks correlates with loss of an ethyl group. Finally, the M-79 peak equates with the loss of the bromine atom.



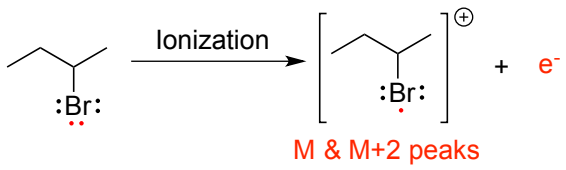
Alkyl halides have two main fragmentation pathways: heterolytic and homolytic cleavage. Heterolytic cleavage breaks the C-Br bond and explains the loss of bromine (M-79 peak). Homolytic cleavage breaks a bond between the α carbon and its neighbor. This can explain the loss of the methyl (M-15) and ethyl (M-29) groups. Assembling the fragments gives us 2-bromobutane:



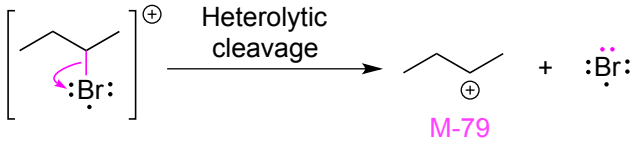
To prepare 2-bromobutane, we would have to start with 2-butanol and treat it with HBr.



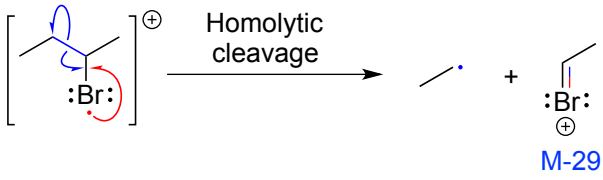
When subjected to mass spectrometry, 2-bromobutane is converted to a molecular ion through ionization. The molecular ion (M) contains ^{79}Br and is accompanied by an M+2 peak for molecular ions containing ^{81}Br.



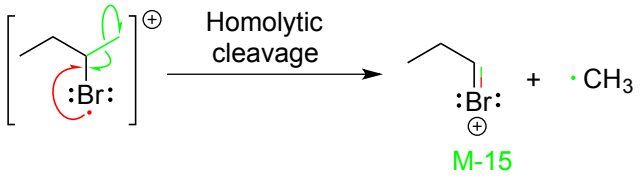
The molecular ion can undergo heterolytic cleavage to generate the M-79 peak.



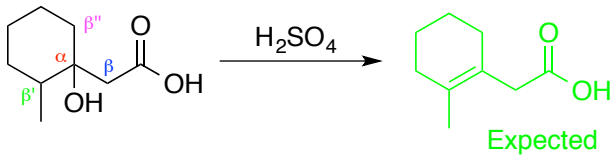
It can also undergo two homolytic pathways. One results in the scission of the ethyl group, giving the M-29 peak.



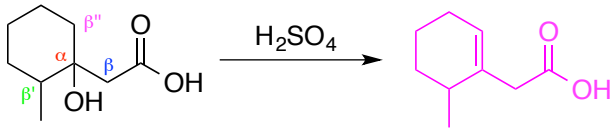
The other results in the loss of a methyl group, thereby explaining the M-15 peak.



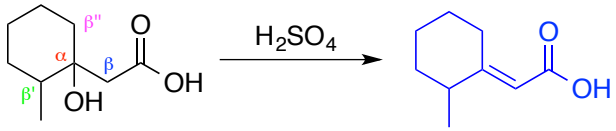
48. Given that this is a dehydration and that dehydration involves the removal of the hydroxyl group from α and a proton from β, there are three possible outcomes. The substrate has three β positions, and a proton could conceivably be lost from any of them. Loss of a proton from β' gives the expected product. We have IR evidence suggesting that this did not occur.



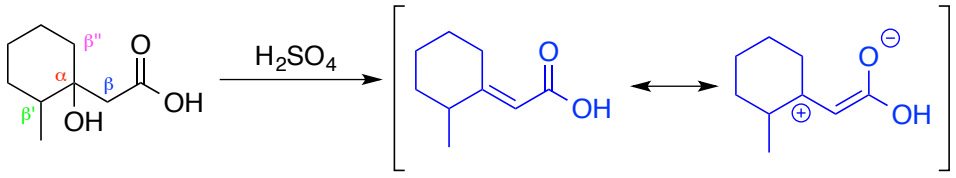
Loss of a proton form β'' seems improbable because we merely obtain a less highly substituted alkene that has no redeeming contributions to stability from other factors.



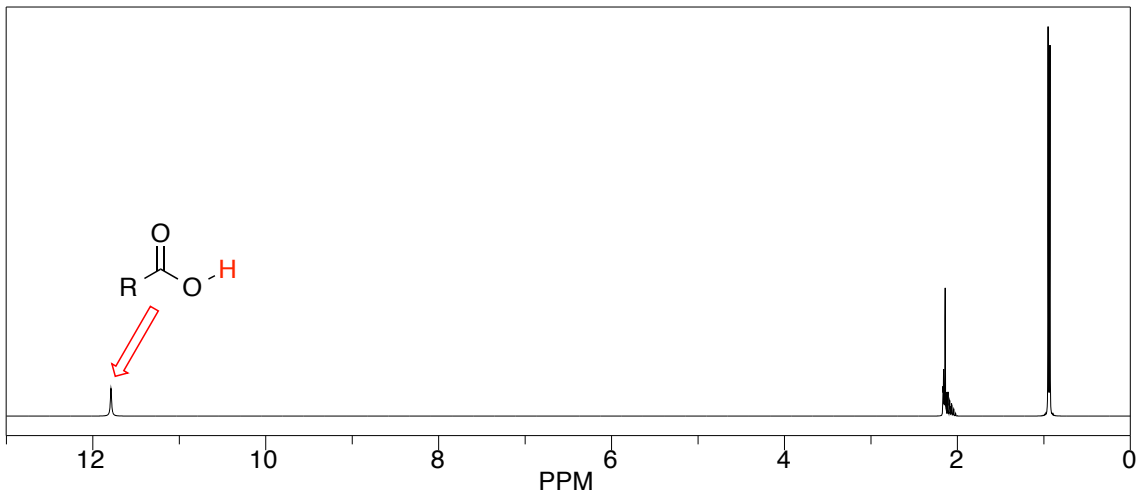
However, the loss of a proton from β yields a conjugated alkene. Although this alkene is merely trisubstituted (as opposed to the expected tetrasubstituted alkene), we know that conjugation allows for resonance delocalization of electrons, which is a powerfully stabilizing factor. Therefore, this pathway seems like a viable alternative to the anticipated one.



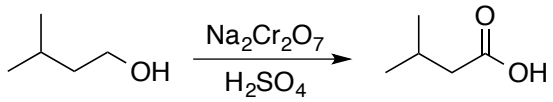
The surprising intensity of this alkene's C=C resonance can be explained through resonance as well. Resonance renders one of the alkene carbons partially positive, while the other alkene carbon retains a formal charge of zero in both resonance structures. This charge disparity heightens the dipole moment of the alkene, thereby enhancing the intensity of its signal in the IR spectrum.



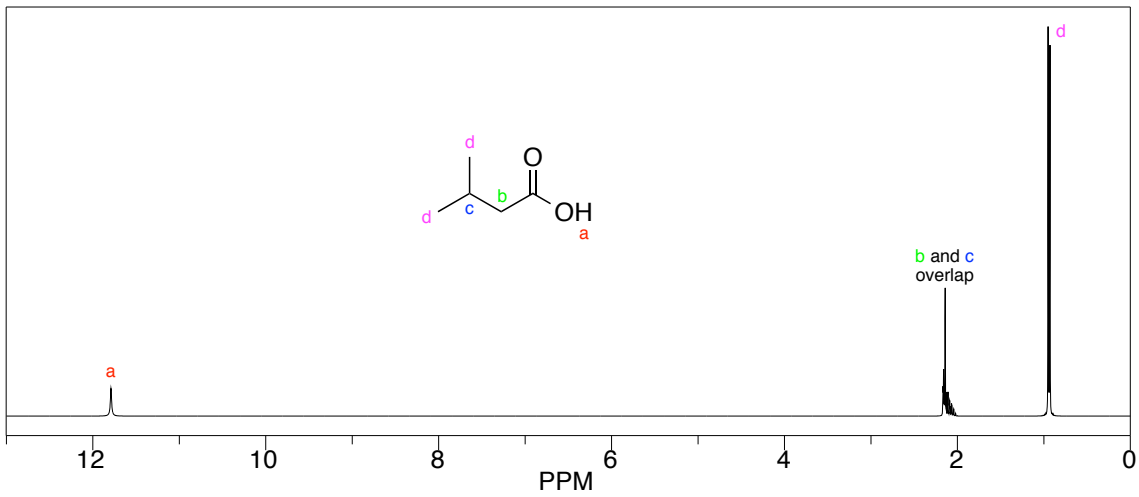
49. While some of the signals in this proton NMR spectrum overlap with one another, it is not necessary to disentangle all of that information in order to solve the problem. The key observation is a simple one. There are only two possible oxidation products (an aldehyde or a carboxylic acid), and the signal near 12 ppm is more consistent with a carboxylic acid proton.



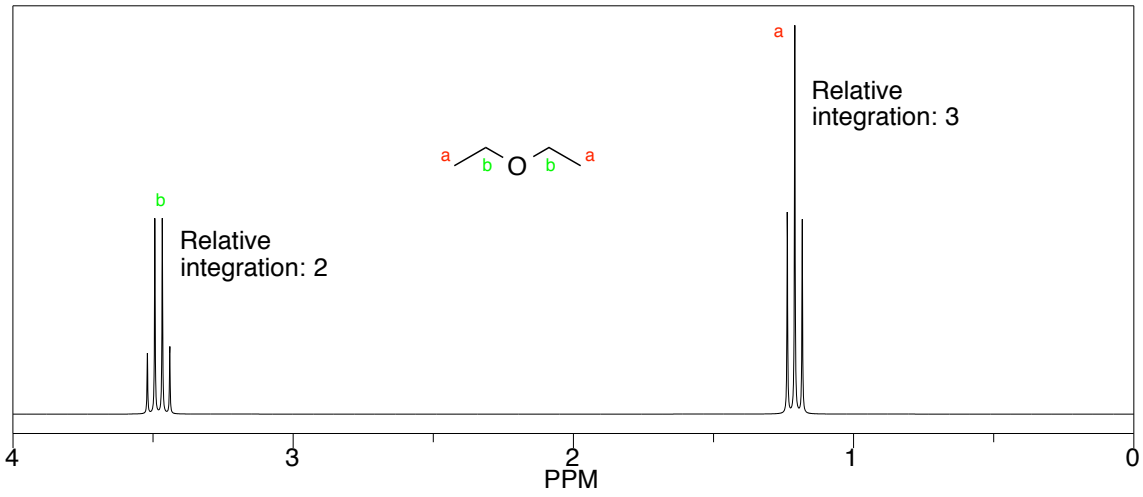
If the alcohol was oxidized to the corresponding acid, then chromic acid was the oxidant. It can be prepared from either sodium dichromate (shown below) or chromium trioxide in sulfuric acid.



To be thorough, all of the peaks are assigned in the following spectrum; however, it was not necessary to do this in order to answer the question.

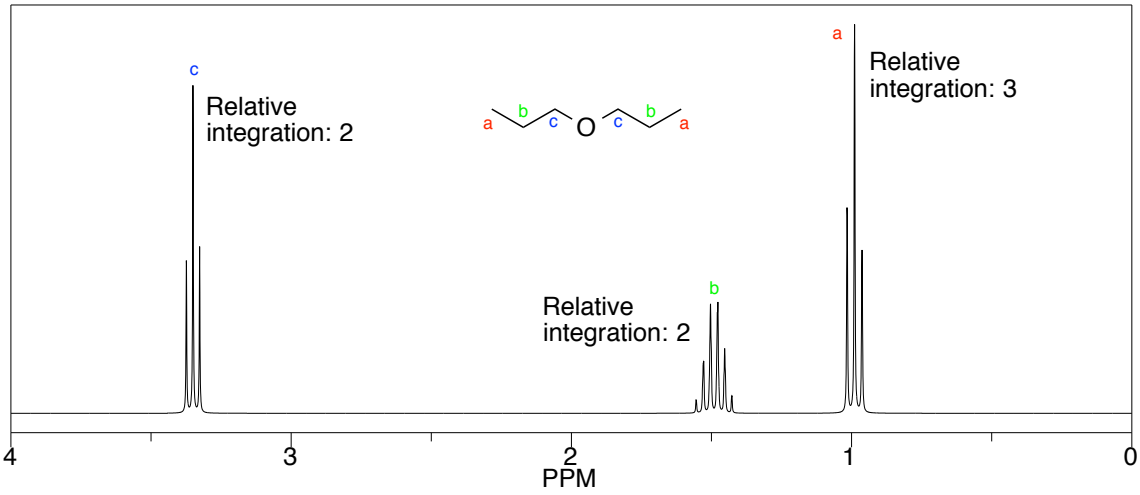


50. It is wise to begin with the simplest of the NMR spectra, which happens to appear first. This spectrum has only two signals, indicating a neighboring CH_3 and CH_2 group. The ethyl group (CH_3CH_2-) is all that appears in the spectrum. Since there is no signal for the alcohol proton, we can surmise that the compound must be an ether bearing two ethyl groups. This compound is therefore diethyl ether.

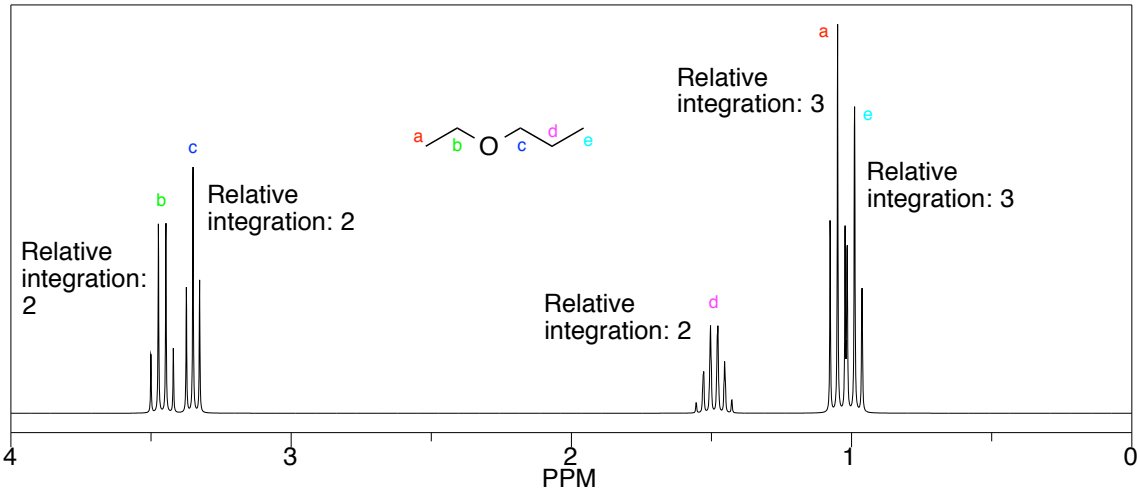


In the next spectrum, there are signals for a methyl group, as well as two methylene (CH_2) groups. Based on the splitting, these fragments must be adjacent to one

another, giving a propyl moiety: $CH_3CH_2CH_2$-. As with the previous spectrum, we can surmise that the compound is dipropyl ether due to the absence of any other signals.

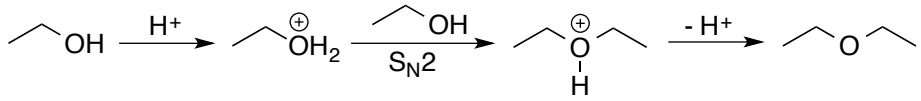


The final spectrum is the most difficult to interpret. It contains two methyl groups and three methylene groups. Both methyl groups are triplets, indicating adjacency to methylenes: CH_3CH_2- and CH_3CH_2-. The green methylene is a quartet, indicating that its three red neighbors are its only neighbors. Additionally, it is so deshielded that it is likely bonded to oxygen: CH_3CH_2O-. The other fragment must contain one more methylene in order to explain the splitting of the purple CH_2 group: $CH_3CH_2CH_2$-. The blue methylene is so deshielded that it too is likely next to oxygen, which enables us to complete the structure: $CH_3CH_2OCH_2CH_2CH_3$. This compound is ethyl propyl ether.

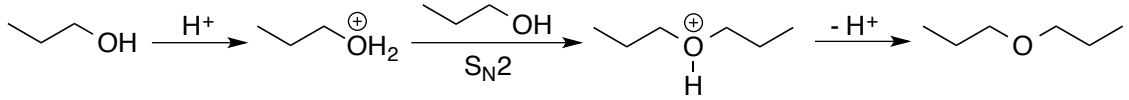


With the structures of the products in hand, we can now identify what transpired during the reaction. Two symmetrical ethers and one unsymmetrical ether were

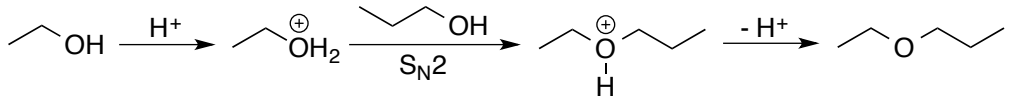
formed. Diethyl ether is formed when both the electrophilic and nucleophilic species are derived from ethyl alcohol.



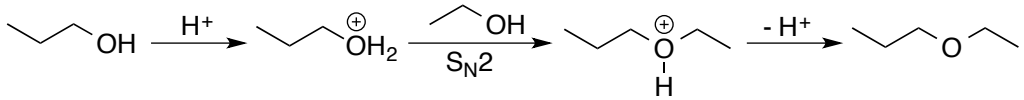
Similarly, dipropyl ether is derived from electrophilic and nucleophilic S_N2 participants that can be traced back to propyl alcohol.



Lastly, ethyl propyl ether is formed when the two different alcohols give rise to the electrophilic and nucleophilic components of the reaction. A protonated molecule of ethyl alcohol can be the electrophile:



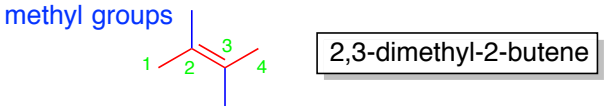
Or, a protonated molecule of propyl alcohol can be the electrophile:



Solutions to Problems for Chapter 10: Alkenes

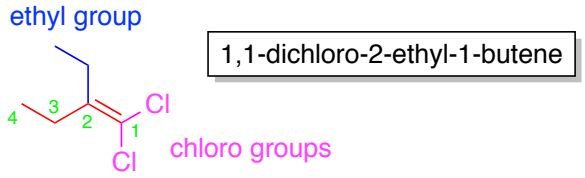
1.

(a)



- Four carbon parent = butane
- Replace "ane" suffix with "ene"
- Provide a number for the site where the double bond begins
- Include the names and numbers for substituents

(b)



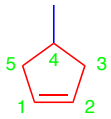
- Four carbon parent = butane
- Replace "ane" suffix with "ene"
- Provide a number for the site where the double bond begins
- Include the names and numbers for substituents

(c)

- Add prefix "cyclo" for cyclic parent
- Six carbon parent = hexane
- Replace "ane" suffix with "ene"

Note that, in this case, no number is needed to denote the site of the alkene because there is no ambiguity in regard to its location. If you were drawing the structure of cyclohexene, you'd first draw a six-membered ring. Then, as you seek to place the pi bond in the ring, you'd see that the location doesn't matter since all of the ring carbons are equivalent.

(d)

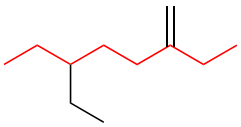


4-methylcyclopentene

- Add prefix "cyclo" for cyclic parent
  - Five carbon parent = pentane
- Replace "ane" suffix with "ene"
  - Add "4-methyl" for substituent

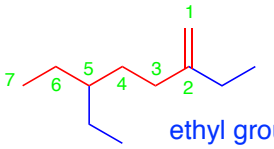
Much as in part (c) above, there is no number needed for the alkene in a cycle. It is understood that, wherever we choose to place the alkene in the ring, the carbon where it begins is C1 and the other alkene carbon is C2. We do, however, need a locant to indicate the position of the methyl group relative to the alkene.

2. In this problem, it may be tempting to select the eight-carbon chain as the parent because it is the longest continuous chain in the molecule. However, it does not contain both carbons of the alkene and is therefore not the correct parent.



Not the parent: does not include both alkene carbons

Given that both alkene carbons must be included in the parent, the longest possible chain is seven.



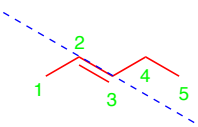
ethyl groups

2,5-diethyl-1-heptene

- Seven carbon parent = heptane
- Replace "ane" suffix with "ene"
  - Provide a number for the site where the double bond begins
- Include the names and numbers for substituents

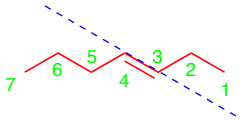
3.

(a) This compound is *trans*-2-pentene.



Groups on opposite sides of axis through and parallel to alkene

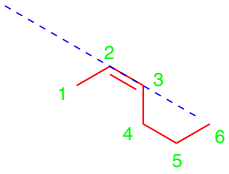
(b) In this instance, we have to be careful to number so as to give the alkene carbons the lowest possible numbers (right-to-left), making this compound *trans*-3-heptene.



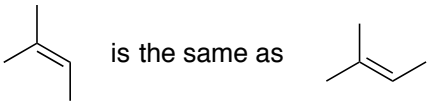
Groups on opposite sides of axis through and parallel to alkene

(c) This compound is *cis*-2-hexene.

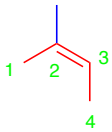
Groups on same side of axis through and parallel to alkene



(d) This compound does not have *cis*/*trans* isomerism—it is *non*-stereoisomeric—because one of the alkene carbons (C2) is bonded to two identical (methyl) groups.

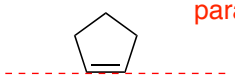


Therefore, its name is simply 2-methyl-2-butene.



4. Cyclopentene does not typically receive a *cis* designation (see Problem 1d). This is due to the fact that the *cis* geometry is implied in small rings (i.e., those less than eight carbons in size).

Groups on same side of axis through and parallel to alkene



A *trans* double bond simply can't be accommodated in a small ring. This becomes evident when you try to draw the molecule. If you draw a *trans* alkene and then try

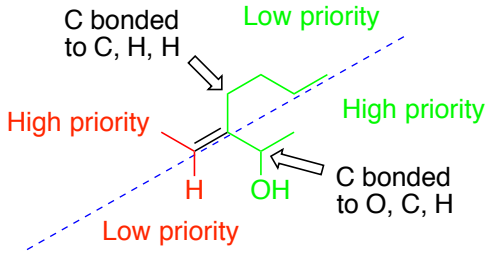
to connect the ends, you notice that the bonds have to be quite long in order to do so. You can further convince yourself of this by attempting to build a model of a five-membered ring containing a *trans* alkene. You won't be able to do it using the standard-length carbon-carbon bonds.

Not a feabile structure:
bond lengths too long

Trans double bonds only become feasible in rings containing eight or more carbons.

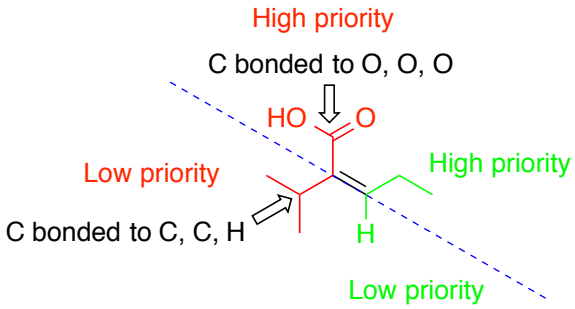
5.

(a) Each carbon of the alkene must be assigned a high and low priority group. On the left-hand alkene carbon, a methyl and a hydrogen are present. The carbon of the methyl group has a higher atomic number than the hydrogen, so the methyl is the high priority group. On the right-hand alkene carbon, there are two alkyl groups. As we compare the first atom of each, we find a tie because they are both carbon. These carbons are bonded to C, H, and H vs. O, C, and H. Oxygen has a higher atomic number than carbon, so the alcohol-bearing group wins the high priority. Since the high priority groups are on opposite sides of an axis passing through and parallel to the alkene, the double bond has *E* geometry.



High priority groups on opposite sides of
axis through and parallel to alkene = *E*

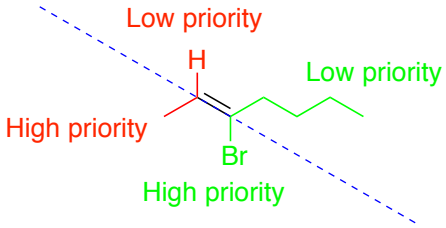
(b) Each carbon of the alkene must be assigned a high and low priority group. On the right-hand alkene carbon, the carbon of the ethyl group beats hydrogen due to carbon's higher atomic number. The left-hand alkene carbon is directly bonded to two carbon atoms, resulting in a tie. This tie is broken by considering the atoms pendent to these carbons. The acid group has a carbon bonded to O, O, and O, while the isopropyl group has a carbon bonded to C, C, and H. Since oxygen's atomic number is higher than that of carbon, the acid group wins high priority. The high priority groups are on the same side of an axis through and parallel to the alkene, making this a *Z* alkene.



High priority groups on same side of axis through and parallel to alkene = *Z*

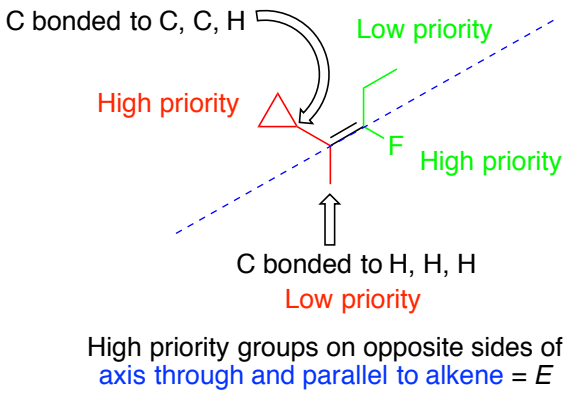
6.

(a) The core of the name is 3-bromo-2-heptene; however, we need to add an *E* or *Z* designation to the beginning of the name to indicate the geometry of the double bond. On the left-hand alkene carbon, the methyl group wins the high priority. On the right-hand alkene carbon, bromine's high atomic number beats the atomic number of the carbon atom of the butyl group, so bromine is the high priority substituent. The high priority groups are on the same side of an axis through and parallel to the alkene, so the double bond has *Z* geometry. The molecule's complete name is therefore (*Z*)-3-bromo-2-heptene.



High priority groups on same side of axis through and parallel to alkene = *Z*

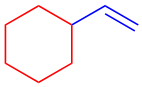
(b) The core of the name is 2-cyclopropyl-3-fluoro-2-pentene, but we also need a stereochemical descriptor. On the left-hand alkene carbon, the cyclopropyl group beats the methyl for high priority because a carbon bonded to C, C, and H beats a carbon bonded to H, H, and H. On the right-hand alkene carbon, fluorine wins the top priority because its atomic number is higher than that of carbon. Since the high priority groups are on opposite sides of an axis through and parallel to the alkene, the geometry is *E*. The complete name is therefore (*E*)-2-cyclopropyl-3-fluoro-2-pentene.



High priority groups on opposite sides of axis through and parallel to alkene = *E*

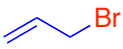
7.

(a) In this instance, the vinyl group can be treated as a substituent on the cyclohexane ring.



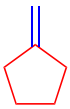
vinylcyclohexane

(b) We can refer to this halide as allyl bromide.



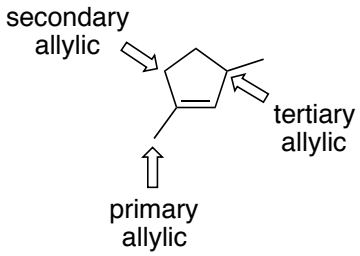
allyl bromide

(c) In this molecule, a methylene group is pendent to the cyclopentane ring.

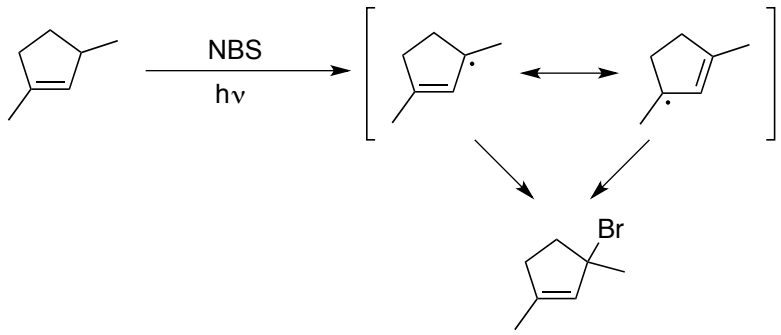


methylenecyclopentane

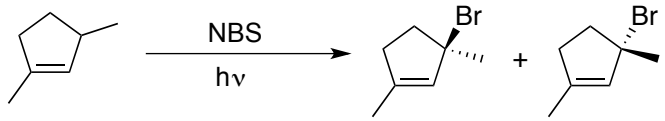
8. It's always important to think mechanistically, even if you aren't asked to draw a complete mechanism for a given reaction. We know that a bromine radical abstracts a hydrogen atom so as to make the most stable radical possible. Although this molecule has three allylic positions, abstraction of a hydrogen from the tertiary position leads to the best radical.



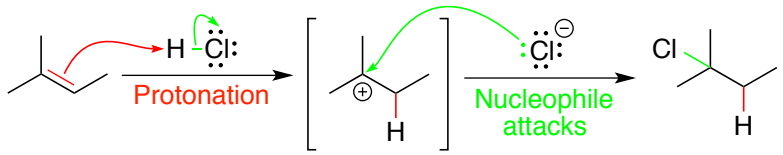
The tertiary allylic radical has two resonance forms, but upon abstraction of a bromine atom from Br_2, they converge on a single constitutional isomer due to the molecule's symmetry.



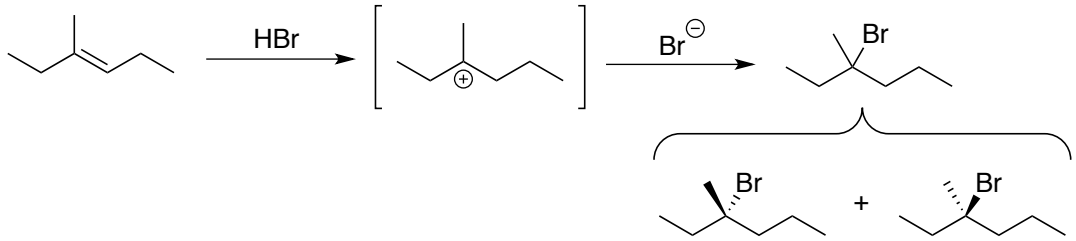
Additionally, a stereocenter was created during the reaction, so we expect to form both enantiomers as a racemic mixture.



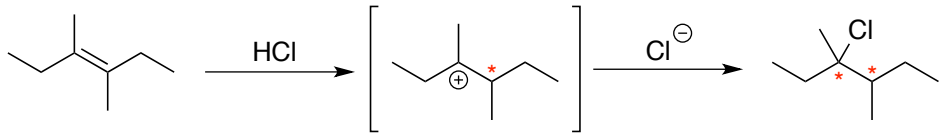
9. The transformation begins with the protonation of the electron-rich alkene pi bond by HCl. The protonation occurs according to Markovnikov's rule so as to afford the more stable tertiary carbocation. Chloride then attacks the carbocation to yield the product.



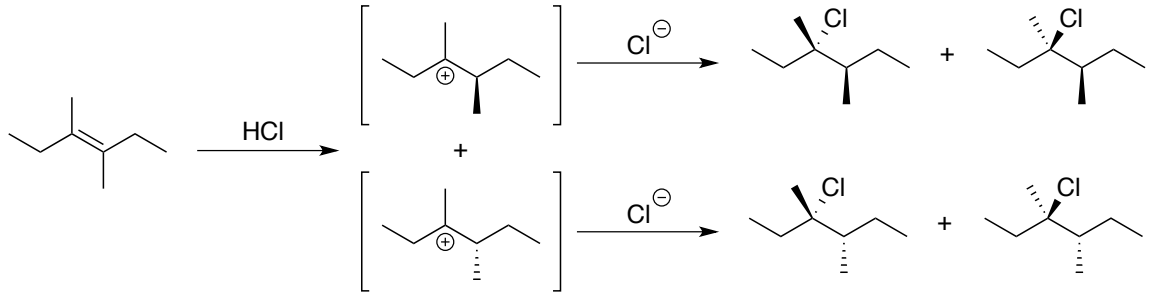
10. The reaction entails protonation of the alkene according to Markovnikov's rule, followed by addition of bromide to the carbocation. Notice that a stereocenter is formed during the reaction. Consequently, the products are a racemic mixture of enantiomers.



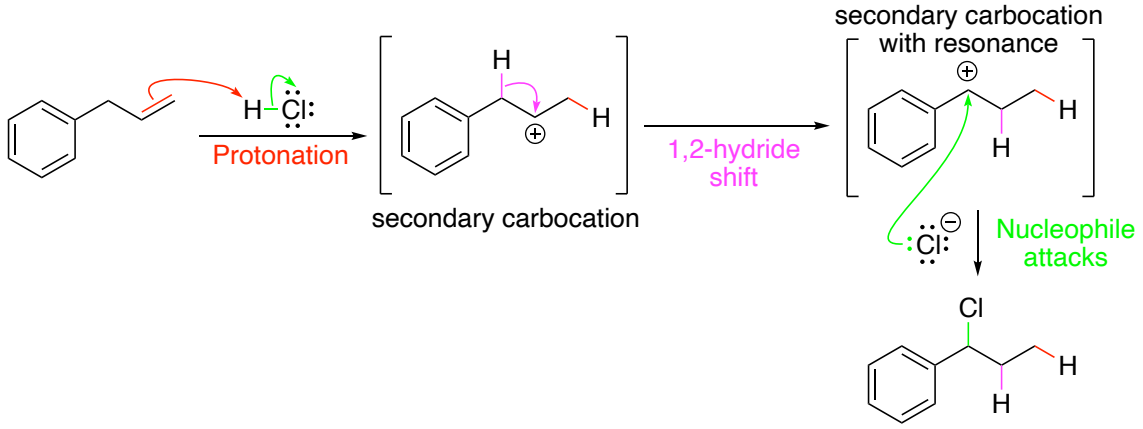
11. In this reaction, the symmetrical alkene can be protonated at either carbon to afford the same tertiary carbocation. Chloride then adds to this carbocation to yield the product. Notice that the product has two stereocenters (*). Therefore, we need to address the stereochemical outcome of this reaction.



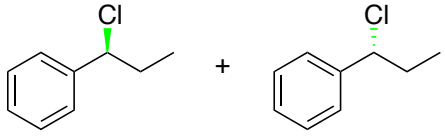
During the initial protonation, the first stereocenter is created. Since the alkene is flat, protonation may occur from either side to give both configurations at this center. During the second step, chloride adds to the flat carbocation from either side. This leads to the formation of two products from each of the two carbocations. All four possible stereoisomers were created in this reaction.



12. The reaction begins with protonation of the alkene in a Markovnikov fashion so as to make the more stable carbocation. This carbocation is secondary, and it resides next to another secondary center. At first glance, it might seem as though this reaction should be immune to carbocation rearrangement; however, it is not. If a 1,2-hydride shift occurs, the new secondary carbocation is also resonance stabilized by the benzene ring. This lends a great deal of additional stability to the carbocation and justifies the rearrangement. Finally, chloride adds to this carbocation to yield the product.

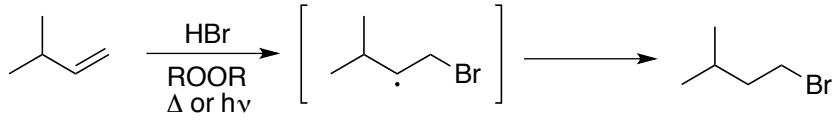


The product contains a single stereocenter, which will be produced in both configurations.



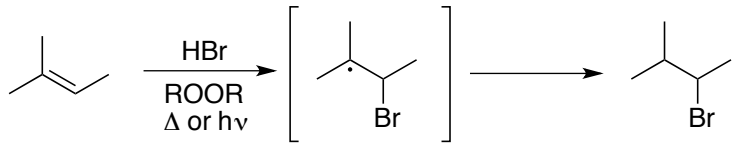
13. In radical hydrohalogenation, bromine radical formed through initiation adds to the alkene to make the more stable radical.

(a) In this case, the more stable radical is at the secondary center. Subsequent, hydrogen abstraction affords the product.

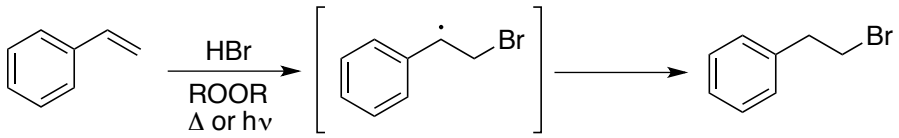


Notice that, unlike carbocations, radicals do <u>not</u> undergo rearrangement.

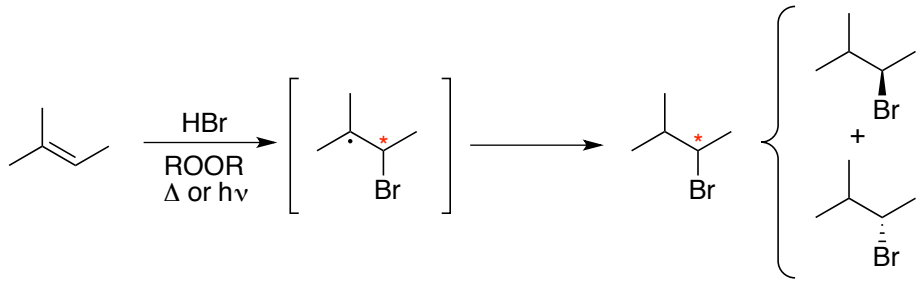
(b) Here it is the tertiary center that provides the better radical intermediate. The product is formed upon hydrogen abstraction.



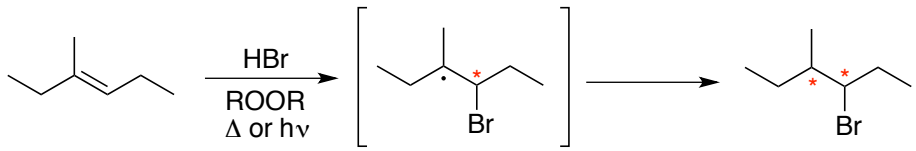
(c) In this case, the secondary radical is preferable not only because of its higher level of substitution but also because of the resonance stabilization provided by the benzene ring. Subsequent hydrogen abstraction leads to product formation.



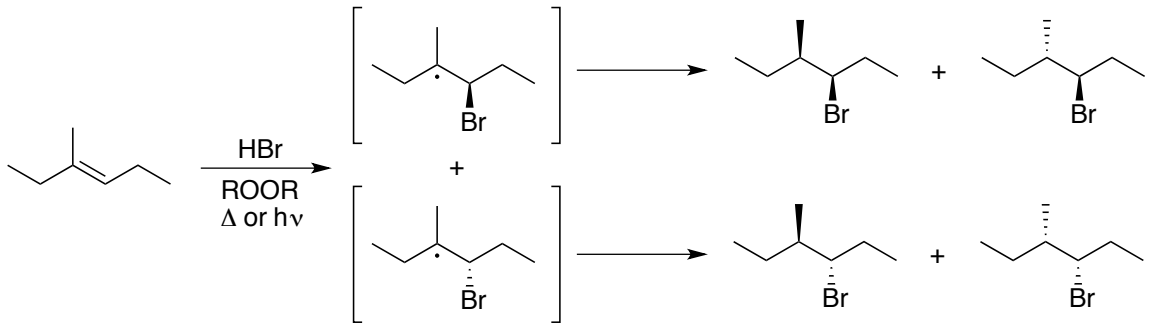
14. When we revisit this reaction from a three-dimensional perspective, we notice that a stereocenter (*) is formed when bromine adds to the alkene. The product contains a single stereocenter and is therefore formed as a mixture of enantiomers.



15. In this transformation, a stereocenter (*) is formed when bromine adds to the alkene, and a second stereocenter is formed when the radical abstracts a hydrogen to form the product.

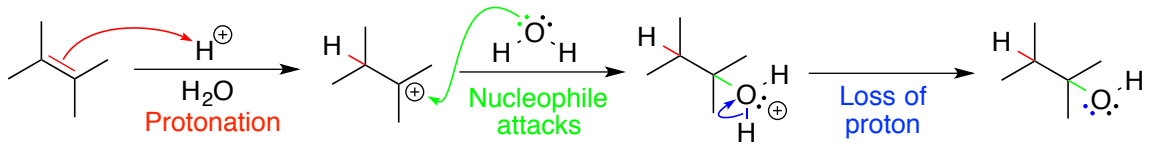


The addition of bromine to the alkene occurs from both sides because the alkene is flat. Similarly, the radical is sp^2 hybridized and therefore flat in shape, so the hydrogen is added from both sides as well. This means that each of the two radicals forms two stereoisomeric products, leading to a total of all four possible stereoisomers.



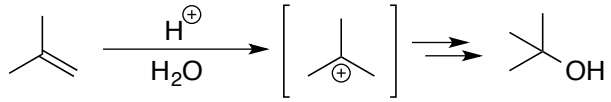
16. Recall that aqueous acid may be represented as H^+ / H_2O, H_3O^+, or H_2SO_4 / H_2O. In this problem, the protonation may occur by attack directly on a proton. Either alkene carbon may be protonated due to the symmetry of the molecule. Water then attacks the carbocation, forming the new C-O bond. Finally, a proton is lost to the

medium to yield the neutral alcohol as the reaction product. When a proton is lost to the medium, sometimes a specific base (in this case, water) is shown removing the proton. However, sometimes we simply show the mechanistic arrow that describes the bond from the substrate to hydrogen being broken, as was done here.

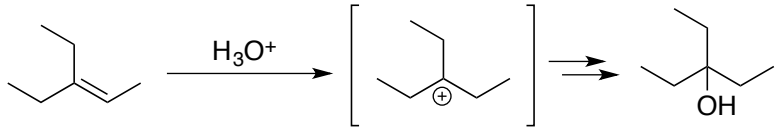


17.

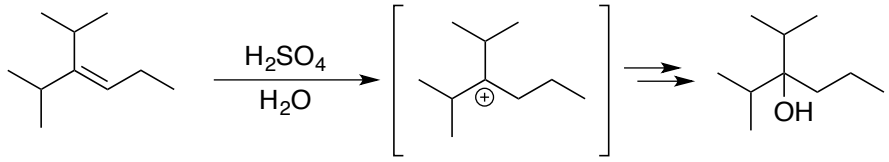
(a) Protonation of the alkene affords the more stable tertiary carbocation. Water adds to this center, and then sheds a proton to form the Markovnikov alcohol.



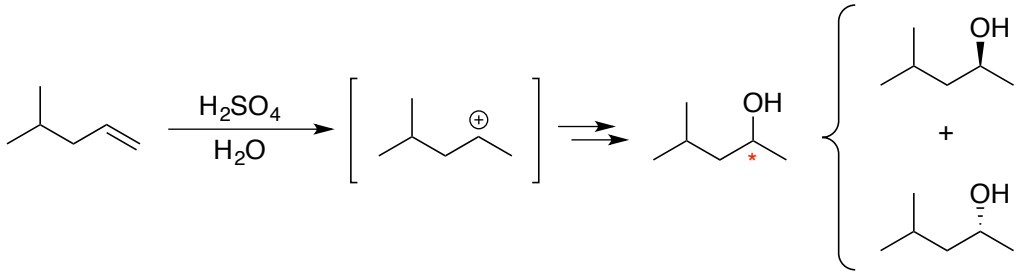
(b) The initial protonation occurs so as to yield the more stable tertiary carbocation. Water adds to this carbocation, and the resulting oxonium ion loses a proton to produce the Markovnikov alcohol.



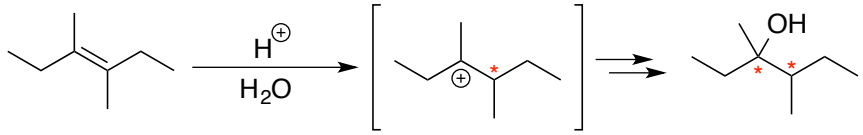
(c) The protonation step occurs according to Markovnikov's rule so as to provide the better tertiary carbocation. After the addition of water and the subsequent loss of a proton, the product is formed.



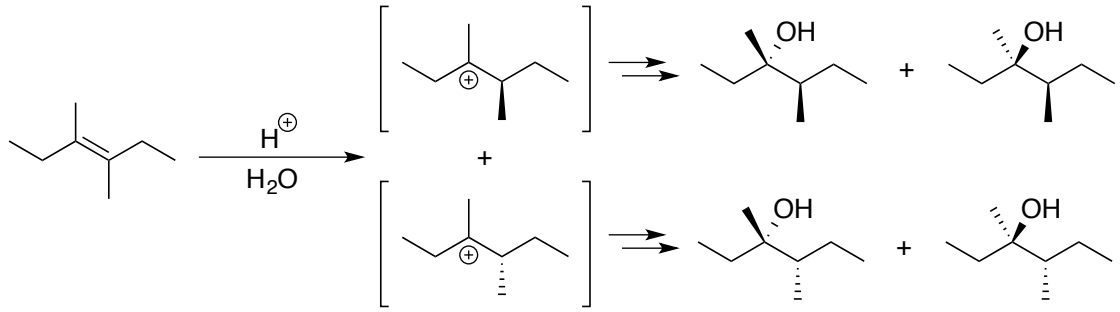
18. The alkene is protonated so as to provide the more stable carbocation. Then, water adds, and a proton is lost from the resulting oxonium ion. The Markovnikov alcohol thus produced contains a stereocenter (*) that was formed during the addition of water to the carbocation. Since the carbocation is sp^2 hybridized (and therefore flat), the addition can occur from either side to produce a racemic mixture of enantiomers.



19. This symmetrical alkene may be protonated on either carbon to produce the same carbocation. Water adds to the carbocation, and a proton is lost to yield the alcohol product. In this instance, two stereocenters have been formed during the reaction, so we must consider the three-dimensionality of the product.

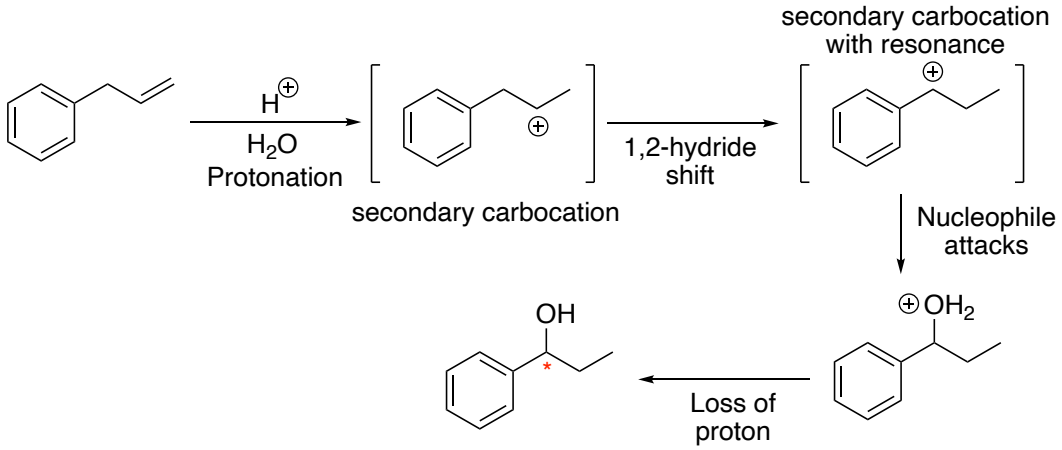


The first stereocenter is produced when the flat alkene is protonated. It may, of course, be protonated from either side, giving two enantiomeric carbocations. Each of these carbocations may then add water from either side, resulting in a total of four reaction products.

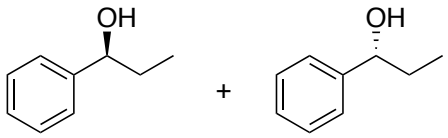


It is worth comparing this problem to Problem 11. The comparison shows that, although ionic hydrohalogenation and acid-catalyzed hydration are different reactions, they have comparable stereochemical outcomes due to their analogous mechanisms (i.e., protonation followed by addition of a nucleophile to the intermediate carbocation).

20. Protonation of the alkene begins the reaction. A secondary carbocation is formed, but it undergoes a 1,2-hydride shift to form a secondary carbocation that also has resonance stabilization. Water attacks the newly formed carbocation, and the oxonium ion loses a proton to yield the alcohol product.



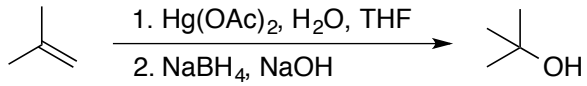
Notice that the alcohol has a single stereocenter (*). Consequently, the product is actually a racemic mixture of enantiomers.



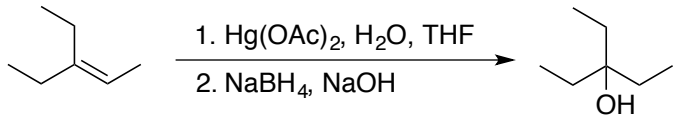
It is a good idea to compare this question to Problem 12. The comparison will further reinforce the similarities of ionic hydrohalogenation and acid-catalyzed hydration.

21. The basic guideline resulting from our mechanistic study of this reaction is that oxymercuration-demercuration yields Markovnikov hydration products. In each of the following examples, the Markovnikov alcohol is formed.

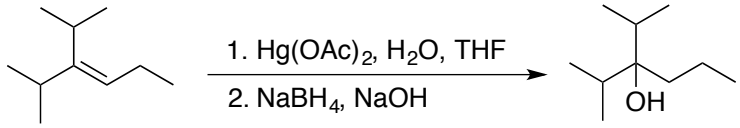
(a)



(b)

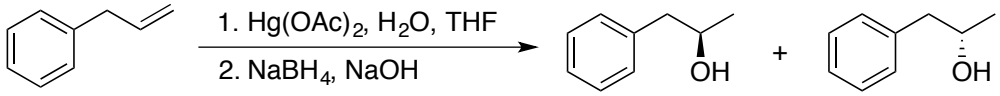


(c)

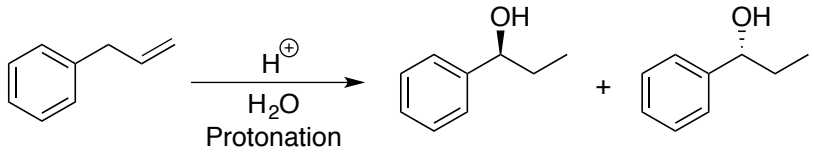


Compare this problem to Problem 17 to see how acid-catalyzed hydration and oxymercuration-demercuration can lead to identical products in some cases. Very soon, we'll see an important distinction between the two reactions.

22. We have now seen that oxymercuration-demercuration provides Markovnikov hydration products *with no chance of rearrangement*. Therefore, the product is simply the Markovnikov alcohol. Since a single stereocenter is formed during this reaction, the product is produced as a pair of enantiomers.



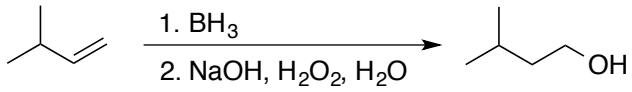
Compare this with the acid-catalyzed hydration in Problem 20 (shown below), which included a carbocation rearrangement.



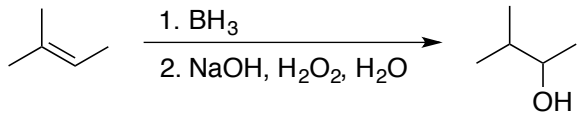
Now, we see a clear distinction between the two sets of reaction conditions. They can, in some cases, yield different products.

23. The guiding principle for hydroboration-oxidation is that it induces anti-Markovnikov hydration. In each of the following three examples, the anti-Markovnikov alcohol is the product.

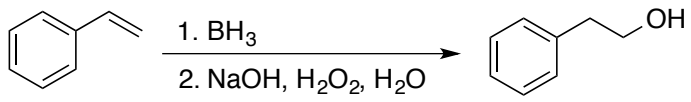
(a)



(b)

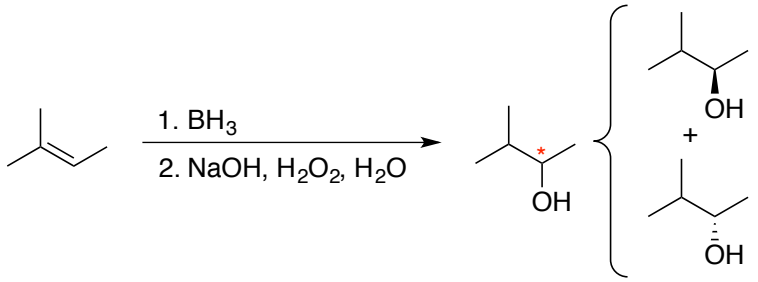


(c)

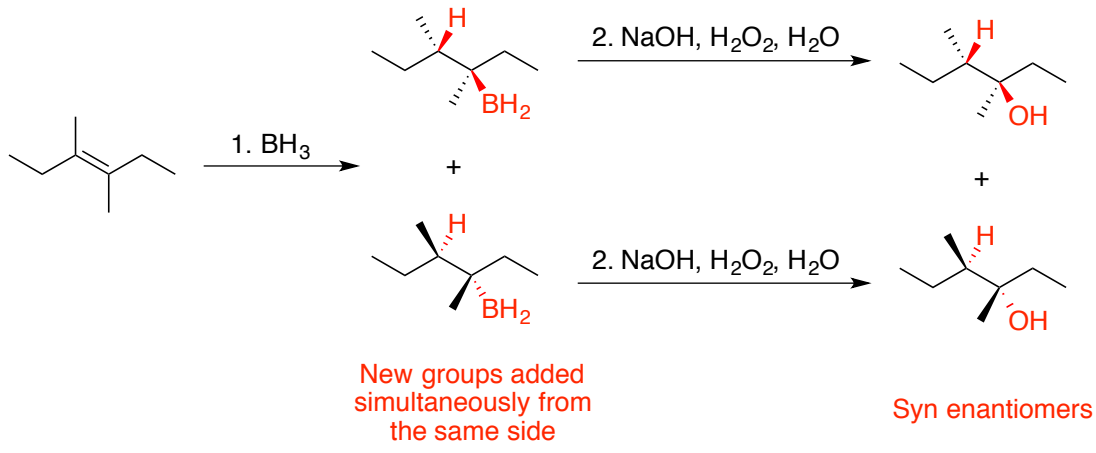


Compare these answers to those for Problem 13. Doing so will highlight the similarity between radical hydrohalogenation and hydroboration-oxidation. Although the two reactions add different groups across the alkene pi bond (HBr vs. H_2O), they both afford anti-Markovnikov regiochemistry.

24. Notice that a stereocenter (*) is formed during this particular hydroboration-oxidation reaction. The product is therefore a mixture of enantiomers.



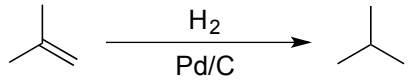
25. The key stereochemical facet of hydroboration-oxidation derives from the concerted addition of BH_3 across the alkene pi bond in step 1 (hydroboration). Since the two new groups add simultaneously, they must add from the same side. In step 2 (oxidation), boron is replaced where it stands by a hydroxyl group, and there is no change in stereochemistry. So, the syn hydroboration products of step 1 become syn alcohols after step 2.



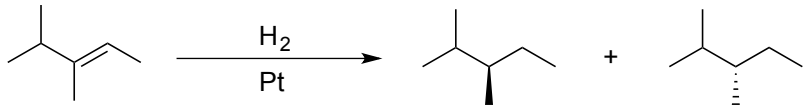
Notice that only two of the four possible stereoisomers were made from this reaction. Compare this result with that of the acid-catalyzed hydration in Problem 19, which created all four stereoisomeric products. *The difference in mechanism between the two reactions accounts for the different stereochemical outcomes.*

26.

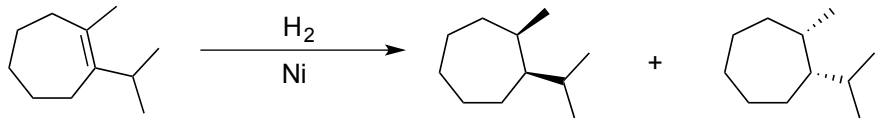
(a) Hydrogen is added across the alkene, and no stereocenters are formed in this reaction.



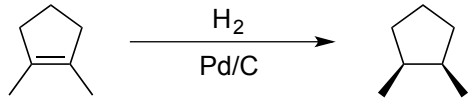
(b) In this reaction, a single stereocenter is formed when hydrogen adds across the alkene pi bond. Therefore, the product is a mixture of enantiomers.



(c) As hydrogen is added across the alkene pi bond, two stereocenters are formed. Since the addition of hydrogen is concerted, both atoms add simultaneously from the same side, meaning that only the syn enantiomers are produced.

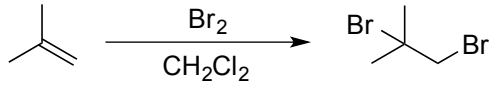


(d) In this reaction, two stereocenters are formed during the addition of hydrogen as well. However, given the syn nature of the addition, the product has an internal plane of symmetry, making it a meso compound. Therefore, there is only a single reaction product because a meso compound has no enantiomer.

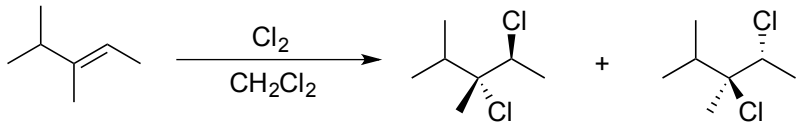


27.

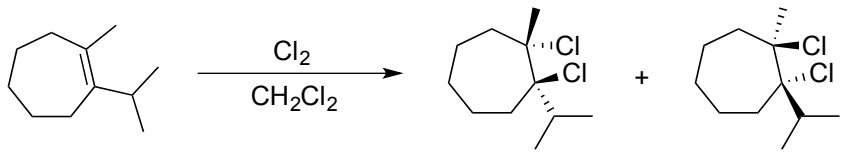
(a) The addition of bromine across the alkene pi bond does not create any stereocenters in this example. There is a single reaction product, the vicinal dibromide.



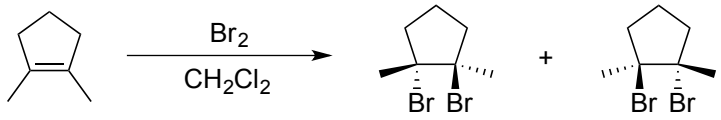
(b) In this reaction, two stereocenters are formed as chlorine adds across the pi bond of the alkene. Since the addition is anti, only two stereoisomers are formed. These are the anti enantiomers.



(c) This chlorination also produces the vicinal dichloride as a pair of anti enantiomers.

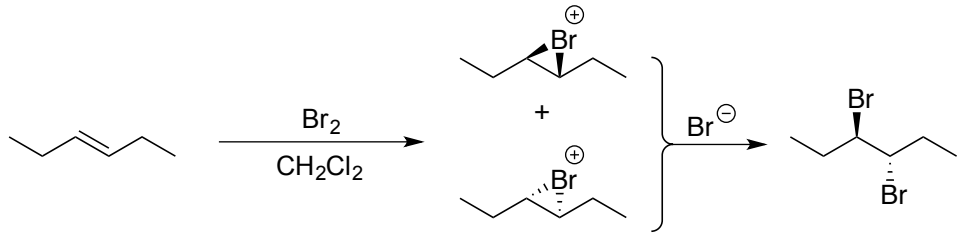


(d) Bromination yields a product with two stereocenters, resulting in a pair of anti enantiomers.

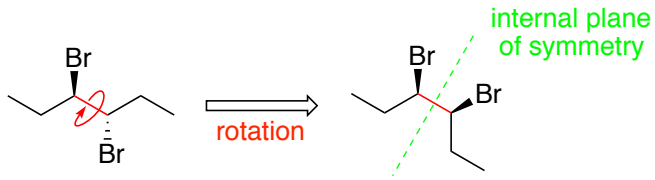


28.

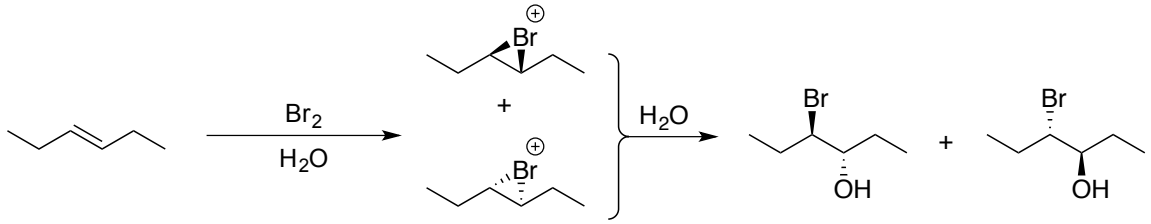
(a) The bromination of *trans*-3-hexene begins with the formation of enantiomeric bromonium ions because bromine can be added from above or below the plane of the alkene. Bromide then opens these bromonium ions in an anti fashion, and as a result, the two bromonium ions converge on a single product.



We know that, at most, halogenation can form a pair of anti enantiomers; the syn enantiomers are *not* produced during halogenation. In this case, we do not obtain a pair of anti enantiomers because the compound possesses internal symmetry. Although it is not obvious in the conformation of the product that was drawn above, rotation about the central carbon-carbon bond leads to a conformation in which the internal symmetry is much more readily apparent.

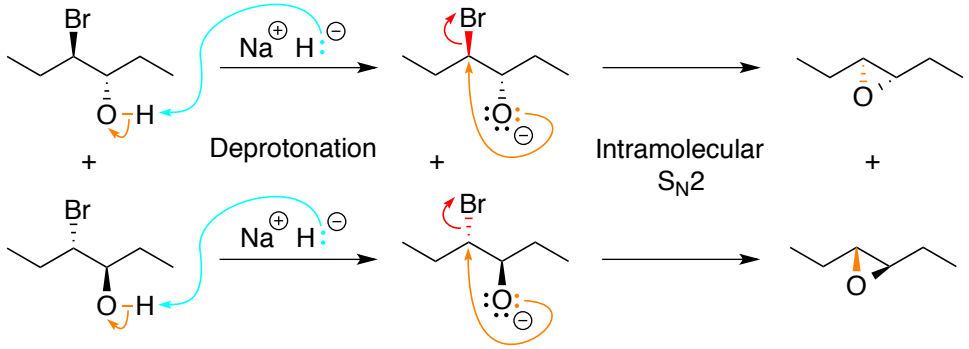


(b) In this halohydrin formation, the same two bromonium ions appear as intermediates. However, when they are opened by the nucleophilic solvent, a pair of anti enantiomers are formed. In this case, there is no internal symmetry because two different groups (Br and OH) were added across the alkene pi bond.

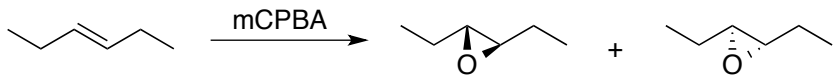


29.

(a) Treatment with sodium hydride leads initially to the complete deprotonation of the hydroxyl group. The anion thus formed can then serve as the nucleophile in an intramolecular S_N2 reaction, which displaces bromide as a good leaving group and closes the epoxide.

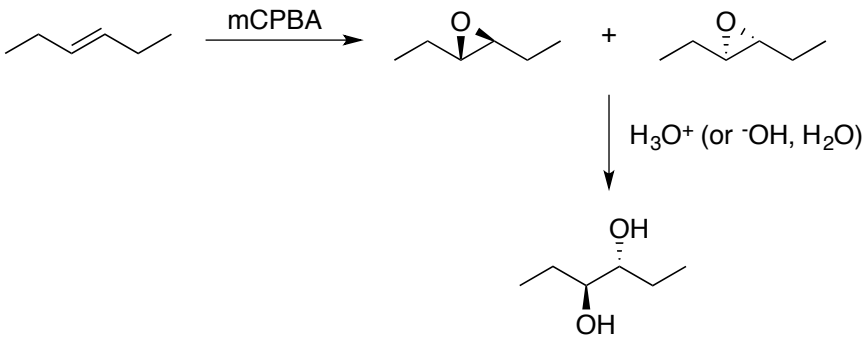


(b) These same enantiomeric epoxides can be made directly from *trans*-3-hexene by epoxidation with a peroxyacid, such as mCPBA.

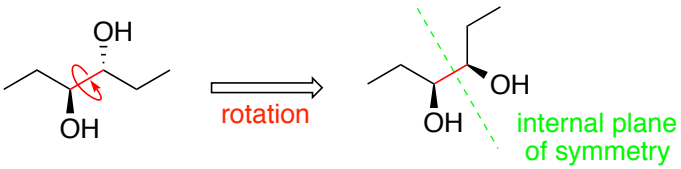


30.

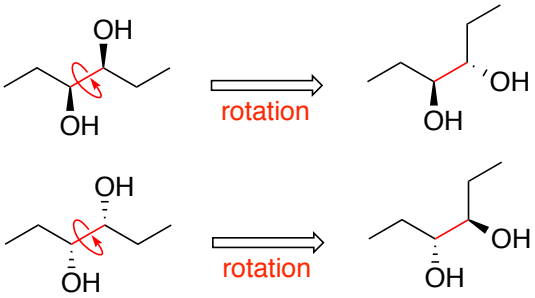
(a) Anti dihydroxylation entails two steps: (1) epoxidation and (2) opening of the epoxide in aqueous acid or base. Since the anti arrangement of the hydroxyl groups is readily apparent in this target, we merely need to choose the corresponding alkene as the reactant. Epoxidation of *trans*-3-hexene yields a pair of epoxide enantiomers that converge on a single diol upon opening in aqueous acid or base.



The reason for this may not be entirely clear until we look more closely for internal symmetry. Remember that it is important to draw a molecule in its most highly symmetrical conformation in order to find internal symmetry when it exists. The conformation given in the original problem happens not to be the most highly symmetrical one, but rotation about the central carbon-carbon bond reveals a more symmetric conformation in which the internal symmetry is clear. This diol is a meso compound, which explains why there is only one product of this reaction. This diol has no enantiomer.

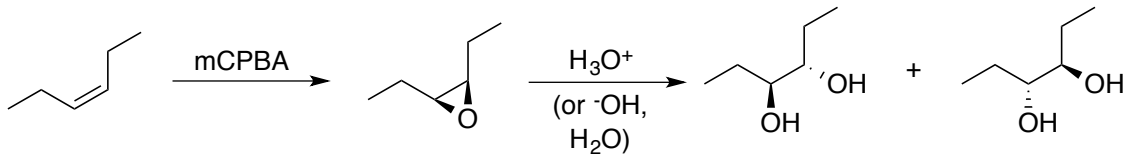


(b) The challenge in this question stems from the fact that the anti arrangement of the hydroxyl groups is not present in the given conformation. However, if we rotate about the central carbon-carbon bond in each of the target molecules, we can find a conformation in which the two hydroxyl groups are anti to one another.



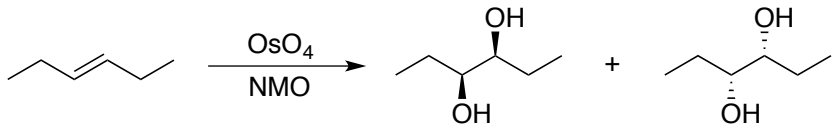
Now, it is apparent how these can be anti vicinal diols. Their synthesis can be achieved through: (1) epoxidation and (2) opening of the epoxide in aqueous acid or base. But, it is important to use an alkene reactant that preserves the correct geometry of the hydrocarbon framework. In other words, *cis*-3-hexene must be used as the substrate. Treatment with a peroxyacid, like mCPBA, gives a single meso epoxide. When the epoxide is opened in aqueous acid or base, a pair of anti

enantiomers is formed. Each one derives from the attack of the nucleophile (water or hydroxide, depending on the method used) on one of the two epoxide carbons.

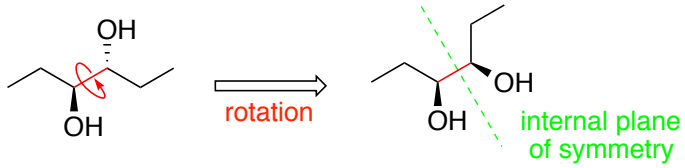


31.

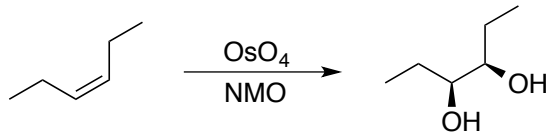
(a) In this instance, the syn arrangement of the hydroxyl groups is readily apparent, so we need only select an alkene that preserves the desired geometry of the hydrocarbon skeleton: *trans*-3-hexene.



(b) In this synthesis problem, there doesn't initially seem to be a syn arrangement of the hydroxyl groups. However, if we rotate about the central carbon-carbon bond, we can locate a conformation in which the hydroxyl groups are syn to one another. Also, notice that this particular conformation illustrates why the target is a meso compound.



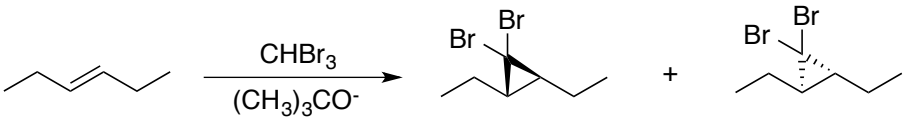
Now that a syn arrangement is apparent, we can choose an alkene reactant that preserves the geometry of the hydrocarbon backbone: *cis*-3-hexene.



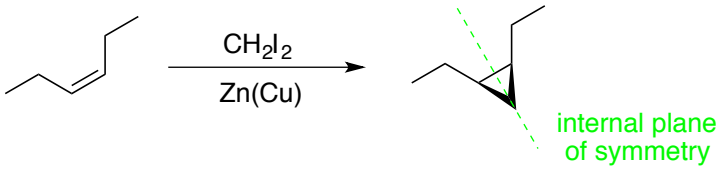
Compare part (a) of this question to Problem 30(b). Then, compare part (b) of this question to Problem 30(a). You'll notice that different alkenes must be used to make the same target molecules due to the difference in stereochemistry between the two dihydroxylation reactions.

32.

(a) Cyclopropanation using bromoform ($CHBr_3$) and *tert*-butoxide proceeds via a dibromocarbene, which adds to the alkene in a concerted fashion. As a result, the addition is syn, and only the syn enantiomers results from this reaction.



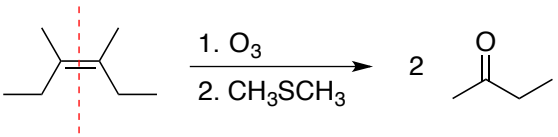
(b) This Simmons-Smith reaction proceeds via a carbenoid, which also adds to the alkene in a concerted fashion, giving the syn product. However, in this case, the cyclopropane derivative formed is a meso compound and has no enantiomer.



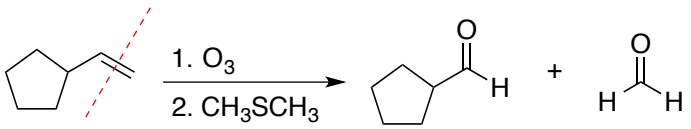
Compare these cyclopropane derivatives to the epoxides formed in Problem 30. You'll notice similar stereochemical outcomes.

33.

(a) From the perspective of simply predicting the products of an ozonolysis reaction, it is most important to remember that the net result of the mechanism was to cleave both bonds of the alkene, separate the resultant fragments, and replace the two bonds to carbon with two bonds to oxygen (i.e., a carbonyl). In the following diagram, the dotted red line signifies where the alkene is cleaved. This symmetrical alkene results in two identical ketones upon reductive workup with dimethyl sulfide.

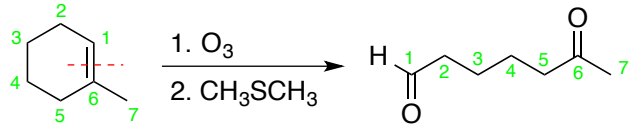


(b) As described in part (a) above, the olefin is cleaved, and two carbonyls are formed. In this case, the alkene is unsymmetrical and yields two different carbonyl-containing products, both of which happen to be aldehydes.



(c) As described in part (a) above, the olefin is cleaved, and two carbonyls are formed. This problem is a bit more challenging because the substrate is a cycloalkane, and as a result, it can be difficult to envision how the molecule unravels as the double bond is cleaved.

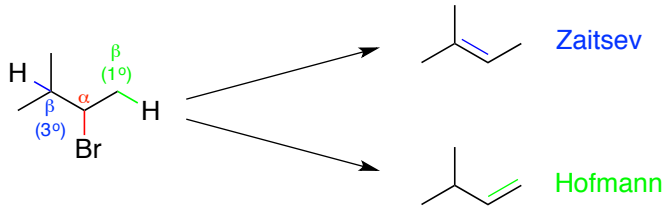
The best and simplest solution is to number the atoms. Note that this number is only for the purposes of tracking the atoms. Consequently, the numbers are arbitrary and have no correlation to IUPAC nomenclature. The numbering makes it easy to draw the seven-carbon backbone of the product and to insert the carbonyls at the correct locations (C1 and C6). Notice that cyclic alkenes afford a single ozonolysis product with two carbonyl-containing functional groups, which in this case happen to be an aldehyde and a ketone.



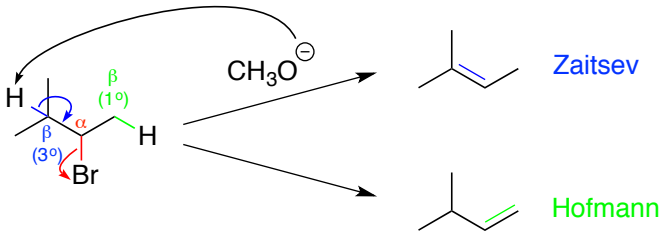
34.

(a) In this question, alkenes are synthesized from alkyl halides, which necessitates elimination. If you are ever stumped on a synthesis problem, try to use simple tools to work past the initial confusion. For instance, molecular formula difference is a simple and powerful tool. If you compare the differences between this substrate and the alkene products, you'll notice that HBr is lost to form the products. HBr is, of course, and acid, so it would make sense that base is needed to effect the conversion.

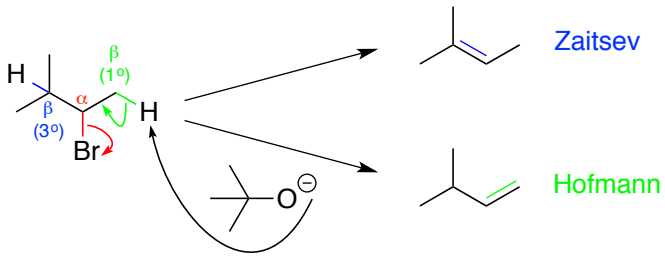
The only question that remains is which bases will give us the desired alkenes. Notice that one alkene is more highly substituted than the other. This is the Zaitsev product, which is trisubstituted in this case. The other alkene is only monosubstituted. Being less substituted, it is known as the Hofmann product.



In order to make the Zaitsev product, we must remove a proton from the more substituted β position, which is tertiary in this case. A small base must be used in order to accomplish this. Its small size allows it to reach the more hindered center to remove the β proton that will give rise to the more stable product.



To make the less stable Hofmann product preferentially, we'll need to use a bulky base that can only successfully approach the less hindered β position, which is primary in this substrate.

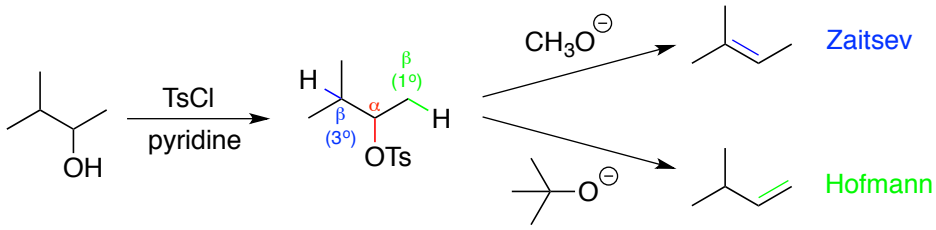


(b) As in part (a) above, molecular formula difference can be a powerful tool for generating ideas during a synthesis problem. Here, the difference in formula between the alcohol reactant and either alkene product is H_2O. This reveals the necessary reaction: dehydration.

It is important to remember that dehydration can be accomplished in multiple ways. One option is direct dehydration using concentrated sulfuric acid; however, this always yields the Zaitsev product as the major product and can suffer from complicating carbocation rearrangement in some cases.

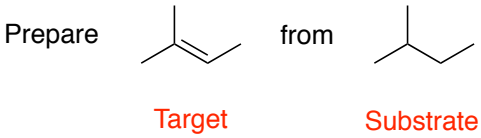
An alternate option that is strategically safer when composing answers to synthesis problems is to convert the alcohol to a tosylate, which can then be treated with a small or large strong base to afford the Zaitsev or Hofmann product, respectively.

Once the poor leaving group (hydroxide) has been converted to a good leaving group (the tosylate), this question is extremely similar to part (a). Methoxide, a small base, provides the Zaitsev product. On the other hand, *tert*-butoxide, a bulky base, gives the Hofmann product.

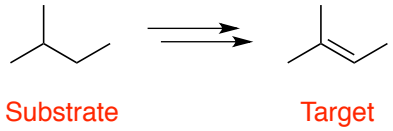


35.

(a) The first step is to make sure that we are properly understanding the question. To do this, label the target and the substrate. The molecule being prepared is the target, while the molecule being used is the substrate.

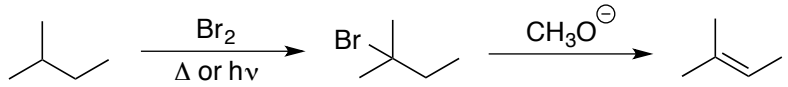


Then, rewrite the question in a fashion with which we are more comfortable (i.e., substrate yields target after some number of steps). This is a trivial but important step because it prevents us from inadvertently trying to complete the synthesis in the opposite of the direction stated in the problem.

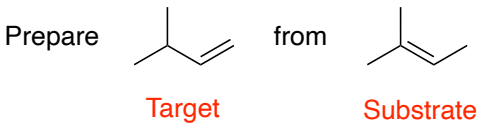


Now, let's think broadly about the challenge. The goal here is to convert an alkane to an alkene. We know no direct method for this. However, we do know that alkanes can be converted to alkyl halides via radical halogenation. And, these alkyl halides can, in turn, be eliminated to provide alkenes.

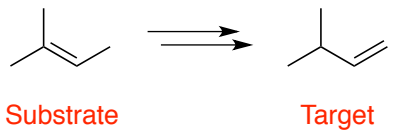
Radical halogenation proceeds through the most substituted (and therefore most stable) radical to give the tertiary alkyl bromide. Subsequent elimination with a small base, such as methoxide, affords the Zaitsev alkene.



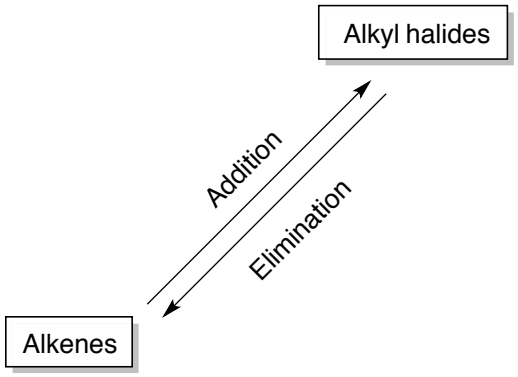
(b) Again, it is useful to make sure that we are doing the problem in the right direction by labeling the target and the substrate.



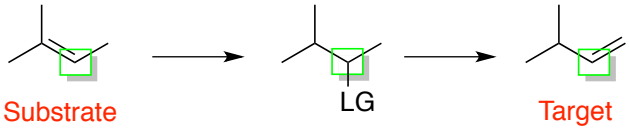
Then, rewriting the problem makes the format look more familiar.



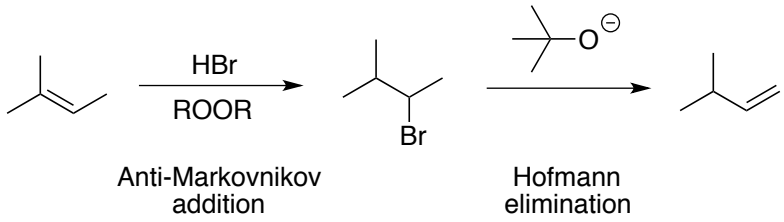
In this instance, we want to make an alkene from an alkene. We have learned no method to directly migrate a pi bond. However, we do know that alkenes can be converted to alkyl halides (or alcohols) and back again to alkenes via a sequence of addition and elimination.



If a leaving group (such as a halide) is to be added to the substrate, it should be added to the one carbon that is functionalized in both the starting material and the target. We need to maintain reactivity at this center throughout the sequence. This necessitates anti-Markovnikov regiochemistry during the addition.

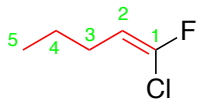


Anti-Markovnikov hydrohalogenation requires radical conditions (HBr and peroxides). This can be followed by Hofmann elimination using a bulky base to remove a proton from the more sterically accessible β position, yielding the desired target molecule.

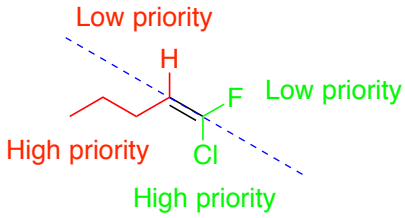


36.

(a) The parent here is a five-carbon chain with the alkene originating at C1, making it a 1-pentene. Adding the substituents to the name, we have 1-chloro-1-fluoro-1-pentene. However, a stereochemical designation is still needed.

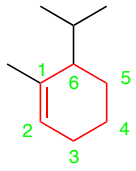


On the left-hand alkene carbon, the propyl group is higher priority than the hydrogen. On the right-hand alkene carbon, the chlorine has a higher priority than fluorine due to chlorine's higher atomic number. Since the high priority groups are on the same side of an axis running through and parallel to the alkene, this is a *Z* alkene. The complete name is therefore (*Z*)-1-chloro-1-fluoro-1-pentene.



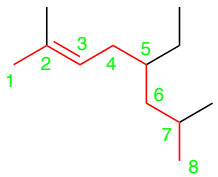
High priority groups on same side of axis through and parallel to alkene = *Z*

(b) The parent is cyclohexene. Remember that a number is not needed to indicate the position of the olefin in a ring because all sites within the ring are equivalent until the double bond is placed. The alkene carbons are C1 and C2, but given that they receive the same numbers regardless of whether we number them clockwise or counterclockwise, we assign the lowest possible number to the first substituent. With the numbers in place, the molecule can be named as 6-isopropyl-1-methylcyclohexene.



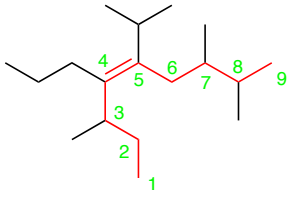
Note that no stereochemical designation is needed for this alkene because cycloalkenes of less than eight carbons in size must have the *cis* configuration.

(c) The eight-carbon chain is the longest continuous carbon chain containing both of the alkene carbons, so it is the parent. We number so as to give the alkene carbons the lowest possible numbers, and the parent therefore becomes 2-octene. Adding the substituents, the name is expanded to 5-ethyl-2,7-dimethyl-2-octene.

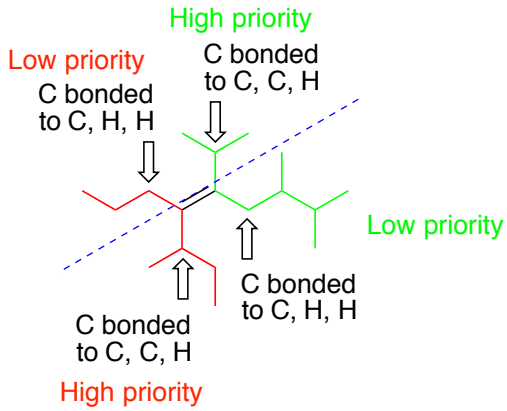


Note that no stereochemical designation is needed in this case because one of the alkene carbons (C2) bears two identical methyl groups. As a result, there is no geometric (E/Z) isomerism in this molecule.

(d) Although it is tempting to select the nine-carbon chain running horizontally as the parent, there is a second nine-carbon chain (highlighted in red below) that possesses a larger number of substituents. Remember that, all other things being equal, the parent that gives more substituents is preferred. We number so as to give the alkene the lowest possible number, and the core of the name can be derived as: 5-isopropyl-3,7,8-trimethyl-4-propyl-4-nonene. However, we still need to add a stereochemical descriptor in order to complete the name.



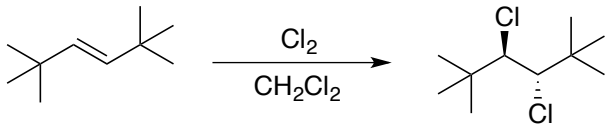
On the left-hand alkene carbon, the *sec*-butyl group is the high priority group. On the right-hand alkene carbon, the isopropyl group is the high priority group. Since the high priority groups are on opposite sides of an axis through and parallel to the alkene, this is an *E* alkene, and the complete name is: (*E*)-5-isopropyl-3,7,8-trimethyl-4-propyl-4-nonene.



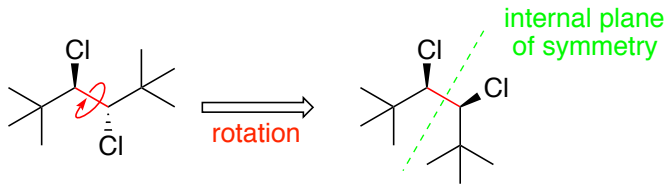
High priority groups on opposite sides of axis through and parallel to alkene = *E*

37.

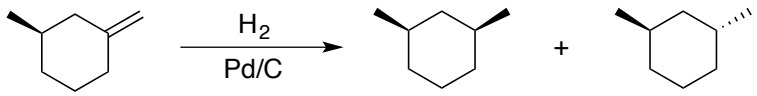
(a) This is a halogenation reaction. A chloronium ion is initially formed as a chlorine atom adds across the alkene pi bond. Then, chloride opens the chloronium ion from the opposite side, yielding an anti addition product.



This is the sole product of the reaction because it is a meso compound. This becomes more apparent upon rotation about the central C-C bond.

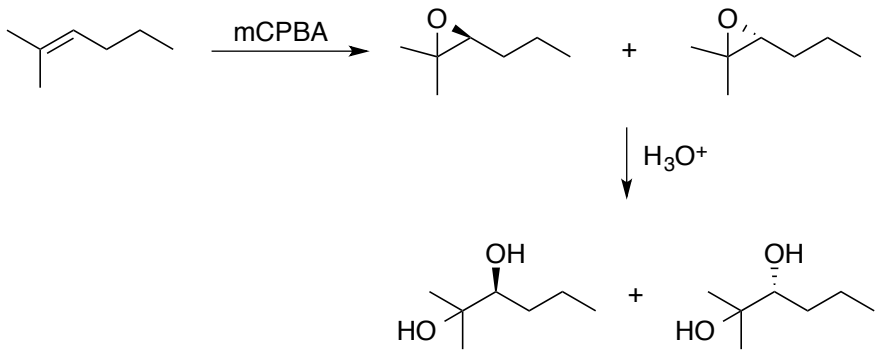


(b) This is hydrogenation, which adds H_2 across the pi bond. In the process, a new stereocenter is formed. Since hydrogen can add from either side of the olefin, the products are the *cis* and *trans* isomers of 1,3-dimethylcyclohexane, which are diastereomers.



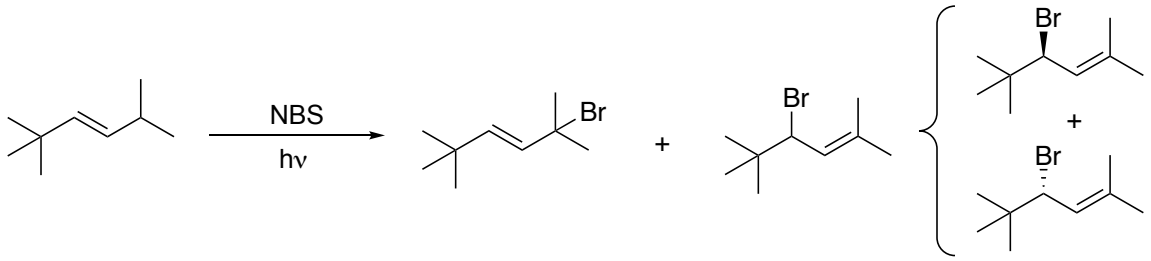
Notice that the preexisting chiral center is unaffected by the transformation because no reaction takes place at that site.

(c) This is an anti-dihydroxylation which entails two steps: (1) epoxidation and (2) acidic opening of the epoxide. Epoxidation with a peroxyacid, like mCPBA, affords enantiomeric epoxides. Both of these are protonated, and the resulting oxonium ion is opened by attack of water at the more substituted center (bearing the greater δ^+). The result is a pair of enantiomeric diols, which contain only a single stereocenter each.

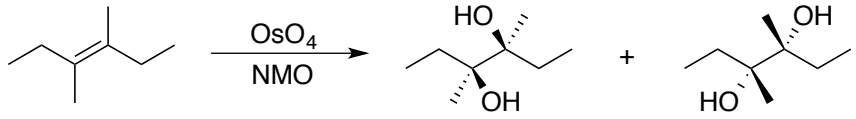


(d) This is allylic bromination. During the first propagation step, a hydrogen is abstracted from an allylic carbon, leading to a resonance-stabilized radical. This implies that at least one allylic hydrogen is required for the reaction. While there are

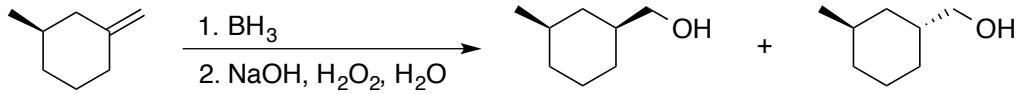
two allylic centers in this substrate, only one has a hydrogen. Either resonance form of the resulting radical can abstract a bromine atom in propagation step 2 leading to two regioisomers, the latter of which is formed as a pair of enantiomers.



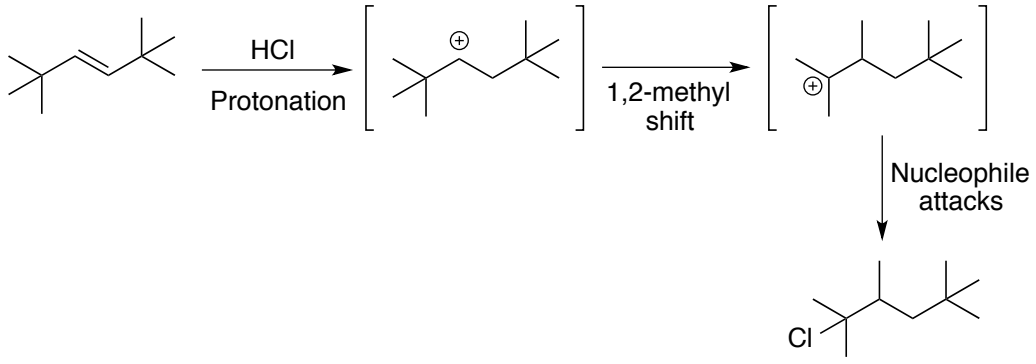
(e) This is a syn-dihydroxylation. Osmium tetraoxide adds across the olefin, forming two stereocenters in a syn fashion. Upon cleavage of the cyclic osmate ester, a pair of syn vicinal diols are formed.



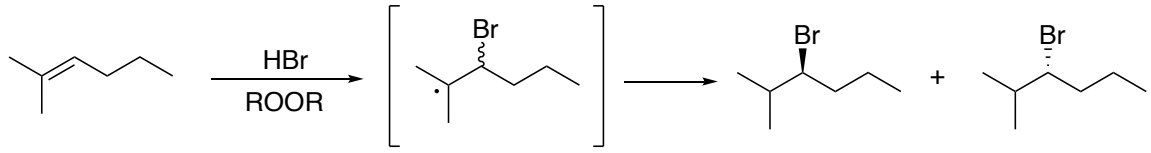
(f) In this hydroboration-oxidation, the alkene is hydrated with anti-Markovnikov regiochemistry. The result is a primary alcohol, containing one new stereocenter. This new stereocenter can have either configuration, but the preexisting stereocenter is unaffected since no reaction happens at that site. The products are diastereomeric alcohols.



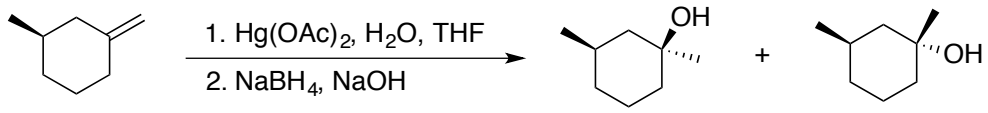
(g) This is an ionic hydrohalogenation, which begins with protonation. Due to the symmetry of the molecule, only one carbocation can be formed, but it readily rearranges to yield a more stable cation. Subsequent attack of the nucleophile affords the alkyl chloride product.



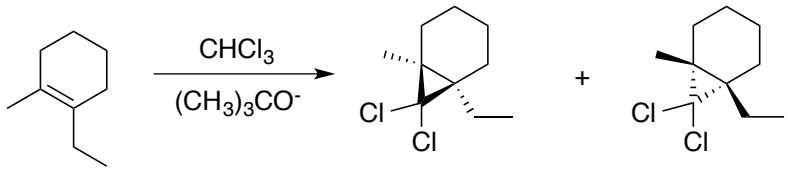
(h) Radical hydrohalogenation proceeds with anti-Markovnikov regiochemistry. This is the result of addition of bromine radical to the alkene so as to form the more stable carbon radical, which is tertiary in this case. Subsequent abstraction of a hydrogen from HBr affords the alkyl bromide product as a pair of enantiomers.



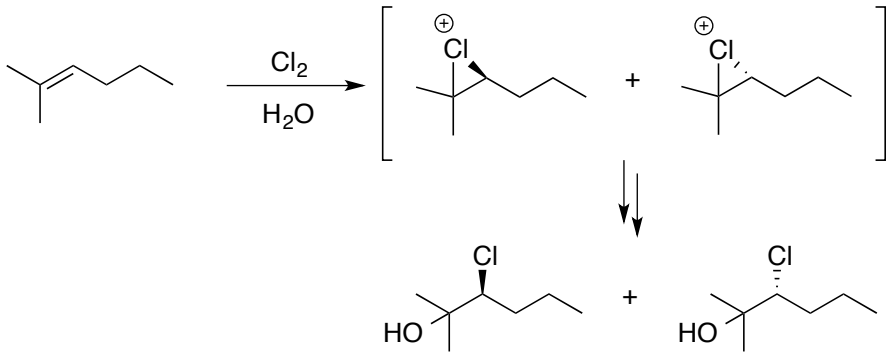
(i) Oxymercuration-demercuration provides Markovnikov regiochemistry. In this case, one new stereocenter is formed, and it can have either configuration. The preexisting chiral center is unaffected because no reaction transpires at that site. The products are therefore diastereomeric alcohols.



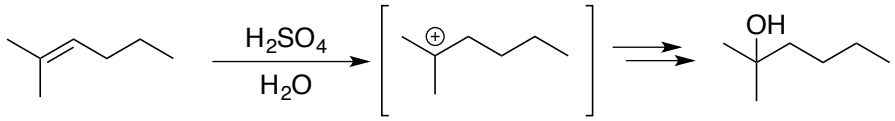
(j) In this cyclopropanation reaction, a dichlorocarbene is formed from the reaction between chloroform ($CHCl_3$) and *tert*-butoxide. The dichlorocarbene ($:CCl_2$) adds across the olefin, creating two new stereocenters in the process. Since the addition is concerted, it occurs with syn stereochemistry, and the products are the syn enantiomers.



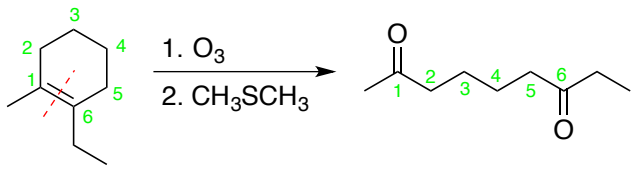
(k) In this transformation, a chloronium ion is initially formed from the reaction between the alkene and chlorine. Since chlorine can add to either side of the alkene, two enantiomeric chloronium ions are formed. They are both opened at the more substituted center (bearing the greater δ^+) by the nucleophilic solvent (H_2O). Enantiomeric halohydrins are formed. Although these are the result of anti addition, it is not readily apparent because each product contains only one stereocenter.



(l) Acid-catalyzed hydration is initiated when the alkene is protonated so as to yield the more stable carbocation intermediate. Water then adds to this site and subsequently sheds a proton to the medium, affording a Markovnikov alcohol.

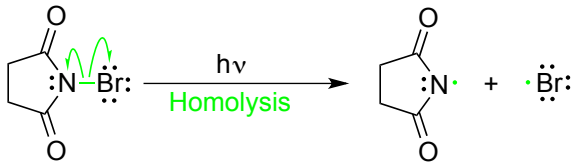


(m) Ozonolysis of cycloalkenes can be tricky because it is difficult to envision the unfolding of the ring as the double bond is cleaved. The simplest solution is numbering for the purpose of keeping track of the atoms (note: this numbering is arbitrary and need not be tied to IUPAC nomenclature). Numbering the ring allows us to easily see that C1 becomes a carbonyl bearing a methyl group, while C6 becomes a carbonyl bearing an ethyl group. The product in this case is a diketone.



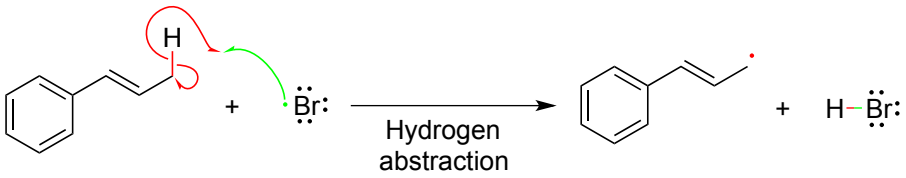
38. This is an allylic halogenation, which begins with the homolysis of a few molecules of NBS upon exposure to light during the initiation step.

Initiation:

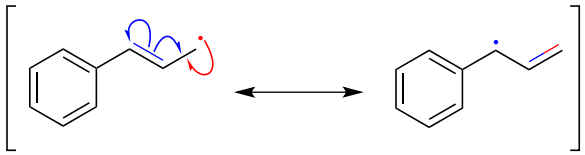


In propagation step 1, the bromine radical formed during initiation abstracts a hydrogen from the allylic center.

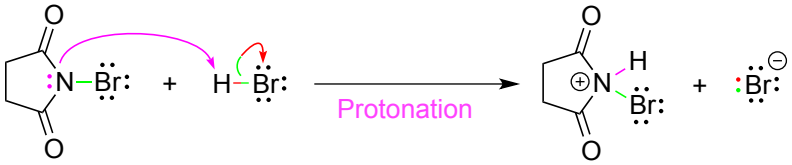
Propagation step 1:



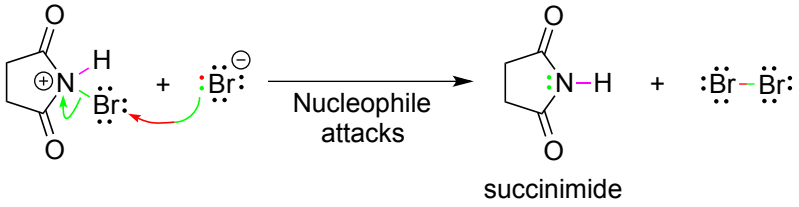
The hydrogen abstraction occurs specifically at the allylic center because the radical that forms as a result has resonance stabilization. There are also additional resonance forms involving the benzene ring.



A series of two ionic steps follow in which the HBr produced in propagation step 1 reacts with NBS so as to ultimately form succinimide and Br_2. NBS is first protonated.

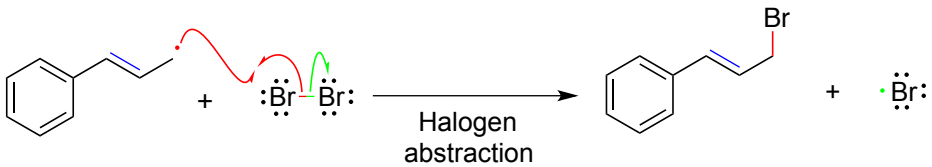


Then, bromide attacks the bromine atom of NBS, cleaving it from the molecule and yielding Br_2. In this way, a slow, steady concentration of Br_2 is introduced into the reaction. Every time that the first propagation step occurs, a molecule of HBr is produced, which in turn reacts with a molecule of NBS to yield a molecule of Br_2.

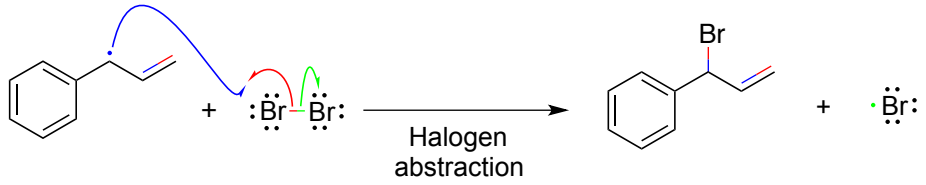


In propagation step 2, the carbon-centered radical abstracts a bromine atom from the newly formed molecule of Br_2. Since there are two centers outside the ring bearing radical character, either may react to yield two allylic bromide products.

Propagation step 2:

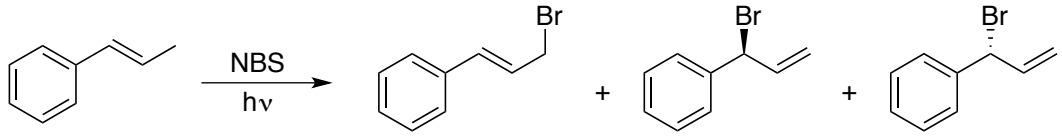


Propagation step 2:

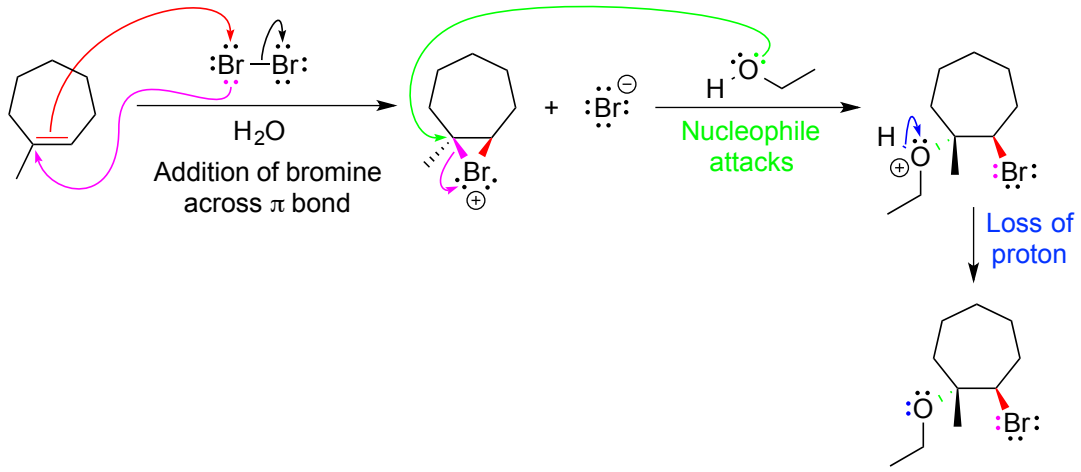


Although there are also centers on the ring bearing radical character, we'll see in the chapter on Aromaticity that there is an energetic advantage to maintaining the pattern of alternating single and double bonds in the ring.

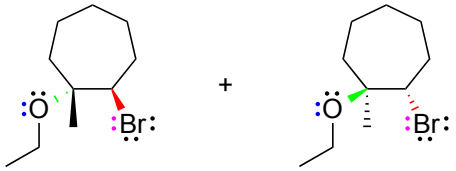
The latter product includes a stereocenter, which can have either configuration, so there are a total of three products of this reaction.



39. The reaction begins with the addition of a bromine atom across the pi bond to yield a bromonium ion. Bromine can add to either side of the flat alkene, so two enantiomeric bromonium ions are formed, one of which is shown below. In this case, ethanol is the solvent. Although it differs from water, it is nucleophilic much like water and can therefore attack the bromonium ion at its more substituted carbon (the one with the greater δ^+). Note that the attack occurs opposite the bromine leaving group. The resulting oxonium ion simply sheds a proton to the medium to provide the product.



The enantiomeric bromonium ion formed in the first step of the mechanism ultimately leads to an enantiomeric product, so this reaction produces a racemic mixture of the following two compounds.



When water was used as the solvent, a halogen and a hydroxyl group were added across the alkene pi bond. When an alcohol is used as the solvent instead, the product is similar, but a halogen and an alkoxy group (OR) are added across the olefin.

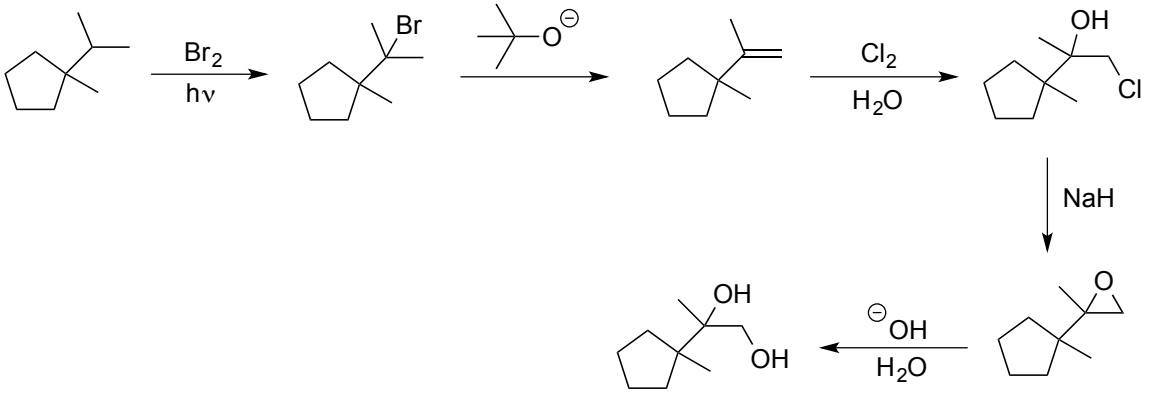
40. The first step is a radical halogenation of an alkane. This proceeds via abstraction of hydrogen from the most highly substituted carbon so as to yield the most stable radical intermediate. There is only one tertiary carbon in the substrate, so it is the site of reaction and ultimately bears the halogen.

Next, *tert*-butoxide (a strong base) incites elimination. The only β positions bearing protons are the methyl groups. Removal of a proton from either leads to the same alkene product.

In order to make a halohydrin, we must add the appropriate halogen (in this case, chlorine) to the alkene along with water, which is a nucleophilic solvent that opens the intermediate chloronium ion.

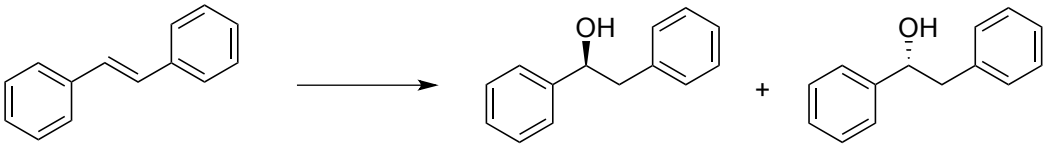
To convert the halohydrin to the epoxide, it is necessary to deprotonate the hydroxyl group. Complete deprotonation of the hydroxyl group requires a very strong base, such as sodium hydride. Once deprotonated, the oxygen anion performs an intramolecular S_N2 reaction, displacing chloride and forming the epoxide.

Finally, in the presence of aqueous hydroxide, the epoxide is opened at its more sterically accessible site to afford the vicinal diol as the final reaction product.

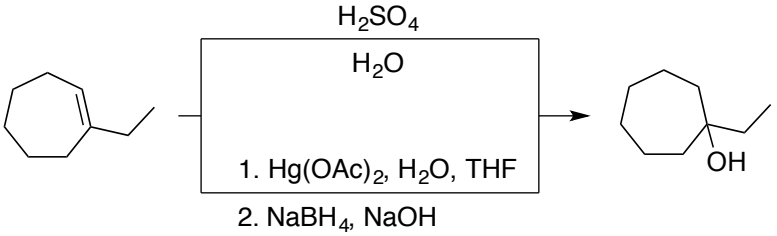


41.

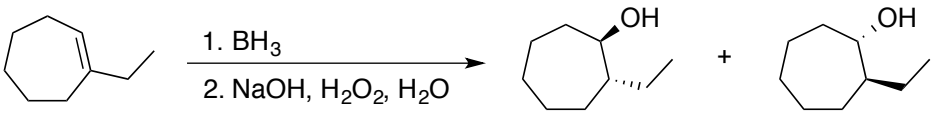
(a) This alkene, known as *trans*-stilbene, is symmetrical, so any of the three methods would lead to the formation of the same racemic mixture of enantiomeric alcohols.



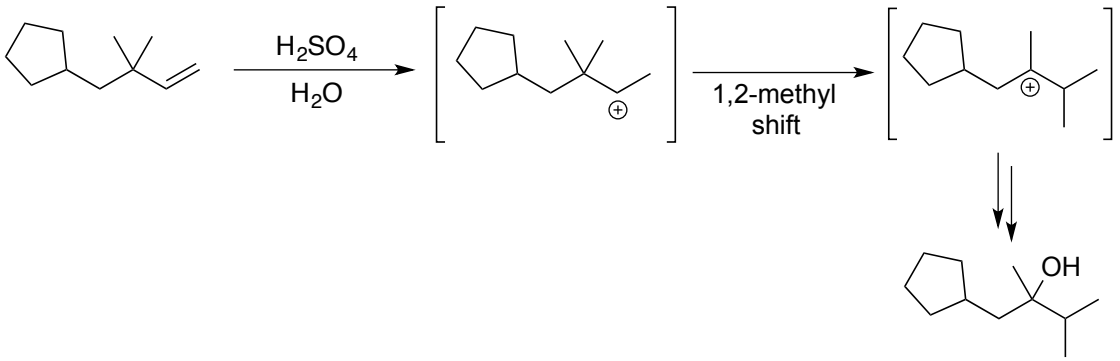
(b) This substrate provides the same Markovnikov alcohol upon either acid-catalyzed hydration or oxymercuration-demercuration. There are no stereocenters in the product.



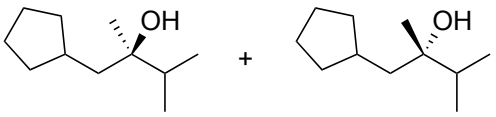
However, hydroboration-oxidation yields an anti-Markovnikov alcohol instead. This product does contain two stereocenters, and given that hydroboration-oxidation occurs with syn stereochemistry, the products that result are the two enantiomers in which the hydroxyl group and the newly added hydrogen (on the carbon bearing the ethyl group) are syn to one another.



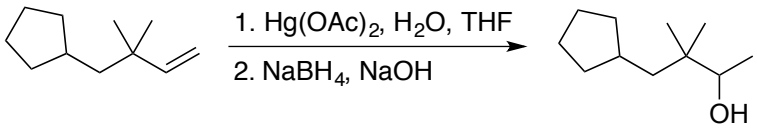
(c) This substrate, on the other hand, gives different products with each of the three methods. Acid-catalyzed hydration proceeds via protonation in a Markovnikov fashion. A 1,2-methyl shift follows, giving a more stable carbocation. Addition of water to this newly formed carbocation and subsequent loss of a proton afford the tertiary alcohol product.



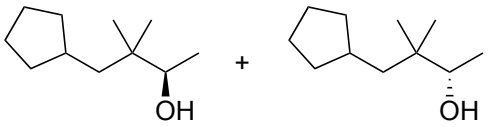
The product contains a single stereocenter, which is formed with either configuration.



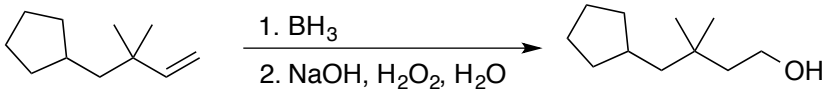
Oxymercuration-demercuration avoids carbocation intermediates and therefore does not suffer from carbocation rearrangement. Consequently, the product is the secondary alcohol resulting from the Markovnikov regiochemistry of this transformation.



Again, the product contains one stereocenter and is therefore a racemic mixture.



On the other hand, hydroboration-oxidation exhibits anti-Markovnikov regiochemistry and gives a primary alcohol without stereocenters as the product.



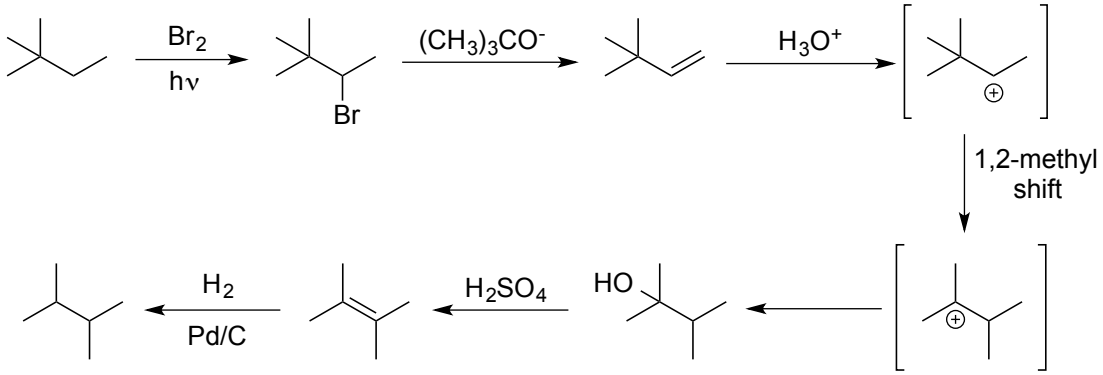
42. We are told that the substrate is an alkane, and we have the structure of the carbon skeleton from the first intermediate. Therefore, we can fill in the structure of the starting alkane: 2,2-dimethylbutane.

Treatment of the alkyl bromide with *tert*-butoxide leads to elimination, and there is only one β position with protons. So, elimination produces 3,3-dimethyl-1-butene.

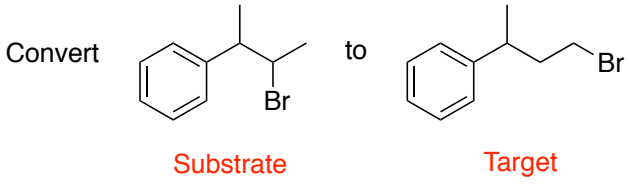
Acid-catalyzed hydration of this alkene begins with protonation, which forms a secondary carbocation. A 1,2-methyl shift gives a more stable tertiary carbocation to which water adds. Upon loss of a proton from the oxonium ion, a tertiary alcohol is formed.

Dehydration with concentrated sulfuric acid gives predominantly the Zaitsev alkene.

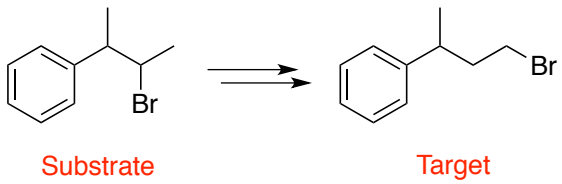
Finally, hydrogenation yields an alkane whose hydrocarbon framework differs from that of the original substrate due to the 1,2-methyl shift that occurred during acid-catalyzed hydration.



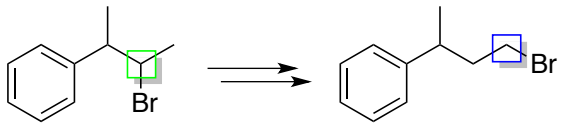
43. It is always useful to begin synthesis problems by labeling the substrate and the target. In this case, the first compound written is the substrate due to the wording of the question.



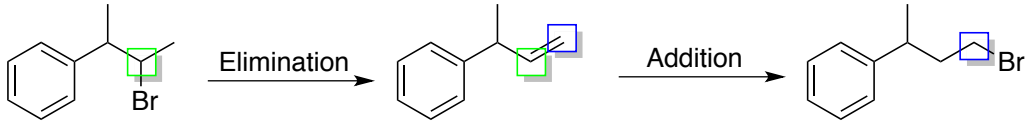
Having identified the substrate and target, we can rewrite the problem in the usual format.



We know no method that directly slides a halogen from one carbon to the adjacent center. However, if adjacent centers need to be functionalized at one time or another in the synthesis, this suggests the intermediacy of an alkene.

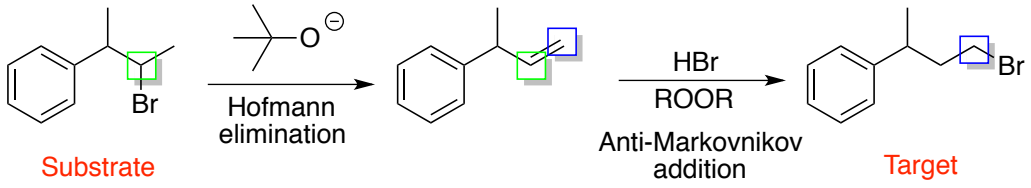


An alkene could be formed by elimination of the substrate, and the alkene could yield the target upon addition.

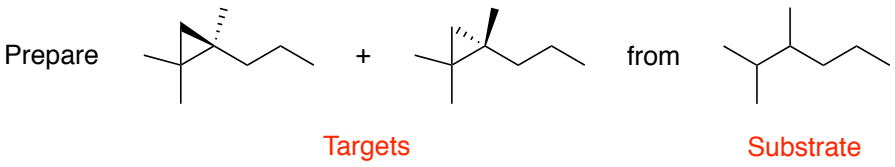


All that remains is to choose the appropriate reagents. For elimination, we must choose Zaitsev or Hofmann regiochemistry. In this case, the desired intermediate is the Hofmann alkene, which is formed when a bulky base is used. The bulky base can only access the less sterically encumbered β position.

For addition, we must choose Markovnikov or anti-Markovnikov regiochemistry. In this case, the desired target has anti-Markovnikov regiochemistry, so the proper reagents to effect this conversion are HBr and peroxides.



44. As always, it is prudent to begin a synthesis problem by assigning the substrate and target(s).

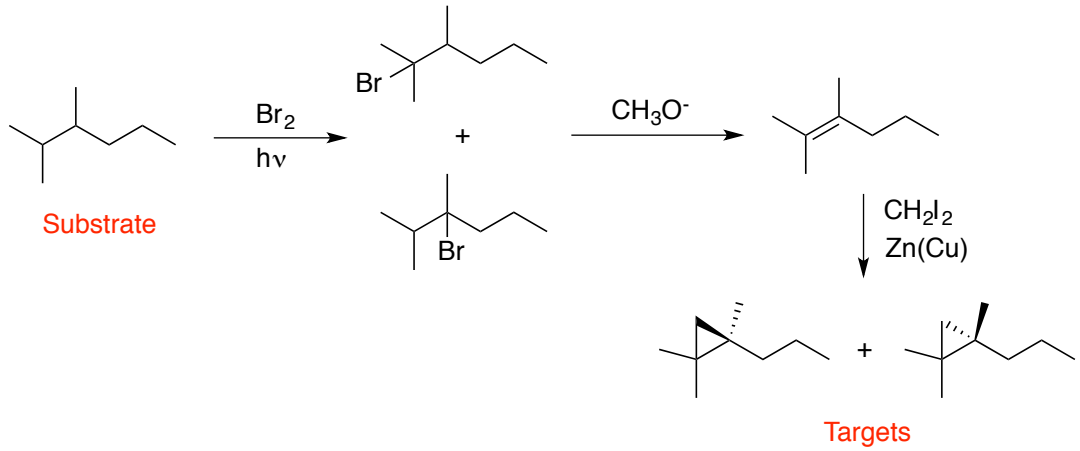


This allows us to rewrite the problem in a more familiar format.

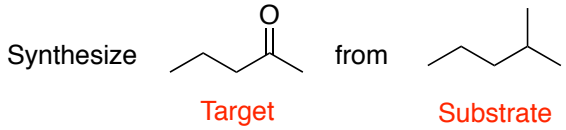
Substrate Targets

Drawing a full retrosynthesis can always be helpful; however, many students aren't comfortable with retrosynthesis and don't want to draw it. At least try to engage in some retrosynthetic thinking though. For instance, we know that cyclopropane rings can be made from Simmons-Smith reaction of an alkene. Therefore, we need to make an alkene in which the double bond spans the two carbons that will be joined by the CH_2 group of the cyclopropane ring.

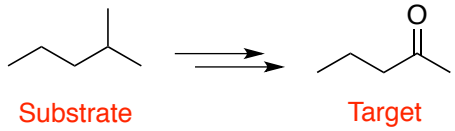
To do so, we must first functionalize the alkane. The only way that we know to functionalize an alkane is radical halogenation, which proceeds via the most stable radical. However, bromination will yield two products in this case because there are two tertiary centers in the molecule. This is of little consequence though because both alkyl bromides can undergo elimination to converge on the same Zaitsev alkene. A small base, like methoxide, should be used to favor the Zaitsev over the Hofmann alkene. Finally, Simmons-Smith reaction yields the substituted cyclopropane of the target. Since one stereocenter is formed in the final reaction, both enantiomers are obtained.



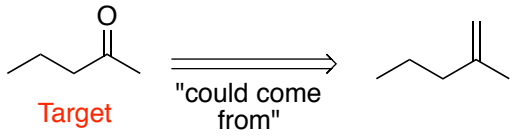
45. We are being asked to synthesize a ketone (2-pentanone) from 2-methylpentane. First, label the target and the substrate.



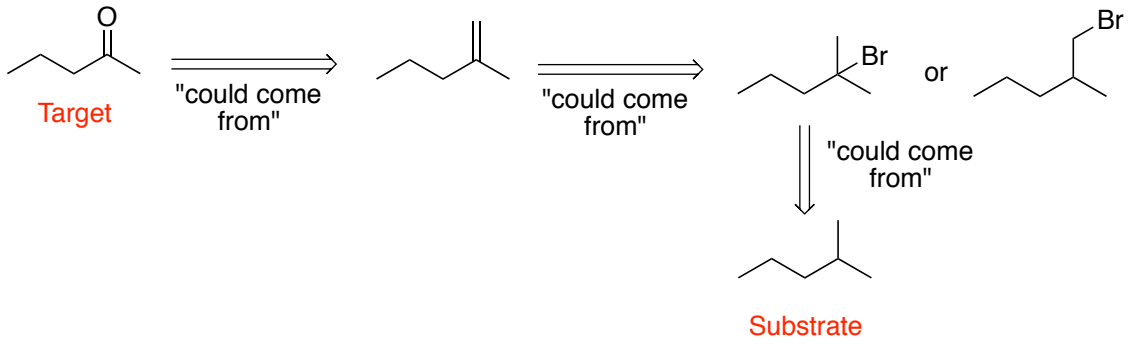
Then, rewrite the problem in a more familiar format.



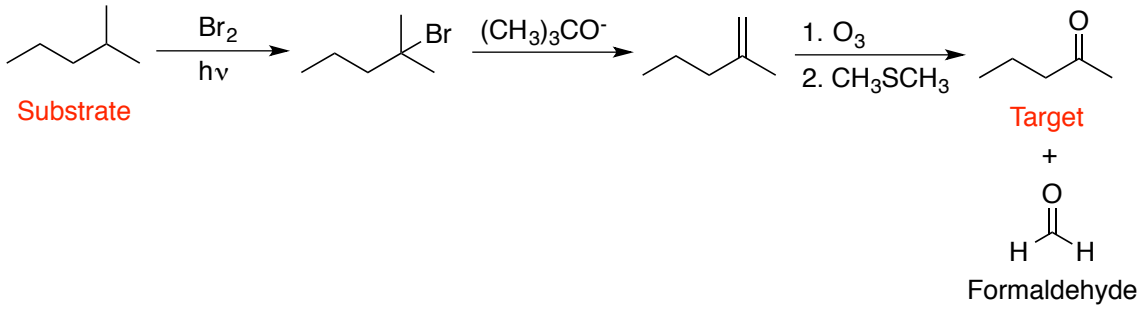
The key realization in this problem is that the target contains fewer carbons than the substrate. The substrate has six carbons, and the target has only five. The only method that we currently know for breaking carbon-carbon bonds is ozonolysis, so it must be used in this synthesis. Furthermore, ozonolysis requires an alkene reactant, so we can write a retrosynthetic step as follows. Remember that the retrosynthetic arrow can be read as "could come from."



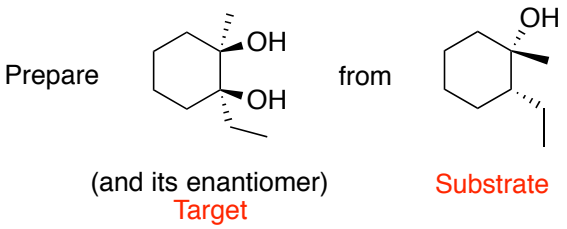
To make the alkene, we need to do an elimination, which necessitates a leaving group, and we can install such a leaving group through radical bromination of the substrate.



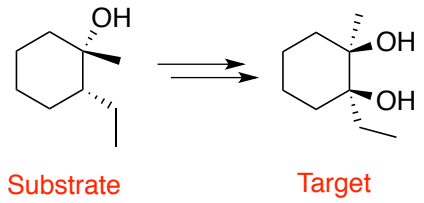
In the forward sense, radical bromination installs a bromine at the tertiary center. Hofmann elimination using a bulky base affords the needed alkene, and ozonolysis degrades that alkene into the target ketone and formaldehyde, which is a byproduct of this synthesis.



46. Always begin by labeling the substrate and the target.

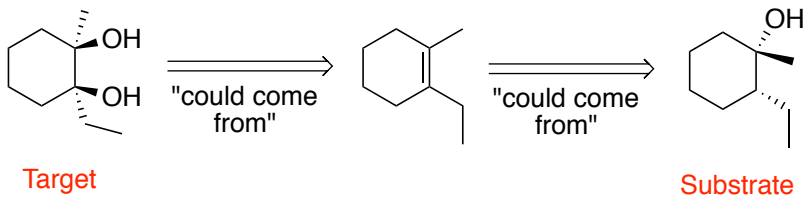


Then rewrite the problem in a more familiar format. Notice that the critical challenge is installing the second hydroxyl group at an unfunctionalized (and therefore seemingly unreactive) center.

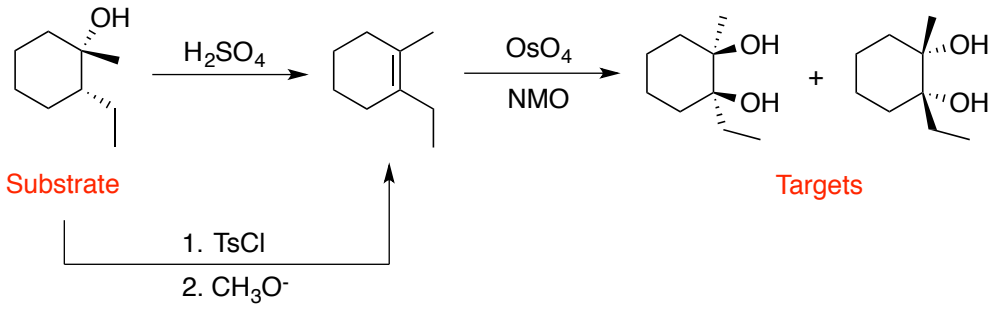


The structure of the substrate can often cloud your judgment. Some students are tempted to think solely in terms of reaction at the carbon bearing the ethyl group. There is a tendency to want to hold onto the hydroxyl group at the carbon bearing the methyl substituent because it is part of the desired target's structure. That's why we are much better served by retrosynthesis.

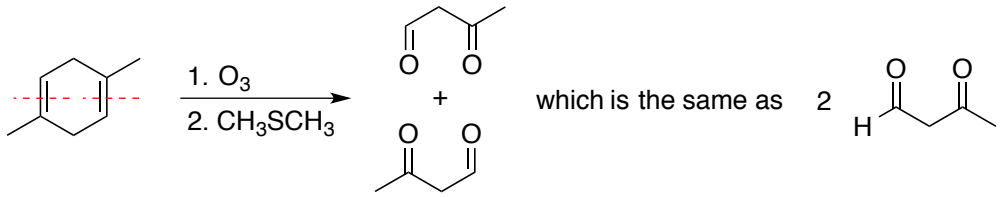
Start by thinking solely in terms of what the target could be made from in a single step. This would likely lead you to the conclusion that an alkene could give rise to the desired vicinal diol via syn-dihydroxylation. The alkene, in turn, could be made from the substrate in a single step: dehydration. Notice that we have to give up the hydroxyl group in the substrate temporarily in order to set the stage for a reaction that adds hydroxyl groups to adjacent centers with the desired stereochemistry.



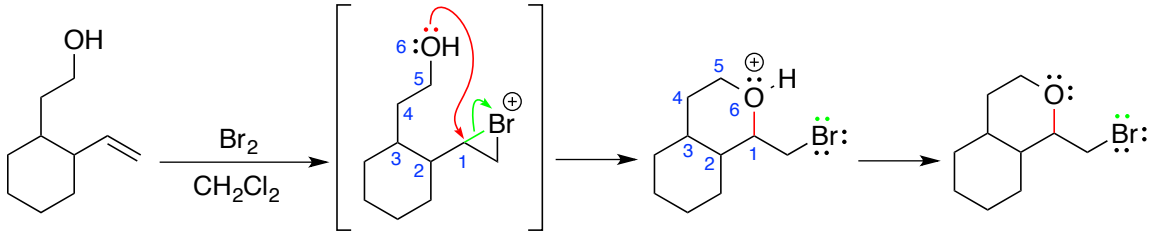
In the forward sense, dehydration of the substrate using concentrated sulfuric acid will provide the needed Zaitsev alkene. Alternatively, the tosylate could be made and treated with a small base (like methoxide) to yield the same alkene. Then, syn-dihydroxylation provides the target compounds.



47. Ozonolysis leads to the cleavage of both the σ and π bonds of an olefin. Both olefins in the reactant undergo this process, thereby breaking the molecule into two identical halves. Each half contains an aldehyde and a ketone, explaining why there are two signals in the carbonyl-stretching region of the IR (around 1700 cm^{-1}).



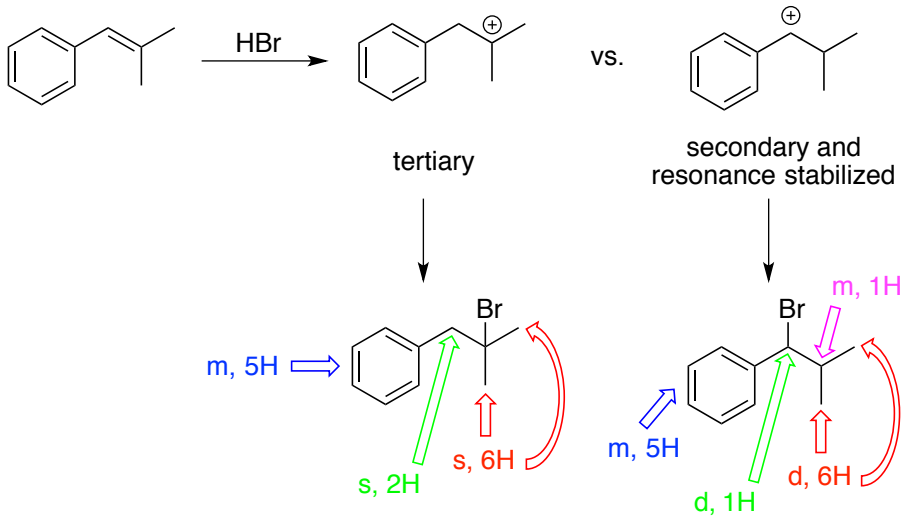
48. The reaction begins as expected with formation of a bromonium ion. We know that nucleophilic solvents, such as water, can open the bromonium ion. We also saw in Problem 39 that an alcohol behaves much like water. This molecule happens to have a tethered alcohol, which can behave in exactly the same fashion as an alcohol solvent would. It attacks the bromonium ion at the carbon bearing the greater δ^+, thereby opening the three-membered ring. The bicyclic oxonium ion thus formed simply sheds a proton to the medium to form the product.



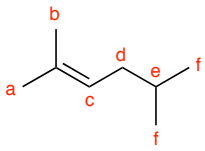
The product contains one bromine atom, so it displays M and M+2 peaks in the mass spectrum for molecules bearing ^{79}Br or ^{81}Br, respectively. However, there are *not* two bromine atoms as we might have expected if we had not thought carefully about the role that the alcohol could play in this reaction.

49. The protonation of the alkene can yield one of two carbocations. Our choices are a tertiary carbocation or a secondary carbocation. We'd certainly expect to form the tertiary carbocation by Markovnikov's rule; however, this fails to take into account the role played by resonance. In this reaction, the secondary carbocation has resonance stabilization, but the tertiary one does not. The resonance-stabilized

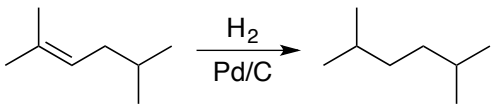
carbocation is preferred, leading to a product that has a structure consistent with the NMR data given.



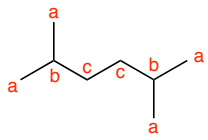
50. The alkene shows a total of six signals in its ^{1}H NMR spectrum. They are labeled a – f below. Note that the two methyl groups stemming directly from the alkene (C_a and C_b) give rise to different signals because one is *cis* to C_d and the other is *trans* to C_d.



Hydrogenation of this alkene affords the alkane shown below: 2,5-dimethylhexane.



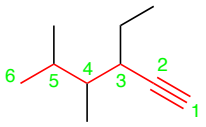
Notice that there is much greater symmetry in the hydrogenation product. Symmetry reduces the number of signals in the NMR spectrum because there are now fewer distinct types of protons in the molecule. They are labeled a – c below.



Solutions to Problems for Chapter 11: Alkynes

1.

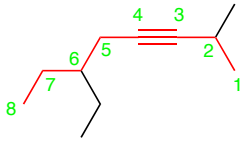
(a) The parent is the longest continuous carbon chain containing the alkyne. It is numbered so as to give the alkyne the lowest possible number, and substituents are named according to the guidelines outlined in earlier chapters.



3-ethyl-4-5-dimethyl-1-hexyne

- Six carbon parent = hexane
- Replace "ane" suffix with "yne"
- Provide a number for the site where the triple bond begins
- Add substituent names and numbers

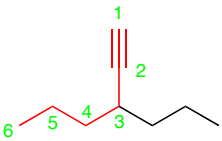
(b) In this problem, it is important to notice that numbering from right-to-left provides the lowest possible number for the alkyne.



6-ethyl-2-methyl-3-octyne

- Eight carbon parent = octane
- Replace "ane" suffix with "yne"
- Provide a number for the site where the triple bond begins
- Add substituent names and numbers

(c) Here, you may be tempted to select the horizontal seven-carbon chain as the parent. However, that heptane chain does not include the alkyne functional group, and the parent must do so. Consequently, the parent is a hexyne instead.

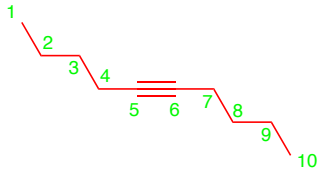


3-propyl-1-hexyne

- Six carbon parent = hexane
- Replace "ane" suffix with "yne"
- Provide a number for the site where the triple bond begins
- Add substituent names and numbers

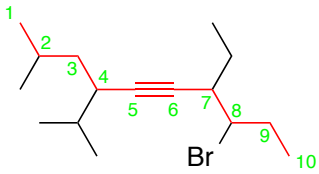
2.

(a) When drawing structures from names, begin at the end of the name. In other words, start by drawing the parent and placing numbers on it.



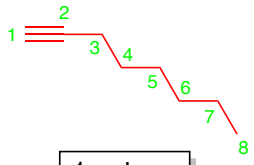
5-decyne

It then becomes relatively trivial to place the substituents.



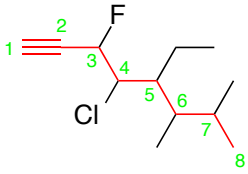
8-bromo-7-ethyl-4-isopropyl-2-methyl-5-decyne

(b) Again, begin by drawing and numbering the parent.



1-octyne

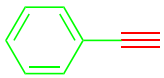
Then, place the substituents to complete the structure.



4-chloro-5-ethyl-3-fluoro-6,7-dimethyl-1-octyne

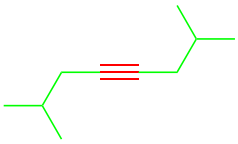
3. Common names are derived by placing the names of the groups connected to the alkyne before the word “acetylene,” which indicates the presence of the triple bond.

(a) Benzene as a substituent is known as a phenyl group.



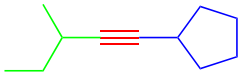
phenylacetylene

(b) In this instance, the two alkyl groups are identical, so they are clustered together as diisobutyl in order to make the name as concise as possible (i.e., *not* isobutylisobutylacetylene).



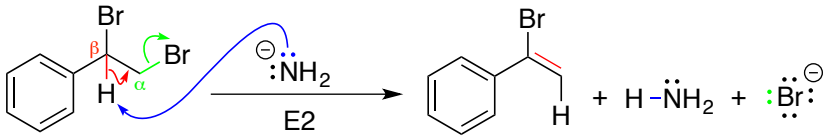
diisobutylacetylene

(c) Here, the two alkyl groups differ in structure. Recall that only iso, cyclo, and neo prefixes count in alphabetization. Therefore, *sec* does not count, and *sec*-butyl appears before cyclopentyl as a result.

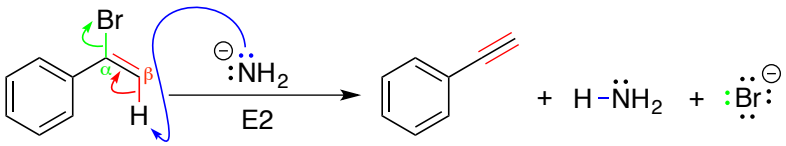


sec-butylcyclopentylacetylene

4. We've already been shown the intermediates in this transformation, and that makes it significantly easier to draw the mechanism. An E2 reaction provides the first intermediate (a vinyl bromide). This occurs as sodamide removes a proton that is β to one of the halogens. The C-H σ bond electrons collapse in between α and β to form the double bond as a bromide is displaced from the molecule.

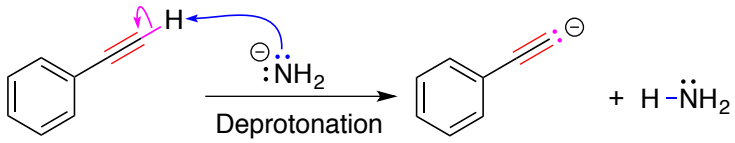


A second E2 reaction occurs in a similar fashion to produce the second π bond.

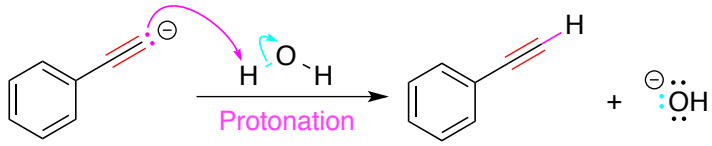


Once the alkyne has been produced, an acid-base reaction happens unavoidably. The pK_a of an alkyne proton is about 25; whereas, the pK_a of ammonia (the conjugate

base of sodamide) is about 35. Consequently, the deprotonation of the alkyne is highly favored since sodamide is such as strong base.



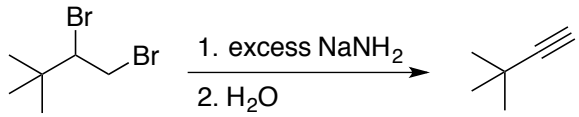
In a second separate step, water is added to the reaction to protonate the alkynide ion.



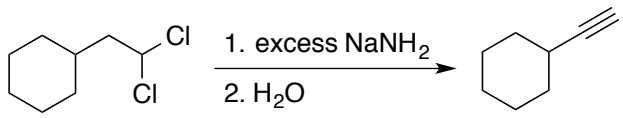
The final two mechanistic steps tend to confuse students. It seems odd that a proton is removed in the penultimate step only to be replaced in the final step. It's important to remember that we aren't choosing to take a proton off and then replace it. These steps are a consequence of the fact that, when an alkyne is formed in such basic media, it will naturally and unavoidably be deprotonated. We simply add water in step 2 to neutralize the carbanion that was formed.

5.

(a) Excess sodamide accomplishes the double elimination of this vicinal dibromide. The terminal alkyne is then deprotonated in this basic medium, but the proton is replaced in step 2 when water is added.

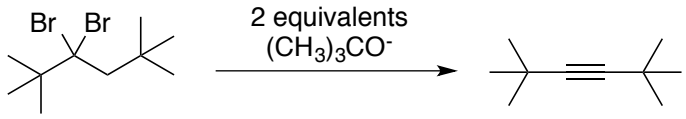


(b) This geminal dichloride can also undergo double elimination in the presence of excess sodamide. The alkyne thus formed is subsequently deprotonated. Step 2 introduces water as a proton source, which neutralizes the alkynide ion.



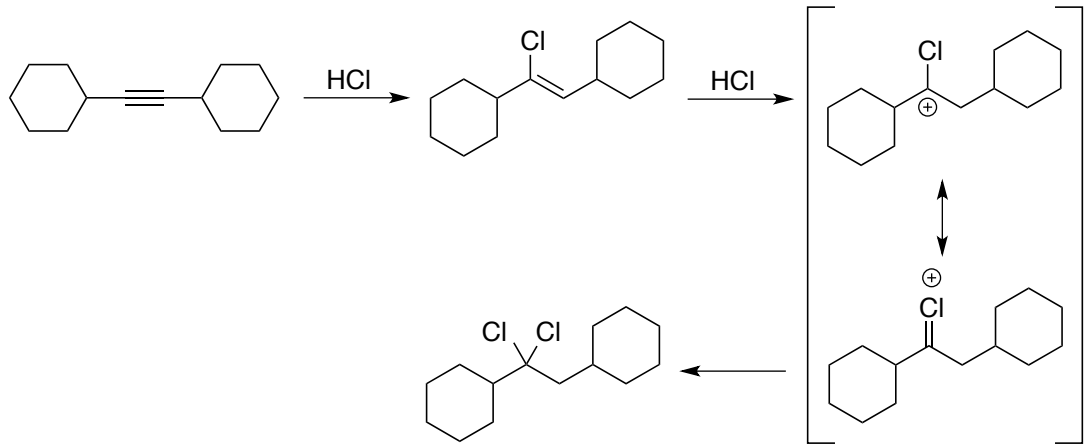
(c) It was mentioned in this section that other strong bases, such as *tert*-butoxide, can sometimes accomplish the double elimination of a vicinal or geminal dihalide. In this case, the geminal dibromide undergoes two successive E2 reactions in the

presence of two equivalents of *tert*-butoxide. The net result is an internal symmetrical alkyne.

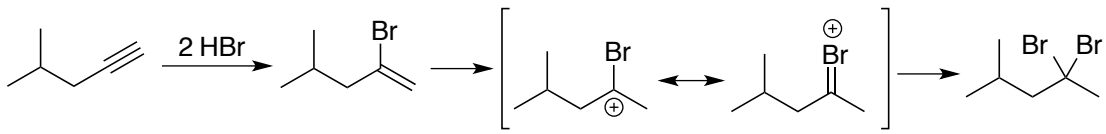


Since this alkyne is not terminal, subsequent deprotonation is not even a consideration. Additionally, although migration of internal alkynes in base was mentioned in this section, this alkyne has no protons on its adjacent centers and is therefore impervious to migration.

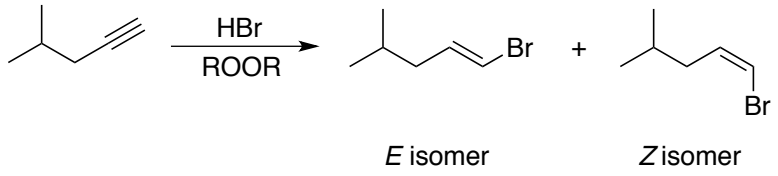
6. Given the symmetry of the reactant, the initial addition of HCl can only give rise to a single vinylic chloride. The second addition of HCl occurs with Markovnikov regiochemistry because it proceeds through the more stable carbocation, which enjoys resonance stabilization provided by the chlorine atom. The ultimate product is a geminal dichloride.



7. Both the first and second additions of HBr occur with Markovnikov regiochemistry. The first addition of HBr adds in a Markovnikov fashion so that the developing δ^+ is on the more substituted carbon. The intermediate vinyl bromide then adds a proton according to Markovnikov's rule so that the more stable carbocation is formed. This cation's stability is due to resonance with the bromine atom. Bromide then adds to yield the geminal dihalide product.

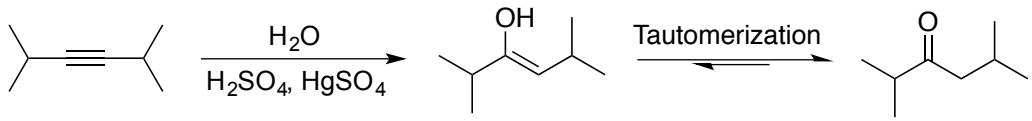


8. This radical hydrohalogenation occurs in an anti-Markovnikov fashion. The resultant vinyl bromide has both *E* and *Z* forms.

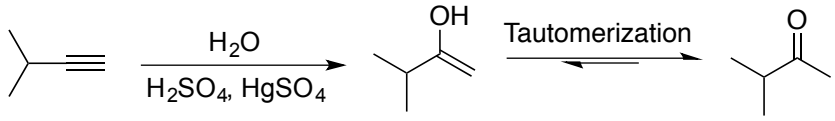


9.

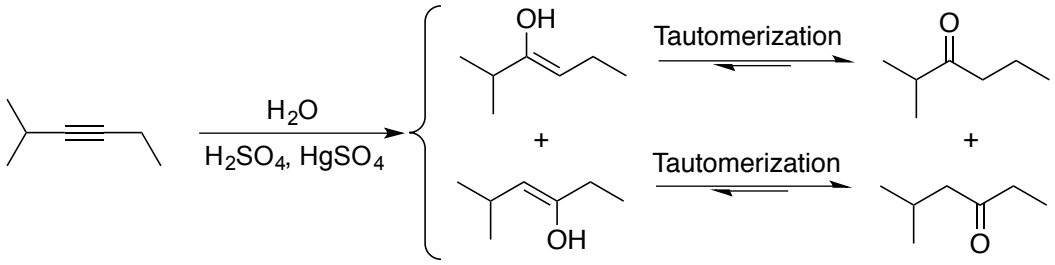
(a) This internal symmetrical alkyne can undergo hydration to give only one enol. The enol, in turn, tautomerizes to yield a single ketone.



(b) This terminal alkyne experiences Markovnikov hydration. The resultant enol then tautomerizes to afford a methyl ketone.

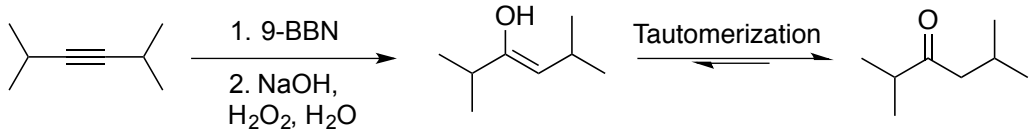


(c) Since both carbons of the triple bond are equally substituted, this internal unsymmetrical alkyne can be hydrated in two different ways to afford two enols, both of which tautomerize resulting in two ketone products.

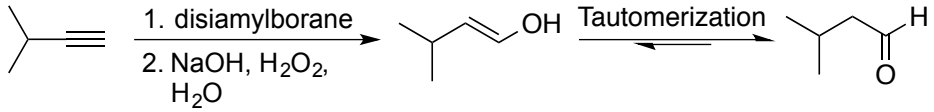


10.

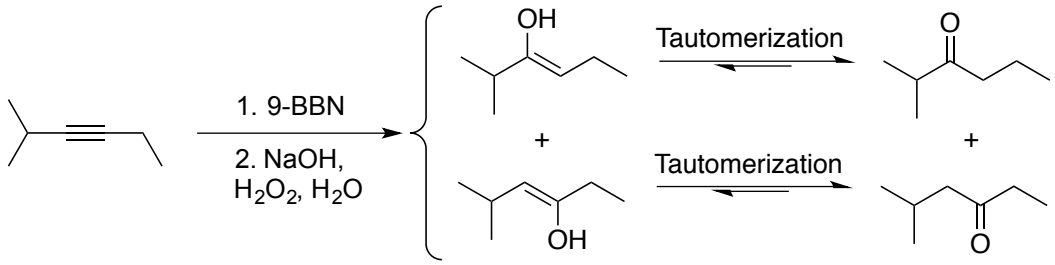
(a) This internal symmetrical alkyne yields the same enol regardless of how it is hydrated. The enol then tautomerizes to provide a single ketone product.



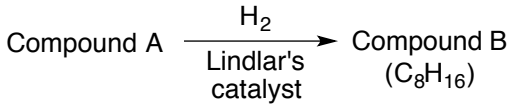
(b) This terminal alkyne is hydrated with anti-Markovnikov regiochemistry. The resultant enol then tautomerizes to afford an aldehyde.



(c) Since both carbons of the triple bond have the same level of substitution, this internal unsymmetrical alkyne can he hydrated in two different ways. The two enols subsequently tautomerize to give a mixture of ketone products.



11. With word problems it is very important to map out the information that is given in the text of the problem. For instance, we are told that Compound A undergoes the following reaction.

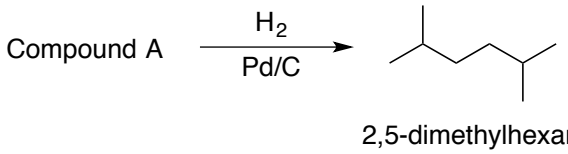


When we see parts of the problem in this format, it is sometimes easier to extract information. In this case, the molecular formula allows us to calculate degrees of unsaturation (DOU) for Compound B.

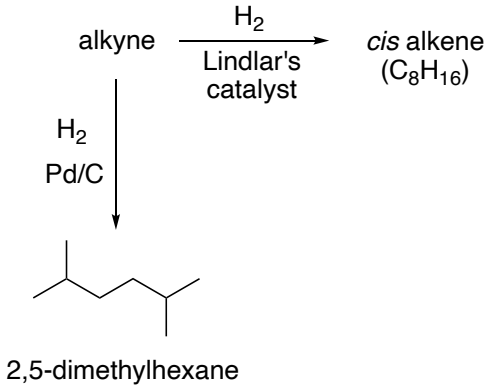
$$DOU = \frac{[2(8) + 2] - 16}{2} = 1$$

While one DOU can mean a ring or a π bond, it is extremely likely that the DOU is a π bond in this case because we know that alkenes, which have one DOU are the products of reduction of alkynes using Lindlar's catalyst. It is probable that Compound A is an alkyne, and Compound B is the *cis* alkene formed from its partial reduction. However, there are a number of isomers that could fit the criteria we have outlined so far.

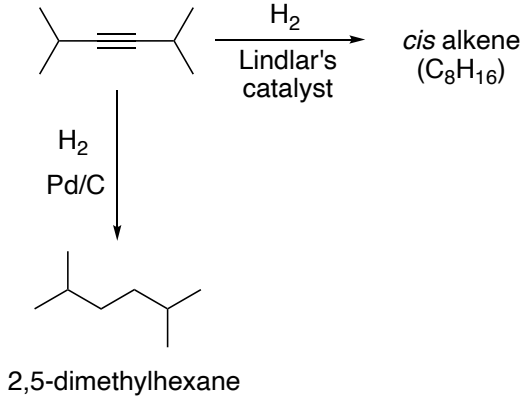
Consequently, we should turn our attention to the other piece of information we've been given. We know that Compound A can be fully reduced to yield 2,5-dimethylhexane. This gives us the structure of the carbon skeleton.



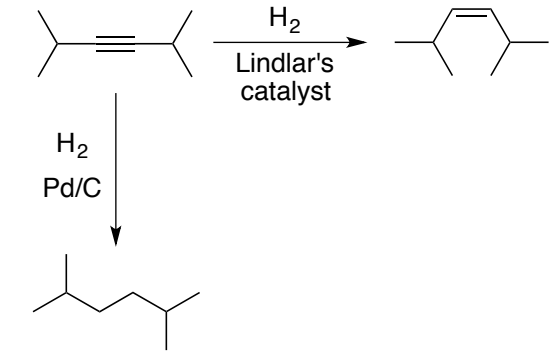
Now, let's compile the information that we know into a single diagram.



The remaining challenge is to use the carbon skeleton given by the alkane to ascertain the structures of Compounds A and B. While there are three different alkenes that could have that carbon framework, there is only a single alkyne possible. No other site in the molecule can sustain a triple bond without exceeding carbon's valence of four.



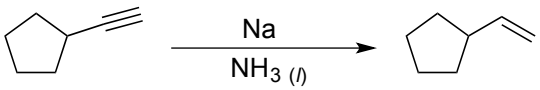
Now that we know the alkyne's structure, we can infer that of the alkene since we know that reduction with Lindlar's catalyst affords the *cis* configuration.



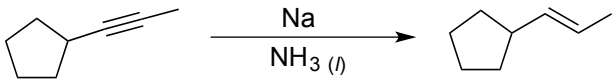
2,5-dimethylhexane

12.

(a) In this reaction, the alkyne is reduced to an alkene that has no *cis*/*trans* isomerism.

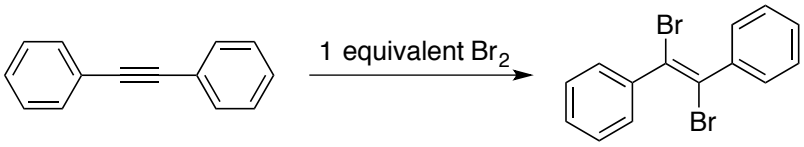


(b) In this dissolving metal reduction, the alkene is produced only in its *trans* configuration.

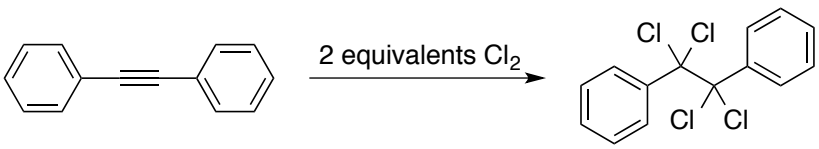


13.

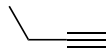
(a) A single equivalent of bromine adds to diphenylacetylene to afford the *E* alkene due to the stereochemistry of halogenation, which is anti.



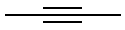
(b) Two equivalents of chlorine add to diphenylacetylene to yield the tetrachloride. Stereochemistry is not an issue here because there are no double bonds or stereocenters.



14. We know that alkynes undergo ozonolysis to produce carboxylic acids and/or carbon dioxide, so Compound A is an alkyne. However, there are two alkynes with the molecular formula given.

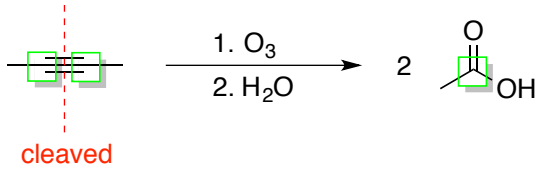


1-butyne

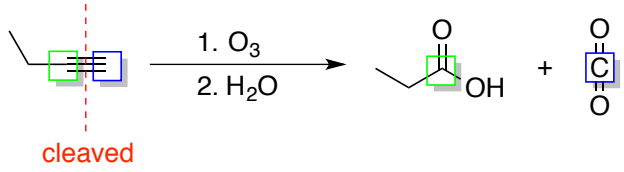


2-butyne

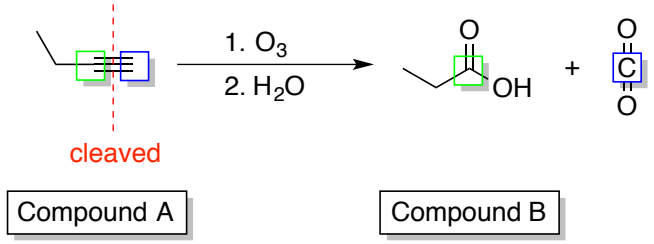
Ozonolysis of 2-butyne would give two equivalents of a single carboxylic acid (acetic acid).



However, ozonolysis of 1-butyne fits with the given information because carbon dioxide is a product.

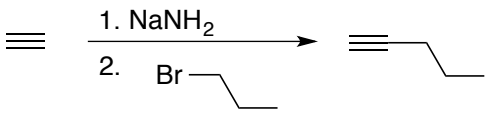


Therefore, Compound A is 1-butyne and Compound B is the three-carbon carboxylic acid (propanoic acid).

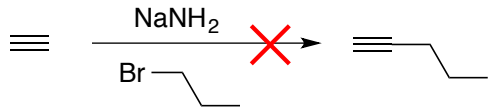


15.

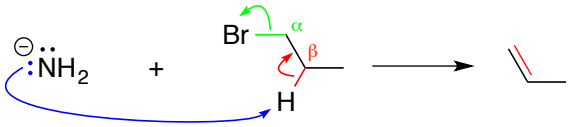
(a) Propylacetylene can be prepared by deprotonating acetylene with sodamide and then adding propyl bromide.



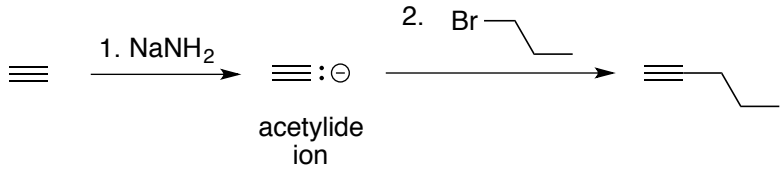
It is very important to include the numbers to indicate that these are two separate steps. If the numbers aren't included, the desired product won't be made in good yield.



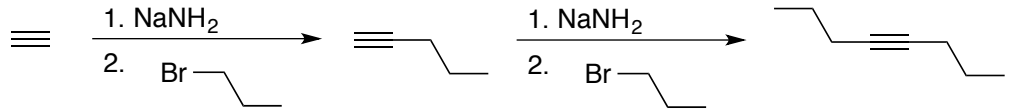
The reason is that sodamide can simply cause propyl bromide to undergo E2 and S_N2 reaction (E2 is shown below). These undesired reactions diminish the amount of desired product significantly.



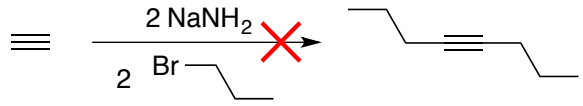
It is important for sodamide to be exposed to acetylene first so that the acetylide ion is made. This carbanion then reacts with propyl bromide to afford the desired product.



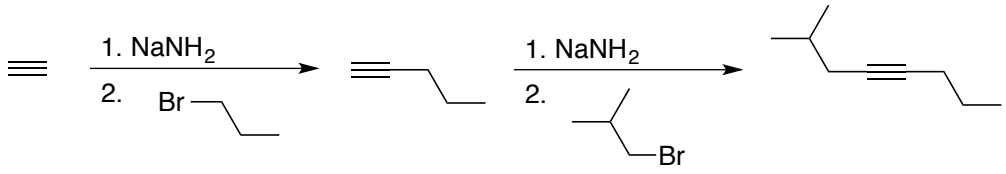
(b) This internal symmetrical alkyne can be prepared by two rounds of deprotonation and alkylation.



It is a common mistake to simply say that two equivalents of sodamide and two equivalents of propyl bromide can be used. This does not work well because of the side reactions discussed in part (a) above.



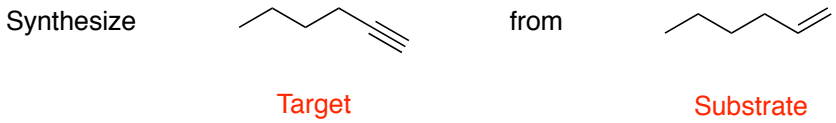
(c) This internal unsymmetrical alkyne can be prepared through two rounds of deprotonation and alkylation as well. However, each alkylation uses different alkyl halides in this case. Alkylation with propyl bromide is followed by alkylation with isobutyl bromide.



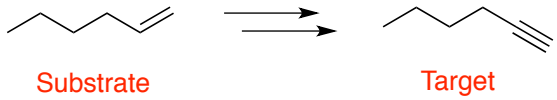
Again, remember that you cannot simply mix all of the reagents with the reactant simultaneously. Doing so will lead to side reactions and low selectivity for the desired transformation.

However, you can reverse the order of the alkylation events. In other words, alkylation with isobutyl bromide could occur prior to alkylation with propyl bromide.

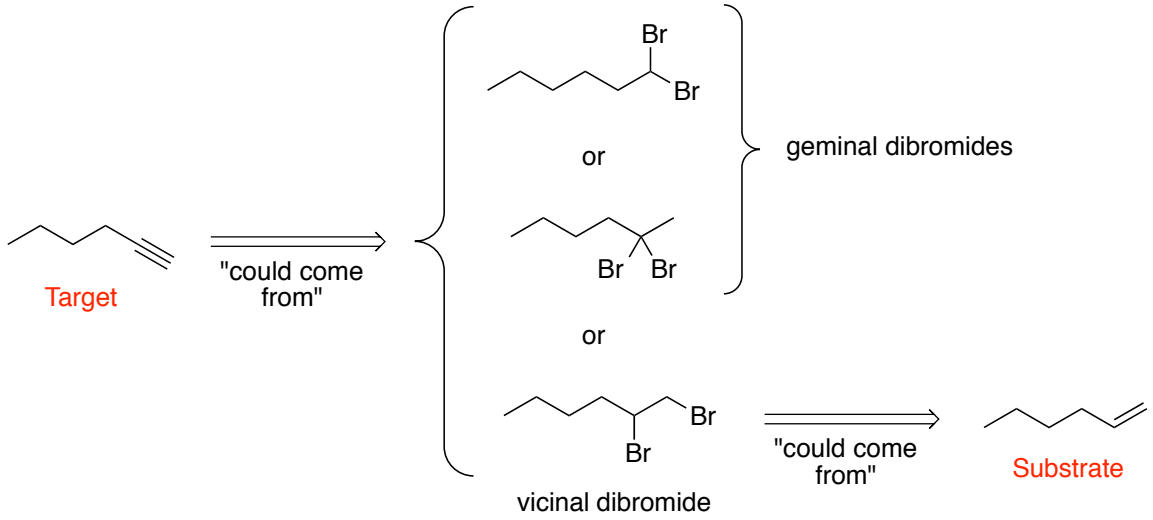
16. In synthesis problems, remember to begin by labeling the target and the substrate.



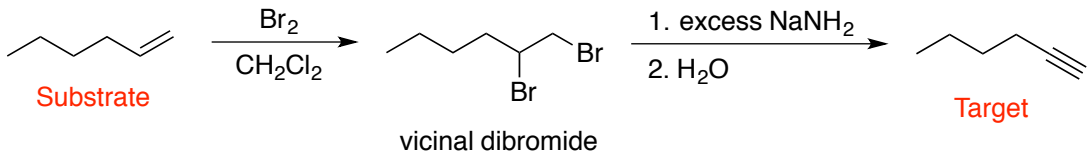
Then, rewrite the problem in the usual fashion.



This allows us to see that the challenge is to convert an alkene into an alkyne. While we know no direct method for doing so, we do know that alkynes can be prepared through double elimination of a geminal or vicinal dihalide. This brings to mind three possible precursors for the alkyne: two geminal dihalides and one vicinal dihalide. We do not know a method to prepare a geminal dihalide from an alkene; however, we do know that vicinal dihalides result from halogenation of alkenes.

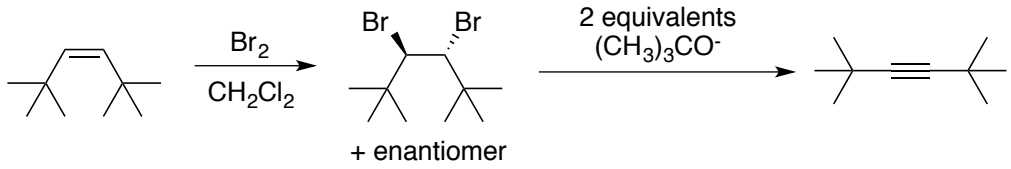


In the forward sense then, bromination of the substrate affords a vicinal dihalide. This vicinal dihalide can then be exposed to an excess of strong base, such as sodamide, to effect double elimination. The resultant alkyne is deprotonated in this strongly basic medium, and the proton is replaced when water is added to the mixture.

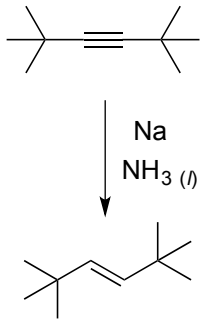


As you learn more and more reactions, the number of combinations (and therefore the number of possible synthesis problems) increases dramatically. You cannot memorize all possible combinations; however, you can file away in your memory synthetic modules. In other words, you can think of short clusters of reactions as modules that allow you to make a particular type of change. We have now seen one such synthetic module is the conversion of an alkene to the corresponding alkyne through halogenation followed by double elimination.

17. Let's deal with the conversion of the alkene to the alkyne first. We are well suited to do this after the previous problem in which we learned a synthetic module for the conversion of alkenes to alkynes: halogenation followed by double elimination.

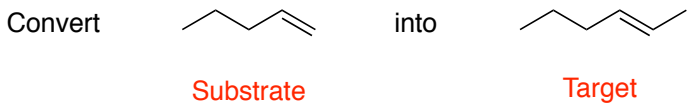


In the second phase of this scheme, the alkyne is treated with sodium in liquid ammonia. These are conditions for dissolving metal reduction, which results in *trans* alkenes.

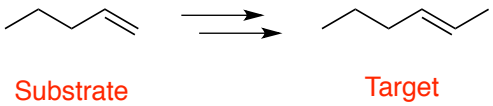


Remember how we set the stage for thinking about synthetic modules in the last problem? In this problem, we've encountered another type of synthetic module. While we don't know a direct method to convert a *cis* alkene to a *trans* alkene or vice versa, we can accomplish this by first converting the alkene to the corresponding alkyne and then choosing either dissolving metal reduction or hydrogenation with Lindlar's catalyst, depending on which alkene configuration is desired.

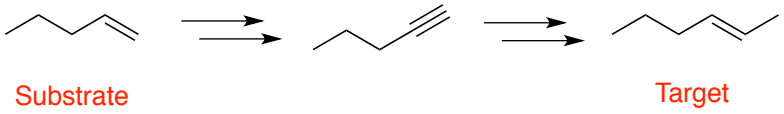
18. Again, it is always prudent to begin a synthesis with the labeling of the substrate and target. In this case, the substrate actually appears first due to the wording of the problem.



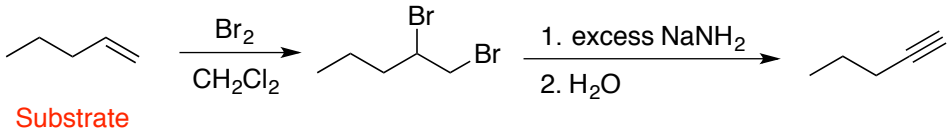
Then, we can draw the task in the typical fashion.



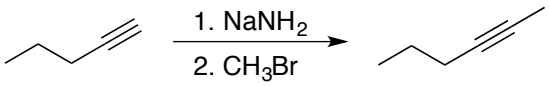
While it isn't always necessary to engage in a full retrosynthesis, some retrosynthetic thinking will always be helpful. In this case, we notice that the target contains one more carbon than the substrate. Therefore, it is necessary to make a carbon-carbon bond at some point in the synthesis. In order to make a carbon-carbon bond, we need an alkyne, which can then be deprotonated and alkylated. This thought process highlights the fact that an alkyne must be an intermediate in the synthesis, so we can now divide the synthesis into two phases: (1) preparing the alkyne and (2) forging the desired carbon framework before adjusting the functionality as needed. Notice that our plan centers around making the correct carbon skeleton. Phase 1 makes the reactant needed for a carbon-carbon bond-forming reaction, and phase 2 includes the new-bond formation.



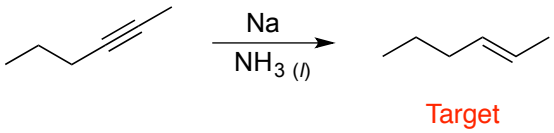
Phase 1 is accomplished using a synthetic module that we delineated earlier in Problem 16. Alkenes can be converted to alkynes by halogenation and subsequent double elimination.



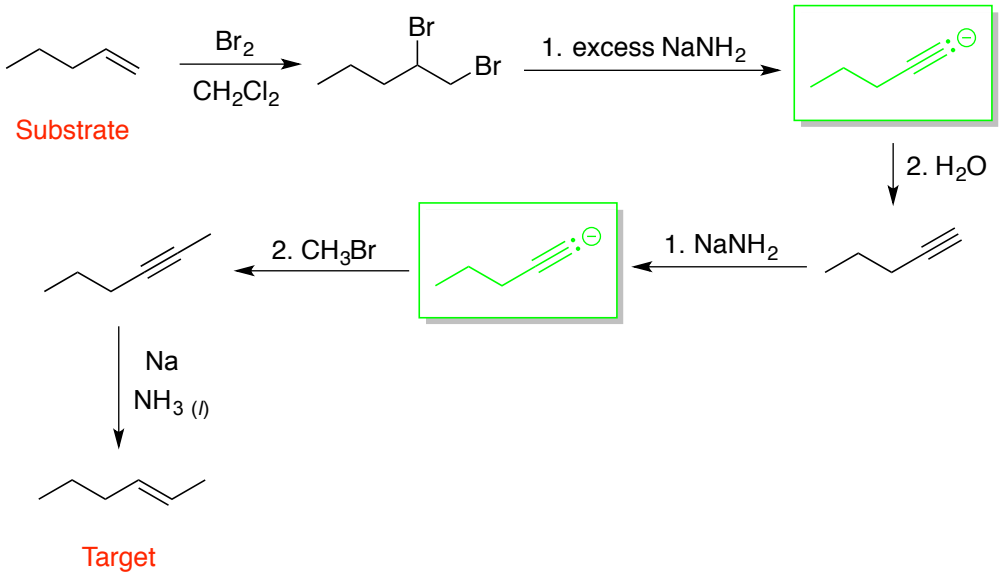
As we enter into phase 2 of the synthesis, we are ready to make the new C-C bond. This is accomplished by deprotonation and alkylation.



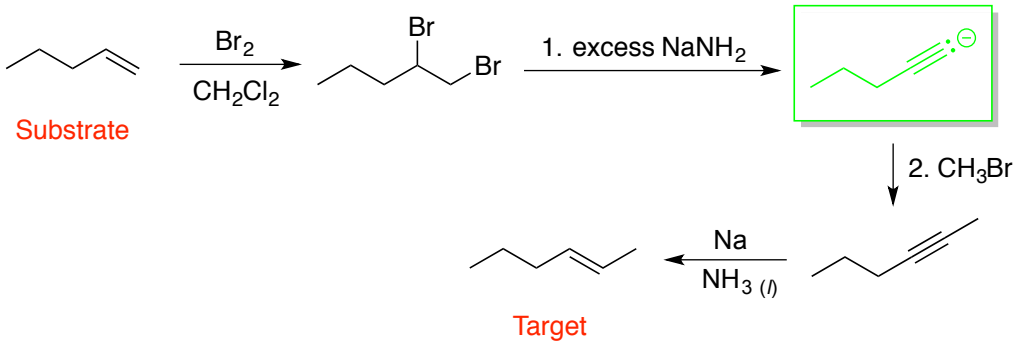
Finally, we adjust the functionality to prepare the target. This requires partial reduction using dissolving metal reduction to afford the *trans* alkene.



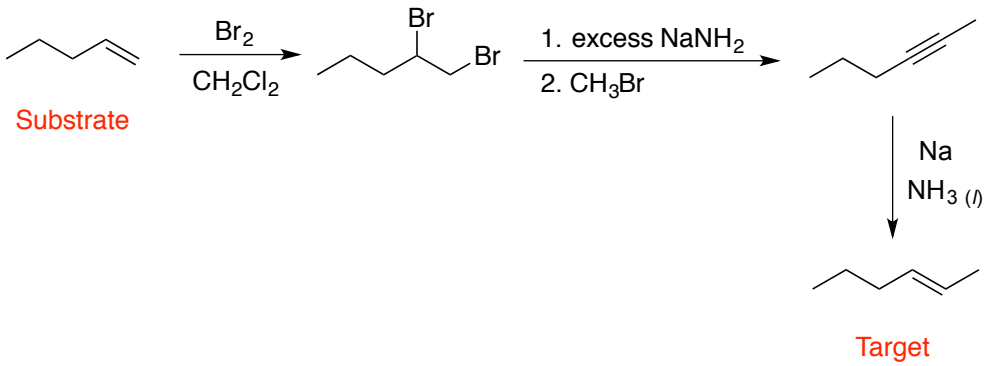
This would be a fine answer to the question; however, there is one efficiency available to us. This efficiency will enable us to reduce the number of steps, which is always desirable because a shorter synthesis is easier to carry out in the laboratory. The efficiency stems from the fact that, during double elimination, an alkynide ion is formed. When water is added, that alkynide ion is quenched. But, we then immediately prepare the same alkynide ion in the subsequent alkylation by first treating with sodamide.



By simply cutting out the intervening steps, we can abbreviate the synthesis by preparing the alkynide ion just once.

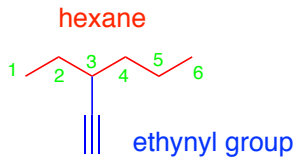


Written in a concise form that does not explicitly show the alkynide ion, the synthesis may appear as follows:

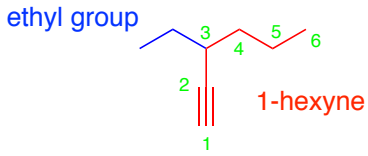


19.

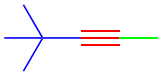
(a) The best way to begin a problem like this is by drawing the structure that is suggested by the given name. We are told that an ethynyl group is attached to a hexane chain at C3.



Now, we can evaluate the name given to this structure. We quickly notice that the parent does not include the functional group, and that must be remedied. The parent should be 1-hexyne, and there is an ethyl group at C3. Therefore, the proper name is 3-ethyl-1-hexyne.



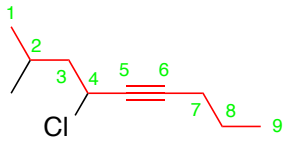
(b) The structure suggested by the name is a substituted acetylene, bearing both a methyl and a *tert*-butyl group.



methyl *tert*-butylacetylene

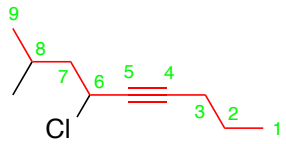
Recall that the only prefixes used in alphabetization are iso, cyclo, and neo. *Tert* is not among this list, so the alphabetization should compare the "m" of methyl to the "b" of *tert*-butyl, making the proper name *tert*-butylmethylacetylene.

(c) The structure suggested by the name follows. We are told that there is a nonyne parent, where the triple bond appears at C5. We are also told of chloro and methyl substituents appearing at C4 and C2, respectively.

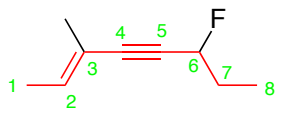


Upon closer examination, it becomes apparent that the parent carbon chain was numbered from left-to-right in order to give the substituents the lowest possible numbers. However, the functional group takes precedence and should be given the lowest possible number.

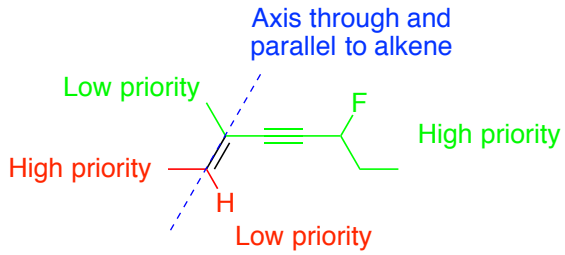
Numbering the parent from right-to-left instead, we now see that the name should be 6-chloro-8-methyl-4-nonyne.



20. The parent is 2-octen-4-yne or oct-2-en-4-yne. The substituents must be added to the name, expanding it to 6-fluoro-3-methyl-2-octen-4-yne.

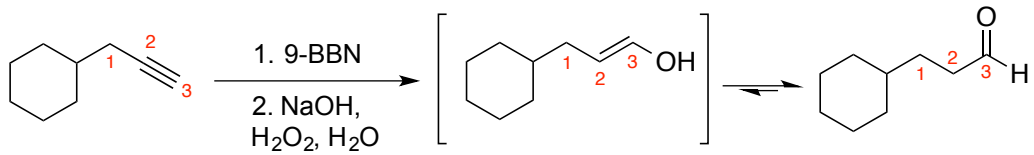


Additionally, we need a stereochemical descriptor for the double bond. Since the high priority groups are on opposite sides of an axis through and parallel to the double bond, it receives the *E* designation: (*E*)-6-fluoro-3-methyl-2-octen-4-yne.



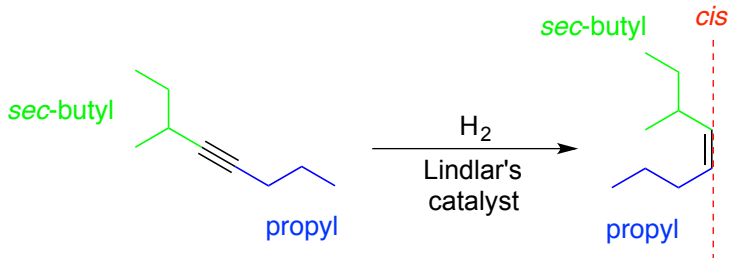
21.

(a) In this hydroboration-oxidation, the alkyne is hydrated in with anti-Markovnikov selectivity to afford a single enol bearing the hydroxyl group on its terminal carbon. This enol then tautomerizes to provide the product as an aldehyde.



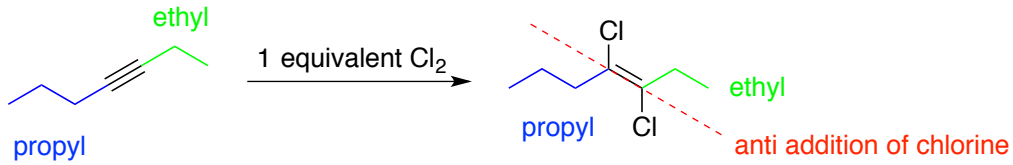
It is common for students to inadvertently add or remove carbons as they draw products in which the carbon framework looks a bit different than it did in the reactant. An easy way to remedy that problem is to letter or number the carbon atoms. If you choose to number the carbons, the numbering is solely for the purpose of keeping track of the atoms and need not have any relationship to IUPAC numbering. In the diagram above, the three carbons pendent to the ring have been numbered in each structure to ensure that the carbon-count is correct.

(b) In this problem, a partial reduction of the alkyne is being conducted with *cis* selectivity through the use of Lindlar's catalyst. Notice that both alkyl groups are on the same side of an axis running through and parallel to the alkene.



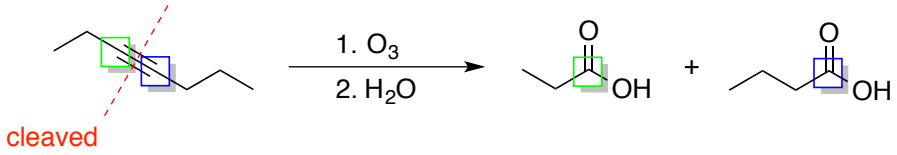
As mentioned in part (a) above, keeping the correct carbon count can be a challenge, particularly when the skeleton looks different in the reactant and product. In part (a), we discussed numbering the atoms to avoid errors. Another method is to check that the groups connected to the reactive site are the same in both the reactant and product. In this problem, the alkyne bears *sec*-butyl and propyl groups. The alkene product bears the same groups, so we can be confident that the carbon count is correct.

(c) This is a halogenation reaction, but only a single equivalent of chlorine has been used. This means that only one of the π bonds will undergo addition. The other π bond remains in the product. The addition of the halogens is anti, much like it was with halogenation of alkenes in the previous chapter.

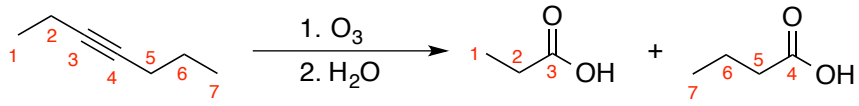


To ensure that the carbon count is correct, we can simply verify that both the reactant and the product bear propyl and ethyl groups.

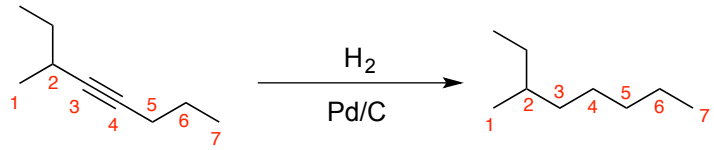
(d) This internal unsymmetrical alkyne undergoes ozonolysis to yield two carboxylic acid products.



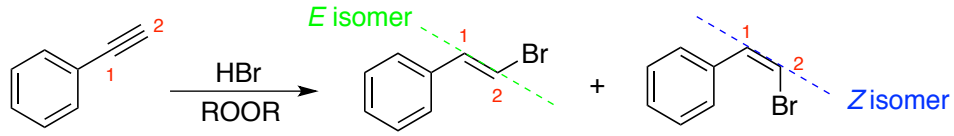
There are a number of ways to double-check the carbon count. Numbering can be quite effective.



(e) This hydrogenation with palladium on carbon (Pd/C) reduces the alkyne completely, giving an alkane as the product. Numbering helps to verify the correct number of carbon atoms.

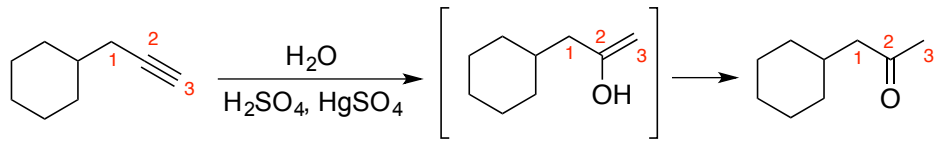


(f) This radical hydrohalogenation proceeds with anti-Markovnikov regioselectivity. The vinyl bromide product is produced as a mixture of *E* and *Z* isomers.



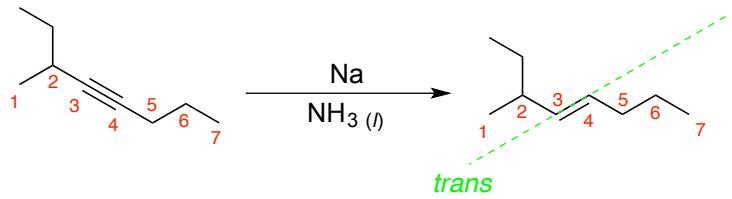
22.

(a) In this Markovnikov hydration, water is added across the alkyne so that the hydroxyl group is placed on the interior carbon. Tautomerization of the intermediate enol affords a methyl ketone. The correct carbon count is verified through numbering.



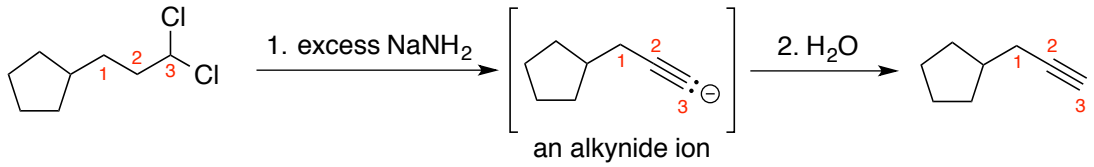
Compare this to Problem 21(a).

(b) Dissolving metal reduction leads to partial reduction of the alkyne that results in a *trans* alkene. Numbering helps to verify the correct carbon skeleton.

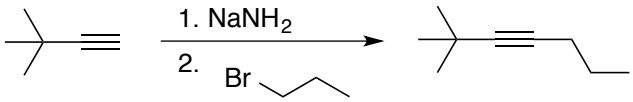


Compare this to Problem 21(b).

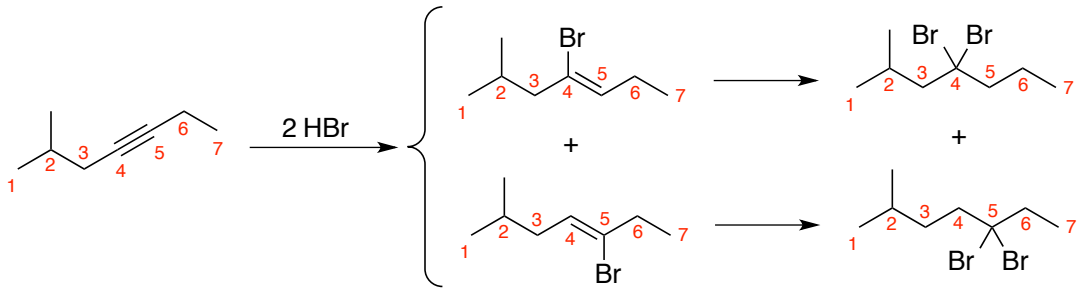
(c) This geminal dihalide undergoes double elimination upon treatment with excess sodamide. The resulting terminal alkyne is deprotonated to afford the alkynide ion as an intermediate. When water is added, the alkynide ion is protonated, and the alkyne is obtained. Numbering throughout the problem helps to verify the correct carbon count.



(d) This is an example of alkylation of a terminal alkyne. Deprotonation with sodamide yields an alkynide ion that displaces the bromide of propyl bromide in S_N2 fashion to provide the product, which is an internal unsymmetrical alkyne.

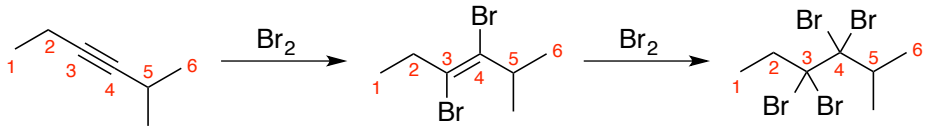


(e) When an alkyne is treated with two equivalents of HX, two hydrohalogenations ensue and consume both of the π bonds. Since this particular alkyne is internal, the addition of HX can occur in two ways because both alkyne carbons have an identical level of substitution. Given that this substrate is also an internal *unsymmetrical* alkyne, the two modes of addition will result in two different geminal dihalide products. The first equivalent of HBr adds with either regiochemistry to afford two vinyl bromides. Both of these add a second equivalent of HBr with Markovnikov regiochemistry, resulting in the two geminal dihalide products.

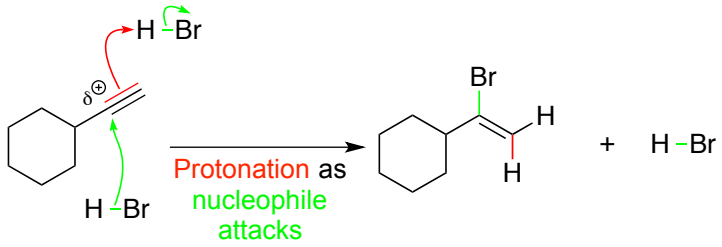


As with the other problems, numbering helps us to keep track of the carbons as the framework is drawn a bit differently.

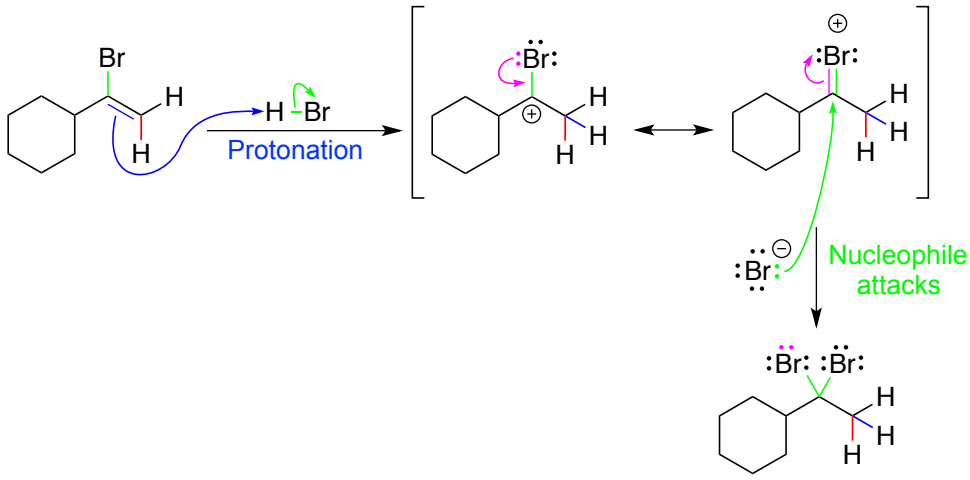
(f) When two equivalents of X_2 are added to an alkyne, it undergoes two successive halogenations. The first occurs with anti stereochemistry. The second yields a tetrabromide. Numbering throughout the problem ensures that no carbons are incorrectly added to or removed from the substrate.



23. The mechanism begins with protonation of the alkyne so as to place the developing δ^+ on the more stable secondary center (Markovnikov). However, since a vinylic carbocation would be especially unstable, bromide concurrently attacks this secondary center bearing a δ^+. The concerted mechanism yields the vinyl bromide intermediate in a single step. Although it initially appears as though 2 equivalents of HBr are used in this step, only one equivalent is actually consumed by addition to the π bond. The residual proton and bromide constitute an unreacted molecule of HBr.

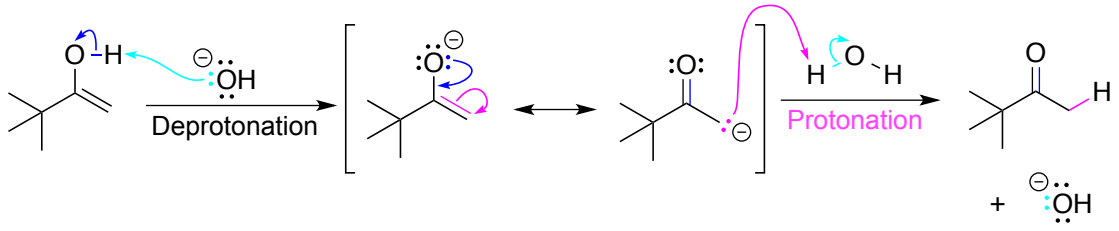


The remaining π bond can also undergo electrophilic addition of HBr. This process begins with protonation. The resonance-stabilized cation is formed, resulting in Markovnikov regiochemistry. Finally, bromide adds to the carbocation to provide the geminal dihalide product.



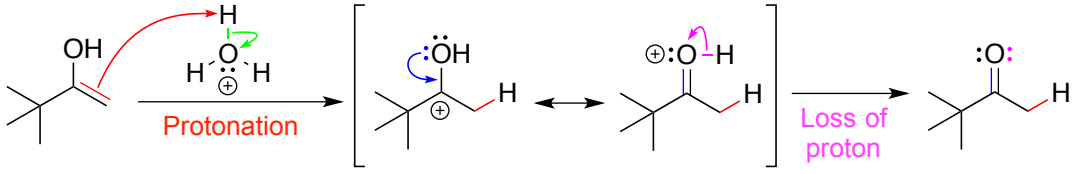
24.

(a) Tautomerization under basic conditions begins with the deprotonation of the enol by hydroxide. The resultant enolate (i.e., the conjugate base of an enol) has resonance stabilization that delocalizes the negative charge onto carbon. Finally, protonation at that electron-rich site affords the keto form of the molecule.



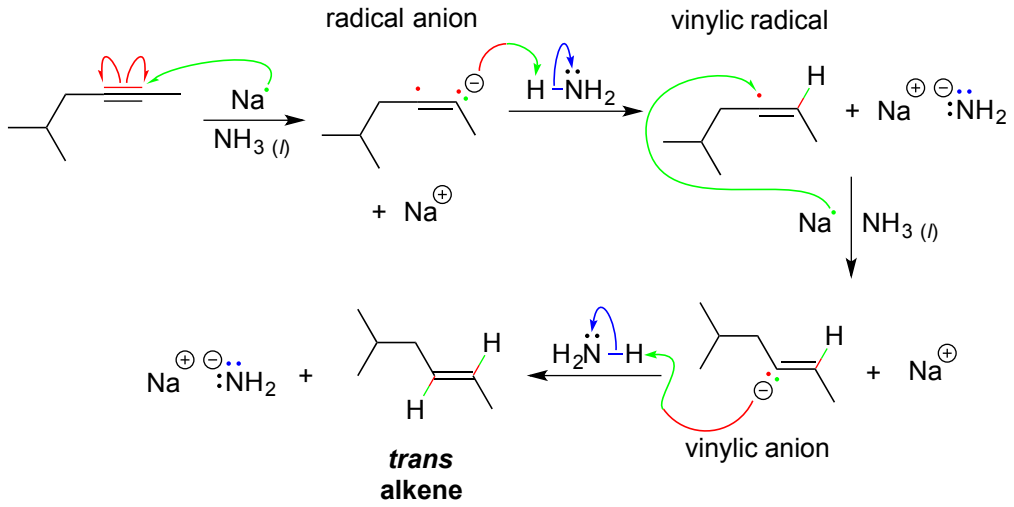
Only a trace of hydroxide is needed because, although hydroxide is consumed during the deprotonation step, it is regenerated during the protonation step.

(b) In acidic media, tautomerization must begin with protonation instead. The enol is protonated so as to produce a resonance-stabilized cation. Subsequent loss of a proton from the oxonium ion results in the keto form of the molecule.

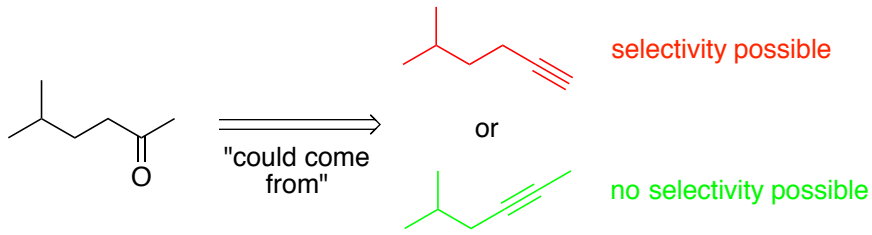


Again, only a trace of acid is needed because, although acid is consumed during protonation, it is re-formed during loss of a proton.

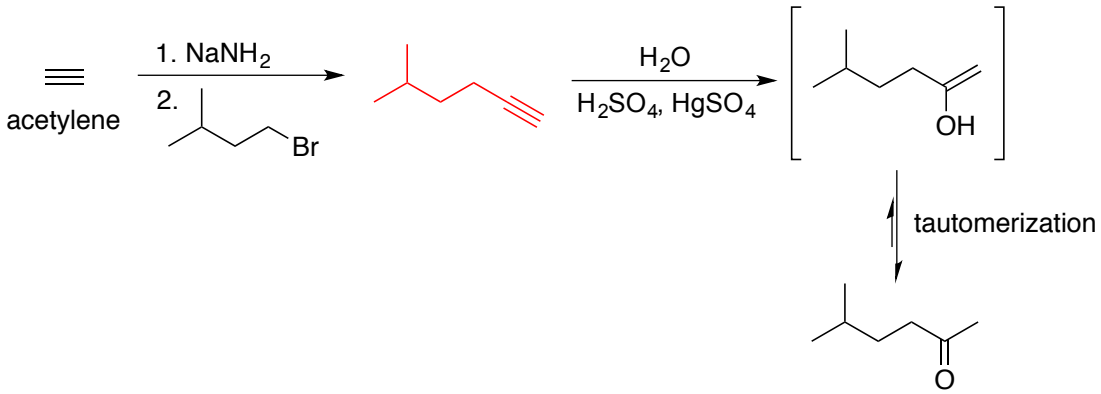
25. Dissolving metal reduction begins with the donation of an electron from sodium to the alkyne. This results in the formation of an intermediate known as a radical anion (i.e., it possesses both an unpaired electron and a negative charge). The vinylic carbanion then deprotonates ammonia. The resulting vinylic radical accepts a second electron from a second atom of sodium. At this stage, the rehybridization that leads to *cis*/*trans* isomerism takes place. Upon accepting an electron, the vinylic radical is rehybridized from sp to sp^2, and the more stable *trans* configuration is adopted. Finally, the vinylic carbanion deprotonates ammonia to yield the *trans* alkene product.



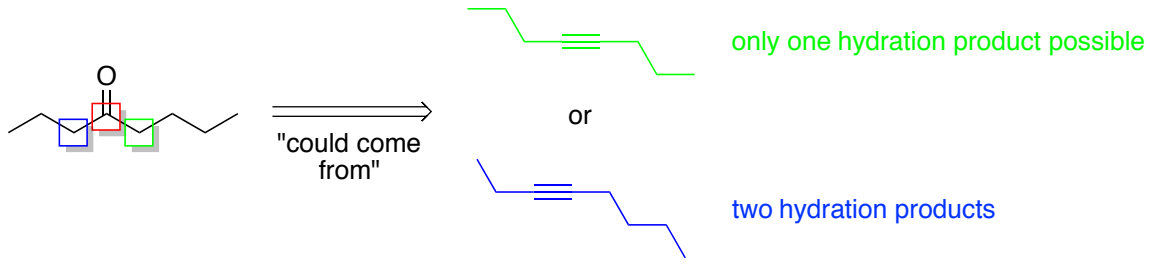
26. This methyl ketone could be made from one of two alkyne precursors. However, only the terminal alkyne allows for selective preparation of just the desired ketone. The internal unsymmetrical alkyne provides no basis for selectivity because both of the alkyne carbons are equally substituted.



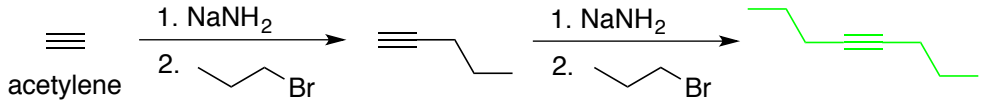
It therefore becomes our goal to prepare the terminal alkyne from acetylene. This requires alkylation, which is achieved through deprotonation followed by treatment with the appropriate alkyl halide. Then, Markovnikov hydration using mercuric sulfate and sulfuric acid in water yields the desired enol, which will spontaneously tautomerize to give the desired ketone.



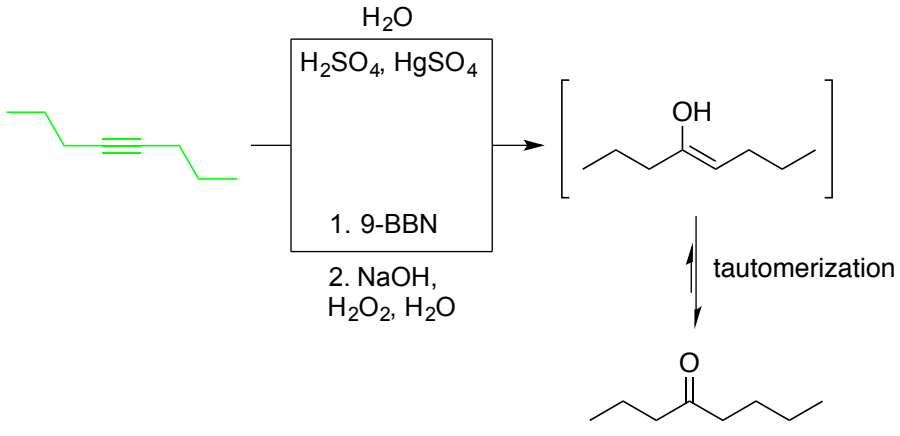
27. This ketone could be prepared from one of two alkyne precursors. The triple bond must involve the red carbon because we need to install a functional group there eventually. However, it could also involve the green carbon or the blue carbon. The internal symmetrical alkyne, 4-octyne, will only yield a single hydration product. However, the internal unsymmetrical alkyne, 3-octyne, will yield two hydration products: the desired ketone and an undesired ketone. Since it is always preferable to prepare the target molecule in the highest possible yield, the internal symmetrical alkyne is our preferred synthetic intermediate.



4-Octyne can be prepared through two rounds of alkylation, each involving deprotonation with sodamide followed by alkylation with propyl bromide.

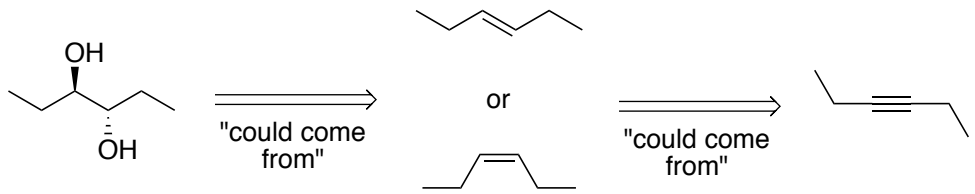


Since the two carbons of the triple bond are equally substituted, both Markovnikov and anti-Markovnikov hydration will give the same result. Since this alkyne is symmetrical, hydration with either regiochemistry affords only one enol, which tautomerizes to the desired ketone product.

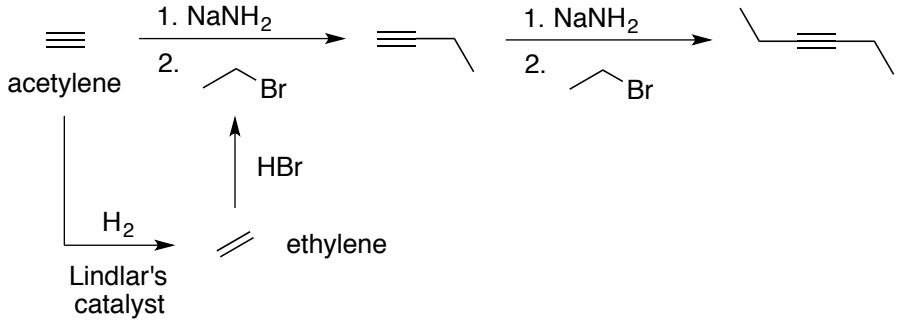


28. As with many synthesis problems, there are multiple approaches that can be successful in this example. The desired diol is a meso compound that can be made through dihydroxylation of an alkene [see Chapter 10, Problems 30(a) and 31(b)].

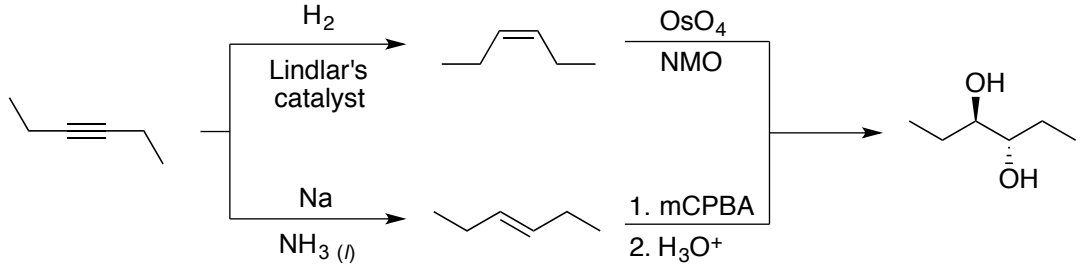
Anti-dihydroxylation of *trans*-3-hexene or syn-dihydroxylation of *cis*-3-hexene will achieve the goal. Either alkene can be prepared from 3-hexyne. So, our first task is to prepare 3-hexyne from acetylene.



A small snag presents itself when we reflect on the fact that we are only allowed to use acetylene as a source of carbon atoms. It is clear that 3-hexyne must be made from acetylene through two rounds of deprotonation and alkylation with ethyl bromide. But, we also have to prepare the ethyl bromide from acetylene. This can be accomplished through partial reduction (H_2 and Lindlar's catalyst or dissolving metal reduction) and hydrohalogenation.

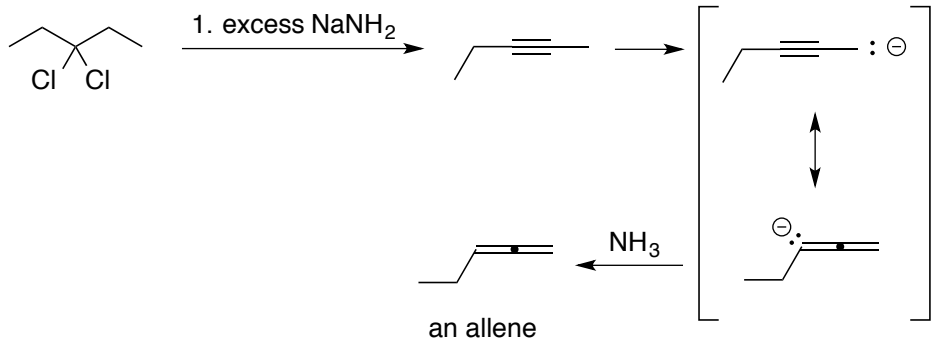


With 3-hexyne in hand, we have two choices for the endgame of the synthesis. One option is to partially reduce via hydrogenation with Lindlar's catalyst. This affords the *cis* alkene, which must then undergo syn-dihydroxylation in order to provide the target compound. Alternatively, dissolving metal reduction of 3-hexyne affords the *trans* alkene, which is converted to the product by anti-hydroxylation.

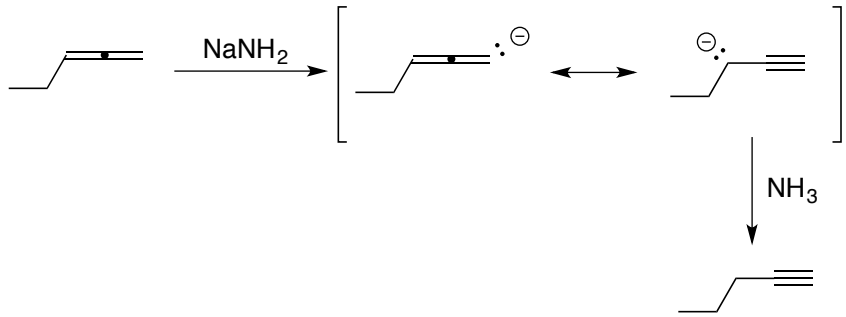


29. In order for the IR to exhibit a signal at ~3300 cm^{-1} for a ≡C-H bond, the initially formed alkyne (2-pentyne) must have isomerized to a terminal alkyne. As indicated at the end of Section 2, this can happen through a series of deprotonation and

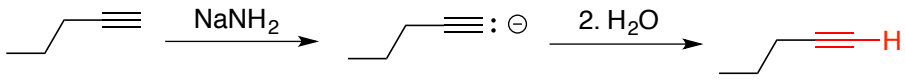
reprotonation events. If the alkyne is deprotonated at the adjacent methyl group, a resonance-stabilized anion is formed. If this carbanion is protonated at a different δ^- site, it can form a functional group known as an allene (C=C=C). These two steps have effectively isomerized one of the alkyne π bonds to the terminus of the chain.



The allene can be deprotonated again to afford another resonance-stabilized anion. If it too is protonated at a new δ^- site, the other π bond is isomerized to the molecule's terminus, creating a terminal alkyne.

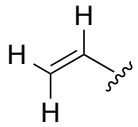


The equilibrium is driven in this direction by the ultimate deprotonation of the terminal alkyne, which has the most acidic proton in the system. Upon addition of water in the second step of the reaction, the alkynide ion is neutralized and the ≡C-H bond responsible for the unexpected IR signal is formed.

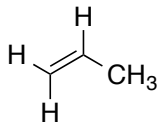


Note that this alkyne is a constitutional isomer of the expected one, which explains why the mass spectrum gave the anticipated signal at *m/z* 68.

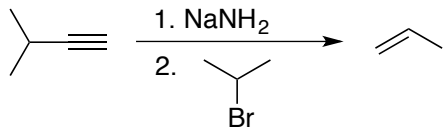
30. One of the striking features of the ^{1}H NMR is the appearance of vinyl protons with chemical shifts between 4.5 and 6 ppm. We did not expect to see any such protons in the intended target, diisopropylacetylene, because it contains no alkene. Given the integration values of the vinyl protons, we can construct a small fragment:



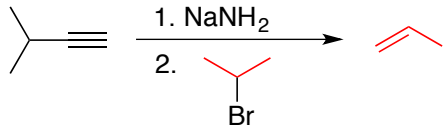
We can expand this fragment by considering the last signal in the NMR, which integrates for 3, suggesting that it is a methyl group.



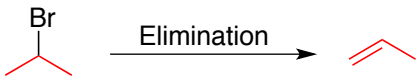
Now we know what happened in the reaction:



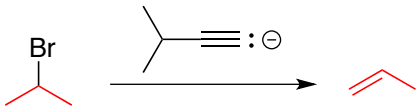
The question that remains is: Why did this happen? The three carbons of the product, propylene, seem much more likely to have derived from the three-carbon alkyl halide (isopropyl bromide) than from isopropylacetylene.



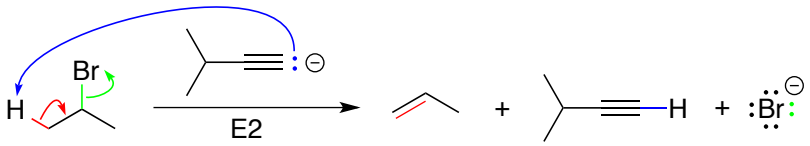
In order for isopropyl bromide to become propylene, it must undergo elimination.



This can happen if a strong base is present, and that is precisely what the other reagent (the alkynide ion) is.



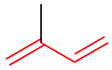
The alkynide ion was formed from the reactant upon treatment with sodamide. The investigator expected it to behave as a nucleophile and displace bromide from the alkyl halide to afford a substitution product. However, this alkyl halide is secondary. With increased steric hindrance, the rate of S_N2 declines and E2 becomes a competitive reaction.


Br
H
E2
+
H
+
:Br:

Solutions to Problems for Chapter 12: Dienes

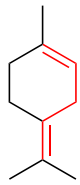
1.

(a) Isoprene contains a conjugated π system. The alkenes are separated by exactly one single bond.



isoprene

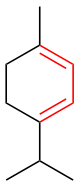
(b) Terpinolene contains an isolated diene because the π bonds are separated by more than one single bond.



terpinolene

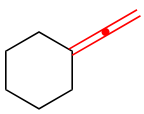
A tip for these problems is to look for the shortest possible distance between the two π bonds.

(c) α-Terpinene contains a conjugated diene due to the fact that the π bonds are separated by exactly one single bond.

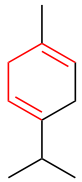


α-terpinene

(d) This molecule contains a cumulated diene because the two alkenes share a carbon in common. That carbon is highlighted by the dot between the double bonds.

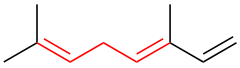


(e) γ-Terpinene contains an isolated diene because the alkenes are separated by more than one single bond.



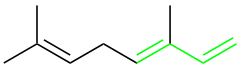
γ-terpinene

(f) *Trans*-β-ocimene contains three π bonds, which makes the analysis a bit more involved. On the left-hand side of the molecule is a pair of alkenes separated by more than one single bond, so these alkenes are isolated from each other.



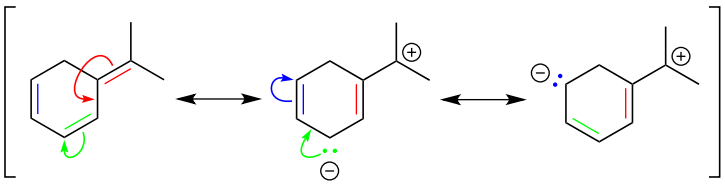
trans-β-ocimene

The right-hand side of the molecule, however, contains a conjugated π system because the two alkenes have exactly one single bond between them.

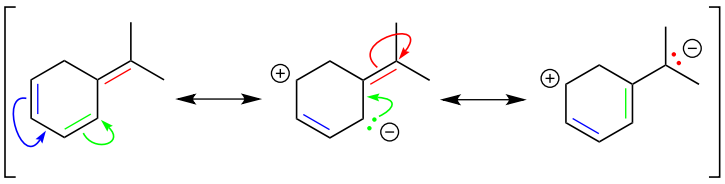


trans-β-ocimene

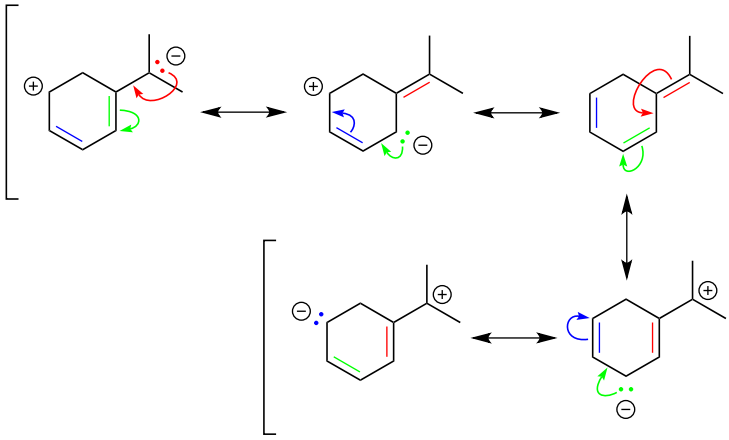
2. It is probably easiest to begin drawing resonance structures by moving electrons from one terminus of the π system. Let's start with the red π bond on the right-hand side of the molecule. These electrons can be moved into the ring, displacing the green π electrons onto the adjacent carbon. The green electrons can then be moved toward the blue π bond to generate a third resonance form.



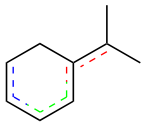
Alternatively, we could have begun with the blue π electrons on the left-hand side of the molecule to produce two more resonance forms in a similar fashion.



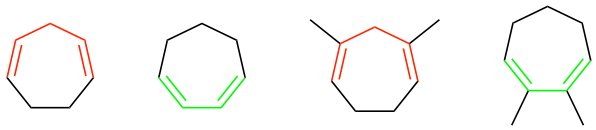
All of these resonance structures can be placed in the same diagram, showing the extensive delocalization of π electrons in this compound.



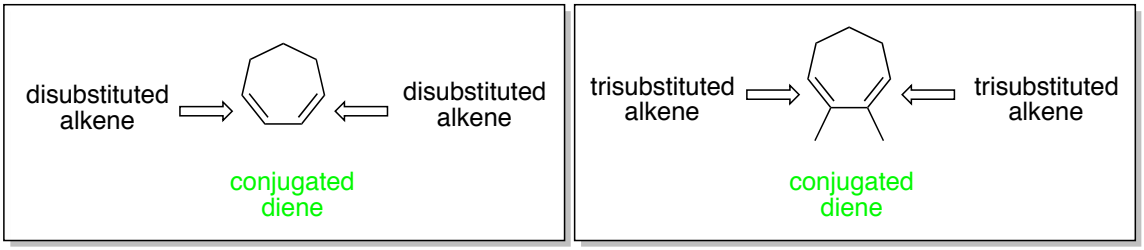
The resonance hybrid shows dashed lines throughout the portion of the structure involved in resonance so as to reflect the fact that these bonds have partial single bond character as well as partial double bond character. In other words, they have a bond order between 1 and 2.



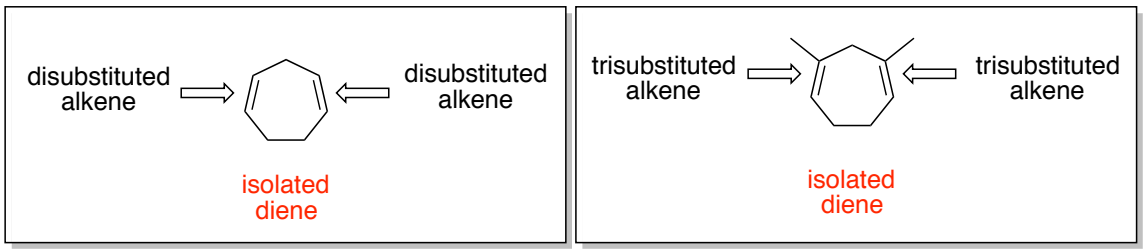
3. In this section, we've seen that conjugated dienes are more stable than isolated dienes. The most stable compound must therefore be one of the two conjugated dienes.



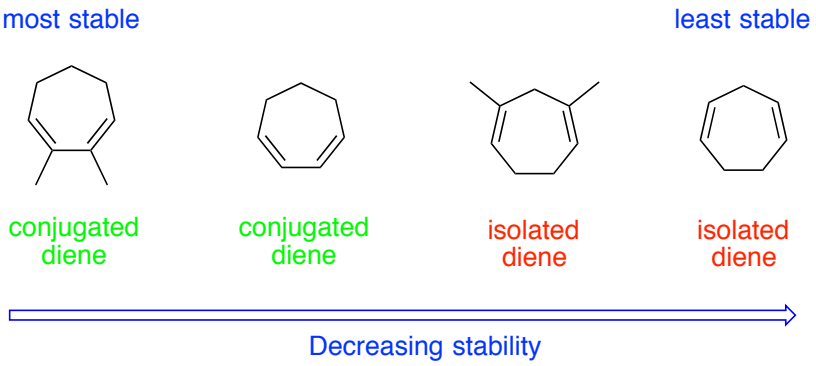
Of the two conjugated dienes, one contains two disubstituted alkenes, while the other possesses two trisubstituted alkenes. As we learned in Chapter 7, the more highly substituted an alkene is the more stable it will be. Therefore, the conjugated diene containing two trisubstituted alkenes is the most stable compound and is followed by the conjugated diene containing disubstituted alkenes.



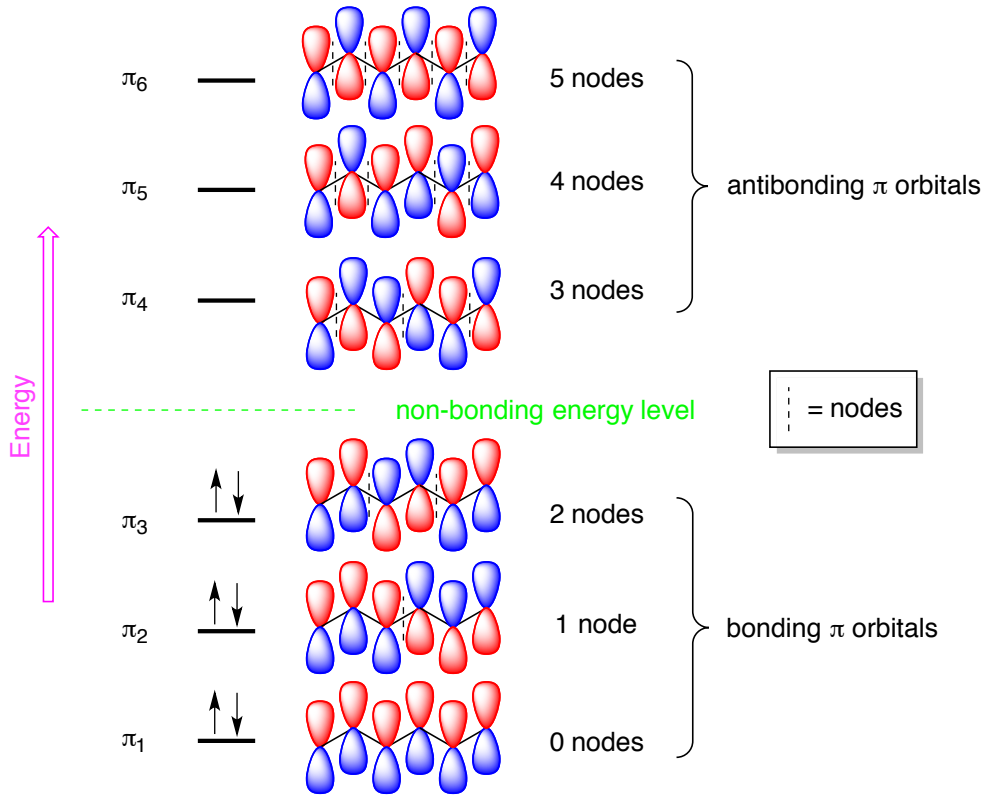
The isolated dienes will be less stable than the conjugated ones. To differentiate between the two isolated dienes, we can again use the substitution of their individual alkenes. The isolated diene containing two trisubstituted olefins is more stable than its counterpart bearing disubstituted alkenes.



To summarize, the alkenes are ranked below in order of decreasing stability.

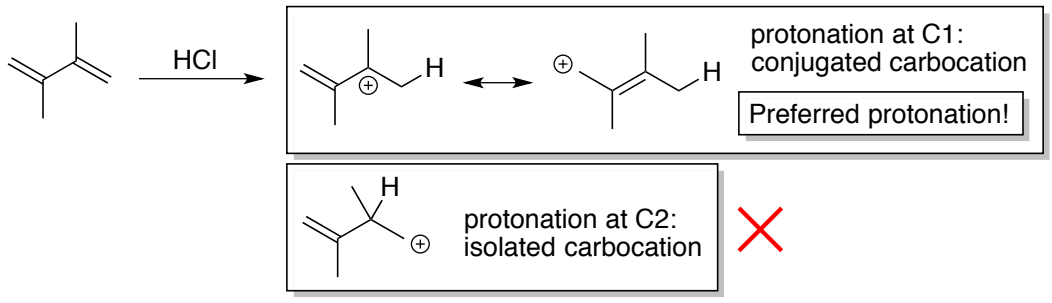


4. The six p orbitals of the six carbons of 1,3,5-hexatriene translate into six molecular π orbitals, their energy increasing according to the number of nodes. The molecular orbital with zero nodes (all in phase) is the lowest in energy, while the molecular orbital with five nodes (all out of phase) is the highest in energy. Since the molecular orbitals are symmetrically situated around the non-bonding energy level, π_1, π_2, and π_3 fall below this energy and are bonding orbitals. On the other hand, π_4, π_5, and π_6 are above this energy and are antibonding orbitals. Each carbon atom contributes one electron to the π system, and these six electrons fill the three bonding orbitals.

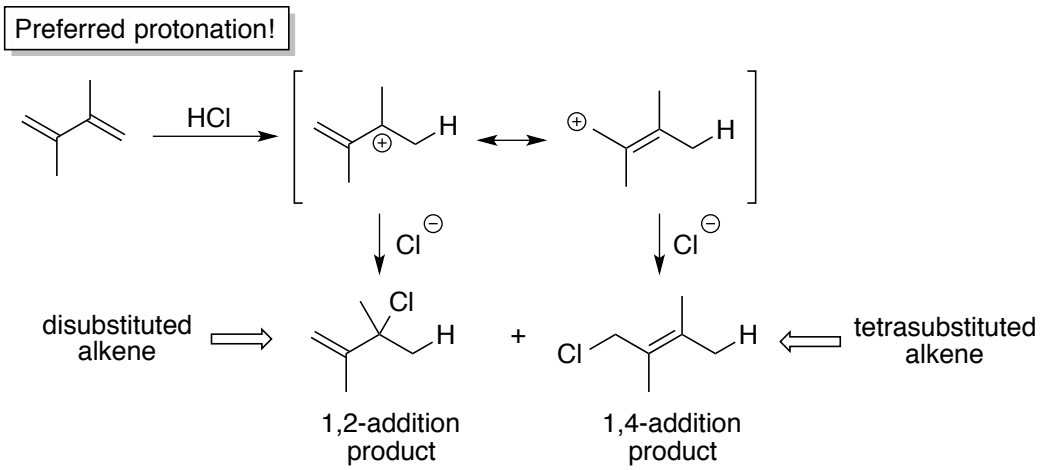


The frontier molecular orbitals are π_3 and π_4. π_3 is the highest occupied molecular orbital, while π_4 is the lowest unoccupied molecular orbital.

5. This symmetrical diene can be protonated in one of two ways. Protonation at C1 yields a conjugated carbocation with resonance stabilization, and this is preferred over protonation at C2, which yields an isolated carbocation with no such resonance stabilization.



The carbocation formed from protonation at C1 can then undergo the addition of chloride at either of its partially positive carbons. This results in the formation of 1,2- and 1,4-addition products.

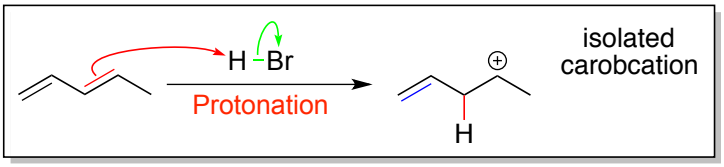


The 1,2-addition product is the kinetic product due to the proximity effect, and it is favored at lower reaction temperatures. However, the 1,4-addition product contains the more highly substituted alkene, making it the thermodynamic product. This product is favored at higher reaction temperatures.

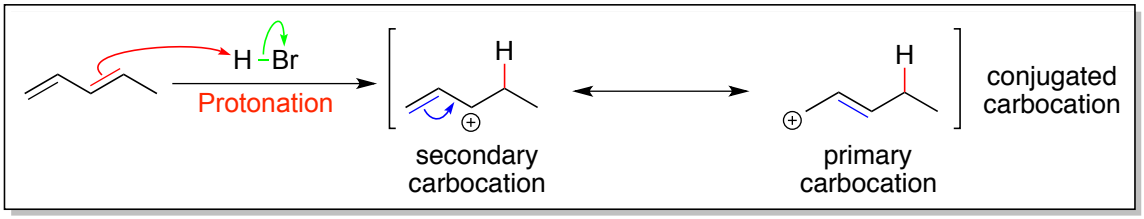
6.

(a) It is most systematic to consider the protonation of each carbon of the π system in turn. Then, we can compare the stability of the carbocations formed to determine which site of protonation is most favorable.

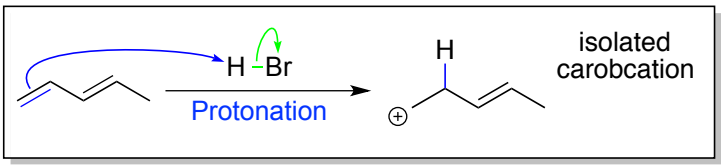
If the red π bond acts as the base, it is possible that C3 could be protonated. This would yield an isolated carbocation. Due to the lack of resonance stabilization, this is an undesirable outcome.



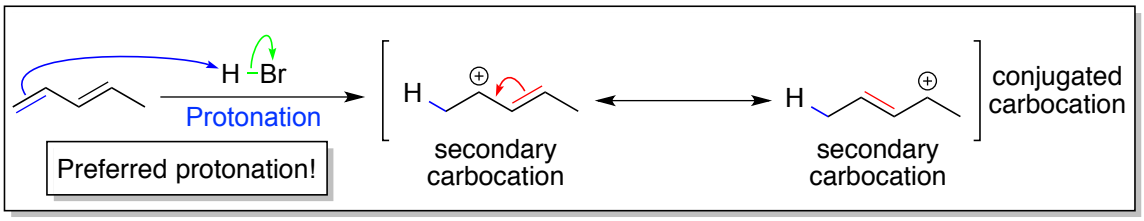
Alternatively, C4 could be protonated through the same mechanism. This leads to a conjugated (i.e., resonance-stabilized) carbocation, which is a much better result due to its enhanced stability. Note that the two resonance contributors consist of a secondary and primary allylic carbocation.



If the blue π bond acts as the base, it is possible that C2 could be protonated. However, this would lead to an undesirable isolated carbocation.

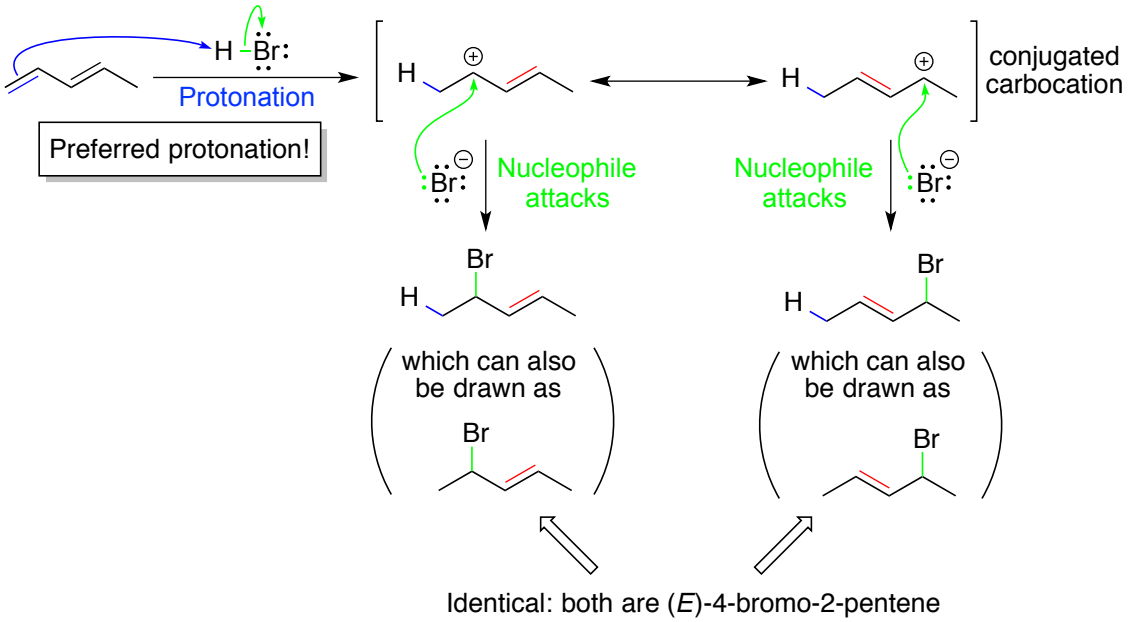


Alternatively, C1 could be protonated via the same mechanism, and this would lead to a conjugated carbocation. The two resonance forms in this instance both include secondary carbocations.

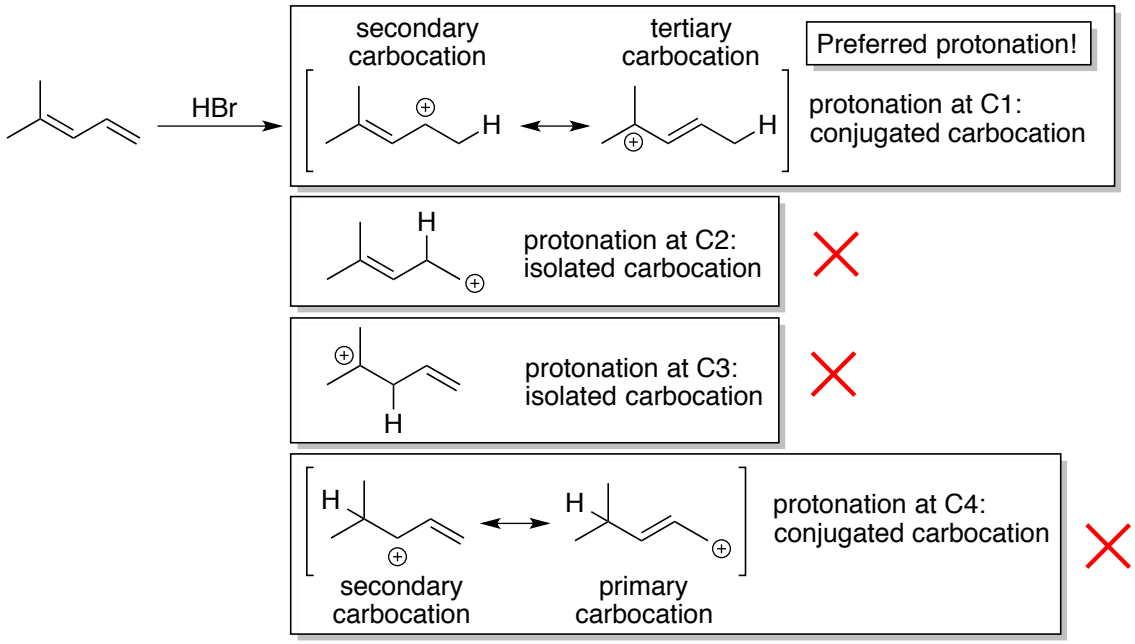


Of the two protonation events that led to resonance-stabilized carbocations, the latter (protonation at C1) is the lowest energy pathway because it has the most substituted carbocations in its two resonance contributors.

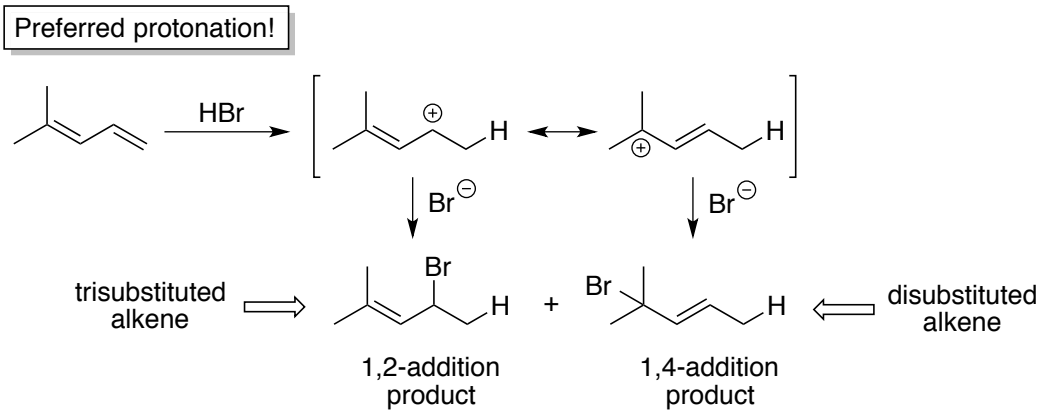
(b) In the second step of the mechanism, bromide can attack either of the two carbons with δ^+ charges. However, this just so happens to lead to the exact same molecule, (*E*)-4-bromo-2-pentene, in either case.



7. To determine the principal products of this reaction, we should consider each possible protonation event to determine which is the most favorable. Protonation at C2 or C3 would lead to isolated carbocations with no resonance stabilization. These outcomes are not favorable. Protonation at C1 or C4 would lead to conjugated carbocations that do have resonance stabilization, making these outcomes more favorable. Of the two, the most favorable protonation is at C1 because it results in resonance contributors with more highly substituted carbocations.



Now that we have determined the preferred mode of protonation, we can predict the two principal products by considering the addition of bromide to either partially positive carbon of the carbocation intermediate. This results in the 1,2- and 1,4-addition products.

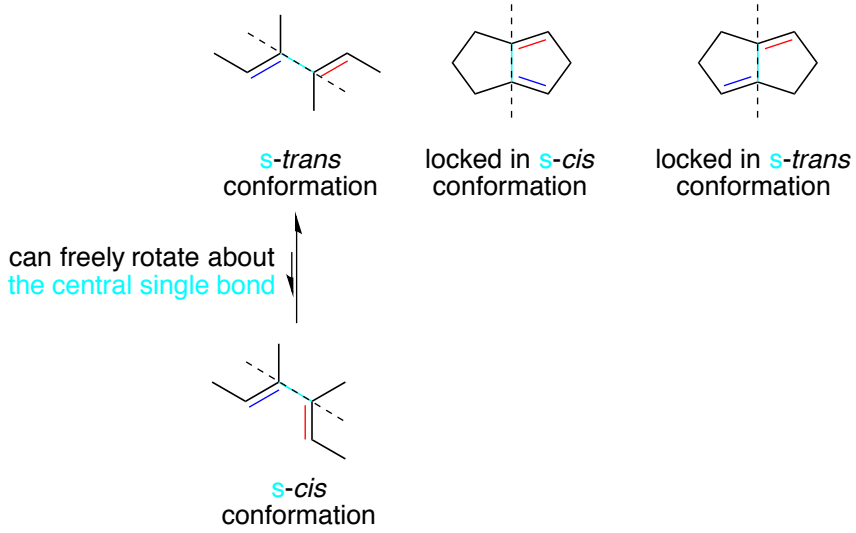


The 1,2-addition product is always the kinetic product due to the proximity effect. However, in this case, it is also the thermodynamic product because it contains the

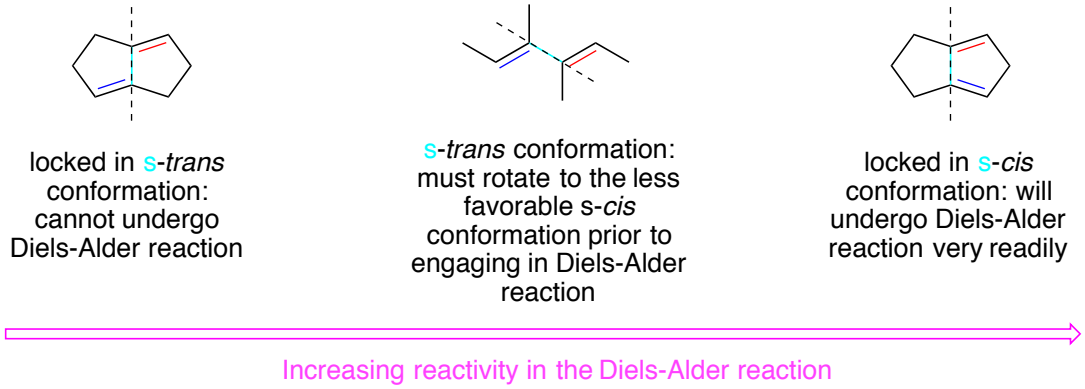
more highly substituted alkene. Therefore, the 1,2-addition product will be favored regardless of the temperature at which the reaction is conducted.

8. The issue in this question is whether or not the dienes have (or can achieve) the proper conformation for the Diels-Alder reaction. In order to undergo Diels-Alder reaction, the diene must be in the s-*cis* conformation.

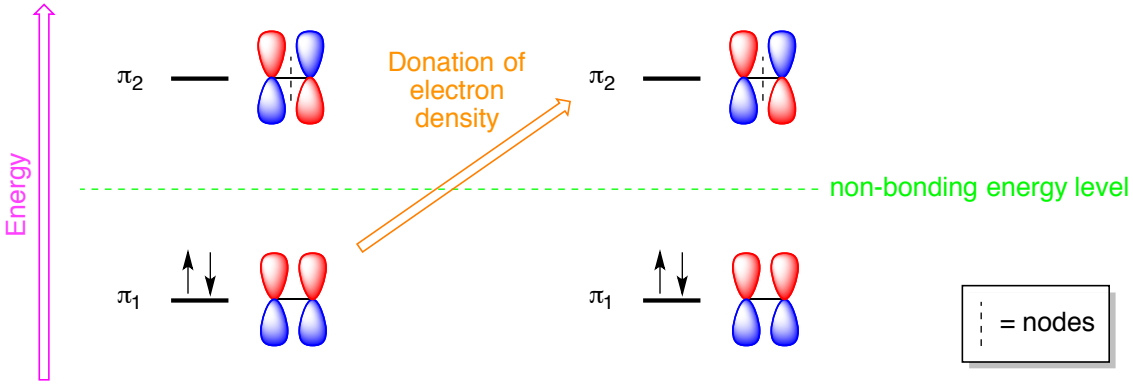
The acyclic diene is in the s-*trans* conformation; however, it can undergo rotation about the central single bond in order to achieve the needed s-*cis* conformation. The first of the cyclic dienes is actually locked in the s-*cis* conformation. Due to the conformational constraint imposed by the rings, it cannot undergo rotation about the central single bond. This conformational constraint is also in place in the second of the cyclic dienes; however, it serves to lock this one in the s-*trans* conformation.



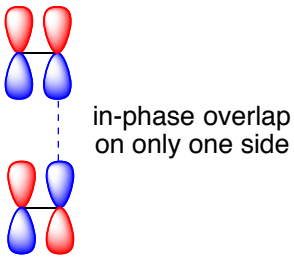
Each of these situations exerts a different impact on the molecule's ability to undergo the Diels-Alder reaction. The compound that is locked in the s-*trans* conformation simply cannot engage in the Diels-Alder reaction; therefore, it has the lowest reactivity. The acyclic diene does not have the necessary conformation, but given time, it can rotate so as to attain the needed s-*cis* arrangement. This means that it can undergo Diels-Alder reaction. However, it will not do so as quickly as the cyclic diene that is locked in the necessary s-*cis* conformation.



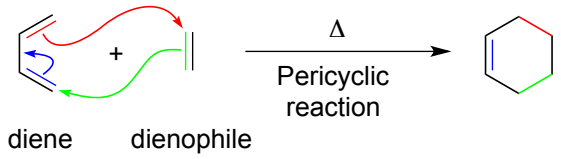
9. We utilized ethylene earlier in this very section. However, now we are considering two of these molecules undergoing cycloaddition. As we saw for the Diels-Alder reaction, it is necessary for a filled and an unfilled orbital to interact. In other words, the highest occupied molecular orbital (π_1) of one reactant must interact with the lowest unoccupied molecular orbital (π_2) of the other reactant.



The problem arises when we align the HOMO and the LUMO of the reactants. There is constructive interference on only one side. The other side experiences destructive interference that does not lead to new bond formation.

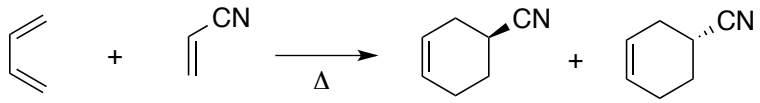


10. The motif for all four examples is exactly the same as for the simple Diels-Alder reactions covered thus far. The diene and the dienophile unite to form a cyclohexene ring.

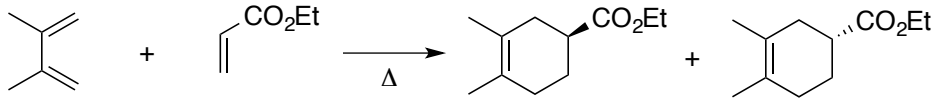


The substituents do not fundamentally alter the reaction in any way. They must merely be placed on the appropriate carbons of the cyclohexene product.

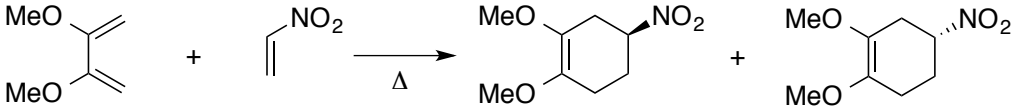
(a) In this reaction, a new stereocenter is formed, so the product is obtained as a mixture of enantiomers.



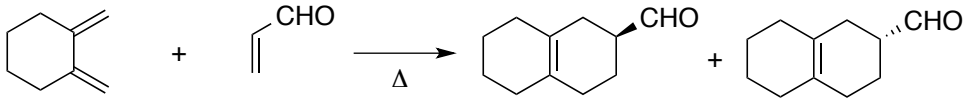
(b) Similarly, a new stereocenter is formed during this transformation. Therefore, the product is a racemic mixture.



(c) Yet again, a new stereocenter has been produced during the reaction, so the resulting product mixture is racemic.

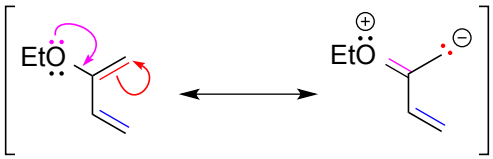


(d) In this final example, a stereocenter is also created, so the product is once again a 50/50 mixture of enantiomers.

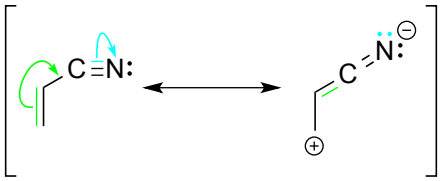


11.

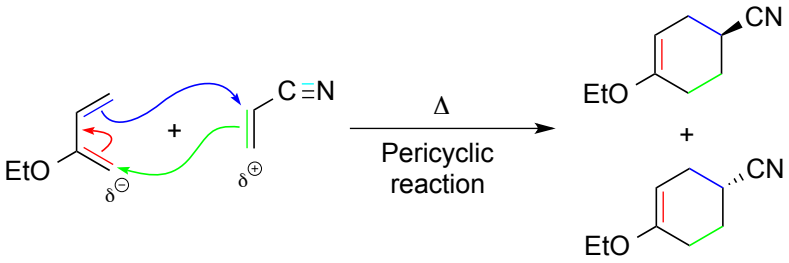
(a) This diene is very similar to the one used in the example in this section. Donation of a lone pair from the ethoxy group into the diene adds electron density to one terminus of the diene.



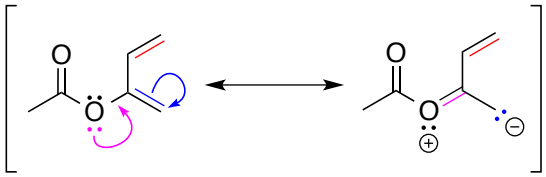
The dienophile bears a nitrile, which is an electron-withdrawing group. Resonance pulls electrons out of the alkene as electron density flows toward nitrogen.



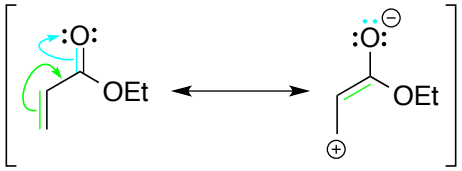
The diene and the dienophile align with complementary partial charges. When the Diels-Alder reaction takes place, a new stereocenter is formed, so a racemic mixture is obtained.



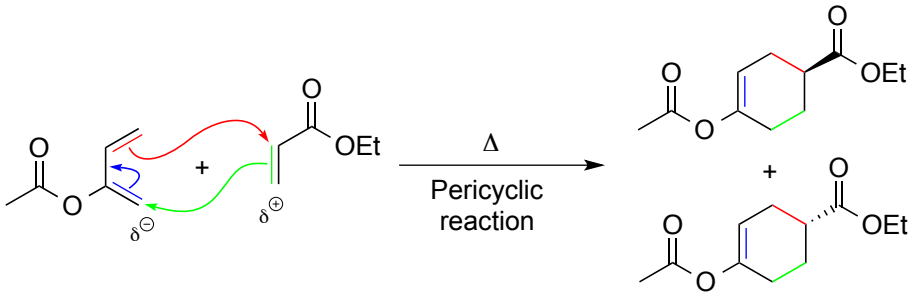
(b) The diene in this reaction bears an electron-donating ester group. Donation of a lone pair of electrons from the carboxyl oxygen places enhanced electron density on one end of the diene.



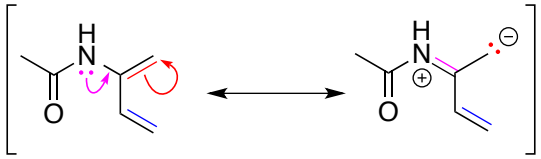
The dienophile also has an ester as a substituent. However, it is the carbonyl of the ester (rather than the carboxyl oxygen) that faces the π system. This makes the ester an electron-withdrawing group on the dienophile. It pulls electron density from the alkene as electrons flow onto the carbonyl oxygen. Notice how this effect differs from that exerted by the ester attached to the diene.



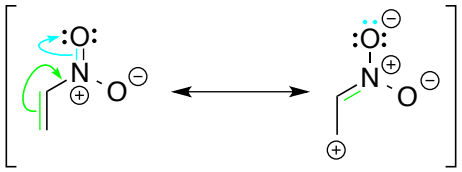
The reactants align with complementary partial charges as the pericyclic reaction commences. The product is obtained as a racemic mixture of enantiomers.



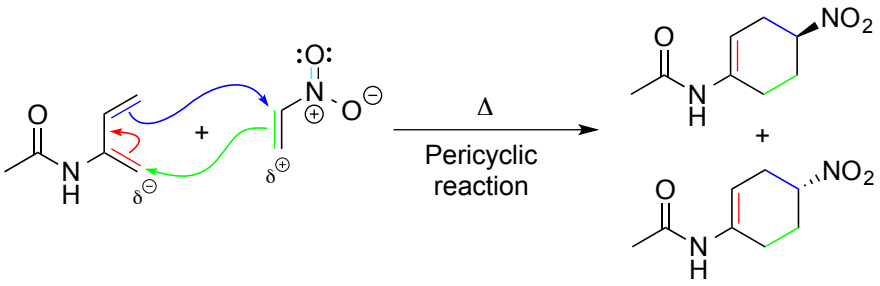
(c) The amide substituent on the diene is analogous to the ester substituent on the diene in part (b) above. The nitrogen atom can donate a pair of electrons to the diene, thereby enriching the electron density of one terminus of the π system.



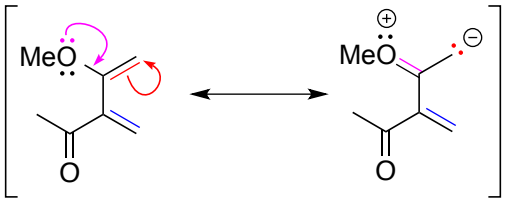
The nitro group is an electron-withdrawing group. Although it looks very different from a carbonyl, the nitrogen-oxygen double bond withdraws electron density through resonance much like a carbonyl does. As electrons are pulled from the dienophile, a partial positive charge develops on one side.



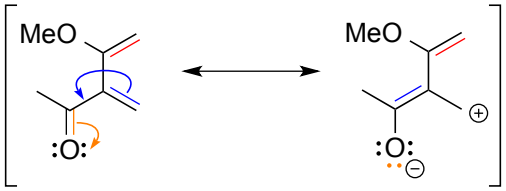
The diene and the dienophile align so that their partial charges are complementary. The Diels-Alder product is a racemic mixture.



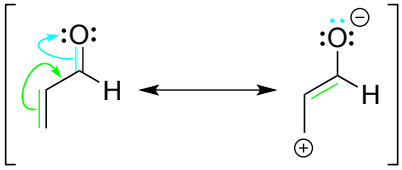
(d) This diene has two substituents, so we should consider the effect of each. We've seen the methoxy group before, and we know that it donates electron density to the diene.



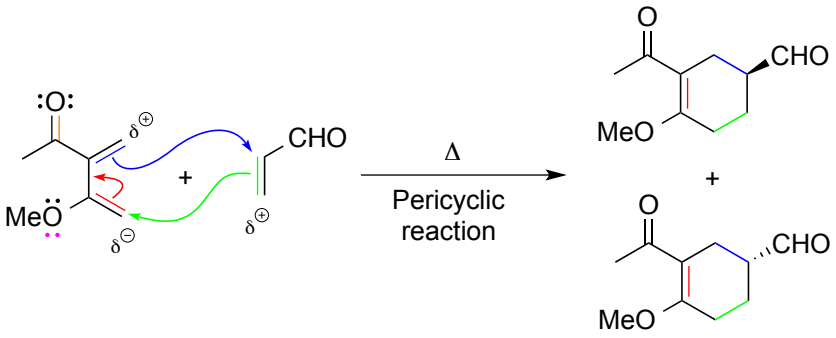
We've also seen that a carbonyl will withdraw electron density through resonance.



The dienophile also bears a carbonyl-containing functional group (an aldehyde in this case). The carbonyl withdraws electron density from the alkene.

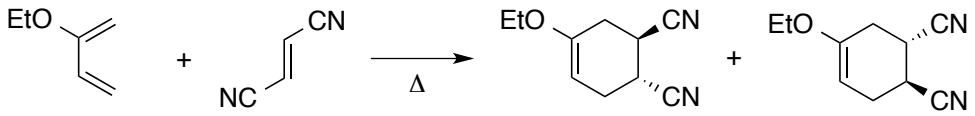


The reactants are, as usual, aligned with complementary partial charges. The more elaborate diene used in this problem merely has a partial charge at each end of the π system. The product is once again a racemic mixture.

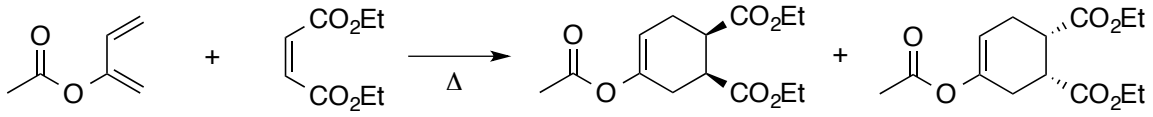


12.

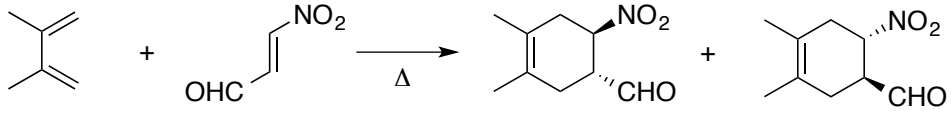
(a) In this reaction, the dienophile has the *trans* geometry, which is preserved in the products. Only the *trans* enantiomers of the Diels-Alder adduct are formed.



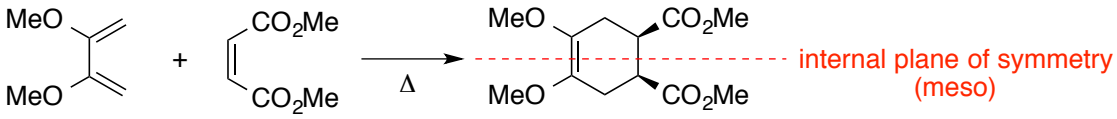
(b) The dienophile used in this instance has the *cis* configuration. Even though the esters are on the same side of the Diels-Alder adduct, the product is not a meso compound because the ester of the diene has broken the product's symmetry. Therefore, we obtain both *cis* enantiomers as products.



(c) The nitro group and the aldehyde are on opposite sides of the dienophile, and this *trans* geometry is retained in the enantiomeric Diels-Alder adducts.

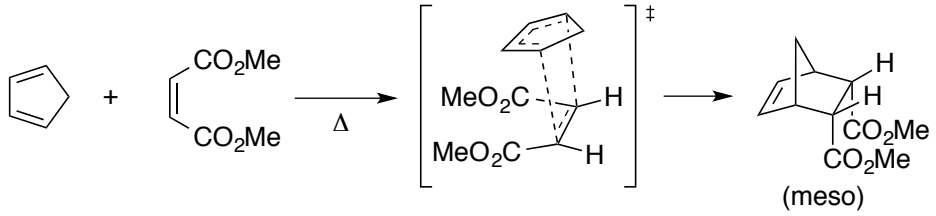


(d) The *cis* configuration of the dienophile is preserved in the Diels-Alder product. In this case, the product has internal symmetry, so it is a meso compound. Consequently, there is only a single reaction product.

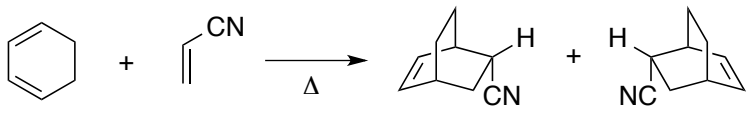


13.

(a) This problem is quite similar to the example used in this section. The only significant difference is that the dienophile bears *two* carbonyl-containing groups. As expected, the dienophile approaches the diene so that these carbonyls are tucked under the π system, which allows for additional orbital overlap. The result is an endo adduct that has the esters closer to the longer two-carbon bridge.

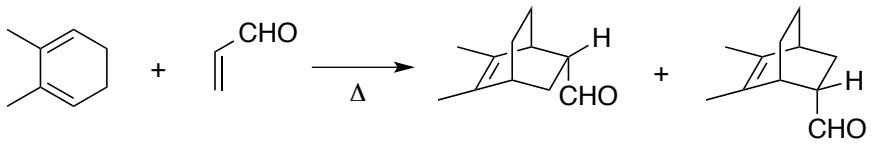


(b) The Diels-Alder adduct formed from this reaction has two bridges of the same length, which may initially appear to blur the distinction between exo and endo. However, the motif is the same as in part (a) above. Due to the favorability of additional orbital overlap in the transition state, the substituent ends up closer to the bridge containing the π bond.



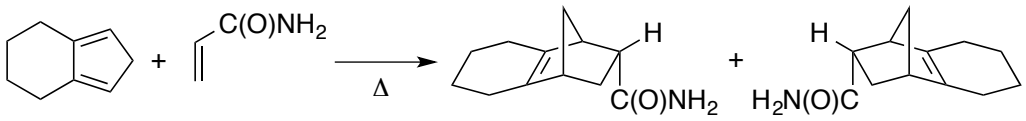
The product is a racemic mixture of enantiomers. In this case, the enantiomers have been drawn to highlight the fact that they are mirror images.

(c) The diene is substituted in this example, but that doesn't change the preference for endo addition. As in part (b) above, the substituent is closer to the bridge containing the π bond in the Diels-Alder adduct.



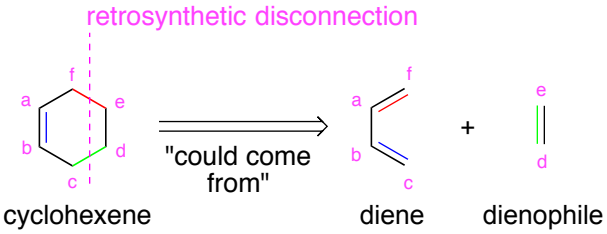
The Diels-Alder adduct is obtained as an equal mixture of enantiomers. In this case, the second enantiomer drawn is the mirror image rotated by 180°.

(d) In this final reaction, the diene is fused to a six-membered ring, but that doesn't alter anything about the course of the transformation. The endo product is formed such that the amide substituent of the dienophile is closer to the longer bridge in the adduct.

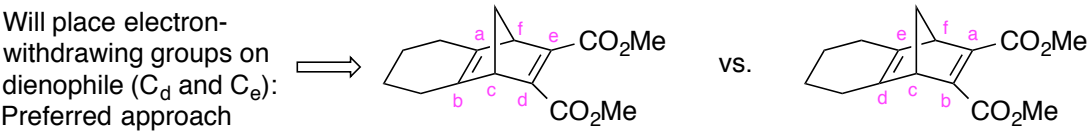


Both enantiomers are formed, and they are drawn above so as to highlight the fact that they are mirror images.

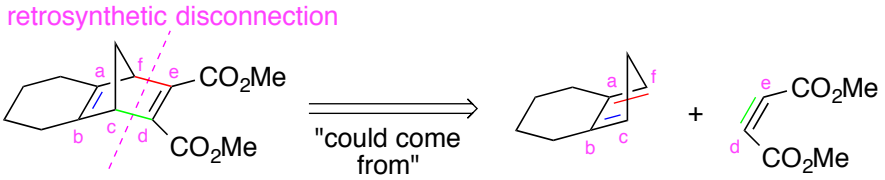
14. Remember to always use the model of the simplest possible Diels-Alder reaction as a guide.



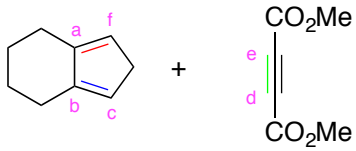
We begin by identifying the cyclohexene ring and labeling it according to the simple model (i.e., with C_a and C_b as the alkene carbons). In this instance, there are two possible ways to achieve this; however, only one labeling scheme places electron-withdrawing groups on carbons d and e, which come from the dienophile, so this is the preferred approach.



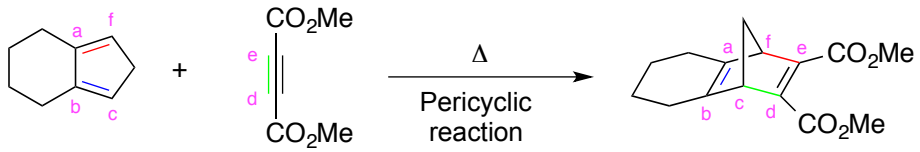
Next, we can use the same color-coding as in the simple Diels-Alder reaction to highlight those bonds that are formed during the cycloaddition. This shows us that the retrosynthetic disconnections should occur between C_c and C_d as well as between C_e and C_f. The two fragments are separated, and the π bonds are placed between the same carbons as in our model diene and dienophile. In other words, the red π bond appears between carbons a and f of the diene, the blue π bond appears between carbons b and c of the diene, and the green π bond appears between carbons d and e of the dienophile. Once we have established the proper connectivity, we can clean up the structures.



which could be drawn more neatly as:

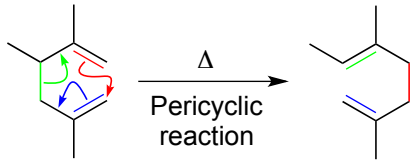


All that remains is to draw the reaction that converts the necessary diene and dienophile into the Diels-Alder adduct.

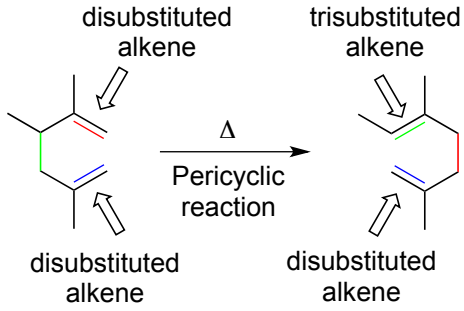


Notice that, in this reaction, the dienophile is an alkyne rather than an alkene. The presence of an additional π bond in the dienophile does not change the fundamental nature of the reaction taking place. It is, in essence, merely one more substituent to be carried through the process.

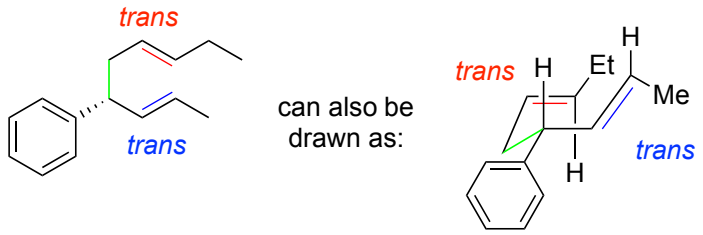
15. One of the π bonds attacks the carbon six atoms away, thereby forming a new σ bond. This displaces the second π bond, and as that π bond migrates, a σ bond is cleaved and becomes a π bond.



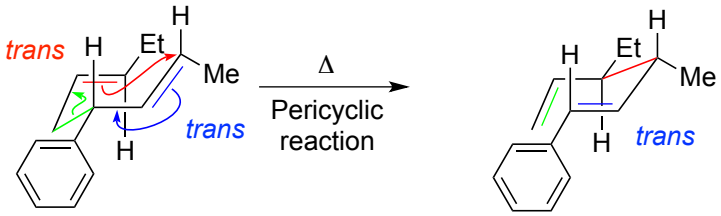
The reactant contains two disubstituted alkenes, while the product contains a disubstituted and a trisubstituted alkene. More highly substituted alkenes are more stable, so the product is favored at equilibrium.



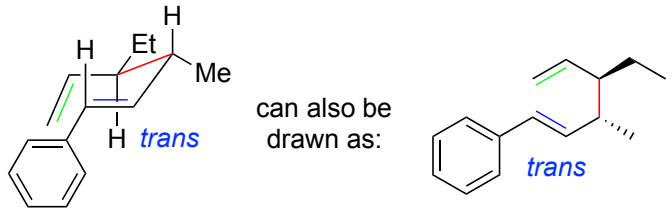
16. When the reactant is drawn in a chair-like conformation, the *trans* geometry of the two alkenes allows placement of the ethyl and methyl groups in pseudo-equatorial positions. Similarly, the configuration of the stereocenter results in the placement of the phenyl group on a pseudo-equatorial bond as well.



The mechanism begins when one π bond attacks the carbon that is six atoms away. A π bond is shifted as a result, and this incites the cleavage of a σ bond, which completes the mechanism.

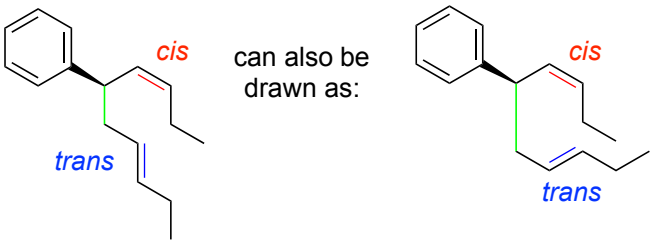


As the product's rendition is converted into a more traditional skeletal structure, it is important to take note of the *trans* nature of the disubstituted olefin. Additionally, two new stereocenters have been generated. If we redraw the product with the carbon backbone in the same orientation, then the ethyl group resides on a wedge because it was facing upward in the chair-like conformation. The methyl group, on the other hand, would be on a dash because it occupied a downward bond in the chair-like conformation.

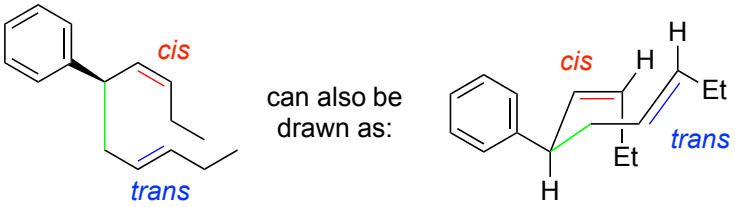


The formation of a conjugated alkene drives this reaction forward.

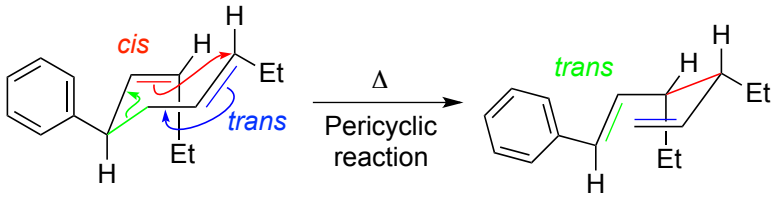
17. The first step in this problem is to redraw the reactant in a way that places the termini of the two alkenes relatively close to each other. This helps to emphasize the Cope rearrangement that is about to take place. As you do this, be careful to preserve the geometry of the olefins.



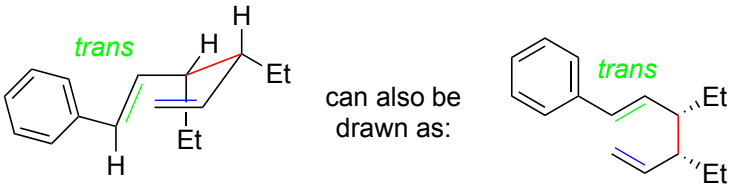
Then, the substrate can be drawn in a chair-like conformation. The *cis* orientation of one alkene results in one ethyl group occupying a pseudo-axial position. However, due to the configuration of the stereocenter and the *trans* geometry of the other alkene, both the phenyl group and the other ethyl group reside on pseudo-equatorial bonds.



The mechanism begins with the attack of one olefin on the terminus of the other that is six atoms away. A π bond is shifted in the process, and this necessitates the cleavage of a single bond to complete the pericyclic process.

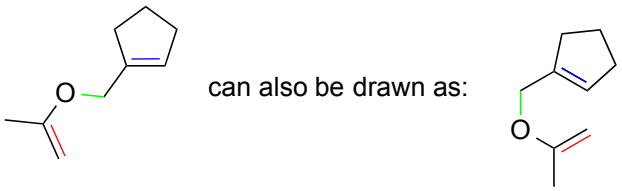


We can now convert the chair-like conformation back into a more traditional representation. As we do so, it is important to preserve the *trans* configuration of the disubstituted alkene. Additionally, provided that we draw the carbon backbone in the same orientation, the two ethyl groups are on dashed bonds because they both face downward in the chair-like rendition.

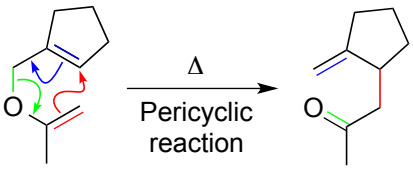


The reaction is also driven by the generation of a conjugated olefin.

18. It can be helpful to begin by redrawing the allyl vinyl ether so as to emphasize the incipient Claisen rearrangement by placing the termini of the two alkenes close together.

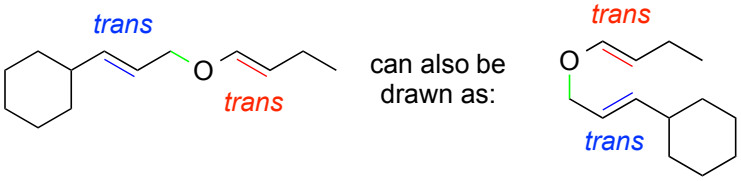


The Claisen rearrangement begins when the π bond of the vinyl ether attacks the alkene carbon that is six atoms away. This shifts the π bond of the allyl group toward oxygen, breaking a carbon-oxygen bond in the process to form the carbonyl.

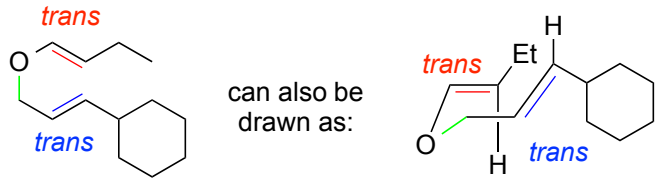


19.

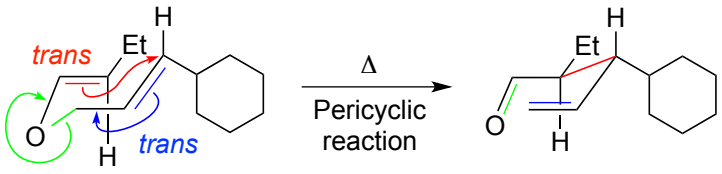
(a) It can be helpful to begin by drawing the substrate in a way that is more suggestive of the impeding Claisen rearrangement. This is done by orienting the molecule so that the termini of the alkenes are in close proximity. Be careful to maintain the configuration of each olefin though.



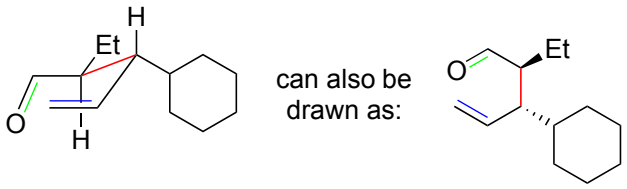
The substrate can now be redrawn in a chair-like conformation. The *trans* geometry of the two olefins results in the ethyl and cyclohexyl groups occupying pseudo-equatorial positions.



The Claisen rearrangement occurs when the π bond of the vinyl ether attacks the carbon that is six atoms away. This shifts of the π bond in the allyl group toward oxygen, causing the carbon-oxygen σ bond to break and generate the carbonyl.

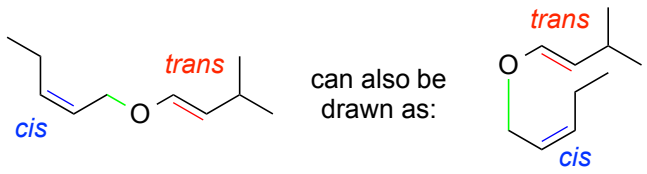


Finally, the product can be redrawn in a more traditional fashion. If the backbone is kept in the same orientation, the ethyl group occupies a wedge because it faces upward in the chair-like conformation. Additionally, the cyclohexyl group resides on a dash because it faces downward in the chair-like conformation.

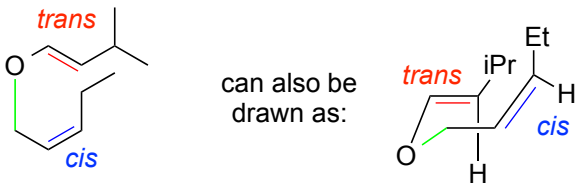


It is also important to note that the product is actually a racemic mixture. The enantiomeric product is formed through the enantiomeric chair-like transition state.

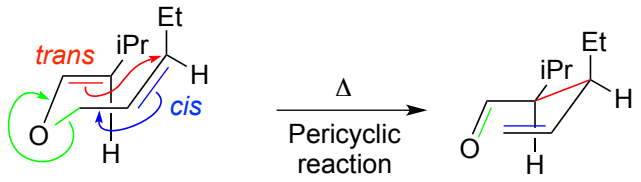
(b) Again, it is usually helpful to begin by redrawing the allyl vinyl ether so as to emphasize the conformation relevant for Claisen rearrangement. In doing so, we place the termini of the olefins in close proximity, and pay special attention to retaining their configurations.



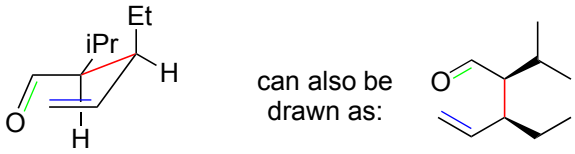
Now, the chair-like conformation can be drawn readily. The *trans* geometry of the vinyl group results in a pseudo-equatorial placement of the isopropyl substituent (iPr). Conversely, the *cis* geometry of the allyl moiety translates into a pseudo-axial placement of the ethyl group. Notice that the bigger group (the branched isopropyl substituent) has been placed in the pseudo-equatorial position.



The [3,3]sigmatropic rearrangement entails the attack of the vinyl group on the carbon six atoms removed. The shift of the allylic π bond necessitates the cleavage of the carbon-oxygen σ bond, which results in the formation of a carbonyl.

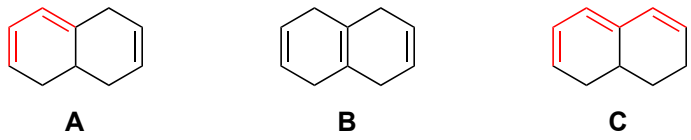


The product can now be redrawn in a more typical fashion. Assuming that we keep the backbone in the same orientation, both the isopropyl and ethyl groups reside on wedges because they are both on upward-facing bonds in the chair-like conformation.

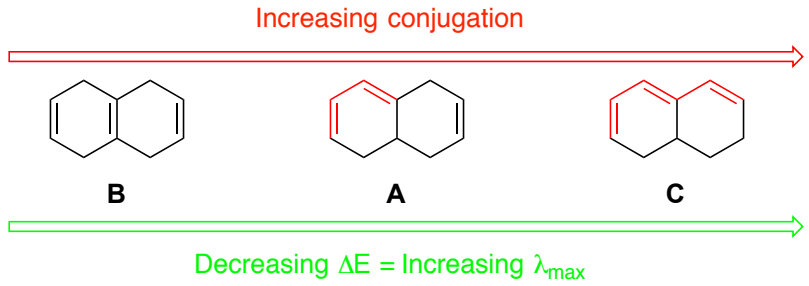


Note that the enantiomer is also formed in an equal amount from the enantiomeric chair-like transition state.

20. In compound A, two of the alkenes are conjugated, while the third is isolated. In compound B, all three olefins are isolated. However, in compound C, all three alkenes are conjugated.

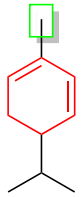


As the conjugation increases so does the λ_{max} value.



21.

(a) α-Phellandrene has a 1,3-cyclohexadiene moiety at its core, so the base λ_{max} value is 253 nm. Additionally, there is one alkyl group bonded to a carbon of the conjugated π system, which adds 5 nm to the λ_{max} for an approximate final value of 258 nm.

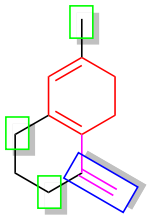


α-phellandrene

Core structure: 253 nm
One alkyl group: 5 nm

Expected λ_{max} = 258 nm

(b) This molecule also contains a 1,3-cyclohexadiene fragment at its core, giving it a base λ_{max} value of 253 nm. There is one additional conjugated π bond, which elevates the λ_{max} by 30 nm. The three alkyl groups bonded to carbons of the π system each add 5 nm, as does the fact that one of the π bonds is exocyclic. These additions bring the approximate λ_{max} value to 303 nm.



Core structure: 253 nm
Additional conjugated π bond: 30 nm
Three alkyl groups: 3 x 5 nm
Exocyclic double bond: 5 nm

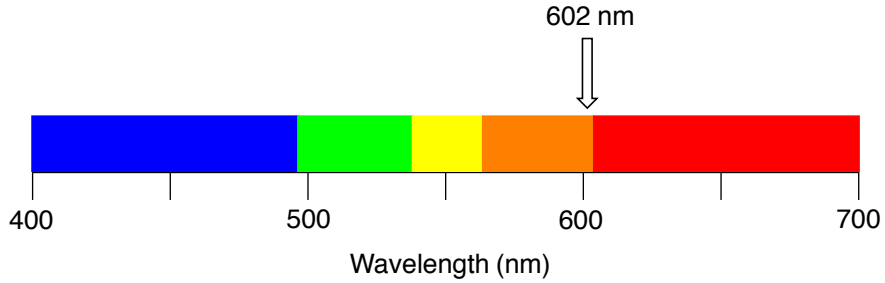
Expected λ_{max} = 303 nm

(c) In this compound, the core π system is a 1,3-butadiene fragment, resulting in a base λ_{max} value of 217 nm. The π system includes one additional conjugated alkene, which increases that value by 30 nm. Finally, there are four alkyl groups bonded to carbons of the π system, and each adds 5 nm to the λ_{max}. These adjustments bring the approximate λ_{max} to 267 nm.

Core structure: 217 nm
Additional conjugated π bond: 30 nm
Four alkyl groups: 4 x 5 nm

Expected λ_{max} = 267 nm

22. A λ_{max} of 602 nm falls within the orange range, approaching red light.

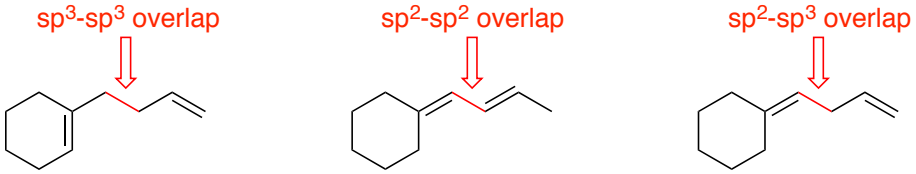


The complement of this reddish-orange light is blue, so the compound is expected to be blue in appearance. The reddish-orange light and the surrounding wavelengths are absorbed, while the complementary blue light is reflected to the observer's eye.

[1]

This compound is called indigo, and the name reflects the observed color.

23. The indicated σ bond in each structure is formed from the overlap of different hybrid orbitals. In the first molecule, it is the overlap of two sp^3 orbitals that forms the σ bond. In the second structure, it is the overlap of two sp^2 orbitals that gives rise to this bond. And, in the third and final compound, an sp^2 hybrid overlaps with an sp^3 hybrid to generate the σ bond.

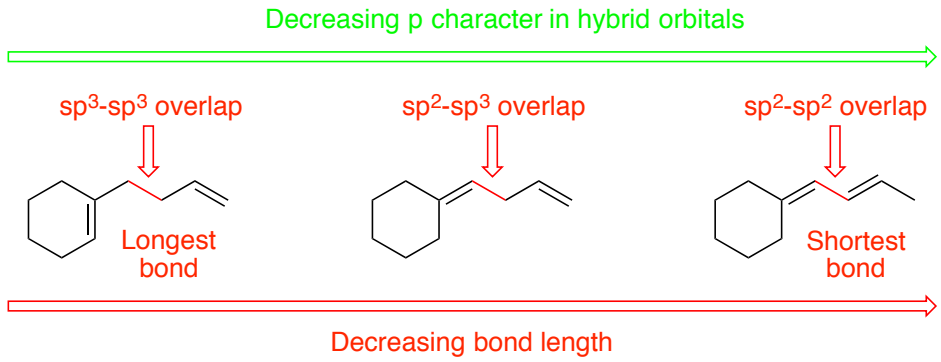


The shapes of the orbitals that are hybridized impact the length of the resulting hybrid orbital. An s orbital is spherical and shorter than a p orbital in the same shell. Consequently, hybrid orbitals with more p character are longer.

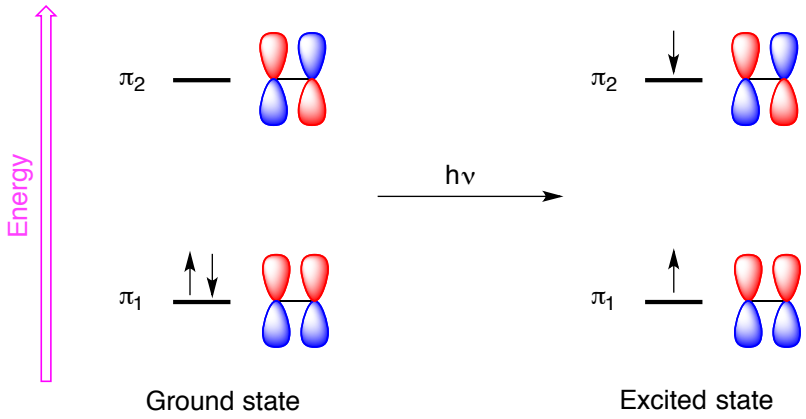
[1] Color wheel image:
http://commons.wikimedia.org/wiki/File:BYR_color_wheel.svg

sp	50% s character	shortest hybrid orbital
sp^2	33% s character	longer hybrid orbital
sp^3	25% s character	longest hybrid orbital

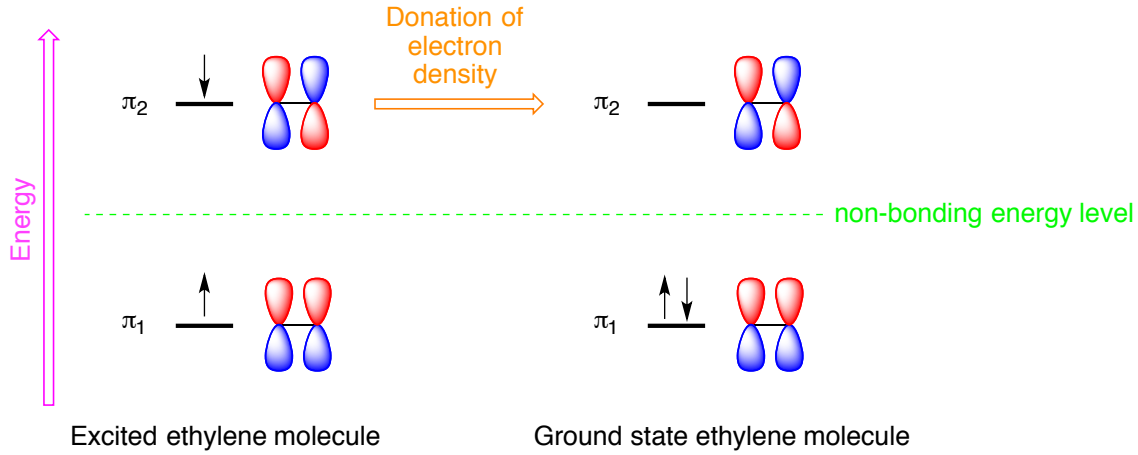
Therefore, the longest of the three bonds is the one made from two sp^3 orbitals, since they are the longest hybrids. Conversely, the shortest of the three bonds is the one made from two sp^2 orbitals, since they are the shortest hybrids.



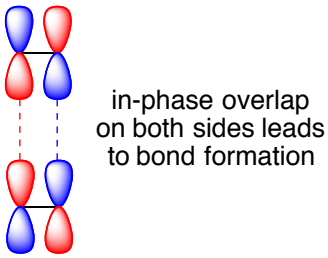
24. As stated in the text of the problem, light promotes an electron of some ethylene molecules from the HOMO to the LUMO. As shown below, this produces an ethylene molecule in the excited state.



It was also stated in the problem that the newly occupied molecular π orbital then interacts with the LUMO of a ground state ethylene molecule. That interaction is shown below.



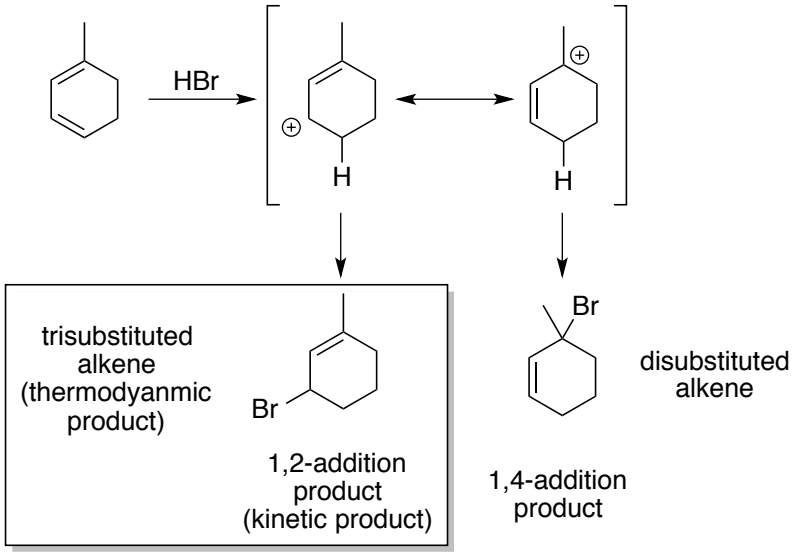
It is possible to align these two molecular π orbitals so that there is constructive (i.e., in-phase) interference between both termini, which results in the formation of the two new bonds produced during this [2+2]cycloaddition.



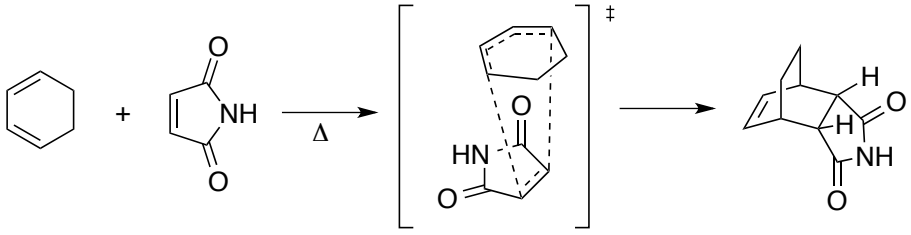
25.

(a) This reaction is an ionic hydrohalogenation. The conjugated diene preferentially adds a proton so as to make the most stable carbocation intermediate possible. This is the conjugated carbocation whose resonance hybrid has contributors bearing secondary and tertiary carbocation character.

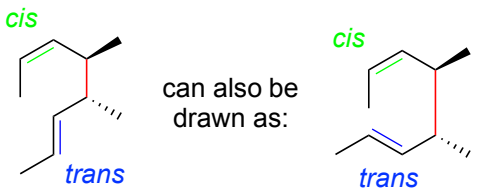
If we consider adding bromide to either δ^+ site, we can then evaluate the two possible products. The 1,2-addition product is always kinetically favored due to the proximity effect. In this particular instance, the 1,2-addition product also happens to contain the more highly substituted olefin, which makes it the thermodynamically favored product as well. As a result, the 1,2-addition product is expected to be the major product at any temperature.



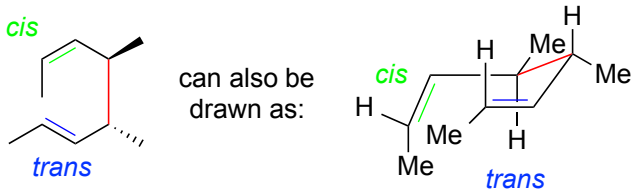
(b) This is a Diels-Alder reaction. Regiochemistry is not a concern in this case due to the symmetry of the reactants. However, stereochemistry is a consideration. Due to the preference for endo addition, the reactants approach one another so that the carbonyls of the dienophile are tucked under the π system of the diene. This allows for additional orbital overlap that stabilizes the transition state. The resulting product is a meso compound. Due to its internal plane of symmetry, it possesses no enantiomer and is the sole reaction product.



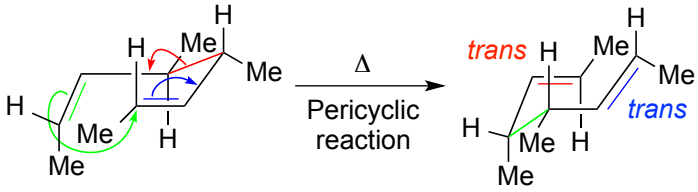
(c) This is a Cope rearrangement. The clues include the fact that the reactant is a 1,5-diene and that there is no oxygen in the backbone (as we would expect for a Claisen rearrangement). We can begin by redrawing the reactant with the termini of the π system in close proximity so as to accentuate the impending [3,3]sigmatropic shift. In so doing, we must be careful to preserve the alkene geometry.



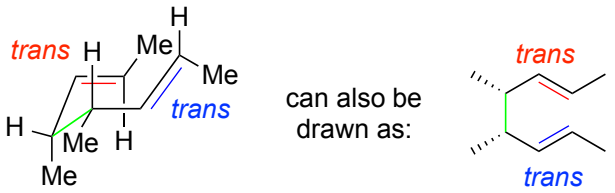
The reactant may now be drawn in the chair-like conformation through which the Cope rearrangement proceeds. Due to the configurations of the stereocenters and the alkenes, three of the four methyl groups reside in a pseudo-equatorial position.



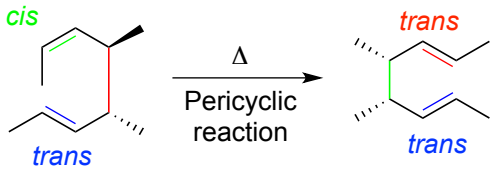
Then, the transformation ensues, giving rise to two new alkenes, both of which have the *trans* geometry.



We may now redraw the product in a more traditional fashion. If we keep the backbone in the same orientation, the methyl groups on the two new stereocenters will both occupy dashed bonds.



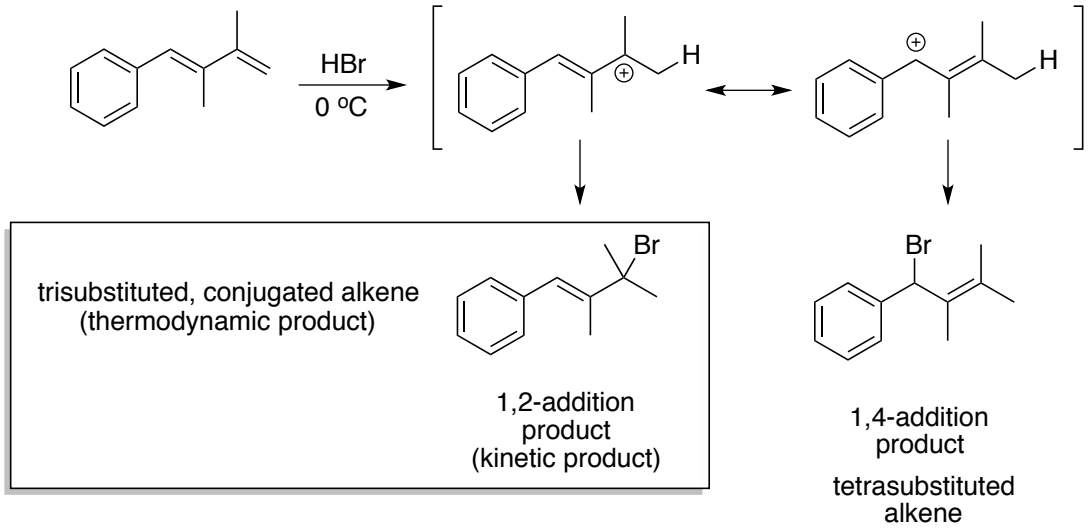
Overall, we can summarize the reaction as follows.



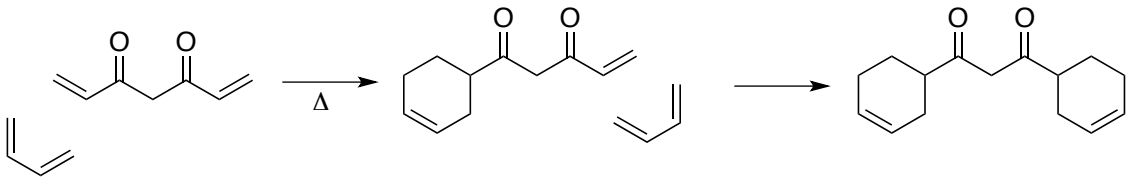
(d) In this ionic hydrohalogenation, we begin by protonating the conjugated diene. The preferred protonation leads to the most stable carbocation, which is not only resonance stabilized but also has resonance structures bearing tertiary and secondary, benzylic carbocation character.

We can generate both possible products by simply adding bromide to either of the partially positive sites. The 1,2-addition product is kinetically favored by the proximity effect. In this case, it is also thermodynamically favored. Although it has a

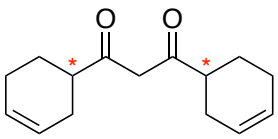
slightly less substituted alkene, the conjugation of that olefin to the aromatic ring is highly stabilizing. Since the 1,2-addition product also happens to contain the more stable alkene, it is the thermodynamic product as well. Being both the kinetically and thermodynamically favored compound, the 1,2-addition product is expected to predominate at any temperature.



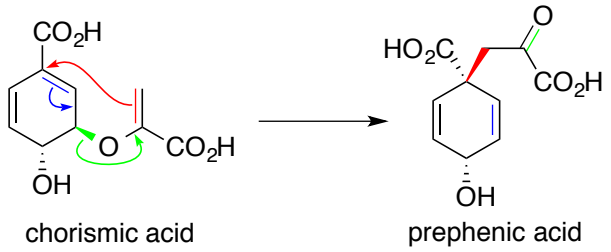
(e) This Diels-Alder reaction is slightly unusual in that we see the use of two equivalents of diene. The dienophile contains not just one but two reactive sites, which explains the use of additional diene. First, a Diels-Alder reaction occurs at one of the dienophilic termini of the diketone. Then, another Diels-Alder reaction takes place at the other terminus.



Two new stereocenters (*) are generated during this reaction. Each center is formed with either configuration. The two Diels-Alder reactions are independent of one another, so any combination of configurations may be formed. This leads to a total of three stereoisomers of the product: a pair of enantiomers and a meso compound.



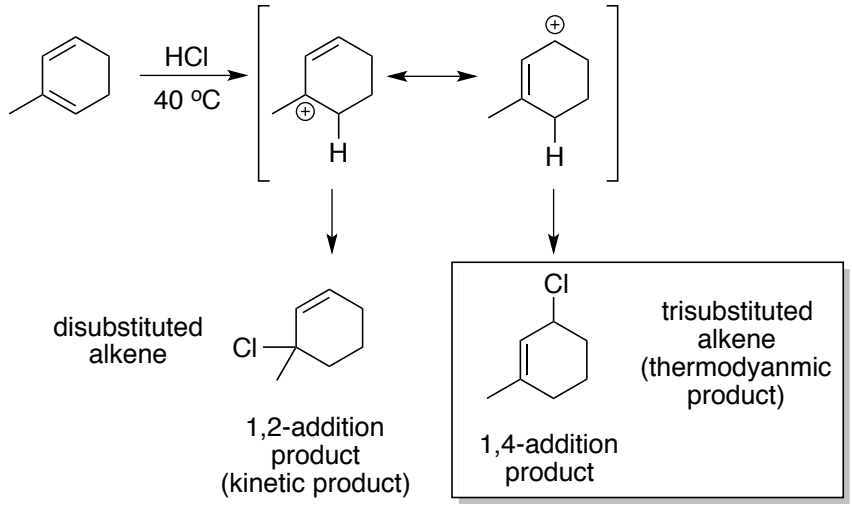
(f) This more complex substrate still contains the allyl vinyl ether moiety that is emblematic of a Claisen rearrangement. The typical Claisen mechanism provides the product, which happens to be known as prephenic acid.



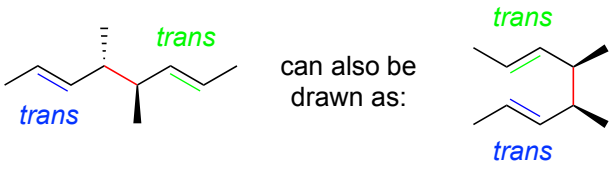
chorismic acid prephenic acid

(g) In this ionic hydrohalogenation, the conjugated diene preferentially undergoes addition of a proton so as to generate the most stable carbocation possible. This carbocation is resonance stabilized, and the resonance contributors to the hybrid have secondary and tertiary carbocation character.

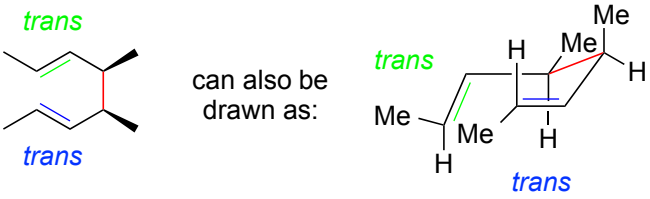
We can then consider the addition of chloride to either of the partially positive sites, giving the two possible products. The 1,2-addition product is always the kinetic product due to the proximity effect. However, the 1,4-addition product contains the more substituted alkene, which makes it the thermodynamically favored product. Since this reaction is conducted at a higher temperature, it is the thermodynamic product that predominates.



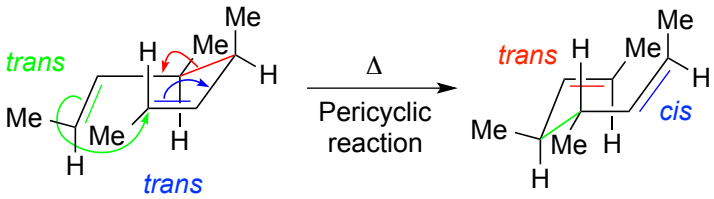
(h) The presence of a 1,5-diene and the absence of any oxygen atoms in the backbone suggest a Cope rearrangement. However, the reactant was not drawn to accentuate the transformation. We can begin by doing that. This entails drawing the termini of the alkenes in close proximity to one another. As we manipulate the structure, it is important to preserve the olefin configurations.



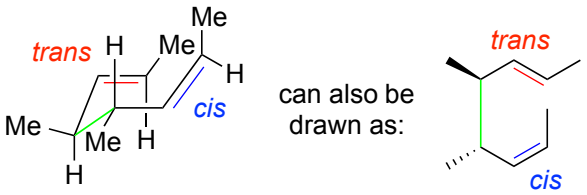
Now, we can proceed by drawing the chair-like conformation through which the Cope rearrangement occurs. Due to the configurations of the stereocenters and alkenes, three of the four methyl groups are in the pseudo-equatorial position.



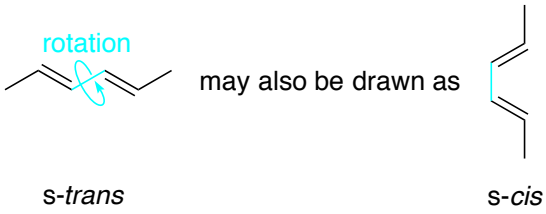
The reaction yields a new 1,5-diene with one *trans* alkene and one *cis* alkene.



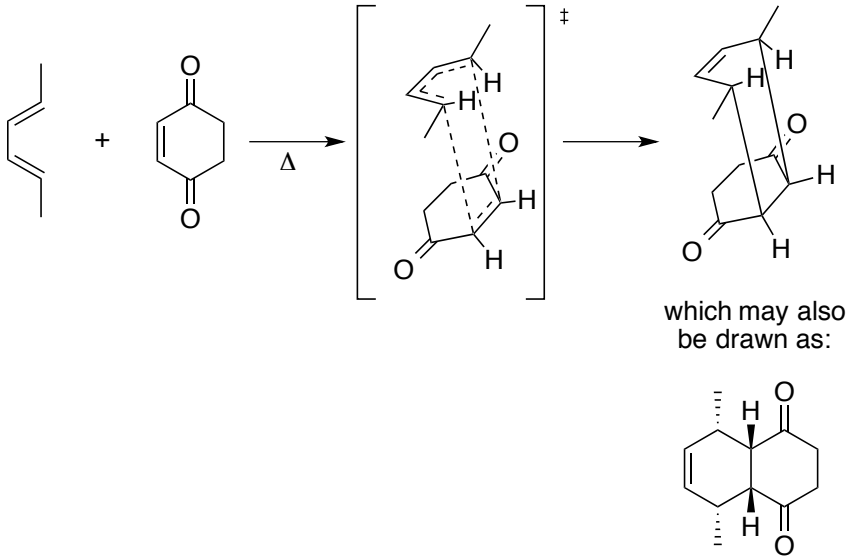
Finally, we can convert the chair-like conformation of the product to a more traditional drawing. Provided that the backbone is kept in the same orientation, the two methyl groups on the new stereocenters will occupy different sides of the molecule. The product drawn below is obtained along with its enantiomer, which results from the enantiomeric chair-like transition state.



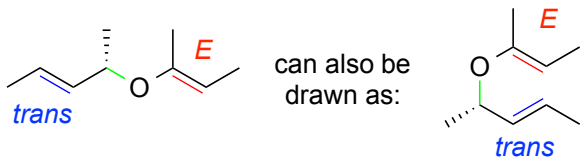
(i) This is a Diels-Alder reaction; however, the diene is drawn in such a way that it does not accentuate the reaction. Rotation about the central single bond converts the s-*trans* conformation to the s-*cis* conformation needed for successful reaction. Be careful though to preserve the *trans* configuration of each of the alkenes.



Due to the preference for endo addition, the dienophile approaches the diene with the carbonyls tucked under the diene's π system. This allows for additional stabilizing orbital overlap. Several hydrogen atoms are drawn in the transition state below for clarity. In the product, we can see that all four indicated hydrogens are on the same side of the molecule, while the two methyl groups are on the opposite side from the hydrogens. This is similarly reflected in the more traditional drawing of the product's structure. Since it is a meso compound, the product has no enantiomer.

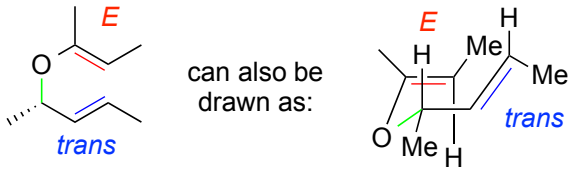


(j) This substrate contains the allyl vinyl ether fragment that is indicative of a Claisen rearrangement; however, it is not drawn so as to highlight the impending reaction. We can begin by redrawing it with the termini of the alkenes in close proximity. Be careful to maintain the configurations of the alkenes as you redraw the substrate.

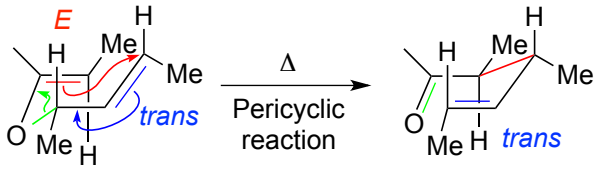


The substrate can now be redrawn in the chair-like transition state through which the Claisen rearrangement proceeds. Due to the configurations of the stereocenter and the alkenes, three methyl groups occupy pseudo-equatorial positions. The

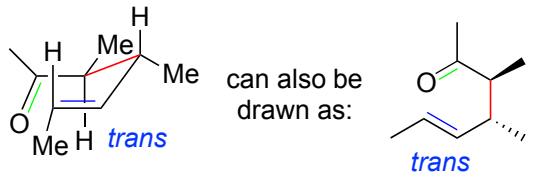
methyl group directly adjacent to oxygen on the vinyl fragment is neither pseudo-axial nor pseudo-equatorial.



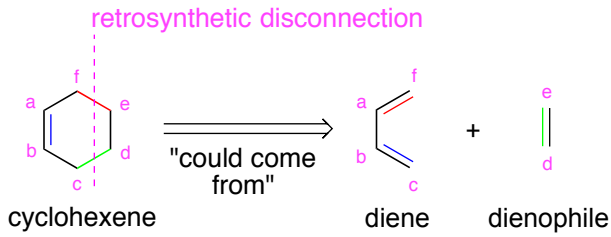
When the reaction occurs, a new alkene is formed with *trans* geometry.



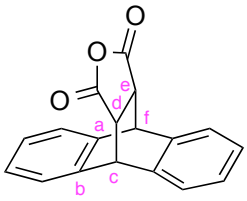
Finally, we can redraw the product in a more traditional way. If the backbone is kept in the same orientation, the methyl groups on the two new stereocenters will reside on opposite sides of the molecule.



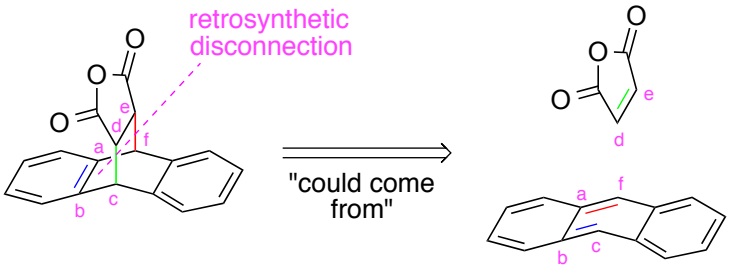
26. Remember that it is always wise to use the simplest possible Diels-Alder reaction as a model when tackling more complex Diels-Alder synthesis problems.



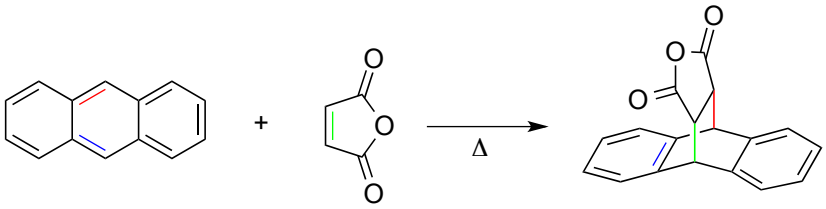
(a) We begin by identifying the cyclohexene ring in the target and labeling it so that C_a and C_b correspond to the alkene carbons. In cases such as this one where it is possible to identify more than one cyclohexene ring in the product, we are guided by that fact that the dienophile carbons (C_d and C_e) should bear electron-withdrawing groups if possible.



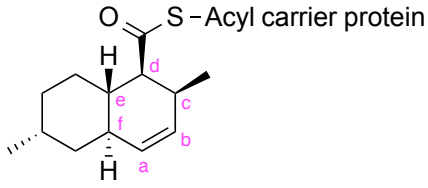
With the labeling in place, we can apply the same color-coding as in the model reaction to highlight those bonds that are newly formed from the Diels-Alder reaction. This shows us where the retrosynthetic disconnections should be made. We then slide the fragments apart and place the three π bonds in the same sites they occupied in the model reaction.



All that remains is to clean up the structures of the reactants and draw the reaction in the forward sense.

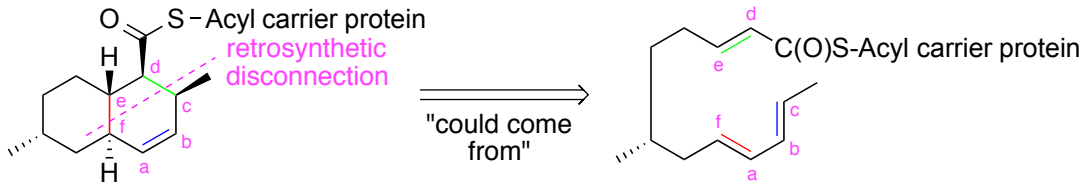


(b) It is fairly straightforward to identify the cyclohexene ring in this target. Once again, we can apply the labeling from the simple model Diels-Alder reaction. Be sure to assign C_a and C_b as the alkene carbons.

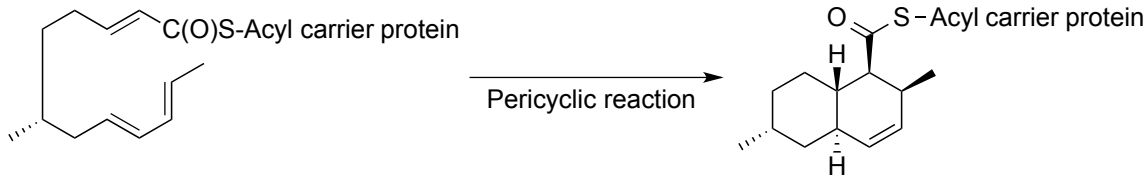


With the labeling in place, we can introduce the same color-coding used in the model reaction to highlight those bonds formed during the [4+2]cycloaddition. The retrosynthetic disconnections are made across the newly formed σ bonds, and we can then separate the fragments and place the π bonds according to the labeling of

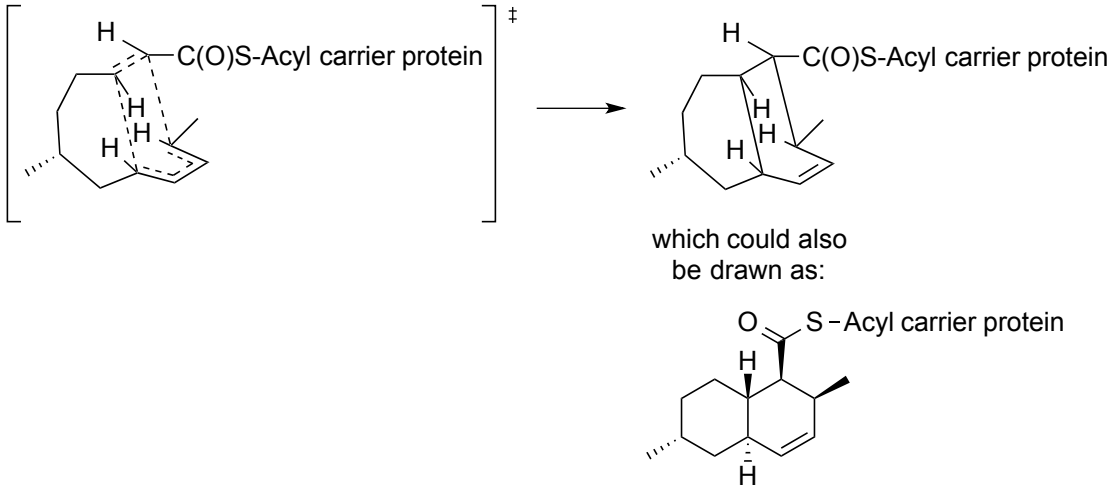
the reactants in the simple reference Diels-Alder reaction. In this instance, there is a tether between the diene and the dienophile, so the reactant is a single molecule.



All that remains is to show the reaction in the forward sense. Since this [4+2]cycloaddition takes place between a diene and dienophile in the same substrate, it is an *intramolecular* Diels-Alder reaction.



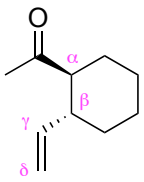
The stereochemistry of the process is a subtle point. All three alkenes must have the *trans* geometry in order to yield the desired stereochemistry. The transition state shown below reveals how this all *trans* substrate gives rise to the observed stereochemistry of the product.



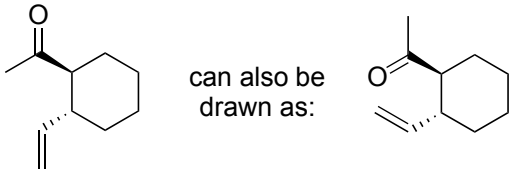
As shown, the product could be accompanied by a diastereomer, resulting from a transition state in which the dienophile approaches the diene from underneath. However, if this reaction were catalyzed by an enzyme (a so-called "Diels-Alderase"), it would take place in the chiral environment that is the enzyme's active site. Under such conditions, a single stereoisomer could be produced.

27.

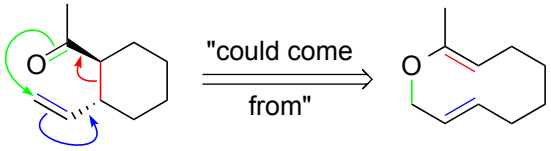
(a) This target certainly contains the γ,δ-unsaturated carbonyl that results from a Claisen rearrangement; however, its structure has not been drawn in a way that emphasizes the pericyclic reaction that made it.



We can begin by redrawing the target molecule so that the carbonyl oxygen and the terminus of the γ,δ-unsaturation are in close proximity.

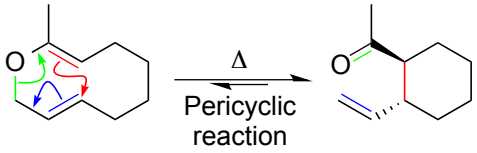


This makes it easier to envision the *retro*-Claisen rearrangement. In other words, we can draw the three arrows of this pericyclic reaction, but now we are using them to show us which reactant is needed to generate the target structure. The retro-Claisen rearrangement reveals the allyl vinyl ether needed for this synthesis.

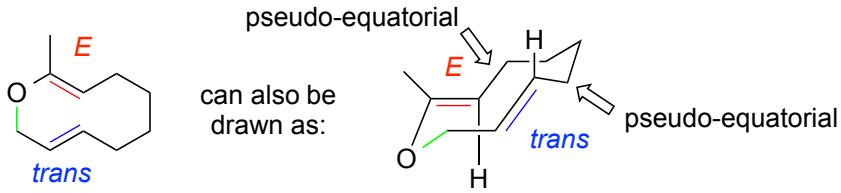


retro-Claisen rearrangement

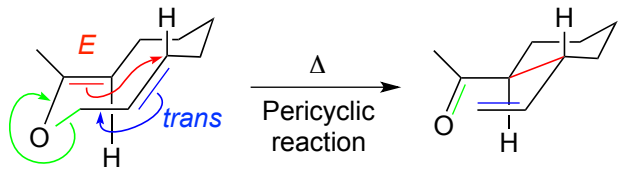
All that remains is to show the reaction in the forward sense.



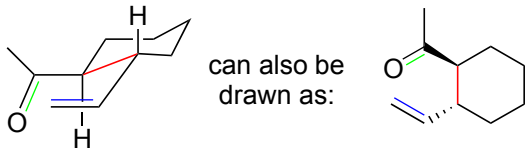
However, we have not yet explicitly checked the stereochemistry, and we should do so to be sure that the reactant we drew has the double bond geometry needed to give the desired stereochemistry in the target. Let's draw the reactant in the chair-like conformation through which the Claisen rearrangement proceeds. Be careful to preserve the olefin geometry. Due to the configuration of the olefins, the four-carbon bridge joining the alkenes resides solely on pseudo-equatorial bonds.



When the Claisen rearrangement takes place, two stereocenters are formed.

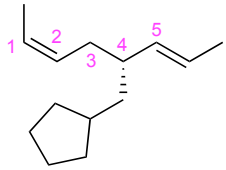


As the product is redrawn in a more conventional fashion, we can see that the two substituents do indeed occupy opposite sides of the cyclohexane ring.

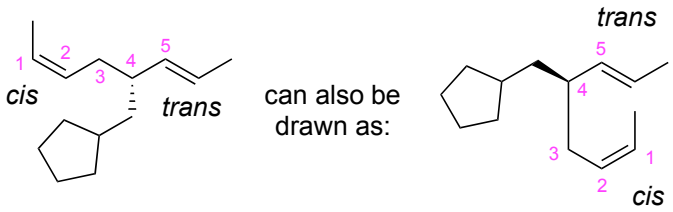


The enantiomeric product is also produced from the enantiomeric transition state.

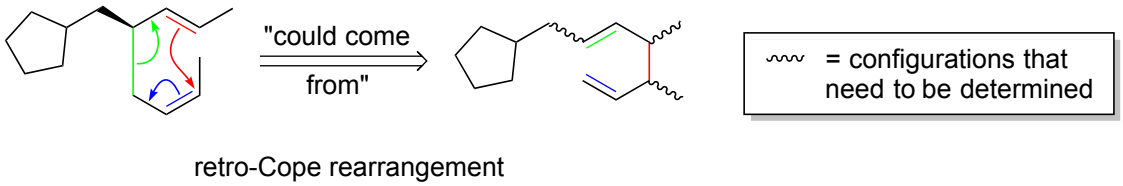
(b) This target does contain the 1,5-diene that is emblematic of both a Cope rearrangement reactant and product. However, the molecule has not been drawn in a way that would emphasize the reaction.



It is helpful to begin by redrawing the target so that the termini of the alkenes are in close proximity. This makes the Cope transformation more apparent. Be careful to preserve the olefin geometry though.

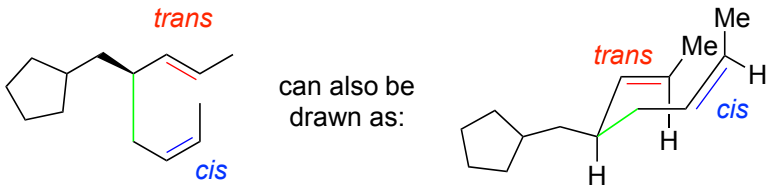


We can now draw the arrows of the Cope rearrangement, but here we are using them to deduce the structure of the reactant that gives rise to this product. In this sense, it is referred to as a *retro*-Cope rearrangement because we are, in essence, using it in the reverse of the synthetic direction. The proposed reactant has an olefin with either *cis* or *trans* geometry and stereocenters with configurations that need to be defined.

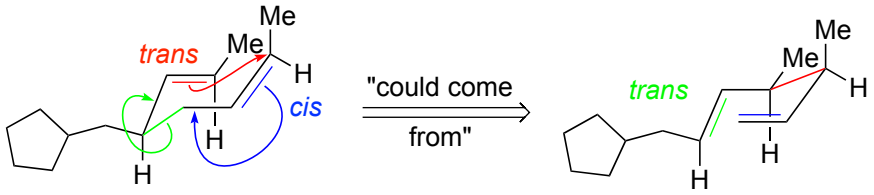


retro-Cope rearrangement

We can use the chair-like transition state (again working backwards) to deduce the proper orientations. Let's begin by drawing the target in the chair-like conformation in which it is formed at the conclusion of the Cope rearrangement. We must be careful to preserve the configuration of the two alkenes and the single stereocenter. Notice that the R group and one of the methyl groups occupy pseudo-equatorial positions while the other methyl group occupies the pseudo-axial position.

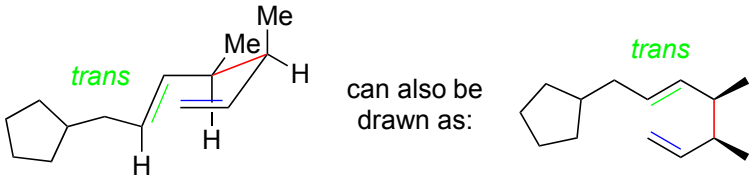


Now, we can once again draw the arrows for the retro-Cope rearrangement. This allows us to make the bonds present in the reactant. In so doing, we have also determined all of the necessary configurations.

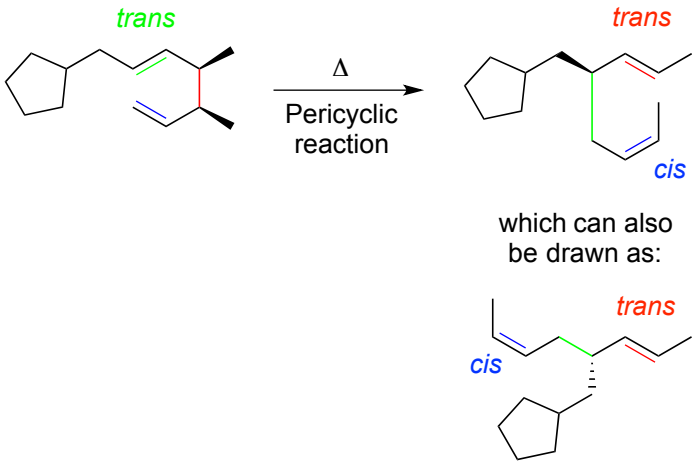


retro-Cope rearrangement

The reactant can now be redrawn in a more conventional way. The disubstituted alkene is *trans*, and the two methyl groups reside on the same side of the molecule provided that we draw the backbone in the same orientation.



To finish the problem, we need only draw the reaction in the forward sense.



The enantiomeric reactant would give the enantiomeric product.

28. Recall from our discussions in Chapter 6, that the change in Gibbs free energy allows us to predict which side of a reaction is favored at equilibrium.

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

For this reaction, the change in entropy is negligible because one reactant molecule is rearranging to yield one product molecule that is roughly comparable in structure. Therefore, we may continue to assume that the change in Gibbs free energy is approximately equal to the change in enthalpy.

$$\Delta G^\circ \approx \Delta H^\circ$$

The change in enthalpy can be calculated using bond dissociation energies. Recall that the change in enthalpy is the difference in energy between the bonds broken and formed during the transformation.

$$\Delta H^\circ = \sum [H^\circ \, bonds \, broken] - \sum [H^\circ \, bonds \, formed]$$

During Claisen rearrangement, two carbon-carbon π bonds and one carbon-oxygen σ bond are broken. By the conclusion of the reaction, a carbon-carbon π bond, a carbon-carbon σ bond, and a carbon-oxygen π bond have been formed.

$$\Delta H^{\circ} = [2 \times (carbon - carbon\,\pi) + (C - O)] - [(carbon - carbon\,\pi) + (C - C) + (carbon - oxygen\,\pi)]$$

Notice that the table provided does not include the bond dissociation energies of just the π bonds. The values listed for the double bonds include the energy needed to break both the σ and the π bond. Nevertheless, we can derive the bond dissociation energy for the π bonds by merely taking the difference between the bond dissociation energy for the double and single bonds:

Bond dissociation energy (BDE) of carbon-carbon π bond = (BDE C=C) – (BDE C-C) = 146 – 83 = 63 kcal/mole

Bond dissociation energy (BDE) of carbon-oxygen π bond = (BDE C=O) – (BDE C-O) = 177 – 85.5 = 91.5 kcal/mole

Now, we have all of the values needed to complete the calculation of the change in enthalpy.

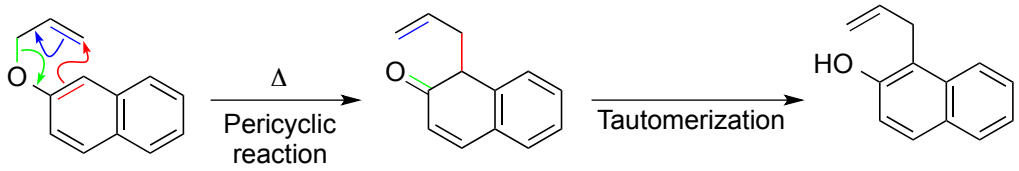
$$\Delta H^{\circ} = [2 \times (carbon - carbon\,\pi) + (C - O)] - [(carbon - carbon\,\pi) + (C - C) + (carbon - oxygen\,\pi)]$$

$$\Delta H^{\circ} = [2 \times (63) + 85.5] - [63 + 83 + 91.5] = -26\ kcal/mole$$

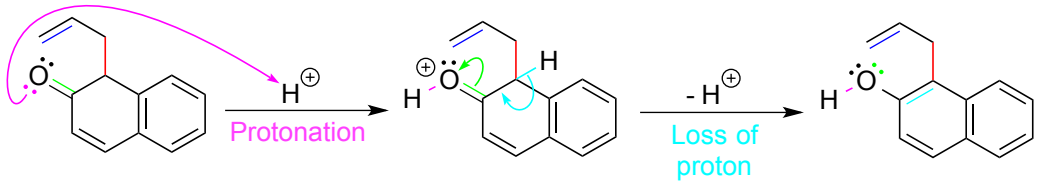
This reaction is therefore exothermic ($-\Delta H^{\circ}$). Since the change in enthalpy is expected to predict the change in Gibbs free energy reasonably well, we also expect the reaction to be exergonic ($-\Delta G^{\circ}$), meaning that the products are favored at equilibrium.

29. We know that a chemical change did indeed occur because the reactant would not be expected to show any broad signals in the heteroatom-to-hydrogen stretching region of the IR. However, we may be a bit surprised by this outcome, which is consistent with a product containing an O-H group (IR signal at ~3300 cm^{-1}). Claisen rearrangements typically yield carbonyl-containing products, but no signal was observed at 1700 cm^{-1}.

Let's begin by drawing the expected Claisen rearrangement. One of the π bonds of the ring functions just as the π bond of the vinyl group usually does. It attacks the terminus of the allyl group, shifting that π bond toward oxygen, and ultimately cleaving the carbon-oxygen σ bond to form the carbonyl. The unusual part of this reaction is that the carbonyl-containing intermediate can then tautomerize so as to re-form a second aromatic, or "benzene-like," ring.

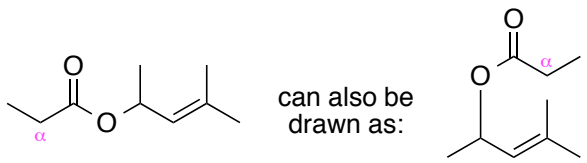


Tautomerization occurs with merely a trace of acid or base. The acid-catalyzed mechanism is shown below. It begins with protonation of the carbonyl oxygen. A proton is then lost from the adjacent sp^3 hybridized carbon, and electrons flow toward the carbonyl oxygen to neutralize its charge.

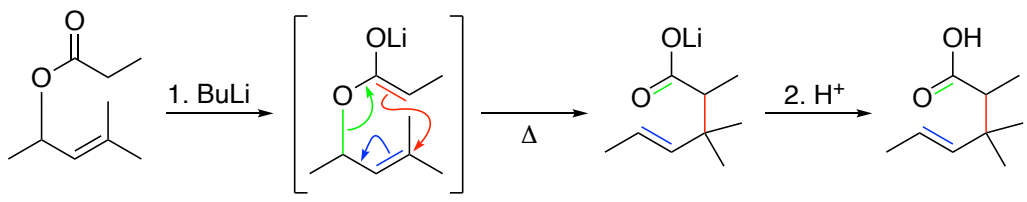


The product contains a phenolic hydroxyl group whose O-H stretch explains the signal at 3300 cm^{-1} in the IR spectrum. The tautomerization also explains why no carbonyl resonance is observed.

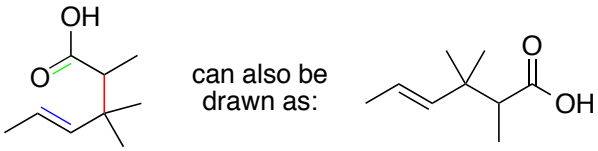
30. The reactant is an allylic ester, but it is not drawn in a way that will accentuate the pericyclic rearrangement to come. We can therefore begin by redrawing its structure so as to place the α carbon in close proximity to the terminus of the allyl group.



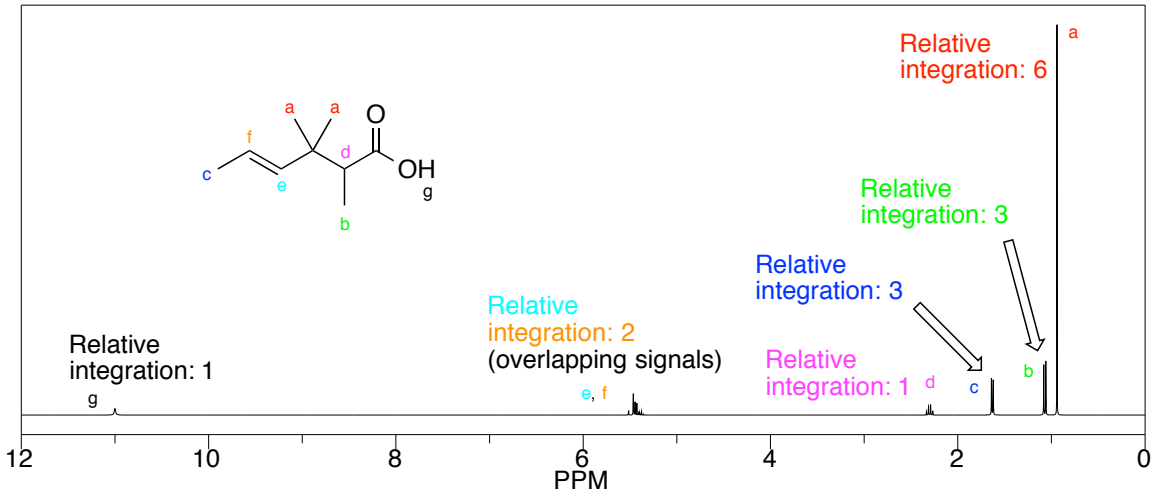
The α carbon is deprotonated in the first step of the Ireland-Claisen reaction. This generates the electronic core structure necessary for the [3,3]sigmatropic shift. The rearrangement occurs to yield a carboxylate, which is protonated in the second step of the reaction.



The product may also be drawn as follows.

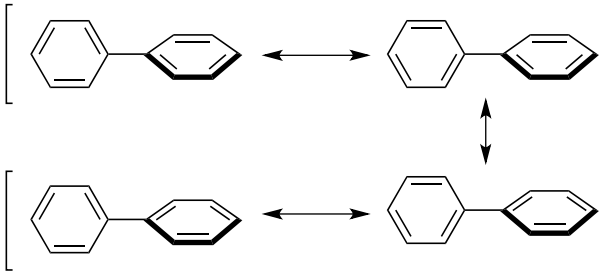


To assign the signals in the proton NMR spectrum, we should first identify the different types of protons in the molecule. There are seven types of protons (labeled a–g below). The signal integrating for 6 hydrogens clearly corresponds to the two identical methyl groups (a). Both b and c are methyl groups with a single neighbor; however, c is closer to a π bond, making it slightly more deshielded than b. The methine (CH) labeled d is unique in that it integrates for 1 hydrogen and is fairly shielded. The two vinyl protons (e and f) happen to overlap within the chemical shift region corresponding to vinyl protons. Finally, the carboxylic acid proton (g) is quite deshielded.

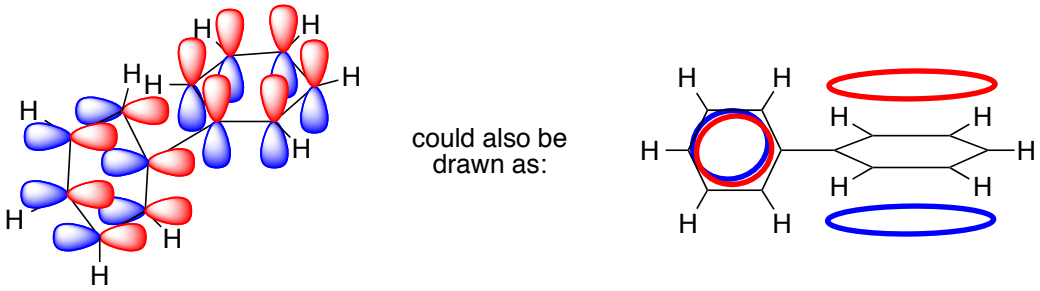


Solutions to Problems for Chapter 13: Aromaticity

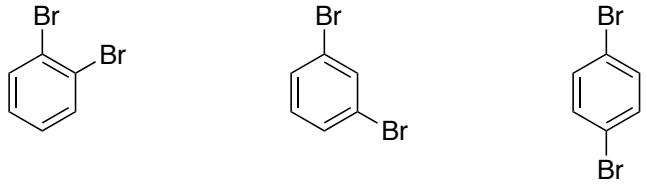
1. There are two Kekulé forms for each ring, so there are four combinations leading to four resonance structures.



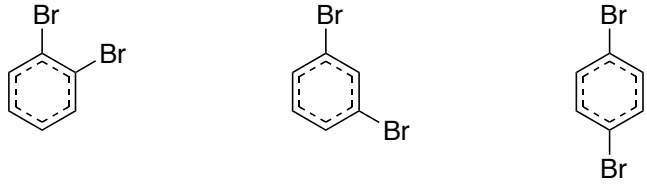
Since the rings are perpendicular, the π systems are as well. The π systems can be illustrated using the individual p orbitals of each carbon or by showing the delocalization of electrons in a π cloud found above and below each ring.



2. There are three isomers of dibromobenzene. The bromine atoms can be on adjacent sites. There can be an intervening carbon, or the bromines can be on opposite sides of the ring.



To highlight the fact that the placement of the double bonds in the ring does not impact the number of isomers, we can also draw these three isomers using their resonance hybrids.



3. Naphthalene contains five π bonds, so at a simplistic level, we would expect its complete hydrogenation to liberate five times as much energy as that of cyclohexene.

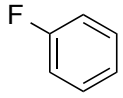
Expected heat of hydrogenation = 5 x (-28.6kcal/mole) = -143 kcal/mole

However, as stated in the problem, the hydrogenation of naphthalene releases only about 82 kcal/mole. Resonance energy accounts for the difference in the two values.

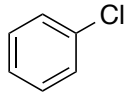
Resonance energy = (-82 kcal mole) – (-143 kcal/mole) = 61 kcal/mole

4.

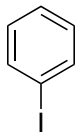
(a) Fluorine as a substituent is denoted by the fluoro prefix, so this is fluorobenzene. No number is needed to indicate the location of a substituent on a monosubstituted ring because all sites on benzene are identical.



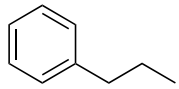
(b) This compound is chlorobenzene.



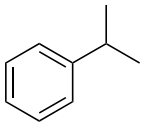
(c) This is iodobenzene.



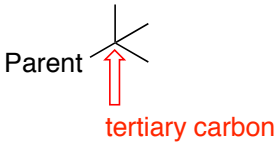
(d) This is an alkylbenzene. The alkyl group contains three carbons, and they are connected to the ring through a terminal carbon. This is therefore a propyl group, and the compound is propylbenzene.



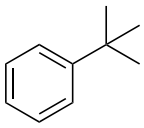
(e) This alkylbenzene also has a three-carbon substituent, but this time the alkyl group is connected to the ring through the central carbon. Consequently, it is an isopropyl group, and the molecule is isopropylbenzene.



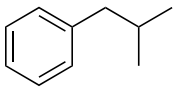
(f) This alkylbenzene bears a four-carbon substituent. The carbon of the substituent that is connected to the parent is tertiary, so this is a *tert*-butyl group. Remember that we only consider the carbons within the substituent when determining the substitution of the carbon bonded to the parent.



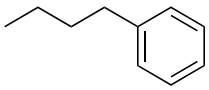
The molecule is therefore *tert*-butylbenzene.



(g) This alkylbenzene has a four-carbon substituent that branches into two methyl groups at the end of the chain. It is therefore an isobutyl group, and this is isobutylbenzene.

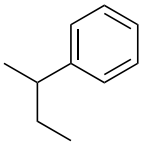


(h) The alkyl group in this molecule contains four carbons in a linear array, making it a butyl group. The compound is therefore butylbenzene.



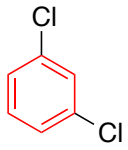
(i) In this instance, the four-carbon substituent is bonded to the parent through a secondary carbon, so it is a *sec*-butyl group. Again, note that we only count the carbons within the substituent when determining the substitution of the carbon connected to the parent.

The molecule is therefore *sec*-butylbenzene.



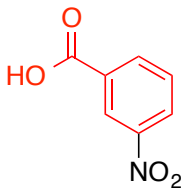
5.

(a) This molecule contains two chlorine substituents on a benzene parent, making it a dichlorobenzene. However, we also need to describe the relative location of the two chloro groups. This can be done use the *meta* prefix or using numbers. Therefore, the two possible names for this compound are: *meta*-dichlorobenzene or 1,3-dichlorobenzene.



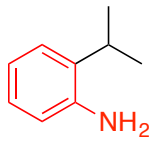
meta-dichlorobenzene
or
1,3-dichlorobenzene

(b) Recall that, if a parent larger than benzene with its own commonly accepted name exists, we must identify and use it. Consequently, the parent in the following molecule is benzoic acid. The nitro group is *meta* to the acid, so one name is *meta*-nitrobenzoic acid. Alternatively, we may call this compound 3-nitrobenzoic acid. Note that the position of the acid is implied to be C1 since it is part of the parent.



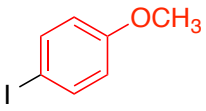
meta-nitrobenzoic acid
or
3-nitrobenzoic acid

(c) The parent in this compound is aniline. There is an isopropyl substituent adjacent to the amino group of aniline. This can be denoted using the prefix *ortho* or by using the locant 2. The possible names are therefore *ortho*-isopropylaniline or 2-isopropylaniline.



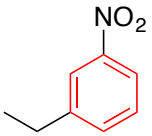
ortho-isopropylaniline
or
2-isopropylaniline

(d) The parent within this compound is anisole, and there is an iodo group *para* to it. Consequently, one possible name is *para*-iodoanisole. If we choose to use locants instead, the name is 4-iodoanisole.



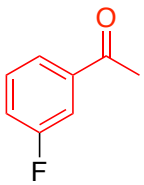
para-iodoanisole
or
4-iodoanisole

(e) The parent in this compound is simply benzene. The ethyl and nitro groups are *meta* to one another, so the name can be *meta*-ethylnitrobenzene. Alternatively, if numbers are used, the name is 1-ethyl-3-nitrobenzene. Note that the substituents get the locants 1 and 3 regardless of the direction of numbering. We therefore give the alphabetically first substituent the number 1.



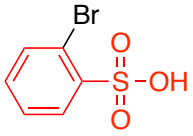
meta-ethylnitrobenzene
or
1-ethyl-3-nitrobenzene

(f) Acetophenone is the parent in this structure, and it has a fluorine in the *meta* position or on C3'.



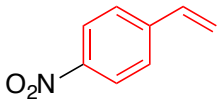
meta-fluoroacetophenone
or
3'-fluoroacetophenone

(g) Benzenesulfonic acid is the parent in this compound. It contains a bromine in the *ortho* position or on C2.



ortho-bromobenzenesulfonic acid
or
2-bromobenzenesulfonic acid

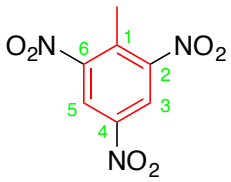
(h) The parent in this molecule is styrene. The nitro group is in the *para* position or on C4.



para-nitrostyrene
or
4-nitrostyrene

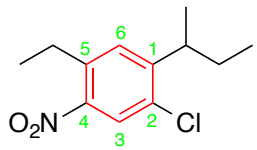
6.

(a) The parent in this compound is toluene. The carbon bearing the methyl group is C1. In this instance, it makes no difference which direction the ring is numbered. The nitro groups are located on C2, C4, and C6 either way. The molecule's complete name is 2,4,6-trinitrotoluene. It is the explosive more commonly known by its abbreviation TNT.



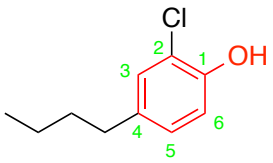
2,4,6-trinitrotoluene (also known as TNT)

(b) The parent in this molecule is simply benzene. There are a variety of ways that we could number it so as to obtain the locants 1, 2, 4, and 5 for its substituents. We decide between them by giving the alphabetically first substituent (*sec*-butyl, which is alphabetized by the b) the number 1, making this compound 1-*sec*-butyl-2-chloro-5-ethyl-4-nitrobenzene.



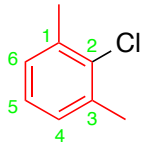
1-*sec*-butyl-2-chloro-5-ethyl-4-nitrobenzene

(c) The parent in this structure is phenol. The carbon bearing the hydroxyl group is C1. The ring is then numbered counterclockwise so as to give the second substituent the lowest possible number. The compound's name is therefore 4-butyl-2-chlorophenol.



4-butyl-2-chlorophenol

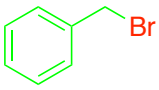
(d) The parent in this structure is *meta*-xylene. One of its methyl groups resides at C1, and the other is at C3. Therefore, the complete name is 2-chloro-*meta*-xylene.



2-chloro-*meta*-xylene

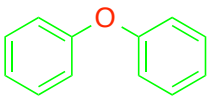
7.

(a) This alkyl halide has a benzyl group bonded to bromine, so it is benzyl bromide.



benzyl bromide

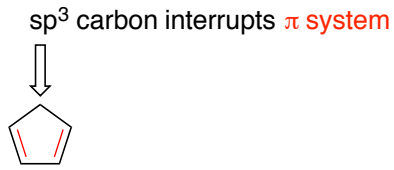
(b) This ether has two phenyl groups, so it is diphenyl ether.



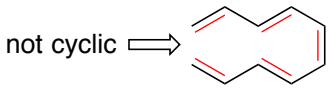
diphenyl ether

8.

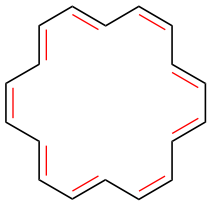
(a) 1,3-Cyclopentadiene is cyclic, but it does not have a p orbital on each and every ring atom. The sp^3 hybridized carbon of the ring introduces a break in the π system, so the molecule is non-aromatic.



(b) This 1,3,5,7,9-decapentaene has a completely conjugated π system, but the molecule is not cyclic. Consequently, it is non-aromatic.



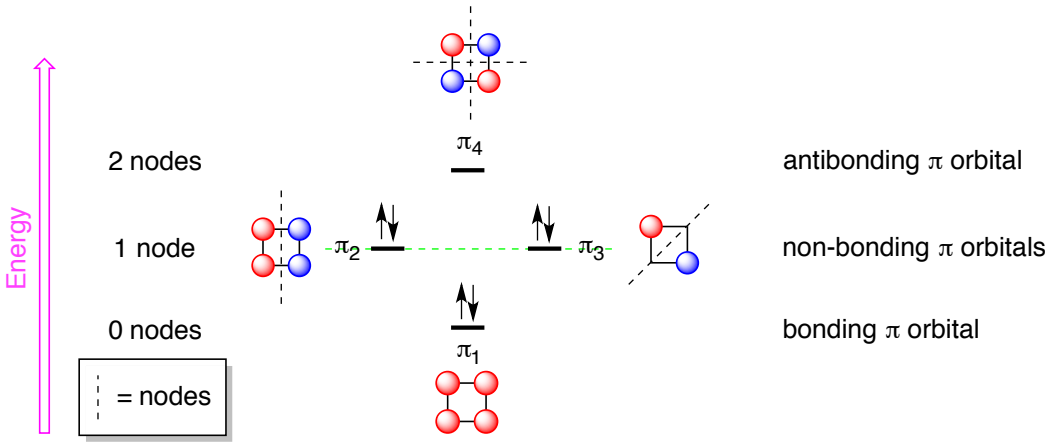
(c) This annulene is cyclic, and it has a p orbital on each and every ring atom. It can also be planar. Since the molecule can possess a continuous, cyclic array of parallel p orbitals, we can consider the number of π electrons. This annulene has a total of 18 π electrons. This is a 4n + 2 value (when n = 4), so the compound is aromatic.



Since being planar leads to a favorable outcome (aromaticity), this annulene adopts a planar conformation. Had planarity led to an unfavorable result (antiaromaticity), it would have bent out of the plane to avoid that fate.

(d) This annulene is cyclic and has a p orbital on each and every ring atom; however, it is clearly not planar. The p orbitals of the π system are not all parallel to one another, so it is therefore a non-aromatic structure.

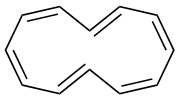
9. Cyclobutadiene has four electrons in its π system. If two additional electrons are added to the π system as the problem states, then there will be a total of six π electrons. The first two fill π_1, and the next four fill π_2 and π_3.



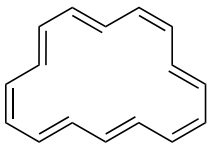
In cyclobutadiene, π_2 and π_3 were each half filled, which was a source of instability. Now, with two additional electrons in the π system, these molecular orbitals are completely filled. There is no longer any instability associated with unpaired electrons. Additionally, two of the electrons in the π system (those in π_1) are stabilized relative to the non-bonding energy level.

10. All of these compounds are annulenes, meaning that they are all cyclic and they all have a p orbital on each and every ring atom. Additionally, for this problem, we are making the assumption that the rings are planar. Therefore, none of our answers will be non-aromatic. In each case, we will consider the number of π electrons to see whether it is a 4n or 4n + 2 value.

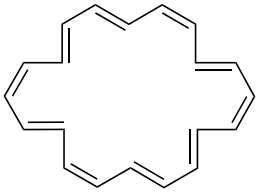
(a) This compound is a [12]annulene. It contains six π bonds for a total of 12 π electrons. This is a 4n value (when n = 3), so if it were planar, the compound would be expected to be antiaromatic.



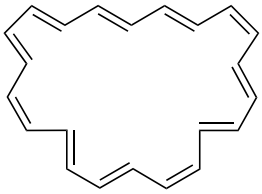
(b) This is a [16]annulene. It has eight π bonds and, therefore, a total of 16 π electrons. This too is a 4n value (when n = 4), so if it were planar, it would be antiaromatic.



(c) The following compound is a [20]annulene. With its 10 π bonds, it has a total of 20 π electrons. That is a 4n value (when n = 5). Consequently, if it were planar, it too would be antiaromatic.

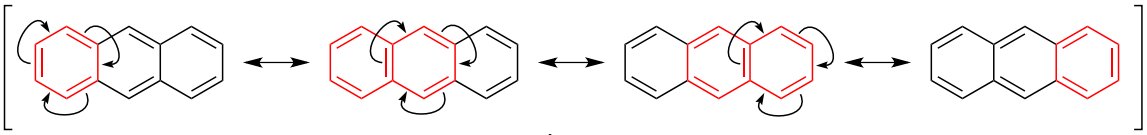


(d) This is a [22]annulene. Since it contains 11 π bonds, it has a total of 22 π electrons. This is a 4n + 2 value (when n = 5), so this annulene is expected to be aromatic.



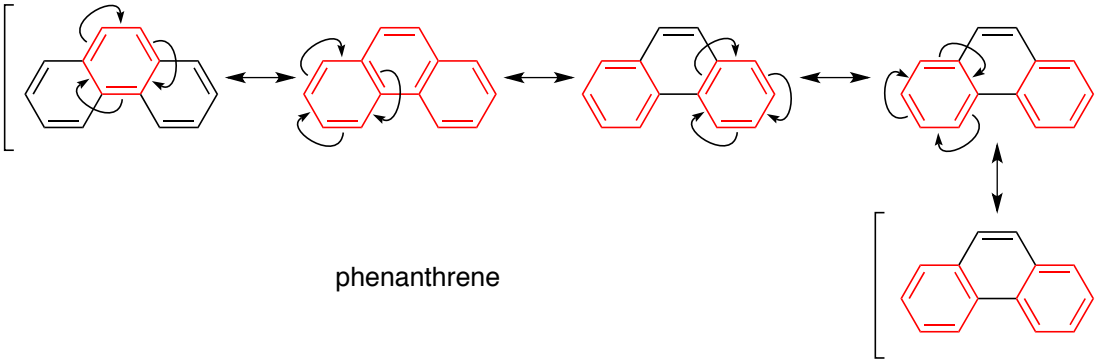
11. It can be daunting to consider all of the major resonance forms of compounds with so many π bonds, but there is a simple way to conceptualize this task so that you have a clear path to the answer. Each ring has two possible Kekulé forms. Systematically work through the resonance structures so that you show both Kekulé forms of each ring.

For anthracene, if we begin with the resonance form shown on the left below, we can start by "spinning the double bonds" in the left-hand ring to derive its other Kekulé form. This then enables us to do the same for the central ring and finally for the right-hand ring, giving a total of four resonance structures. The fully aromatic rings in each structure are highlighted in red.



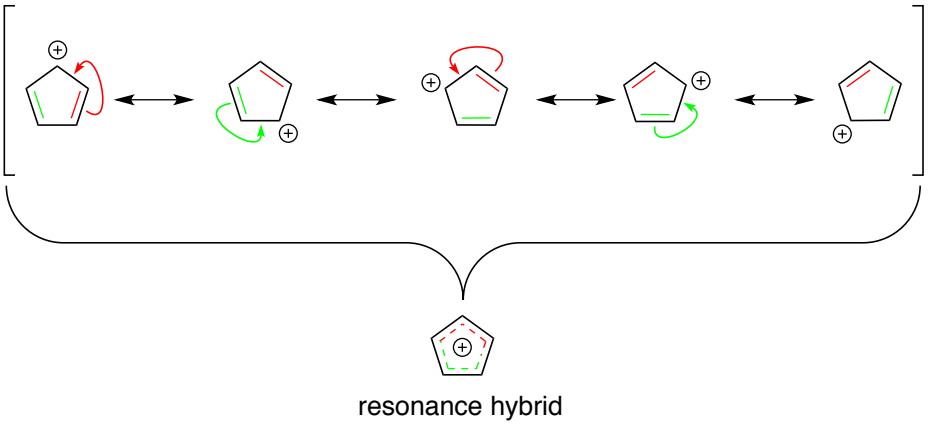
anthracene

For phenanthrene, if we begin with the resonance structure shown on the left below, we can start by "spinning the double bonds" in the central ring to obtain its other Kekulé form. Then, we can do the same for the left-hand ring, followed by the right-hand ring. Finally, we can "spin the double bonds" in the left-hand ring one more time to derive a resonance form that we have not yet drawn. A total of five resonance structures are produced, and the fully aromatic rings are highlighted in red in each.



We have shown the full complement of resonance structures for each molecule, but we have yet to address the difference in resonance energy. To do this, we need to reflect on how frequently each ring is fully aromatic in the resonance forms shown above. For anthracene, each ring is fully aromatic in one half (50%) of the resonance structures. For phenanthrene, the terminal rings are fully aromatic in four out of five resonance structures (80%), and the central ring is aromatic in two of the five resonance forms (40%). Overall, the rings in phenanthrene are fully aromatic in a greater percentage of the resonance structures, which explains why it has a greater resonance energy than anthracene.

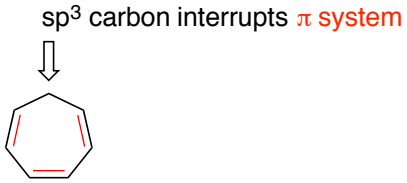
12. We can begin by delocalizing the cyclopentadienyl cation's positive charge using the red π bond. Then, the green π bond can be used to move the charge to a new site on the ring. Similarly, another iteration of delocalization using the red then green π bonds places the positive charge on two more unique locations on the ring. Ultimately, all five of the ring carbons bear partial positive charge in the resonance hybrid.



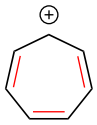
Notice that simply having a ring with a resonance-delocalized charge does *not* tell us anything about that ring's stability. The cyclopentadienyl anion is aromatic, while the cyclopentadienyl cation is antiaromatic. Yet, both possess extensive resonance delocalization of their charges. In fact, each compound has the exact same number of

resonance forms, so the extent of the resonance delocalization is also *not* a predictor of aromaticity.

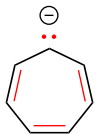
13. 1,3,5-Cycloheptatriene has a single sp^3 hybridized carbon in the ring. The lack of a p orbital on this atom interrupts the π system and renders the compound non-aromatic.



The cycloheptatrienyl cation is often called the tropylium ion. Since the carbocation has an empty p orbital, this cyclic compound does in fact have a p orbital on each and every ring atom. Its π system contains a total of six electrons in its three π bonds. Six is a 4n + 2 value (when n = 1), so the tropylium ion is aromatic.



The cycloheptatrienyl anion contains a lone pair of electrons. If they were held in a p orbital so that they could be delocalized through the π system, this π system would include a total of eight electrons. As such, it would be antiaromatic.

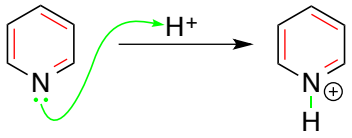


Consequently, the anion actually adopts an sp^3 hybridization instead. This keeps the lone pair out of the π system and interrupts the π system as well. The result is a non-aromatic anion. This outcome is preferable to the extreme instability of antiaromaticity.

To make it easier to deal with complicated decisions like this one, you can think of hybridization as a choice. If placing a lone pair into the π system by adopting sp^2 hybridization would lead to antiaromaticity, the atom will "choose" not to do so. Instead, it will be sp^3 hybridized. This interrupts the π system and makes the molecule non-aromatic instead, which is a better outcome.

14. When pyridine acts as a base, the lone pair on nitrogen is used to form a new bond to a proton. Since nitrogen's lone pair was not part of the π system, this has no consequence for the molecule's aromaticity. Pyridine is aromatic, and after

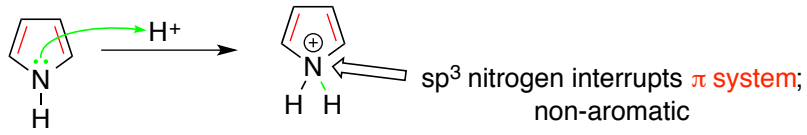
protonation, its conjugate acid (the pyridinium ion) is still aromatic. Since pyridine can act as a base without disrupting its aromaticity, it freely does so.



pyridine
6 π electrons
(a 4n + 2 value)
aromatic

pyridinium ion
6 π electrons
(a 4n + 2 value)
aromatic

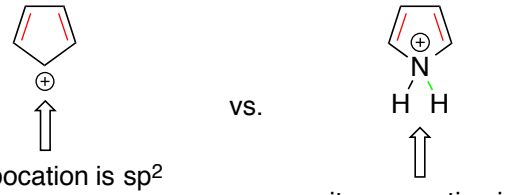
On the other hand, if pyrrole were to use its lone pair to acquire a new proton, this would have a consequence for aromaticity. By acquiring a fourth σ bond, nitrogen would become sp^3 hybridized, and as such, it would interrupt the π system. Therefore, pyrrole's conjugate acid is non-aromatic. Granted, non-aromatic compounds not as unstable as antiaromatic ones, but the ring would nevertheless lose it aromaticity through protonation. The high energetic cost of protonation therefore prevents pyrrole from acting as a base.



sp^3 nitrogen interrupts π system;
non-aromatic

6 π electrons
(4 in π bonds and
2 in the lone pair)
a 4n + 2 value;
aromatic

Students often reach the incorrect conclusion that the conjugate acid of pyrrole is antiaromatic. Since carbocations have an empty p orbital, some students assume that a nitrogen cation would as well. But, as we have seen in this problem, that is not necessarily the case.

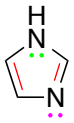


carbocation is sp^2
hybridized and has
an empty p orbital

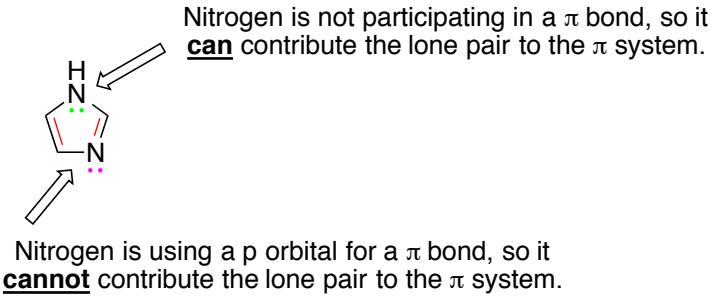
nitrogen cation is
sp^3 hybridized and
has no p orbital

15. Imidazole is a cyclic molecule with a p orbital on each and every ring atom. The presence of a p orbital on the four atoms participating in π bonds is immediately clear. Additionally, the nitrogen atom that is not participating in a π bond can place

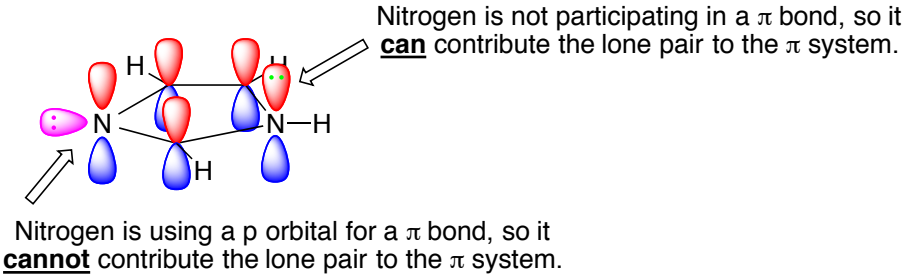
its lone pair into a p orbital to delocalize it. The ring is also planar due to its small size and the hybridization of its atoms.



Since imidazole contains a continuous, cyclic array of parallel p orbitals, it is either aromatic or antiaromatic depending on the number of π electrons it possesses. The four electrons in the two π bonds are certainly part of the π system. The more difficult question is whether the nitrogen lone pairs are also a part of the π system. The two nitrogen atoms are different in this regard. One nitrogen atom is participating in a π bond, so it is already using a p orbital for that purpose and therefore cannot donate its lone pair to the π system. Conversely, the other nitrogen atom is not participating in a π bond, so it is able to place its lone pair into a p orbital that is parallel to the others.



The π system can also be represented using the following orbital diagram.

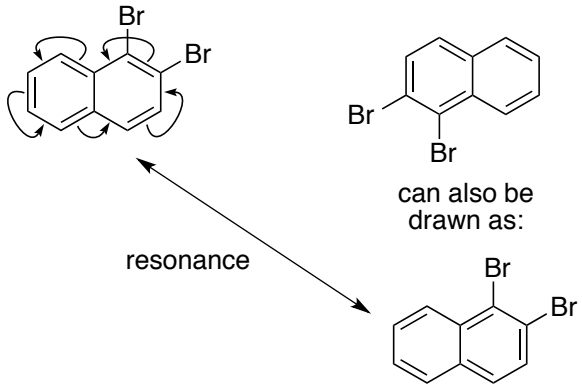


We can now say that the π system includes the four electrons in the two π bonds as well as one nitrogen atom's lone pair, for a total of six. Imidazole therefore has a 4n + 2 value of π electrons and is aromatic.

16.

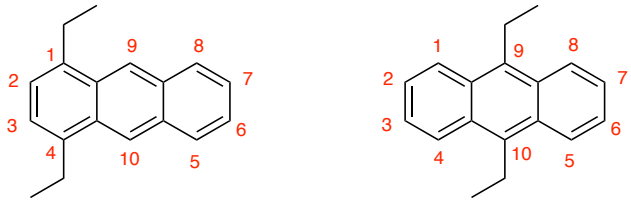
(a) This problem can be made easier by rotating one of the structures to align the molecules with the bromine atoms in the same locations. Then, it is easier to see

that all that differs between these two representations is the placement of the π bonds. They are resonance structures of one another.

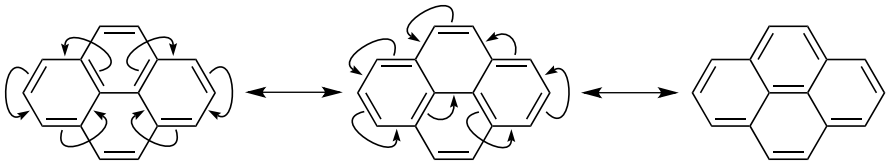


(b) These diethylanthracene derivatives differ in connectivity. In one compound, the ethyl groups reside on a terminal ring. In the other, they are located on the central ring. Due to the difference in connectivity, these are constitutional isomers.

Numbering can help to illustrate a difference in connectivity. The two isomeric anthracenes are numbered below according to IUPAC rules. However, there is no need to know or use IUPAC numbering to answer this question. The molecules can be numbered in any fashion, as long as it is done consistently from one structure to the other. The numbering clearly shows that the ethyl groups reside at different locations in the two structures.

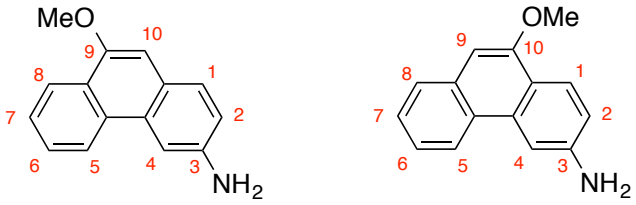


(c) This polyaromatic hydrocarbon is known as pyrene. The three structures shown differ only in the placement of their π bonds. They are resonance forms, and their interconversion is shown below.



(d) These compounds actually differ in connectivity and are therefore constitutional isomers. Numbering can help to illustrate this point. The two phenanthrenes are numbered below according to IUPAC rules; however, it is not necessary to know or use IUPAC numbering to deduce that these are isomers. You can apply any

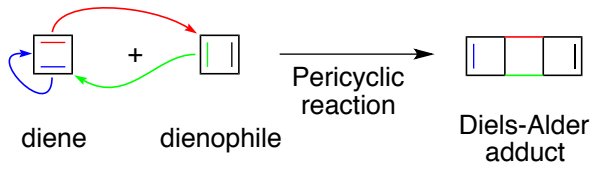
numbering to the two molecules, as long as it is consistent. The numbering highlights the fact that the methoxy group is bonded to a different carbon in each isomer.



17.

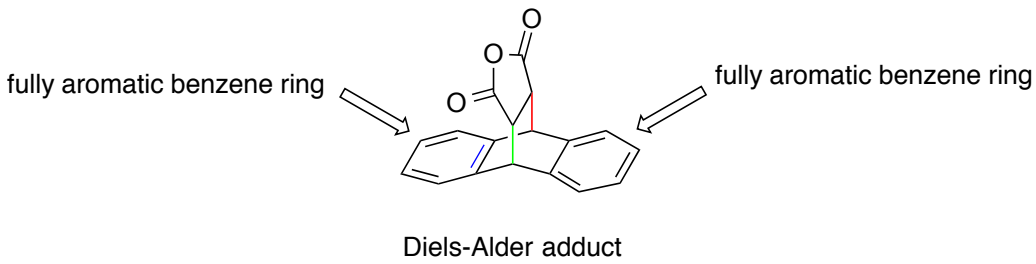
(a) Benzene's resistance to hydrogenation stems from the fact that reduction results in the loss of aromaticity.

(b) Cyclobutadiene reacts quite readily because it is antiaromatic and therefore highly unstable. The question stated that a Diels-Alder reaction takes place in which one molecule of cyclobutadiene acts as the diene, while another molecule acts as the dienophile. That cycloaddition is shown below.

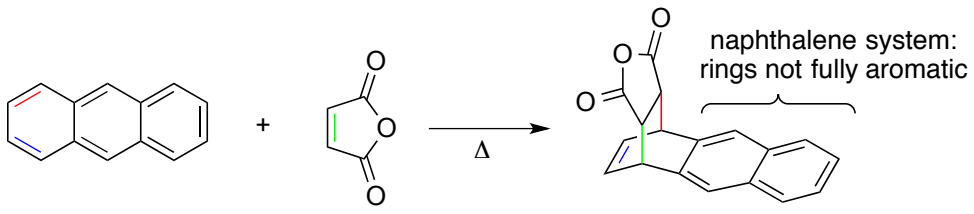


18. Phenanthrene has seven π bonds. If they were all treated as isolated π bonds, then we would expect phenanthrene's heat of hydrogenation to be seven times that of cyclohexene (7 * -28.6 kcal/mole = -200.2 kcal/mole). However, phenanthrene has a resonance energy of 92 kcal/mole, which means that it releases 92 kcal/mole less than expected (-200.2 kcal/mole + 92 kcal/mole = -108.2 kcal/mole). Therefore, the actual heat of hydrogenation of phenanthrene is -108.2 kcal/mole.

19. The middle ring of anthracene is more reactive than the outer rings. The reason is that reaction of the middle ring leaves two intact fully aromatic benzene rings on either side of the molecule.



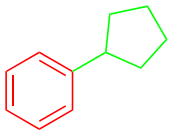
Had the Diels-Alder reaction occurred on a terminal ring, the adduct would contain a naphthalene ring system in which the two rings are not both fully aromatic in all of their resonance forms.



anthracene | maleic anhydride | Diels-Alder adduct

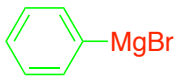
20.

(a) This compound contains a benzene ring bearing a cyclopentyl substituent. It is therefore cyclopentylbenzene. No number is need because all of the sites on benzene are equivalent until a substituent is added.



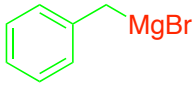
cyclopentylbenzene

(b) When a benzene ring is a substituent, it is termed "phenyl". This Grignard reagent is therefore phenylmagnesium bromide.



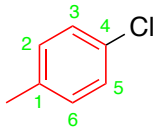
phenylmagnesium bromide

(c) This Grignard reagent contains a benzyl group, and is consequently named benzylmagnesium bromide.



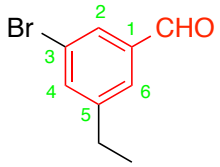
benzylmagnesium bromide

(d) The parent in this structure is toluene. The chlorine can be described as *para* to the methyl group or on C4.



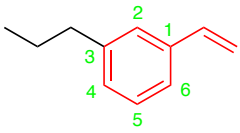
para-chlorotoluene
or
4-chlorotoluene

(e) The parent in this compound is benzaldehyde. The carbon bearing the aldehyde is C1. The numbers 3 and 5 will be obtained for the substituents regardless of the direction of numbering, so we give the locant 3 to the substituent that appears first in alphabetical order.



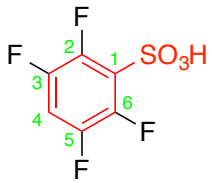
3-bromo-5-ethylbenzaldehyde

(f) The parent in this molecule is styrene. The propyl group is *meta* to the vinyl group. Alternatively, you may say that the propyl group is on C3.



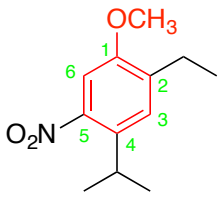
meta-propylstyrene
or
3-propylstyrene

(g) The parent here is benzenesulfonic acid. The direction of numbering makes no difference in this case.



2,3,5,6-tetrafluorobenzenesulfonic acid

(h) This compound's parent is anisole. The methoxy group of the parent resides on C1, and we number so as to give the lowest possible number to the second substituent. This results in a locant of 2 for the ethyl group. The isopropyl and nitro groups therefore receive locants of 4 and 5, respectively.



2-ethyl-4-isopropyl-5-nitroanisole

21.

(a) Cyclopropene is a non-aromatic compound because it has an sp^3 hybridized carbon in the ring. There is no p orbital on this atom, which results in an interruption of the π system.

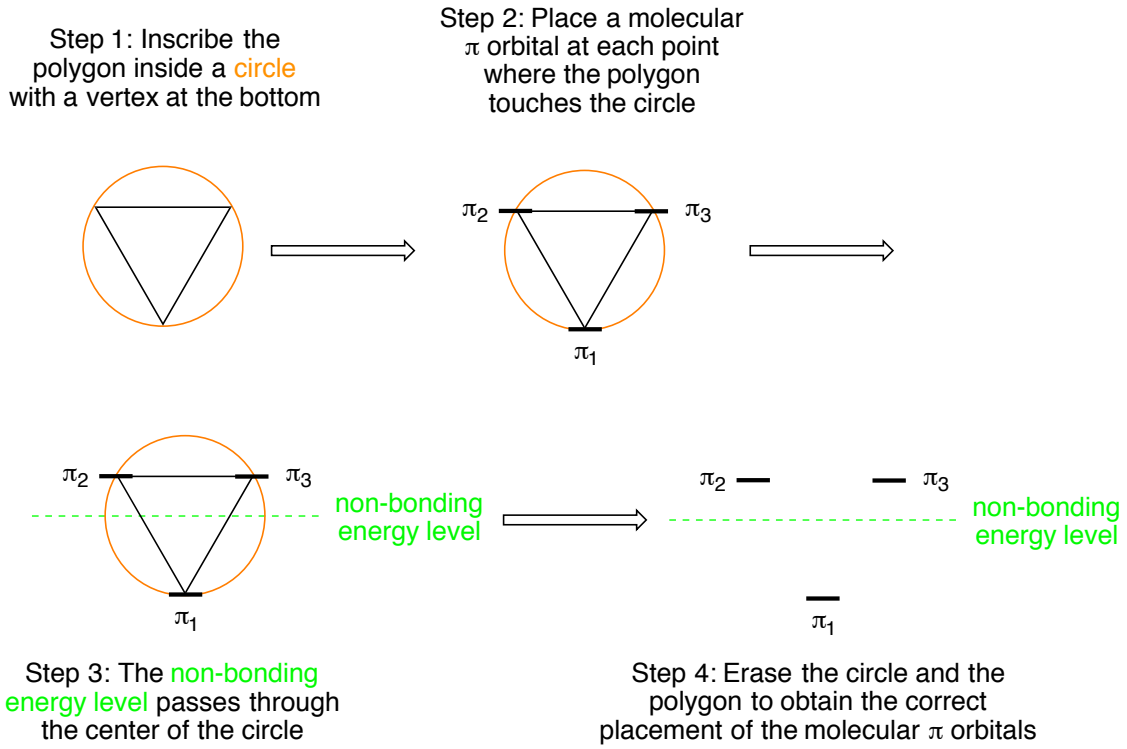
sp^3 carbon interrupts π system

That same carbon atom is sp^2 hybridized in the cyclopropenyl cation. Therefore, there is a continuous, cyclic array of parallel p orbitals. The molecule has only two π electrons, which is a 4n + 2 value (when n = 0), so this cation is aromatic.

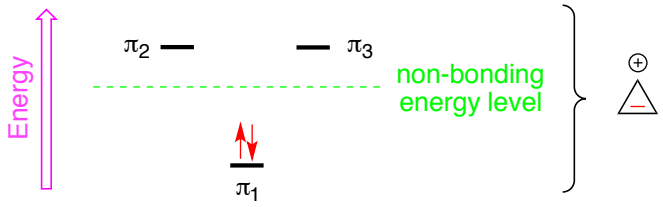
The cyclopropenyl anion has a lone pair. If it were housed in a p orbital so that it could be delocalized throughout the π system, this would be a four-π-electron system (a 4n value), making the anion antiaromatic.

Consequently, the anion adopts sp^3 hybridization, thereby interrupting the π system and making the it non-aromatic instead. As we saw in Problem 13, we can make complicated situations like this easier by thinking of hybridization as a choice. If adopting sp^2 hybridization to place a lone pair into a p orbital results in antiaromaticity, the atom will not do so. Instead, it will opt for sp^3 hybridization, which keeps the lone pair out of the π system. This results in non-aromaticity, which is preferable to antiaromaticity.

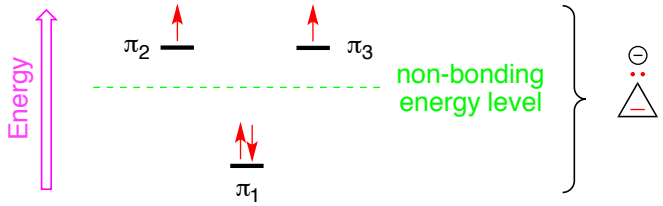
(b) To provide a molecular orbital justification for the answers in part (a), we must first derive the number and energies of the molecular π orbitals using the Frost-circle method.



For the cyclopropenyl cation, its two π electrons fill π_1. These electrons are paired and stabilized relative to the non-bonding level, which accounts for the aromatic *stabilization* of this cation.



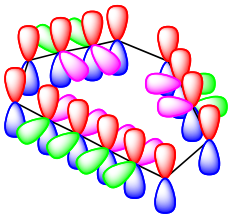
If we treated the lone pair as part of the π system, the cyclopropenyl anion would have two additional π electrons, and these would be placed in π_2 and π_3 according to Hund's rule. Consequently, the anion would have two unpaired electrons that also happen to be at an elevated energy. This would lead to antiaromatic *destabilization*. As we noted in part (a) though, the anion would adopt sp^3 hybridization to avoid this fate.



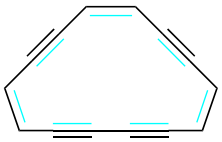
22.

(a) The methylene bridge holds this [10]annulene in a nearly planar conformation, allowing it to attain a continuous, cyclic array of parallel p orbitals. With 10 electrons in its π system (a 4n + 2 value, when n = 2), this molecule is expected to be aromatic.

(b) This annulene has a continuous, cyclic array of parallel p orbitals. The challenge is determining how many electrons are in the π system: should we include two or four electrons from each alkyne? The answer is readily apparent when you consider the geometry of the orbitals. One π bond of each alkyne consists of p orbitals (shaded red and blue) that are parallel to those of the alkenes (also shaded red and blue). However, the second π bond of each alkyne consists of p orbitals (shaded green and purple) that are orthogonal to those of the alkenes. The electrons in these latter π bonds are not a part of the larger π system of the annulene.

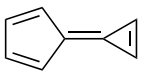


Therefore, each alkyne contributes only two electrons to the π system, making this a 14 π electron molecule (a 4n + 2 value, when n = 3). Consequently, this compound is expected to be aromatic.



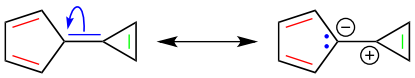
23.

(a) This molecule happens to be known as calicene. It is an example of a fulvalene, a type of compound in which two rings are conjugated through a shared exocyclic olefin. It is important to remember that Hückel's rule applies only to single rings because, if we simply counted the π electrons in calicene (of which there are eight), we would reach the *incorrect* conclusion that it is antiaromatic.

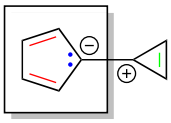


The red π electrons are clearly within the five-membered ring, and the green π electrons are definitely within the three-membered ring. It is less clear where the blue π electrons belong. However, as the hint suggested, we can consider a charged

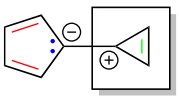
resonance form that takes the blue π electrons from one ring and gives them to the other. These electrons could be donated to the cyclopentadienyl or cyclopropenyl ring, but only one of these donations is consistent with the observed aromaticity of the compound.



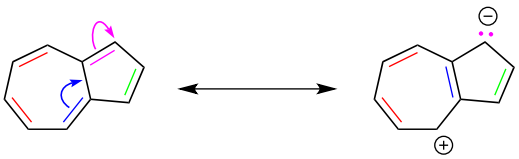
If the blue electron pair is donated to a carbon as a lone pair, then the cyclopentadienyl ring contains a total of six π electrons (four in its two π bonds and two in the lone pair). This makes it an aromatic ion as we saw in Section 7.



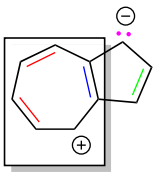
When the blue electrons are clearly taken away from the three-membered ring, the resultant cyclopropenyl cation has only two π electrons in its one π bond. This renders it aromatic as well, as we saw in Problem 21.



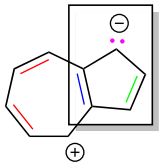
(b) This compound happens to be known as azulene. A charged resonance form can be drawn by moving the blue and purple π electrons in such a way that they are more clearly identified with a specific ring. As in part (a), there are two ways to do this, but only one will be compatible with the observation of aromatic character.



On the left-hand side of this resonance form, there is a tropylium ion. As we saw in Problem 13, this six π electron system is aromatic. The six π electrons include the those in the two red and one blue π bonds.

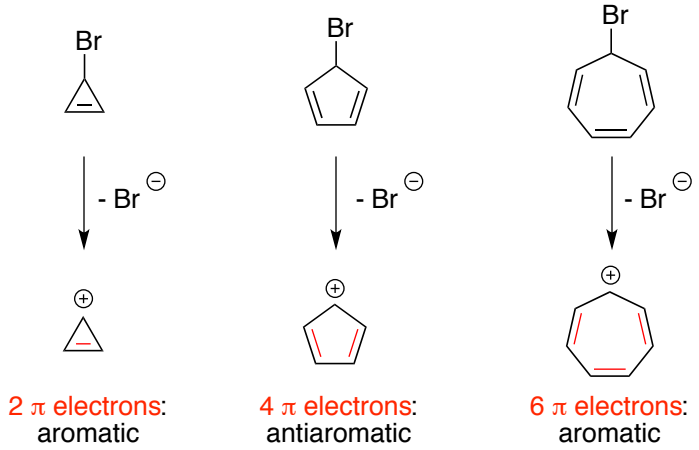


On the right-hand side of this resonance structure is a cyclopentadienyl anion. We saw this aromatic ion in Section 7. It has six π electrons as well, which are found in the green and blue π bonds along with the purple lone pair. This ring therefore has aromatic character too.

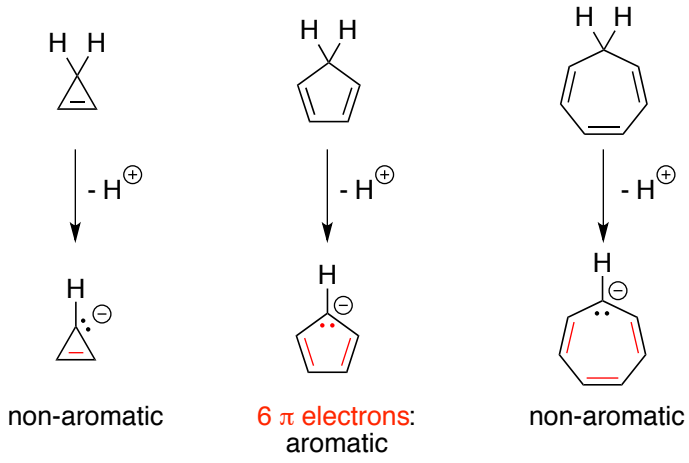


24.

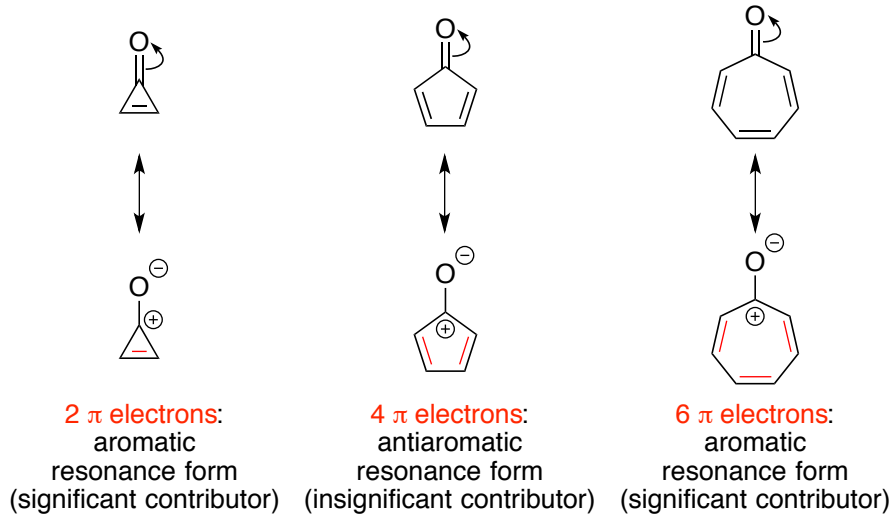
(a) The dissociation of each bromide is shown below. The stability of the carbocations formed dictates how facile each dissociation will be. The carbocations all have a continuous, cyclic array of parallel p orbitals. The cyclopropenyl cation has two π electrons, so it is aromatic. The cyclopentadienyl cation has four π electrons, making it antiaromatic. And, the tropylium ion contains six π electrons, resulting in aromaticity. The ionizations that lead to aromatic carbocations will occur readily, but 5-bromo-1,3-cyclopentadiene will be reluctant to ionize because doing so will generate a highly *unstable* antiaromatic carbocation.



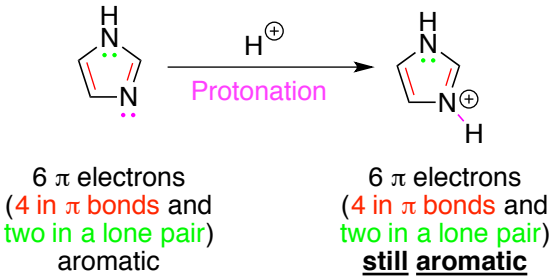
(b) The loss of a proton from each molecule is shown below. The stability of the conjugate bases impacts the pK_a of the parent acids. As we saw in Problem 21, the cyclopropenyl anion is non-aromatic because the anion adopts sp^3 hybridization to avoid the extreme instability of antiaromaticity. The cycloheptatrienyl anion behaves similarly as we noted in Problem 13. In contrast, the cyclopentadienyl anion has six π electrons and is therefore aromatic. Due to its aromaticity, the cyclopentadienyl anion is the most stable of the three conjugate bases. Therefore, 1,3-cyclopentadiene is the strongest acid, which has the lowest pK_a value.



(c) The carbonyl is the most polarized portion of the following three molecules. The answer to the question lies in the extent of each carbonyl's polarization. The resonance forms that contain charge separation are the most polarized representation of the carbonyl possible. Notice that the three- and seven-membered rings are aromatic in these resonance forms. Therefore, we expect these to be significant contributors to the resonance hybrid. On the other hand, the five-membered ring has an antiaromatic resonance form, which would not be expected to contribute to the hybrid in any significant way. Cyclopentadienone (the five-membered, cyclic ketone) is therefore the least polar of the three compounds.



(d) As we saw in Problem 15, one of imidazole's nitrogens contributes its lone pair to the π system while the other does not. The lone pair that is a part of the π system cannot be used to make a new bond without resulting in the loss of aromaticity, so that lone pair is relatively unreactive. However, the lone pair that is not part of the π system can be used for protonation without impacting the ring's stability, so this is the basic site.

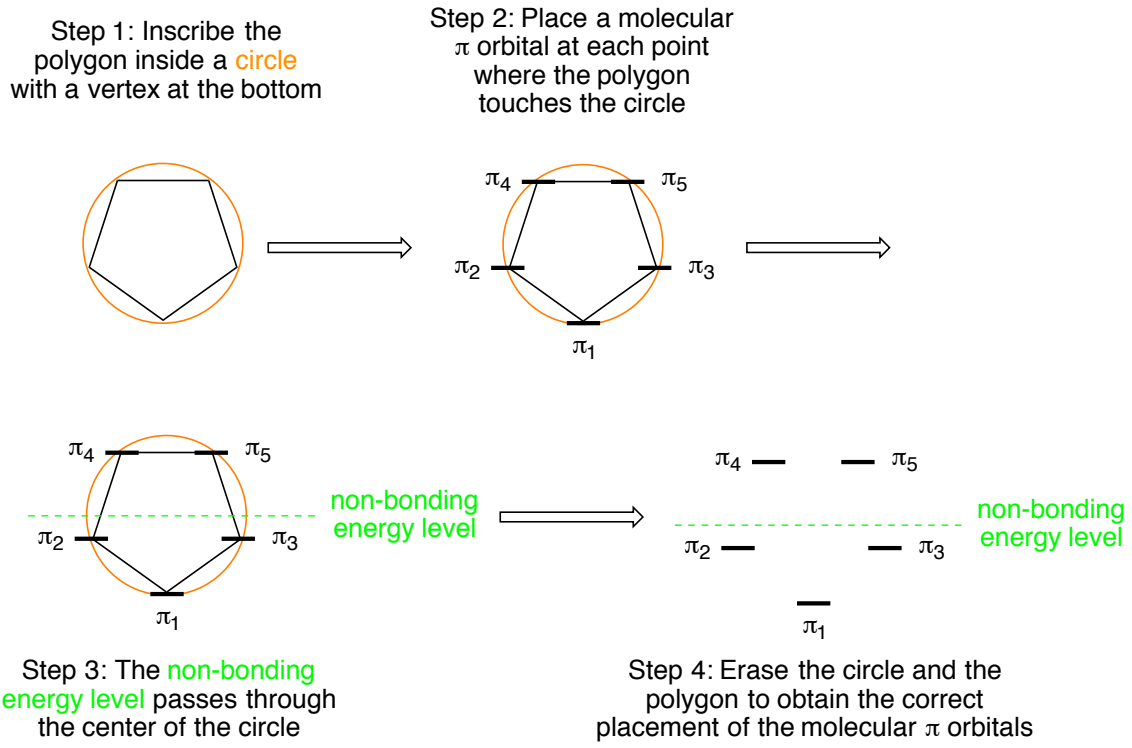


6 π electrons (4 in π bonds and two in a lone pair) aromatic

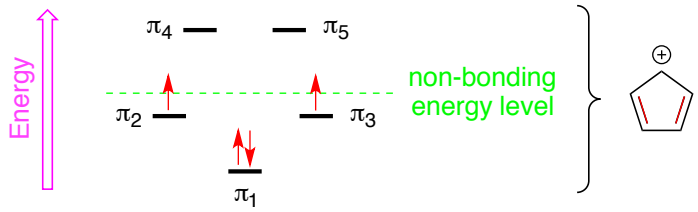
6 π electrons (4 in π bonds and two in a lone pair) **still aromatic**

25.

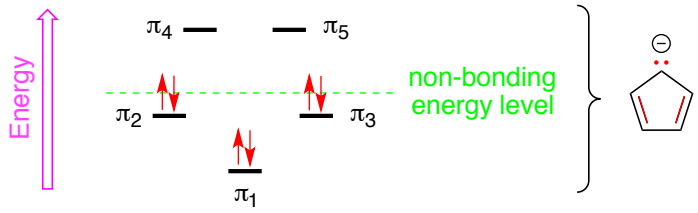
(a) First, we must derive the proper number and placement of molecular π orbitals. This can be done quickly and easily using the Frost-circle mnemonic. First, we inscribe a pentagon inside a circle with a point facing downward. At each place where the pentagon touches the circle, a molecular π orbital is placed. Finally, the non-bonding energy level passes through the center of the circle.



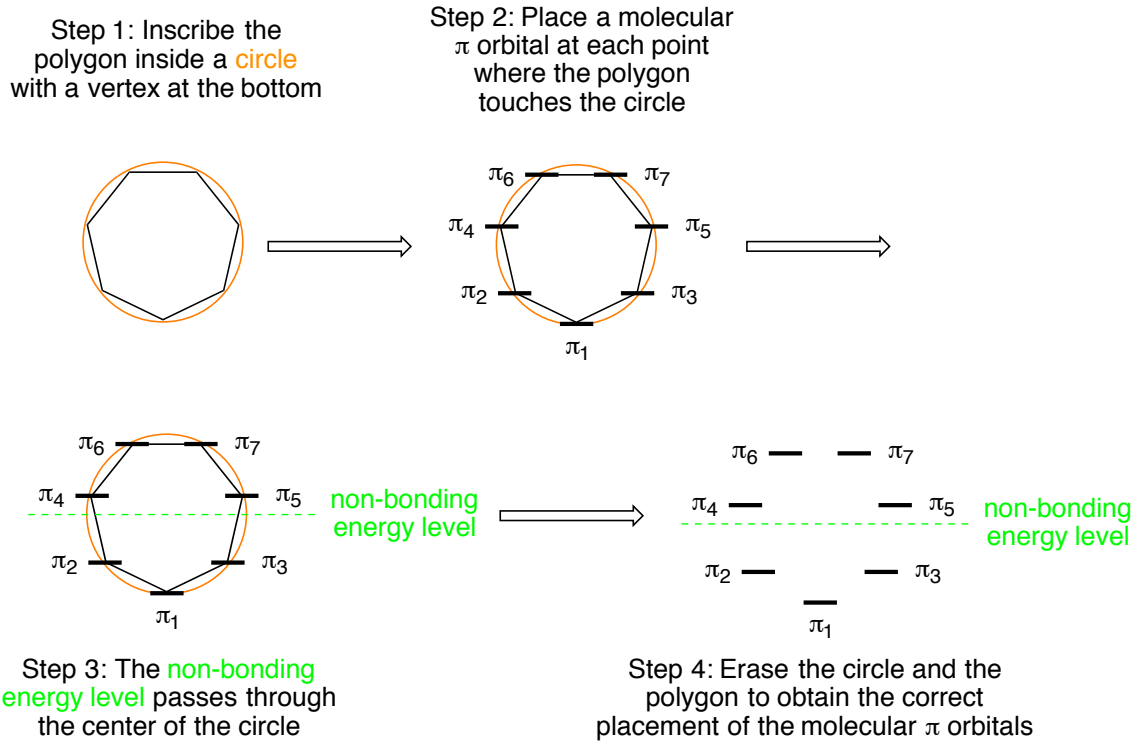
The cyclopentadienyl cation has only four π electrons. The first two fill π_1, but when we place the remaining two according to Hund's rule, the degenerate orbitals π_2 and π_3 each receive only a single electron. Since this ion has two unpaired electrons (i.e., diradical character), it is unstable and therefore antiaromatic.



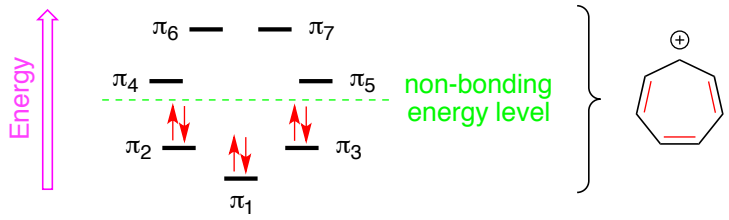
The cyclopentadienyl anion has two additional electrons in its π system, bring the total to six π electrons. As a result, π_2 and π_3 are completely filled. This ion has all of its π electrons paired and residing in bonding orbitals that are lower in energy than the non-bonding level. These two factors lead to aromatic stabilization.



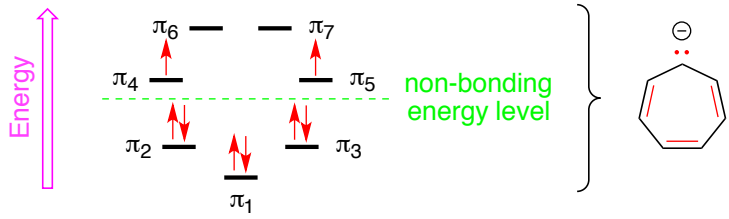
(b) We first need to use the Frost-circle method to ascertain the correct number and placement of the molecular π orbitals. The seven-sided polygon is inscribed inside a circle with a vertex pointing down. Then, a molecular π orbital is placed at each location where the polygon touches the circle. Finally, the non-bonding energy level passes through the center of the circle.



The tropylium ion has six π electrons that fill the bonding molecular π orbitals (π_1 – π_3). Since all of the electrons are paired and reside in orbitals below the non-bonding energy level, this ion is stabilized and therefore aromatic.



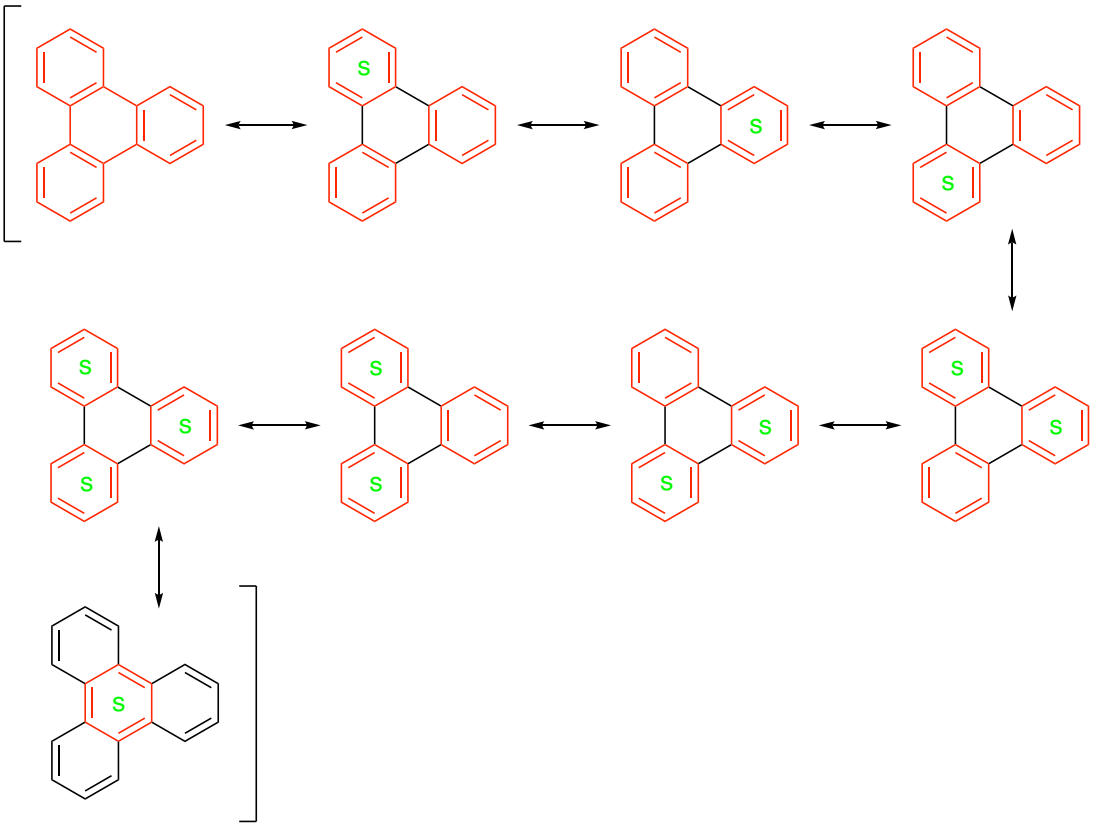
Its anionic counterpart has a lone pair. If these electrons were part of the π system, they would be placed according to Hund's rule, and π_4 and π_5 would each be singly occupied. The presence of two unpaired electrons, which also happen to be above the non-bonding energy level, would destabilize the molecule, making it antiaromatic.



As we noted in Problem 13 though, the anion adopts sp^3 hybridization to avoid this fate. It is non-aromatic instead.

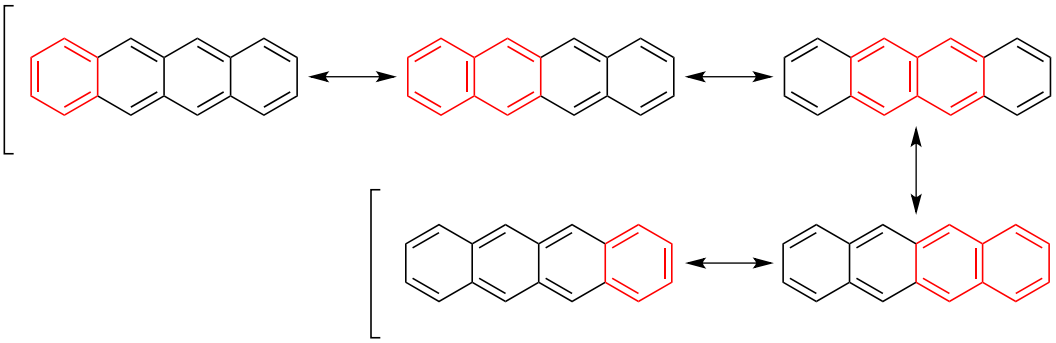
26.

(a) Triphenylene has a number of resonance structures. To explain how they can be derived in a systematic fashion, consider "spinning" the double bonds in a benzene ring to convert it from one Kekulé form to the other. In the diagram below, a green "s" is used to denote which ring(s) was/were converted to the other Kekulé form *when compared to the original resonance form*. We can start by "spinning" the double bonds in each of the three exterior rings one at a time. Then, we can derive three more resonance forms by "spinning" the double bonds in two of the exterior rings. Another resonance form is obtained by "spinning" the double bonds in all three exterior rings. Finally, one last resonance form is obtained by "spinning" the double bonds in the central ring.



Notice that the three exterior rings of triphenylene are fully aromatic in eight out of nine resonance structures (~90%). These rings have almost as much aromatic stabilization as benzene, while the interior ring has very little aromatic character since it is fully aromatic in only two of the nine resonance forms (~20%).

In tetracene, the resonance structures can be derived by "spinning" the double bonds in the first ring, then the second, third, and fourth. Each ring is fully aromatic in two out of five resonance forms (40%). This is a much lower percentage than for the outer rings of triphenylene, which explains the difference in resonance energy.

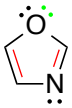


(b) Graphene is a series of fused benzene rings that simply extends very far in two dimensions. Since benzene is aromatic, we expect this series of fused benzene rings to have at least some aromatic character as well.

27. Thiophene has four π electrons in its two π bonds. Additionally, sulfur can contribute one lone pair to the π system by placing it in a p orbital. The result is a six-π-electron system (a 4n + 2 value), which is aromatic.

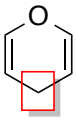
thiophene

Oxazole also has four π electrons in its two π bonds. Nitrogen is already using a p orbital for a π bond, so it is unable to place its lone pair into a p orbital that would align with the rest of the π system. On the other hand, oxygen can place one lone pair into a p orbital that is parallel to the π system. This leads to a six-π-electron system (a 4n + 2 value), which is aromatic.



oxazole

4*H*-Pyran contains one ring atom that is sp^3 hybridized. This interrupts the π system, causing the compound to be non-aromatic.



4*H*-pyran

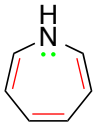
2*H*-Azirine also has one ring atom that is sp^3 hybridized, so it too is non-aromatic.

2*H*-azirine

Azete's nitrogen atom is unable to contribute its lone pair to the π system. Since the nitrogen atom is already using a p orbital for its π bond, it cannot place the lone pair into a p orbital that would align with the π system. As such, azete is a four-π-electron system and is antiaromatic.

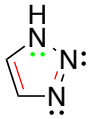
azete

Azepine has six π electrons in its three π bonds. If nitrogen were to contribute its lone pair to the π system, the ring would have eight π electrons and would be antiaromatic. Since this is an undesirable attribute, the nitrogen adopts sp^3 hybridization thereby causing an interruption in the π system. The result is a non-aromatic molecule.



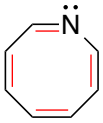
azepine

1,2,3-Triazole contains two π bonds that contribute a total of four electrons to the π system. The two nitrogen atoms that are participating in a π bond are unable to donate their lone pairs to the π system. However, the sole nitrogen that is not participating in a π bond can place its lone pair into a p orbital that aligns with the others. 1,2,3-Triazole therefore has six π electrons (a 4n + 2 value) and is aromatic.



1,2,3-triazole

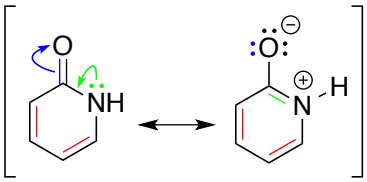
Azocine has eight π electrons resulting from its four π bonds. Nitrogen is already participating in the π system through a π bond, so it is unable to contribute its lone pair. Azocine would therefore be antiaromatic if it were planar, but much like cyclooctatetraene, it bends out of planarity to avoid this fate. It is non-aromatic instead.



azocine

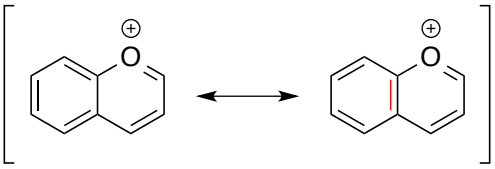
2-Pyridone can be difficult to analyze because the relationship of the carbonyl π bond to the ring is unclear in the resonance form given in the problem. However, there is another resonance form that places nitrogen's lone pair squarely in the ring's π system and the carbonyl π bond decidedly outside the ring. The ring

therefore has a total of six π electrons (four from the alkenes and two from nitrogen) and is aromatic as a result.



2-pyridone

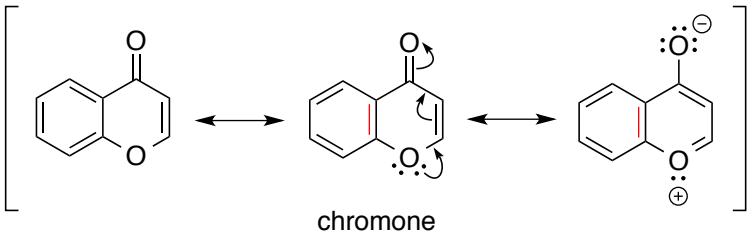
28. When analyzing each structure, it is helpful to utilize a resonance form that clearly shows any electrons that may be shared between multiple rings.



1-benzopyrylium ion

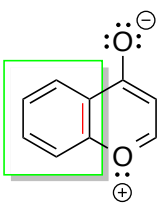
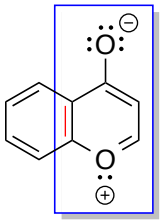
Then, we can consider each ring separately. The benzene ring is aromatic. Its oxygen-containing analogue, the pyrylium ring, is also aromatic. Although the oxonium ion has one lone pair remaining, that lone pair cannot be contributed to the π system since oxygen is already using a p orbital for its π bond. Since 1-benzopyrylium consists of two fused aromatic rings, we expect it to be aromatic as well.

For chromone, we can begin similarly by showing a resonance form that highlights electrons shared between the rings. Additionally, it is helpful to illustrate the conjugation between the oxygen in the ring and the carbonyl (much as we did for 2-pyridone in the previous problem).

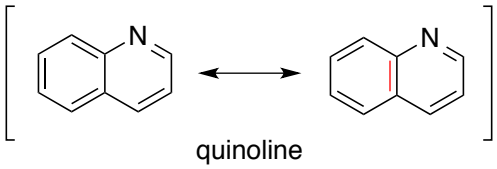


chromone

The benzene ring is, of course, aromatic, as is the 4-pyranone ring. Since chromone consists of two fused aromatic rings, we expect it to be aromatic too.

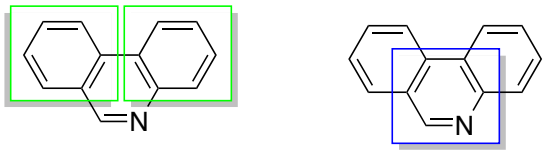



With quinoline, we should begin by drawing a resonance form that clearly reveals the electrons shared between the rings.

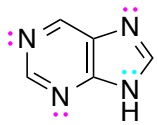


The benzene and pyridine rings are both aromatic, so quinoline is an aromatic ring as well. Recall that, while nitrogen bears a lone pair in pyridine, that lone pair is not part of the π system because nitrogen is already using a p orbital for its π bond.

Dibenzopyridine has conveniently been drawn in a way that the electrons shared between rings are already apparent, so we can proceed directly to analysis of the individual rings. Both benzene rings are certainly aromatic, as is the pyridine ring. Therefore, the molecule as a whole is expected to be aromatic.

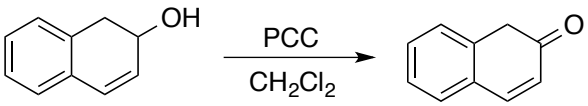


Purine is a component of the nitrogenous bases adenine and guanine that appear in nucleotides in DNA and RNA. Purine contains four nitrogen atoms, each with a lone pair of electrons. Three of these nitrogens are participating in a π bond and are therefore unable to contribute their lone pairs to the π system. There is one nitrogen atom though that is not participating in a π bond, so it is able to contribute its lone pair to the π system by placing it into a p orbital.



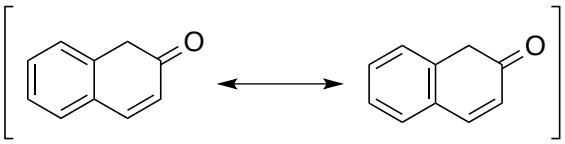
Thus, when we analyze the individual rings, we find that the pyrimidine ring is aromatic. It is a six-π-electron system where all six electrons come from the π bonds and none are donated by nitrogen atoms. The imidazole ring is also aromatic. It too is a six-π-electron system, but its electrons come from the four in its π bonds and two from a lone pair. Since purine is a fusion of two aromatic rings, we expect it to be aromatic as well.

29. The expected oxidation product is the ketone shown below.

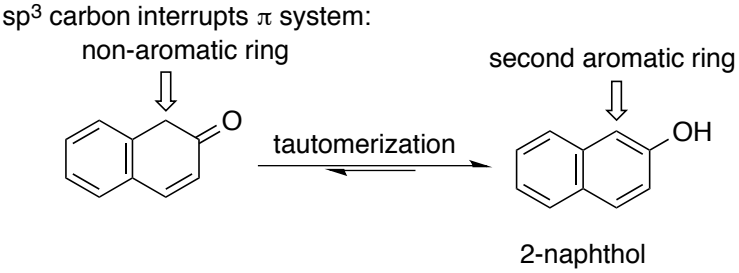


However, this compound would exhibit a carbonyl resonance in the IR spectrum. It would be a bit below 1700 cm^{-1} due to the carbonyl's conjugation, but it would be present in this general vicinity. The absence of any type of carbonyl signal causes a reconsideration of this product.

Notice that the carbonyl-containing ring already has a π bond and shares a π bond with the fused benzene ring. It is close to being aromatic, but the sp^3 hybridized carbon interrupts the π system and makes it a non-aromatic ring as drawn.



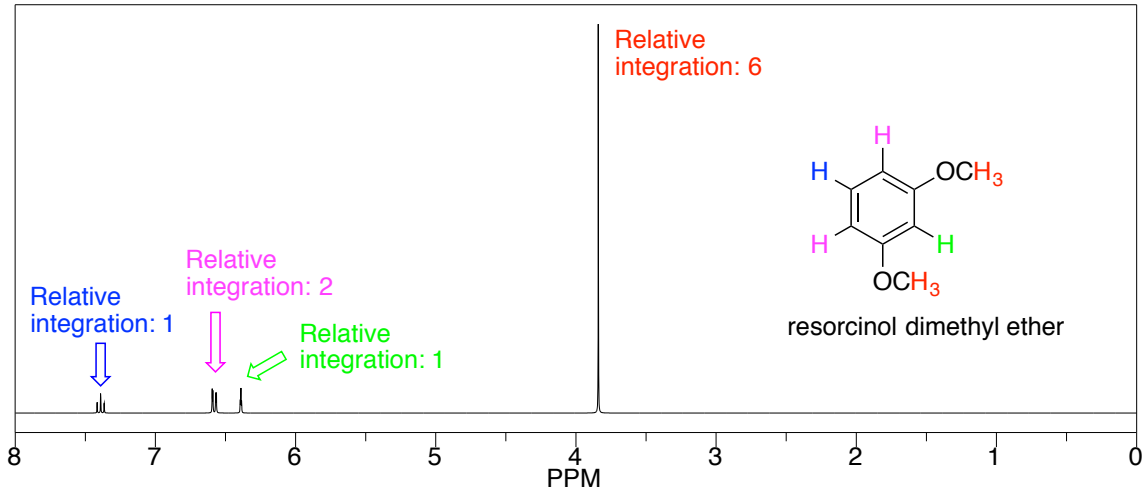
We learned about tautomerism in Chapter 11. Normally, the carbonyl-containing tautomer (i.e., the keto form) is favored. However, in this instance, the enol form contains a second aromatic ring (a phenol), which tips the balance in its favor.



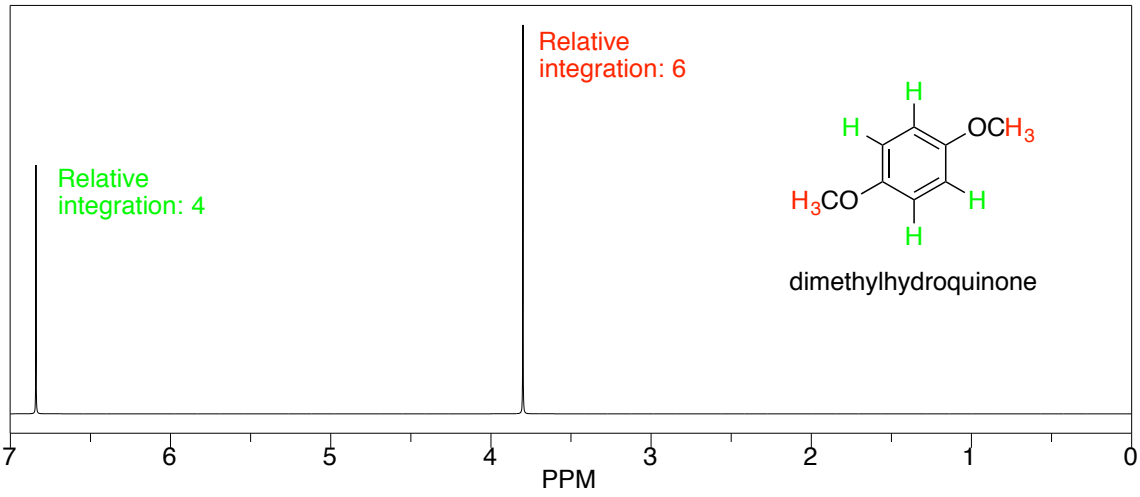
This compound, which happens to be known as 2-naphthol, is consistent with the observed IR data. The phenolic hydroxyl group results in a broad O-H stretch around 3300 cm^{-1}, and the sp^2 C-H stretching causes the signals just above 3000 cm^{-1}. Additionally, there is no carbonyl in 2-naphthol.

30. In all three compounds, the methyl groups are equivalent and give rise to a singlet integrating for six hydrogens. This structural feature is therefore not particularly useful in differentiating the spectra.

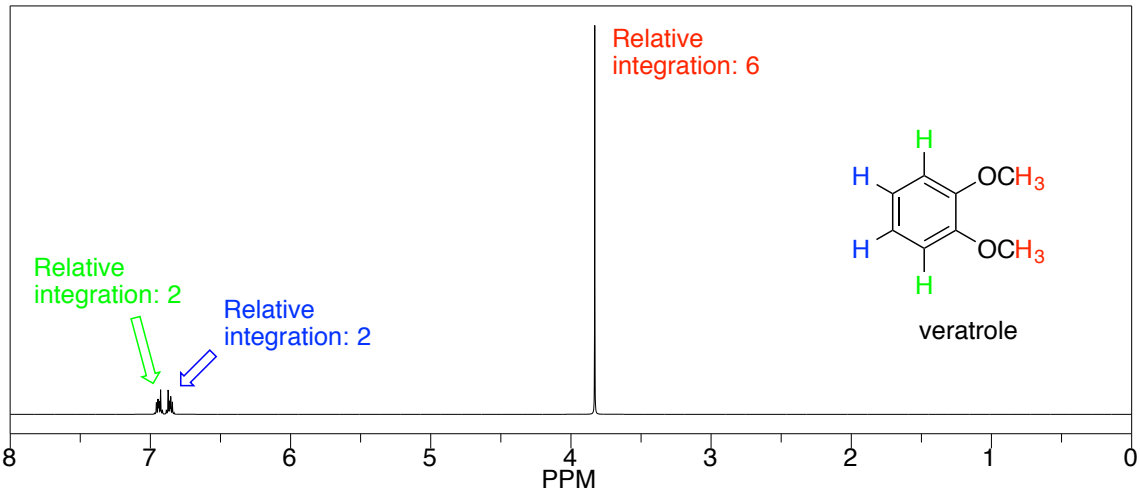
On the other hand, each isomer has a distinct array of aryl protons that will allow us to match the spectra with the molecules. The first spectrum has three aryl signals, and only the *meta* isomer, resorcinol dimethyl ether, has three types of aryl protons. The proton flanked by two methoxy groups has only weak *meta* coupling, so it nearly appears as a singlet. If you look closely, you can see some modest splitting into a triplet. The two protons adjacent to a single methoxy group give rise to one signal that appears to be a doublet at first glance. If you look very closely, you can see some additional splitting resulting from weak *meta* coupling to the green proton. Finally, the proton that is not adjacent to any methoxy groups is a triplet.



The second spectrum has only one signal in the aryl region, and this is consistent only with the *para* isomer, dimethylhydroquinone. All four of the aryl protons are in the exact same chemical environment, so they cause a single signal.

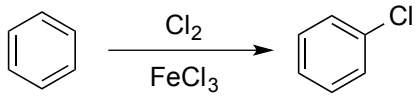


The final spectrum has two aryl signals. This matches the *ortho* isomer, veratrole. Both signals are complex due to long range splitting and second-order coupling as well. The green protons are slightly more deshielded as a result of the inductive electron withdrawal by the oxygen atoms, which are in closer proximity to them.

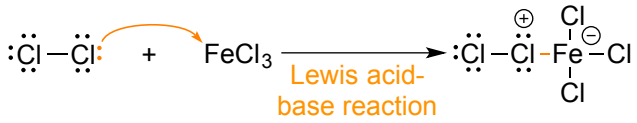


Solutions to Problems for Chapter 14: Reactions of Aromatic Compounds

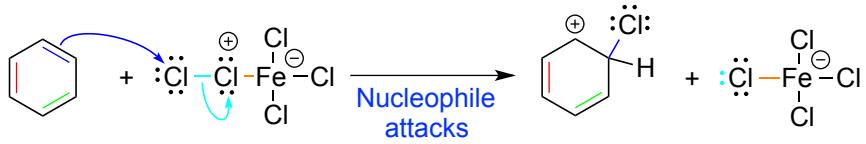
1. We are asked to draw the mechanism for the chlorination of benzene.



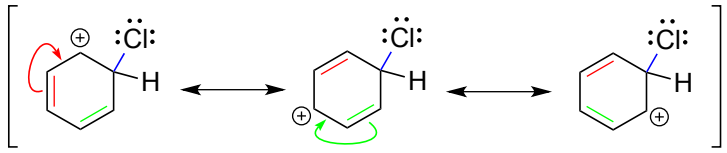
Chlorine is not sufficiently electrophilic to incite a reaction with benzene, so it is the initial Lewis acid-base reaction between chlorine and iron trichloride (or aluminum trichloride) that creates the potent electrophile needed for this reaction.



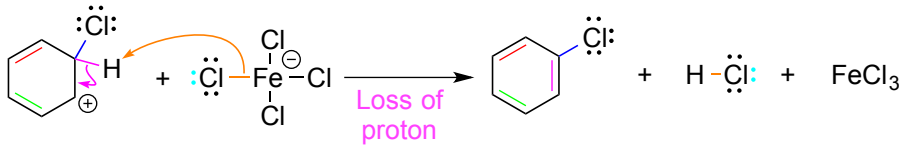
The terminal chlorine atom of the Lewis acid-base complex is attacked by a pi bond of the aromatic ring. This allows electrons to be pushed onto the interior chlorine atom to neutralize its charge.



The sigma complex thus formed has a total of three contributors to the resonance hybrid.

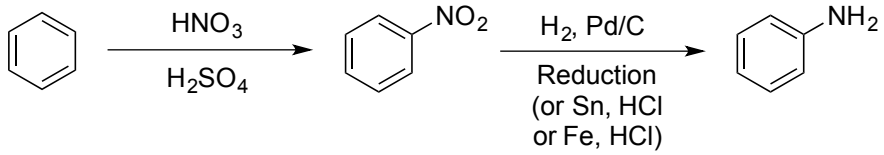


The reaction concludes with the loss of a proton to restore aromaticity to the ring. This is a step where students sometimes get tripped up. It is easy to remove a proton from an incorrect location when drawing this part of the mechanism. Remember that the sigma complex is non-aromatic. This can be attributed to the break in conjugation caused by the sp^3 hybridized carbon atom that bears both the new group and a proton. The proton must be lost from the only ring atom that is sp^3 hybridized in order to reestablish aromaticity. Loss of a proton from any other site on the ring would not accomplish this goal.

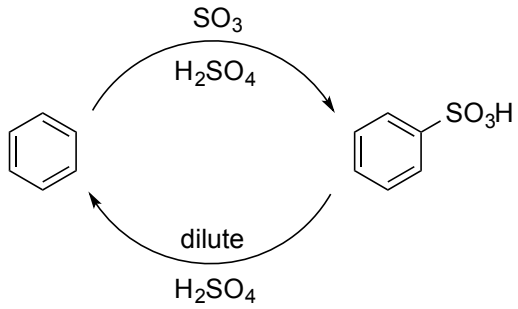


The product is chlorobenzene, and it is formed along with hydrochloric acid as a byproduct. Notice that the last step also regenerates the iron trichloride catalyst.

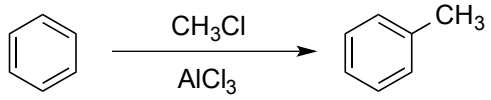
2. Recall that aniline is a benzene ring bearing an amino group. The amino group cannot be directly installed on the ring via EAS. However, a nitrogen atom can be connected to the ring through nitration. The nitrobenzene thus produced can be reduced to aniline using a variety of methods, such as hydrogenation.



3. Sulfonation is the addition of a sulfonic acid group to an aromatic ring. This reaction requires sulfur trioxide and sulfuric acid. The removal of the sulfonic acid group from the ring is known as desulfonation, and this transformation necessitates dilute sulfuric acid.

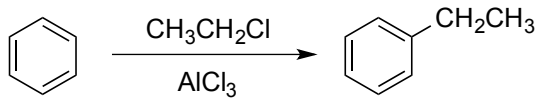


4. Treatment of benzene with methyl chloride and aluminum trichloride yields toluene.

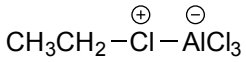


5.

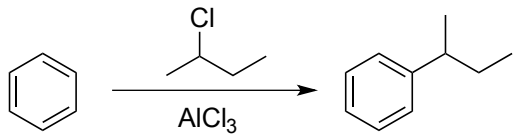
(a) We saw this transformation in the section entitled “Installation of an ethyl group.” The product is ethylbenzene.



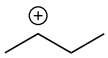
Since ethyl chloride is a primary alkyl halide and would yield an unstable primary carbocation if dissociation were to occur, *no* carbocation intermediate is present in the mechanism. The electrophile that is attacked by the benzene ring is the Lewis acid-base complex:



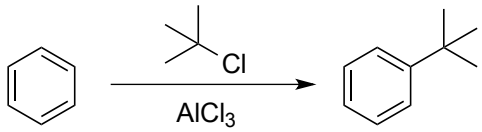
(b) This Friedel-Crafts alkylation generates *sec*-butylbenzene.



Since *sec*-butyl chloride is a secondary alkyl halide, dissociation does occur after complexation with $AlCl_3$ to produce a reasonably stable secondary carbocation that serves as the potent electrophile in this reaction:



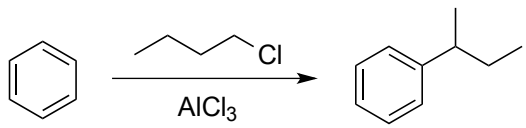
(c) This alkylation reaction affords *tert*-butylbenzene.



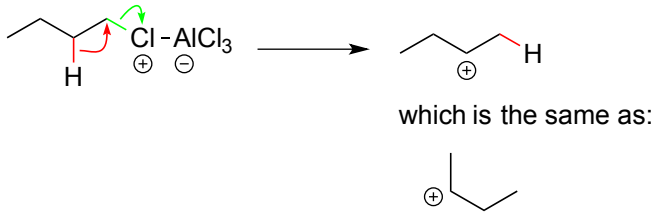
Tert-butyl chloride is a tertiary alkyl halide. Dissociation subsequent to complexation with the Lewis acid yields a stable tertiary carbocation, which serves as the electrophile in this transformation:

6.

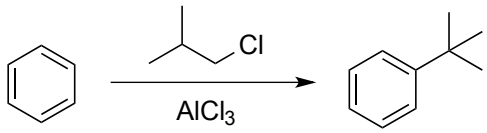
(a) This reaction yields *sec*-butylbenzene as the major product.



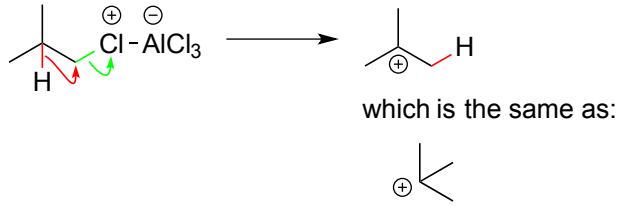
The initial Lewis acid-base adduct undergoes rearrangement to produce a secondary carbocation, which serves as the electrophile in this reaction.



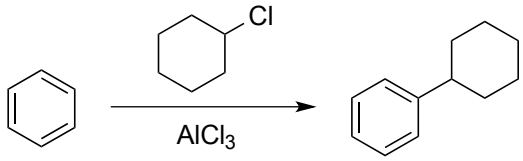
(b) This reaction produces *tert*-butylbenzene as the major product.



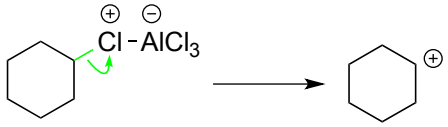
The Lewis acid-base complex undergoes a hydride shift to yield a tertiary carbocation. This cation is the potent electrophile in the alkylation:



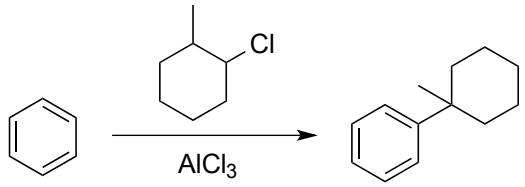
(c) This alkylation reaction affords cyclohexylbenzene.



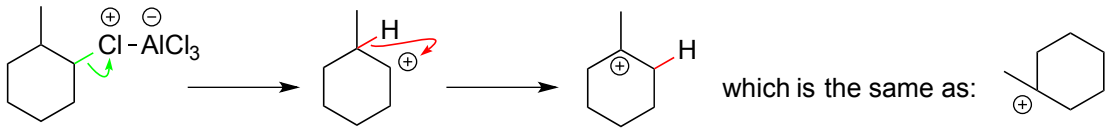
There is no rearrangement in this instance. A secondary carbocation is formed when the $AlCl_4^-$ dissociates, and rearrangement would not lead to any improvement in stability:



(d) This alkylation reaction does involve a rearrangement, leading to the following major product:

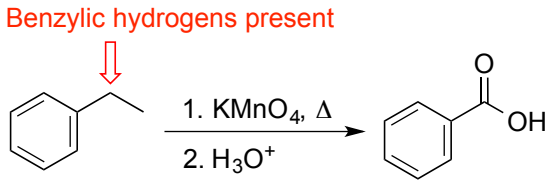


When $AlCl_4^-$ dissociates, a secondary carbocation is formed as we saw in part (c). However, this secondary cation resides next to a tertiary center. A 1,2-hydride shift affords a more stable tertiary carbocation, which serves as the electrophile in this transformation:

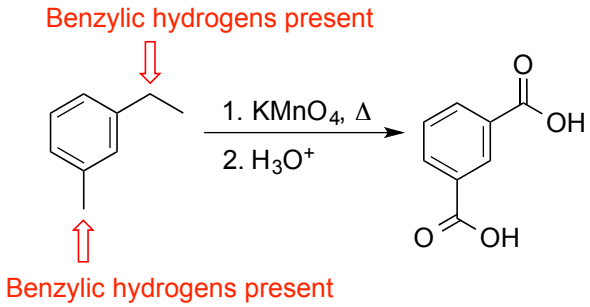


7.

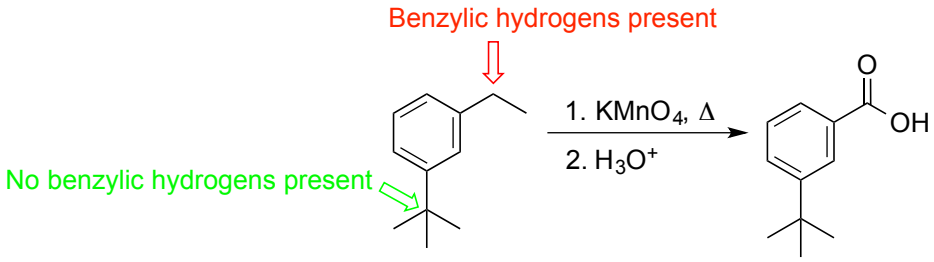
(a) At least one benzylic hydrogen (i.e., a hydrogen atom on the carbon adjacent to the benzene ring) is required in order for benzylic oxidation to occur. Ethylbenzene does possess benzylic hydrogens, so it undergoes benzylic oxidation to provide benzoic acid.



(b) 1-Ethyl-3-methylbenzene has hydrogens at both of its benzylic centers. Therefore, oxidation occurs at both sites yielding a compound known as isophthalic acid.

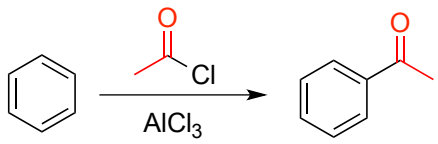


(c) 1-*Tert*-butyl-3-ethylbenzene has benzylic hydrogens on the ethyl group but *not* on the *tert*-butyl group. Since at least one benzylic hydrogen is necessary in order for benzylic oxidation to occur, only the ethyl group is oxidized.

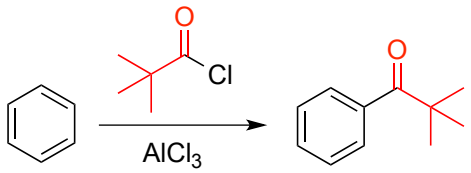


8. In each case, we merely need to choose the appropriate acid chloride corresponding to the acyl group that needs to be installed.

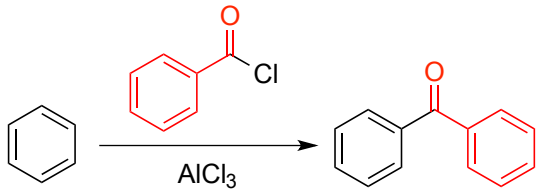
(a)



(b)

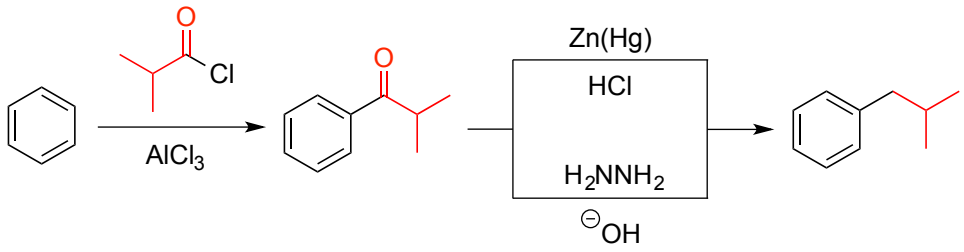


(c)

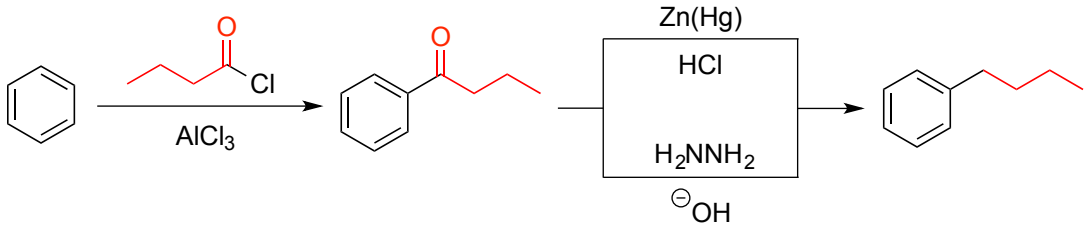


9.

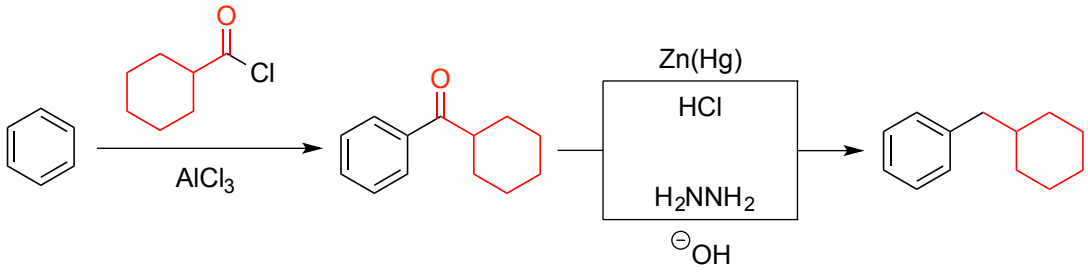
(a) Since the target compound has a primary alkyl group attached to the ring, it *cannot* be made directly through Friedel-Crafts alkylation because rearrangement would occur (see Problem 6b). Instead, we must circumvent the rearrangement issue by performing a Friedel-Crafts acylation. Recall that acylations will not suffer from rearrangement because the acylium ion is resonance stabilized. The acylation should be performed with an acid chloride having the same number of carbons connected in the same fashion as the target alkyl group. Then, the carbonyl of the ketone product is reduced using either the Clemmensen or Wolff-Kishner reaction.



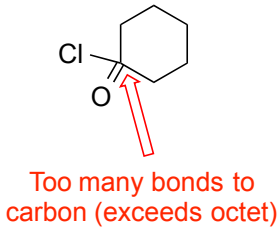
(b) As in the part (a), this question entails the installation of a primary alkyl group, which *cannot* be performed directly through alkylation due to the tendency for rearrangement (see Problem 6a). Instead, acylation is performed using an acid chloride having the same carbon skeleton as the desired alkyl group. Subsequent to acylation, the ketone is removed by the Clemmensen or Wolff-Kishner reduction.



(c) As in parts (a) and (b) above, direct addition of the primary alkyl group through alkylation would *not* provide the intended product as the major product because of rearrangement. However, acylation with an acid chloride having the desired carbon skeleton affords a ketone that can be reduced to the target molecule using the Clemmensen or Wolff-Kishner reaction.

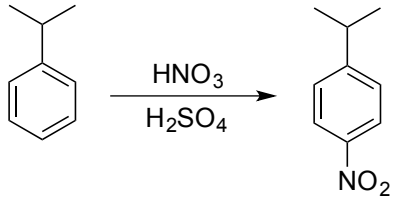


(d) This compound cannot be made using Friedel-Crafts acylation. The reason is that the center to be connected to the benzene ring cannot accommodate the bonds necessary for an acid chloride:

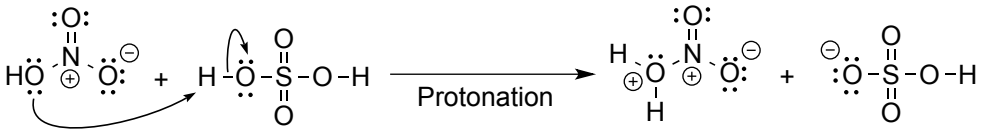


However, this compound can be made directly through Friedel-Crafts alkylation (see Problem 6c).

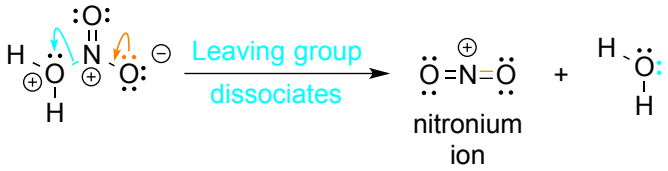
10. Isopropylbenzene bears a substituent that is electron donating. For this reason, the ring is activated, and EAS is directed to the *ortho* and *para* positions. Furthermore, the steric bulk of the isopropyl group suggests that the major product will result from nitration at the more accessible *para* position.



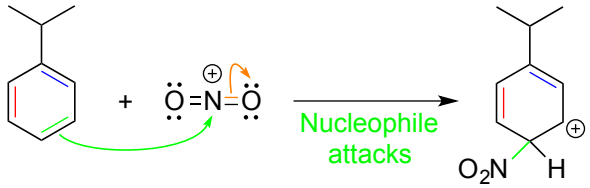
The mechanism begins with the protonation of nitric acid by sulfuric acid. This protonation occurs on the hydroxyl group and converts it into a good leaving group.



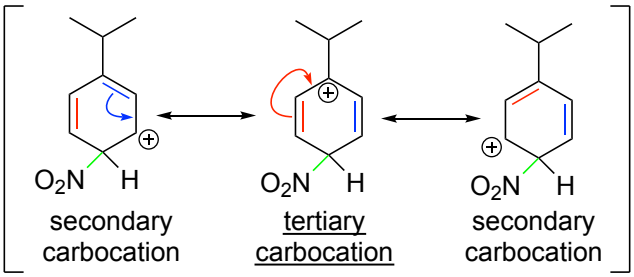
Water is then displaced as a leaving group to form the nitronium ion, which serves as the potent electrophile in this EAS reaction.



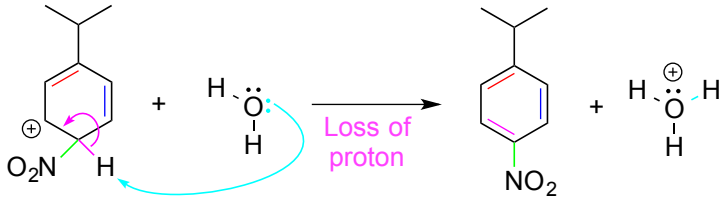
A pi bond of the ring then attacks the nitronium ion to yield the sigma complex as an intermediate in this reaction mechanism.



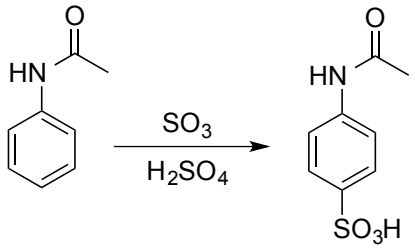
This sigma complex has three resonance forms, and when the sigma complex results from *ortho* or *para* attack, one of those resonance forms is particularly stable due to the tertiary carbocation. Such a resonance contributor is not available from the *meta* pathway.



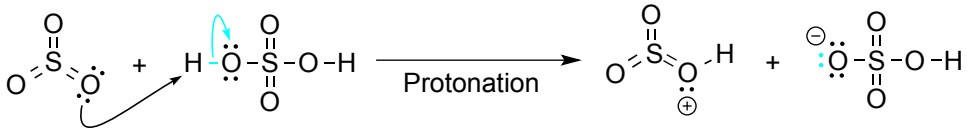
The mechanism concludes with the loss of a proton from the sp^3 hybridized carbon of the ring to restore aromaticity to the system.



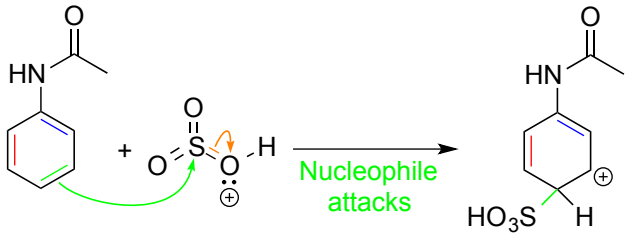
11. This amide serves as an electron-donating group by resonance. As a result, it is both activating and an *ortho*, *para* director. For steric reasons, the *para* product is expected to predominate.



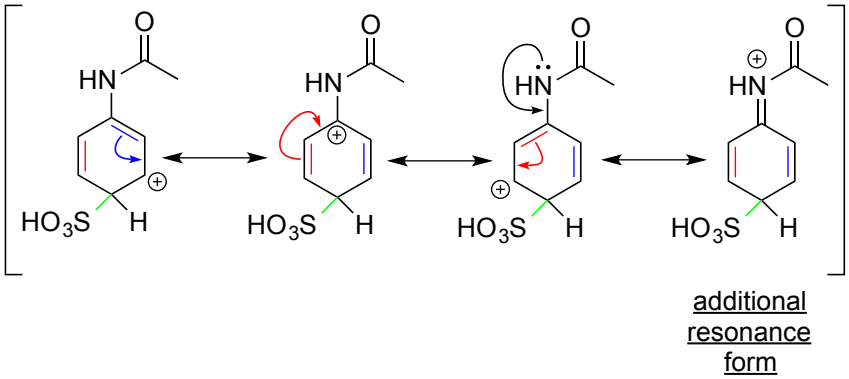
The mechanism more clearly illustrates why the amide is an *ortho*, *para* director. It begins with the protonation of sulfur trioxide by sulfuric acid to generate a potent electrophile.



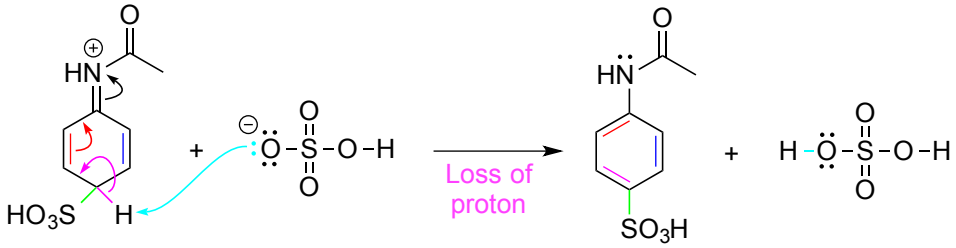
The electrophile is then attacked by a pi bond of the aromatic ring, resulting in the formation of a sigma complex.



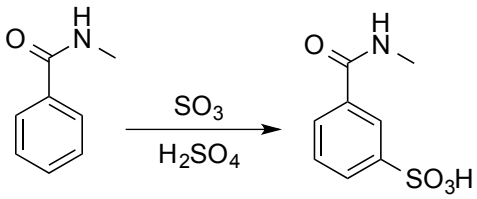
The *ortho* and *para* pathways lead to sigma complexes in which there is an additional resonance structure resulting from the donation of electrons into the ring by the amide nitrogen. This extra delocalization of the positive charge, which is not available in the *meta* pathway, is particularly stabilizing because all atoms possess a complete octet of electrons when the nitrogen atom bears the positive charge.



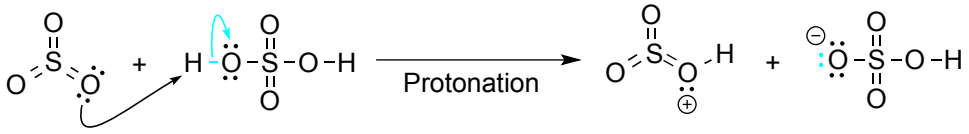
Finally, loss of a proton from the sp^3 hybridized carbon of the ring restores aromaticity to the ring.



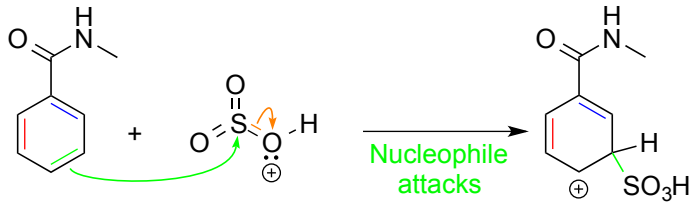
12. The carbonyl of the amide is conjugated to the ring and can therefore withdraw electron density from it. The majority of electron-withdrawing groups are *meta* directors, so we expect to obtain the *meta* regioisomer as the predominant product.



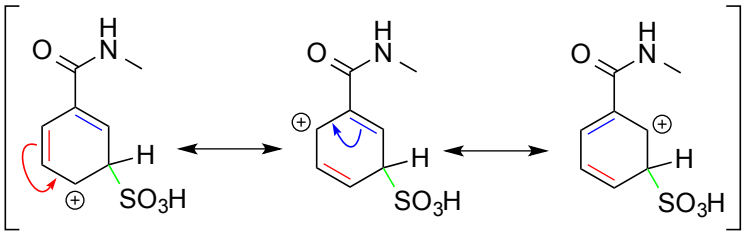
The mechanism more fully explains this result. When sulfur trioxide is protonated by sulfuric acid, a potent electrophile is formed.



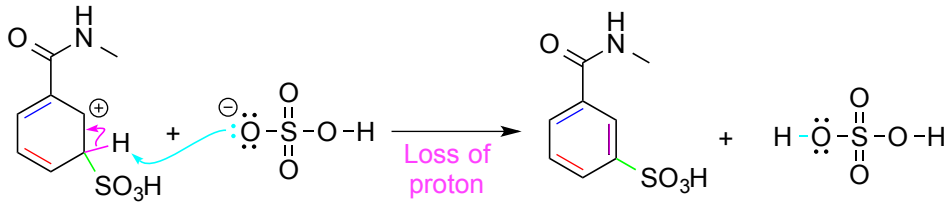
This electrophile is then attacked by a pi bond of the ring, yielding a sigma complex.



This sigma complex has the three usual resonance forms. What is important about these resonance structures is that the positive charge is never placed directly adjacent to the partially positive carbonyl carbon. As a result, a destabilizing repulsive force is avoided in the *meta* pathway. However, in the *ortho* and *para* pathways that repulsive interaction destabilizes the sigma complex.

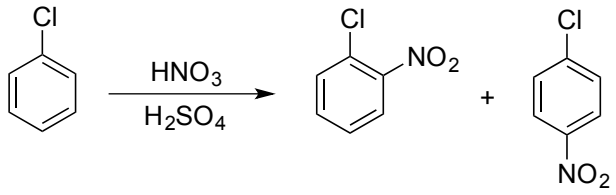


Finally, the loss of a proton from the sp^3 hybridized carbon of the ring restores aromaticity.



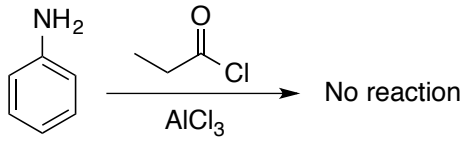
Compare this problem to Problem 11. *Notice how the reversal of the amide group changes the nature of the substituent entirely.* When nitrogen's lone pair is conjugated to the ring (as in Problem 11), the amide is an activating *ortho*, *para* director. However, when the carbonyl is conjugated to the ring (as in Problem 12), the amide is a deactivating *meta* director.

13. As we saw in this section, the halogens exhibit unusual behavior in that they are deactivating by induction but are *ortho*, *para* directing based on their ability to donate electron density to the ring through resonance. Consequently, we expect the products of the reaction to be the *ortho* and *para* regioisomers. Since the chloro group is small, steric hindrance is not a significant consideration, and therefore both products are expected.

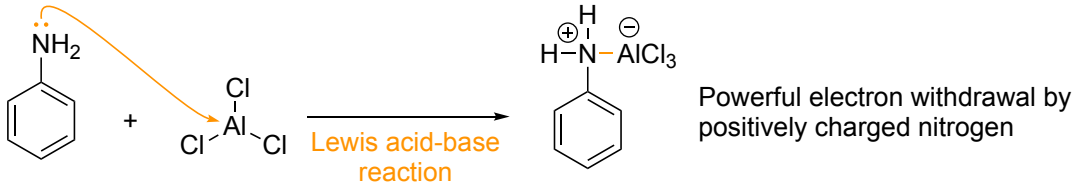


14.

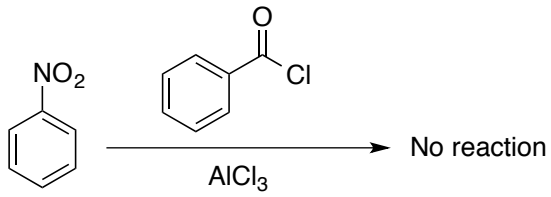
(a) As we learned in this section, Friedel-Crafts reactions (alkylation and acylation) do not work on rings bearing amino groups, so this reaction will fail.



The reason is the Lewis acid-base reaction that occurs between the amino group and aluminum trichloride. The adduct bears a powerfully electron-withdrawing group due to the inductive withdrawal by the positively charged nitrogen atom.

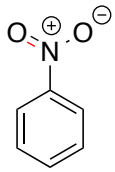


(b) We also learned in this section that nitro groups are too powerfully electron withdrawing to allow Friedel-Crafts reaction to occur. As a result, this reaction fails as well.

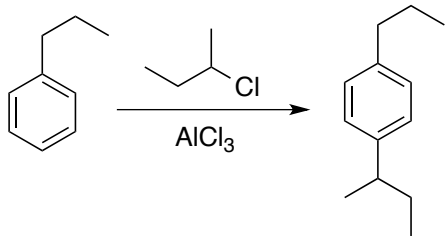


The reason is that the nitro group withdraws electron density from the ring through induction and resonance. The inductive electron withdrawal is due to the positive

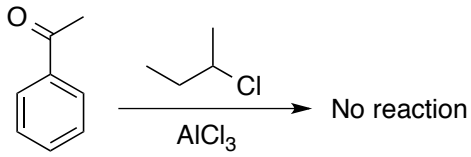
charge on the nitrogen atom. The nitrogen-oxygen pi bond is also conjugated to the ring, allowing for withdrawal of electron density from the ring by resonance.



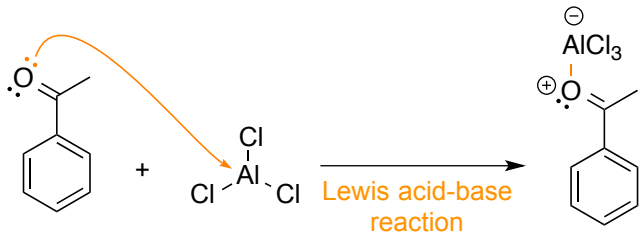
(c) Friedel-Crafts reactions are compatible with alkyl groups, so this reaction does proceed. The alkyl group on the ring directs substitution to the *ortho* and *para* positions; however, the *ortho* position is less accessible for steric reasons. Therefore, the major product is expected to be the *para* isomer.



(d) As was also mentioned in this section, Friedel-Crafts reactions are problematic with rings that have carbonyls conjugated to the ring, so this reaction will fail because the ketone is conjugated to the ring.



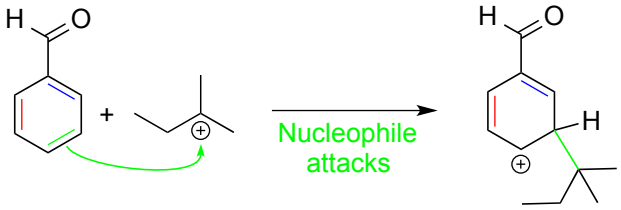
The reason is that a lone pair of the ketone oxygen can complex with the Lewis acid. The resulting adduct is too deactivated for Friedel-Crafts reaction because the ketone's electron-withdrawing nature has been enhanced by the placement of a positive charge on oxygen.



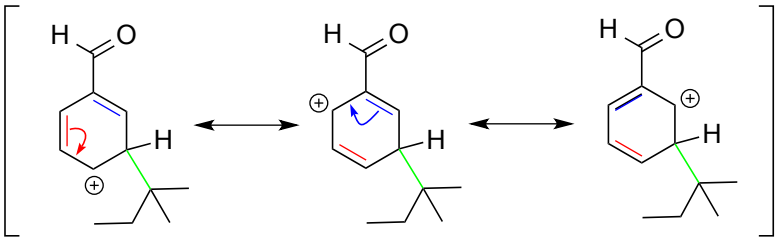
15. Recall from the chapter on alcohols that the hydroxyl group can be protonated by a strong acid, such as sulfuric acid.

Once it is protonated, a good leaving group (water) is present. Its dissociation leads to the formation of a tertiary carbocation.

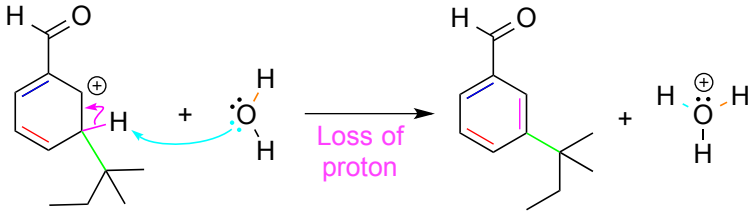
Carbocations can serve as potent electrophiles in Friedel-Crafts alkylations, and it doesn't matter how the carbocation is produced. This is merely an alternative way of forming the carbocation. It is subsequently attacked by a pi bond of the aromatic ring. The aldehyde is an electron-withdrawing group, and electron-withdrawing groups (other than the halogens) are *meta* directors. Therefore, the alkyl group is added to the *meta* site.



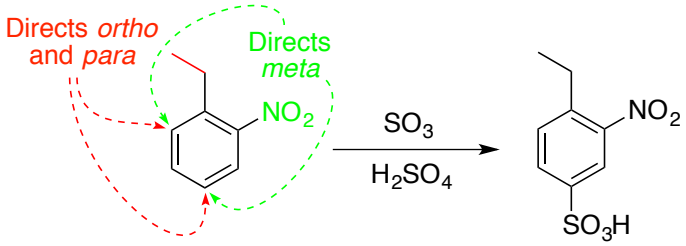
The sigma complex thus formed has three resonance structures, none of which place the positive charge directly adjacent to the aldehyde. Consequently, a repulsive electrostatic interaction is avoided in the *meta* pathway.



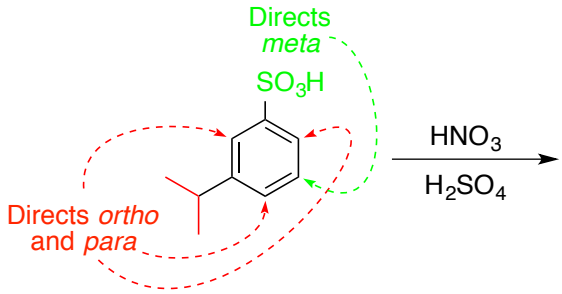
The final step is the loss of a proton from the sp^3 hybridized carbon of the ring to reestablish aromaticity.



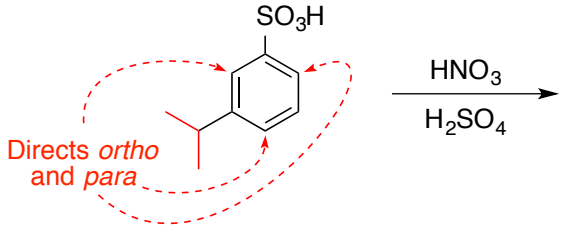
16. The ethyl group directs *ortho* and *para* to itself; however, one of its *ortho* positions is already occupied by the nitro group. On the other hand, the nitro group directs *meta* to itself. Both substituents direct the sulfonation to the same locations, but the site adjacent to the ethyl group is less sterically accessible. Therefore, the major product is 4-ethyl-3-nitrobenzenesulfonic acid.



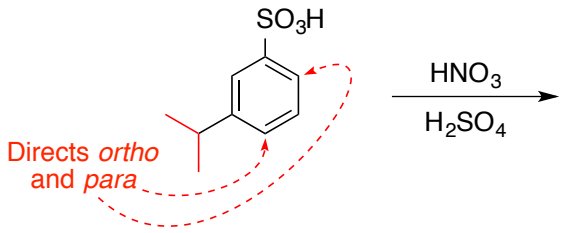
17. The isopropyl group directs *ortho* and *para* to itself, while the sulfonic acid group directs *meta* to itself. As a result, each location on the ring that does not already possess a substituent appears to be a candidate for nitration.



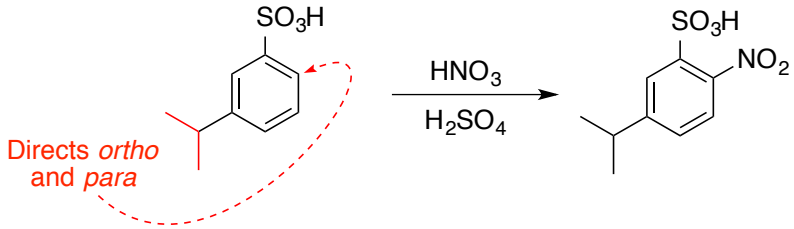
The first guideline for narrowing the choices is that the most activating group on the ring controls the regiochemistry of electrophilic aromatic substitution. The alkyl group is electron donating and therefore activating, but the sulfonic acid group is electron withdrawing and consequently deactivating. So, it is the isopropyl group that controls the EAS reaction. This narrows the choices from four sites to three.



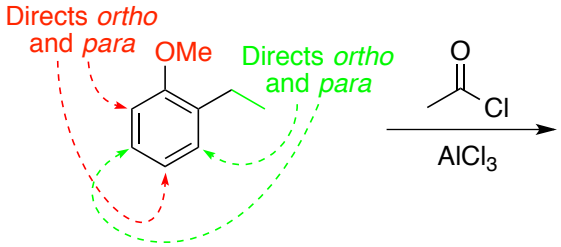
The second guideline is that EAS does not occur between two groups for steric reasons. This narrows the choices from three to two.



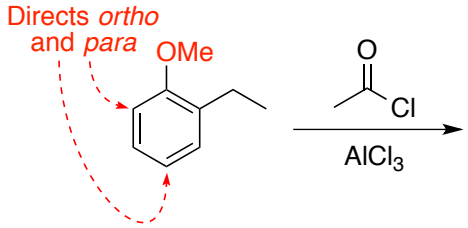
Finally, the steric bulk of the isopropyl group disfavors substitution at its *ortho* position and allows us to determine where nitration will occur preferentially.



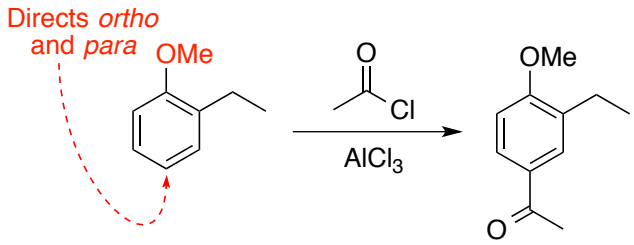
18. In this case, both groups are *ortho*, *para* directors. Between the two directing effects, it seems that any of the four open locations on the ring are eligible for acylation.



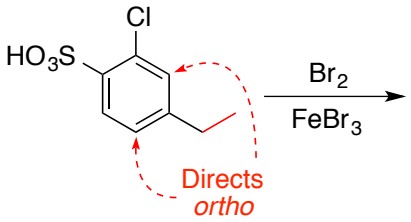
However, our first guideline for narrowing the choices is that the <u>most</u> activating group on the ring controls the regiochemistry of EAS. While both the ethyl and the methoxy group are activators, the ethyl group donates electron density to the ring merely through induction. Induction is a weaker effect than resonance, and the methoxy group activates the ring through resonance (donation of a lone pair into the ring's pi system). Consequently, it is the methoxy group that is the stronger activating group, and it controls the regiochemistry of the EAS reaction.



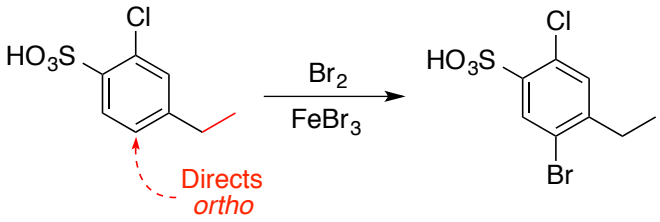
Of the two positions activated by the methoxy group, it is the *para* position that is more sterically accessible. Therefore, the predominant product is 3-ethyl-4-methoxyacetophenone.



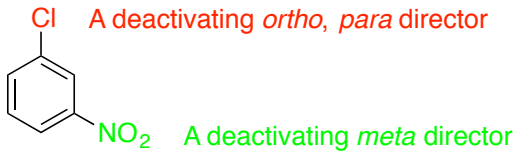
19. EAS reactions of polysubstituted rings follow the same basic guidelines. First, it is the most activating group on the ring that controls the EAS. Both the sulfonic acid and chloro groups are electron withdrawing and therefore deactivating. Only the ethyl group is electron donating and activating, so the ethyl group controls the regiochemistry of the reaction. It directs *ortho* and *para*; however, its *para* position is already occupied.



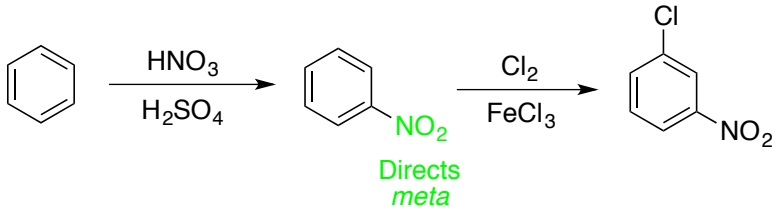
The second guideline is that EAS does not occur between two substituents for steric reasons. This allows us to eliminate one of the choices and predict the major product of the reaction.



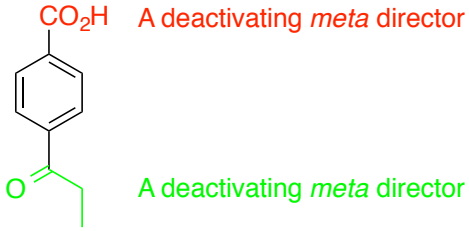
20. We should begin this problem by drawing the structure of the target and considering the directing effects of the substituents. The nitro group is deactivating, and like most deactivating groups, it is a *meta* director. Chlorine is also deactivating, but recall that the halogens are the only deactivating groups that direct *ortho* and *para.*



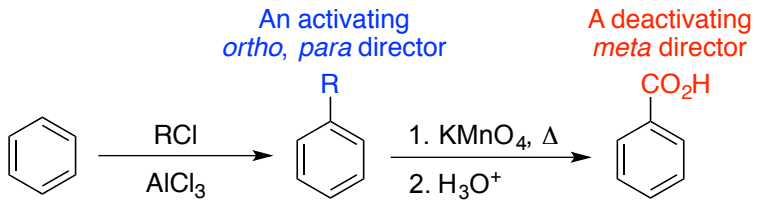
Since the desired regiochemistry is *meta*, we should install the *meta* director first. Subsequent chlorination provides the target molecule.



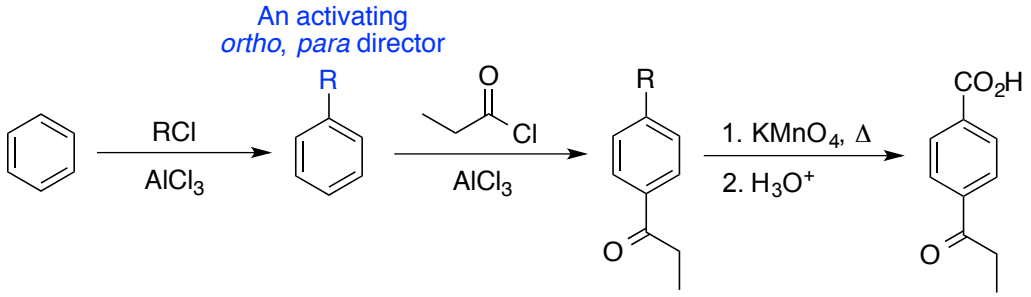
21. Analysis of the directing effects of the substituents leads to the conclusion that both are deactivating *meta* directors. Since the desired regiochemistry in the target is *para*, we know that at least one of the groups must be installed via a multi-step process, where an intermediate will have the directing capability that we need.



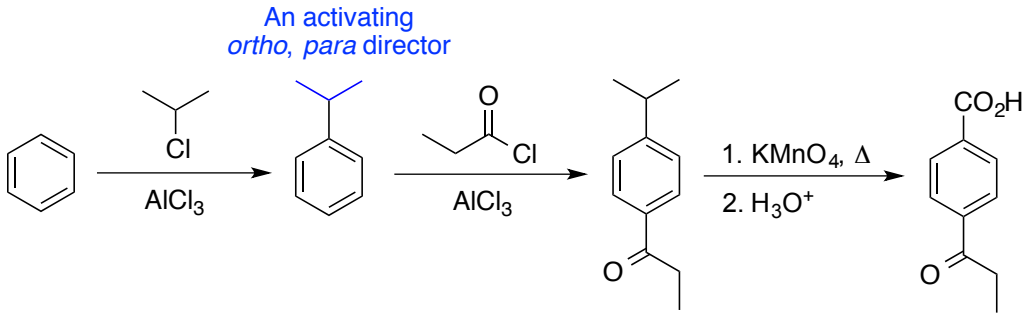
The acyl group is installed through just one step: Friedel-Crafts acylation. However, there is no single-step method for the addition of a carboxylic acid to the ring. Carboxylic acids are added by a two-step process: Friedel-Crafts alkylation followed by benzylic oxidation.



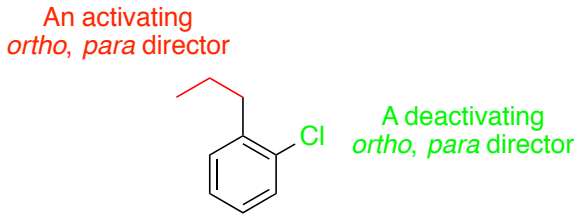
The key to this problem is recognizing that the two steps need not be conducted back-to-back. We can pause in the middle of this two-step sequence to take advantage of the *ortho*, *para* directing capability of the R group, which allows us to place the acyl group in the correct location.



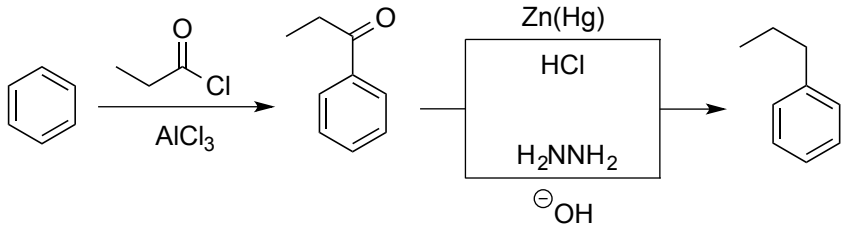
All that remains is to select a specific R group. There are two factors affecting our choice: (1) The R group must have at least one benzylic hydrogen in order for benzylic oxidation to work, and (2) the bulkier the R group, the higher the yield of the desired *para* isomer (rather than *ortho*) will be. An isopropyl group is a good choice for R because it leads to an alkylbenzene with one benzylic hydrogen, allowing benzylic oxidation to occur when we later treat with potassium permanganate. Additionally, the branching of the isopropyl group increases steric bulk and disfavors *ortho* substitution during the acylation.



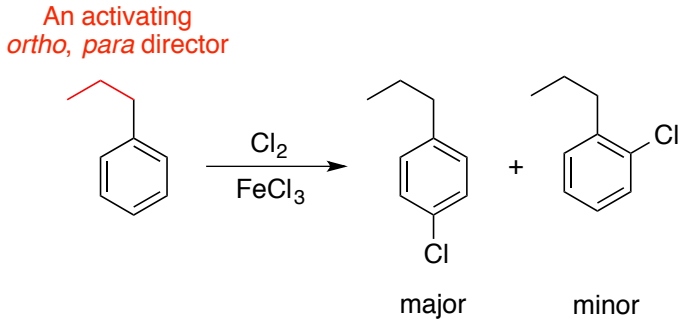
22. In this synthesis problem, both groups are *ortho*, *para* directors. However, the propyl group is activating, and the chloro group is deactivating. While either group could be used to achieve the desired regiochemistry, *it is preferable to use activated rings in EAS reactions.* Remember that activated rings undergo EAS more quickly than deactivated ones, so the reactions of activated rings are better reactions.



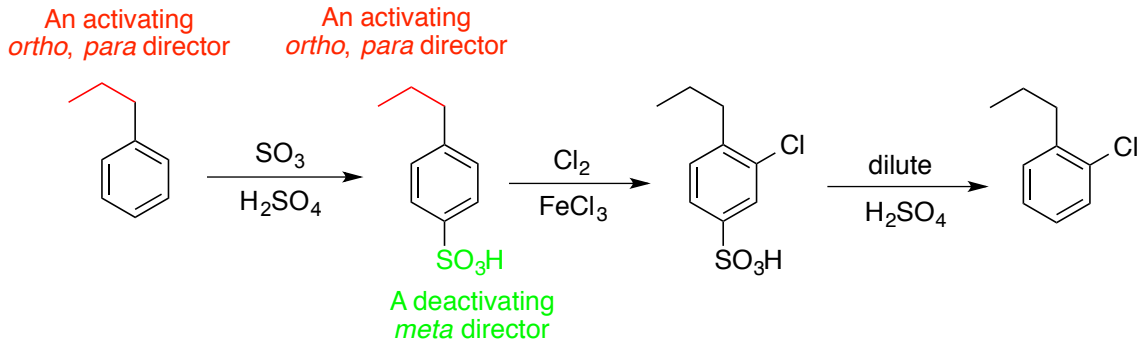
Since the propyl group is a primary alkyl group, it cannot be installed directly using Friedel-Crafts alkylation due to rearrangement that would lead to isopropyl benzene rather than propyl benzene. We must use a two-step sequence to add the propyl group to the ring: acylation and reduction.



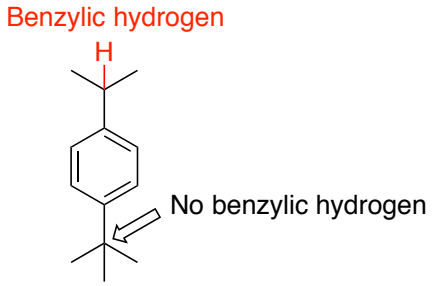
However, if we then chlorinate the ring directly, the major product is expected to be the *para* product. *It is always preferable to produce the maximum possible yield of the target compound, so this synthesis is flawed.*



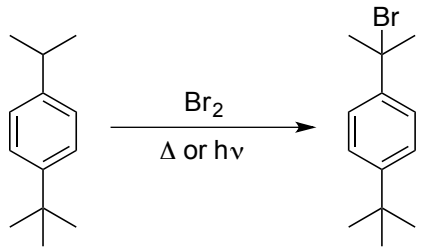
We can easily remedy the situation using the sulfonic acid group as a blocking group. The propyl group directs sulfonation predominantly to the *para* position. Subsequent chlorination can then only occur *ortho* to the propyl group. Finally, dilute sulfuric acid removes the blocking group to afford the desired compound.



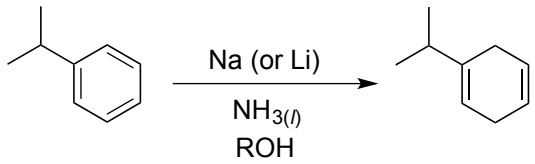
23. It is always important to think mechanistically, even when you aren't asked to draw the mechanism for a reaction. Recall that during benzylic bromination a hydrogen atom is abstracted from the benzylic carbon. Therefore, it is necessary to have at least one benzylic hydrogen in order for bromination to occur. There are two benzylic carbons in this substrate, but only one has a hydrogen atom. The isopropyl group has a benzylic hydrogen atom, but the *tert*-butyl group does not.



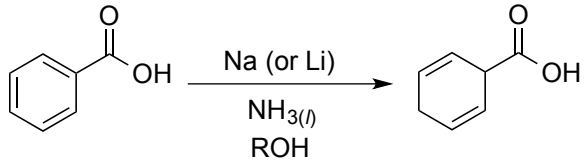
As a result, only the isopropyl group undergoes bromination at the benzylic position.



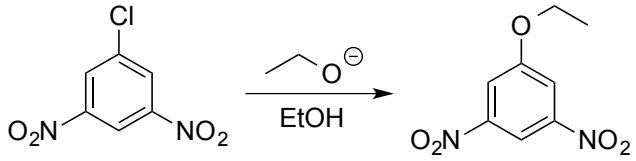
24. When benzene derivatives bearing electron-donating groups are subjected to Birch reduction, the electron-donating group resides on a double bond in the product. This is driven by avoiding placement of the carbanion intermediate adjacent to the electron-donating group, which would be destabilizing.



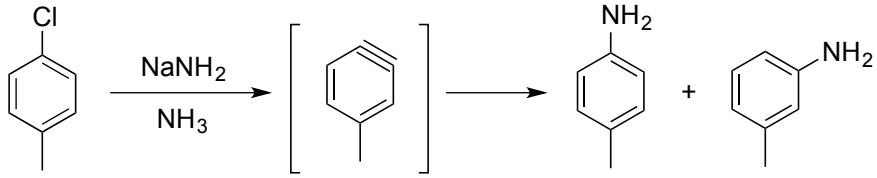
25. Benzene derivatives bearing electron-withdrawing groups yield Birch-reduction products in which the substituent does not reside on a double bond. This is driven by placing the carbanion intermediate adjacent to the electron-withdrawing group by which it is stabilized.



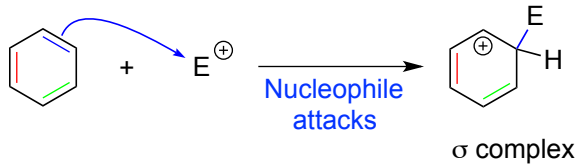
26. Chloride will serve as the leaving group in this nucleophilic aromatic substitution. The nitro groups, being electron-withdrawing, are activating for S_NAr, although they were deactivating for EAS reactions which have the opposite electronics. Ethoxide acts as the nucleophile and displaces chloride to yield the product.



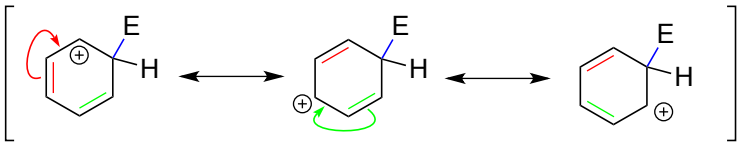
27. We know that this will be an elimination-addition reaction because of the absence of electron-withdrawing groups on the aromatic ring. In the presence of electron-withdrawing groups, S_NAr is a mechanistic possibility, but in their absence elimination-addition is more likely. A benzyne is formed through elimination, and the subsequent addition can occur at either the *meta* or *para* positions to yield two regioisomeric products.



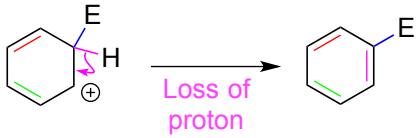
28. The reaction begins with the attack of a pi bond of the ring on the electrophile (E^+). This forms the sigma complex, which has one additional sigma bond relative to the substrate.



The positive charge of the sigma complex is delocalized to three sites on the ring.



The loss of a proton from the sp^3 hybridized carbon of the ring restores aromaticity.

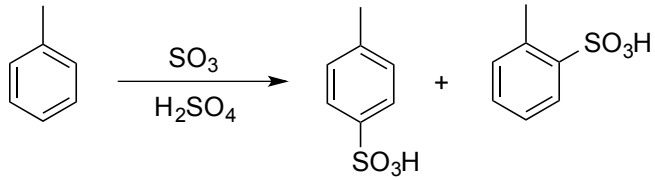


The five EAS reactions mentioned (halogenation, nitration, sulfonation, Friedel-Crafts alkylation, and Friedel-Crafts acylation) all follow the same mechanism because they differ only in how the potent electrophile is prepared. Once an

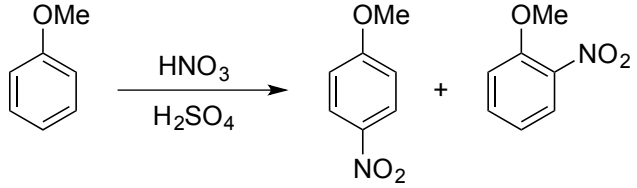
electrophile is formed, it doesn't really matter whether it is a nitronium ion or an acylium ion from a mechanistic standpoint. Each electrophile is attacked by the ring in the same fashion to form the same type of sigma complex, which loses a proton in the same way to reestablish aromaticity.

29.

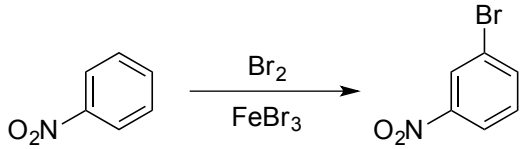
(a) This is a sulfonation reaction, which requires sulfur trioxide and sulfuric acid (also known as fuming sulfuric acid).



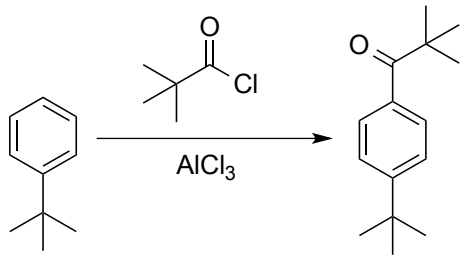
(b) This is a nitration reaction, requiring nitric and sulfuric acid.



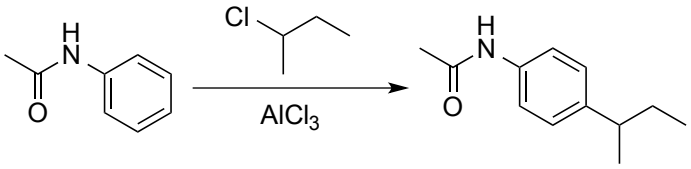
(c) This is a bromination reaction, which necessitates bromine and iron tribromide.



(d) To complete this Friedel-Crafts acylation, it is necessary to use the appropriate acid halide, as well as aluminum trichloride.

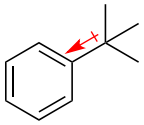


(e) For Friedel-Crafts alkylation, an appropriate alkyl chloride is used, as is aluminum trichloride.

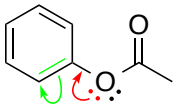


30.

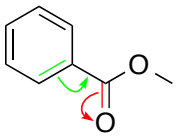
(a) We know that alkyl groups are electron donating, as highlighted by the dipole below. All electron-donating groups are activating for EAS.



(b) The sp^3 hybridized oxygen of the ester is conjugated to the ring, which means that it can donate a lone pair of electrons into the ring by resonance. This ring is therefore activated toward EAS.

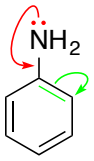


(c) The carbonyl of this ester is conjugated to the ring, which means that it can withdraw electrons from the ring through resonance. This ring is therefore deactivated toward EAS.

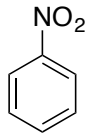


Compare parts (b) and (c). Notice how a simple reversal of the ester changes its activating/deactivating behavior. This is why it is best to consider fundamental principles, such as resonance, rather than attempting to memorize the behavior of each group. Groups that look very similar may actually have different attributes, which are easy to uncover by drawing a bit of resonance.

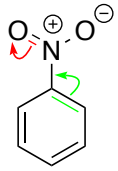
(d) The amino group is electron donating by resonance, which activates the ring toward EAS.



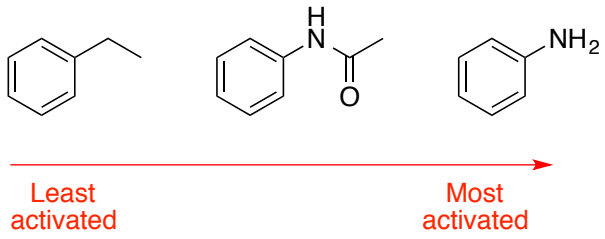
(e) This problem is another example of why it is better to draw structures and resonance to illustrate the nature of a group, rather than to attempt to memorize. Some students make the mistake of assuming that the nitro group behaves like the amino group (part d above) simply because the nitrogens in both groups are connected to two other atoms.



However, when the Lewis structure for the nitro group is drawn, you can see that it is totally different from the amino group. The nitro group withdraws electron density from the ring by resonance and induction, making it a deactivating group in EAS.

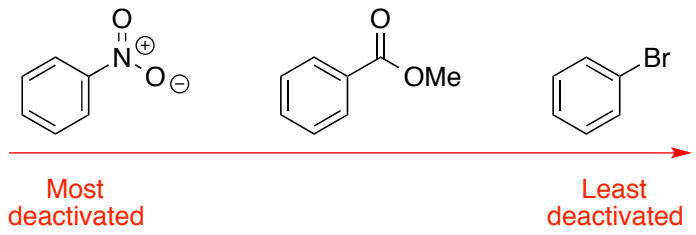


31. All of these rings are activated but to varying degrees. The ethyl group is electron donating but only through induction. Consequently, ethyl benzene is weakly activated. The amide can donate electron density into the ring by resonance, which is a more powerful activating effect. However, the activation by the amide nitrogen is tempered by the fact that its lone pair can also be delocalized into the carbonyl. Since the amide nitrogen's lone pair can be delocalized into both the ring and the carbonyl, the donation of electron density to the ring is only moderate. On the other hand, the amine of aniline has a lone pair that can be delocalized only into the ring. This results in a greater enhancement of electron density in the ring and consequently the most activated ring.



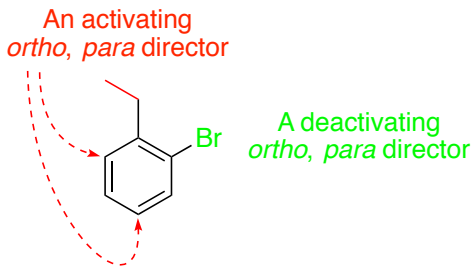
32. The nitro group is the most deactivating of the three because it can withdraw electron density through both induction and resonance. The positive charge on nitrogen results in an inductive electron withdrawal from the ring, while the nitrogen-oxygen pi bond is conjugated to the ring and results in electron withdrawal by resonance. The ester also withdraws electron density from the ring but only through resonance involving the carbonyl. It is therefore more moderately

deactivating. Finally, bromine is the least deactivating substituent because its electron withdrawal is merely through induction.

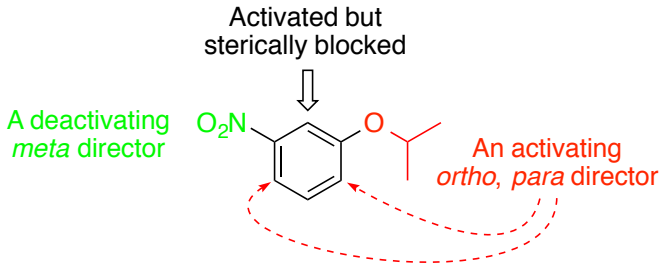


33. The primary guideline for rings with multiple substituents is that the most activating group on the ring controls the regiochemistry of EAS reaction.

(a) The ethyl group is activating, while the halogen is deactivating. Therefore, the ethyl group directs EAS to the positions *ortho* and *para* to itself. The *para* position is less sterically encumbered and would be the predominant site for reaction.

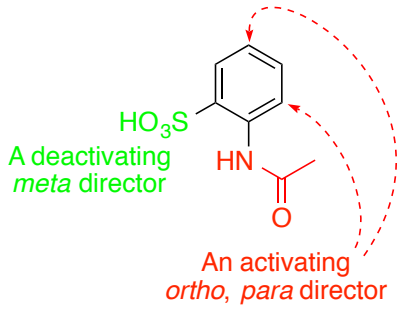


(b) The nitro group withdraws electron density from the ring, but the isopropoxy group can donate electron density to the ring by resonance. Therefore, the isopropoxy group is activating and controls the regiochemistry of EAS. It directs to the positions *ortho* and *para* to itself. However, the position between the two substituents is too sterically encumbered for reaction. The position *para* to the isopropoxy group suffers from the least steric hindrance, so most reaction would be expected at that site.

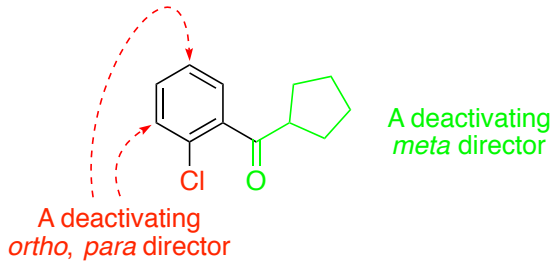


(c) The sulfonic acid group is electron withdrawing and therefore deactivating, but the amide can donate electron density to the ring through resonance, making it an activating group. The amide therefore controls the regiochemistry of EAS, directing

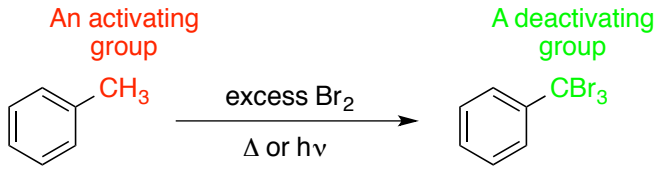
reaction to the positions *ortho* and *para* to itself. The *para* position is the most accessible, leading to the major product of EAS reaction.



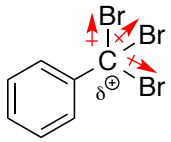
(d) The acyl group withdraws electron density from the ring by resonance and is therefore deactivating. The chlorine atom also withdraws electron density from the ring, so in this case both groups are deactivating. However, the halogen deactivates the ring to a lesser extent because its electron withdrawal is merely through induction. Consequently, the halogen (being weakly deactivating) is closer to being an activating group than the acyl group, which moderately deactivates the ring through resonance. The halogen controls the regiochemistry of EAS as a result, directing substitution to the sites *ortho* and *para* to itself.



34. As we know, the methyl group, like other alkyl groups, is electron donating by induction and therefore activating. However, the question is stating that exhaustive bromination converts this group into a deactivator. This might be puzzling at first glance because the tribromomethyl group could still be classified as an alkyl group.

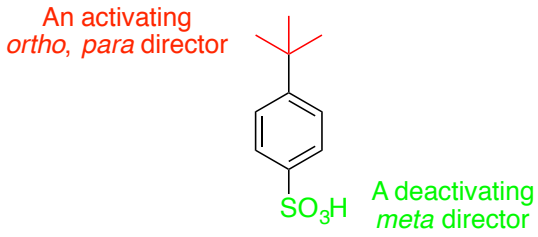


However, upon closer examination, the reason becomes clear. Each of the halogens withdraws electron density from the benzylic carbon, rendering it partially positive. As a consequence, the benzylic carbon will, in turn, pull electron density from the ring through induction and deactivate it.

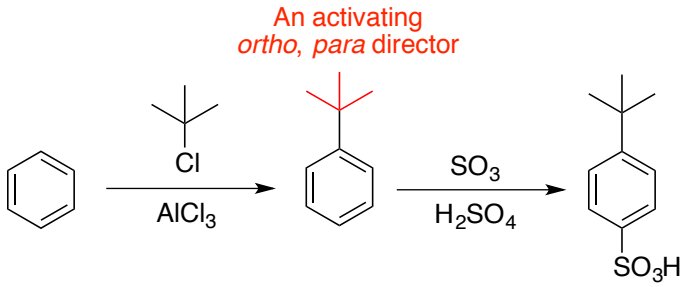


35.

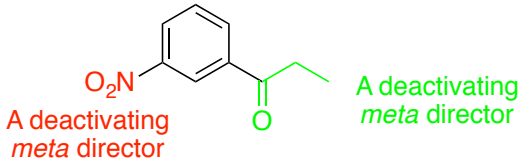
(a) It is always best to begin a synthesis problem with an analysis of the directing capabilities of the substituents on the target compound. In the first problem, the *tert*-butyl group is an activating *ortho*, *para* director, while the sulfonic acid group deactivates and directs *meta*.



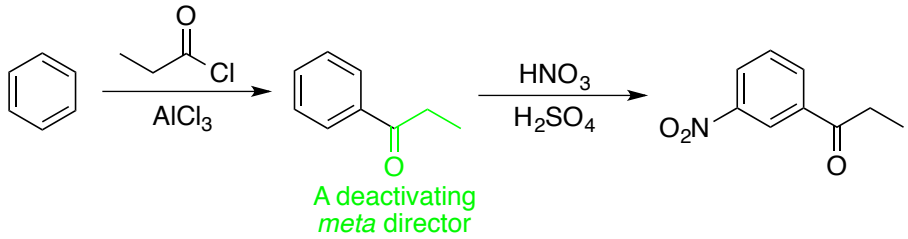
Given that the desired regiochemistry is *para*, the *tert*-butyl group should be placed on the ring first. It then directs the sulfonation to the desired location.



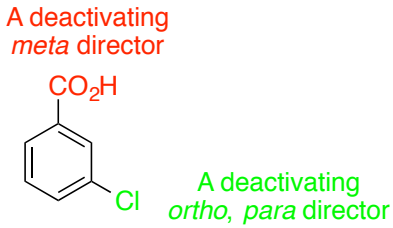
(b) In this target, we have two deactivating *meta* directors, so it might initially seem as though either can be placed on the ring first and allowed to direct the second EAS to the desired location. However, it is important to recall the limitations of the Friedel-Crafts reactions. They fail on nitrobenzene because the ring is too powerfully deactivated. As a result, we must first acylate.



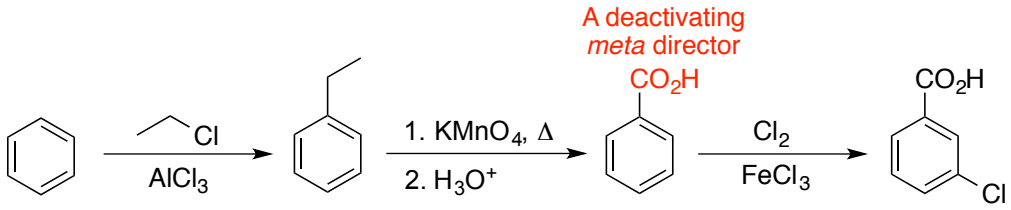
The acylation provides a ring with the reactivity and directing capability to not only successfully undergo nitration but also to place the nitro group in the desired location.



(c) In this question, the carboxylic acid is a deactivating *meta* director, while the halogen is also deactivating but directs to the *ortho* and *para* positions. Since the desired regiochemistry is *meta*, the carboxylic acid should be installed first.

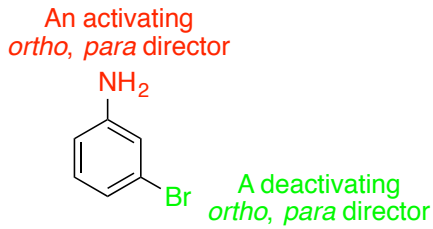


However, there is no single reaction to place a carboxylic acid on the ring. Instead, we must add the acid through a two-step sequence involving alkylation and benzylic oxidation. The alkylation can utilize many different alkyl groups. As long as the R group added to the ring has at least one benzylic hydrogen, it will be suitable for the subsequent oxidation. In this case, Friedel-Crafts alkylation was conducted with ethyl chloride in order to place an ethyl group on the ring. Its oxidation affords benzoic acid, which directs halogenation to the correct location.

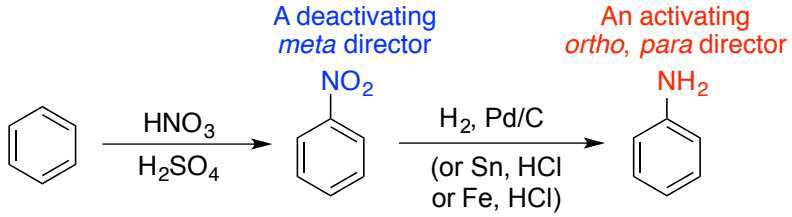


36.

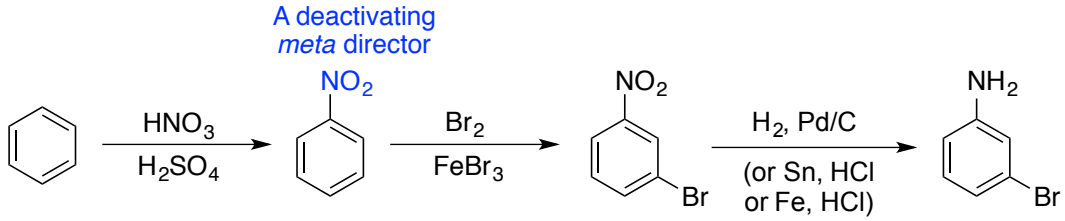
(a) This problem is an example of the seemingly impossible substituent pattern. Both the amino and bromo groups are *ortho*, *para* directors, so it is unclear how either could possibly direct substitution to the desired location.



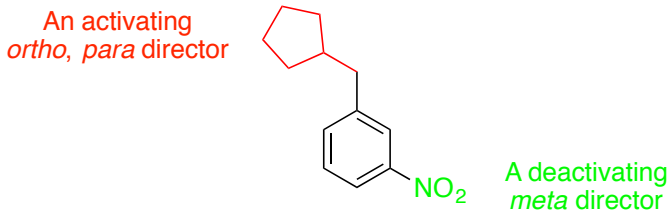
When this sort of situation arises, one of the groups must be installed via a multi-step sequence in which an intermediate provides the desired directing capability. In fact, we quickly notice that the amino group cannot be added directly to the ring. It is added through a two-step process: nitration and reduction.



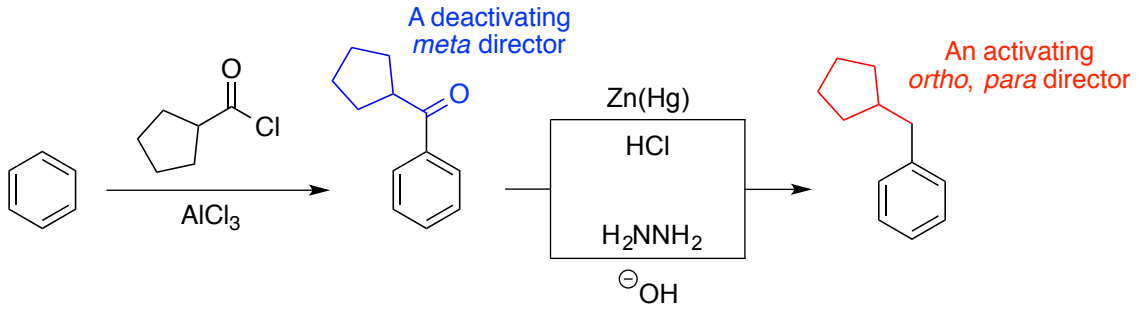
The key to solving this problem is recognizing that these two steps need not be conducted back-to-back. The intermediate, nitrobenzene, has the desired *meta* directing capability, so we can pause at that stage to exploit this fact. The bromine is installed in the desired location, and the final reduction affords the target molecule.



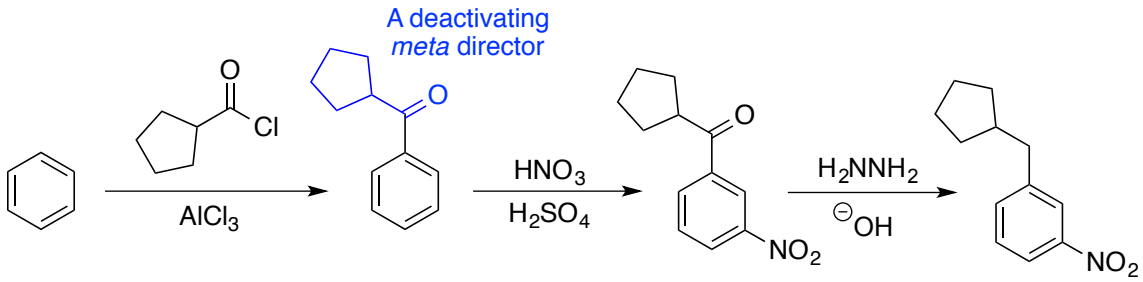
(b) At first glance, this problem may seem straightforward. The desired regiochemistry is *meta*, and there is a *meta* director on the target. So, it is tempting to install the nitro group and allow it to direct substitution to the desired location. However, one of the limitations of the Friedel-Crafts reactions is that they do not work on nitrobenzene since the ring is too highly deactivated.



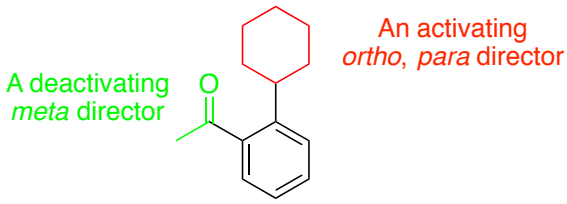
The dilemma then becomes how to attain the desired substituent pattern without ignoring an important limitation of the Friedel-Crafts reactions. We can resolve this conundrum by turning our attention to the alkyl group. Though it is an *ortho*, *para* director, alkyl groups can also be added to the ring via two steps: acylation and reduction. In fact, in this case where we wish to install a primary alkyl group, the two-step method is a necessity in order to avoid rearrangement.



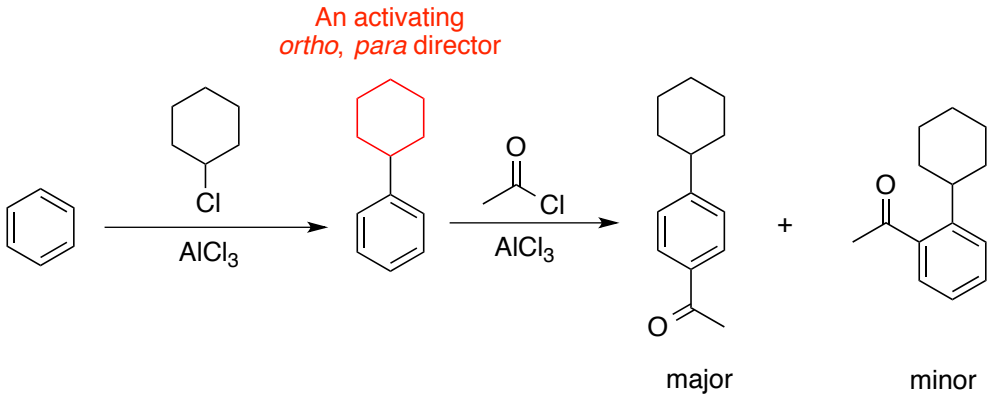
Again, the key to solving the problem is recognizing that these two steps do not need to be conducted back-to-back. We can pause after the acylation to take advantage of the acyl group's *meta* directing effect, which allows nitration to occur at the desired location. Then, a reduction, such as the Wolff-Kishner reaction, completes the synthesis.



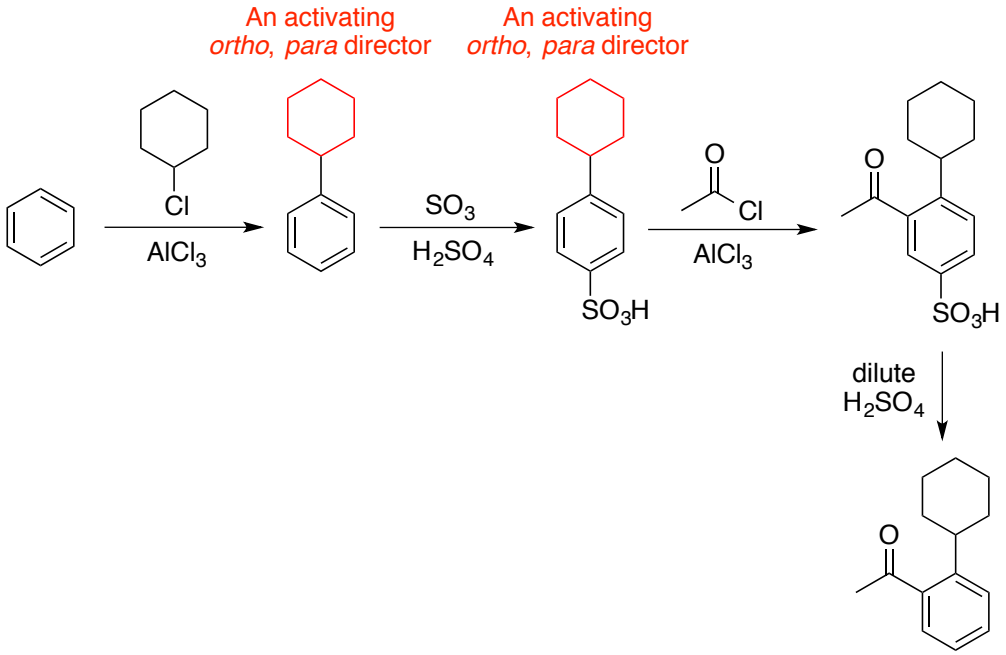
(c) In this instance, the alkyl group is *ortho*, *para* directing, while the acyl group is *meta* directing. The alkyl group has the ability to direct EAS to the desired location, so it should be placed on the ring first.



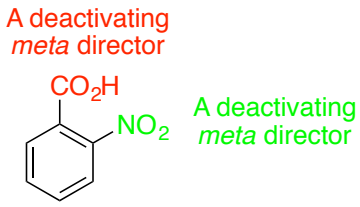
However, acylation will occur predominantly at the more sterically accessible *para* position, providing the target molecule as only a minor product. This outcome is undesirable.



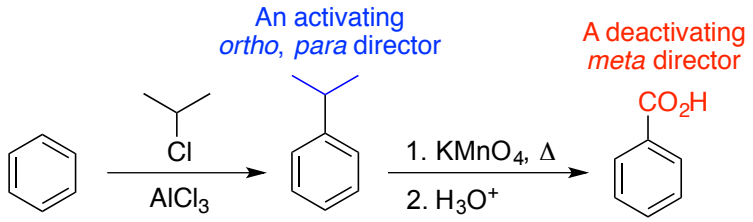
A blocking group can be used to improve the yield of the desired compound. After alkylation, sulfonation is directed *ortho* and *para*; however, the *para* product predominates for steric reasons. Then, acylation occurs at the only unoccupied, activated position, which is *ortho* to the alkyl group. Treatment with dilute sulfuric acid will remove the blocking group and complete the synthesis.



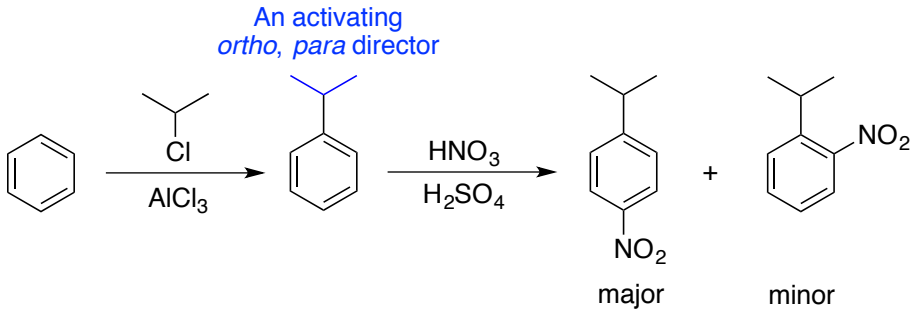
(d) In this case, both of the groups are deactivating *meta* directors. Since the desired substituent pattern is *ortho*, one of the groups must be installed via a multi-step sequence in which an intermediate has the desired directing effect.



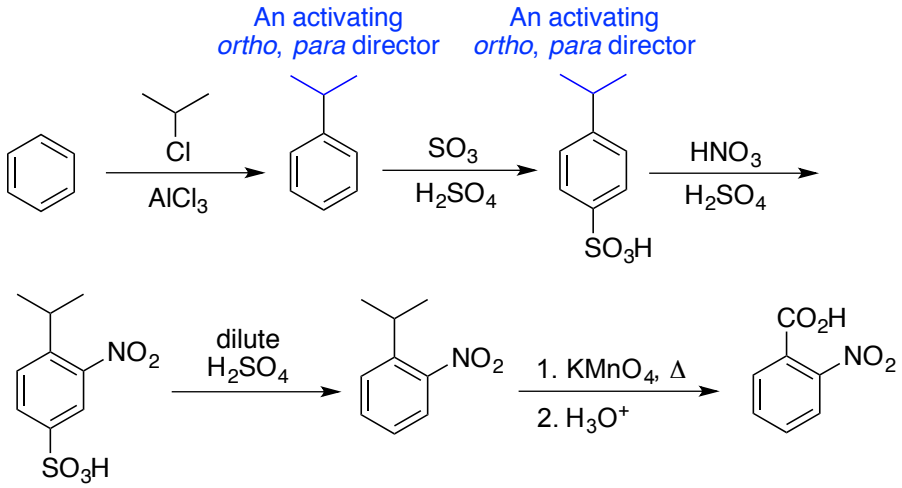
The nitro group can be added directly to the ring in a single step via nitration. However, such is not the case for the carboxylic acid. It must be placed on the ring over the course of two-steps: alkylation and benzylic oxidation.



The intermediate alkylbenzene has the desired directing effect; however, nitration will yield mostly *para* product for steric reasons. The desired *ortho* regiochemistry is obtained only as a minor product. Even if we decrease the size of the alkyl group to methyl, there will still be an appreciable amount of undesired *para* product.

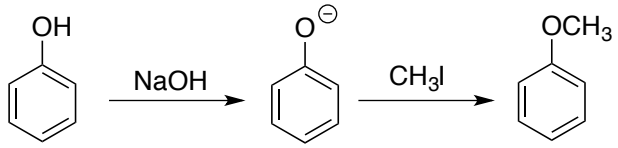


To circumvent this problem, we can employ a blocking group. Isopropylbenzene is sulfonated predominantly in the more accessible *para* position. Nitration then proceeds at the only unoccupied, activated position: *ortho* to the isopropyl group. Having served its purpose, the blocking group can now be removed using dilute sulfuric acid. Lastly, oxidation with potassium permanganate provides the desired compound, 2-nitrobenzoic acid.

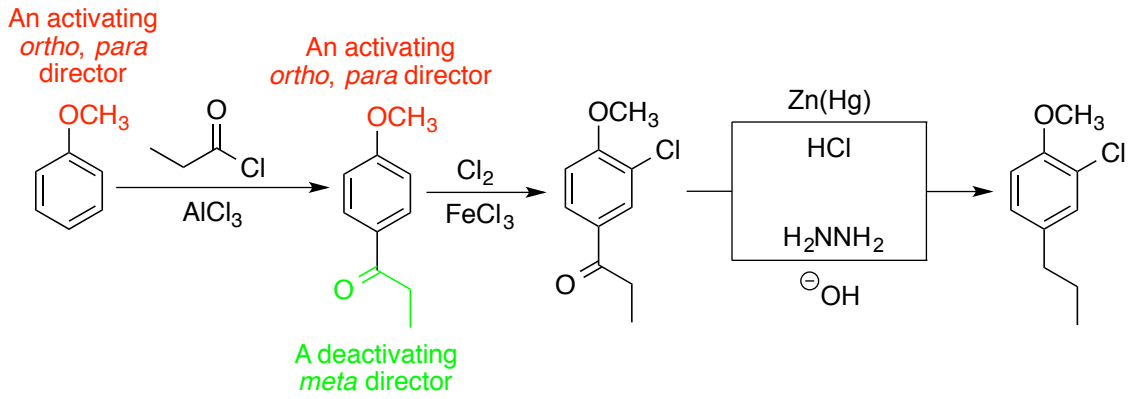


37.

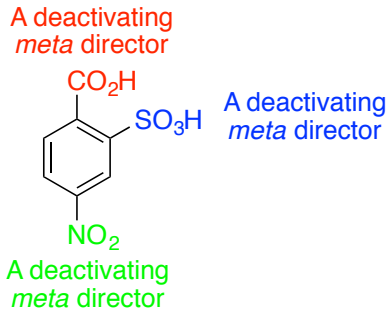
(a) The first thing that strikes us about this problem is that the hydroxyl group of phenol is not present anywhere on the target molecule. However, there is an oxygen in the methoxy group of the target, which suggests that the hydroxyl group was covalently modified to form the methoxy group. This can be easily accomplished using acid-base and substitution chemistry. We know that phenol is fairly acidic, so it can be deprotonated with a base such as hydroxide. The resultant phenoxide ion can serve as a nucleophile in S_N2 reaction with methyl iodide to yield anisole. This was essentially a Williamson ether synthesis (see Chapter 9 Section 7).



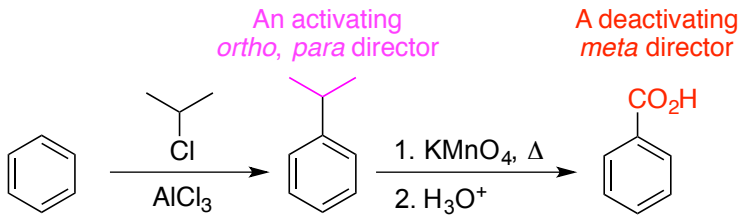
Anisole bears an *ortho*, *para* directing methoxy group, which can direct acylation in large part to the *para* position. Between the two substituents, the methoxy group controls the regiochemistry of further EAS reaction, but it is also convenient that the methoxy and acyl groups direct to the same location anyway. This is therefore a good point in the synthesis for chlorination. Finally, Clemmensen or Wolff-Kishner reduction provides the desired product.



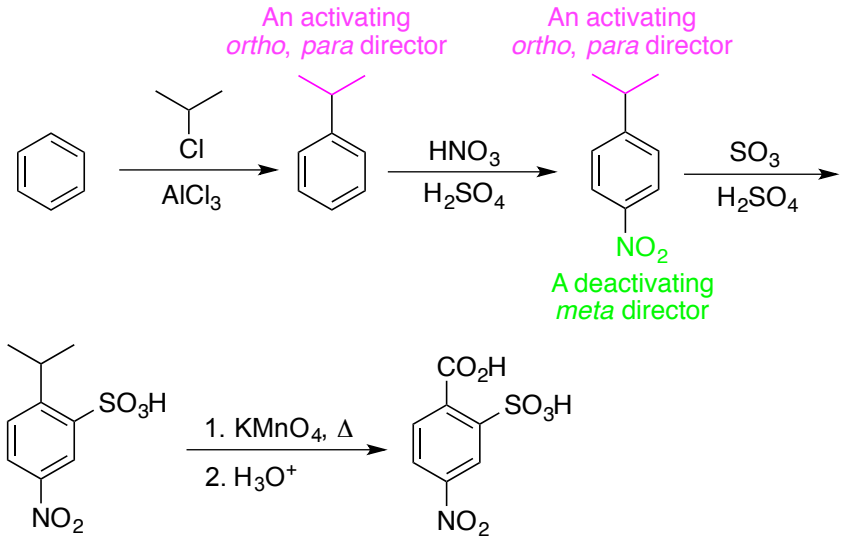
(b) The striking feature of this synthesis problem is that all three groups are *meta* directors, but the regiochemistry is not exclusively *meta*. Therefore, one of the groups must be installed through a multi-step sequence in which an intermediate has the needed directing capability.



Unlike the other two substituents, the carboxylic acid cannot be added directly to the ring. It is installed via alkylation followed by benzylic oxidation.

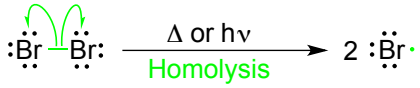


However, these two steps do not need to be conducted back-to-back. We can pause after alkylation to exploit the *ortho*, *para* directing effect of the isopropyl group. The next EAS reaction will occur predominantly at the *para* position due to steric considerations, so it should be nitration. The final EAS reaction, sulfonation, occurs at the only remaining activated center: *ortho* to the isopropyl group. Lastly, benzylic oxidation with potassium permanganate affords the target.



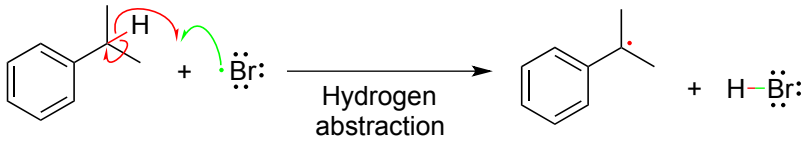
38. The reaction begins with initiation, in which the bromine-bromine bond of a few Br_2 molecules homolyzes upon exposure to heat or light. This generates a small quantity of bromine radicals.

Initiation:

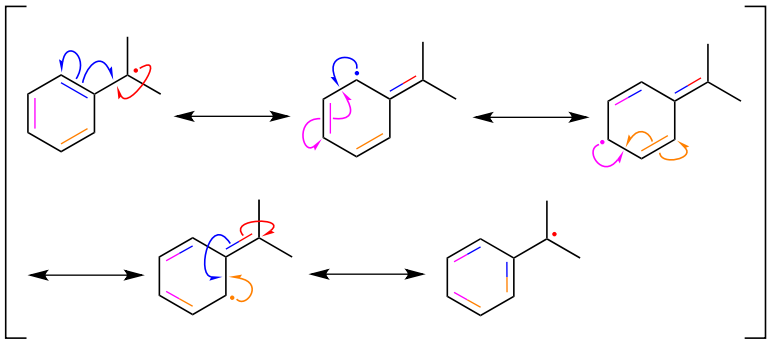


Next, a bromine radical abstracts a hydrogen atom from the benzylic position in the first propagation step.

Propagation step 1:

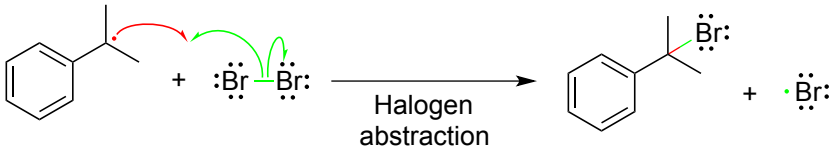


There are several hydrogens in the molecule, but only the benzylic hydrogen is abstracted because the resulting radical is conjugated to the ring and therefore resonance stabilized. This explains the regiochemistry of bromination (i.e., why it does not occur at any other locations).



Finally, the carbon-centered radical encounters an unreacted molecule of bromine, from which it abstracts a bromine atom to yield the product.

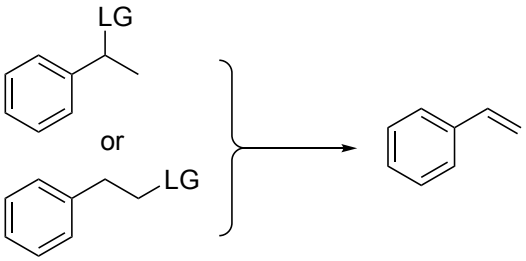
Propagation step 2:



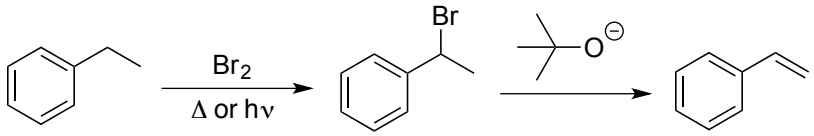
Termination steps are not especially important to this mechanism because the vast majority of product is formed during propagation step 2. The termination steps merely serve to explain the fate of the few radicals that remain at the end of the reaction when substrate has been mostly consumed. In a termination step, any two radicals from the mechanism can combine.

39.

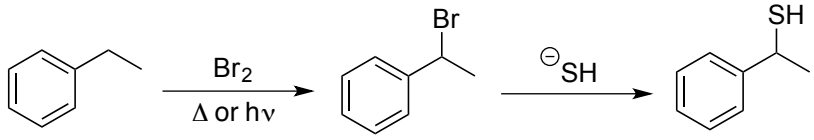
(a) This transformation leads to the formation of an alkene. We know that alkenes are commonly formed through elimination, which requires a leaving group (LG). This suggests one of the two following precursors to the target alkene.



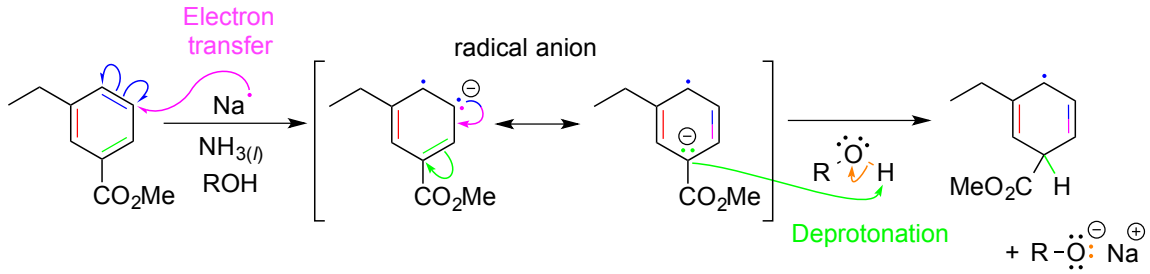
We haven't seen any ways to functionalize alkyl groups at sites distant from the ring; however, we do know that benzylic bromination can install bromine (a good leaving group) at the benzylic carbon. With a leaving group on the substrate, a strong base can incite E2 reaction. We can use a bulky base, such as *tert*-butoxide, to minimize the amount of substitution product.



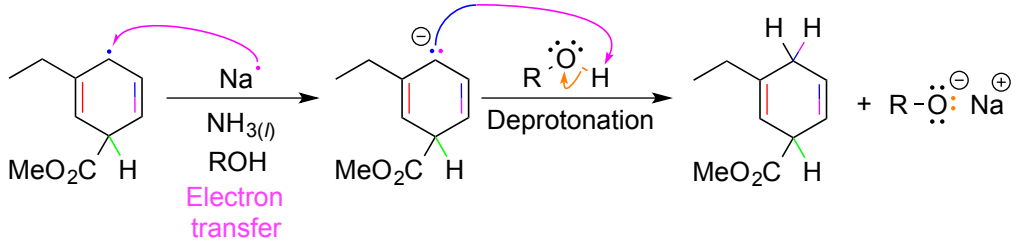
(b) While we have not seen a way to functionalize the benzylic center with sulfur directly, we can perform benzylic bromination to make that site reactive. Then, S_N2 reaction can convert the benzylic halide to the corresponding thiol.



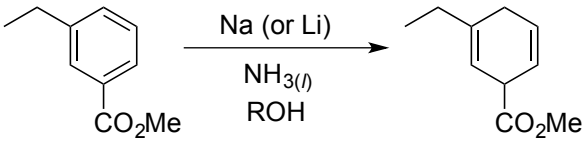
40. The reaction begins with the transfer of an electron from sodium to the substrate. This produces a radical anion, which possesses a resonance form that places the negative charge adjacent to the electron-withdrawing ester. This is a stabilizing resonance form and helps to explain the regiochemical outcome of the transformation. The radical anion then deprotonates the alcohol to afford a radical intermediate.



A second electron transfer takes place at this stage and converts the electron-deficient radical to a carbanion. Finally, the carbanion removes a proton from another molecule of alcohol to provide the neutral reaction product.



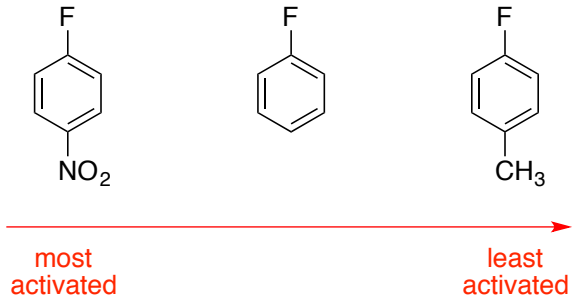
When considering the overall transformation, notice that the guidelines we developed earlier regarding the Birch reduction are both followed. Electron-donating groups reside on a double bond in the product, while electron-withdrawing groups do not reside on a double bond in the product.



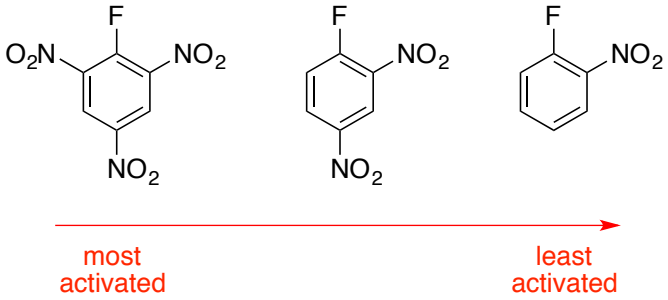
As you reexamine the mechanism, notice how this regiochemical outcome results from avoiding placement of the initial anion adjacent to the electron-donating alkyl group (which would be destabilizing) and instead placing the initial anion adjacent to the electron-withdrawing ester (which is stabilizing).

41.

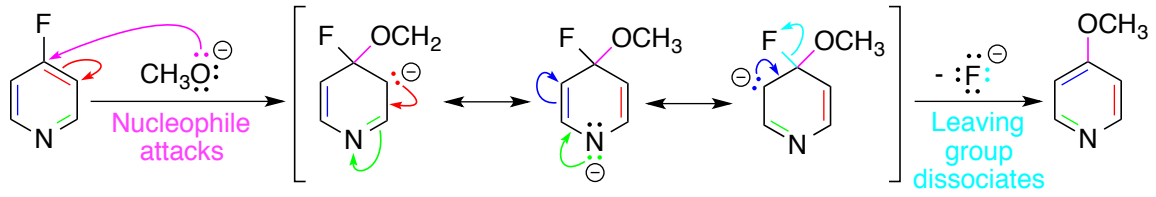
(a) In nucleophilic aromatic substitution (S_NAr), electron-withdrawing groups are activating. Recall that the ring acts as an electrophile in this mechanism, and a more electron-poor electrophile is a better electrophile. The nitro group is powerfully electron withdrawing, so it activates the ring toward S_NAr; however, the methyl group is electron donating and deactivates the ring toward this reaction.



(b) In this question, all of the rings bear electron-withdrawing groups. All that differs is the number of electron-withdrawing nitro groups. A greater number of electron-withdrawing groups will better stabilize the negative charge in the Meisenheimer complex.

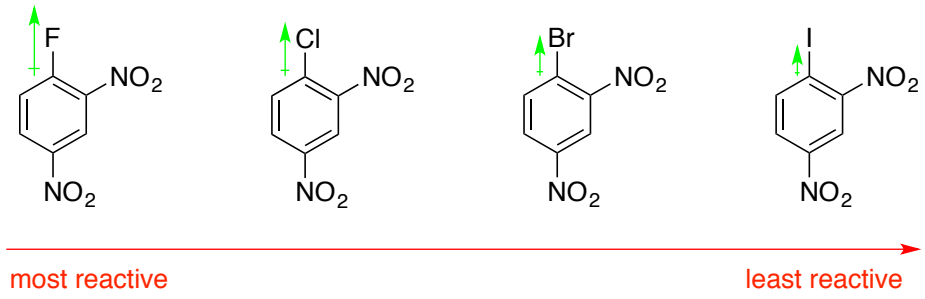


42. S_NAr reactions begin with the attack of a nucleophile on the carbon of the aromatic ring bearing a leaving group. This forms the resonance-stabilized Meisenheimer complex. The leaving group is ultimately ejected from this intermediate to yield the product.



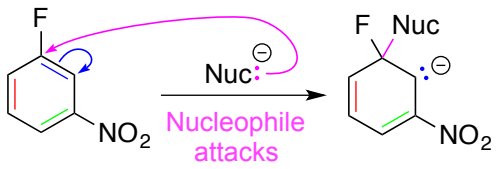
In this reaction, the Meisenheimer complex has one resonance form in which the negative charge is placed on nitrogen, which is more electronegative than carbon. Consequently, the nitrogen atom acts as electron-withdrawing group within the ring itself, thereby allowing S_NAr to proceed.

43. The rate-determining step of S_NAr reaction is the attack of the nucleophile on the ring to form the Meisenheimer complex. The more electrophilic the site of attack, the more quickly this step will proceed. Therefore, the most electronegative halogen, which creates the greatest δ^+ on the reactive center, gives the fastest reaction. The dipoles in the structures below get progressively smaller as we move from fluorine to chlorine to bromine to iodine, illustrating the diminishing δ^+ on the reactive carbon.

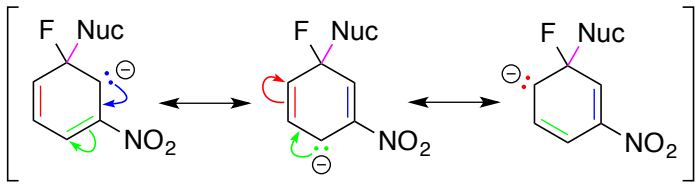


This answer may be surprising based on your knowledge of S_N1 and S_N2 reactions, where the trend would be reversed (i.e., an alkyl iodide would be the most reactive). However, it is important to remember that, in S_N1 and S_N2 reactions, the loss of leaving group is involved in the rate-determining step. Consequently, in those reactions, the better the leaving group, the more rapid the reaction. In S_NAr though, the loss of leaving group is not a part of the rate-determining step, so the electronegativity of the halogen ends up being more important than its leaving group ability.

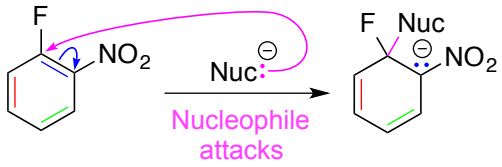
44. The answer to this question lies in the stabilization of the Meisenheimer complex. In the *meta* substrate, the initial nucleophilic attack affords the anionic Meisenheimer complex as expected.



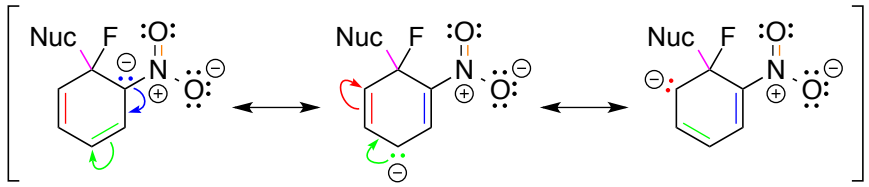
The anion is resonance stabilized by delocalization to a total of three locations on the ring. Notice, however, that the anion never resides on the carbon adjacent to the nitro group, and as a result, there is no resonance involving the nitro group.



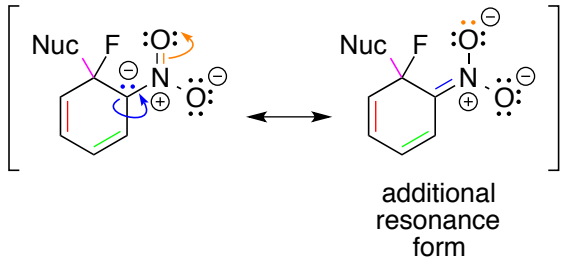
If we turn our attention to the *ortho* substrate, we see the anionic Meisenheimer complex being formed through nucleophilic attack as expected.



This anion is also delocalized onto three ring carbons, but one of the resonance forms places the negative charge next to the nitro group.



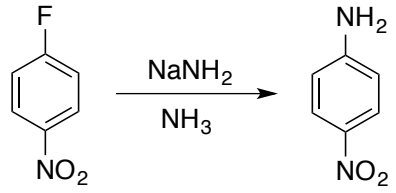
Therefore, there is an additional opportunity for delocalization. The anion can be moved into the nitro group, and this affords a particularly stable resonance form in which the negative charge resides on a more electronegative oxygen atom.



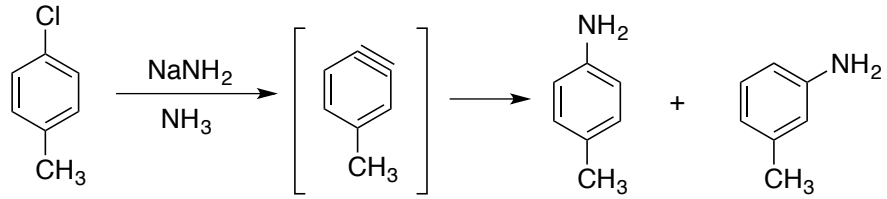
Due to this additional stabilizing resonance, the Meisenheimer complex formed from the *ortho* substrate is lower in energy. As a result of this lower-energy intermediate, the *ortho* substrate is more reactive.

45.

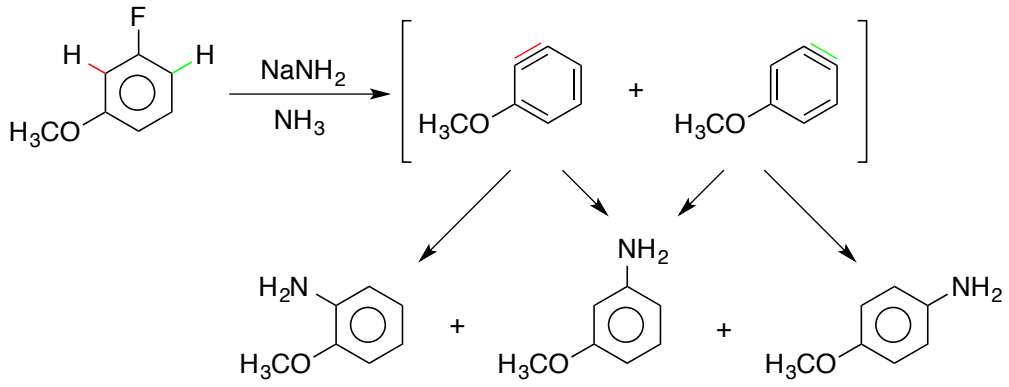
(a) This substrate bears an electron-withdrawing group, so it can undergo S_NAr. The nucleophile attacks the carbon bearing fluoride and ultimately displaces it, via the Meisenheimer complex.



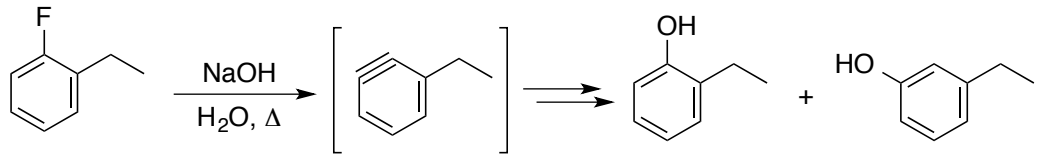
(b) Since this ring bears an electron-donating group, it will not readily undergo S_NAr. The anionic Meisenheimer complex would be too destabilized by the electron donation from the methyl group. Instead, the reaction proceeds via elimination-addition. A benzyne intermediate is formed, and addition then occurs at either carbon of the triple bond to afford two regioisomeric products.



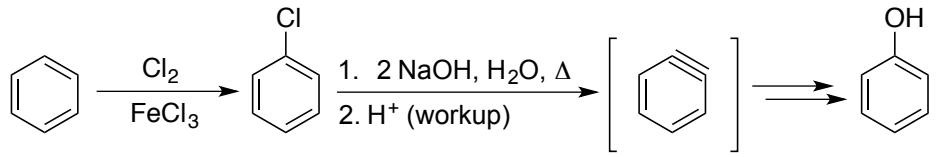
(c) This ring also bears an electron-donating (by resonance) group and is therefore more suitable for elimination-addition. In this instance, regioisomeric benzyne intermediates can be formed depending upon which β-proton is removed. Each of these intermediates can undergo addition at either carbon of the triple bond, leading to a total of three regioisomeric products.



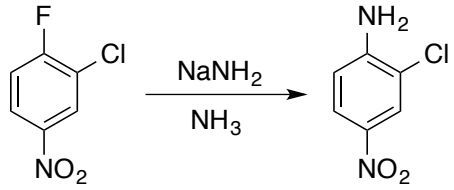
46. This ring is not suitable for S_NAr because of its electron-donating group. However, although sodium hydroxide is not as reactive as sodamide ($NaNH_2$), it can induce elimination-addition with sufficient heating. A benzyne intermediate is formed, and the nucleophile (hydroxide in this case) adds to either carbon of the triple bond, resulting in two regioisomeric phenols after workup.



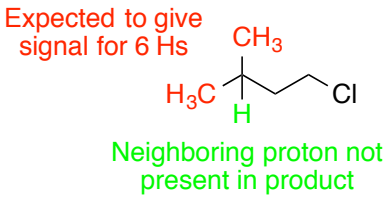
47. While we have not learned a reaction that will add a hydroxyl group directly to the ring, we have now seen in Problem 46 that phenols can be produced via elimination-addition. In order for the elimination to occur, a leaving group is needed, and we can install one onto the ring via EAS halogenation. Subsequent treatment with aqueous hydroxide at high temperature forms benzyne, and hydroxide adds to benzyne to yield phenol after workup.



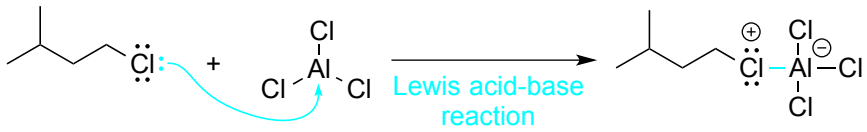
48. This ring possesses an electron-withdrawing nitro group and is therefore suitable for S_NAr. The question is which halide will be displaced during the reaction. Problems 43 and 44 give some insight into this issue, but so does the mass spectral data. If the product has M and M+2 peaks in a ratio of roughly 3:1, it suggests that the chlorine atom is still present. The isotope pattern results from the presence of ^{35}Cl and ^{37}Cl. Therefore, it is the fluorine atom that was displaced by sodamide.



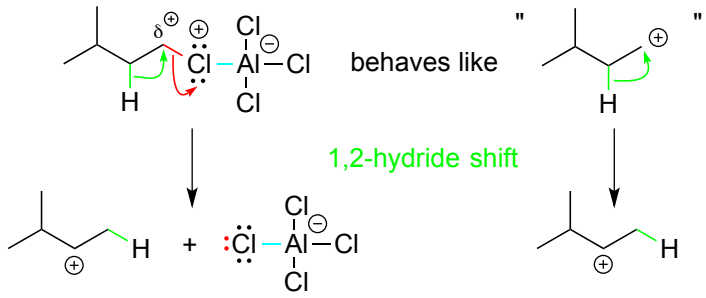
49. A striking feature of the NMR is that the signal for 6 hydrogens is a singlet. We expect this signal to correspond to the two methyl groups branching off of the same carbon; however, they have one neighbor in the reactant alkyl chloride that no longer appears to be present in the product.



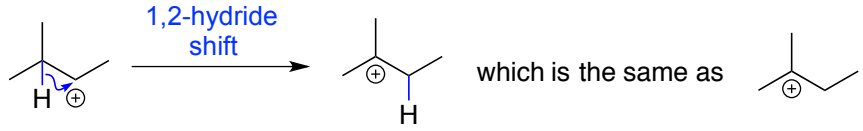
Noticing that the methyl groups and the neighbor in question all branch from a tertiary center should lead us to think about carbocation rearrangement, which plays a role in this reaction. The initial Lewis acid-base reaction forms the expected adduct.



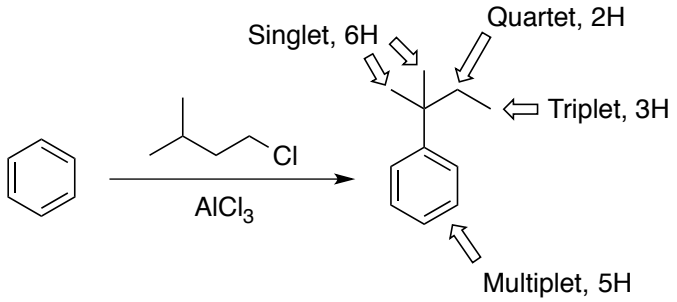
However, the significant partial positive charge on the primary center causes it to behave much as though it were a carbocation. Hence, rearrangement occurs.



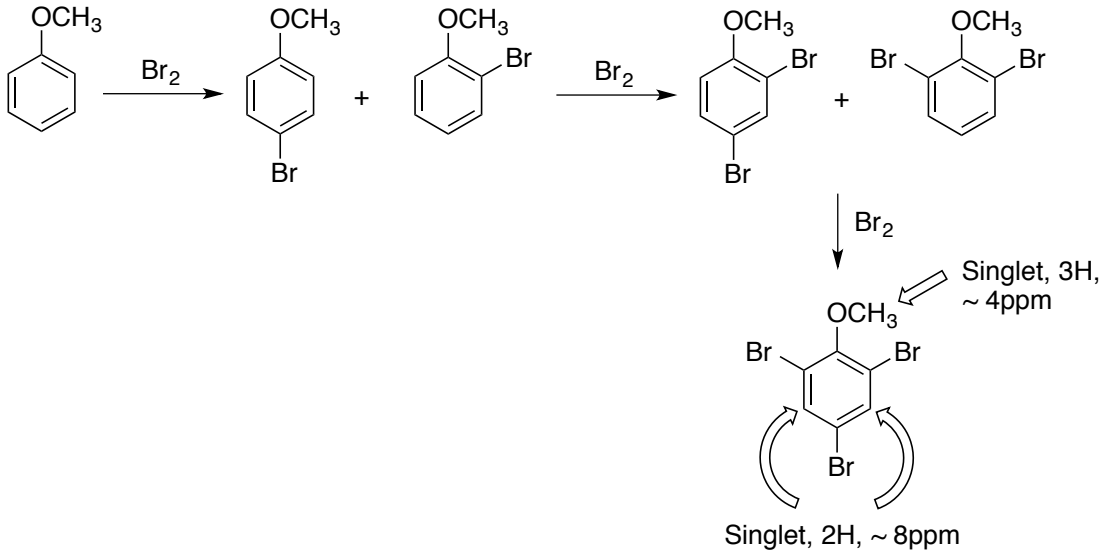
The secondary carbocation thus formed resides next to a tertiary center, which provides an opportunity for a second carbocation rearrangement. The resulting tertiary carbocation is the electrophile that is attacked by the aromatic ring in this Friedel-Crafts alkylation.



The reaction product produces an NMR spectrum consistent with the data provided.



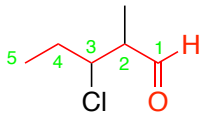
50. A key feature of the NMR data is the presence of only one signal for aromatic hydrogens that integrates for merely 2 protons. This shows that three of the ring hydrogens have been replaced, so bromination must have occurred three times. During each successive bromination event, the methoxy group will control the regiochemistry since it is the activating group. Therefore, the three bromine atoms will be placed *ortho* and *para* to the methoxy group, ultimately occupying all of these activated positions.



Solutions to Problems for Chapter 15: Aldehydes and Ketones

1.

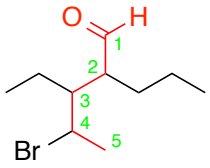
(a) The longest continuous carbon chain is five carbons in length, making the parent pentanal. The aldehyde carbon is implicitly C1, and the substituents are named and numbered accordingly.



3-chloro-2-methylpentanal

- Five carbon parent = pentane
- Replace "e" of suffix with "al"
- Number the aldehyde carbon as 1
- Add substituent names and numbers

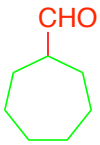
(b) In this problem, it may be tempting to select the horizontal seven-carbon chain as the parent. However, that chain does not contain the aldehyde. There are three five-carbon chains containing the functional group. The one with the largest number of substituents is the preferred parent. The aldehyde receives an implied locant of 1, and the substituents are named and numbered accordingly.



4-bromo-3-ethyl-2-propylpentanal

- Five carbon parent = pentane
- Replace "e" of suffix with "al"
- Number the aldehyde carbon as 1
- Add substituent names and numbers

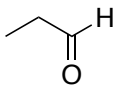
(c) In this example, the aldehyde is pendent to a ring. Consequently, the ring is named, and the word "carbaldehyde" follows.



cycloheptanecarbaldehyde

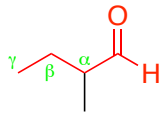
2.

(a) This three-carbon aldehyde can be termed "propionaldehyde."



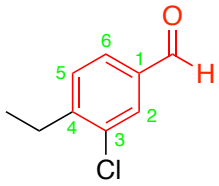
propionaldehyde

(b) A four-carbon aldehyde has the common name "butyraldehyde." Greek letters may be used to describe the location of substituents. The α carbon is adjacent to the carbonyl carbon, making this α-methylbutyraldehyde.



α-methylbutyraldehyde

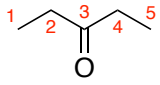
(c) Benzaldehyde is the parent in this molecule. It is numbered to as to give the carbon bearing the aldehyde the locant 1. Then, the ring is numbered clockwise in order to provide the lowest possible number for the first substituent.



3-chloro-4-ethylbenzaldehyde

3.

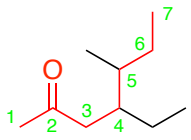
(a) In this simple example, the parent is a pentanone; however, a number is also needed to indicate the location of the ketone on the parent carbon chain, making this 3-pentanone.



3-pentanone

- Five carbon parent = pentane
- Replace "e" of suffix with "one"
- Number so as to give the ketone's carbonyl carbon the lowest possible number

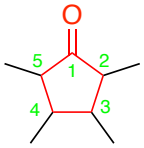
(b) It is sometimes tempting to simply select the chain drawn horizontally as the parent; however, in this case, that chain has only six carbons. There is a longer chain containing the parent, so this is a heptanone. The parent is numbered so as to give the ketone the lowest possible number. That number is added to the name, along with names and numbers for the substituents.



4-ethyl-5-methyl-2-heptanone

- Seven carbon parent = heptane
- Replace "e" of suffix with "one"
- Number so as to give the ketone's carbonyl carbon the lowest possible number
- Add substituent names and numbers

(c) In this instance, the parent is a cyclic ketone. Cyclic ketones do not need a number to place the carbonyl; wherever it is placed on the ring is assumed to be C1. The substituents receive the same numbers whether the numbering is clockwise or counterclockwise. The four methyl groups are condensed into the designation "tetramethyl," and each one is given a number.

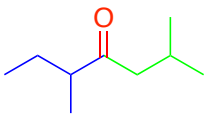


2,3,4,5-tetramethylcyclopentanone

- Five carbon, cyclic parent = cyclopentane
- Replace "e" of suffix with "one"
- Number so as to give the ketone's carbonyl carbon the lowest possible number
- Add substituent names and numbers

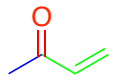
4.

(a) The common names for ketones are derived from the names of the two alkyl groups connected to the carbonyl carbon placed before the word "ketone." In this instance, the two alkyl groups are *sec*-butyl and isobutyl. Only the prefixes iso, cyclo, and neo are used in alphabetization, so we are comparing the "b" of *sec*-butyl to the "i" of isobutyl.



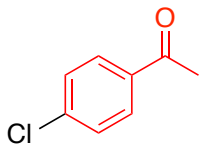
sec-butyl isobutyl ketone

(b) To name this ketone, we must remember from the alkenes chapter that the smallest alkene-containing substituent is known as the vinyl group.



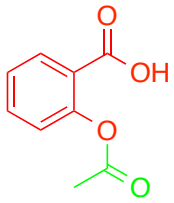
methyl vinyl ketone

(c) In this example, acetophenone is the parent. Since the halogen is opposite the acyl group on the ring, this molecule can be named as *para*-chloroacetophenone.



para-chloroacetophenone

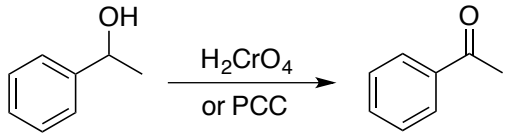
5. We are told that aspirin is salicyclic acid to which an acetyl group has been added. Furthermore, the problem states that the acetyl group is added specifically to the phenol when aspirin is made. These facts allow us to derive the structure of aspirin. The proton of the phenol is replaced by an acetyl group.



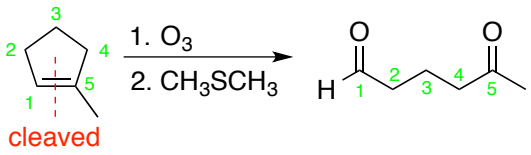
acetylsalicylic acid

6.

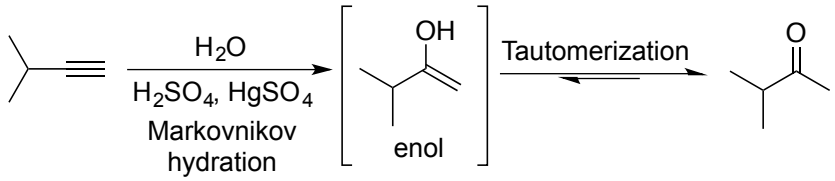
(a) Secondary alcohols can be oxidized to ketones using either chromic acid or PCC. Chromic acid is prepared from chromium trioxide or sodium dichromate and sulfuric acid.



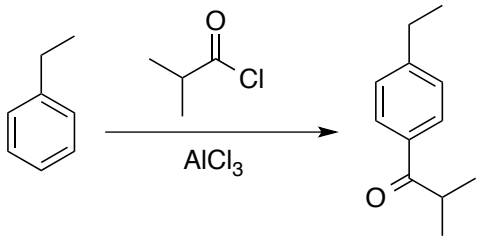
(b) Alkenes can be converted to aldehydes and/or ketones via ozonolysis. In this instance, the cycloalkene is cleaved to provide both an aldehyde and a ketone, which are tethered to one another by a three-carbon (C2 – C4) bridge.



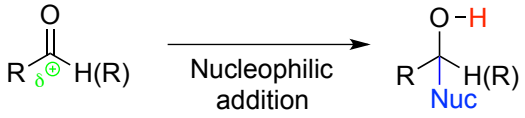
(c) Terminal alkynes are transformed into methyl ketones through Markovnikov hydration. The initial hydration product is an enol, which subsequently tautomerizes to yield the ketone.



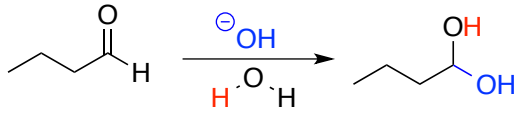
(d) This Friedel-Crafts acylation necessitates an acid chloride and aluminum trichloride. The *para* product is expected to predominate for steric reasons, but some of the *ortho* isomer would be produced as well.



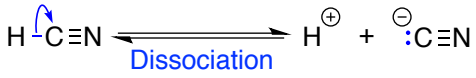
7. Recall that, regardless of the mechanism (acidic vs. basic conditions), the pattern of nucleophilic addition is the introduction of a nucleophile to the carbonyl carbon and a proton to the carbonyl oxygen. In each part below, we merely need to identify the nucleophile in order to answer the question.



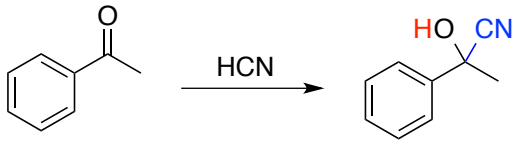
(a) Here, the nucleophile is clearly hydroxide. It is added to the carbonyl carbon, and a proton is added to the carbonyl oxygen.



(b) In this part, the nucleophile is less obvious. However, if we consider the structure of HCN, it is possible for dissociation to occur to provide a proton and the nucleophile cyanide.



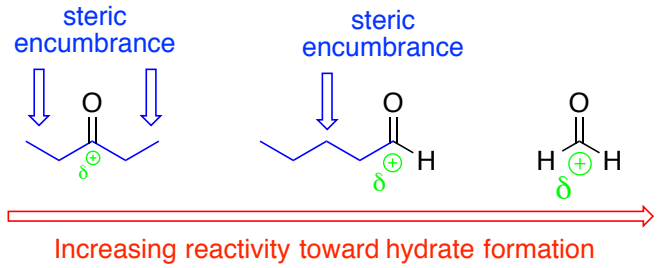
Therefore, cyanide adds to the carbonyl carbon as the nucleophile, and a proton is added to the carbonyl oxygen.



8. At the beginning of this section, it was noted that "The position of equilibrium depends on the electrophilicity of the carbonyl carbon and the steric encumbrance around it. As a result, aldehydes are more likely to form hydrates than ketones."

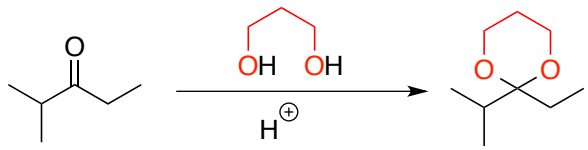
The greater the δ^+ on the carbonyl carbon, the more effectively it draws in a nucleophile. This makes hydrate formation more favorable. Additionally, the less hindered the carbonyl is, the more facile nucleophilic attack will be. Consequently, the compound with the largest δ^+ and the least steric hindrance will form the most hydrate.

Formaldehyde has the largest δ^+ since it bears no electron-donating R groups. Similarly, formaldehyde has the least steric hindrance due to the absence of R groups. Therefore, this compound is the most reactive in hydrate formation.

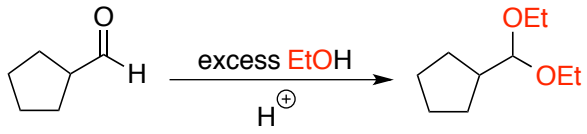


9.

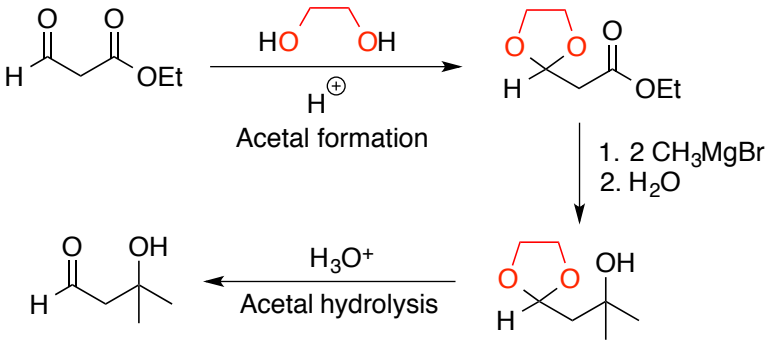
(a) Since the reagent used in this transformation is a diol, a cyclic acetal will be formed.



(b) This reaction leads to the formation of a diethyl acetal. The use of excess alcohol drives the reaction to completion.

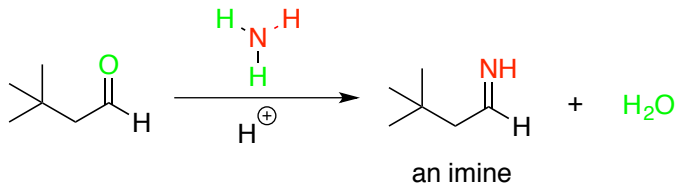


(c) In this problem, we must first select the reagents needed to prepare the cyclic acetal. Making a cyclic acetal necessitates a diol. The number of carbons between the two alcohols is dictated by the length of the bridge in the desired cyclic acetal, which is two carbons in this case. Then, in the last step of this sequence, aqueous acid hydrolyzes the acetal, unveiling the original aldehyde functional group.

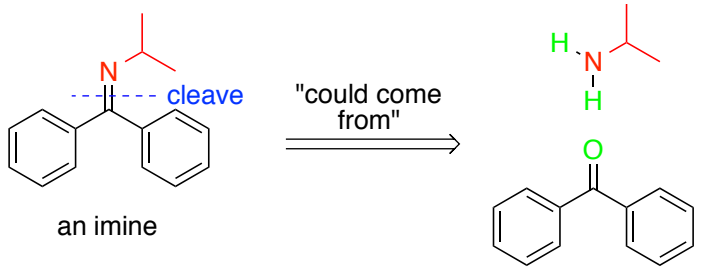


10.

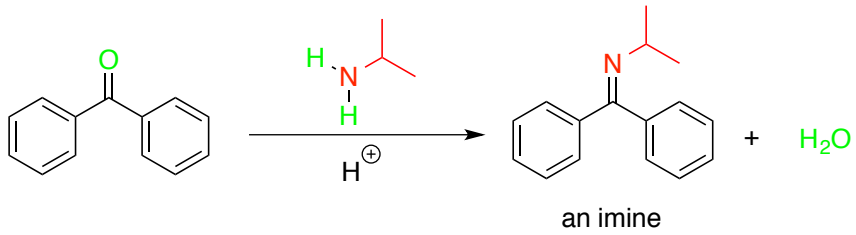
(a) In this instance, we are asked to predict the reaction product. The treatment of aldehydes or ketones with ammonia leads to the formation of an imine. As we saw in this section, a molecule of water is lost as a consequence of the mechanism of the reaction.



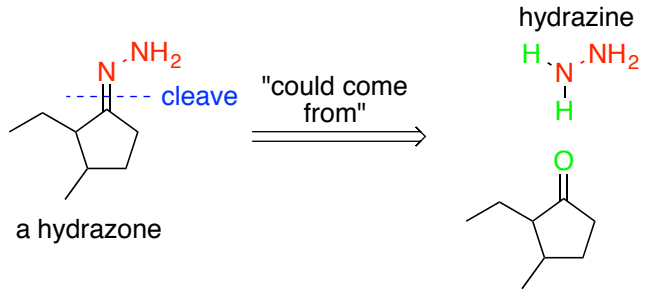
(b) Similarly, we saw in this section that aldehydes or ketones can undergo reaction with primary amines (rather than ammonia) to yield imines as well. The reaction also occurs with the loss of water. To solve a problem like this, you can envision cleaving the carbon-nitrogen double bond and separating the halves of the target molecule. The nitrogen's valence is satisfied by the addition of two hydrogen atoms to deduce the reagent's structure. The carbon's valence is satisfied by the incorporation of a carbonyl oxygen, and this provides the reactant's structure.



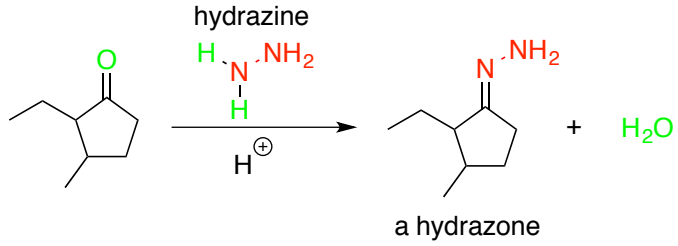
In the forward sense, the reaction appears as follows.



(c) In this problem, a hydrazone is prepared. As we saw in part (b) above, a little retrosynthesis assists with the selection of the necessary reagent. We imagine cleaving the carbon-nitrogen double bond and separating the two halves of the molecule. The carbon becomes a carbonyl carbon and matches the reactant with which we were provided. The nitrogen's valence is filled using hydrogens. In this way, we have derived the structure of the needed reagent, hydrazine.

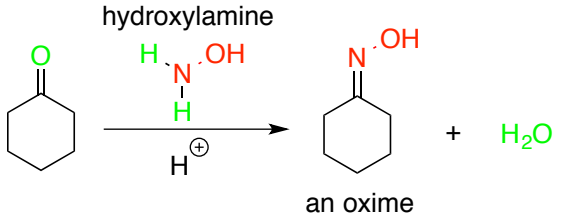


As we saw at the end of this section, hydrazine can be used to prepare a hydrazone. The reaction is directly analogous to imine formation.

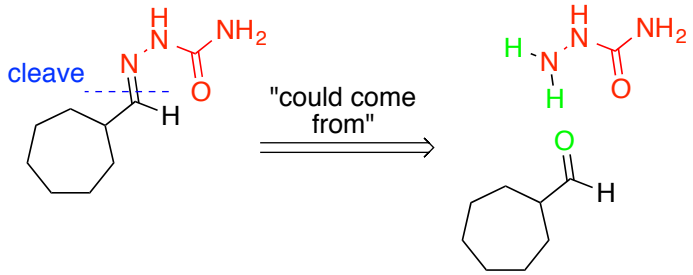


(d) In this question, we are simply predicting the product of the transformation. Recall that, even when an unusual reactant (such as hydroxylamine) is used, the

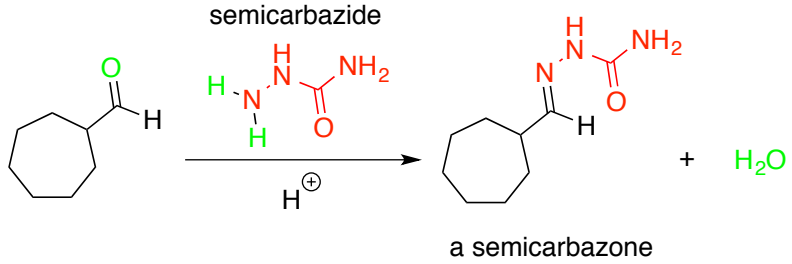
reaction is very similar to imine formation. Water is lost as the carbon-nitrogen double bond is created. In this instance, an oxime is prepared.



(e) A brief retrosynthesis will help us with the selection of the proper reagent for this transformation, which is unlike any of the others that we have seen in this section. Nevertheless, the method used in the parts (b) and (c) works equally well here. Imagine cleaving the carbon-nitrogen double bond and sliding the two halves of the molecule apart. The carbon becomes a carbonyl carbon, and we derive the structure of the reactant we were given. The nitrogen's valence is filled with hydrogens to deduce the structure of the necessary reagent.



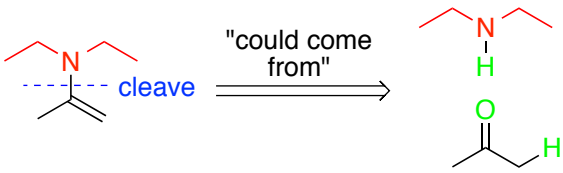
Although this reagent, which is known as semicarbazide, is different from any of the others we've used thus far, the reaction mechanism is essentially identical to that for imine formation. Semicarbazide combines with the aldehyde to form a product known as a semicarbazone, and water is lost in the process.



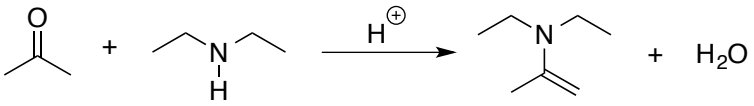
11. During enamine formation, the bond between nitrogen and the alkene carbon is forged. As we saw in this section, the mechanism proceeds with the eventual loss of water. A proton is lost from nitrogen and the position α to the carbonyl. Additionally, the carbonyl oxygen is lost as part of water.

Therefore, in each of the following examples, we imagine cleaving the nitrogen-to-alkene bond. The two halves of the target enamine are then separated. Nitrogen's valence is filled with a proton. The carbon that was bonded to nitrogen is the site of the original carbonyl, and its α position is the site of the proton lost in the final step of the mechanism.

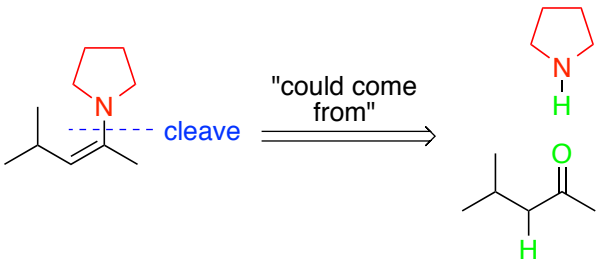
(a) As stated in the introduction to this solution, the nitrogen-to-alkene bond is retrosynthetically cleaved. The halves are separated. Nitrogen's valence is filled with a proton, and the carbon that was bonded to nitrogen is the site of the original carbonyl.



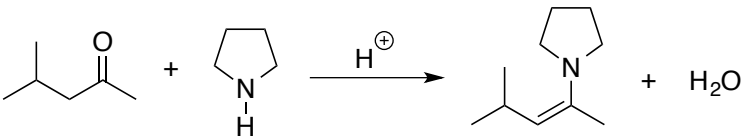
Written in the forward sense, the enamine preparation would look like this.



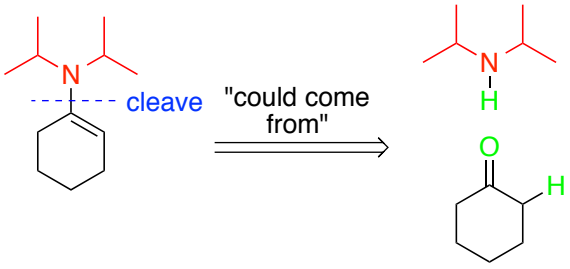
(b) As was noted in the introduction to this problem's solution, the nitrogen-to-alkene bond is broken retrosynthetically. The halves are separated to derive the original secondary amine and carbonyl-containing substrate.



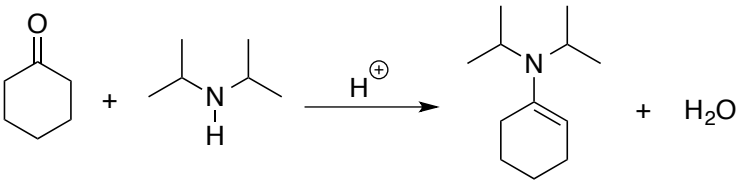
The reaction to prepare this enamine is as follows.



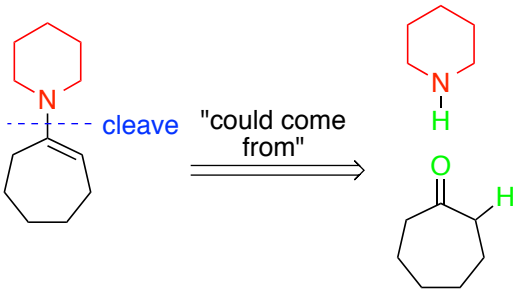
(c) As stated at the outset of this solution, we begin by imagining scission of the nitrogen-to-alkene bond. Then, separate the halves to provide the structural basis for the original secondary amine and carbonyl-containing compound.



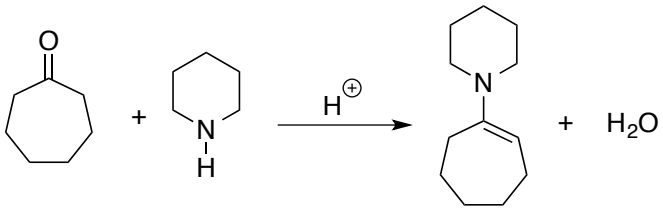
The enamine synthesis is as follows.



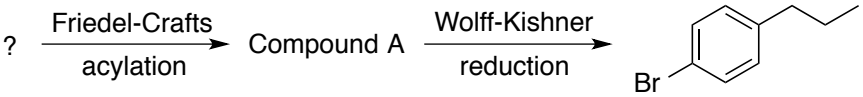
(d) As noted at the outset of this problem's solution, it is best to begin to retrosynthetically cutting the nitrogen-to-alkene bond. The resultant halves are separated to derive structures of the necessary reactants.



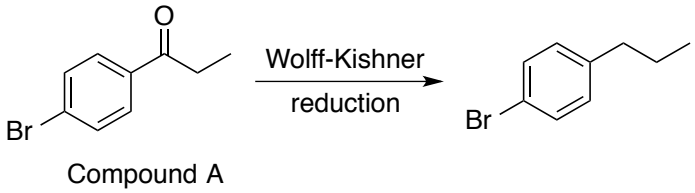
The reaction to prepare this enamine is as follows.



12. As with any word problem, we are usually well served by compiling the information given in a graphical format. We are told that Compound A is the product of Friedel-Crafts acylation of some unknown precursor. Additionally, we are told that Wolff-Kishner reduction of Compound A affords 1-bromo-4-propylbenzene.

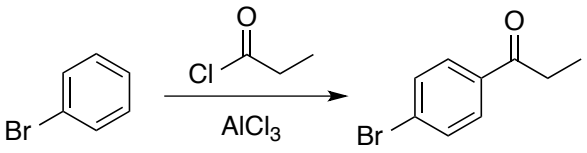


Working backwards from the Wolff-Kishner reduction product, we can deduce the structure of Compound A. It must have a carbonyl that is reduced by the Wolff-Kishner reaction. Furthermore, if Compound A derived from Friedel-Crafts acylation, then that carbonyl must be adjacent to the ring.



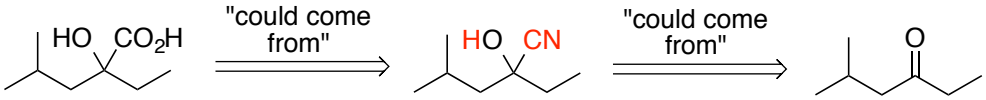
Compound A

The Friedel-Crafts reaction to form Compound A must therefore utilize bromobenzene as the reactant.

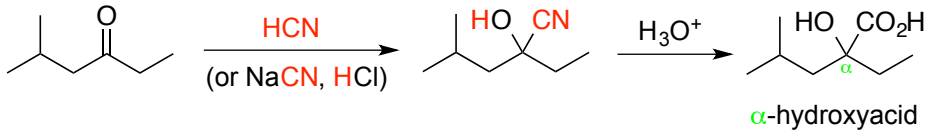


Compound A

13. As we just saw at the end of this section, an α-hydroxyacid can be prepared from the corresponding cyanohydrin. Cyanohydrins, in turn, are prepared by the net addition of HCN across a carbonyl π bond. This train of thought leads us to a suitable ketone.



The synthesis would entail treating the ketone with HCN (or NaCN and HCl) in order to prepare the cyanohydrin via nucleophilic addition. Then, hydrolysis in aqueous acid converts the cyanohydrin to the α-hydroxyacid.

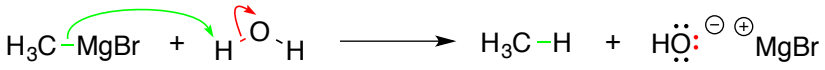


α-hydroxyacid

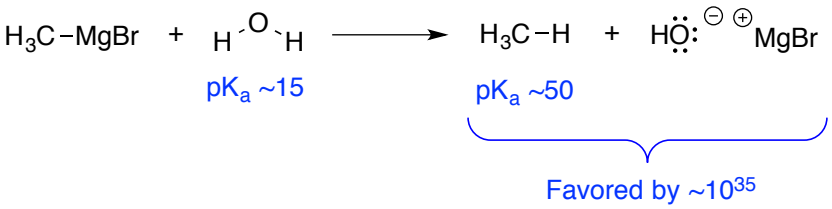
14.

(a) Methylmagnesium bromide behaves as though it were a methyl carbanion. This means that it is quite a strong base.

If exposed to water, methylmagnesium bromide will undergo a Brønsted-Lowry acid-base reaction. It deprotonates water to afford methane. Hydroxide is also produced and forms an ionic bond with the magnesium bromide cation. This type of reaction is typically undesired because the reactivity of the Grignard reagent has been quenched by converting it to the alkane.



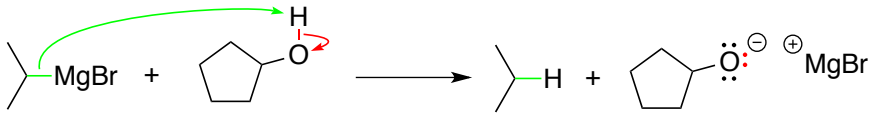
The pK_a of methane is ~50, while the pK_a of water is ~15. Therefore, the products are favored by $\sim 10^{35}$! Recall that equilibrium favors the side with the weaker acid (which has the higher pK_a value) and that this side is favored by 10 to the difference in the pK_a values.



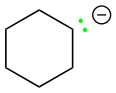
Note that the green arrow begins at the green σ bond. The arrow must begin at the site where the electrons used in the transformation actually reside. If the arrow is drawn from carbon or magnesium, it is incorrect because neither atom possesses lone pair electrons that could be used in this reaction.

(b) Isopropylmagnesium bromide behaves as though it were the isopropyl carbanion because the electrons in the carbon-magnesium bond are polarized toward carbon.

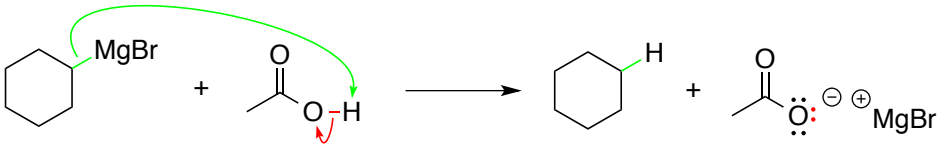
Given the high electron density on this carbon, it serves as a strong base. Alcohols are roughly as acidic as water [see part (a) above], meaning that cyclopentanol can serve as a proton source. The Grignard reagent's reactivity is quenched as it is converted to propane, and an alkoxide is the byproduct.



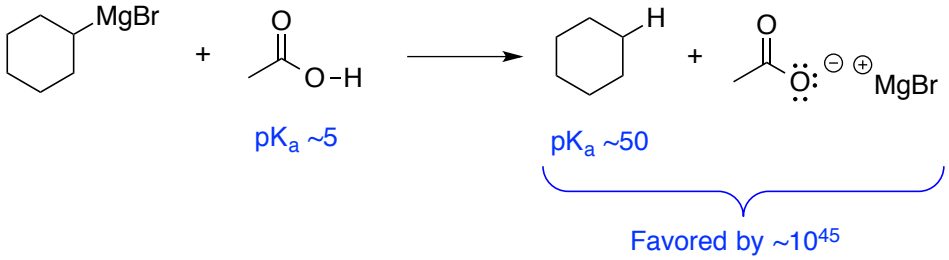
(c) This Grignard reagent behaves as though it were the cyclohexyl carbanion. As a result, it is quite basic.



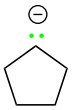
Since carboxylic acids are quite acidic, a Brønsted-Lowry acid-base reaction ensues. This destroys the reactivity of the Grignard reagent by converting it to cyclohexane. The carboxylate is a byproduct.



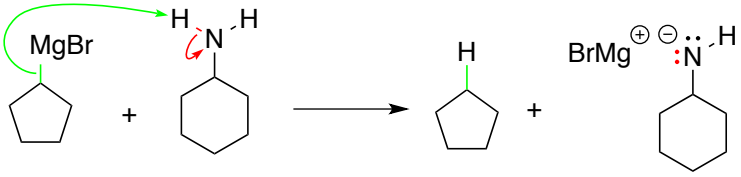
Since carboxylic acids have a pK_a of ~5 and alkanes have a pK_a of ~50, the products are favored by about 10^{45}!



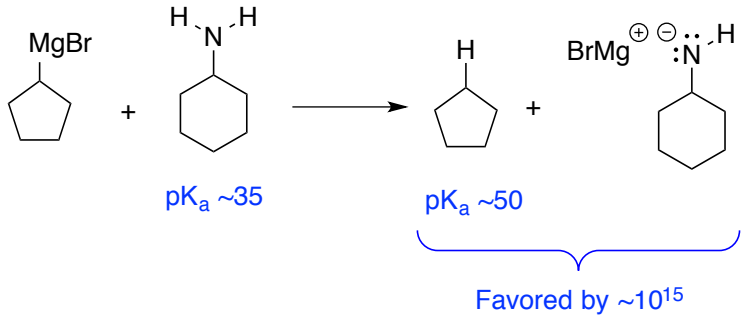
(d) Cyclopentylmagnesium bromide also behaves as though it were a carbanion. As a result, it is a powerful base.



Although amines are less acidic than the compounds in parts (a) – (c) above, they are still acidic enough to quench a Grignard reagent through proton transfer.

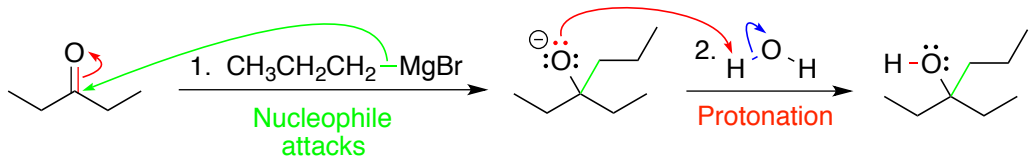


In this case, the products are favored by approximately 10^{15}.

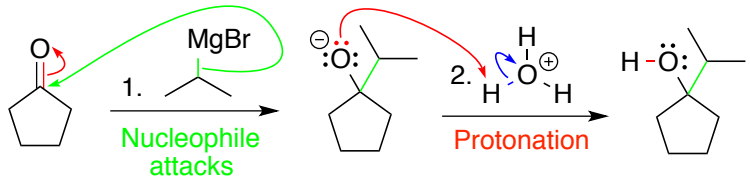


15.

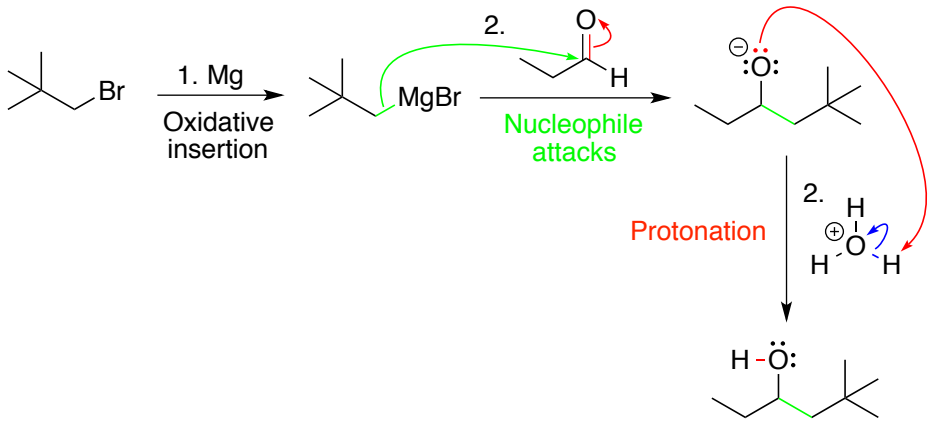
(a) Propylmagnesium bromide is drawn to the electrophilic carbonyl carbon of the ketone. As it attacks, the π bond is displaced onto oxygen as a lone pair. In step 2, the alkoxide is quenched when it deprotonates water.



(b) Isopropylmagnesium bromide is attracted to the δ+ of the ketone's carbonyl carbon. It nucleophilically attacks, and the π bond is pushed onto oxygen. In step 2, aqueous acid is added and serves as the proton source for the alkoxide.

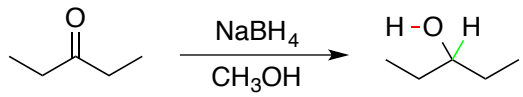


(c) In this problem, we see the transformation from the perspective of the alkyl halide. It first undergoes oxidative insertion of magnesium into the carbon-bromine bond. The Grignard reagent thus formed then attacks the electrophilic carbonyl carbon in step 2 of the reaction. Finally, aqueous acid is used to quench the alkoxide in the last step.

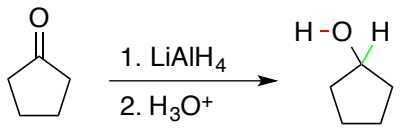


16.

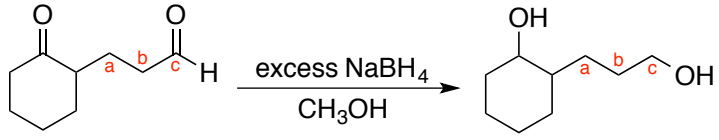
(a) The ketone is reduced to a secondary alcohol in this reaction. Compare this to Problem 15(a) to highlight how similar Grignard reactions and hydride reductions are. The only difference is that in this reaction hydride ($H:^-$) was added to the carbonyl, as opposed to $R:^-$ which was added during the Grignard reaction. The two solutions are color coded similarly to enhance the comparison.



(b) Cyclopentanone is reduced to cyclopentanol in this lithium aluminum hydride reduction. Compare this question to Problem 15(b) to further reinforce the similarity of hydride reductions and Grignard reactions. The two solutions are color coded similarly to highlight that the only difference is whether $H:^-$ or $R:^-$ is added.

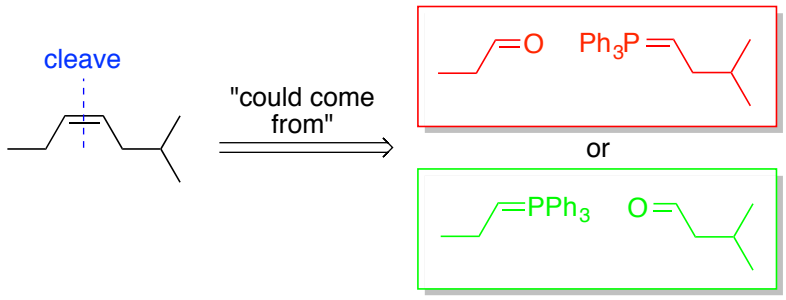


(c) With the use of excess reducing agent, both the aldehyde and the ketone can be reduced to the corresponding alcohols. Remember that, anytime you are concerned about inadvertently changing the carbon count, you can always label the carbons to ensure that you draw the proper framework.

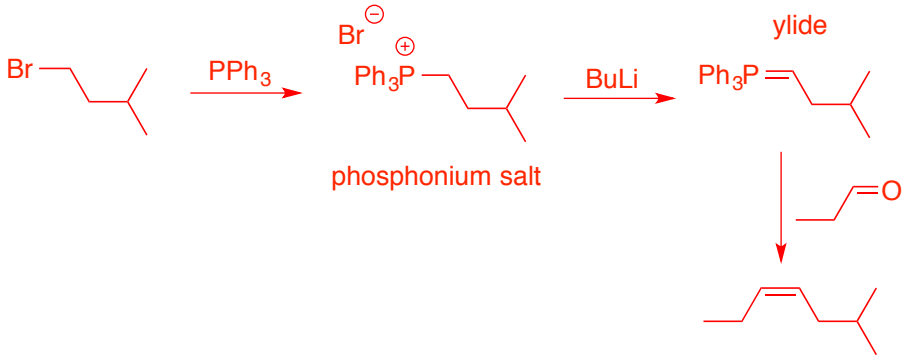


17. Remember that both the σ and the π bonds of the alkene are formed during the Wittig reaction. Therefore, when using this reaction synthetically, imagine

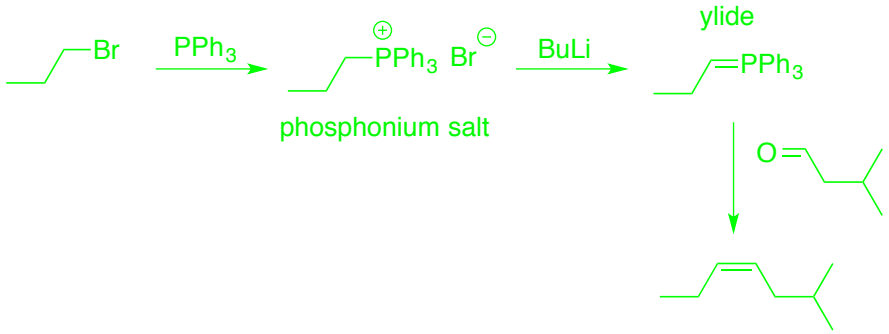
disconnecting the target molecule at the site of the double bond. Then, separate the two halves, one of which must be a ketone or aldehyde and the other of which must be the ylide. This provides us with two options for the synthesis of the target alkene. Either half can be the aldehyde, and either half can be the ylide.



The first path to the target necessitates an ylide that must be prepared from the corresponding alkyl halide having the same carbon skeleton. The alkyl halide is treated with triphenylphosphine to form a phosphonium salt, which is deprotonated by butyllithium to prepare the desired ylide. Subsequent addition of the aldehyde affords the target molecule.



The second synthetic option entails the preparation of a different ylide from propyl bromide. Propyl bromide is first converted to the phosphonium salt by triphenylphosphine. Then, addition of butyllithium converts the phosphonium salt to the ylide. Finally, addition of the appropriate aldehyde completes the synthesis.



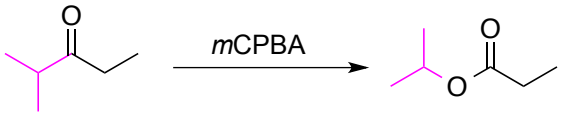
18. For this problem, it is especially important to recall the migratory aptitude discussed in this section. The group that migrates more readily will be found on the carboxyl oxygen (i.e., the sp^3 hybridized oxygen) in the product.

Migrates fastest ⟹ Migrates slowest

Tertiary > Secondary > Aryl > Primary > Methyl

(a) We know that an ester will be formed in this reaction and that the group that migrates more readily will be bonded to the carboxyl (sp^3) oxygen, so we must first compare the substitution of the groups on the ketone. In this instance, there are secondary (2°) and primary (1°) R groups.

The secondary group migrates more readily and is therefore bonded to the carboxyl oxygen in the product.

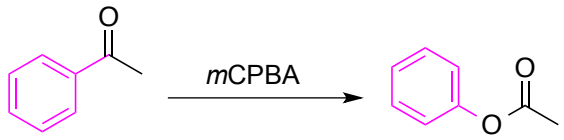


(b) Again, we expect an ester to be formed in which the group that migrates more readily is bonded to the carboxyl (sp^3) oxygen. This ketone has tertiary (3°) and secondary (2°) R groups.

The tertiary R group is more electron-rich. It migrates more readily and is bonded to the carboxyl oxygen in the product.

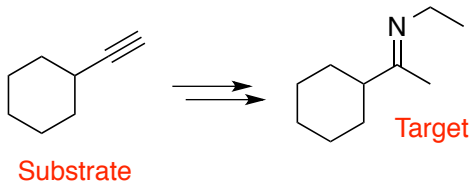
(c) As with any Baeyer-Villiger oxidation, we expect to form an ester product in which the group with the greater migratory aptitude is bonded to the carboxyl (sp^3) oxygen. This ketone has aryl and methyl groups.

It is the aryl group that possesses the greater migratory aptitude and ends up on the carboxyl oxygen of the ester.

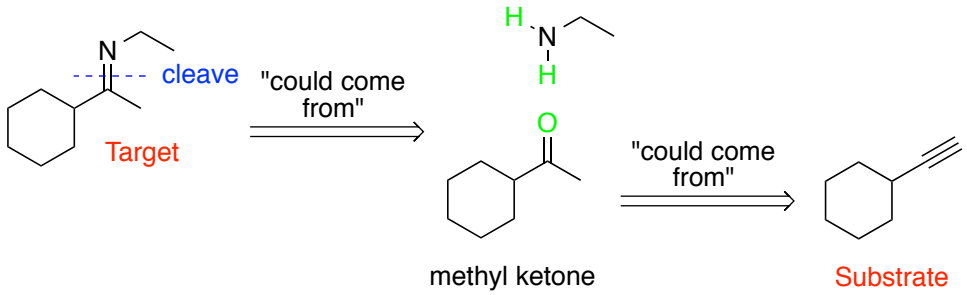


19. In any synthesis problem, it is prudent to begin by labeling the substrate and the target.

Then, draw the question in a more familiar format. This reveals that our goal is to convert an alkyne to an imine. We have seen no direct way to accomplish this.

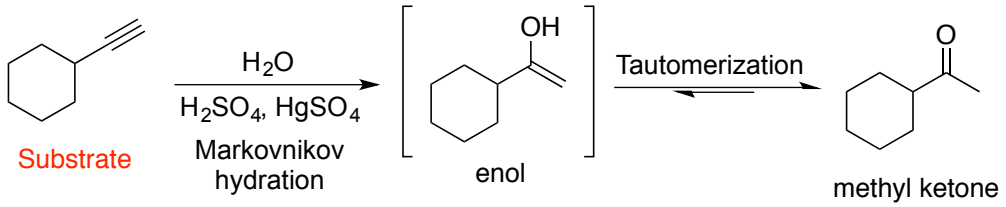


However, we do know that imines are prepared from ketones or aldehydes. Additionally, in Problem 10, we learned how to conduct retrosynthesis on an imine. We imagine disconnecting the carbon-nitrogen double bond. The two halves of the molecule are separated, and the valences of nitrogen and carbon are satisfied by bonds to hydrogen and oxygen, respectively. The atoms that we've added correspond to the water molecule that is lost during imine formation. As we learned in the alkynes chapter, the methyl ketone that we need for this synthesis can be prepared from the alkyne that is our substrate.

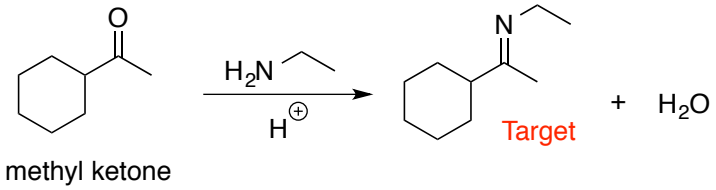


Alkynes can be hydrated with Markovnikov or anti-Markovnikov regiochemistry. In this instance, it is Markovnikov regiochemistry that we want, so mercuric sulfate

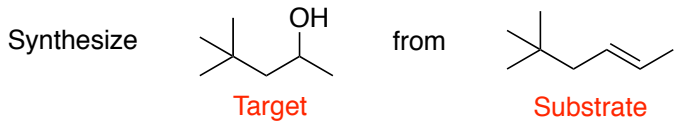
and sulfuric acid in water are used to hydrate the alkyne. A Markovnikov enol is formed initially, and it tautomerizes to the desired methyl ketone.



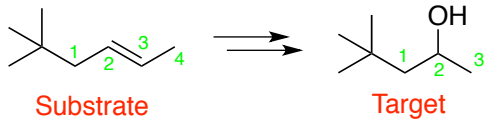
Upon treatment with ethylamine under moderately acidic conditions, the imine can then be formed. Since this is a freely reversible reaction, there is usually some measure taken to remove water from the system so as to drive the equilibrium toward the desired imine product. An example would be the use of a Dean-Stark trap.



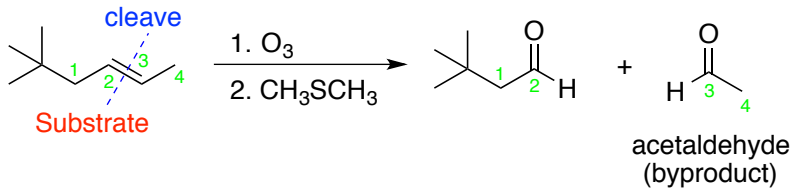
20. Begin by labeling the substrate and the target.



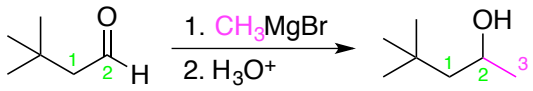
Then, draw the objective in the usual format. This reveals that a change is indeed occurring to the carbon skeleton during this synthesis. However, the change is a bit perplexing at first glance. It appears that we need to cleave the C3-C4 bond, but we know of no way to cleave a bond adjacent to an alkene. The only method that we know to cleave the carbon skeleton of an alkene is ozonolysis, and it cleaves the σ and π bonds of the alkene itself.



Since ozonolysis is the only method we know for cleaving the carbon backbone of alkenes, we should attempt to use it, even though it doesn't initially seem perfectly suited to our ultimate goal. Ozonolysis cleaves the C2-C3 bond, freeing carbons 3 and 4 in the form of acetaldehyde (a byproduct of this synthesis).



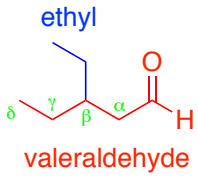
To complete the synthesis, we need to accomplish two things: (1) the addition of a carbon atom to the aldehyde and (2) the conversion of the aldehyde to an alcohol. When we consider the various ways to make carbon-carbon bonds, we realize that a Grignard reaction is perfectly suited to accomplish both of these goals. Grignard reaction with methylmagnesium bromide adds a new C3 to the molecule, and in the process, the aldehyde is transformed into a secondary alcohol.



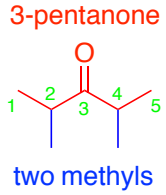
In retrospect, we see that this synthesis necessitated both a carbon-carbon bond cleavage and a carbon-carbon bond formation. This underscores the fact that changes to the carbon skeleton may sometimes be attained in stages, rather than in a single reaction.

21.

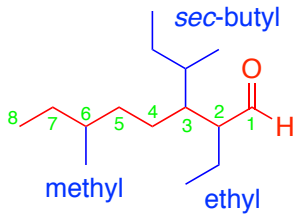
(a) Valeraldehyde is the common name for a five-carbon aldehyde. The carbons of the parent can be assigned Greek letters beginning with α for the site *adjacent* to the carbonyl. The ethyl group appears on the β carbon.



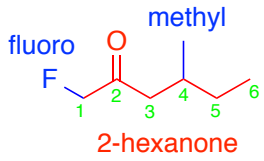
(b) 3-Pentanone is a five-carbon chain bearing a ketone at C3. The name also indicates methyl groups at C2 and C4.



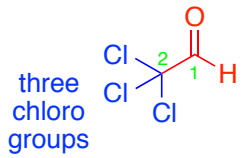
(c) Octanal is an eight-carbon aldehyde. The aldehyde implicitly appears at C1. There are also substituents (*sec*-butyl, ethyl, and methyl) located at C3, C2, and C6, respectively.



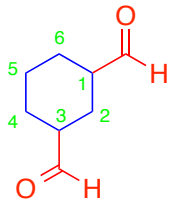
(d) 2-Hexanone consists of a six-carbon chain with a ketone at C2. This particular compound also has fluoro and methyl groups at C1 and C4, respectively.



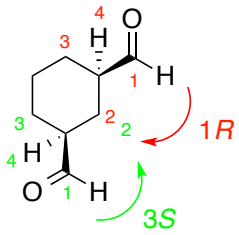
(e) Acetaldehyde is the common name for a two-carbon aldehyde. Although there are no numbers to specify the locations of the three chloro groups, there is only one carbon (C2) where they could be placed.



(f) The cyclohexane ring is substituted at C1 and C3 with aldehydes.

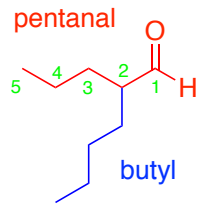


When we add the stereochemistry to our drawing, it becomes apparent that this is a meso compound since it has the *cis* configuration. The priorities of each group on the two stereocenters are indicated by numbers in the drawing below.

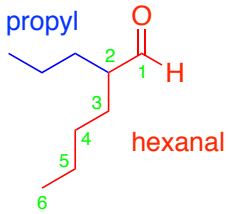


22.

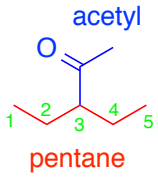
(a) We should begin by drawing the structure that is suggested by the name we've been given. Pentanal is a five-carbon aldehyde. This molecule has a butyl group at C2.



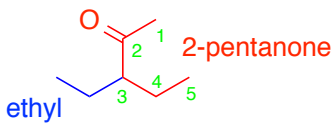
Upon closer inspection, the error becomes apparent. The longest carbon chain is not five carbons, but six. Therefore, the parent should be hexanal. This compound has a propyl group at C2, so its proper name should be 2-propylhexanal.



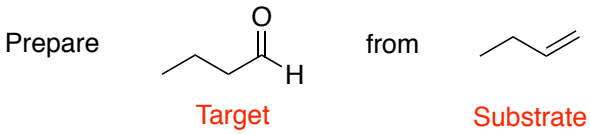
(b) Our first step is to draw the structure suggested by the name. Pentane is a five-carbon chain. The acetyl group is connected to C3.



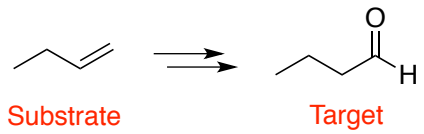
The problem with this name is that the parent, while it is of the proper length, does not contain the functional group. If we select the longest parent containing the functional group, it is 2-pentanone. There is an ethyl group at C3, making the full name 3-ethyl-2-pentanone.



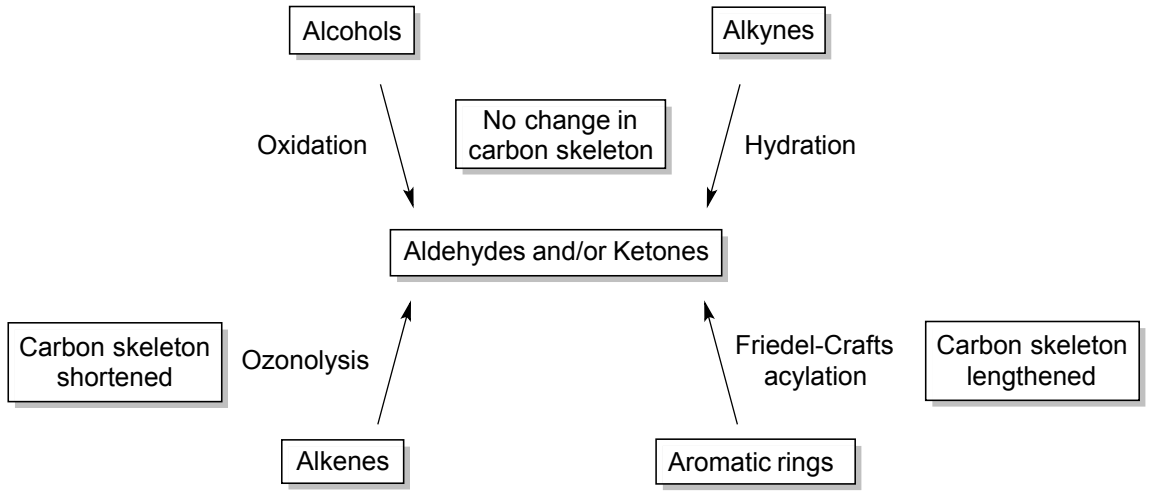
23. We begin our synthesis, as usual, by labeling the substrate and target.



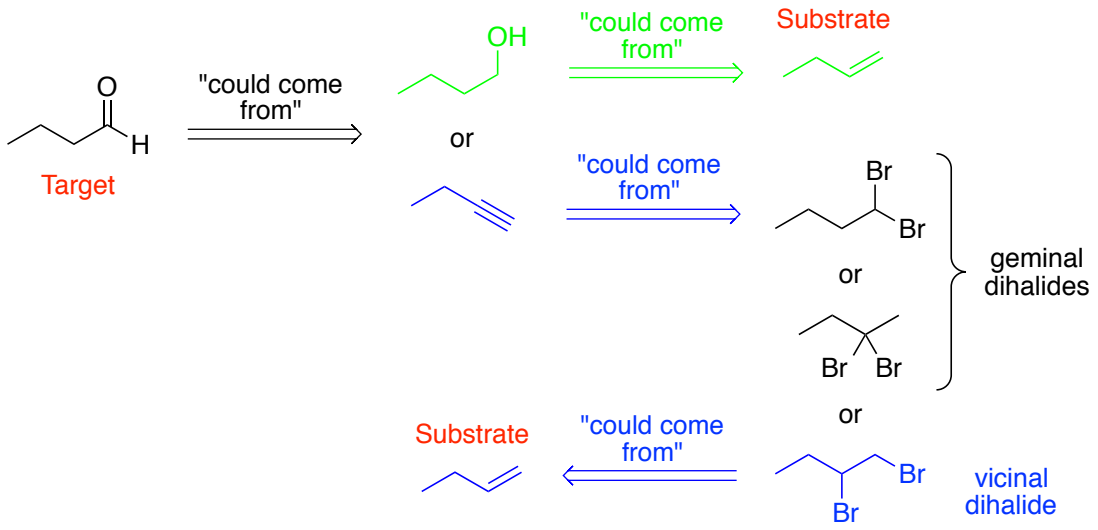
Redrawing the task in the usual format reveals that our goal is to convert an alkene to an aldehyde. There is no direct way to do this without altering the carbon skeleton (through ozonolysis), which is undesirable in this case.



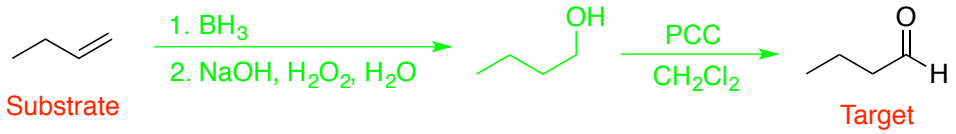
However, in the section on preparation of aldehydes and ketones, we saw several viable methods. If we eliminate the two methods that alter the carbon skeleton (ozonolysis and Friedel-Crafts acylation), we are left with preparation of the aldehyde from an alcohol or an alkyne.



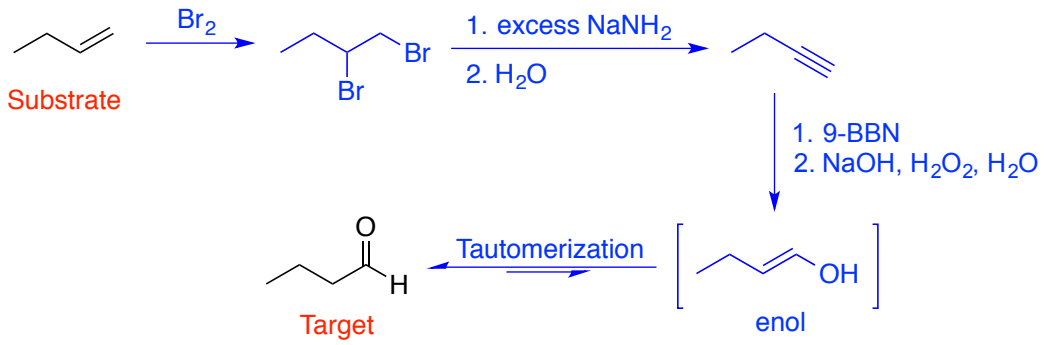
We can sketch out these options in a retrosynthesis. The target aldehyde can be made from an appropriate alcohol (green path) or alkyne (blue path). Let's focus on the green path first. The appropriate alcohol would be one in which the oxygen is connected to the terminal carbon, just like it is in the aldehyde. This alcohol could in turn be made from the alkene substrate with which we were provided. Alternatively, in the blue path, a terminal alkyne could be used to prepare the target aldehyde. This alkyne can be made from the allowed substrate using a synthetic module that we learned in the alkynes chapter: (1) halogenation followed by (2) double elimination. Any one of three dihalides (two geminal and one vicinal) would be suitable for double elimination to make the alkyne, but only the vicinal dihalide can be made from an alkene.



In the forward sense, the green path begins with hydroboration-oxidation to afford the anti-Markovnikov alcohol. Subsequent oxidation with PCC (to avoid overoxidation to the carboxylic acid) yields the target aldehyde.



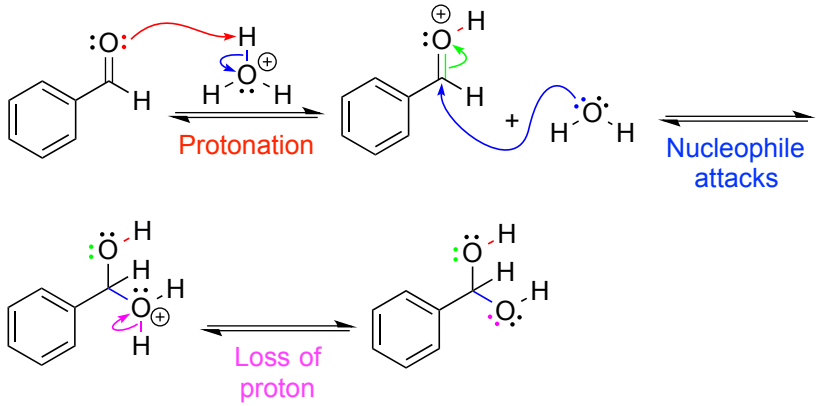
Alternatively, the blue path begins with halogenation of the alkene. Treatment with excess sodamide leads to double elimination and deprotonation of the terminal alkyne, once it is formed. The addition of water quenches the alkynide ion, and the terminal alkyne can then be subjected to hydroboration-oxidation. This gives an ephemeral anti-Markovnikov enol that readily tautomerizes to yield the target aldehyde.



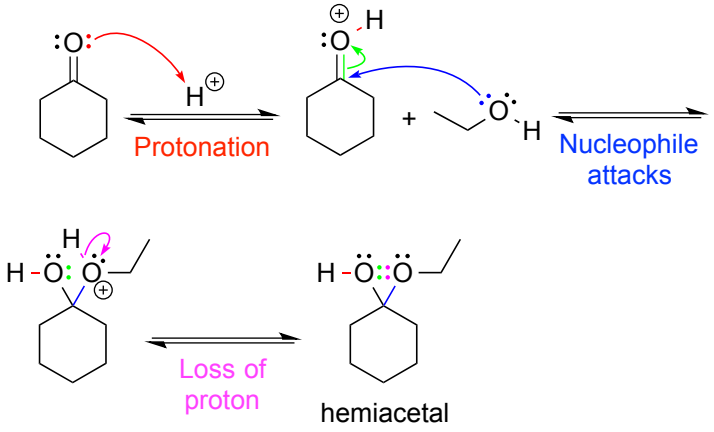
The green path is likely preferable since it requires only two steps, as opposed to the three steps in the blue path.

24. The mechanism begins with protonation of the carbonyl oxygen. This enhances the electrophilicity of the carbonyl, making it more susceptible to nucleophilic

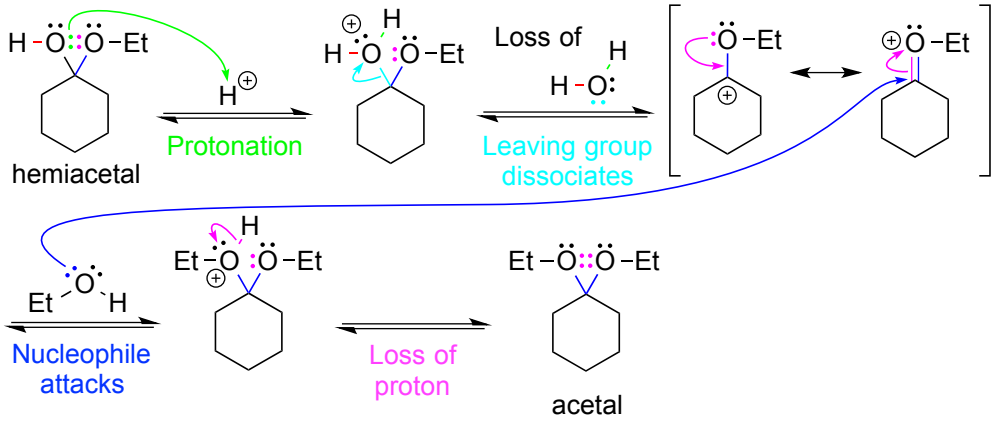
attack of even a weak nucleophile, such as water. This attack displaces the carbonyl π electrons onto oxygen as a lone pair. The resulting oxonium ion loses a proton to afford the hydrate.



25. The first stage of acetal formation is the preparation of the hemiacetal. It is initiated by protonation of the carbonyl oxygen. This enhances the electrophilicity of the carbonyl carbon, making it more vulnerable to attack of even weak nucleophiles, such as ethanol. Since the goal of this problem is to prepare a diethyl acetal, we must use an alcohol bearing an ethyl group, hence ethanol. This nucleophilic attack pushes the carbonyl π electrons onto oxygen, and the resultant oxonium ion sheds a proton to the medium to yield the hemiacetal.

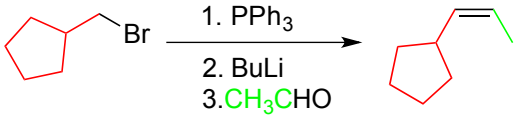


Phase two of the mechanism is the formation of the acetal, itself. This phase is also initiated by protonation. Protonation of the hydroxyl group makes it a good leaving group. Its dissociation leaves behind a resonance-stabilized carbocation to which a second molecule of ethanol adds. Finally, the loss of a proton from the oxonium ion neutralizes the charge on oxygen and provides the diethyl acetal.

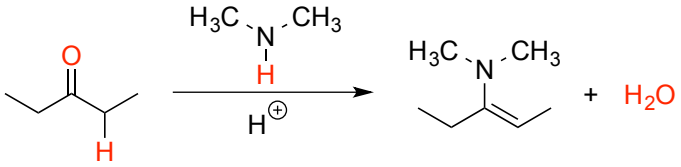


26.

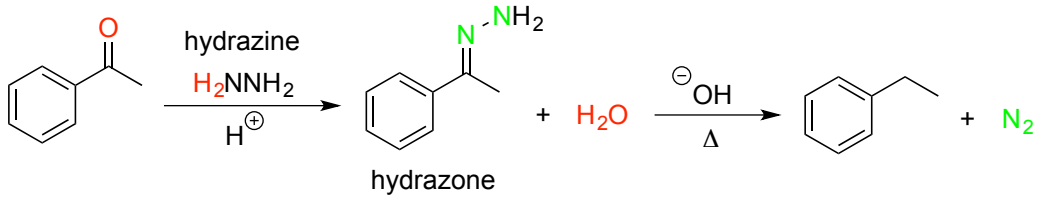
(a) This is a Wittig reaction. The alkyl bromide is transformed into a phosphonium salt by treatment with triphenylphosphine. Deprotonation with butyllithium then gives the ylide. The ylide and the aldehyde combine to provide the *cis* alkene as the product.



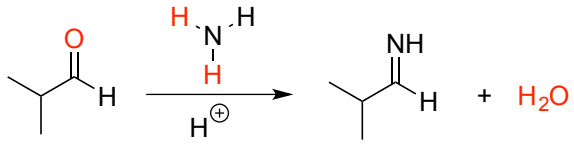
(b) When a secondary amine reacts with a ketone (or aldehyde), an enamine is formed. Remember that acetal, imine, and enamine formation all result in the loss of water from the reactants. In this case, the water molecule is formed from the carbonyl oxygen, the proton of the amine, and a proton from the position α to the carbonyl.



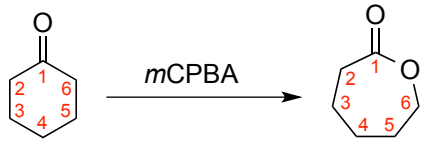
(c) This is a Wolff-Kishner reduction, which begins with the formation of a hydrazone from the ketone and hydrazine. Much like imine formation, this transformation occurs with the loss of water (the carbonyl oxygen and two protons from hydrazine). Subsequent treatment with hydroxide results in the expulsion of nitrogen gas upon heating. The product is ethylbenzene.



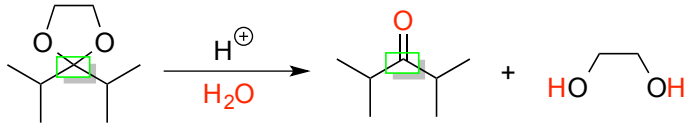
(d) This is an imine formation. Imines are formed when aldehydes (or ketones) are condensed with ammonia (or primary amines). The process results in the loss of water from the reactants (the carbonyl oxygen and two protons from ammonia).



(e) This is a Baeyer-Villiger oxidation. A cyclic ketone behaves no differently than an acyclic one in this transformation. Since C2 and C6 are totally equivalent, either one can migrate (migration of C6 is shown below) to afford a cyclic ester. Cyclic esters are known as lactones. The ring has been enlarged by one atom: the oxygen that was incorporated during the oxidation.

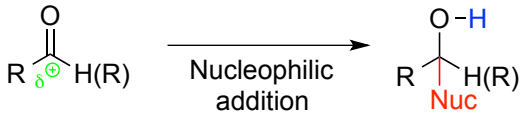


(f) This is the hydrolysis of an acetal. Acetal hydrolysis occurs in aqueous acid and results in the addition of water as the acetal is broken into the carbonyl-containing reactant and two alcohols, which happen to be tethered in this case.

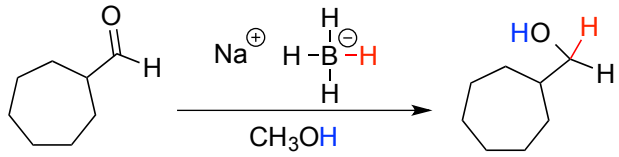


It is helpful to note that this reaction occurs with no change in oxidation state. As a result, the only carbon atom in the acetal that possesses two bonds to oxygen still has two bonds to oxygen in the ketone product.

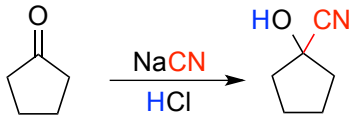
27. In this problem, it will be helpful to keep in mind the general paradigm for nucleophilic addition. Remember that a nucleophile adds to the electrophilic carbonyl carbon, and a proton is added to the carbonyl oxygen during transformations of this type.



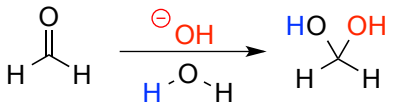
(a) This is a reduction with sodium borohydride. Hydride ($H:^-$) is the nucleophile that adds to the carbonyl, and the carbonyl oxygen acquires a proton from methanol during the second step of the mechanism. There is a net addition of H_2 across the carbonyl π bond.



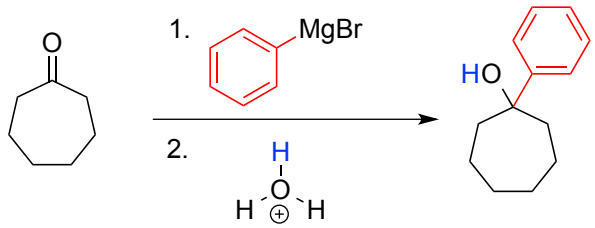
(b) This is an example of cyanohydrin formation. The net addition of HCN occurs across the carbonyl π bond.



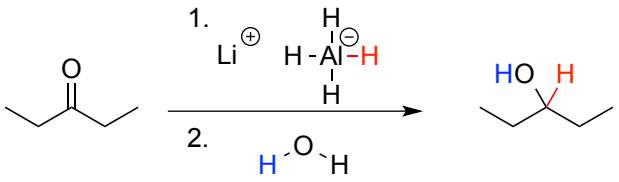
(c) This is hydrate formation under basic conditions. There is a net addition of water across the π bond, with the hydroxyl group coming from hydroxide and the proton coming from water in the second step of the mechanism.



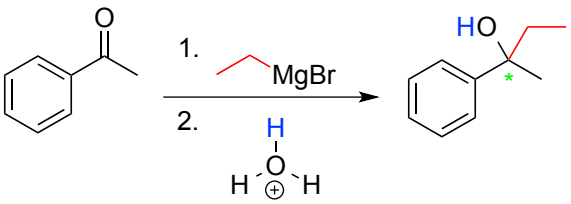
(d) This is a Grignard reaction. The nucleophilic Grignard reagent adds to the carbonyl carbon in the first step of the mechanism. This is followed by protonation of the resulting alkoxide in the second step of the mechanism.



(e) This is a reduction using lithium aluminum hydride. Hydride ($H:^-$) is the nucleophile that adds to the electrophilic carbonyl carbon, and the carbonyl oxygen then acquires a proton from water during the second step of the mechanism. There is a net addition of H_2 across the carbonyl π bond.

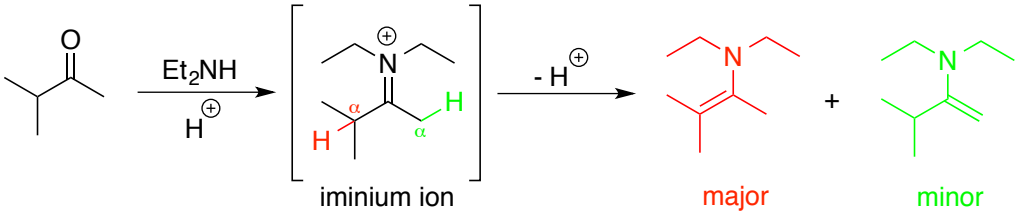


(f) This is another Grignard reaction. Ethylmagnesium bromide adds to the electrophilic carbonyl carbon, and this is followed by protonation of the alkoxide intermediate in the second step. In this instance, a stereocenter is formed during the reaction.

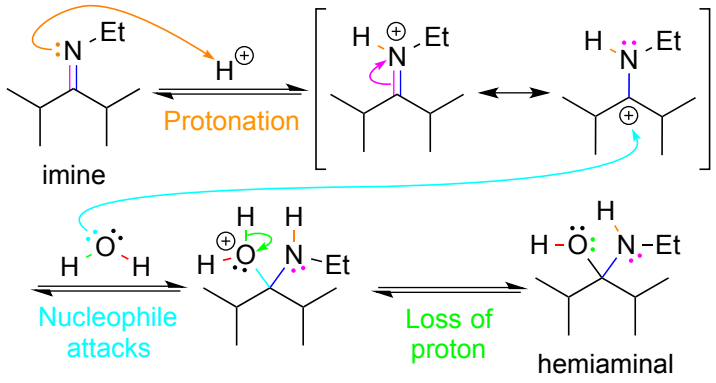


The ketone is flat (sp^2 hybridized) at the site of reaction. Consequently, there is no preference for attack of Grignard reagent from above or below the plane of the carbonyl, and the product is produced as a racemic mixture of enantiomers.

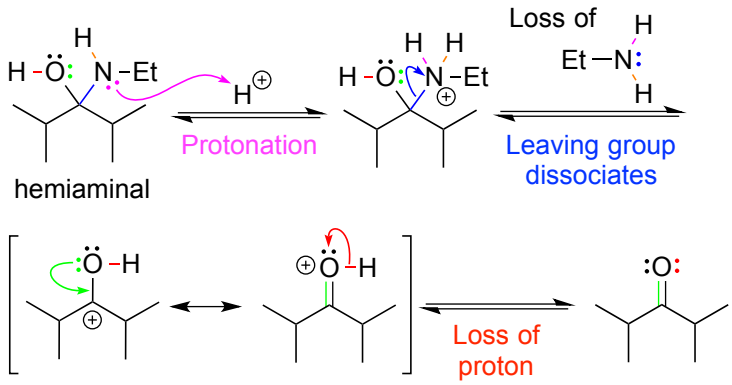
28. This unsymmetrical ketone condenses with diethylamine to yield an iminium ion intermediate. In the final mechanistic step of the reaction, the iminium ion can lose a proton from either of its α carbons. Loss of a proton from the more highly substituted tertiary α carbon leads to the more highly substituted alkene and therefore the major enamine product.



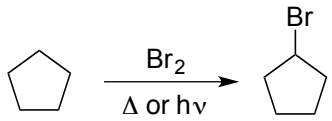
29. This is the hydrolysis of an imine. The first phase of the mechanism is reversion to the hemiaminal. This stage begins with protonation at the only site bearing lone pair electrons: the imine nitrogen. Water then attacks the resonance-stabilized iminium ion. A proton is subsequently lost from the oxonium ion to afford the hemiaminal.



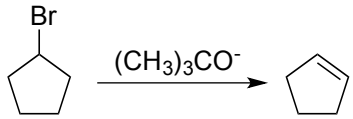
Although the hemiaminal may look like a reasonable final product, there is more that can happen to it under the reaction conditions (aqueous acid). Protonation on nitrogen affords a new intermediate bearing a good leaving group. This good leaving group (ethylamine) dissociates from the molecule to provide a resonance-stabilized carbocation. The cation sheds a proton from oxygen to yield the ketone as the final hydrolysis product.



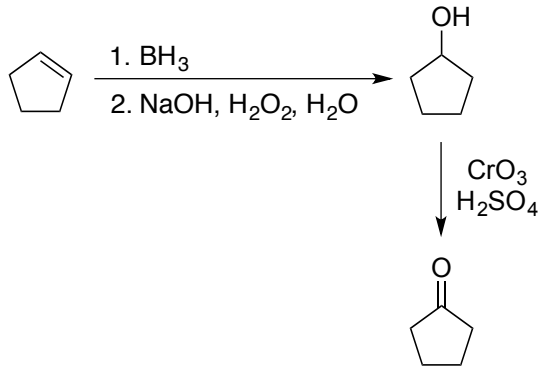
30. This scheme begins with a radical bromination of cyclopentane, which yields bromocyclopentane.



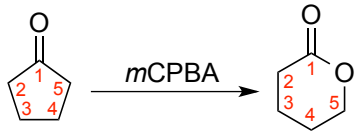
In order to convert bromocyclopentane to cyclopentene, an elimination must be performed. Although there are multiple ways to achieve this outcome, E2 is common approach. Since regiochemistry is not an issue in this scenario, we can simply use a bulky base, such as *tert*-butoxide, to minimize the amount of competing substitution byproduct.



Upon hydroboration-oxidation, cyclopentanol is produced, and it can be oxidized by chromic acid (formed from chromium trioxide and sulfuric acid) to generate the corresponding ketone: cyclopentanone.

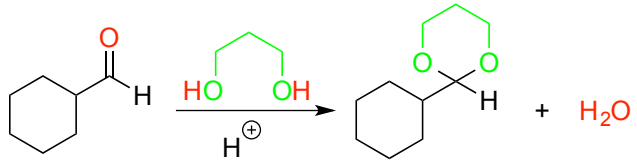


Finally, cyclopentanone undergoes Baeyer-Villiger oxidation when treated with *m*CPBA. This cyclic substrate proceeds through Baeyer-Villiger oxidation just as any other substrate would, but when the R group migrates, the net result is ring expansion. See Problem 26(e) for a similar example. Numbering is useful to ensure the correct carbon count in the product.



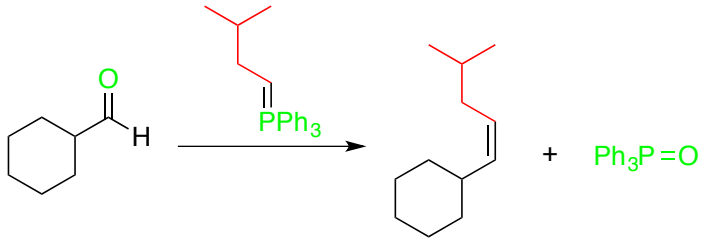
31.

(a) The desired product is an acetal. This means that the reagent must be an alcohol or a diol. Given that the desired acetal is cyclic, the reagent should be a diol. The number of intervening carbons between the two hydroxyl groups should match that in the product. Acid catalysis is required for this transformation as well. Recall that this reaction proceeds with the loss of water.

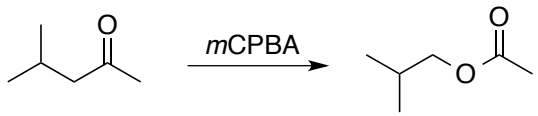


(b) The Wittig reaction is the shortest route from an aldehyde to a *cis* alkene. This necessitates treating the aldehyde with the appropriate ylide. The ylide's R group

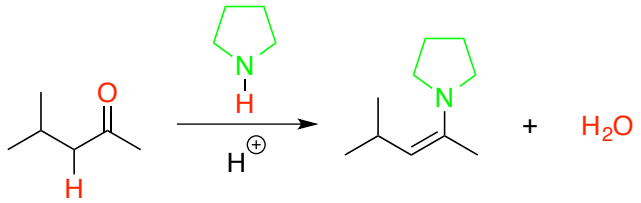
should match that of the newly formed alkene. Triphenylphosphine oxide is a byproduct of this reaction.



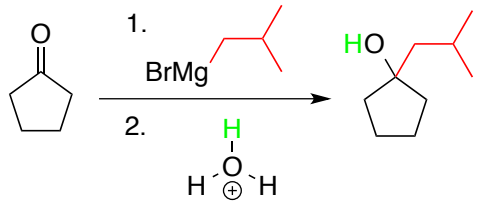
(c) Esters are produced from ketones using the Baeyer-Villiger reaction, which requires a peroxyacid such as *m*CPBA.



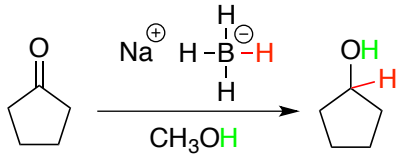
(d) To form an enamine, the ketone must be treated with a secondary amine. In this case, the desired secondary amine is cyclic. Much like acetal and imine formation, water is also lost during this transformation.



(e) The Grignard reaction can be used to add nearly any R group to a ketone (or aldehyde), thereby converting it to an alcohol in the process. The Grignard reagent donates its R group to the carbonyl carbon, and in the second step of the reaction, the alkoxide intermediate is protonated by the hydronium ion (or water if that is used instead).



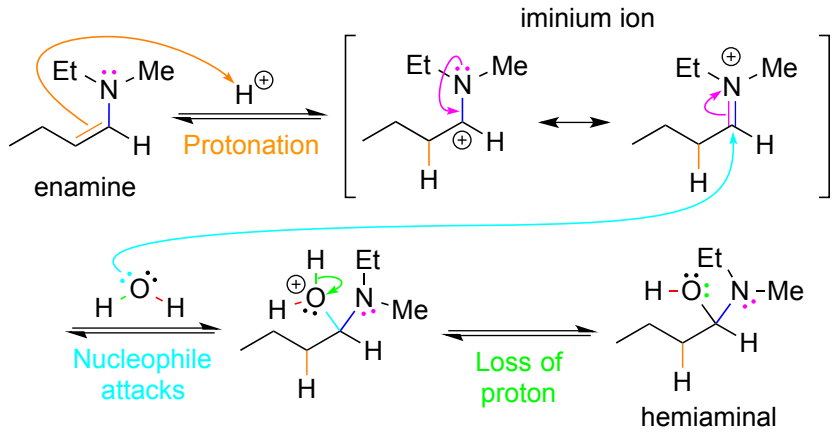
(f) To reduce a ketone to the corresponding alcohol, we may use sodium borohydride or lithium aluminum hydride. As shown below, sodium borohydride will donate a hydride ($H:^-$) to the carbonyl carbon. The alkoxide intermediate is subsequently protonated by methanol (the use of a different alcohol or water as the solvent is acceptable too).



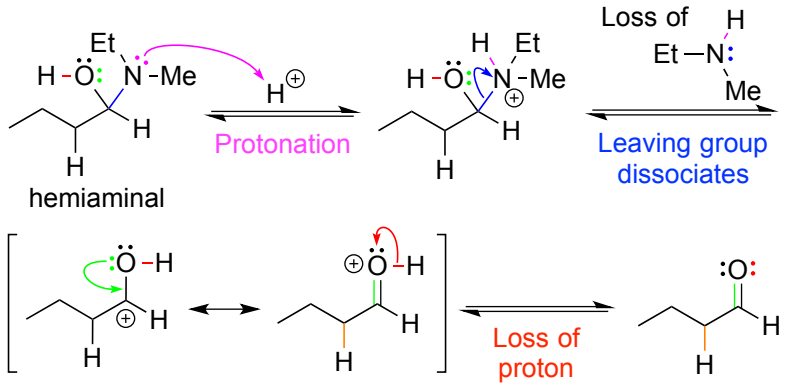
If lithium aluminum hydride were used instead, the reaction would be similar. However, water needs to be added in a second, separate step because lithium aluminum hydride is very reactive and therefore incompatible with water's reasonably acidic protons.

32. This enamine hydrolysis consists of two stages, much like imine hydrolysis does (see Problem 29). The first stage is reversion of the enamine to the hemiaminal. The second stage is the conversion of the hemiaminal to the carbonyl compound (an aldehyde or ketone).

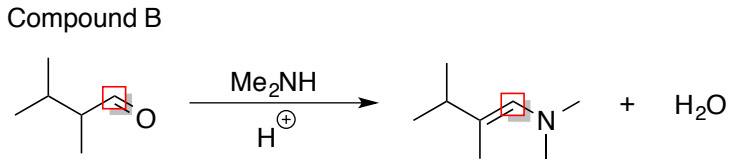
The first stage is initiated by protonation. While we normally protonate on an atom with lone pair electrons, doing so in this case would lead to an ammonium ion (positively charged nitrogen) without any resonance stabilization. There is a better option in this case. Protonation of the alkene can lead to a resonance-stabilized cation, which is a more stable intermediate. Attack of water on the electron-deficient carbon is followed by loss of a proton from the resultant oxonium ion. The hemiaminal is formed in this way.



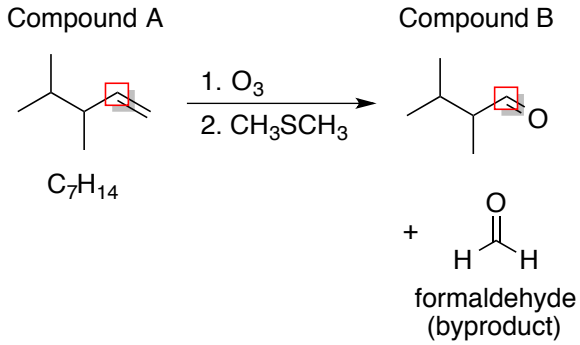
The hemiaminal may appear to be a reasonable stopping point at first glance. However, there is more that it can do in these reaction conditions (aqueous acid). Protonation of the amine yields a new intermediate that bears a good leaving group (ethylmethylamine). Dissociation of this leaving group produces a resonance-stabilized carbocation. Finally, loss of a proton from water provides the aldehyde as the final hydrolysis product.



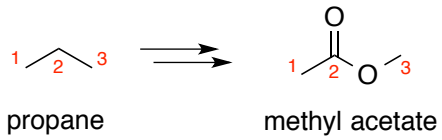
33. The enamine is generated from dimethylamine and a compound bearing a carbonyl. The carbonyl must be located at the same site as the dimethylamino group in the enamine. This means that Compound B is an aldehyde. The reaction is referred to as a condensation in the problem because two reactants unite with the loss of a small molecule, which in this case is water.



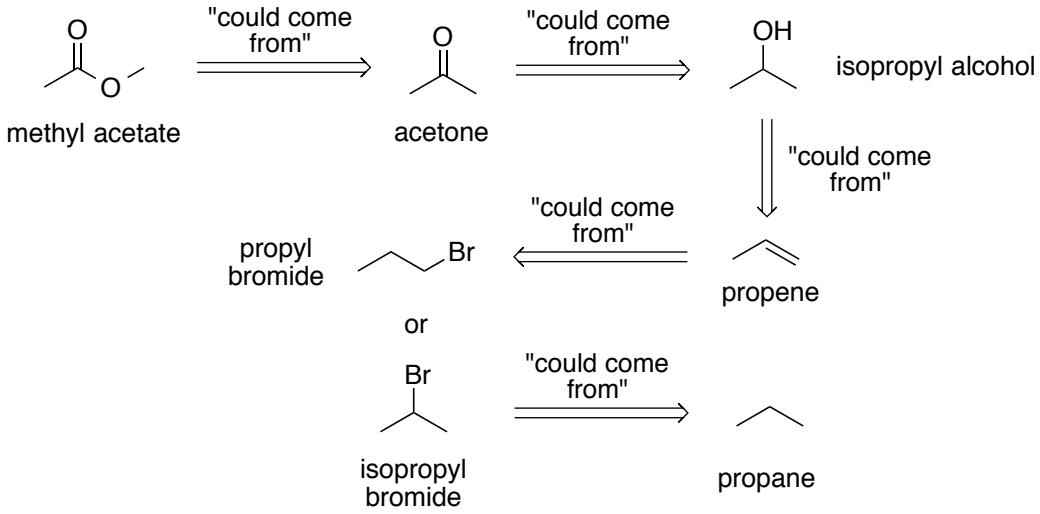
Compound B results from the ozonolysis of Compound A, which contains one additional carbon based on its molecular formula. Therefore, Compound A must be the alkene shown below, and the byproduct formed during ozonolysis is formaldehyde.



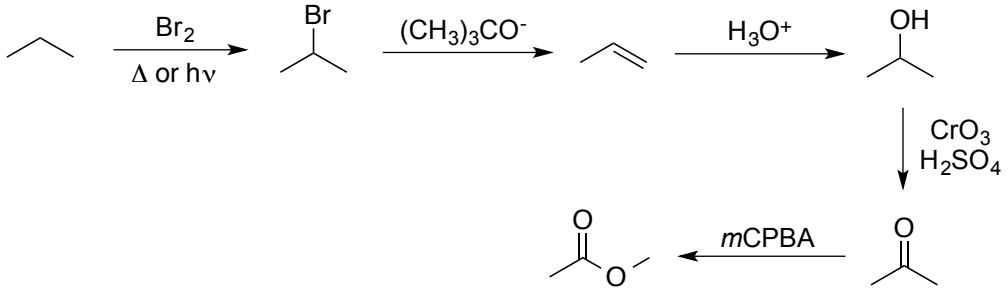
34. We are asked to prepare methyl acetate from propane in this problem. Upon analyzing the carbon skeleton, it becomes evident that cleavage of a carbon-carbon bond has occurred at some point in the synthesis. We know that ozonolysis and Baeyer-Villiger oxidation both lead to cleavage of carbon-carbon bonds; however, only Baeyer-Villiger oxidation produces esters directly.



Consequently, it seems reasonable to assume that a late-stage Baeyer-Villiger oxidation will produce methyl acetate from the corresponding three-carbon ketone, acetone. Acetone can be made by oxidation of isopropyl alcohol, which in turn can result from the hydration of propene. Since alkene π bonds are formed through elimination, either propyl or isopropyl bromide would be an appropriate precursor; however, only isopropyl bromide can be made in good yield from propane by radical halogenation.

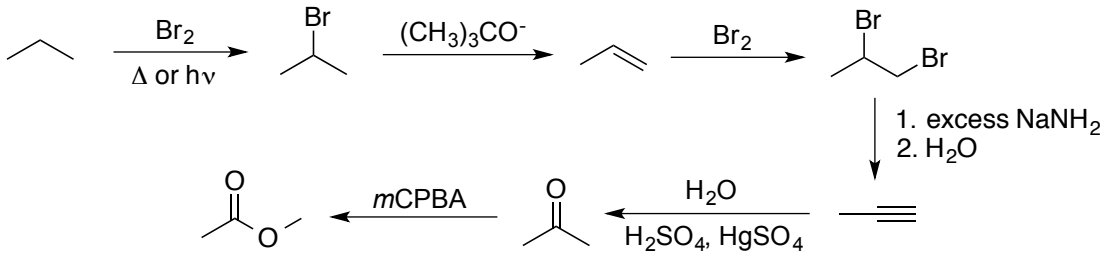


In the forward sense, we begin with the free radical bromination of propane to produce isopropyl bromide. A subsequent elimination will afford propene. Since regiochemistry is not a concern in this step, we can use a bulky base to minimize any side products due to undesired substitution. Propene can then be hydrated simply through the addition of aqueous acid. Alternatively, oxymercuration-demercuration would also yield isopropyl alcohol. Oxidation with chromic acid (from chromium trioxide or sodium dichromate and sulfuric acid) or PCC provides acetone, which undergoes the key Baeyer-Villiger oxidation when treated with *m*CPBA.

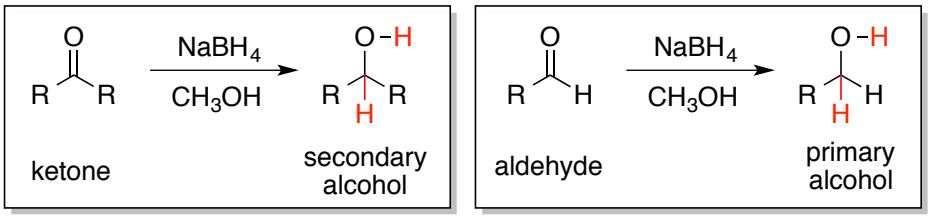


Note that this synthesis is similar to the sequence of events in Problem 30. It may be useful to compare these problems side-by-side to reinforce your understanding of both.

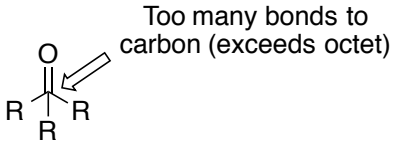
As an aside, there are often multiple ways to go about a synthesis. For instance, in this problem, we could have prepared acetone by hydration of propyne instead. Propyne could be prepared by double elimination of a vicinal dihalide resulting from propene.



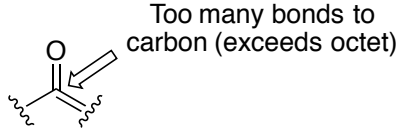
35. The reduction of ketones affords secondary alcohols, while the reduction of aldehydes provides primary alcohols. In both cases, there is a net addition of H_2 across the carbonyl π bond.



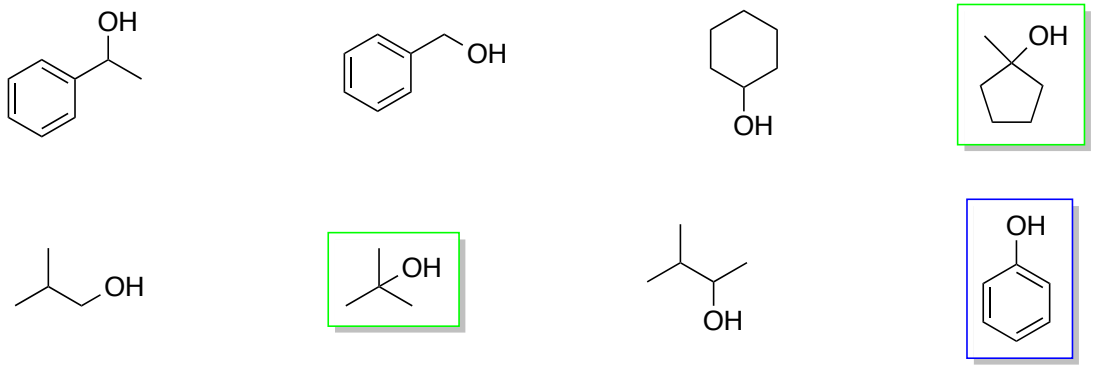
Notice that neither of these reactions yields a tertiary alcohol. Therefore, we can state that the tertiary alcohols cannot be prepared by sodium borohydride reduction of a ketone or aldehyde. The fundamental reason is that a tertiary center does not have enough free valences to support a carbonyl.



Similarly, a vinyl or aryl carbon does not have enough free valences to support a carbonyl either.

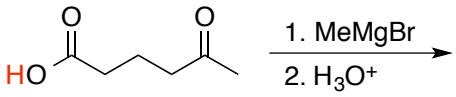


Therefore, among the list of compounds we were given, the tertiary alcohols and the phenol cannot be made by hydride reduction of an aldehyde or ketone.

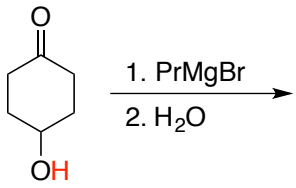


36. We've seen previously that Grignard reagents are not compatible with even mildly acidic protons (see Problem 14).

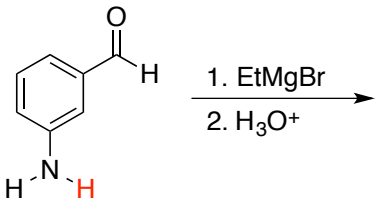
(a) In this reaction, the acidic proton of the carboxylic acid (pK_a ~5) will quench the Grignard reagent.



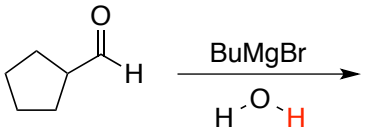
(b) In this instance, the mildly acidic alcohol proton (pK_a ~15) will quench the Grignard reagent.



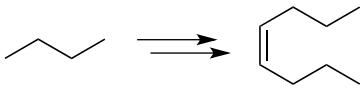
(c) In this example, the weakly acidic proton of the amine (pK_a ~35) can quench the Grignard reagent.



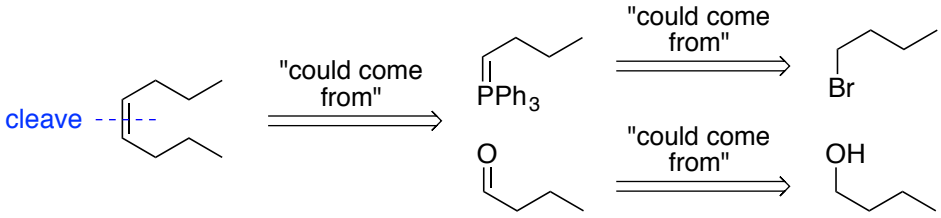
(d) In this reaction, the steps 1 and 2 have not been designated, which suggests that the substrate, butylmagnesium bromide, and water are all being combined at once. This is problematic because the mildly acidic proton of water (pK_a ~15) will quench the Grignard reagent.



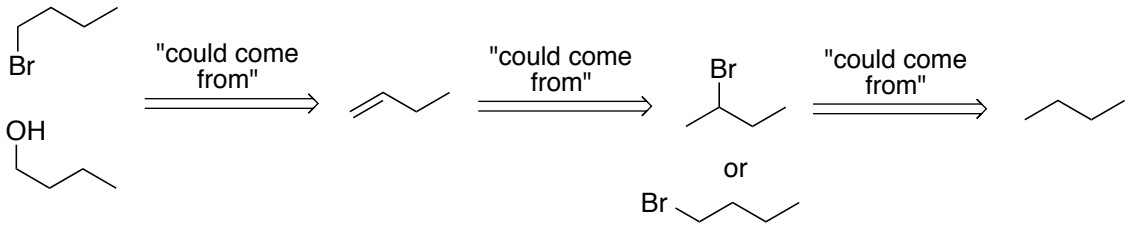
37. The challenge of this problem is two prepare an eight-carbon *cis* alkene using a single four-carbon reactant.



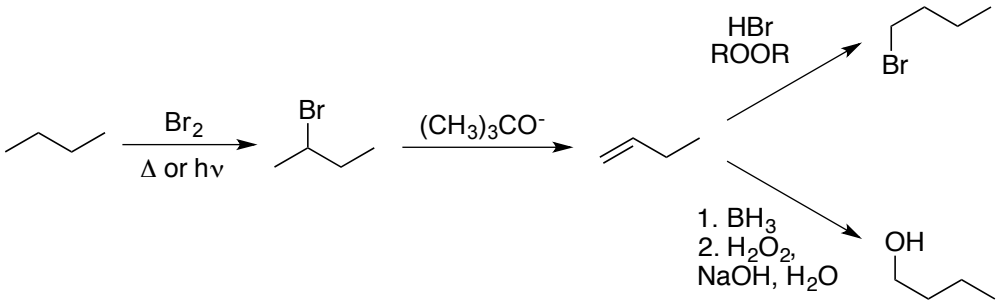
We need to make a carbon-carbon double bond, and Wittig reactions not only do this but also provide the *cis* configuration. Therefore, our first retrosynthetic disconnection is through the alkene to provide an ylide and an aldehyde as precursors. The ylide is prepared from a corresponding alkyl bromide, and the aldehyde can be prepared from a primary alcohol.



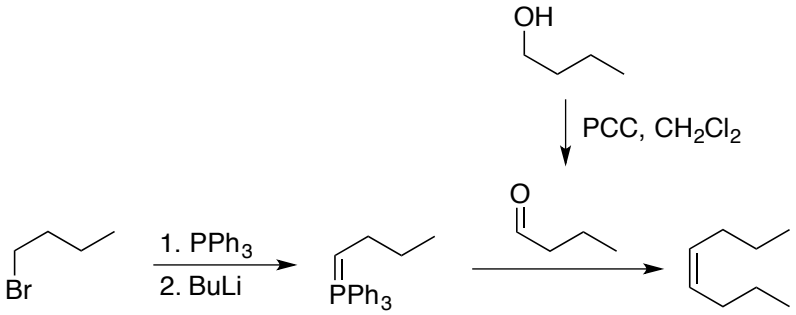
Both of these synthetic intermediates can be made from 1-butene through anti-Markovnikov additions. 1-Butene, in turn, is prepared from elimination of an alkyl bromide. Either 1-bromobutane or 2-bromobutane could serve this purpose, but only 2-bromobutane can be prepared in good yield from butane by free radical halogenation.



With a plan in place, we can now proceed with the synthesis. Butane is brominated under free radical conditions to provide 2-bromobutane. Hofmann elimination using a bulky base, such as *tert*-butoxide, affords 1-butene. This alkene can then undergo the anti-Markovnikov addition of HBr or water to provide the two necessary fragments.

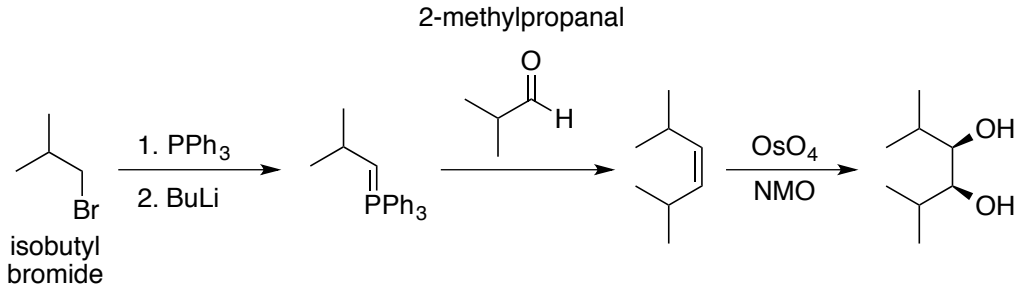


1-Bromobutane is treated with triphenylphosphine to prepare the phosphonium salt, which is then deprotonated by butyllithium to generate the ylide. 1-Butanol is oxidized using PCC (to avoid overoxidation to the carboxylic acid) to produce butyraldehyde. At this stage, the ylide and aldehyde can undergo Wittig reaction to yield the desired product.

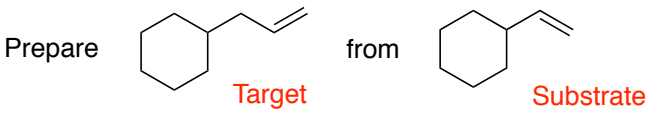


38. This problem provides a lot of clues about the sequence of events, but the information is provided in the form of text rather than graphics. In such cases, it is usually a good idea to convert the textual information into graphical information. To do this, simply take each piece of information one at a time.

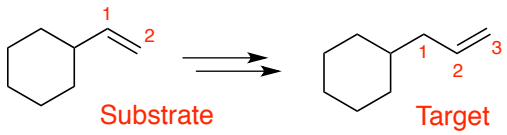
In other words, we begin by drawing isobutyl bromide. It is treated with triphenylphosphine (PPh_3) followed by butyllithium (BuLi) to yield an ylide. The ylide then undergoes a Wittig reaction with 2-methylpropanal. If we first draw the structure of this aldehyde, it then becomes clear what alkene is formed form the Wittig reaction. Finally, treatment with osmium tetraoxide (OsO_4) and NMO affords a diol. These are the conditions for syn-dihydroxylation, so a single meso diol results from the reaction.



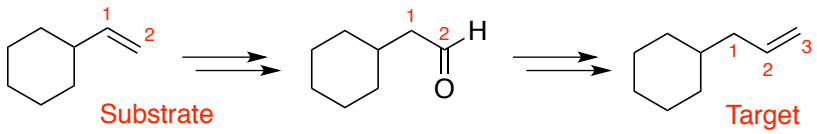
39. It is always prudent to begin a synthesis problem by labeling the substrate and target.



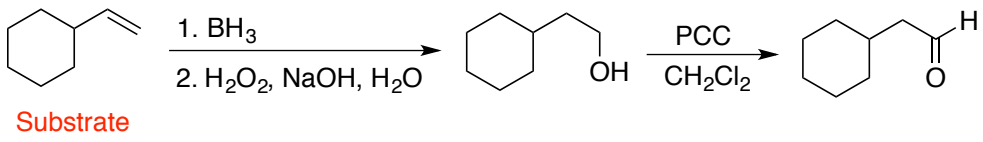
Then, we can redraw our task in the typical format. A little numbering highlights the fact that we need to install a new carbon-carbon bond during this synthesis. Of our carbon-carbon bond forming reactions, the Grignard reaction seems best suited to this task. As for the alternative C-C bond forming reactions, the use of cyanide could add one carbon, but it would be difficult to manipulate the nitrile (C≡N) into an alkene since we don't yet know reactions of nitriles. The use of an alkynide ion would add more carbons than needed because at least two carbons are necessary in an alkyne. The Diels-Alder and Friedel-Crafts reactions are not suited to the types of changes being made here (i.e., we don't want to install a cyclohexene or an aromatic ring).



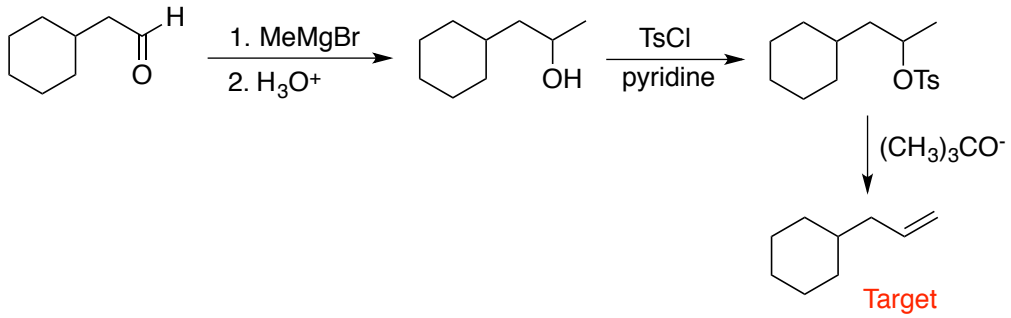
While a full retrosynthesis is always useful, sometimes a partial retrosynthesis is sufficient to develop a plan. We know that Grignard reactions require carbonyl-containing reactants, and the carbonyl must be present at the site where new bond formation should occur (C2). Therefore, it is clear that an aldehyde must be a key intermediate in our synthesis. Knowing this divides the synthesis into two phases: (1) prepare the aldehyde and (2) perform the Grignard reaction and manipulate functionality as needed.



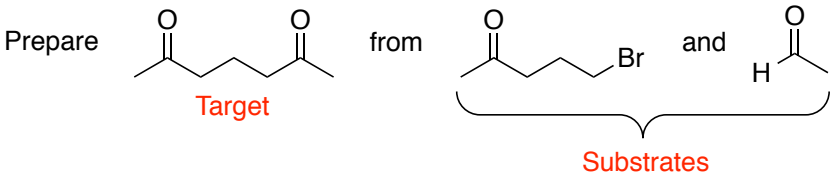
Phase 1 (preparation of the aldehyde) begins with hydration of the alkene in an anti-Markovnikov fashion using hydroboration-oxidation. This installs oxygen onto the molecule where it is needed. A subsequent oxidation with PCC (to avoid overoxidation to the carboxylic acid) provides the needed aldehyde.



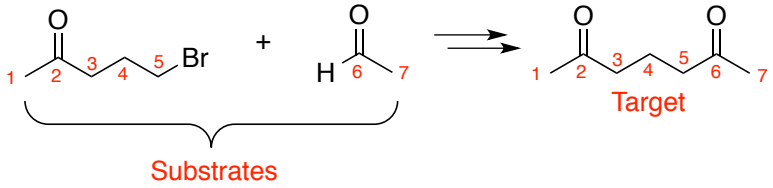
To install a single carbon atom, the Grignard reagent of choice is methylmagnesium bromide. With the desired carbon framework now in place, all that remains is to dehydrate in order to obtain the target alkene. Dehydration cannot be performed directly (with sulfuric acid) though because the desired alkene is the Hofmann product. Therefore, the alcohol is converted to the tosylate (a good leaving group), and E2 reaction is performed with a bulky base to ensure that the Hofmann product predominates.



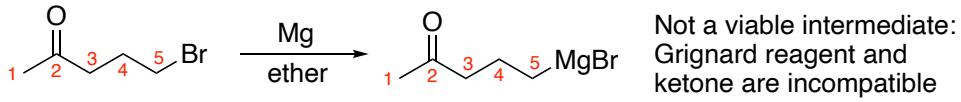
40. It is always useful to label the substrate and target.



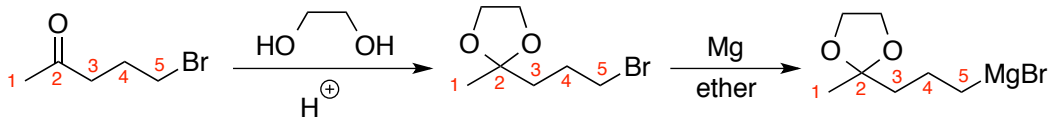
Then, rewrite the problem in the usual format. This highlights the fact that we are asked to make a seven-carbon diketone from five and two-carbon reactants. Clearly, these reactants must be joined to make the C5-C6 bond.



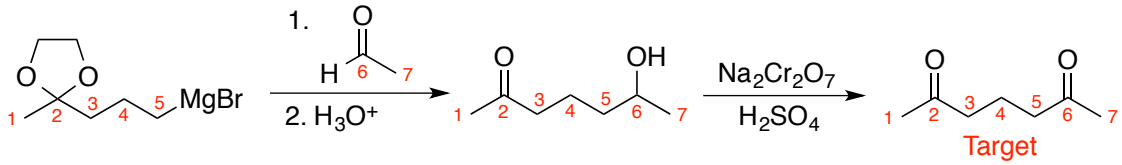
A Grignard reagent would seem to be an ideal solution because an alkyl bromide can be converted to a Grignard reagent, which can then react with the C6 aldehyde. However, when we look a bit deeper, we encounter a problem. The desired Grignard reagent will not be viable because it is not compatible with the C2 ketone. Remember that Grignard reagents react with ketones as well as aldehydes.



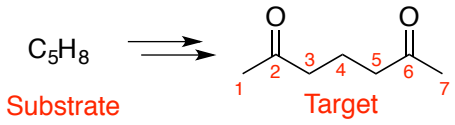
The hint helps us to solve what would otherwise be an intractable problem. In the section on acetals, we learned that acetals can be used to protect aldehydes or ketones from undesired reactions. In this case, we can exploit that fact. The ketone is first converted to an acetal. Any acetal would suffice; however, it is common to see cyclic acetals used in this capacity because they are fairly robust protecting groups. With the ketone carbonyl thus masked, the Grignard reagent can be safely prepared. Grignard reagents react with carbonyls but *not* with acetals.



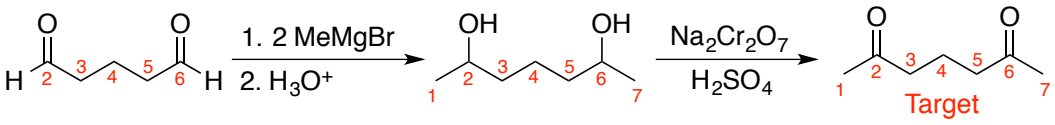
The Grignard reagent can then undergo reaction with acetaldehyde (our other allowed substrate). If we use aqueous acid during the second step of the Grignard reaction, it will not only protonate the alkoxide intermediate but also hydrolyze the cyclic acetal to unveil the ketone. Finally, the alcohol can be oxidized by chromic acid (or PCC) to give the target diketone.



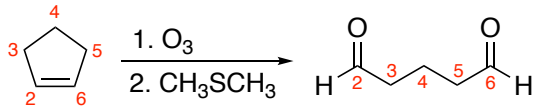
41. This synthesis problem is a bit more open-ended than usual. We are merely given a formula for the reactant, rather than its structure. Nevertheless, it is readily apparent that two carbons are added in the course of this synthesis. They could be added as one two-carbon block or as two single-carbon units. Given the symmetry of the molecule, it would be attractive to add the two carbons at the termini (C1 and C7) because this would entail performing the same reaction two times.



If we were to add both C1 and C7 to a precursor to the target compound, it would likely be through two Grignard reactions. These would initially yield alcohols at C2 and C6, but those could readily be oxidized to the ketones, yielding the target structure.



The question that remains is how to derive the dialdehyde from a reactant with the formula C_5H_8. When in doubt, it is useful to compare molecular formulas. Notice that the dialdehyde has the formula $C_5H_8O_2$. If we literally removed the two oxygens and linked C2 to C6, we'd have a compound with the formula stipulated: cyclopentene. Cyclopentene can be readily converted to the needed dialdehyde through ozonolysis [see Problem 6(b) for a similar reaction].

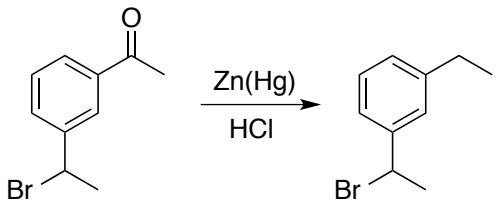


C_5H_8

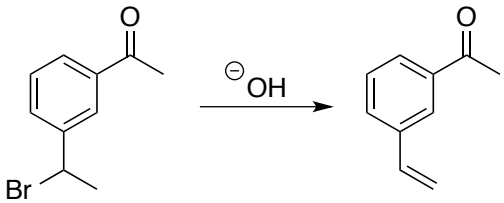
Substrate

42.

(a) To reduce the ketone to the methylene without altering the benzylic bromide, it is best to use the Clemmensen reduction.

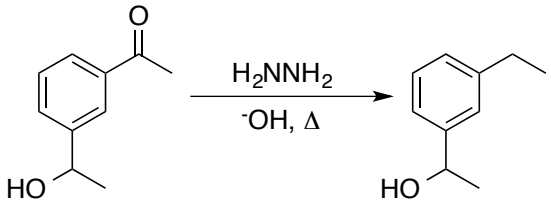


The Wolff-Kishner reduction takes place in base, and under basic conditions substitution and/or elimination (the latter is shown below) can take place giving undesired side products.

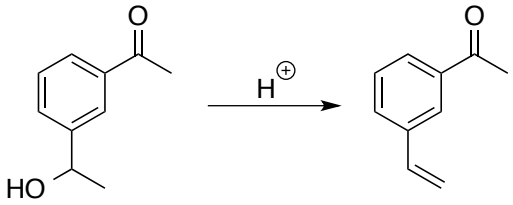


Note that this was not a concern in Problem 12 because the reduction substrate was an aryl halide rather than an alkyl halide. S_N2 and E2 are not a concern when the leaving group is on an sp^2 hybridized carbon.

(b) To reduce the ketone to the methylene without altering the benzylic alcohol, it is best to use the Wolff-Kishner reduction. In this chapter, we showed the Wolff-Kishner reduction in a stepwise fashion (hydrazone formation followed by treatment with base) to highlight the analogy to mechanisms like imine formation; however, recall from the last chapter that the Wolff-Kishner reduction can also be performed simply by heating with hydrazine and hydroxide.

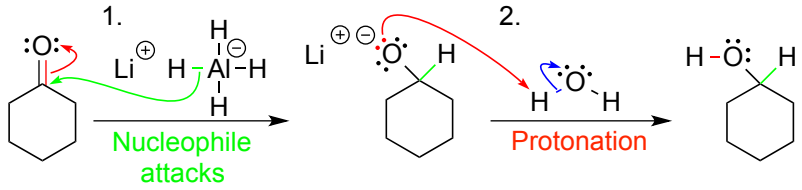


The Clemmensen reduction takes place in acidic media. In acid, the alcohol could undergo acid-catalyzed dehydration. This would be an undesired side reaction.

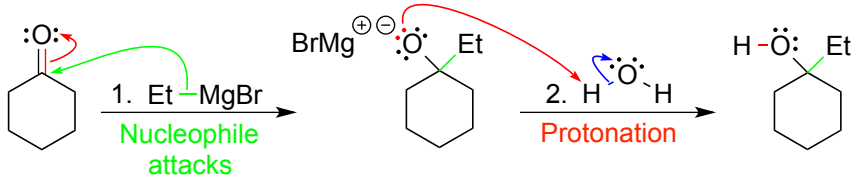


43.

(a) This reduction begins with the nucleophilic attack of hydride (donated from lithium aluminum hydride) on the electrophilic carbonyl carbon. The electrons of the π bond are displaced onto oxygen to form an alkoxide. This alkoxide is neutralized through protonation in step 2 when water is added.



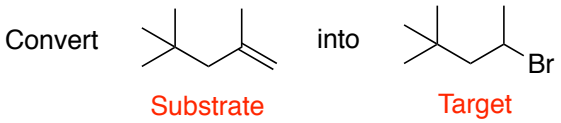
(b) This Grignard reaction begins with the attack of the nucleophilic ethyl group of ethylmagnesium bromide on the electrophilic carbonyl carbon. In the process, the π-bonding electrons are displaced onto oxygen, yielding an alkoxide. This alkoxide is neutralized through protonation in step 2 when water is added.



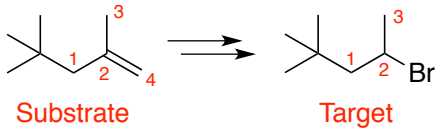
Upon comparison, we see that $LiAlH_4$ reduction and Grignard reaction share a great deal of mechanistic similarity. Both reactions begin with nucleophilic attack on the electrophilic carbonyl carbon. In both instances, the carbonyl π electrons are displaced onto oxygen to give an alkoxide intermediate. And, in both reactions, that

alkoxide is protonated in step 2 when water (or aqueous acid) is added. The only difference is whether the nucleophile is hydride ($H:^-$) or a carbanion ($R:^-$).

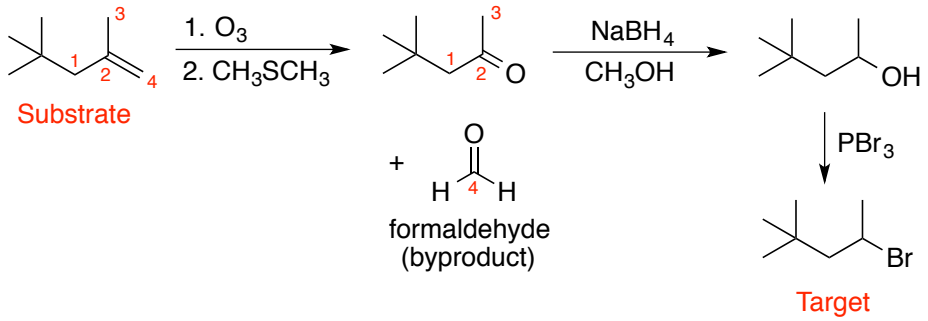
44. It is safest to begin by labeling the substrate and target. In this instance, the substrate appears first due to the wording of the problem.



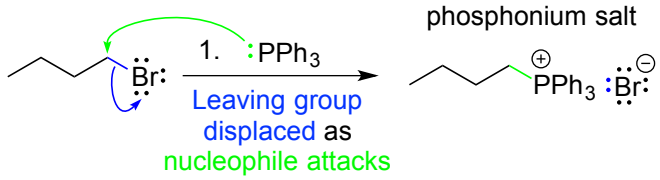
Writing the task in the usual format and numbering highlights the change to the carbon skeleton during this synthesis. A C=C is cleaved. The reaction that this brings to mind is ozonolysis, so we begin our synthesis there.



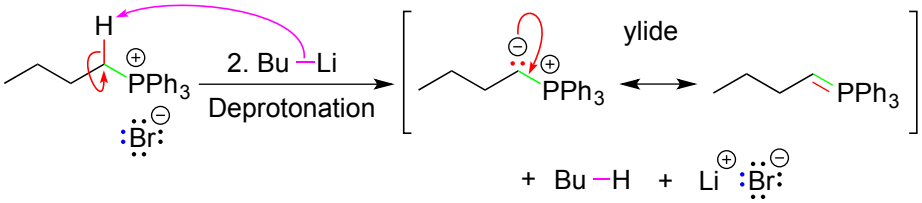
Ozonolysis of the substrate cleaves off C4 in the form of formaldehyde, a byproduct of this synthesis. With the correct carbon skeleton in place, all that remains is to convert the ketone to an alkyl halide. This requires a change in oxidation state. The alkyl halide is at a lower oxidation state (0) than the ketone (+2), so a reduction is needed. Treatment with sodium borohydride in methanol (or $LiAlH_4$ followed by water) provides the necessary reduction. Lastly, the alcohol can be converted to the alkyl bromide using phosphorus tribromide.



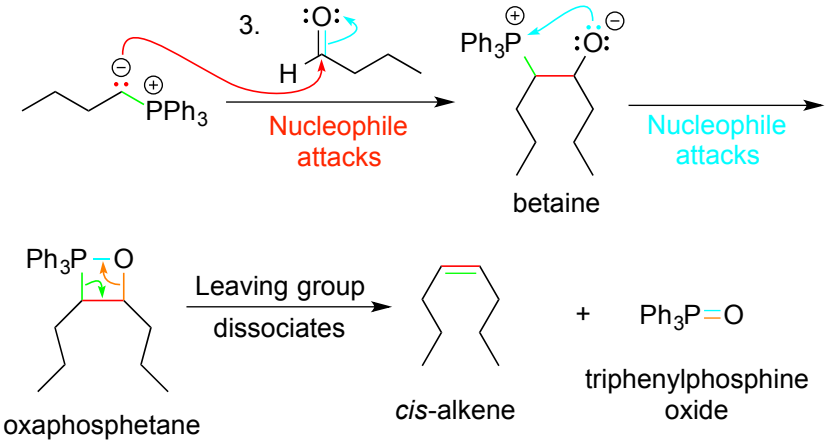
45. The reaction begins with the displacement of bromide by the attack of triphenylphosphine. This generates the phosphonium salt as the first intermediate.



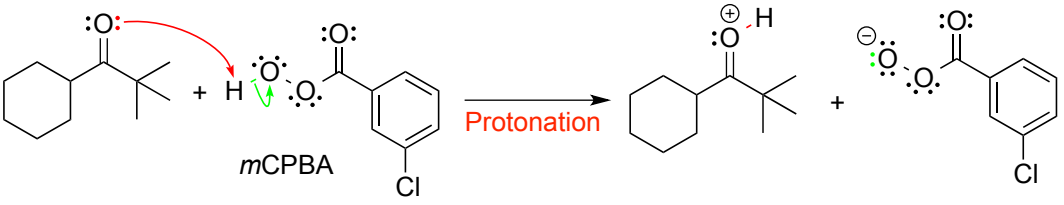
Upon treatment with butyllithium, the phosphonium salt is deprotonated to form the resonance-stabilized ylide.



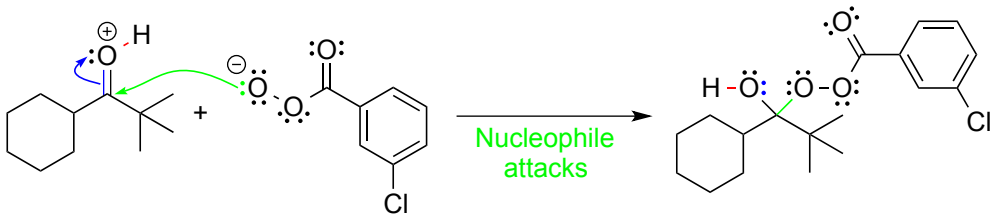
In the final phase of the Wittig reaction, the ylide and the aldehyde are combined. The nucleophilic ylide attacks the electrophilic carbonyl carbon of the aldehyde, displacing the carbonyl π electrons onto oxygen. The intermediate that results is known as a betaine, and it undergoes an intramolecular attack of the nucleophilic alkoxide on the electrophilic phosphonium ion. The oxaphosphetane then extrudes triphenylphosphine oxide as the alkene product is formed.



46. This Baeyer-Villiger oxidation can begin with protonation of the ketone by *m*CPBA.



With the ketone's electrophilicity thus enhanced, the conjugate base of *m*CPBA attacks the carbonyl carbon, displacing the π electrons onto oxygen.

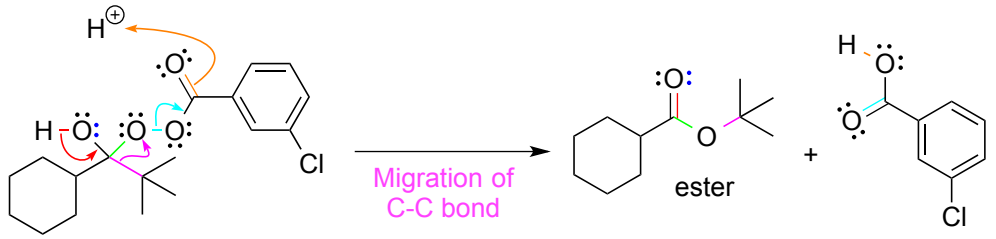


At this stage the carbonyl will re-form as an R group migrates from the carbonyl carbon to what is about to become the carboxyl (sp^3) oxygen. The migratory-aptitude ranking places tertiary before secondary. This is because a tertiary R group is more electron rich and therefore a better nucleophile.

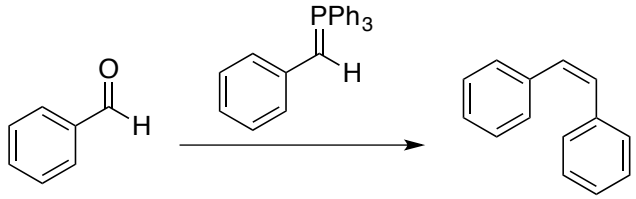
Migrates fastest ⟹ Migrates slowest

Tertiary > Secondary > Aryl > Primary > Methyl

Consequently, the *tert*-butyl group migrates as the carbonyl is re-formed. In the process, *meta*-chlorobenzoate is displaced as a good leaving group. It acquires a proton as it is ejected, leading to the formation of *meta*-chlorobenzoic acid as a byproduct of the reaction. The newly formed ester is the product of interest.

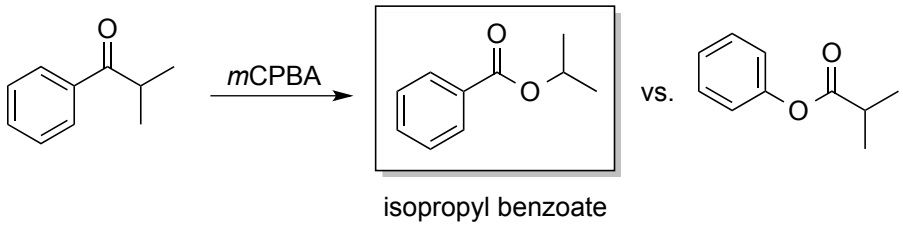


47. The Wittig reaction produces *cis* alkenes, not *trans* alkenes. The investigator was simply expecting to produce the more stable *trans* isomer and forgot about the stereochemistry of the Wittig reaction. Unfortunately, the mass spectrum was not helpful in uncovering the error because *cis* and *trans*-stilbene are isomers and therefore produce the same molecular ion peak. The actual reaction that took place was:

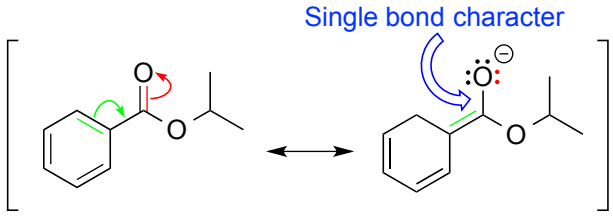


48. When isopropyl phenyl ketone is treated with *m*CPBA, two esters could be formed, depending on whether the isopropyl group or the phenyl group migrates. However, secondary R groups have a greater migratory aptitude than aryl groups,

so we expect the isopropyl group to migrate, providing an ester known as isopropyl benzoate as the major product.

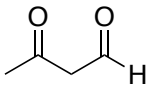


The carbonyl of isopropyl benzoate is part of an ester functional group; however, it is also conjugated to the aromatic ring. This lends single bond character to the carbonyl via resonance. Single bonds oscillate at a lower frequency than double bonds, which explains the reduction of 30 cm^{-1} in the carbonyl-stretching resonance.

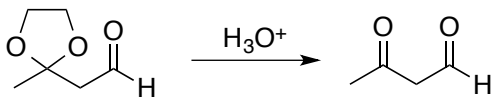


49. Let's begin with an analysis of the ^1H NMR spectrum. The signal between 9 and 10 ppm is suggestive of an aldehyde.

There are also NMR signals suggesting methyl (CH_3) and methylene (CH_2) groups based on their relative integration values. Furthermore, the methyl group's chemical shift indicates that it is adjacent to a carbonyl. The methylene is even more deshielded, so it is likely next to two electron-withdrawing groups (e.g., two carbonyls). All of these data point toward the following structure:



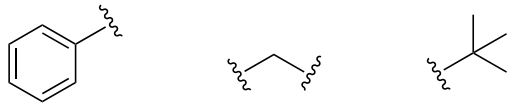
This means that the intended hydrate formation actually led to acetal hydrolysis instead. In retrospect, this makes sense because aqueous acid corresponds to the conditions for acetal hydrolysis.



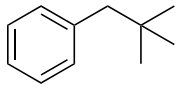
The investigator might have had better luck with base-catalyzed hydrate formation, since acetals are stable in base. Although in Chapter 17 we'll learn about the aldol reaction, which could also occur under such conditions.

50. This problem can be solved in one of two ways. We could work our way through the reaction sequence and then verify that the NMR matches the expected product. Or, we could determine the product's structure based on the NMR and then verify that this makes sense given the sequence of chemical transformations that took place. Since this NMR spectrum is fairly simple, let's try the latter method.

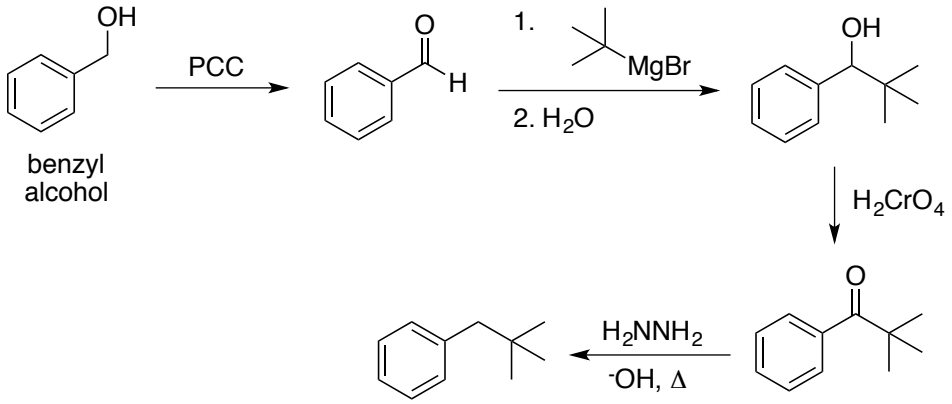
The NMR includes three signals. The singlet for nine hydrogens is very likely a *tert*-butyl group. The singlet for two hydrogens is probably a methylene (CH_2) group. Finally, the multiplet for five hydrogens in the aromatic region corresponds to a monosubstituted benzene ring.



It quickly becomes apparent that there is only one way to put these fragments together.



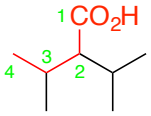
Now, let's see if this product makes sense in light of the reaction sequence, which begins with benzyl alcohol. PCC oxidation would afford benzaldehyde. Grignard reaction with *tert*-butylmagnesium bromide then produces a new benzylic alcohol bearing a *tert*-butyl group on the benzylic carbon. Chromic acid oxidation of this secondary alcohol generates a ketone, whose Wolff-Kishner reduction product does indeed match the structure determined from the NMR data.



Solutions to Problems for Chapter 16: Carboxylic Acids and Their Derivatives

1.

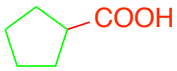
(a) In this molecule, the longest continuous carbon chain is four-carbons in length. The parent is therefore butanoic acid. No "1" is needed to indicate the location of the acid. It is assumed to be at C1. The substituents receive names and numbers as expected though.



2-isopropyl-3-methylbutanoic acid

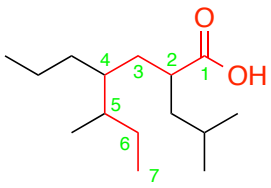
- Four carbon parent = butane
- Replace "e" of suffix with "oic acid"
- Number the carboxylic acid carbon as 1
- Add substituent names and numbers

(b) When a carboxylic acid is a substituent on a cycloalkane, the ring's name is followed by the word "carboxylic acid".



cyclopentanecarboxylic acid

(c) There are two possible seven-carbon parents that include the carboxylic acid. The one with the greater number of substituents is the preferred parent. This heptanoic acid parent needs no locant to identify the placement of the acid. It is assumed to reside at C1. The substituents are named and numbered as anticipated.

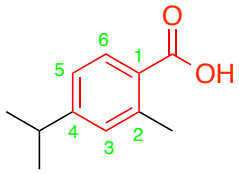


2-isobutyl-5-methyl-4-propylheptanoic acid

- Seven carbon parent = heptane
- Replace "e" of suffix with "oic acid"
- Number the carboxylic acid carbon as 1
- Add substituent names and numbers

2.

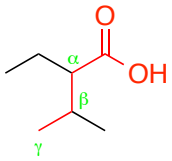
(a) The parent is benzoic acid. The ring carbon bearing the acid is C1, and we number the rest of the ring so as to give the first substituent (methyl) the lowest possible number.



4-isopropyl-2-methylbenzoic acid

- Parent = benzoic acid
- Number the site bearing the carboxylic acid as 1
- Number clockwise to give the first substituent the lowest possible number
- Add substituent names and numbers

(b) The parent is the butyric acid bearing the larger number of substituents. Greek letters can be used to designate the locations of the substituents.

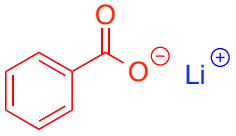


α-ethyl-β-methylbutyric acid

- Parent = butyric acid
- Assign Greek letters to the carbons of the parent, beginning with α as the site next to the carbonyl
- Add substituent names and locations

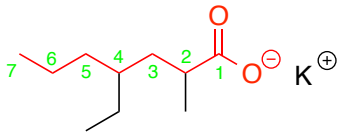
3.

(a) The carboxylate derived from benzoic acid is benzoate. The name of its counterion, lithium in this case, is placed in front of the name.



lithium benzoate

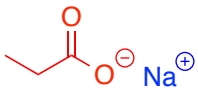
(b) The parent acid is heptanoic acid, making the name of this carboxylate "heptanoate". Just as with a carboxylic acid, the carboxylate carbon is C1, but that is not stated. The substituent names and numbers are added as expected, and finally the name of the counterion is placed in front of the carboxylate name.



potassium 4-ethyl-2-methylheptanoate

- Seven-carbon carboxylic acid parent = heptanoic acid
  - Replace "ic acid" of suffix with "ate"
  - Number the carboxylate carbon as 1
  - Add substituent names and numbers
  - Add counterion's name as a prefix

(c) In this instance, we may choose to provide a systematic or a common name. All that differs between the two methods is whether the parent acid's name is designated as propanoic acid or propionic acid. In either case, the "ic acid" ending is replaced by "ate", and the counterion's name is placed at the front of the name.

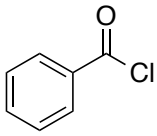


IUPAC name: sodium propanoate

Common name: sodium propionate

4.

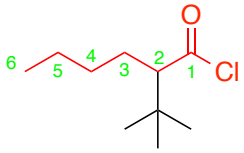
(a) In this case, the parent acid is benzoic acid. The "ic acid" suffix is replaced by "yl chloride" to provide benzoyl chloride as the compound's name.



benzoyl chloride

- Carboxylic acid parent = benzoic acid
- Replace "ic acid" of suffix with "yl chloride"

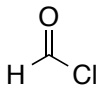
(b) This six-carbon acid chloride is hexanoyl chloride. The carbonyl carbon is numbered as C1, but that number is not stated. The substituent is given a name and number as expected though.



2-*tert*-butylhexanoyl chloride

- Six-carbon carboxylic acid parent = hexanoic acid
  - Replace "ic acid" of suffix with "yl chloride"
  - Number the carbonyl carbon as 1
  - Add substituent names and numbers

(c) This small acid chloride may be named in a systematic or common fashion. All that differs is the name of the parent acid. In the systematic method, it will be methanoic acid; however, the common name is formic acid. In either case, the "ic acid" ending is simply replaced by "yl chloride".

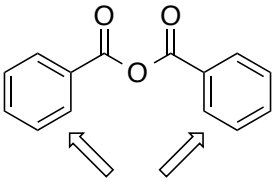


IUPAC name: methanoyl chloride

Common name: formyl chloride

5.

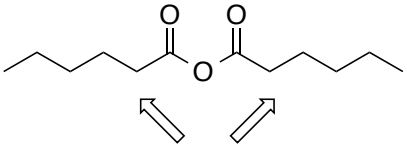
(a) This symmetrical anhydride consists of halves derived from benzoic acid, making it benzoic anhydride.



benzoic anhydride

benzoic acid fragments

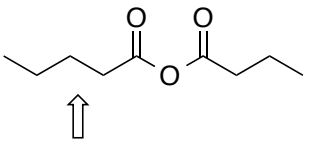
(b) This symmetrical anhydride is built from two hexanoic acid fragments, making it hexanoic anhydride.



hexanoic anhydride

hexanoic acid fragments

(c) This unsymmetrical anhydride is constructed from a four-carbon and five-carbon acid. Each of these may be named using the systematic or common approach. Therefore, the molecule can be given an IUPAC name of butanoic pentanoic anhydride or a common name of butyric valeric anhydride.



butanoic (systematic) or
butyric (common) acid fragment

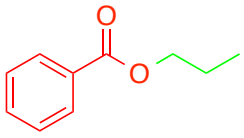
pentanoic (systematic) or
valeric (common) acid fragment

IUPAC name: butanoic pentanoic anhydride

Common name: butyric valeric anhydride

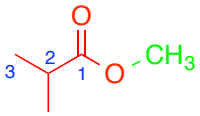
6.

(a) This ester consists of a propyl group bonded to the carboxyl oxygen of benzoate.



propyl benzoate

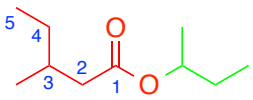
(b) This ester bears a methyl group on the carboxyl oxygen. The other half of the molecule is 2-methylpropanoate if the systematic method is used or α-methylpropionate if a common name is applied.



IUPAC name: methyl 2-methylpropanoate

Common name: methyl α-methylpropionate

(c) This ester has a *sec*-butyl group on the carboxyl oxygen. The other portion of the molecule is 3-methylpentanoate or β-methylvalerate depending on whether the systematic or common name is used. Remember to choose the longest continuous carbon chain for the parent (i.e., the horizontal four-carbon carboxylate is *not* the correct parent).

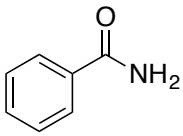


IUPAC name: *sec*-butyl 3-methylpentanoate

Common name: *sec*-butyl β-methylvalerate

7.

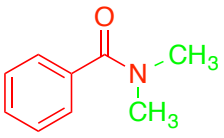
(a) Benzoic acid is the parent carboxylic acid. The "oic acid" ending is removed and replaced with "amide" to give benzamide as the name.



benzamide

- Carboxylic acid parent = benzoic acid
- Replace "oic acid" of suffix with "amide"

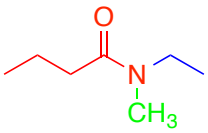
(b) This molecule also has a benzamide parent. However, there are also two methyl substituents on the nitrogen atom. Their location must be designated using "*N*." Remember, that each of the two substituents needs a locant, so the name is *N*,*N*-dimethylbenzamide, *not N*-dimethylbenzamide.



N,N-dimethylbenzamide

- Carboxylic acid parent = benzoic acid
- Replace "oic acid" of suffix with "amide"
- Substituents on nitrogen have location designated using *N*

(c) This parent may be named butanamide or butyramide. In either case, there are ethyl and methyl substituents on the nitrogen atom, whose locations are designated using the locant "*N*."



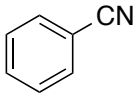
IUPAC name: *N*-ethyl-*N*-methylbutanamide

Common name: *N*-ethyl-*N*-methylbutyramide

- Four-carbon carboxylic acid parent = butanoic (systematic) or butyric (common) acid
- Replace "oic or ic acid" of suffix with "amide"
- Substituents on nitrogen have location designated using *N*

8.

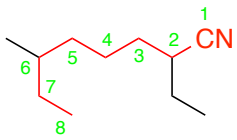
(a) The parent acid is benzoic acid. The "oic acid" suffix is removed and replaced with "onitrile" to generate the name benzonitrile.



benzonitrile

- Carboxylic acid parent = benzoic acid
- Replace "oic acid" of suffix with "onitrile"

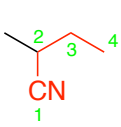
(b) The longest continuous carbon chain containing the nitrile functional group is eight carbons in length, making the parent octanonitrile. The nitrile carbon is numbered C1, but that number is merely implied. It is not stated. Substituent names and numbers are applied as usual though.



2-ethyl-6-methyloctanonitrile

- Eight-carbon carboxylic acid parent = octanoic acid
- Replace "oic acid" of suffix with "onitrile"
- Number the nitrile carbon as 1
- Add substituent names and numbers

(c) The longest continuous carbon chain that includes the parent is four-carbons long. Therefore, the parent is butanonitrile if the IUPAC method is used or butyronitrile if the common name is applied. The substituent's location can be designated using a number or a Greek letter, depending on the method used.



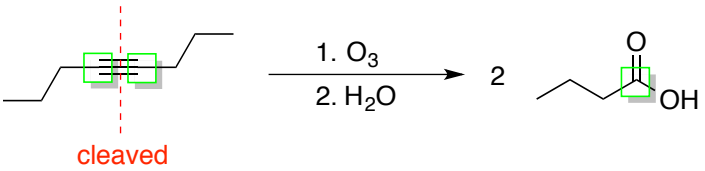
IUPAC name: 2-methylbutanonitrile

Common name: α-methylbutyronitrile

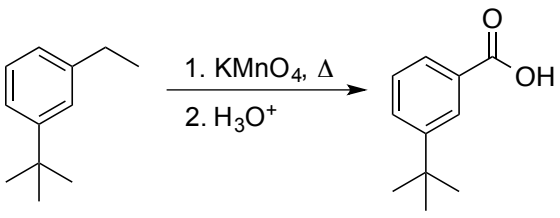
- Four-carbon carboxylic acid parent = butanoic (systematic) or butyric (common) acid
- Replace the "oic or ic acid" suffix with "onitrile"
- Add substituent names and numbers

9.

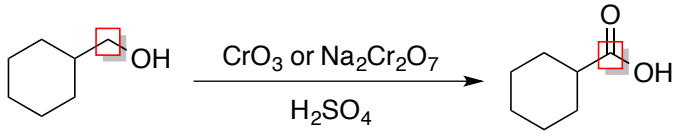
(a) We are told that an alkyne must be used to prepare two equivalents of a carboxylic acid. This is a clear indication that the alkyne subjected to ozonolysis must be symmetrical. Since there are four carbons in the acid product, each half of the symmetrical alkyne must contain four carbons as well.



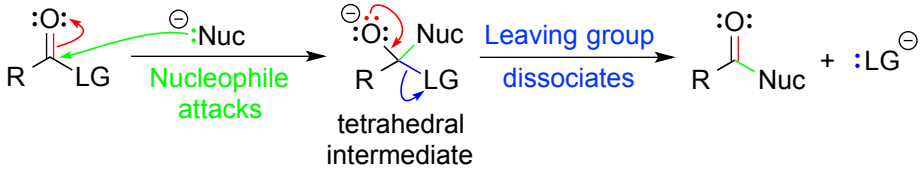
(b) The preparation of a benzoic acid suggests benzylic oxidation using potassium permanganate. Many different reactants could yield this product, but we are constrained by the given molecular formula ($C_{12}H_{18}$), which shows that the reactant can possess only one more carbon than the product. Therefore, the reactant bears an ethyl group at the site of reaction. Notice that the *tert*-butyl group is unaffected by this transformation because it lacks benzylic hydrogens.



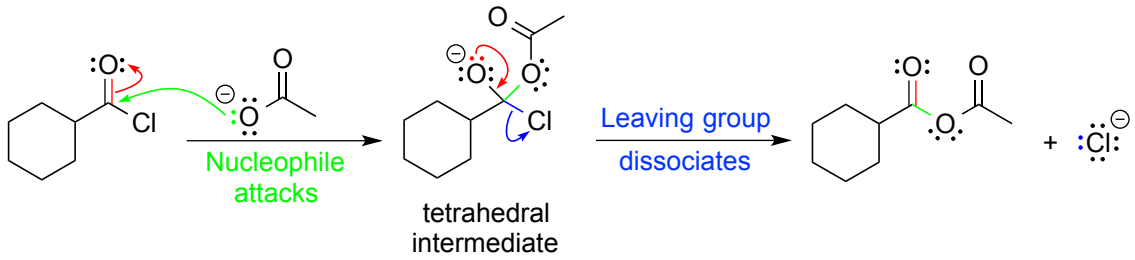
(c) We are told that the reactant is an alcohol. This suggests that the reaction is a chromic acid oxidation, where the chromic acid is prepared *in situ* from chromium trioxide or sodium dichromate and sulfuric acid. The necessary alcohol reactant must have the exact same carbon count as the product, so be sure to include the single carbon pendent to the cyclohexane ring.



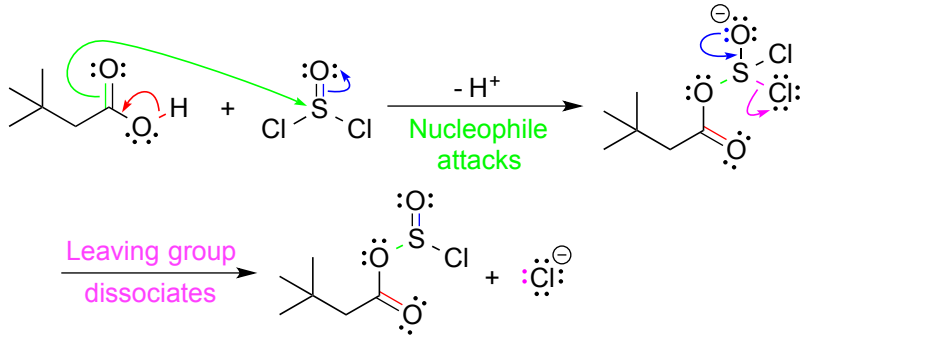
10. Given the presence of a negatively charged nucleophile and the absence of acid catalysis, this appears to be a situation in which the leaving group is particularly good and the conditions are neutral or basic. Such mechanisms follow the generic model shown below.



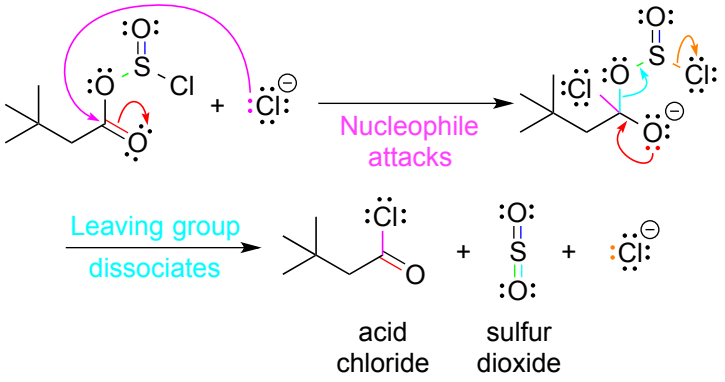
The mechanism for this specific reaction entails the attack of the carboxylate on the carbonyl carbon of the acid chloride. This pushes the carbonyl π-bonding electrons onto oxygen. A tetrahedral intermediate is formed due to the addition of a fourth group to the carbonyl carbon. This tetrahedral intermediate collapses to re-form the carbonyl, and chloride is simultaneously ejected from the substrate. The product is an anhydride, and chloride is a byproduct.



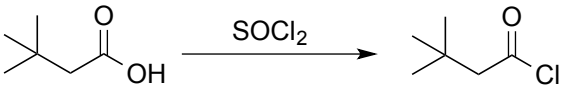
11. The reaction begins when the carboxylic acid loses a proton and attacks thionyl chloride. In the process the sulfur-oxygen π-bonding electrons are displaced onto oxygen. These electrons then re-form the sulfur-oxygen π bond as chloride is displaced. The net result of this phase of the mechanism was to convert the poor leaving group on the carbonyl (hydroxide) into a good one.



The second phase of the mechanism is nucleophilic acyl substitution. Chloride attacks the carbonyl carbon, displacing the π-bonding electrons onto oxygen. The tetrahedral intermediate thus formed then collapses to re-form the carbonyl. The good leaving group is simultaneously displaced. However, rather than simply being lost as an anion, the electrons from the C-O bond fall between sulfur and oxygen to form the second π bond of sulfur dioxide. Chloride is ultimately the anion that is displaced. This fragmentation of the leaving group serves to place the negative charge on a halogen, while also increasing the entropy of the system by releasing sulfur dioxide as a gas.

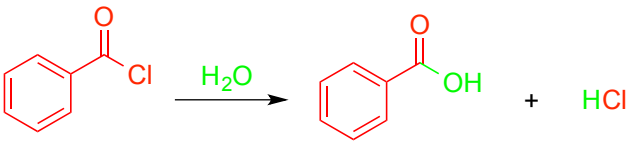


The overall reaction converted the carboxylic acid to an acid chloride.

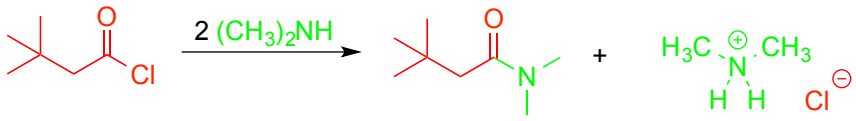


12.

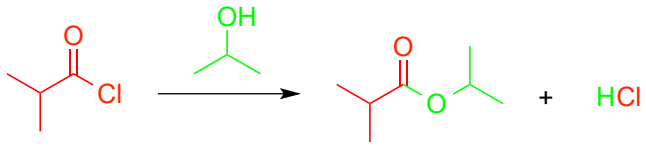
(a) Water nucleophilically attacks the carbonyl carbon, ultimately displacing chloride and losing a proton to provide the carboxylic acid as the hydrolysis product. Hydrochloric acid is a byproduct of this reaction.



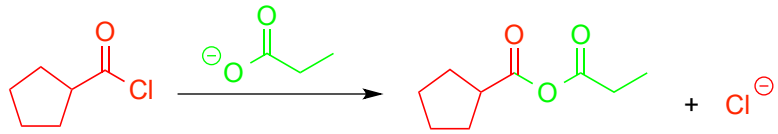
(b) A molecule of dimethylamine nucleophilically attacks the carbonyl carbon, eventually losing a proton and displacing chloride. This yields the amide as the product of interest. The hydrochloric acid byproduct reacts with a sacrificial equivalent of amine, forming a salt as well.



(c) Isopropyl alcohol nucleophilically attacks the carbonyl carbon. Eventually, a proton is lost and chloride is displaced. The product is an ester, and HCl is a byproduct.

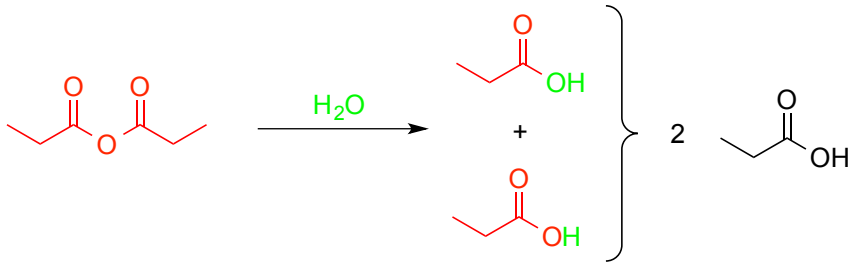


(d) The carboxylate nucleophilically attacks the carbonyl carbon. Upon collapse of the tetrahedral intermediate, chloride is displaced, and an anhydride is generated.



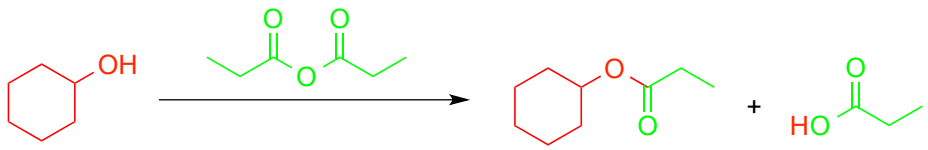
13.

(a) Water hydrolyzes the anhydride by attacking one of the two carbonyl carbons. Ultimately, a proton is lost and a carboxylate is displaced. Since this anhydride is symmetrical, two equivalents of the same carboxylic acid are produced upon hydrolysis.



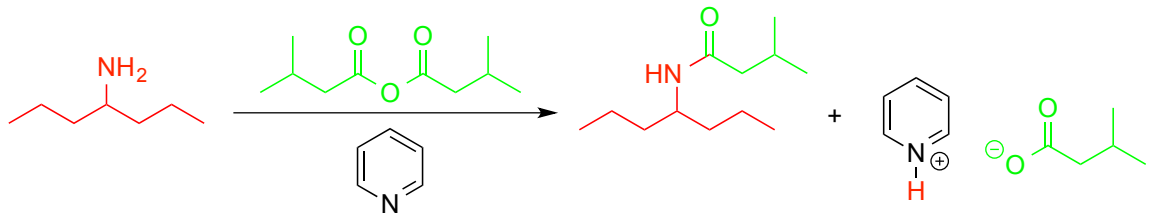
(b) The setup of this problem highlights the fact that the anhydride may sometimes be viewed as a reagent. Another compound, such as cyclohexanol, can be thought of as the reactant. This is largely semantic because both the alcohol and the anhydride are truly reactants. Sometimes, organic chemists will view the alcohol as the molecule of interest. In such cases, it will be written as the reactant, and the anhydride, which is merely modifying the substrate of interest, is written over the arrow.

The alcohol nucleophilically attacks one of the two carbonyl carbons. A tetrahedral intermediate is formed. Eventually, a proton is lost and a carboxylate is displaced. The net result is the formation of an ester, which is the product of interest, and a carboxylic acid as a byproduct.



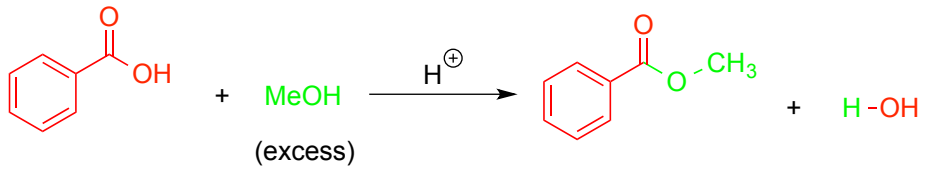
(c) This combination affords no reaction. Chloride can attack the carbonyl carbon, leading to the formation of a tetrahedral intermediate. However, as the best leaving group, it is ejected from the molecule when the tetrahedral intermediate collapses. Consequently, there is no observable transformation.

(d) This is another situation in which the anhydride is being viewed as a reagent. The reactant of interest is the amine. It attacks one of the two carbonyl carbons, forming a tetrahedral intermediate that ultimately loses a proton and a carboxylate. The end result is the formation of an amide, which is the product of interest. The carboxylic acid byproduct undergoes acid-base reaction with pyridine, forming a salt. This is a way of consuming the acid using the cheap and widely available reagent pyridine. If pyridine were not used, a second (sacrificial) equivalent of amine would be necessary to consume the acid liberated during the reaction.

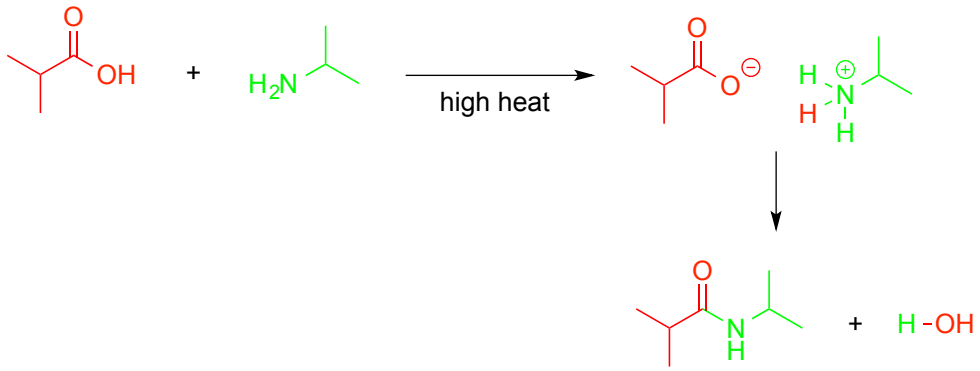


14.

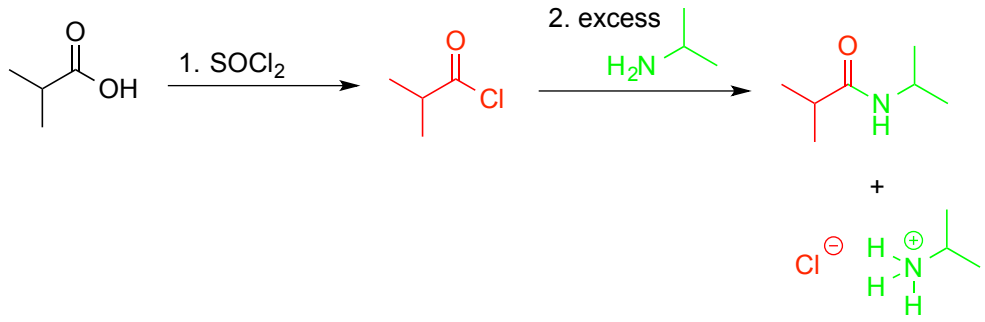
(a) This is a Fischer esterification, in which the acid undergoes nucleophilic acyl substitution in the presence of catalytic acid. Methanol serves as the nucleophile. Methyl benzoate is the end product, and water is released as a byproduct. Since this reaction is freely reversible, an excess of methanol would likely be used to drive the equilibrium toward product.



(b) This nucleophilic acyl substitution only works at very high temperatures. The initial acid-base reaction between the acid and the amine yields a salt that is unreactive in nucleophilic acyl substitution. To counteract this lack of reactivity, extremely high temperatures must be used, and these reaction conditions are generally undesirable.

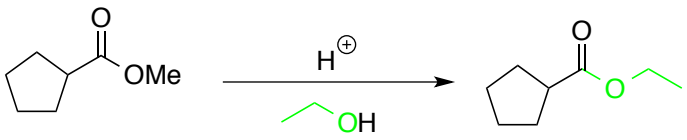


(c) This problem presents a milder method for generating the amide. The carboxylic acid is first converted to the acid chloride. Then, this much more reactive compound readily undergoes nucleophilic acyl substitution with the amine added in step 2. The amine attacks the carbonyl carbon, forming a tetrahedral intermediate that ultimately loses a proton and chloride. The product of interest is the amide. The HCl byproduct is consumed by a second (sacrificial) equivalent of amine to form a salt.

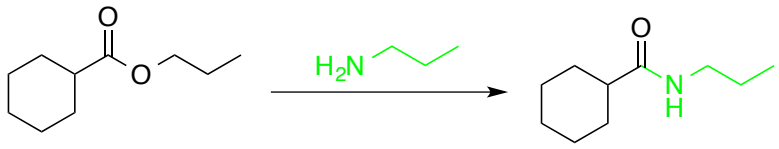


15.

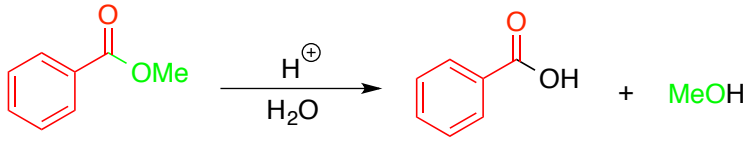
(a) This is a transesterification because the alkyl group bonded to the carboxyl oxygen of the ester is changed. Furthermore, it is acid-catalyzed transesterification because we are shown H^+. We need only add the alcohol that serves as the nucleophile in this nucleophilic acyl substitution: ethanol.



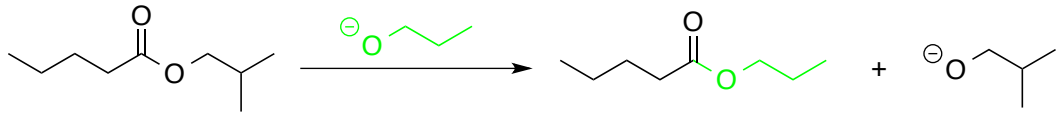
(b) This is an aminolysis reaction. The reagent must be the amine bearing the desired R group, which in this case is propyl. Notice that the displaced alcohol (propanol) was not shown since it is not a product of interest. Sometimes the displaced alcohol will be shown, and sometimes it is omitted.



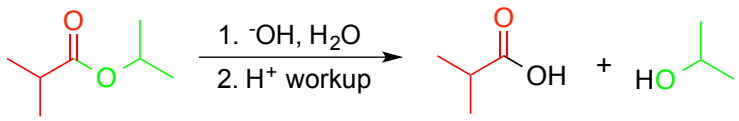
(c) This is an acid-catalyzed hydrolysis since the reagents used are H^+ and water. As a result, the methyl ester will be cleaved into the carboxylic acid (benzoic acid) and methanol as the elements of water are effectively added across the carbonyl carbon-carboxyl oxygen bond.



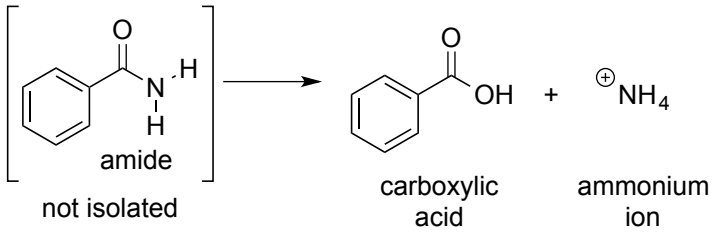
(d) This is a transesterification, and it must be a basic transesterification because the displaced group is an alkoxide rather than a neutral alcohol. As a result, the reagent needed is the alkoxide bearing the desired R group, which is propyl.



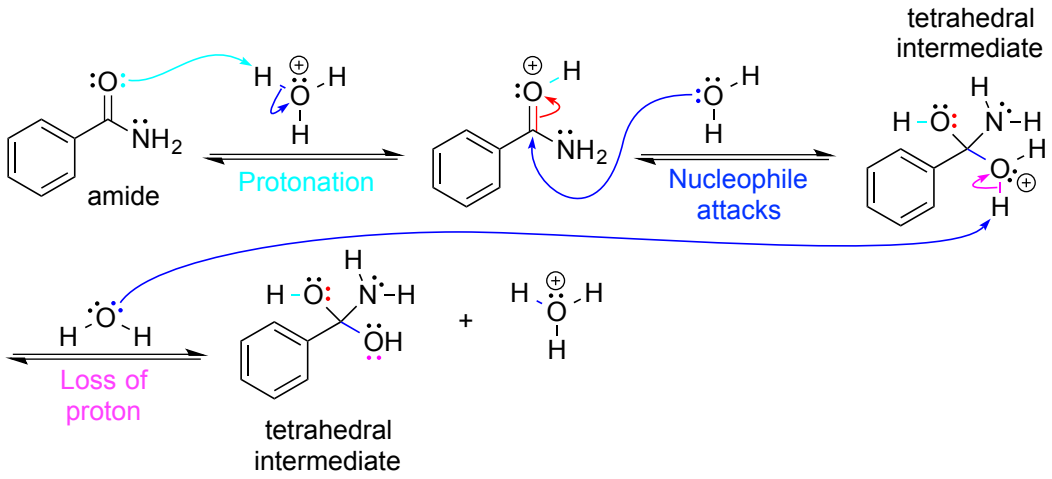
(e) This is a basic hydrolysis, or saponification, because aqueous base is used. The elements of water will ultimately be added across the carbonyl carbon-carboxyl oxygen bond, liberating the carboxylic acid and alcohol fragments of the ester.



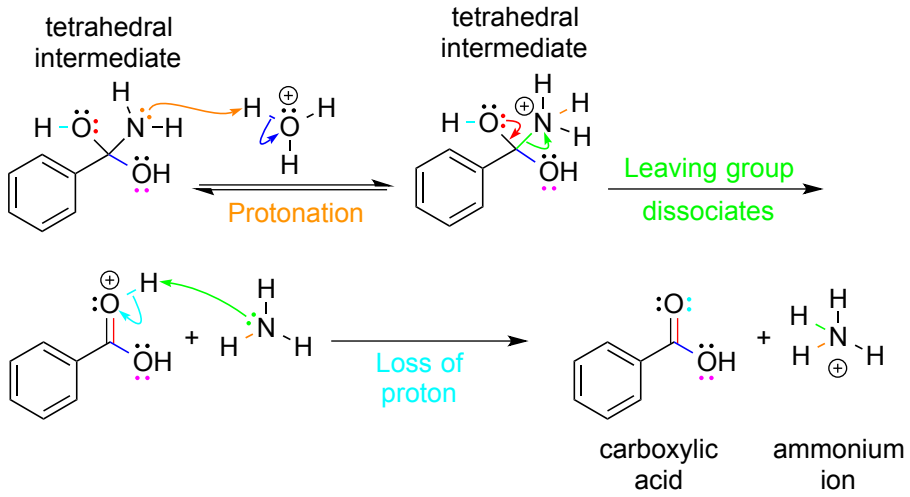
16. For right now we are focused only on the second half of the reaction: the hydrolysis of the amide to the carboxylic acid and the ammonium ion. The conditions are aqueous acid (shown in the first half of this same reaction).



In aqueous acid, the amide can be protonated on the carbonyl oxygen to give a resonance-stabilized cation. Either H^+ or H_3O^+ can be used as the proton source. With the electrophilicity of the carbonyl carbon thus enhanced, water attacks. A proton is then lost to afford a neutral tetrahedral intermediate.

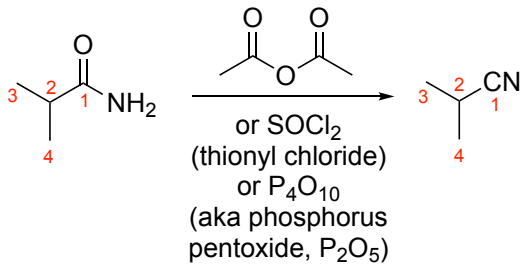


Although this neutral tetrahedral intermediate may look like a reasonable stopping point, there is more that can happen to it under the reaction conditions, so we must explore those possibilities. Protonation on the nitrogen generates an intermediate that we have not yet seen. This positively charged tetrahedral intermediate has a good leaving group (ammonia), which dissociates as the carbonyl is re-formed. Subsequently, loss of a proton affords the carboxylic acid and the conjugate acid of ammonia.

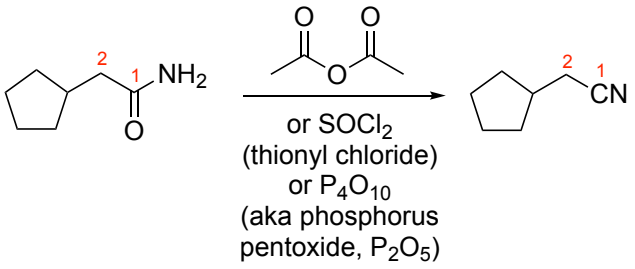


17.

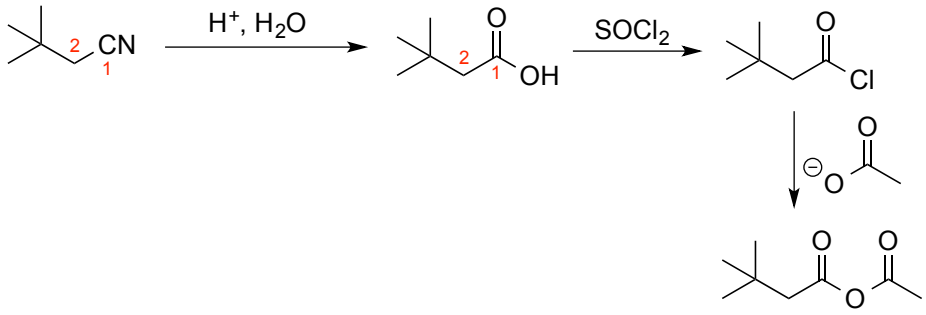
(a) We know that primary amides [i.e., those amides taking the form $RC(O)NH_2$] can be dehydrated using a variety of reagents to yield nitriles. The greatest concern when choosing the reactant is maintaining the correct carbon count. No carbons are added or lost during this transformation, so the reactant must have the same number of carbons as the desired product. A bit of numbering can help to ensure to proper carbon count.



(b) As with part (a) above, the greatest concern is having the proper carbon skeleton in the reactant. Numbering both the reactant and the product can help to ensure that the correct number of carbons is present. Notice that you don't necessarily need to apply numbers or letters to every carbon atom. You need only label those portions of the molecule that might prove to be tricky. In this problem, the five-membered ring is distinctive and easy to draw properly. Only the carbons pendent to the ring have been numbered because that is the site where inadvertently adding or deleting a carbon is most likely to occur.

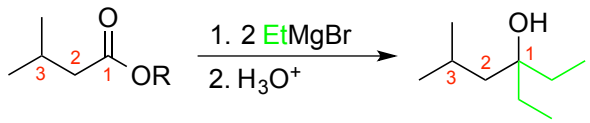


18. We know of no way to prepare an anhydride directly from a nitrile. However, we do know that nitriles can be hydrolyzed to carboxylic acids and that acids can be manipulated in a variety of ways. Consequently, hydrolysis in aqueous acid or base is a logical place to begin. Numbering the carbon skeleton helps to ensure that the proper carbon count is maintained. It is difficult to make an unsymmetrical anhydride in good yield directly from the carboxylic acid, so conversion to the acid chloride provides greater synthetic flexibility. The acid chloride can then be treated with acetate to generate the desired anhydride.



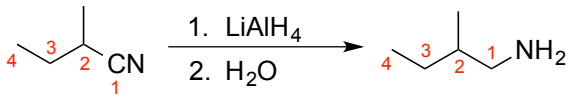
19.

(a) In this problem, we are told to use an ester to prepare a tertiary alcohol bearing two identical alkyl groups. When Grignard reagents react with esters, there are two successive additions to the carbonyl. The first is a nucleophilic acyl substitution that yields the ketone, and the second is a nucleophilic addition that affords the alkoxide. Upon workup, the alkoxide is protonated to provide the alcohol. Therefore, we select an ester in which the carbonyl resides at the site that becomes an alcohol in the product. The identity of the ester's R group is irrelevant because the alkoxide bearing it is displaced during this reaction. We then choose two equivalents of the Grignard reagent that will deliver the appropriate alkyl groups.

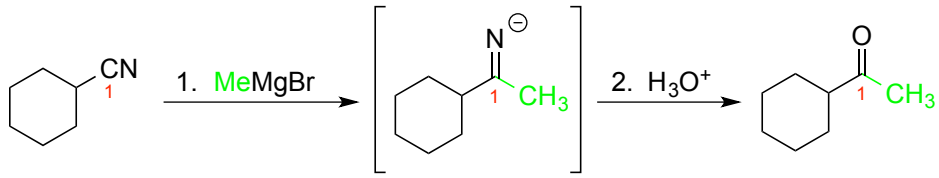


(b) We know that both amides and nitriles can be reduced to amines. However, the given formula for the reactant contains no oxygen, so the reactant must be a nitrile

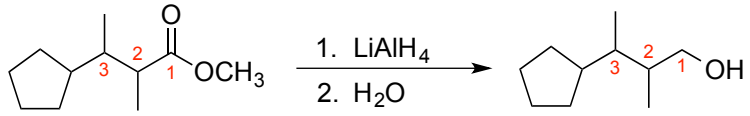
rather than an amide. Since no carbons are gained or lost during this transformation, numbering helps us to maintain a consistent carbon count.



(c) Ketones can be prepared by the reaction of Grignard reagents with nitriles. The nitrile carbon is the one that ultimately becomes the carbonyl carbon of the ketone. The Grignard reagent adds one of the ketone's R groups. Since the reactant should contain seven carbons, it already possesses the cyclohexane ring and one additional carbon, which is the nitrile carbon. Methylmagnesium bromide adds one more carbon to the nitrile. Upon workup, the nitrogen anion is protonated and the resulting imine is hydrolyzed to the ketone.

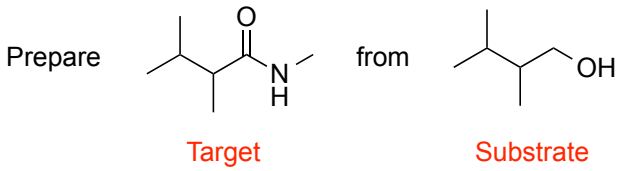


(d) Alcohols can result from the reduction of carboxylic acids or esters. Since the reactant has one more carbon than the product, it must not only be an ester but specifically a methyl ester. Methoxide is displaced during the reduction, explaining the loss of a carbon from the formula. The reduction consists of two successive hydride additions. The first is a nucleophilic acyl substitution yielding the aldehyde, and the second is a nucleophilic addition that forms the alkoxide, which is protonated upon workup.

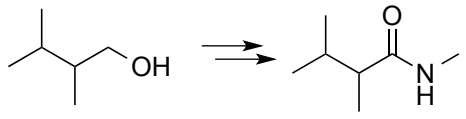


20.

(a) It is always wise to begin a synthesis problem by labeling the substrate and target based on the phrasing of the question.

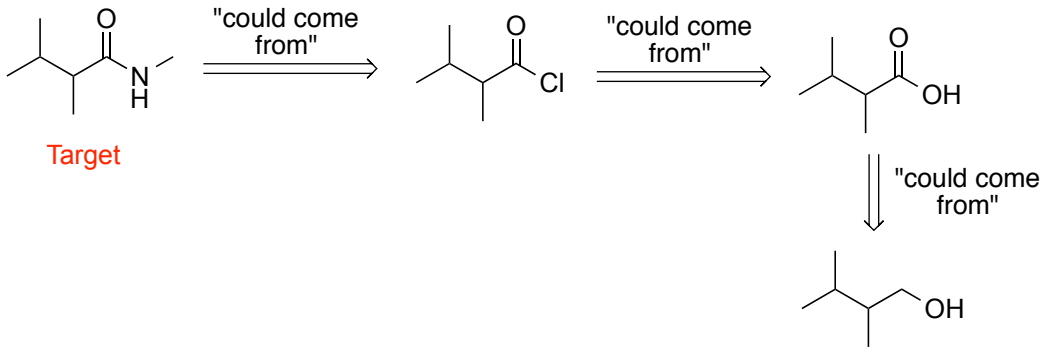


Then, we can rewrite the question in the usual format.



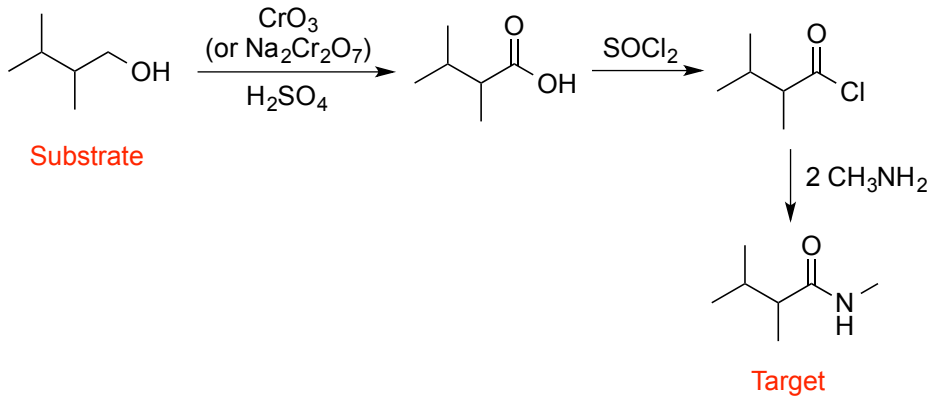
Substrate Target

Amides are most commonly prepared from acid chlorides, which in turn are prepared from carboxylic acids. The needed carboxylic acid can be made by oxidation of the corresponding alcohol, which happens to be our allowed substrate.



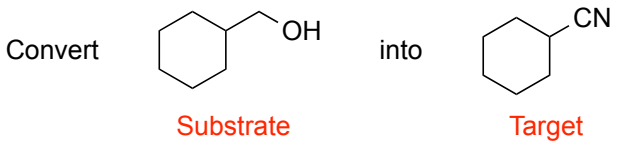
Target Substrate

We want to oxidize this primary alcohol fully, so a chromic acid oxidation is performed. The carboxylic acid is then treated with thionyl chloride to obtain the acid chloride. Treatment with at least two equivalents of methylamine then provides the target amide. The excess methylamine is consumed by reaction with HCl liberated during this final nucleophilic acyl substitution.

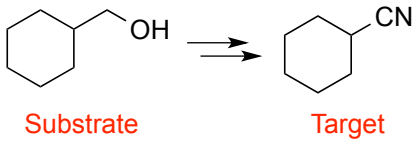


Substrate Target

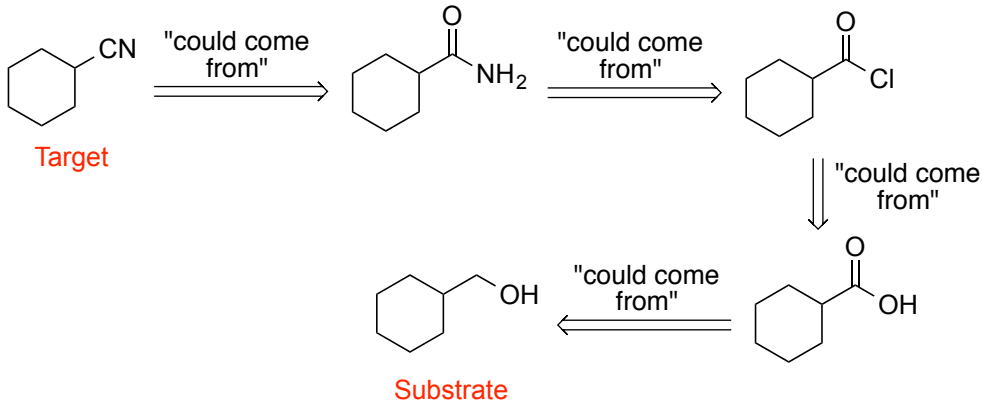
(b) Again, we begin by labeling the substrate and the target. Due to the phrasing of this question, the substrate appears first.



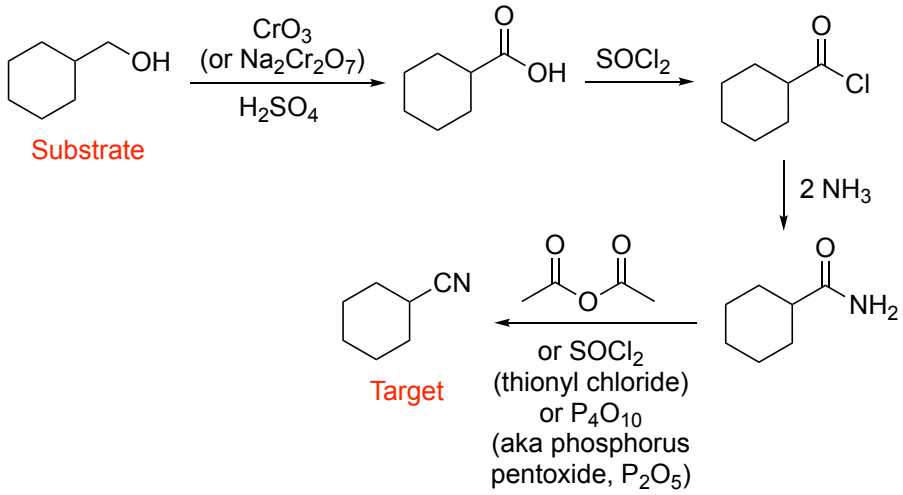
Then, rewrite the question in the usual format.



Notice that the substrate and the target have the same number of carbons: the six-membered ring plus one carbon in the chain attached to the ring. This is an important clue. Although nitriles can be prepared from S_N2 reaction of alkyl halides with cyanide, that would add one carbon to the chain and is therefore not useful in this case. Consequently, we direct our attention instead to the preparation of the nitrile by dehydration of a corresponding amide. In the previous problem, we saw a method to prepare an amide from an alcohol via oxidation, conversion to the acid chloride, and nucleophilic acyl substitution. We can use that same approach here.

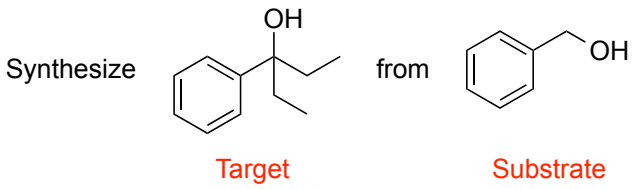


The alcohol is first oxidized to the acid by treatment with chromic acid prepared *in situ* from chromium trioxide or sodium dichromate in sulfuric acid. The acid is then converted to the acid chloride upon treatment with thionyl chloride. Subsequent addition of excess ammonia affords the primary amide, which can finally be dehydrated to yield the nitrile by application of an anhydride, thionyl chloride, or phosphorus pentoxide.

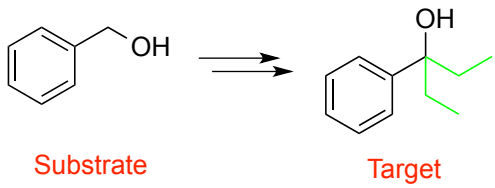


21.

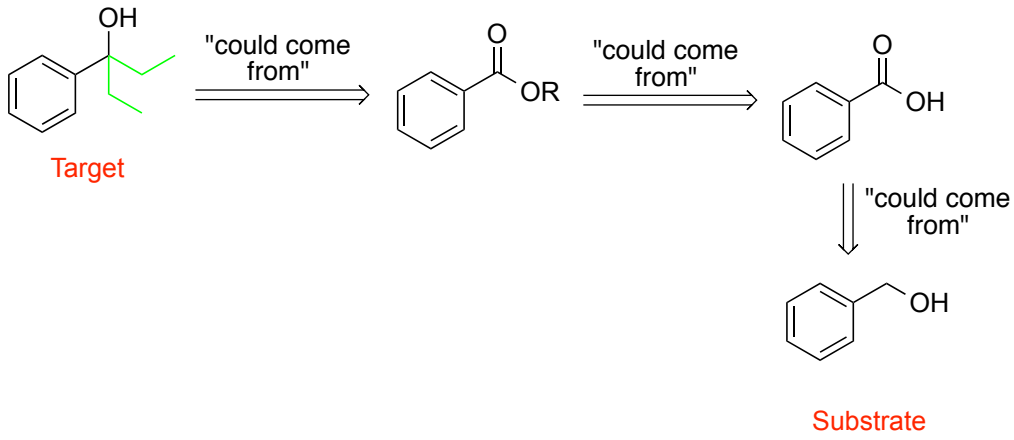
(a) We begin by labeling the substrate and the target.



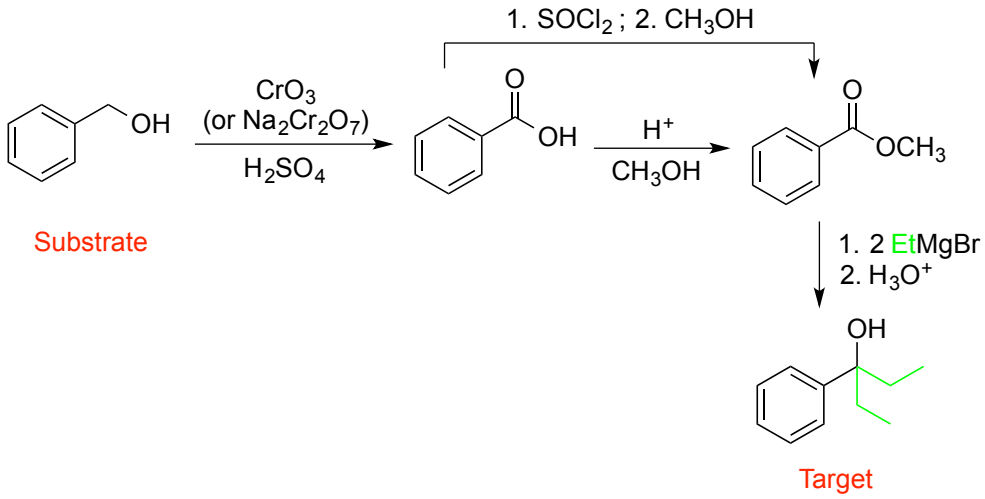
The problem is then rewritten in the typical format. This highlights that two ethyl groups are added to the substrate during this synthesis. We know of no way to add alkyl groups directly to the α-carbon of an alcohol. However, we do know that, when esters react with excess Grignard reagent, two identical alkyl groups are added to the carbonyl, resulting in a tertiary alcohol. This seems ideally suited to the task at hand.



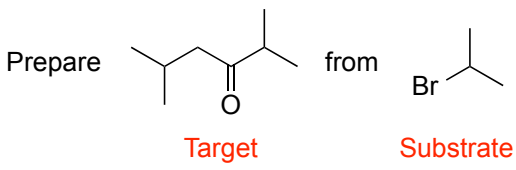
Consequently, we surmise that the tertiary alcohol with two identical alkyl groups can be derived from a corresponding ester. The ester, in turn, can be made from a carboxylic acid, and carboxylic acids are easily prepared by oxidation of primary alcohols, such as our given substrate.



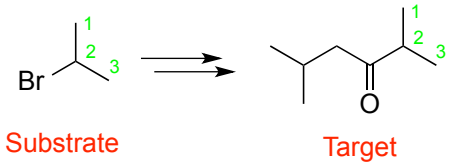
The synthesis begins with chromic acid oxidation of benzyl alcohol to yield benzoic acid. Benzoic acid can be converted to any ester. The identity of the alkyl group bonded to the carboxyl oxygen is irrelevant since it will be displaced as part of an alkoxide during the Grignard reaction. That being the case, we can make a simple ester, such as a methyl ester. This can be done through Fischer esterification. Alternatively, the acid can be converted to the acid chloride, which can then be treated with methanol to yield the same ester. The methyl ester can then be treated with two equivalents of ethylmagnesium bromide to provide the target alcohol. See Problem 19(a) for a similar reaction that provides a tertiary alcohol bearing two ethyl groups.



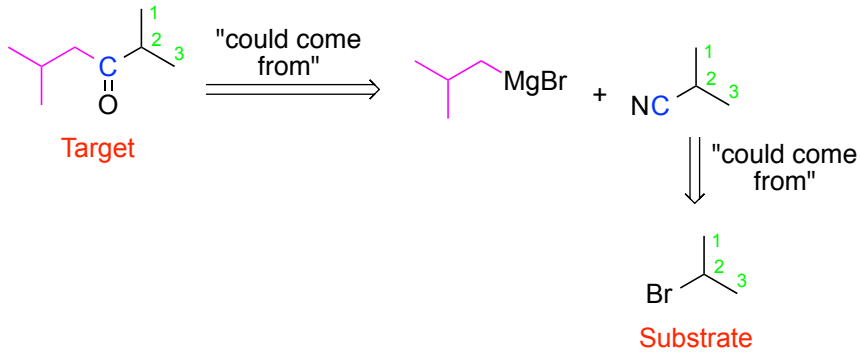
(b) Begin by labeling the substrate and the target based on the phrasing of the question.



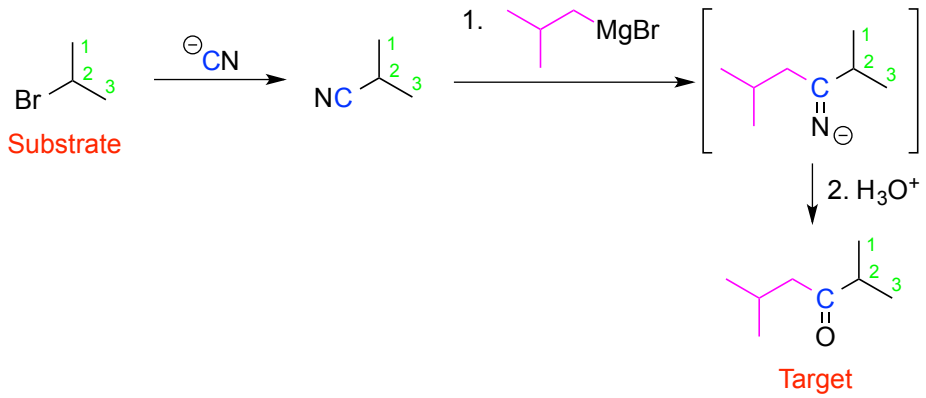
Then, rewrite the task in the usual format. There is an obvious change to the carbon skeleton, and the question is how best to achieve it. We know that the Grignard reaction provides a versatile method for the extension of a molecule's carbon framework; however, ketones are not often the product of Grignard reactions because ketones, themselves, are reactive with Grignard reagents.



An exception is the reaction of nitriles with Grignard reagents. This type of reaction does afford a ketone product. The needed nitrile can be obtained from the S_N2 reaction of isopropyl bromide with cyanide.

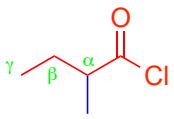


The S_N2 reaction is the starting point for this synthesis, in which the carbon of cyanide will serve as a linchpin for the connection of the isopropyl group of the alkyl halide with the isobutyl group of the Grignard reagent.



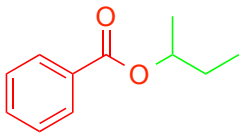
22.

(a) The parent is a four-carbon acid chloride, bearing the common name butyryl chloride. In common nomenclature, the carbons of the parent can be labeled with Greek letters, beginning with α for the carbon adjacent to the carbonyl carbon. The methyl group resides on the α carbon.



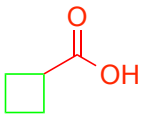
α-methylbutyryl chloride

(b) The parent in this ester is the carboxylate benzoate. The *sec*-butyl group resides on the carboxyl oxygen.



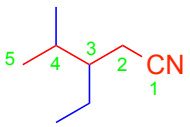
sec-butylbenzoate

(c) This carboxylic acid is pendent to a cyclobutane ring.



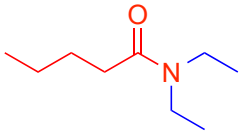
cyclobutanecarboxylic acid

(d) This molecule has a five-carbon parent, in which C1 is part of a nitrile functional group. C3 bears an ethyl group, and C4 bears a methyl group.



3-ethyl-4-methylpentanonitrile

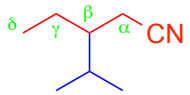
(e) This amide is given the common name valeramide, denoting the present of five carbons in the parent chain. There are two ethyl groups, both of which are given the locant *N* to indicate their attachment to the amide nitrogen.



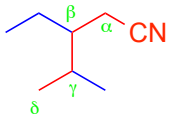
N,*N*-diethylvaleramide

23.

(a) We should begin by drawing the structure indicated by the name. Valeronitrile is the common name for a five-carbon nitrile. This compound bears an isopropyl group at the β carbon.

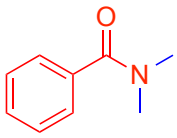


Five carbons is the correct length for the parent chain; however, there are two possible five-carbon parents in this molecule. The other five-carbon parent (shown below) has a larger number of substituents, making it the preferred parent. As a result, the proper name for this compound is β-ethyl-γ-methylvaleronitrile.

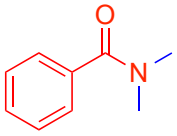


β-ethyl-γ-methylvaleronitrile

(b) Benzamide is the name for the amide derived from benzoic acid. This benzamide has two methyl groups. However, we've been provided with only one locant. The most logical assumption would be that both methyls reside on the amide nitrogen.

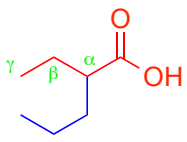


The proper name for such a molecule is *N*,*N*-dimethylbenzamide. Notice that there are two locants (both *N*), one for each substituent.

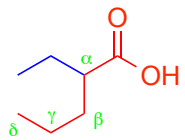


N,*N*-dimethylbenzamide

(c) Butyric acid is the common name for a four-carbon carboxylic acid. There is a propyl group attached to the α carbon.

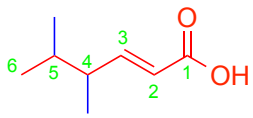


Upon closer inspection, it becomes apparent that four carbons is not the proper length for the parent. There is a longer chain of five carbons, making this a valeric acid derivative in which an ethyl group resides on the α carbon.

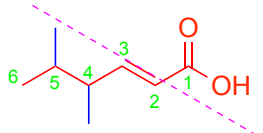


α-ethylvaleric acid

24. The longest continuous carbon chain possesses six carbons. Such an alkene would be known as a "hexene". To indicate the presence of the carboxylic acid, the "e" of the suffix is removed and replaced by "oic acid", making this a hexenoic acid parent. Since the acid has priority, it is given the number 1. Therefore, this is more specifically a 2-hexenoic acid. Remember that no number is needed for the acid. It is assumed to be at C1. However, the alkene could appear at multiple locations, so it must be given a locant. Then, we add substituents and their numbers, giving 4,5-dimethyl-2-hexenoic acid.



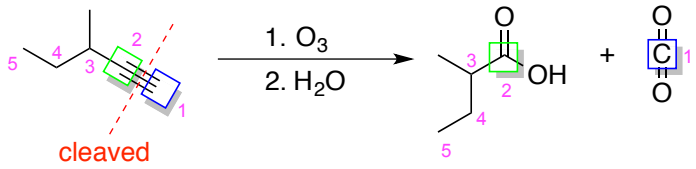
Finally, we must insert (*E*) as a prefix to show the double bond geometry. The complete name is therefore (*E*)-4,5-dimethyl-2-hexenoic acid.



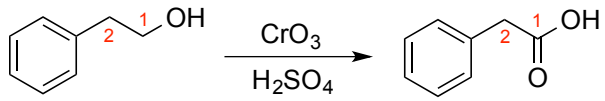
High priority groups on opposite sides of an axis through and parallel to the alkene = *E*

25. All three of these transformations are methods for the preparation of carboxylic acids.

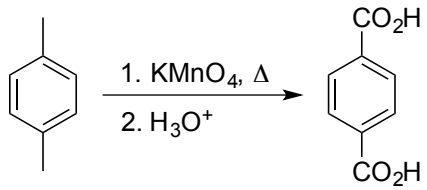
(a) During ozonolysis of a terminal alkyne, the triple bond is cleaved, liberating a carboxylic acid and carbon dioxide. A bit of numbering is useful to keep track of the carbons. In this case, C1 becomes carbon dioxide, and C2 becomes the carboxylic acid.



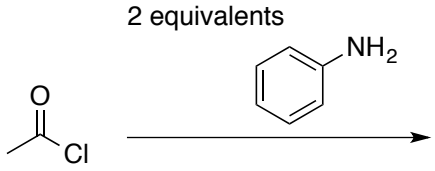
(b) Chromic acid oxidation of a primary alcohol generates a carboxylic acid having the same carbon skeleton as the reactant.



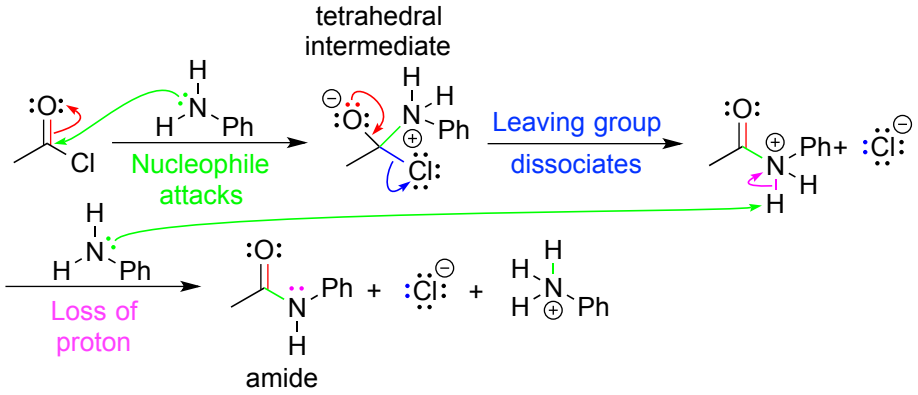
(c) Benzylic oxidation leads to the oxidation of any benzylic carbon having at least one hydrogen. The end product of this oxidation is a carboxylic acid. In this case, both of the benzylic carbons are methyl groups, so they are both oxidized to the corresponding acids.



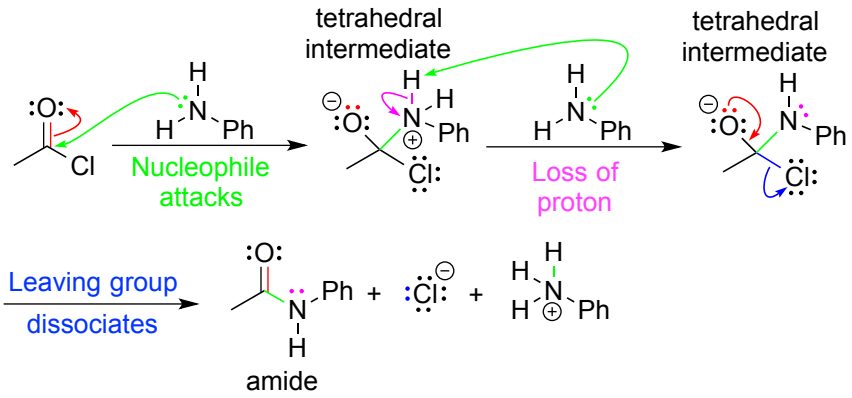
26. The construction of this problem illustrates that there is more than one way to phrase a particular chemical reaction. The treatment of 1 equivalent of an amine with 0.5 equivalents of acid chloride is mathematically the same as the treatment of 1 equivalent of acid chloride with 2 equivalents of amine. The latter phrasing is what we have seen more frequently in this chapter, and if you wish, the problem can be rewritten in that fashion.



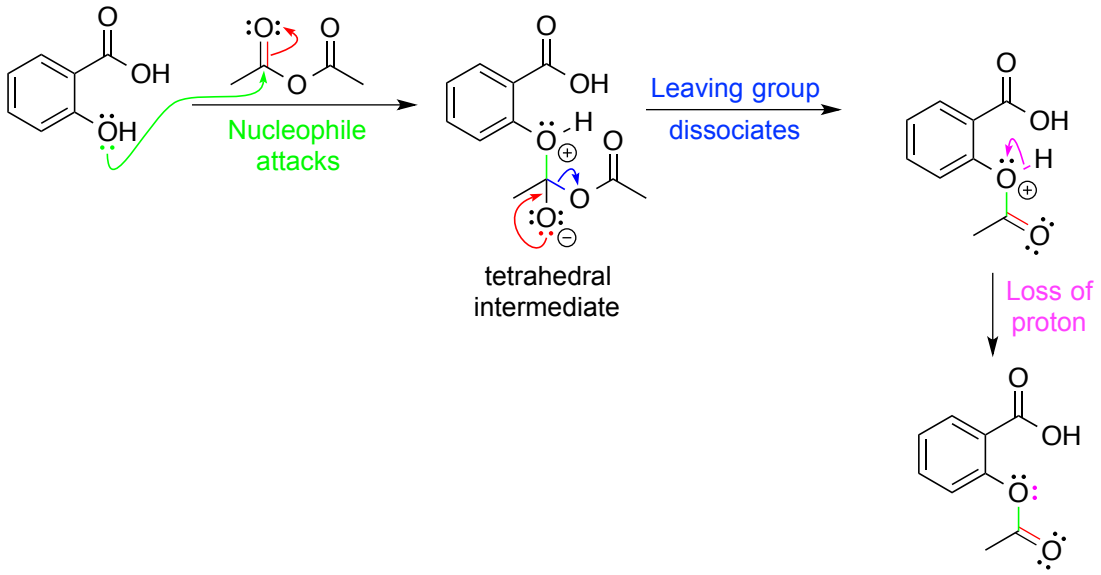
In any event, there is twice as much amine as acid chloride, which will be important at the end of this mechanism. This is a nucleophilic acyl substitution of an acid chloride, which begins with the attack of the amine ($PhNH_2$) on the carbonyl carbon. The π bond is displaced onto oxygen, and the tetrahedral intermediate thus formed subsequently collapses and displaces chloride in the process. The loss of a proton from nitrogen completes the reaction, and the HCl liberated during this process has been consumed by the second equivalent of amine. In other words, the HCl salt of the amine is a byproduct of this reaction, and it is the reason that a sacrificial equivalent of amine is necessary.



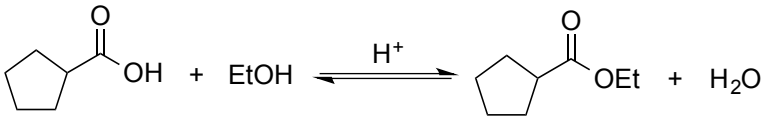
It is also worth noting that the final two mechanistic steps can be reversed. It is similarly reasonable to show the loss of a proton prior to the collapse of the tetrahedral intermediate and the concomitant displacement of the leaving group.



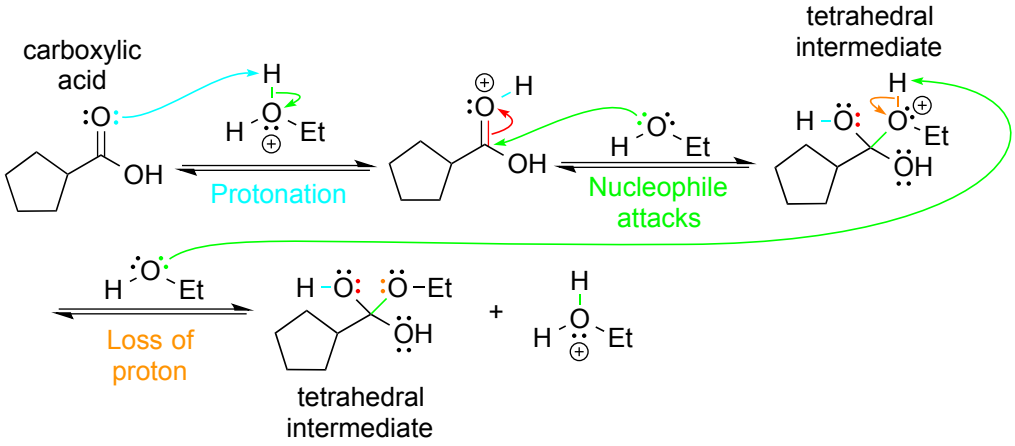
27. The reaction begins with the nucleophilic attack of the phenolic hydroxyl group on one of the two carbonyl carbons of acetic anhydride. The carbonyl π-bonding electrons are displaced onto oxygen, forming a tetrahedral intermediate. This tetrahedral intermediate then collapses and displaces the carboxylate as a good leaving group. Finally, a proton is lost to neutralize the oxonium ion. The proton may be removed by the carboxylate that was displaced in the penultimate step of the mechanism; however, it is also common to simply show a proton being lost to the medium (i.e., without a specified base removing it).



28. The Fischer esterification that would make the desired ethyl ester is the reaction of cyclopentanecarboxylic acid with ethanol in the presence of catalytic acid. Since the reaction is freely reversible, the equilibrium would have to be driven toward products, likely by using excess ethanol.

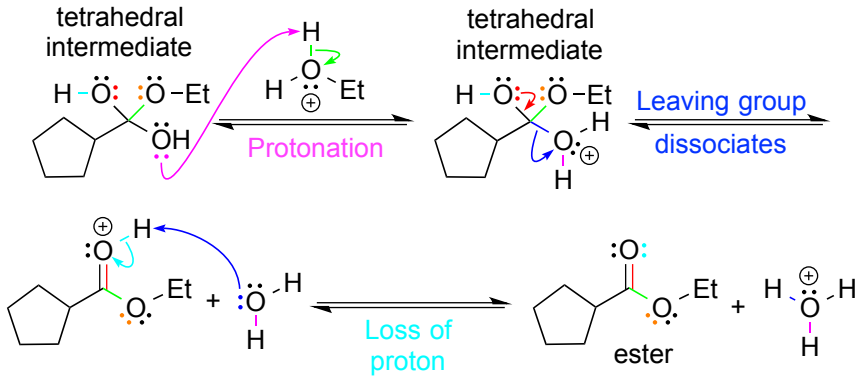


The mechanism begins with the protonation of the carboxylic acid on the carbonyl oxygen. This makes the carbonyl carbon even more electrophilic, and it is therefore attacked by ethanol to form a tetrahedral intermediate. Loss of a proton from the oxonium ion affords a neutral tetrahedral intermediate.

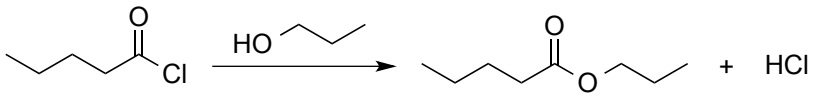


Although this neutral tetrahedral intermediate might appear to be a reasonable stopping point, there is more that can happen to it under the reaction conditions

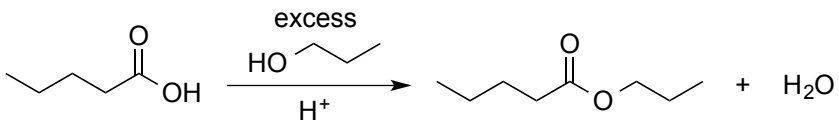
(catalytic acid). One of the two equivalent hydroxyl groups can be protonated to yield an intermediate that we have not yet encountered. The good leaving group (water) dissociates as the carbonyl is re-formed. Finally, the loss of a proton generates the neutral ester product. This proton may be lost to ethanol or water. Alternatively, it is also possible that the specific base that removes the proton may not be shown.



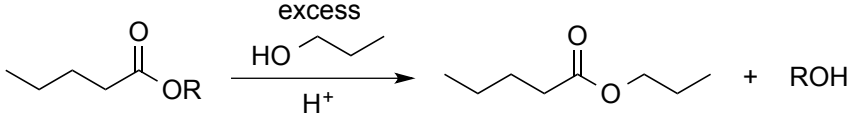
29. Esters can be prepared in a variety of ways. One method is the treatment of an acid chloride (or anhydride) with an alcohol.



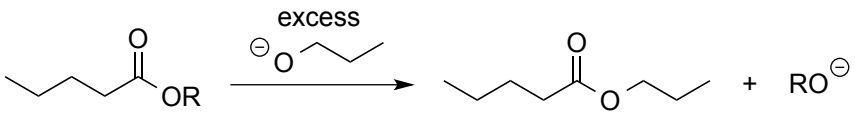
An alternative method is Fischer esterification, in which a carboxylic acid and an alcohol are treated with catalytic acid. This reaction is freely reversible, so an excess of the alcohol is commonly employed to push the reaction toward the products.



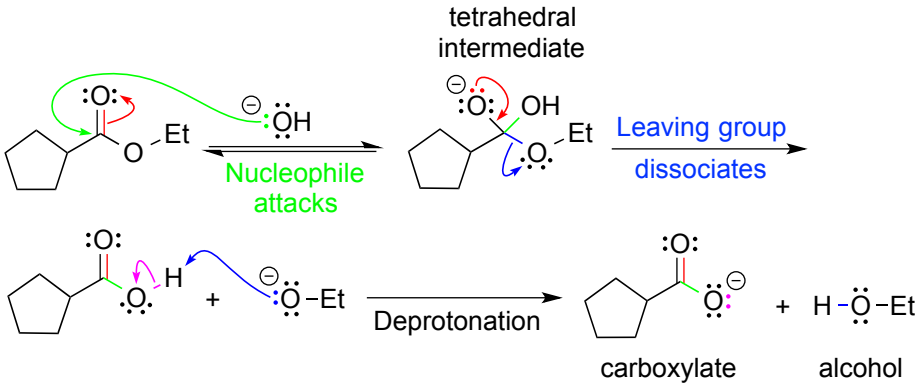
Transesterification is yet another option for the preparation of esters. Transesterification can be conducted under acidic or basic conditions. Acid-catalyzed transesterification is much like Fischer esterification, except that the reactant is an ester. The new alcohol is incorporated during the course of the reaction. This too is a freely reversible process that is commonly driven to completion using an excess of the desired alcohol.



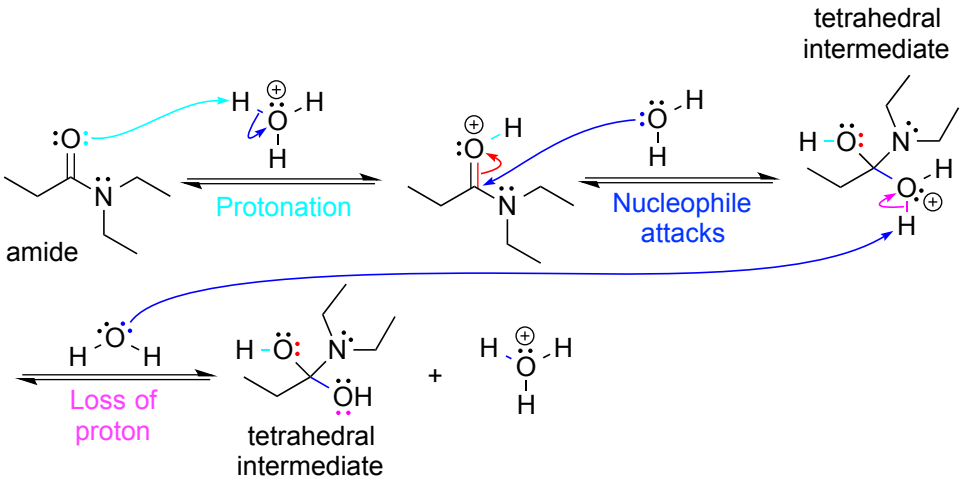
Basic transesterification would use an excess of the desired alkoxide to drive the reaction in the preferred direction.



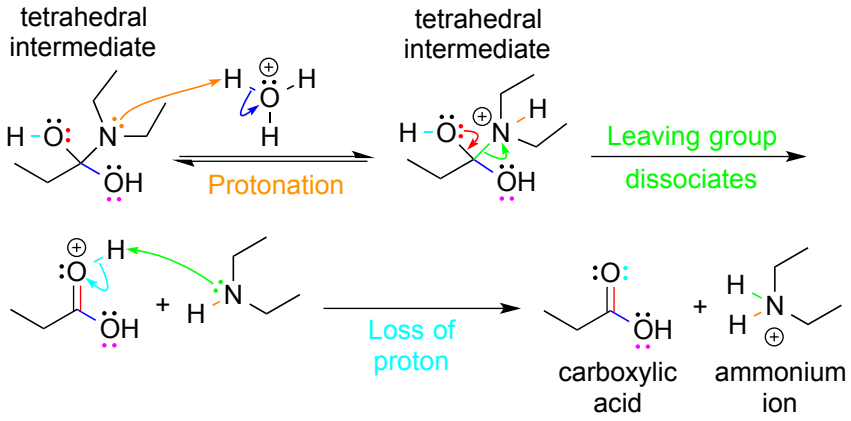
30. Saponification begins with the attack of hydroxide on the electrophilic carbonyl carbon. This displaces the π-bonding electrons onto oxygen as a tetrahedral intermediate is formed. The tetrahedral intermediate then collapses to re-form the carbonyl as the alkoxide (ethoxide in this case) is displaced. Once displaced, ethoxide is basic enough to readily deprotonate the newly formed carboxylic acid, yielding cyclopentanecarboxylate (a carboxylate) and ethanol (an alcohol) as the products.



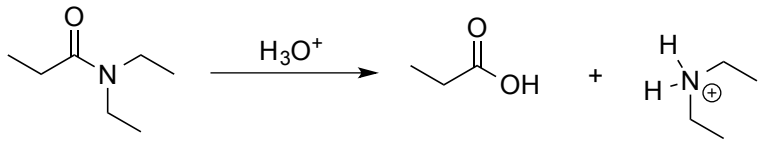
31. The acidic hydrolysis of an amide begins much like the other reactions of carboxylic acid derivatives in acidic media: with the protonation of the carbonyl oxygen. With the carbonyl carbon's electrophilicity thus enhanced, water attacks and displaces the π-bonding electrons onto oxygen. The tetrahedral intermediate then loses a proton to neutralize the charge on the oxonium ion.



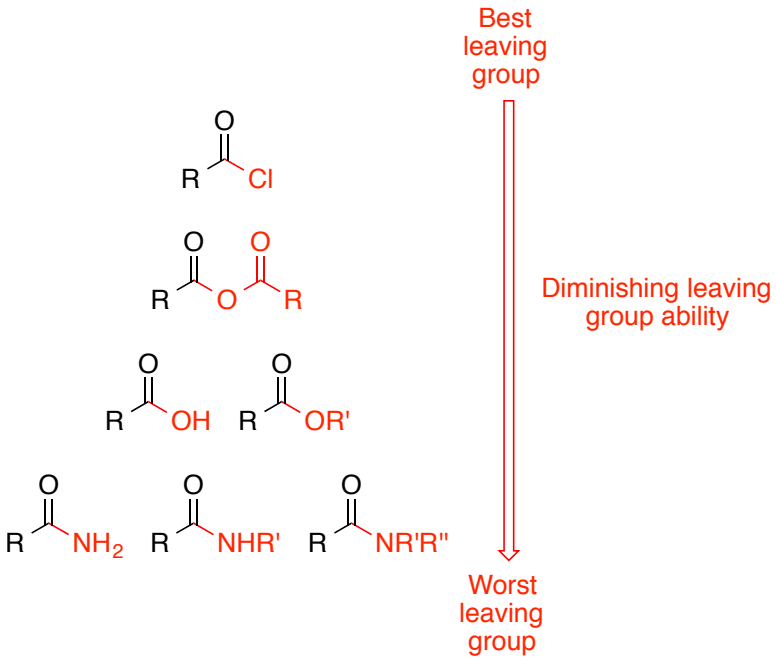
Although this may seem like a reasonable stopping point, remember that it is always important to ask whether any new intermediates can be formed under the reaction conditions. In this case, protonation of the amino group yields a new reaction intermediate whose reactivity we must explore. Upon protonation, the amino group becomes a good leaving group. Diethylamine then dissociates as the carbonyl is re-formed. Finally, a proton transfer neutralizes the carboxylic acid and yields an ammonium ion as well.



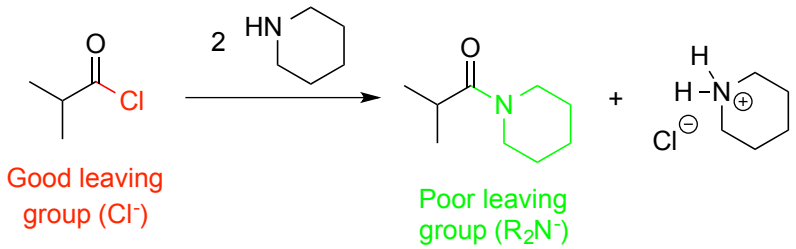
The net hydrolysis reaction is shown below.



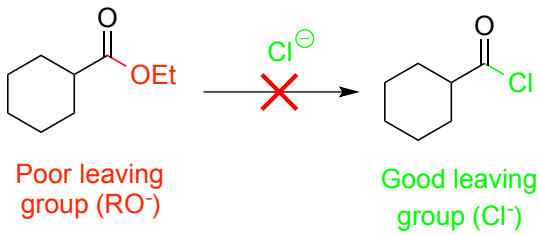
32. Throughout this problem, it will be useful to keep in mind the order of reactivity developed earlier in this chapter. When considering single-step transformations, in general you can move down this reactivity ladder. Moving up the ladder is sometimes possible (i.e., hydrolysis of an amide) but is far less common in single-step conversions.



(a) This reaction can be accomplished in a single step. Chloride is an excellent leaving group. As such, acid chlorides are at the top of the reactivity ladder. Consequently, they can be converted into any of the other carboxylic acid derivatives through direct nucleophilic acyl substitution. In this case, the amide is made by treatment of the acid chloride with excess amine. One equivalent of the amine is incorporated into the amide, and the other consumes the HCl liberated during this reaction.

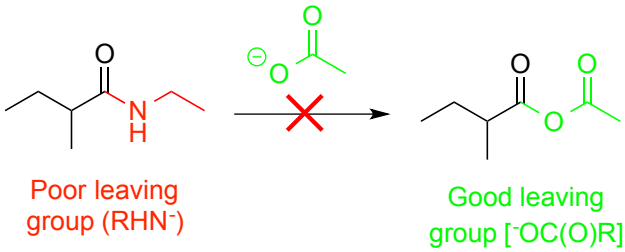


(b) This transformation cannot be accomplished in a single step. The reason is that the ester bears a relatively poor leaving group (ethoxide). Ethoxide *cannot* be directly displaced by chloride.



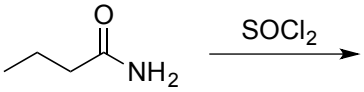
It is worth noting that this conversion can be accomplished, but it requires multiple steps. The ester could be hydrolyzed to give the acid, which can then be converted to the acid chloride upon treatment with thionyl chloride.

(c) This conversion also cannot be attained in a single step. The amide bears a poor leaving group. The nitrogen anion *cannot* be displaced by a carboxylate.



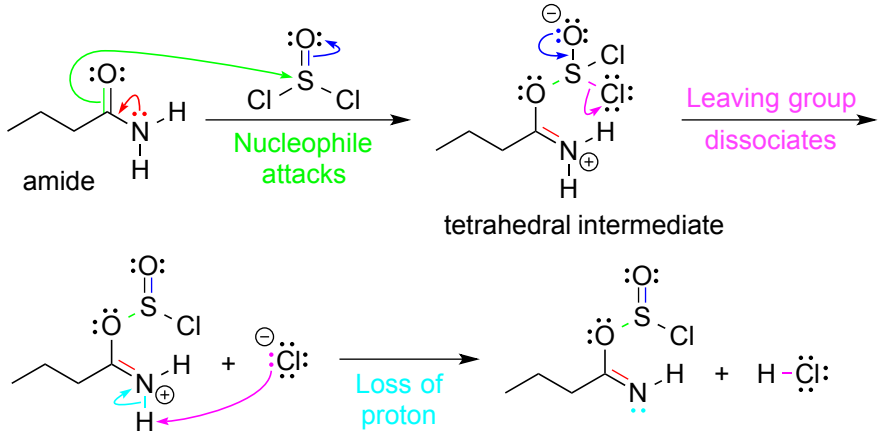
Again, it's worth noting that it is possible to complete this synthesis, but it would require a series of steps to do so. The amide can be hydrolyzed to produce the corresponding carboxylic acid. The acid can be converted to the acid chloride using $SOCl_2$. Finally, treatment of the acid chloride with acetate ($CH_3CO_2^-$) would afford the anhydride.

33. In this question, we are asked to treat butyramide with thionyl chloride ($SOCl_2$). This is one of the acceptable sets of conditions for dehydration of an amide to obtain a nitrile.

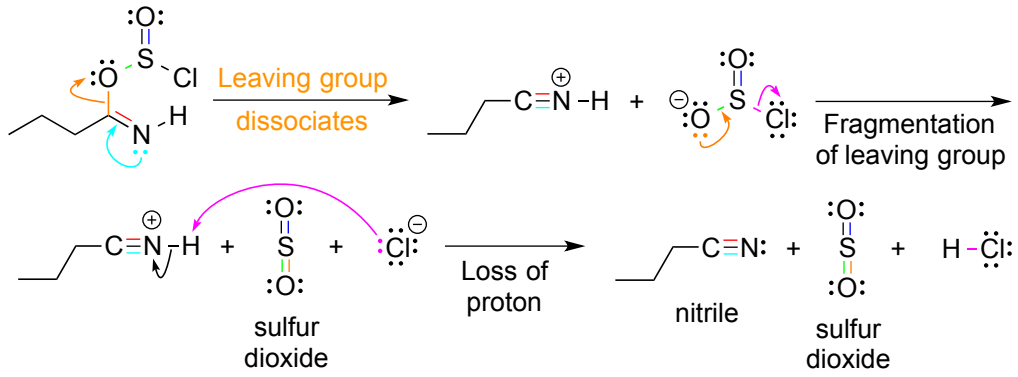


butyramide

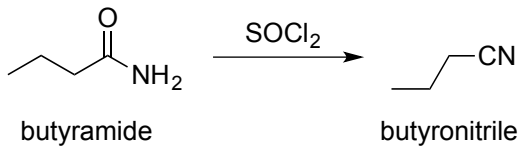
The reaction begins with attack of the carbonyl oxygen on the electrophilic sulfur of thionyl chloride. This has some similarity to protonation, which is a common opening mechanistic gambit. In both types of steps, the carbonyl oxygen attacks an electrophilic entity (δ^+ sulfur in this case vs. H^+ in protonation). During this step, nitrogen donates electrons to the adjacent carbon in order to help it maintain a consistent valence. In this way, the first π bond of the nitrile is formed. The attack also displaces the sulfur-oxygen π-bonding electrons onto oxygen. The sulfur-oxygen π bond then re-forms as chloride is displaced from the molecule. The first phase of the mechanism ends with the loss of a proton from the positively charged nitrogen. This part of the mechanism has served to convert the carbonyl oxygen into a good leaving group.



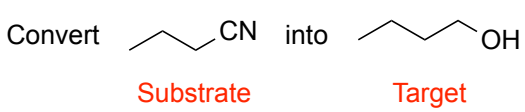
The second phase of the mechanism begins with displacement of that good leaving group by a lone pair of electrons on nitrogen. This forms the second π bond of the nitrile. The mechanism concludes with fragmentation of the leaving group (into sulfur dioxide and chloride) and with the loss of a proton from the substrate to afford the neutral nitrile product.



The overall reaction is shown below.

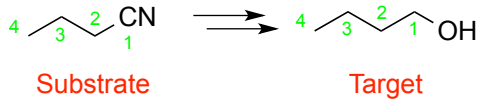


34. We begin by labeling the substrate and the target based on the phrasing of the question. In this instance, the substrate appears first.

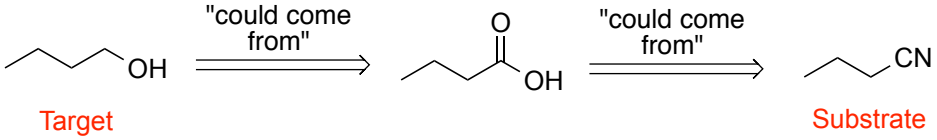


Rewriting the task in the usual fashion highlights that this is merely a functional group interconversion. The substrate and the target have the same number of

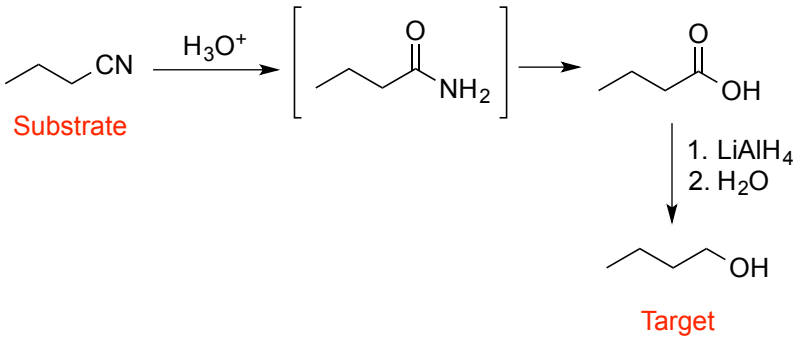
carbons, so there is no need to make or break carbon-carbon bonds during this synthesis.



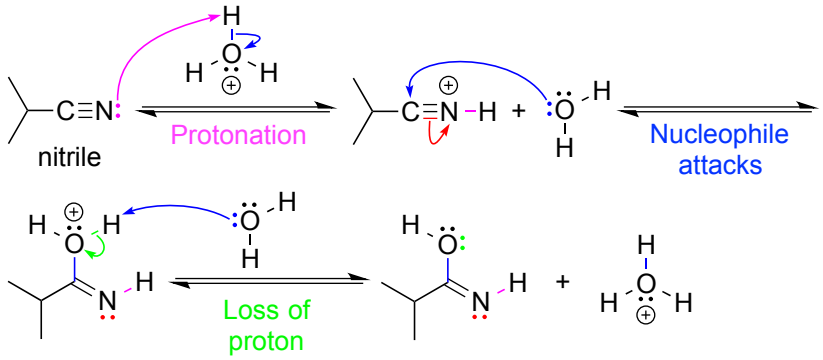
A bit of retrosynthesis helps to clarify our approach to this transformation. We know that alcohols can be made through the reduction of esters or carboxylic acids. However, only the latter can be made directly from nitriles, like our substrate.



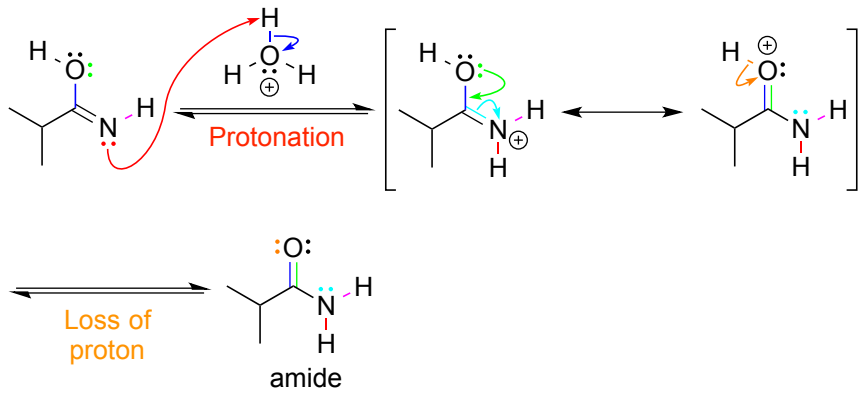
Consequently, the synthesis begins with the hydrolysis of the nitrile. Aqueous acid or base could be used. Acidic hydrolysis is shown below. The nitrile is first hydrated to give the amide, and the amide is subsequently hydrolyzed to afford butyric acid. Butyric acid is then reduced to 1-butanol using lithium aluminum hydride.



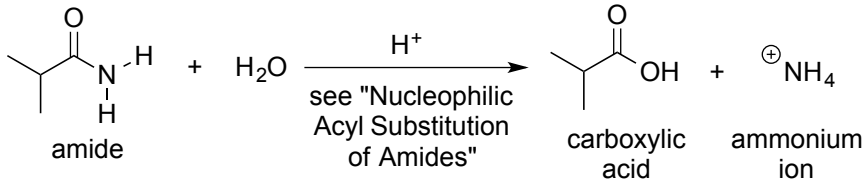
35. This is the hydrolysis of a nitrile, which has two main parts: (1) hydration of the nitrile to yield the amide and (2) hydrolysis of the amide to give the carboxylic acid. The reaction begins with protonation of the nitrile. This enhances the electrophilicity of the molecule, enabling water to attack the nitrile carbon. A proton is then lost to yield a neutral intermediate, which happens to be the tautomer of an amide.



Tautomerization in acid occurs through protonation of nitrogen to yield a resonance stabilized cation. A proton is then lost from the carbonyl oxygen to provide the amide. Water may be shown removing this proton, or the proton's loss may simply be shown. In the latter case (shown below), the assumption is that the proton is lost to the medium, which is aqueous.

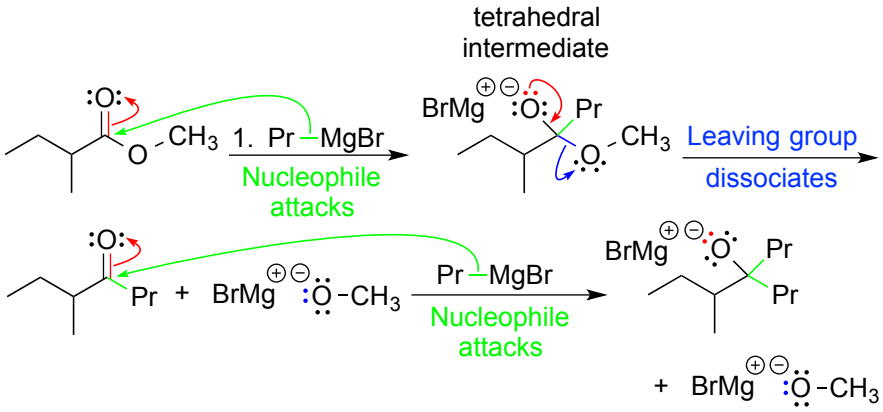


In the second part of the mechanism, the amide hydrolyzes under these conditions. Problem 31 provides the mechanism for a similar amide hydrolysis. The end result of the reaction is the carboxylic acid and the ammonium ion.

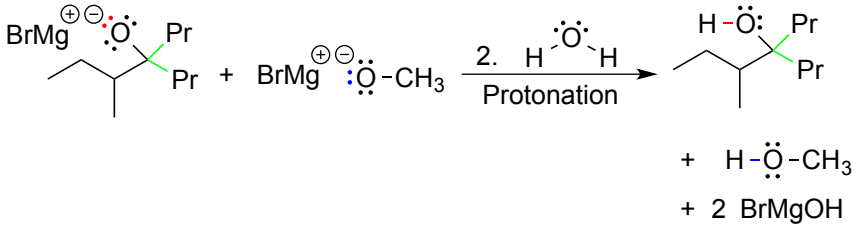


36. Since the Grignard reagent contains a carbon with a powerful δ^-, it is nucleophilic enough to attack the carbonyl carbon directly. This displaces the π-bonding electrons onto oxygen as a tetrahedral intermediate is formed. The carbonyl then re-forms as methoxide is displaced. The resultant intermediate is a ketone, and ketones are also reactive with Grignard reagents. Consequently, a second equivalent of propylmagnesium bromide adds to the ketone's carbonyl

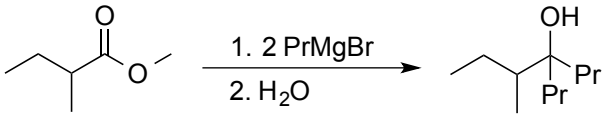
carbon. The resulting alkoxide bears no reasonable leaving groups, so it merely persists until workup.



When water or aqueous acid is added, protonation of both alkoxides affords the tertiary alcohol and methanol as the final products.



The overall reaction is shown below. Since the tertiary alcohol is likely the product of interest, it is shown, and methanol may sometimes be omitted.



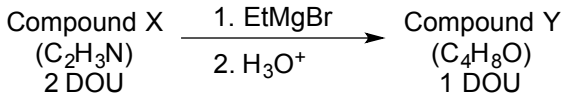
37. Molecular formula can always give us some clues about structural features, namely degrees of unsaturation. Given its molecular formula, Compound X has two degrees of unsaturation. Remember that nitrogen counts as one half of a carbon in the degrees of unsaturation calculation. These degrees of unsaturation could be rings or π bonds or one of each.

$$Degrees\ of\ unsaturation = \frac{[2(2.5) + 2] - 3}{2} = 2$$

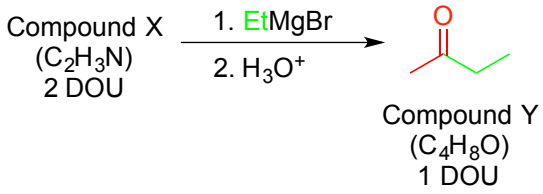
Compound Y has one degree of unsaturation.

$$Degrees\ of\ unsaturation = \frac{[2(4) + 2] - 8}{2} = 1$$

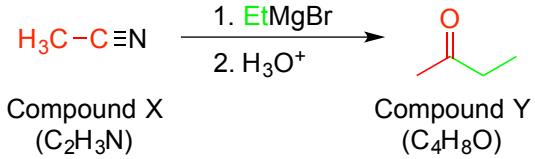
Again, this degree of unsaturation could be a ring or a π bond. However, let's also keep in mind the reaction that we are considering. A compound with two degrees of unsaturation (DOU) adds a Grignard reagent to yield a compound with only one degree of unsaturation.



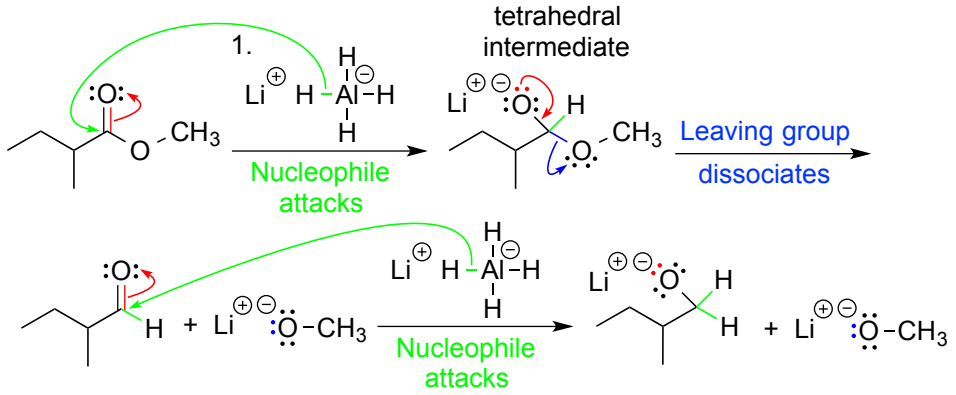
Compound Y must contain the ethyl group of the Grignard reagent, so the remaining two carbons are very likely an acetyl group.



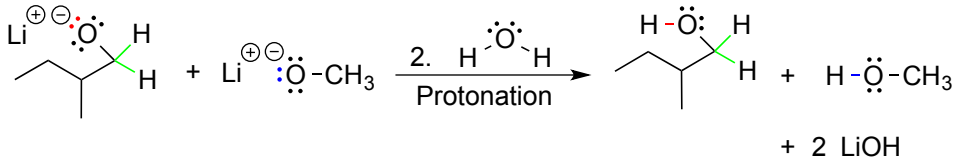
When we consider reactants that could engage in such a transformation, only nitriles come to mind.



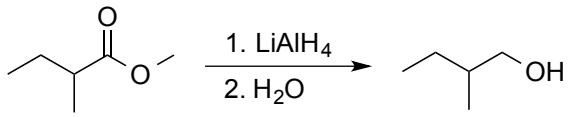
38. LAH (lithium aluminum hydride) is a hydride ($H:^-$) donor. The mechanism begins with the attack of hydride on the ester's carbonyl carbon. This displaces the π-bonding electrons onto oxygen, forming a tetrahedral intermediate. Subsequent collapse of the tetrahedral intermediate re-forms the carbonyl and expels methoxide. An aldehyde is formed as the next reaction intermediate; however, aldehydes are also reactive with lithium aluminum hydride (as we saw in the previous chapter). Consequently, a second hydride adds to the carbonyl carbon, displacing the π electrons onto oxygen. The resulting alkoxide has no reasonable leaving groups, so it persists until workup.



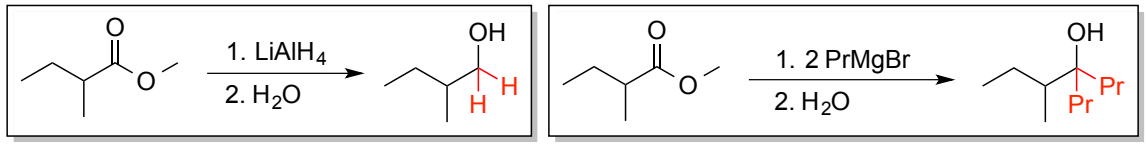
Upon workup, both alkoxides are protonated by water to afford the primary alcohol and methanol as the final reaction products.



The overall reaction is drawn below. Since the primary alcohol is likely the product of interest, it may be the only product shown.

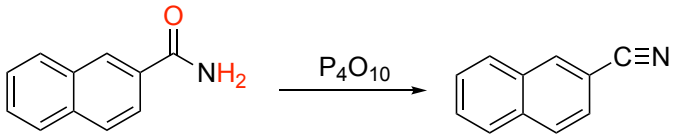


When you compare the mechanisms in this problem and in Problem 36, you see that they involve comparable steps. The only difference is whether $H:^-$ or $R:^-$ is added.

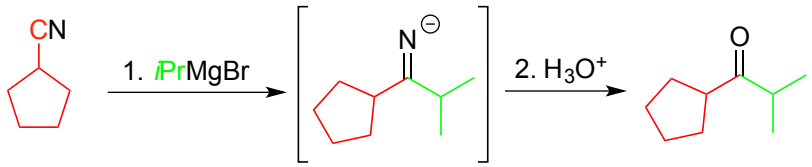


39.

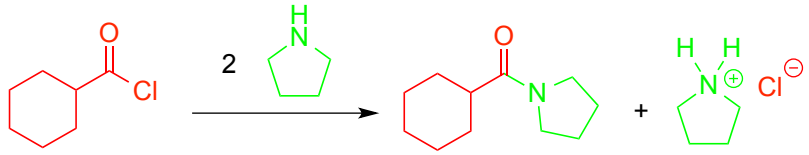
(a) This is the dehydration of an amide to form a nitrile. Phosphorus pentoxide removes water from the amide, and the two additional π bonds of the nitrile are formed as a consequence.



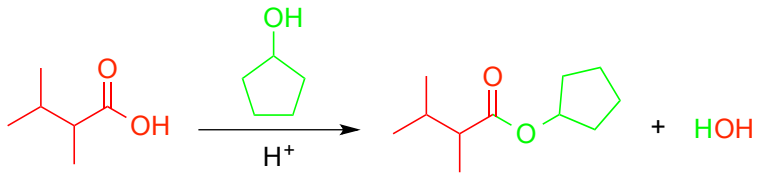
(b) This is a Grignard reaction of a nitrile. Isopropylmagnesium bromide adds to the nitrile carbon. Upon workup, the nitrogen anion is quenched through protonation, and the resulting imine hydrolyzes to provide the ketone.



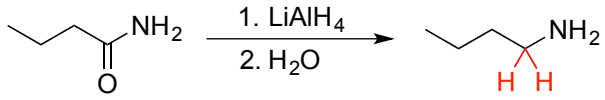
(c) This is a nucleophilic acyl substitution of an acid chloride in which an amine adds to the carbonyl carbon, forming a tetrahedral intermediate that ultimately loses both chloride and a proton. The product of interest is the amide, and the liberated HCl is consumed by a second (sacrificial) equivalent of amine.



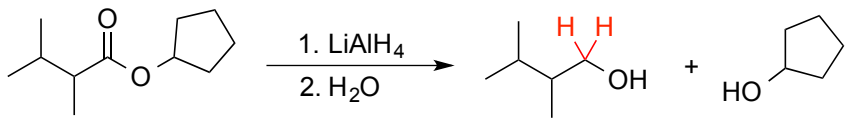
(d) This is a Fischer esterification, in which an acid and an alcohol are united under acid catalysis with the loss of water. The product of interest is the ester.



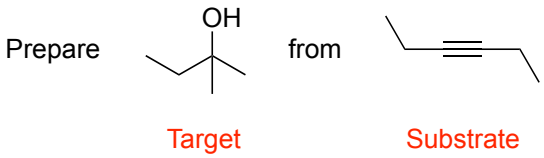
(e) This reduction yields an amine. Two equivalents of hydride are added to the carbonyl carbon during the reduction of the amide reactant.



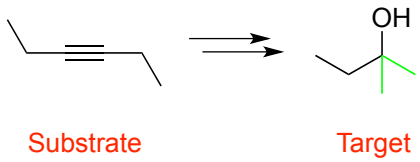
(f) This reduction breaks the ester into two halves. The carbonyl carbon undergoes the addition of two equivalents of hydride during the reaction to yield the product typically considered to be the one of interest. Cyclopentanol is released during the first round of reduction, which follows the paradigm of nucleophilic acyl substitution.



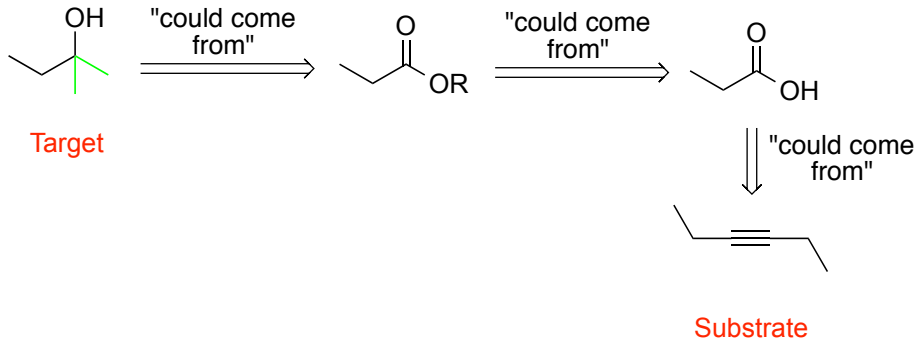
40. It is always prudent to begin a synthesis by labeling the target and the substrate.



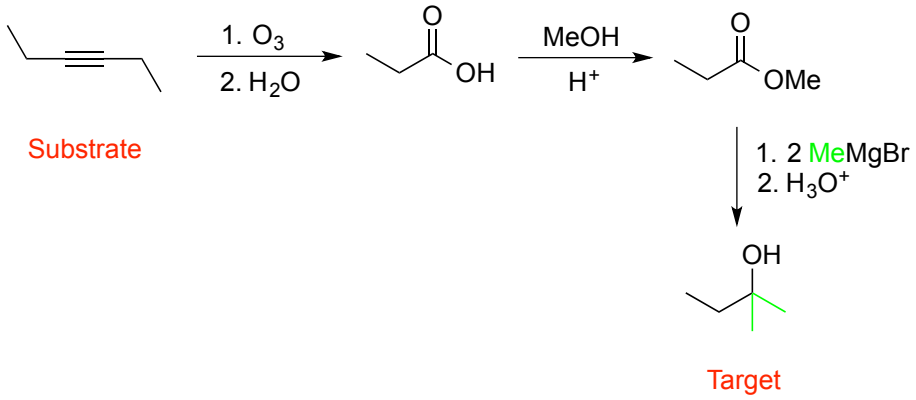
Then, rewrite the task in the usual fashion. In this case, doing so reveals on significant clue. The target is a tertiary alcohol bearing two identical alkyl groups. We know that molecules of this type can be prepared by the Grignard reaction of esters.



This insight provides us with the first step in a retrosynthesis. The rest of the retrosynthesis follows quite readily. We know that esters are commonly prepared from carboxylic acids, and the desired propionic acid could result from ozonolysis of the symmetrical six-carbon alkyne (3-hexyne) that is our allowed starting material.

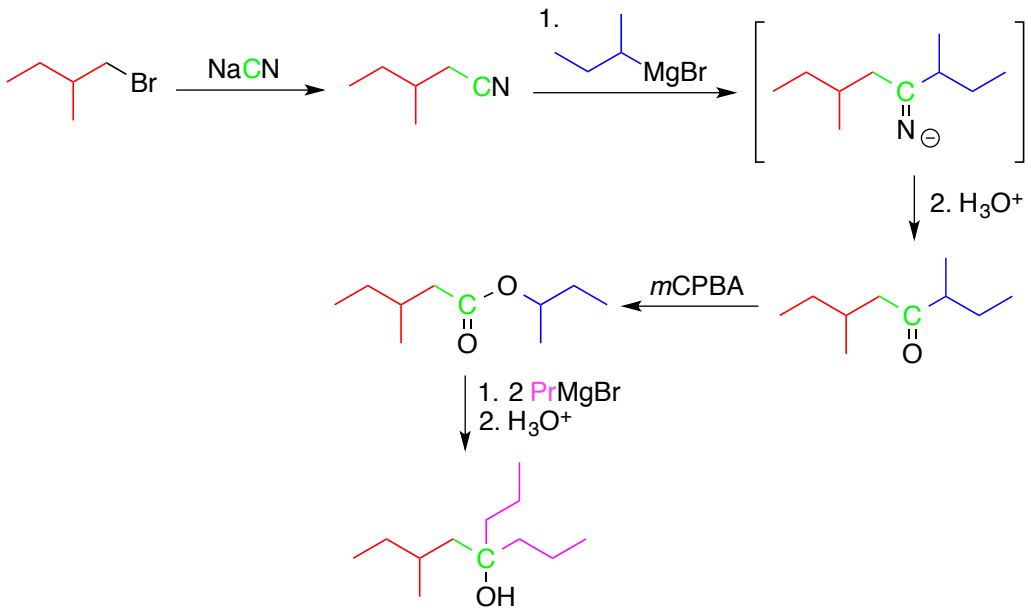


Ozonolysis of the alkyne substrate provides a single product, propionic acid. Propionic acid can then be converted into any ester of our choosing. The alkyl group on the carboxyl oxygen doesn't really matter because it will be displaced as part of an alkoxide during the subsequent Grignard reaction. In this case, the acid was converted to the methyl ester using standard Fischer esterification conditions. Finally, Grignard reaction with two equivalents of methylmagnesium bromide affords the desired tertiary alcohol.



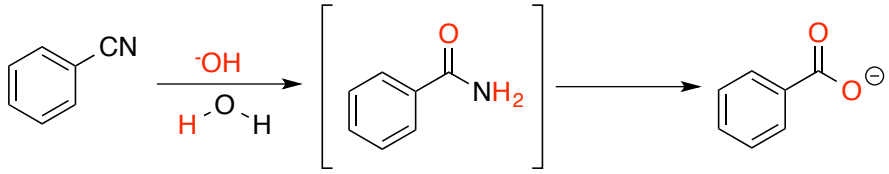
Notice that this synthesis incorporates both the cleavage and the formation of carbon-carbon bonds.

41. The sequence begins with an S_N2 reaction between an alkyl bromide and the cyanide ($^-$:CN) from sodium cyanide. The result is a nitrile containing one more carbon than the original substrate. Then, the Grignard reagent (*sec*-butylmagnesium bromide) adds to the nitrile. Upon workup the nitrogen anion is protonated, and the resulting imine is hydrolyzed, giving a ketone product. This ketone then undergoes Baeyer-Villiger oxidation to afford an ester. Recall that the more electron-rich alkyl group is the one to shift onto oxygen during the Baeyer-Villiger oxidation. In this case, that is the secondary *sec*-butyl group. Finally, the ester undergoes the successive addition of two equivalents of propylmagnesium bromide to yield a tertiary alcohol bearing two identical alkyl groups.

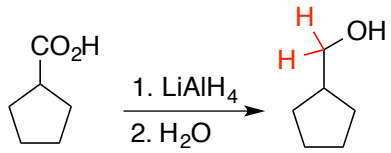


42.

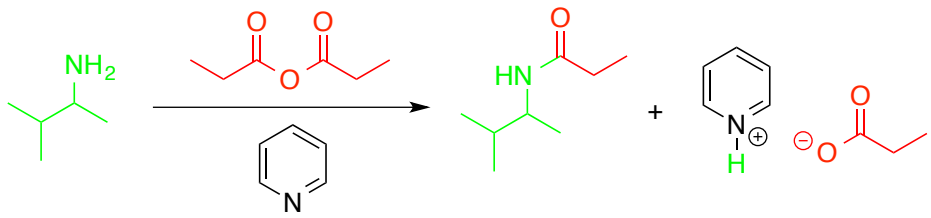
(a) This is the basic hydrolysis of a nitrile. The nitrile is first hydrated to afford the amide. Then, the amide is hydrolyzed under basic conditions, providing the carboxylate as the final product.



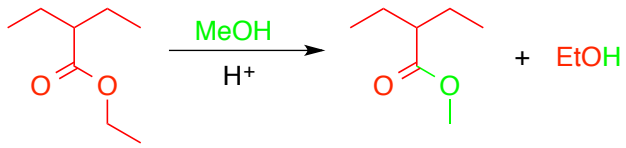
(b) In this reduction, two equivalents of hydride ($H:^-$) add to the carbonyl, ultimately reducing it to the alcohol.



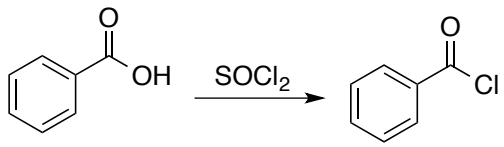
(c) This is a nucleophilic acyl substitution of an anhydride. The amine nucleophilically attacks a carbonyl carbon, forming a tetrahedral intermediate from which a carboxylate and a proton are ultimately lost. The end product is an amide, and pyridine consumes the carboxylic acid liberated during this transformation.



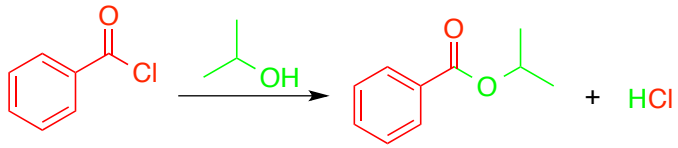
(d) This is an acid-catalyzed transesterification. The mechanism is much like that of acid-catalyzed hydrolysis of an ester. The only difference is that an alcohol (in this case, methanol) adopts the role played by water in hydrolysis.



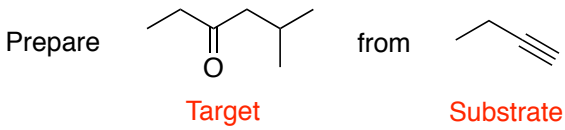
(e) In this transformation, the carboxylic acid is converted to an acid chloride.



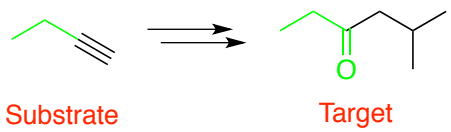
(f) This is a nucleophilic acyl substitution of an acid chloride. Isopropyl alcohol nucleophilically attacks the carbonyl carbon. This forms a tetrahedral intermediate that loses both chloride and a proton to finally yield the isopropyl ester, along with HCl as a byproduct.



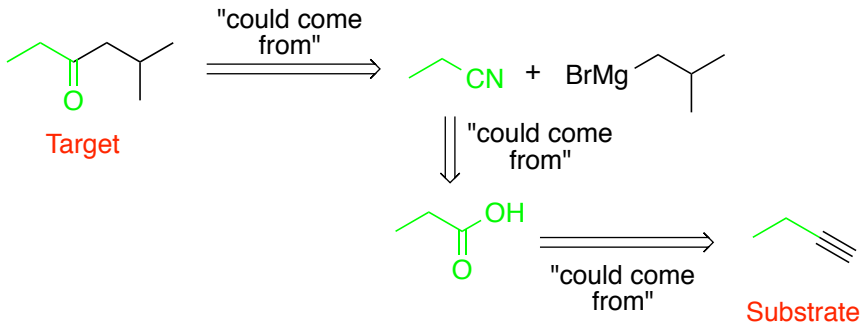
43. It is always wise to begin a synthesis by labeling the substrate and the target.



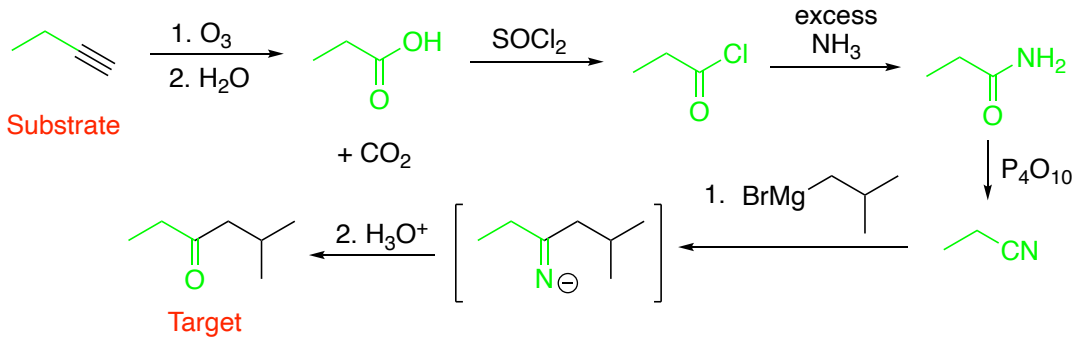
Then, rewrite the problem in the usual fashion. In this instance, we might notice that the three left-hand carbons of the substrate could correspond to the three left-hand carbons of the target, at the end of which a carbonyl resides. This is a useful clue because we know that alkynes can be cleaved by ozonolysis to afford carboxylic acids, which can then be manipulated in a variety of ways that we learned about in this chapter. It is also clear that carbon-carbon bond formation must take place during this synthesis.



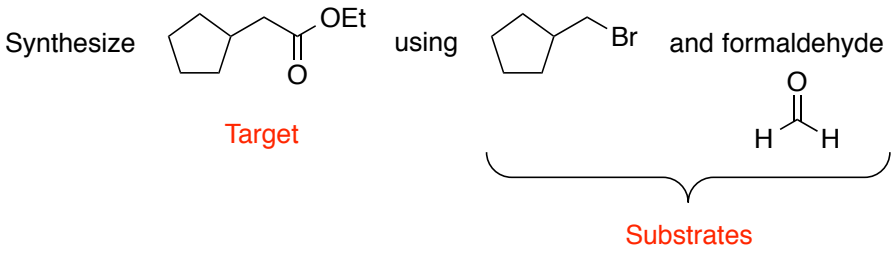
Retrosynthetically, we know that ketones can be made through Grignard reaction of nitriles. This provides a convenient method for the extension of the carbon skeleton required during this problem. The nitrile, in turn, can be made from a corresponding carboxylic acid through a few manipulations. This acid can be accessed by ozonolysis of the substrate.



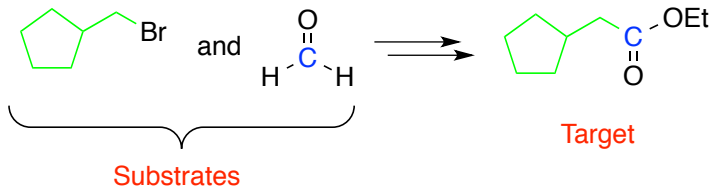
The synthesis begins with ozonolysis, which produces the needed acid and releases one carbon in the form of carbon dioxide. The carboxylic acid can then be converted to the corresponding nitrile through a three-step sequence involving: (1) reaction with thionyl chloride to give the acid chloride; (2) reaction with excess ammonia to produce the primary amide; and (3) dehydration of that amide with phosphorus pentoxide (or thionyl chloride or an anhydride). Finally, Grignard reaction with isobutylmagnesium bromide installs the rest of the carbon framework. During workup, the nitrogen anion is protonated and the resulting imine is hydrolyzed to provide the ketone.



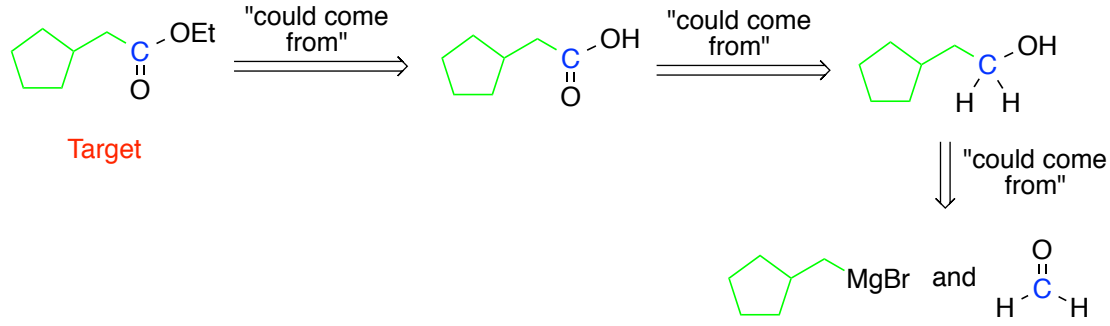
44. We begin by labeling the substrate and the target. It is also useful to draw the structure of formaldehyde.



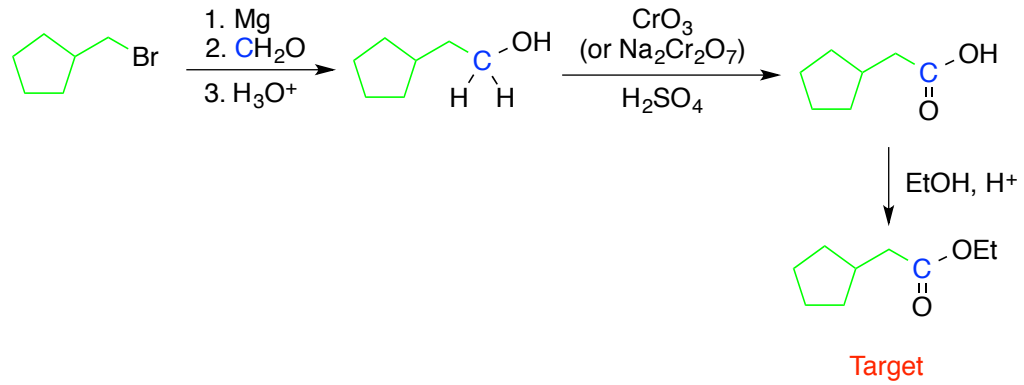
Then, rewrite the question in the usual format. By comparing the structures of the substrates and the target, it is clear that carbon-carbon bond formation must occur since the target has more continuous carbons than either of the substrates. Furthermore, it appears that the carbonyl carbon of the target ester should derive from formaldehyde. A Grignard reaction would be an ideal way to connect the two substrates.



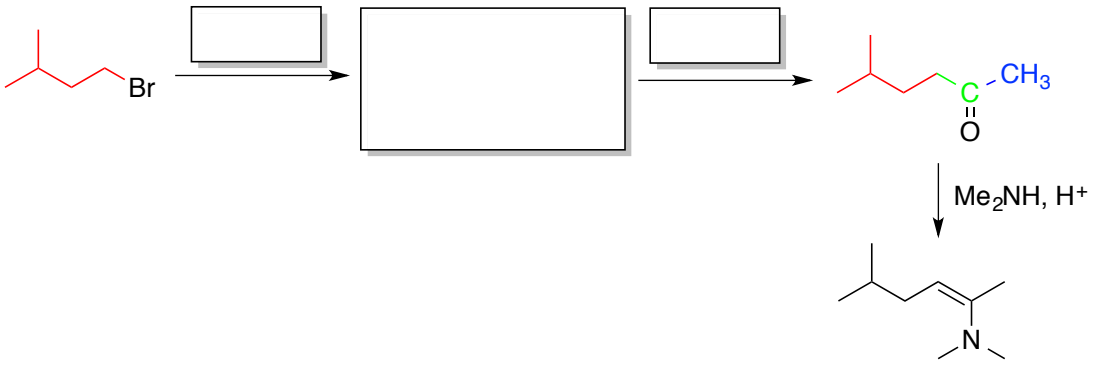
Retrosynthetically, we know that esters can be prepared from carboxylic acids. Since we are considering a Grignard reaction and Grignard reactions often yield alcohols, we can surmise that the carboxylic acid could be prepared by oxidation of the corresponding alcohol. This alcohol, in turn, would result from Grignard reaction between formaldehyde and the Grignard reagent derived from the supplied alkyl bromide.



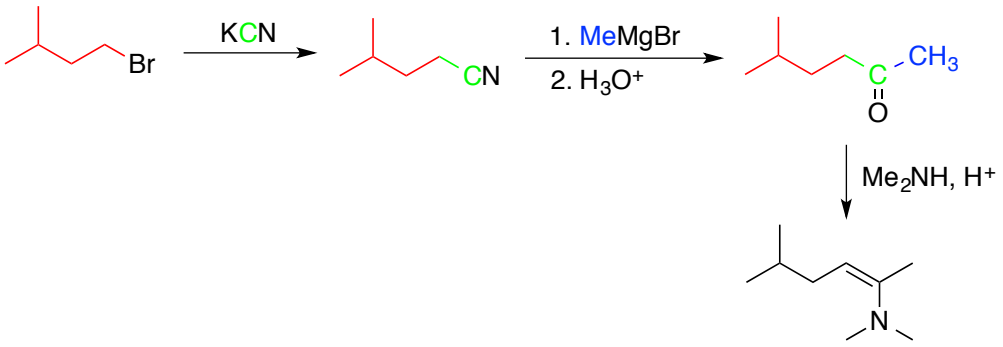
The synthesis begins by treating the alkyl bromide with magnesium to form the Grignard reagent. Then, formaldehyde is added, and the key carbon-carbon bond formation takes place. The Grignard reaction is then quenched with aqueous acid (or simply water). The alcohol can then be oxidized to the acid using chromic acid prepared *in situ*. Finally, a Fischer esterification provides the shortest route from the acid to its ethyl ester. Note that you could also convert the acid to the acid chloride and then add ethanol to achieve the same end result.



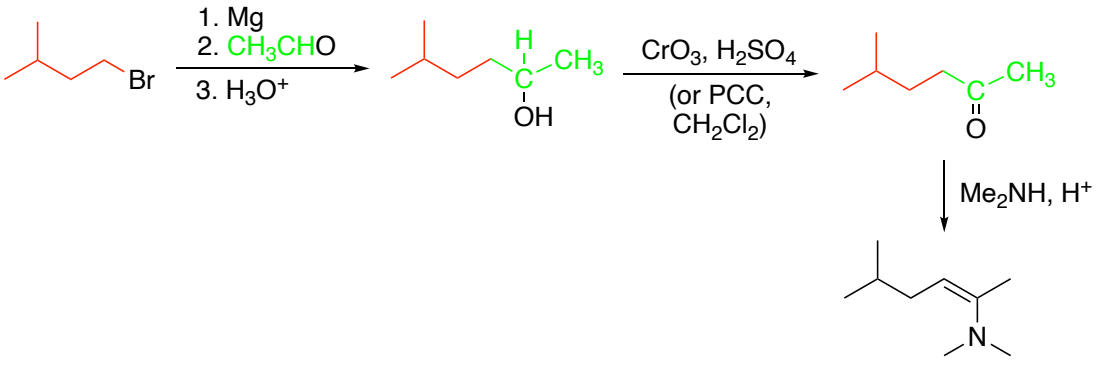
45. There is a good deal of information missing from this synthetic scheme. As a result, it is probably easiest to work our way backwards from the end of the synthesis. We know that enamines are prepared from the condensation of secondary amines with ketones or aldehydes. Given the structure of this particular enamine, we can deduce the structure of the ketone from which it was prepared. Then, we can compare the structure of this ketone to that of the original reactant. There is a net addition of two carbons during the first two steps.



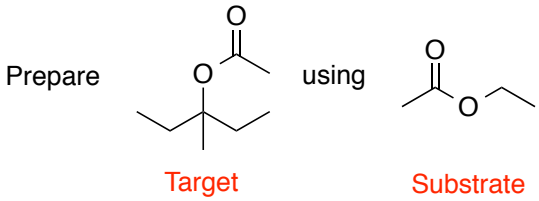
One way to achieve this is by using the carbon of cyanide as a linchpin to join an alkyl halide and a Grignard reagent. This approach views the addition of the two carbons as two separate events.



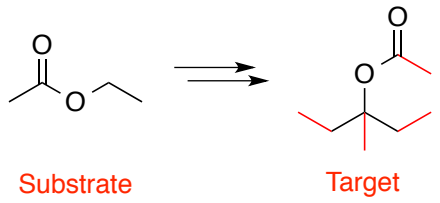
Alternatively, you could also view the addition of the two carbons as a single event, in which case the reactant alkyl halide would be converted to a Grignard reagent and treated with acetaldehyde. This would give a secondary alcohol after workup, and the alcohol can be oxidized to the needed ketone.



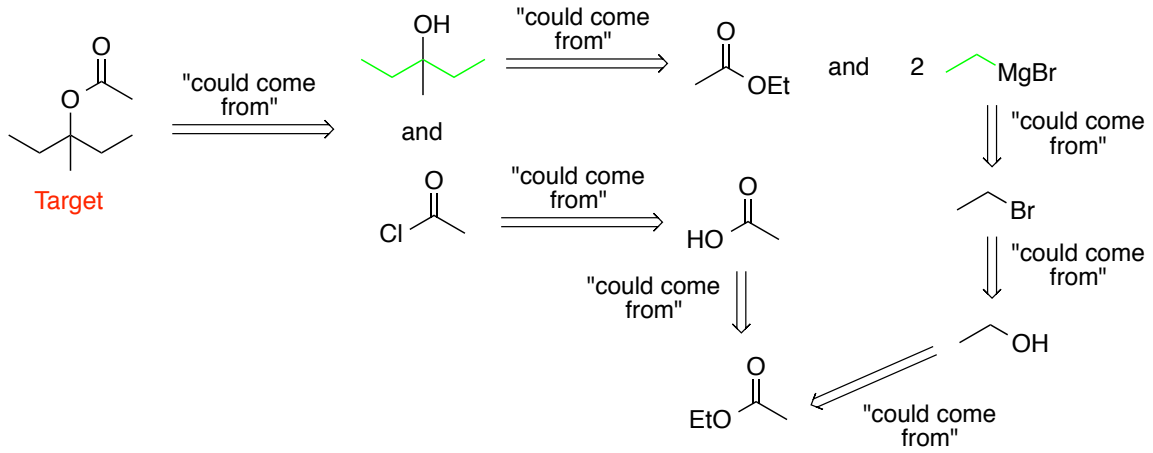
46. We begin by drawing the structure of ethyl acetate and by labeling the substrate and the target.



Then, rewrite the problem in the usual fashion. We are only allowed to use ethyl acetate as a source of carbon atoms, and ethyl acetate has only two continuous carbons. Therefore, it is useful to look for two-carbon fragments in the target. We can easily identify four two-carbon fragments in the target, each of which is derived from a molecule of ethyl acetate.

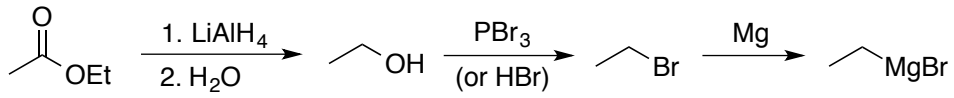


Retrosynthetically, we know that esters can be prepared from alcohols and acid chlorides (or anhydrides). The acid chloride is readily derived from the corresponding acid, which in turn can be made from ethyl acetate. The needed alcohol happens to be a tertiary alcohol bearing two identical alkyl groups. This suggests that it could be made by Grignard reaction between an ester and two equivalents of ethylmagnesium bromide. The ethylmagnesium bromide must be made from ethyl acetate as well. This can be achieved through the alcohol, which is formed upon reduction of ethyl acetate.

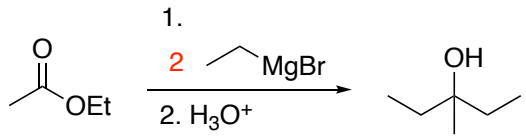


Our synthetic plan has three principal phases: (1) make the Grignard reagent; (2) conduct the Grignard reaction; and (3) form the final ester linkage of the target. Phase one begins with reduction of ethyl acetate using lithium aluminum hydride. This yields a single alcohol product: ethanol. Ethanol can be converted to ethyl

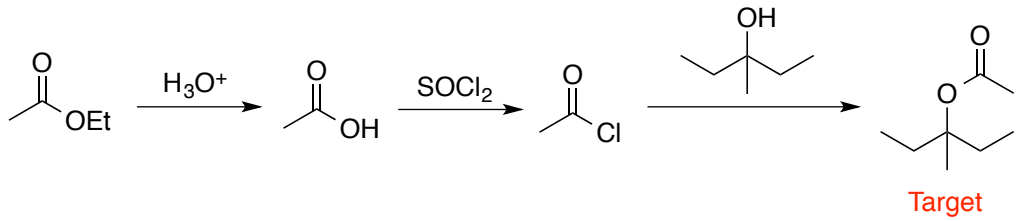
bromide using phosphorus tribromide or HBr. Finally, addition of magnesium provides the necessary Grignard reagent.



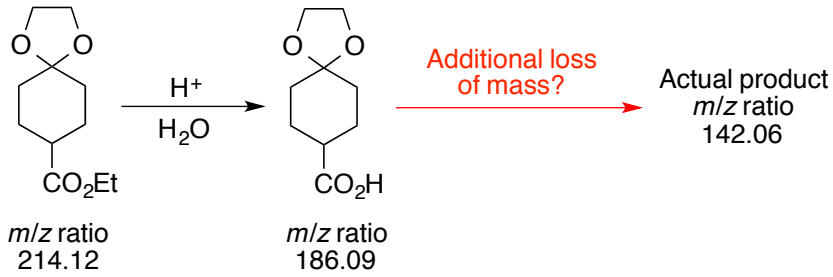
In phase two of our synthesis, ethyl acetate is treated with two equivalents of the Grignard reagent. Two successive additions occur. The first is a nucleophilic acyl substitution giving a ketone, and the second is a nucleophilic addition that results in a tertiary alcohol bearing two ethyl groups.



Finally, ethyl acetate can be hydrolyzed (in acid or base) to yield acetic acid. Acetic acid forms acetyl chloride upon treatment with thionyl chloride, and addition of the tertiary alcohol then provides the target through nucleophilic acyl substitution.

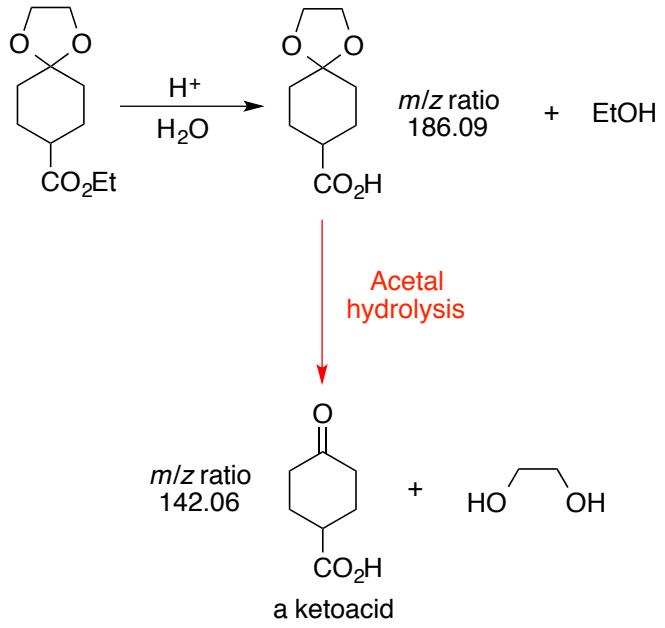


47. In this transformation, a loss of mass is anticipated due to the replacement of an ethoxy group by a hydroxyl group during the ester hydrolysis. However, even more mass than anticipated was lost in this transformation.



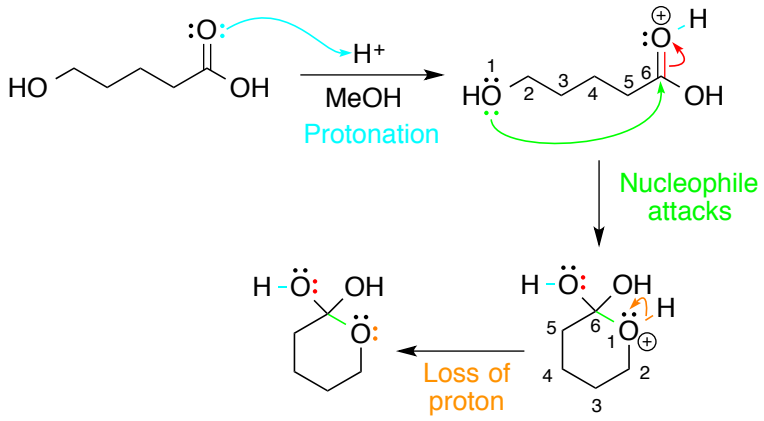
It is improbable that the investigator was wrong about the ester hydrolysis because we learned in this chapter that esters are indeed hydrolyzed by aqueous acid. It is possible though that something additional has occurred. When we examine the entire molecule, the acetal stands out as another potentially reactive functional group. In fact, we learned in the previous chapter that acetals are also hydrolyzed by aqueous acid, so it is likely that both the ester and the acetal were hydrolyzed under

the reaction conditions. In fact, the ketoacid does have a mass consistent with that observed in the mass spectrum.

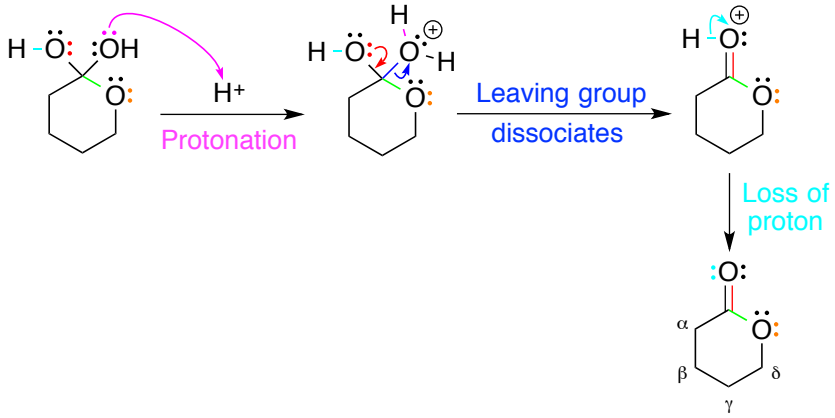


48. The alcohol could not simply have disappeared. It must therefore be the case that the alcohol underwent a reaction. Notice that the intended Fischer esterification would involve an alcohol (methanol). What if the alcohol in the substrate played the role that we thought methanol would play in this reaction? In other words, it is possible to have an *intramolecular* Fischer esterification take place.

Such a transformation would begin, like any other Fischer esterification, with the protonation of the carbonyl oxygen. The only difference is that the nucleophilic attack of an alcohol occurs from within the substrate itself. This forms a ring, which can be challenging to visualize. Numbering the atoms from nucleophile to electrophile highlights that the ring is six-atoms in size. Additionally, the numbering helps us to draw the cyclic reaction intermediate correctly. A proton is then lost to neutralize the charge of the oxonium ion.

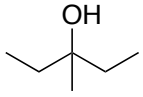


Although this might appear to be a reasonable stopping point, there is more that can happen under these reaction conditions. Protonation of either equivalent hydroxyl group will yield an intermediate that we haven't seen yet, and we must explore its reactivity. The newly formed good leaving group (water) dissociates as the carbonyl is re-formed. Finally, the loss of a proton gives a cyclic ester. Cyclic esters are known as lactones, and this specific one is δ-valerolactone.

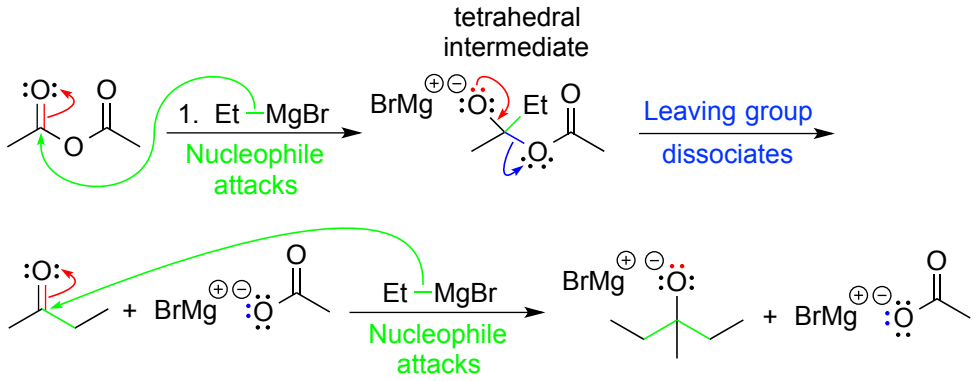


This explains why the alcohol stretch is absent and why we see only sp^3 C-H stretching and an ester C=O stretch in the product's IR spectrum.

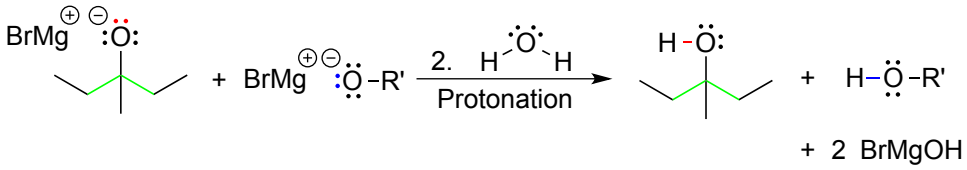
49. The proton NMR spectrum does display the expected singlet integrating for three hydrogens that would correspond to a methyl group with no neighbors. However, instead of a single ethyl group, the integration values (of 6 and 4) suggest that there are actually two ethyl groups in the product. Finally, there is a broad singlet integrating for one hydrogen that is suggestive of an alcohol. There is only one way to fit all of these fragments together.



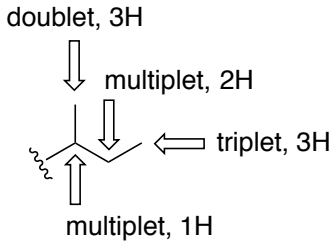
It appears that the substrate has undergone the addition of two equivalents of Grignard reagent, rather than just one. In retrospect, this makes a great deal of sense. An anhydride possesses a leaving group on the carbonyl carbon. As a result, it will react much like an ester (or an acid chloride) in the Grignard reaction. The first equivalent of Grignard reagent attacks the carbonyl carbon, and the resultant tetrahedral intermediate expels the carboxylate leaving group to produce ethyl methyl ketone (the intended product). However, ketones are also reactive with Grignard reagents, so a second equivalent adds to the ketone's carbonyl carbon. The resulting alkoxide has no reasonable leaving groups, so it persists until workup.



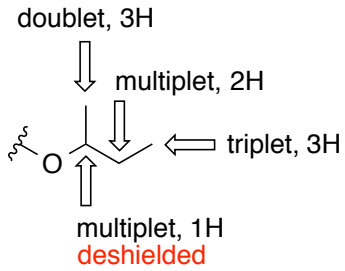
Upon workup, the alkoxides are protonated to afford the product suggested by the NMR spectrum.



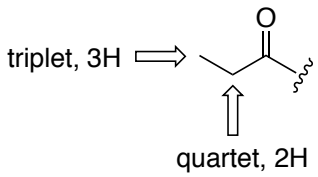
50. There are multiple approaches to a problem like this. One of our options is to begin with an interpretation of the NMR spectrum. However, our job can be made much easier by taking clues from the reaction sequence. For instance, *sec*-butylmagnesium bromide is used in the second step. Therefore, it is highly probable that a *sec*-butyl group has been incorporated into the product's structure. Let's consider the signals that such a group would cause.



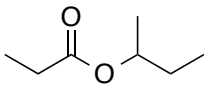
Notice that there is only one signal in the NMR spectrum that integrates for one hydrogen. This must be the methine (CH group) of the *sec*-butyl moiety. Also, notice that this signal is fairly deshielded. Its chemical shift suggests that it is adjacent to an electron-withdrawing group, such as an oxygen atom. Given the types of reactions conducted in this sequence, oxygen would appear to be the most logical candidate for a deshielding element.



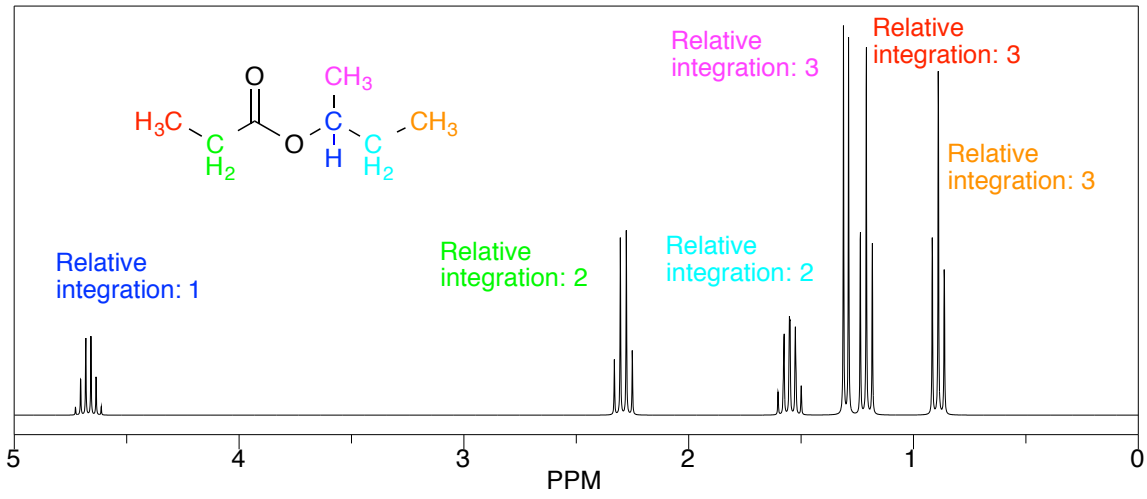
There are only two remaining NMR signals: an additional CH_3 (triplet) and CH_2 (quartet) group. Based on their splitting, they must constitute and ethyl group. Also, given that the *sec*-butyl's CH_2 group should be fairly shielded, the CH_2 of the ethyl group is comparatively deshielded. Its chemical shift suggests adjacency to a carbonyl.



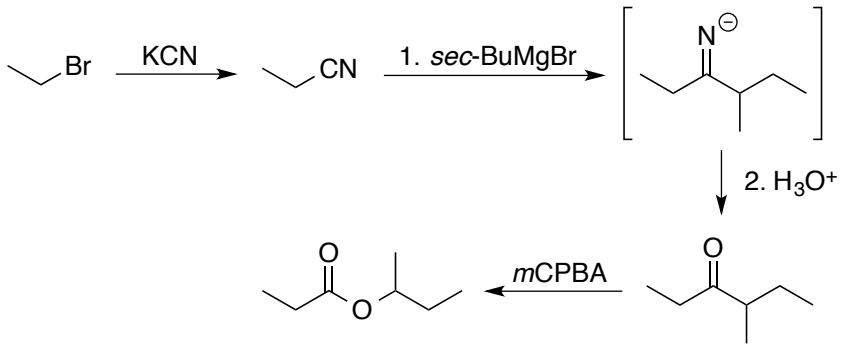
The union of these fragments gives an ester as the final product of the reaction sequence.



The assignments made in preceding discussion are summarized in this labeled NMR spectrum.

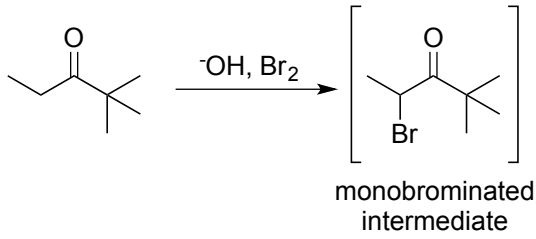


This ester is consistent with the final product we can expect from the reaction sequence. Ethyl bromide first undergoes S_N2 reaction with cyanide ($^-$:CN) supplied by potassium cyanide to yield propiononitrile. The Grignard reaction produces *sec*-butyl ethyl ketone. Lastly, Baeyer-Villiger oxidation yields an ester in which the more electron-rich secondary alkyl group migrates onto oxygen. The final product is *sec*-butyl propionate, just as we deduced from the NMR spectrum.

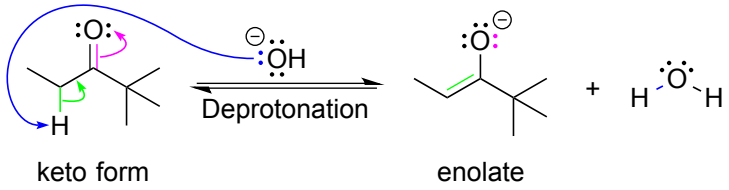


Solutions to Problems for Chapter 17: Reactions of Carbonyl Compounds at the Alpha Carbon

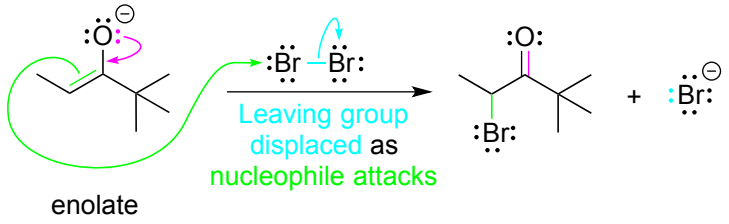
1. In this problem, we are focusing on the first portion of the reaction: the formation of the monobrominated intermediate. This reaction takes place in base. Due to the use of hydroxide, we expect the reaction to proceed through the enolate.



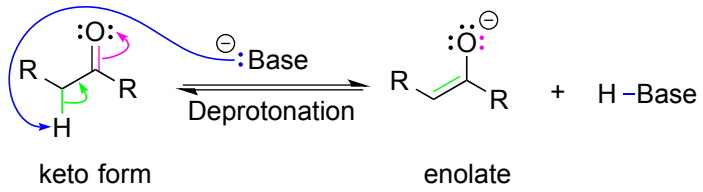
The enolate is formed when hydroxide deprotonates the only α-carbon bearing protons. Electrons from the C-H bond flow toward the carbonyl, ultimately depositing the negative charge on oxygen.



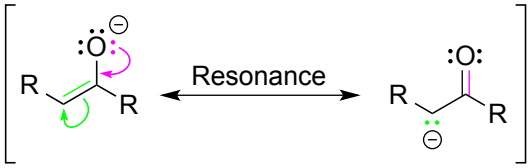
As the only other reaction component, bromine must play the role of the electrophile in this transformation. The enolate attacks one of the two bromine atoms while the carbonyl π bond is re-formed. As bromine is attacked, the Br-Br bond is cleaved and bromide is ejected as a leaving group.



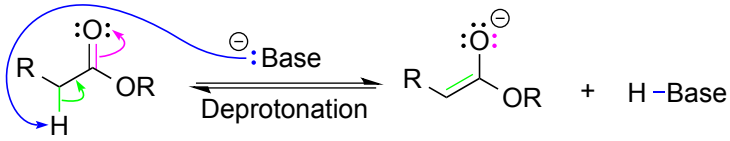
2. When a ketone (or aldehyde) is deprotonated, the corresponding enolate is formed.



This enolate has resonance delocalization so that the negative charge is shared by the carbonyl oxygen and the α-carbon.

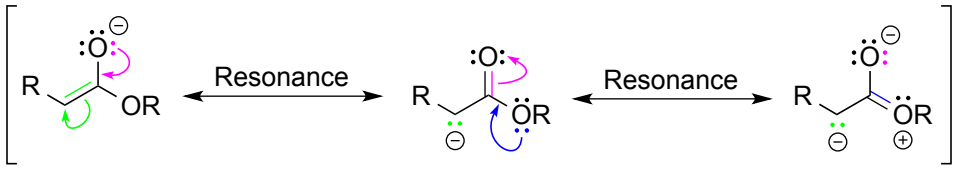


When an ester is deprotonated, it similarly forms the corresponding enolate.



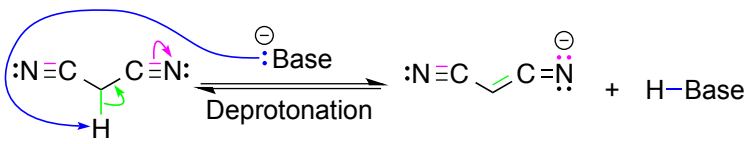
keto form enolate

This enolate also shares the negative charge between the carbonyl oxygen and the α-carbon. However, the presence of the carboxyl oxygen complicates matters. It too can delocalize electrons into the carbonyl, which leads to a third resonance structure. In a sense, the α-carbon and the carboxyl oxygen compete for delocalization of their electrons into the carbonyl. This phenomenon is called cross-conjugation. It reduces the efficiency of stabilization provided for the enolate anion and explains why it is less acidic.

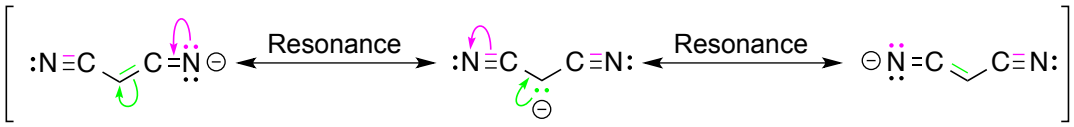


3.

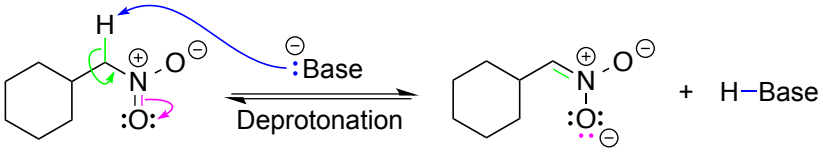
(a) This dinitrile has carbon-nitrogen π bonds that can play the same role as the carbon-oxygen π bond of a carbonyl. When the α-carbon is deprotonated, the electrons from the C-H bond can flow toward the nitrile, ultimately depositing the negative charge onto nitrogen.



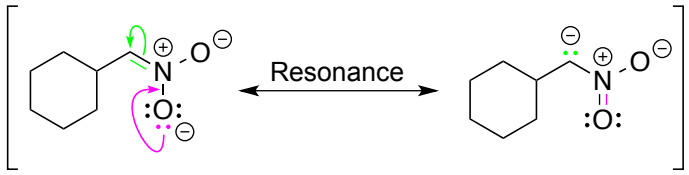
This anion shares the negative charge between both nitrile nitrogens and the α-carbon. This makes it akin to an enolate bearing two carbonyls. In fact, the pK_a of this dinitrile is about 11.



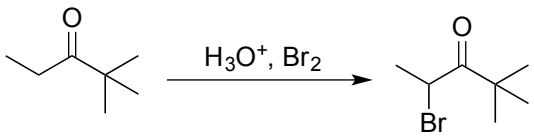
(b) The nitro group possesses a nitrogen-oxygen π bond that can play the same role as a carbonyl's π bond. As the α-carbon is deprotonated, electrons from the breaking C-H bond flow toward the nitro group, and the charge is placed on an oxygen atom.



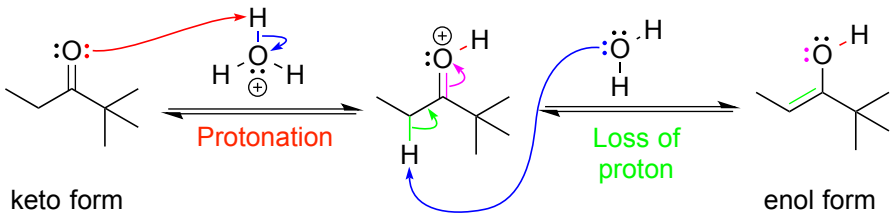
The conjugate base has resonance forms that highlight the sharing of electron density between the oxygen atom and the α-carbon. As we saw in the chapter on the reactions of aromatic compounds, the nitro group is powerfully electron withdrawing. Not only does it withdraw electron density through resonance, but it also inductively withdraws electron density due to the nitrogen's positive charge. As a result, the nitro group makes the α-carbon quite acidic (pK_a ~10).



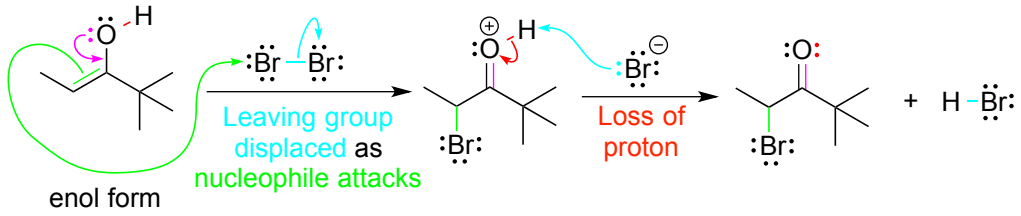
4. The acidic α-bromination of *tert*-butyl ethyl ketone involves treatment with bromine in acidic media.



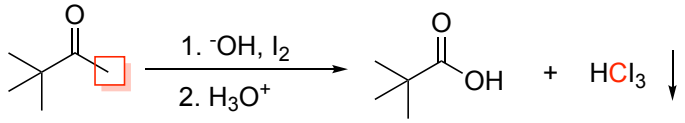
The reaction begins with tautomerization to the enol via (1) protonation of the carbonyl oxygen and (2) loss of an α-proton.



The enol then attacks Br_2 as the carbonyl π bond is re-formed. The attack on Br_2 causes bromide to be expelled as a leaving group. Finally, a proton is shed so as to form the monobrominated ketone.

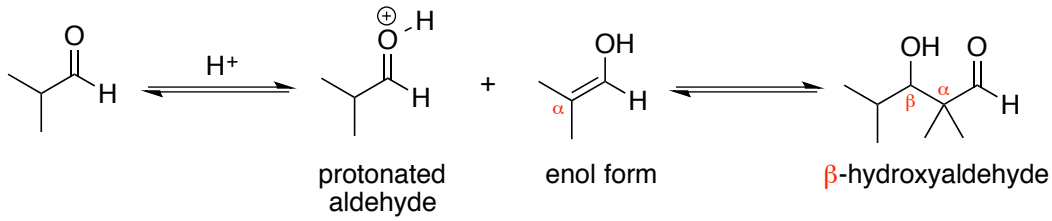


5. Although this ketone possesses four methyl groups, only the methyl group α to the carbonyl is reactive in the haloform reaction. That carbon is ultimately cleaved from the substrate to produce a carboxylic acid. Since this is the iodoform reaction specifically, there is visual evidence of the reaction's occurrence. It takes the form of the precipitation (↓) of the iodoform byproduct as a yellow solid.

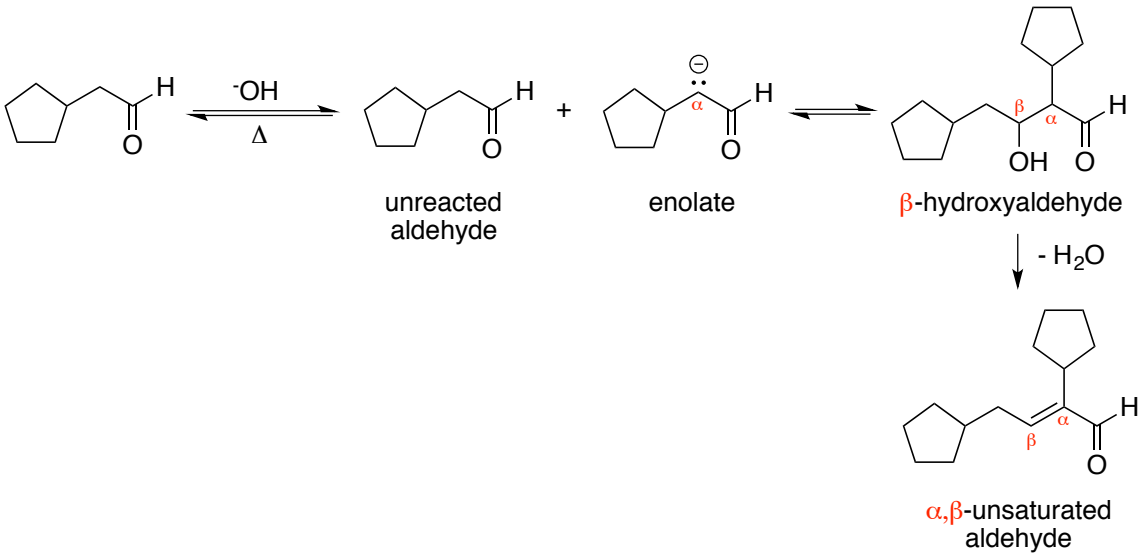


6.

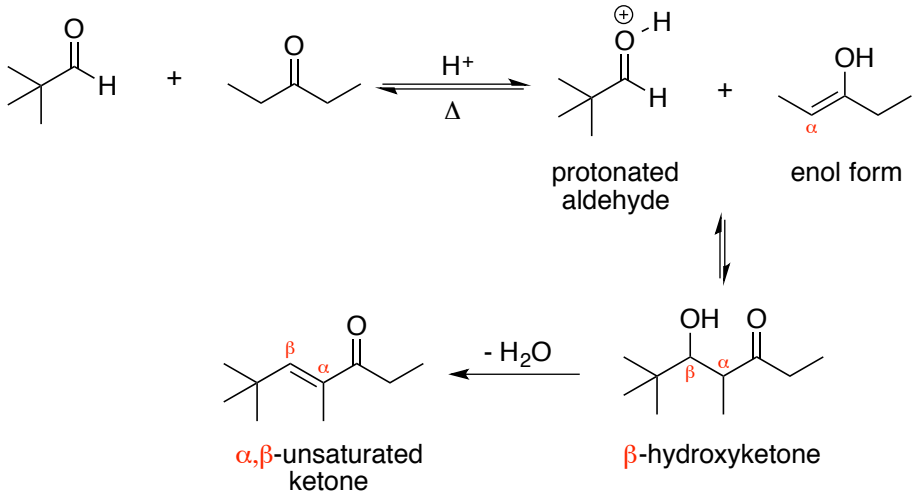
(a) This is an aldol reaction in acidic media. A molecule of aldehyde is converted to its enol form, which is nucleophilic at the α-carbon. Another molecule of aldehyde is protonated on the carbonyl oxygen, making its carbonyl carbon particularly electrophilic. The two centers are joined due to their opposite polarities, and this yields a β-hydroxyaldehyde. The reaction halts at this stage because no heat is applied.



(b) This is an aldol condensation in basic media. It begins with the deprotonation of a small amount of aldehyde to yield the corresponding enolate. The enolate is nucleophilic at its α-carbon. The unreacted aldehyde is electrophilic at its carbonyl carbon. Consequently, the two centers form a bond to give a β-hydroxyaldehyde. Since this reaction is heated, dehydration follows and pushes the equilibrium toward the product, an α,β-unsaturated aldehyde.

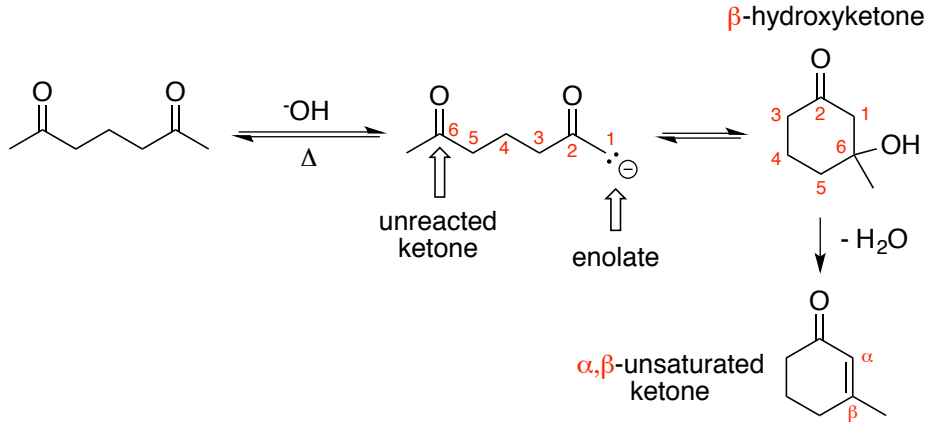


(c) This crossed-aldol condensation takes place in acidic media. It begins with conversion of the only substrate bearing α-protons to its enol form, which is nucleophilic at the α-carbon. The non-enolizable substrate is protonated, making its carbonyl carbon even more electrophilic. The nucleophilic α-carbon of the enol attacks the electrophilic carbonyl carbon of the protonated aldehyde to yield a β-hydroxyketone. Since this reaction is heated, subsequent dehydration occurs and drives the equilibrium to the α,β-unsaturated ketone product.

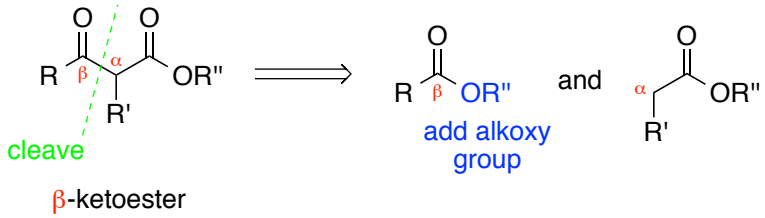


(d) This intramolecular aldol condensation takes place in base. It begins with the deprotonation of an α-carbon. While there are two types of α positions in this molecule, only deprotonation of the α-methyl group will lead to a reasonable ring size. The enolate is nucleophilic, so it attacks the unreacted ketone, which just happens to be tethered to it in this instance. The intramolecular aldol reaction yields a β-hydroxyketone. Numbering the atoms from the nucleophilic center to the electrophilic one highlights the fact that a six-membered ring is formed. It also helps

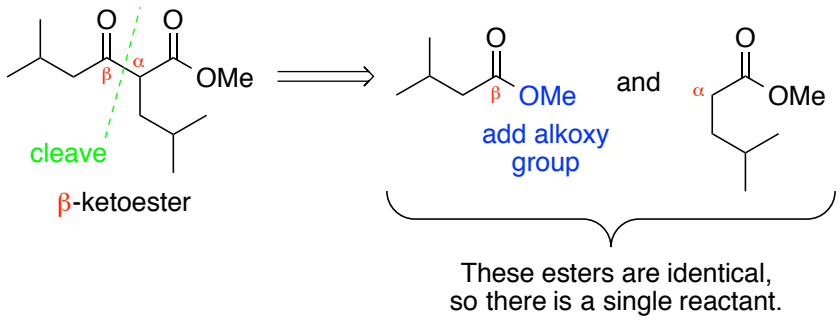
us to draw the product properly. Finally, since this reaction is heated, dehydration follows to give the α,β-unsaturated ketone.



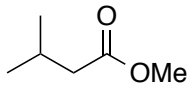
7. Throughout this problem, it will be useful to have a consistent, systematic approach. The best strategy comes from recognizing that the Claisen condensation yields β-ketoesters. The reaction itself joins two ester reactants through the formation of the α-β bond. Therefore, to derive the ester reactants through retrosynthesis, you should cleave the α-β bond, slide apart the two halves of the molecule, and add an alkoxy group to the β carbon.



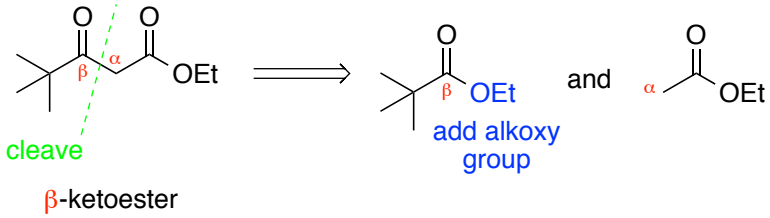
(a) We can apply the method described above by first identifying the ester. Then, label its α and β positions, with the β carbon corresponding to the carbonyl carbon of the keto group. Next, cleave the α-β bond retrosynthetically. Separate the halves, and add an alkoxy group to the β carbon. The specific identity of the alkoxy group (i.e., methoxy vs. ethoxy, etc.) may not matter because it is displaced during the reaction anyway. However, it is expedient to make it the same as the alkoxy group of the other ester, which in this case is methoxy. This leads to a single ester reactant (simply drawn in two different ways).



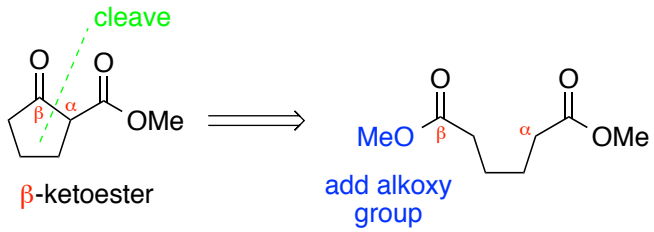
Consequently, there is only one ester needed for this Claisen condensation.



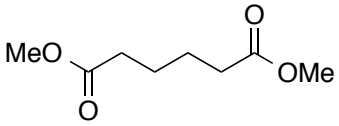
(b) Applying the procedure described above results in two distinct esters in this problem. This is therefore a crossed-Claisen condensation.



(c) When we apply the same protocol to the retrosynthesis of this β-ketoester, we discover a slight twist. The two esters are tethered to one another. This is therefore a Dieckmann condensation (i.e., an intramolecular Claisen condensation).

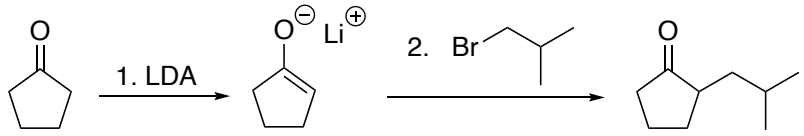


As such, it requires only a single diester reactant.

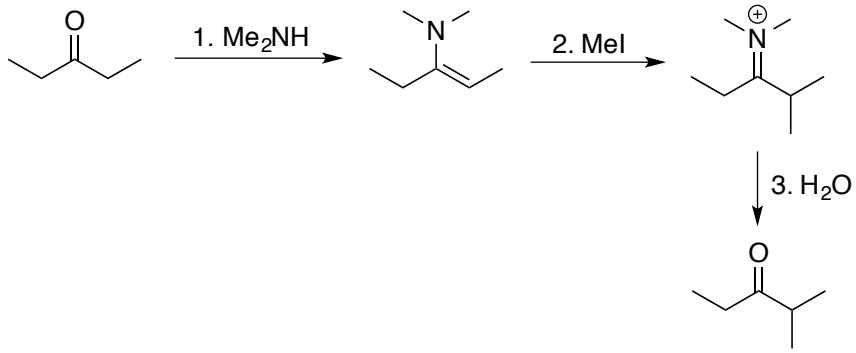


8.

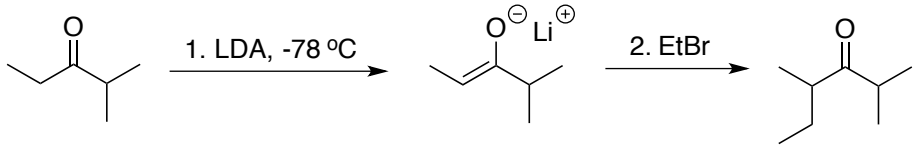
(a) In this sequence, LDA deprotonates the symmetrical ketone at either α position, forming the corresponding enolate. The enolate is then alkylated using isobutyl bromide to prepare the product.



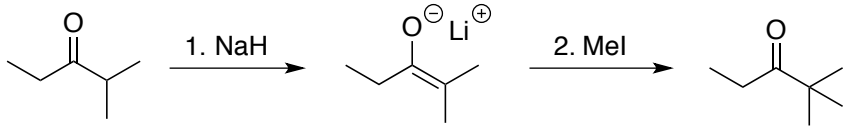
(b) This alpha alkylation involves the intermediacy of an enamine, formed from the ketone and dimethylamine. The enamine is alkylated using methyl iodide, and the resulting iminium ion is hydrolyzed to afford the ketone product.



(c) At low temperature, LDA deprotonates the more sterically accessible α position, forming the kinetic enolate. Subsequent alkylation with ethyl bromide affords the product.



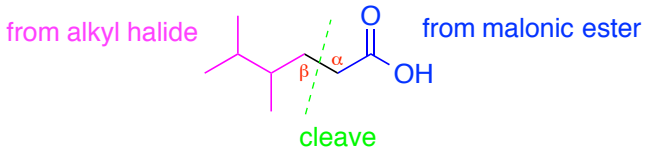
(d) Sodium hydride deprotonates the unsymmetrical ketone so as to form the thermodynamic enolate, which is then alkylated by methyl iodide.



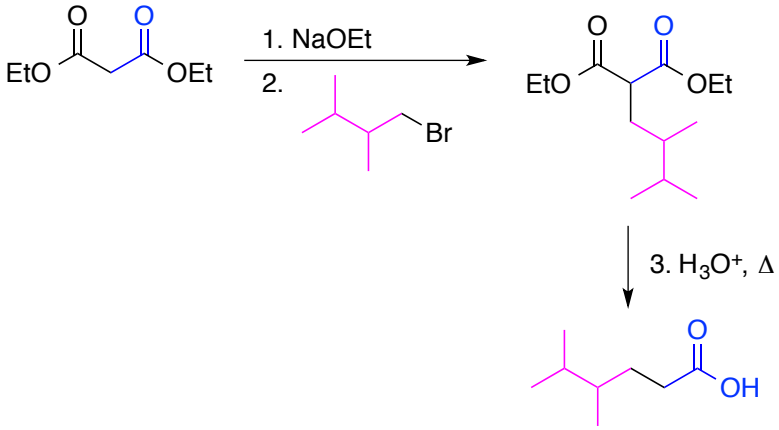
9.

(a) When using a malonic ester synthesis to prepare a specific target, it is best to begin with an analysis of the desired product. First, label the α and β-carbons. The α-β bond is made during the malonic ester synthesis, so this is where we retrosynthetically disconnect the target. The carboxylic acid and the α-carbon derive

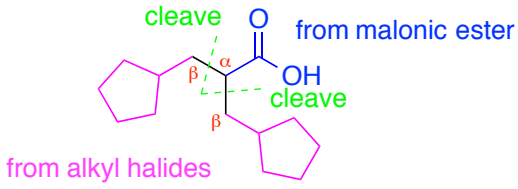
from the malonic ester itself. The β-carbon and its substituent come from the alkyl halide used during the alkylation. This retrosynthetic analysis allows us to begin the malonic ester synthesis with a clear plan in mind.



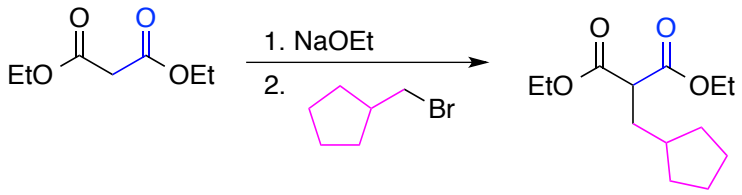
Diethyl malonate is treated with sodium ethoxide to deprotonate the α-carbon. Then, the necessary alkyl halide is added to complete the alkylation. Finally, hydrolysis of both esters is followed by decarboxylation to yield the monosubstituted acetic acid derivative.



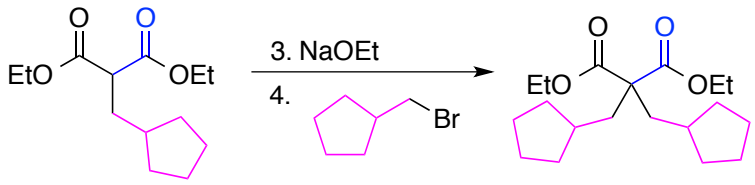
(b) In this problem, we similarly begin by labeling the α-carbon and both β positions. Any α-β bonds are made during the malonic ester synthesis, so we must retrosynthetically disconnect both α-β bonds. As in part (a), the carboxylic acid and the α-carbon come from the malonic ester. The β-carbons and their substituents come from alkyl halides. Since the two purple fragments are identical, a single alkyl halide can be used in both alkylation events.



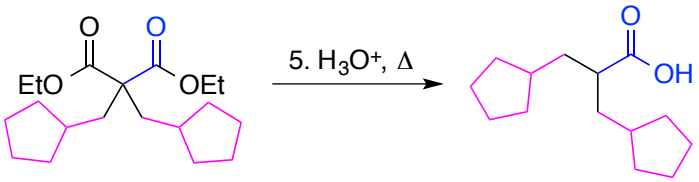
The sequence begins with deprotonation of diethyl malonate using sodium ethoxide. The enolate is then alkylated for the first time.



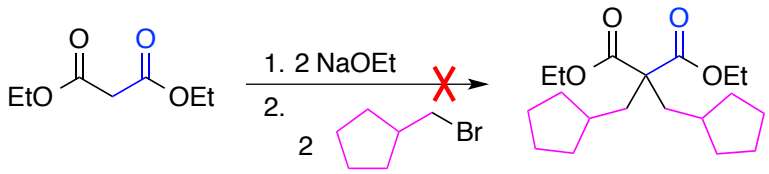
Treatment with sodium ethoxide once again deprotonates the α-carbon, and a second alkylation installs the last needed fragment of the target molecule.



The synthesis concludes with hydrolysis and decarboxylation to yield the desired disubstituted acetic acid derivative.



Note that this synthesis is a five-step sequence. Even though both alkylations happen to use the same alkyl halide, you *cannot* condense the first four steps as follows.

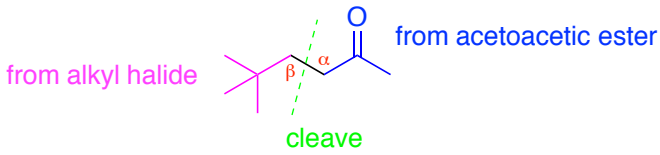


Formation of a dianion in step 1 is not possible because such a dianion would be too high in energy. As a consequence, there would be residual ethoxide present when the alkyl halide is added in step 2. The remaining ethoxide could cause the alkyl halide to undergo undesired substitution and/or elimination reactions.

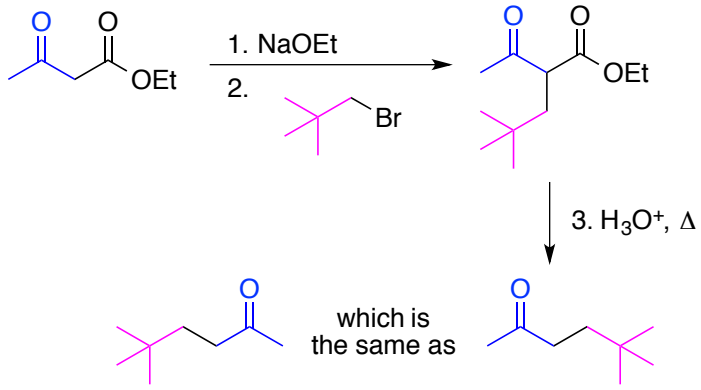
10.

(a) When using the acetoacetic ester synthesis, it is best to begin by carefully analyzing the target. Start by labeling the α and β positions. The α-β bond is the one made during the acetoacetic ester synthesis, so retrosynthetically disconnect at this location. The fragment bearing the α-carbon comes from ethyl acetoacetate itself.

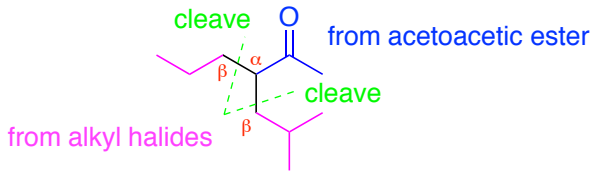
The fragment containing the β-carbon derives from the alkyl halide used during the alkylation.



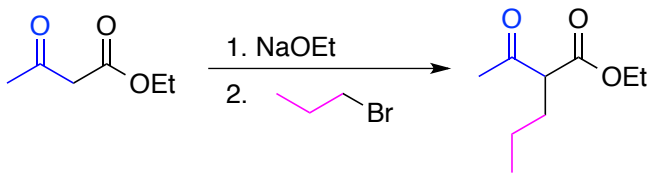
We can now embark on the synthesis with a clear plan in mind. Ethyl acetoacetate is first deprotonated using ethoxide. Then the enolate is alkylated using the requisite alkyl halide. Finally, heating in aqueous acid hydrolyzes the ester and decarboxylates to afford the monosubstituted acetone derivative.



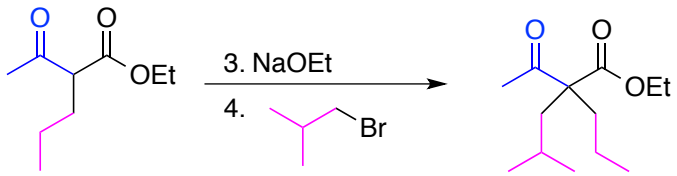
(b) In this problem, we also begin by labeling the α-carbon and both β positions. Any α-β bonds are made during the acetoacetic ester synthesis, so we must retrosynthetically cleave both α-β bonds. As in part (a), the fragment containing the α-carbon comes from ethyl acetoacetate. The fragments containing the β-carbons are derived from the alkyl halides used in the two alkylation events.



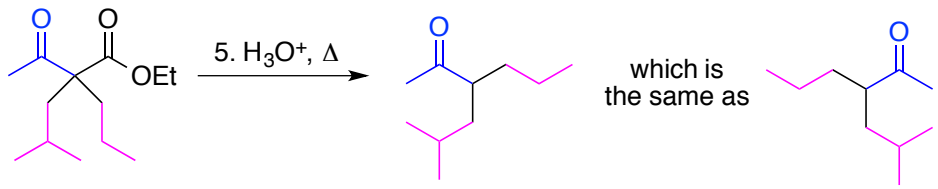
We begin the synthesis with deprotonation of ethyl acetoacetate using ethoxide. The resulting enolate can then be alkylated with either of the necessary alkyl halides. The order in which the alkyl groups are added is irrelevant.



The monoalkylated compound is deprotonated a second time and then treated with the other alkyl halide to install the last fragment needed.

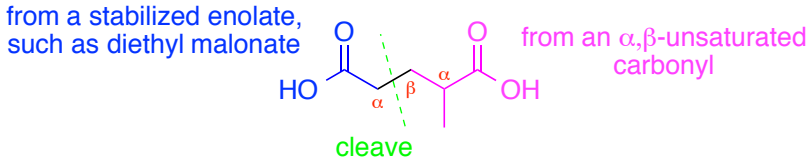


Lastly, heating in aqueous acid hydrolyzes the ester. The β-ketoacid thus formed decarboxylates at the elevated temperatures used in this transformation, and the result is the desired disubstituted acetone derivative.

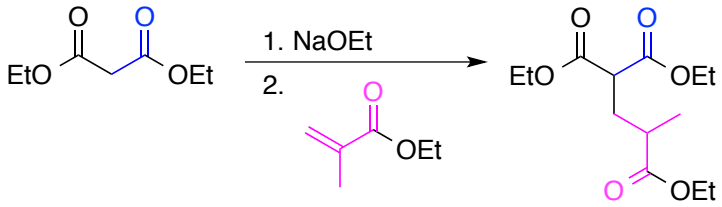


11.

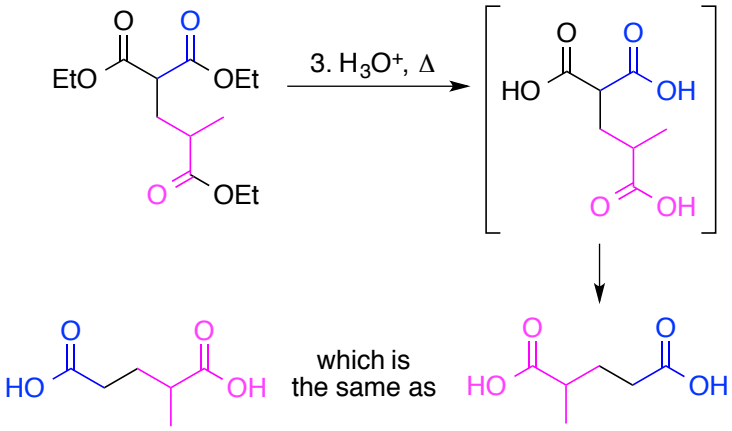
(a) Since the target possesses a 1,5-dicarbonyl, it is clear that a Michael reaction has been used. Begin by labeling the α-carbons and the β position. During the Michael reaction the α-carbon of a stabilized enolate is united with the β position of an α,β-unsaturated carbonyl compound. As such, we could retrosynthetically disconnect either α-β bond. The fragment containing only an α position derives from the stabilized enolate. The fragment containing both α and β positions results from the α,β-unsaturated system.



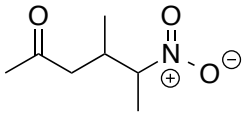
We can now begin the synthesis with a clear plan in mind. The stabilized enolate usually possesses two carbonyls (or similar functionalities) that delocalize the charge on the α-carbon. Furthermore, to make the desired target, we have to be able to remove one of the groups (through decarboxylation) while the other remains as an acid. Therefore, a malonic ester, such as diethyl malonate, is a logical choice. Note that we cannot use a diacid because the acidic protons would present a problem during the deprotonation step. Once the enolate is formed through treatment with ethoxide, the Michael reaction can be conducted when an α,β-unsaturated ester is added. Notice that, yet again, we must use an ester rather than an acid because the acid's labile proton would simply quench the enolate.



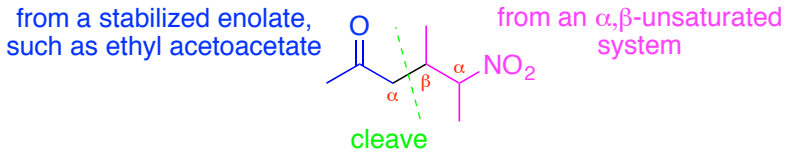
With the Michael adduct in hand, we can now hydrolyze all three esters by heating in aqueous acid. Once the triacid is formed, it will spontaneously decarboxylate at this elevated temperature. Remember that, in order to decarboxylate, an acid must have a carbonyl in the β position. So, only a single decarboxylation occurs, and it occurs on the malonic acid fragment. The end result is the target diacid.



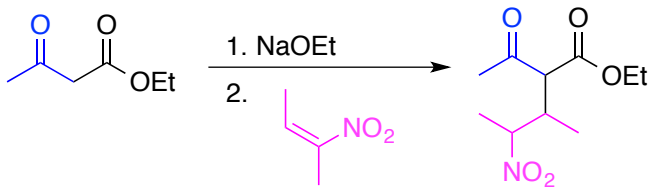
(b) This target does not contain a 1,5-dicarbonyl; however, there is a nitrogen-oxygen π bond five atoms from the ketone. Therefore, this is electronically quite similar to a 1,5-dicarbonyl, signaling the use of a Michael reaction.



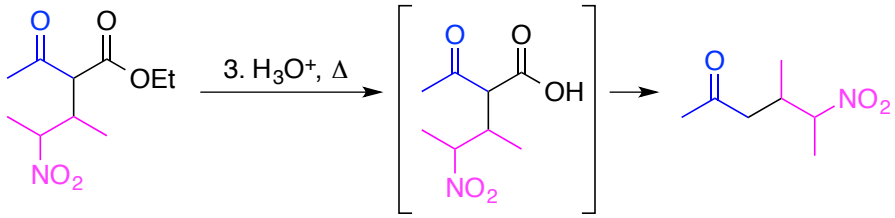
To analyze the target, we should first label the α positions and the β position. Since the α-β bond is made during a Michael reaction, we can cleave retrosynthetically at either α-β bond. Our choice can be guided by the selection of familiar reagents. If the cleavage below is made, the stabilized enolate could be ethyl acetoacetate, which we know can undergo decarboxylation to shed the carboxylate and leave only the acetone fragment. The section of the target containing both the α and β positions can be traced back to an α,β-unsaturated system.



The synthesis begins with the deprotonation of ethyl acetoacetate. The enolate thus formed can then add to the β position of an α,β-unsaturated nitro compound.

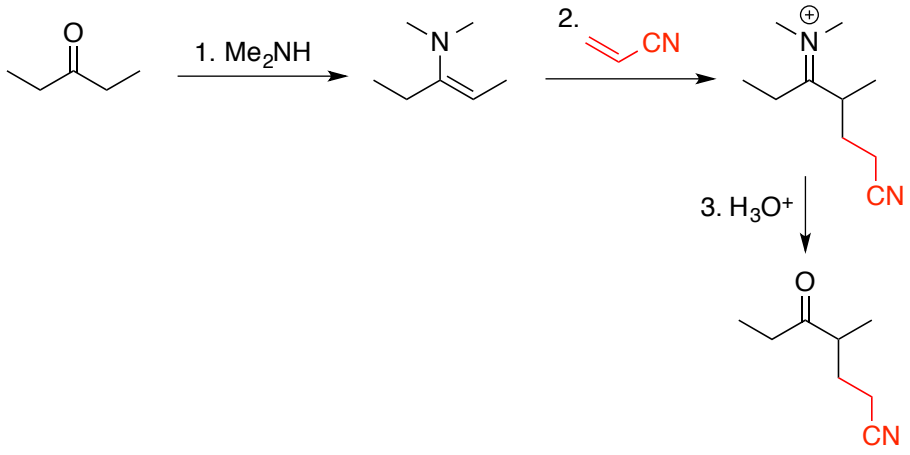


With all the key portions of the molecule in place, the ester can be hydrolyzed in aqueous acid at elevated temperature. This is immediately followed by spontaneous decarboxylation to afford the target molecule.



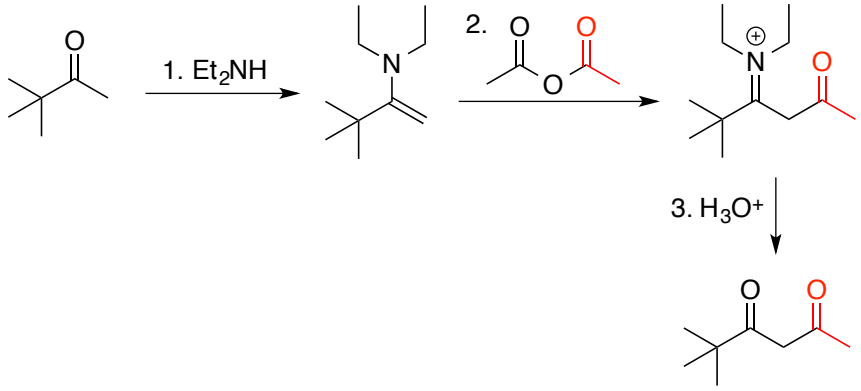
12.

(a) This reaction begins with enamine formation between 3-pentanone and dimethylamine. The enamine is nucleophilic on its α-carbon, which therefore adds to the electrophilic β position of the α,β-unsaturated nitrile. The resultant iminium ion is then hydrolyzed to afford the ketone as the final product.



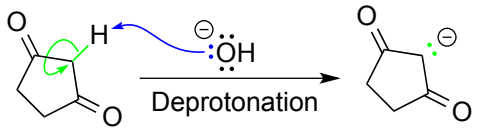
You might be concerned about hydrolysis of the nitrile in the last step. However, as we learned in Chapter 16, it takes fairly strong acid (and often heating) to hydrolyze a nitrile. Therefore, if the acid used is dilute, the much more labile iminium ion can be hydrolyzed without impacting the nitrile.

(b) This transformation begins with enamine formation as well. Only one of the original ketone's α positions is enolizable, so only one enamine can be formed. The nucleophilic α-carbon of the enamine then attacks one of the electrophilic carbonyls of the anhydride. This amounts to a nucleophilic acyl substitution of an anhydride. We are simply using a new nucleophile (the enamine) that we have not previously used in this capacity. In this fashion, an acetyl group is added to the substrate, and the iminium ion is then hydrolyzed to afford the 1,3-diketone product.

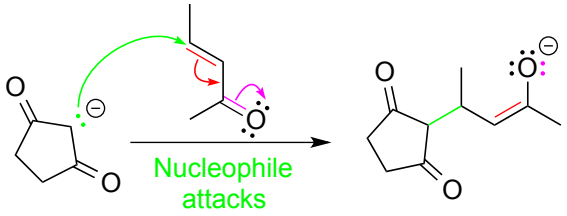


13. Since the Robinson annulation has a fairly lengthy mechanism, it helpful to remember that it has two main phases: (1) Michael reaction and (2) intramolecular aldol condensation. We can even further subdivide the intramolecular aldol condensation into two parts: intramolecular aldol reaction followed by dehydration. This breaks the mechanism into three small, manageable segments: (1) Michael reaction, (2) intramolecular aldol reaction, and (3) dehydration.

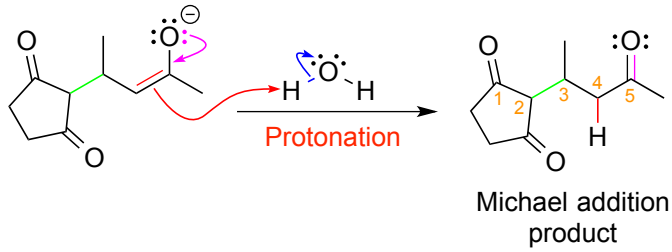
The first segment is Michael reaction, which begins with the formation of a stabilized enolate. Although there are multiple α positions in the two reactants, only one is doubly stabilized by two adjacent carbonyls. This is the site of the initial deprotonation.



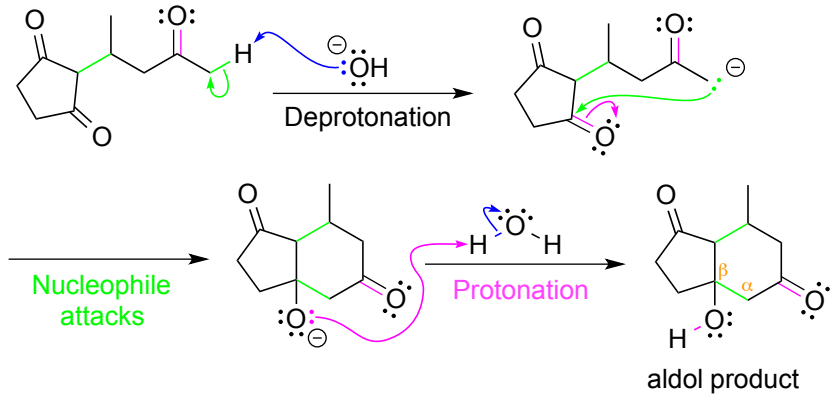
The stabilized enolate then adds to the β position of the α,β-unsaturated ketone. Electrons from the alkene flow toward the carbonyl, and the negative charge is ultimately deposited on the carbonyl oxygen.



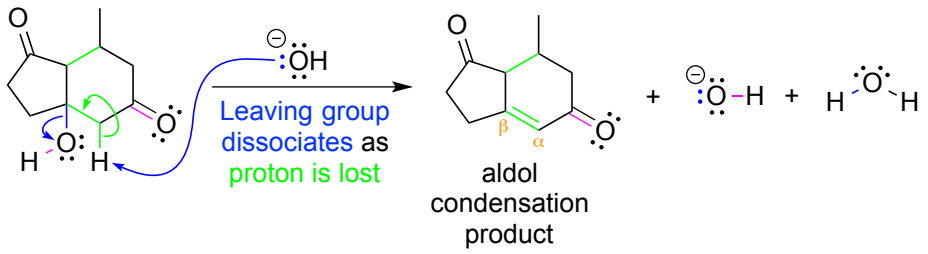
The new enolate then removes a proton from the solvent (water in this case) to provide the neutral Michael adduct with a 1,5-dicarbonyl.



In the second phase of the Robinson annulation, an intramolecular aldol reaction occurs. This too begins with deprotonation. While there are multiple α positions present, there is only one enolate that could cyclize onto another carbonyl to yield an unstrained, six-membered ring. That is the enolate formed from deprotonation of the terminal methyl group. It cyclizes onto one of the two remaining carbonyls to yield a new six-membered ring. The alkoxide removes a proton from the solvent to yield the product of the intramolecular aldol reaction. Notice that this product is a β-hydroxyketone. This core fragment is emblematic of an aldol reaction product, which always contains a hydroxyl group β to a carbonyl.

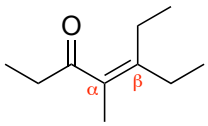


The third and final portion of the Robinson annulation is the dehydration of the aldol product. This occurs through removal of an α-proton and simultaneous expulsion of the β-hydroxyl group as the α,β-unsaturation is installed. The increase in entropy drives this process forward.

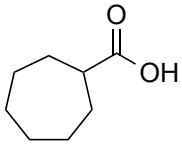


14.

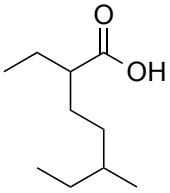
(a) This compound is an α,β-unsaturated ketone, which means that an aldol condensation would be ideally suited for its preparation.



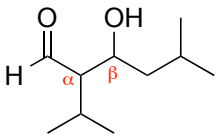
(b) This carboxylic acid could be prepared by a haloform reaction of a substrate bearing one additional carbon in the form of a methyl ketone, or alternatively it may be made using a malonic ester synthesis.



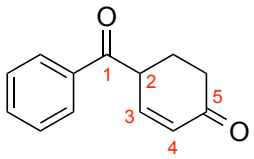
(c) This carboxylic acid could also be prepared using either a haloform reaction or a malonic ester synthesis.



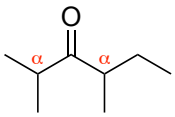
(d) This is a β-hydroxyaldehyde, which can be made using an aldol reaction.



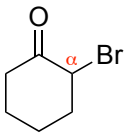
(e) This target contains a 1,5-diketone. Since the path from one carbonyl to the other also entails a ring, it is likely that Robinson annulation would be a good choice for its preparation.



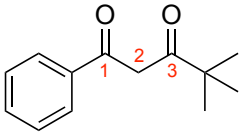
(f) This ketone could be prepared via α-alkylation, which could be used to install any of the substituents branching off of either α-carbon.



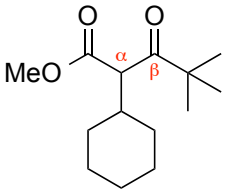
(g) This cyclohexanone bearing a bromine on the α carbon would likely be produced using α-halogenation.



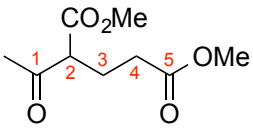
(h) This 1,3-diketone could be prepared using a Stork enamine reaction.



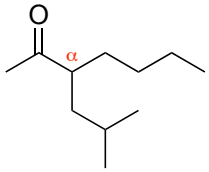
(i) The Claisen condensation would be ideally suited to the preparation of this β-ketoester.



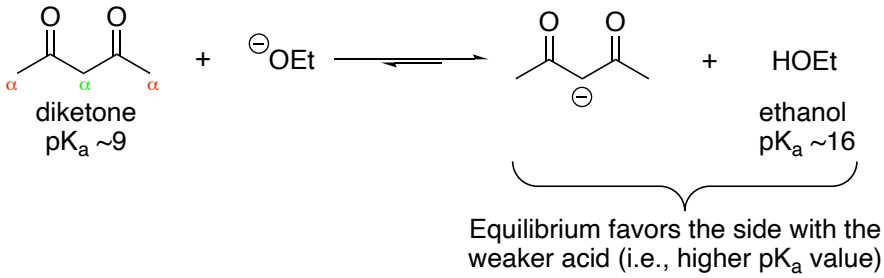
(j) This 1,5-dicarbonyl could be prepared using a Michael reaction or a Stork enamine reaction.



(k) This geminally disubstituted acetone derivative could be prepared via the acetoacetic ester synthesis.



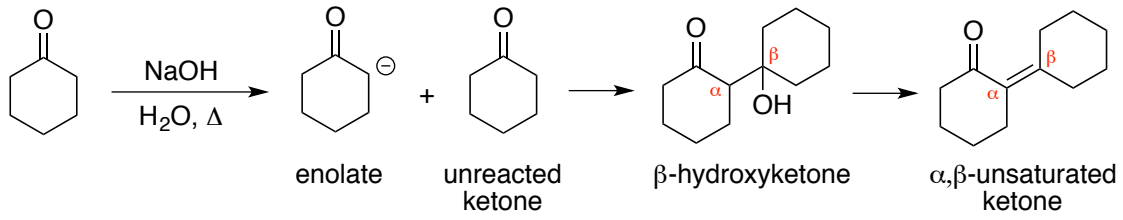
15. The diketone has three α-carbons, amounting to two distinct options for the site of deprotonation. The central α-protons are more acidic than the terminal α-protons. The reason is that the enolate formed at the central α position enjoys resonance delocalization into two carbonyls; whereas, an enolate formed at a terminal α position would benefit from resonance into only one of the two carbonyls. Consequently, ethoxide deprotonates the central α-carbon to form the most stable enolate and ethanol as products.



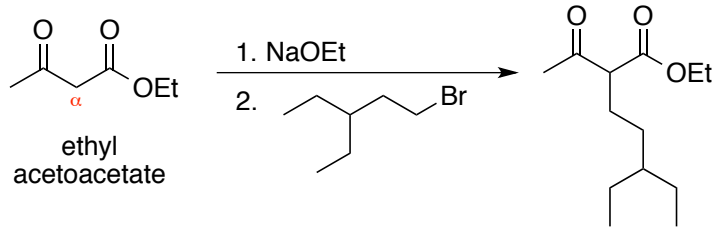
Equilibrium favors the products because that is the side with the weaker acid. Recall that the weaker acid possesses the higher pK_a value. The products are favored by 10 to the difference in the pK_a values, or 10^7.

16.

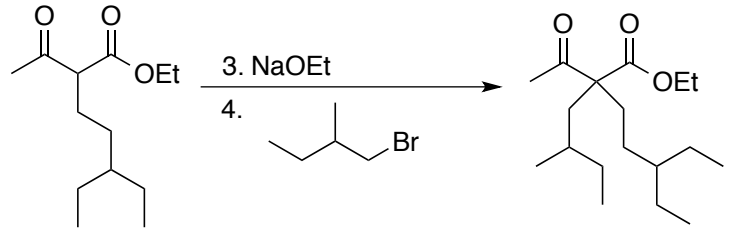
(a) This is an aldol condensation under basic conditions. The ketone is partially deprotonated at its α position. In other words, hydroxide is only strong enough to deprotonate some molecules of cyclohexanone. Much of the cyclohexanone is unchanged by the base. Given that both the enolate and unreacted ketone will be present in the reaction mixture, a self-condensation can occur. The enolate attacks the ketone, and the resulting alkoxide removes a proton from water to yield a β-hydroxyketone. At the elevated temperatures used, dehydration will follow to afford the α,β-unsaturated ketone as the final product.



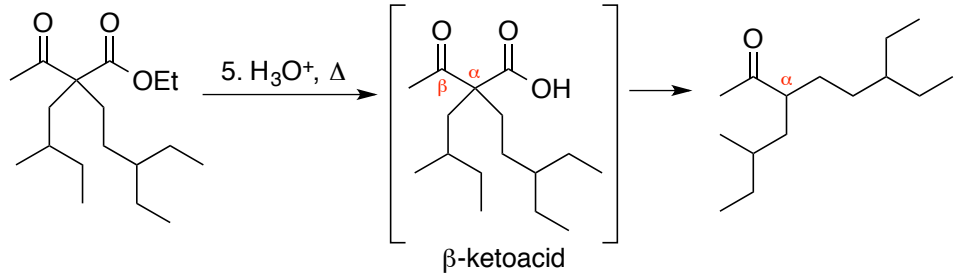
(b) This is an acetoacetic ester synthesis, which begins with the substrate ethyl acetoacetate. The especially acidic position that is α to two carbonyls is deprotonated by sodium ethoxide. The resultant enolate is then alkylated.



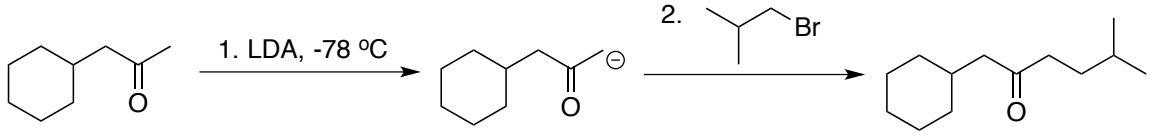
Since one proton remains at the acidic, doubly activated α position, it can be deprotonated and alkylated once again.



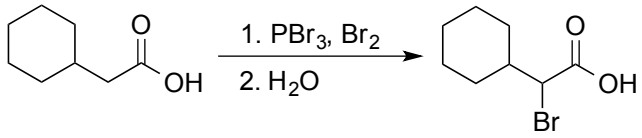
Finally, the ester is hydrolyzed, and the β-ketoacid that results spontaneously decarboxylates to provide the final product: a geminally disubstituted acetone derivative.



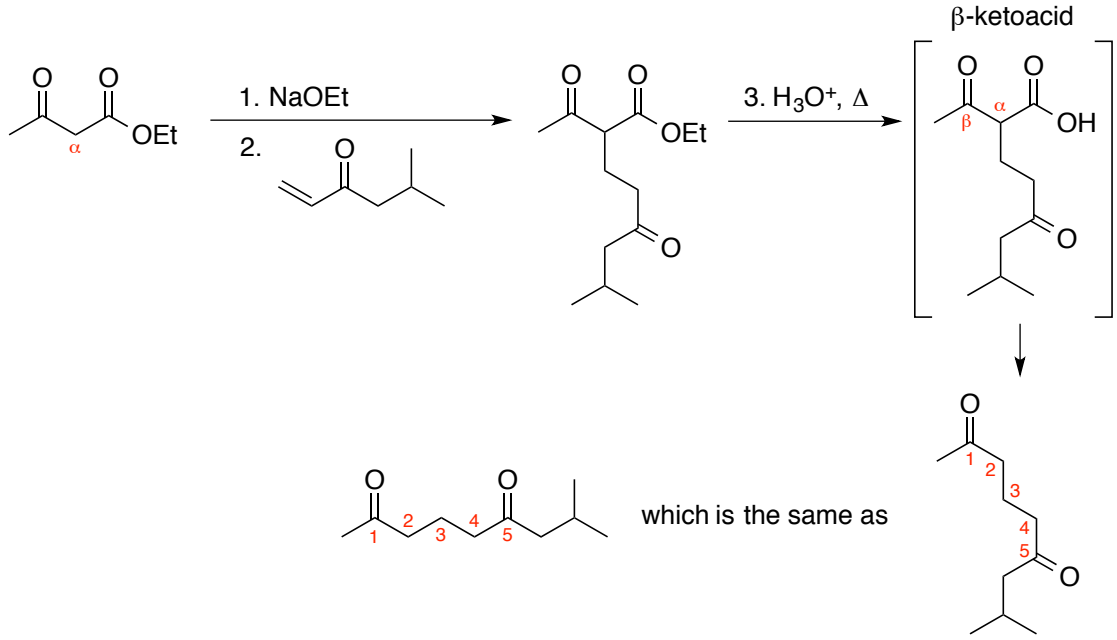
(c) This is an α-alkylation that is under kinetic control. At low temperatures, the sterically hindered base LDA removes only the more accessible α-proton to provide the kinetic enolate. This enolate is then alkylated to provide the product.



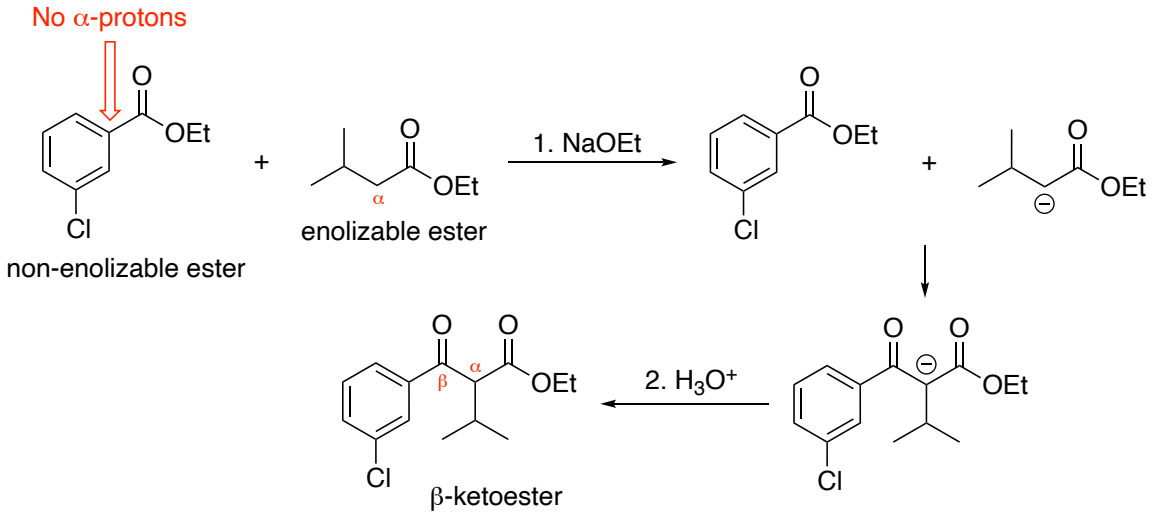
(d) In this Hell-Volhard-Zelinsky reaction, the carboxylic acid is halogenated in the α position.



(e) This sequence begins with the deprotonation of ethyl acetoacetate at the doubly activated α-carbon. The stabilized enolate then adds to the α,β-unsaturated ketone in a Michael reaction. The resultant enolate removes a proton from the solvent to afford the Michael product. Upon heating with aqueous acid, the ester is hydrolyzed, and the β-ketoacid then spontaneously decarboxylates to provide the 1,5-diketone as the final product.

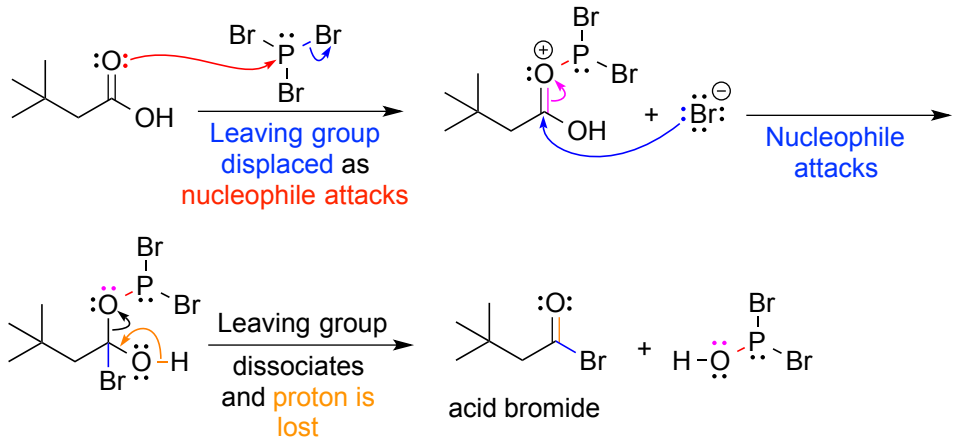


(f) This is a crossed-Claisen condensation. When treated with sodium ethoxide, only one of the two esters can enolize because only one of the two esters possesses α-protons. The enolate thus formed attacks the non-enolizable ester. This amounts to a nucleophilic acyl substitution of ethyl *meta*-chlorobenzoate, in which the enolate is the nucleophile. The β-ketoester that results has a doubly activated (and therefore much more acidic) α position. Consequently, it readily loses a proton in this basic medium. Upon treatment with acid in step 2, the enolate is protonated to afford the neutral β-ketoester as the final product.

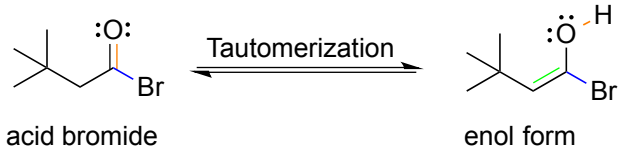


17. The treatment of a carboxylic acid with phosphorus tribromide and bromine followed by water is an α-bromination known specifically as the Hell-Volhard-Zelinsky (HVZ) reaction. The HVZ reaction has three principal phases: (1) conversion of the carboxylic acid to the acid bromide; (2) α-bromination; and (3) hydrolysis of the acid bromide. Learning the reaction in this fashion makes the fairly lengthy mechanism more manageable.

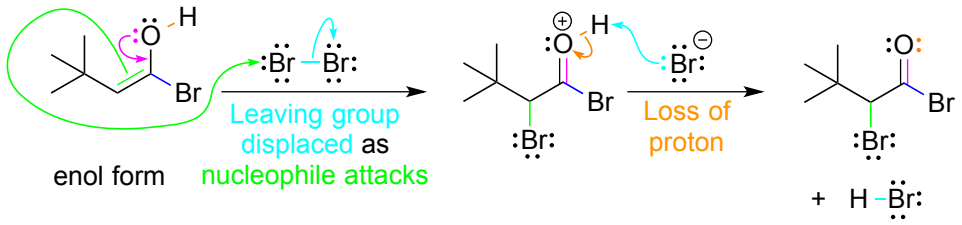
The first phase of the mechanism begins with the attack of the carbonyl oxygen on the electrophilic phosphorus of PBr_3. A bromide is displaced in the process, and it subsequently attacks the carbonyl carbon, pushing the π electrons onto oxygen. The tetrahedral intermediate thus formed loses a good leaving group as a new carbonyl is formed. The result is the acid bromide.



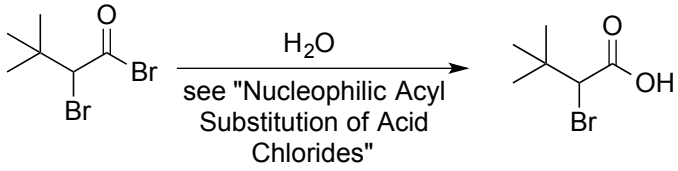
The acid bromide tautomerizes more readily than the original carboxylic acid. This provides some of the enol form, which is nucleophilic on its α-carbon.



Then, as the carbonyl is re-formed, the nucleophilic enol attacks bromine and displaces bromide. The oxonium ion then sheds a proton to yield the neutral α-brominated acid bromide.

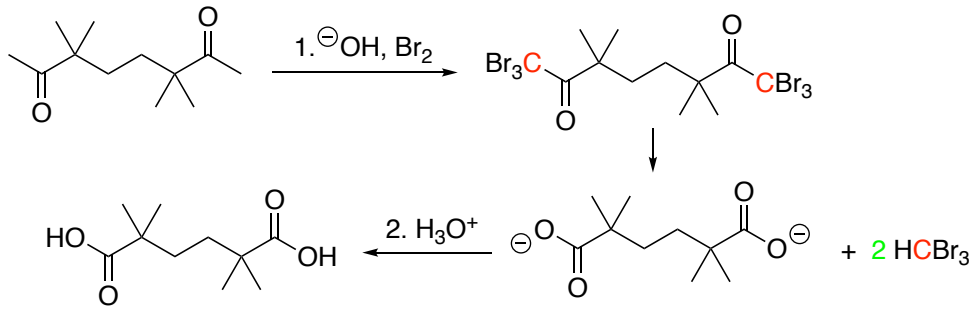


Finally, when water is added to the mixture, the acid bromide is hydrolyzed much as an acid chloride would be hydrolyzed. This occurs through nucleophilic acyl substitution.



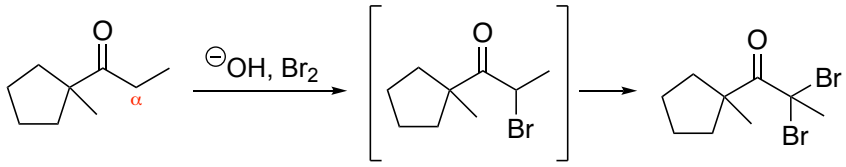
18.

(a) The treatment of a methyl ketone with hydroxide and bromine followed by acid is the bromoform reaction (a specific example of the haloform reaction). The reaction begins with the exhaustive bromination of the methyl ketones. Then $^{-}$:CBr_3 is displaced as a good leaving group in a nucleophilic acyl substitution in which hydroxide acts as the nucleophile. The newly formed carboxylic acids are deprotonated in this basic medium to yield two equivalents of bromoform and the carboxylates, which are protonated upon acidic workup.

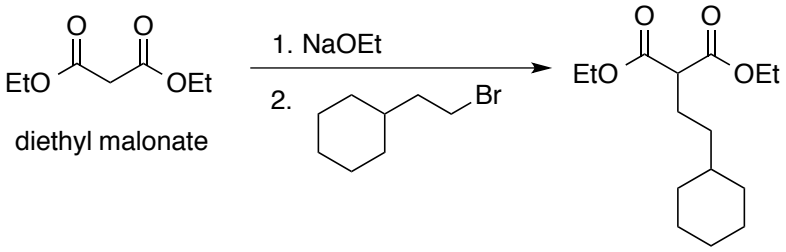


Notice that each occurrence of the bromoform reaction shortens the carbon chain by one. Since the substrate contained two methyl ketones, the product has lost two carbons in the two equivalents of bromoform released during the transformation.

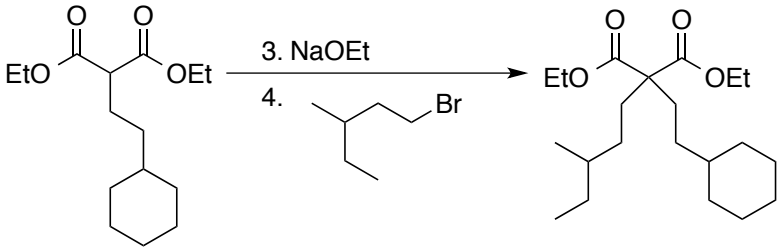
(b) The treatment of an enolizable ketone or aldehyde with bromine in base leads to α-bromination. The α-carbon bearing protons is deprotonated to yield an enolate, which then reacts with bromine. The monobrominated ketone still possesses an α-proton, and due to the electron-withdrawing nature of bromine, this remaining α-proton is now even more acidic than the original α-protons were. Consequently, a second deprotonation occurs readily. The second enolate then reacts with more bromine, leading to a dibrominated ketone product.



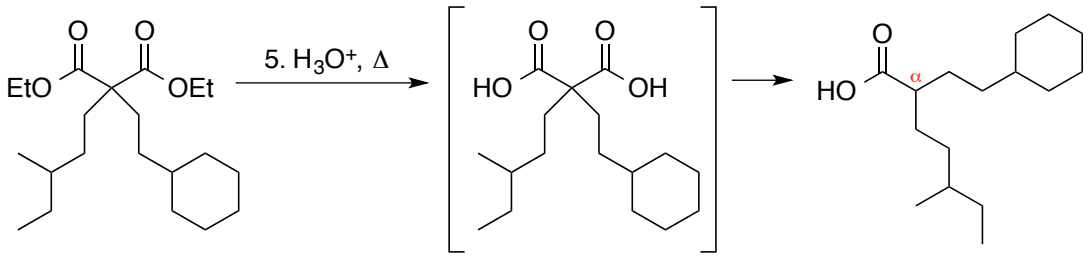
(c) The appearance of diethyl malonate, followed by two alkylation events is a clear indication that this sequence is a malonic ester synthesis. The process begins with deprotonation of the α-carbon and subsequent alkylation.



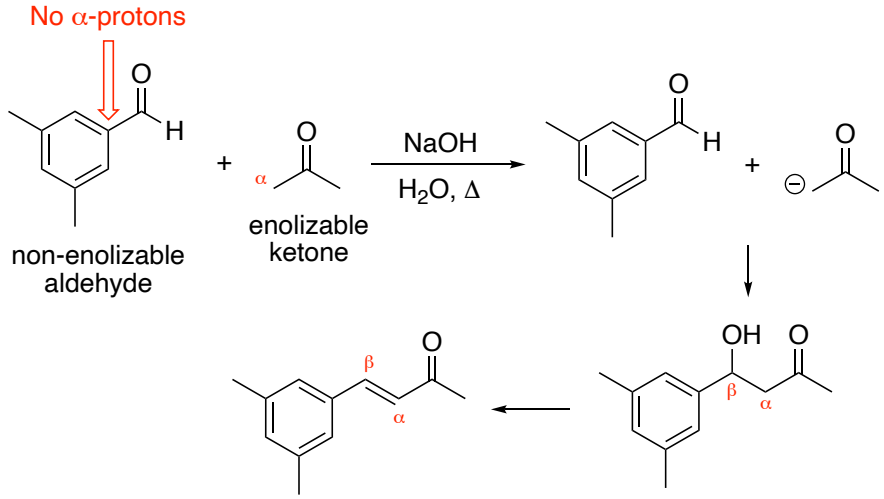
Since one α-proton remains, it is possible to conduct a second alkylation.



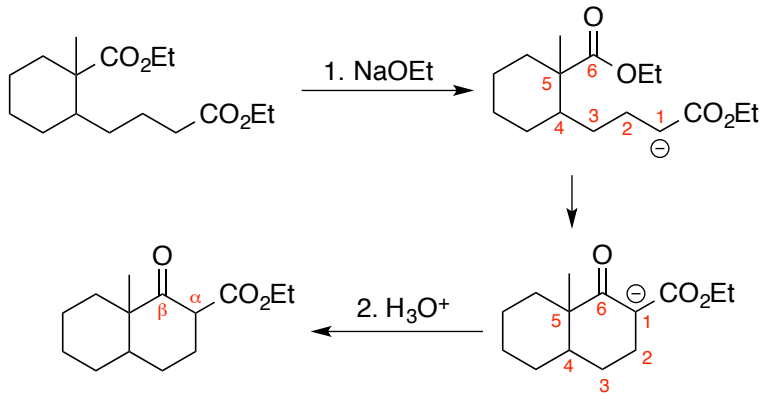
Finally, heating in aqueous acid hydrolyzes both esters. The diacid that is formed spontaneously decarboxylates to give a disubstituted acetic acid derivative.



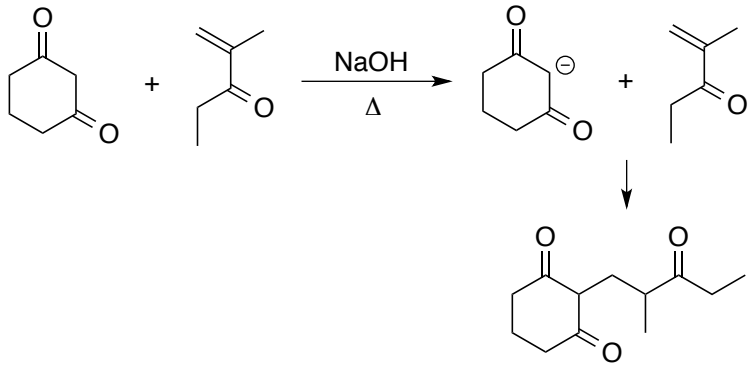
(d) The reactants include one enolizable ketone and one aldehyde that bears no α-protons and is therefore non-enolizable. In base, a crossed-aldol reaction will occur. It begins with enolate formation. The enolate then attacks the non-enolizable aldehyde. After the resulting alkoxide removes a proton from water, a β-hydroxyketone is produced. At the elevated temperatures used in this reaction, dehydration follows to give the α,β-unsaturated system.



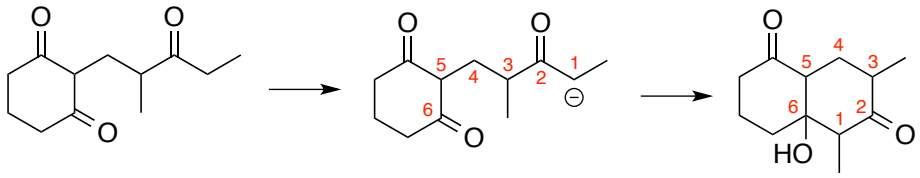
(e) The substrate contains two esters, one of which has α-protons (and is therefore enolizable). Upon treatment with base, an *intramolecular* Claisen condensation can occur. This is termed the Dieckmann condensation. The transformation begins with enolate formation. The enolate is six atoms from the electrophilic carbonyl of the other ester. Cyclization takes place through nucleophilic acyl substitution on the electrophilic ester. Numbering helps to determine the size of the ring formed and to draw that ring with the substituents in the correct locations. The resulting β-ketoester has a doubly activated α position that is quite acidic, so it is readily deprotonated under the reaction conditions. Upon workup however, that proton is restored to yield the neutral, cyclic β-ketoester.



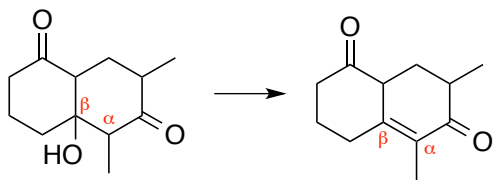
(f) There are a few indications that this is a Robinson annulation. First, a stabilized enolate can be formed, and it can then undergo Michael reaction with the α,β-unsaturated ketone.



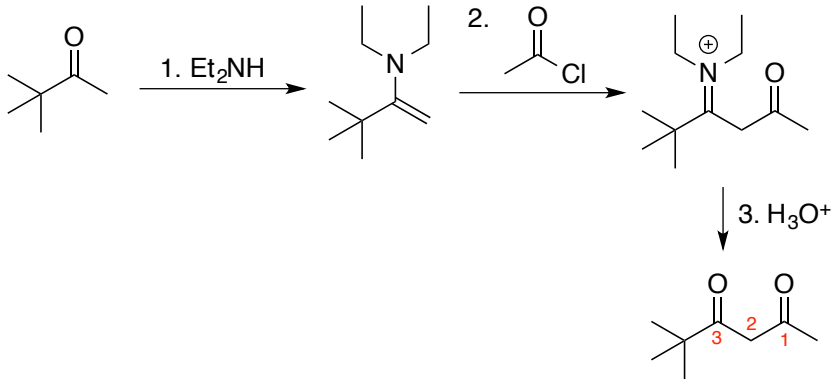
Secondly, the Michael adduct has α-protons, so it can be deprotonated, leading to an intramolecular aldol reaction that will form a ring. Note that numbering helps us to draw the correct ring size and to place the substituents in the appropriate locations.



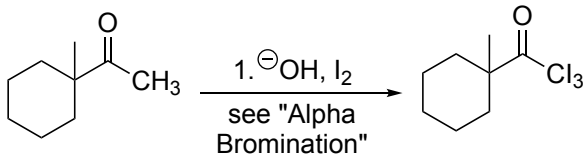
Finally, under the elevated temperatures used for this transformation, the β-hydroxyketone dehydrates, installing an α,β-unsaturation and completing an aldol *condensation*.



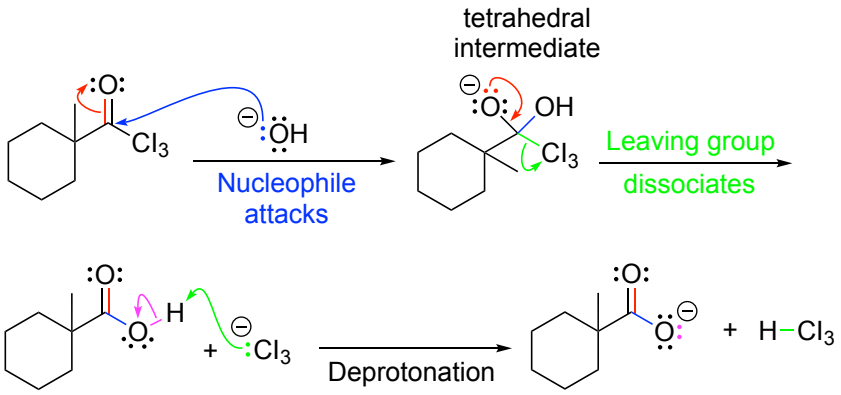
(g) This reaction entails the formation of an enamine, which suggests a Stork enamine reaction. The enamine formed in step 1 is nucleophilic at its α-carbon. Consequently, it serves as the nucleophile in a nucleophilic acyl substitution on acetyl chloride. The resultant iminium ion is readily hydrolyzed in aqueous acid, and the product is a 1,3-diketone.



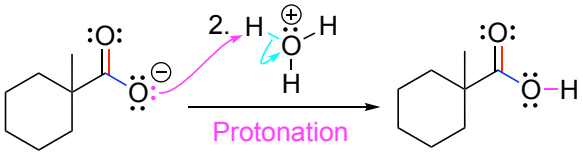
19. This is a haloform reaction, specifically the iodoform reaction. The process begins with the exhaustive iodination of the methyl ketone. This occurs through a mechanism that is essentially identical to that of α-bromination under basic conditions.



Then, hydroxide attacks the carbonyl carbon, displacing the π electrons onto oxygen and forming a tetrahedral intermediate. Although a carbanion is not usually a reasonable leaving group, the electron-withdrawing nature of the halogens makes the triiodomethyl carbanion a reasonable leaving group. It is displaced as the carbonyl is re-formed. Finally, the newly formed carboxylic acid is deprotonated under these basic conditions to yield a carboxylate and iodoform.

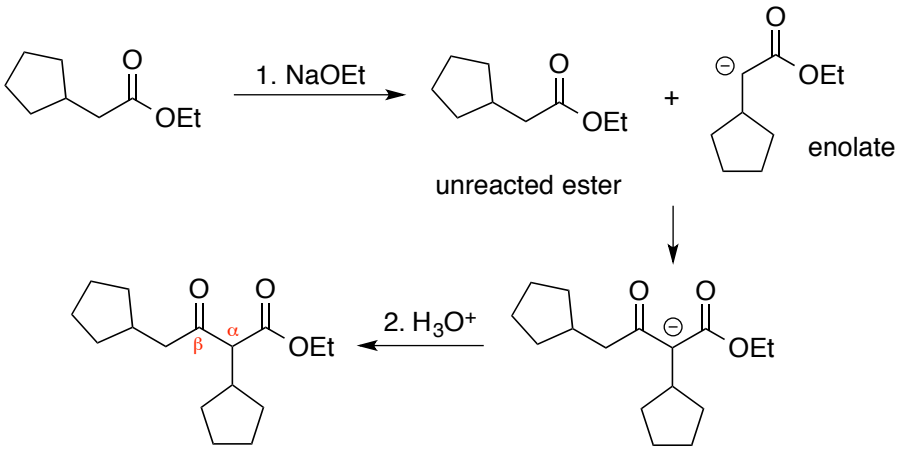


Upon workup, the carboxylate is protonated to provide a carboxylic acid whose carbon skeleton has been reduced by one.



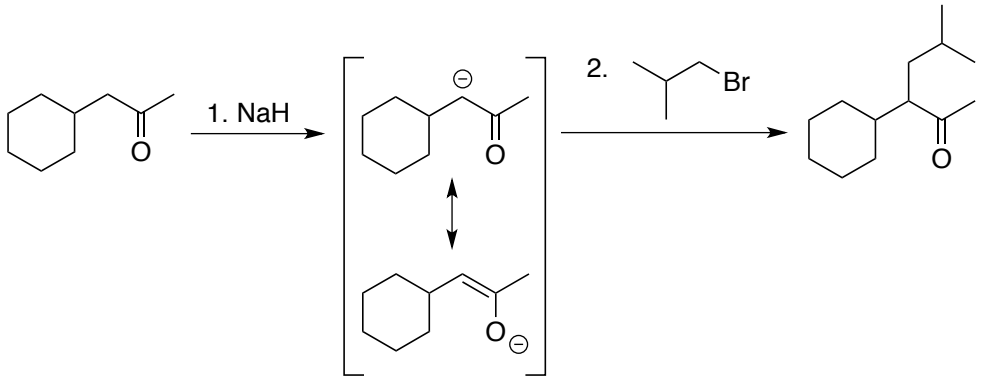
20.

(a) The presence of an enolizable ester along with base suggests the Claisen condensation. Since a modest base (ethoxide) is used, some of the ester is deprotonated but much remains unaltered. The enolate is nucleophilic and attacks the electrophilic carbonyl carbon of the unreacted ester. What follows is simply a nucleophilic acyl substitution of an ester, in which an enolate plays the role of the nucleophile. A β-ketoester is produced, but its doubly activated α position readily loses a proton in this basic medium. That proton is replaced upon workup with acid.



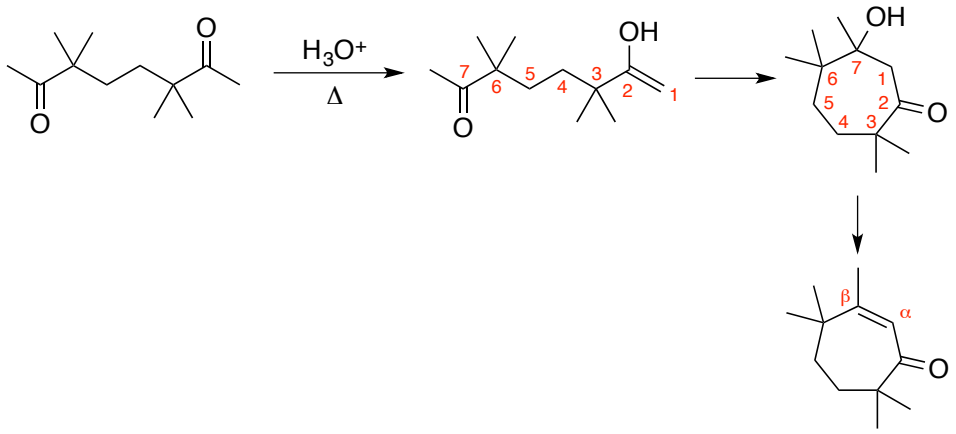
(b) This is an α-alkylation performed under thermodynamic control. Sodium hydride deprotonates the ketone at the more substituted α position because this

leads to the more substituted (and therefore more stable) double bond in the resultant enolate. This thermodynamically favored enolate is then alkylated.

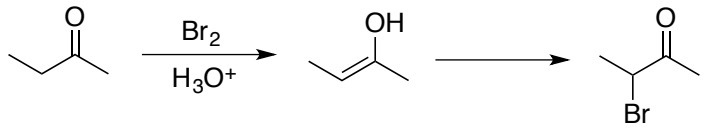


Contrast this outcome with that of Problem 16(c), which is under kinetic control instead.

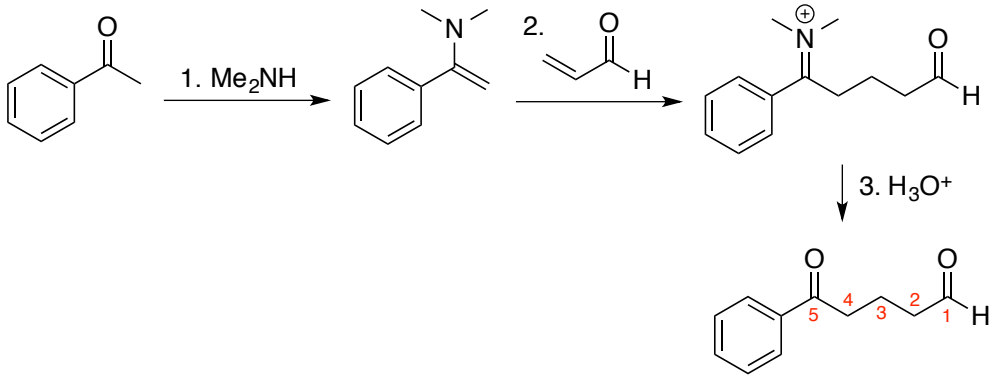
(c) The heating of enolizable ketones with acid suggests an acidic aldol condensation. Furthermore, since these ketones are tethered to one another, we can predict an *intramolecular* reaction. The transformation begins when one ketone enolizes. The enol is nucleophilic on its α-carbon, and it attacks the carbonyl carbon of the other ketone (once protonated). Numbering helps us to deduce the proper ring size and place substituents accordingly. The initial product, though cyclic, is a β-hydroxyketone just as we would expect from an aldol reaction. Due to the heating, this will ultimately be an aldol *condensation*. Dehydration occurs to install the α,β-unsaturation.



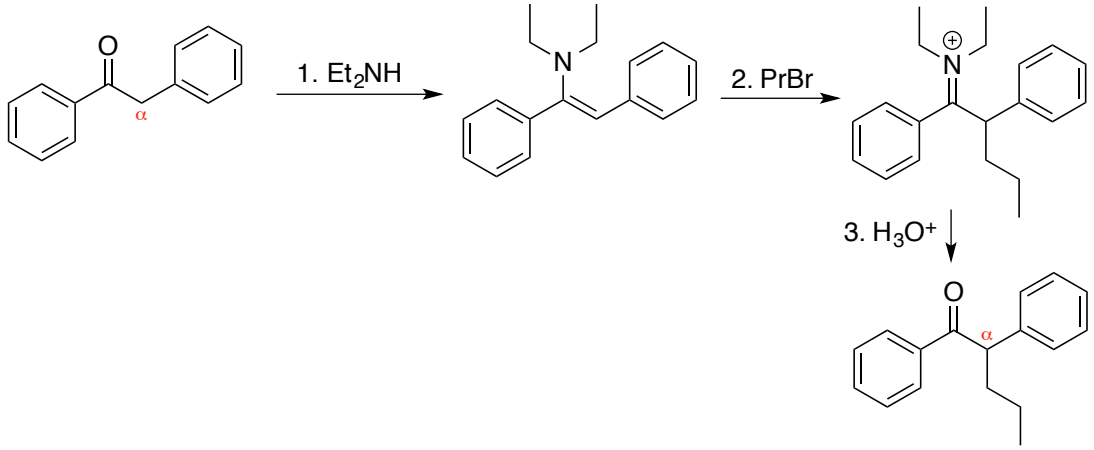
(d) The treatment of an enolizable ketone with bromine and acid implies α-bromination. The reaction proceeds through the enol. The more stable enol (containing the more highly substituted double bond) is formed preferentially. The enol then attacks bromine from its α-carbon to afford the product.



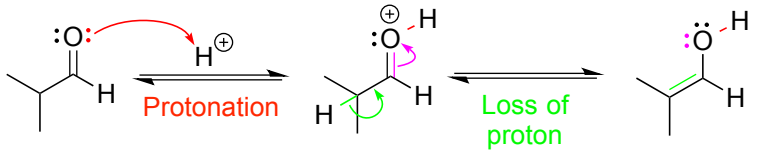
(e) The formation of an enamine in step 1 hints at a Stork enamine reaction. The enamine, being nucleophilic on its α-carbon, attacks the β position of the α,β-unsaturated aldehyde added in step 2. The resulting iminium ion is hydrolyzed in aqueous acid to yield the product as a 1,5-dicarbonyl.



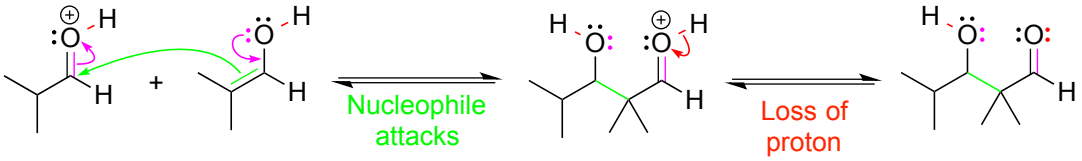
(f) This is an α-alkylation that occurs through the intermediacy of an enamine. The enamine is formed in step 1. In step 2, its nucleophilic α-carbon attacks the electrophilic propyl bromide. The iminium ion that results is hydrolyzed in step 3 to unveil the ketone bearing a new α-substituent.



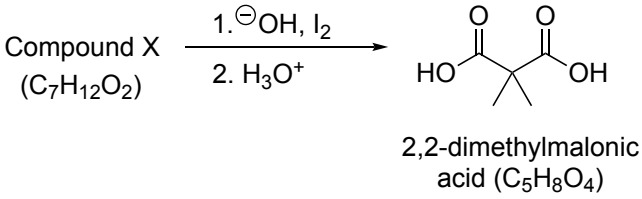
21. This aldol reaction begins with tautomerization. Tautomerization involves protonation of the carbonyl oxygen, followed by loss of an α-proton.



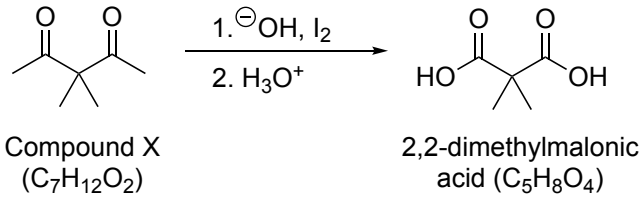
The enol thus formed is nucleophilic on its α-carbon, which therefore attacks the electrophilic carbonyl carbon of another (protonated) molecule of reactant. The carbonyl π-bonding electrons are pushed onto oxygen during this nucleophilic addition. Finally, loss of a proton neutralizes the oxonium ion and yields the β-hydroxyaldehyde.



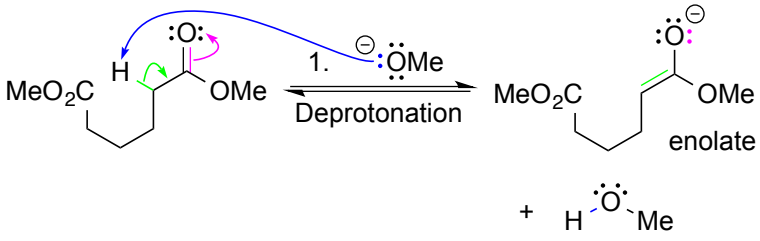
22. In word problems, it is always best to diagram the information provided. We are told that Compound X undergoes iodoform reaction to yield 2,2-dimethylmalonic acid after workup.



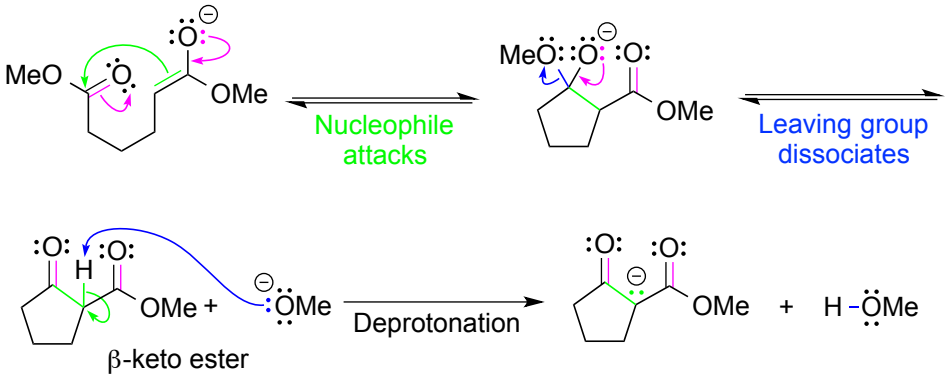
Notice that the product contains not just one, but *two* carbons fewer than the reactant. This means that two carbons are lost during the iodoform reaction. Therefore, Compound X must contain two methyl ketones that become the two carboxylic acids of the malonic acid derivative. Compound X is therefore 3,3-dimethyl-2,4-pentanedione.



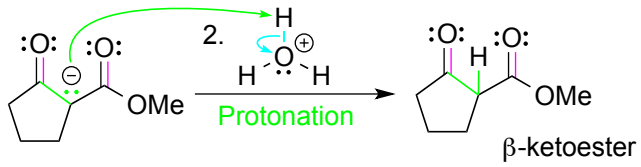
23. The Dieckmann condensation begins exactly as the Claisen condensation does: with the removal of an α-proton. Since the reactant is symmetrical, either α-carbon may be deprotonated to form the same enolate.



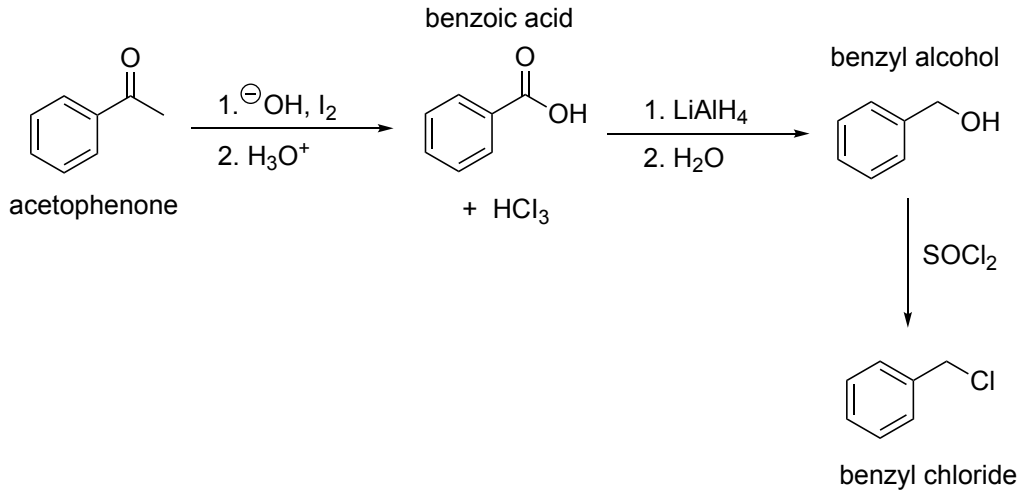
The enolate is nucleophilic and therefore attacks the ester carbonyl carbon that is five-atoms removed. This intramolecular attack is all that differentiates the Dieckmann from the Claisen condensation. As the carbonyl π electrons are pushed onto oxygen, a tetrahedral intermediate is generated. It subsequently collapses, re-forming the carbonyl and displacing methoxide in the process. The β-ketoester that results has a particularly acidic α-proton since it is doubly activated by two adjacent carbonyls. This proton is unavoidably lost in this basic medium.



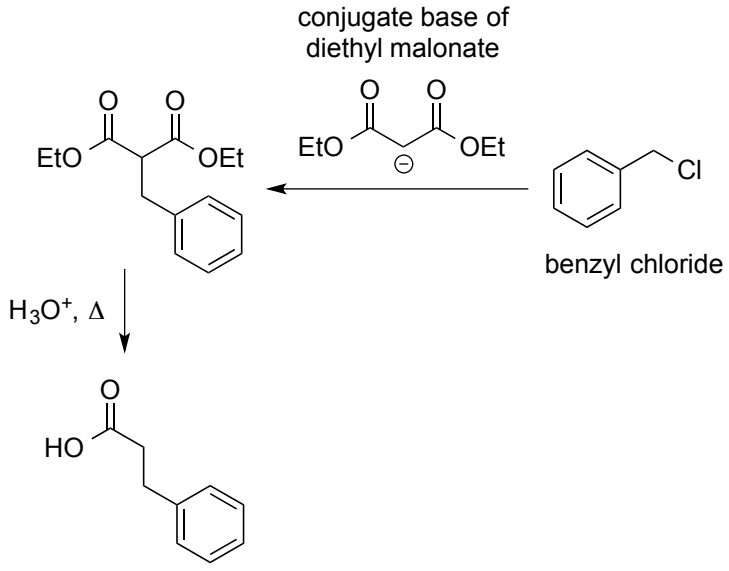
Upon workup, the enolate is quenched to yield the neutral β-ketoester as the final product.



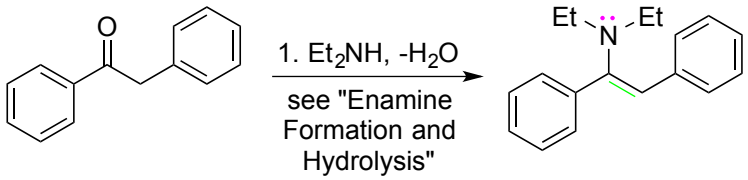
24. Since the reactant is missing, we are best served by working backwards from the first intermediate given, benzyl chloride. Alcohols can be converted to alkyl chlorides using thionyl chloride ($SOCl_2$), so the precursor to benzyl chloride must be benzyl alcohol. Benzyl alcohol could be produced from the lithium aluminum hydride reduction of benzaldehyde or benzoic acid, but only benzoic acid can be produced from an iodoform reaction. This allows us to firmly establish that benzoic acid is the second compound in the sequence. It would be the product of iodoform reaction of acetophenone.



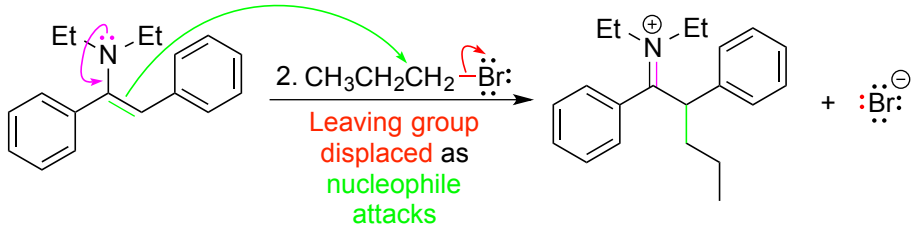
With the first half of the sequence sorted out, we can now turn our attention to the endgame of the synthesis. Two carbons are ultimately added to benzyl chloride to form a carboxylic acid as the final product. Notice that this carboxylic acid could be described as a monosubstituted acetic acid derivative. This suggests that the malonic ester synthesis was used. Since benzyl chloride is an electrophile, the missing reagent must be the conjugate base of diethyl malonate. Once the alkylation is complete, hydrolysis at elevated temperatures would be followed by spontaneous decarboxylation to afford the indicated product.



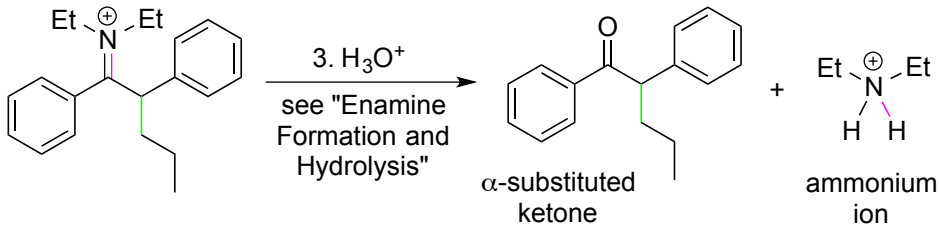
25. This α-alkylation begins with the formation of an enamine.



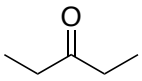
In step 2, the nucleophilic enamine is alkylated. The lone pair on nitrogen forms a nitrogen-carbon π bond, thereby freeing the electrons in the double bond to attack the electrophilic center of propyl bromide. Bromide is displaced in the process.



The iminium ion that was formed in step 2 is then hydrolyzed in step 3 to unveil the ketone, which is now alkylated in the α position.

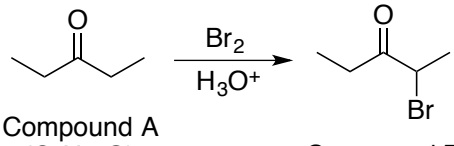


26. It is probably easiest to begin by deducing the structure of Compound A. There is only one *symmetrical* ketone with the indicated formula.



Compound A
($C_5H_{10}O$)

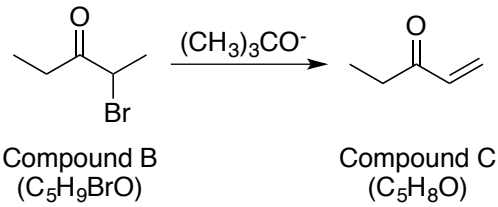
The α-halogenation of Compound A then occurs in acidic media.



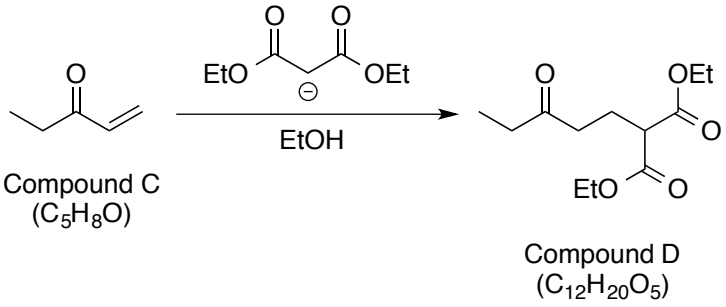
Compound A
($C_5H_{10}O$)

Compound B
(C_5H_9BrO)

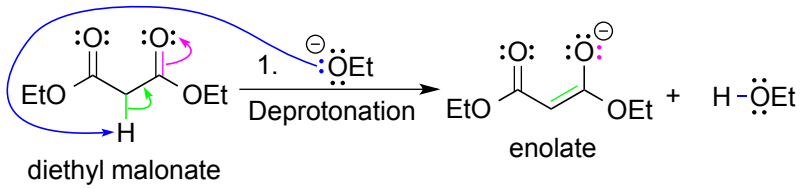
In a small twist, Compound B is then treated with *tert*-butoxide. We have not encountered reactions with *tert*-butoxide in this chapter, but a comparison of the molecular formulas of Compounds B and C shows that HBr has been removed. This suggests an elimination, which makes a great deal of sense in retrospect. We've often used *tert*-butoxide to perform eliminations. Here, E2 reaction creates Compound C.



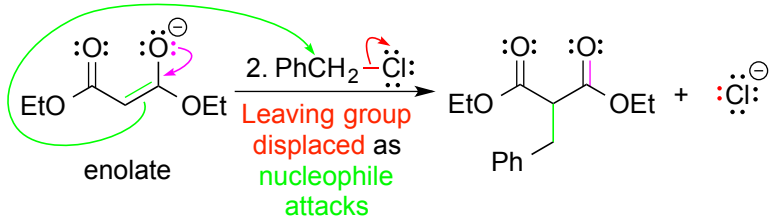
Compound C, it turns out, is an α,β-unsaturated ketone. Such systems are susceptible to Michael addition. The conjugate base of diethyl malonate is a stabilized enolate and therefore a prototypical Michael donor. The product contains the 1,5-dicarbonyl that is the hallmark of many Michael adducts.



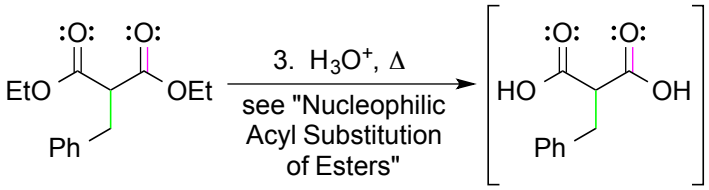
27. The choice of diethyl malonate as a reactant suggests a malonic ester synthesis, which begins with deprotonation of the α-carbon by ethoxide.



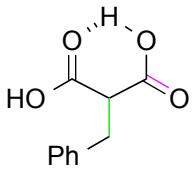
When the electrophile is added in step 2, the carbonyl is re-formed as the enolate attacks benzyl chloride and displaces chloride in S_N2 fashion.



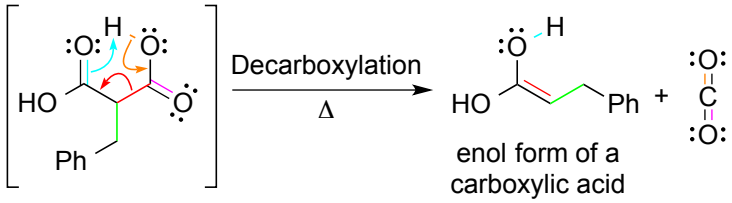
Step 3 begins with the hydrolysis of the esters. These are nucleophilic acyl substitution reactions as we learned in the previous chapter.



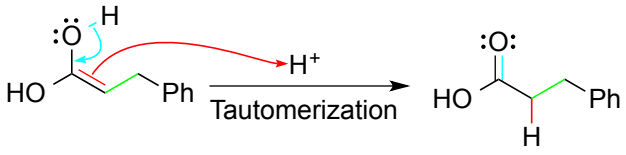
Once the diacid is formed, intramolecular hydrogen bonding takes place between the labile proton of one acid and the carbonyl oxygen of the other. This sets the stage for the subsequent decarboxylation.



During decarboxylation, the carbonyl π-bonding electrons are used to convert the hydrogen bond into a complete covalent bond. This frees the electrons in the O-H bond to form the second π bond of carbon dioxide. As this new π bond is made, the α-carbon to carbonyl carbon bond is broken. The electrons from that bond flow toward the other carbonyl in order to keep it at a consistent valence. The product of this step is the enol form of a carboxylic acid.

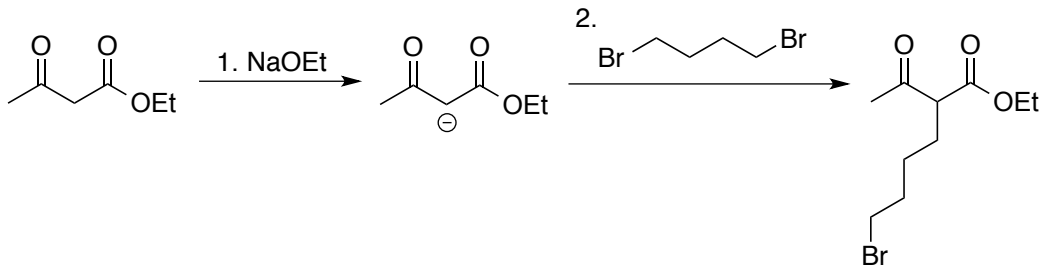


Lastly, tautomerization takes place when the enol is protonated and sheds a proton from the carbonyl oxygen. The final product is a monosubstituted acetic acid derivative.

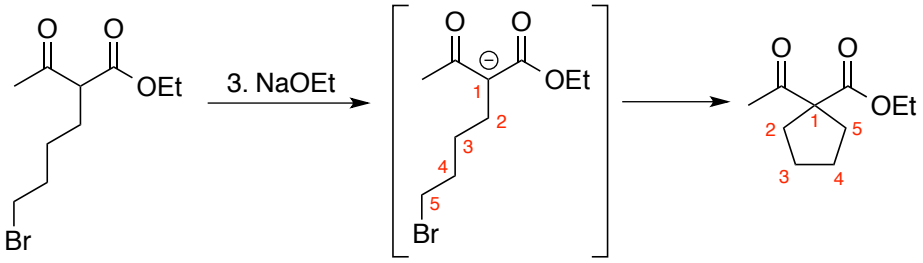


Notice that this is the mechanism for the final two steps of Problem 24.

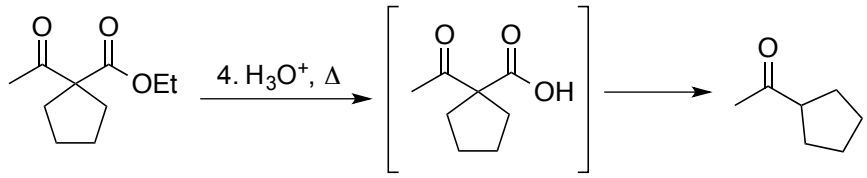
28. Based on the fact that ethyl acetoacetate is used as a reactant and alkylation follows, this appears to be an acetoacetic ester synthesis. Step 1 entails enolate formation. In step 2, the enolate is alkylated by 1,4-dibromobutane.



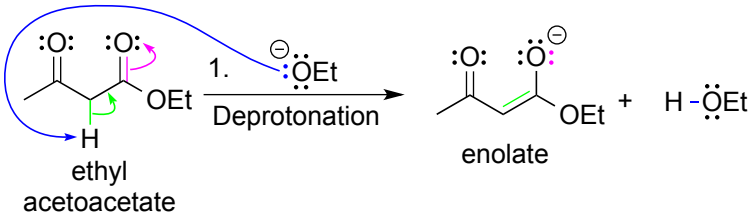
In step 3, sodium ethoxide is added once again, which generates another stabilized enolate. It may initially be puzzling that a new alkyl halide is *not* added in step 4. However, when we examine the substrate closely, we see that there is, of course, an alkyl halide already present within it. This allows for *intramolecular* S_N2 alkylation, and a cyclic adduct results.



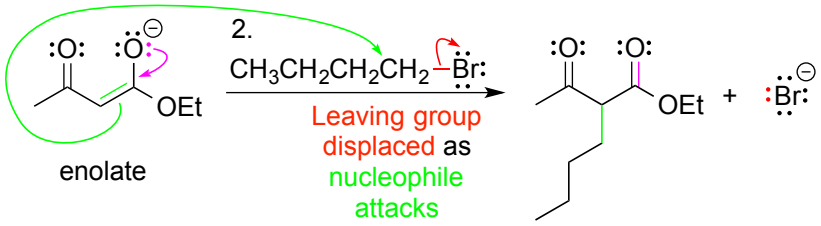
In step 4, the ester is hydrolyzed and decarboxylation follows to yield a geminally disubstituted acetone derivative, just as we would expect from an acetoacetic ester synthesis with two rounds of alkylation. The only difference is that the two alkyl halides were tethered, resulting in a cyclic product.



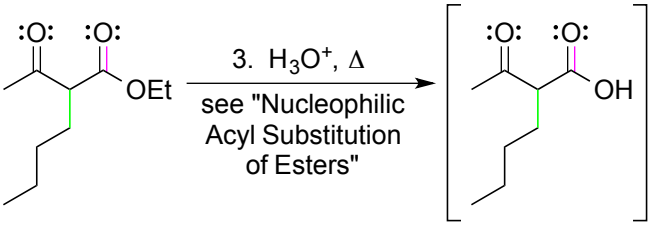
29. The use of ethyl acetoacetate as the reactant implies that this may well be an acetoacetic ester synthesis. The sequence begins with the deprotonation of the doubly activated α position by ethoxide.



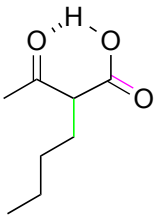
The nucleophilic enolate then attacks butyl bromide in S_N2 fashion, displacing bromide.



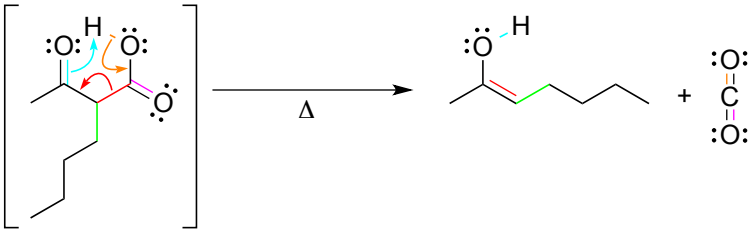
Upon heating with aqueous acid, the ester is hydrolyzed through a nucleophilic acyl substitution, which we learned about in the previous chapter.



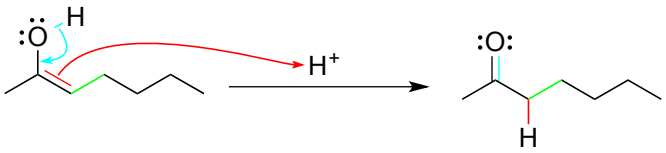
Once the β-ketoacid is formed, intramolecular hydrogen bonding takes place between the labile proton of the acid and the carbonyl oxygen of the ketone. This sets the stage for decarboxylation.



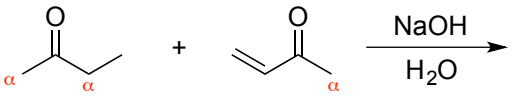
Decarboxylation begins when the ketone π bond is used to convert the hydrogen bond into a complete covalent bond. This frees a σ-bonding pair of electrons to create the second π bond of carbon dioxide. As CO_2 is formed, it is freed from the molecule when a carbon-carbon bond breaks. These electrons are used to replace the bond that was lost by the ketone carbonyl carbon. This process yields the product but in its enol form.



Tautomerization occurs spontaneously in acid when the enol is protonated and a proton is shed from oxygen. The final product of the sequence is a monosubstituted acetone derivative.

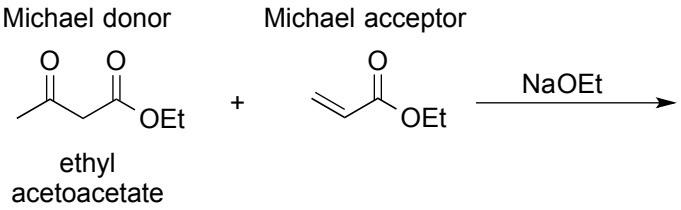


30. One of the problems associated with this reaction is the availability of multiple α positions of comparable acidity. This could lead to a mixture of enolates, which will result in a mixture of products.

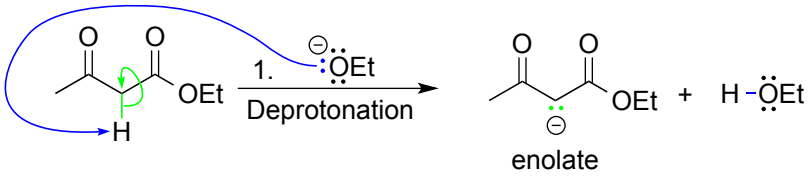


Additionally, we know that simple enolates frequently add to the carbonyl carbon, as in aldol or Claisen condensations. In Michael reaction, the stabilized enolate adds to the β position instead. In the absence of a stabilized enolate, aldol reaction can compete with Michael reaction in this case, leading to undesired products.

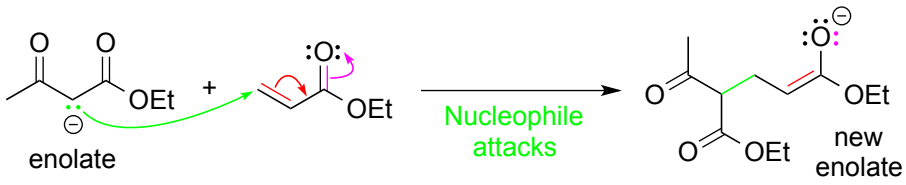
31. The presence of ethyl acetoacetate may lead us to suspect an acetoacetic ester synthesis. However, there is no alkyl halide to be used for alkylation. Instead, the reactive partner is an α,β-unsaturated ester, and we know that α,β-unsaturated systems can accept stabilized nucleophiles through the Michael reaction.



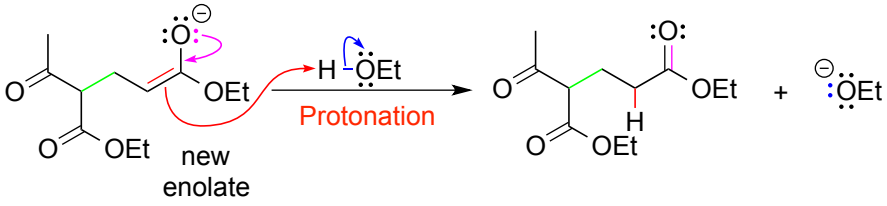
The process begins when ethyl acetoacetate is deprotonated by ethoxide. This forms a stabilized enolate. In other words, the extensive resonance delocalization of the charge into not just one but two carbonyls provides significant stabilization.



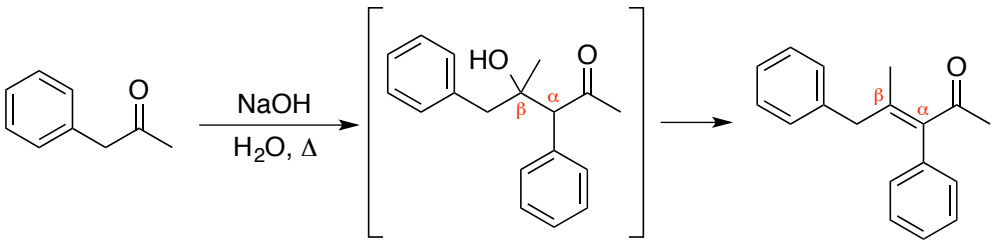
The stabilized enolate then attacks the β position of the unsaturated ester. This pushes the π electrons toward the carbonyl so that the negative charge can ultimately be deposited on the carbonyl oxygen. In this way, a new enolate is formed.



This enolate is more basic than the first because it has less resonance stabilization. It therefore removes a proton from the solvent (ethanol). Remember that, when an alkoxide is used as a reagent, the corresponding alcohol is frequently employed as the solvent. Additionally, ethanol was formed in step 1 of this mechanism. The adduct contains the 1,5-dicarbonyl that is commonly observed in Michael reaction products.

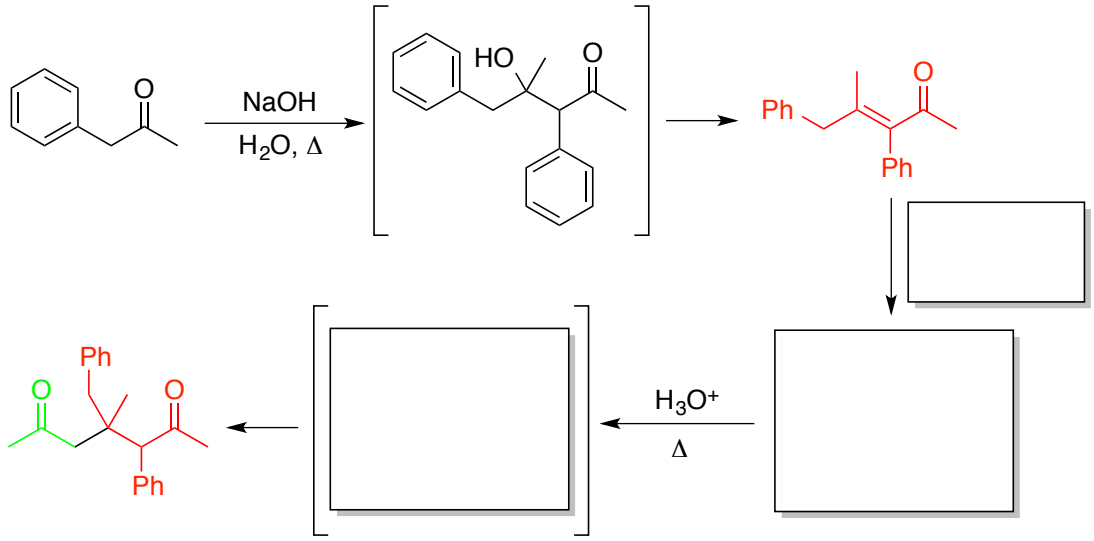


32. The scheme begins with an aldol self-condensation. As anticipated, this process proceeds through the β-hydroxyketone, which then dehydrates at elevated temperatures to afford an α,β-unsaturated ketone.

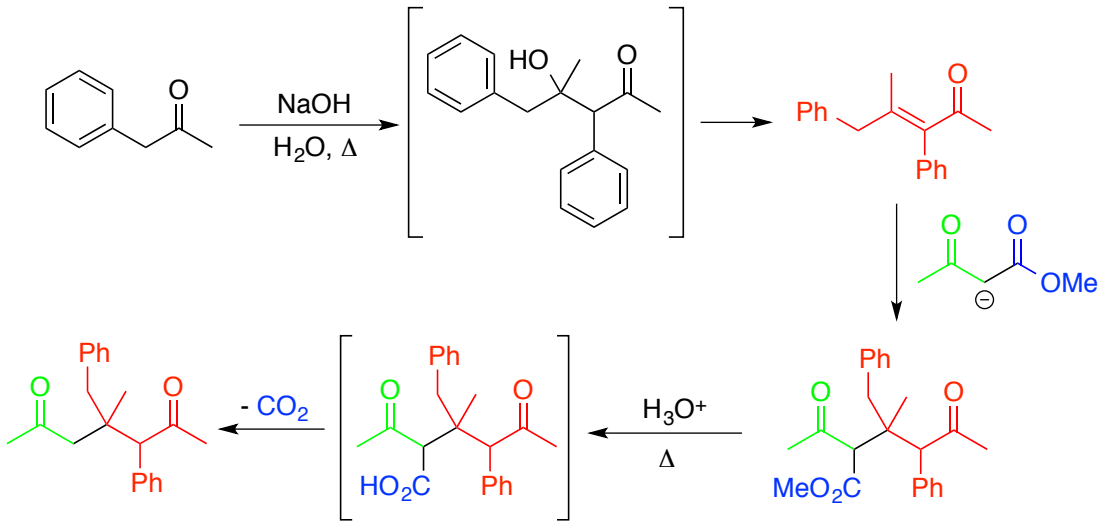


As we approach the second part of the scheme, there are two useful tools to add clarity to the path forward. First, redraw the aldol condensation product using the abbreviation Ph for phenyl because this makes it more clearly resemble the final product. Secondly, match up the aldol condensation product to the corresponding

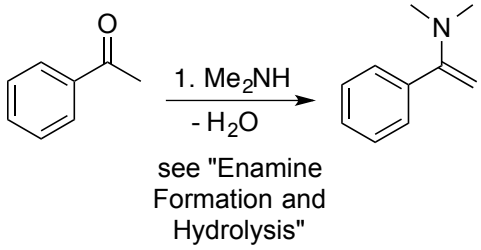
fragment of the final product, and then examine what has been added to it. Doing so illustrates that we have added a fragment corresponding to acetone.



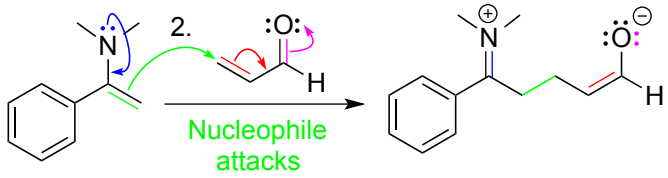
It might be tempting to simply add the enolate of acetone to achieve the transformation via Michael addition, but remember that Michael addition works best when the enolate is stabilized by resonance into not just one but two carbonyls. Therefore, we need a second carbonyl to stabilize the enolate, but it must also be one that can be removed once it has served its purpose. This is reminiscent of the use of ethyl acetoacetate in an acetoacetic ester synthesis. The enolate of ethyl acetoacetate adds the the α,β-unsaturated ketone in a Michael fashion. The ester is then hydrolyzed, and the β-ketoacid decarboxylates, losing the unwanted carboxyl group as carbon dioxide.



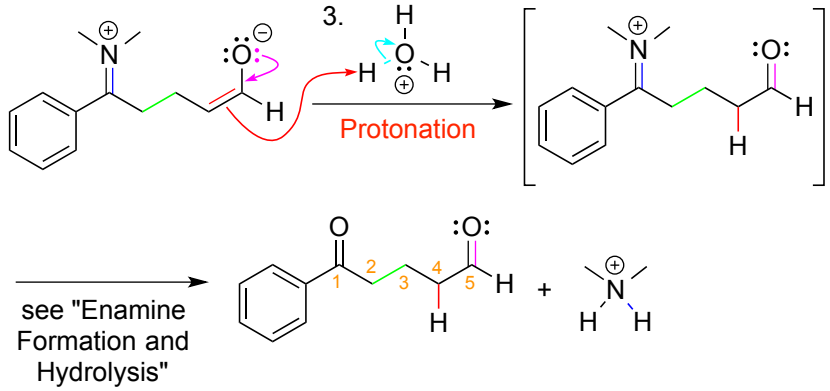
33. This is a Stork enamine reaction, which begins with the formation of an enamine from acetophenone and dimethylamine. This mechanism was covered in Chapter 15.



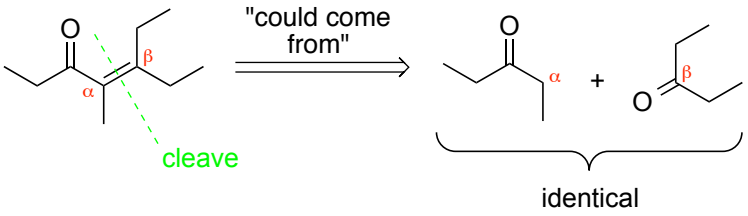
In step 2, the nucleophilic enamine attacks the β position of the α,β-unsaturated aldehyde. To maintain a consistent valence for the carbons of the enamine, nitrogen's lone pair compensates the adajcent carbon for the bond that it loses. The α,β-unsaturation is pushed toward the carbonyl so that the negative charge may ultimately be placed on the carbonyl oxygen.



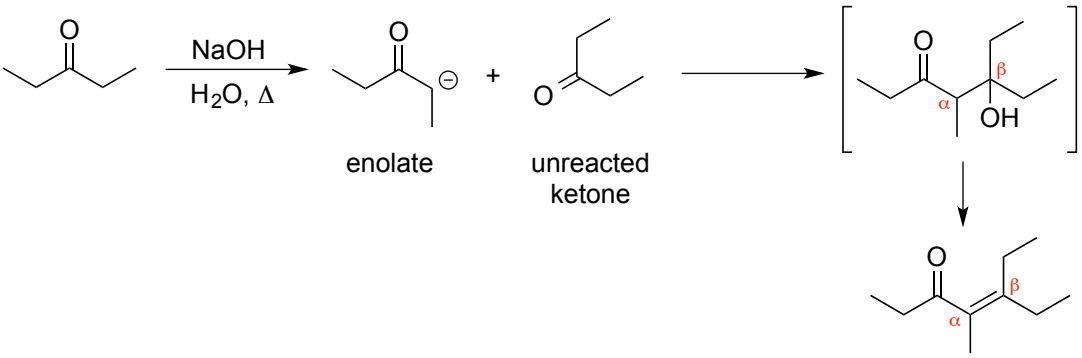
The enolate thus formed is protonated by the aqueous acid added in step 3. Under these conditions, the iminium ion is also hydrolyzed as discussed in Chapter 15 to unveil a 1,5-dicarbonyl.



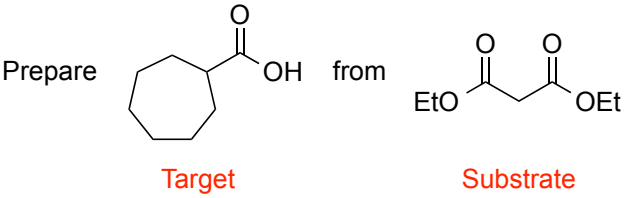
34. As we identified in Problem 14(a), α,β-unsaturated ketones are commonly prepared via the aldol condensation. To perform a retrosynthesis on this target, we need to recognize that both the σ and π bonds of the α,β-unsaturation are formed during an aldol condensation. Therefore, this is the site where retrosynthetic disconnection should take place. We slide the two halves of the molecule apart, and place a carbonyl on what used to be the β carbon. In this instance, the two precursors are identical, so it is an aldol *self*-condensation that is required.



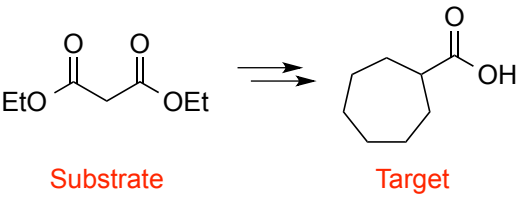
To achieve the synthesis 3-pentanone is simply treated with aqueous base (or acid) at elevated temperatures. In base, the enolate is formed in the presence of much unreacted ketone. The aldol reaction yields a β-hydroxyketone, which dehydrates at elevated temperature to produce the desired target.



35. When both the substrate and target are specified, it is wise to begin by labeling both based on the wording of the question.

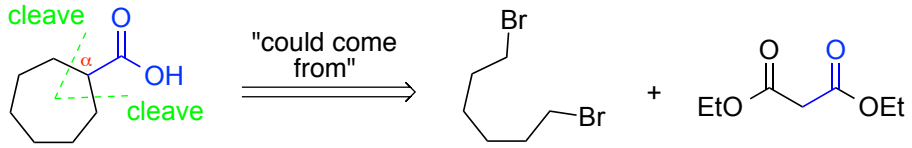


Then, we can rewrite the problem in the usual fashion.

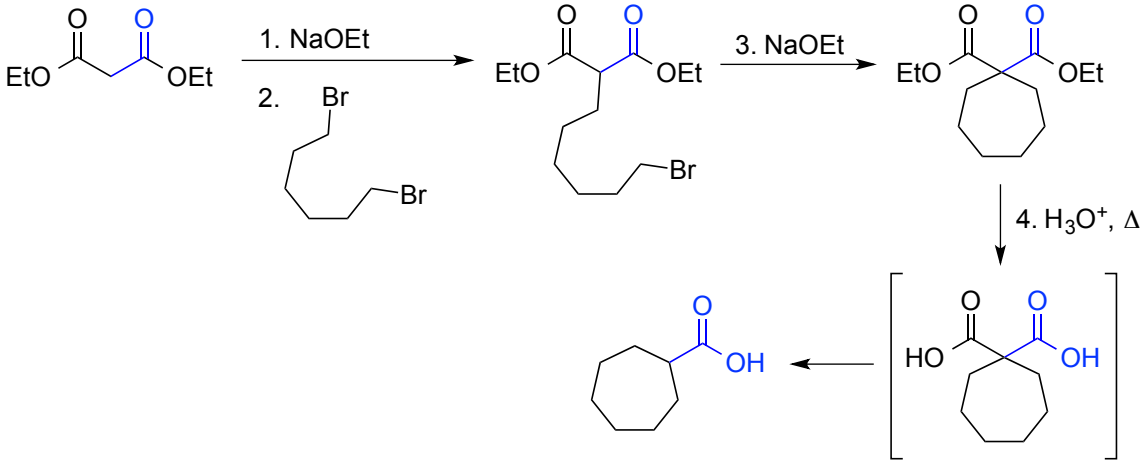


Since diethyl malonate is the substrate, we are performing a malonic ester synthesis, one of the two options for the preparation of this target acid that were identified in Problem 14(b). The malonic ester synthesis produces acetic acid derivatives, in which any alkyl groups attached to the α-carbon were installed during the reaction. From the retrosynthetic perspective, we therefore disconnect both the α-carbon to

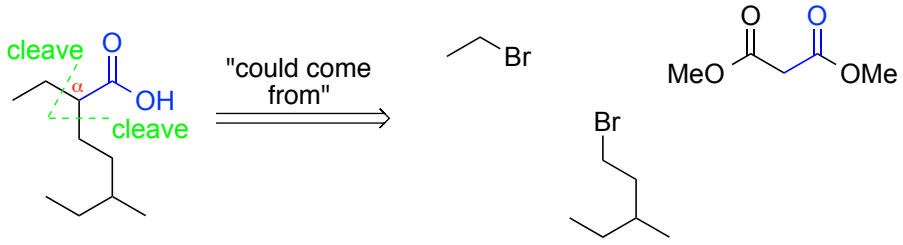
R group bonds. The fragments are then separated. The alkyl groups installed during the reaction must be electrophilic, so leaving groups are added (bromine was chosen in this instance). The two carbons of the acetic acid residue derive from diethyl malonate.



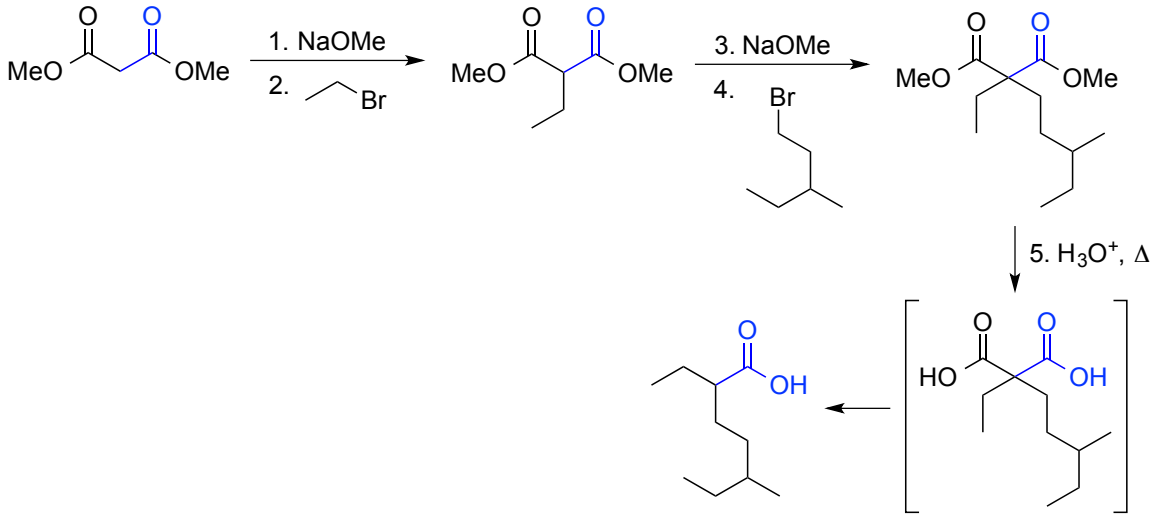
Having identified all of the necessary reactants, we can now embark on the synthesis. It begins with deprotonation and alkylation. In this instance, the alkyl group that we've installed possesses another electrophilic center. Therefore, treatment with a second equivalent of base forms a new enolate, and an *intramolecular* S_N2 reaction follows to create the ring. Finally, the esters are hydrolyzed, and the resulting diacid decarboxylates to yield the target molecule.



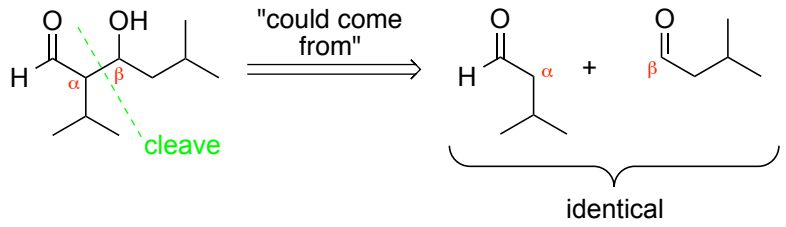
36. As we saw above, α-substituted acetic acid derivatives are commonly prepared through the malonic ester synthesis. Any R groups attached to the α-carbon are retrosynthetically cleaved. The R groups come from alkyl halides used in the alkylation steps, and the two carbons of the acetic acid moiety stem from a malonate ester. In order to remaining within the six-carbon limit stipulated in the problem, we must use dimethyl malonate rather than diethyl malonate, which has been used in several previous problems.



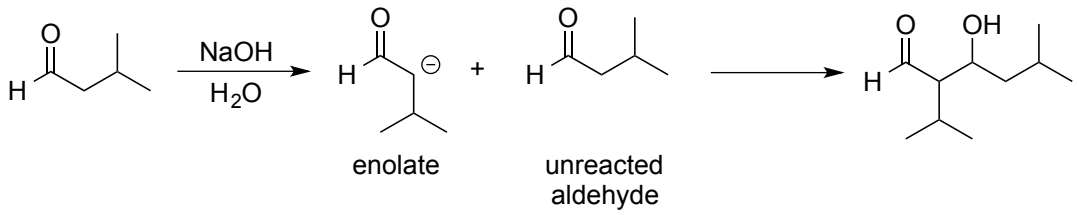
The synthesis begins with deprotonation using methoxide and alkylation. Either R group can be added first. The order of the alkylation events makes no difference. In another round of alkylation, the second R group is added. Then, the esters are hydrolyzed, and decarboxylation follows to afford the target.



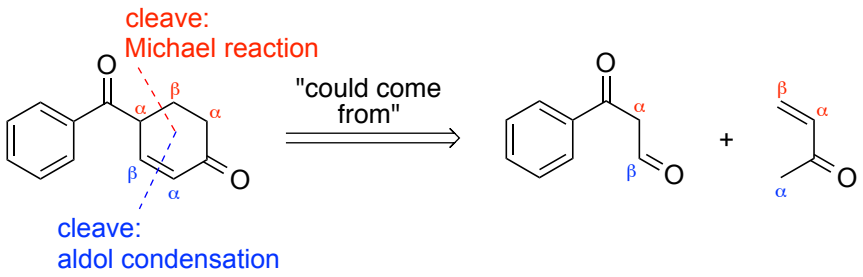
37. A β-hydroxyaldehyde can be prepared by an aldol reaction. The most important thing to keep in mind is that it is the α-β bond that is made during the reaction, so this is the site for a retrosynthetic disconnection. The fragments are separated, and what use to be the β-carbon is given a carbonyl. In this case, the two requisite aldehydes are identical, so only a single reactant is needed.



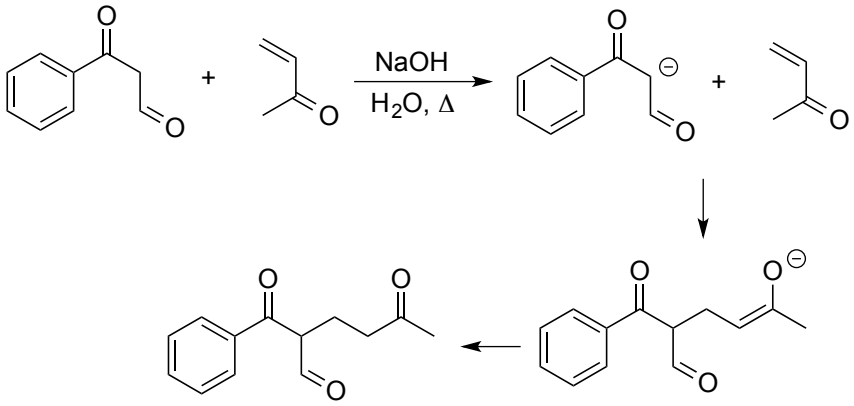
The reaction entails the treatment of 3-methylbutanal with aqueous base (or acid). In base, some enolate is formed in the presence of a great deal of unreacted aldehyde. The nucleophilic attack of the enolate on the aldehyde's carbonyl carbon joins the fragments, ultimately creating the desired β-hydroxyaldehyde.



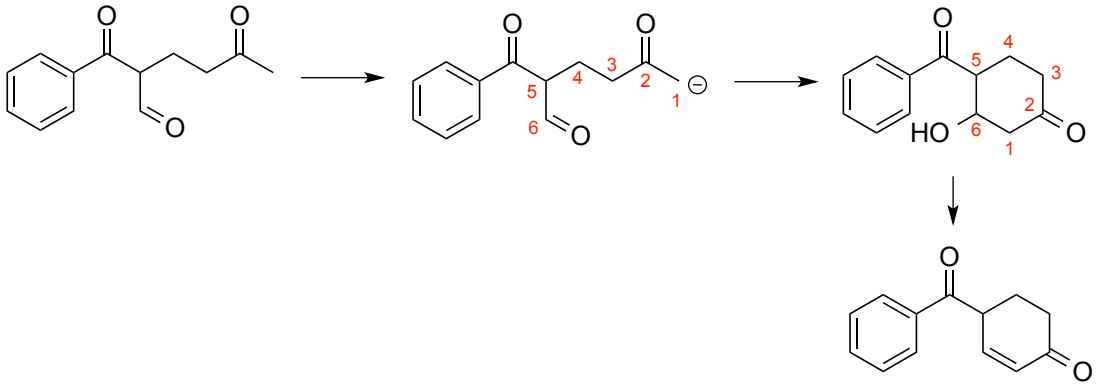
38. In Problem 14(e), you decided that the Robinson annulation would be an ideal way to prepare this target because it contains a 1,5-diketone and the path from one carbonyl to the other also includes a ring. To derive the necessary reactants through retrosynthesis, it is useful for us to view the Robinson annulation as the combination of two other reactions: a Michael reaction and an intramolecular aldol condensation. The Michael reaction can be used to retrosynthetically disconnect an α-β bond of the 1,5-diketone. The aldol condensation can be used to retrosynthetically cleave both the σ and the π bonds of the α,β-unsaturated ketone. Two two halves of the target are then separated. Where the Michael disconnection was made, we must add an α,β-unsaturation, and where the aldol disconnection was made we must add a carbonyl at what was the β-carbon. Now, we have the reactants needed for this transformation.



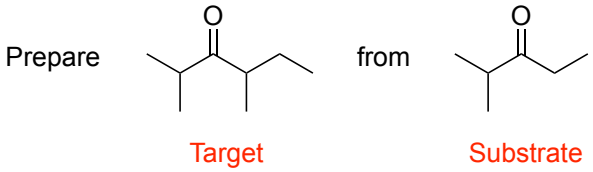
The synthesis simply entails heating these reactants with aqueous base. However, the intermediates are shown below for clarity. The reaction begins with deprotonation of the most acidic (doubly activated) α position. The stabilized enolate then adds to the β position of the α,β-unsaturated ketone. The resulting enolate removes a proton from water to yield the Michael adduct.



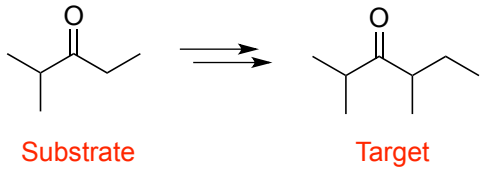
The Michael Adduct has multiple α positions, but only deprotonation at the terminal methyl group can lead to the formation of an unstrained, six-membered ring. The enolate cyclizes onto the more electrophilic and less sterically encumbered aldehyde (as opposed to the ketone) to generate a β-hydroxyketone. Dehydration follows to provide the Robinson annulation product.



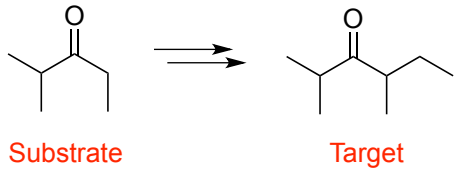
39. As usual, it is wise to begin by labeling the substrate and target.



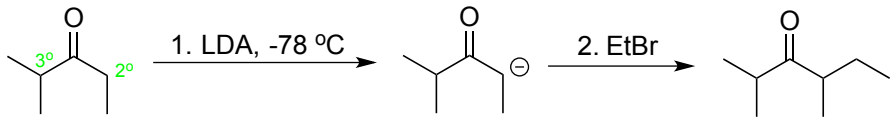
Then, rewrite the problem in the usual way.



It might even be helpful to draw the substrate so that it matches up with the target as closely as possible.

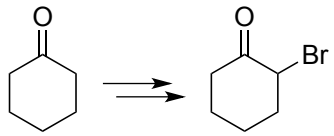


This problem necessitates an α-alkylation. Additionally, we have to consider the selectivity of enolate formation. The enolate must be formed at the more sterically accessible secondary (2°) center. This kinetic enolate can be formed using LDA at low temperature. The enolate is then alkylated with ethyl bromide to afford the desired ketone.

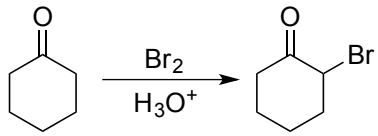


Substrate Target

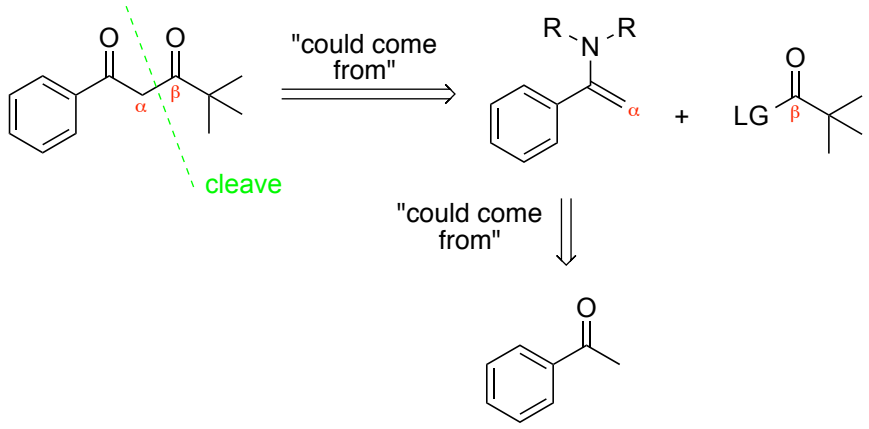
40. This problem requires an α-bromination.



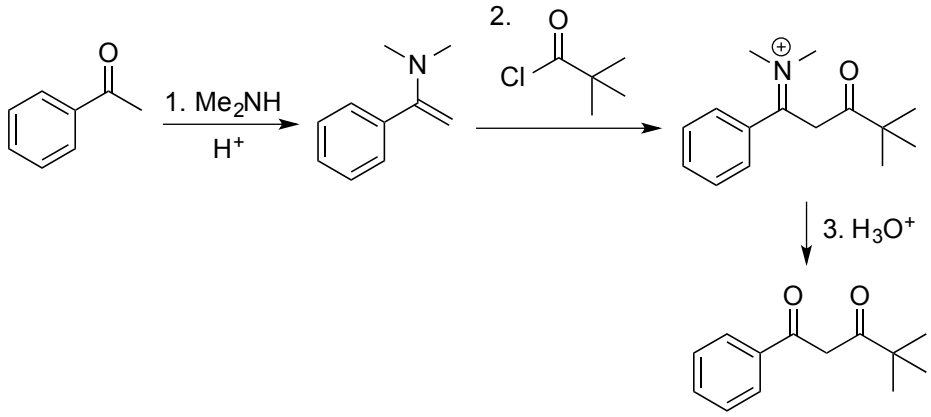
It is better to use acidic conditions so as to avoid exhaustive bromination, which arises under basic conditions.



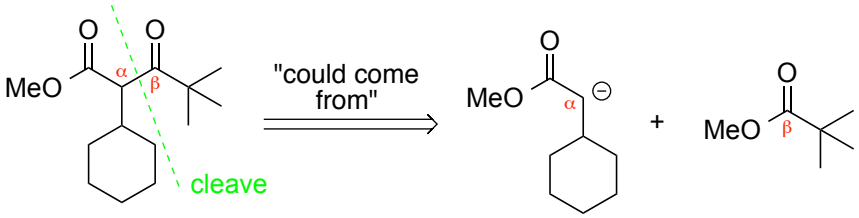
41. The Stork enamine reaction is ideally suited to the preparation of a 1,3-diketone. During a Stork enamine reaction, it is the α-β bond that is formed, so this is the site for a retrosynthetic disconnection. The fragment bearing the α carbon would derive from an enamine, and the piece containing the β carbon must be provided with a leaving group. The necessary enamine can, in turn, be prepared from acetophenone.



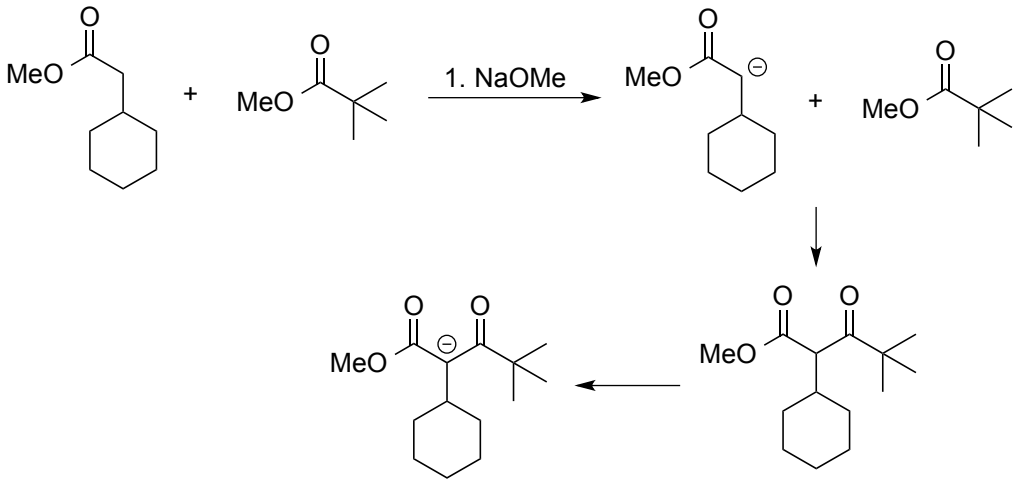
The synthesis begins with enamine formation between acetophenone and a secondary amine, such as dimethylamine. Acid catalysis aids the transformation, and a Dean-Stark trap would likely be used to assist with the removal of water. The enamine is then treated with an acid chloride (or anhydride) to install the desired acyl group through nucleophilic acyl substitution. The iminium ion that results is hydrolyzed to afford the desired diketone.



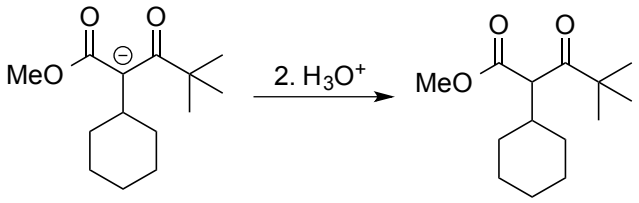
42. The Claisen condensation offers a common method for the preparation of β-ketoesters. The α-β bond is made during a Claisen condensation, so this is the appropriate site for a retrosynthetic disconnection. The fragment containing the α-carbon was the enolate, while the segment that includes the β-carbon was the ester that served as the electrophile during the reaction.



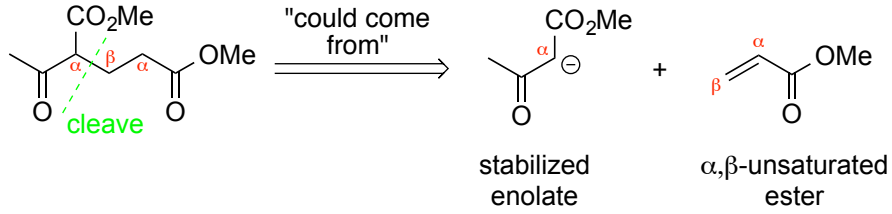
The reaction begins when the esters are treated with methoxide. Note that only one of the two esters is enolizable. It becomes the enolate, and then nucleophilically attacks the other ester. The β-ketoester that results has a doubly activated (and therefore especially acidic) α position, which readily loses a proton in this basic medium thereby driving the reaction to completion.



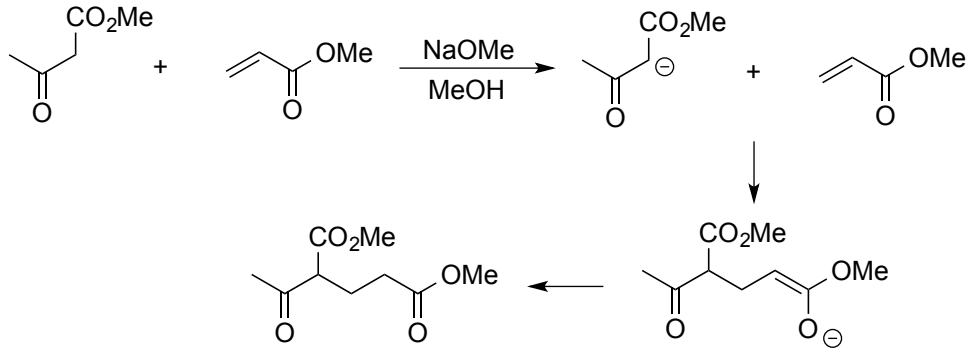
Upon workup with aqueous acid, the α-carbon is protonated to provide the neutral β-ketoester.



43. Molecules containing 1,5-dicarbonyls, like this one, are readily prepared through Michael reaction. During the Michael reaction, the α-β bond is made between a stabilized enolate and an α,β-unsaturated system. There are two conceivable α-β disconnections that could be made; however, it is important to remember that a *stabilized* enolate must be used for the Michael reaction. This narrows our choice to a single retrosynthetic disconnection.

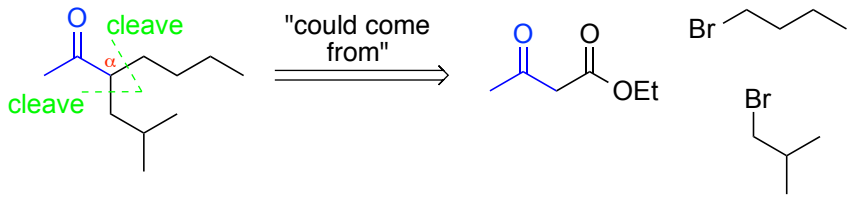


The reaction begins with deprotonation of the most acidic α-carbon in the system. This is the α-carbon that is activated by two adjacent carbonyls. The stabilized enolate thus formed then adds to the β position of the α,β-unsaturated ester. A new enolate is formed, and this more basic enolate deprotonates the solvent (methanol) to yield the Michael adduct.

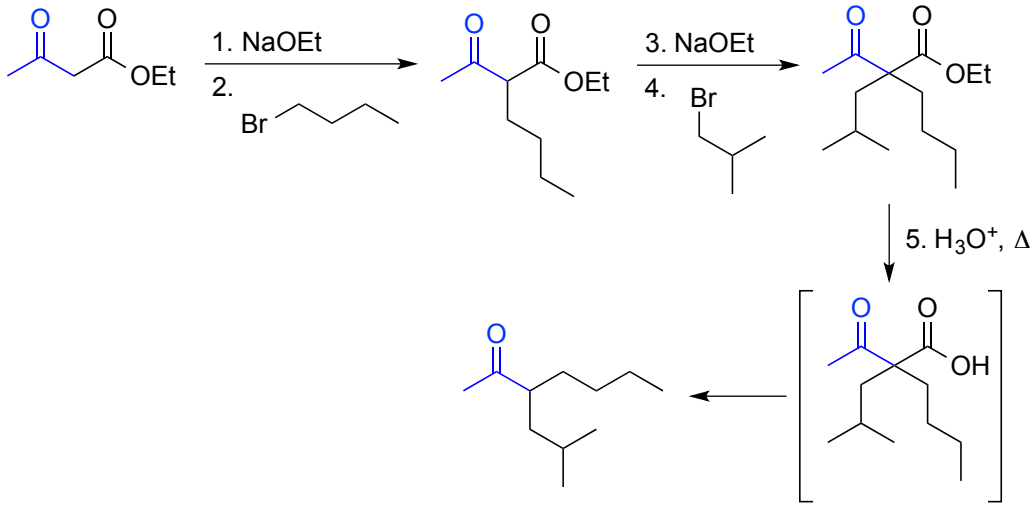


44. The target molecule is a geminally disubstituted acetone derivative, and such molecules can be prepared using the acetoacetic ester synthesis. During this process, the bonds between the α-carbon and its substituents are made, so these are the sites for retrosynthetic disconnection. The three carbons of the acetone moiety come from the acetoacetic ester used as a reactant. The substituents adding during

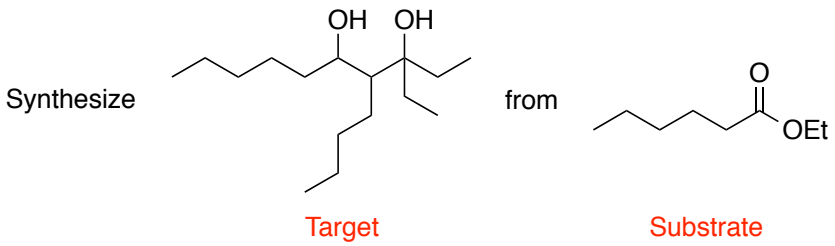
the course of the synthesis must be electrophilic, so alkyl halides are used as the other reagents.



The synthesis begins with the deprotonation of ethyl acetoacetate. It is then alkylated with either of the necessary electrophiles. The order of the two alkylation events is immaterial. The monoalkylated compound goes through another round of deprotonation and alkylation. Then, hydrolysis of the ester is followed by spontaneous decarboxylation to afford the target compound.

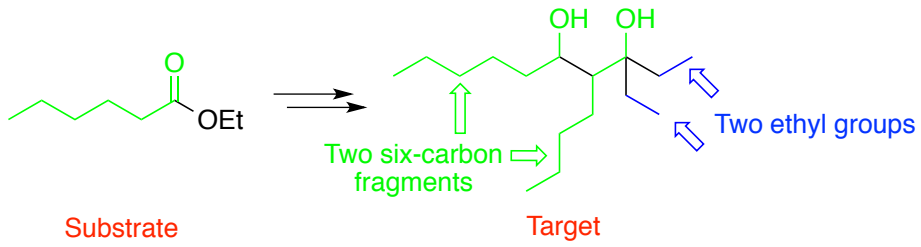


45. It is always a good idea to begin by labeling the substrate and the target.

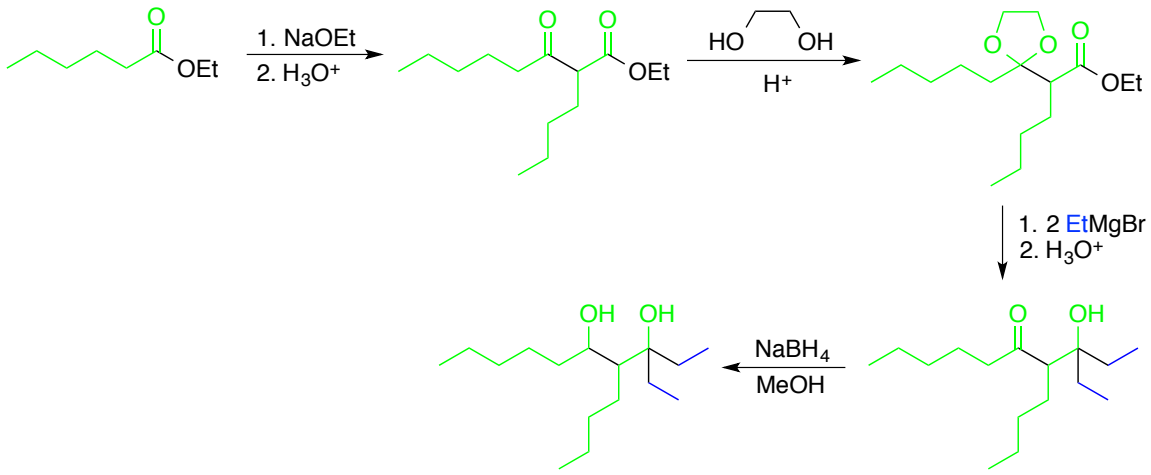


Then, rewrite the problem in the usual fashion. A formal retrosynthesis is also always beneficial. However, sometimes engaging in some retrosynthetic thinking may be sufficient. You may not always need to draw out a complete retrosynthesis. For instance, when we analyze the target, we can identify two six-carbon fragments that likely derive from the reactant. It is also clear that two ethyl groups needed to be added at some point in the synthesis. Since we are beginning with an ester and

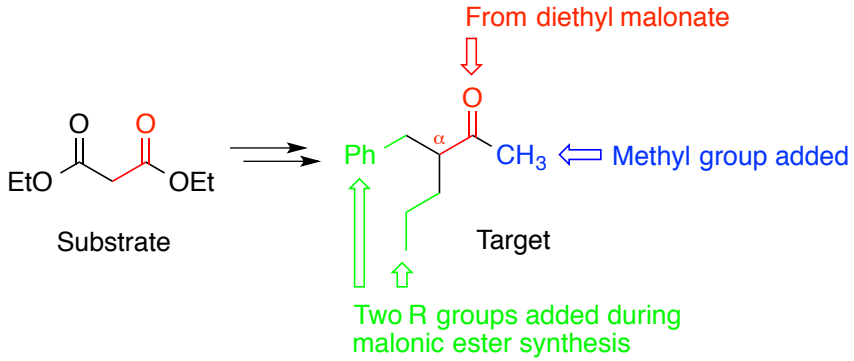
we know that the Claisen condensation will unite two molecules of this ester, that is a good place to begin.



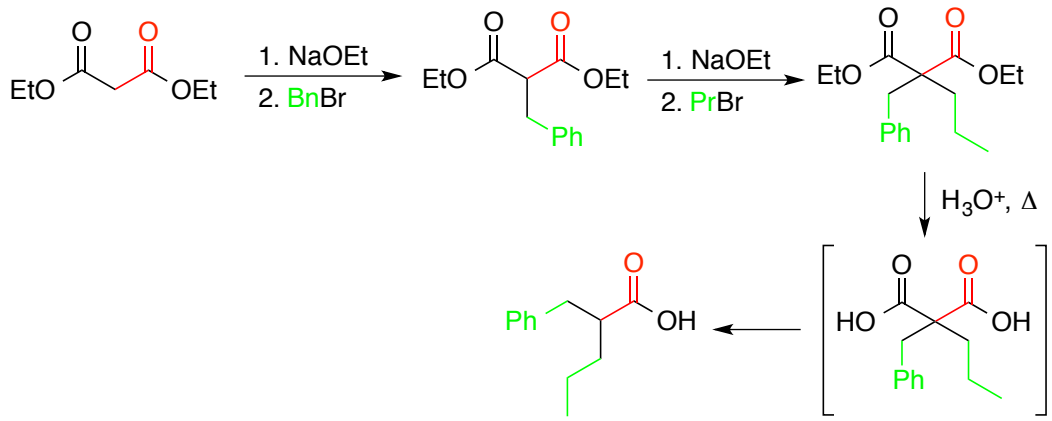
The Claisen condensation stitches together two equivalents of the ester to yield a β-ketoester. A Grignard reaction would be an ideal way to add the two ethyl groups to the ester. However, since Grignard reagents also react with ketones, it is necessary to protect the ketone as an acetal first. You need not necessarily use a cyclic acetal. Any acetal will suffice. Once the ketone is protected, Grignard reaction with two equivalents of ethylmagnesium bromide converts the ester to a tertiary alcohol bearing two ethyl groups. During the workup with aqueous acid, the acetal can also be hydrolyzed. Finally, the ketone can be reduced to a secondary alcohol upon treatment with sodium borohydride.



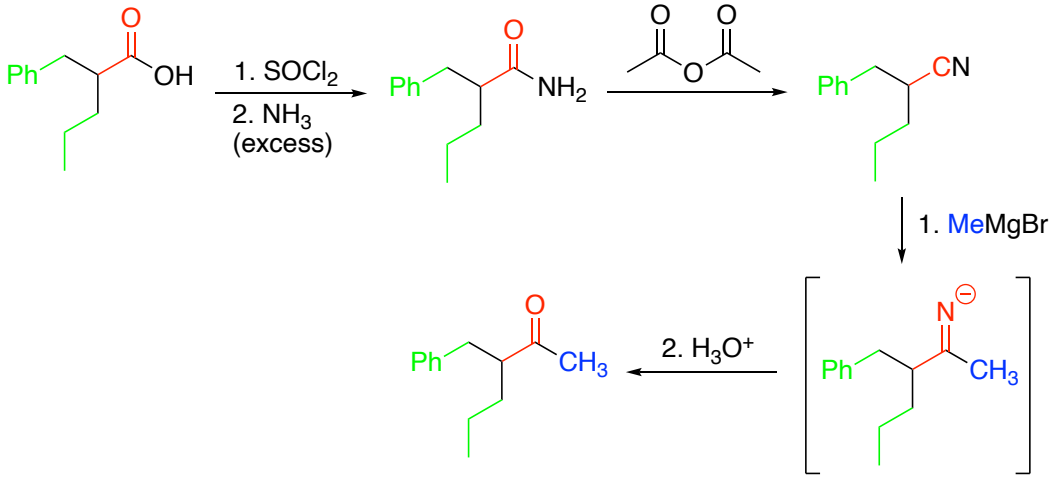
46. In this problem, we are asked to use diethyl malonate as a substrate from which to prepare the given ketone. Retrosynthetic analysis of the target will give us direction on how best to proceed. We know that diethyl malonate can be used in malonic ester syntheses to generate mono or disubstituted acetic acid derivatives. Although there is no acetic acid residue in the target, we can identify the carbonyl and the α-carbon as likely deriving from diethyl malonate. Therefore, the benzyl and propyl groups bonded to the α-carbon could be installed during the alkylation steps of the malonic ester synthesis. At a late stage of the synthesis, we'll also need to determine a way to add the methyl group of the methyl ketone.



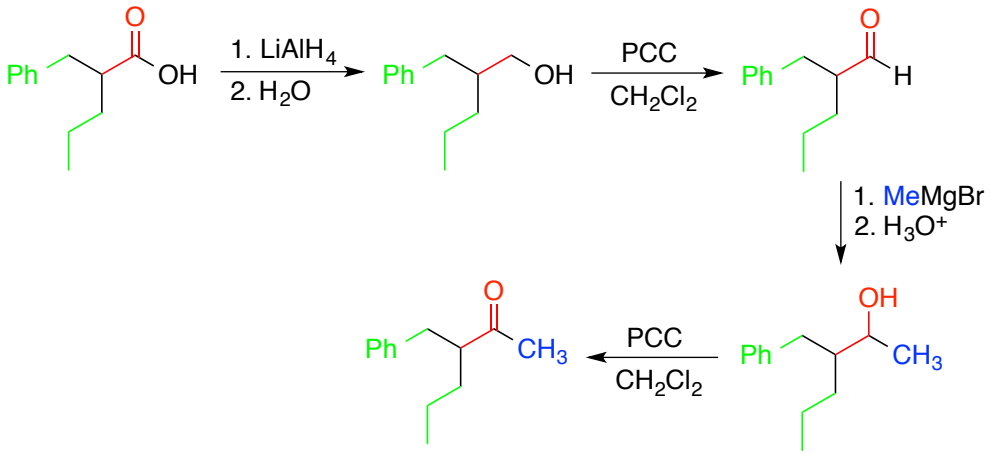
With this outline in mind, we can embark on the first part of the route: the malonic ester synthesis. Two rounds of deprotonation and alkylation will install the benzyl and propyl groups. The order in which these alkylations take place is irrelevant. Then, hydrolysis of the esters and decarboxylation provides a disubstituted acetic acid derivative.



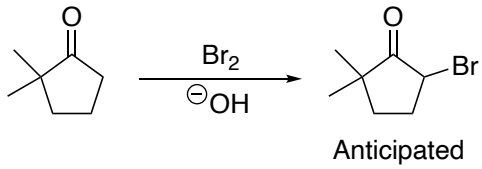
Now, we need to decide how to add the methyl group of the target's methyl ketone. There is more than one way to go about this. One option is based on the fact that Grignard reactions of nitriles afford ketones. To that end, we could convert the carboxylic acid to the primary amide via the acid chloride. Then, the amide can be dehydrated using an anhydride (or thionyl chloride or phosphorus pentoxide). At this stage, methylmagnesium bromide will add to the nitrile to afford the methyl ketone after workup.



An alternative approach to the endgame of the synthesis would be to reduce the disubstituted acetic acid derivative prepared from the malonic ester synthesis. The resulting alcohol can then be oxidized with PCC to the aldehyde. The aldehyde will undergo nucleophilic addition when treated with methylmagnesium bromide to give a secondary alcohol, which can then be oxidized to the target using PCC (or chromic acid).

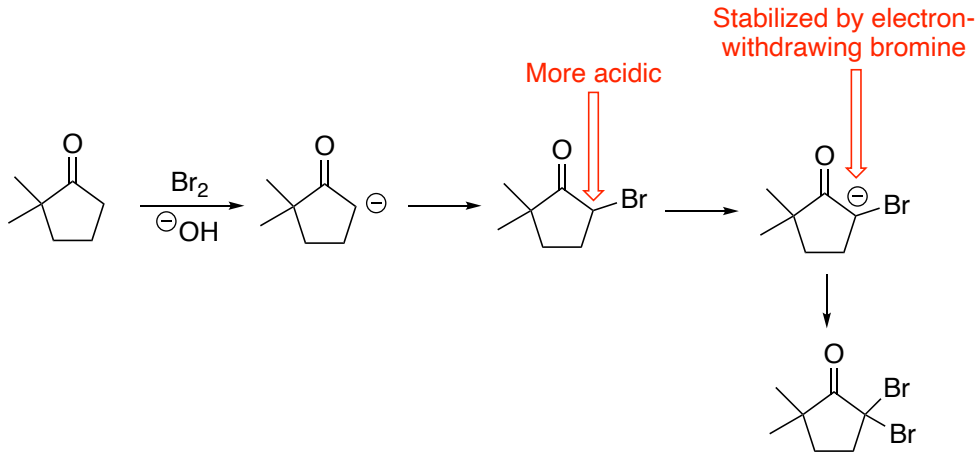


47. The anticipated product would display M and M+2 signals due to the presence of bromine, which has two isotopes (^{79}Br and ^{81}Br) that differ in mass by 2. These isotopes are present in roughly equal abundance, resulting in a 1:1 ratio of the M and M+2 peaks.

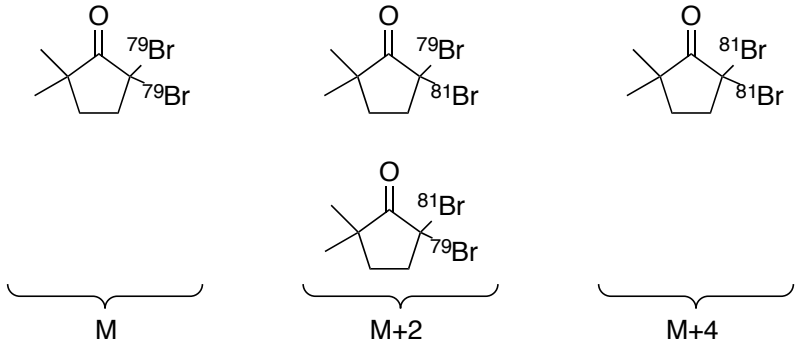


If two bromine atoms were present in the product instead of just one, then the possible combinations would be: ^{79}Br and ^{79}Br, ^{79}Br and ^{81}Br, and ^{81}Br and ^{81}Br. In other words, there would be M, M+2, and M+4 peaks exactly as observed in the mass spectrum of the product that was actually obtained.

The investigator forgot that basic α-bromination is susceptible to exhaustive bromination because each remaining α-proton is more acidic than the previous one due to the electron-withdrawing effect of the added halogens.



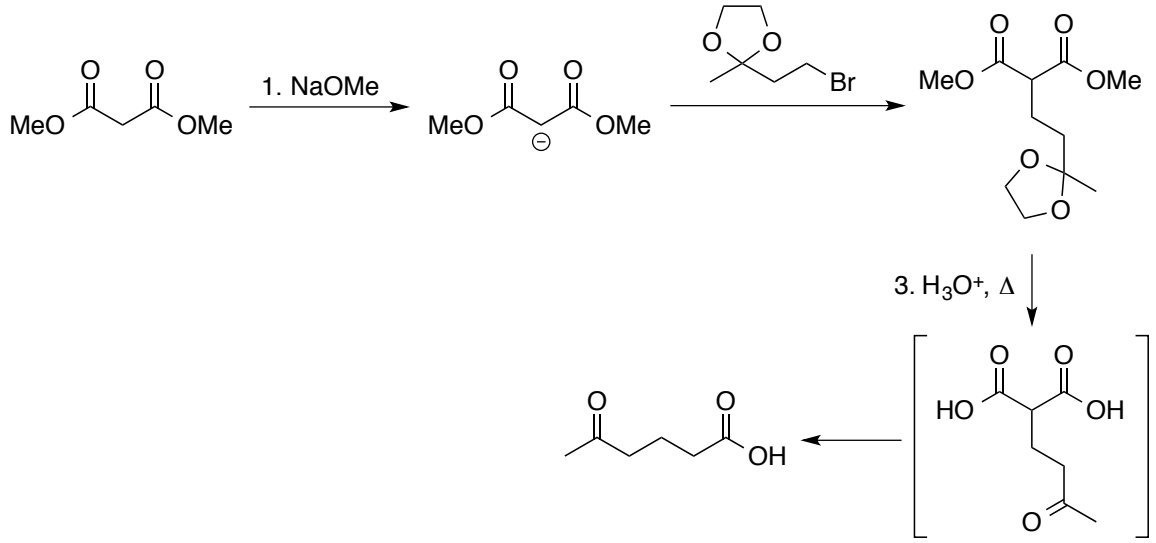
The product thus obtained can exhibit the following array of isotopes:



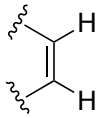
Notice that there are two ways to arrive at the M+2 peak, making it twice as prominent as the other two. This explains the 1:2:1 intensity pattern observed in the mass spectrum.

48. The general flow of this sequence is sound. It is a seemingly standard malonic ester synthesis involving: deprotonation, alkylation, ester hydrolysis, and decarboxylation. There's no reason to believe that the investigator's prediction of the product is way off base. More likely a subtlety has been overlooked. Upon closer examination of the alkyl halide's R group, we see that an acetal is present. Acetals are also subject to hydrolysis in aqueous acid. Therefore, in step 3, not only the

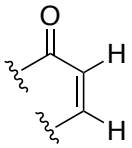
esters but also the acetal will be hydrolyzed. This unveils a ketone, which explains the presence of the second carbonyl resonance in the IR spectrum.



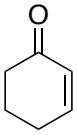
49. The NMR spectrum clearly does not match that of the anticipated product. There are not enough protons, particularly in the aromatic region of the NMR spectrum. We clearly see a vinyl proton just above 6 ppm. This suggests that the proton at approximately 7.5 ppm is also a vinyl proton, giving us the following fragment.



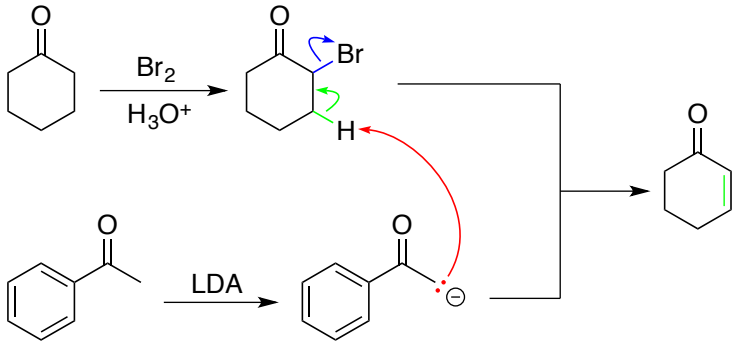
We can expand this fragment by explaining the chemical shift difference between the two vinyl protons. There must be a deshielding moiety that affects one more than the other. Given the structures of the reactants, the deshielding moiety is likely a carbonyl. Resonance places a δ^+ on the β position, deshielding the proton at that location significantly.



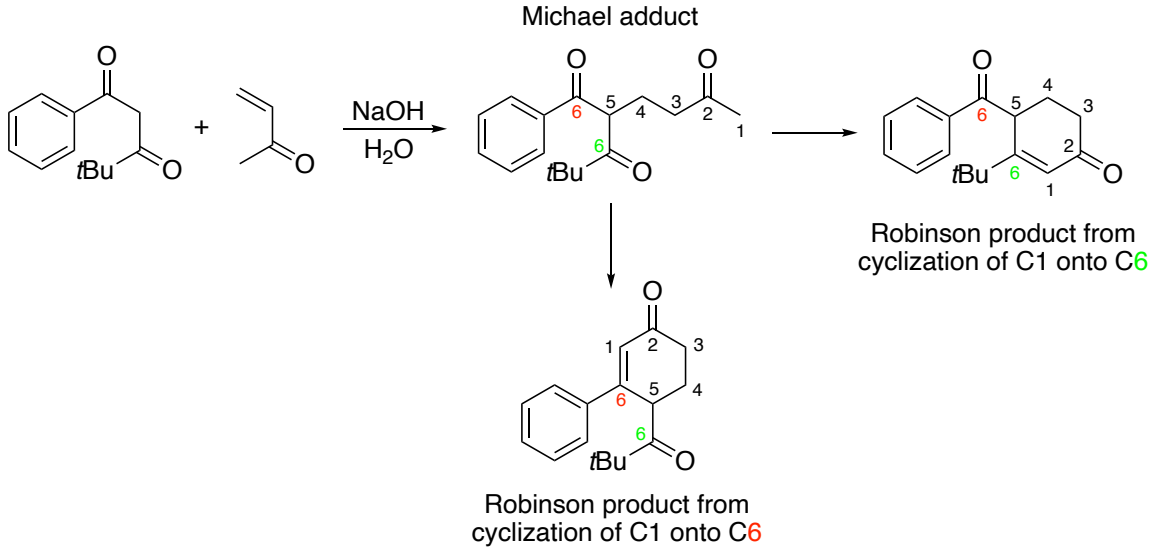
Finally, all that remains in the NMR spectrum is a set of three methylene (CH_2) groups. This allows us to flesh out the product's structure.



This product has an unanticipated π bond, and π bonds are frequently formed through elimination. To form this product, the enolate acted as a base, removing the proton adjacent to the carbon bearing bromine. The electrons in the C-H σ bond formed the π bond of the alkene, and bromide was displaced as a leaving group. 2-Cyclohexenone was formed through E2 elimination. The slightly increased steric hindrance of the secondary alkyl halide and the development of conjugation led to the formation of this α,β-unsaturated ketone as one of the reaction products.



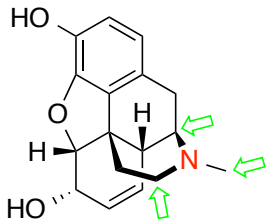
50. The first phase of a Robinson annulation is a Michael addition. This yields a single Michael adduct when the stabilized enolate formed from the diketone adds to the β-carbon of the Michael acceptor (methyl vinyl ketone). The remaining portions of the Robinson annulation are intramolecular aldol reaction and dehydration. Together these amount to intramolecular aldol *condensation*. C1 of the Michael adduct will become the nucleophilic enolate because it leads to the formation of an unstrained ring. However, cyclization onto either remaining ketone (C6 or C6) will provide a six-membered ring, so two Robinson annulation products can result from this transformation.



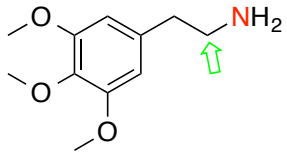
Solutions to Problems for Chapter 18: Amines

1.

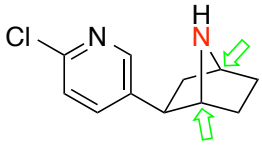
(a) The amino group in morphine possesses a nitrogen atom bonded to three alkyl groups, making it a tertiary amine.



(b) The amino group of mescaline has a nitrogen bonded to only one alkyl group, which makes it a primary amine.

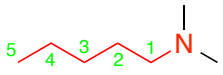


(c) The *aliphatic* amine in epibatidine contains a nitrogen atom bearing two alkyl groups, which makes it a secondary amine.



2.

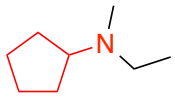
(a) The longest, continuous carbon chain including the amine is five-carbons in length. This molecule is therefore a pentanamine. The carbon skeleton is numbered so as to give the amine the lowest possible number, making this more specifically a 1-pentanamine. Finally, the location of the two methyl groups on nitrogen is designated using the locant *N*. The complete name is therefore *N*,*N*-dimethyl-1-pentanamine.



N,*N*-dimethyl-1-pentanamine

- Five carbon parent = pentane
- Replace "e" of suffix with "amine"
- Number so as to give the amine the lowest possible number
- Add substituent names and numbers

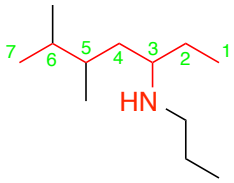
(b) The parent in this case is a cyclopentanamine. Recall that, when there is no ambiguity about the placement of the amine, no locant is needed. Since all of the positions on the ring are equivalent, nitrogen cannot be placed incorrectly, so no number is used to designate its location. The ethyl and methyl groups reside on nitrogen, which is communicated using the locant *N*.



N-ethyl-*N*-methylcyclopentanamine

- Five carbon, cyclic parent = cyclopentane
- Replace "e" of suffix with "amine"
- Add substituent names and locants

(c) Here, the longest, continuous carbon chain that includes the amine is seven-carbons in size. The chain is numbered from right to left because that assigns the lowest number possible to the amine. The parent is therefore 3-heptanamine. There are two methyl groups at C5 and C6, as well as a propyl group on the amine. These substituents and their locants are added to finalize the name.

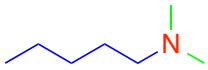


5,6-dimethyl-*N*-propyl-3-heptanamine

- Seven carbon parent = heptane
- Replace "e" of suffix with "amine"
- Number so as to give the amine the lowest possible number
- Add substituent names and numbers

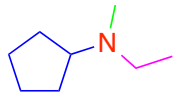
3.

(a) This compound was given a systematic name in Problem 2(a). Common names are created by placing the names of the alkyl groups bonded to nitrogen before the word “amine.”



dimethylpentylamine

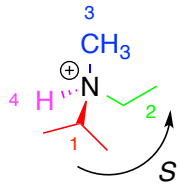
(b) This compound was named using the IUPAC method in Problem 2(b). The common name is derived when the alkyl group names are alphabetized before the word “amine.” “Cyclo” is one of the few prefixes (iso, cyclo, and neo) that count in alphabetization, so the cyclopentyl group appears first in the list.



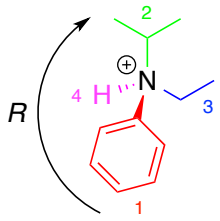
cyclopentylethylmethylamine

4.

(a) The carbon of the isopropyl group is bonded to two other carbons, making it the highest priority group. The carbon of the ethyl group is bonded to one other carbon, so it ranks as the second highest priority. The carbon of the methyl group is bonded to no other carbons, so it is priority 3. Finally, the hydrogen is priority 4. The lowest priority group is positioned on the dash as it should be. The arrow from 1 to 2 (without passing through 3) goes counterclockwise, so the configuration is *S*.



(b) The carbon of the phenyl group has three bonds to other carbons, so it ranks as the top priority group. The carbon of the isopropyl group is bonded to two other carbons, so it is the second highest priority. The carbon of the ethyl group has only one bond to another carbon, making it priority number 3. Finally, the hydrogen is priority 4. The lowest priority group is appropriately positioned on the dash. The arrow from priority 1 to 2 (without passing through 3) goes clockwise, so the configuration is *R*.

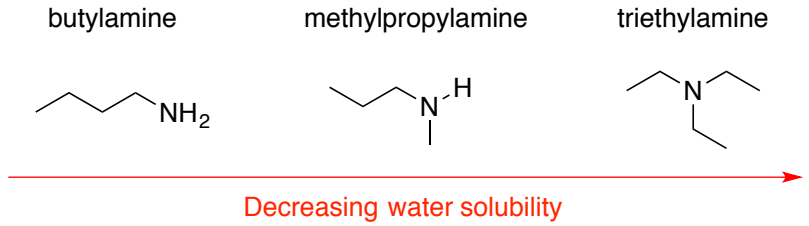


5. One factor in making the determination is the carbon count of each amine. We know that, in general, more carbons equate with reduced water solubility. Two of these amines (butylamine and methylpropylamine) contain four carbons, and one (triethylamine) contains six carbons.

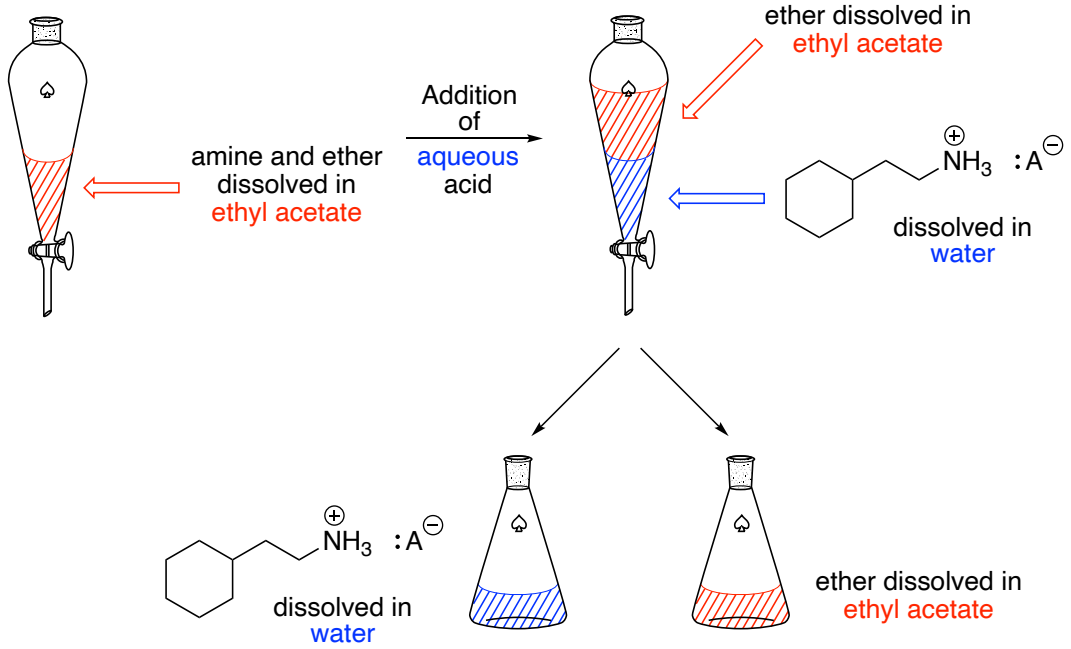
A second factor to consider is hydrogen bonding. All three amines can serve as hydrogen bond acceptors due to the presence of nitrogen with a lone pair of electrons. Butylamine has two N-H bonds, which are hydrogen bond donors. Methylpropylamine has one fewer hydrogen bond donor, and triethylamine has no

hydrogen bond donors. As the number of hydrogen bond donors diminishes, so does water solubility.

Taking both factors into account, we can state that butylamine should be the most water soluble. It is tied for the lowest carbon count and also has the greatest hydrogen-bonding capability. Methylpropylamine has the same carbon count but fewer hydrogen bond donors, so it is expected to be less water soluble. Finally, triethylamine has more carbons and the least hydrogen-bonding capability, making it the least water soluble of the three.

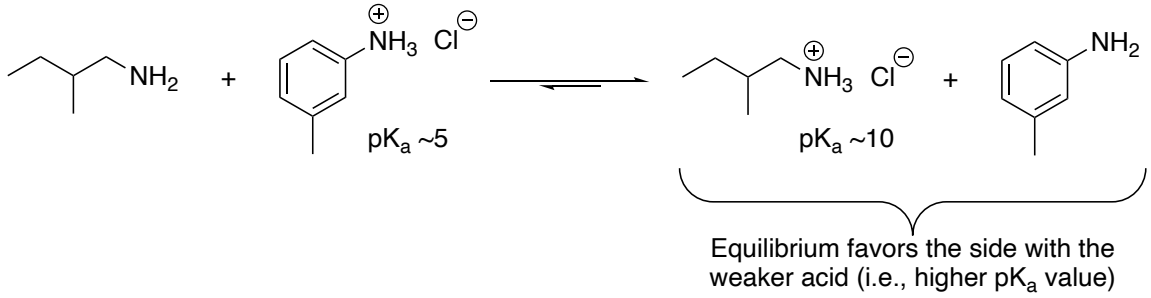


6. First, the mixture of the amine and the ether can be dissolved in an organic solvent, such as ethyl acetate. This solution is transferred to a separatory funnel. Then, aqueous acid is added. The separatory funnel is shaken to allow mixing of the layers, and then the layers are allowed to separate. The acid will have protonated the amine, thereby enhancing its water solubility. As a result, much of the protonated amine will now reside in the aqueous layer. In contrast, the ether has no significant basicity. It remains neutral and therefore dissolved in the organic layer. The layers are drained from the separatory funnel into different flasks. Now, we have a solution of the protonated amine separate from a solution of the ether.

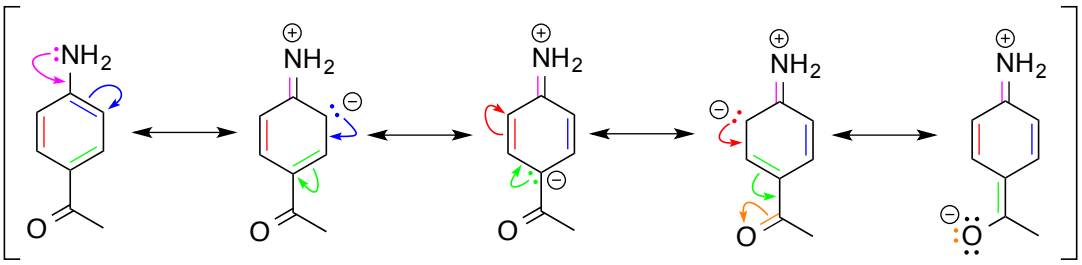


It is worth noting that solubility is not typically an "all-or-nothing" scenario. In other words, much of the amine was removed from the organic layer by washing it with acid; however, some amine will still remain in the organic layer. Therefore, we would typically perform multiple washings with aqueous acid in order to remove all of the amine from the organic layer.

7. This acid-base reaction involves the transfer of a proton from the arylamine to the aliphatic amine. As we learned in this section, protonated arylamines have pK_a values of approximately 5, while protonated aliphatic amines have pK_a values of about 10. Equilibrium favors the products in this instance because the protonated aliphatic amine is the weaker acid (i.e., it has the higher pK_a value). The products are favored by 10 to the difference in the pK_a values, or 10^5.



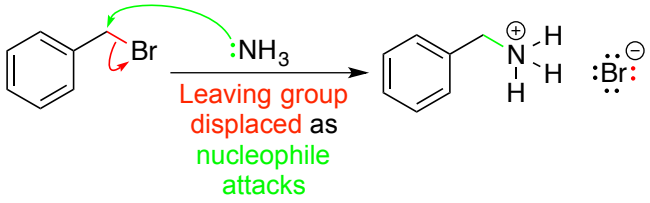
8. The distinguishing feature of the arylamine is resonance. The effect of that resonance is to draw electron density from the amino group into the ring and, in this case, into the carbonyl. Since electron density is removed from the amino group in this fashion, it will be rendered *less* nucleophilic than the aliphatic amine, which has a lone pair that resides exclusively on nitrogen.



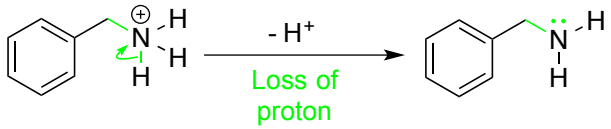
9.

(a) This reaction is written so as to show that you may see the alkyl halide being treated as the reactant, while ammonia can be thought of as a reagent. This is the reverse of the presentation in the text of this section. However, the difference is immaterial because both substances are, in actuality, reactants.

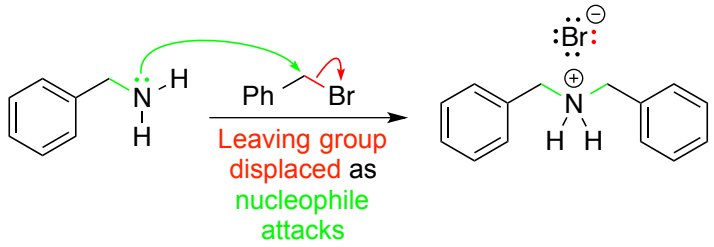
The transformation begins with the displacement of bromide from benzyl bromide as it is attacked by ammonia.



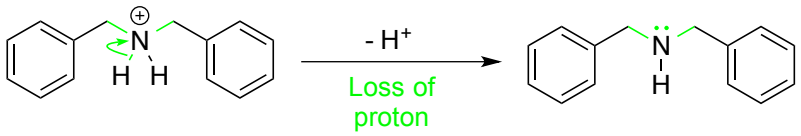
The resulting ammonium ion then sheds a proton. Ammonia would likely be the base responsible for removing this proton, since it is the most basic entity in the medium. However, as we've seen many times previously, we sometimes show only the loss of a proton from the substrate and omit the identity of the specific base that takes the proton.



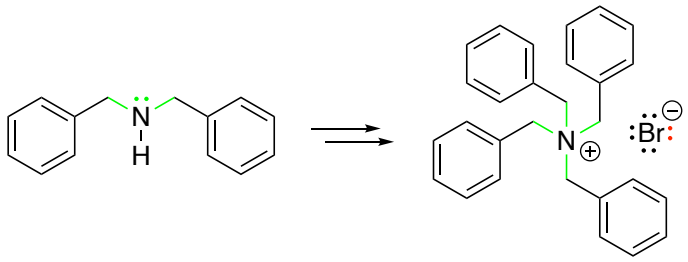
The benzylamine that was just formed is more nucleophilic than ammonia due to the electron-donating effect of the alkyl group. Consequently, benzylamine is more likely to react with another molecule of benzyl bromide than ammonia is. In other words, once a little benzylamine is formed, it consumes remaining benzyl bromide more rapidly than ammonia can. A new round of alkylation ensues when benzylamine attacks benzyl bromide and displaces bromide.



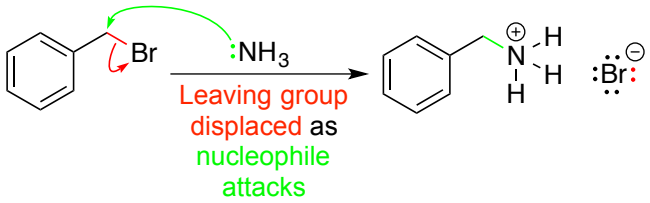
The new ammonia ion sheds a proton to the medium.



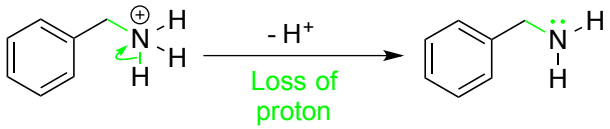
The newly formed dibenzylamine is even more electron rich, and therefore more nucleophilic, than its predecessors. So, two additional rounds of alkylation and proton loss follow until nitrogen has been exhaustively alkylated, forming a quaternary ammonium cation.



(b) When the reaction is conducted with excess ammonia, the initial alkylation is identical.

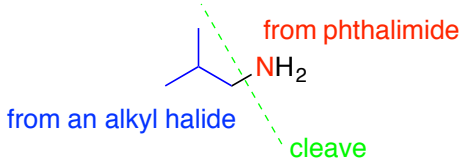


This is followed by loss of a proton, as expected.



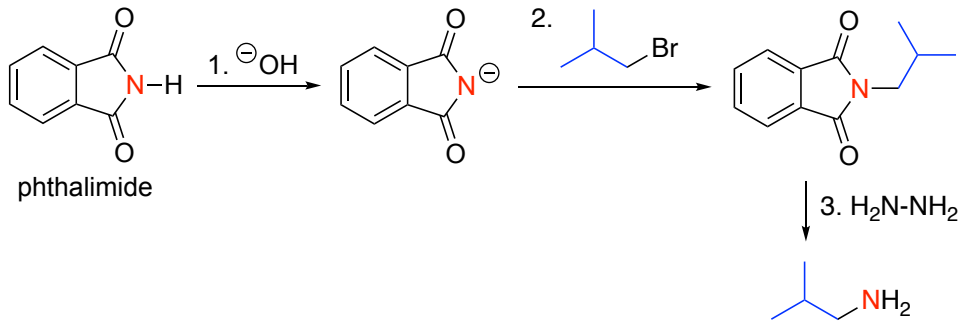
While benzylamine is more nucleophilic than ammonia [as discussed in part (a) above], the excess of ammonia is an additional factor that must be considered. Benzylamine is the better nucleophile, but there is simply a great deal more ammonia present. As a result, ammonia is more likely to encounter and react with any remaining benzyl bromide, and overalkylation does *not* take place in this scenario.

10. The Gabriel synthesis entails the preparation of a primary amine from phthalimide. From a retrosynthetic standpoint, the nitrogen of the target amine derives from phthalimide, while the amine's alkyl group comes from the alkyl halide used during the alkylation step of the Gabriel synthesis. This means that we should disconnect the target between the amino and R groups.



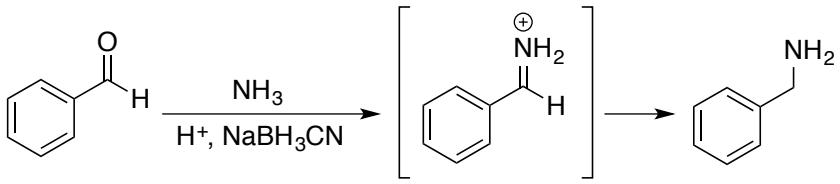
All Gabriel syntheses begin with the deprotonation of phthalimide using a base, such as hydroxide. Then, an isobutyl halide is added to install the needed R group on

nitrogen. Finally, one of the three methods discussed in this section is used to cleave the substituted phthalimide and liberate the desired primary amine.

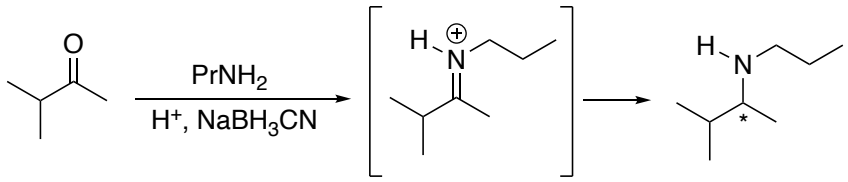


11.

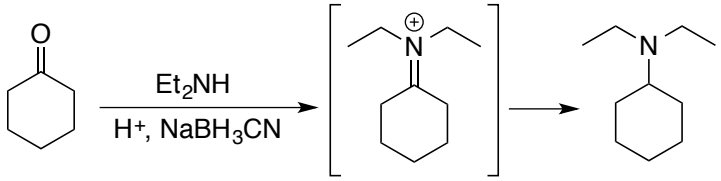
(a) Benzaldehyde first condenses with ammonia to afford an iminium ion. This iminium ion is then reduced by sodium cyanoborohydride to yield a primary amine as the product.



(b) The ketone condenses with propylamine to yield an iminium ion. *In situ* reduction with sodium cyanoborohydride affords a product that is a secondary amine. Since a stereocenter (*) is formed, the product would be a racemic mixture.



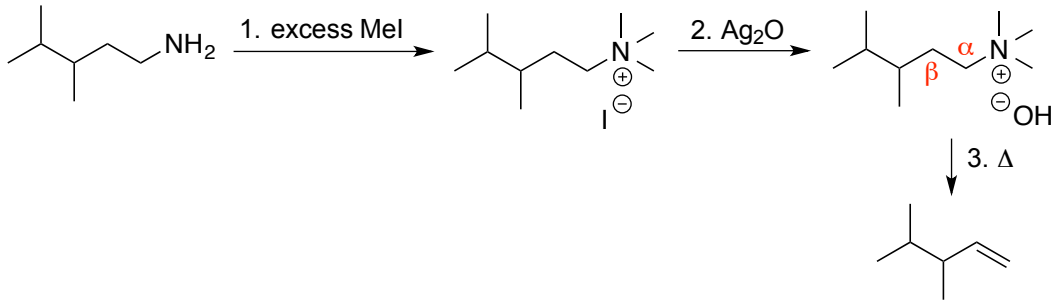
(c) Cyclohexanone and diethylamine condense to create an iminium ion that is susceptible to reduction by sodium cyanoborohydride. The final product is a tertiary amine.



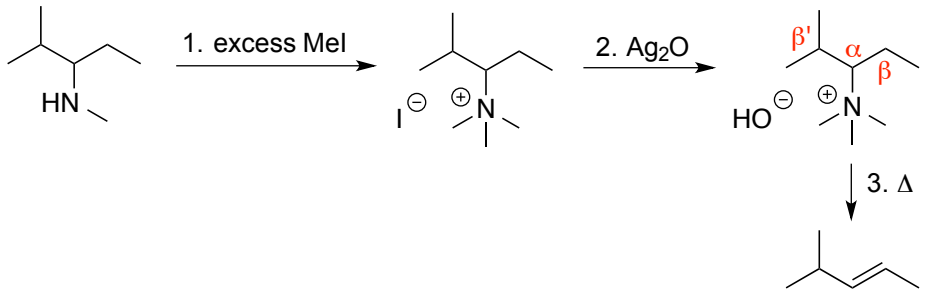
Before leaving this problem, it is useful to pause and compare parts (a), (b), and (c), which produce primary, secondary, and tertiary amines, respectively.

12.

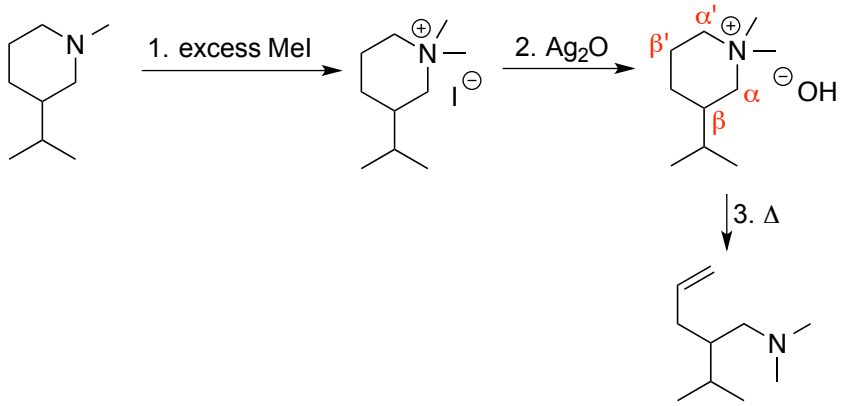
(a) The Hoffman elimination begins with exhaustive methylation, yielding the quaternary ammonium cation. Upon treatment with silver oxide, a counterion swap occurs. Finally, when heated, β-elimination leads to the formation of an alkene. In this case, there is only one β-carbon from which the proton can be removed. As the electrons from the β-carbon to hydrogen bond collapse in between the α and β positions to form the new alkene π bond, trimethylamine is ejected from α as a leaving group.



(b) The transformation begins with exhaustive methylation. Since this secondary amine begins with more R groups than the primary amine in part (a), fewer methylations are required to form the quaternary ammonium cation. In step 2, the counterion is exchanged. Upon heating, the β-elimination takes place. In this instance there are two β positions (β and β'). One position, β, is secondary, while the other, β', is tertiary. It is the less hindered β position that loses a proton during the E2 reaction.

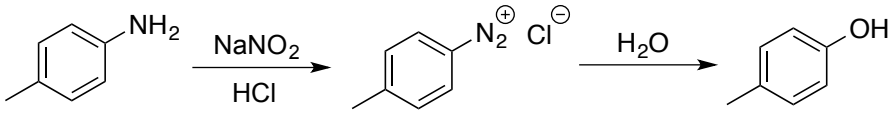


(c) In this reaction, the tertiary amine requires even fewer methylations than the primary and secondary amines seen in parts (a) and (b) above. A single methylation yields the quaternary ammonium cation. After the counterion exchange occurs, E2 takes place. This substrate also possesses two β positions. The β position is tertiary, while the β' position is secondary. The proton is removed from the less hindered β' center to yield the alkene product.

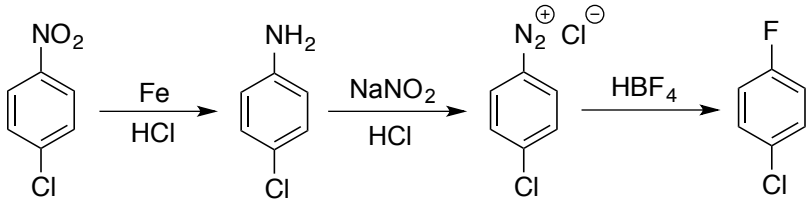


13.

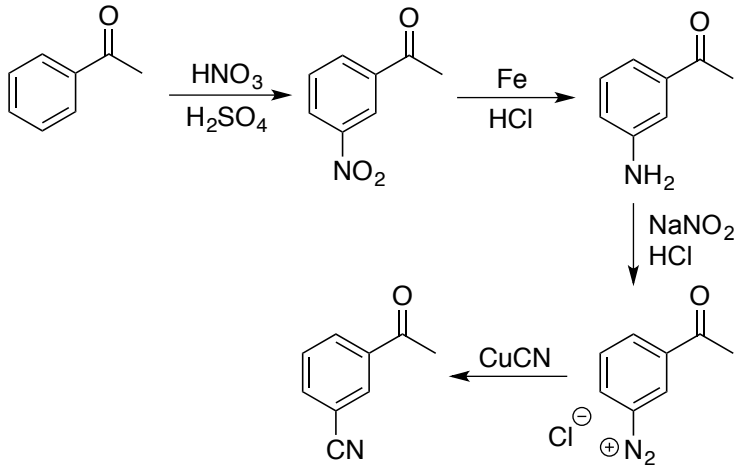
(a) In this problem, we begin with the requisite amino group in place, so it can be immediately diazotized by treatment with sodium nitrite and hydrochloric acid. Then, when water is added, the diazonium ion is replaced by a hydroxyl group, giving the desired phenol as the product.



(b) The substrate for this sequence does not possess the amino group needed for diazotization. However, it does have a nitrogen-containing group: the nitro group. We learned in Chapter 14 that nitro groups on aromatic rings can be reduced using hydrogenation or active-metal reduction (Sn or Fe and HCl). This affords the amino group needed for diazotization. Finally, the Schiemann reaction provides the aryl fluoride.

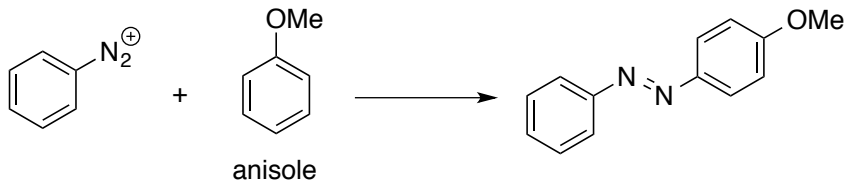


(c) In this problem, there are no nitrogen-containing groups on the ring, so we must install one using an EAS reaction. Nitration places a nitro group on the ring in the proper position because the ketone of acetophenone is a *meta* director. With the nitro group in place, reduction and diazotization yield the diazonium salt. Sandmeyer reaction with copper(I) cyanide then provides the desired nitrile.

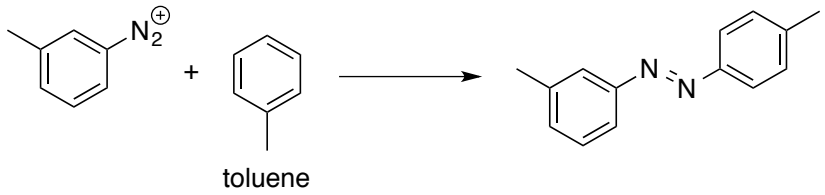


14.

(a) Recall that diazo coupling amounts to an EAS reaction of the ring bearing an electron-donating group. The diazonium ion is merely a new electrophile that we did not use in Chapter 14 when we first learned about EAS reaction. Anisole has an electron-donating methoxy group. As we learned in Chapter 14, all electron-donating groups are *ortho*, *para* directors. Given the size of not only the methoxy group but also the large electrophile being added to the ring, the substitution occurs predominantly at the *para* position, which is less sterically encumbered.

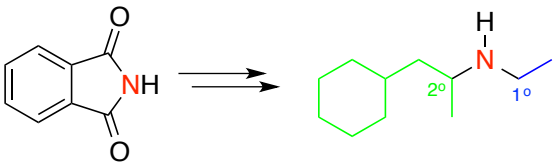


(b) In this reaction, it is toluene that serves as the nucleophile in the EAS reaction. Like anisole, it bears an electron-donating *ortho*, *para* director. The substitution again occurs *para* to the methyl group so as to minimize steric hindrance. Even though the diazonium ion also possesses a substituent, there are no regiochemical decisions to be made with regard to that ring because the nucleophilic aromatic compound always attacks the terminal nitrogen of the diazonium ion.



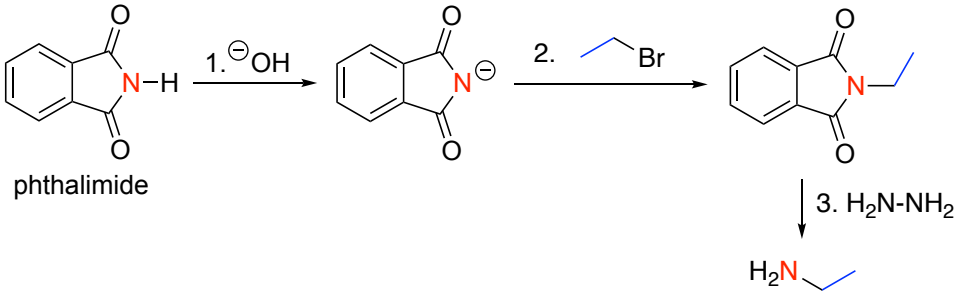
15. It's useful to begin by diagramming the task at hand. We are charged with converting phthalimide to the target amine. Since phthalimide is the reactant for a Gabriel synthesis, that would seem to be part of the solution. The nitrogen of the

target amine will be derived from phthalimide. Although the target amine bears two R groups, we can only install one of these using the Gabriel synthesis. Since the Gabriel synthesis entails an S_N2 reaction, it would be prudent to select the less hindered primary alkyl group for installation using that technique. Reductive amination is another tool for constructing amines that can be used later in the synthesis to add the more hindered secondary alkyl group.



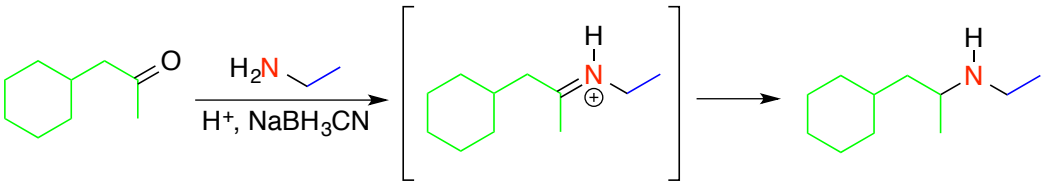
phthalimide

The Gabriel synthesis begins with deprotonation of phthalimide. The anion thus formed serves as a nucleophile in S_N2 reaction with ethyl bromide. Finally, ethylamine is liberated upon treatment with hydrazine (or one of the other hydrolysis options).



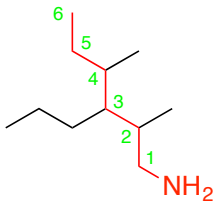
phthalimide

To install the second alkyl group, we must use reductive amination. Ethylamine condenses with the necessary ketone to afford an iminium ion that is subsequently reduced by sodium cyanoborohydride to yield the target amine.



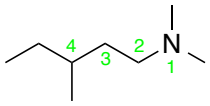
16.

(a) The parent is a hexanamine but not the one used in the given name. The hexanamine that was chosen has two substituents. There is another hexanamine that would have three substituents. When two parents of identical length are identified, it is the one with more substituents that is preferred.



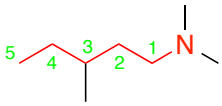
2,4-dimethyl-3-propyl-1-hexanamine

(b) The given name suggests that nitrogen was assigned the number 1; however, only carbons should receive numbers.



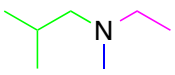
1,1,4-trimethylpentanamine

When the five carbons of the parent are numbered properly, it becomes clear that we must use the locant "*N*" to identify the location of two of the methyl groups.



N,*N*,3-trimethyl-1-pentanamine

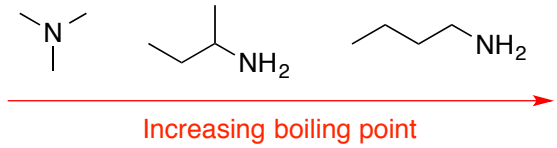
(c) The four-carbon alkyl group was misidentified as a *sec*-butyl group. In fact, it is an isobutyl group. "Iso" is one of the few substituents used in alphabetization, so this change in the name of the alkyl group also changes the order in which the alkyl groups appear in the common name.



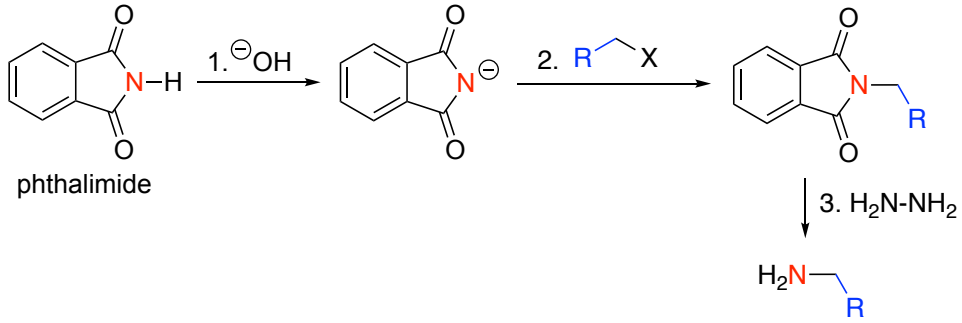
ethylisobutylmethylamine

17. Trimethylamine is the only one of the three amines that is unable to hydrogen bond in a neat sample since it has no hydrogen bond donor. Additionally, trimethylamine is the smallest of the three amines. It has only three carbons; whereas, the other two amines have four carbons each. This means that trimethylamine has the smallest amount of van der Waals interactions as well. These two factors combined reveal that trimethylamine has the smallest amount of intermolecular forces. It is therefore expected to have the lowest boiling point of the three.

Both *sec*-butylamine and butylamine have equivalent hydrogen bonding potential. They both have two hydrogen bond donors and can serve as hydrogen bond acceptors. The only difference between them is the branching in the *sec*-butyl chain. Recall that branching reduces van der Waals interactions. Therefore, *sec*-butylamine is expected to boil at a lower temperature than butylamine.

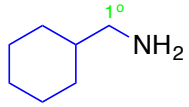


18. The Gabriel synthesis can be used to prepare primary amines only. Phthalimide is deprotonated to give the corresponding anion. The phthalimide anion then serves as the nucleophile in an S_N2 reaction with an alkyl halide. The alkyl halide must be *unhindered* since S_N2 reactions are sensitive to steric hindrance. The alkylated phthalimide has no remaining protons on nitrogen. Therefore, it cannot be deprotonated a second time in order to add another alkyl group. Furthermore, the lone pair on nitrogen is not nucleophilic because it is delocalized through resonance into the two adjacent carbonyls. Thus, when the amine is liberated from phthalimide through nucleophilic acyl substitution, it will bear one and only one alkyl group.

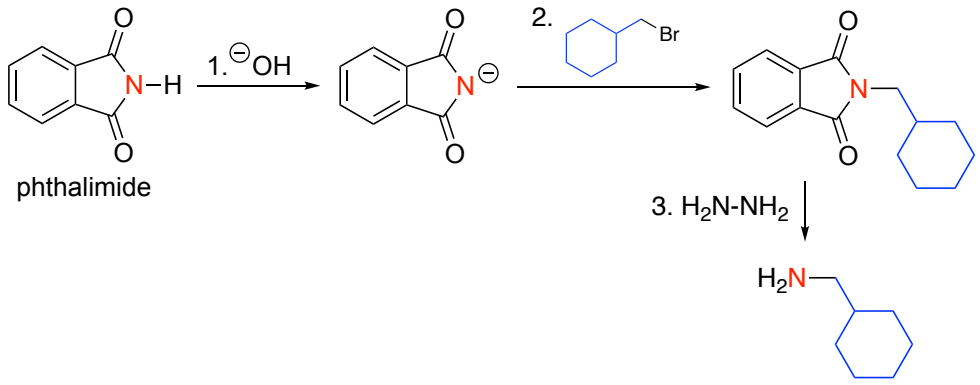


The first amine is a secondary amine. It bears two alkyl groups and cannot therefore be prepared using the Gabriel synthesis alone.

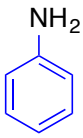
The second amine bears a single alkyl group, and that alkyl group is primary and therefore unhindered. So, this amine could be prepared using the Gabriel synthesis.



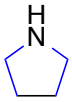
Its preparation is shown below.



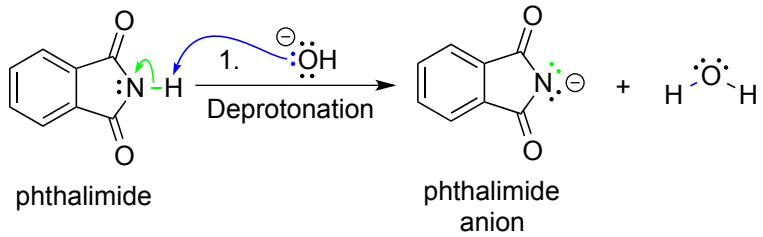
The third amine is aniline. It bears only one group, but that group is an aryl group rather than an alkyl group. Since S_N2 reaction does not occur on sp^2 hybridized centers, aniline cannot be prepared via the Gabriel synthesis.



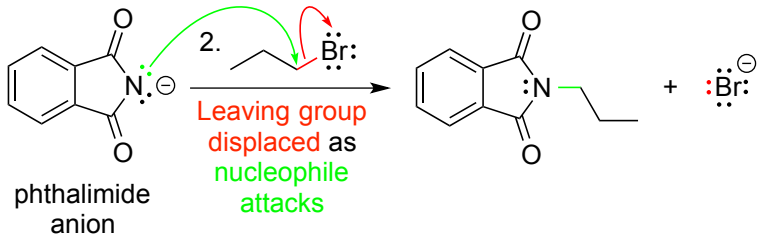
The final amine is known as pyrrolidine. The nitrogen atom is bonded to two carbons, making it a secondary amine. As such, it cannot be prepared using the Gabriel synthesis alone.



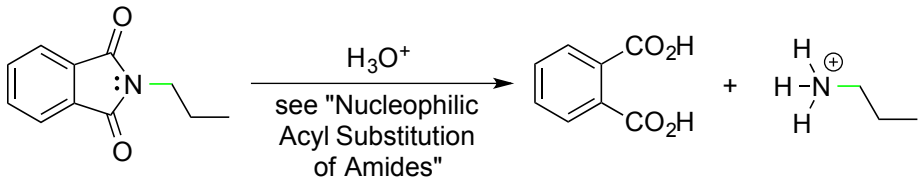
19. In the first step of the Gabriel synthesis, phthalimide is deprotonated to give the nucleophilic phthalimide anion.



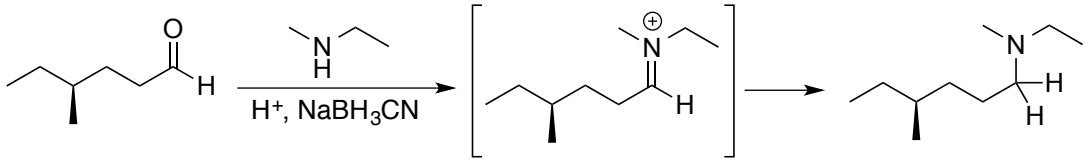
When propyl bromide is added, an S_N2 reaction ensues and results in an alkylated phthalimide.



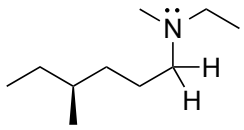
Finally, hydrolysis in aqueous acid proceeds via nucleophilic acyl substitution. This is exactly the same as the hydrolysis of an amide in aqueous acid, as we saw in Chapter 16. It merely occurs twice to cleave each nitrogen to carbonyl carbon bond. Propylamine is thus released, but it is obtained as its conjugate acid since the reaction conditions are acidic.



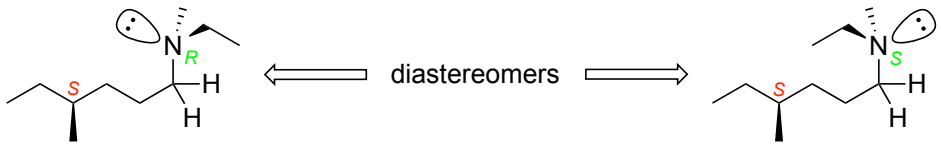
20. This is a reductive amination that produces a tertiary amine.



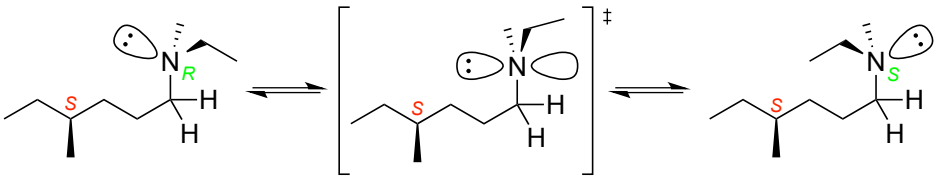
This particular tertiary amine has three unique alkyl groups on nitrogen. Considering that the nitrogen atom also has a lone pair of electrons, it bears four different groups and is therefore a chiral center.



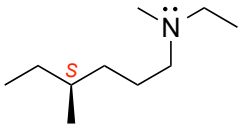
The investigator expected to obtain diastereomers because the nitrogen could have either configuration, while the configuration of the stereogenic carbon is unaltered during the reaction. For clarity, the configurations of both centers are labeling in the diagram below. When assigning the configuration of nitrogen, it is important to know that the lone pair is the lowest priority substituent possible.



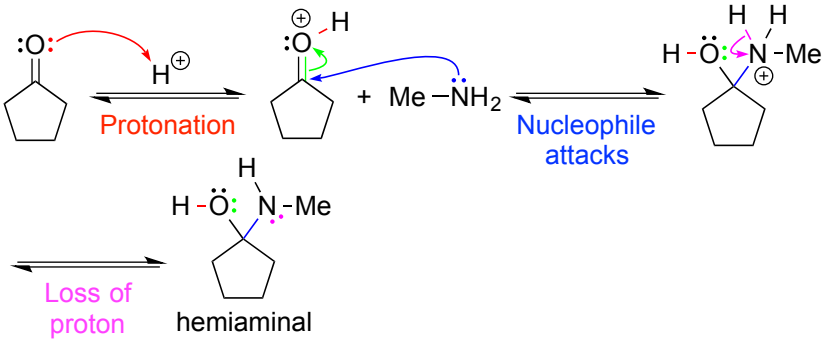
The investigator forgot about pyramidal inversion though. While it is true that nitrogen can have two possible configurations, they rapidly interconvert at room temperature.



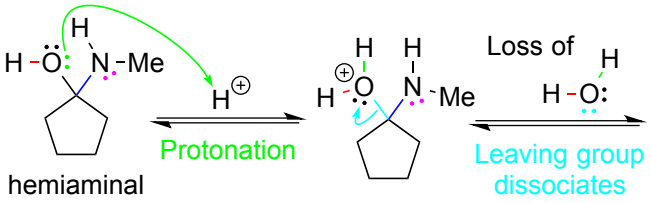
For practical purposes, the nitrogen's chirality can be ignored, and the product can simply be represented as:

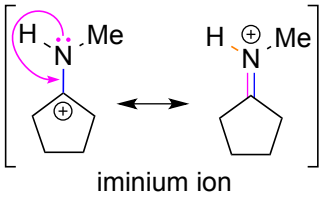


21. This reductive amination begins with formation of an iminium ion, which proceeds through the hemiaminal. The process starts with protonation of the carbonyl oxygen. The amine then attacks the carbonyl carbon, whose electrophilicity was enhanced by protonation of the neighboring oxygen. The ammonium ion thus formed then sheds a proton to the medium to yield the hemiaminal.

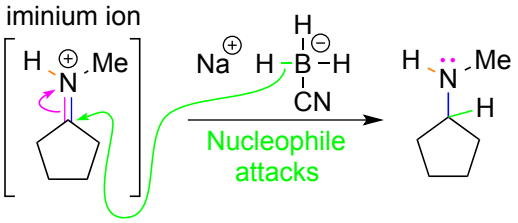


Under the reaction conditions (aqueous acid), there is more that can happen to the hemiaminal. Protonation of the hydroxyl group transforms it into a good leaving group. Water dissociates, and the resultant iminium ion is stabilized by resonance.



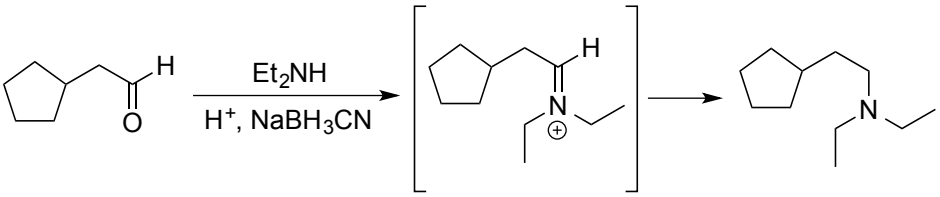


The iminium ion is electrophilic enough to attract a hydride from the weak hydride donor sodium cyanoborohydride. This leads to the formation of an amine as the final reaction product.

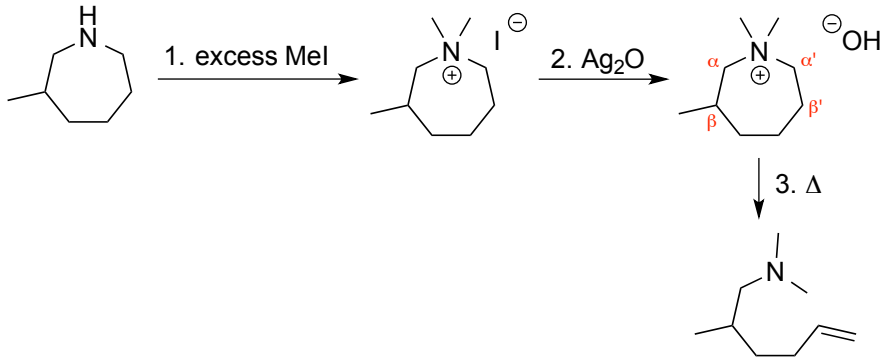


22.

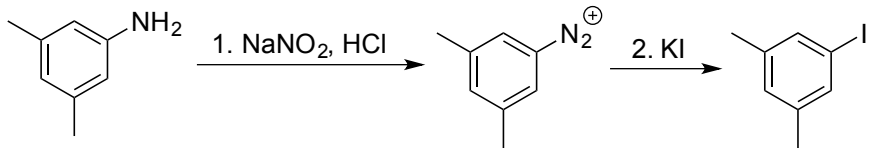
(a) This reductive amination begins with the condensation of the aldehyde and diethylamine, which generates an iminium ion. The iminium ion is then reduced *in situ* to the tertiary amine.



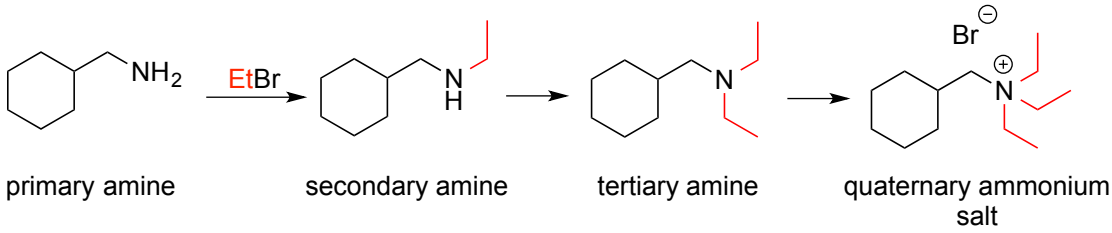
(b) This Hofmann elimination begins with the exhaustive methylation of the secondary amine. The quaternary ammonium cation then experiences a counterion swap, from iodide to hydroxide, when silver oxide is added. Finally, β-elimination occurs when the mixture is heated. Hydroxide removes a proton from the less hindered β' position. The electrons from the C-H σ bond collapse between α' and β' to form the alkene π bond, and the amine is expelled as a leaving group. Since the amine was cyclic, it remains tethered to the alkene formed during the reaction.



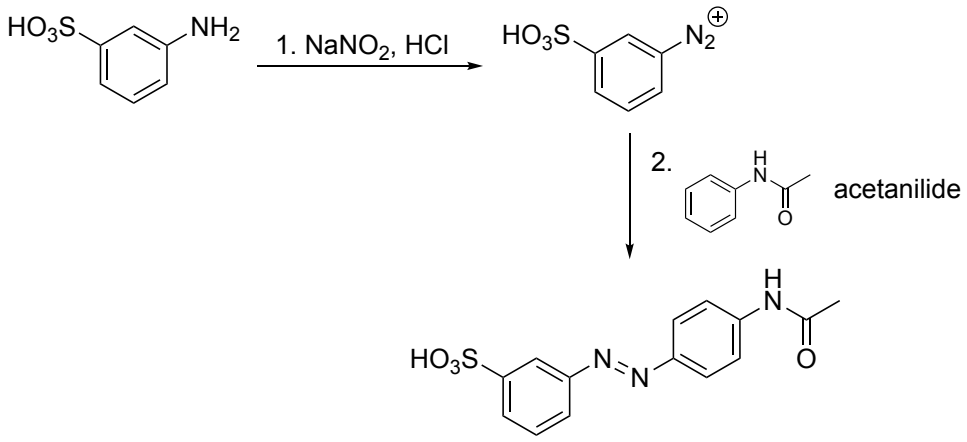
(c) This sequence begins with diazotization. The diazonium ion is then treated with potassium iodide to yield an aryl iodide product.



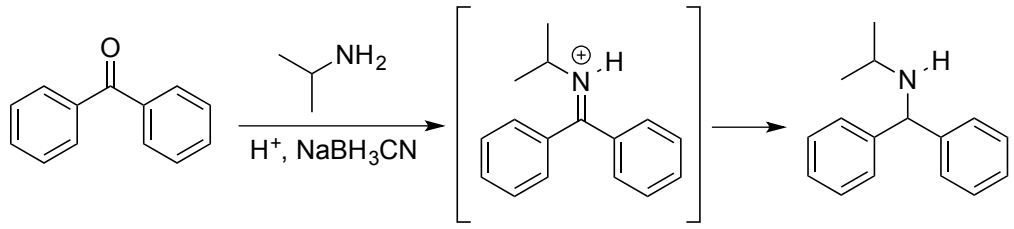
(d) This is direct alkylation of an amine. S_N2 reaction transpires between the primary amine and ethyl bromide. However, the reaction does not stop there. Once a proton is shed, the secondary amine is even more nucleophilic than the original primary amine was, so another S_N2 reaction occurs. After a proton is lost, a tertiary amine is formed, and it too is more nucleophilic than its predecessors. Consequently, one more S_N2 reaction takes place, yielding the quaternary ammonium salt as the final product. There will also be unreacted primary amine left if the stoichiometry of the reactant to ethyl bromide was 1:1. Some molecules of reactant consumed more than their fair share of ethyl bromide as successive alkylations took place. Therefore, the ethyl bromide will be consumed before all of the reactant can be alkylated.



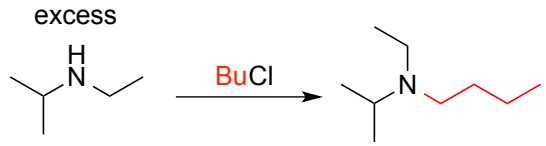
(e) This sequence begins with diazotization. The diazonium ion then serves as the electrophile in an EAS reaction with acetanilide. Acetanilide is most nucleophilic on the carbons *ortho* and *para* to the amide. The EAS reaction takes places at the more sterically accessible *para* position to give the diazo coupling product.



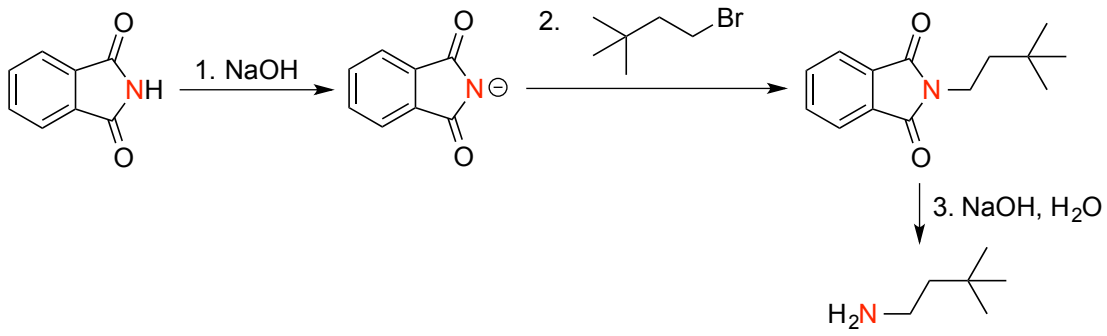
(f) This reductive amination begins when benzophenone and isopropylamine condense to yield an iminium ion intermediate. This iminium ion is subsequently reduced by sodium cyanoborohydride to afford the product as a secondary amine.



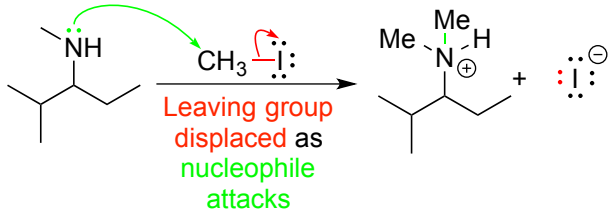
(g) This is a direct alkylation of an amine. Unlike part (d) above, this reaction utilizes an excess of the reactant amine. This ensures that only a single butyl group can be added to any molecule of amine because the likelihood of the butylated amine encountering another molecule of butyl chloride is low.



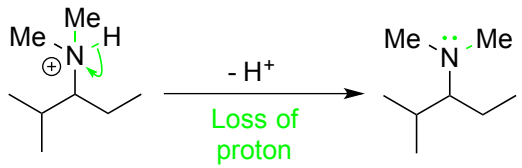
(h) This Gabriel synthesis begins with formation of the phthalimide anion, which then engages in an S_N2 reaction with the alkyl bromide. Finally, basic hydrolysis of both amide linkages liberates the primary amine product.



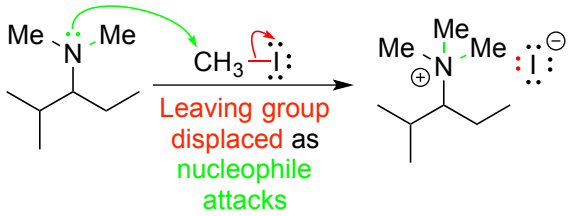
23. This Hofmann elimination begins with exhaustive alkylation. This will entail two rounds of alkylation since the reactant is a secondary amine. The amine attacks methyl iodide, displacing iodide as a good leaving group in S_N2 fashion.



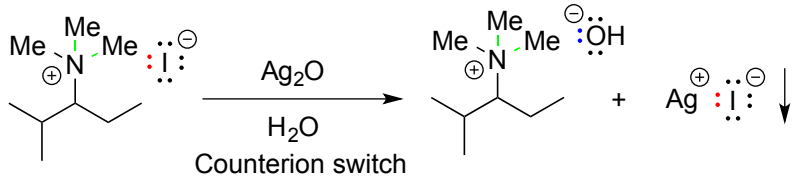
The ammonium cation then sheds a proton to the medium.



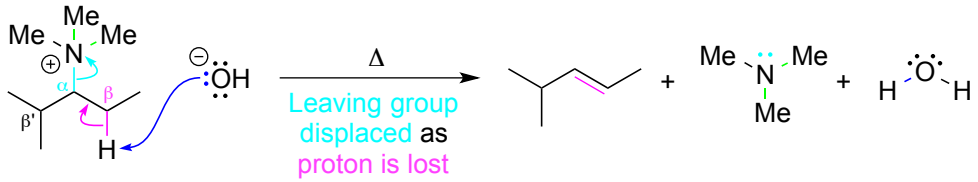
This tertiary amine then attacks another molecule of methyl iodide, again displacing iodide in S_N2 fashion. A quaternary ammonium salt is formed.



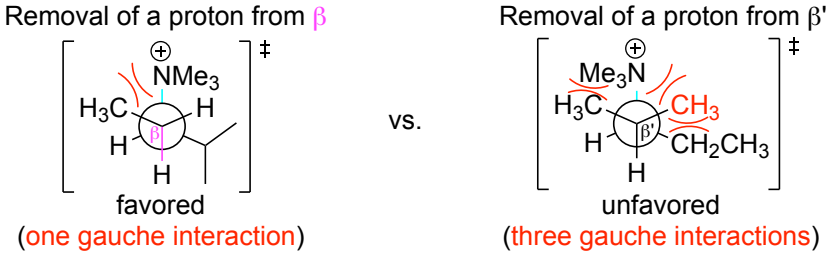
The next step induces a counterion swap. When silver oxide is added, silver iodide is formed and precipitates (↓). The hydroxide formed from silver oxide in water then complexes with the quaternary ammonium cation.



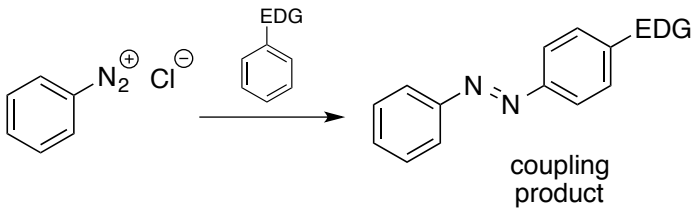
Finally, when heated, β-elimination occurs. There are two positions from which a proton could be removed, but β is less hindered than β' and is therefore the site of proton removal by hydroxide. The π bond is formed as trimethylamine is displaced as a good leaving group.



To further justify why the proton was removed from β rather than β', we can examine the transition state for each pathway. Recall that the proton removed during this E2 reaction must be anti-periplanar to the trimethylamino leaving group. As such, when a proton is removed from β, there is an unavoidable gauche interaction between the methyl group on β and the trimethylamino group. However, if we were to remove a proton from β', there would be additional gauche interactions.

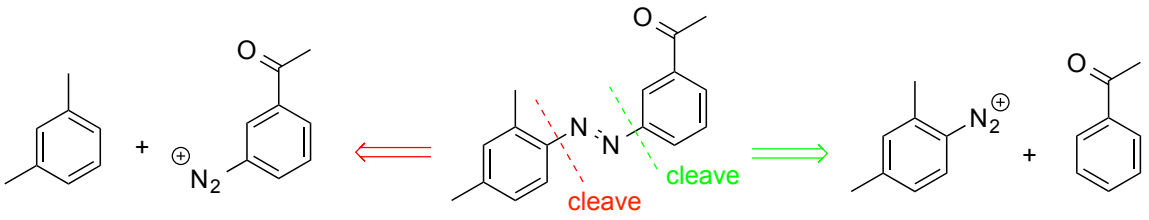


24. The key to this problem is that diazo coupling requires that the nucleophilic ring (i.e., the one that does *not* bear the diazonium ion) must possess an electron-donating group.

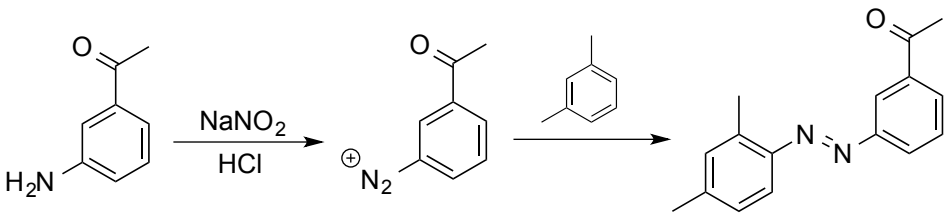


It is the bond between an aromatic ring and a nitrogen atom that is made during diazo coupling, so there are two possible retrosynthetic disconnections. However,

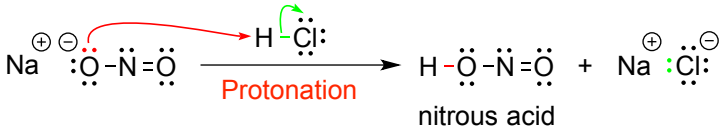
the green pathway is unacceptable because it would lead to a "nucleophilic" ring bearing an electron-withdrawing ketone. Such a ring would actually be a poor nucleophile for the diazo coupling. However, the red path leads to a nucleophilic ring that is, indeed, electron rich due to the presence of its two methyl groups.



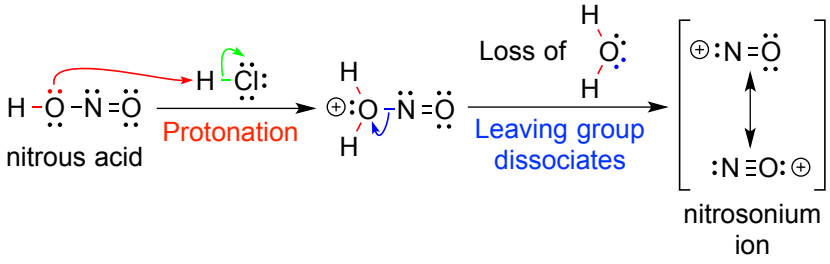
Therefore, *meta*-aminoacetophenone can be diazotized to yield the requisite diazonium ion. Then, treatment with *meta*-xylene affords the desired product. The positions *ortho* and *para* to the methyl groups of xylene are the most nucleophilic, but remember that EAS never occurs between two substituents.



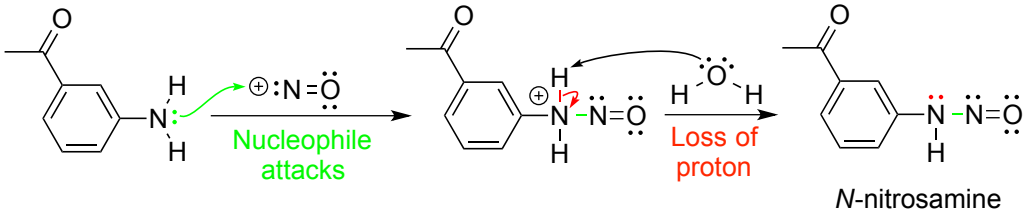
25. The reaction sequence begins with *in situ* formation of the nitrosonium ion. Sodium nitrite is protonated by hydrochloric acid to yield nitrous acid.



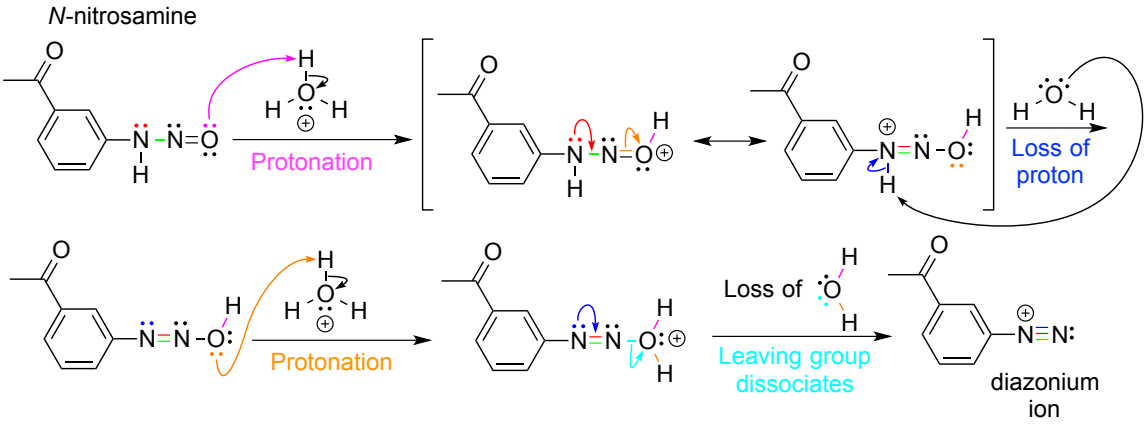
Nitrous acid is then protonated on its hydroxyl group. This forms a good leaving group, and when water dissociates, the nitrosonium ion is produced.



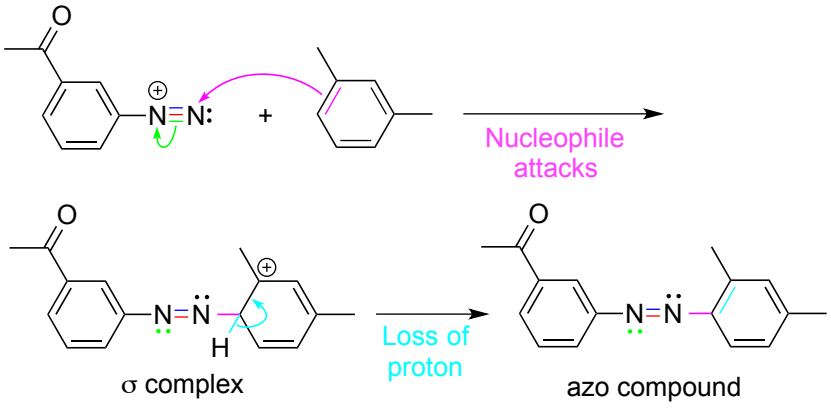
The arylamine then attacks the nitrosonium ion. A proton is subsequently lost to afford an *N*-nitrosamine.



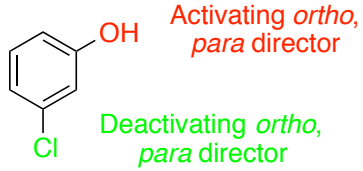
Through a series of proton transfers, the oxygen of the *N*-nitrosamine is converted into a good leaving group, and the π bonds of the diazonium ion are formed. This begins with protonation of the oxygen. The resulting oxonium ion has a resonance form in which nitrogen bears the charge. A proton is then lost from this nitrogen atom. Notice how the oxygen became a hydroxyl group due to these two proton transfers, and the first nitrogen-nitrogen π bond was concurrently formed. Now, the hydroxyl group is protonated to yield a good leaving group. The second nitrogen-nitrogen π bond is formed as water dissociates. The result is the aryl diazonium ion.



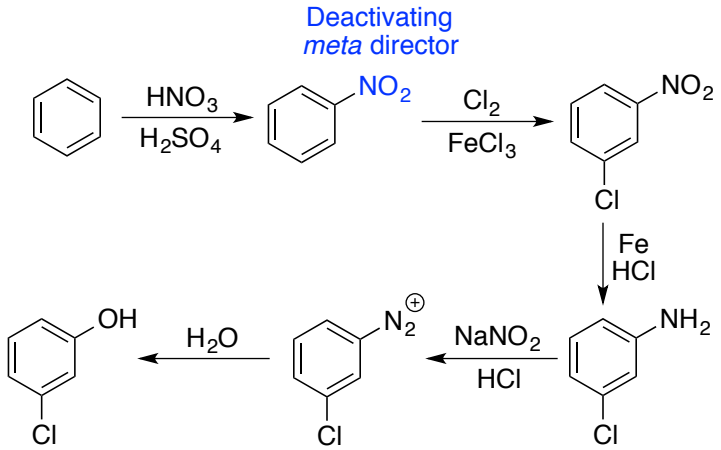
To the diazonium ion, *meta*-xylene is added, and EAS reaction follows. A π bond of *meta*-xylene attacks the terminal nitrogen of the diazonium ion, thereby pushing electrons onto the internal nitrogen to neutralize its charge. A σ complex is formed in the process, and it then loses a proton to restore aromaticity, yielding the azo compound.



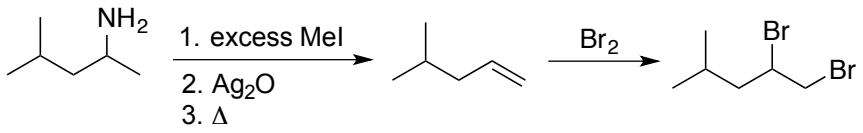
26. In Chapter 14, we saw that, when considering the synthesis of aromatic molecules, it is best to begin with an analysis of the directing capabilities of the substituents. In this case, both groups are *ortho*, *para* directors despite the fact that they differ in whether they are activating or deactivating. This presents a challenge because it appears as though the desired *meta* substitution pattern will be difficult to obtain. When we encountered situations like this in Chapter 14, the solution resided in the fact that at least one substituent would require more than a single step for installation. One of the intermediates would have the needed directing capability.



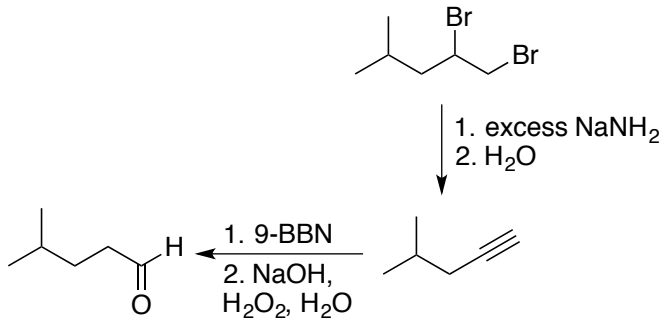
In this problem, chlorine could be added to the ring in as little as one step; however, the hydroxyl group definitely requires a multi-step installation. Therefore, we should begin this process and look for an intermediate that can direct to the *meta* position. Phenols are prepared from diazonium ions, so we must start the process of installing a diazonium ion. This begins with nitration. The nitro group is a *meta* director, so we can pause at this stage to place the chlorine through EAS chlorination. Then, the nitro group can be reduced, and the resulting amine can be diazotized. Finally, addition of water yields the desired phenol.



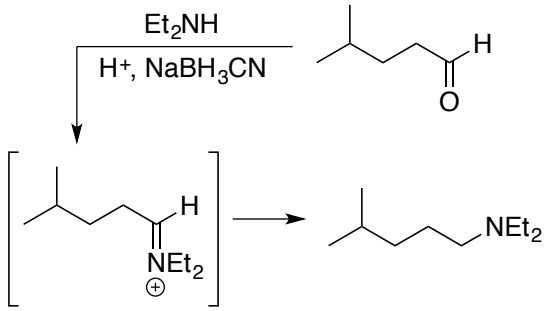
27. We should begin by working backwards from the first intermediate given: the vicinal dibromide. Vicinal dibromides are made from the corresponding alkenes, in which the same two carbons are functionalized. This alkene (4-methyl-1-pentene) would result from Hofmann elimination of 4-methyl-2-pentanamine.



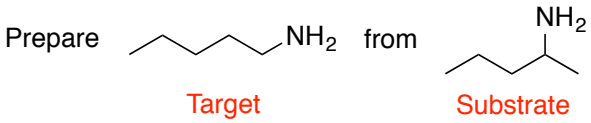
In the next part of the scheme, the vicinal dibromide is converted to an aldehyde. Vicinal dibromides can undergo two eliminations to yield alkynes, and alkynes in turn can be hydrated with anti-Markovnikov regioselectivity to yield aldehydes.



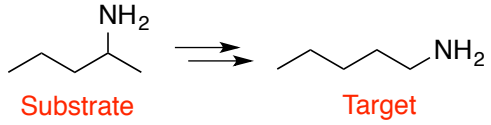
Finally, a reductive amination completes the sequence.



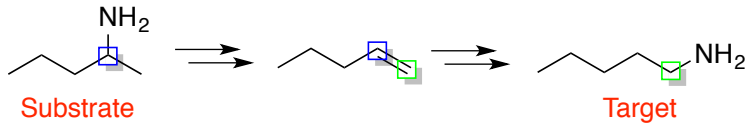
28. As usual, it is a good idea to label the substrate and the target.



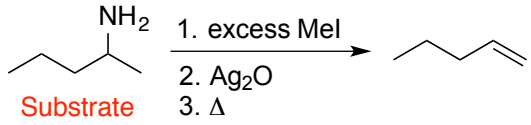
Then, write the problem in the typical fashion. This highlights the fact that the central challenge of the synthesis is transposing the amine from one carbon to the adjacent center.



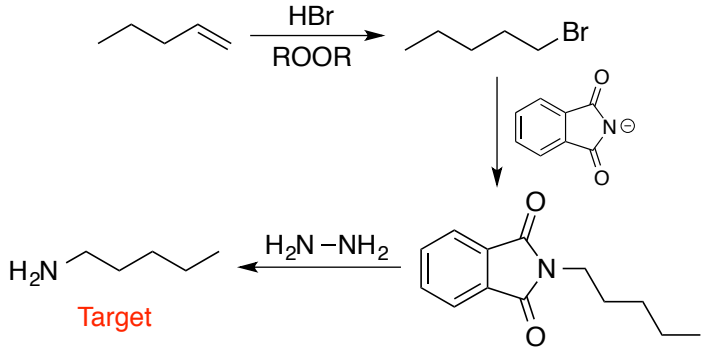
There is no method to accomplish this directly. However, in other chapters, we've seen similar challenges. Whenever two adjacent centers are the focus of our attention, it suggests the intermediacy of an alkene, which has two adjacent carbons that are functionalized. This observation breaks the synthesis into two phases: (1) elimination and (2) addition to the alkene with the desired regiochemistry.



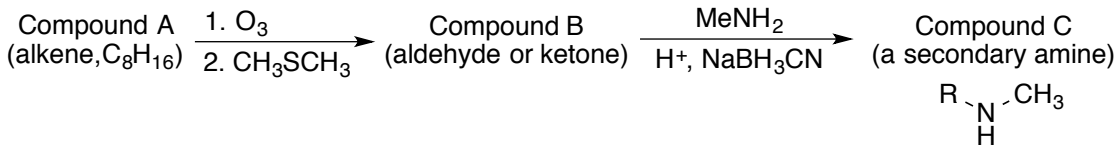
Phase 1 is the more straightforward of the two. We have learned that the Hofmann elimination converts an amine into the less substituted (Hofmann) alkene.



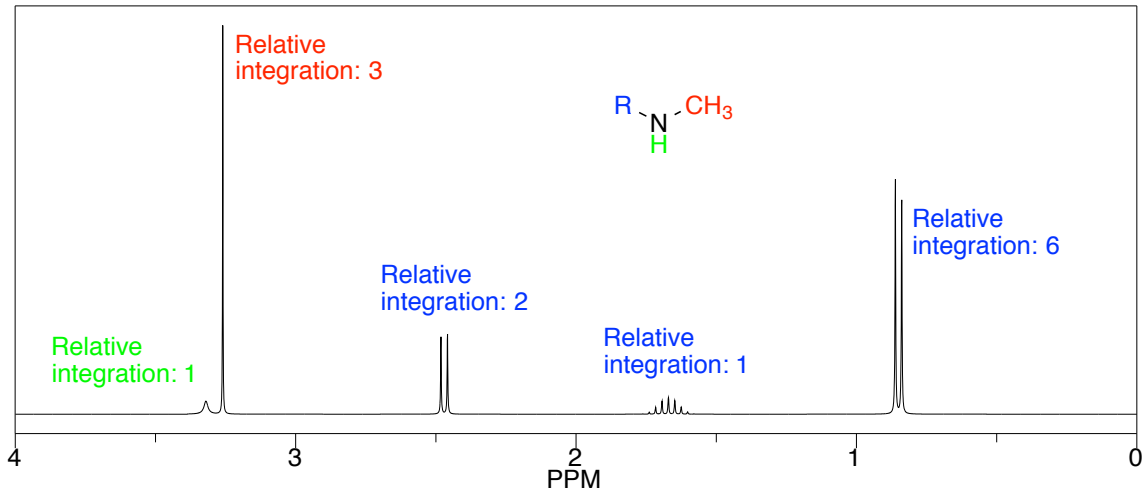
Phase 2 entails anti-Markovnikov addition to the alkene. However, we are unable to add ammonia (NH_3) across the alkene. We've learned no such amination reaction. On the other hand, we do know that the Gabriel synthesis allows for the preparation of primary amines. The alkene can be converted to 1-bromopentane through anti-Markovnikov addition of HBr across the π bond of 1-pentene. Subsequent treatment with the phthalimide anion yields an alkylated phthalimide. Nucleophilic acyl substitution using hydrazine then frees 1-pentanamine from the phthalimide.



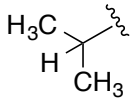
29. It is always helpful to map out the information supplied in a word problem. We know the formula for Compound A and the fact that it is an alkene. Additionally, we know that alkenes yield aldehydes or ketones upon ozonolysis followed by a reductive workup with dimethyl sulfide. Finally, since Compound C is clearly prepared via reductive amination, we can safely conclude that it is a secondary amine in which the amine bears a methyl group and an R group corresponding to Compound B's framework.



There are several possible structures for Compound A based on the molecular formula alone, so we should begin by analyzing the NMR of Compound C and then work our way backward to the structures of Compounds A and B. However, our job is made easier by the rough outline of Compound C's structure that we derived above. We can quickly identify the methyl group and the hydrogen on nitrogen (recall that hydrogen bonding protons often yield broad singlets). The remaining three signals must reveal the structure of the amine's R group.

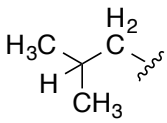


The doublet integrating for six hydrogens most likely represents two methyl groups with a single neighbor.

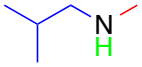


The multiplet integrating for one hydrogen fits nicely with this hypothesis, since it is exactly what we would expect for the methine (CH) of an isopropyl fragment.

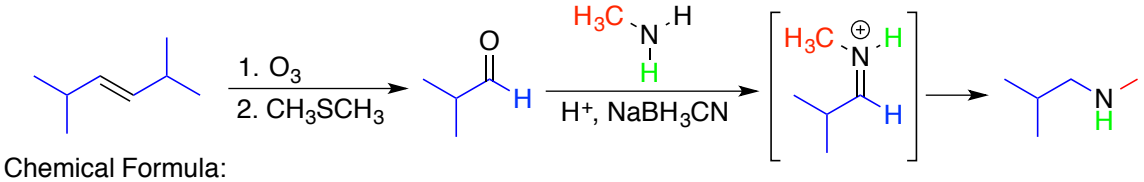
Finally, the doublet integrating for two hydrogens correlates with a methylene (CH_2) adjacent to the methine.



This allows us to identify the remaining R group on nitrogen as an isobutyl group.

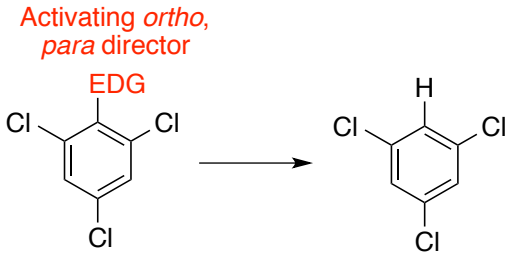


Now, we can work backwards to the structures of Compounds A and B. The reductive amination must utilize α-methylpropionaldehyde (Compound B) in order to yield the correct secondary amine product. Compound A must therefore be a symmetrical alkene that, when cleaved, yields two equivalents of the aldehyde.

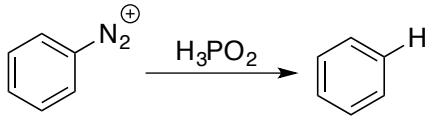


Chemical Formula: C_8H_{16}

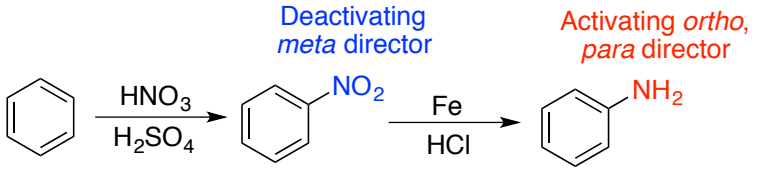
30. The challenge of this problem is that the chlorines are all deactivating *ortho*, *para* directors. Consequently, they won't end up mutually *meta* to each other if we simply use EAS chlorination. The hint suggests a removable directing group that could orchestrate the chlorinations. If there were an activating *ortho*, *para* director on the ring, it would control all of the EAS reactions, directing chlorination *ortho* and *para* to itself. If this directing group could subsequently be replaced with hydrogen, then it would effectively be erased by the end of the synthesis.



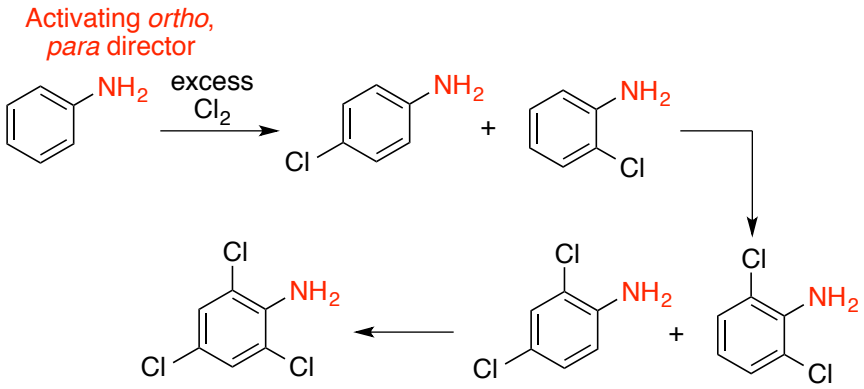
We know that a diazonium ion can be replaced by hydrogen when treated with hypophosphorous acid, so any precursor to the diazonium ion could be the removable directing group that we want.



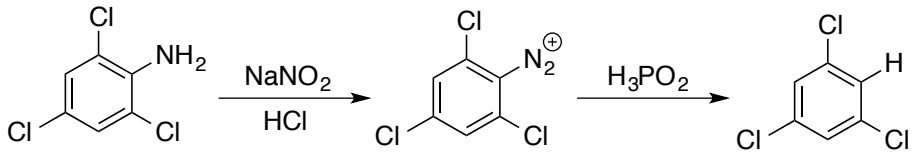
As we begin the process of installing a diazonium ion on the ring, it becomes apparent that the nitro group does *not* possess the desired directing capability. However, the amino group does.



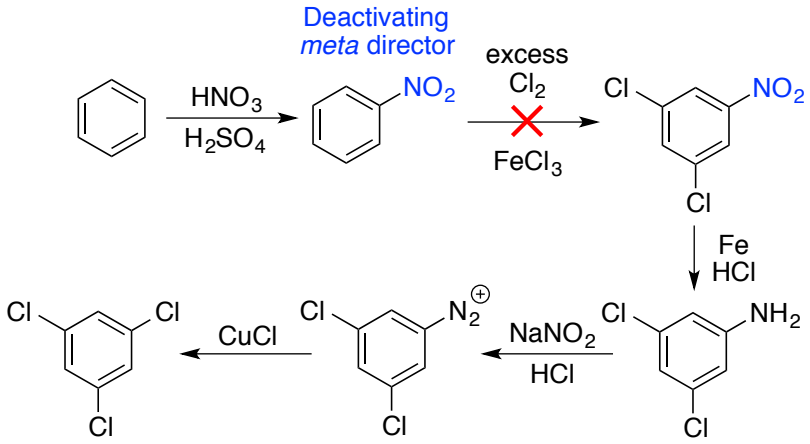
Therefore, aniline can be exhaustively chlorinated. In fact, it is activated enough that we don't even need to add iron trichloride for this EAS reaction. While the intermediates may be mixtures of isomers, they all converge on a single trichlorinated product.



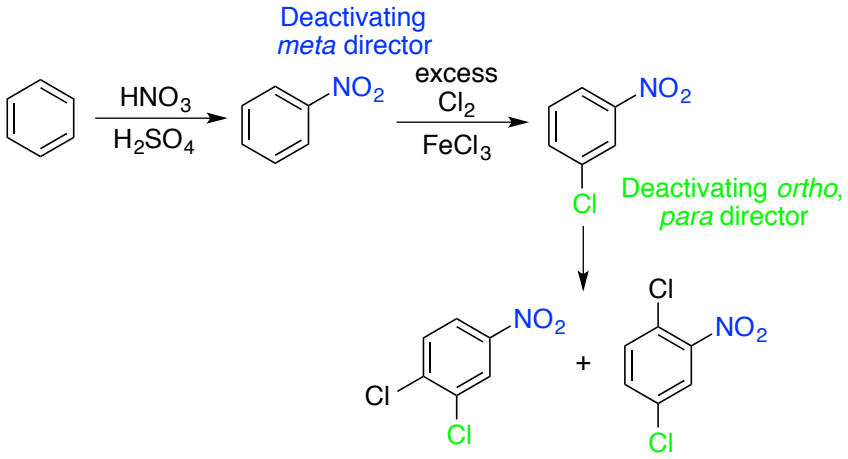
Now that the amino group has served its purpose, it can be removed through conversion to the diazonium ion and treatment with hypophosphorous acid.



It is worth noting a common error before we finish with this problem. Some students are tempted to approach the synthesis differently. They believe that the nitro group can direct two chlorines to its *meta* positions and that the nitro group can then ultimately be replaced by the third chlorine via Sandmeyer reaction. The problem is that the EAS chlorination does not work as anticipated.



The first chlorination will indeed go *meta* to the nitro group. However, at this stage, things go awry. The chlorine atom is only weakly deactivating; whereas, the nitro group is strongly deactivating. Therefore, it is the chlorine (*not* the nitro group) that controls the second chlorination. Chlorine directs *ortho* and *para* to itself, and an incorrect substituent pattern is obtained as a result.



Credits

The following infrared spectra found in Chapter 5:

1-hexene
cyclohexane
m-toluic acid
isopropyl butyrate
4'-methoxyacetophenone
1-butanol
2-butanone
1-pentene
butyraldehyde
butyric acid
isobutyramide
acetophenone
phenylacetaldehyde
2,2,4-trimethylcyclopentanone
cyclohexanol
cyclohexyl amine
N-methyl cyclohexyl amine
N-methylbenzamide
isobutyric acid
pivalic acid
N-ethylacetanilide
phenylacetylene
butyronitrile
hexane
2-acetyl-N-tert-butyl-2-butenamide
1,4-dioxane
isobutyl isobutyrate
cis-3-hexene
trans-3-hexene
2,3-dimethyl-2-butene
2-methylbutanal
2-pentanol
ethylisopropylamine
3,3-dimethyl-2-butanone
1-pentyne
3,4-dihydro-2(1*H*)-naphthalenone

and the following infrared spectrum used in Chapter 7:

isopropenylbenzene

were obtained from the Spectral Database for Organic Compounds, SDBSWeb (http://sdbs.db.aist.go.jp/), National Institute of Advanced Industrial Science and Technology, 2014 – 2015.