organic chemistry I

Manisha Nigam
University of Pittsburgh - Johnstown

Organic Chemistry-I eBook

About the book:

This open textbook is suitable for the college-level first semester of Organic Chemistry. This book covers basic concepts of organic molecules' structures and reactivities with plenty of solved examples. Besides the fundamental concepts, topics of organic acids-bases, kinetics, thermodynamics of reaction, and stereochemistry, this book covers the preparation and reactions of alkyl halides, alkenes, alkynes, and alcohols. Understanding organic chemistry requires **active studying**. Studying Organic chemistry is akin to playing a new video game or learning to play an instrument. It just doesn’t come easy naturally. One cannot watch other people play piano/video games/teach Organic chemistry and become an expert on it. One must actively play/draw structures using a pencil and paper to draw and redraw structures, write reactions, and explore stereochemistry. Like a painting class!

About the author:

Dr. Manisha Nigam is an Associate Professor at the Department of Chemistry, University of Pittsburgh Johnstown since 2002. Other than teaching sophomore-level Organic Chemistry lectures and laboratory courses, she has also been actively involved in the curriculum development of a new course Green Chemistry and Sustainability.

Author’s note:

I would like to dedicate this section to all my undergraduate students, past and present. I appreciate their commitment to finding content errors in this textbook. They have always done more than expected and given so much of their time and effort to support the final draft.

The Office of the Provost, University of Pittsburgh for providing funding for this project.

About the cover: Aditi Sridhar, my daughter designed the cover for this OER.

Table of Contents

Chapter 1: Structure and Bonding- A Review from General Chemistry

1.1 Study of carbon-containing compounds

Organic chemistry is the study of compounds that contain carbon. What makes carbon unique is that bonds between carbon atoms are stable, allowing chains of carbon atoms to be formed, with each carbon atom of a chain being capable of joining other atoms such as hydrogen, oxygen, sulfur, nitrogen, and halogens.

1.2 Atomic Structure

Before you further your reading, you should review your own, because it will be assumed that you already understand some basic chemistry concepts. It would be a good idea to return to your introductory chemistry textbook or watch the video tutorials on Canvas.

The number of protons in the nucleus determines an element's chemical properties. It is the electrons that take part in chemical bonding. Figure 1.1 shows the atomic structure of the carbon atom. The protons and neutrons constitute the nucleus (almost all the mass is in the nucleus). The electrons reside in the orbitals that are outside the nucleus. The first shell has only two electrons in the s orbital ($1s^2$). The second shell that constitutes s and p orbitals ($2s^22p^2$) has a total of 4 electrons. This is also known as the valence shell. Since it has 4 electrons, the Carbon atom resides in group IV of the periodic table. Good news!! We will only explore elements that have valence electrons in s and p orbitals in Organic chemistry!

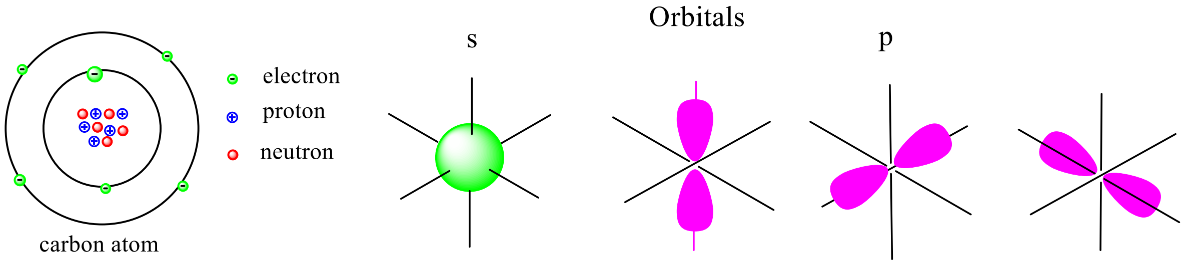


Figure 1.1

Exercise 1.1: The electron configuration of a carbon atom is $1s^22s^22p^2$, and that of a sodium cation ($Na^{\oplus}$) is $1s^22s^22p^6$. Using a periodic table, show the electron configuration for

a. a nitrogen atom
b. an oxygen atom
c. a fluorine atom
d. a magnesium atom
e. a potassium atom
f. a potassium ion ($K^{\oplus}$)
g. a chloride anion ($Cl^{\ominus}$)
h. a sulfur atom
i. a lithium cation ($Li^{\oplus}$)
j. a calcium cation ($Ca^{2\oplus}$)

1.3 Bond Formation and Ionic vs. Covalent Bonding

The elements in the second row of the periodic table are:

Group number	I	II	III	IV	V	VI	VII	VIII
Elements	**Li**	**Be**	**B**	**C**	**N**	**O**	**F**	**Ne**
Number of valence electrons	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Number of bonds	**1**	**2**	**3**	**4**	**3**	**2**	**1**	**0**

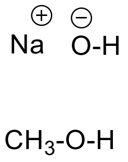
Lithium and beryllium can form positive ions by the loss of one or two electrons, respectively. Boron is in an intermediate position and its somewhat unusual bonding properties are considered later in the book. Carbon, nitrogen, oxygen, and fluorine all can form covalent bonds because each can complete its octet by sharing electrons with other atoms.

Ionic Bonds: Bonds that are formed by the complete transfer of electrons from one atom (metal) to another atom (non-metal). E.g., metallic sodium reacts with chlorine by completely transferring an electron to it to form $Na^{\oplus}$ and $Cl^{\ominus}$ which holds a crystal of sodium chloride together. Each $Na^{\oplus}$ in the crystal feels a force of attraction to each $Cl^{\ominus}$.

Covalent bonds: Covalent bond involves the 'sharing' of a pair of electrons between two atoms. These two atoms are typically both non-metals. Some examples of bonds between carbon and oxygen or carbon and nitrogen etc.
It is important to point out that the difference between an ionic versus a covalent bond is how you write the structures.

NaOH and CH_3OH may seem very similar-looking compounds, with a big difference! NaOH has an ionic bond between Na and O while CH_3OH has a covalent bond between C and O. This is important to point out especially when acid-base equilibrium will be discussed (in Chapter 2).

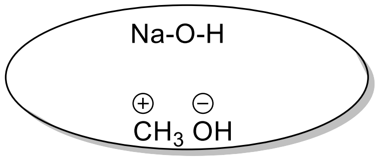
NaOH really should be written as $Na^{\oplus}\ {}^{\ominus}O\text{-}H$ (there is a formal charge on Na and O), writing NaOH as Na-O-H would be a very wrong representation. On the other hand, in CH_3OH, there is a covalent bond between $H_3C\text{-}O\text{-}H$.



$\overset{\oplus}{Na}\ \overset{\ominus}{O}\text{-}H$

$CH_3\text{-}O\text{-}H$

Correct representation of ionic (NaOH) and covalent CH_3OH bond



Na-O-H

$\overset{\oplus}{CH_3}\ \overset{\ominus}{O}H$

The two right structures are incorrect

1.4 Lewis Structure

Follow the common bonding patterns of uncharged molecules containing carbon, nitrogen, oxygen, halogen):

	C	**N**	**O**	**Halides (F,Cl,Br,I**
Valence electrons	**4**	**5**	**6**	**7**
# of bonds	**4**	**3**	**2**	**1**
# of lone pairs	**0**	**1**	**2**	**3**

Step 1: Determine the total number of valence electrons.

This process involves calculating the number of valence electrons of every atom in the molecule or ion. For a neutral molecule, this is nothing more than the sum of the valence electrons on each atom. If the molecule carries an electric charge, **we add** one electron for each negative charge or **subtract** an electron for each positive charge.

Step 2: Write the skeleton structure of the molecule. Use two valence electrons to form each bond in the skeleton structure. In Organic chemistry, hydrogen and halogen atoms tend to appear on the outside of the molecule and are rarely the central atom.

Step 3: Try to satisfy the octets of the atoms by distributing the remaining valence electrons as nonbonding electrons. **<u>Important:</u>** Octet may **<u>NOT</u>** be satisfied for positively charged species. Positive charge implies a lack of electrons!

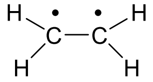
Exercise 1.2: Draw Lewis structures for the following species (use lines to denote bonds and dots for lone-pair electrons). All atoms should have a complete valence shell of electrons. For now, do not worry about showing accurate bond angles.

a. NH_3
b. $NH_4^{\oplus}$
c. $NH_2^{\ominus}$
d. CH_2CHCH_3
e. $CHCCH_3$
f. CH_3NH_2
g. CH_3CH_2OH
h. CH_3OCH_3

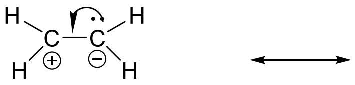
1.5 Multiple Bonding

Multiple bonds are formed when there are not enough electrons to distribute between atoms. The electrons get shared between two atoms to make a double or triple bond.

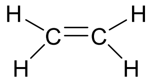
E.g. C_2H_4 has 12 valence electrons. Some suggested structures are shown below.



A Lewis structure where both the carbon's octet is not complete.



A Lewis structure where the left carbon's octet is not complete. Formal charges are indicated



A Lewis structure where both the carbon's octet is complete. There is no formal charges on any atom.

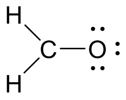
This is the most accurate Lewis structure.

Occasionally we encounter a molecule that does not seem to have enough valence electrons. If we cannot get a satisfactory Lewis structure by sharing a single pair of electrons, it may be possible to achieve this goal by sharing two or even three pairs of electrons.

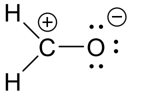
Example: Consider formaldehyde (H_2CO) which contains 12 valence electrons.

$$H_2CO: 2(1) + 4 + 6 = 12$$

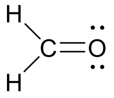
The formula of this molecule suggests the following skeleton structures.



A Lewis structure where the carbon's octet is not complete. Formal charges are not indicated



A Lewis structure where the carbon's octet is not complete. Formal charges are indicated



A Lewis structure where the carbon's octet is complete. There is no formal charges on any atom.

This is the most accurate Lewis structure.

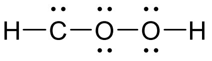
There are three covalent bonds in this skeleton structure, which means that six valence electrons must be used as bonding electrons. This leaves six nonbonding electrons. It is impossible, however, to satisfy the octets of the atoms in this molecule with six nonbonding electrons. When the nonbonding electrons are used to satisfy the octet of the oxygen atom, the carbon atom has a total of only six valence electrons.

We therefore assume that the carbon and oxygen atoms share two pairs of electrons. There are now four bonds in the skeleton structure, which leaves only four nonbonding electrons. This is enough, however, to satisfy the octets of the carbon and oxygen atoms.

Let us take another example of compounds with multiple bonds.

HCOOH has **18** valence electrons. A typical student will try to write the structure as follows:

H—C—O—O—H This structure has only considered 8 electrons. We will need to place 10 electrons as 5 lone pairs.

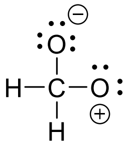
So, the student then suggests the following structure: 

$\mathrm{H{-}\ddot{C}{-}\underset{\cdot\cdot}{\ddot{O}}{-}\underset{\cdot\cdot}{\ddot{O}}{-}H}$

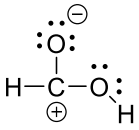
However, right away, one can see that carbon is making only two bonds and has one lone pair. Carbon's octet is not complete and wasn't carbon supposed to make 4 bonds? There are no formal charges in the molecule, so every atom should follow the octet (except hydrogen, of course!).

How can this structure be fixed to a) satisfy the octet, b) follow the common bonding pattern, and c) have no formal charge on any atom?

Let us give it another try. Just remember, carbon must make four bonds. So, the student tries one more time:

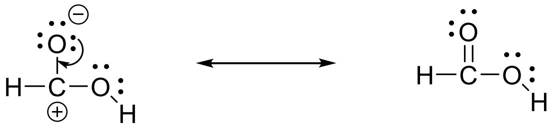


In this case, all have octets except the right oxygen. So, this must not be the correct Lewis structure either. Although formal charges are canceled out. The arrangement of the atoms must be fixed such that all atoms obey the octet. If we move the hydrogen atom to the right oxygen with the electron, the right oxygen would be happy. Let's try:



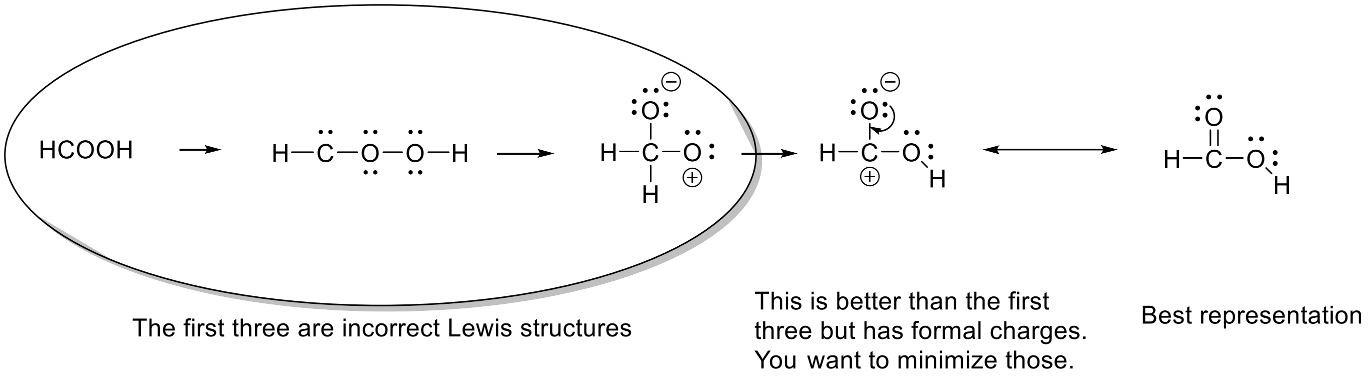
In this structure, the carbon has an incomplete octet, and the top oxygen has too many electrons. What if oxygen shares two electrons with the carbon atom? Then the net formal charge would disappear, and both will be happy with the octet! In the future, if you ever see two bonded adjacent atoms, one with a positive charge and the other with a negative one, just make a bond between the two, and that is what makes multiple bonds.

Let us try again!



Note: We will soon learn the arrow pushing in section 1.9 (resonance uses double headed arrows like shown in above picture). This will be one of the most important topics right after writing correct Lewis structures. The two structures are resonance forms, and the second structure is a better representative of the Lewis structure since we have minimized the formal charges.

So, there was some playing around we did and after several such problems, you will start to get the idea. Our overall approach was as follows:



Condensed Formulas: Deciphering What the Parentheses Means

Parentheses help in two ways. They can

1. Reduces the amount of work

$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_3$ and $CH_3(CH_2)_6CH_3$. Much less work, right?

2. Removes ambiguity.

A second use of parentheses is to reduce ambiguity. Consider a case where you have four CH_3 groups attached to a carbon. You would **NOT** write it $CH_3CH_3CH_3CH_3C$: writing it like that implies a chain, and each of those CH_3 groups can only be attached to one thing. So put the CH_3 groups in parentheses and write $C(CH_3)_4$. This has no ambiguity. An equivalent way to write the structure would be $CH_3C(CH_3)_3$.

Exercise 1.3: For the given compound/ion, draw the Lewis Dot Structure. Formal charges on each atom is **zero** unless stated otherwise.

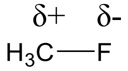
a. C_2H_6
b. NH_3
c. C_2H_4
d. $(CH_3)_3CBr$
e. $CH_3(CH_2)_2OH$
f. $CH_3CH_2COCH_2CH_3$
g. CH_3CH_2COOH
h. CH_3CHO
i. $CH_3CH_2OCH_2CH_3$
j. CH_3CH_2CCH
k. $CH_3CH_2COOCH_3$
l. CH_3CN
m. CH_2NH
n. $(CH_3)_4N^{\oplus}$
o. $(CH_3)_2CH^{\ominus}$
p. $CH_2{=}N{=}N$ (has formal charges)

1.6 Electronegativity and Bond Polarity

The degree of sharing of electrons in a covalent bond will not be exactly equal if the elements being linked are different. The relative attractive power exerted by an element on the electrons in a covalent bond can be expressed by its **electronegativity.** In one quantitative definition of electronegativity, we have an increase in electronegativity along the series toward fluorine as follows:

C	N	O	F
2.5	3.0	3.5	4.0

The electronegativity of hydrogen is 2.0, close to that of carbon. Each covalent bond between elements with different electronegativities will have the bonding electrons unequally shared between them, which leads to what is called polar character. In a carbon-fluorine bond, the pair of electrons are attracted more to the fluorine nucleus than to the carbon nucleus. The regions of space occupied by electrons are called **orbitals** and, in a molecule such as CF_4, the pair of electrons in the orbital that represents each covalent bond will not be divided equally between the carbon and fluorine but will be polarized towards fluorine.

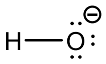


$\overset{\delta+}{H_3C}-\overset{\delta-}{F}$

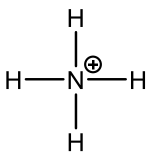
1.7 Formal Charges

Good news! In Organic Chemistry, the formal charge on an atom is it is either +1 or -1. Once you have a **correct** Lewis Structure, the formal charge can be found by a formula:

Formal Charge = # of valence electron – (# of dots + # of bonds)

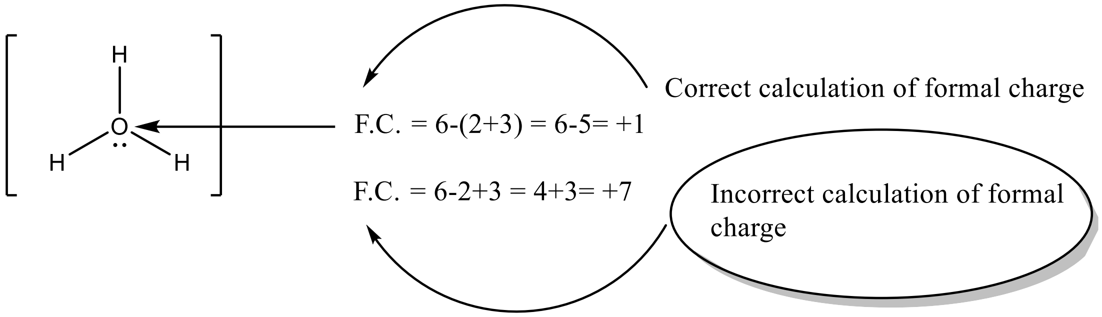


F.C. = 6-(6+1) = 6-7 = -1



F.C. = 5-(4+0) = 5-4 = +1

Note: The use of brackets in the formula is very important. If brackets are missing, your calculation would be wrong. Let's see how.



Always indicate charges inside a circle, either as ⊕ or ⊖

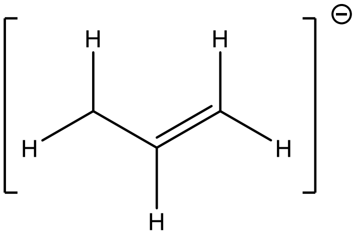
Exercise 1.4: Fill in all missing lone pair electrons and formal charges in the structures below. Net charges are shown outside the brackets. Unless the charge is positive, assume that all atoms have a complete valence shell of electrons.

a. $NO_3^{\ominus}$

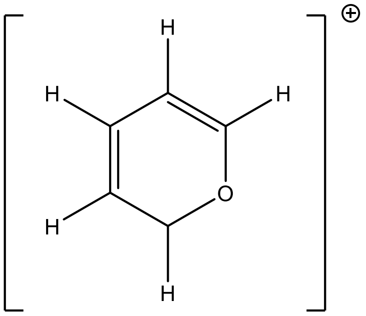
b. $PO_4^{\ominus 3}$

c. $CO_3^{\ominus 2}$

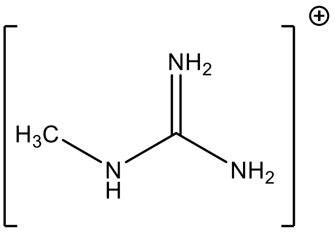
d.



e.



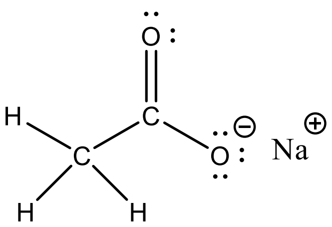
f.



1.8 Ionic Structures

Some organic compounds contain both covalent and ionic bonds. For example, the Lewis structure of sodium acetate is a combination of covalent and ionic bonds.

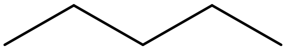
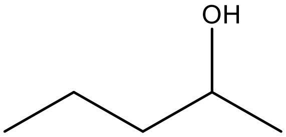
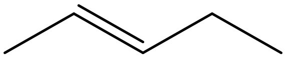
CH_3COONa is written as



The bond between oxygen and sodium is ionic in nature (like in NaOH).

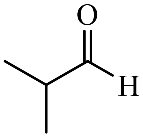
1.9 Line Formula

A line formula has no carbons or hydrogens written. Lines represent bonds, and carbon atoms are inferred at each **bend or end**. The number of hydrogen atoms is inferred based on the octet rule. Hetero atoms (atoms other than carbon and hydrogen) are always indicated. It takes practice to understand how many hydrogens are present on each of the carbon atom.

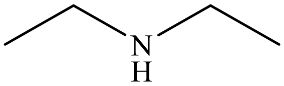
Condensed structure	Line structure
$CH_3(CH_2)_3CH_3$	
$CH_3(CH_2)_2CHOHCH_3$	
$CH_3CH=CHCH_2CH_3$	

Exercise 1.5: A good way to test your understanding of the line structure convention is to determine the number of hydrogen atoms in a molecule from its line structure. Draw out the hydrogen atom for each of the structures shown below.

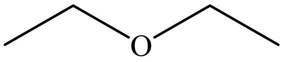
a.



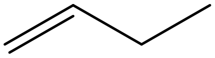
b.



c.



d.



1.10 Resonance: Principals of Arrow Pushing

Resonance is a way of describing delocalized electrons within certain molecules or polyatomic ions where the bonding cannot be expressed by one single Lewis **structure**.

- Atoms never move.
- You can **only move electrons in π bonds or lone pairs** (that are in p orbitals)
- The overall charge of the system must remain the same.
- The bonding framework of a molecule must remain intact.

Rules for drawing resonance structures

1. When you see two different resonance contributors, you are *not* seeing a chemical reaction! Rather, you are seeing the exact same molecule or ion depicted in two different ways.

2. Resonance contributors involve the ‘imaginary movement’ of pi (π) bonded electrons or of lone-pair electrons that are adjacent to (*i.e.* conjugated to) π bonds. You can *never* shift the location of electrons in sigma (σ) bonds – if you show a (σ) bond forming or breaking, you are showing a chemical reaction taking place (see rule # 1). Likewise, the positions of *atoms* in the molecule cannot change between two resonance contributors.

3. All resonance contributors for a molecule or ion must have the same *net* charge.

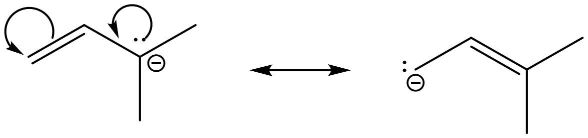
4. All resonance contributors must be drawn as proper Lewis structures, with correct formal charges. Never show curved 'electron movement' arrows that would lead to a situation where a second-row element (i.e. carbon, nitrogen, or oxygen) has more than eight electrons: this would break the 'octet rule'. Sometimes, however, we will draw resonance contributors in which a carbon atom has only six electrons (i.e. a carbocation). In general, all oxygen, nitrogen and halogens should have a complete octet of valence electrons.

Techniques for drawing resonance structure systematically.

Step 1: Always draw out the electron pairs!
Step 2: Draw the correct number of hydrogens on each carbon, so you don’t “accidentally” exceed the octet of the carbon (at least do that until you come comfortable with the line formula).
Step 3: The movement of the arrow is always from **electron-rich** species (lone pairs or pi (π) bonds.

How you use curved arrows to draw different resonance structures will depend upon whether a positive charge or negative charge is being delocalized. Shown below are different scenarios.

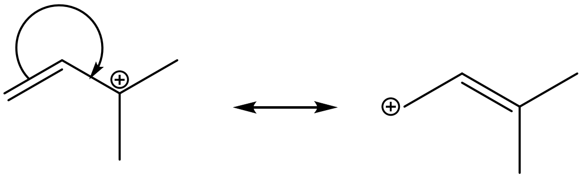
Scenario 1: When there is a lone pair (hence a negative charge) next to the pi (π) bond.
“Lone pairs become pi bonds and pi bonds become lone pairs”



Check to see if this option can be performed again.

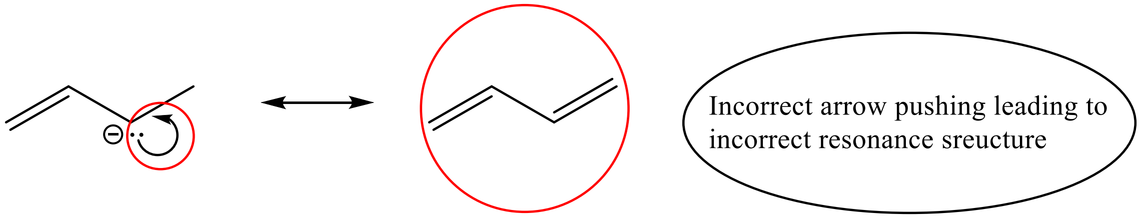
Scenario 2: When there is a pi (π) bond next to a positive charge

“Fill a hole (positive charge) and create a new hole”

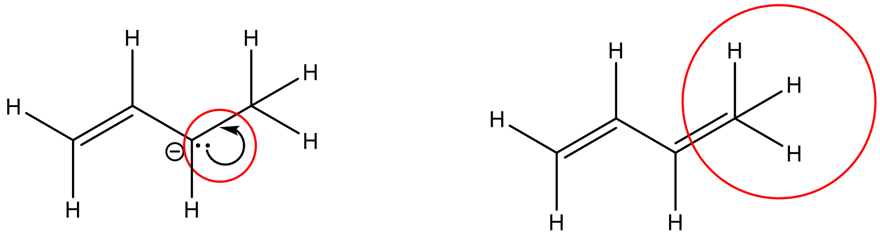


“Fill a hole (positive charge) and create a new hole”

Common mistake: If one is not paying attention to the number of hydrogen atoms on each carbon, it is easy to make 5 bonds on the carbon atom.

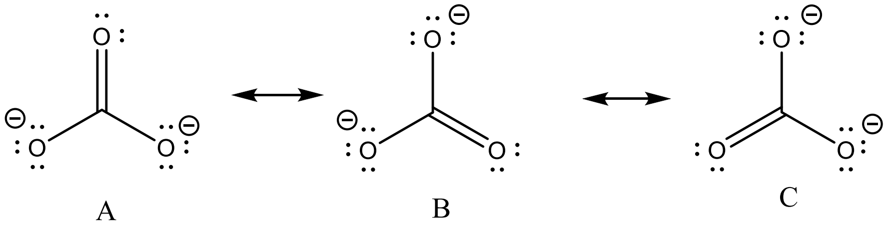

Incorrect arrow pushing leading to incorrect resonance sreucture

Why is the structure on the right incorrect? After placing the correct number of hydrogen atoms on every carbon, do you see why this arrow pushing would be incorrect? It would lead to the right carbon having 5 bonds (is it possible? Octet on carbon can NEVER be exceeded).



Consider the Lewis structure of the carbonate ion, CO_3^{2-}. The Lewis structure for this ion has a carbon-oxygen double bond, and two carbon-oxygen single bonds. Each of the singly bonded oxygen atoms bears a formal charge of 1^-. (Review the formal charge if needed.). But which of the three oxygens forms the double bond? There are three possibilities:

The negative charge is delocalized to all three oxygens



⟷ *double-headed resonance arrow is used going from one resonance structure to another.*

These structures are similar in that they have the same types of bonds and electron positions, but they are not identical. The position of the carbon-oxygen double bond makes them different. In structure **A,** the double bond is with the top oxygen atom, in **B** with the right-hand oxygen atom, and **C** with the left-hand oxygen atom. These oxygen atoms are at different places in space, so these are different structures.

It is very important to be clear that in drawing two (or more) resonance contributors, we are not drawing two different molecules: they are simply *different depictions of the exact same molecule*.

Furthermore, the double-headed resonance arrow does NOT mean that a chemical reaction has taken place.

Arrow pushing during resonance. The movement of arrow is always from an **electron rich** species to **electron deficient** species.

1. Let us first look at the **wrong arrow pushing** which are highlighted in red font in (Figure 1)

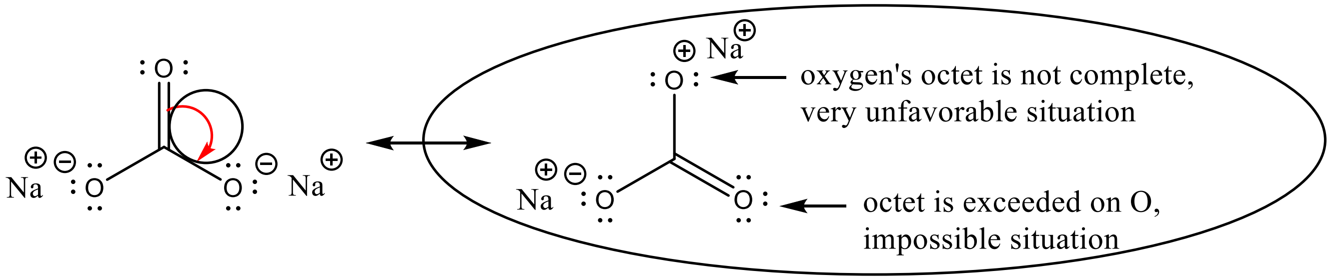


Figure 1. Resonance forms of Sodium Carbonate (Incorrect Arrows)

If you were moving arrows in that direction (shown above), wouldn't you be exceeding the octet on the oxygen?

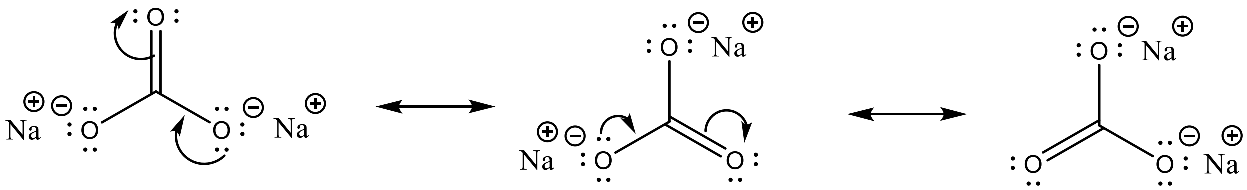


Figure 2. Resonance forms of Sodium Carbonate (Corrected Arrows)

2. For positive charges, use lone pairs or pi bond and create a new pi bond to fill the hole (positive charge).

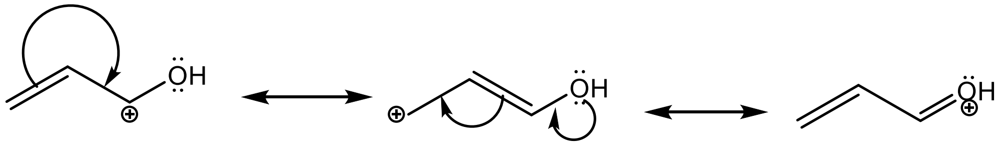
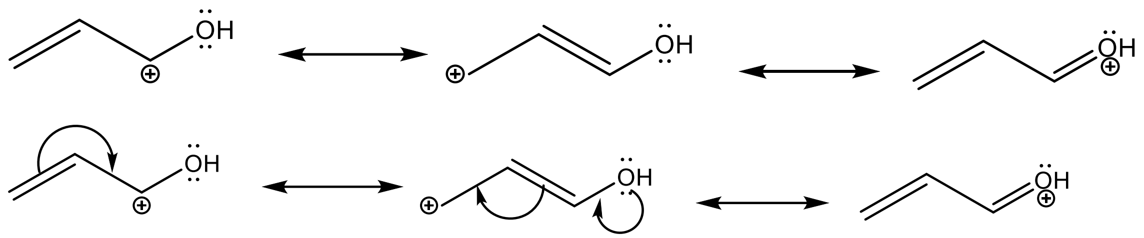


Figure 3. Arrow pushing for cations (positive charges)

Predicting major resonance contributing structures: To predict major resonance contributing structure, use the following criteria beginning with the most important.

1. **As many octets as possible (valid for positive charge only).**
2. **As many bonds as possible.**
3. **As little charge separation.**
4. **Any negative charge on electronegative atoms (only for negative charges)**

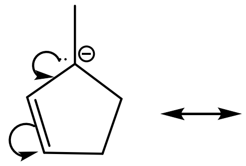


I II III

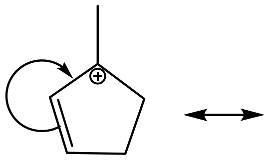
Which is the major resonance contributing structure here? Structure I and II have positive charge on the carbon atom that has three sigma bonds (recall, in line formula, hydrogen atoms are not explicitly drawn) hence carbon's octet is not complete. In structure III, oxygen has a positive charge, however oxygen's octet is complete. Structure III will be **major** as all atoms have octet complete.

Exercise 1.6: Draw the resonance contributors that correspond to the curved, two electrons movement arrows in the resonance expressions below.

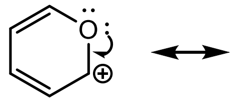
a.



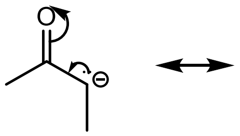
b.



c.

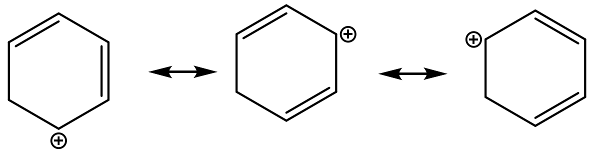


d.

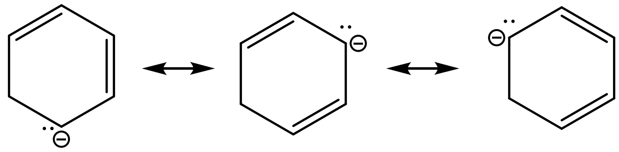


Exercise 1.7: For the following resonance structures drawn, provide the arrows that are required to go from one structure to the other. **If** there is any major resonance contributing structure, circle it. Explain why it is a major form.

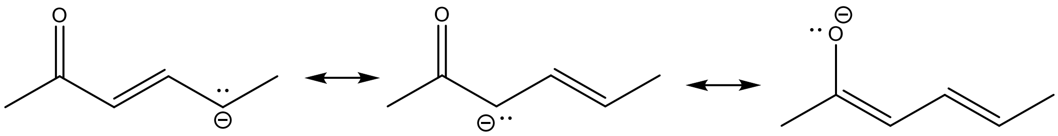
a.



b.

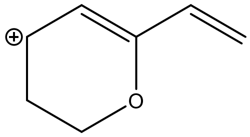


c.

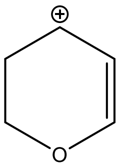


Exercise 1.8: **<u>Using curved arrows</u>**, write **all** important resonance structures of the species shown below. **If** there is any major resonance contributing structure, circle it. Explain why it is major.

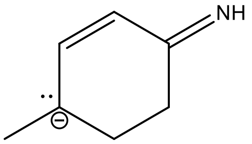
a.



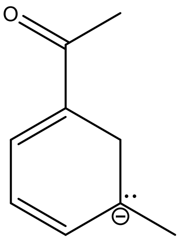
b.



c.

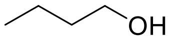


d.

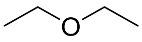


1.11 Molecular Formula

A molecular formula simply gives the number of atoms of each element in one molecule of the compound. For example: a compound having a molecular formula $C_4H_{10}O$ can have many possible structures. Two compounds are drawn below with the same formula. The only thing common between them is their molecular formula. They are also called structural isomers (more in section 1.19).



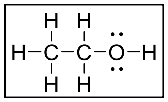
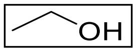
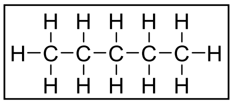
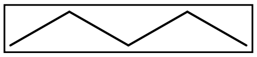
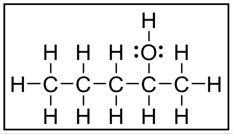
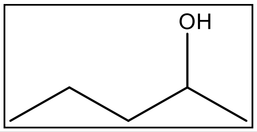
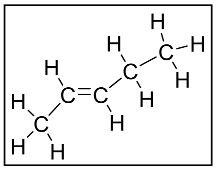
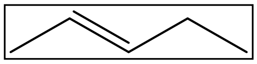
$C_4H_{10}O$



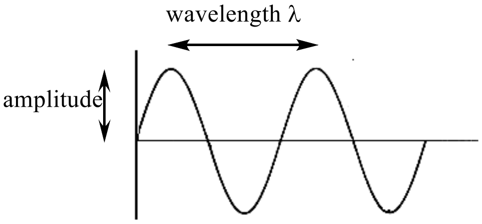
$C_4H_{10}O$

1.12 Structural Formula

Structural formula shows which atoms are bonded to other atoms. Structural formula can be represented as Lewis structure (as discussed in section 1.4), where bonding pairs are represented by dash (—) and lone pairs as a pair of dots. Condensed structure (formula does not show all individual bonds. And line formula is represented by stick like figures where every end and every bend is a carbon that is not explicitly drawn and neither are the hydrogens.

Lewis Structure	Condensed structure	Line structure
	CH_3CH_2OH	
	$CH_3(CH_2)_3CH_3$	
	$CH_3(CH_2)_2CHOHCH_3$	
	$CH_3CH{=}CHCH_2CH_3$	

1.13 Wave Properties of Electrons



The orbitals (*s* and *p*) can be described by their wave function ψ which is a mathematical description of the shape of the waves as it vibrates. There is a positive amplitude and a negative amplitude. The electron density at any point is given by ψ^2. The plus sign and minus sign of these waves are **not** charges, but the phase of the constantly changing wave function.

An orbital is a region of space where the probability of finding an electron is high. All s orbitals are spherical. All p orbitals are shaped like dumbbells with a nodal plane separating the two lobes of a p-orbital, and the three p orbitals of a given energy level are arranged along the x, y, and z axes.

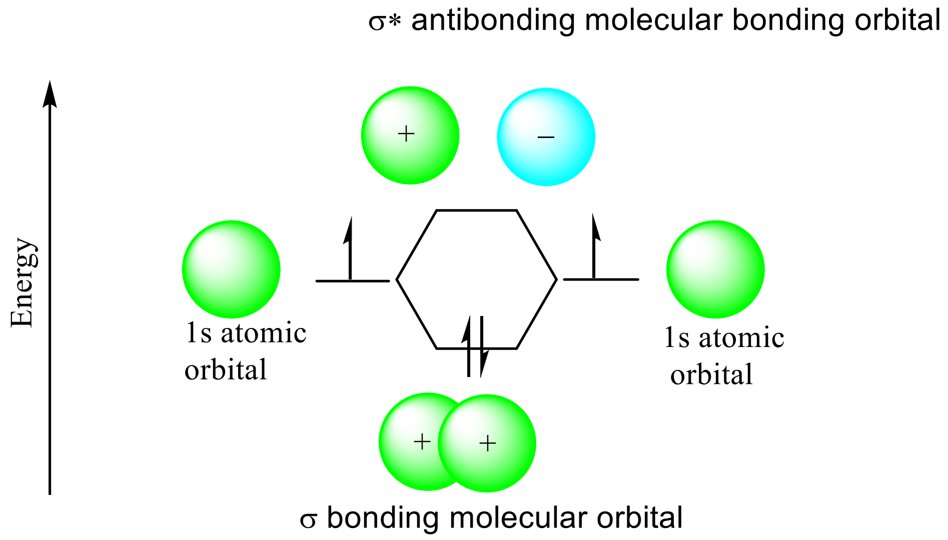
Linear combination of atomic orbitals (LCAO) can take place two possible ways:

1. When orbitals of **different** atoms interact, they produce molecular orbitals (MOs) that can lead to bonding or antibonding (*) molecular orbitals. Two atomic orbitals will generate 2 molecular orbitals.
2. When the orbitals on the **same** atom interact, they result in hybrid atomic orbitals that defines the geometry of the bonds (more in section 1.16)

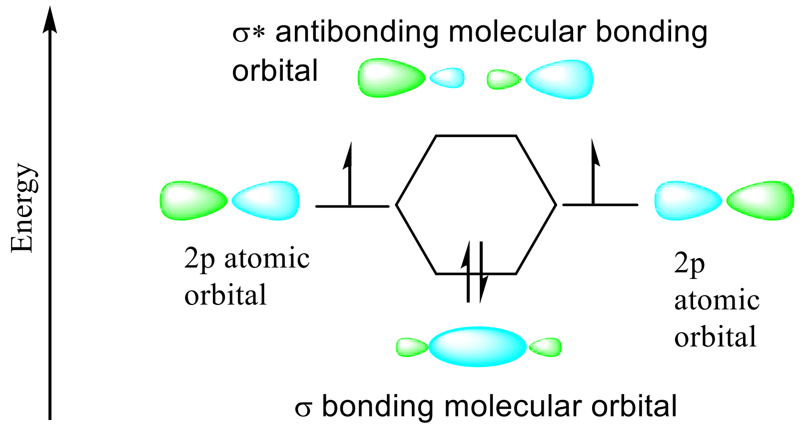
1.14 Molecular Orbital

When the orbitals with the same phase sign interact, constructive overlap takes place and reinforces the amplitude of the resultant wave which results in bonding MO. When orbitals with opposite phase signs interact, destructive overlap takes place and subtract the amplitude of the resultant wave which results in antibonding (*) MO.

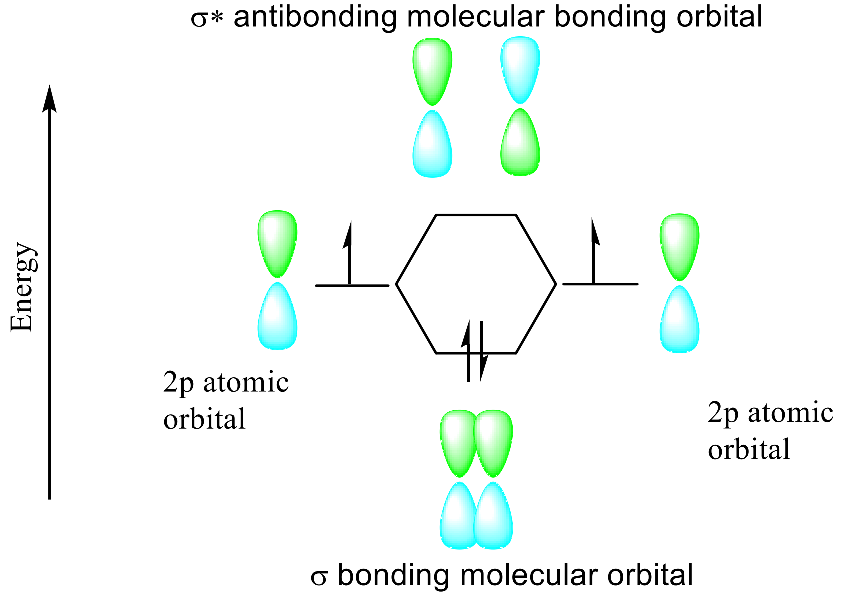
Overlap of s orbitals: The above picture shows sigma bonding in the hydrogen molecule due to the overlap of two atomic s orbitals of each hydrogen atom. When the orbitals overlap constructively give σ bonding MO, and when they overlap destructively give σ* antibonding MO.



Head-on overlap of p-orbitals: Figure below shows two possible ways p orbitals can overlap to give either σ bonding MO or σ* antibonding MO.

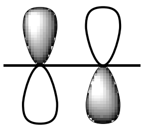


Sideways overlap of p-orbitals: When two parallel p orbitals overlap sideways, they give rise to pi (π) bonds. When the orbitals overlap sideways constructively give π bonding MO, and when they overlap destructively give π* antibonding MO.



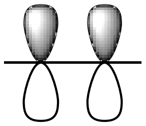
Exercise 1.9: For each of the orbital overlap shown below, what type of bond is formed? σ, σ*, π or π*.

a.



b.

c.



d.

1.15 Hybridization and Molecular Shapes, Geometry

Hybridization is the concept of **mixing** of atomic orbitals of an atom into new hybrid orbitals (with different energies, shapes than the component atomic orbitals) suitable for the pairing of electrons to form chemical bonds in valence bond theory. Since the mixing of the orbitals takes place of an atom, **Hybridization is always talked about an atom (not a molecule)**.

<u>Most important</u>: Before trying to figure out hybridization of an atom, draw CORRECT Lewis dot structure.

Hybridization can be calculated based on Steric number, which belongs to an atom (not a molecule), which means we will be talking about hybridization of an atom. Note: Hydrogen atom do not hybridize.

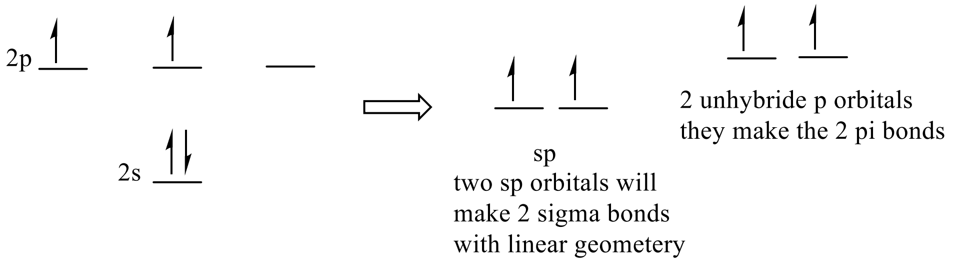
Steric Number (SN #) = # of sigma bonds + lone pairs

Steric Number (SN)	Hybridization	Geometry	Lone pairs	Shape	Bond Angle (approx.)	# of pi bonds
2	**s+p= sp**	**Linear**	**N/A**	**Linear**	**180°**	**2**
3	**s+p+p= sp2**	**Trigonal planar**	**0**	**Trigonal planar**	**120°**	**1**
			1	**Bent**		
4	**s+p+p+p= sp3**	**Tetrahedral**	**0**	**Tetrahedral**	**109.5°**	**0**
			1	**Trigonal pyramidal**		
			2	**bent**		

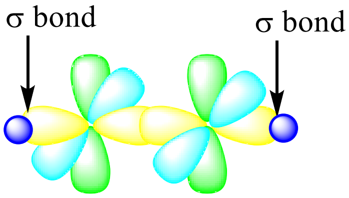
sp (SN = 2, electron geometry = linear)

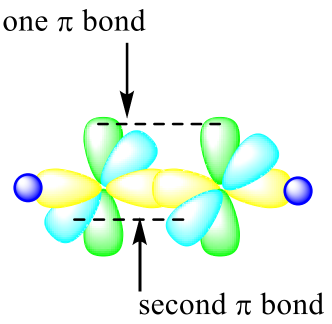
sp hybridization is made up of a single s orbital and a single p orbital, leaving 2 p orbitals unhybridized (that will be responsible for making the pi bond). Since electrons reside in these two sp orbitals, they want to be far away from each other, hence the expected linear geometry.

Let us look at carbon.



There are only 2 unpaired electrons in the hybridized orbitals, indicating the formation of 2 σ bonds. The 2 unpaired electrons in the 2p orbital indicate the formation of 2 π bonds. These π bonds are going to be 90 ° to each other and 90 ° to the σ bonds. Overall, each carbon is forming 4 bonds.





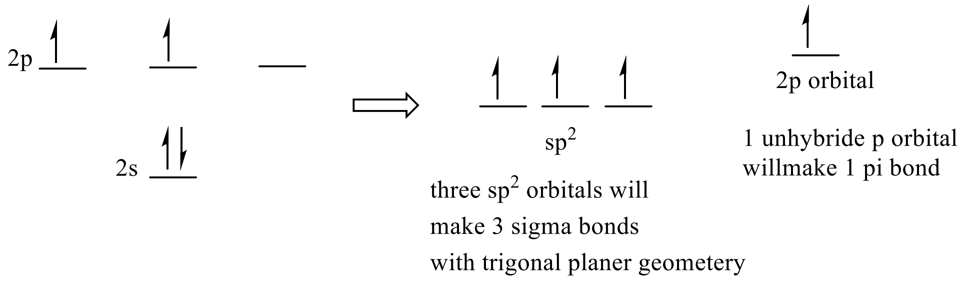
$H-C\equiv C-H$

The yellow orbitals lie 180° from each other (the sp orbitals). The green and light blue orbitals are the non-hybrid p orbitals responsible for making the pi (π) bond and lie 90° from each other and are not hybridized (p orbitals). As there is both one σ and a two π bond, these carbons are connected by a triple bond.

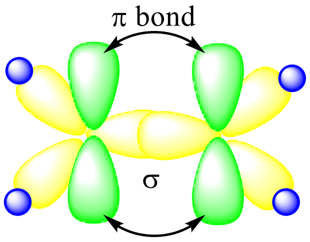
sp^2 (SN = 3, electron geometry = trigonal planar)

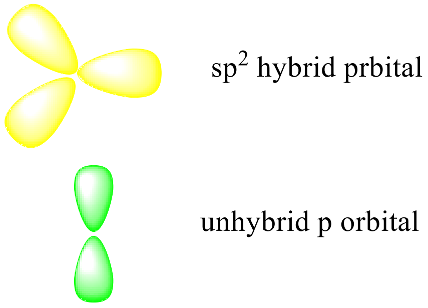
sp^2 hybridization is made up of a single s orbital and two p orbital, leaving one p orbitals unhybridized (that will be responsible for making the pi bond). Since electrons reside in these two sp^2 orbitals, they want to be far away from each other, hence the expected trigonal planer geometry.

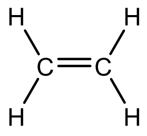
Let us look at carbon.



There are only 3 unpaired electrons in the hybridized orbitals, indicating the formation of 3 σ bonds. The 1 unpaired electron in the p orbital indicate the formation of 1 π bond. This π bonds is going to be 90° to the σ bonds. Overall, carbon is forming 4 bonds.



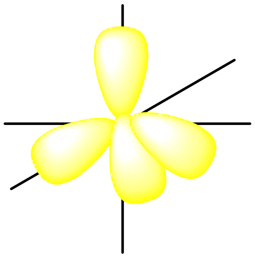




The yellow sp^2 orbitals lie 120° from each other. The green orbital is the un hybrid p orbital responsible for making the pi (π) bond. The π bond between the two carbon atoms is green. The σ bonds from carbon are along the yellow lobes, bonding to the 1s orbital of hydrogen. As there is both a σ and a π bond, these carbons are connected by a double bond.

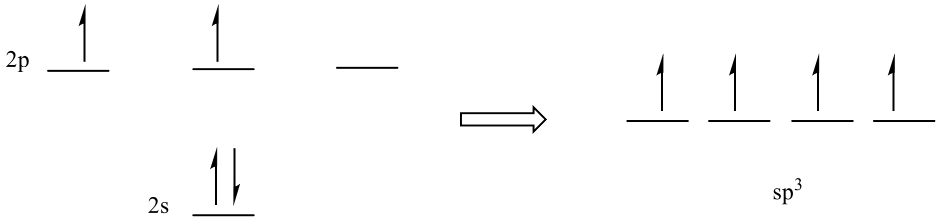
sp^3 (SN = 4, electron geometry = tetrahedral)

sp^3 hybridization is made up of one s orbital and all three p orbitals



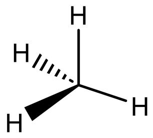
Each lobe lies at 109.5 ° to the others and can form a σ bond or contain a lone pair.
Let us look at carbon.

Electron configuration for C is $1s^2 2s^2 2p^2$. So, we're looking at 4 valence electrons.
Since we're dealing with sp^3 orbitals, we use the s orbital and the 3 p orbitals to form sp^3.



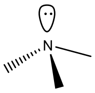
four sp^3 orbitals will
make 4 sigma bonds with
tetrahedral geometery

There are 4 unpaired electrons in the sp^3 orbital from carbon, indicating the formation of *4 σ bonds*. An sp^3 hybridized carbon will therefore have 4 σ bonds (carbon forming 4 bonds total). These may come from other elements (of various hybridization), but an easy way to visualize this is with CH_4.



As each bond is only a single σ bond, there are only single bonds present in this molecule. **There can be no pi bonds on a carbon that is sp3 hybridized.**

<u>Geometry/Shape</u>: Once you know the Steric Number and Hybridization, the geometry can be easily found. To find geometry, include the lone pairs; do not include the lone pairs for shapes. E.g. NH_3 has three sigma bonds and a lone pair:



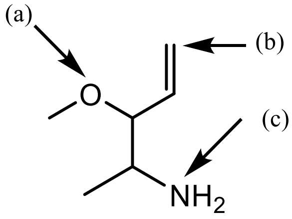
It has a tetrahedral <u>geometry</u> and a trigonal pyramidal <u>shape</u>.

Exercise 1.10: For the given compound/ion

A. Draw the Lewis Dot Structure. Formal charges on each atom is **<u>zero</u>**.
B. Hybridization (sp, sp^2, sp^3) across the central atom (or <u>underlined</u> atom)
C. Find the <u>shape</u> of the compound/ion (pyramidal, tetrahedral, bent etc.) across the atom that is <u>underlined</u>)

a. $\underline{C}_2H_6$
b. $CH_3(CH_2)_2\underline{O}H$
c. $\underline{C}_2H_4$
d. $(CH_3)_3\underline{C}Br$
e. $CH_3\underline{C}HO$
f. $CH_3CH_2\underline{C}OCH_2CH_3$
g. $CH_3CH_2\underline{C}OOH$
h. $CH_2\underline{N}H$

Exercise 1.11: For the line formula given below, indicate the hybridization of each of the atom indicated. Place lone pairs on N and O to answer those questions. Recall, in line formula, hydrogen atoms are not explicitly drawn.



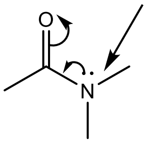
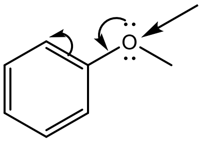
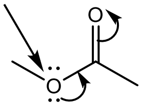
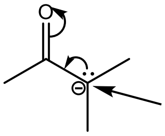
(a): ______ (b): ______ (c): ______

1.16 Important Exception to Hybridization in Organic Chemistry

Any time lone pairs are capable of resonance, the lone pairs reside in non-hybrid p-orbitals that changes the geometry of that atom. If the expected hybridization was sp^3, the actual would be sp^2. If the expected hybridization was sp^2, the actual would be sp (or one less than expected).

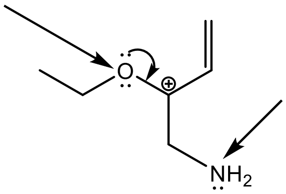
Scenario # 1: Lone Pairs Adjacent to Pi-bonds

The main exception is for atoms bearing lone pairs that are adjacent to pi bonds. Lone pairs adjacent to pi-bonds (and pi-systems) tend to be in non-hybridized p orbitals, rather than in hybridized sp^2 or sp^3 orbitals. When a nitrogen that you might expect to be trigonal pyramidal sp^3 is adjacent to a pi bond, its hybridization is sp^2 (trigonal planar). This is due to the ability of lone pairs that are capable of resonance,

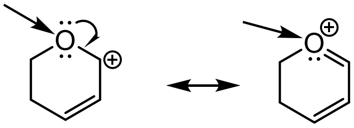
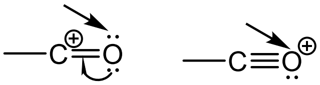
	Expected Hybridization	Actual Hybridization
	sp3	sp2
	sp3	sp2
	sp3	sp2
	sp3	sp2

Scenario #2: Lone Pairs Adjacent to a Positively Charged Carbon:

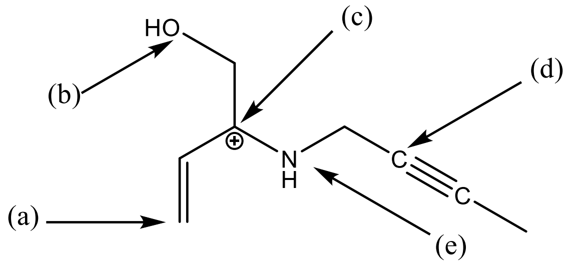
When atoms having lone pairs are next to a positively charged carbon atom (whose octet is not satisfied), the lone pairs can be involved in resonance to satisfy the octet by making a pi bond.


Lone pair on O is capable of resonance so the actual hybridization sp^2 (not sp^3)

lone pair is not capable of resonance, so N remains sp^3

	Expected Hybridization	Actual Hybridization
	sp^3	sp^2
	sp^2	sp

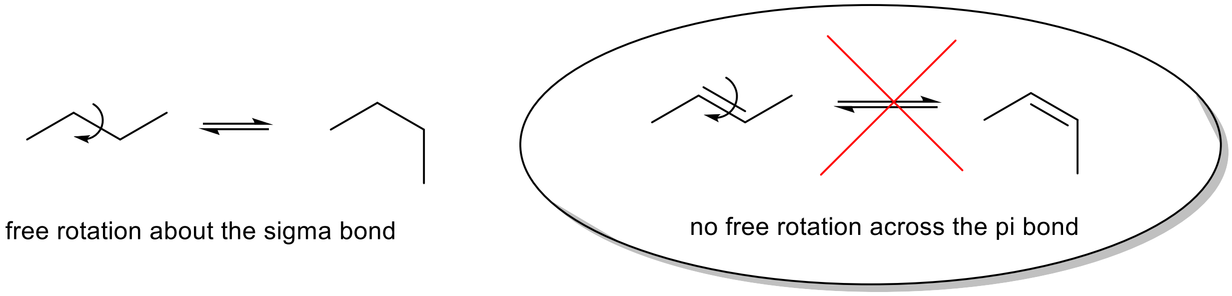
Exercise 1.12: For the line formula given below, indicate the hybridization of each of the atom indicated. Place lone pairs on N and O to answer those questions.



(a): ___ (b): ___ (c): ___ (d): _____ (e): ___

1.17 Bond Rotation

In sp^3 hybridized atom like carbon, there are only sigma bonds. There is free rotation that requires very little energy. Double (and triple) bonds have pi bonds that are rigid. At room temperature, there is no free rotation about the pi bond. If there is a rotation the p orbitals will not overlap



free rotation about the sigma bond

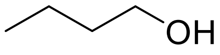
no free rotation across the pi bond

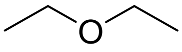
In pi bond, the rotation would disrupt the overlap of the p orbitals. The right two molecules are isomers whereas the left two are conformers (identical, for all practical purposes).

1.18 Isomerism

Isomers are compounds that have the same molecular formula but are different. In chapter 5, we will discuss many more types of isomers, but for now, there are the following two broad categories: structural (constitutional) isomers and stereoisomers.

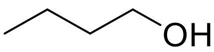
Structural Isomers: Compounds that have same molecular formula but differ in their bonding sequence. The only thing common to them is the molecular formula. For example, the two molecules with formula $C_4H_{10}O$ are drawn below:

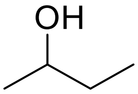




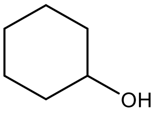
These two compounds have same formula, but the connectively of atoms is different.
Two other examples are shown below. Both have same formula, but they have different connectivity. The arrangements of atom are different.

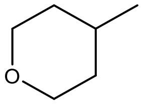
e.g.





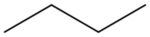
e.g.

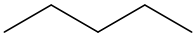




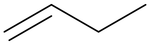
Exercise 1.13: Which of the following pairs are structural isomers?

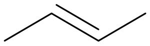
a.



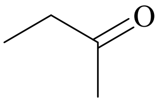


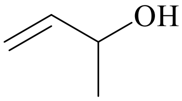
b.



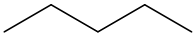


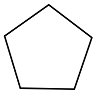
c.



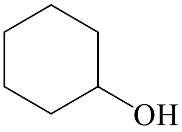


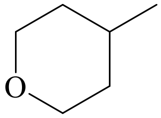
d.



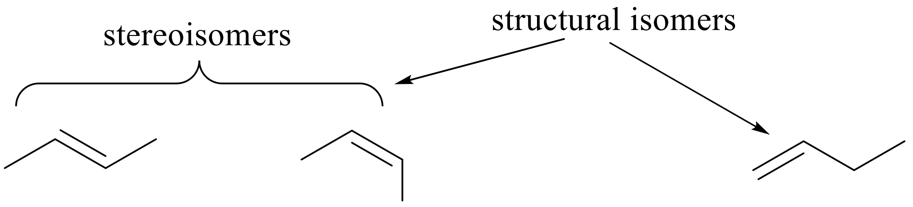


e.





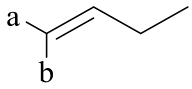
Stereoisomers: Compounds that have same molecular formula, same connectivity but different orientation in space are stereoisomers. *Cis*- and *trans*- isomers are examples of stereoisomers. There are other examples that will be discussed in chapter 5.



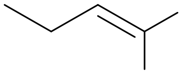
trans-but-2-ene *cis*-but-2-ene but-1-ene

Cis and *trans* isomers are also called geometric isomers because they differ in the geometry of the groups on the double bond.

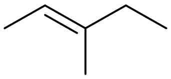
For a molecule to exhibit as cis or trans compound, there must be two different groups on **<u>each</u>** end of the double bond.



if a=b, the compound can not exist as *cis/trans*



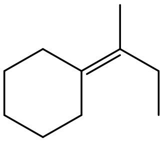
The right carbon that is doubly bonded has two identical -CH_3 groups. Therefore, this molecule cannot exist as *cis/trans*.



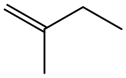
On each of the carbon that is doubly bonded, there are two different groups. The left carbon has -H and -CH_3 group attached to it while the right carbon has -CH_3 and -CH_2CH_3 groups attached to it. Therefore, this molecule can exist as cis/trans.

Exercise 1.14: Which of the following compounds show cis/trans isomerism?

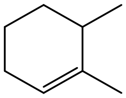
a.



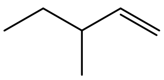
b.



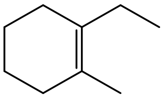
c.



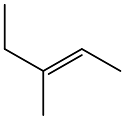
d.



e.

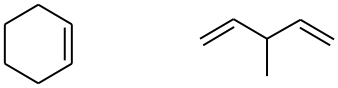


f.



Exercise 1.15: Which of the following best describes the relationship between the two structures shown? Choose from <u>stereoisomers</u>, <u>structural isomers</u>, <u>identical</u> or <u>not isomers</u>.

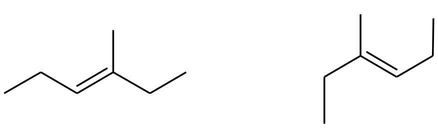
a.



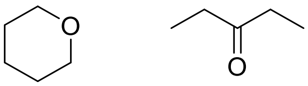
b.

c.

d.



e.

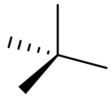


Chapter 2: Acids and Bases; Functional Groups

2.1 Polarity of Bonds and Molecules

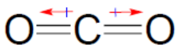
Bond polarity can range from non-polar covalent, polar covalent to totally ionic. If an electronegativity difference exists between two bonded atoms, and they are not large enough to produce an ionic bond, the electrons are not shared equally and produce a polar covalent bond. If there is a partial charge (δ+ or δ-) on an atom, the molecule ends up having a dipole moment. A molecule with a dipole moment is known as a polar molecule. The direction of polarity of a polar bond can be symbolized by +⟶ with the cross being the positive end and the arrowhead being the partially negative end. A molecule can have polar covalent bonds and still be nonpolar due to symmetry in its molecular geometry.

To understand molecular dipole moment, the 3D structure of a molecule must be understood. In organic chemistry, we will only focus on 3 types of hybridization, sp (linear geometry), sp^2 (trigonal planar geometry), and sp^3, tetrahedral geometry. While the former two can be easily drawn on paper, as they are on the plane of the paper, tetrahedral geometry is 3 dimensional and must be represented as follows:

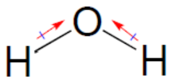


In this notation, two bonds are drawn in the plane of the page (sticks), one bond is drawn coming toward you, out of the page (wedged, ▬), and one bond is drawn going away from you, behind the page (dashed, ⋯).

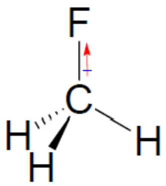
Most molecules contain both polar and nonpolar covalent bonds. Depending on the location of polar bonds and bonding **geometry**, molecules may possess a net polarity, called a **molecular dipole moment**. As you probably recall, water has a dipole moment resulting from the combined dipoles of its two oxygen-hydrogen bonds. The following examples show the molecular dipole moment is affected by the 3D structure of the molecules.



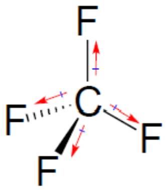
zero dipole moment



non-zero dipole moment



non-zero dipole moment



zero dipole moment

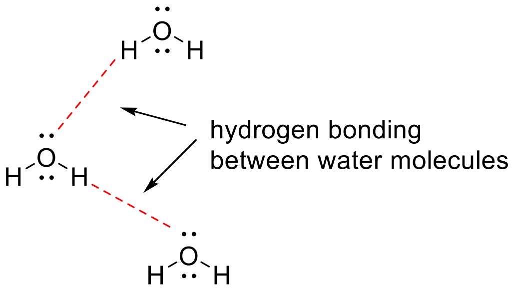
2.2 Intermolecular Forces

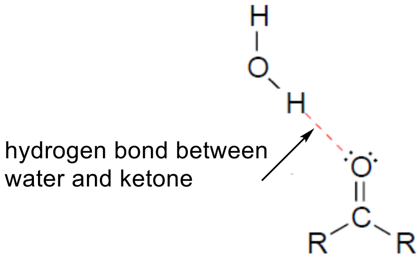
Attractions between molecules are particularly important liquids. In this phase, the molecules are continuously in contact with each other. The boiling points roughly indicate the strength of intermolecular forces, because those forces must be overcome to boil the compound. There are three types of intermolecular forces that affect the boiling points and solubilities of organic compounds

1. the "hydrogen bonds" that link molecules having — OH or — NH groups.
2. the dipole-dipole forces of polar molecules
3. the London dispersion forces that affect all molecules.

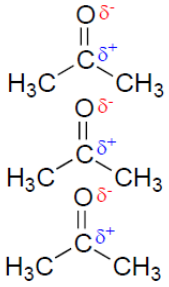
Higher the intermolecular forces, the higher the boiling point of the liquid.

A hydrogen bond is the strongest Intermolecular Force (IMF) that results from the interaction between a hydrogen bonded to an electronegative heteroatom, specifically nitrogen or oxygen, and a lone pair of electrons on nitrogen or oxygen, of a neighboring molecule or functional group. In a polar bond, a hydrogen atom can form a strong interaction with a lone pair on a **neighboring** electronegative atom. Hydrogen bonds are the strongest intermolecular forces but are still considerably weaker than covalent bonds.



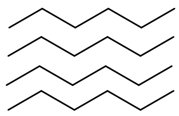


Dipole-Dipole is due to a permanent dipole moment resulting from a nonuniform distribution of bonding electrons in polar molecules. Polar molecules that have an overall dipole moment, can align themselves in such a way as to allow their respective positive and negative poles to interact with each other.

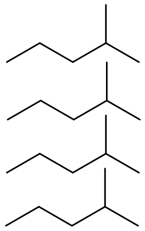


London dispersion forces (also called Van der Waals forces) are the weakest IMF. London dispersion forces result from the constantly shifting electron density in any molecule. Even a nonpolar molecule will, at any given moment, have a weak, short-lived dipole. This temporary dipole will induce a neighboring nonpolar molecule to develop a corresponding temporary dipole of its own, with the result that a temporary dipole-dipole interaction is formed. These London dispersion **forces** are relatively weak but constantly form and dissipate among closely packed **nonpolar molecules**.

A higher molecular weight increases boiling point because there is higher energy needed to reach necessary velocities and because there is more surface area. Molecules that are longer and flatter (long chains) have more surface area and thus have larger dispersion forces.



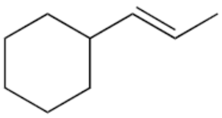
larger srface contact area
(stronger IMF)



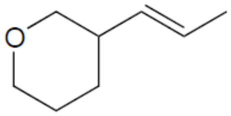
smaller srface contact area
(weaker IMF)

Exercise 2.1: Classify the structures below as (a) capable of participating in hydrogen bonding, (b) capable of dipole-dipole interactions (c) capable of only London dispersion forces.

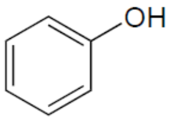
(a)



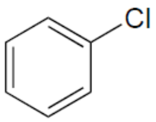
(b)



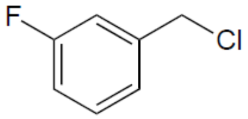
(c)



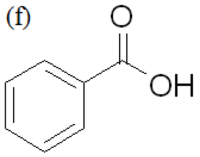
(d)



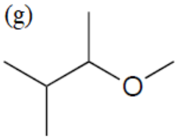
(e)



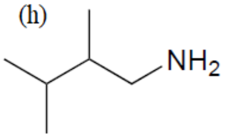
(f)



(g)



(h)



Exercise 2.2: Rank the following compounds in the order of increasing boiling points. Compound with the lowest boiling point first.

$CH_3CH_2OCH_2CH_3$ $CH_3CH_2OCH_3$ $CH_3CH_2CH_2CH_3$ $CH_3CH_2CH_2CH_2NH_2$

2.3 Polarity Effects on Solubility

"Like dissolves like"
Hydrophobic means incompatible with water while hydrophilic means compatible with water. Polar compounds will dissolve in polar solvents and non-polar compounds in non-polar solvents. Hydrocarbons (compounds containing only carbon and hydrogen) are hydrophobic and are not soluble in water (which is polar). The hydrophobic effect is when a hydrocarbon chain, for

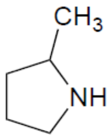
instance, with a large hydrophobic portion does not dissolve in a polar solvent even though it has a hydrophilic functional group like -OH

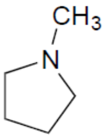
With soaps and detergents, there is a long hydrophobic chain with a strong hydrophilic group at the end of the chain. The long chain embeds itself in the oily layer of what we wash while the hydrophilic ion portion attracts the polar water molecules.

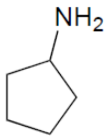
Compounds with one to three carbon atoms are water soluble if the compound has only one hydrophilic group. Compounds with four to five carbons are borderline, and compounds with six or more carbons are insoluble in water.

Exercise 2.3: Rank the set of three compounds below according to their solubility in water (least soluble to most)

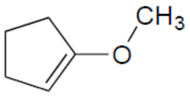
a)

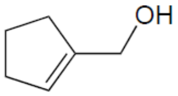


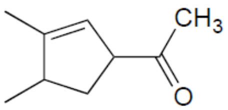




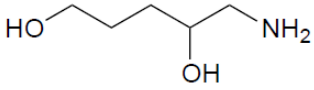
b)

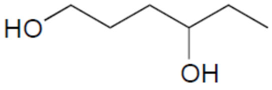


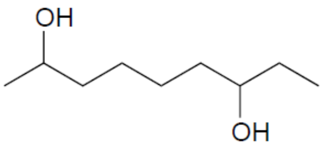




c)







2.4 Brønsted Lowry Acids and Bases

Brønsted-Lowry acid-base reactions involve the transfer of protons ($H^{\oplus}$)

A Brønsted-Lowry acid is a substance that can donate a proton - Proton Donor is Acid (**PDA**)
A Brønsted-Lowry base is a substance that can accept a proton - Proton Acceptor is Base (**PAB**)
When an acid loses a $H^{\oplus}$, the molecule or ion that forms are its conjugate base
When a base accepts a $H^{\oplus}$, the molecule or ion that forms are the conjugate acid

The conjugate base of H_2O is $HO^{\ominus}$ The conjugate acid of H_2O is $H_3O^{\oplus}$

Exercise 2.4: Draw the conjugate base of the following molecules/ions:

a. NH_3 b. CH_3OH c. $[CH_3NH_3]^{\oplus}$ d. $H_3O^{\oplus}$

Exercise 2.5: Draw the conjugate acid of the following molecules/ions:

b. NH_3 b. CH_3OH c. $CH_3CH_2^{\ominus}$ d. H_2O

2.5 Electron Stabilizing Forces (PRECHI)

Six electron stabilizing forces that determines the species as acid or base. These are listed in the order of importance.

1. **P**o- polarizability (the bigger the electron cloud, the more stable the electrons)
2. **R**e- resonance (more resonance structures give greater stability)
3. **E**l- electronegativity (the more electronegative, the more stable)
4. **C**h- charge (uncharged is more stable than charged)
5. **H**y- hybridization (only for carbon- the more s in the orbital the more stable)
6. **I**e- inductive effects (dipoles pull electron density **away** (only) spreading the electrons out and making them more stable)

In short, use **PRECHI*** to determine the relative strengths of acids or bases.

***This general trend is not always perfectly applicable. However, it is usually a very good indicator of acidities.**

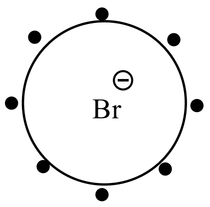
Problem-Solving Tips:

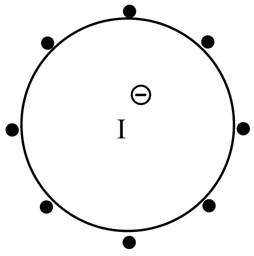
For Acids: Acids don't have electrons, so draw the conjugate base of both acids. Look at the stability of electrons on the conjugate base. More stable the electrons on the conjugate base, weaker the base and stronger the corresponding acid.

For Bases: Look at the electrons on the basic atom. The more stable the electrons on the basic atom, the less reactive (the weaker) the base.

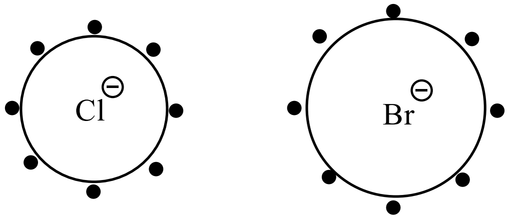
1. **Polarizability (Po)** applies to only elements in row three or higher rows. The bigger the electron cloud, the more stable the electrons on the atom)

If you are asked, which is a stronger acid H-Br or H-I? Firstly, draw the conjugate base (CB) of both. CB of H-Br is $Br^{\ominus}$, CB of H-I is $I^{\ominus}$. The size of I is larger than the size of Br. Since electrons are farther apart in $I^{\ominus}$, the electrons are more stable on $I^{\ominus}$, hence H-I is a stronger acid. <u>*More stable the electrons on the CB, the stronger the acid.*</u>





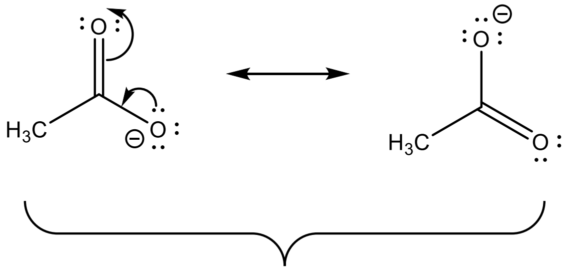
If you are asked, which is more basic, $Cl^{\ominus}$ or $Br^{\ominus}$? Since we are looking at the basicity, simply look at the electrons on basic atom. Cl and Br are in different rows so there is a difference in their size, Br being in row 4 so larger size.



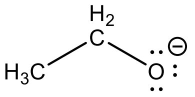
Since electrons on $Br^{\ominus}$ are farther apart, the electrons are more stable. Electrons on $Cl^{\ominus}$ are less stable therefore $Cl^{\ominus}$ is a stronger base due to SMALLER polarizability.

2. Resonance (Re) (more resonance structures give greater stability)

Which is a weaker base? $CH_3COO^{\ominus}$ or $CH_3CH_2O^{\ominus}$? Since we are looking at the basicity, simply look at the electrons on basic atom. the Lewis structure of each of these bases should be written out to understand the structure.



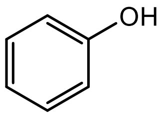
two resonance form of $CH_3COO^{\ominus}$



no resonance in $CH_3CH_2O^{\ominus}$

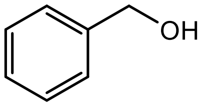
Resonance will stabilize the electrons on the oxygen in $CH_3COO^{\ominus}$ which will make the electrons more stable hence a weaker base.

Which is a stronger acid? Phenol or benzyl alcohol?



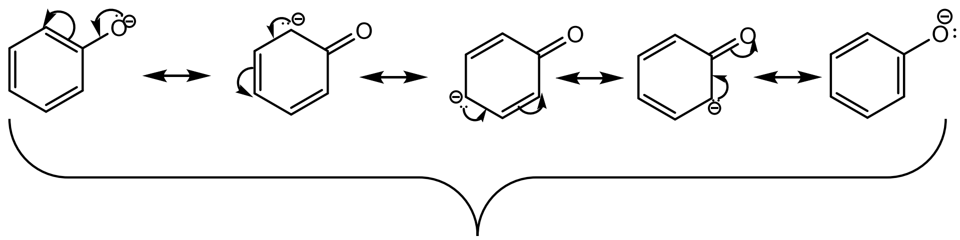
phenol

or

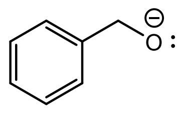


benzyl alcohol

Once again, since the question is posed for acidity, draw out the conjugate base of both species. More stable the electrons on the CB, stronger the corresponding acid.



many resonance form of CB of phenol



no resonance in the
CB of benzyl alcohol

Since CB of phenol has so man resonance forms, the electrons on the CB of phenol are more stable (also a weaker base), hence phenol itself would be a stronger acid.

3. **E**l- electronegativity (electrons on more electronegative atoms are more stable)

Which is a stronger acid? CH_4 (methane) or NH_3 (ammonia)?

Once again, since the question is posed for acidity, draw out the conjugate base of both species. More stable the electrons on the CB, stronger the corresponding acid.

$:\overset{\ominus}{C}H_3$ $:\overset{\ominus}{N}H_2$

Electrons on which atom are more stable? Since Nitrogen is more electronegative than carbon, electrons on N are more stable. Therefore, the corresponding acid, NH_3 is a stronger acid than CH_4

Which is a stronger base? $H_2\ddot{\underset{\cdot\cdot}{O}}$ (water) or $:NH_3$ (ammonia)

Since we are looking at the basicity, simply look at the electrons on basic atom. O is more electronegative than N, electrons on O are more stable, and electrons on N are less stable. The less stable the electrons, the more reactive and stronger the base. Hence NH_3 is a stronger base than H_2O.

4. **C**h- charge (electrons on the uncharged atom are more stable than on charged atom)

Which is a stronger acid?

$H_3O^{\oplus}$ (hydronium ion) or H_2O (water)

Once again, since the question is posed for acidity, draw out the conjugate base of both species. More stable the electrons on the CB, the stronger the corresponding acid.

H_2O $H\ddot{O}^{\ominus}$

The electrons on uncharged O are more stable electrons on charged oxygen. Therefore, the corresponding acid, $H_3O^{\oplus}$ is a stronger acid than H_2O.

Which is a stronger base?

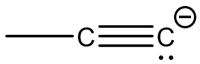
$CH_3CH_2\overset{\ominus}{O}$ (ethoxide ion) or CH_3CH_2OH (ethanol)

Since we are looking at the basicity, simply look at the electrons on basic atom. Charge is the only difference between the two bases. Since the oxygen with the negative charge in ethoxide ion will be less stable, the O atom would be more reactive and more basic

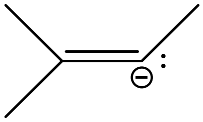
5. **H**y- hybridization (only for carbon atom in Organic 1- the more *s*-character in the orbital the more stable the electrons).

We will focus on three types of hybridization: sp^3 (25% s-character), sp^2 (33.3% s-character) and sp (50% s-character). The more the *s*-character in the hybrid orbital the more stable the electrons.

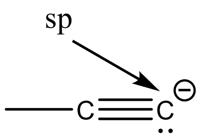
Which is a stronger base?



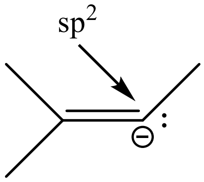
or



Since we are looking at the basicity, simply look at the electrons on basic atom. The only difference in each case is the hybridization on the carbon atom bearing the negative charge.

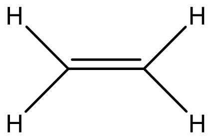


or



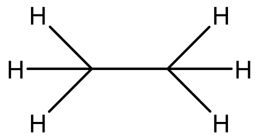
The sp carbon (left anion) has more s-character hence its electrons are more stable. The sp^2 carbon (right anion) has lesser s-character therefore these electrons are less stable, more reactive and more basic.

Which is a stronger acid?



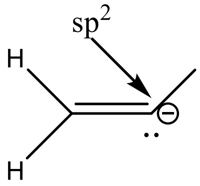
(alkene)

or

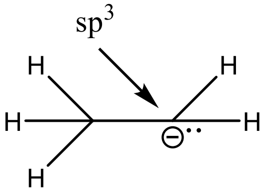


(alkane)

Once again, since the question is posed for acidity, draw out the conjugate base of both species. More stable the electrons on the CB, stronger the corresponding acid.



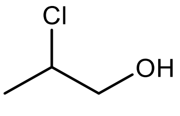
or



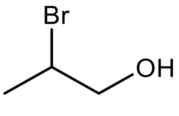
The CB of alkene (left ion) with sp^2 carbon has more s-character than the CB of alkane (right anion), hence the CB of alkene (left) is more stable. Therefore, the corresponding acid, alkene is more acidic than the alkane.

6. **I**e- inductive effects (dipoles pull electron density **away** (only) spreading the electrons out and making them more stable). Inductive effect reduces with distance.

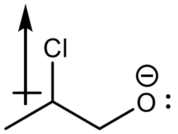
Which is a stronger acid?



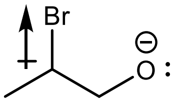
or



Once again, since the question is posed for acidity, draw out the conjugate base of both species. More stable the electrons on the CB, stronger the corresponding acid.



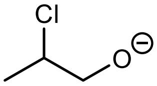
or



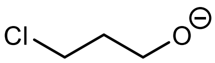
A stronger Inductive effect will stabilize the electrons on oxygen as Cl is more electronegative than Br

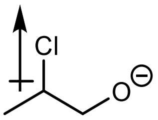
The Inductive effect will weaker and the electrons on oxygen are less stable as Br is less electronegative than Cl

Which is a stronger base?
Since we are looking at the basicity, simply look at the electrons on basic atom.

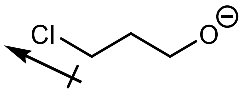


or





or



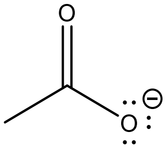
The size of the dipole is the same, however, the distance of the Cl atom is different. Since Inductive effect goes down with distance, the electrons on the right ion are less stable (Cl being farther away from O), the right ion would be more reactive and more basic.
Till now, we were comparing the same Electron stabilizing force (ESF) in determining acidity/basicity. Let’s look at examples where a more than two ESF will be used to determine the strength of acid/base.

Solved problem 2.1 Rank the following in the order of increasing basicity (least basic first)

CH_3OH CH_3NH_2 $CH_3COO^{\ominus}$

Since we are looking at the basicity, simply look at the electrons on basic atom. It is important to understand that acidity/basicity is dependent upon structure. Lewis structures are drawn to check for resonance.

$CH_3\underset{\cdot\cdot}{\ddot{O}}H$ $CH_3\ddot{N}H_2$



A B C

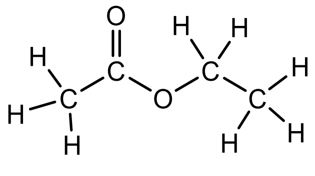
Use PRECHI to answer his question. Ion C has electrons on O that are capable of resonance, hence those are most stable electrons (least basic). Between A and B, the difference is between electronegativity between O and N. Since O in B is more electronegative, its electrons are more stable than electrons on N in B.

So, ranking would be: C<A<B

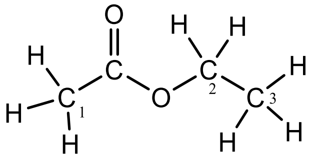
Exercise 2.6: Rank the following in the order of increasing acidity (least acidic first):

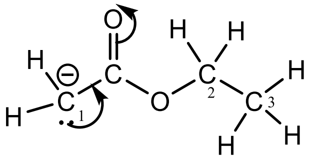
CH_3CH_2OH CH_3NH_2 HBr $BrCH_2CH_2OH$ CH_3SH

Solved Problem 2.2: Which is the most acidic hydrogen in the molecule shown below?

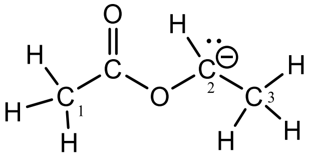


Hint: If you don’t know where to begin, draw the CB by removing each type of proton and drawing the CB and seeing if any of those CB are more stable than the other. Since there are three types of hydrogen atoms (each on carbon 1, 2 and 3), draw three different CB and see which is more stable. Use PRECHI to decide.

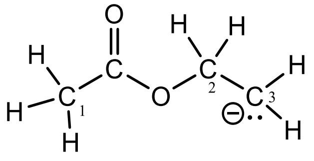




CB from C_1



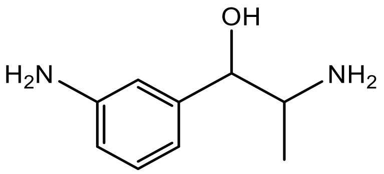
CB from C_2



CB from C_3

Removal of a proton from C1 gives a CB that is resonance stabilized hence most stable CB. Hence protons bonded to C_1 atom are most acidic.

Exercise 2.7: Which is the most basic atom in the molecule shown below?



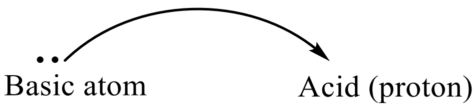
2.6 Acid-Base Mechanism

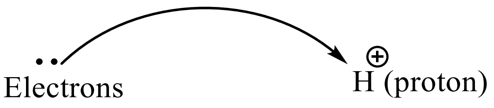
When ionic bonds are involved, the spectator ions (such as sodium ($Na^{\oplus}$) or potassium ($K^{\oplus}$) do not play a part in an acid-base reaction.

Let us take an example of a reaction you have seen many times in general chemistry 1.

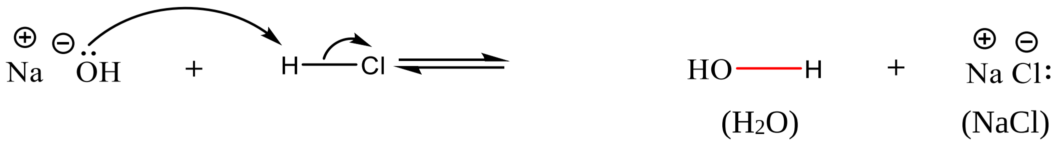
$$NaOH \quad + \quad HCl \rightleftharpoons NaCl \quad + \quad H_2O$$

Now we will write the same reaction properly using arrows and using proper formal charges. But there is a very specific way of arrow pushing. Arrow starts from electrons on the base (electron rich species) and picks up the proton of the acid (electron deficient species).

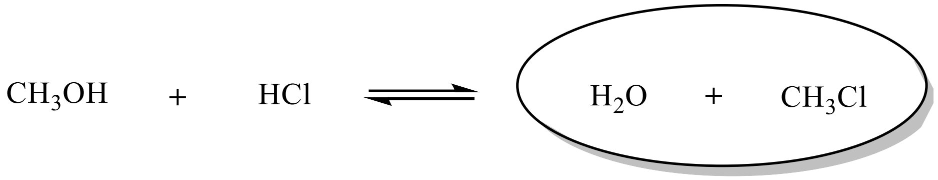




Writing the above acid-base reaction. We first draw the formal charges and then use arrows:

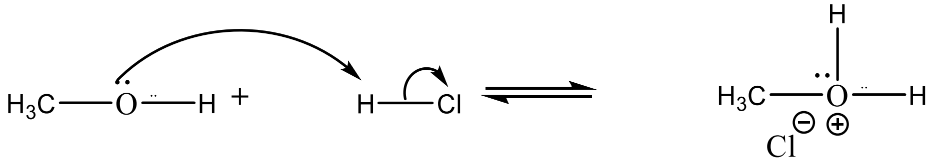


Another example:



Incorrect products. Why?

Why is the right side of equilibrium incorrect? NaOH has an ionic bond. But CH_3OH has only covalent bonds. CH_3OH is the base and HCl is the acid (why?). Based on how the arrows are pushed, the reaction should be written as:



The right side has the correct product(s) a mixture of covalent and ionic bonds.

Directions of how to use arrows and draw the acid-base mechanisms

1. Draw charges. (Be sure to keep them close to the atom that bears the charge to avoid confusion.)

2. Decide which molecule is the acid (A) and which is the base (B). Label accordingly.

3. Determine which specific hydrogen in the acid molecule is the most acidic hydrogen. Determine which pair of electrons in the basic molecule is the most basic (draw them).

4. Draw an arrow from the basic electrons to the acidic hydrogen (this shows the formation of the new bond being formed). Then, for the acidic hydrogen to leave, its bond to the remainder of the acid must break. Do this by drawing an arrow from the pair of electrons in this bond (middle) to the non-hydrogen atom of the bond. (This step illustrates the acid base reaction in mechanistic form.)

5. This now creates the two products. Draw each.

6. Determine which molecule on the right (the ones you just drew) is the acid and which is the base and label them accordingly (A = acid, B = base).

7. Look at the electron pair on each of the bases (the one on the right and the one on the left of the reaction). Determine which one is more/less stable using one the six electron stabilizing forces (see below). Remember: more stable = the less reactive = conjugate base.

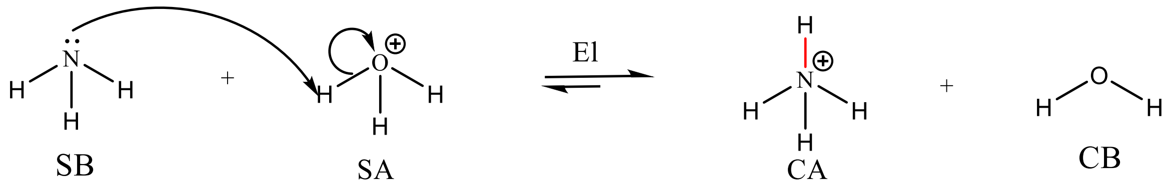
8. Label the A's and B's as strong (S) or conjugate (C). (Remember S's on one side, C's on the other)

9. Draw the appropriate equilibrium arrows (use the line provided as the "long" arrow) Remember- equilibrium favors the weak /conjugate.)

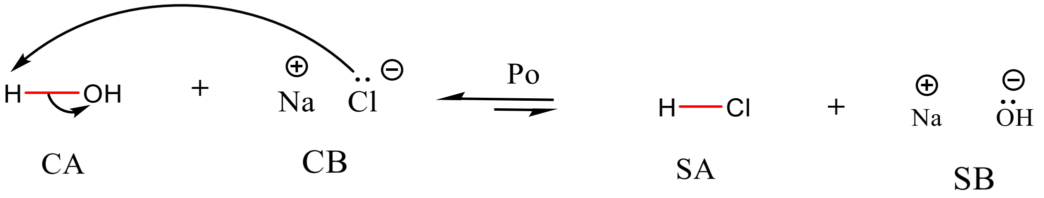
10. Over the equilibrium arrows, write the two-letter abbreviation for the stabilizing force that is in play.

Mechanisms: the first two mechanisms have been done for you and should serve as an example.

1.

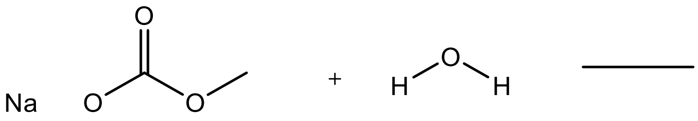


2.

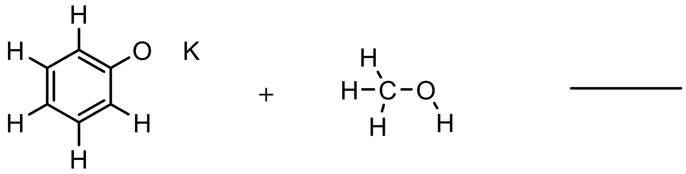


Exercise 2.8: Using arrows, draw the product of the following acid-base mechanism then indicate which electron stabilizing force (ESF) will decide the direction of equilibrium. Include formal charge, if any.

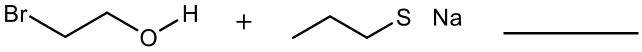
1.



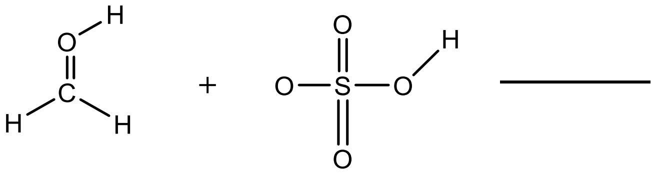
2.



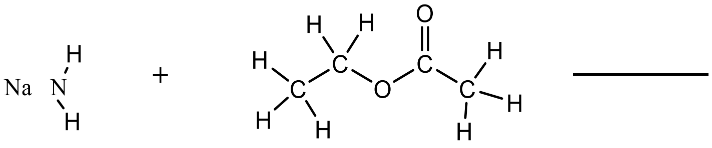
3.



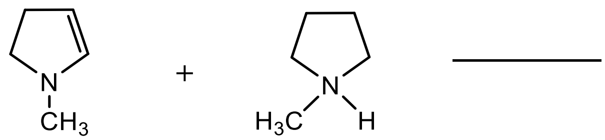
4.



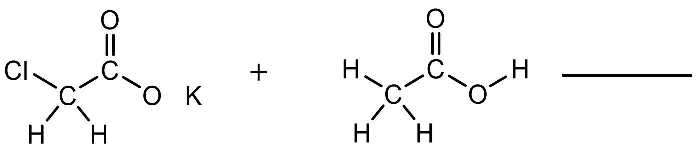
5.



6.



7.



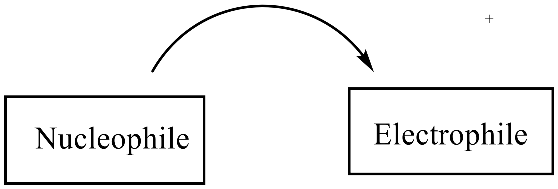
2.7 Lewis Acid (Electrophile) and Lewis Base (Nucleophile)

Electrophiles are electron deficient species. **Nucleophiles** are electron rich species.

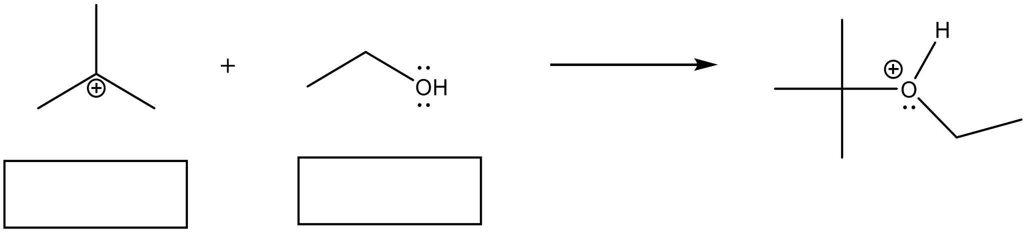
Since Lewis Acids are electron deficient species and they accept electrons *Lewis Acid Accepts Electrons* (**laae**), they are **Electrophiles**.

Since Lewis Bases are electron rich species and they donate electrons *Lewis Base Donates Electrons* (**lbde**), they are **Nucleophiles**.

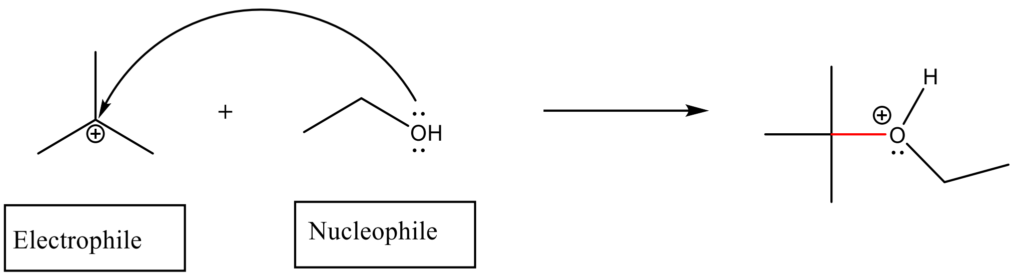
Since flow of electrons is always from electron rich to electron deficient, the arrows should always start from **Nucleophile (Lewis Base)** and point to the **Electrophile (Lewis Acid)**.



<u>Solved Problem 2.3:</u> Label each species as Nucleophile or Electrophile that explains the product of this Lewis Acid-Base reaction. Explain why this is not a Brønsted-Lowry Acid-Base reaction.

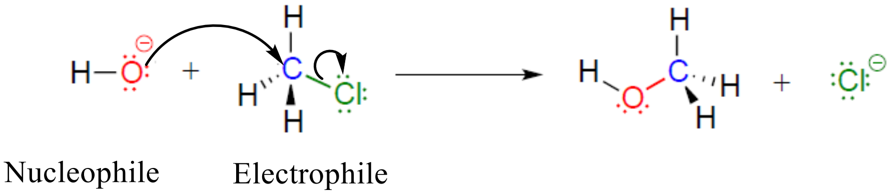


The left species is electron deficient (center carbon has a positive charge), therefore this is the Electrophile (Lewis Acid). The right species has lone pair of electrons on the oxygen atom that makes is electron rich (Nucleophile and Lewis Base). Electrons always flow from Nucleophile to Electrophile; therefore arrows should start from the lone pair of electrons on the oxygen atom to the to the central atom that has the positive charge. This indicates a new bond being formed between the oxygen atom and the carbon atom. Since the left central carbon atom's octet is not complete, it happily accepts the electrons from the oxygen and now its octet is complete. The oxygen on the other hand is now making three bonds hence it will have a formal charge of plus 1. In this case, the base is not picking up a proton, therefore this is **<u>not</u>** a Brønsted-Lowry acid-base reaction. This is a Lewis acid-base reaction.



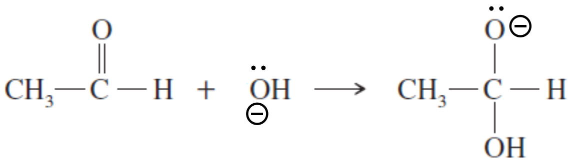
Solved Problem 2.4: For the reaction shown below, label each species as Nucleophile and Electrophile then use arrows that will explain this Lewis acid-base mechanism.

The left species has oxygen having a minus charge, so this oxygen must be the Nucleophile. In the right species, it is not obvious which is the electron deficient atom as octet on all atoms are complete. However, the carbon bonded to the chloride atom has a polar covalent bond where the dipole is pointing towards the more electronegative chlorine atom. This makes the carbon atom more electron deficient (Electrophile). When we use arrows from nucleophilic oxygen to electrophilic carbon, we will be suggesting making a bond between oxygen and carbon. But carbon's octet will exceed, so while a new bond is being formed, an old bond must be broken. The most obvious choice would be the C-Cl bond to be broken since it is anyway a polar covalent bond.

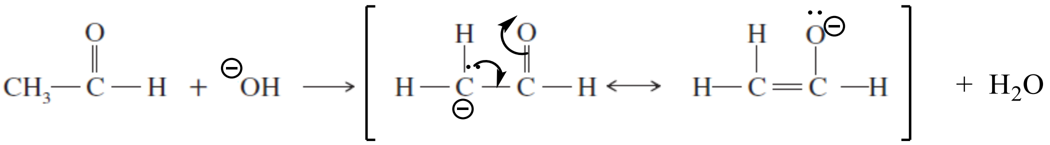


Exercise 2.9: In the following acid–base reactions:

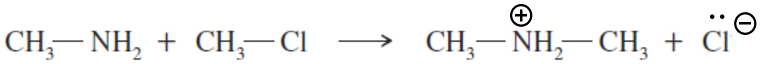
A. determine which species are acting as electrophiles (acids) and which are acting as nucleophiles (bases) on the left side of arrows.
B. use the curved-arrow formalism to show the movement of electron pairs in these reactions.
a.



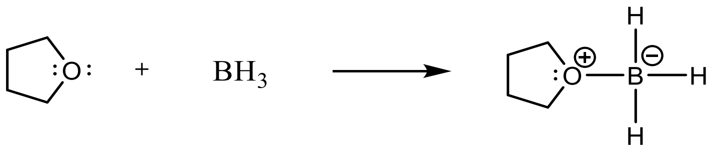
b.



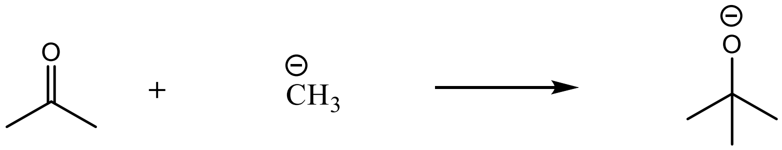
c.



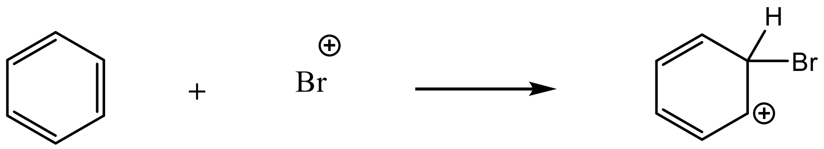
d.



e.



f.



Exercise 2.10: For the following molecules, state whether they are Lewis acid or base and whether they are Brønsted-Lowry acid or base.

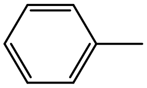
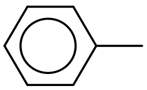
BH_3 $\overset{\oplus}{NH_4}$

2.8 Functional Groups and Classes of Compounds

In organic chemistry, **functional groups** are distinct chemical units, such as double bonds, hydroxyl groups, or halogen atoms, that are reactive and that are responsible for the characteristic chemical reactions of those molecules. The same functional group will undergo the same or similar chemical reaction(s) regardless of the size of the molecule it is a part of. This allows for systematic prediction of chemical reactions and behavior of chemical compounds and design of chemical syntheses.

Alkyl groups are the functional groups that we identify for purposes of naming compounds if a hydrogen atom is removed from the alkane. For example, for methane, CH_4, the alkyl group is methyl, CH_3-, with an abbreviation of Me-), for ethane, CH_3CH_3, the alkyl group is ethyl, CH_3CH_2-, with an abbreviation of Et-)

When a benzene ring is attached to some other group of atoms it is called a phenyl group and can be represented by some of the following ways:

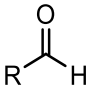
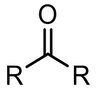

,

, Phenyl- or Ph-

Hydrocarbons representative Alkanes, Alkenes, Alkynes, and Aromatic Compounds
Hydrocarbons are compounds that contain only hydrogen and carbon
Alkanes are hydrocarbons that are entirely composed of single bonds, C–C, between carbon atoms (members of this family have suffixes of -ane)
Alkenes contain at least one $C{=}C$ bond (members of this family have suffixes of -ene)
Alkynes contain at least one $C{\equiv}C$ bond (members of this family have suffixes of -yne)
Aromatic compounds contain a special type of ring, the most common being a **benzene** ring.

Compounds with only single bonds are known as saturated compounds because they contain a maximum number of hydrogen atoms. Compounds with multiple bonds are known as unsaturated compounds because they contain fewer than the maximum possible number of hydrogen atoms.

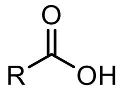
Alkyl halides, or haloalkanes, are compounds in which a halogen atom replaces a hydrogen atom of an alkane (ie: RX)

An **alcohol** has the functional group known as a hydroxyl group, ROH, that attaches to a sp^3 hybridized carbon atom.
Ethers have the general formula of R-O-R where the two groups are composed of same or different alkyl or phenyl groups

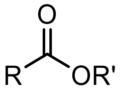
An **aldehyde** can be classified as  while a **ketone** can be classified as 

Both aldehydes and ketones have the carbonyl group, which is the carbon atom double bonded to the oxygen (C=O). The carbonyl group of an aldehyde is bonded to one hydrogen atom and one carbon atom except for formaldehyde, which is the only aldehyde bearing two hydrogen atoms (R group is H). The carbonyl group of a ketone is bonded to two carbon atoms.

Carboxylic acids have a carboxyl group, which is represented as -COOH, since it comes from the carbonyl group and a hydroxyl group. Carboxylic acids thus are classified as RCOOH

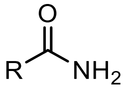
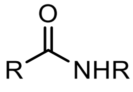
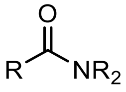


Esters have the general formula of RCOOR, with a carbonyl group bonded to an alkoxyl group

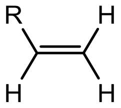
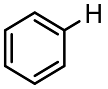
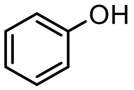
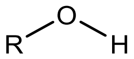
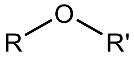
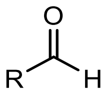
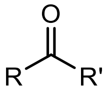
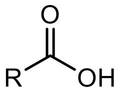
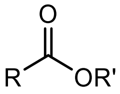
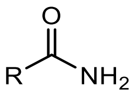
(-OR) 

Amines have the functional group of R-NH_2, R_2NH, or R_3N

Amides have a carbonyl (look for that C=O group bonded to a nitrogen atom bearing hydrogen and/or alkyl groups and therefore have the possible general formulas of $RCONH_2$, RCONHR or $RCONR_2$

A **nitrile** has a cyanide group attached to the carbon to make a general formula of R-CN with linear sp hybridization. Examples of common functional groups in organic chemistry.

Class of compounds	General	Line Structure
Alkanes	**R-H**	R—H
Alkenes	**$RCHCH_2$**	
Alkynes	**RCCH**	$R—C\equiv CH$
Aromatics (Benzene ring)	**Ph-H**	
Phenol	**Ph-OH**	
Alcohols	**R-OH**	
Ethers	**R-O-R'**	
Aldehydes	**RCHO**	
Ketones	**RCOR**	
Carboxylic Acids	**RCOOH**	
Esters	**RCOOR'**	
Amines	**$R-NH_2$**	$R—NH_2$
Amides	**$RCONH_2$**	
Nitrile	**RCN**	$R—C\equiv N$

Chapter 3: Structure and Stereochemistry of Alkanes

3.1 Classification of Hydrocarbons (Review)

Hydrocarbons are compounds containing only carbons and hydrogen.

Hydrocarbons are representative Alkanes, Alkenes, Alkynes, and Aromatic Compounds
Hydrocarbons are compounds that contain only hydrogen and carbon

Alkanes are hydrocarbons that are entirely composed of single bonds, C─C, between carbon atoms (members of this family have suffixes of -ane)
Alkenes contain at least one $C=C$ bond (members of this family have suffixes of -ene)
Alkynes contain at least one $C\equiv C$ bond (members of this family have suffixes of -yne)
Aromatic compounds contain a special type of ring, the most common being a **benzene** ring.

An **alkane** is a hydrocarbon that contains only single bonds. The alkanes are the simplest and least reactive class of organic compounds because they contain only hydrogen and *sp*^{3} hybridized carbon, and they have no reactive functional groups. Compounds with only single bonds are known as saturated compounds because they contain a maximum number of hydrogen atoms.

Alkanes are poor acids and bases, and they are poor electrophiles and nucleophiles as well. Although alkanes undergo reactions such as cracking and combustion at high temperatures, they are much less reactive than other classes of compounds that have functional groups. Compounds with only single bonds are known as saturated compounds because they contain a maximum number of hydrogen atoms. Compounds with multiple bonds (alkene, alkyne etc.) are known as unsaturated compounds because they contain fewer than the maximum possible number of hydrogen atoms.

3.2 Molecular Formulas of Alkanes

Alkanes have the molecular formula $\mathbf{C_nH_{2n+2}}$, which means for every n number of the carbon atom, the alkane can have only a maximum number of 2n+2 hydrogens. An alkane containing 6 carbon atoms can contain a maximum of 14 hydrogen atoms.

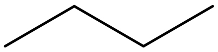
Cycloalkanes are alkanes that are in a ring and have two fewer hydrogens compared to their alkane counterpart, hence the molecular formula of cycloalkanes is $\mathbf{C_nH_{2n}}$**.**

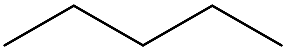
	Alkane	**Cycloalkane**
Molecular formula	$\mathbf{C_nH_{2n+2}}$	$\mathbf{C_nH_{2n}}$

3.3 Nomenclature of Alkanes

Alkanes name ends with "ane". Depending upon the number of carbon atoms an alkane has, the nomenclature will change. You need to know only the first ten alkanes. The first four need to be memorized and the remaining 6 are based on Greek and Latin (mixed language series) nomenclature of numbering, which makes it easier to memorize.

# of carbon	Nomenclature
1	**methane**
2	**ethane**
3	**propane**
4	**butane**
5	**pentane**
6	**hexane**
7	**heptane**
8	**octane**
9	**nonane**
10	**decane**

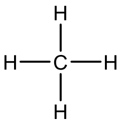

butane

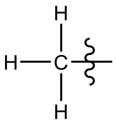

pentane

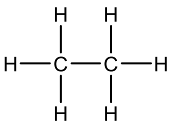

hexane

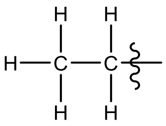
The naming of alkyl groups:

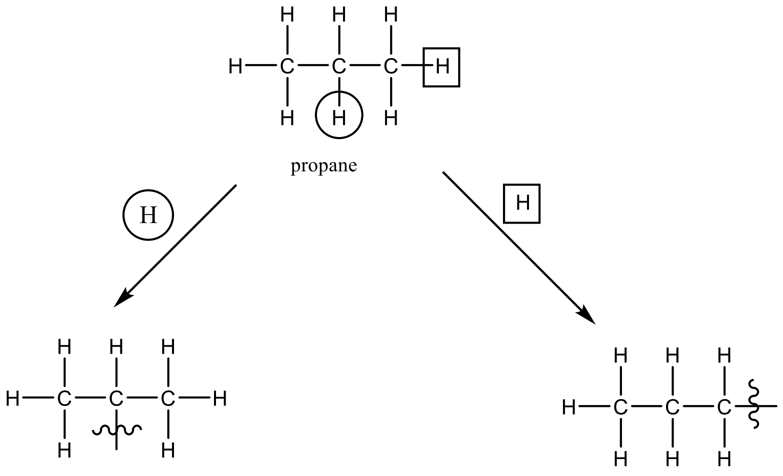
Alkyl groups are the functional groups that we identify for purposes of naming compounds if a hydrogen atom is removed from the alkane. For example, for methane, CH_4, the alkyl group is methyl, CH_3-, with an abbreviation of Me-), for ethane, CH_3CH_3, the alkyl group is ethyl, CH_3CH_2-, with an abbreviation of Et-)


methane


methyl


ethane

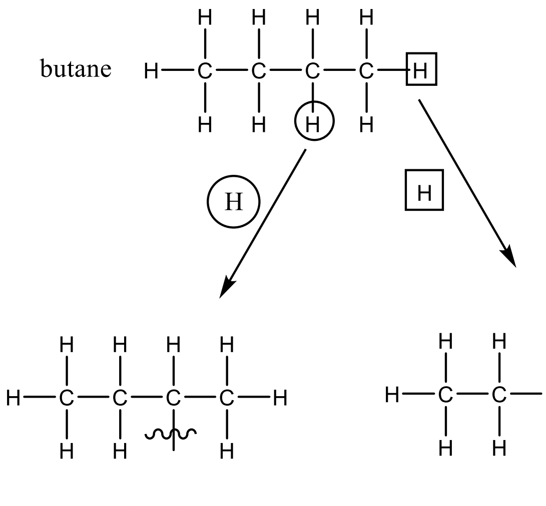

ethyl



propane

isopropyl

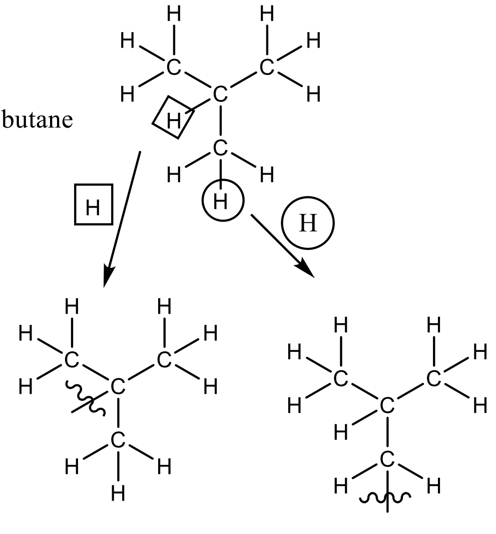
propyl



butane

sec-butyl

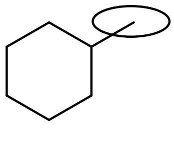
butyl



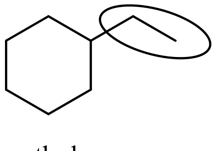
isobutane

t-butyl

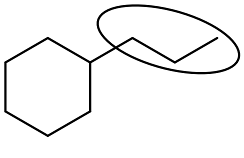
isobutyl



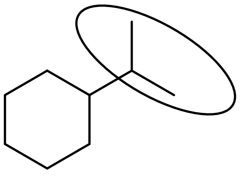
methyl



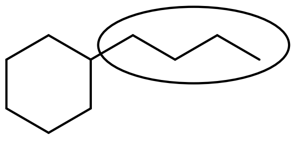
ethyl



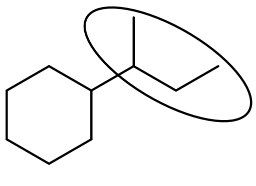
propyl



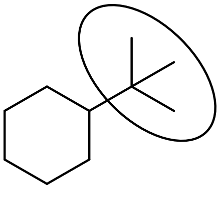
isopropyl



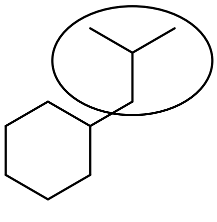
butyl



sec-butyl



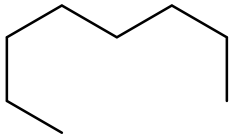
t-butyl



isobutyl

International Union of Pure and Applied Chemistry (IUPAC) Rules for Naming Alkanes

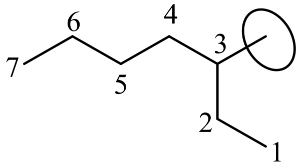
1. Identify the longest **<u>continuous</u>** chain of carbon atoms; this “parent chain” provides the root name. Indicate the number of carbon atoms in the chain with a prefix followed by the ending *-ane*.



For this unbranched molecule, there are eight carbon connected continuously to each other so the name of this molecule will be octane.

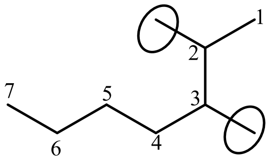
2. For branched chain alkanes, number the longest chain, beginning with the end of the chain nearest a substituent.

e.g.

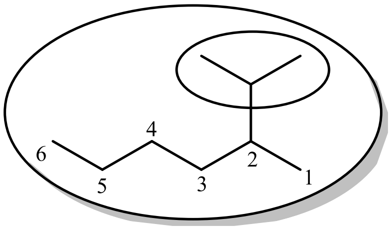


The circled substituent is the branch.

e.g.



I

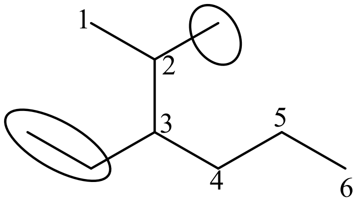


II (incorrect)

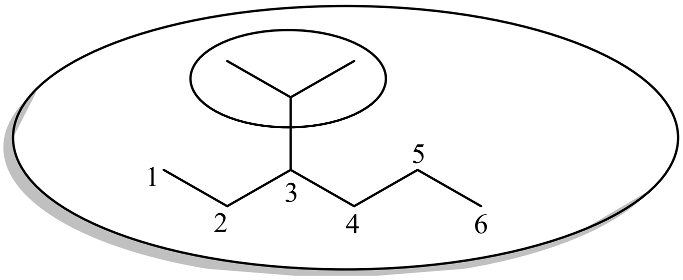
Structure I show correct numbering while structure II shows incorrect numbering, as the longest continuous chain is 7 carbon, not 6.

3. When there are two or more parent chains of identical length, choose the parent chain with the greater number of substituents.

e.g.



I (correct)



II (Incorrect)

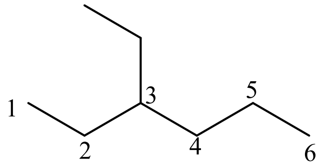
Both structure I and II have longest chain as 6 carbons. In structure I, we chose the longest chain that gives 2 branches. In structure II, we chose the longest chain that gives us only one branch. Due to this structure II numbering will give us incorrect nomenclature.

4. Identify and name the substituent(s).

   methyl for -CH_3, ethyl for CH_3CH_2- etc.

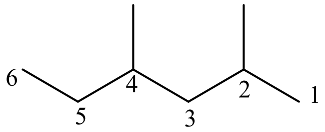
5. Number the parent chain.

- **One substituent**: number from the end that gives the substituent the lower number. *Use a hyphen to connect the number to the name.*



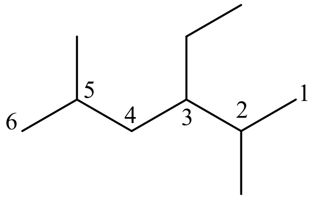
3-ethylhexane

- **Two or more identical substituents**: number from the end that gives the lower number to the substituent encountered first. *The number of times the substituent occurs is indicated by the prefixes di-, tri-, tetra-, penta-, hexa-, and so on. A comma is used to separate position numbers.*



2,4-dimethylhexane

- **Two or more different substituents**: list the substituents in alphabetical order and the number from the end that gives the lower number to the substituent encountered first. If there are different substituents in equivalent positions at opposite ends of the parent chain, give the substituent of lower alphabetical order the lower number. *Prefixes such as di-, tri-, tetra-, penta-, hexa-, and so on are not included in alphabetizing.*

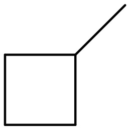


3-ethyl-2,5-dimethylhexane (*alphabetically, e comes before m,* ***di*** *doesn't count*)

Nomenclature of Cycloalkanes

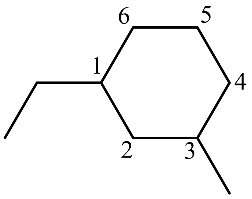
1. Prefix the name of the corresponding straight chain alkane with *cyclo*-.
2. Identify and name the substituent(s) on the ring.
3. Number the ring.

- One substituent: no number necessary (i.e., "1" is assumed).

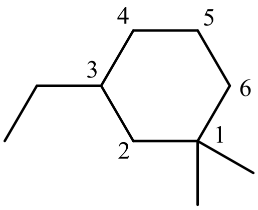


methylcyclobutane

- Two substituents: number so that substituent with lower alphabetical order given lower number. Three or more substituents: number in order to give the substituents the *lowest set* of numbers.



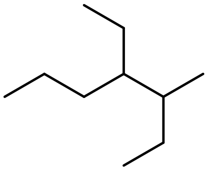
1-ethyl-3-methylcyclohexane



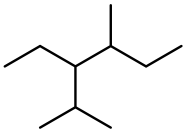
3-ethyl-1,1-dimethylcyclohexane

Exercise 3.1: Give these alkanes proper IUPAC names:

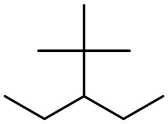
a.



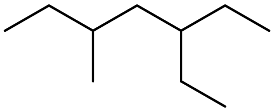
b.



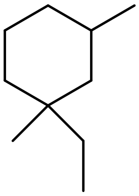
c.



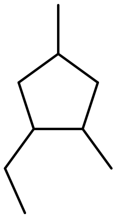
d.



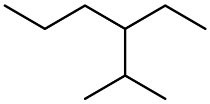
e.



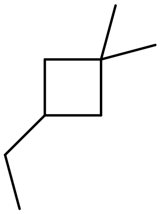
f.



g.



h.



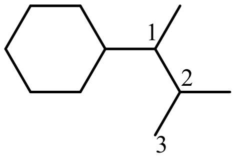
Exercise 3.2: All the following names are incorrect or incomplete. In each case, draw the structure (or a possible structure) and name it correctly.

a. 2-methylethylpentane
b. 2-ethyl-3-methylpentane
c. 3-dimethylhexane
d. 4-isobutylheptane
e. 1-methyl-3-ethylbutane
f. 2-diethyl-3-methylhexane

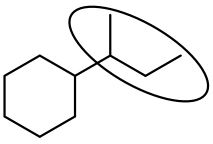
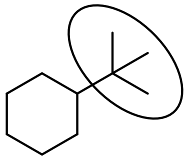
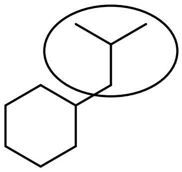
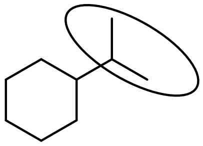
Complex naming of alkyl groups.

When a branch has a branch, use complex nomenclature.

Complex Substituents Complex alkyl groups are named by a systematic method using the longest alkyl chain as the base alkyl group. The base alkyl group is numbered beginning with the carbon atom (the "head carbon") bonded to the main chain. The substituents on the base alkyl group are listed with appropriate numbers, and parentheses are used to set off the name of the complex alkyl group. The following examples illustrate the systematic method for naming complex alkyl groups.



To give a complex name to the alkyl group, label the carbon attached to the main chain as # 1 and count outwards away from the main chain. In the above example, three continuous carbon atoms are attached to the main chain. Carbon 1 and 2, of the complex alkyl group, have two methyl groups respectively. The complex name of this branch would be (1,2-dimethylpropyl). Since this complex branch is attached to the main chain of cyclohexane, the complete IUPAC name of the above molecule would be (1,2-dimethylpropyl) cyclohexane.

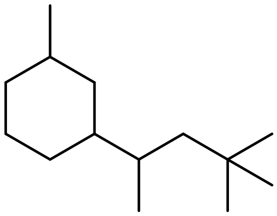
				
common name	sec-butyl	t-butyl	isobutyl	isopropyl
complex name	1-methlypropyl	1,1-dimethylethyl	2-methylpropyl	1-methylethyl

Exercise 3.3: Draw the structures of the following groups and give their more common names.

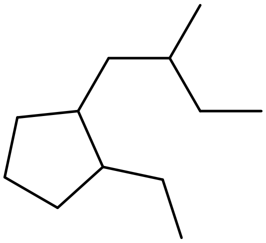
a. the (1-methylethyl) group
b. the (2-methylpropyl) group
c. the (1-methylpropyl) group
d. the (1,1-dimethylethyl) group

Exercise 3.4: Give these alkanes proper IUPAC names. Use complex naming for the branches.

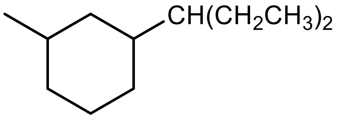
a.



b.



c.



3.4 Physical Properties of Alkanes

Alkanes are said to be **hydrophobic** ("water hating") because they do not dissolve in water. Alkanes are nonpolar, so they dissolve in nonpolar or weakly polar organic solvents. Alkanes are good lubricants. The boiling points increase smoothly with increasing numbers of carbon atoms and increasing molecular weights. Larger molecules have larger surface areas, resulting in increased intermolecular van der Waals attractions. In general, a branched alkane boils at a lower temperature than the *n*-alkane with the same number of carbon atoms. This difference in boiling points arises because branched alkanes have less surface area for London force interactions.

3.5 Uses of Alkanes

Alkanes are important raw materials in the chemical industry and the principal constituent of gasoline and lubricating oils. Natural gas mainly contains methane and ethane and is used for heating and cooking purposes. For transportation purposes, natural gas may be liquefied by applying pressure and cooling it (liquefied petroleum gas or LPG).

Crude oil is separated into its components by fractional distillation at oil refineries. The different "fractions" of crude oil have different boiling points and consist mostly of alkanes of similar chain lengths (the higher the boiling point the more carbon atoms the components of a fraction contain).

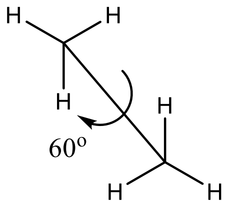
3.6 Reactions of Alkanes

Alkanes undergo combustion, which is the reaction of alkanes with oxygen to produce carbon dioxide and water, and a lot of energy. They also undergo catalytic **cracking** where large hydrocarbons at high temperatures produce smaller hydrocarbons. The cracking process usually operates under conditions that give the maximum yields of gasoline. These two reactions are less significant to organic chemists compared to the free radical halogenation reaction. Heat or light is usually needed to initiate this **halogenation.** Reactions of alkanes with chlorine and bromine proceed at moderate rates and are easily controlled. We will discuss the halogenation of alkanes in Chapter 4.

$$CH_4 \quad + \quad Cl_2 \quad \xrightarrow[\text{or hv}]{\Delta} \quad CH_3Cl \quad + \quad HCl$$

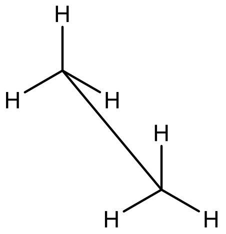
3.7 Structure and Conformations of Alkanes

Two conformers of ethane, CH_3CH_3 are drawn. I and II are the saw-horse projection and II and IV are Newman projections.



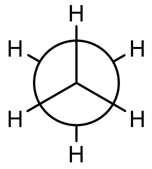
sawhorse staggered

I



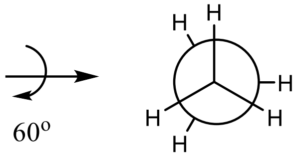
sawhorse eclipsed

II



Newman staggered

III

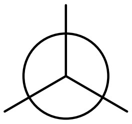


Newman eclipsed

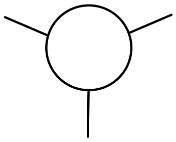
IV

Conforms differ only in the temporary way the molecule happens to arrange itself and can easily be interconverted just by rotating around bonds. No bonds are broken.

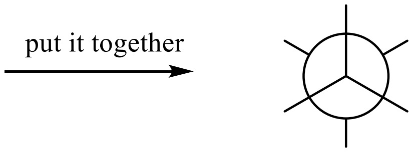
In drawing conformations, we often use **Newman projections,** a way of drawing a 3D molecule in 2D. You are looking straight down at the bond connecting two carbon atoms (see figure above). The front carbon atom is in the center of the circle and three lines (three bonds) come off it. The back carbon is represented by the center of the circle with three bonds pointing out from it (in a Y shape)



front carbon is in the center



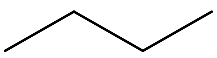
back carbon is at the center



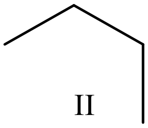
most stable staggered form of Newman projection

Until you become familiar with Newman projections, you should make models and compare your models with the drawings. The more stable form is the staggered form as the electron cloud is farthest apart.

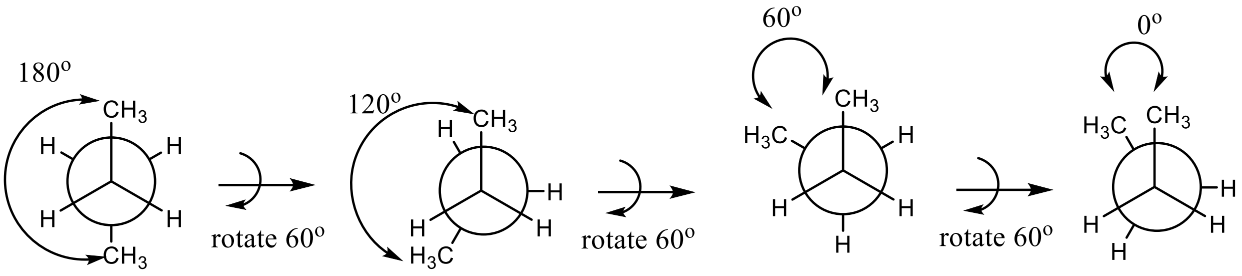
Two conformers of butane are drawn below. Structure I is staggered while II is eclipsed.



I



II



completely staggered
most stable "anti"

A

eclipsed

B

Gauche staggered

C

totally eclipsed
least stable

D

Looking along the central bond, for four conformations of butane. Notice that we have defined the dihedral angle as the angle between the two end methyl groups.

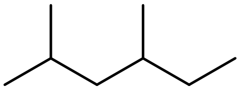
In structure A, the methyl groups are pointed in the opposite directions, with dihedral angle at 180° and this is the most stable completely staggered form. This conformation is called **anti** because the methyl groups are “opposed.” Structure B is obtained by rotating the back carbon of A by 60° clockwise. This is the eclipsed form where the two methyl groups have a dihedral angle of 120°. Structure C is obtained by rotating the back carbon of B by 60° clockwise. This results in a staggered form of C. The two methyl groups have a dihedral angle of 60°. Structure D is obtained by rotating the back carbon of C by 60° clockwise. This leads to a completely eclipsed form where the two methyl groups are pointed in the same direction, they eclipse each other. This conformation is called totally eclipsed (D) and the two methyl groups have a dihedral angle of 0°.

If one had to rank the order of stability in increasing order (least stable first), look at the **staggered form that would be always more stable than the eclipsed form**. Only after that, look at the dihedral angle between the methyl groups.

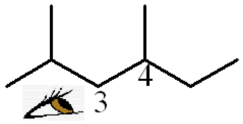
Based upon this, the ranking would be as follows: (least stable first): **D<B<C<A**

We can apply the same principle to any higher alkane. ***Make sure the groups that have the biggest electron cloud are “anti” or completely staggered.***

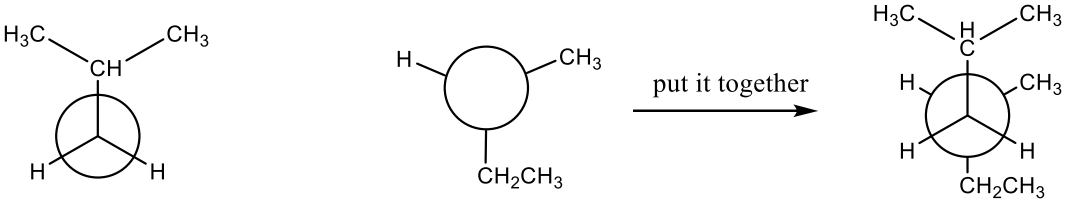
Solved Problem 3.1: Draw the most stable Newman projection of the molecule shown below while viewing it from $C_3 \rightarrow C_4$ (C_3 in front).



Since the directions clearly say to draw most stable form while viewing from $C_3 \rightarrow C_4$, the eye must be placed such that C_3 is in the front and C_4 is in the back of Newman projection.



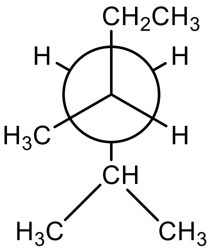
The front carbon has isopropyl group and 2 hydrogen, that should be drawn as the inverted letter Y on a circle. The back carbon has an ethyl group, methyl group and a hydrogen atom. For most stable Newman projection, draw the two biggest electron cloud group (isopropyl on C_3) and ethyl (on C_4) such that they have a 180^o bond angle (farthest apart).



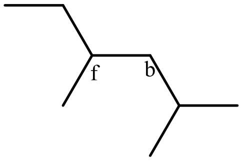
front carbon (C3) is in the center back carbon (C4) is also at the center most stable Newman projection

Converting Newman projections to line formula can be achieved as well. The starting pint is to know the front and back carbons and what are attached to them.

Solved Problem 3.2: Draw the line formula of the following Newman Projection and provide the IUPAC name.



In the Newman Projection, the front carbon is at the center of the front circle and the back carbon is at the center of back circle (that can't be seen). First draw a line and label each end of the line as f and b f ——— b Now to each f and b carbon, add the groups that are attached. The front carbon has ethyl, methyl and hydrogen attached to it, while the back carbon has isopropyl and 2 hydrogens.

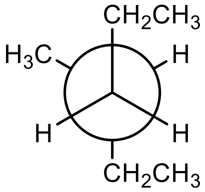


The IUPAC name is 2,4-dimethylhexane

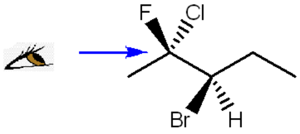
Exercise 3.5: Draw the most stable Newman projection conformation of:

- **a.** 3-methylhexane while viewing the molecule from $C_3 \rightarrow C_4$ (C_3 in front)
- **b.** 2-methylbutane while viewing the molecule from $C_2 \rightarrow C_3$ (C_2 in front)

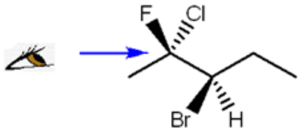
Exercise 3.6: Draw the line formula and provide the IUPAC name of the following Newman projection.



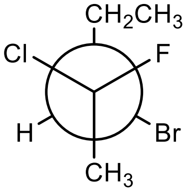
Conformations using 3D perspective must be understood so that the three-dimensional structure of molecules can be interpreted when they are drawn on a piece of paper. In this molecule shown below, viewing it from left to write, the fluorine on C_2 and bromine on C_3 are draw with wedges (coming out of the plane of the paper) while chlorine on C_2 and hydrogen on C_3 are drawn with dash lines (going behind the plane of paper).



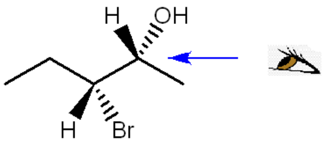
To draw this molecule using Newman projection, viewed from the direction of blue arrow, just rotate the 3D perspective by 90° such that the front carbon is facing you. Upon doing that fluorine and bromine would be on the right side of C2 and C3 respectively and chlorine and hydrogen would be on the left side of C2 and C3 respectively in the Newman projection.

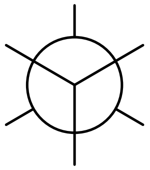


converts to

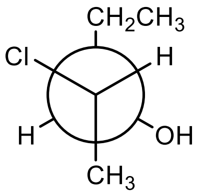


Exercise 3.7: Draw the Newman projection of the following molecule in the direction of blue arrow. Newman's "wheel" has been drawn for your convenience.

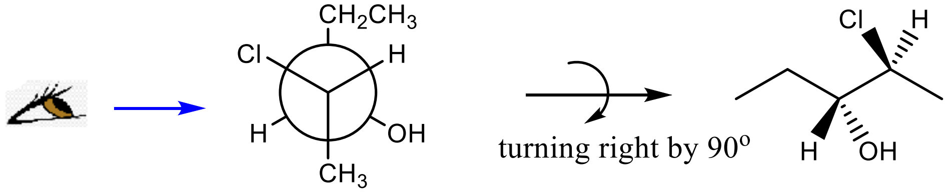




Solved Problem 3.3: Convert the Newman Projection to 3D-perspective using dash and wedges. There is more than one possible correct way of drawing this, depending upon which direction you turn this Newman projection, so that you have a sideways view of the molecule for you to be able to convert it to 3D perspective,

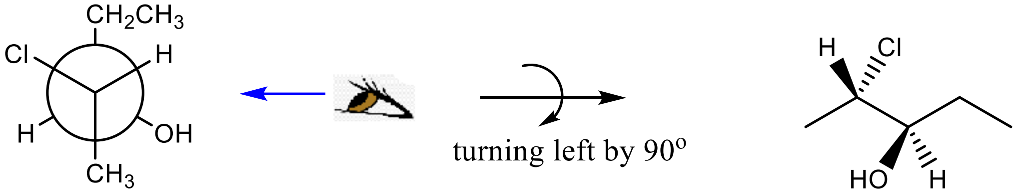


Viewing the molecule from left side.



I

Or viewing the molecule from the right side.

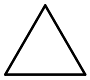


II

Both I and II are correct answers.

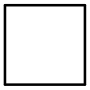
3.8 Cycloalkanes

The general formula of cycloalkanes is C_nH_{2n}. There are two less hydrogen atoms in cycloalkane compared to their open chain counterpart.



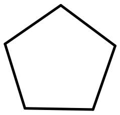
cyclopropane

C_3H_6



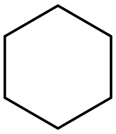
cyclobutane

C_4H_8



cyclopentane

C_5H_{10}



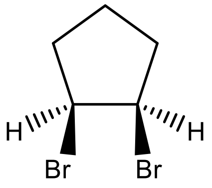
cyclohexane

C_6H_{12}

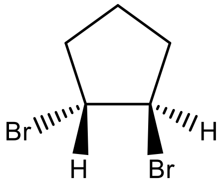
Most cycloalkanes resemble the **acyclic** (noncyclic), open-chain alkanes in their physical properties and chemical properties.

3.9 Cis-trans Isomerism in Cycloalkanes

Unlike acyclic alkanes, cycloalkanes are do not have a free rotation about the sigma bond. In that aspect, In the cyclic structure shown above is that atoms or groups bonded to tetrahedral ring carbons are either pointing up (out of the plane of the page) or down (into the plane of the page), as indicated by the use of dashed or solid wedge bonds. When two substituents on the same ring are both pointing toward the same side of the ring, they are said to be ***cis*** to each other. When they are pointed to opposite sides, they are said to be ***trans*** to each other. These **stereoisomers** cannot interconvert without breaking and re-forming bonds.



cis



trans

Exercise 3.8: Which of the following cycloalkanes are capable of stereo (cis-trans) isomerism? Draw the cis and trans isomers.

a. 3-ethyl-1,1-dimethylcyclohexane

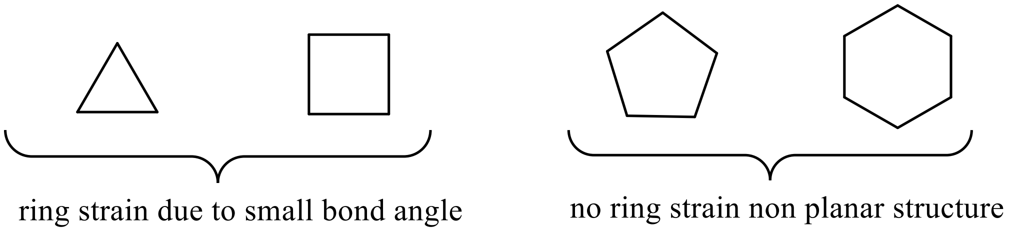
b.1-ethyl-3-methylcycloheptane

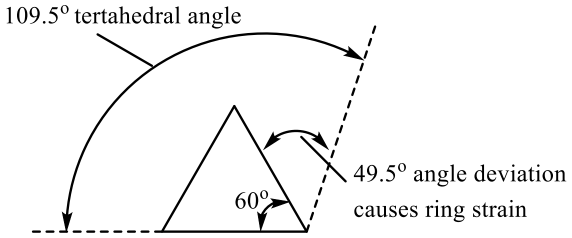
c. 1-ethyl-3-methylcyclopentane

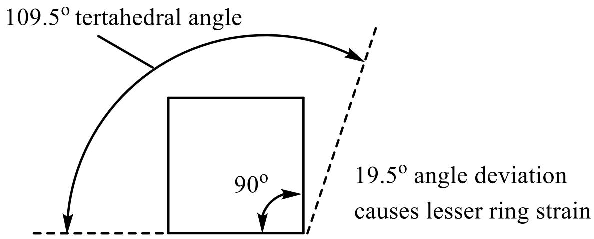
d. 1-cyclopropyl-2-methylcyclohexane

3.10 Stabilities of Cycloalkanes; Ring Strain

Ring strain is mainly composed of angle strain. Angle strain is the result of deviation from ideal bond angles caused by structural constraints (lack of sigma bond rotation).





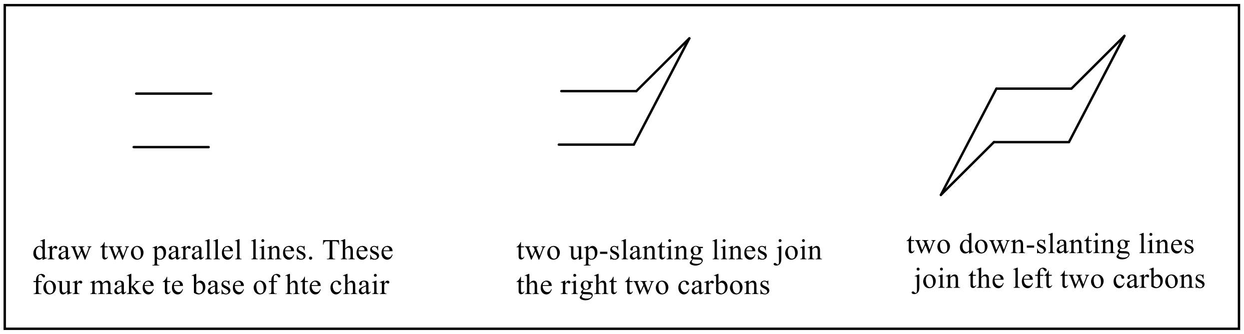


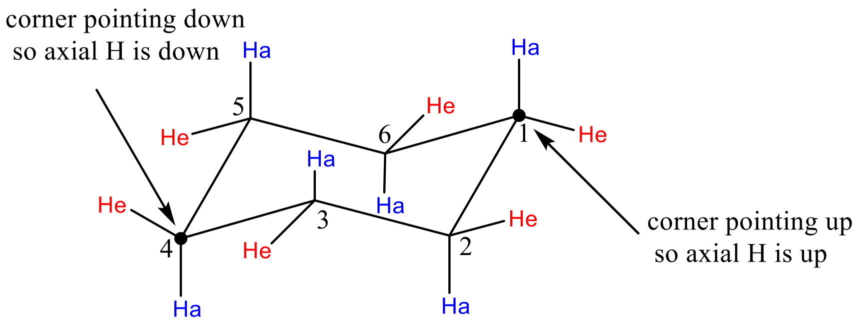
Cyclopropane has more angle strain than cyclobutane as the deviation from the bond angle of (~109.5°) sp^3 hybridized carbon is larger (~49.5°) than in case of cyclobutane (~19.5°). Both are almost planar unlike cyclopentane and cyclohexane that are not planar.

3.11 Cyclohexane Conformations-Chair conformations

In six-membered cycloalkane structures, bonding angles are close to tetrahedral, and thus ring strain is not a factor – these rings are very stable. However, the ‘flat’ drawings we have been using up to now do not accurately show the actual three-dimensional shape of a five- or six-membered ring. If cyclohexane were indeed flat, the bond angles must be distorted from 109.5° to 120°. If you build a model, you will find that when you rotate the carbon-carbon bonds so as to put the ring into a shape that resembles a recliner (chair) and there is no ring strain.

How to draw the chair conformation”



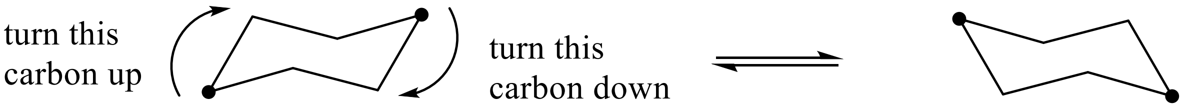

corner pointing down so axial H is down

corner pointing up so axial H is up

If you look carefully at the above model of cyclohexane in the chair conformation, you will see that all twelve hydrogens are not equivalent in terms of their three-dimensional arrangement in space. Six hydrogens are **axial** (in blue) that is, they are pointing either straight up or straight down relative to the ring. The other six hydrogens are **equatorial** (in red), meaning that they are pointing away from the perimeter of the ring, either slightly up or slightly down.

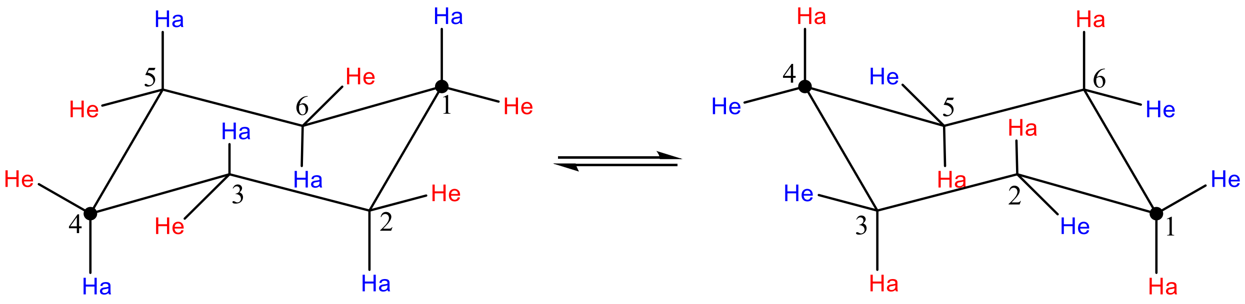
An easy way to figure out axial or equatorial hydrogens on a carbon are to see the following pattern. Take the top-right carbon and label as C1. If C1 has an axial bond upward and an equatorial bond downward. C2 will have an equatorial bond upward and an axial bond downward. The pattern alternates. If the odd-numbered carbon atoms have axial bonds up and equatorial bonds down, the even-numbered carbons will have equatorial bonds up and axial bonds down.

This is not the only possible chair conformation for cyclohexane. On your model, turn one of the 'up' carbons down, and one of the 'down' carbons up. You now have a new, alternate chair conformation – this process is called **ring inversion**. These two structures are conformers.


turn this carbon up

turn this carbon down

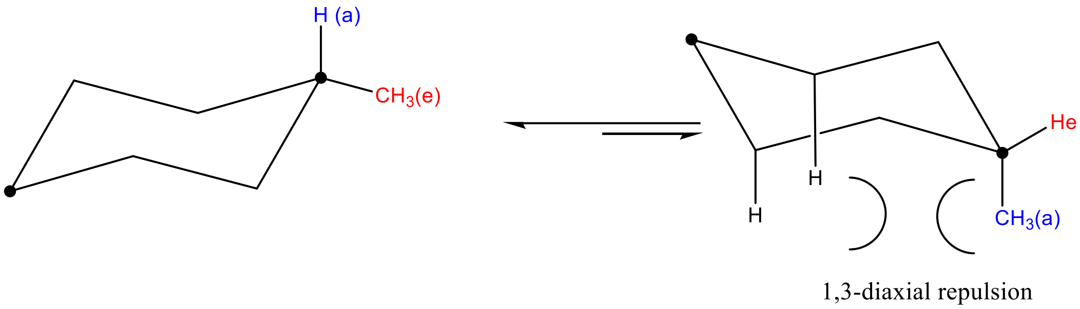
This ring inversion is now shown with the axial and equatorial hydrogens.



Note the color change of Ha and He As a result of the ring inversion process, all the axial and equatorial hydrogens have traded positions: axial hydrogens have become equatorial, and vice-versa. Notice, however, at the 'down' hydrogens are still pointing down, and the 'up' hydrogens are still pointing up regardless of whether they are axial or equatorial. This interconversion is constantly taking place for pure cyclohexane.

3.12 Conformations of Monosubstituted Cyclohexane

What happens to the relative energies of chair conformers when the ring has a substituent, such as a methyl group? Now, the two chair conformations are quite different: in one, the methyl group is equatorial and in the other it is axial.

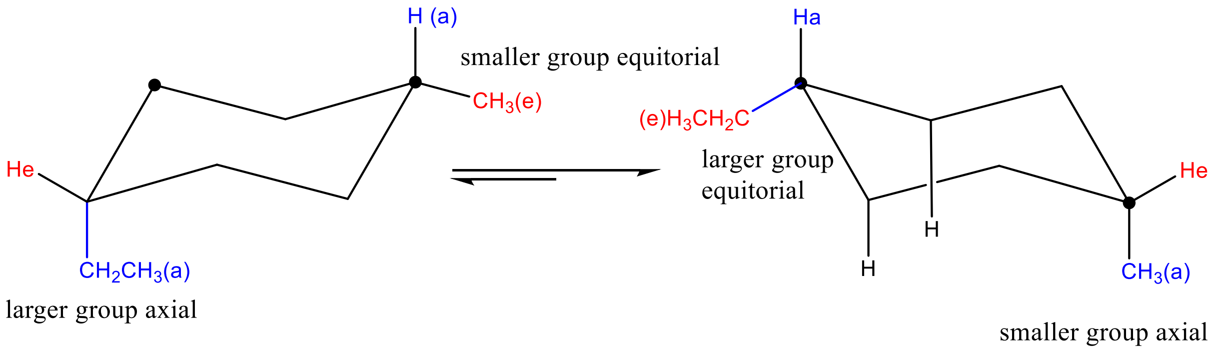


When the methyl group is in the axial position, it is brought close enough to the axial hydrogens on carbons two bonds away to cause destabilizing steric repulsion: this is referred to as **1,3-diaxial repulsion**.

Bottomline is: if one group is present, the group prefers to be in the equatorial position to avoid 1,3-diaxial repulsion.

3.13 Conformations of Disubstituted Cyclohexane

In disubstituted cyclohexane ring in which both substituents cannot be equatorial, the lower energy conformation generally places the bulkier substituent in the equatorial position. This is since the bulkier groups will experience larger 1,3-diaxial repulsion.

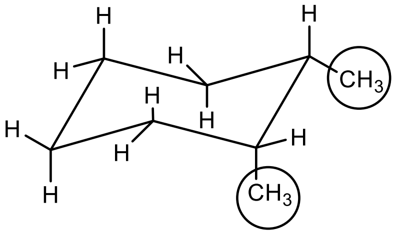


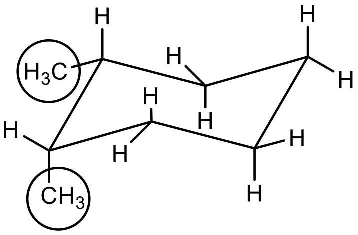
As a rule, the most stable chair conformation of a chair conformation will be that in which the bulkiest groups are in the equatorial position.

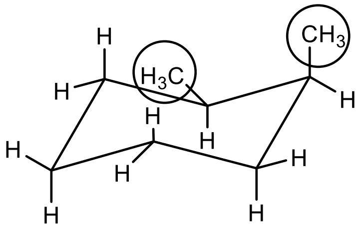
__Common Mistakes__: A very common mistake made by students as they begin to learn about chair conformations is to confuse the terms axial and equatorial with the terms *cis* and *trans*. **These are completely different**! For example, when two substituents on a ring are *cis* in relation to one another, it means that they are pointed to the same side of the ring (both up or both down). Depending on their positions on the ring, they might both be axial, both be equatorial, or one of each. Do not make the mistake of calling two substituents *trans* to each other merely because one is equatorial and one is axial, or *cis* because they are both axial or both equatorial.

Solved Problem 3.4: Draw the most stable chair conformations of each of the molecules: Chairs are drawn for your convenience. Place the hydrogens on the remaining positions to complete the picture. Note: there are many possible correct answers as any carbon on the chair can be # 1.

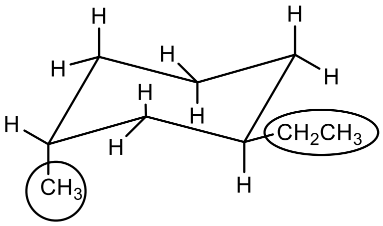
a. cis-1,2-dimethylcyclohexane. All three are correct answers as they all have the two methyl groups on the same side. In the first two cases, they are going down, in the third case, they are going up.

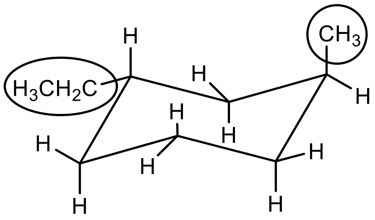


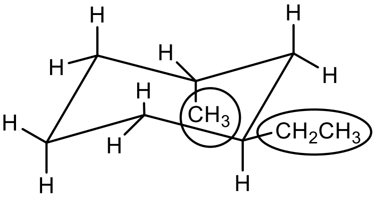




b. trans-1-ethyl-3-methylcyclohexane. Between ethyl and methyl, ethyl is bulkier and would prefer to occupy the equatorial position to avoid 1,3-diaxial repulsions. Show below are a few correct answers.

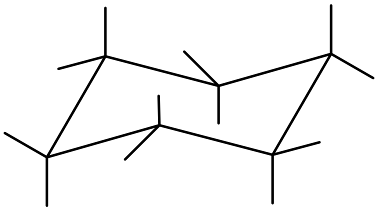




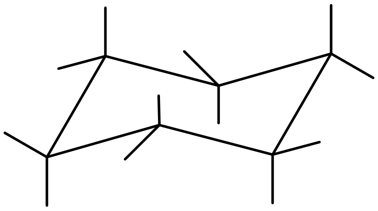


Exercise 3.8: Draw the most stable chair conformations of each of the molecules: Chairs are drawn for your convenience. Place the hydrogens on the remaining positions to complete the picture. Note: there are many possible correct answers as any carbon on the chair can be # 1.

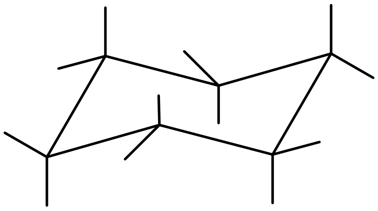
a. trans-1-ethyl-3-propylylcyclohexane



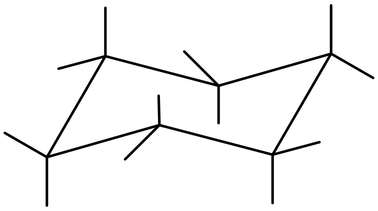
b. trans-1-ethyl-3-methylcyclohexane



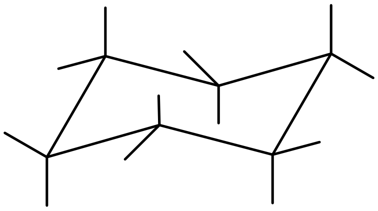
c. trans-1,2-dimethylcyclohexane



d. trans-1-ethyl-4-isopropylylcyclohexane

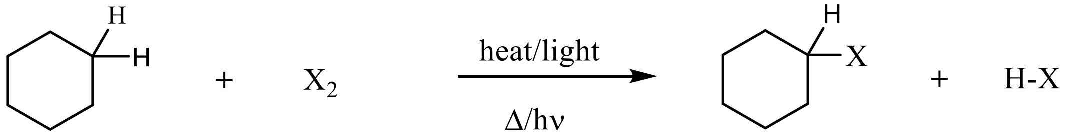


e. cis-1-ethyl-3-methylcyclohexane



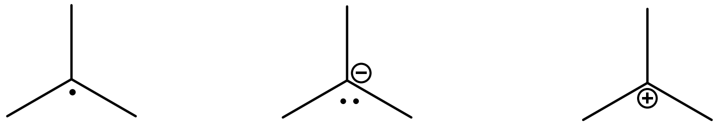
Chapter 4: The Study of Chemical Reactions

4.1 Halogenation of Methane



This is called a free radical substitution reaction. Here, X_2 is a halogen like Cl_2 or Br_2. The reaction works best with these two. The reaction takes place in presence of heat or light (/Δ/hυ). In this chapter, you will be learning about reactive Intermediates (R.I.), species that are short-lived (unstable) because they react as quickly as they are formed.

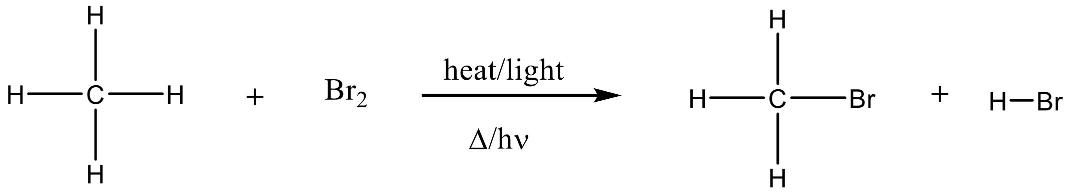
Some of the common reactive intermediates contain carbon atoms with only three bonds, compared with carbon's four bonds in its stable compounds. The three most common types of organic R.I. are:



free radical carbanion carbocation

4.2 Free-Radical Halogenation Mechanism

We will explore the bromination of methane as a tool to study the reaction mechanism. A **mechanism** is a step-by-step direction using arrows that describes which bonds break, which bonds form, and in what order to give the observed products.



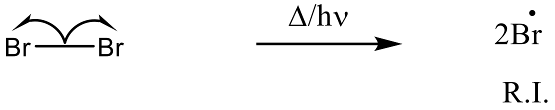
monohalogenated product

In this chapter, we will only focus on the monohalogenated product (single substitution).

There are three steps associated with the above reaction:

1. **Initiation step,** which generates a reactive intermediate (R.I.).
2. **Propagation steps,** in which the reactive intermediate reacts with a stable molecule to form a product and another reactive intermediate, allowing the chain to continue until the reactive intermediate is destroyed.
3. **Termination steps,** side reactions that destroy reactive intermediates and tend to slow or stop the reaction.

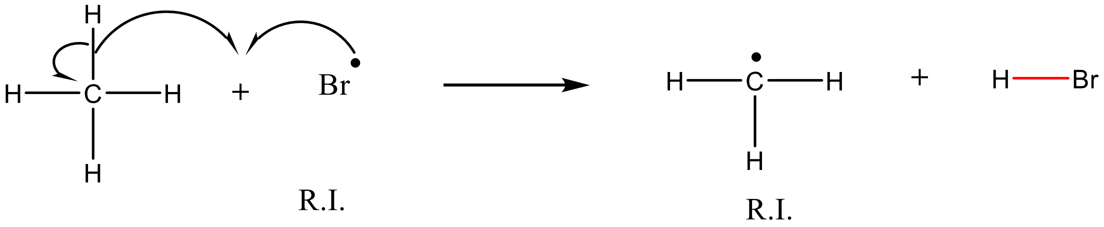
1. Initiation: This step shows that the bond between two bromine atoms breaks.



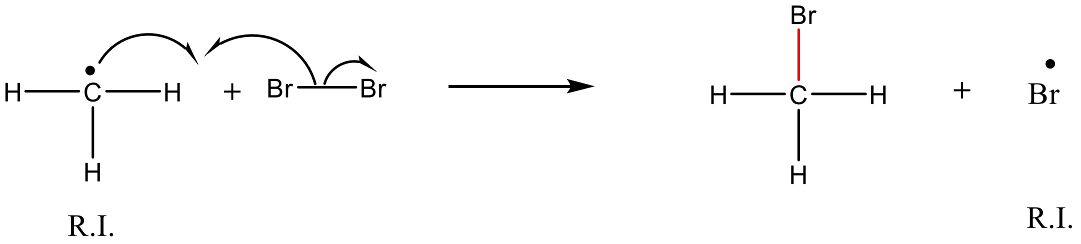
Notice the fishhook-shaped half-arrows  used to show the movement of single unpaired electrons. We use these curved half-arrows to represent the movement of single electrons. These half arrows show that the two electrons in the bond between two bromine atoms separate, and one leaves with each bromine atom.

1. Propagation: There are two steps to it:

(a) In the first propagation step, a bromine radical collides with a methane molecule and abstracts (removes) a hydrogen atom from methane. One of the electrons in the bond remains on carbon while the other combines with the odd electron on the bromine atom to form the H-Br bond.



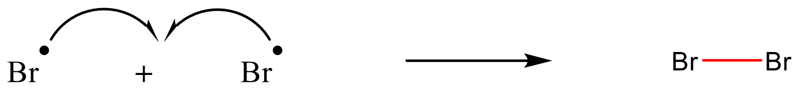
(b) In the second propagation step, the methyl radical reacts with a molecule of bromine to form bromomethane (stable), and the chlorine atom is left with the odd electron (generating a R.I.).



The bromine radical formed in step 2 goes on to react in step 1, continuing the chain.

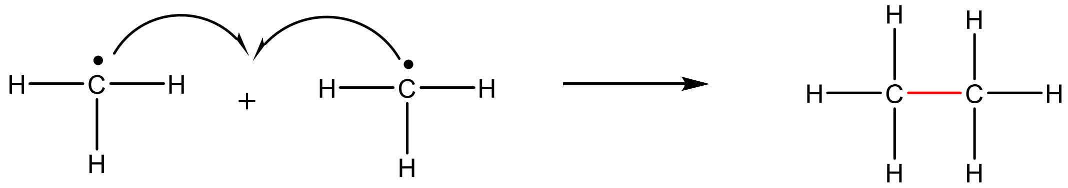
2. Termination: There are three possible ways this reaction could end (terminate). There are only two types of free radicals that are generated in this reaction and they can collide in three possible ways to terminate the reaction.

(a)



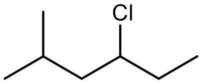
(b)

(c)

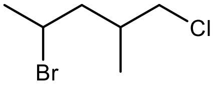


4.3 Nomenclature and Classification of Alkyl Halides

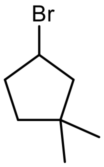
The systematic (IUPAC) nomenclature treats an alkyl halide as an alkane with a *halo-substituent*: Fluorine is *fluoro-*, chlorine is *chloro-*, bromine is *bromo-*, and iodine is *iodo-*. This results in a systematic **haloalkane** name.



4-chloro-2-methylhexane

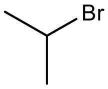


4-bromo-1-chloro-2-methylhexane

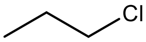


3-bromo-1,1,-dimethylcyclopentane

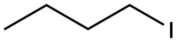
Common or "trivial" names are constructed by naming the alkyl group and then the halide, as in "isopropyl bromide." This is the origin of the term *alkyl halide*. Common names are useful only for simple alkyl halides, such as the following:



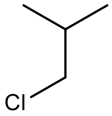
isopropyl bromide



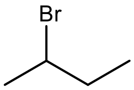
propyl chloride



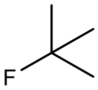
butyl iodide



isobutyl chloride



sec-butyl bromide



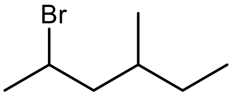
t-butyl flouride

Alkyl halides are classified according to the nature of the carbon atom bonded to the halogen. If the halogen-bearing carbon is bonded to one carbon atom, it is **primary** (1°) and the alkyl halide is a primary halide. If two carbon atoms are bonded to the halogen-bearing carbon, it is secondary (2°) and the compound is a secondary halide. If the halogen-bearing carbon is bonded to three carbon atoms, it is a tertiary halide (3°). If the halogen-bearing carbon atom is a methyl group (bonded to no other carbon atoms), the compound is a *methyl halide*.

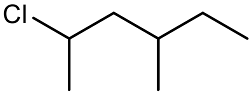
Exercise 4.1: For each of the following compounds:

1. Give the IUPAC name.
2. Classify the compound as a methyl, primary, secondary, or tertiary halide.

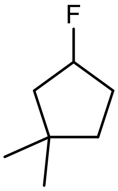
a.



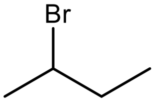
b.



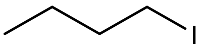
c.



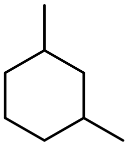
d.



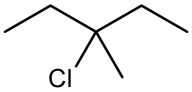
e.



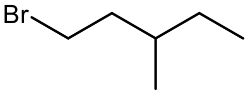
f.



g.



h.



4.4 Energy Diagram of a one-step reaction.

For a one-step reaction, a representative energy diagram is drawn.

$$A + B \longrightarrow C + D$$

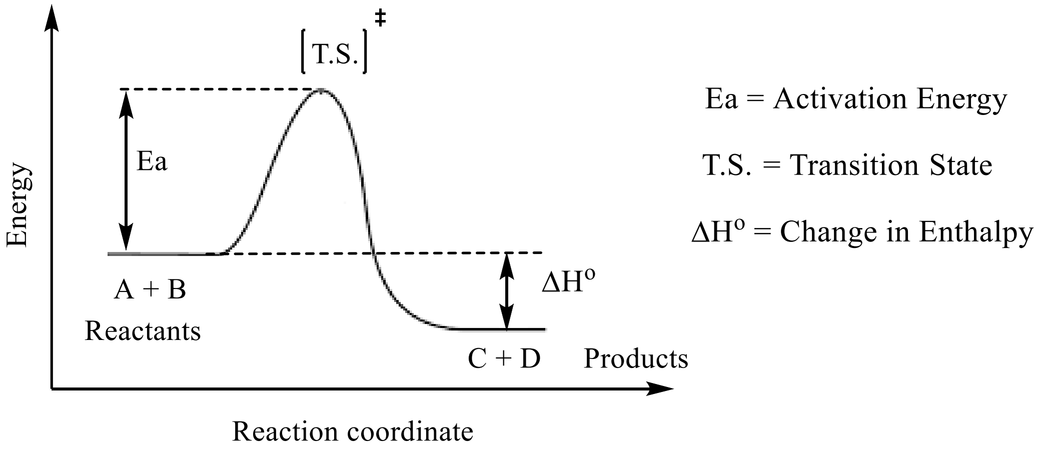


Figure 4.1: Energy diagram of a one-step reaction

The activation energy Ea represents the energy difference between the reactants and the **transition state,** the highest point in the energy diagram. For a reaction to go forward, the activation energy barrier must be overcome. The value of is always positive. The term transition state implies that this configuration is the transition between the reactants and products, and the molecules can either go on to products or return to reactants. Unlike the reactants or products, a transition state is unstable and cannot be isolated. The transition state is symbolized by a superscript double dagger (‡). Transition states have high energies because bonds must begin to break before other bonds can form. The enthalpy of the reaction (ΔH^o) is the difference in energy between the reactants and the products.

4.5 Rates of multiple-step reaction

Let us take an example of the propagation step of the free radical halogenation reaction of alkanes from the previous section. There are two steps in the propagation steps and one of them has higher activation energy (Ea).

In a multistep reaction, each step has its own characteristic rate. The overall reaction rate is controlled by the slow, **rate-determining step** (rds). The rds is the *highest energy* step of a multistep reaction. If we have the reaction-energy diagram, it is simple: The highest point in the energy diagram is the transition state with the highest energy, generally the transition state for the rate-limiting step. Propagation steps in the chlorination of methane are shown here,

(a) $CH_4 + Cl^{\bullet} \overset{\text{rds}}{\rightleftharpoons} {}^{\bullet}CH_3 + HCl$

(b) ${}^{\bullet}CH_3 + Cl_2 \xrightarrow{\text{fast}} CH_3Cl + Cl^{\bullet}$

ΔH^o (kcal)	Ea (kcal)
+2 kcal	4 kcal
-27 kcal	1 kcal

The step with the highest Ea in the energy diagram of the chlorination of methane (Figure 4.1) is the transition state for the reaction of methane with a chlorine radical (step 1). This step must be rate determining step.

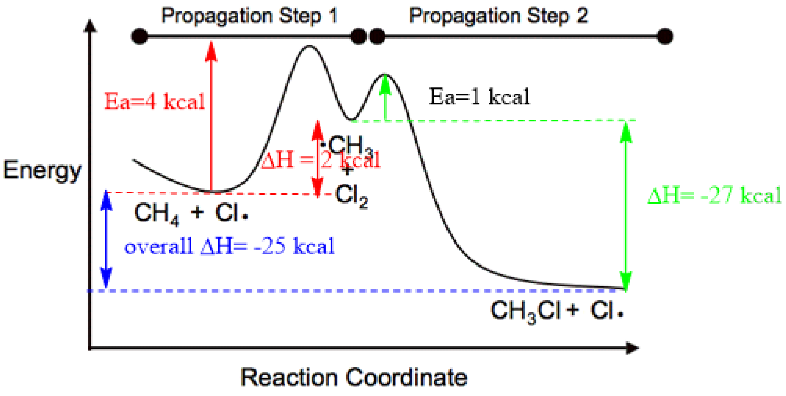
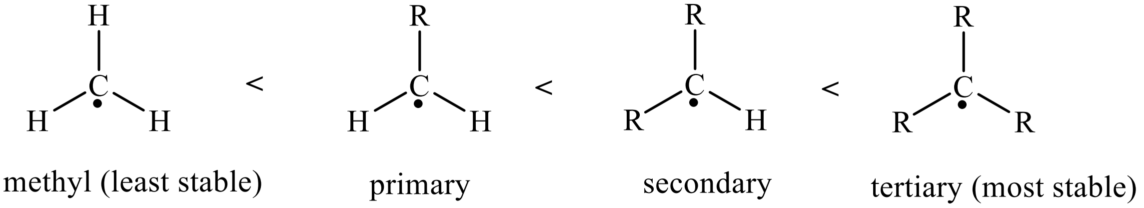


Figure 4.2: Energy Diagram for propagation steps during chlorination of propane

4.6 Free Radical stabilities

During the first propagation step of alkanes, an alkyl free radical is formed in the rds. The more stable the radical, the lower its Ea and faster the reaction. Figure 4.1 shows the energy required (BDE) to form a free radical by breaking a bond between a hydrogen atom and a carbon atom. Based upon the Table 4.1, this energy is greatest for a methyl carbon, and it decreases for a primary carbon, a secondary carbon, and a tertiary carbon. The more highly substituted the carbon atom, the less energy is required to form the free radical.

The following free radicals are listed in increasing order of stability.



4.7 Enthalpy

The enthalpy change (ΔH) is a measure of the relative strength of bonding in the products and reactants. Reactions tend to favor products with the strongest bonds. If weaker bonds are broken and stronger bonds are formed, heat is evolved, and the reaction is **exothermic** (negative value of ΔH). If stronger bonds are broken and weaker bonds are formed, then energy is consumed in the reaction, and the reaction is **endothermic** (positive value of ΔH).

4.8 Bond-Dissociation Enthalpies

The **bond-dissociation energy (BDE)** is the amount of enthalpy required to break a bond **homolytically** (equally). Energy is released when bonds are formed, and energy is consumed to break bonds. Therefore, bond-dissociation enthalpies are always positive (endothermic). The overall enthalpy change (ΔH^o) for a reaction is the sum of the dissociation enthalpies of the bonds broken minus the sum of the dissociation enthalpies of the bonds formed.

$$\mathbf{\Delta H^o = \Sigma\ (BDE\ of\ bonds\ broken) - \Sigma\ (BDE\ of\ bonds\ formed)}$$

If you have a hard time remembering which goes first in the formula, just remember that bonds are broken first and then bonds are formed. Having the formula backward will give you the wrong sign in the value of ΔH^o**.** For the hypothetical reaction:

$$\mathrm{A{-}B} \quad + \quad \mathrm{C{-}D} \longrightarrow \mathrm{A{-}C} \quad + \quad \mathrm{B{-}D}$$

$$\mathbf{\Delta H^o = \Sigma\ (BDE\ A\text{-}B + BDE\ of\ C\text{-}D) - \Sigma\ (BDE\ of\ A\text{-}C + BDE\ of\ B\text{-}D)}$$

By studying the heats of reaction for many different reactions, chemists have developed reliable tables of bond-dissociation enthalpies. Table 4.1 gives the bond-dissociation enthalpies in a variety of molecules.

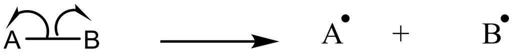
			
Bond	Bond Disassociation Enthalpy (kcal/mol)	Bond	Bond Disassociation Enthalpy (kcal/mol)
$H-X$ and $X-X$ **bonds**		**Bonds to secondary carbon**	
$H-H$	104	$(CH_3)_2CH-H$	95
$D-D$	106	$(CH_3)_2CH-F$	106
$F-F$	38	$(CH_3)_2CH-Cl$	80
$Cl-Cl$	58	$(CH_3)_2CH-Br$	68
$Br-Br$	46	$(CH_3)_2CH-I$	53
$I-I$	36		
$H-F$	136	**Bonds to tertiary carbon**	
$H-Cl$	103	$(CH_3)_3C-H$	91
$H-Br$	88	$(CH_3)_3C-F$	106
$H-I$	71	$(CH_3)_3C-Cl$	79
$OH-H$	119	$(CH_3)_3C-Br$	65
$HO-OH$	51	$(CH_3)_3C-I$	50
Methyl bonds		**Other C-H bonds**	
CH_3-H	104	$PhCH_2-H$ (benzylic)	85
CH_3-F	109	$CH_2{=}CHCH_2-H$ (allylic)	87
CH_3-Cl	84	$CH_2{=}CH-H$ (vinyl)	111
CH_3-Br	70	$Ph-H$ (aromatic)	113
CH_3-I	56	$HC{\equiv}C-H$ (acetylenic)	125
Bonds to primary carbon		**C-C bonds**	
CH_3CH_2-H	98	CH_3-CH_3	88
CH_3CH_2-F	107	$CH_3CH_2-CH_3$	85
CH_3CH_2-Cl	81	$CH_3CH_2-CH_2CH_3$	82
CH_3CH_2-Br	68	$(CH_3)_2CH-CH_3$	84
CH_3CH_2-I	53	$(CH_3)_3C-CH_3$	81

Table 4.1

Exercise 4.2: Using the table 4.1, calculate the overall ΔH° of the following reaction:

$$CH_3CH_3 \quad + \quad Br_2 \quad \xrightarrow{\Delta/h\nu} \quad CH_3CH_2Br \quad + \quad HBr$$

Exercise 4.3: Given the bond dissociation energies below (in kcal), calculate the ΔH^o for the propagation step. Include units.

$(CH_3)_2CH\cdot + Cl_2$ ---------> $(CH_3)_2CHCl + Cl\cdot$

$CH_3CH_2CH_2$-H	98
$(CH_3)_2CH$-H	95
Cl-Cl	58
H-Cl	103
$CH_3CH_2CH_2$-Cl	81
(CH3)$_2$CH-Cl	80

4.9 Kinetics and the Rate Equation

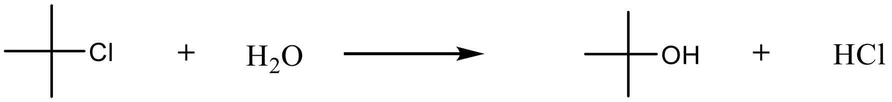
For the reaction shown below:

$$CH_3Br + \overset{\oplus}{Na}\ \overset{\ominus}{OH} \longrightarrow CH_3OH + \overset{\oplus}{Na}\ \overset{\ominus}{Br}$$

The rate of this reaction was experimentally found to be expressed with the following rate equation. Rate = $k\ [CH_3Br]^1 [NaOH]^1$ where k is a rate constant.

By adding the exponents, we can say the reaction is overall second order. Looking at the rate equation, one can predict the effect of concentration on rate. Rate will double if you double the concentration of CH_3Br, but not NaOH. If you double the concentration of both CH_3Br and NaOH, the rate quadruples. If you triple concentration of both CH_3Br and NaOH, the rate increases by nine time.

For the reaction shown below:



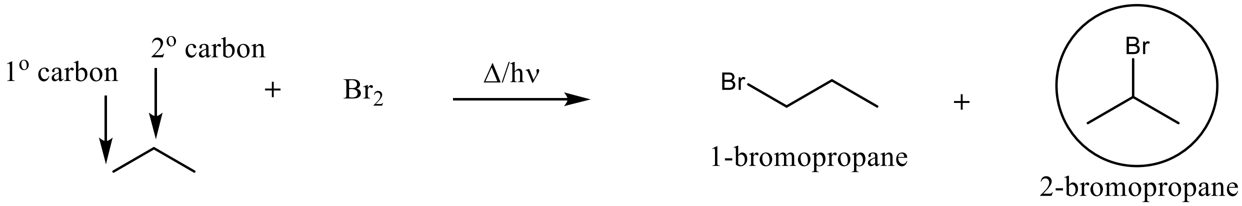
The rate of this reaction was experimentally found to be expressed with the following rate equation.

Rate = $k\ [(CH_3)_3Cl]^1 [H_2O]^0$ where k is a rate constant.

By adding the exponents, we can say the reaction is overall first order. Looking at the rate equation, one can predict the effect of concentration on rate. Rate will double if you double the concentration of CH_3Cl, but do not change the concentration of H_2O. If you double the concentration of both CH_3Cl and H_2O, the rate will still double. If you triple concentration of both CH_3Cl and H_2O, the rate triples. In other words, one can say that the rate is independent upon the concentration of H_2O.

4.10 Halogenation of higher alkanes

When propane undergoes free radical halogenation reaction, two products are formed. There are two unique types of hydrogens. The hydrogens on carbon 1 and 3 are identical and the hydrogen on the central carbon (carbon 2) is chemically different. Since, there are two unique types of hydrogens, there are two products. The formation of alkyl radical is the rds, when propane makes propyl (1°) radical vs. when it makes isopropyl (2°) radical, the Ea will be lower to make a more stable isopropyl (2°) radical.



2-bromoproane is the major product. This is due to the formation of a 2° free radical formed in the rds, which has a lower Ea, and is also more stable.

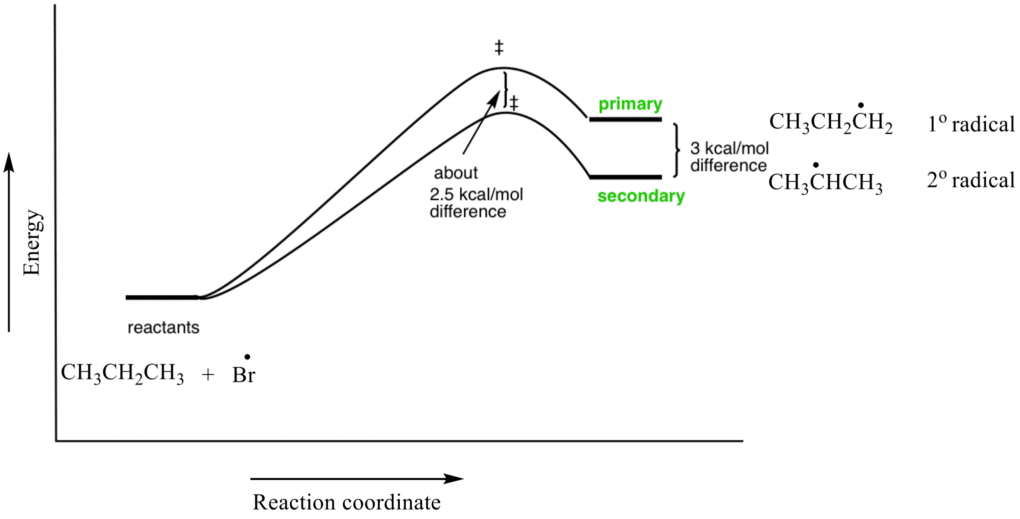
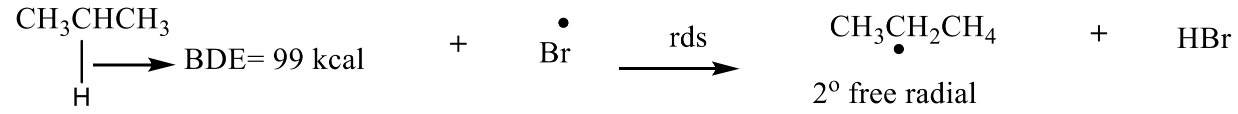


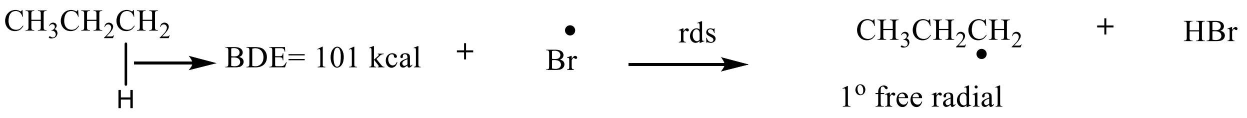
Figure 4.3: Energy diagram of rate determining step during bromination of propane

The difference in Ea of formation of 1° vs. 2° free radical is a result of the difference in the bond dissociation energy of breaking a 2° C-H bond vs. a 2° C-H bond.



$$CH_3\underset{H}{\underset{|}{C}}HCH_3 \longrightarrow \text{BDE= 99 kcal} \quad + \quad \dot{Br} \xrightarrow{\text{rds}} CH_3\underset{\bullet}{C}H_2CH_4 \quad + \quad HBr$$

2° free radial

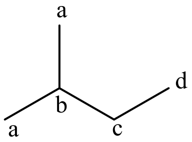


$$CH_3CH_2\underset{H}{\underset{|}{C}}H_2 \longrightarrow \text{BDE= 101 kcal} \quad + \quad \dot{Br} \xrightarrow{\text{rds}} CH_3CH_2\underset{\bullet}{C}H_2 \quad + \quad HBr$$

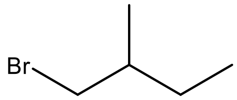
1° free radial

Solved Problem 4.1: How many monobrominated products would form when 2-methylbutane undergo free radical bromination in presence of light. Draw all the unique products, provide the IUPAC names and circle the major product.

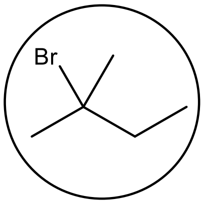
In order to predict how many products will form, we must carefully see the chemically different types of hydrogens that can be removed by bromine radical in the rate determining step.



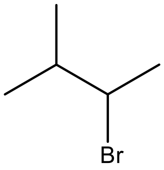
The two methyl groups (carbon a) attached to carbon b are identical, since they have the same connectivity. Upon removal of a hydrogen, a 1^o radical will form. Carbon b has 1 hydrogen which upon removal will form a 3^o radical. Removal of hydrogen on carbon c will give a 2^o radical. And removal of hydrogen on carbon d will give a 1^o radical.



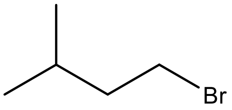
1-bromo-2-methylbutane



2-bromo-2-methylbutane



2-bromo-3-methylbutane



1-bromo-3-methylbutane

The major product is circled. It is major as the free radical would be formed on a 3^o radical.

Common mistake: One may think that hydrogen atoms on carbon a and d (both 1^o carbon) are identical, look at their connectivity. Carbon a is bonded to a tertiary carbon while carbon d is bonded to a secondary carbon. One must pay attention to the full structure of the molecule to be able to decide the unique number of hydrogens, hence the unique number monohalogenated products. Giving a proper IUPAC name will help you eliminate the redundant structures.

Exercise 4.4: How many monobrominated products would form when the following alkanes undergo free radical bromination in presence of light. Draw all the unique products and circle the major product.

(a) cyclopentane (b) 2-methylpropane (c) 3-methylpentane (d) 2,2-dimethylbutane

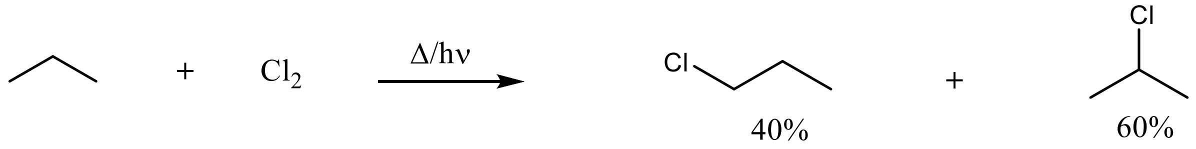
Exercise 4.5: The bromination of methane proceeds through the following propagation steps.

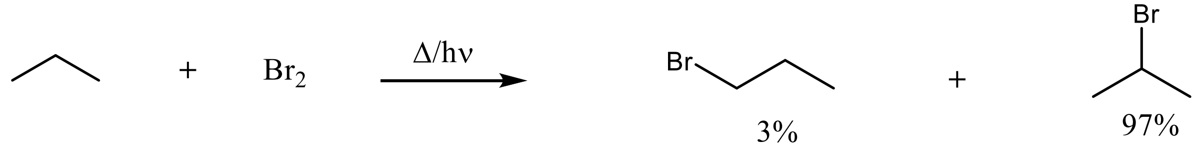
	ΔH° (per mole)	E_a (per mole)
$CH_4 + Br\cdot \rightarrow \cdot CH_3 + HBr$	(16 kcal)	(18 kcal)
$\cdot CH_3 + Br_2 \rightarrow CH_3Br + Br\cdot$	(−24 kcal)	(1 kcal)

a. Draw a complete reaction-energy diagram for this reaction.
b. Label the rate determining step.
c. Calculate the overall value of ΔH° for the bromination.

4.11 Selectivity in Halogenation

A side-by-side comparison of chlorination vs. bromination yielded interesting results when it came to the ratio of products being formed. Pat attention to the percent of products being formed. Bromination is a lot more "**selective**" compared to chlorination it makes a LOT more of 2-bromopropane than chlorine making 2-chloropropane. Why is that?





This observation was explained by the energy diagram of the propagation step of chlorination vs. bromination. The energy differences between chlorination and bromination result from the difference in the bond-dissociation enthalpies of H-Cl (103 kcal) and H-Br (88 kcal). The HBr bond is weaker, and abstraction of a hydrogen atom by is endothermic. This endothermic step explains why bromination is much slower than chlorination. The transition states forming the 1° and 2° radicals for the endothermic bromination have a larger energy difference than those for the exothermic chlorination.

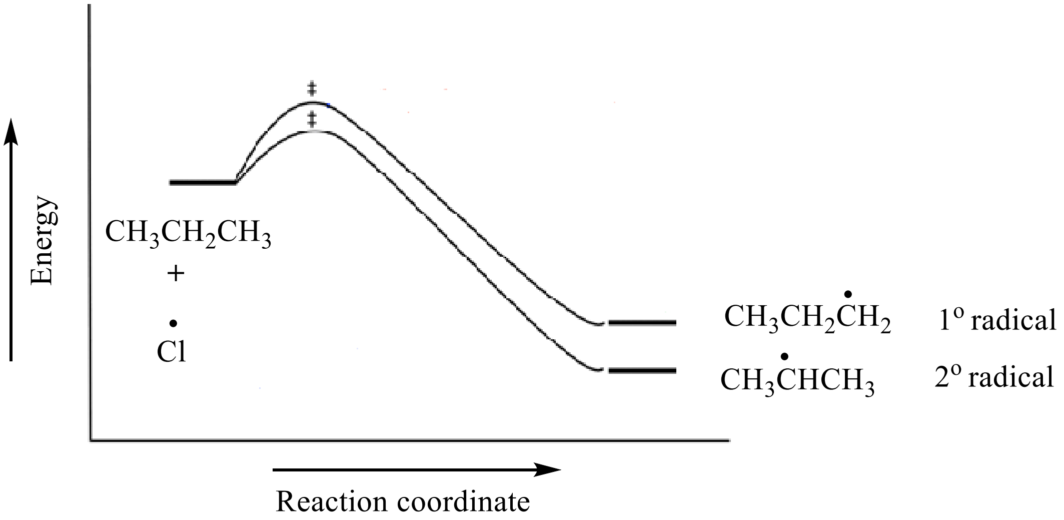


Figure 4.4: Energy diagram of chlorination of propane

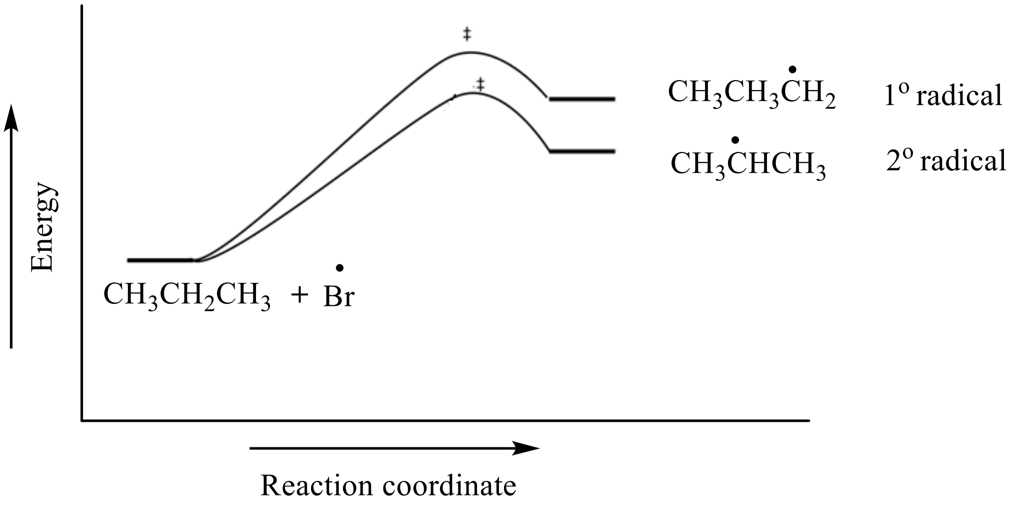
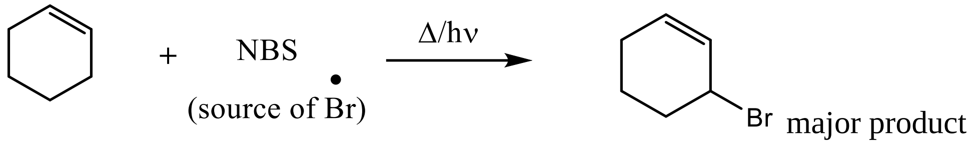


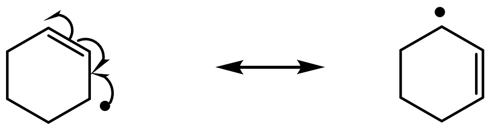
Figure 4.5: Energy diagram of bromination of propane

4.12 Free radical halogenation of alkenes

Instead of using Br_2, N-bromosuccinamide) (NBS) is used during free radical halogenation of alkenes. Since Br_2 can add across the double bond of alkene (more in chapter 8), NBS is used to provide a low concentration of bromine radical. Its mechanism is identical to the free radical halogenation of alkanes with Br_2 or Cl_2.



By now, we know that the free radical mechanism takes place with the formation of most stable free radical during the rds. With alkenes, the most stable free radical will be adjacent to the pi bond (also called **allylic** position) so that when the radical forms, it will be capable of resonance. In case of cyclohexene (shown above) you can use either of the carbons that are adjacent to the pi bond, them being identical.

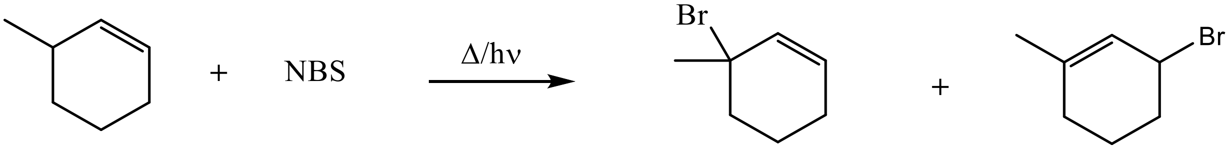


Since these two resonance forms are of equal energy, only one product is formed.

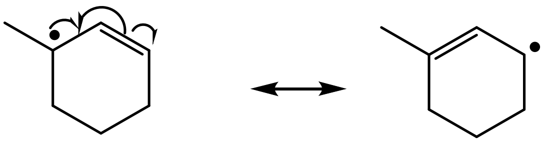
Note (1): Since free radical has a lone electron, we use fishhook-shaped half-arrows ↷. During resonance, there is a delocalization of 3 electrons, so three of the fishhook arrows will be used to show the movement of these three electrons.

Note: (2): The free radicals on sp2 and sp carbons are highly unstable and will not be formed.

Solved Problem 4.2: When the given alkene undergoes free radical halogenation with NBS in presence of heat/light, two structural isomers are formed as the major products. Explain how.



There are two carbons adjacent to the pi bond, one that is 3^o and one that is 2^o. We already know from stabilities of radicals that a 3^o radical is more stable than a 2^o radical, therefore, the most stable radical adjacent to the double bond on a 3^o carbon would form in the rds.



I II

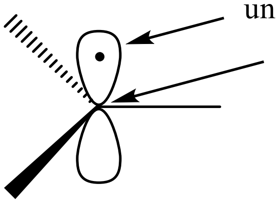
This radical is capable of resonance. Looking carefully at the structure of radical I and II, they are of different stabilities. For now, draw both the products coming from each of these radicals. We will wait until Organic II lecture to find out which forms as a major product, as that depends upon the temperature.

Exercise 4.6: When the given alkene undergoes free radical halogenation with NBS in presence of heat/light, two structural isomers are formed as the major products. Draw both.

4.13 Reactive Intermediates

Some of the common reactive intermediates contain carbon atoms with only three bonds, compared with carbon's four bonds in its stable compounds. The three most common type of organic R.I. are:

1. <u>**Free radical**</u> (carbon with three bonds <u>and</u> a single electron)

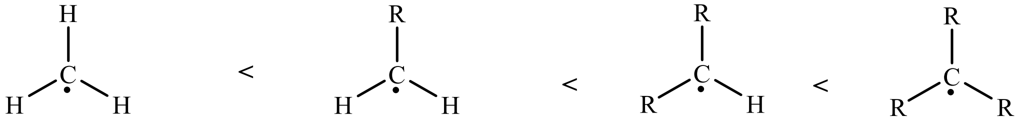


unhybrid p-orbital where the unpaired electron resides

sp2, 120^o bond angle, trigonal planar geometry

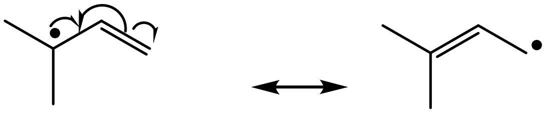
There are two ways the stability of free radicals can be discussed. (a): Indictive Effect and (b):, Resonance effect.

The **inductive effect** is a donation of electron density through the sigma bonds of the molecule. The electron deficient carbon atom of the free radical is stabilized from the alkyl groups bonded to it. The more alkyl groups attached to it, the more stable the free radical.



methyl (least stable) primary secondary tertiary (most stable)

Resonance effect is the delocalization of the single electron adjacent to the pi bond.

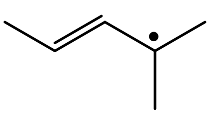


I

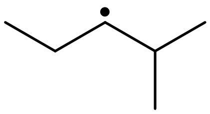
more stable free radical

II

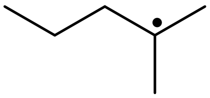
Exercise 4.7: Rank the free radicals (**A-C**) shown below in order of <u>decreasing</u> stability (i.e., from most stable to least stable).



A

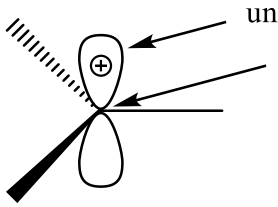


B



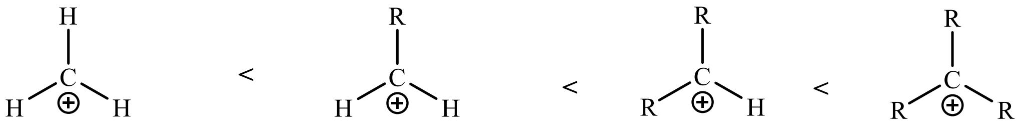
C

2. **<u>Carbocation</u>** (carbon with three bonds and no electrons, incomplete octet and a positive



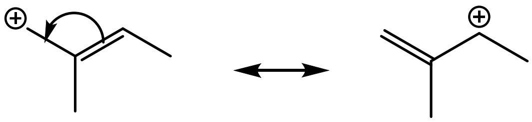
Like in case of free radicals, there are two ways the stability of carbocations can be discussed. (a): Indictive Effect and (b): Resonance effect.

The electron deficient carbon atom of the carbocation is stabilized from the alkyl groups bonded to it. The more alkyl groups attached to it, the more stable the carbocation.



methyl (least stable) primary secondary tertiary (most stable)

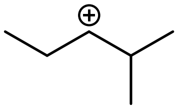
Resonance effect is the delocalization of the positive charge on the carbocation.



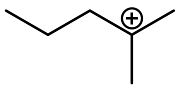
I

II more stable carbocation

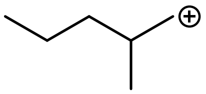
Exercise 4.8: Rank the following in the order of increasing stability (least stable first).



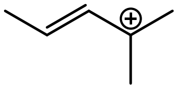
A



B

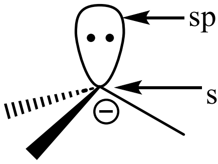


C



D

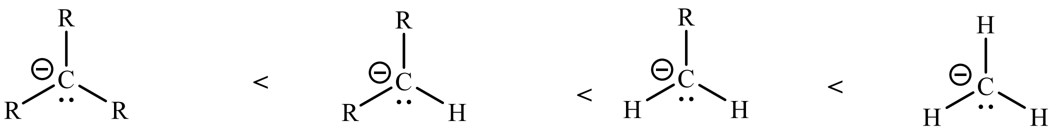
3. **<u>Carbanion</u>** (carbon with three bonds <u>and</u> a lone pair, hence a formal negative charge)


sp3 orbital in which electrons reside

sp3, 109.5^o bond angle, tetrahedral geometry

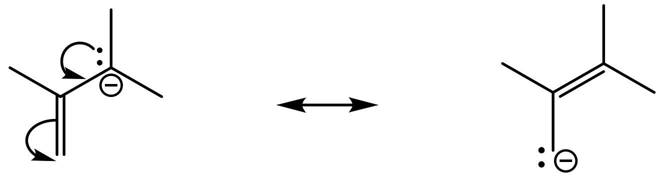
Note the hybridization of carbanion! Due to which the bond angle, geometry and
Like in case of free radicals and carbocations, there are two ways the stability of carbanions can be discussed. (a): Indictive Effect and (b): Resonance effect.

The electron rich carbon atom of the carbanion is **destabilized** from the alkyl groups bonded to it. The more alkyl groups attached to it, the more unstable the carbanion. **In that aspect, carbanion is opposite to free radicals and carbocation.**



tertiary (least stable) secondary primary methyl (most stable)

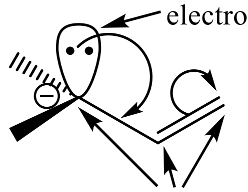
Resonance effect is the delocalization of the negative charge and the lone pairs on the carbanion.



I

II more stable carbocation

Important Exception to Hybridization. In structure I and II above, the lone pairs are capable of resonance, the lone pairs will reside in the unhybrid p-orbitals and hence the carbon with the lone pairs will be sp2 hybridized and will have 120 bond angle and a trigonal planar geometry.



electrons reside in unhybrid p-orbital due to resonance

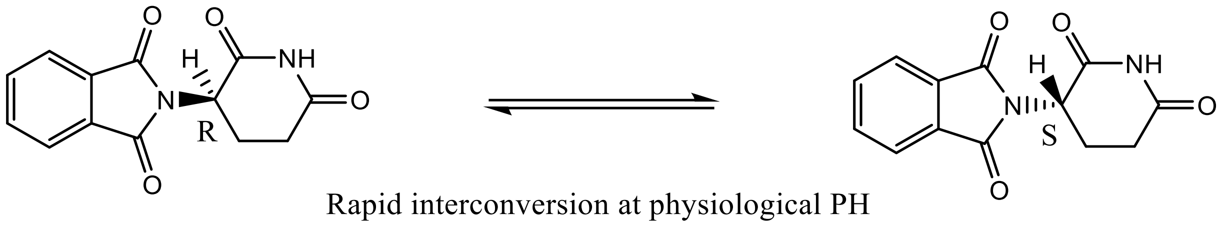
sp2 hybridized carbons, 120^{o} bond angle, trigonal planar geometry

Chapter 5: Stereochemistry

5.1 Background information

Stereochemistry is the study of three-dimensional structures of molecules. For simplicity, we will only discuss stereochemistry on a sp3 hybridized carbon atom.

More than 60 years after the drug thalidomide caused birth defects in thousands of children whose mothers took the drug while pregnant, the million-dollar question remained: “How did the drug produce such severe fetal harm”?

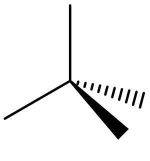


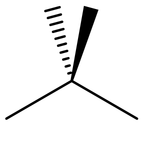
R-thalidomide

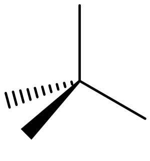
S-thalidomide

S-thalidomide is teratogenic (any agent that can disturb the development of an embryo or fetus and may cause a birth defect in the child). However, the drug can convert (racemize) between enantiomeric states at physiological pH, and it is very difficult to make a stable form that is nonteratogenic. Researchers have found that thalidomide acts by promoting the degradation of an unexpectedly wide range of transcription factors – cell proteins that help switch genes on or off – including one called SALL4. The result is the complete removal of SALL4 from cells. Individuals who carry a mutation in the gene for SALL4 are often born with missing thumbs, underdeveloped limbs, eye and ear defects, and congenital heart disease – problems that mirror those in children exposed to thalidomide in the womb.

Before going further, it is important to know the correct way of representing a 3D molecule on a piece of paper:

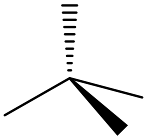


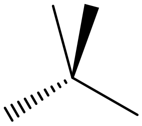


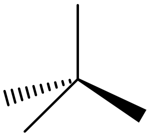


The two bonds on the plane are drawn together while the wedge and dash are drawn together.

Incorrect way to represent a 3-D molecule:

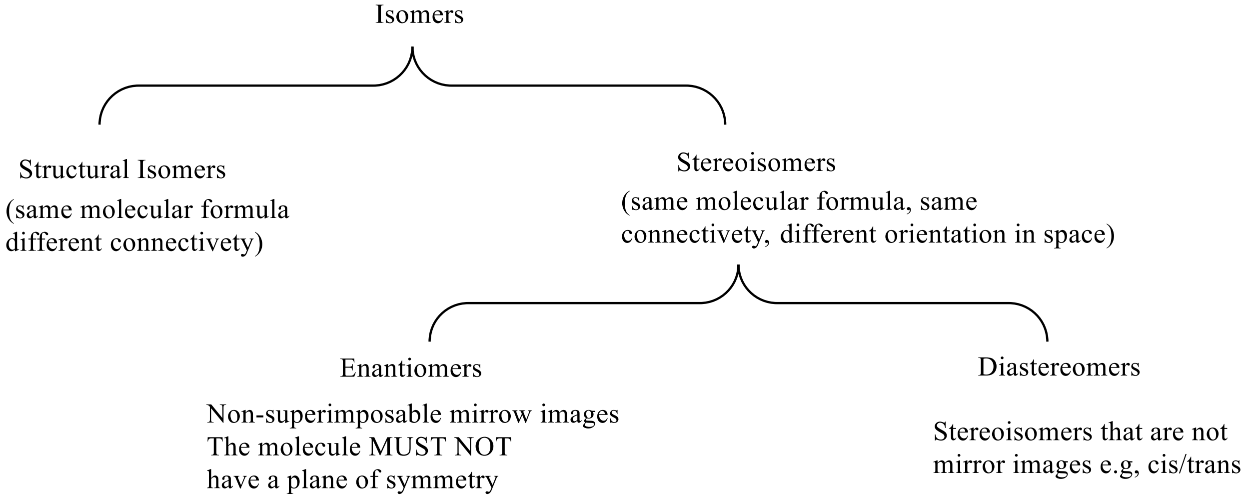






This is incorrect as the two bonds on the plane are NOT drawn together and the wedge and dash are NOT drawn together.

Enantiomers and **diastereomers** are two types of stereoisomers.



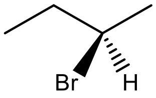
Isomers

Structural Isomers
(same molecular formula
different connectivety)

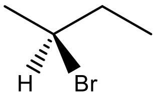
Stereoisomers
(same molecular formula, same
connectivety, different orientation in space)

Enantiomers
Non-superimposable mirrow images
The molecule MUST NOT
have a plane of symmetry

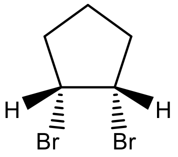
Diastereomers
Stereoisomers that are not
mirror images e.g, cis/trans



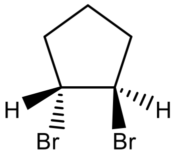
A



B



C



D

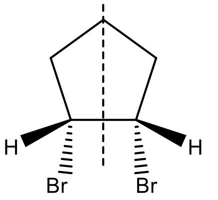
A & B are non-superimposable mirror images, therefore **enantiomers**. C (cis) and D (trans) are examples of stereoisomers that are not mirror images, therefore C and D are **diastereomers**.

5.2 Chirality

Molecules that demonstrate handedness are called **chiral** molecules. In other words, we can say that the molecules that lack a plane of symmetry (an imaginary plane that cuts the molecule in two equal halves) are **chiral**.

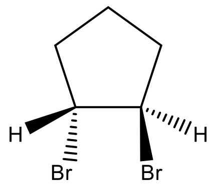
Since the hand lacks a plane of symmetry, it will be considered chiral.

Look carefully at molecule A. This molecule has a plane of symmetry; hence this molecule will not be chiral, or it will be **achiral**. Molecule B on the other hand lacks a plane of symmetry and hence it would be chiral.



A

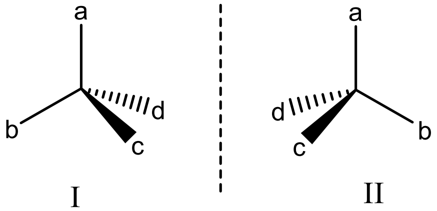
achiral



B

chiral

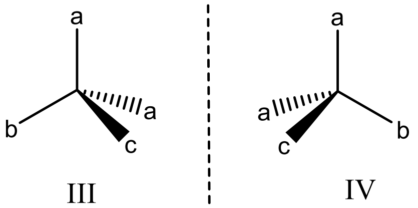
How can we easily figure out the plane of symmetry? What if the plane of symmetry is not obvious? Let us simplify and state the following: The condition for a compound with one **chiral** carbon is that it must be attached to four different groups. If all four groups are different, the carbon is called an **asymmetric** carbon and a **chiral** center. When that happens, the molecule and its mirror image are non-superimposable and are called **enantiomers.** In the image below, molecule I and II are non-superimposable mirror images and as the four groups are different, they are **enantiomers**.



I II

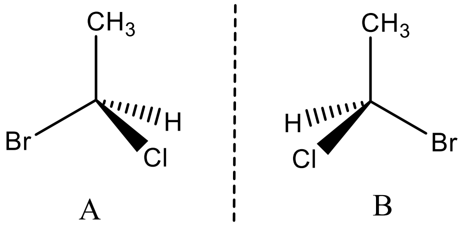
$a \neq b \neq c \neq d$

The moment two of these 4 groups are identical, the molecule is no longer chiral. It becomes achiral.



III IV

In III and IV, two of the four groups are identical, therefore III and IV must be identical and are achiral.



A B

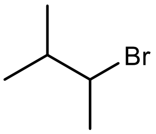
A has four different groups and B is its mirror image. These mirror images must be non-superimposable and hence A and B are enantiomers.

Exercise 5.1: Which of the following molecules are chiral?

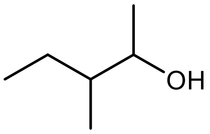
a. 2-chloropropane **b.** *cis*-1,2-dibromocyclobutane **c.** 1,2-dichloropropane
d. *trans*-1,2-dibromocyclobutane e. trans-1,4-dichlorocyclohexane

Exercise 5.2: Locate all the chiral centers (there may be more than one in a molecule). If there are no chiral center, indicate so.

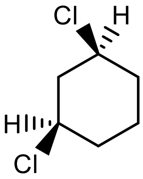
a.



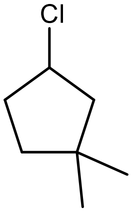
b.



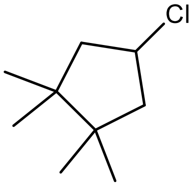
c.



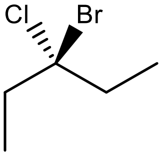
d.



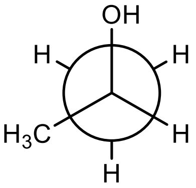
e.



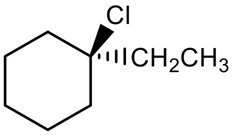
f.



g.

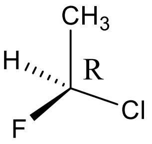


h.

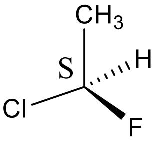


5.3 (R) and (S) Nomenclature of Asymmetric Carbon Atoms

To distinguish one stereoisomer from another, the **Cahn-Ingold-Prelog (CIP) system** is used, which is a set of rules that allows us to unambiguously define the stereochemical configuration of any stereocenter, using the designations '***R***' (from the Latin *rectus*, meaning right-handed) or '***S***' (from the Latin *sinister*, meaning left-handed).



A



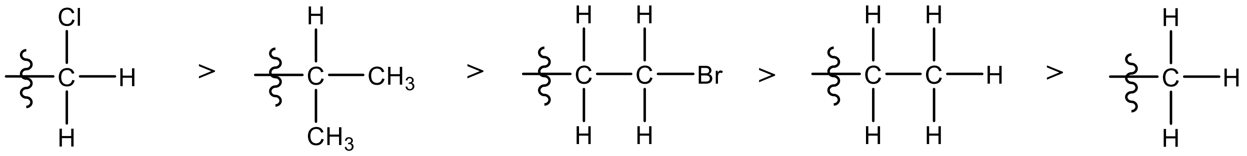
B

A and B are two enantiomers. A has R stereochemistry, and B has S stereochemistry.
The rules for assigning an R/S designation to a chiral center are as follows:

1: Assign priorities to the four substituents, with #1 being the highest priority and #4 the lowest. Priorities are based on the atomic number. Higher the atomic number, higher the priority. Br>Cl>F>O>N>C>H

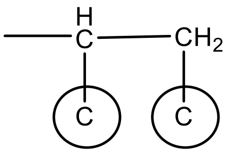
2. If there is a tie, use the next atom until a decision is made.

We assign higher priority to chloromethyl ($-CH_2Cl$), then isopropyl $-CH(CH_3)_2$ then bromoethyl ($-CH_2CH_2Br$), then ethyl ($-CH_2CH_3$) then methyl ($-CH_3$). One high-priority atom takes priority over any number of lower-priority atoms.



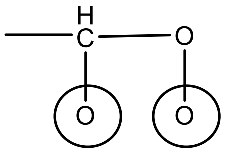
3. Double and triple bonds should be treated as if each were a bond to a separate atom. For this method, imagine that each pi bond is broken and the atoms at both ends are duplicated. Note that when you break a bond, you always add two imaginary atoms. (Circle the "imaginary" atoms)

$-CH{=}CH_2$ becomes



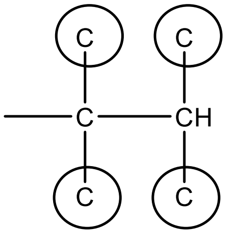
break the double bond and duplicate

$-CH{=}O$ becomes



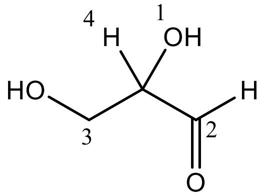
break the double bond and duplicate

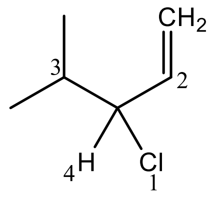
$-C{\equiv}CH$ becomes

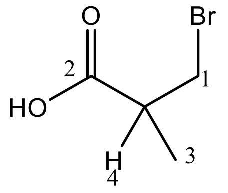


break the triple bond and duplicate

Examples of assigned priorities groups on a chiral center.

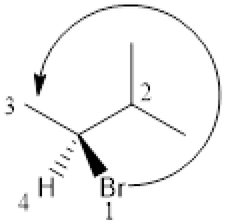






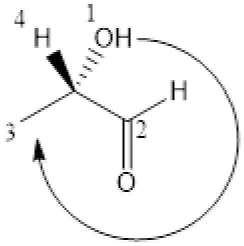
To assign R/S priorities:

1. **If the orientation of the #4 priority group is going behind (dash line)**, trace a circle from #1 to #2 to #3. A clockwise circle corresponds to the *R* configuration, while a counterclockwise circle corresponds to the *S* configuration.



The lowest priority is going behind and making a circle from 1->2->3 is going counterclockwise, therefore this must be “S”.

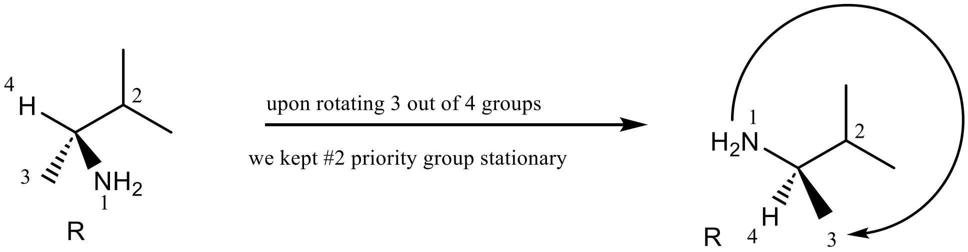
2. **If the orientation of the #4 priority group is coming towards you (wedges),** trace a circle from #1 to #2 to #3. Figure out R/S, and the **<u>opposite</u>** stereochemistry would be the correct one (since you are viewing the molecule from the backside).



Although the 1->2->3 is going clockwise, the lowest priority group is coming towards you (wedges), so the correct stereochemistry would be the opposite, it would be “S”.

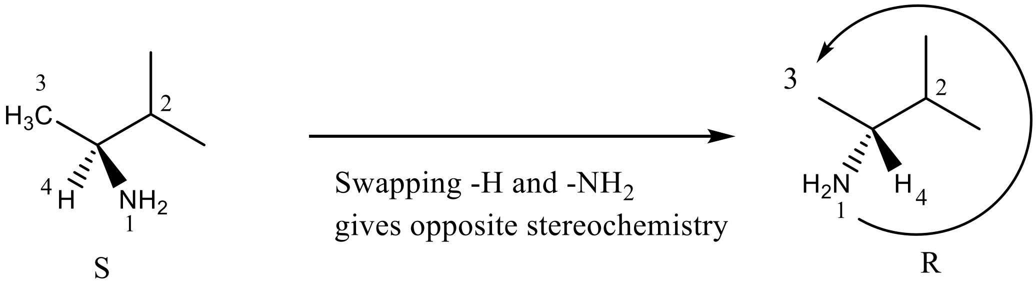
Notes: Some other useful tips

A. Rotating 3 out of 4 groups gives you the same stereochemistry. If the lowest priority group is on the plane, rotate three out of four groups such that it goes behind the plane (dash line) and figure out R/S.



H takes the place of CH_3, CH_3 takes the place of NH_2 and NH_2 takes the place of H (the isopropyl group was kept stationary).

B. Swapping two groups once gives you the opposite stereochemistry.

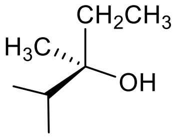


(lowest priority is coming towards you, so opposite streochemistry is correct)

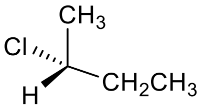
When you swap two groups, the stereochemistry becomes opposite (R becomes S and S becomes R). In this case swapping H and NH_2 will give the opposite stereochemistry.

Exercise 5.3: For each of the following chiral centers, give priority from 1-4 to all the groups attached to the chiral center (1 for the group with the highest priority, 4 for the lowest), then assign R/S stereochemistry to each chiral carbon.

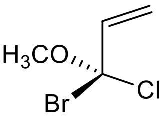
a.



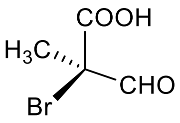
b.



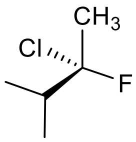
c.



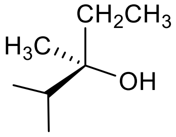
d.



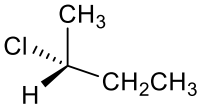
e.



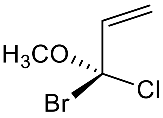
f.



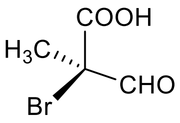
g.



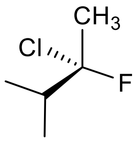
h.



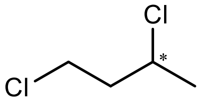
i.



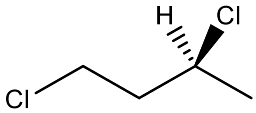
j.



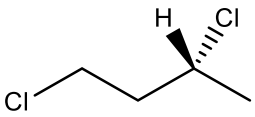
Solved Problem 5.1: Draw the enantiomers of 1,3-dichlorobutane and label them as (*R*) and (*S*).



has only one chiral center that has been labeled as *. To draw one enantiomer, we use wedges and dash line at the chiral center. In one case, Cl on the chiral center will be drawn up (with a wedge) and the hydrogen not shown in the line formula will be drawn going down (with dash line). This structure ends up with "S" stereochemistry. To draw its enantiomer, redraw the structure, but swap the stereochemistry of Cl and H and you will end up with the "R" stereochemistry.



(S)-1,3-dichlorobutane



(R)-1,3-dichlorobutane

5.4 Optical Activity

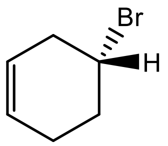
Any chiral compound is optically active. An optically active compound rotates plane polarized light. To find out if a compound is chiral or optically active look for two things:

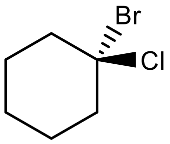
a. Does it have a chiral center (four different groups on the carbon atom)?
b. Does the molecule lack plane of symmetry?

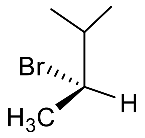
If you answer yes to both questions, the compound is chiral. For cyclohexane, do not use the chair conformations (as they will have two chairs). Use planar cyclohexane for chirality.

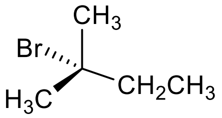
For compounds with only one chiral center: If the carbon atom has four different groups, it will be chiral as it cannot have a plane of symmetry.

Solved Problem 5.2: Which of the following are chiral?


A

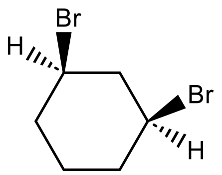

B

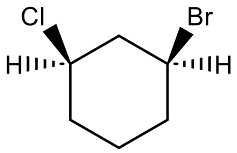

C

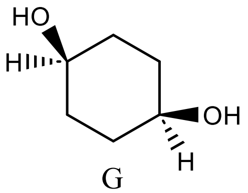

D

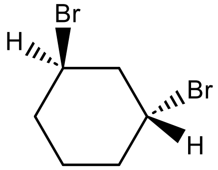
Compounds A and C have carbon atom that have 4 different groups attached to it, so A and C are chiral compounds, hence they are also optically active. Compounds B and D do not have a carbon with 4 different groups; hence, compounds B and D are achiral and optically inactive.

Solved Problem 5.2: Which of the following compounds are chiral?


E


F

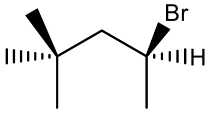

G


H

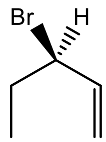
Compounds E, F and H have chiral centers, but compound G does not, so compound G is achiral as it does not have any chiral center. Compound F and H lacks the plane of symmetry; F and H will be chiral and optically active. Although E has chiral centers, the compound is achiral due to plane of symmetry. The compounds that have chiral center but are achiral due to plane of symmetry are called **meso** compounds.

Exercise 5.4: Which of the following compounds are chiral (optically active)?

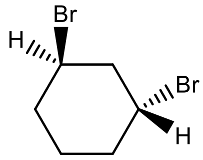
a.



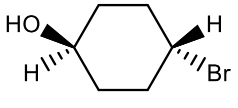
b.



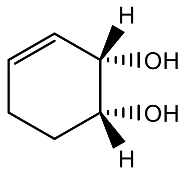
c.



d.

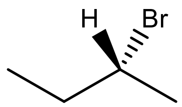


e.

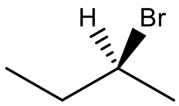


5.5 Racemic Mixtures

Equal mixture of two enantiomers makes a racemic mixture. If in a test tube, you have 50% of (S)-2-bromobutane and 50% of (R)-2-bromobutane, you would call it racemic mixture.



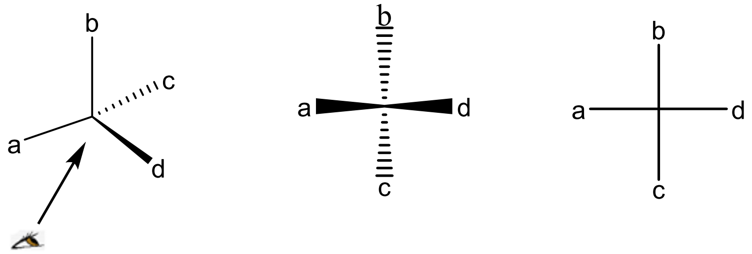
(R)-2-bromobutane



(S)-2-bromobutane

5.6 Fischer Projections

Fischer Projections are a 2-D representation of a 3-D molecule.

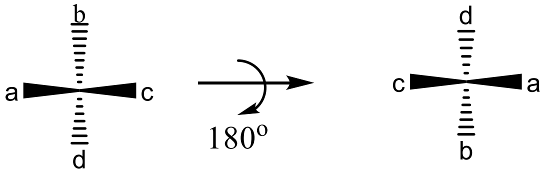


view from this angle

The Fischer projection looks like a cross, with the chiral carbon at the center of the cross. The horizontal lines (will also be referred as arms) are bonds coming towards you (wedges). The vertical lines (will also be referred as North and South) are bonds going away from you (dashed lines). Due to these very specific conditions as how you write Fischer Projections, a few things must be kept in mind:

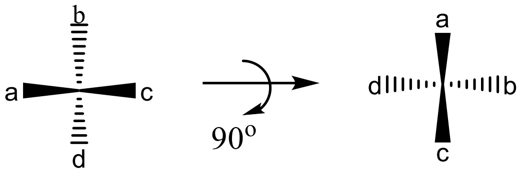
1. ***Rotation by 180^o is allowed***
2. ***Rotation by 90^o is NOT allowed.***
3. ***Flipping the Fischer projection like a burger is NOT allowed.***
4. ***If the lowest priority group is on the arm, figure out R/S and the opposite stereochemistry would be the correct one, as the lowest priority group is coming towards you.***

- Rotating by 180^o is allowed as it results in arms still going up.



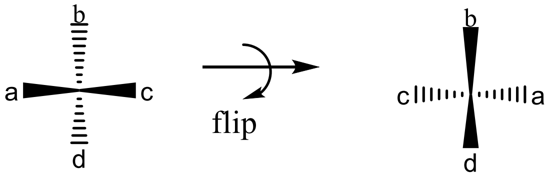
arms remains as wedges

- Rotating by 90^o is **NOT allowed** as it results in arms going down, which is not allowed in Fischer Projection.



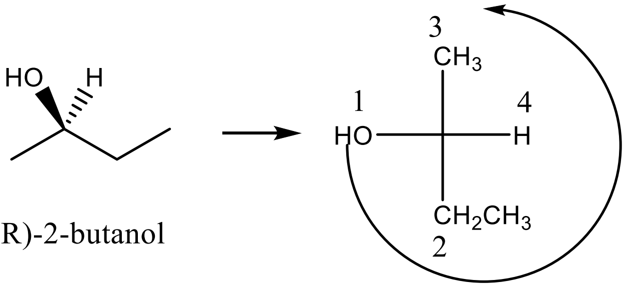
arms are no longer wedges

- Flipping the molecule like a burger is NOT allowed.



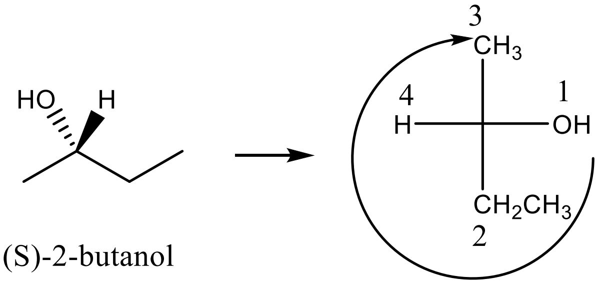
arms are no longer wedges

- If the lowest priority group is on the arm, figure out R/S and the opposite stereochemistry would be the correct one, as the lowest priority group is coming towards you.



(R)-2-butanol

In here, although 1->2->3 priority groups are going counterclockwise (S), the correct stereochemistry is R as the lowest priority group is on the arm (coming towards you. What if you wanted to draw its enantiomer (S)-2-butanol? Just swap the arms, and you will end up with the enantiomer!



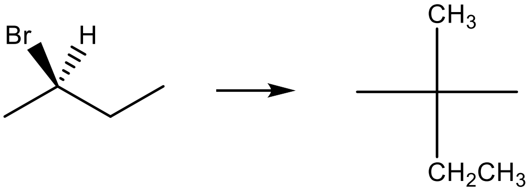
(S)-2-butanol

(S)-2-butanol

The final rule for drawing Fischer projections is that the carbon chain is drawn along the vertical line of the Fischer projection, with the IUPAC numbering from top to bottom. In most cases, this numbering places the most highly oxidized carbon (**carbon with more oxygen attached to it**) substituent at the top.

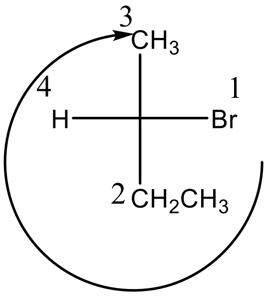
Solved Problem 5.3: Write the Fischer Projection of (R)-2-bromobutane.

To write the correct Fischer Projection of (R)-2-bromobutane make sure the longest carbon chain goes from North to South. Then draw the remaining two groups on the chiral center.

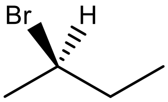


At this point, without the models it becomes challenging to know which group, H or Br should be on the right side. I would say randomly draw the Br on the right side and H on the left and then check stereochemistry.

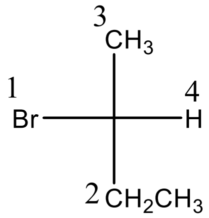
if drawn like this



What is the stereochemistry of this Fischer projection? Is this R? Since hydrogen, (the lowest priority group is on the arm), we have to reverse the stereochemistry. Since 1->2->3-> goes clockwise, it is NOT R, but S. So how can we fix this structure so that we have (R)-2-bromobutane? Just flip the arms (don't flip the north and south as that would not give you the longest chain going from north to south).



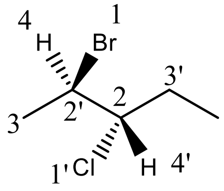
should be drawn like this



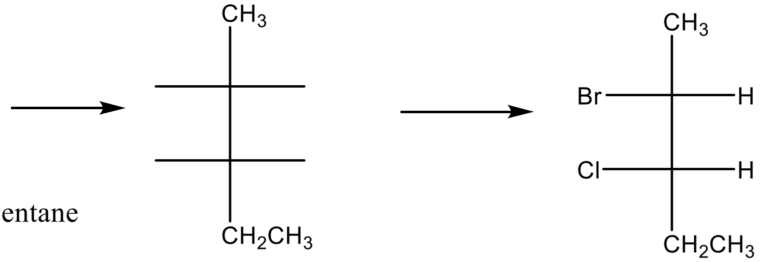
(R)-2-bromobutane

Solved Problem 5.4: Write the Fischer Projection of (2R,3S)-2-bromo-3-chloropentane.

Fischer projection of compounds with more than one (2 or more) chiral center will have the same principle. To begin with, assign priorities to all the groups on each chiral center (1,2,3,4 is used for chiral carbon #2 and 1'2'3'4' is used for chiral carbon #. This is followed by writing the Fischer crossbar such that the longest chain goes from north to south. Since the arms will have a hydrogen atom which has the lowest priority, figure out R /S and reverse will be the correct stereochemistry. If you place Br on the right arm, 1->2->3 will be going clockwise (but S) as H is coming towards you. So, place the Br on the left arm instead. Do the same with the second stereocenter. Cl on right side would give you S stereochemistry.

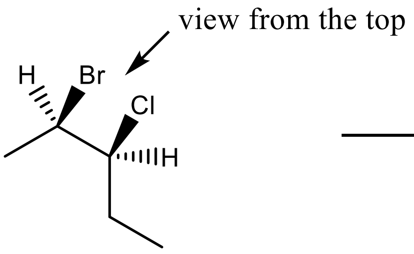


(2R,3S)-2-bromo-3-chloropentane

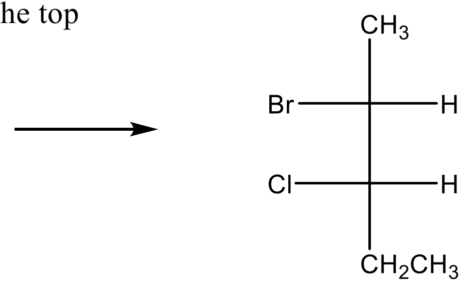


(2R,3S)-2-bromo-3-chloropentane

Do not be confused by the 3D perspective having Br and Cl in the opposite side while in Fischer projections they are on the same side. This happens because in Fischer projections, arms always come towards you. In other words, Fischer is the least stable Newman. Making models will really help here.



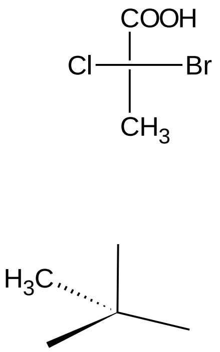
(2R,3S)-2-bromo-3-chloropentane



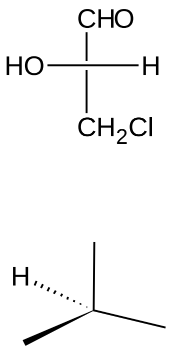
(2R,3S)-2-bromo-3-chloropentane

Exercise 5.5: Figure out the stereochemistry for each of these Fischer Projections and convert each of them in the correct 3-D perspective formula.

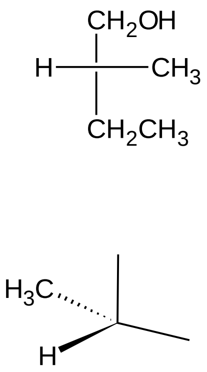
a.



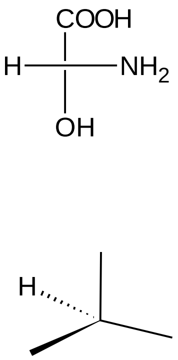
b.



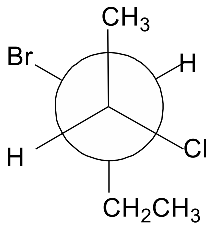
c.

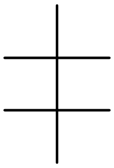


d.



Exercise 5.6: Draw the following molecules in Fischer Projections.



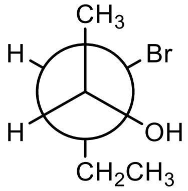


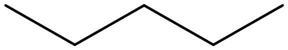
Exercise 5.7: Draw the following molecules in 3-D perspective.

(a) (2R,3S)-2,3-dibromohexane

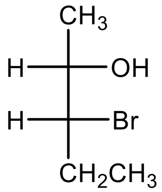
(b) (1S,3R)-1-ethyl-3-isopropylcyclopentane

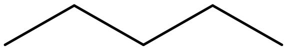
(c)





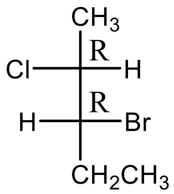
(d)



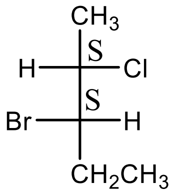


Drawing mirror images of Fischer projections:

Although the mirror image of Fischer projection can be drawn many ways, the easiest is to pretend a mirror on the paper. Unless the mirror image is identical (due to plane of symmetry), the stereochemistry of mirror images will always be opposite. I and II are enantiomers as they are non-superimposable mirror images.



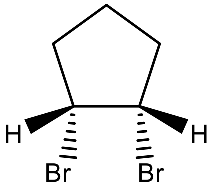
(2R, 3R)-2-chloro-3-bromopentane
I



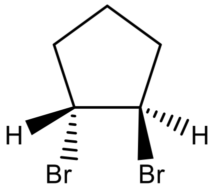
(2S, 3S)-2-chloro-3-bromopentane
II

5.7 Diastereomers

Earlier, we defined diastereomers as stereoisomers that are not mirror images. Cis/trans isomers are examples of diastereomers as they have the same connectivity, but they are not mirror images. There are other types of diastereomers other than cis/trans.



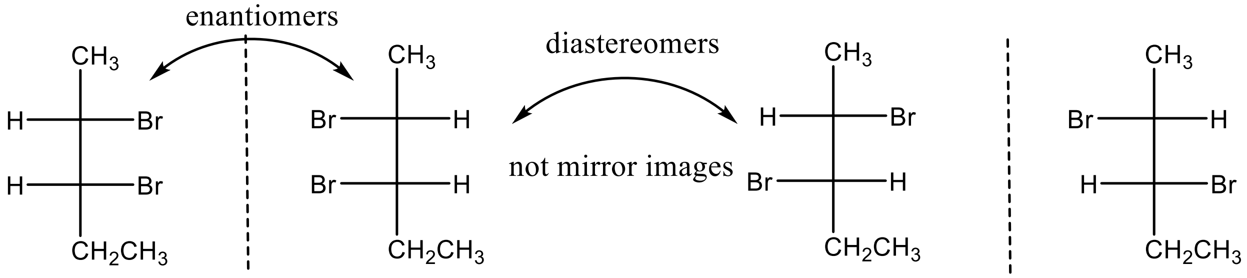
A



B

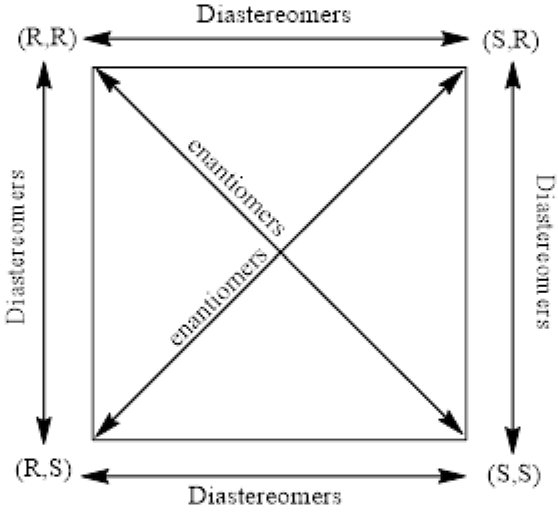
Maximum number of stereoisomers with n chiral center = 2^n

For only one chiral center, there will be only two stereoisomers that will be enantiomers. But then there are 2 chiral centers, there can be a maximum of 4 stereoisomers. Let us explore different stereo isomers of 2,3-dibromopentane.



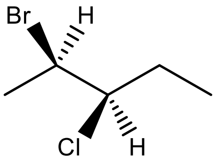
(2S, 3R) (2R, 3S) (2S, 3S) (2R, 3R)

I **II** **III** **IV**

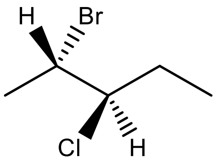


Looking at the stereochemistry of each of the four compounds, it is evident that I and II are mirror images and so are III and IV. However, I and III; II and III; I and IV; II and IV are not mirror images. They are stereoisomers that are not mirror images, therefore they are diastereomers. An easy way to figure out relationships between stereoisomers if they are enantiomers or diastereomers is to look at their stereochemistry. We will use the image below to explain relationships between compounds. Within the diagonal of the square shown below, the stereochemistry of both chiral center inverts, therefore, they will be enantiomers. Outside the perimeter of the square, only one center inverts, therefore the perimeter compounds will be diastereomers.

Solved problem 5.4: What is the relationship between the two molecules shown below? Choose from structural isomers, enantiomers, diastereomers, identical, not isomers.



A

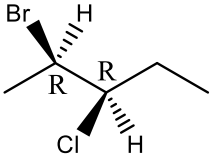


B

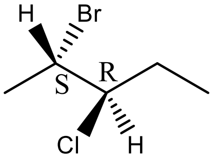
A few things you should be asking is as follows:

1. Do they have same molecular formula? If yes, they are isomers, if no, they are not isomers.
2. Do they have the same connectivity? If yes, they are stereoisomers, if no, they are structural isomers.
3. If they have same connectivity, are they mirror images? If yes, do they have a plane of symmetry? If yes, the two are identical. If no, they are enantiomers.
4. If they have same connectivity but are not mirror images, they are diastereomers.

A is (2R, 3R) while B is (2S, 3R), therefore these stereoisomers that are not mirror images, therefore they are diastereomers.



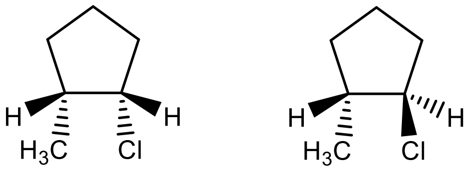
A



B

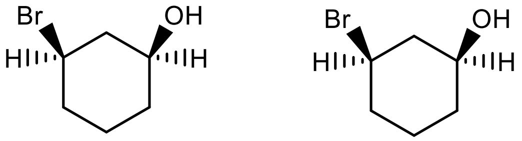
Exercise 5.8: For each pair, give the relationship between the two compounds. Choose from structural isomers, enantiomers, diastereomers, identical, not isomers.

a.

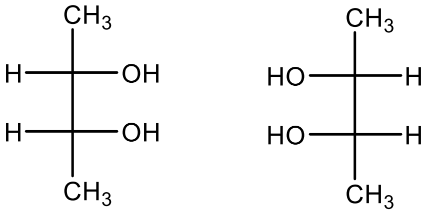


b.

c.

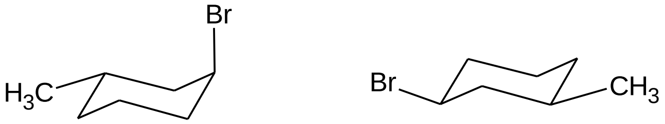


d.



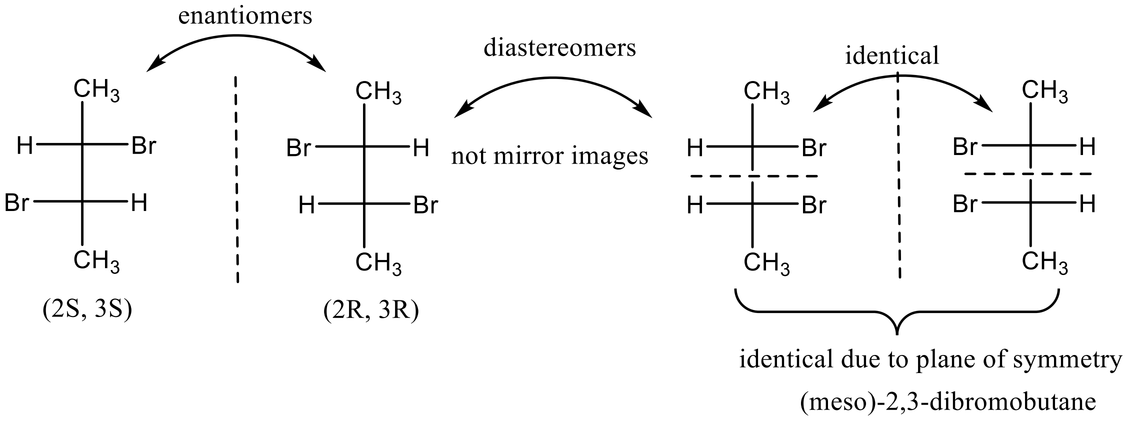
e.

f.



5.8 Meso Compounds

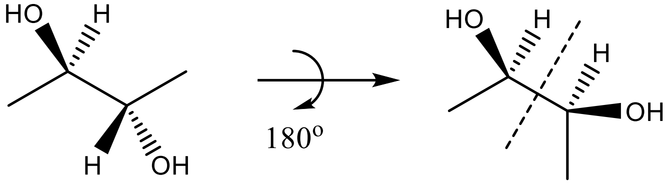
Compounds that have chiral centers but are achiral due to plane of symmetry are called **meso** compounds. Because they are achiral, they are optically inactive.
Let us take example of 2,3-dibromobutane. Drawing Fischer projections of all its stereoisomers results in not 4 but three stereoisomers.



I II III IV

I and II are enantiomers. III and IV are identical and are called **meso**. Although they are mirror images, they are identical as they have a plane of symmetry. It is easier to see the plane of symmetry in Fischer projections, so you can draw a 3-D perspective to a Fischer projection to see the plane of symmetry. Otherwise, convert a 3-D perspective such that you can see the plane of symmetry by drawing the compound in its eclipsed form.

e.g. In the example below, it is difficult to see the plane of symmetry in the 3-D perspective of compound I drawn in the staggered form (conformer I). By rotating the right carbon by 180°, it is easy to see the plane of symmetry in the eclipsed form (conformer II). Hence this compound is **meso**, as is evident by the plane of symmetry it exhibits.

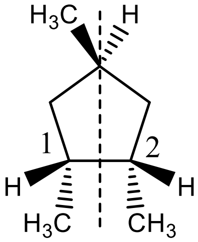


I

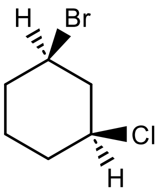
II

For a compound to be meso, the two (or more) chiral centers must have the same identical four groups.

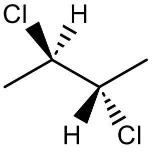
e.g., in the compounds shown below, there are two chiral centers, 1 and 2. Both centers have the same 4 groups attached and there is a plane of symmetry, therefore this compound is meso.



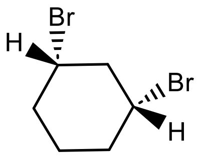
Exercise 5.9: Which of the following are expected to be meso:



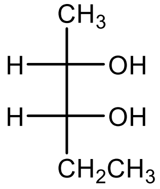
A



B



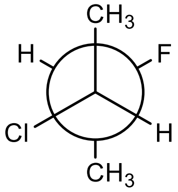
C



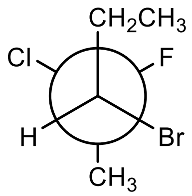
D

Exercise 5.10: Draw the Newman projections in 3D perspective to figure or R/S.

a.

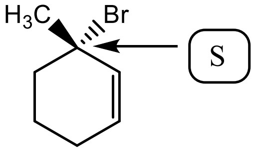


b.

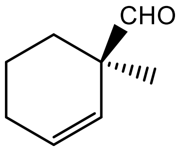


Exercise 5.11: Assign R/S stereochemistry at each chiral center. If not applicable, write N/A. First one is shown as an example.

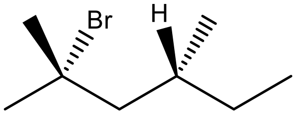
a.



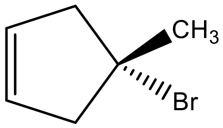
b.



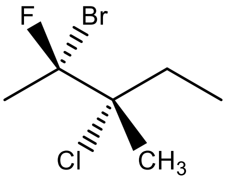
c.



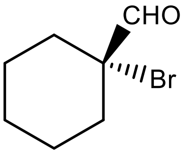
d.



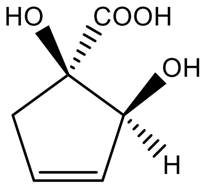
e.



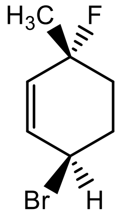
f.



g.

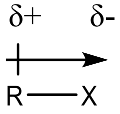


h.



Chapter 6: Alkyl Halides and Nucleophilic Substitution and Elimination Reaction

6.1 Functional group, nomenclature, and classification of Alkyl halides

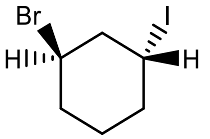


where X = F, Cl, Br, or I

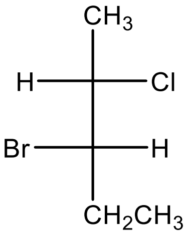
The carbon bonded to halogen is less electronegative than the halogen, hence there is a partial positive charge on the carbon, or it is **electrophilic**. Most reactions of alkyl halides result from breaking this polar covalent bond. Section 4.3 discusses the nomenclature and classification of alkyl halides as primary, secondary, and tertiary.

Exercise 6.1: Provide the IUPAC name of the following compounds including stereochemistry.

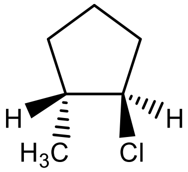
a.



b.



c.

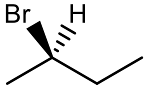


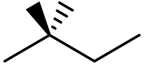
6.2 Preparation of Alkyl Halides-A review from Chapter 4

When butane undergoes a free radical halogenation reaction, two products are formed. 2-bromobutane is the major product. This is due to the formation of a 2° free radical formed in the rds, which has a lower Ea.

major product

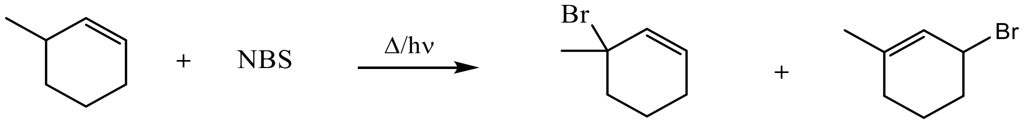
The carbon marked with a * is a chiral center and this reaction gives a mixture of R and S stereoisomers of 2-bromobutane. This is due to the trigonal planar sp2 hybridized free radical formed during the rate-determining step. The bromine can approach this free radical from either top or bottom to give a racemic mixture of (R)-2-bromobutane and (S)-2-bromobutane.



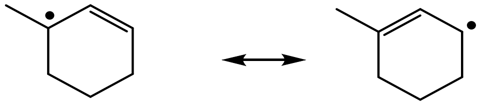


6.3 Allylic Bromination

To avoid the addition of Br_2 across the C=C pi bond, N-bromosuccinamide (NBS) is used during the free radical halogenation of alkenes. In the example shown below, two products are formed via the formation of the most stable (resonance stabilized) allylic free radical.



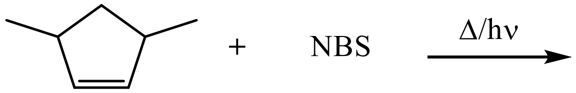
Later in the Organic II lecture, we find out which product forms a major product, as that is temperature dependent.



I

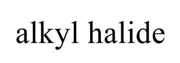
II

Exercise 6.2: Two structural isomers are formed as major products when the reaction shown below takes place. Draw both products.

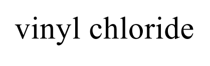


6.4 Reactions of Alkyl Halides: Substitution and Elimination

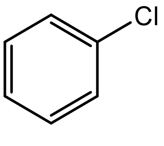
There are three major classes of halogenated organic compounds: the alkyl halides, the vinyl halides, and the aryl halides. An **alkyl halide** simply has a halogen atom bonded to one of the carbon atoms of an alkyl group (sp3 carbon). A **vinyl halide** has a halogen atom bonded to one of the carbon atoms of an alkene (sp2 carbon). An **aryl halide** has a halogen atom bonded to one of the carbon atoms of an aromatic ring (sp2 carbon). The chemistry of vinyl halides and aryl halides is different from that of alkyl halides because their bonding and hybridization are different. ***In this chapter, we will only explore the reactions of alkyl halides.***



alkyl halide



vinyl chloride

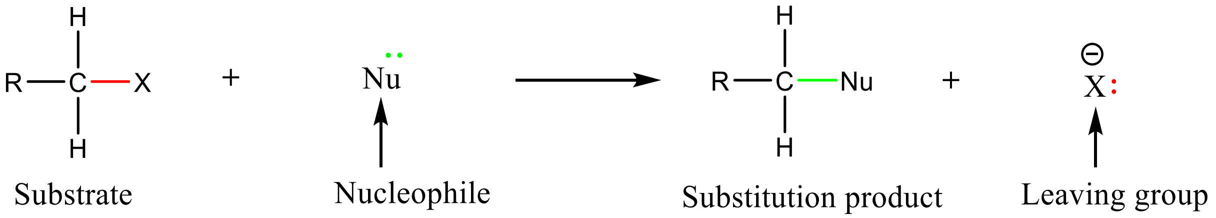


aryl chloride

There are four types of reactions of alkyl halides. Two of them are substitution reactions and the other two are elimination reactions.

S_N1, S_N2 (Substitution Reactions) E1, E2 (Elimination reactions)

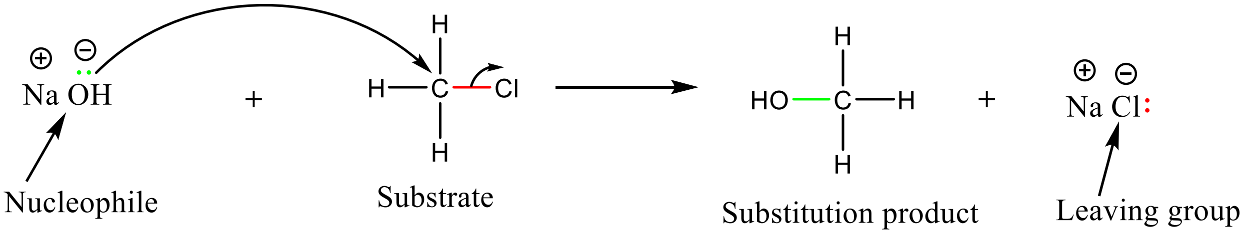
6.5 Bimolecular Nucleophilic Substitution: The S_N2 Reaction



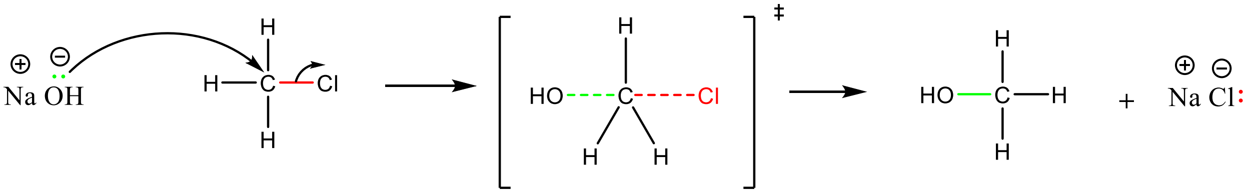
The alkyl halide is called a substrate, and the species it reacts with is the electron-rich species called the nucleophile. During the S_N2 reaction, the bond between nucleophile and substrate is formed (green color), and the bond between carbon and halogen breaks (red color). Once that bond breaks, the halogen leaves with the electron on the bond and is called the leaving group. Notice nucleophile provides the electrons to make the new bond (green) and the leaving group X leaves with the electrons (red).

6.6 S_N2 Mechanism: Arrow pushing during the one-step mechanism of S_N2 reaction.

Bond Making: *The arrow starts from the electrons (not the atom) on the nucleophile and points to the electrophilic atom. This suggests a bond is being made between the two atoms with the help of the electrons on the nucleophile.*
Bond Breaking: *The arrow starts* ***from the bond*** *between electrophilic carbon and halogen and ends up on the halogen atom. This suggests that the bond is being broken and the electrons that were originally between the bonds now end up with the halogen which is the leaving group.*



The oxygen with lone pairs is the nucleophile, the carbon bonded to chlorine is electrophile, and $Cl^{\ominus}$ is the leaving group. Recall, curved arrows always start from nucleophile to electrophile and not the other way around. Here, curved arrows are used to show hydroxide ion $HO^{\ominus}$ attacking the back side of the electrophilic carbon atom, donating a pair of electrons to form a new bond. Since carbon can only have eight electrons, a bond must break. The C-Cl bond is the most polar, and it breaks as a new bond is formed. This is expressed as a transition state of the reaction shown as a ‡symbol. Ultimately, Cl leaves with the electrons and is the leaving group.

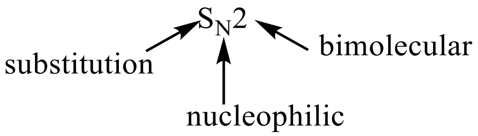


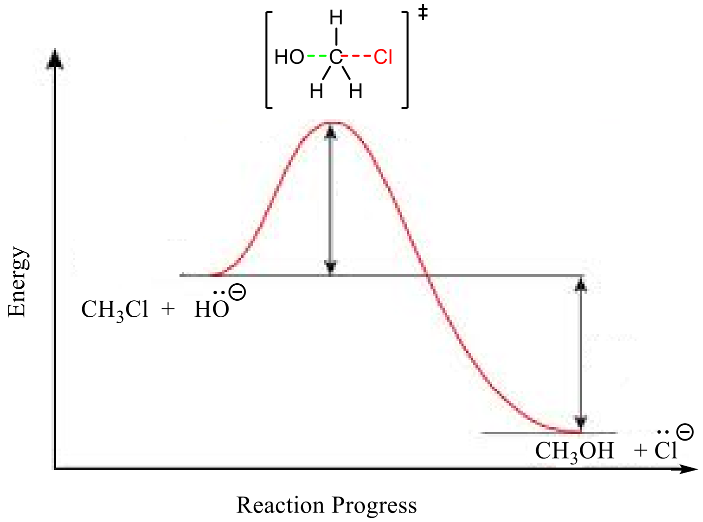
transition state

One can vary the concentrations of the reactants and observe the effects on the reaction rate. The rate is found to double when the concentration of **either** reactant is doubled. The reaction is therefore first order with respect to each of the reactants and second order overall. The rate equation has the following form:

Rate = k $[NaOH]^1[CH_3Cl]^1$ where k is a rate constant.

For all S_N2 reactions, the terminology is

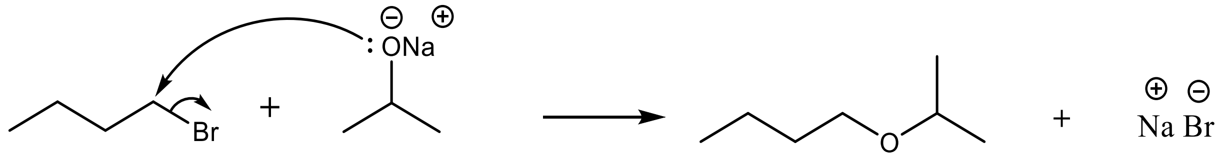


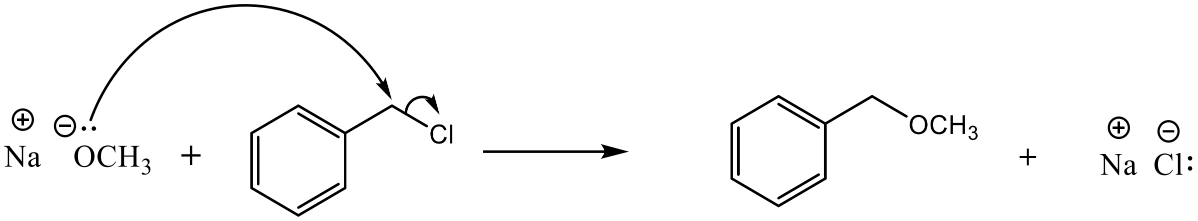


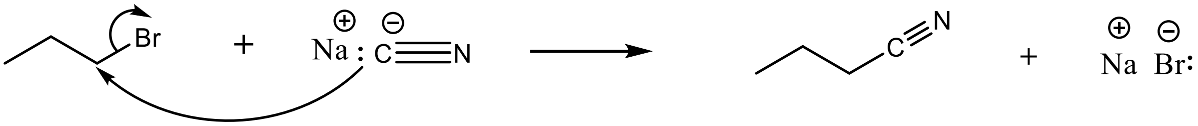
The term bimolecular means that the transition state of the rate-determining step (the only step in this reaction) depends upon the concentration of both reactants. Bimolecular reactions usually have rate equations that are second order overall. S_N2 reaction is a **concerted reaction,** taking place in a single step with bonds breaking and forming at the same time.

6.7 Generality of the S_N2 Reaction

Shown below are examples of S_N2 reactions. These examples illustrate the mechanism, with arrows starting from nucleophile to electrophile, followed by the arrow showing bond breaking between carbon and halogen with electrons going towards the halogen, which is the leaving group. All S_N2 reactions undergo the same mechanism.







Exercise 6.3: Predict the S_N2 product of the following reaction. Use arrow and propose a mechanism.

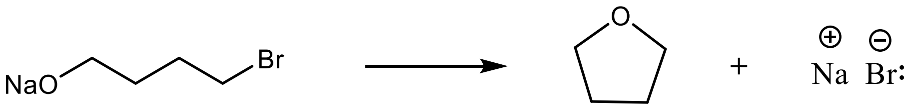
What happens to the rate if the concentration of?

a. 1-iodopropane is tripled and sodium hydroxide remains the same?

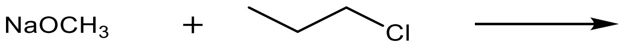
b. 1-iodopropane remains the same and sodium hydroxide is doubled?

c. 1-iodopropane is doubled and the concentration of sodium hydroxide tripled?

Exercise 6.4: Sometimes a nucleophile and leaving group can be in the same molecule. Here, an intra-molecular SN2 reaction occurs. Draw the mechanism:



Exercise 6.5: Predict the S_N2 product of the following reaction. Use arrow and propose a mechanism.



6.8 Factors Affecting SN2 Reactions:

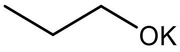
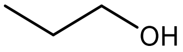
a. Strength of Nucleophile

In general, a species with a negative charge is a stronger nucleophile than a similar, neutral species. A stronger nucleophile is an ion or molecule that reacts faster in the reaction than a weaker nucleophile under the same conditions. A strong nucleophile is much more effective than a weak one in attacking an electrophilic carbon atom. For example, both methanol (CH_3OH) and methoxide ion (CH_3ONa) have easily shared pairs of nonbonding electrons, but methoxide ion reacts with electrophiles much faster than methanol. So, bases are stronger nucleophiles than their corresponding conjugate acid.

CH_3OH is a weaker nucleophile than CH_3ONa

Keep in mind that in CH_3ONa, there is an ionic bond between oxygen (that has a negative charge) and sodium (that has a positive charge). So, ideally, you should write CH_3ONa as

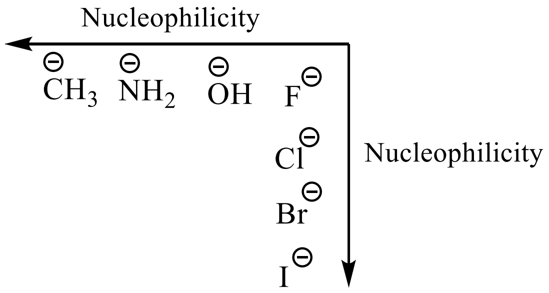
$CH_3\overset{\ominus}{O}\overset{\oplus}{Na}$

Likewise,  is a stronger nucleophile than 

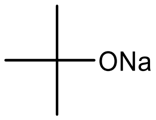
When comparing two different atoms, the more electronegative elements have more tightly held nonbonding electrons that are **less** reactive toward forming new bonds. Therefore, nucleophilicity decreases from left to right in the periodic table.

b. Nucleophilicity Trend

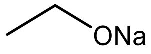
Nucleophilicity increases down the periodic table (as there is a decrease in electronegativity). As we go down a column in the periodic table, the atoms become larger and their electrons are more loosely held, and the atom is more **polarizable.** Its electrons can move more freely toward a positive charge, resulting in stronger bonding with the electrophile. This increased availability of electrons of larger atoms enhances its ability to begin to form a bond at a relatively long distance.



c. Steric effects in Nucleophilicity



vs.



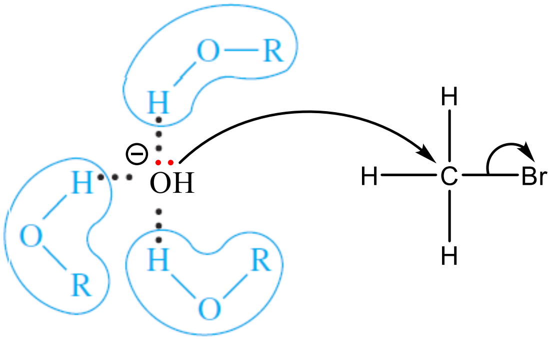
sodium t-butoxide

sodium ethoxide

Sodium t-butoxide (a bulky nucleophile) will experience a larger steric hinderance in the transition state than the less hindered sodium ethoxide.

d. Solvent Effects on Nucleophilicity

Polar **protic** solvents are a source of acidic hydrogen and do not favor SN2 reactions as they start interacting with the nucleophile, which slows down the SN2 reaction. Polar aprotic solvents do not have the acidic hydrogen; hence they cannot interact with the nucleophile, hence the nucleophile is 100% available to react with the electrophile. Examples of polar protic and aprotic solvents are given below.

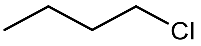


Polar protic solvents	Polar aprotic solvents
H_2O (water)	CH_3CN (acetonitrile)
CH_3OH (methanol)	$(CH_3)_2SO$ (DMSO)
CH_3CH_2OH (ethanol)	$(CH_3)_2CO$ (acetone)

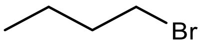
6.9 Reactivity of the Substrate in SN2 Reactions

a. Leaving Groups

Substitution reactions must have the substrate that has a good leaving group. The better the leaving group, faster the reaction. But qualifies as the good leaving group? The electrons on the atom that is the leaving group must be stable. We will use PRECHI electron stabilizing force to identify whether one leaving group is better than the other. *<u>The more stable the electrons on the leaving group, better the leaving group. Or a weaker base is a better leaving group.</u>* Between 1-chlorobutane and 1-bromobutane, which will react faster in S_N2 reaction? The only difference between the two is that A has chlorine as a leaving group and B has bromine as a leaving group. Due to the larger size of bromine atom (polarizability), the electrons on $Br^{\ominus}$ are more stable than on $Cl^{\ominus}$. Hence B will react faster than A.



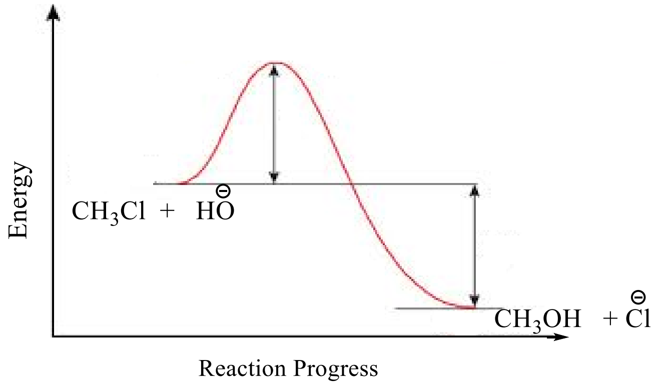
A



B

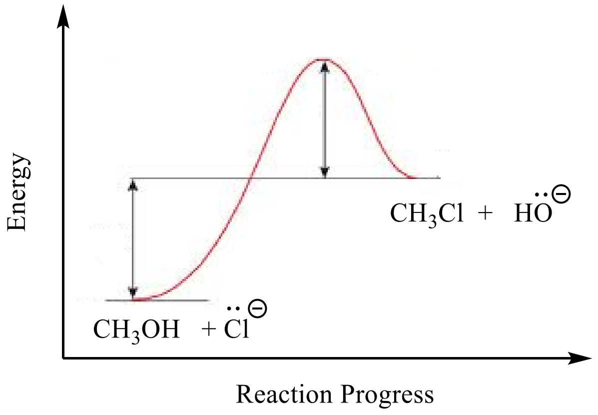
Let us look at the reaction shown below and its energy diagram.

$CH_3Cl + \overset{\ominus}{OH} \longrightarrow CH_3OH + Cl^{\ominus}$



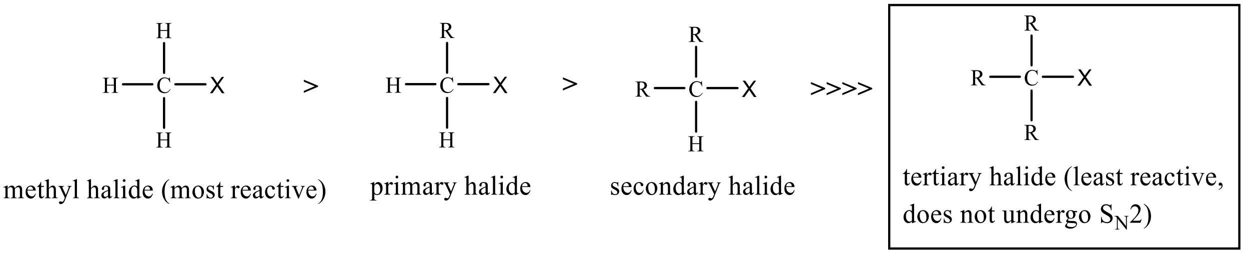
Will the reverse reaction take place? The reverse reaction is not energetically favored as it would be endothermic. The leaving group of reverse reaction will be $HO^{\ominus}$ which is a stronger base than $Cl^{\ominus}$ hence the reverse reaction will **not** take place.

$CH_3OH + Cl^{\ominus} \not\longrightarrow CH_3Cl + \overset{\ominus}{OH}$



b. Steric Effects of Substrate

Looking at the transition state of S_N2 reactions, the less crowded the transition state, the faster the S_N2 reaction. This is also called the transition state having least amount of steric hinderance.



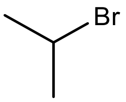
methyl halide (most reactive)

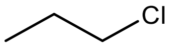
primary halide

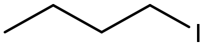
secondary halide

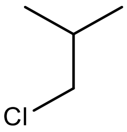
tertiary halide (least reactive, does not undergo S_N2)

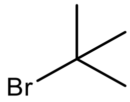
Exercise 6.6: Rank these alkyl halides in the order of increasing reactivity (least reactive first) during S_N2 reaction.


A


B

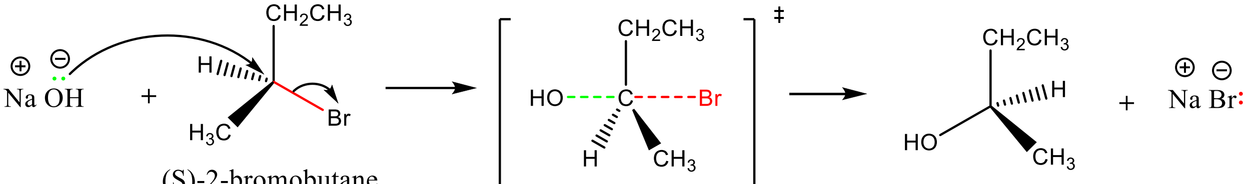

C


D


E

6.10 Stereochemistry of the S_N2 Reaction

During the S_N2 mechanism, the nucleophile approaches the substrate from the opposite side of leaving group. This results in an inversion of stereochemistry (assuming that the priority of the nucleophile and the leaving are the same during R/S nomenclature).

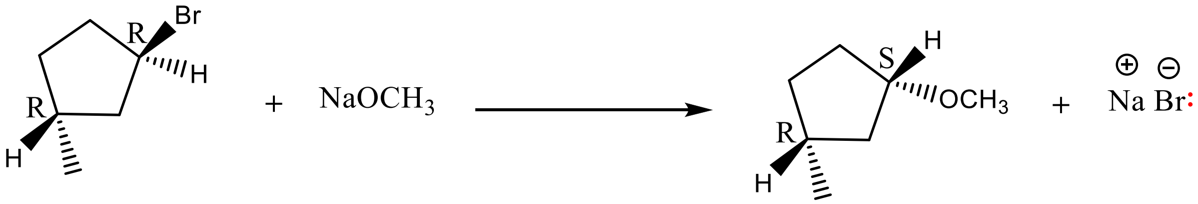

(S)-2-bromobutane

transition state

(R)-2-butanol

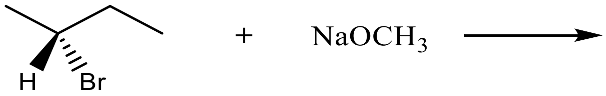
This causes an inversion of configuration at the stereocenter where the reaction takes place.

e.g.

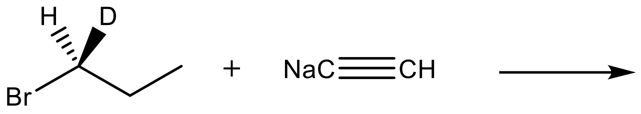


Exercise 6.7: Draw the organic SN2 product with correct stereochemistry of the reactions shown below.

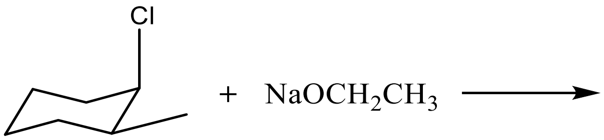
a.



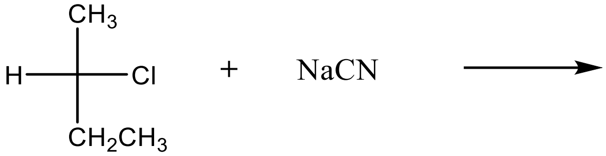
b.



c.

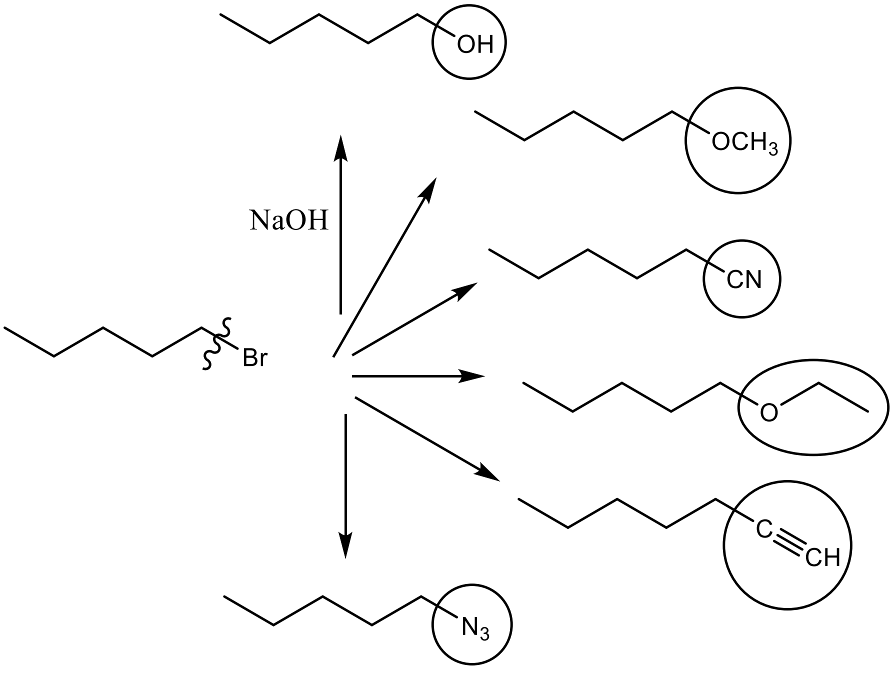


d.



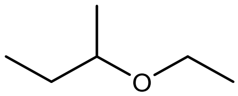
6.11 Planning a synthesis during S_N2 reactions.

During S_N2 reactions, planning a synthesis is important. Let us take one starting material and see how you can convert it into many different products using S_N2 reaction.

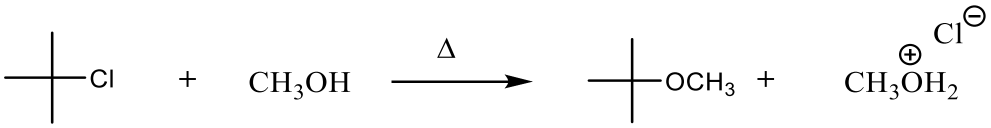


In each case, we are breaking the C-Br bond and replacing it with a C-nucleophile bond in the product. Depending upon the product, use an anion of the circled species. The first one is solved for you.

Exercise 6.8: Propose the structure of and alkyl bromide and a nucleophile that would synthesize the following compound.



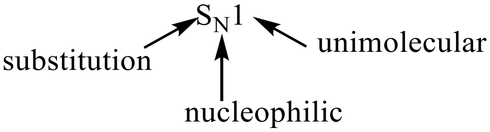
6.12 First-Order Nucleophilic Substitution: The S_N1 Reaction



Rate = k $[(CH_3)_3Cl]^1$ $[CH_3OH]^0$ = k $[(CH_3)_3Cl]^1$ where k is a rate constant.

Looking at the rate equation, one can predict the effect of concentration on rate. Rate will double if you double the concentration of CH_3Cl, but do not change the concentration of CH_3OH. If you double the concentration of both CH_3Cl and CH_3OH, the rate will still double. If you triple concentration of both CH_3Cl and CH_3OH, the rate triples. In other words, one can say that the rate is independent upon the concentration of CH_3OH.

For all SN1 reaction, the terminology is

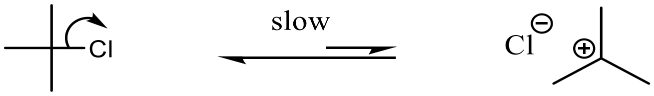


The term *unimolecular* means there is only one molecule involved in the transition state of the rate-determining step.

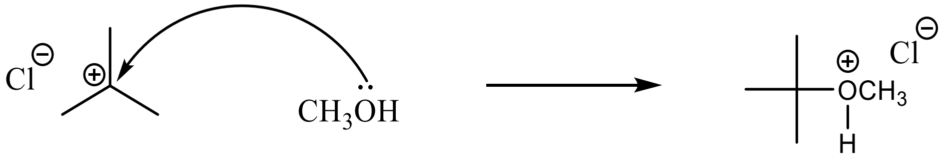
6.13 The S_N1 Reaction Mechanism

The mechanism of the reaction of *t*-butyl chloride with methanol is shown here. Ionization of the alkyl halide (the first step) to form the carbocation is the rate-determining step.

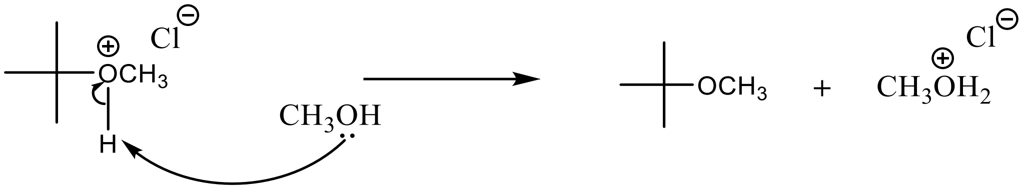
Step 1: Formation of the carbocation is the slow, rds.



Step 2: Nucleophile attacks the carbocation (electrophile)

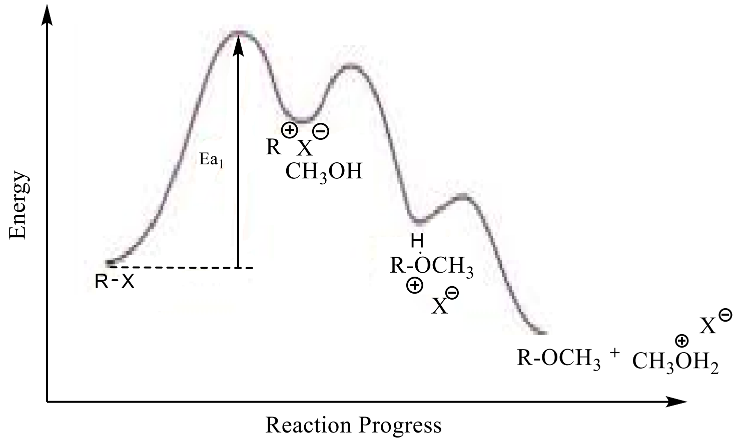


Step 3: The solvent picks up the proton to give uncharged SN1 product.



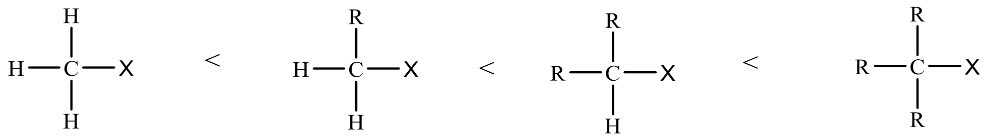
The energy diagram of the SN1 reaction shows why the rate does not depend on the strength or concentration of the nucleophile. The formation of carbocation is highly endothermic, and its large activation energy determines the overall reaction rate. Since the first step does not involve the nucleophile, the rate is independent upon the concentration of the nucleophile.

The nucleophilic attack (second step) is strongly exothermic, with a lower-energy transition state. In effect, a nucleophile reacts with the carbocation almost as soon as it forms.
The SN1 reaction are also referred to as ***solvolysis*** *reaction since the nucleophile can be in large amount without effecting the rate.* Since SN1 reaction goes via carbocation formation, use of heat is often used in SN1 reactions to cross the energy barrier.



a. Substituent effect on SN1 reaction

The rds of SN1 reaction is the formation of carbocation. The more stable the carbocation, the faster its formation. In chapter 4, we saw that alkyl groups stabilize carbocations by donating electrons through sigma bonds (the inductive effect). Highly substituted carbocations are therefore more stable and will be formed faster in the rds. Therefore, for SN1 reaction, the order of reactivity of alkyl halides is: 3^o RX > 2^o RX > 1^o RX > CH_3X. This is opposite to that of SN2 reaction.



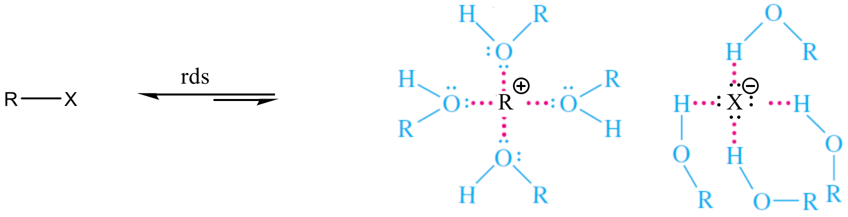
methyl halide (least reactive) primary halide secondary halide tertiary halide (most reactive)

b. Leaving group ability

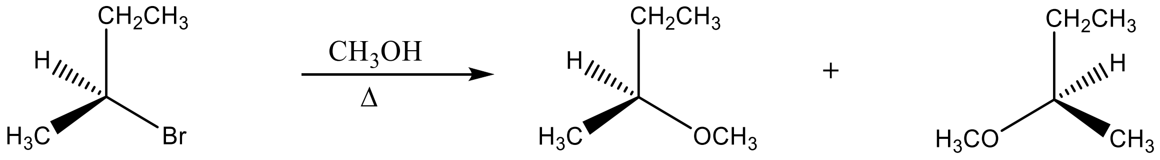
Like in SN2 reaction, SN1 reactions require good leaving groups (weaker base, or more stable electrons on the leaving group).

c. Solvent effect

Polar protic solvents favor SN1 reactions as they stabilize both the carbocation and the leaving group in the rds.

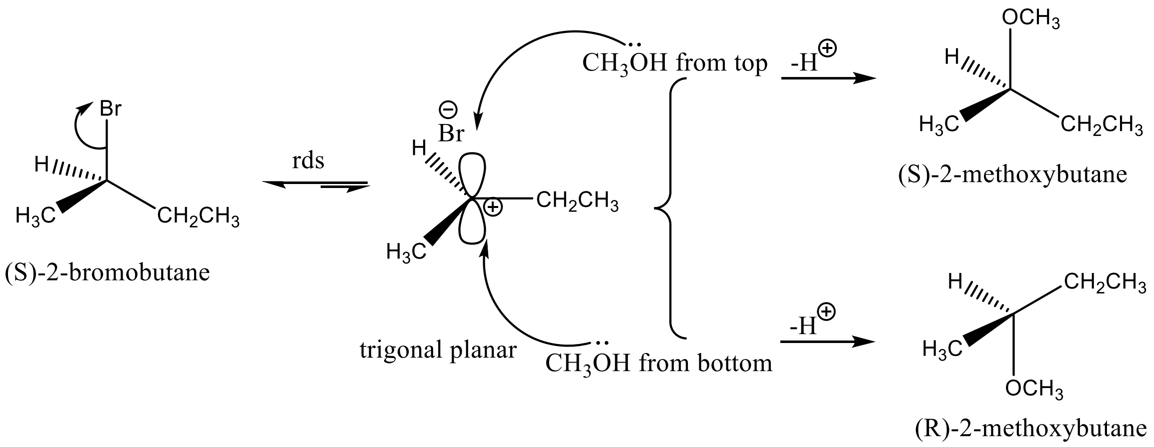


6.14 Stereochemistry of the SN1 Reaction

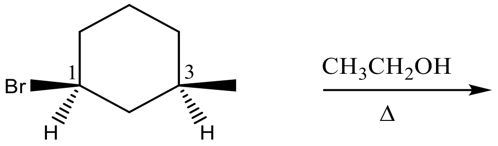


(S)-2-bromobutane (S)-2-methoxybutane (R)-2-methoxybutane

When (S)-2-bromobutane undergoes SN1 reaction with methanol (CH_3OH), there ae two stereoisomers formed (R)-2-methoxybutane and (S)-2-methoxybutane in equal amounts. In order to understand why a mixture of products are formed, look at the carbocation formed in the rds. The carbocation has a trigonal planar geometry. Upon breaking of C-Br bond in the rds, the nucleophile can approach the carbocation from either side of trigonal planar shape. If the nucleophile approaches from the top side, the stereochemistry of the product is (S), but when it approaches the carbocation from the bottom side, the stereochemistry of the product is (R). This ends up with equal mixture of enantiomers, or a racemic mixture.



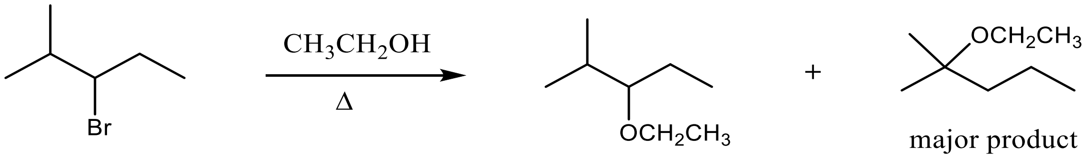
Exercise 6.9: Draw the organic product(s) of the reaction shown below. Pay attention to stereochemistry. What is the relationship between the two stereoisomers?



(1S,3R)-1-bromo-3-methylcyclohexane

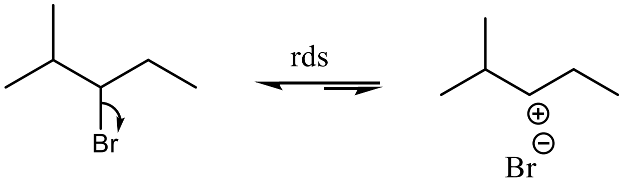
6.15 Rearrangements in the S_N1 Reactions

Carbocations frequently undergo structural changes, called **rearrangements,** to form more stable carbocations. Rearrangement occurs after a carbocation has formed. Rearrangements are often seen in reactions, where carbocation is formed. S_N2 reaction will never see a rearrangement as it does not proceed via carbocation formation. For the following reaction, an unexpected product was formed as the major product.

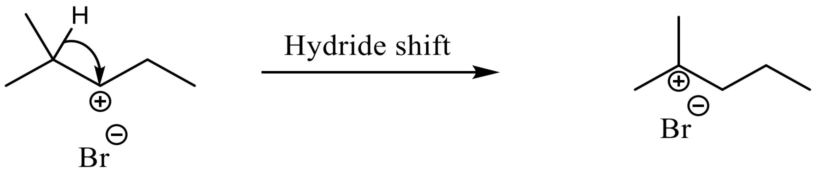


The structural change takes place only if there is an incentive for a more stable carbocation to be formed. It will not form a less stable carbocation. This rearrangement can take place via a hydride shift (hydrogen atom with its electrons) or via a methyl shift (methyl group with its electrons). Mechanism for formation of the major product of above reaction.

Step 1: Formation of carbocation.



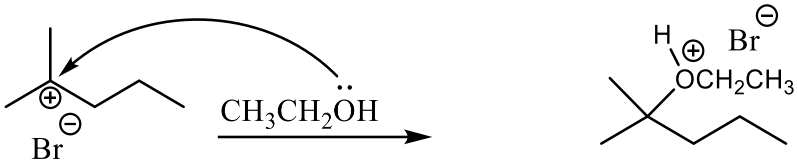
Step 2: Hydride shift



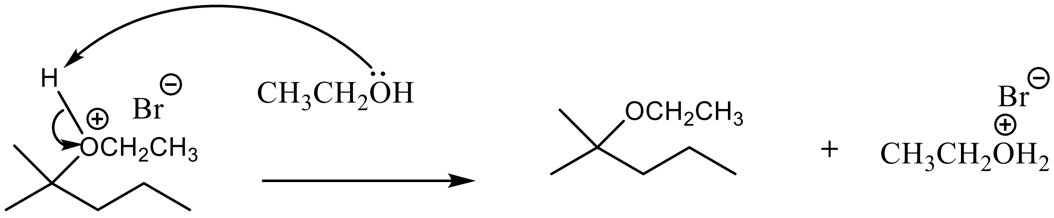
2° carbocation

3° carbocation

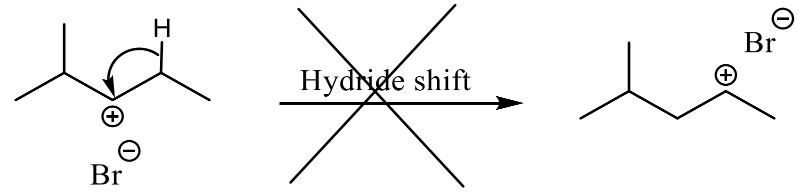
Step 3: Nucleophile attacks the carbocation



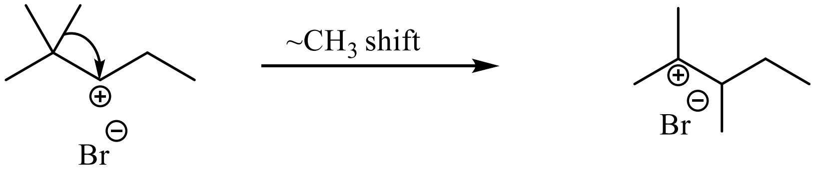
Step 4: The solvent picks up the proton to give this uncharged major SN1 product.



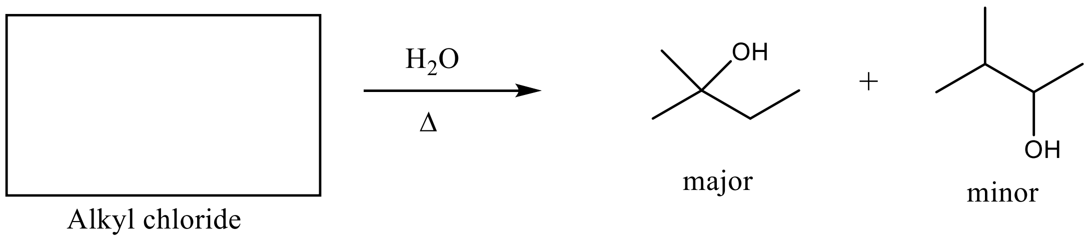
When do a hydride shift/methyl shift rearrangement take place? Only when it ends up giving a more stable carbocation. Also, hydride shift is referred to as ~H and a methyl shift is represented as ~CH$_3$.



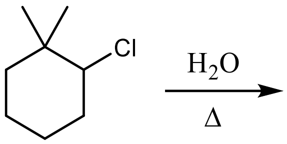
e.g. of a methyl shift



Exercise 6.10: Inside the box, draw the structure of the alkyl chloride starting material that will undergo SN1 reaction to give the following two products.



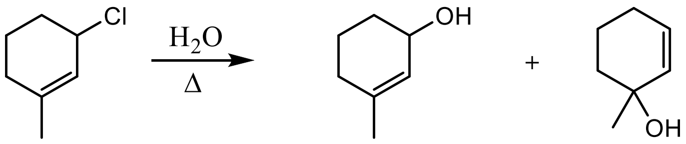
Exercise 6.11: Draw the major organic product of the reaction shown below.



6.16 Resonance in the S_N1 Reactions

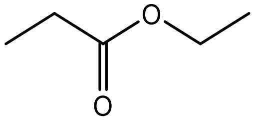
Resonance stabilization of the carbocation can also promote the reaction. This resonance may also result in formation of two possible structural isomers that would not be possible in S_N2 reactions.

Exercise 6.12: Explain how the two products are formed in the reaction shown below.

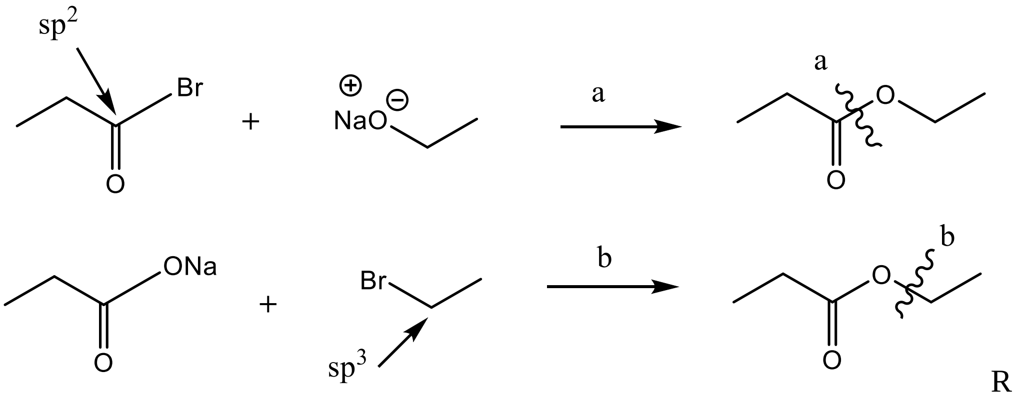


Note: S_N1 and S_N2 reactions take place only on sp^3 carbon. They do not take place on an alkyl halide where the halogen is on sp or sp^2 carbon.

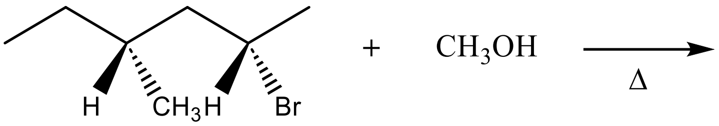
Solved Problem 6.1: Propose the structure of nucleophile and alkyl bromide that will synthesize the compound below using S_N2 reaction.



We have seen C-O bond being easily being made using an alkyl halide. There are two possible (a and b) C-O bonds, but can both ways are viable S_N2 reactions? Pathway a is not a viable S_N2 as the alkyl halide is on a sp^2 carbon.



Exercise 6.13: Draw the product(s) of the reaction.



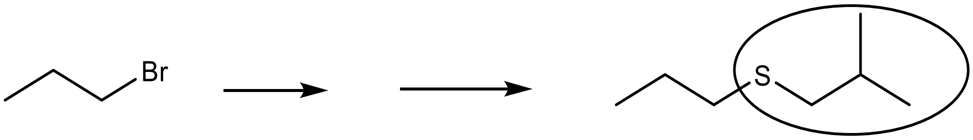
6.17 Comparison of S_N1 and S_N2 Reactions

The table below shows the summary of comparison between S_N1 and S_N2 reactions:

Factors	S_N1	S_N2
Nucleophile	Usually weak	Strong
Substrate	3° RX >2° RX >1° RX > CH_3-X	CH_3-X >1° RX > 2° RX > 3° RX
Rate Law	Rate = k [Substrate]^1	Rate = k [Substrate]^1 [Nucleophile]^1
Solvent	Polar protic	Polar aprotic
Stereochemistry	Mixture of stereoisomer	Inversion of stereochemistry
Rearrangements	common	Can never take place

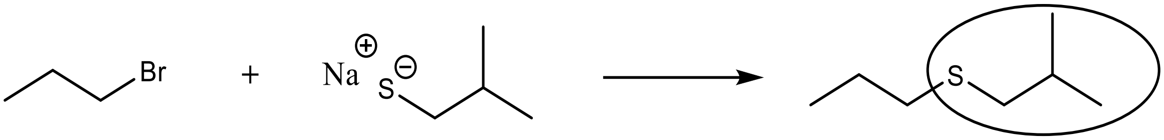
6.18 Synthesis during S_N1 and S_N2 Reactions

a. What functional group is present on the *reactant*?
b. What functional group is present on the *product*?
c. What has changed from reactant to product?
d. Which reactions do I know to convert from one to the other?



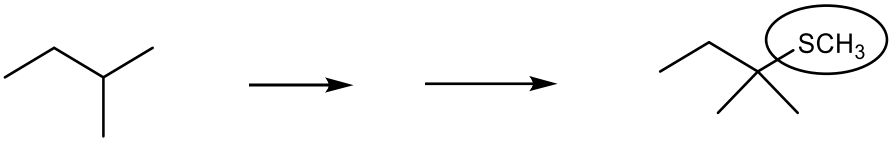
During solving this synthesis problem, focus on what has changed.

a. C-Br bond is broken and is replaced by C-$SCH_2CH(CH_3)_2$ bond. Focus on the bond where the change has taken place.
b. This seems to be the simple case of substitution reaction. We have seen two kinds, S_N1 and S_N2. Which one will it be? Not sure?
c. Look at the alkyl halide. This R-X is 1°, which favors S_N2 reaction.
d. What should be the structure of the nucleophile? Simply look at the rest of the structure in the product. The rest of the structure is circled. The whole circled structure is nucleophile and the sulfur atom is the nucleophilic atom. Make sure you have the sulfur atom charged as SN2 reactions require strong nucleophile.

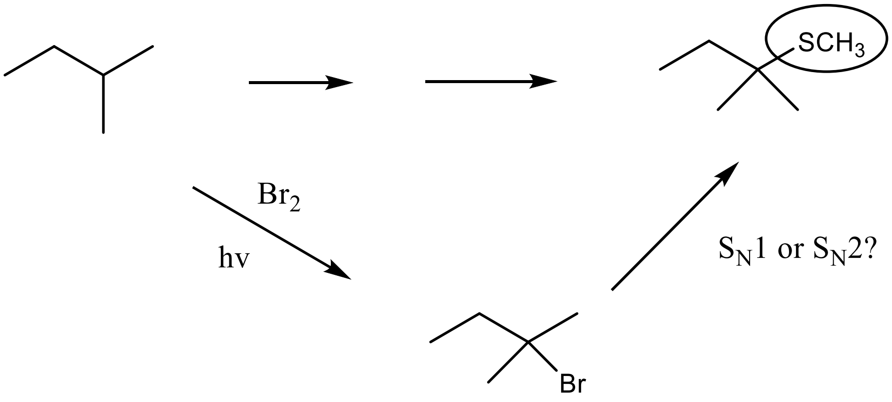


This is an example of one-step synthesis. What if a synthesis involves more than one step?

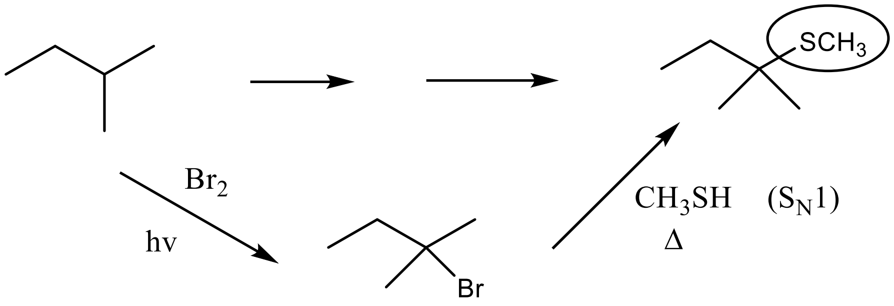
Solved Problem 6.2: Propose the synthesis of the following product from the starting material provided.



a. In this case, the starting material is an alkane (not an alkyl halide). However, it seems this reaction also involves a substitution reaction where a hydrogen has been substituted by a -SCH_3 group.
b. However, we know that only alkyl halide undergoes S_N1 or S_N2 types of substitution reaction. This starting material is an alkane, not an alkyl halide.
c. From chapter 4, we know alkanes can be easily converted to alkyl halides using free radical halogenation reaction. (**Note**: This will be a repeated reaction that you will be seeing during synthesis starting from alkanes/alkenes).
d. This thought process made you realize that this synthesis can not be done in one step. You must manipulate the functional group alkane to first convert to an alkyl halide and then convert the alkyl halide into the desired product.

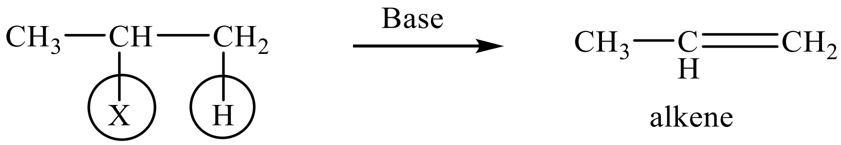


In the first step, the free radical halogenation goes via formation of the most stable free radical (in this case, a tertiary free radical which yields 2-bromo-2-methylbutane as the major product).
Once you have synthesized the alkyl halide, it is easy to see the substitution reaction that has taken place. But is it S_N1 and S_N2? Which one will it be? Look at the alkyl halide. It is 3^o R-X. S_N2 reactions are NOT favored on a 3^o alkyl halide, hence this conversion best takes place using a S_N1 reaction. Use of a weak nucleophile will favor S_N1 reaction, so do not use charged nucleophile (on sulfur atom). Since SN1 reaction goes via carbocation formation, use of heat is often used in S_N1 reactions to cross the energy barrier.



6.19 Elimination Reactions of Alkyl Halides

When alkyl halides are reacted with bases, they undergo dehydrohalogenation reaction (removal of a hydrogen and halogen) and makes a pi bond (alkene) in the process. This is represented as:

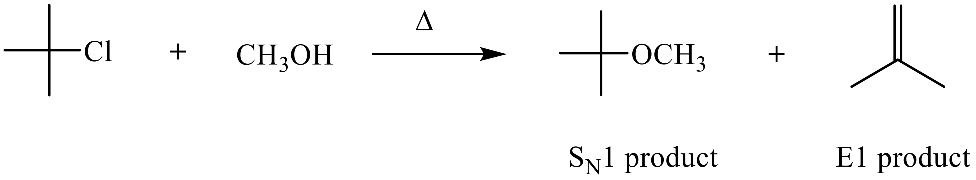


loss of H and Br from alkyl halides is dehydrohalgenation

Since a hydrogen and a halogen is being removed from the alkyl halide, this is called an elimination reaction. Depending on the reagents and conditions involved, an elimination might be a first order **E1** (like S_N1, E1 reaction takes place via formation of a carbocation) or second order **E2** (like S_N2 reaction, E2 reaction undergoes without formation of a carbocation).

6.20 The Unimolecular Elimination (E1) Reaction

When the following reaction takes place, two organic products are formed. The substitution product is formed via the S_N1 mechanism. The elimination product (alkene) is formed via E1 mechanism.



In section 6.13, we have already discussed the mechanism of S_N1 product. To understand the elimination reaction, let us tale a look at nucleophile here. CH_3OH is a weak nucleophile but can also behave like a weak base. Since bases like protons, during elimination reaction, the base can abstract a proton from a carbon atom that is next to the carbocation formed during E1 reaction. The rate of the E1 reaction was found to be:

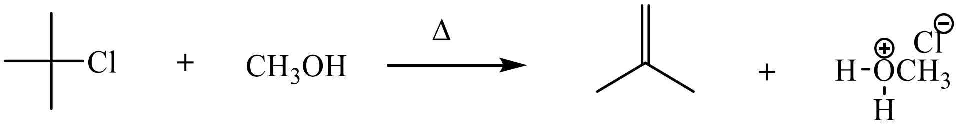
Rate = $k\ [(CH_3)_3Cl]^1\ [CH_3OH]^0$ Rate $= k$ [alkyl halide]^1 where k is a rate constant.

Looking at the rate equation, one can predict the effect of concentration on rate. Rate will double if you double the concentration of $(CH_3)_3Cl$, but do not change the concentration of CH_3OH. If you double the concentration of both $(CH_3)_3Cl$ and CH_3OH, the rate will still double. If you triple concentration of both CH_3Cl and CH_3OH, the rate triples. In other words, one can say that the rate is independent upon the concentration of nucleophile.

For all E1elimination reaction, the terminology is

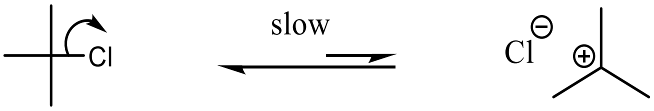
6.21 The E1 Reaction Mechanism

The E1 mechanism of the reaction of *t*-butyl chloride with methanol is shown here. Ionization of the alkyl halide (the first step) to form the carbocation is the rate-determining step.

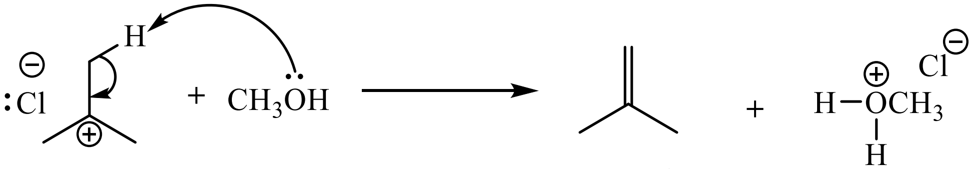


E1 product

Step 1: Formation of the carbocation is the slow, rds.

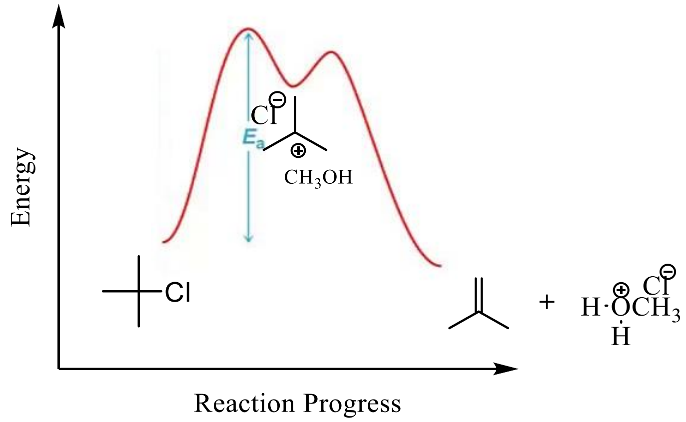


Step 2: Base picks up the proton from the carbon next to the carbocation, which results in a new pi bond between the carbocation carbon and the carbon where the base abstracted the proton from.



E1 product

The energy diagram of the E1 reaction shows why the rate does not depend on the strength or concentration of the base (CH_3OH). The formation of carbocation is highly endothermic, and its large activation energy determines the overall reaction rate. Since the first step does not involve the base, the rate is independent upon the concentration of the base.



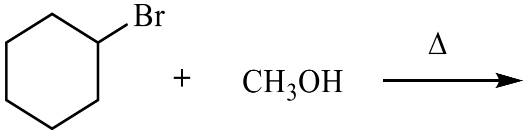
a. Substituent effect on E1 reaction

The rds of E1 reaction is the formation of carbocation. The more stable the carbocation, the faster its formation. Highly substituted carbocations are therefore more stable and will be formed faster in the rds. Therefore, for both E1 and S_N1 reaction, the order of reactivity of alkyl halides is:
S_N1: 3° RX > 2° RX > 1° RX > CH_3X.

E1: 3° RX > 2° RX > 1° RX > CH_3X.

> The E1 reaction almost always competes with the reaction. Whenever a carbocation is formed, it can undergo either substitution or elimination, and mixtures of products often result.

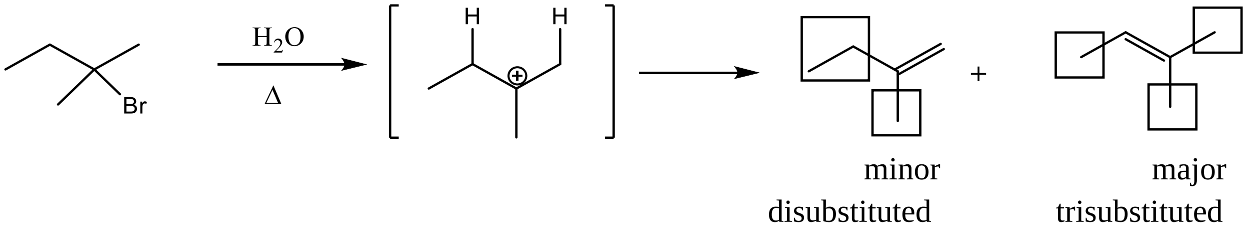
Exercise 6.14: Draw the organic product(s) of the reaction shown below.



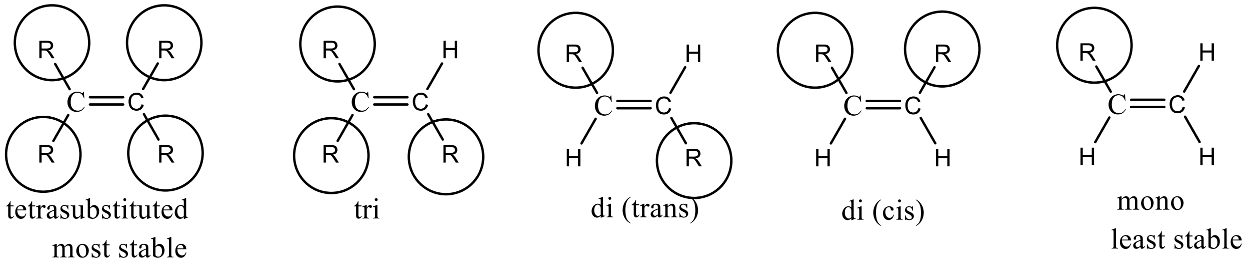
Note: the nucleophile/base is weak so S_N2 reaction will not take place. Both SN1 and E1 products will form.

6.22 Positional Orientation of Elimination: Zaitsev's Rule

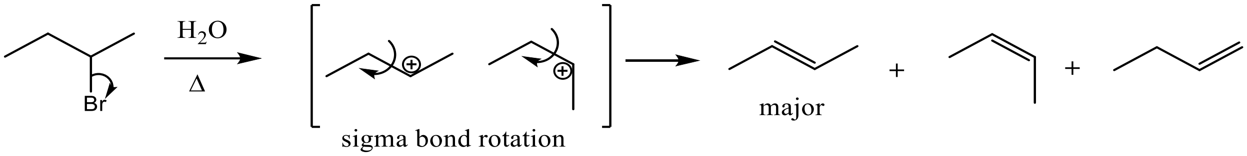
Many alkyl halides can eliminate in more than one way, to give mixtures of alkenes. In many cases, we can predict which elimination product will predominate. In the example below, the carbocation formed in the rds can lose a proton on either of two adjacent carbon atoms.



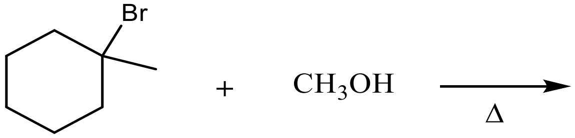
The first product has a disubstituted double bond and the second product has a trisubstituted double bond. In E1 reaction, the product with the more substituted double bond is more stable and hence would be the major product. This is called Zaitsev's rule. So according to Zaitsev's rule, in E1 reaction, more stable alkene will be major product. Between cis and trans, trans is more stable



e.g., when 2-bromobutane undergoes E1 reaction, three possible products are formed.

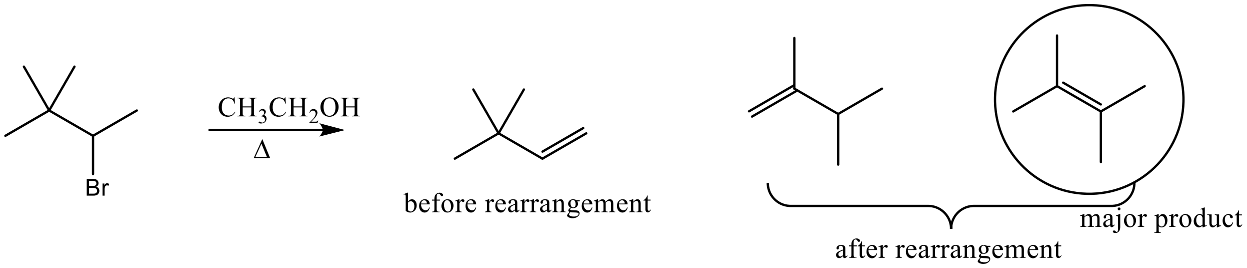


Exercise 6.15: Draw all the alkenes formed during the reaction shown below. Circle the major product.



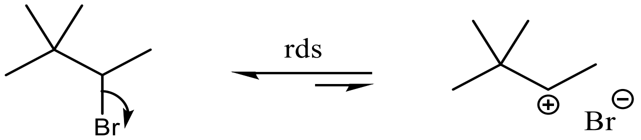
6.23 Rearrangement in an E1 Reaction

Like in SN1 reactions, carbocations can undergo **rearrangements,** to form more stable carbocations. For the following reaction, the major product formed is circled. The structural change takes place only if there is an incentive for a more stable carbocation to be formed. It will not form a less stable carbocation. This rearrangement can take place via a hydride shift (hydrogen atom with its electrons) or via a methyl shift (methyl group with its electrons).

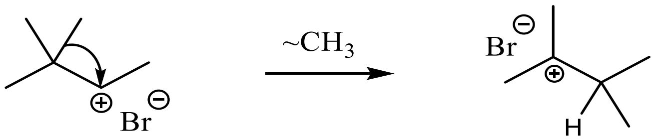


Mechanism for formation of the major product of above reaction is sown below:

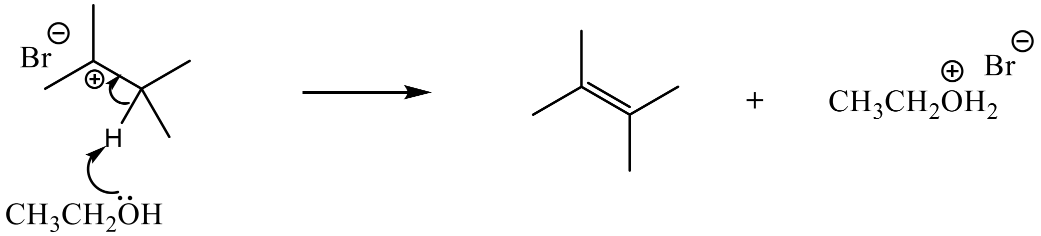
Step 1: Formation of the carbocation



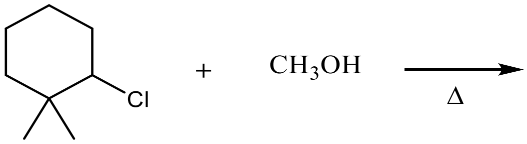
Step 2: Carbocation rearranges via methyl shift (~CH_3).



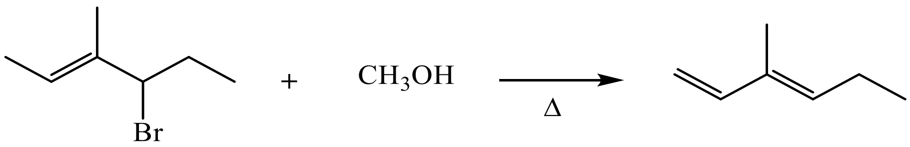
Step 3: Base picks up a proton adjacent to the carbocation to give the most substituted alkene as the major product.



Exercise 6.16: Draw all the elimination products that are formed during the reaction shown below. Circle the major product.

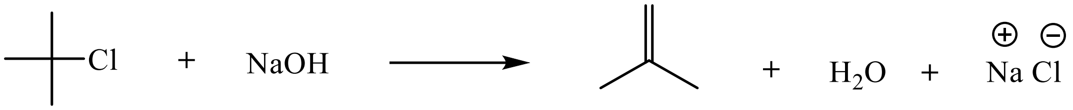


Exercise 6.17: Using arrows, write a mechanism that explains how this alkene is formed during the elimination reaction shown below.



6.24 Second-Order Elimination: The E2 Reaction

Eliminations can also take place under second-order conditions with a strong base present. As an example, consider the reaction of *tert*-butyl chloride with sodium hydroxide in water as a solvent.



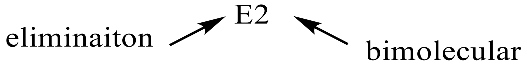
E2 product

This is a second-order reaction because hydroxide ion is a strong base as well as a strong nucleophile. It attacks the alkyl halide faster than the halide can ionize to give a first-order reaction. No S_N2 product is observed, however. The S_N2 cannot take place because the tertiary alkyl halide is too sterically hindered (has a crowded transition state). The observed product is 2-methylpropene, resulting from elimination of HBr and formation of a double bond. Unlike E1 reaction, no carbocation is formed, and the mechanism is concerted (one-step) with all bond breaking and bond forming taking place simultaneously.

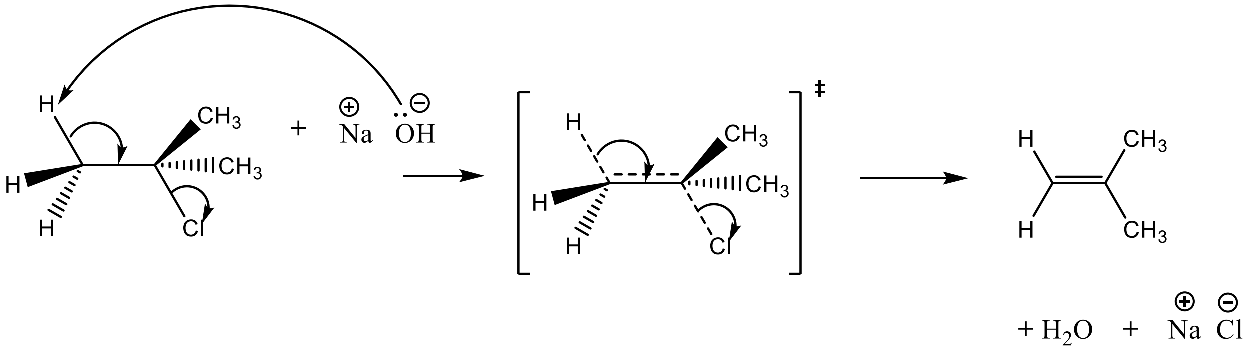
Rate = k $[(CH_3)_3Cl]^1$ $[NaOH]^1$ Rate = k [Alkyl halidel]^1 [Base]^1 where k is a rate constant.

Looking at the rate equation, one can predict the effect of concentration on rate. Rate will double if you double the concentration of $(CH_3)_3Cl$, but do not change the concentration of NaOH. If you double the concentration of both $(CH_3)_3Cl$ and NaOH, the rate will quadruple. If you triple concentration of both CH_3Cl and NaOH, the rate increases by nine times. In other words, one can say that the rate is dependent upon the concentration of both substrate and base

For all E2 elimination reaction, the terminology is



6.25 The E2 Reaction Mechanism



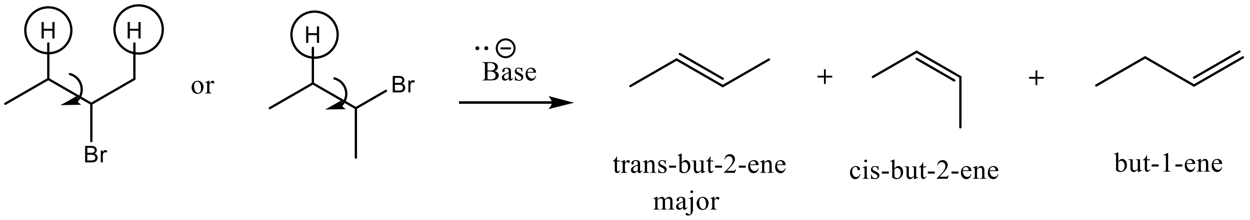
Three arrows are used to represent the E2 mechanism. The mechanism is concerted (one-step) with all bond breaking and bond forming taking place simultaneously. The electrons from the base pick up a proton from the carbon adjacent to the carbon bearing the halogen (also called as the β hydrogen). This is a second-order reaction because hydroxide ion is a strong base as well as a strong nucleophile.

The order of reactivity of alkyl halides toward E2 dehydrohalogenation is found to be

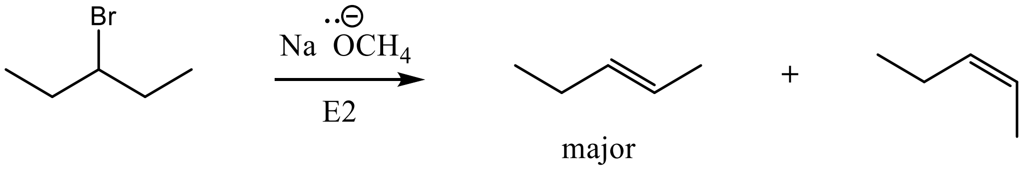
3^{o} RX > 2^{o} RX > 1^{o} RX >

Elimination of a tertiary halide gives a more substituted alkene than elimination of a secondary halide, which gives a more substituted alkene than a primary halide.

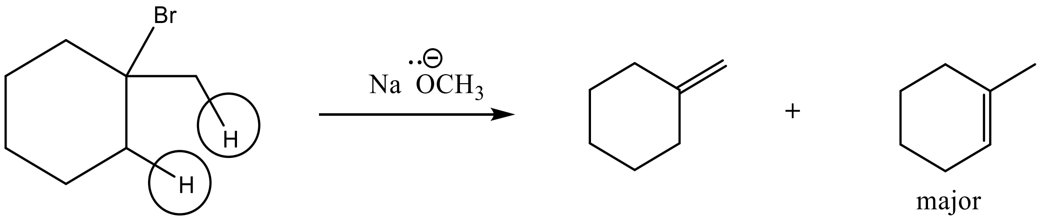
Mixtures of Products in the E2: The E2 reaction requires abstraction of a proton on a carbon atom next to the carbon bearing the halogen (β hydrogen). If there are two or more possibilities, mixtures of products may result. In most cases, Zaitsev's rule predicts which of the possible products will be the major product: the most substituted alkene. For example, the E2 reaction of 2-bromobutane with potassium hydroxide gives a mixture of three products, but-1-ene (a monosubstituted alkene), cis-but-2-ene (a disubstituted alkene) and trans-but-2-ene (a disubstituted alkene). As predicted by Zaitsev's rule, the disubstituted isomer trans-but-2-ene is the major product.



When an option of cis and trans alkene is there, like in 2-bromopentane, trans alkene will be major.



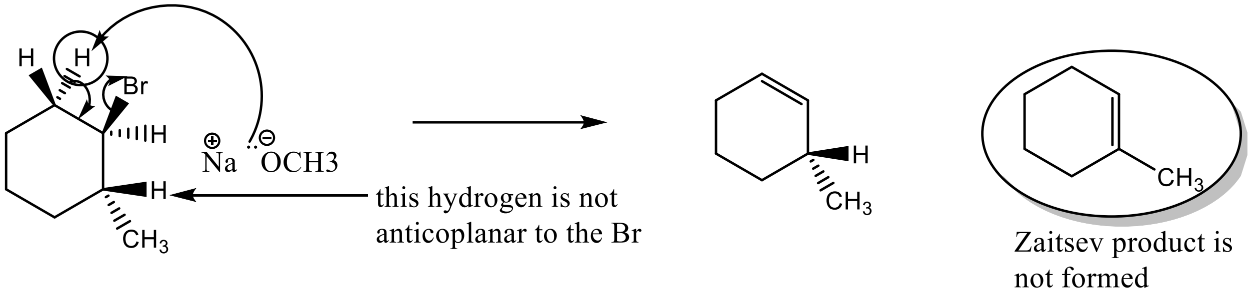
In 1-bromo-1-methylyclohexane, there are two β hydrogens that the base can abstract. Therefore, two possible products are formed. The major product is the trisubstituted alkene.



6.26 Stereochemistry of the E2 Reaction

"Anticoplanar transition state" is required for E2 reaction to take place. The β hydrogen that the base picks up must be anticoplanar to the halogen. Pay attention to stereochemistry any time stereochemistry is provided in the starting alkyl halide.

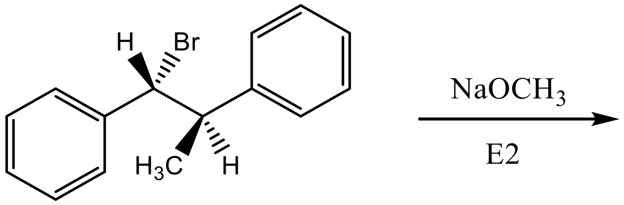
In the example below, there are two β hydrogen (hydrogens on adjacent carbon to the halogen), however only the circled hydrogen is anticoplanar to Br, so in this case, the Zaitsev product is not formed.

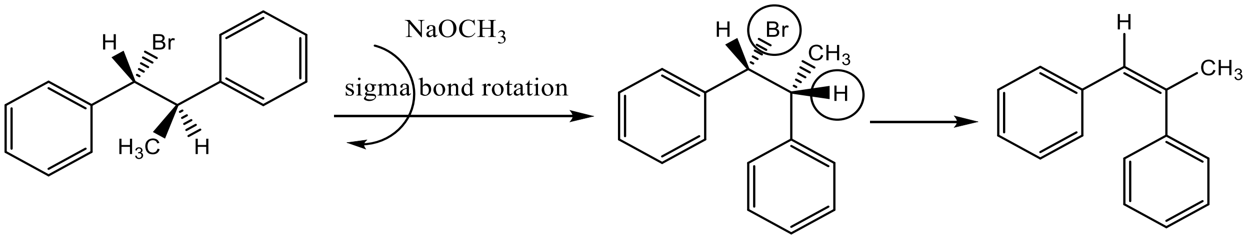


this hydrogen is not anticoplanar to the Br

Zaitsev product is not formed

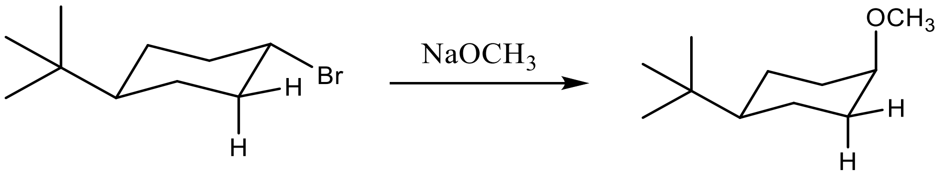
In the example below, during E2 reaction shown below, the only β hydrogen is not anticoplanar to the halogen (leaving group). However, recall sigma bond rotation is possible.





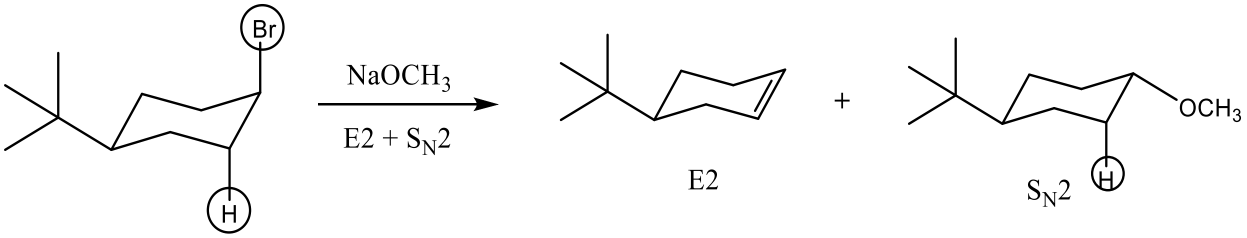
> *Problem solving strategies: If the stereochemistry is shown, pay attention to it and make sure anticoplanar condition is satisfied for the β hydrogen and the halogen. Remember, rotating three out of four groups also gives you the same stereochemistry, so you can either have a sigma bond rotation by 180^o or rotating three out of four groups to achieve anticoplanar condition. If neither can happen, E2 reaction cannot take place.*

For chair conformations, when the halogen is on the equatorial position, the β hydrogen are not anticoplanar to the halogen. In this case, no E2 reaction takes place. However, since $NaOCH_3$ is a strong nucleophile and strong base, it can undergo S_N2 reaction. So, in this case, only S_N2 reaction takes place.



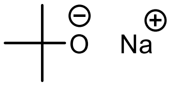
only S_N2, no E2

In a chair conformation, the anticoplanar requirement is satisfied only when the halogen is on axial position.

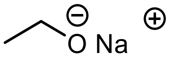


6.27 Bulky bases in E2 reactions

Bulky bases like sodium t-butoxide can also accomplish dehydrohalogenations that do not follow the Zaitsev rule. Bulky bases experience a significant amount of steric hindrance that prevents it from abstracting the proton that leads to the most highly substituted alkene.

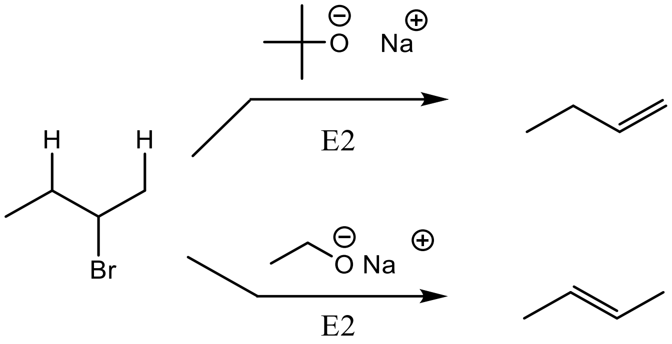


sodium *t*-butoxide
bulky base



sodium ethoxide
non-bulky base

In these cases, it abstracts a less hindered proton (a proton on a less substituted carbon), often the one that leads to formation of the less substituted product, called the **Hofmann product.** The following reaction gives mostly the **Zaitsev product** with the relatively unhindered ethoxide ion, but mostly the Hofmann product with the bulky *tert*-butoxide ion.



Hoffman product

Zaitsev product

If the substrate is prone to substitution, a bulky base can minimize the amount of substitution. Bulky base hinders its approach to attack a carbon atom (substitution) of alkyl halide, yet it can easily abstract a proton from β carbon and favor elimination.

6.28 Comparison of E1 and E2 Elimination Mechanisms

The table below shows the summary of comparison between E1 and E2 reactions:

Factors	**E1**	**E2**
Base	Usually weak bases	Strong base requires
Substrate	3^o RX >2^o RX >1^o RX	3^o RX >2^o RX >1^o RX
Rate Law	Rate = k $[\text{Substrate}]^1$	Rate = k $[\text{Substrate}]^1 [\text{Base}]^1$
Solvent	Polar protic	Polar aprotic
Stereochemistry	Not specific (Zaitsev major product)	coplanar transition state required
Rearrangements	common	Can never take place

6.29 Comparison of Substitution and Elimination Mechanisms

Substitution and elimination reactions are almost always in competition with each other. In order to predict the products of a reaction, it is necessary to determine which mechanisms are likely to occur. Do not fall into the trap of thinking that there must always be one clear winner. Sometimes there is, but sometimes there are multiple products. The goal is to predict which products are major. To accomplish this goal, these steps are required:

a. Analyze the nucleophile/base. Charged (strong) nucleophiles/base favoring S_N2 or E2 reaction and uncharged (weak) nucleophiles/base favoring S_N1 or E1 reaction.
b. Looks at the nature of substrate. The order of reactivity of alkyl halides towards all four mechanism are as follows:

$$\left.\begin{array}{ll} S_N1 & 3^o\ RX > 2^o\ RX > 1^o\ RX \\ E1 & 3^o\ RX > 2^o\ RX > 1^o\ RX \end{array}\right\}\ \text{favored by uncharged (weak) nucleophile/base}$$

Looking at the reactivity, S_N1 and E1 always compete.

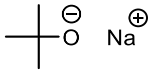
$$\left.\begin{array}{ll} S_N2 & CH_3\text{-}X > 1^{o}\,RX > \boxed{2^{o}\,RX} > 3^{o}\,RX \\ E_2 & 3^{o}\,RX > \boxed{2^{o}\,RX} > 1^{o}\,RX \end{array}\right\}\text{favored by charged (strong) nucleophile/base}$$

Since the reactivity of alkyl halide is opposite of S_N2 and E2 reactions, technically they compete only when the substrate is 2^{o} RX.

$$\underbrace{CH_3\text{-}X \qquad 1^{o}\,RX}_{S_N2\text{ only}} \qquad \underbrace{2^{o}\,RX}_{S_N2 + E2} \qquad \underbrace{3^{o}\,RX}_{E2\text{ only}}$$

c. Nucleophilicity vs. Basicity

We will now inspect the nucleophile/base to see what will happen. We can divide nucleophiles /bases into categories.

Nucleophile only	Base only	Nucleophile/Base	Weak Nucleophile/ Weak Base
$RS^{\ominus}$ $Cl^{\ominus}$ $HS^{\ominus}$ $Br^{\ominus}$ $I^{\ominus}$	$NaH\ (\ddot{H}^{\ominus})$ 	$HO\colon^{\ominus}$ $CH_3O\colon^{\ominus}$ $CH_3CH_2O\colon^{\ominus}$	H_2O CH_3OH CH_3CH_2OH

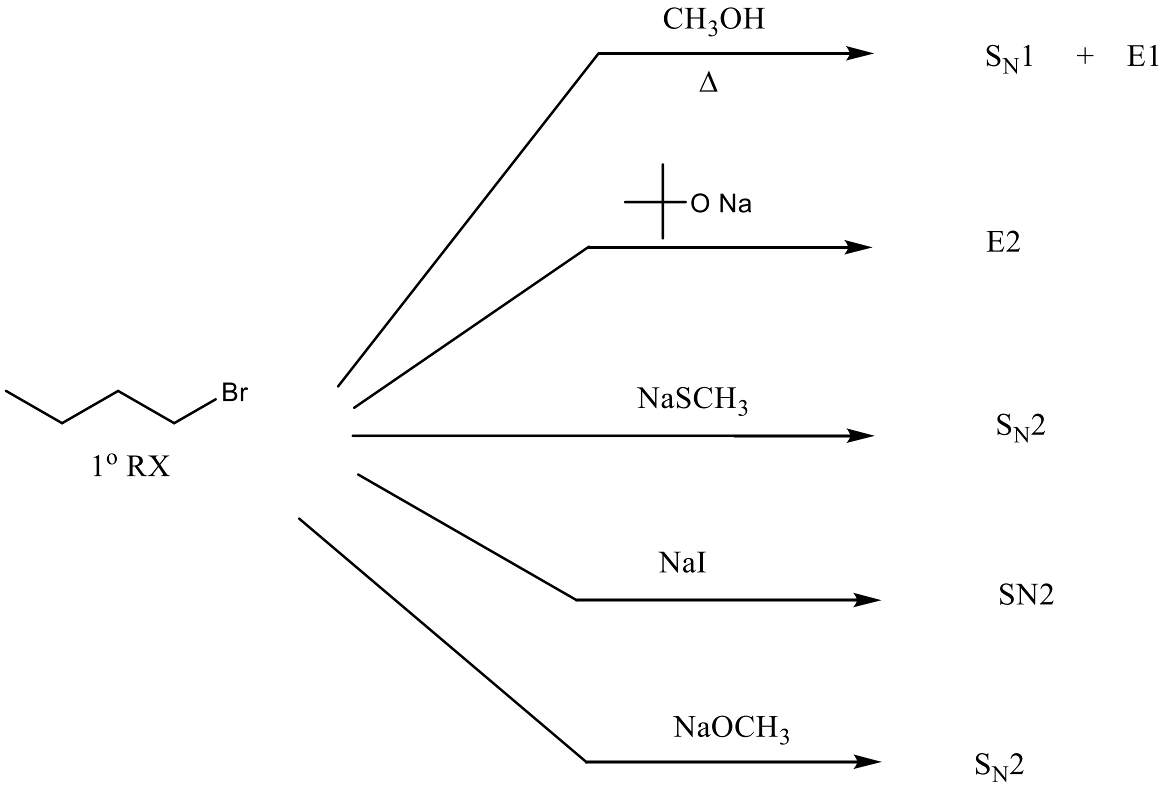
Depending upon the alkyl halide, each of these categories will react to give the possible products.

$$\boxed{\text{Nucleophile only}} \quad \left.\begin{array}{l} CH_3\text{-}X \\ 1^{o}\,RX \\ 2^{o}\,RX \end{array}\right\} S_N2\text{ only} \qquad \boxed{\text{Base only}} \quad \left.\begin{array}{l} 1^{o}\,RX \\ 2^{o}\,RX \\ 3^{o}\,RX \end{array}\right\} E2\text{ only}$$

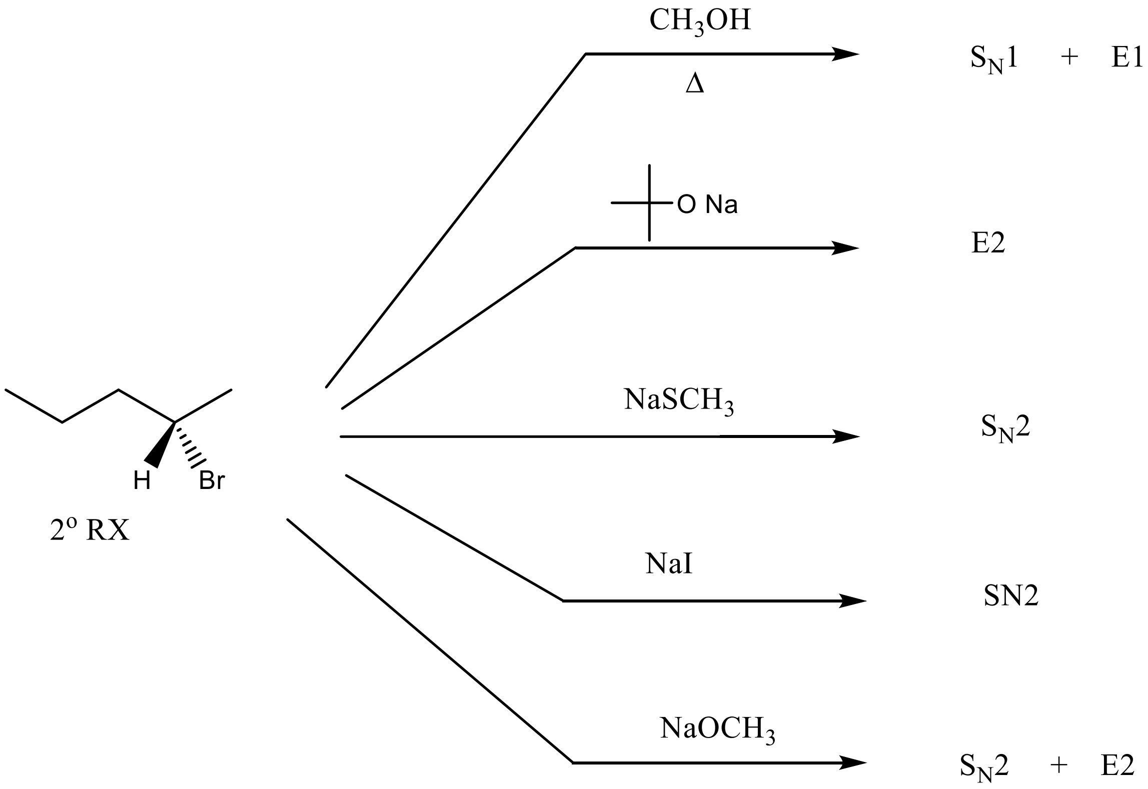
$$\boxed{\text{Strong Nucleophile/Base}} \quad \begin{array}{l} \left.\begin{array}{l} CH_3\text{-}X \\ 1^{o}\,RX \end{array}\right\} S_N2\text{ only} \\ \left.2^{o}\,RX\right\} S_N2 + E2 \\ \left.3^{o}\,RX\right\} E2\text{ only} \end{array} \qquad \boxed{\text{Weak Nucleophile/Base}} \quad \left.\begin{array}{l} 1^{o}\,RX \\ 2^{o}\,RX \\ 3^{o}\,RX \end{array}\right\} \begin{array}{l} S_N1\text{ and} \\ E1 \end{array}$$

These are grossly simplified for this class.

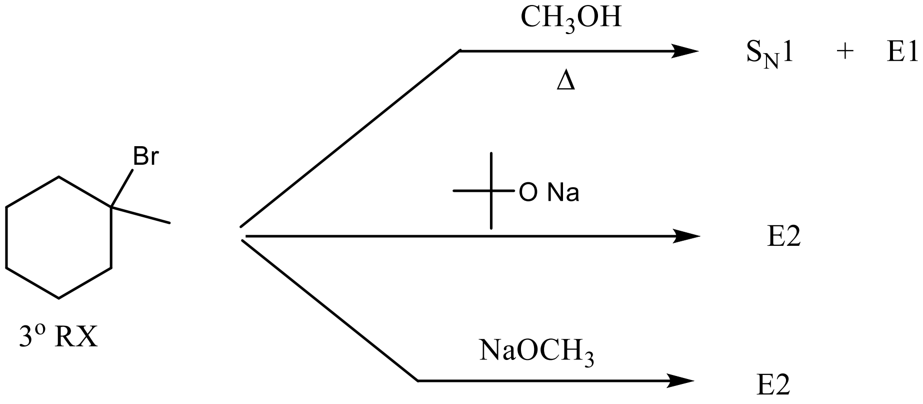
Examples:



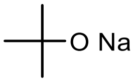
1° RX



2° RX



Commonly used abbreviations.

Me = $-CH_3$ Et = $-CH_2CH_3$ t-BuONa = 

Exercise 6.18: Identify the mechanism when 1-bromobutane is treated with the following:

a. NaOH b. NaSH c. *t*-BuONa d. NaOMe

Exercise 6.19: Identify the mechanism when 2-bromopentane is treated with the following:

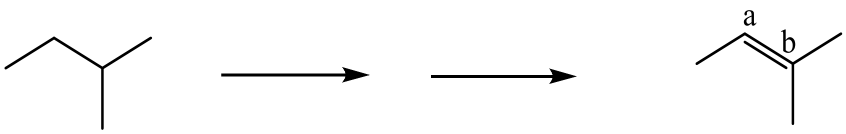
a. NaOEt b. NaI c. *t*-BuONa d. NaOH

Exercise 6.20: Identify the mechanism when 2-bromo-2-methylpentane is treated with the following:

a. NaOEt b. NaOH c. *t*-BuONa d. MeOH, Δ

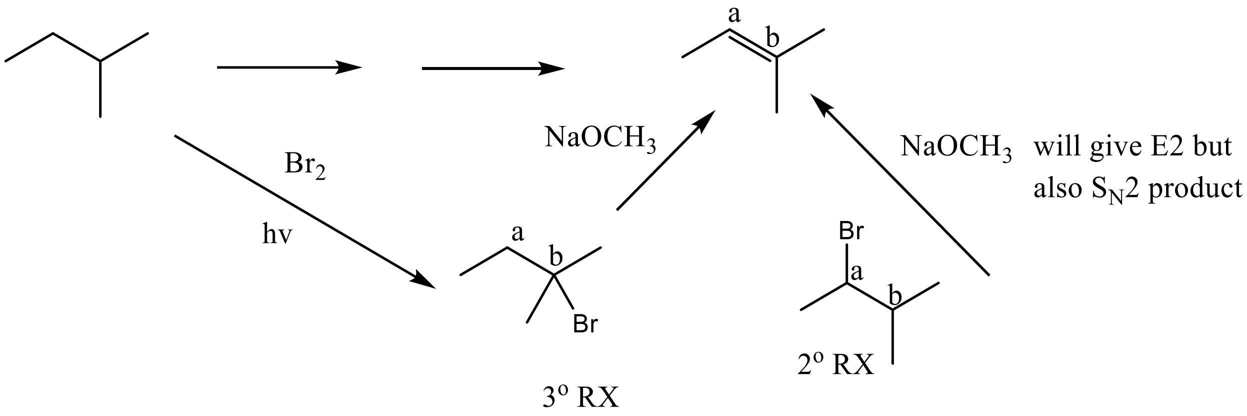
6.30 Synthesis of Alkenes from Alkanes

Synthesis of alkenes from alkyl halides can be performed by the two of the elimination mechanism E1 and E2 reaction we saw in this chapter. During a synthesis, do NOT use E1 method as E1 always competes with S_N1 reaction, no matter the classification of alkyl halide. You want to avoid any unwanted side-reaction during synthesis although sometimes it can not be avoided. Only use E2 reaction (strong base, either bulky or non-bulky).

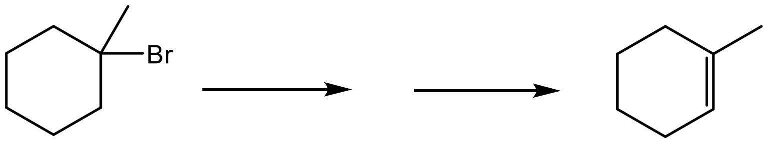


During this synthesis, pay attention to where the pi bond is. Recall this pi bond can be made from an alkyl halide using E2 reaction. But which atom will the halogen be on a or b? Does it matter? If the halogen is on atom a, the halide would be on a 2^o carbon. If the halogen is on atom b, the halide would be on a 3^o carbon.

Yes, it does as we have been asked to start from the alkane that first need to be converted to alkyl halide using free radical halogenation. Since that reaction goes via free radical formation in the rds, the more stable 3^o free radical (atom b) will have the lowest Ea and will form the most to give the 3 ^{o} RX (3-bromo-3-methylbutane).



Exercise 6.21: Synthesize the following alkene from the starting alkane using any reagents.

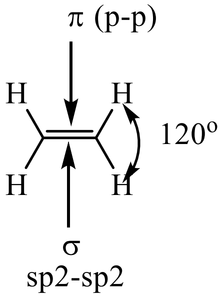


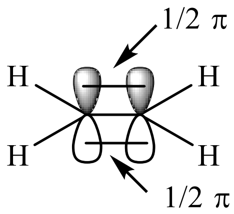
Exercise 6.22: Synthesize the following alkene from the starting alkane using any reagents.

Chapter 7: Structure and Synthesis of Alkenes

7.1 The Orbital Description of the Alkene Double Bond

Alkenes are a functional group where a carbon is doubly bonded to another carbon. The smallest alkene has two carbons. The double bond between the two carbon atoms is made up of one sigma bond and one pi bond. The sigma bond between the two carbon atoms is formed by the overlap of hybrid orbitals on each carbon. Since each carbon is sp2 hybridized, the sigma bond is formed by the overlap of sp2 orbitals on each carbon. The pi bonds are always formed by the sideways overlap of unhybridized p-orbitals. The two top and bottom lobes of the p orbital make one pi (π) bond.



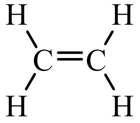


The H-C-H bond angle is 120° and the alkene has a trigonal planar geometry.

7.2 Elements of Unsaturation

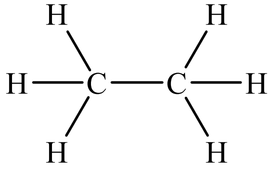
The molecular formula of alkenes is C_nH_{2n}. So, alkenes have two fewer hydrogen atoms compared to their alkane counterpart. This is called Elements of Unsaturation or Index of Hydrogen deficiency (IHD). Use the C_nH_{2n+2} formula to figure out the number of hydrogens for the saturated counterpart.

E.g. ethene (C_2H_4) has 2 lesser hydrogens compared to its fully saturated ethane (C_2H_6) counterpart.



C_2H_4

ethene



C_2H_6

ethane

Mathematically, IHD can be calculated using the formula:

$$\text{IHD} = \frac{\text{\# of hydrogens for saturated} - \text{\# of hydrogen for unsaturated}}{2}$$

In this case, IHD of C_2H_4 = $\frac{(6-4)}{2}$ = 1

Problem-solving:

a triple bond = two elements of unsaturation
a ring = one element of unsaturation
a double bond = one element of unsaturation

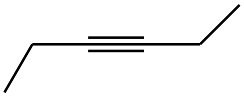
IHD of 1 can be achieved by either one double bond or one ring. If a molecule has two rings and one double bond, it will have IHD=3.

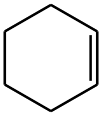
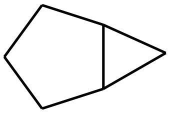
Solved Problems 7.1: Calculate the Element of Unsaturation (IHD) implied by the molecular formula C_6H_{10}.

Comparing C_6H_{10} from its saturated counterpart C_6H_{14} (we used C_nH_{2n+2} formula),

IHD = $\frac{(14-10)}{2}$ = 2

This molecule can have two double bonds, two rings, or 1 ring and one pi bond. A few of the proposed structures of compounds with the C_6H_{10} formula are:



Exercise 7.1: Calculate the Element of Unsaturation (IHD) implied by the molecular formula C_4H_8.

Exercise 7.2: Give four examples of structures with the formula C_5H_{10}. At least one should contain a ring, and at least one a double bond.

Exercise 7.3: If a hydrocarbon has ten carbon atoms, three double bonds, and one ring, how many hydrogen atoms must it have?

For molecules containing heteroatoms, we will treat atoms belonging to each group separately.

(i) <u>For compounds containing Oxygen or Sulfur</u>.

For calculating IHD, we will ignore the presence of O/S.

e.g. You are asked to calculate the IHD of a compound molecular formula $C_5H_{10}O$. For calculating IHD, we will ignore the O atom and compare the formula with a fully saturated counterpart.

C_5H_{10} vs. C_5H_{12}. The IHD = $\frac{(12-10)}{2}$ = 1

Exercise 7.4: Calculate the IHD for a compound with the molecular formula $C_7H_{12}O$.

(ii) For compounds containing Halogens (Fluorine, Chlorine, Bromine, Iodine.

For calculating IHD, we will add one hydrogen for every halogen present in the compound.

e.g., You are asked to calculate the IHD of a compound molecular formula $C_6H_{11}Cl$. For calculating IHD, we will add one hydrogen atom (for one Cl atom) and compare the formula with a fully saturated counterpart.

C_6H_{12} vs. C_6H_{14}. The IHD = $\frac{(14-12)}{2} = 1$

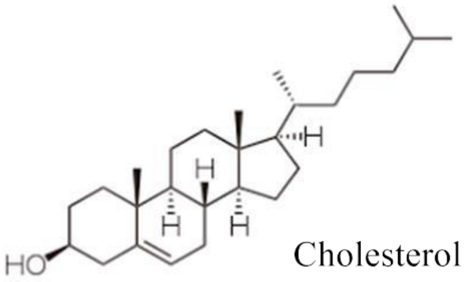
(iii) For compounds containing Nitrogen or Phosphorous.

For calculating IHD, we will subtract one hydrogen for every N/P present in the compound.

e.g., You are asked to calculate the IHD of a compound molecular formula $C_6H_{11}N$. For calculating IHD, we will subtract one hydrogen atom (for one N atom) and compare the formula with a fully saturated counterpart.

C_6H_{10} vs. C_6H_{14}. The IHD = $\frac{(14-10)}{2} = 2$

Exercise 7.5: Calculate the IHD for cholesterol whose structure is shown below.

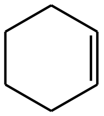


Exercise 7.6: For each of the following molecular formulas, determine the IHD.

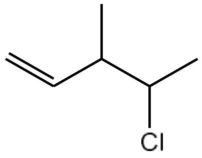
a. $C_4H_4Cl_2$ **b.** $C_7H_{14}O$ c. $C_6H_8O_2$ d. $C_5H_5NO_2$ e. $C_6H_3NCl_2$

7.3 Nomenclature of Alkenes

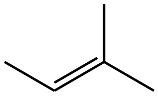
1. Simple alkenes are named much like alkanes, using the root name of the longest chain containing the double bond. During alkene nomenclature, the name of alkenes ends with “ene”
2. The C=C must be a part of the longest continuous chain.
3. The C=C must be given the smallest possible number.
4. Cycloalkenes are assumed to have a double bond in the number 1 position.



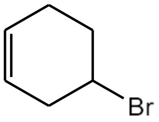
cyclohexene



4-chloro-3-methylpent-1-ene

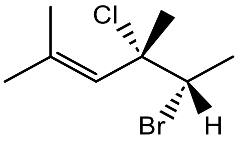


2-methylbut-2-ene



4-bromocyclohexene

Exercise 7.7: Provide the IUPAC nomenclature for the compound below. Include stereochemistry.



Exercise 7.8: Draw the structure represented by the incorrect name (or a consistent structure if the name is ambiguous) and give your drawing the correct name.

a. *cis*-2,3-dimethyl-2-pentene

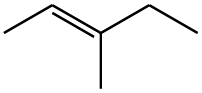
b. 2-methylcyclopentene

c. 2,5-dimethylcyclohexene

d. *cis*-2,5-dibromo-3-ethylpent-2-ene

7.4 Nomenclature of Cis-Trans Isomers

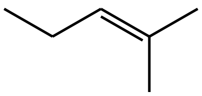
In previous chapters, we saw how the lack of rotation of double bonds between C=C gives rise to cis-trans isomerism. If two identical or substantial groups are on the same side of the double bond, the compound can be designated with *cis* if they are on the same side or *trans* if they are on opposite sides. If applicable, always indicate *cis* and *trans* with a double bond on a hydrocarbon chain



cis-3-methylpent-2-ene.

In this case, the two -CH3 groups are on the same side of the double bond so this is a cis isomer.

Not all alkenes can show cis-trans isomerism. For a molecule to exhibit as a cis or trans compound, there must be two different groups on **each** end of the double bond.



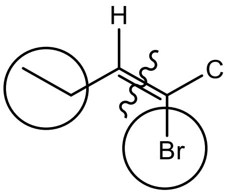
The right carbon that is doubly bonded has two identical -CH3 groups. Therefore, this molecule cannot exist as *cis/trans*. Trans cycloalkenes are unstable unless the ring is large enough (at least eight carbon atoms) to accommodate the trans-double bond. Therefore, all cycloalkenes are assumed to be cis unless they are specifically named trans.

E/Z nomenclature of alkenes:

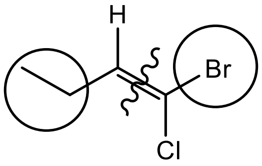
The cis-trans nomenclature for geometric isomers sometimes gives an ambiguous name. For example, the isomers of 1-bromo-1-chlorobut-1-ene are not clearly cis or trans because it is not obvious which substituents are referred to as cis or trans.

stereoisomers of 1-bromo-1-chlorobut-1-ene

To deal with this conflict, we use the ***E-Z* system** of nomenclature (pun intended) for cis-trans isomers, which is patterned after the Cahn–Ingold–Prelog convention for asymmetric carbon atoms. It assigns a unique configuration of either *E* or *Z* to any double bond capable of geometric isomerism. To name an alkene by the *E-Z* system, mentally separate the double bond into its two ends. Remember how you assigned relative priorities to groups on an asymmetric carbon atom so you could name it (*R*) or (*S*)? Consider each end of the double bond separately and use those same rules to assign first and second priorities to the two substituent groups on each end. If the two first-priority atoms are on the same side of the double bond, you have the ***Z*** isomer. If the two first-priority atoms are on *opposite* sides of the double bond, you have the ***E*** isomer.

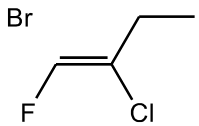


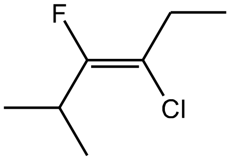
Z- 1-bromo-1-chlorobut-1-ene

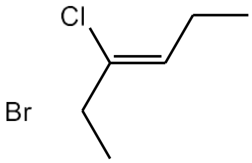


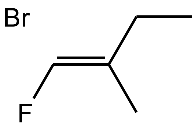
E- 1-bromo-1-chlorobut-1-ene

Exercise 7.9: Provide the IUPAC nomenclature for the compound below. Include E/Z stereochemistry.









Exercise 7.10: Some of the following examples can show geometric isomerism, and some cannot. For the ones that can, draw all the geometric isomers, and assign complete names using the *E-Z* system.

a. 3-bromo-2-chloropent-2-ene

b. 3-ethyl-5-methyloct-3-ene

c. 3-bromo-2-methylhex-3-ene

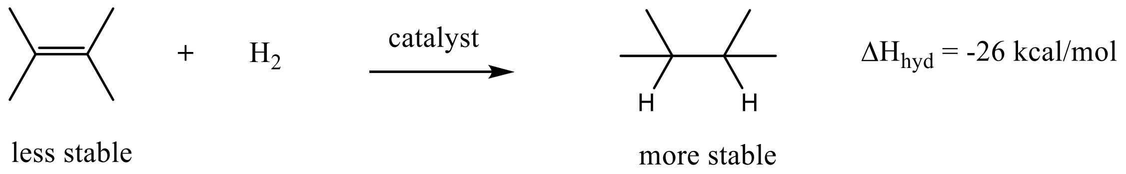
d. 4-bromo-3-chlorohept-3-ene

7.5 Commercial Importance of Alkenes

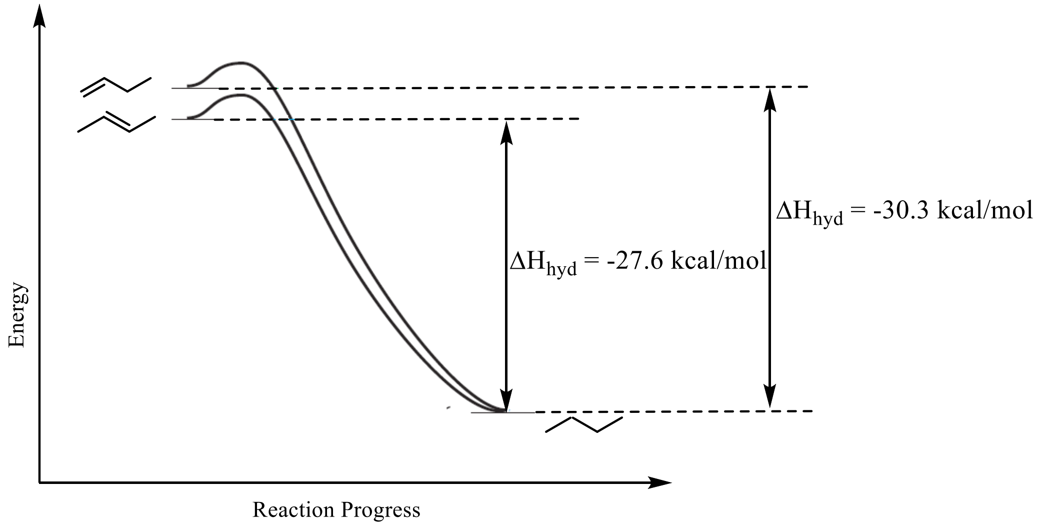
Alkenes are important intermediates in the synthesis of polymers, drugs, pesticides, and other valuable chemicals. We will see in Chapter 8 that the carbon-carbon double bond of alkenes can easily be converted to other functional groups. The smallest alkene ethene (common name ethylene) is the organic compound produced in the largest volume, at around 160 billion pounds per year worldwide. Most of this ethylene is polymerized to form polyethylene.

7.6 Stability of Alkenes

Alkenes are less stable than their alkane counterparts. This was quantitatively observed by studying the heat of hydrogenation. The reaction is exothermic, and the energy diagram is shown below.

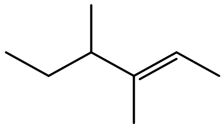


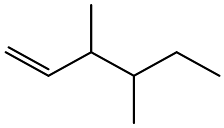
In the presence of catalysts like Pt, Ni, and Pd metal.
It was quantitatively observed that but-1-ene is less stable than *trans*-but-2-ene by 2.7 kcal mol. This difference in stability was calculated by the difference in ΔH_{hyd} of the two alkenes.

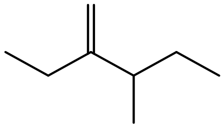


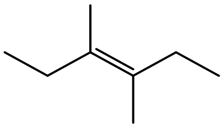
We can use the heat of hydrogenation to compare the stabilities of different alkenes if they hydrogenate to give alkanes of similar energies. The observation would be that the more stable the alkene, the smaller the ΔH_{hyd}. Recall, more substituted alkenes are more stable than less substituted alkenes. Also, the trans isomer is more stable than the cis isomer and the E isomer is more stable than the Z isomer.

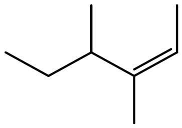
Exercise 7.11: Rank the following alkenes in the order of increasing heat of hydrogenation (ΔH_{hyd}). Compound with lowest ΔH_{hyd} first.


A


B

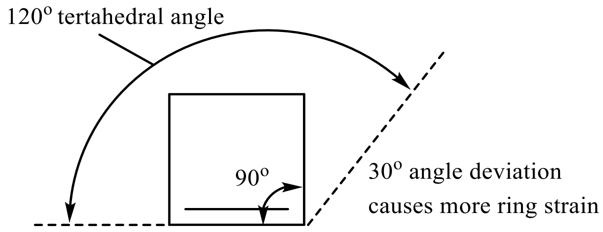

C

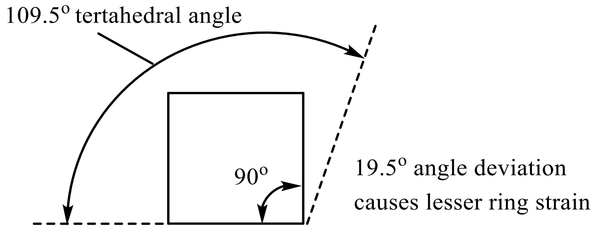

D


E

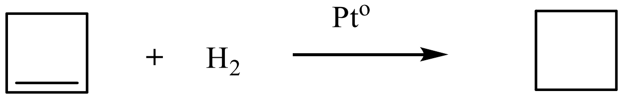
Ring Strain in cycloalkenes:

Smaller cycloalkenes have a larger ring strain than their cycloalkane counterpart.

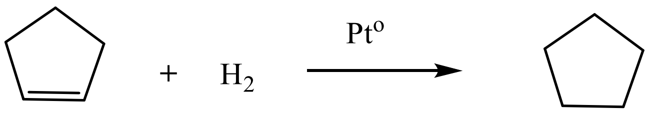




ΔH_{hyd} of cyclobutene is higher by 4.1 kcal/mol compared to ΔH_{hyd} of cyclopentene. The extra ring strain in cyclobutene makes its double bond more reactive than a typical double bond.



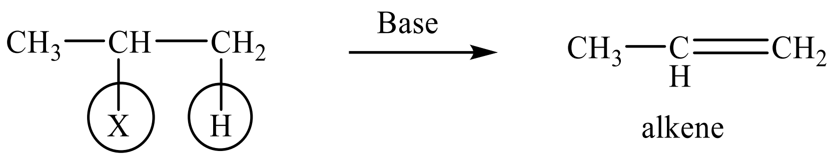
ΔH_{hyd} = -30.7 kcal/mol



ΔH_{hyd} = -26.6 kcal/mol

7.7 Alkene Synthesis by Elimination of Alkyl Halides-A Review from Chapter 6.

When alkyl halides are reacted with bases, they undergo a dehydrohalogenation reaction (removal of hydrogen and halogen) and make a pi bond (alkene) in the process. This is represented as:

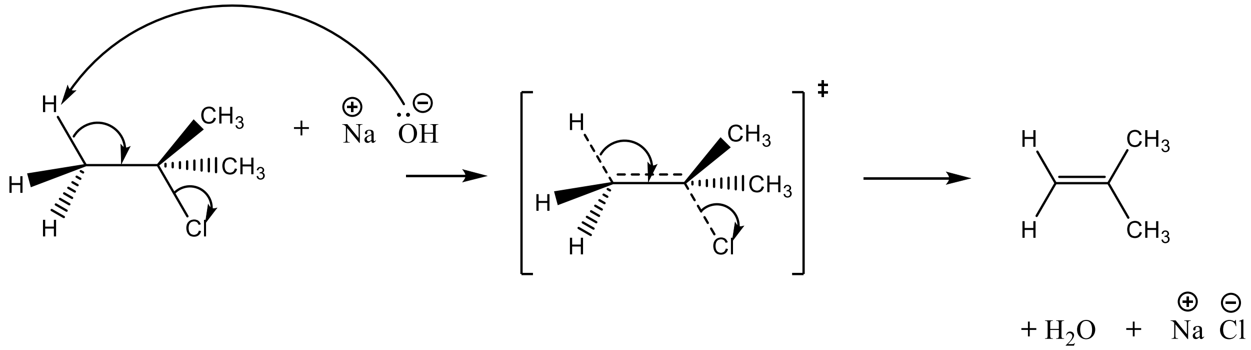


$$CH_3-\underset{\textcircled{X}}{CH}-\underset{\textcircled{H}}{CH_2} \xrightarrow{\text{Base}} CH_3-\underset{H}{C}=CH_2$$

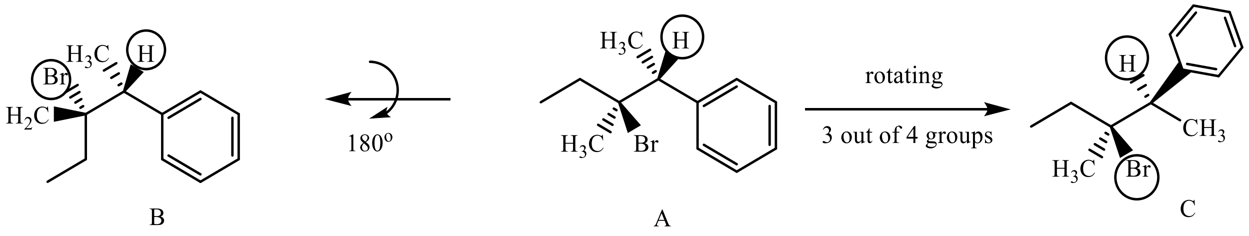
Since hydrogen and a halogen is being removed from the alkyl halide, this is called an elimination reaction. In Chapter 6 we saw how dehydrohalogenation can take place through the E1 and E2 mechanisms. The second-order elimination (E2) is usually better for synthetic purposes because the E1 always competes with the SN1 reaction. In the next section, we will review the E2 reaction as it is synthetically more useful to make alkenes from a secondary or a tertiary RX. You should also keep in mind the competing reactions of the SN2 and E2 mechanisms (mostly for 2° RX).

7.8 The E2 Reaction Mechanism and stereochemistry of E2 reaction.

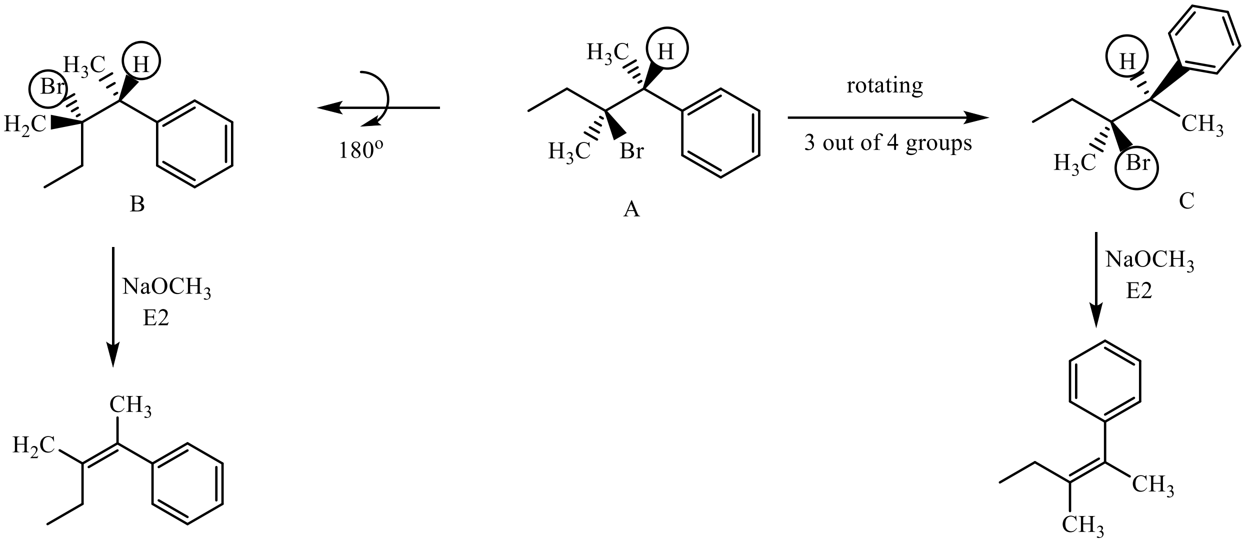
"Anti-coplanar transition state" is required for E2 reaction to take place. The β hydrogen that the base picks up must be anti-coplanar to the halogen. Pay attention to stereochemistry any time stereochemistry is provided in the starting alkyl halide.



The anti-coplanar transition state can be achieved by a rotation of three out of four groups or via sigma bond rotation in acyclic alkyl halides. For the E2 reaction of the given secondary halide A, to form the major product (tetra-substituted alkene), the circled hydrogen is not an anti-coplanar transition state. Rotating three out of four groups or rotating the molecule by 180° is necessary to achieve the anti-coplanar transition state, such that the circled hydrogen atom is anti-coplanar to the bromine atom. Here A, B, and C are the same molecules with different representations.

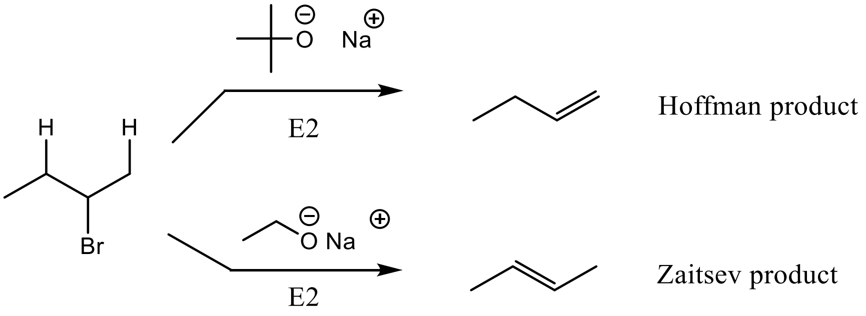


The major E2 product resulting would be the Z isomer. E isomer would not be formed.



7.9 Bulky bases in E2 reactions

Bulky bases like (CH3)3CONa (sodium *t*-butoxide) abstracts a less hindered proton (a proton on a less substituted carbon), often the one that leads to the formation of the less substituted product, called the **Hofmann product.** The following reaction gives mostly the **Zaitsev product** with the relatively unhindered sodium ethoxide, but mostly the Hofmann product with the bulky sodium *t*-butoxide.

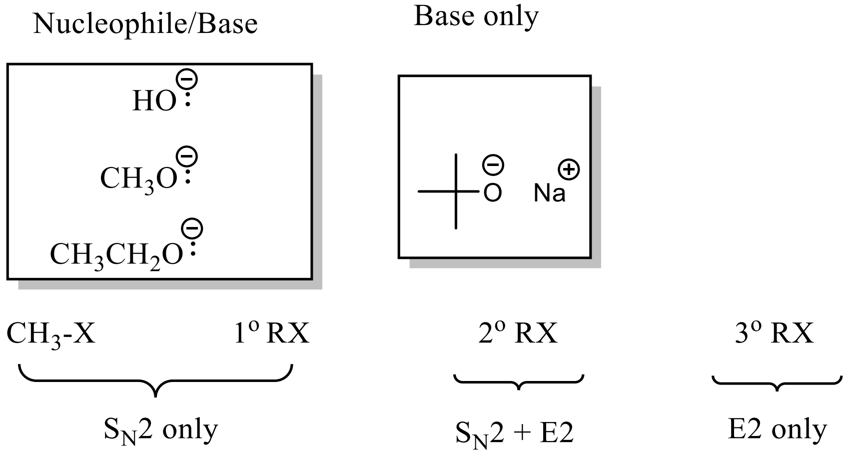


7.10 Reactivity of Alkyl Halides in E2 reactions:

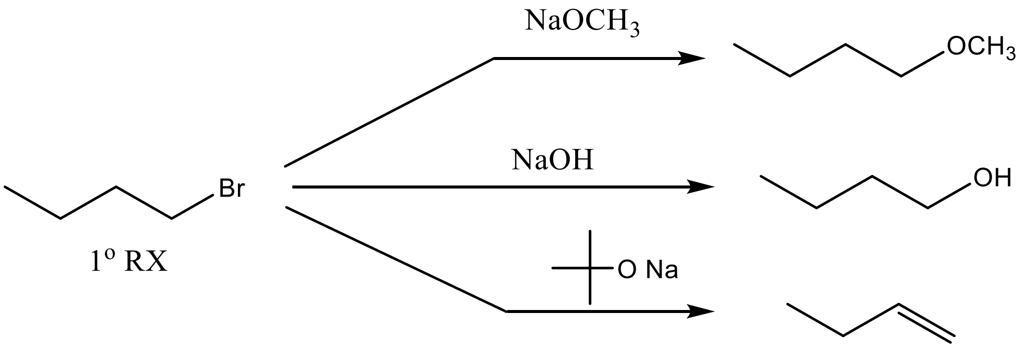
$$\left.\begin{array}{ll} S_N2 & CH_3\text{-}X > 1^o\,RX > \boxed{2^o\,RX} > 3^o\,RX \\ E_2 & 3^o\,RX > \boxed{2^o\,RX} > 1^o\,RX \end{array}\right\}\ \text{favored by charged (strong) nucleophile/base}$$

Since the reactivity of alkyl halide is opposite of S_N2 and E2 reactions, technically they compete only when the substrate is 2^o RX.

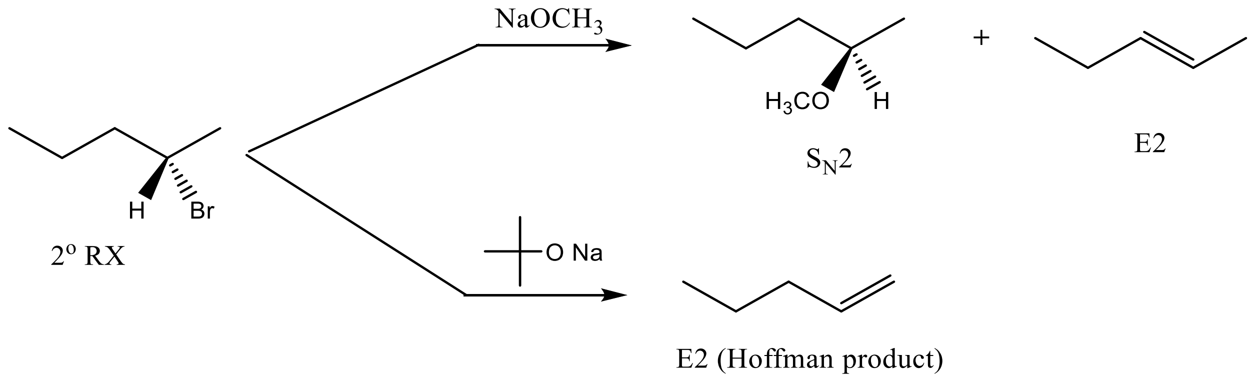
The following bases are used to synthesize alkenes from alkyl halides. The left column is both strong nucleophiles and strong bases. The right column (which contains a bulky base) is a strong base and is too bulky to act like a nucleophile.



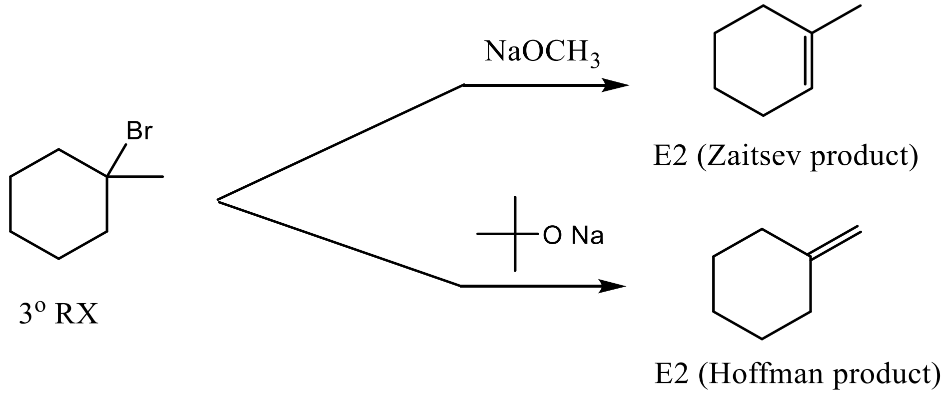
For 1° RX



For 2° RX

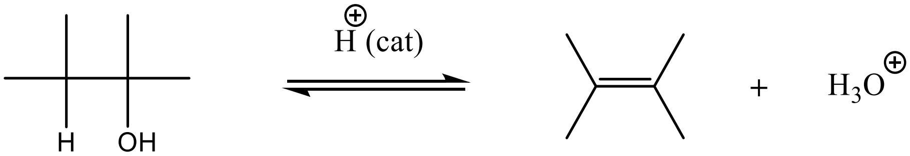


For 3° RX

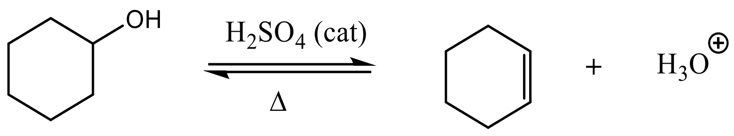


7.11 Acid-Catalyzed Dehydration of an Alcohol

When alcohols are heated in presence of catalytic amount of acid like H_2SO_4 or H_3PO_4, a dehydration reaction takes place. Dehydration implies loss of water (H_2O), so in essence, the alcohol loses water and forms an alkene. This reaction is an equilibrium reaction and the equilibrium can be favored to the right side (Le Chatelier's principle) by an experimental technique called distillation, where a mixture of two liquids can isolate based on their boiling points. The alkene boils at a lower temperature than the alcohol because the alcohol is hydrogen bonded. A carefully controlled distillation removes the alkene while leaving the alcohol in the reaction mixture.



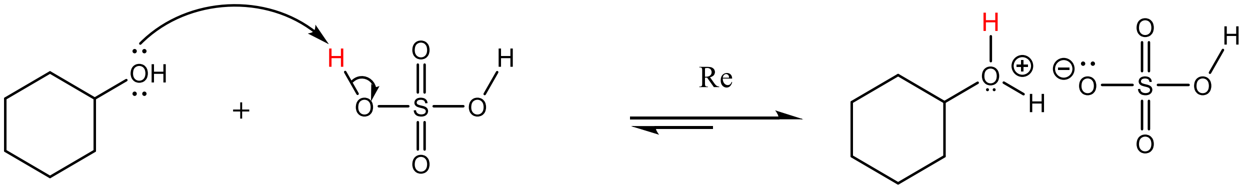
e.g., cyclohexanol undergoes a dehydration reaction when it is heated in the presence of an acid catalyst such as H_2SO_4 or H_3PO_4 (but **<u>NOT</u>** HCl, HBr).



b.p. 162°C b.p. 83°C

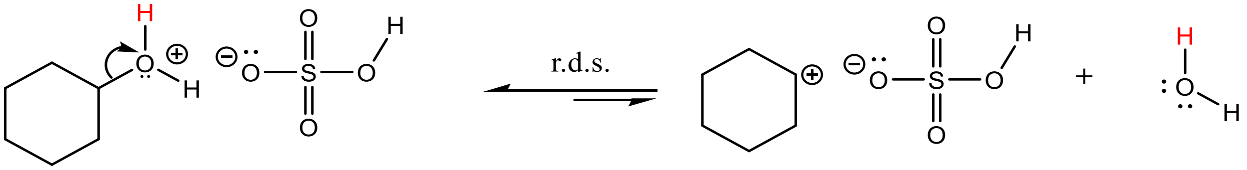
The mechanism of this reaction is shown below. The first step is an acid-base reaction between the alcohol and the sulfuric acid (H_2SO_4). Recall, that sulfur can have an expanded octet.

Step 1: Acid-Base reaction

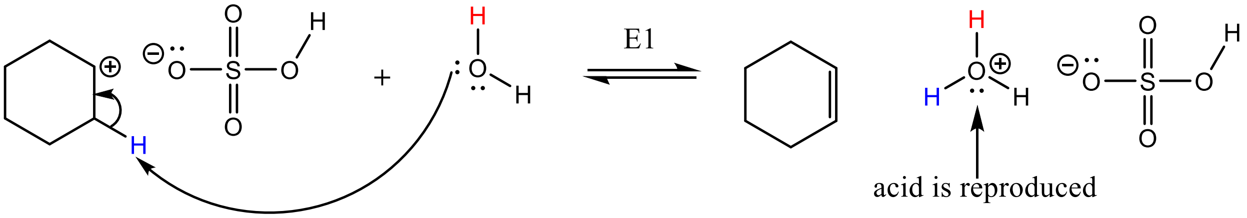


SB SA CA CB

Step 2: Loss of water from protonated alcohol. This is the slowest rate determining step of the reaction as a reactive intermediate (carbocation) is formed.

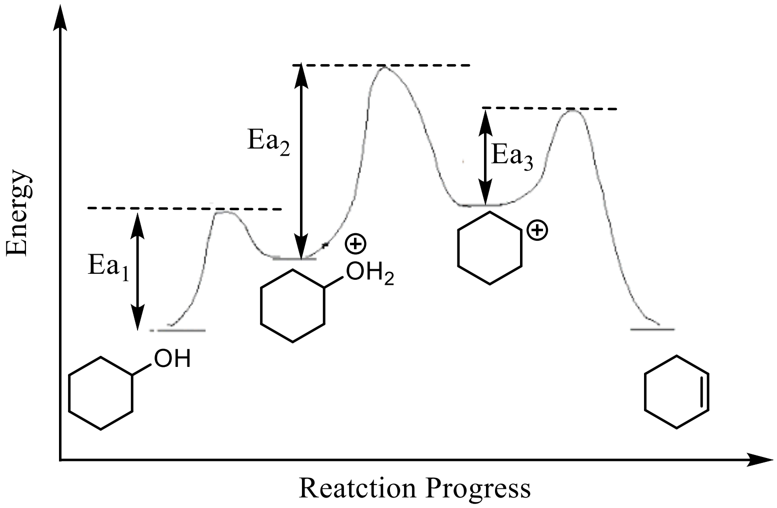


Step 3: Loss of a proton from the carbon adjacent to the carbocation is the E1 mechanism. The loss of the proton takes place by H_2O produced in the second step and **<u>not</u>** $HSO_4^{\ominus}$. Between the two, $HSO_4^{\ominus}$ is a weaker base as its electrons are stabilized via resonance.



acid is reproduced

The energy diagram for the formation of cyclohexene is shown below. The rds is the formation of carbocation (Step 2) that has the highest activation energy (Ea_2).

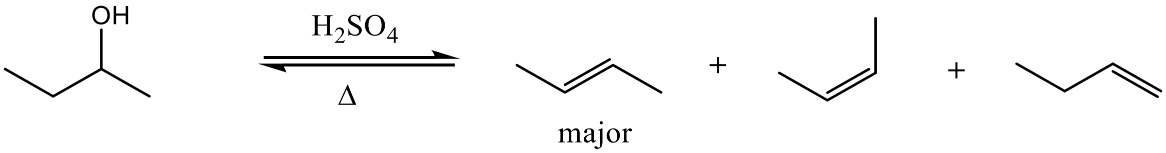


Reactivity of alcohols: The formation of carbocation is the rate determining step. Due to which the more stable the carbocation, the lower the Ea of its formation and faster the reaction.

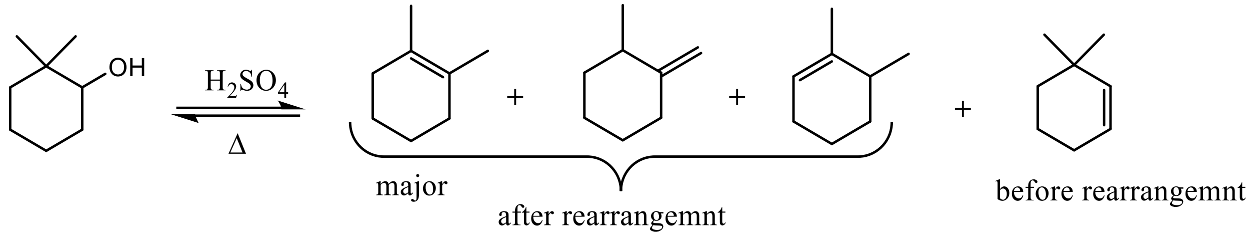
Therefore, the reactivity of alcohols is as follows:

3^o ROH > 2^o ROH > 1^o ROH >
most reactive least reactive

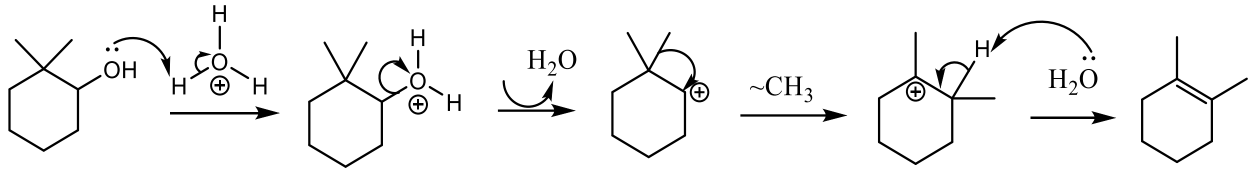
Formation of alkene: This is an E1 elimination mechanism, hence the most stable alkene is always the major product. When butan-2-ol undergoes dehydration reaction, three alkenes are forms and of the three the major product is *trans*-but-2-ene.



Rearrangements during dehydration of alcohols: Carbocation formation implies that rearrangements are possible.

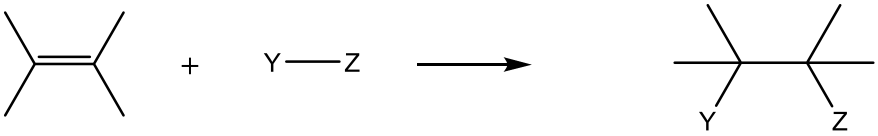


Formation of the major product, 1,2-dimethylcyclohexene is shown below. The acid in the first step has been abbreviated as $H_3O^{\oplus}$.



8.1 Reactivity of the Carbon-Carbon Double Bond

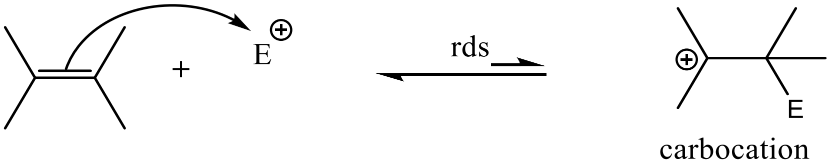
Alkenes undergo addition reactions very easily due to the reactivity of the pi bond. A representative example is given below:



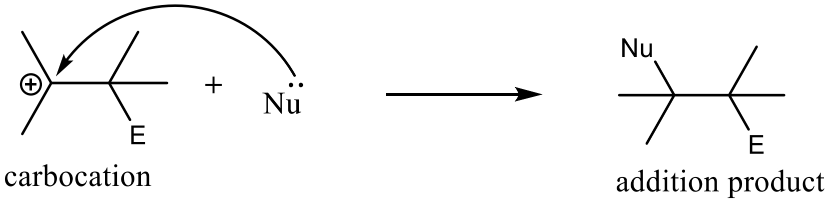
Addition across the pi bond of alkene is its most common reaction of alkenes. In this chapter, we will explore additions to alkenes in detail which results in a wide variety of functional groups. This takes place through the addition of suitable reagents to the double bonds of alkenes.

8.2 Electrophilic Addition to Alkenes

The pi electrons of alkenes make them very reactive as they are more loosely held by carbon atoms. A strong electrophile is attracted to these loosely held electrons. It can pull them away to form a new bond. The arrow starts from the middle of the pi bonds (the electrons) and one of the carbon atoms makes the bond with the electrophile. This leaves the other carbon atom with only three bonds and a positive charge: **carbocation**. In this process the double bond (the electrons of the pi bond acts like a nucleophile that donates a pair of electrons to the electrophile.



Most addition reactions involve a second step in which a nucleophile attacks the carbocation (as in the second step of the reaction), forming a stable addition product. In the product, both the electrophile and the nucleophile are bonded to the carbon atoms that were connected by the double bond.

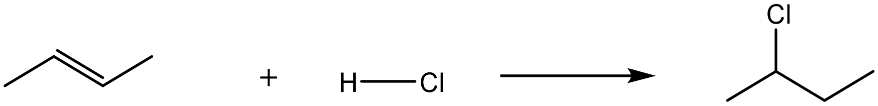


This type of reaction requires a strong electrophile to attract the electrons of the pi bond and generate a carbocation in the rate-limiting step. Most alkene reactions fall into this large class of **electrophilic additions** to alkenes.

8.3 Addition of Hydrogen Halides to Alkenes

Halo acids (HX) add across the C=C in an electrophilic manner. In the $\overset{\delta+}{\mathrm{H}}-\overset{\delta-}{\mathrm{X}}$, the hydrogen bonded to halogen (X) is electrophilic as the halogen is more electronegative.

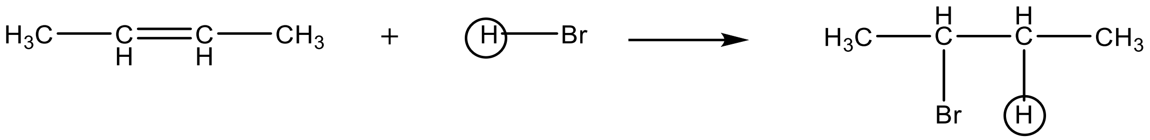
In the line formula:



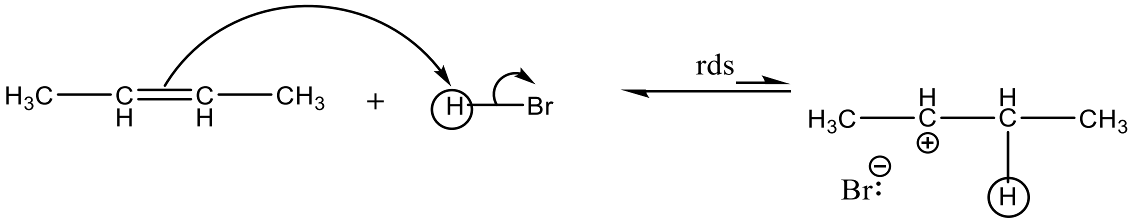
Pay attention to the change in the products. The H and Cl add across the double bond.

8.4 Ionic Addition of HX to an Alkene

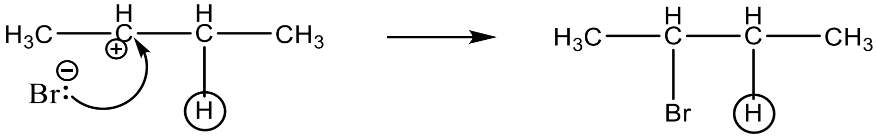
The mechanism of the addition of H-Br to but-2-ene is shown below. The hydrogen atom belonging to the halo acid HBr has been circled so you can see how the reaction mechanism proceeds in the first step.



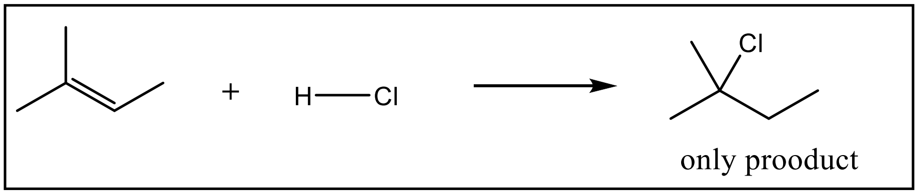
Step 1:

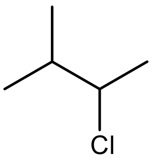


Step 2:



When 2-methylbut-2-ene reacts with HCl, only one product is formed. 2-chloro-2-methylbutane. In other words, we can say that H of HCl goes to the less substituted carbon and Cl goes to the more substituted carbon.

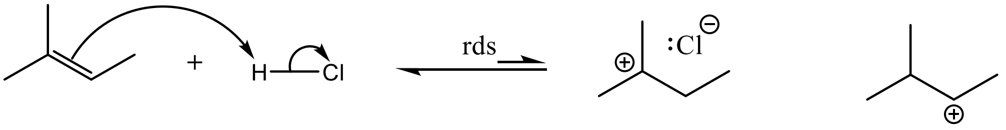




does not form

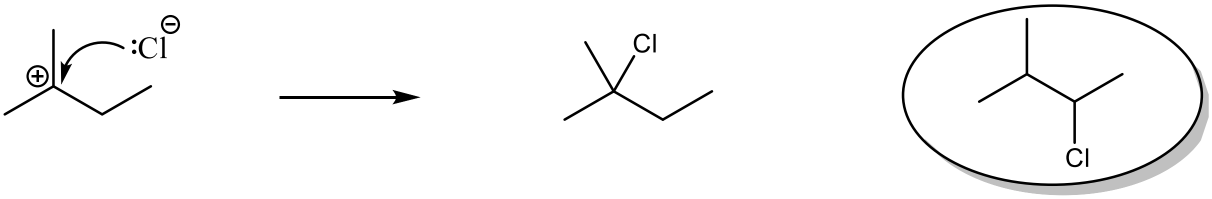
Since the first step is the formation of a carbocation (the rds), the more stable 3^o carbocation forms and 2^o carbocation does not form, leading to only one product. Recall from Chapter 4 that a more substituted carbocation is more stable due to inductive effects.

Step 1:



3^o carbocation forms 2^o carbocation does not form

Step 2:



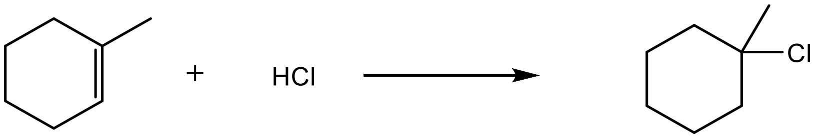
does not form

Markovnikov was a Russian scientist who observed all alkene reactions undergoing similar reactions and it later became **Markovnikov Rule**:

The addition of a proton acid to the double bond of an alkene results in a product with the acid proton bonded to the less substituted carbon (carbon atom that holds the greater number of hydrogen atoms).

This was restated: An electrophilic addition to an alkene, the electrophile adds in such a way as to generate the most stable reactive intermediate.

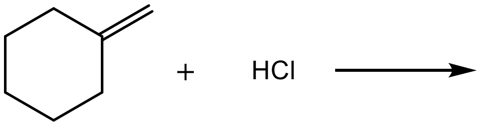
When 1-methylcyclohexene undergoes an addition reaction with HCl, the Markovnikov product is 1-chloro-1-methylcyclohexene.



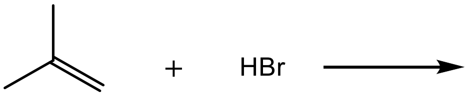
Markovnikov product

Exercise 8.1: Draw the product of the following reaction and propose a mechanism.

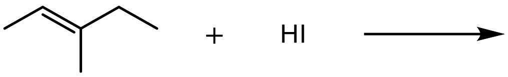
a.



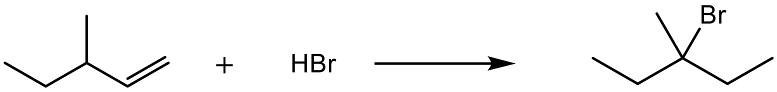
b.



c.



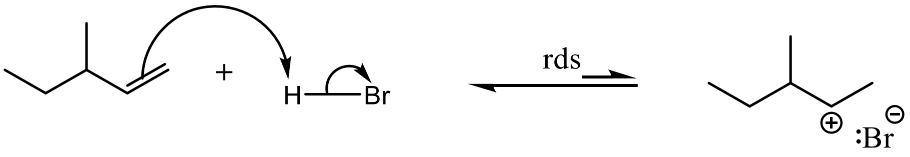
Rearrangements are often observed during addition reactions. Since carbocation is formed in the addition reaction of halo acids, rearrangements are often observed. When the reaction below takes place, an unexpected product was formed as a major product.



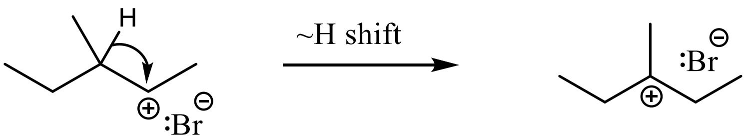
major product

Based upon the reaction mechanism, it is obvious that the major product is formed after carbocation rearrangement takes place.

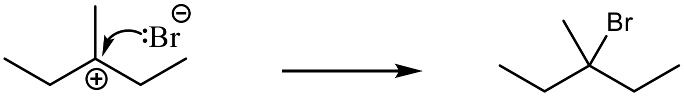
Step 1:



Step 2:

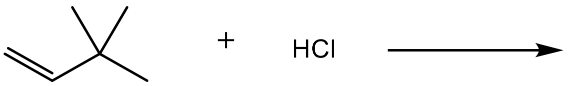


Step 3:



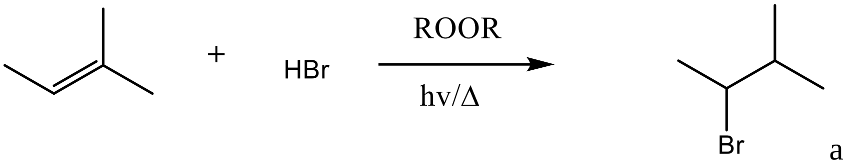
major product

Exercise 8.2: Draw the major product of the following reaction and propose a mechanism.



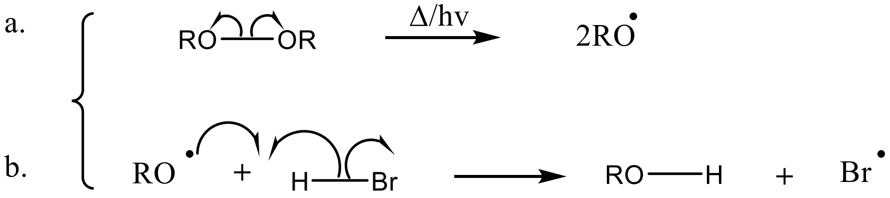
8.5 Free-Radical Addition of HBr to Alkenes

In 1933, Kharasch and Mayo found that some additions of HBr (but not HCl or HI) to alkenes gave products that were opposite to those expected from Markovnikov's rule. These **anti-Markovnikov** reactions took place in presence of alkyl peroxides (ROOR). Peroxides give rise to free radicals that initiate the addition, causing it to occur by a free radical mechanism.

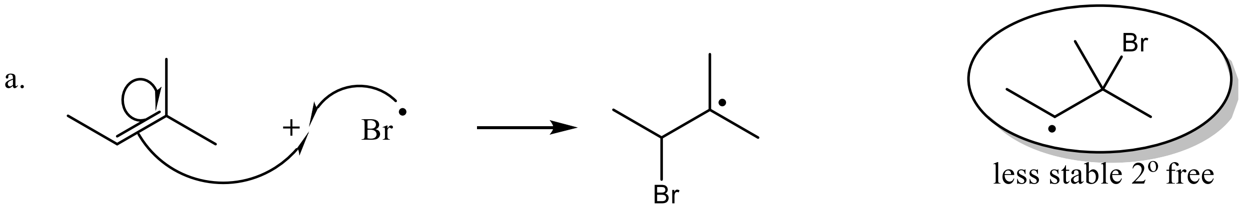


anti-Markovnikov product

Step 1: Initiation steps

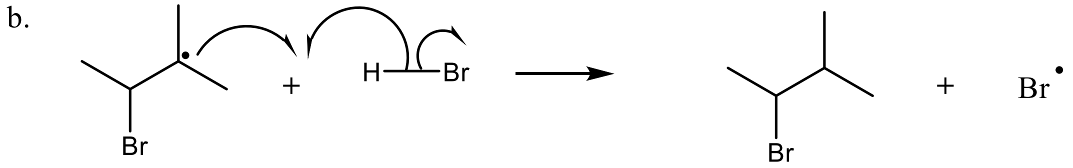


Step 2: Propagation steps



3^o free radical

less stable 2^o free radical not formed

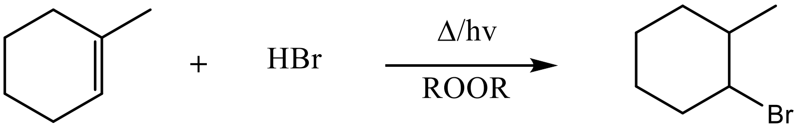


anti Markovnikov product

Step 3: Termination steps

Three possible termination steps due to two types of free radicals colliding with each other or themselves.

e.g.

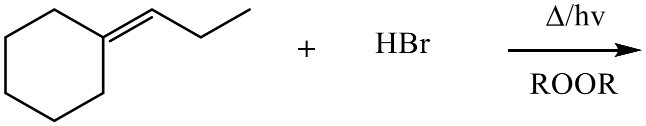


Notes:

1. This reaction takes place only with HBr. The reaction is not energetically favored for HCl and HI.
2. This is a free radical mechanism. The reaction takes place with the formation of a more stable free radical.
3. The sequence of addition of HBr is opposite to that of carbocation mechanism. The Br adds first then H (unlike the carbocation mechanism where H adds first and then Br).
4. The resulting product is formed by the addition of HBr across the C=C in **anti-Markovnikov** manner. H adds to the more substituted carbon and Br adds to the less substituted carbon.

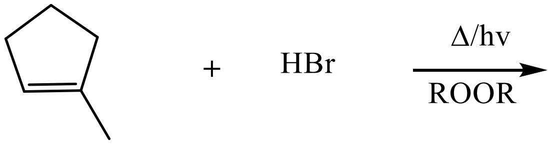
Exercise 8.3: Draw the major product of the following reactions.

a.

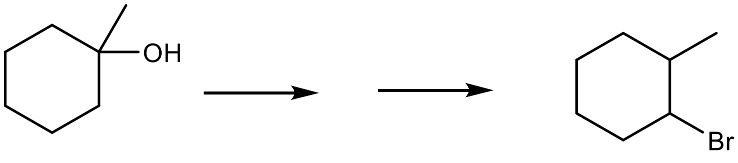


b.

c.



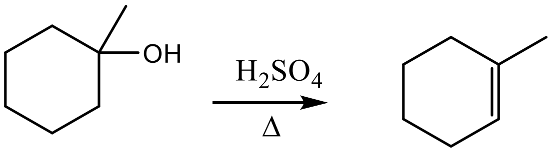
Solved Problem 8.1: Show how you would accomplish the following synthetic conversions.



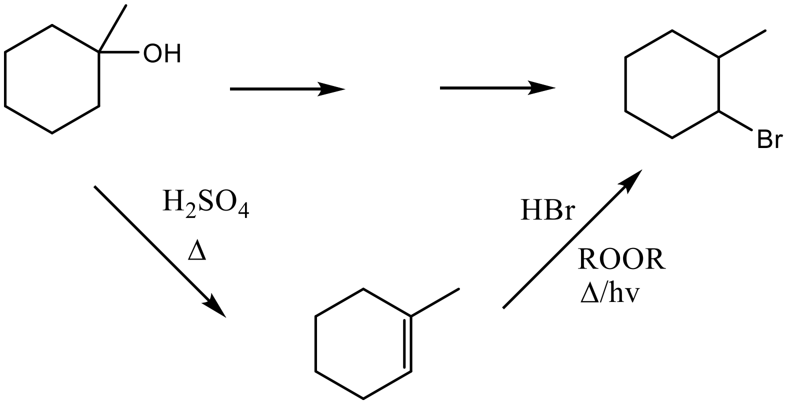
A few questions to ask:

e. What **functional group** is present on the *reactant*?
f. What **functional group** is present on the *product*?
g. What has changed from reactant to product?
h. Which reactions do I know to **convert** from one to the other?

Approach:
The starting material is alcohol.
The product is an alkyl halide where the halogen is on a **less** substituted carbon.
We only know one reaction of alcohol, dehydration of alcohol to give alkene. This takes place in presence of acid like H_2SO_4 as a catalyst. That alkene is formed such that the major product is a more substituted alkene.

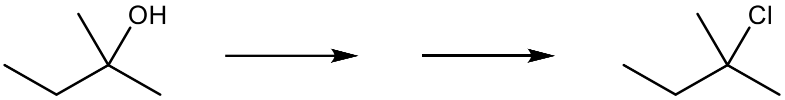


Can this alkene then be converted to the alkyl halide? See the double bond has disappeared in N the product, therefore we must be adding H and Br across the C=C. The HBr has added in an anti-Markovnikov manner. Therefore, this synthesis can be achieved in two steps as shown below:

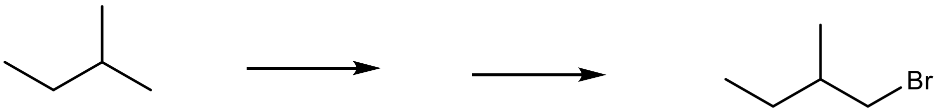


Exercise 8.4: Show how you would accomplish the following synthetic conversions

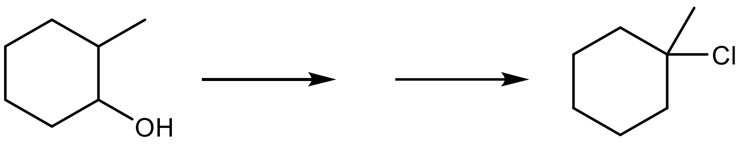
a.



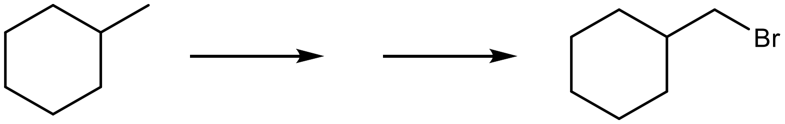
b.



c.



d.

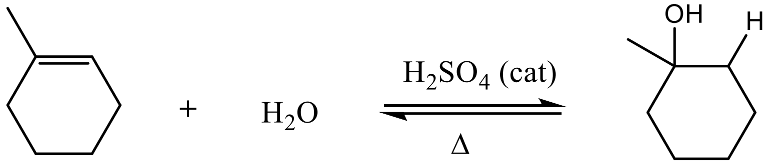


8.6 Addition of Water: Hydration of Alkenes

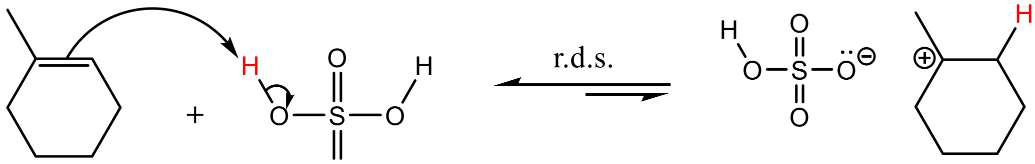
An alkene may react with water in the presence of a strongly acidic catalyst to form an alcohol. Formally, this reaction is a **hydration** (the addition of water), with a hydrogen atom adding to one carbon and a alcohol (-OH) group adding to the other.

8.7 Acid-Catalyzed Hydration of an Alkene: Direct Hydration

In chapter 7, we saw the dehydration of alcohol to give alkene. That was a reversible reaction. The hydration of alkene is the same reaction in the opposite direction. Every step of the mechanism is in equilibrium and the equilibrium can be forced to the right by using Le Chatelier's principle. The first step of the mechanism is the rds (formation of carbocation). Due to this, the addition of water takes place in a Markovnikov manner.

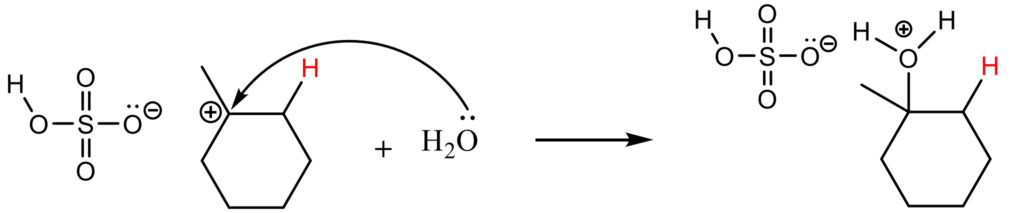


Step 1: The alkene electrons provide the electrons that picks up the acidic proton from the H_2SO_4 (marked red).

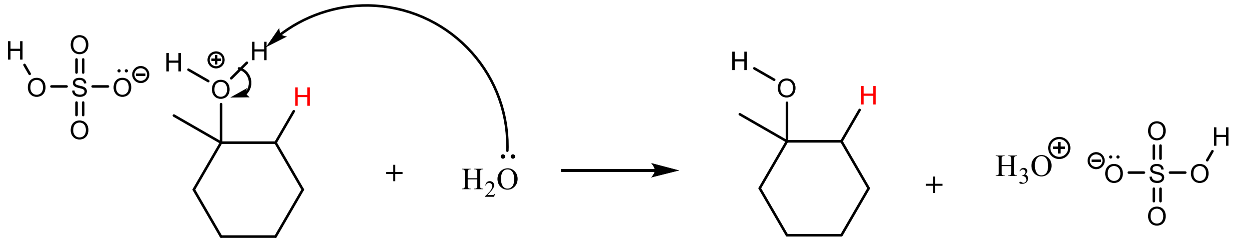


more stable 3° carbocation

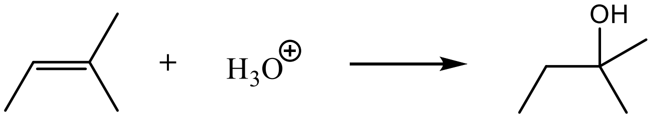
Step 2: The lone pair on water attacks the carbocation and which results in the formation of C-O bond.



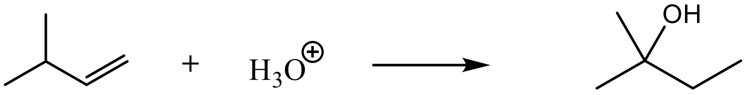
Step 3: The loss of the proton takes place by H_2O and **<u>not</u>** $HSO_4^{\ominus}$. Between the two, $HSO_4^{\ominus}$ is a weaker base as its electrons are stabilized via resonance.



Often, $H_3O^{\oplus}$ is used to indicate the use of catalytic amount of acid with water.
e.g.



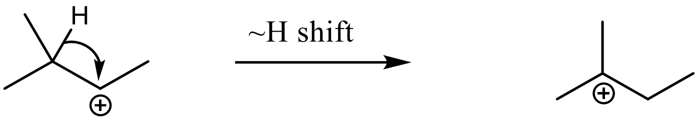
Rearrangements can take place during addition reactions. Since carbocation is formed during hydration of alkenes in catalytic acid, rearrangements are often observed. When the reaction below takes place, an unexpected product was formed as a major product.



major product

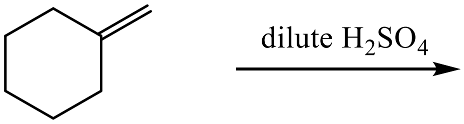
major product

The reaction takes place via formation of more substituted carbocation which undergoes a rearrangement as shown below. This explains the formation of the major product.

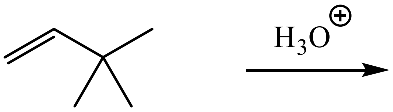


Exercise 8.5: Draw the major product of the following reactions.

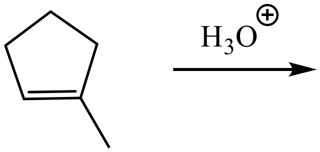
a.



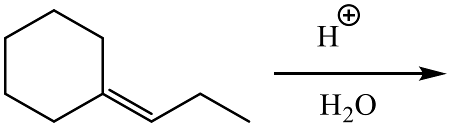
b.



c.



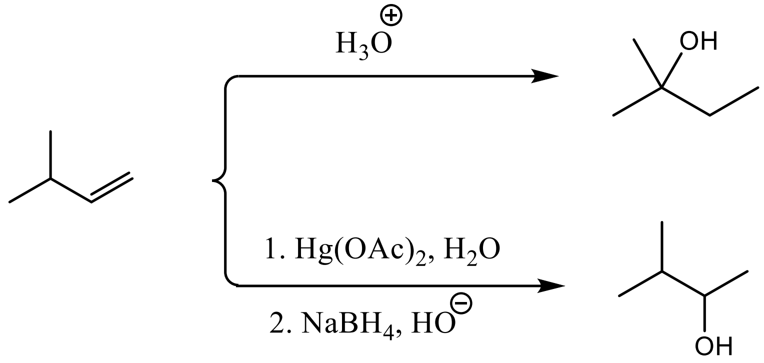
d.



Limitations of direct hydration:

1. The hydrophobic alkene may not be very soluble in hydrophilic water and acid.
2. Carbocation rearrangements are possible, which means the alcohol may not be formed at the double bond of alkene.

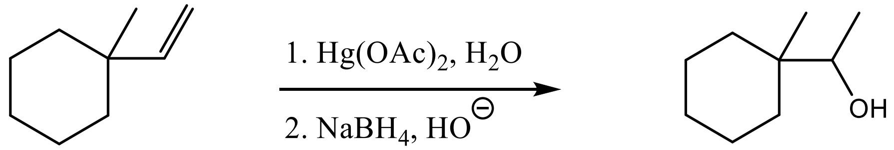
8.8 Indirect Hydration by Oxymercuration–Demercuration (OMD)



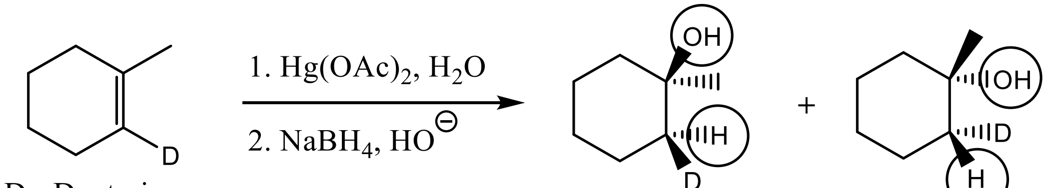
Carbocation rearranges
Markovnikov alcohol

Markovnikov alcohol
no carbocation rearrangement

The second reaction is called Oxymercuration-Demercuration. Looking at the product formed, the reaction is addition of water in a Markovnikov manner without formation of carbocation (since no rearrangement takes place).
e.g.

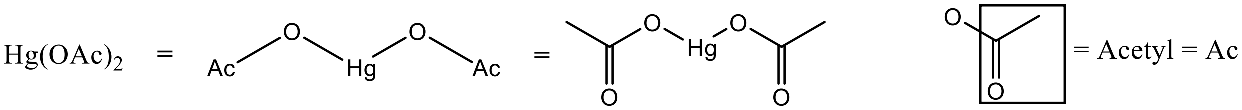


The example below shows Oxymercuration-Demercuration with stereochemistry. The overall reaction is addition of H_2O in a **Markovnikov** and ***trans*** manner.



D= Deuterium

The product shows two enantiomers that are formed. Once mechanism is explored, you will know why.

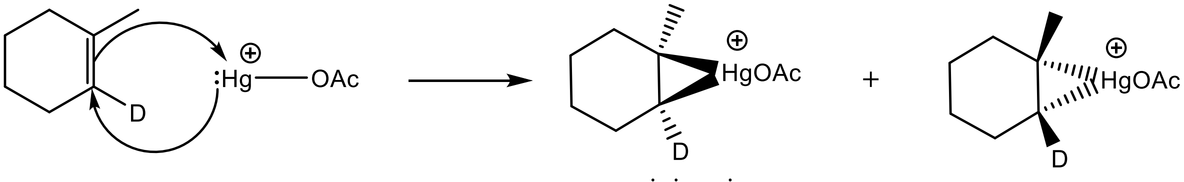


Mercury Acetate [Hg(OAc)2] disassociates to make the electrophile before it reacts with the alkene.

Mechanism of Oxymercuration of an Alkene

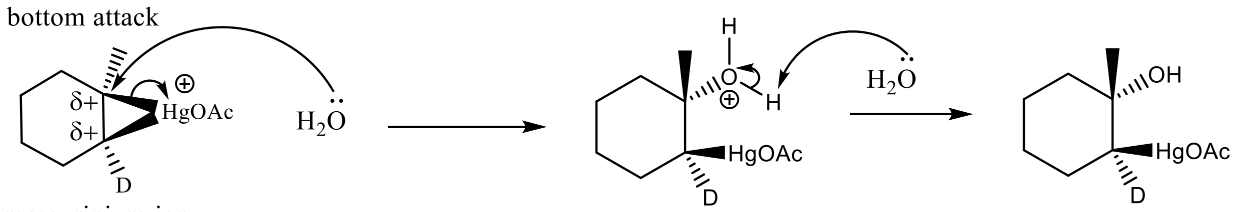
Step 1a Oxymercuration: This step involves attack of the double to the electrophilic positively charged mercury atom while the d-electrons on the mercury atom makes a bond with the other carbon. The product is a mercurinium ion, an organometallic cation containing a three-membered ring, with mercury atom bearing a full positive charge.

Since alkene is trigonal planar, the mercurinium ion can be formed on either side of the double bond (top or bottom), hence two enantiomers of mercurinium ion are formed.



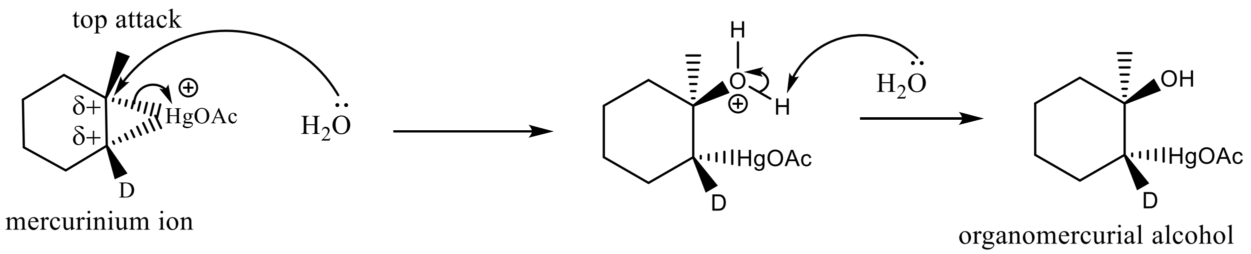
mercurinium ion mercurinium ion

Step 1b Oxymercuration: Due to positive charge on mercury atom, each of the carbon bears a partial positive charge. The more substituted carbon handles the positive charge better, so water attacks the more substituted carbon from the side opposite to the mercurinium ion. This results in an inversion of stereochemistry at the more substituted carbon. Pay attention to stereochemistry of organomercurial alcohol.

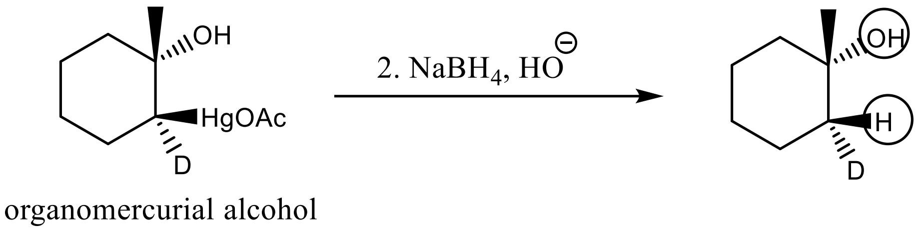


organomercurial alcohol

The same can happen with the other enantiomer.

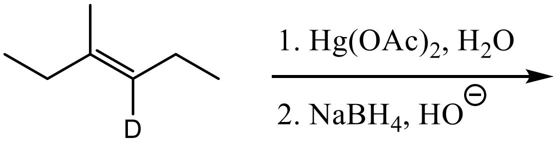


Demercuration of Organomercurial alcohol (no mechanism)**:** NaBH4 is a reducing agent which reduces the C-Hg bond to C-H bond without changing the stereochemistry. No mechanism for this reaction.

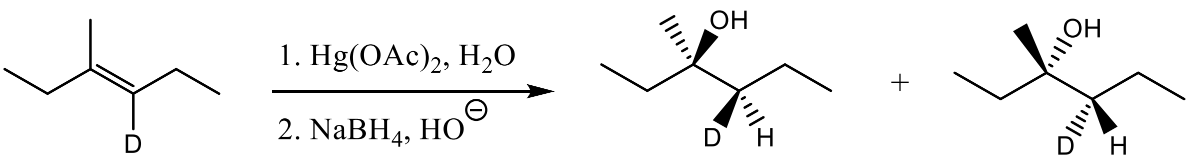


The Oxymercuration-Demercuration reaction is addition of water to an alkene in a **Markovnikov** and ***trans*** manner.

Solved Problem 8.2: Draw the product(s) of the reaction shown below with correct stereochemistry.



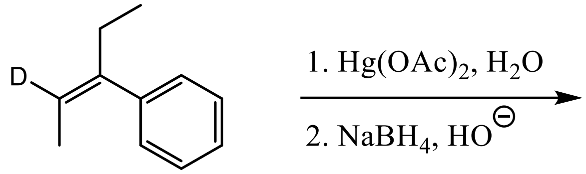
Approach: This reaction is Oxymercuration-Demercuration (OMD) reaction, where water adds across the C=C pi bond in a Markovnikov and *trans* manner. In this alkene the left alkene of the double bond is more substituted (D is deuterium, isotope of hydrogen, so the right carbon bearing D is less substituted). So, add water such that OH goes to the left carbon and H goes to the right carbon. Then draw the stereochemistry such that they are trans.



When to show stereochemistry? When there are two adjacent carbons, both having stereocenters.

Exercise 8.6: Draw the major product(s) with correct stereochemistry.

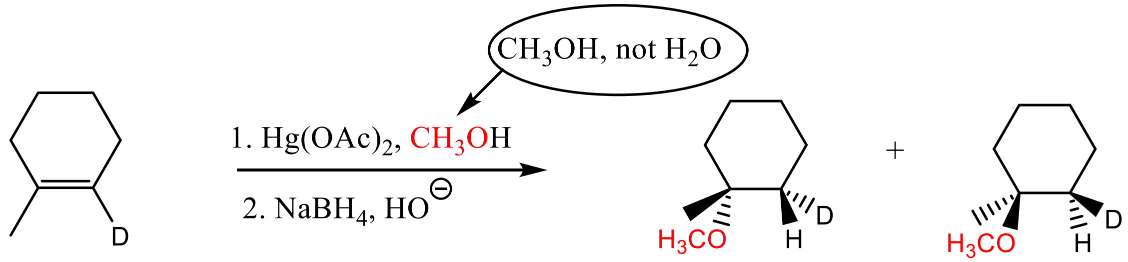
a.



Double bonds of benzene are extremely stable and do not under **addition** reactions like the non-aromatic C=C.

8.9 Alkoxymercuration–Demercuration (AMD)

When mercuration takes place in an alcohol instead of water, the alcohol serves as a nucleophile to attack the mercurinium ion. The resulting product contains an -OR (**alkoxy**) group. In effect, Alkoxymercuration-Demercuration (AMD) converts alkenes to **ethers** by adding an alcohol across the double bond of the alkene. The reaction mechanism is identical to AMD reaction discussed in section 8.8.

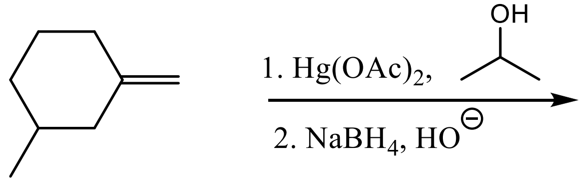


The addition of CH_3OH takes place across the C=C pi bond. CH_3OH adds across **Markovnikov** and ***trans*** manner. The resulting product is an **ether**.

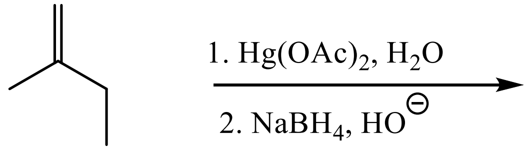
When H_2O was used as a nucleophile, the reaction is OMD. When an alcohol is used as a nucleophile, the reaction is AMD.

Exercise 8.6: Draw the major product(s).

a.

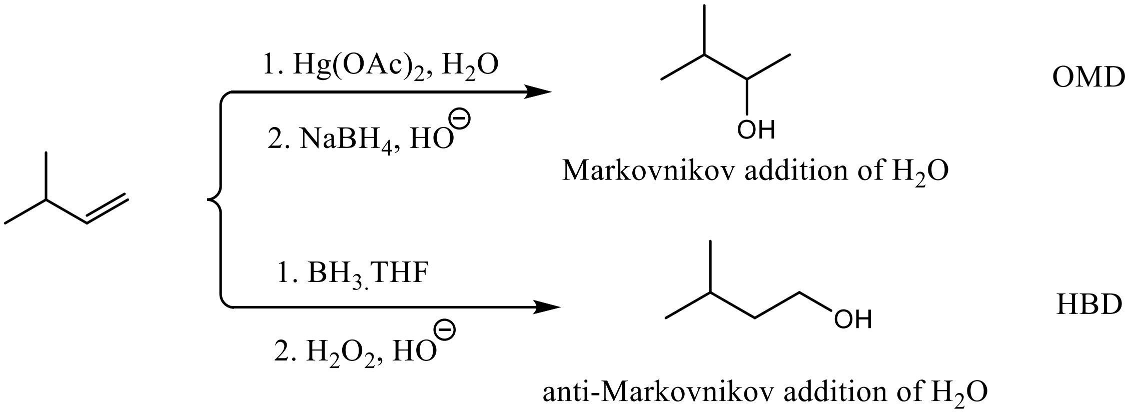


b.

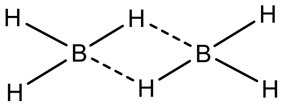


8.10 Hydroboration-Deboration of Alkenes (HBD)

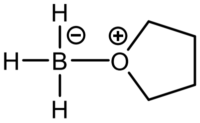
We have seen two methods for hydrating an alkene with Markovnikov orientation. In the reaction shown below, the top reaction is Oxymercuration-Demercuration (OMD) reaction that converts an alkene to a Markovnikov alcohol. What if we need to convert an alkene to the anti-Markovnikov alcohol? Hydroboration-Deboration (HBD) is a reaction that adds water across a C=C in an anti-Markovnikov manner.



Diborane is a dimer composed of two molecules of borane (BH_3). However, B_2H_6 is a toxic, flammable, and explosive gas. BH_3 is more easily used as a complex with tetrahydrofuran (THF), a cyclic ether. This complex (BH_3.THF) reacts like diborane, yet the solution is easy to handle in a laboratory setting.



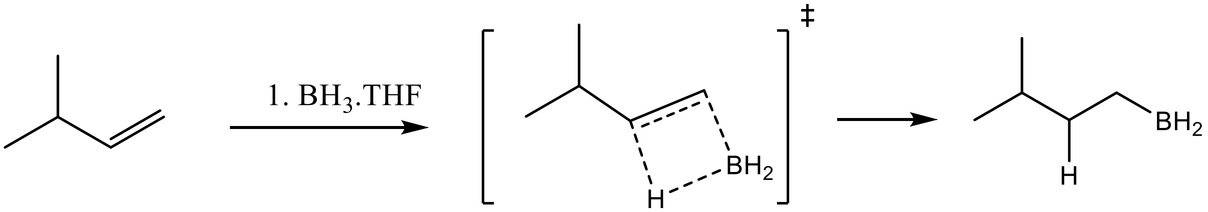
$=B_2H_6$



$=BH_3$.THF

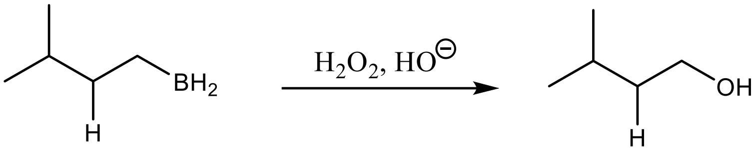
Borane (BH_3) is an electron-deficient compound. It has only six valence electrons, so the boron atom in cannot have an octet. Due to which, it is a strong electrophile, capable of adding to a double bond.

Hydroboration (no arrows): This **hydroboration** of the double bond is thought to occur in one step, with the boron atom adding to the less substituted end of the double bond



Deboration (no arrows):

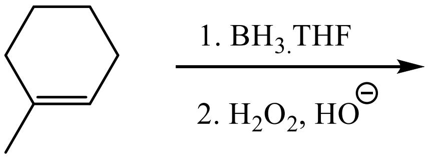
The C-B bond is oxidized to C-OH bond by using hydrogen peroxide (HOOH or H_2O_2) in aqueous NaOH without changing the stereochemistry.



Since BH3 is trigonal planar and so is the alkene, the addition of BH3 to alkene takes place from the same side of the double bond.

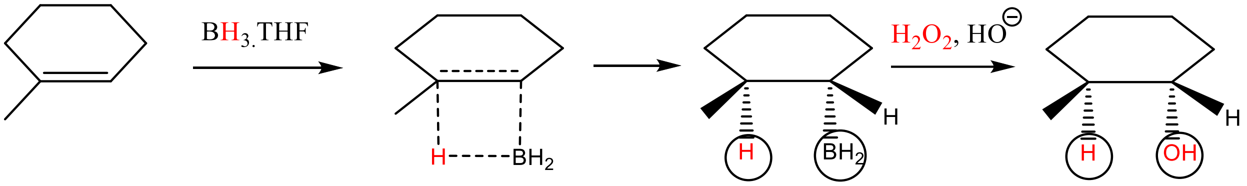
The **Hyroboration-Deboration** reaction is addition of water to an alkene in an **anti-Markovnikov** and ***cis*** manner.

Solved Problem 8.3: Draw the major product(s) of the reaction and indicate the stereochemistry.

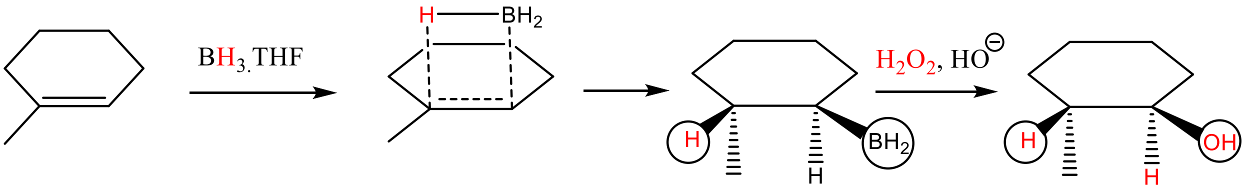


Approach: This is the Hydroboration-Deboration (HBD) reaction where the alkene is converted to an **anti-Markovnikov** alcohol. The H and OH add across in a **cis** manner. Since both carbon of the pi bond will end up with a stereocenter, it is important to show stereochemistry. The right carbon of the double bond is less substituted, and the left is more substituted. So, the OH goes to the right carbon and H to the left. This both add either from the bottom side of double bond in cis manner or top side, resulting in a pair of enantiomers (shown below).

BH3 adding to the pi bond form the **bottom** side.

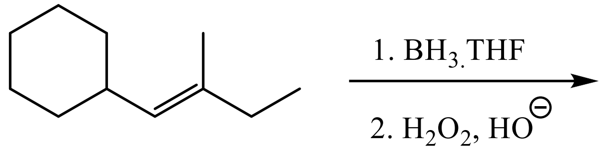


BH3 adding to the pi bond form the **top** side.

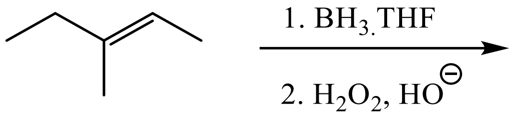


Exercise 8.7: Draw the major product(s). Pay attention to stereochemistry.

a.



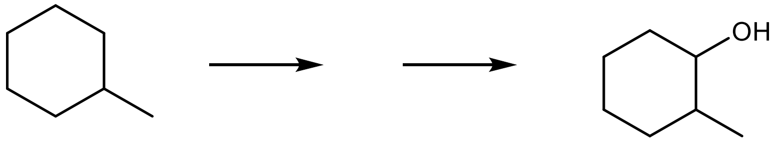
b.



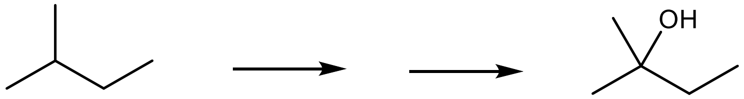
Exercise 8.8: Show how you would accomplish the following synthetic conversions

a.

b.

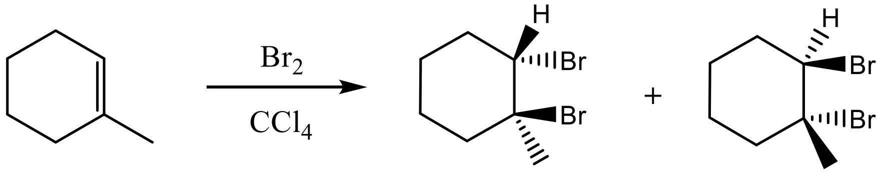


c.



8.11 Addition of Halogens to Alkenes

When alkenes undergo reactions with halogens (Cl_2, Br_2, I_2) in presence of inert solvents like CCl_4, an addition reaction takes place such that each halogen atom is added across a C=C pi bond. The resulting product is called a **vicinal dihalide** (two halogens on two adjacent atoms).

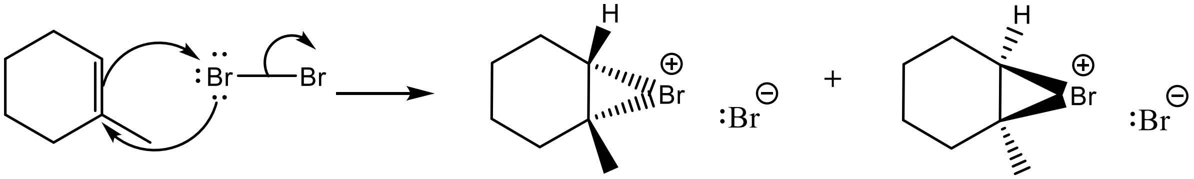


A pair of enantiomers are formed and the addition of halogens across the C=C pi bond takes place in a **trans** manner.

Mechanism of bromination of alkene.

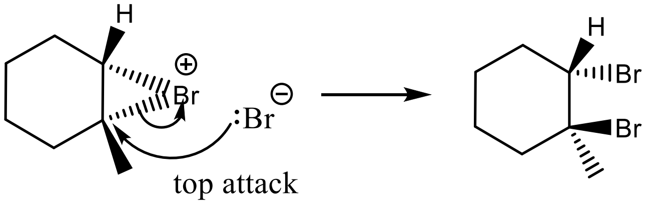
Step 1: The pi electrons of an alkene attack one of the bromine atom and one lone pair of the same atom makes a bond with the other carbon. In this process, the other bromine atom expels as a bromide ion. A concerted movement of three arrows shows formation of **bromonium ion**, containing a three-membered ring with a positive charge on the bromine atom. This bromonium ion is similar in structure to the mercurinium ion discussed in Section 8.8.

Since alkene is trigonal planar, the bromonium ion can be formed on either side of the double bond (top or bottom), hence two enantiomers of bromonium ion are formed.

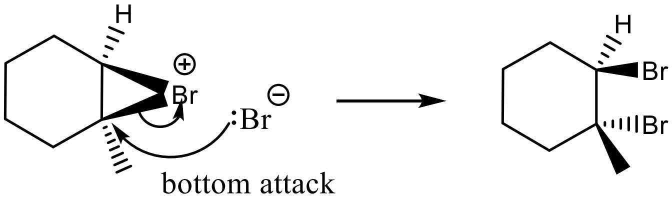


bromonium ion bromonium ion

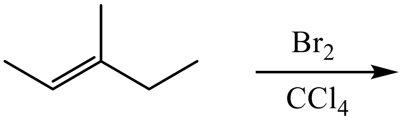
Step 2: The bromide ion Br$^{\ominus}$ then attacks the **more substituted carbon**, similar to attack of a nucleophile to a mercurinium ion. In this process, there is an inversion of stereochemistry taking place as the bromide ion attacks the bromonium ion from the opposite side. This eventually results in a trans addition of two bromine atoms across the C=C pi bond.
Bromide ion attacks more substituted carbon of the bromonium ion from the opposite side.



The same can happen with the other enantiomer.



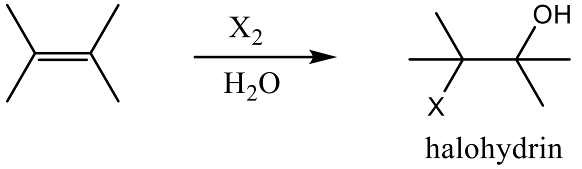
Exercise 8.9: Draw the major product(s). Pay attention to stereochemistry.



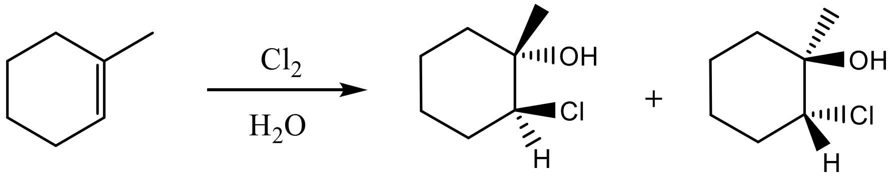
Exercise 8.10: When cis-but-2-ene and trans-but-2-ene undergo bromination, one diastereomer gives a (meso)-2,3-dibromobutane. Which one will it be? Explain using structures.

8.12 Formation of Halohydrins

When an alcohol and halogen are on adjacent carbon atoms, it is called a **halohydrin**. In the presence of **water**, halogens add to alkenes to form halohydrins.

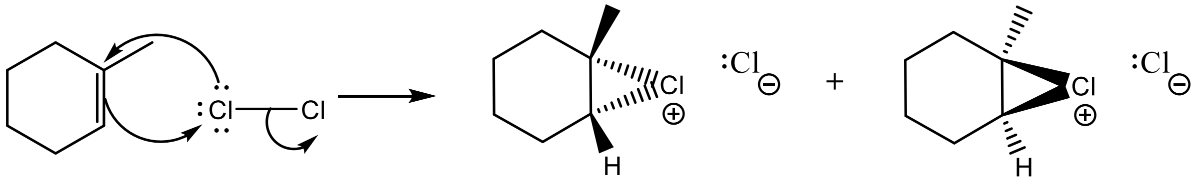


In the example shown below, H_2O acts like a nucleophile and attacks the more substituted carbon of chloronium ion to form the halohydrin. Note: -OH group appears on the more **more substituted** carbon.



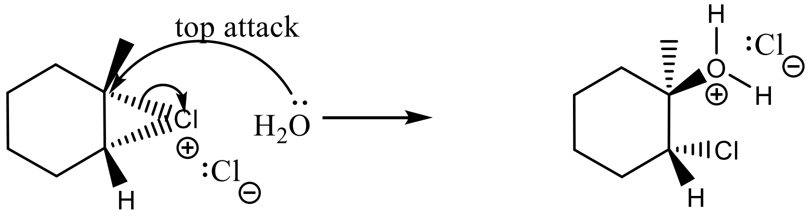
Mechanism of halohydrin formation.

Step 1: The pi electrons of an alkene attack one of the bromine atom and one lone pair of the same atom makes a bond with the other carbon. In this process, the other bromine atom expels as a bromide ion. A concerted movement of three arrows shows formation of **chloronium ion**, containing a three-membered ring with a positive charge on the chlorine atom.

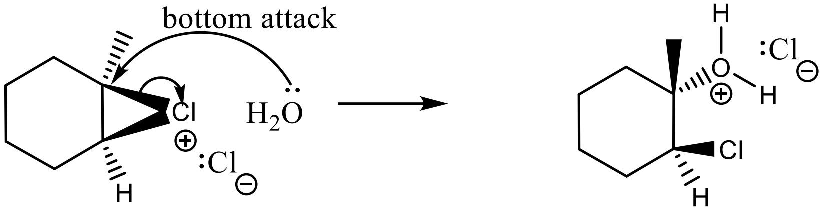


Step 2: The H_2O then attacks the **more substituted carbon**, like the attack of a nucleophile to a mercurinium ion. In this process, there is an inversion of stereochemistry taking place as the bromide ion attacks the bromonium ion from the opposite side. This eventually results in a trans addition of two bromine atoms across the C=C pi bond.

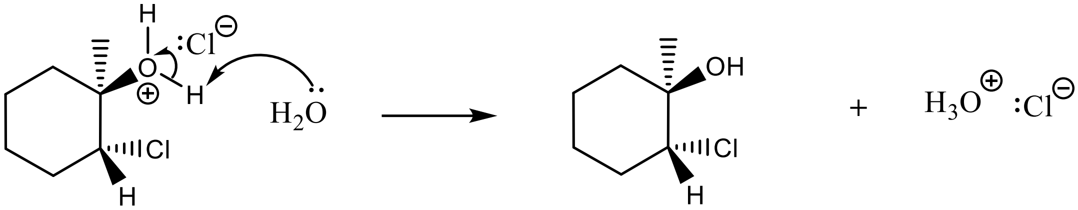
Attack of H_2O to the more substituted carbon from opposite side of chloronium ion



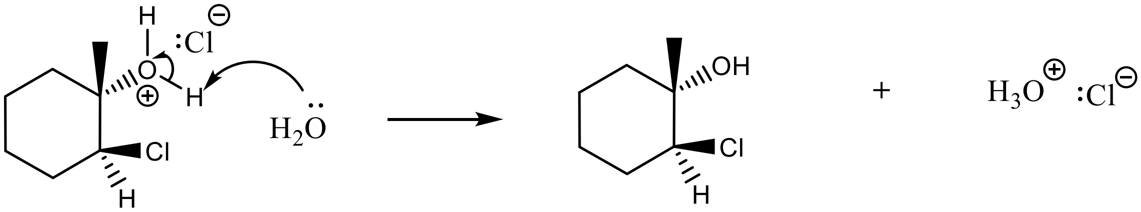
The same can happen with the other enantiomer.



Step 3: Deprotonation of the halohydrin is a required step for the reaction to end in the formation of halohydrin. This takes place with excess H_2O (which is also a solvent, hence on the bottom of the arrow). Removal of proton to yield halohydrin.

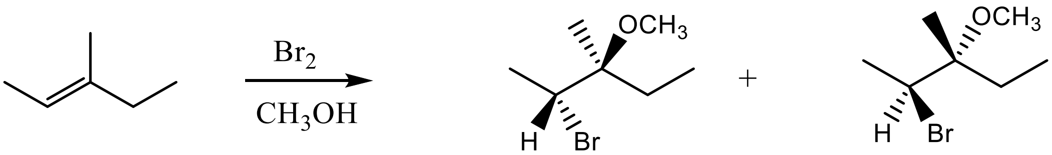


Removal of proton to from the other enantiomer to yield halohydrin.



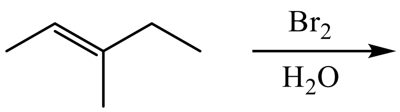
Formation of **halo ether** when alcohol is used as a solvent with halogens:

When alcohol (ROH) are used as a solvent with halogens instead of H_2O, product is not a halohydrin, it is **halo ether**. The mechanism is the same as halohydrin formation, except the -OR group appears in the product instead of -OH group.

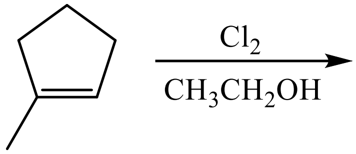


Exercise 8.11: Draw the major product(s). Pay attention to stereochemistry.

a.

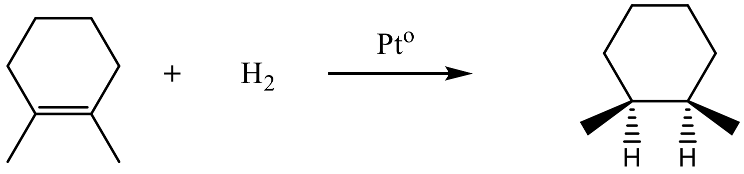


b.



8.13 Catalytic Hydrogenation of Alkenes

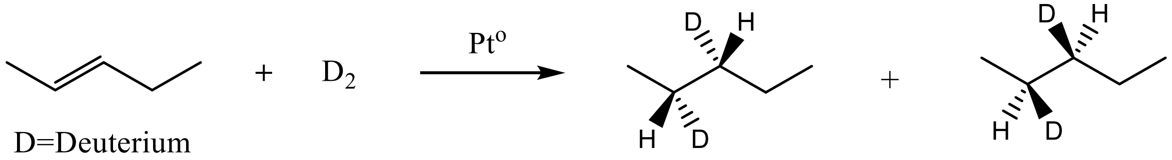
Hydrogenation of alkenes takes place at the surface of the metal catalyst like Pt^o, Ni^o, Pd^o, Ru^o and Rh^o where the liquid solution of the alkene reacts with the hydrogen gas and the catalyst. Without the catalyst, the activation energy of this reaction is very high. These transitional metal catalysts are in their elemental form (not ionic). Hydrogen gas is adsorbed onto the surface of the metal catalyst, which weakens the H-H bond. The addition of the hydrogen gas takes place from the same side of the double bond (**cis addition**).
This reaction is also called a reduction reaction as the number of C-H bond has increased for both carbons of alkene (more about oxidation/reduction in the next section).



(meso)-1,2-dimethylcyclohexane

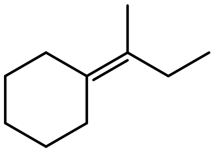
For the above reaction, the enantiomer is **not** formed as the product has a **plane of symmetry**. This would not be the case of the alkene was not symmetric.

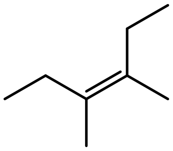
When pent-2-ene undergoes hydrogenation with D2 in presence of platinum as a catalyst, two enantiomers are formed.

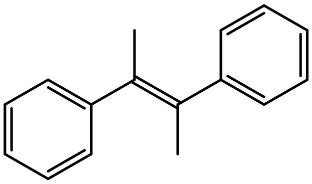


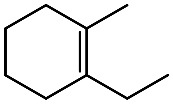
The **Hydrogenation** reaction is addition of hydrogens to an alkene in a and ***cis*** manner.

Exercise 8.12: Draw the major product(s) of the when the following alkenes undergo hydrogenation reactions with hydrogen gas in palladium catalyst. Include stereochemistry where applicable.


A


B

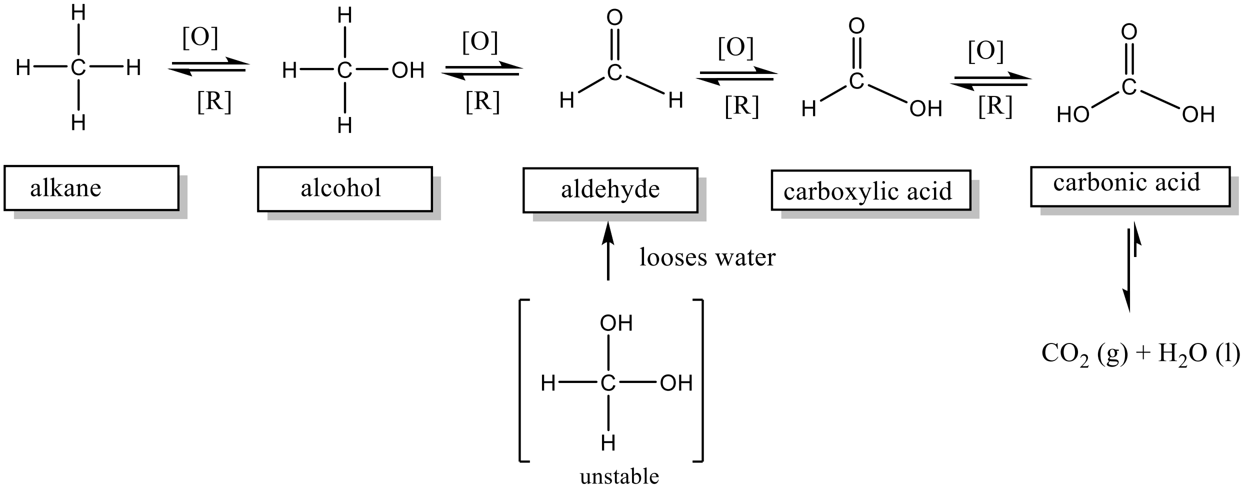

C


D

Which of the following alkenes will form enantiomers?

8.14 Oxidation-Reduction reactions in Organic Chemistry

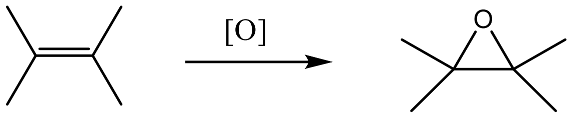
In Organic Chemistry, as the number of C-O bond increase, a molecule is more **oxidized**. As the number of C-H bond increase a molecule is more **reduced**.



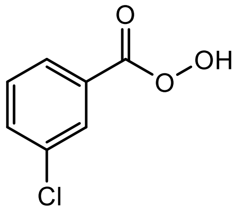
In the scheme above, as we increase the number of C-O bonds, oxidation is taking place (from left to right). Reduction is taking place in the opposite direction.

8.15 Epoxidation of Alkenes

An **epoxide** is a three-membered cyclic ether. Epoxides are valuable synthetic intermediates used for converting alkenes to a variety of other functional groups. An alkene is converted to an epoxide by a **peroxyacid** (RCO_3H). Peroxy acids have one extra oxygen atom compared to carboxylic acids (RCO_2H).

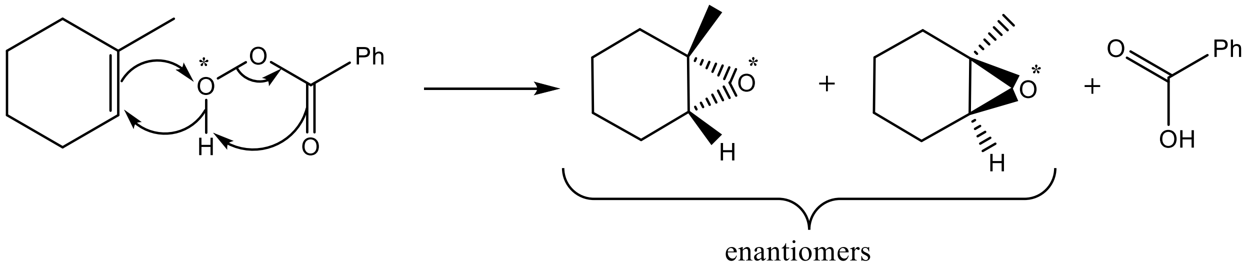


This reaction is called epoxidation of alkenes and is an oxidation reaction. The popular reagent that converts the alkene to epoxide is ***m***_eta_-**c**hloro**p**er**b**enzoic **a**cid which has an acronym *m*CPBA (or $PhCO_3H$).

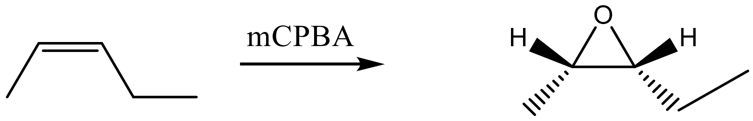


mCPBA = $PhCO_3H$

Reaction of alkene with mCPBA is a concerted mechanism where the oxygen that has been labeled with a * in mCPBA inserts between two carbons of alkene to make an epoxide.



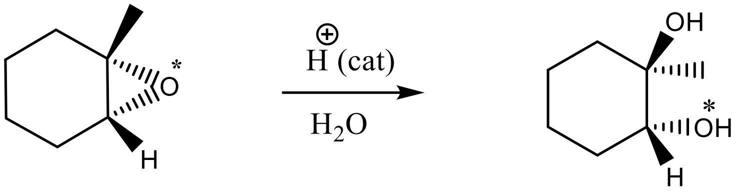
Because this is a concerted mechanism, a cis alkene will produce an epoxide where the two alkyl groups will be cis.



A trans alkene will produce an epoxide where the two alkyl groups will be trans.

8.16 Acid-Catalyzed Opening of Epoxides

Most epoxides are stable under neutral conditions. Under acidic or basic conditions, epoxide undergo ring opening reactions readily. Any moderately strong acid protonates the epoxide, however. Water attacks the protonated epoxide, opening the ring and forming a 1,2-diol

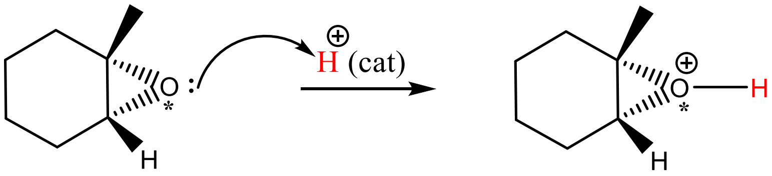


trans-diol

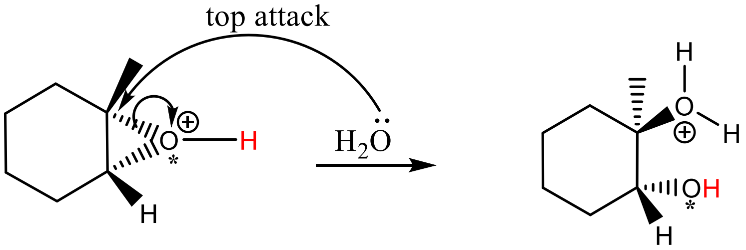
This acid catalyzed ring opening reaction is very similar to mercurinum ion and bromonium ion ring opening mechanism.

Mechanism of Acid-Catalyzed Opening of Epoxides: For the ease of keeping track of the acid and the epoxide oxygen, the acidic hydrogen is labeled red and

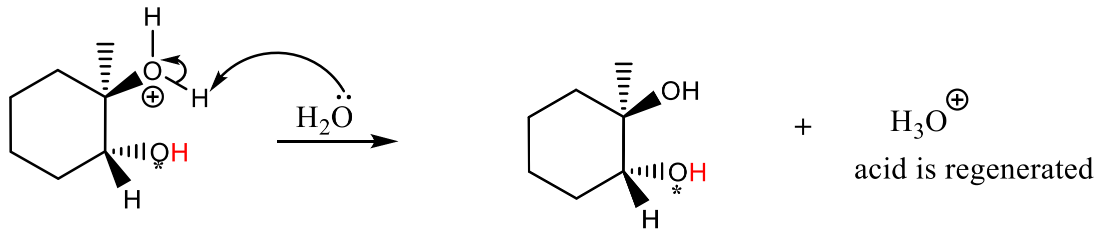
Step 1: The first step is the protonation of the epoxide by the acid.



Step 2: The nucleophile (H_2O in this case) attacks the more substituted carbon from the opposite side of the epoxide. Since the original epoxide has oxygen going down, the H_2O attacks the more substituted carbon from the top side.



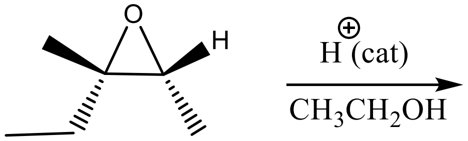
Step 3: Deprotonation of the diol is a required step for the reaction to end in the formation of trans-diol. This takes place with excess H_2O (which is also a solvent, hence on the bottom of the arrow).


acid is regenerated

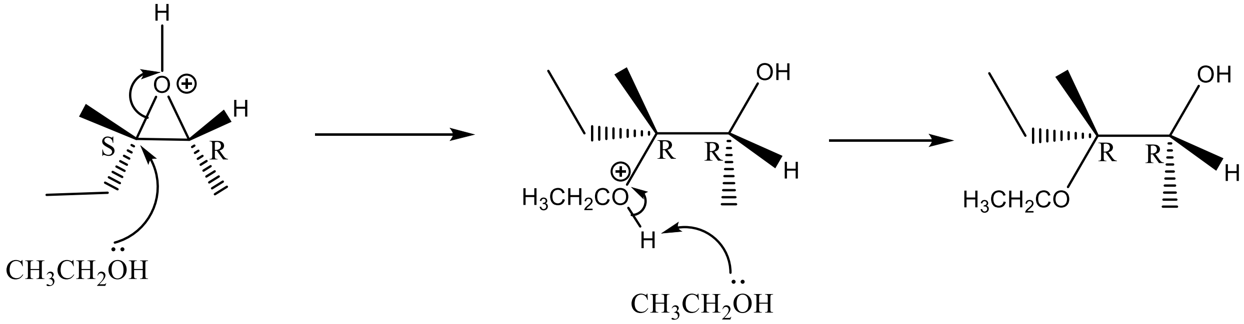
Note: The acid is regenerated in the last step, hence this is an **acid-catalyzed** reaction.

Since the starting epoxide has a very specific stereochemistry, therefore only this product with this stereochemistry is formed and the enantiomer is **NOT** formed.

Solved Problem 8.4: Draw the mechanism and the major product(s) of the when the following reaction takes place. Include stereochemistry at the stereocenter of the product.



Approach: This is an acid-catalyzed ring opening reaction of epoxide with ethanol (CH_3CH_2OH) as a nucleophile. Since the epoxide is drawn on the plane, the nucleophile CH_3CH_2OH will approach the more substituted carbon (left carbon) from the opposite side of epoxide (but still on the plane) after it has been protonated by acid.

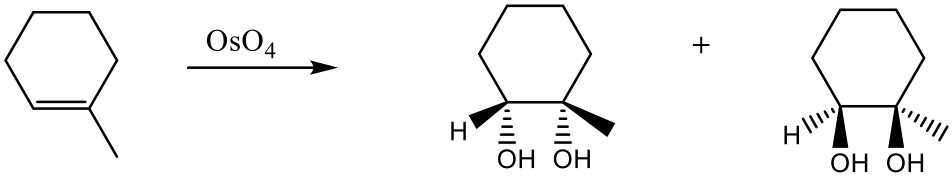


Note the change in stereochemistry of the chiral center where the reaction is taking place. It has been inverted. No other stereoisomer is formed.

8.17 Syn Dihydroxylation of Alkenes

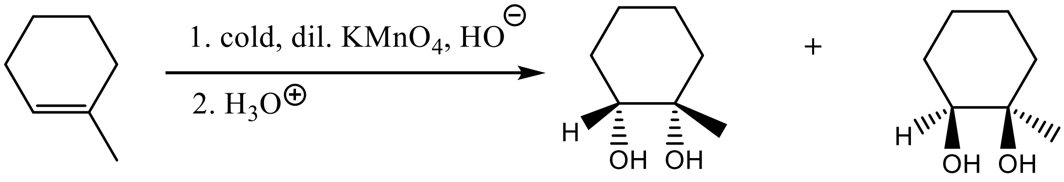
We have seen that epoxidation of an alkene, followed by acidic hydrolysis, gives ***trans*-diol** (dehydroxylated product). Reagents are also available for the dihydroxylation of alkenes with *cis* stereochemistry.

Osmium tetroxide (**OsO_4**) or Potassium permanganate (**$KMnO_4$**) are oxidizing agents that add two -OH groups across C=C to give cis-diol.



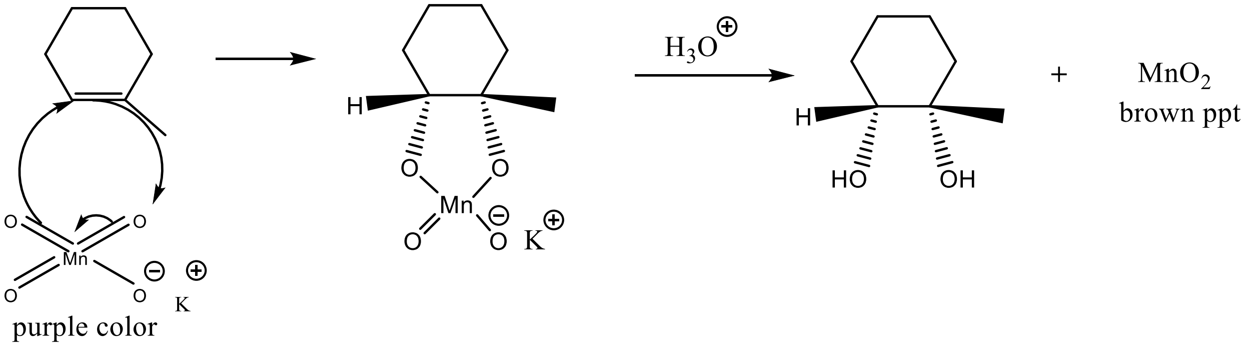
cis-diol cis-diol

Osmium tetroxide (**OsO_4**) is very toxic, so cold, dilute $KMnO_4$ is often used in a basic solution.



cis-diol cis-diol

In this case, enantiomers are formed as the KMnO4 can approach either from the top or the bottom of the double bond to give *cis* diol.



The permanganate oxidation of alkenes provides a simple chemical test for the presence of an alkene. When an alkene is added to a clear, deep purple aqueous solution of potassium permanganate, the solution loses its purple color and becomes the murky, opaque brown color of MnO_2.

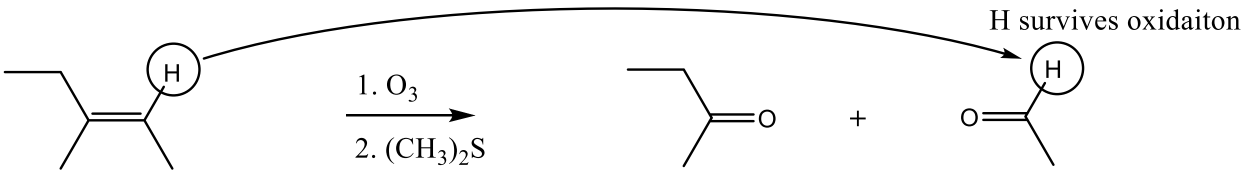
$KMnO_4$ (cold, dilute) oxidation is addition of two hydroxyl groups to an alkene in a ***cis*** manner.

8.18 Oxidative Cleavage of Alkenes the C=C bond (σ and π)

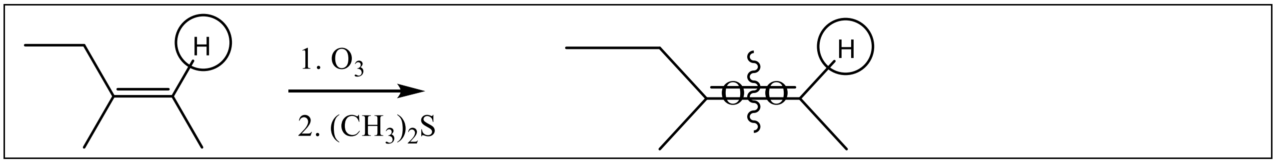
There are two types of reagents that make a pi and sigma bond of alkene undergo cleavage (breaking of both bonds) and replacing it with oxygen. Since C=C is becoming C=O, this is an oxidation reaction, and it takes place with the following two reagents:

$$\xrightarrow[\text{2. } H_3O^{\oplus}]{\text{1. hot, conc. } KMnO_4,\ HO^{\ominus}} \qquad\qquad \xrightarrow[\text{2. } (CH_3)_2S]{\text{1. } O_3}$$

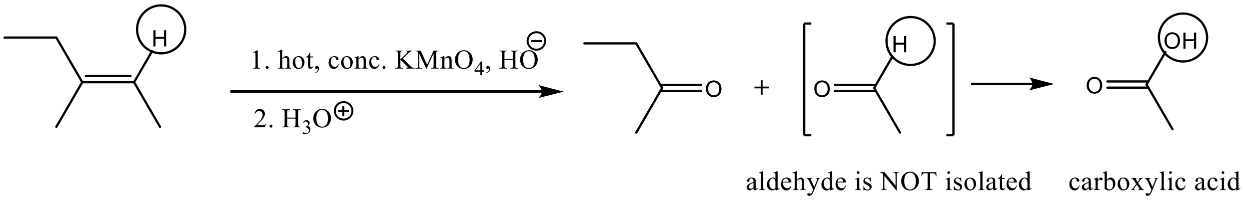
(a) This is called ozonolysis reaction (reaction of alkene with ozone, O_3).



This is an oxidative cleavage reaction where C=C is becoming C=O. Note the aldehyde is formed as one of the products. The circled hydrogen survives the oxidation. In other words, the following happens:

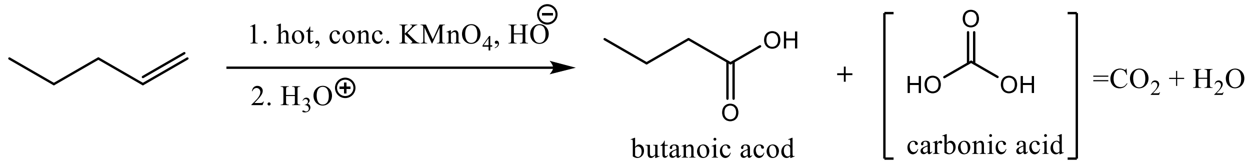


(b) With a stronger oxidizing agent, the circled hydrogen is further oxidized to carboxylic acid.

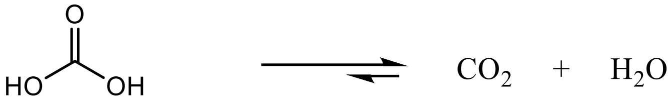


This is also an oxidative cleavage reaction where C=C is becoming C=O. Note the aldehyde formed as an intermediate is further oxidized to form carboxylic acid. Based upon these two observations, which is a stronger oxidizing agent, Ozone or KMnO4?

When pent-1-ene (terminal alkene) undergoes oxidative cleavage with hot, concentrated $KMnO_4$, butanoic acid and CO_2 are formed as organic products.

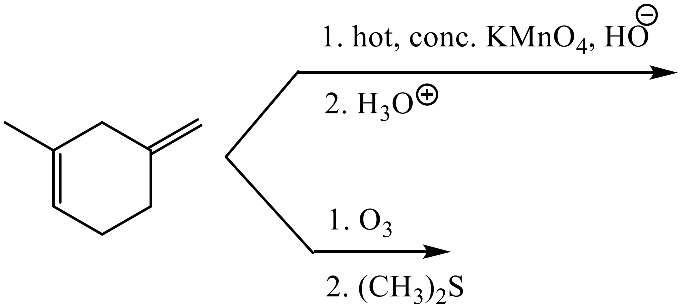


Carbonic acid (H_2CO_3) is unstable and decomposes to give carbon dioxide and water (CO_2 and H_2O).

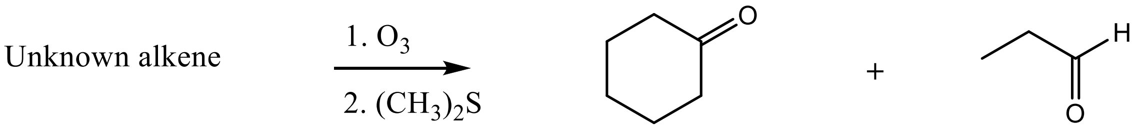


carbonic acid, H_2CO_3

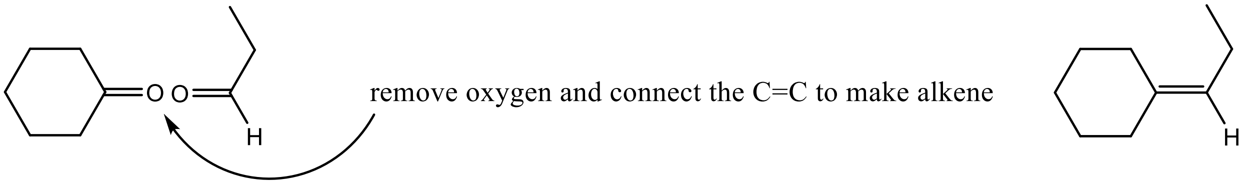
Exercise 8.13: Draw the major product(s) of the when the given alkene undergoes the two oxidative cleavage reactions.



Solved problem 8.5: An unknown alkene undergoes ozonolysis reaction and makes the following two compounds. Propose the structure of the unknown alkene.

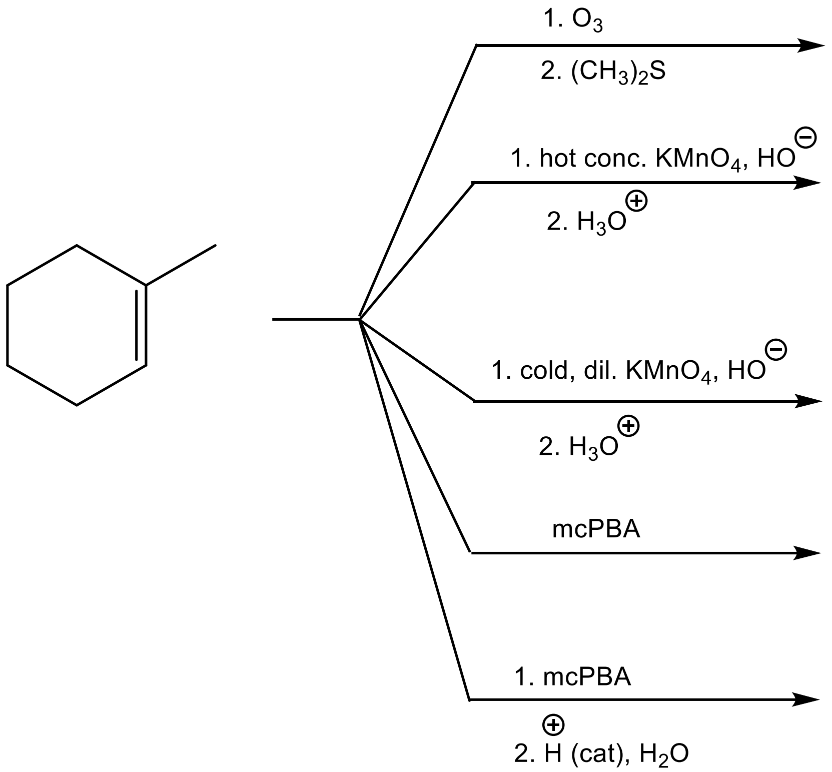


Approach: We can reconstruct the alkene by removing the two oxygen atoms of the carbonyl groups (C=O) and connecting the remaining carbon atoms with a double bond.



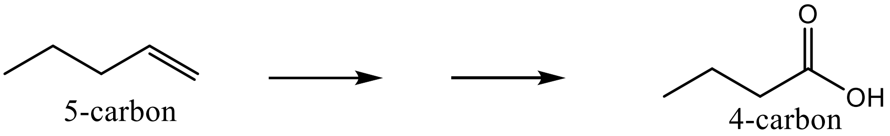
This reaction will not differentiate between cis/trans alkene as both with give the same products. If more than one double bond is present, both will undergo oxidative cleavage.

Exercise 8.14: Draw the most likely product(s) that result from the treatment of 1-methylcyclohexene with each reagent listed. All of these are oxidation reactions.

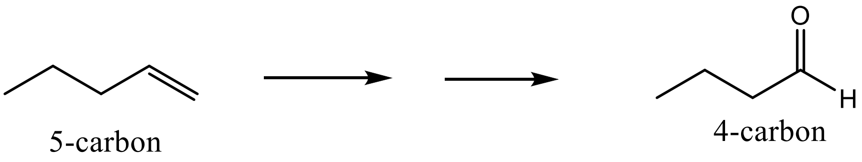


Exercise 8.15: Using pent-1-ene as your starting material, show how you would synthesize the following compounds.

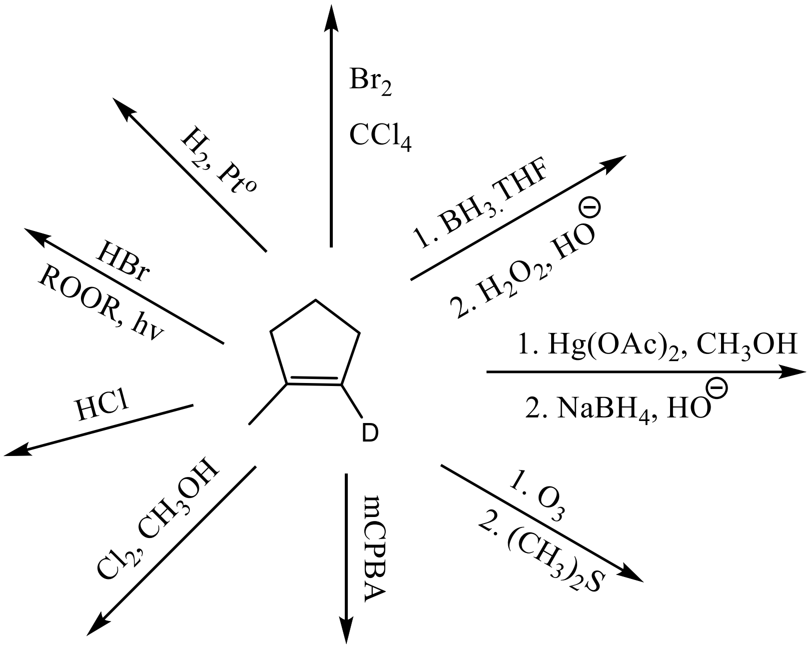
a.



b.



Exercise 8.16: Draw the major product(s) of the when the given alkene undergoes the following reactions. Pay attention to stereochemistry. If enantiomers are formed draw both.



Chapter 9: Alkynes

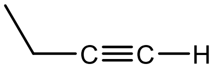
9.1 Introduction

Alkynes are hydrocarbons that contain carbon-carbon triple bonds. The chemistry of the carbon-carbon triple bond is like that of the double bond. Most of the additions and oxidation reactions of alkynes are like that of alkenes. The smallest alkyne has two carbons, and its common name is acetylene.

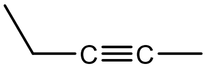
$H-C\equiv C-H$

Acetylene

If the alkyne is at the end of the chain, it is referred to as terminal alkyne. Otherwise, it is called internal alkyne.



terminal alkyne

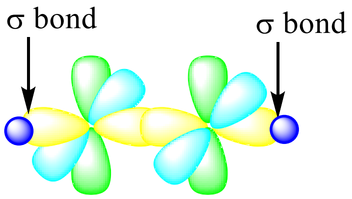


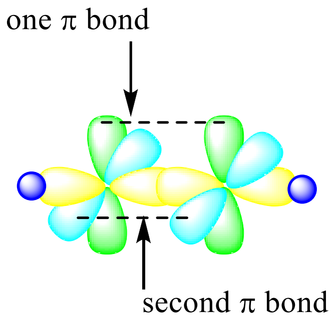
internal alkyne

9.2 Electronic Structure of Alkynes

$H-C\equiv C-H$

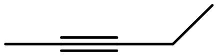
Each carbon of the acetylene molecule atom is bonded to two other atoms, and each carbon is sp hybridized. Overlap of these *sp* hybrid orbitals (yellow color) with each other and with the hydrogen *s* orbitals gives the sigma bond framework. This results in a linear structure with a 180° bond angle. In the figure below, orbitals in green and blue are the unhybrid *p*-orbitals that are parallel and overlapping sideways to form pi (π) bonds. These two pi bonds are perpendicular to each other and the sigma framework. The one in green is going up and down the sigma framework and the one in blue is coming front and going back of the plane of the paper.



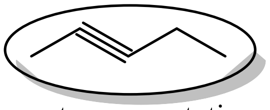


$H-C\equiv C-H$

Due to the 180° bond angle, the triple bond should be written in a linear format and shown below are the correct (and incorrect) ways of drawing alkynes in the line formula.



correct representation of pent-2-yne

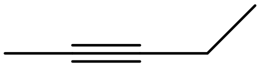


incorrect representation of pent-2-yne

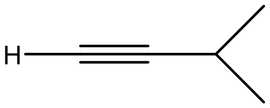
Alkynes do not appear in a ring unless the ring is larger than eight carbons.

9.3 Nomenclature of Alkynes

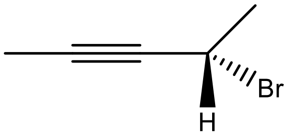
IUPAC naming of alkynes ends with "yne". Find the longest continuous chain of carbon atoms that includes the triple bond and change the *-ane* ending of the parent alkane to *–yne*. The chain is numbered from the end closest to the triple bond, and the position of the triple bond is designated by its lower-numbered carbon atom.



pent-2-yne



3-methylbut-1-yne



(S)-4-bromopent-2-yne

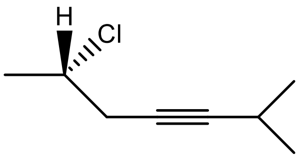
When an additional functional group like alkene is present, the suffixes are combined to produce the compound names of the *enynes* (a double bond and a triple bond). Regarding how to number the enynes, if the double bond and the triple bond are the same distance from the ends of the chain, number the chain so that the double bond receives a lower number than the triple bond (ene before yne).

Do not forget to drop the second e of ene when combining it with yne to give enyne.

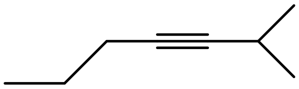
Exercise 9.1: Provide the IUPAC name of the following alkynes.

a.

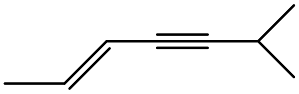
c.



b.



d.

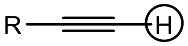


Exercise 9.2: For the molecular formula C_5H_8, draw all the isomeric alkynes (three isomers), and give their IUPAC names.

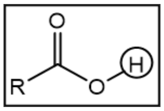
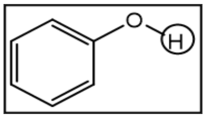
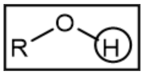
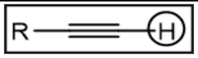
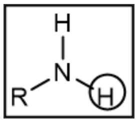
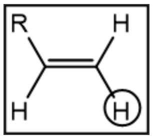
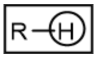
Exercise 9.3: Calculate the IHD and draw structural formulas of at least two alkynes of each molecular formula.

a. C_6H_{10} **b.** C_8H_{12}

9.4 Acidity of Terminal Alkynes

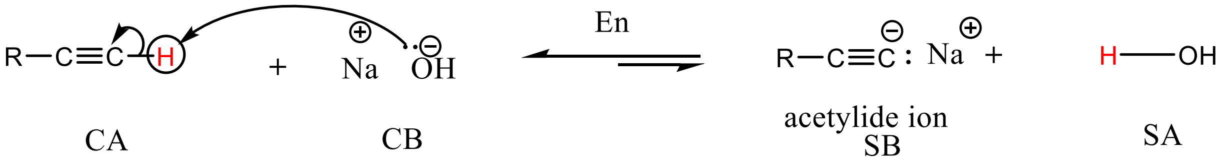
Many of an alkyne's chemical properties depend on whether it is internal or terminal. A terminal alkyne has a triple bond coming at the end of a carbon chain. .
The circled hydrogen of a terminal alkyne has a significant acidity compared to its alkene or alkane counterpart. Removal of this proton to form an **acetylide ion** plays a central role in alkyne chemistry. The acidity of acetylenic hydrogen stems from the nature of the *sp* bond. The electrons on the conjugate base of terminal alkyne, the acetylide anion has electrons in sp orbital that have more s character (electrons are closer to the nucleus, hence more stable).
Remember that a **smaller** value of PKa corresponds to a stronger acid as pKa = -log Ka. The table below shows how the acidity of different functional groups.

Functional Group	Compound	Pka	

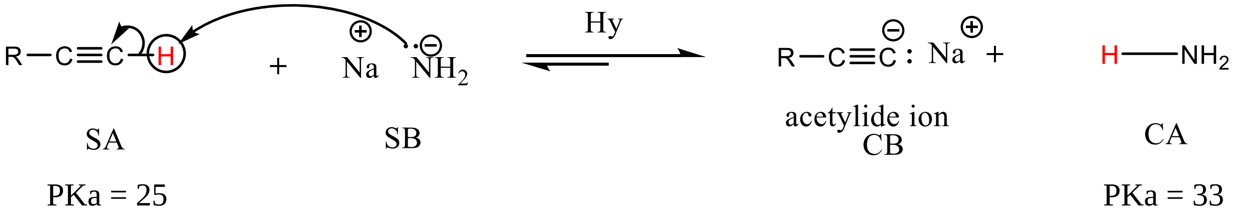
Carboxylic acid		**5**	most acidic ↑ least acidic
Phenol		**10**	
Alcohol		**16**	
Alkyne (terminal)		**25**	
Amine		**33**	
Alkene		**44**	
Alkane		**50**	

9.5 Formation of Acetylide Ions

When a base like NaOH is used to deprotonate the terminal hydrogen, the reaction is not favored to make the acetylide anion. Writing an acid-base mechanism between the two is shown below:



A stronger base than NaOH will be $NaNH_2$ (common name **sodamide**) will be required to deprotonate the terminal hydrogen of alkyne:



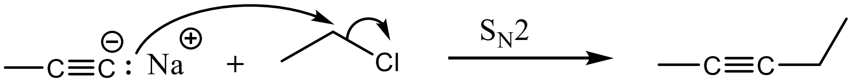
This acid-base mechanism DOES NOT follow PRECHI. The sp hybridization on carbon makes the electrons more stable on the acetylide ion, hence equilibrium favors to the right side. Looking at PKa values, the equilibrium favors to the right side (the weaker acid/base).

Throughout this chapter, you will see the use of sodamide ($NaNH_2$) as a base to form acetylide ion.

9.6 Synthesis of Alkynes from Acetylides: Formation of C-C bond!!

Acetylide ions are strong nucleophiles. The best methods for increasing the carbon chain of the alkyne is a nucleophilic attack by an acetylide ion on an unhindered alkyl halide (CH_3-X or a 1° RX). This can take place only if the starting alkyne is terminal.

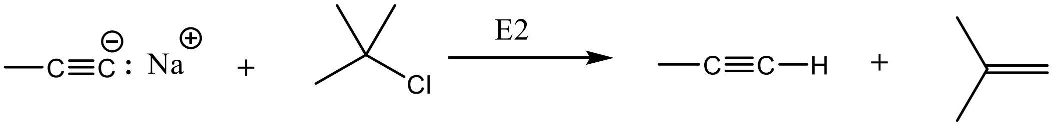
Mechanism:



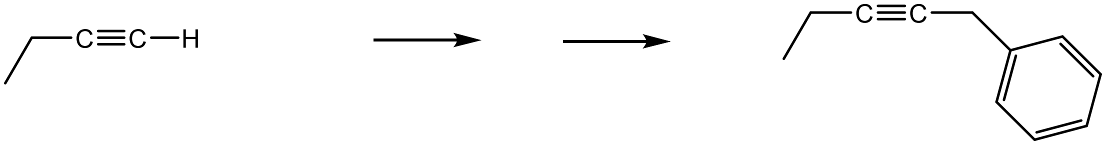
3-carbons 5 carbons

These are important reaction as it allows you to synthesize from a smaller molecule to a larger molecule. Since the carbon chain has increased, keep track of where the change is taking place and by how many carbons. ***Count the carbons if it helps***!

If the back-side approach is sterically hindered like in a 3° RX, the acetylide ion may abstract a proton, giving elimination by the E2 mechanism. 2° RX will give a mixture of S_N2 and E2 products(s).



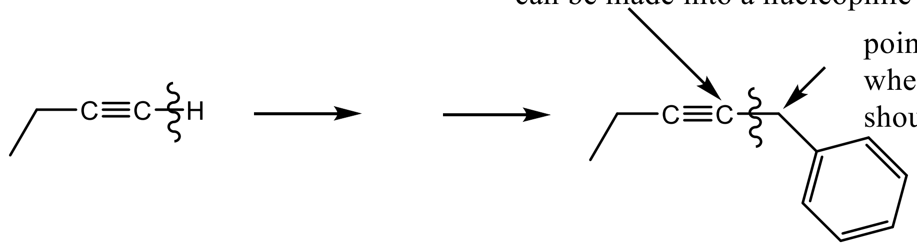
Solved Problem 9.1: Show the necessary steps required to have the following conversion. Use any reagent you can choose.



Approach:

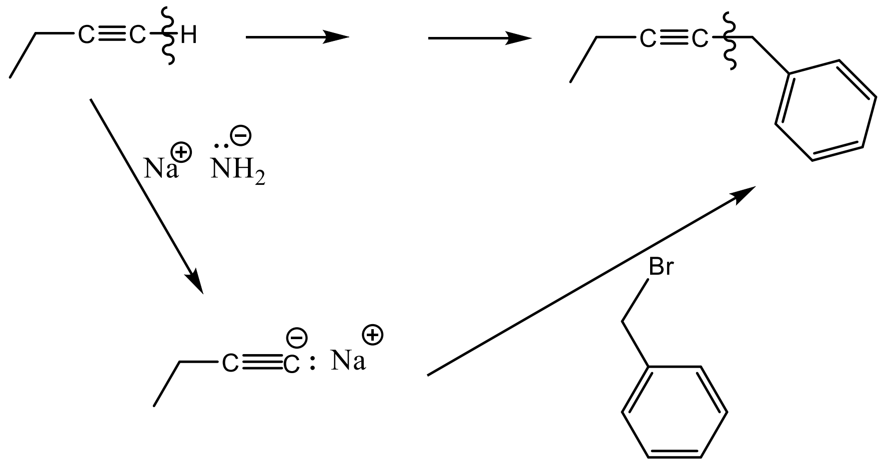
i. What **functional group** is present on the *reactant*?
j. What **functional group** is present on the *product*?
k. What has changed from reactant to product?
l. Which reactions do I know to **convert** from one to the other?
m. Has the overall length of the alkyne changed? (YES, in this case!)

First mark where the change has happened.


can be made into a nucleophile

point of connection, thats where the halogen of RX should be

In the first step, use $NaNH_2$ (sodaminde) to give acetylide ion followed by its reaction with $PhCH_2Br$.

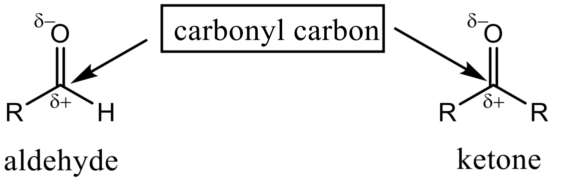


Exercise 9.4: Show how you might synthesize the following compounds, using acetylene and any suitable alkyl halides as your starting materials.

(a) pent-1-yne **(b)** hex-2-yne **(c)** hept-3-yne

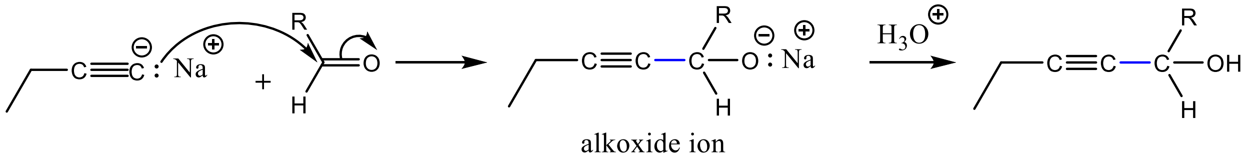
9.7 Addition of Acetylide Ions to Carbonyl Groups: Formation of C-C bond!!

Acetylide ions also undergo addition reactions to aldehydes and ketones.



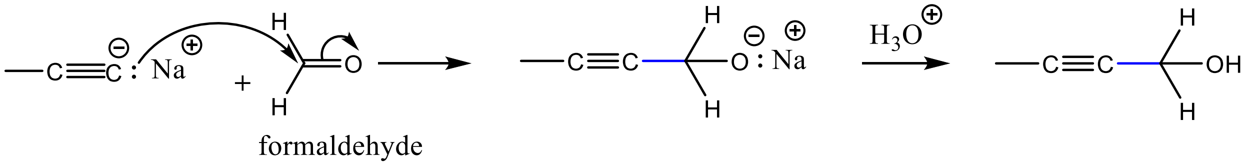
The carbonyl carbon of aldehydes and ketones is very electrophilic and the nucleophilic acetylide ion can attack the carbonyl carbon. This makes a new bond between the nucleophilic acetylide carbon and electrophilic carbonyl carbon.

Mechanism: The acetylide anion attacks the carbonyl carbon. To offset the formation of a new C-C bond, the pi bond (which is the weakest bond) breaks and electrons move to the more electronegative oxygen. This results in a minus charge on the oxygen and the product of this nucleophilic attack is an alkoxide ion, a strong base. (An **alkoxide ion** is the conjugate base of alcohol, a weak acid). The addition of a dilute acid protonates the alkoxide to give the neutral alcohol.



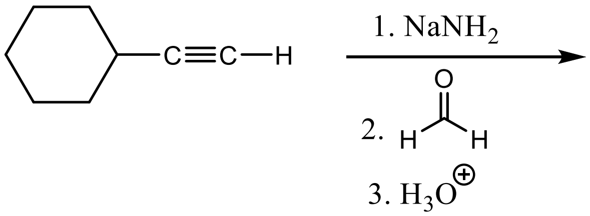
Note: The product has two functional groups: alkyne, and alcohol. The -OH group will always appear on the carbon that was originally the carbonyl carbon and will be next to the triply bonded carbon.

Formation of primary alcohol: An acetylide ion adds to formaldehyde (one carbon aldehyde) to give (after the protonation step) a primary alcohol with one more carbon atom than there was in the acetylide ion. So, the carbon chain increases only by one carbon.



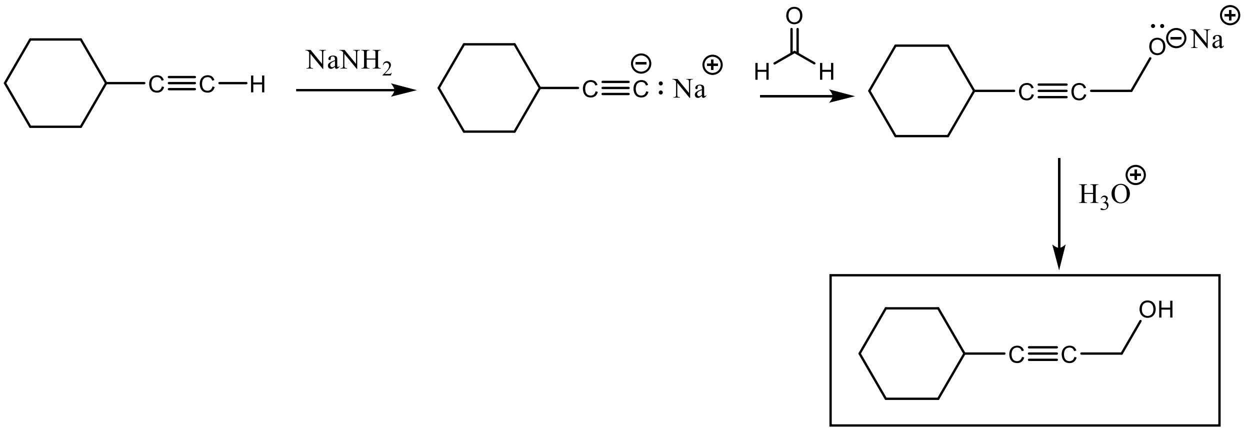
Count the carbons if it helps! Since the carbon chain has increased, keep track of where the change is taking place and by how many carbons.

Solved Problem 9.2: Draw the final organic product of the reaction.

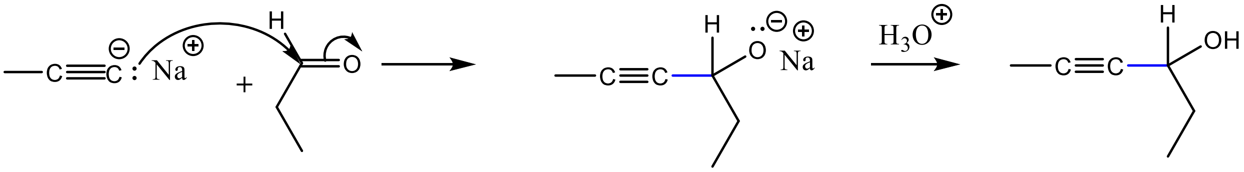


Approach: Numbers 1.,2., 3., etc. are used to show a sequence of separate reactions over a single arrow. If the numbers were omitted, it would incorrectly imply mixing all these reagents together, rather than adding them in separate steps.

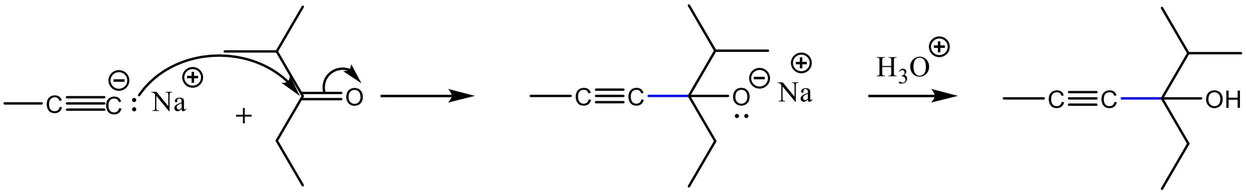
It is best to break down each step so you can see what the intermediate products are formed after every step.



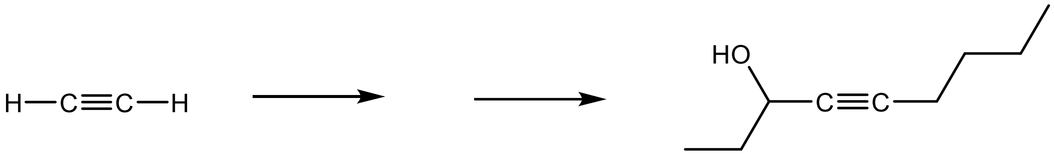
Formation of secondary alcohol: An acetylide ion adds to an aldehyde to give (after the protonation step) a secondary alcohol. The increase in carbon chain will depend upon the structure of the aldehyde.



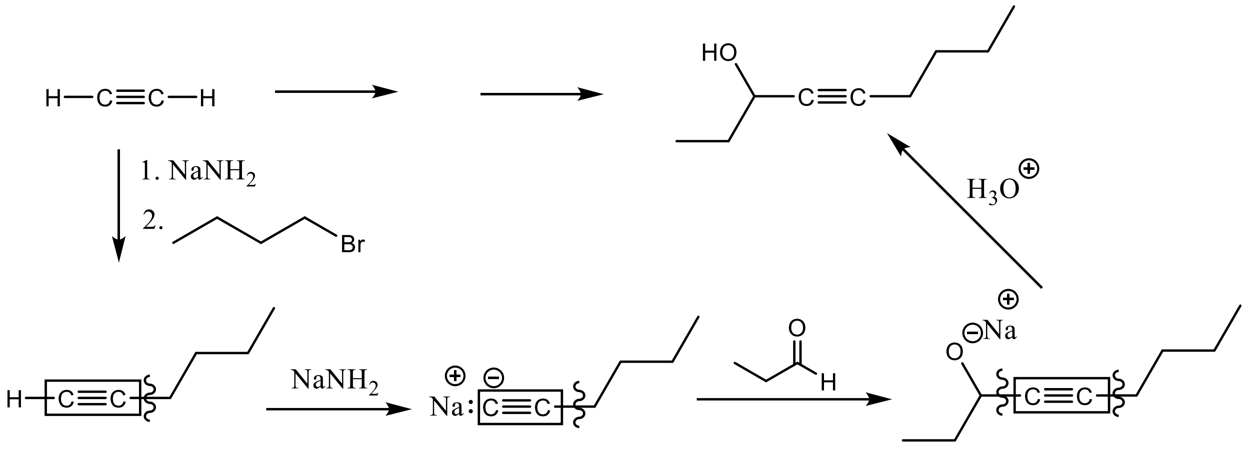
Formation of tertiary alcohol: An acetylide ion adds to a ketone to give (after the protonation step) a tertiary alcohol. The increase in carbon chain will depend upon the structure of the ketone.



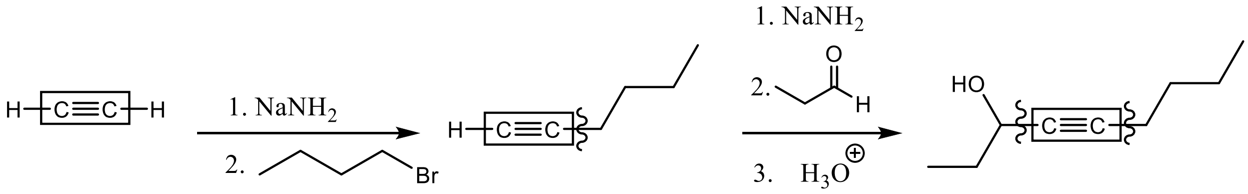
Solved Problem 9.3: Show how you would synthesize the following compound, beginning with acetylene and any necessary additional reagents.



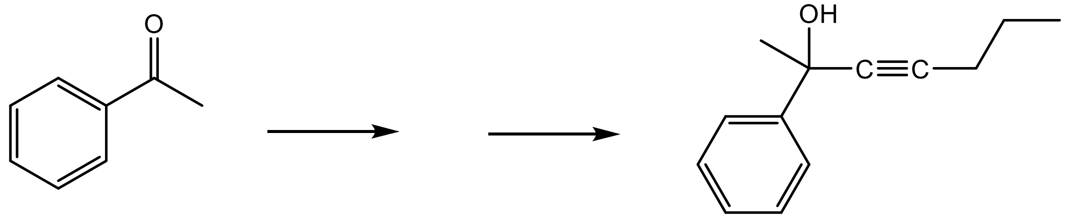
Approach: We need to add two groups to acetylene: a butyl group (the right side of triple bond) and a three-carbon aldehyde (the left side of triple bond) to form the secondary alcohol. We should add the less reactive butyl group first and add the alcohol group later. If we formed the alcohol group first, the weakly acidic group would interfere when sodamide (NaNH$_2$) is used to place butyl group as the -OH group is more acidic than the hydrogen of terminal alkyne $R-C\equiv C-H$.



The same synthesis can also be written as:

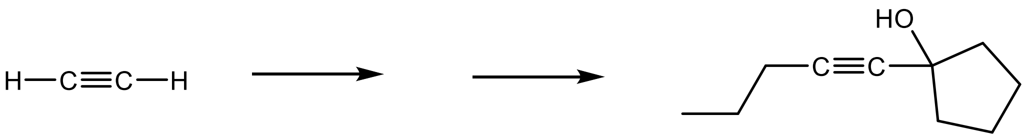


Exercise 9.5: Show how you would synthesize the following compound, beginning with acetophenone (structure shown below) and any necessary additional reagents.

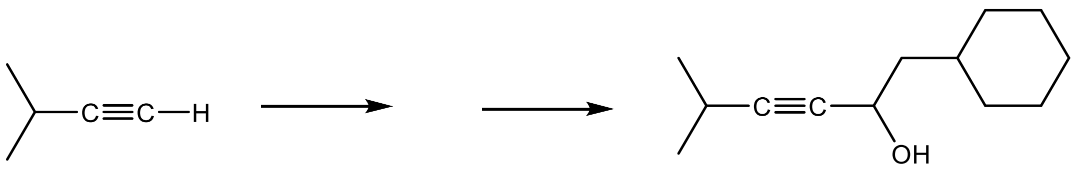


Exercise 9.6: Show how you would synthesize the following compound, beginning with acetylene and any necessary additional reagents.

a.

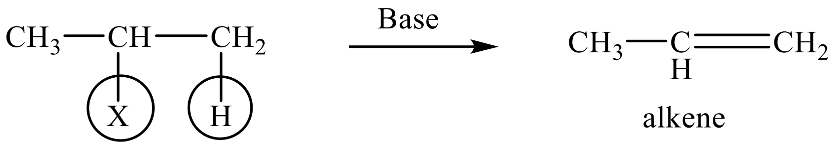


b.



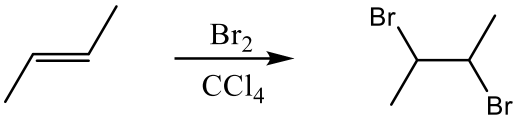
9.8 Synthesis of Alkynes by Elimination Reactions

In chapter 7, we saw elimination reaction of alkyl halide with bases that undergoes dehydrohalogenation reaction to make an alkene. This is represented as:

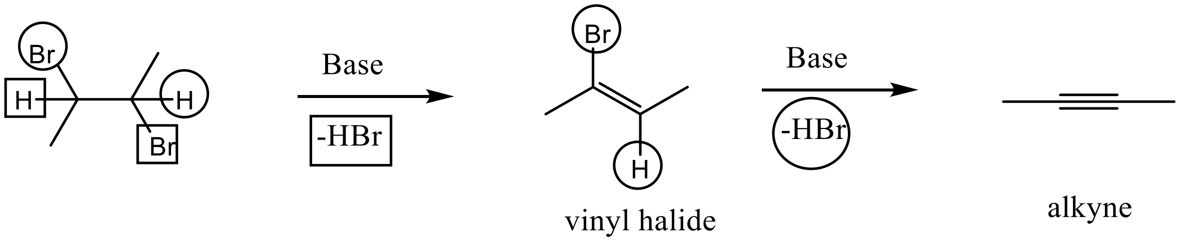


loss of H and Br from alkyl halides is dehydrohalgenation

In chapter 8, we saw formation of vicinal dihalides from alkenes.



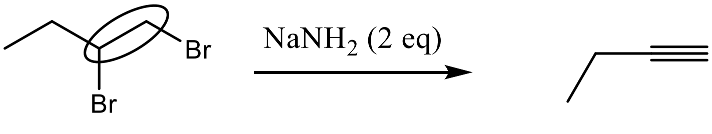
If a vicinal dihalide undergoes dehydrohalogenation twice, it produces an alkyne. You will need two equivalents of base.



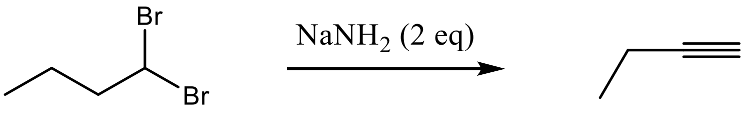
We have already seen many examples of dehydrohalogenation of alkyl halides in chapter 6. The second step is new, however, because it involves dehydrohalogenation of a vinyl halide to give an alkyne. This second dehydrohalogenation occurs only under extremely basic conditions. There are two reagents that do this double dehydrohalogenation.

fused KOH (2 eq)
Δ

$NaNH_2$ (2 eq)

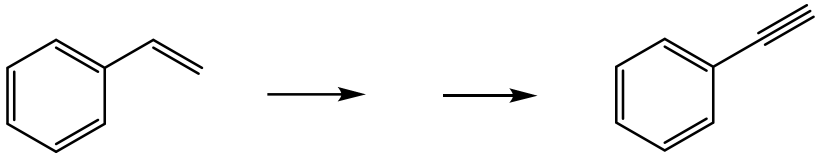


Note: The triple bond is formed between the carbons where the two bromine atoms were in the vicinal dihalide. The same reaction can also take place when the dihalide is geminal (two halogens on the same carbon).



Importance of alkyne formation in synthesis:

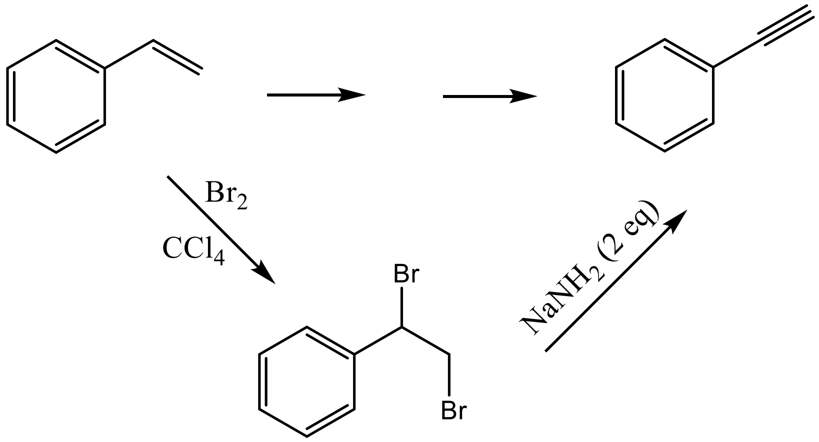
Solved Problem 9.4: Show how you would synthesize the following compound, beginning with styrene (shown below) and any necessary additional reagents.



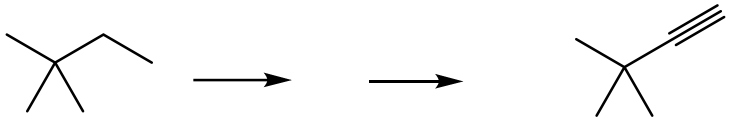
Approach: Once again, we asked ourselves:

a. What **functional group** is present on the *reactant*?
b. What **functional group** is present on the *product*?
c. What has changed from reactant to product?
d. Which reactions do I know to **convert** from one to the other?
e. Has the overall length of the alkyne changed? (NO, in this case!)

1. Going from alkene to alkyne, two hydrogens have been removed. We do not know any reaction how we can remove to hydrogens, so this cannot be achieved in a single step.
2. Look at the alkyne and let us review how many ways an alkyne can be synthesized. The alkyne length can be increase by using the acidity of terminal alkyne. But this synthesis does not involve an increase in carbon chain, so we cannot use that reaction. Another way of making an alkyne is via double dehydrohalogenation. For that we need a vicinal (or geminal halide). Since our starting material is an alkene, we can make a vicinal halide by simply adding the halogen across the C=C pi bond in presence of an inert solvent (do not use polar protic solvents like H_2O or CH_3OH).

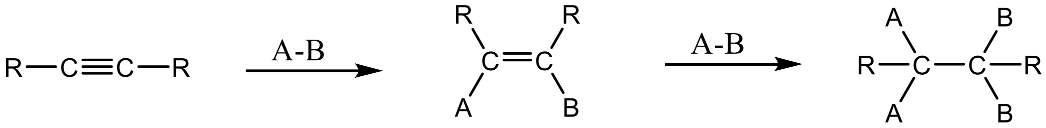


Exercise 9.7: Show how you would synthesize the following compound, beginning with 2,2,-dimethylbutane and any necessary additional reagents.



9.9 Addition Reactions of Alkynes

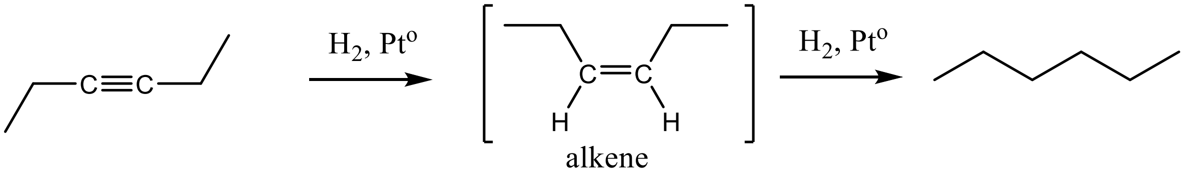
Reagents add across the triple bonds of alkynes just as they add across the double bonds of alkenes. Since alkynes have two pi bonds, a reagent can twice across the triple bond.



Depending upon the reagent, you can add it cis or trans. Some conditions may allow the reaction to stop after a single addition, while other conditions give double addition.

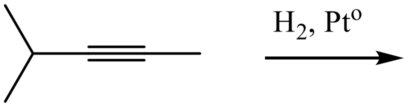
9.10 Catalytic Hydrogenation to Alkanes

Catalytic hydrogenation takes place in two stages, with an alkene intermediate, however it is usually impossible to stop the reaction at the alkene stage with efficient catalysts such as platinum, palladium, or nickel.



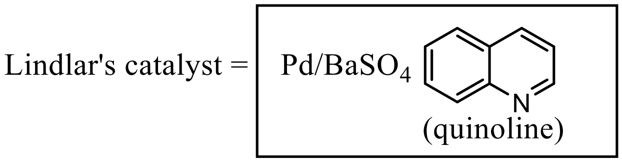
Alkene cannot be isolated. For best results, excess of hydrogen gas is used to go directly from alkyne to alkane.

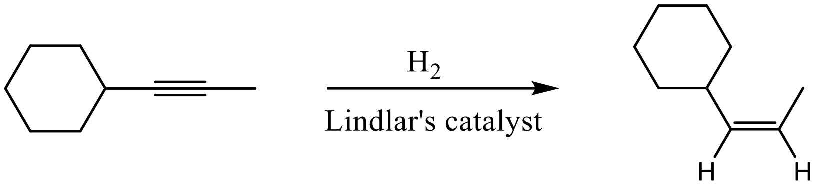
Exercise 9.8: Draw the product of the reaction shown below. Assume excess reagent.



9.11 Catalytic Hydrogenation to cis Alkenes

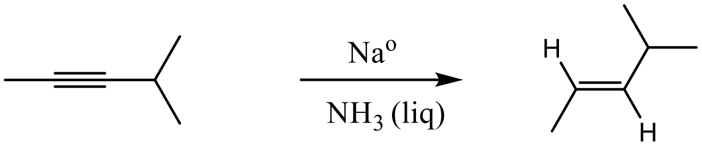
Hydrogenation of an alkyne can be stopped at the alkene stage by using a "poisoned" catalyst made by treating palladium with a compound that makes the catalyst less effective. **Lindlar's catalyst** is a poisoned palladium catalyst, which is barium sulfate coated with palladium, poisoned with quinoline. The hydrogens add to the alkyne from the same side to yield a cis alkene.





9.12 Metal–Ammonia Reduction of an Alkyne

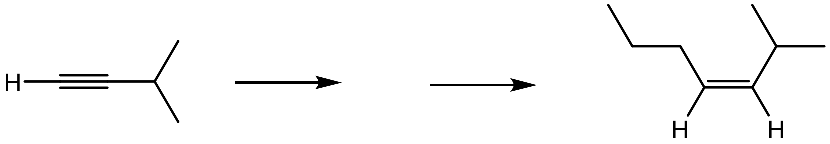
To form a trans alkene, two hydrogens must be added to the alkyne with anti (trans) stereochemistry. Sodium (or Lithium) metal in liquid ammonia reduces alkynes to give trans-alkene.



Exercise 9.9: Show how you would perform the following transformations.

a. hept-3-yne to *cis*-hept-3-ene **b.** hex-2-yne to *trans*-hex-2-ene

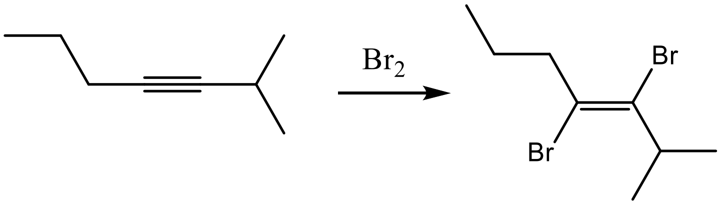
Exercise 9.10: Show how you would synthesize the following compound, beginning with 3-methylbut-1-yne and any necessary additional reagents.



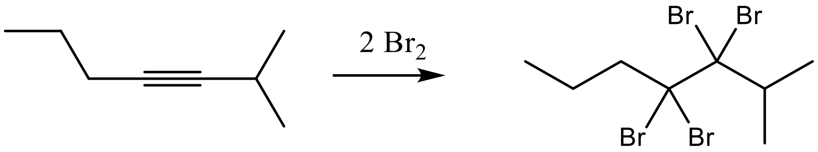
9.13 Addition of Halogens

Bromine and chlorine add to alkynes just as they add to alkenes. If 1 mole of halogen adds to 1 mole of an alkyne, the product is a dihaloalkene.

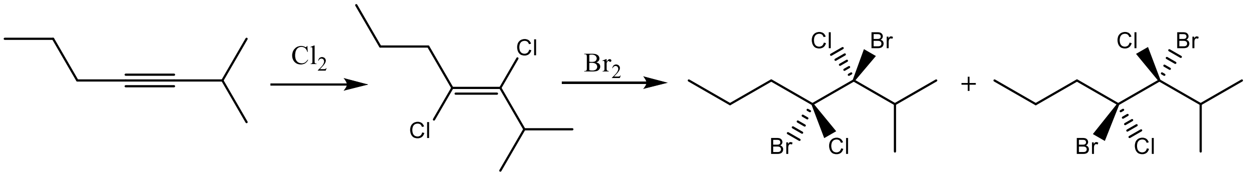
The stereochemistry of addition may be either cis or trans, and the products are often mixtures of cis and trans isomers, trans product being the major.



When 2 moles of halogen add to 1 mole of an alkyne, a tetrahalide results.

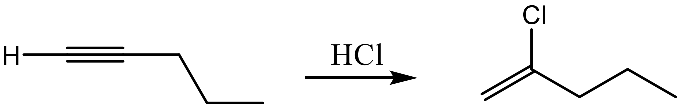


In the example below, the first step forms E-isomer. A sequence of addition of first chlorine followed by bromine can give a mixture of enantiomers.



9.14 Markovnikov Addition of Hydrogen Halides

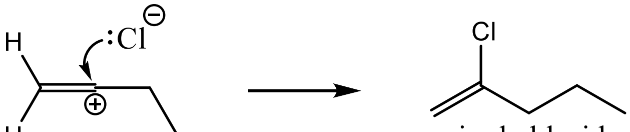
When a hydrogen halide (HX) adds to a terminal alkyne, addition takes place in a Markovnikov manner. A second molecule of HX adds with the same orientation as the first. This is due to the carbocation formed in each case on a more substituted carbon.



Marvovnikov addition of HCl

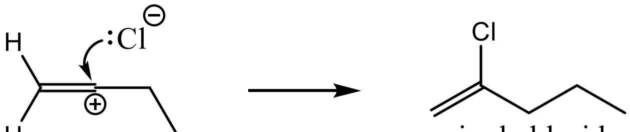
Mechanism:

Step 1: Formation of more stable carbocation.



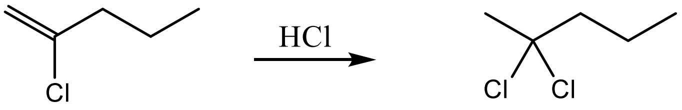
vinyl chloride

Step 2: Attack of chloride ion to the carbocation resulting in a Markovnikov addition of HCl.



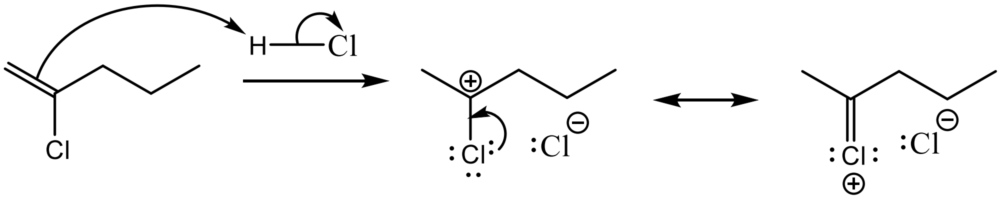
vinyl chloride

If 2 mol of HCl is present for every 1 mol of alkyne, the reaction can continue by another Markovnikov addition to vinyl chloride. This forms **geminal dihalide** (two halogens on the same carbon).



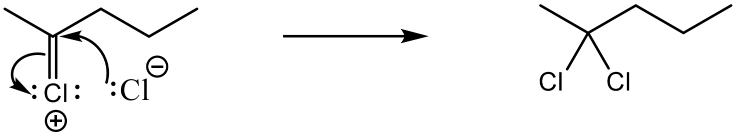
geminal dihalide

Step 1: Formation of a resonance stabilized carbocation. The right form is major contributing structure due to octet rule.



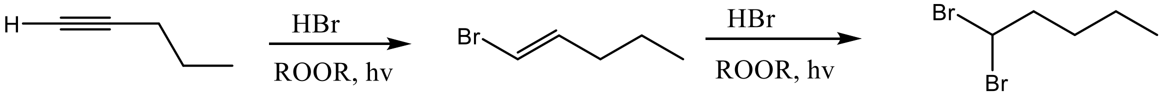
resonance stabilized carbocation

Step 2: Attack of chloride ion to the carbocation resulting in a Markovnikov addition of HCl.



9.15 Anti-Markovnikov addition of Hydrogen Bromide (Only HBr, not HCl or HI).

In chapter 8, we saw the effect of peroxides on the addition of HBr to alkenes. This is a free-radical chain reaction that adds HBr across the double bond of an alkene in the anti-Markovnikov manner. A similar reaction occurs with alkynes, with addition of HBr taking place in an anti-Markovnikov manner.

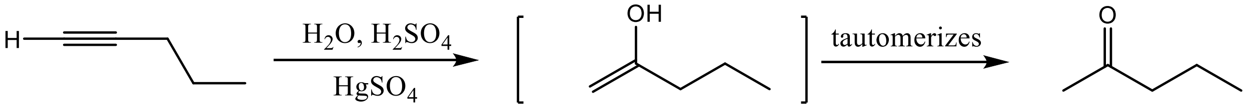


anti-Marvovnikov addition of HBr

geminal dihalide
anti-Marvovnikov addition of HBr

9.16 Markovnikov Hydration of Alkynes

When a terminal alkyne undergoes acid-catalyzed hydration reaction, it requires $HgSO_4$ as a catalyst. The H_2O adds in a Markovnikov manner to produce an unstable intermediate "enol". This enol **cannot** be isolated. The enol undergoes a rearrangement called tautomerism that converts it to a ketone.

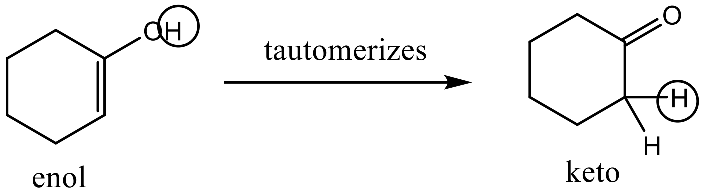


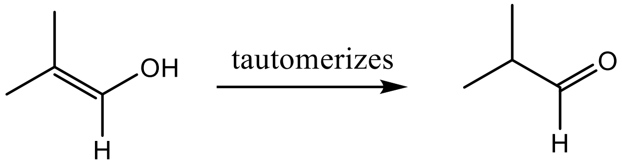
enol
unstable

ketone

The word **enol** comes from the functional groups of alkenes (**en**) and alcohol (**ol**) on the **same** carbon. In general, keto forms are more stable than the enol form. Enol form cannot be isolated.

Depending upon the structure of enol, upon tautomerism, they convert to either **aldehyde** or **ketone**. In the example below, enol to keto tautomers is shown. The hydrogen on the oxygen of enol ends up on the adjacent carbon that belonged to the double of enol.

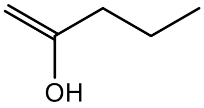




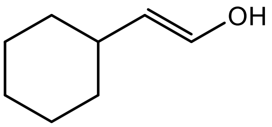
When the -OH group of an enol is at the end of the carbon chain, the resulting tautomer will be an aldehyde. When the -OH group of an enol is on an internal carbon, the resulting tautomer will be ketone.

Exercise 9.11: Draw the tautomer of each of these enols and then name the functional group (ketone or aldehyde).

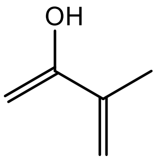
a.



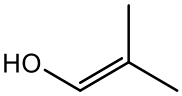
b.



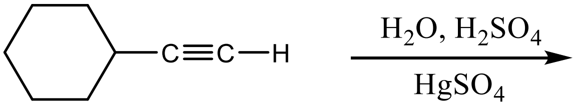
c.



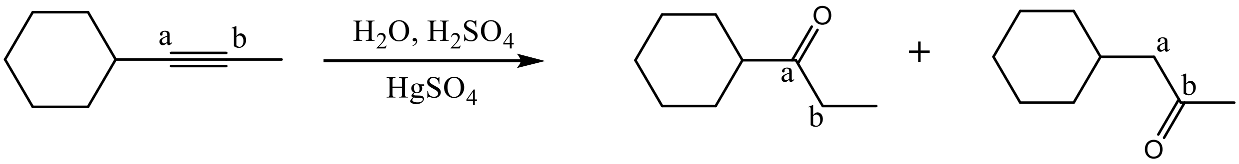
d.



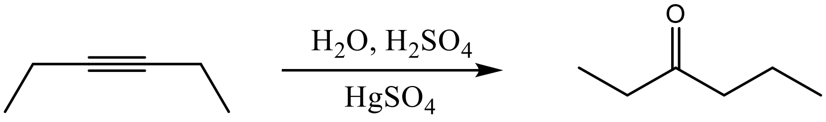
Exercise 9.12: Draw the final organic product when the following reaction takes place. [*Note: It helps to first draw the enol and then draw the final product*].



When an asymmetric internal alkyne undergoes the same reaction, two products are formed.



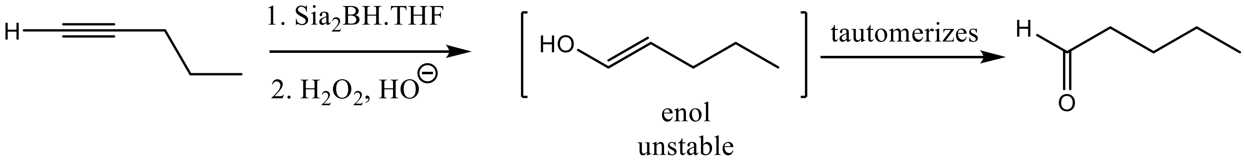
In the example above, the triply bonded carbon a and b are equally substituted. Due to which addition of water can take place two possible ways. Synthetically, it is not useful to make a ketone from an asymmetric internal alkyne. A symmetric alkyne results in only one product.



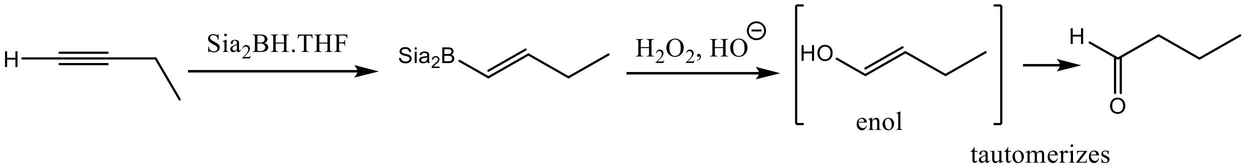
Synthetically, making a ketone is useful only if the alkyne is terminal or if it is a symmetric internal alkyne.

9.17 Anti-Markovnikov Addition of Water via Hydroboration–Deboration (Oxidation)

In chapter 8, we saw that Hydroboration–Deboration reaction adds water across the double bonds of alkenes with anti-Markovnikov orientation. A similar reaction takes place with alkynes, except a modified reagent disiamylborane (Sia_2BH) is be used.



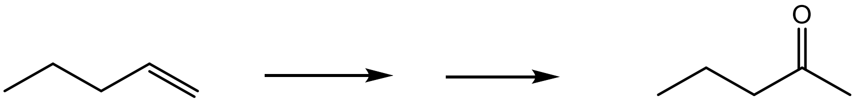
In a terminal alkyne, the boron atom bonds to the terminal carbon atom and H adds to the more substituted carbon. During the second Deboration step, H_2O_2 (hydrogen peroxide) oxidized the C-B bond to C-OH bond. This forma an enol that tautomerizes to give an aldehyde as the final organic product.



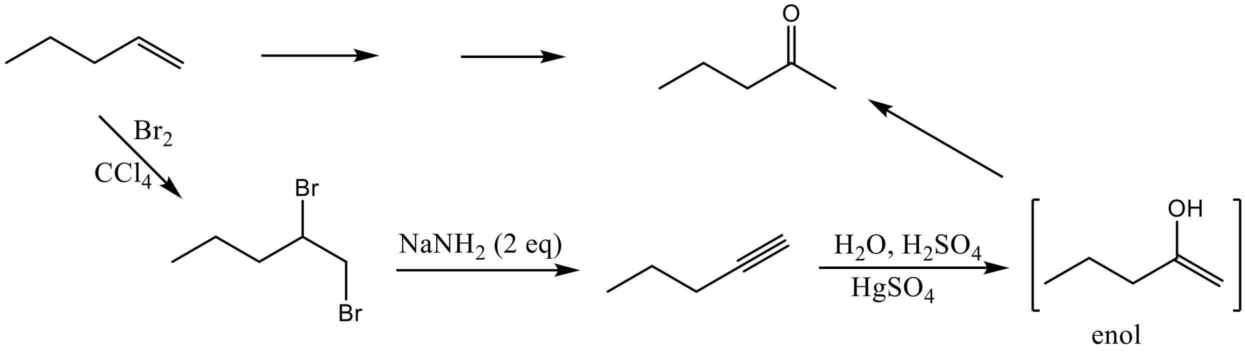
This sequence is an excellent method for converting terminal alkynes to aldehydes.

It is important to note that the aldehyde will **NEVER** form if the alkyne is internal.

Solved Problem 9.5: Show how you would synthesize the following compound, beginning with pent-1-ene (shown below) and any necessary additional reagents.

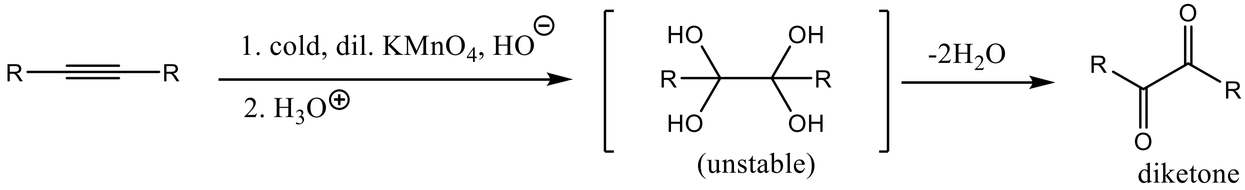


Approach: The alkene is being converted to a ketone. We know two ways to make a ketone. The first one is oxidative cleavage of alkene. But that breaks C=C bond and in this case, the number of carbon atoms are the same in the starting alkene and the ketone product. The second method to synthesize a ketone is by hydrating an alkyne where the H_2O adds Markovnikov manner. For which, the last step should be to have pent-1-yne react with H_2O, H_2SO_4 and $HgSO_4$ to give the final product.
This brings up to the question, can we convert the alkene to alkyne? Two hydrogens are removed from alkene to give alkyne. Look at solved problem 9.4 where we converted an alkene to an alkyne.

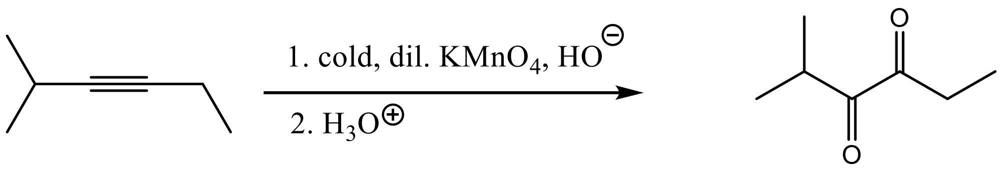


9.18 Mild Oxidation of Alkynes

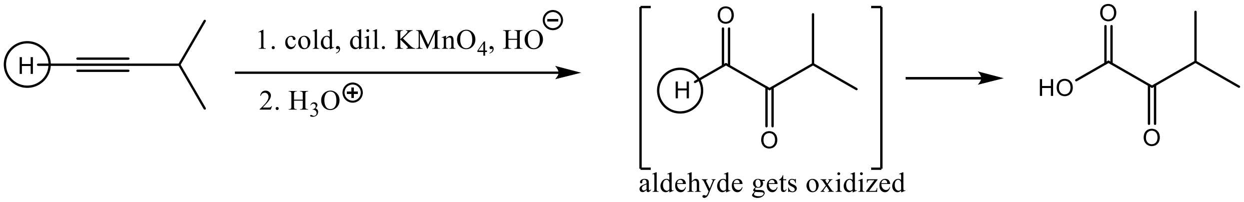
In chapter 8, we the oxidation of alkenes potassium permanganate (cold and dilute) to give diol (compounds with two -OH groups on adjacent carbon atoms. A similar reaction occurs with alkynes. If an alkyne is treated with cold, aqueous potassium permanganate solution followed by aqueous workup, a diketone is formed. This is conceptually the same as hydroxylating each of the two pi bonds of the alkyne, then losing two molecules of water to give the diketone.



When 2-methylhex-3-yne reacts with cold, dilute $KMnO_4$, the following diketone is formed.



When a terminal alkyne undergoes the same reaction, initially it forms a keto-aldehyde, but the aldehyde quickly oxidizes to an acid under these conditions. This is like the oxidation of alkenes with cold, dilute $KMnO_4$. The circled hydrogen on alkyne (or alkene) doesn't survive and is further oxidized to carboxylic acid.

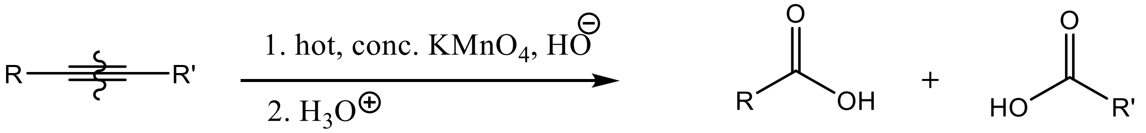


9.19 Oxidative Cleavage of Alkyne

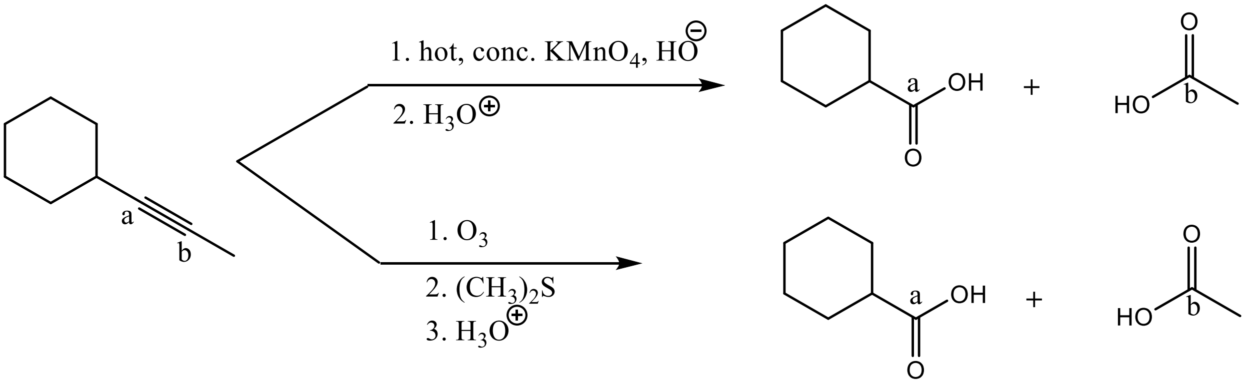
Like alkenes, alkynes undergo oxidative cleavage such that the triple bond breaks. The reagents are:

$$\boxed{\xrightarrow[\text{2. } H_3O^{\oplus}]{\text{1. hot, conc. } KMnO_4,\ HO^{\ominus}}} \qquad \boxed{\xrightarrow[\substack{\text{2. } (CH_3)_2S \\ \text{3. } H_3O^{\oplus}}]{\text{1. } O_3}}$$

With cold, dilute $KMnO_4$, an internal alkyne forms a diketone. If you heat up that reaction and increase the concentration of $KMnO_4$, the diketone further, oxidative cleavage takes place. Since we are breaking three carbon-carbon bonds, they should be replaced by three carbon-oxygen bonds. Two of them are C=O and one of them is C-O, which results in the formation of carboxylic acid. Both the above reagents produce carboxylic acid with internal alkynes when the triple bond breaks.

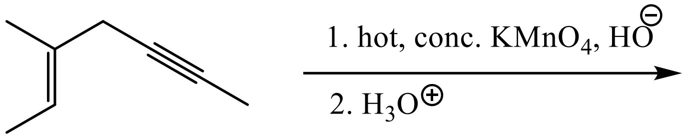


For example, when the following alkyne undergoes oxidative cleavage with each of the above reagent, the same products are formed in each case

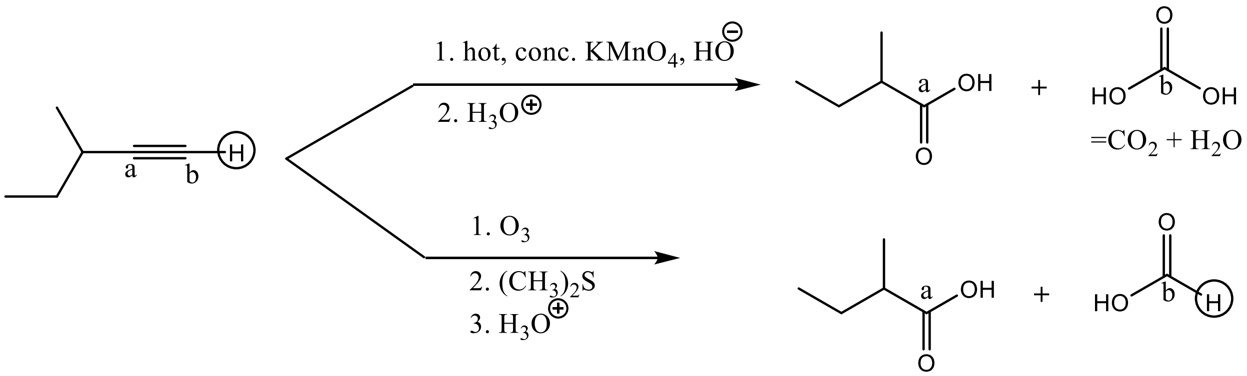


A carboxylic acid is formed when the carbon-carbon triple bond undergoes the oxidative cleavage

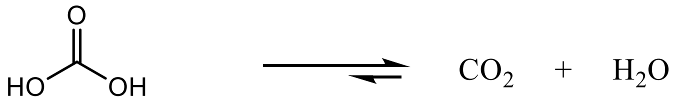
Exercise 9.13: Draw the organic product(s) of the following reaction. Assume excess of reagent.



With terminal alkynes, the products are not the same:



Carbonic acid (H_2CO_3) is unstable and decomposes to give carbon dioxide and water (CO_2 and H_2O).



carbonic acid, H_2CO_3

9.20 Multistep Synthesis

Building upon the previous approach of multi-step synthesis, asking the following:

a. What **functional group** is present on the *reactant*?

b. What **functional group** is present on the *product*?

c. What has changed from reactant to product?

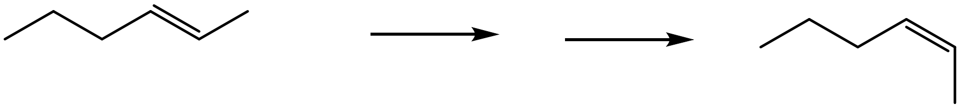
d. Has the overall length of the alkyne changed? If yes, you must use the **acidity of a terminal alkyne** (make **acetylide** ion) to extend a carbon chain.

e. Work backward through as many steps as necessary. Compare methods for synthesizing the reactants needed for assembly of the key intermediate with the correct carbon skeleton and functionality.

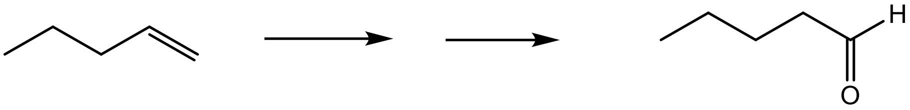
f. Summarize the complete synthesis in the forward direction, including all steps and all reagents, and check it for errors and omissions.

Exercise 9.14: Using the given starting material, show how you would synthesize the following compounds.

c.

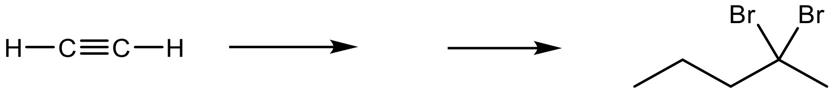


d.



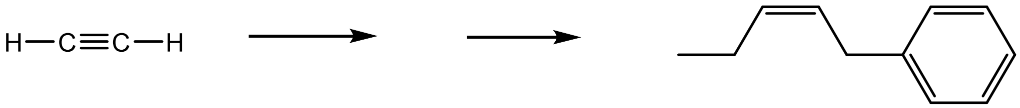
Exercise 9.15: Using acetylene as your starting material, show how you would synthesize the following compounds.

a.



b.

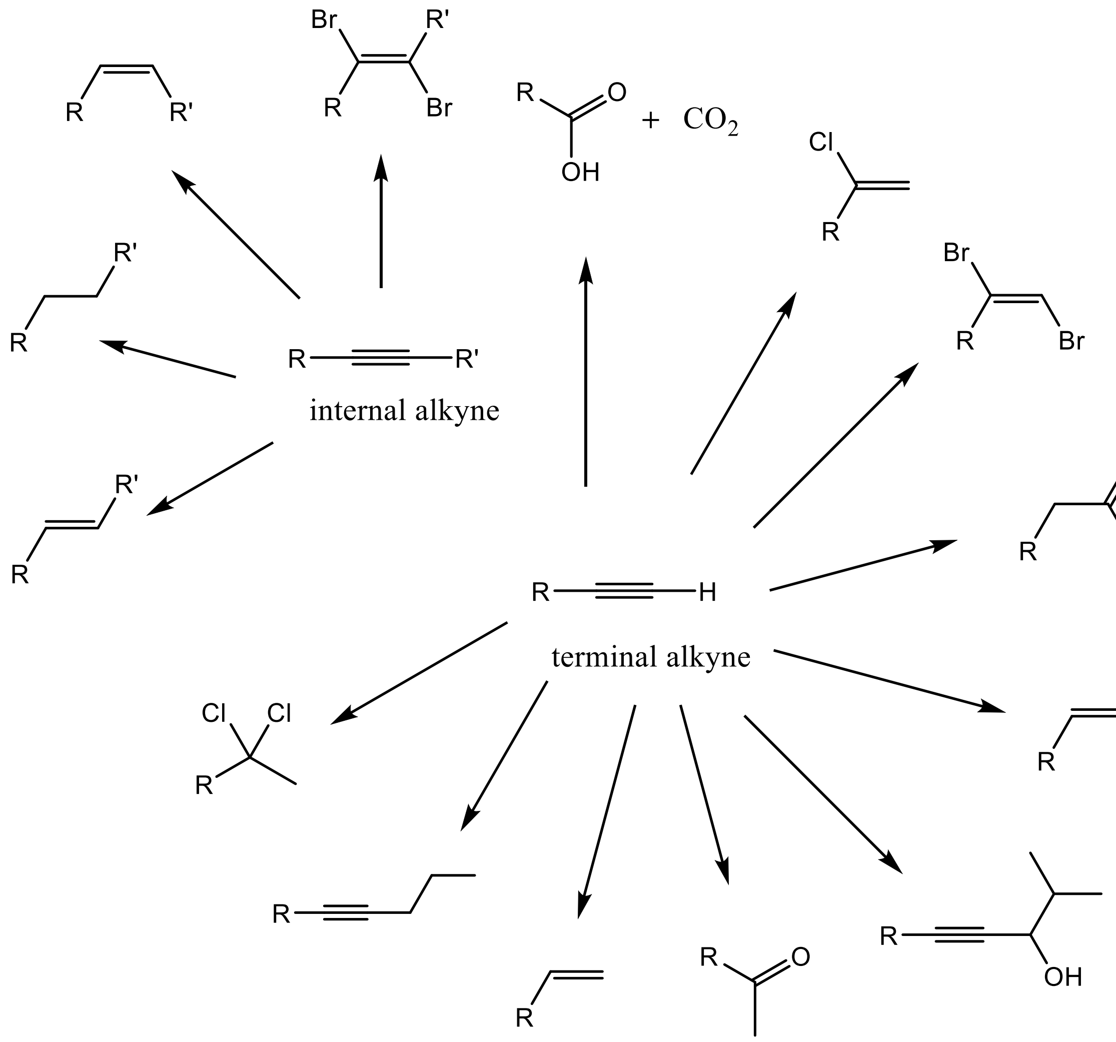
c.



Exercise 9.16: Using hex-1-ene as your starting material, show how you would synthesize the following compounds.

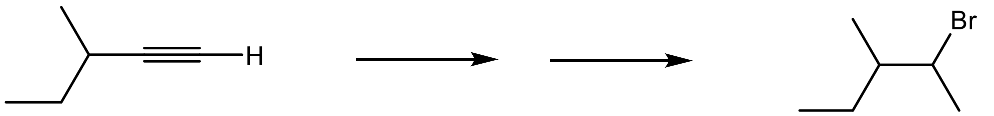
- **a.** 1,2-dibromohexane
- **b.** hex-1-yne
- **c.** 2,2-dibromohexane

Exercise 9.18: Identify the reagents for each of the following reactions of internal and terminal alkynes.

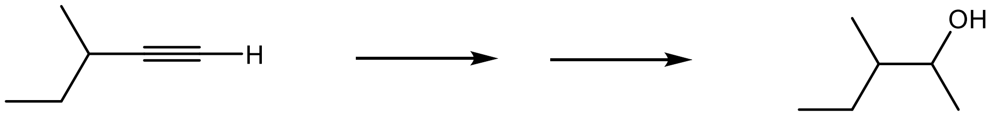


Exercise 9.19: Show how you would synthesize the following compounds from the alkyne provided below.

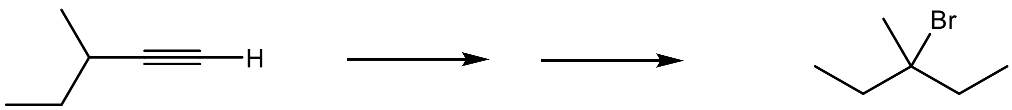
a.



b.



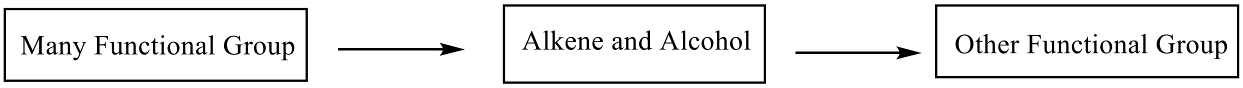
c.



Chapter 10: Structure and Synthesis of Alcohol

10.1 Introduction

An alcohol functional group is an alkyl group attached to the hydroxyl (-OH) group. The smallest alcohol is methanol, CH_3OH. Ethanol is CH_3CH_2OH and is found in alcoholic beverages, cosmetics, drug preparation, etc. Rubbing alcohol is isopropanol, used for cleaning the skin prior to injections and for minor cuts.
Like alkenes, the alcohol functional group is very important as many functional groups can be converted from one to another with the help of alkene and alcohol.



10.2 Structure and Classification of Alcohols

The structure of alcohol resembles the structure of water, with an alkyl group replacing one of the hydrogen atoms of water.

sp3 hybridized
~109.5 ° bond angle
tetrahedral geometry
bent shape

Alcohols can be classified as primary (1°), secondary (2°), and tertiary(3°) like alkyl halides. If the carbon atom bonded to the -OH group is primary, the compound is a primary alcohol. Similarly, if the carbon atom bonded to the -OH group is secondary, the alcohol is secondary.

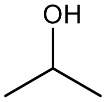
When the -OH group is directly attached to a benzene ring, the alcohol has a specific name called phenol. Below are a few alcohols that are commonly used commercially.

CH_3OH

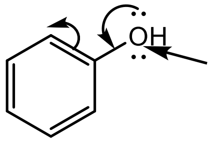
methanol

CH_3CH_2OH

ethanol



isopropyl alcohol



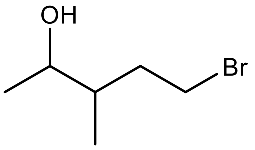
phenol

O is sp2 hybridized
due to resonance

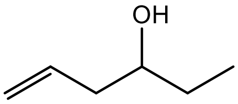
10.3 IUPAC Nomenclature of Alcohols and Phenols

1. Name the longest carbon chain that contains the carbon atom bearing the group. Drop the final *-e* from the alkane name and add the suffix *-ol* to give the root name.
2. Number the longest carbon chain starting at the end nearest the -OH group and use the appropriate number to indicate the position of the group. (For numbering, the -OH group takes precedence over double and triple bonds).
3. Name all the substituents and give their numbers, as you would for an alkane or an alkene.

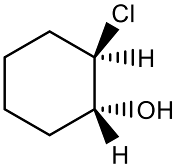
4. Cyclic alcohols are named using the prefix *cyclo-*; the hydroxyl group is assumed to be on carbon 1.



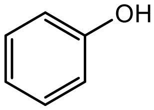
5-bromo-3-methylpent-2-ol



hex-5-en-3-ol



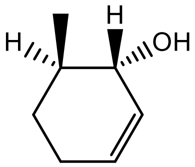
(1R, 2R)-2-chlorocyclohexanol



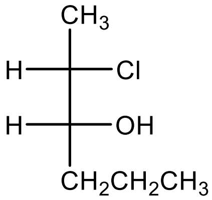
phenol

Exercise 10.1: Provide a proper IUPAC name for the following compounds. Include stereochemistry where appropriate.

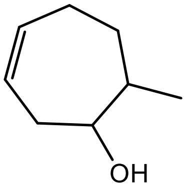
a.



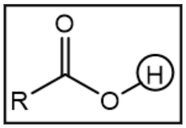
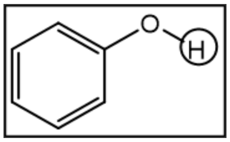
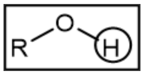
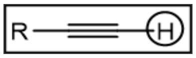
b.



c.

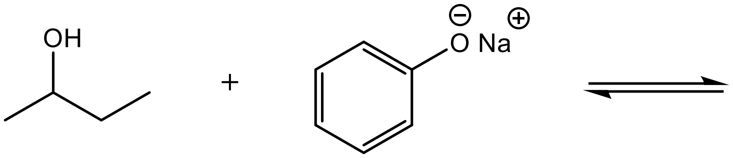


10.4 Acidity of Alcohols and Phenols

Functional Group	Compound	Pka	
Carboxylic acid		**5**	most acidic
Phenol		**10**	
Alcohol		**16**	
Alkyne (terminal)		**25**	least acidic

Exercise 10.2: Explain why phenol is so much more acidic than ethanol.

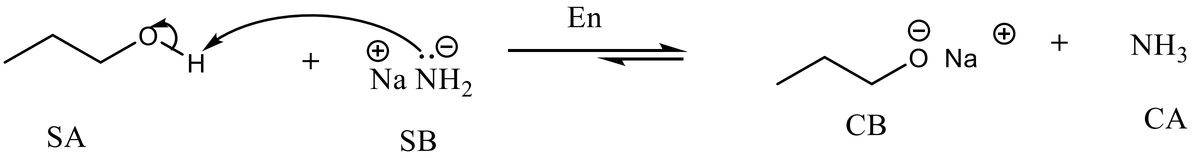
Exercise 10.3: Draw the acid-base mechanism of the reaction shown below. Which direction is the equilibrium favored? Why? Under each species of reactants and products, write SA, SB, CA, or CB.



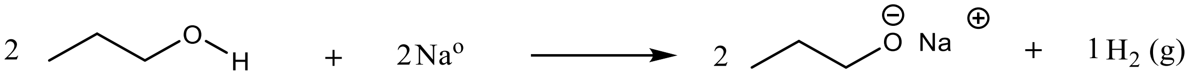
Exercise 10.4: Predict which member of each pair will be more acidic. Explain your answers.

- **(a)** methanol or 2,2-dimethylpronan-2-ol
- **(b)** 2-chloropropan-1-ol or 2-bromopropan-1-ol
- **(c)** 2-chloroethanol or 2,2-dichloroethanol

To synthesize an alkoxide ion from alcohol, a strong base like $NaNH_2$ (sodamide) should be used.



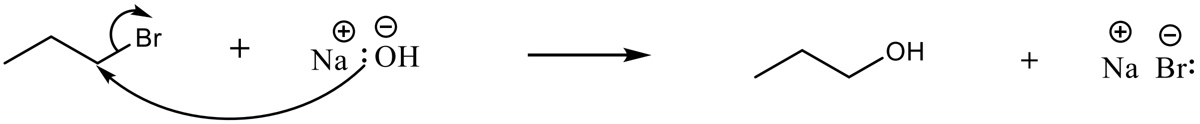
Often alkali metals like lithium or sodium are used with alcohol to produce alkoxide ion. This is a redox reaction where the hydrogen ion gets reduced, and sodium (or potassium) metal gets oxidized.



10.5 Synthesis of Alcohols: A Review

a. S_N2 reaction between a primary alkyl halide and hydroxide ion (Chapter 6)

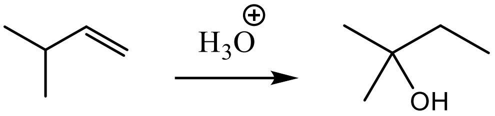
Section 6.5-6.10 discusses SN2 reactions of alkyl halides. When strong nucleophiles like hydroxide ions are used with primary alkyl halides, the product is an alcohol.



Since NaOH is a strong nucleophile/base, the alcohol formation takes place best with a primary RX. With secondary RX, S_N2 and E2 reactions compete whereas, with a tertiary RX, only the E2 reaction takes place.

b. Acid-catalyzed direct hydration of alkenes (Markovnikov addition of water)

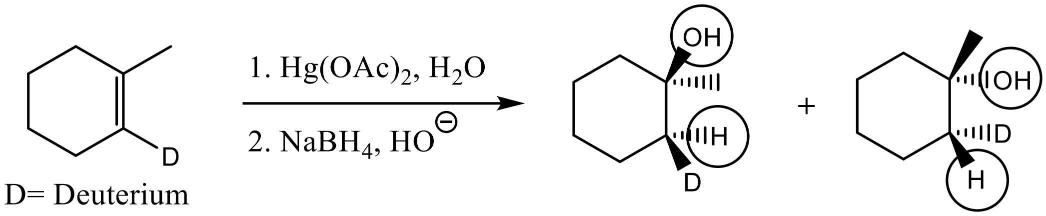
Section 8.7 discussed the direct hydration of alkenes with water in the presence of H_2SO_4 as a catalyst. The reaction proceeds via the formation of carbocation and rearrangements are often observed.



Carbocation rearranges
Markovnikov alcohol

c. Oxymercuration-Demercuration of alkenes (Markovnikov addition of water)

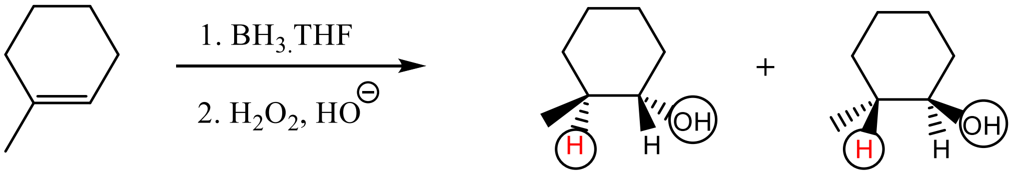
Section 8.8 discussed indirect hydration via Oxymercuration-Demercuration.



Stereochemistry: ***Markovnikov's*** *addition of water takes place in a* ***trans*** *manner.*

d. Hydroboration-Deboration of alkenes (anti-Markovnikov addition of water)

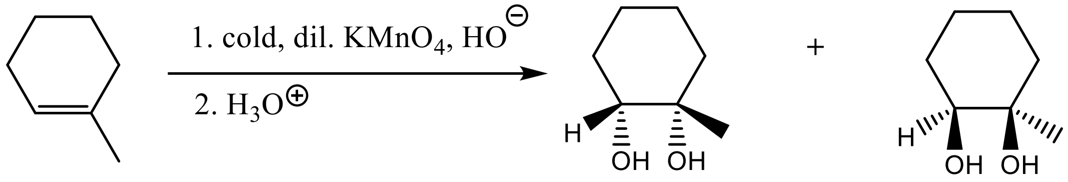
Section 8.10 discussed hydration via Hydroboration-Deboration.



Anti-Markovnikov *addition of water takes place in a* ***cis*** *manner.*

e. Synthesis of *cis* diol

Section 8.17 discussed oxidation of alcohol to give *cis*-diol with cold, dilute $KMnO_4$.

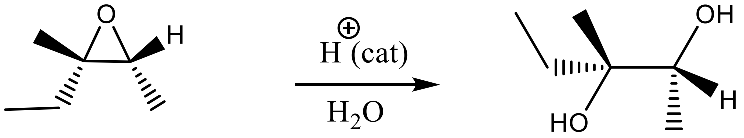


cis-diol cis-diol

KMnO4 (cold, dilute) oxidation is addition of two hydroxyl groups to an alkene in a ***cis*** manner.

f. Synthesis of *trans*-diol

Section 8.16 discussed the ring opening of epoxide under acidic conditions to give *trans*-diol.

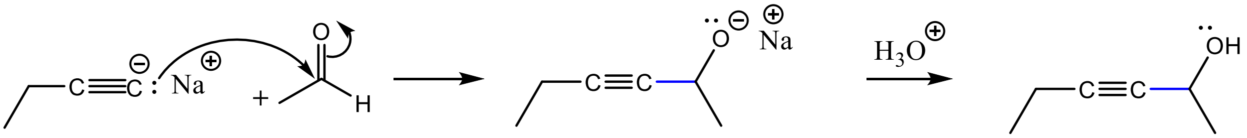


Hydrolysis of epoxide results in the addition of two hydroxyl groups to an alkene in a ***trans*** manner.

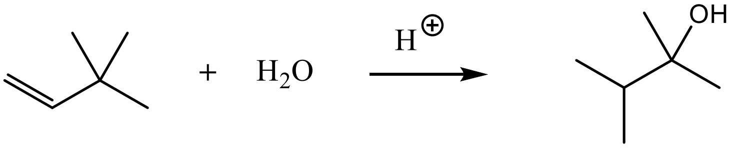
g. Alcohol from acetylide anion

Section 9.7 discussed the reaction of acetylide ions with formaldehyde, aldehyde, and ketone to yield 1°, 2°, and 3° alcohol, respectively. These are C-C bond formation reactions that increase the carbon chain hence these reactions will be synthetically important.

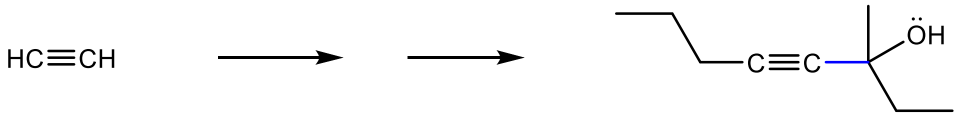
The example below shows the formation of a 2° alcohol.



Exercise 10.5: Draw a step-by-step mechanism for the reaction shown below that will explain the formation of the product.

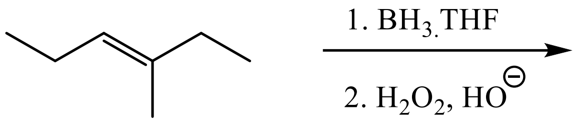


Exercise 10.6: Show how you would synthesize the following compound, beginning with acetylene and any necessary additional reagents.

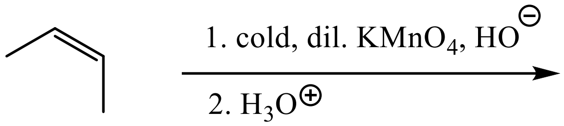


Exercise 10.7: Draw the final organic product(s) of the reaction. Will the product form an enantiomer? Explain.

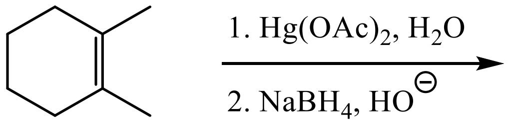
a.



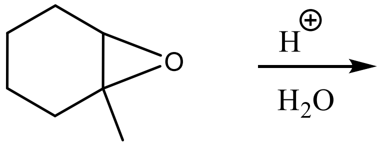
b.



c.

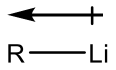


d.

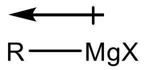


10.6 Organometallic Reagents for Alcohol Synthesis

Organometallic compounds (R-M, where M is a metal like **lithium** and **magnesium**) contain highly polar covalent bonds between carbon atoms and metal atoms.



Organolithium

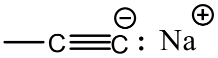


Grignard reagent

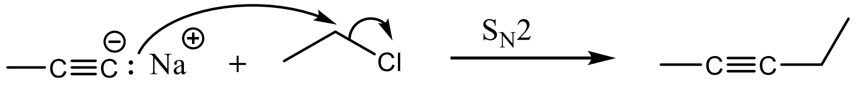
Although the bond is between a metal and a non-metal, notice, that it is written as a polar covalent bond and not ionic.

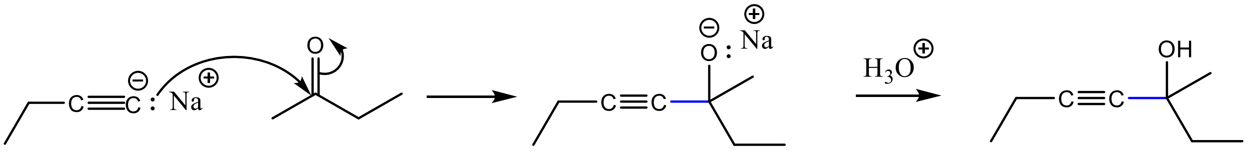
The difference in electronegativity between carbon and lithium (or magnesium) is not large enough to qualify it to be an ionic bond, but it is large enough to have a highly polar covalent bond character, where the carbon atom is highly nucleophilic (and basic). This contrasts with the electrophilic carbon atoms of alkyl halides.

We have already encountered acetylide ion as an organometallic compound.

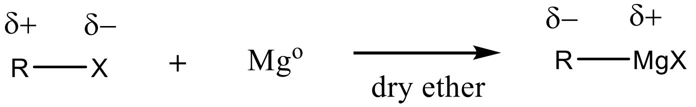


Terminal alkynes are weakly acidic, and they are converted to sodium acetylides by treatment with a strong base, sodamide ($NaNH_2$). These acetylide ions are useful nucleophiles, reacting with alkyl halides and carbonyl compounds to form new carbon-carbon bonds.





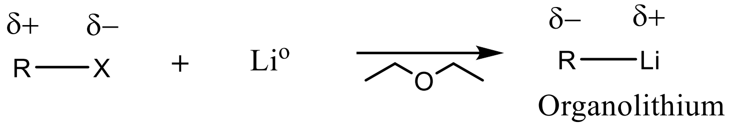
Alkanes and Alkenes are not acidic enough to be deprotonated by sodamide ($NaNH_2$), but they can be made into organomagnesium (also known as **Grignard** reagent) and organolithium reagents. These two are very useful for the synthesis of alcohols.



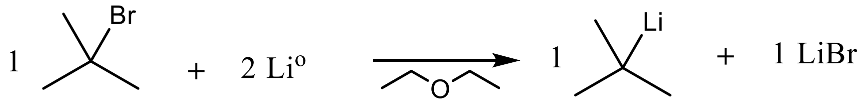
Grignard reagent

There is no limitation to the nature of alkyl halide. All kinds of halides, 1°, 2°, 3°, on any hybrid carbon (sp2, etc.) react with magnesium metal in the presence of dry ether. The dry ether stabilizes the **Grignard** reagent.

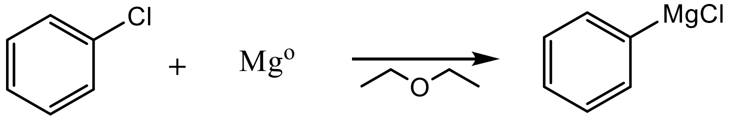
Organolithium can be similarly synthesized from a reaction of alkyl halide with lithium metal in the presence of dry ether. Diethyl ether is a popular solvent for organometallic synthesis.



In contrast with the electrophilic carbon atoms of alkyl halides, the carbon atom of Grignard reagent is highly nucleophilic and reacts with aldehydes and ketones to yield alcohols.
e.g.



e.g.

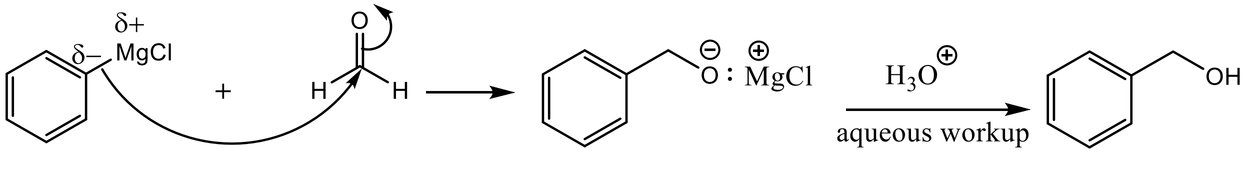


In Organic Chemistry I course, these two organometallics can be used interchangeably.

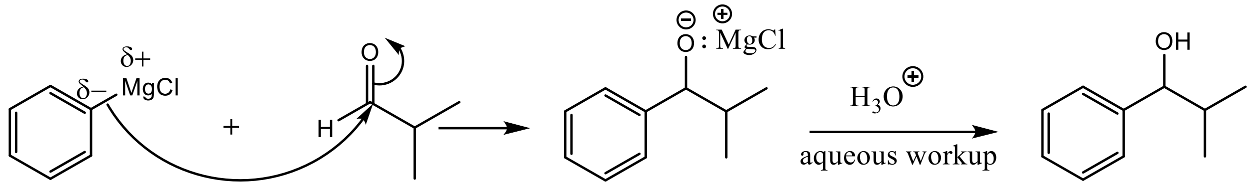
10.7 Addition of Organometallic Reagents to Carbonyl Compounds to Synthesize 1°, 2° and 3° alcohol.

Mechanism: The nucleophilic carbon bonded to magnesium is covalently bonded. Place partial charges on the carbon (δ-) and magnesium (δ+) to indicate that the carbon bonded to magnesium is nucleophilic. As the electrons are in between the polar covalent bond, the arrow should start from the bond. The Grignard attacks the carbonyl carbon. To offset the formation of a new C-C bond, the pi bond breaks and electrons move to the more electronegative oxygen. This results in a minus charge on the oxygen and the product of this nucleophilic attack is an alkoxide ion, a strong base. (An alkoxide ion is the conjugate base of alcohol, a weak acid). The addition of a dilute acid protonates the alkoxide to give the neutral alcohol.

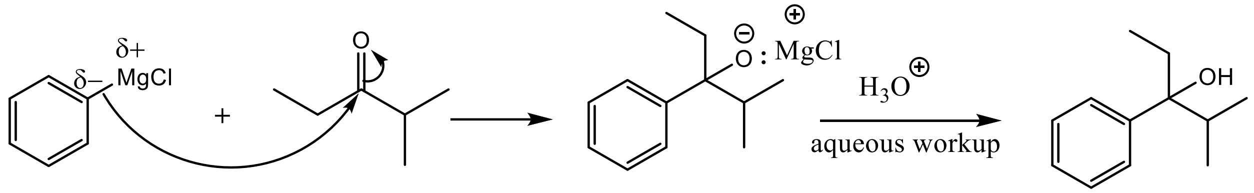
Synthesis of primary alcohol: A Grignard (or organolithium) adds to formaldehyde (one carbon aldehyde) to give primary alcohol (after the protonation step) with one more carbon atom than there was in the Grignard. So, the carbon chain increases only by one carbon.



Synthesis of secondary alcohol: An organometallic reagent adds to an aldehyde to give (after the protonation step) a secondary alcohol. The increase in carbon chain will depend upon the structure of the aldehyde.

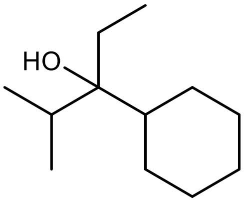


Synthesis of tertiary alcohol: An organometallic reagent adds to a ketone to give (after the protonation step) a secondary alcohol. The increase in carbon chain will depend upon the structure of the ketone.

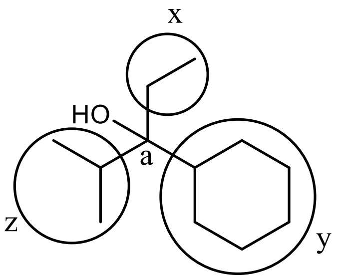


Count the carbons: It helps! Since the carbon chain has increased, keep track of where the change is taking place and by how many carbons.

Solved problem 10.1: Propose a structure of an organometallic compound and a carbonyl compound that will react to give the following alcohol after aqueous workup.

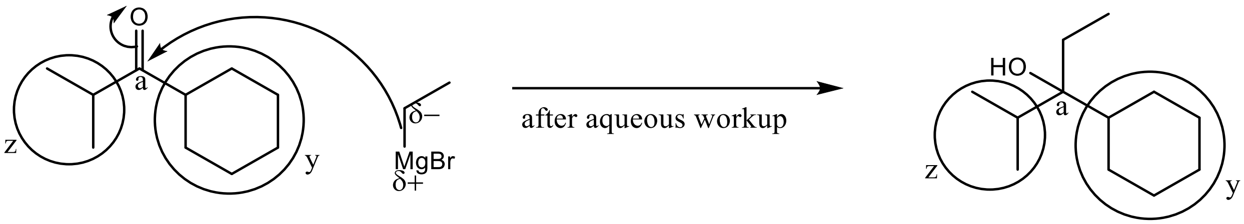


Approach: From this section, we have the knowledge that alcohol can be synthesized from a reaction of an organometallic with a carbonyl compound like an aldehyde or ketone. Since this is a tertiary alcohol, the carbonyl must be a ketone. How do we know what is the structure of carbonyl? One thing is certain: The carbon bearing the -OH group (labeled a), must be the carbonyl carbon. On carbon a, there are three alkyl groups, that have been circled as x, y, and z. If two of these belong to the carbonyl, the third one will belong to the organometallic.

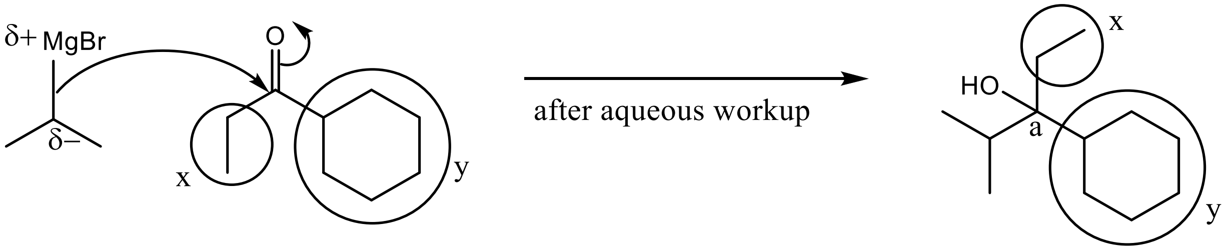


There are three possible correct answers, as **any** two groups can belong to the carbonyl carbon.

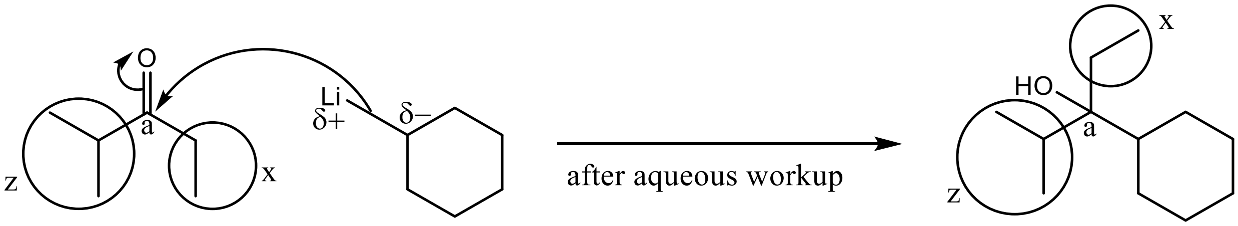
If y and z are part of the carbonyl, x will be a part of the organometallic (Grignard or organolithium).



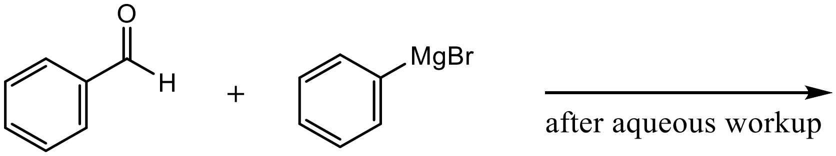
If x and y are part of the carbonyl, z will be a part of the organometallic (Grignard or organolithium).



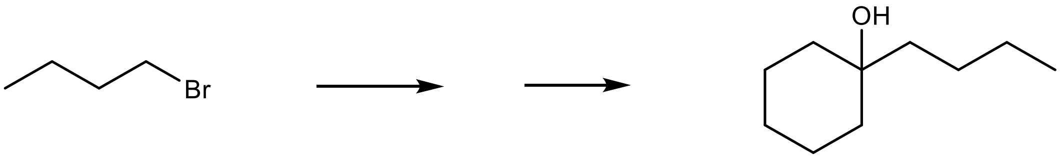
If x and z are part of the carbonyl, y will be a part of the organometallic (Grignard or organolithium).



Exercise 10.8: Using arrows, propose a mechanism for the reaction shown below. Then draw the product after aqueous workup.



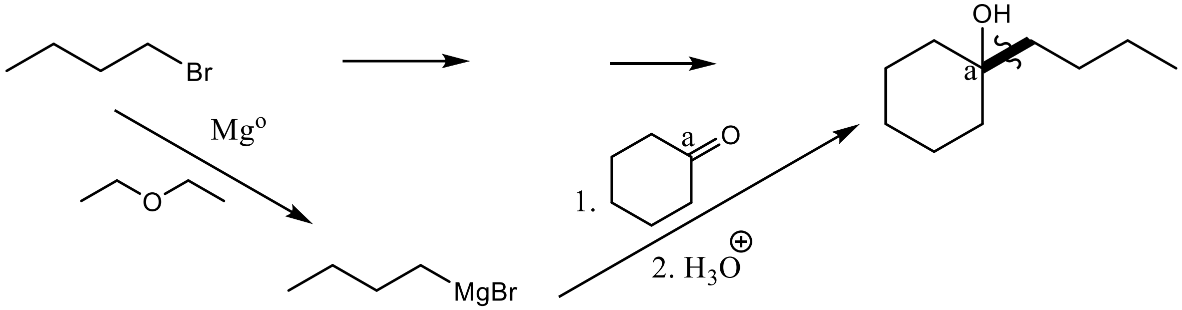
Solved problem 10.2: Show how you would synthesize the following compound, beginning with 1-bromobutane and any necessary additional reagents.



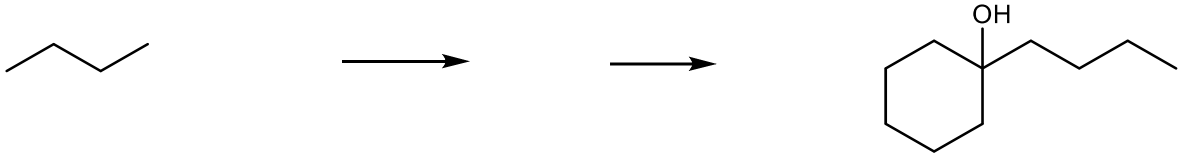
Approach: As always, we begin by asking the following questions during synthesis:

f. Has the overall length of the compound changed? (YES, in this case!)
g. If new C-C bond is formed highlight the bond and if alcohol is the product, the carbon containing the -OH group must be the carbonyl carbon that reacts with an organometallic.
h. What **functional group** is present on the *reactant*?
i. What **functional group** is present on the *product*?

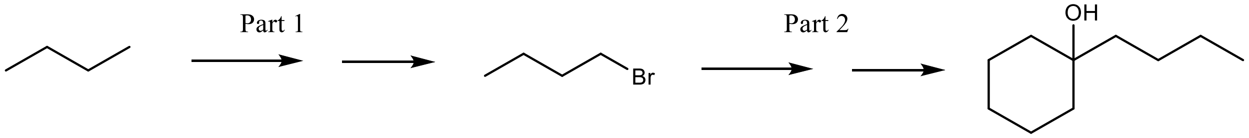
The most important observation is that a new C-C bond is formed for which an organometallic reagent (like Grignard) must be used. The -OH group appears on the ring (carbon a) so the carbon where the -OH group must be the carbonyl carbon (ketone).



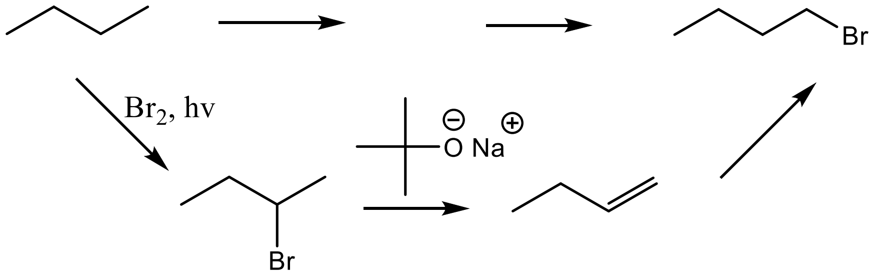
First figure out the last step, the structure of ketone (ketone is required as the alcohol is tertiary). If we want to synthesize of same compound starting from butane.



This can be broken up into two parts:



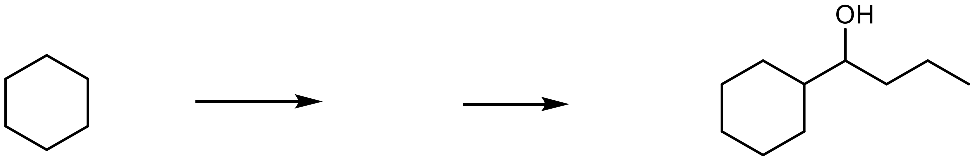
Part 1: This synthesis uses your knowledge of chapters 4, 6 and 8.



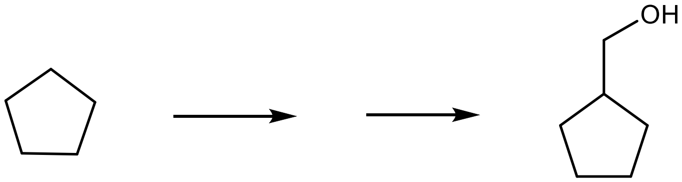
Part 2: See solved problem 10.2 for part 2.

Exercise 10.9: Show how you would synthesize the following compound, provided starting material and any necessary additional reagents.

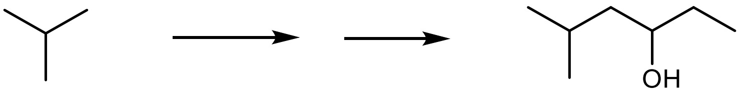
a.



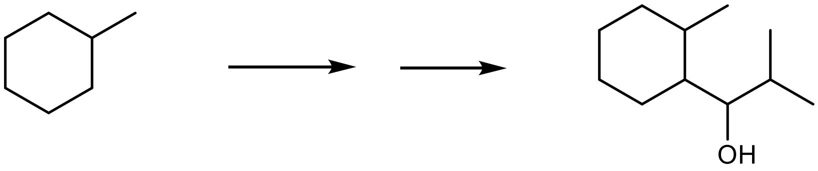
b.



c.

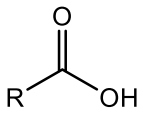


d.

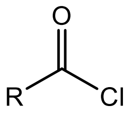


10.8 Reaction of Organometallics with Acid chloride and Esters to synthesize tertiary alcohol

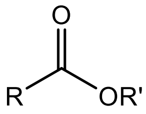
Both acid chlorides and esters react with two equivalents of organolithium or Grignard to give tertiary alcohol. Acid chloride and esters are considered derivatives of carboxylic acid.



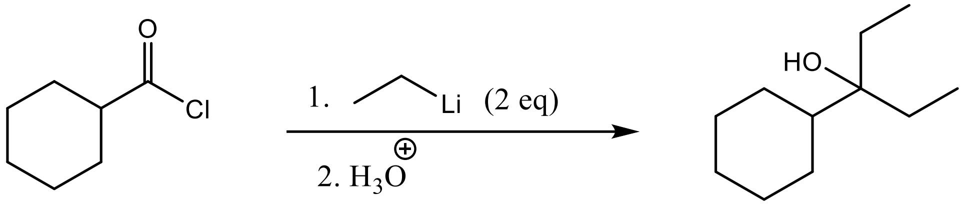
Carboxylic acid



Acid chloride

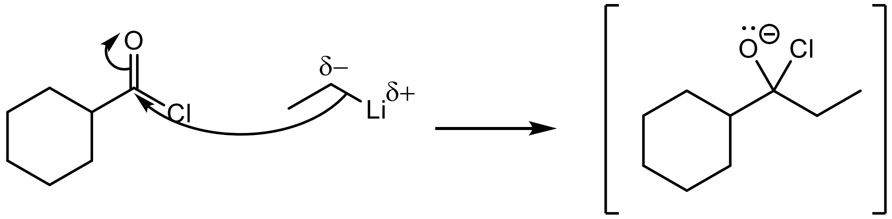


Ester



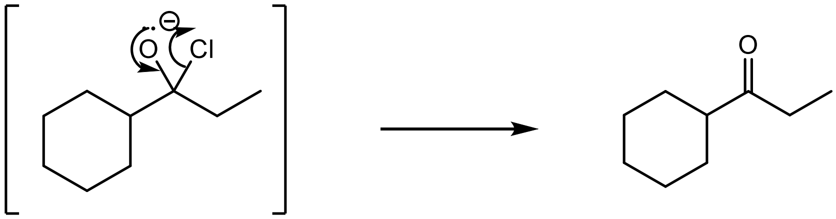
Mechanism:

Step 1: The first equivalent of the nucleophilic carbon of organolithium attacks the electrophilic carbonyl carbon which results in a tetrahedral intermediate that is unstable.



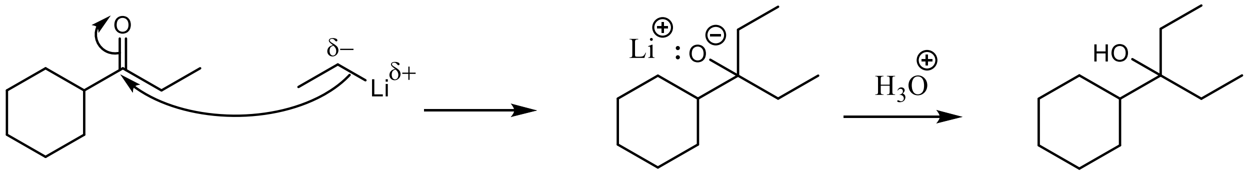
tetrahedral intermediate

Step 2: The tetrahedral intermediate is unstable as chloride ion (in the acid chloride) or an alkoxide ion (in the ester) are good leaving group. The lone pair on oxygen remakes the C-O double bond and in that process, ejects the chloride ion (in the acid chloride) or an alkoxide ion (in the ester), to give a ketone.

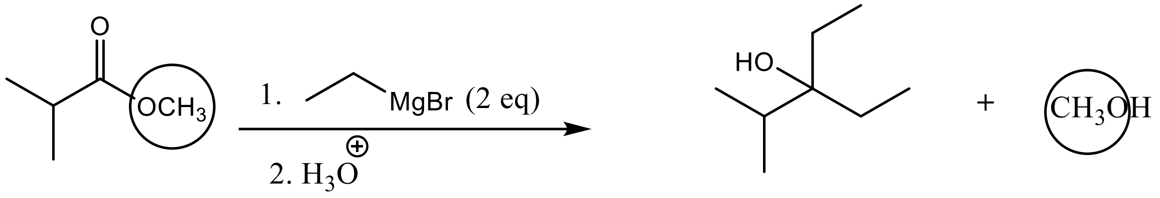


tetrahedral intermediate

Step 3: The ketone reacts with a second equivalent of the organolithium, forming the lithium salt of a tertiary alkoxide. Protonation gives a tertiary alcohol with one of its alkyl groups derived from the acid chloride or ester, and the other two derived from the organolithium.

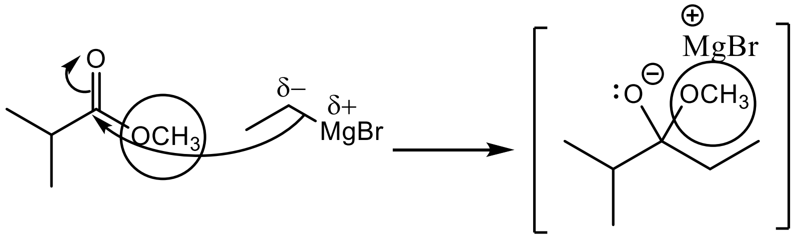


Esters undergo the same mechanism as acid chlorides. The only difference is that depending upon the OR group on the ester (it has been circled in the image below), there would be ROH formed after the aqueous workup.



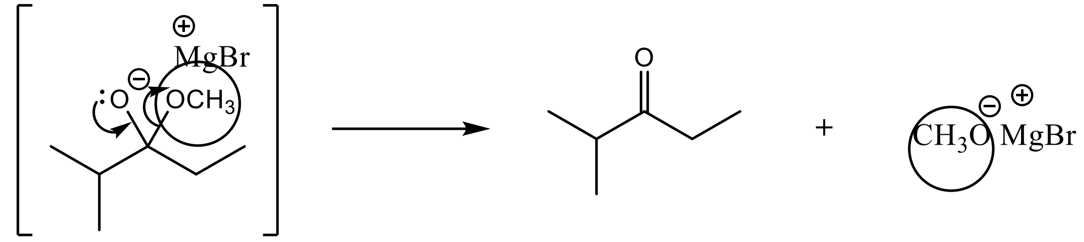
Mechanism:

Step 1: The first equivalent of the nucleophilic carbon of Grignard attacks the electrophilic carbonyl carbon which results in a tetrahedral intermediate that is unstable.



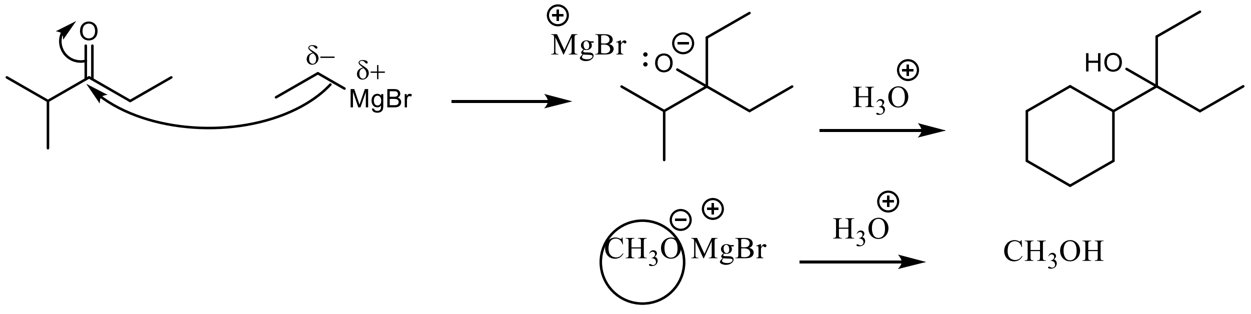
tetrahedral intermediate

Step 2: The tetrahedral intermediate is unstable and the lone pair on oxygen remakes the C-O double bond and in that process, ejects the methoxide ion (in the ester), to give a ketone.



tetrahedral intermediate

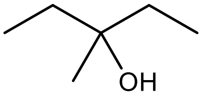
Step 3: The ketone reacts with a second equivalent of the Grignard reagent, forming the magnesium salt of salt of a tertiary alkoxide. Protonation gives a tertiary alcohol and methanol (CH3OH), which was formed by the protonation of the methoxide ion that was ejected in the second step of the mechanism.



Note:

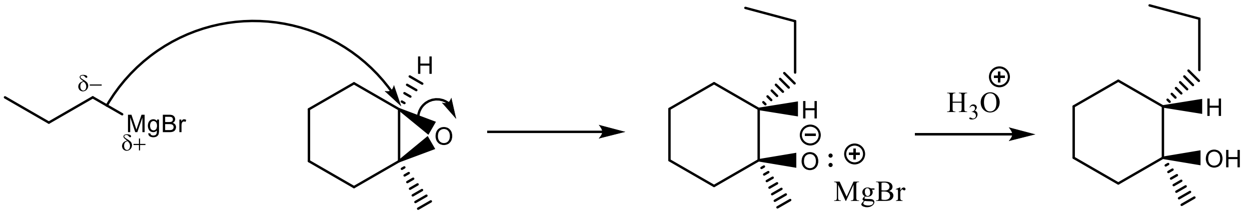
1. **The -OCH3 group of esters (circled above) does not appear in the tertiary alcohol.**
2. **The reaction cannot be stopped at the ketone, so for best results, use at least two equivalents of organometallic.**

Exercise 10.10: Synthesize the following alcohol starting from any ester and a Grignard reagent.



10.9 Reaction of Organometallics with epoxide.

Organometallics also react with the epoxides to give alcohol. The nature of alcohol will depend upon the structure of the epoxide.
Mechanism: The Grignard attacks the less substituted carbon from the opposite side of epoxide. This is followed by aqueous workup to produce the neutral alcohol.

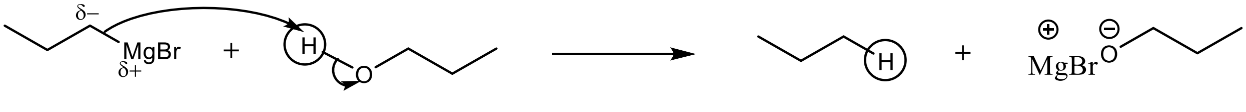


In the mechanism shown above, the Grignard is the nucleophile and since it is a strong base, the Grignard attacks the less substituted carbon (**BAL**, for base attacks less substituted side). It attacks from the opposite side of epoxide oxygen. Since the epoxide shown here is coming towards you (shown as a wedge), the nucleophile approaches from the bottom side (shown as dash line). This results in an inversion of stereochemistry at the carbon where the reaction takes place but not on the other carbon, where the -OH group appears. The product of this reaction is an alcohol with a new C-C bond formation.

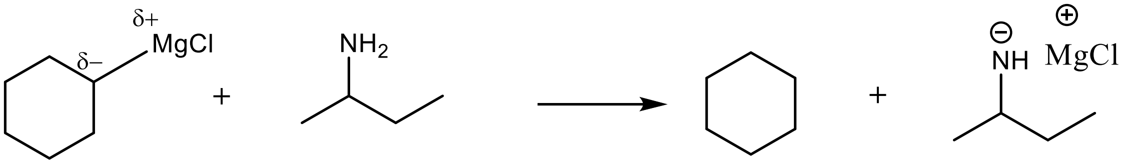
-OH group appears one carbon away from the new C-C bond. This happens ONLY when the organometallic reacts with an epoxide.
When the organometallic reacts with, any carbonyl containing compounds such as aldehyde, ketone, acid chloride and ester, the -OH group appears on where the new C-C bond is formed.

10.10 Side Reactions of Organometallic Reagents: Reduction of Alkyl Halides

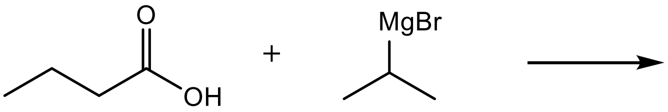
Organometallics are strong nucleophiles, but also very strong bases and can easily deprotonate an acidic proton. In other words, while synthesizing them, dry ether is used and protic solvents like water or alcohol should NOT be used, as these will destroy the organometallic.



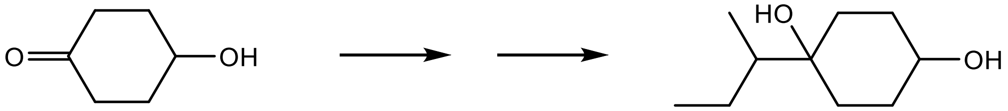
They are strong enough bases that they can deprotonate even the N-H bonds in amines.



Exercise 10.11: Draw the product(s) of the reaction shown below.

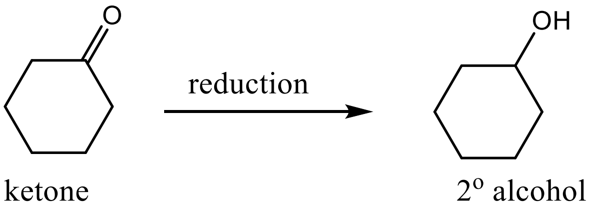


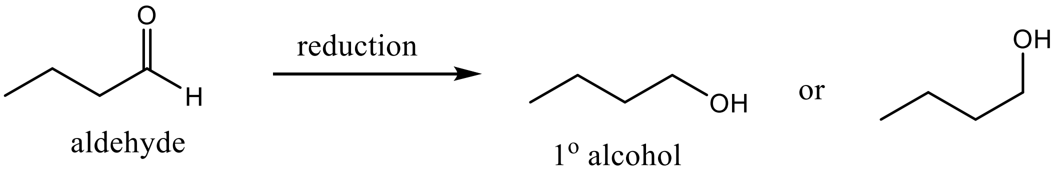
Exercise 10.12: A student wanted to perform the following synthesis, but the reaction failed. Explain what happened.



10.11 Reduction of the Carbonyl Group: Synthesis of 1° and 2° Alcohols

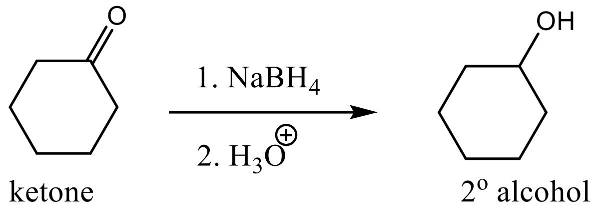
Aldehydes and ketones can easily be reduced by reducing agents to form either primary or secondary alcohol, respectively.

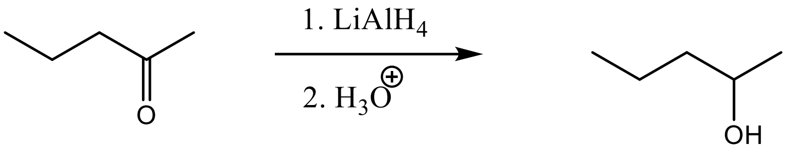




The overall is addition of two hydrogens across the C=O to yield an alcohol. Whether the alcohol is primary or secondary will depend upon the structure of carbonyl (if it is an aldehyde or a ketone).

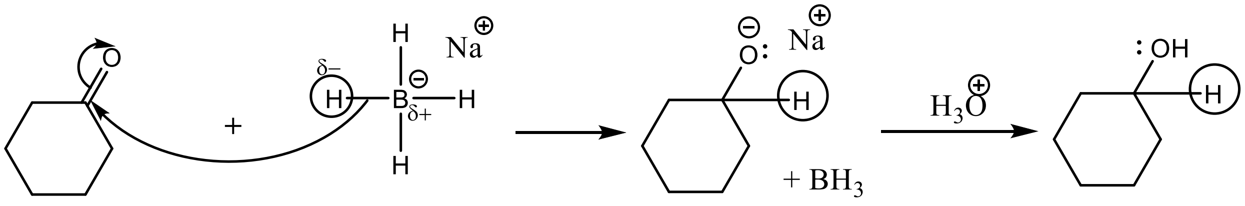
There are two types of reducing agents that perform this conversion. Sodium Boro Hydride ($NaBH_4$) or Lithium Aluminum Hydride ($LiAlH_4$). These both are reducing agents that react with aldehyde and ketone the same way.





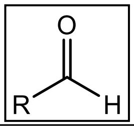
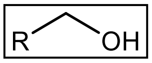
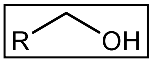
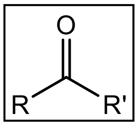
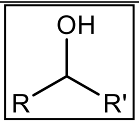
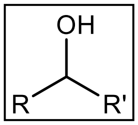
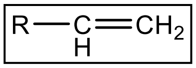
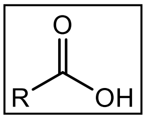
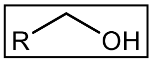
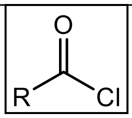
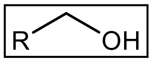
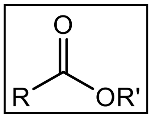
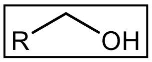
These complex hydrides (rather than sodium hydride or lithium hydride) are better nucleophiles. The hydrogen bonded to the boron (in $NaBH_4$) or lithium (in $LiAlH_4$) is more electronegative than the boron or aluminum, hence very nucleophilic.

Mechanism: The nucleophilic hydride attacks the electrophilic carbonyl carbon. To offset the formation of a new C-H bond, the pi bond breaks and electrons move to the more electronegative oxygen. This results in a minus charge on the oxygen and the formation of alkoxide ion. Addition of a dilute acid protonates the alkoxide to give the neutral alcohol.

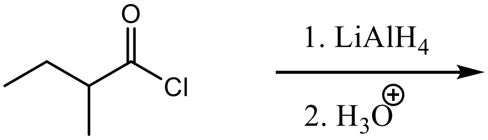


The mechanism of $NaBH_4$ and $LiAlH_4$ reduction are identical for aldehyde and ketone. However, other $NaBH_4$ is less reactive and more selective. It reduces only aldehyde and ketone. $LiAlH_4$ is more reactive and reduces other functional groups, such as carboxylic acid, acid chloride and esters to yield **primary alcohol**. A summary of reactions of functionals groups that react or do not react with the two reducing agents is shown in the table below.

10.12 Summary: Reactions of $LiAlH_4$ and $NaBH_4$

Functional Group	**Structure**	**$NaBH_4$**	**$LiAlH_4$**
Aldehyde			
Ketone			
Alkene	 $R-\underset{H}{C}=CH_2$	**NR**	**NR**
Carboxylic acid		**NR**	 **primary alcohol**
Acid Chloride		**NR**	 **primary alcohol**
Ester		**NR**	 **primary alcohol**

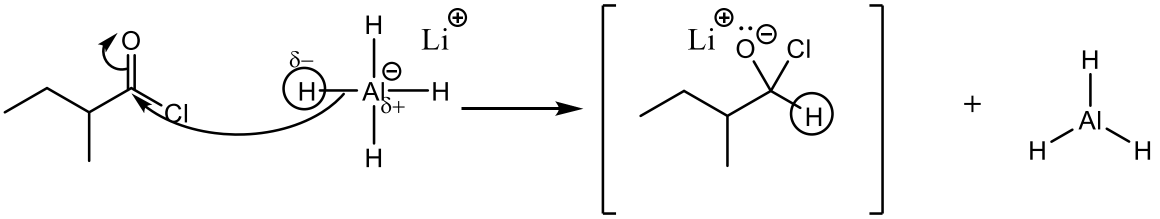
Solved problem 10.3: Draw the organic product(s) of the reaction shown below and a step by step mechanism that will explain its formation.



Approach: This is an acid chloride reacting with $LiAlH_4$, which is a stronger reducing agent than $NaBH_4$. The product of the reaction should be a primary alcohol. If we explore the mechanism, we can see how that is formed.

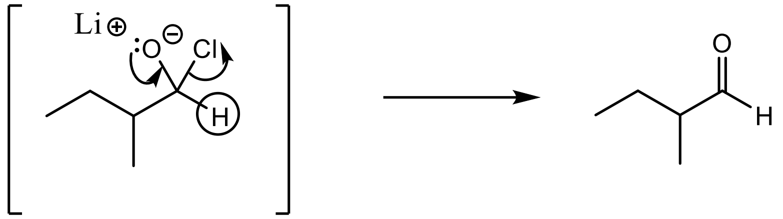
Mechanism:

Step 1: The first equivalent of the nucleophilic hydrogen of reducing agent $LiAlH_4$ attacks the electrophilic carbonyl carbon which results in a tetrahedral intermediate that is unstable.



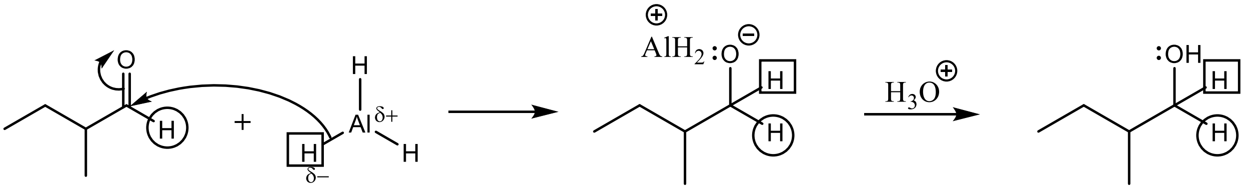
tetrahedral intermediate

Step 2: The tetrahedral intermediate is unstable as chloride ion (in the acid chloride) or an alkoxide ion (in the ester) are good leaving group. The lone pair on oxygen remakes the C-O double bond and in that process, ejects the chloride ion (in the acid chloride) or an alkoxide ion (in the ester), to yield an aldehyde.



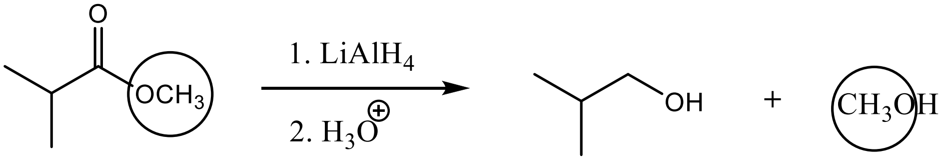
tetrahedral intermediate

Step 3: The aldehyde reacts with AlH_3 formed in step 1, forming the lithium salt of a primary alkoxide. Protonation with acid gives primary alcohol.



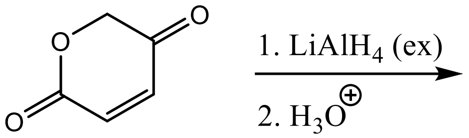
Note: The source of circled and boxed hydrogen on the final product is the reducing agent $LiAlH_4$.

Esters undergo the same mechanism as acid chlorides. The only difference is that depending upon the OR group on the ester (it has been circled in the image below), there would be ROH formed after the aqueous workup.

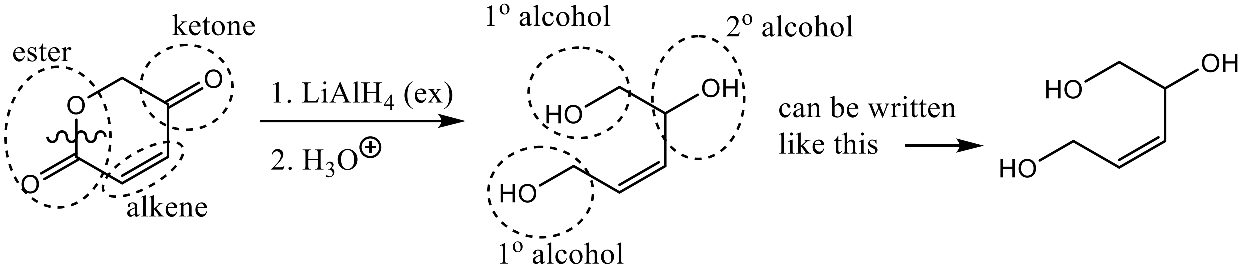


The source of the two hydrogens on the primary carbon bearing the -OH group is from the reducing agent, $LiAlH_4$.

Solved problem 10.4: Draw the final organic product(s) of the reaction shown below.

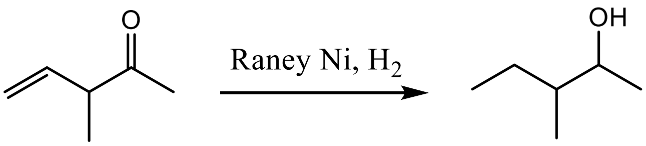


Approach: The first thing to identify is the functional group and the nature of the reducing agent. There are three functional groups present here. There is an ester, alkene, and a ketone. Keeping mechanism in mind, the single bond of C-O of ester breaks (shown as ∿∿∿ in the figure below). The carbonyl carbon of ester becomes a primary alcohol; however, the carbonyl carbon of the ketone will become the secondary alcohol. The alkene is untouched by this reducing agent.

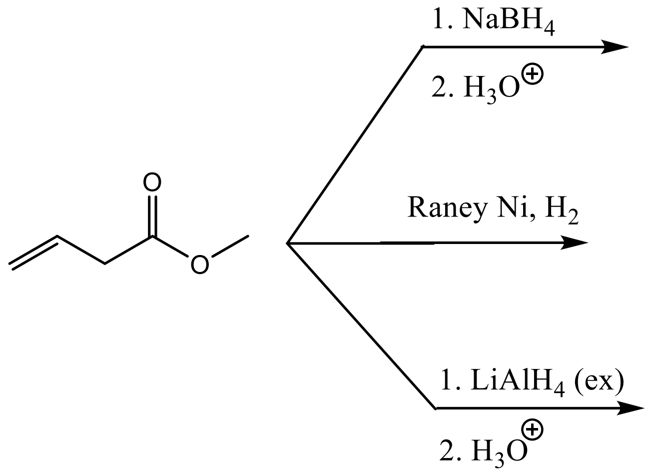


10.13 Reduction of a Carbonyl Group and Alkene using Raney Nickle.

A reducing agent that reduces both C=O of aldehydes and ketone and C=C of alkenes is hydrogen gas in presence of a specialized catalyst called Raney Nickel.

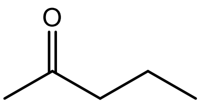


Exercise 10.13: Draw the organic product(s) of the reaction when the given compound reacts with each of these reducing agents.

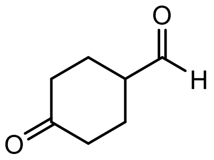


Exercise 10.14: Draw the organic product(s) of the reaction when the given compound reacts with NaBH4 followed by aqueous workup.

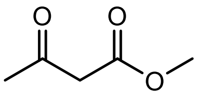
a.



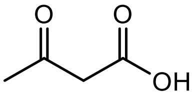
b.



c.

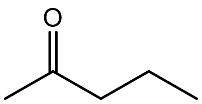


d.

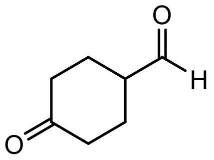


Exercise 10.15: Draw the organic product(s) of the reaction when the given compound reacts with LiAlH4 followed by aqueous workup.

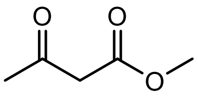
a.



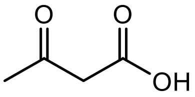
b.



c.



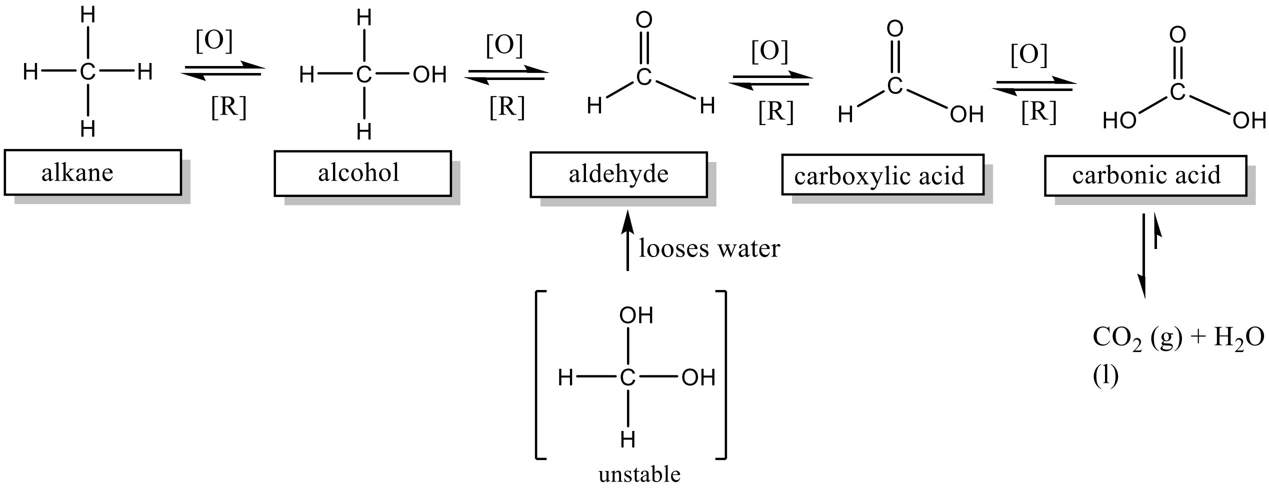
d.



Chapter 11: Reactions of Alcohol

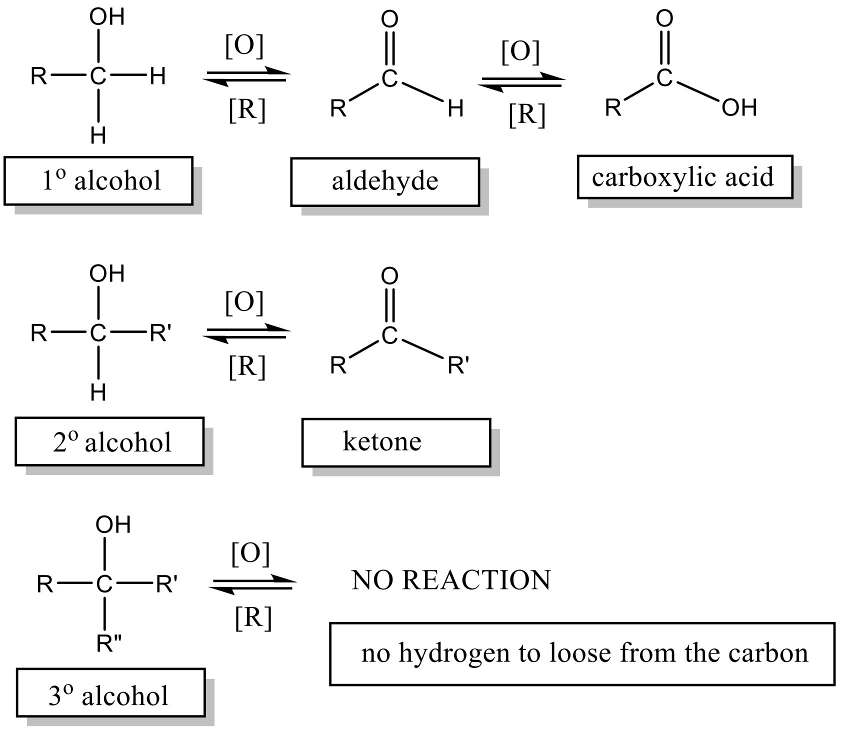
11.1 Oxidation of Alcohols

In Chapter 8 we saw that as the number of C-O bond increase, a molecule is more **oxidized**. As the number of C-H bond increase a molecule is **reduced**.

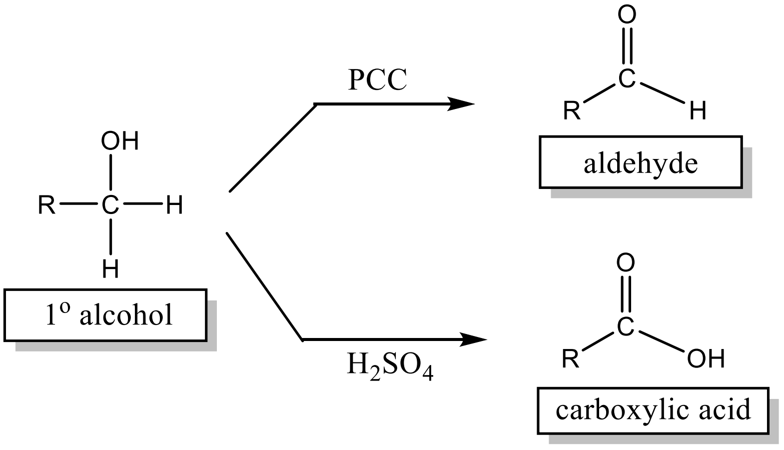


In the scheme above, as we increase the number of C-O bonds, oxidation is taking place (from left to right). Based on this flow diagram, depending upon the nature of alcohol, different functional groups are formed as a product.

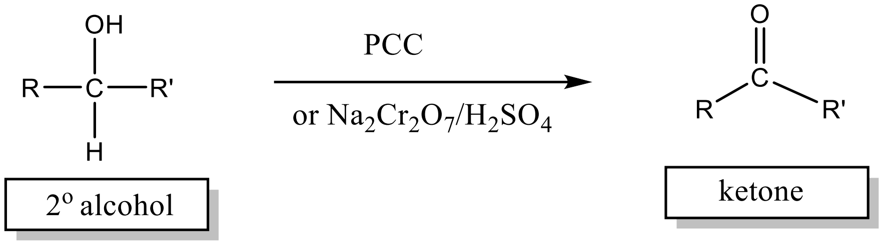
Oxidation results in the removal of two hydrogens, one from carbon and one from oxygen.



Oxidation of primary alcohol: Primary alcohol can be oxidized to two possible functional groups; aldehyde or ketone. The milder oxidizing agent is Pyridinium Chloro Chromate (**PCC**) stops the oxidation at the aldehyde and does not allow the aldehyde to get further oxidized. Chromic acid (H_2CrO_4) is a stronger oxidizing agent and oxidizes the primary alcohol all the way to carboxylic acid. Since chromic acid is toxic, it is generated in situ (in the reaction pot) by using **$Na_2Cr_2O_7$** and **H_2SO_4**.



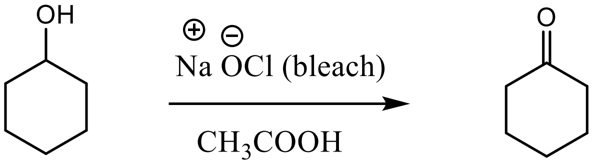
Oxidation of secondary alcohol: Secondary alcohols can be oxidized to give ketone.



Oxidation of tertiary alcohol: Tertiary alcohols do not undergo oxidation as the tertiary carbon has no hydrogen that can be oxidized.

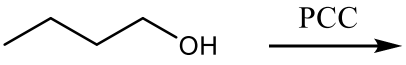
11.2 Additional Methods for Oxidizing Alcohols

The oxidizing agents containing chromium produce by-products that produce chromium salts that must be collected as hazardous waste. These are toxic and are known to cause cancer. Use of simple household bleach (NaOCl) can be used as an oxidizing agent. This is a known “greener” oxidizing agent and works very with **secondary alcohol** to give **ketone**. This mechanism will be discussed in the laboratory course.

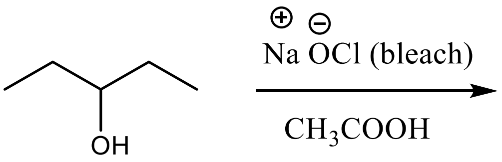


Exercise 11.1: Draw the organic product(s) of the reactions shown below.

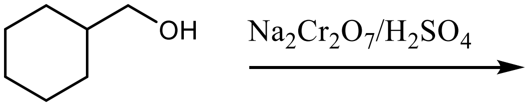
a.



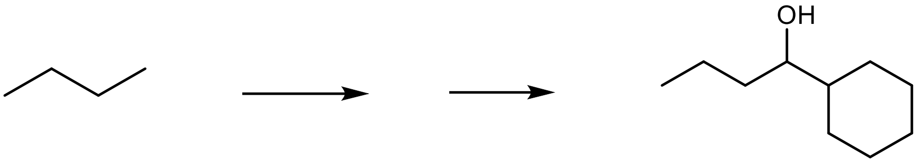
b.



c.

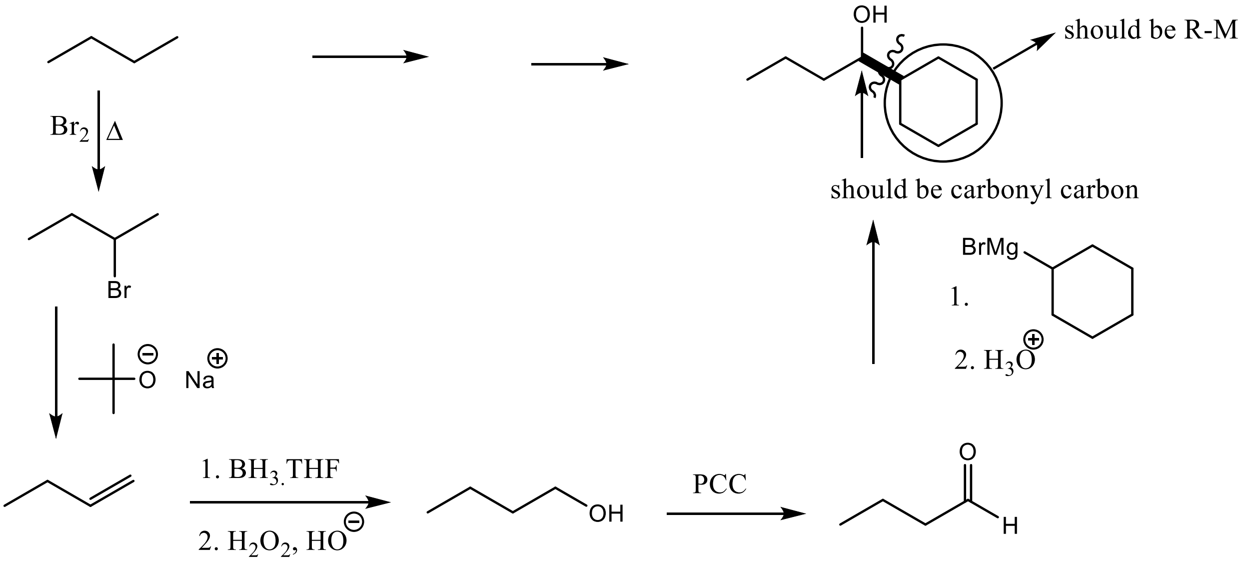


Solved problem 11.1: Show how you would synthesize the following compound, beginning with butane and any necessary additional reagents.



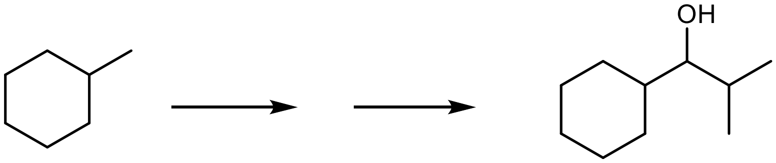
Approach: As always, we begin by asking the following questions during synthesis:

j. Has the overall length of the compound changed? (YES, in this case!)
k. If a new C-C bond is formed highlight the bond and if alcohol is the product, the carbon-containing -OH group must be the carbonyl carbon that reacts with an organometallic.
l. What **functional group** is present in the *reactant*?
m. What **functional group** is present in the *product*?
n. What is the last step that will give you the final product?

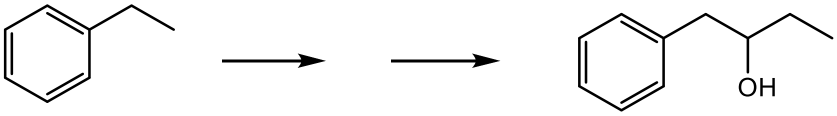


Exercise 11.2: Using any reagents, how will you perform the following synthesis.

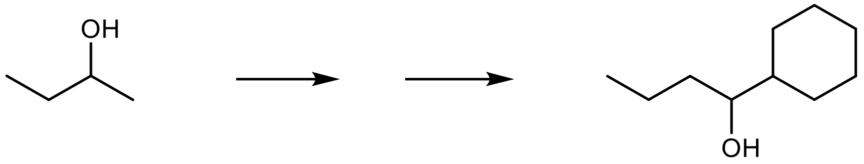
a.



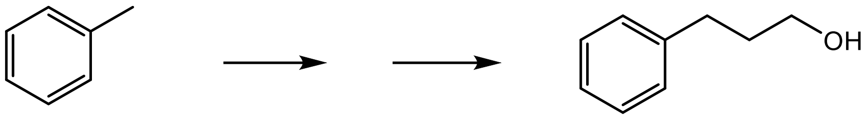
b.



c.

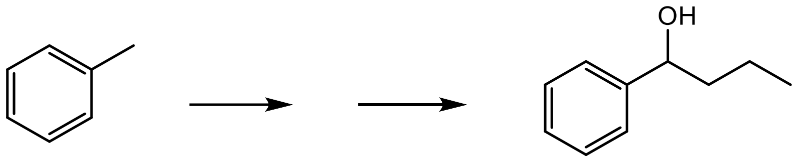


d.



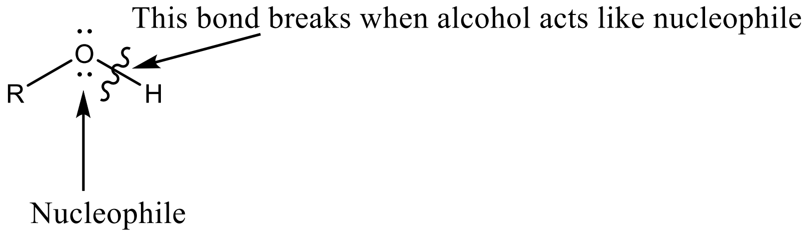
hint: use epoxide

e.

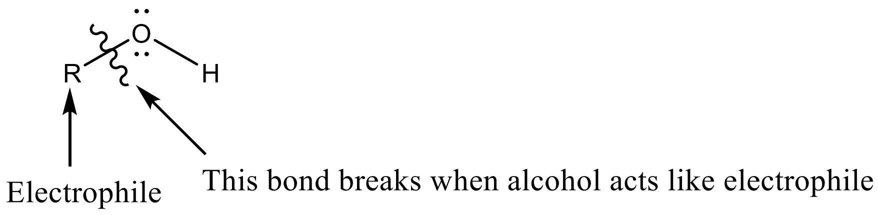


11.3 Alcohols as Nucleophiles and Electrophiles; Formation of Tosylates

We have already seen alcohol as a weak nucleophile during S_N1, or a strong nucleophile in S_N2 reactions. Pay attention to the bond that breaks during this. The O-H bond breaks when the alcohol acts like a nucleophile.

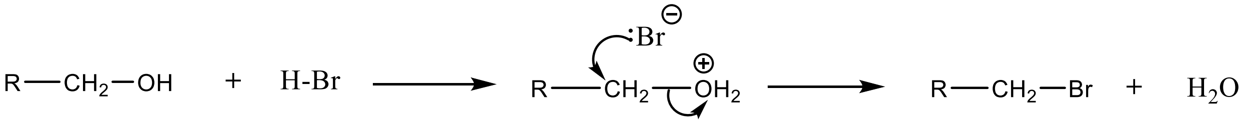


When the alcohol acts like an electrophile, the C-O bond breaks.

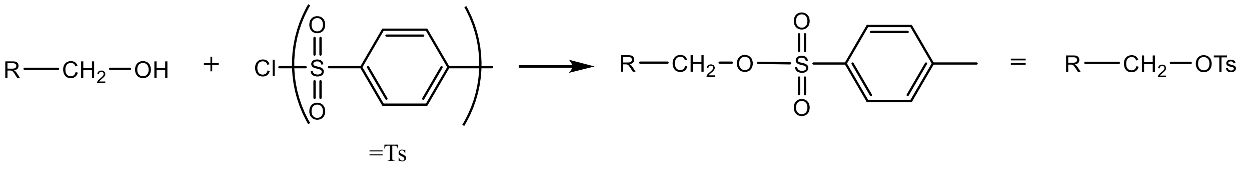


Since -OH is a poor leaving group, there are two ways R-OH bond breaks:

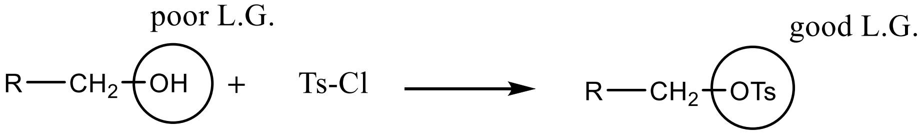
a. This takes place only when the alcohol is protonated



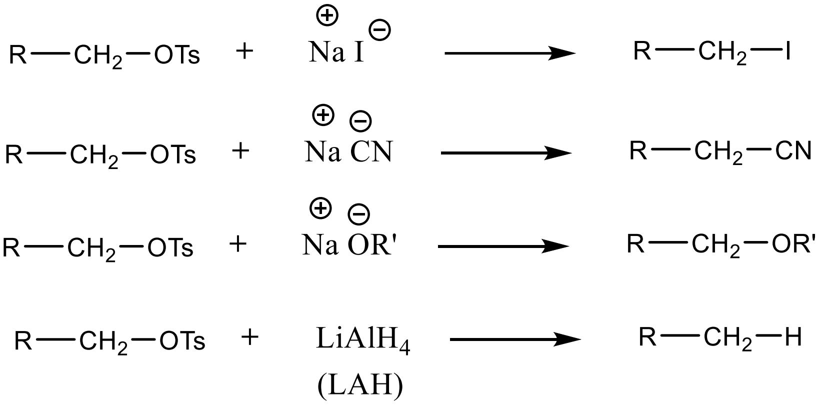
b. when the alcohol is made into a good leaving group using tosyl chloride (Ts-Cl)



In other words, by reacting the alcohol with Ts-Cl, you are converting a poor leaving group into a good leaving group.



-OTs group behaves like a halide and undergoes the typical SN2 reactions (with primary carbon) like alkyl halides.



$$R—CH_2—OTs + \overset{\oplus}{Na}\,\overset{\ominus}{I} \longrightarrow R—CH_2—I$$

$$R—CH_2—OTs + \overset{\oplus}{Na}\,\overset{\ominus}{CN} \longrightarrow R—CH_2—CN$$

$$R—CH_2—OTs + \overset{\oplus}{Na}\,\overset{\ominus}{OR'} \longrightarrow R—CH_2—OR'$$

$$R—CH_2—OTs + \underset{(LAH)}{LiAlH_4} \longrightarrow R—CH_2—H$$

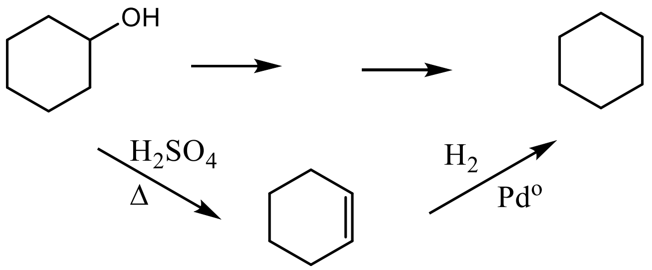
One useful reaction of tosylates is that it reacts with reducing agent such as Lithium Aluminum chloride ($LiAlH_4$) and gives an alkane. This results in a reduction of tosylates.

11.4 Reduction of Alcohols

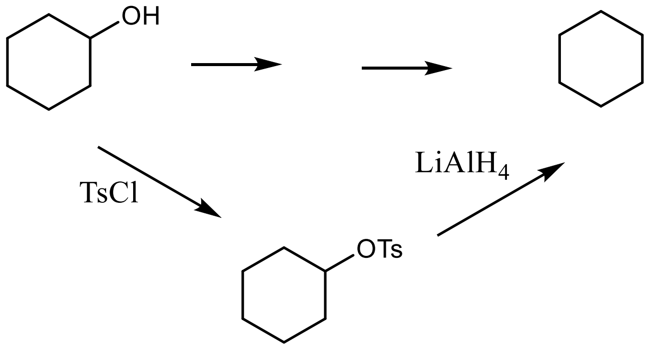
One useful reaction of tosylates is that it reacts with reducing agent such as Lithium Aluminum chloride ($LiAlH_4$) and gives an alkane.

$$R—CH_2—OTs \xrightarrow{LiAlH_4} R—CH_2—H$$

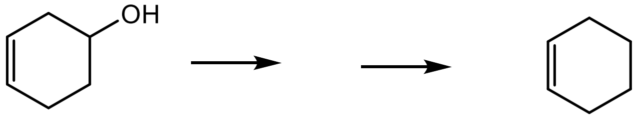
To convert cyclohexanol to cyclohexane, one can dehydrate the alcohol to alkene and then reduce the alkene to alkane.



Another route to the same problem is to convert the cyclohexanol to tosylate and then reduce the tosylate to alkane.

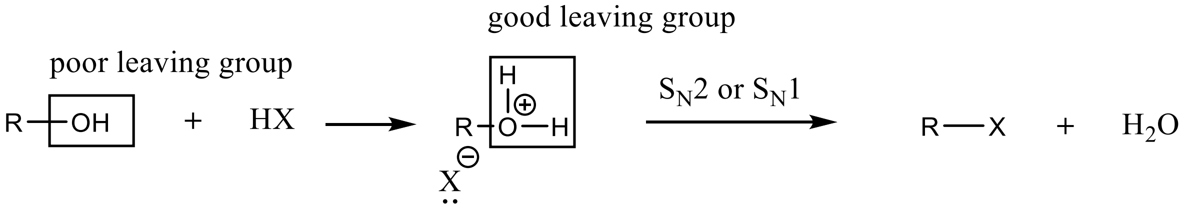


Exercise 11.3: Perform the following conversion. Of the above two methods, which one would work better. Why?



11.5 Reactions of Alcohols with Halo acids (HX)

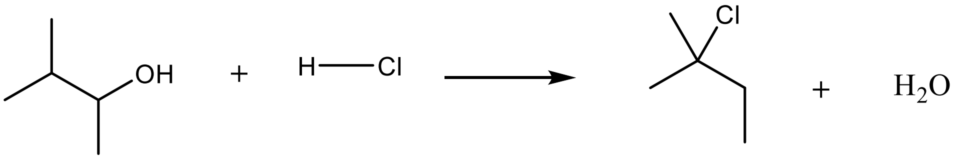
When alcohol react with halo acids (HX), the alcohol gets protonated. This converts the hydroxyl group ($\mathrm{HO}^{\ominus}$) from a poor leaving group to a good leaving group (H_2O). Once the alcohol is protonated, all the usual substitution reactions are feasible, depending on the structure (1°, 2°, 3°) of the alcohol. Since halides are poor bases (they are conjugate base of strong acids), only substitution reactions take place, not elimination reactions.



with 1^{o} ROH, the reaction is S_N2, with 2^{o} and 3^{o} ROH, the reaction is S_N1

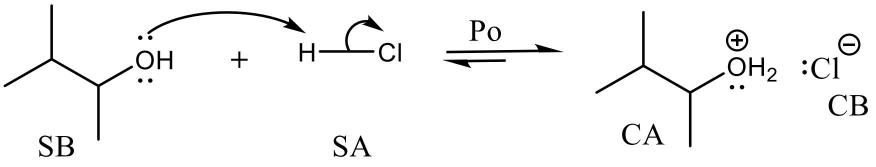
11.6 Reaction of a Tertiary and Secondary Alcohol with HBr (S_N1)

When 2° and 3° alcohol undergo this reaction with halo acids, the reaction goes vis S_N1 mechanism (formation of carbocation is the rds).

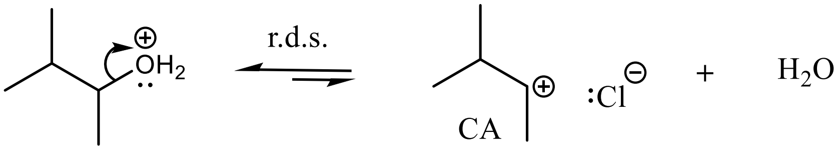


Mechanism:

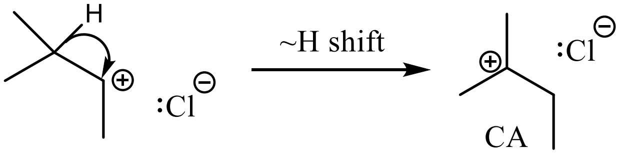
Step 1: Acid-base reaction converts the alcohol -OH into a good leaving group.



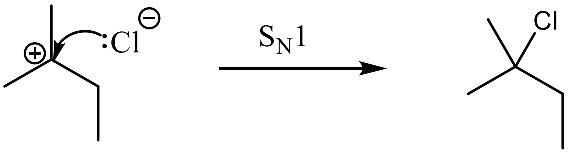
Step 2: Formation of carbocation is the rds.



Step 3: Carbocation undergoes rearrangement to give a more stable 3° carbocation.

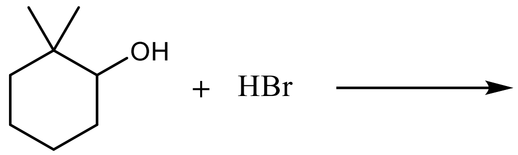


Step 4:

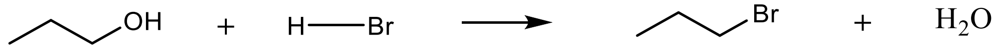


Exercise 11.4: When *trans*-2-methylcyclohexanol reacts with the HBr, the major product is 1-chloro-1-methylcyclohexane. Propose a mechanism to explain the formation of this product.

Exercise 11.5: Draw the major organic product of the S_N1 reaction between 2,2-dimethylcyclohexanol and HBr.

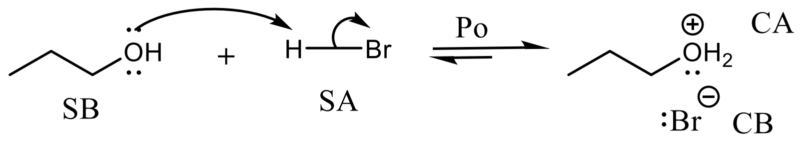


11.7 Reaction of a Primary Alcohol with HBr (SN2)

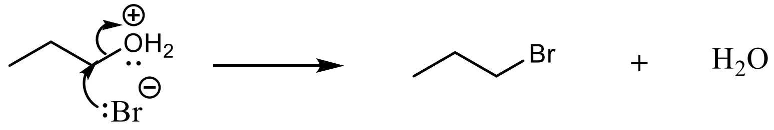


Mechanism:

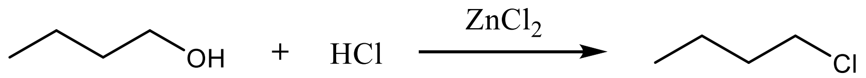
Step 1: Acid-base reaction converts the alcohol -OH into a good leaving group.



Step 2: Bromide ion undergoes an S_N2 reaction (for primary alcohol only) and displaces water.



Reactions of 1° alcohol with HCl is very slow and to promote the reaction to go fast, a Lewis acid catalyst like $ZnCl_2$ is often used. The combination of HCl and $ZnCl_2$ is called Lucas reagent. In lab, Lucas reagent is often used as a test to distinguish between 1°, 2° and 3° alcohol.

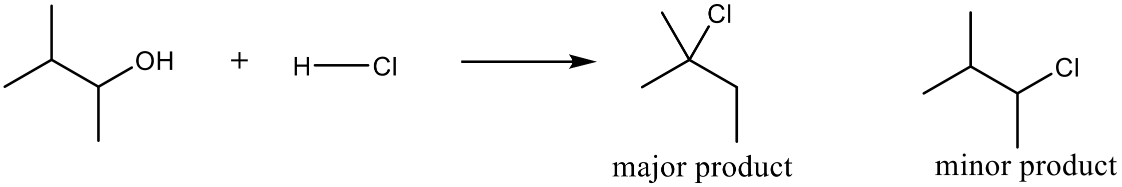


While 1° alcohol with Lucas reagent undergoes the reaction via S_N2 mechanism, 2° and 3° alcohol with Lucas reagent undergoes the reaction via S_N1 mechanism.

Alcohol classification	Reaction time with Lucas reagent
1° alcohol	Greater than 6 minutes
2° alcohol	1-5 minutes
3° alcohol	Less than 1 minute

Limitations of Alcohol reaction with halo acids (HX).

1. The reaction of 1^o alcohol with HCl is very slow and often poor yields of the alkyl halide product is formed.
2. Halo acids (HX) may also react with additional functional groups present in the molecule. E.g., if alkene or alkyne is present along with the alcohol, the halo acid (HX) will also react with these functional groups.
3. Carbocation formation during SN1 mechanism of a 2^o alcohol may result in a rearrangement.



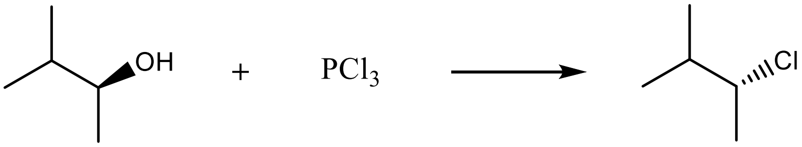
What if you wanted to synthesize 2-chloro-3-methylbutane as the major product? Then we cannot use the halo acid (HCl) in above example.

Use of phosphorus halide (PX_3 or PX_5) takes of care of these above listed limitations.

11.8 Reactions of Alcohols with Phosphorus Halides (A better pathway?)

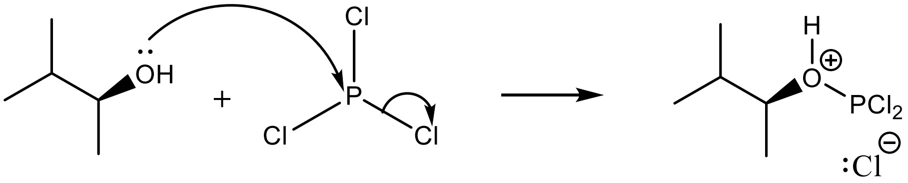
PX_3: PCl_3 or PBr_3
PX_5: PCl_5 or PBr_5
P/I_2

PI_3 is unstable and is generated by adding elemental phosphorus to iodine.
The above three reagents convert a 1^o and 2^o alcohol (**but not 3^o alcohol**) to alkyl halide successfully, without any rearrangements.

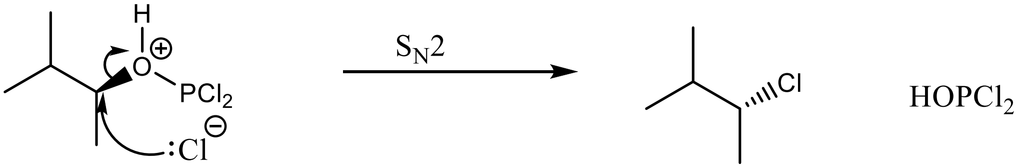


Mechanism: The mechanism of the reaction of alcohols with phosphorus trihalides explains why rearrangements are not observed and why phosphorus halides work poorly with tertiary alcohols. The mechanism is shown here using PCl_3 as the reagent; and PBr_3 and P/I_2 react in a similar manner.

Step 1: The phosphorus atom of PBr_3 is a strong electrophile and the nucleophilic oxygen of the alcohol attacks the phosphorus and ejects one chlorine atom as a leaving group.



Step 2: The chloride ion displaces the leaving group in an S_N2 manner, to form the alkyl halide with the opposite stereochemistry of the alcohol.

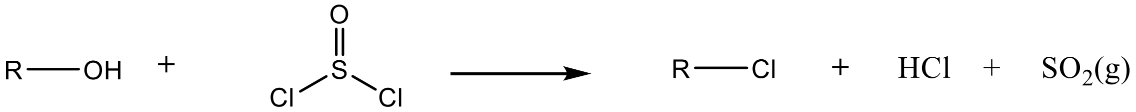


Exercise 11.6: Give the structures of the products you would expect when each alcohol reacts with (1) HBr; (2) PBr_3 (3) P/I_2. If no reaction takes place, write NR.

a. butan-1-ol **b.** 2-methylbutan-2-ol **c.** *cis*-3-methylcyclopentanol

11.9 Reactions of Alcohols with Thionyl Chloride ($SOCl_2$)

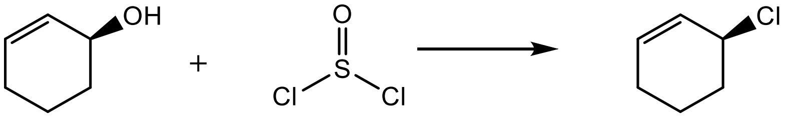
Thionyl chloride ($SOCl_2$) is often the best reagent for converting an alcohol to an alkyl chloride.



$$R{-}OH + SOCl_2 \longrightarrow R{-}Cl + HCl + SO_2(g)$$

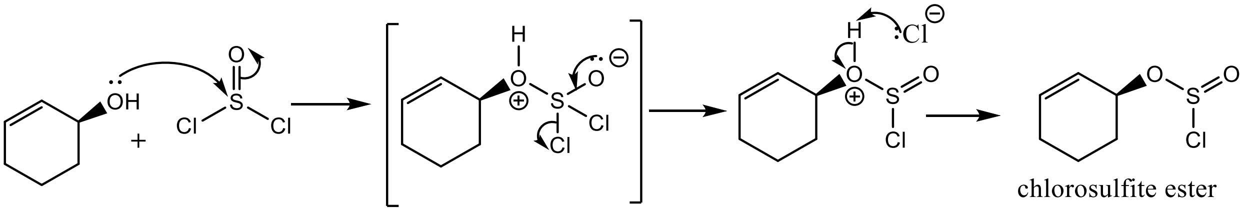
The by-products are SO_2 (gas) and HCl and the alkyl halide as the organic product can easily be isolated. There is no limitation on the nature of alcohol. All types of alcohol, 1°, 2° and 3° alcohol can be easily converted to alkyl chloride.

Reaction of alcohol with thionyl chloride undergoes via retention of stereochemistry.

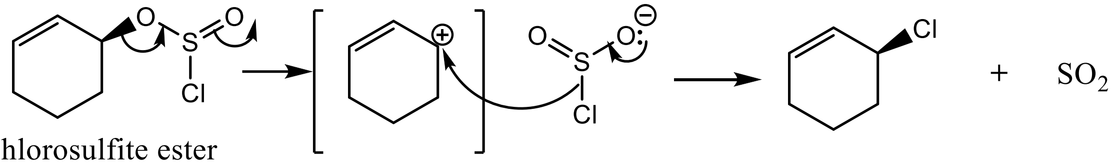


Mechanism:

Step 1: The electrons of the hydroxyl oxygen atom attack the electrophilic sulfur atom of thionyl chloride. A chloride ion is expelled, and a proton is lost to give a chlorosulfite ester.



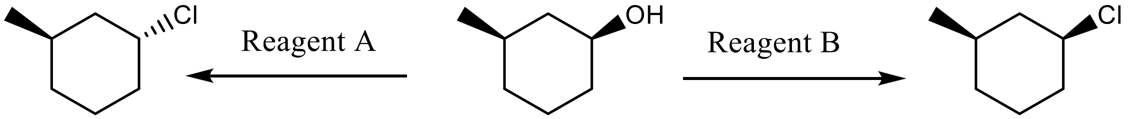
Step 2: The chlorosulfite ester forms a carbocation (when R = 2° or 3°), and the sulfur atom quickly delivers chloride to the carbocation. When R is primary, chloride probably bonds to carbon while the C-O bond is breaking.



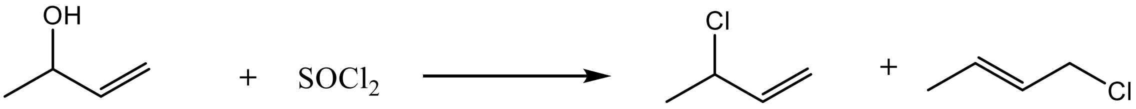
chlorosulfite ester

Once mechanism is explored, it is evident that the retention of stereochemistry takes place as the nucleophile (chloride ion) is delivered to the carbocation by the same side as the leaving group.

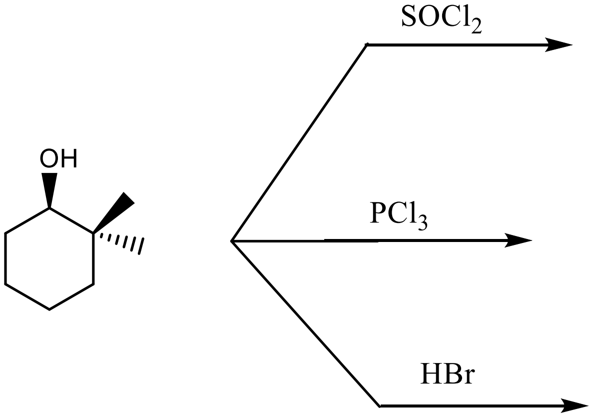
Exercise 11.7: What is reagent A and B that will perform the following transformation?



Exercise 11.7: During the reaction of given alcohol, two products are formed. Explain how.



Exercise 11.8: Draw the major organic product(s) of the reaction of given alcohol with each of these reagents, Pay attention to stereochemistry.



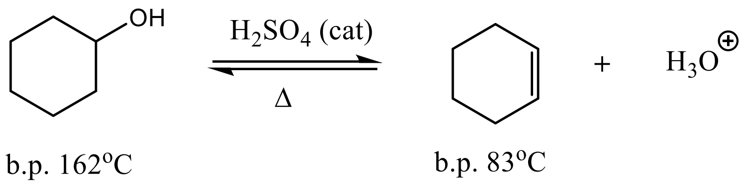
(4 stereoisomers)

A summary of reagents for alcohol reactions depending upon classification is shown below:

R-OH	R-Cl	R-Br	R-I
1^o	PCl_3, PCl_5, $SOCl_2$	PBr_3, PBr_5	P/I_2
2^o	PCl_3, PCl_5, $SOCl_2$	PBr_3, PBr_5	P/I_2
3^o	$SOCl_2$	HBr	HI

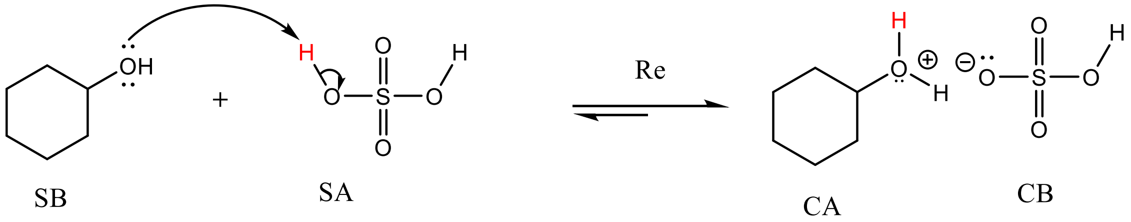
11.10 Unimolecular Dehydration Reactions of Alcohols (A Review)

In chapter 7, we saw unimolecular dehydration of alcohol. When alcohols are heated in presence of catalytic amount of acid like H_2SO_4 or H_3PO_4, a dehydration reaction takes place, resulting in a loss of water from alcohol to form an alkene. When cyclohexanol undergoes a dehydration reaction when it is heated in presence of an acid catalyst such as H_2SO_4 or H_3PO_4, cycloalkene is formed.

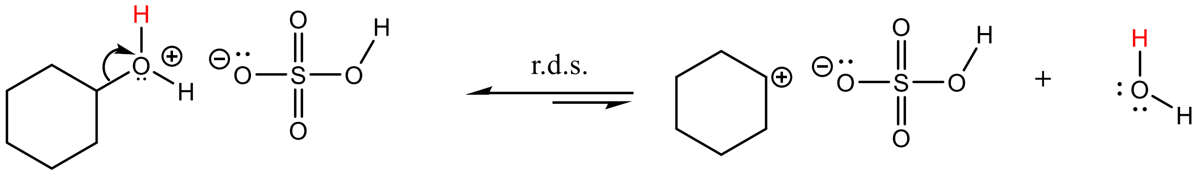


Mechanism:

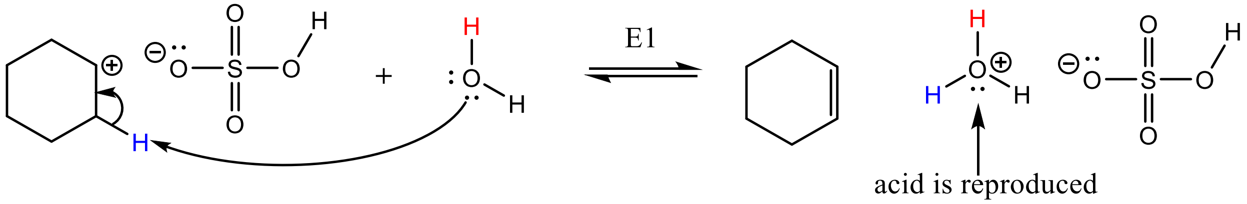
Step 1: Acid-Base reaction



Step 2: Loss of water from protonated alcohol. This is the slowest rate determining step of the reaction as a reactive intermediate (carbocation) is formed.



Step 3: Loss of a proton from the carbon adjacent to the carbocation is the E1 mechanism. The loss of the proton takes place by H_2O produced in the second step and **<u>not</u>** $HSO_4^{\ominus}$. Between the two, $HSO_4^{\ominus}$ is a weaker base as its electrons are stabilized via resonance.



Reactivity of alcohols: The formation of carbocation is the rate determining step. Due to which the more stable the carbocation, the lower the Ea of its formation and faster the reaction. Therefore, the reactivity of alcohols is as follows:

3^o ROH > 2^o ROH > 1^o ROH >
most reactive least reactive

When primary alcohol undergoes this reaction, the temperature at which they dehydrate is very high (180°C, as it requires a higher activation energy to form the carbocation). At a lower temperature of 140°C, a bimolecular dehydration of alcohol starts taking place to give an ether as a product instead of an alkene.

$$CH_3CH_2OH \xrightarrow[180^oC]{H_2SO_4\ (cat)} \underset{\text{ethene}}{H_2C{=}CH_2} \quad \text{unimolecular dehydration}$$

$$2\ CH_3CH_2OH \xrightarrow[140^oC]{H_2SO_4\ (cat)} \underset{\text{diethylether}}{CH_3CH_2OCH_2CH_3} \quad \text{bimolecular dehydration}$$

In the next section, we will explore the bimolecular dehydration.

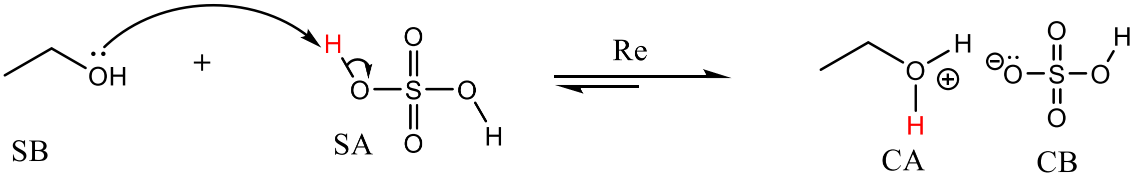
11.11 Bimolecular Dehydration of an Alcohol: Industrial Synthesis of Symmetric ethers

In the previous section, we saw unimolecular dehydration. During the industrial synthesis of diethylether, ethanol (CH_3CH_2OH) is heated at 140°C with H_2SO_4. Overall water is lost form two molecules of ethanol. During bimolecular dehydration, a protonated primary alcohol is attacked by another molecule of the alcohol and undergo a SN2 displacement reaction.

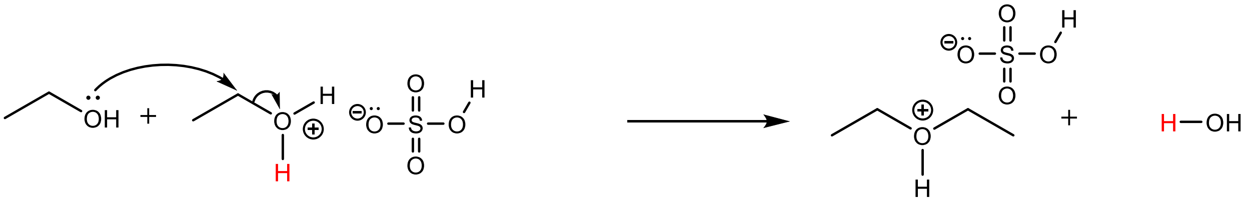
$$CH_3CH_2O\boxed{H \quad + \quad HO}CH_2CH_3 \xrightarrow[140^oC]{H_2SO_4\ (cat)} CH_3CH_2OCH_2CH_3 \quad + \quad H_2O$$

Mechanism:

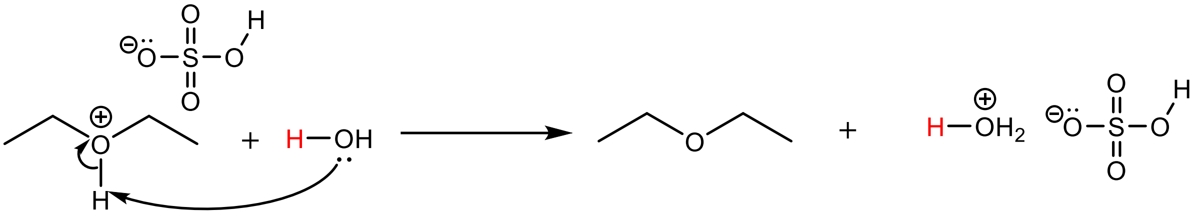
Step 1: Acid-base mechanism.



Step 2: SN2 reaction of another molecule of ethanol with the protonated alcohol.



Step 3: An acid-base reaction is again needed to produce the uncharged ether. The loss of the proton takes place by H_2O produced in the second step and **<u>not</u>** $HSO_4^{\ominus}$ (as it is a weaker base as its electrons are stabilized via resonance).



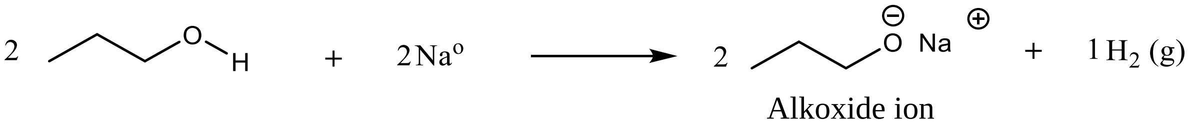
Since the acid is regenerated in form of $H_3O^{\oplus}$ in the last step, this is also an acid-catalyzed reaction.

Exercise 11.9: Explain why the acid-catalyzed condensation is a poor method for the synthesis of an unsymmetrical ether such as ethyl propyl ether, $CH_3CH_2OCH_2CH_2CH_3$.

Exercise 11.10: Draw the product of the reaction when propan-1-ol undergoes a bimolecular dehydration reaction in presence of catalytic amount of H_2SO_4.

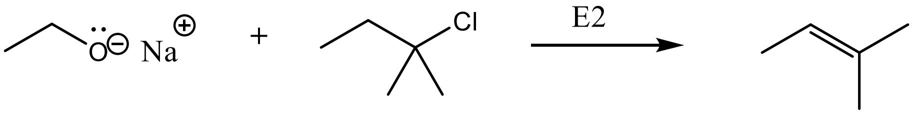
11.12 Reactions of Alkoxides: Williamson Ether Synthesis

In Section 10.4, we learned to remove the hydroxyl proton from an alcohol by reduction with an alkali metal such as sodium or potassium. This reaction generates a sodium or potassium salt of an **alkoxide ion** and hydrogen gas.



In chapter 6, we saw the alkoxide ion is a strong nucleophile as well as a strong base. Unlike the alcohol itself, the alkoxide ion reacts with primary alkyl halides and tosylates to form **ethers.** This general reaction, called the **Williamson ether synthesis,** is a S_N2 displacement reaction. Bothe symmetric and asymmetric ethers can be synthesized using Williamson ether synthesis.

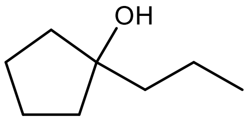
The alkyl halide (or tosylate) must be primary so that a back-side attack is not hindered. When the alkyl halide is not primary, elimination usually results.



11.13 Problem-Solving Strategy: Multistep Synthesis

Convergent synthesis: When a molecule is asked to be synthesized from two different starting materials.

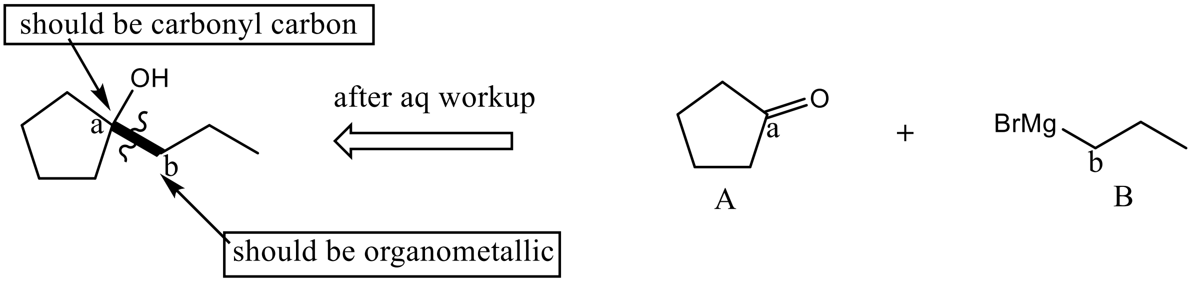
Solved problem 11.2: Show how you would synthesize the alcohol given below starting from cyclopentanol and any other alcohol.



Approach: As always, we begin by asking the following questions during synthesis:

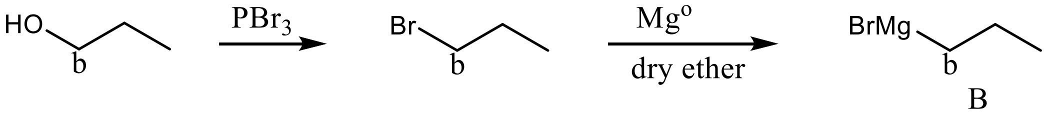
a. Has the overall length of the compound changed? (YES, in this case!)
b. If new C-C bond is formed highlight the bond and if alcohol is the product, the carbon containing the -OH group must be the carbonyl carbon that reacts with an organometallic.
c. What **functional group** is present on the *reactant*?
d. What **functional group** is present on the *product*?

The most important observation is that a new C-C bond is formed for which an organometallic reagent (like Grignard) must be used. The -OH group appears on the ring (carbon a) so the carbon where the -OH group must be the carbonyl carbon (ketone). In the flow diagram below, we have recognized the last step which gives the final product.

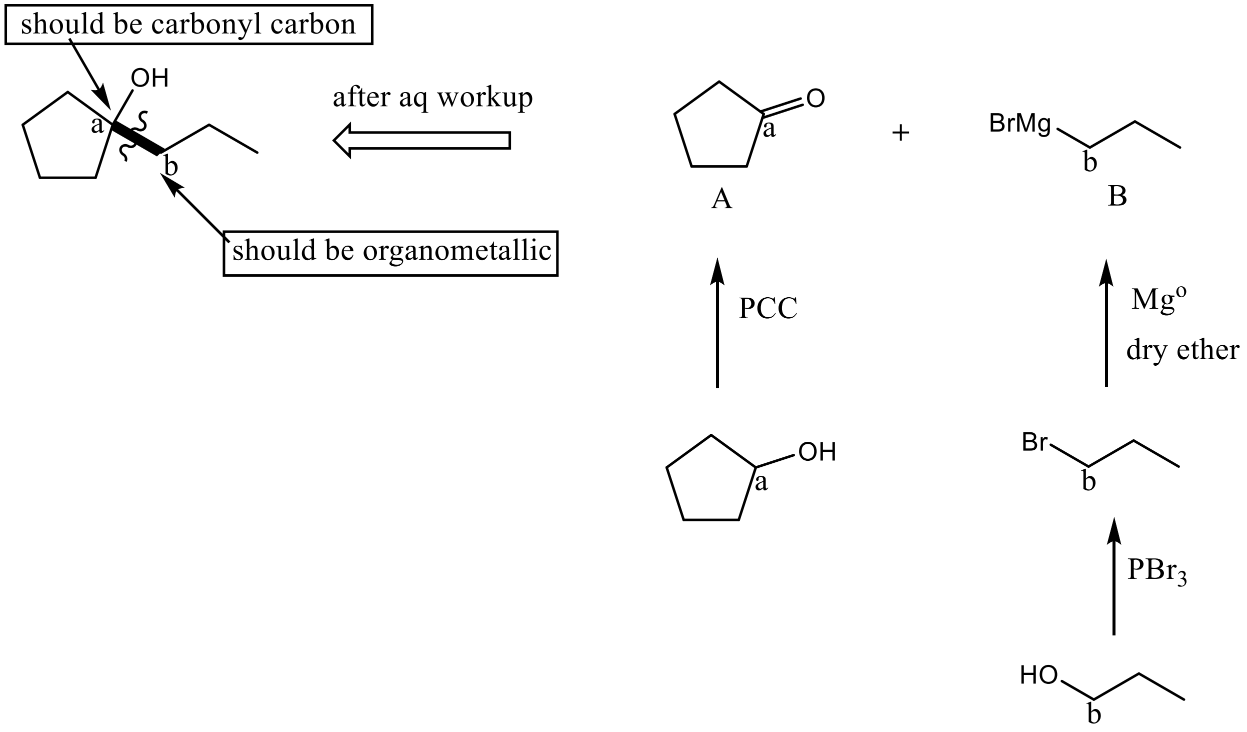


To make the ketone A from an alcohol:
We now must figure out how to make the cyclic ketone form cylopentanol. If you pay attention to functional groups, the secondary alcohol can be oxidized to a ketone. PCC or $NaOCl/CH_3COOH$ or $Na_2Cr_2O_7/H_2SO_4$, either of the three oxidizing reagents will perform the oxidation.

To make Grignard from an alcohol:
Grignard are made from alkyl halide, and alkyl halides can be made from alcohols.

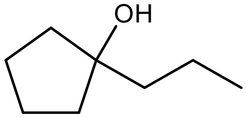


Putting all together, the convergent synthesis can be written as:



Exercise 11.10: Show how you would synthesize the compounds given below.

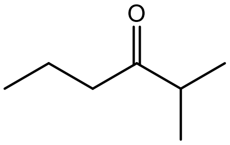
a.



starting from cyclopentane and any other alkane.

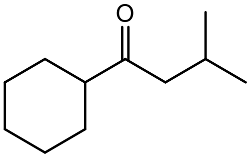
[Note: This is the same problem as solved problem 11.2, except the starting material is an alkane, not an alcohol].

b.



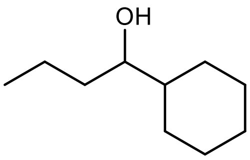
starting from alcohol of 4 carbon or less.

c.



starting from cyclohexane and any other alcohol.

d.

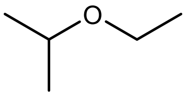


starting form methylcyclohexane and any other alkane.

Chapter 12: Ethers and Epoxide

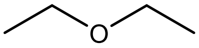
12.1 Introduction

Ethers have the general formula of R-O-R' where the two groups are composed of the same or different alkyl or phenyl groups. If the two R groups are identical, it is a symmetric ether. Otherwise, it is asymmetric. Some ethers and their common names are given below.



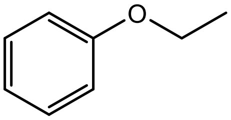
ethylisopropylether

asymmetric ether



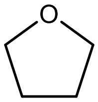
diethylether

symmetric ether



ethylphenylether

asymmetric ether

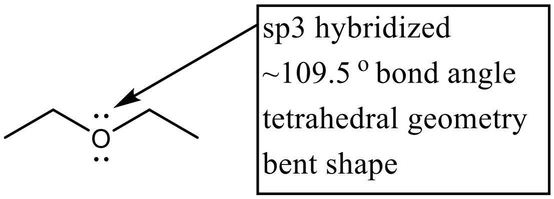


tetrahydrofuran (THF)

symmetric, cyclic ether

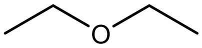
12.2 Physical Properties of Ethers

Other than epoxides, ethers are relatively unreactive. Because they are stable, ethers are commonly used as solvents for organic reactions. Ethers dissolve both non-polar and mildly polar solutes and do not react with weak acids, bases, oxidizing agents, and reducing agents.

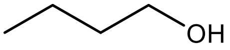


sp3 hybridized
~109.5 ° bond angle
tetrahedral geometry
bent shape

Ethers have a lower boiling point than their alcohol counterparts. Alcohols exhibit hydrogen bonding as the intermolecular forces that is lacking in ethers.



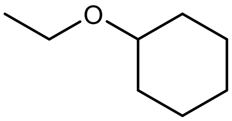
diethylether
b.p. ~35°C



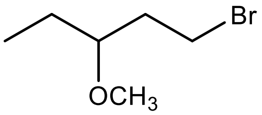
butan-1-ol
b.p. ~118°C

12.3 Nomenclature of Ethers

IUPAC name of ethers use the more complex alkyl group as the root name, and the rest of the ether as an alkoxy group.



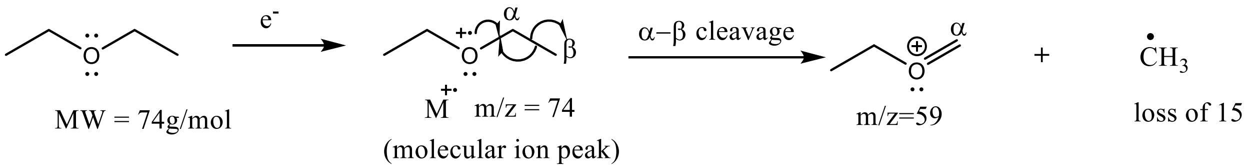
ethoxycyclohexane



1-bromo-3-methoxypentane

12.4 Spectroscopy of Ethers (A review from the laboratory course)

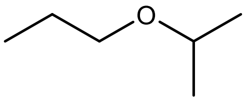
Mass Spectroscopy shows the typical α-β cleavage.



^{1}H NMR of ethers is also typical. Given the structure of ether, you should be able to find:

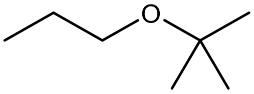
1. Unique number of hydrogens
2. Splitting pattern of each hydrogen
3. Identify the most deshielded proton

Problem 12.1: Starting from the molecular ion peak, and using arrows, draw a mechanism that will explain the peak at m/z of 73 for the following compound.



Problem 12.2: Answer the following questions for the ether shown below:

1. How many unique numbers of hydrogens are present in the ether? Label them as a,b,c, etc. going from left to right.
2. What is the splitting pattern of each unique hydrogen?
3. Identify the most deshielded hydrogen.

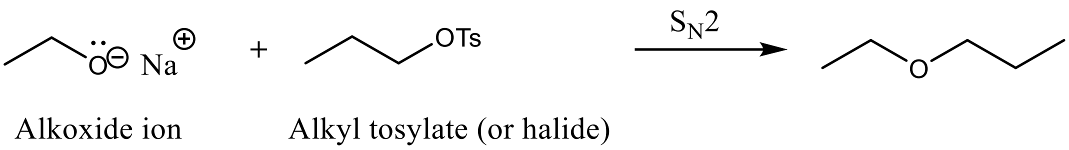


12.5 The Williamson Ether Synthesis (A Review)

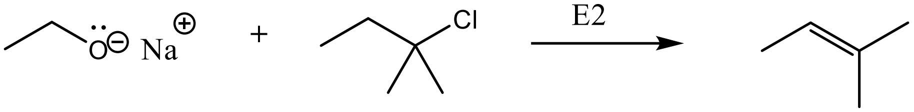
In **section 10.4**, we learned to remove the hydroxyl proton from alcohol by reduction with an alkali metal such as sodium or potassium. This reaction generates a sodium or potassium salt of an **alkoxide ion** and hydrogen gas.

Alkoxide ion

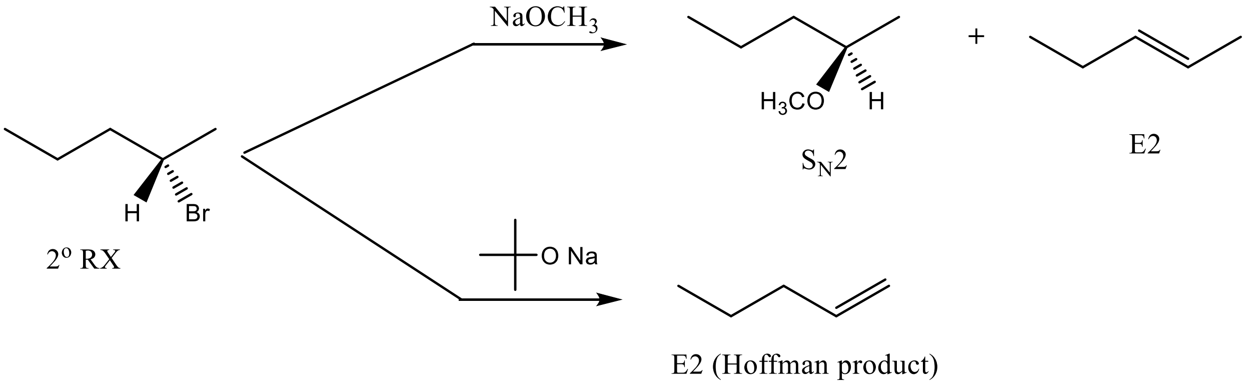
In **section 6.6**, we saw the alkoxide ion is a strong nucleophile as well as a strong base. Unlike the alcohol itself, the alkoxide ion reacts with primary alkyl halides and tosylates to form **ethers.** This general reaction called the **Williamson ether synthesis,** is an S_N2 displacement reaction. In **section 11.12**, we saw Williamson ether synthesis. Both symmetric and asymmetric ethers can be synthesized using Williamson ether synthesis.



The alkyl halide (or tosylate) must be primary so that a back-side attack is not hindered. When the alkyl halide is tertiary, only an elimination reaction results.

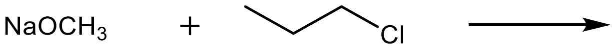


With secondary halides, both S_N2 and E2 products are formed (or with bulky base, only the E2 product is formed), and thus the reaction does not work well with secondary halides as well.

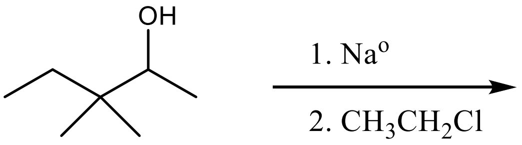


Exercise 12.3: Predict the product of the following reaction. Use the arrows and propose a mechanism. Provide an IUPAC name for the organic product.

a.

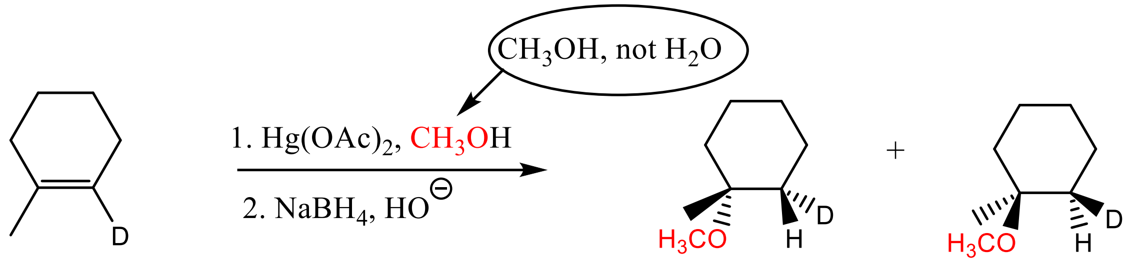


b.

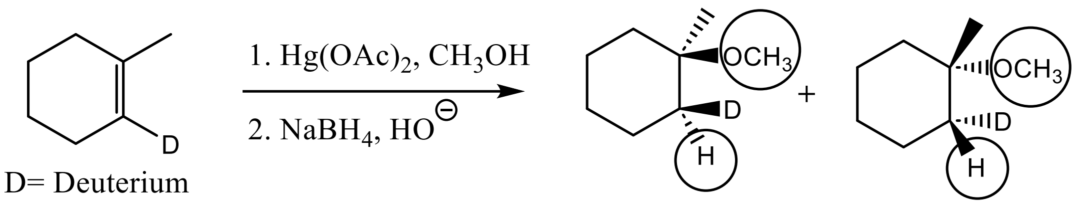


12.6 Synthesis of Ethers by Alkoxymercuration–Demercuration (A Review)

In **section 8.9** we saw the Alkoxymercuration-Demercuration (AMD) reaction of alkene. When mercuration takes place in alcohol, the alcohol serves as a nucleophile to attack the mercurinium ion. The resulting product contains an -OR (**alkoxy**) group. In effect, Alkoxymercuration-Demercuration (AMD) converts alkenes to **ethers** by adding alcohol across the double bond of the alkene. The reaction mechanism is identical to the AMD reaction discussed in **section 8.8**.

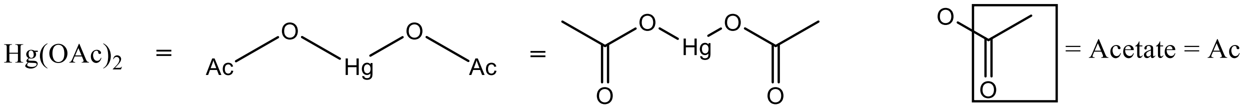


The addition of CH_3OH takes place across the C=C pi bond. CH_3OH adds across **Markovnikov** and ***trans*** manner. The resulting product is an **ether**.



D= Deuterium

The product shows two enantiomers that are formed. Once mechanism is explored, you will know why.

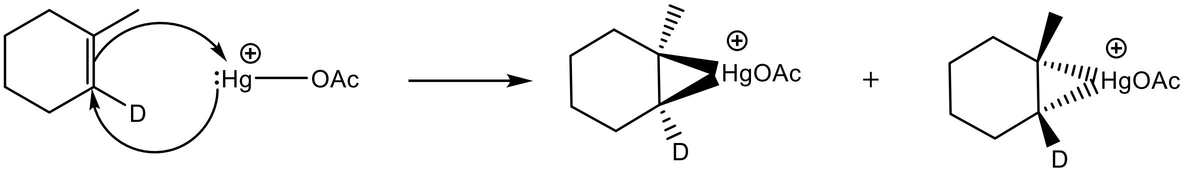


Mercury Acetate [$Hg(OAc)_2$] disassociates to make the electrophile before it reacts with the alkene.

Mechanism of Alkoxymercuration of an Alkene

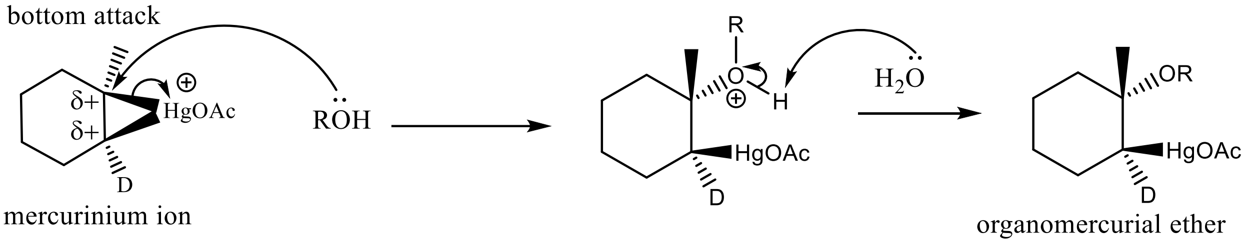
Step 1a Alkoxymercuration: This step involves the attack of the double to the electrophilic positively charged mercury atom while the d-electrons on the mercury atom make a bond with the other carbon. The product is a mercurinium *ion*, an organometallic cation containing a three-membered ring, with a mercury atom bearing a full positive charge.

Since alkene is trigonal planar, the mercurinium ion can be formed on either side of the double bond (top or bottom), hence two enantiomers of mercurinium ion are formed.

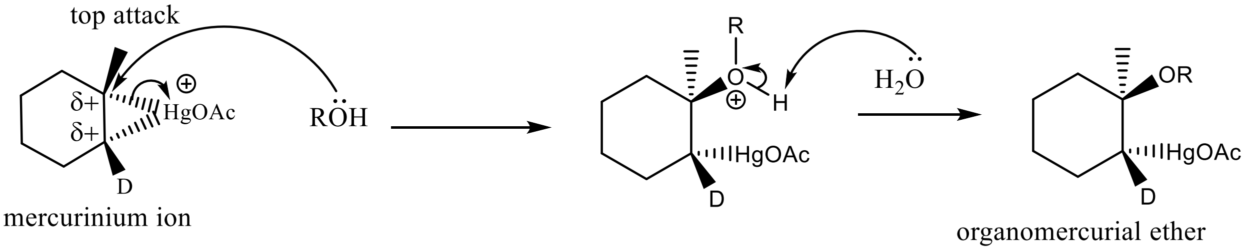


mercurinium ion   mercurinium ion

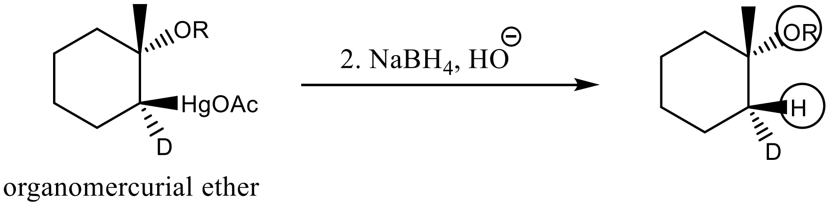
Step 1b Alkoxymercuration: Due to the positive charge on the mercury atom, each of the carbon bears a partial positive charge. The more substituted carbon handles the positive charge better, so **alcohol** attacks the more substituted carbon from the side opposite to the mercurinium ion. This results in an inversion of stereochemistry at the more substituted carbon. Pay attention to stereochemistry of organomercurial ether.



The same can happen with the other enantiomer.



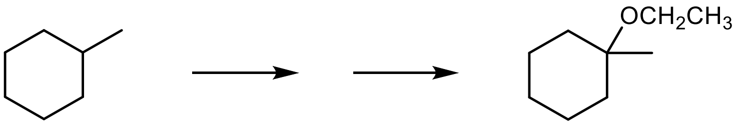
Demercuration of Organomercurial ether (no mechanism)**:** NaBH4 is a reducing agent which reduces the C-Hg bond to C-H bond without changing the stereochemistry. You are not responsible for the mechanism for this reaction.



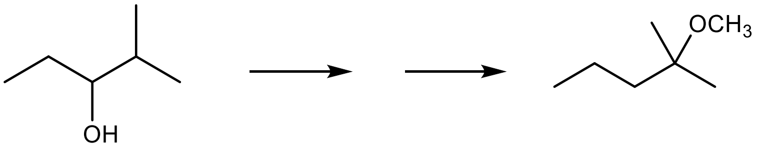
The Alkoxymercuration-Demercuration reaction is addition of an alcohol to an alkene in a **Markovnikov** and ***trans*** manner.

Exercise 12.4: Show how you would perform the following synthesis starting from the given compound and any other reagents.

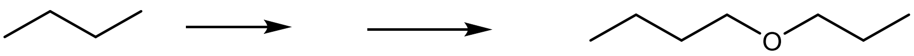
a.



b.



c.



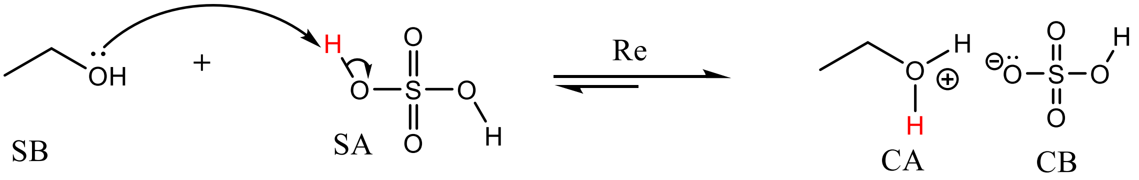
12.7 Industrial Synthesis: Bimolecular Dehydration of Alcohols (A Review)

In the **section 11.11**, we saw bimolecular dehydration. During the industrial synthesis of diethylether, ethanol (CH_3CH_2OH) is heated at 140°C with H_2SO_4. Overall water is lost form two molecules of ethanol. During bimolecular dehydration, a protonated primary alcohol is attacked by another molecule of the alcohol and undergo a S_N2 displacement reaction.

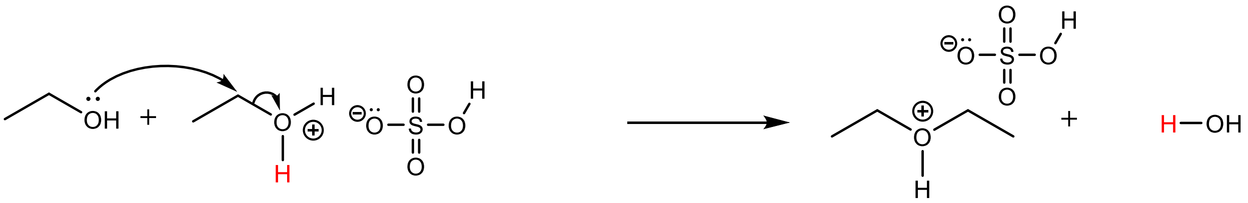
$$CH_3CH_2O\boxed{H \quad + \quad HO}CH_2CH_3 \xrightarrow[140^{o}C]{H_2SO_4\ (cat)} CH_3CH_2OCH_2CH_3 \quad + \quad H_2O$$

Mechanism:

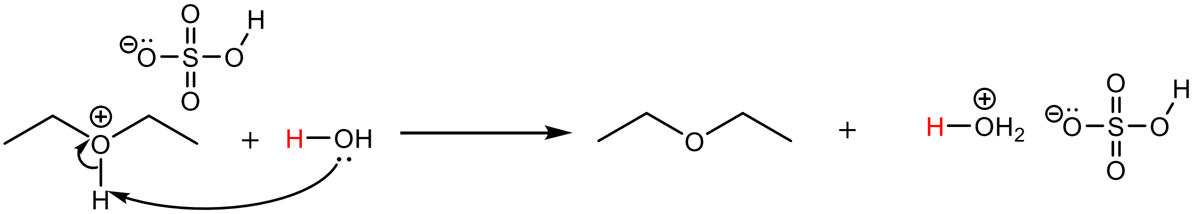
Step 1: Acid-base mechanism.



Step 2: S_N2 reaction of another molecule of ethanol with the protonated alcohol.



Step 3: An acid-base reaction is again needed to produce the uncharged ether. The loss of the proton takes place by H_2O produced in the second step and **<u>not</u>** $HSO_4^{\ominus}$ (as it is a weaker base as its electrons are stabilized via resonance).



Since the acid is regenerated in form of $H_3O^{\oplus}$ in the last step, this is also an acid-catalyzed reaction.

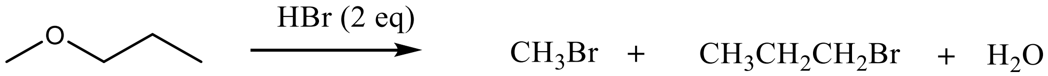
Exercise 12.5: Explain why the acid-catalyzed condensation is a poor method for the synthesis of an unsymmetrical ether such as ethyl propyl ether, $CH_3CH_2OCH_2CH_2CH_3$.

Exercise 12.6: Draw the product of the reaction when propan-1-ol undergoes a bimolecular dehydration reaction in the presence of a catalytic amount of H_2SO_4.

12.8 Cleavage of Ethers by HBr and HI

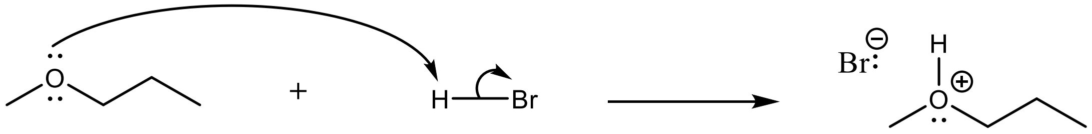
Here, HX=HI, HBr. The reaction of HCl is very slow.

Here R and R' can only be on sp3 carbon to give an alkyl halide as the product. If R or R' are on sp2 or sp carbon, alkyl halide is not formed. [When we explore the mechanism, it will be clear as to why].

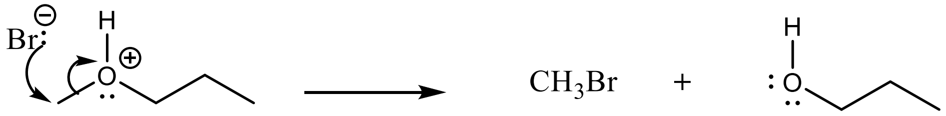


Mechanism:

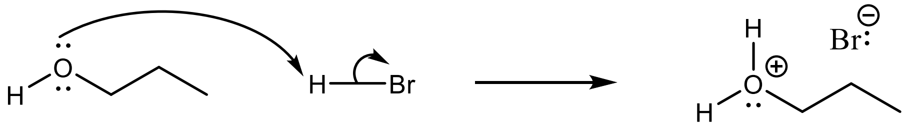
Step 1: Acid-Base reaction between the ether and the strong halo acid. The protonation of ether makes it into a good leaving group.



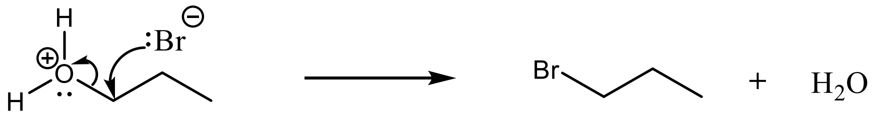
Step 2: Cleavage of the protonated ether. Since the less hindered side is on the left, the bromide ion attacks the less hindered carbon and the leaving group leaves as alcohol.



Step 3: The alcohol formed in step 2 reacts with excess HBr and an acid-base reaction takes place.

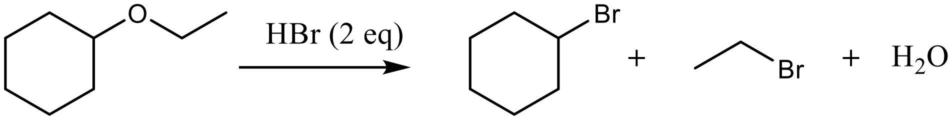


Step 4: Conversion of alcohol to alkyl halide in presence of excess HBr, takes place in a typical fashion that you have observed in **section 11.7**. Since this alcohol is a primary, the reaction takes place via S_N2 reaction, after the protonation of alcohol.

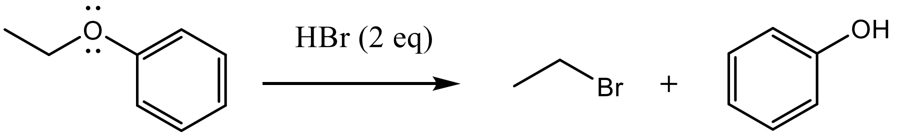


If the alcohol formed in step 3 is secondary or tertiary, the Step 4 takes place in S_N1 fashion.

Exercise 12.7: Draw a step-by-step mechanism that will explain the formation of the products. Refer to section **11.6** for the S_N1 mechanism between secondary alcohol and HBr.

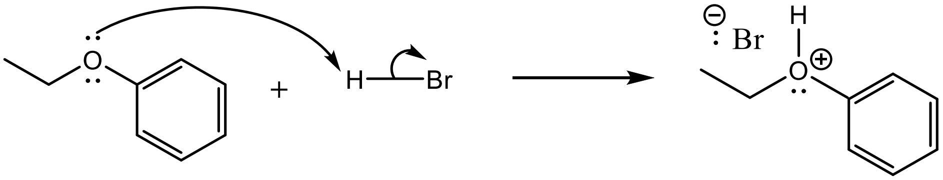


Since S_N1 and S_N2 reaction do not take place on sp2 or sp carbon, if one of the R group is on a sp2 or sp carbon, even in presence of excess HBr, the products of the reaction are an alcohol and an alkyl halide.
e.g.

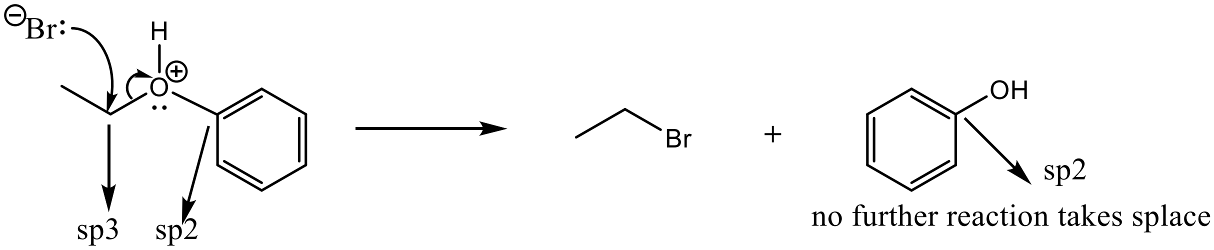


phenol (no further alkylation)

Mechanism: Step 1: Acid-Base reaction between the ether and the strong halo acid. The protonation of ether makes it into a good leaving group.

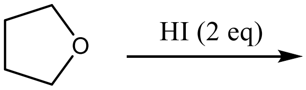


Step 2: Cleavage of the protonated ether. Since the carbon capable of undergoing the S_N2 reaction is the sp3 carbon (carbon on the right side of the oxygen), the bromide ion attacks the right carbon, and the leaving group leaves as alcohol (phenol). Since phenol is on a sp2 carbon, no further reaction of phenol takes place with HBr.

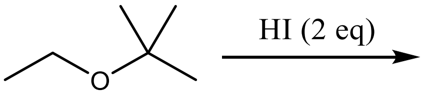


Exercise 12.8: Predict the products of the following reactions. An excess of acid is available in each case.

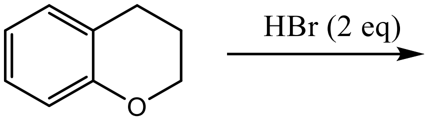
a.



b.

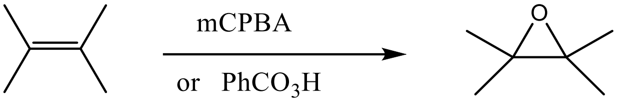


c.

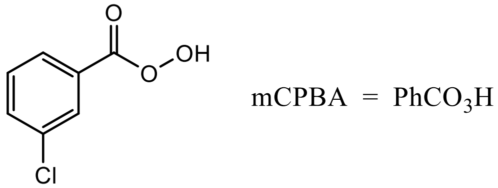


12.9 Synthesis of Epoxides

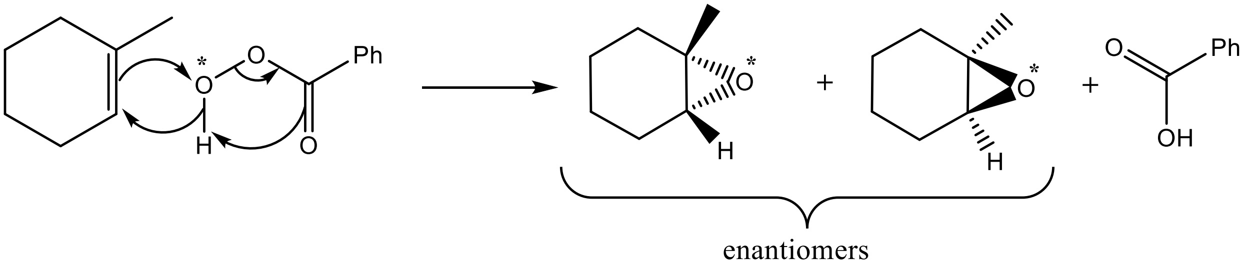
An **epoxide** is a three-membered cyclic ether. Epoxides are valuable synthetic intermediates used for converting alkenes to a variety of other functional groups. An alkene is converted to an epoxide by a **peroxyacid** (RCO_3H). Peroxy acids have one extra oxygen atom compared to carboxylic acids (RCO_2H).



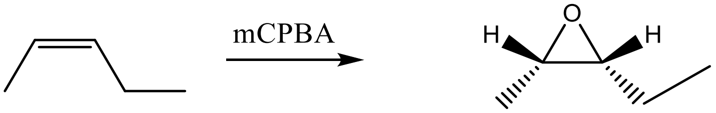
This reaction is called epoxidation of alkenes and is an oxidation reaction. The popular reagent that converts the alkene to epoxide is ***m**eta*-**c**hloro**p**er**b**enzoic **a**cid which has an acronym *m*CPBA (or $PhCO_3H$).



Reaction of alkene with mCPBA is a concerted mechanism where the oxygen that has been labeled with a * in mCPBA inserts between two carbons of alkene to make an epoxide.

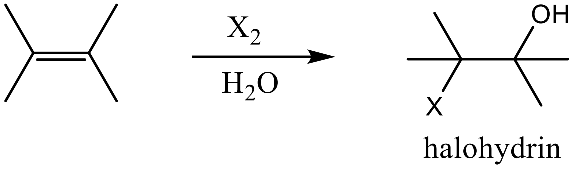


Because this is a concerted mechanism, a cis alkene will produce an epoxide where the two alkyl groups will be cis.

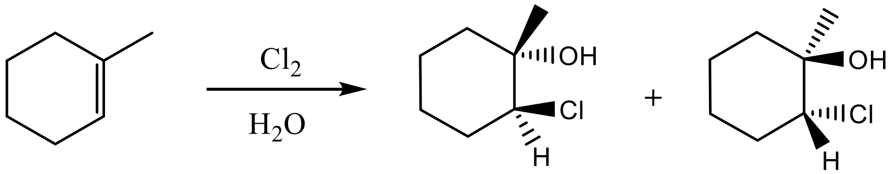


A trans alkene will produce an epoxide where the two alkyl groups will be trans.

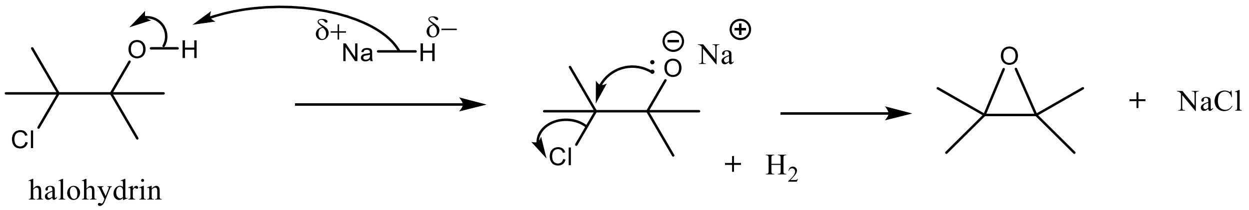
Epoxides can also be synthesized from halohydrins. In section 8.12, we saw formation of halohydrin. When an alcohol and halogen are on adjacent carbon atoms, it is called a **halohydrin**. In the presence of **water**, halogens add to alkenes to form halohydrins.



In the example shown below, H_2O acts like a nucleophile and attacks the more substituted carbon of chloronium ion to form the halohydrin. Note: -OH group appears on the **more substituted** carbon.

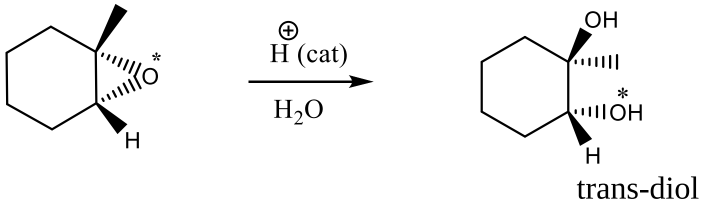


Once the halohydrin are formed, a base is used to deprotonate the acidic proton of alcohol, which in turn does an intramolecular SN2 reaction to form an epoxide. A base like NaH (sodium hydride) or 2,6-lutidine is used to deprotonate the acidic hydrogen.



12.10 Acid-Catalyzed Ring Opening of Epoxides (A Review)

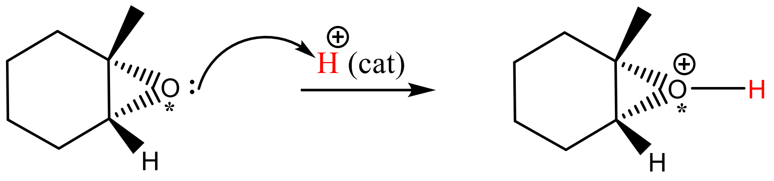
In section 8.16, we saw the acid catalyzed ring opening of epoxides. Most epoxides are stable under neutral conditions. Under acidic or basic conditions, epoxide undergo ring opening reactions readily. Any moderately strong acid protonates the epoxide, however. Water attacks the protonated epoxide, opening the ring and forming a 1,2-diol.



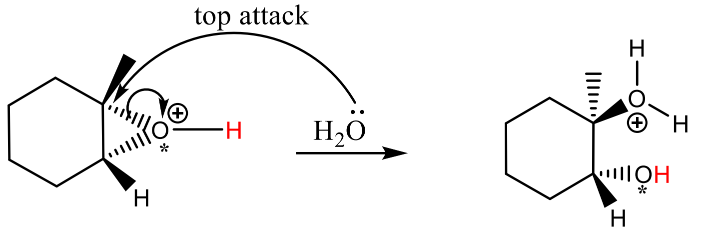
This acid catalyzed ring opening reaction is very similar to mercurinum ion and bromonium ion ring opening mechanism.

Mechanism of Acid-Catalyzed Opening of Epoxides: For the ease of keeping track of the acid and the epoxide oxygen, the acidic hydrogen is labeled red and

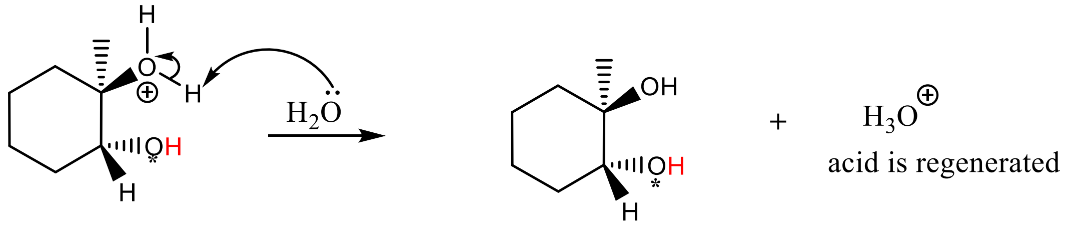
Step 1: The first step is the protonation of the epoxide by the acid.



Step 2: The nucleophile (H_2O in this case) attacks the more substituted carbon from the opposite side of the epoxide. Since the original epoxide has oxygen going down, the H_2O attacks the more substituted carbon from the top side.



Step 3: Deprotonation of the diol is a required step for the reaction to end in the formation of trans-diol. This takes place with excess H_2O (which is also a solvent, hence on the bottom of the arrow).



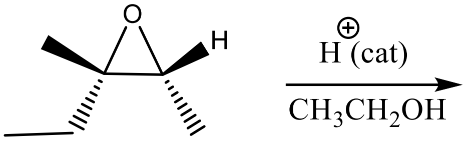
Note: The acid is regenerated in the last step, hence this is an **acid-catalyzed** reaction.

Since the starting epoxide has a very specific stereochemistry, therefore only this product with this stereochemistry is formed and the enantiomer is **NOT** formed.

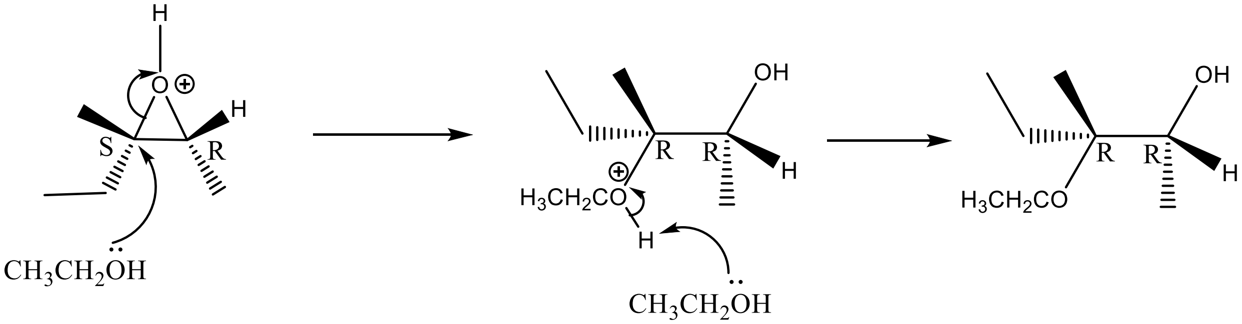
12.11 Acid-Catalyzed Opening of an Epoxide in an Alcohol Solution (A Review)

When an alcohol (ROH) is used as a solvent instead of H_2O, product is not a trans-diol, it is **an ether alcohol**. The mechanism is the same as halohydrin formation, except the -OR group appears in the product instead of -OH group.

Solved Problem 12.1: Draw the mechanism and the major product(s) of the when the following reaction takes place. Include stereochemistry at the stereocenter of the product.



Approach: This is an acid-catalyzed ring opening reaction of epoxide with ethanol (CH_3CH_2OH) as a nucleophile. Since the epoxide is drawn on the plane, the nucleophile CH_3CH_2OH will approach the more substituted carbon (left carbon) from the opposite side of epoxide (but still on the plane) after it has been protonated by acid.

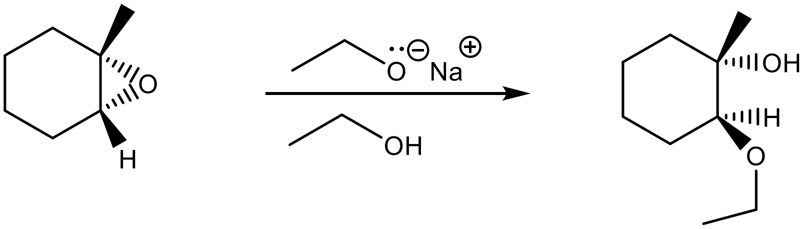


Note the change in stereochemistry of the chiral center where the reaction is taking place. It has been inverted. No other stereoisomer is formed.

12.12 Base-Catalyzed Ring Opening of Epoxides

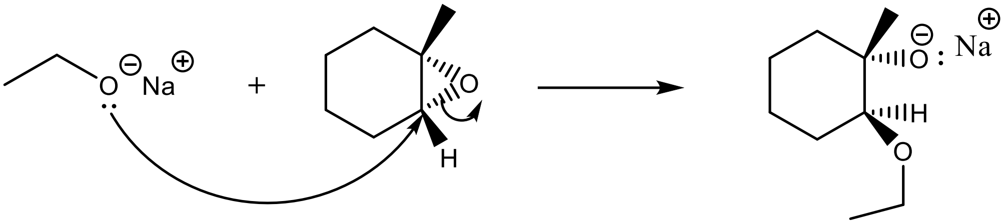
When epoxide undergo ring opening reactions under basic conditions, the strong nucleophile attacks the less substituted carbon from the opposite side of epoxide. This results in an inversion of stereochemistry at the carbon where the reaction takes place but not on the other carbon, where the -OH group appears.

Under basic conditions, the strong (charged) nucleophile is dissolved in the conjugate acid as a solvent. (NaOH will be dissolved in H_2O, CH_3ONa will be dissolved in CH_3OH etc.)

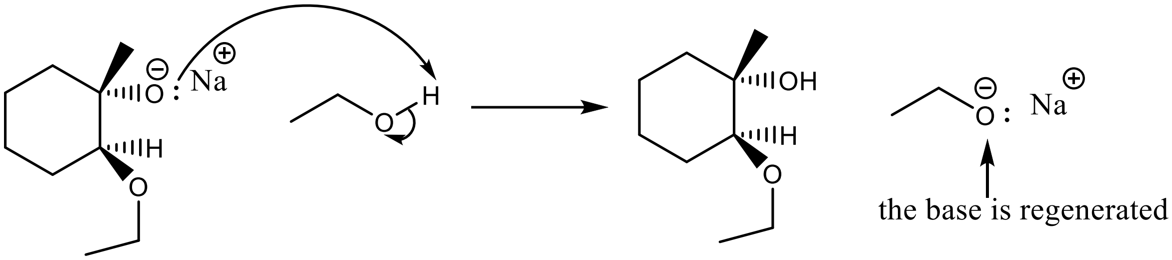


Mechanism:

Step 1: Under basic conditions, the charged nucleophile attacks the less substituted carbon from the opposite side of epoxide. This results in an inversion of stereochemistry at the carbon where the reaction takes place



Step 2: An acid-base reaction takes place where the solvent provides the proton to form the final product. The base is regenerated and hence this is called a base-**catalyzed** ring opening reaction.



12.13 Orientation of Epoxide Ring Opening

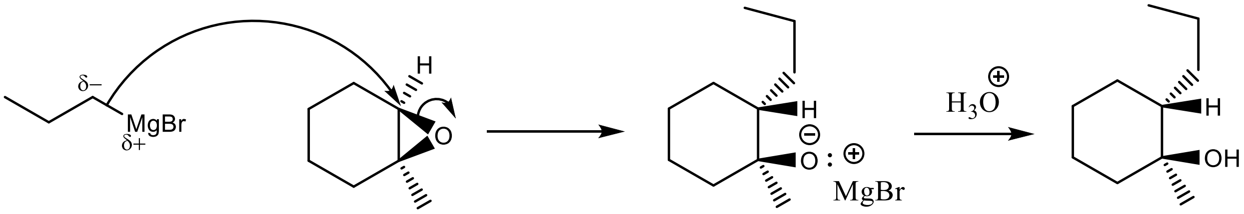
Under acidic conditions, the nucleophile attacks the more substituted carbon of the epoxide.

Under basic conditions, the nucleophile attacks the less substituted carbon of the epoxide. (**BAL**)

12.14 Reactions of Epoxides with Grignard and Organolithium Reagents (A Review)

In **section 10.9**, we saw how organometallics like Grignard and Organolithium react with the epoxides to give alcohol. The nature of alcohol will depend upon the structure of the epoxide.

Mechanism: The Grignard attacks the less substituted carbon from the opposite side of epoxide. This is followed by aqueous workup to produce the neutral alcohol.



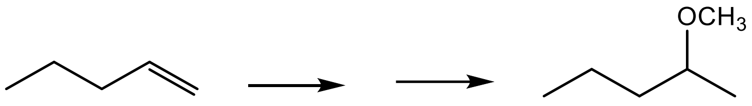
In the mechanism shown above, the Grignard is the nucleophile and since it is a strong base, the Grignard attacks the less substituted carbon (**BAL**, for base attacks less substituted side). It attacks from the opposite side of epoxide oxygen. Since the epoxide shown here is coming towards you (shown as a wedge), the nucleophile approaches from the bottom side (shown as dash line). This results in an inversion of stereochemistry at the carbon where the reaction takes place but not on the other carbon, where the -OH group appears. The product of this reaction is an alcohol with a new C-C bond formation.

-OH group appears one carbon away from the new C-C bond. This happens ONLY when the organometallic reacts with an epoxide.

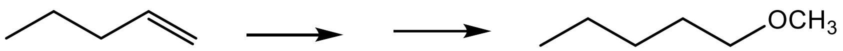
When the organometallic reacts with, any carbonyl containing compounds such as aldehyde, ketone, acid chloride and ester, the -OH group appears on where the new C-C bond is formed.

Exercise 12.9: Propose a synthesis of the following compounds starting from pent-1-ene and any other reagent.

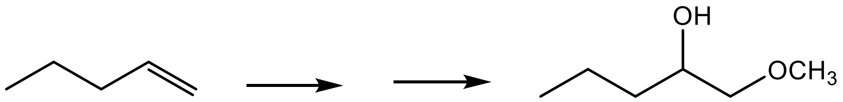
a.



b.



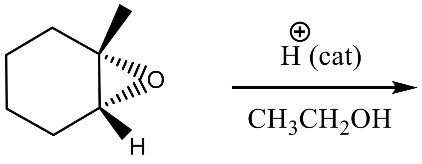
c.



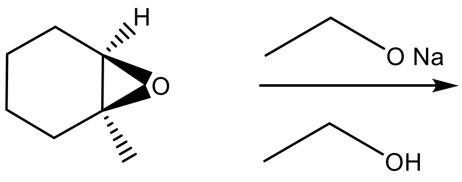
d.

Exercise 12.10: Draw the organic product(s) of the reaction shown below. Pay attention to stereochemistry, where appropriate.

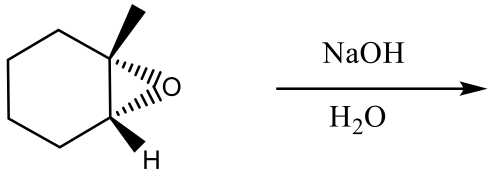
a.



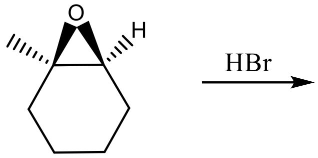
b.



c.



d.



Exercise 12.11: Starting from molecular ion peak and using arrow, show the fragmentations that will account for the following peaks observed in the mass spectrum of 2-methoxypentane: 102, 87 and 59.

Exercise 12.12: Show how would you synthesize the given ether form cyclohexanol and propan-1-ol. This is a convergent synthesis.