

# Organic Chemistry I



# Organic Chemistry I

*XIN LIU*

KWANTLEN POLYTECHNIC UNIVERSITY  
SURREY, BC



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# Introduction

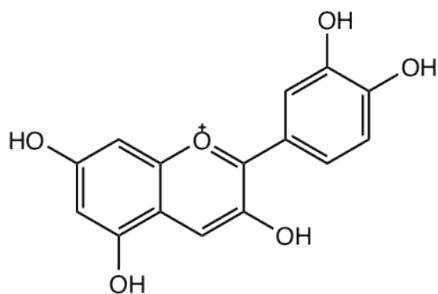
## What is Organic Chemistry and Why is it Important?

On a lovely Saturday afternoon in April, you are relaxing in a garden whilst enjoying a hot cup of coffee. Colourful spring blossoms lace the air with a pleasant aroma, and the green grass, warm sunshine and rich espresso make the afternoon a charming occasion.

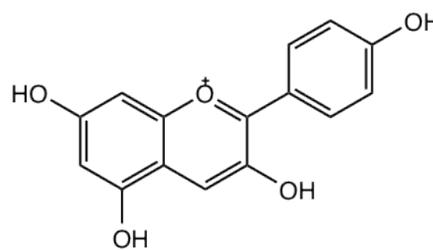
Your mind begins to drift as you contemplate the combination of scents, colours and tastes that surround you in this moment and how they make up the human experience's unique and fascinating complexities.

If you have ever wondered about the origins of nature's vibrant hues or the reasoning behind the alluring flavour of coffee, you will be able to find every answer within the elaborate spectrum of knowledge in the study of organic chemistry.

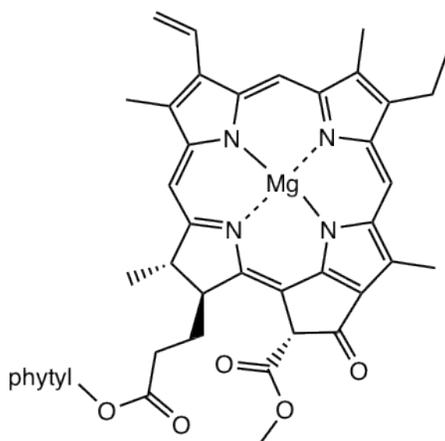
Organic chemistry is the chemistry of compounds containing the carbon element: the common element of all living organisms. Anthocyanins are the pigments that give flowers their various colours, chlorophyll is responsible for the green shades of grass and is involved in the photosynthesis process of plants, and caffeine is what makes coffee function the way it does. All these substances contain carbon, and they are all organic compounds.



**Cyanidin:** an anthocyanin in reddish color



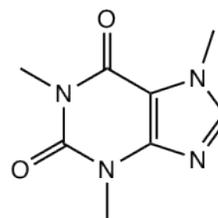
**Pelargonidin:** an anthocyanin in orange color



**Chlorophyll a**



Image of a Cyanidin, Pelargonidin, Chlorophyll a, and Caffeine



**Caffeine**

The root of the term organic dates back to over two hundred years ago, when its original meaning did not even involve the element of carbon. The word organic was first introduced in 1807 by Jöns Jakob Berzelius, a Swedish chemist, and was used to refer to compounds derived from living organisms. It was once believed that organic compounds could only be obtained directly from nature as they contained a mystical essence of life known as “vita force”, therefore making it impossible to create organic compounds artificially. This theory was shattered by a famous experiment conducted by German chemist Friedrich Wohler in 1828. In his experiment, Wohler successfully synthesized crystals of urea by heating ammonia and cyanic acid together. The synthesis of urea marked a new era in the history of organic chemistry, not only redefining the term organic, but also rerouting organic chemistry into a completely new scientific discipline. The contemporary definition of organic being carbon-containing compounds is now the scientific way of describing the term. However, it has remained true over the years that organic compounds are essential to every known lifeform, as an abundance of organic molecules constitute all living organisms.

There are two additional notes regarding the modern definition of *organic*. Firstly, while it is true that organic compounds are those containing the element carbon, it is important to note that not all compounds that contain carbon are organic compounds. For example, calcium carbonate ( $\text{CaCO}_3$ ), the primary component in certain rocks and chalk, can never be labelled as organic. Secondly, the “organic” food often found in supermarkets refers to the fact that these agricultural products were grown without the use of artificial pesticides, herbicides, or synthetic fertilizers and has nothing to do with the presence of carbon in their chemical structures. This use of the word organic is possibly derived from the old definition, implying that the products came from nature, without human intervention.

As you may be able to deduce, organic chemistry can be found in every corner of the world around us. From the food we eat (the carbohydrates in bread, the protein in meat, the fructose in fruit, and more), to the fabric we wear (cotton, nylon, polyester), and the fuels that power the technology around us (gasoline, natural gas, coal), the list of organic compounds involved in our lives is endless. An important factor in the application of organic chemistry is its critical role in the development of medicine and pharmaceuticals. The active ingredients found in medicine are usually organic compounds that are either isolated from naturally occurring materials or synthesized in a lab. Just a few well-known examples include Aspirin, Tylenol, penicillin, insulin, Warfarin, and Tamiflu. The rapid development of the pharmaceutical industry, in which organic chemistry has acted as a major driver, has saved millions of lives and dramatically improved our quality of life.

The magic element that is the key to organic chemistry and all living organisms is carbon. What is it about the carbon element that makes it so unique? Mainly, it is carbon's special bonding ability. Carbon atoms can form strong covalent bonds with other carbon atoms in the form of chains and rings, and they also form strong bonds with other elements such as hydrogen, oxygen, nitrogen, sulfur and more. As a result, the structures of organic compounds are hugely diverse and can be highly complex.

## Tips for Studying Organic Chemistry

Learning organic chemistry can be both exciting and challenging. A common misleading learning strategy is the notion that “I can be successful by simply memorizing everything”. While memorization may be necessary at times, it is but a small fraction of what is needed to learn organic chemistry; the more important factor is your understanding. There are many structures, reactions and mechanisms involved in the course, and surface-level memorization will not carry you all the way through. However, if you know the connections between the structures, understand the underlying principles of the reactivity of certain compounds, and can recognize the similarities and differences between different mechanisms, you will find that it becomes much easier. A few suggestions for learning are:

- Rewrite your own notes when studying. For example, restate the concepts in your own words or write a map of concepts that are related.
- Practice makes perfect. Do as many practice questions as you can and try to make your own questions to double-

check your understanding.

- Use molecule model sets for certain topics.

## About the Book

Due to the high price barrier, about half of organic chemistry students at KPU do not have access to the textbook. This has become a serious issue that significantly affects learning outcomes for the course. The creation of this open textbook is intended to provide a solution to this problem and help students have success in this course.

The book contains ten chapters, with the content covering from basic concepts on chemical bonding and functional groups to stereochemistry, spectroscopy for structure determination (IR and NMR) and organic reactions (nucleophilic substitution, elimination, radical substitution of alkanes, addition and oxidation reactions of alkenes, preparation and reactions of alkynes).

Organic chemistry is a challenging subject for many students. To help the readers understand the concepts more easily, simple and concise language is intentionally used in the book. Featured shaded textbox areas are frequently included in the book in which readers can find useful learning tips, reminders of common errors, and comparisons between similar concepts. To help readers develop problem-solving skills, small sections labelled as “strategy” are usually given for examples in the book. Readers are encouraged to try solving the problems by themselves with the helpful hints provided in the “strategy” and then compare their work with the detailed solutions provided afterwards.

# Acknowledgements

It was my great honour to be granted educational leave and an OER creation grant at KPU, as this open textbook project would not have been possible without this funding support. Special thanks to Dr. Rajiv Jhangiani, Mr. Todd Mundle and Dr. Fergal Callaghan for their advice and their help on the grant applications. I would also like to show my appreciation to Dr. Elizabeth Worobec and Dr. Joel Murray, the deans of the Faculty of Science and Horticulture, for their support for this project since the very beginning. Furthermore, I wish to extend my thanks to my colleagues Suzanne Pearce, for sharing her experience in working with open textbooks, and Dr. Deepani Indurugalla, Dr. Richard Popoff and Dr. David Sud, for their feedback as well as everyone in the Chemistry Department for their comments and help.

The Organic Chemistry I open textbook was made possible through in-kind support and project funding from KPU's Open Educational Resources Grant Program and sustained by KPU Library's Open Publishing Suite (OPUS). The help received from Urooj Nizami, Karen Meijer-Kline and Caroline Daniels is greatly appreciated, as their patience and professionalism allowed this project to be completed.

# CHAPTER 1: BASIC CONCEPTS IN CHEMICAL BONDING AND ORGANIC MOLECULES

Before starting the journey in Organic Chemistry, reviewing some basic knowledge from the General Chemistry course will be very helpful and important. We will begin with chemical bonding and review how to draw a Lewis Structure to show and predict the bonding in a chemical species followed by Valence Bond Theory and Hybridization to explain how the bonds are formed.

Learning Objectives for this chapter:

- Explain and describe chemical bonding using Valence Bond Theory and hybridization.
- Draw plausible Lewis structure, recognize bonding and non-bonding (lone pair) electrons, and count formal charges.
- Draw major resonance structures of simple organic molecules, compare the relative stability of different resonance contributors, and use this information to determine the relative stability of organic molecules and ions.
- Apply VSEPR theory to explain the shape of simple organic molecules.



# 1.1 Chemical Bonding

To summarize simply, a chemical bond is the attractive force holding atoms or ions together. This attractive interaction leads to a more stable state for the whole system compared to individual atoms.

Valence electrons play a fundamental role in chemical bonding. In the electron configuration of an atom, the outermost shell is called the valence shell, and the electrons in the valence shell (outermost shell) are known as valence electrons. Take the carbon atom for example: the electron configuration of carbon is  $1s^2 2s^2 2p^2$ . The outermost shell is the 2<sup>nd</sup> principal shell, so there are 4 valence electrons in carbon. Valence electrons are the electrons that are the furthest away from the nucleus, and thus they experience the least attraction from the nucleus and are the most reactive. They play the most important role in chemical bonding.

## Exercises 1.1

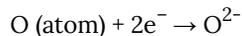
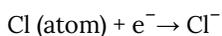
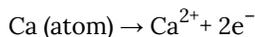
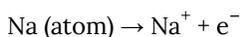
Determine the number of valence electrons for following elements: B, N, O, Cl, Mg.

Answers to Chapter 1 Practice Questions

## Ionic Bonds and Covalent Bonds

There are two major types of chemical bonds: ionic bonds and covalent bonds. An ionic bond is an interaction that results from the electrostatic attraction (force) between ions of opposite charges. Ionic bonds apply to ionic compounds, such as sodium chloride (NaCl).

In simple ionic compounds, the metal element loses valence electron(s) to form the cation and the non-metal element gains electron(s) to form the anion. With the proper number of electron(s) lost or gained, both the cation and the anion achieve a full outer shell that contains eight electrons, as in the following examples of  $\text{Na}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Cl}^-$  and  $\text{O}^{2-}$ . According to Lewis's Theory, an atom is most stable if its outer shell is filled or contains eight electrons. This is also called the octet rule.



A covalent bond is a bond formed through the sharing of electron pairs between the two bonding atoms. The shared electron pairs are mutually attracted by the nuclei of both atoms. By sharing the electron pairs, both atoms also gain a filled outer shell, or an octet. Almost all the bonds involved in organic compounds are covalent bonds.

Covalent bonds can be non-polar or polar.

For covalent bonds formed between two identical atoms, the electron pairs are shared equally between the two nuclei. Electron density is distributed evenly through the bond, making it a non-polar bond. Examples include all homonuclear molecules, such as H-H, Cl-Cl, O=O, N≡N.



- The EN of C (2.5) and H (2.1) is close, which makes the C-H bond (the bond involved in all organic compounds) technically non-polar.

With the introduction to the concept of EN, bond polarity can be represented with the EN difference between the two bonding atoms, which is known as  $\Delta EN$ . For non-polar bonds,  $\Delta EN$  equals to zero, and for polar bonds,  $\Delta EN$  is not zero. The greater the  $\Delta EN$ , the more polar the bond is.

### Exercises 1.2

- Identify the following bonds as “polar” or “non-polar”: C-C, C-H, B-F, O-O, C=N
- Rank the following bonds in order of increasing bonding polarity: C-S, C-O, C-F (referring to the trend of EN, you do not need to use the exact EN values).

### Answers to Chapter 1 Practice Questions

Because of the EN difference, the atom with the higher EN attracts the shared electron pairs more strongly, therefore bearing a slightly negative charge ( $\delta^-$ ). The other atom with a lower EN bears a slightly positive charge ( $\delta^+$ ). The direction of the bond polarity can be indicated with an arrow, with the head of the arrow pointing to the negative end and a short perpendicular line near the tail of the arrow marking the positive end. The following example of an H-Cl molecule indicates how to show the bond polarity and partial charges of the polar bond.

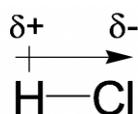


Fig. 1.1b Polarity of H-Cl bond

## 1.2 Lewis Structure

A Lewis structure shows the bonding between atoms as short lines (some books use pairs of dots) and non-bonding valence electrons as dots.

### 1.2.1 Lewis Structure of Diatomic Molecules

To learn about Lewis structures, we will start with the Lewis symbol. The Lewis symbol is the chemical symbol of an element with valence electrons represented as dots. The Lewis symbols of some elements are shown here:

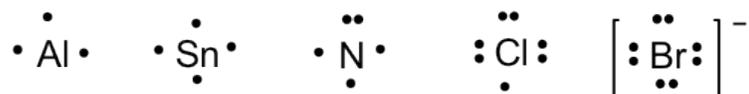


Figure 1.2a The Lewis structures of aluminum, tin, nitrogen, chlorine and bromine

For simple diatomic molecules, combining the Lewis symbols of each element gives its Lewis structure.

H<sub>2</sub> example: (H only needs two electrons; this is usually referred to as a duet.)

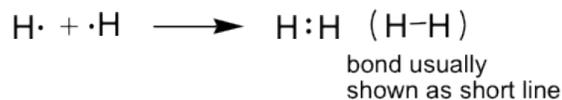


Figure 1.2b The Lewis structure of Hydrogen

F<sub>2</sub> example:

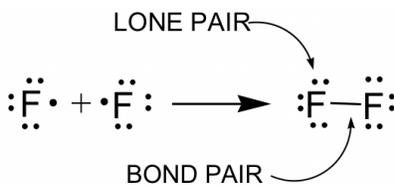


Figure 1.2c The Lewis structure of the Fluorine molecule

Terms used in Lewis structures (see example of F<sub>2</sub>):

- Bonding pair: The pair of valence electrons involved in a covalent bond. The covalent bonds are drawn as short lines in this book, and one covalent bond means one pair of bonding electrons, that is, 2 electrons. Single bonds and multiple bonds (double or triple bonds) may be involved.
- Lone pair: The pairs of valence electrons not involved in a covalent bond. Lone pair electrons can also be called non-bonding electron pairs.

Special note: Non-bonding electrons can also be unpaired (single) electrons. A species with one or more unpaired (single) electrons is called a radical (free radical). More examples of radicals with single electrons will be given in section 1.2.5 and Chapter 9.

### HCl example:

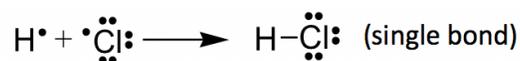


Figure 1.2d The Lewis structure of covalent bond between hydrogen and chlorine

### O<sub>2</sub> example:

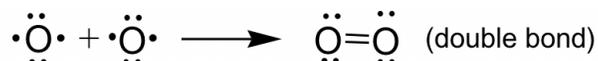


Figure 1.2e The Lewis structure of a covalent bond between two oxygen atoms

#### Exercises 1.3

Draw the Lewis structure of the N<sub>2</sub> molecule.

## 1.2.2 Lewis Structures of Polyatomic Molecules or Ions

For more complicated polyatomic molecules and ions, the Lewis structures cannot be obtained by simply combining Lewis symbols. A specific procedure with certain steps has to be followed. It is very important that you use the following procedure to get the correct Lewis structures for polyatomic molecules and ions.

### Lewis Structure Drawing Procedure for Polyatomic Molecules and Ions

- 1. Calculate the total number of valence electrons. For ions, make sure charges are properly included in the calculation. For example, for an  $\text{NH}_4^+$  cation:
  - the total number of electrons = 5 (N atom) + 4×1 (four H atoms) -1 (minus the charge for cation) = 8 valence electrons
- 2. Write a plausible skeletal structure using the following steps:
  - a) Write atomic symbols for the central and terminal atoms.
    - Hydrogen atoms are always terminal.
    - Central atoms are generally those with the lowest EN.
    - Carbon atoms are always central.
  - b) Connect the central atom with each of the terminal atoms by drawing a single bond.
- 3. For each single bond, subtract two electrons from the total number of valence electrons.
- 4. Using the remaining valence electrons, complete the octets of the terminal atoms first, then complete as many as possible for the central atoms.
- 5. If you have used up all the valence electrons to complete octets for all the atoms, you are done.
- 6. If not, then complete the octets of all central atoms by moving lone pairs from terminal atoms to form multiple bonds.
- 7. Calculate the Formal Charges on all atoms and label the non-zero formal charges in the structure:

Formal Charge on an atom = No. of valence electrons in free atoms - No. of lone pair electrons -  $\frac{1}{2}$  (No. of bonding electrons)

### Formula 1.1

**Examples:** Here we will take  $\text{CO}_2$  molecule as an example to explain the **procedure** step by step:

1. Total number of valence electrons: 4 (C atom) + 2×6 (2 O atoms) = 16

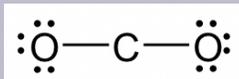
Always DOUBLE CHECK: In the correct Lewis structure, the total number of electrons involved (bonding plus non-bonding electrons) must be equal to this number, less or more are both incorrect!!

2. Write a plausible skeletal structure:

Carbon atoms are always central, so the skeletal structure is: O – C – O

3. Four electrons are used so far, and there are  $16 - 4 = 12$  electrons remained.

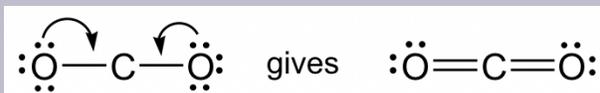
4. The remaining 12 electrons must be used to complete the octet for both terminal O atoms first, and no electrons left after that.



It is very important to keep in mind that the remaining electrons should be used to give the octet of terminal atoms first!

5. The central C atom does not get octet yet, we should do next step.

6. Moving one lone pair from each terminal O atom, the following structure is obtained.



this is the complete Lewis structure of CO<sub>2</sub>.

For Lewis structure purposes, the lone-pairs can only be moved from terminal atoms to the central atom to form multiple bonds, not the other way around.

7. Formal charges check: all atoms have formal charges equals to 0 in this structure.

$$\text{FC (C)} = 4 - \frac{1}{2} \times (4 \times 2) = 0$$

$$\text{FC (O)} = 6 - 4 - \frac{1}{2} \times (2 \times 2) = 0$$

Since the two oxygen atoms have the same bonding, one calculation is enough for both oxygen atoms.

### 1.2.3 Guidelines about Formal Charges in Lewis Structures

The purpose of formal charges is to compare the difference between the number of valence electrons in the free atom and the number of electrons the atom “owns” when it is bonded. The smaller the difference, the “happier” (more stable) the atom is. The atom owns all of the lone pair (non-bonding) electrons and half of the bonding (shared) electrons, which is why the formula is given in the way shown in Formula 1.1.

Formal charges can be used as guidelines to determine the plausibility of Lewis structures by comparing the stability of non-equivalent resonance structures, which is particularly important for organic species. The rules about formal charges are:

- The sum of the formal charges must equal to the total charge on the molecule or ion.
- Formal charges should be as small as possible (comparing the absolute value of formal charges for such purposes).
- “-” FC usually appears on the most electronegative atoms (with the stronger ability to pull the shared electrons; this atom is “winning” electrons in the sharing).
- “+” FC usually appears on least electronegative atoms (with the weaker ability to pull the shared electrons; this atom is “losing” electrons in the sharing).
- Structures having formal charges of the same sign on adjacent atoms is unlikely.

There is a *derived way* for calculating formal charges: since each bond contains 2 electrons, half of the bonding electrons simply equals the number of bonds. So, the formal charge can also be calculated based on the derived version of the formula:

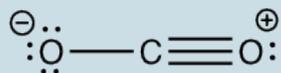
Formal Charge on an atom = No. of valence electrons in free atoms - No. of lone pair electrons - No. of covalent bonds around the atom

Formula 1.2

Double bonds count as 2 and triple bonds count as 3 in Formula 1.2. Both Formula 1.1 and 1.2 work for counting the formal charge; you can choose either one for your convenience. While almost all other textbooks show Formula 1.1 as the official way, Formula 1.2 is easier to use and can be regarded as the most practical one based on experience.

#### Exercises 1.4

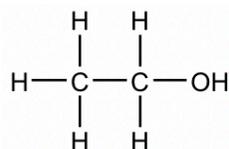
Why is the following structure not the best way to show the Lewis structure of CO<sub>2</sub>?



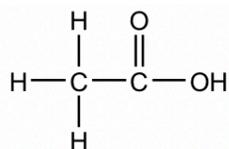
#### Answers to Chapter 1 Practice Questions

#### 1.2.4 Kekulé Structures vs Lewis Structures

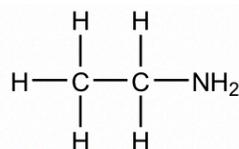
The complete Lewis structure always has to include all the bonding electrons and lone pair electrons. However, organic species are usually shown as Kekulé structures (further discussion will be given in Chapter 2) with all the lone pair electrons completely omitted (with exception to the lone pairs shown to highlight special properties). Therefore, when viewing Kekulé structures, it is helpful to keep in mind that atoms other than C and H should have a certain number of lone pairs. Examples of Kekulé structures of some compounds are given here:



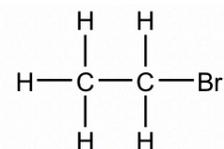
ethanol



acetic acid



ethyl amine



ethyl bromide

Figure 1.2f The Kekulé structures of ethanol, acetic acid, ethyl amine, and ethyl bromide

To count how many lone pairs should be involved on a certain atom, apply the octet rule. All of the atoms (except H) should have 8 electrons around it, therefore, N usually has 1 lone pair, O has 2 lone pairs and halogens have 3 lone pairs.

## 1.2.5 Exceptions to the Octet Rule in Lewis Structure

So far, we have always been applying the octet rule in Lewis structures; however, there are some cases in which this rule does not apply. For example, H only needs 2 electrons. Here, we will see some other cases in which the octet rule is compromised.

- Odd number of electrons

If the total number of valence electrons is an odd number, the octet rule can not be applied to all atoms in the species. Examples could include NO (nitrogen monoxide or nitric oxide), NO<sub>2</sub> (nitrogen dioxide) and alkyl radicals.

NO molecule: Although NO is a diatomic molecule, it is possible to draw the Lewis structure by following the procedure in section 1.2.2. Depending on which atom is given the octet first in Step 4, you may get two possible structures. By applying the formal charge guideline, we can decide that the first structure is the better choice with zero formal charges.

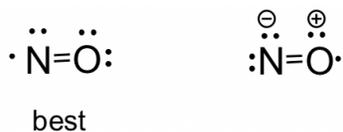


Figure 1.2g NO molecule Lewis structure

NO<sub>2</sub> molecule: The Lewis structure of an NO<sub>2</sub> molecule is shown below.

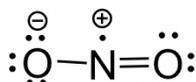


Figure 1.2h NO<sub>2</sub> molecule Lewis structure

The above molecules all contain unpaired (single) electrons. The neutral species that contain an unpaired electron are called radicals (or free radicals). When the carbon atom of an alkyl group has an unpaired electron, the species is the alkyl radical.

Alkyl radicals: The simplest example of an alkyl radical is •CH<sub>3</sub> with the total number of valence electrons as 7. The structure is:

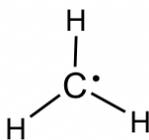


Figure 1.2i CH<sub>3</sub>  
Lewis structure

Further discussions about the properties and reactions of radicals will be included in Chapter 9.

- Incomplete Octet

An incomplete octet means the atom has less than 8 electrons involved. This could be because the total number of valence electrons is less than 8 or due to formal charge concerns.

BH<sub>3</sub> molecule: The total number of valence electrons is 6, so the central boron atom does not get an octet.

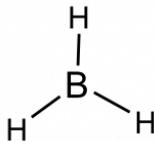


Figure 1.2j BH<sub>3</sub>  
molecule Lewis  
structure

BF<sub>3</sub> molecule: Even though all the atoms do have a chance to get octets in the structure of BF<sub>3</sub>, the actual structure of BF<sub>3</sub> keeps the incomplete octet. Applying the FC guideline explains why the first structure is the better choice. Similar examples include BeF<sub>2</sub> and AlCl<sub>3</sub>.

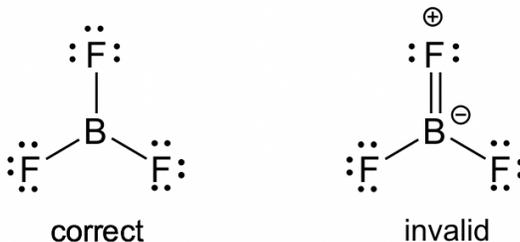


Figure 1.2k BF<sub>3</sub> molecule Lewis structure

F is the atom with the highest electronegativity; therefore, F atom NEVER has the “+” formal charge in any plausible Lewis structure!

CH<sub>3</sub><sup>+</sup>: This is another reactive intermediate in organic reactions (further discussions in Chapter 8). FC calculations

indicate that the “+” charge lies on the C atom, so such a species is also called a carbocation. Carbon has an incomplete octet.

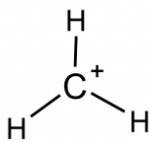


Figure 1.2l CH<sub>3</sub><sup>+</sup> molecule Lewis structure

- Expanded Valence Shell

For elements in Period 3 or higher, they can have more than 8 electrons if it helps to lower the formal charges. Common examples involve species with P, S, Cl, etc. as central atoms. Sometimes multiple double bonds are necessary to minimize the formal charge of the central atom. The structure of the phosphate anion, PO<sub>4</sub><sup>3-</sup>, is given here as an example.

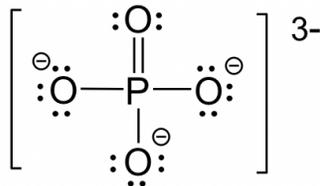


Figure 1.2m phosphate anion Lewis structure

Elements in Period 3 (or higher) have 3 (or more than 3) principal shells, so the *d* orbital is available in the valence shell. That is why they can accommodate more than 8 electrons.

#### Key Takeaways

For elements in 2<sup>nd</sup> period, C, N, O, F and Ne, the maximum number of electrons involved in Lewis structure is eight!!!

## 1.3 Resonance Structures

In cases in which more than one reasonable (plausible) Lewis structure can be drawn for a species, these structures are called resonance structures or resonance contributors. Resonance structures can be either equivalent or non-equivalent.

### Equivalent Resonance Structures

Let's consider the example of the carbonate anion,  $\text{CO}_3^{2-}$ :

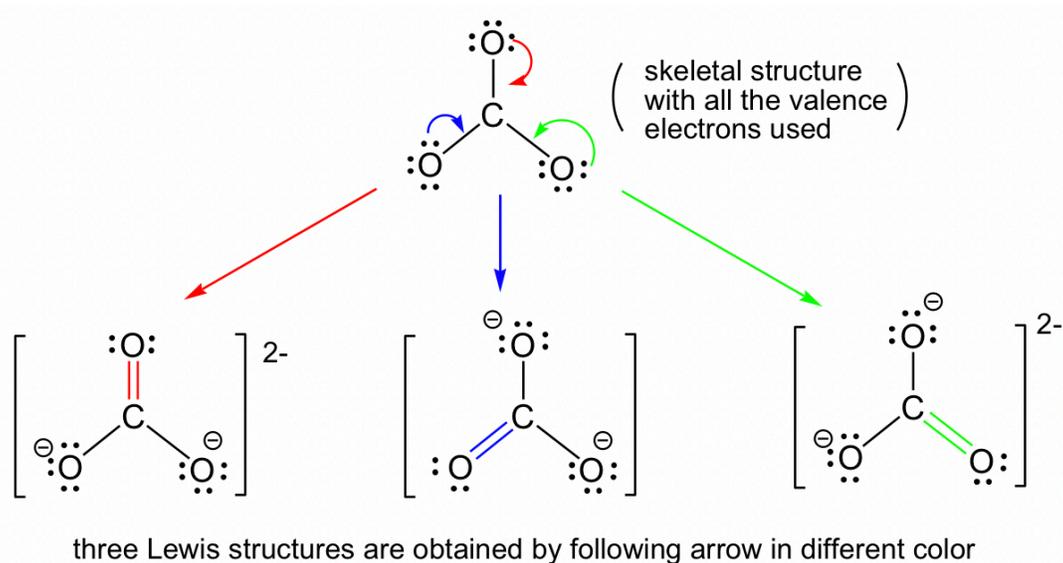
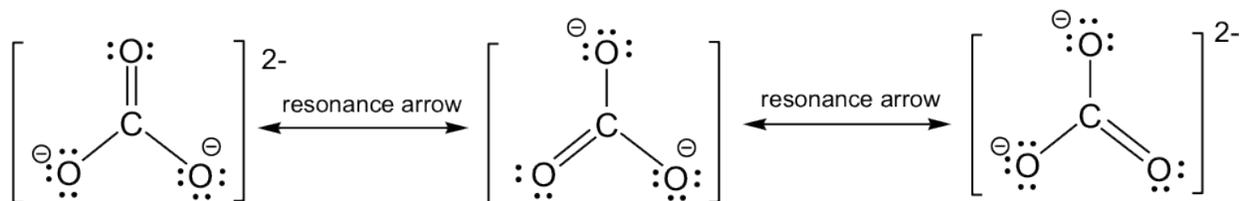


Figure 1.3a Versions of the carbonate anion Lewis structure

By following Step 6 in the Lewis structure drawing procedure, the double bond can be built between the central C and any of the terminal O's to generate three structures, and they all look "the same". However, they are not really identical (or the same), they are just equivalent. Each structure is called a resonance structure, and they can be connected by the double-headed resonance arrow. There are three equivalent resonance structures for  $\text{CO}_3^{2-}$ , and the actual structure of  $\text{CO}_3^{2-}$  is a hybrid of the three resonance contributors.



### three equivalent resonance contributors of carbonate anion

Figure 1.3b Three equivalent resonance contributors of carbonate anion

The arrows used here to connect between resonance structures is the “resonance arrow”, which has double arrow heads. Resonance structures have to be connected using resonance arrows.

Since the resonance structures are equivalent, they are all in the same level of energy and have the same stability, so they make the same contributions to the actual structure of  $\text{CO}_3^{2-}$ . This is supported by experimental evidence showing that all the carbon-oxygen bonds in  $\text{CO}_3^{2-}$  are the same bond length, which is longer than a regular double bond but shorter than a single bond. As a result of the resonance structures, the two negative charges in  $\text{CO}_3^{2-}$  are not localized on any oxygen atoms, but are spread evenly among all three oxygen atoms, and this is called charge delocalization. Because of charge delocalization, each oxygen atom has two-thirds of a full negative charge. Charge delocalization helps stabilize the whole species. The stability a species gains from having charge delocalization through resonance contributors is called the resonance stabilization effect. The greater the number of resonance contributors, the greater the resonance stabilization effect and the more stable the species is.

The actual structure of the carbonate anion is a combination of all three equivalent resonance structures, which can be called a hybrid. What does the actual structure look like, and can we draw one structure on paper to show the actual structure? The actual structure can not be shown with a conventional Lewis structure because the regular Lewis structures do not include partial charges, and there are two-thirds of a full negative charge on each oxygen atom in  $\text{CO}_3^{2-}$ . An attempt to show the hybrid structure can be done by using dashed lines to show that the bond between carbon and oxygen is somewhere between a single and double bond, and each oxygen atom has partial charges.

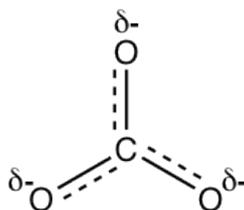


Figure 1.3c Dashed lines drawn on the carbonate anion Lewis structure to show the actual structure and partial charges

The delocalized charges can also be represented by the calculated electrostatic potential map of the electron density in the  $\text{CO}_3^{2-}$  anion. In an electrostatic potential map, regions with different charges are shown in different colours. More specifically, colours trending towards red mean higher negative charges, while colours trending toward blue mean more positive charges (the colour system generated by different types of software might not be the same, but they will follow the same trend). In the electrostatic potential map of the carbonate anion below, the same shade of red of all three oxygen atoms indicates the equal charge distribution at the three oxygen atoms.

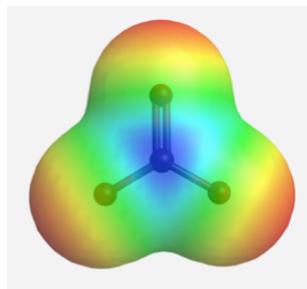


Figure 1.3d The electrostatic potential map of carbonate anion

### Exercises 1.5

Draw all the equivalent resonance structures for following species. Include any non-zero formal charges in the structures.

- O<sub>3</sub> molecule
- nitrate anion NO<sub>3</sub><sup>-</sup>
- chlorate anion ClO<sub>3</sub><sup>-</sup>.

### Answers to Chapter 1 Practice Questions

#### Non-equivalent Resonance Structures

Resonance structures can also be non-equivalent. For the example of OCN<sup>-</sup>, there are three non-equivalent resonance structures, depending on how the multiple bonds are formed in Step 6 of the Lewis structure drawing procedure.

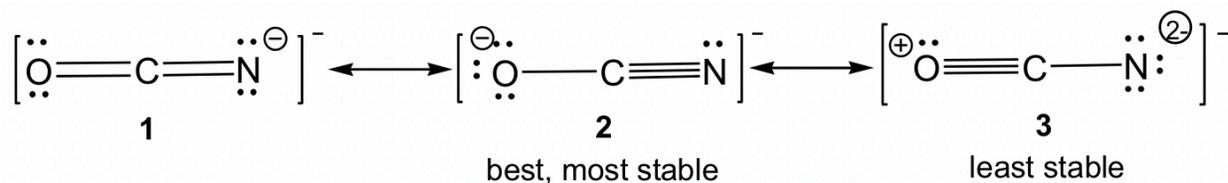


Figure 1.3e Three non-equivalent resonance structure contributors of OCN<sup>-</sup>

For non-equivalent resonance structures, the bonding and charge distributions are different, so they are in different energy levels. Some are more stable (better) resonance structures than others. The guidelines for comparing the relative stability between non-equivalent resonance structures are the lower the energy, the more stable the structure is, and vice versa:

- A structure with complete octets is usually more stable, except in the cases given in section 1.2.4 "Exceptions to the

Octet Rule”.

- A structure involving the smaller formal charges is more stable.
- Negative charges should be preferentially located on atoms with greater EN, and positive charges should be preferentially located on atoms with less EN
- Charge separation decreases the stability (increases the energy).

By applying the rules above, we can predict that for  $\text{OCN}^-$ , structure 3 is the least stable since it has the highest formal charges. For both structures 1 and 2, the formal charge is “-1”. It is preferable for negative formal charges to be on oxygen, the more electronegative atom; therefore, structure 2 is the most stable.

#### Exercises 1.6

Draw all of the resonance structures for azide anion,  $\text{N}_3^-$ , and indicate the most stable one.

Answers to Chapter 1 Practice Questions

## 1.4 Resonance Structures in Organic Chemistry

The Resonance stabilization effect (also known as the resonance effect), as briefly mentioned in Section 1.3, is one of the fundamental concepts of Organic Chemistry and has broad applications. The discussion of the resonance effect heavily relies on the understanding of resonance structures. Here, we will focus on how to draw resonance structures (or resonance contributors) for organic chemistry species and how to compare the relative stabilities between the structures.

According to the resonance effect, the greater the number of resonance contributors, the greater the resonance stabilization effect, and the more stable the species is. Therefore, to predict whether the resonance effect applies or not, we usually need to construct “new” resonance structures (contributors) based on the “original” one available. Some very important rules need to be followed for such purposes.

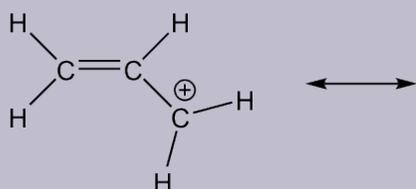
### Guidelines for Drawing Resonance Structures:

- All resonance structures must be valid Lewis structures. (Keep in mind that all the rules applied to Lewis structures still apply here!)
- All resonance structures must have the same atom connectivity and only differ in the electron arrangement. (Atoms NEVER move; only electrons move.)
- All resonance structures have the same number of electrons and net charge. (Formal charges on individual atoms could be different, but the net charge, which is the sum of all the charges, must be the same.) To move electrons, only  $\pi$  electrons and lone pair electrons (NEVER move  $\sigma$  bonds!) can be moved from a higher electron density area to a lower electron density area by following one of the three transformations:
  - a  $\pi$  bond forms another  $\pi$  bond;
  - a  $\pi$  bond forms the lone pair electrons; and
  - lone pair electrons form a  $\pi$  bond.
- Use curved arrows to indicate the electron movement in the “original” resonance structure. The “new” resonance structure should be a “product” automatically obtained by following the arrows.
- Calculate the formal charge in the “new” structure and label any non-zero formal charges.

The way to use curved arrows to show electron transfer is also called arrow pushing, and it is a very important fundamental skill you need to master in organic chemistry. To construct “new” resonance structures, arrows have to be shown in the “original” structure.

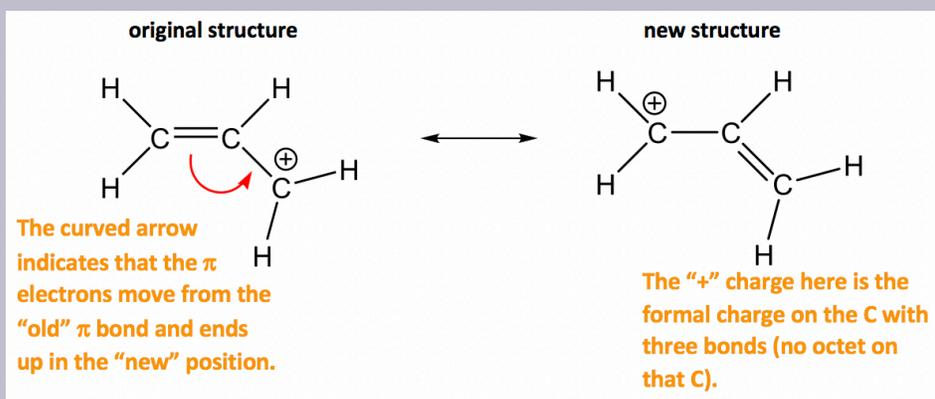
*Examples: Draw another resonance structure based on the given one.*

1.

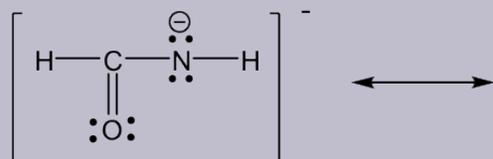


Approach: There is only one  $\pi$  bond in this example, and no any lone pairs, so only the  $\pi$  electrons can be moved around. There is a carbocation beside the  $\pi$  bond, which is the low electron density spot. Therefore it is reasonable to move the  $\pi$  electrons to the position beside carbocation to form another  $\pi$  bond, and that gives the “new” structure. The two resonance structures here are equivalent.

Solution:

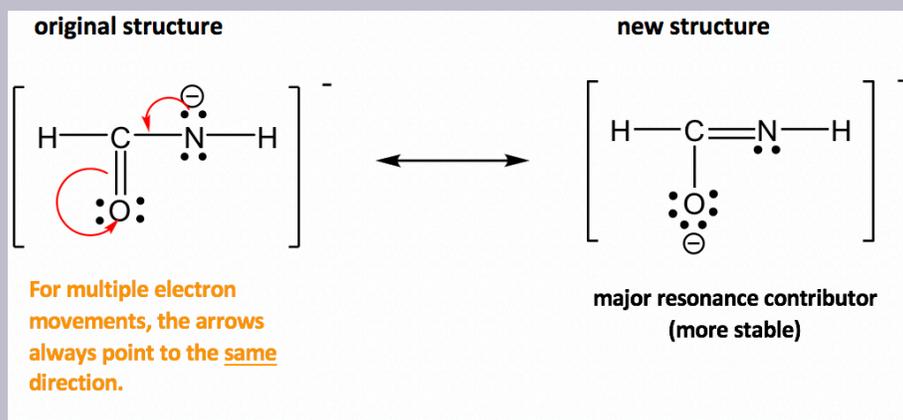


2.



Approach: More electrons available for movement in this example: several lone pairs and one  $\pi$  bond. The guideline of “move electrons from the higher electron density area to the lower electron density area” provides a useful hint about where to start. The nitrogen atom has a “-” formal charge, meaning it has a relatively high electron density, higher than other neutral spots. So it is reasonable to move the lone pair on nitrogen away to form a  $\pi$  bond (keep in mind that lone pair can only form  $\pi$  bond, *not* another lone pair). However, when the new  $\pi$  bond is formed around the carbon atom, there are 5 bonds (10 electrons) on that carbon, which is not allowed. So, another electron pair has to be moved away, and the only available electron pair to be moved is the  $\pi$  electrons in C=O bond. It can be moved onto the oxygen atom and become another lone pair on the oxygen atom.

Solution:



The two resonance structures in this example are *non-equivalent*, so one is more stable than the other. By applying the formal charge guideline, the “-“ formal charge is more preferable on oxygen, which is more electronegative than nitrogen, so the 2<sup>nd</sup> structure is the more stable one with lower energy, and makes more contribution to the actual structure in this species. The more stable structure can also be called as the major resonance contributor.

Comparing the relative stability of different resonance contributors:

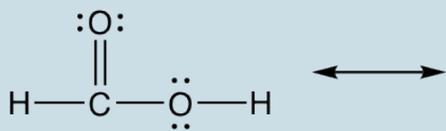
- Structures with a maximum of octets are the most important.
- Charge separation usually decreases the stability (increases the energy of the contributor).
- Negative charges should be preferentially located on atoms with greater electronegativity, and positive charges should be preferentially located on atoms with less electronegativity.

Common errors in drawing resonance structures:

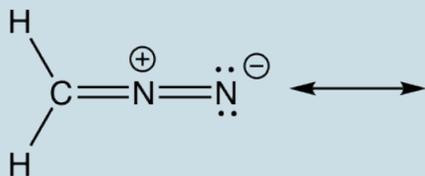
1.  $\sigma$  bond is moved.
2. An Atom is moved.
3. There are more than eight electrons located around C, N or O.
4. Arrows are not shown in the proper way.
5. Electron pairs are moved too far away; they should only be moved to the next position/atom.

Exercises 1.7 Draw new resonance structure and compare the relative stability, show arrows in the original structure.

1.



2.



Answers to Chapter 1 Practice Questions

# 1.5 Valence-Shell Electron-Pair Repulsion Theory (VSEPR)

The Valence-Shell Electron-Pair Repulsion (VSEPR) theory helps us understand and predict the geometry (shape) of molecules or ions. The theory states that:

- Electron pairs repel each other whether they are in chemical bonds or lone pairs.
- Valence electron pairs are oriented to be as far apart as possible to minimize repulsions.

Based on this theory, depending on the number of electron pairs (both bonding pairs and lone pairs) around the central atom, a certain shape is adopted to minimize the repulsion between electron pairs, as summarized in Table 1.2 below:

Total number of electron groups (electron pairs) around the central atom	Geometry (Shape) of electron groups (electron pairs)
2	linear
3	trigonal planar
4	tetrahedral
5	trigonal bipyramidal
6	octahedral

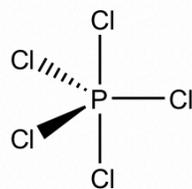
Table 1.2 Basic VSEPR Shapes

Notes:

- For VSEPR purposes, the terms “shape” and “geometry” are interchangeable; “electron pair” and “electron group” are also interchangeable.
- Multiple bonds (double or triple bonds) are regarded as one electron group for VSEPR purposes.

For species that do not have any lone pair electrons (LPs), the geometry (shape) of the species is the same as the geometry of the electron groups.

For the example of the  $\text{PCl}_5$  molecule, there are five electron groups on the central phosphorous, and they are all bonding pairs (BPs). The shape of the electron groups is trigonal bipyramidal, and the shape of the  $\text{PCl}_5$  molecule is trigonal bipyramidal as well. The trigonal bipyramidal shape can be drawn on paper using solid and dashed wedges: the three bonds that lie within the paper plane are shown as ordinary lines, the solid wedge represents a bond that points out of the paper plane, and the dashed wedge represents a bond that points behind the paper plane.

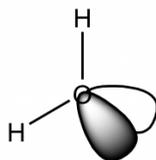


### **trigonal bipyramidal shape of $\text{PCl}_5$ molecule**

*Figure 1.5a Trigonal bipyramidal shape of  $\text{PCl}_5$  molecule*

However, for the species that has lone pair electrons on the central atom, the shape of the species will be different from the shape of the electron groups. The reason is that even though the lone pairs occupy the space, there are no terminal atoms connected with the lone pairs, so the lone pairs become “invisible” for the shape of the species.

For the example of the water ( $\text{H}_2\text{O}$ ) molecule, the central oxygen atom has two BPs and two LPs, and the shape of all the electron groups is tetrahedral. The shape of a water molecule is bent because only the atoms are counted towards the molecular shape, not the lone pair electrons.



### **bent shape of $\text{H}_2\text{O}$ molecule**

*Figure 1.5b Bent shape of  $\text{H}_2\text{O}$  molecule*

The VSEPR shapes can be highly diverse, considering the different numbers of total electron pairs together with the different numbers of lone pairs involved. The most common shapes are summarized in the following table (Table 1.3). To describe a certain shape, the specific name has to be used properly, and the bond angle information is important as well.

Total number of e-groups	Geometry (shape) of all the electron groups	# of Bonding Pairs (BP) and Lone Pairs (LP)	Geometry (shape) of the species	Angles (°)
2	linear	2BP	linear	180
3	trigonal planar	3BP	trigonal planar	120
		2BP, 1LP	bent	<120
4	tetrahedral	4BP	tetrahedral	109.5
		3BP, 1LP	trigonal pyramidal	<109.5
		2BP, 2LP	bent	<109.5
5	trigonal bipyramidal	5BP	trigonal bipyramidal	120, 90, 180
		4BP, 1LP	see-saw	<120, 90, 180
		3BP, 2LP	T-shape	90, 180
		2BP, 3LP	linear	180
6	octahedral	6BP	octahedral	90, 180
		5BP, 1LP	square pyramidal	90, 180
		4BP, 2LP	square planar	90, 180

Table 1.3 Summary of specific VSEPR shapes

The website Molecule Shapes [https://phet.colorado.edu/sims/html/molecule-shapes/latest/molecule-shapes\\_en.html](https://phet.colorado.edu/sims/html/molecule-shapes/latest/molecule-shapes_en.html) provides good resources for visualizing and practicing VSEPR topics.

We will see more applications of VSEPR in organic compounds in the next section.

# 1.6 Valence Bond Theory and Hybridization

## 1.6.1 Valence Bond Theory

We have discussed how covalent bonds are formed through the sharing of a pair of electrons; here we will apply the valence bond theory to explain in more detail how the sharing happens. The valence bond theory describes the covalent bond formed from the overlap of two half-filled atomic orbitals on different atoms.

Let's start with the simple molecule  $H_2$ . The atomic electron configuration of a hydrogen atom is  $1s^1$ , meaning there is one electron (which is also the valence electron) in the sphere-shaped  $1s$  orbital.

When two hydrogen atoms are approaching each other, the two  $1s$  orbitals overlap, allowing the two electrons (each H donates 1 electron) to pair up for the bonding with the overlapping orbitals. The shared pair of electrons are under the attraction of both hydrogen nuclei simultaneously, resulting in them acting as a "glue" that holds the two nuclei together.

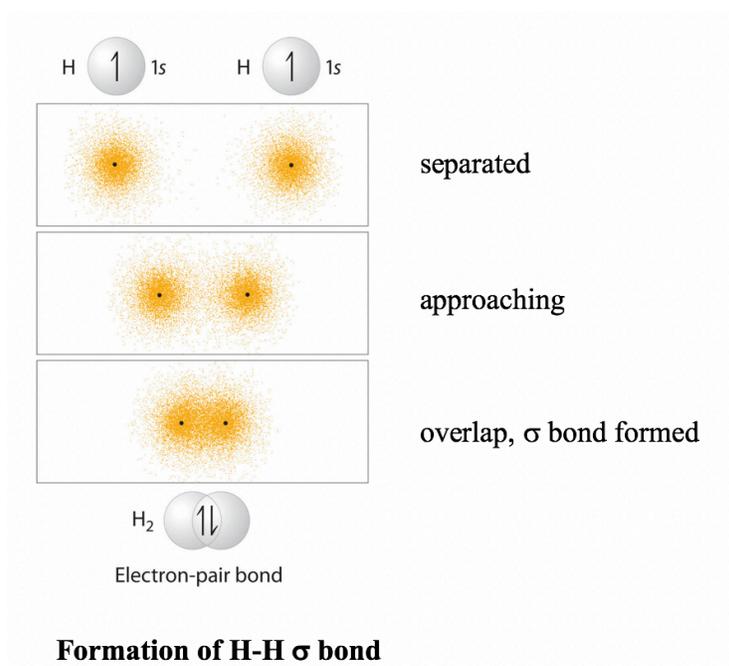


Figure 1.6a Formation of H-H bond

The overall energy changes of the system *versus* the distance between the two hydrogen nuclei can be summarized in the energy diagram below.

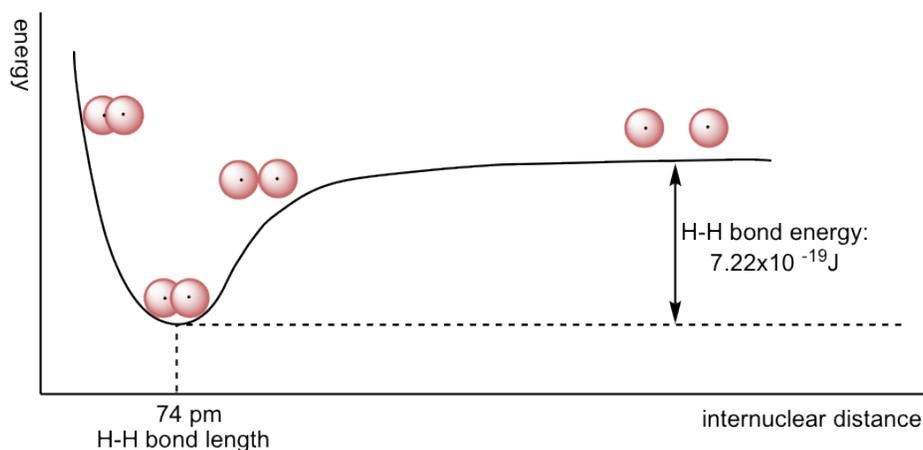


Figure 1.6b Potential energy of the hydrogen molecule as a function of internuclear distance

When the two atoms are separate, there is no overlap and no interaction. As they get closer, orbitals start to overlap, and there is attraction between the nucleus of one atom and the electron of the other atom, so the total energy of the system lowers. The energy lowers to its minimum level when the two atoms approach the optimal distance. The optimal distance is also defined as the bond length. H<sub>2</sub> molecules have a bond length of 74 pm (often referred to as 0.74 Å, 1Å= 10<sup>-10</sup>m). The energy difference between the most stable state (lowest energy state with optimum distance) and the state in which the two atoms are completely separated is called the bond (dissociation) energy. The bond energy is 7.22×10<sup>-19</sup> J for one H-H bond or 435 kJ/mol.

When the two atoms get closer than the optimal distance, the repulsion between the two nuclei becomes predominant, and the energy of the system becomes even higher.

Another important character of the covalent bond in H<sub>2</sub> is that the two 1s orbitals overlap in a way that is referred to as head-to-head. The bond formed by head-to-head overlap is called σ (sigma) bond. σ bonds are cylindrically symmetrical, meaning if a cross-sectional plane is taken of the bond at any point, it will form a circle.

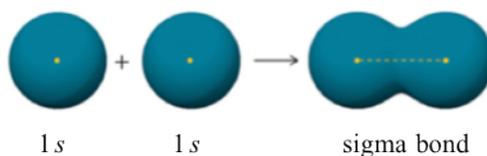


Figure 1.6c Cylindrical symmetry property of σ bond

The valence bond theory works well to explain the bonding in HF as well, with the 2p orbital of fluorine atom involved in the overlapping.

The fluorine atom has the valence electron configuration of 2s<sup>2</sup>2p<sup>5</sup> as shown in the orbital diagram.

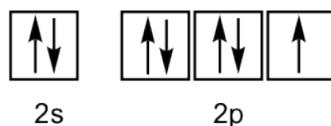


Figure 1.6d Orbital diagram of valence electrons in fluorine atom

For the three 2p orbitals, two of them are filled, and the other one is half-filled with one single electron. The filled orbital cannot form bonds, so only the half-filled 2p is available for overlap. Therefore, the 1s orbital of the hydrogen atom overlaps head-to-head with the half-filled 2p orbital of the fluorine atom to form the H-F  $\sigma$  bond, as shown below.

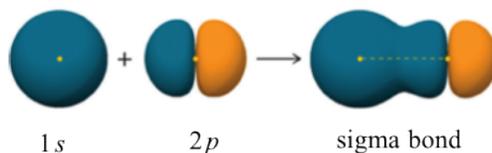


Figure 1.6e H-F  $\sigma$  bond

A  $\sigma$  bond can also be formed through the overlap of two p orbitals. The covalent bond in molecular fluorine,  $F_2$ , is a  $\sigma$  bond formed by the overlap of two half-filled 2p orbitals, one from each fluorine atom as shown here.

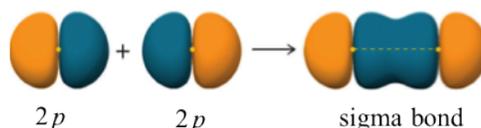


Figure 1.6f  $F_2$   $\sigma$  bond

However, when the valence bond theory is applied to organic molecules, for instance  $CH_4$ , it does not work. The valence electron configuration of a carbon atom is  $2s^2 2p^2$  as shown in the orbital diagram.

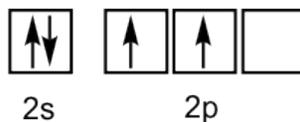


Figure 1.6g Orbital diagram of valence electrons in carbon atom

Based on the valence bond theory, with two half-filled orbitals available, the carbon atom should be able to form two bonds. However, carbon always has four bonds in any stable organic compound. To explain the bonding of carbon and other atoms that cannot fit into the simple valence bond theory, a new theory called orbital hybridization will be introduced as a supplement to the valence bond theory.

## 1.6.2 Hybridization and the Structure of $CH_4$

Simply speaking, hybridization refers to the mathematical combination of several orbitals to generate a set of new hybrid orbitals.

In the hybridization for  $CH_4$ , the 2s and three 2p orbitals are combined to give a new set of four identical orbitals

that are called  $sp^3$  hybrid orbitals. The symbol  $sp^3$  here identifies the numbers and types of orbitals involved in the hybridization: one  $s$  and three  $p$  orbitals. For the hybridization process,

$$\text{number of hybrid orbitals} = \text{the total number of atomic orbitals that are combined}$$

It means that with a total of four orbitals combined, four new hybrid orbitals are generated, and they are all named  $sp^3$  hybrid orbitals. These new hybrid orbitals are all in the same energy level between those of  $2s$  and  $2p$  orbitals and are directed in a tetrahedral shape overall with the angle between any two orbitals as  $109.5^\circ$ . Each  $sp^3$  hybrid orbital has two lobes that are very different in size. The lobe with the larger size is in the positive phase and is responsible for bonding.

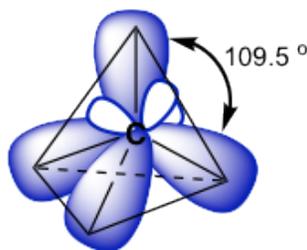
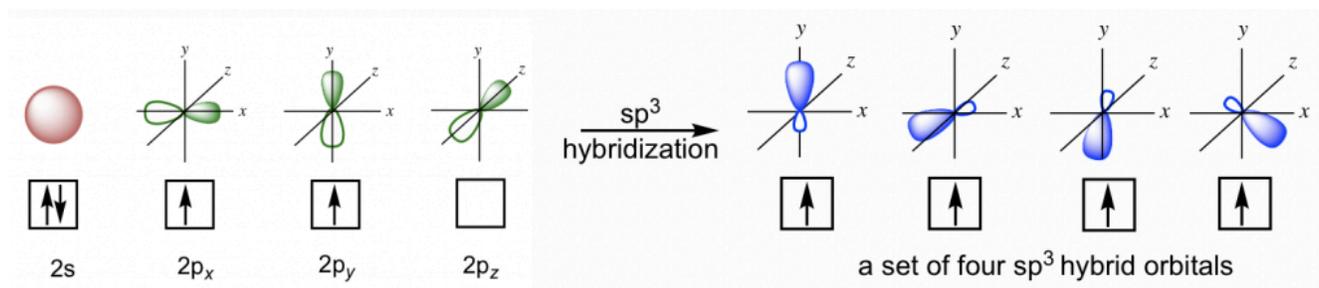


Figure 1.6h Four  $sp^3$  hybrid orbitals oriented in tetrahedral shape

Since there are four  $sp^3$  hybrid orbitals available, each of the four valence electrons occupies one of them, so there are four half-filled  $sp^3$  orbitals in the carbon atom that are able to form four bonds. Therefore, the C-H bond of  $CH_4$  is formed by the overlapping between the  $1s$  orbital in the hydrogen atom and the  $sp^3$  orbital in the carbon atom.

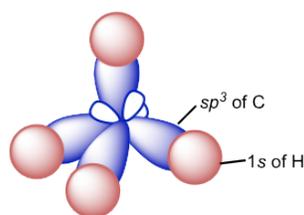


Figure 1.6i Orbital overlap of C-H bonds in methane

Because the arrangement of the four  $sp^3$  hybrid orbitals is in a tetrahedral shape, the shape of the  $CH_4$  molecule is also tetrahedral, which is consistent with the shape predicted by VSEPR. The tetrahedral shape of the  $sp^3$  carbon can usually be drawn using solid and dashed wedges. Out of the four bonds, the two bonds that lie within the paper plane are shown as ordinary lines, the solid wedge represents a bond that points out of the paper plane, and the dashed wedge represents a bond that points behind the paper plane. These perspective drawings that show the 3D tetrahedral shape are particularly important in the discussion of stereochemistry in Chapter 5.

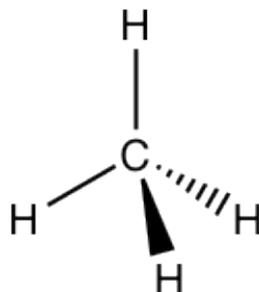


Figure 1.6j Tetrahedral shape of methane with solid and dashed wedges drawing

### 1.6.3 Hybridization and VSEPR

Other than  $sp^3$  hybridization, there are also other types of hybridization that include  $sp$ ,  $sp^2$ ,  $sp^3d$  and  $sp^3d^2$ . Usually, the hybridization on a certain atom can simply be determined by counting the total number of electron groups (bonding pairs and lone pairs). The total number of electron groups equals the total number of orbitals involved in the specific hybridization. For example, in a  $CH_4$  molecule, the central carbon atom has four bonding pairs, so the hybridization of carbon is  $sp^3$  (one  $s$  and three  $p$  orbitals,  $1+3=4$ ). If a central atom has a total of five electron groups (bonding pairs and lone pairs altogether), then the hybridization is  $sp^3d$  (one  $s$ , three  $p$  and one  $d$  orbitals,  $1+3+1=5$ ).

This correlation may remind you of VSEPR. Hybridization and VSEPR are two separate concepts, but they can be correlated together via the number of electron groups in common. The following table (Table 1.4) is very useful in correlating the hybridization and VSEPR shape/bond angles around the central atom and the total number of electron groups together.

Hybridization on the central atom	Total number of electron pairs (BP and LP) around the central atom	Geometry (Shape) of electron groups (electron pairs)
sp	2	linear
sp <sup>2</sup>	3	trigonal planar
sp <sup>3</sup>	4	tetrahedral
sp <sup>3</sup> d	5	trigonal bipyramidal
sp <sup>3</sup> d <sup>2</sup>	6	octahedral

Table 1.4 Correlation between Hybridization and VSEPR

### Exercises 1.8

1. What is the hybridization of the oxygen atom in H<sub>2</sub>O molecule?
2. What is the hybridization of the xenon atom in XeF<sub>4</sub> molecule, and what is the shape of the whole molecule?

Answers to Chapter 1 Practice Questions

## 1.6.4 The Hybridization and VSEPR in Organic Molecules

Organic molecules usually contain more than one central atom, so it is not practical to name the shape of the whole molecule; instead, we can talk about the shape/bond angle of each central atom individually. For such purposes, we must make sure to include the lone pairs that are usually left out in the organic structures (refer to section 1.2.4). The different structural formulas of ethanol, acetic acid and ethanenitrile molecules are shown in the table below. The 3D molecular model for each compound is shown as well to help you visualize the spatial arrangement. We can see that the hybridization and VSEPR shapes need to be separately indicated for each internal atom. Taking the oxygen atom in the OH group of ethanol as an example, since there are two pairs of lone pair electrons on the oxygen atom as well (these are omitted in the structures in the table), the oxygen has sp<sup>3</sup> hybridization and is in a tetrahedral shape.

	<u>Kekulé structures</u>	Perspective formula with hybridization and shape of central atoms	3D models
ethanol	$\begin{array}{c} \text{H} & & \text{H} \\   & &   \\ \text{H}-\text{C} & - & \text{C}-\text{OH} \\   & &   \\ \text{H} & & \text{H} \end{array}$		
acetic acid	$\begin{array}{c} \text{H} & & \text{O} \\   & &    \\ \text{H}-\text{C} & - & \text{C}-\text{OH} \\   & & \\ \text{H} & & \end{array}$		
ethanenitrile (acetonitrile)	$\begin{array}{c} \text{H} \\   \\ \text{H}-\text{C}-\text{C}\equiv\text{N} \\   \\ \text{H} \end{array}$		

Table 1.5 Hybridization and VSEPR of organic molecule examples [Image Description]

## 1.6.5 Multiple Bonds in Organic Structures

Ethene ( $\text{C}_2\text{H}_4$ )

We will take Ethene ( $\text{C}_2\text{H}_4$ ) as an example for understanding the structure of a double bond.

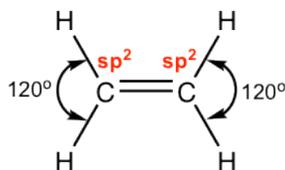


Figure 1.6k Ethene hybridization

According to the structure formula of  $\text{C}_2\text{H}_4$ , there are three electron groups around each carbon. By referring to Table 1.3, it is determined that both carbons are in  $sp^2$  hybridization, with the trigonal planar shape and a  $120^\circ$  bond angle. What does the  $sp^2$  hybridization mean to the carbon atom in this compound? It means that only three orbitals are involved in the hybridization (one 2s and two of 2p orbitals) out of the total four, and there is one 2p orbital left out or not included in the hybridization, which is called the unhybridized 2p.

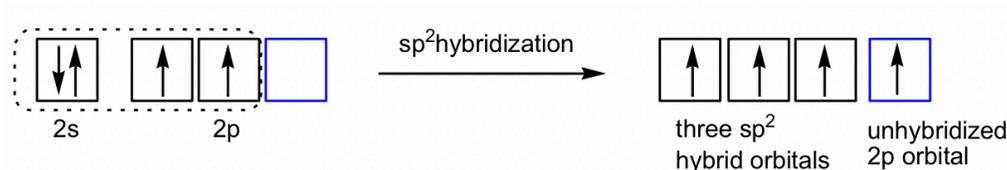
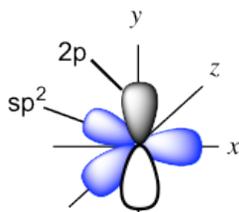


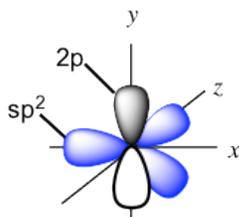
Figure 1.6l Orbital hybridization diagram of valence electrons in Ethene

The three new  $sp^2$  hybrid orbitals and the unhybridized 2p are directed in the following arrangement: the three  $sp^2$  hybrid orbitals are in a trigonal planar shape, and the unhybridized 2p is in a position perpendicular to the plane. Each orbital has one single electron, so all the orbitals are half-filled and are available for bonding. Both carbon atoms have the same set of orbitals (three  $sp^2$  hybrid orbitals and one unhybridized 2p) as shown below.



the set of orbitals:  $sp^2 + 2p$

Figure 1.6m The set of orbitals:  $sp^2 + 2p$



the set of orbitals:  $sp^2 + 2p$

Figure 1.6n The set of orbitals  $sp^2 + 2p$

When the two carbons approach each other, the  $sp^2$  on the x-axis overlaps head-to-head to form the C-C  $\sigma$  sigma bond, and the “unhybridized” 2p overlaps side-by-side to form another new bond. The side-by-side orbital overlapping forms the  $\pi$  (pi) bond.

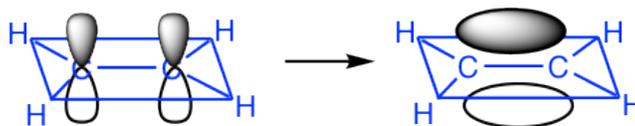


Figure 1.6o Side-by-side overlap of p orbitals leading to pi ( $\pi$ ) bond

So now we understand that the C=C double bond contains two different bonds: the  $\sigma$  (sigma) bond from  $sp^2-sp^2$  orbital overlapping and the  $\pi$  (pi) bond from 2p-2p overlapping. Because of the  $\pi$  bond, the overall shape of the whole C<sub>2</sub>H<sub>4</sub> molecule is co-planar.

The other  $sp^2$  hybrid orbitals on each carbon atom overlap with 1s orbital of H atoms and give a total of four C-H  $\sigma$  (sigma) bonds.

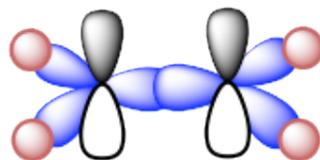


Figure 1.6p Sigma ( $\sigma$ ) bond framework of C<sub>2</sub>H<sub>4</sub>

Ethyne (C<sub>2</sub>H<sub>2</sub>)

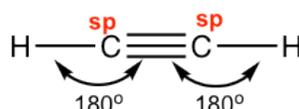


Figure 1.6q Ethyne hybridization

Ethyne C<sub>2</sub>H<sub>2</sub> (common name is acetylene) has a C $\equiv$ C triple bond. Generally, triple bonds involve one  $\sigma$  sigma bond and two  $\pi$  (pi) bonds. Both carbon atoms are in  $sp$  hybridization and in a linear shape. With  $sp$  hybridization, each carbon has two  $sp$  hybrid orbitals and two unhybridized 2p orbitals. Each carbon uses one  $sp$  hybrid orbital to overlap head-to-head and gives the C-C the  $\sigma$  sigma bond; meanwhile, the 2p orbitals overlap side-by-side to give two  $\pi$  bonds as shown in the diagram below. The other  $sp$  orbitals are used for overlapping with 1s of hydrogen atoms to form C-H  $\sigma$  bonds.

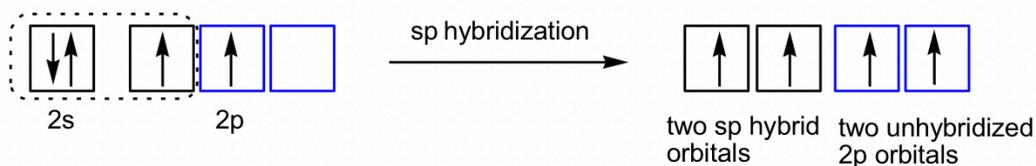
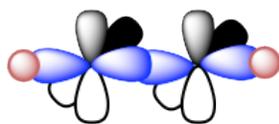
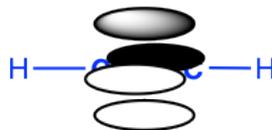


Figure 1.6r Orbital hybridization diagram of valence electrons in Ethyne



sigma ( $\sigma$ ) bond framework of C<sub>2</sub>H<sub>2</sub>



two pi ( $\pi$ ) bonds in C<sub>2</sub>H<sub>2</sub>

Figure 1.6s Sigma ( $\sigma$ ) bond framework of Ethyne and two pi ( $\pi$ ) binds of Ethyne

## Image Descriptions

Table 1.5 image description: Ethanol's CH<sub>3</sub>, CH<sub>2</sub>, and OH are all in a sp<sup>3</sup> tetrahedral shape. Acetic acid's CH<sub>3</sub> and OH are in a sp<sup>3</sup> tetrahedral shape, and CO is in a sp<sup>2</sup> trigonal planar. Lastly, ethanenitrile's (acetonitrile) CH<sub>3</sub> is in a sp<sup>3</sup> tetrahedral shape, and CN is in a sp linear shape. [Return to Table 1.5]

# Answers to Chapter 1 Practice Questions

## I.1

Number of valence electrons:

B: 3 valence electrons

N: 5 valence electrons

O: 6 valence electrons

Cl: 7 valence electrons

Mg: 2 valence electrons

## I.2

- Identify whether the following bond is “polar” or “non-polar”.

C-C: non-polar      C-H: non-polar (very close electronegativity for C and H)

B-F: polar      O-O: non-polar      C=N: polar

- Rank the following bonds in the order of increasing bonding polarity: C-S, C-O, C-F (referring to the trend of EN, no need to use the exact EN values).

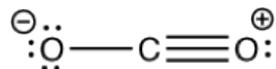
bonding polarity: C-S < C-O < C-F

## I.3

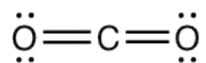
Draw the Lewis structure of an N<sub>2</sub> molecule:  $\text{:N}\equiv\text{N:}$

## I.4

Why is the following structure is not the best way to show the Lewis structure of CO<sub>2</sub>?



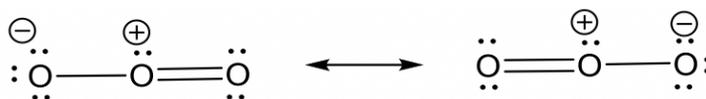
Because the formal charges are not minimized in the above structure. The formal charge in the best Lewis structure of CO<sub>2</sub> are all zero, and the best Lewis structure of CO<sub>2</sub> is shown here:



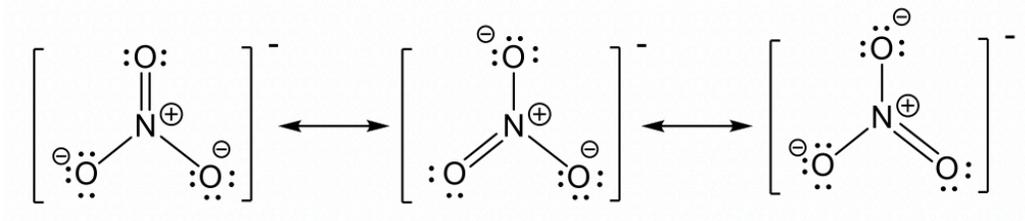
## I.5

Draw all the equivalent resonance structures for the following species. Include any non-zero formal charges in the structures.

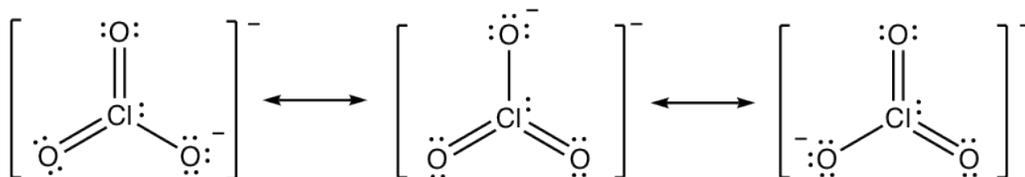
- O<sub>3</sub> molecule



- nitrate anion NO<sub>3</sub><sup>-</sup>

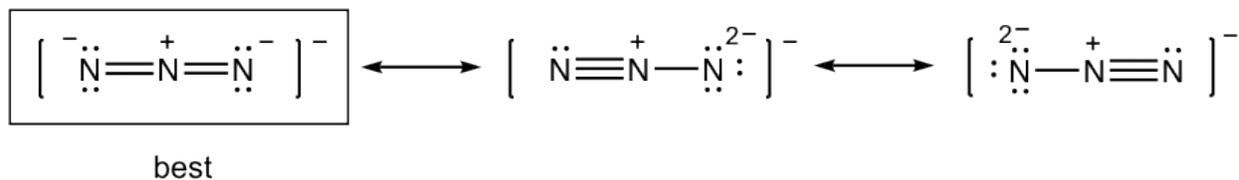


- chlorate anion ClO<sub>3</sub><sup>-</sup>



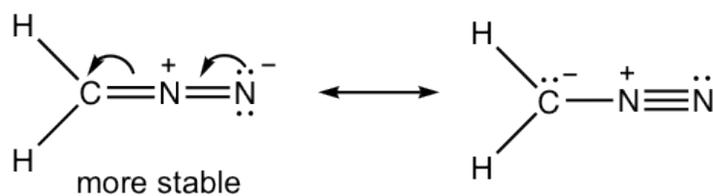
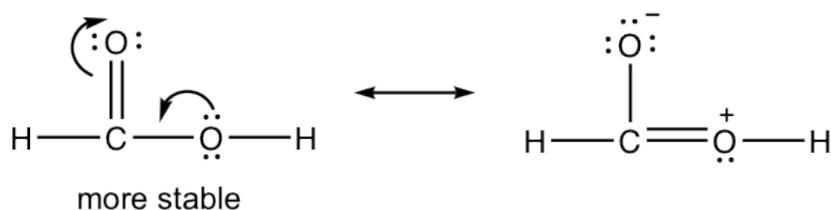
## I.6

Draw all the resonance structures for the azide anion, N<sub>3</sub><sup>-</sup>, and indicate the most stable one.



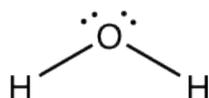
### I.7

Draw a new resonance structure and compare the relative stability; show the arrows in the original structure.



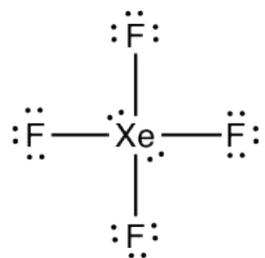
### I.8

- What is the hybridization of the oxygen atom in a H<sub>2</sub>O molecule?



four electron groups around central oxygen (2 BP, 2 LP),  
the oxygen is in  $sp^3$  hybridization

- What is the hybridization of the xenon atom in an XeF<sub>4</sub> molecule, and what is the shape of the whole molecule?



six electron groups around central oxygen (4 BP, 2 LP),  
the oxygen is in  $sp^3d^2$  hybridization



# CHAPTER 2: FUNDAMENTALS OF ORGANIC STRUCTURES

In this chapter, we will discuss the fundamental structural features of organic compounds, the categorization and drawing of organic structures, functional groups, and nomenclatures.

Learning Objectives for this chapter:

- Draw, recognize and read different structure formulas that represent organic molecules correctly and skillfully.
- Understand and be able to recognize constitutional isomers. Draw all constitutional isomers with a given formula, by applying both structure knowledge and degree of unsaturation concept.
- Recognize and name simple organic molecules with common functional groups by applying IUPAC nomenclature.
- Understand the nature and structure effect on different intermolecular forces, and be able to predict and explain the physical property of substance based on the intermolecular force knowledge.

## Organic Compounds Overview

Organic compounds are compounds that contain the carbonelement. The simplest organic compound is a hydrocarbon, which is a compound containing only the elements carbon and hydrogen. Hydrocarbons are composed of several sub-categories: alkane, alkene, alkyne and aromatic, depending on the type of carbon-carbon bonds involved.

Hydrocarbons can be in chains (straight-chains or branched-chains) or rings. The hydrocarbon chain and ring form the “carbon backbone” of organic compounds, and functional groups connected to the backbone allow for a great diversity of organic structures. Functional groups are common and specific arrangements of atoms, usually heteroatoms (atoms other than carbon and hydrogen) like N, O, and Cl that show specific and relatively high reactivities. Knowledge about the common functional groups in this chapter will prepare us for the later discussion on organic reactions.

## Hydrocarbons:

- Alkane and cycloalkane: contain only C-C (single) bonds
- Alkene and cycloalkene: contain one or more C=C (double) bonds
- Alkyne: contains one or more C≡C (triple) bonds
- Aromatic: contains a benzene ring and its derivative

Alkene, alkyne and aromatic rings are categorized as hydrocarbon functional groups because of the presence of multiple bonds, even without heteroatoms.

Functional Groups involving heteroatoms (see details in Table 2.2, section 2.3):

- Alkyl halides (haloalkanes), alcohol, ether, nitrile, nitro, amine, aldehyde, ketone, carboxylic acid, ester, amide,

anhydride

## 2.1 Structures of Alkenes

### 2.1.1 Structures and Different Structure Formulas

Alkane is the simplest hydrocarbon with only C-C single bonds. The chain alkane fits the general formula of  $C_nH_{2n+2}$  (n: positive integer), and the number of H atoms reaches the maximum level in chain alkanes. The names and structures of straight-chain alkanes up to ten carbons are listed in Table 2.1 below.

Number of Carbons	Name	Formula ( $C_nH_{2n+2}$ )	Condensed Structure
1	methane	CH <sub>4</sub>	CH <sub>4</sub>
2	ethane	C <sub>2</sub> H <sub>6</sub>	CH <sub>3</sub> CH <sub>3</sub>
3	propane	C <sub>3</sub> H <sub>8</sub>	CH <sub>3</sub> CH <sub>2</sub> CH <sub>3</sub>
4	butane	C <sub>4</sub> H <sub>10</sub>	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
5	pentane	C <sub>5</sub> H <sub>12</sub>	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
6	hexane	C <sub>6</sub> H <sub>14</sub>	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
7	heptane	C <sub>7</sub> H <sub>16</sub>	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
8	octane	C <sub>8</sub> H <sub>18</sub>	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
9	nonane	C <sub>9</sub> H <sub>20</sub>	CH <sub>3</sub> CH <sub>2</sub> CH <sub>3</sub>
10	decane	C <sub>10</sub> H <sub>22</sub>	CH <sub>3</sub> CH <sub>2</sub> CH <sub>3</sub>

Table 2.1 Names and Structures of Straight-Chain Alkanes

The primary sources of alkanes are natural gas and petroleum. Natural gas contains mainly methane (70–90%) and some ethane. Petroleum refining separates crude oil into different fractions, and each fraction consists of alkanes of a similar number of carbons. Propane and butane are common fuels in propane gas burners and cigarette lighters. Alkanes with 5 to 8 carbons are the major components of gasoline, while diesel contains alkanes ranging from 9 to 16 carbons. As the number of carbons increases, the boiling point and viscosity of alkanes increase.

There are a variety of formats to show the structural formulas of organic compounds, and it is important to be able to recognize different formula drawings and use them correctly to represent the structures.

### Kekulé Structure

We have had some discussions on Kekulé structures in section 1.2.4. They are similar to Lewis structures with all the bonding electrons shown in short lines and all the atoms included as element symbols. However, the lone pair electrons are left out in Kekulé structures, which is the major difference between Kekulé structures of organic compounds and Lewis structures.

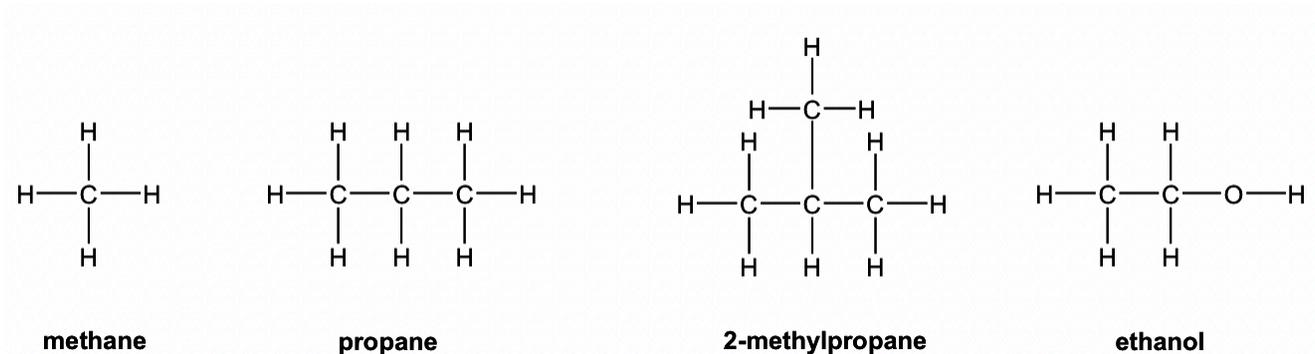


Figure 2.1a Examples of Kekulé Structures

## Condensed Structure Formula

In condensed structure formulas, the C-H bonds are omitted, and all the H atoms attached to a certain carbon (or other atoms) are usually shown as a group like CH<sub>3</sub>, CH<sub>2</sub>, NH<sub>2</sub>, and OH. The structures in Table 2.1 are shown as condensed structures. The C-C bond sometimes can be omitted as well (as for 2-methylpropane and 2-hexanol in the examples below). Usually, if the structure has a branch, the bonding between the parent structure to the branch needs to be shown with a short line. It is faster to draw a structure with a condensed structure formula, and it does not look as bulky as Kekulé structures.

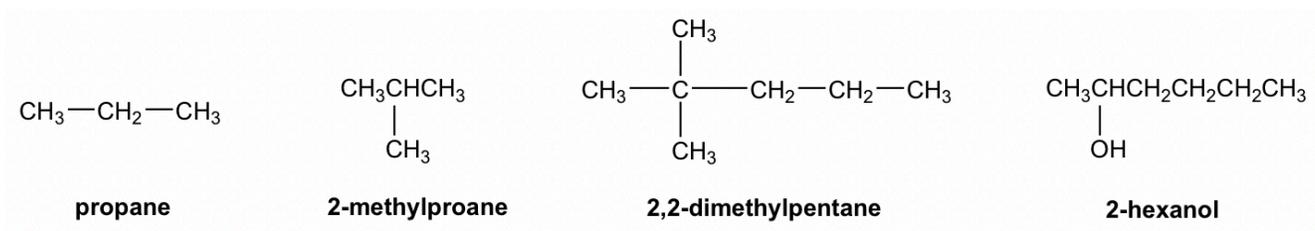
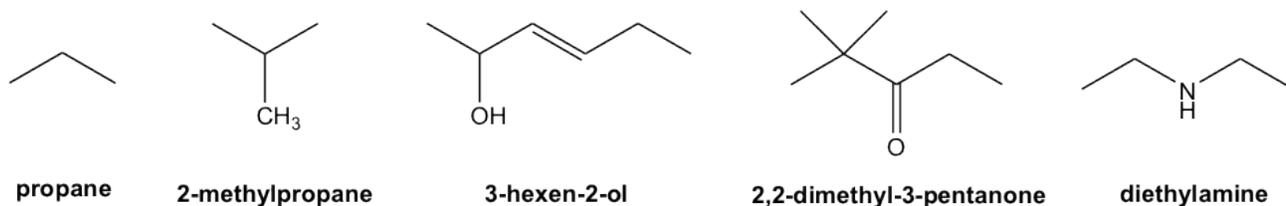


Figure 2.1b Examples of Condensed Structures

## Short-Line Structure Formula

The structure drawing can be further simplified by a short-line structure (or “bond-line structure”, “skeletal formula” in other books) with most atoms omitted; this is also a very common type of structure formula used in organic chemistry because of its simplicity. To apply and interpret the short-line structures correctly, it is important to clearly understand the conventions of this type of drawing.

- Each short line represents a bond.
- The carbon chains are shown in a zig-zag way.
- No carbon atoms are shown (as an exception, it is optional to show the CH<sub>3</sub> group at the end of the chain or as a branch); each bend in a line or terminus of a line represents a carbon atom unless another atom is shown explicitly.
- Hydrogen atoms bonded to carbons are not shown; hydrogen atoms bonded to other atoms are shown explicitly.
- Atoms other than C and H, for example, N, O, and Cl, need to be shown explicitly.
-



### Examples of Short-line Structures

Figure 2.1c Examples of Short-line structures

In short-line structures, the number of hydrogen atoms attached to each carbon can be *calculated* by applying the octet rule and checking the formal charges involved.

### Perspective Formula of 3D Structure

When it is necessary to highlight the spatial arrangement of groups around a tetrahedral  $sp^3$  carbon for conformation (Chapter 4) or stereochemistry (Chapter 5) purposes, a perspective formula with solid and dashed wedges is used. Of the four bonds on a tetrahedral carbon, two bonds lie within the paper plane and are shown as ordinary lines, the solid wedge represents a bond that points out of the paper plane, and the dashed wedge represents a bond that points behind the paper plane.

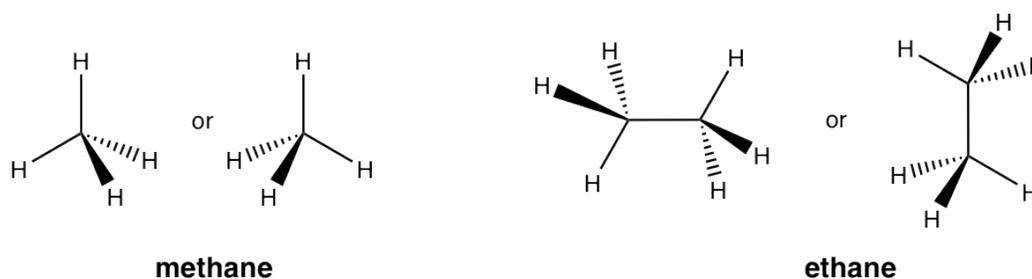


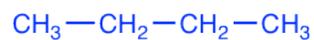
Figure 2.1d Examples of Perspective Formula

### 2.1.2 Constitutional Isomers

For methane, ethane and propane, there is only one type of carbon arrangement. As the number of carbon increases to 4, there are two ways for the carbon atoms to be connected: as a straight-chain (blue structure below) and as a branch on the chain (red structure below).

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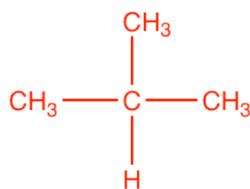
Two Constitutional Isomers with Formula C<sub>4</sub>H<sub>10</sub>



Butane

b.p. = 0°C

density: 0.622 g/mL



Isobutane (i-butane)  
"iso" means "isomeric"

b.p. = -12°C

density: 0.604 g/mL

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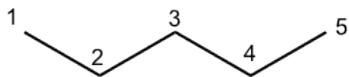
As we can see, these two different structures represent two different compounds, with different names and different physical properties; however, they both have the same formula of C<sub>4</sub>H<sub>10</sub>, and they are called constitutional (structural) isomers. Constitutional (structural) isomers are different compounds with the same molecular formula, but their atoms are arranged in a different order (i.e. the atoms are bonded in different ways).

Let's see some more examples of constitutional isomers.

For alkanes with 5 carbons, there are a total of three constitutional isomers. The strategies for building constitutional isomers are given in the notes beside the structures.

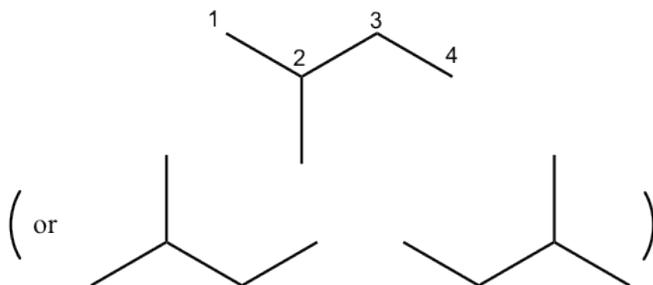
## Constitutional isomers of C<sub>5</sub>H<sub>12</sub>

Isomer I



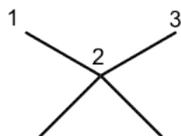
The basic one, with carbons connected one after the other.

Isomer II



“Chop” one carbon off the basic chain, so the backbone has only 4 carbons. Then put the chopped carbon back, it has to be connected on the middle carbon in order to give a new structure. Attention: the drawings in parentheses are for the same structure of Isomer II.

Isomer III

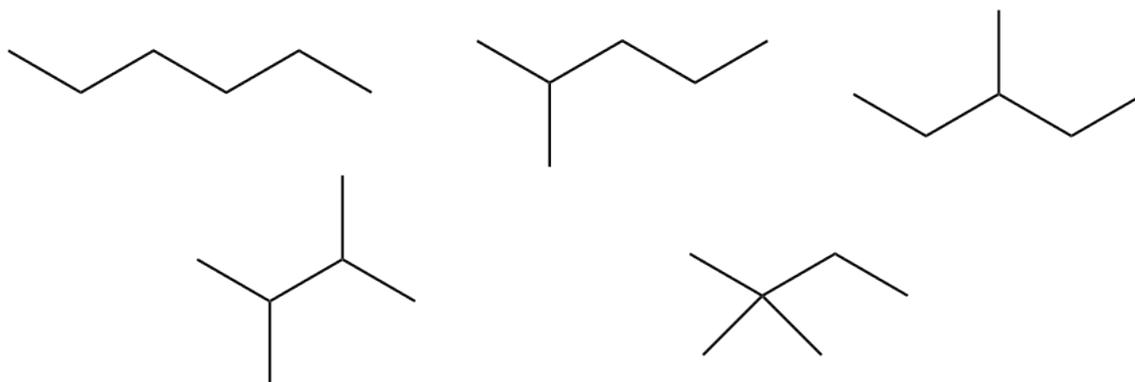


“Chop” two carbons off, so the backbone has only 3 carbons. To put the two carbons back, they both should be connected on the same carbon in order to give a new structure.

Figure 2.1e Constitutional isomers of C<sub>5</sub>H<sub>12</sub>

For alkanes with 6 carbons, there are a total of five constitutional isomers.

## Constitutional isomers of C<sub>6</sub>H<sub>14</sub>



Draw all the constitutional isomers with a formula of  $C_7H_{16}$ .

### Answers to Chapter 2 Practice Questions

The constitutional isomers we have discussed so far have different lengths of carbon “backbones” and are also called skeletal constitutional isomers. The other possible situations include positional and functional constitutional isomers, which we will encounter later.

As the number of carbons increases, the number of constitutional isomers increases dramatically. For the example of alkanes with 20 carbons, that is  $C_{20}H_{42}$ , there are 366,319 constitutional isomers. While there is no simple formula that allows us to predict the total number of isomers for a certain number of carbons, the phenomena of constitutional isomers partially explain the high diversity of organic structures.

### 2.1.3 Recognition of $1^\circ$ , $2^\circ$ , $3^\circ$ , $4^\circ$ carbons

The carbon atoms in organic structures can be categorized as primary ( $1^\circ$ ), secondary ( $2^\circ$ ), tertiary ( $3^\circ$ ) and quaternary ( $4^\circ$ ), depending on how many other carbons it connects with. Specifically:

- Primary ( $1^\circ$ ) carbon: attached directly to only one other C atom
- Secondary ( $2^\circ$ ) carbon: attached directly to two other C atoms
- Tertiary ( $3^\circ$ ) carbon: attached directly to three other C atoms
- Quaternary ( $4^\circ$ ) carbon: attached to four other C atoms

The hydrogen atoms attached to  $1^\circ$ ,  $2^\circ$  and  $3^\circ$  carbon are labeled as  $1^\circ$ ,  $2^\circ$  and  $3^\circ$  hydrogen respectively.

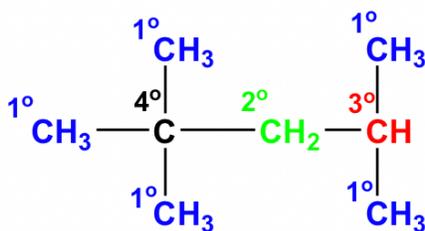


Figure 2.1f Hydrogen atoms attached on  $1^\circ$ ,  $2^\circ$  and  $3^\circ$  carbon

In one compound, carbons (or hydrogens) that belong to different categories show different structural and reactive properties. This concept has many more applications in later sections.

## 2.2 Nomenclature of Alkanes

As it has been shown that the number of constitutional isomers increases dramatically as the number of carbons increases, it is impossible to give each structure its own common name, like isobutane. As a result, a systematic method with certain rules is necessary when it comes to naming organic compounds. In this book, we will learn about IUPAC nomenclature; it is also the systematic nomenclature that has been widely adopted internationally. **IUPAC** nomenclature was initially designed by a commission for the International Union of Pure and Applied Chemistry in 1892, and it has been continually revised by the commission since then.

### IUPAC NOMENCLATURE of ALKANES

1. Identify the *longest continuous carbon chain* as the parent chain. This chain determines the parent name (or last name) of the alkane.
  - If there are two choices of the same length, then the parent chain is the longest chain with the greatest number of “branches”. The term substituent will be used from now on as the official name for “branch”.
2. Number the chain beginning at the end that is closest to any substituents, thus ensuring the lowest possible numbers for the positions of substituents.
3. Use these numbers to designate the location of the substituent groups, whose names are obtained by changing the “-ane” suffix to “-yl”.

The substituents derived from alkane are also called alkyl groups.

#### Normal alkyl groups:

$\text{CH}_3\text{—}$	methyl (Me-)
$\text{CH}_3\text{CH}_2\text{—}$	ethyl (Et-)
$\text{CH}_3\text{CH}_2\text{CH}_2\text{—}$	propyl (Pr-)
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{—}$	butyl (Bu-)

Figure 2.2a Normal alkyl groups

### Branched alkyl groups:

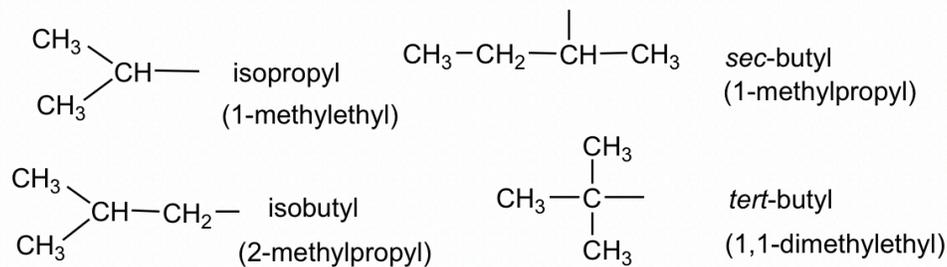
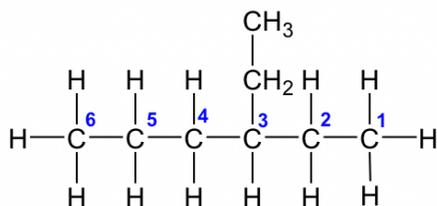


Figure 2.2b Branched alkyl groups

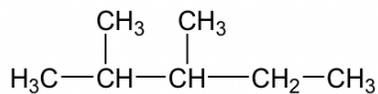
4. If an alkyl substituent group appears more than once, use the prefixes di, tri, tetra, penta, and hexa (meaning 2, 3, 4, 5, and 6 respectively) for each type of alkyl group.
5. List the substituent groups alphabetically (use the substituent group name from step 3, ignore the prefixes from 4, but include “iso” and “cyclo”).
6. Write the name as a single word. Numbers are separated from letters by “-”; numbers are separated by “,”.

### Alkane Naming Examples:



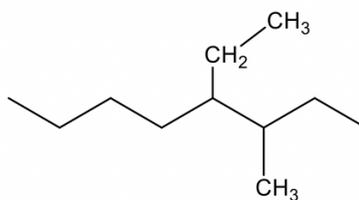
#### **3-ethylhexane**

Figure 2.2c 3-ethylhexane



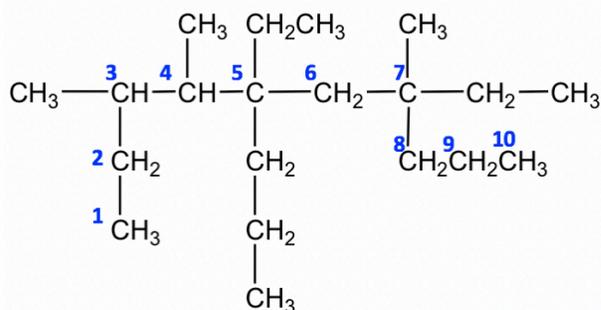
#### **2,3-dimethylpentane**

Figure 2.2d 2,3-dimethylpentane



### 4-ethyl-3-methyloctane

Figure 2.2e 4-ethyl-3-methyloctane



Find the parent chain correctly is the key step for naming this structure.

### 5,7-diethyl-3,4,7-trimethyl-5-propyldecane

Figure 2.2f 5,7-diethyl-3,4,7-trimethyl-5-propyldecane

## More notes about the branched alkyl groups:

The common names of the branched alkyl groups have been used broadly, and are adopted as part of the IUPAC system. Understanding the origin of these common names is very helpful in distinguishing and memorizing the names.

## Three-carbon branched alkyl groups

Both of the two 3-carbon branched alkyl groups come from propane. Since propane has two types of hydrogens, primary ( $1^\circ$ ) and secondary ( $2^\circ$ ), so there are two alkyl groups depending on which H is removed.

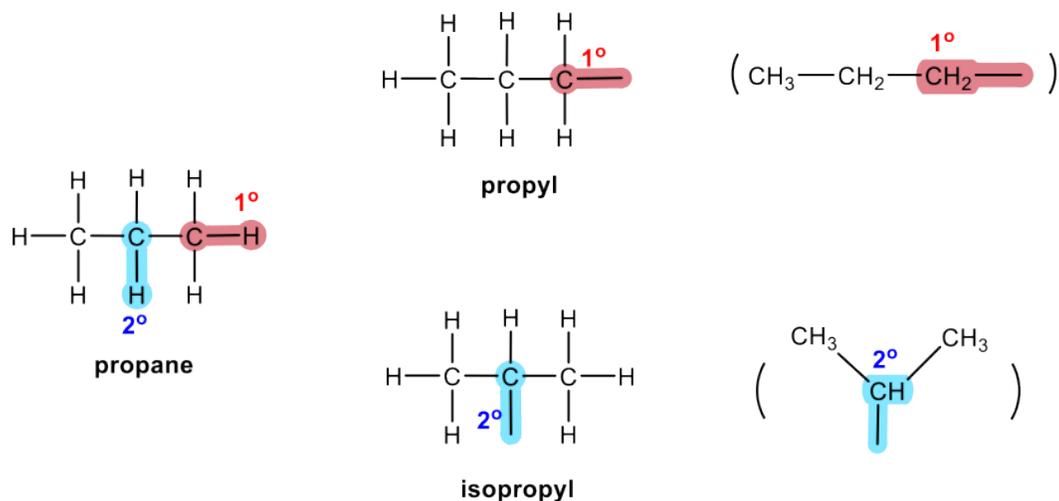


Figure 2.2g The primary and secondary hydrogen of propane

## Four-carbon branched alkyl groups

Out of the four 4-carbon branched alkyl groups, two come from butane and the other two come from isobutane (or 2-methylpropane).

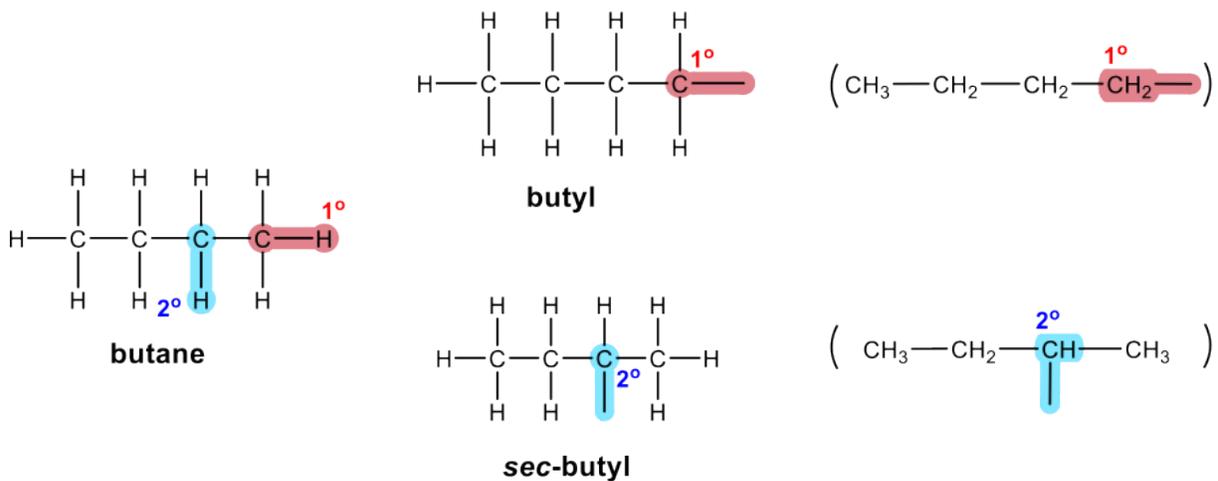


Figure 2.2h The primary and secondary hydrogen of butane

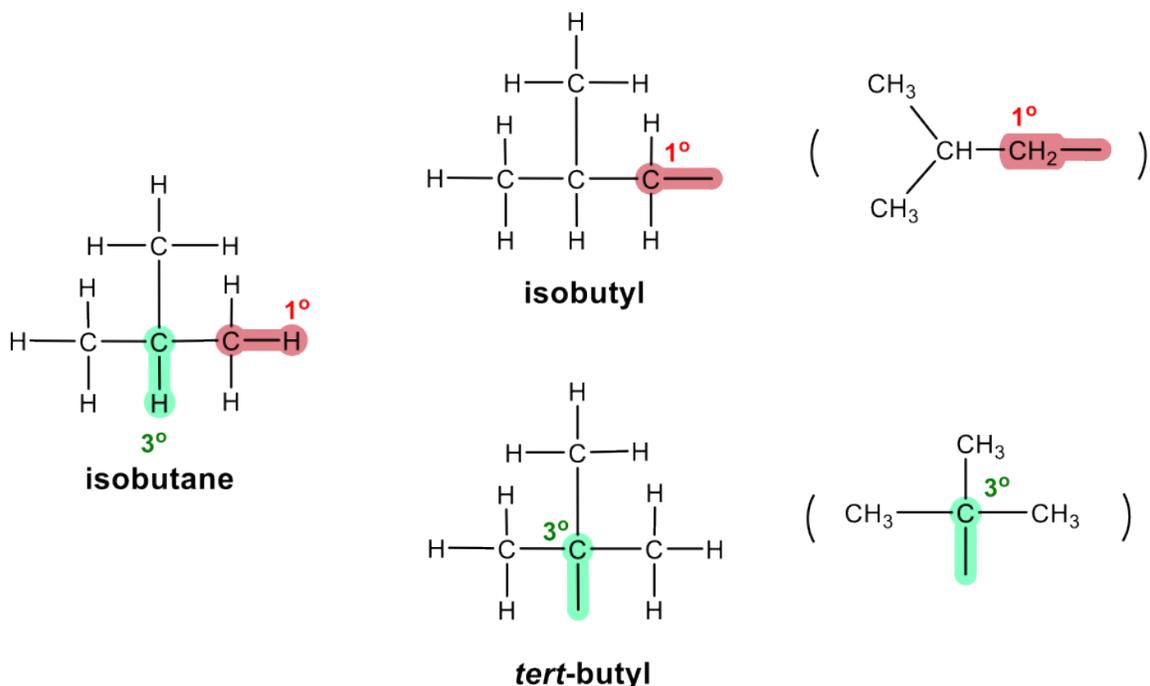


Figure 2.2i The primary and tertiary hydrogen of isobutane

## IUPAC name of branched alkyl groups

The branched alkyl groups can also be named by IUPAC rules. To do that, they are treated as if they were a compound. Begin numbering at the point of attachment to the parent chain, and the same number of branches as before to avoid confusion. The complex substituent name is put in parentheses when the name of the complete molecule is written.

For the example of isobutyl below, the part that connects directly to the parent chain has 3 carbons, so it is “propyl”. There is another CH<sub>3</sub> on the 2nd carbon of propyl; therefore, the whole group is called “2-methylpropyl”.

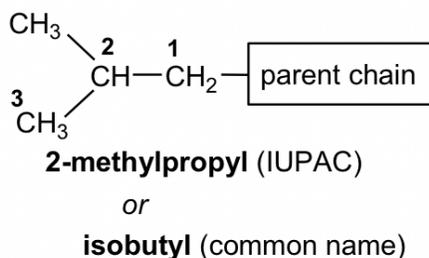


Figure 2.2j 2-methylpropyl or isobutyl

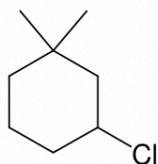
## Naming of Cycloalkanes

Cycloalkanes are alkanes that contain a ring(s) as part of the structure. For a cycloalkane that contains one ring, there are two fewer hydrogens than the non-cyclic alkane, so the general formula of cycloalkanes with one ring is **C<sub>n</sub>H<sub>2n</sub>**.

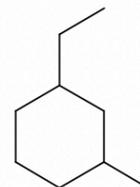
## IUPAC NOMENCLATURE of CYCLOALKANES

1. The parent name is “cycloalkane”.
2. Number the ring to provide the lowest possible numbering sequence (when two such sequences are possible, cite substituents in alphabetical order, and the No. 1 position is given to the first cited substituent).

Example:



**3-chloro-1,1-dimethylcyclohexane**

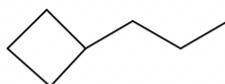


**1-ethyl-3-methylcyclohexane**

*Figure 2.2k 3-chloro-1,1-dimethylcyclohexane & 1-ethyl-3-methylcyclohexane*

3. When both the ring and chain are included in the structure, compare the number of carbons in the ring vs the chain and select the one with more carbons as the parent structure; the other is treated as a substituent.

Example:

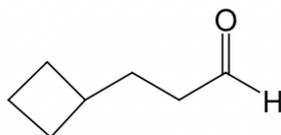


**propylcyclobutane**

*Figure 2.2l propylcyclobutane*

4. When higher-priority functional groups are present (more in section 2.2), parent structure will contain that functional group.

Example:



**3-cyclobutylpropanal**

*Figure 2.2m 3-cyclobutylpropanal*

## 2.3 Functional Groups

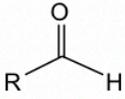
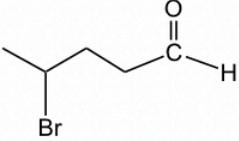
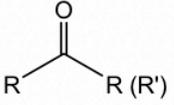
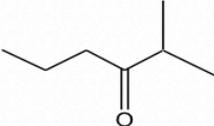
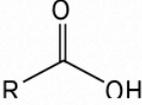
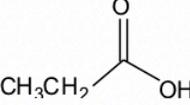
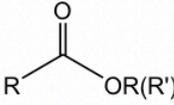
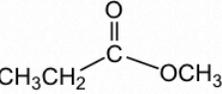
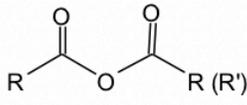
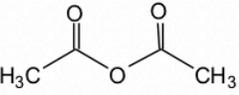
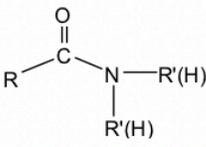
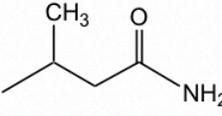
Functional groups are the most reactive parts in organic compounds and determine the major properties of compounds. A summary of common functional groups is included in Table 2.2. Knowing the functional groups well is one of the fundamental skills required for this course. This is required for students to quickly identify and name the functional groups included in molecules as well as to understand, interpret and draw the specific structure of each functional group clearly. The IUPAC naming of compounds containing several functional groups is required as well.

Class of Compounds	General Structure*	Specific Example	Notes
Alkene	$\begin{array}{c} \text{(H)R} \quad \text{R (H)} \\ \diagdown \quad / \\ \text{C} = \text{C} \\ / \quad \diagdown \\ \text{(H)R} \quad \text{R (H)} \end{array}$		
Alkyne	$\text{(H)R} \text{---} \text{C} \equiv \text{C} \text{---} \text{R (H)}$		
Aromatic ring			
Alkyl halide (Haloalkane)	$\text{R-X}$ $\text{X: F, Cl, Br or I}$		$\text{R-CH}_2\text{-X}$ : 1° halide $\text{R}_2\text{-CH-X}$ : 2° halide $\text{R}_3\text{-C-X}$ : 3° halide
Alcohol	$\text{R-OH}$		$\text{R-CH}_2\text{-OH}$ : 1° alcohol $\text{R}_2\text{-CH-OH}$ : 2° alcohol $\text{R}_3\text{-C-OH}$ : 3° alcohol
Ether	$\text{R-O-R}'$	$\text{CH}_3\text{---O---CH}_2\text{CH}_3$ ethyl methyl ether (common name)	<b>Common name:**</b> Alkyl <u>alkyl</u> ether (alphabetic order)
Nitrile	$\text{R-C}\equiv\text{N}$	$\text{H}_3\text{C-C}\equiv\text{N}$	
Nitro	$\text{R-NO}_2$		
Amine	$\text{RNH}_2$ $\text{R}_2\text{NH}$ $\text{R}_3\text{N}$	$\text{CH}_3\text{CH}_2\text{NH}_2$ : ethyl amine (common name) $(\text{CH}_3\text{CH}_2)_3\text{N}$ : triethyl amine (common name)	<b>Common name:**</b> Alkyl <u>alkyl alkyl</u> amine (alphabetic order)

\* R: hydrocarbon group, alkyl or phenyl; for structure with multiple R, they can be same or different groups.

\*\* These common names are accepted by IUPAC.

Table 2.2 Common Organic Functional Groups

Class of Compounds	General Structure	Specific Example	Notes
Aldehyde	 or: R-CHO		C=O double bond is usually called as a “ <b>carbonyl</b> ” group. The function groups on this page all contain carbonyl group.
Ketone			
Carboxylic acid	 or: R-COOH		Reaction with base gives salt of carboxylic acid, RCOO <sup>-</sup> M <sup>+</sup>
Ester			Carboxylic acid derivative.
Anhydride			Carboxylic acid derivative.
Amide			Carboxylic acid derivative

**Table 2.2** Common Organic Functional Groups (continued)

Alkene and alkynes are hydrocarbon functional groups; the  $\pi$  bond in multiple bonds accounts for the reactivity of alkenes and alkynes.

Benzene rings (C<sub>6</sub>H<sub>6</sub>) are a special type of hydrocarbon. Historically, because of the special aroma (sweet smell) that benzene and its derivatives release, they are called aromatic compounds. The structure of benzene can be represented as three C=C double bonds alternating with single bonds; however, the actual structure of benzene has nothing to do with alkenes. The structure of benzene, which is a big conjugation system, and the chemistry definitions of aromatic/aromaticity will be discussed in detail in Organic Chemistry II. Benzene rings can be shown with any of the following structure drawings.

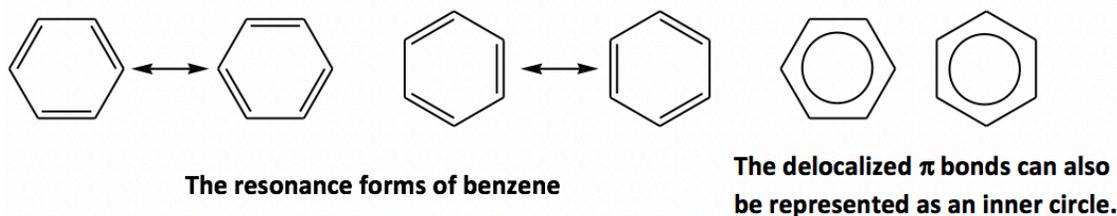


Figure 2.3a Benzene

When a halogen is connected with carbon, the group is called alkyl halide (or haloalkane). The halide can be categorized as a primary ( $1^\circ$ ), secondary ( $2^\circ$ ) or tertiary ( $3^\circ$ ) halide, depending on what category the carbon connected with the halogen is in.

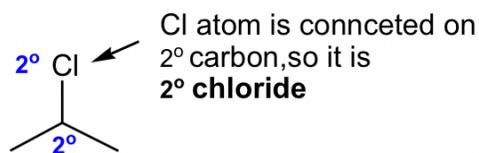


Figure 2.3b  $2^\circ$  chloride

Alcohol is a functional group that you are probably familiar with. In organic chemistry, the term alcohol refers to a compound containing the OH (hydroxy) group. Depending on the position of the OH group, alcohols can also be categorized as primary ( $1^\circ$ ), secondary ( $2^\circ$ ) or tertiary ( $3^\circ$ ).

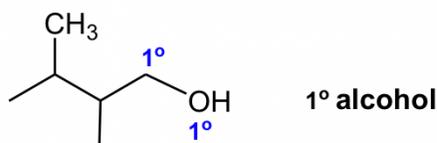


Figure 2.3c  $1^\circ$  alcohol

Another functional group that contains the oxygen atom in single bonds is ether. In ether, the O atom connects with two carbon-containing R groups through two C-O  $\sigma$  bonds. Compounds with ether as the only functional group are usually referred to with the common name "alkyl alkyl ether". When the two alkyl groups are the same, they can be combined as "dialkyl".

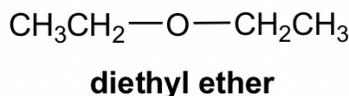
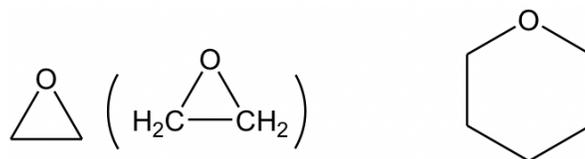


Figure 2.3d diethyl ether

Ether can be in a cyclic structure as well. It may not be that intuitive to recognize the following structure as ether, and labelling the carbon atom will be helpful for identification.

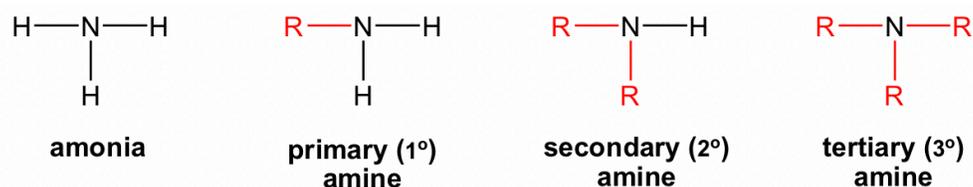


### cyclic ether examples

Figure 2.3e Cyclic ether examples

Both nitrile and nitro groups contain nitrogen atoms, and they can be easily confused. Nitrile has a  $C\equiv N$  triple bond, and therefore can only be at the end of a structure, while nitro ( $NO_2$ ) can be in any position on the carbon chain or ring.

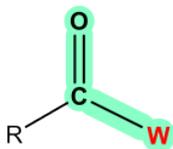
Amine is the organic derivative of ammonia,  $NH_3$ . When the hydrogen atom(s) in  $NH_3$  is replaced with R groups, it produces amine. Amine can be primary ( $1^\circ$ ), secondary ( $2^\circ$ ) or tertiary ( $3^\circ$ ) depending on how many R groups are connected with nitrogen. Amines can also be referred to with common names.



for  $2^\circ$  and  $3^\circ$  amine, R can be any alkyl or phenyl group, they don't have to be the same group

Figure 2.3f Primary, secondary, & tertiary amine

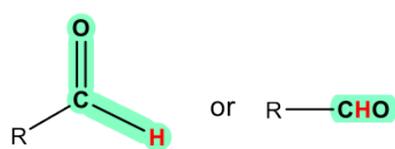
For the functional groups in the 2<sup>nd</sup> part of Table 2.2, they all have a common structural unit of a carbonyl group  $C=O$ ; the different structure of "W" in the general formula determines the nature of the functional group. It is usually more challenging to identify and draw these functional groups correctly because they are similar. More practice is needed.



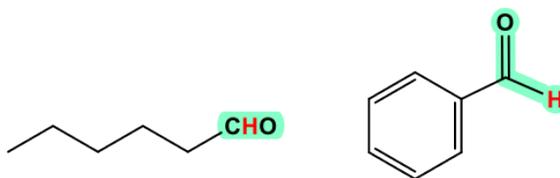
### General structure of functional groups containing $C=O$ bond

Figure 2.3g General structure of functional groups containing  $c=O$  bond

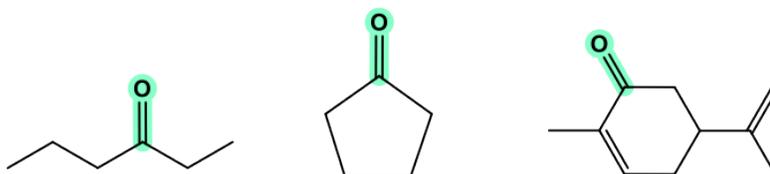
Aldehyde and ketone are similar in terms of their structures and properties. Aldehyde can be regarded as a special case of ketone since "H" can be regarded as an R with zero carbon. Because H has to be connected on one side of the  $C=O$  group in aldehyde, aldehyde can only be at the end of a structure. Ketone, on the other hand, must be in the middle position to ensure both sides of the  $C=O$  groups are connected with R groups. Ketone can also be in a cyclic structure.



**aldehyde**



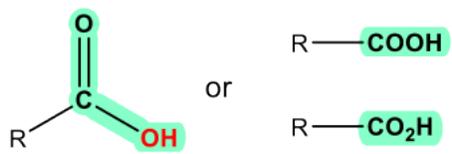
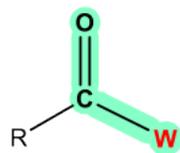
**aldehyde examples  
(CHO group must be on terminal)**



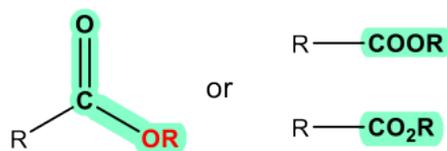
**ketone and cyclic ketone examples**

*Figure 2.3h Ketone and cyclic ketone examples*

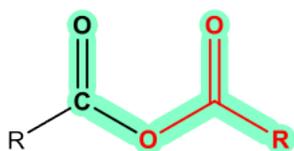
The last four functional groups are related in terms of structures and chemical properties. When an OH group is connected with C=O, the whole COOH is called a carboxylic acid functional group. The other three: ester, anhydride and amide, are all derivatives of carboxylic acid, meaning they can be prepared with carboxylic acid as the starting material. For these three functional groups, it is important to remember that the “W” part has to be considered together with the C=O, since overall they define the functional group. For example, the COOR is ester; it can not be recognized as a “ketone” plus an “ether”.



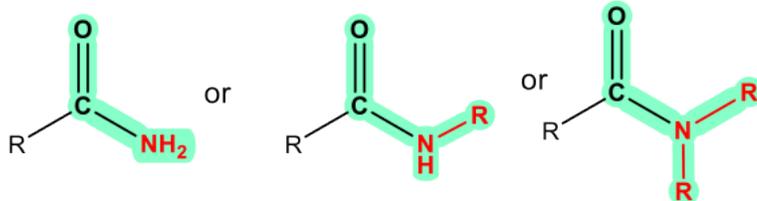
**carboxylic acid**



**ester**



**anhydride**



**amide**

Figure 2.3i Carboxylic acid (COOH/CO<sub>2</sub>H), ester (COOR/CO<sub>2</sub>R), anhydride, and amide

## 2.4 IUPAC Naming of Organic Compounds with Functional Groups

With the ability to identify functional groups, next we will learn how to give IUPAC names to compounds containing several functional groups by following a set of rules.

### IUPAC NOMENCLATURE of COMPOUNDS with FUNCTIONAL GROUPS

1. Find the longest carbon chain containing the functional group with the highest priority (see Table 2.3). This chain determines the parent name of the compound.
2. Change the ending of the parent alkane/alkene/alkyne to the suffix of the highest priority group, which gives the parent name of the compound (usually, drop the last letter “e” before adding the suffix, except for nitrile where the “e” is kept).
3. Number the chain from the end closest to the highest functional group.
4. The other groups are named as substituents by using the appropriate prefixes.
5. Assign stereochemistry, E/Z or R/S, as necessary (details in Chapter 5).

For naming purposes, the functional groups are assigned with priorities (Table 2.3). If the compound includes more than one functional group, the one with the highest priority is the “parent structure” and determines the “parent name”; the other groups will be regarded as “substituents”. The “suffix” is used to indicate the name of the parent structure, and the “prefix” is for the substituent. The order of the groups listed in Table 2.3 is based on the decreasing order of priority, where the carboxylic acid group is in the highest priority. The groups in the subordinate table (Table 2.4) have no difference in terms of priority, and they are usually listed in alphabetic order.

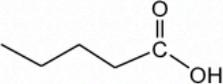
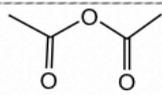
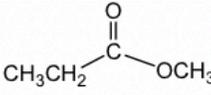
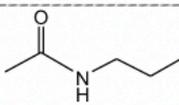
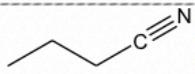
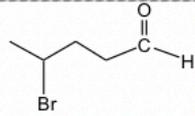
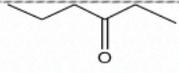
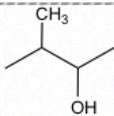
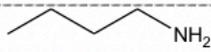
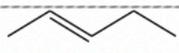
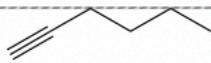
Functional group	Prefix	Suffix	Examples	Name of Example
carboxylic acid	carboxy	-oic acid -carboxylic acid		pentanoic acid
acid anhydride	—	-oic anhydride -carboxylic anhydride		ethanoic anhydride
carboxylic ester	alkoxycarbonyl	-oate -carboxylate		methyl propanoate
amide	amido	-amide -carboxamide		N-propylethanamide
nitrile	cyano	-nitrile (keep "e") -carbonitrile		butanenitrile
aldehyde	oxo	-al -carbaldehyde		4-bromo-pentanal
ketone	oxo	-one		3-hexanone
alcohol	hydroxy	-ol		3-methyl-2-butanol
amine	amino	-amine		butylamine (common name)
alkene	enyl	-ene		2-pentene
alkyne	ynyl	-yne		1-hexyne
alkyl	yl	-ane		2,2-dimethylbutane

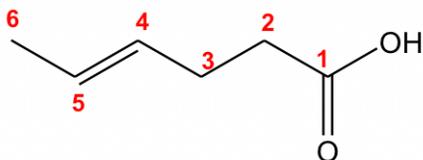
Table 2.3 Naming Priorities of Common Functional Groups

Functional group	Structure	Prefix	Suffix
alkyl halide	R—X (X: F, Br, Cl, I)	halo (fluoro, bromo, chloro, iodo)	—
ether	R—O—R	oxy	ether
sulfide	R—S—R	alkylthio	sulfide
nitro	—NO <sub>2</sub>	nitro	—
benzene		phenyl	benzene

Table 2.4 Subordinate Groups

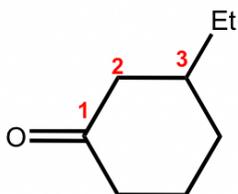
We will go through several examples for more details about the naming rules.

1.



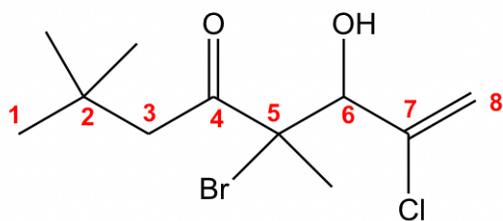
The parent structure is the 6-carbon carboxylic acid with a double bond, so the last name comes from “hexene”. To add the suffix, the last letter “e” will be dropped, so the parent name is “hexeneoicacid”. A number is necessary to indicate the position of the double bond, so the name is “4-hexenoic acid”. The carboxylic acid group is always in the #1 position, so it is NOT necessary to include that number for the position.

2.



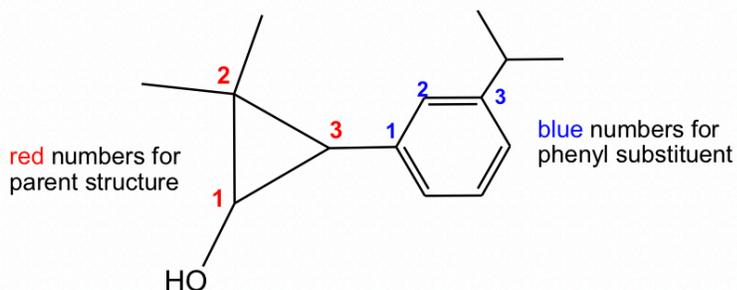
This is a ketone based on a cycloalkane, so the last name comes from “cyclohexane”. By adding the suffix, it becomes “cyclohexanone”, and the complete name is “3-ethylcyclohexanone”.

3.



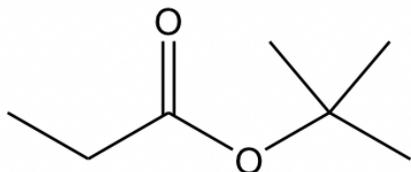
With the multiple groups involved, the ketone has the highest priority, so it decides the last name. The 8-carbon alkene chain with ketone should be named “octenone”. The numbers on the chain should start from the left side to ensure that ketone has the lowest number. When the OH group is regarded as a substituent, it is indicated by the prefix “hydroxy”. So the complete name is “5-bromo-7-chloro-6-hydroxy-2,2,5-trimethyl-7-octen-4-one”.

4.



For this compound, it is not difficult to find the parent structure, which is a cyclic alcohol, so the last name is “cyclopropanol”. The naming of the substituent with the benzene ring is a bit more challenging. When benzene is a “substituent”, it is called “phenyl”; and since there is an isopropyl group on the “phenyl”, the whole substituent is called “3-isopropylphenyl”, and the complete name of the compound is “2,2-dimethyl-3-(3-isopropylphenyl)cyclopropanol”.

5.



In ester, an OR group replaces the OH group of a carboxylic acid. When naming the ester, the name of the R in the OR group is stated first, followed by the name of the acid, with “oic acid” replaced by “oate”. As a net result, the R in the OR is regarded as the “substituent”, even though it is not. So, the complete name of the ester above is “tert-butyl propanoate”.

## Naming of substituted benzene and benzene derivatives

For substituted benzene, the benzene ring is regarded as the parent structure, and the positions and names of substituents are added to the front.

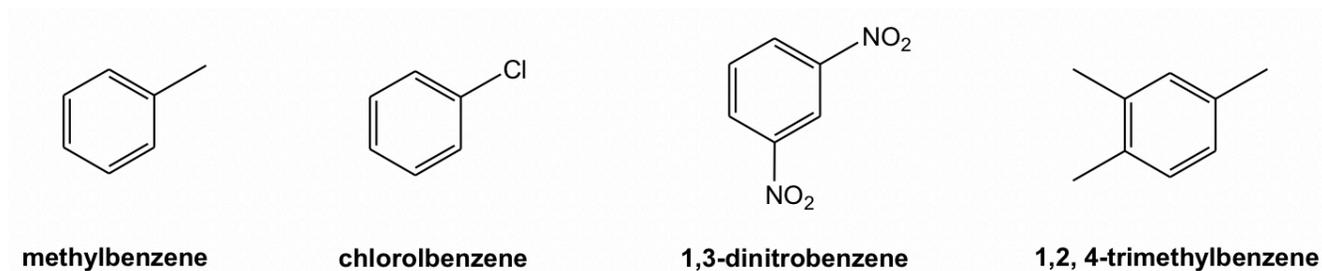
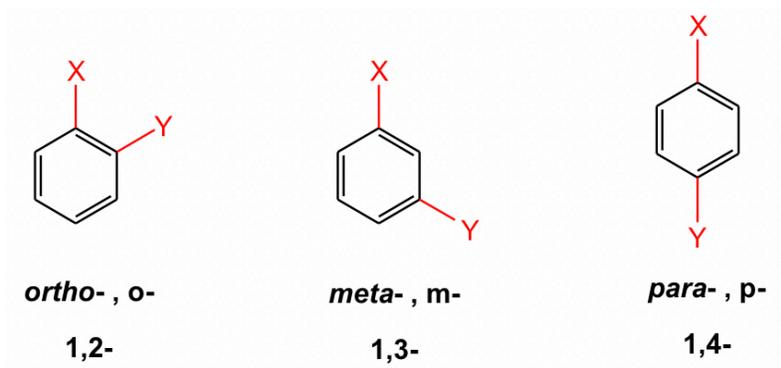


Figure 2.4a Methylbenzene, chlorobenzene, 1,3-dinitrobenzene, & 1,2,4-trimethylbenzene

For di-substituted benzene, there is another unique way to indicate the relative position of the two substituents by using ortho-, meta- and para-. This o-, m-, p- system is the common naming system for benzene derivatives, however, they have been applied broadly in books and academic literature.

- *ortho-* (*o-*): 1,2- (next to each other in a benzene ring)
- *meta-* (*m*): 1,3- (separated by one carbon in a benzene ring)
- *para-* (*p*): 1,4- (across from each other in a benzene ring)



For the mono-substituted benzene derivatives: phenol, benzoic acid and benzaldehyde, their common names are adopted in the IUPAC system.

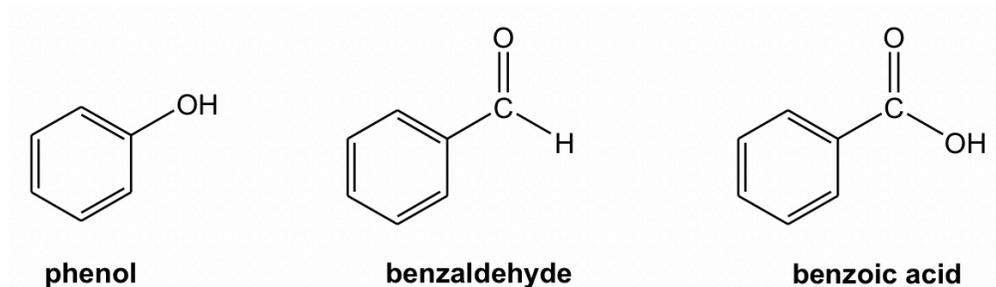
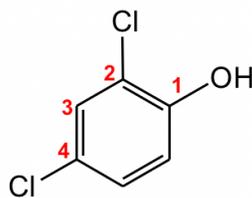


Figure 2.4b Phenol, benzaldehyde, benzoic acid

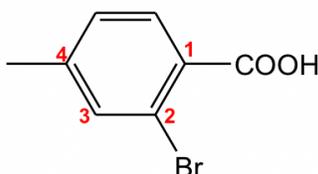
When other substituents are introduced into those benzene derivatives, the common name will be used as the parent

name of the compound with the base functional group (OH for phenol, COOH for benzoic acid and CHO for benzaldehyde) given the #1 position. For example:



**2,4-dichlorophenol**

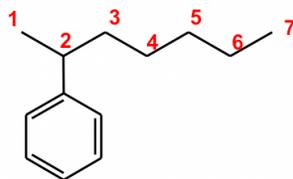
Figure 2.4c 2,4-dichlorophenol



**2-bromo-4-methylbenzoic acid**

Figure 2.4d 2-bromo-4-methylbenzoic acid

When benzene is connected with a carbon chain that has six or more carbons, the carbon chain should be regarded as the parent structure, and the benzene ring becomes the substituent and will be indicated with the prefix “phenyl”. An example is given here:



**2-phenylheptane**

Figure 2.4e 2-phenylheptane

## 2.5 Degree of Unsaturation/Index of Hydrogen Deficiency

Now that many functional groups have been introduced, the extent of constitutional isomers will be greatly expanded. To further explore the phenomena of constitutional isomers, we will need to understand the concept of Degree of Unsaturation (or: Index of Hydrogen Deficiency/IHD).

First, let's compare three compounds: pentane, 1-pentene and cyclopentane

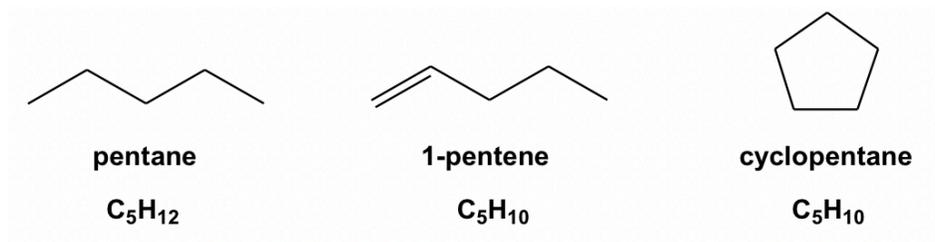


Figure 2.5a Pentane, 1-pentene, & cyclopentane

The formula for pentane is  $C_5H_{12}$ . For a compound containing 5 carbons, the maximum number of hydrogens is 12, so the structure of pentane is saturated (no more hydrogen atoms can be added in), or we can say that pentane has zero degrees of unsaturation.

For 1-pentene  $C_5H_{10}$ , there are two fewer hydrogens than the saturated level (pentane), which means the 1-pentene has one degree of unsaturation. With a ring introduced, cyclopentane ( $C_5H_{10}$ ) also has to sacrifice two hydrogens, so cyclopentane also has one degree of unsaturation. The trend is that when a double bond (essentially a  $\pi$  bond) or a ring is involved in the structure, it leads to one degree of unsaturation of the compound.

Formula	Degree of Unsaturation/ Index of Hydrogen Deficiency (IHD)*	Structure Unit Involved
$C_nH_{2n+2}$	0	chain alkane only
$C_nH_{2n}$	1	1 double bond or 1 ring
$C_nH_{2n-2}$	2	2 double bonds or 2 rings or 1 double bond plus 1 ring or 1 triple bond

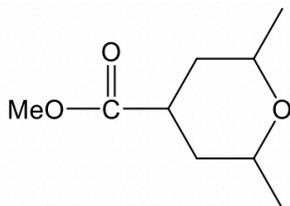
Table 2.5 Summary of the degree of unsaturation/IHD vs structure unit involved

The degree of unsaturation could be accumulated, and Table 2.5 summarizes the situations up to two degrees. As we

can see, adding 1 ring or 1  $\pi$  bond contributes to one degree of unsaturation. Therefore, the essential meaning of the degree of unsaturation is the “number of rings plus  $\pi$  bonds” in a structure.

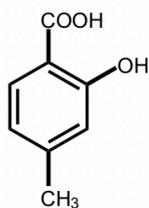
If the structure of a compound is available, the total degrees of unsaturation can simply be counted by inspecting the structure.

### Example:



This compound has one ring and one double bond, so the total degree of unsaturation is 2.

Figure 2.5b Total degree of unsaturation is 2



Benzene ring means 4 unsaturation degrees (3 double bonds and 1 ring); COOH also include one C=O bond. Total degree of unsaturation is 5.

Figure 2.5c Total degree of unsaturation is 5

If the formula of a compound is given, we can also calculate the degree of unsaturation by comparing the number of hydrogens vs the saturated level by using the equation:

$$\text{Degree of unsaturation} = \frac{(2n+2)-X}{2}$$

(n: number of carbons; X = number of H + number of Halogen – number of N)

This is a general equation that accounts for the presence of heteroatoms as well. Please note that oxygen atoms are ignored in this calculation.

For example, for a compound with a formula given as  $C_4H_7NO$ , it is calculated that the degree of unsaturation is 2 for

$$\frac{(2n+2)-X}{2} = \frac{(2 \times 4 + 2) - (7 - 1)}{2} = 2$$

this compound:

Now, we are ready to solve constitutional isomer questions with the application of degrees of unsaturation. Usually, the formula information is available to us for such questions, and we will need to build constitutional isomers based on the given formula together with other requirements. This type of question can be solved strategically by following certain steps:

- Calculate the degree of unsaturation based on the given formula.
- With the value of this specific unsaturation degree, how many double bonds or rings might be included in the structure?
- Combine your knowledge of functional groups with the degree of unsaturation, as well as with certain atoms included in the formula, to see what functional group(s) may be possible.
- Build constitutional isomers according to the above information (separate the isomers by different functional groups).

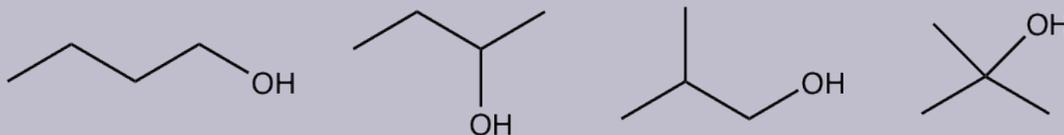
Examples: Draw and name all the constitutional isomers with the molecular formula  $C_4H_{10}O$ .

Approach: Answering the following questions lead you to the solution.

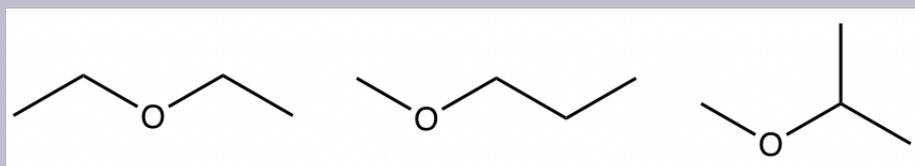
- What is the degree of unsaturation for the formula  $C_4H_{10}O$ ? **0**
- How many double bonds, or rings, could be involved? **none**
- What are the possible functional groups that match with that degree of unsaturation, and include one oxygen atom? **alcohol or ether**
- With these hints, we can try to “build” the constitutional isomers for each functional group separately.  
**total seven structures**

### Solutions:

alcohols:



ethers:



Exercises 2.2

Draw all the constitutional isomers that include a C=O bond with formula the  $C_5H_{10}O$ .

Answers to Chapter 2 Practice Questions

## 2.6 Intermolecular Force and Physical Properties of Organic Compounds

### 2.6.1 Intermolecular Forces

In organic chemistry, the understanding of the physical properties of organic compounds, for instance, boiling point (b.p.), molecular polarity and solubility, is very important, as it provides us with helpful information about how to deal with a substance in the proper way. Those physical properties are determined by the intermolecular forces involved. Intermolecular forces are the attractive forces between molecules that hold the molecules together; they are an electrical force in nature. We will focus on three types of intermolecular forces: dispersion forces, dipole-dipole forces and hydrogen bonds.

#### Dispersion Forces

Dispersion forces (also called London forces) result from the instantaneous dipole and induced dipole of the molecules. For nonpolar molecules, the constant shifting and distortion of electron density leads to a weak, short-lived dipole at a given moment, which is called an instantaneous dipole. Such temporary dipoles also induce the electrons in a neighbouring molecule to be distorted, and this molecule develops a corresponding transient dipole of its own, which is the induced dipole. At the end, all nonpolar molecules are attracted together via the two types of temporary dipoles as shown in Fig. 2.6a. The dispersion force is weak in nature and is the weakest intermolecular force. However, since it applies to all types of molecules (it is the only intermolecular force for nonpolar molecules), dispersion forces are also the most fundamental intermolecular force.

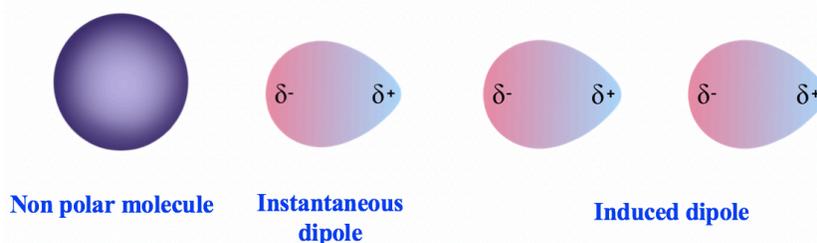


Figure 2.6a Instantaneous Dipole and Induced Dipole

The magnitude of dispersion forces depends on two factors:

- The relative polarizability of electrons – The simple understanding of polarizability is how easily the electrons get distorted. For larger atoms, there are more electrons in a larger space; therefore the electrons are more loosely held and more easily polarized, so the dispersion force is stronger. Generally, the larger the molar mass of the molecule, the stronger the dispersion force.
- The relative surface area of the molecule – Molecules with longer, flatter or cylindrical shapes have a greater surface area compared to the bulky, branched molecules, and therefore have a stronger dispersion force. Taking

the two constitutional isomers of C<sub>4</sub>H<sub>10</sub> (section 2.1.2), butane and isobutane as an example, the dispersion force of butane is stronger than that of isobutane.

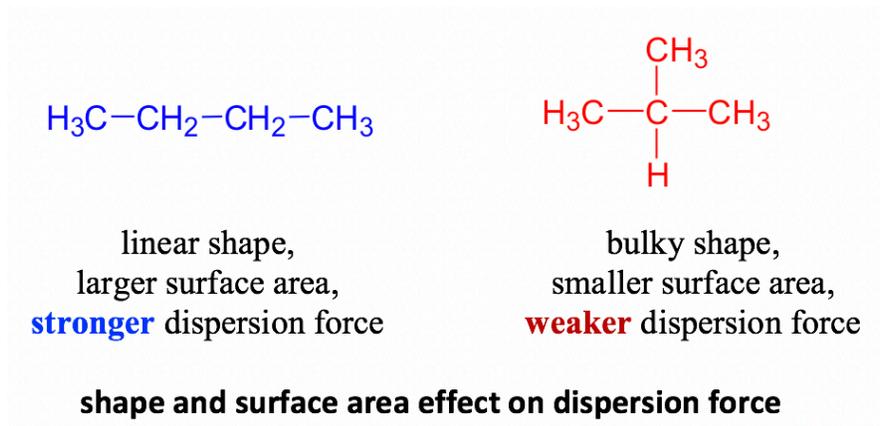
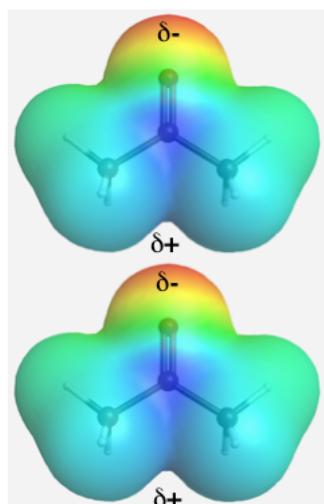


Figure 2.6b Shape and surface area effect on dispersion force

## Dipole-Dipole Force

For polar molecules, molecules are attracted to each other because of a permanent dipole, this type of attractive force is called a dipole-dipole force. As shown below in the electrostatic potential map of acetone, one end of acetone has a partial negative charge (red), and the other end has a partial positive charge (blue). The dipole-dipole force is an attraction force between the positive end of one molecule and the negative end of the neighbouring molecule.



electrostatic potential map of acetone

Figure 2.6c Electrostatic potential map of acetone

## Hydrogen Bonds

First of all, do not let the name mislead you! Although it is called a “bond”, a hydrogen bond is not a covalent bond, it is a type of intermolecular force. The hydrogen bond is the force between an H atom that is bonded to O, N or F (atoms with high EN) and the neighbouring electronegative atom. It can be shown in a general way as:

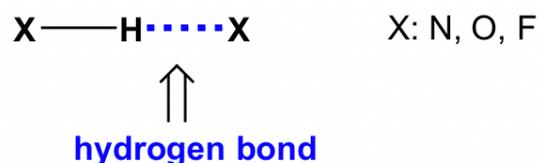


Figure 2.6d Hydrogen bond

The most common example of hydrogen bonding is for water molecules. Water has two O-H bonds, and both are available as hydrogen bond donors for neighbouring molecules. This explains the extraordinarily high b.p. of water (100°C) considering the rather small molar mass of 18.0 g/mol. As a comparison, a methane molecule CH<sub>4</sub> with a similar size has a b.p. of -167.7°C.

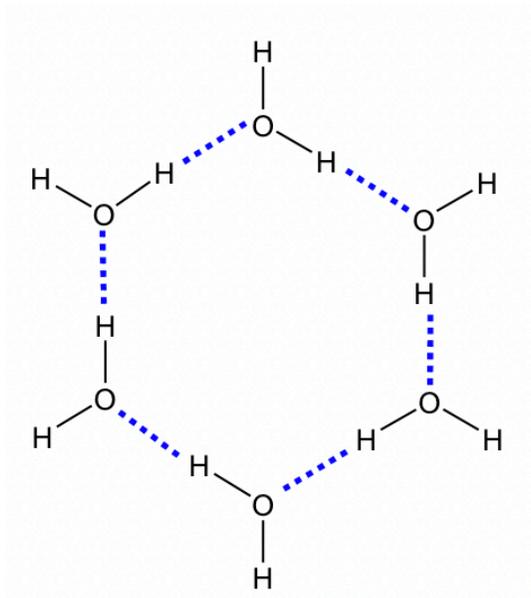


Figure 2.6e Simplified Diagram of Hydrogen Bonds between Water Molecules

For organic compounds, hydrogen bonds play important roles in determining the properties of compounds with OH or NH bonds, for example, alcohol (R-OH), carboxylic acid (R-COOH), amine (R-NH<sub>2</sub>) and amide RCONH<sub>2</sub>.

The three major types of intermolecular forces are summarized and compared in Table 2.6.

Type of Force	Applied to	Strength
Dispersion Forces	All molecules	0.1 – 5 kJ/mol
Dipole-dipole Forces	Polar molecules	5 – 20 kJ/mol
Hydrogen Bonding	Polar molecules with N – H, O – H or F – H bond	5 – 50 kJ/mol

**Table 2.6** Summary of the Three Major Intermolecular Forces

## Polar vs Non-Polar molecules

As indicated in Table 2.6, the nature of molecular polarity determines the types of force(s) applied to a certain substance. So here we will have discussions about how to tell whether a molecule is polar or non-polar.

The polarity of the compound can be determined by its formula and shape.

For diatomic molecules, the molecular polarity is the same as the bonding polarity. That means all homonuclear molecules, like  $H_2$ ,  $N_2$ ,  $O_2$ , and  $F_2$ , are non-polar because of their non-polar bond, while all heteronuclear molecules, like HF and HCl, are polar.

For polyatomic molecules, the molecular polarity depends on the shape (refer to VSEPR in Section 1.5) of the molecule as well. Let's see some examples of  $H_2O$  and  $CO_2$ .

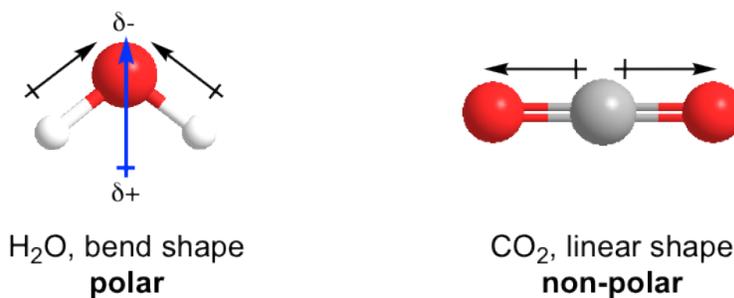


Figure 2.6f Polar and non-polar

Both  $H_2O$  and  $CO_2$  have two polar bonds.  $H_2O$  is in a bent shape, so the bond polarities of the two O-H bonds add up to give the molecular polarity of the whole molecule (shown above); therefore,  $H_2O$  is a polar molecule. On the other hand, the shape of  $CO_2$  is linear, and the bond polarities of the two C=O bonds cancel out, so the whole  $CO_2$  molecule is non-polar.

There are other examples of non-polar molecules where the bond polarity cancels out, such as  $BF_3$ ,  $CCl_4$ ,  $PCl_5$ , and  $XeO_4$ .

For organic compounds, the hydrocarbons ( $C_xH_y$ ) are always non-polar. This is mainly because of the small EN difference between carbon atoms and hydrogen atoms, making C-H bonds technically non-polar bonds.

For other organic compounds that contain functional groups with heteroatoms, like R-O-R, C=O, OH, and NH, they are all polar molecules.

The diagram here (Fig. 2.6g) provides a summary of all the discussions about molecular polarities.

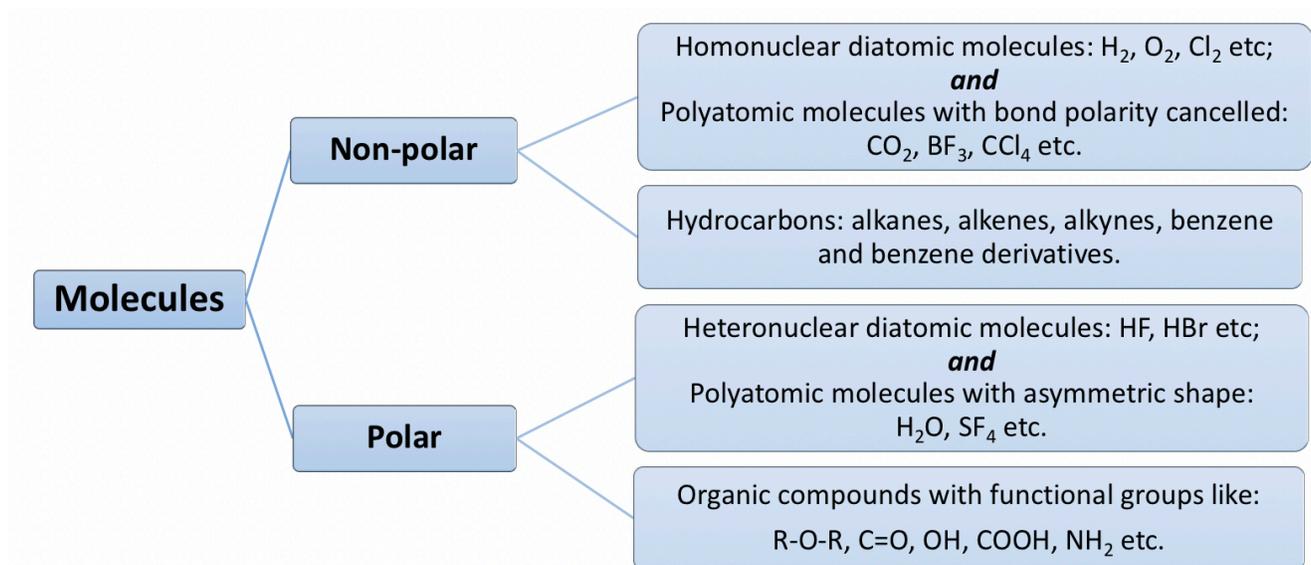


Figure 2.6g Summary of Molecular Polarities

Other than the three types of intermolecular forces, another interaction is very important for understanding the physical property of a compound, which is the ion-dipole force.

## Ion-Dipole Force

The ion-dipole force is not categorized as an intermolecular force, as it is an important non-covalent force that is responsible for the interaction between ions and other polar substances. A simple example is the dissolving of an ionic solid, or salt, in water. When table salt (NaCl) is dissolved in water, the interactions between the ions and water molecules are strong enough to overcome the ionic bond that holds the ions in the crystal lattice. As a result, the cations and anions are separated completely, and each ion is surrounded by a cluster of water molecules. This is called a solvation process. The solvation occurs through the strong ion-dipole force. Many salts, or ionic compounds, are soluble in water because of such interactions.

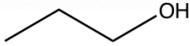
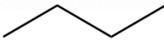
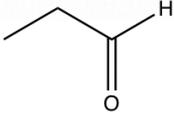
## 2.6.2 Physical Properties and Intermolecular Forces

The comprehension of intermolecular forces helps us understand and explain the physical properties of substances since intermolecular forces account for physical properties such as phases, boiling points, melting points, and viscosities. For organic chemistry purposes, we will focus on b.p. and solubility.

## Boiling point (b.p.):

The b.p. trend of different substances directly correlates with the total intermolecular forces. Generally speaking, the stronger the overall intermolecular force applied to a certain substance, the higher the b.p. of the substance. The b.p. is the temperature at which the liquid phase of the substance vaporizes to become a gas. To vaporize a liquid, the intermolecular forces that hold the molecules together must be overcome. The stronger the forces, the more energy that is needed to overcome the forces, and a higher temperature is required, thus leading to a higher b.p.

Example:

		
<b>propanol</b>	<b>butane</b>	<b>propanal</b>
<b>b.p.:</b> 97 °C	<b>-0.5 °C</b>	<b>48 °C</b>
<b>MM:</b> 60 <b>(g/mol)</b>	<b>58</b>	<b>58</b>

All three compounds here have similar molar masses, so the dispersion forces are at a similar level. However, the three compounds have different molecular polarities. Butane is a non-polar substance that only has dispersion forces, propanal is a polar molecule with both dispersion forces and dipole-dipole forces, and propanol is a polar molecule with an OH bond, so all three types of forces apply. Therefore, the overall amount of intermolecular force is strongest for propanol and weakest for butane, which is in the same order as their boiling points.

## Solubility:

A general rule for solubility is summarized by the expression “like dissolves like”. This means that one substance can dissolve in another with a similar polarity and, as a result, with similar intermolecular forces. More specifically:

- Nonpolar substances are usually soluble in nonpolar solvents.
- Polar and ionic substances are usually soluble in polar solvents.
- Polar and nonpolar substances are insoluble to each other.

Determining the polarity of a substance has already been summarized in an earlier part of this section (Fig. 2.6g). Water, methanol and ethanol are examples of very polar solvents that can form hydrogen bonds. Ether, ketone, halide and esters are polar solvents as well, but they are not as polar as water or methanol. Non-polar solvents include hydrocarbons like hexane, benzene, and toluene.

For large organic molecules, however, it may not be so easy to simply call them polar or non-polar because part of a compound may be polar while another part may be nonpolar. Such polar or nonpolar parts of a compound are often described as hydrophilic or hydrophobic.

- Hydrophilic (*hydro*, water; *philic*: loving or seeking) means it likes water, or is soluble in water.

- Hydrophobic (*hydro*, water; *phobic*: fearing or avoiding) meaning it does not like water, or is insoluble in water.

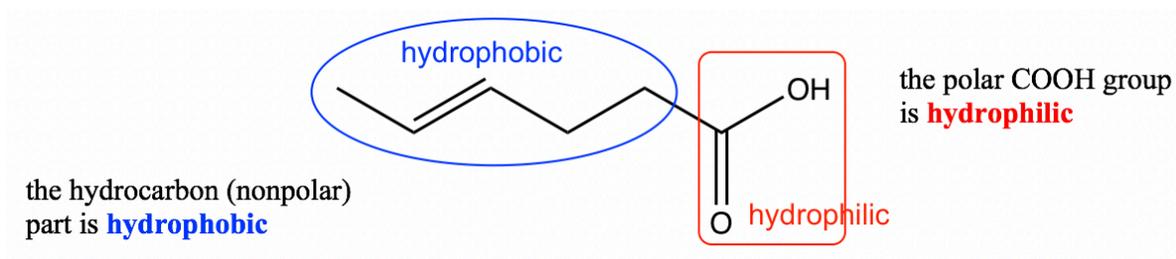


Figure 2.6h Hydrophobic and Hydrophilic

The hydrocarbon part of an organic compound is *hydrophobic* because it is nonpolar and therefore does not dissolve in polar water. The functional group of OH, COOH, NH<sub>2</sub>, etc. is polar and is therefore *hydrophilic*. With both hydrophobic and hydrophilic parts present in an organic compound, the overall polarity depends on whichever part is the major one. If the carbon chain is short (1-3 carbons), the hydrophilic effect of the polar group is the major one, so the whole compound is soluble in water; with carbon chains of 4-5 carbons, the hydrophobic effect begins to overcome the hydrophilic effect, and water solubility is lost.

The solubility differences of different alcohols demonstrate this trend clearly; as the length of the carbon chain increases, the solubility of alcohol in water decreases dramatically (Table 2.7):

Alcohol	Solubility in water (g/100mL)
methanol, ethanol, propanol (CH <sub>3</sub> OH, CH <sub>3</sub> CH <sub>2</sub> OH, CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> OH)	miscible (dissolve in all proportions)
1-butanol (CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH)	9
1-pentanol (CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OH)	2.7
1-octanol (CH <sub>3</sub> CH <sub>2</sub> OH)	0.06

Table 2.7 Solubility of different alcohols in water

For organic compounds that are water-insoluble, they can sometimes be converted to the “salt derivative” via a proper reaction and thus can become water-soluble. This method is commonly used in labs for the separation of organic compounds.

Example:

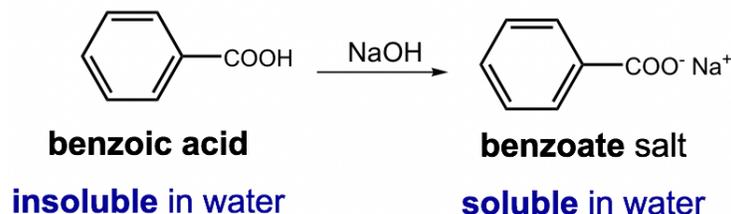


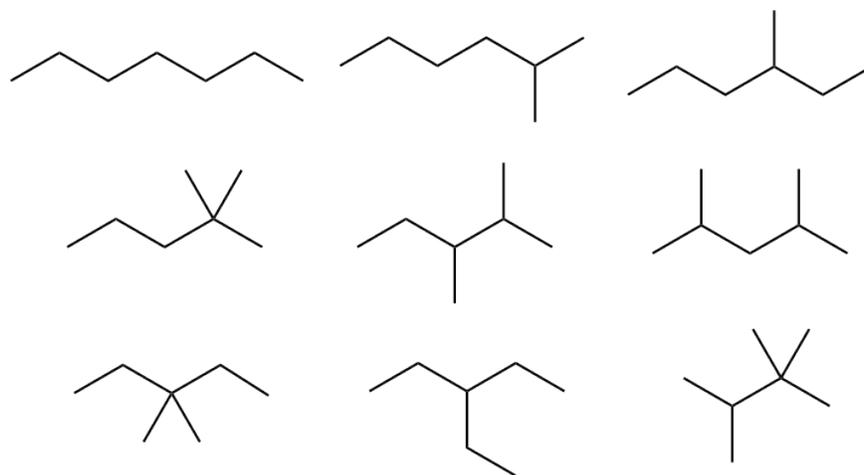
Figure 2.6i Convert insoluble organic compound to the soluble salt derivative

Applying acid-base reactions is the most common way of achieving such purposes. As shown in the above example, by adding a strong base to the benzoic acid, an acid-base reaction occurs and benzoic acid is converted to its salt, sodium benzoate, which is water soluble (because of the ion-dipole force, as we learned earlier). The benzoic acid can therefore be brought into the water (aqueous) phase and separated from other organic compounds that do not have similar properties.

# Answers to Chapter 2 Practice Questions

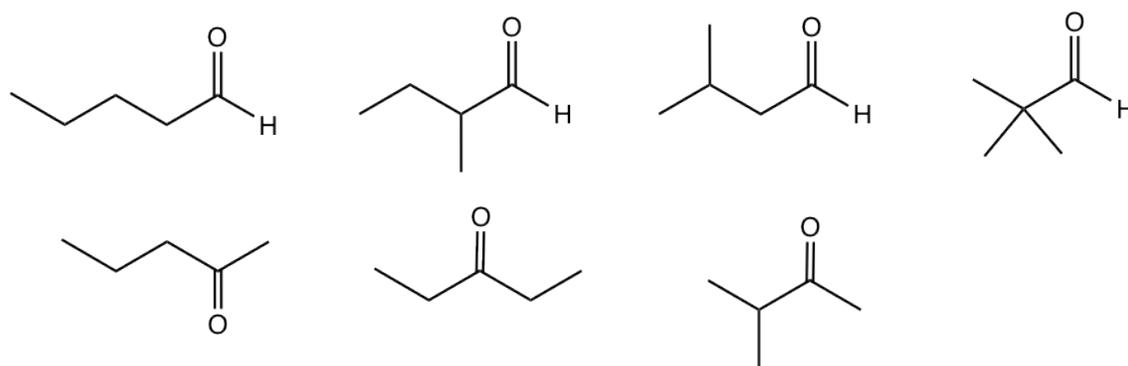
## 2.1

Draw all the constitutional isomers with a formula of  $C_7H_{16}$



## 2.2

Draw all the constitutional isomers that include a  $C=O$  bond with the formula  $C_5H_{10}O$ .



# CHAPTER 3: ACIDS AND BASES: INTRODUCTION TO ORGANIC REACTION MECHANISM INTRODUCTION

Acids and bases are topics that we are familiar with from first-year general chemistry courses. In this chapter, we will first review the basic concepts of acids and bases, and then apply those concepts to the context of organic chemistry. We will learn how to understand organic reactions from the perspective of acids and bases and take a detailed look at the organic reactions in terms of their reaction mechanisms.

Learning Objectives for this chapter:

- Describe, define and recognize acids and bases based on Bronsted-Lowry or Lewis acid-base definitions.
- Compare the relative acidity or basicity of organic functional groups qualitatively and quantitatively ( $pK_a$ ), and be able to apply such information to predict the products and direction of equilibrium for organic reactions.
- Understand and explain the structural effects on the acidity and basicity of organic compounds.

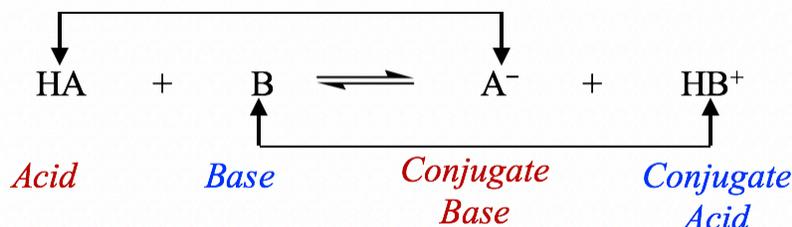


## 3.1 Review of Acids and Bases and $K_a$

The most commonly applied definition of acids and bases is the Brønsted-Lowry definition:

- Brønsted-Lowry Acid: a substance that can donate a proton ( $H^+$ )
- Brønsted-Lowry Base: a substance that can accept a proton ( $H^+$ )

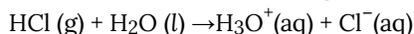
Therefore, according to the Brønsted-Lowry definition, an acid-base reaction is a proton transfer process in which the acid gives away a proton and the base accepts a proton as shown in the general equation:



General equation for acid-base reaction

The species that forms when an acid loses its proton is called the conjugate base of that acid; similarly, the species that forms when a base accepts a proton is called the conjugate acid of that base. In the general equation above, HA is the conjugate acid of  $A^-$ , and  $A^-$  is the conjugate base of HA. HA and  $A^-$  can also be called a conjugate acid-base pair; another pair is  $HB^+$  and B.

A strong acid donates the proton completely, and the arrow " $\rightarrow$ " can be used in the reaction equation to indicate that the reaction goes to completion. The dissociation reaction of the strong acid HCl in water is used as an example here:



For weak acids (HA is used as a general formula), the proton is only partially donated and the reaction stays at equilibrium. The equilibrium arrow " $\rightleftharpoons$ " will be needed in the reaction equation to indicate the equilibrium status:



The equilibrium constant for the above reaction is called the acid dissociation constant,  $K_a$ . It is a constant to measure the relative strength of an acid. The expression for  $K_a$  is:

$$K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

The larger the  $K_a$  value, the stronger the ability of the acid to donate protons, and the stronger the acid is. (Technically, when the  $K_a$  value is larger than 10, the acid can be regarded as a strong acid.)

For the conjugate acid-base pair, the stronger the acid, the weaker the conjugate base is, and vice versa.

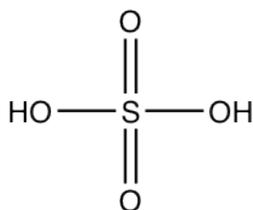
## 3.2 Organic Acids and Bases and Organic Reaction Mechanism

### 3.2.1 Organic Acids

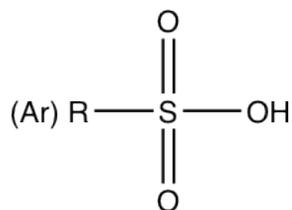
The acids we discussed in general chemistry usually refer to inorganic acids, such as HCl, H<sub>2</sub>SO<sub>4</sub>, and HF. If the structure of the acid contains a “carbon” part, then it is an organic acid. Organic acids donate protons in the same way as inorganic acids, but their structure may be more complicated due to the nature of organic structures.

Carboxylic acid, with the general formula of R-COOH, is the most common organic acid we are familiar with. Acetic acid (CH<sub>3</sub>COOH), an ingredient in vinegar, is a simple example of a carboxylic acid. The K<sub>a</sub> of acetic acid is 1.8×10<sup>-5</sup>.

Another common organic acid is the organic derivative of sulfuric acid H<sub>2</sub>SO<sub>4</sub>.



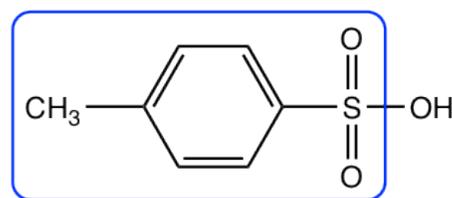
**sulfuric acid, H<sub>2</sub>SO<sub>4</sub>**



**sulfonic acid, RSO<sub>3</sub>H or ArSO<sub>3</sub>H**

The replacement of one OH group in H<sub>2</sub>SO<sub>4</sub> with a carbon-containing R (alkyl) or Ar (aromatic) group leads to the organic acid named “sulfonic acid” with the general formula of RSO<sub>3</sub>H, or ArSO<sub>3</sub>H. Sulfonic acid is a strong organic acid with a K<sub>a</sub> in the range of 10<sup>6</sup>. The structure of a specific sulfonic acid example called *p*-toluenesulfonic acid is shown here:

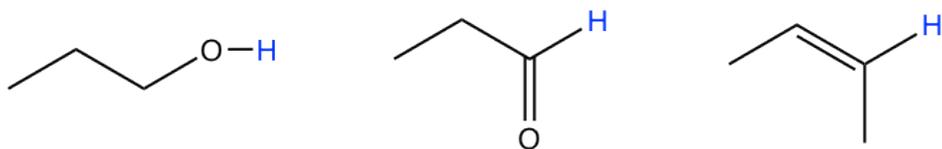
The common name is tosylic acid, and the circled part is known as the “**tosyl**” group, that is abbreviated as “**Ts**”. So the formula of tosylic acid can also be **TsOH**.



***p*-toluenesulfonic acid, TsOH  
(common name: tosylic acid)**

Figure 3.1a CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>H Tosylic acid

Other than the acids mentioned here, technically, any organic compound could be an acid because organic compounds always have hydrogen atoms that could potentially be donated as H<sup>+</sup>. A few examples are shown here with the hydrogen atoms highlighted in blue:



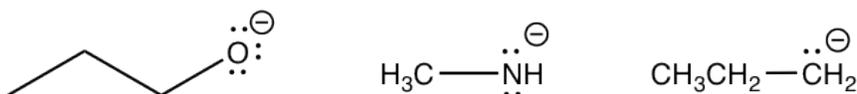
### More examples of organic acids

Therefore, the scope of acids has been extended to be broadly extended in an organic chemistry context. We will have further discussions on the acidity of organic compounds in section 3.3, and we will see more acid-base reactions applied to organic compounds later in this chapter.

### 3.2.2 Organic Bases

While it is relatively straightforward to identify an organic acid since hydrogen atoms are always involved, it is not always easy to identify organic bases. According to the definition, a base is a species that is able to accept protons. Organic bases may involve a variety of different structures, but they must all share the common feature of having electron pairs that are able to accept protons. The electron pairs could be lone pair electrons on a neutral or negatively charged species or  $\pi$  electron pairs. Organic bases could therefore involve the following types:

- Negatively charged organic bases:  $\text{RO}^-$  (alkoxide),  $\text{RNH}^-$  (amide), and  $\text{R}^-$  (alkide, the conjugate base of alkane). Since the negatively charged bases have a high electron density, they are usually stronger bases than the neutral ones.



#### Examples of negatively charged organic bases with lone pair electrons shown in the structure

Note: Keep in mind that lone pairs are usually omitted in organic structures as mentioned before. For example, with the formula of  $\text{CH}_3\text{NH}^-$  given, you should understand that the N actually has two pairs of lone pair electrons (as shown in the above structure) and it is a base.

- Neutral organic bases, for example, amine,  $\text{C}=\text{O}$  group and  $\text{C}=\text{C}$  group
  - Amine:  $\text{RNH}_2$ ,  $\text{R}_2\text{NH}$ ,  $\text{R}_3\text{N}$ ,  $\text{ArNH}_2$ , etc. (section 2.3). As organic derivatives of  $\text{NH}_3$ , which is an inorganic weak base, amines are organic weak bases with lone pair electrons on N that are able to accept the protons.

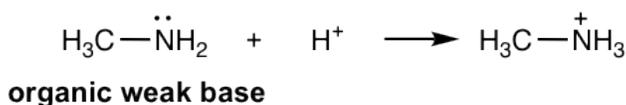
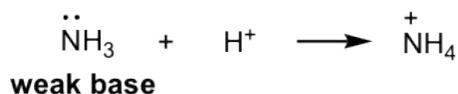


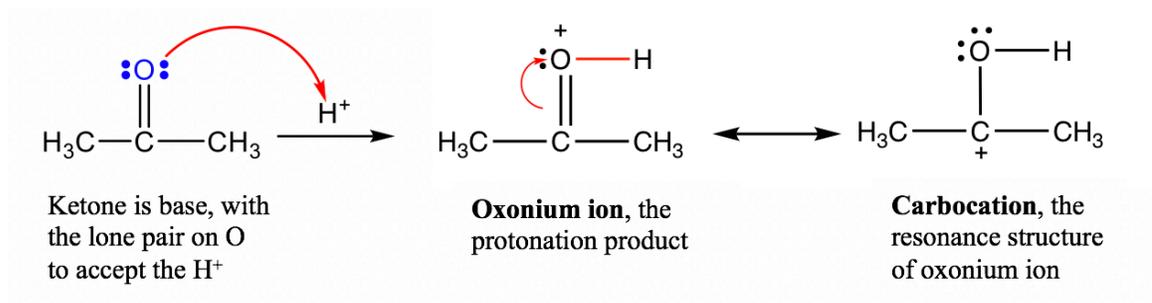
Figure 3.1b weak base and organic weak base

- Functional groups containing oxygen atoms: carbonyl group C=O, alcohol R-OH, and ether R-O-R. The lone pair electrons on O in these groups are able to accept the protons, so functional groups like aldehyde, ketone, alcohol and ether are all organic bases. It may not be easy to accept this concept at first because these groups do not really look like bases. However, they are bases according to the definition because they are able to accept the proton with the lone pair on the oxygen atom.

Adjust your thinking here to embrace the broader scope of acids and bases in an organic chemistry context.

Here, we will take the reaction between acetone and  $\text{H}^+$  as an example, to understand the reaction deeply by exploring the reaction mechanism, and learn how to use the curved arrows to show it.

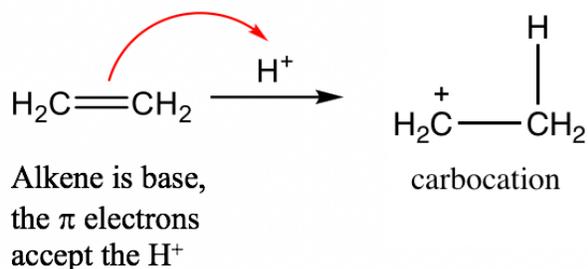
A reaction mechanism is a step-by-step electron transfer process that converts reactants to products. *Curved arrows* are used to illustrate the reaction mechanism. Curved arrows should always start at the electrons, and end in the spot that is receiving the electrons. The curved arrows used here are similar to those for resonance structures (section 1.4) but are not exactly the same though. Please note that in resonance structures, curved arrows are used to show how the electrons are transferred within the molecule, leading to another resonance structure. For mechanism purposes, there must be arrows that connect between species.



### Notes for the above mechanism:

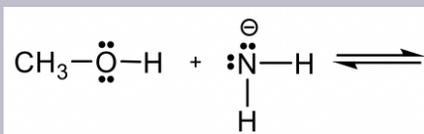
- For the acid-base reaction between the C=O group and the proton, the arrow starts from the electron pair on O and points to the H<sup>+</sup> that is receiving the electron pair. A new O-H bond is formed as a result of this electron pair movement.
- In this acid-base reaction, the ketone is protonated by H<sup>+</sup> so this reaction can also be called the “protonation of ketone”.
- The product of the protonation is called an “oxonium ion”, which is stabilized with another resonance structure, carbocation.

- Alkene (C=C): Although there are no lone pair electrons in the C=C bond of alkene, the π electrons of the C=C double bond are able to accept protons and act as a base. For example:



*Example: Organic acid and base reaction*

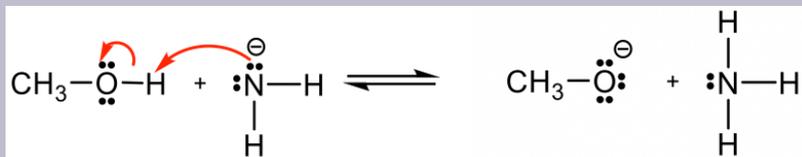
Predict and draw the products of the following reaction and use the curved arrow to show the mechanism.



Approach: If H<sup>+</sup> is the acid as in previous examples, it is rather easy to predict how the reaction will proceed. However, if there is no obvious acid (or base) as in this example, how do you determine which is the acid, and which is the base?

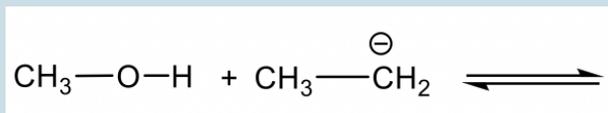
Methanol  $\text{CH}_3\text{OH}$  is neutral, and the other reactant,  $\text{NH}_2^-$ , is a negatively charged amide. The amide with a negative charge has higher electron density than the neutral methanol, therefore amide  $\text{NH}_2^-$  should act as base, and  $\text{CH}_3\text{OH}$  is the acid that donates  $\text{H}^+$ .

Solution:



### Exercises 3.1

Predict and draw the products of the following reaction and use a curved arrow to show the mechanism.



Answers to Chapter 3 Practice Questions

## 3.3 pK<sub>a</sub> of Organic Acids and Application of pK<sub>a</sub> to Predict Acid-Base Reaction Outcome

As we mentioned before, all organic compounds could be acids because they all have hydrogen atoms that could potentially be donated. Most organic acids are weak acids with a small  $K_a$ . For example, acetic acid  $\text{CH}_3\text{COOH}$  has a  $K_a$  of  $1.8 \times 10^{-5}$ . Many other organic acids are even weaker than acetic acid, and it is this weak acidity that makes it difficult to realize that some organic compounds are actually acids.

However, this weak acidity is very important in Organic Chemistry. Since it is inconvenient to have to say or to remember  $K_a$  values like  $1.8 \times 10^{-5}$ ,  $\text{p}K_a$  is used more often in Organic Chemistry to refer to the relative acidity of different acids. The definition of  $\text{p}K_a$  is:

$$\text{p}K_a = -\log K_a$$

The smaller the  $\text{p}K_a$  value, the larger the  $K_a$ , and the stronger the acidity is.

The  $\text{p}K_a$  of most organic acids ranges between 5 ~ 60. While it is impossible to know the  $\text{p}K_a$  of every organic compound, it is very useful to understand the  $\text{p}K_a$  (and acidity) based on the functional groups involved because the same functional groups usually have similar  $\text{p}K_a$ s. The approximate ranges of  $\text{p}K_a$  values for seven major functional groups are listed in Table 3.1, which serves as a valuable starting point for us to predict and understand the acidity of any organic molecule. The strongest organic acid listed here is carboxylic acid with a  $\text{p}K_a$  of about 5; the weakest organic acids are the alkanes with  $\text{p}K_a$  values of over 50. Since approximate ranges of  $\text{p}K_a$  values are listed in the table, the exact  $\text{p}K_a$  value of a group varies for different compounds because of the structural differences. Fortunately, however, it is usually not necessary to know the exact  $\text{p}K_a$  values for most cases in organic chemistry, and the approximate range is good enough.

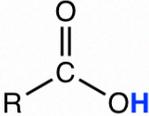
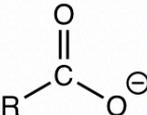
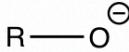
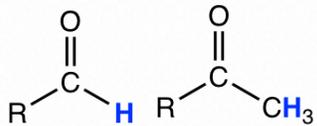
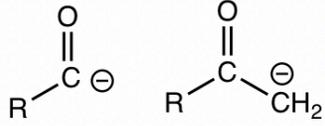
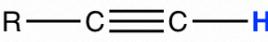
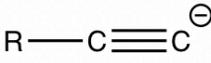
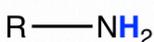
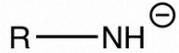
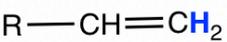
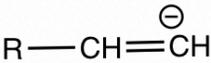
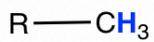
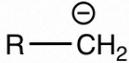
Acidic Hydrogen in Functional Groups	Approximate Range of pKa	Conjugate Base
Carboxylic acid 	~5	
Alcohol R—OH 	~16 (H <sub>2</sub> O: ~16; Phenol: ~10)	
Aldehyde/Ketone 	~16 to ~20	
Alkyne 	~25	
Amine 	~35 to 40 (NH <sub>3</sub> : ~38)	
Alkene 	~45	
Alkane 	>50	

Table 3.1: Approximate ranges of pK<sub>a</sub> values for common organic functional groups

### Notes for the pK<sub>a</sub> values in Table 3.1:

- Acidity is the ability of a compound to donate H<sup>+</sup>, so when we talk about the acidity (K<sub>a</sub> and pK<sub>a</sub>) of an organic compound, it must be about a specific H atom (highlighted in blue in the table). For different H atoms in the same compound, the acidity and pK<sub>a</sub> are different. As for the example of methanol:

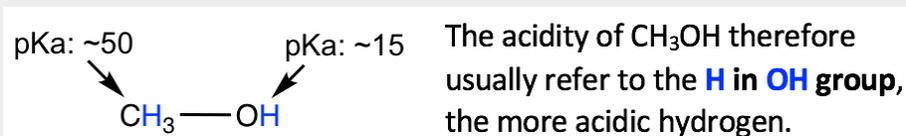


Figure 3.3a Methanol

- It is useful to memorize the approximate ranges of  $\text{pK}_a$  listed in Table 3.1.
- The acidity of the functional groups in the table decreases from top to bottom, and the basicity of the conjugate bases in the last column increases from top to bottom because the stronger the acid, the weaker the conjugate base is.

#### Predict the Outcomes of Organic Acid-Base Reactions – Use $\text{pK}_a$ as a Criterion

With our knowledge of acidity and  $\text{pK}_a$ , we are now ready to see how to apply this information to the understanding of organic reactions from an acid-base perspective.

The following reaction is an example in Section 3.2. If you take a closer look at the reactants and products, you will find that the “product” side also contains an acid (ammonia  $\text{NH}_3$ ) and a base (methoxide  $\text{CH}_3\text{O}^-$ ). Now the question is, how can we be so sure that the reaction proceeds to the “product” side as written? The question can also be asked in a different way: if an equilibrium is established for the reaction mixture, which side will the position of the equilibrium predominantly favour? Left or right?

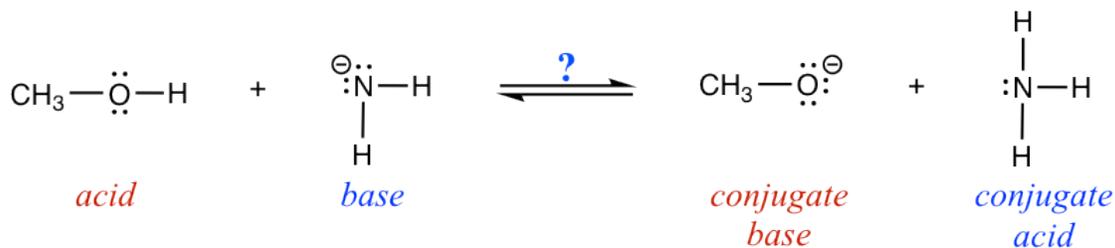


Figure 3.3b Acid-Base Reaction

To answer that question, we will learn about a general rule for acid-base reactions: Acid-base reactions always favour the formation of the weaker acid and the weaker base. This is because the equilibrium always favours the formation of more stable products, and weaker acids and bases are more stable than stronger ones.

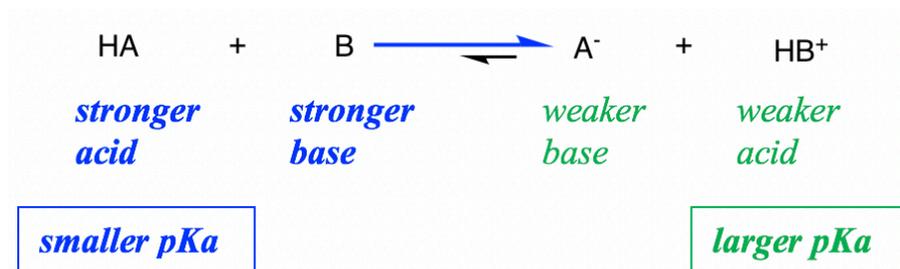


Figure 3.3c Smaller pK<sub>a</sub> and larger pK<sub>a</sub>

With pK<sub>a</sub> values available at hand, the relative acidity of reactants vs products can be compared by comparing their pK<sub>a</sub> values, and the reaction will proceed to the side of the acid with a larger pK<sub>a</sub> (larger pK<sub>a</sub> means smaller K<sub>a</sub>, and thus a weaker acid).

So for this reaction, the pK<sub>a</sub> check indicates that ammonia NH<sub>3</sub> is a weaker acid than methanol CH<sub>3</sub>OH, so the reaction does proceed to the right side with CH<sub>3</sub>O<sup>-</sup> and NH<sub>3</sub> as the major products.

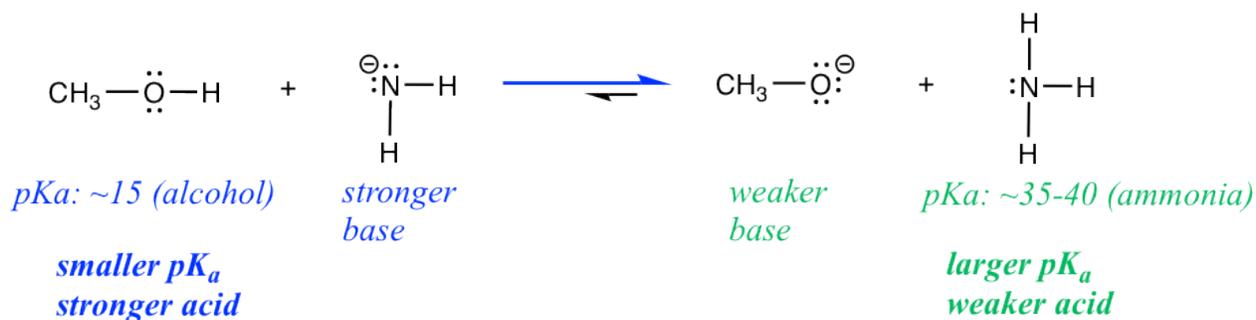


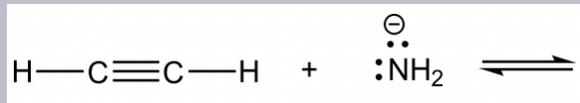
Figure 3.3d Which direction does the reaction go?

Notes: Only comparing acids is good enough for this purpose because if CH<sub>3</sub>OH is stronger than NH<sub>3</sub>, then the conjugate base CH<sub>3</sub>O<sup>-</sup> must be weaker than the other base NH<sub>2</sub><sup>-</sup>.

### Examples

Show the products of the following reactions and predict the predominant side of the equilibrium.

### Reaction 1

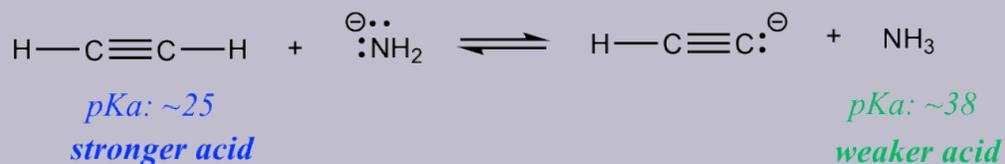


### Reaction 2



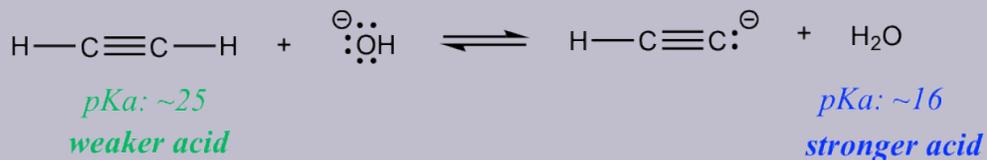
### Solutions:

#### Reaction 1



the equilibrium favors the **products (right) side** of the reaction

#### Reaction 2



the equilibrium favors the **reactants (left) side** of the reaction

Are there any practical applications for such a prediction? Yes! Let's compare the two reactions in the exercises above. Reaction 1 indicates that if ethyne (HC≡CH) and amide (NH<sub>2</sub><sup>−</sup>) are mixed together, the reaction does proceed to the

product side, meaning  $\text{HC}\equiv\text{CH}$  could be deprotonated by amide  $\text{NH}_2^-$ . However, if  $\text{HC}\equiv\text{CH}$  and hydroxide  $\text{OH}^-$  are mixed as shown in reaction 2, no reaction occurs, or we can say that  $\text{HC}\equiv\text{CH}$  can not be deprotonated by  $\text{OH}^-$  because  $\text{OH}^-$  is not strong enough! So if you are working in the lab and have the option of choosing between  $\text{NH}_2^-$  or  $\text{OH}^-$  to deprotonate  $\text{HC}\equiv\text{CH}$ , you now know which one to choose.

The idea that  $\text{OH}^-$  is not a strong enough base may bother you a lot, since it conflicts with the “common knowledge” that we learned in General Chemistry, where  $\text{OH}^-$  is a strong base. Generally speaking,  $\text{OH}^-$  is a pretty strong base; however, it is just barely not strong enough to deprotonate  $\text{HC}\equiv\text{CH}$ , which is a very weak acid, with a  $\text{p}K_a$  of about ~25. Since  $\text{HC}\equiv\text{CH}$  is much weaker than the “weak acids” we learned in General Chemistry, a much stronger base, like  $\text{NH}_2^-$ , is required to deprotonate it.

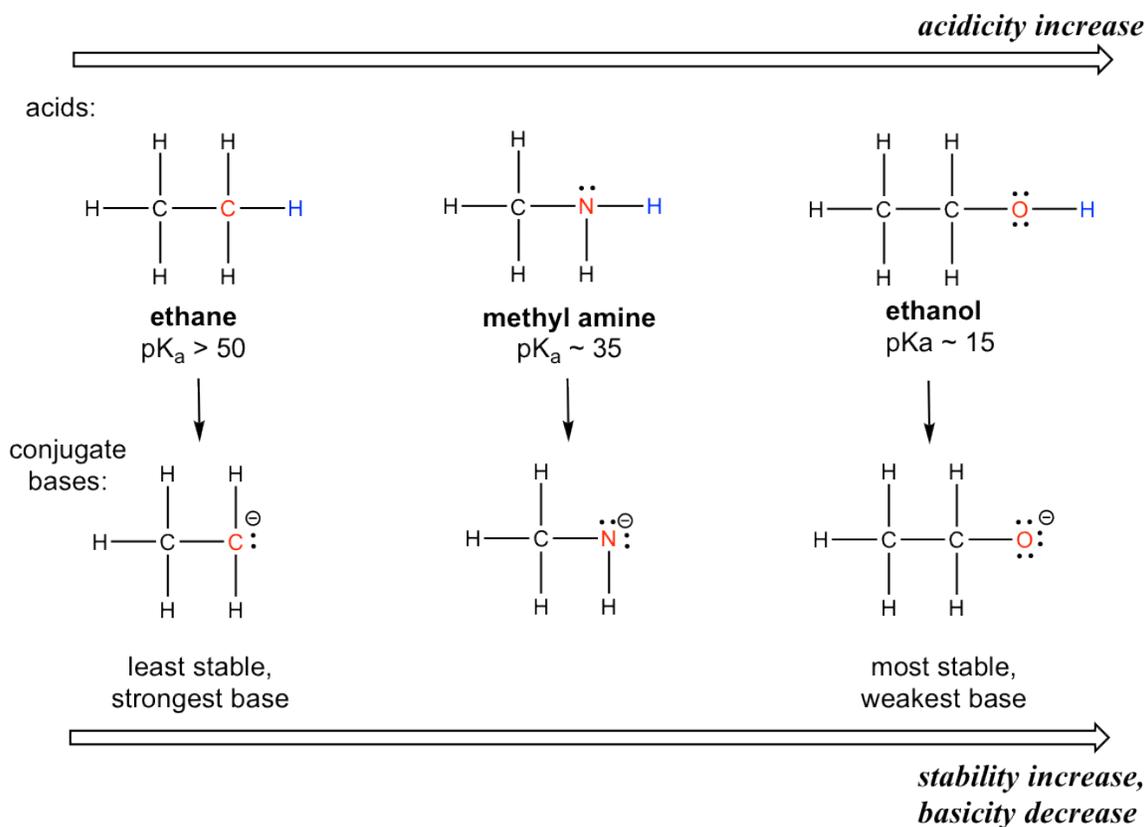
## 3.4 Structural Effects on Acidity and Basicity

We have learned that different functional groups have different strengths in terms of acidity. In this section, we will gain an understanding of the fundamental reasons behind this, which is why one group is more acidic than the other. Many of the concepts we will learn here will continue to be applied throughout this course as we tackle other organic topics.

### 3.4.1 Element Effect

#### A. Periodic Trend: Electronegativity

The element effect is about the individual atom that connects with the hydrogen (keep in mind that acidity is about the ability to donate certain hydrogen). Let's compare the acidity of hydrogens in ethane, methylamine and ethanol as shown below.



A clear trend in the acidity of these compounds is that the acidity increases for the elements from left to right along the second row of the periodic table, C to N, and then to O. This is consistent with the increasing trend of EN along the period from left to right. The connection between EN and acidity can be explained as the atom with a higher EN being better able to accommodate the negative charge of the conjugate base, thereby stabilizing the conjugate base in a better

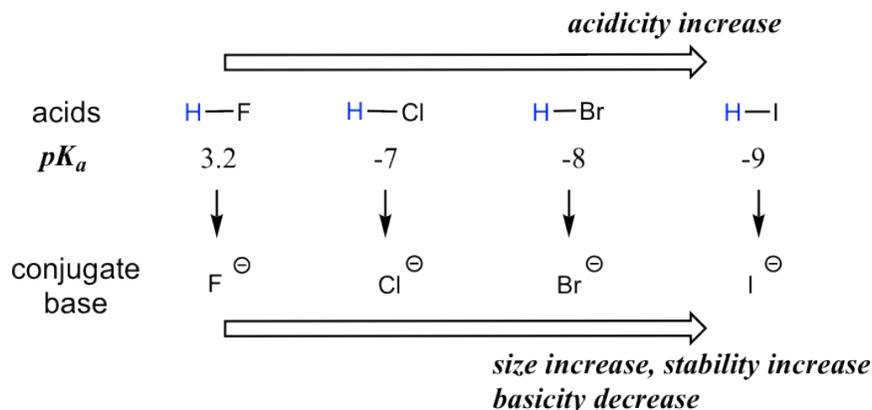
way. Therefore, the more stable the conjugate base, the weaker the conjugate base is, and the stronger the acid is. For the discussion in this section, the trend in the stability (or basicity) of the conjugate bases often helps explain the trend of the acidity.

The relative acidity of elements in the same period is:

For elements in the same period, the more electronegative an atom, the stronger the acid is; the acidity increases from left to right across the period.

## B. Group (vertical) Trend: Size of the atom

When moving vertically within a given group on the periodic table, the trend is that acidity increases from top to bottom. This can be illustrated with the haloacids HX and halides as shown below: the acidity of HX increases from top to bottom, and the basicity of the conjugate bases  $X^-$  decreases from top to bottom.



The acidity of the H in the thiol SH group is also stronger than the corresponding alcohol OH group following the same trend. For example, the  $pK_a$  of  $CH_3CH_2SH$  is ~10, which is much more acidic than ethanol  $CH_3CH_2OH$  which has a  $pK_a$  of ~16.

To make sense of this trend, we will once again consider the stability of the conjugate bases. When moving vertically in the same group of the periodic table, the size of the atom overrides its EN with regard to basicity. The atomic radius of iodine is approximately twice that of fluorine, so in an iodide ion, the negative charge is spread out over a significantly larger volume, so  $I^-$  is more stable and less basic, making HI more acidic.



**larger volume of  $I^-$  helps the negative charge to be better spread out, so  $I^-$  is more stable than  $F^-$**

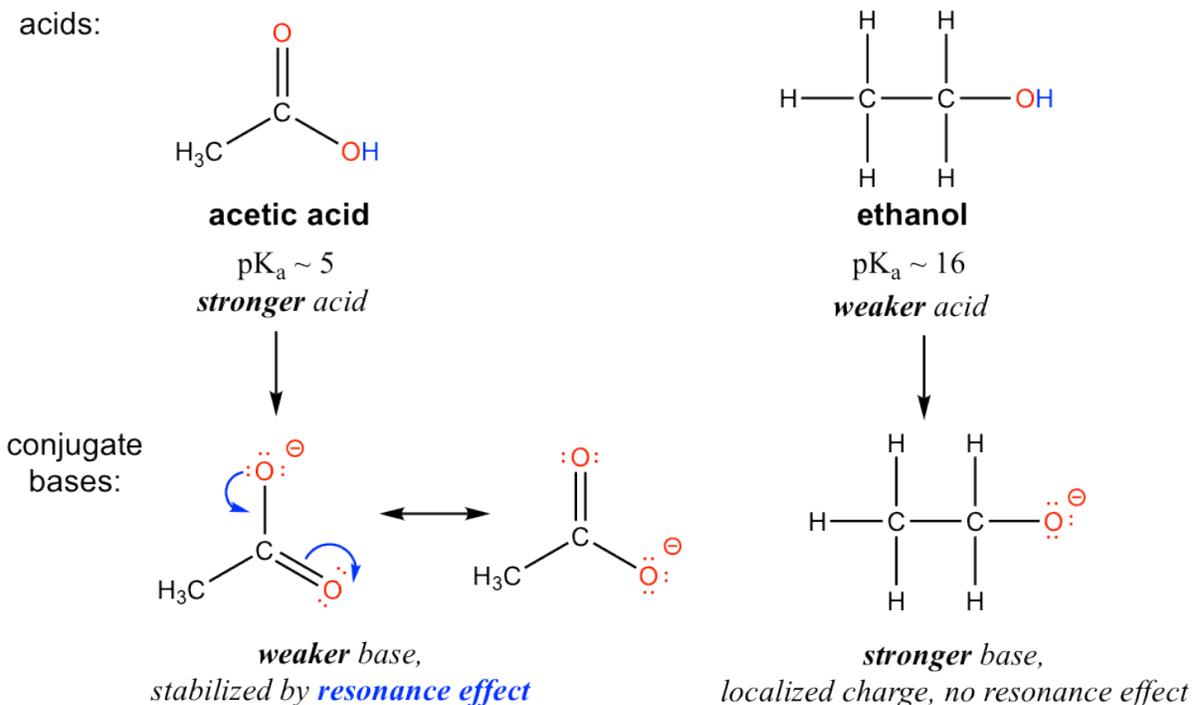
Figure 3.4a Stability of fluorine and iodide ion

The relative acidity of elements in the same group is:

For elements in the same group, the larger the size of the atom, the stronger the acid is; the acidity increases from top to bottom along the group.

### 3.4.2. Resonance Effect

The resonance effect accounts for the acidity difference between ethanol and acetic acid. For both ethanol and acetic acid, the hydrogen is bonded with the oxygen atom, so there is no element effect that matters. However, the  $pK_a$  values (and the acidity) of ethanol and acetic acid are very different. What makes a carboxylic acid so much more acidic than an alcohol? As stated before, we begin by considering the stability of the conjugate bases, remembering that a more stable (weaker) conjugate base corresponds to a stronger acid.



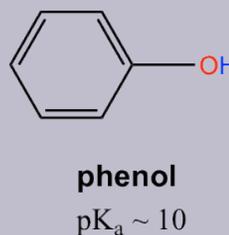
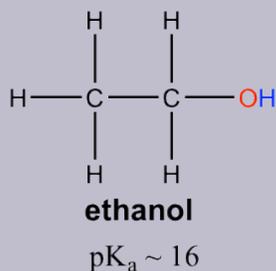
For acetate, the conjugate base of acetic acid, two resonance contributors can be drawn and therefore the negative charge can be delocalized (shared) over two oxygen atoms. However, no other resonance contributor is available in the ethoxide ion, the conjugate base of ethanol, so the negative charge is localized on the oxygen atom. As we have learned in section 1.3, the species that has more resonance contributors gains stability; therefore acetate is more stable than ethoxide and is weaker as the base, so acetic acid is a stronger acid than ethanol.

The charge delocalization by resonance has a powerful effect on the reactivity of organic molecules, enough to

account for the significant difference of over 10  $pK_a$  units between ethanol and acetic acid.  $pK_a = -\log K_a$ , which means that there is a factor of about  $10^{10}$  between the  $K_a$  values for the two molecules!

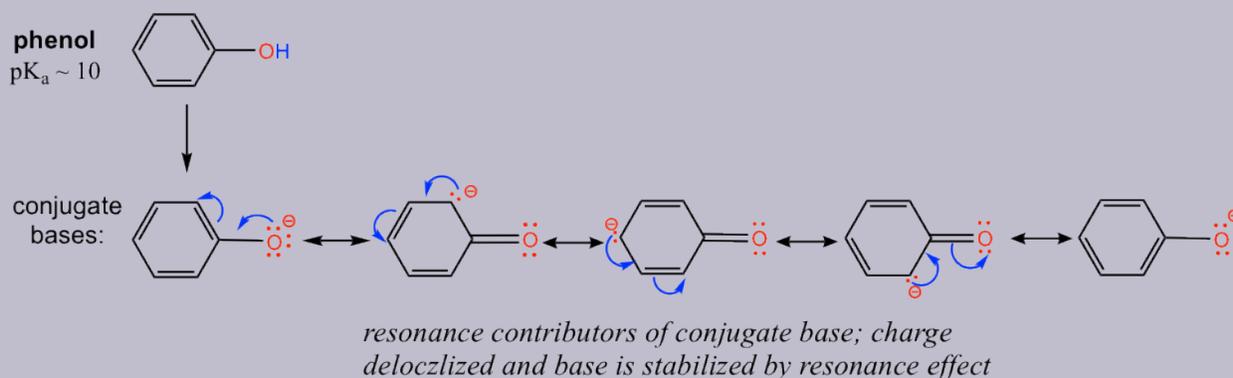
### Examples

The  $pK_a$  of the OH group in alcohol is about 15, however OH in phenol (OH group connected on a benzene ring) has a  $pK_a$  of about 10, which is much stronger in acidity than other alcohols. Explain the difference.



### Solution:

The difference can be explained by the resonance effect. There is no resonance effect on the conjugate base of ethanol, as mentioned before. However, the conjugate base of phenol is stabilized by the resonance effect with four more resonance contributors, and the negative charge is delocalized on the benzene ring, so the conjugate base of phenol is much more stable and is a weaker base. Therefore phenol is much more acidic than other alcohols.

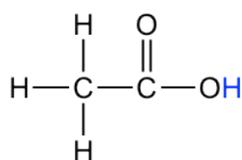


- Practice drawing the resonance structures of the conjugate base of phenol by yourself!
- It is because of the special acidity of phenol (and other aromatic alcohols), that NaOH can be used to deprotonate phenol effectively, but not to normal alcohols, like ethanol. Show the reaction equations of these reactions and explain the difference by applying the  $pK_a$  values.

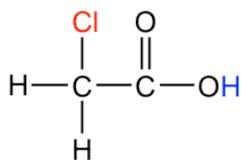
## Answers to Chapter 3 Practice Questions

## 3.4.3 Inductive Effect

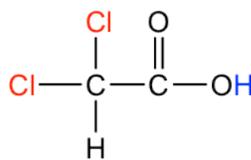
Let's compare the  $pK_a$  values of acetic acid and its mono-, di-, and tri-chlorinated derivatives:

**acetic acid**

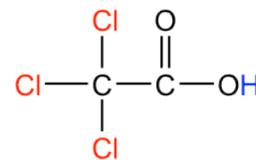
$pK_a = 4.8$

**monochloroacetic acid**

$pK_a = 2.8$

**dichloroacetic acid**

$pK_a = 1.3$

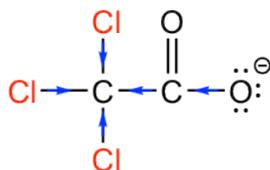
**trichloroacetic acid**

$pK_a = 0.64$

Figure 3.4b Acetic acid and its mono-, di-, and tri-chlorinated derivatives

The presence of the chlorine atoms clearly increases the acidity of the carboxylic acid group, and the trend here apparently can not be explained by the element effect. The resonance effect does not apply here either, because no additional resonance contributors can be drawn for the chlorinated molecules. Rather, the explanation for this phenomenon involves something called the inductive effect. A chlorine atom is more electronegative than hydrogen and is thus able to 'induce' or 'pull' electron density towards itself via  $\sigma$  bonds in between, and therefore it helps spread out the electron density of the conjugate base, the carboxylate, and stabilize it. The chlorine substituent can be referred to as an electron-withdrawing group because of the inductive effect.

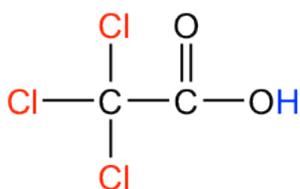
The inductive effect is the charge dispersal effect of electronegative atoms through  $\sigma$  bonds. The inductive effect is additive; more chlorine atoms have an overall stronger effect, which explains the increasing acidity from mono, to di-, to tri-chlorinated acetic acid. The following diagram shows the inductive effect of trichloro acetate as an example.



trichloro acetate was stabilized by inductive effect:  
chlorine atoms pull electrons through  $\sigma$  bonds to help  
charge dispersal

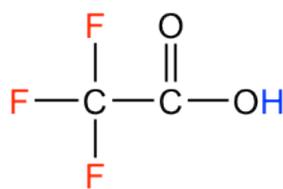
Figure 3.4c Trichloro acetate was stabilized by inductive effect

Because the inductive effect depends on EN, fluorine substituents have a stronger inductive effect than chlorine substituents, making trifluoroacetic acid (TFA) a very strong organic acid.



**trichloroacetic acid**

$$\text{pK}_a = 0.64$$

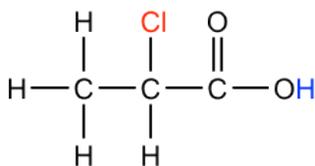


**trifluoroacetic acid  
(TFA)**

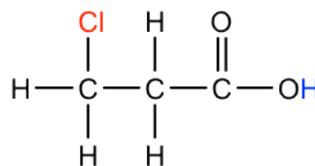
$$\text{pK}_a = -0.25$$

Figure 3.4d trichloroacetic acid ( $\text{pK}_a = 0.64$ ) and trifluoroacetic acid (TFA) ( $\text{pK}_a = -0.25$ )

In addition, because the inductive effect takes place through covalent bonds, its influence decreases significantly with distance – thus a chlorine that is two carbons away from a carboxylic acid group has a weaker effect compared to a chlorine just one carbon away.



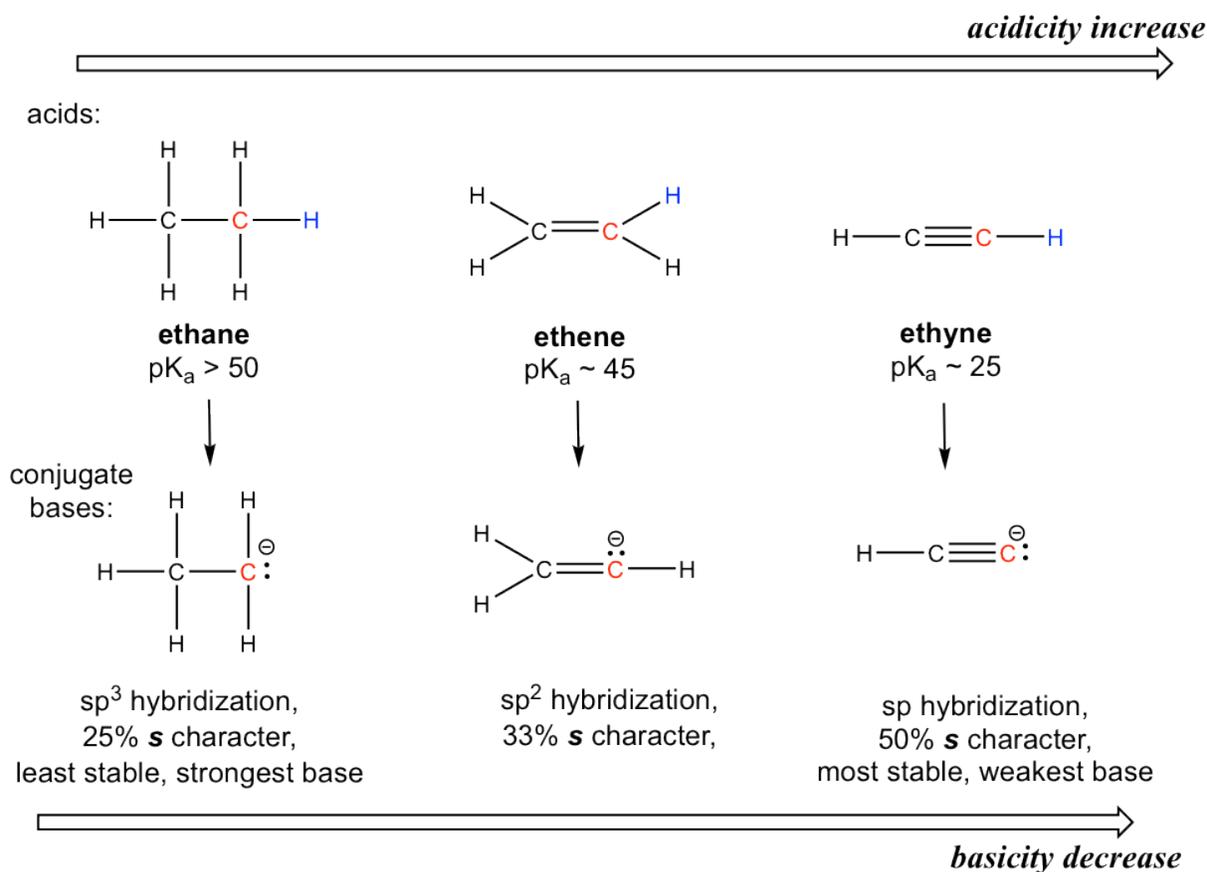
***stronger acid***



***weaker acid***

### 3.4.4 Hybridization Effect

To introduce the hybridization effect, we will take a look at the acidity difference between alkane, alkene and alkyne.



The hydrogen atom is bonded with a carbon atom in all three functional groups, so the element effect does not occur. Also, considering the conjugate base of each, there is no possible extra resonance contributor.

The key difference between the conjugate base anions is the hybridization of the carbon atom, which is sp<sup>3</sup>, sp<sup>2</sup> and sp for alkane, alkene and alkyne, respectively. Different hybridizations lead to different s character, which is the percent of s orbitals out of the total number of orbitals. The sp<sup>3</sup> hybridization means 25% s character (one s and three p orbitals, so s character is 1/4 = 25%), sp<sup>2</sup> hybridization has 33.3% s character, and the number is 50% for sp hybridization. Electrons of 2s orbitals are in a lower energy level than those of 2p orbitals because 2s is much closer to the nucleus. So, for an anion with more s character, the electrons are closer to the nucleus and experience stronger attraction; therefore, the anion has lower energy and is more stable.

The relative stability of the three anions (conjugate bases) can also be illustrated by the electrostatic potential map, in which the lighter color (less red) indicates less electron density of the anion and higher stability.

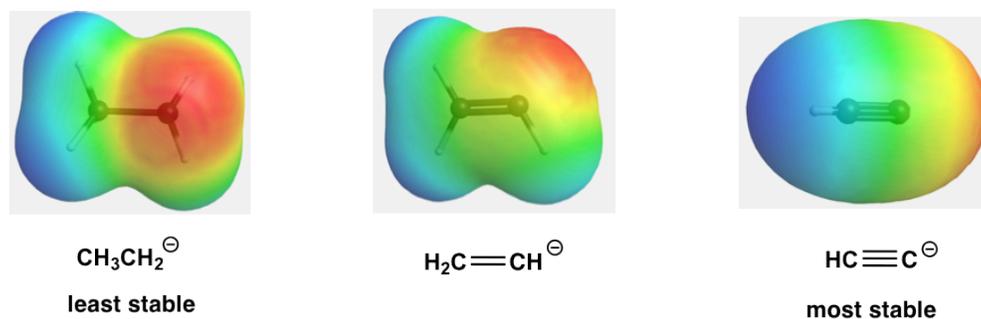


Figure 3.4e Electrostatic potential map of the conj. bases

This can also be stated in a more general way as more s character in the hybrid orbitals makes the atom more electronegative. For the same atom, an sp hybridized atom is more electronegative than an sp<sup>2</sup> hybridized atom, which is more electronegative than an sp<sup>3</sup> hybridized atom.

## 3.5 Lewis Acids and Lewis Bases

The Brønsted-Lowry definition works well for the reactions we have learned so far, but it also limits the scope of acid-base reactions in a way in which the proton  $\text{H}^+$  must be involved. Lewis acids and Lewis bases are defined in a more inclusive way that was first introduced by G.N. Lewis in 1923.

Lewis Acid: a species that can accept an electron pair

Lewis Base: a species that can donate an electron pair

All Brønsted-Lowry acids and bases fit into the Lewis definition because the proton transfer process is essentially the reaction where the base uses its electron pair to accept a proton, as indicated by the mechanism arrow that we learned about earlier. Therefore in the following reaction, the BL acid,  $\text{H}^+$ , is also the Lewis acid, and the BL base,  $\text{NH}_3$ , also fits the definition of the Lewis base.

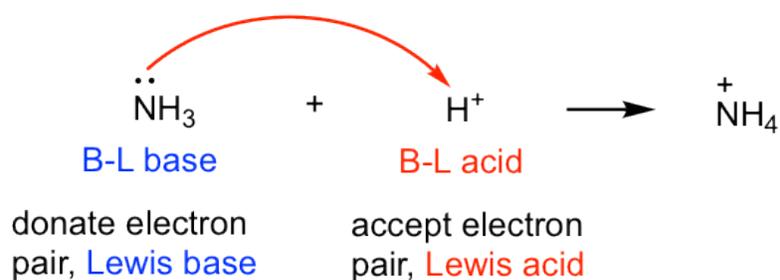


Figure 3.5a Lewis base & Lewis acid reaction

However, the Lewis definition is broader and covers more situations. For the following reaction,  $\text{B}(\text{CH}_3)_3$  is the Lewis acid because boron has an incomplete octet, and the empty 2p orbital on boron is able to accept electrons.  $(\text{CH}_3)_3\text{N}$  behaves as the Lewis base with the lone pair electron on N that is able to be donated.

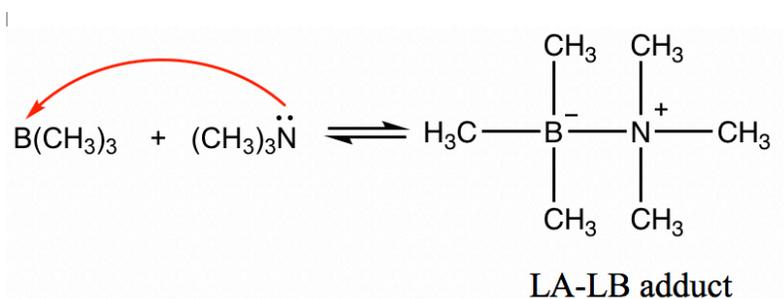


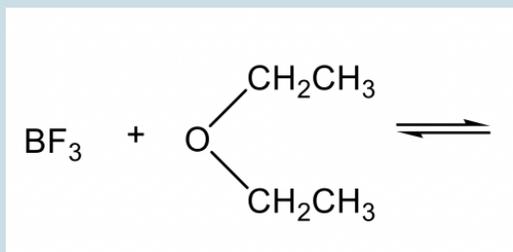
Figure 3.5b LA-LB adduct

The product between Lewis acids and Lewis bases is usually a species that has the acid and base joined together, and this product is called the “LA-LB adduct”.

Other examples of Lewis acids include electron-deficient species, such as  $\text{H}^+$ ,  $\text{M}^+$ ,  $\text{M}^{2+}$ ,  $\text{BH}_3$ ,  $\text{BF}_3$ , and  $\text{AlCl}_3$ . Lewis bases can be amine, ether, or other species that have lone pair electrons to donate.

Exercises 3.3

Show the product of the following LA-LB reaction:

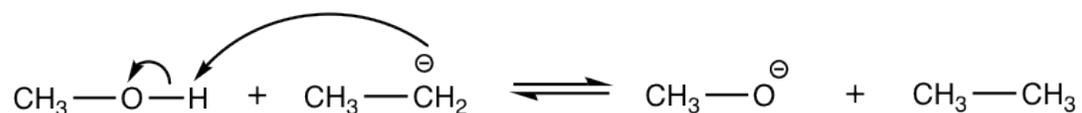


Answers to Chapter 3 Practice Questions

# Answers to Chapter 3 Practice Questions

3.1

Predict and draw the products of the following reaction; use curved arrows to show the mechanism.



3.2

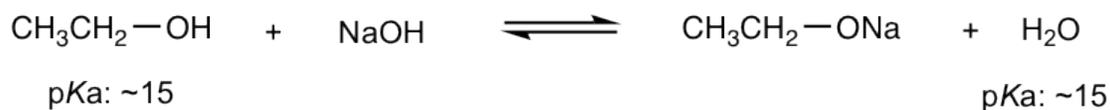
Practice drawing the resonance structures of the conjugate base of phenol by yourself!

Solutions are included in the section.

- It is the special acidity of phenol (and other aromatic alcohol) that allows NaOH to be used to deprotonate phenol effectively, but this is not the case for normal alcohols, like ethanol. Show the reaction equations of these reactions and explain the difference by applying the  $\text{pK}_a$  values.



the equilibrium lies on the **product side**, so NaOH is able to deprotonate phenol



stay at equilibrium, so NaOH is **not** able to deprotonate ethanol effectively

3.3

Show the product of the following LA-LB reaction:





# CHAPTER 4: CONFORMATIONS OF ALKANES AND CYCLOALKANES

The structure and naming of alkanes and cycloalkanes have been discussed in Chapter 2. Here we will learn another property of alkanes and cycloalkanes that comes from the bond rotation.

Learning Objectives for this chapter:

- Understand the nature and properties of conformational isomers, and conduct conformation analysis of simple alkanes.
- Rationalize and compare the relative stability of different cycloalkanes by understanding the three-dimensional structure of cycloalkanes and different types of strains.
- Draw and recognize the chair conformation of cyclohexane; understand the orientation and property of axial and equatorial positions; explain the conformation interconversion process, and conduct conformation analysis of multi-substituted cyclohexane.
- Understand and draw Newman projection of the chair conformation of cyclohexane.
- Understand, identify and draw the geometric isomer and conformational isomer of multi-substituted cyclohexane.



# 4.I Conformation Analysis of Alkanes

## 4.I.I Conformation

At a molecular level, a property of  $\sigma$  (sigma) bonds in alkane is that the bonds keep on rotating. For the example of ethane ( $\text{CH}_3\text{CH}_3$ ), one methyl ( $\text{CH}_3$ ) group is able to rotate around the C-C bond freely without any obstacles.

It is highly recommended that the molecular model is used here to “see” the bond rotation. With a molecular model on hand, you can hold one methyl group steady, and rotate the other methyl group.

The C-C bond is formed by the  $\text{sp}^3\text{-sp}^3$  orbitals overlapping and the bond is cylindrically symmetrical, so rotation about the bond can occur easily and the molecule does not seem to change. However, a closer look indicates that the rotation of the C-C bond does result in a different spatial arrangement of hydrogen atoms in the molecule, as shown below:

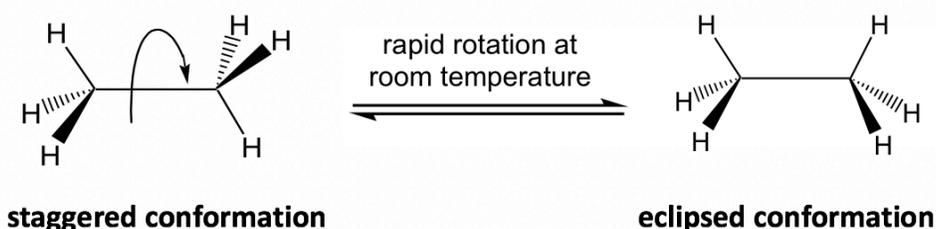


Figure 4.1a Two conformers of ethane in perspective formulas

The different spatial arrangements of the atoms/groups that result from the single bond rotation are called conformations. Molecules with different conformations are called conformational isomers or conformers. The two extreme conformations of ethane coming from the C-C rotation shown above are: the staggered conformation with all of the H atoms spread out and the eclipsed conformation with all of the H atoms overlapped.

In the study of conformation, it is convenient to use certain types of structural formulas. The formula used in the drawing above is the perspective formula (see section 2.1.1) that shows the side-view of the molecule. In perspective formulas, solid and dashed wedges are used to show the spatial arrangement of atoms (or groups) around the  $\text{sp}^3$  carbons.

Another structural formula is the sawhorse formula which shows the tilted top-view of the molecule.

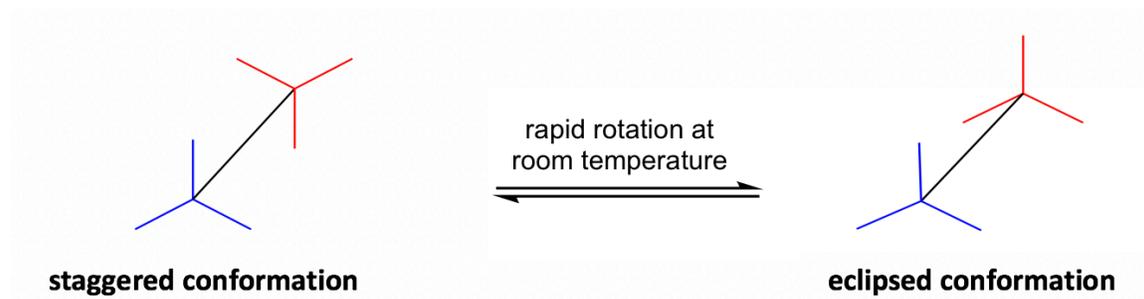


Figure 4.1b Two conformers of ethane in sawhorse formulas

The most commonly applied formula in conformation analysis is the Newman projection formula.

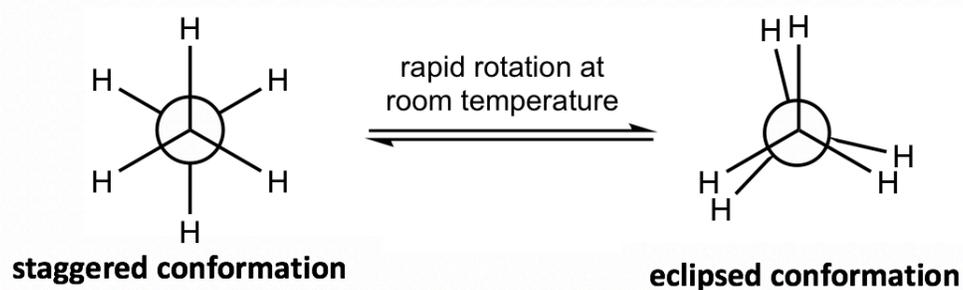


Figure 4.1c Two conformers of ethane in Newman projections

## How to draw a Newman projection

To draw a Newman projection, we will imagine viewing the molecule from one carbon to the next carbon atom directly along a selected C-C bond, as shown below, and follow the rules:

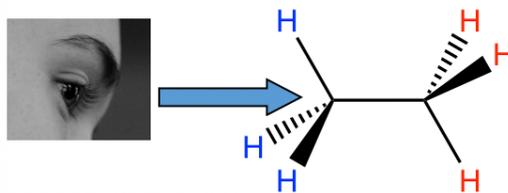


Figure 4.1d Viewing of the molecule

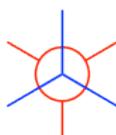
- The front carbon atom is shown as a point with three other bonds:



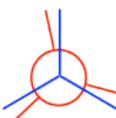
- The rear carbon atom is shown as a circle with three other bonds:



- Put the two carbons together to get the Newman projection of the staggered conformation:



- From the staggered conformation, fix the front carbon in place and rotate the rear carbon by 60° to get the eclipsed conformation:



Note: In eclipsed conformers, the C-H bonds are supposed to be completely overlapped; however, to make the rear groups still visible, the bonds on the rear carbon are intentionally drawn slightly tilted.

### 4.1.2 Conformation Analysis of Ethane

Next, we will do a conformation analysis of ethane by using the Newman projections. A conformation analysis is an investigation of the energy differences and relative stabilities of the different conformations of a compound.

The two conformations of ethane, staggered and eclipsed, are different and therefore should be in different energy levels. You may also intuitively predict that the staggered conformation is more stable and has lower energy because the C-H bonds are arranged as far apart as possible in that conformation. That is correct! In eclipsed conformations, the H atoms on the front carbon overlap with the H atoms on the rear carbon, and this arrangement causes the repulsion between the electrons of the C-H bonds of the two carbons. This type of repulsion is called torsional strain, also known as eclipsing strain. Due to torsional strain, the eclipsed conformer is in an energy level that is 12 kJ/mol (or about 2.9 kcal/mol) higher than the staggered one. This can be represented graphically in a potential energy diagram as shown in Figure 4.1f.

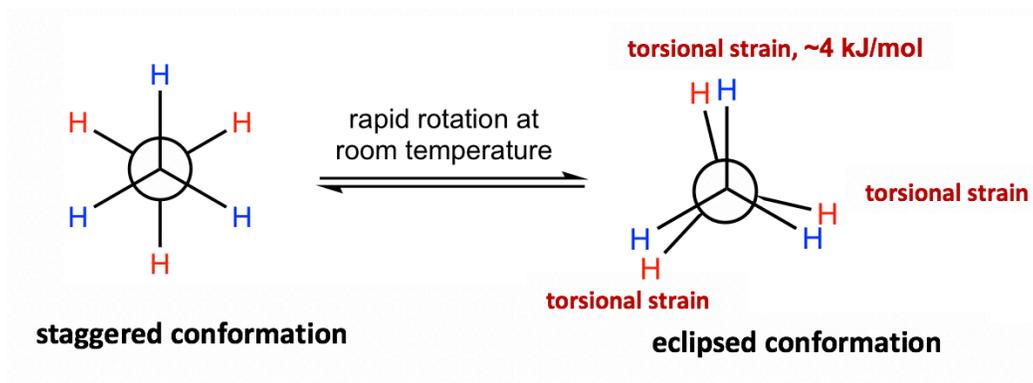


Figure 4.1e Staggered vs. eclipsed conformation

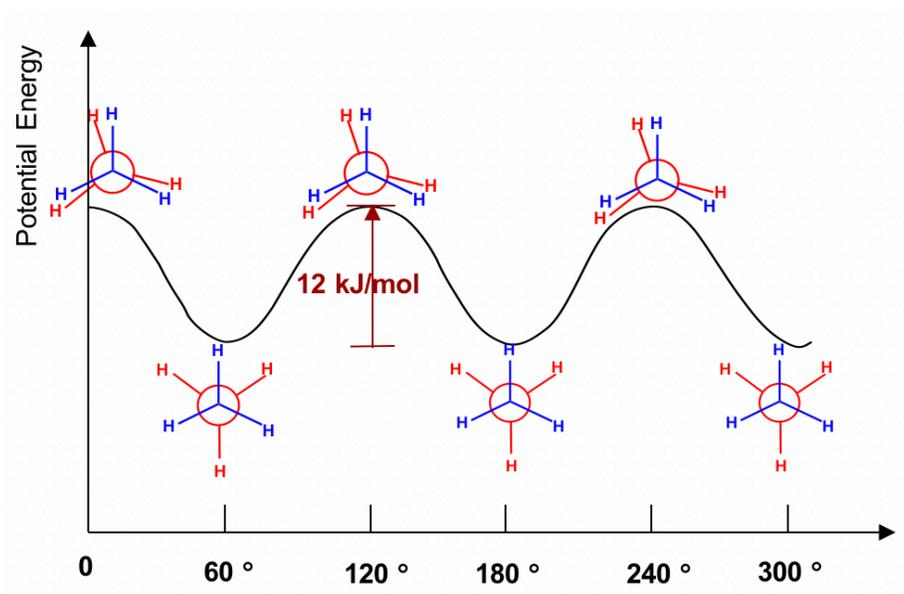


Fig. 4.1f Potential Energy of Ethane vs the Angle of Rotation about the C-C bond

Because of this energy difference, an energy barrier must be overcome when rotation about the C-C bond occurs. However, this energy difference in ethane is small, and the kinetic energy of molecules at room temperature is high enough to cover it. So, at room temperature, the changes from staggered to eclipsed conformers occur millions of times per second. Because of these continuous interconversions, these two conformers cannot be separated from each other. However, at any given moment, about 99% of the ethane molecules will be in a staggered conformation because of their higher stability.

### 4.1.3 Conformation Analysis of Propane

A similar analysis can be applied to propane as well. There are still two types of conformations: staggered and eclipsed

resulting from the rotation. The difference between propane and ethane is that there is a methyl ( $\text{CH}_3$ ) group connected to the rear carbon for propane. However, that does not affect the relative stability, and the staggered conformer is more stable and has lower energy.

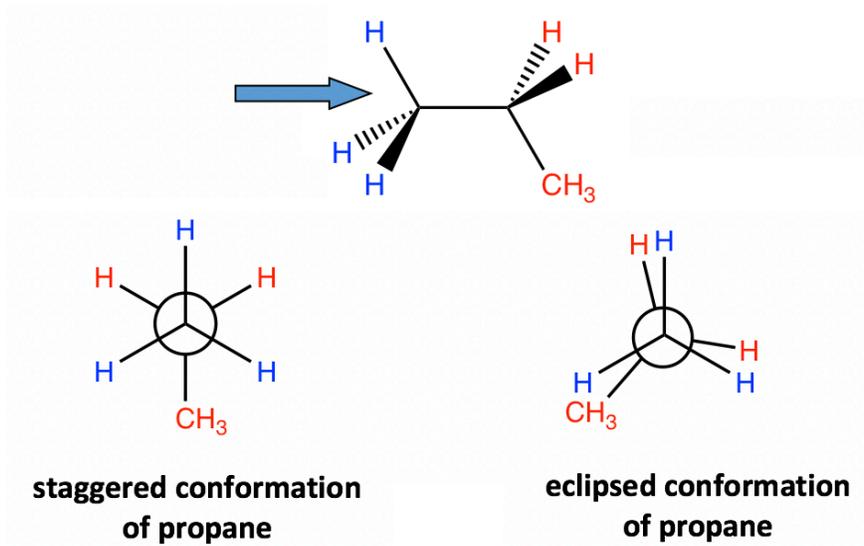


Figure 4.1g Staggered and eclipsed conformation of propane

#### 4.1.4 Conformation Analysis of Butane

There are three C-C bonds in butane, and rotation can occur about each of them. If we choose C1-C2 (or C3-C4) for the study, the situation is almost the same as propane, with the ethyl  $\text{CH}_2\text{CH}_3$  group replacing the  $\text{CH}_3$  group. However, if we consider the rotation along the C2-C3 bond, the situation will be much more complex.

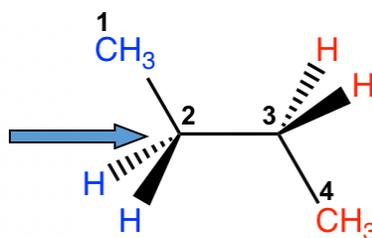


Figure 4.1h Conformation analysis of butane by viewing along C2-C3 bond

For both carbon atoms, C2 and C3, there are two hydrogen atoms and one methyl  $\text{CH}_3$  group bonded. We can start with the conformer in which the two  $\text{CH}_3$  groups are opposite to each other, then fix the front carbon and do  $60^\circ$  rotations of the rear carbon to investigate all the possible conformations.

Exercises 4.1: Draw all the possible conformers of butane from viewing along the C2-C3 bond. Finish this practice by yourself before continue reading!

Tips for drawing all the possible conformers about a certain C-C bond:

- View along that C-C bond; circle and decide what atoms/groups are connected on each carbon;
- Start with the staggered conformation in which the largest groups on each carbon are opposite (far away) to each other (this is called the “anti” conformation as we will learn later);
- Keep the groups on one carbon “fixed”, and rotate the groups on the other carbon at 60° angles. Repeat the rotation five times, and you should get a total of six conformers.

Answers to Chapter 4 Practice Questions

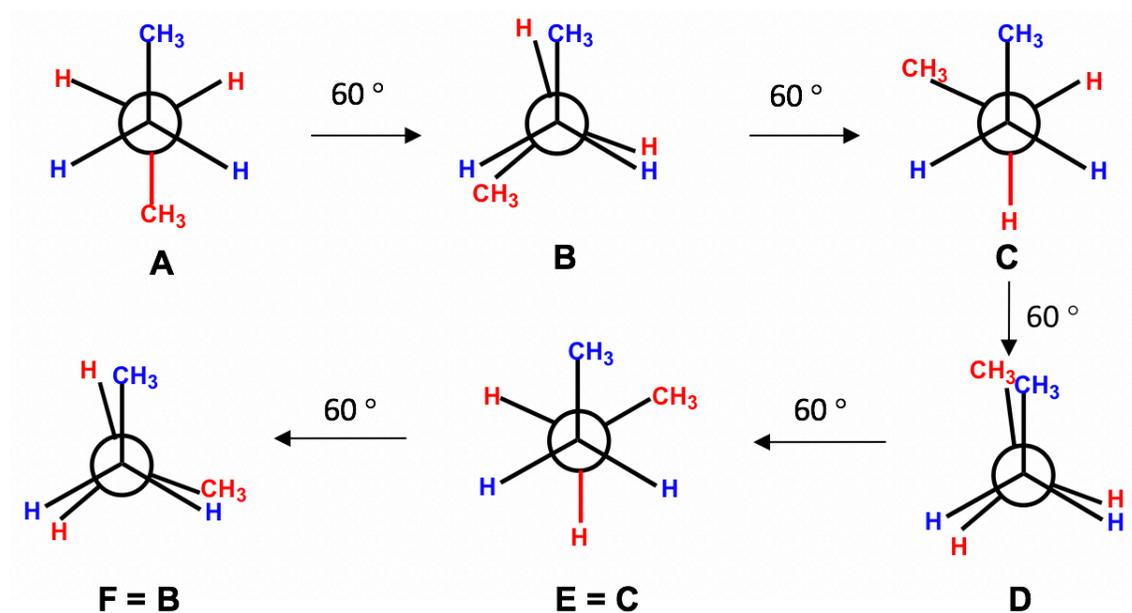


Figure 4.1i All the conformers of butane by viewing along C2-C3 bond

Among all six conformers obtained, there are three staggered and three eclipsed. Staggered conformations **C** and **E** should be in the same energy level because the groups are arranged in an equivalent way between these two conformers. Similarly, eclipsed conformations **F** and **B** are also in the same energy level. So, our studies can be focused on the four conformers: **A**, **B**, **C** and **D**, which are different in terms of energy and stability.

Between the two staggered conformers **A** and **C**, **A** is more stable than **C** because the two methyl CH<sub>3</sub> groups in **A** are as far apart as possible. This most stable staggered conformation is called the anti-conformation (anti is Greek for “opposite”). In anti-conformations, the largest groups on the front and rear carbon are 180° opposite to each other. The other staggered conformation **C** is called a gauche conformation, in which the two large groups are adjacent and are 60° to each other. With the large groups being close to each other in gauche conformers, the molecule experiences steric

strain. Steric strain is the strain that is caused when atoms (or groups) are close enough together that their electron clouds repel each other. Steric strain only matters when the groups are close to each other (less or equal to  $60^\circ$ ), so steric strain does not apply in anti-conformations. The magnitude of steric strain also depends on the size of the group: the larger the size, the higher the steric strain. As a result, there is no steric strain between two small hydrogen atoms, even if they are close to each other.

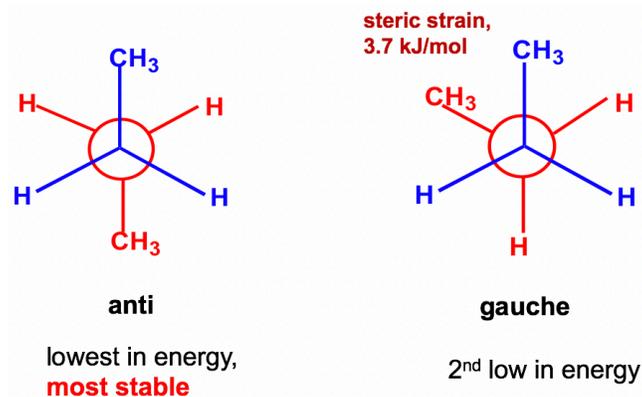


Figure 4.1j Anti and gauche conformations

Between the two eclipsed conformers **B** and **D**, **D** is less stable than **B** because the two  $\text{CH}_3$  groups are eclipsing (overlapping) each other in **D**, causing both torsional and steric strains.

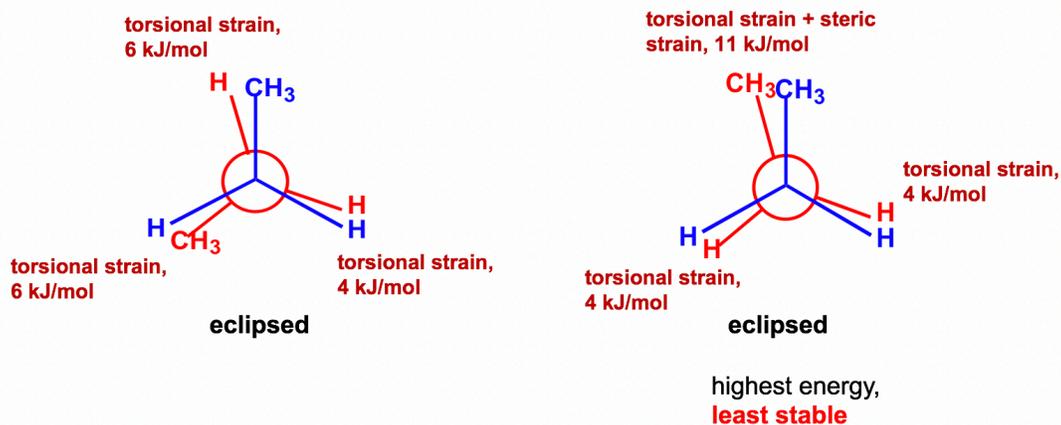


Figure 4.1k Comparison between the two eclipsed conformations

The energy difference of all the conformers obtained from the rotation about the  $\text{C}_2\text{-C}_3$  bond are shown in the potential energy diagram Fig. 4.1l. The curve is more complex than that of ethane since there are four different energy levels corresponding to four conformers with different stabilities. Even though the energy barriers for the rotations are larger than that of ethane, they are still not high enough to stop rotation at room temperature.

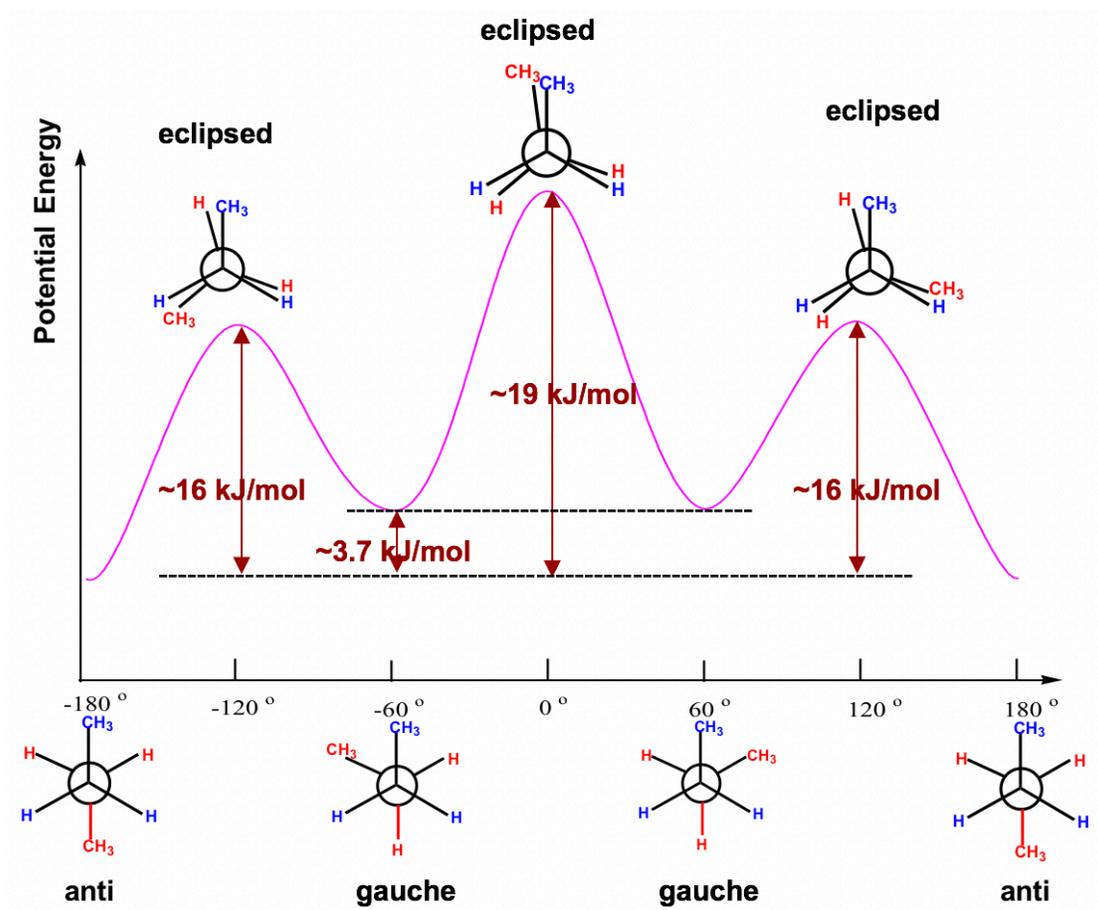


Figure 4.1l Potential Energy of Butane vs the Angle of Rotation about the C2-C3 bond

#### Exercises 4.2

Draw all conformers for 3-methylpentane by viewing along the C2-C3 bond, and order them from the most stable to least stable.

#### Answers to Chapter 4 Practice Questions

## 4.2 Cycloalkanes and Their Relative Stabilities

While the open chain alkanes have conformational isomers because of bond rotation, will this apply to cycloalkanes as well? In this section, we will take a look at the properties of cycloalkanes first, then investigate how the different conformers of cycloalkanes contribute to the different stabilities.

The short line structural formulas of cycloalkanes simply look like shapes such as a triangle, square, etc. The internal angles of the shapes can be calculated with geometry, as shown below.

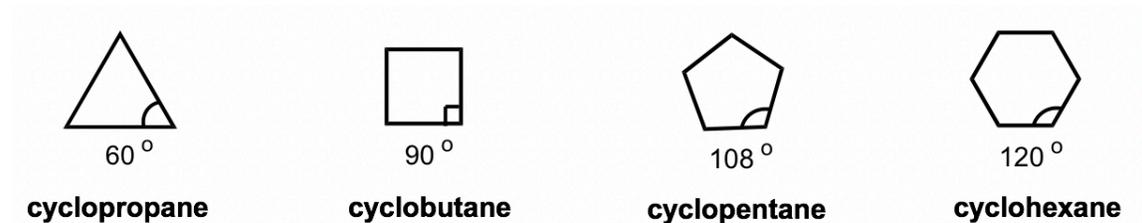


Figure 4.2a Short line structural formula of cycloalkanes

An interesting fact about the cycloalkanes is that they have different relative stabilities, and the stability depends on the size of the ring. It has been observed that cyclic compounds found in nature are usually in 5- or 6-membered rings and 3- or 4-membered rings are rare.

To explain this stability difference, German chemist Adolf von Baeyer proposed the “Bayer Strain Theory”. By assuming all the rings are in a *flat* (or planar) shape, Bayer Theory suggests that the difference between the ideal bond angle (which is 109.5° for  $sp^3$  carbon) and the angle in the planer cycloalkane causes the strain, which is called angle strain. According to the Bayer Theory, cyclopentane would be the most stable because its bond angle, 108°, is closest to the ideal angle of 109.5°. Cyclopropane would be the least stable one since it has the largest angle deviation of 49.5° (60° vs 109.5°). It was also predicted that cyclohexane would be less stable than cyclopentane because of the larger angle deviation (10.5° deviation for cyclohexane vs 1.5° for cyclopentane), and as the number of sides in the cycloalkanes increases beyond six, the stability decreases.

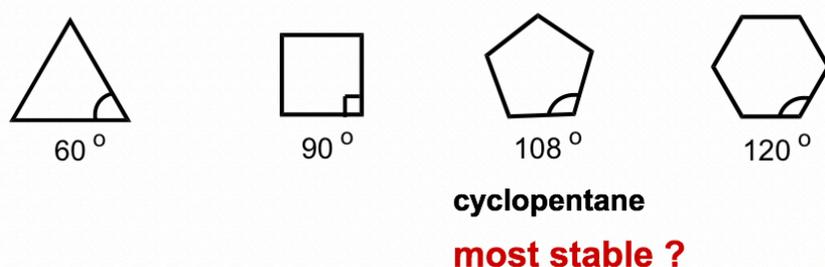


Figure 4.2b Which cyclo is stable?

However, experimental results show a different trend. It turns out that cyclohexane is the most stable ring that is strain-free and is as stable as a chain alkane. Furthermore, cyclic compounds do not become less and less stable as the number of rings increases.

To measure the relative stability of cycloalkanes, the heat of combustion ( $\Delta H_{\text{comb}}$ ) for each cycloalkane was measured. The heat of combustion is the amount of heat released when the compounds burn completely with oxygen. The

cycloalkanes will be in higher energy levels than corresponding chain alkanes because of strain energy. Therefore, when cycloalkane burns, more heat will be released, so the difference of  $\Delta H_{\text{comb}}$  between cycloalkane vs the “strainless” chain alkane is just the amount of strain energy, as shown below. The larger the difference, the higher the strain energy of the cycloalkane. The strain energy for different cycloalkanes measured by this method is listed in Table 4.1.

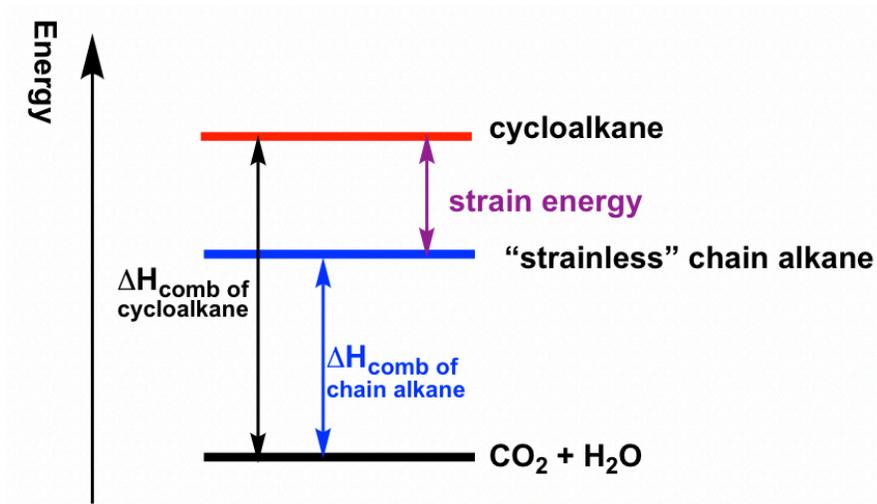
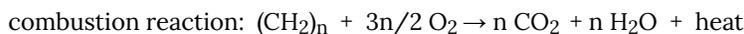


Figure 4.2c The relationship between the heat of combustion and strain energy

	cyclopropane	cyclobutane	cyclopentane	cyclohexane
Strain Energy (KJ/mol)	114	110	25	0

Table 4.1 Strain Energies of Cycloalkanes

The major drawback of the Baeyer Theory is that we must assume that all the rings are flat. The highest stability of cyclohexane from experimental results indicates that the rings may not be in a planar shape. We will have a closer look at the actual shape and conformation of 3-, 4-, 5- and 6-membered cycloalkanes.

## Cyclopropane

With three carbons for the ring, cyclopropane must be planar.

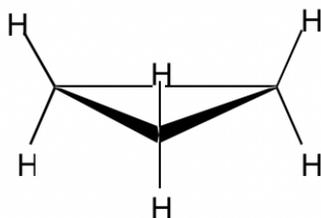
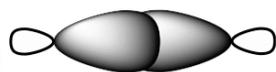


Figure 4.2d Cyclopropane

The bond angle in cyclopropane is  $60^\circ$ , derived significantly from the optimal angle of  $109.5^\circ$ , so it has very high angle strains. The  $sp^3-sp^3$  orbitals can only overlap partially because of the angle deviation, so the overlapping is not as effective as it should be, and as a result, the C-C bond in cyclopropane is relatively weak.



**effective overlap,  
normal strong bond**



**poor overlap,  
weak bond in cyclopropane**

Because of the poor overlapping of  $sp^3-sp^3$  orbitals, the bonds formed in cyclopropane resemble the shape of a banana and are sometimes called banana bonds.

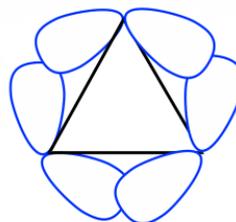
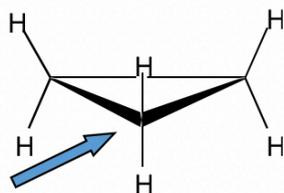
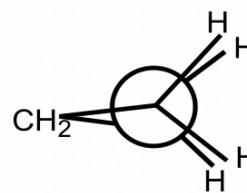


Figure 4.2e "Banana bonds" of cyclopropane

Other than the angle strains, all the adjacent C-H bonds are eclipsed in cyclopropane; therefore, the torsional strains are applied as well. Such strains can be "viewed" more clearly from the Newman projection of cyclopropane.



**viewing along the C-C bond with blue  
arrow to draw the Newman projection**



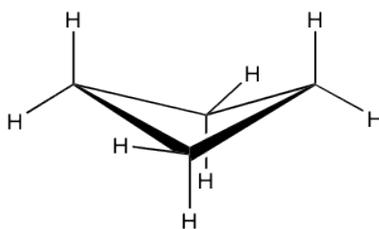
**Newman projection of cyclopropane**

The Newman projection of cyclopropane might seem unusual at first glance. For cyclopropane, there are three carbons, so the CH<sub>2</sub> group connects with both the front and rear carbons of the Newman projection.

Because of the high level of angle strains and torsional strains, 3-membered rings are unstable. They rarely exist in nature and undergo ring-opening reactions easily to release the strains.

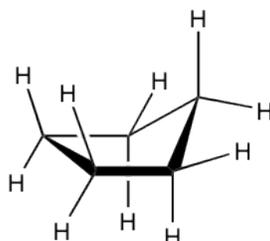
## Cyclobutane

Cyclobutane is not planar. The ring puckers (or folds) slightly due to the efforts of releasing some torsional strain. Meanwhile, cyclobutane still has a considerable number of angle strains as the internal angles become about  $88^\circ$  with the folded shape. Overall, cyclobutane is an unstable structure with a high level of strain.

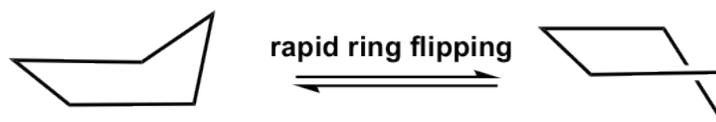


## Cyclopentane

Cyclopentane is also not planar, and the total level of strain is significantly lowered. It also puckers and adopts a bent conformation where one carbon atom sticks out of the plane of the others, which helps to release the torsional strain by allowing some hydrogen atoms to become almost staggered.



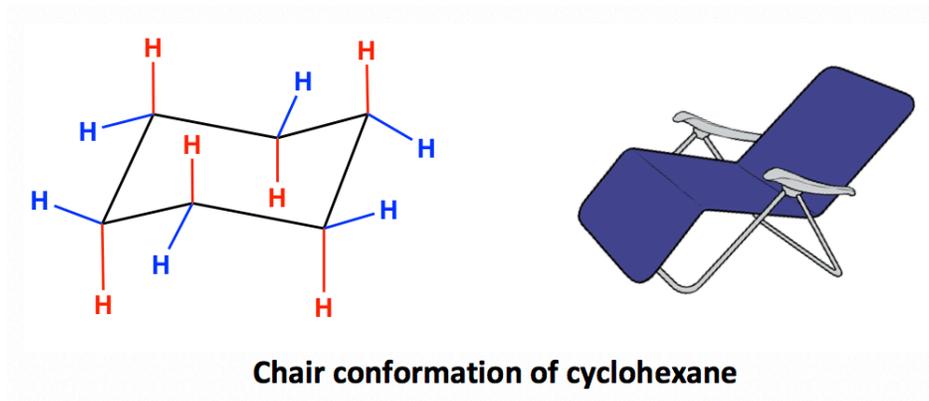
This bent shape of cyclopentane is also called the “envelope” conformation. The envelope conformation can undergo a process called “ring flipping” as a result of C–C bond rotation. Further discussion about ring flipping will be included in the section on cyclohexane.



## 4.3 Conformation Analysis of Cyclohexane

### Chair conformation of cyclohexane

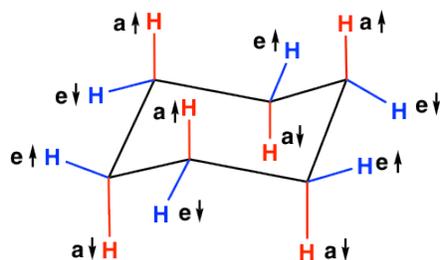
Cyclohexane is the most stable cycloalkane. It is strain-free, meaning neither angle strains nor torsional strains apply, and it shows the same stability as chain alkanes. This special stability is due to a unique conformation it adopts. The most stable conformation of cyclohexane is called the “chair” conformation, since it somewhat resembles a chair.



In the chair conformation of cyclohexane, all the carbons are at  $109.5^\circ$  bond angles, so no angle strain applies. The hydrogens on adjacent carbons are also arranged in a perfectly staggered conformation that makes the ring free of torsional strain as well. This will be illustrated more clearly later when we learn about the Newman projection of the chair conformation.

### Properties of the chair conformation

In the chair conformation of cyclohexane, the twelve C-H bonds can be divided into two categories based on the orientations, which are axial (“a”) and equatorial (“e”). In the structure below, the six red-coloured bonds are axial, and the six blue-coloured bonds are equatorial. Axial bonds are vertical and perpendicular to the average plane of the ring, while the equatorial bonds are more “flat” and extend from the perimeter of the ring. For both “a” and “e”, they can either point up  $\uparrow$  (above the ring), or point down  $\downarrow$  (below the ring). The trending of “a” and “e” bonds in the chair conformation can be summarized as:

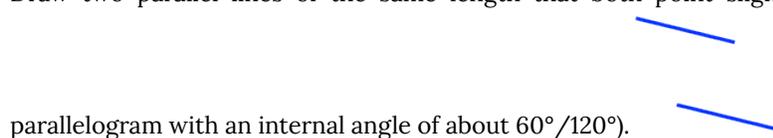


- Each carbon has one “a” bond and one “e” bond; if one bond points up ↑(above the ring), the other has to point down ↓(below the ring)
- For the same type of bonds, the orientation up ↑ and down ↓ alternates from one carbon to the adjacent carbon, meaning if a certain carbon has a ↑, then the adjacent carbon must have a ↓
- For the twelve C-H bonds: 3a↑ , 3 a↓, 3 e↑ , and 3 e↓.

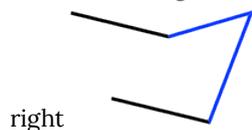
## How to draw the chair conformation

It is important to understand and recognize all the bonds in the chair conformation, and you are also expected to be able to draw the conformation correctly and quickly. The procedure is:

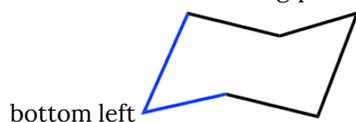
1. Draw two parallel lines of the same length that both point slightly down (if connected, they would form a



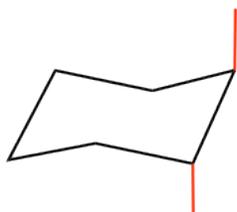
2. Connect the right ending points of the two lines with a “V” shape so that the vertex of the V points to the upper



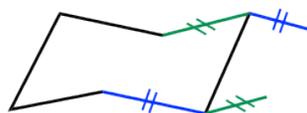
3. Connect the left starting points of the two lines with another “V” shape so that the vertex of the V points to the



4. Add up all of the “a” bonds on each carbon as the vertical lines, and follow the alternating trend on adjacent carbons



5. Add all of the “e” bonds by following the trend in which on a certain carbon, if an “a” bond points up, then an “e” bond must point down, and vice versa. Also notice that the “e” bond is parallel to the C-C bond which is one bond away, as shown below. The “green e” is parallel to the “green C-C bond”, and the “blue e” is parallel to the “blue C-C bond”. (It is more challenging to draw “e” bonds, and following the above trend makes it easier).



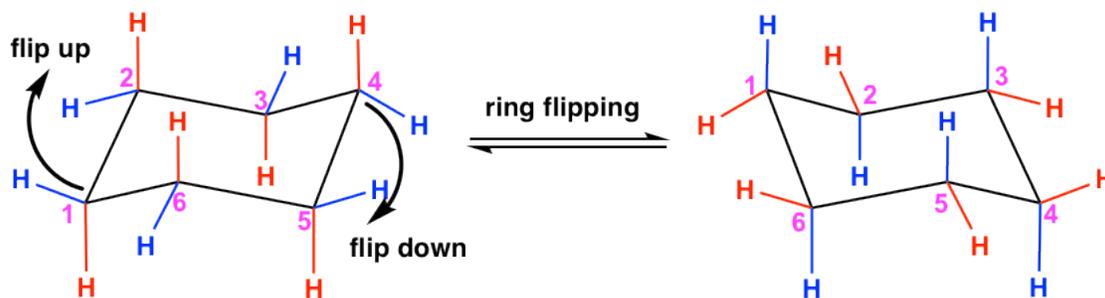
It is highly recommended that a molecular model set is used as a study tool in this section. Assemble a cyclohexane ring with the model and become familiar with all the bonds in the chair conformation.

Practice makes perfect! A lot of practice is required to become skilled in drawing and understanding the chair conformation.

## Ring flipping

When a cyclohexane ring undergoes a chair-chair conformation conversion, this is known as ring flipping. Ring flipping comes from C-C bond rotation, but since all of the bonds are limited within the ring, the rotation can only partially occur, which leads to the ring “flipping”. Cyclohexane rapidly interconverts between two stable chair conformations because of the ease of bond rotation. The energy barrier is about 45 kJ/mol, and the thermal energies of the molecules at room temperature are high enough to cause about 1 million interconversions to occur per second.

For cyclohexane, the ring after flipping still appears almost identical to the original ring, but some changes happen on the C-H bonds. Specifically, all the “a” bonds become “e” bonds, and all the “e” bonds become “a” bonds; however, their relative positions in terms of the ring, up or down, remain the same. The ring flipping is shown in the equation below. Compare the carbon with the same numbering in the two structures to see what happened to the bonds due to ring flipping.



Taking C #1 as an example, you will notice that the red a↓ converted to a red e↓, and the blue e↑ converted to a blue a↑ after ring flipping.

### Summary of ring flipping for chair conformation:

- This is NOT rotation, but ring flipping
- The two structures are conformation isomers (or conformers)

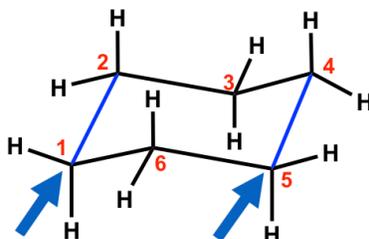
- All “a” bonds become “e” bonds and all “e” bonds become “a” bonds
- These two conformations are equivalent for the cyclohexane ring itself (without any substituents), with the same energy level.

A molecular model is very useful for understanding ring flipping.

## Newman projection of the chair conformation

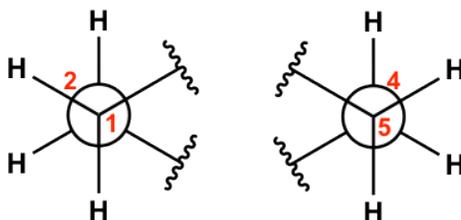
The chair conformation is strain-free, with all the C-H bonds in a staggered position. However, it is not easy to see the staggered conformation in the drawings we have so far, and a Newman projection helps for this purpose.

To draw Newman projections for the chair conformation of cyclohexane, we also need to pick up the C-C bonds to view along, just as we did for alkanes. Since there are a total of six C-C bonds, we will pick two of them, and these two need to be parallel to each other.

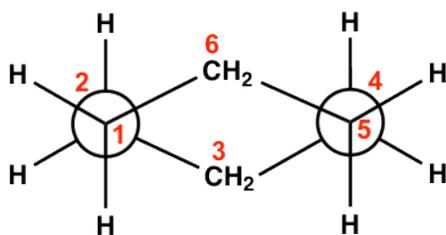


For the chair conformation example here, the two blue parallel C-C bonds, C1-C2 and C5-C4, are chosen for viewing. (There are 3 pairs of parallel bonds in the chair conformation, and any pair can be chosen with the resulting Newman projection looking the same).

For the C1-C2 bond, C1 is the ‘front’ carbon and C2 is the ‘rear’ carbon. For the C5-C4 bond, C5 is the ‘front’ carbon and C4 is the ‘rear’ carbon. These two bonds will be represented by two “Newman projections” we are familiar with (two circle things), and each represents two carbons, as shown below:



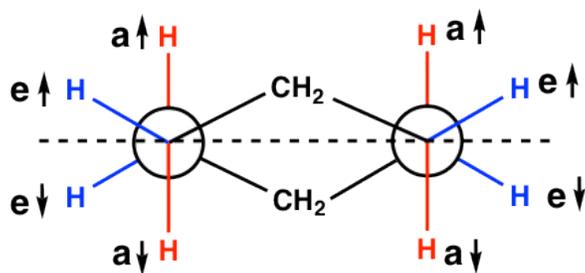
Keep in mind that there are a total of six carbons in the ring, and the drawing above only shows four of them with C3 and C6 being left out. Additionally, the two “separated” Newman projections above are actually connected to both C3 and C6, so the overall Newman projection of the chair conformation of cyclohexane looks like this:



The *staggered* conformation of hydrogens is clearly shown in the Newman projection here!

Notes for Newman projections of the chair conformation (refer to the drawing below):

- The “a” or “e” bonds on four carbons (C1, C2, C4 and C5) are shown explicitly, while the bonds on C3 and C6 are just shown as CH<sub>2</sub>.
- The vertical red C-H bonds are the “a” bonds, and the “flat” blue C-H bonds are the “e” bonds.
- The dashed line in the drawing below can be regarded as the average plane of the ring. Those above the line are the bonds that point up ↑, and those below the line are the bonds that point down ↓.
- 



## Other conformation of cyclohexane

The chair conformation is the most stable one with the lowest energy, but it is not the only conformation for cyclohexane. During the ring flipping from one chair conformation to another, the ring goes through several other conformations, and we will only briefly discuss the boat conformation here.

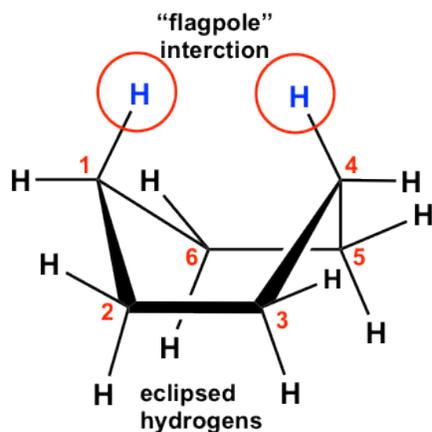


Figure 4.3a Boat conformation of cyclohexane

The boat conformation comes from partial C-C bond rotations (only flipping one carbon up to convert the chair to a boat) of the chair conformation, and all the carbons still have  $109.5^\circ$  bond angles, so there are no angle strains. However, the hydrogens on the base of the boat are all in eclipsed positions, so there are torsional strains. This can be illustrated by the Newman projection below. The Newman projection is drawn by viewing along C6-C5 and C2-C3 bonds of the above boat conformation.

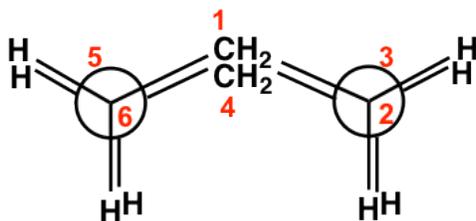


Figure 4.3b Newman projection of boat conformation

Other than that, the two hydrogen atoms on C1 and C4 are very close to each other and cause steric strain. This is also called the "flagpole" interaction of the boat conformation. The two types of strains make the boat conformation have considerably higher energy (about 30 kJ/mol) than the chair conformation.

## 4.4 Substituted Cyclohexanes

### Monosubstituted cyclohexane

For the cyclohexane ring itself, the two conformers from the ring flipping are equivalent in terms of energy since there are always six hydrogens in the axial position and six hydrogens in the equatorial position. For substituted cyclohexane, however, the two chair conformations are not equivalent anymore. Let's see the example of methylcyclohexane.

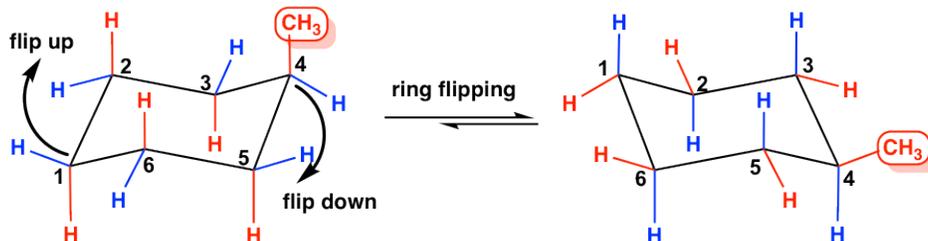


Figure 4.4a (Left one) I, less stable & (Right one) II, more stable

Methylcyclohexane has two chair conformations that are interconvertible through the ring flipping. In conformation **I**, the methyl group occupies an axial position, and in conformation **II** the methyl group occupies an equatorial position. Studies indicate that the conformer **II** with the equatorial-methyl is more stable, with an energy of about 7.6 kJ/mol lower than the other conformer.

This difference is due to the “1,3-diaxial interaction”. In axial-methyl conformation, the methyl  $\text{CH}_3$  group (regarded as #1 position) is very close to the axial hydrogens that are one carbon away (regarded as #3 position), and it causes repulsion between the two, which is called the 1,3-diaxial interaction. This type of repulsion is essentially the same as the gauche steric strain because the  $\text{CH}_3$  group and the  $\text{CH}$  are in a gauche position. For the equatorial-methyl conformer, no such strains are applied because the  $\text{CH}_3$  group and the  $\text{CH}$  are in an anti-position. This interaction can be illustrated more clearly by a Newman projection.

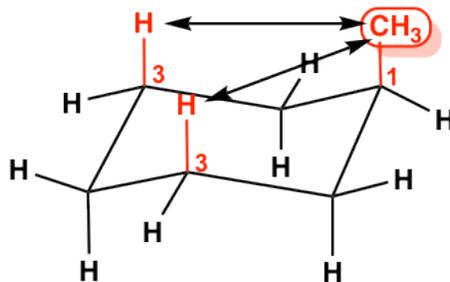
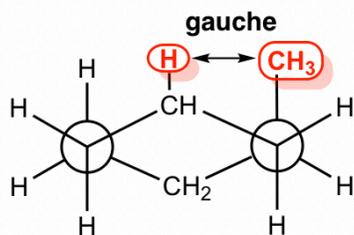
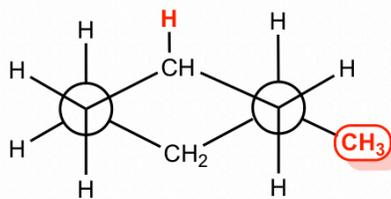


Figure 4.4b 1,3-diaxial interaction



CH<sub>3</sub> group in *axial* position:  
cause “1,3-diaxial interaction”,  
that is the gauche steric strain  
between CH<sub>3</sub> and CH

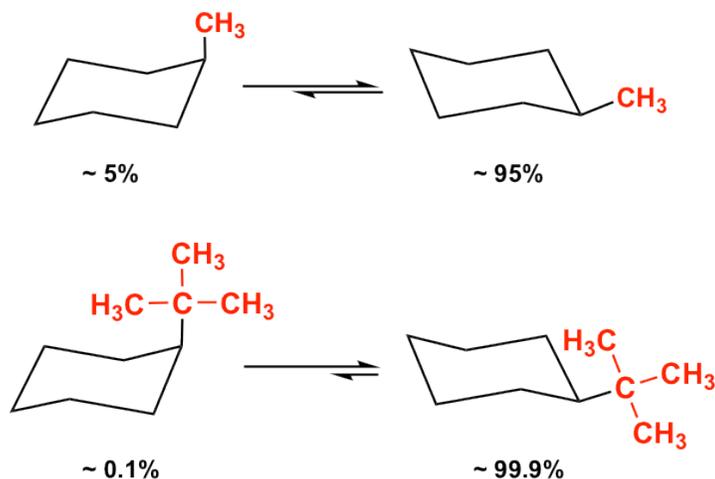


CH<sub>3</sub> group in *equatorial*  
position: CH<sub>3</sub> and CH are “anti”,  
no gauche steric strain applied,  
**more stable**

For mono-substituted cyclohexane, the equatorial-conformer is more stable than the axial-conformer because of the 1,3-diaxial interaction.

Since the 1,3-diaxial interaction is essentially the steric strain, the larger the size of the substituent, the greater the interaction is. For *t*-butylcyclohexane, the conformation with the *t*-butyl group in the equatorial position is about 21 kJ/mol more stable than the axial conformation.

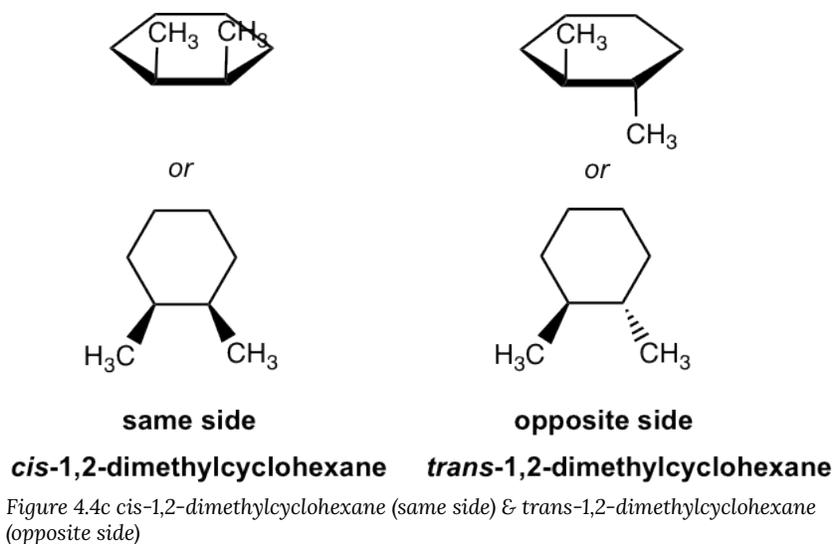
Because of the stability difference between the two chair conformers, the *equatorial* conformation is always the predominant one in the equilibrium mixture. The larger the size of the substituent, the larger the energy difference and the equilibrium constant **K**, so the equilibrium lies more toward the “equatorial” side. For methylcyclohexane, there is about 95% *equatorial* conformer in the mixture, and the percentage is about 99.9% for *t*-butylcyclohexane.



## Disubstituted cyclohexane

When there are two substituents on different carbons of a cycloalkane, there are two possible relative positions between

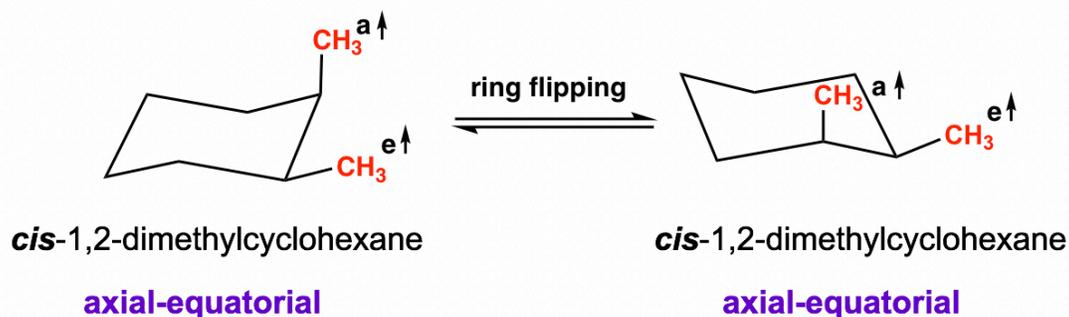
the two groups – they can be either on the same side or the opposite side of the ring – that are called geometric isomers, a type of stereoisomer (further discussed in Chapter 5). The isomer with two groups on the same side of the ring is the “cis” isomer, and the one with two groups on the opposite side is called the “trans” isomer. Because the C-C bond can not rotate freely due to the restriction of the ring, the two geometric isomers can not be interconverted.



So now when considering the conformational isomer, the stereoisomers should be taken into account as well. The general guideline for determining the relative stability of conformers for a certain isomer is:

- The steric effects of all substituents are cumulative, and the more substituents in equatorial positions, when possible, the more stable the conformation isomer will be.
- For different substituents, the conformer with the larger substituent in the equatorial position is more stable.

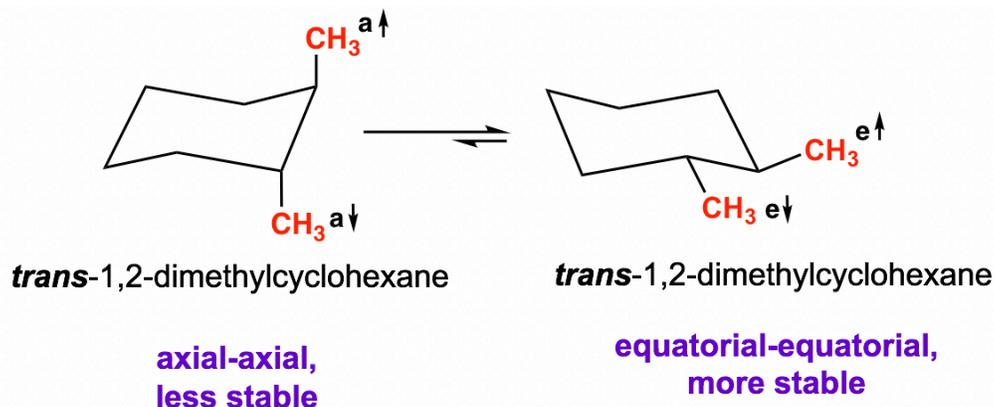
Let us start with cis-1,2-dimethylcyclohexane and compare between the two possible chair conformations:



For both conformations, there is one methyl group in the equatorial and the other methyl group in axial, so the two conformers are equivalent and have the same energy and stability level.

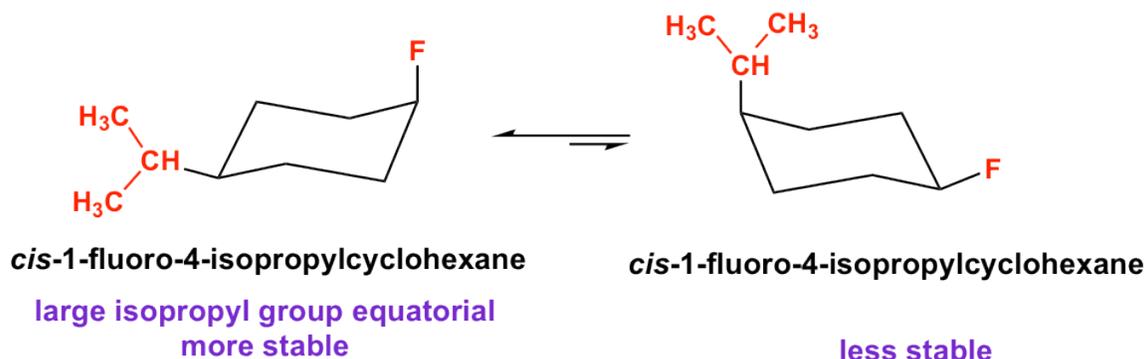
How can you tell whether an isomer in the chair conformation is cis or trans? A general way to recognize this is to check whether a group attached by the bond is above the ring ( $\uparrow$ , point up) or below the ring ( $\downarrow$ , point down). If both groups point to the same side, the compound is a *cis* isomer; otherwise, it is a *trans* isomer.

How about the *trans*-1,2-dimethylcyclohexane? There are also two possible chair conformations:



In one conformation both methyl groups are axial, and in the other conformation, both methyl groups are equatorial. These two conformers are not equivalent, and the di-equatorial one is the more stable conformation as we would expect.

*cis*-1-fluoro-4-isopropylcyclohexane is the structure with two different substituents. Both chair conformations have one *axial* substituent and one equatorial substituent. According to the guideline, the conformer with the larger substituent in equatorial is more stable because if the large group is axial, a stronger steric strain will be generated and it is less stable.



Determine which is the more stable isomer, *cis*-1-ethyl-2-methylcyclohexane or *trans*-1-ethyl-2-methylcyclohexane?

Tips: draw all the chair conformers of each isomer, and decide which is the most stable one.

Answers to Chapter 4 Practice Questions

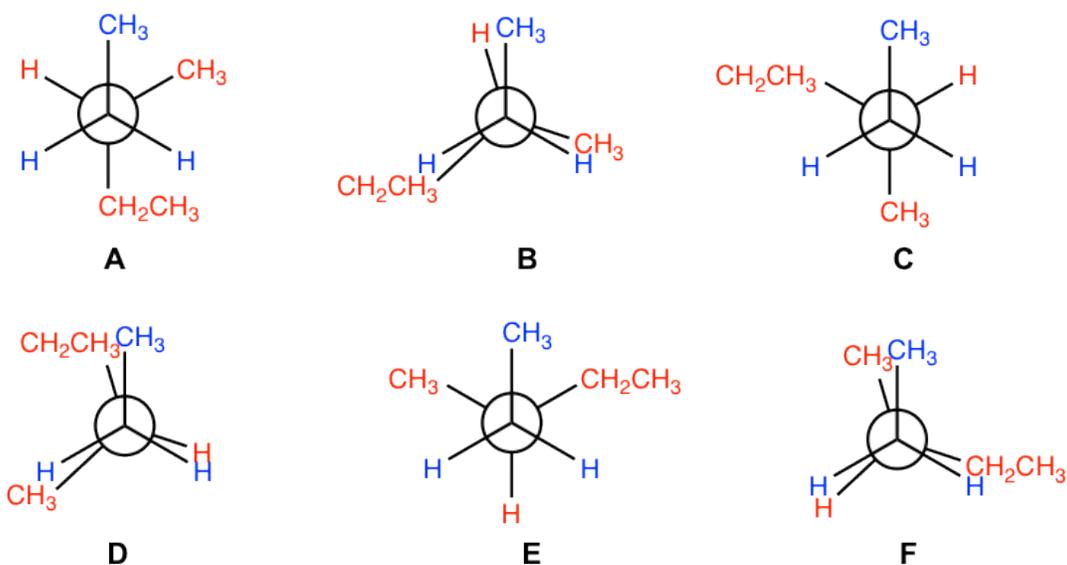
# Answers to Chapter 4 Practice Questions

## 4.1

Solutions included in the section.

## 4.2

Draw all conformers for 3-methylpentane by viewing along the C2-C3 bond, and order them from the most stable to the least stable.



**stability: A > C > E > B > F > D**

**most stable**

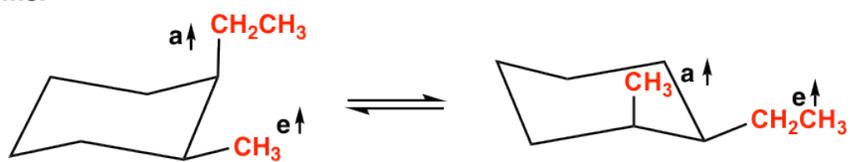
**least stable**

## 4.3

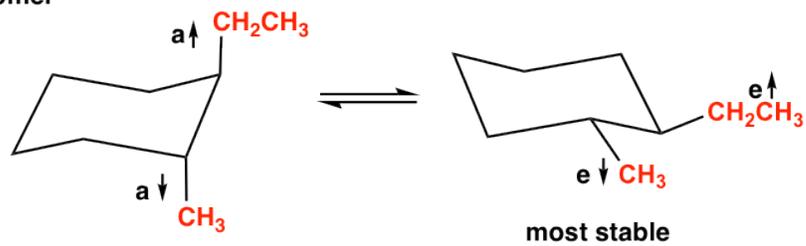
Determine which is the more stable isomer: *cis*-1-ethyl-2-methylcyclohexane or *trans*-1-ethyl-2-methylcyclohexane.

The *trans*-isomer has the most stable conformer with both substituents at equatorial positions; therefore, the *trans*-isomer is the more stable one.

*cis*-isomer



*trans*-isomer





# CHAPTER 5: STEREOCHEMISTRY

The term stereoisomer has been introduced in Chapter 4, on the topic of cis/trans isomer of disubstituted cycloalkane. Stereoisomers are interesting phenomenon that exist in nature, and also have great impacts on the properties of organic molecules. In this chapter, we will have in-depth discussions on stereoisomers and stereochemistry.

Learning Objectives for this chapter:

- Understand and apply the concepts of different types of isomers.
- Recognize, draw and name geometric isomers with the E/Z naming system.
- Explain chirality and identify chirality carbon and chiral molecules.
- Understand and describe the optical activity of chiral molecules and do calculations related to optical activity.
- Determine the absolute configuration (R/S) of chirality carbon with the C.I.P rule.
- Draw and recognize molecules with one or more chirality centers by different types of formulas, for example, perspective formula, Fisher projection, Newman projection, to show and determine the configuration of chirality carbons correctly.
- Understand and identify the *meso* compound and determine the chirality of molecules with more than one chiral centers.
- Identify the isomeric relationship, for example, constitutional isomers, geometric isomers, enantiomers and diastereomers, between different molecules.



## 5.1 Summary of Isomers

In discussing stereochemistry, we will learn more about different types of isomers. To clarify the concepts, it is a good idea to have a summary of the isomers in organic chemistry. There are two major types of isomers: constitutional isomers and stereoisomers. We had detailed discussions of constitutional isomers in Chapter 2 and will focus on stereoisomers in this chapter. Stereoisomers are molecules with the same bonding, but groups are in different spatial arrangements. At the beginning of this chapter, we will learn more about geometric isomers in alkenes and the E/Z naming system. Then, we will move on to a brand-new category of stereoisomers – isomers with a chirality center. The flowchart here (Fig. 5.1a) shows the correlations and differences between different types of isomers (pay attention to the definitions included) and provides a useful guideline.

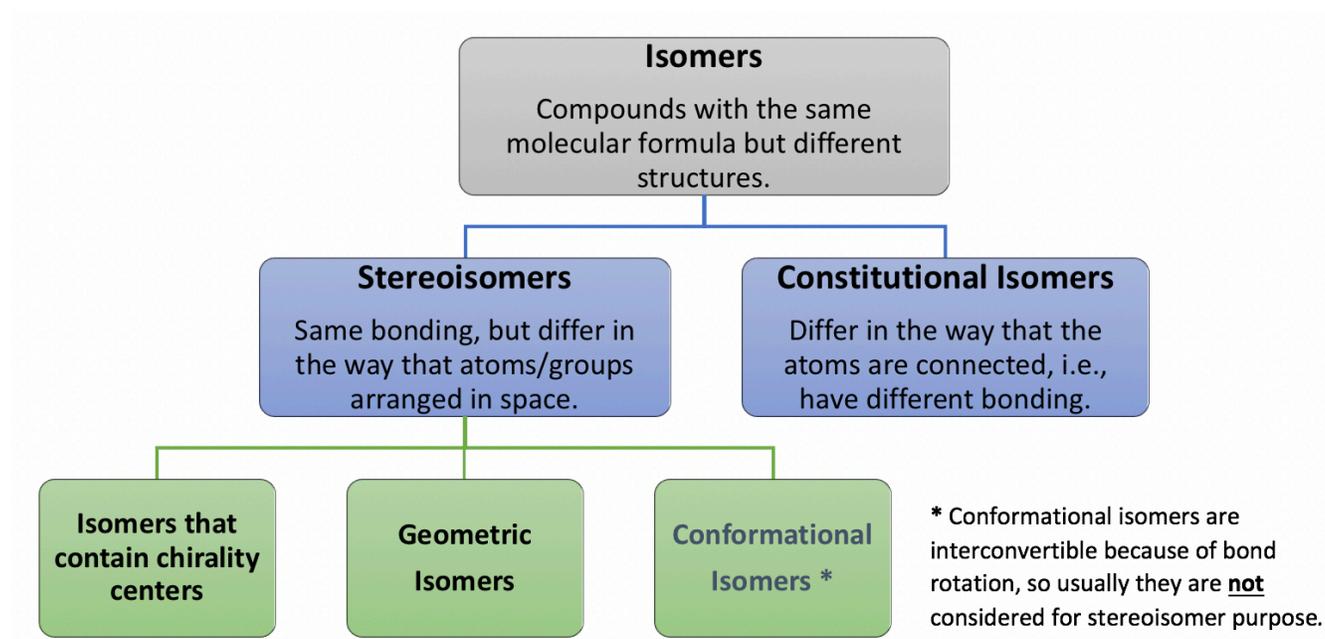


Fig. 5.1a Summarization of Isomers

## 5.2 Geometric Isomers and the E/Z Naming System

### Geometric Isomers of Alkenes

In the discussions about 1,2-dimethylcyclohexane in Chapter 4, we learned that there are two geometric isomers possible for that compound: *cis* and *trans*. The restricted C-C bond rotation of the cyclic structure results in the *cis* or *trans* isomer of 1,2-dimethylcyclohexane. Restricted rotation also can be caused by a double bond, so geometric isomers apply to some alkenes as well.

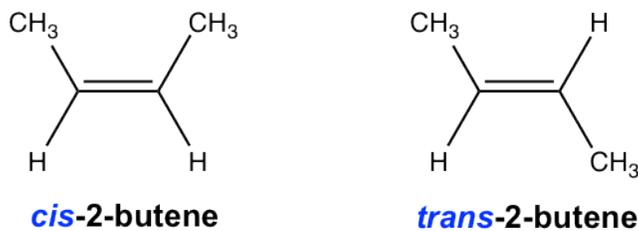


***cis*-1,2-dimethylcyclohexane**

***trans*-1,2-dimethylcyclohexane**

Figure 5.2a Geometric isomers of disubstituted cycloalkanes

For the example of 2-butene, the condensed structural formula CH<sub>3</sub>-CH=CH-CH<sub>3</sub> does not represent the trigonal planar shape of the sp<sup>2</sup> carbons with double bonds. To show the shape explicitly, we need to draw a Kekulé structure that shows all the bond angles. Then, it will be noted that there are two different shapes of 2-butene, with the CH<sub>3</sub> groups on either the same side or the opposite side of the double bond.



***cis*-2-butene**

***trans*-2-butene**

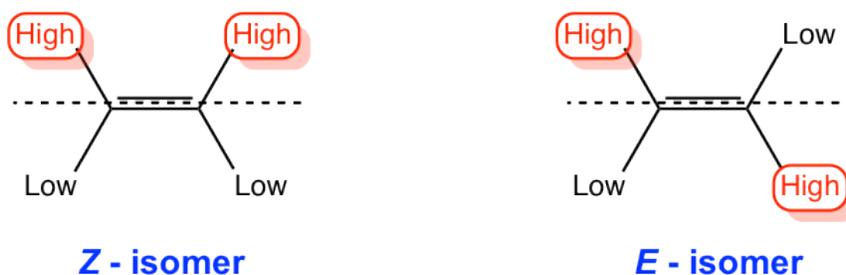
Figure 5.2b Geometric isomers of some alkenes

They are geometric isomers and can be labeled as *cis* or *trans* in a similar way as disubstituted cycloalkane. *Cis/trans* is the common designation for geometric isomers and might be ambiguous for some structures. Here, we will learn the IUPAC naming system for the geometric isomers of alkene, which is the *E/Z* naming system.

### *E/Z* Naming System

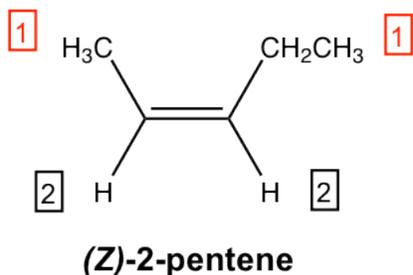
To do the *E/Z* designation, first, the groups connected on each sp<sup>2</sup> double bond carbon will be assigned priority based

on the atomic number (see the following guidelines for details). Then, the isomer with the same priority group on the same side of the double bond is assigned “Z”, and the isomer with the same priority group on the opposite side of the double bond is called “E”. Both E and Z come from German: “Zusammen” means “same side” and “Entgegen” means “opposite”.



## The guidelines for assigning group priority in E/Z naming system

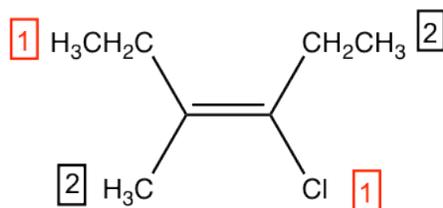
1. Priority is assigned based on the atomic number of the atoms bonded directly to the  $sp^2$  double bond carbon – the larger the atomic number, the higher the priority (isotopes with a higher mass number have higher priority). For example:  $S > O > N > C > H$ .



For the above structure of 2-pentene: on the left-side  $sp^2$  carbon, the methyl group  $CH_3$  is higher than the hydrogen atom because  $C > H$ ; on the right-side  $sp^2$  carbon, the ethyl group  $CH_2CH_3$  is also higher than hydrogen. With higher priority groups on both sides of the double bond, this is the Z isomer, and the complete name of the compound is (Z)-2-pentene.

The group with higher priority is labelled as #1, and the group with lower priority is labelled as #2 in this book.

2. If the two groups bonded directly on an  $sp^2$  carbon start with the same atom, it means there is a tie from step 1. Then, we move on to the atoms connected to the “tied” atom, and priority increases as the atomic number of the next attached atom increases.



**(E)-3-chloro-4-methyl-3-hexene**

For the above structure, it is obvious that Cl is higher than C (C of CH<sub>2</sub>CH<sub>3</sub> group) on the right-side sp<sup>2</sup> carbon.

On the left-side sp<sup>2</sup> carbon, we need to compare between the methyl CH<sub>3</sub> group and ethyl CH<sub>2</sub>CH<sub>3</sub> group. Both groups have carbon atoms attached directly to the sp<sup>2</sup> carbon, which is a tie. In the CH<sub>3</sub> group, the carbon atom is bonded to H, H, H, while in the CH<sub>2</sub>CH<sub>3</sub> group the carbon atom is bonded with H, H, C. So, ethyl CH<sub>2</sub>CH<sub>3</sub> is higher than methyl CH<sub>3</sub> (see the Note below). Since the higher priority groups are on the opposite side of the double bond, this is the E isomer, and the complete name of the compound is (E)-3-chloro-4-methyl-3-hexene.

**Note #1:**

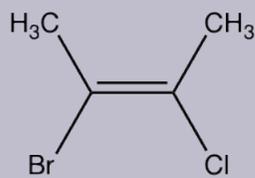
For this round of comparison between H, H, H and H, H, C, compare the single atom with the greatest number in one group *versus* the single atom with the greatest number in the other group. So, it is H in one group versus C in the other group, since C > H; therefore, CH<sub>2</sub>CH<sub>3</sub> is higher than CH<sub>3</sub>. Remember, do not add the atomic numbers. For example, if one group has C, C, C, and the other group has C, O, H, then the C, O, H side is higher because O is higher than C.

**Note #2:**

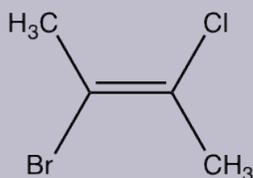
The above compound is a *cis*-isomer if using the *cis/trans* naming system (both ethyl groups are on the same side of the double bond), but it is an *E*-isomer for the *E/Z* system. So, *cis/trans* and *E/Z* are two different naming systems, but they do not always match.

3. Repeat step 2 if necessary until the priority is assigned.

Examples: What is the correct structural formula of (E)-2-bromo-3-chloro-2-butene?



**A**

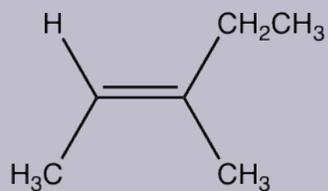


**B**

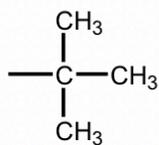
The answer is B.

Examples: Draw the structure of (E)-3-methyl-2-pentene

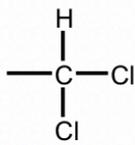
Answer:



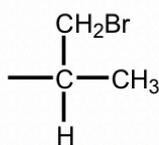
Examples: Order the following groups based on increasing priority.



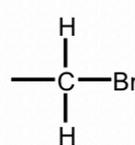
**A**



**B**



**C**



**D**

**Approach:**

1<sup>st</sup> round: C, C, C, C (tie);

2<sup>nd</sup> round:

A: C bonded to C, C, C; (3<sup>rd</sup>)

**B:** C bonded to H, Cl, Cl; (Cl is the 2<sup>nd</sup> high)

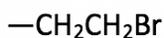
**C:** C bonded to H, C, C; (4<sup>th</sup>)

**D:** C bonded to H, H, Br (Br is the highest)

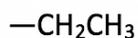
**Solution:** C < A < B < D

### Exercises 5.1

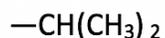
Order the following groups based on decreasing priority for E/Z naming purposes.



**A**



**B**



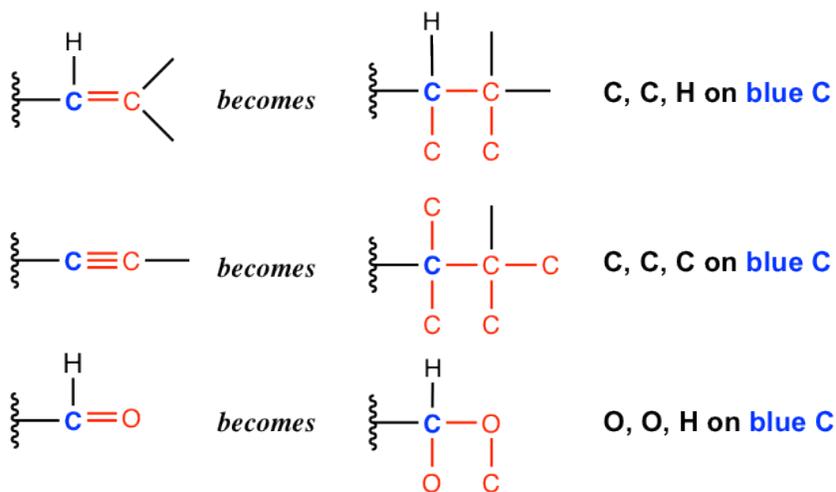
**C**



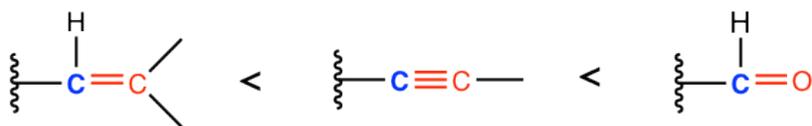
**D**

### Answers to Chapter 5 Practice Questions

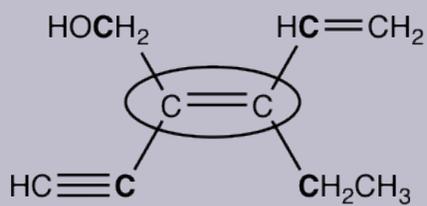
4. When a multiple bond is part of the group, the multiple bond is treated as if it was singly bonded to several of those atoms. Specifically:



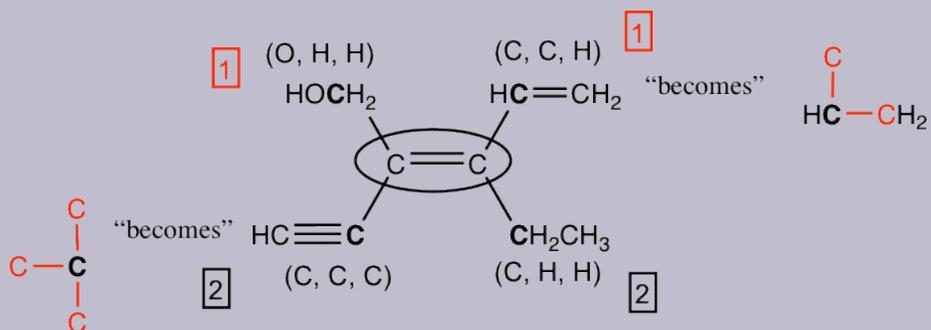
For these three groups that involve multiple bonds, they all start with the carbon atom (the carbon atom is highlighted in blue color), and we should compare the group of atoms that connected to the blue carbon by converting the multiple bonds to “multiple single bonds”, as shown above. So, if we compare the order of these three groups, it is:



Examples: Assign E/Z of the circled double bond.



Thinking:



The answer is Z-isomer.

## 5.3 Chirality and the R/S Naming System

Other than geometric isomers, there is another type of stereoisomer that is related to a special property called chirality. We will start with the basic concepts of chirality, and then expand the topic further from there.

### 5.3.1 Chiral and Chirality

To talk about chirality, let's first take a closer look at our left hand and our right hand. The left hand can be regarded as a mirror image of the right hand, and vice versa. Now, let's try to superimpose (overlay) the left hand on the right hand. Can you do that?

No! No matter how hard you try, the left hand can not be superimposed on the right hand. This is because of the special property of the hand that is called chirality. Both the left and right hand are chiral (*ky-ral*) and show chirality. Chiral is derived from the Greek word *cheir*, which means "hand", and chirality means "handedness".

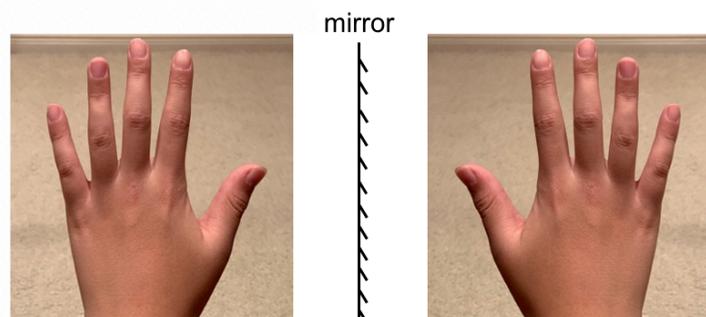


Figure 5.3a Left hand and right hand are non-superimposable mirror images

The definition of chirality is the property of any object (molecule) being non-superimposable on its mirror image. The left and right hand are mirror images of each other, and they are not superimposable, so both the left hand and right hand are chiral. You can also find many other objects in daily life that show chirality as well.



Figure 5.3b Book is chiral

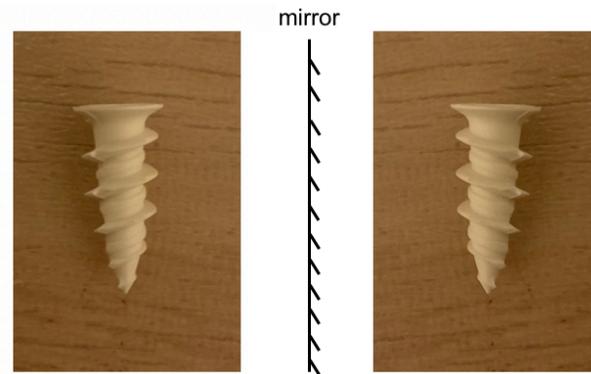


Figure 5.3c Screw is chiral

If an object is superimposable on its mirror image (in such a case, the object and its mirror image are exactly identical), then this object is not chiral, and it is referred to as achiral.

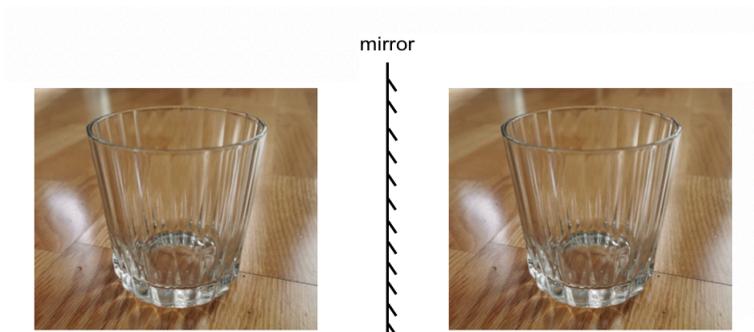


Figure 5.3d Cup is achiral

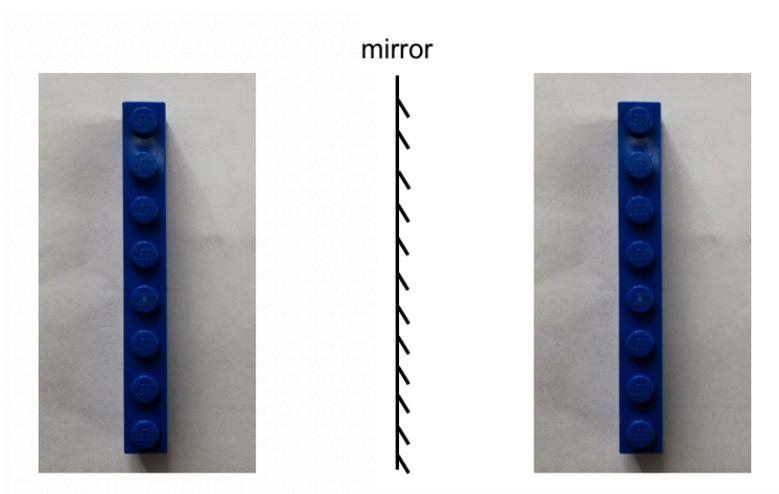
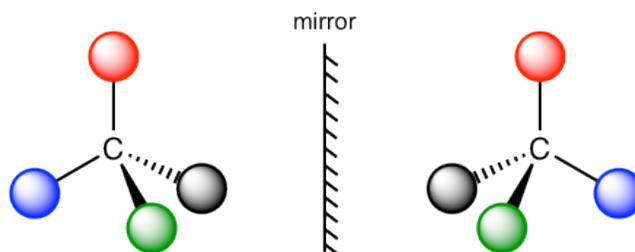


Figure 5.3e Lego piece is achiral

In organic chemistry, we are interested in organic molecules that are chiral. Let's see the following molecular models that represent a molecule and its mirror image.



In the models here, the four balls with different colors represent four different substituents, and the two structures are mirror images of each other. The effort of trying to superimpose one structure on the other does not work. Therefore, according to the definition of chiral/chirality, both molecules are non-superimposable on the mirror image, so they are both chiral and show chirality.

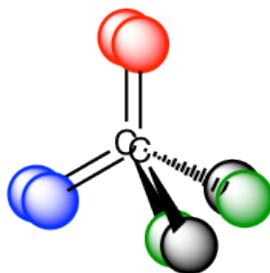


Figure 5.3f The two structures can not be superimposed to each other

The chirality of the molecule results from the structure of the central carbon. When the central carbon is  $sp^3$  carbon and bonded with four different groups (represented by four different colors in the model), the molecule is chiral. The central carbon is called the chirality center (or asymmetric center). A molecule with one chirality center must be chiral. The chirality center can also be called the asymmetric center. We will use the term chirality center in this book.

It is highly recommended that the molecular model set is used as a learning tool in this chapter. Assemble the model as shown above to understand the concept of chiral and chirality. The model is also very useful for the R/S assignment later in this section.

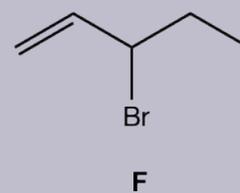
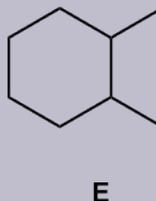
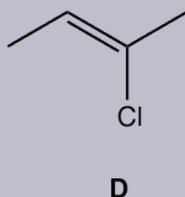
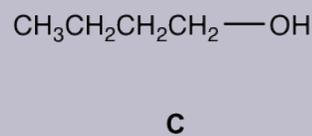
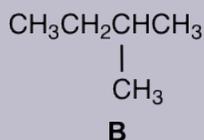
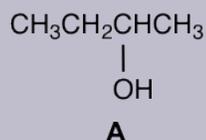
In summary, a chirality (asymmetric) center should meet two requirements:

- $sp^3$  carbon;

- bonded with four different groups.

### Examples

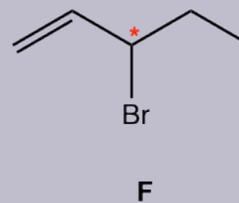
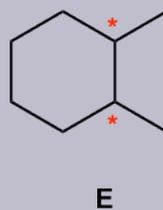
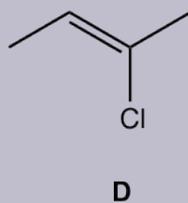
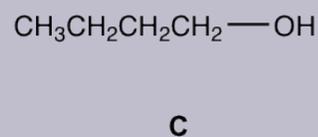
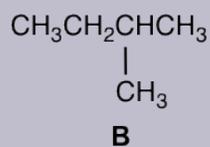
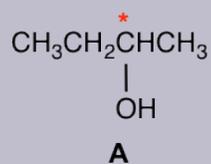
For following compounds, label each of the chirality center with a star.



Approach:

- The carbons in  $\text{CH}_3$  or  $\text{CH}_2$  are NEVER chirality centers. The chirality center must be the carbon bonded with a branch (or branches).
- $\text{sp}^2$  double bond carbon is NEVER a chirality center.
- Carbon in a ring can also be chirality center as long as it meet the two requirements.
- Not all the above compounds have a chirality center.

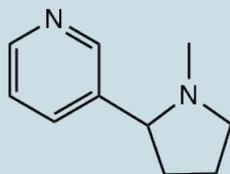
Solution:



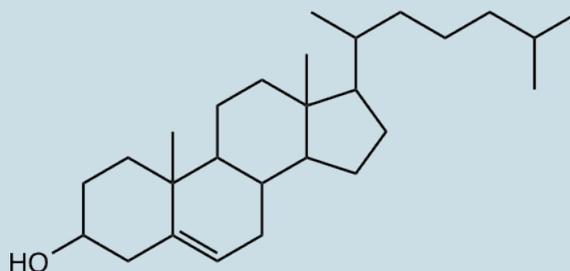
## Exercises 5.2

- 1. Draw the structure of the following compounds, determine which one has a chirality center, and label it with a star.
  - a) 1-bromobutane,
  - b) 1-pentanol,
  - c) 2-pentanol,
  - d) 3-pentanol,
  - e) 2-bromopropanoic acid
  - f) 2-methyl cyclohexanone

2. Label all the chirality centers in the following molecules.



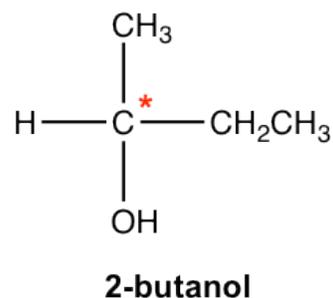
nicotine



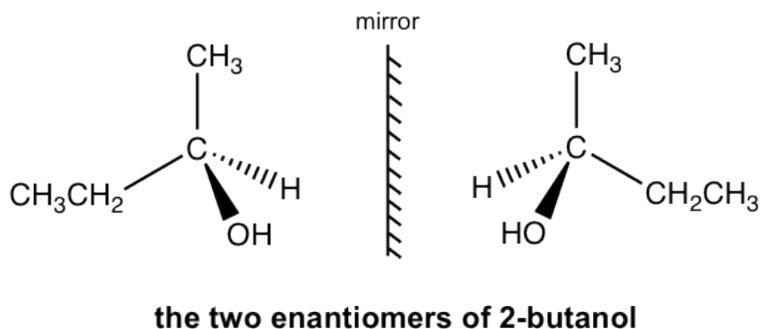
cholesterol

### 5.3.2 Stereoisomer with One Chirality Center — Enantiomers

For 2-butanol, we can recognize that C2 is the chirality center.



The perspective formula shows the 3D structure of 2-butanol in two different ways, and they are non-superimposable mirror images of each other.



The two mirror images are different molecules. They have the same bonding but differ in the way the atoms are arranged in space. So, the two molecules are stereoisomers. This specific type of stereoisomer is defined as an enantiomer. Molecules that are a pair of non-superimposable mirror images of each other are called enantiomers.

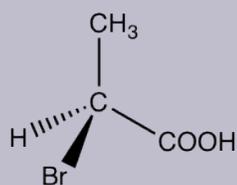
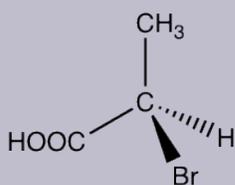
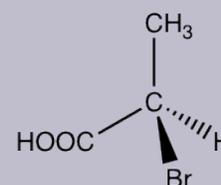
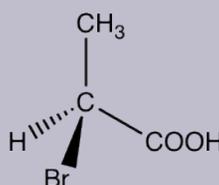
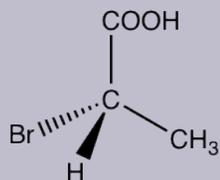
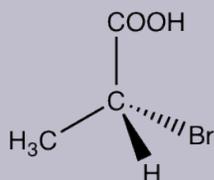
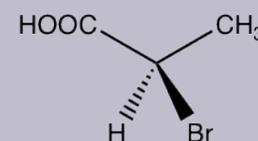
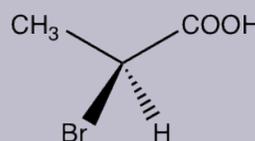
## Important Properties of Enantiomers:

- Enantiomers are a pair of non-superimposable mirror images.
- Enantiomers are a pair of molecules that are both chiral and show chirality (Enantiomers must be chiral).
- For any chiral molecule, it must have its enantiomer, that is, the mirror image of the molecule.
- Achiral molecules do not have enantiomers. The mirror image of an achiral molecule is an identical molecule to itself.

## Approach:

To draw the 3D structure of any enantiomer, we need to use a perspective formula with solid and dashed wedges to show the tetrahedral arrangements of groups around the  $sp^3$  carbon (refer to section 2.11). Out of the four bonds on tetrahedral carbon, two bonds lie within the paper plane are shown as ordinary lines, the solid wedge represents a bond that points out of the paper plane, and the dashed wedge represents a bond that points behind the paper plane. For the first enantiomer, you can draw the four groups with *any* arrangement, then draw the other enantiomer by drawing the *mirror image* of the first one. Please note, that although it seems there are different ways to show the enantiomers, there are only a total of two enantiomers, we will learn in the next section how to identify and designate each of them.

Several possible ways to show the structures are included in the answer here. However, your answer can be different from any of them, as long as a pair of mirror images is shown.

**solution I:****solution II:****solution III:****solution IV:**

## Exercises 5.3

Draw the pair of enantiomers of 2-chloro-1-propanol.

## Answers to Chapter 5 Practice Questions

## 5.3.3 R/S Naming System of the Chirality Center

The two enantiomers are different compounds, though they are very similar; therefore, we need a nomenclature system to distinguish between them, to give each one a different designation so that we know which one we are talking about. That is the *R/S* naming system defined in IUPAC. The *R/S* designation can be determined by following the Cahn-Ingold-Prelog rule, the rule devised by R. S Cahn, C. Ingold, and V. Prelog.

For a pair of enantiomers with one chirality center, one enantiomer has the *R* configuration and the other one has the *S* configuration.

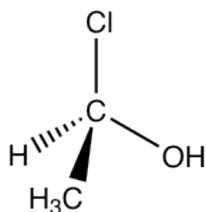
## Cahn-Ingold-Prelog Rule:

1. Assign priorities of the groups (or atoms) bonded to the chirality center by following the same priority rules as for the E/Z system (section 5.2). The highest priority group is labeled as #1, and the lowest priority group is labeled as #4 in this book.
2. Orient the molecule in a way that the lowest priority group (#4) is pointing away from you.
3. Look at the direction in which the priority decreases for the other three groups, that is 1→2→3.

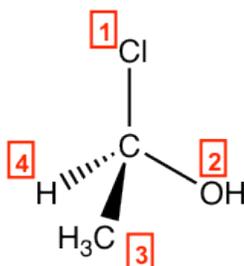
For the clockwise direction, the designation is R-, *rectus*, which means “right” in Latin.

For the counterclockwise direction, the designation is S-, *sinister*, which means “left” in Latin.

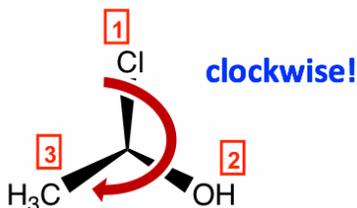
Let's take the following molecule as an example to practice the rule:



Step 1: The priorities are assigned.

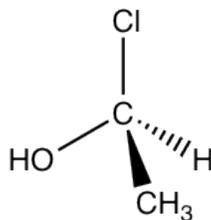


Step 2: Re-orient the molecule, so H (#4, lowest priority) is in the position away from us. Then, the other three groups will be arranged in this way:

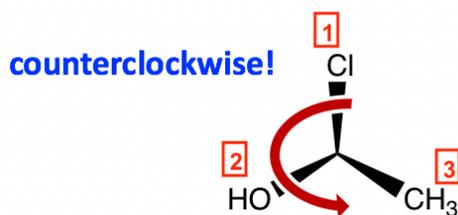


Step 3: Go along the direction from #1→#2→#3; it is in the clockwise direction, so this enantiomer is assigned an R configuration, and the complete name of the molecule is (R)-1-chloroethanol.

Now, let's assign the configuration of the other enantiomer:



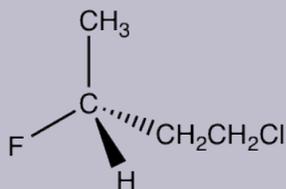
Following the same steps, put H away from us, and the arrangement of the other three groups is:



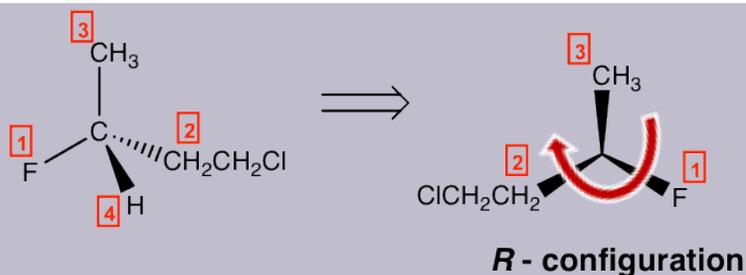
The counterclockwise direction gives the S configuration, and the complete name of the molecule is (S)-1-chloroethanol.

Examples: Assign R/S configuration of the chirality center.

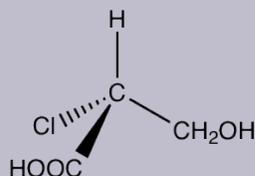
1.



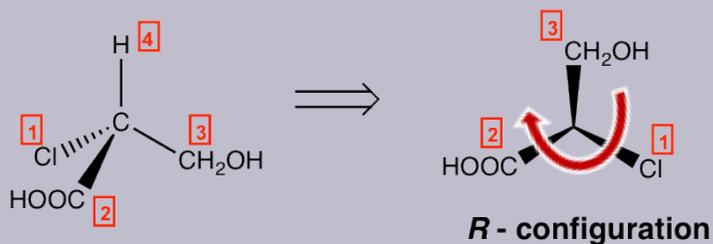
Solution:



2.



Solution:

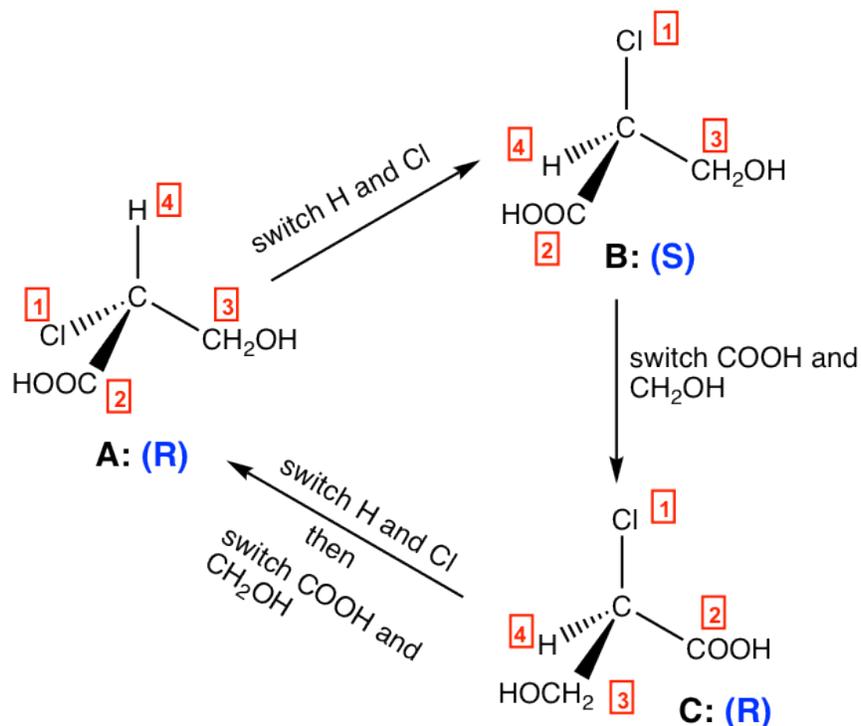


More practical hints about R/S assignment with the Cahn-Ingold-Prelog rule:

- Assigning priority is the first possible challenge for applying the C.I.P. rule. Review and practice the guidelines in section 5.2.
- The second challenge is to re-orient the molecule (to arrange the #4 group away from you). The molecule model will be very helpful for this purpose. Assemble a molecular model with four different colors connected to the carbon. Compare your model to the given structure and match the assigned priority to each color; for example, red is #1, blue is #2, etc. Then, rotate the model to arrange the lowest (#4) group away from you and see how the other groups are located to get the answer.

For the perspective formula of enantiomers, it is important to know the following properties:

- One (odd number of) switch (interchanging) for a pair of groups inverts the configuration of the chirality center.
- Two (even number of) switches get the original configuration back.
-



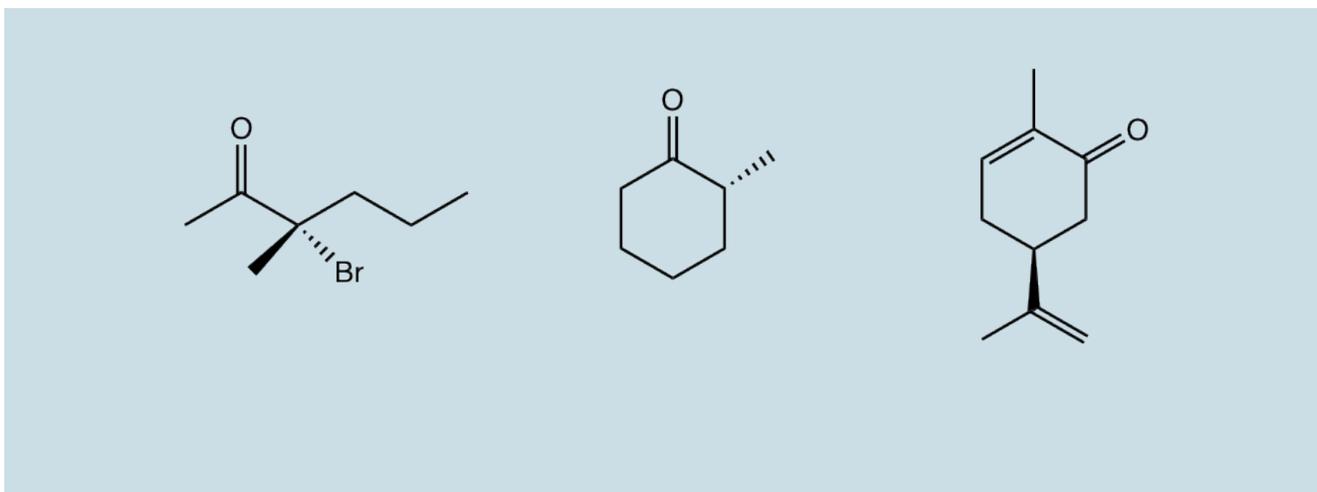
For the structures above:

- One switch of **A** leads to **B**, **A** is **R** and **B** is **S**, so **A** and **B** are **enantiomers**.
- One switch of **B** leads to **C**, **B** is **S** and **C** is **R**, so **B** and **C** are **enantiomers**.
- Two switches of **C** lead to **A**, and both **C** and **A** are **R**, so **C** and **A** are **identical**.

When you switch between a pair of groups, do it with caution. Do not switch unless it is really necessary because it is quite easy to get lost. Do R/S assignment is a safer (and easier for most cases) way to compare the relationship between two structures.

#### Exercises 5.4

Determine the R/S configuration of the chirality center in following compounds.

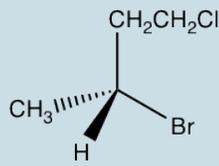
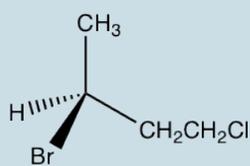


Answers to Chapter 5 Practice Questions

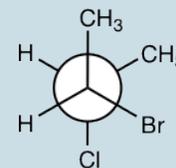
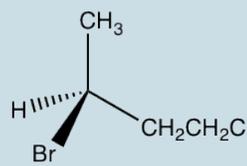
Exercises 5.5

Determine the relationship for each pair of molecules: enantiomers, identical, constitutional isomers, non-isomer:

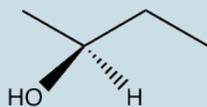
1)



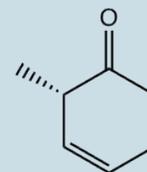
2)



3)



4)



## 5.4 Optical Activity

The two enantiomers are mirror images of each other. They are very alike and share many properties in common, such as the same b.p., m.p., density, color, and solubility. In fact, the pair of enantiomers have the same physical properties, except the way they interact with plane-polarized light.

In normal light, the electric field oscillates in all directions. When normal light passes through a polarizing filter, only light oscillating in one single plane can go through, and the resulting light that oscillates in one single direction is called plane-polarized light.

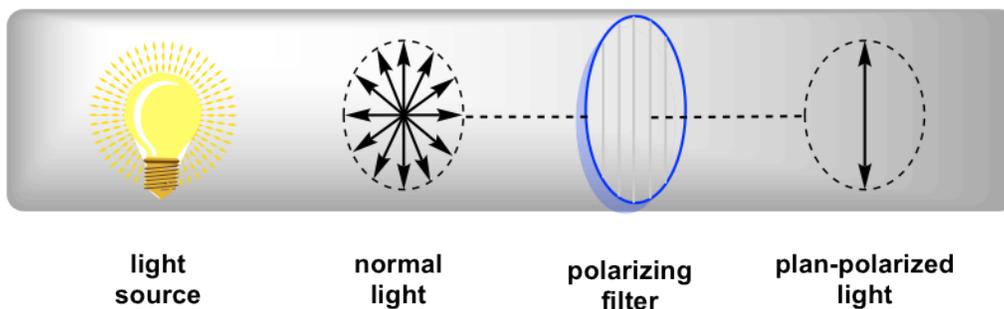


Figure 5.4a Generation of Plane-Polarized Light

When plane-polarized light interacts with chiral molecules, the plane of polarization will be rotated by the chiral substances. It was first discovered by Jean-Baptiste Biot in 1815 that some naturally occurring organic substances, like camphor, are able to rotate the plane of polarization of plane-polarized light. He also noted that some compounds rotated the plane clockwise and others counterclockwise. Further studies indicate that the rotation is caused by the chirality of the substances.

The property of a compound being able to rotate the plane of polarization of plane-polarized light is called optical activity, and a compound with such activity is labeled as optical active. A stereoisomer that is optical active is also called an optical isomer.

Chiral compound is optical active. Achiral compound is optical inactive.

The sample containing a chiral compound rotates the plane of polarization of plane-polarized light, and the direction and angles of the rotation depend on the nature and concentration of the chiral substances. The rotation angles can be measured using a polarimeter (later in this section).

For a pair of enantiomers with the same concentration, under the same conditions, they rotate the plane of polarization with the same angles but in the opposite direction. One is clockwise, and the other is counterclockwise.

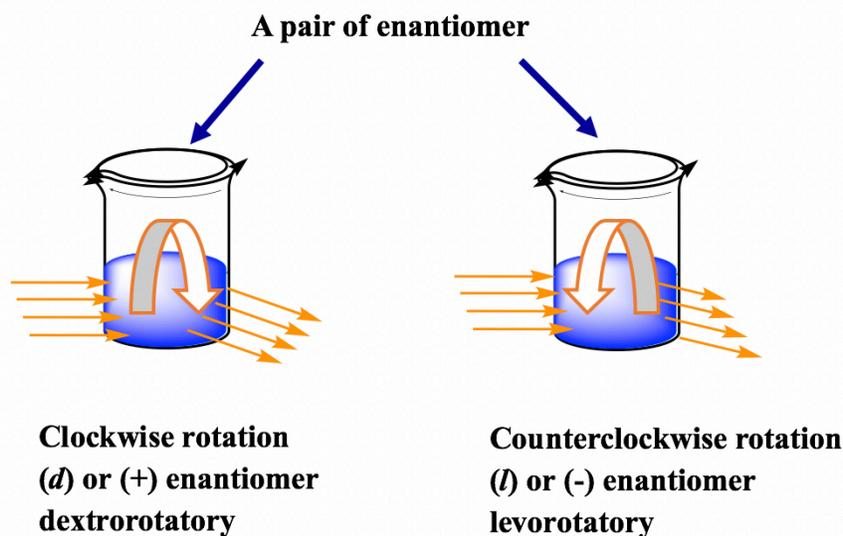
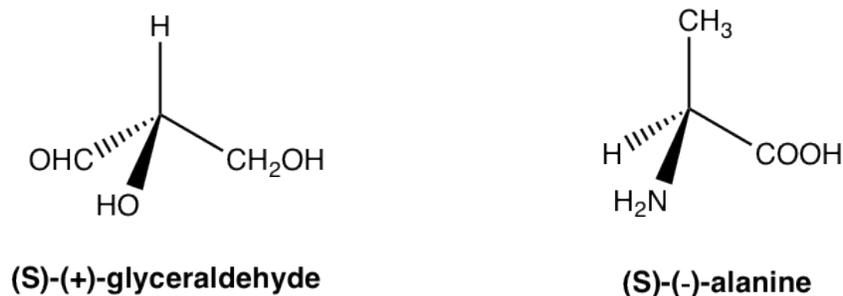


Figure 5.4b Clockwise rotation/enantiomer dextrorotatory vs. counterclockwise rotation/enantiomer levorotary

The enantiomer rotates the plane of polarization clockwise and is said to be dextrorotatory (*Latin*, which means to the right), and it is labeled with the prefix (*d*) or (+). The enantiomer rotates the plane of polarization counterclockwise and is said to be levorotatory (*Latin*, which means to the left), and it is labeled with the prefix (*l*) or (-). The *d/l* (or +/-) indicates the direction in which an optical active compound rotates the plane of polarization of plane-polarized light, which has to be determined by an experiment to measure the optical rotation. The *d/l* (or +/-) symbol has nothing to do with *R/S*. *R/S* indicates the arrangement of the groups around the chirality center, which can be determined by knowing the exact spatial arrangement of the groups. That means a compound with an **R** configuration can be either *d* or *l*, and a compound with an **S** configuration can also be either *d* or *l*. For the examples below, both compounds are *S*-isomers, but one is *d* (+) and the other is *l* (-).



The only thing we can be sure of is that for a pair of enantiomers, if one enantiomer has been determined as *d*, then the other enantiomer must be *l*, and vice versa.

## Measurement of Optical Rotation

The polarimeter is an instrument that measures the direction and angles of rotation of plane-polarized light. The plane-

polarized light passes through the sample tube containing the solution of a sample, and the angle of rotations will be received and recorded by the analyzer, as summarized in Fig. 5.4c.

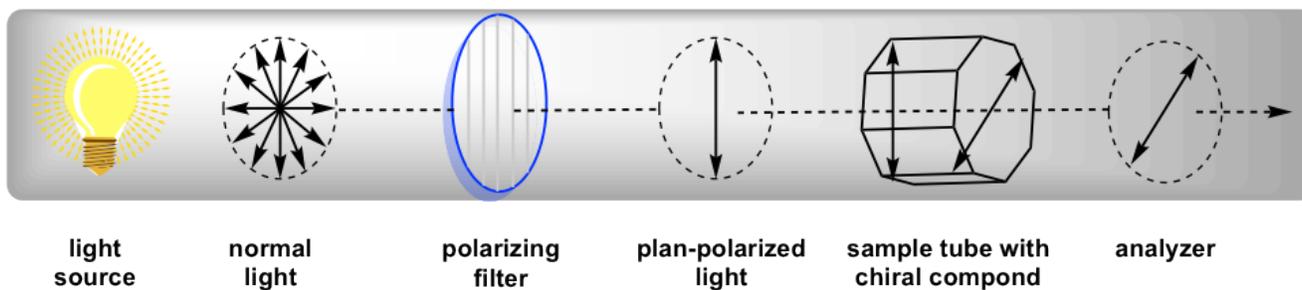


Figure 5.4c Measurement of Optical Rotation with Polarimeter

Since the measurement results vary with the wavelength of the light being used, the specific light from a sodium atomic spectrum with the wavelength of 589 nm, which is called the sodium D-line, is used for most polarimeters. The rotation degree measured by the polarimeter is called the observed rotation ( $\alpha$ ), and the observed rotation depends on the length of the sample tube, the concentration of the sample and the temperature.

To compare the optical rotation between different compounds under consistent conditions, the specific rotation  $[\alpha]_D^{20^\circ C}$  ( $[\alpha]_D^T$ ) is used. Specific rotation is the rotation caused by a solution with a concentration of 1.0 g/mL in a sample tube of 1.0 dm length. The temperature is usually at 20°C. Based on this definition, the specific rotation can be calculated from the observed rotation by applying the formula:

$$[\alpha]_D^T = \frac{\alpha}{l \times c}$$

T: usually at 20 °C

$\alpha$ : observed rotation in degree;

$l$ : length of the sample cell (**dm**);

$c$ : concentration (**g/mL**)

Figure 5.4d Specific rotation equation

Please note: In this formula, the unit of concentration (g/mL) and length of the sample tube (dm) are not the units we are familiar with. Also, the unit of the specific rotation is in degree (°), don't need to worry about the unit cancellation in this formula.

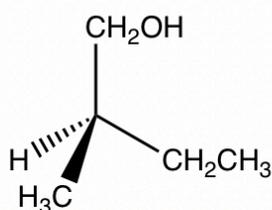
Examples: Calculate the specific rotation.

The observed rotation of 10.0g of (**R**)-2-methyl-1-butnaol in 50mL of solution in a 20-cm polarimeter tube is +2.3° at 20 °C, what is the specific rotation of the compound?

Solution:

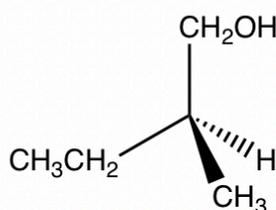
$$[\alpha]_D^{20^\circ C} = \frac{\alpha}{l \times c} = \frac{+2.3}{2dm \times \frac{10.0g}{50 mL}} = 5.75$$

Specific rotation is the characteristic property of an optical active compound. The specific rotation value of the authentic compound in literature can be used to confirm the identity of an unknown compound. For the example here, if it has been measured that the specific rotation of (**R**)-2-methyl-1-butnaol is +5.75°, then we can tell that the other enantiomer (**S**)-2-methyl-1-butnaol must have the specific rotation of -5.75°, without further measurement necessary.



**(R)-2-methyl-1-butnaol**

$$[\alpha]_D^{20^\circ C} = +5.75^\circ$$



**(S)-2-methyl-1-butnaol**

$$[\alpha]_D^{20^\circ C} = -5.75^\circ$$

## Optical Activity of Different Samples

When a sample under measurement only contains one enantiomer, this sample is called enantiomerically pure, which means only one enantiomer is present in the sample.

The sample may also consist of a mixture of a pair of enantiomers. For such a mixture sample, the observed rotation value of the mixture, together with the information on the specific rotation of one of the enantiomers allows us to calculate the percentage (%) of each enantiomer in the mixture. To do such a calculation, the concept of enantiomer excess (ee) will be needed. The enantiomeric excess (**ee**) tells how much of an excess of one enantiomer is in the mixture, and it can be calculated as:

$$ee = \frac{\text{observed rotation}}{\text{specific rotation of pure enantiomer}}$$

We will use a series of hypothetical examples in the next table for a detailed explanation.

If the specific rotation of a (+)-enantiomer is +100°, then the observed rotation of the following samples are (assume the sample tube has a length of 1 dm, and the concentration for each sample is 1.0 g/mL):

Sample Number	Sample	Observed rotation (°)
1	pure (+) enantiomer	+100
2	Pure (-)-enantiomer	-100
3	Racemic mixture of 50% (+)-enantiomer and 50% (-)-enantiomer	0
4	A mixture of 75% (+)-enantiomer and 25% (-)-enantiomer	+50
4	A Mixture of 20% (+)-enantiomer and 80% (-)-enantiomer	-60

Sample #1 and #2 are straightforward.

Sample #3 is for a mixture with an equal amount of two enantiomers, and such a mixture is called a racemic mixture or racemate. Racemic mixtures do not rotate the plane of polarization of plane-polarized light, which means racemic mixtures are optical inactive and have an observed rotation of zero! This is because for every molecule in the mixture that rotates the plane of polarization in one direction, there is an enantiomer molecule that rotates the plane of polarization in the *opposite* direction with the same angle, and the rotation gets canceled out. As a net result, no rotation is observed for the overall racemic mixture. The symbol ( $\pm$ ) sometimes is used to indicate that a mixture is racemic.

In Sample #4, the (+)-enantiomer is in excess. Since there are 75% (+)-enantiomer and 25%(-)-enantiomer, the enantiomeric excess (ee) value of (+)-enantiomer is 75% - 25% = 50%; this can also be calculated by the formula: ee =

$$\frac{\text{observed rotation}}{\text{specific rotation of pure enantiomer}} = \frac{50}{100} = 0.5 = 50\%$$

In this sample of the mixture, the rotation of the (-)-enantiomer is *canceled* by the rotation caused by part of the (+)-enantiomer, so the overall net observed rotation depends on how much “net amount” of (+)-enantiomer is present. This can be shown in the diagram below.

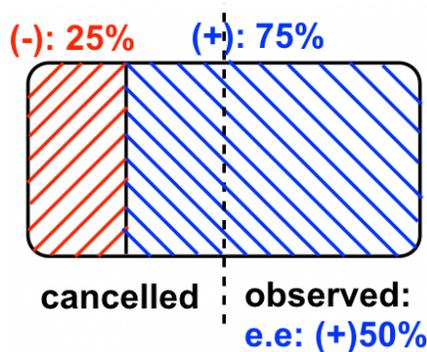


Figure 5.4e Cancelled & observed

In Sample #5, the (-)-enantiomer is in excess, and because there is 80% (-)-enantiomer and 20% (+)-enantiomer, the enantiomeric excess (ee) value of the (-)-enantiomer is  $80\% - 20\% = 60\%$ ; this can also be calculated by the formula: ee

$$= \frac{\text{observed rotation}}{\text{specific rotation of pure enantiomer}} = \frac{60}{100} = 0.6 = 60\%$$

Please note: To calculate the e.e value, it is not necessary to include the sign of the rotation angle, as long as keep in mind that the sign (+ or -) of the observed rotation indicates which enantiomer is in excess.

#### Exercises 5.6

Draw the diagram for Sample #5 by referring to the diagram for Sample #4.

#### Answers to Practice Questions Chapter 5

Examples: An advanced level of calculation.

The (+)-enantiomer of a compound has a specific rotation ( $[\alpha]_{\text{D}}^{20}$ ) of  $+100^\circ$ . For a sample (1 g/ml in 1dm cell) that is a mixture of (+) and (-) enantiomers, the observed rotation  $\alpha$  is  $-45^\circ$ , what is the percentage of (+) enantiomer present in this sample?

Solution:

The observed rotation is in “-”, so the (-)-enantiomer is in excess.

ee of (-)-enantiomer is: 
$$e.e = \frac{\text{observed rotation}}{\text{specific rotation of pure enantiomer}} = \frac{45}{100} = 0.45 = 45\%$$

From here, we will see two ways of solving such type of question:

Method I: solving algebra

% of (-)-enantiomer is set as “x”; % of (+)-enantiomer is set as “y”

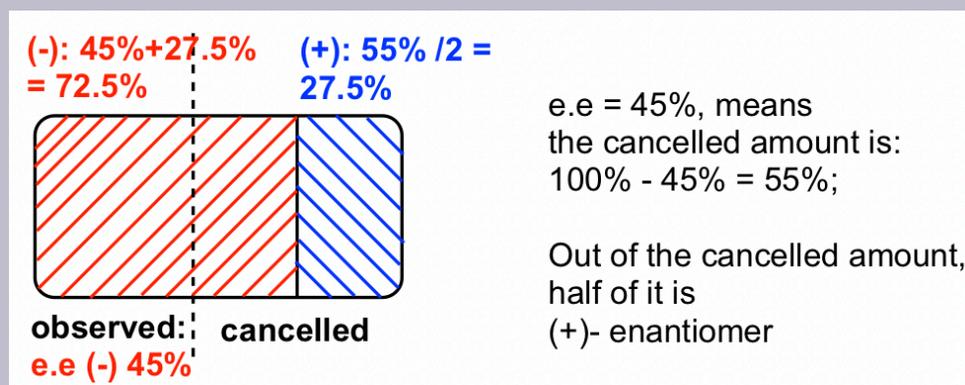
$$x + y = 100\%$$

$$x - y = 45\%$$

Solve  $x = 72.5\%$ ;  $y = 27.5\%$ ;

So there is 72.5% (-)-enantiomer and 27.5% of (+)-enantiomer in the sample.

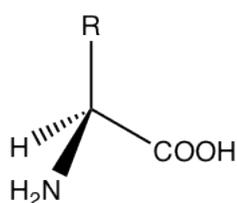
Method II: using the diagram, the answer is in blue color, there is 27.5% of (+)-enantiomer.



## Chirality and Biological Properties

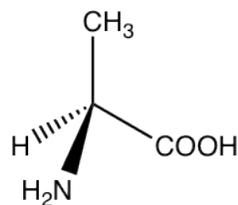
Other than the optical activity difference, the different enantiomers of a chiral molecule usually show different properties when interacting with other chiral substances. This can be understood by using the analogue example of fitting a hand into its respective glove: the right hand only fits into the right glove, and it feels weird and uncomfortable if you wear a left glove on the right hand. This is because both the right hand and right glove are chiral. A chiral object only fits into a specific chiral environment.

In the human body, biological functions are modulated by enzymes and receptors. Enzymes and receptors are essentially proteins, and proteins are made up of amino acids. Amino acids are examples of naturally occurring chiral substances. With the general formula given below, the carbon with an amino (NH<sub>2</sub>) group is the chirality (asymmetric) center for most amino acids, and only one enantiomer (usually an S-enantiomer) exists in nature. A few examples of amino acids are given below with the general formula.

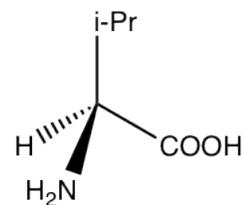


**General formula of  $\alpha$ -amino acid**

Figure 5.4f Chirality center of amino acids



**(S)-alanine**



**(S)-valine**

Because amino acids are chiral, proteins are chiral, so enzymes and receptors are chiral as well. The enzymes or receptors therefore form the chiral environment in the human body that distinguishes between R or S enantiomers. Such selectivity can be illustrated by the simple diagram below.

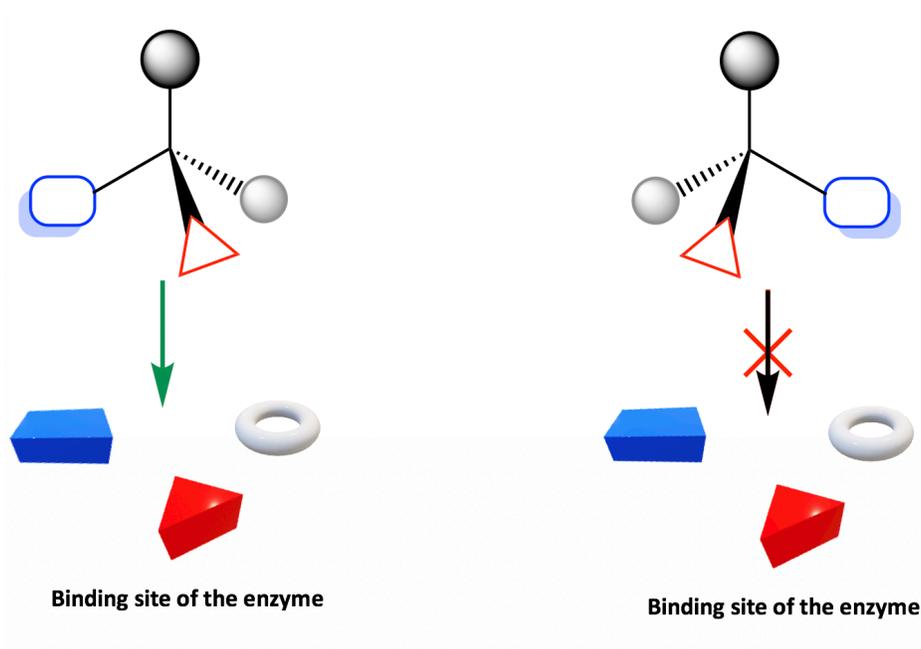
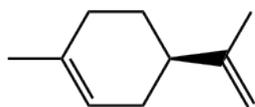


Figure 5.4g Binding site of the enzyme

The binding site of an enzyme or receptor is chiral, so it only binds with the enantiomer whose groups are in proper positions to fit into the binding site. As shown in the diagram, only one enantiomer binds with the site, but not the other enantiomer.

A couple of common examples to showcase such binding selectivity of different enantiomers may include limonene and carvone.

Limonene has two enantiomers, and they smell completely different to human beings because they interact with different receptors located in the nerve cells in the nose. The (R)-(+)-limonene is responsible for the smell of oranges, and the (S)-(-)-limonene gives the smell of lemon.



**(R)-(+)-limonene**

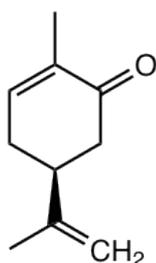
**the enantiomer of  
limonene found in  
oranges**



**(S)-(-)-limonene**

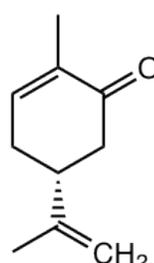
**the enantiomer of  
limonene found in  
lemons**

If you like caraway bread, this smell is due to the (S)-(+)-carvone, and the (R)-(-)-carvone that is found in spearmint oil gives it a much different odor.



**(S)-(+)-carvone**

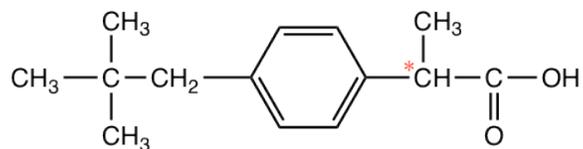
**caraway seed oil**



**(R)-(-)-carvone**

**spearmint oil**

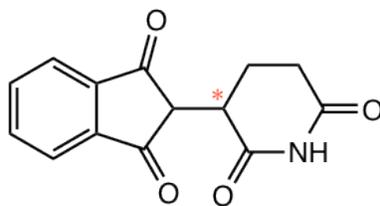
More dramatic examples of how chirality plays an important role in biological properties are found in many medicines. For the common over-the-counter anti-inflammatory drug ibuprofen (Advil), for example, only the (S)-enantiomer is the active agent, while the (R)-enantiomer has no anti-inflammatory effects. Fortunately, the (R)-enantiomer does not have any harmful side effects and slowly converts to the (S)-enantiomer in the body. Ibuprofen is usually marketed as a racemate form.



**(±) Ibuprofen**

The issue of chiral drugs (drugs that contain a single enantiomer, not as a racemate) did not gain the attention of the drug discovery industry until 1960. Back then, drugs were approved in racemate form if a chirality center was involved, and there was no further study on the biological differences of different enantiomers. These were all changed by the tragic case of thalidomide. Thalidomide was a drug sold in more than 40 countries, mainly in Europe, in the early 1960s as a sleeping aid and to pregnant women as an antiemetic (a drug that prevents vomiting) to combat morning sickness. It was not recognized at that time that only the R-enantiomer has the antiemetic property, while the S-enantiomer was

a teratogen that causes congenital deformations. The drug was marketed as a racemic mixture and caused damage in about 10,000 children before it was withdrawn from the market in Nov. 1961. This drug was not approved in the US, but it was attributed to Dr. Frances O. Kelsey, who was a physician for the Food and Drug Administration at that time and had insisted on additional tests on some side effects. Thousands of lives were saved by Dr. Kelsey, and she was awarded the President's Medal in 1962 for preventing the sale of thalidomide.

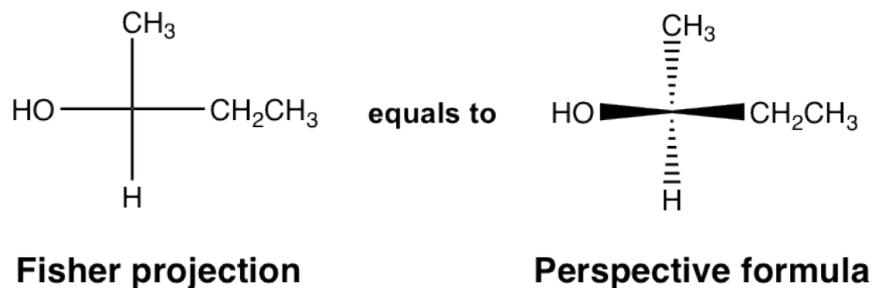


**(±) Thalidomide**

## 5.5 Fisher Projection

For the discussions so far, the perspective formula with solid and dashed wedges has been used to represent the 3D arrangement of groups bonded to a chirality center. In addition, there is another broadly applied formula for that purpose: the Fisher projection. A Fisher projection is a shortcut for showing the spatial group arrangement of a chirality center; it is easier to draw and recognize and is particularly useful for showing structures with more than one chirality center.

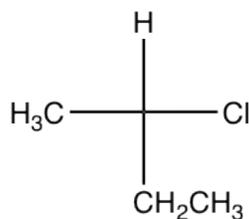
In a Fisher projection, the chirality center is shown as the intersection of two perpendicular lines. The horizontal lines represent the bonds that point out of the plane, and the vertical lines represent the bonds that point behind the plane.



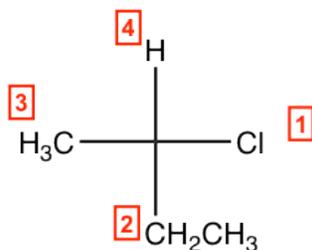
It is very important to keep in mind that the lines in Fisher projection are not just bonds, they represent the bonds with specific spatial arrangements and stereochemistry.

### Assigning an R/S Configuration in a Fisher projection

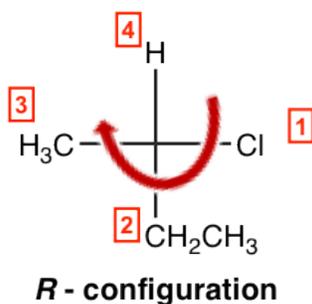
Taking the following compound as an example:



1. Assign group priority as we usually do.

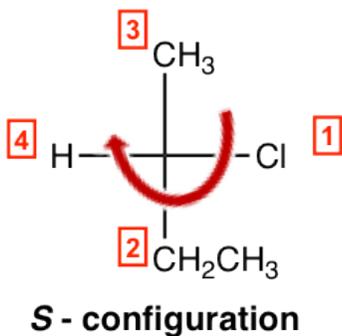


2. If the lowest priority group (#4 group) is on a vertical bond, determine the priority decrease direction from #1→#2→#3 as usual to get the configuration; clockwise is **R** and counterclockwise is **S**.
- 3.



So, the example here is an **R**-isomer, and the complete name of the compound is (**R**)-2-chlorobutane.

3. If the lowest priority group is on a horizontal bond (as is the case in the following structure), determine the priority decrease direction as in step 2, then reverse the answer to the oppositeway to get the final configuration.



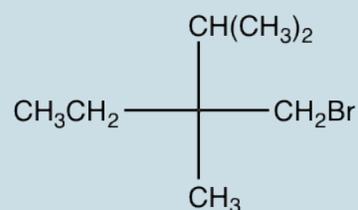
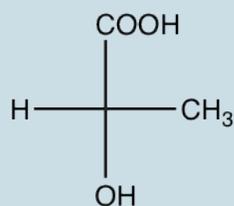
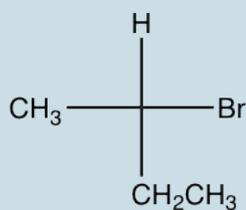
“clockwise”; **however** since the #4 group is at horizontal bond, the answer need to be **reversed**, and the final answer is “**S**”

So, the example here is a **S**-isomer, and the complete name of the compound is (**S**)-2-chlorobutane.

Explain why in step 3 of the above procedure, the answer should be reversed to get the final (actual) configuration.

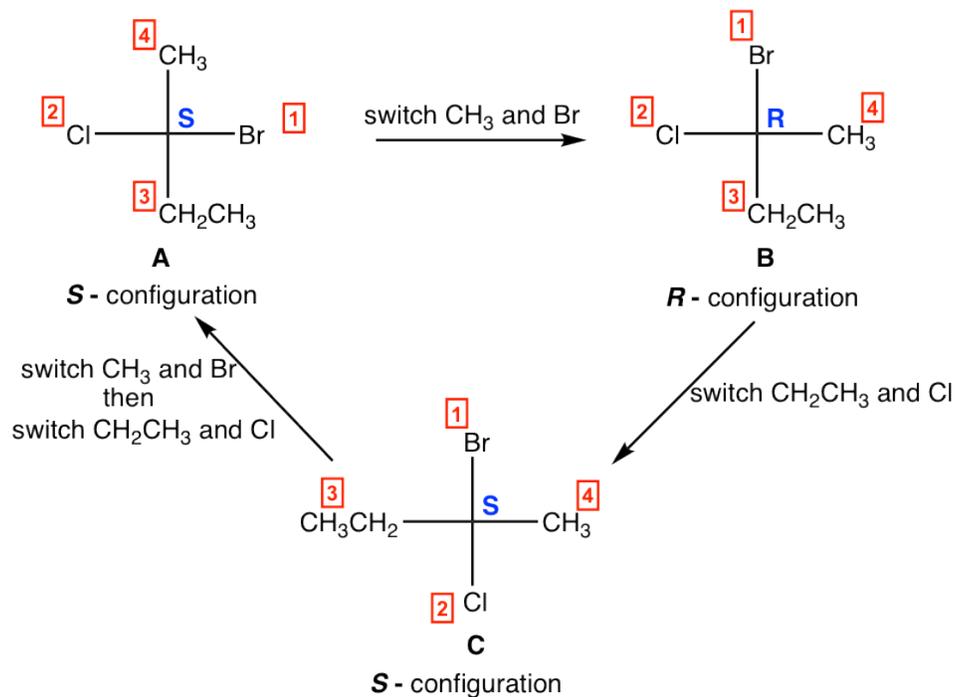
## Answers to Chapter 5 Practice Questions

Exercises 5.7: Indicate the configuration of the following structures.



### Properties of a Fisher projection:

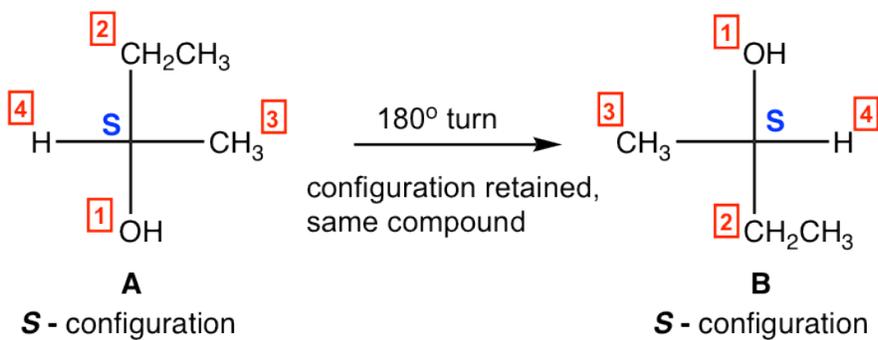
1. One switch (interchange) of two groups in a Fisher projection inverts the configuration, and two switches bring the original isomer back.



For the above structures:

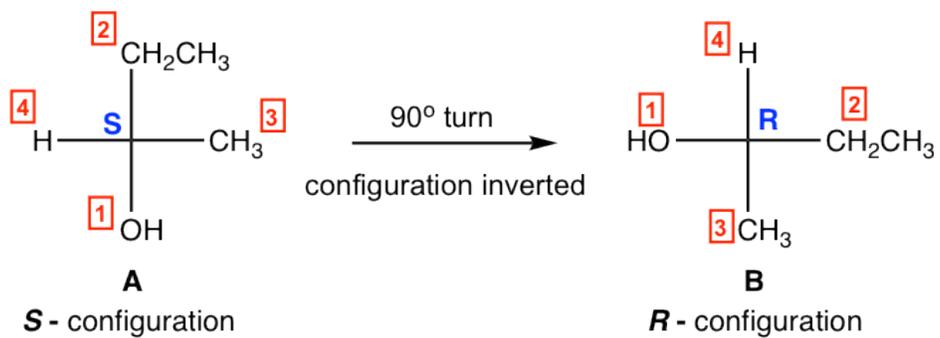
- one switch of A leads to B, and A and B are enantiomers.
- one switch of B leads to C, and B and C are enantiomers.
- two switches of C lead to A, and A and C are identical.

2. Rotate the Fisher projection 180° to get the same structure, with the configuration retained.



- A 180° rotation of A leads to B, and A and B are identical.

3. Rotate the Fisher projection 90° to get the configuration inverted.



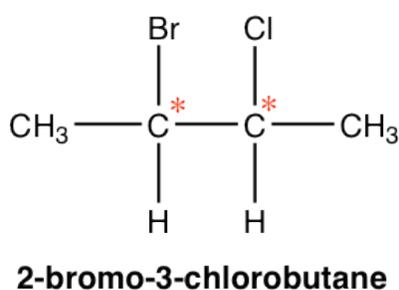
- 90° rotation of A leads to B, and A and B are enantiomers.

Do NOT rotate the Fisher projection 90°, unless you have to. Keep in mind that the configuration gets inverted by a 90° rotation.

# 5.6 Compounds with More Than One Chirality Centers

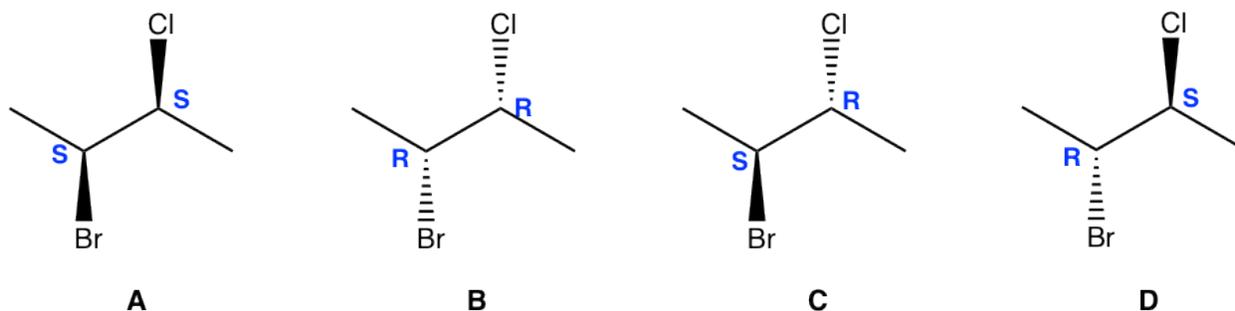
## 5.6.1 Diastereomers

It is very common for there to be more than one chirality centers in an organic compound. For the example of 2-bromo-3-chlorobutane below, there are 2 chirality centers, C2 and C3. As each chirality center has two possible configurations, R and S, the total number of possible stereoisomers for this compound is four, with configurations on C2 and C3 as RR, SS, RS and SR, respectively.

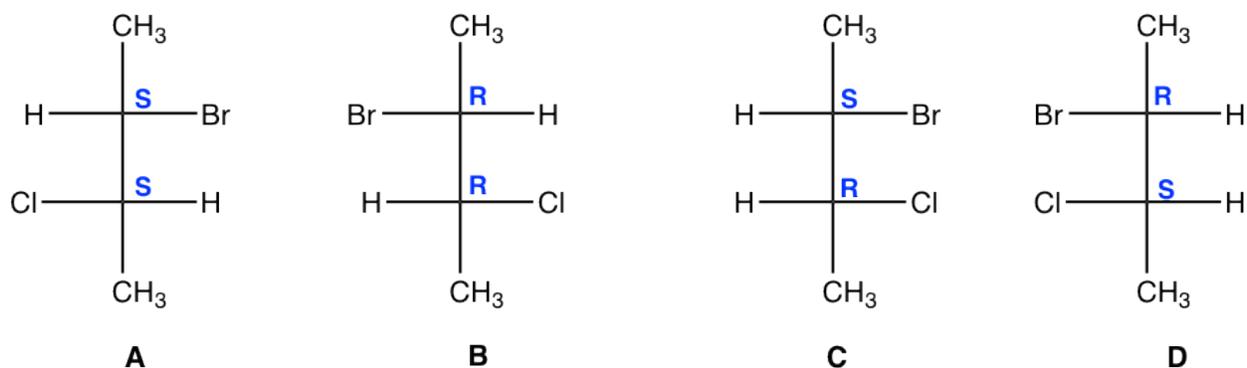


As a general rule, for a compound that has  $n$  chirality centers, the maximum number of stereoisomers for that compound is  $2^n$ .

The four stereoisomers of 2-bromo-3-chlorobutane consist of two pairs of enantiomers. Stereoisomers A and B are a pair of non-superimposable mirror images, so they are enantiomers. So are the isomers C and D. What then is the relationship between isomers A and C?

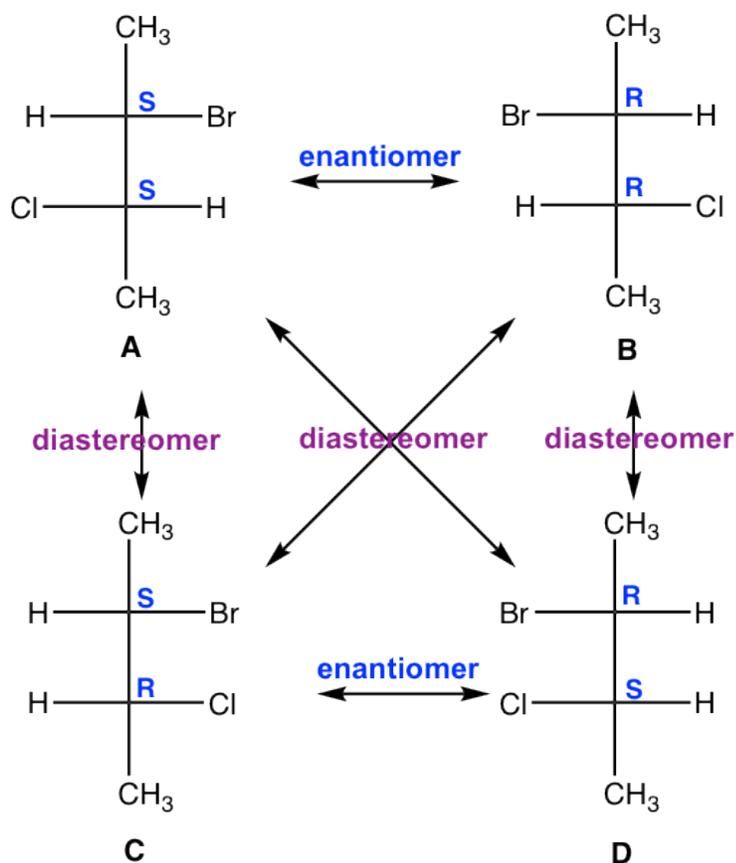


**Four stereoisomers of 2-bromo-3-chlorobutane in perspective formula**



**Four stereoisomers of 2-bromo-3-chlorobutane in Fisher projection**

A and C are not identical, not enantiomers, and they are stereoisomers (have the same bonding but differ in the spatial arrangement of groups). This type of stereoisomer is defined as a diastereomer. Diastereomers are stereoisomers that are not enantiomers. For the four stereoisomers here, there are four pairs of diastereomers: A and C, A and D, B and C, and B and D. The relationship between the four stereoisomers can be summarized as:



**Relationships between the four stereoisomers of 2-bromo-3-chlorobutane**

With the introduction of the diastereomer concept, the way to categorize isomers can be revised, and the summary

in Fig. 5.1a can be replaced by the updated version in Fig. 5.6a. The stereoisomer then has two sub-types; enantiomers and diastereomers, because any stereoisomers that are not enantiomers can always be called diastereomers. Based on such a definition, the geometric isomers we learned about earlier also belong to the diastereomer category.

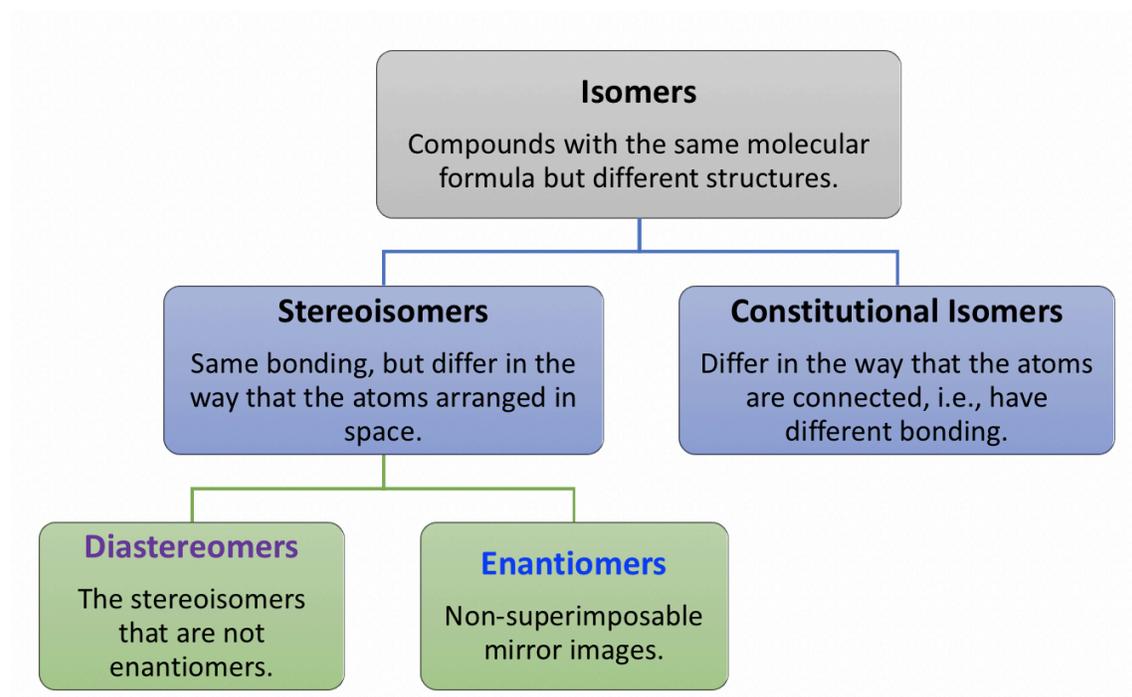
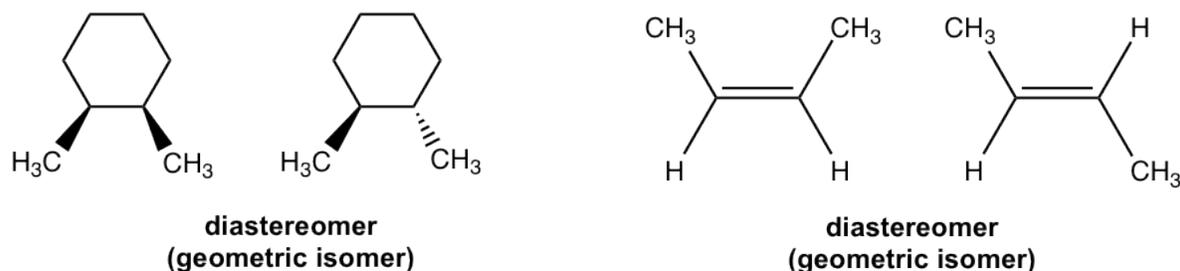


Figure 5.6a Updated Summarization of isomers

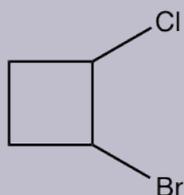
As mentioned earlier, enantiomers are very similar to each other, and they share the same physical properties except optical activity (the opposite sign for a specific rotation). Enantiomers also generally have same chemical properties, except for the reaction with other chiral reagents (not topics in this course).

However, diastereomers are not that closely related. Diastereomers have different physical properties, for example, different b.p., color, density, polarity, solubility, etc. They also have different chemical properties.

Next, we will go through examples of cyclic compounds to see how the new concept of the diastereomer relates to the knowledge of cyclic compounds we learned before.

### Examples

Draw the structures of all the stereoisomers for 1-bromo-2-chlorocyclobutane, and indicate the relationship between any two stereoisomers.



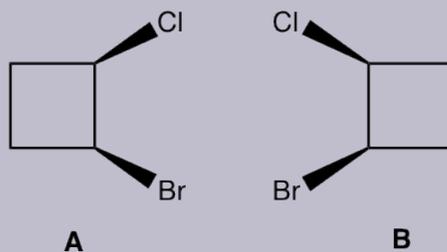
**1-bromo-2-chlorocyclobutane**

### Approach:

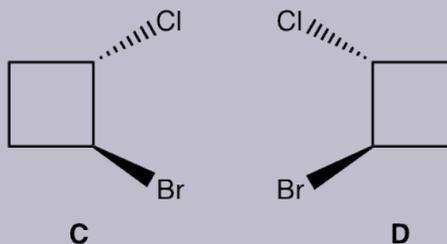
There are two chirality centers for a 1-bromo-2-chlorocyclobutane molecule. So, the maximum number of stereoisomers is four. To work on the stereoisomers for cyclic compounds, we can start with a cis/trans isomer and then check whether the enantiomer applies to each case.

### Solution:

#### *cis*-1-bromo-2-chlorocyclobutane:



#### *trans*-1-bromo-2-chlorocyclobutane:



There are two *cis*-isomers: A and B, and they are enantiomers of each other; similarly, there are also two *trans*-isomers: C and D that are enantiomers of each other as well.

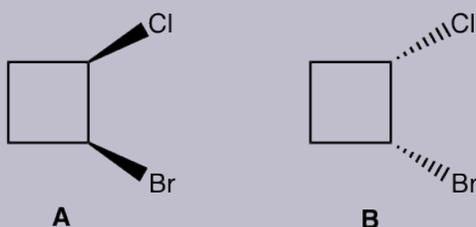
The relationship between *any* of the *cis*-isomers to *any* of the *trans*-isomers is diastereomers (A and C, A and D, B and C, and B and D). Since they are geometric isomers, and as we learned earlier geometric isomers can also be called diastereomers.

All geometric isomers are diastereomers (it is always correct to call a pair of geometric isomers diastereomers); however, not all diastereomers are geometric isomers!

Examples:

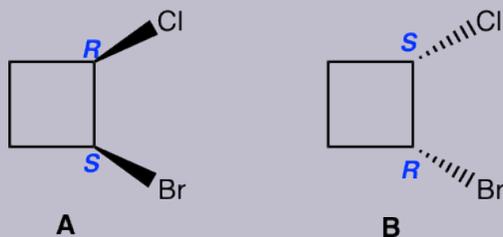
What is the relationship between the following pair of compounds, enantiomers, identical, diastereomers, constitutional isomers, and non-isomers?

1.



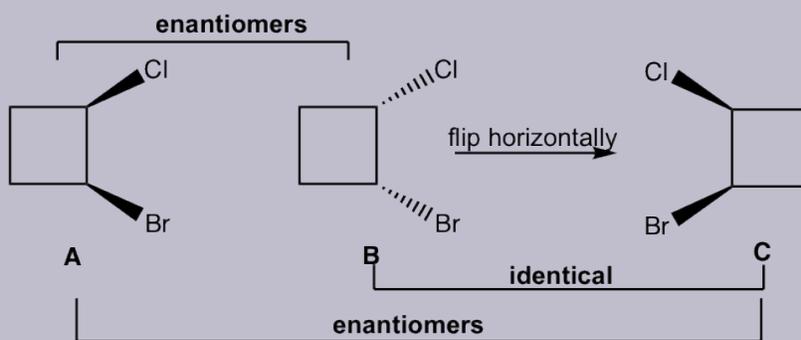
### Method I:

The basic way is to determine the configuration of each chirality center. As shown below the configuration for both chirality centers are right opposite between the structure A and B. So they are enantiomers.



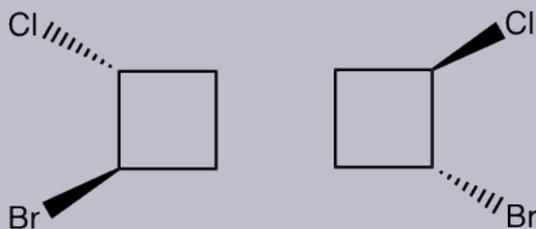
## Method II:

For the cyclic structures, sometimes rotating or flipping a given structure in a certain way helps us to tell the relationship (using the molecular model helps the rotate or flip part). For this example, flipping structure B horizontally leads to structure C, B and C are identical. Then it is easy to tell that A and C are just non-superimposable mirror images of each other, so A and C are enantiomers, then A and B are enantiomers as well.



If this method looks confusing to you, then you can stick to Method I.

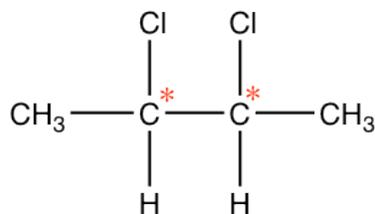
2.



You can use either of the above methods, the answer is "identical".

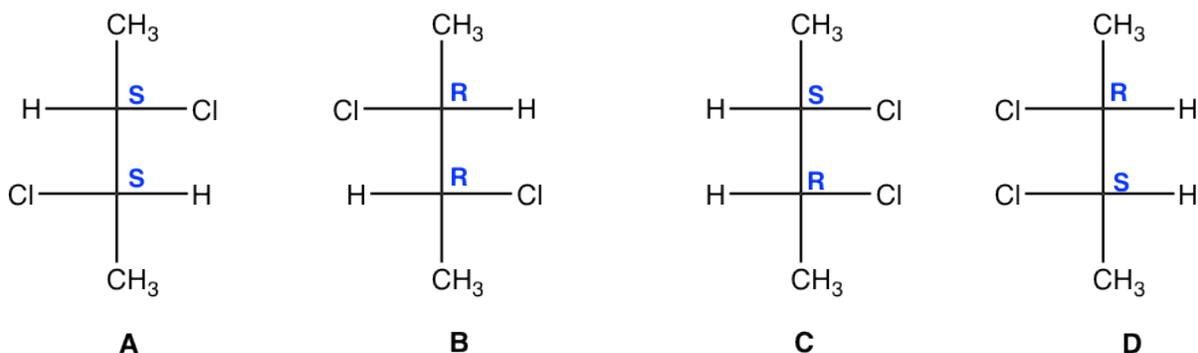
## 5.6.2 Meso compound

Next, we will see another example of a compound containing two chirality centers, 2,3-dichlorobutane, a compound that has the same substituents on C2 and C3 carbons.



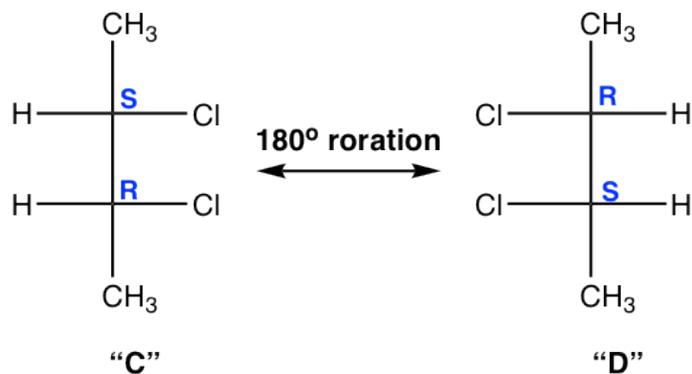
**2,3-dichlorobutane**

Theoretically, there are a maximum of four stereoisomers, and the structures are shown here by Fisher projections.



Stereoisomers A and B are non-superimposable mirror images, so they are enantiomers.

We will take a detailed look at stereoisomers C and D. Yes, they are mirror images, but are they non-superimposable? If isomer C is rotated 180° (180° rotation still gets the same structure back for a Fisher projection), then it could get superimposed on isomer D. So, isomer C and D are superimposable mirror images, which means they are the same, identical!



**superimposable mirror image;  
identical;  
meso compound**

Then “C” and “D” are just different drawings for the same stereoisomer. The next question is whether this

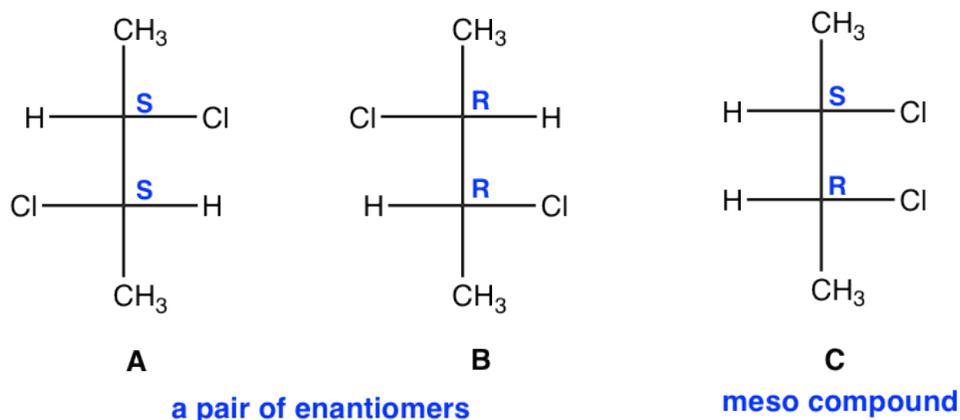
stereoisomer is chiral. We have confirmed that this isomer does get superimposed on its mirror image, which means it is achiral.

This is so weird! Can a compound that contains two chirality centers (C2 and C3) be achiral?

Yes, it can! A compound that is achiral but contains chirality centers is called a meso compound. A meso compound is achiral and optical inactive (it does NOT rotate the plane of polarization of plane-polarized light), but it does have multiple chirality centers.

Because that one stereoisomer is a meso compound, the total number of stereoisomers for 2,3-dichlorobutane is three.

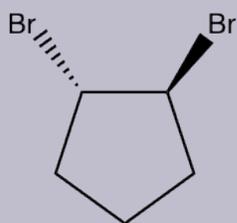
Attention,  $2^n$  is the maximum number of stereoisomers. Some compounds may have less than the maximum, because of the existence of meso compounds.



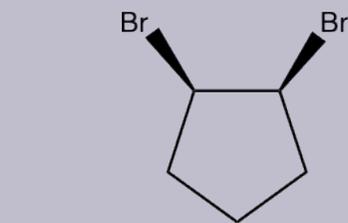
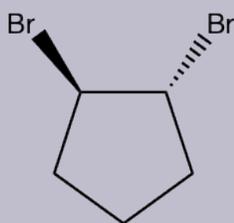
**Three stereoisomers of 2,3-dichlorobutane**

*Examples: Draw all the stereoisomers of 1,2-dibromocyclopentane.*

Solutions: there are a total of three stereoisomers.



two *trans*-isomers, a pair enantiomers



one *cis*-isomer, meso compound

### Exercises 5.8

- Draw all stereoisomers for 1-ethyl-3-methylcyclohexane.
- Draw all stereoisomers for 1-ethyl-4-methylcyclohexane.
- Draw all stereoisomers for 1,2-dimethylcyclohexane.

### Answers to Chapter 5 Practice Questions

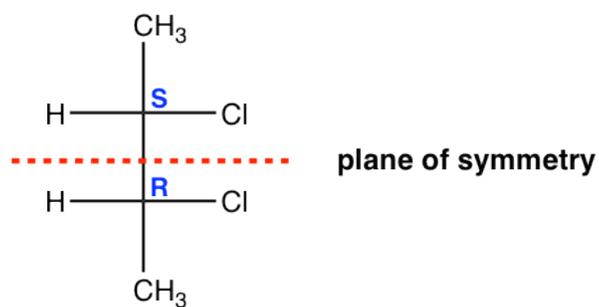
#### 5.6.3 Chiral or achiral by looking for Plane of symmetry

The existence of chirality centers does not guarantee the chirality of a molecule, for example, of the meso compound. Following the definition of chirality always involves the comparison between the original structure and its mirror image, which requires extra work. Is there any easier way to tell whether a molecule is chiral or achiral?

We can check the plane of symmetry. The plane of symmetry is a plane that cuts the molecule in half, and each half is the mirror image of the other.

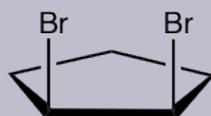
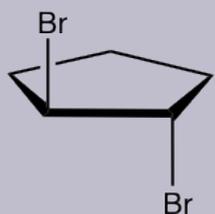
- If a molecule does have a plan of symmetry, then the molecule is achiral.
- A molecule that does not have a plane of symmetry in any conformation is chiral.

For the meso isomer of 2,3-dichlorobutane, the plane of symmetry is the plane that is labeled in the structure below.

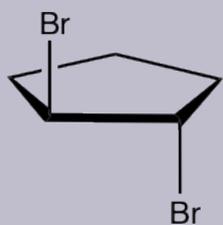


Examples:

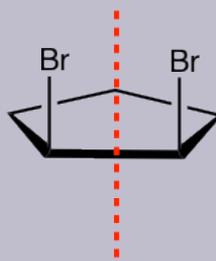
Determine whether the following molecule is chiral or achiral.



Solution:



**chiral,  
no plane of symmetry**

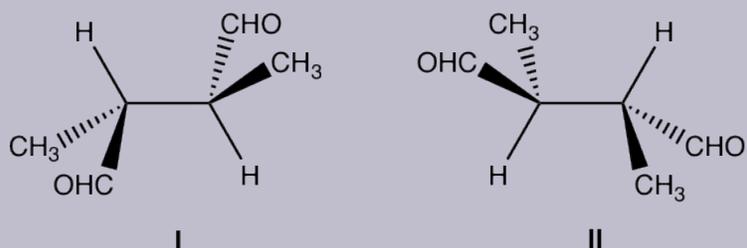


**achiral,  
has plane of symmetry**

Checking the plane of symmetry provides a quick way to determine the chirality of a molecule. But sometimes you may

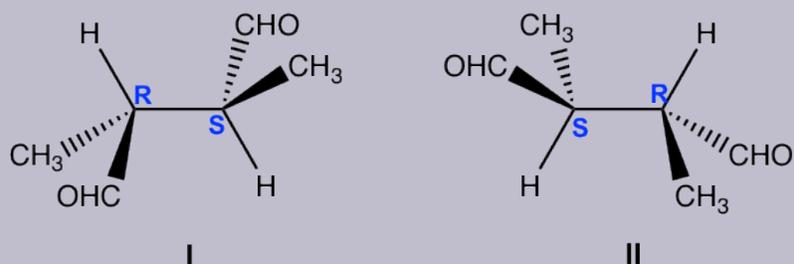
need to look for the proper conformation to get the plane of symmetry. See the following example.

Examples: What is the relationship of the following pair of structures?



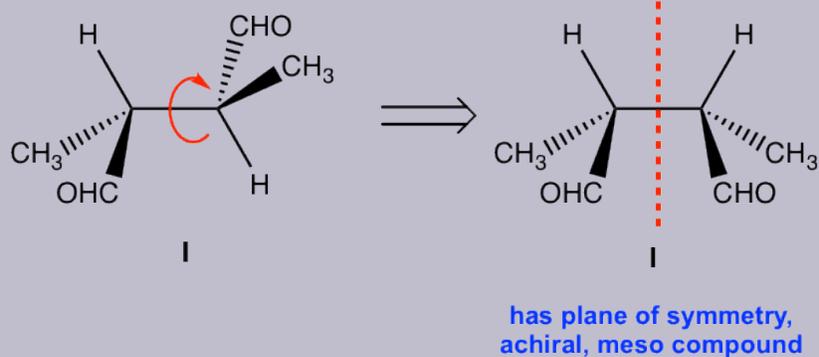
### Approach:

Determine the R/S configuration of each carbon.



For both structures, the chirality centers are bonded with the same groups, and structure **I** has R and S, and structure **II** has S and R. Are they enantiomers?

A bit further investigation is necessary to get the conclusion. Let's rotate the groups around the 2<sup>nd</sup> chirality centre of structure **I** (you can use the molecular model to do the rotation, which is very helpful for visualizing the spatial arrangement of the groups):



Rotation of the groups around the chirality centre does not change the configuration, however, it does change the conformation to eclipsed conformation. In the eclipsed conformation, it is easier to tell that the structure has a plane of symmetry, so it is a meso compound that is achiral. Achiral compound does not have an enantiomer, so structure II is also a meso compound that is identical to the structure I.

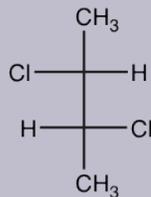
### Solution:

Identical

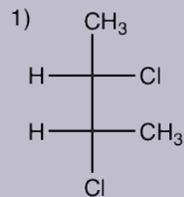
(You can rotate, or do switches to compare between the two structures, but make sure to keep track of any action. If it is easy to get lost by rotating or switching, assigning R/S configuration is a safer way.)

*Examples*

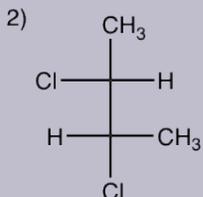
If the specific rotation of this molecule is  $+50^\circ$  (hypothetic value), determine the specific rotation of molecules in following questions:



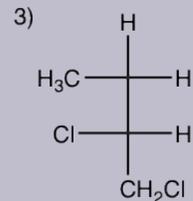
specific rotation is  $+50^\circ$



- a)  $+50^\circ$
- b)  $-50^\circ$
- c)  $0^\circ$
- d) not enough information to decide



- a)  $+50^\circ$
- b)  $-50^\circ$
- c)  $0^\circ$
- d) not enough information to decide



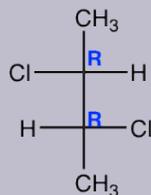
- a)  $+50^\circ$
- b)  $-50^\circ$
- c)  $0^\circ$
- d) not enough information to decide

### Thinking:

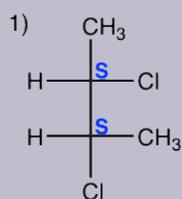
Determine the relationship between the molecule in each question with the given one, and apply the knowledge of specific rotation.

## Solutions:

If the specific rotation of this molecule is  $+50^\circ$  (hypothetic value), determine the specific rotation of molecules in following questions:



specific rotation is  $+50^\circ$



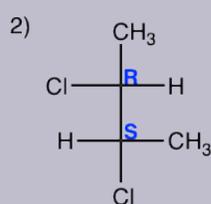
a)  $+50^\circ$

b)  $-50^\circ$

c)  $0^\circ$

d) not enough information to decide

this molecule is **enantiomer** to the given molecule, so the specific rotation has the same value, but opposite sign



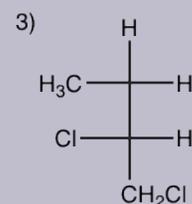
a)  $+50^\circ$

b)  $-50^\circ$

c)  $0^\circ$

d) not enough information to decide

this molecule is **diastereomer** to the given molecule, and it is a meso compound, so **achiral**



a)  $+50^\circ$

b)  $-50^\circ$

c)  $0^\circ$

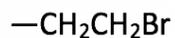
d) not enough information to decide

this molecule is **constitutional isomer** to the given molecule, so the specific rotation has no connection to each other

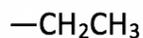
# Answers to Chapter 5 Practice Questions

## 5.1

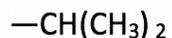
Order the following groups based on decreasing priority for E/Z naming purpose.



**A**



**B**



**C**



**D**

Answer:  $\text{D} > \text{C} > \text{A} > \text{B}$

## 5.2

1. Draw the structure of the following compounds. Determine which one has a chirality center and label it with a star.

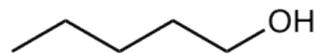
a) 1-bromobutane

no



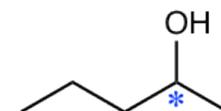
b) 1-pentanol

no



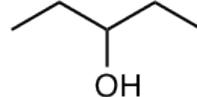
c) 2-pentanol

yes



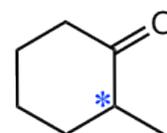
d) 3-pentanol

no



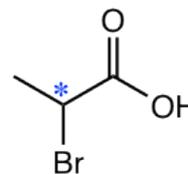
e) 2-bromopropanoic acid

yes

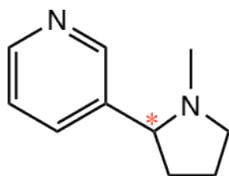


f) 2-methyl cyclohexanone

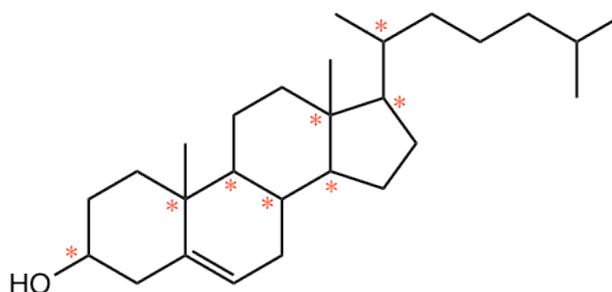
yes



2. Label all the chirality centers in the following molecules.



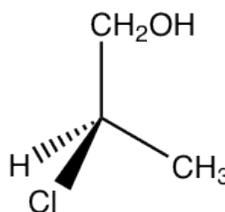
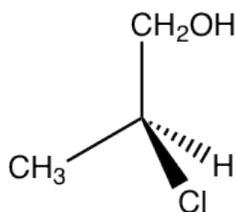
nicotine



cholesterol

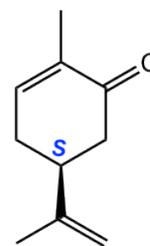
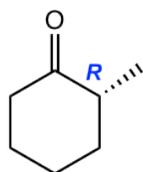
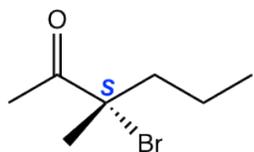
5.3

Draw the pair of enantiomers of 2-chloro-1-propanol.



5.4

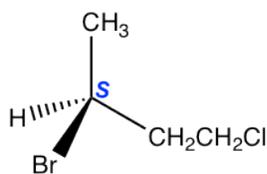
Determine the R/S configuration of the chirality center in following compounds.



5.5

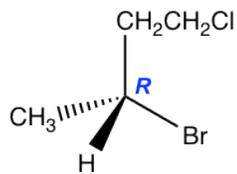
Determine the relationship for each pair of molecules: enantiomers, identical, constitutional isomers, non-isomers:

1)

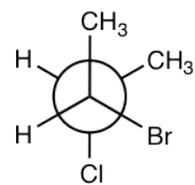
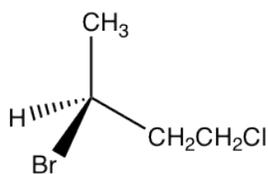


enantiomers

2)



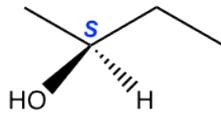
constitutional isomers



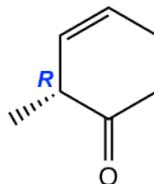
3)



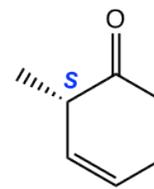
identical



4)



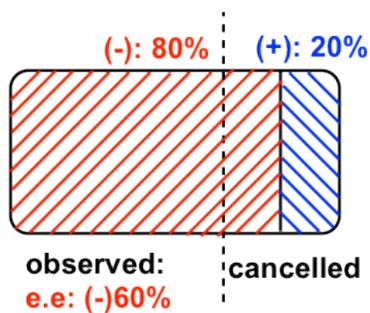
enantiomers



5.6

Draw the diagram for Sample #5 by referring to the diagram for Sample #4.

Sample #5



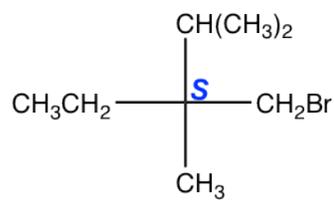
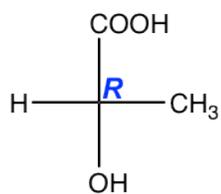
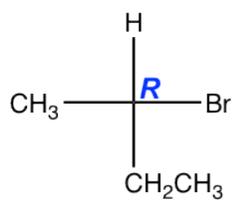
5.7

Explain why, in step 3 of the above procedure, the answer should be reversed to get the final (actual) configuration?

According to the definition of a Fisher projection, the horizontal bond is the bond pointing towards the viewer. Therefore, when the lowest priority group is on a horizontal bond, it is on the position just opposite to the way defined by the Cahn-Ingold-Prelog rule, so the actual configuration should be the reversed version of whatever is initially obtained.

5.8

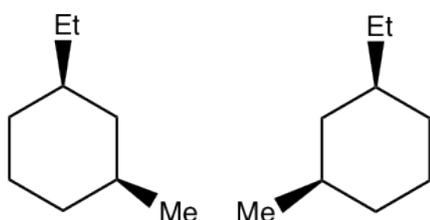
Indicate the configuration of the following compounds.



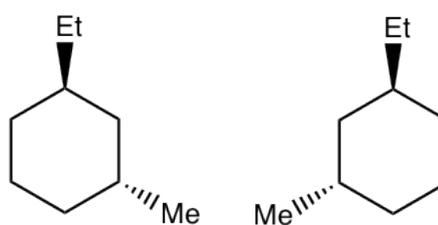
## 5.9

- Draw all stereoisomers for 1-ethyl-3-methylcyclohexane.

*cis*

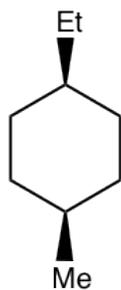


*trans*

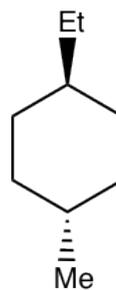


- Draw all stereoisomers for 1-ethyl-4-methylcyclohexane.

*cis*

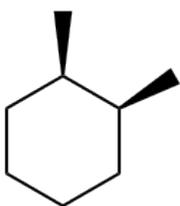


*trans*

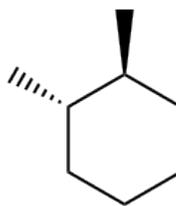
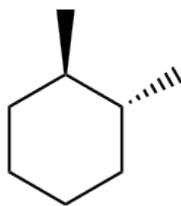


- Draw all stereoisomers for 1,2-dimethylcyclohexane.

*cis*



*trans*



**meso compound**



# CHAPTER 6: STRUCTURAL IDENTIFICATION OF ORGANIC COMPOUNDS: IR AND NMR SPECTROSCOPY

In this chapter, we will focus on the methods for chemists to determine the structure of organic compounds. As part of the efforts for scientists to search for new compounds for medical, material or new energy resource purposes, determining the structures of the new compounds is a very critical step. A number of instrumental spectroscopy techniques have been used broadly for such purposes. Spectroscopy is the study of the interaction of matter and electromagnetic radiation, and how these interactions can be quantified, analyzed, and interpreted to gain information about the structure of matter. To identify the structures of organic compounds, we will specifically study how molecules interact with electromagnetic radiation, so the spectroscopy techniques in our discussions here can also be called molecular spectroscopy.

Specifically, we will have discussions about infrared (IR) spectroscopy and nuclear magnetic resonance (NMR) spectroscopy in this Chapter. IR spectroscopy is a technique applied widely in organic chemistry to detect the presence or absence of a certain functional group, and NMR spectroscopy is a powerful analytical technique that can determine the bonding arrangement, or the structure, of a molecule.

## Learning Objectives for this chapter:

- Understand and explain the principle of Infrared (IR) spectroscopy.
- Be able to identify the bands of major organic functional groups in IR spectra.
- Understand and explain the principle of Nuclear Magnetic Resonance (NMR) spectroscopy, including the NMR active nuclei, spin state and magnetic resonance, shielding and de-shielding effects and chemical shift.
- Interpret the NMR spectra of a certain compound by assigning the peaks based on groups of signals, chemical shifts, splitting patterns, and integration.
- Predict the number of peaks expected in the  $^1\text{H}$  or  $^{13}\text{C}$  NMR spectrum of a given compound.
- Determine the structures of unknown compounds based on the structural information given together with IR and NMR spectra.



# 6.1 Electromagnetic Radiation and Molecular Spectroscopy

Electromagnetic radiation is radiation composed of oscillating electrical and magnetic fields. The whole electromagnetic spectrum covers radiation in a broad range from gamma rays (emitted by the nuclei of certain radioactive elements), X-rays (used for the medical examination of bones), to ultraviolet (UV) light (is responsible for sunburns and can also be used for disinfection purposes), microwaves, and radio-frequency waves (used for radio and television communication and for cell phone signals). Visible light, the radiation that is visible to our eyes and what we commonly refer to as “light”, accounts for only a very narrow band of the full electromagnetic spectrum.

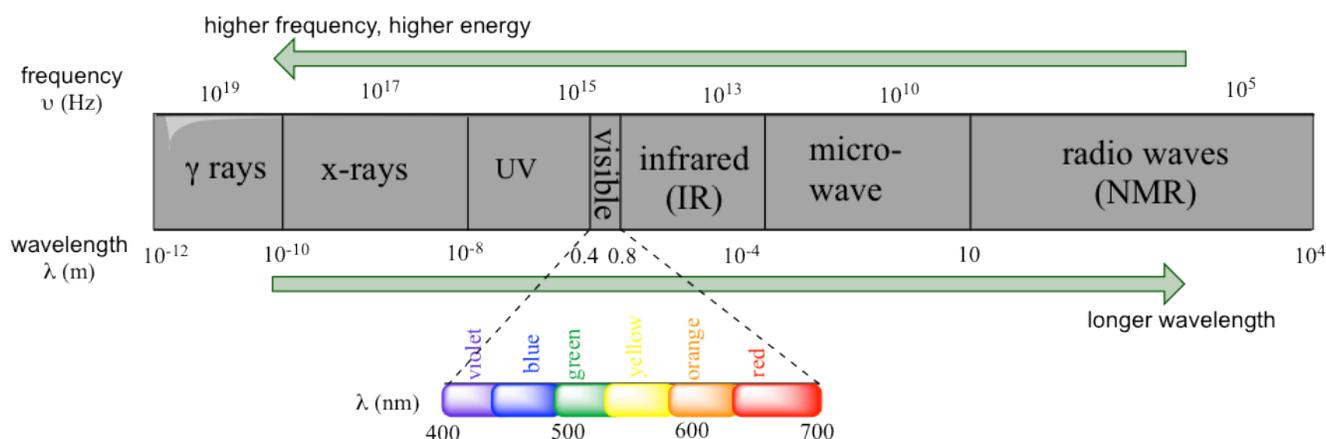


Figure 6.1a The Electromagnetic Spectrum

Electromagnetic radiation exhibits wave-like properties. As a general property of waves, the wavelength ( $\lambda$ , Greek ‘lambda’) and frequency ( $\nu$ , Greek ‘nu’, in a unit of Hz or  $s^{-1}$ ,  $1\text{Hz} = 1s^{-1}$ ) of electromagnetic radiation fits the formula of:

$$c = \lambda\nu \quad \text{Formula 6.1}$$

where  $c$  is the speed, usually referred to as the “speed of light”, with the constant value of  $2.998 \times 10^8 \text{m/s}$  in vacuum (the speed of light in air is a little bit slower than this constant but is usually regarded as the same). Because electromagnetic radiation travels at a constant speed, the wavelength ( $\lambda$ ) and frequency ( $\nu$ ) are inversely proportional to each other: the longer waves have lower frequencies, and shorter waves have higher frequencies.

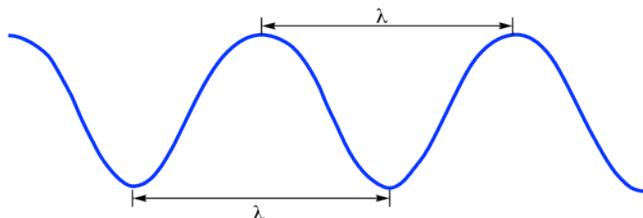


Figure 6.1b Wavelength

The energy of electromagnetic radiation can be calculated based on the formula:

$$E = h\nu = hc/\lambda$$

Formula 6.2

where  $E$  is the energy of each photon in the unit of Joule (J) and  $h$  is the Planck's constant with a value of  $6.626 \times 10^{-34}$  J.s.

So, radiation with higher frequencies corresponds to higher energy. High energy radiation, such as gamma radiation and X-rays, is composed of very short waves – as short as 10 ~ 16m. Longer wavelengths are much less energetic and thus are less harmful to living things. Visible light waves are in the range of 400–700 nm (nanometer, 1 nm =  $10^{-9}$ m), while radio waves can be several hundred meters in length.

In a molecular spectroscopy experiment, the electromagnetic radiation of a specified range of wavelengths is allowed to pass through a sample containing a compound of interest. The sample molecules absorb energy from some of the wavelengths and as a result jump from a lower energy 'ground state' to a higher energy 'excited state'. Other wavelengths are not absorbed by the sample molecule, and they pass through. A detector records which wavelengths were absorbed and how much was absorbed.

As we will see in this chapter, we can learn a lot about the structure of an organic molecule by quantifying how it absorbs (or does not absorb) different wavelengths in the electromagnetic spectrum. IR spectroscopy involves the absorption of radiations in the infrared region, and radio waves are applied in the NMR technique.

## 6.2 Infrared (IR) Spectroscopy Theory

In IR spectroscopy, how the vibration mode of covalent bonds is affected by absorbing IR electromagnetic radiation is studied. Covalent bonds in organic molecules are not like rigid sticks; instead, they behave as if they were vibrating springs. At room temperature, organic molecules are always in motion, which involves several vibration modes, such as stretching, bending, and twisting as illustrated in Fig. 6.2a.

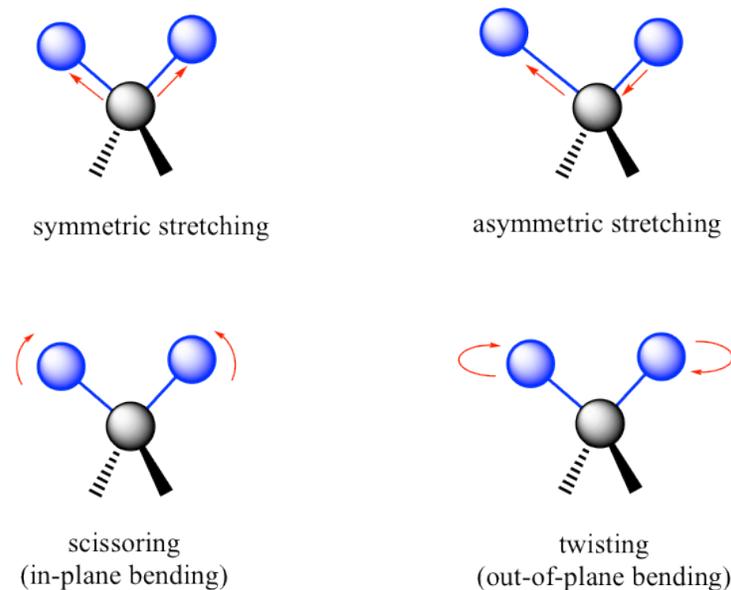


Figure 6.2a Vibration Modes of Bonds

Stretching is the vibration occurring along the line of the bond that changes the bond length. Bending is the vibration that, like a swing, does not occur along the line, but changes the bond angles. The specific bending mode is often referred to by descriptive terms like scissoring, twisting, etc.

One covalent bond may vibrate in different vibrational modes; for example, the C-H bond can be in a stretching and bending mode. Each vibrational mode for a given bond occurs with a characteristic ground state frequency that corresponds to the frequency of the IR region (1013 to 1014Hz, or 2.5 to 17  $\mu\text{m}$  in wavelength) of the electromagnetic spectrum. If a molecule is exposed to IR radiation, it will absorb the radiation that matches the frequency of the vibration of one of its bonds. The IR radiation absorbed allows the bond to vibrate a bit more, that is, increases the amplitude of vibration, but the vibrational frequency will remain the same.

In an infrared spectrophotometer (Fig. 6.2b), a beam of IR radiation passes through the sample, and some radiation is absorbed by the sample, while the remaining radiation goes through it. Another beam of IR radiation passes through the cell with a blank (no sample, no absorption) and all the light goes through it. The detector in the instrument records and compares the radiation transmitted through the sample with that transmitted in the absence of the sample. Any frequencies absorbed by the sample will be apparent by the difference. The computer plots the result as a graph showing transmittance vs frequency (in the format of wavenumber, which will be explained next).

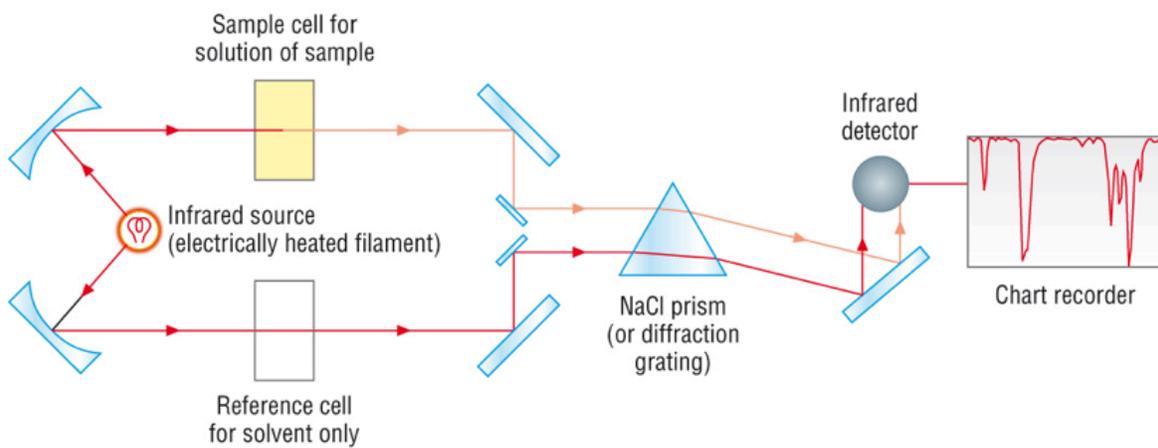


Fig. 6.2b Diagram of the IR Spectrometer

## 6.3 IR Spectrum and Characteristic Absorption Bands

With a basic understanding of IR theory, we will now take a look at the actual output from IR spectroscopy experiments and learn how to get structural information from the IR spectrum. Below is the IR spectrum for 2-hexanone.

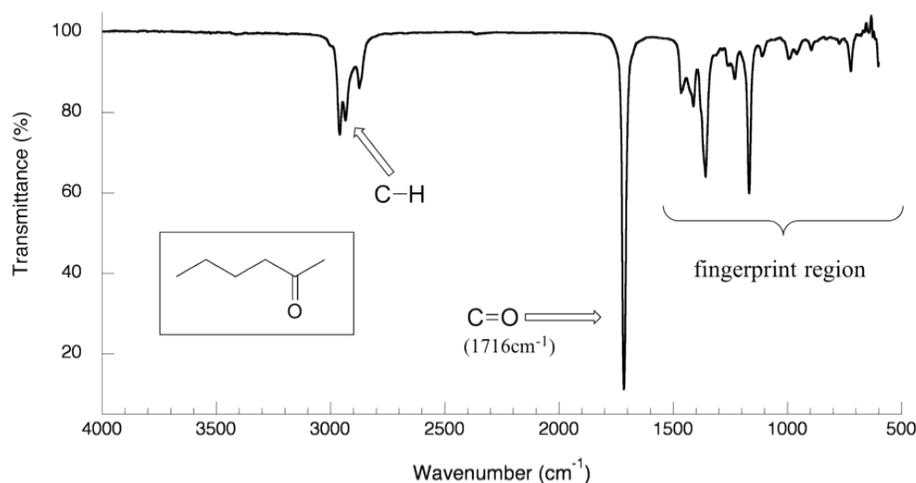


Figure 6.3a IR Spectrum of 2-hexanone

Notes for interpreting IR spectra:

- The vertical axis is '% transmittance', which indicates how strongly light was absorbed at each frequency. The solid line traces the values of % transmittance for every wavelength passed through the sample. At the high end of the axis, 100% transmittance means no absorption occurred at that frequency. Lower values of % transmittance mean that some of the energy is absorbed by the compound and gives downward spikes. The spikes are called absorption bands in the IR spectrum. A molecule has a variety of covalent bonds, and each bond has different vibration modes, so the IR spectrum of a compound usually shows multiple absorption bands.
- The horizontal axis indicates the position of an absorption band, but instead of using frequency to show the absorbed radiation, wavenumbers ( $\bar{\nu}$ , in the unit of  $\text{cm}^{-1}$ ) are used as a conventional way in IR spectra. The wavenumber is defined as the reciprocal of wavelength (Formula 6.3), and the wavenumbers of IR radiation are normally in the range of  $4000 \text{ cm}^{-1}$  to  $600 \text{ cm}^{-1}$  (approximately corresponds to the wavelength range of  $2.5 \mu\text{m}$  to  $17 \mu\text{m}$  of IR radiation).

$$\begin{aligned}\text{wavenumber } (\bar{\nu}, \text{ cm}^{-1}) &= 1 / \lambda \text{ (with } \lambda \text{ in cm)} \\ &= 1 / 100\lambda \text{ (with } \lambda \text{ in m)} \\ &= 10^4 / \lambda \text{ (with } \lambda \text{ in nm)}\end{aligned}$$

**Formula 6.3**

Formula 6.3 Wavenumber

Please note that the direction of the horizontal axis (wavenumber) in IR spectra *decreases* from left to right. The larger wavenumbers (shorter wavelengths) are associated with higher frequencies and higher energy.

The power of infrared spectroscopy arises from the observation that the covalent bonds characterizing different functional groups have different characteristic absorption frequencies (in wavenumber, Table 6.1). The technique is therefore very useful as a means of identifying which functional groups are present in a molecule of interest.

For example, the most characteristic absorption band in the spectrum of 2-hexanone (Figure 6.3a) is that from the stretching vibration of carbonyl double bond C=O at 1716 cm<sup>-1</sup>. It is a very strong band compared to the others on the spectrum. A strong absorbance band in the 1650–1750 cm<sup>-1</sup> region indicates that a carbonyl group (C=O) is present. Within that range, carboxylic acids, esters, ketones and aldehydes tend to absorb in the higher wavenumber/frequency end (1700–1750 cm<sup>-1</sup>), while conjugated unsaturated ketones and amides tend to absorb on the lower wavenumber/frequency end (1650–1700 cm<sup>-1</sup>).

## Stretching Vibrations

Generally, stretching vibrations require more energy and show absorption bands in the higher wavenumber/frequency region. The characteristics of stretching vibration bands associated with the bonds in some common functional groups are summarized in Table 6.1.

Formula	Bond	Characteristic IR Frequency range (cm <sup>-1</sup> )
alcohol	O-H stretching	3200-3600 (broad)
carbonyl	C=O stretching	1650-1750 (strong)
aldehyde	C-H stretching	~ 2800 and ~ 2700 (medium)
carboxylic acid	C=O stretching	1700-1725 (strong)
	O-H stretching	2500-3300 (broad)
alkene	C=C stretching	1620-1680 (weak)
	vinyl =C-H stretching	3020-3080
benzene	C=C stretching	~ 1600 and 1500-1430 (strong to weak)
alkyne	C≡C stretching	2100-2250 (weak)
	terminal ≡C-H stretching	3250-3350
alkane	C-H stretching	2850-2950
amine	N-H stretching	3300-3500 (medium)

Table 6.1 Characteristic IR Frequencies of Stretching Vibrations

The information in Table 6.1 can be summarized in the diagram for easier identification (Figure 6.3b), in which the IR spectrum is divided into several regions, with the characteristic band of certain groups labeled.

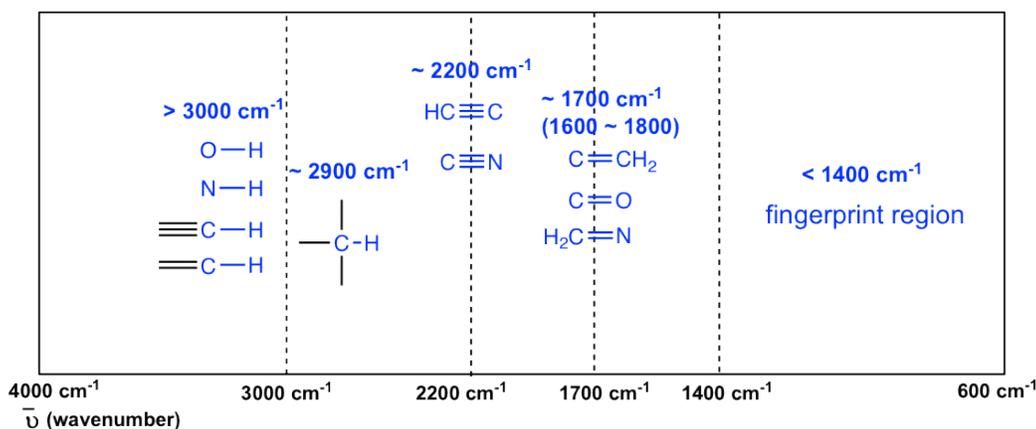


Figure 6.3b Approximate IR Absorption Range

The absorption bands in IR spectra have different intensities that can usually be referred to as strong (s), medium (m), weak (w), broad and sharp. The intensity of an absorption band depends on the polarity of the bond, and a bond with a higher polarity will show a more intense absorption band. The intensity also depends on the number of bonds responsible for the absorption, and an absorption band with more bonds involved has a higher intensity.

The polar O-H bond (in alcohol and carboxylic acid) usually shows strong and broad absorption bands that are easy to identify. The broad shape of the absorption band results from the hydrogen bonding of the OH groups between molecules. The OH bond of an alcohol group usually has absorption in the range of 3200–3600  $\text{cm}^{-1}$ , while the OH bond of the carboxylic acid group occurs at about 2500–3300  $\text{cm}^{-1}$  (Figure 6.4a and Figure 6.4c).

The polarity of the N-H bond (in amine and amide) is weaker than the OH bond, so the absorption band of N-H is not as intense or as broad as O-H, and the position is in the 3300–3500  $\text{cm}^{-1}$  region.

The C-H bond stretching of all hydrocarbons occurs in the range of 2800–3300  $\text{cm}^{-1}$ , and the exact location can be used to distinguish between alkane, alkene and alkyne. Specifically:

- $\equiv\text{C-H}$  ( $\text{sp}$  C-H) bond of terminal alkyne gives absorption at about 3300  $\text{cm}^{-1}$
- $=\text{C-H}$  ( $\text{sp}^2$  C-H) bond of alkene gives absorption at about 3000–3100  $\text{cm}^{-1}$
- $-\text{C-H}$  ( $\text{sp}^3$  C-H) bond of alkane gives absorption at about  $\sim 2900$   $\text{cm}^{-1}$  (see the example of the IR spectrum of 2-hexanone in Figure 6.3a; the C-H absorption band at about 2900  $\text{cm}^{-1}$ )

A special note should be made for the C-H bond stretching of an aldehyde group that shows two absorption bands: one at  $\sim 2800$   $\text{cm}^{-1}$  and the other at  $\sim 2700$   $\text{cm}^{-1}$ . It is therefore relatively easy to identify the aldehyde group (together with the C=O stretching at about 1700  $\text{cm}^{-1}$ ) since essentially no other absorptions occur at these wavenumbers (see the example of the IR spectrum of butanal in Figure 6.4d).

The stretching vibration of triple bonds  $\text{C}\equiv\text{C}$  and  $\text{C}\equiv\text{N}$  have absorption bands of about 2100–2200  $\text{cm}^{-1}$ . The band intensity is at a medium to weak level. The alkynes can generally be identified with the characteristic weak but sharp IR absorbance bands in the range of 2100–2250  $\text{cm}^{-1}$  due to stretching of the  $\text{C}\equiv\text{C}$  triple bond, and terminal alkynes can be identified by their absorbance at about 3300  $\text{cm}^{-1}$  due to stretching of  $\text{sp}$  C-H.

As mentioned earlier, the C=O stretching has a strong absorption band in the 1650–1750  $\text{cm}^{-1}$  region. Other double bonds like C=C and C=N have absorptions in lower frequency regions of about 1550–1650  $\text{cm}^{-1}$ . The C=C stretching of an alkene only shows one band at  $\sim 1600$   $\text{cm}^{-1}$  (Figure 6.4b), while a benzene ring is indicated by two sharp absorption bands: one at  $\sim 1600$   $\text{cm}^{-1}$  and one at 1500–1430  $\text{cm}^{-1}$  (see the example of the IR spectrum of ethyl benzene in Figure 6.4e).

You will notice in Figures 6.3a and 6.3b that a region with a lower frequency of  $400\text{--}1400\text{ cm}^{-1}$  in the IR spectrum is called the fingerprint region. Similar to a human fingerprint, the pattern of absorbance bands in the fingerprint region is characteristic of the compound as a whole. Even if two different molecules have the same functional groups, their IR spectra will not be identical, and such a difference will be reflected in the bands in the fingerprint region. Therefore, the IR from an unknown sample can be compared to a database of IR spectra of known standards to confirm the identification of the unknown sample.

## 6.4 IR Spectrum Interpretation Practice

Now, let's take a look at the IR spectrum for examples. It is very important to keep in mind that we generally do not try to identify all the absorption bands in an IR spectrum. Instead, we will look at the characteristic absorption band to confirm the presence or absence of a functional group. An IR spectrum usually does not provide enough information for us to determine the complete structure of a molecule, and other instrumental methods have to be applied in conjunction, such as NMR, which is a more powerful analytical method to give more specific information about molecular structures that we will learn about in later sections.

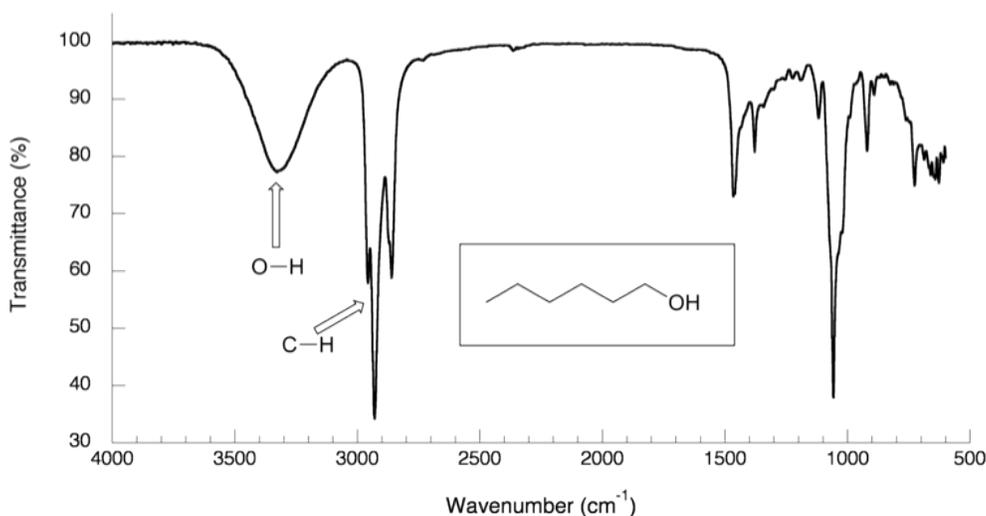


Figure 6.4a IR Spectrum of 1-hexanol

In the IR spectrum of 1-hexanol in Fig. 6.4a, there are  $sp^3$  C-H stretching bands of alkane at about  $2800\text{--}3000\text{ cm}^{-1}$  as expected. Other than that, there is a very broad peak centered at about  $3400\text{ cm}^{-1}$  which is the characteristic band of the O-H stretching mode of alcohols.

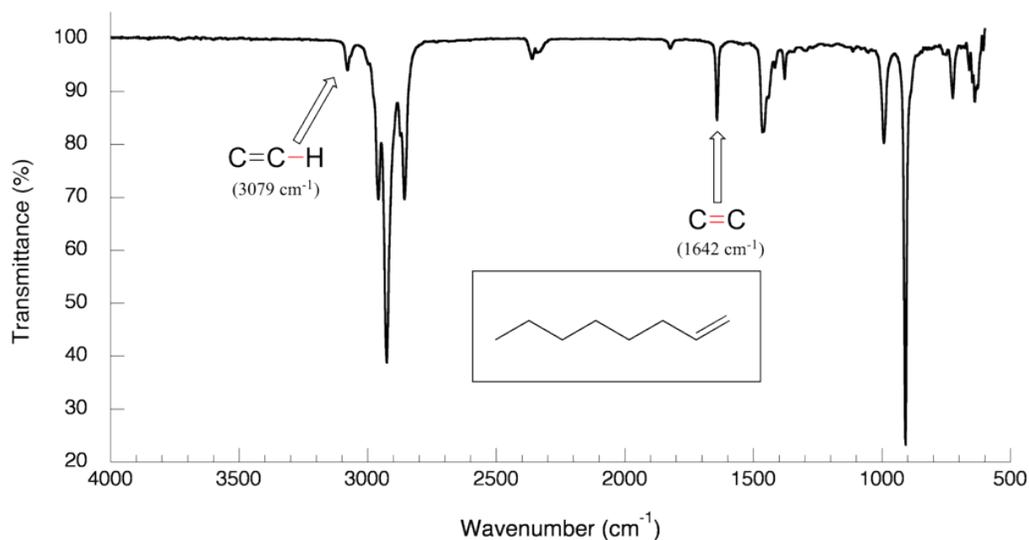


Figure 6.4b IR Spectrum of 1-octene

The spectrum for 1-octene (Fig. 6.4b) shows two bands that are characteristic of alkenes: the one at 1642 cm<sup>-1</sup> is due to stretching of the carbon-carbon double bond, and the one at 3079 cm<sup>-1</sup> is due to stretching of the  $\sigma$  bond between the sp<sup>2</sup>-hybridized alkene carbons and their attached hydrogens.

The following IR spectra are taken from Spectral Database for Organic Compounds, a free organic compounds spectral database. The key bands for each compound are labeled on the spectra.

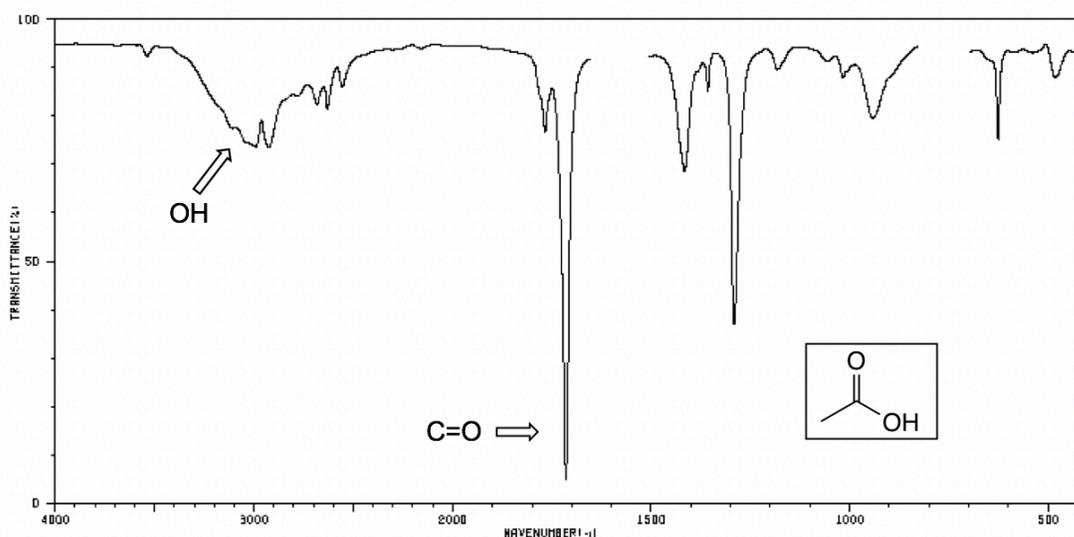


Figure 6.4c IR Spectrum of acetic acid

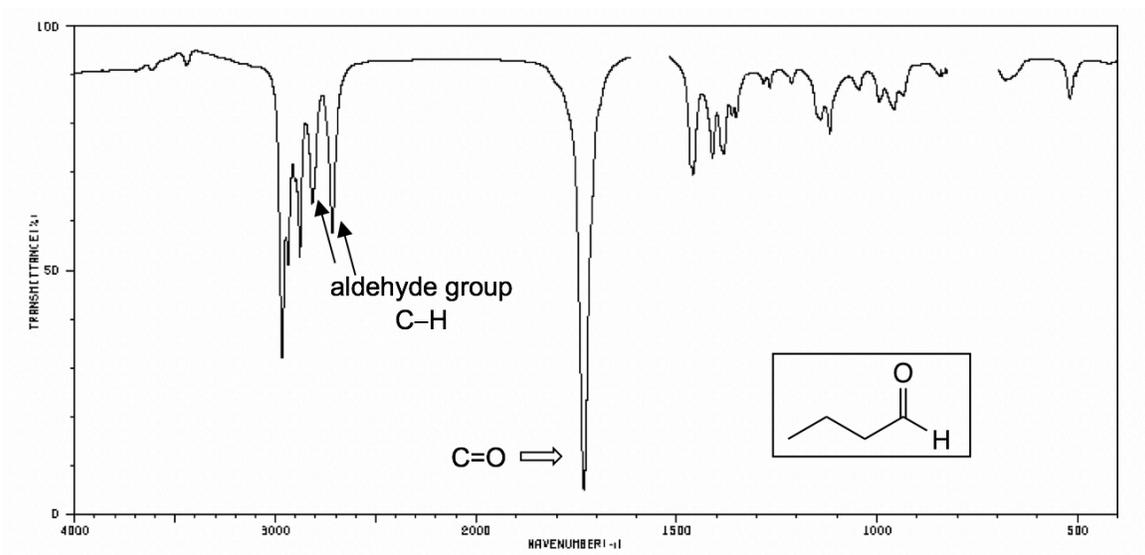


Figure 6.4d IR Spectrum of butanal

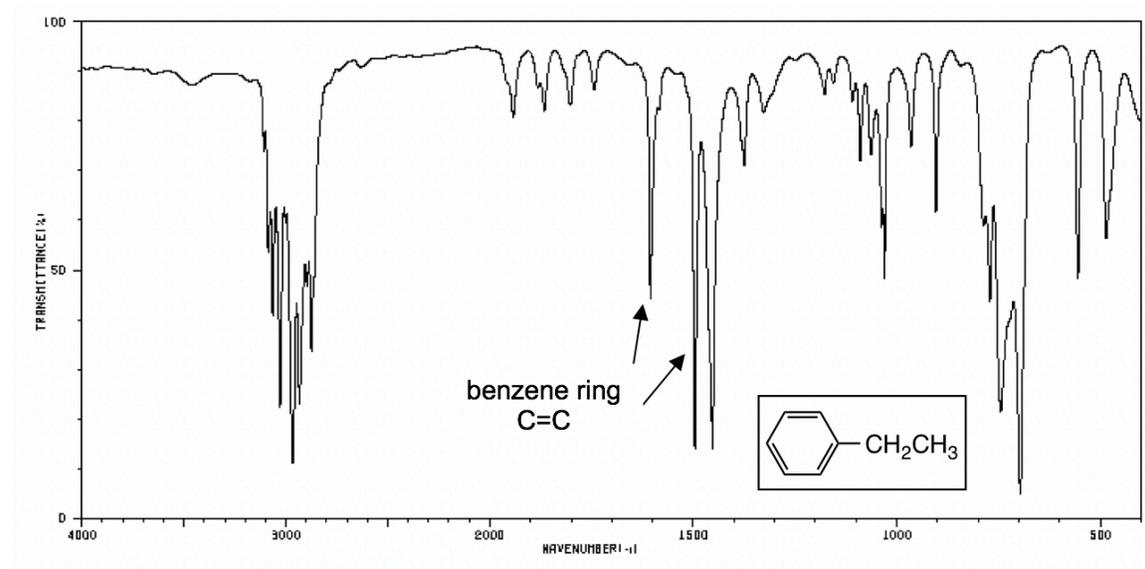


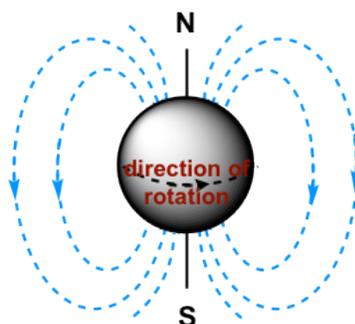
Figure 6.4e IR Spectrum of ethyl benzene

## 6.5 NMR Theory and Experiment

Although the other techniques provide valuable information about a molecule, they do not tell us about the overall molecular structure or the framework of C-C and C-H bonds. Nuclear magnetic resonance (NMR) spectroscopy is an immensely powerful analytical technique that provides such information. NMR works by the same principles as a magnetic resonance imaging (MRI) scanner in hospitals. MRI is a scanning technique used to detect hidden medical problems without causing any harm or pain to the patient. While doctors use MRI to peer inside the human body, we will see how NMR allows organic chemists to piece together, atom by atom and bond by bond, the structure of an organic molecule.

### NMR-active Nuclei

The basis for NMR is a phenomenon in which some atomic nuclei spin about their axes and as a result, generate their own magnetic field or magnetic moment; these nuclei are called NMR-active. Not all nuclei have a magnetic moment though, as only nuclei with an odd number of protons and/or neutrons have one. Fortunately, nuclei that are important for organic compounds, such as the  $^1\text{H}$  isotope of hydrogen, the  $^{13}\text{C}$  isotope of carbon, the  $^{14}\text{N}$  isotope of nitrogen,  $^{19}\text{F}$  and  $^{31}\text{P}$  are all NMR-active and therefore can be observed by NMR. Other nuclei, such as the common  $^{12}\text{C}$  isotope of carbon and  $^{16}\text{O}$  isotope of oxygen, do not have magnetic moments and cannot be directly observed by NMR.



**the magnetic field associated with a spinning nucleus**

*Figure 6.5a The magnetic field*

In practice, the  $^1\text{H}$  and  $^{13}\text{C}$  nuclei are most commonly observed by NMR spectroscopy, and we will focus on these techniques in this chapter, beginning with  $^1\text{H}$  NMR.  $^1\text{H}$  NMR is usually called proton NMR because the nucleus of the  $^1\text{H}$  atom is actually a single proton. The words 'proton' and 'hydrogen' will be used interchangeably in this chapter for  $^1\text{H}$  NMR purposes.

### Spin State and Magnetic Resonance

We will take a proton, the nucleus of a  $^1\text{H}$  atom, as an example for the discussions here.

When a sample of an organic compound is sitting in a flask on a laboratory bench, the magnetic moments of all of its

protons are oriented randomly. However, when the same sample is placed within the field of a strong magnet in an NMR instrument (this field is referred to as the applied external magnetic field,  $B_0$ , in NMR), each proton will assume one of two possible orientations with respect to the external magnetic field. These two orientations correspond to the two spin states that can be labeled as  $\alpha$  and  $\beta$ . In the  $\alpha$  spin state, the proton's magnetic moment is aligned with the direction of the external magnetic field  $B_0$ , while in the  $\beta$  spin state, it is aligned as opposed to the direction of  $B_0$  (Fig. 6.5b).

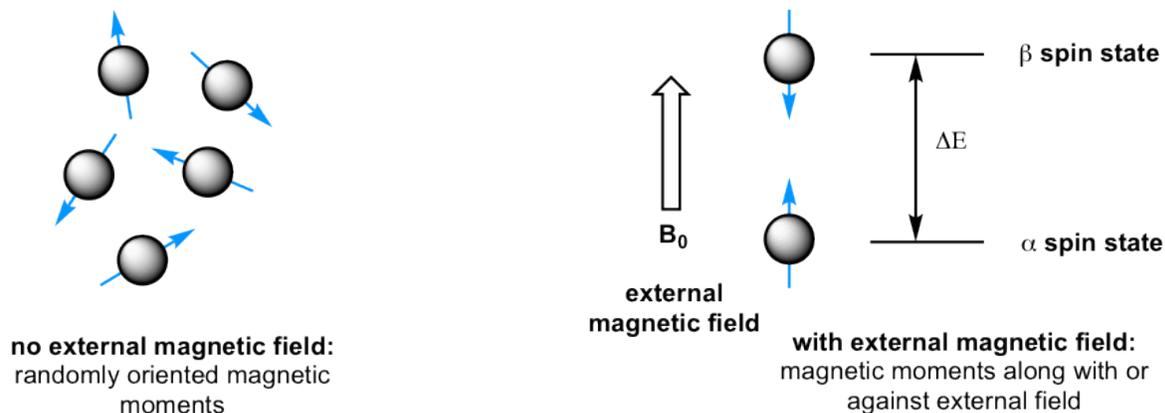


Figure 6.5b Orientations of magnetic moments of protons without and with external magnetic field

The  $\alpha$  spin state is slightly lower in energy than the  $\beta$  state, and the energy gap between them,  $\Delta E$ , depends upon the strength of  $B_0$ : a stronger applied external magnetic field results in a larger  $\Delta E$ . For a large population of organic molecules in an external magnetic field, slightly more than half of the protons will occupy the lower energy  $\alpha$  spin state, while slightly less than half will occupy the higher energy  $\beta$  spin state. It is this population difference between the two spin states that is exploited by NMR, and the difference increases with the strength of the applied magnetic field  $B_0$ .

Energy is required to excite the proton from the lower energy state ( $\alpha$  spin state) to the higher energy state ( $\beta$  spin state). In an NMR spectrometer, the energy is supplied by electromagnetic radiation in the radio frequency (RF) region. When a proton in an external magnetic field is exposed to RF radiation with the energy that matches the energy gap  $\Delta E$ , the energy of the RF is absorbed and the proton will flip its magnetic moment from the lower energy state ( $\alpha$  spin state) to the higher energy state ( $\beta$  spin state), and the nuclei are said to be in resonance with the electromagnetic radiation.

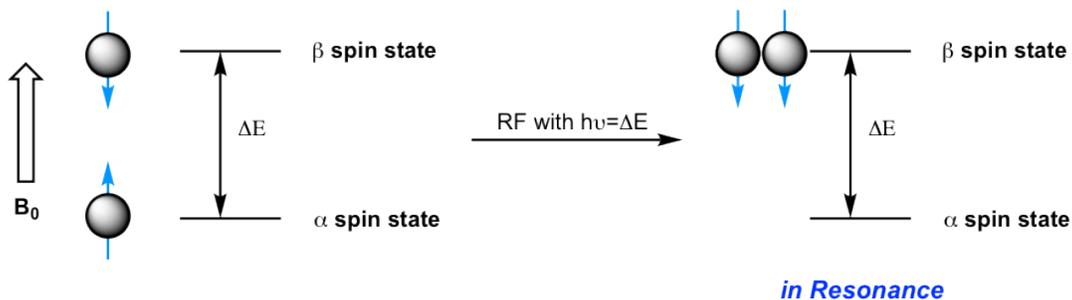


Figure 6.5c Resonance

The frequency of radiation absorbed by a proton (or any other nucleus) during a spin transition in an NMR experiment is called its resonance frequency,  $\nu$ . As a result, the resonance frequency also depends on  $B_0$ ; the larger the  $B_0$  the higher

the resonance frequency, and the relationship fits the specific formula (Formula 6.4 is for your information purposes only):

$$\nu = \frac{\gamma B_0}{2\pi} \quad \text{Formula 6.4}$$

$\gamma$  is the magnetogyric (or gyromagnetic) ratio, and different nuclei have different values of  $\gamma$ . For a proton, the  $\gamma$  value is  $26.753 \text{ rad} \cdot \text{s}^{-1} \cdot \text{tesla}^{-1}$ .

Calculations indicate that if an external magnetic field  $B_0 \approx 1.41$  Tesla, the energy difference corresponds to RF with the frequency of  $60 \times 10^6$  Hz (60 MHz) for a proton; when  $B_0 \approx 7.04$  Tesla, the corresponding RF frequency is  $300 \times 10^6$  Hz (300 MHz) for a proton. This frequency is the most important parameter for an NMR spectrometer (the instrument that runs NMR experiments); the higher the frequency, the more sensitive the instrument and the higher resolution the resulting NMR spectrum is.

## The NMR Experiment

In this book, we will explain how the NMR experiment and NMR spectrometer work in a simplified way (again with a proton as an example). The full version is outside the scope of this course.

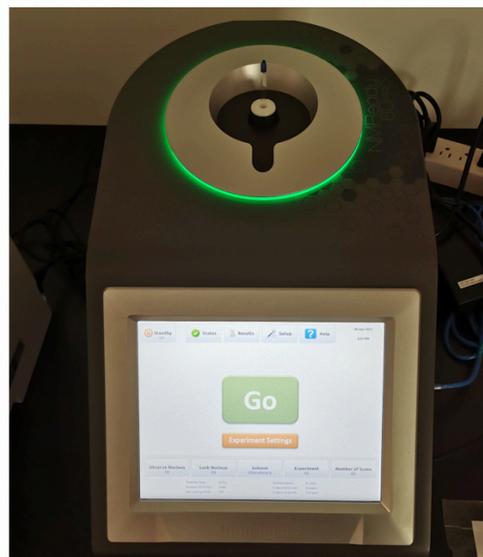
When a sample with a compound is placed in the strong external magnetic field  $B_0$  of the instrument, the protons begin to spin with one of the two spin states. Initially, slightly more than half of the protons have magnetic moments in a-spin states (aligned with  $B_0$ ), and slightly less than half are in b-spin states (aligned against  $B_0$ ). Then, the sample is exposed to a range of radio frequencies. Out of all of the frequencies that hit the sample, only the frequencies that match the resonance frequency of the protons are absorbed, causing those protons that are aligned with  $B_0$  to 'spin flip' so that they align themselves against  $B_0$ . When the 'flipped' protons flip back down to their ground state, they emit energy, again in the form of radio-frequency radiation. The NMR instrument detects and records the frequency and intensity of this radiation by making use of a mathematical technique known as a Fourier transform (FT). FT converts the signal from time versus amplitude signals to frequency versus amplitude signals, which is what we observe in an NMR spectrum.



Figure 6.5d Simplified diagrams to illustrate the NMR experiment

Most modern FT-NMR spectrometers use superconducting magnets that have very high magnetic fields and thus

operate with a high resonance frequency from 100 MHz to 800 MHz. Superconducting magnets operate in a bath of liquid nitrogen or liquid helium at a very low temperature.



**FT-NMR with superconducting magnet**

**A model of bench top NMR: NMReady-60**

Figure 6.5e FT-NMR with superconducting magnet and a model of benchtop NMR: NMReady-60

Despite the high power and resolution of high-frequency NMR spectrometers, the purchase and maintenance of the instrument are very costly. For teaching purposes, the benchtop NMR is becoming more and more popular. The frequency of a benchtop NMR is usually in the range of 60–90 MHz; however, it can provide spectra with good resolution for many basic organic structures used for undergraduate organic chemistry classes. With a low-cost benchtop NMR available, students have the chance to gain hands-on NMR experience in sample preparation, instrument operation and spectrum processing.

## Shielding and Deshielding

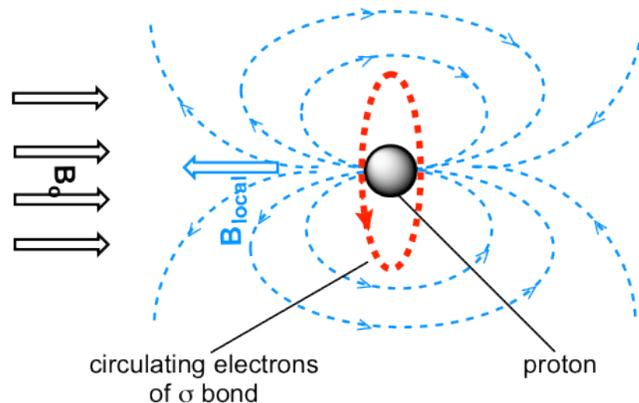
If all hydrogen atoms (and protons) in organic molecules had the same resonance frequency, then they would all show the same signal, and NMR spectroscopy would not be that useful for chemists. Fortunately, resonance frequencies are different for different protons in a molecule. Specifically, the resonance frequency varies according to the electronic environment a given proton inhabits.

For hydrogen atoms in any bonds, such as C-H, O-H, etc., the external magnetic field  $B_0$  causes the s electrons to circulate in a way that generates an induced local magnetic field ( $B_{local}$ ) at the proton, and the direction of the local field  $B_{local}$  is opposite to the external field  $B_0$ . The proton thus experiences a net magnetic field, which is called  $B_{eff}$  that is smaller than the applied magnetic field:

$$B_{eff} = B_0 - B_{local}$$

As a result, the proton responds to a lower frequency (resonance frequency is proportional to the magnetic field as mentioned earlier). This  $B_{local}$ , to a small but significant degree, shields the proton from experiencing the full force of

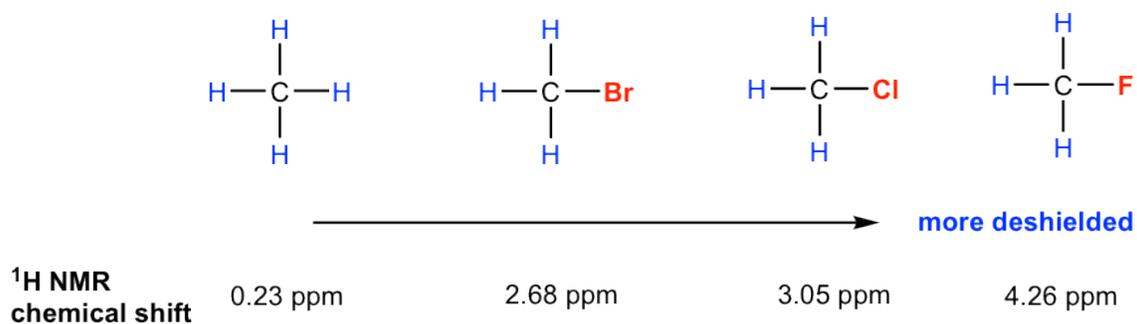
$B_0$ , so this effect is called the shielding effect. Different hydrogen atoms in organic structures are in different electronic environments and have different electron densities, so they have different  $B_{\text{local}}$  and different  $B_{\text{eff}}$  as well. That is why different hydrogens (and protons) are in different resonance frequencies and show different signals in the spectrum.



**Shielding effect:  $B_{\text{local}}$  generated by the circulation electrons of  $\sigma$  bond shield the proton from the external magnetic field  $B_0$ .**

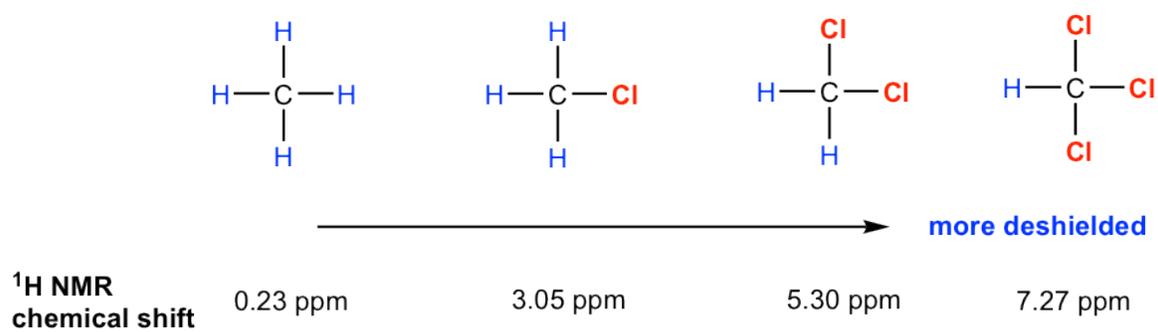
Figure 6.5f Shielding effect

For hydrogen atoms close to electronegative groups, electronegative groups withdraw electron density from nearby atoms, thereby diminishing the shielding of the protons by circulating electrons. The hydrogen atoms near electronegative groups are said to be deshielded from the external magnetic field and have a higher resonance frequency than shielded protons. As the EN of the substituent increases, so does the extent of the deshielding effect (and so the chemical shift, see section 6.6.2 for further discussion about the chemical shift) as shown in the examples below.



**H atoms get more deshielded with electronegativity of substituent increase**

Figure 6.5g H atoms get more deshielded with electronegativity of substituent increase



**H atoms get more deshielded with more electronegative substituents involved**

Figure 6.5h H atoms get more deshielded with more electronegativity substituents involved

## 6.6 $^1\text{H}$ NMR Spectra and Interpretation (Part I)

Understanding the basics of NMR theory gets us ready to move on to the most important and practical part of this section, which is how to understand the  $^1\text{H}$  NMR spectrum and elucidate the structure of a compound from  $^1\text{H}$  NMR spectrum information. Let's first take a look at an actual  $^1\text{H}$  NMR spectrum, the spectrum of methyl acetate in Fig. 6.6a.

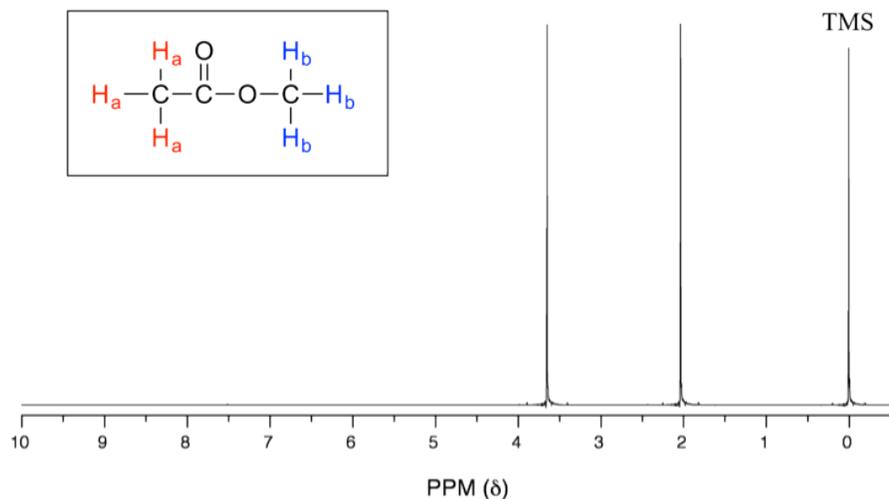


Fig. 6.6a The  $^1\text{H}$  NMR spectrum of methyl acetate

Generally, information about the structure of a molecule can be obtained from four aspects of a typical  $^1\text{H}$  NMR spectrum:

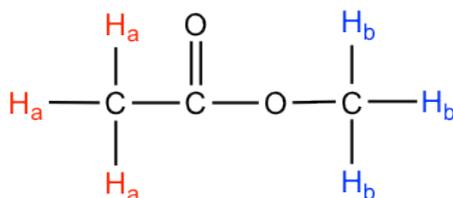
- Chemical equivalent and non-equivalent protons (total number of signals)
- Chemical shift
- Integration
- Signal splitting

### 6.6.1 Chemical Equivalent and Non-Equivalent Protons

In the above  $^1\text{H}$  NMR spectrum of methyl acetate (Fig. 6.6a), we can see that there are three signals. The peak at the far right is for the standard reference compound tetramethylsilane (TMS, which is further discussed in the chemical shift section 6.6.2), not for the compound. So, the compound methyl acetate shows two signals in the  $^1\text{H}$  NMR spectrum. Why are there only two signals for a compound containing a total of six hydrogens?

This is because of chemical equivalence. The six hydrogens can be divided into two groups, the three  $\text{H}_a$  protons in the methyl group that bonded with  $\text{C}=\text{O}$  are all in the same chemical environment, so they are chemical equivalent. All chemical equivalent hydrogens have the same resonance frequency when applied to an external magnetic field, so they show only one signal in the  $^1\text{H}$  NMR spectrum. The three  $\text{H}_b$  protons in the methyl group bonded with the O atom

are chemical equivalent as well and show the other signal. That is why there are two signals for the compound methyl acetate.



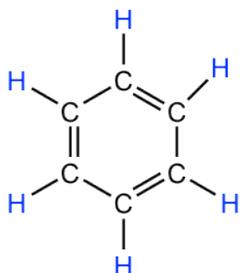
the three  $\text{H}_a$ s are  
chemical equivalent

the three  $\text{H}_b$ s are  
chemical equivalent

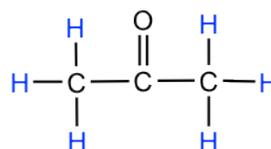
The ability to recognize chemical equivalent and non-equivalent protons in a molecule is very important to understanding the NMR spectrum. For the compound with the structure given, we should be able to predict how many signals there are in the  $^1\text{H}$  NMR spectrum. On the other hand, if the  $^1\text{H}$  NMR spectrum is available for an unknown compound, counting the number of signals in the spectrum tells us the number of different sets of protons in the molecule, and that is very important information for determining the structure of the compound.

Here, we will go through several examples for the first situation, which is to predict the number of signals in the  $^1\text{H}$  NMR spectrum with the structure of a compound given. To do that, we need to count how many distinct proton sets are included in the molecule.

For each of the following molecules, the chemically equivalent protons are labeled in the same color to facilitate understanding.



benzene

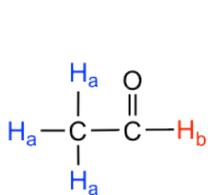


acetone

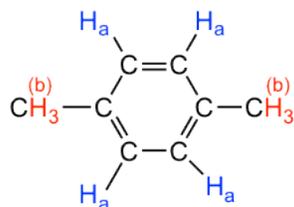
- Benzene: all six protons are chemical equivalent (have the same bonding and are in the same chemical environment) to each other and have the same resonance frequency in a  $^1\text{H}$  NMR experiment; therefore, they show only one signal.
- Acetone: both methyl groups (two  $\text{CH}_3$ ) bonded with a  $\text{C}=\text{O}$  bond, so they are in the same chemical environment, and as a result, all six protons are chemical equivalent and show only one signal.

Notes: As you have probably already realized, chemical equivalence or non-equivalence in NMR is closely related to symmetry. Protons that are symmetric to each other by a certain plane of symmetry are chemical equivalent.

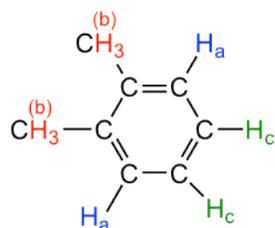
The molecules in the next figure contain more sets of chemically equivalent protons.



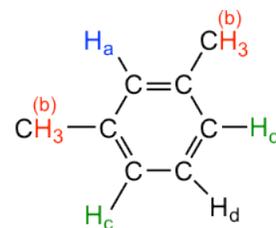
acetaldehyde



1,4-dimethylbenzene



1,2-dimethylbenzene

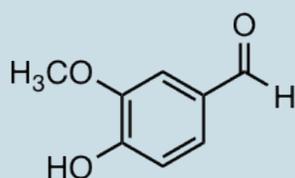
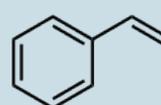
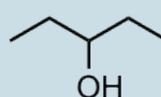
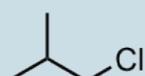


1,3-dimethylbenzene

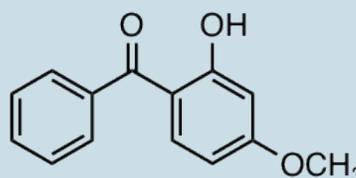
- Acetaldehyde: The three  $H_a$  protons in the methyl group are chemical equivalent, and they all bonded to an  $sp^3$ -hybridized carbon; but they are different from the  $H_b$  proton that is bonded to an  $sp^2$ -hybridized carbonyl carbon. There are two total signals in the  $^1H$  NMR spectrum.
- 1,4-dimethylbenzene: all four aromatic protons are chemically equivalent because of the symmetry. The two methyl groups are equivalent to each other as well. There are two signals in total in the  $^1H$  NMR spectrum.
- 1,2-dimethylbenzene: both  $H_a$  protons are adjacent to a methyl substituent, while both  $H_c$  protons are two carbons away. So, the four aromatic protons are divided into *two* sets. Both methyl groups are in the same bonding and are symmetric to each other; they are equivalent. There are three signals in total in the  $^1H$  NMR spectrum.
- 1,3-dimethylbenzene:  $H_b$  is situated between two methyl groups, the two  $H_c$  protons are one carbon away from a methyl group, and  $H_d$  is two carbons away from a methyl group. Therefore, the four aromatic protons can be divided into *three* sets. The two methyl groups are equivalent. There are four signals in total in the  $^1H$  NMR spectrum.

### Exercises 6.1

How many  $^1H$  NMR signals would you predict for each of the following molecules?



vanillin



oxybenzone

## 6.6.2 Chemical Shift

As seen in the  $^1\text{H}$  NMR spectrum of methyl acetate (Fig. 6.6a), the x-axis units of the NMR spectrum are in ppm (not in Hz, as we would expect for frequency), and the two signals stand at different positions along the x-axis. Let's explain how that works and what information can be obtained.

The position of a signal along the x-axis of an NMR spectra is called the chemical shift, or  $\delta$ , of the signal. Chemical shift is determined by the structural electronic environment of the nuclei producing that signal. Protons in different chemical environments (non-equivalent) show signals at different chemical shifts. The *direction* of the chemical shift scale in the x-axis is opposite to what we are familiar with; that is, the smaller value is at the right-hand side, and the larger value is at the left-hand side (Fig. 6.6b).

- Smaller chemical shift ( $\delta$ ) values correspond with a lower resonance frequency.
- Larger chemical shift ( $\delta$ ) values correspond with a higher resonance frequency.

By convention, the right-hand side of an NMR spectrum with smaller chemical shift values is called upfield, and the left-hand direction is called downfield (Fig. 6.6b).

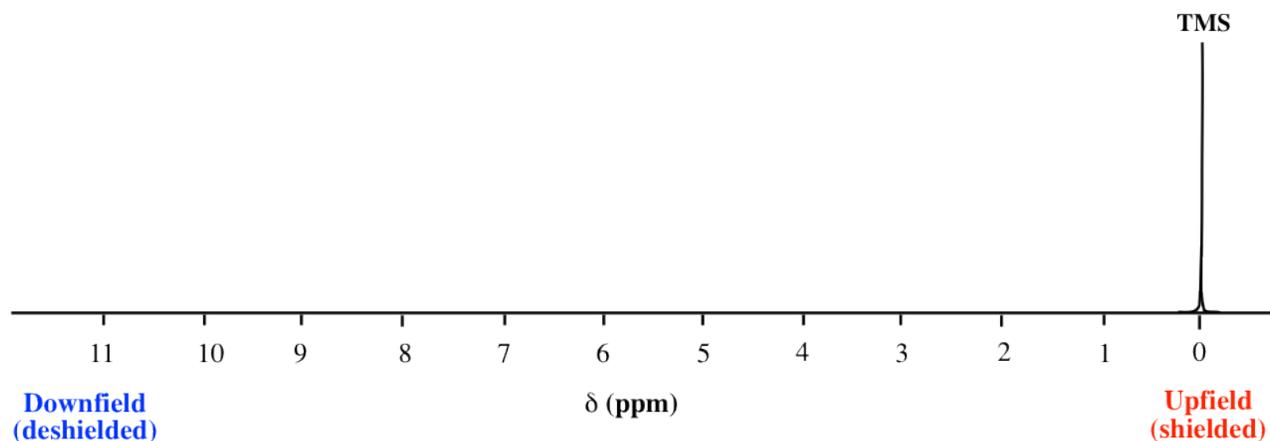


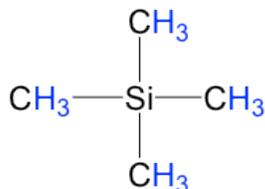
Figure 6.6b The chemical shift scale in  $^1\text{H}$  NMR spectra

For protons that are shielded, because of the  $B_{\text{local}}$  caused by circulating electrons, the magnetic field experienced by the proton,  $B_{\text{eff}}$ , is smaller than the applied external field,  $B_0$ , so the protons have a lower resonance frequency and have smaller chemical shift values.

- Shielded protons have a lower resonance frequency and smaller chemical shift ( $\delta$ ) values.
- Deshielded protons have a higher resonance frequency and larger chemical shift ( $\delta$ ) values.

In the  $^1\text{H}$  NMR spectrum, the absorption of the protons of TMS (tetramethylsilane) is defined as “zero” on the chemical shift ( $\delta$ ) scale, and the absorption of other protons is reported as a relative shift compared with that of TMS.

TMS was chosen as a reference compound and defined as “zero” for several reasons. Since silicon is less electronegative than carbon, the hydrogens of TMS are in a high electron-density environment; therefore, they are highly shielded with a very low resonance frequency and rarely interfere with the signals of other compounds. Also, there are twelve equivalent hydrogens in TMS that show a single signal, so the signal is strong, even with a very small amount of TMS. TMS is also quite inert and easy to be removed with a b.p. of  $27^\circ\text{C}$ . A small amount of TMS was added in the sample as an internal standard for NMR measurement and removed by evaporation afterwards. However, for a contemporary NMR spectrometer (including a benchtop NMR), it is no longer necessary to actually add TMS since the computer can calibrate the chemical shift electronically based on the resonance frequencies of the solvent used.



**tetramethylsilane (TMS)**

The unit of chemical shift ( $\delta$ ) is ppm. The ‘ppm’ label stands for ‘parts per million’. The chemical shift relative to TMS in ppm is defined as the formula below.

$$\delta = \frac{\text{distance of peak from TMS in Hz}}{\text{spectrometer frequency in MHz}}$$

The reason for using a relative value of chemical shift in ppm rather than the actual resonance frequency in Hz is that every NMR instrument will have a different magnetic field strength, so the actual value of resonance frequencies expressed in Hz will be different on different instruments – remember that the  $\Delta E$  for the magnetic transition of a nucleus depends upon the strength of the externally applied magnetic field  $B_0$ . However, the chemical shift expressed in ppm will always be the same whether measured with an instrument operating at 400 MHz or 60 MHz. In the  $^1\text{H}$  NMR of methyl acetate, the two signals are at 2.0 and 3.6 ppm and represent the two sets of protons in methyl acetate that have resonance frequencies of about 2.0 and 3.6 parts per million higher than the resonance frequencies of the TMS protons. If, for example, the spectrum is measured by the 400-MHz NMR spectrometer, then the chemical shift in Hz will be 800 Hz and 1440 Hz, respectively.

Most protons in organic compounds have chemical shift values between 0 and 12 ppm relative to TMS, though values below 0 ppm and above 12 ppm are occasionally observed. The chemical shift value of hydrogens in a certain structural environment or common organic functional groups is listed in the chart (Fig. 6.6c) and table (Table 6.2) below.

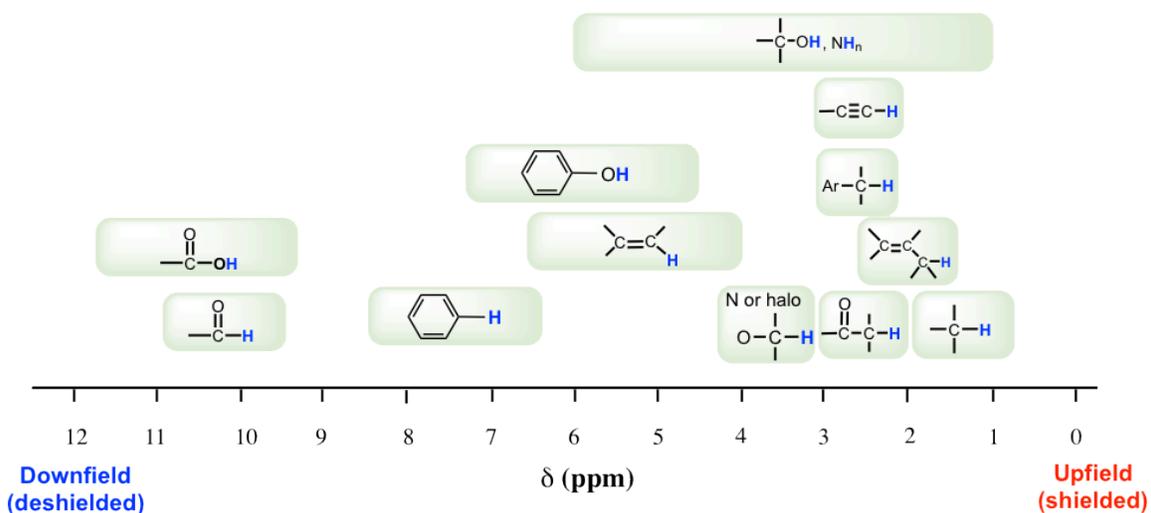


Figure 6.6c Chart of Approximate proton chemical shifts

Type of Proton	Chemical Shift (ppm)	Type of Proton	Chemical Shift (ppm)
R-CH <sub>3</sub>	0.9 – 1.2	X-CH <sub>2</sub> R (X: Cl, Br, I)	3.1 – 3.8
R-CH <sub>2</sub> -R	1.2 – 1.5	R-OH	variable, 1 – 5
R-CH-R	1.4 – 1.9	R-NH <sub>2</sub>	variable, 1 – 5
R <sub>2</sub> C=CHR <sub>2</sub>	1.5 – 2.5	R <sub>2</sub> C=CH-R	4.5 – 6.0
R-C(=O)-CH <sub>3</sub>	2.0 – 2.6	Ar-H	6.0 – 8.5
Ar-CH <sub>3</sub>	2.2 – 2.5	R-C(=O)-H	9.5 – 10.5
R-C≡C-H	2.5 – 3.0	R-C(=O)-OH	10 – 13
(H)R-O-CH <sub>3</sub>	3.3 – 4.0		

Table 6.2 Approximate Proton Chemical Shifts of Common Functional Groups

The importance of chemical shift information is that it gives critical clues about molecular *structures*. Several highlights should be noted:

- Usually, the hydrogens in a C-H bond, without any other functional groups nearby, are in the range of 1–2 ppm;
- for hydrogen in a C-H bond besides a double bond, like a C=C or C=O bond, the signal goes downfield to 2–2.5 ppm;
- with electronegative atoms connected on the carbon, like O-C-H, the hydrogens get deshielded and the chemical shift moves further downfield to 3–4 ppm;
- the hydrogens bonded directly to double bond carbon have a chemical shift at around 4.5–6 ppm;
- the aromatic hydrogens (H on the benzene ring) show a chemical shift of around 7 ppm;
- the chemical shift of hydrogens in the OH (alcohol) or NH (amine) group varies in a large range, from 1–5 ppm; and
- the hydrogen in the aldehyde (-CHO) and carboxylic acid (COOH) group has a chemical shift rather downfield at about 9–10 ppm and 10–12 ppm, respectively.

When referring to the chemical shift table (or chart) for a certain compound, it is useful to keep in mind that the exact value may vary to the given range, and sometimes a difference up to 0.5 ppm unit may happen depending on the specific structure and the solvent used.

With chemical shift information available, we can now assign the signals in the  $^1\text{H}$  NMR spectrum of methyl acetate. According to Fig. 6.6c, the protons in the  $\text{CH}_3$  group beside the  $\text{C}=\text{O}$  bond are supposed to be in the range of 2–3 ppm, and protons in the  $\text{CH}_3$  group connected with O directly have  $\delta$  value of about 3–4 ppm. So, the 2.0-ppm signal is for the  $\text{H}_a$  group, and the 3.6-ppm signal is for the  $\text{H}_b$  group.

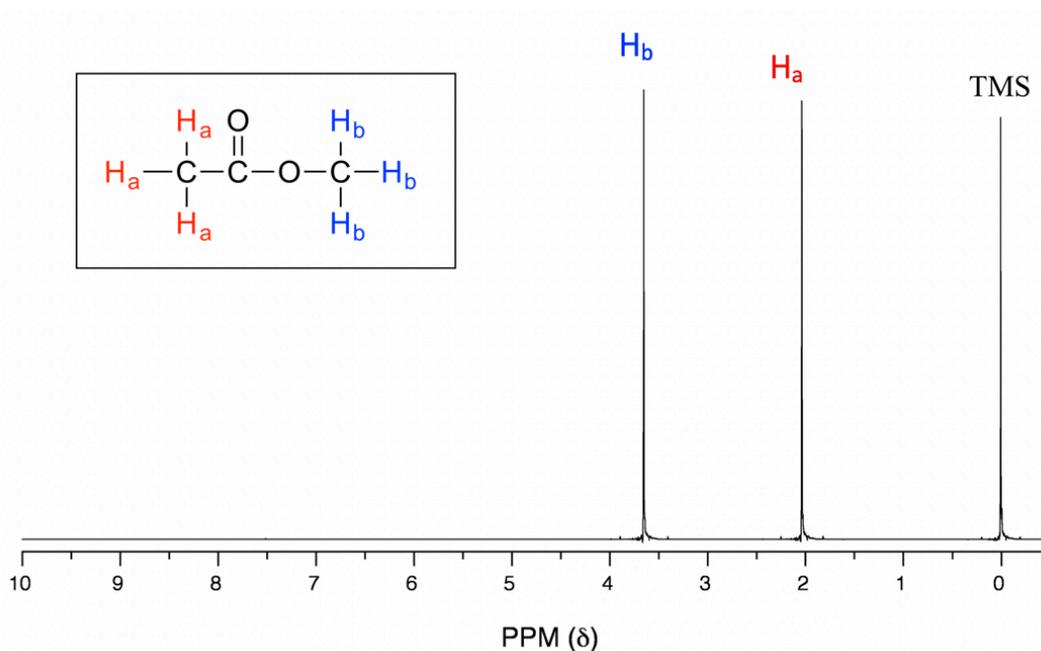
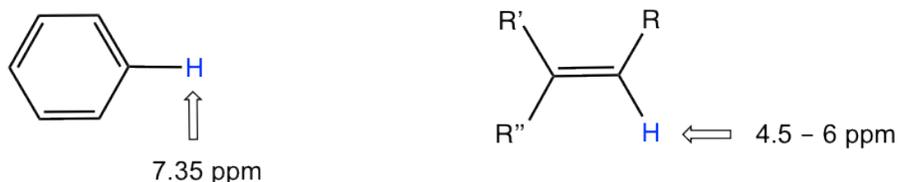


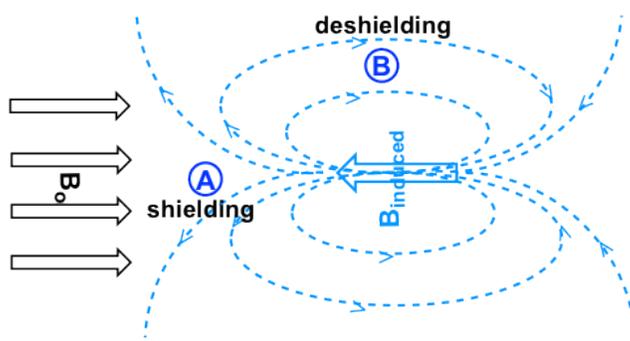
Fig. 6.6d The  $^1\text{H}$  NMR spectrum of methyl acetate with signals assignment

## Chemical Shift of Protons Near $\pi$ Electrons — Anisotropy Effect

The chemical shift values of aromatic protons and vinylic protons (those directly bonded to an alkene carbon) resonate much further downfield (higher frequency, higher chemical shift) than can be accounted for simply by the deshielding effect of nearby electronegative atoms. These chemical shifts result from the anisotropy effect.



Let's investigate the aromatic protons first. In a benzene ring (and many other aromatic structures), a total of six  $\pi$  electrons form a delocalized big  $\pi$  bond around the ring (further discussion in Organic II). When the molecule is exposed to the external magnetic field  $B_0$ , these  $\pi$  electrons begin to circulate in a ring current and generate their own induced magnetic field,  $B_{\text{induced}}$ . Whether shielding or deshielding occurs depends on the *location* of the protons in the induced magnetic field, and this is called an anisotropy (means "non-uniformity") effect. This can be illustrated specifically in Fig. 6.6e below by comparing between points A and B.

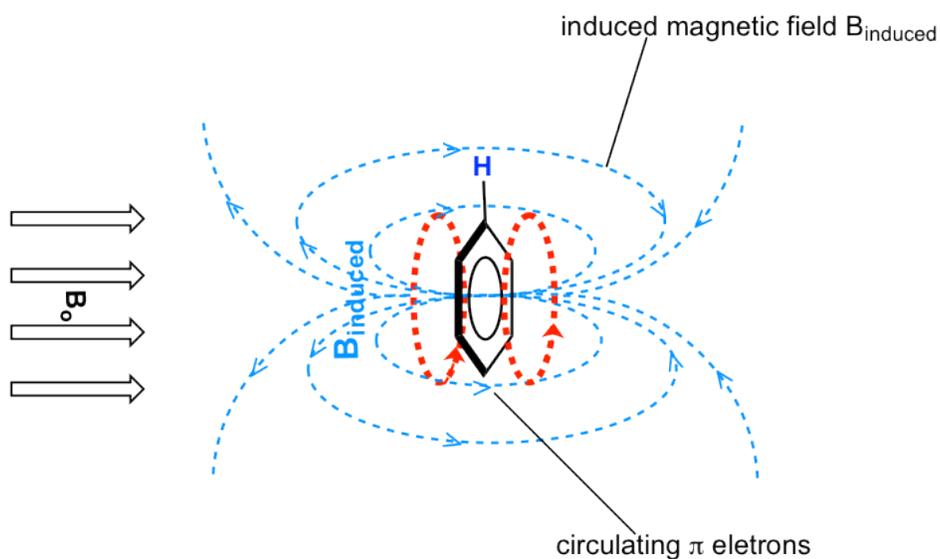


### Anisotropy effect of the induced magnetic field $B_{\text{induced}}$

Figure 6.6e Anisotropy effect of the induced magnetic field  $B_{\text{induced}}$

If a proton is at point A, it feels the induced magnetic field pointing to the opposite direction of  $B_0$ , so the proton experiences a shielding effect. For the proton at point B, however, it feels the induced magnetic field to the same direction as  $B_0$ , so the proton experiences a deshielding effect.

The protons on a benzene ring are at the position equivalent of 'point B', which means the induced current in this region of space is oriented in the same direction as  $B_0$ , so it adds to  $B_0$  and results in a deshielding effect and the benzene protons resonate at a higher frequency and has larger chemical shifts.

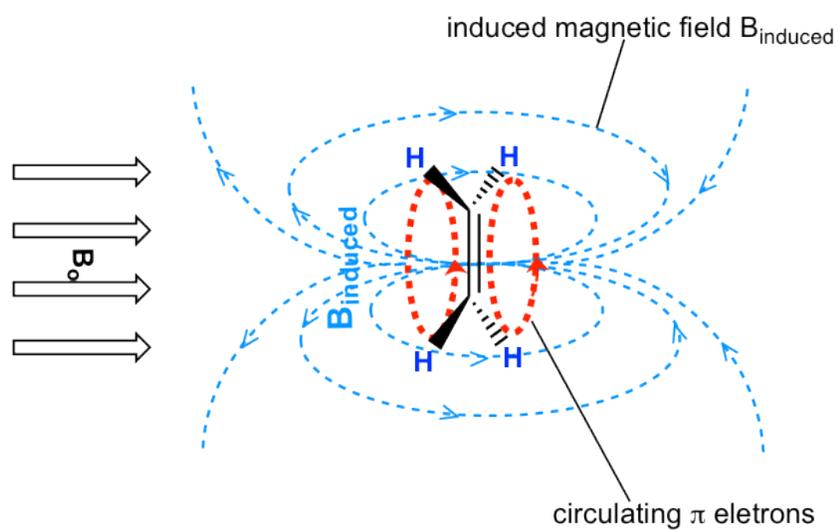


**Anisotropy Effect of Benzene ring:**  
 aromatic protons are at the location with **deshielding effect**, where the  $B_{\text{induced}}$  is in the same direction as the  $B_0$

*Figure 6.6f Anisotropy effect of Benzene ring: aromatic protons are at the location with deshielding effect, where the  $B(\text{induced})$  is in the same direction as the  $B(O)$*

As a result, due to the anisotropy of the induced field generated by the circulating  $\pi$  electrons, the benzene protons are highly deshielded. Their chemical shift is far downfield, in the range of 6.5–8.5 ppm.

Anisotropy is also responsible for the downfield (high frequency) chemical shifts of vinylic protons (4–6.5 ppm) and aldehyde protons (9.5–11 ppm). The  $\pi$  electrons in these groups also circulate in such a way to generate an induced magnetic field that adds to the external field  $B_0$  in the spots occupied by the protons. Carboxylic acid protons are even further downfield (9.5–12 ppm) due to the combined influence of the electronegative oxygen atom and the nearby  $\pi$  bond.



**Anisotropy Effect of Alkene:**

vinyllic protons are at the location with **deshielding effect**, where the  $B_{\text{induced}}$  is in the same direction as the  $B_0$

Figure 6.6g Anisotropy Effect of Alkene: Vinyllic protons are at the location with deshielding effect, where the  $B_{\text{induced}}$  is in the same direction as the  $B_0$

## 6.7 $^1\text{H}$ NMR Spectra and Interpretation (Part II)

### 6.7.1 Integration of Signal Areas

The computer in the NMR instrument can be instructed to mathematically integrate the area under a signal or group of signals. The signal integration process is very useful in the  $^1\text{H}$  NMR spectrum because the area under a signal is proportional to the number of protons to which the signal corresponds.

Fig. 6.7a shows the  $^1\text{H}$  NMR spectrum of 1,4-dimethylbenzene with an integration line (blue lines). The integration line generated by the computer is always in a curved shape that resembles steps. The integration numbers are also generated by the computer together with the curve, which shows the relative area of each signal (the integration numbers in the actual spectra are usually with decimals, but whole numbers are shown here for simplicity).

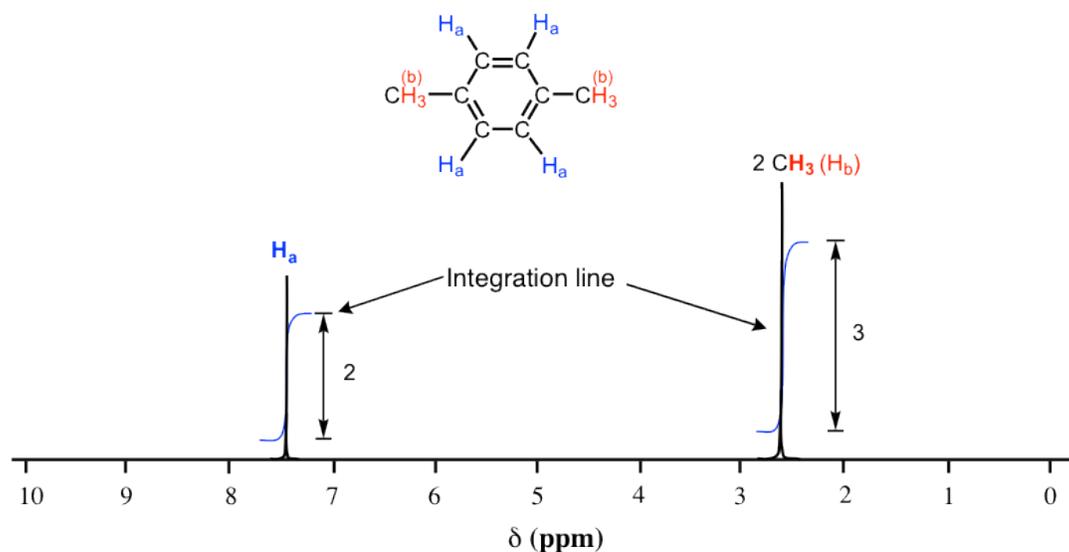


Figure 6.7a The  $^1\text{H}$  NMR spectrum of 1,4-dimethylbenzene with integration

As we discussed earlier, the molecule of 1,4-dimethylbenzene has two sets of equivalent protons: the four aromatic ( $\text{H}_a$ ) protons and the six methyl ( $\text{H}_b$ ) protons. The integration of the area under the peak at 2.6 ppm is 1.5 times greater than the area under the peak at 7.4 ppm. Please note that the integration number shows the relative ratio of the number of protons, not the actual number. The ratio of 3 to 2 here matches the ratio of the actual number 6 to 4. This integration information, along with the chemical shift knowledge we have learned before allows us to assign the peaks: the peak at 7.4 ppm corresponds to protons ( $\text{H}_a$ ) on the benzene ring, and the peak at 2.6 ppm corresponds to two methyl groups ( $\text{H}_b$ ).

### 6.7.2 Signal Splitting (Coupling)

In the  $^1\text{H}$  NMR spectra we have seen so far, each set of protons generates a single NMR signal. This is not that common for  $^1\text{H}$ NMR. In fact, the  $^1\text{H}$  NMR spectra of most organic molecules contain signals that are 'split' into two or more peaks,

which is called splitting (or coupling). The spectra with peak splitting may look more complicated, but this splitting behavior provides very useful information about the structure of a compound.

Let's consider the spectrum for 1,1,2-trichloroethane (Fig. 6.7b). In this and in other spectra to follow, the expansions of individual signals are shown so that the splitting patterns are recognizable.

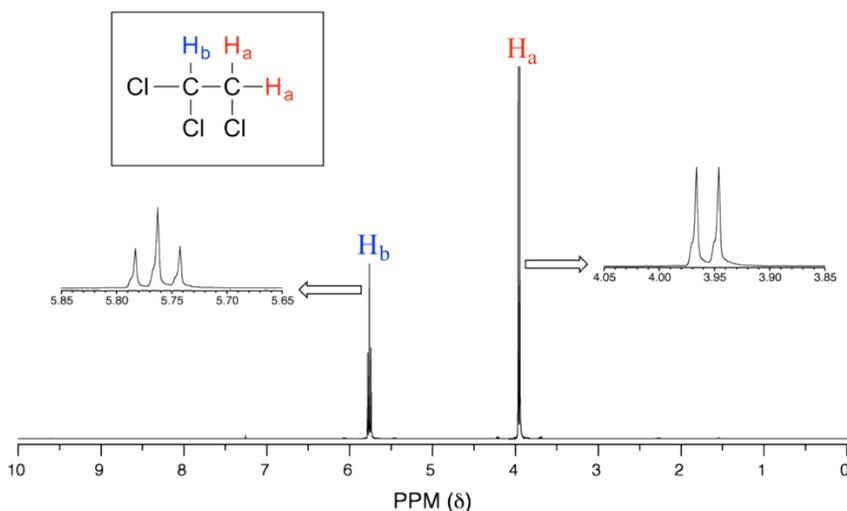
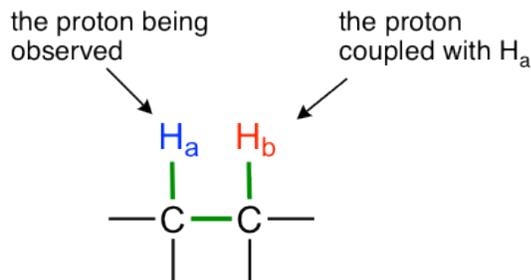


Fig. 6.7b The  $^1\text{H}$  NMR spectrum of 1,1,2-trichloroethane with signal splitting

The signal at 3.96 ppm, corresponding to the two  $\text{H}_a$  protons, is split into two peaks of equal height (and area) – this is referred to as a doublet. The  $\text{H}_b$  signal at 5.76 ppm, on the other hand, is split into three peaks, with the middle peak higher than the two outside peaks, and the integration ratio between the three peaks is 1:2:1. Such a splitting signal is called a triplet.

Signal splitting is caused by spin-spin coupling, a term that describes the magnetic interactions between non-equivalent hydrogen atoms that are separated by 2 or 3  $\sigma$  bonds. The nearby protons have a magnetic moment that can be either against or with the external magnetic field; therefore, the energy levels of the protons whose signal is being observed are split, and this results in the splitting of the signal into multiple peaks (the terms 'splitting' and 'coupling' are often used interchangeably when discussing NMR).

The most typical coupling we observed in this course is from non-equivalent vicinal hydrogens that are 3 bonds away, that is the hydrogens on adjacent carbons. This is also called vicinal coupling or three-bond coupling.



**Vicinal Coupling:**

$\text{H}_b$  is 3-bond away from  $\text{H}_a$ , and causes splitting of the signal for  $\text{H}_a$

Figure 6.7c Vicinal Coupling

A simple rule that applies for predicting the number of peaks (or splitting pattern) expected from coupling and the rule in  $^1\text{H}$  NMR is:

$$\text{number of peaks} = n + 1$$

( $n$  is the number of vicinal non-equivalent hydrogens)

We will examine the splitting pattern with a different number of  $n$ :

- When  $n=0$ , the signal is a singlet, or has only one peak, such as the signals observed in Fig. 6.6d and Fig. 6.7a.
- When  $n=1$ , the signal is a doublet with two peaks. The area ratio of the two peaks for a doublet is 1:1. The space between the two peaks is called the coupling constant,  $J_{ab}$ , which is measured in Hz.

For the example of compound 1,1,2-trichloromethane, the signal of  $\text{H}_a$  protons fits into this situation. With only one vicinal proton,  $\text{H}_b$ , on the adjacent carbon, the signal of  $\text{H}_a$  shows as a doublet.

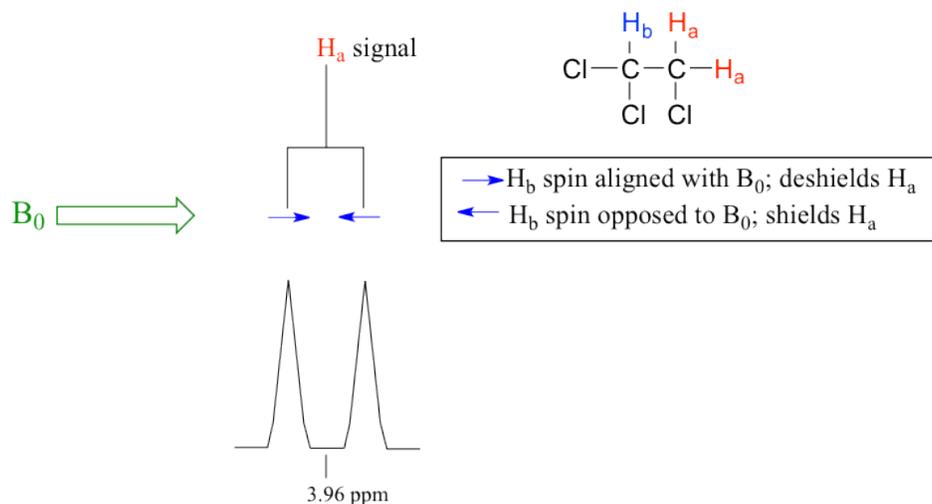
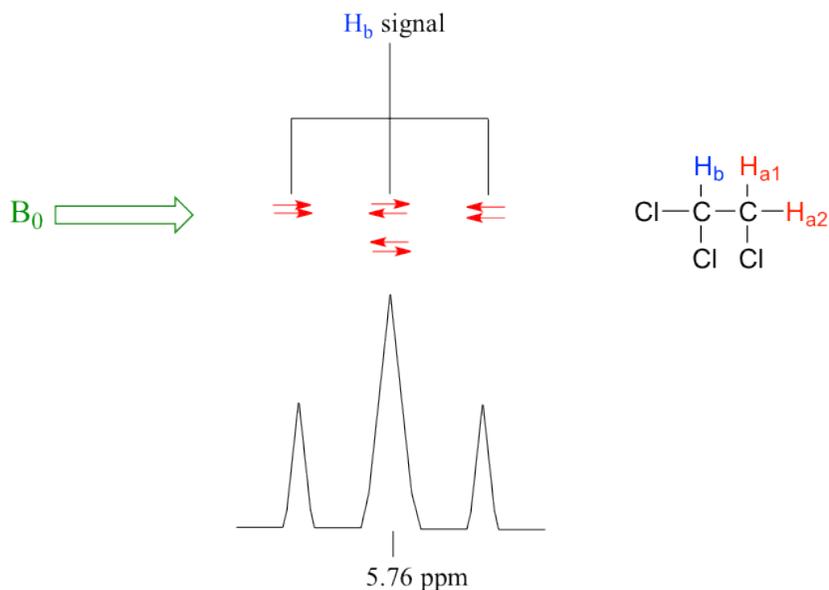


Figure 6.7d 1,1,2-trichloromethane

- When  $n=2$ , the signal is a triplet with three peaks. The three peaks of the triplet have a ratio of the area of 1:2:1.

In the same compound 1,1,2-trichloromethane, the signal of the  $\text{H}_b$  proton fits into this situation. With two vicinal protons,  $2\text{H}_a$ , on the adjacent carbon, the signal of  $\text{H}_b$  shows as a triplet.



- When  $n=3$ , the signal is a quartet, which means it has four peaks. The four peaks of the quartet have an area ratio of 1:3:3:1. For the spectrum of ethyl acetate (Fig. 6.7e), the signal of  $H_b$  is a quartet because there are three vicinal protons  $3H_c$  on the adjacent carbon. Please note that the carbon with  $H_b$  is connected with oxygen on the other side, and there are no hydrogen atoms on that oxygen atom, so only the coupling with three vicinal protons applies.

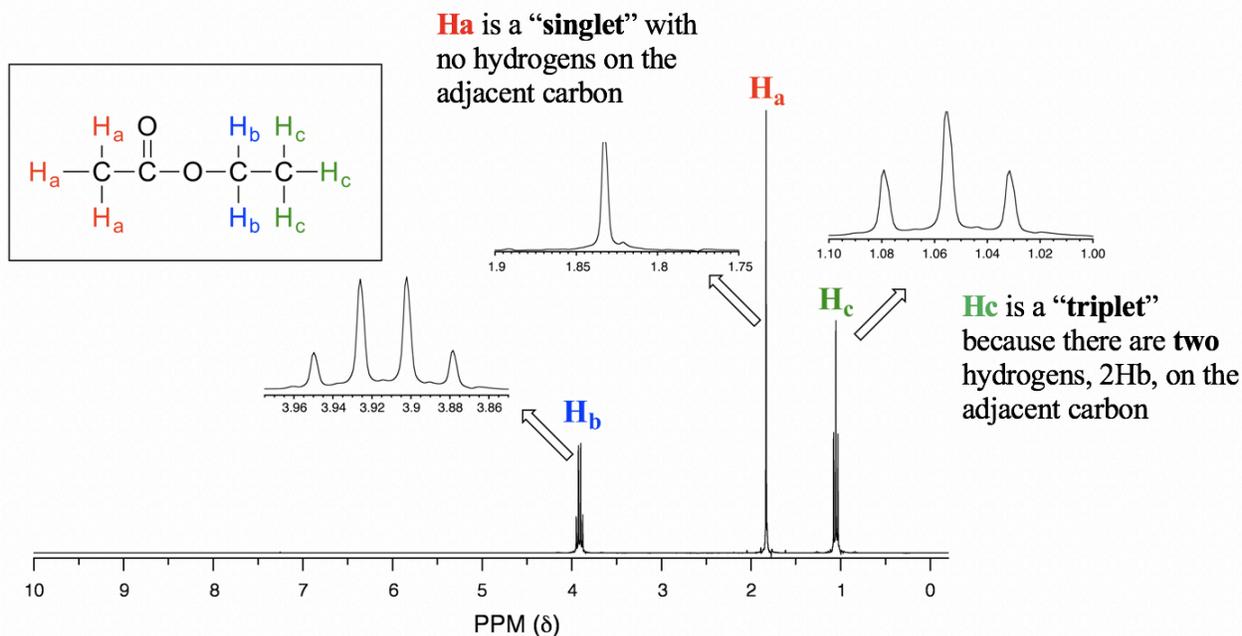


Figure 6.7e The  $^1\text{H}$  NMR spectrum of ethyl acetate with signals splitting

- When  $n \geq 4$ , the signal can be called a multiplet. Theoretically, with  $n$  increase the signal splits into more peaks and the total number of peaks is " $n+1$ ". However, the small peaks on the sides may or may not be able to be observed

since they might be merged into noise. The signals with more than four peaks are generally called multiplets, and it is not that critical to tell exactly how many peaks are involved in a multiplet.

### Extra notes about signal splitting:

1. Splitting (coupling) only occurs between nonequivalent protons. For equivalent protons, there is no coupling. In the spectrum of succinic acid (Fig. 6.7f), for example, the protons on the two middle carbons are equivalent ( $H_a$ ), so there is no coupling between them and they show a singlet.

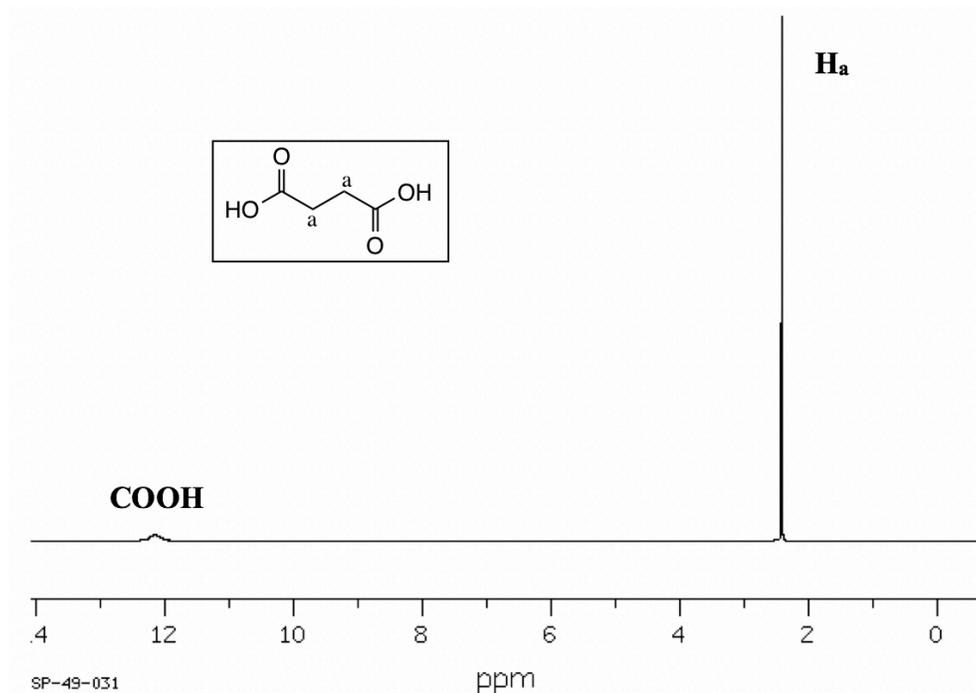


Figure 6.7f  $^1\text{H}$  NMR spectrum of succinic acid

2. Protons in OH or NH generally do not couple with vicinal hydrogens. OH and NH protons are acidic enough to rapidly exchange between different molecules, so the neighboring protons never actually 'feel' their influence. See the specific example of the 1-heptanol spectrum in Fig. 6.7g.

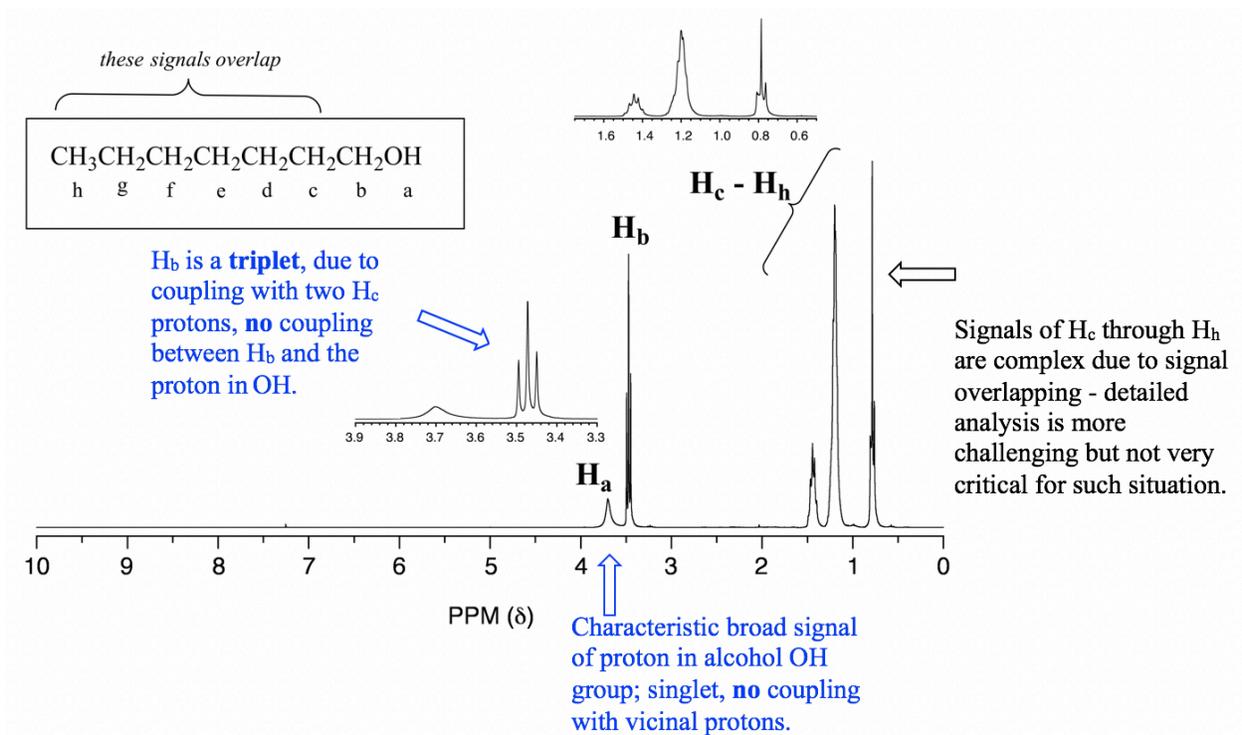


Figure 6.7g The  $^1\text{H}$ NMR spectrum of 1-heptanol

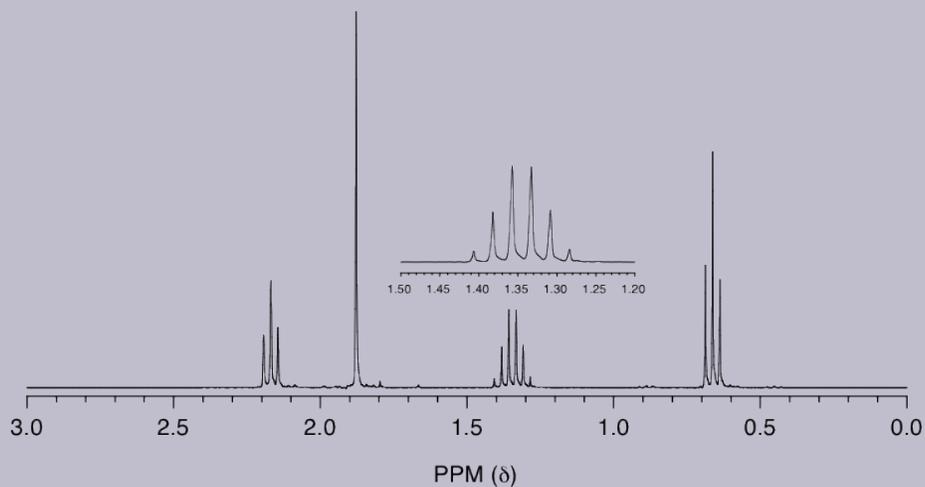
### 6.7.3 $^1\text{H}$ NMR Practice

#### Signal assignment based on the given structure

With the structure of a compound given, we can apply all the knowledge about  $^1\text{H}$  NMR to assign the signals in the spectrum to identify which signals come from which hydrogen(s).

#### Examples

Match the  $^1\text{H}$  NMR spectrum below to its corresponding compound, and assign all of the signals.



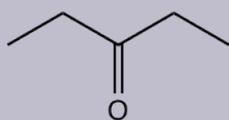
- a) cyclopentanone b) 3-pentanone c) butanal d) 2-pentanone  
 e) 4-heptanone f) 1-butene

### Approach:

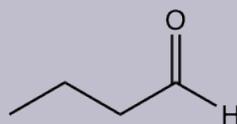
It is a good idea to draw the structure of each compound and try to see which matches the spectrum.



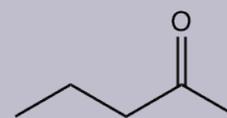
a) 2 signals



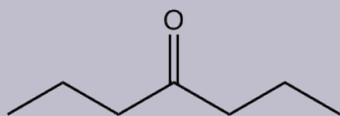
b) 2 signals



c) 4 signals



d) 4 signals



e) 3 signals



f) 4 signals

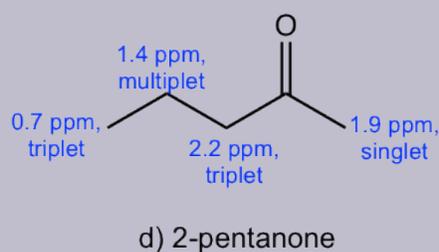
The spectrum has four signals: triplet (~0.7 ppm), multiplet (~1.4 ppm), singlet (~1.9 ppm) and triplet (~2.2 ppm)

ppm). Based on the structure of each compound, compound c), d) and f) should have four signals in the  $^1\text{H}$  NMR spectrum.

- There is no signals at about 9 ppm for the aldehyde hydrogens in the spectra, so the spectrum is not for compound c), butaldehyde.
- There is no signals at about 4~5 ppm for the alkene hydrogens in the spectra, so the spectrum is not for compound f), 1-butene.
- The signals in the spectrum match with what are expected for compound d), 2-pentanone.

Solution:

The spectrum is for 2-pentanone.



## Structure Determination based on $^1\text{H}$ NMR spectrum

For an advanced level of practice, we are supposed to be able to determine the exact structure of a compound with the  $^1\text{H}$  NMR spectrum given (and other necessary information). As we have learned, much valuable information about the structure of a compound can be obtained from a  $^1\text{H}$  NMR spectrum. In summary, analyzing the four features of the spectrum is critical to elucidate the structure of a compound:

- The number of signals indicates how many different sets of protons there are in the molecule.
- The chemical shift of the signal tells us about the electronic environment of each set of protons.
- The integration under each signal provides information about how many protons there are in the set being measured (keep in mind that the integration values are for the *ratio*, not the actual number of protons).
- The splitting pattern of each signal indicates the number of protons on atoms *adjacent* to the one whose signal is being measured.

We will see examples of structure determination in section 6.9.

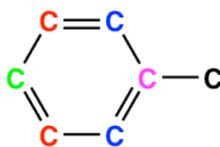
## 6.8 $^{13}\text{C}$ NMR Spectroscopy

For a carbon element, the most abundant isotope  $^{12}\text{C}$  (with ~99% natural abundance) does not have a nuclear magnetic moment and thus is NMR-inactive. The C NMR is therefore based on the  $^{13}\text{C}$  isotope, which accounts for about 1% of carbon atoms in nature and has a magnetic dipole moment just like a proton. The theories we have learned about  $^1\text{H}$  NMR spectroscopy also apply to  $^{13}\text{C}$  NMR, but with several important differences in the spectrum.

The magnetic moment of a  $^{13}\text{C}$  nucleus is much weaker than that of a proton, meaning that  $^{13}\text{C}$  NMR signals are inherently much weaker than proton signals. This, combined with the low natural abundance of  $^{13}\text{C}$ , means that it is much more difficult to observe carbon signals. Usually, samples with a high concentration and large number of scans (thousands or more) are required to bring the signal-to-noise ratio down to acceptable levels for  $^{13}\text{C}$  NMR spectra.

### Chemical Equivalent

For carbons that are chemical equivalent, they only show one signal in  $^{13}\text{C}$  NMR, similar to protons for  $^1\text{H}$ NMR. Considering this, it is very important to be able to identify equivalent carbons in the structure to interpret the  $^{13}\text{C}$  NMR spectrum correctly. Taking toluene as an example, there are five sets of different carbon atoms (shown in different colors), so there are five signals in the  $^{13}\text{C}$  NMR spectrum of toluene.



**toluene molecule has 5 different sets of carbon atoms  
(hydrogen atoms are omitted)**

### Chemical Shift

$^{13}\text{C}$  nuclei have a different value of  $g$  (the magnetogyric ratio) compared to  $^1\text{H}$  nuclei, so the resonance frequencies of  $^{13}\text{C}$  nuclei are different from those of protons in the same applied field (referring to formula 6.4, in section 6.5). In an instrument with a 7.05 Tesla magnet, protons resonate at about 300 MHz, while carbons resonate at about 75 MHz. This allows us to look at  $^{13}\text{C}$  signals using a completely separate 'window' of radio frequencies. Just like in  $^1\text{H}$  NMR, tetramethylsilane (TMS) is also used as the standard compound in  $^{13}\text{C}$  NMR experiments to define the 0 ppm; however, it is the signal from the four equivalent carbon atoms in TMS that serves as the standard. Chemical shifts for  $^{13}\text{C}$  nuclei in organic molecules are spread out over a much wider range of about 220 ppm (see Table 6.3).

Type of Carbon	Chemical Shift (ppm)	Type of Carbon	Chemical Shift (ppm)
$R-CH_3$	0 – 35		80 – 150
	15 – 55		110 – 170
	25 – 55		165 – 175
	30 – 40		175 – 185
	10 – 65		190 – 200
(X: Cl, Br or N)			200 – 220
	50 – 90		
	70 – 90		

**Table 6.3 Approximate  $^{13}\text{C}$  NMR chemical shifts of some common groups**

Table 6.3 Approximate  $^{13}\text{C}$  NMR chemical shifts of some common groups

The chemical shift of a  $^{13}\text{C}$  nucleus is influenced by essentially the same factors that influence the chemical shift of a proton: the deshielding effect of electronegative atoms and anisotropy effects tend to shift signals downfield (higher resonance frequency, with higher chemical shifts). In addition,  $sp^2$  hybridization results in a large downfield shift. The  $^{13}\text{C}$  NMR signals for carbonyl carbons are generally the furthest downfield (170–220 ppm) due to both  $sp^2$  hybridization and the double bond to oxygen.

## Integration and Coupling in $^{13}\text{C}$ NMR

Unlike  $^1\text{H}$  NMR, the area under a  $^{13}\text{C}$  NMR signal cannot easily be used to determine the number of carbons to which it corresponds. The signals for some types of carbons are inherently weaker than for other types; for example, peaks corresponding to carbonyl carbons are much smaller than those for methyl or methylene ( $\text{CH}_2$ ) peaks. For this reason, signal integration is generally not useful in  $^{13}\text{C}$  NMR spectroscopy.

Because of the low natural abundance of  $^{13}\text{C}$  nuclei, the spin-spin coupling between two nonequivalent  $^{13}\text{C}$  atoms is negligible.  $^{13}\text{C}$  nuclei are coupled to nearby protons, which results in complicated spectra. For clarity, chemists generally use a technique called broadband decoupling, which essentially ‘turns off’ C-H coupling, resulting in a spectrum in which all carbon signals are singlets. Below is the proton-decoupled  $^{13}\text{C}$  NMR spectrum of ethyl acetate in  $\text{CDCl}_3$  (Fig. 6.8a), showing the expected four signals, one for each of the carbons.

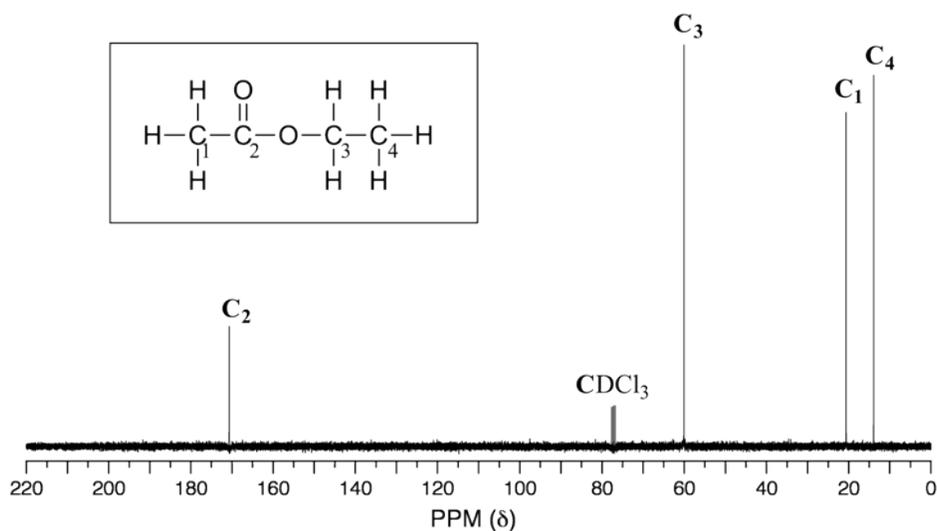
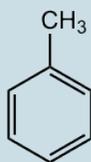


Figure 6.8a The  $^{13}\text{C}$  NMR spectrum of ethyl acetate

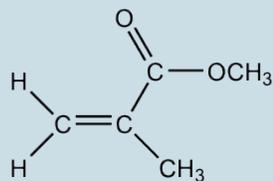
For our purposes,  $^{13}\text{C}$  NMR spectra are usually used as supporting information to confirm the structure of a compound.

### Exercises 6.2

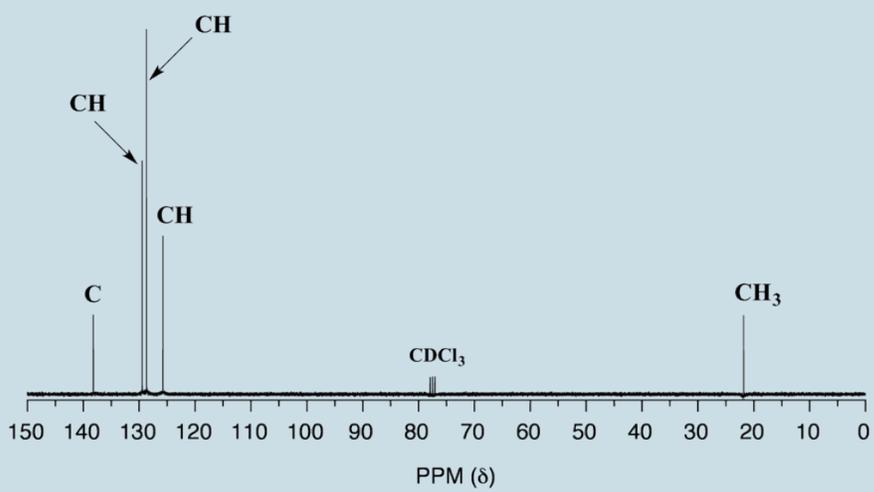
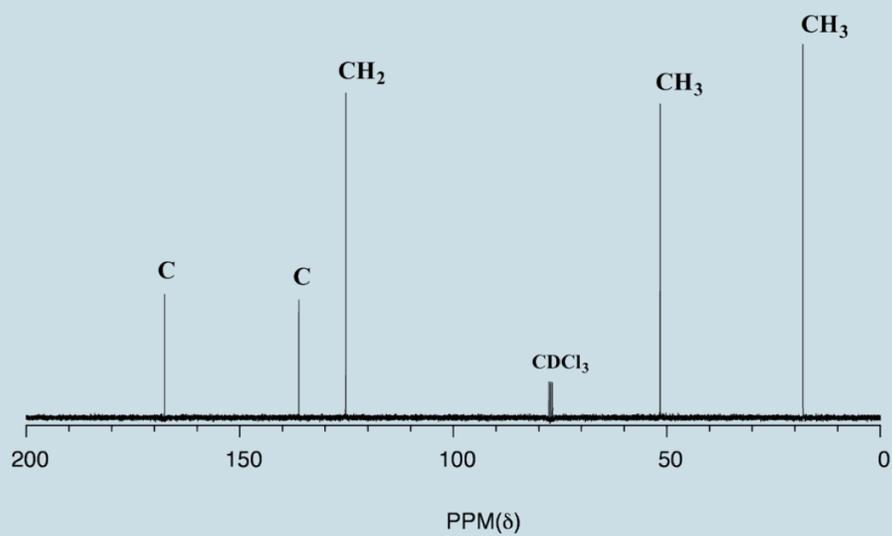
Below are  $^{13}\text{C}$  NMR spectra for methylbenzene (common name toluene) and methyl methacrylate. Refer to Table 6.3 to match the spectra to the correct structure.



toluene



methyl methacrylate



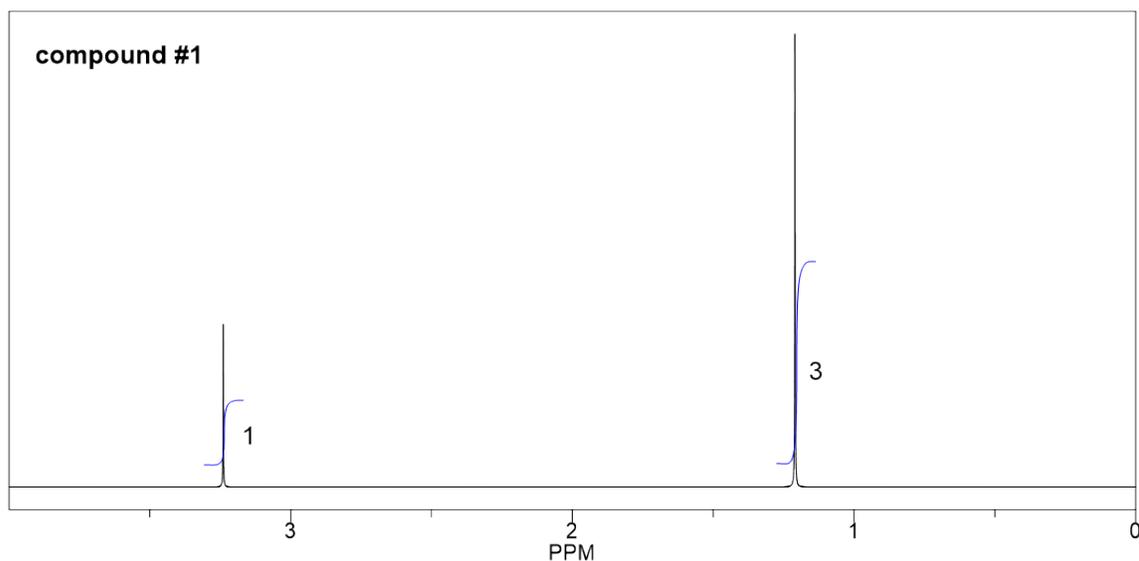
Answers to Chapter 6 Practice Questions

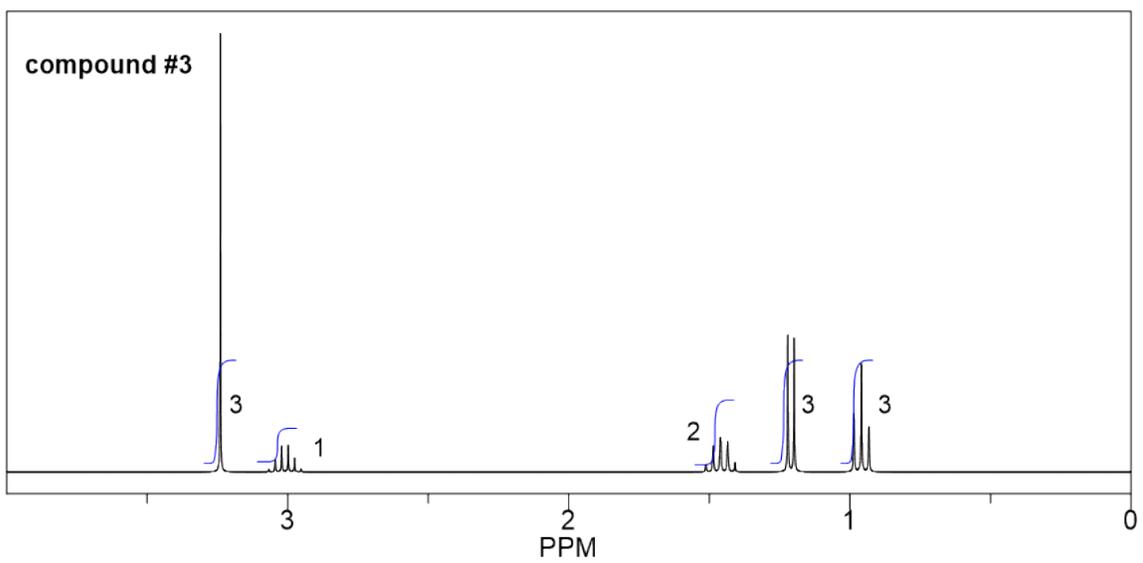
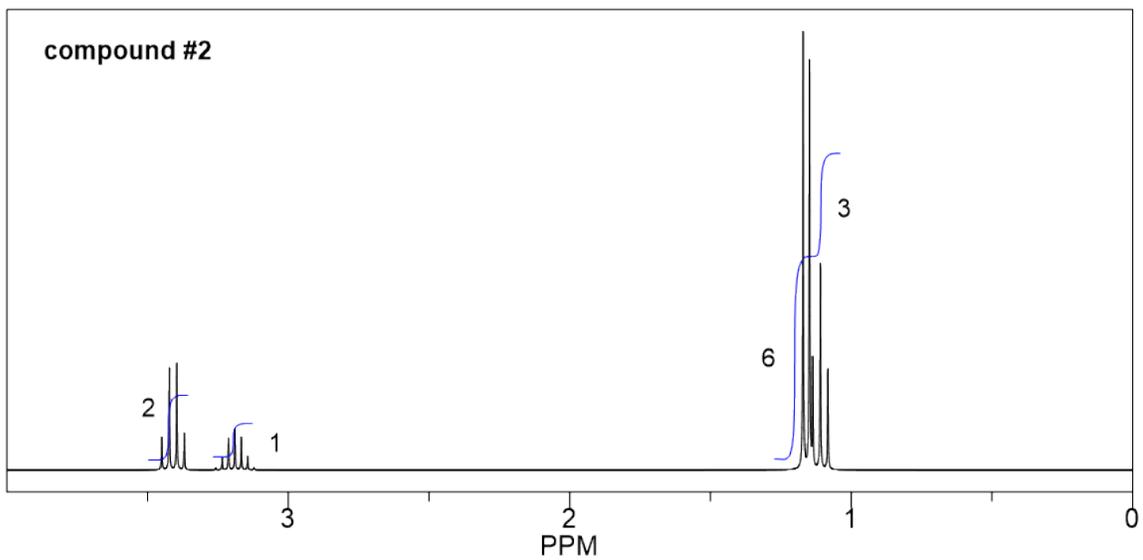
## 6.9 Structure Determination Practice

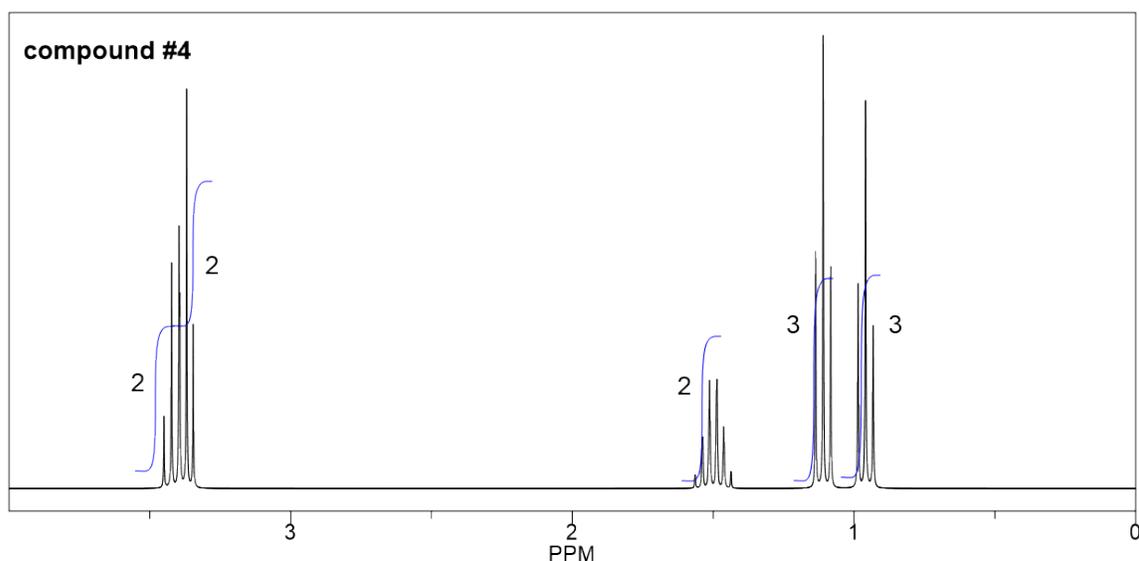
$^1\text{H}$  NMR provides a powerful tool for determining the structure of unknown compounds. Other than that  $^1\text{H}$  NMR, additional information that is usually provided includes the molecular formula, IR and  $^{13}\text{C}$  NMR spectrum. Solving the structure of an unknown compound based on all the given information is an important type of question we will work on for this chapter. We will take the  $\text{C}_5\text{H}_{12}\text{O}$  constitutional isomer as an example to go through the strategy for solving this type of question.

### Example: Constitutional Isomers with Formula $\text{C}_5\text{H}_{12}\text{O}$

The  $^1\text{H}$  NMR below are all for compounds with a molecular formula of  $\text{C}_5\text{H}_{12}\text{O}$  (the relative integration area for each signal is given as numbers on the spectra). The IR spectra of these compounds do not have any strong band at above  $3000\text{ cm}^{-1}$ , nor are there strong bands at  $1700\text{ cm}^{-1}$ . Propose a reasonable structure for each compound that is consistent with the data given.







## Approach:

Step 1: Calculate the degree of unsaturation (or IHD, section 2.3) based on the given molecular formula, and get hints about the structure/functional group according to the degree of unsaturation. This is usually the first step to solving this type of question.

$$\frac{(2n+2)-X}{2} = \frac{(2 \times 5 + 2) - 12}{2} = 0$$

Degree of unsaturation =

From what we learned about the degree of unsaturation, zero degree means there is no ring nor double bond in the structure, which means all the compounds in this question have *open chain structures with single bonds* only. With one oxygen atom involved, the possible functional group, therefore, will be open-chain alcohol, or open-chain ether.

Step 2: Narrow down the possible functional groups with IR information.

IR indicates that there are no strong bands above  $3000\text{ cm}^{-1}$  for the compound, that exclude the option of alcohol, so the only choice left is the open chain ether.

Step 3: Use available spectroscopy data (mainly  $^1\text{H}$  NMR, with  $^{13}\text{C}$  NMR as supporting if available) to identify discrete parts of the structure.

Step 4: Try to put the pieces of the puzzle together, and double-check if everything fits the available data.

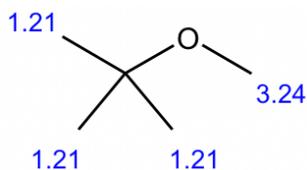
Step 3 and 4 are the most challenging parts since there is no simple rule to follow about how to do that. It takes practice to do the interpretation of  $^1\text{H}$  NMR signals and translate them into the structure of the unknown compound. Checking the four aspects of  $^1\text{H}$  NMR as we learned in section 6.6.5. The relative integration areas are given for this question to make it a bit easier.

## Solutions:

### Compound 1:

We can start with the simplest spectrum that has the least signals:

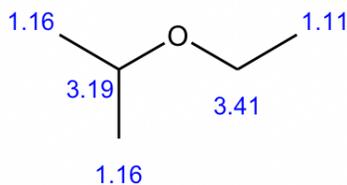
- There are only two signals (both are singlet) in this spectrum, indicating that there are two sets of non-equivalent hydrogens.
- The integrations of the two signals are 3 and 1, which means the ratio of the number of hydrogens in these two sets is 3:1. And since there are a total of 12 hydrogens, the actual number of hydrogens should be 9 and 3 in each group.
- 3 hydrogens imply a CH<sub>3</sub> methyl group, and 9 hydrogens could be three CH<sub>3</sub> groups. Also since all the 9 hydrogens are equivalent, that means the three CH<sub>3</sub> groups are equivalent. The only way to have three equivalent CH<sub>3</sub> groups is that there is a *t*-butyl group.
- So the structure is the ether with a methyl group and a *t*-butyl group connected with the oxygen atom.
- The structure of compound 1 is given below, with the chemical shift value included.



For the remaining compounds, the integration for each signal could be a very good starting point, since generally, the integration value indicates the possible structural unit like CH<sub>3</sub>, CH<sub>2</sub> or CH. Then the structural units can be put together in a logical way like putting pieces of a puzzle together.

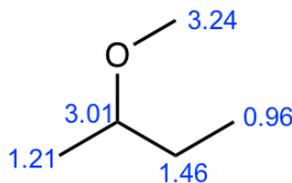
### Compound 2:

- Based on the integration, it is determined that there are:
  - one CH<sub>3</sub> group shows a triplet;
  - two equivalent CH<sub>3</sub> groups show a doublet;
  - one CH group shows a multiplet;
  - one CH<sub>2</sub> group shows a quartet.
- The triplet CH<sub>3</sub> could connect with quartet CH<sub>2</sub> as a CH<sub>2</sub>CH<sub>3</sub> ethyl group, which makes sense based on the splitting pattern.
- Also, the two equivalent CH<sub>3</sub> groups with a CH could give an isopropyl group, that is consistent to the splitting pattern.
- So the overall structure of compound 2 is isopropyl ethyl ether.



### Compound 3:

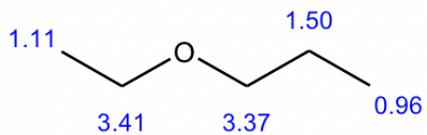
- Based on the integration, it is determined that there are:
  - one CH<sub>3</sub> group shows a triplet;
  - one CH<sub>3</sub> group shows a doublet;
  - one CH<sub>2</sub> group shows a multiplet;
  - one CH group shows a quartet;
  - one CH<sub>3</sub> group shows a singlet.
- The singlet means the CH<sub>3</sub> has no other hydrogens bonded on adjacent atoms, so the CH<sub>3</sub> group should be bonded with the oxygen atom, and the value of chemical shift (about 3.2 ppm) confirms this.
- The triplet CH<sub>3</sub> could connect with quartet CH<sub>2</sub> as a CH<sub>2</sub>CH<sub>3</sub> ethyl group, which makes sense based on the splitting pattern.
- The doublet CH<sub>3</sub> groups should connect with a CH group, that is consistent to the splitting pattern.
- The chemical shift (about 3 ppm) and splitting of the CH group (quartet) indicate it should connect to the oxygen atom.
- Put all the above pieces together, the structure of compound 3 is sec-butyl methyl ether.



### Compound 4

- Based on the integration, it is determined that there are:
  - one CH<sub>3</sub> group shows a triplet;
  - another CH<sub>3</sub> groups show a triplet;
  - one CH<sub>2</sub> group shows a multiplet;
  - two CH<sub>2</sub> groups with signals overlapping
- The two CH<sub>3</sub> groups both as triplets indicate that they both connect with CH<sub>2</sub>, so there are two ethyl CH<sub>2</sub>CH<sub>3</sub> groups in the structure, and they are not equivalent.
- Therefore there is only one more CH<sub>2</sub> group left.

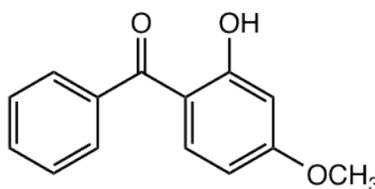
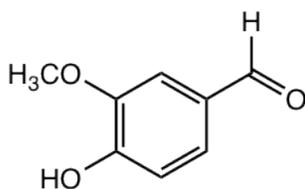
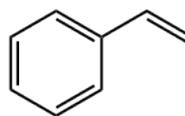
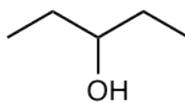
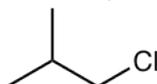
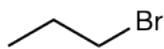
- There is only one possible structure with two  $\text{CH}_2\text{CH}_3$  groups, one  $\text{CH}_2$  group and one oxygen atom, so the structure of compound 4 is ethyl methyl ether.



# Answers to Chapter 6 Practice Questions

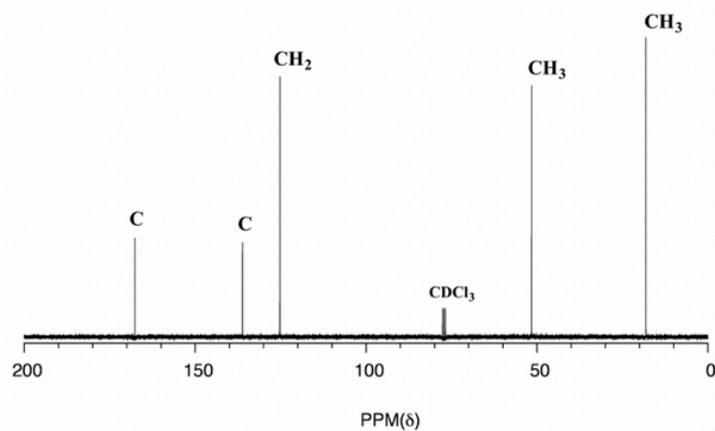
## 6.1

How many  $^1\text{H}$  NMR signals would you predict for each of the following molecules?

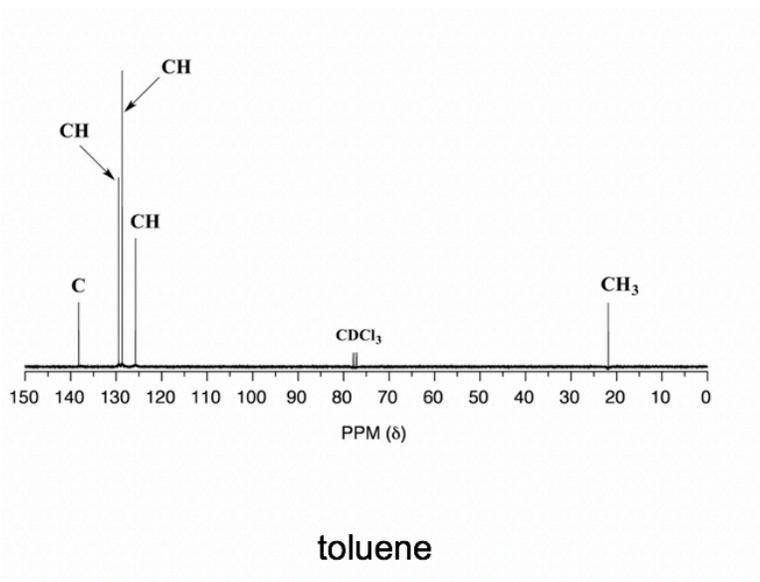


## 6.2

Below are  $^{13}\text{C}$  NMR spectra for methylbenzene (common name toluene) and methyl methacrylate. Refer to Table 6.3 to match the spectra to the correct structure.



methyl methacrylate





# CHAPTER 7: NUCLEOPHILIC SUBSTITUTION REACTIONS

With the foundations that have been built on the basic concepts in Organic Chemistry, we are now ready to learn about organic reactions. Organic reactions are mainly about the transformation of one functional group to the other, which aims to introduce a new functional group into the product. As the reactivity center of a compound, a functional group has unique properties and undergoes certain types of reactions. We will explore the specific rules that govern the reactivity of each functional group and learn why different functional groups show different reactivities. In this chapter, we will start with the substitution reaction of alkyl halide and in the next chapter, the elimination reaction.

## Learning Objectives for Chapters 7 and 8

- Understand, explain, and show the mechanism of nucleophilic substitution and elimination reaction, including intermediates, transition state, reaction coordination diagram, and extra add up to the basic mechanism. Be able to use the proper terms and curved arrows to show and explain the SN1, SN2, E1, E2 mechanisms.
- Predict the major/minor products of a given reaction with certain reactants, reagents and reaction conditions.
- Be able to compare the relative reactivity of different substrates, and the effects of different factors on each reaction mechanism, such as nucleophiles, leaving group and solvent.
- Apply and draw the proper reaction mechanism to explain or predict the product(s) of reactions, including the stereochemistry of the product.
- Provide the proper reaction conditions in order to prepare a particular product.



# 7.1 Nucleophilic Substitution Reactions Overview

Let's start with a simple substitution reaction example:

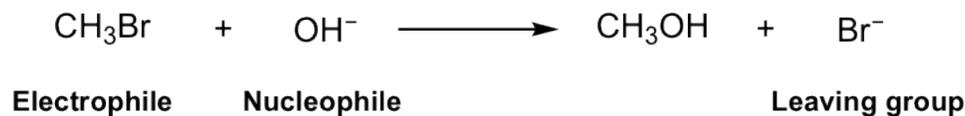


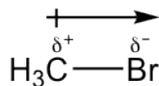
Figure 7.1a Substitution reaction

In this reaction, the Br in the reactant methylbromide ( $\text{CH}_3\text{Br}$ ) is replaced by the OH group, and methanol ( $\text{CH}_3\text{OH}$ ) is the major product, together with bromide  $\text{Br}^-$ , the side product. It is easy to understand that this is a substitution reaction because Br is substituted by OH.

Further discussion on this simple reaction requires the introduction of some key terms that are critical for understanding why and how the reaction proceeds in this way. These terms are electrophile, nucleophile, and leaving group.

## Electrophile

The reactant  $\text{CH}_3\text{Br}$  is an alkyl halide. The C-X bond (X: F, Cl, and Br) in an alkyl halide is polar because halogen is more electronegative than carbon, and as a result carbon has a partial positive charge and halogen has a partial negative charge.



Because of the partial positive charge on carbon, the carbon atom in the C-X bond is electron-deficient, and it is going to seek an electron-rich reagent to connect with. Such an electron-deficient species is called an electrophile (*phile* is a Greek suffix meaning “love”, which indicates it is a species that loves electrons). Electron-deficient species are usually electrophiles. Other electrophile examples include positively charged ions and atoms with incomplete octets, for example,  $\text{H}^+$ ,  $\text{CH}_3^+$ ,  $\text{BH}_3$ ,  $\text{BeF}_2$ , and  $\text{AlCl}_3$ .

For  $\text{CH}_3\text{Br}$  in this reaction, it is the carbon atom that acts as the electrophile, and the carbon can be called an electrophilic carbon.

The compound  $\text{CH}_3\text{Br}$  that undergoes the substitution usually can be called the substrate.

## Nucleophile

The hydroxide,  $\text{OH}^-$ , is another reactant in the above reaction. It is shown clearly with the Lewis structure of  $\text{OH}^-$  that the oxygen atom has three lone pair electrons and is negatively charged, so it is an electron-rich species with a high electron density.



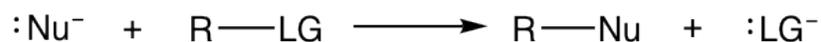
An electron-rich species is called a nucleophile (“nucleo” comes from nucleus, which means positive charge), which is a reagent seeking positively charged or electron-poor species to react with.  $\text{OH}^-$  is the nucleophile for the above reaction. Generally, any species with an electron pair available for sharing can be a nucleophile. A nucleophile can be either negatively charged ( $\text{Nu}^-$ ), or neutral ( $\text{Nu}$ ), for example:  $\text{OR}^-$ ,  $\text{H}_2\text{O}$ ,  $\text{ROH}$ ,  $\text{NH}_3$ ,  $\text{RNH}_2$ , and  $\text{RCOO}^-$  are all possible nucleophiles.

Based on the understanding of the concepts of electrophile and nucleophile, you have probably realized that a nucleophile can react with an electrophile! Yes, that is a very important and fundamental rule for organic reactions: *when electron-rich nucleophiles meet with electron-deficient electrophiles, organic reactions can occur.*

## Leaving Group

To ensure the above substitution occurs, another critical factor is that the Br must leave together with the electron pairs in C-Br bonds, and the bromide,  $\text{Br}^-$ , is called the leaving group. The leaving group (LG) leaves with the bonding pair of electrons and is replaced by the nucleophile in the substitution reaction. Without a proper leaving group, even a nucleophile is attracted to an electrophile, and the substitution reaction still cannot move forward. Leaving groups can be negatively charged or neutral, as we will see in detailed discussions later.

Applying the three key terms, the above substitution reaction can be summarized as: the nucleophile displaces the leaving group in a substrate, so such a reaction is called a nucleophilic substitution reaction. A nucleophilic substitution reaction can therefore be shown in a more general way:



Note: the nucleophile and leaving group are not necessarily negatively charged, as they could be neutral as mentioned earlier.

## Kinetics of Nucleophilic Substitution Reaction

Kinetics is the study of the rate of a chemical reaction or how fast the reaction occurs. Reaction rate data helps shed light on the understanding of reaction mechanisms or the step-by-step electron transfer process. Kinetic studies on nucleophilic substitution reactions indicate that there are two different rate law expressions for such reactions. For the two reactions below, reaction 1 is in the second order, while reaction 2 is in the first order. The only reason for the different kinetic rates is that the reactions go through different reaction mechanisms.

### Reaction 1:

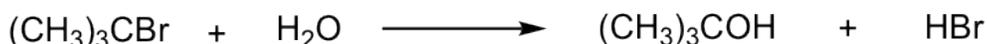


$$\text{Reaction Rate} = k \times [\text{CH}_3\text{Br}] \times [\text{OH}^-] \quad \text{second-order reaction}$$

Figure 7.1b Reaction 1: second-order reaction

Reaction 1 is the substitution reaction we are already familiar with. It is a second-order reaction. That means the reaction rate depends on the concentration of *both* the substrate  $\text{CH}_3\text{Br}$  and nucleophile  $\text{OH}^-$ . If the concentration of  $\text{CH}_3\text{Br}$  is doubled, the reaction rate gets doubled, and if the concentration of  $\text{OH}^-$  is doubled, the reaction rate is doubled as well. When the concentration of both  $\text{CH}_3\text{Br}$  and  $\text{OH}^-$  are doubled, the reaction rate increases by a factor of *four*.

### Reaction 2:



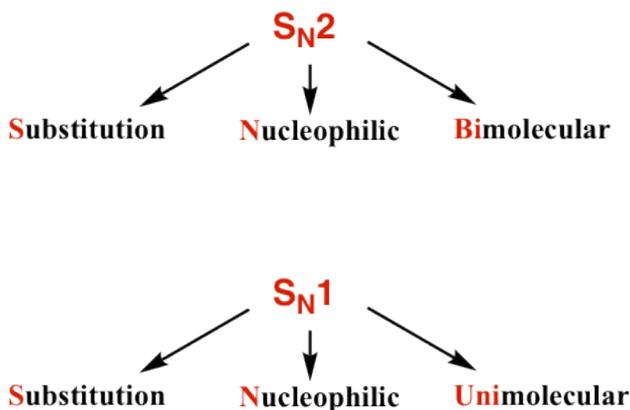
$$\text{Reaction Rate} = k \times [(\text{CH}_3)_3\text{CBr}] \quad \text{first-order reaction}$$

Figure 7.1c Reaction 2: first-order reaction

Reaction 2 is another substitution reaction example. The substrate here is a tertiary bromide and the nucleophile is a neutral water molecule. As a first-order reaction, the reaction rate depends only on the concentration of the substrate  $(\text{CH}_3)_3\text{CBr}$  and has nothing to do with nucleophiles.

The two types of reactions correspond to two types of reaction mechanisms:

- A second-order reaction goes through the bimolecular reaction mechanism that is called an  $\text{S}_{\text{N}}2$  reaction, meaning Substitution, Nucleophilic and Bimolecular.
- A first-order reaction goes through the unimolecular reaction mechanism that is called an  $\text{S}_{\text{N}}1$  reaction, meaning Substitution, Nucleophilic and Unimolecular.



We will have detailed discussions on  $S_N2$  and  $S_N1$  mechanisms respectively, and then compare the similarities and differences between them.,.

## 7.2 S<sub>N</sub>2 Reaction Mechanisms, Energy Diagram and Stereochemistry

### S<sub>N</sub>2 Reaction Mechanism

Let's still take the reaction between CH<sub>3</sub>Br and OH<sup>-</sup> as an example of an S<sub>N</sub>2 mechanism.



**Mechanism:**

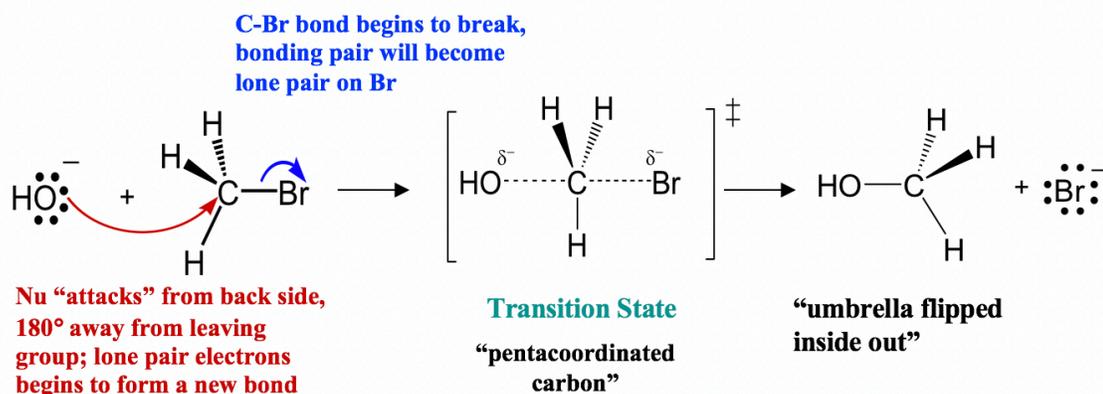


Fig. 7.2a S<sub>N</sub>2 reaction mechanism between CH<sub>3</sub>Br and OH<sup>-</sup>

An S<sub>N</sub>2 mechanism involves two electron pair transfers that occur at the same time; nucleophile attacking (red arrow) and leave group leaving (blue arrow). The nucleophile OH<sup>-</sup> approaches the electrophilic carbon from the back side, the side that is opposite to the direction that the leaving group Br leaves. With the nucleophile OH<sup>-</sup> getting closer, the Br starts to leave as well. The new C—OH bond formation and the old C—Br bond breaking occur *at the same time*. In a very short transient moment, the carbon atom is *partially* connected with *both* OH and Br, which gives the highest energy level state of the whole process called the transition state. In the transition state of an S<sub>N</sub>2 reaction, there are five groups around the carbon and the carbon can be called "pentacoordinated". As the OH<sup>-</sup> continues to get closer to the carbon, the Br moves further away from it with the bonding electron pair. Eventually, the new bond is completely formed and the old bond is completely broken, which gives the product CH<sub>3</sub>OH.

In the mechanism, the reaction proceeds in a single step that involves both the nucleophile and the substrate, so increasing the concentration of either increases the possibility of a collision, which explains the second-order kinetics of an S<sub>N</sub>2 reaction. With both nucleophile attacking and leaving group leaving happen at the same time, S<sub>N</sub>2 is also said to be a concerted mechanism, as concerted means simultaneous.

## Notes for drawing an S<sub>N</sub>2 mechanism:

- The two arrows must be shown when drawing the S<sub>N</sub>2 mechanism. Both have to be shown with the proper direction: nucleophile attack from the direction that is opposite to the leaving group leaves, i.e., backside attack.
- The transition state is optional (depending on the requirement of the question). However, it is important to understand that the reaction process goes through the transition state before producing the products.
- Please pay attention to the fact that for the product, the positions of the three hydrogens around the carbon are all pushed to the other side, and the overall configuration of the carbon gets inverted, like an umbrella flipped inside out in a windstorm. It seems to not really matter for the product (CH<sub>3</sub>OH) in this reaction, but it does make a difference if the carbon is a chirality center.

## Energy Diagram of the S<sub>N</sub>2 Mechanism

The energy changes for the above reaction can be represented in the energy diagram shown in Fig. 7.2b. S<sub>N</sub>2 is a single-step reaction, so the diagram has only one curve. The products CH<sub>3</sub>OH and Br<sup>-</sup> are in lower energy than the reactants CH<sub>3</sub>Br and OH<sup>-</sup>, which indicates that the overall reaction is exothermic and the products are more stable.

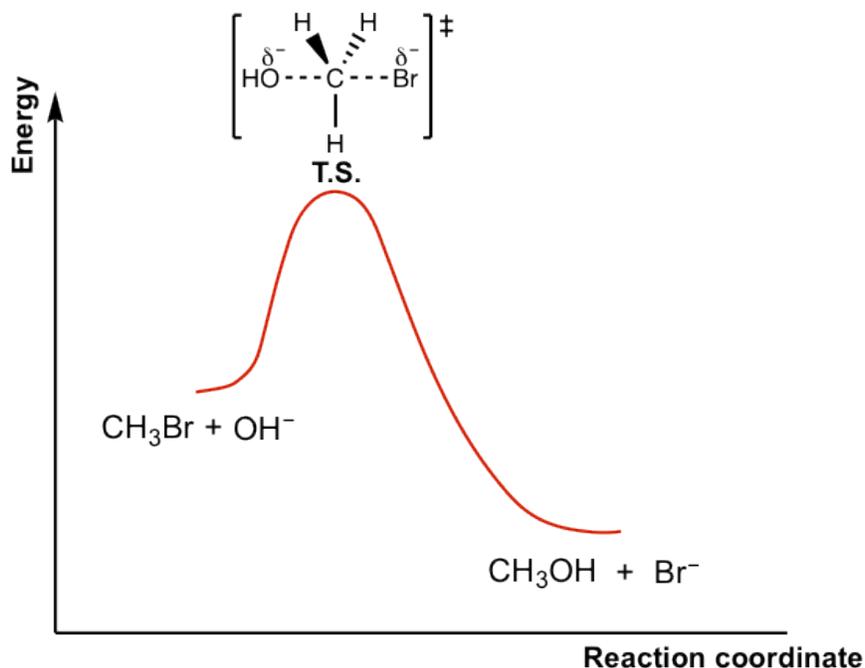


Fig. 7.2b Energy diagram of S<sub>N</sub>2 reaction between CH<sub>3</sub>Br and OH<sup>-</sup>

The top of the curve corresponds to the transition state, which is the highest-energy structure involved in the reaction. A transition state always involves partial bonds, partially formed bonds and partially broken bonds, and therefore it is very unstable with no appreciable lifetime. The transition state therefore can never be isolated. The structure of the transition states is usually shown in a square bracket with a double-dagger superscript.

## The Effect of Alkyl Halide Structure on S<sub>N</sub>2 the Reaction Rate

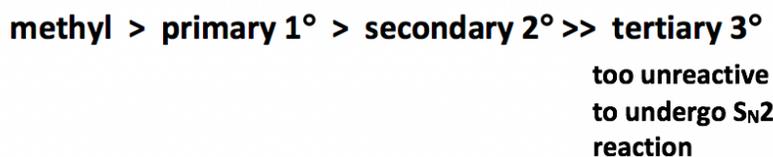
For the discussions on the S<sub>N</sub>2 mechanism so far, we focused on the reaction of methylbromide CH<sub>3</sub>Br. Other alkyl halides could undergo S<sub>N</sub>2 reactions as well. The studies on the reaction rate for S<sub>N</sub>2 indicate that the structure category of electrophilic carbon in alkyl halide dramatically affects the reaction rate.

Type of Alkyl Halide	Alkyl Halide Structure	Relative Rate
Methyl	CH <sub>3</sub> X	30
Primary (1°)	RCH <sub>2</sub> -X	1
Secondary (2°)	$\begin{array}{c} \text{R} \\ \diagdown \\ \text{CH}-\text{X} \\ \diagup \\ \text{R}' \end{array}$	0.03
Tertiary (3°) (no S <sub>N</sub> 2 reaction)	$\begin{array}{c} \text{R}' \\   \\ \text{R}-\text{C}-\text{X} \\   \\ \text{R}'' \end{array}$	negligible

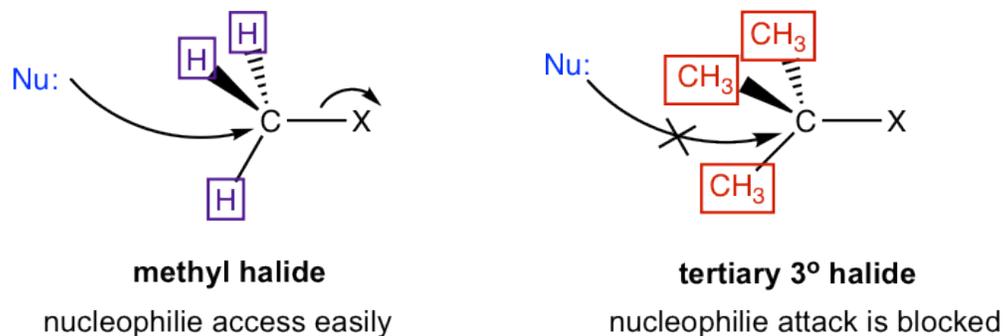
Table 7.1 Relative Reaction Rate of S<sub>N</sub>2 for Different Types of Alkyl Halide

As shown in Table 7.1, methyl and primary halides are the substrates with the highest rate, the rate decreases a lot for secondary halides, and the tertiary halides do not undergo an S<sub>N</sub>2 reaction at all because the rate is too low to be practical.

The relative reactivity of alkyl halides towards S<sub>N</sub>2 reaction can therefore be summarized as:

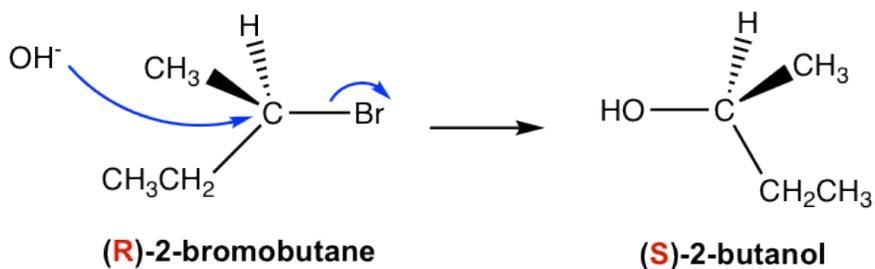


Why is the trend like this? This can be explained by the mechanism of the  $S_N2$  reaction. Actually, this is among the experimental evidence scientists used for proposing the mechanism. A key feature in the  $S_N2$  mechanism is that the nucleophile attacks from the back side. When nucleophiles approach the carbon, it is easiest to get close to the methyl carbon because the hydrogen atoms connected to carbon are small in size. With the size of the groups connected to the carbon getting larger, it becomes more difficult to access the carbon, and such an approach is completely blocked for tertiary carbons with three bulky alkyl groups connected. Therefore, the reactivity difference is essentially caused by the steric effect. The steric effect is based on the steric size or volume of a group. Because of the steric hindrance of bulky groups on the electrophilic carbon, it is less accessible for nucleophiles to do back-side attacks, so the  $S_N2$  reaction rate of secondary ( $2^\circ$ ) and tertiary ( $3^\circ$ ) substrates dramatically decreases. The  $3^\circ$  substrates never go with the  $S_N2$  reaction mechanism because the reaction rate is too slow.



## The Stereochemistry of $S_N2$ Reaction

Another feature of the  $S_N2$  reaction mechanism is that the overall configuration of the carbon in the product gets inverted compared to that of the reactant, as an umbrella flipped inside out. Such inversion of the configuration is called *Walden inversion*. Let's see what are the stereochemistry consequences for such inversion.

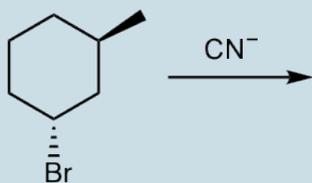


Start with the (R)-2-bromobutane. The  $S_N2$  reaction produces only one enantiomer of the 2-butanol product, and it is predictable that the configuration of the product is supposed to be S because of the configuration inversion.

Note: Inversion means the arrangement of the groups gets inverted, not necessarily means the absolute configuration, R/S, is inverted. The product does get an inverted R/S configuration compared to the reactant for lot cases, but not guaranteed. The actual configuration of the product has to be determined accordingly.

Exercises 7.1

Show the product of the following  $S_N2$  reaction ( $CN^-$  is the nucleophile):



Answers to Chapter 7 Practice Questions

## 7.3 Other Factors that Affect S<sub>N</sub>2 Reactions

### Leaving Group

When alkyl halides undergo nucleophilic substitution reactions, halogen is the leaving group. Not only halogens can be the leaving group, but other appropriate groups can be leaving groups as well. Generally speaking, a nucleophilic substitution reaction requires a good leaving group. The question then is how to decide whether a leaving group is good or not.

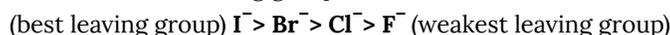
When a leaving group departs, it takes the electron pair from the broken bond together with it. So, the good leaving group should be one that can accommodate the electron pair very well, that is, the good leaving group should be the group that is stable with the pair of electrons.

The stability of a group with a pair of electrons is related to the basicity of the group since basicity refers to the ability of the species to share its electron pair. As a result, a strong base has high reactivity to share the electron pair, so it is not stable and cannot be a good leaving group. On the other side, a weak base with a low tendency to share the electron pair is a more stable base and therefore is a good leaving group. So, the general trend is:

The weaker the basicity of a group, the better the leaving group is.

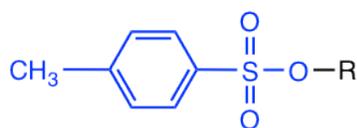
Our knowledge of acid-base topics will be very helpful here to compare the strength between different leaving groups.

For alkyl halides, the relative reactivities as a leaving group are:

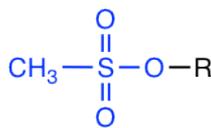


This order matches the relative basicity of halide anions. I<sup>-</sup> is the weakest base and also the best leaving group.

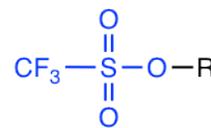
Besides halides, other groups can be leaving groups as well. In the acid-base chapter, we have learned about some examples of strong organic acids, for example, tosylic acid, TsOH, etc. Since the conjugate base of strong acid is a very weak base, the conjugate bases of those acids are good choices for leaving groups as well. Examples include (the leaving group is highlighted in blue):



leaving group: TsO<sup>-</sup>, tosylate



leaving group: MsO<sup>-</sup>, mesylate



leaving group: TfO<sup>-</sup>, triflate

#### Examples of good leaving groups: conjugate bases of strong organic acids

Figure 7.3a Examples of good leaving groups: Conjugate bases of strong organic acids

Strong bases such as OH<sup>-</sup>, RO<sup>-</sup>, NH<sub>2</sub><sup>-</sup>, and R<sup>-</sup> are therefore very poor leaving groups and cannot go with nucleophilic substitution reactions. For OH<sup>-</sup> or RO<sup>-</sup>, however, upon protonation they can be converted to neutral H<sub>2</sub>O or ROH molecules, which are leaving groups suitable for substitution. This topic will be covered in section 7.6.

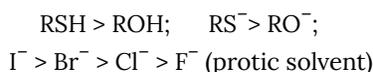
Note: with the scope of leaving group expanded, the substitution reaction is not only limited to alkyl halide. Any compounds with a good leaving group can undergo nucleophilic substitution.

# Nucleophile

For an  $S_N2$  reaction, the nucleophile is one of the rate-determining factors; therefore, strong nucleophiles help to speed up  $S_N2$  reactions.

The relative strength of a nucleophile is called nucleophilicity. The nucleophilicity of a nucleophile is measured in terms of the relative rate of its  $S_N2$  reaction with the same substrate. Generally speaking, the nucleophilicity trend depends on several structural features of the nucleophile.

- A nucleophile with a negative charge is always stronger than the corresponding neutral one. For example:  $\text{OH}^- > \text{H}_2\text{O}$ ;  $\text{RO}^- > \text{ROH}$ .
- Nucleophilicity decreases across a period. For example:  $\text{NH}_3 > \text{H}_2\text{O}$ ;  $\text{RNH}_2 > \text{ROH}$
- Nucleophilicity increases across a group. For example:



- A smaller group is a better nucleophile than a bulky group.

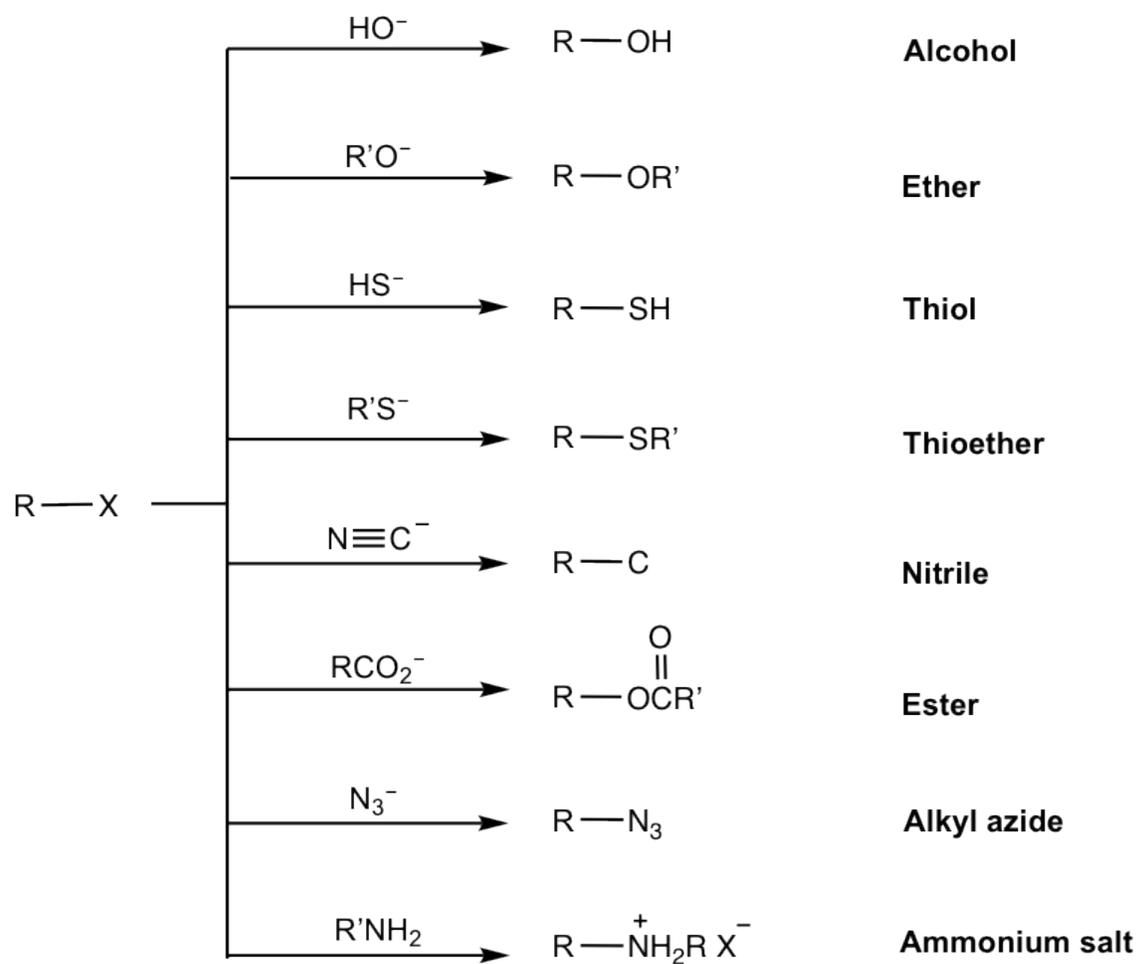
For example,  $t\text{-BuO}^-$   $\left( \begin{array}{c} \text{CH}_3 \\ | \\ \text{CH}_3 - \text{C} - \text{O}^- \\ | \\ \text{CH}_3 \end{array} \right)$  is a very poor nucleophile because of its bulky size.

To make it more convenient for studying purposes, the commonly applied strong and weak nucleophiles are listed here:

Strong (good) nucleophile:  $\text{OH}^-$ ,  $\text{RO}^-$  (small alkoxide),  $\text{RS}^-$  (thiolate),  $\text{N}_3^-$  (azide),  $\text{CN}^-$  (cyanide),  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$  (halide),  $\text{RCO}_2^-$  (carboxylate),  $\text{RNH}_2$  (amine)

Weak (poor) nucleophile:  $\text{ROH}$ ,  $\text{H}_2\text{O}$ ,  $t\text{-BuO}^-$

With the structure of nucleophiles being so diverse,  $S_N2$  reactions can be used to synthesize compounds with a variety of functional groups, as shown here.



### Functional group interconversions via $S_N2$ reactions

Figure 7.3b Functional group interconversions via  $S_N2$  reactions

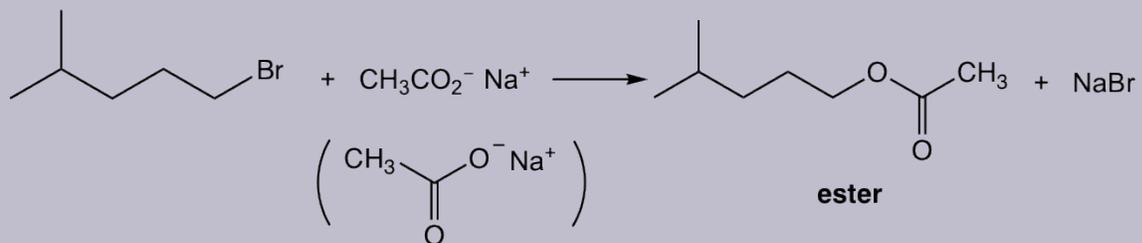
Examples

**synthesis of ether**



**ether**

**synthesis of ester**



Exercises 7.2

Show the reaction mechanism of the above reactions.

Answers to Chapter 7 Practice Questions

# 7.4 S<sub>N</sub>1 Reaction Mechanisms, Energy Diagram and Stereochemistry

## S<sub>N</sub>1 Reaction Mechanism

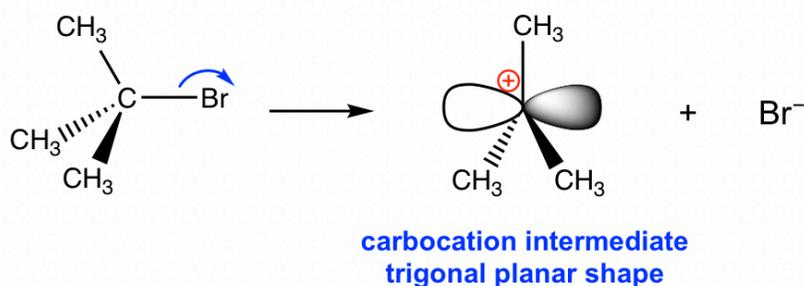
The reaction between *tert*-butylbromide and water proceeds via the S<sub>N</sub>1 mechanism. Unlike S<sub>N</sub>2 which is a single-step reaction, S<sub>N</sub>1 reaction involves multiple steps. Reaction: (CH<sub>3</sub>)<sub>3</sub>CBr + H<sub>2</sub>O → (CH<sub>3</sub>)<sub>3</sub>COH + HBr



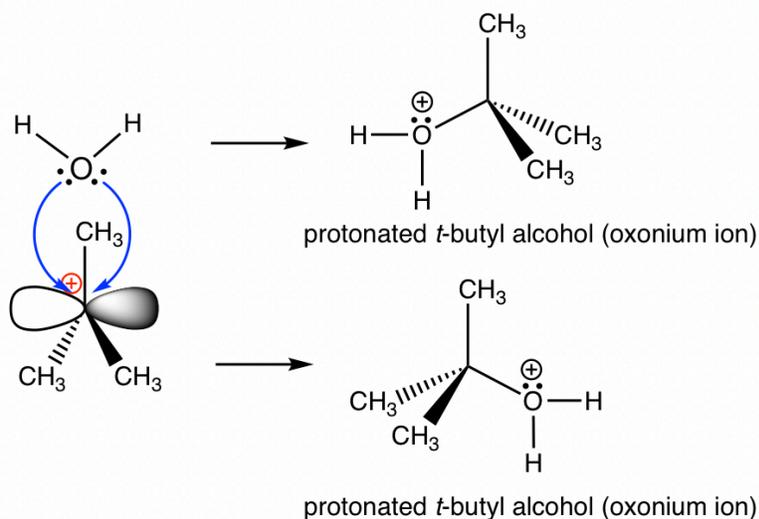
### Mechanism:

**Step 1** Cleavage of C–Br bond **slowly** to form the carbocation intermediate.

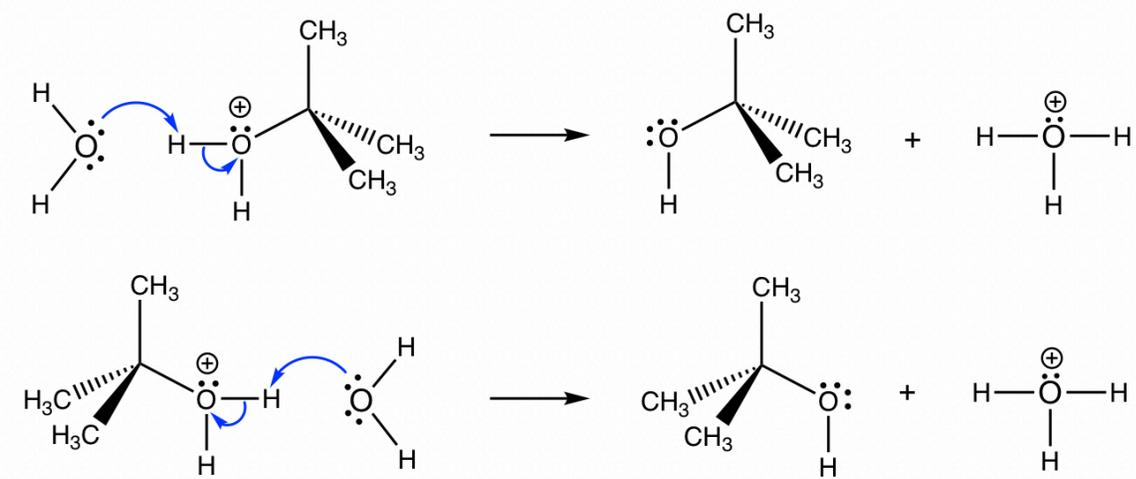
Step 1 is the **rate-determining step**.



**Step 2** Rapid reaction between carbocation intermediate and nucleophile H<sub>2</sub>O; H<sub>2</sub>O attacks from both sides of the planar carbocation.



**Step 3** Rapid deprotonation to produce neutral final product *t*-butyl alcohol (very fast step, and sometimes can be combined with step 2 together as one step).



In step 1, the C–Br bond breaks and Br departs with the bonding electron pair to produce a tertiary carbocation and bromide anion  $\text{Br}^-$ . This step only involves a highly endothermic bond-breaking process, and this is the slowest step in the whole mechanism. In the multiple-step mechanism, the overall reaction rate is determined by the slowest step, and such a step is therefore called the rate-determining step. In an  $\text{S}_{\text{N}}1$  reaction, step 1 is the slowest step and therefore the rate-determining step. The rate-determining step only involves the alkyl halide substrate, which is why the overall rate law is in the first order, because nucleophiles do not participate in the rate-determining step.

The product of step 1, carbocation, will be the reactant of the next step and is called the intermediate for an  $\text{S}_{\text{N}}1$  reaction. An intermediate is an unstable, highly reactive species with a very short lifetime. The carbocation intermediate is in a trigonal planar shape, with the empty 2p orbital particular to the plane. The central carbon is  $\text{sp}^2$  hybridized and has an incomplete octet, so carbocation is the highly reactive intermediate, which is also the electrophile.

Step 2 is the nucleophilic attack step, that the nucleophile  $\text{H}_2\text{O}$  uses its lone pair to react with the carbocation intermediate, and produces the protonated *t*-butyl alcohol (oxonium ion). Because of the planar shape of the carbocation intermediate, there is the same possibility for the nucleophile to attack from either side of the plane, so possible products are generated with the same amounts. For this reaction, attacking from either side gives the same product (both are still shown for the purpose of illustrating the concept); however, it gives different stereoisomers if the electrophilic carbon is the chirality center.

In step 3, a water molecule acts as a Bronsted base to accept the proton from the oxonium ion, and the final neutral product *t*-butyl alcohol is produced. This deprotonation step is very fast, and sometimes can be combined with step 2 together as one step (i.e. step 3 may not be regarded as an individual step).

## Energy diagram of $\text{S}_{\text{N}}1$ mechanism

$\text{S}_{\text{N}}1$  is a multiple-step reaction so the diagram has multiple curves, and each step can be represented by one curve. Out of the three steps, the activation energy for step 1 is the highest; therefore, step 1 is the slowest step, which is the rate-determining step.

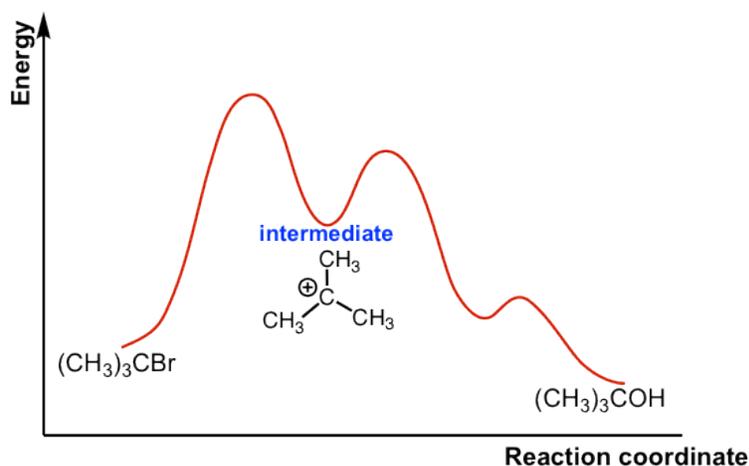


Figure 7.4a Energy diagram for  $S_N1$  reaction between  $(CH_3)_3CBr$  and  $H_2O$

The connection between the first two curves represents the carbocation intermediate. Generally, the intermediate is the product of one step of a reaction and the reactant for the next step. The intermediate is at a relatively lower energy level compared to the transition state (which is at the peak of a curve), but the intermediate is also highly reactive and unstable.

## The Effect of the Substrate Structure on the $S_N1$ Reaction Rate

Different substrates have different reaction rates towards the  $S_N1$  reaction, and the relative reactivity of substrates towards the  $S_N1$  reaction can be summarized as:

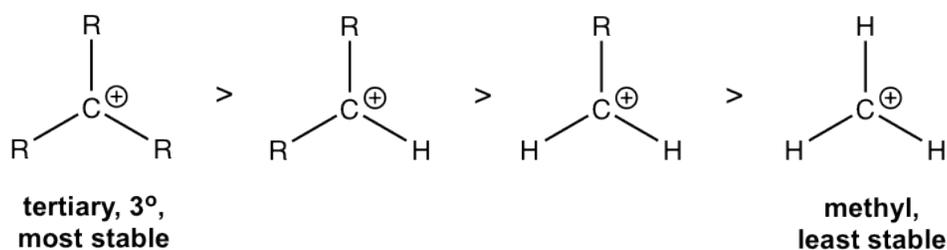
**tertiary  $3^\circ$  > secondary  $2^\circ$  > primary  $1^\circ$  and methyl**      **too unreactive to undergo  $S_N1$  reaction**

Figure 7.4b Relative reactivity of substrates towards  $S_N1$  reaction

Comparing this trend to that of  $S_N2$  reaction, you will probably realize that they are opposite. A tertiary substrate is the most reactive towards  $S_N1$ , but it does not undergo  $S_N2$  at all; primary and methyl substrates are unreactive for  $S_N1$ , but they are the best substrates for  $S_N2$ . This comparison is very important and useful for us to choose the proper reaction condition for different substrates as we will see in the next section. For now, we will need to understand the reasoning behind the trend for  $S_N1$ .

This is because of the stability of the carbocation intermediate. The mechanism shows that a carbocation is formed in the rate-determining step, so the more stable the carbocation, the more easily it is formed, and the more it facilitates the rate-determining step and speeds up the whole reaction. Therefore, the more stable the carbocation intermediate, the faster the rate of an  $S_N1$  reaction.

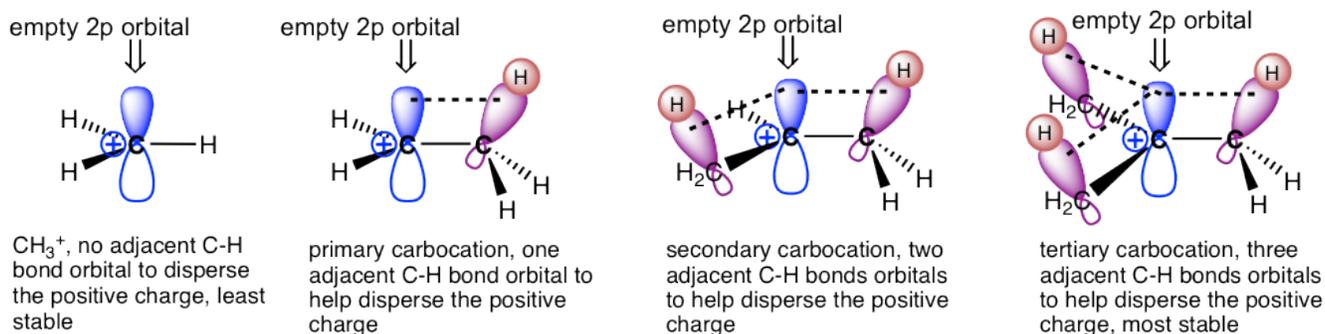
The relative stability of carbocation is given below, in which the tertiary carbocations are the most stable and methyl carbocation is the least stable.



### the relative stability of carbocations

Figure 7.4c The relative stability of carbocations

The relative stability of carbocations can be explained by the hyperconjugation effect. Hyperconjugation is the partial orbital overlap between a filled bonding orbital to an adjacent unfilled (or half-filled) orbital. The carbocation is an electron-deficient species that has an incomplete octet and empty 2p orbital. If there is an alkyl group connected with a carbocation, then there are C-C or C-H sigma bonds besides the carbocation carbon, so the filled orbitals of sigma bonds will be able to partially overlap with the empty 2p orbital. This allows sharing of the electron density with the carbocation, which stabilizes the carbocation. The more R groups involved, the stronger the hyperconjugation effect is. So, the tertiary (3°) carbocation is the most stable one. While there is no R group in the methyl carbocation,  $\text{CH}_3^+$ , it is the least stable.

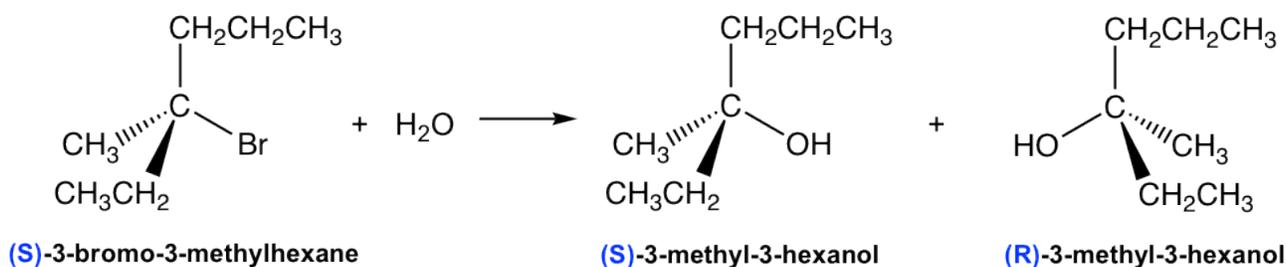


**Hyperconjugation effect:** electron delocalized from filled C-H orbitals to adjacent empty orbital, and helps to disperse and stabilize the positive charge

Figure 7.4d Hyperconjugation effect

## Stereochemistry of the $\text{S}_{\text{N}}1$ mechanism

The stereochemistry feature of the  $\text{S}_{\text{N}}1$  reaction is very different from that of  $\text{S}_{\text{N}}2$ , and of course, this can be explained well with the  $\text{S}_{\text{N}}1$  mechanism.



Starting with (S)-3-bromo-3-methylhexane reactant, the S<sub>N</sub>1 reaction produces a 50:50 mixture of both R and S enantiomers of 3-methyl-3-hexanol, which is the racemic mixture product. This is because the carbocation formed in the first step of an S<sub>N</sub>1 reaction has a trigonal planar shape. When it reacts with nucleophiles, it may react from either the front side or the back side, and each side gives one enantiomer. There is an equal possibility for a reaction to occur from either side, so the two enantiomers are formed with the same amount, and the product is a racemic mixture.

A reaction that converts an optically active compound into a racemic form is said to proceed with racemization. For an S<sub>N</sub>1 reaction that starts with (an optical active) one enantiomer as the reactant and the chirality center is also the electrophilic carbon (i.e. the reaction occurs on the chirality center), it proceeds with racemization as shown above.

### Exercises 7.3

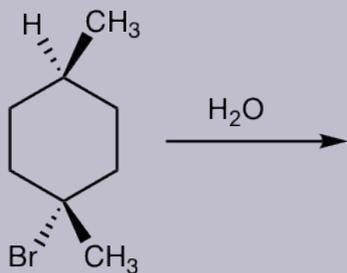
Show the detailed mechanism for the above reaction of (S)-3-bromo-3-methylhexane and water.

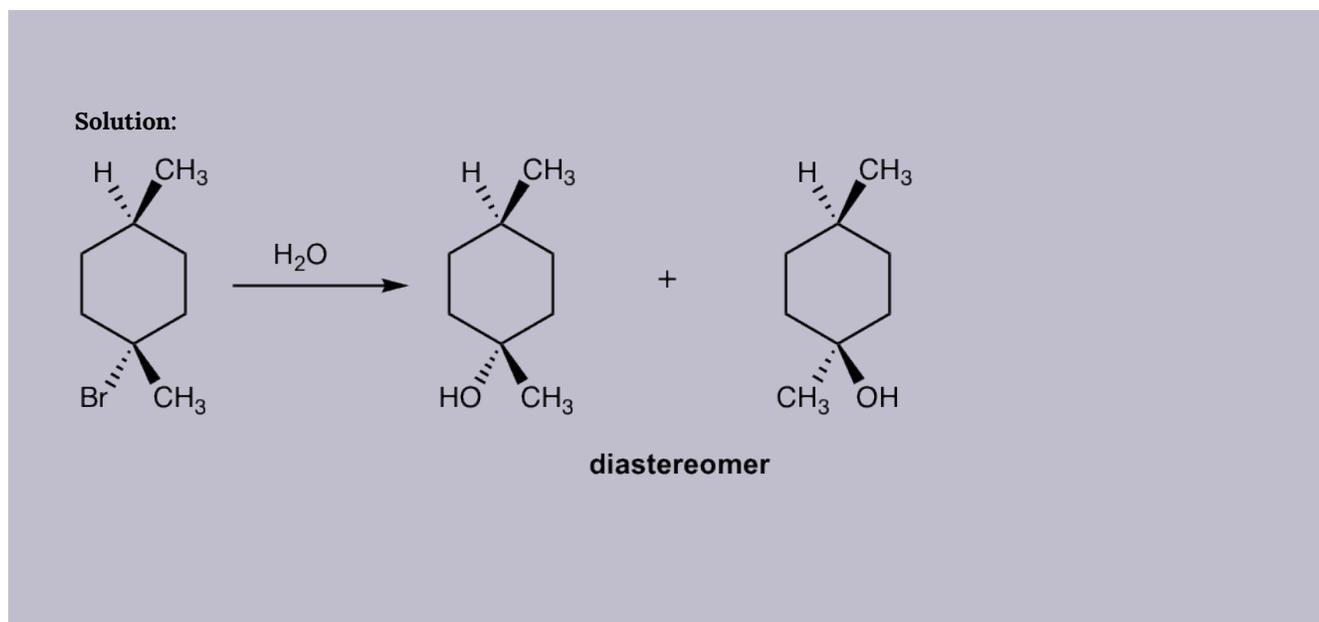
### Answers to Chapter 7 Practice Questions

Please note that if the chirality center of the reactant is not the reaction center, or if there is more than one chirality center in the reactant, the S<sub>N</sub>1 reaction does not produce the racemic mixture as shown in the example below.

### Examples

Show product(s) of the following S<sub>N</sub>1 reaction:





## Leaving Group Effect on $S_N1$

As is the case for the  $S_N2$  reaction, a good leaving group is also required for the  $S_N1$  mechanism, and all the discussions we had in section 7.3 still apply.

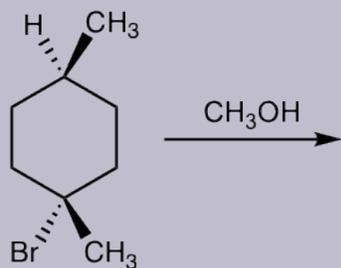
## Nucleophile

Unlike an  $S_N2$  reaction, the rate-determining step of the  $S_N1$  reaction does not include nucleophiles, so theoretically, the strength of a nucleophile does not affect the  $S_N1$  reaction. However, a strong nucleophile has a high tendency to go with the  $S_N2$  reaction instead of  $S_N1$ , so a weaker nucleophile is a better choice for  $S_N1$ . For the examples we have seen so far,  $H_2O$  is the nucleophile.

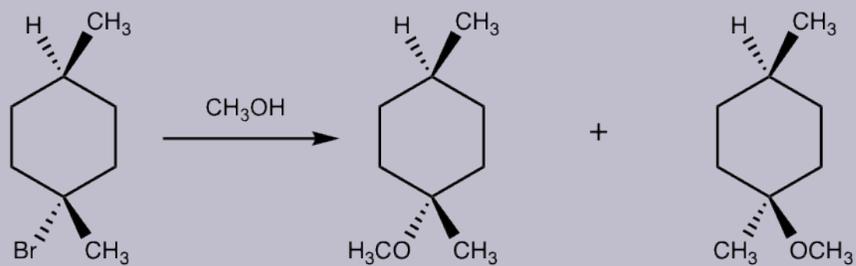
In practice, neutral substances such as  $H_2O$ ,  $ROH$ , and  $RCOOH$  are usually used as nucleophiles in  $S_N1$  reactions. When these substances are applied in the reaction, they serve another function as solvents. So, they are used as *both* nucleophiles and solvents for the  $S_N1$  reaction, and such a reaction is also called a solvolysis reaction. A solvolysis reaction is a nucleophilic substitution in which the nucleophile is a molecule of the solvent as well. The term solvolysis comes from *solvent*+*lysis*, which means cleavage by the solvent. An  $S_N1$  reaction is usually a solvolysis reaction.

### Examples

Show the structures of the products for the following solvolysis reaction.



**Solution:**



**diastereomer**

## 7.5 S<sub>N</sub>I vs S<sub>N</sub>2

### 7.5.1 Comparison Between S<sub>N</sub>I and S<sub>N</sub>2 Reactions

As of now, we have finished with the basic concepts of S<sub>N</sub>1 and S<sub>N</sub>2 reactions. You have probably already noticed that the two types of reactions have some similarities, but they are also quite different. It will be very helpful to put them together for comparison. To help you get an in-depth understanding of the two types of mechanisms, it is highly recommended that you have a summary in your own way. The following comparison is provided here for your reference.

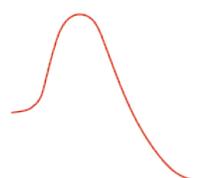
	S <sub>N</sub> 1	S <sub>N</sub> 2
Rate law	Rate = k[electrophile]	Rate = k[nucleophile]×[electrophile]
Mechanism	multiple steps with carbocation intermediate	one step, concerted
Reaction Diagram		
Stereochemistry	racemization on reaction center	inversion on reaction center
Electrophilic Substrate	tertiary 3° > secondary 2° > primary 1° and methyl	primary 1° and methyl > secondary 2° > tertiary 3°
Nucleophile	weak nucleophile, solvolysis	strong nucleophile

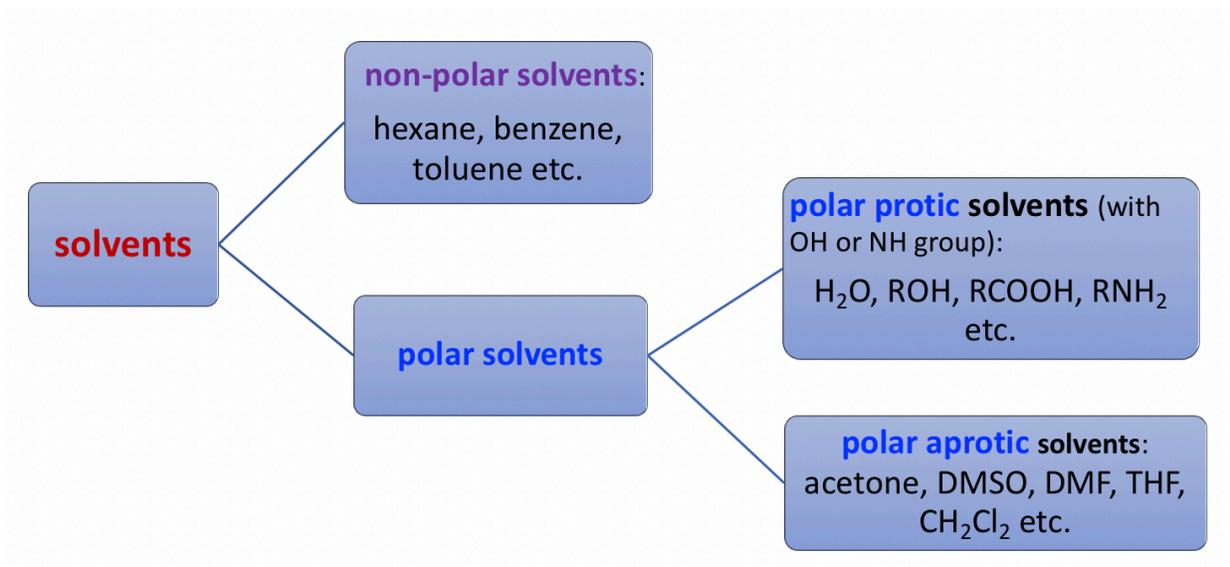
Table 7.2 Comparison between S<sub>N</sub>1 and S<sub>N</sub>2 reactions

### 7.5.2 Solvent Effect on S<sub>N</sub>1 and S<sub>N</sub>2 Reactions

Other than the factors we have talked about so far, solvents are another key factor that affect nucleophilic substitution reactions. A proper solvent is required to facilitate a certain mechanism. For some cases, choosing the appropriate solvent is an effective way to control on which pathway the reaction proceeds.

To understand the solvent effect, we first need to have more detailed discussions about solvents, then learn how to choose a good solvent for a specific reaction.

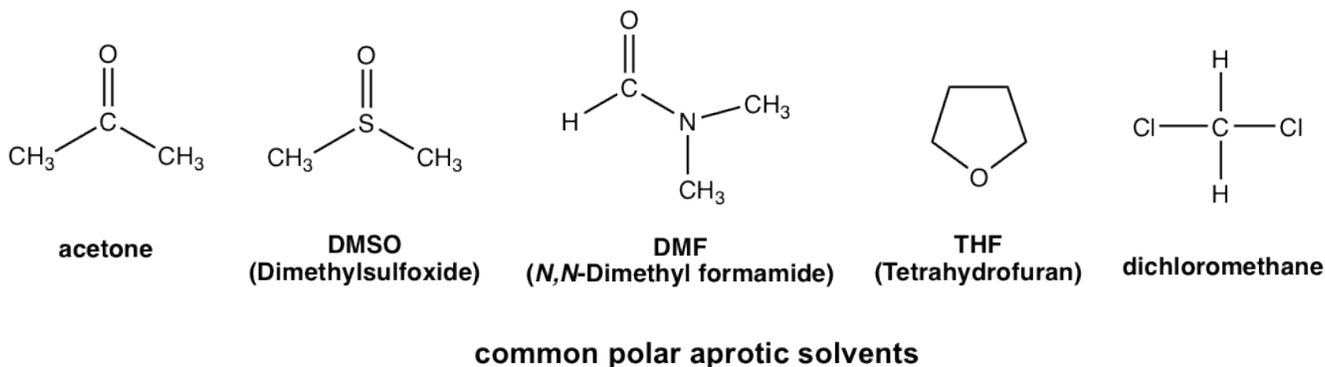
Solvents can be divided into three major categories based on the structures and polarities: non-polar, polar protic and polar aprotic solvents.



Non-polar solvents are non-polar compounds (hexane, benzene, toluene, etc.)

Polar protic solvents are compounds containing OH or NH groups that are able to form hydrogen bonds. Polar protic solvents are highly polar because of the OH or NH group.

Polar aprotic solvents are group solvents with a medium range of polarity. They are polar because of polar bonds like C=O or S=O, but the polarity is not as high as the OH or NH group. Typical examples of polar aprotic solvents include acetone, DMSO, DMF, THF, and CH<sub>2</sub>Cl<sub>2</sub>.



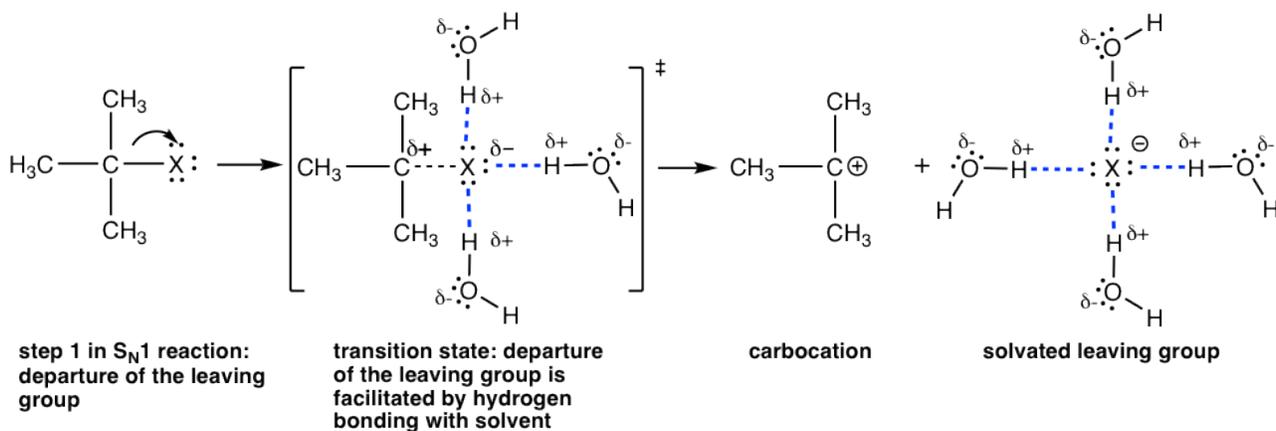
The general guideline for solvents regarding the nucleophilic substitution reaction is:

- S<sub>N</sub>1 reactions are favored by polar protic solvents (H<sub>2</sub>O, ROH, etc.), and usually are solvolysis reactions.
- S<sub>N</sub>2 reactions are favored by polar aprotic solvents (acetone, DMSO, DMF, etc.).

## Polar Protic Solvents Favor S<sub>N</sub>1 Reactions

In an S<sub>N</sub>1 reaction, the leaving group leaves and a carbocation is formed in the first step, which is also the rate-determining step. The polar solvent, such as water, and MeOH, can form hydrogen bonding with the leaving group in

the transition state of the first step, thereby lowering the energy of the transition state that leads to the carbocation and speeding up the rate-determining step. As a result, polar protic solvents facilitate  $S_N1$  reactions. It is very common that polar protic solvents also serve as nucleophiles for  $S_N1$  reactions so  $S_N1$  reactions are usually solvolysis reactions, as we learned earlier.



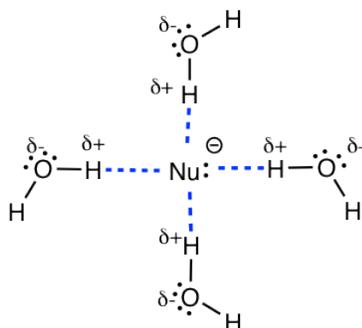
### protic solvent ( $H_2O$ as an example) facilitates the formation of carbocation intermediate in $S_N1$ reaction

Figure 7.5a Protic solvent (ex.  $H_2O$ ) facilitates the formation of carbocation intermediate in  $S_N1$  reaction

## Polar Aprotic Solvents Favor $S_N2$ Reactions

Strong nucleophiles are required in  $S_N2$  reactions, and strong nucleophiles are usually negatively charged species, such as  $OH^-$ ,  $CH_3O^-$ , and  $CN^-$ . These anions must stay with cations in a salt format like  $NaOH$  or  $CH_3ONa$ . Since salts are insoluble in a non-polar solvent, non-polar solvents are not appropriate choices, and we need polar solvents that can dissolve the salts.

The issue for polar protic solvents is that the nucleophile anions will be surrounded by a layer of solvent molecules with hydrogen bonds, and this is called the solvation effect. The solvation effect stabilizes (or encumbers) the nucleophiles and hinders their reactivities in an  $S_N2$  reaction. Therefore, polar protic solvents are not suitable for  $S_N2$  reactions.



### protic solvent does not work for $S_N2$ : nucleophile is solvated and encumbered by protic solvent

Figure 7.5b Protic solvent does not work for  $S_N2$ : nucleophile is solvated and encumbered by protic solvent

As a result, polar aprotic solvents, such as acetone and DMSO are the best choice for  $S_N2$  reactions. They are polar enough to dissolve the salt format nucleophiles and they also do not interact as strongly with anions to hinder their reactivities. The nucleophile anions still move around freely in polar aprotic solvents to act as nucleophiles.

The reaction rates for  $S_N2$  reactions in different solvents are provided in Table 7.3 below, and the polar aprotic solvent DMF proved to be the best choice that speeds up the reaction significantly.

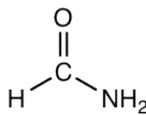
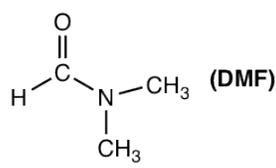
<b>reaction:</b> $\text{CH}_3\text{I} + \text{Cl}^- \rightarrow \text{CH}_3\text{Cl} + \text{I}^-$	
<b>solvent</b>	<b>relative rate</b>
$\text{CH}_3\text{OH}$	1
	12.5
 (DMF)	1,200,000

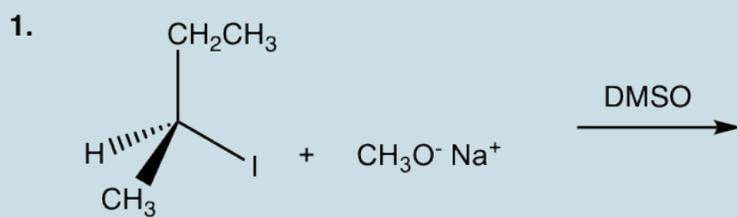
Table 7.3 The rate comparison of  $S_N2$  reactions in different solvents

### 7.5.3 The Choice of Reaction Pathway: $S_N1$ or $S_N2$ ?

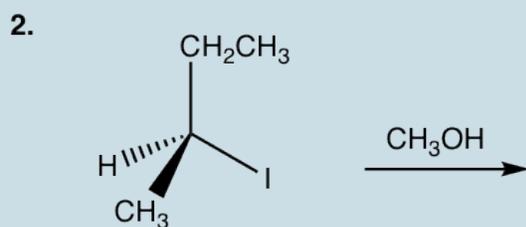
With all the knowledge we have learned about  $S_N1$ ,  $S_N2$  reactions and reaction conditions, we should be able to determine whether a given reaction goes with the  $S_N1$  or  $S_N2$  pathway or design a proper reaction that will produce the desired product(s). The reaction pathway predominantly depends on the nature of the substrates (primary, secondary, or tertiary), and the choice of proper reaction condition serves as a way to facilitate the process.

- Primary and methyl substrates predominantly undergo  $S_N2$  reactions.
- Tertiary substrates go with the  $S_N1$  process.
- The reaction of secondary substrates mainly relies on the conditions applied. The conditions include nucleophiles, solvents, etc.

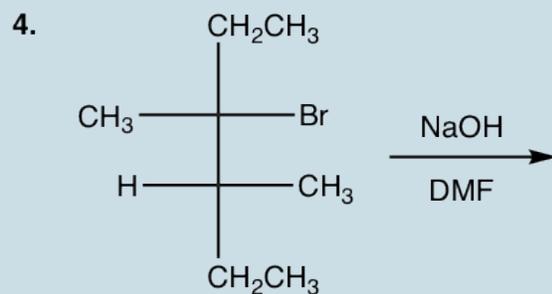
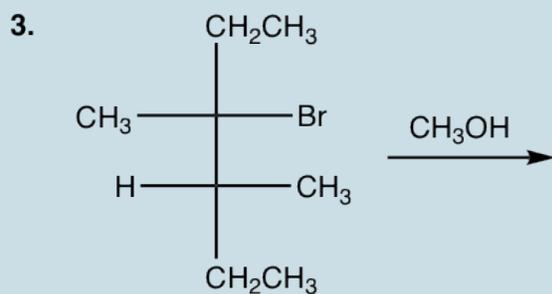
Show the product(s) of the following reactions:



(S)-2-iodobutane

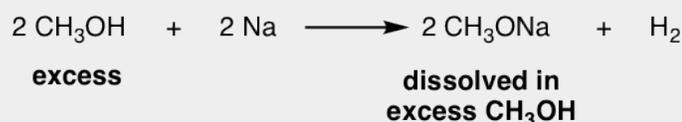


(S)-2-iodobutane



## Some practical tips for working on S<sub>N</sub>1, and S<sub>N</sub>2 reactions:

1. As we understand, strong nucleophiles are required for S<sub>N</sub>2 reactions, and most of the strong nucleophiles are those with negative charges, for example, OH<sup>-</sup> and OR<sup>-</sup>. These nucleophiles can be either shown as anions OH<sup>-</sup>, CH<sub>3</sub>O<sup>-</sup>, C<sub>2</sub>H<sub>5</sub>O<sup>-</sup>, or in a salt format like NaOH, KOH, CH<sub>3</sub>ONa, or C<sub>2</sub>H<sub>5</sub>ONa in the reaction conditions. You should understand that it is the same thing. The anion format is easy to identify and also highlights the nature of these species; however, since anions must stay together with counter cations as salt, the salt format shows the actual chemical formula of the compound used in the reaction.
2. Since a polar aprotic solvent favors S<sub>N</sub>2 reactions, any of the above anions or salt can be used together with DMSO, DMF, etc., such as OH<sup>-</sup>/DMSO or CH<sub>3</sub>ONa/DMF. However, sometimes you may see a combination like CH<sub>3</sub>ONa/CH<sub>3</sub>OH, which is the combination of CH<sub>3</sub>O<sup>-</sup> together with its conjugate acid CH<sub>3</sub>OH. It may seem contradictory, so why is a strong nucleophile for S<sub>N</sub>2 combined with a solvent for S<sub>N</sub>1? The reality is that CH<sub>3</sub>ONa here still acts as a strong nucleophile and can be used for an S<sub>N</sub>2 reaction, and CH<sub>3</sub>OH is the solvent for CH<sub>3</sub>ONa. The reason why CH<sub>3</sub>OH is used together as a solvent is that the CH<sub>3</sub>ONa can be prepared by treating an alcohol with Na. For example:



Other alcohols can also react with Na metal (or potassium metal, K) to generate the corresponding R<sub>2</sub>ONa.

The reaction between alcohol and NaH can be used as well.



Since alcohol is in excess in the above reactions, it is also a good solvent for the resulting alkoxide, and an RO<sup>-</sup>/ROH combination is used commonly together. The RO<sup>-</sup> in this combination can be used as a strong nucleophile for an S<sub>N</sub>2 reaction or a base in an elimination reaction (Chapter 8).

## 7.6 Extra Topics on Nucleophilic Substitution Reactions

Our discussions so far have focused on fundamental concepts about  $S_N1$  and  $S_N2$  mechanisms, and the reactions we have learned about proceed regularly. Some other conditions can be “added” to the basic nucleophilic substitution reactions to make the reaction look different or more challenging. However, understanding the basic concepts well is very helpful for us to deal with various situations. The reaction may look different, but it is essentially still the same.

### 7.6.1 $S_N1$ Reaction with Carbocation Rearrangement

Let's take a look at an  $S_N1$  reaction.

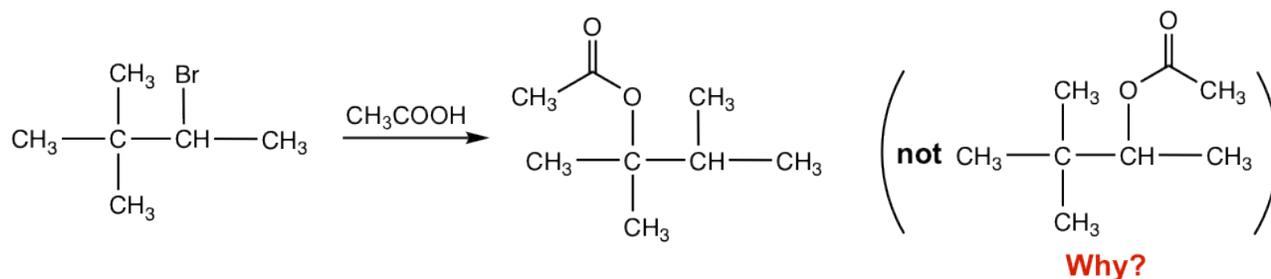


Figure 7.6a Reaction with Carbocation Rearrangement

With the secondary substrate and neutral nucleophile ( $\text{CH}_3\text{COOH}$ ), this is an  $S_N1$  reaction, also the solvolysis that  $\text{CH}_3\text{COOH}$  acts as both a solvent and nucleophile. It is supposed to give the acetate as a product, with the acetate replacing the Br. However, as shown in the reaction equation, the acetate was not introduced on the carbon with the leaving group Br but was connected to the next carbon instead. What is the reason for the unexpected structure of the product?

For reactions involving a carbocation intermediate, it is a common phenomenon that the carbocation *might* rearrange if such a rearrangement leads to a more stable carbocation; this is called carbocation rearrangement. Because of the carbocation rearrangement, the product of the above reaction is different than expected. This can be explained with the step-by-step mechanism below.

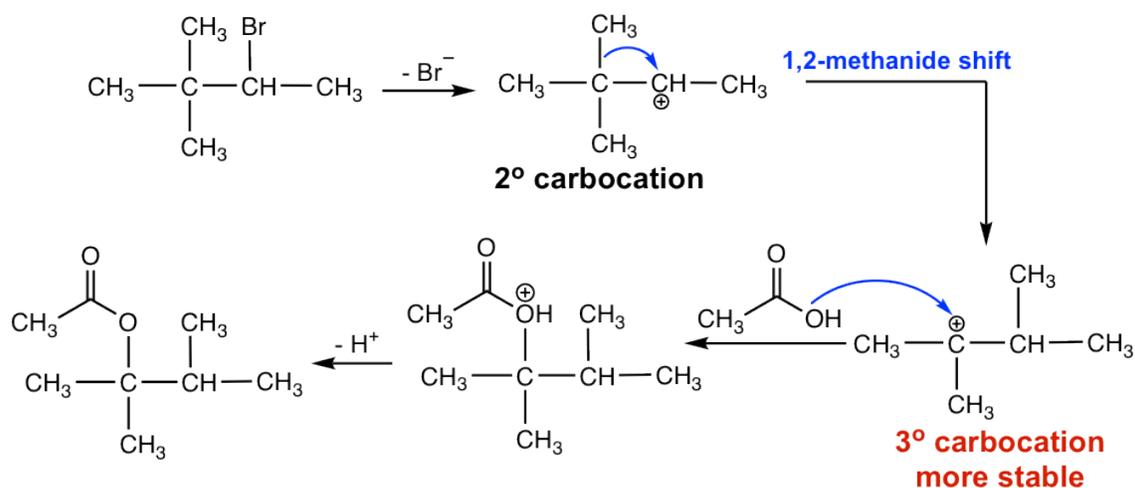


Figure 7.6b Step-by-step carbocation rearrangement

When  $\text{Br}^-$  leaves, the initial carbocation formed is a secondary one. The  $\text{CH}_3$  group on the next carbon then shifts with its bonding electrons to the positively charged carbon and creates a new, more stable tertiary carbocation. The tertiary carbocation then reacts with nucleophile  $\text{CH}_3\text{COOH}$  to give the final acetate product. The  $\text{CH}_3$  group shifts with the electron pair, and such a move is called 1,2-methanideshift. “1,2-” here refers to the movement that occurs between two adjacent carbons, but not necessarily C1 and C2.

Other than the  $\text{CH}_3$  group, the H atom in other reactions could shift as well with the electron pair if such a shift can lead to a more stable carbocation. The shift of hydrogen is called a 1,2-hydride shift. A couple of notes about the carbocation rearrangement:

- Any reaction that involves a carbocation intermediate might have a rearrangement.
- Not all carbocations rearrange. Carbocations only rearrange if they become more stable as a result of the rearrangement.
- The shift is usually a 1,2-shift, which means it occurs between two adjacent carbons.

## 7.6.2 Intramolecular Nucleophilic Substitution Reaction

For the reactions we learned before, the substrate with a leaving group and the nucleophile are always two separate compounds. It is actually possible for one compound to contain both a leaving group and nucleophile, and the reaction occurs within the same molecule. Such a reaction is called an intramolecular (*intra*, Latin for “within”) reaction. A cyclic product is obtained from an intramolecular reaction.

Let’s talk about the reaction mechanism that rationalizes the structure and stereochemistry of the product for the following reaction.

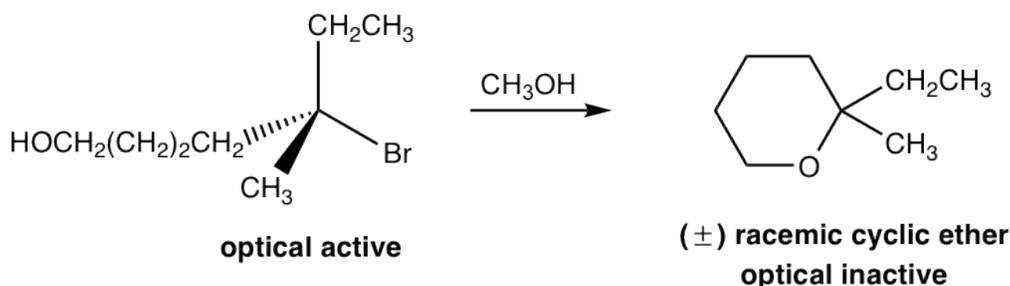


Figure 7.6c Intramolecular Nucleophilic Substitution Reaction

### Mechanism

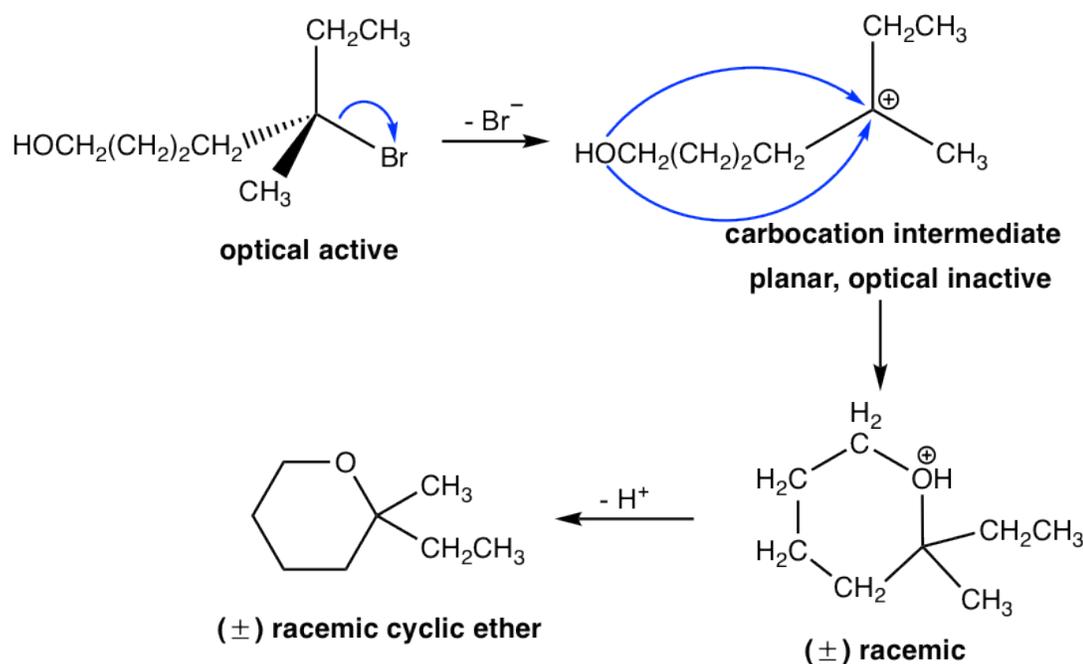


Figure 7.6d Intramolecular Mechanism

In the above reaction, the reactant has two functional groups, bromide (Br) and alcohol (OH). A compound with two functional groups is called a bifunctional molecule. In this reactant, Br is connected to a tertiary carbon, which is a good substrate for an  $\text{S}_{\text{N}}1$  reaction, and OH is a good nucleophile for  $\text{S}_{\text{N}}1$  as well, so the substitution reaction can occur within the same molecule via the  $\text{S}_{\text{N}}1$  mechanism. So, the reaction occurs between one end of the molecule, Br, which acts as the leaving group, and the other part of the molecule, OH, which acts as the nucleophile. As a result, a six-membered cyclic ether is formed as the product.

Since the reaction occurs with the  $\text{S}_{\text{N}}1$  mechanism, the carbocation intermediate is in a trigonal planar shape, and the nucleophile can attack from either side of the carbocation to give both enantiomers. Therefore, the product is a racemic mixture that is optical inactive. This is consistent with the stereochemistry feature of the  $\text{S}_{\text{N}}1$  reaction we learned about before.

Usually, if an intramolecular reaction can produce a five- or six-membered ring as the product, the reaction will be highly favored because of the special stability of five- or six-membered rings.

## 7.6.3 Converting a Poor Leaving Group to a Good Leaving Group

In early discussions about leaving groups (section 7.3), we mentioned the importance of a good leaving group for both  $S_N1$  and  $S_N2$  reactions and that the substitution reaction will not occur if a poor leaving group is present. For some situations, however, a poor leaving group could be converted to a good leaving group to make the reaction feasible. We will see a couple of strategies for such a purpose.

### By Acid Catalyst $H^+$

Example: Propose the mechanism to rationalize the reaction.

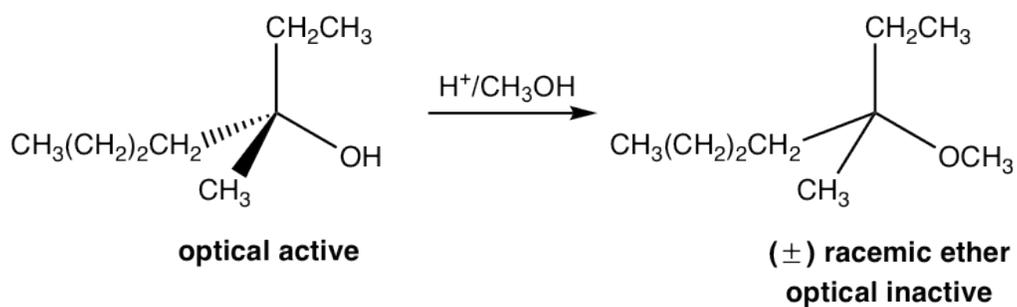
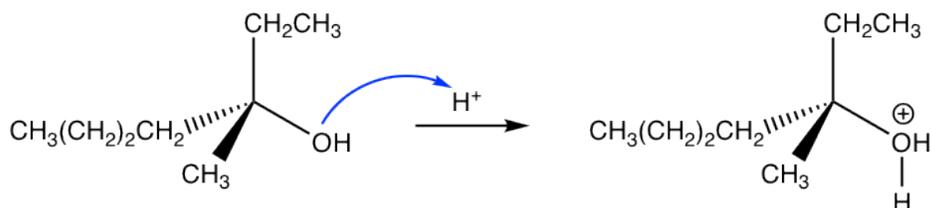


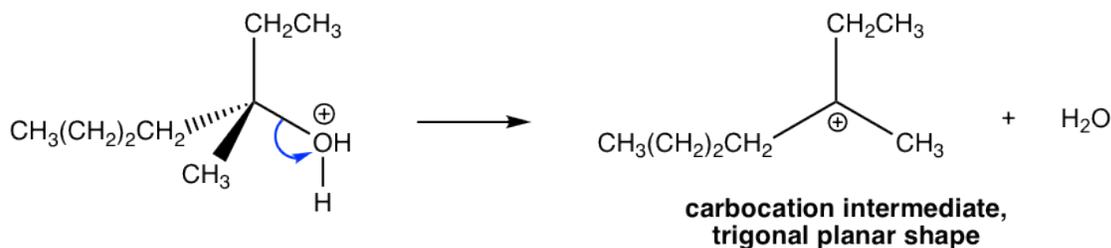
Figure 7.6e Reaction

## Mechanism:

### Step 1: protonation of OH



### Step 2: H<sub>2</sub>O departs as leaving group



### Step 3: CH<sub>3</sub>OH attacks carbocation



### Step 4: Deprotonation to give neutral product

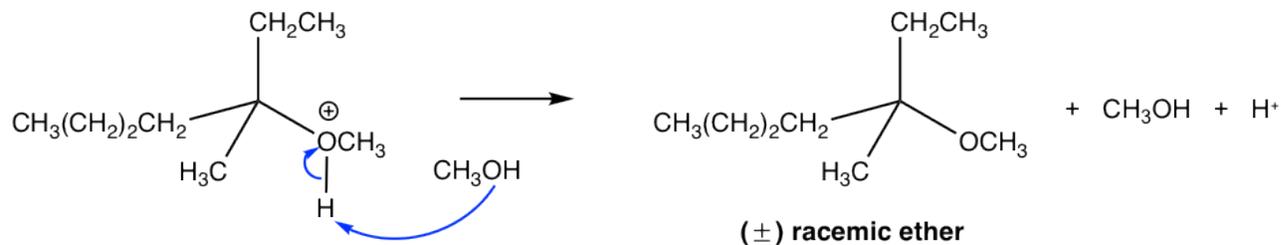


Figure 7.6f Mechanism

The last three steps in the above mechanism are the standard steps of the S<sub>N</sub>1 mechanism. However, the reaction will not proceed without the first step. In the first step, which is an acid-base reaction, a proton is rapidly transferred to the OH group and the alcohol gets protonated. By protonation, the OH group is converted to H<sub>2</sub>O, which is a much weaker base and therefore a good leaving group. In step 2, a water molecule departs with the electron pair and leaves behind a carbocation intermediate. The following steps are just S<sub>N</sub>1, which explains why the product is a racemic mixture. The acid H<sup>+</sup> was regenerated in step 4 and can be reused for further reactions; therefore, only a catalytical amount of H<sup>+</sup> is necessary to start the process.

## By Sulfonyl Chloride

Another commonly applied method for converting an OH group to a better leaving group is by introducing a sulfonate ester. When alcohol reacts with sulfonyl chloride, with the presence of a weak base, the sulfonate ester is formed.

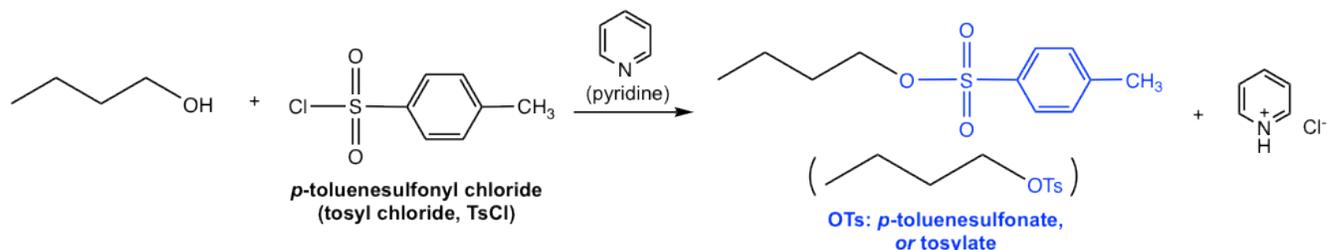


Figure 7.6g Alcohol reacting with tosyl chloride to produce tosylate

As the example shown above, when *p*-toluenesulfonyl chloride (tosyl chloride, TsCl) is used, the resulting ester is *p*-toluenesulfonate (tosylate, OTs). Does the tosyl group look familiar to you? It should, as we learned about this species in section 3.2. As the conjugate base of strong acid *p*-toluenesulfonic acid (TsOH), OTs is a very weak base and therefore an excellent leaving group. Pyridine here acts as a weak base to neutralize the side product HCl and facilitate the reaction to completion. The detailed mechanism for this reaction is not required in this course.

Other than introducing OTs, other commonly applied sulfonyl chlorides include MsCl and TfCl, and the sulfonate ester OMs (mesylate) and OTf (triflate) are formed respectively.

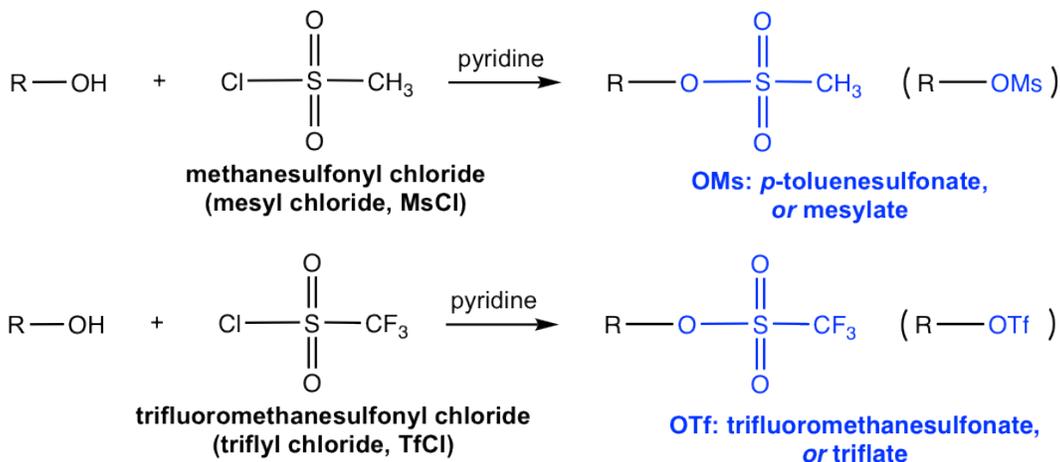


Figure 7.6h Conversion of Alcohol to Mesylate or Triflate

Once the primary alcohol has been converted to OTs (or OMs, OTf), it is then a good substrate for an S<sub>N</sub>2 reaction. With the appropriate nucleophile added in a separate step, for example, CH<sub>3</sub>O<sup>-</sup>, the S<sub>N</sub>2 reaction takes place readily to give ether as the final product, as shown below.

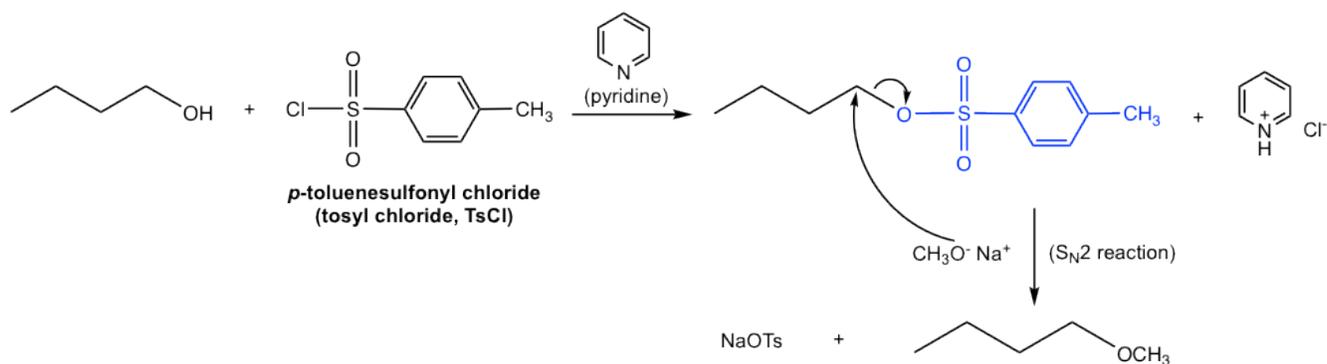


Figure 7.6i Step-by-step synthesis scheme of butyl methyl ether from 1-butanol (with structures of intermediates shown)

The overall synthesis of butyl methyl ether from 1-butanol involves two separate steps: the conversion of OH to OTs and then the replacement of OTs by  $\text{CH}_3\text{O}$  through an  $\text{S}_{\text{N}}2$  reaction. The two steps have to be carried out one after the other; however, the whole synthesis scheme can also be shown below:

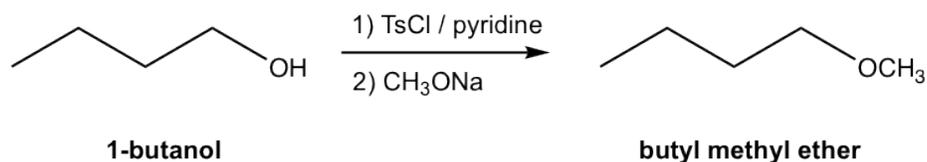
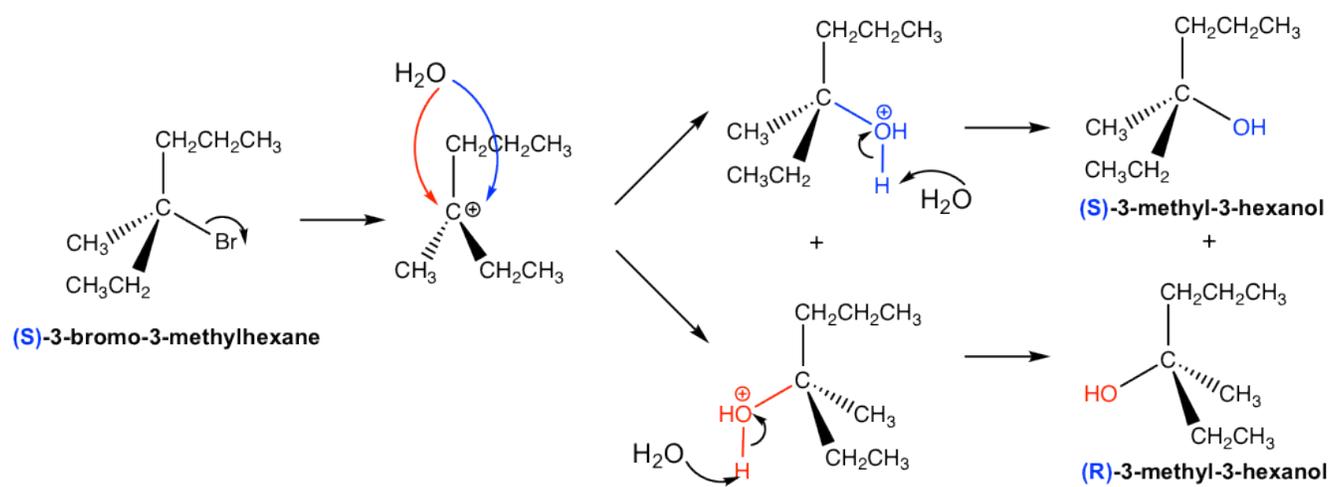


Figure 7.6j Synthesis scheme of butyl methyl ether from 1-butanol (structures of intermediates are NOT shown)

Note:

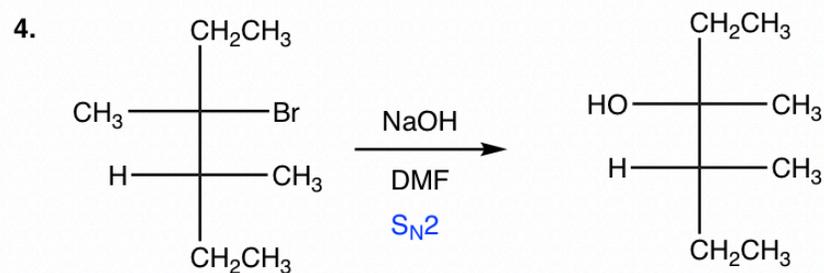
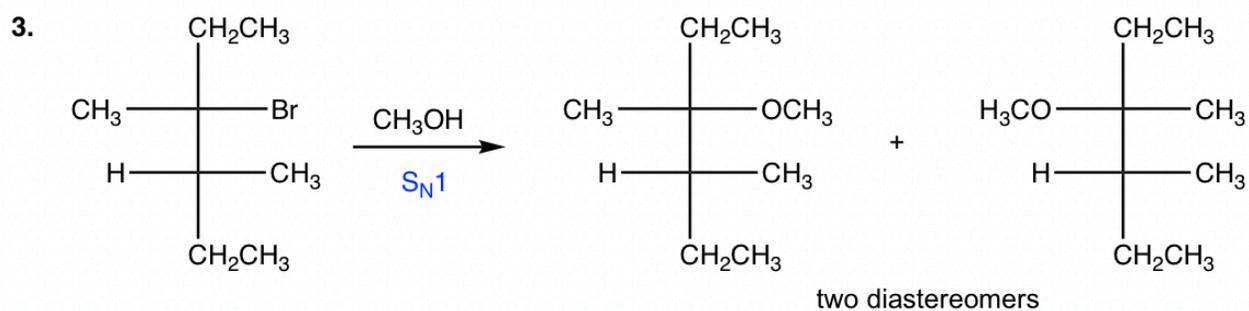
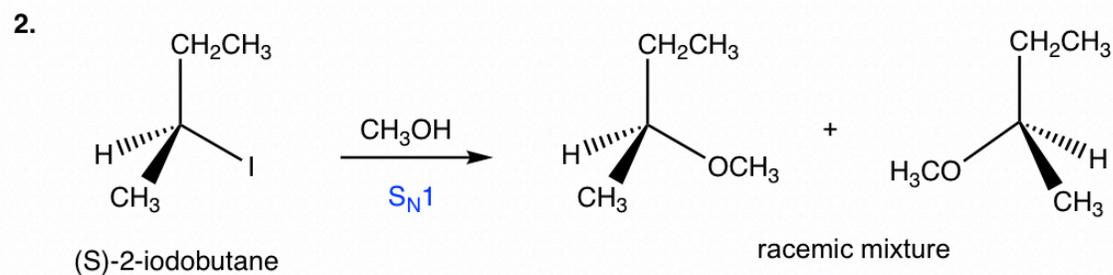
- Figure 7.6j represents the common and conventional way to show multiple-step synthesis in organic chemistry. The reaction conditions (reagent, catalyst, solvent, temperature, etc.) for each step are shown on top and bottom of the equation arrow. Only the structures of the starting material and final product(s) are shown, and the structures of the intermediate products for each step are not included.
- The individual steps need to be labeled as 1), 2), etc. for the proper order, and they can not be mixed together.





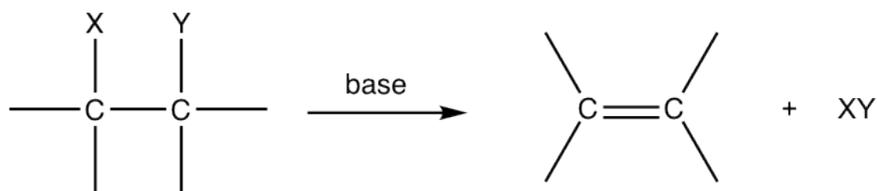
7.4

Show the product(s) of the following reactions:



# CHAPTER 8: ELIMINATION REACTIONS

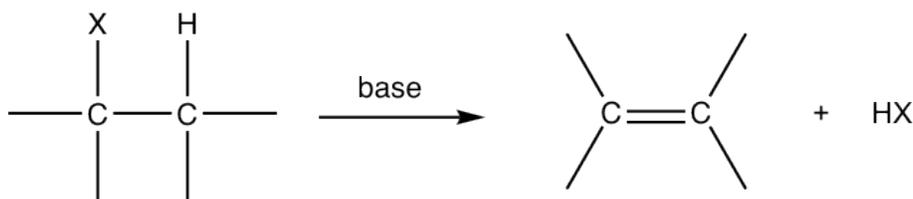
A nucleophilic substitution reaction is not the only possible reaction for alkyl halides and other substrates with a good leaving group. These substrates can also undergo elimination reactions. In an elimination reaction, a small molecule (XY) is removed from two adjacent atoms of the reactant, and a multiple bond is formed in the product:



## General equation of elimination reaction

Figure 8.0a General equation of elimination reaction

For an elimination reaction of alkyl halides, the major product alkene is produced together with the small HX (X is halogen) molecule, which is the side inorganic product. Such reaction with removal of a proton and a halide ion is called dehydrohalogenation. Dehydrohalogenation is a commonly applied method for the synthesis of alkene.



## Dehydrohalogenation of alkyl halide

Figure 8.0b Dehydrohalogenation of alkyl halide

In the discussions of elimination reactions, the carbon atom that bonded to the leaving group (halogen for alkyl halide) is called the alpha ( $\alpha$ ) carbon atom, and the carbon atom adjacent to  $\alpha$ -carbon is called the beta ( $\beta$ ) carbon atom. In dehydrohalogenation, the hydrogen atom on  $\beta$ -carbon is eliminated together with halogen, as HX; therefore, the reaction is often called  $\beta$ -elimination or 1,2-elimination. (The number 1,2- indicates that the atoms being removed are on two adjacent carbons and not necessarily C1 and C2 atoms.)

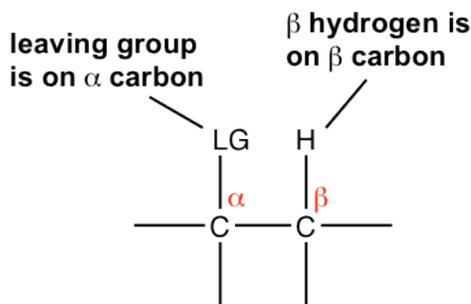


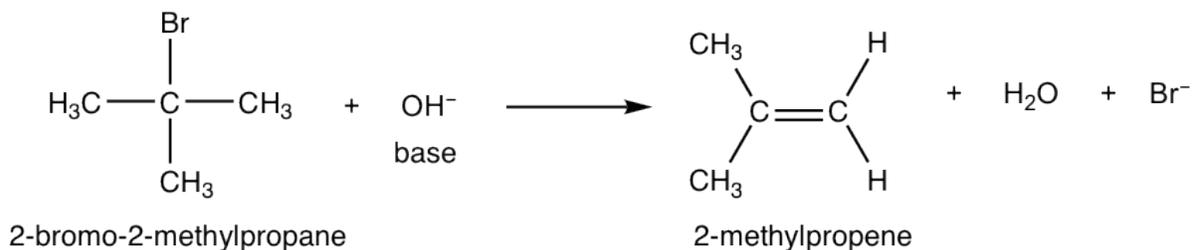
Figure 8.0c Alpha and Beta carbon

Beside the substrate, a base is required for elimination reactions other than the nucleophile for substitution. Similar to substitution reactions, elimination reactions also have different rate laws, and therefore involve different mechanisms. The elimination mechanisms are E1 and E2. You may expect that E1 is a unimolecular reaction with the first order rate law and E2 is the second order bimolecular reaction. That is correct. We will go through the mechanism in detail first, then compare between elimination and substitution.

# 8.1 E2 Reactions

## 8.1.1 E2 Mechanism

The E2 mechanism is the bimolecular elimination mechanism, and the reaction rate depends on the concentration of both the substrate and base. We will take the elimination reaction of 2-bromo-2-methylpropane as an example for discussion.



$$\text{Reaction Rate} = k \times [(\text{CH}_3)_3\text{Br}] \times [\text{OH}^-]$$

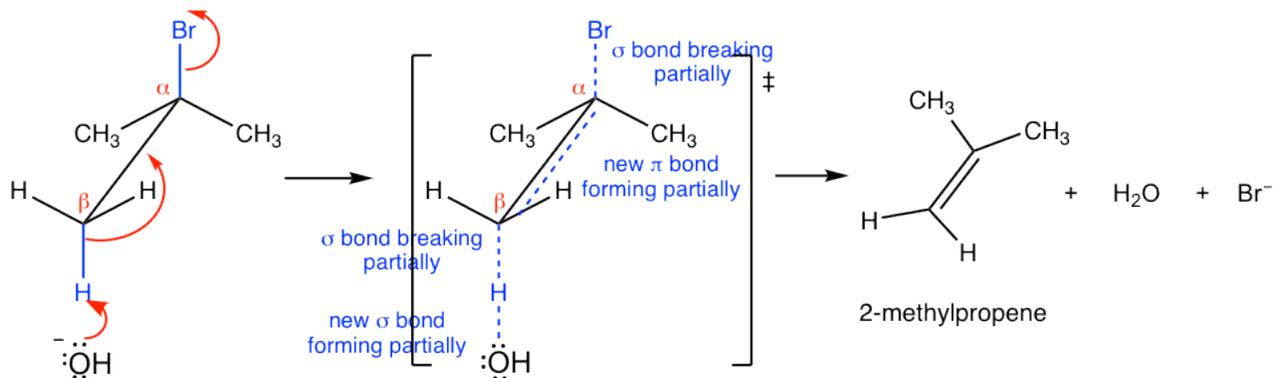
**second-order reaction**

Figure 8.1a Bimolecular Elimination Reaction

It was mentioned earlier that HX is the side product of dehydrohalogenation, why there is no HX (HBr for this reaction) in the reaction equation? It could be understood that with the presence of an excess base (OH<sup>-</sup>) in the reaction mixture, HBr reacts with OH<sup>-</sup> to give H<sub>2</sub>O and Br<sup>-</sup>. The following discussion of the mechanism will help you to understand this better.

The E2 mechanism is also a single-step concerted reaction, similar to S<sub>N</sub>2, with multiple electron pair transfers that happen at the same time.

## E2 Reaction Mechanism:



2-bromo-2-methylpropane

Figure 8.1b E2 Reaction Mechanism

The base,  $\text{OH}^-$ , uses its electron pair to attack a  $\beta$ -hydrogen on  $\beta$ -carbon and starts to form a bond; at the same time, the  $\beta$  C-H  $\sigma$  bond begins to move in to become the  $\pi$  bond of a double bond, and meanwhile, Br begins to depart by taking the bonding electrons with it. A transition state is formed in the reaction process with partially breaking and partially forming bonds. At the completion of the reaction, the C=C double bond and  $\text{H}_2\text{O}$  molecule are fully formed, with  $\text{Br}^-$  leaving completely.

Since both the substrate (halide) and the base are involved in the single-step mechanism, E2 is the second-order reaction.

### 8.1.2 Regioselectivity of E2 reaction: Zaitsev's Rule vs Hofmann's Rule

For the reaction we talked about in the above section, there are three  $\beta$ -carbons in the substrate 2-bromo-2-methylpropane; however, they are all identical so the reaction gives only one single elimination product: 2-methylpropene.

For other alkyl halides, if there are different  $\beta$ -carbons in the substrate, then the elimination reaction may yield more than one product. For example, the dehydrohalogenation of 2-bromo-2-methylbutane can produce two products: 2-methyl-2-butene and 2-methyl-1-butene by following two different pathways.

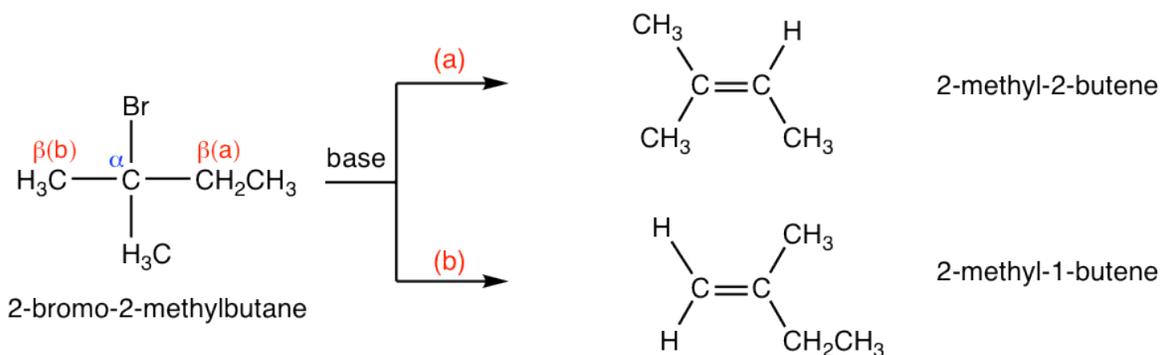


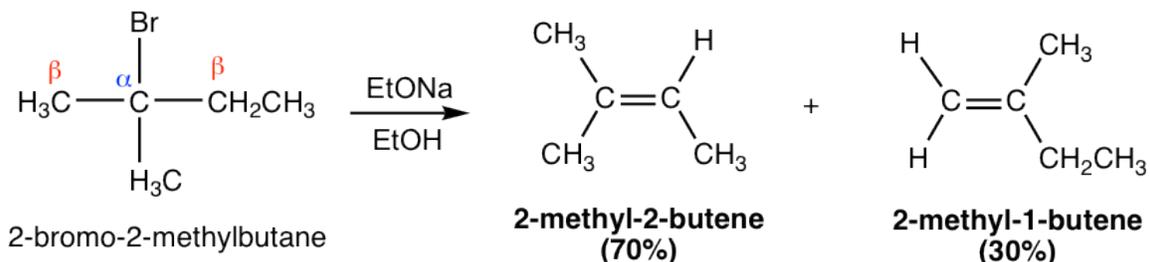
Figure 8.1c Regioselectivity of E2 reaction

Between the two possible products, 2-methyl-2-butene is a trisubstituted alkene, whereas 2-methyl-1-butene is monosubstituted. For alkenes, the more alkyl groups bonded on the double bond carbons, the more stable the alkene is. Generally, the relative stability of alkenes with a different number of substituents is:

tetrasubstituted > trisubstituted > disubstituted > monosubstituted > ethene

Therefore, 2-methyl-2-butene is more stable than 2-methyl-1-butene. When a small-sized base is used for the elimination reaction, such as  $\text{OH}^-$ ,  $\text{CH}_3\text{O}^-$ , or  $\text{EtO}^-$ , the relative stability of the product is the key factor in determining the major product. As a result, 2-methyl-2-butene is the major product of the above reaction.

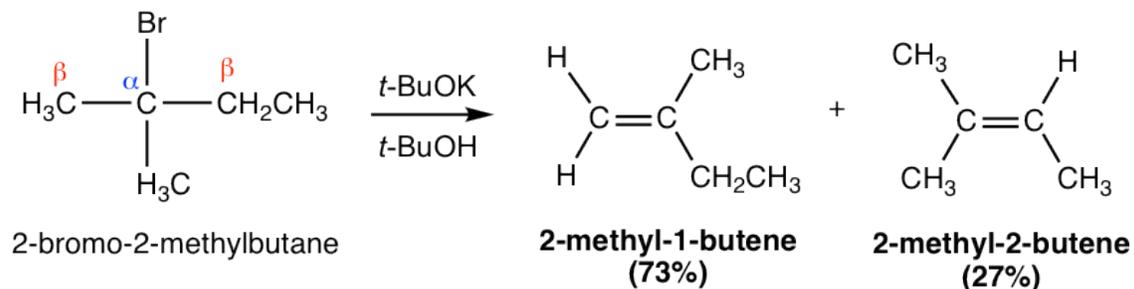
As a general trend, when a small base is applied, the elimination products can be predicted by Zaitsev's rule, that said the more substituted alkene is obtained preferably. So, Zaitsev's rule essentially can be explained by the higher stability of the more substituted alkenes.



### Elimination reaction occurs by following Zaitsev's rule with small base applied

Figure 8.1d Elimination reaction occurs by following Zaitsev's rule with a small base applied

However, if a bulky base is applied in the elimination, such as  $t\text{-BuOK}$ , the reaction favors the formation of less substituted alkenes.



### Elimination reaction occurs by following Hofmann rule with bulky base applied

Figure 8.1e Elimination reaction occurs following Hofmann rule with bulky base applied

This is mainly because of steric hindrance. With  $t\text{-BuO}^-$  attacking the  $\beta$ -hydrogen, it is difficult for this big, bulky base to approach the hydrogens from the  $\beta$ -carbon that is bonded with more substituents (as shown in the pathway (a) below), while the hydrogen of the methyl group is much easier to access (in the pathway (b) instead). When the elimination yields the less substituted alkene, it is said that it follows Hofmann's rule.

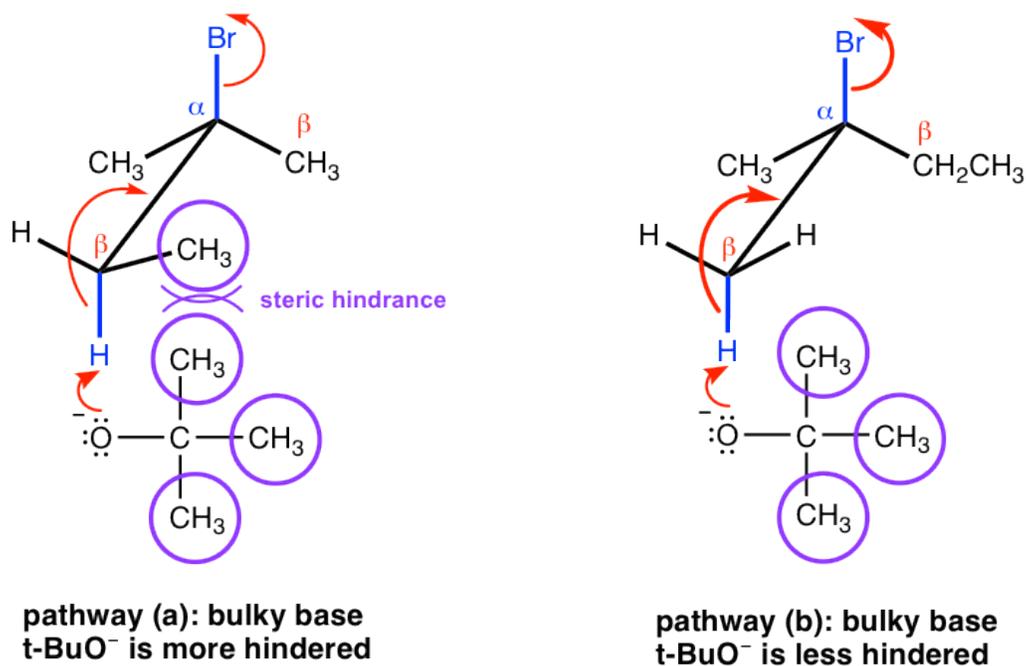
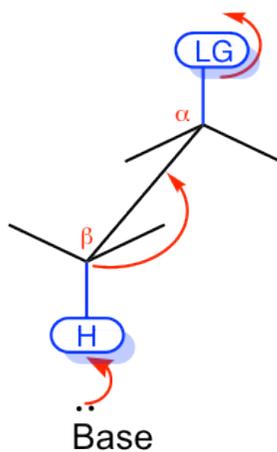


Figure 8.1f Hofmann rule: Bulky base  $t\text{-BuO}^-$  (pathway a), Bulky base  $t\text{-BuO}^-$  is less hindered

### 8.1.3 Stereochemistry of the E2 Reaction

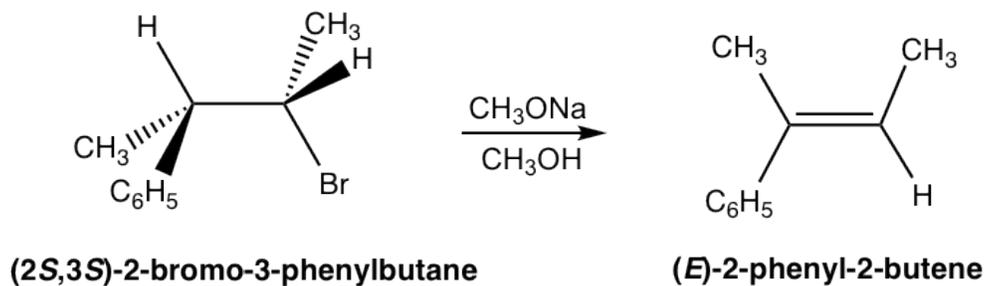
The E2 mechanism has special stereochemistry requirements to ensure it proceeds. First, the bond connected with the leaving group and the bond connected with the H must be in the same plane to allow the proper orbital overlapping of the two carbons in the formation of the  $\pi$  bond of the alkene product. Second, the leaving group and H must be in anti-position to each other. This is because the anti-position allows the transition state of the reaction to be in the more stable staggered conformation, which helps to lower the energy level of the transition state and speed up the reaction. Overall, the E2 reaction proceeds with the leaving group, and H is in an anti-coplanar conformation.



**Anti coplanar conformation of H and LG is required in E2 mechanism**

Figure 8.1g Anti-coplanar conformation of H and LG is required in E2 mechanism

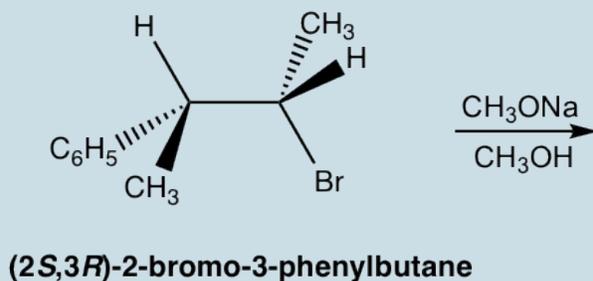
Because of the anti-coplanar conformation requirement for the E2 reaction, one stereoisomer will be produced preferably over the other, and this is called stereoselectivity. For the following example, the elimination of (2*S*,3*S*)-2-bromo-3-phenylbutane produces the *E* isomer specifically, not the *Z* isomer at all. This is because when H is in an anti-position to the leaving group Br, the whole compound is in a staggered conformation, and the other groups retain their relative position in elimination which leads to the *E* isomer.



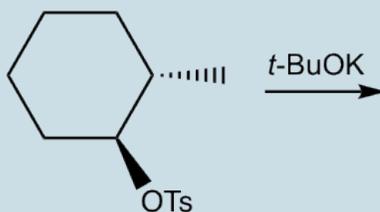
### Exercises 8.1

Show elimination product of the following reactions

I.



2.



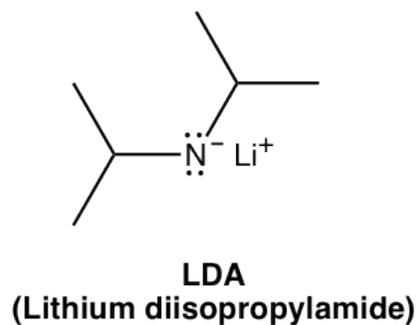
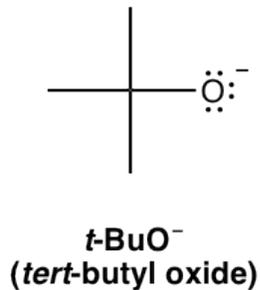
Answers to Chapter 8 Practice Questions

### 8.1.4 Bases in E2 Reactions (Brief Summary)

The most commonly applied bases in an E2 reaction are hydroxide  $\text{OH}^-$  and alkoxide  $\text{RO}^-$ . Specifically, the combination of a base with the corresponding alcohol is used broadly, such as  $\text{CH}_3\text{ONa}/\text{CH}_3\text{OH}$  or  $\text{C}_2\text{H}_5\text{ONa}/\text{C}_2\text{H}_5\text{OH}$ .

Examples of small bases:  $\text{OH}^-$ ,  $\text{CH}_3\text{O}^-$ ,  $\text{C}_2\text{H}_5\text{O}^-$ , and  $\text{NH}_2^-$

Examples of big bulky bases:  $t\text{-BuO}^-$  and LDA (lithium diisopropylamide) with the structures shown below.



## 8.2 E<sub>I</sub> Reactions

### E<sub>I</sub> Mechanism

Similar to substitutions, some elimination reactions show first-order kinetics. These reactions go through the E<sub>I</sub> mechanism, which is the multiple-step mechanism that includes the carbocation intermediate.

When t-butyl bromide reacts with ethanol, a small amount of elimination products is obtained via the E<sub>I</sub> mechanism.

#### Reaction



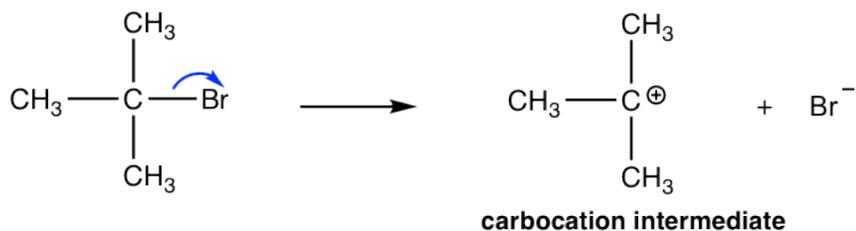
$$\text{Reaction Rate} = k \times [(\text{CH}_3)_3\text{Br}]$$

**first-order** reaction

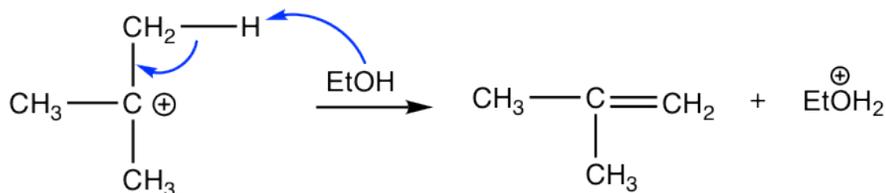
The overall elimination involves two steps:

#### Mechanism

**Step 1:** Cleavage of C-Br bond **slowly** to form the carbocation intermediate.



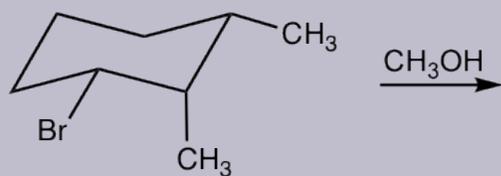
**Step 2:** base (EtOH) removes H from a β-carbon, and double bond produced.



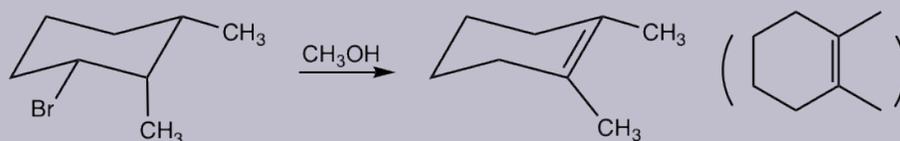
Step 1: The bromide dissociates and forms a tertiary (3°) carbocation. This is a slow bond-breaking step, and it is also the rate-determining step for the whole reaction. Since only the bromide substrate was involved in the rate-determining



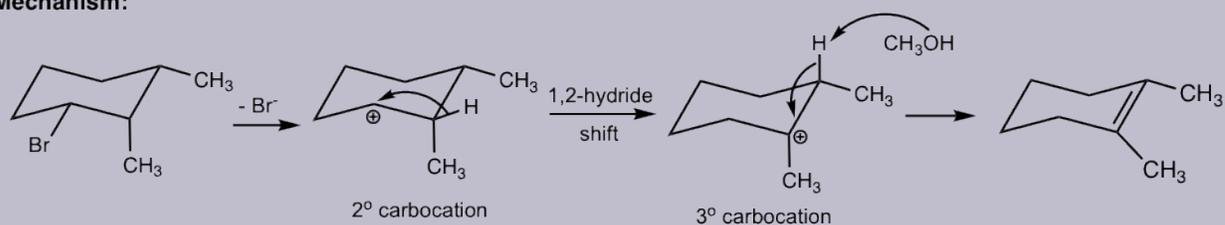
Examples: Show elimination product of the following reaction.



**Answer:**



**Mechanism:**



## 8.3 E1/E2 Summary

The comparison between E1 and E2, in terms of the rate law, mechanism, reaction condition, etc., can be summarized in Table 8.1.

	E1	E2
Rate law	Rate = $k \times [\text{substrate}]$	Rate = $k \times [\text{substrate}] \times [\text{base}]$
Mechanism	multiple steps with carbocation intermediate	one step, concerted
Product	More substituted, more stable alkenes	small base: more substituted alkenes (Zaitsev's rule) bulky base: less substituted alkenes (Hoffmann rule)
Substrate	tertiary 3° > secondary 2° > primary 1° (no E1)	tertiary 3° > secondary 2° > primary 1°
Base	weak base, (H <sub>2</sub> O, ROH)	strong base (OH <sup>-</sup> , RO <sup>-</sup> , etc.)

Table 8.1 Comparison between E1 and E2 mechanism

The competition between E1 and E2, or whether a substrate goes through E1 or E2, mainly depends on the nature of the substrate, that is:

- Primary 1° substrates go with E2 only, because primary carbocations are too unstable to be formed.
- Secondary 2° and tertiary 3° substrates can go with either an E1 or E2 reaction, and appropriate reaction conditions are necessary to facilitate a specific mechanism. The E2 reaction is favored by a high concentration of a strong base (OH<sup>-</sup>, RO<sup>-</sup>, or NH<sub>2</sub><sup>-</sup>) and a polar aprotic solvent. The E1 reaction is favored by a weak base, and a polar protic compound, H<sub>2</sub>O, ROH, can be both a base and a solvent (solvolysis).

For study purposes, a comparison between the E1 and E2 mechanisms helps us understand the two processes in depth. In practice, however, the competition between E1 and E2 will not be an issue because they require rather different reaction conditions. More important actually, it is a competition between elimination and substitution. Next, we will have detailed discussions on the comparison and competition between all four types of reactions: S<sub>N</sub>1, S<sub>N</sub>2, E1 and E2.

## 8.4 Comparison and Competition Between S<sub>N</sub>1, S<sub>N</sub>2, E<sub>1</sub> and E<sub>2</sub>

For a certain substrate, it may have a chance to go through any of the four reaction pathways. So it seems rather challenging to predict the outcome of a certain reaction. We will talk about the strategies that can be applied in solving such a problem, and explain the reasoning behind them.

It is important to understand that the structural nature of a substrate (primary, secondary, or tertiary) is the most critical factor in determining which reaction pathway it goes through. For example, primary substrates never go with S<sub>N</sub>1 or E<sub>1</sub> because the primary carbocations are too unstable. If the substrate could go with a couple of different reaction pathways, then the reaction conditions, including the basicity/nucleophilicity of the reagent, temperature, solvent, etc., play an important role in determining which pathway is the major one. Our discussions therefore will start with the different types of substrates, then explore the condition effects on that substrate.

### Methyl

This is the easiest case. A methyl substrate only goes with S<sub>N</sub>2 reaction, if any reaction occurs. Elimination is not possible for methyl substrates, and no S<sub>N</sub>1 reaction is possible either because CH<sub>3</sub><sup>+</sup> is too unreactive to be formed, so the only possible way is S<sub>N</sub>2.

### Primary (1°)

Primary (1°) substrates cannot go with any unimolecular reaction, that is no S<sub>N</sub>1/E<sub>1</sub>, because primary carbocations are too unstable to be formed. Since primary substrates are very good candidates for S<sub>N</sub>2 reactions, S<sub>N</sub>2 is the predominant pathway when a good nucleophile is used. The only exception is that when a big bulky base/nucleophile is used, E<sub>2</sub> becomes the major reaction.

Examples of reactions for primary substrates:

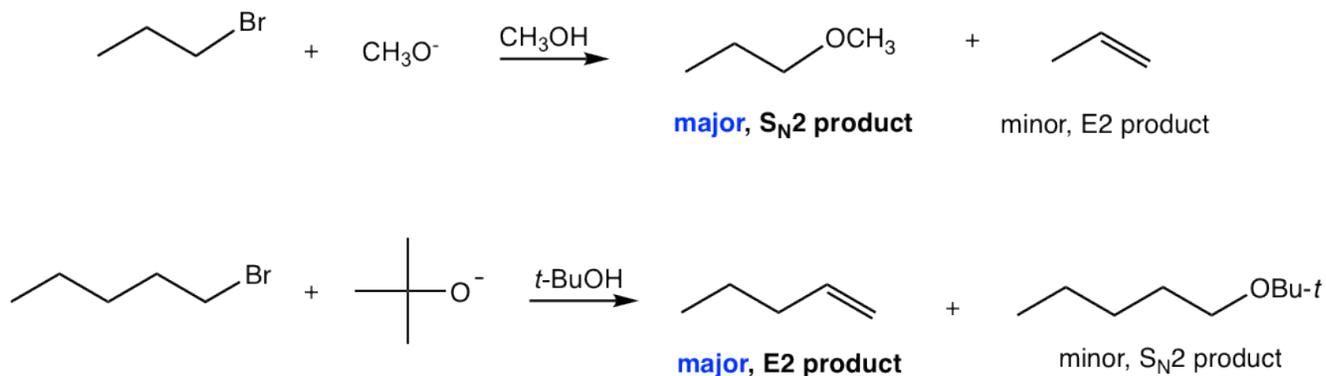


Figure 8.4a Reactions for primary substrates

## Secondary (2°)

It is most complicated or challenging to predict the reaction of a secondary substrate (2°) because all the pathways are possible. The reaction conditions then become a key factor. The four types of reactions can be separated into three pathways:

E2: favored by a strong base

S<sub>N</sub>2: favored by a good nucleophile (relatively weaker base)

S<sub>N</sub>1/E1: It is hard to separate S<sub>N</sub>1 and E1 completely because they both go through carbocation intermediates and are favored by a poor nucleophile/weak base, for example, H<sub>2</sub>O or ROH (solvolysis). Under such neutral conditions, S<sub>N</sub>1 and E1 usually occur together for secondary substrates, and increasing the reaction temperature favors E1 over S<sub>N</sub>1.

It is relatively easy to separate S<sub>N</sub>2 and E2 pathways from S<sub>N</sub>1/E1 since both S<sub>N</sub>2 and E2 require a strong nucleophile or strong base, which are usually negatively charged species, while S<sub>N</sub>1/E1 requires neutral conditions.

To distinguish S<sub>N</sub>2 from E2, we need to determine whether a negatively charged anion is a strong nucleophile (for S<sub>N</sub>2) or a strong base (for E2). All nucleophiles are potential bases, and all bases are potential nucleophiles because the reactive part of both the nucleophile and base are lone pair electrons. Whether an anion is a better nucleophile or a better base depends on its basicity, size, and polarizability. Generally speaking, the relatively stronger bases have the tendency to act as bases, and relatively weaker bases with a small size and good polarizability have the tendency to act as nucleophiles. See the list given below.

Strong bases: OH<sup>-</sup>, RO<sup>-</sup> (R: small size alkyl group), NH<sub>2</sub><sup>-</sup>

Good nucleophiles (relatively weaker bases): Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>, RS<sup>-</sup>, N<sub>3</sub><sup>-</sup>, CN<sup>-</sup>, RCO<sub>2</sub><sup>-</sup>, RNH<sub>2</sub>

Please note that bulky bases, such as t-BuO<sup>-</sup> and LDA, always favor E2 and generate elimination products that follow Hofmann's rule because they are too big to do a back-side attack in S<sub>N</sub>2.

Examples of reactions for secondary substrates:

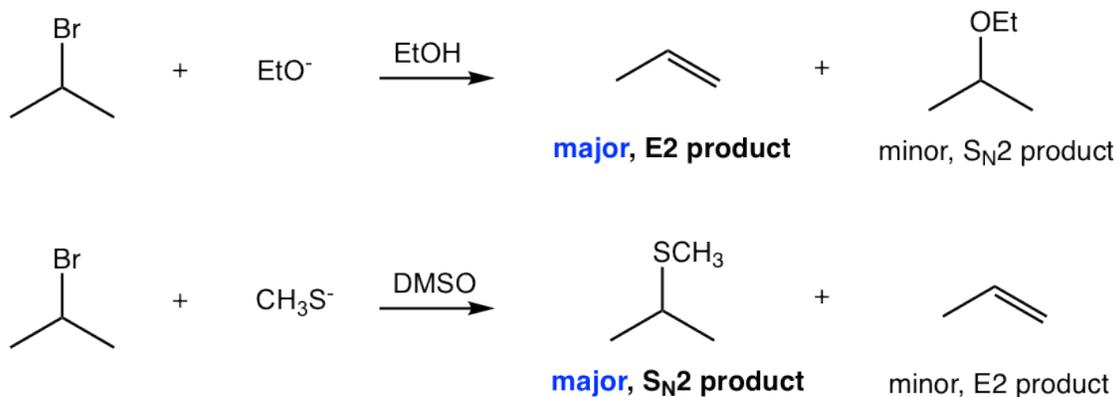


Figure 8.4b Reactions for secondary substrates

## Tertiary (3°)

Tertiary (3°) substrates do not go with S<sub>N</sub>2 reactions because of steric hindrance. So an E2 reaction is the choice when a strong base is applied or an S<sub>N</sub>1/E1 pathway with neutral conditions (poor nucleophile/weak base). Theoretically speaking, E2 and E1 are supposed to give the same elimination product. However, to synthesize an alkene from a tertiary substrate, it is a better choice to use a strong base that encourages the E2 process rather than E1. This is because E1 always combines together with S<sub>N</sub>1, and it is almost impossible to avoid the substitution product.

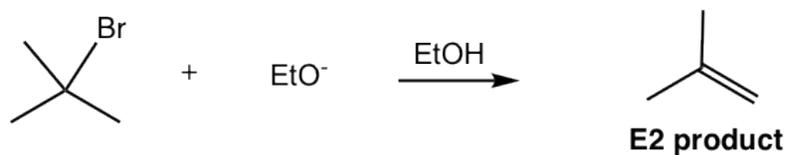


Figure 8.4c Reaction for tertiary substrates

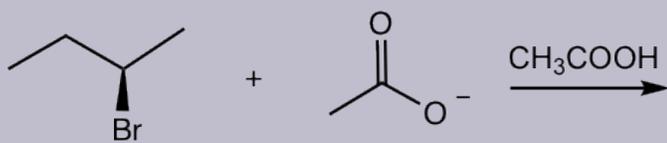
The above discussions can be briefly summarized in Table 8.2 below, followed by several examples. To predict the reaction outcome or to design a synthesis route for a certain case, it is highly recommended that you do the analysis by following the logic mentioned above, instead of just referring to the table. Also, practice makes perfect!

Substrate	Preferred Reaction Pathways
Methyl	$S_N2$ reaction
Primary	Predominantly $S_N2$ reaction; Exception: E2 reaction for bulky base
Secondary	$S_N2$ reaction with a good nucleophile (e.g., $RS^-$ , $RCO_2^-$ , etc) E2 reaction with a strong base (e.g., $OH^-$ , $OR^-$ ) $S_N1/E1$ with neutral condition (e.g., $H_2O$ , $ROH$ )
Tertiary	E2 reaction with a strong base (e.g., $OH^-$ , $OR^-$ ) $S_N1/E1$ with neutral condition (e.g., $H_2O$ , $ROH$ )

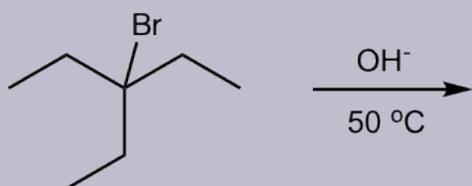
Table 8.2 Preferred reaction pathways for different types of substrate

Examples: Show major organic product(s) for following reactions.

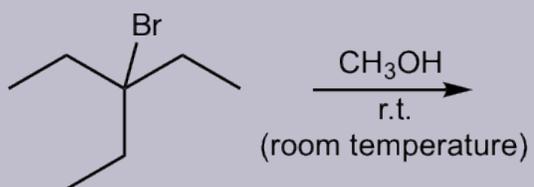
1.



2.

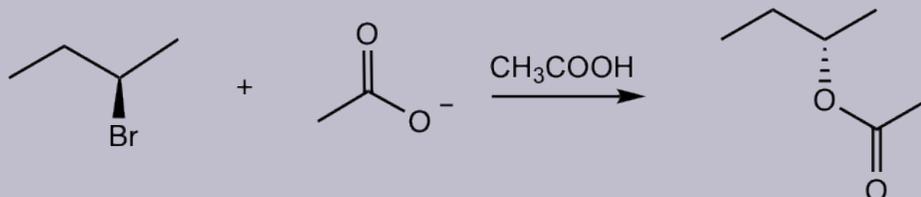


3.



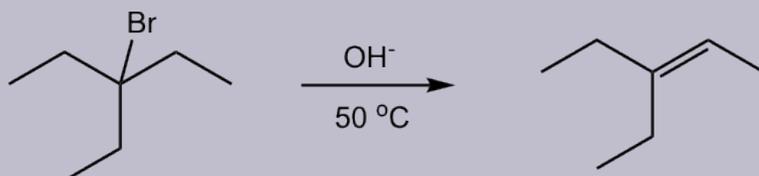
## Solutions:

1.



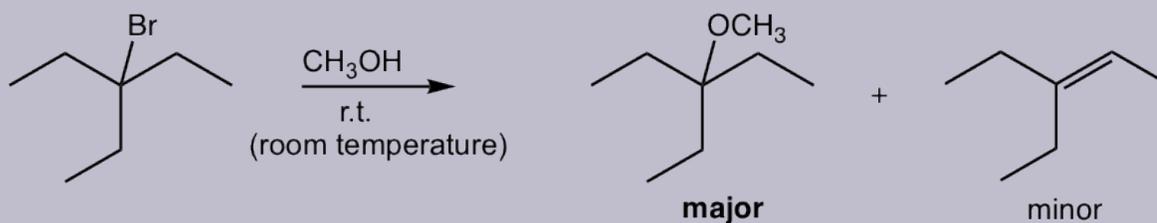
Secondary substrate, with good nucleophile, acetate, which is weak base, so  $\text{S}_{\text{N}}2$  is the major pathway. Configuration inverted at the chirality center.

2.



Tertiary substrate with strong base  $\text{OH}^-$ , therefore E2 is the major pathway. The high temperature facilitates the E2 reaction.

3.



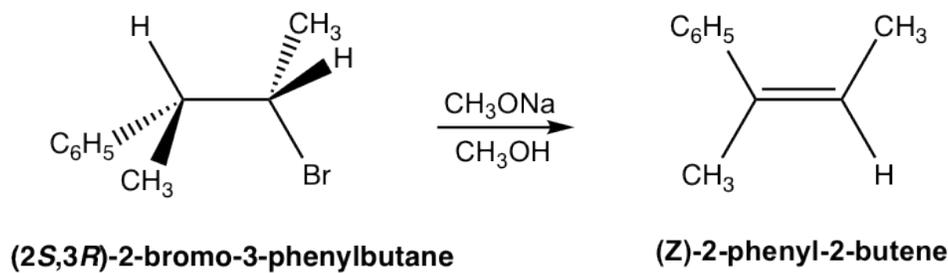
Tertiary substrate in neutral condition, this is solvolysis.  $\text{CH}_3\text{OH}$  is weak nucleophile/weak base and the solvent, so the possible reactions are  $\text{S}_{\text{N}}1$  and E1. At this low temperature,  $\text{S}_{\text{N}}1$  is the major pathway, with bit E1 product obtained.

# Answers to Chapter 8 Practice Questions

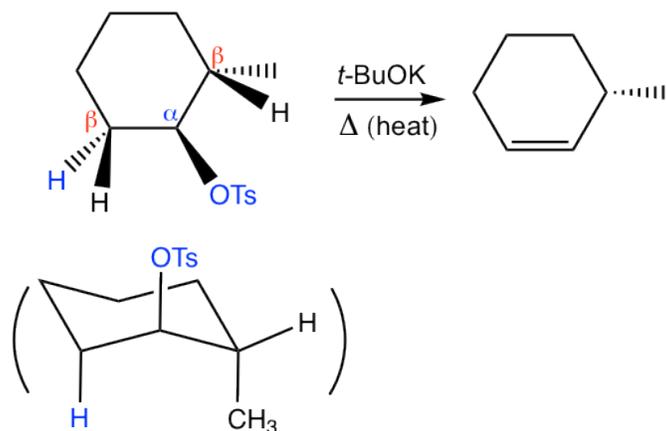
## 8.I

Show the elimination product of the following reactions.

1.



2.



The anti-coplanar conformation of H and leaving group OTs are shown more clearly in the chair conformation of the cyclohexane. Please note that the other  $\beta\text{-H}$  can not be anti to the leaving group OTs. Also, to fit to the anti-coplanar requirement, both H and OTs have to be in axial positions so this conformation is the one that undergoes the elimination, though it is not the most stable one. Since the most stable conformation does not fit the E2 stereochemistry requirement, the elimination has to go through the less stable conformation. Heat is preferred to facilitate the reaction.

# CHAPTER 9: FREE RADICAL SUBSTITUTION REACTION OF ALKANES

Generally speaking, alkane is the type of compound that is inert in most organic reactions. There are only C-C and C-H  $\sigma$  bonds involved in the structure of alkanes. A  $\sigma$  bond is formed by head-to-head orbital overlapping, which is the most effective way of overlapping, as it makes the bond strong and stable. Furthermore, both C-C and C-H bonds are non-polar, so none of the atoms has any significant charges, which means no nucleophile nor electrophile is possible in alkanes. Overall, alkanes are rather unreactive compounds, and they rarely undergo any organic reactions. One exception is the reaction we will learn about in this chapter, which is halogenation substitution via a radical mechanism. We will first talk about how to produce radicals and then see radicals promote the substitution reaction of alkanes.

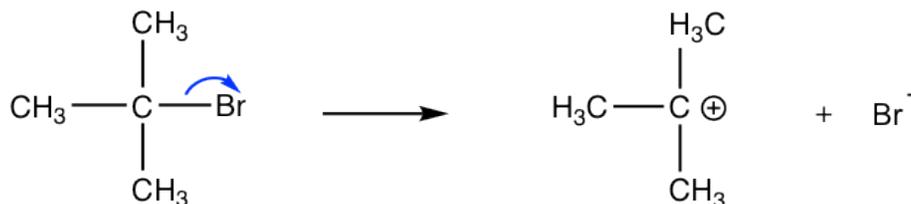
Learning Objectives for this chapter:

- Understand, explain and show the radical substitution mechanism of alkanes, including the intermediates, transition state and reaction coordination diagram.
- Explain the process of radical formation, and compare the properties, stability and reactivity of different types of alkyl radicals.
- Understand the reactivity difference between different halogens, and how the difference affects the application of radical substitution reaction.



## 9.1 Homolytic and Heterolytic Cleavage

For the reactions we learned about so far, bond breaking occurs when one part of the bond takes both electrons (the electron pair) of the bond away. For example, for an  $S_N1$  reaction, the leaving group Br leaves with the electron pair to form  $Br^-$  and carbocation intermediate.



### example of heterolytic bond cleavage

This process is called heterolytic bond cleavage, and the  $\sigma$  bond breaks heterolytically. As before, an arrow with double-barbs is used to show heterolytic cleavage, which is the transfer of the electron pair specifically:



Fig. 9.1a  
Double-barbs  
arrow for  
heterolytic bond  
cleavage

There is another type of bond-breaking process, in which each part of the  $\sigma$  bond takes one electron away, as shown below:



### homolytic bond cleavage

This is called homolytic cleavage or homolysis. The electron pair separates evenly to each part, and as a result, both products contain a single electron. The species that contains one or more single electrons is called a radical (or free radical). Radicals are produced from homolytic cleavage. The arrow with a sing-barb (like the shape of a fishhook) is used to show homolytic cleavage, which is single electron transfer specifically:



Fig. 9.1b Sing-barb  
arrow for  
homolytic bond  
cleavage

Homolysis occurs mainly for non-polar bonds, and heat or light ( $\Delta$  is the symbol for heat;  $h\nu$  is used to show light) is needed to provide enough energy to initiate the process. Two examples of radicals generated from homolysis are shown below.

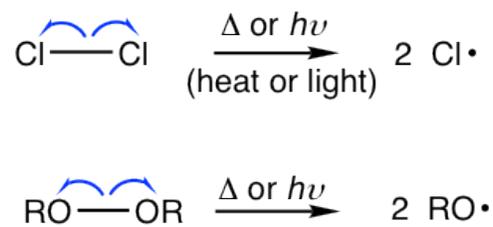


Fig. 9.1c Homolytic cleavage to generate radicals

A radical is another highly reactive reaction intermediate, because of the lack of an octet. The substitution reaction we will learn about in this chapter involves the radical intermediate.

## 9.2 Halogenation Reaction of Alkanes

When alkanes react with halogen ( $\text{Cl}_2$  or  $\text{Br}_2$ ), with heat or light, the hydrogen atom of the alkane is replaced by a halogen atom, and alkyl halide is produced as a product. This can be generally shown as:

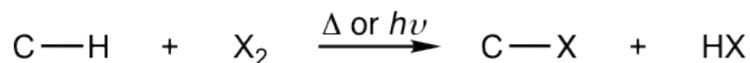


Fig. 9.2a General reaction equation of halogenation for alkane

A specific example is:

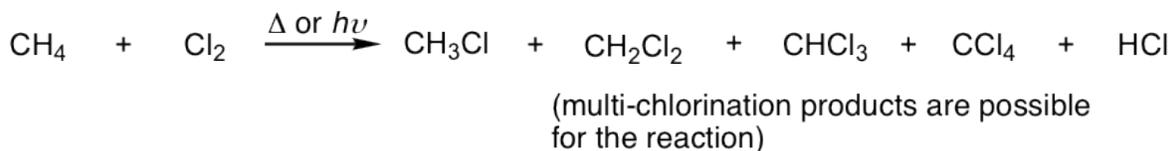
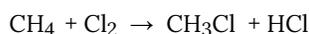


Fig. 9.2b Chlorination of methane

Such a type of reaction can be called substitution because hydrogen is substituted by halogen; it can also be called halogenation because halogen is introduced into the product. For this book, both terms are used in this chapter, interchangeably.

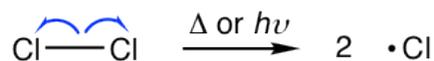
The net reaction for halogenation seems straightforward, but the mechanism is more complicated though, as it goes through multiple steps, including initiation, propagation, and termination.

We will take the following example of the mono-chlorination of methane for the discussion of reaction mechanisms.



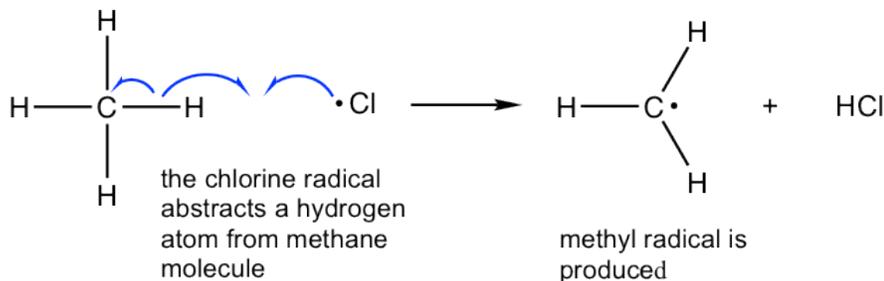
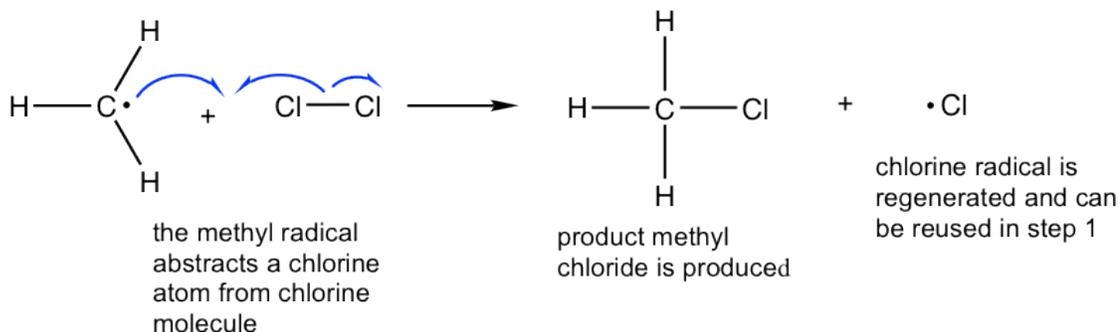
### Mechanism for the mono-chlorination of methane:

Initiation: Production of radicals



With the energy provided by heat or light, chlorine molecules dissociate homolytically, and each chlorine atom takes one of the bonding electrons, and two highly reactive chlorine radicals,  $\text{Cl}\cdot$ , are produced.

Propagation: Formation of the product and regeneration of radicals

**step 1:****step 2:**

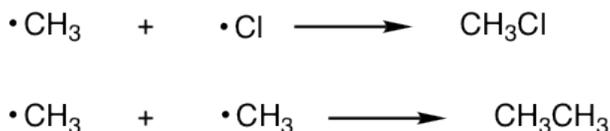
The propagation step involves two sub-steps. In the 1<sup>st</sup> step, the Cl• takes a hydrogen atom from the methane molecule (this is also called hydrogen abstraction by Cl•), and the C-H single bond breaks homolytically. A new  $\sigma$  bond is formed by Cl and H, with each donating one electron and HCl is produced as the side product. The CH<sub>3</sub> radical, CH<sub>3</sub>•, the critical intermediate for the formation of the product in the next step, is formed as well.

In the 2<sup>nd</sup> step, the CH<sub>3</sub>• abstracts a chlorine atom to give the final CH<sub>3</sub>Cl product together with another Cl•. The regenerated Cl• can attack another methane molecule and cause the repetition of step 1, then step 2 is repeated, and so forth. Therefore, the regeneration of the Cl• is particularly significant, as it makes the propagation step self-repeat hundreds or thousands of times. The propagation step is therefore called the self-sustaining step, and only a small amount of Cl• is required at the beginning to initiate the process.

Initiation and propagation are productive steps for the formation of a product. This type of sequential, step-wise mechanism in which the earlier step generates the intermediate that causes the next step of the reaction to occur, is called a chain reaction.

The chain reaction will not continue forever though, because of the termination steps.

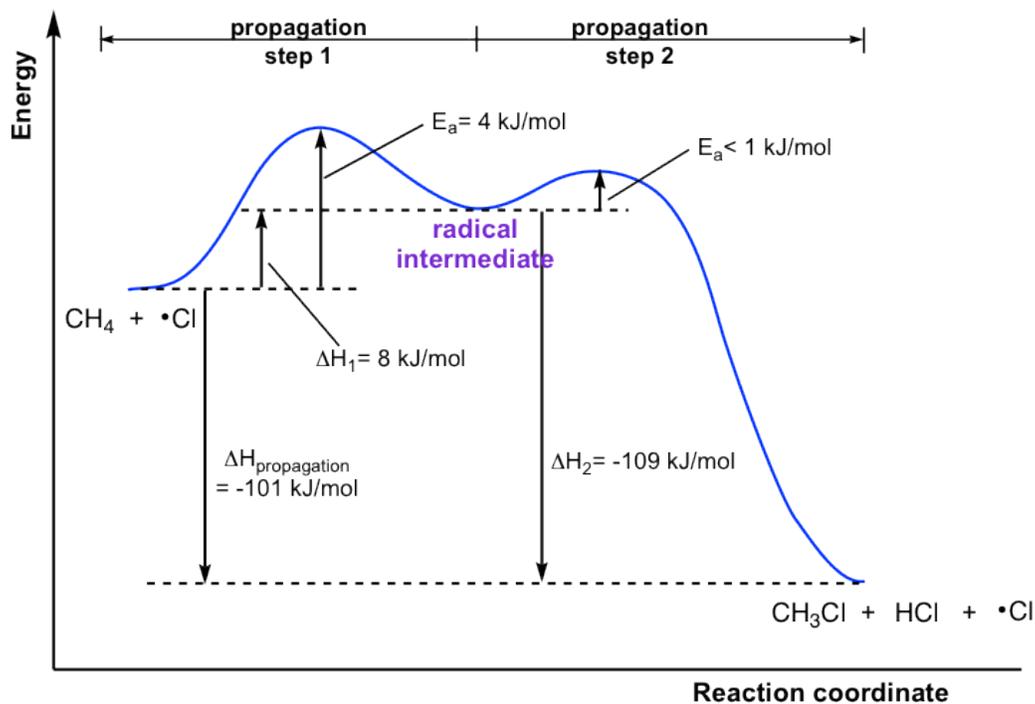
Termination: Consumption of radicals



When two radicals in the reaction mixture meet with each other, they combine to form a stable molecule. The combination of radicals leads to a decrease in the number of radicals available to propagate the reaction, and the reaction slows and stops eventually, so the combination process is called the termination step. A few examples of termination are given above, and other combinations are possible as well.

The propagation steps are the core steps in halogenation. The energy level diagram helps to provide a further understanding of the propagation process.

The 1<sup>st</sup> step in propagation is endothermic, while the energy absorbed can be offset by the 2<sup>nd</sup> exothermic step. Therefore, the overall propagation is an exothermic process, and the products are at a lower energy level than the reactants.



**Energy diagram of mono-chlorination of methane**

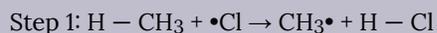
The reaction heat (enthalpy) for each of the propagation steps can also be calculated by referring to the homolytic bond dissociation energies (Table 9.1). For such a calculation, energy is absorbed for the bond-breaking step, so the bond energy is given a “+” sign, and for the energy released for the bond-forming step the “-” sign is applied.

Bond	kJ/mol	Bond	kJ/mol	Bond	kJ/mol
A – B → A • + B •					
F – F	159	H – Br	366	CH <sub>3</sub> – I	240
Cl – Cl	243	H – I	298	CH <sub>3</sub> CH <sub>2</sub> – H	421
Br – Br	193	CH <sub>3</sub> – H	440	CH <sub>3</sub> CH <sub>2</sub> – F	444
I – I	151	CH <sub>3</sub> – F	461	CH <sub>3</sub> CH <sub>2</sub> – Cl	353
H – F	570	CH <sub>3</sub> – Cl	352	CH <sub>3</sub> CH <sub>2</sub> – Br	295
H – Cl	432	CH <sub>3</sub> – Br	293	CH <sub>3</sub> CH <sub>2</sub> – I	233

Table 9.1 Homolytic Bond Dissociation Energies for Some Single Bonds

Examples: Calculate the reaction energy for the propagation step of mono-chlorination of methane (referring to the corresponding bond energies in Table 9.1).

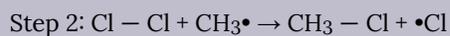
### Solution:



The H - CH<sub>3</sub> bond broken, absorb energy, so +440 kJ

The H - Cl bond formed, release energy, so - 432 kJ

$$\Delta H_1 = +440 + (-432) = +8 \text{ kJ}$$

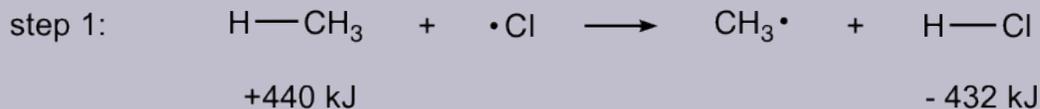


The Cl - Cl bond broken, absorb energy, so +243 kJ

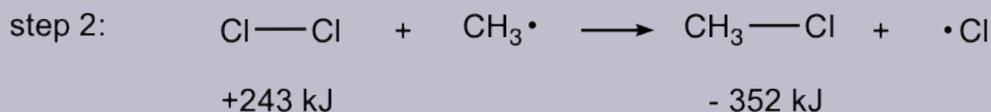
The CH<sub>3</sub> - Cl formed, release energy, so -352kJ

$$\Delta H_2 = +243 + (-352) = -109 \text{ kJ}$$

$$\Delta H_{\text{propagation}} = \Delta H_1 + \Delta H_2 = +8 + (-109) = -101 \text{ kJ}$$



$$\Delta H_1 = +440 + (-432) = +8 \text{ kJ}$$



$$\Delta H_2 = +243 + (-352) = -109 \text{ kJ}$$

$$\Delta H_{\text{propagation}} = \Delta H_1 + \Delta H_2 = +8 + (-109) = -101 \text{ kJ}$$

The calculated data does match with the data from the energy diagram.

## Reactivity Comparison of Halogenation

The energy changes for halogenation (substitution) with the other halogens can be calculated similarly. The results are summarized in Table 9.2.

Reaction	F <sub>2</sub>	Cl <sub>2</sub>	Br <sub>2</sub>	I <sub>2</sub>
Step 1:				
$\text{H} - \text{CH}_3 + \bullet\text{X} \rightarrow \text{CH}_3\bullet + \text{H} - \text{X}$	-130	+8	+74	-142
Step 2:				
$\text{X} - \text{X} + \text{CH}_3\bullet \rightarrow \text{CH}_3 - \text{X} + \bullet\text{X}$	-322	-109	-100	-89
Overall propagation:				
$\text{H} - \text{CH}_3 + \text{X} - \text{X} \rightarrow \text{CH}_3 - \text{X} + \text{HX}$	-452	-101	-26	+53

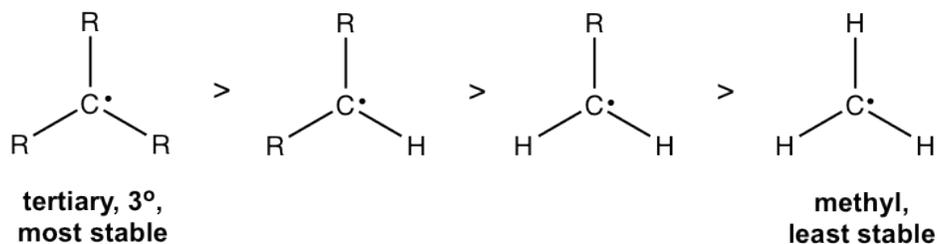
Table 9.2. Enthalpy of the Propagation Steps in Mono-halogenation of Methane (kJ/mol)

The data above indicate that the halogen radicals have different reactivity; fluorine is the most reactive, and iodine is the least reactive. The iodine radical is very unreactive with overall “+” enthalpy, so iodine does not react with alkane at all. On the other side, the extremely high reactivity of fluorine is not a benefit either. The reaction for fluorine radical is vigorous and even dangerous with a lot of heat released, and it is not practical to apply this reaction for any application because it is hard to control. So, Cl<sub>2</sub> and Br<sub>2</sub>, with reactivity in the medium range, are used for halogen substitutions of alkanes. Apparently, Cl<sub>2</sub> is more reactive than Br<sub>2</sub>, and this leads to the different selectivity and application between the two halogens. This is further discussed in section 9.4.

## 9.3 Stability of Alkyl Radicals

The alkyl radical is the key intermediate for the halogenation reaction of alkanes, so the relative stability of radicals determines the relative reactivity. Based on the energy diagram, the alkane that generates the more stable carbon radical exhibits higher reactivity.

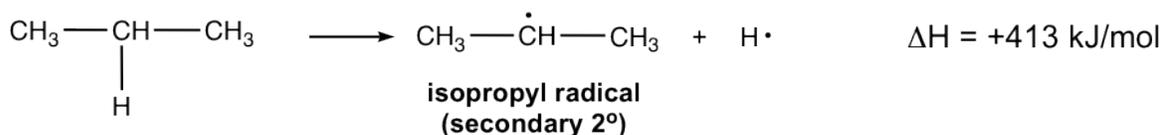
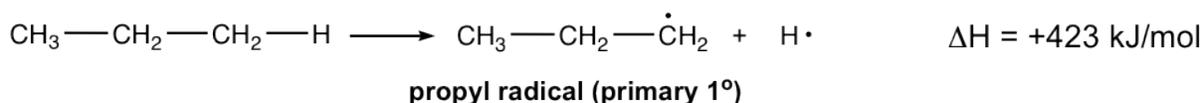
The alkyl radicals with different structures show different stabilities. Specifically, tertiary radicals are the most stable, and primary and methyl radicals are the least stable, which follows the same trend as the stability of carbocations.



### the relative stability of alkyl radicals

This trend can be explained by two reasons:

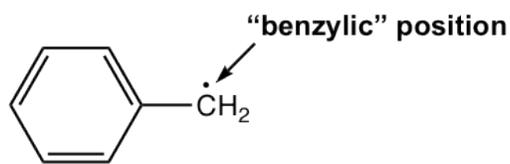
- The Hyperconjugation effect of the alkyl (R) group: alkyl groups are electron-donating groups through the hyperconjugation effect (refer to section 7.4), which is the electron density of C-C or C-H  $\sigma$  bond overlap with the half-filled p orbital of carbon radicals. Similar to the carbocation, the carbon radical is also an electron-deficient species, so the electron-donating effect of alkyl groups helps stabilize it. With more alkyl groups involved, the radical is more stable.
- Homolytic bond dissociation energy comparison: Homolytic cleavage of the C-H bond produces carbon radicals. The C-H bond in different structures has different bond dissociation energy. Let's compare two different types below – primary vs secondary:



Since both radicals come from the same compound, propane, the higher the homolytic bond dissociation energy, the higher the energy level of the resulting carbon radical. The bond energy of the 1° C-H is 10 kJ/mol higher in energy than the bond energy of the 2° C-H; therefore, the secondary radical is more stable than the primary one.

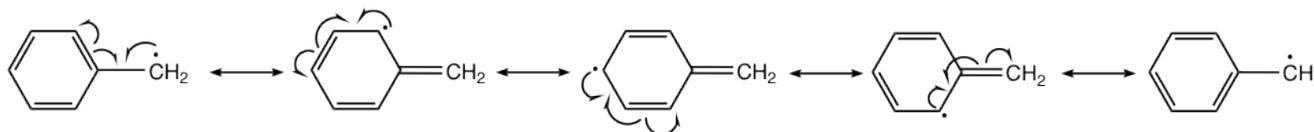
Other than the above reasons, there is another effect that impacts the stability of radicals. For example, the following

radical exhibits special stability and is even more stable than other regular tertiary radicals, even though it is a primary radical. Why? This is because of another effect – the resonance effect!



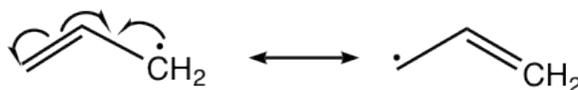
### benzylic radical

The radical here is not a regular primary radical, as it is on the position beside the benzene ring. The position right next to the benzene ring is called the benzylic position, and this radical is a benzylic radical. Because of the presence of the benzene ring, the benzylic radical has a total of five resonance contributors. According to the resonance effect, the more resonance contributors available, the better the electron density will be dispersed, and the more stable the species will be.



**resonance effect: benzylic radical is stabilized by resonance structures**

The resonance effect also helps to stabilize the allylic radical. The carbon that is right next to the C=C double bond is the allylic position. The resonance structures of an allylic radical example are shown below. Both benzylic and allylic radicals are more stable than tertiary alkyl radicals because of resonance effects.



**allylic radical is stabilized by resonance structures**

## 9.4 Chlorination vs Bromination

### 9.4.1 Monochlorination

First, we will focus on the monochlorination product by assuming that chlorination only occurs once. Since chlorine is a rather reactive reagent, it shows relatively low selectivity, which means  $\text{Cl}_2$  does not discriminate greatly among the different types of hydrogen atoms (primary, secondary, or tertiary) in an alkane. As a result, for the reaction of alkane with different hydrogen atoms, a mixture of isomeric monochlorinated products is obtained.

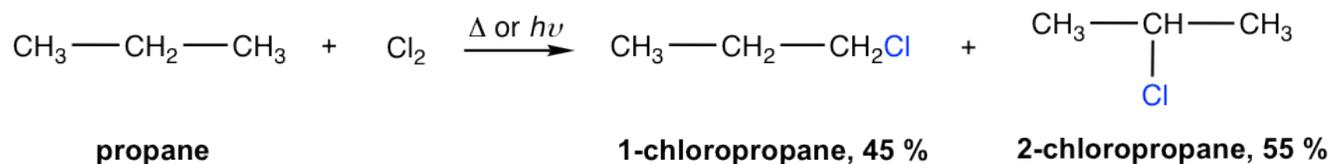


Figure 9.4a Monochlorination products

The experimental results of the monochlorination of propane indicate that 45% primary chloride (1-chloropropane) and 55% secondary chloride (2-chloropropane) are produced. How can this result be explained?

To predict the relative amount of different chlorination products, we need to consider two factors at the same time: reactivity and probability.

It has been discussed in section 9.3 that different radicals (primary, secondary or tertiary) have different stability and reactivity. The relative reaction rate of alkyl radicals for chlorination has been measured and has the approximate values of:

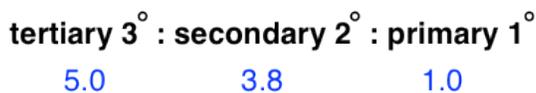


Figure 9.4b Relative reaction rate of alkyl radicals for chlorination

Probability simply depends on how many hydrogen atoms there are for each type. With more hydrogen atoms available, the chance for that type of hydrogen to react is statistically higher.

So, the overall amount of each isomeric product should be estimated by accounting for both reactivity and probability; that is:

The amount of a certain type of product = the number of that type of hydrogens  $\times$  relative reactivity

For the example of the monochlorination of propane, the calculation is:

Amount of 1-chloropropane: 6 (number of  $1^\circ$  hydrogens)  $\times$  1.0 (relative reactivity) = 6.0

Amount of 2-chloropropane: 2 (number of  $2^\circ$  hydrogens)  $\times$  3.8 (relative reactivity) = 7.6

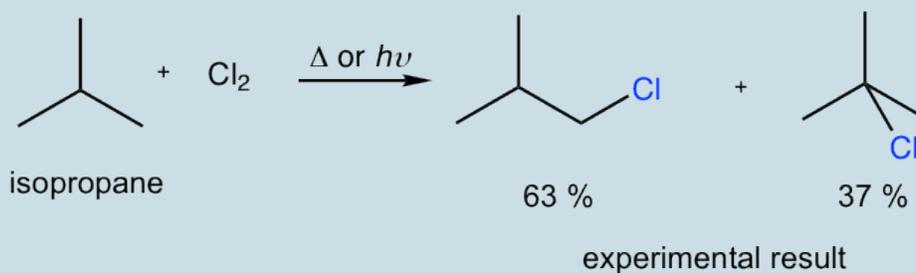
yield % of 1-chloropropane:  $6.0/13.6 = 44\%$

yield % of 2-chloropropane:  $7.6/13.6 = 56\%$

The calculated values are consistent with the experiment results.

### Exercises 9.1

Predict the percentage yield of each product for monochlorination of isobutane by calculation, and compare your calculated numbers to the experiment results. Are they consistent?



### Answers to Chapter 9 Practice Questions

For an alkane with only one type of hydrogen, the problem of isomeric mixture can be prevented since only one product is produced. For the following chlorination of cyclopentane, only one monochloride is produced.

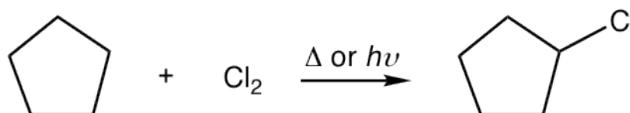


Figure 9.4c Chlorination of cyclopentane

### 9.4.2 Multichlorination

Although we assume that chlorination occurs once, as the last section discusses, this is not the actual case. A common issue with chlorination is that multiple substitution always happens. A simple example is the chlorination of methane, in which a mixture of multiple chlorination products is obtained, as we learned before.

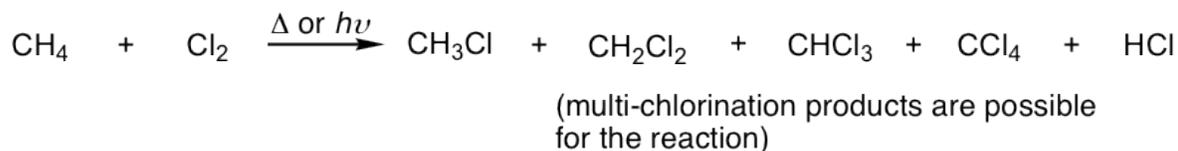


Figure 9.4d Example of multichlorination products

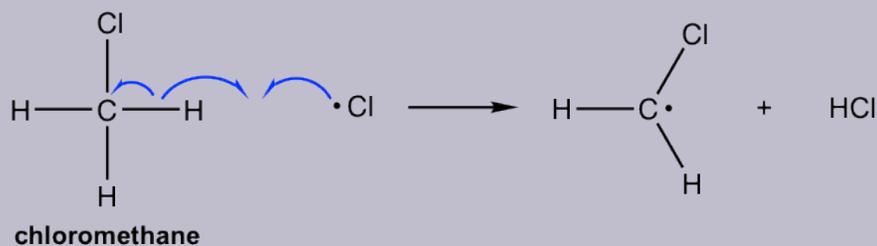
The mechanism for the formation of a multichlorination product is similar to that of monochloride. When chloromethane (or methyl chloride) reacts with  $\text{Cl}_2$ , another hydrogen is replaced by a chlorine atom to give dichloromethane, dichloromethane reacts with  $\text{Cl}_2$  again to give trichloromethane, and trichloromethane reacts further to produce tetrachloromethane. All the reactions still go through similar propagation steps with the radical mechanism.

### Examples

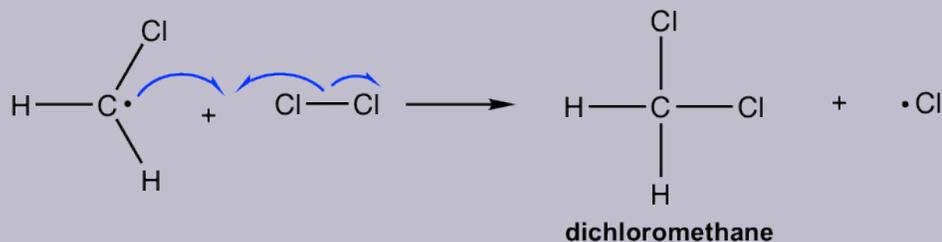
Show the mechanism of propagation steps for the formation of dichloromethane from chloromethane.

### Solution:

#### propagation step 1:



#### step 2:



Practically, to minimize the problem of multichlorination products, the reaction conditions can be controlled in certain ways, for example:

- Use the high concentration of alkane relative to  $\text{Cl}_2$ , to decrease the possibility of multichlorination;
- Control the reaction time: stop the reaction after a “short” time to favor the monochlorination product.

These methods help reduce the number of multichlorination products, but the problem still cannot be completely avoided.

### 9.4.3 Bromination

Because of the two major problems of chlorination: the lack of selectivity and multi-substitution, chlorination is not useful as a synthesis method to prepare a specific alkyl halide product. Instead, bromination with Br<sub>2</sub> can be applied for that purpose. The relative lower reactivity of bromine makes it exhibit a much greater selectivity. Bromine is less reactive, which means it reacts more slowly; therefore, it has the chance to differentiate between the different types of hydrogens, and selectively reacts with the most reactive one. The relative reaction rate of bromination for different radicals is shown here, and you can see the big difference to that of chlorination:



Figure 9.4e Relative reaction rate of bromination

For bromination, the reactivity difference between different types of positions is so high that the reactivity factor becomes predominant for determining the product. Therefore, bromination usually occurs *selectively* on the most reactive position (the position that forms the most stable carbon radical intermediate) and gives one major product exclusively, as shown in the example here for the bromination of isobutane.

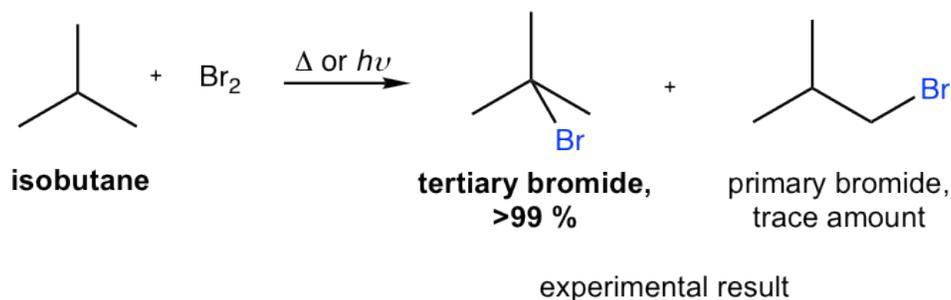
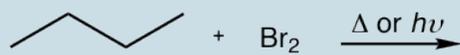
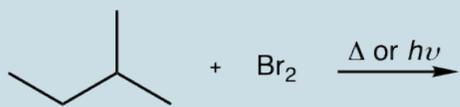


Figure 9.4f An example of the bromination of isobutane

As a result, bromination has the greatest utility synthesis of alkyl halide.

#### Exercises 9.2

Show the major bromination product of the following reactions.



Answers to Chapter 9 Practice Questions

## 9.5 Stereochemistry for the Halogenation of Alkanes

For a substitution reaction in which a stereocenter is generated, the stereochemistry can be explained by the structure feature of the radical intermediate.

In the structure of a carbon radical, carbon has three bonds and one single electron. Based on VSEPR, there are a total of four electron groups, and the radical should be in a tetrahedral shape. However, experimental evidence indicates that the geometric shape of most alkyl radicals is a trigonal planar shape, with the carbon in  $sp^2$  hybridization, and there is one single unpaired electron in the unhybridized 2p orbital.

We will take the bromination reaction of ( $\pm$ )-3-methylhexane to explain the stereochemistry. The experiment results indicate that the racemic mixture of R and S 3-bromo-3-methylhexane was obtained with the bromination.

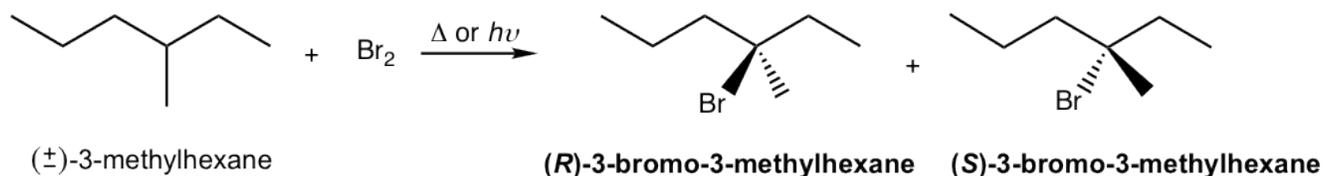
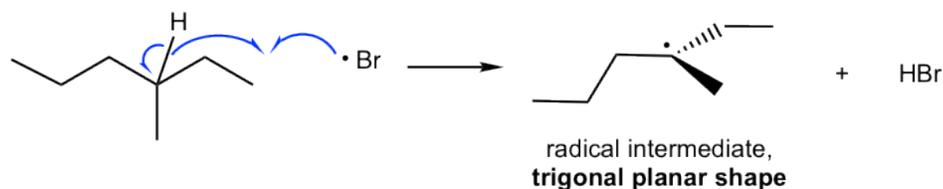


Figure 9.5a Bromination reaction of ( $\pm$ )-3-methylhexane

This can be explained by the stereochemistry of the propagation steps in the mechanism. The carbon radical generated in step 1 is in a trigonal planar shape as mentioned earlier. When the radical reacts with bromine in step 2, the reaction can occur at either side of the plane. Because both sides are identical, the probability of the reaction by either side is the same; therefore, an equal amount of the R- and S- enantiomers are obtained as a racemic mixture.

### propagation step 1:



### step 2:

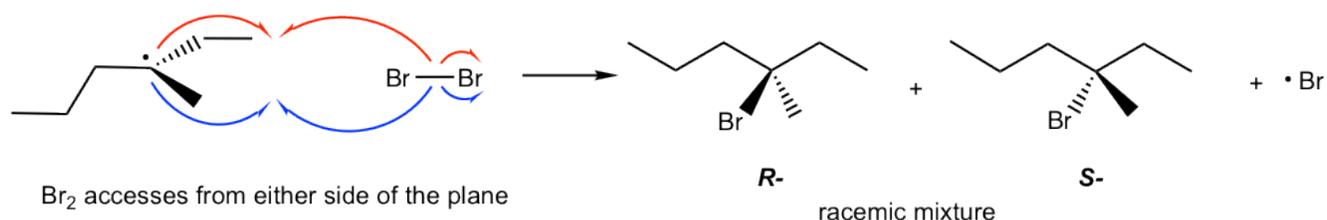
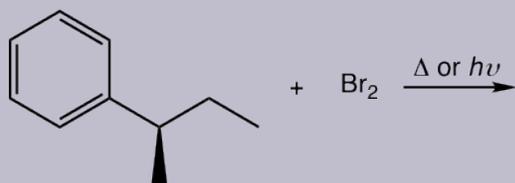


Figure 9.5b Propagation steps

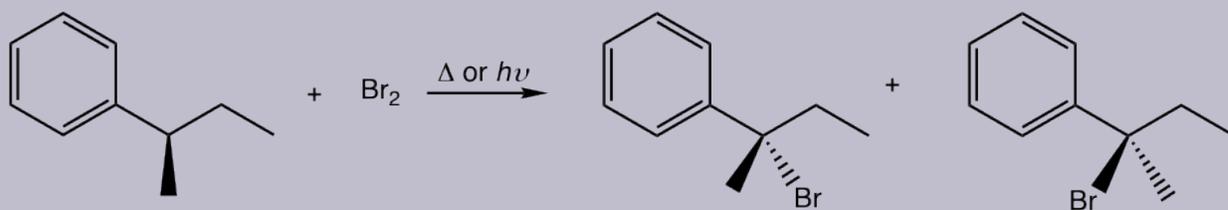
The stereochemistry of the radical substitution is similar to that of the  $S_N1$  reaction because both carbon radical and carbocation are in a trigonal planar shape.

## Examples

Show the bromination product(s) with stereoisomers when applied.



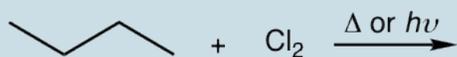
**Solutions:**



The racemic mixture is obtained.

## Exercises 9.3

Show all the mono-chlorination products of butane with any stereoisomers when applied.



Answers to Chapter 9 Practice Questions

## 9.6 Synthesis of Target Molecules: Introduction to Retrosynthetic Analysis

So far, we have learned three major types of reactions: nucleophilic substitution, elimination, and the halogenation of alkane (radical substitution). Now, we will see how to put the knowledge of these reactions together for application, that is, how to design a synthesis route for a target (desired) compound from available starting materials.

Building larger, complex organic molecules from smaller, simple molecules is the goal of organic synthesis. Organic synthesis has great importance for many reasons, from testing the newly developed reaction mechanism or method to replicating the molecules of living nature, to producing new molecules that have potential applications in energy, material, or medicinal fields.

It usually takes multiple steps, from a few to 20 or more, to synthesize a desired compound, and therefore it would be challenging to visualize from the start all the steps necessary. A common strategy for designing a synthesis is to work backward; that is, instead of looking at the starting material and deciding how to do the first step, we look at the product and decide how to do the last step. This process is called retrosynthetic analysis, a technique frequently applied in organic synthesis. We will introduce the basic ideas of retrosynthetic analysis here, and for practice purposes, the starting material will always be defined for our examples.

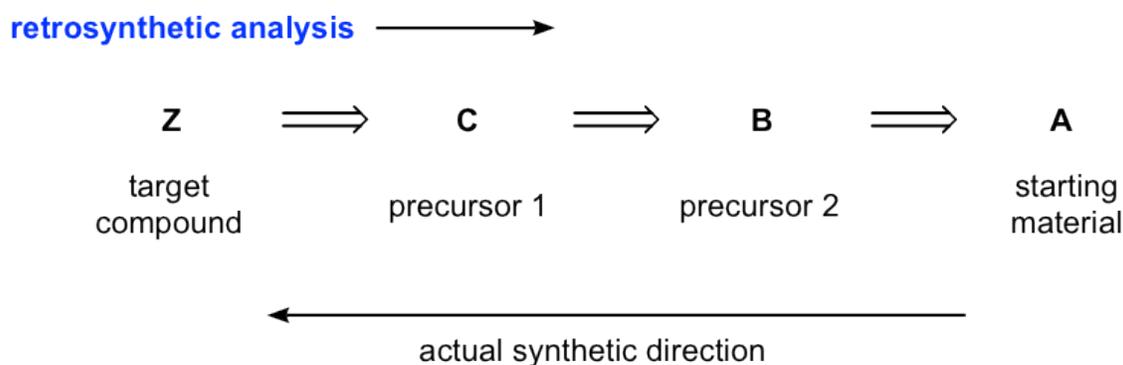
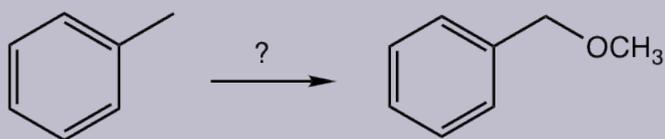


Figure 9.6a Retrosynthetic analysis

Retrosynthetic analysis can usually be shown in the above way, with the open arrows indicating that the analysis is backward. We first identify precursor 1 that could react in one step to make the target compound, then identify the next precursor that could react to give precursor 1, and repeat the process until we reach the starting material. Please note that the analysis is done in this way to show the “thinking or ideas” for solving the problem, so typically the reagents/conditions required for each step are not specified until the synthesis route is written in the forward direction. Also, you may come up with multiple routes sometimes, with different precursors, and then the most efficient synthesis route can be determined by evaluating the possible benefits and disadvantages of each path.

Examples

Design the synthesis route of methoxymethylbenzene starting from toluene.

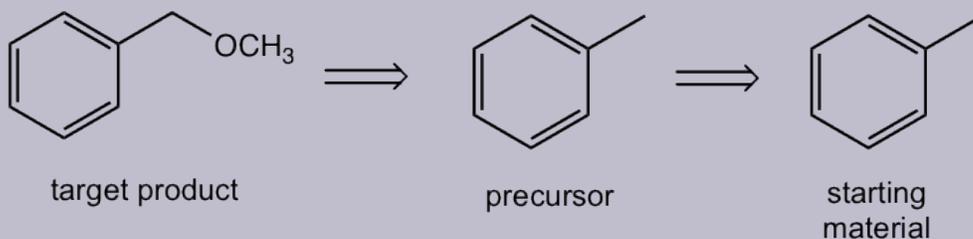


starting material

target product

Approach: The target compound is an ether. We have learned that the  $S_N2$  reaction is a reasonable way to introduce different functional groups by applying different nucleophiles (section 7.3), that said the reaction between  $\text{CH}_3\text{O}^-$  (nucleophile) and halide gives the desired ether, and the halide can be the "precursor 1". The halide precursor can then be directly connected with the starting material, toluene, through the halogenation that we just learned in this chapter. This is an easy example that only involves two steps.

### retrosynthetic analysis



target product

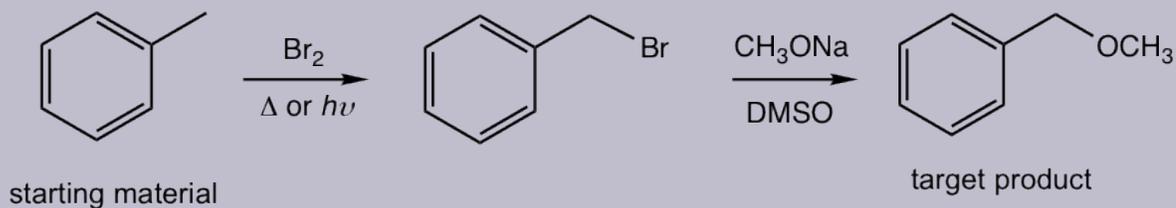
precursor

starting material

### Solutions:

The analysis can then be transferred to the solution of the question by showing the reactions in forward direction and include the reagents/condition for each step.

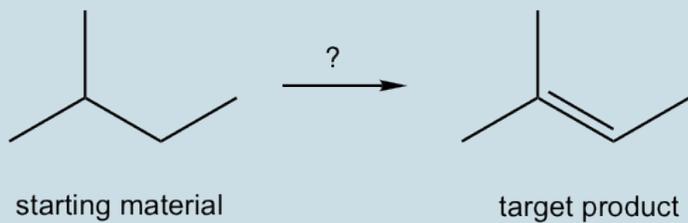
### synthesis



Synthesis route design is a challenging topic that requires a lot of practice. To do it well, you should be very familiar with all types of reactions in terms of how the functional groups are transformed and what reagents and conditions are

involved. Sometimes, some reaction features, like stereochemistry, will be useful as well.

Exercises 9.4 Design the synthesis route.

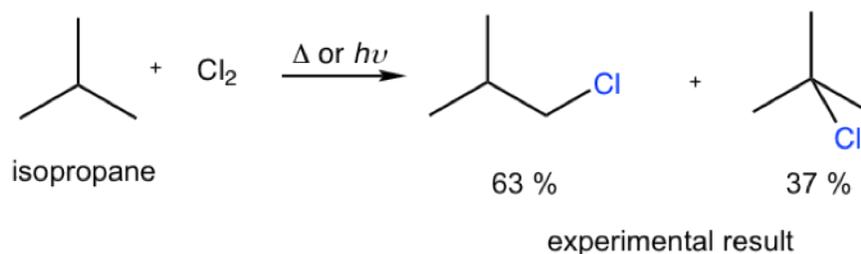


Answers to Chapter 9 Practice Questions

# Answers to Chapter 9 Practice Questions

## 9.1

Predict the percentage yield of each product for the monochlorination of isobutane by calculation and compare your calculated numbers to the experiment results. Are they consistent?



### Calculation:

The amount of 1°-chloride: 9 (number of 1°hydrogens) × 1.0 (relative reactivity) = 9.0

The amount of 3°-chloride: 1 (number of 3°hydrogens) × 3.8 (relative reactivity) = 3.8

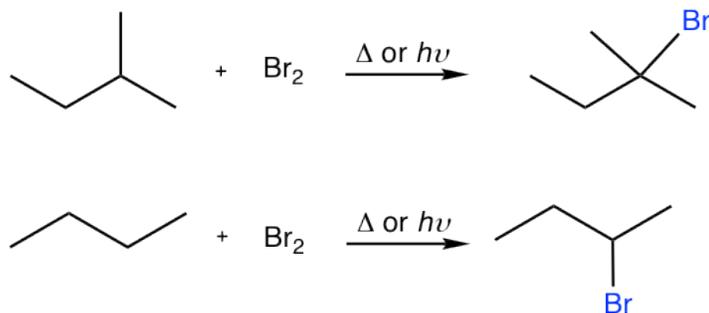
yield% of 1°-chloride: 8.0/12.8 = 70.3%

yield% of 3°-chloride 3.8/12.8 = 29.7%

The calculated values are consistent with the experiment results, but not exactly the same though.

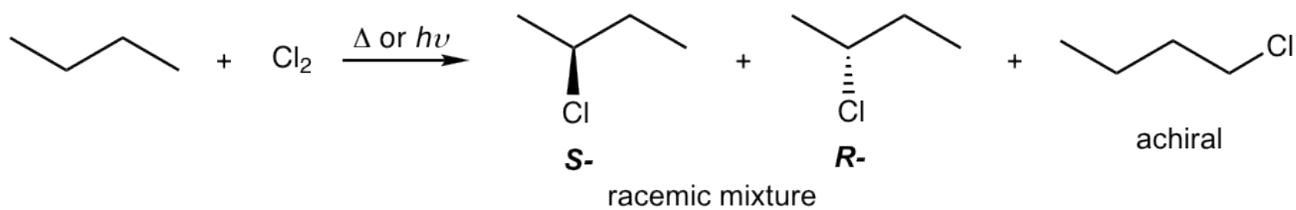
## 9.2

Show the major bromination product of the following reactions.



## 9.3

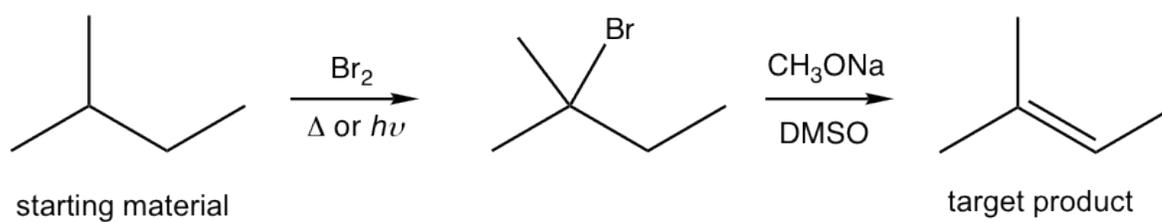
Show all the mono-chlorination products of butane with any stereoisomers when applied.



9.4

Design the synthesis route.

**synthesis**





# CHAPTER 10: ALKENES AND ALKYNES

Alkenes are hydrocarbons that contain C=C double bonds. The topics of naming, structure features, and geometric isomers of alkene have been covered in Chapters 2 and 7. In this chapter, we will first discuss how to synthesize alkenes and then investigate the chemical reactivities of alkenes. Furthermore, the second part of this chapter will cover the synthesis and reactions of alkynes, the hydrocarbon that contains a C≡C triple bond.

Learning Objectives for this chapter:

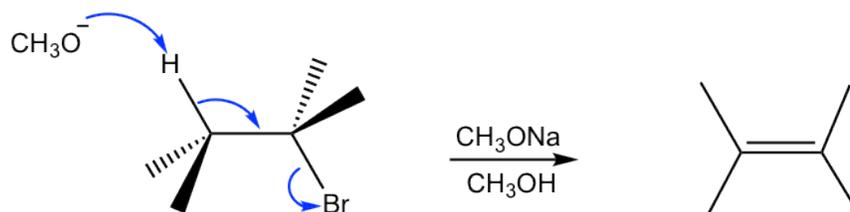
- Be able to prepare alkenes and alkynes by elimination reactions.
- Understand, explain, and apply the addition and oxidation reactions of alkenes and alkynes with different reagents, including the detailed mechanism, intermediates involved, and the stereochemistry of the products.
- Determine the reaction products for a variety of addition and oxidation reactions of alkenes and alkynes.
- Design the synthesis route for organic compounds by applying the reactions learned in this course.



## 10.1 Synthesis of Alkenes

### 10.1.1 Dehydrohalogenation of Alkyl Halide

The E2 elimination reaction of alkyl halide is one of the most useful methods for synthesizing alkene.



#### E2 elimination of alkyl halide to synthesize alkene

Figure 10.1a E2 elimination of alkyl halide to synthesize alkene

The mechanism and stereochemistry of the E2 reaction are thoroughly discussed in Chapter 8. Here are a few practical hints on making use of the E2 reaction to prepare alkene as the desired product:

- Choose a secondary or tertiary substrate if possible, since they prefer E2.
- If a primary substrate is necessary, choose a bulky base such as  $\text{t-BuO}^-$  to avoid a competition of substitution reaction. As mentioned earlier (section 8.4), the primary substrate undergoes an  $\text{S}_{\text{N}}2$  reaction with a small species like  $\text{OH}^-$ , which is also a good nucleophile.
- A high concentration of a strong base at an elevated temperature favors the E2 reaction.
- Keep in mind that a small base produces Zaitsev's product (more substituted alkene), while a bulky base produces Hofmann's product (less substituted alkene).

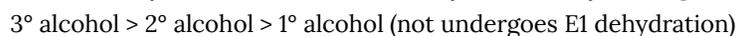
### 10.1.2 Dehydration of Alcohol

Other than alkyl halides, alcohols can also be the substrates for elimination to produce alkenes. Most alcohols undergo elimination by losing the  $\text{OH}$  group and an  $\text{H}$  atom from an adjacent carbon. Since a water molecule is eliminated for the overall reaction, the reaction is also called dehydration. Two dehydration reactions are shown below for synthesizing alkene from alcohol. Dehydration of an alcohol requires a strong acid with heat. Concentrated sulfuric acid ( $\text{H}_2\text{SO}_4$ ) or phosphoric acid ( $\text{H}_3\text{PO}_4$ ) are the most commonly used acids in the lab.



The elimination mechanism involves the carbocation intermediate, so it is essentially an E1 mechanism. However, it is not a typical E1, since it starts with the protonation step. We have learned in the substitution reaction chapter (section 7.6) that the OH group is a poor leaving group, so it never leaves. However, with the presence of strong acid ( $\text{H}_3\text{O}^+$ ,  $\text{H}_2\text{SO}_4$ , etc.), the OH group is protonated by acid and therefore is converted to the good leaving group  $\text{H}_2\text{O}$ . The same concepts apply here in elimination as well. Step 1 in the mechanism is the acid-base reaction for the purpose of converting the poor leaving group OH to the good leaving group  $\text{H}_2\text{O}$ . Steps 2 and 3 are typical steps for an E1 mechanism. The overall dehydration reaction can be regarded as the E1 reaction of a protonated alcohol.

For the E1 mechanism, the rate-determining step is the formation of carbocation, so the relative stability of carbocation defines the relative reactivity of alcohol towards E1 dehydration. As you can predict, the trend is:



Another observation in the dehydration reaction is that rearrangement occurs. This makes sense because the mechanism involves the formation of carbocation. We have learned the concept in section 7.6, that a carbocation will rearrange if the rearrangement produces a more stable carbocation. An example of dehydration with rearrangement is given below:

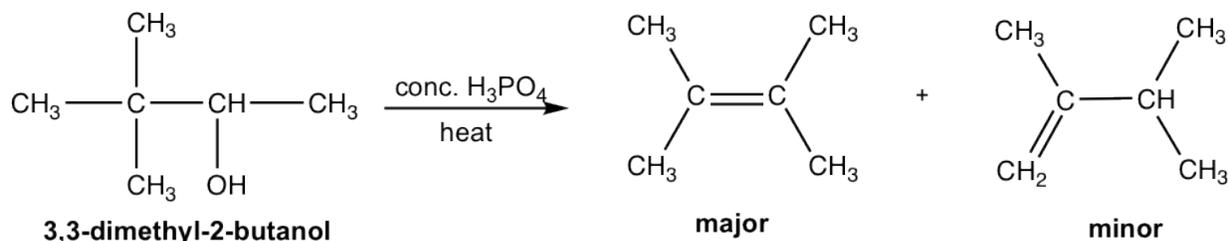
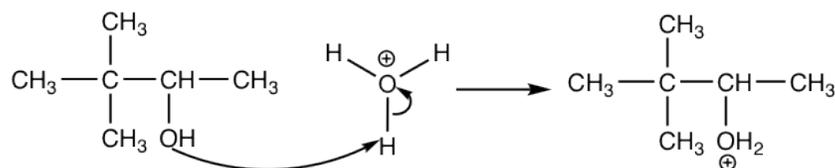


Figure 10.1d Example of dehydration with rearrangement

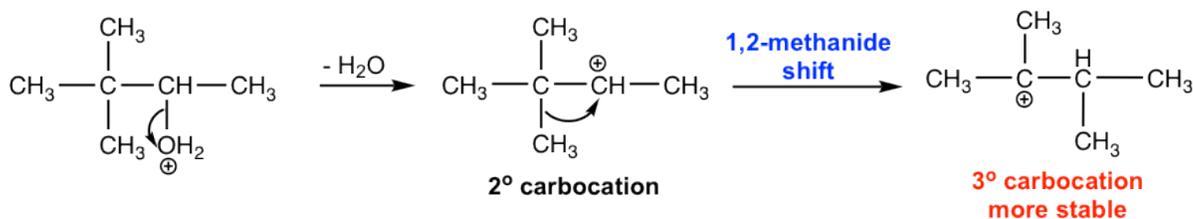
For the dehydration of 3,3-dimethyl-2-butanol, two alkenes are obtained with 2,3-dimethyl-2-butene as the major product. However, both products have a different carbon skeleton compared to that of the reactant. This is due to the rearrangement of the carbocation intermediate, which is shown explicitly in the mechanism below.

## Mechanism: Dehydration of 3,3-dimethyl-2-butanol

Step 1:



Step 2:



Step 3:

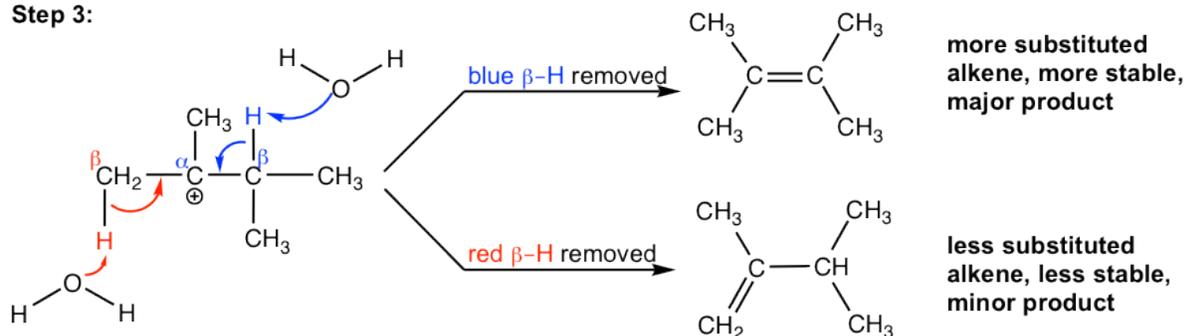


Figure 10.1e Dehydration of 3,3-dimethyl-2-butanol

In step 2 of the mechanism, the initially formed secondary carbocation undergoes rearrangement, 1,2-methanide shift, to produce the more stable tertiary carbocation.

In step 3, there are two  $\beta$ -hydrogens available in the tertiary carbocation for removal. The more substituted alkene, which is more stable, is the major product.

## Primary Alcohol Elimination

The primary alcohol can also undergo dehydration, however through an E2 mechanism because the primary carbocations are too unstable to be formed. The first step of the mechanism still involves the protonation of the OH group, to convert the poor leaving group to a good leaving group. The second step is the actual E2 of the protonated primary alcohol.

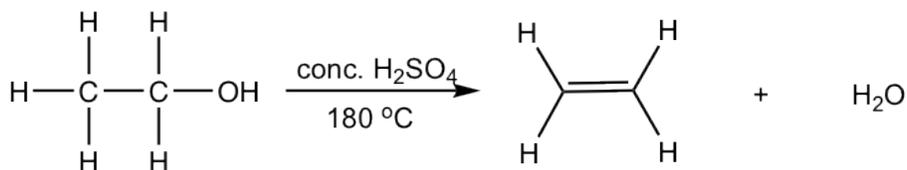


Figure 10.1f Example of a Primary Alcohol Elimination

### Mechanism: Dehydration of ethanol

#### Step 1: protonation of OH group



#### Step 2: E2, base removes a hydrogen from the $\beta$ -carbon, double bond forms, and water leaves.

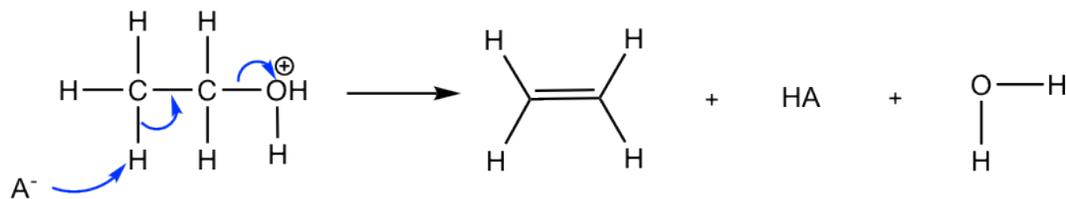
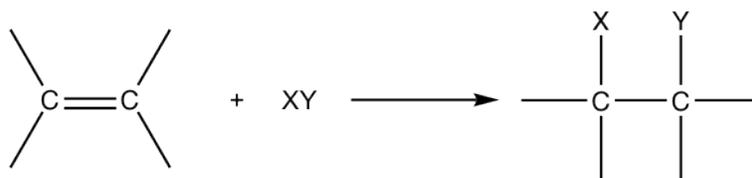


Figure 10.1g Dehydration of ethanol mechanism

## 10.2 Reactions of Alkenes: Addition of Hydrogen Halide to Alkenes

Alkenes undergo a wide variety of reactions. At first glance, these reactions appear to be quite different, but detailed studies indicate that the different mechanisms all share some common features. The double bond is the reactivity center of alkene; this is mainly because of the relatively loosely held  $\pi$  electrons of the double bond. The  $\pi$  bond is formed by side-by-side overlapping, a relatively weak overlapping mode, so the  $\pi$  bond is weak and exhibits high reactivity. The  $\pi$  electrons also make the double bond carbons electron-rich and have the tendency to be attracted to an electrophile. The high reactivity makes alkenes an important type of organic compound, and they can be used to synthesize a wide variety of other compounds, such as halides, alcohols, ethers, and alkanes.

The most common type of reaction for alkene is the addition reaction to a C=C double bond. In addition reaction, a small molecule is added to multiple bonds, and one  $\pi$  bond is converted to two  $\sigma$  bonds (unsaturation degree decreases) as a result of the addition. An addition reaction is the opposite process of elimination.



**General equation for addition reaction of alkene**

Figure 10.2a General equation for addition reaction of alkene

The addition reactions can generally be categorized depending on what small molecule is added, our following discussions will also be based on that.

### 10.2.1 Addition of Hydrogen Halide to Alkenes

The addition reaction of a hydrogen halide to an alkene produces an alkyl halide as a product. For examples:

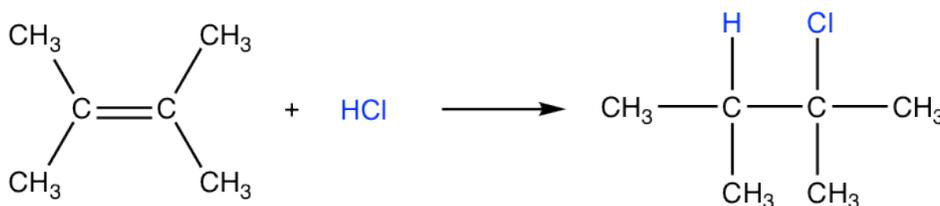


Figure 10.2b Addition reaction of a hydrogen halide to an alkene

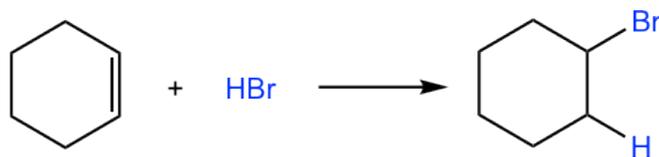


Figure 10.2c Addition reaction of a hydrogen halide to an alkene

In the above reactions, the alkenes are in symmetric structures, which means it does not matter which carbon bonded with hydrogen and which carbon bonded with the halogen, as the same product will be obtained either way.

For the alkene that does not have a symmetric structure, the double bond carbons have different substituents so the question of which carbon gets the hydrogen is critical. For the example of the following reaction, two possible products could be produced: 2-bromo-2-methylpropane and 1-bromo-2-methylpropane. Which one is actually formed? Or are both formed?

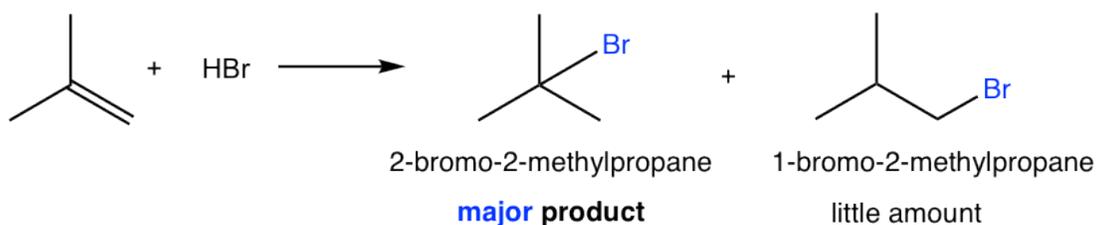


Figure 10.2d Which product is formed?

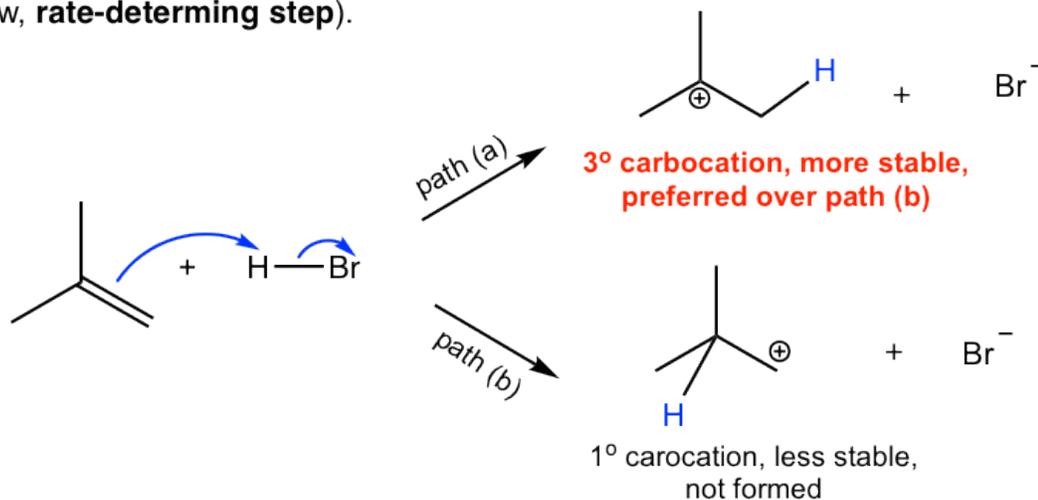
It turns out that 2-bromo-2-methylpropane is the main product of the reaction. To explain and understand the outcome of the reaction, we need to look at the mechanism of the reaction.

The mechanism of the addition reaction involves two steps (shown below). In the first step, the  $\pi$  electrons of the alkene act as nucleophiles and are attracted to the partially positively charged hydrogen (electrophile) of HBr. As the  $\pi$  electrons of the alkenes move toward the hydrogen, the H-Br bond breaks, Br moves away with the bonding electrons, and a new  $\sigma$  bond is formed between one double bond carbon and hydrogen. A carbocation and a bromide,  $\text{Br}^-$ , are formed in this step.

In the second step, the bromide,  $\text{Br}^-$ , reacts with the positively charged carbocation to give the final product. This step is similar to the second step of the  $\text{S}_{\text{N}}1$  reaction, in which a nucleophile reacts with an electrophile (carbocation).

## Mechanism: Electrophilic addition of HBr to 2-methylpropene

**Step 1:** Electrophilic attack of HBr to the alkene, carbocation intermediate formed (slow, rate-determining step).



**Step 2:** Halide anion reacts with the carbocation (fast).

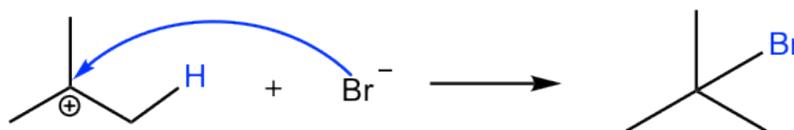


Figure 10.2e Mechanism: Electrophilic addition of HBr to 2-methylpropene

When the new bond is formed between the double bond carbon and hydrogen in the first step, the hydrogen could possibly be bonded with either carbon, as shown in paths (a) and (b), and carbocations with a different structure will be produced. It is obvious that the tertiary carbocation formed in the path (a) is much more stable than the primary carbocation in the path (b) and will be produced preferably. The tertiary carbocation is then attacked by the  $\text{Br}^-$  in the second step, which produces the product 2-bromo-2-methylpropane. It is the stability difference between two carbocations in the first step that accounts for the selective formation of 2-bromo-2-methylpropane in the overall reaction.

Because the first step of the above reaction is the addition of an electrophile ( $\text{H}^+$ ) to the alkene, the reaction is called an electrophilic addition reaction. An electrophilic addition reaction is a characteristic type of reaction of alkenes, and several other addition reactions, as we will see later, also belong to this category.

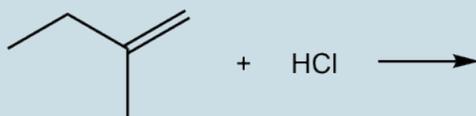
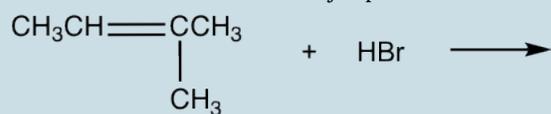
The two possible products of this reaction are constitutional isomers to each other. For the reaction in which two or more constitutional isomers could be obtained as products, but one predominates, the reaction is said to be a regioselective reaction. *Regio* comes from the Latin word *regionem*, which means direction. The regioselectivity trend of the electrophilic addition of HX to alkenes was summarized as Markovnikov's rule by Russian chemist Vladimir Markovnikov. One way to state Markovnikov's rule is that in the addition of HX to an alkene, the hydrogen atom adds to the double bond carbon that has the greater number of hydrogen atoms.

The underlying reasoning for Markovnikov's rule is the stability of the carbocation intermediate involved in the reaction mechanism. It may seem easy to just memorize the rule or memorize the fact that 2-bromo-2-methylpropane is the product of the above reaction without understanding why. However, you would quickly notice that your memorization would be overwhelmed and mixed up with the many reactions coming up. The proper way to study

organic reactions is to learn and understand the mechanism and unify the principles of the reactions based on mechanisms. The mastery of the contents will be much easier and a lot more fun in this way.

### Exercises 10.1

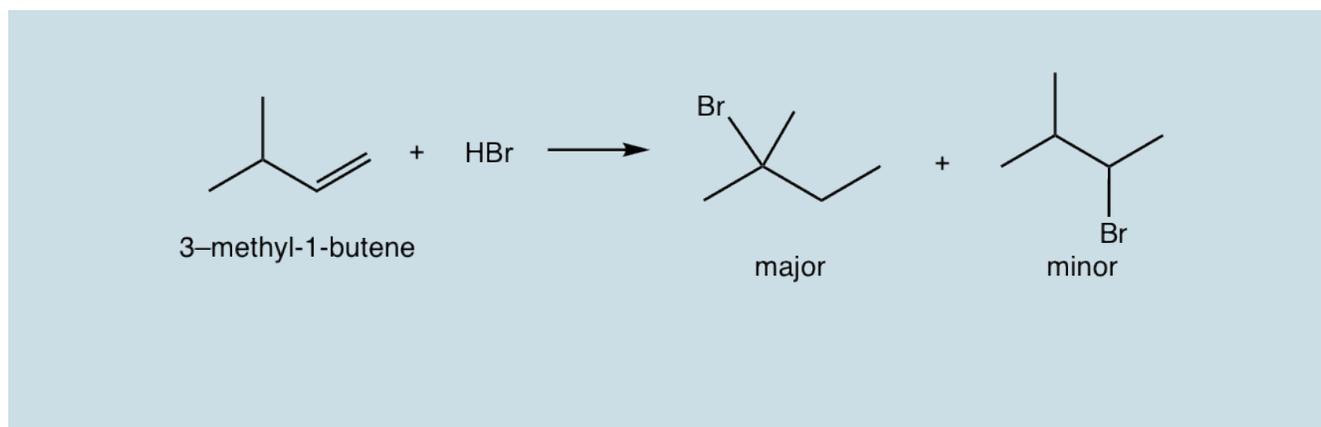
Show the structure of the major product for following addition reactions.



### Answers to Chapter 10 Practice Questions

### Exercises 10.2

For the addition of HBr to 3-methyl-1-butene, two products were observed. Show the reaction mechanism to explain the formation of both products.



## 10.2.2 Radical Addition of HBr to Alkenes

In the last section, we learned that the electrophilic addition of HX to alkene gives addition products that follow Markovnikov's rule. Here, we will learn that hydrobromide, HBr, can also be added to alkene in a way that gives an anti-Markovnikov product.

**electrophilic addition:**



**radical addition:**

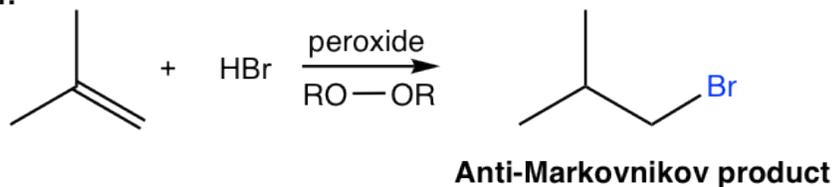


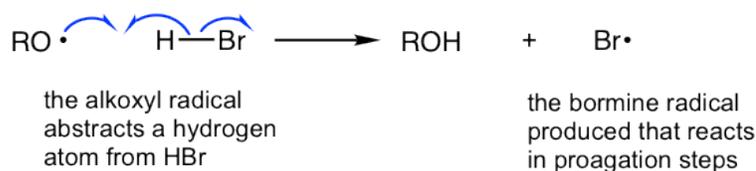
Figure 10.2f Electrophilic addition produces Markovnikov product & radical addition produces Anti-Markovnikov product

The anti-Markovnikov product is obtained through a different mechanism, which is the radical mechanism. To initiate the radical mechanism, peroxide must be involved to generate the radical in the initiation step of the mechanism. The O-O bond of peroxide is weak (with a bond energy of about 150 kJ/mol), and it undergoes homolytic cleavage readily with heat to produce alkoxy radicals. The peroxide therefore acts as a radical initiator by generating radicals, and the addition is called radical addition. The detailed radical addition mechanism of the above addition of HBr to 2-methylpropene is given here.

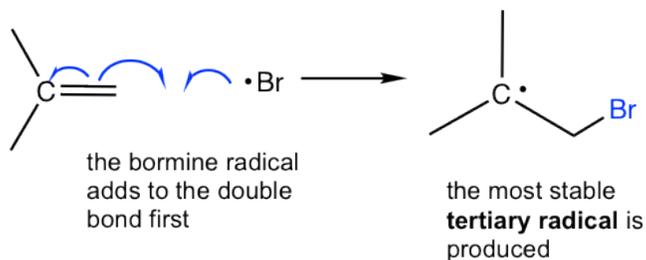
**Initiation step 1:**



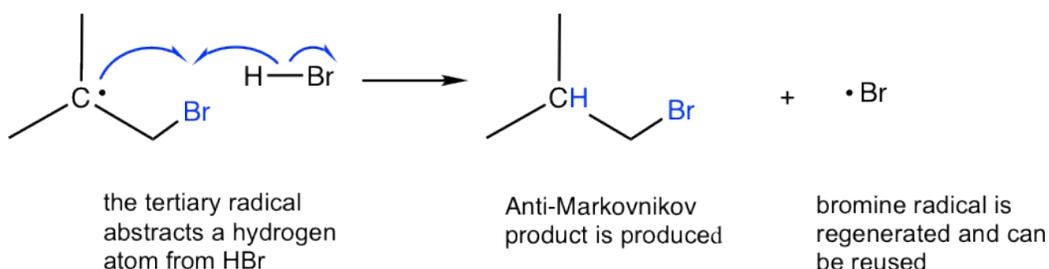
**step 2:**



**Propagation step 1:**



**step 2:**



**Termination steps:**

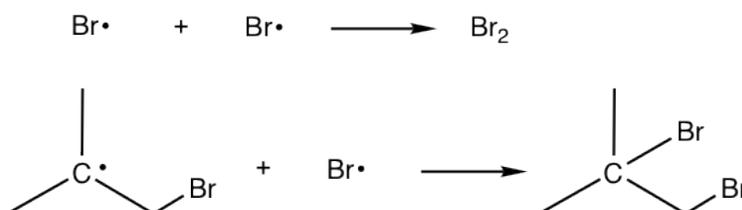


Figure 10.2g Radical Addition Mechanism

The initiation involves two steps for the radical addition mechanism. The alkoxy radical generated in step 1 reacts with H-Br to generate the bromine radical, Br·, which reacts with an alkene to initiate the chain reaction in the propagation steps. It is shown clearly in the propagation steps that the order of the addition is reversed in radical addition compared to that of electrophilic addition. Specifically, the bromine radical (Br) is added to the double bond first followed by the abstraction of hydrogen atoms (H); therefore, the anti-Markovnikov product is produced as a result.

One more note is that only HBr proceeds with radical addition in the presence of peroxide, not HCl or HI.

## 10.3 Reactions of Alkenes: Addition of Water (or Alcohol) to Alkenes

### Addition of Water to Alkenes (Hydration of Alkenes)

An alkene does not react with pure water since water is not acidic enough to allow the hydrogen to act as an electrophile to start a reaction. However, with the presence of a small amount of an acid, the reaction does occur with a water molecule added to the double bond of alkene, and the product is an alcohol. This is the acid-catalyzed addition reaction of water to alkene (also called hydration), and this reaction has great utility in the large-scale industrial production of certain low-molecular-weight alcohols.

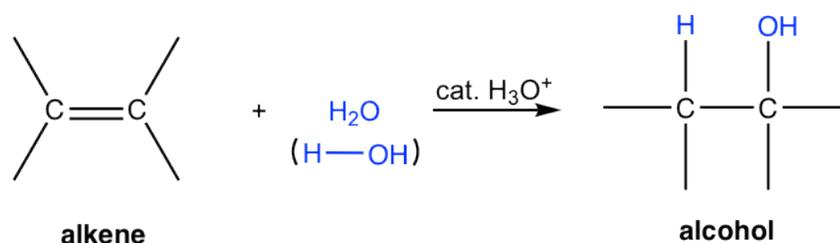
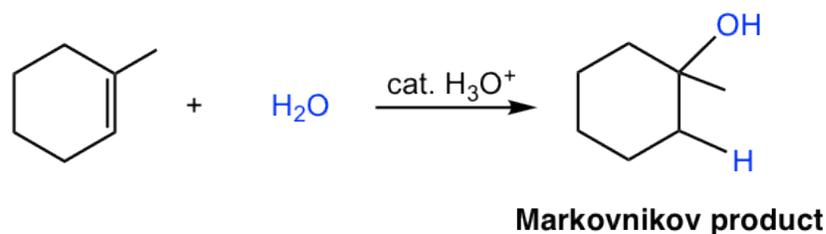


Figure 10.3a Hydration Reaction

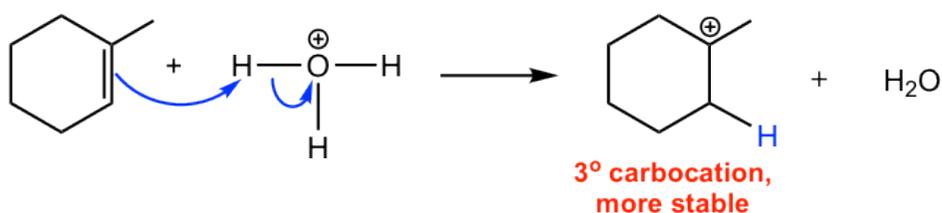
The acid most commonly applied to catalyze this reaction is the dilute aqueous solution of sulfuric acid ( $\text{H}_2\text{SO}_4$ ). Sulfuric acid dissociates completely in an aqueous solution and the hydronium ion ( $\text{H}_3\text{O}^+$ ) generated participates in the reaction. A strong organic acid, tosyl acid ( $\text{TsOH}$ ), is sometimes used as well.

The mechanism for the acid-catalyzed hydration of alkene is essentially the same as the mechanism for the addition of hydrogen halide,  $\text{HX}$ , to alkenes, and the reaction therefore also follows Markovnikov's rule in terms of regioselectivity. The hydration of 1-methylcyclohexene and the reaction mechanism is shown below.

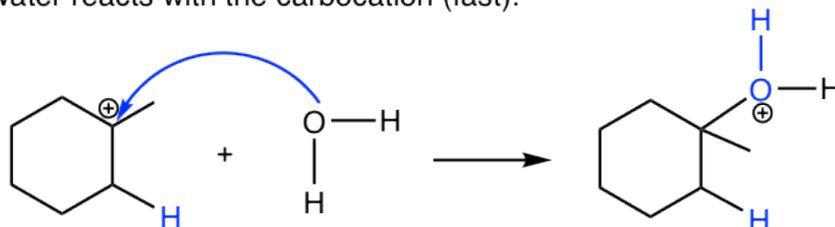


### Mechanism

**Step 1:** Electrophilic attack of  $\text{H}_3\text{O}^+$  to the alkene, carbocation intermediate formed (slow).



**Step 2:** Water reacts with the carbocation (fast).



**Step 3:** Deprotonation to get neutral product (fast).

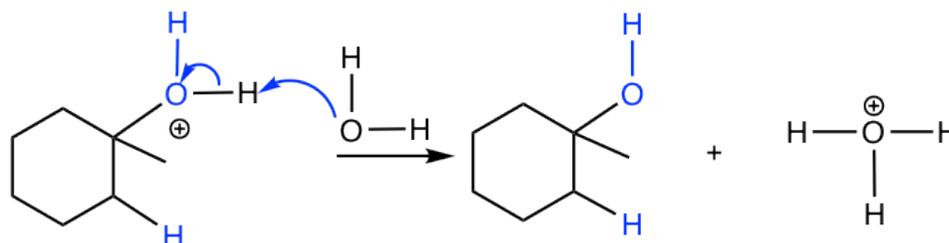


Figure 10.3b Mechanism for acid-catalyzed hydration of alkene

Since a water molecule can be regarded as  $\text{H}-\text{OH}$ , the regioselectivity of alcohol product that follows Markovnikov's rule means the hydrogen atom connects to the double bond carbon that has more hydrogen atoms, and the  $\text{OH}$  group adds to the carbon that has fewer hydrogen atoms. This can be explained again by the formation of a more stable carbocation in the first step of the mechanism. The acidic hydronium ion ( $\text{H}_3\text{O}^+$ ) is regenerated in the last deprotonation step, so only a small amount of acid is required to initiate the reaction. The acid therefore is a catalyst.

When comparing the hydration reaction of alkene to the dehydration reaction of alcohol in section 10.1.2, you will recognize that they are reverse reactions, as one is addition, and the other is elimination. To produce alcohol from alkene via hydration, water should be in excess to ensure the reaction goes to completion. While preparing alkene from alcohol through dehydration, a high concentration of acid with an elevated temperature favors the elimination process, and the product can be removed by distillation as it is formed to push the equilibrium to the alkene side.

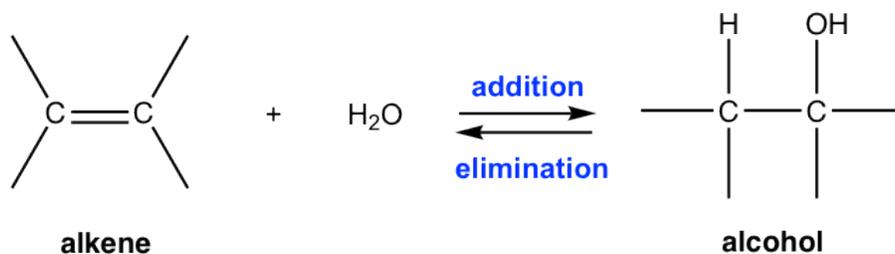


Figure 10.3c Hydration reaction of alkene vs. dehydration reaction of alcohol

## Addition of Alcohol to Alkenes

With the presence of acid, an alcohol can be added to the alkene in the same way that water can be, and ether is formed as a product. For example:

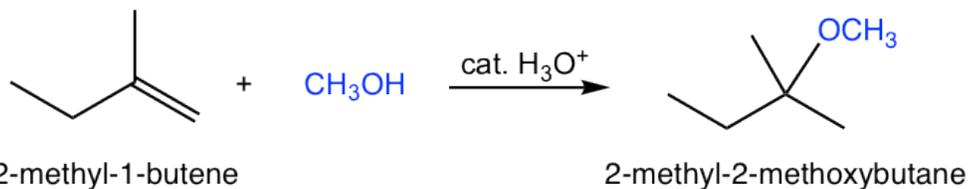


Figure 10.3d Example of addition of Alcohol to Alkenes

Examples:

Show the mechanism for the above addition reaction of methanol to 2-methyl-1-butene. Refer to the hydration mechanism.

### Solutions:

Mechanism: addition of methanol to 2-methyl-1-butene

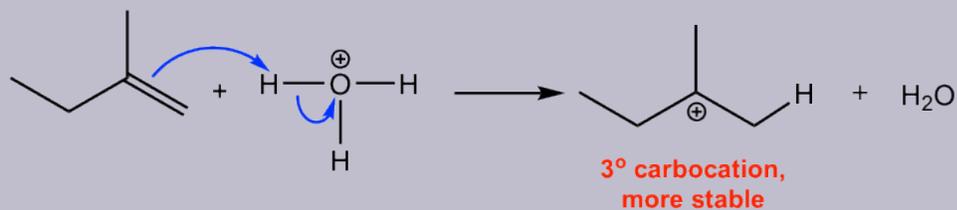
Step 1: Electrophilic attack of  $\text{H}_3\text{O}^+$  to the alkene, carbocation intermediate formed

Step 2: Methanol reacts with the carbocation

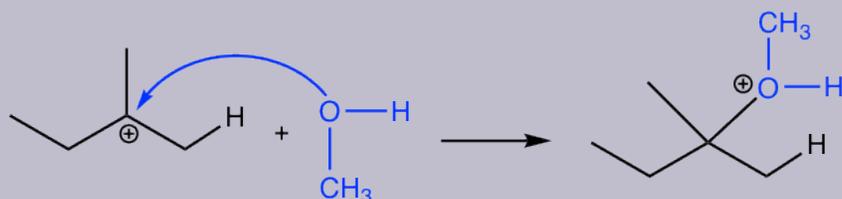
Step 3: Deprotonation to get the neutral product

### Mechanism: addition of methanol to 2-methyl-1-butene

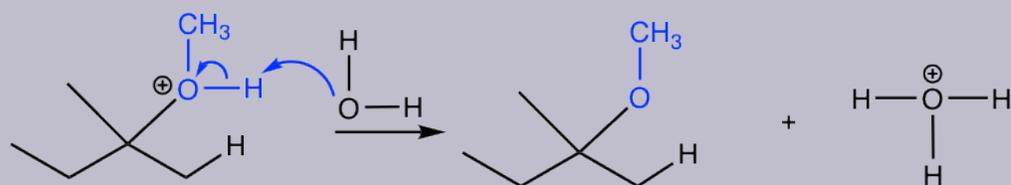
**Step 1:** Electrophilic attack of  $\text{H}_3\text{O}^+$  to the alkene, carbocation intermediate formed



**Step 2:** Methanol reacts with the carbocation



**Step 3:** Deprotonation to get neutral product

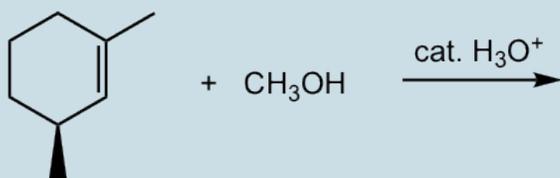
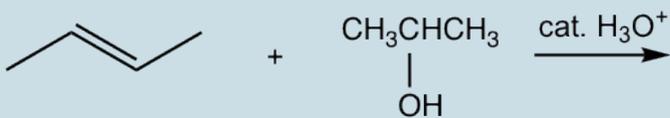
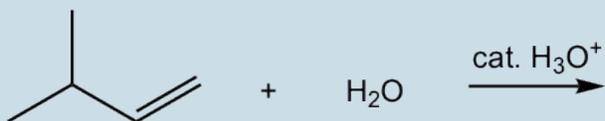


Note:

Please keep in mind that for the reaction that involves carbocation intermediate, the rearrangement of carbocation is always an option. Therefore the addition of water/alcohol to alkenes may involve carbocation rearrangement if possible.

#### Exercises 10.3

Show major product(s) for the following reactions.



Answers to Chapter 10 Practice Questions

## 10.4 Reactions of Alkenes: Addition of Bromine and Chlorine to Alkenes

An addition reaction also easily occurs between halogens ( $\text{Br}_2$  and  $\text{Cl}_2$ ) and alkenes. In the presence of aprotic solvent, the product is a vicinal dihalide, as shown here for the addition of chlorine to propene.

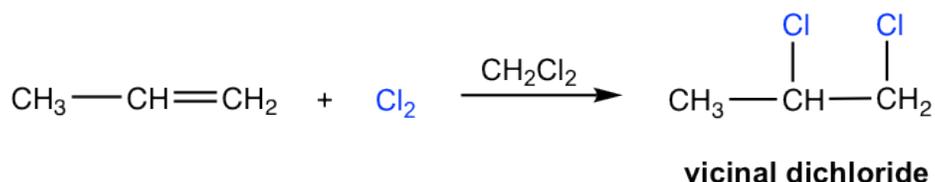
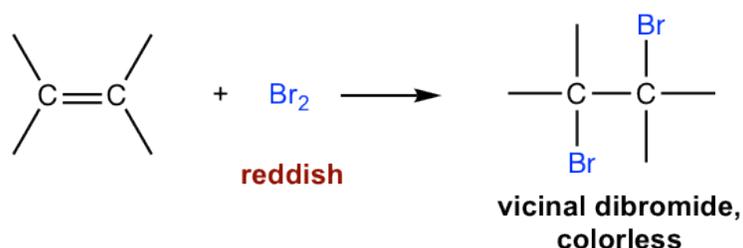


Figure 10.4a Addition reaction

The reaction between a C=C double bond and bromine ( $\text{Br}_2$ ) can be used as a test for the presence of alkene in an unknown sample. The bromine reagent is in a reddish color, and the product vicinal dibromide is colorless. When bromine is added to the sample, if the reddish color disappears, it means the sample contains an alkene. The addition reaction occurs to get reddish bromine consumed and a colorless product is formed, so the color fades off.



### Mechanism for the Addition of Halogen to Alkenes

The products for the addition of halogen to alkenes seem straightforward, with each halogen added to each double bond carbon. However, the addition proceeds with a unique stereochemistry feature that needs special attention. It turns out that the halogen atoms are added via **anti-addition** to the double bond, as shown in the examples here:

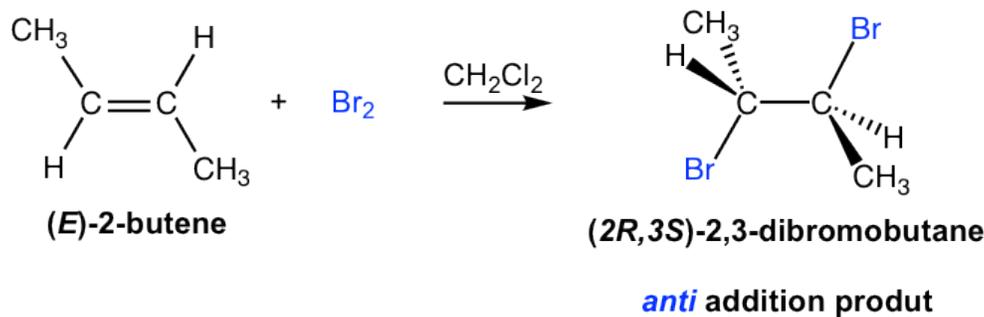
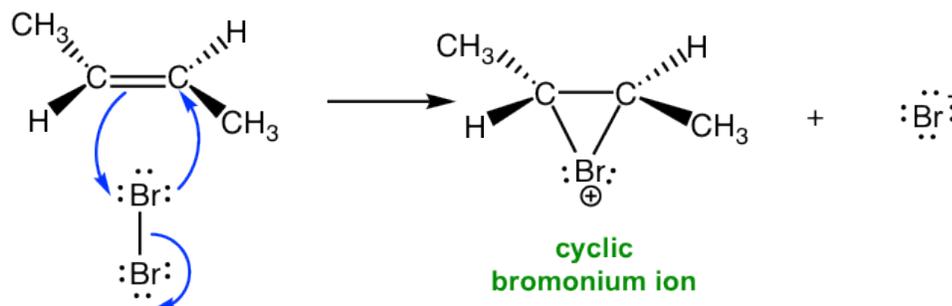


Figure 10.4b Anti addition product

The mechanism that accounts for the anti-addition of halogen involves the electron pairs transferred in a way that is different to what we are familiar with and the formation of the cyclic halonium ion intermediate. We will take the addition of bromine to (*E*)-2-butene as an example to explain the mechanism.

### Mechanism: addition of Br<sub>2</sub> to *E*-2-butene

#### Step 1: formation of bromonium ion



#### Step 2: Br<sup>-</sup> attacks from the direction that is **anti** to bromonium ion

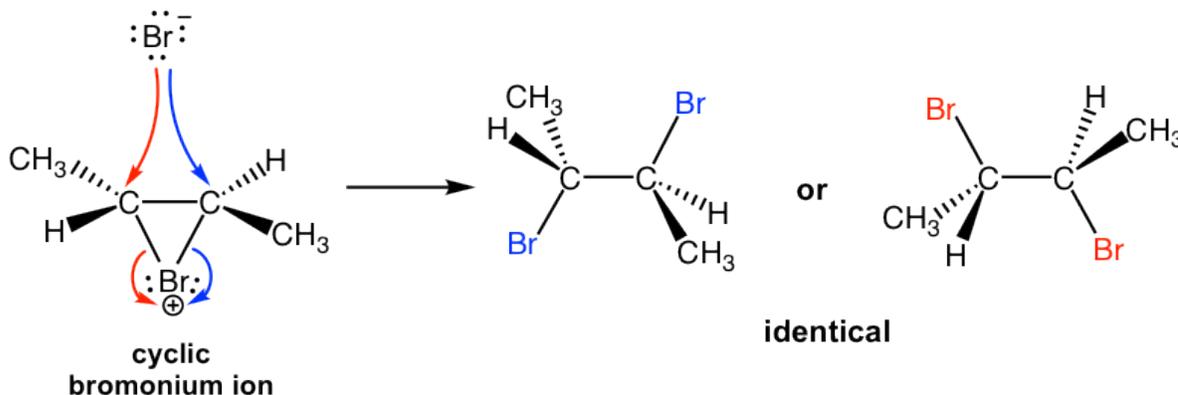


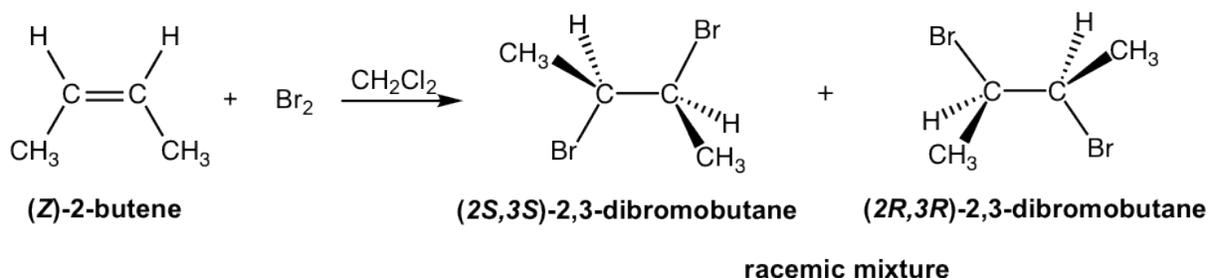
Figure 10.4c Mechanism for addition of Br<sub>2</sub> to *E*-2-butene

When a Br<sub>2</sub> molecule approaches alkene in the first step, the electron density of the  $\pi$  bond in alkene repels the electron density in the bromine, polarizing the bromine molecule and making the bromine atom closer to the double bond electrophilic. The alkene donates a pair of  $\pi$  electrons to the closer bromine, causing the displacement of the bromine atom, which is further away. The lone pair on the closer bromine atom then acts as a nucleophile to attack the other  $sp^2$  carbon. Thus, the same bromine atom is both an electrophile and a nucleophile, and two single bonds are formed between the two  $sp^2$  carbons and the closer bromine that gives the cyclic bromonium ion intermediate.

In the second step, the nucleophilic bromide, Br<sup>-</sup> (generated in step 1), attacks the carbon of the cyclic intermediate. Since the bottom side of the intermediate is blocked by the ring, the Br<sup>-</sup> can only attack from the top side, which results in the anti-position of the two Br in the product. The attack is similar to the S<sub>N</sub>2 reaction and causes the ring to open and the formation of vicinal dibromide. For the above example, the two carbons in the bromonium ion intermediate are in the same chemical environment, so they both have the same chance of being attacked by Br<sup>-</sup>, as shown in the blue and red arrows. The two attacks result in the same product, the meso compound (2*R*,3*S*)-2,3-dibromobutane, in this reaction.

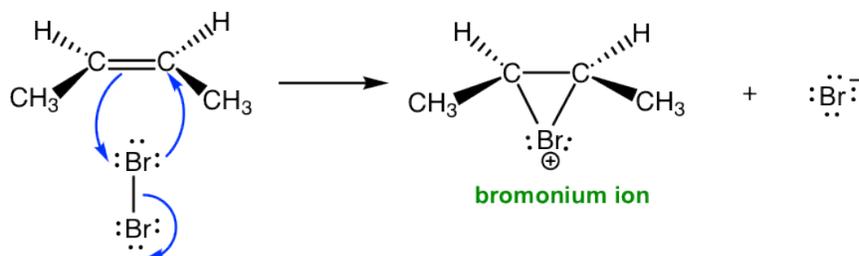
Next, let's examine the addition of bromine to (*Z*)-2-butene. As you may expect, the reaction goes through the same

mechanism that involves the cyclic bromonium ion intermediate; however, the products have different stereochemistry features.



**Mechanism: addition of Br<sub>2</sub> to (Z)-2-butene**

**Step 1: formation of bromonium ion**



**Step 2: attack of Br<sup>-</sup> to bromonium ion from anti direction**

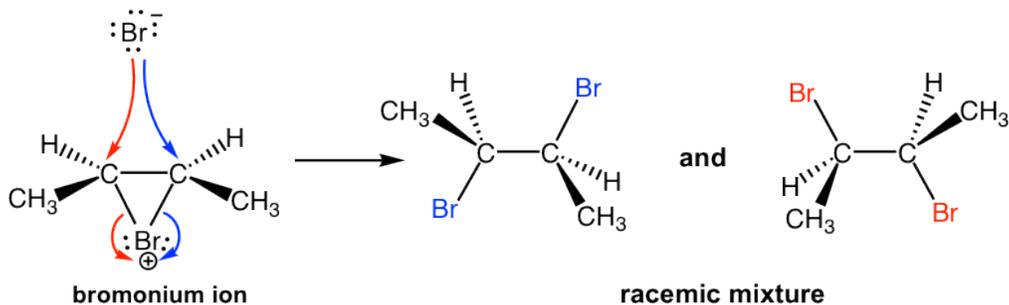
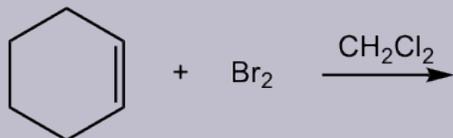


Figure 10.4d Mechanism: addition of Br<sub>2</sub> to (Z)-2-butene

In the addition of Br<sub>2</sub> to (Z)-2-butene, the attack of Br<sup>-</sup> to either carbon in a bromonium ion by following the blue or red arrow results in a different enantiomer (step 2 in the above mechanism). Since both carbons have the same chance of being attacked, the product is a 50:50 racemic mixture of the two enantiomers.

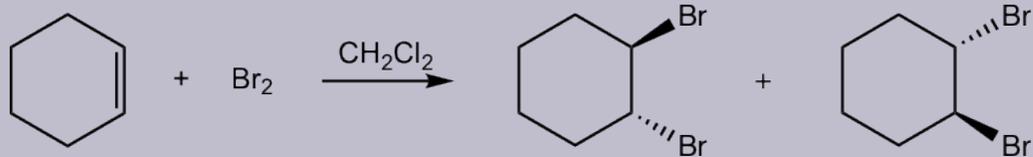
The addition reaction of Br<sub>2</sub> to different reactants, (E)-2-butene and (Z)-2-butene, generates different stereoisomers as products. The addition of (E)-2-butene gives one product, the meso compound (2R,3S)-2,3-dibromobutane, while the addition of (Z)-2-butene produces the racemic mixture of two enantiomers, (2S,3S)-2,3-dibromobutane and (2R,3R)-2,3-dibromobutane. Such a reaction, the one in which a particular stereoisomer of the starting material yields a specific stereoisomer of the product, is called a stereospecific reaction. The anti-addition of a halogen to an alkene is an example of a stereospecific reaction.

Show the product of the following addition.



**cyclohexene**

Solutions:



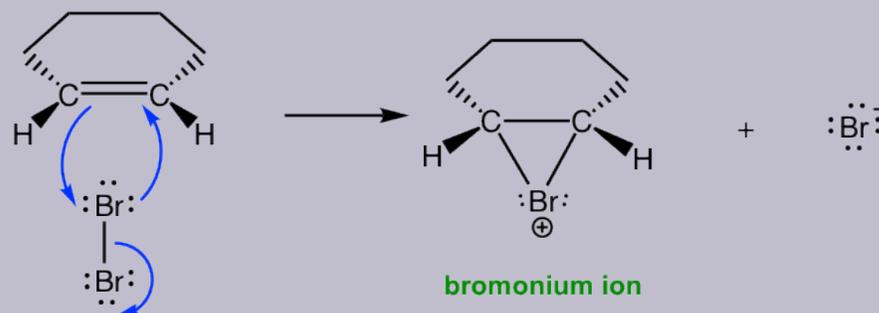
**cyclohexene**

**racemic mixture: two enantiomers of  
*trans*-1,2-dibromocyclohexane**

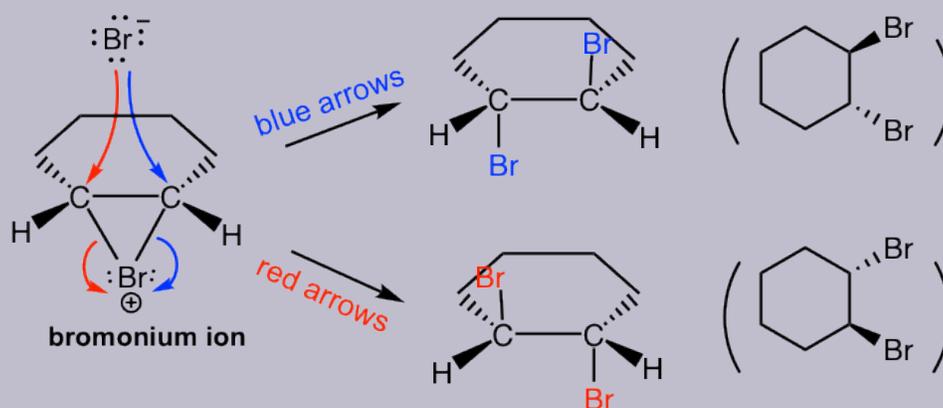
The formation of the racemic mixture product can be explained by the mechanism:

## Mechanism

### Step 1:



### Step 2:



## Formation of Halohydrin

If water is used as a solvent in the reaction, rather than  $\text{CH}_2\text{Cl}_2$  water takes in part of the reaction and acts as a nucleophile to attack the cyclic halonium intermediate in the second step. The major product of the addition will be a vicinal halohydrin as a result. A vicinal halohydrin is a compound that contains a halogen and an OH group on two adjacent carbons.

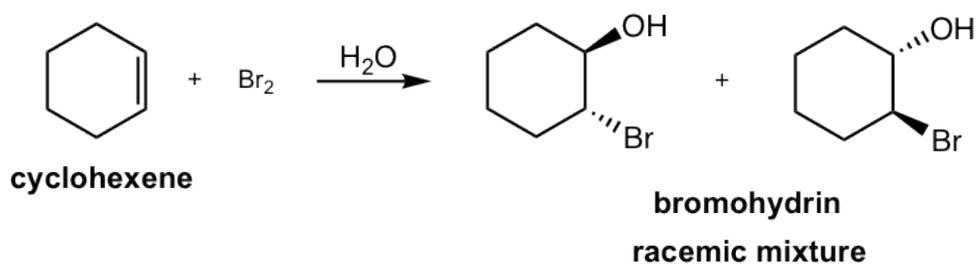


Figure 10.4e Formation of Halohydrin

## Mechanism: reaction of bromine water with cyclohexene

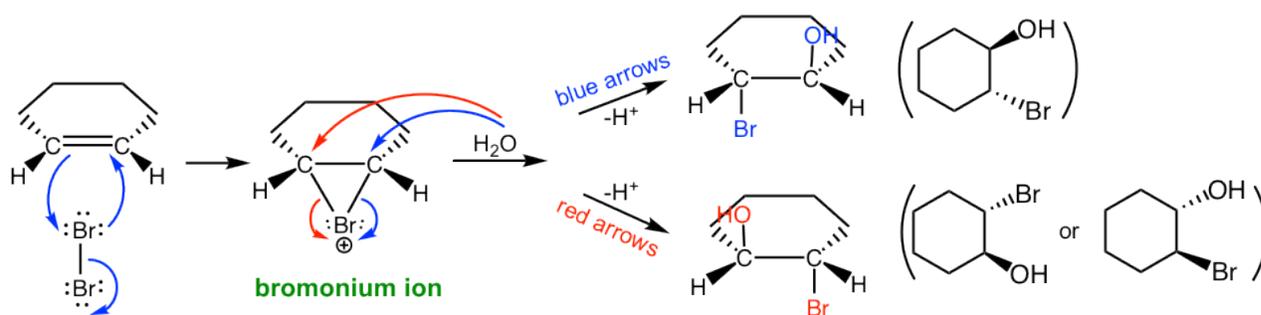
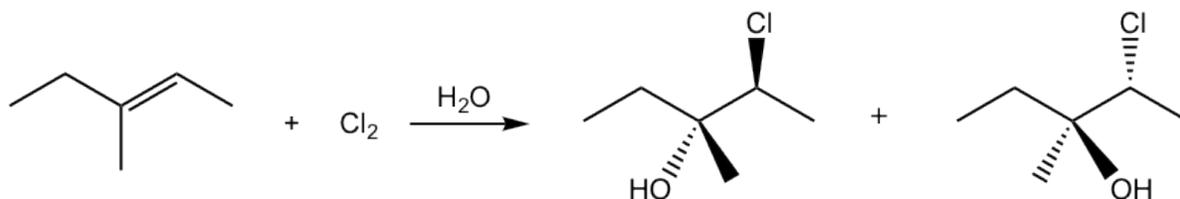


Figure 10.4f Mechanism: reaction of bromine water with cyclohexene

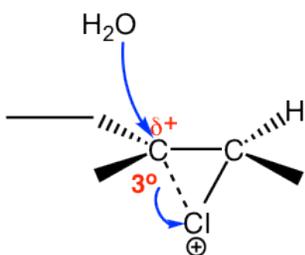
In the second step of the mechanism, both  $\text{H}_2\text{O}$  (solvent) and  $\text{Br}^-$  (produced in the first step) are nucleophiles and have the chance to react with the cyclic bromonium ion. However since  $\text{H}_2\text{O}$  is the solvent, its concentration is much higher than that of  $\text{Br}^-$ , so the major products come from the attack of  $\text{H}_2\text{O}$ .

This reaction is still the stereospecific reaction in which the anti-addition occurs, as the halogen and OH group are in an anti-position. For the above example, the addition of bromine water to cyclohexene, a racemic mixture with both enantiomers is obtained.

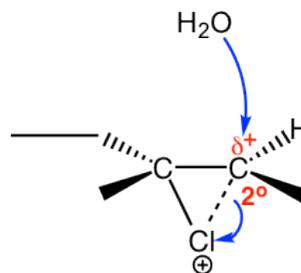
If the alkene is not in a symmetric structure, it is observed that the addition shows the regioselectivity as well, specifically, the halogen adds on the carbon atom with the greater number of hydrogen atoms, and the OH group ends up on the double bond carbon with fewer hydrogen atoms. How can this be explained?



This is due to the difference between the two double-bond carbons in the cyclic intermediate. When nucleophile water attacks, the  $\text{C-Br}$  bond starts to break and the carbon atom has partial positive charges. The carbon atom with two substituents bears more positive charges, and it resembles the more stable tertiary carbocation, and the other carbon atom with one substituent shows a secondary carbocation character. As a result, the attack on the carbon with more tertiary carbocation character is preferable.



partial positive charge is accommodated better on **tertiary carbon, preferred**

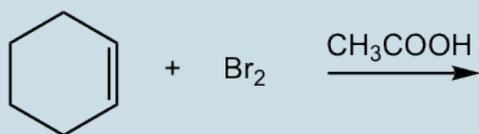


secondary carbon not accommodate partial positive charged that well, not preferred

Figure 10.4g tertiary carbon vs. secondary carbon

#### Exercises 10.4

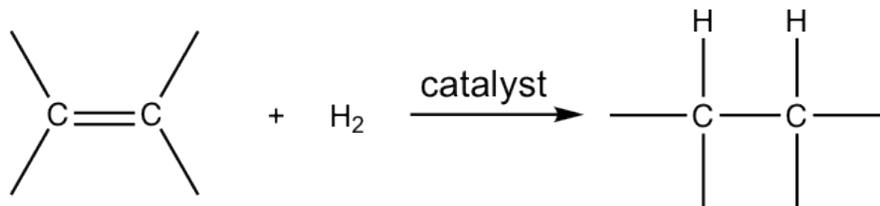
Show major product(s) of the following reactions:



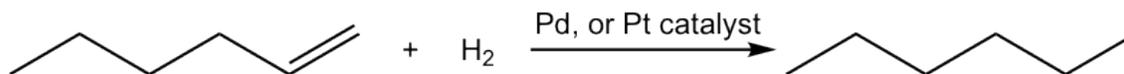
Answers to Chapter 10 Practice Questions

## 10.5 Reaction of Alkenes: Hydrogenation

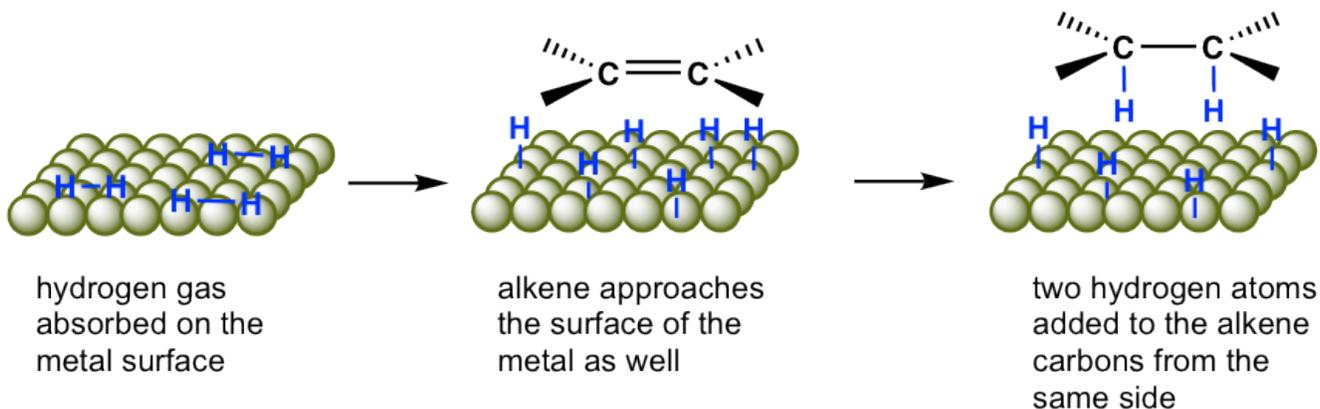
When alkenes react with hydrogen gas in the presence of a variety of metal catalysts, a hydrogen molecule will be added to the double bond in a way that each carbon atom bonds with one hydrogen atom. Such an addition reaction is called hydrogenation.



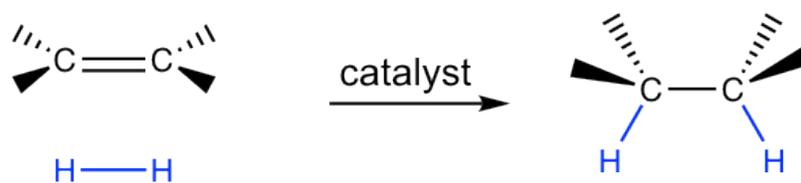
Catalysts are a must-have for hydrogenation, so the reaction can also be called catalytic hydrogenation. Commonly applied metal catalysts include palladium and platinum. Palladium, which is used as a powder absorbed on charcoal to maximize the surface area, is the most common catalyst and is referred to as palladium on charcoal (Pd/carbon). Platinum, which is usually used as oxide PtO<sub>2</sub>, is also employed frequently and referred to as Adams' catalyst. These metal catalysts are not soluble in the reaction mixture and therefore are described as heterogeneous catalysts. The heterogeneous catalyst can be easily filtered out of the reaction mixture after the reaction and then recycled and reused.



The hydrogenation reaction does not take place without a catalyst because of the enormous activation energy. The catalysts lower the activation energy by weakening the H-H bond and making the reaction feasible at room temperature. The details of the mechanism of catalytic hydrogenation are not completely clear. What was understood was that hydrogen gas is adsorbed on the surface of the metal, and the alkene also complexes with the metal by overlapping its  $\pi$  orbitals with vacant orbitals of the metal. The reaction occurs on the surface of the metal catalyst, with both hydrogen atoms added from the same side of the alkene to give alkane as the product that diffuses away from the metal surface. This mode of addition that the atoms added from the same side of the alkene is called the syn addition.

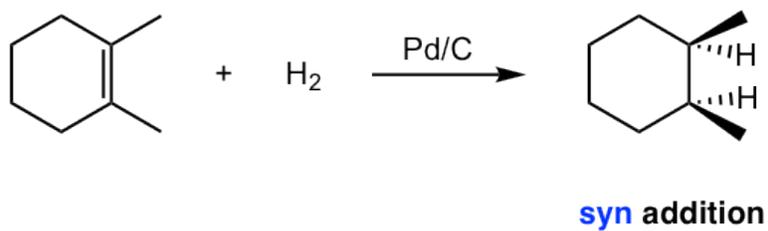


**simplified diagram for catalytic hydrogenation of alkene**



**catalytic hydrogenation: *syn* addition**

Example:



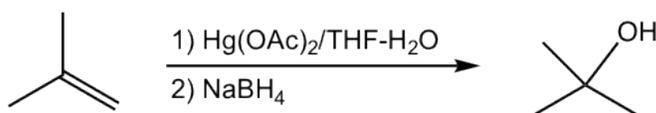
## 10.6 Two Other Hydration Reactions of Alkenes

As we learned in section 10.2.2, the acid-catalyzed hydration (addition of water) to alkene produces alcohol that follows Markovnikov's regioselectivity. Here, we will investigate two other methods for the hydration of alkene via different reaction conditions and mechanisms and produce either Markovnikov or anti-Markovnikov alcohol products, respectively.

### 10.6.1 Oxymercuration-Demercuration of Alkenes

The oxymercuration-demercuration of alkenes provides an alternative way to synthesize Markovnikov's alcohol from an alkene. It is a fast reaction with lots of applications in laboratories, and the yield is usually greater than 90%. Compared to acid-catalyzed hydration, the benefits of oxymercuration-demercuration are: no strong acids required and no carbocation rearrangements involved. The only reason that limits the wide application of this method is the environmental concern since mercury (Hg) waste is produced.

Oxymercuration-demercuration is a two-step procedure, as shown explicitly below:

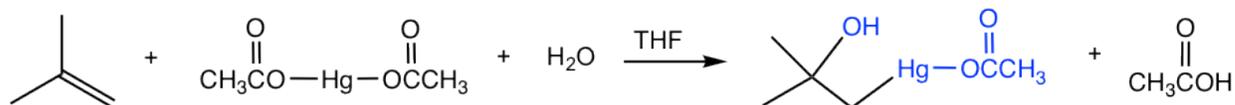


$\text{Hg}(\text{OAc})_2$ : mercuric acetate,  $\text{CH}_3\text{CO}-\overset{\text{O}}{\parallel}{\text{C}}-\text{Hg}-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3$ ; the acetate group,  $\text{CH}_3\overset{\text{O}}{\parallel}{\text{C}}-$ , is abbreviated as OAc

THF: tetrahydrofuran, the co-solvent

$\text{NaBH}_4$ : sodium borohydride,  $\text{H}-\overset{\text{H}}{\underset{\text{H}}{\text{B}}}-\text{H} \text{Na}^\oplus$ , the reducing agent

**Step 1 Oxymercuration:** mercuric acetate and water add to the double bond



**Step 2 Demercuration:** the mercuric group is reduced and replaced with hydrogen



Figure 10.6a 1. Oxymercuration-Demercuration process

The mechanism in the oxymercuration step involves mercury acting as a reagent attacking the alkene double bond to form a cyclic mercurinium ion intermediate. Because no carbocation intermediate is involved, rearrangements are not observed in a such reaction. Then, a water molecule attacks the most substituted carbon to open the mercurinium ion bridge followed by proton transfer to a solvent water molecule. For the same reasoning that the water molecule attacks the more substituted carbon of the cyclic halonium ion in a halohydrin formation (section 10.2.4), the water molecule in this mechanism also attacks the more substituted carbon preferentially, as the partial positive charge is better accommodated on a tertiary carbon than on a primary carbon (if the attack occurs on the other carbon).

**Mechanism of Oxymercuration:**

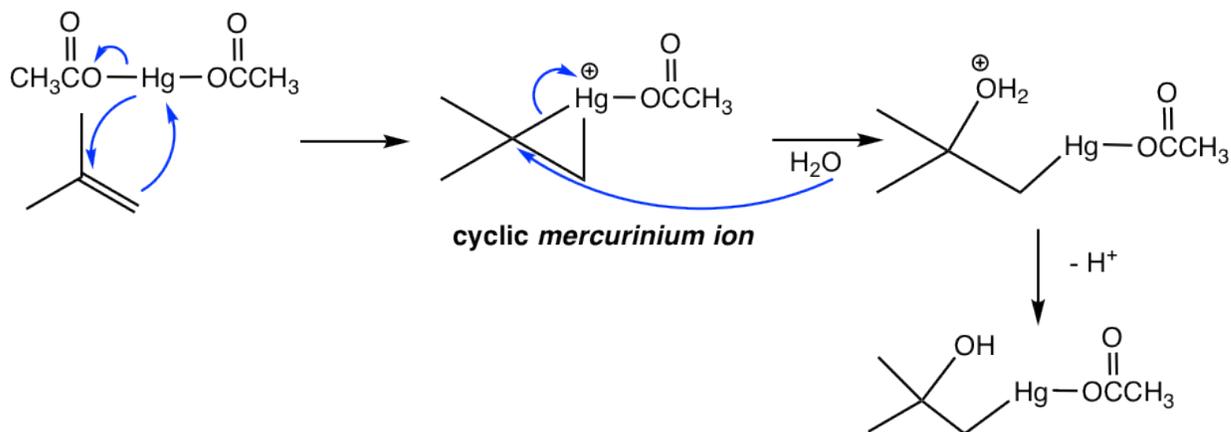


Figure 10.6b Mechanism of Oxymercuration

The organomercury intermediate is then reduced by sodium borohydride. The mechanism for this final step is beyond the scope of our discussions here. Notice that the overall oxymercuration-demercuration mechanism follows Markovnikov's rule with the OH group attached to the most substituted carbon, and the hydrogen atom adds to the less substituted carbon.

## 10.6.2 Hydroboration-Oxidation of Alkenes

Hydroboration-oxidation is another method for converting alkene to alcohol; however, in anti-Markovnikov regioselectivity, OH is bonded to the carbon with a greater number of hydrogens, and the hydrogen atom is bonded to the carbon with fewer hydrogens.

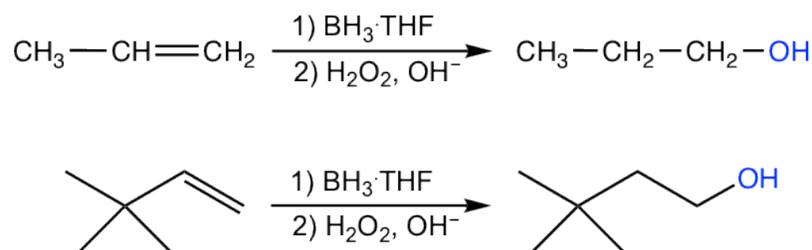


Figure 10.6c Hydroboration-Oxidation of Alkenes

The overall reaction is also a two-step process:

- The first step is hydroboration, which is the addition of boron atoms and hydrogen atoms to the alkene.
- The second step is oxidation and hydrolysis of the alkylborane formed in step 1 to produce alcohol.

The borane reagent used in the first step is usually available as the solution containing a  $\text{BH}_3 \cdot \text{THF}$  complex. Borane,  $\text{BH}_3$ , is an electron-deficient species because the boron atom has an incomplete octet with only six electrons. When  $\text{BH}_3$  is introduced to THF, they react to form a Lewis acid-Lewis base adduct (Chapter 3), which is more stable and relatively easy to handle and store. The solution containing  $\text{BH}_3 \cdot \text{THF}$  is still sensitive and must be used in an inert atmosphere (nitrogen or argon) and with care.

Because of the incomplete octet of the boron atom in  $\text{BH}_3$ , it is a good electrophile that reacts with alkene. The mechanism of the hydroboration step is illustrated below with propene as the example.

## Mechanism of Hydroboration

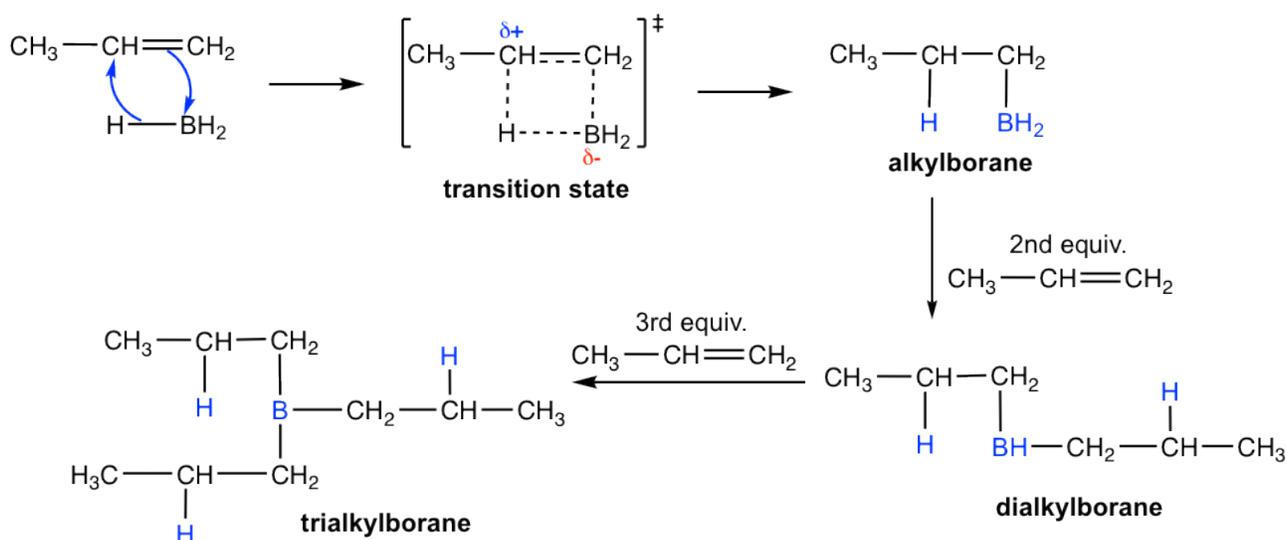


Figure 10.6d Mechanism of Hydroboration

When a terminal alkene, for example, propene, is treated with BH<sub>3</sub>·THF, the BH<sub>3</sub> molecule adds successively to the C=C double bond of three alkene molecules to form a trialkylborane. In each additional step, the boron atom becomes attached to the *less substituted* double bond carbon, and a hydrogen atom is transferred from the BH<sub>3</sub> to the more substituted carbon. In the second step (oxidation and hydrolysis) of the whole process, the borane is oxidized and hydrolyzed to the OH group. So, the regioselectivity of the hydroboration step defines the anti-Markovnikov regioselectivity of the overall reaction.

Such regioselectivity of the hydroboration step can be explained by both electronic and steric effects. In terms of the steric factor, the boron-containing group is more bulky than the hydrogen atom, so they can approach the less substituted carbon more easily. The electronic effect lies in the transition state structure for the formation of alkylborane. As shown above, the π electrons from the double bond are donated to the π orbital of boron and a four-atom ring cyclic transition state is approached. In the transition state, electrons shift in the direction of the boron atom and away from the carbon that is not connected to the boron. This makes the carbon not connected to the boron bear a partial positive charge, which is better accommodated on the more substituted carbon. As a result, the electronic effect also favors the addition of boron on the less substituted carbon.

## Stereochemistry of Hydroboration

Hydroboration-oxidation takes place with syn stereochemistry, in which the OH group and the hydrogen atom add to the same side of the double bond, as shown in the following example.

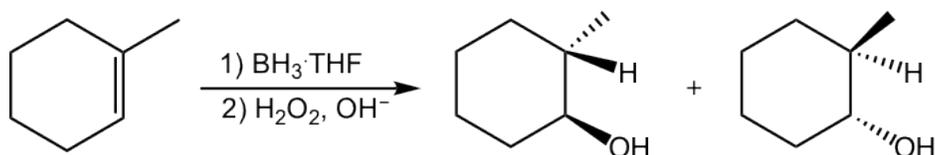


Figure 10.6e Stereochemistry of Hydroboration

This can be explained by the mechanism of the hydroboration step. The four-membered ring transition state requires that the boron atom and the hydrogen atom approach the same surface of the alkene double bond so they are added in the syn position to the double bond. Since the boron part is converted to the OH group in the second step, it results in the syn addition of OH and H in the product.

## Oxidation and Hydrolysis of trialkylboranes

When the hydroboration reaction is over, the trialkylboranes are usually not isolated; they are oxidized and hydrolyzed with the addition of hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) in a basic aqueous solution. The mechanism for the oxidation and hydrolysis of trialkylboranes is complicated and could be an optional topic, but the net result is that the boron initially bonded on the carbon is replaced by the hydroxy OH group.

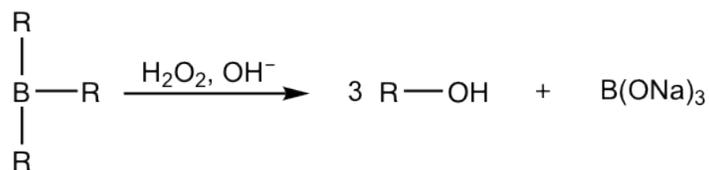
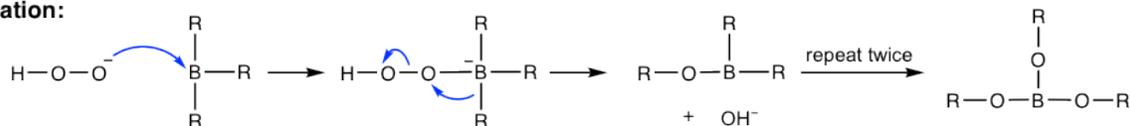


Figure 10.6f Oxidation and Hydrolysis of trialkylboranes

### Mechanism: Oxidation and Hydrolysis of trialkylboranes

#### Oxidation:



#### Hydrolysis:

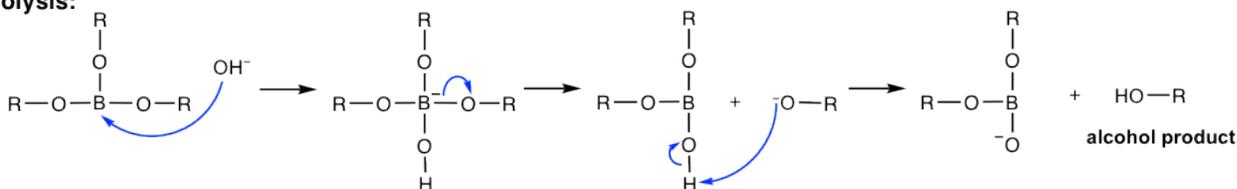


Figure 10.6g Mechanism: Oxidation and Hydrolysis of trialkylboranes

## Summary: Hydration Methods of Alkene

Overall, there are three methods for converting alkene to alcohol via addition: acid-catalyzed hydration, oxymercuration-demercuration, and hydroboration-oxidation, as summarized in Table 10.1. Each method has its benefits and drawbacks. The proper method can be chosen based on the need.

	Acid-catalyzed hydration	Oxymercuration-demercuration	Hydroboration-oxidation
<b>Reaction Conditions</b>	cat. H <sup>+</sup> /H <sub>2</sub> O	1)Hg(OAc) <sub>2</sub> /THF·H <sub>2</sub> O 2)NaBH <sub>4</sub>	1) BH <sub>3</sub> ·THF 2) NaBH <sub>4</sub>
<b>Regioselectivity</b>	Markovnikov	Markovnikov	Anti-Markovnikov
<b>Stereochemistry</b>	Not controlled	Not controlled	syn-addition
<b>Rearrangement</b>	Yes	No	No

Table 10.1 Summary of methods for conversion of alkene to alcohol

## 10.7 Oxidation Reactions of Alkenes

Alkenes undergo a number of reactions in which the C=C double bond is oxidized. For organic compounds, a conventional way to tell whether oxidation or reduction occurs is to check the number of C–O bonds or C–H bonds. An oxidation reaction increases the number of C–O bonds or decreases the number of C–H bonds. On the other side, a reduction reaction increases the number of C–H bonds or decreases the number of C–O bonds. The relative oxidation states of some common organic functional groups are listed here based on the trend.

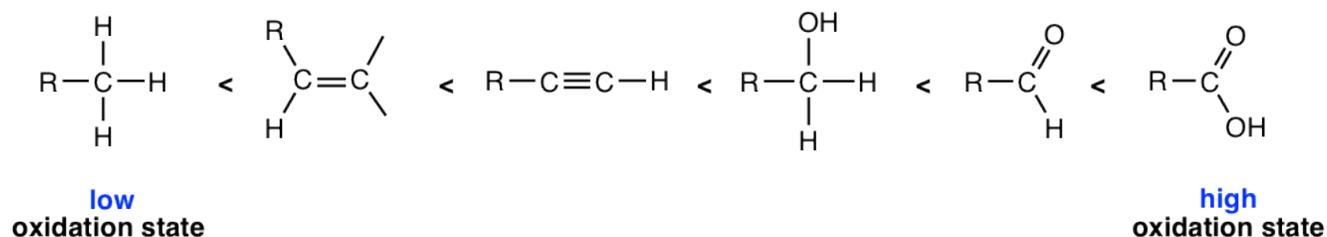


Figure 10.7a The relative oxidation state of some common organic functional groups

### 10.7.1 Syn 1,2-Dihydroxylation

1,2-Dihydroxylation, the conversion of the C=C double bond to 1,2-diol, is an oxidative addition reaction of alkene. Osmium tetroxide ( $\text{OsO}_4$ ) is a widely used oxidizing agent for such purpose. Potassium permanganate can be used as well, though further oxidation is prone to occur to cleave the diol because it is a stronger oxidizing agent (10.7.2).

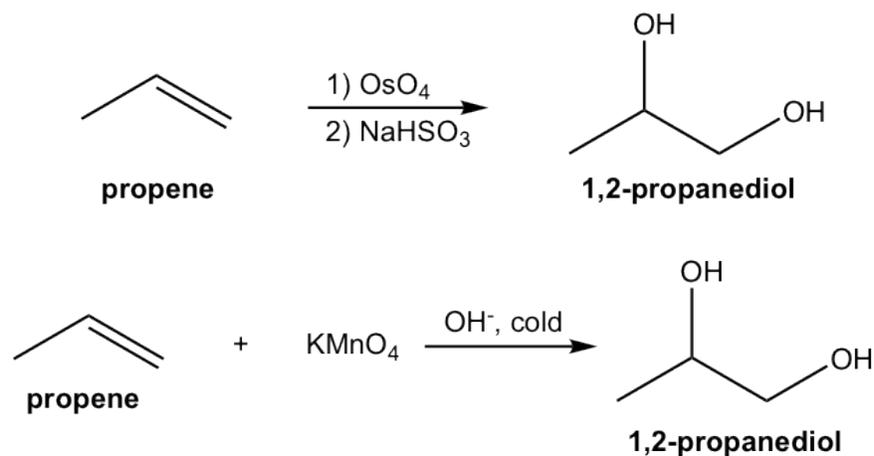


Figure 10.7b Example of 1,2-Dihydroxylation

The traditional method of 1,2-dihydroxylation with osmium tetroxide is a two-step procedure. Osmium tetroxide first reacts with alkene to form a cyclic osmate ester intermediate, and this cyclic intermediate involves the syn addition of  $\text{OsO}_4$  to the double bond. The cleavage of the O–Os bond of the intermediate then takes place in the second step with the reducing agent  $\text{NaHSO}_3$  without modifying the stereochemistry of the C–O bond. The diol formed therefore has the syn stereochemistry property.

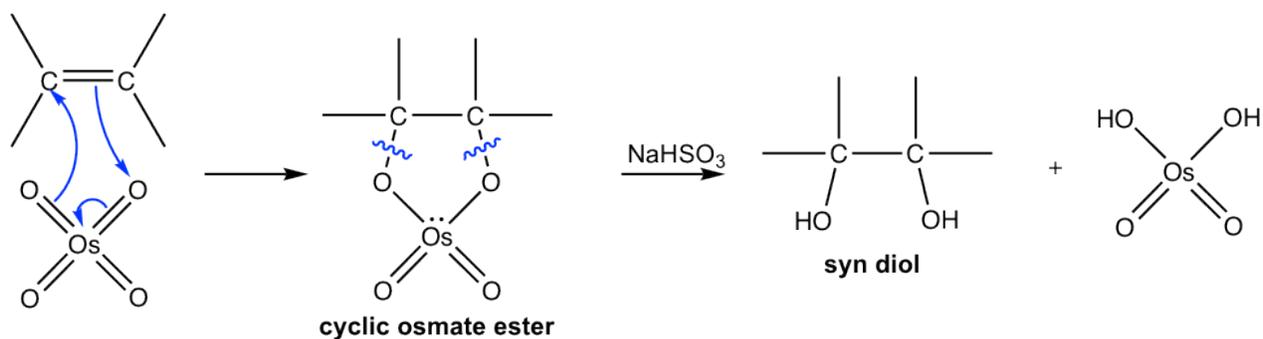
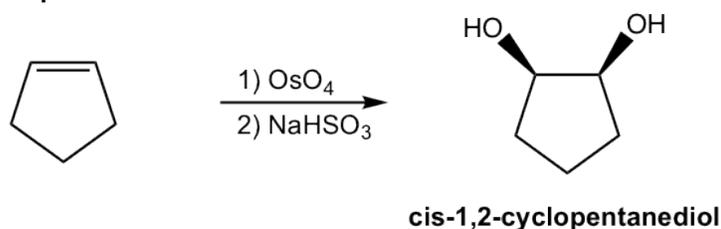


Figure 10.7c 1,2-dihydroxylation mechanism

example:



## Catalytic OsO<sub>4</sub> 1,2-Dihydroxylation

The 1,2-dihydroxylation with osmium tetroxide is a reaction that is often used in labs for preparing diol from alkene effectively. However, this method has major drawbacks because osmium tetroxide is a highly toxic, volatile and expensive reagent. Improved methods have been developed that allow only a catalytic amount of OsO<sub>4</sub> to be used in conjunction with a co-oxidant in a stoichiometric amount. *N*-methylmorpholine *N*-oxide (NMO) is one of the most commonly employed co-oxidants. In such conditions, osmium compounds are re-oxidized by NMO and can be reused to react with more alkenes, so only a small molar percentage of OsO<sub>4</sub> is necessary in the reaction mixture. The reaction proceeds smoothly with syn diols produced in good yield.

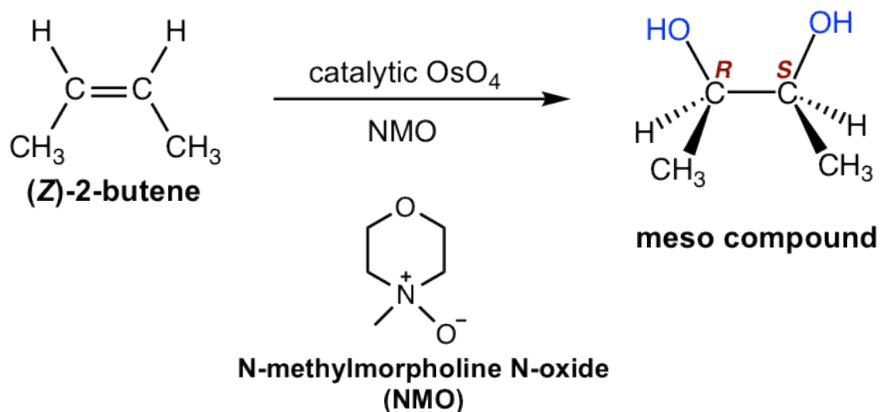
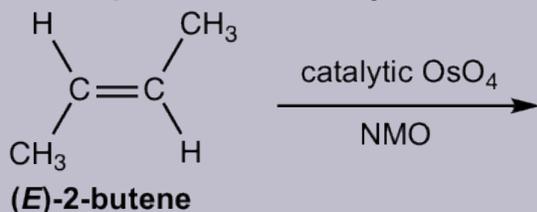


Figure 10.7d Example of a Catalytic OsO<sub>4</sub> 1,2-Dihydroxylation

In terms of the stereochemistry of the product, although the syn addition could occur on either side of the alkene plane, it gives the same product, which is the meso compound. This can be identified by either looking for the plane of symmetry of the product or by assigning the absolute configuration on the chirality centers. Review the stereochemistry knowledge.

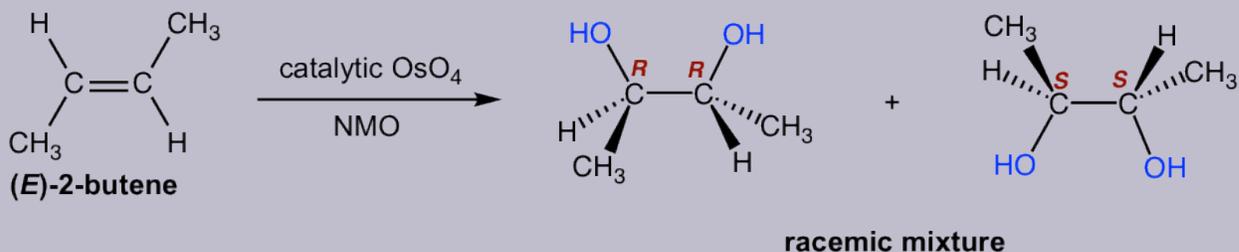
### Examples

Show the product of the following reaction:



### Solution:

The syn addition occurs on either side of the alkene plane, so both enantiomers are obtained with the same amount as a racemic mixture.



## 10.7.2 Oxidative Cleavage of Alkenes

### Cleavage with Ozone

With a stronger oxidizing agent being applied, the C=C double bond of alkenes can be oxidatively cleaved, and the alkene molecule is cleaved into smaller molecules.

The most effective way to cleave alkene is to use ozone,  $\text{O}_3$ , through a two-step process. Alkene first reacts with ozone at a very low temperature ( $-78^\circ\text{C}$ ) and then is treated with dimethyl sulfide  $(\text{CH}_3)_2\text{S}$ , (or  $\text{Zn}/\text{CH}_3\text{COOH}$ ) to give the cleavage products. The whole process is called ozonolysis.

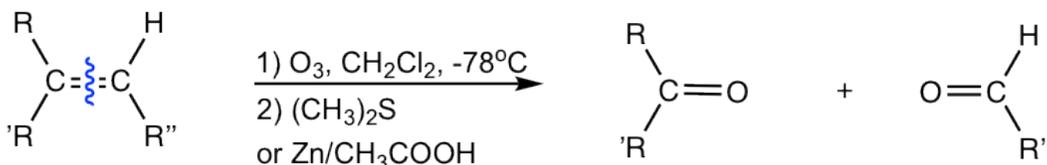


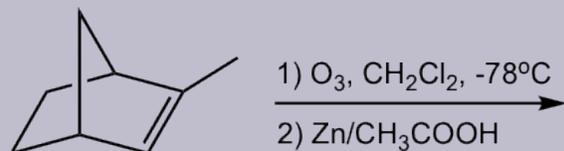
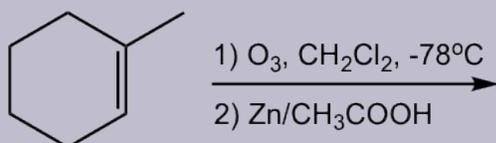
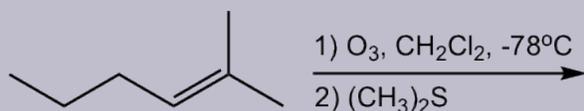
Figure 10.7e The process of Cleavage with Ozone

Ozonolysis results in the cleavage of the double bond, and each double bond carbon gets bonded to an oxygen atom with a new double bond. The products of ozonolysis are aldehyde(s) and/or ketone(s), and the exact structures of the products depend on the structure of the initial alkene:

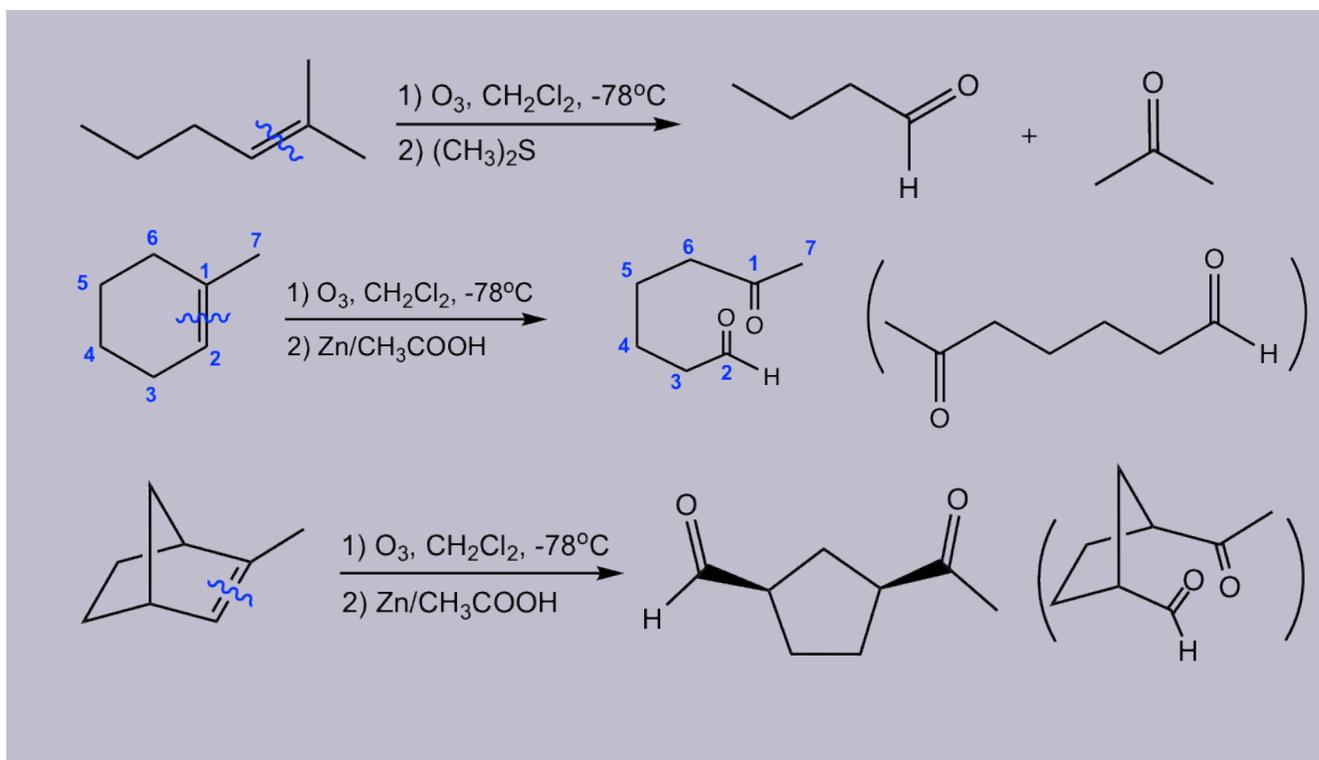
- Disubstituted alkene carbons are oxidatively cleaved to ketone.
- Monosubstituted alkene carbons are oxidatively cleaved to aldehyde.
- Unsubstituted alkene carbons are oxidatively cleaved to formaldehyde (HCHO).

### Examples

Show ozonolysis products of the following reactions:



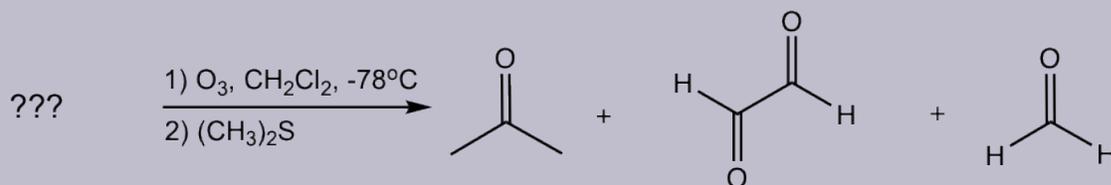
Hint: To figure out the structure of ozonolysis product(s), “cut” the double bond, then “add” a “=O” (double bonded oxygen) to each carbon.



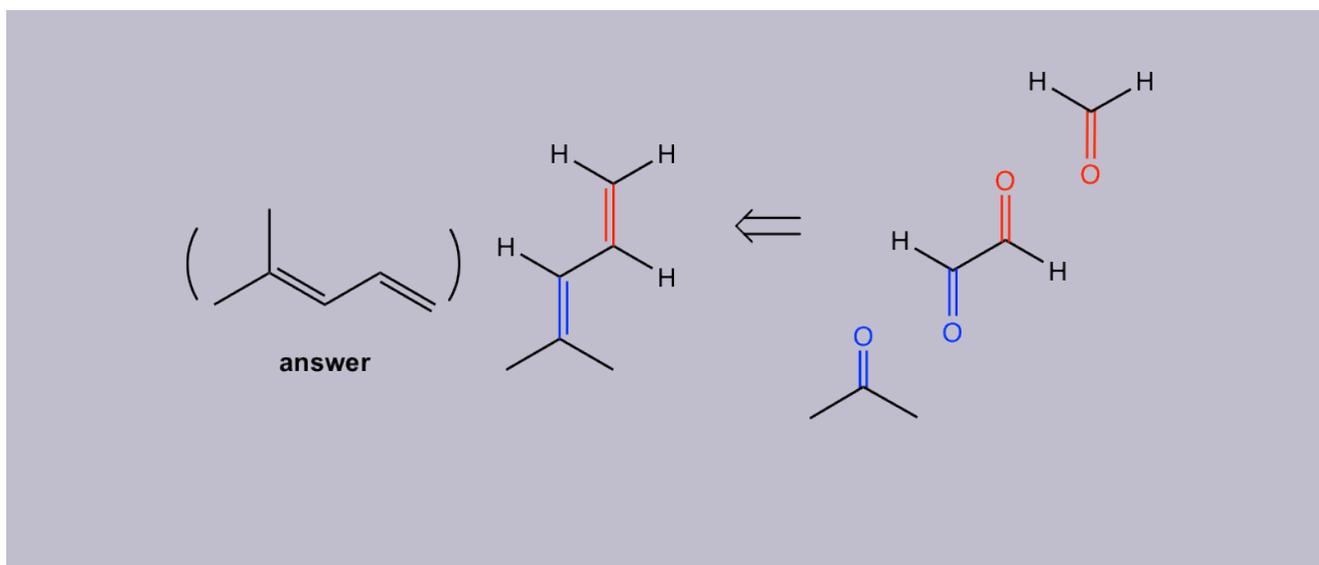
As shown in the above examples, the ozonolysis reaction is useful as a synthetic tool for certain aldehydes and ketones. Meanwhile, it is also a method for determining the position of double bonds in an alkene by working backward from the structure of the products.

### Examples

Determine the structure of the alkene:



Approach: To determine the structure of the initial alkene, we can work backward by connecting two C=O bonds in the products together. The two C=O bonds are “connected” to give a C=C bond with all oxygen atoms “removed”. In this example, the two blue C=O bonds give the blue C=C bond, and the two red C=O bonds give the red C=C bond.



## Mechanism for Ozonolysis

The hints mentioned earlier help us solve the problems with ozonolysis reactions, not the reaction mechanism. The mechanism of the ozonolysis reaction is complicated and involves the formation of an initial cyclic ozonide that decomposes into fragments, and the fragments recombine to form a new cyclic ozonide, which is reduced to give products.

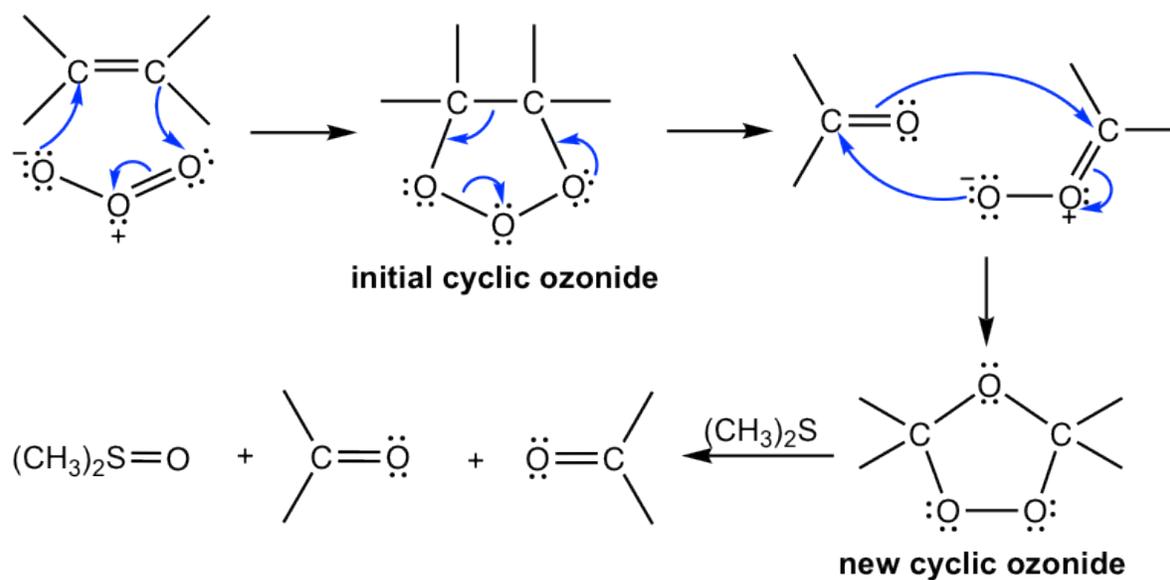


Figure 10.7f Mechanism for Ozonolysis

## Cleavage with Potassium Permanganate $\text{KMnO}_4$

Potassium permanganate,  $\text{KMnO}_4$ , is another oxidizing agent that cleaves the  $\text{C}=\text{C}$  double bond of an alkene. Under hot basic conditions, the oxidative cleavage products of alkenes could involve ketone, salt of carboxylic acid or carbon dioxide depending on the different substituent patterns on the alkene:

- Disubstituted alkene carbons are oxidatively cleaved to ketone.
- Monosubstituted alkene carbons are oxidatively cleaved to the carboxylic acid (in salt format).
- Unsubstituted alkene carbons are oxidatively cleaved to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ .

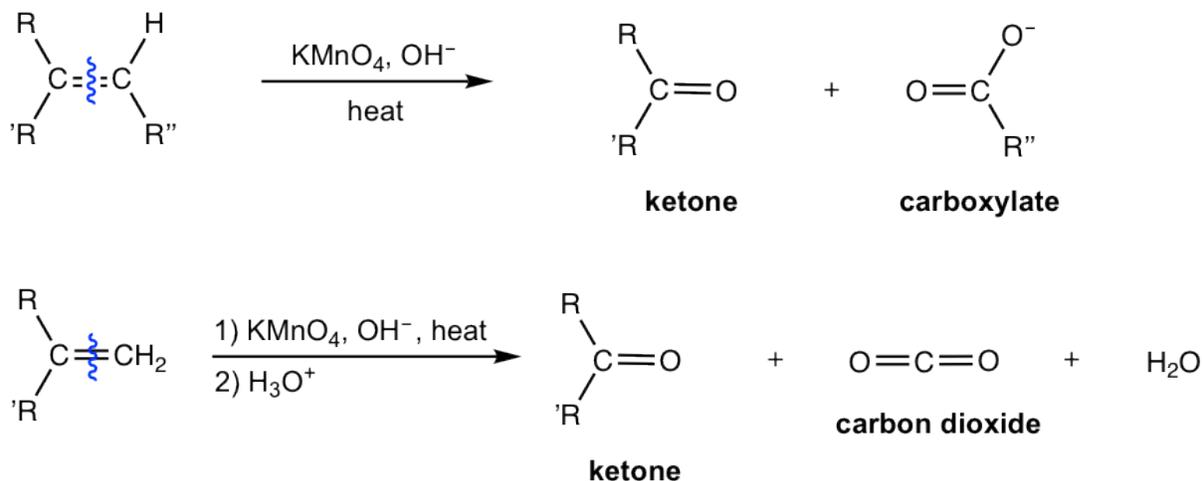


Figure 10.7g Cleavage with Potassium Permanganate  $\text{KMnO}_4$

$\text{KMnO}_4$  is a stronger oxidizing agent that further oxidizes the initial cleavage products, therefore aldehyde is further oxidized to carboxylic acid (in salt format under basic conditions). For terminal unsubstituted alkene carbons, the initial product is  $\text{HCHO}$ , which is then further oxidized to carboxylate  $\text{CO}_3^{2-}$  in basic conditions. The acidification of  $\text{CO}_3^{2-}$  produces  $\text{H}_2\text{CO}_3$  which decomposes to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . Because of over oxidation,  $\text{KMnO}_4$  is not a useful reagent for the synthesis of aldehyde/ketone from alkenes.

## 10.8 Alkynes

Alkyne is a hydrocarbon that contains a C≡C triple bond. In this section, we will explore methods for the synthesis of alkyne and the chemical reactions of alkynes.

### 10.8.1 Acidity of Terminal Alkynes and Related Reactions

In the discussions of acids and bases (Chapter 3), we have learned that the hydrogen atom bonded to the terminal alkyne carbon shows higher acidity than the hydrogen atoms bonded to the carbons of an alkene or alkane, and the  $pK_a$  value of the terminal alkyne hydrogen is about 25.

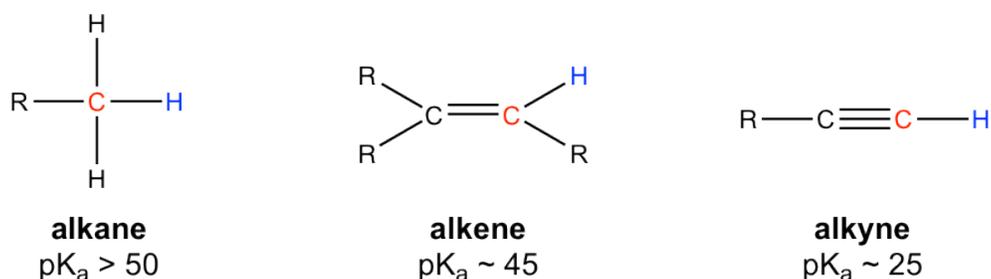


Figure 10.8a Acidity of terminal Alkynes

Because of the relatively high acidity, the terminal alkynes can be deprotonated by appropriate strong bases, such as NaH, and NaNH<sub>2</sub>.

**deprotonation of terminal alkyne:**

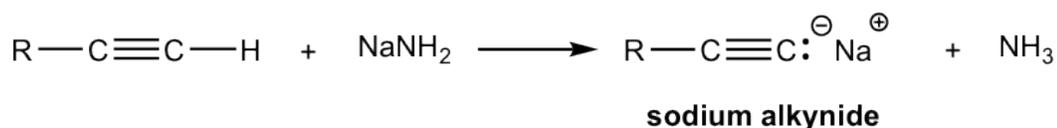


Figure 10.8b Deprotonation of terminal alkyne

The product of the above deprotonation, alkynide anion, is a good nucleophile that can be used in an S<sub>N</sub>2 reaction with primary substrates (since primary substrates work best for such S<sub>N</sub>2 reactions as we have learned):

**S<sub>N</sub>2 reaction:**

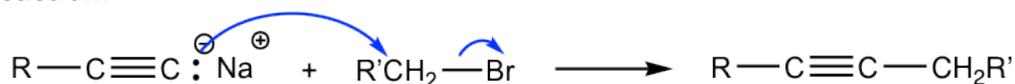


Figure 10.8c S<sub>N</sub>2 reaction



### Mechanism: Double dehydrohalogenation of vicinal dibromide

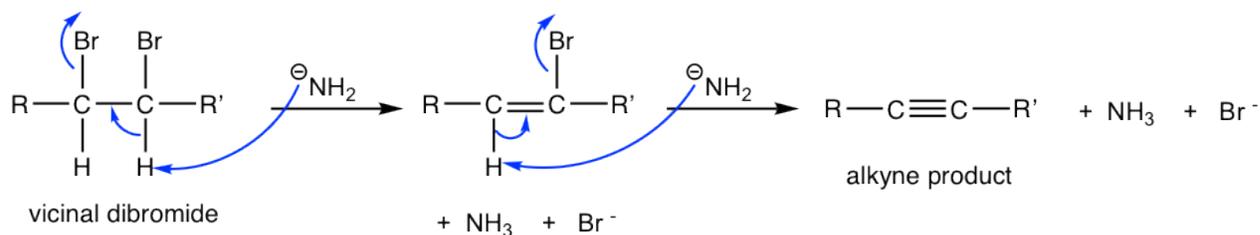
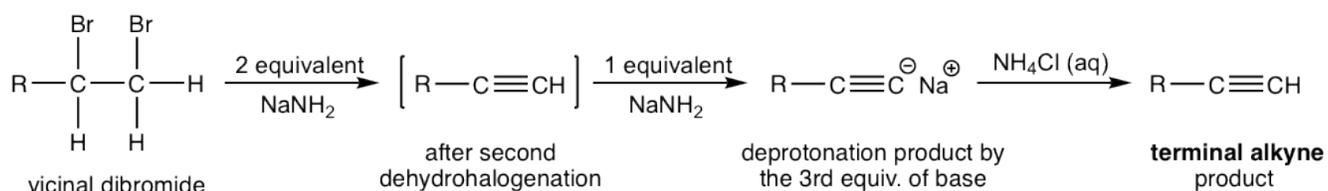


Figure 10.8f Mechanism: Double dehydrohalogenation

If a terminal alkyne is the desired product, then three molar equivalents of a base are required. The terminal alkyne produced after double dehydrohalogenation is deprotonated by sodium amide, and the third mole of the base is to ensure that the deprotonation occurs completely and all the terminal alkynes convert to the salt format. The salt of alkynide was then treated with ammonium chloride (or water, as a source of protons) to produce terminal alkyne as the final desired product.



### synthesis of terminal alkyne

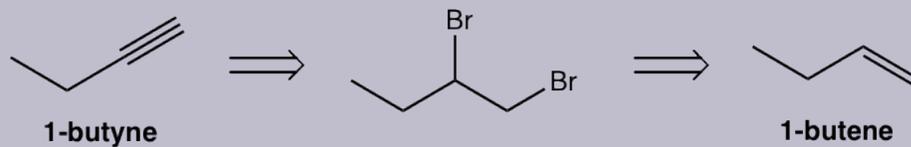
Figure 10.8g Synthesis of terminal alkyne

#### Examples

Design the synthesis route of 1-butyne from 1-butene.

#### Approach:

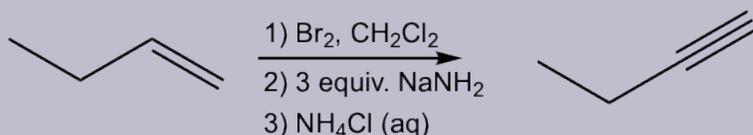
Use retro-synthetic analysis:



That analysis can be translated to the step-by-step synthesis as:



Solution: (show the steps together in the proper order, without showing intermediates for each step)



### 10.8.3 Reactions of Alkynes

#### Hydrogenation of Alkynes

Catalytic hydrogenation applies to the  $\pi$  bonds of  $\text{C}\equiv\text{C}$  triple bonds as well. Depending on the conditions and catalysts employed, one or two molar equivalents of hydrogen will be added to a triple bond, and alkene or alkane is produced as the product, respectively.

When platinum or palladium catalysts are applied, the final product of the hydrogenation is an alkane with sufficient hydrogen provided. The initial product is an alkene, which undergoes the reaction successively to give alkane as the final product.

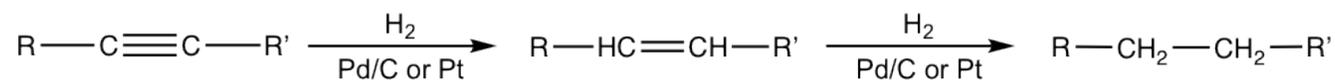


Figure 10.8h Hydrogenation

With a certain catalyst used, the hydrogenation of alkyne can be stopped at the alkene stage. The most commonly employed catalyst is the Lindlar catalyst. The Lindlar catalyst is prepared by precipitating palladium on calcium

carbonate and then treating it with lead (II) acetate and quinoline. The special treatment modifies the surface of the palladium metal by partially deactivating it and making it more effective at catalyzing the hydrogenation to a triple bond rather than to a double bond.

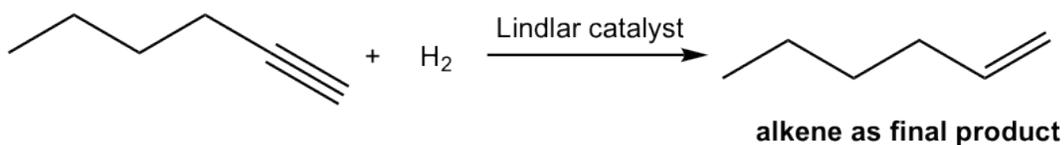


Figure 10.8i Lindlar catalyst

The mechanism for the catalytic hydrogenation of alkyne is almost the same as that of alkene (10.5). Since both hydrogen atoms are delivered from the surface of the catalyst, they are delivered to the same side of the triple bond; therefore, syn-addition occurs. So, the hydrogenation of an internal alkyne produces *cis*-alkene with the Lindlar catalyst.

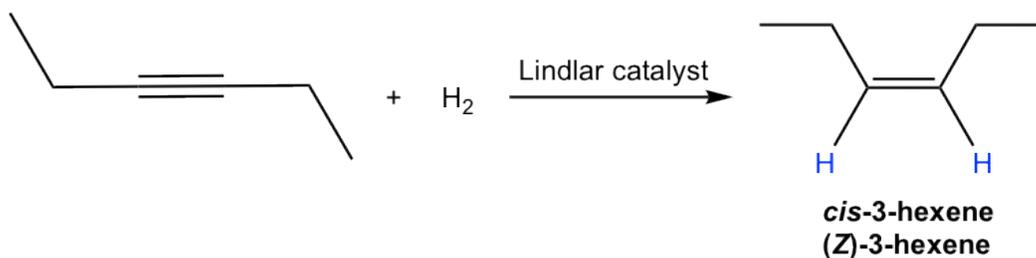


Figure 10.8j Hydrogenation of an internal alkyne produces *cis*-alkene with the Lindlar catalyst.

Internal alkyne can be converted into *trans*-alkene using sodium (or lithium) in liquid ammonia. The mechanism for this reaction involves successive single electron transfers from the metal (sodium or lithium) and proton transfers from ammonia, with radical intermediates. The sodium metal (or lithium) reacts more rapidly with triple bonds than double bonds, so the reaction stops at the alkene stage. A low temperature ( $-78^{\circ}\text{C}$ ) is necessary to keep ammonia in the liquid state.

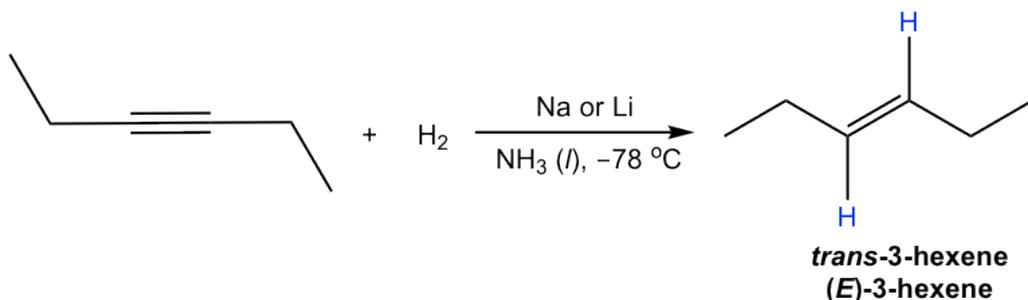


Figure 10.8k Internal alkyne converted to *trans*-alkene using sodium (or lithium) in liquid ammonia.

The *trans*-vinylic anion is formed preferentially because of the higher stability with two R groups farther apart. Protonation of the *trans*-vinylic anion leads to the *trans*-alkene.

## Mechanism: Hydrogenation (Reduction) of Alkyne by Metal

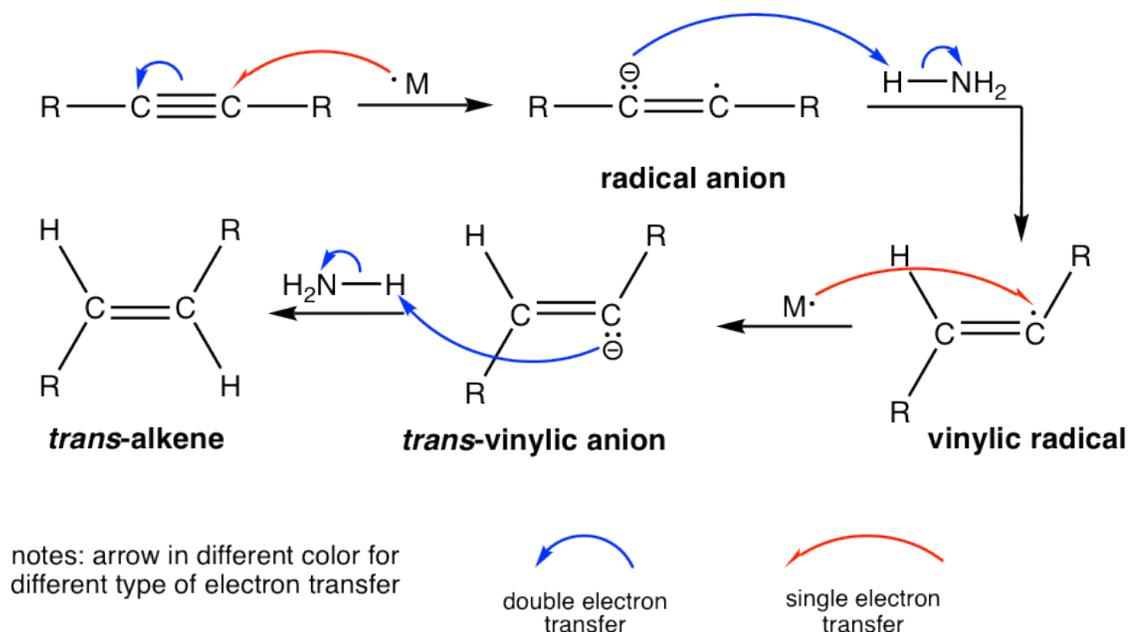


Figure 10.8l Mechanism: Hydrogenation (Reduction) of Alkyne by Metal

## Hydrohalogenation of Alkynes

An alkyne is an electron-rich molecule with a high density of pi electrons; therefore, it is a good nucleophile that reacts readily with electrophiles. Thus, alkynes, like alkenes, also undergo electrophilic addition with hydrogen halide.

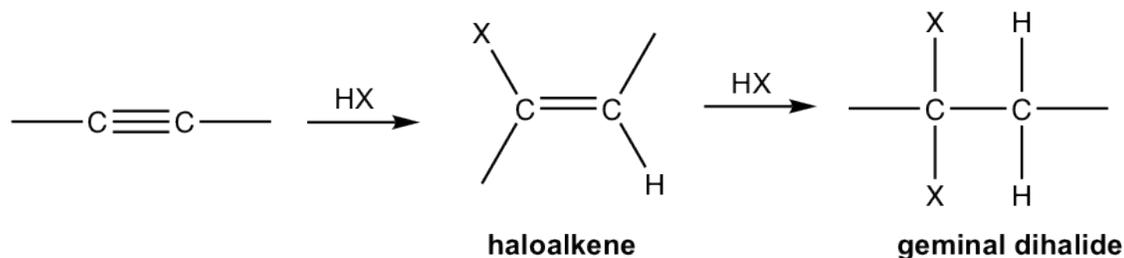


Figure 10.8m Haloalkene and geminal dihalide

- Alkyne reacts with one mole of HX to form haloalkene and with two moles of HX to form geminal dihalides, a dihalide with both halogens attached to the same carbon. “Geminal” comes from *geminus*, which in Latin means “twin”.
- Both additions follow Markovnikov’s rule in terms of regioselectivity. If one molar equivalent of HX is available, the addition can be stopped at the first addition to haloalkene. The halo-substituted alkene is less reactive than alkyne for electrophilic addition because a halogen substituent withdraws electrons inductively, thereby decreasing the nucleophilicity of the double bond.

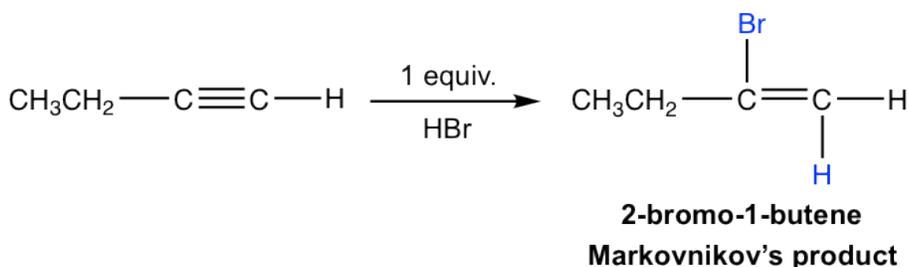


Figure 10.8n 2-bromo-1-butene Markovnikov's product

The mechanism for the electrophilic addition to alkyne is similar to the addition of alkene, with protonation as the first step. For terminal alkyne, if the protonation occurs on different triple bond carbons, the primary or secondary vinylic cation intermediate will be formed. The higher stability of the secondary vinylic cation leads to Markovnikov's regioselectivity, in which the hydrogen atom attached to the carbon has the greater number of hydrogen atoms.

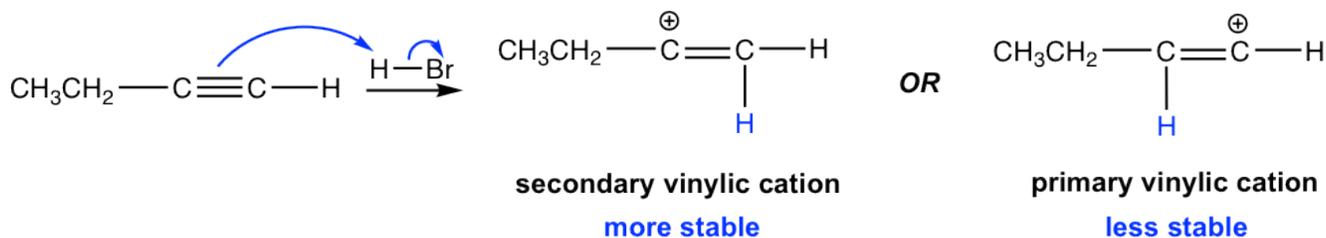


Figure 10.8o Secondary and Primary vinylic cation

If excess hydro halide is present, the addition to alkyne occurs twice to give geminal halide that follows Markovnikov's regioselectivity.

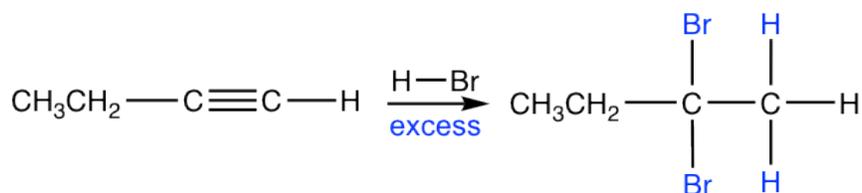


Figure 10.8p Excess hydro halide

## Hydration of Alkynes

Alkynes also undergo the acid-catalyzed addition of water (hydration), similar to alkenes. As a result, the H is added to one triple bond carbon and OH is added to the other triple bond carbon, and the product formed is called an enol ("en" comes from "ene" which means a double bond, and "ol" means OH group). An enol is a compound with a carbon-carbon double bond and an OH group connected to one of the double bond carbons.



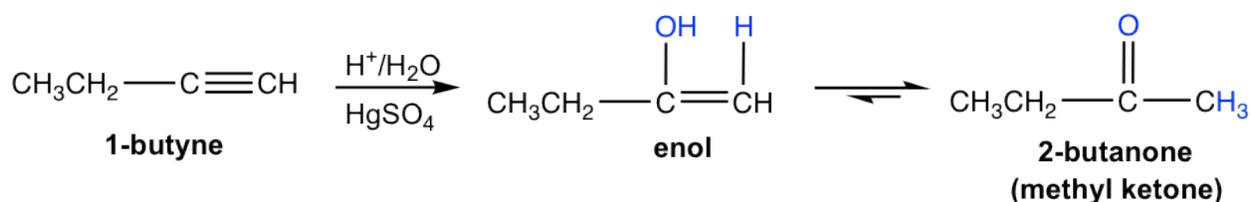


Figure 10.8t Mercuric ion as a catalyst

## Hydroboration-Oxidation of Alkynes:

Hydroboration-oxidation also applies to alkyne in a similar way as to alkene. The two-step process results in the enol, which goes through tautomerization to give a carbonyl compound.

Meanwhile, the addition of borane to a terminal alkyne shows the same regioselectivity as observed in borane addition to an alkene. That is, boron adds preferentially to the terminal triple bond (sp) carbon (the carbon with more hydrogen atoms), or the terminal carbon with fewer substituents. After oxidation, the boron-containing group is converted to the OH group, so the enol is produced in the anti-Markovnikov way, with OH connected to the terminal carbon. The tautomerization of such enol generates aldehyde as the final product.

Comparing the two hydration methods of alkyne, hydroboration-oxidation produces aldehyde from terminal alkyne, while acid-catalyzed hydration converts terminal alkyne to methyl ketone.

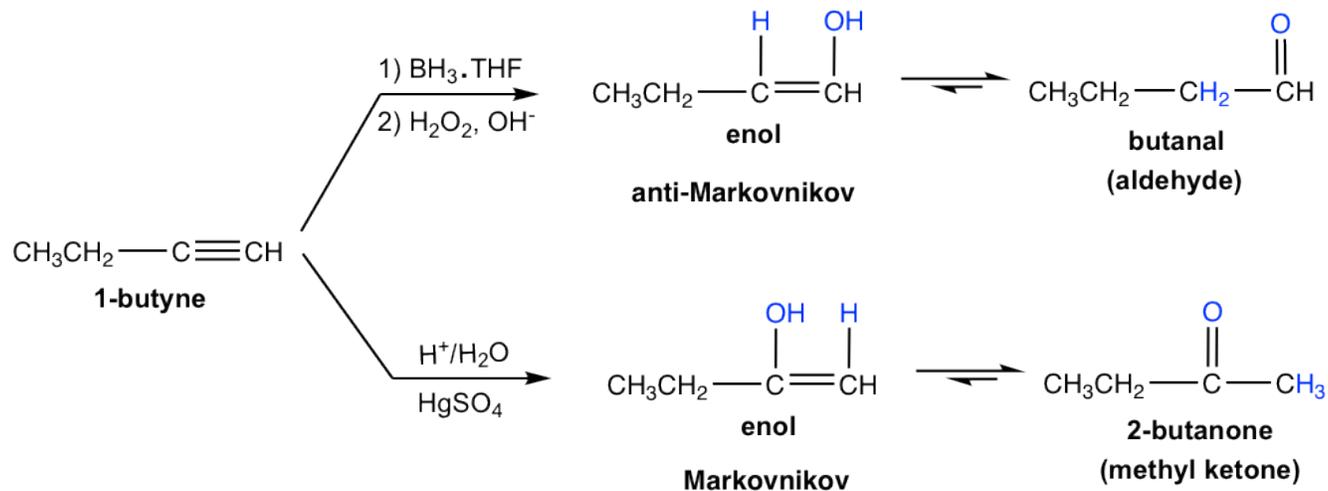
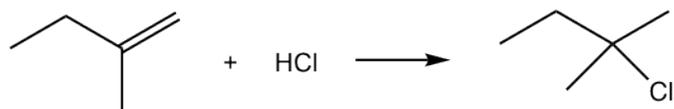
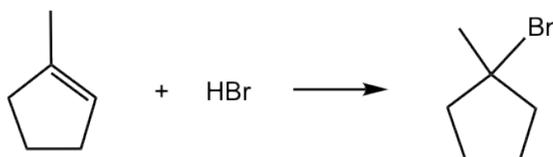
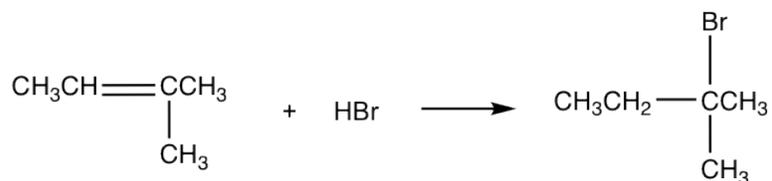


Figure 10.8u Hydroboration-Oxidation of Alkyne

# Answers to Chapter 10 Practice Questions

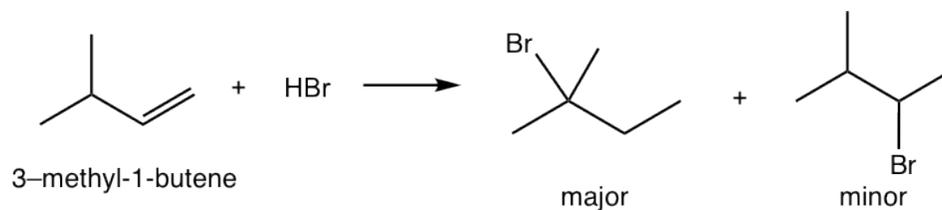
## 10.1

Show the structure of the major product for the following addition reactions.

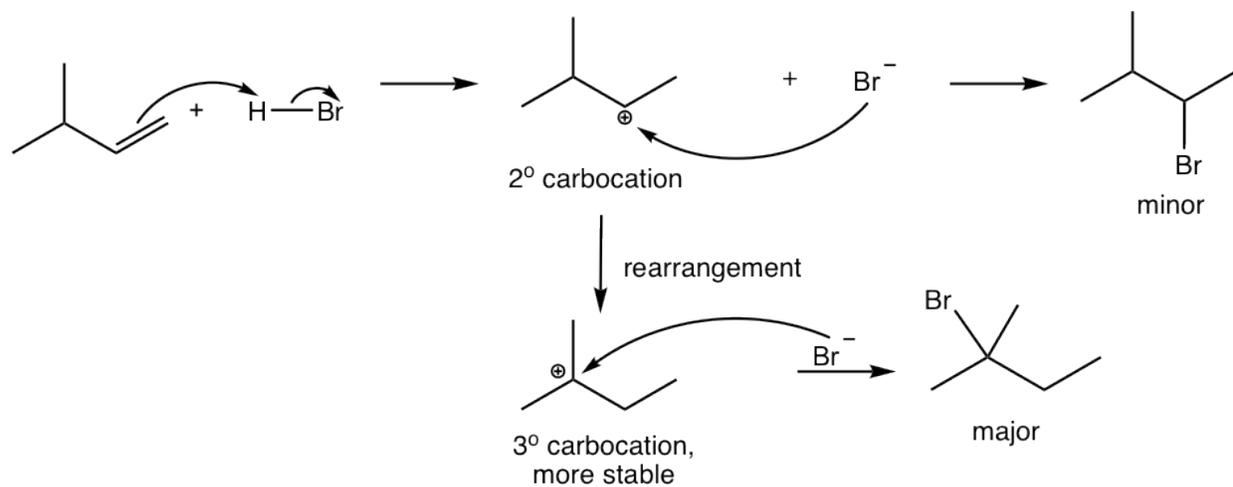


## 10.2

For the addition of HBr to 3-methyl-1-butene, two products were observed. Show the reaction mechanism to explain the formation of both products.

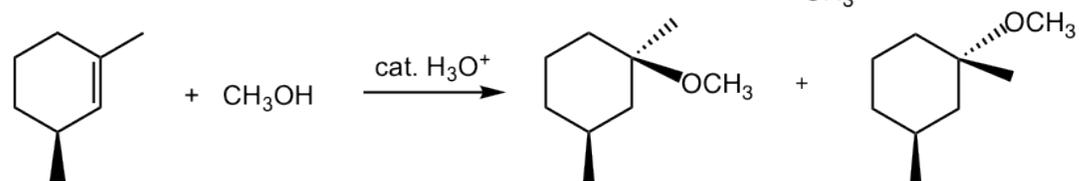
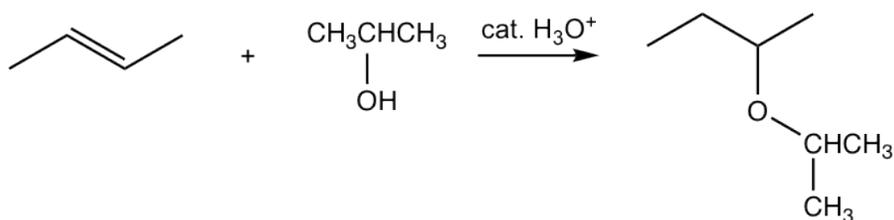
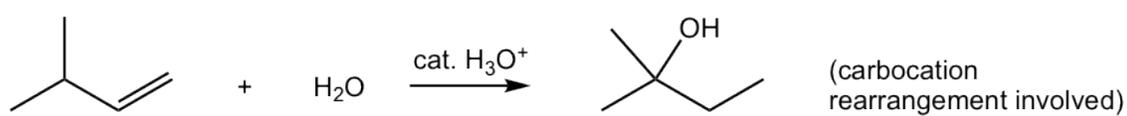


**Mechanism:**



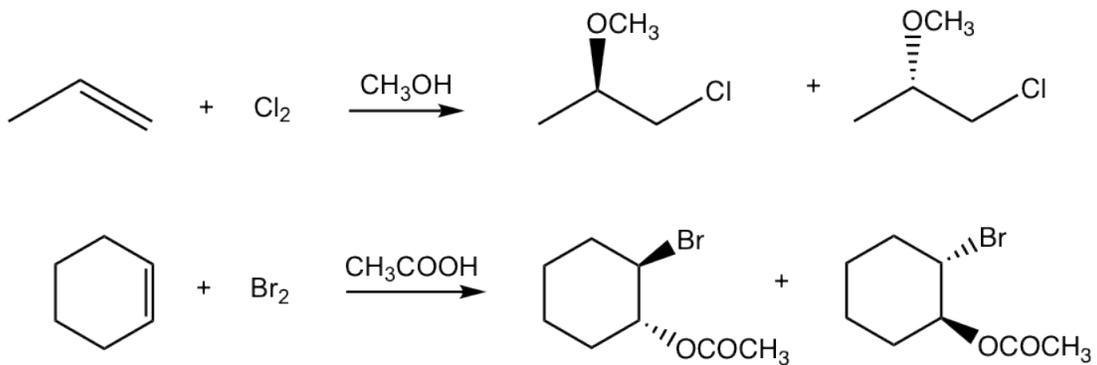
### 10.3

Show major product(s) for the following reactions.



### 10.4

Show major product(s) of the following reactions.



# About the Author

## Xin Liu, Kwantlen Polytechnic University

xin.liu@kpu.ca



*Dr. Xin Liu, Author*

Dr. Xin Liu has been a faculty member at the Department of Chemistry, KPU since 2008. Other than teaching Organic Chemistry and first-year General Chemistry courses, she has also been actively involved in curriculum review and new course development. Having a keen interest in Open Education Resources, Dr. Liu hopes to make more contributions to this fast-growing area to make learning accessible to everyone.