PEOPLE'S DEMOCRATIC REPUBLIC OF ALGERIA

MINISTRY OF HIGHER EDUCATION AND

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ESSA-Tlemcen

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The Organic Chemistry Fundamentals with Illustrated Applications

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PREFACE

The Organic Chemistry Fundamentals with Illustrated Applications is a new book intended for undergraduate students enrolled in the first cycle of university, college and institution and constitutes an interesting support for chemistry teachers.

The book is subdivided to four parts comprising the essential four organic chemistry chapters such as; Nomenclature, Stereochemistry, Electronic Effects, and Reaction Mechanisms, taught and learnt in the first cycle of university, college and institution. Each chapter is followed by a series of exercises illustrating and explaining with more details and examples about the sections given and treated. The answers are given at the last part of each chapter.

In this book, the student will learn, in a first chapter, a certain number of essential rules and bases adopted by the International Union of Pure and Applied Chemistry (IUPAC) through multiple exercises to practice systematic and official nomenclature. These rules will allow him to name molecules in organic chemistry whether simple, multiple or even mixed with more than one function.

In a second chapter, he will become familiar with the representations of molecules in 3D space and the different spatial arrangements known in chemistry in general. The notion of conformations treating simple molecules such as butane or cyclic molecules such as cyclohexane are well studied and their possible stability is largely detailed. On the other hand, the different types of configurations as well as the Cahn-Ingold-Prelog (CIP) sequential rules explaining them are also addressed to enable him to properly determine the geometric configurations *E* and *Z* or absolute configurations *R* and *S* and finally, the great notion of chirality and all that unfolds and derives from it such as; enantiomerism, diastereoisomerism and Fischer projection of optically active molecules are illustrated by explanatory diagrams.

A third chapter is devoted to the study of the different electronic effects, namely the inductive electronic effects and the mesomeric electronic effects as well as their different applications in the explanation of different chemical properties such as the acidity and basicity of organic compounds and also the study of the stability of the reaction intermediates that enter into the reaction mechanisms. Good demonstration exercises are given, well explained and discussed in details.

The fourth chapter encompasses the application of all the concepts learned in the three precedent chapters of applications cited above and is intended for the study of large classes of basic reactions known in organic chemistry such as: substitution, elimination and addition. These reactions will allow students to acquire the basic concepts necessary for understanding the reaction mechanisms of organic chemistry reactions

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Hybridization

Hybridization in chemistry is defined as the concept of mixing two atomic orbitals to give rise to a new type of hybridized orbitals. This intermixing usually results in the formation of hybrid orbitals having entirely different energies, shapes, etc. The atomic orbitals of the same energy level mainly take part in hybridization. However, both fully filled and half-filled orbitals can also take part in this process, provided they have equal energy.

On the other hand, it can be said that the concept of hybridization is an extension of the valence bond theory and it helps to understand the formation of bonds, bond energies and bond lengths.

Definition

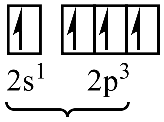
Hybridization can be defined as the redistribution of the energy of orbitals of individual atoms to give orbitals of equivalent energy. This happens when two atomic orbitals combine to form a hybrid orbital in a molecule. This process is called hybridization.

During this process, the atomic orbitals of comparable energies are mixed together and mostly involves the merging of two "s" orbitals or two "p" orbitals or mixing of an "s" orbital with a "p" orbital as well as "s" orbital with a "d" orbital. The new orbitals thus formed are known as hybrid orbitals.

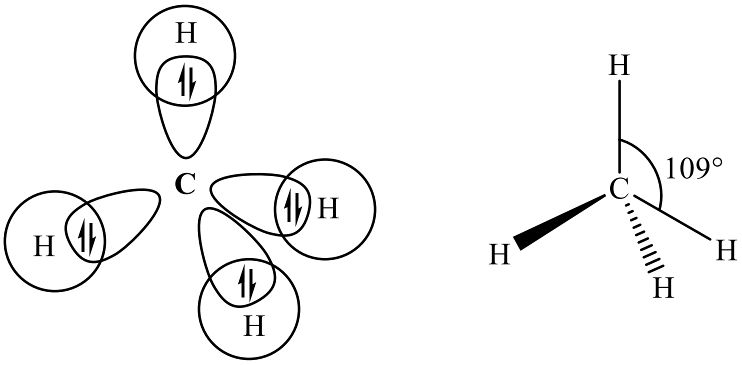
More significantly, hybrid orbitals are quite useful in explaining atomic bonding properties and molecular geometry.

As an example for this, the carbon atom can be treated. This atom forms four single bonds wherein the valence-shell "s" orbital mixes with three valence-shell p orbitals.

This combination leads to the formation of four equivalent sp^3 mixtures. These will have a tetrahedral arrangement around the carbon which is bonded to four different atoms.



sp^3 hybridization
(four σ-bonds)



Tetrahedral structure of methane

It is worthy to note that hybridization takes place only during the bond formation and not in an isolated gaseous atom, and once the hybridization is known, the shape of the molecule can be predicted. The bigger lobe of the hybrid orbital always has a positive sign, while the smaller one has a negative sign.

Types of hybridization

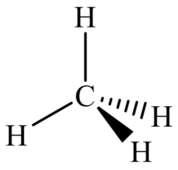
Based on the types of orbitals involved in mixing, the hybridization can be classified as sp^3, sp^2, or sp for the carbon atom.

Hybridization sp^3

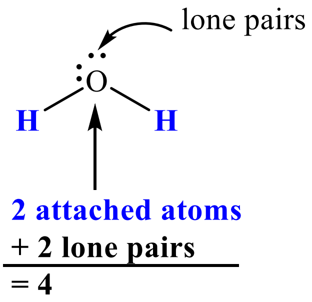
When one s orbital and three p orbitals belonging to the same shell of an atom mix together to form four new equivalent orbitals, the type of hybridization is called a tetrahedral hybridization or sp^3. The new formed orbitals are called sp^3 hybrid orbitals.

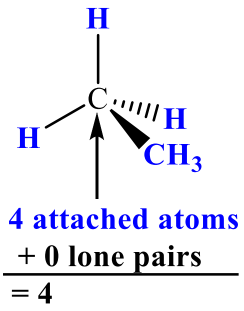
Example:

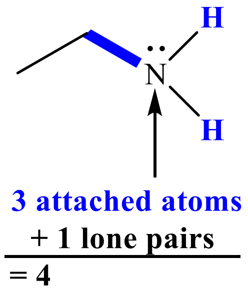
Methane molecule.



To find the sp^3 hybridization, it is possible to do the sum of attached atoms to the atom you want to know its hybridization type plus the sum of lone pairs and here for the sp^3 hybridization the total should be 4 as shown in the following examples.







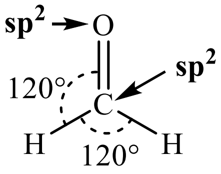
For instance, for the ethanamine molecule, the nitrogen atom is bonded to two hydrogens and one $-CH_2$ so the sum of attached atoms is 3 and of course it has one lone pairs. The total is $3 + 1$ which is 4. Hence, the hybridization type is sp^3.

Hybridization sp^2

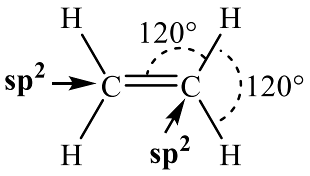
The sp^2 hybridization is observed when one s and two p orbitals of the same shell of an atom mix to form three equivalent orbitals. The new formed orbitals are called sp^2 hybrid orbitals.

Example:

Formaldehyde and ethene molecules.



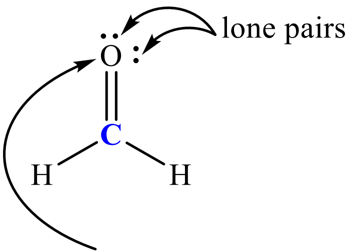
Formaldehyde



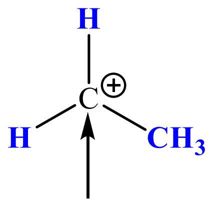
Ethene

sp^2 hybridization is also called trigonal hybridization. It involves mixing of one s orbital and two p orbitals of equal energy to give a new hybrid orbital known as sp^2. A mixture of s and p orbitals formed in trigonal symmetry and is maintained at 120°. All the three hybrid orbitals remain in one plane and make an angle of 120° with one another. Each of the hybrid orbitals formed has 33.33% of s character and 66.66% of p character. The molecules in which the central atom is linked to three atoms and is sp^2 hybridized have a triangular planar shape.

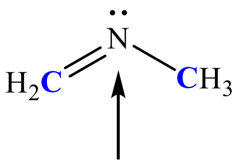
In order to find the sp^2 hybridization, it is easy to do the sum of attached atoms to the atom you want to know its hybridization type plus the sum of lone pairs and here for the sp^2 hybridization the total should be 3.



1 attached atoms
+ 2 lone pairs
= 3



3 attached atoms
+ 0 lone pairs
= 3



2 attached atoms
+ 1 lone pairs
= 3

In the formaldehyde molecule, the oxygen atom possesses two lone pairs and is attached to one carbon atom (bold in blue); so, the sum is $2 + 1 = 3$. For the same molecule, the carbon atom has the sp^2 hybridization since it is bonded to three atoms; two hydrogens and one oxygen.

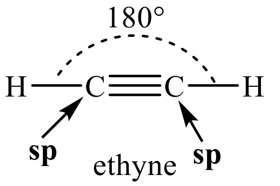
Hybridization *sp*

The *sp* hybridization is observed when one "*s*" and one "*p*" orbital in the same main shell of an atom mix to form two new equivalent orbitals. The new formed orbitals are simply called *sp* hybridized orbitals. It forms linear molecules with an angle of 180°.

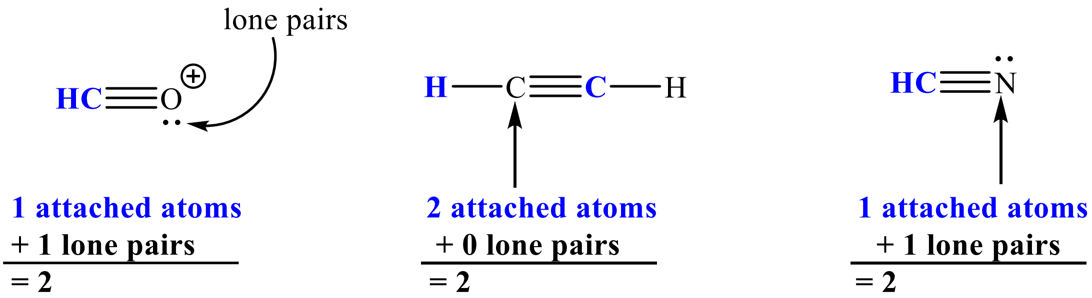
The *sp* hybridization is also called diagonal hybridization. Each *sp* has an equal amount of *s* and *p* character i.e. 50% *s* and 50% *p* character.

Example:

C_2H_2 molecule where the two carbon atoms are linked with a triple bond.



For the *sp* hybridization, the sum of attached atoms to the atom you want to know its hybridization type plus the sum of lone pairs should be 2.

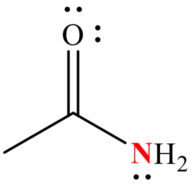


For the ethyne molecule, the carbon in black is bonded to one carbon atom (bold in blue) and one hydrogen. The sum here is 2 so it is *sp* hybridization type.

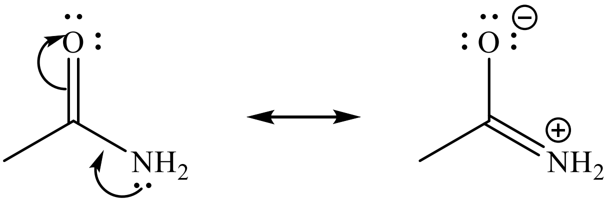
Exceptions

Some exceptions exist whenever lone pairs are adjacent to π-bonds and some examples are given below.

a/ In the acetamide, the expected hybridization of nitrogen atom (bold in red) is sp^3 but actually it is sp^2.

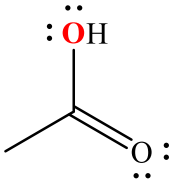


The reason here is the conjugated π-electron system.

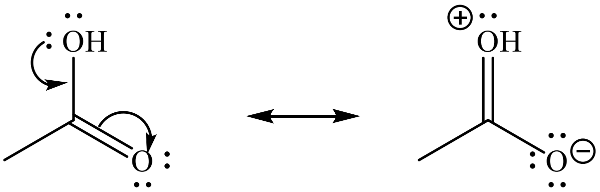


In the second possible resonance structure of acetamide, the nitrogen atom lost its lone pairs is attached to two hydrogen atoms and one carbon atom. This gives the sp^2 hybridization.

2/ The same thing is observed for the acetic acid molecule (conjugated π-electron system).



The two possible resonance structures are:



In the second possible resonance structure of acetic acid, the oxygen atom has only one lone pairs and attached to one hydrogen atom and one carbon atom. Again, this gives the sp^2 hybridization.

Chapter I : Nomenclature

Introduction

Organic molecules not only constitute the majority of living matter (proteins, sugars, fats) but are also present in common consumer products (food, medicines, etc.).

An organic molecule is often defined to contain not only carbon, but at least one other element, which is often hydrogen. Even though they are composed of only two types of atoms, there is a wide variety of hydrocarbons because they may consist of varying lengths of chains, branched chains, and rings of carbon atoms, or combinations of these structures.

Hence, molecules can contain both double or triple bonds and many other functional groups (e.g. an alkene and an alcohol functional group in one molecule - prop**en**ol). The existence of so many organic molecules is a consequence of the ability of carbon atoms to form up to four strong bonds to other carbon atoms, resulting in chains and rings of many different sizes, shapes, and complexities. This leads to differences in geometries and in the hybridization of the carbon orbitals.

Hydrocarbons are classified according to the structures of the carbon chain and according to the degree of saturation of the carbon atom: alkanes, alkenes, alkynes and benzene (Scheme 1).

Due to the increasing number of organic compounds identified every day, and due to the fact that each compound may present many possible isomers, it was more than necessary the creation and development of a nomenclature system to be able to name all these compounds and distinguish them.

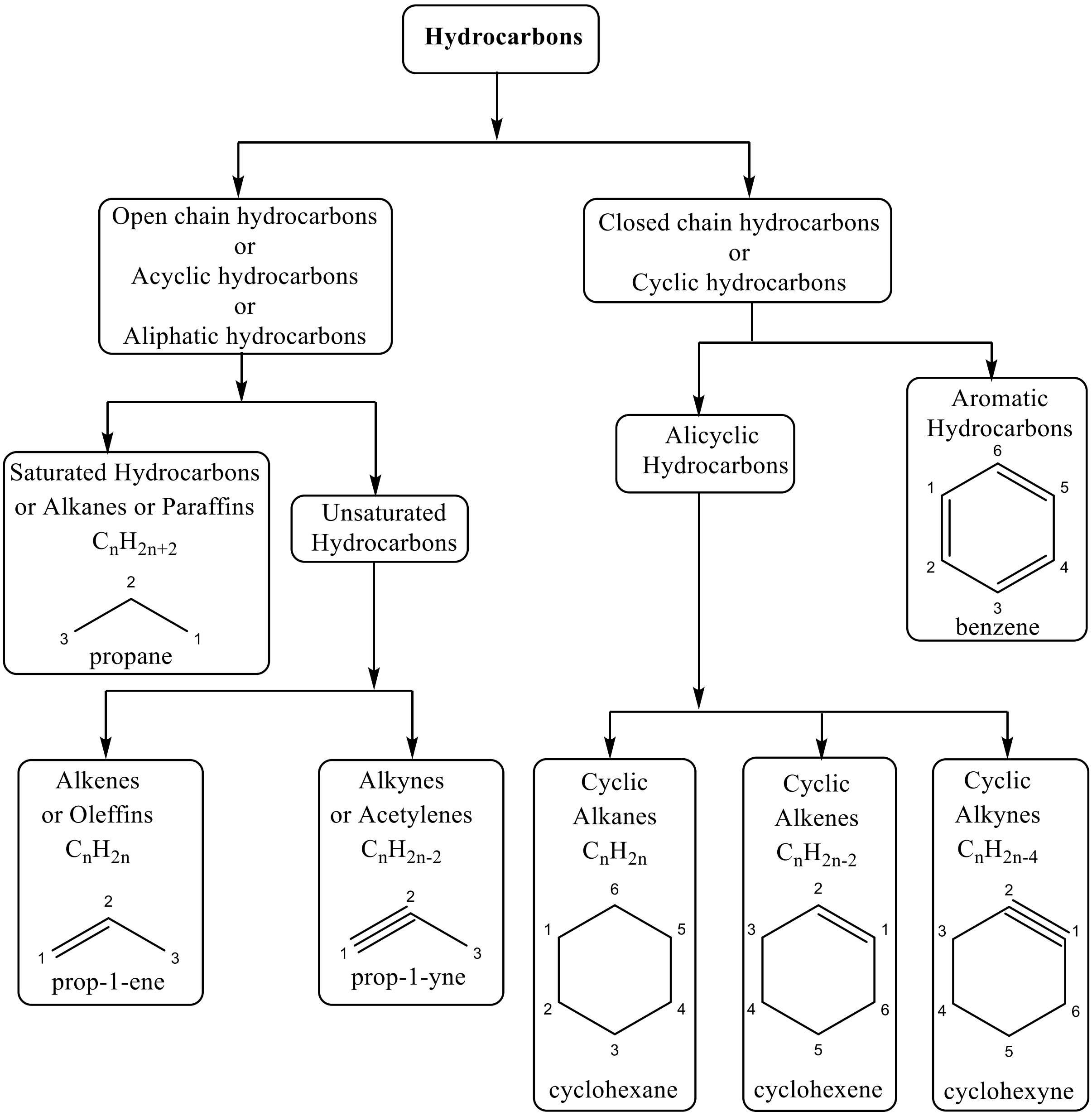
To better understand the naming system of various compounds, the International Union of Pure and Applied Chemistry (IUPAC) nomenclature has been established and is used.

In a simple way, the IUPAC system for naming is something that is very similar to addressing a person with his complete designation.

According to IUPAC system, naming of organic compounds has some standard process may be called naming method in which anything about naming of molecule is given in a systematic way.

The purpose of the IUPAC system of nomenclature is to establish an international standard of naming compounds to facilitate communication. The goal of the system is to give each structure a unique and unambiguous name, and to correlate each name with a unique and unambiguous structure.

The fundamental principle of IUPAC nomenclature is based on naming a molecule's longest chain of carbons connected by single bonds, whether in a continuous chain or in a ring. All deviations, either multiple bonds or atoms other than carbon and hydrogen, are indicated by prefixes or suffixes according to a specific set of priorities.



Scheme 1: Classification diagram of hydrocarbons.

1. Representation of molecules

Organic molecules can be represented in different ways, more or less detailed.

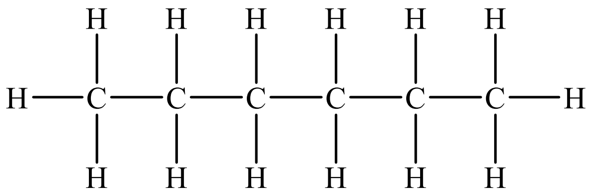
a-The crude formula of a compound gives its composition in each of the elements constituting it.

Example:

C_2H_6O for ethanol, $C_8H_9O_2N$ for paracetamol.

b-The structural formula specifies the arrangement of the atoms within the molecule. It shows all the bonds while respecting the valence of each atom (4 for C, 1 for H, 2 for O, 3 for N...).

Example: C_6H_{14}



$$\begin{array}{ccccccccccccc} & & H & & H & & H & & H & & H & & H & & \\ & & | & & | & & | & & | & & | & & | & & \\ H & - & C & - & C & - & C & - & C & - & C & - & C & - & H \\ & & | & & | & & | & & | & & | & & | & & \\ & & H & & H & & H & & H & & H & & H & & \end{array}$$

N.B: Structural formulas are rarely used. Less bulky semi-developed formulas are preferable and more used.

c-The semi-structural formula

This type is obtained by not representing the bonds of the hydrogen atoms with the other atoms.

Example: C_6H_{14}

$$CH_3 - CH_2 - CH_2 - CH_2 - CH_2 - CH_3$$

d-The condensed formula

The $C - C$ and $C - H$ bonds do not appear.

Example: C_6H_{14}

$$CH_3CH_2CH_2CH_2CH_2CH_3$$

e-The topological formula

The carbon chain is arranged in a zigzag with possibly branches and double or triple segments for multiple bonds. The C and H atoms are not shown. Hetero-atoms are mentioned as well as the hydrogen atoms attached to them.

Example: $C_{10}H_{22}$

Each end of segment corresponds to a carbon atom C.

2. Nomenclature

The first organic molecules were extracted from natural products and bore the name of their discoverer or a name recalling their origin. This name gave no information about the structure of the molecule.

With the explosion of extraction methods and especially organic synthesis, a considerable number of molecules have appeared, requiring the introduction of systematic nomenclature rules.

Nomenclature is a set of rules allowing a given compound to be named by specifying the sequence of its carbon atoms, as well as the nature and position of the different functions it contains.

A systematic nomenclature has been established by an international organization, the IUPAC (International Union of Pure and Applied Chemistry), often referred to by its English name IUPAC.

The name of the molecule must contain all the information about the organization of the atoms in the molecule, namely:

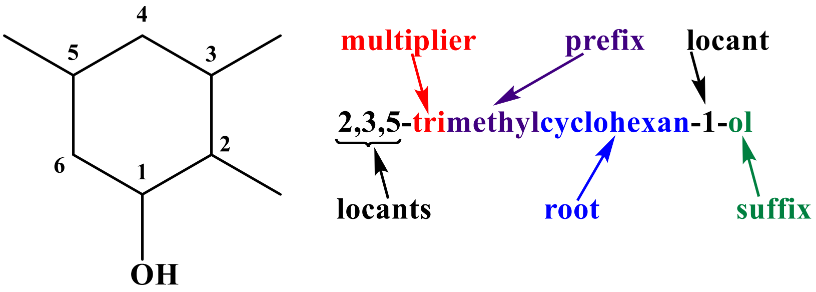
1. Presence of the main chemical functional group
2. Longest carbon chain with the main functional group (parent chain)
3. Presence of substituents in alphabetical order and secondary functional groups
4. Indication of stereochemistry

The general formula for naming organic compounds is:

Locant Multiplier (Substituent Prefix)-ROOT (Parent Chain) Locant-Suffix (Principal Group)
lowest priority *highest priority*

- The **root** denotes the number of carbon atoms present in the primary chain (or the longest possible chain of carbon atoms). For example, '*Oct*' in 'Octane', refers to a chain of eight (8) carbon atoms length.
- The **prefix** is the part of the IUPAC name which appears before the root word. For example, '*cyclo*' is the prefix for the compound of 'cyclopropane', and is used to make the difference between a cyclic compound from an acyclic compound.
- The **suffix** refers to the main functional group and the multiple bonds present within an organic compound. For example, '*ol*' in 'alcohol', refers to the specific class of the organic compound.
- The **locant** is a natural number attributed to substituents or functional group to show its position on the parent chain.

Example:



3. Alkanes

Alkanes are saturated hydrocarbons or paraffin (not very reactive) in which the carbon atoms are linked by σ (sigma) bonds ($-C-C-$). Their hybridization type is sp^3.

They have the general formula C_nH_{2n+2} (straight or branched acyclic) and C_nH_{2n} (monocyclic).

They are represented by $R-H$, R being the alkyl group such that: $R = C_nH_{2n+1}$-

3.1 Straight-chain alkanes

The name of straight-chain alkanes is composed of a prefix indicating the number of carbon atoms followed by the ending "*ane*". They are also referred to as "normal" alkanes (preceded by "*n*").

Table 1: Prefixes indicating the number of carbon atoms.

$1C$	$2C$	$3C$	$4C$	$5C$	$6C$	$7C$	$8C$	$9C$	$10C$	$11C$
meth	*eth*	*prop*	*but*	*pent*	*hex*	*hept*	*oct*	*non*	*dec*	*undec*

The first terms of straight-chain alkanes have the following names:

CH_4 methane, CH_3CH_3 ethane, $CH_3CH_2CH_3$ propane, $CH_3(CH_2)_2CH_3$ butane,

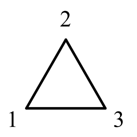
$CH_3(CH_2)_3CH_3$ pentane or *n*-pentane, $CH_3(CH_2)_4CH_3$ hexane or *n*-hexane, $CH_3(CH_2)_5CH_3$ heptane….

NB: The letter "*n*" stands for a normal alkane.

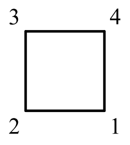
3.2 Cycloalkanes

They are named as the same name as the straight-chain alkane corresponding to the same number of carbon atoms preceded by the prefix "*cyclo*".

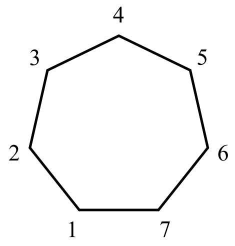
Examples:



cyclopropane



cyclobutane

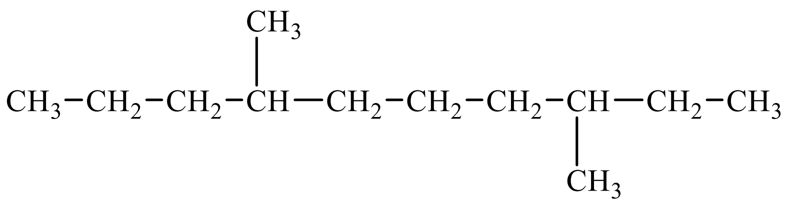


cycloheptane

3.3 Branched-chain alkanes

A branched alkane can be viewed as a straight alkane where the main carbon chain has one or more branches of alky groups (substituents).

Example:



$$CH_3-CH_2-CH_2-\overset{\displaystyle CH_3}{\overset{|}{C}H}-CH_2-CH_2-CH_2-\underset{\displaystyle CH_3}{\underset{|}{C}H}-CH_2-CH_3$$

3.3.1 Normal alkyl groups or normal substituents

They result from the removal of a hydrogen atom from a normal alkane. For a given normal alkane, the corresponding normal alkyl or substituent formula is C_nH_{2n+1}. Their names derive from the corresponding alkane by replacing the ending $-ane$ with the suffix $-yl$.

Table 2: Normal alkyl groups.

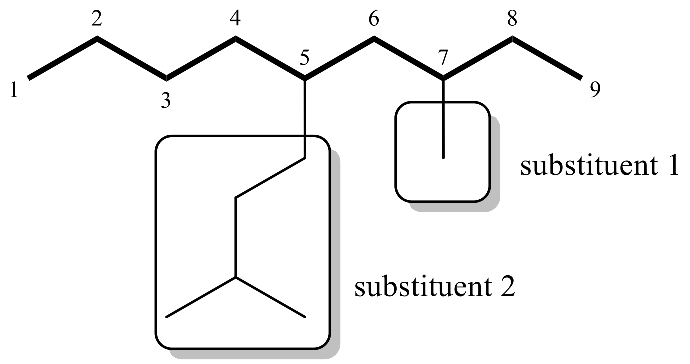
C_nH_{2n+2}	**Alkane**	$C_nH_{2n+1}-$	**Alkyl**
CH_4	methane	CH_3-	methyl or abbreviated to Me
C_2H_6	ethane	C_2H_5-	Ethyl or abbreviated to Et
C_3H_8	propane	C_3H_7-	$CH_3-CH_2-CH_2-$ propyl, Pr or *n*-Pr

3.3.2 IUPAC nomenclature rules

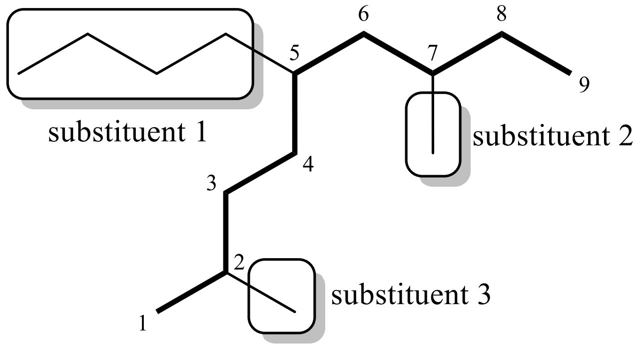
IUPAC rule #1

The parent chain is always the longest carbon chain; it is named after the corresponding alkane. If a molecule has two or more chains of the same length, the parent chain is chosen to be the one with the greatest number of substituents.

Example:



The longest chain with just two substituents

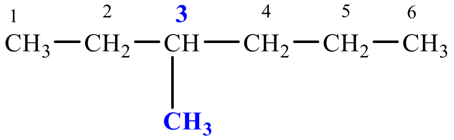


The longest chain with three substituents is more correct

IUPAC rule # 2

The name of the alkyl group attached to the parent chain is added as a prefix. The smallest index is given to the carbon carrying this alkyl group.

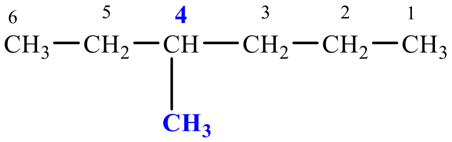
Example:



$\overset{1}{CH_3}-\overset{2}{CH_2}-\underset{\underset{\textstyle CH_3}{|}}{\overset{3}{CH}}-\overset{4}{CH_2}-\overset{5}{CH_2}-\overset{6}{CH_3}$

3-methylhexane

and not

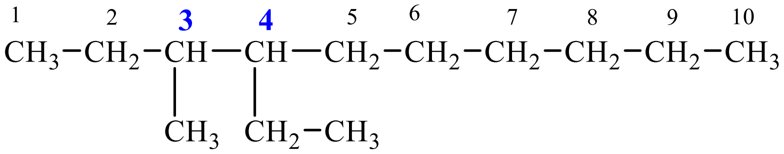


$\overset{6}{CH_3}-\overset{5}{CH_2}-\underset{\underset{\textstyle CH_3}{|}}{\overset{4}{CH}}-\overset{3}{CH_2}-\overset{2}{CH_2}-\overset{1}{CH_3}$

4-methylhexane

When many groups are present, the parent chain is numbered in the direction that gives the lowest locants of the two possible numbering ways.

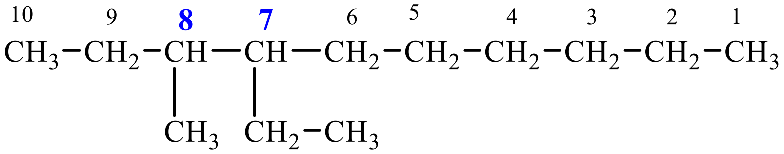
Example:



$\overset{1}{CH_3}-\overset{2}{CH_2}-\underset{\underset{\textstyle CH_3}{|}}{\overset{3}{CH}}-\underset{\underset{\textstyle CH_2-CH_3}{|}}{\overset{4}{CH}}-\overset{5}{CH_2}-\overset{6}{CH_2}-\overset{7}{CH_2}-\overset{8}{CH_2}-\overset{9}{CH_2}-\overset{10}{CH_3}$

4-ethyl-**3**-methyldecane

and not



$\overset{10}{CH_3}-\overset{9}{CH_2}-\underset{\underset{\textstyle CH_3}{|}}{\overset{8}{CH}}-\underset{\underset{\textstyle CH_2-CH_3}{|}}{\overset{7}{CH}}-\overset{6}{CH_2}-\overset{5}{CH_2}-\overset{4}{CH_2}-\overset{3}{CH_2}-\overset{2}{CH_2}-\overset{1}{CH_3}$

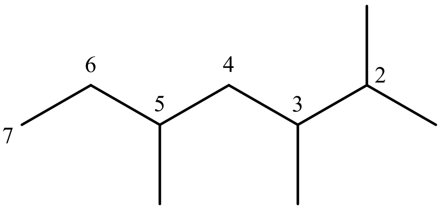
7-ethyl-**8**-methyldecane

In the first numbering, we have the set of numbers (3,4) and in the second (7,8). However, the set of numbers (3,4) is preferable because it presents the lowest locants *i.e.* 3 at the first opportunity of difference compared to the other set (7,8).

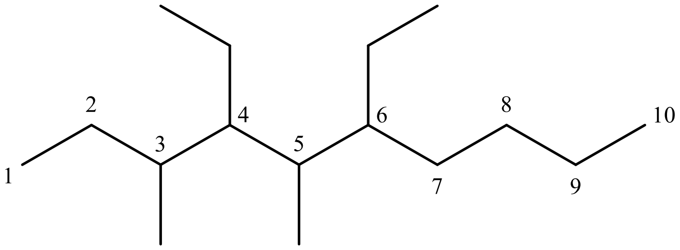
IUPAC rule # 3

When there are several identical groups, the numerical multiplier prefixes: *di*, *tri*, *tetra*, *penta*, *hexa*, *hepta*, *octa*, *nona*, *deca*… are used before the name of the alkyl group.

Example:



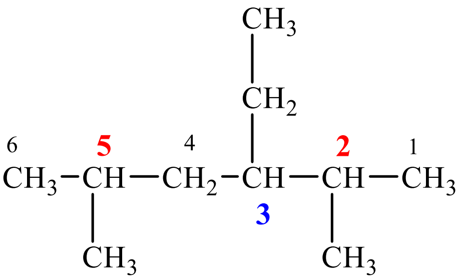
2,3,5-**tri**methylheptane



4,6-**di**ethyl-3,5-**di**methyldecane

Note that the terms *di*, *tri*, *tetra*, etc., are not taken into account in the alphabetical order.

Example:



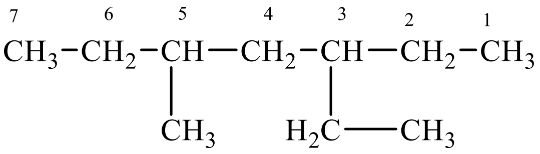
3-**e**thyl-**2**,**5**-**dim**ethylhexane

In the example given above, the letter “***d***” of the prefix « ***di*** » is not considered in the alphabetical order even though it precedes the letter “***m***” of methyl in the alphabetical order. So, the correct order in IUPAC naming is “***e***” in ethyl and then “***m***” in methyl and not “***d***”.

IUPAC rule # 4

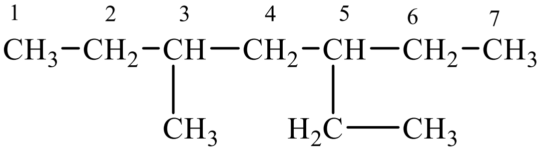
When there are several side chains, the substituents are arranged in alphabetical order. When possible, the smallest locant is given to the group first placed in alphabetical order.

Example:



3-ethyl-5-methylheptane

and not



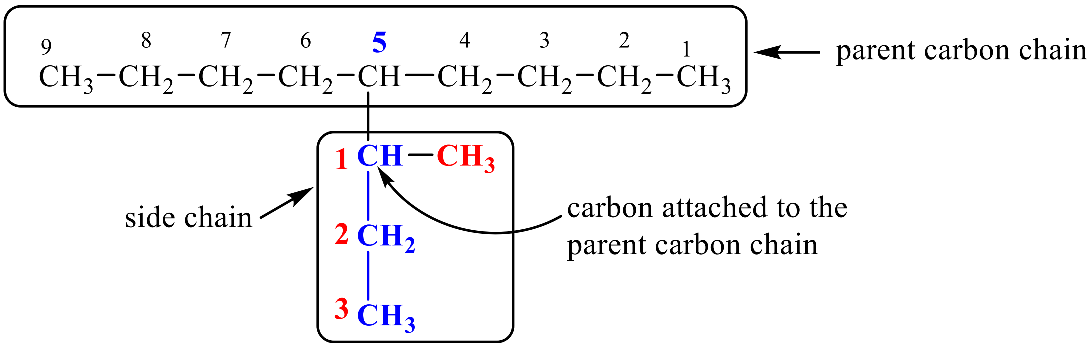
5-ethyl-3-methylheptane

Hence, when the locants of the alkyl groups are the same in both numbering directions *i.e.* from left to right and from right to left, the first alphabetically named (*ethyl* in this example) will receive the lowest locant.

IUPAC rule # 5

The nomenclature of side chains (substituents) follows the same rules as that of the parent chains with the only exception that the carbon attached to the parent chain is numbered 1.

Example:

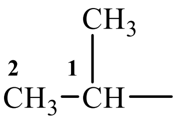
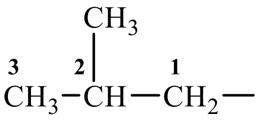
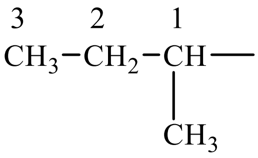
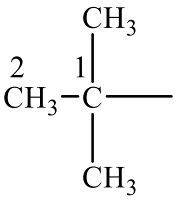


5-(**1**-**methylpropyl**)nonane

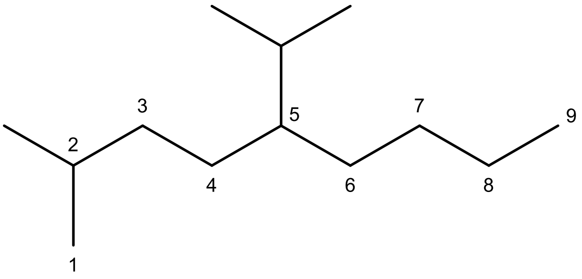
3.3.3 Complex alkyl groups (or complex substituents)

Complex alkyl groups are alkyl groups bearing themselves smaller alkyl groups. Some examples of such groups are given in Table 3.

Table 3: Complex alkyl groups.

Alkyl Group	Usual Name	IUPAC Name
 $\overset{2}{CH_3}-\overset{\overset{CH_3}{\vert}}{\overset{1}{CH}}-$	isopropyl (*i*-Pr)	1-methylethyle
 $\overset{3}{CH_3}-\overset{\overset{CH_3}{\vert}}{\overset{2}{CH}}-\overset{1}{CH_2}-$	isobutyl (*i*-Bu)	2-methylpropyle
 $\overset{3}{CH_3}-\overset{2}{CH_2}-\underset{\underset{CH_3}{\vert}}{\overset{1}{CH}}-$	*sec*-butyl (secondary butyl) (*s*-Bu)	1-methylpropyle
 $\overset{2}{CH_3}-\underset{\underset{CH_3}{\vert}}{\overset{\overset{CH_3}{\vert}}{\overset{1}{C}}}-$	*tert*-butyl (tertiary butyl) (*t*-Bu)	1,1-dimethylethyle

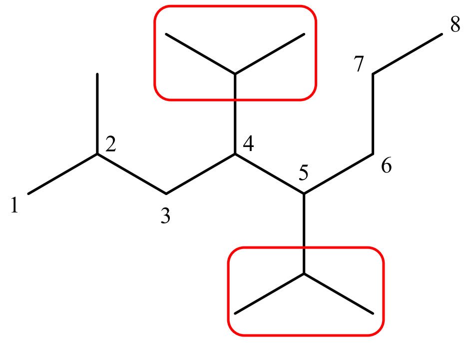
Example:



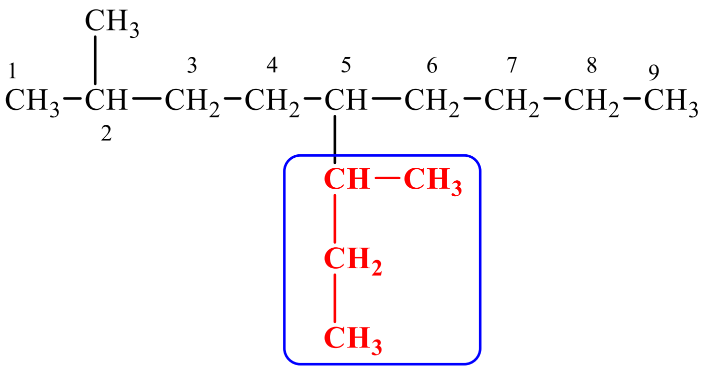
5-isopropyl-2-methylnonane

The terms *sec*, *tert* are ignored in the alphabetical order. However, *iso*- is used and is taken into account in the alphabetical order.

Example:

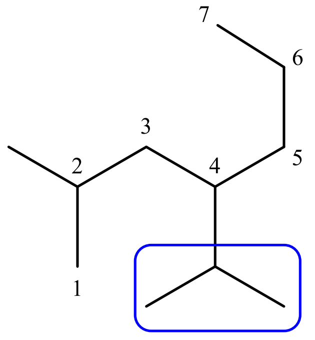


4,5-**diisopropyl**-2-methyloctane

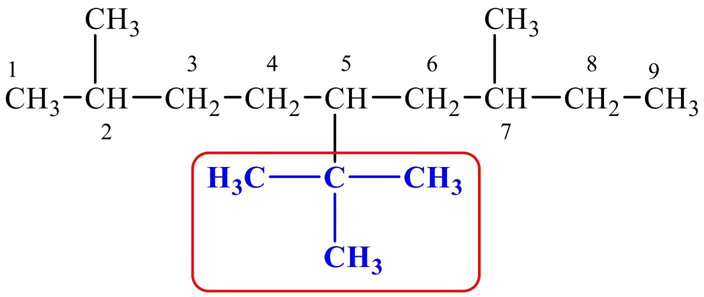


$$\begin{array}{l} \quad\; CH_3 \\ CH_3-\overset{|}{C}H-CH_2-CH_2-CH-CH_2-CH_2-CH_2-CH_3 \\ \qquad\qquad\qquad\qquad\quad\; \begin{array}{l} | \\ CH-CH_3 \\ | \\ CH_2 \\ | \\ CH_3 \end{array} \end{array}$$

5-(***sec*-butyl**)-2-methylnonane



4-**isopropyl**-2-methylheptane

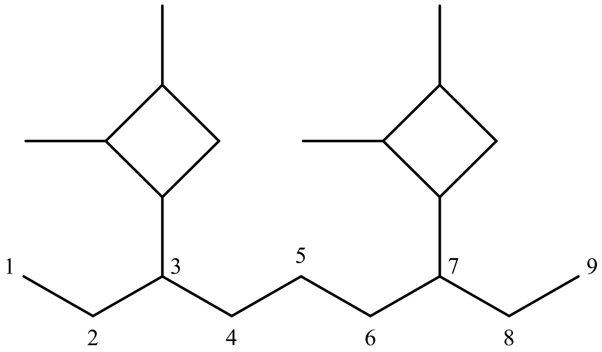


$$\begin{array}{l} \quad\; CH_3 \qquad\qquad\qquad\qquad\qquad\qquad\quad CH_3 \\ CH_3-\overset{|}{C}H-CH_2-CH_2-CH-CH_2-\overset{|}{C}H-CH_2-CH_3 \\ \qquad\qquad\qquad\qquad\; \begin{array}{c} | \\ H_3C-C-CH_3 \\ | \\ CH_3 \end{array} \end{array}$$

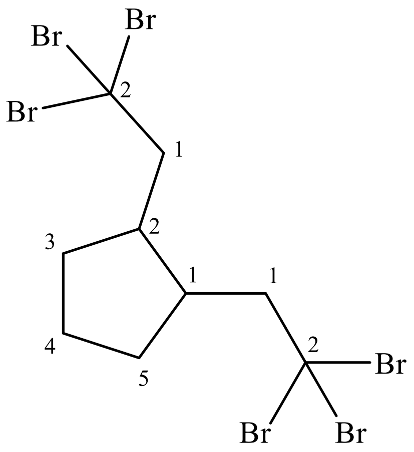
5-(***tert*-butyl**)-2,7-dimethylnonane

Numerical multiplier prefixes (*bis*, *tris*, *tetrakis*, etc.) are used when two or more identical complex groups (substituted substituents) are present where their names already contain the prefixes: *di*, *tri*, etc.

Examples:



3,7-bis(2,3-dimethylcyclobutyl)nonane



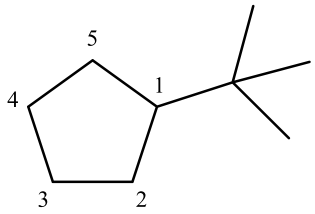
1,2-bis(2,2,2-tribromoethyl)cyclopentane

In the examples given above, in the name of the first molecule on the left “$3,7-bis(2,3-dimethylcyclobutyl)nonane$”, the substituent “$2,3-dimethylcyclobutyl$” is found twice in the compound structure and in its name, it can be seen that the numerical multiplier “*di*” is already used. So, it is not possible to use the same multiplier prefix to show the presence of two identical side chains. In this sense, the numerical multiplier “*bis*” is used to avoid any possible confusion.

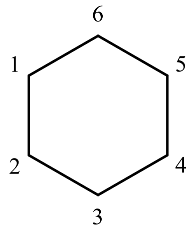
3.4 Substituted cycloalkanes

The names of cycloalkanes follow the same nomenclature rules as for straight alkanes with preceding their names by the prefix “*cyclo*”.

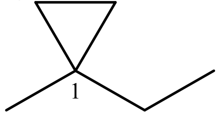
Examples:



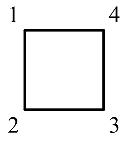
tert-butylcyclopentane



cyclohexane



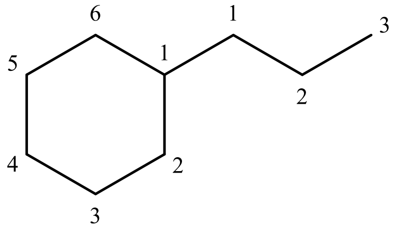
1-ethyl-1-methylcyclopropane



cyclobutane

i. If the carbon number of the cycloalkane is greater than that of the side chain, then the compound is called an alkyl-substituted cycloalkane.

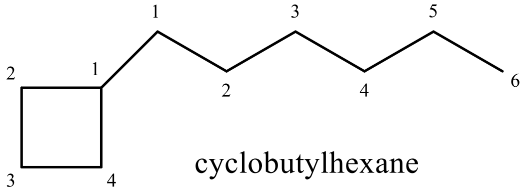
Example:



propylcyclohexane

ii. If the number of carbons in the side chain is higher, then the compound is called a cycloalkyl-substituted alkane.

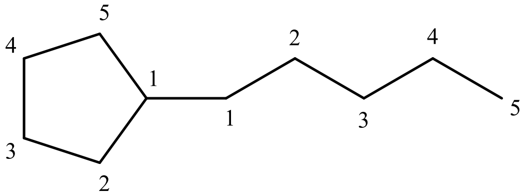
Example:



cyclobutylhexane

iii. But if they have equal number of carbon atoms then the ring has priority over the side chain $i.e.$ it should be named as alkyl substituted cycloalkane.

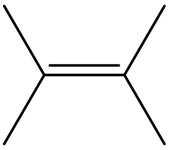
Example:



pentylcyclopentane

4. Alkene nomenclature

Alkenes are hydrocarbons containing a double bond (unsaturated compounds). They are characterized by sp^2 hybridization. The family suffix is: $-ene$. Their general formula is C_nH_{2n} with $n \geq 2$.



4.1 Straight and branched-chain alkenes

Their name is formed as $alc\ (\cancel{\boldsymbol{ane}}) + ene$.

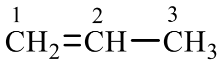
The first term, “ethene” is commonly called ethylene, hence the use of the name “ethylenic compounds” given to alkenes.

For $n = 3$, $C_3H_6, CH_2 = CH - CH_3$ propene

For $n = 4$, $C_4H_8, CH_2 = CH - CH_2 - CH_3$ butene

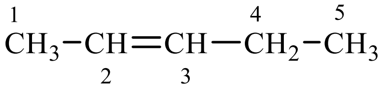
1. The parent chain is numbered from the closest side to the double bond.
2. If the double bond has the same number regardless of the numbering direction of the parent chain, the substituents will be assigned the lowest possible numbers (locants).

Examples:



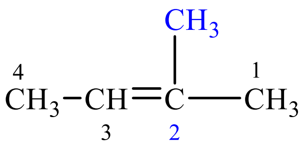
$CH_2=CH-CH_3$

prop-1-ene



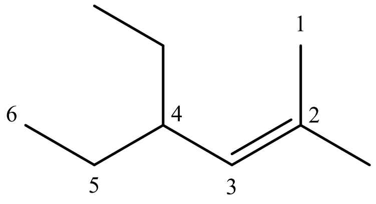
$CH_3-CH=CH-CH_2-CH_3$

pent-2-ene

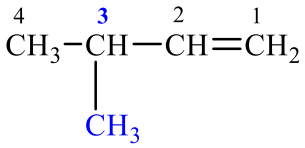


$CH_3-CH=\overset{CH_3}{\overset{|}{C}}-CH_3$

2-methylbut-2-ene



4-ethyl-2-methylhex-2-ene

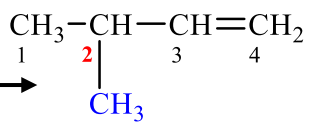


$CH_3-\underset{CH_3}{\underset{|}{CH}}-CH=CH_2$

3-methylbut-1-ene

and not

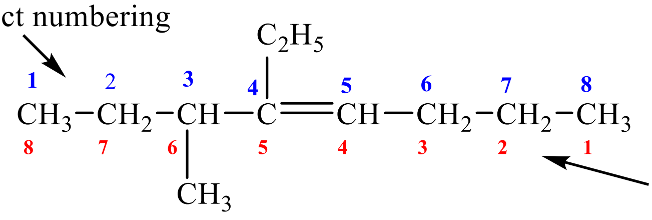
(The smallest number must be first given to the double bond which is the functional group here and not to the methyl substituent.)



$CH_3-\underset{CH_3}{\underset{|}{CH}}-CH=CH_2$

2-methylbut-3-ene

correct numbering



$CH_3-CH_2-\underset{CH_3}{\underset{|}{CH}}-\overset{C_2H_5}{\overset{|}{C}}=CH-CH_2-CH_2-CH_3$

false numbering

4-ethyl-**3**-methyloct-**4**-ene

The name of an unsaturated radical deriving from an alkene is obtained by replacing the suffix "*ene*" with "*enyl*". However, the simplest terms have been given special names:

$-CH=CH_2$: **vinyl** instead of **ethenyl**

$-CH_2-CH=CH_2$ **: allyl** instead of **prop-2-enyl**

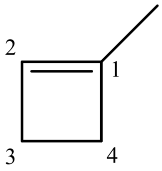
4.2 Cycloalkenes

Cycloalkenes are hydrocarbons with a ring holding a double bond inside. Their general formula is C_nH_{2n-2} .They are named as:

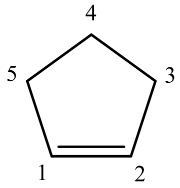
1. The prefix "*cyclo*" is used before the word "*alkene*" is used to indicate the cycloalkene "$cyclo + alk + ene$".

2. The numbering begins first from the carbons of the double bond $C = C$ and goes on through the whole ring.

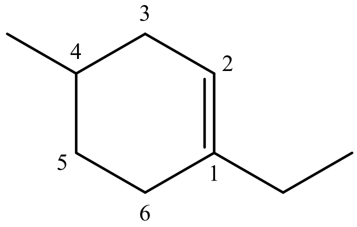
3. If two or more substituents are attached to the ring, the two possible directions of numbering are considered in order to assign the lowest possible locants to substituents.



1-methylcyclobut-1-ene



cyclopentene



1-ethyl-4-methylcyclohex-1-ene

5. Alkyne nomenclature

5.1 Straight and branched-chain alkynes

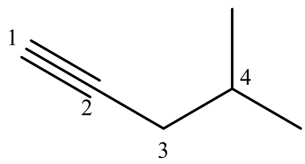
Alkynes are hydrocarbons containing a triple bond and have sp hybridization. They are characterized with a linear geometry. The family suffix is $-yne$. Their general formula is C_nH_{2n-2} with $n \geq 2$. For $n = 2$, we have C_2H_2; for $n = 3$, it is C_3H_4. The first term is ethyne (commonly named "acetylene"), hence the name "acetylenic compounds" given to alkynes. Their nomenclature is the same as that of alkenes except the suffix $-yne$ replaces $-ene$.

1. The parent chain is the longest chain with the maximum number of carbon atoms and necessarily includes the triple bond.
2. The numbering is done by affecting the lowest locants to the carbons of the triple bond $C \equiv C$ $i.e.$ the numbering begins from the nearest side to the triple bond.
3. In the case of triple bond in the middle of the parent chain of branched alkynes, the lowest locants are assigned to the possible substituents.

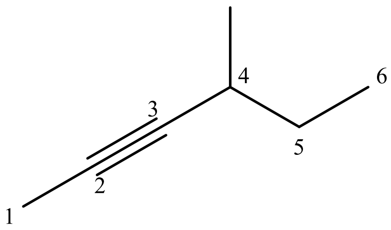
Examples:

$HC \equiv CH$ ethyne (acetylene)

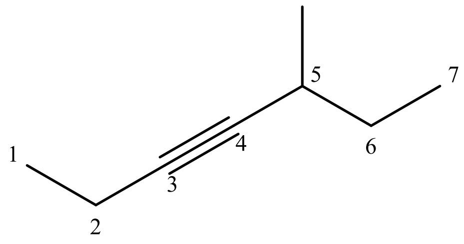
$CH_3 - C \equiv C - CH_3$ but-2-yne



4-methylpent-1-yne



4-methylhex-2-yne



5-methylhept-3-yne

Groups derived from alkynes have the "$ynyl$" ending.

Examples:

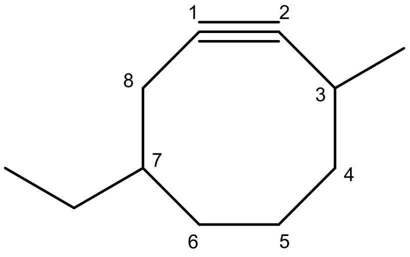
$HC \equiv C -$	ethynyl
$HC \equiv C - CH_2 -$	propargyl
$H_3C - C \equiv C -$	propynyl

5.2 Cycloalkynes

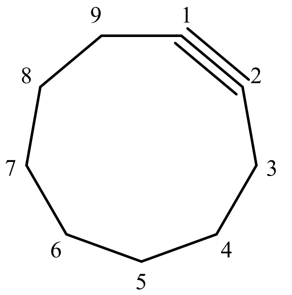
Cycloalkynes are hydrocarbons with a ring holding a triple bond inside. Their general formula is C_nH_{2n-4} .They are named as:

1. The prefix “$cyclo$” is used before the word “$alkyne$” is used to indicate the cycloalkyne “$cyclo + alk + yne$”.
2. The numbering begins first from the carbons of the triple bond $C \equiv C$ and goes on through the whole ring.
3. If two or more substituents are attached to the ring, the two possible directions of numbering are considered in order to assign the lowest possible locants to substituents.

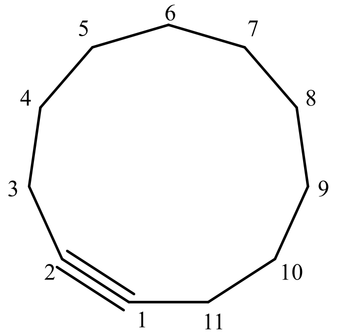
Example:



7-ethyl-3-methylcyclooct-1-yne



cyclononyne



cycloundecyne

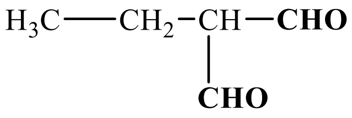
6. Nomenclature of organic functional groups

Functional groups are groups of atoms in organic molecules that are responsible for the characteristic chemical reactions of those molecules. Different possible types of organic compounds could be distinguished.

- Organic molecules containing a single functional group.
- Organic molecules containing two or more identical functional groups.
- Organic molecules containing two or more different functional groups.

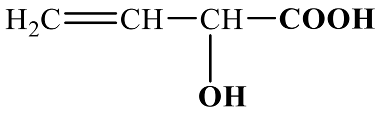
Examples:

$CH_3-CH_2-\mathbf{COOH}$	One functional group



$H_3C-CH_2-CH(\mathbf{CHO})-\mathbf{CHO}$

two identical functional groups



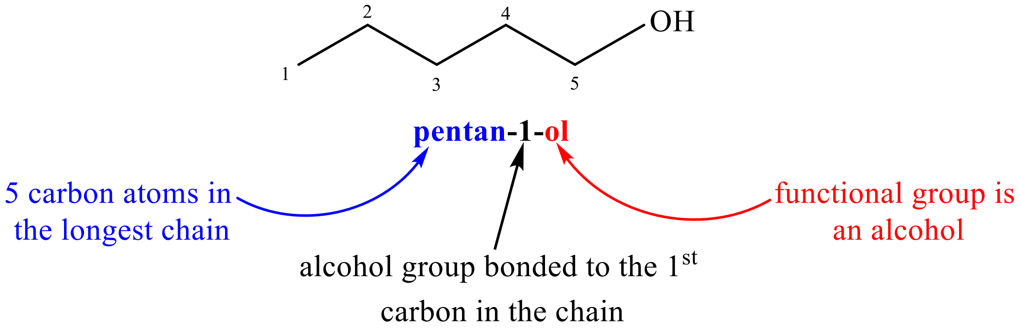
$H_2C=CH-CH(\mathbf{OH})-\mathbf{COOH}$

different functional groups

6.1 Nomenclature of simple organic functional groups

6.1.1 Nomenclature of alcohols ($R-OH$)

The functional group of an alcohol is the hydroxyl group $-OH$.



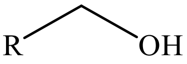
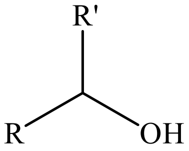
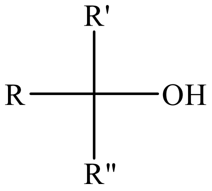
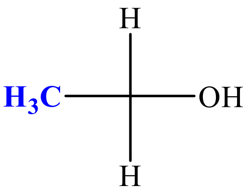
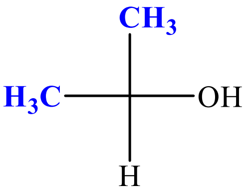
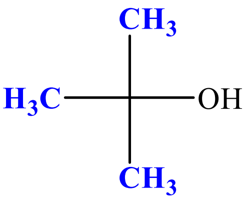
pentan-1-ol

5 carbon atoms in the longest chain

functional group is an alcohol

alcohol group bonded to the 1st carbon in the chain

Classification of alcohols is determined by the number of alkyl groups attached to the carbon bonded to the hydroxyl group. Thus, three classes of alcohols can be defined.

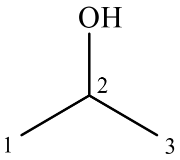
Primary alcohol (1°) **1 group**	**Secondary alcohol (2°)** **2 groups**	**Tertiary alcohol (3°)** **3 groups**
		
		

To name an alcohol, the “e” of the corresponding alkane is replaced by the prefix “ol”.

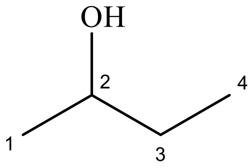
Formula	**IUPAC**	**Formula**	**IUPAC**
CH_4	methan**e**	CH_3-OH	methan**ol**
CH_3-CH_3	ethan**e**	CH_3-CH_2-OH	ethan**ol**
$CH_3-CH_2-CH_3$	propan**e**	$CH_3-CH_2-CH_2-OH$	propan**ol**
$CH_3-CH_2-CH_2-CH_3$	butan**e**	$CH_3-CH_2-CH_2-CH_2-OH$	butan**ol**
$CH_3-CH_2-CH_2-CH_2-CH_3$	pentan**e**	$CH_3-CH_2-CH_2-CH_2-CH_2-OH$	pentan**ol**

From propanol, it is necessary to indicate the position of "OH" in the name just before suffix "ol" since isomers notion enter into account for the carbon chain starting from three carbons and so on.

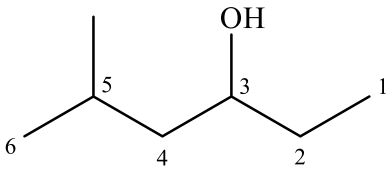
Example:



propan-2-ol



butan-2-ol

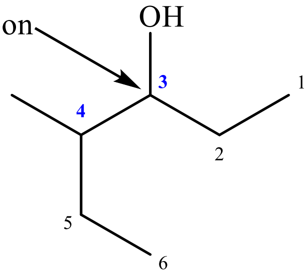


5-methylhexan-3-ol

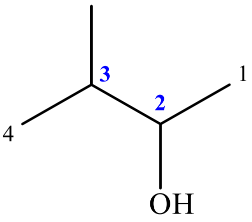
IUPAC names for longer branched chains are given by numbering the longest chain from the nearest end to the $-OH$ group.

Example:

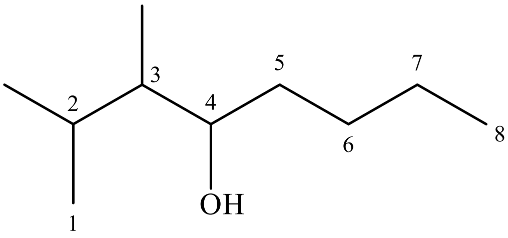
The parent chain necessarily includes this carbon



4-methylhexan-**3**-ol (and not 3-methylhexan-4-ol)



3-methylbutan-**2**-ol
(and not 2-methylbutan-3-ol)



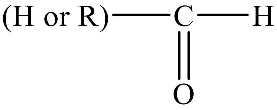
2,3-dimethyloctan-4-ol

6.1.2 Nomenclature of aldehydes and ketones

Aldehydes and ketones are carbonyl derivatives (They hold "$C = O$" carbonyl group).

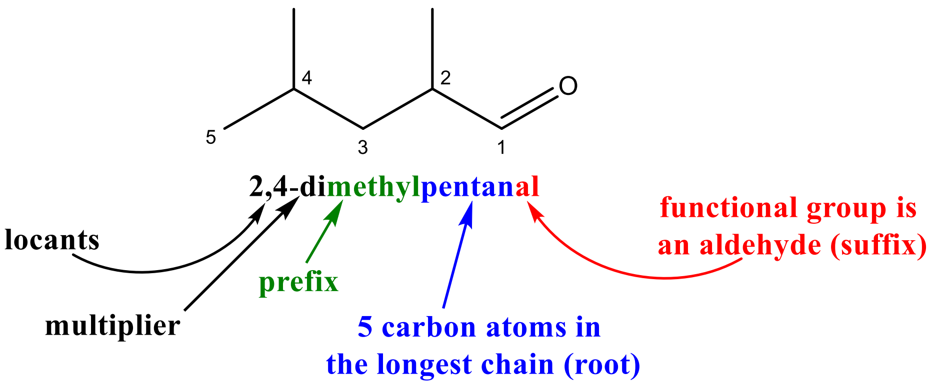
a- Aldehydes

The aldehyde general structure is:



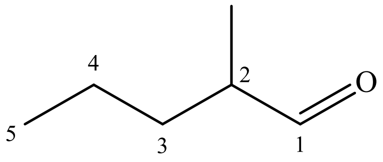
$$(\text{H or R})-\underset{\underset{\text{O}}{\|}}{\text{C}}-\text{H}$$

The name of the aldehyde derives from that of the corresponding alkane by replacing the suffix "$-ane$" with "$-al$". The carbon in the $CH = O$ group always takes the number 1.



Examples:

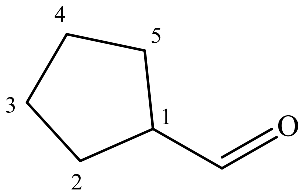
$CH_3 - CHO$	ethanal
$CH_3 - CH_2 - CHO$	propanal
$CH_3 - CH_2 - CH_2 - CHO$	butanal



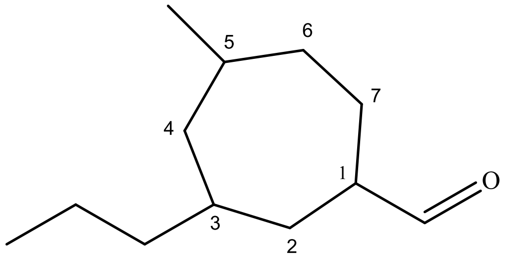
2-methylpentanal

The aldehyde functional group is a "*terminal*" functional group (always at the end of carbon chain). In the case of an aldehyde functional group attached to a ring, the suffix "$-carbaldehyde$" is used.

Example:



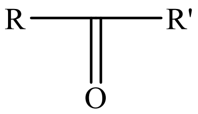
cyclopentanecarbaldehyde



5-methyl-3-propylcycloheptane-1-carbaldehyde

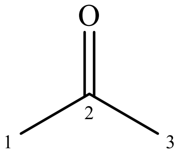
b-Ketones

The ketone structure is:



The name has the suffix "*one*" (instead of *ane*) preceded by the locant of the functional group $-C = O$.

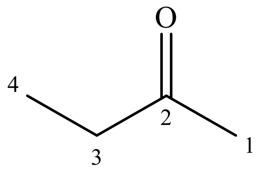
The first ketone molecule is propan-2-one commonly named as acetone:



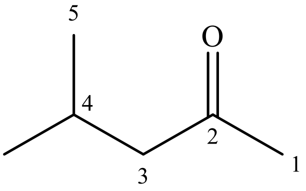
propan-2-one

The parent chain is the longest of the chains containing the group ($C = O$) with the lowest possible locant.

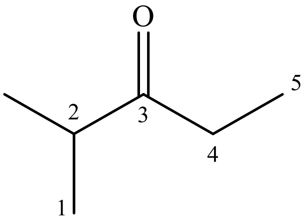
Examples:



butan-2-one



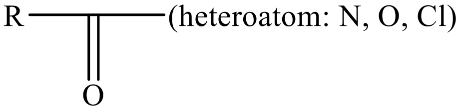
4-methylpentan-2-one



2-methylpentan-3-one

6.1.3 Nomenclature of carboxylic acids and derivatives

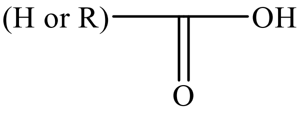
The carboxylic acid and its derivatives have the general structure:



$$R-\underset{\displaystyle O}{\underset{\|}{C}}-\text{(heteroatom: N, O, Cl)}$$

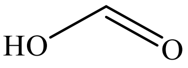
6.1.3.1 Carboxylic acids

A carboxylic acid is:



$$\text{(H or R)}-\underset{\displaystyle O}{\underset{\|}{C}}-OH$$

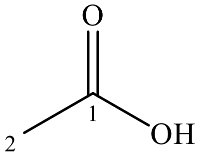
The family suffix is $-anoic$, but many acids have common names.



$HCOOH$

methanoic acid

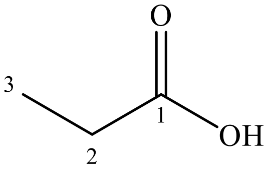
formic acid



CH_3COOH

ethanoic acid

acetic acid



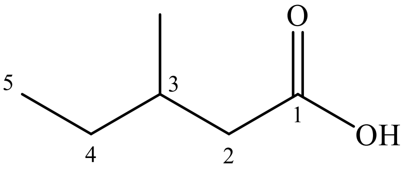
CH_3CH_2COOH

propanoic acid

propionic acid

The carboxylic acid is a "*terminal*" functional group. The carbon of the functional group is always numbered 1. The numbering is then continued on the longest continuous carbon chain.

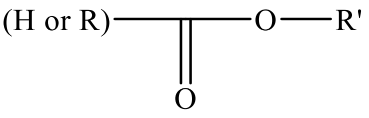
Example:



3-methylpentanoic acid

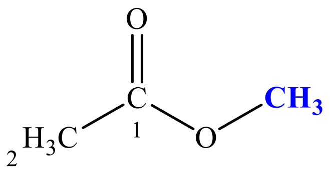
6.1.3.2 Esters

An ester is characterized by the sequence:

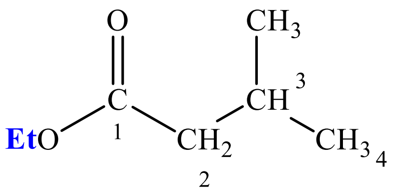


The family suffix is $-alkyl\ anoate$. The carbon of the $-COO-$ functional group has always the locant number 1. The longest carbon chain is numbered from the carbon bearing the ester functional group.

Examples:



methyl ethanotate or methyl acetate



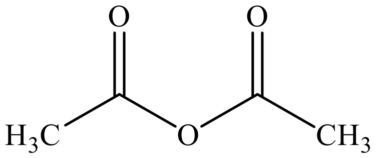
ethyl 3-methylbutanoate

6.1.3.3 Acid anhydrides

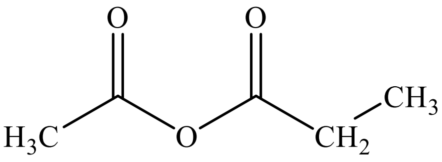
An acid anhydride results from the reaction of two molecules of carboxylic acid with elimination of water molecule.

The name derives from the corresponding acid name by replacing the term "*acid*" by "*anhydride*".

Examples:



ethanoic anhydride or acetic anhydride

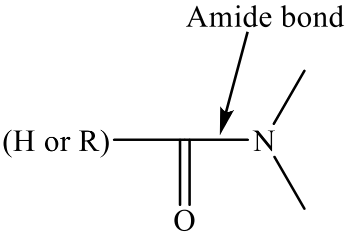


ethanoic propanoic anhydride
or acetic propionic anhydride

6.1.3.4 Amides

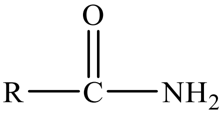
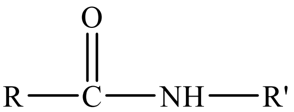
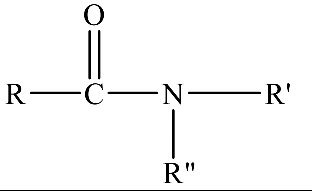
Amides are derivatives of carboxylic acids resulting from the reaction of carboxylic acids with amines.

An amide is characterized by the sequence:



The family suffix is $-anamide$. Like amines, the amides can be classified into three categories.

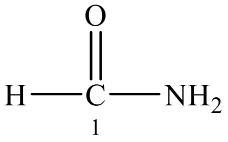
They are classified according to the number of substituents (non-hydrogen-like groups) attached to the nitrogen of the amide group.

Structure	 $R-\overset{\overset{O}{\|}}{C}-NH_2$	 $R-\overset{\overset{O}{\|}}{C}-NH-R'$	 $R-\overset{\overset{O}{\|}}{C}-\underset{\underset{R''}{\|}}{N}-R'$
Number of groups on nitrogen	one	two	three
Classification	Primary amide	Secondary amide	Tertiary amide

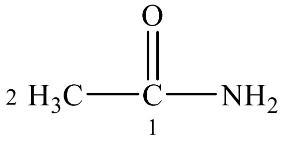
Unlike to alcohols, the classification of amides relates to the substitution at the nitrogen rather than substitution on carbon.

The carbon in $C = O$ is always numbered 1.

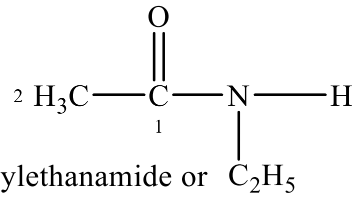
Examples:


$H-\overset{\overset{O}{\|}}{\underset{1}{C}}-NH_2$

methanamide or formamide


$\overset{2}{}H_3C-\overset{\overset{O}{\|}}{\underset{1}{C}}-NH_2$

ethanamide or acetamide

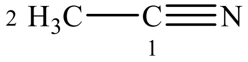

$\overset{2}{}H_3C-\overset{\overset{O}{\|}}{\underset{1}{C}}-\underset{\underset{C_2H_5}{|}}{N}-H$

N-ethylethanamide or N-ethylacetamide

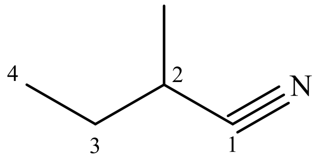
6.1.3.5 Nitriles

The family suffix is $-anenitrile$. The name derives from the corresponding alkane ($+\ nitrile\ suffix$).

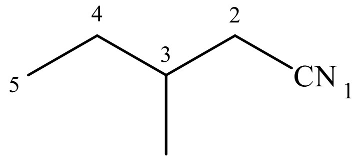
Example:


$\overset{2}{}H_3C-\underset{1}{C}\equiv N$

ethanenitrile or acetonitrile



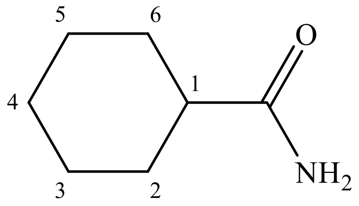
2-methylbutanenitrile



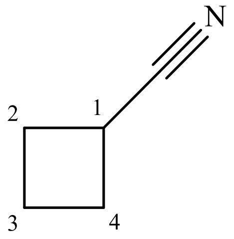
3-methylpentanenitrile

The suffixes $-carboxylic\ acid$, $-carboxamide$ and $-carbonitrile$ are used when more than two carboxylic acid, aldehyde, amide or nitrile functional groups, respectively, are attached to straight chains or in the case where one or more groups are attached to rings.

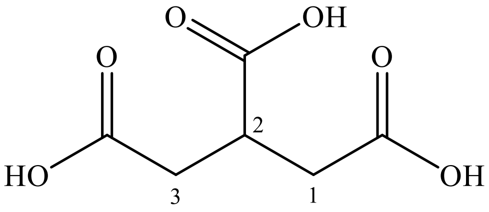
Examples:



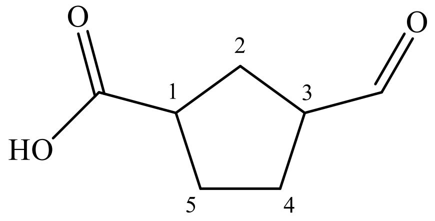
cyclohexanecarboxamide



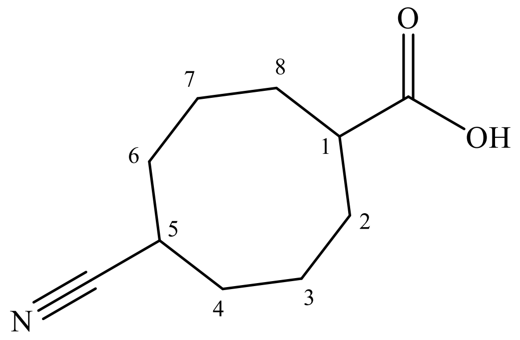
cyclobutanecarbonitrile



propane-1,2,3-tricarboxylic acid



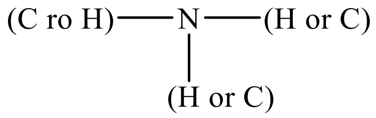
3-formylcyclopentane-1-carboxylic acid



5-cyanocyclooctane-1-carboxylic acid

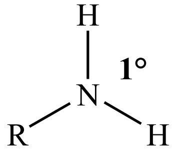
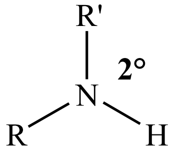
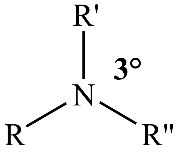
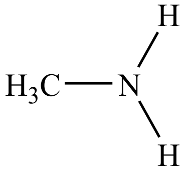
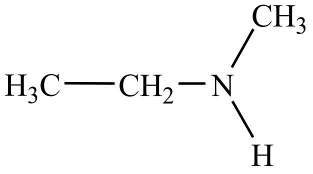
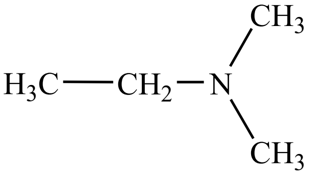
6.1.4 Nomenclature of amines

Amines are compounds containing a nitrogen, linked to carbons or hydrogens.



$$(C\ ro\ H)-\underset{(H\ or\ C)}{\underset{|}{N}}-(H\ or\ C)$$

Amines are classified according to the number of carbon atoms bonded directly to the nitrogen atom. There are three major groups of amines and they are classified as primary (RNH_2), secondary (R_2NH), or tertiary (R_3N), depending on the number of organic substituents attached to nitrogen.

Primary amine (1°) one group	Secondary amine (2°) two groups	Tertiary amine (3°) three groups
		
		

The suffix of the family is $-anamine$, or $-an-x-amine$, x being the locant of the carbon connected to the nitrogen.

6.1.4.1 Primary amines ($R-NH_2$)

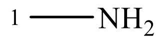
IUPAC system allows two different ways of naming primary amines. They can either be named as $alkylamines$ or as $alkanamines$. Most primary amines which are attached to straight-chain alkanes, cycloalkanes, and alkyl groups with common names tend to be named as alkylamines.

The general steps applied for such nomenclature:

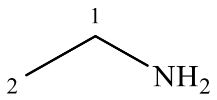
1. Identify the longest carbon chain bonded to the nitrogen.

2. Identify the substituents.
3. Number the parent chain, giving the lowest possible locant to the carbon linked to nitrogen atom.
4. Put all together and ensure that the substituents are in alphabetical order.

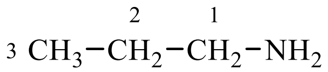
Examples:



methanamine

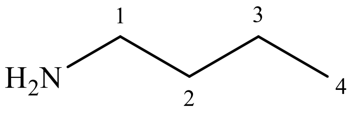


ethanamine



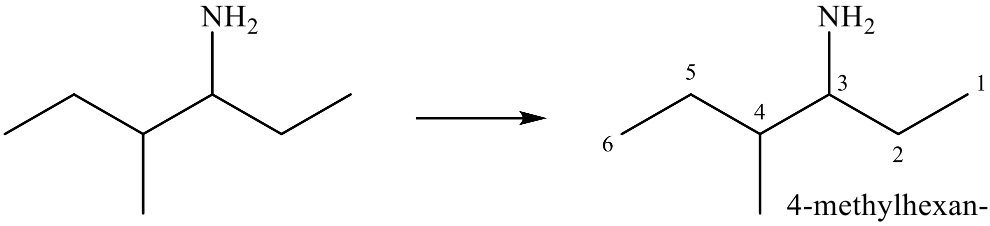
$$\overset{3}{CH_3}-\overset{2}{CH_2}-\overset{1}{CH_2}-NH_2$$

propan-1-amine



butan-1-amine

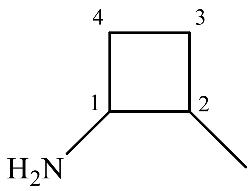
To name the following amine:



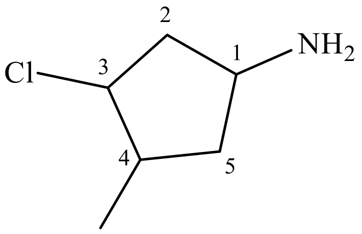
4-methylhexan-3-amine

For the amines attached to a ring, the prefix: *cyclo* is added as *cycloalkanamine*.

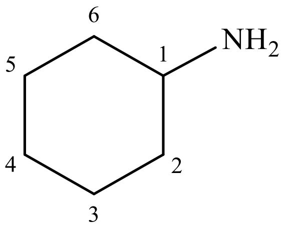
Example:



2-methylcyclobutan-1-amine



3-chloro-4-methylcyclopentan-1-amine

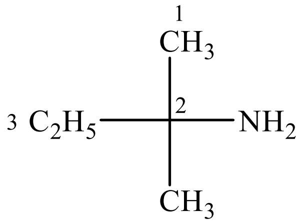


cyclohexanamine

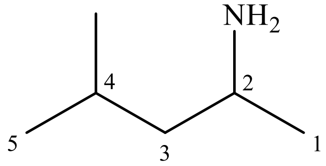
Alternatively, primary amines tend to be named as alkylamine following the rules:

1. Identify the longest carbon chain bonded to the nitrogen of the amine group.
2. The alkyl group is named as a substituent ($prefix + alkyl$).
3. The suffix amine is added at the end of the name.
4. Assign the lowest possible locants first to the carbon linked to the nitrogen, then to the possible substituents.

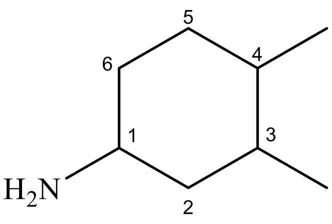
Example:



2-methylbutyl-2-amine



4-methylpentyl-2-amine



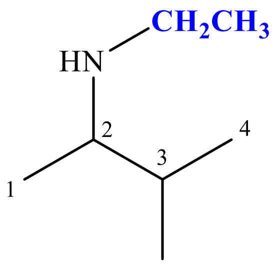
3,4-dimethylcyclohexyl-1-amine

6.1.4.2 Secondary ($R-NH-R'$) and tertiary amines $(R)_3N$

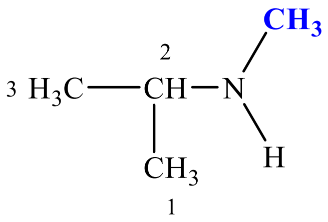
The longest chain containing the nitrogen $-N$ gives the root of the name ($alkan-x-amine$ where "x" is the position index or locant of the nitrogen) preceded by the name of the substituent.

1. The name of the substituent is preceded by *N*- to indicate that it is linked to the nitrogen.
2. The names of the other groups are given in alphabetical order before that of the amine.

Example:



N-**ethyl**-3-methylbutan-2-amine

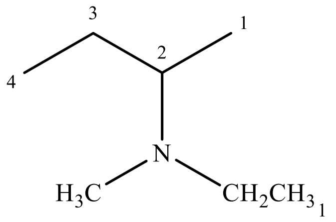


N-**methyl**propan-2-amine

3. If there are two or more identical alkyl substituents, the ≪ $N,N-\ di.....yl...$ ≫ is used.

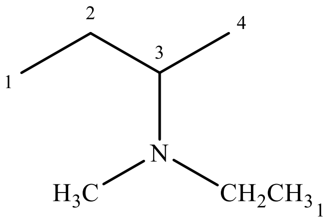
Examples:

The numbering is set by assigning the smallest possible locant to the carbon connected to *N*.

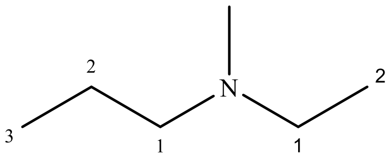


N-ethyl-*N*-methylbutan-2-amine

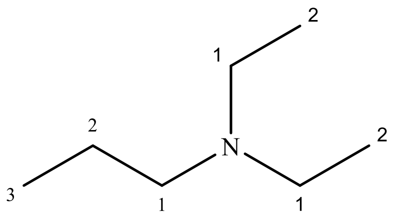
and not



N-ethyl-*N*-methylbutan-3-amine



N-ethyl-*N*-methylpropan-1-amine

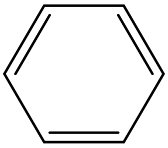


N,*N*-diethylpropan-1-amine

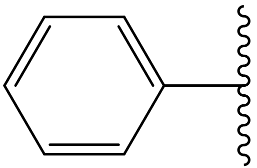
6.1.5 Nomenclature of substituted benzenes

Benzene (C_6H_6) is a fundamental aromatic compound with a cyclic and planar structure containing delocalized π electrons (Conjugated π system). It is a six-membered ring with sp^2 hybridized carbon atoms bonded to one hydrogen atom each.

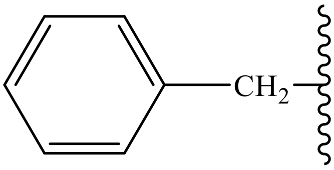
Substituents derived from benzene are:



benzene



phenyl



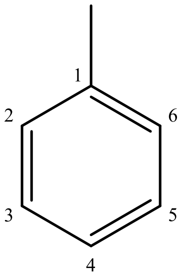
benzyl

As in aliphatic hydrocarbons nomenclature described earlier in this chapter, the nomenclature of aromatic compounds is based on determining the root name of the parent ring first; then assigning priority, name, and position number of substituents; and finally assembling the name in alphabetical order. Functional group priority order remains the same in aliphatic and aromatic nomenclature.

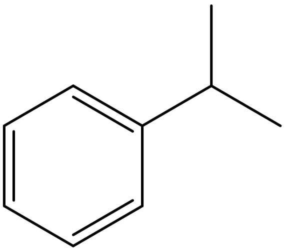
6.1.5.1 Monosubstituted benzenes

In a simple aromatic molecule, benzene becomes the parent chain. The names of the side chains linked to benzene are given as prefixes.

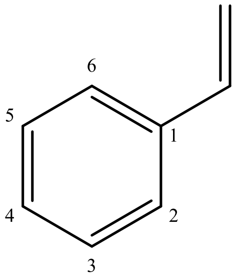
Examples:



methylbenzene (toluene)



isopropylbenzene (cumene)

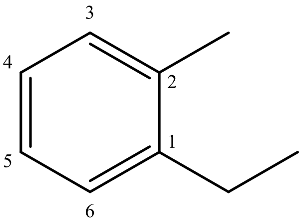


vinylbenzene (styrene)

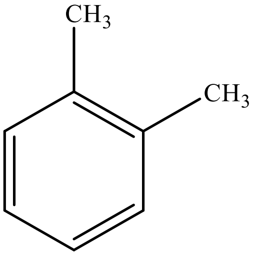
6.1.5.2 Disubstituted benzenes

Disubstituted benzene derivatives can exist in three isomeric forms, for which the prefixes *ortho*, *meta* and *para*, often abbreviated to "*o*, *m* and *p*", are used instead of "1,2", "1,3" and "1,4", respectively.

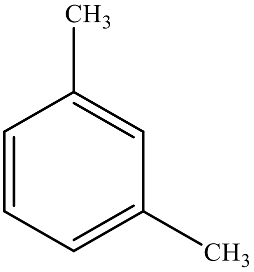
Examples:



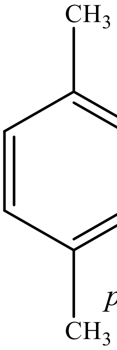
1-ethyl-2-methylbenzene



o-xylene



m-xylene



p-xylene

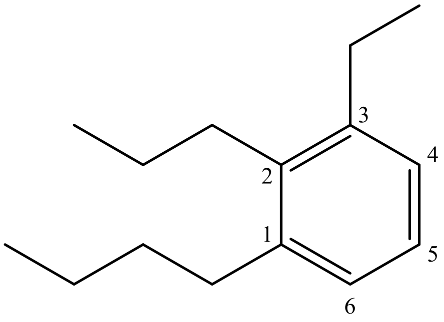
6.1.5.3 Polysubstituted benzenes

Polysubstituted benzene are substituted benzene with more than two substituents (three and so on).

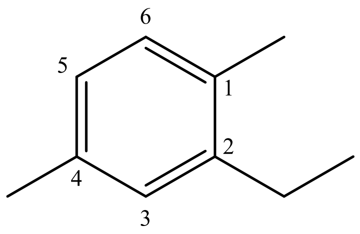
1. The set of locants of the substituents is chosen in the lowest possible way.
2. The substituents are listed in alphabetic order.

3. The carbon of benzene takes the position number 1 in case it is attached to a functional group ($-NH_2$, $-OH$, $-COOH$,…) or has a common special name such as toluene (when attached to $-CH_3$) for example.

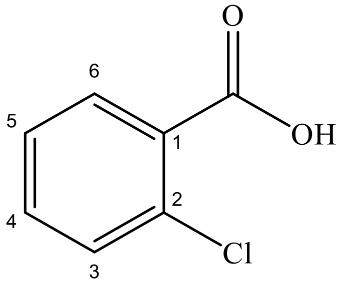
Examples:



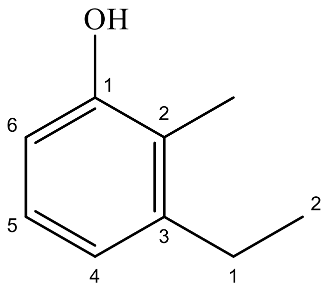
1-butyl-3-ethyl-2-propylbenzene



2-ethyl-1,4-dimethylbenzene

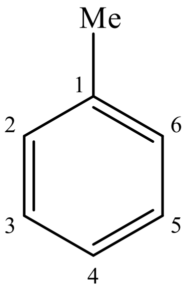


2-chlorobenzoic acid

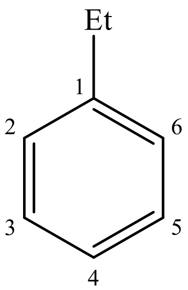


3-ethyl-2-methylphenol

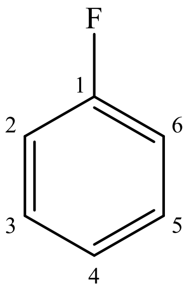
Some common IUPAC retained parent names for substituted benzene are listed below:



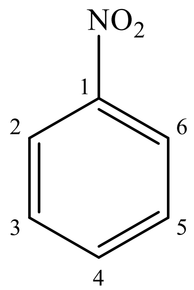
toluene



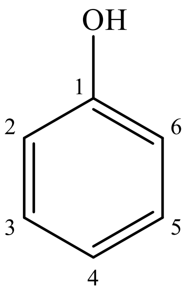
ethylbenzene



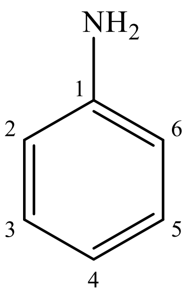
fluorobenzene



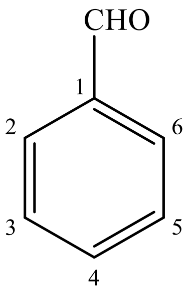
nitrobenzene



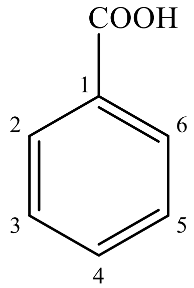
phenol



aniline



benzaldehyde

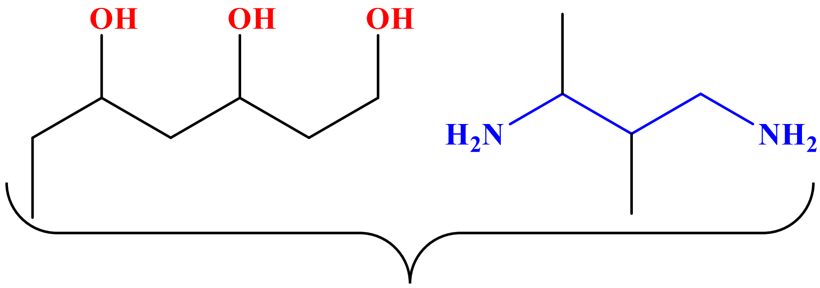


benzoic acid

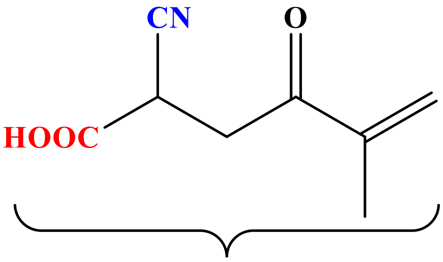
6.2 Nomenclature of polyfunctional compounds

Polyfunctional compounds are compounds which contain two or more than two functional groups in an organic compound. The polyfunctional compound can hold the same or identical functional groups as it can contain different functional groups.

Example:



Compound containing the same functional groups



Compound containing different functional groups

In the IUPAC nomenclature system, the functional groups of the polyfunctional compound are classified into primary and secondary functional group according to their priority. In order to do this classification, a system of priorities is used to determine the main functional group, which determines the identity of the compound. All other functional groups are treated as substituents. Hence, the functional group with the highest priority is selected as the principal functional group.

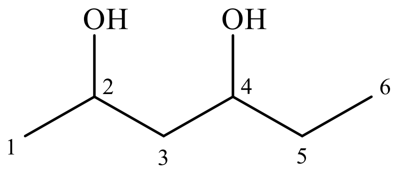
6.2.1 Polyfunctional compounds containing identical functional groups

1. The numerical multipliers prefixes di, tri, $tetra$, $penta$, $hexa$, etc. are placed before the suffix and preceded by the locants of the functional groups.

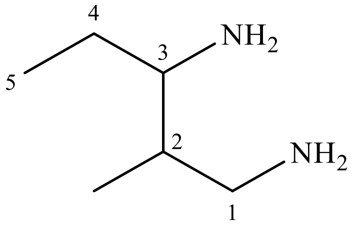
2. The parent chain is the longest carbon chain containing either all the carbons of the functional groups (for functional groups such as $-COOH$, $-CHO$, etc.), or all the carbons carrying the functional group (for functional groups such as $-OH$, $-NH_2$, etc.).

3. The lowest possible locants are assigned to the carbons of the functional groups (or to the carbons carrying the functional group).

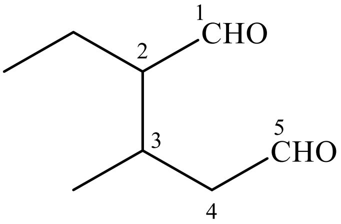
Examples:



hexane-2,4-diol

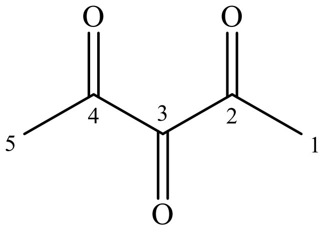


2-methylpentane-1,3-diamine

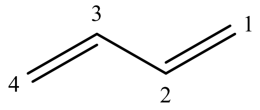


2-ethyl-3-methylpentanedial

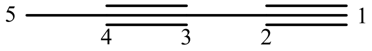
Note 1: compared to propan-1-ol for example, we add an "*e*" after "*an*" because it is followed by a consonant (as in hexanediol).



pentane-2,3,4-trione

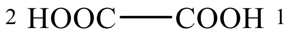


buta-1,3-diene

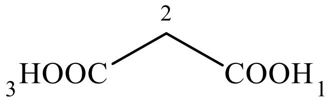


penta-1,3-diyne

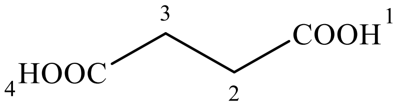
Note 2: compared to but-2-ene for example, we add an "*a*" after "but" because it is followed by a consonant (as in butadiene).



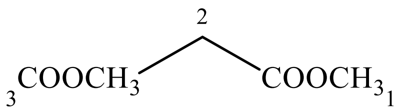
ethanedioic acid



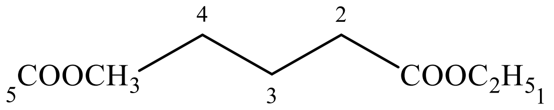
propanedioic acid



butanedioic acid



dimethyl propanedioate



ethyl methyl pentanedioate

6.2.2 Polyfunctional compounds containing different functional groups

In the case of polyfunctional compounds containing two or more different functional groups, one of the functional groups will have the highest priority and stands as principal group and its suffix will appear at the end of the name.

The remaining functional groups will be the secondary functional groups and they will appear in the name as substituents (in the prefix). The procedure for naming functional groups is as follow:

1. Find the longest carbon chain which will give the root of the name
2. The parent carbon chain must contain the carbon of the main functional group
3. It must contain the maximum of the multiple bonds present (double or triple bond)
4. The parent chain does not necessarily contain the secondary functional groups since they are treated as substituents

The priority order of the most common used functional groups is given in the following Table 4.

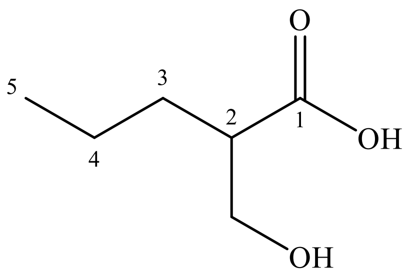
Table 4: Priority order of common functional groups.

Functional group	Prefix	Suffix
Carboxylic acid ($-COOH$)	carboxy-	-oic acid
Ester ($-COOR$)	alkoxycarbonyl-	oate
Amide ($-CONR_2$)	carbamoyl-	-amide
Nitrile ($-C \equiv N$)	cyano-	-nitrile
Aldehyde ($-CHO$)	formyl- or oxo-	-al or -carbaldehyde
Ketone ($> C = O$)	oxo-	-one
Alcohol ($-OH$)	hydroxy-	-ol
Amine ($-NR_2$)	amino-	-amine
Alkene $> C = C <$	enyl-	-ene
Alkyne ($-C \equiv C -$)	ynyl-	-yne
Alkane ($-C - C -$)	yl-	-ane

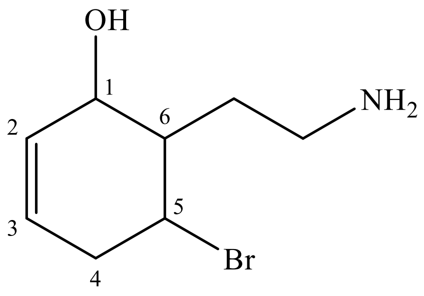
Table 5: Classification of common functional groups.

	Functional group	
Trivalent functional groups	1- Carboxylic acids	$-COOH$
	2- Esters	$-COOR$
	3- Amides	$-CONR_2$
	4-Nitriles	$-CN$
Divalent functional groups	5- Aldehydes	$-CHO$
	6- Ketones	$-CO$
Monovalent functional groups	7-Alcohols	$-OH$
	8-Amines	$-NR_2$

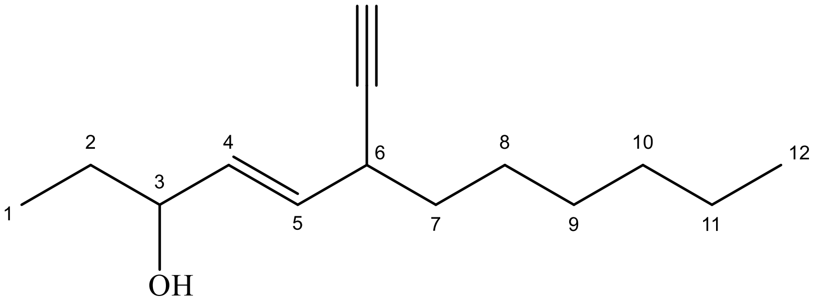
Examples:



2-(hydroxymethyl)pentanoic acid



6-(2-aminoethyl)-5-bromocyclohex-2-en-1-ol

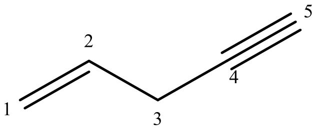


6-ethynyldodec-4-en-3-ol

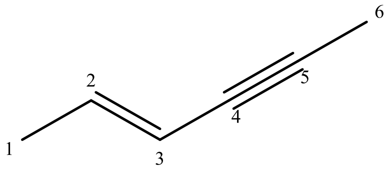
In the previous examples, the indication of the double bond (en) comes before the indication of the alcohol suffix (ol) as "$enol$". Hence, in the alphabetical order the letter "e" in "en" comes before "o" in "ol".

Likewise, in a given name, the indication of a double bond (en) is always placed before the indication of the triple bond (yn) as "$enyne$". Again, in the alphabetical order the letter "e" comes before "y".

Example 1:

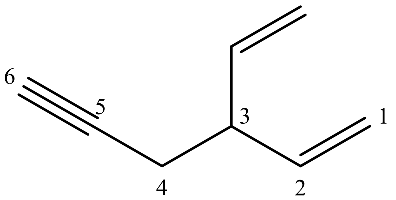


pent-1-en-4-yne



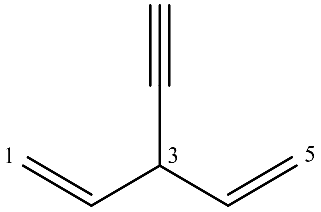
hex-2-en-4-yne

Example 2:



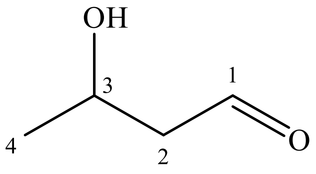
3-vinylhex-1-en-5-yne

Example 3:

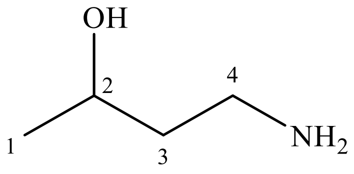


3-ethynylpenta-1,4-diene

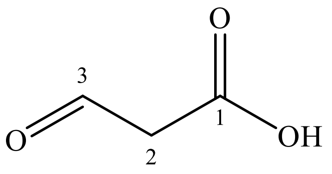
For this compound (example 3), a maximum of two multiple bonds can be included in the parent chain: one double + the triple, or both doubles. The number of carbons is equivalent in both cases ($C5$). In this case, priority is given to the double bond.



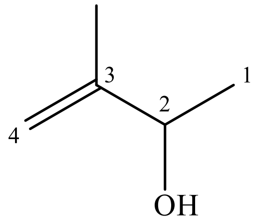
3-hydroxybutanal



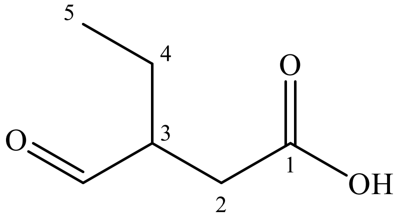
4-aminobutan-2-ol



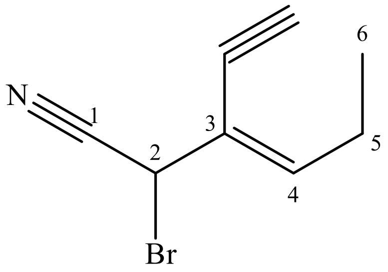
3-oxopropanoic acid



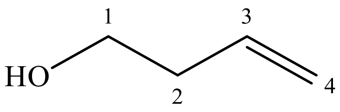
3-methylbut-3-en-2-ol



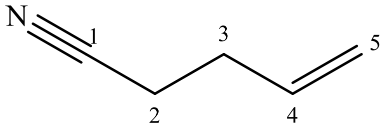
3-formylpentanoic acid



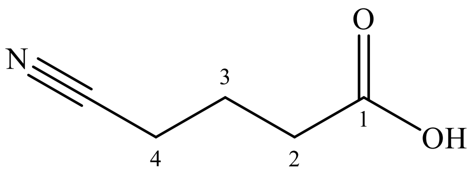
2-bromo-3-ethynylhex-3-enenitrile



but-3-en-1-ol



pent-4-enenitrile



4-cyanobutanoic acid

In 4-cyanobutanoic acid, the term "$cyano$" represents the $-CN$ group, and the carbon of this group is already indicated in the prefix, so it is not considered in the parent chain.

Naming of halogen derivatives (Halo compounds)

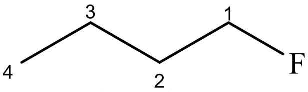
Halogens never have priority; they are always substituents and are named as $fluoro-$ for fuorine, $chloro-$ for chlorine, $bromo-$ for bromine, and finally $iodo-$ for iodine. To name the haloalkane, the procedure used is:

1. Number the chain from the nearest end to the halogen
2. Write prefix ($halogen + root + suffix$).
3. If more than one halogen is present, the alphabetical order is applicable.
4. If there are two or more identical halogens are present, use the numerical multiplier prefixes $di-$, $tri-$, $tetra-$, etc.

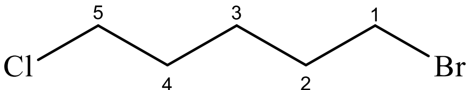
Examples:

$_3\,CH_3-\overset{2}{CH_2}-\overset{1}{CH_2}-Cl$

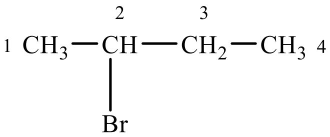
1-chloropropane



1-fluorobutane

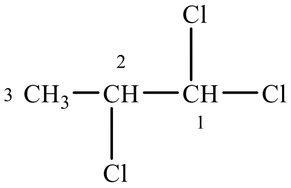


1-bromo-5-chloropentane



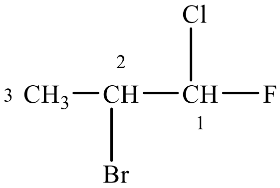
$_1\,CH_3-\underset{Br}{\overset{2}{CH}}-\overset{3}{CH_2}-CH_3\,_4$

2-bromobutane



$_3\,CH_3-\underset{Cl}{\overset{2}{CH}}-\underset{1}{\overset{Cl}{CH}}-Cl$

1,1,2-trichloropropane

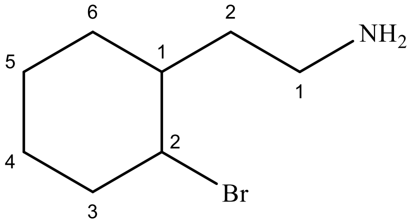


$_3\,CH_3-\underset{Br}{\overset{2}{CH}}-\underset{1}{\overset{Cl}{CH}}-F$

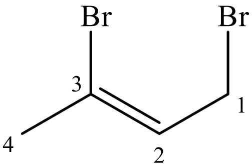
2-bromo-1-chloro-1-fluoropropane

In the case of haloalkenes, haloalkynes and all other functional groups, the highest priority is given first to the functional group while numbering and then to halogens treated as substituents.

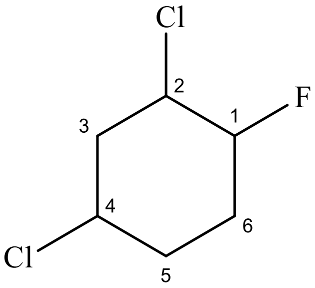
Examples:



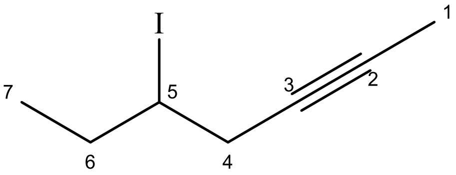
2-(2-bromocyclohexyl)ethan-1-amine



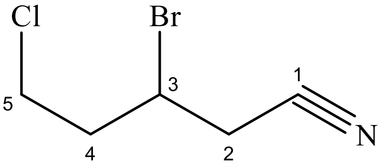
1,3-dibromobut-2-ene



2,4-dichloro-1-fluorocyclohexane



5-iodohept-2-yne

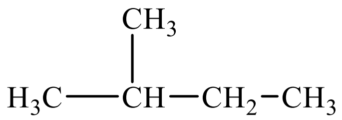


3-bromo-5-chloropentanenitrile

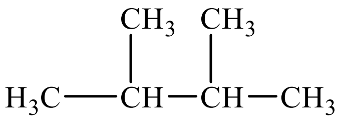
EXERCISES:

Exercise 1:

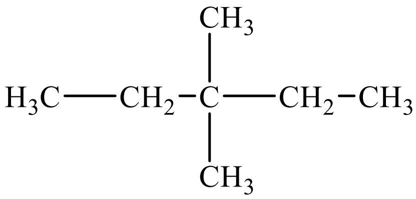
Give the IUPAC name for each of the following:



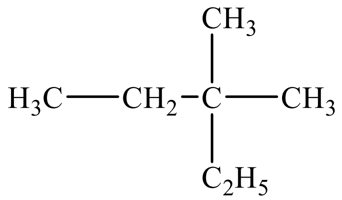
$H_3C-\overset{CH_3}{\overset{|}{CH}}-CH_2-CH_3$



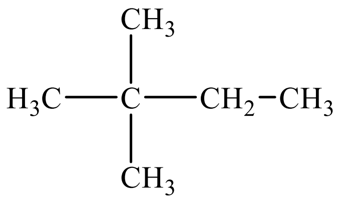
$H_3C-\overset{CH_3}{\overset{|}{CH}}-\overset{CH_3}{\overset{|}{CH}}-CH_3$



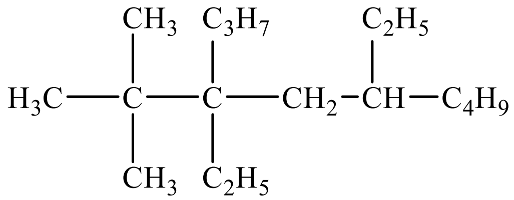
$H_3C-CH_2-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2-CH_3$



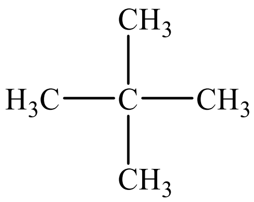
$H_3C-CH_2-\underset{\underset{C_2H_5}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_3$



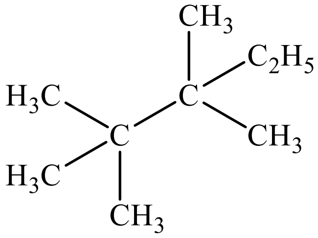
$H_3C-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_2-CH_3$

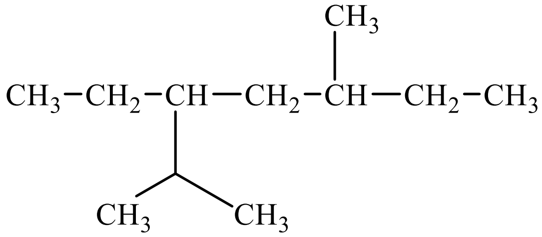


$H_3C-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-\underset{\underset{C_2H_5}{|}}{\overset{\overset{C_3H_7}{|}}{C}}-CH_2-\overset{C_2H_5}{\overset{|}{CH}}-C_4H_9$



$H_3C-\underset{\underset{CH_3}{|}}{\overset{\overset{CH_3}{|}}{C}}-CH_3$





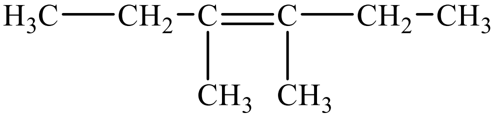
Exercise 2:

Write the structural formula for each of the following:

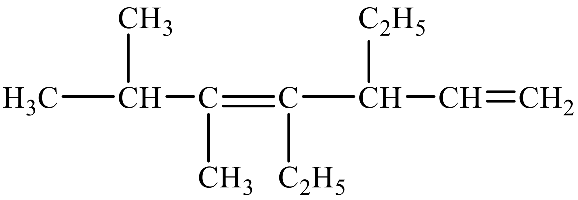
1. 2,3,4-trimethyloctane
2. 2,3-dimethylbutane
3. 2,4-dimethyl-4-ethylheptane
4. 1,3-dipropylcyclohexane
5. 1,2,4-triethylcyclobutane

Exercise 3:

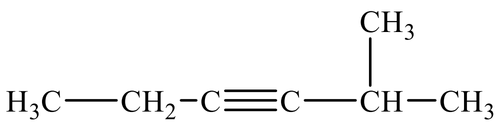
Give the IUPAC name for each of the following unsaturated compounds:

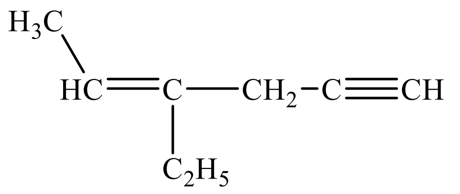


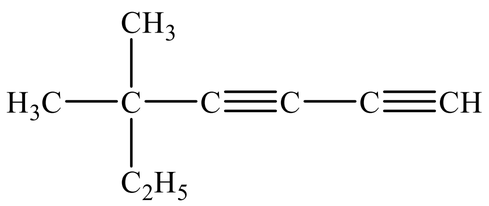
$H_3C-CH_2-\underset{CH_3}{\underset{|}{C}}=\underset{CH_3}{\underset{|}{C}}-CH_2-CH_3$

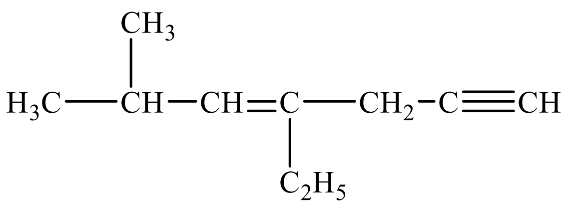


$H_3C-\overset{CH_3}{\overset{|}{CH}}-\underset{CH_3}{\underset{|}{C}}=\underset{C_2H_5}{\underset{|}{C}}-\overset{C_2H_5}{\overset{|}{CH}}-CH=CH_2$


$H_3C-CH_2-C\equiv C-CH(CH_3)-CH_3$


$H_3C-HC=C(C_2H_5)-CH_2-C\equiv CH$


$H_3C-C(CH_3)(C_2H_5)-C\equiv C-C\equiv CH$


$H_3C-CH(CH_3)-CH=C(C_2H_5)-CH_2-C\equiv CH$

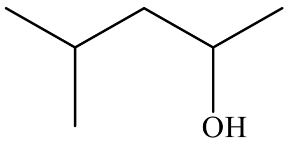
Exercise 4:

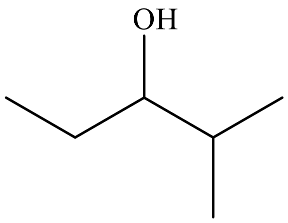
Write the structural formula for each of the following molecules:

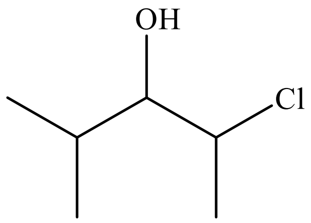
1. 2,6-dimethylhept-3-yne
2. 3-methylcyclobutene
3. 4-ethyl-3-methylhex-3-ene
4. 5-ethyl-3-methylcyclohex-1-yne
5. 1-chloro-3-bromo-4-methylcyclopentene

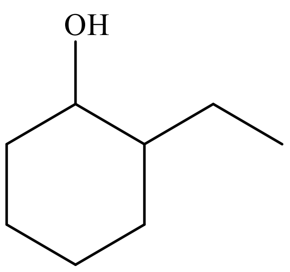
Exercise 5:

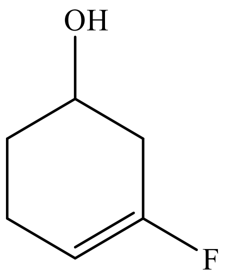
Provide an IUPAC name for each of the following alcohols.

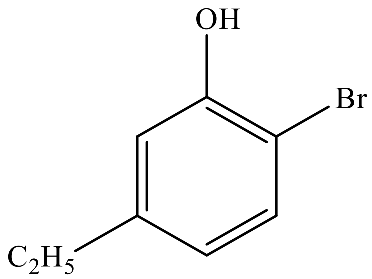






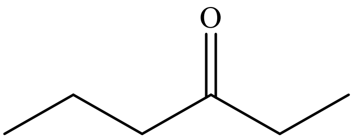


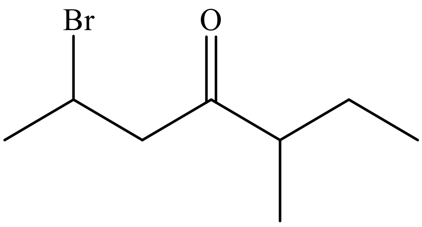


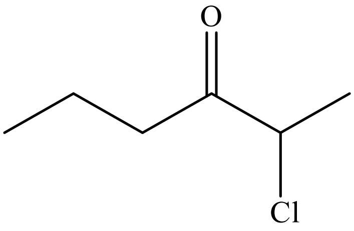


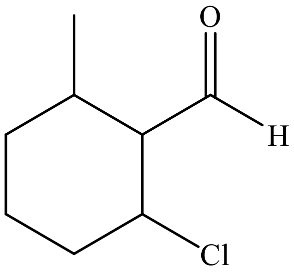
Exercise 6:

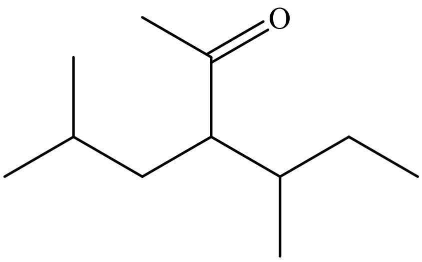
Assign a systematic IUPAC name to each of the following aldehydes and ketones:

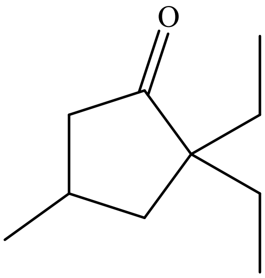


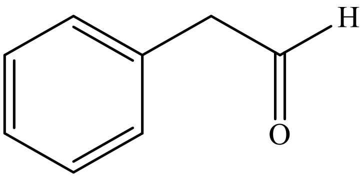


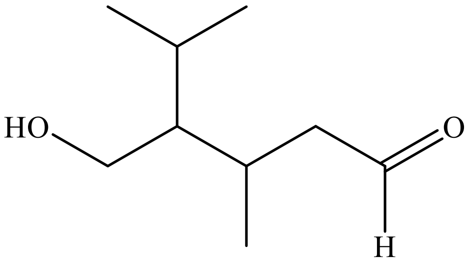


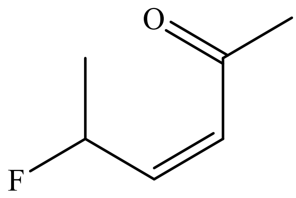












Exercise 7:

Draw the following carboxylic acids:

a- 4-methylhexanoic acid

b- 3-ethyl-6-methyloct-3-enoic acid

c- 3-methylbutanoic acid

d- 2,6-dimethylheptanoic acid

e- 2-methyl-3-isopropylpentanoic acid

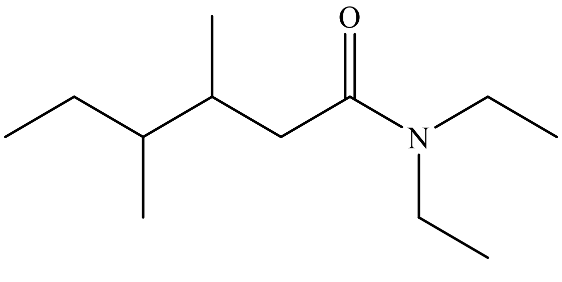
f- 4-methylpent-2-enoic acid

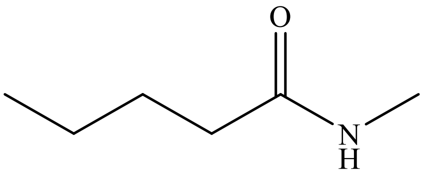
g- 3-ethylnon-5-enoic acid

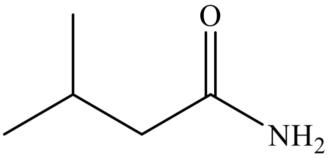
h- 2-ethylcyclopentane-1-carboxylic acid

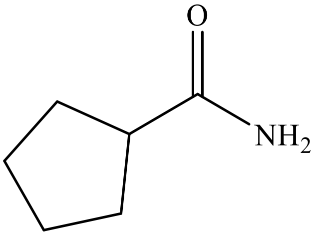
Exercise 8:

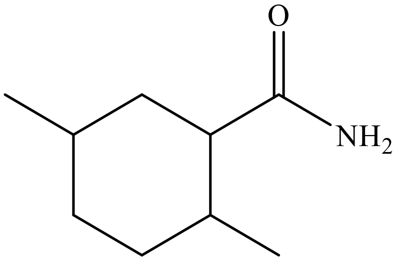
a- Provide the IUPAC name of the following amides.









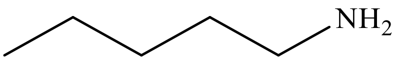


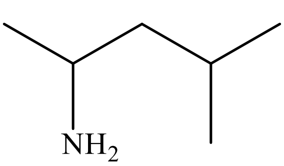
b- Draw the structure of the following amides.

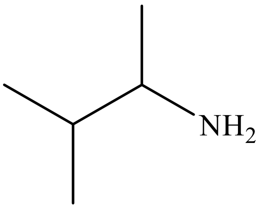
1) *N*-isobutylpropanamide
2) *N,N*-diethylpentanamide
3) 3-chloro-2,4-dimethylheptanamide
4) *N,N*-diisobutylformamide

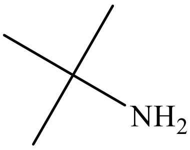
Exercise 9:

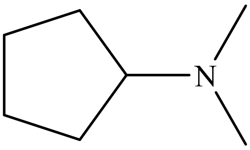
Name using IUPAC the following amine structures.

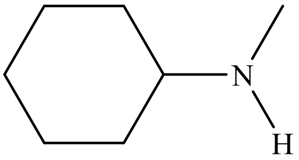


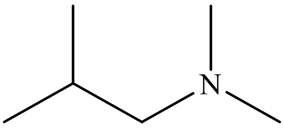


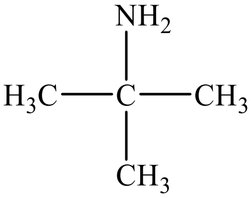




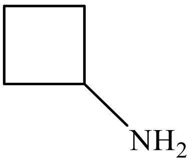


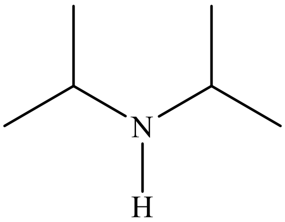


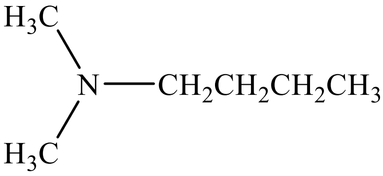


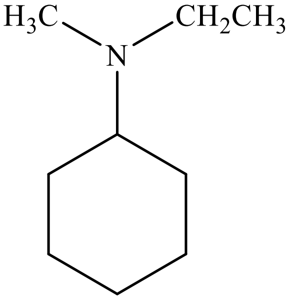


$H_3C-\overset{\overset{NH_2}{|}}{\underset{\underset{CH_3}{|}}{C}}-CH_3$



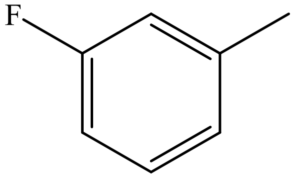


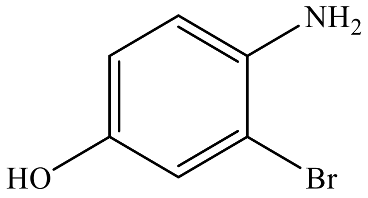


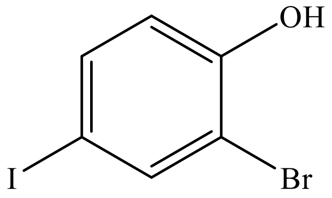


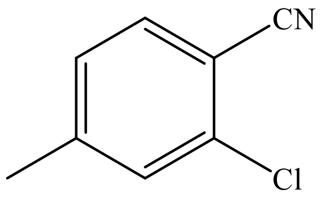
Exercise 10:

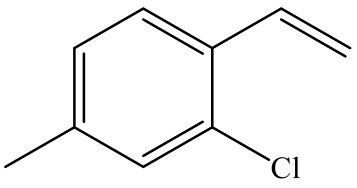
Give the IUPAC name for each of the following aromatic compounds.

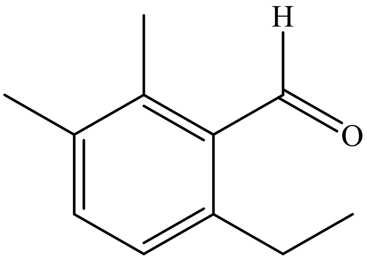


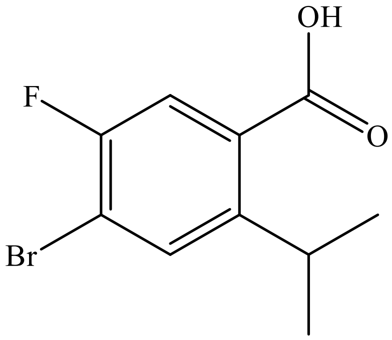


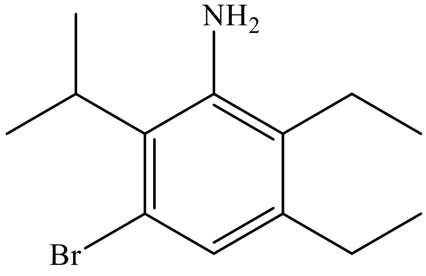


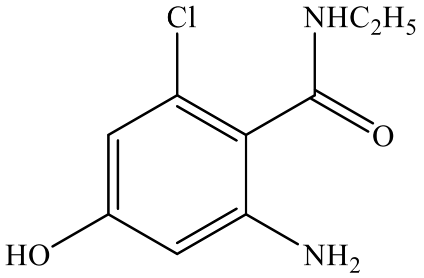






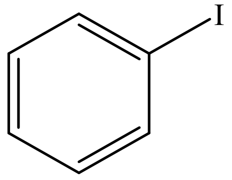


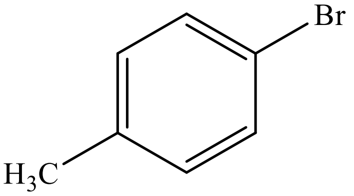


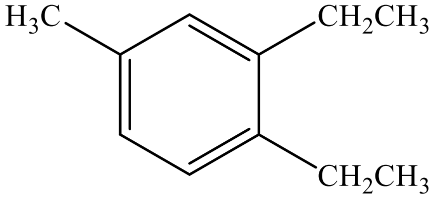


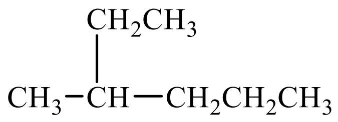
Exercise 11:

Provide the IUPAC name of the following molecules.

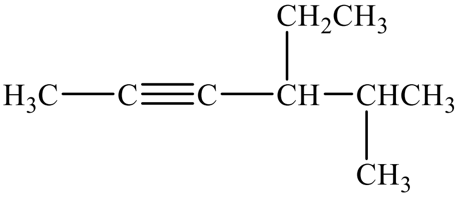




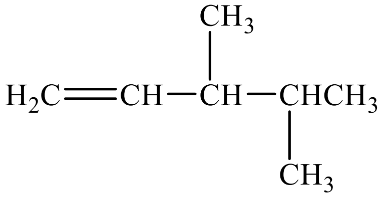




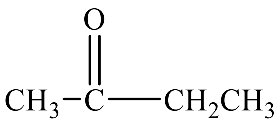
$CH_3-\overset{CH_2CH_3}{\overset{|}{CH}}-CH_2CH_2CH_3$



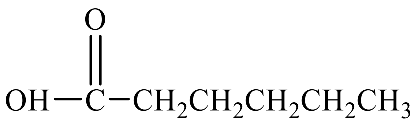
$H_3C-C\equiv C-\overset{CH_2CH_3}{\overset{|}{CH}}-\underset{\underset{CH_3}{|}}{CH}CH_3$



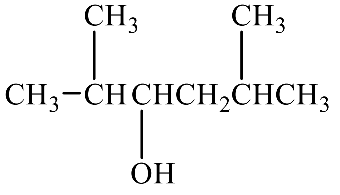
$H_2C=CH-\overset{CH_3}{\overset{|}{CH}}-\underset{\underset{CH_3}{|}}{CH}CH_3$



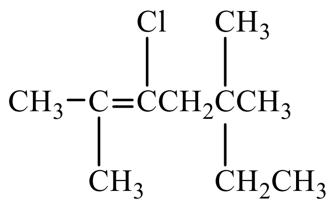
$CH_3-\overset{\overset{O}{\|}}{C}-CH_2CH_3$



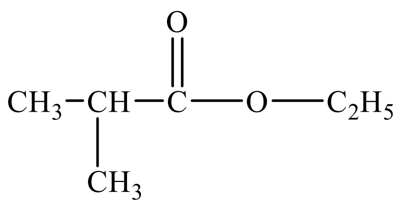
$OH-\overset{\overset{O}{\|}}{C}-CH_2CH_2CH_2CH_2CH_3$



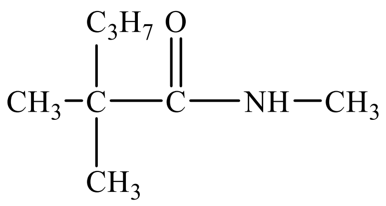
$CH_3-\overset{CH_3}{\overset{|}{CH}}\underset{\underset{OH}{|}}{CH}CH_2\overset{CH_3}{\overset{|}{CH}}CH_3$



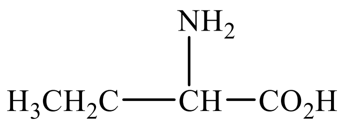
$CH_3-\underset{CH_3}{\overset{Cl}{C}}=CCH_2\underset{CH_2CH_3}{\overset{CH_3}{C}}CH_3$



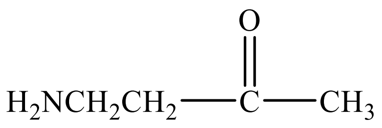
$CH_3-\underset{CH_3}{CH}-\overset{O}{\overset{\|}{C}}-O-C_2H_5$



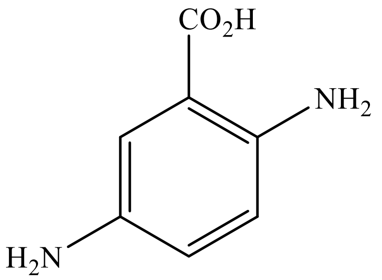
$CH_3-\underset{CH_3}{\overset{C_3H_7}{C}}-\overset{O}{\overset{\|}{C}}-NH-CH_3$



$H_3CH_2C-\overset{NH_2}{CH}-CO_2H$



$H_2NCH_2CH_2-\overset{O}{\overset{\|}{C}}-CH_3$



Exercise 12:

Draw the structural formulas for the following compounds:

1) pent-1-ene
2) prop-2-yn-1-ylbenzene
3) 2,3-dichloro-4-ethylhex-2-ene
4) *m*-bromophenol
5) 3-ethyl-2,3-dimethylpentan-2-ol
6) 2,4-dinitrotoluene
7) 2-methylhept-3-yne
8) 3-ethyl-4,5-dimethylpentane
9) 4-methylhexanoic acid
10) 5-chloro-4-methylheptan-3-one
11) 2-ethylpentan-1-ol
12) 3,3,6,6-tetraethyloct-4-yne

Exercise 13:

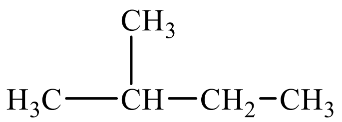
Give the structure of the following molecules:

1) 3-bromobutanoic acid
2) 3-ethylhexan-1-ol
3) 4-ethyl-2-methylnonane
4) 3,3-dimethylpentane
5) 5-ethyl-2-methylhept-3-yne
6) hex-3-ene
7) ethanoic acid
8) butanone
9) 4-aminopentanal
10) pent-2-yne
11) 2-chloropropan-1-ol
12) 1-bromo-1,2-dichloropropane
13) 3-methylhexanoic acid
14) 2,3,3-trimethylhexane
15) octan-4-ylbenzene

SOLUTIONS

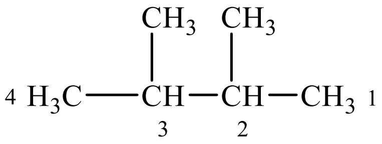
Exercise 1:

We give the IUPAC name for each of the following:



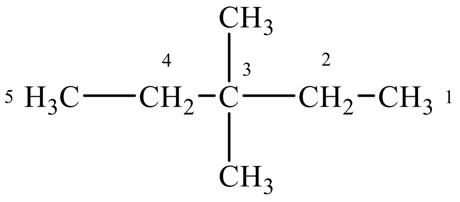
$H_3C-\overset{\overset{\displaystyle CH_3}{|}}{C}H-CH_2-CH_3$

isopentane



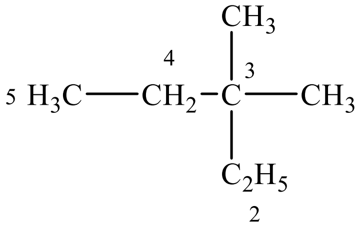
$\overset{4}{H_3C}-\overset{\overset{\displaystyle CH_3}{|}}{\underset{3}{C}H}-\overset{\overset{\displaystyle CH_3}{|}}{\underset{2}{C}H}-\overset{1}{CH_3}$

2,3-dimethylbutane



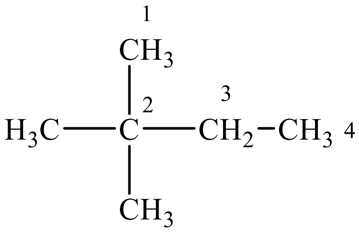
$\overset{5}{H_3C}-\overset{4}{CH_2}-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{\overset{3}{C}}}-\overset{2}{CH_2}-\overset{1}{CH_3}$

3,3-dimethylpentane



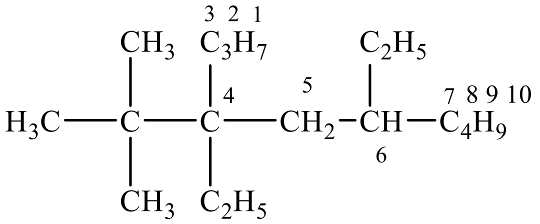
$\overset{5}{H_3C}-\overset{4}{CH_2}-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle \underset{2}{C_2H_5}}{|}}{\overset{3}{C}}}-CH_3$

3,3-dimethylpentane



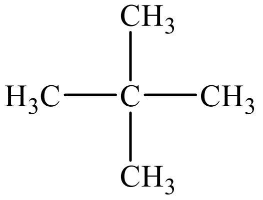
$H_3C-\overset{\overset{\displaystyle \overset{1}{CH_3}}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{\overset{2}{C}}}-\overset{3}{CH_2}-\overset{4}{CH_3}$

2,2-dimethylbutane



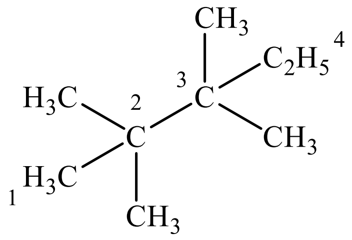
$H_3C-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-\overset{\overset{\displaystyle \overset{3\,2\,1}{C_3H_7}}{|}}{\underset{\underset{\displaystyle C_2H_5}{|}}{\overset{4}{C}}}-\overset{5}{CH_2}-\overset{\overset{\displaystyle C_2H_5}{|}}{\underset{6}{C}H}-\overset{7\,8\,9\,10}{C_4H_9}$

4-(*tert*-butyl)-4,6-diethyldecane

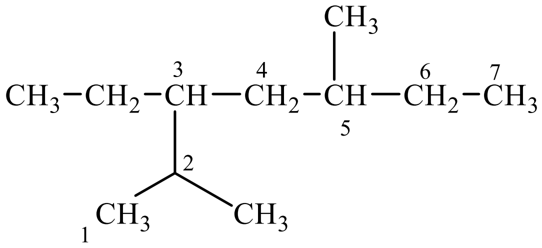


$H_3C-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-CH_3$

neopentane



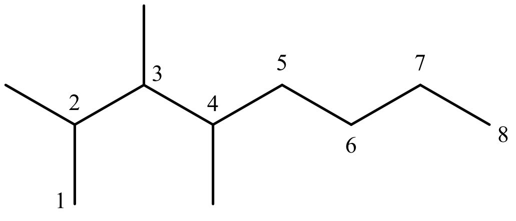
2,2,3,3-tetramethylpentane



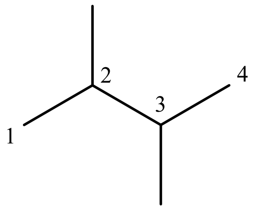
3-ethyl-2,5-dimethylheptane

Exercise 2:

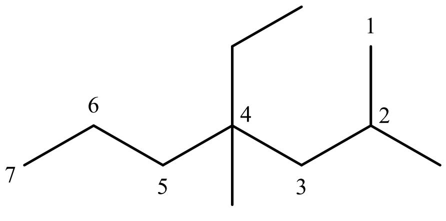
We write the structural formula for each of the following:



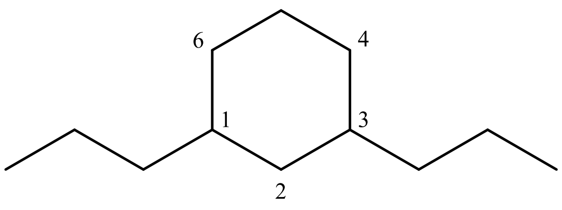
1. 2,3,4-trimethyloctane



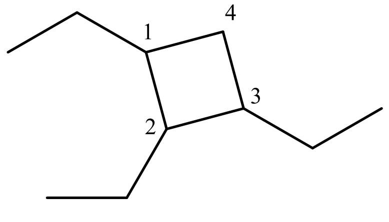
2. 2,3-dimethylbutane



3. 2,4-dimethyl-4-ethylheptane



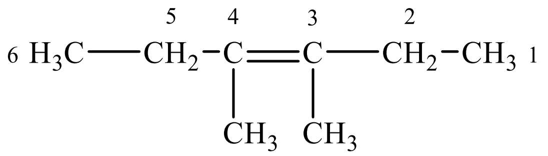
4. 1,3-dipropylcyclohexane



5. 1,2,4-triethylcyclobutane

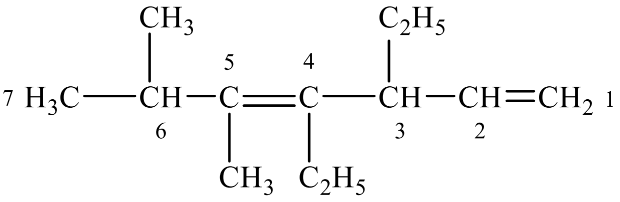
Exercise 3:

We give the IUPAC name for each of the following unsaturated compounds:



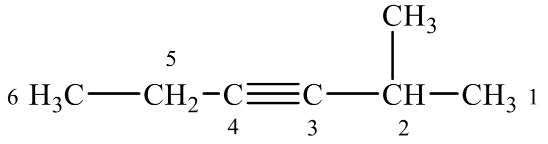
$H_3C-CH_2-\underset{CH_3}{C}=\underset{CH_3}{C}-CH_2-CH_3$

3,4-dimethylhex-3-ene



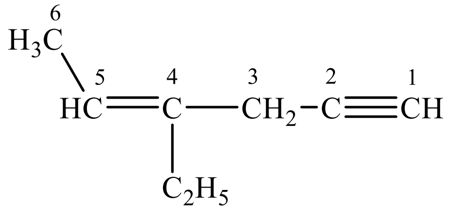
$H_3C-\overset{CH_3}{CH}-\underset{CH_3}{C}=\underset{C_2H_5}{C}-\overset{C_2H_5}{CH}-CH=CH_2$

3,4-diethyl-5,6-dimethylhepta-1,4-diene



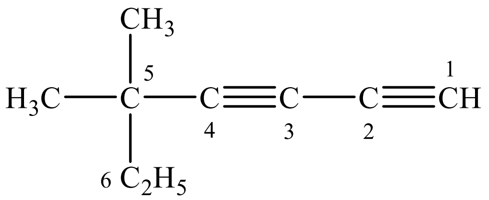
$H_3C-CH_2-C\equiv C-\overset{CH_3}{CH}-CH_3$

2-methylhex-3-yne



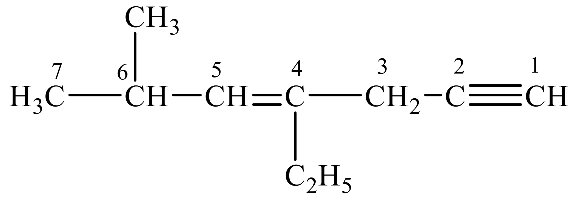
$\overset{H_3C}{HC}=\underset{C_2H_5}{C}-CH_2-C\equiv CH$

4-ethylhex-4-en-1-yne



$H_3C-\overset{CH_3}{\underset{C_2H_5}{C}}-C\equiv C-C\equiv CH$

5,5-dimethylhepta-1,3-diyne

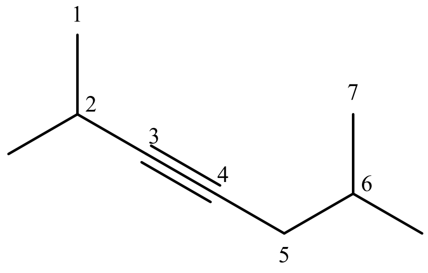


$H_3C-\overset{CH_3}{CH}-CH=\underset{C_2H_5}{C}-CH_2-C\equiv CH$

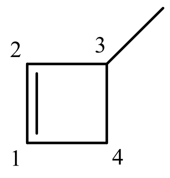
4-ethyl-6-methylhept-4-en-1-yne

Exercise 4:

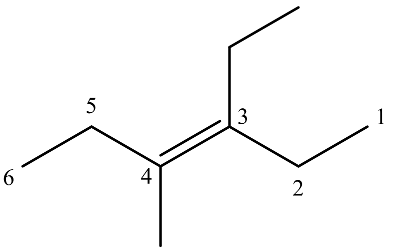
We write the structural formula for each of the following molecules:



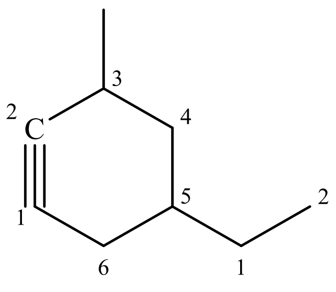
1. 2,6-dimethylhept-3-yne



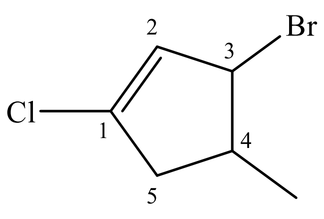
2. 3-methylcyclobutene



3. 4-ethyl-3-methylhex-3-ene



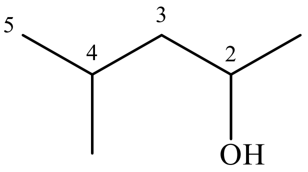
4. 5-ethyl-3-methylcyclohex-1-yne



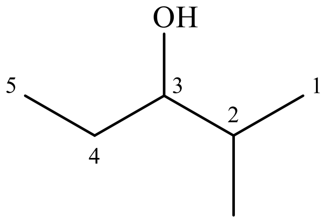
5.1-chloro-3-bromo-4-methylcyclopentene

Exercise 5:

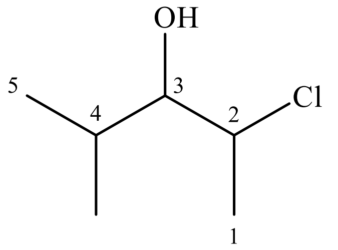
We provide an IUPAC name for each of the following alcohols.



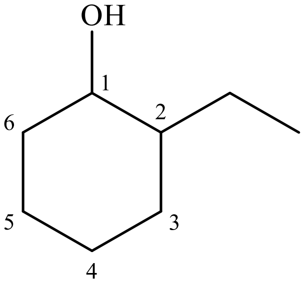
4-methylpentan-2-ol



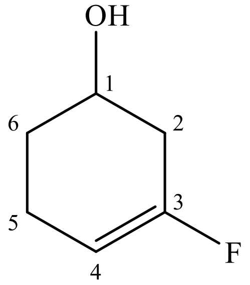
2-methylpentan-3-ol



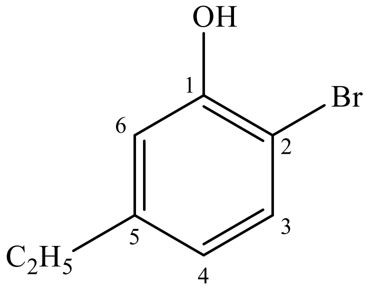
2-chloro-4-methylpentan-3-ol



2-ethylcyclohexan-1-ol



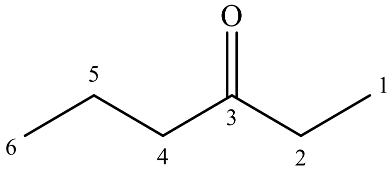
3-fluorocyclohex-3-en-1-ol



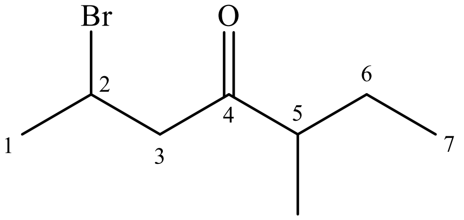
2-bromo-5-ethylphenol

Exercise 6:

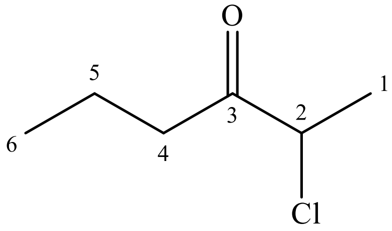
We assign a systematic IUPAC name to each of the following aldehydes and ketones:



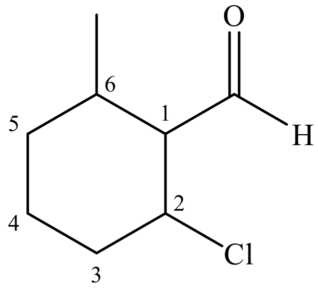
hexan-3-one



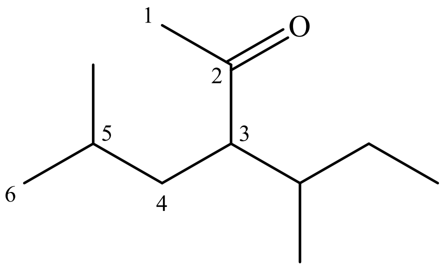
2-bromo-5-methylheptan-4-one



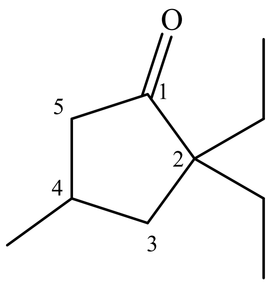
2-chlorohexan-3-one



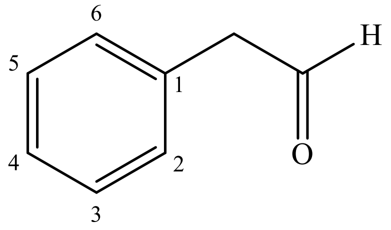
2-chloro-6-methylcyclohexane-1-carbaldehyde



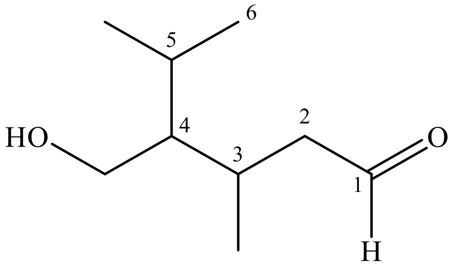
3-(*sec*-butyl)-5-methylhexan-2-one



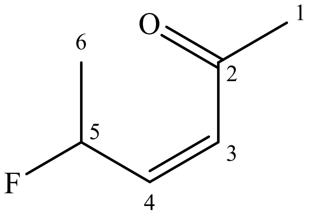
2,2-diethyl-4-methylcyclopentan-1-one



2-phenylacetaldehyde



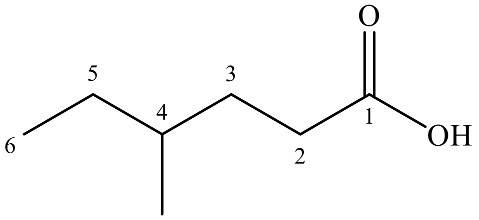
4-(hydroxymethyl)-3,5-dimethylhexanal



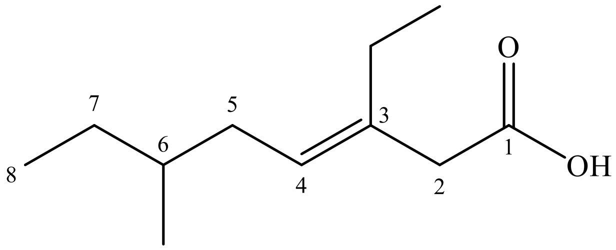
5-fluorohex-3-en-2-one

Exercise 7:

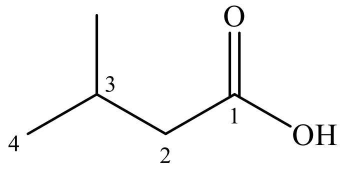
We draw the following carboxylic acids:



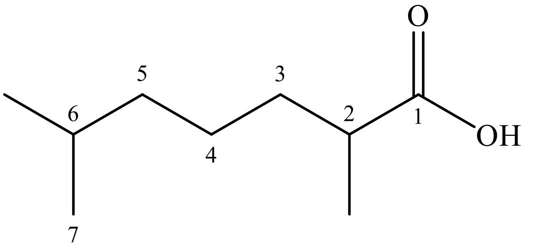
a- 4-methylhexanoic acid



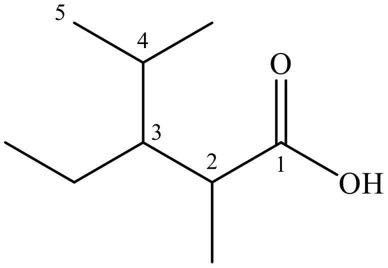
b- 3-ethyl-6-methyloct-3-enoic acid



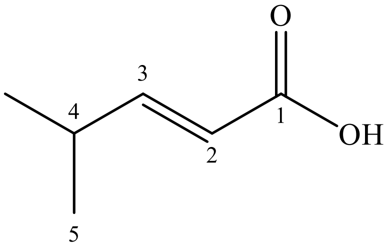
c- 3-methylbutanoic acid



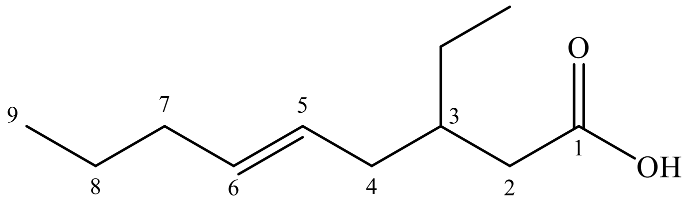
d- 2,6-dimethylheptanoic acid



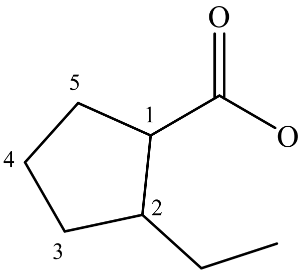
e- 2-methyl-3-isopropylpentanoic acid



f- 4-methylpent-2-enoic acid



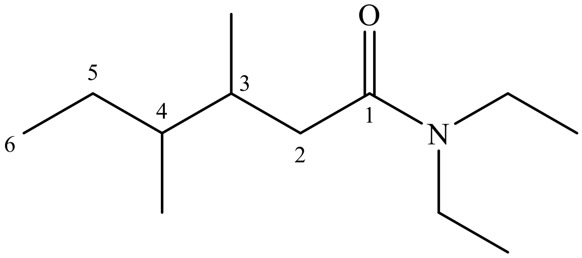
g- 3-ethylnon-5-enoic acid



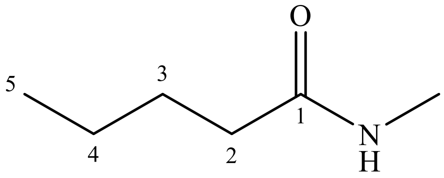
h- 2-ethylcyclopentane-1-carboxylic acid

Exercise 8:

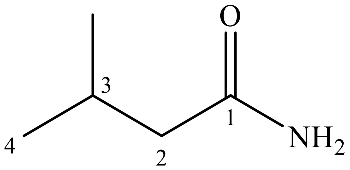
a- We provide the IUPAC name of the following amides.



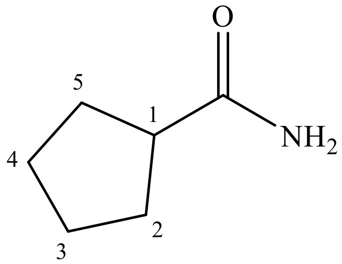
N,*N*-diethyl-3,4-dimethylhexanamide



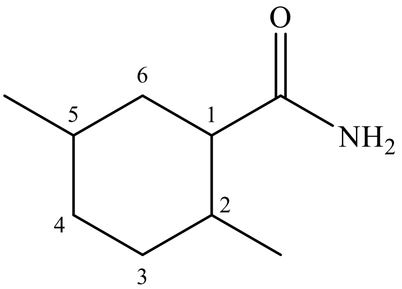
N-methylpentanamide



3-methylbutanamide

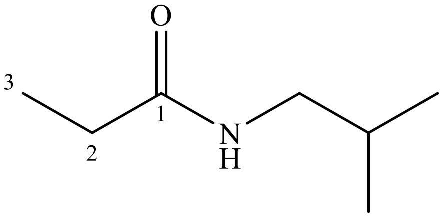


cyclopentanecarboxamide

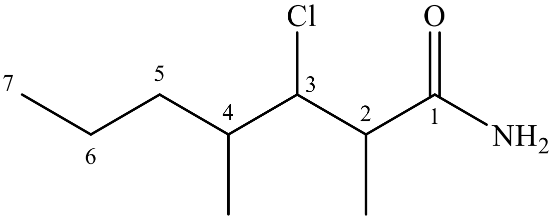


2,5-dimethylcyclohexane-1-carboxamide

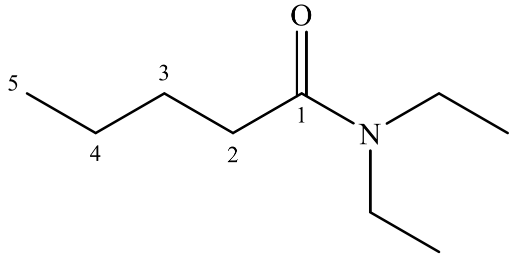
b- We draw the structure of the following amides.



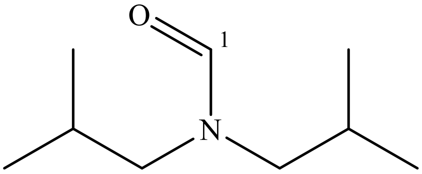
1) *N*-isobutylpropanamide



3) 3-chloro-2,4-dimethylheptanamide



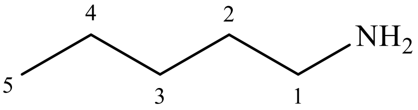
2) *N,N*-diethylpentanamide



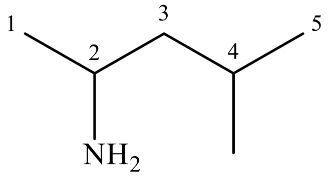
4) *N,N*-diisobutylformamide

Exercise 9:

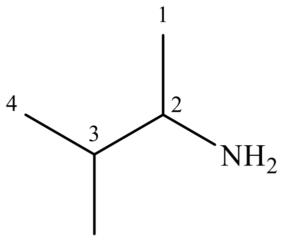
We name using IUPAC the following amine structures.



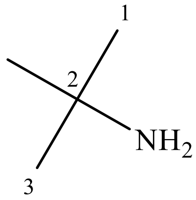
pentan-1-amine



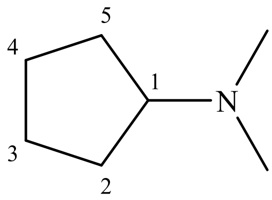
4-methylpentan-2-amine



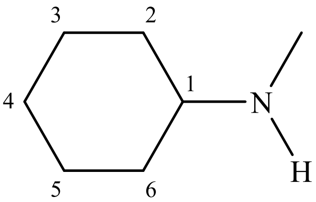
3-methylbutan-2-amine



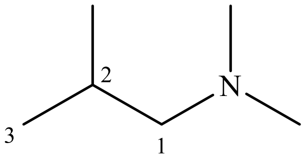
2-methylpropan-2-amine



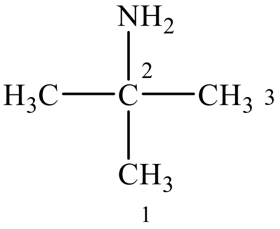
N,*N*-dimethylcyclopentanamine



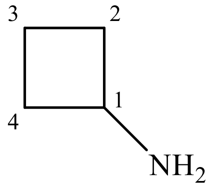
N-methylcyclohexanamine



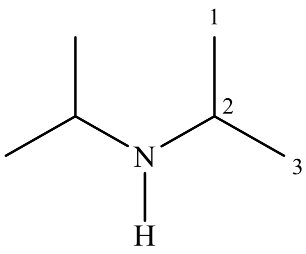
N,*N*,2-trimethylpropan-1-amine



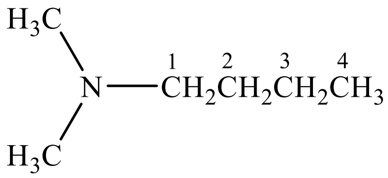
2-methylpropan-2-amine



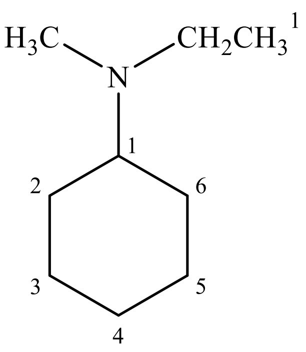
cyclobutanamine



diisopropylamine



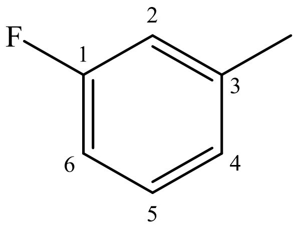
N,*N*-dimethylbutan-1-amine



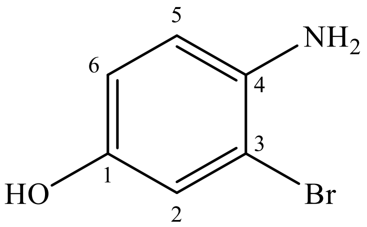
N-ethyl-*N*-methylcyclohexanamine

Exercise 10:

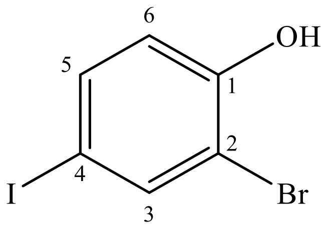
We give the IUPAC name for each of the following aromatic compounds.



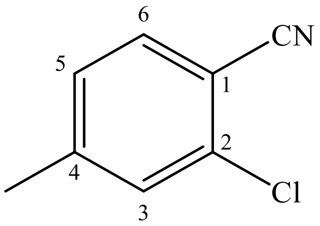
1-fluoro-3-methylbenzene



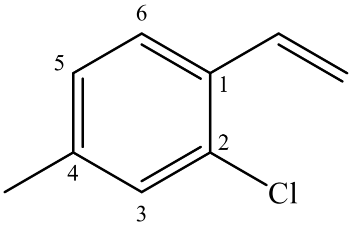
4-amino-3-bromophenol



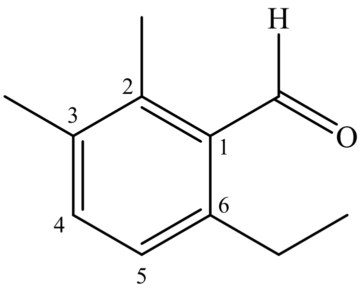
2-bromo-4-iodophenol



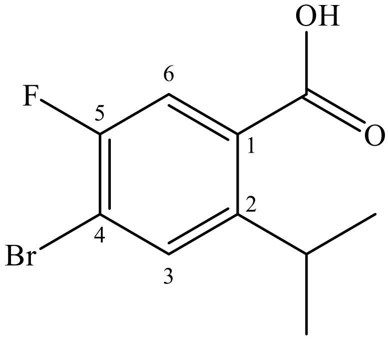
2-chloro-4-methylbenzonitrile



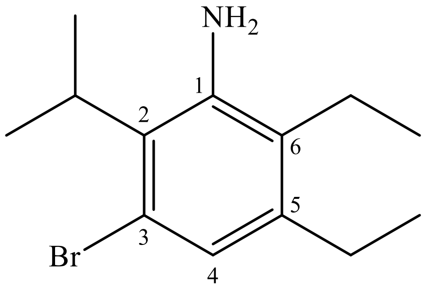
2-chloro-4-methyl-1-vinylbenzene



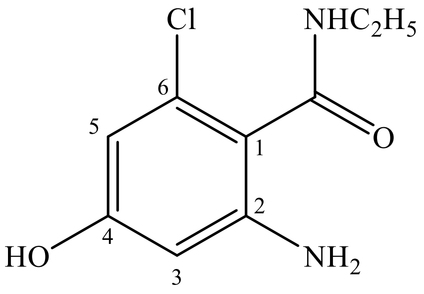
6-ethyl-2,3-dimethylbenzaldehyde



4-bromo-5-fluoro-2-isopropylbenzoic acid



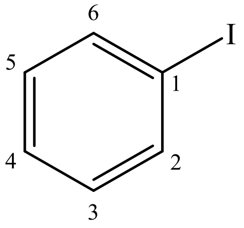
3-bromo-5,6-diethyl-2-isopropylaniline



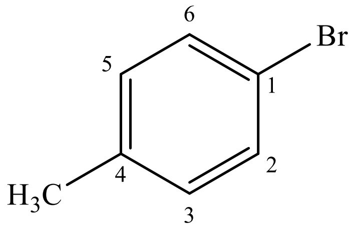
2-amino-6-chloro-*N*-ethyl-4-hydroxybenzamide

Exercise 11:

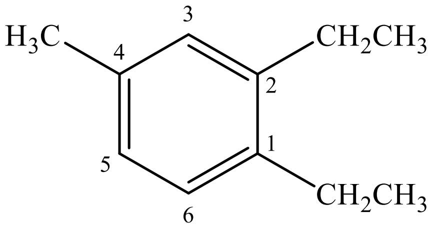
We provide the IUPAC name of the following molecules.



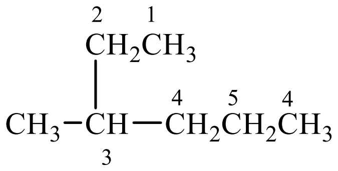
iodobenzene



1-bromo-4-methylbenzene

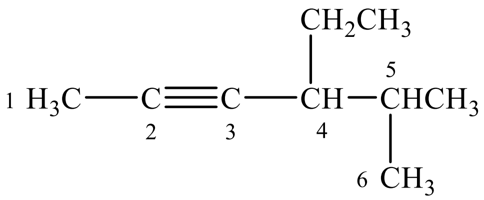


1,2-diethyl-4-methylbenzene



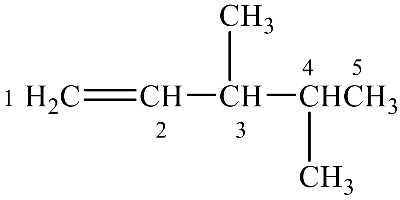
$CH_3-\overset{\overset{CH_2CH_3}{|}}{CH}-CH_2CH_2CH_3$

3-methylhexane



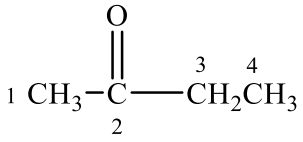
$H_3C-C\equiv C-\overset{\overset{CH_2CH_3}{|}}{CH}-\underset{\underset{CH_3}{|}}{CH}CH_3$

4-ethyl-5-methylhex-2-yne



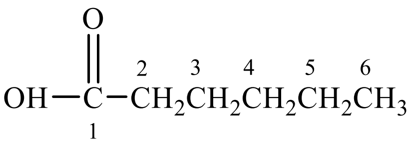
$H_2C=CH-\overset{\overset{CH_3}{|}}{CH}-\underset{\underset{CH_3}{|}}{CH}CH_3$

3,4-dimethylpent-1-ene



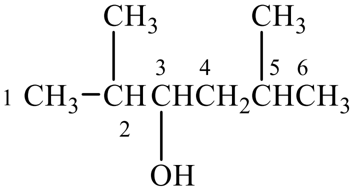
$CH_3-\overset{\overset{O}{\|}}{C}-CH_2CH_3$

butan-2-one



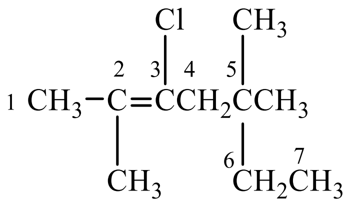
$OH-\overset{\overset{O}{\|}}{C}-CH_2CH_2CH_2CH_2CH_3$

hexanoic acid



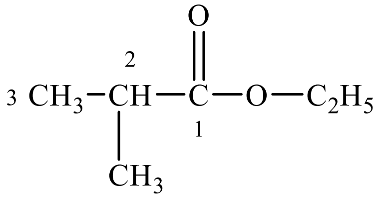
$CH_3-\overset{\overset{CH_3}{|}}{CH}\underset{\underset{OH}{|}}{CH}CH_2\overset{\overset{CH_3}{|}}{CH}CH_3$

2,5-dimethylhexan-3-ol



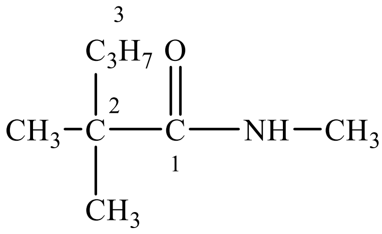
$CH_3-\underset{\underset{CH_3}{|}}{C}=\overset{\overset{Cl}{|}}{C}CH_2\overset{\overset{CH_3}{|}}{\underset{\underset{CH_2CH_3}{|}}{C}}CH_3$

3-chloro-2,5,5-trimethylhept-2-ene



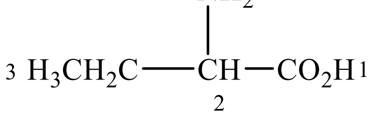
$CH_3-\underset{\underset{CH_3}{|}}{CH}-\overset{\overset{O}{\|}}{C}-O-C_2H_5$

ethyl 2-methylpropanoate



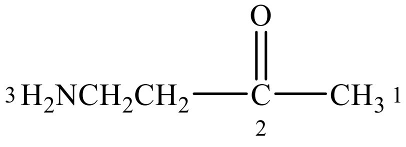
$CH_3-\overset{\overset{C_3H_7}{|}}{\underset{\underset{CH_3}{|}}{C}}-\overset{\overset{O}{\|}}{C}-NH-CH_3$

N,2,2-trimethylpentanamide



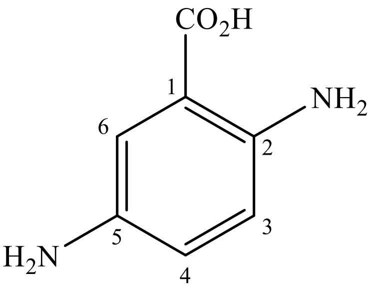
$H_3CH_2C-\overset{\overset{NH_2}{|}}{CH}-CO_2H$

2-aminobutanoic acid



$H_2NCH_2CH_2-\overset{\overset{O}{\|}}{C}-CH_3$

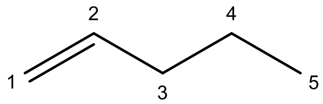
4-aminobutan-2-one



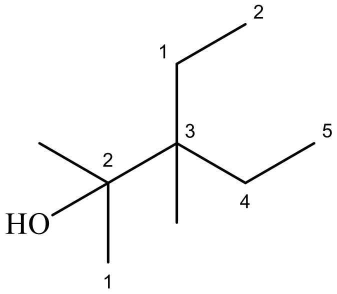
2,5-diaminobenzoic acid

Exercise 12:

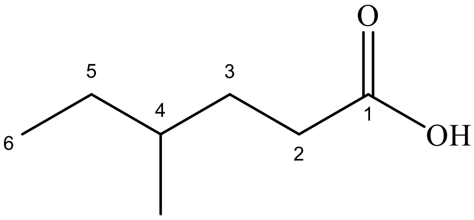
We draw the structural formulas for the following compounds:



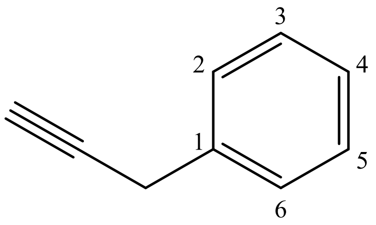
1) pent-1-ene



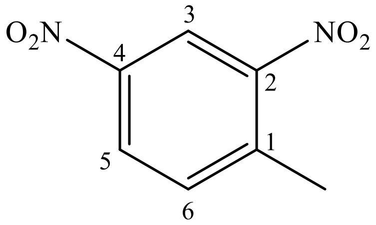
5) 3-ethyl-2,3-dimethylpentan-2-ol



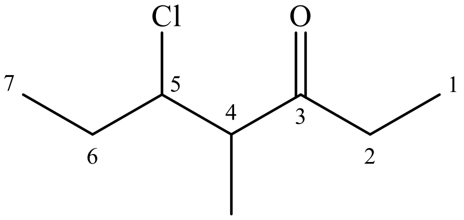
9) 4-methylhexanoic acid



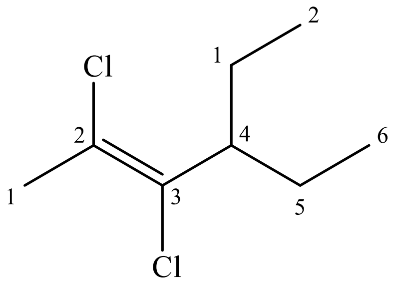
2) prop-2-yn-1-ylbenzene



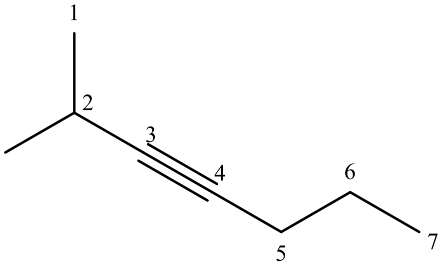
6) 2,4-dinitrotoluene



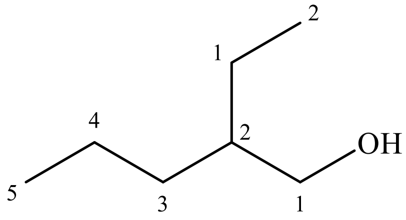
10) 5-chloro-4-methylheptan-3-one



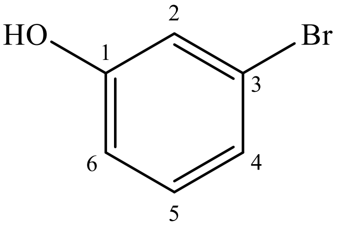
3) 2,3-dichloro-4-ethylhex-2-ene



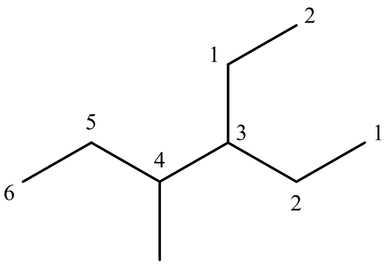
7) 2-methylhept-3-yne



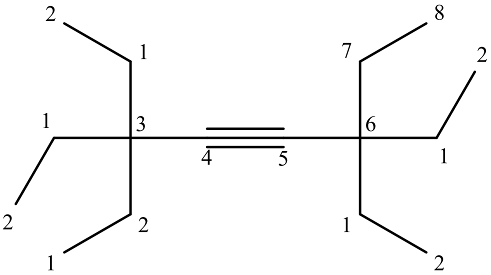
11) 2-ethylpentan-1-ol



4) *m*-bromophenol



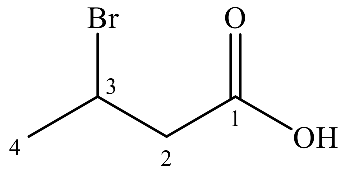
8) 3-ethyl-4,5-dimethylpentane



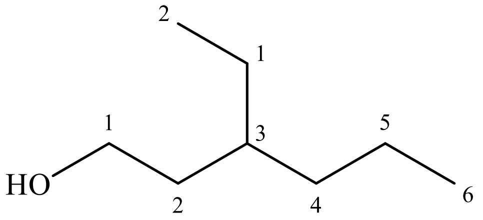
12) 3,3,6,6-tetraethyloct-4-yne

Exercise 13:

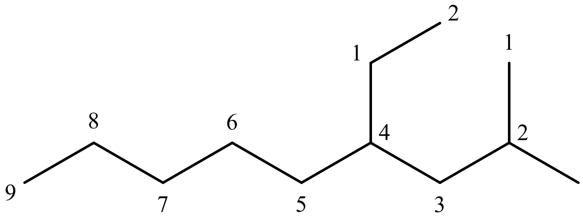
We give the structure of the following molecules:



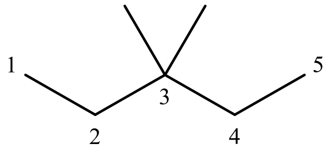
1) 3-bromobutanoic acid



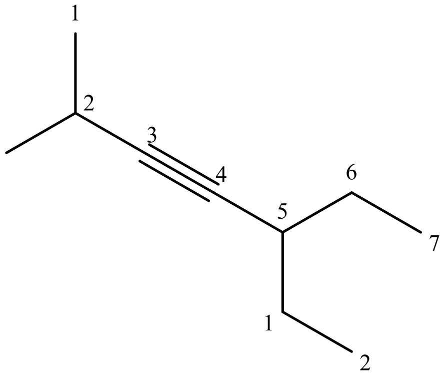
2) 3-ethylhexan-1-ol



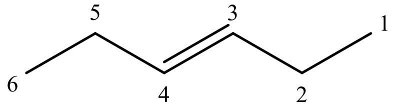
3) 4-ethyl-2-methylnonane



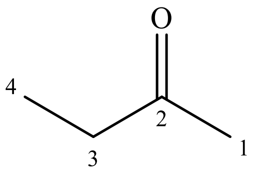
4) 3,3-dimethylpentane



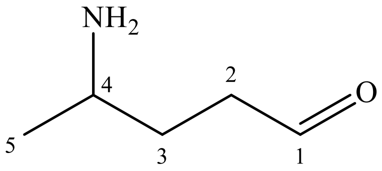
5) 5-ethyl-2-methylhept-3-yne



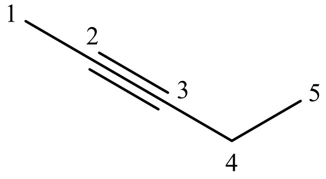
6) hex-3-ene



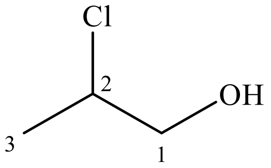
8) butan-2-one



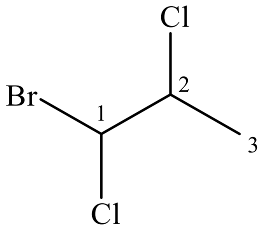
9) 4-aminopentanal



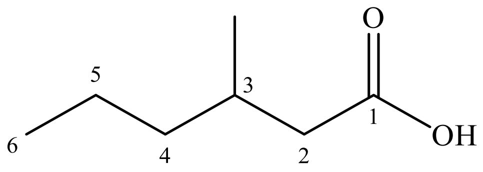
10) pent-2-yne



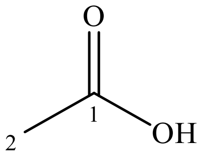
11) 2-chloropropan-1-ol



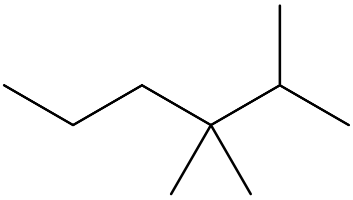
12) 1-bromo-1,2-dichloropropane



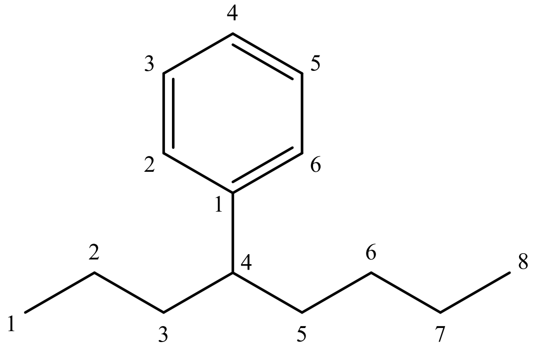
13) 3-methylhexanoic acid



7) ethanoic acid



14) 2,3,3-trimethylhexane



15) octan-4-ylbenzene

Chapter II : Stereochemistry

Introduction

Stereochemistry specifies more specifically the spatial arrangement of atoms in molecules. It is a three-dimensional study of the arrangements in space of the atoms of a given structure (well-defined constitution).

The number of atoms known at present is relatively small compared to the molecules that already exist and others that have been synthesized. This means that for the same given empirical formula, several molecules can be given and presented. In order to differentiate them well, we use their representation in space. Hence the birth of what is called stereochemistry, which aims to study the properties dependent on the geometry of molecules. This discipline gives a broad spatial description of molecules based on the notions of conformation and configuration while specifying the arrangement of atoms in space and how this can vary over time. Conformational analysis, based on the study of the degrees of freedom of the different possible movements, seeks to know the degree of flexibility in order to find the most stable forms with a lower energy. Configuration analysis, which requires a significant energy barrier to pass from one configuration to another, allows us to distinguish the structures of stereoisomers and also to establish enantiomerism and diastereoisomerism relationships. Hence, isomerism plays an important role in organic chemistry, pharmaceuticals, and biochemistry because different isomers can show different reactivity, boiling points, and biological effects.

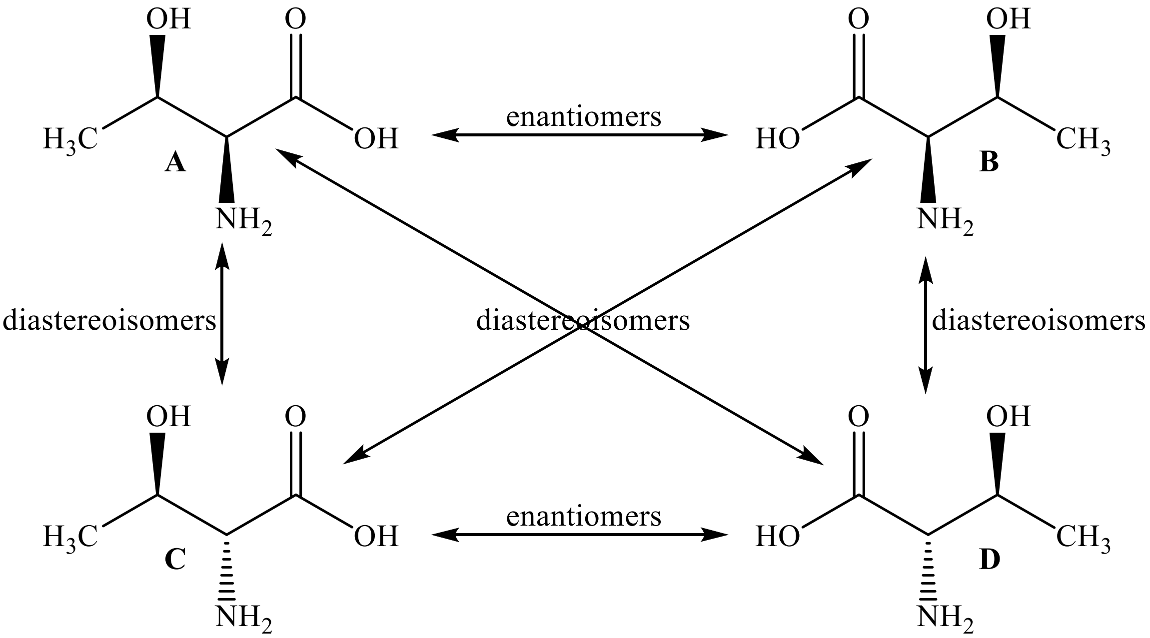
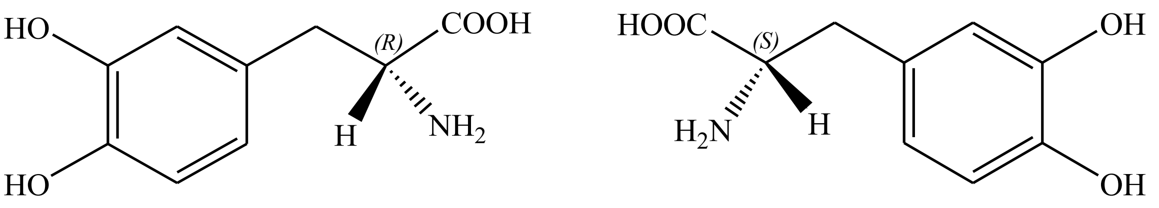


Figure 1: Enantiomerism and diastereoisomerism.

Optical activity is also covered in this chapter. For example, the DOPA molecule has a chiral center. Consequently, two optical isomers are possible: the (*R*)-DOPA form and the (*S*)-DOPA form.



D-DOPA (Inactive) **L-DOPA** (Active)

Figure 2: Chemical structure of the two enantiomer forms of DOPA.

The two optical isomers (*R*) and (*S*) of DOPA have different biological effects. The (*S*) isomer is of great interest in medicine because it is pharmacologically active and is used for the treatment of Parkinson's disease. On the other hand, the (*R*) configuration has no biological effect and is therefore inactive.

In this chapter, course reminders dealing mainly with stereochemistry were discussed in detail.

The different types of isomerism are summarized and given in the following Figure 3.

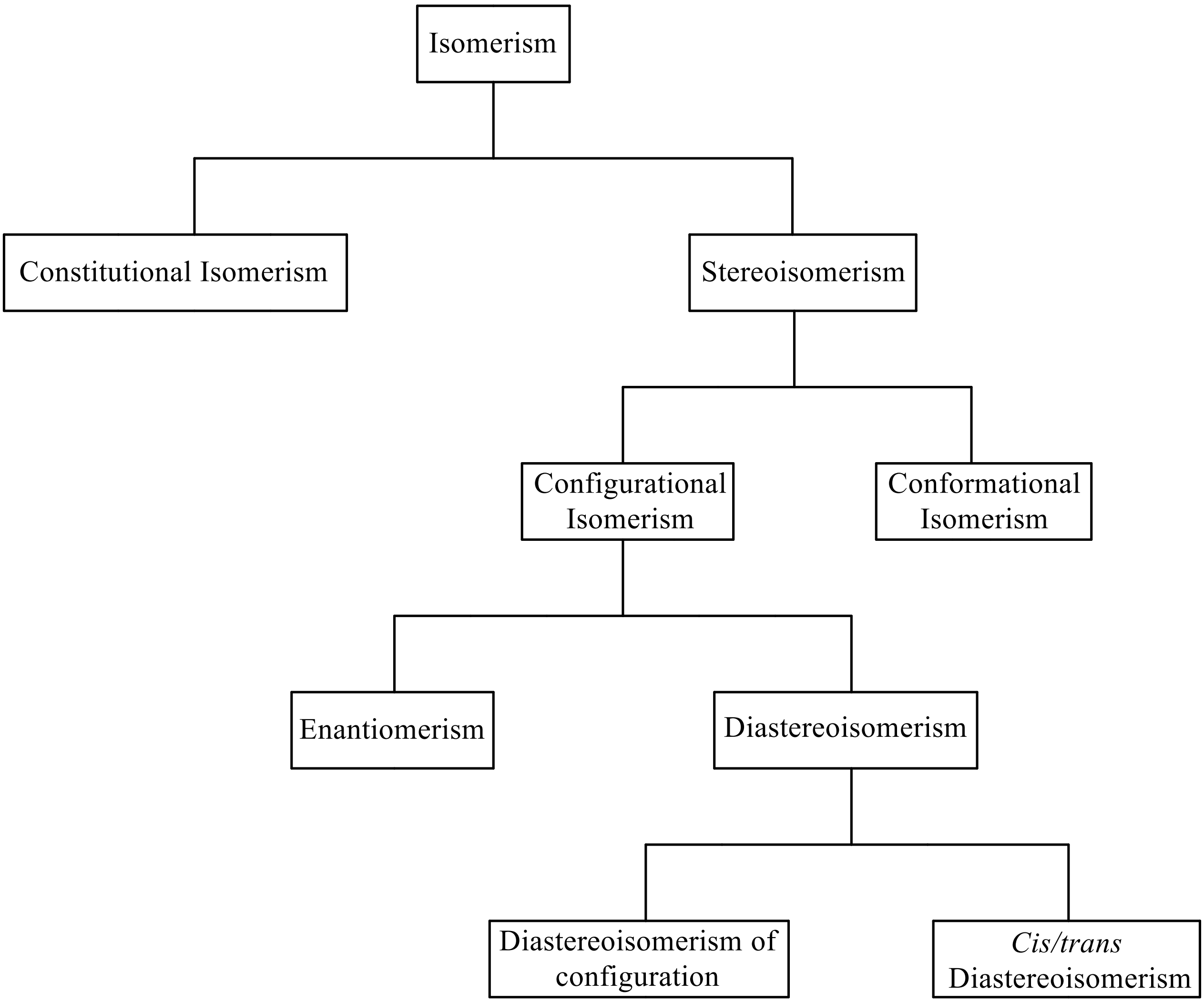


Figure 3: Types of isomerism.

1. Isomerism

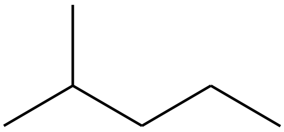
Molecules which have the same molecular formula but of different developed structures (order & nature of connection, arrangement).

There are two main types of isomerism: constitutional isomerism and stereoisomerism.

1.1 Constitutional isomerism

Atoms are connected in different ways, thus giving different molecules within the same molecular formula.

Example:



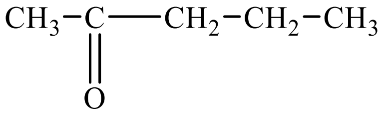
Within the notion of constitutional isomerism, three types can be distinguished.

1.1.1 Skeletal or chain isomerism

The compounds differ by the carbon chain arrangement.

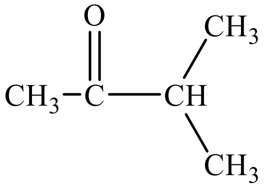
Examples:

a)



$CH_3-\underset{\underset{O}{\|}}{C}-CH_2-CH_2-CH_3$

pentan-2-one

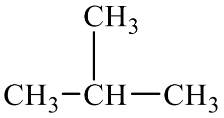


$CH_3-\overset{\overset{O}{\|}}{C}-CH(CH_3)_2$

3-methylbutan-2-one

b) $CH_3-CH_2-CH_2-CH_3$

butane



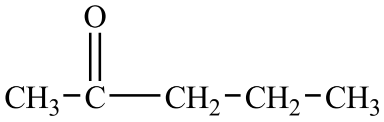
$CH_3-\overset{\overset{CH_3}{|}}{CH}-CH_3$

2-methylpropane

1.1.2 Position isomerism

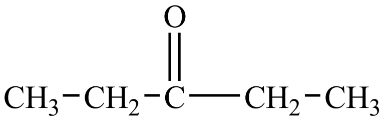
The compounds differ by the position of the functional group.

Examples:



$CH_3-\overset{\overset{O}{\|}}{C}-CH_2-CH_2-CH_3$

pentan-2-one



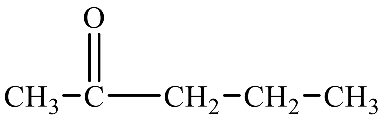
$CH_3-CH_2-\overset{\overset{O}{\|}}{C}-CH_2-CH_3$

pentan-3-one

1.1.3 Functional group isomerism

The compounds differ by the nature of the functional group.

Examples:


$CH_3-\overset{\overset{O}{\|}}{C}-CH_2-CH_2-CH_3$

pentan-2-one

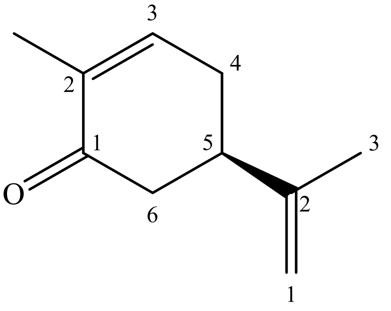
$CH_2{=}CH-CH_2-CH_2-CH_2-OH$

pent-4-en-1-ol

1.2 Stereoisomerism

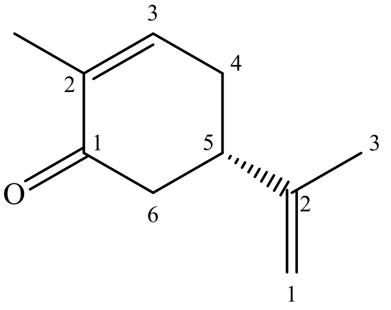
Atoms are connected identically, but their geometries (spatial representations) are different. Isomers that differ only in the spatial orientation of their component atoms are called stereoisomers. In order to indicate their spatial orientation, stereoisomers always require that an additional nomenclature prefix be added to the IUPAC name.

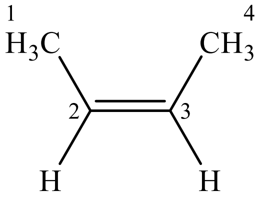
Example:



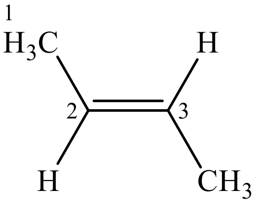
(*R*)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one

(*S*)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one





(*Z*)-but-2-ene



(*E*)-but-2-ene

2. Degree of unsaturation

The degree (number) of unsaturation corresponds to the number of π bonds and cycles present in a molecule.

To do this, you just need to know the crude formula of the compound.

$$N_i = (2n_C + 2 - n_H + n_N - n_X)/2$$

N_i is the degree of unsaturations or cycles.

Where:

n_C : The number of carbon atoms

n_H : The number of hydrogen atoms

n_N : The number of nitrogen atoms

n_X : The number of halogen atoms

Notice, here, that the number of oxygen atoms does not fit into taken into account in the calculation.

Examples:

1- C_5H_{12} :

$N_i = (2n_C + 2 - n_H + n_N - n_X)/2 = (2x5 + 2 - 12)/2 = 0$ unsaturation, thus the molecule is saturated.

2- C_5H_{10} :

$N_i = (2n_C + 2 - n_H + n_N - n_X)/2 = (2x5 + 2 - 10)/2 = 1$ unsaturation, we say this compound possesses a double bond or a cycle.

3- $C_6H_9BrO_2$:

$N_i = (2n_C + 2 - n_H + n_N - n_X)/2 = (2x6 + 2 - 9 - 1)/2 = 2$ unsaturations, so, we can set three possibilities:

- two double bonds or a triple bond
- a double bond + a cycle
- or two cycles

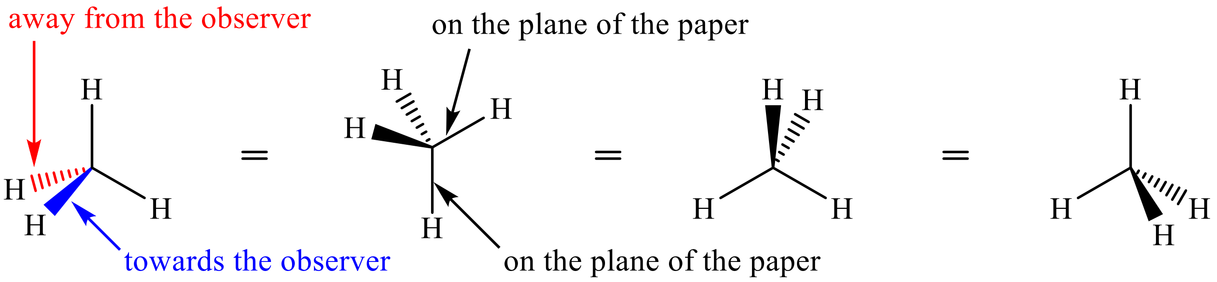
3. Representation of organic molecules

3.1 Wedge and dash representation (*Cram*)

The *wedge and dash* representation, also known as *Cram* representation in French, allows to visualize organic molecules in space.

- The connections or bonds on the paper plane are represented with full lines ——
- Connections forward are represented with a wedge (a full elongated triangle) ◀
- Backward connections are represented with dash lines (a dashed elongated triangle) ||||||||

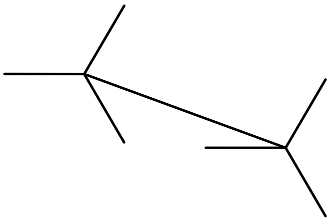
Example: Methane: CH_4

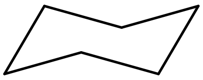


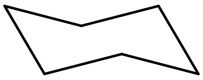
3.2 Sawhorse representation

In the sawhorse projection, bonds are represented by lines that represent the perspective of the molecule. The line of observation makes an angle of 45° with the carbon-carbon bond. The carbon closest to the observer is below and to the right, however, the farthest one is on the top left. This type of representation is also known as projection in perspective and it is used to represent cyclic molecules too, especially cyclohexane and its derivatives.

Example:



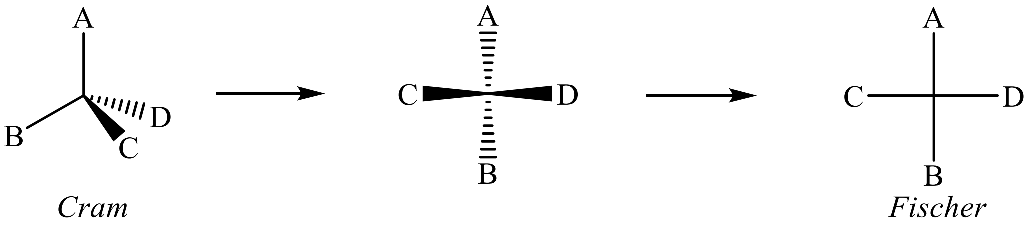




3.3 *Fischer* projection

The *Fischer* projection is a planar representation of a three-dimensional organic molecule.

Example:



The vertical lines represent the connections behind the plane of the figure.

The horizontal lines represent the connections in front of the plane of the figure.

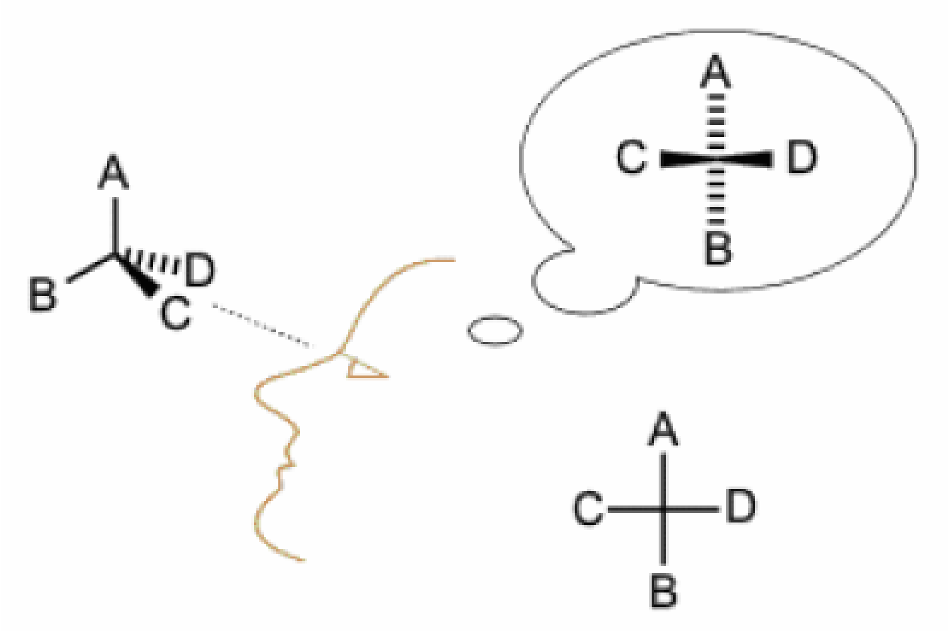


Figure 4: Passage from *Cram* to *Fischer*.

The longest carbon chain is placed vertically and numbered from top to bottom.

The functional group with the lowest index (most often associated with the most oxidized carbon) is placed at the top.

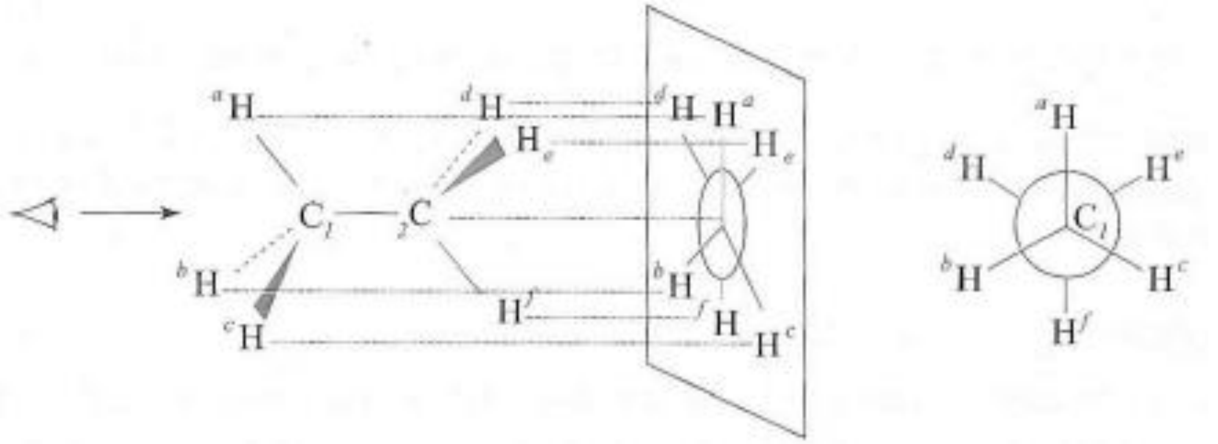
3.4 *Newman* projection

The Newman projection is used to show the relative arrangement of bonds formed by two adjacent carbon atoms.

The molecule is viewed along the axis of the bond studied. Then, it is projected into the plane of the paper (blackboard). The atom in front represented by a point, the one behind is masked by the one in front and is represented by a circle.

Example:

Ethane molecule (C_2H_6)



4. Stereoisomerism

4.1 Conformational stereoisomerism

4.1.1 Definition

Structures that differ only by rotation around a single bond are called conformations of the molecule (or conformers). In other words, the variable spatial orientation of the atoms of a molecule to each other that occurs by rotation or twisting of bonds. Different conformations are interconverted without breaking covalent bonds.

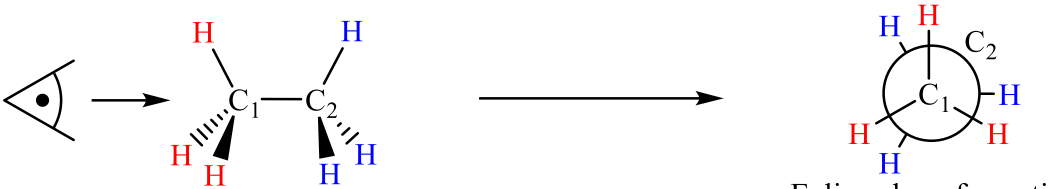
4.1.2 Conformational analysis

The study of the energy changes that occur during the rotations about σ bonds $i.e.$ the study of the equilibrium between the different conformations of the same molecule. The energy barrier to cross to move from one conformation to another is low, which explains why the molecules rotate freely around the $C-C$ bond.

4.1.3 Straight-chain hydrocarbons

Example: Conformations of ethane

Staggered conformation



Eclipsed conformation

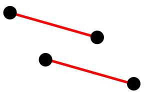
In the eclipsed form, the dihedral angle is 0°, while in the staggered form, the dihedral angle is 180°. In ethane molecule, the difference in energy between the eclipsed and staggered form is 12 kJ/mol. This small barrier to rotation is commonly called torsional barrier. The conformers keeps on changing from one form to another.

Of all conformations of ethane, staggered form has the least torsional strain and the eclipsed form has the highest torsional strain. Hence, eclipsed form of ethane is the least stable conformation (maximum potential energy) and staggered form of ethane is the most stable conformation (minimum potential energy).

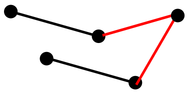
4.1.4 Cycloalkanes: Cyclohexane

First, it is necessary to know how to draw cyclohexane.

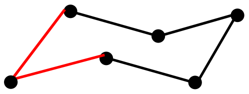
Step 1: draw two parallel lines, slanted downward and slightly off-set from each other. This means that four of the cyclohexane carbons lie in a plane.



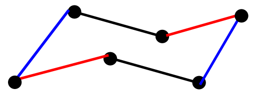
Step 2: place the topmost carbon atom above and the right of the plane of the other four, and connect the bonds.



Step 3: place the bottommost carbon atom below and to the left of the plane of the middle four, and connect the bonds.

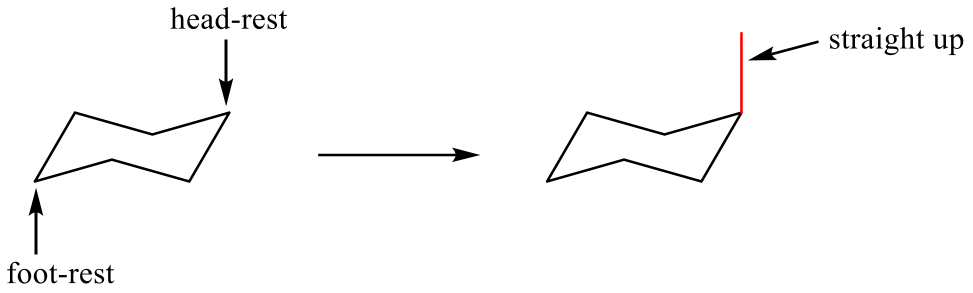


Note that the bonds to the bottommost carbon atom are parallel to the bonds to the topmost carbon.

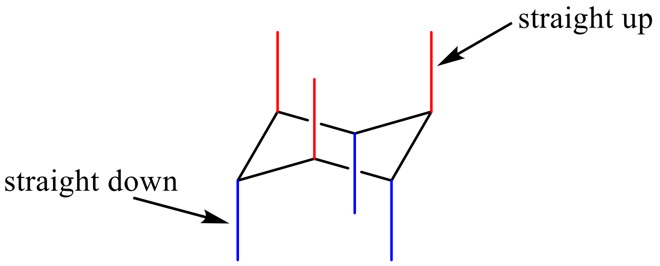


Now, in order to draw in the corresponding substituents:

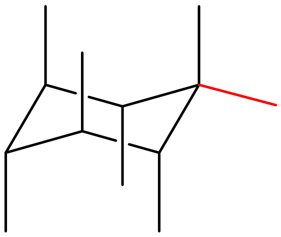
1/ start by drawing a line pointing straight up from the head-rest of the chair



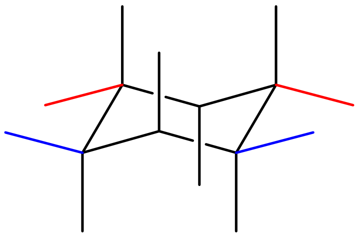
2/ fill in the rest of the axial groups by alternating straight up and down



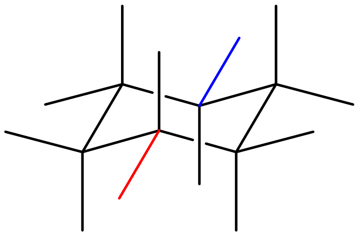
3/draw a line going down about 15° from the head-rest



4/alternate drawing lines going up 15° and down 15° on the two sides

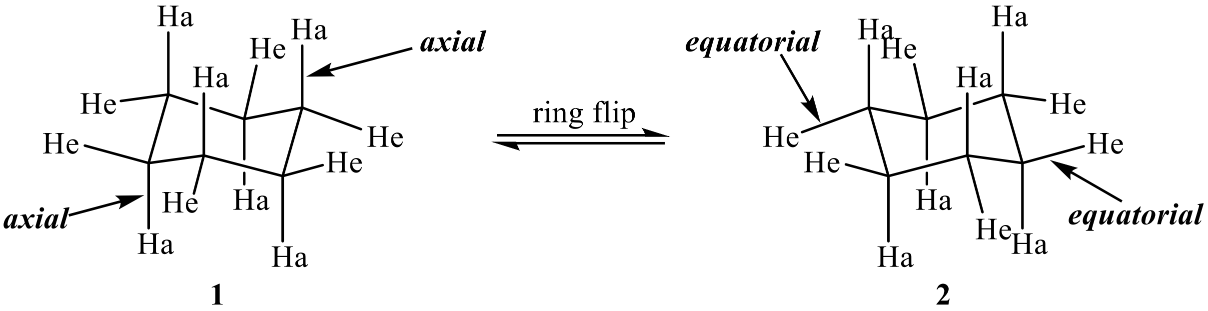


5/ the middle two bonds are at 60° again (parallel to sides)



There are two preferred conformations for cyclohexane: the chair conformation and the boat conformation.

a. The chair conformation



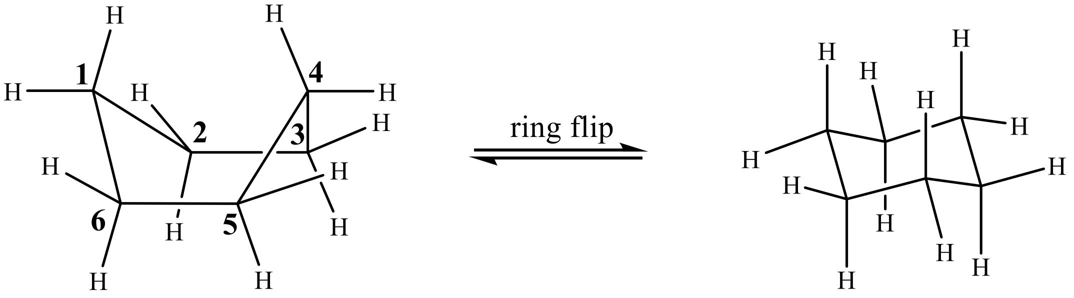
In the chair conformation there are two types of $C-H$ bonds:

--- 6 bonds perpendicular to the average plane of the cycle are called axial.

--- 6 bonds which extend laterally outside the cycle, are called equatorial.

There is an interchange between the two chair conformers **1** and **2** passing through the boat conformer. During this interchange, all axial groups become equatorial and all equatorial groups become axial.

b. The boat conformation



boat conformer *chair conformer*

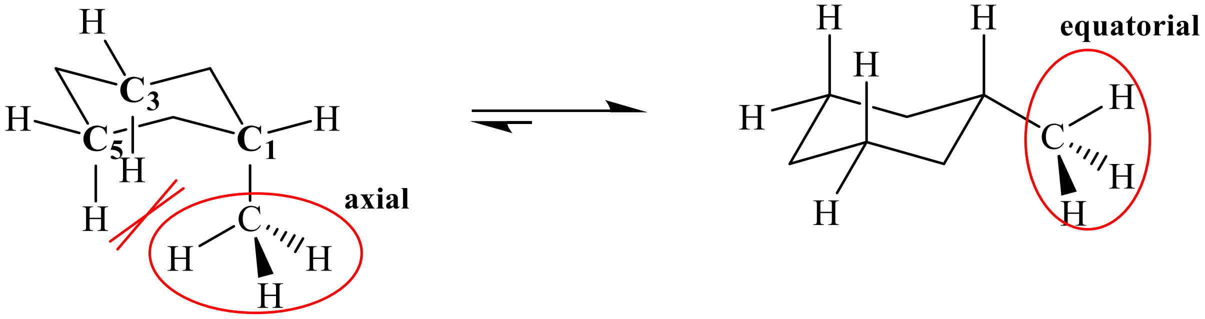
In the sawhorse representation, the four carbon atoms C_2, C_3, C_5 and C_6 are in the same plane.

The other two are below and above this plane for the chair conformation and above this plane for the boat conformation.

The chair conformation is staggered, while the boat conformation is eclipsed. Thus, the chair conformation is the most stable one.

4.1.5 1,3-Diaxial interaction

The "methyl" substituent in the axial position interferes with the axial hydrogens in positions 3 (C_3) and 5 (C_5).



1,3-diaxial interaction

more stable with 7.1 kJ/mol (1.7 kcal/mol)

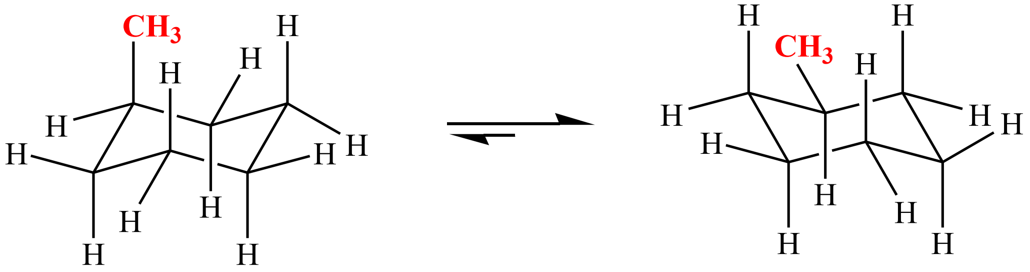
This interference is called: 1,3-diaxial interaction.

Note that the larger the substituent, the greater the 1,3-diaxial interaction (steric hindrance).

4.1.5.1 Monosubstituted cyclohexane

Example 01: methylcyclohexane

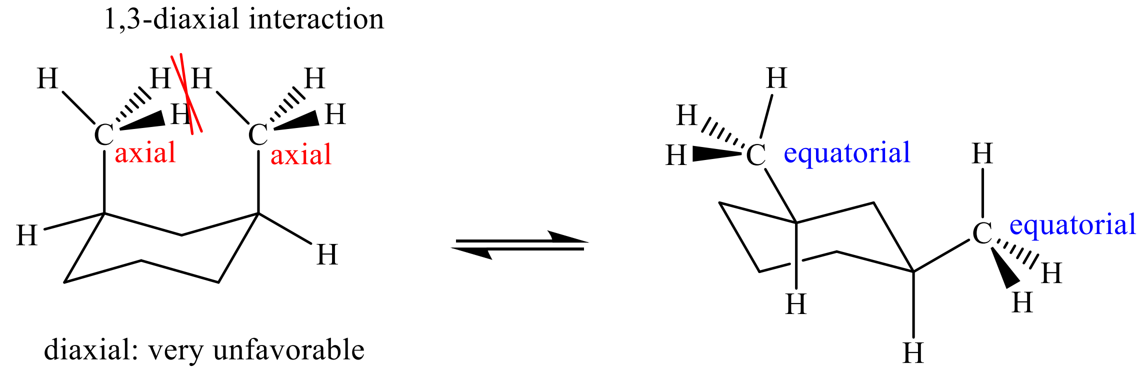
Methyl can be placed in an axial or equatorial position.



4.1.5.2 Disubstituted cyclohexane

Example 01: *Cis*-1,3-dimethylcyclohexane

Cis-1,3-dimethylcyclohexane can have both methyls in the axial position or both in the equatorial position.

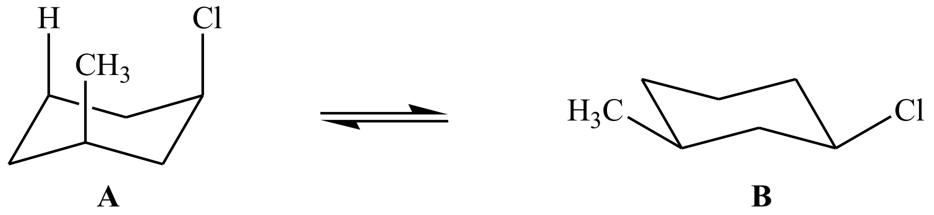


diaxial: very unfavorable because of the important repulsion

diequatorial: very stable

In fact, the conformer with the two methyls in the equatorial position is more stable.

Example 02: 1-chloro-3-methylcyclohexane



Conformer **A** holds three possible 1,3-diaxial interactions; Me/H, Cl/H, and Me/Cl. On the other hand, the **B** conformer does not have any 1,3-diaxial interaction.

Thus, the conformer **B** with methyl and chloride groups in equatorial positions is more stable than **A** with an energy difference of 3.7 kcal/mol.

5. Configuration stereoisomerism (geometrical and optical isomerism)

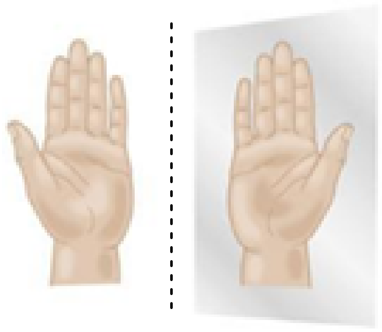
5.1 Configuration

The permanent spatial relationship of the atoms of a molecule to each other. Different configurations are interconverted only by breaking and reforming covalent bonds. This information is given in a stereo-formula, and is also provided by a prefix to the IUPAC name (eg. *cis* & *trans*).

5.2 Chirality

Chirality (from the Greek “χειρ” which means the hand) is the non-superposition of the object and its image in relation to a plane mirror.

Example: left hand and right hand.



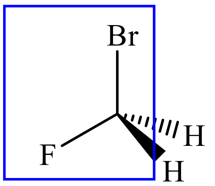
left hand right hand

In other words, the molecule is chiral if it…

- has neither center nor plane of symmetry.
- contains a stereocenter.

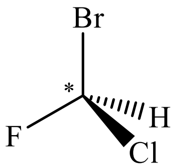
A plane of symmetry is an imaginary plane passing through an object dividing it into two parts such that one half is the mirror image of the other half.

Example:



Plane of symmetry

1-bromo-1-fluoromethane



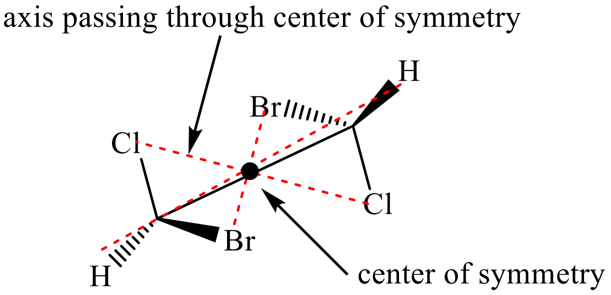
No plane of symmetry

bromochlorofluoromethane

In this example, in the molecule of 1-bromo-1-fluoromethane, the plane of symmetry (in blue) passes by the bromine and fluorine and thus divide the molecule into two parts where the hydrogen is on one side and the second hydrogen is on the other side. However, for the bromochlorofluoromethane there is no way to find a plane of symmetry.

A center of symmetry is a point situated in the center of the object (molecule) that identical components of the object are located equidistant from the point along any axis passing through the point.

Example:

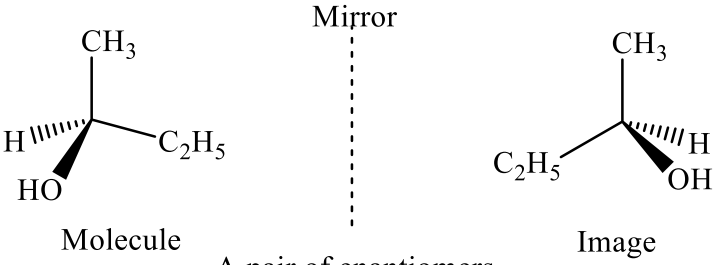


5.3 Enantiomerism

Enantiomers are two chemically identical molecular species that are made up of the same atoms which are bonded to each other identically but differ from each other as they are not superposable on their mirror images.

The molecule and its image form a pair of enantiomers (or optical or even inverse optical isomers).

Example:



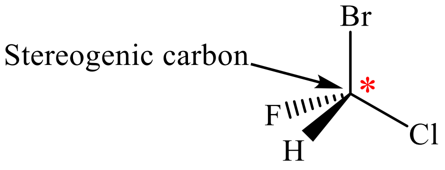
A pair of enantiomers

5.4 Stereocenter

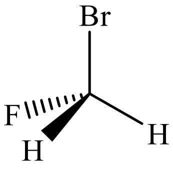
For the molecule to be chiral, it must have an asymmetric carbon or stereocenter.

An asymmetric or stereocenter carbon is an sp^3 carbon which has four different substituents and no plane of symmetry. It is noted as C^*.

Example:



Chiral molecule



Achiral molecule

Examples of carbons that are not stereocenters: CH_2, CH_3, $C = C$, $C \equiv C$, and $C = O$.

5.5 Chirality types

In a chiral molecule, the spatial arrangement of the four substituents of the asymmetric carbon C^* is called absolute configuration.

5.5.1 Molecules with one chiral carbon

To distinguish the two enantiomers of a chiral compound, we determine the absolute configuration of the C^* of each enantiomer. This determination is made according to the following procedure:

1°) we classify the four substituents of C^* in order of decreasing priority according to the *C.I.P* rules $(1 > 2 > 3 > 4)$.

2°) we look at the C^* along the axis opposite to the 4th ranked substituent.

3°) if when going from the 1st substituent to the 2nd substituent then to the 3rd, the direction of rotation is clockwise, then the configuration is *R* (Rectus: right).

If the direction is in the opposite way $i.e.$ counterclockwise, then it is *S* (Sinister: left).

4°) Cahn-Ingold-Prelog (*C.I.P*) sequence rules as given below:

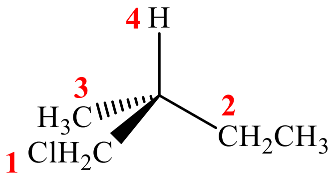
Rule 1:

The priority of atoms decreases when the atomic number decreases (Z increases, then the priority increases as well).

$$Cl > O > N > C > H \quad \text{and} \quad {}^{3}_{1}H > {}^{2}_{1}H > {}^{1}_{1}H$$

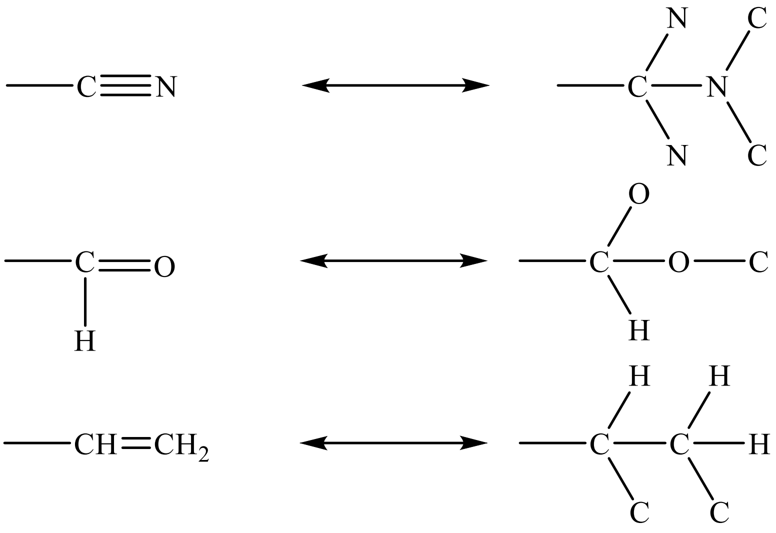
Rule 2:

In the case of equality (identical atoms) in the first rank 1, rule 1 is applied with the atoms of rank 2.



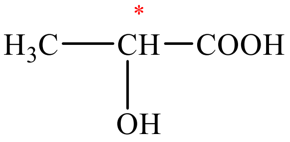
Rule 3:

A multiple bond is equivalent to several single bonds between two atoms (duplication rule).



Example:

2-hydroxypropanoic acid

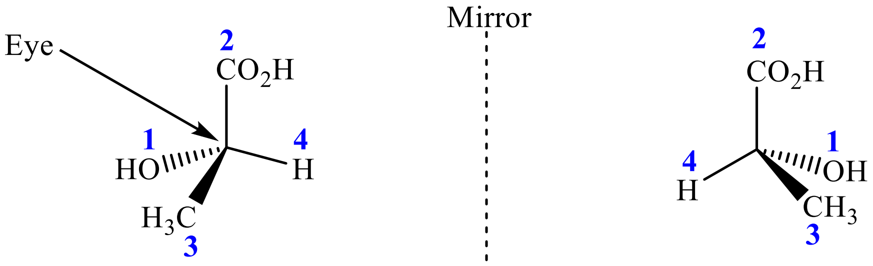


$$H_3C-\overset{*}{C}H(OH)-COOH$$

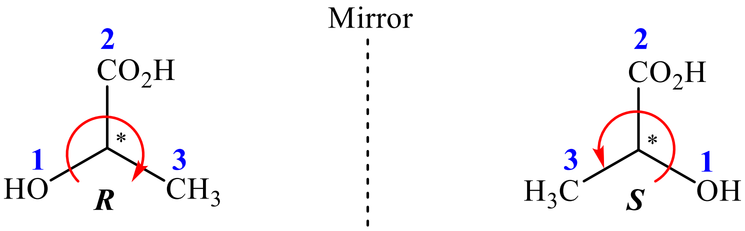
1C^* → two enantiomers

According to *C.I.P*: $OH > CO_2H > CH_3 > H$

Representation of the two enantiomers according to *Cram* is given as:



And the corresponding absolute configurations are:



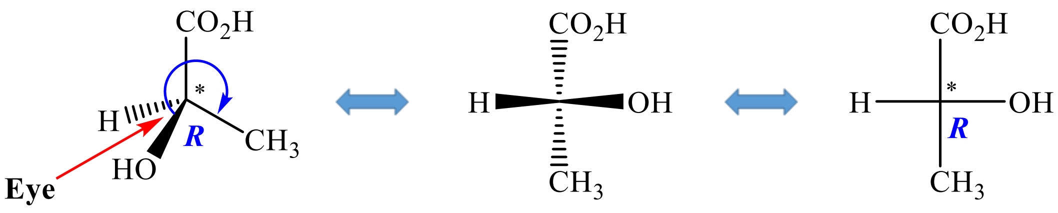
Note:

It is possible to determine the absolute configuration on the *Fischer* projection following the steps:

If the substituent 4 is placed vertically we read directly the sequence 1 → 2 → 3 (towards the right it is *R*, towards the left it is *S*).

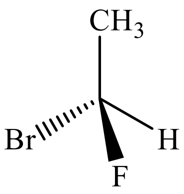
If the substituent 4 is on the horizontal we look at the direction 1 → 2 → 3 then we reverse this direction to find either *R* or *S*.

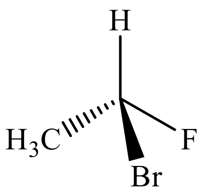
Example: Passage from *Cram* to *Fischer*



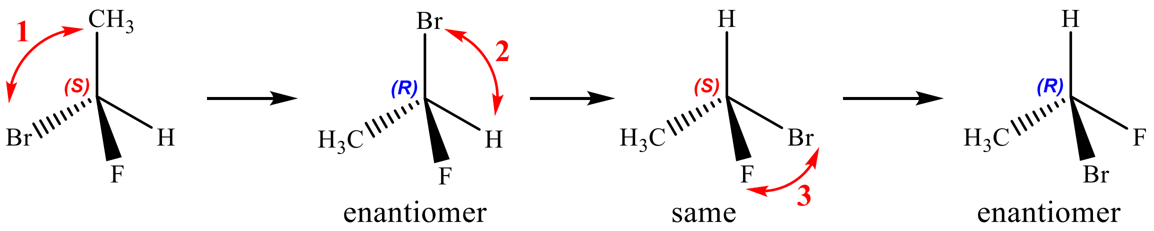
A question might be raised about whether two molecules are identical (meaning the same) or enantiomer. In order to answer this question, interchanges method can be used.

Example: Are the following two molecules identical or enantiomer?





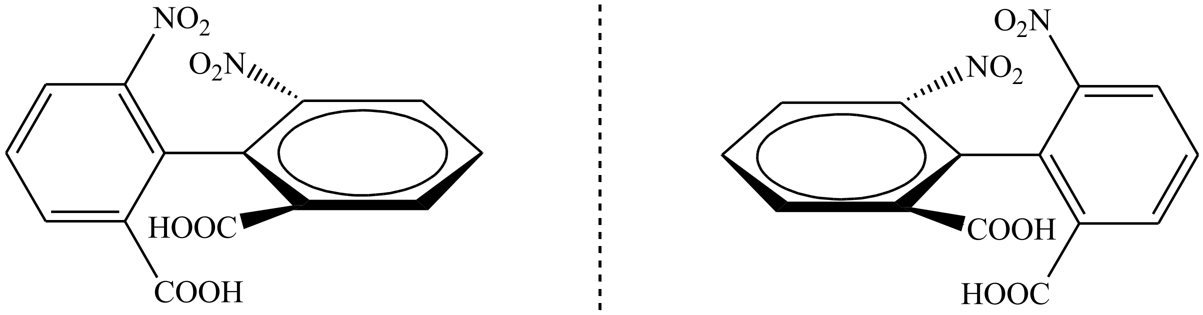
Let's use the interchange method!

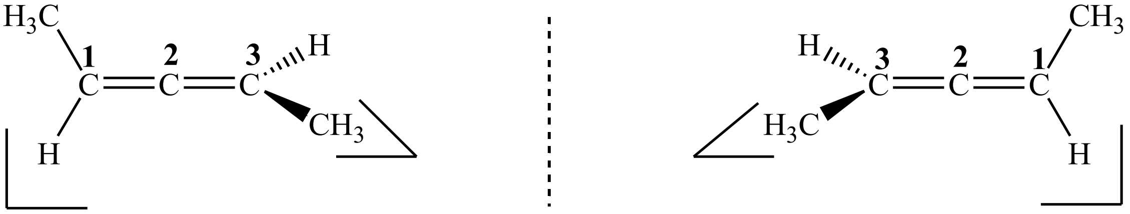


So, it can be said that if the number of interchange operations is odd $i.e.$ 1, 3, 5, $etc.$ the corresponding molecule is enantiomer. However, if the number of interchange operations is even $i.e.$ 2, 4, 6, $etc.$ the corresponding molecule is the same or the original molecule.

On the other hand, some molecules can be chiral, without having an asymmetric carbon.

Examples:





In conclusion, chirality is a global property of the molecule; we should not focus on the presence or absence of asymmetric carbon, even if the presence of the latter very often makes the molecule chiral.

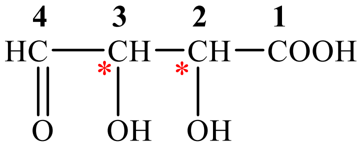
5.5.2 Molecules with more than one chiral carbon

Diastereomerism is due to the presence of two (or more) C^* in a molecule. Such molecules are common in nature and particularly in natural compounds: sugars, amino acids, *etc*.

If the molecule contains n asymmetric carbons, the maximum number of possible stereoisomers is 2^n.

A molecule containing more than one asymmetric carbon is not necessarily chiral. For a given structure, there is only one mirror image molecule; other possible structures are diastereoisomers or also known as diastereomers.

Example:



$$\overset{4}{\underset{\underset{\displaystyle O}{\|}}{\mathrm{HC}}}-\overset{3}{\underset{\underset{\displaystyle OH}{|}}{\overset{*}{\mathrm{C}}\mathrm{H}}}-\overset{2}{\underset{\underset{\displaystyle OH}{|}}{\overset{*}{\mathrm{C}}\mathrm{H}}}-\overset{1}{\mathrm{COOH}}$$

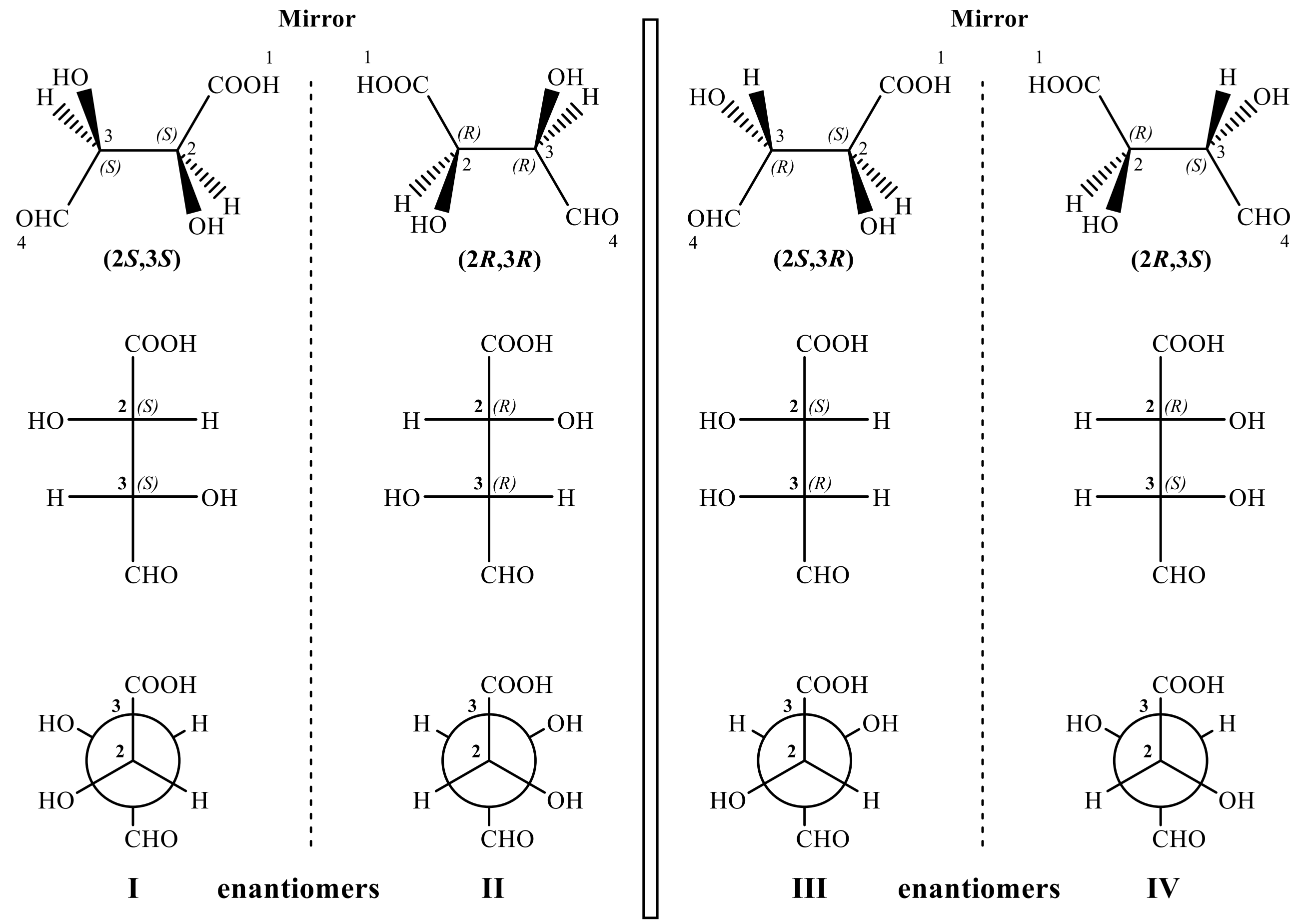
Two asymmetric carbons C_2^* and $C_3^* \rightarrow 2^2 = 4$ stereoisomers.

- Classification of the four substituents of each C^* (*C.I.P*)

$C_2^* : OH > CO_2H > C_3 > H$ and for $C_3^* : OH > CHO > C_2 > H$

The four possible couples of stereoisomers are:

(2*R*, 3*R*); (2*S*, 3*S*); (2*R*, 3*S*); (2*S*, 3*R*).



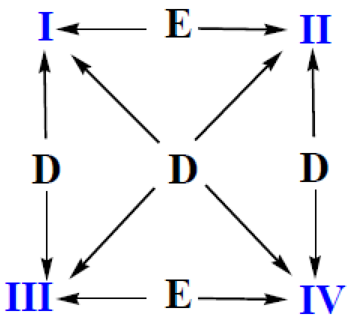
I **enantiomers** **II** **III** **enantiomers** **IV**

- (I, II) and (III, IV) are pairs of enantiomers

- The stereoisomers of each of the following pairs:

(I, III); (I, IV); (II, III) and (II, IV) differ from each other by the absolute configuration of a single C^*. They form pairs of diastereoisomers.

- Two diastereoisomers have different physical and chemical properties. Their equimolar mixture is optically active. Their separation is done by classic methods (distillation, *etc.*)



where;

E: Enantiomers

D: Diastereoisomers

The distinction between enantiomers and diastereoisomers is therefore geometric in nature.

5.6 Optical activity

Two enantiomers of a molecule have identical physical and chemical properties but opposite activities on polarized light. What will distinguish two enantiomers of a molecule is the rotational power (physical property).

The solution of an enantiomer deflects polarized light by an angle α. The solution of the other enantiomer, at the same temperature and at the same concentration, deflects or rotate polarized light by an angle – α. When the deviation of the plane of polarization of polarized light is towards the right or in a clockwise direction (α is positive), the enantiomer is said to be: dextrorotatory or (*d*) or (+).

Otherwise, it is levorotatory or (*l*) or (-) when the rotation of the polarized light is in a counter-clockwise manner (α is negative). The prefixes *dextro* and *levo* come from the Latin *dexter*, meaning right, and *laevus*, for left. Each enantiomer of a stereoisomeric pair is optically active and has an equal but opposite-in-sign specific rotation. Hence, they are called optical isomers or optical inverse. The substance is then said to be optically active or chiral.

The polarimeter, shown in Figure 5, is a device that measures the optical rotation of the optically active substance.

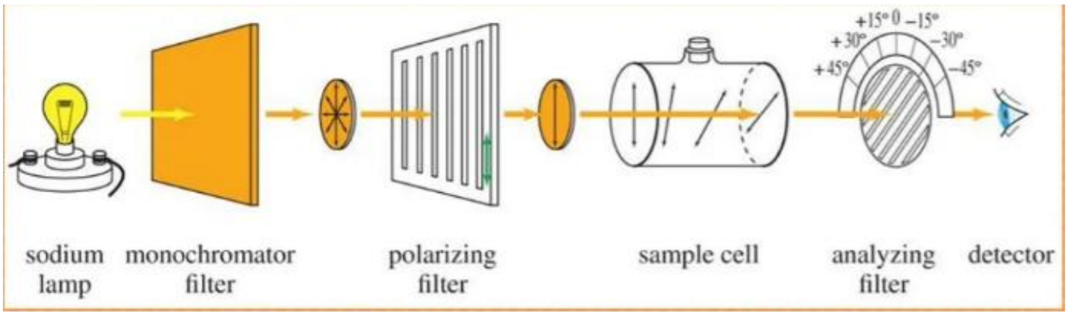


Figure 5: Polarimeter apparatus scheme.

For each of the two enantiomers of a chiral molecule, a specific rotation can be determined using Biot's law defined as:

$$Biot's\ law\ \ [\alpha]_{\lambda}^{T} = \frac{\alpha}{l.C}$$

α: observed optical rotation angle or the specific rotation of the solution (in degrees)

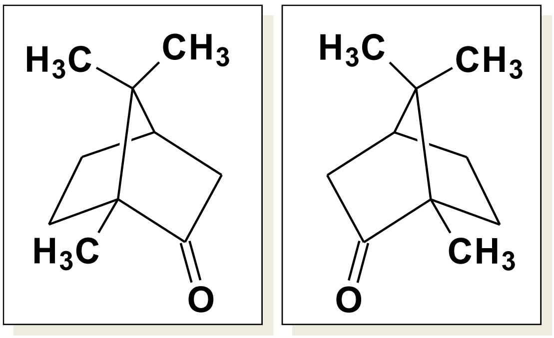
l: length of the cell containing the solution (in dm).

C: concentration of the solution (in g/mL).

T: temperature ($°C$)

$[\alpha]_{\lambda}^{T}$ is the specific rotation (standard) which itself depends on the temperature, the wavelength used, and the solvent in particular (this specific rotating power is often given in the tables at 20 $°C$ and for the length of wave of the yellow sodium line at 589.3 nm).

Specific rotations are useful in that they are experimentally determined constants that characterize and identify pure enantiomers.



Rotational power of *R*-camphor = + 44.26º Rotational power of *S*-camphor = - 44.26º

A mixture of equal concentrations or 50:50 mixture of the two enantiomers, called a racemic mixture, has a specific rotation of 0º and is optically inactive. They do not rotate the polarized light. Such mixtures are called racemates and are designated (±).

6. Relative configuration

6.1 *Erythro* and *Threo* nomenclature

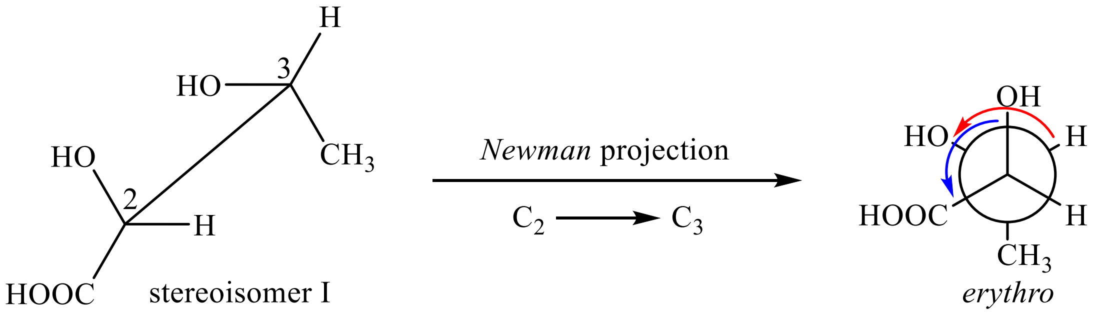
To designate diastereoisomers, chemists often use a particular nomenclature which, although not part of the international nomenclature, is universally used.

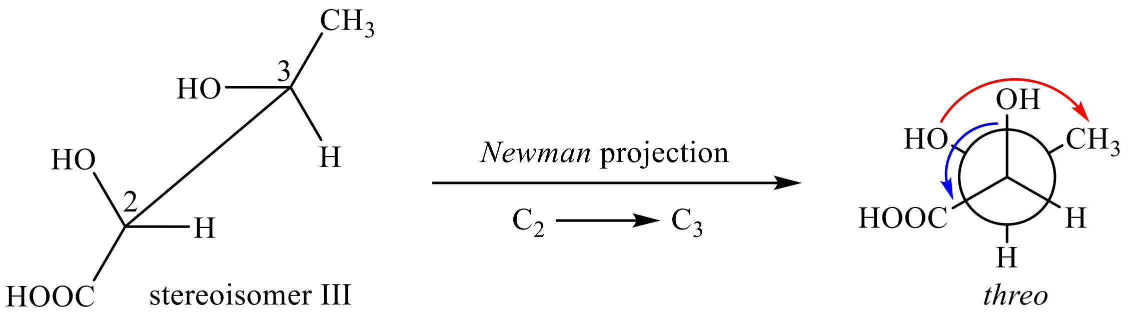
6.1.1 In *Newman* projection

Look at the molecule in the axis $C_n^* \rightarrow C_{n+1\ or\ n-1}^*$, then project into the plane of the sheet. Classify the substituents on each C^* in descending order according to the rules of *Cahn - Ingold - Prelog*.

If the rotations are in the same direction on each C^*, the compound is called "*erythro*", if they are in opposite directions the compound is called "*threo*".

Example:

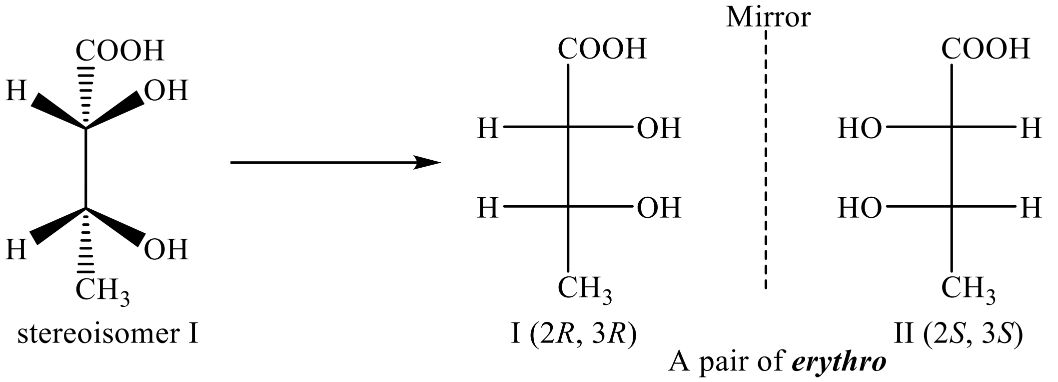




6.1.2 In *Fischer* projection

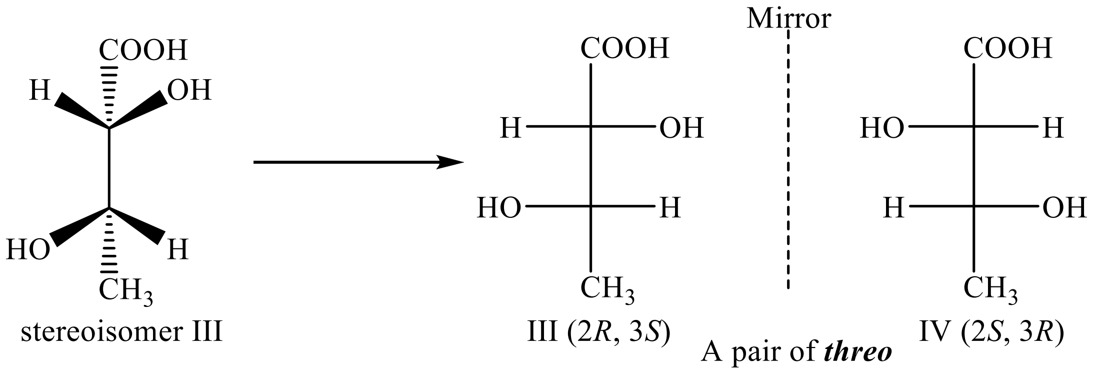
When identical substituents are on the same side of the carbon chain, the compounds are called *erythro*.

Example:

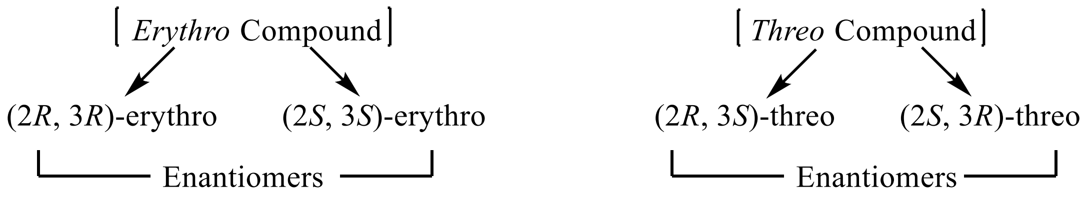


If, on the other hand, these substituents are found on either side of the carbon chain, they are called *threo*.

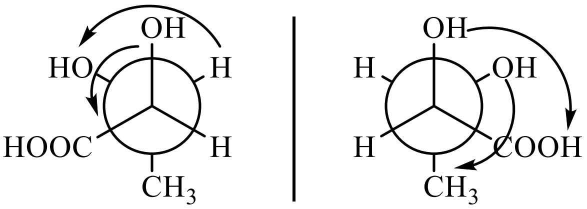
Example:



The *erythro* and *threo* compounds are two diastereomers and each one forms two enantiomers. The enantiomer of *threo* is *threo*, and the enantiomer of *erythro* is *erythro*.

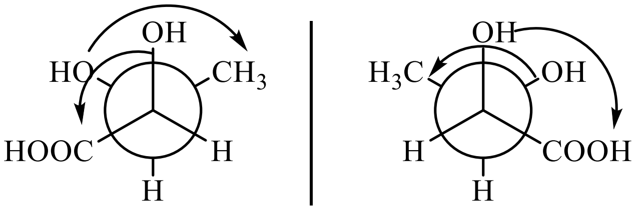


Example:



I **II**

A pair of ***erythro***



III **IV**

A pair of ***threo***

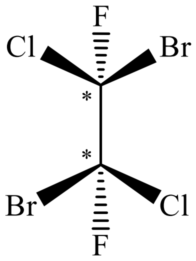
- To determine the absolute configuration *R* or *S* of a C^*, you must look in the axis ($C^* \rightarrow$ least priority substituent) and not in the axis $C_n^* \rightarrow C_{n+1\ or\ n-1}^*$, the directions of rotation are not necessarily the same.

- To determine the *Erythro-Threo* nomenclature, it is not necessary to know the absolute configurations.

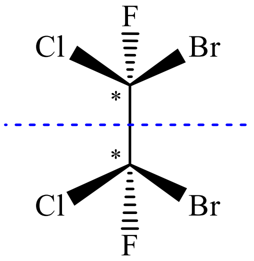
6.2 *Meso* nomenclature

The *meso* compound is a special case of the *erythro* compound. "*Meso*" compounds, even if they have asymmetric carbons, have no action on polarized light (optically inactive). These are compounds that have a plane of symmetry. A "*meso*" compound is identified by the presence of a plane of symmetry.

Example:

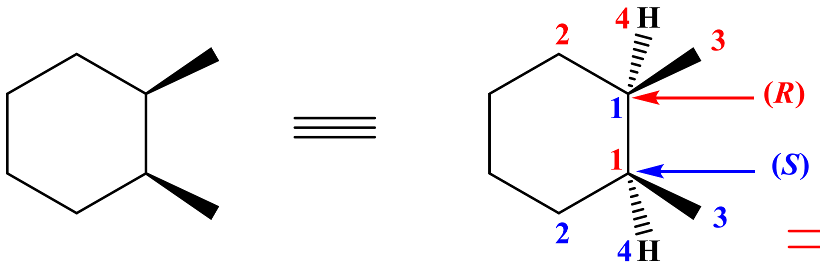


No plane of symmetry, therefore
no meso compound.



Plane of symmetry so it is a meso compound.

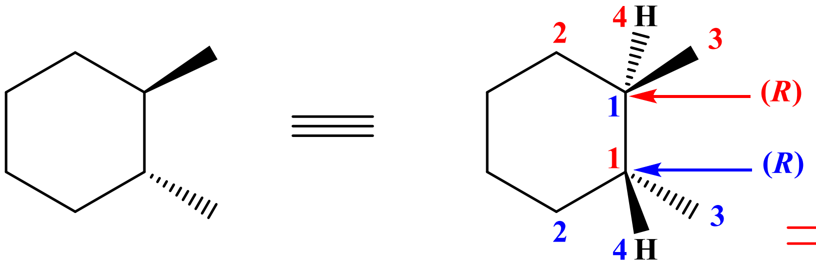
Identification of a *meso* compound by *R/S*



Substituents are disposed symmetrically

Stereocenters are of different chirality

⟹ ***Meso* (Achiral molecule)**



Substituents are disposed symmetrically

Stereocenters are of the same absolute configuration

⟹ ***Not Meso* (Chiral molecule)**

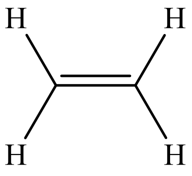
7. Geometrical stereoisomerism

7.1 *Cis-Trans* isomerism

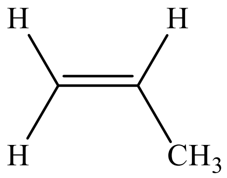
Cis and *Trans* isomers are geometrical isomers used for alkenes. *Cis-Trans* isomerism is a stereoisomerism. This type of isomerism arises due to restricted rotation of the $C = C$ double bond.

Cis is a Latin word which means “on the same side”. However, *Trans* which is also a Latin word means “across”. *Cis-Trans* isomerism is possible for di-substituted alkenes. “Di-substituted” means that the double bond has two substituents other than hydrogen on both carbons.

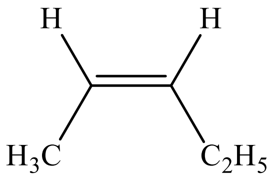
Example:



not disubstituted



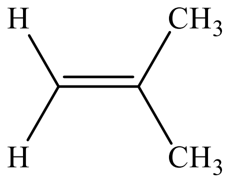
monosubstituted



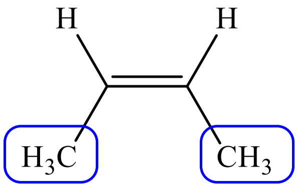
disubstituted

Cis-Trans isomerism requires that both carbons of the double bond be substituted, respectively.

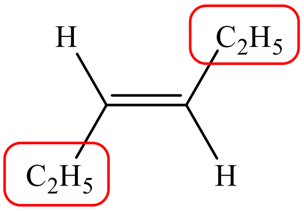
Example:



cannot say *cis* or *trans*



cis-but-2-ene



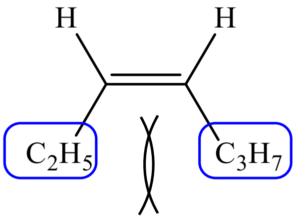
trans-hex-3-ene

Note that *cis* and *trans* isomers attribution is not possible because two substituents on a sp^2 carbon are the same (first example on the left).

The *trans* isomer is more stable than the *cis* because of the steric hindrance.

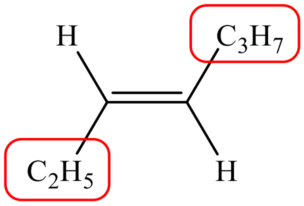
Example:

cis-hept-3-ene



steric interaction

trans-hept-3-ene



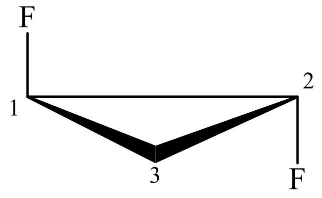
more stable

Due to difference in configuration, *cis* and *trans* isomers differ in physical properties like melting point, boiling point, dipole moment, *etc*.

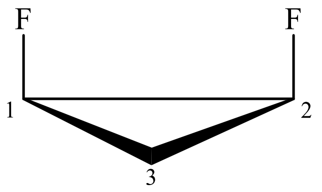
7.2 Cycloalkane isomerism

Cis-trans isomerism is also used for rings with two identical substituents. The same principle of *cis* and *trans* applies to cyclic compounds, where *cis* means both functional groups above or below the ring structure and *trans* means one functional group above and the other below the ring structure.

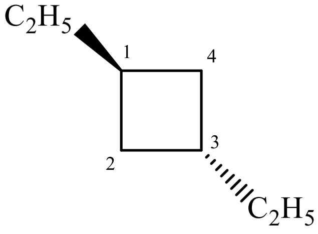
Example:



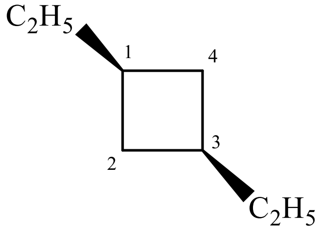
trans-1,2-difluorocyclopropane



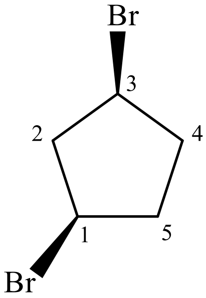
cis-1,2-difluorocyclopropane



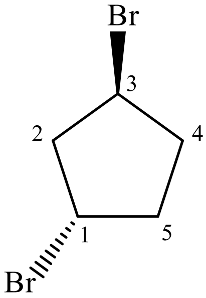
trans-1,3-diethylcyclobutane



cis-1,3-diethylcyclobutane

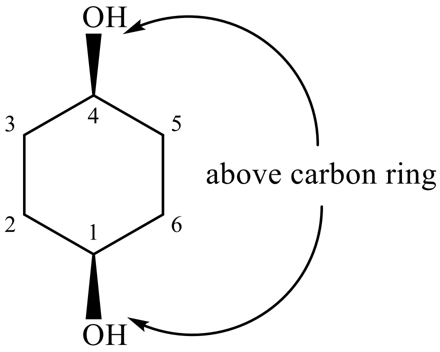


cis-1,3-dibromocyclopentane

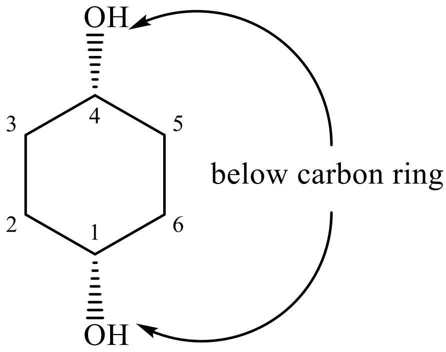


trans-1,3-dibromocyclopentane

For cyclohexane, it can be discussed as shown below. For the *cis* conformation:

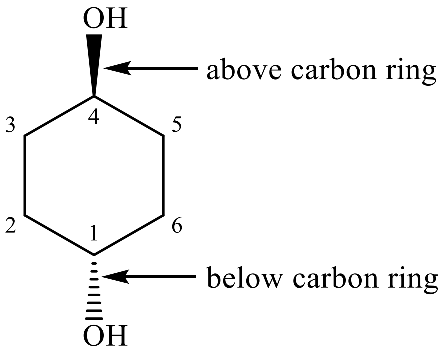


cis-cyclohexane-1,4-diol

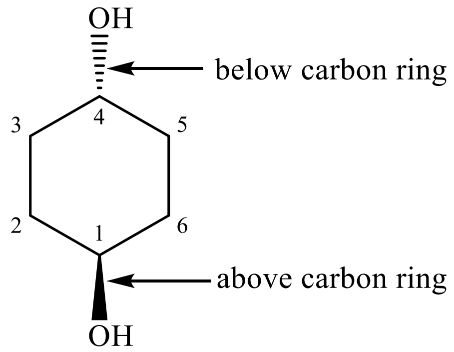


cis-cyclohexane-1,4-diol

For the *trans* conformation:

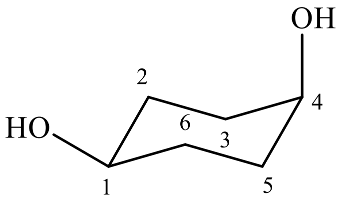


trans-cyclohexane-1,4-diol

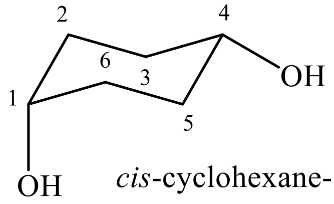


trans-cyclohexane-1,4-diol

For the *cis/trans* of the chair conformation, when one of the substituents of the cyclohexane is axial and the other one is equatorial $i.e.$ (a, e) or (e, a) the configuration is then *cis*.

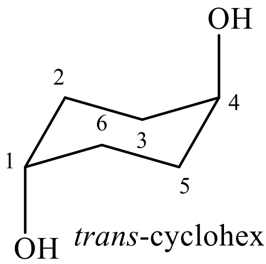


cis-cyclohexane-1,4-diol

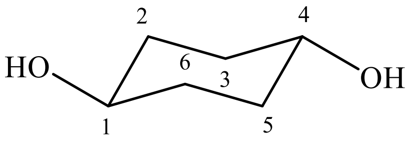


cis-cyclohexane-1,4-diol

However, when the two substituents of the cyclohexane are axial (a, a) or equatorial (e, e) the configuration is then *trans*.



trans-cyclohexane-1,4-diol



trans-cyclohexane-1,4-diol

In other words, if the two substituents are up or the two are down, then it is the *cis* conformation. If one substituent is up and the other one is down, then the conformation is *trans*.

7.3 *E* and *Z* nomenclature

This kind of nomenclature can be used to specify the configuration of any carbon-carbon double bond using the set of *C.I.P* rules.

The *E* and *Z* nomenclature is used instead of *cis* and *trans* for *tri*-substituted and *tetra*-substituted alkenes.

E is taken from German word "*entgegen*" (means opposite). If the two groups of highest priority are on either side of the double bond (opposite sides), then the double bond is assigned as *E* configuration.

Z is taken from the German word "*Zusammen*" (means together). If the two groups of highest priority are on the same side of the double bond, then the double bond is assigned as *Z* configuration.

To do this, the *C.I.P* rules must be followed.

- Analyze the two groups at each end of the double bond and rank them using *C.I.P* priority rules. This is based on classifying the first atoms of each substituent in descending order of their atomic number.
- Then, see whether the higher priority group at one end of the double bond and the higher priority group at the other end of the double bond are on the same side so it is *Z* configuration or on opposite sides with respect to the double bond so it is *E*.

Rule 1

The higher the atomic number, the higher the priority.

$$-\underset{53}{\mathrm{I}} > -\underset{35}{\mathrm{Br}} > -\underset{17}{\mathrm{Cl}} > -\underset{16}{\mathrm{SH}} > -\underset{8}{\mathrm{OH}} > -\underset{7}{\mathrm{NH_2}} > -\underset{6}{\mathrm{CH_3}} > -\underset{1}{\mathrm{H}}$$

Highest priority $\longrightarrow$ **Lowest priority**

Rule 2

In the case of isotopes, the higher the atomic mass, the higher the priority.

$$^{18}\mathrm{O} > {}^{17}\mathrm{O} > {}^{16}\mathrm{O} > {}^{14}\mathrm{C} > {}^{13}\mathrm{C} > {}^{12}\mathrm{C} > {}^{3}\mathrm{H} > {}^{2}\mathrm{H} > {}^{1}\mathrm{H}$$

Highest priority $\longrightarrow$ **Lowest priority**

Rule 3

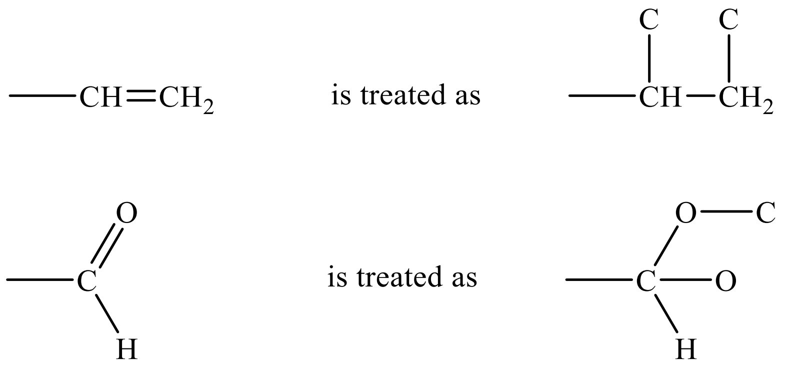
Whenever the priority cannot be assigned using the previous rules, it is recommended to consider the first atom of a group, then look at the next set of atoms and continue until a priority can be found. Hence, the priority can be assigned at the first point of difference. So, if the atoms directly linked to the double bond are the same, then look to the second atom, third atom, *etc*.

$$-\overset{\mathbf{17}}{\mathrm{CH_2Cl}} > -\overset{\mathbf{8}}{\mathrm{CH_2OH}} > -\overset{\mathbf{7}}{\mathrm{CH_2NH_2}} > -\overset{\mathbf{6}}{\mathrm{CH_2CH_3}} > -\overset{\mathbf{2}}{\mathrm{CH_2D}} > -\overset{\mathbf{1}}{\mathrm{CH_2H}}$$

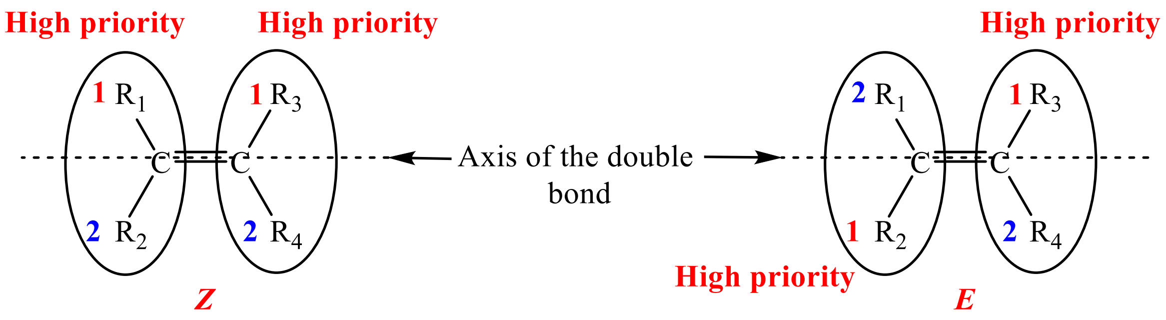
Highest priority $\longrightarrow$ **Lowest priority**

Rule 4

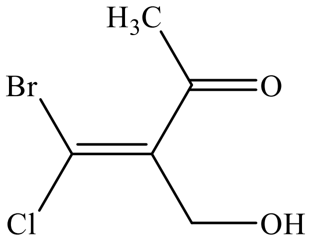
In the case of double or triple bonds, atoms forming the double or triple bond are considered to be bonded to an equivalent number of similar atoms by single bonds, *i.e.* atoms of double and triple bonds are duplicated or triplicated.



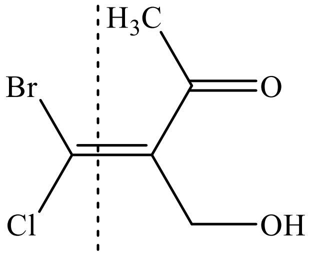
Finally, in order to assign *E*-*Z* configuration, first it is necessary to determine the groups of highest priority on each carbon atom of the double bond. If the two groups with higher priority are on the same side of the double bond $i.e.$ the two groups of higher priority are above or the two are below the axis of the double bond, then the configuration is called *Z*. if they are on opposite sides of the double bond $i.e.$ one group of higher priority is above the axis of the double bond and the second one is below the axis of the double bond, then the configuration is called *E*.



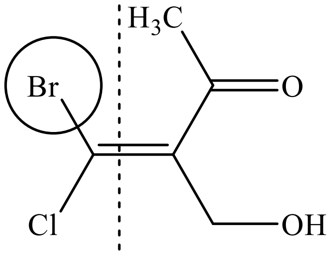
Let’s do an example! Let’s be the following alkene



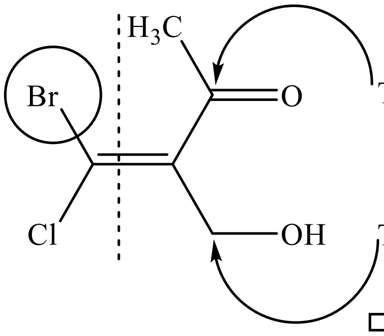
(1) Divide the alkene down the center.



(2) Look at the left end of the alkene. Determine which group has the highest priority. On the left end of this alkene, we have a bromine atom and a chlorine atom. Bromine has an atomic number of 35 while chlorine has an atomic number of 17. Since bromine has the higher atomic number, it will be given the higher priority. Circle the atom you determine to have higher priority.



(3) Look at the right end of the alkene. Determine which group has the highest priority. Here is a situation where the same atom, in this case it is carbon, is bonded to the same end of the double bond. The priority of the groups cannot be determined using the atomic number of the atoms directly attached to the double bond since they are the same. In cases like this, it is customary to compare the next group of atoms, with any double bonds being duplicated (and triple bonds triplicated) with imaginary atoms.

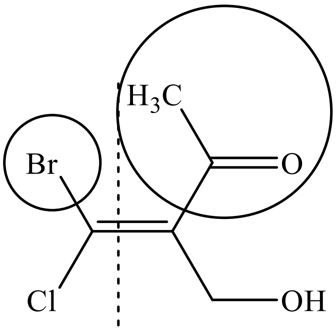


This carbon is attached to a H, O, O.

This carbon is attached to a H, H, O.

⇒ H, O, O is given the higher priority over H, H, O.

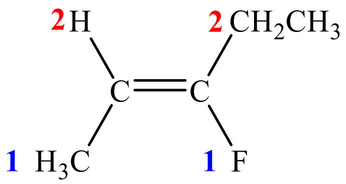
The aldehyde group is therefore given the higher priority.



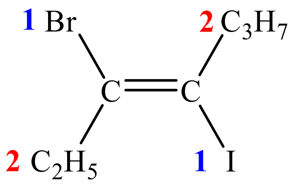
Since both groups of higher priority are on the same side of the bond, the alkene’s configuration is *Z*.

Example:

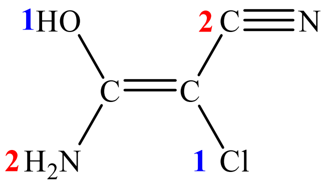
In the following examples, the number **1** refers to higher priority and number **2** refers to lower priority.



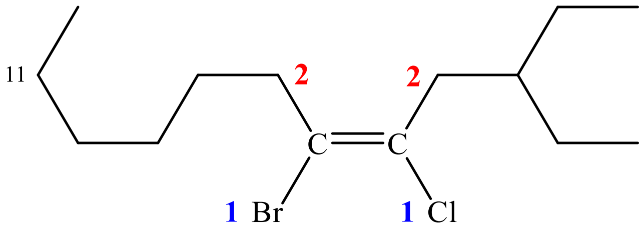
Z



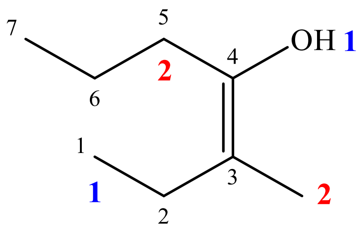
E



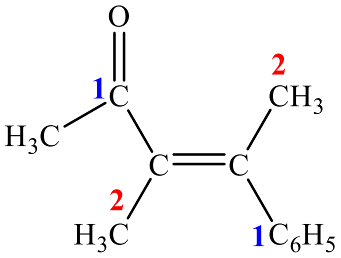
E



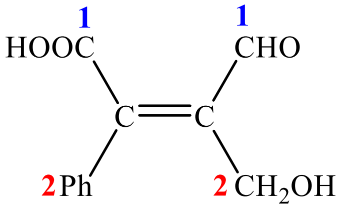
(***Z***)-6-bromo-5-chloro-3-ethyldodec-5-ene



(***E***)-3-methylhept-3-en-4-ol



(***E***)-3-methyl-4-phenylpent-3-en-2-one

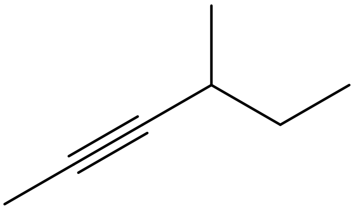


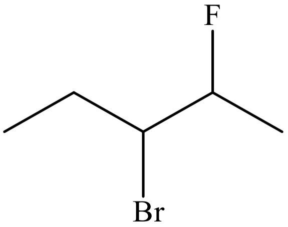
(***Z***)-3-formyl-4-hydroxy-2-phenylbut-2-enoic acid

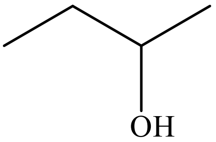
EXERCISES

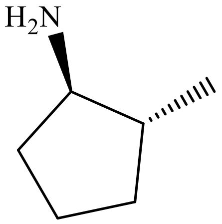
Exercise 1:

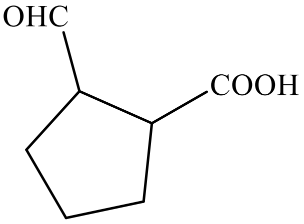
For each compound below, identify all chirality (asymmetric) centers with an asterisk (*).

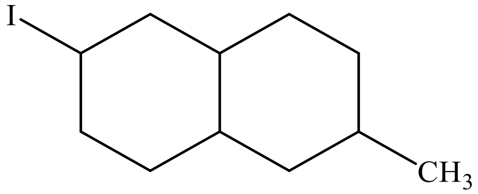


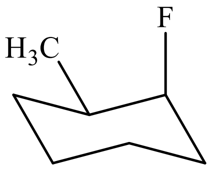


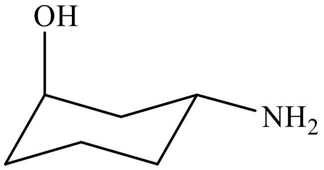












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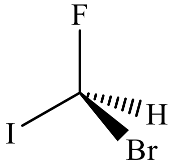
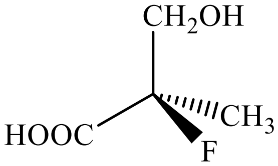
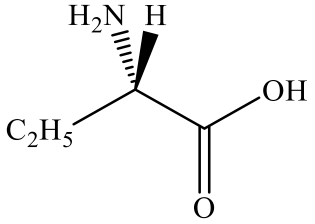
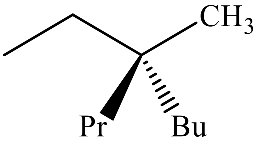
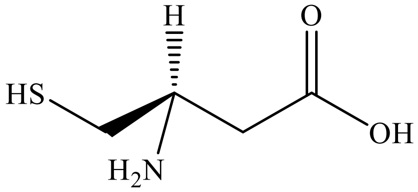
Assign all chiral centers as *R* or *S*.

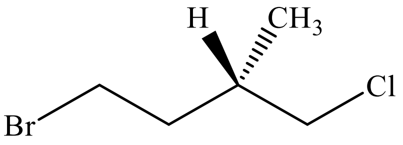


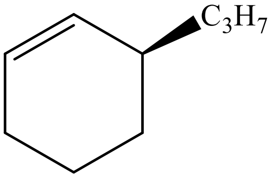


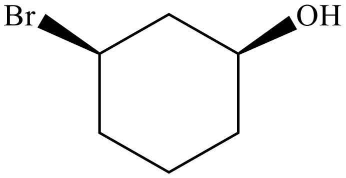


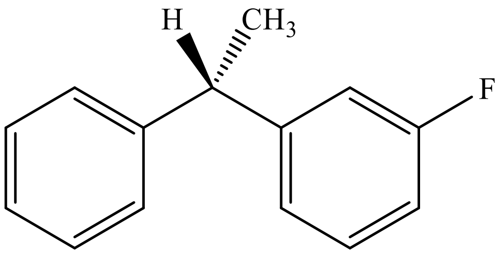






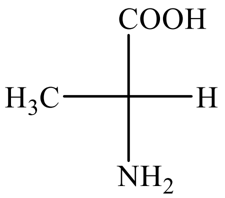


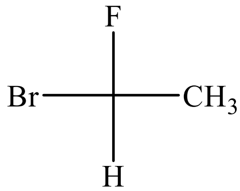


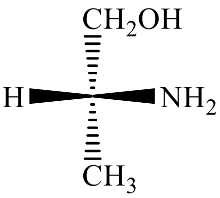


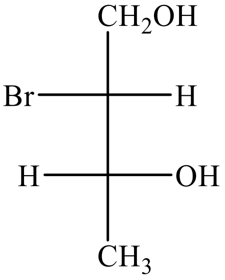
Exercise 3:

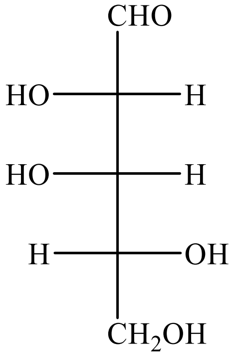
Assign *R* or *S* to the indicated chiral center in these *Fischer* projections.

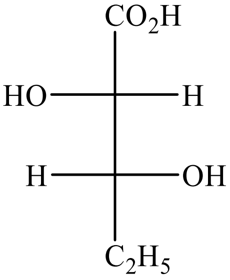






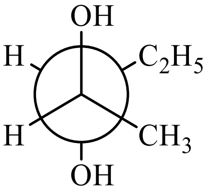


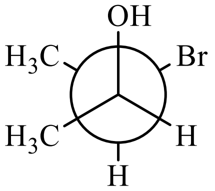


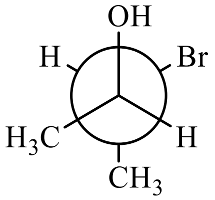


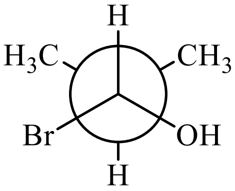
Exercise 4:

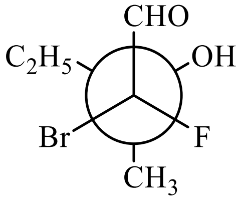
Assign *R* or *S* to the chiral centers in these *Newman* projections.

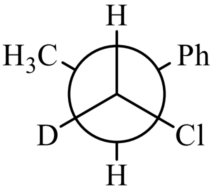






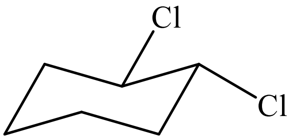


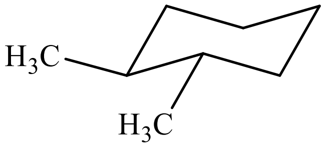


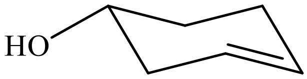


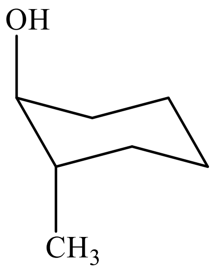
Exercise 5:

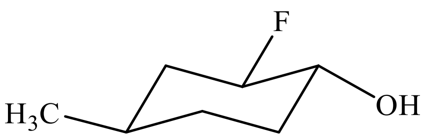
Assign *R* or *S* to the chiral centers in these cyclohexane chairs.

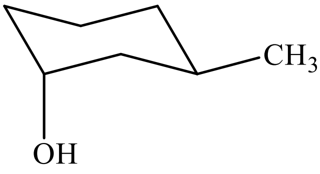






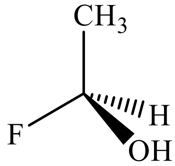


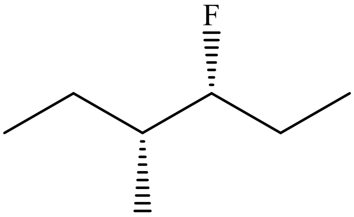


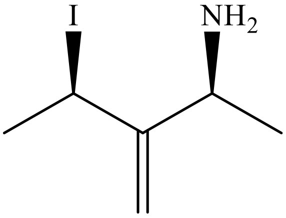


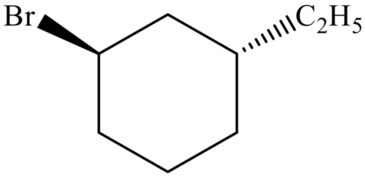
Exercise 6:

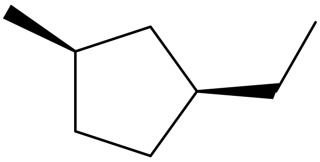
Draw the enantiomer of each compound below.

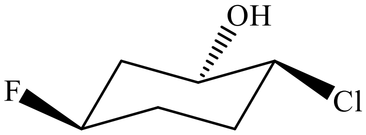


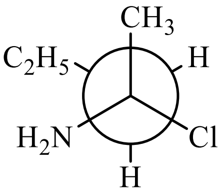


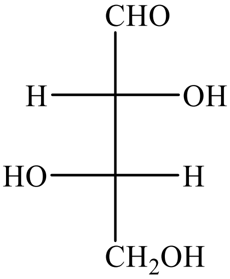


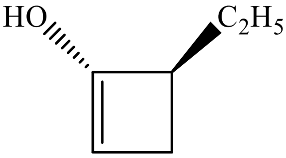


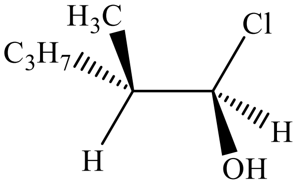






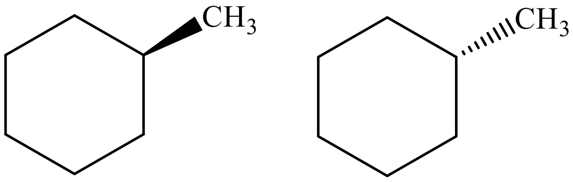
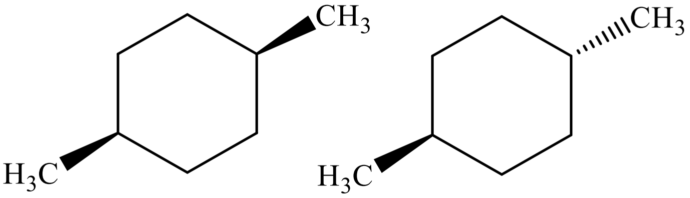
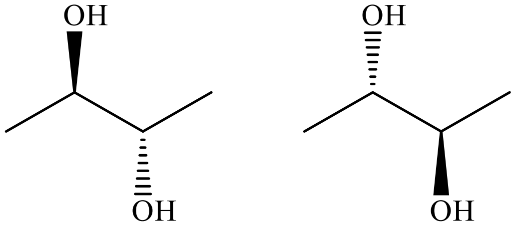
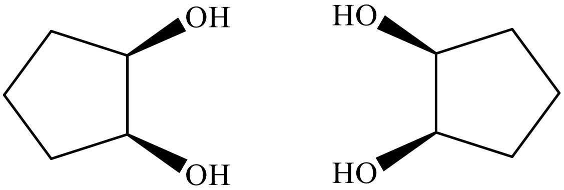
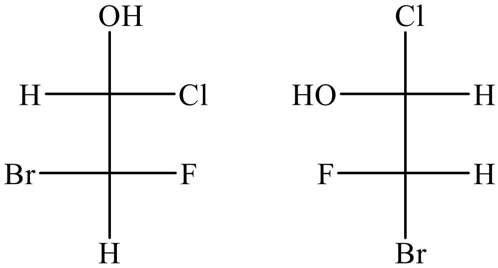
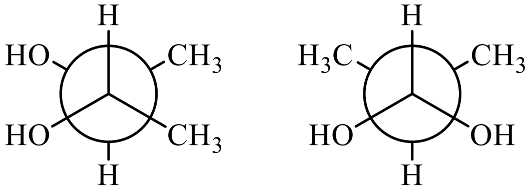
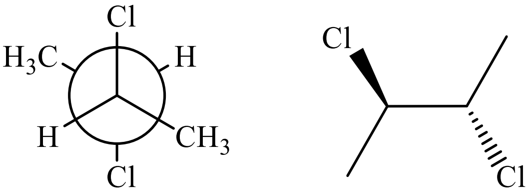
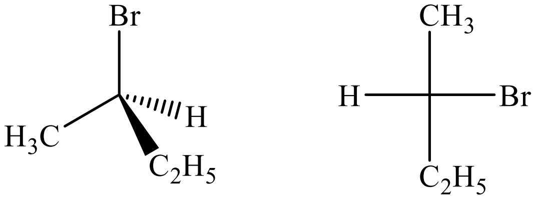






Exercise 7:

Decide if these molecules are enantiomers, diastereomers, same, or constitutional isomers?

Exercise 8:

Given these names, draw the following molecules:

(S)-2-Chlorobutane

(*S*)-1-bromo-1-chloropropane

2-((3*R*)-3-methylcyclohexyl)acetic acid

(2R,3R)-3-Chloropentan-2-ol

(1R,2S)-2-Amino-1-phenylpropan-1-ol

(2*R*,3*S*)-2,3-dichloropentane

Exercise 9:

Based on the name only, decide if these molecules are enantiomers or diastereomers.

1) (*R*)-Butan-2-ol and (*S*)-Butan-2-ol

2) (2*R,*3*R*)-2-Bromo-3-chlorobutane and (2*S,*3*S*)-2-Bromo-3-chlorobutane

3) (*R,R*)-Tartaric acid and (*R,S*)-Tartaric acid

4) (*E*)-Hex-3-ene and (*Z*)-Hex-3-ene

5) (*R,E*)-4-Hexen-2-ol and (*S,Z*)-4-Hexen-2-ol

6) (*R,E*)-4-Hexen-2-ol and (*R,Z*)-4-Hexen-2-ol

7) (*R,E*)-4-Hexen-2-ol and (*S,E*)-4-Hexen-2-ol

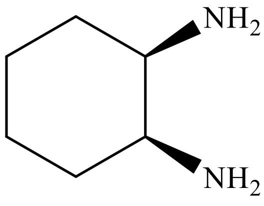
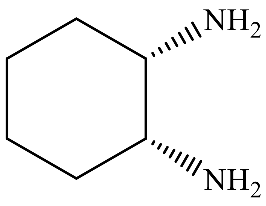
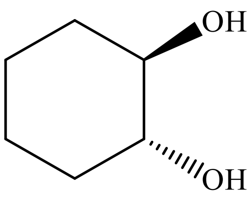
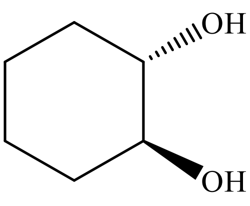
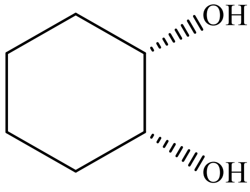
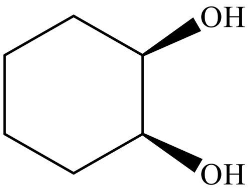
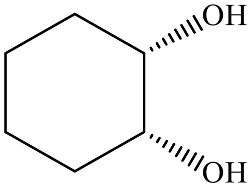
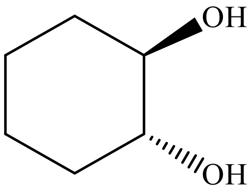
8) *(1R,2S)*-1,2-Dimethylcyclohexane and *(1S, 2R)*-1,2-Dimethylcyclohexane

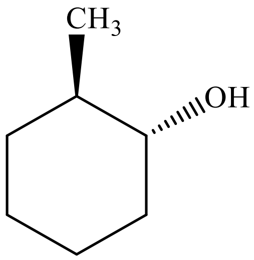
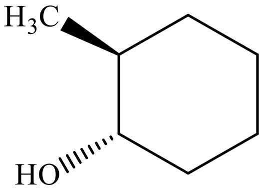
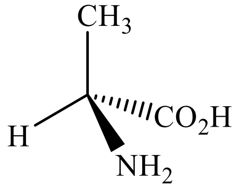
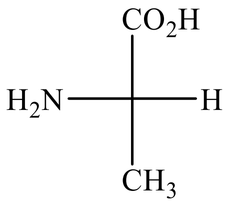
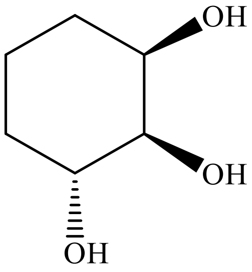
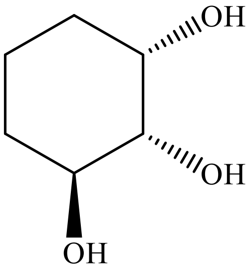
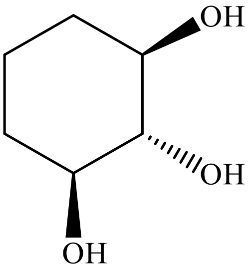
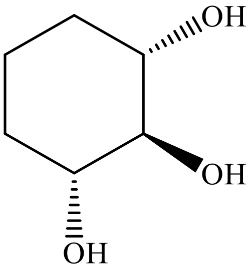
9) *cis*-1,2-Dimethylcyclohexane and *trans*-1,3-Dimethylcyclohexane

10) (*R,S*)-2,3-Dichlorobutane and (*S,R*)-2,3-Dichlorobutane

Exercise 10:

Mark the relationships between the following structures as either "same", "*meso*", "enantiomers", or "diastereomers".

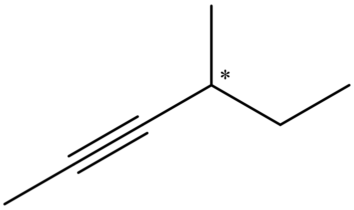
 	 
 	 

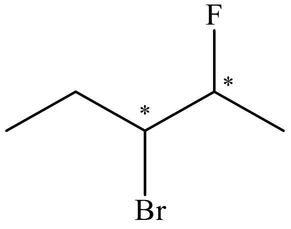
 	 
 	 

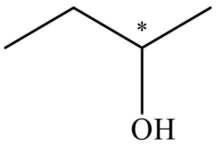
SOLUTIONS

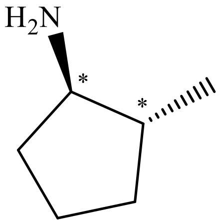
Exercise 1:

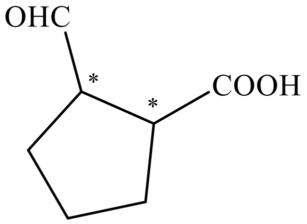
For each compound below, we identify all chirality (asymmetric) centers with an asterisk (*).

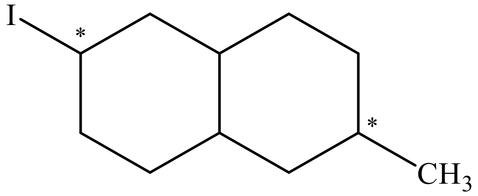


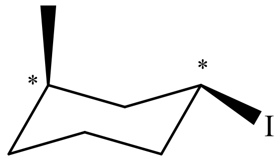


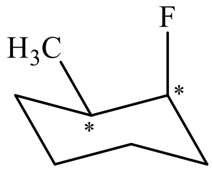


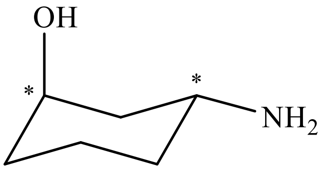






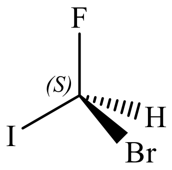


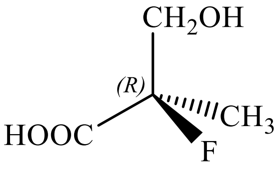


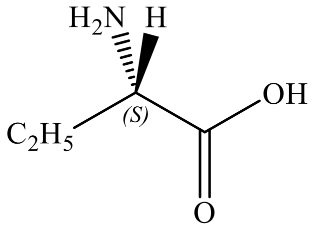


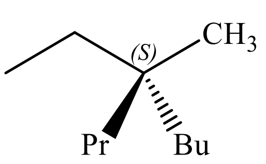
Exercise 2:

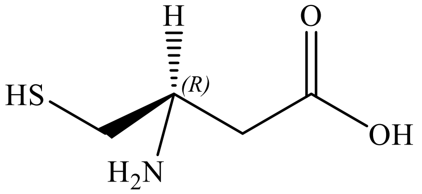
We assign all chiral centers as *R* or *S*.

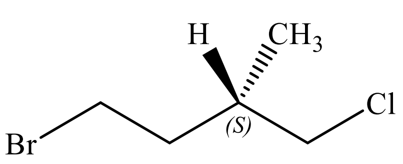


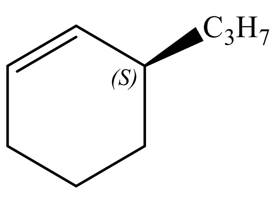


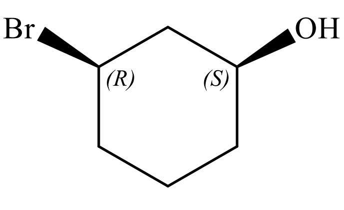


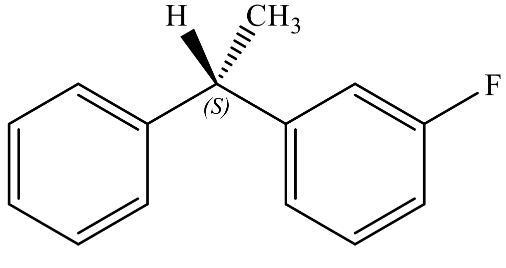






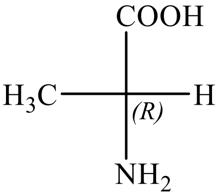


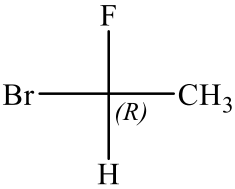


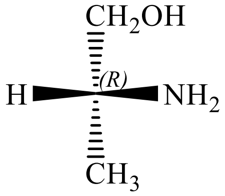


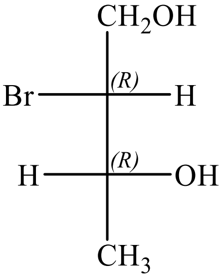
Exercise 3:

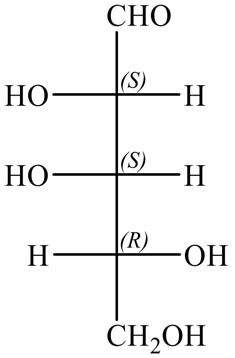
We assign *R* or *S* to the indicated chiral center in these *Fischer* projections.

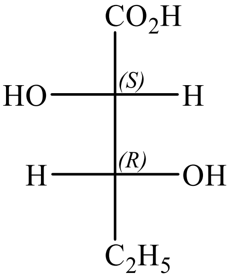






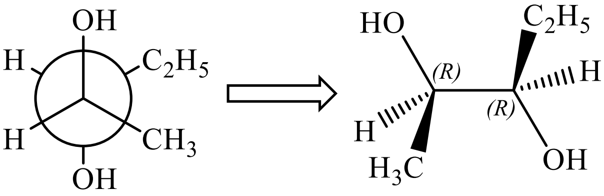


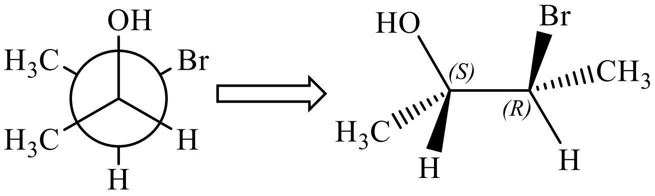


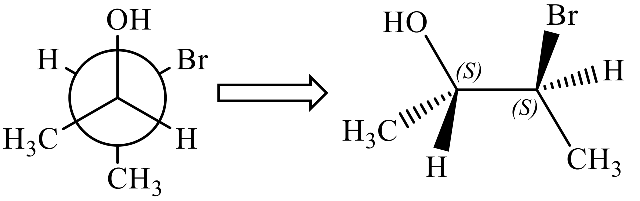


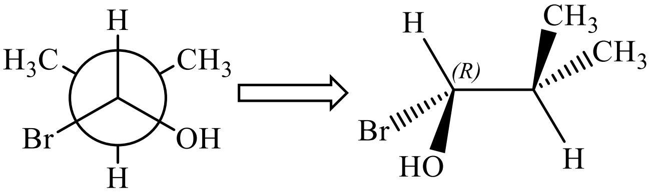
Exercise 4:

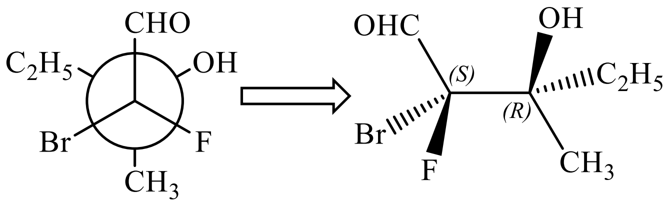
We assign *R* or *S* to the chiral centers in these *Newman* projections.

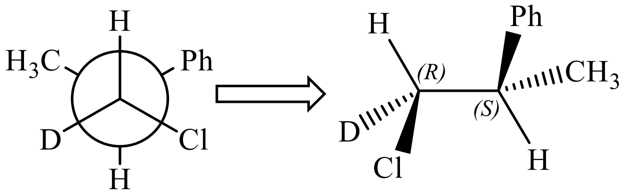






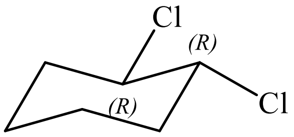


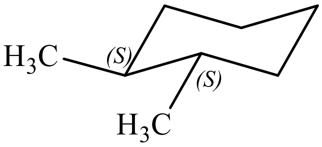


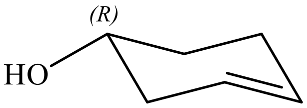


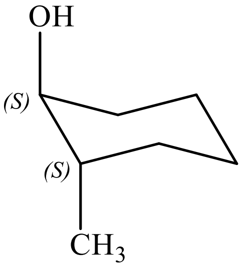
Exercise 5:

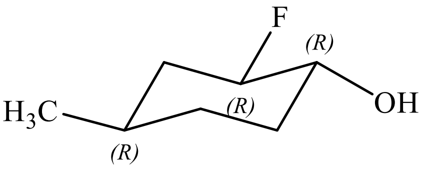
We assign *R* or *S* to the chiral centers in these cyclohexane chairs.

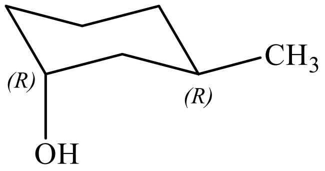






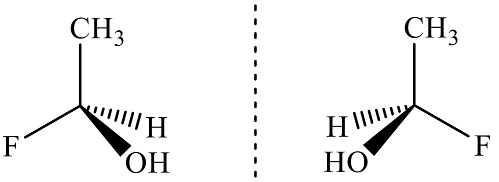


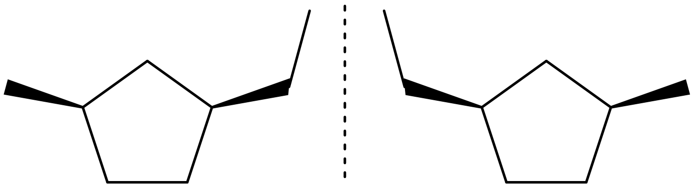


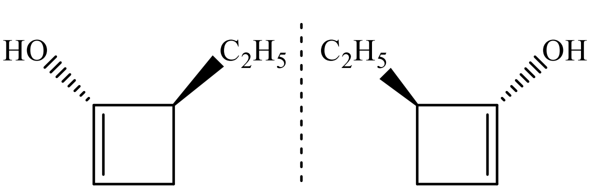


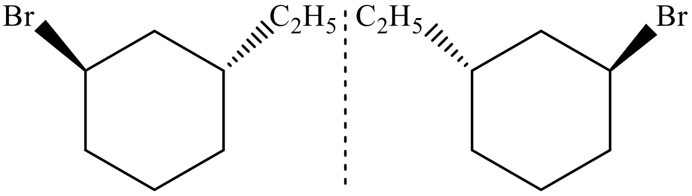
Exercise 6:

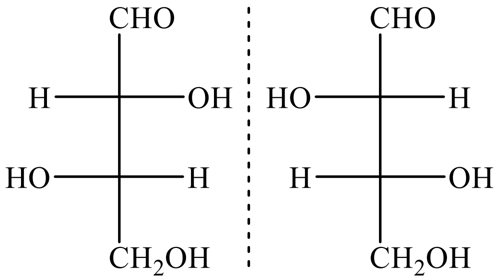
We draw the enantiomer of each compound below.

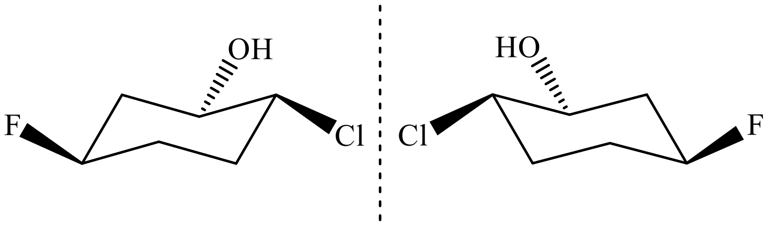


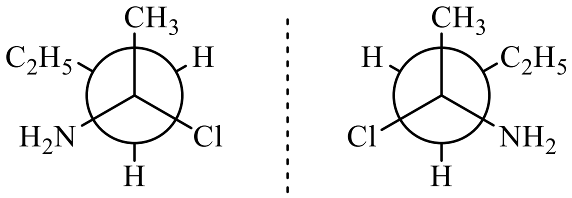


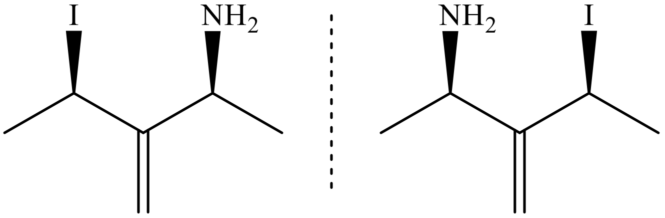


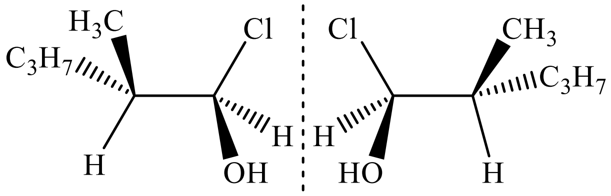


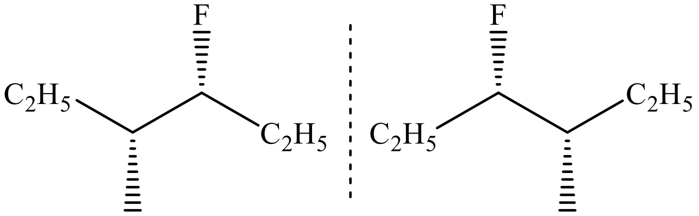






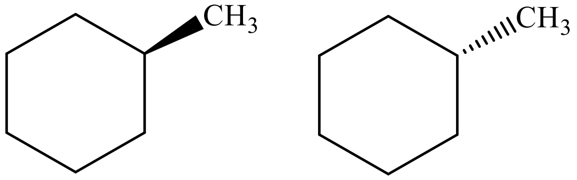




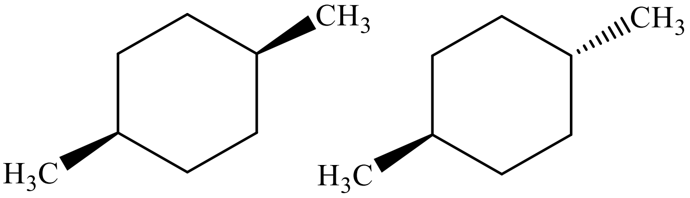


Exercise 7:

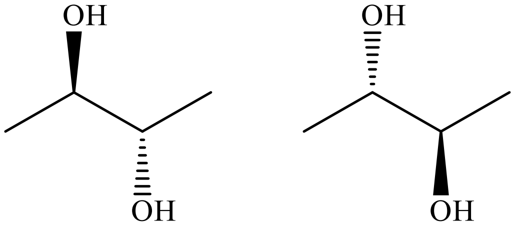
We decide if these molecules are enantiomers, diastereoisomers, same, or constitutional isomers.



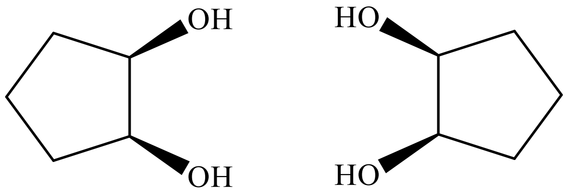
same



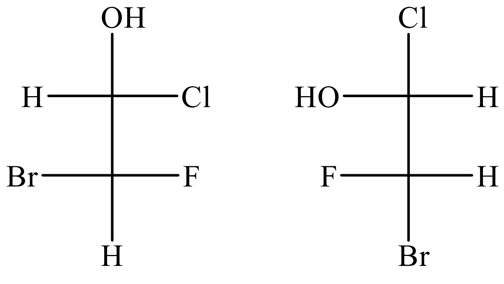
diastereoisomers



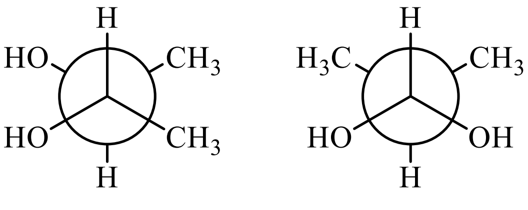
enantiomers



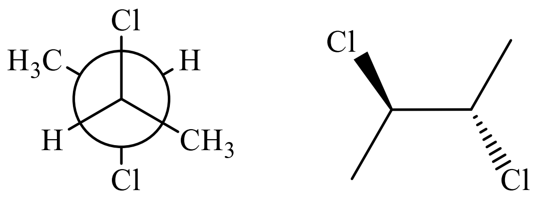
enantiomers



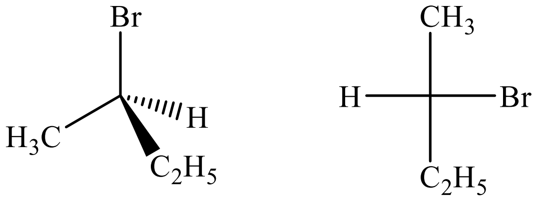
same



constitutional isomers



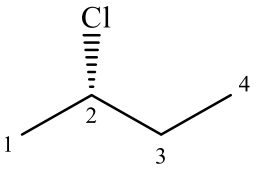
same



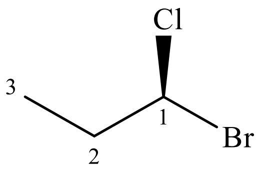
enantiomers

Exercise 8:

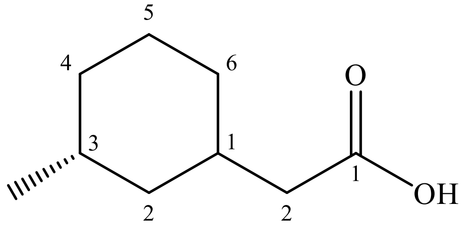
Given the names, we draw the following molecules:



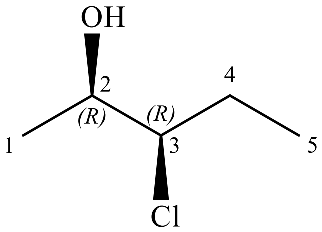
(S)-2-chlorobutane



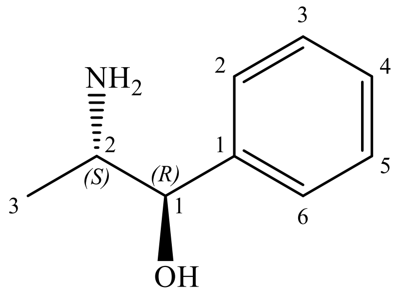
(S)-1-bromo-1-chloropropane



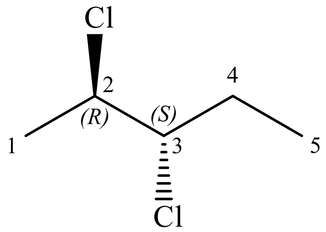
2-((3R)-3-methylcyclohexyl)acetic acid



(2R,3R)-3-chloropentan-2-ol



(1R,2S)-2-amino-1-phenylpropan-1-ol



(2R,3S)-2,3-dichloropentane

Exercise 9:

Based on the name only, we decide if these molecules are enantiomers or diastereoisomers**.**

1) (R)-Butan-2-ol and (S)-Butan-2-ol: enantiomers

2) (2R,3R)-2-Bromo-3-chlorobutane and (2S,3S)-2-Bromo-3-chlorobutane: enantiomers

3) (R,R)-Tartaric acid and (R,S)-Tartaric acid: diastereoisomers

4) (E)-Hex-3-ene and (Z)-Hex-3-ene: diastereoisomers

5) (R,E)-4-Hexen-2-ol and (S,Z)-4-Hexen-2-ol: diastereoisomers

6) (R,E)-4-Hexen-2-ol and (R,Z)-4-Hexen-2-ol: diastereoisomers

7) (R,E)-4-Hexen-2-ol and (S,E)-4-Hexen-2-ol: enantiomers

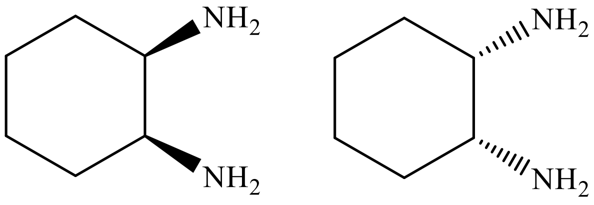
8) (1R,2S)-1,2-Dimethylcyclohexane and (1S, 2R)-1,2-Dimethylcyclohexane: enantiomers

9) *cis*-1,2-Dimethylcyclohexane and *trans*-1,3-Dimethylcyclohexane: diastereoisomers

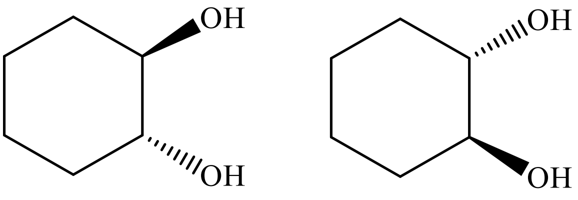
10) (R,S)-2,3-Dichlorobutane and (S,R)-2,3-Dichlorobutane: enantiomers

Exercise 10:

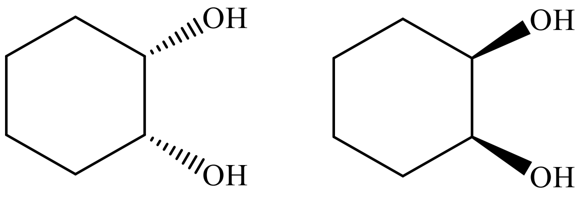
We mark the relationships between the following structures as either "same", "*meso*", "enantiomers", or "diastereomers".



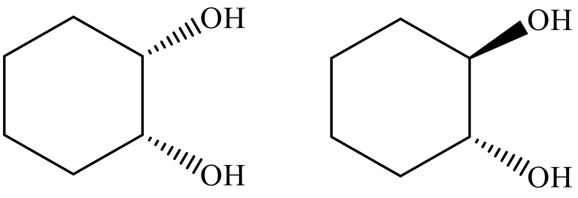
Meso (same compound)



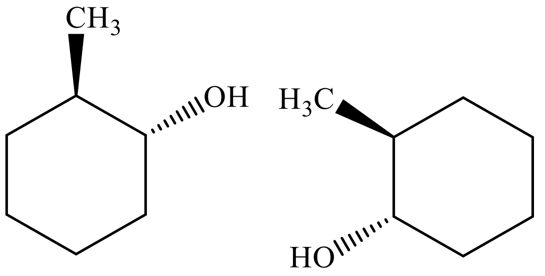
Enantiomers



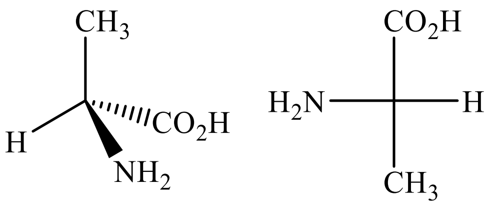
Meso (same compound)



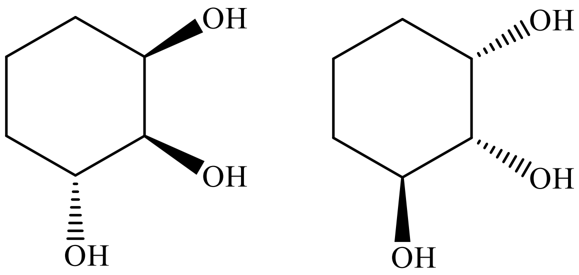
Diastereomers



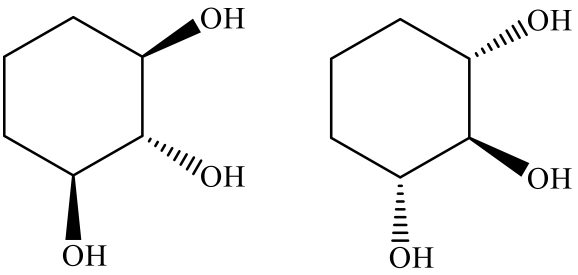
Enantiomers



Same



Enantiomers



Meso (same compound)

Chapter III :
Electronic Effects

Introduction

A wide range of keywords can be drawn from the topic “electronic effects in organic chemistry” since a lot of topics are connected with this area. While it is simple to define organic chemistry – see any textbooks on general chemistry – it is much more difficult to define electronic effects, especially if we want to avoid simply repeating the terms “effects which are governed by electrons”. What can be considered as such electronic effects? All consequences concerning changes caused by the (valence) electrons of organic molecules?

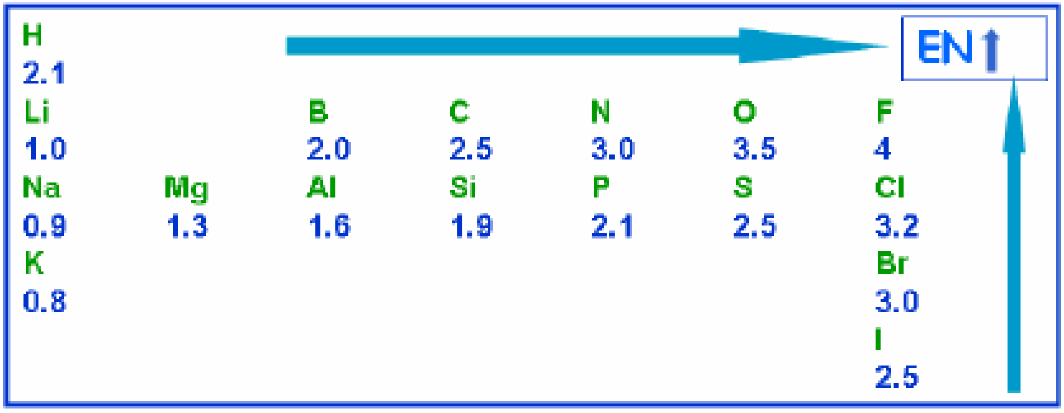
This volume deals with the concepts of electronic structure and associated methods in the context of organic chemistry and provides some answers to the questions above. As all authors are considering some kind of electronic effects, the main emphasis of the book lies in theoretical contributions, because one of the most important sections in theoretical chemistry is electronic structure theory. Nevertheless, important experimental work is highlighted or reviewed at the appropriate position. Hydrogen bonding always plays an important role when it comes to electronic effects, and throughout the book hydrogen bonding always emerges on the surface or plays an indirect role.

1. Polarization and electronegativity

In a covalent bond, the electrons will be more strongly attracted to one of the two atoms in the bond ↔ this bond will be said to be polar or polarized.

The polarization of a covalent bond is linked to electronegativity, the capacity of an atom to be able to take electrons from a covalent bond towards itself.

Keep in mind that electronegativity increases from left to right over the same period, and from bottom to top on the same column.



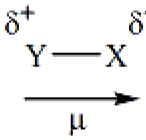
H 2.1						
Li 1.0		B 2.0	C 2.5	N 3.0	O 3.5	F 4
Na 0.9	Mg 1.3	Al 1.6	Si 1.9	P 2.1	S 2.5	Cl 3.2
K 0.8						Br 3.0
						I 2.5

Figure 1: Electronegativity scale.

When a covalent bond is formed by two identical atoms ($X - X$), the pair of electrons is shared between the two atoms. The electron cloud is distributed equally among the two atoms. Therefore, there is no polarity ($\mu = 0$).

2. Dipole moment

The polarization of a bond gives rise to an electric dipole characterized by a dipole moment. The greater the difference in electronegativity of the atoms (or linked groups), the greater the dipole moment of the bond.



μ: dipole moment, function of the charge δ (Coulomb C) and l (Angstrom $A°$) the distance between the center of the positive charges and that of the negative charges. $\mu = \delta . l \; in \; Debye$, where:

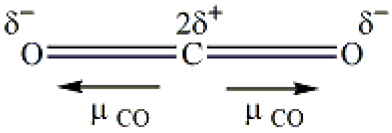
$$1Debye = 3.33.10^{-30} \; C.m$$

Note:

A molecule with a center of symmetry has no dipole moment.

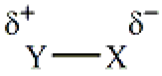
Example:

In the case of the CO_2 molecule, we see that due to its linear and symmetrical geometry, the two $C = O$ bonding moments are compensated. The resulting dipole moment is therefore zero.



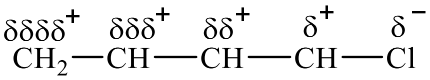
3. Inductive effect

It is permanent but weak effect involving displacement of σ electrons towards more electronegative species. It can be transmitted along the chain of carbon. It is the polarization of sigma bonded electrons towards atom of higher electronegativity. The inductive effect is directly related to electronegativity. The standard reference is hydrogen atom.



δ^- is a negative formal charge and δ^+ is a positive formal charge.

Decrease in inductive effect is shown by a greater number of δ.



It is very important to note that the inductive effect only has an effect on the σ bonds!

Inductive effect is useful in describing many phenomena in organic molecules

- Polarization
- Changing in bond lengths
- Boiling points/ melting points
- Solubility
- Acidity
- Magnitude of acidity
- Basicity and magnitude of basicity
- Reactivity
- Stabilization / destabilization of reactive intermediates

3.1 Types of inductive effect

We will define two types of inductive effects:

a) Negative inductive effect -I: for atoms or groups of atoms having an electronegativity greater than that of carbon having an electron-withdrawing effect (EWG). In general, functional groups are electrons withdrawing groups.

Example:

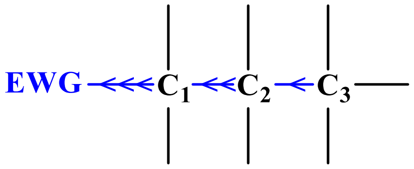
$-F, -Cl, -Br, -OH, -NH_2, -CN, -NO_2$.

b) Positive inductive effect +I: for atoms or groups of atoms having an electronegativity lower than that of carbon, having an electron-donating or electron-releasing effect (EDG). In general, alkyl groups are electrons donating groups.

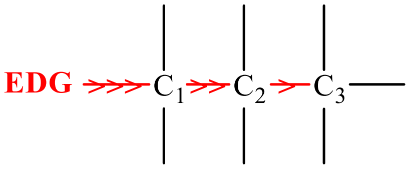
Example:

Metals (Na, Mg, etc.), alkyl groups (CH_3, C_2H_5, $(CH_3)_3C$, etc.)

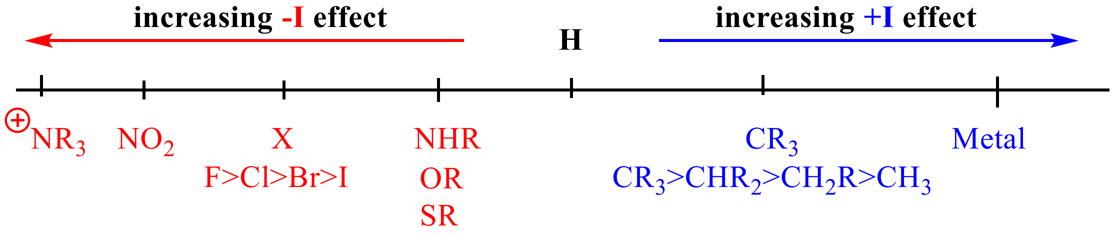
The -I and +I effects decrease rapidly with distance (practically vanishes beyond three to four bonds).



Negative inductive effect -I



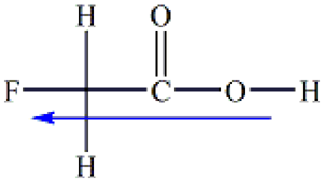
Positive inductive effect +I



4. Factors affecting inductive effect

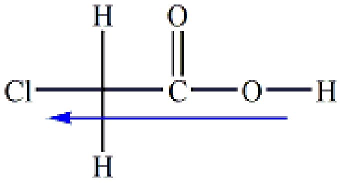
a. Electronegativity

The magnitude or value of the fractional charges δ^+ and δ^- increases with the increase in the electronegativity of the halogen.



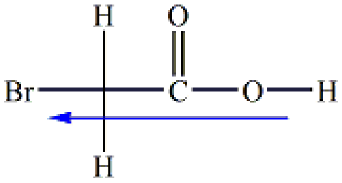
2-fluoroethanoic acid

$pK_a = 2.6$



2-chloroethanoic acid

$pK_a = 2.8$



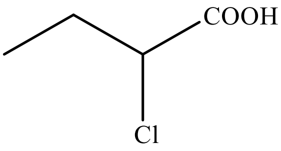
2-bromoethanoic acid

$pK_a = 2.9$

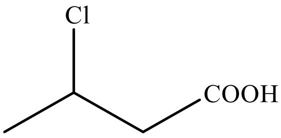
The electronegativity order for halogens is: $F > Cl > Br > I$, which further increases the acidity of the molecule from F to Br. The negative inductive effect is less and less important from F to Cl to Br.

b. Distance

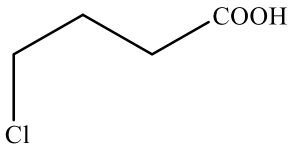
The inductive effect weakens away along the chain and is not significant and becomes negligible beyond the third carbon atom. The same phenomenon can be observed with cyclic molecules.



2-chlorobutanoic acid
$pK_a = 2.89$



3-chlorobutanoic acid
$pK_a = 4.05$

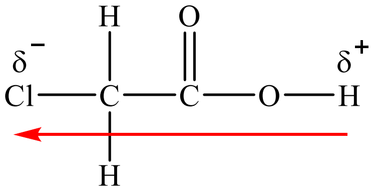


4-chlorobutanoic acid
$pK_a = 4.53$

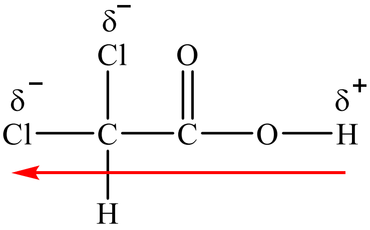
c. Number of groups

The inductive effect is additive. From one, to two, to three chlorine atoms the acidic character of a given molecule increases considerably.

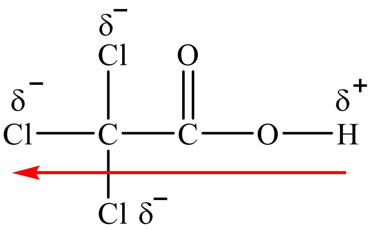
Example:



2-chloroethanoic acid
$pK_a = 2.82$



2,2-chloroethanoic acid
$pK_a = 1.30$

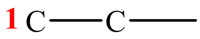


2,2,2-chloroethanoic acid
$pK_a = 0.70$

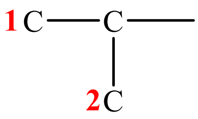
d. Degree of carbon

The inductive effect increases from primary to secondary to tertiary carbon.

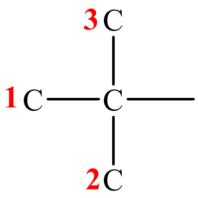
Tertiary > Secondary > Primary



1° Carbon



2° Carbon

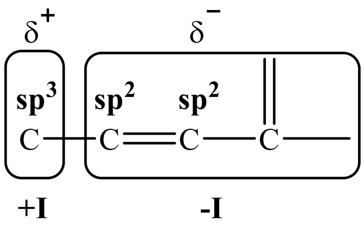


3° Carbon

e. Hybridization

Inductive effect increases with hybridization. The more is the s-character, the more is the $-I$ inductive effect.

$$\mathbf{sp} > \mathbf{sp^2} > \mathbf{sp^3}$$



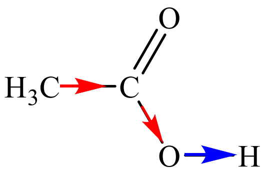
5. Relationship between pK_a and inductive effect

5.1 Inductive effects and acidity

Acidic nature of carboxylic acids depends on the ease of H^+ removal and stability of $R-COO^-$ ion. Electron withdrawing groups disperse negative charge over the molecule and increase stability and acidic nature ($-I$ effect). However, electron releasing groups disperse less negative charge over the molecule and decreases stability and acidic nature ($+I$ effect).

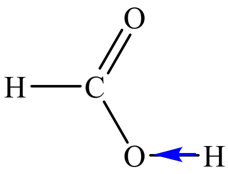
In other words, the presence of a withdrawing group ($-I$ effect) will increase the acidity because the electron-hungry oxygen (very electronegative) will attract the electron pair of the $O-H$ bond even more strongly. The polarization of the $O-H$ bond will increase, this bond will therefore free a proton (H^+) much more easily, and the compound will be more acidic.

Example:



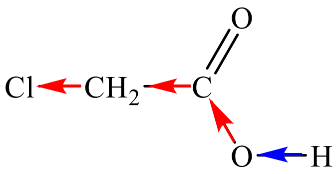
pKa = 4.7

+I effect of methyle



3.8

no effects



2.8

-I effect of chlorine

The inductive electron-withdrawing effect $(-I)$ of a group weakens the $O-H$ bond in $-COOH$ and promotes the ionization of the carboxylic acid ↔ the proton will leave more easily ↔ the acidity increases ↔ the pK_a decreases.

The inductive electron-donating effect $(+I)$ of a group strengthens the $O-H$ bond in $-COOH$ and disadvantages the ionization of the carboxylic acid ↔ the proton will leave more difficult ↔ the acidity decreases ↔ the pK_a increases.

Table 1: Inductive electron-donating effect $(+I)$: $R-COOH$

$\boldsymbol{R-}$	$\boldsymbol{H-}$	$\boldsymbol{H_3C-}$	$\boldsymbol{H_3C-CH_2-CH_2-}$
$\boldsymbol{pK_a}$	3.75	4.76	4.82

The alkyl groups induce an effect $(+I)$ that reduces the acidity.

Table 2: Inductive electron-withdrawing effect $(-I)$: Y-CH_2-COOH

$\boldsymbol{Y-}$	$\boldsymbol{H-}$	$\boldsymbol{Br-}$	$\boldsymbol{Cl-}$	$\boldsymbol{F-}$	$\boldsymbol{NO_2-}$
$\boldsymbol{pK_a}$	4.76	2.90	2.87	2.59	1.68

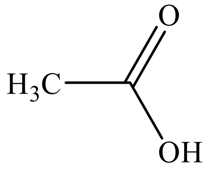
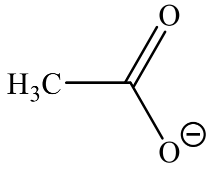
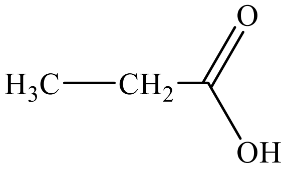
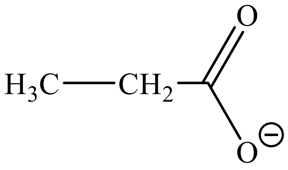
The $(-I)$ effect induces an increase in acidity. The effect $(-I)$ increases with the electronegativity of the atom or with its charge.

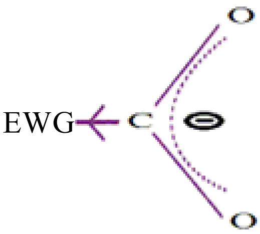
5.2 Inductive effect and basicity

Electron-donating effects increase basicity, whereas electron-withdrawing effects decrease basicity.

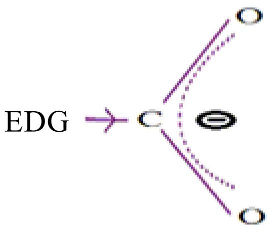
Acid Strength Comparison

To compare the strength of acids, we must see the strength of the conjugate base, and more particularly, in our case, the electron density on oxygen. The higher the density, the stronger the base, the weaker the conjugate acid will be.

Acid	**Conjugate Base**	$\boldsymbol{pK_a}$
		4.75
		4.86



-I stabilizes the $-COO^{\ominus}$ and increases acidity



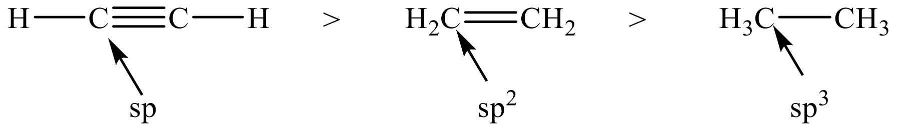
+I destabilizes the $-COO^{\ominus}$ and decreases acidity

For the attractor groups we have: ($NO_2 > F > Cl > Br > I$) which means that Br is more attractant than I, therefore for the conjugated bases, the electron density on the oxygen will be greater in the case of I than in the case of Br, which explains the pKa of their respective acids.

Acid	Electronegativity of X (I, Br, Cl, F)	pK_a
$I—CH_2-COOH$	2.5	3.17
$Br—CH_2-COOH$	2.8	2.87
$Cl—CH_2-COOH$	3.0	2.85
$F—CH_2-COOH$	4.0	2.66

To check the acidity of unsaturated compounds, check the hybridization of the carbon involved. The greater the s character on the carbon, the greater its electronegativity and consequently, its acidity increases.

Therefore, the most acidic among alkynes, alkenes and alkanes is: Alkynes > Alkenes > Alkanes



$$\underset{sp}{H—C{\equiv}C—H} \quad > \quad \underset{sp^2}{H_2C{=}CH_2} \quad > \quad \underset{sp^3}{H_3C—CH_3}$$

6. Mesomeric effect (M)/Resonance effect (R)

The mesomeric (M) or even called resonance effect (R) is a delocalization of electrons on the molecular skeleton. It easily propagates on the molecular backbone by conjugation, resulting in resonance hybrids. It is a property of being able to give or accept a free lone pair of electrons.

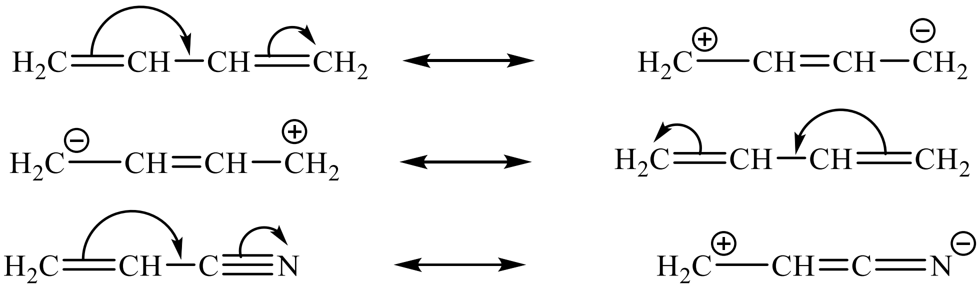
Mesomeric effects result from π-electron delocalization, and contribute significantly to changes in the strength of acids and bases caused by remote substituents, especially via double bonds in conjugation with the ionizable center, including *ortho* or *para* (but not *meta*) substituents in aromatic or heteroaromatic systems.

The mesomeric effect concerns:

- ✓ the π electrons of double or triple bonds

- ✓ the lone pairs of electrons (non-bonding) of heteroatoms (O, N, S,…)
- ✓ charged species such as anions for example

Example:



Resonance structures (or even canonical structures)

The canonical structures are imaginary. There is delocalization whenever there is:

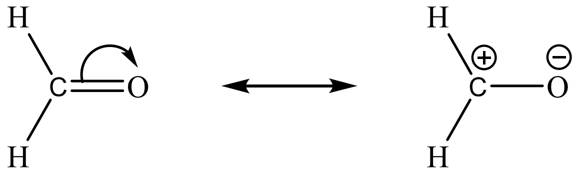
– π electrons of double or triple bonds

– Lone pairs of electrons of heteroatoms (non-bonding electrons of O, N, S, etc.), or anions.

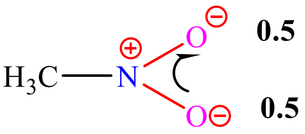
Resonance conditions are:

- ✓ The molecule can be represented by several correct Lewis structures.
- ✓ All resonance structures should differ only in the positions of the electrons and not in the positions of the atoms or nuclei.
- ✓ All structures must have an equal number of valence electrons and unpaired electrons.

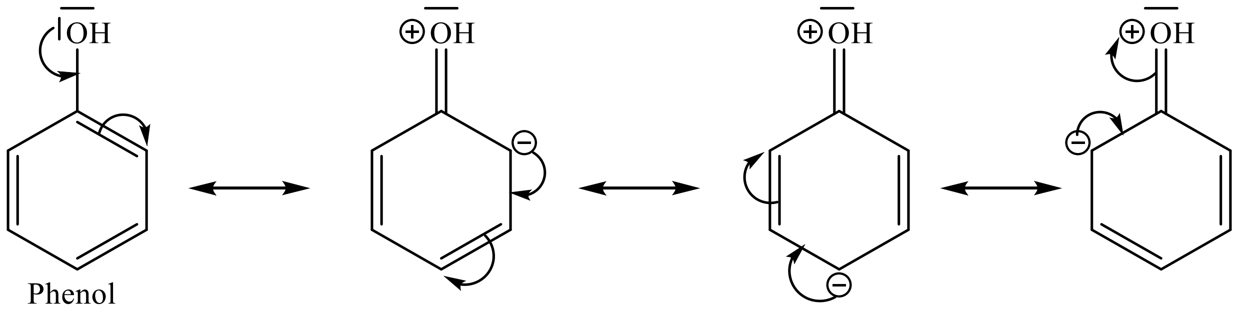
Let’s study the following examples to understand what this means:

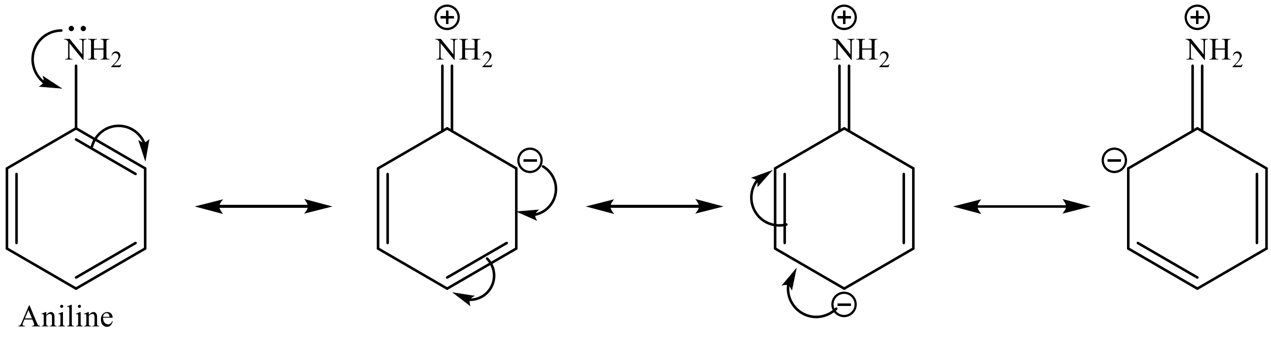


The formaldehyde molecule is said to have two canonical or resonance structures.



Resonance hybrid





Resonance in a given molecule results in a significant increase in its stability compared to the same molecule considered arbitrarily as non-resonant.

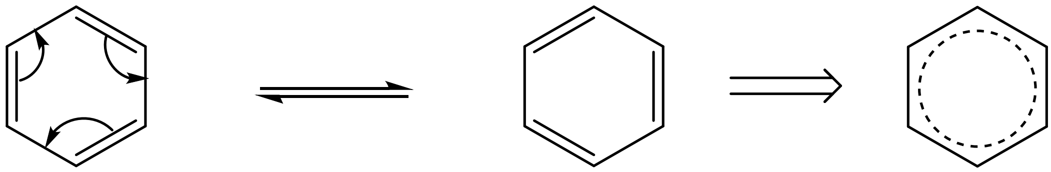
Electronic delocalization on the different atoms constituting a molecule contributes to its stability, the stabilization energy being higher as the dispersion of charges is greater.

As a result, the stabilization energy of a molecule is higher as this molecule has a greater number of resonance or canonical structures and the energy of each canonical structure is greater than that of the actual molecule, because resonance has the property of stabilizing the molecule and therefore reducing its energy.

6.1 Resonance energy

The energy of actual structure of the molecule (the resonance hybrid) is lower than that of any of the canonical structures. The difference in energy between the actual structure (hybrid structure) and the lowest energy resonance structure is called the resonance stabilization energy or even more commonly the resonance energy. The resonance energy of a compound is a measure of the *extra stability* of the conjugated system compared to the corresponding number of isolated double bonds. This energy can be calculated from experimental measurements. The more the number of important contributing structures, the more is the resonance energy.

For example, benzene has two resonance structures and the real structure is the resonance hybrid.



The following diagram shows the experimental heats of hydrogenation, ΔH_h, for the molecules, benzene, cyclohexatriene, 1,3-cyclohexadiene and cyclohexene.

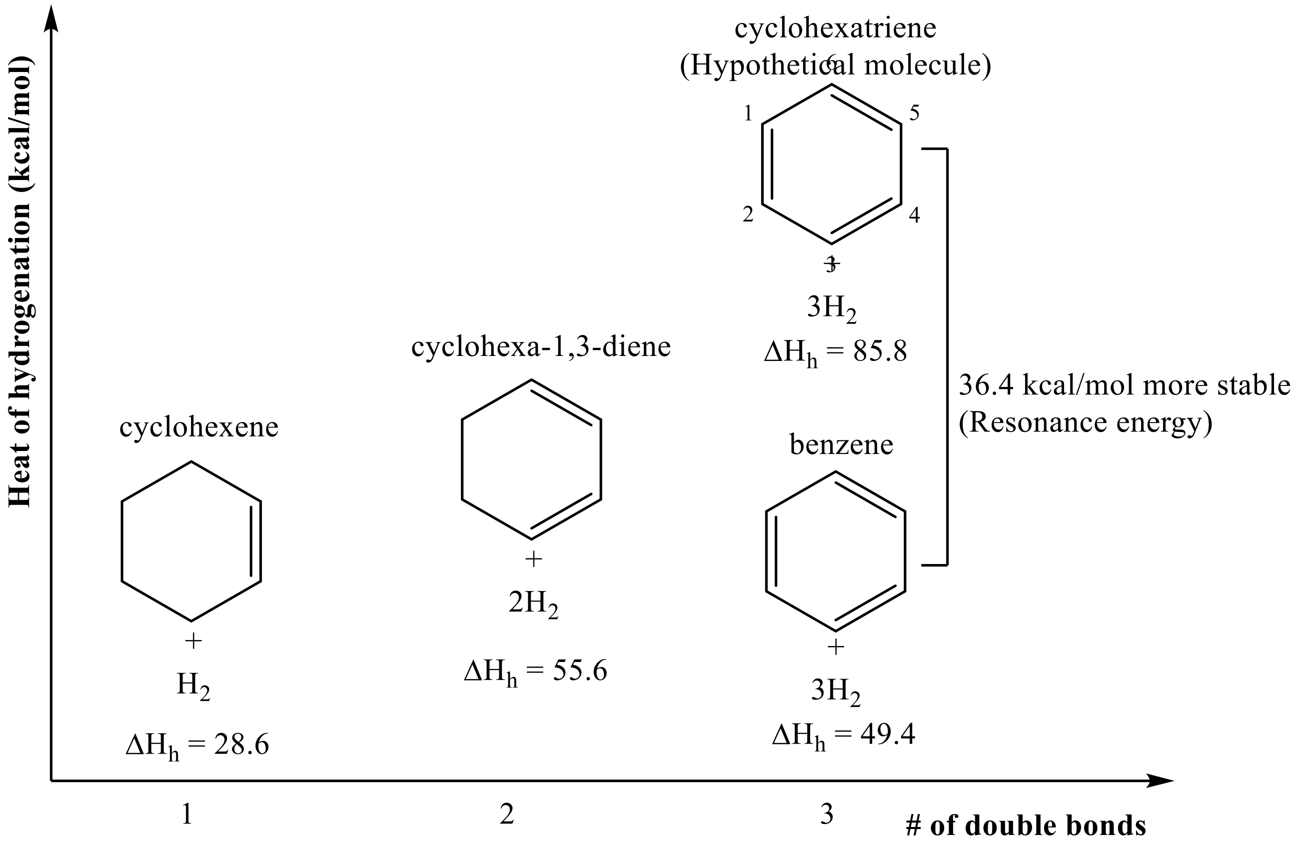


Figure 2: Resonance energy of benzene.

The ΔH_h for "cyclohexatriene", a theoretical molecule in which the double bonds are assumed to be isolated from each other, is calculated to be three times the value for cyclohexene. This value reflects the energy we could expect to be released from three isolated $\boldsymbol{C = C}$.

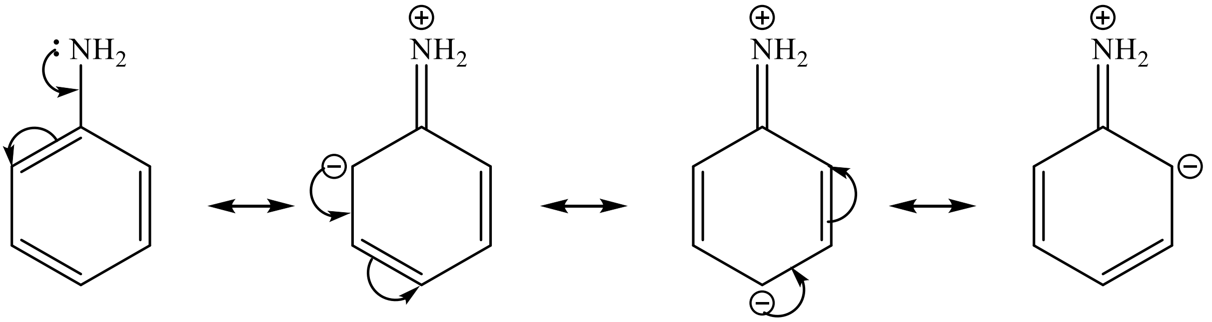
By comparing this value with the experimental value for benzene, we can conclude that benzene is $36.4\ kcal/mol$ more stable than the hypothetical system. This is the ***resonance energy*** for benzene.

6.2 Types of resonance effect

Two types of mesomeric effects can be defined.

a) Positive resonance effect (+R effect/+M effect)

In this effect, the transfer of electrons is away from an atom of substituent group attached to the conjugated system. This electron displacement makes certain positions in the molecule of high electrons densities. This effect in aniline is shown as:



This effect is observed for electron-donating groups such as;

Alkoxide group $-RO^-$

Halogens (Cl, Br, F, I)

Alcohol group $-OH$

Ether group ROR

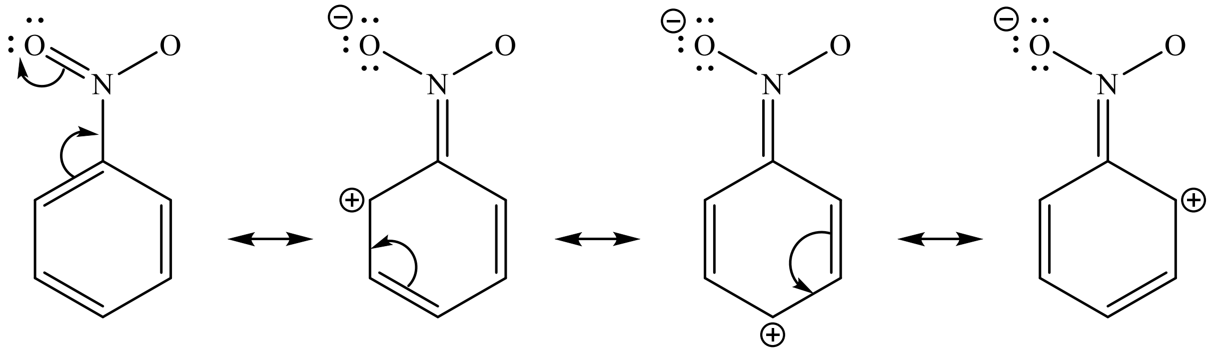
Thioether group RSR

and $-NH_2, -NHR, -NR_2, -NHCOR, -OR, -OCOR$.

- For the $+M$ effect, the group should have either a lone pair of electrons or should have a negative charge.
- The $+M$ effect gives negative charge to the conjugate system which means that the electron density increases on the conjugate system. These conjugate systems show more reactivity towards electrophiles and less reactivity towards a nucleophile.

b) Negative resonance effect (–R effect/-M effect)

This effect is observed when the transfer of electrons is towards the atom or substituent group attached to the conjugated system. This electron displacement makes certain positions in the molecule of low electrons densities. For example, in nitrobenzene, this electron displacement can be depicted as:



This effect is observed for electron-withdrawing groups such as;

Nitro group $-NO_2$

Cyano group $-CN$

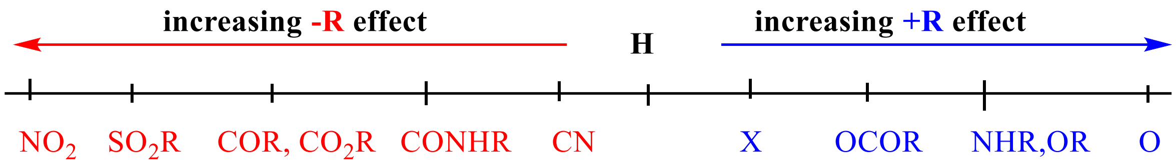
Aldehyde group $-CHO$

Ketone group $> C = O$

Carboxylic acid group $COOH$

Ester group $-COOR$

- For $-M$ effect, the group should have either a positive charge or should have a vacant orbital.
- $-M$ effect makes the compound more reactive towards a nucleophile as it decreases the electron density in the conjugate system and at the same time it is less reactive towards electrophile.



Note:

- The mesomeric effect is always more important than the inductive effect. In the case of a resonance phenomenon, it will be possible to see several resonance structures which reveal the different locations of the charge in the conjugated system.
- Mesomeric effects may enhance or oppose inductive effects.

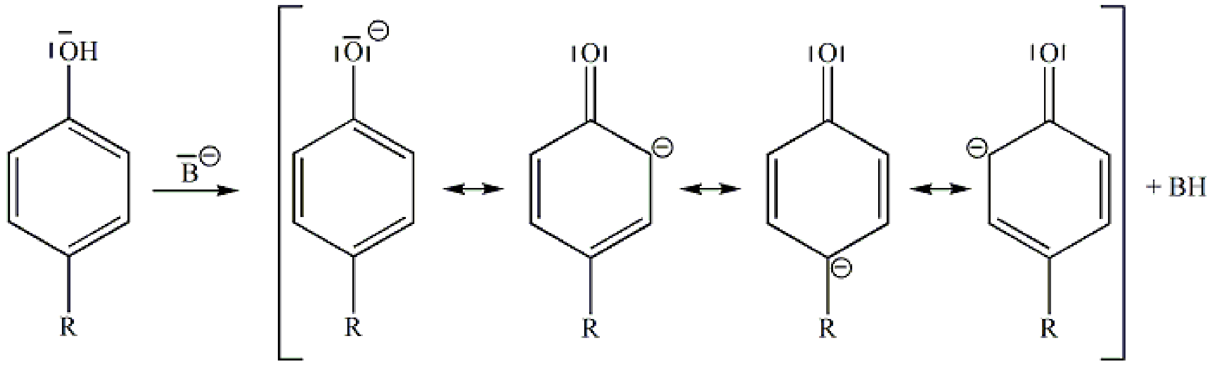
6.3 Mesomeric effect and acidity

a- Acidity of alcohols

Certain groups can have a very great influence on the pK_a of organic compounds. In the case of phenol, it is noticed that the more electron-rich the $O-H$ bond is, the more difficult it will be to break it, therefore the higher the pK_a value will be. On the other hand, the poorer this bond is in electrons, the easier it will be to break it, and therefore the pKa value will be low.

Thus, the existence of an electron-withdrawing group on the phenyl, the $O-H$ bond will become poorer in electrons, therefore easier to break and the pK_a value will decrease (stronger acidity).

While an electron-donating group on phenyl will increase the pK_a value (thus reducing the acidity of the phenol).

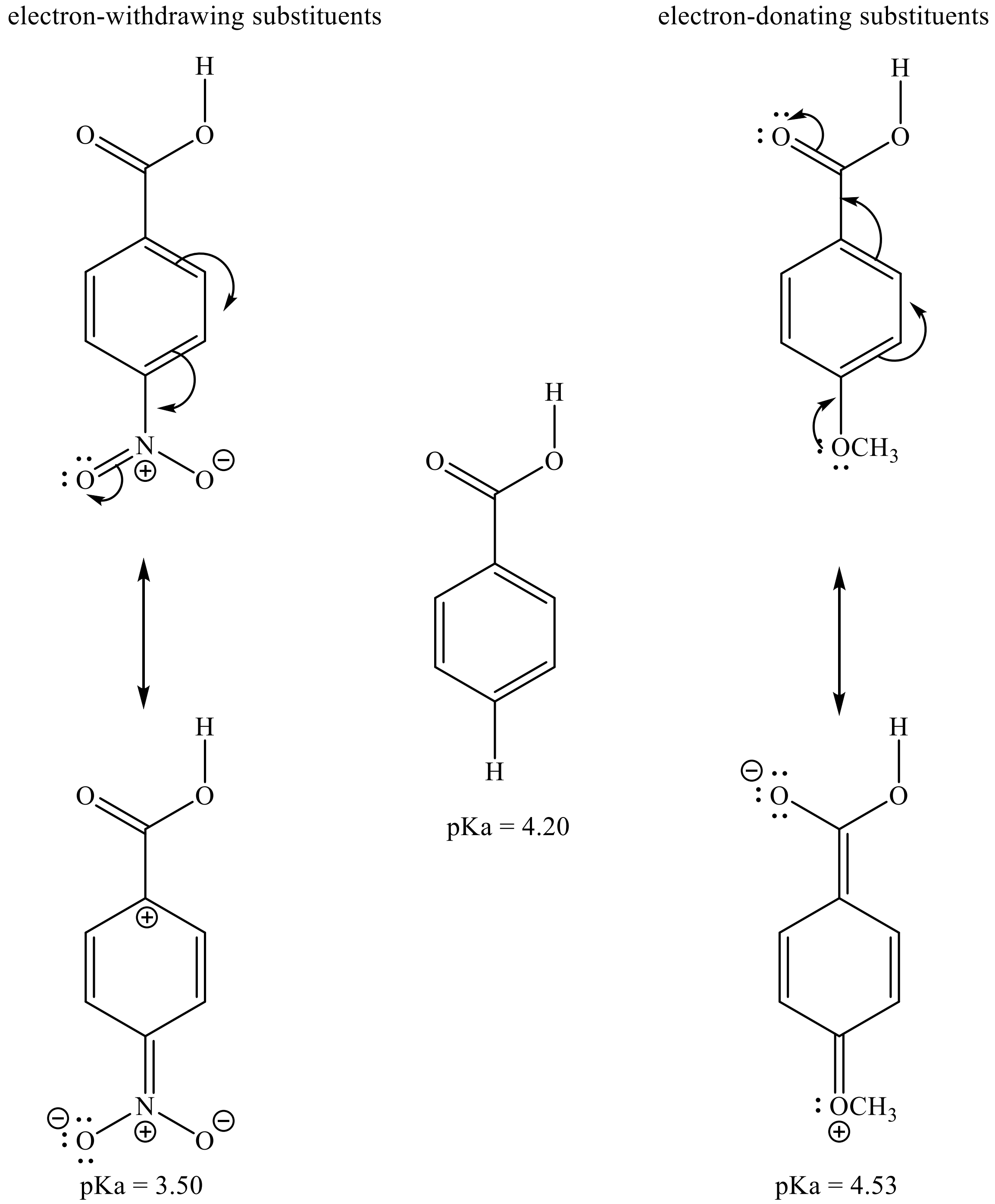


The electronic effect of some groups on phenol is given in the following table.

R	NH_2	OMe	CH_3	H	$COCH_3$	CN	NO_2	$NH(CH_3)_3{}^+$
pK_a	11.2	10.86	10.25	9.89	8.79	8.56	8.24	8.08
Effect	$+M$	$+M$	$+I$		$-M$	$-M$	$-M$	$-I$

b- Acidity of carboxylic acids

In the case of benzoic acids, the presence of mesomeric effects greatly alters the acidity of these products. Thus, in the case of benzoic acids *para*-substituted by an electron-withdrawing group, the electron effect weakens the $O - H$ bond in the acid, and thus increases its acidity. However, an electron-donating group increases the electron density in the acid function group, thereby decreasing the acidity of the compound.

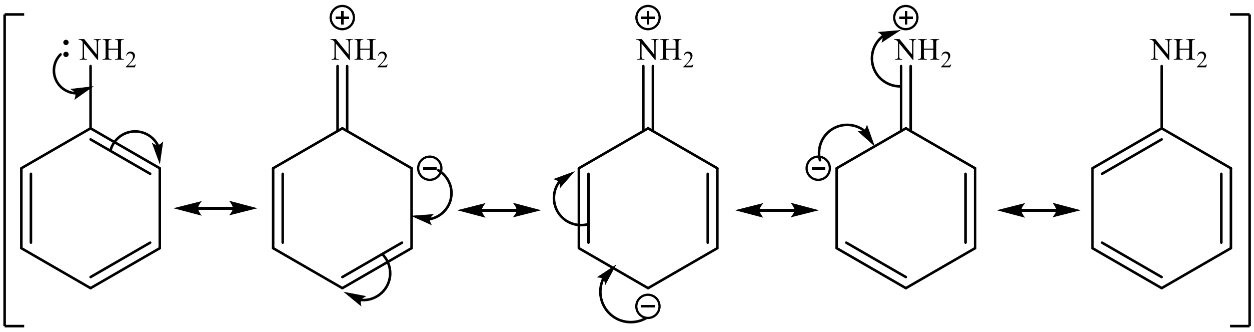


6.4 Mesomeric effect and basicity

Basicity is the property to show basic character. In the case of amines, the basic character is due to the availability of the lone pair on nitrogen.

In general, resonance decreases the basic character of the amines. Especially, aromatic amines are less basic than aliphatic and alicyclic amines. Aromatic amines are compounds that contain an amine functional group ($-NH_2$) attached to an aromatic ring.

The basicity of aniline is lower than that of a typical amine due to the delocalization of electrons caused by resonance. The lone pair of electrons on the nitrogen atom is partially delocalized into the benzene ring, which reduces its availability for donation to a proton.



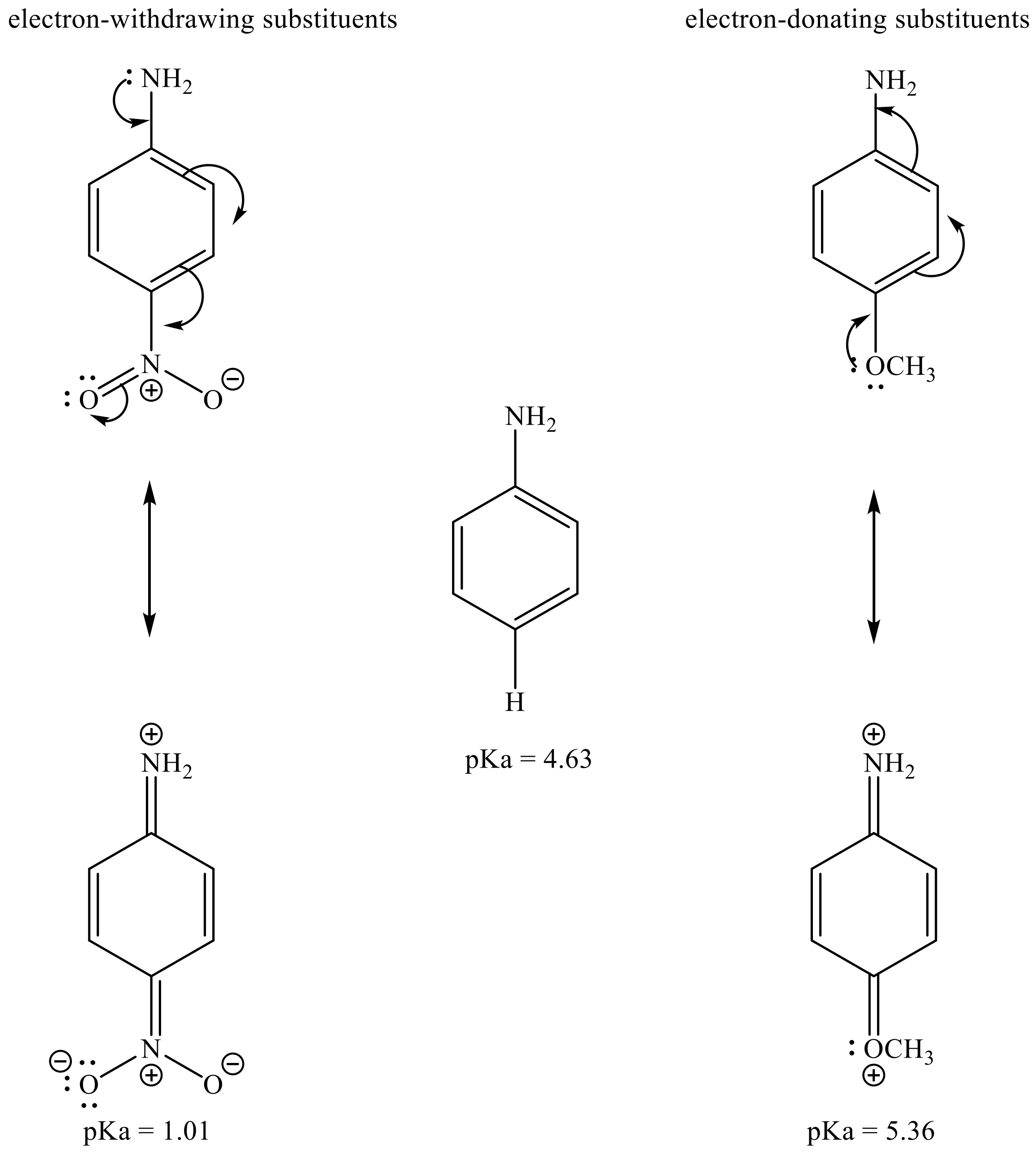
The lone pair of electrons on the N atom of aniline participates in the resonance of the benzene ring, but that of aliphatic amines does not. Therefore, aromatic amines are less basic than aliphatic ones. The reason is that the lone pair of electrons on the nitrogen atom N of aromatic amines is less available to accept a proton (H^+).

However, the basicity of aniline can be increased by substitution on the benzene ring. The effect of substitution on the basicity of aniline depends on the nature and position of the substituent. Electron-donating substituents, such as alkyl groups, increase the basicity of aniline by increasing the electron density on the nitrogen atom. This makes the lone pair of electrons more available for donation to a proton. Electron-withdrawing substituents, such as nitro groups, decrease the basicity of aniline by decreasing the electron density on the nitrogen atom.

Example:

Aniline ($C_6H_5NH_2$) is less basic than methyl amine (CH_3NH_2). This is because, in case of aniline the lone-pair of electrons is involved in resonance with the benzene ring, and hence, not readily available for donation compared to methyl amine in which no resonance occurs.

Electron donating groups in aniline increase the basic character whereas electron withdrawing groups decrease the basic character of the aniline. For example, *para*-nitroaniline is less basic than *para*-methoxyaniline.



7. Reaction intermediates

We have seen that the different effects that the molecule undergoes could result in the formation of carbocation (relative stability is however allowed by resonance), but in certain chemical reactions, there is formation of such compounds due to nucleophilic reagents or electrophiles.

Reaction intermediates are unstable chemical species that appear and disappear quickly during a chemical reaction.

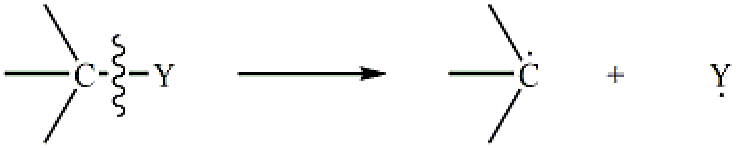
There are four types, among which two are very important:

- the carbocation
- the carbanion

7.1 Radicals

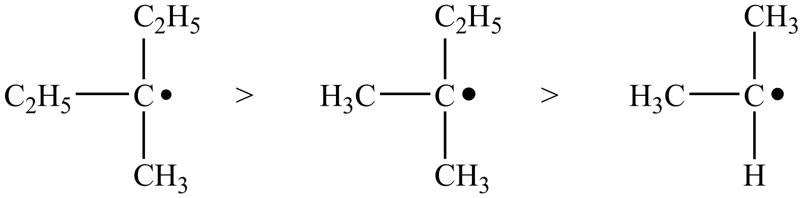
If each atom keeps its electron, the break is homolytic and radicals are formed.

Example:

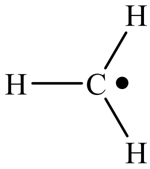


The radicals are generally planar (sp^2, the p_z orbital contains an electron). The more is substituted the radical, the more it is stable.

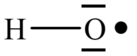
$$\dot{C}_{tertiary} > \dot{C}_{secondary} > \dot{C}_{primary}$$



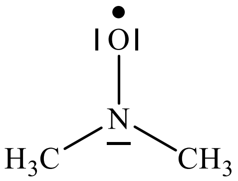
Example:



methyl radical



hydroxyl radical

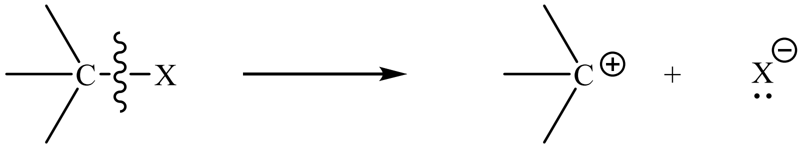


dimethylnitroxyde radical

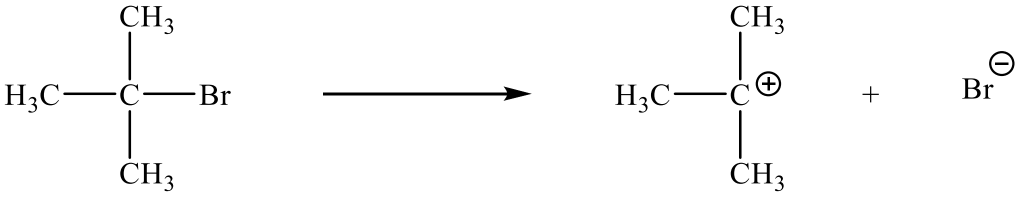
7.2 Carbocations

-If the carbon is linked to a more electronegative atom, the two electrons leave with this atom and the breaking is heterolytic giving rise to the formation of a carbocation.

Example:



carbocation



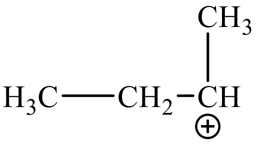
carbocation

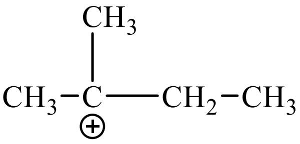
Carbocations are planar (sp^2, p_z orbital is empty) and the more substituted is the carbocation, the more stable it is.

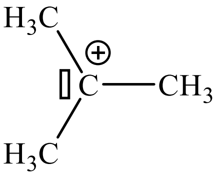
$$C^+_{tertiary} > C^+_{secondary} > C^+_{primary}$$

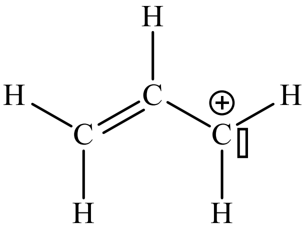
$$(CH_3)_3C^{\oplus} > (CH_3)_2CH^{\oplus} > CH_3CH_2^{\oplus} > CH_3^{\oplus}$$

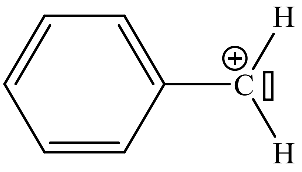
Examples:









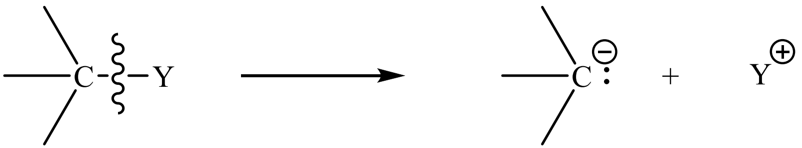


Note:

- Primary carbocation, having two hydrogens is the least stable of all
- Secondary carbocation, having only one hydrogen
- Tertiary carbocation, having no hydrogens is the most stable of all
- CH_3^+ is much more unstable than the primary carbocation.

7.3 Carbanions

If the carbon is linked to a less electronegative atom, the two electrons remain on the carbon, the break is heterolytic and a carbanion is formed.



Examples:

$$R—CH_2{-}MgBr \longrightarrow R—CH_2^{\ominus} + MgBr^{\oplus}$$

Carbanions are tetrahedral (sp^3, p_z orbital contains two electrons) and they are more stable when they are less substituted.

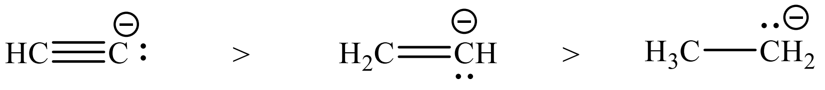
$$C^-_{primary} > C^-_{secondary} > C^-_{tertiary}$$

$$CH_3^{\ominus} > CH_3CH_2^{\ominus} > (CH_3)_2CH^{\ominus} > (CH_3)_3C^{\ominus}$$

Stability of carbanions on the basis of hybridization

The nature and type of hybridization effect can be used to rationalize the relative stability of different carbanions.

As the s-character of carbon bearing negative charge increases, the lone pair gets more and more stabilized; and therefore, overall carbanion stability also increases.



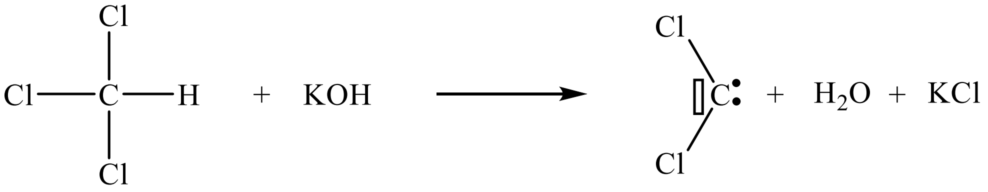
$$HC{\equiv}\overset{\ominus}{C}: \; > \; H_2C{=}\overset{\ominus}{\underset{\cdot\cdot}{C}H} \; > \; H_3C{-}\overset{\cdot\cdot\ominus}{C}H_2$$

50% *s*-character (*sp*-hybridization)	33% *s*-character (*sp*^{2}-hybridization)	25% *s*-character (*sp*^{3}-hybridization)

7.4 Carbenes and nitrenes

Carbenes are neutral chemical species where one carbon atom is divalent (bonded to two atoms). They have a lone pair of electrons and a free unoccupied orbital. Carbenes are generally electrophilic. They mainly attack π double bonds.

Example:



$$CHCl_3 + KOH \longrightarrow :CCl_2 + H_2O + KCl$$

dichlorocarbene

8. Acid-base theory

8.1 Acid-base theory of Bronsted

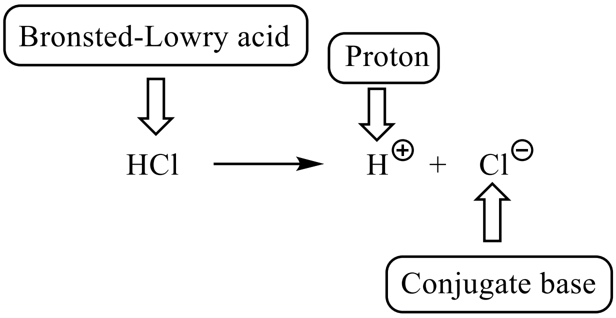
Bronsted-Lowry theory or even called the Proton Theory of Acid and Base, is a theory that explains the concept of acid and base. In the Bronsted-Lowry theory, acids and bases are defined based on proton transfer.

a- Bronsted-Lowry acid definition

Bronsted-Lowry acids are substances which donate a proton or H^+ ion to another compound. In other words, Bronsted acids are proton donors.

$$\boldsymbol{Acid \leftrightharpoons Proton + Conjugate\ Base}$$

Example:

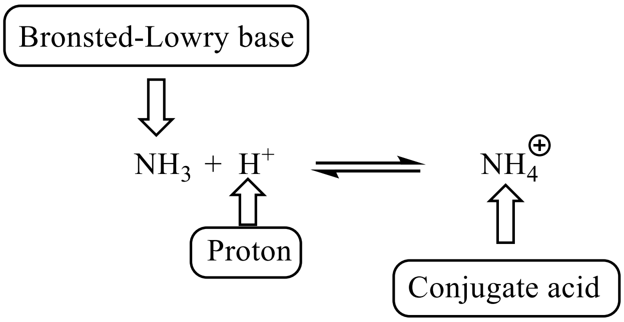


b- Bronsted Lowry base definition

Bronsted-Lowry bases are substances which accept a proton or H^+ ion from another compound. In other words, Bronsted bases are proton acceptors.

$$\boldsymbol{Base + Protons \leftrightharpoons Conjugate\ Acid}$$

Example:



Some examples of reaction with Bronsted-Lowry acids and bases are:

Bronsted-Lowry acid	+	Bronsted-Lowry base		Conjugate base	+	Conjugate acid
HCl	+	NH_3	$\longrightarrow$	$Cl^{\ominus}$	+	$NH_4^{\oplus}$
H_2SO_4	+	H_2O	$\longrightarrow$	$HSO_4^{\ominus}$	+	$H_3O^{\oplus}$
HNO_3	+	CH_3OH	$\longrightarrow$	$NO_3^{\ominus}$	+	$CH_3OH_2^{\oplus}$

8.2 Acid-base theory of Lewis

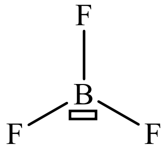
The Lewis acid-base theory is focused on the transfer of electrons between molecules. This theory is widely applicable in various solvents and complex reactions involving non-aqueous systems.

a- Lewis acid definition:

Lewis acids are acceptors of electron lone pairs.

Example:

Reagents which can accept at least one pair of electrons. They are characterized by a vacant orbital (incomplete octet).



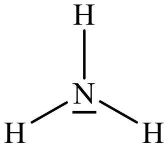
Other examples of Lewis acids are: H^+, Cu^+, Mg^{2+}, Li^+, Al^{3+}, Fe^{3+}, $AlCl_3$, CH_3CO^+, etc.

b- Lewis base definition

Lewis bases are donors of electron lone pairs.

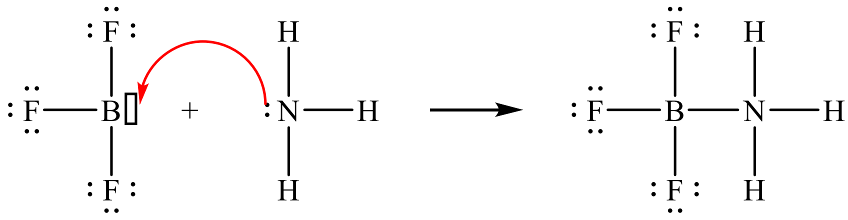
Example:

Reagents which can donate at least one lone pair of electrons such the nitrogen atom.



Other examples of Lewis bases are: Cl^-, OH^-, CH_3^-, SO_4^{2-}, NO_3^-, H_2O, etc.

The reaction between BF_3 and NH_3 lead to:



In this example, the trifluoroborane BF_3 would be the Lewis acid because it has a vacant orbital and then it accepts the electron pair from ammonia NH_3. The NH_3 molecule would be considered as a Lewis base because it donates an electron pair to form the bond between nitrogen and borane.

9. Nucleophilicity and electrophilicity

Nucleophilicity refers to the ability of a nucleophile to displace a leaving group in a substitution reaction. Most common nucleophiles have a negative charge. However, it is the nonbonding electron pair that is important. For example, water, alcohols, ammonia, and amines are nucleophiles even though they are electrically neutral.

Nucleophilicity and basicity reflect the same property, namely the ability to share the lone electron pair (or pairs) with an electron acceptor; thus, to combine with an electrophilic substrate. Nucleophilicity is a kinetic phenomenon and is determined at kinetically controlled conditions whereas basicity is determined at conditions controlled thermodynamically.

Definition

Electrophilicity is defined as the ability of an electrophile to acquire additional electronic charge.

9.1 Nucleophiles / electrophiles

The inductive and mesomeric effects lead to inequalities inside the molecules, consequently centers rich in energy and others poor in energy appear.

Definition

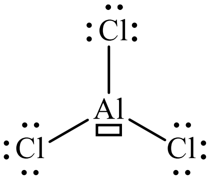
Nucleophile (Nu^-): center rich in electrons (anionic or molecule having a non-bonding doublet): reaction with a center poor in electrons (electrophile)

Example: $CN-$, $Cl-$, $R-$, NH_3, $R-OH$, ….

Electrophile (E^+): electron-poor center (cationic or molecule with an electron-deficient center): reaction with an electron-rich center (nucleophile)

Example: NO_2^+, H^+, R^+, $AlCl_3$, BF_3, $ZnCl_2$….

In the $AlCl_3$ molecule, all chlorine atoms have full octets (three lone pairs of electrons and a bond with the aluminum each). Aluminum, however, only has three bonds with the chlorine atoms (six bonding electrons) and thus does not respect the octet rule. In other words, aluminum is deficient in electrons. For this reason, aluminum tries to gain electrons and therefore acts as an electrophile.



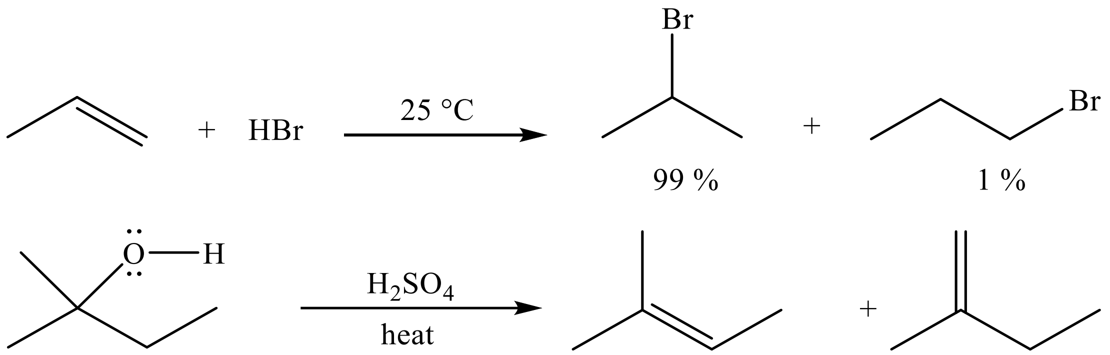
Similarly, BF_3 and $FeCl_3$ also act as electrophiles because B and Fe are electron deficient in these molecules.

10. Orientation of reactions (selectivity)

10.1 Regioselectivity

A reaction is said to be regioselective if, being able to give two (or more) constitutional isomers, it gives one (or some) in the majority.

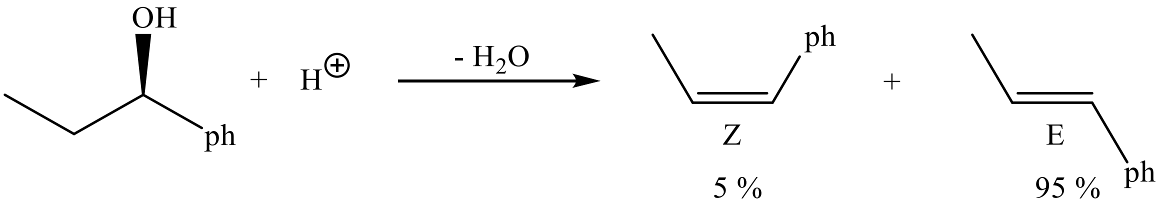
Example:



10.2 Stereoselectivity

A reaction is said to be stereoselective if, being able to give several configurational stereoisomers, it gives some of them mainly (or even exclusively).

Example:

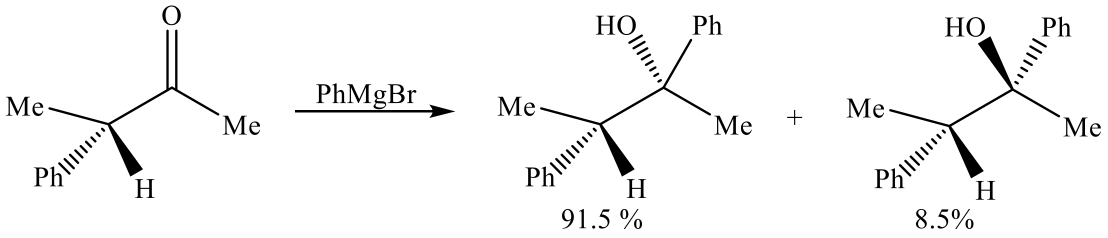


When talking about stereoselectivity two cases can be distinguished: diastereoselectivity and enantioselectivity.

a- Diastereoselective reaction

A stereogenic center is introduced into a molecule in such a way that diastereomers are produced in unequal amounts.

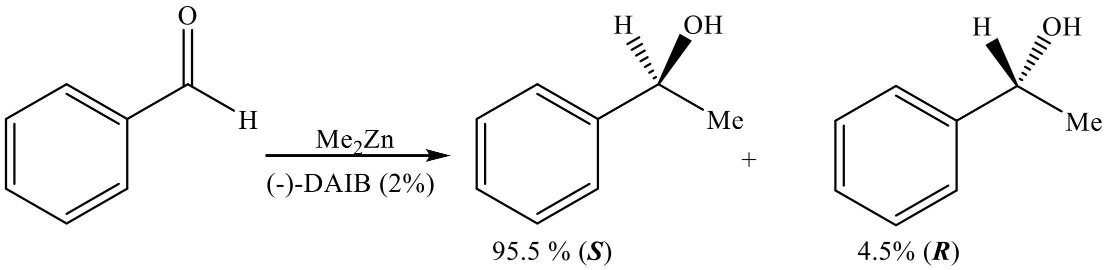
Example:



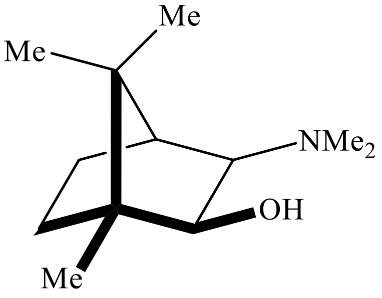
b- Enantioselective reaction

It is a reaction that produces two enantiomers of a product in unequal amounts. Enantioselectivity is achieved by using chiral substrate, reagent, catalyst or solvent.

Example:



The (-)-DAIB structure is:



(-)-DAIB

To show the stereoselectivity of a reaction, the reactants and products must be represented in 3D.

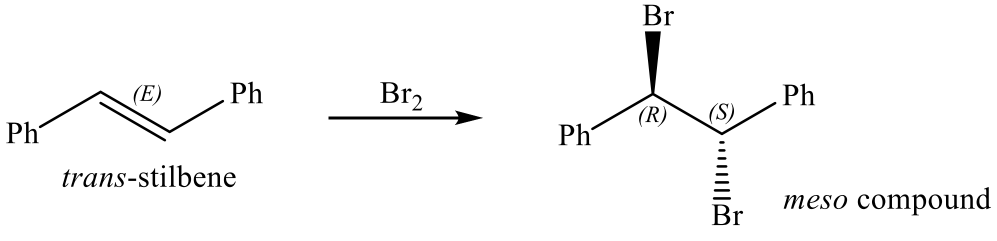
10.3 Stereospecificity

A reaction is said to be stereospecific if the configuration of the products depends on that of the reactants. To show the stereospecificity of a reaction, it is necessary to choose two reagents of different configurations and show that the products obtained from each of the two reagents are then of different configurations.

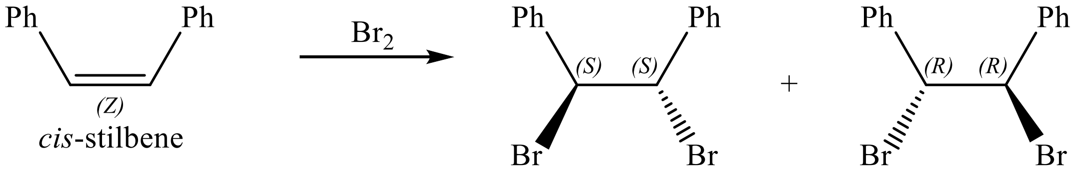
A stereospecific reaction is necessarily stereoselective but not every stereoselective reaction is stereospecific.

Example:

Reaction 1:



Reaction 2:



enantiomers

In the example above, we have a situation where a specific stereoisomer of the starting compound (*trans*-stilbene) gives a specific stereoisomer for the product (a *meso* compound).

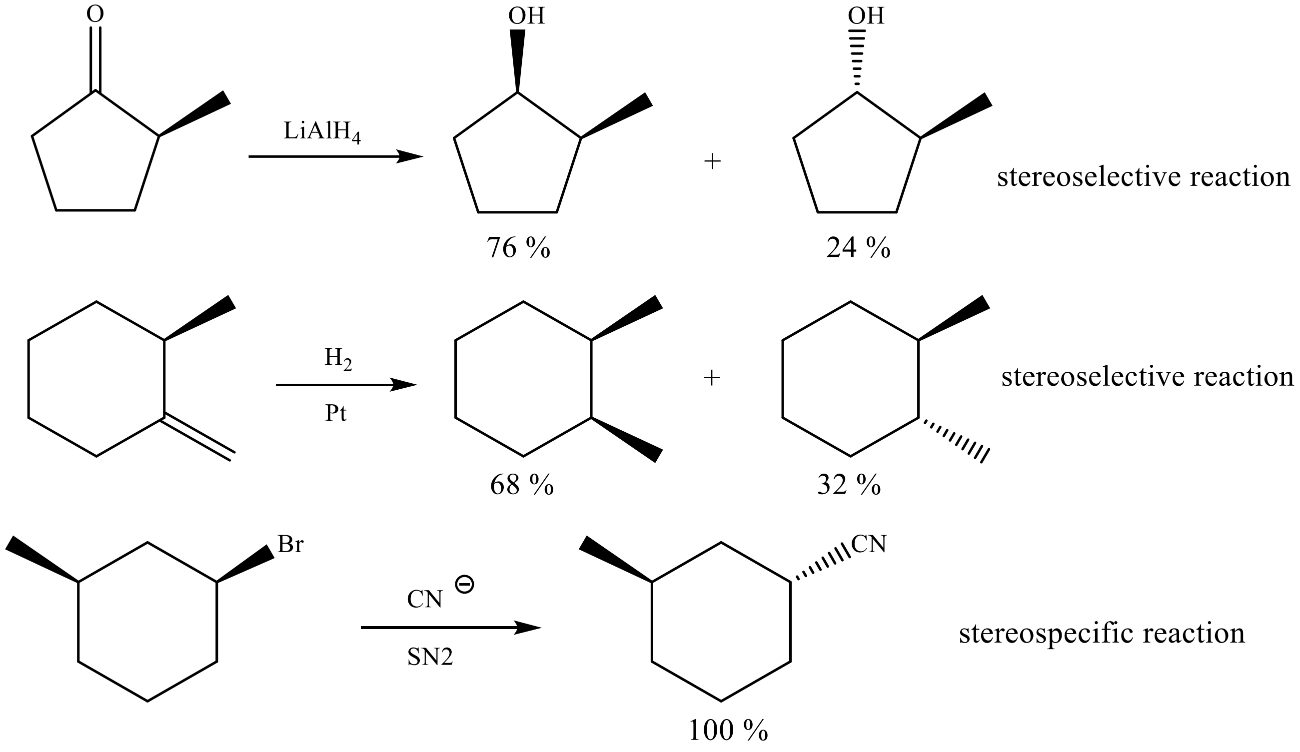
Likewise, the starting compound *cis*-stilbene, specifically, yields a pair of enantiomers. Note that due to the stereospecificity of the halogenation (anti-addition) reaction mechanism, *trans*-stilbene will never give you an enantiomer pair while *cis*-stilbene will never give you the *meso* compound.

So, essentially, if the reaction is stereospecific and the starting molecules are diastereomeric, the products will also be diastereomeric.

Something very important to keep in mind: stereospecific is the description of the reaction mechanism, while stereoselective is the description of the reaction result!

Thus, the reaction can be both stereospecific and stereoselective since the terms describe different aspects of the reaction.

Example: Stereoselectivity and stereospecificity



The first two reaction gives you two stereoisomers with different amount *i.e.* one is major and the other one is minor. These two reactions give a remarkable preference to one stereoisomer over another. So, they are stereoselective. The third reaction, however, gives exclusively one stereoisomer. Thus, it is called stereo***specific***.

11. Solvents

In chemistry, solvents – which are generally in liquid form – are used to dissolve, suspend or extract other materials, usually without chemically changing either the solvents or the other materials.

11.1 Definition of solvent

Solvent can be defined as a substance (usually a liquid) added to dissolve other substance(s).

Solvents can be organic or inorganic. Organic solvents are described as carbon-based substances capable of dissolving or dispersing one or more other substances. In other words, it is a compound that is capable of breaking apart the solute particles. These chemicals include aliphatic hydrocarbons, halogenated hydrocarbons, aliphatic alcohols, glycols and glycol ethers, and aromatic hydrocarbons.

Organic solvents are used to dissolve organic compounds. Different organic solvents can dissolve different kinds of organic compounds. In organic synthesis, specific solvents must be used with respect to the nature of the reaction conditions being used.

Solvents are commonly characterized with the dielectric constant symbolized as ε.

11.2 Dielectric constant

The dielectric constant, also known as the relative permittivity, is a dimensionless constant that describes how a material behaves in an electric field compared to vacuum. It reflects the material's response to an electric field and is related to its polarity.

$$F = \frac{q_1 q_2}{4\pi \varepsilon_r r^2}$$

Where F is the Coulomb force, q_1 and q_2 represent ion charges, ε_r is the dielectric constant, and r is the internuclear distance between ions.

The dielectric constant measures the polarity of a given solvent. The higher the dielectric constant of a solvent, the more polar it is.

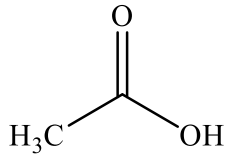
11.3 Classification of solvents

Solvents can be classified to two main categories, polar with high dielectric constant (generally $\varepsilon > 10$) and nonpolar with low dielectric constant (generally $\varepsilon < 10$). Polar solvents have a molecular structure that has a high dipole moment, which facilitates the solubilization of polar molecules (molecules presenting a dipole) by intermolecular associations between dipoles. The polar category is divided into protic and aprotic solvents.

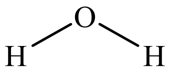
Thus, a protic solvent is a solvent made up of molecules potentially donating H^+ protons (possessing a positively polarized hydrogen atom H). An aprotic solvent does not have this property.

a- Polar protic solvents have large dipole moments and high dielectric constants (polar) and contain $O-H$ or $N-H$ bonds (protic). They have the ability to form hydrogen bonds.

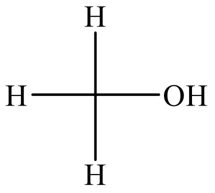
Acetic acid is a polar protic solvent and can form hydrogen bonds with molecules since it has $O-H$ bond. Therefore, it has a higher solubility in water.



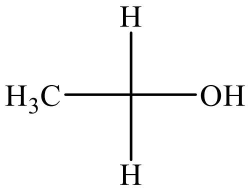
Examples:



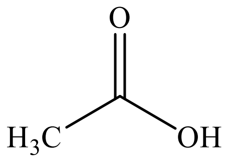
Water



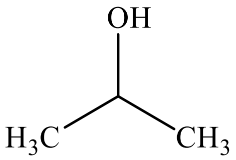
Methanol



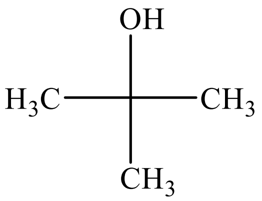
Ethanol



Acetic acid



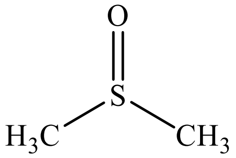
Isopropanol



Tert-butanol

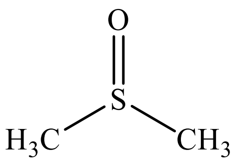
b- Polar aprotic solvents do not have acidic protons and so they do not act as donors during hydrogen bonding. Their dielectric constants and dipole moments are intermediate and low. Unlike polar protic solvents, they do not have $N-H$ bonds and $O-H$ bonds.

Dimethylsulfoxide or DMSO is a good example of a polar aprotic solvent. Its structure is given below.

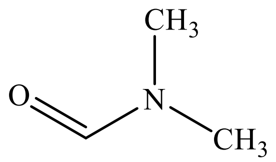


Remember that aprotic solvents are those that are not capable of forming hydrogen bonding interactions. As you can see from the structure, DMSO does not contain $N-H$ or $O-H$ bonds that are needed for the formation of hydrogen bonds.

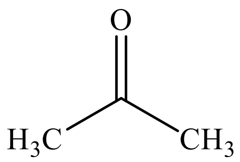
Examples:



Dimethylsulfoxide



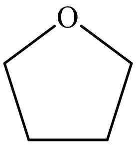
N,N-Dimethylformamide



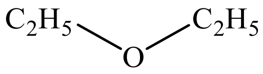
Acetone

c- Non-polar solvents are compounds that have low dielectric constants and are not miscible with water such as carbon tetrachloride (CCl_4). Hydrocarbon solvents are nonpolar (toluene, benzene, hexane, etc.). This kind of solvents contains atoms with similar or comparable electronegativity, such as carbon and hydrogen. Such atoms form bonds with a noticeable lack of positive and negative partial charges which makes these molecules "non-polar".

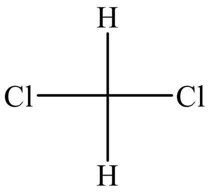
Examples:



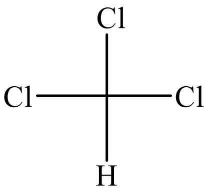
Tetrahydrofuran



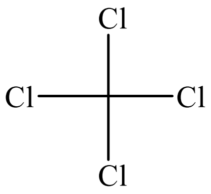
Diethylether



Dichloromethane

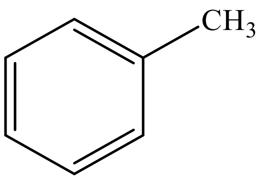


trichloromethane

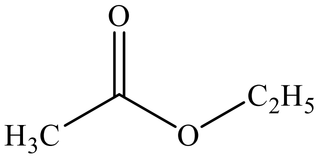


tetrachloromethane

hexane



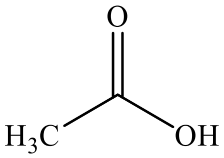
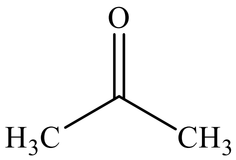
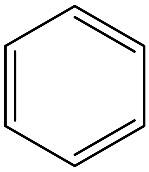
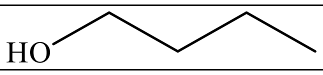
toluene

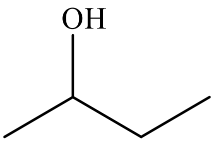
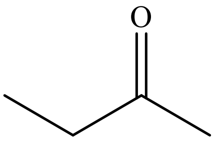
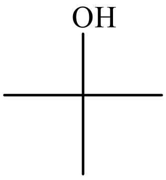
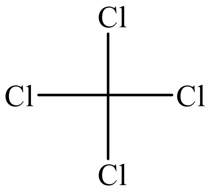
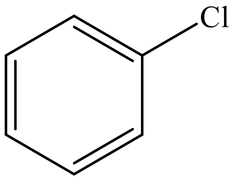
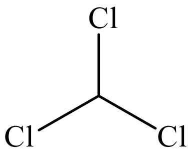
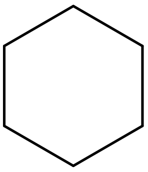
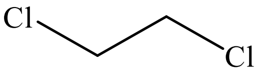
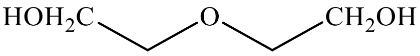
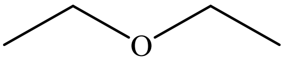
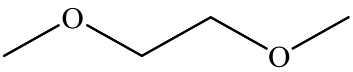
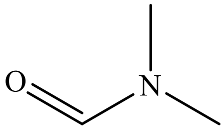
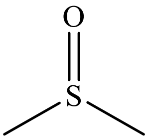


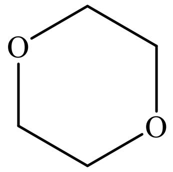
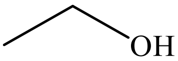
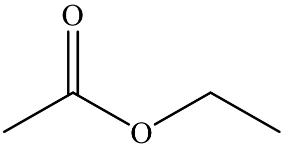
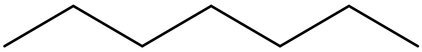
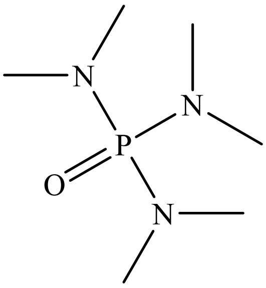
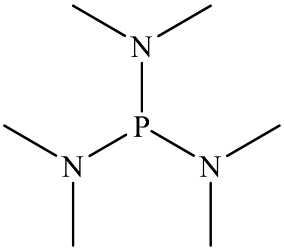
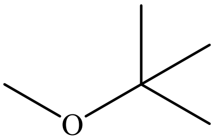
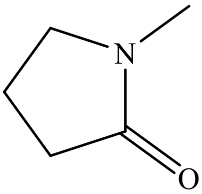
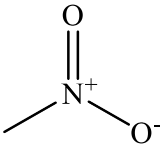
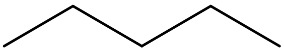
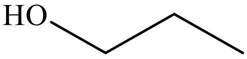
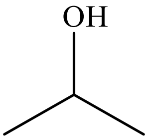
Ethylacetate

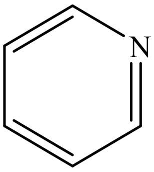
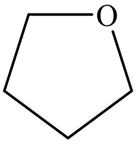
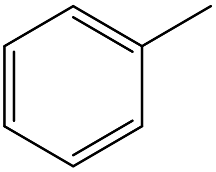
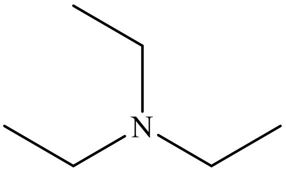
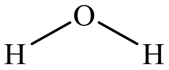
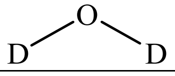
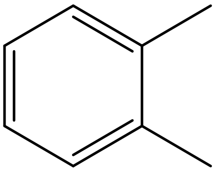
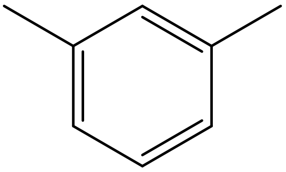
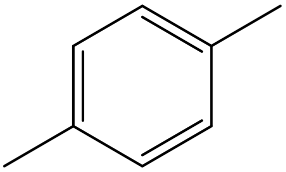
The following table shows some common solvents used in an organic chemistry laboratory.

Table 3: Common solvents used in organic chemistry.

Solvent	Formula	Structure
acetic acid	$C_2H_4O_2$	
acetone	C_3H_6O	
acetonitrile	C_2H_3N	$N\equiv CH_3$
benzene	C_6H_6	
1-butanol	$C_4H_{10}O$	

2-butanol	$C_4H_{10}O$	
2-butanone	C_4H_8O	
t-butyl alcohol	$C_4H_{10}O$	
carbon tetrachloride	CCl_4	
chlorobenzene	C_6H_5Cl	
chloroform	$CHCl_3$	
cyclohexane	C_6H_{12}	
1,2-dichloroethane	$C_2H_4Cl_2$	
diethylene glycol	$C_4H_{10}O_3$	
diethylether	$C_4H_{10}O$	
1,2-dimethoxyethane (glyme, DME)	$C_4H_{10}O_2$	
dimethylformamide (DMF)	C_3H_7NO	
dimethylsulfoxide (DMSO)	C_2H_6OS	

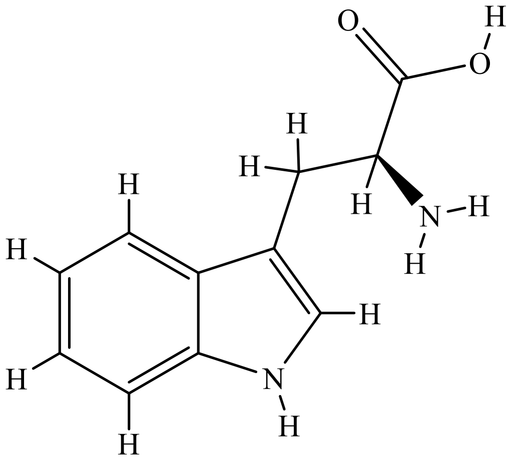
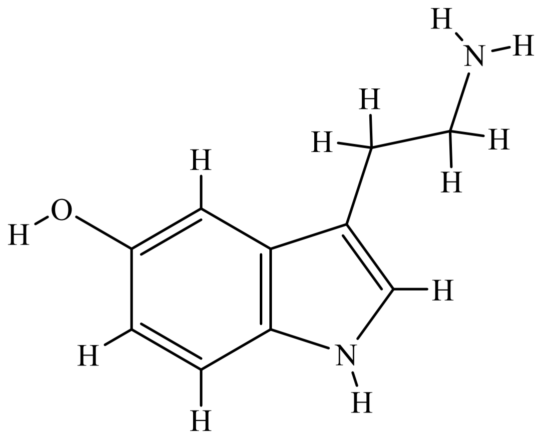
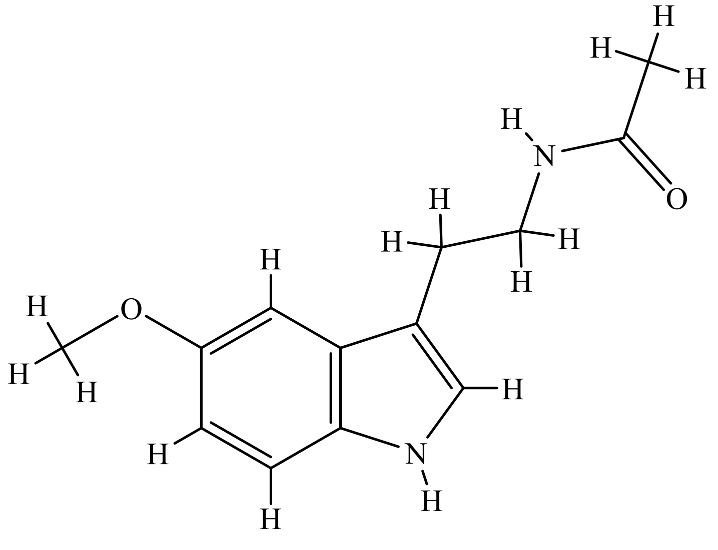
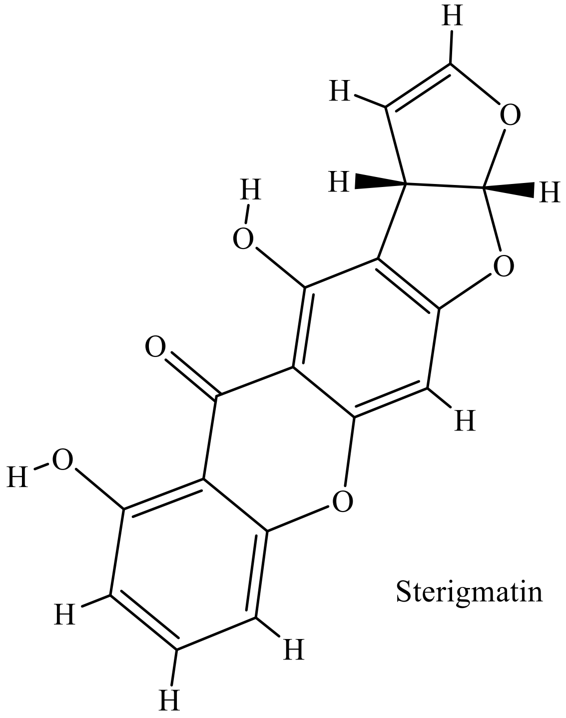
1,4-dioxane	$C_4H_8O_2$	
ethanol	C_2H_6O	
ethylacetate	$C_4H_8O_2$	
heptane	C_7H_{16}	
hexamethylphosphoramide (HMPA)	$C_6H_{18}N_3OP$	
hexamethylphosphorous triamide (HMPT)	$C_6H_{18}N_3P$	
hexane	C_6H_{14}	
methyl *t*-butylether (MTBE)	$C_5H_{12}O$	
N-methyl-2-pyrrolidinone (NMP)	C_5H_9NO	
nitromethane	CH_3NO_2	
pentane	C_5H_{12}	
1-propanol	C_3H_8O	
2-propanol	C_3H_8O	

pyridine	C_5H_5N	
tetrahydrofuran (THF)	C_4H_8O	
toluene	C_7H_8	
triethyl amine	$C_6H_{15}N$	
water	H_2O	
heavy water	D_2O	
o-xylene	C_8H_{10}	
m-xylene	C_8H_{10}	
p-xylene	C_8H_{10}	

EXERCISES

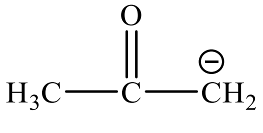
Exercise 1:

For the following molecules, determine the sp^3 and sp^2 hybridized carbons.

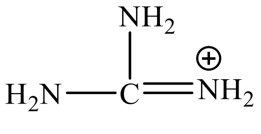
 Tryptophan	 Serotonin
 Melatonin	 Sterigmatin

Exercise 2:

Draw the possible resonance structures for the following species:

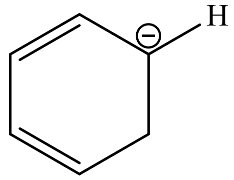


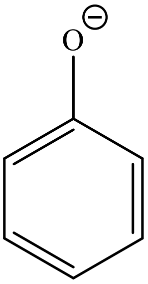
$H_3C-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\ominus}{C}H_2$

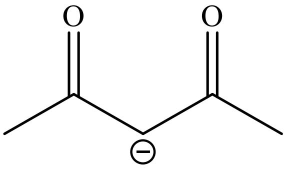


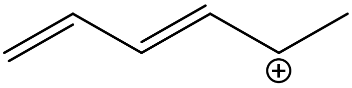
$H_2N-\overset{\overset{\displaystyle NH_2}{|}}{C}=\overset{\oplus}{N}H_2$

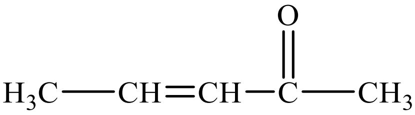
$H_3C-S-\overset{\oplus}{C}H_2$



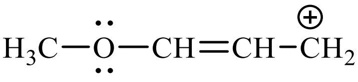




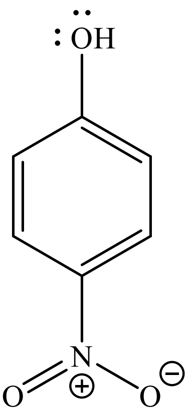




$H_3C-CH=CH-C(=O)-CH_3$



$H_3C-\ddot{O}-CH=CH-\overset{+}{C}H_2$

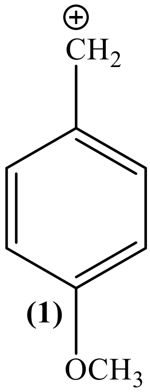


Exercise 3:

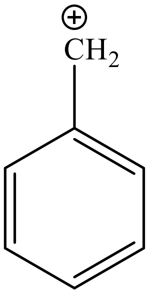
1. Arrange the following carbocation in the increasing order of stability.

$CH_3CH_2^+, (CH_3)_3C^+, (CH_3)_2CH^+, CH_3^+$

2. Give the relative stabilities of the following carbocation in decreasing order.



(1)



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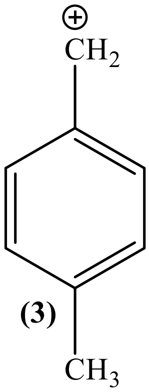

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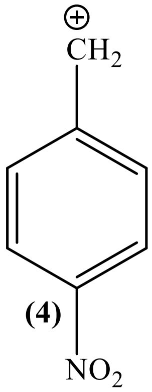
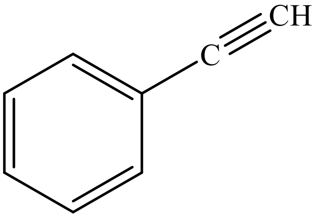
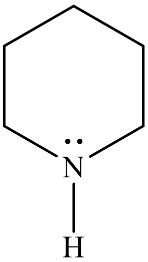


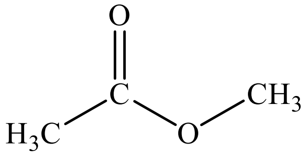
(4)

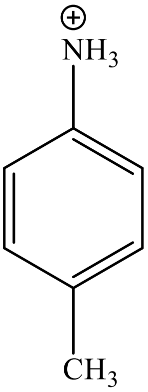
Exercise 4:

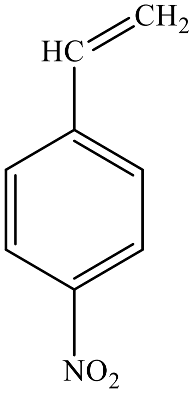
Show the direction of inductive effect in the following compounds:

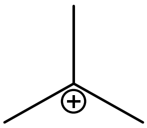






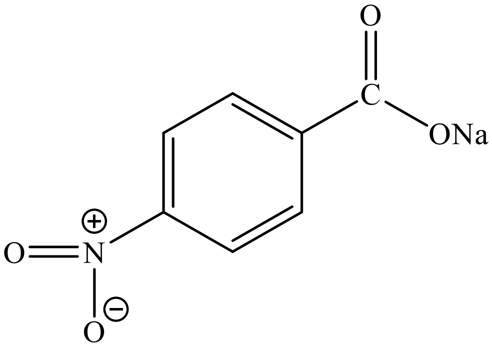


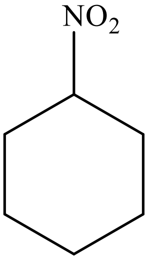


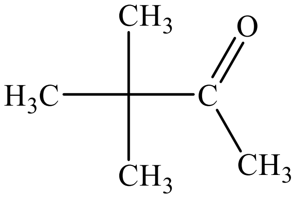


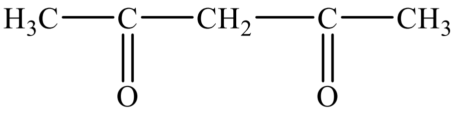
$H_3C—CH_2—CH_2—MgBr$

$H_3C—CH=CH_2$ $H_3C—CH_2—OH$ $H_3C—CH_2—CH_2—Li$



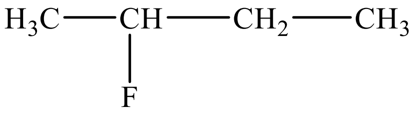






$H_3C—\underset{\|\atop O}{C}—CH_2—\underset{\|\atop O}{C}—CH_3$

$H_3C—COOH$



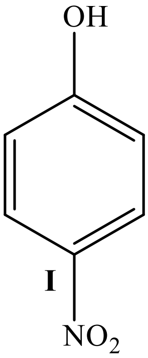
$H_3C—\underset{|\atop F}{CH}—CH_2—CH_3$

$H_3C—CH=CH—NO_2$ $HOOC—CH_2—CH_3$ $^{\ominus}OOC—CH_2—CH_2—CH_3$

Exercise 5:

Give the decreasing acidity order of the following derivatives of phenol.

a)



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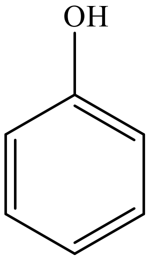

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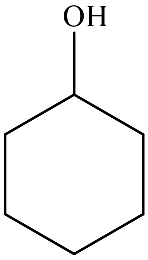

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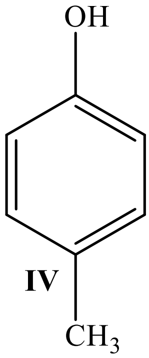

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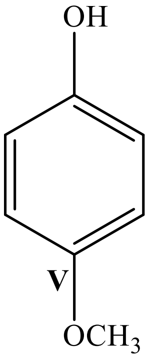
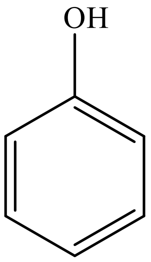


V

b)



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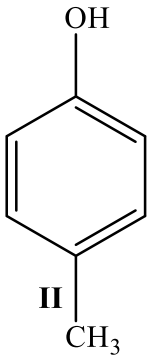

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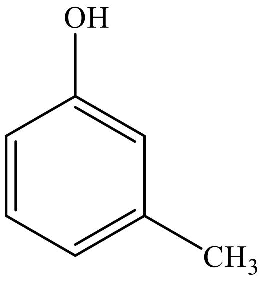

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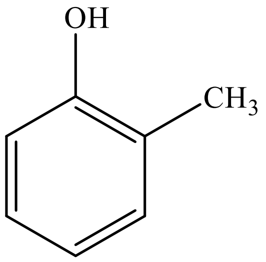
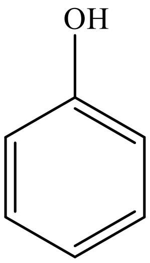


IV

c)



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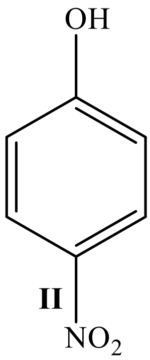

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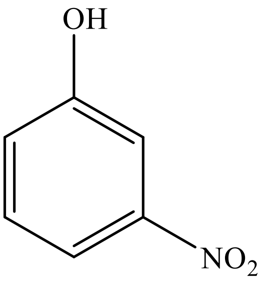

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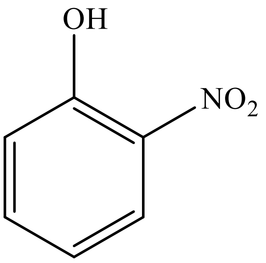


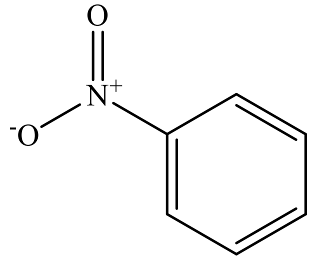
IV

Exercise 6:

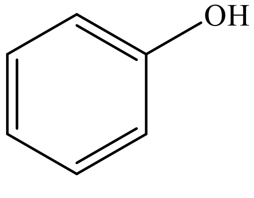
Arrange in order of acidity the following compound: acetic acid, acetone, phenol, acetaldehyde, ethanol, ethyl acetate, 2,4-pentanedione, trifluoroacetic acid.

Exercise 7:

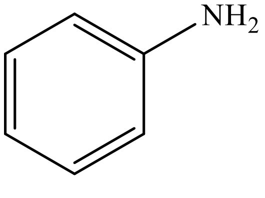
Indicate, based on the corresponding resonant forms, how the functional group (electron-donor or electron-acceptor of charge) affects the hydrocarbon structures: a) nitrobenzene; b) phenol; c) aniline; d) toluene.



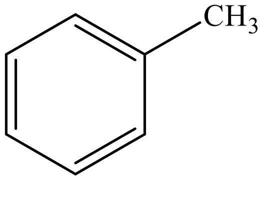
nitrobenzene



phenol



aniline

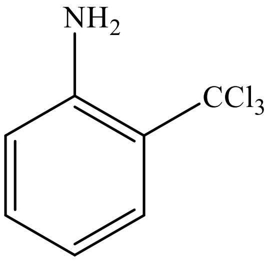


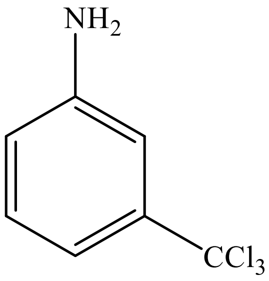
toluene

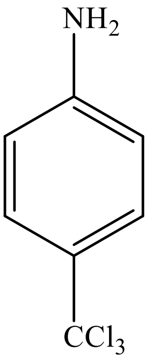
Exercise 8:

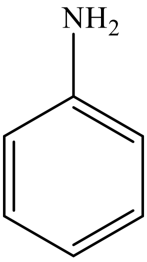
Give the order of decreasing basicity of the following molecules.

a)

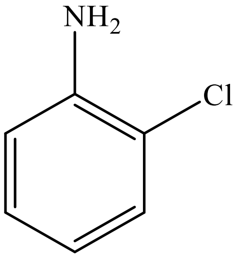


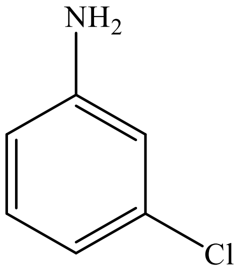


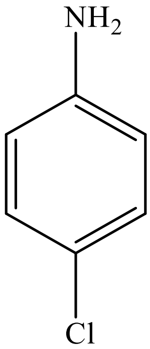


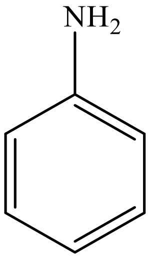


b)









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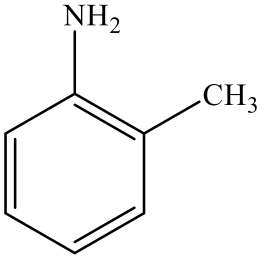

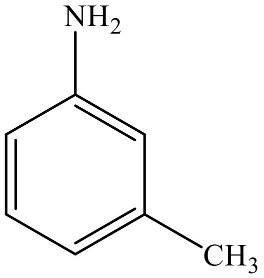

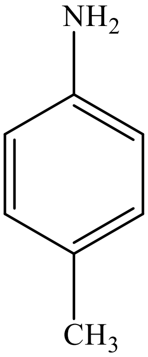

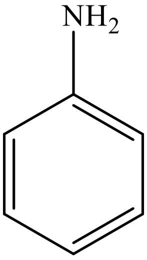

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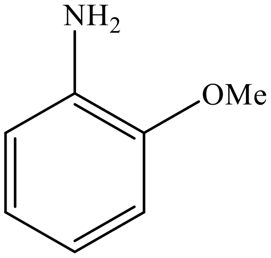
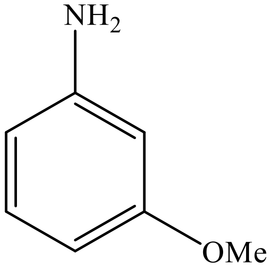
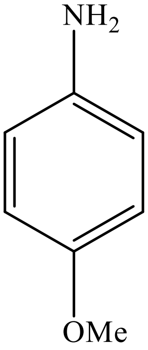
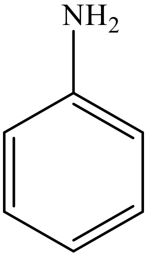


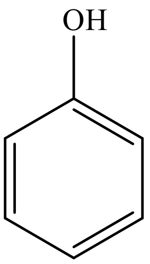




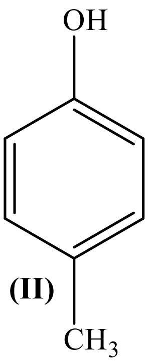


Exercise 9:

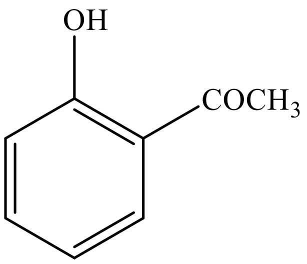
1. Rank the following molecules in order of decreasing acidity.



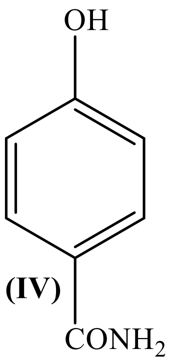
(I)



(II)

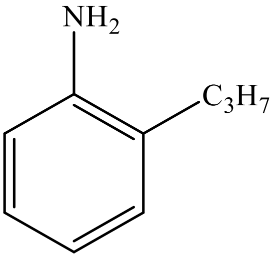


(III)



(IV)

2. Select the basic strength order of the following molecules.



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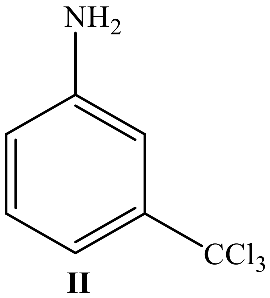

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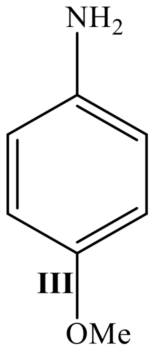

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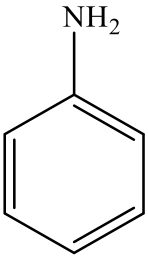
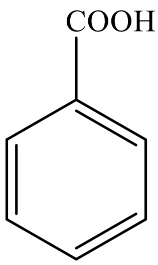


IV

3. Give the right order of decreasing acidity of the following carboxylic acids.



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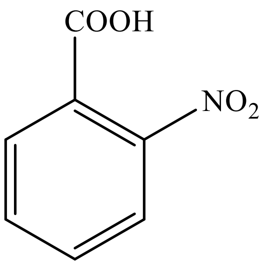

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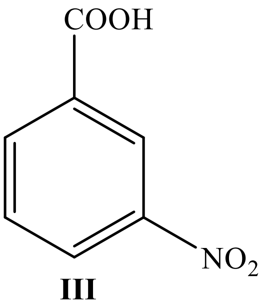

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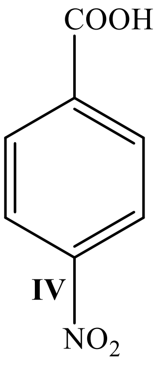
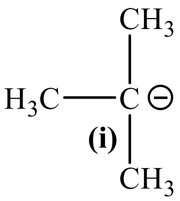


IV

Exercise 10:

a- Give the decreasing order of basicity for the following intermediates (from weak to strong).



$(CH_3)_3C^{\ominus}$

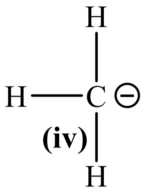
(i)

$H_2C{=}CH{-}\overset{\ominus}{C}H_2$

(ii)

$HC\equiv C^{\ominus}$

(iii)



$H_3C^{\ominus}$

(iv)

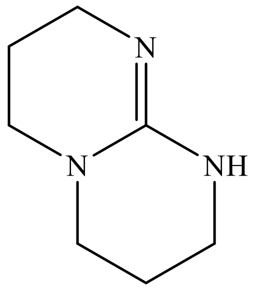
$\overset{\ominus}{C}\equiv N$

(v)

b- Give the decreasing order of pK_b for the following compounds:

$H_2N-CH=NH$

A



B

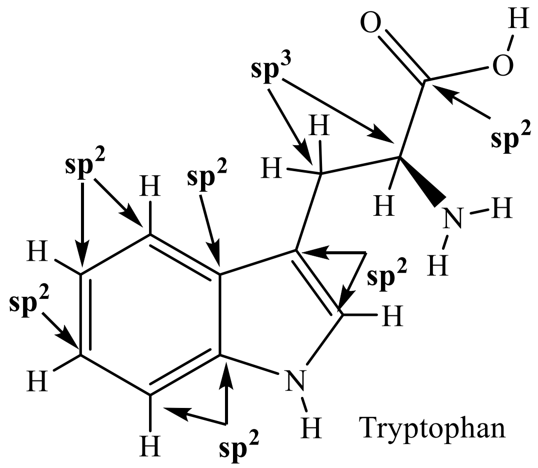
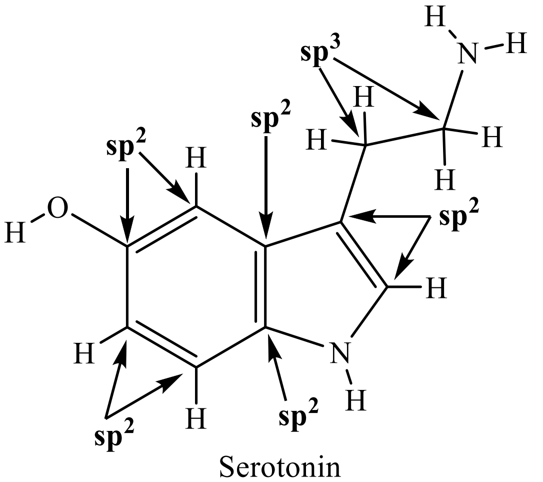
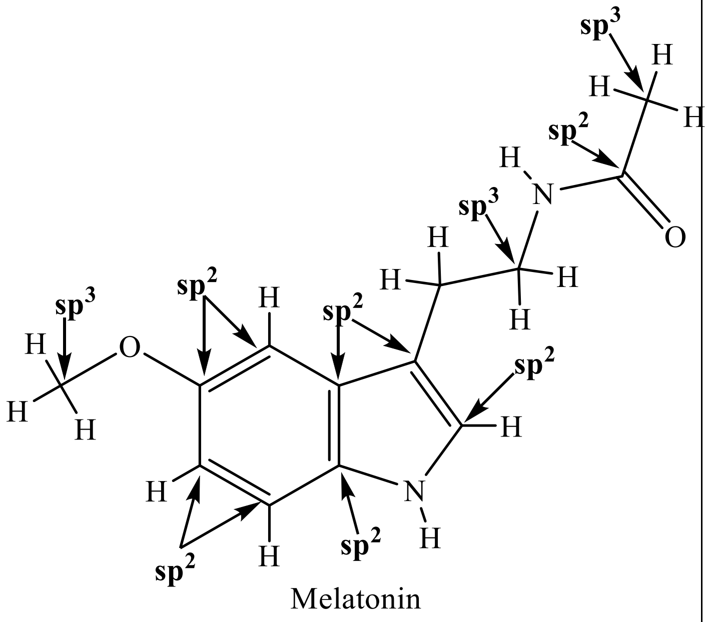
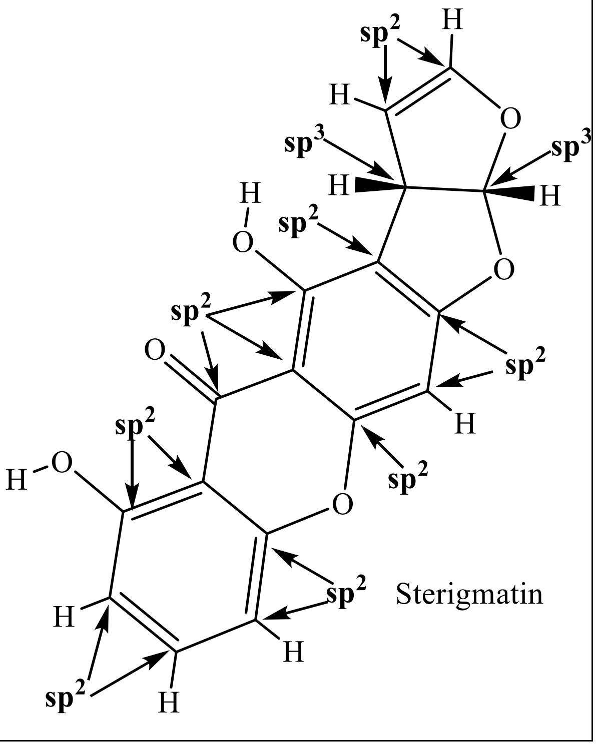
$H_3C-NH-CH_3$

C

SOLUTIONS:

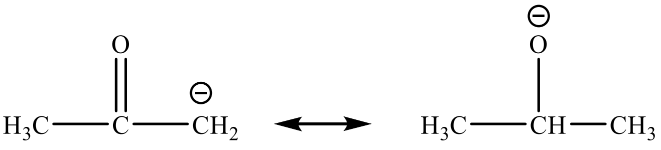
Exercise 1:

For the following molecules, we determine the sp^3 and sp^2 hybridized carbons.

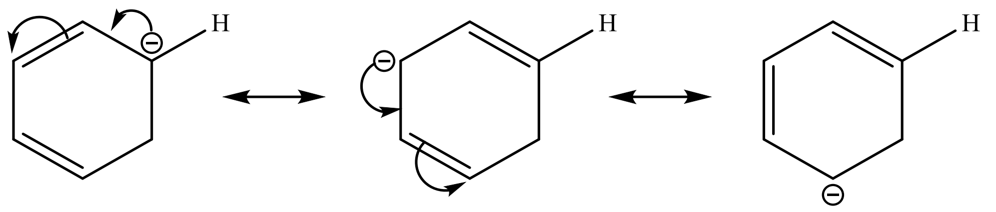
 Tryptophan	 Serotonin
 Melatonin	 Sterigmatin

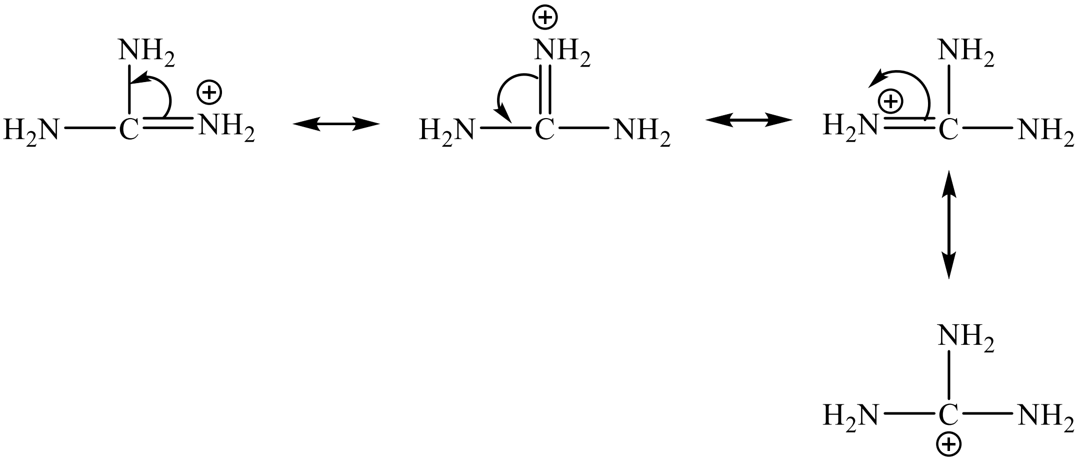
Exercise 2:

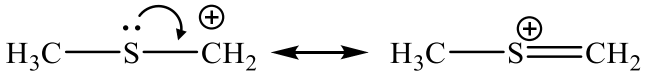
We draw the possible resonance structures for the following species:

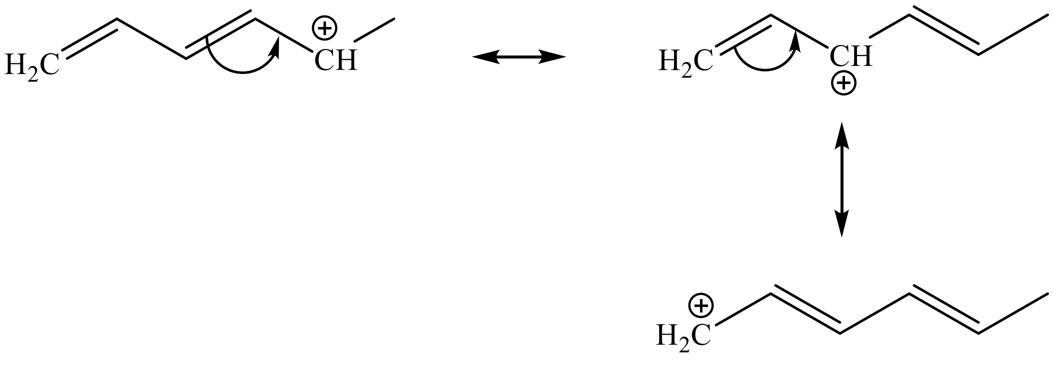


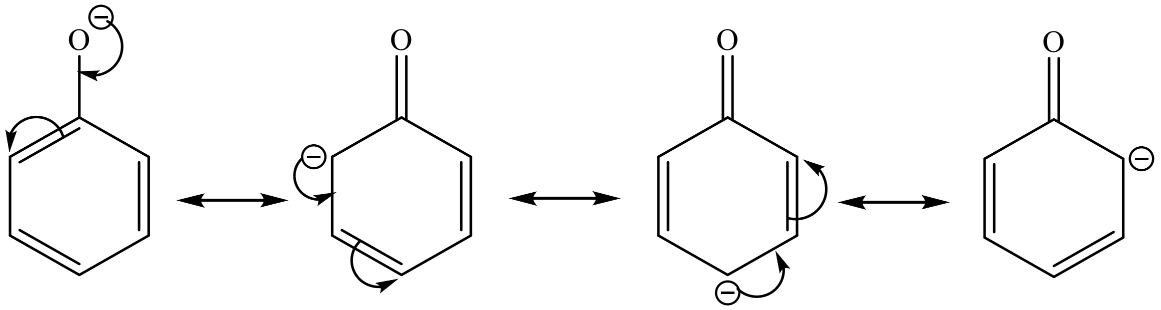
$$H_3C-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\ominus}{C}H_2 \longleftrightarrow H_3C-\overset{\overset{\overset{\ominus}{O}}{|}}{C}H-CH_3$$

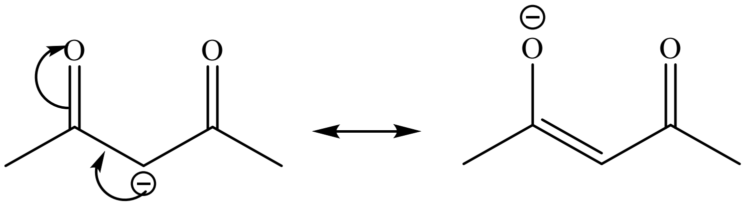




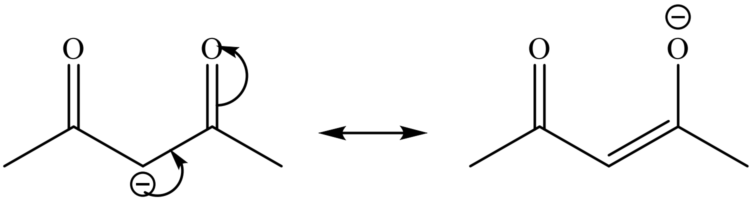


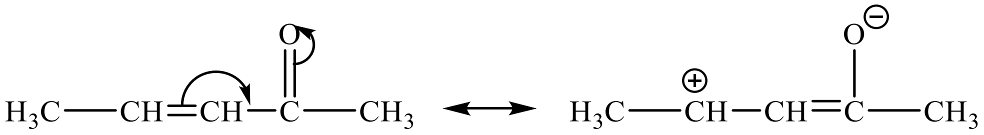




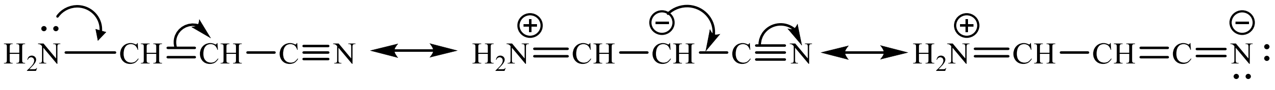


Or, it can be done in the way:

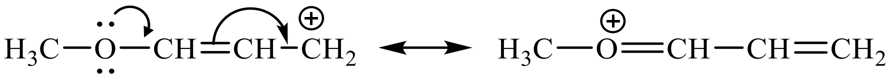




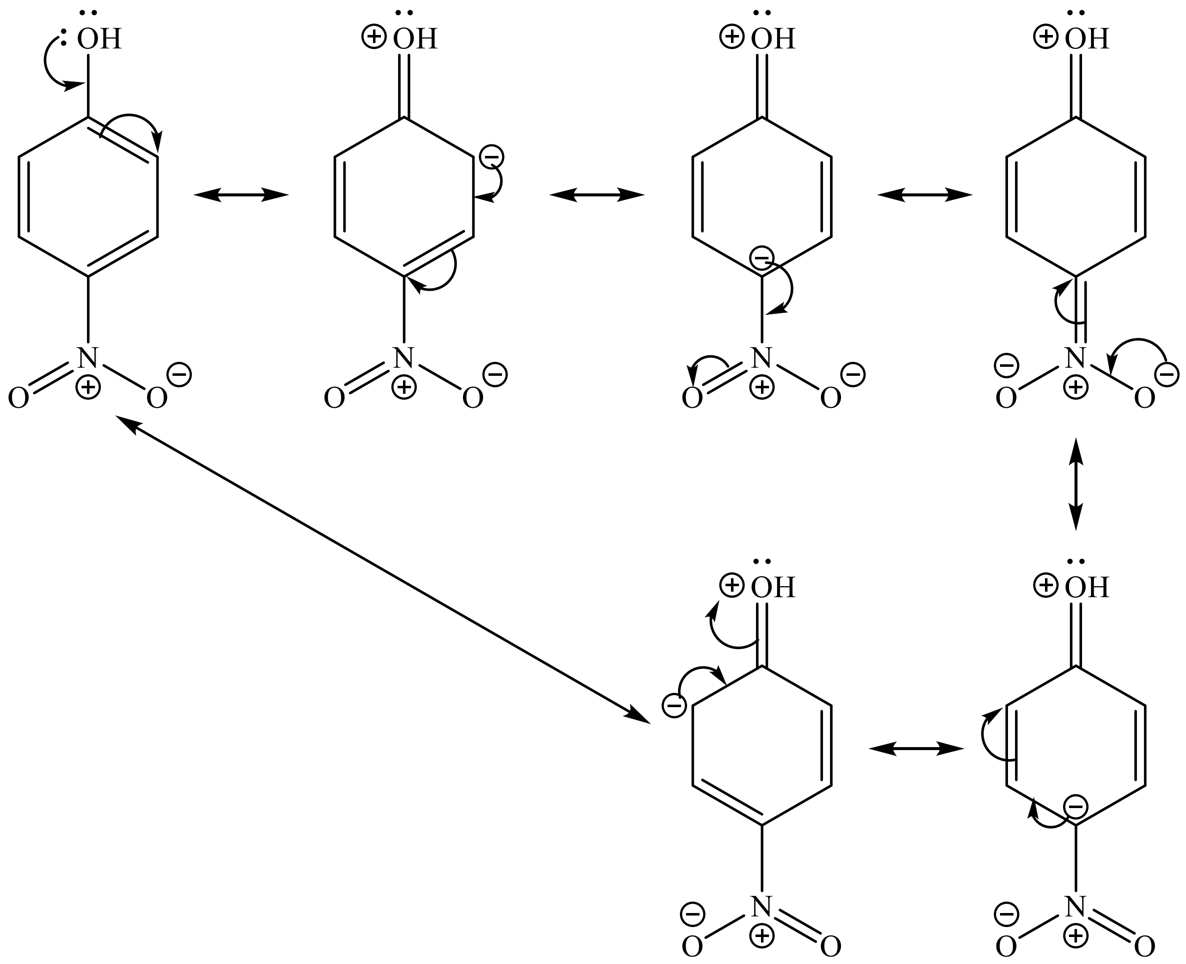
$$H_3C-CH=CH-\overset{\overset{O}{\|}}{C}-CH_3 \longleftrightarrow H_3C-\overset{+}{C}H-CH=\overset{\overset{O^{-}}{|}}{C}-CH_3$$



$$H_2\ddot{N}-CH=CH-C\equiv N \longleftrightarrow H_2\overset{+}{N}=CH-\overset{-}{C}H-C\equiv N \longleftrightarrow H_2\overset{+}{N}=CH-CH=C=\overset{-}{\ddot{N}}:$$

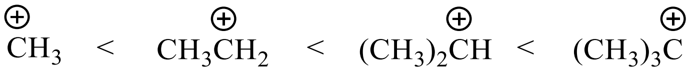


$$H_3C-\underset{..}{\ddot{O}}-CH=CH-\overset{+}{C}H_2 \longleftrightarrow H_3C-\overset{+}{O}=CH-CH=CH_2$$



Exercise 3:

1. We arrange the following carbocation in the increasing order of stability.



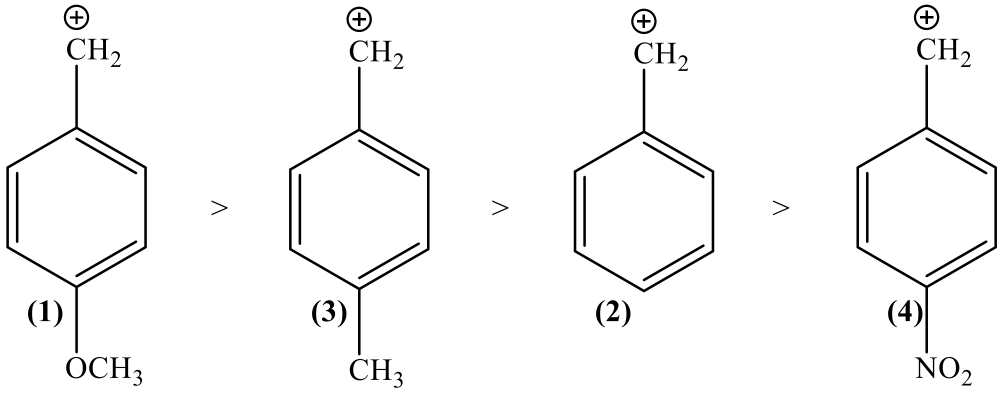
$$\overset{\oplus}{C}H_3 < CH_3\overset{\oplus}{C}H_2 < (CH_3)_2\overset{\oplus}{C}H < (CH_3)_3\overset{\oplus}{C}$$

2. It is commonly known that groups that are $-I$, $-M$ decrease the stability of a carbocation, while groups with $+I$, $+M$ effects increase the stability of a carbocation. Here, the group $-OCH_3$ has a $+M$ effect and thus increases electron density and stabilize the carbocation.

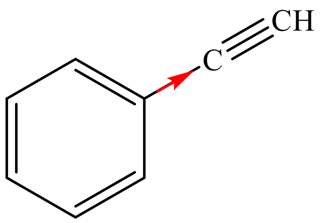
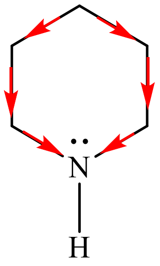
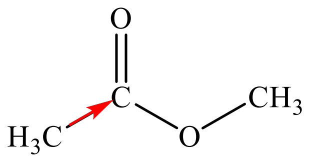
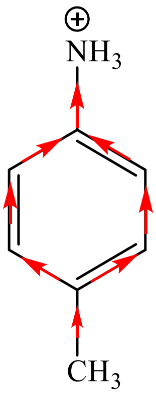
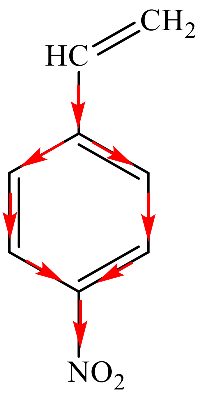
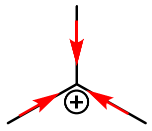
The $-CH_3$ group presents a $+I$ effect, but it is still less inductive than the group holding $+M$ effect.

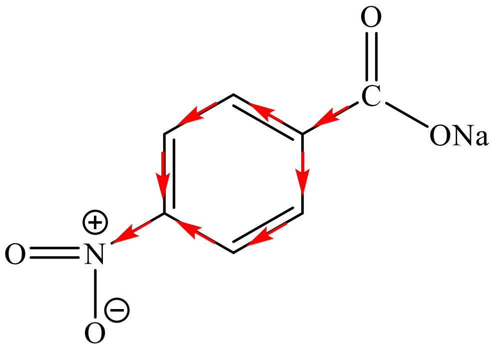
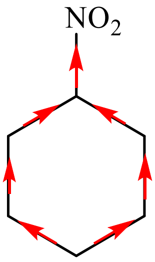
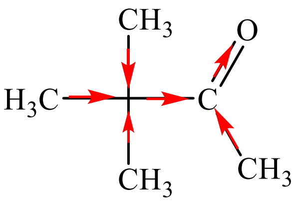
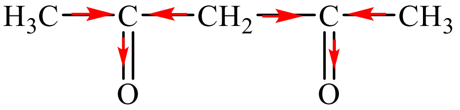
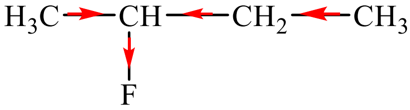
The $-NO_2$ group presents a $-M$ effect, so it destabilizes the carbocation.

So, we have the following decreasing order of stability:



Exercise 4: We show the direction of inductive effect in the following compounds.

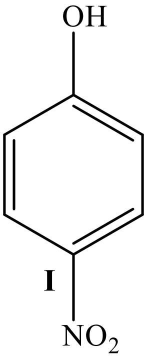
		
		 $H_3C \leftarrow CH_2 \leftarrow CH_2 \leftarrow MgBr$

$H_3C \rightarrow CH{=}CH_2$	$H_3C \rightarrow CH_2 \rightarrow OH$	$H_3C \leftarrow CH_2 \leftarrow CH_2 \leftarrow Li$
		
 $H_3C \rightarrow \underset{\downarrow O}{C} \leftarrow CH_2 \rightarrow \underset{\downarrow O}{C} \leftarrow CH_3$	$H_3C \rightarrow COOH$	 $H_3C \rightarrow \underset{\downarrow F}{CH} \leftarrow CH_2 \leftarrow CH_3$
$H_3C \rightarrow CH \overset{\rightarrow}{=} CH \rightarrow\rightarrow\rightarrow NO_2$	$HOOC \leftarrow CH_2 \leftarrow CH_3$	$^{\ominus}OOC \rightarrow CH_2 \rightarrow CH_2 \rightarrow CH_3$

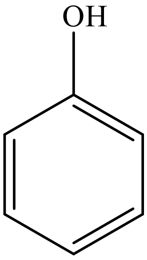
Exercise 5:

We give the decreasing acidity order of the following derivatives of phenol.

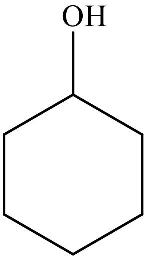
a- Groups with $-I$, $-M$ effects increase the acidic character of phenol because they effectively disperse the negative charge of the phenoxide ion. On the other hand, groups with $+I$, $+M$ effects decrease the acidic strength.



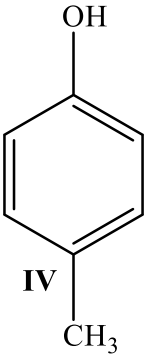
I



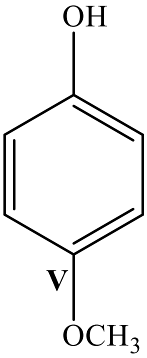
II



III



IV



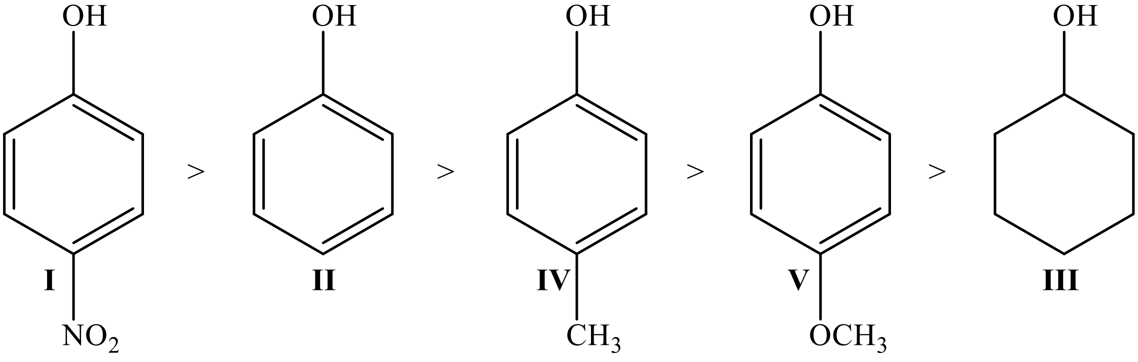
V

The compound ***III*** is the least acidic one since it has no possible dispersion of negative charge (No delocalization). The group has both $-I$ and $-M$ effect, thus it increases acid strength. Hence, it is the most acidic. On the other hand, the $-OCH_3$ group has a $+M$ effect and thus increases electron density hence it decreases the acidic character.

The $-CH_3$ group has a $+I$ effect and thus it decreases the acidic character. The compound ***IV*** is more acidic than ***V*** because the $+M$ effect is more important than $+I$ effect and hence the $+M$ effect decreases acidity more significantly than $+I$ effect.

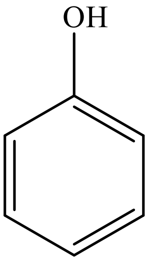
Cyclohexanol will be the least acidic since there is no inductive or mesomeric effect.

So, we will have the following decreasing order of acidity: $\boldsymbol{I > II > IV > V > III}$.

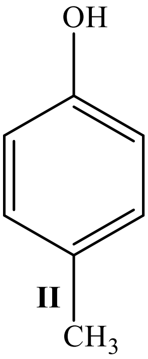


I **II** **IV** **V** **III**

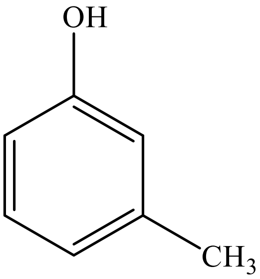
b- In the following series of alcohol, the $-CH_3$ group has $+I$ inductive effect so all methylphenols are less acidic than phenol.



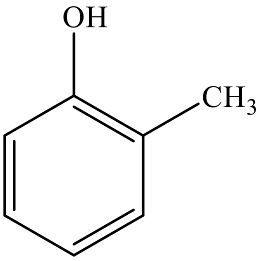
I



II



III

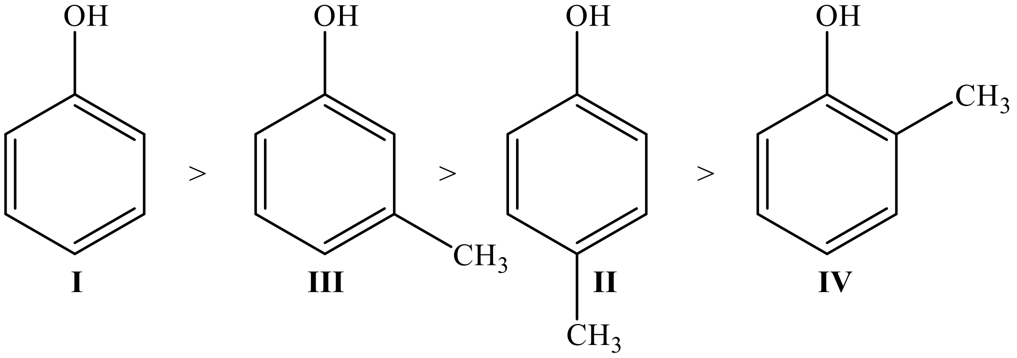


IV

Now, the $o-$ and $p-CH_3$ groups are increasing the electron density due to their hyper conjugation but *ortho* isomer has viable $+I$ effect also, which helps in destabilizing phenoxide ion therefore the *ortho* is the least acidic one.

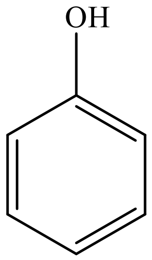
Since at *meta* position only $+I$ effect works it has the least electron density.

In this sense, we will have the following order:

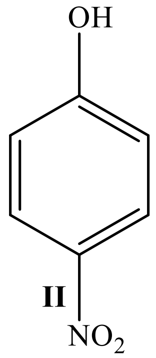


I **III** **II** **IV**

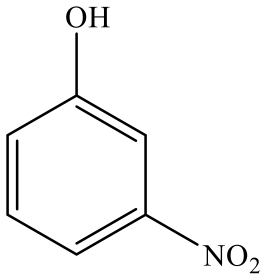
c- We give the acidic strength order for the following phenol derivatives:



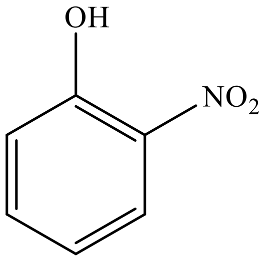
I



II

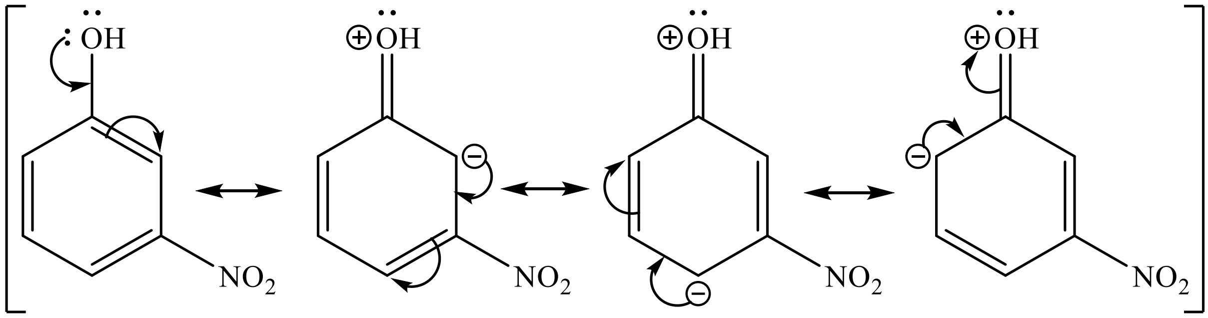


III

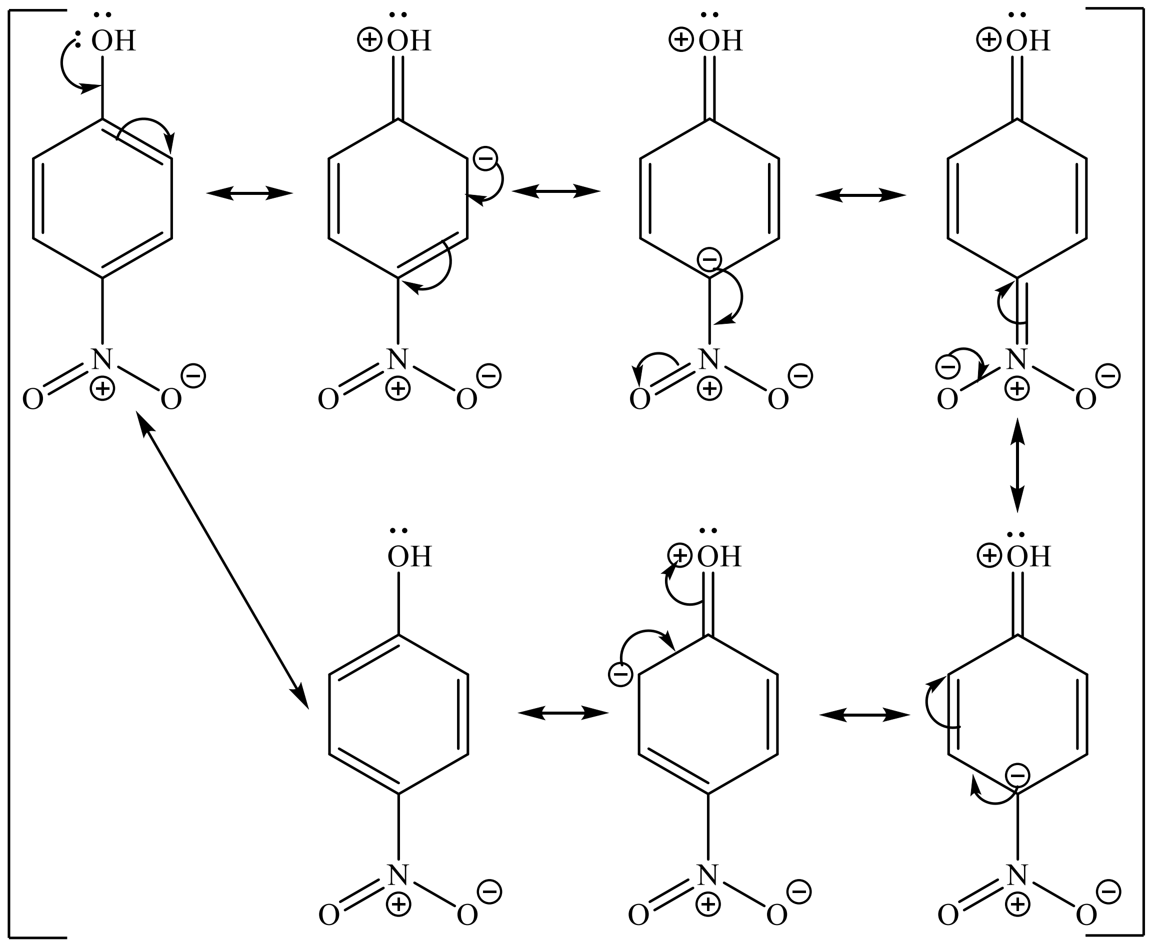


IV

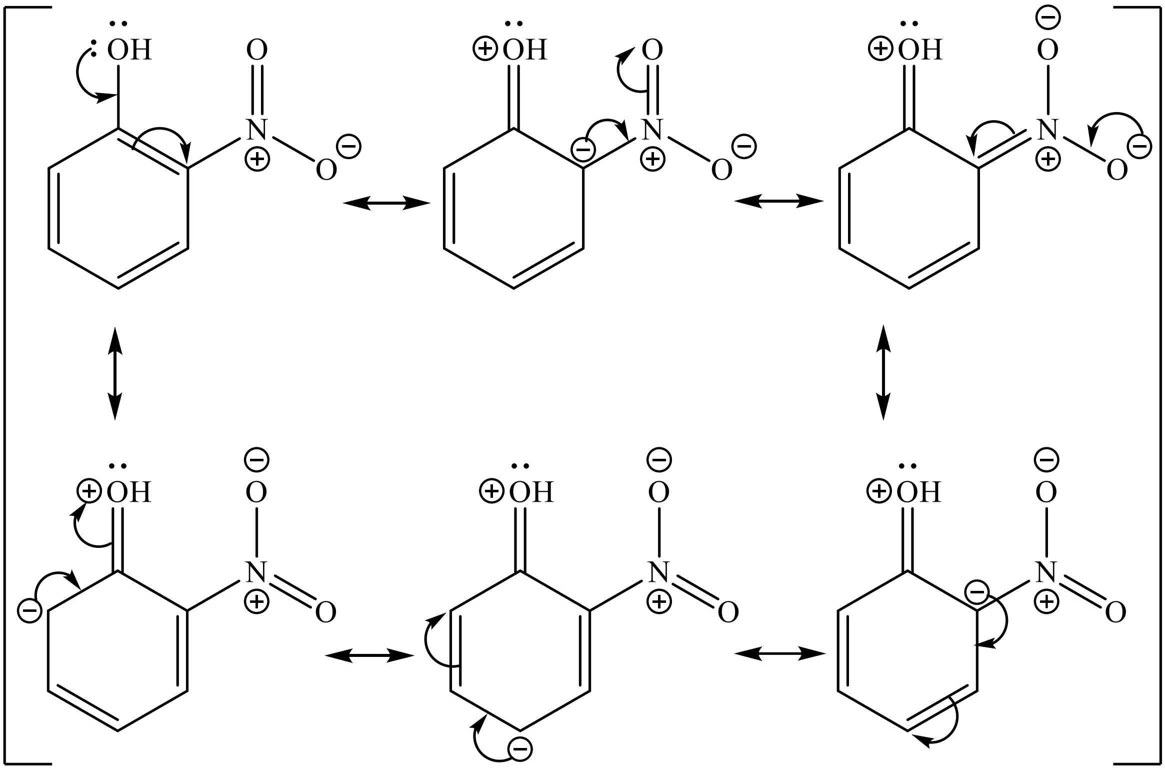
In nitrophenols, the $-NO_2$ group exhibits $-I$ effect which increases acidic strength hence phenol is the least acidic. Only $-I$ effect is applicable in *meta* nitrophenol so it will be number three in the order.



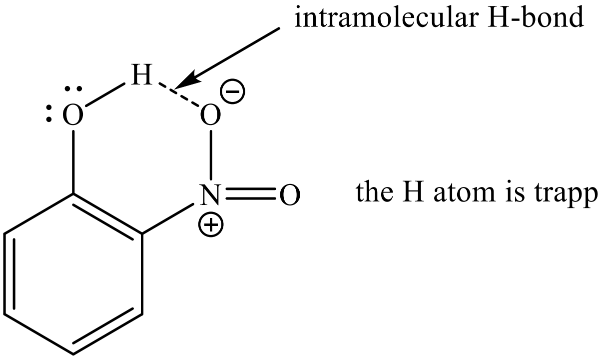
Now, *o*- and *p*- have both $-I$ and $-M$ effect of $-NO_2$ group over OH. For the *para*, we get:



For the *ortho*, we get:

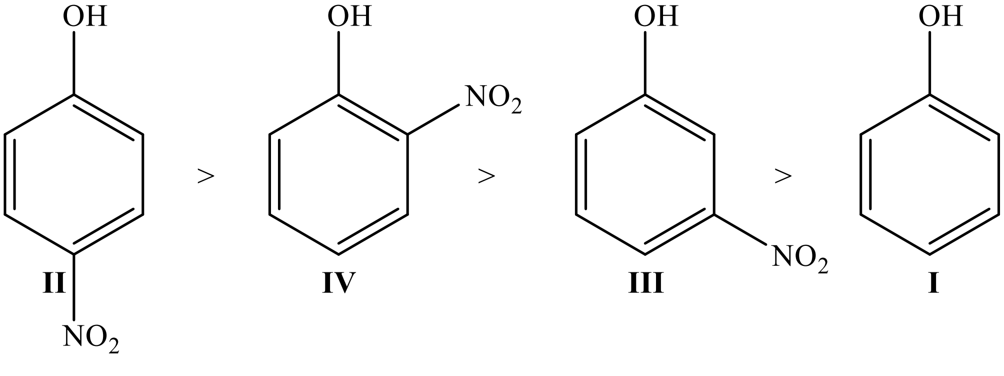


In this particular situation the *para* isomer is more acidic than *ortho* nitrophenol because of intramolecular H −bond.



the H atom is trapped by NO_2 group.

So, we get the following order:

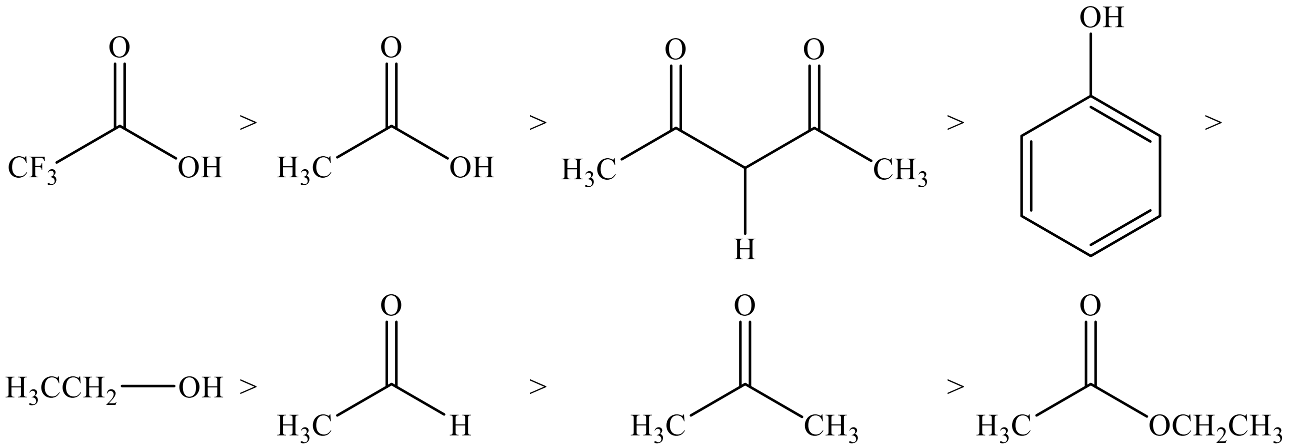


Exercise 6:

We arrange in order of increasing acidity the following compound: acetic acid, acetone, phenol, acetaldehyde, ethanol, ethyl acetate, 2,4-pentanedione, trifluoroacetic acid.

Trifluoroacetic acid is the most acidic because the trifluoroacetate ion formed is the most stable. Phenol exhibits a pronounced acidic character due to the resonance stabilization of the phenolate ion. This phenomenon does not occur in the ethoxide ion (it lacks resonant forms, and the negative charge is concentrated on the oxygen atom). Therefore, phenol is more acidic than ethanol despite both being alcohols.

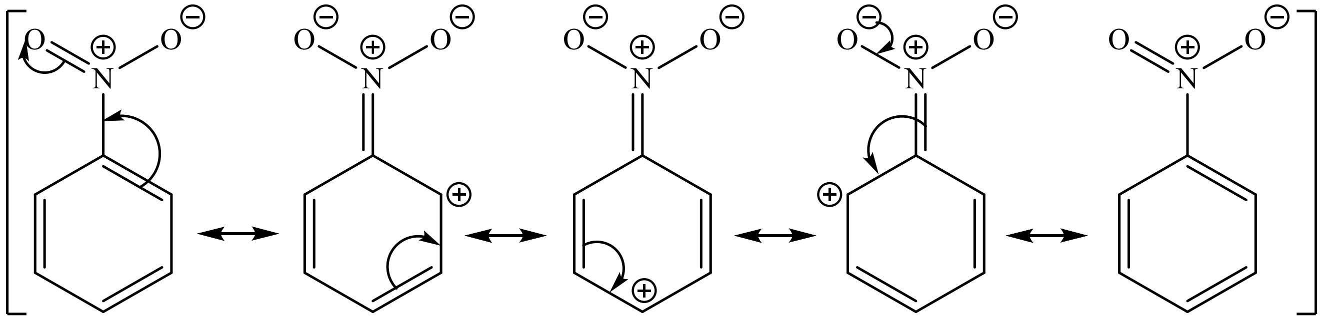
More crucial than the number of resonant forms is their significance. The acetate ion has only two resonant forms, while the phenolate ion has four. However, acetic acid is a stronger acid than phenol. In the case of the acetate ion, the negative charges are located on oxygen atoms, which are more electronegative than carbon. In the case of the phenolate ion, three resonant forms have negative charges on carbon atoms, and these resonant forms are not aromatic.



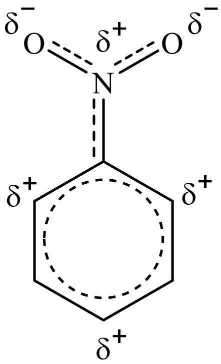
Exercise 7:

We indicate, based on the corresponding resonant forms, how the functional group (electron-donor or electron-acceptor of charge) affects the hydrocarbon structures.

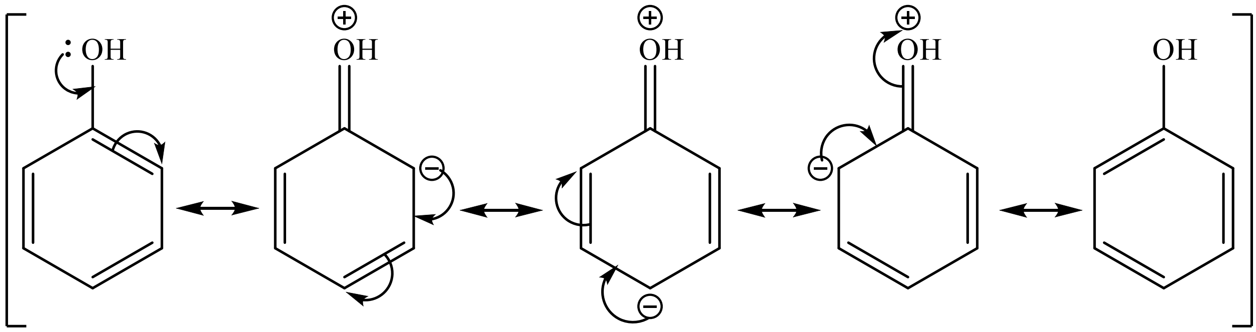
a) The nitro group reduces the electron density of the aromatic ring through delocalization of π electrons (resonance effect being more significant than the inductive effect):



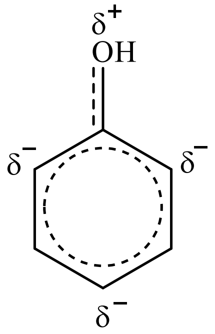
This gives the resonance hybrid:



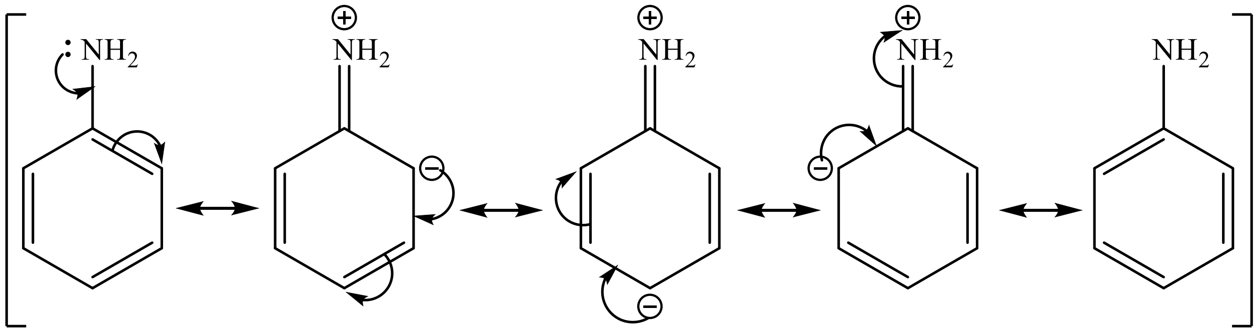
b) The $-OH$ group exerts a positive resonance effect (delocalization of negative charge) and an inductive effect $-I$ due to the electronegativity of oxygen. However, the resonance effect is more dominant than the inductive effect. Therefore, electron density increases at the *ortho* and *para* positions.



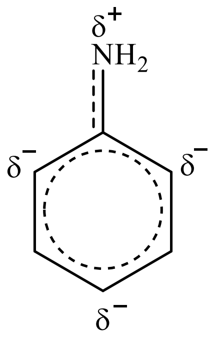
This gives the resonance hybrid:



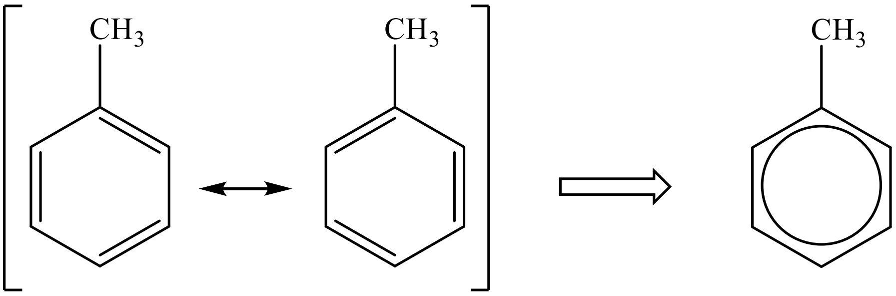
c) Similar to phenol. In this case, it is important to highlight that it decreases the basicity compared to alkyl amines because the lone pair of electrons on nitrogen is delocalized in the aromatic ring.



This gives the resonance hybrid:



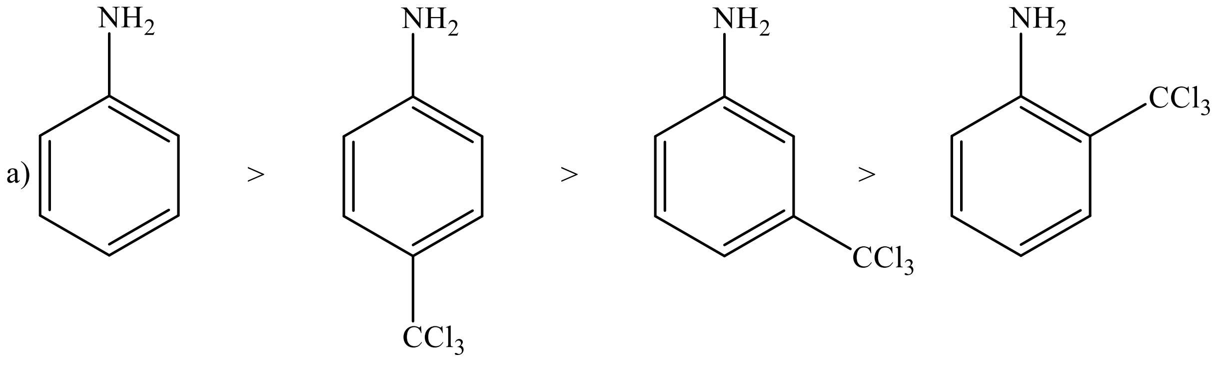
d) Resonance structure of toluene: those generated by the aromatic ring, as the $-CH_3$ group lacks unpaired electrons to conjugate with the π electrons of the aromatic ring.



The methyl group is a weak activator, and although it is evenly distributed on all aromatic carbon atoms in the ring, the orientation for electrophilic aromatic substitution is preferably at the *ortho* and *para* positions.

Exercise 8:

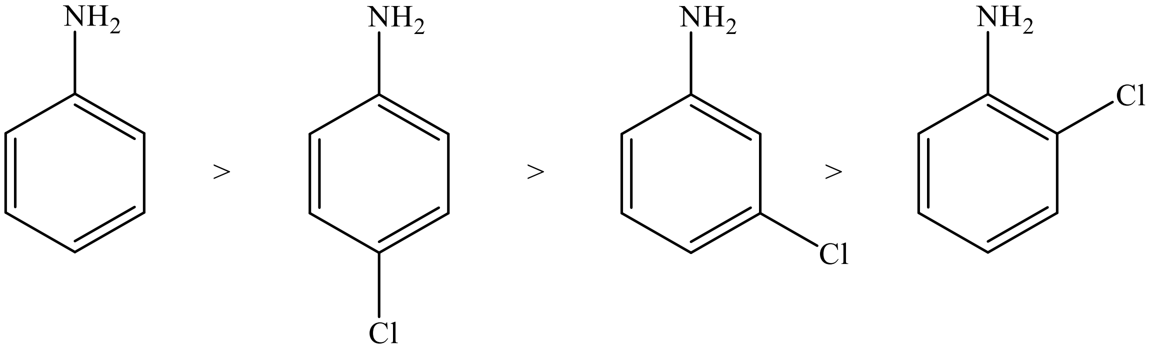
a) The $-CCl_3$ group has the $-I$ effect and only this effect decides the basicity order. Here, it is a matter of distance; the more the $-CCl_3$ group is far from nitrogen atom responsible of basicity, the more the aniline derivative is basic because its effect gets more and more weak because of the distance. So, we get the following order:



b) The $-Cl$ group has both the $-I$ and $+M$ effects. For halogens, the inductive effect $-I$ dominates. So, only this effect decides the basicity order. As in the previous question a), it is a matter of distance too; the more the $-Cl$ group is far from nitrogen atom responsible of basicity, the more the aniline derivative is basic.

The order of decreasing basicity is:

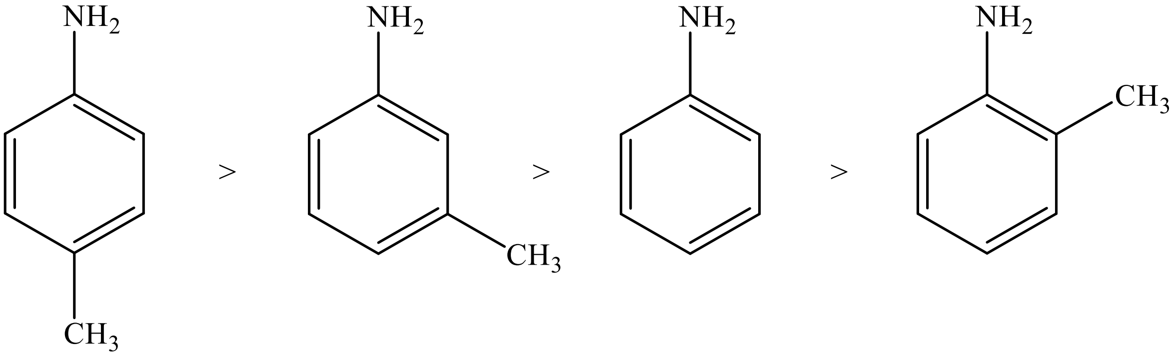
b)



c) The $-CH_3$ group has only the $+I$ effect. As in the previous question a), it is a matter of distance too; the more the $-CH_3$ group is far from nitrogen atom responsible of basicity, the more the aniline derivative is basic.

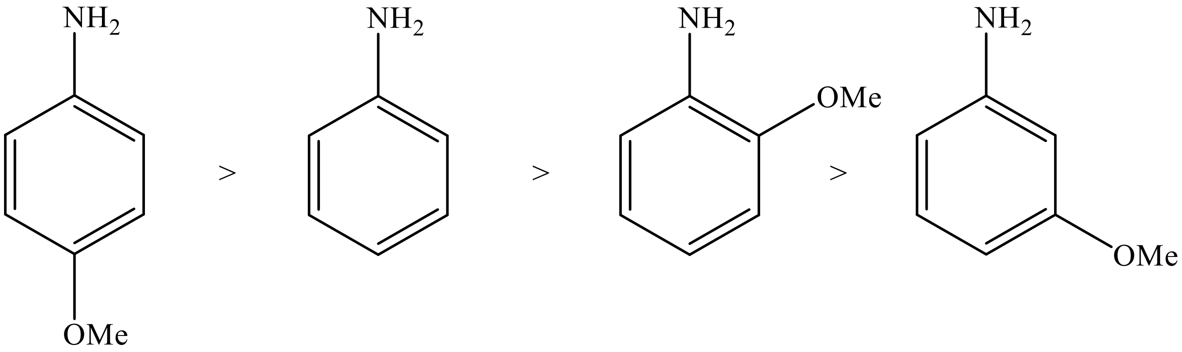
The order of decreasing basicity is:

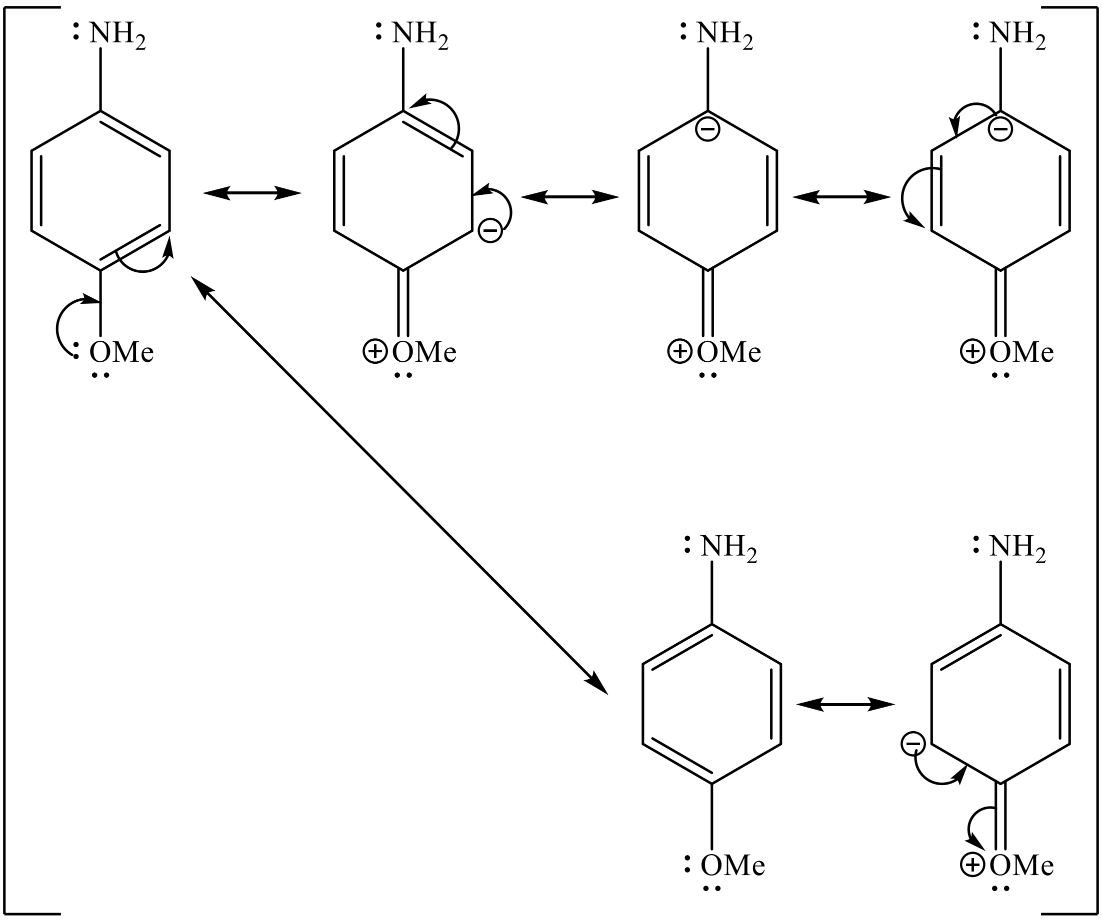
c)

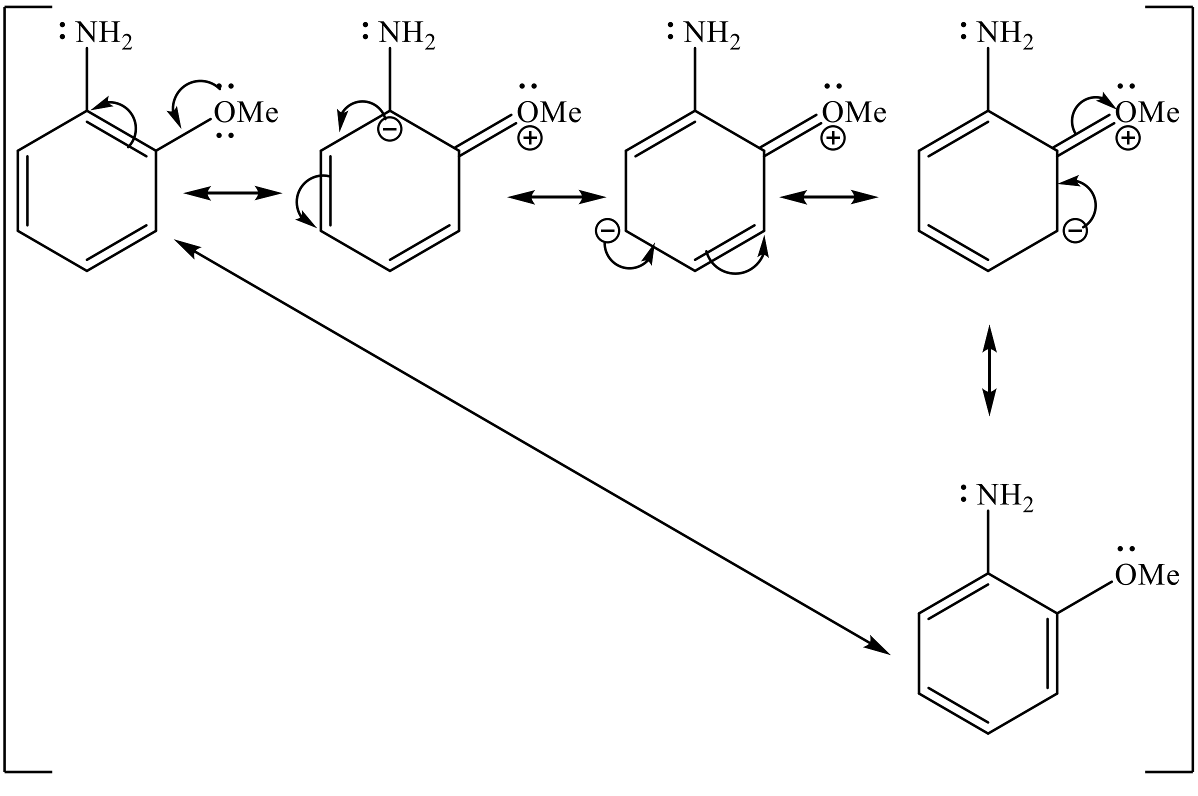


d) The $-OMe$ group has both the $-I$ and $+M$ effects. In the general rule, the $+M$ effect dominates over inductive effect $-I$. So, only this effect decides the basicity order. As in the previous question a), it is a matter of distance too; the more the $-Cl$ group is far from nitrogen atom responsible of basicity, the more the aniline derivative is basic. The order of decreasing basicity is:

d)




:NH₂
OMe
⊕OMe
⊖


:NH₂
OMe
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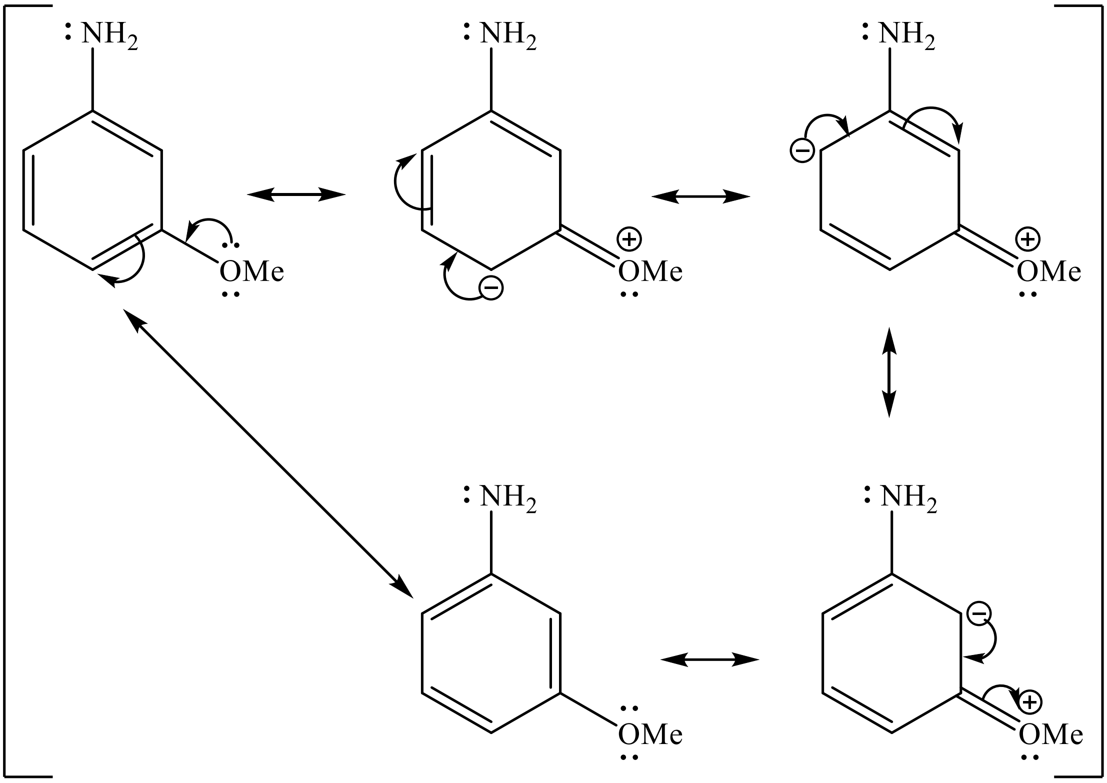
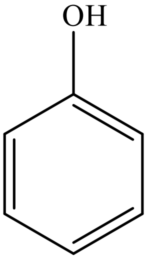
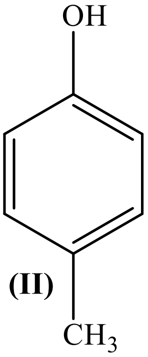


Exercise 9:

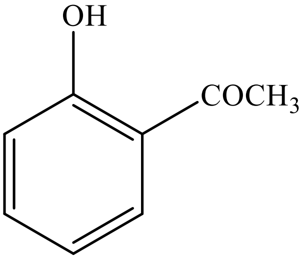
1. Rank the following molecules in order of decreasing acidity.



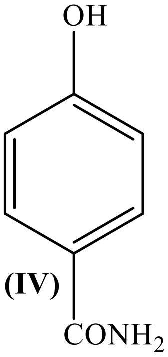
(I)



(II)



(III)



(IV)

An electron-donating group ($+I$ or $+M$) decreases acidity, while an electron-withdrawing group ($-I$ or $-M$) increases it.

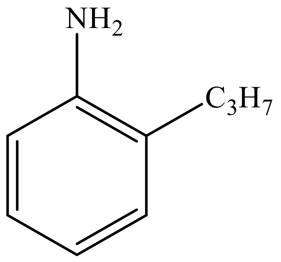
The ($-CH_3$) exerts an inductive electron-donating effect ($+I$)

The acyl group ($-COCH_3$) is a strong electron-withdrawing group by negative mesomeric effect ($-M$) and its *ortho* position reduces greatly the electron density on the nitrogen atom whose free electron pair enters into conjugation with the benzene electrons.

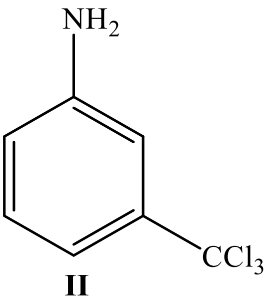
The ($-CONH_2$) group exerts an electron-withdrawing mesomeric effect ($-M$) so compound (**III**) is the most acidic.

Mesomeric effects are stronger than inductive effects. Therefore, compound (**II**) is more acidic than compounds (**I**) and (**IV**).

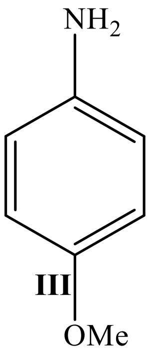
2. Select the basic strength order of the following molecules.



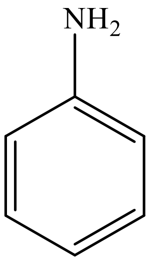
I



II



III



IV

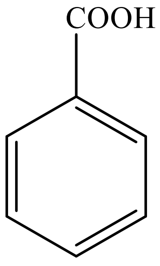
Propyl ($-C_3H_7$) exerts an inductive electron-donating effect ($+I$)

The $-CCl_3$ group has the $-I$ effect and only this effect decides the basicity order.

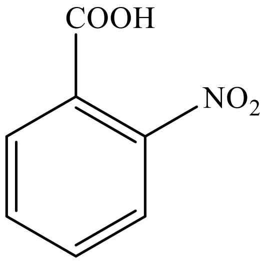
$-OMe$ exerts an electron-donating mesomeric effect ($+M$).

The ($+M$) effect of chlorine is less important than that of $-OMe$, so compound (**I**) is more acidic than compound (**IV**).

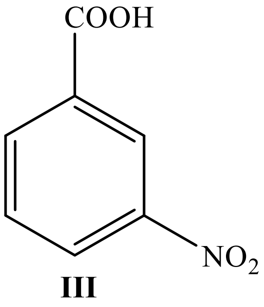
3. We give the right order of decreasing acidity of the following carboxylic acids.



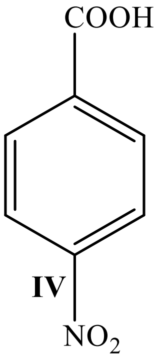
I



II



III

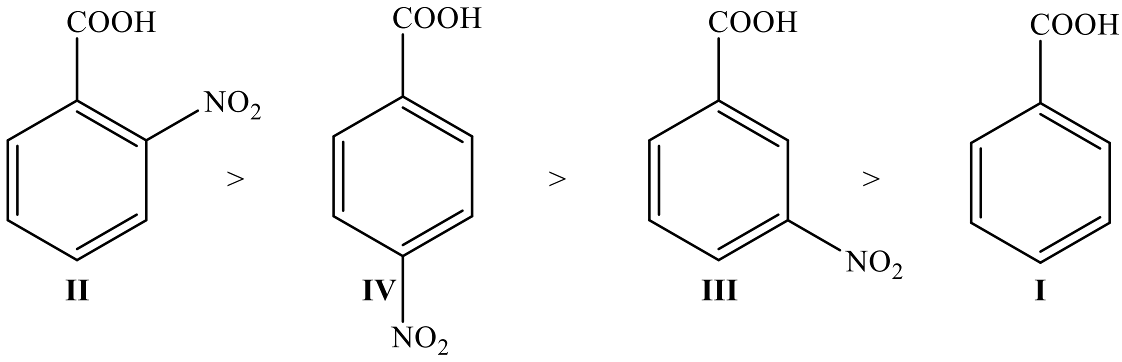


IV

The groups attached to benzene either $-I$ or $-M$ reduces the electron density in conjugation system and make carboxylic group attached to benzene ring more acidic.

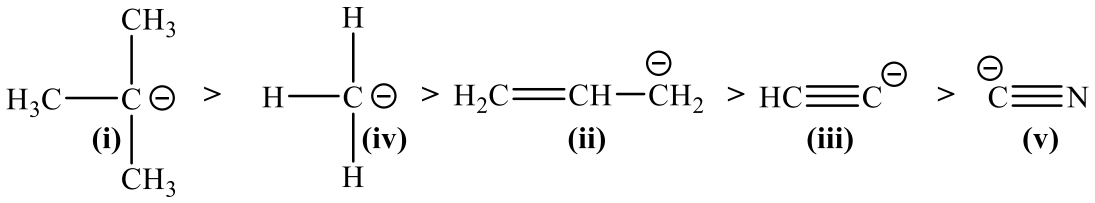
In case of *ortho*-nitrobenzoic acid both $-I$ effect and $-M$ effect strongly applied and making it most acidic among all (due to *ortho* effect).

In *para*-nitrobenzoic acid $-I$ effect is weaker than *ortho*-nitrobenzoic acid, only $-M$ effect is stronger. Hence, the acidity of carboxylic acid is given as:



Exercise 10:

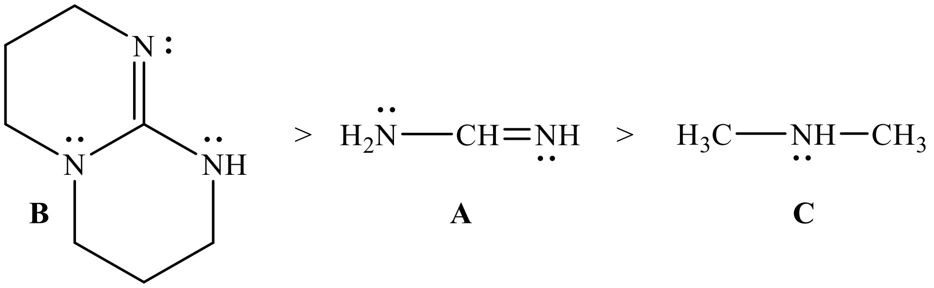
a- The basic strength decreasing order is:



$$\underset{\textbf{(i)}}{(CH_3)_3C^{\ominus}} > \underset{\textbf{(iv)}}{H_3C^{\ominus}} > \underset{\textbf{(ii)}}{H_2C{=}CH{-}\overset{\ominus}{C}H_2} > \underset{\textbf{(iii)}}{HC{\equiv}C^{\ominus}} > \underset{\textbf{(v)}}{{}^{\ominus}C{\equiv}N}$$

b- The strength of decreasing basicity is in the order:

Since the electron lone pair of nitrogen are under conjugation in compounds **A** and **B**, where **B** is the more conjugated one, hence, **A** is more basic than **A**. In compound **C**, the electron lone pair of nitrogen atom is localized and not conjugated so it is the most basic of all. The order of pK_a (acidity) is:



Then, the pK_b order is given as: $\boldsymbol{C} > \boldsymbol{A} > \boldsymbol{B}$.

Chapter IV :
Reaction Mechanisms

Introduction

A chemical reaction is characterized by the formation or breaking of one or more bonds. During the process of forming or breaking a bond, the electron pair, which constitutes the bond, can be distributed equally or unequally between the two fragments while passing through a homolytic or heterolytic bond cleavage.

A reaction is carried out through a series of elementary steps occurring sequentially or in parallel. Kinetic analysis is a very useful tool, which allows, from the measurements of the rates of disappearance of a reactant or the appearance of a product of the reaction, to recognize which is the determining step that imposes the rate, and thus specify a part of the reaction path.

The study of reactions and relevant synthetic applications of organic compounds concerns with the development of powerful and useful reactions, invention of strategies for the construction of defined target molecules. To pursue the objectives general organic reactions are grouped together into some categories based on their kinetic and dynamic characters. The general groups are substitution, addition, elimination and rearrangement reaction. Further each group may be subdivided on the basis of the reactive intermediates involved or the nature of the reaction center. Different types of reactions are accompanied by different stereochemical outcome too.

There are millions of reactions involving naturally occurring as well as synthetic organic molecules. It is very difficult to learn and understand each and every reaction if they are treated and analyzed as unique and isolated process. Using certain generalized basic principles such vast organic reactions can be woven together and fitted neatly into general patterns. Based mainly on the functional groups, electron rich sites, electron deficient sites and weak polar bonds of the molecules, organic reactions may be categorized into four general types: Substitution reaction, Addition reaction, Elimination reaction and rearrangement reaction. In substitution reactions an atom or group bonded to a carbon atom of the reactant molecule is replaced by a new atom or group. In an elimination reaction two atoms or groups are removed from the reactant molecule to form the product. Substitution and elimination take place side by side in a competitive pattern. Addition reactions two reactant molecules or reactant molecule and reagent add together to form a single product without leaving out any other part. In rearrangement reactions there is reorganization of bonds along with atoms and groups of the reactant molecule.

Organic reactions

Enterprises in chemical synthesis concern with the development of powerful and useful reactions, invention of strategies for the construction of defined target molecules. So as to pursue the objectives general nature of the reactions encountered with organic molecules should be thoroughly understood. Here one must be familiar with two aspects: first the structure and representation of organic molecules and secondly the description of the reaction mechanism. From static and dynamic aspects organic reactions may be classified into four general categories mentioned below:

1. Substitution reactions
2. Addition reactions
3. Elimination reactions and
4. Rearrangement reactions

Explanation of thermodynamic quantities

Gibbs free energy change (ΔG)

The energy difference between reactants and products. When ΔG is negative, the reaction is exergonic, has a favorable equilibrium constant, and can occur spontaneously. When ΔG is positive, the reaction is endergonic, has an unfavorable equilibrium constant, and cannot occur spontaneously.

Enthalpy change (ΔH)

The heat of reaction, or difference in strength between the bonds broken and the bonds formed in reaction. When ΔH is negative, the reaction releases heat and is exothermic. When ΔH is positive, the reaction absorbs heat and is endothermic.

Entropy change (ΔS)

It expresses the change in molecular randomness during a reaction. When ΔS is negative, randomness decreases and when ΔS is positive, randomness increases.

1. Transition State Theory

Transition State Theory describes the changes in geometric configuration that occur when molecules with the required critical energy react. It provides a detailed description of the kinetics (rate) of reaction. In other words, it is a theory that provides a basis for understanding the dynamics of chemical reaction. It is often referred to as TST (transition state theory).

The reaction proceeds via a “reaction coordinate,” generally considered to be negative at the reactant, zero at the TS, and positive at the product (Figure 1). The reaction coordinate leads the reactant to the product along a path where the energy is as low as possible, and the TS is the point where the energy is at its maximum (saddle point). In other words, it corresponds to the highest energy point in a reaction step on an energy diagram (Figure 1).

At the molecular scale present at this energy maximum (activated complex), the existing bonds corresponding to the reactants break and new ones are formed (those of the products).

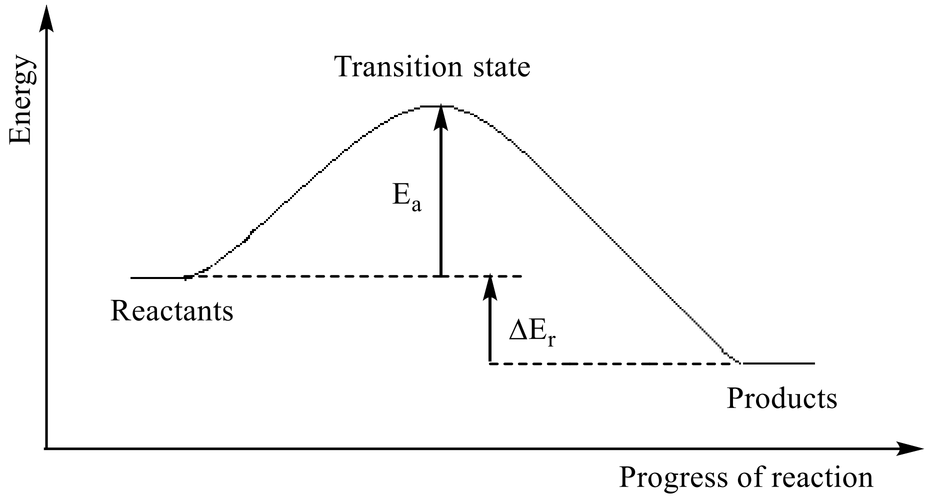
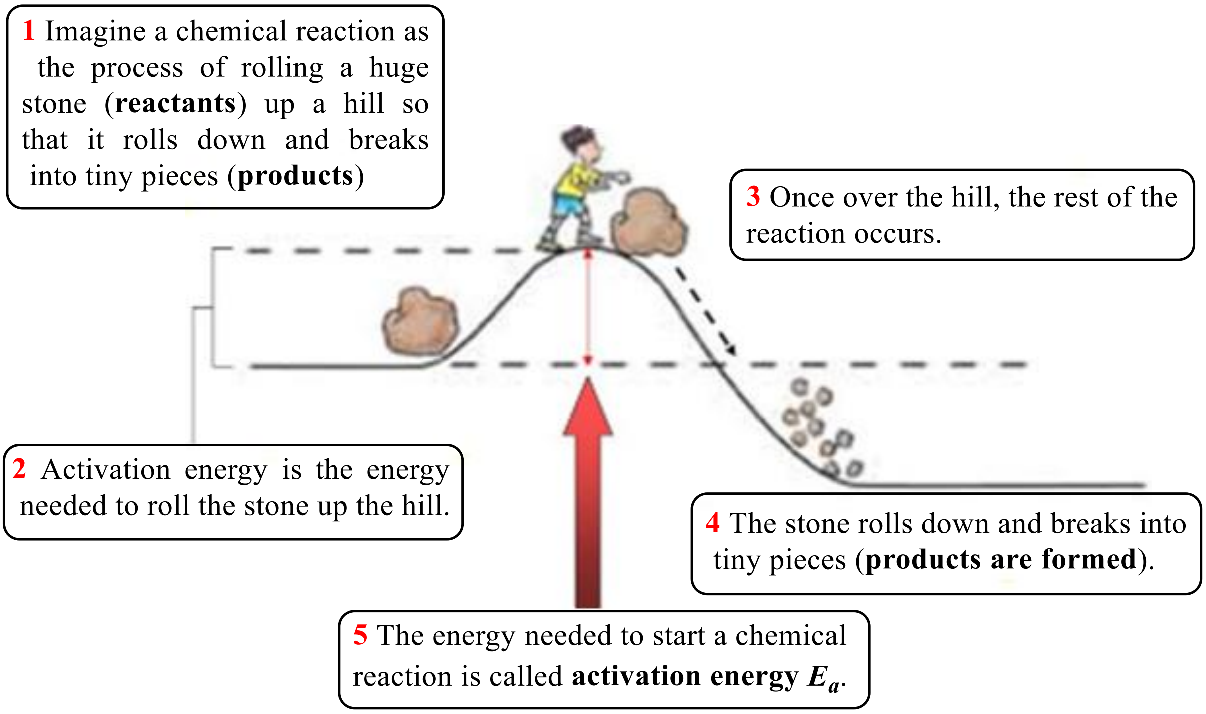


Figure 1: Schematic illustration of the reaction pathway.

2. Activation energy

Activation energy (E_a) is the minimum energy required to be provided to the reactants for a chemical reaction to occur. In other words, it is the minimum energy required to be provided to the reactant molecules to produce efficient collisions (the molecules that collide have an energy $\geq E_a$) thus allowing the formation of the activated complex to reach the transition state followed by the formation of the products (Figure 2).



1 Imagine a chemical reaction as the process of rolling a huge stone (**reactants**) up a hill so that it rolls down and breaks into tiny pieces (**products**)

2 Activation energy is the energy needed to roll the stone up the hill.

3 Once over the hill, the rest of the reaction occurs.

4 The stone rolls down and breaks into tiny pieces (**products are formed**).

5 The energy needed to start a chemical reaction is called **activation energy E_a**.

Figure 2: Illustration of the activation energy.

Activation energy can be calculated as the difference between the energy at the transition state and the energy of the reactants.

The activation energy E_a is a macroscopic quantity defined by the Arrhenius equation:

$$k = A.e^{\frac{-Ea}{RT}}$$

where;

k: rate constant,

A: pre-exponential factor,

Ea: reaction activation energy (in the same units as RT),

R: universal gas constant (8.314 $J.mol^{-1}.K^{-1}$),

T: absolute temperature (in Kelvin).

Similarly, a reaction can only occur if the molecules have sufficient energy to overcome the activation energy barrier.

From this equation, we can see that the rate and the activation energy are inversely proportional. A reaction with a high activation energy is a slow reaction. On the other hand, a reaction with a low activation energy is a fast reaction.

The Arrhenius curve ($\ln k = \ln A - E_a/RT$ shown in Figure 3) shows the relationship between temperature and rate constants for a given reaction. This curve indicates that as the temperature increases, the rate constant k of the reaction increases as well.

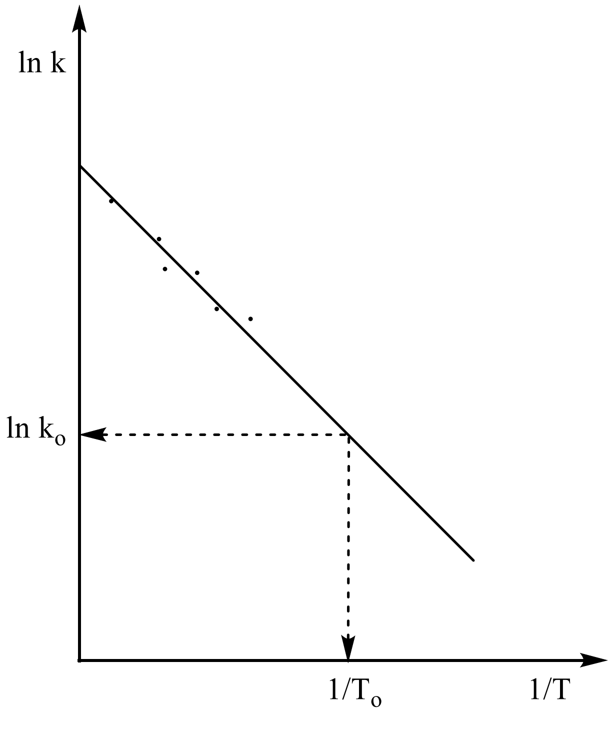


Figure 3: Application of the Arrhenius equation.

3. Rate-determining step

In a multi-step reaction mechanism, each step will have its own rate constant and activation energy and the overall rate of the reaction is determined by the slowest step, which is often referred to as the rate-determining step. This step has the highest activation energy barrier, meaning it proceeds at the slowest rate compared to other steps in the mechanism. Since the overall reaction cannot proceed faster than its slowest step, the rate law must reflect the reactants of that step.

The slowest part of this mechanism is Step 1, meaning the rate law will use the coefficients and reactants of that step (Figure 4).

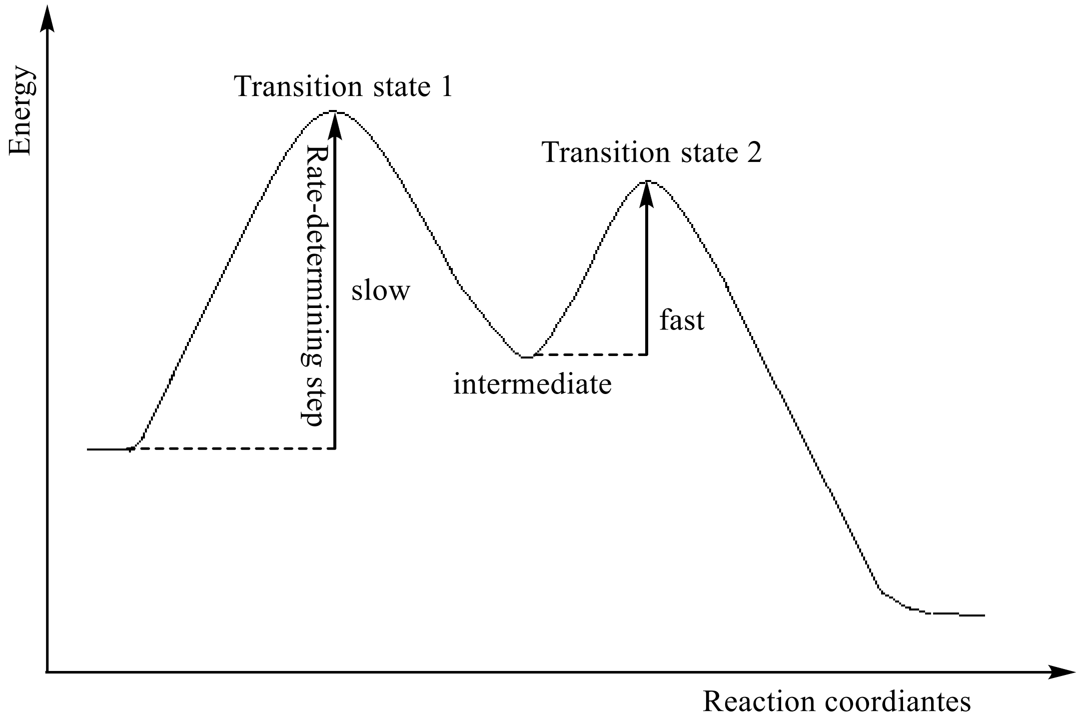


Figure 4: Presentation of the rate-determining step in a reaction pathway.

4. Molecularity

The molecularity of a process indicates how many molecules are involved in this process. In other words, the molecularity of an elementary reaction is the number (an integer) of particles that actually react during this reaction.

It should be noted that the rate law of an elementary reaction is directly based on its molecularity or concentration.

Table 1: Molecularity and rate law of some reactions.

Molecularity	Elementary Reaction	Rate Law
Unimolecular	$A \longrightarrow$ products	$\upsilon = k[A]$
Bimolecular	$A + A \longrightarrow$ products	$\upsilon = k[A]^2$
Bimolecular	$A + B \longrightarrow$ products	$\upsilon = k[A][B]$
Termolecular	$A + A + A \longrightarrow$ products	$\upsilon = k[A]^3$
Termolecular	$A + A + B \longrightarrow$ products	$\upsilon = k[A]^2[B]$
Termolecular	$A + B + C \longrightarrow$ products	$\upsilon = k[A][B][C]$

5. Reaction Mechanism

Chemical reactions last a certain time that can be long or sometimes extremely short, but never zero. The sequence of events that take place during this time constitutes the description of the mechanism of a reaction. In other words, the reaction mechanism can be defined as the set of steps that a reaction can have from the starting point which is the reactants to the arrival point which is the formation the products. Reactions can occur all at once, in a single step, or through several steps. Each step involves the movement of electrons and is known as an elementary reaction or also called an elementary process.

6. Energy profile

The reaction profile represents the changes in the potential energy of the system during the reaction. It is a convenient way to plot the changes in the potential energy of the reacting system when individual molecules interact with each other, as a function of a reaction coordinate, which is an atomic-scale parameter that varies continuously during the transformation. The reaction coordinate can be the distance between two atoms, or an angle between two bonds, etc., that varies during the reaction.

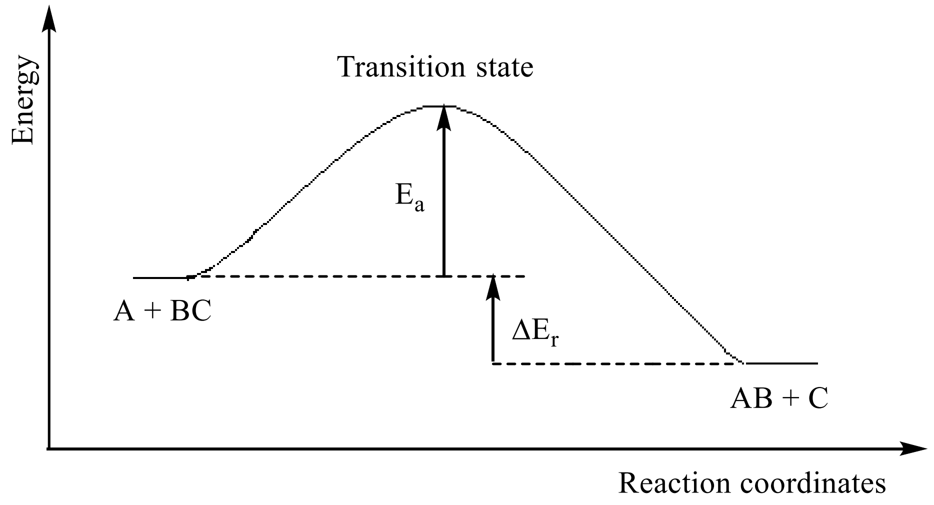


Figure 5: Energy profile of a given reaction.

The vertical axis represents the potential energy which is a set of contributions of the energy stored in the chemical bonds and those associated with the interactions between each species and its environment. As for the horizontal axis, it represents the coordinates of the reaction i.e. the path taken by the reactants according to the products during the reaction. The reaction is said to be endothermic if the enthalpy difference between the reactants and the products is positive and exothermic when the difference is negative.

The following energy diagrams show the progress of a simple reaction:

a) **reaction ($\Delta H < 0$)**

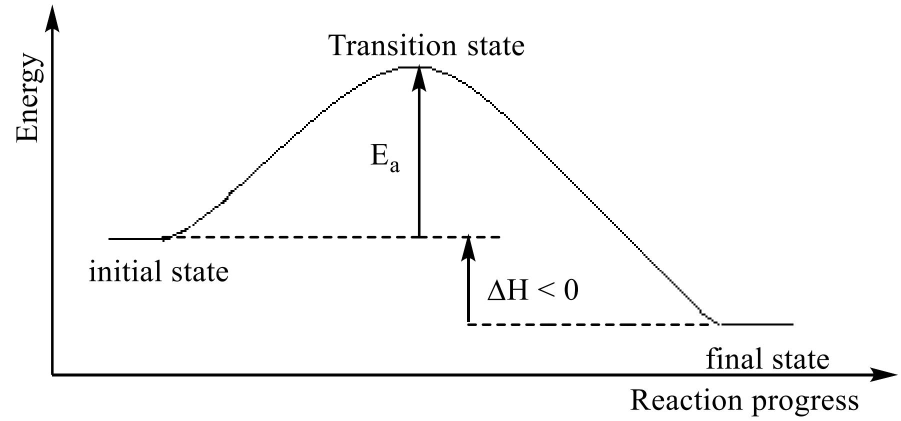


Figure 6: Energy profile of a simple reaction ($\Delta H < 0$).

When the Gibbs free energy of the reaction is negative ($-\Delta G$), then the reaction is said to be exergonic and it is thermodynamically favored.

b) **reaction ($\Delta H > 0$)**

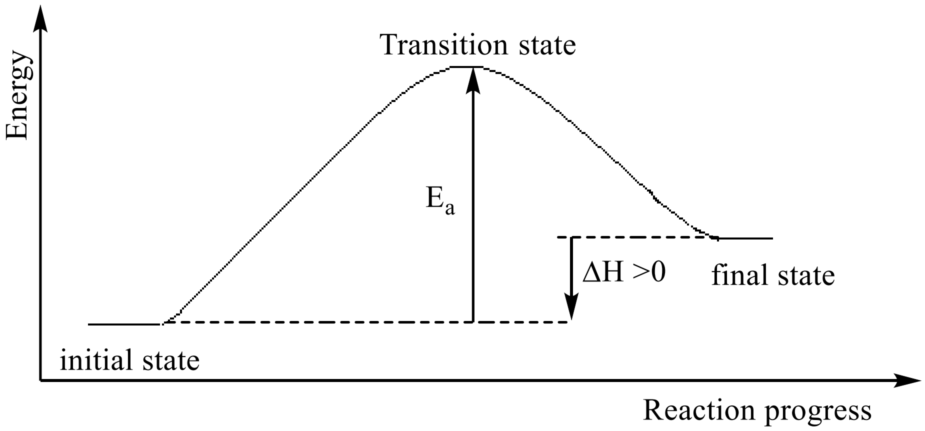


Figure 7: Energy profile of a simple reaction ($\Delta H > 0$).

However, when the Gibbs free energy of the reaction is positive ($+\Delta G$), then the reaction is said to be endergonic and it is thermodynamically not favored.

If a reaction occurs in more than one step, it must involve species that are neither the reactant nor the final product. These are called **reaction intermediates** or simply “intermediates”.

Each step has its own free energy of activation. The complete diagram for the reaction shows the free energy changes associated with an intermediate.

The following energy diagrams show the progress of a complex reaction that occurs in two steps.

c) **reaction ($\Delta H < 0$)**

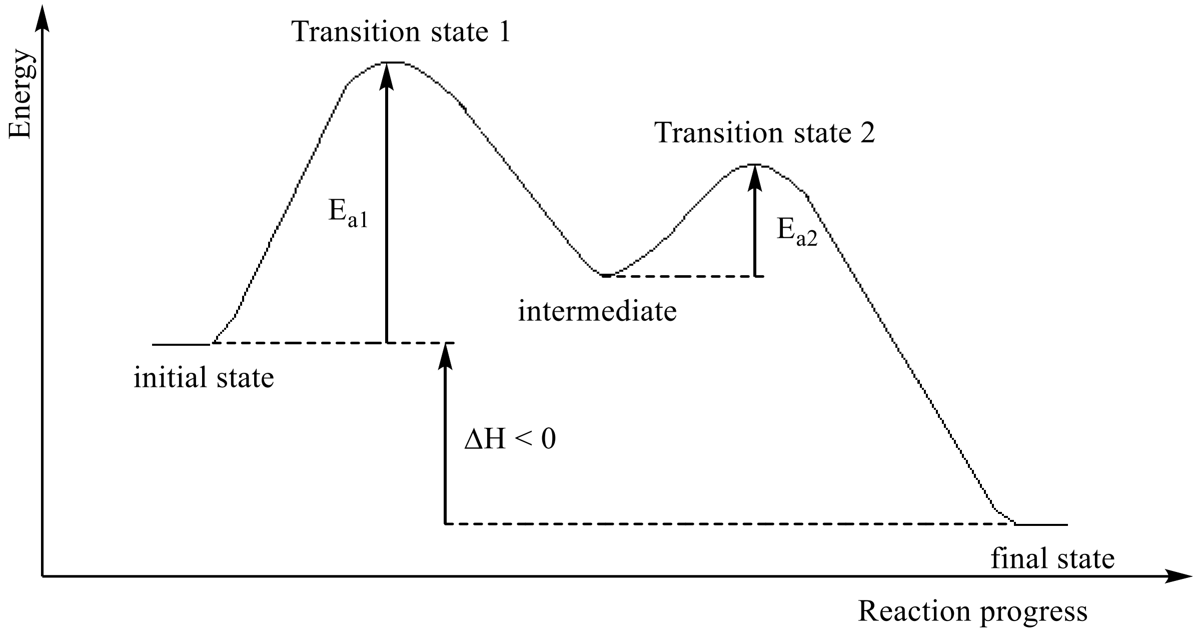


Figure 8: Energy profile of a two-step reaction ($\Delta H < 0$).

d) **reaction ($\Delta H > 0$)**

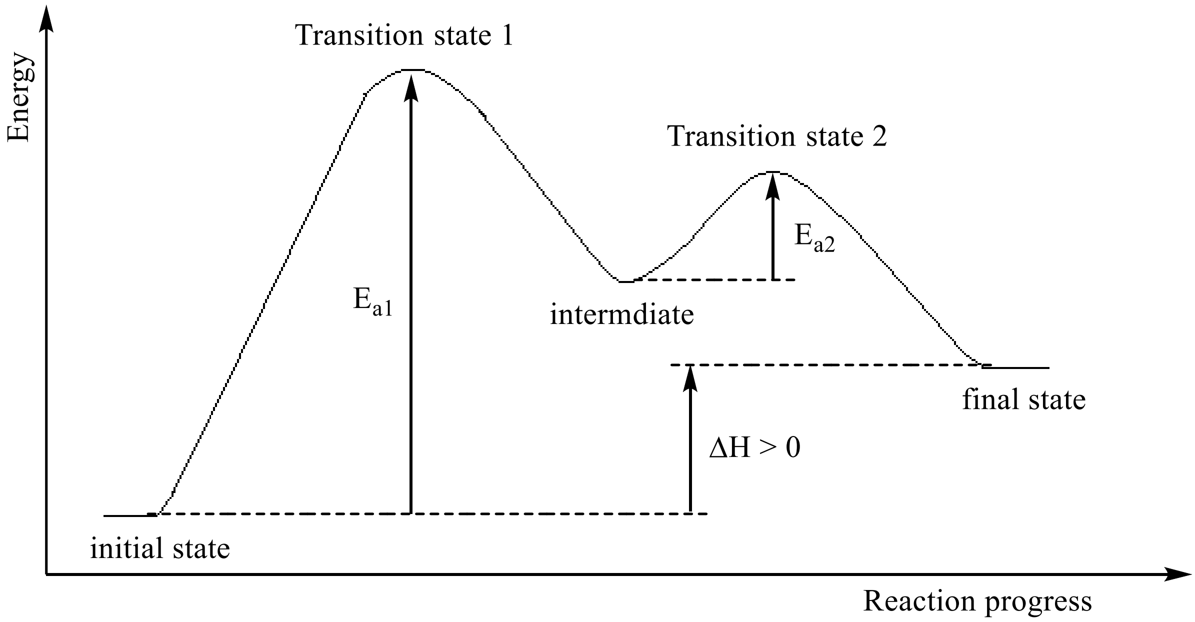


Figure 9: Energy profile of a two-step reaction ($\Delta H > 0$)

7. Kinetic control

In the case of two parallel reactions of the type:

$A + B \rightarrow C$ and $A + B \rightarrow D$, the product that forms the fastest is by definition the kinetic product. This means that one of the elementary steps, for example: $A + B \rightarrow C$ has a transition state much lower in energy (low E_a and high speed) than that of step $A + B \rightarrow D$, and consequently product C is formed in greater quantity than product D (Figure 10).

8. Thermodynamic control

For the same two reactions $A + B \rightarrow C$ and $A + B \rightarrow D$, we say that the reaction is under thermodynamic control if the product that is preferentially formed corresponds to the most thermodynamically stable product. For example, if we consider that D is the thermodynamic product, this means that D has a lower energy level (lower energy) than C and therefore it is more stable (Figure 10).

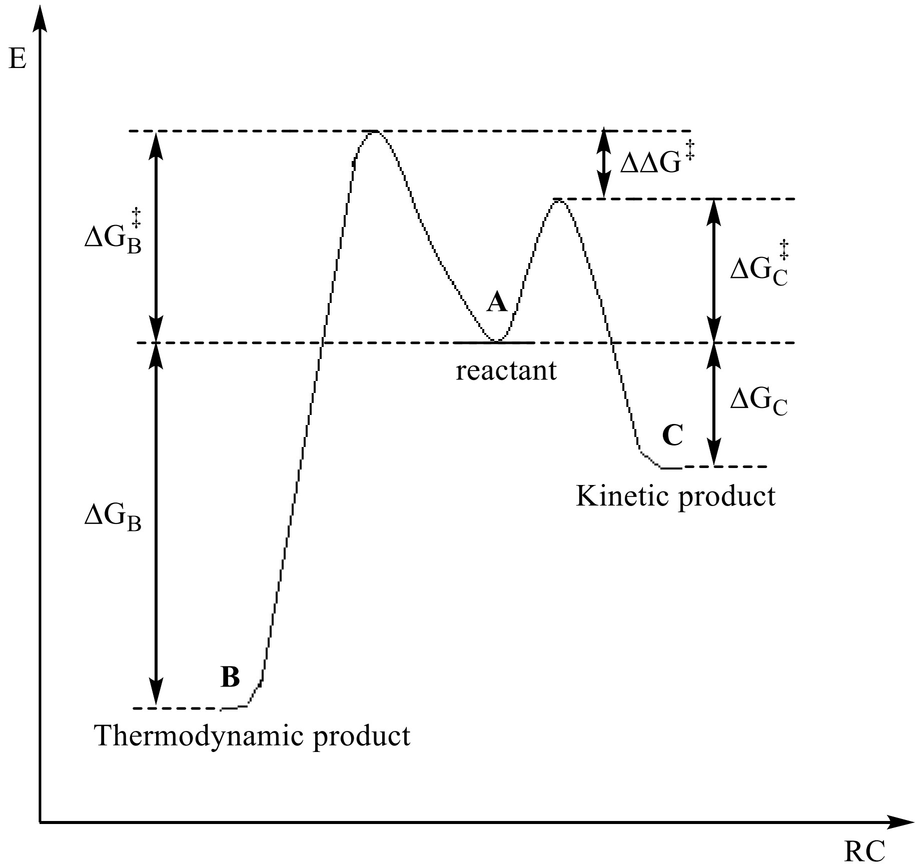


Figure 10: Kinetic and thermodynamic control.

To obtain the thermodynamic product, $i.e.$ the most stable (B in this case), it is necessary to work over long periods of time to reach equilibrium, and at high temperature to promote the passage through the high energy transition state that allows to go from A to B.

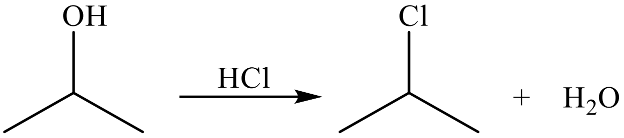
On the other hand, to obtain the kinetic product, the one that forms the most quickly (C product), the experiment must be carried out over a short time interval to avoid reaching equilibrium, and at low temperature to avoid the high energy transition state that allows to go from A to B.

9. Classification of reactions

a. Substitution reactions

An atom or group of atoms replaces another in the initial molecule.

Example:

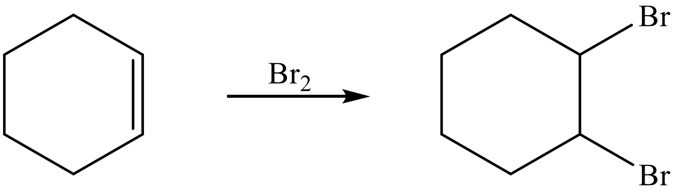


These reactions can be nucleophilic, electrophilic or radical.

b. Addition reactions

A molecule splits into two fragments that attach to an initial molecule.

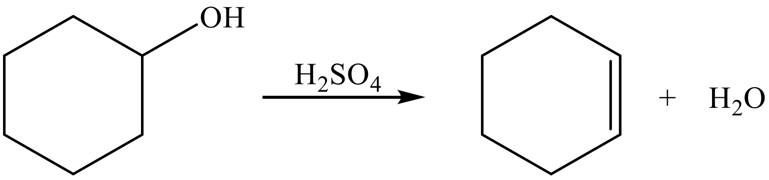
Example:



c. Elimination reactions

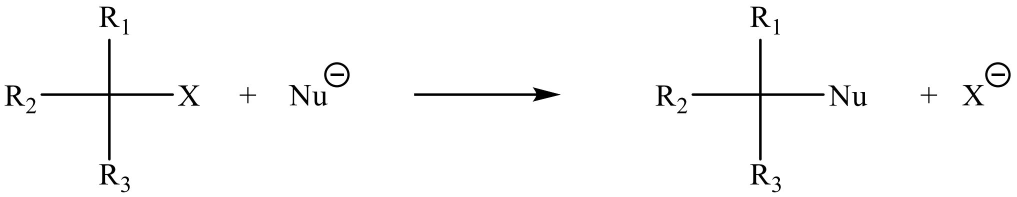
A molecule loses some of its atoms, and a multiple bond is then formed.

Example:

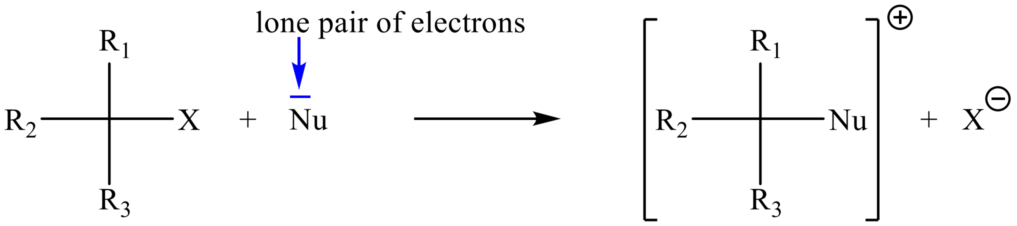


9.1 Nucleophilic substitution reactions

Nucleophilic substitution consists of replacing the halogen with a nucleophilic group $i.e.$ having a negative charge or non-bonding electrons (lone pair of electrons). The overall reaction is:



Nu^-: HO^-, H_2N^-, RO^-.



Nu: H_2O, RNH_2, ROH.

There are two possible mechanisms:

- Unimolecular nucleophilic substitution reactions noted: $SN1$
- Bimolecular nucleophilic substitution reactions noted: $SN2$

9.1.1 Unimolecular nucleophilic substitution $SN1$

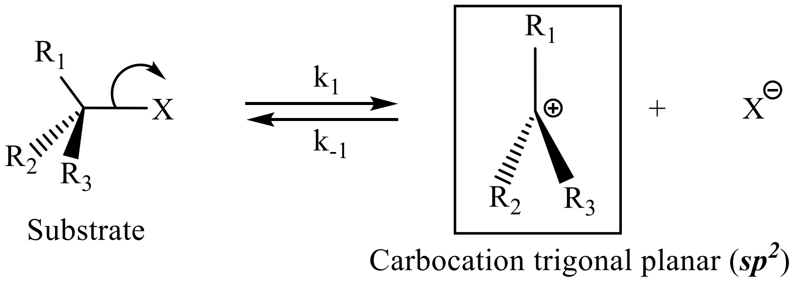
This type of mechanism occurs in two steps and involves a single entity in the slow stage of the reaction:

- Departure of the nucleofuge X^-: slow step, formation of a carbocation trigonal planar shape;
- Attack, of the formed carbocation, by the nucleophile Nu^-: fast step.

9.1.2 Mechanism

The mechanism occurs in two steps; the first step is the formation of the carbocation (C^+), and the second step is the attack of the nucleophile Nu^- on either side of the planar carbocation. The rate-determining step is the one corresponding to the formation of the carbocation. This determining step is unimolecular, hence the name $SN1$.

Since the first step is the rate-determining step, the rate of the reaction depends only on the concentration of the haloalkane (substrate) and thus is independent of that of the nucleophile. The experimental law governing the rate of this reaction is: $v = k[RX]$, first-order reaction with respect to the haloalkane RX.



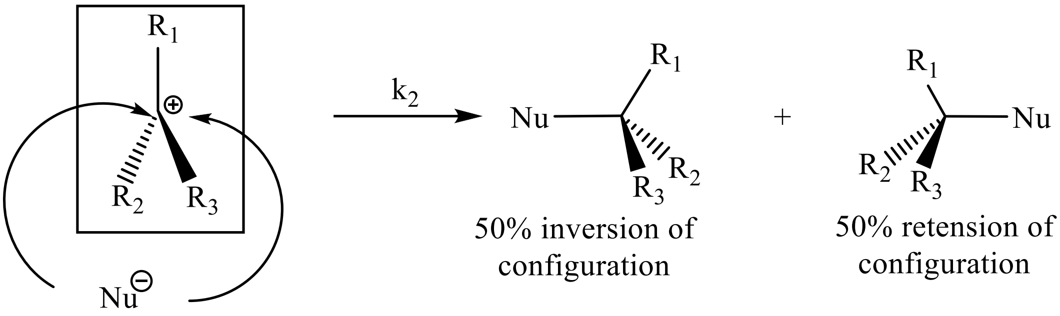


Figure 11: Mechanism of the unimolecular nucleophilic substitution $SN1$.

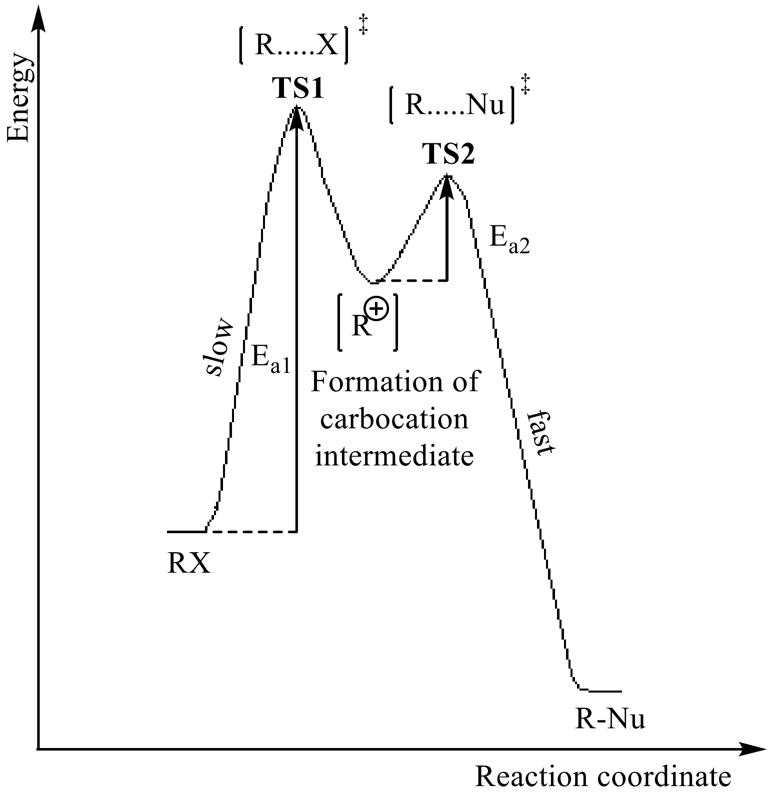


Figure 12: Energy profile of the unimolecular nucleophilic substitution reaction ($SN1$).

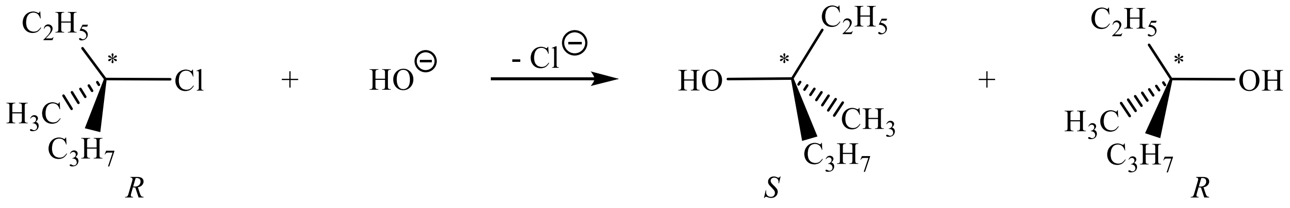
The first step of this mechanism is the most difficult and the most demanding in terms of energy and time because it requires crossing a significant energy barrier so it is slow. While the second step is faster since it overcomes a much lower energy barrier.

9.1.3 Stereochemistry

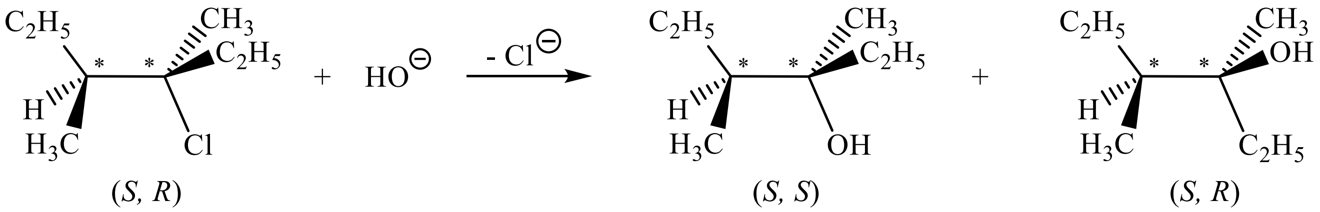
Given the equiprobability of attack of the nucleophile on both sides of the plane carbocation, and to the extent that the starting compound has as its only asymmetric carbon the one on which the substitution occurs, then we obtain at the end of the reaction an equimolar mixture of two products called: racemic mixture.

A racemic mixture is a mixture containing two enantiomers in equal proportions. Racemic mixture is optically inactive and have zero optical rotation. If in a given reaction, 50% of inversion and 50% of retention occurs, the process is then called racemization.

Example:



Two enantiomers in a 50:50 mixture



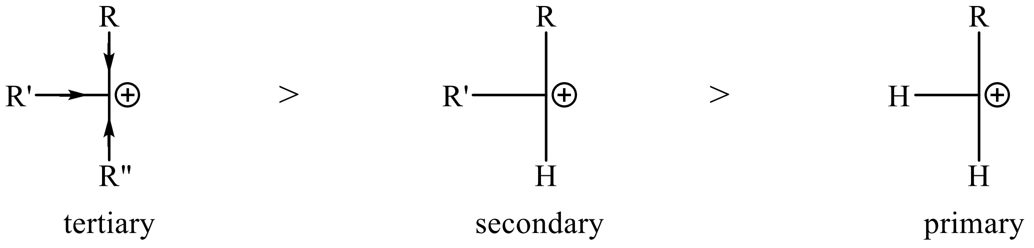
Two diastereoisomers in a 50:50 mixture

We conclude that the $SN1$ reaction is not stereoselective.

9.1.4 Factors influencing $SN1$ reaction

a - Influence of the carbon carrying the leaving group

The $SN1$ reaction is fast whenever the carbocation formed is stable. Alkyl groups with an inductive donor effect further stabilize the carbocation. The reactivity increases in the series:



$SN1$ is favorable on tertiary and secondary halogenoalkanes.

b- Influence of the nucleofuge

The more polarizable the $C - X$ bond is, the more easily it breaks and we will have a good nucleofuge that leaves easily.

c- Influence of the nucleophile

The nucleophile does not intervene in the kinetically determining step of the $SN1$ mechanism. Its influence is therefore weak in this mechanism and is not of great importance given the ease of attack of the carbocation.

d- Influence of the solvent

The solvents used for $SN1$ type reactions are polar protic. In addition, the carbocation formed during the reaction is more stable as it is well solvated. A polar solvent will stabilize the carbocation while a protic solvent will form bonds with the nucleofuge and thus promote the breaking of the $C - X$ bond (C^+ will form more easily) to form two ionic entities R^+ and X^-.

9.1.5 Bimolecular nucleophilic substitution reactions ($SN2$)

This is a single-step mechanism. The approach of the nucleophilic entity Nu^- to the substrate causes the departure of the nucleofugal entity X^-. This approach is done on the opposite side to the $C - X$ bond. As a result, this mechanism leads to a single product unlike the $SN1$ mechanism. If the substrate is an asymmetric carbon, a configuration inversion called Walden inversion takes place.

The inversion of configuration can be encountered when the product formed in a reaction has a stereochemistry opposite to that of reactant.

9.1.5.1 Mechanism

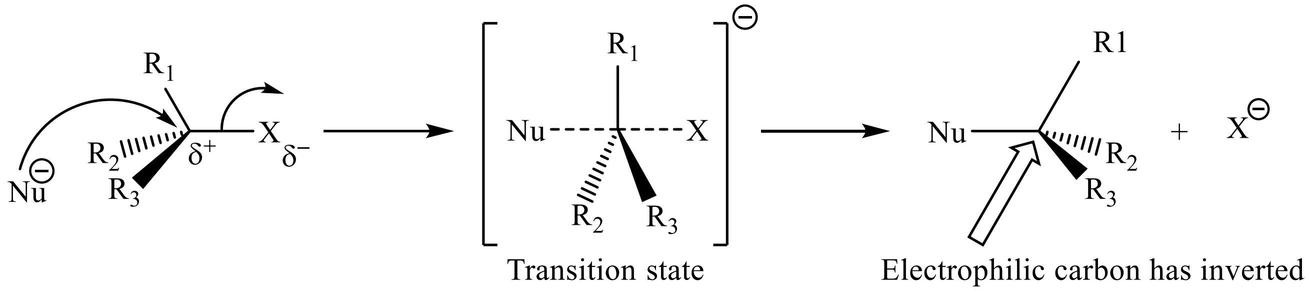


Figure 13: Mechanism of bimolecular nucleophilic substitution $SN2$.

Two molecules of reactants are involved (The molecularity is 2) in this mechanism in a single elementary step, hence the name: bimolecular reaction ($SN2$).

Nu^- attacks the opposite side of X to minimize electrostatic repulsions via the Walden inversion that is easily understood through the representation of the activated complex. The bonds of the intermediate are neither completely formed nor completely broken and the transition state has a five-coordinated carbon where the $C - X$ bond begins to break while the $Nu - C$ bond begins to form $i.e.$ the breaking-formation of bond process is simultaneous or even said to be concerted (at the same time).

The experimental rate law is: $v = k[RX][Nu^-]$.

$[RX]$: represents the concentration of halogenated derivative (expressed in $mol.L^{-1}$)

$[Nu^{-}]$: represents the concentration of base (expressed in $mol.L^{-1}$)

υ: represents the rate of the elimination reaction. It is expressed in $mol.s^{-1}$.

k: is the rate constant. Its unit is given in $L.s^{-1}.mol^{-1}$.

The reaction is of the second order in the general case. These nucleophilic substitution reactions are exothermic and the activation energy E_a is small.

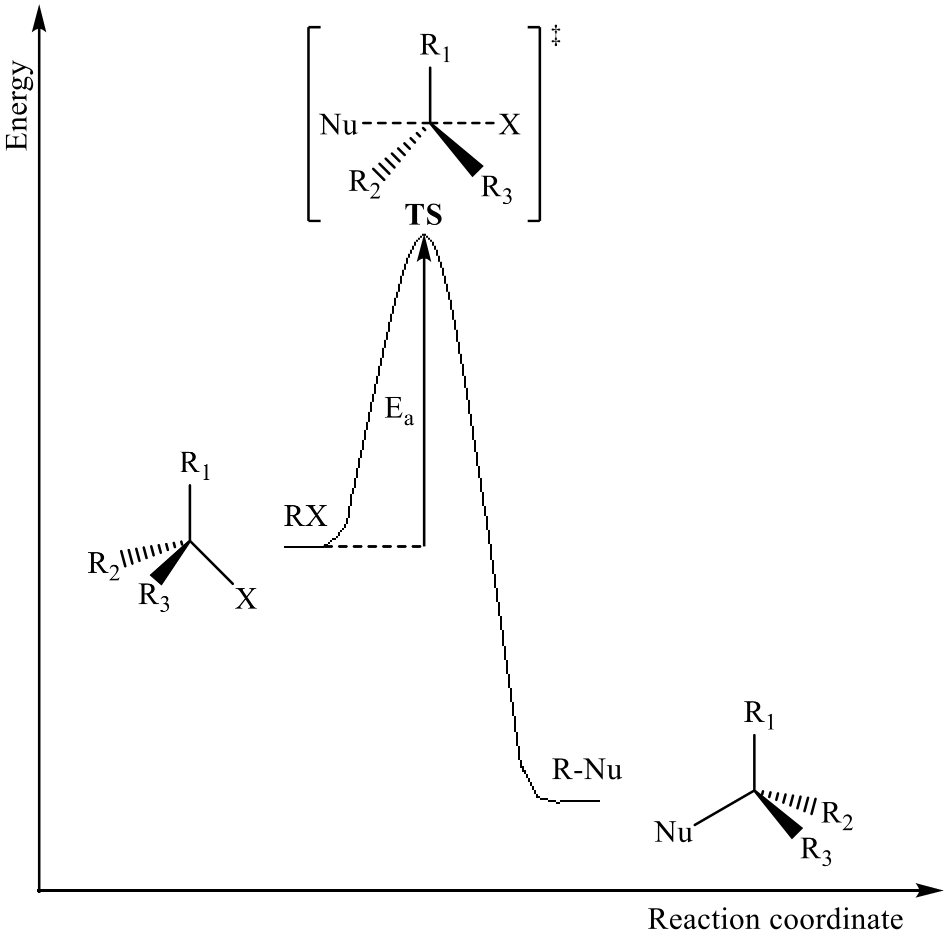
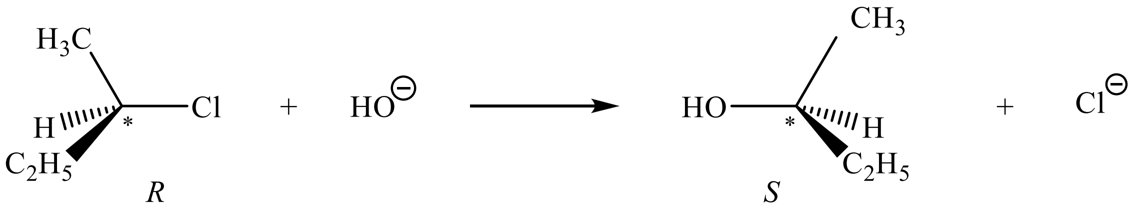
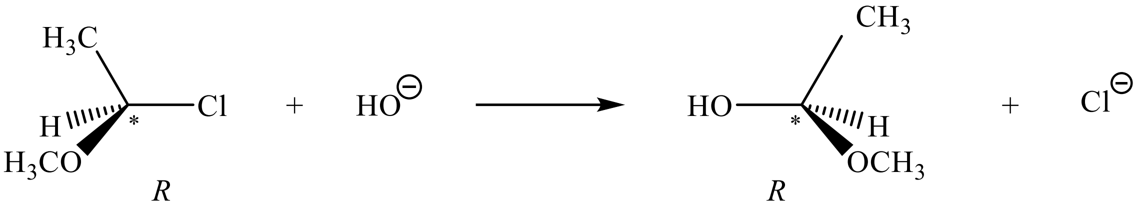


Figure 14: Energy profile of the bimolecular nucleophilic substitution reaction ($SN2$).

9.1.5.2 Stereochemistry

The Walden inversion can involve the inversion of configuration of the asymmetric center on which the reaction takes place, but this is not obligatory.



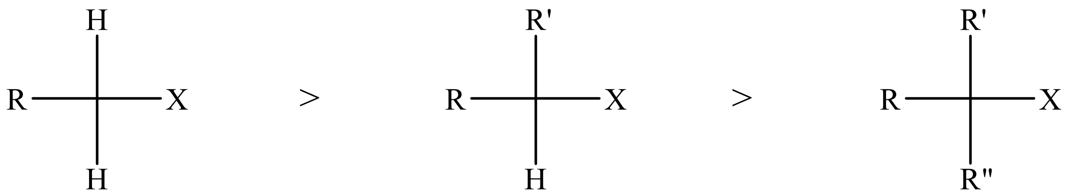


The $SN2$ reaction is stereoselective and stereospecific: from a given absolute configuration for the asymmetric carbon, only one of the two possible products is obtained. The other stereoisomer gives a different product.

9.1.5.3 Factors influencing $SN2$ reaction

a- Influence of the carbon carrying the leaving group

The attack of the nucleophile is hindered by the steric hindrance, hence the order:



b- Influence of the nucleofuge

The nucleofuge or leaving group is the species that leaves the molecule; in this case it is the halogen. It must be able to leave easily. In other words, the more polarizable the $C - X$ bond is, the more easily it breaks.

In the case of halogens, we get the order: $I > Br > Cl > I$

c- Influence of the nucleophile

The attack of the nucleophile triggers the reaction process.

It intervenes in the rate-limiting step of the $SN2$ mechanism favored in the presence of good nucleophiles. The rate of the reaction increases with the nucleophilicity of the nucleophile and decreases with its size. Indeed, a very bulky nucleophile will have more difficulty reacting on the carbon carrying the halogen with respect to a small nucleophile.

Hence the order of priority is: $I > Br > Cl > I$.

d- Influence of the solvent

A polar protic solvent decreases the rate of $SN2$ by solvation of the nucleophile while establishing hydrogen bonds, thus causing a decrease in its nucleophilicity.

On the other hand, a polar or apolar but aprotic solvent (absence of hydrogen bonds) increases the rate of $SN2$ by solvating the cation of the nucleophile. The latter will then remain free in the medium, therefore very reactive.

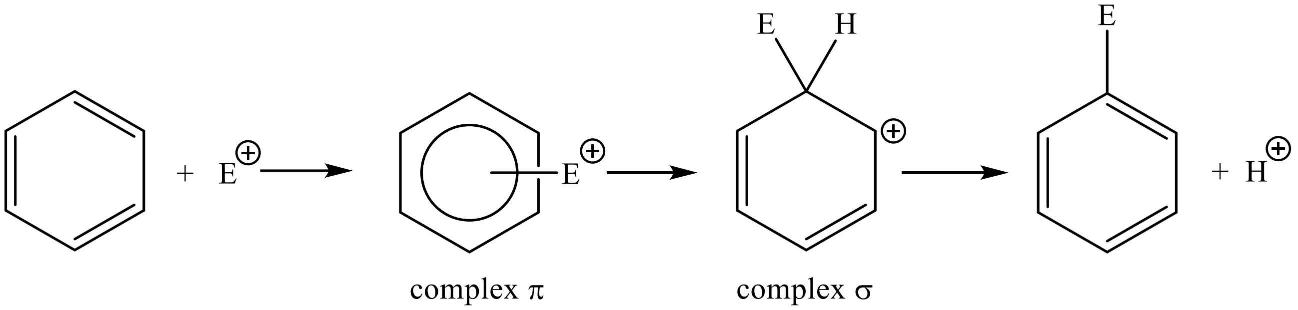
The solvents used for $SN2$ type reactions are polar aprotic such as: dimethyl sulfoxide ($DMSO$), N, N-dimethylformamide (DMF), and acetonitrile.

9.2 Electrophilic substitution reaction

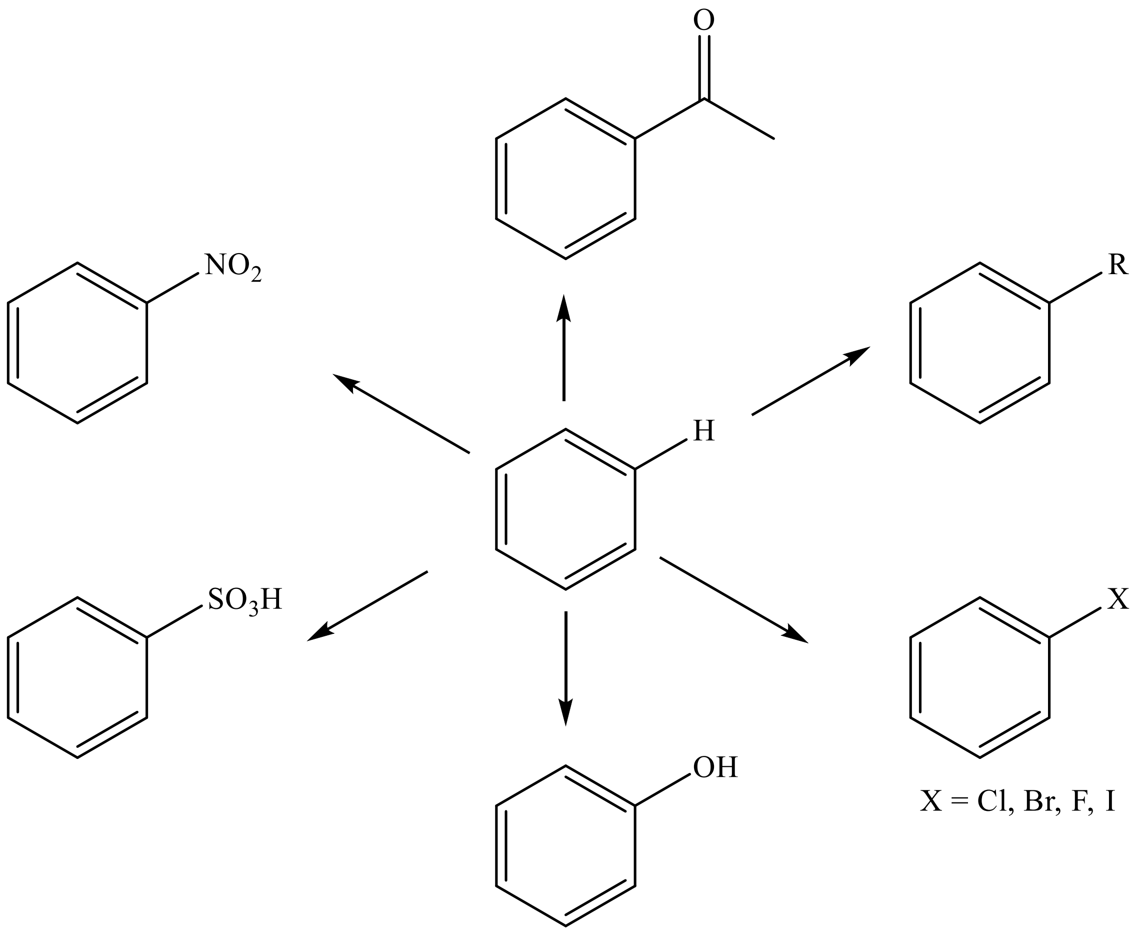
Electrophilic substitution is a reaction between an electrophile (E^+) and a compound rich in π electrons. During such a reaction, there is substitution (replacement) in a molecule of an electrophilic entity (atom or group of atoms poor in electrons) by another electrophilic entity.

This mechanism exists in the aliphatic series as in the aromatic series but more generally on aromatic compounds in the presence of electrophiles. It includes reactions such as chlorination, halogenation, nitration, and sulfonation.

In the aromatic series, during these reactions, which take place in several stages, the aromatic nucleus (cycle with high electron density) attacks an electrophilic entity E^+. This attack leads to a complex called a π complex. The latter evolves towards a σ complex that has lost its aromatic character and which, in turn, regains its aromatic stability by the elimination of a proton. This specific type of electrophilic substitution reactions is called: electrophilic aromatic substitution (EAS).

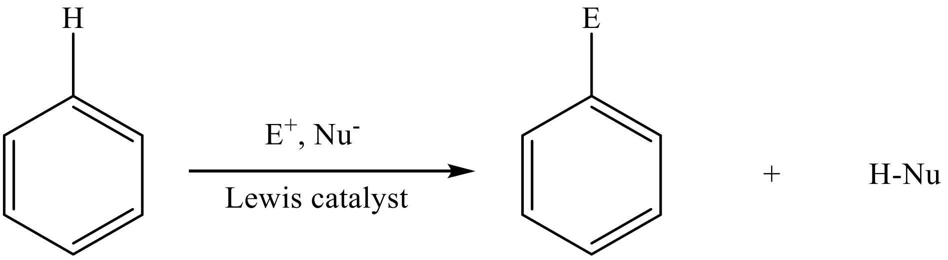


Many different substituents can be introduced onto an aromatic ring through electrophilic substitution. It can be substituted by a halogen ($-Cl, -Br, -I, -F$), a nitro group ($-NO_2$), a sulfonic acid group ($-SO_3H$), a hydroxyl group ($-OH$), an alkyl group ($-R$), or an acyl group ($-COR$), hence it is possible to prepare many thousands of substituted aromatic compounds.



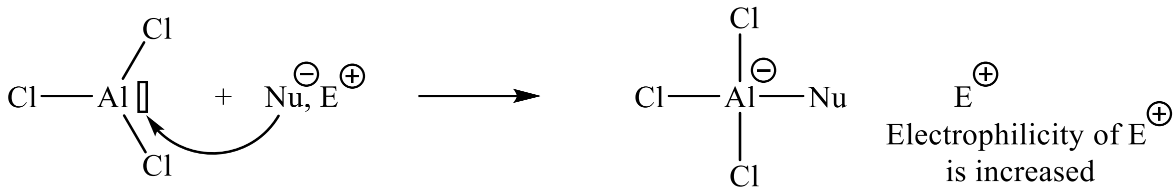
9.2.1 General mechanism of the electrophilic aromatic substitution reaction

The overall electrophilic substitution reaction is:

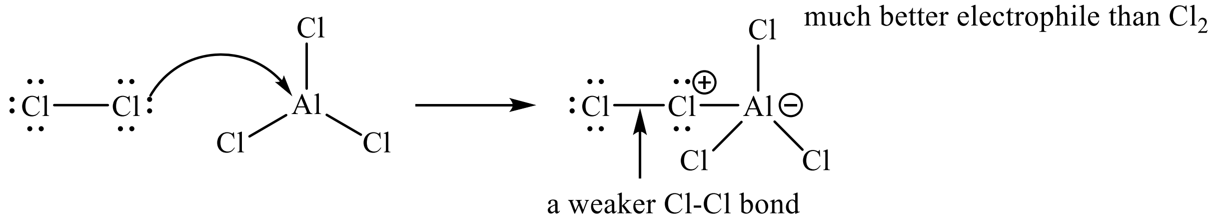


At the end of the reaction, the hydrogen bonds to the nucleophile (Nu^-) that accompanied the electrophile. Examples of Lewis catalysts include aluminum chloride ($AlCl_3$), iron chloride ($FeCl_3$), etc. The catalyst serves to increase the electrophilicity of E^+. The reaction mechanism of the electrophilic aromatic substitution reaction is shown below.

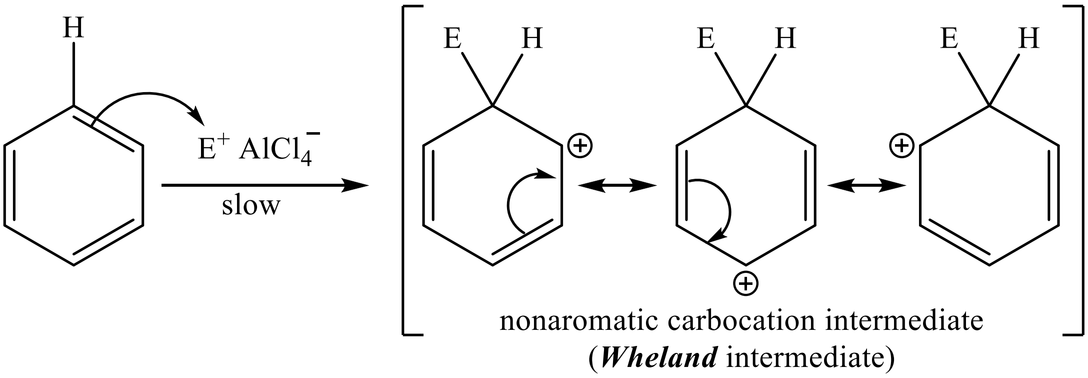
The electrophile exaltation is carried out as:



In the case of chlorination, the Lewis acid $AlCl_3$ accepts a pair of electrons from Cl_2. This weakens the $Cl - Cl$ bond making of it a much better electrophile. Attack by a nucleophile at the distal Cl will not release Cl^-, but the much weaker base $AlCl_4^-$ which is a better leaving group than Cl^-.



Benzene, nucleophile with an electron density of six π electrons, will attack the electrophile. An electron pair from the benzene ring attacks the positively polarized E^+, forming a new $C - E$ bond and leaving a nonaromatic carbocation intermediate.

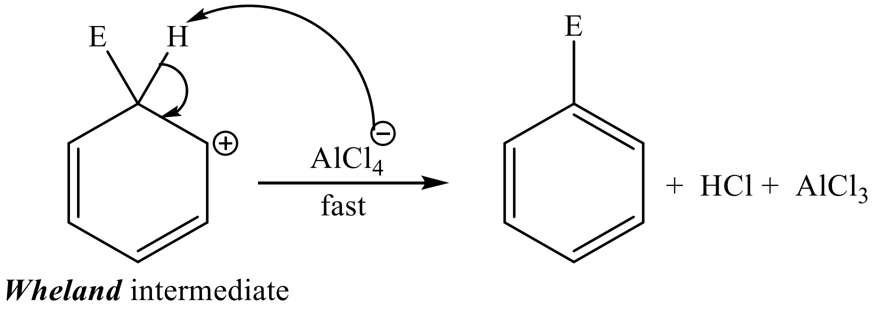


It can be seen that the carbocation intermediate is stabilized by resonance (three possible resonance structures).

The first step of EAS leads to the formation of a σ complex or arenium ion by the attack of the benzene electron pair on the electrophile to lead to a "resonant" carbocation.

This step is slow and constitutes the rate-determining step during which the aromaticity is broken.

The second step is very fast and exothermic, accompanied by a loss of proton and a regeneration of the aromaticity. The intermediate formed, called "Wheland intermediate", releases a proton and the ring regains its aromaticity:



A base removes H^+ from the carbocation intermediate, and the neutral substitution product forms as two electrons from the $C-H$ bond move to re-form the aromatic ring.

Thus, the catalyst $AlCl_3$, in this example, is released of Nu to enhance the electrophilicity of a new molecule E^+, Nu^-.

The energy profile representing the two steps of this reaction is given as:

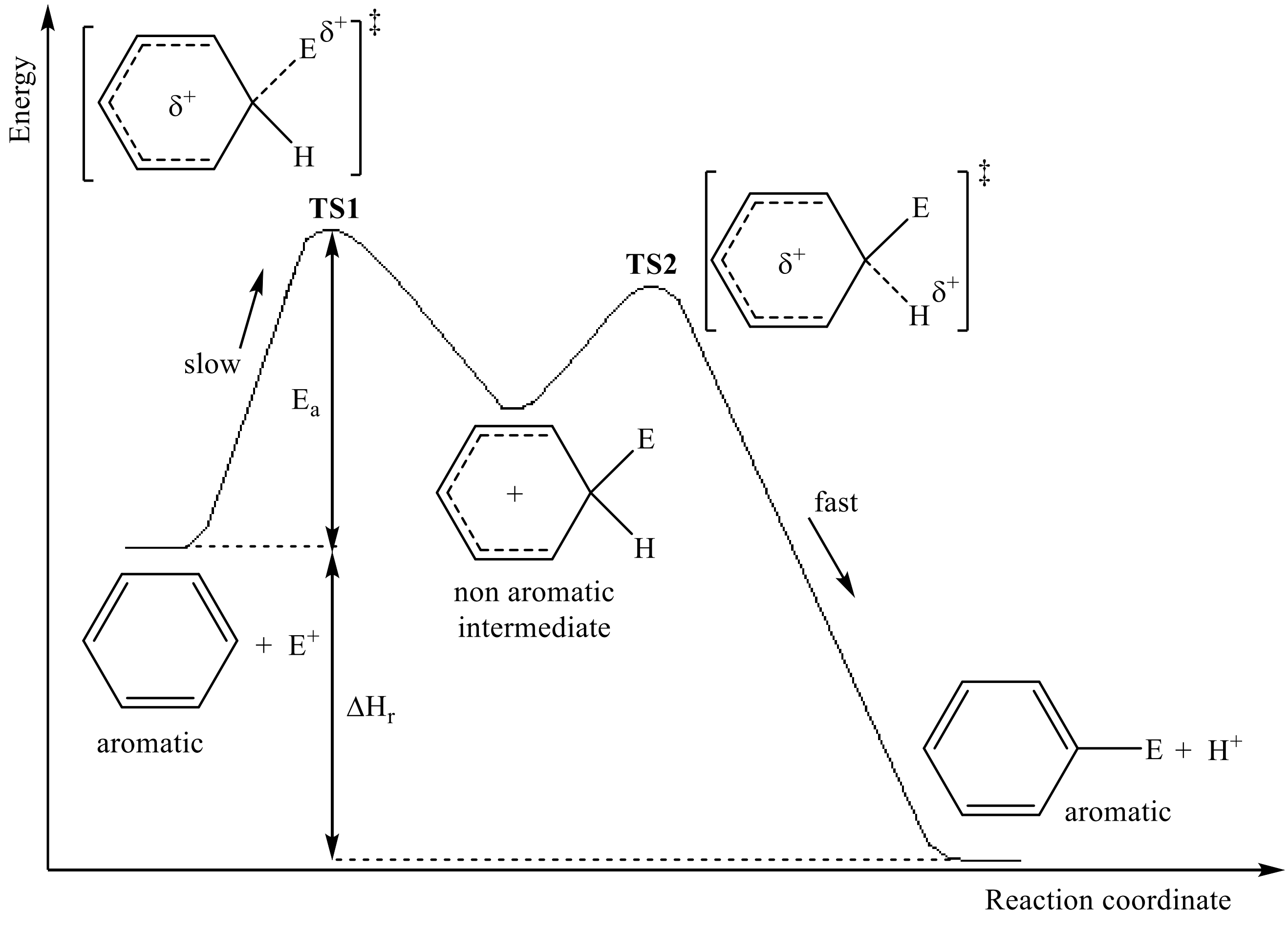


Figure 15: Energy profile of the electrophilic aromatic substitution reaction.

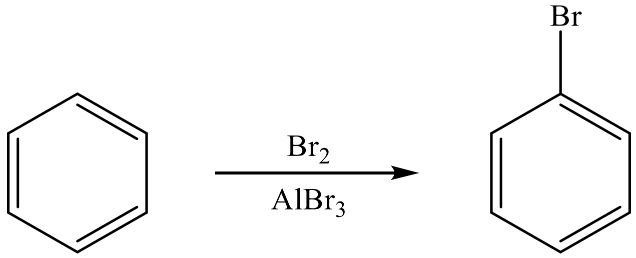
9.2.2 Electrophilic aromatic substitution reactions on benzene

On benzene, all positions are identical because all carbon atoms are linked to a hydrogen.

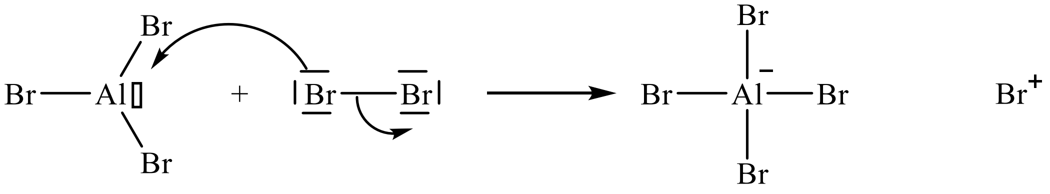
9.2.2.1 Halogenation of benzene

For this kind of reactions, dihalogen, dichlorine or dibromine can be used. The catalysts used are aluminum chloride or aluminum bromide.

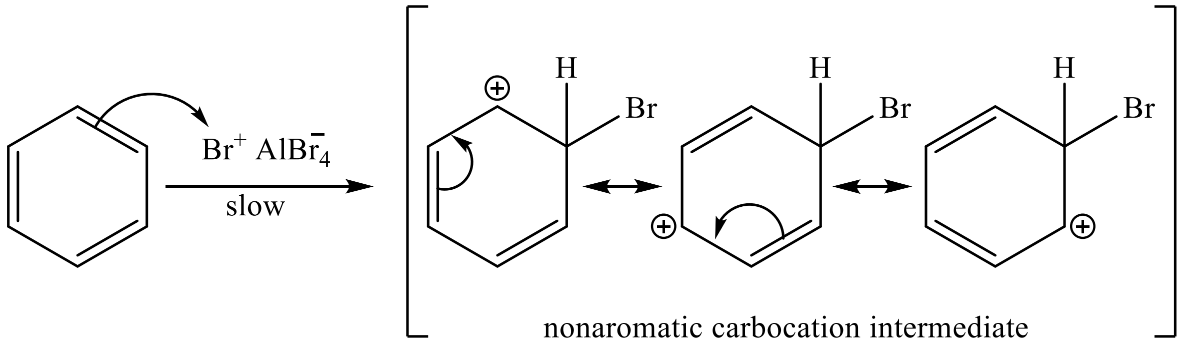
The overall reaction is given as:



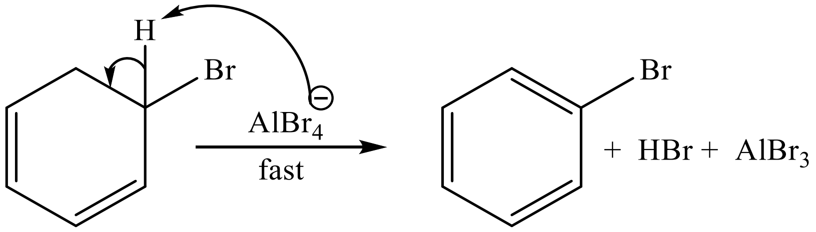
The electrophile exaltation is carried out as follows:



First step:

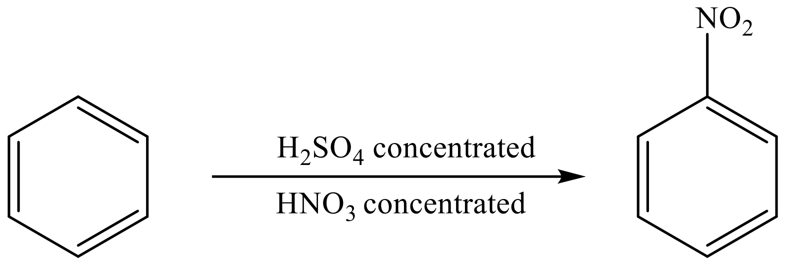


Second step:



9.2.2.2 Nitration of benzene

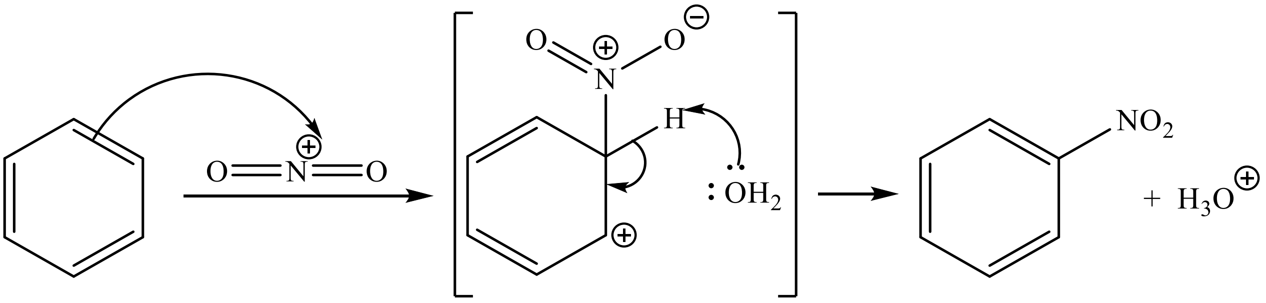
The overall nitration reaction leading to the formation of nitrobenzene is:



nitrobenzene

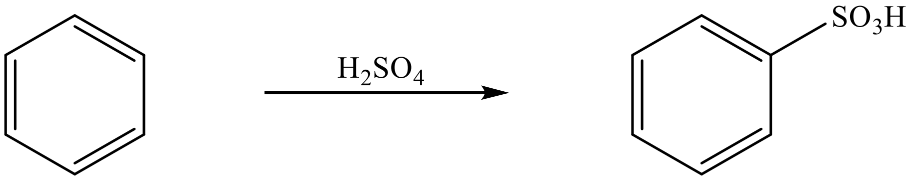
This reaction takes place in the presence of concentrated nitric acid (HNO_3) dissolved in concentrated sulfuric acid (H_2SO_4). This mixture gives rise to the formation of nitronium ion NO_2^+ which is a good electrophilic reagent:

$$2H_2SO_4 + HNO_3 \longrightarrow NO_2^+ + 2HSO_4^- + H_3O^+$$



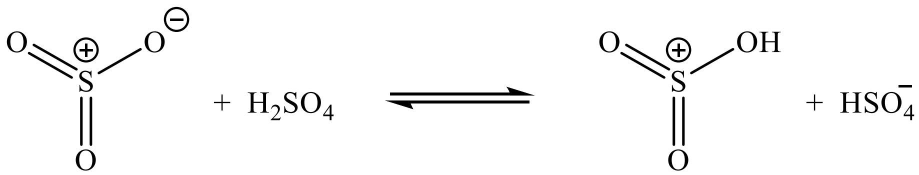
9.2.2.3 Sulfonation of benzene

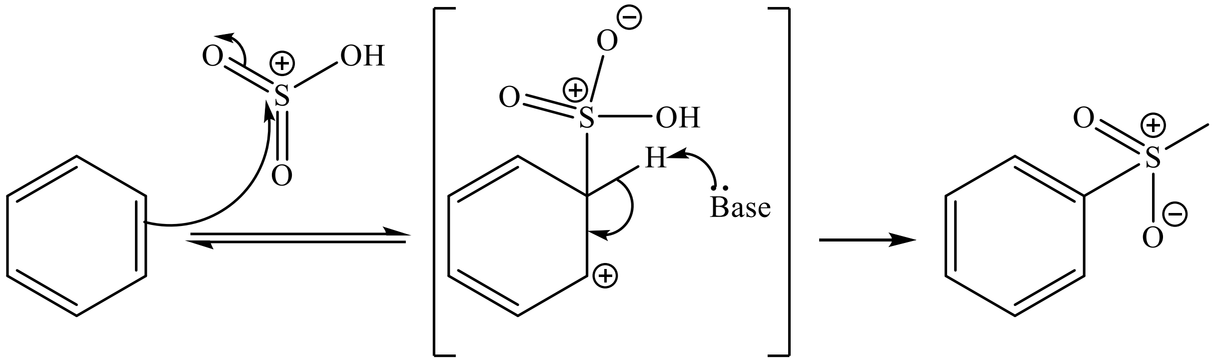
Sulphonation is an electrophilic substitution reaction which takes place in the presence of very concentrated sulfuric acid with benzene to produce benzene sulfonic acid:



benzenesulfonic acid

The mechanism of this reaction is:

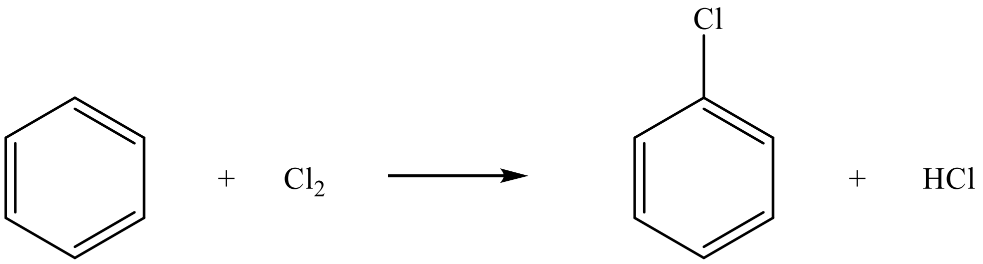




The electrophilic agent in this reaction is sulfite SO_3.

9.2.2.4 Chlorination of benzene

Chlorination is accompanied with the release of hydrochloric gas.



chlorobenzene

The reaction is usually catalyzed by iron, ferric chloride ($FeCl_3$) or other Lewis acids such as aluminum chloride ($AlCl_3$).

The catalyst allows the formation of the electrophile Cl^+ according to:

$$FeCl_3 + Cl_2 \rightleftharpoons [FeCl_4]^{\ominus} + Cl^{\oplus}$$

9.2.2.5 Friedel-Crafts reaction

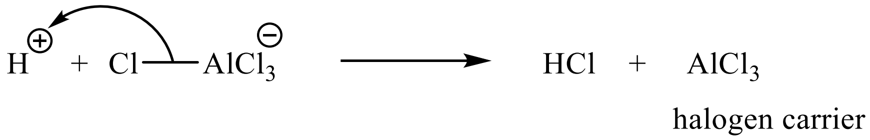
a- Alkylation

It is a simple reaction where an aromatic hydrocarbon (benzene) can be converted to a substituted hydrocarbon by reaction with alkyl halide in presence of Lewis acid like $AlCl_3$ or $FeCl_3$, etc.

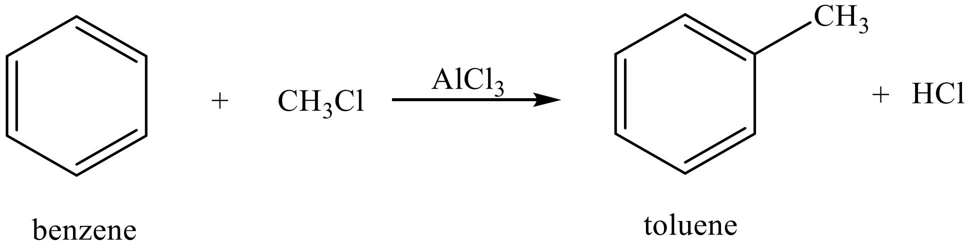
Alkyl ion (R^+) is formed by reacting a halogenoalkane with a halogen carrier ($AlCl_3$).

$$R{-}Cl + \underset{\text{halogen carrier}}{AlCl_3} \longrightarrow \underset{\text{carbocation}}{R^{\oplus}} + AlCl_4^{\ominus}$$

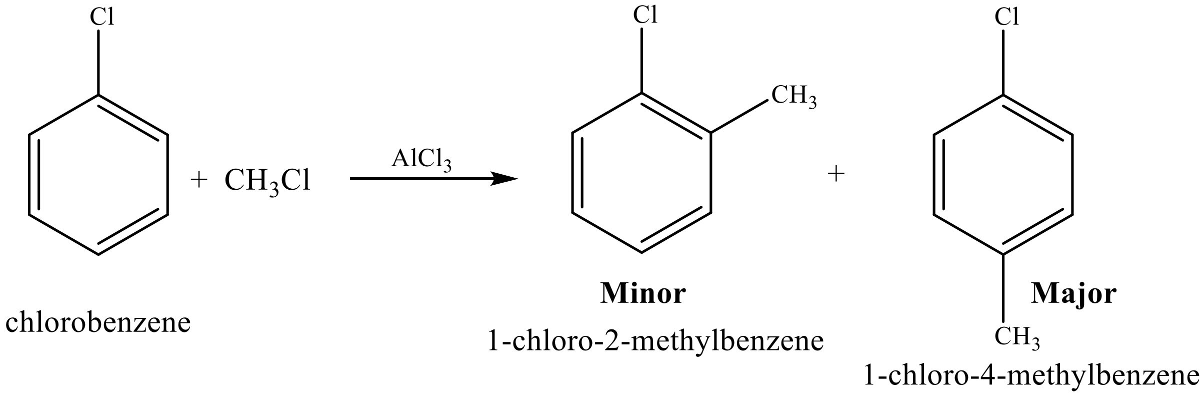
H^+ ion removed from benzene ring combines with $[AlCl_4^-]$ to reform $AlCl_3$ catalyst and HCl is formed.



Example 1:



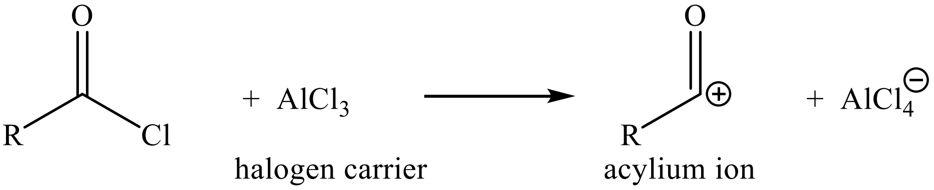
Example 2:



b- Acylation

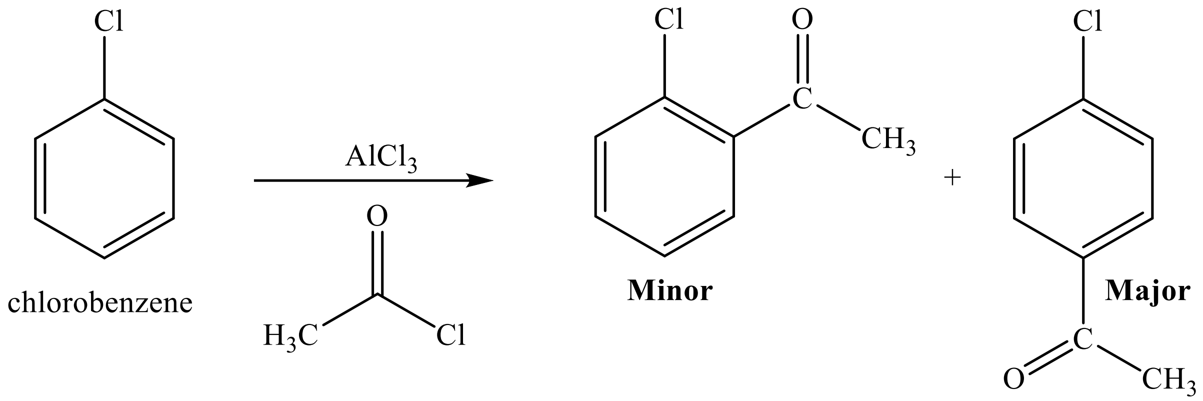
The acylium ion (RCO^+) acts as an electrophile due to its carbocation that can accept an electron pair from the delocalized ring of electrons in the benzene ring. A carbon-carbon bond forms. The carbon-hydrogen bond of benzene breaks to give the electron pair back to the ring of delocalized electrons. The RCO^+ ion replaces H on benzene ring.

Firstly, acylium ion RCO^+ is formed by reacting an acyl chloride with a halogen carrier ($AlCl_3$).



Then, the H^+ ion removed from benzene ring combines with $[AlCl_4^-]$ to reform $AlCl_3$ catalyst and HCl is then formed.

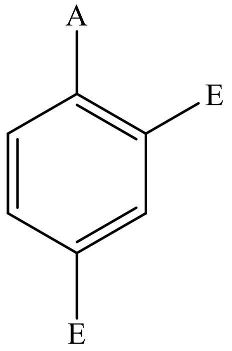
Example:



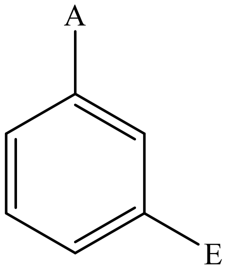
9.2.3 Substitution reactions on substituted benzenes

On a substituted benzene, the positions are different. The electronic effects induced by the atom or the group of atoms carried by the benzene nucleus orient the regioselectivity of the attack of an electrophilic reagent. Depending on the nature of the substituent carried by the benzene nucleus, the substitution will be oriented either toward $ortho$ and $para$, or $meta$, all depending on the inductive or mesomeric effect exerted by this group.

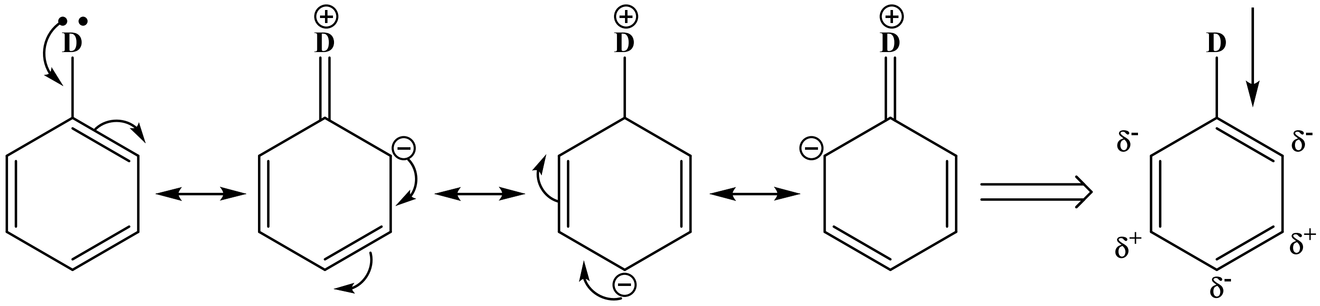
+M, *+I* effect and halogens



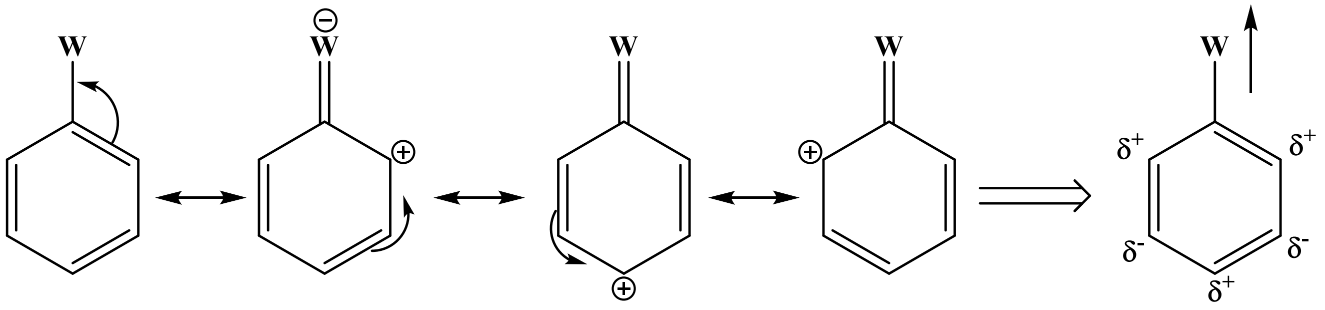
-M and *-I* effect



Thus, when the overall electronic effect (inductive and mesomeric effects), exerted by the substituent, is electron-donating, the nucleus is activated by an increase in its electronic density and the reaction occurs more easily on the $ortho$ and/or $para$ carbon(s).



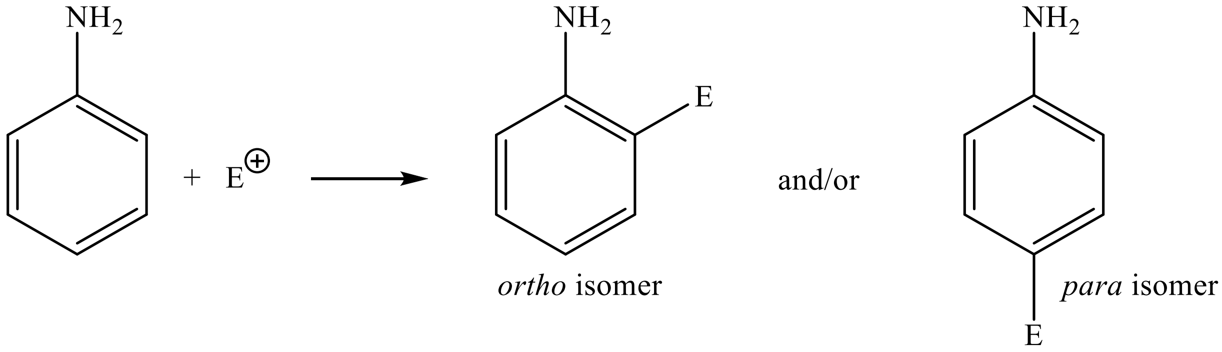
However, when the overall electronic effect of the substituent is electron-withdrawing (mesomeric and inductive), the nucleus is deactivated by a decrease in its electronic density and the reaction can take place on the $meta$ position.



So, to sum up:

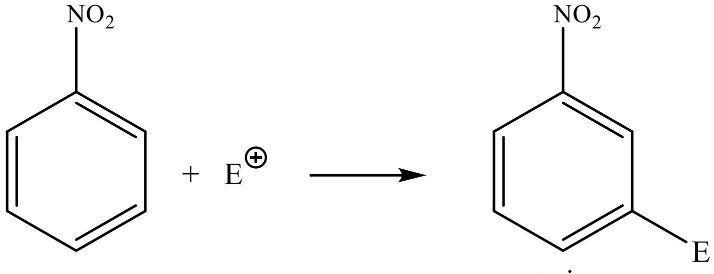
If the group is $(+M)$ or $(+I)$ effect, then the orientation is $ortho$ and $para$.

If the group is $(-M)$ and $(-I)$ effect, then the orientation is $meta$.



ortho isomer

para isomer



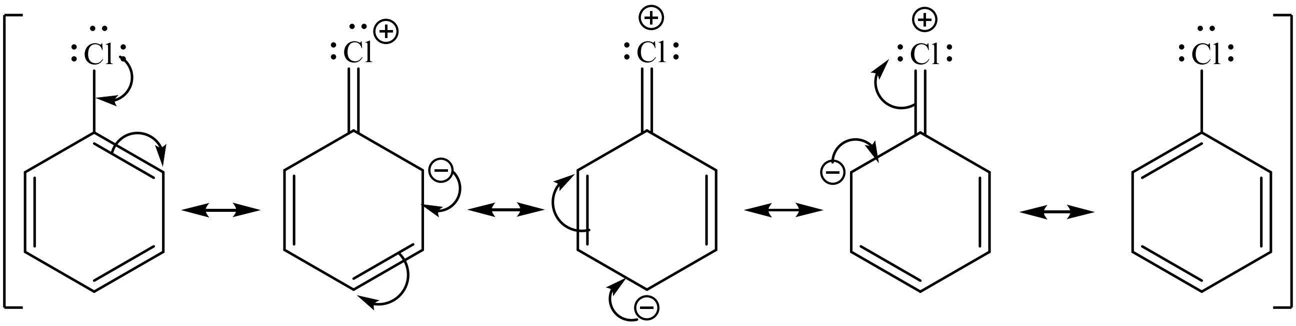
meta isomer

N.B:

1. Halogens direct the electrophilic aromatic substitution in *ortho* and *para*.

Let's take the example of chlorine. The chlorine withdraws electrons through inductive effect $-I$ and releases electrons through resonance effect $+M$.

In chlorobenzene, one of the lone pairs of chlorine atom conjugates with the benzene ring.

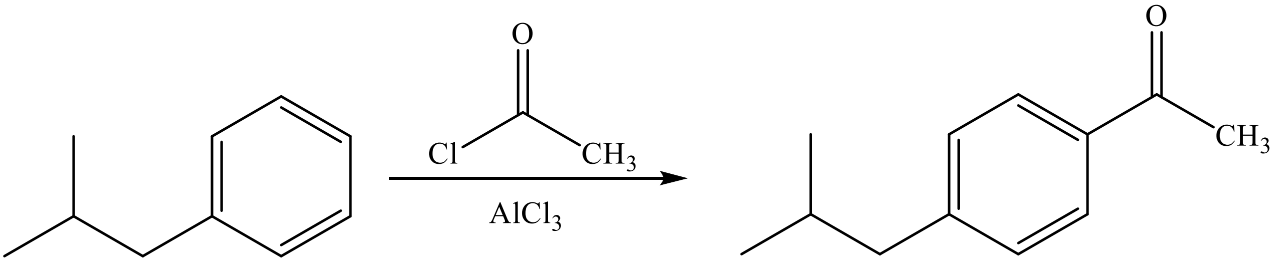


Since the electron density is maximum at $ortho -$ and $para -$ positions due to $+M$ effect, the electrophile can easily attack at each of these positions.

2. Substituents with $(+M)$ or $(+I)$ effects activate the electrophilic substitution reaction, they increase the rate of the reaction. They are said to be activating.
3. Substituents with $(-M)$ or $(-I)$ effects deactivate the electrophilic substitution reaction, they decrease the rate of the reaction. They are said to be deactivating.

Example 1:

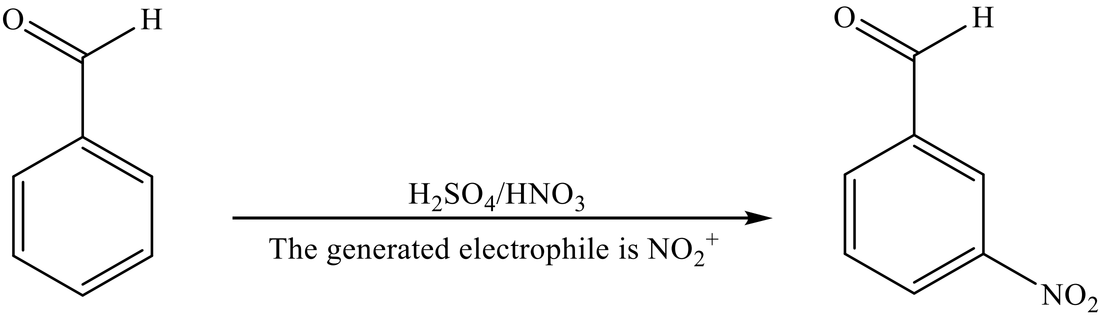
Synthesis of ibuprofen (painkiller):



The $(+I)$ effect of the alkyl group attached to the benzene ring directs the substitution toward $ortho$ and para positions. The $ortho$ position is hindered by the isobutyl group (steric hindrance) so the $para$ position will be favored and will give the major product. This reaction is regioselective.

Example 2:

The $-CHO$ group has a $(-M)$ effect, it will direct the substitution toward $meta$:



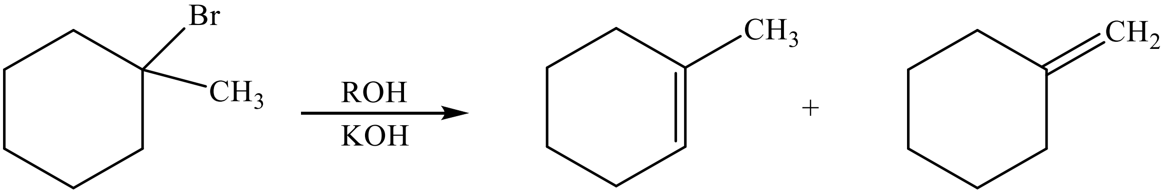
9.3 Elimination reactions

Elimination consists of the departure of the halogen accompanied by a hydrogen in alpha, under the effect of a base. It leads to the formation of an alkene. The overall reaction is:

$$H-CH_2-CH_2-X + B^- \longrightarrow H_2C=CH_2 + BH + X^-$$

These are the reverse reactions of addition reactions. The most frequent ones lead to the formation of a double bond (alkene) following the departure of the halogen accompanied with a hydrogen in alpha, under the effect of a base, by breaking two single bonds carried by two adjacent atoms.

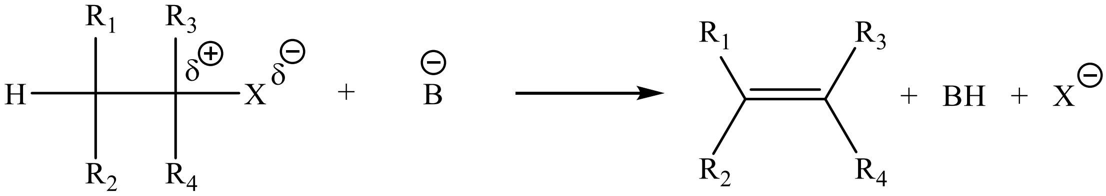
Example:



1-bromo-1-methylcyclohexane 1-methylcyclohex-1-ene methylenecyclohexane

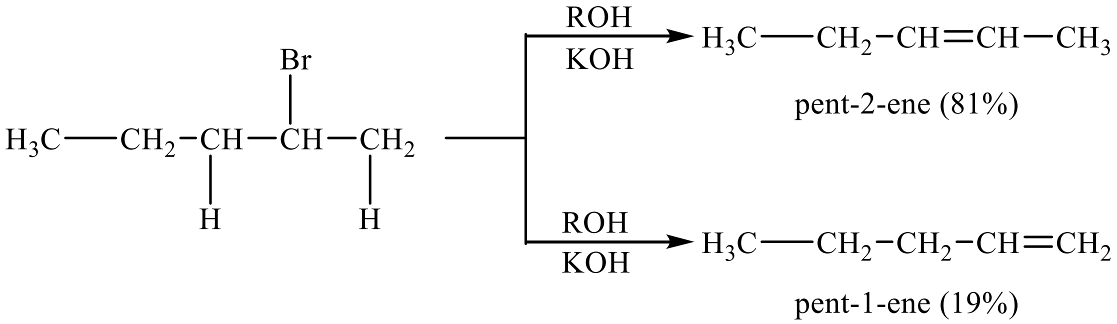
Major **Minor**

9.3.1 General mechanism of elimination reactions (*E*)



The nucleofuge (X) is eliminated at the same time as an H carried by the carbon neighbouring $C-X$, in the presence of a base (B^-).

Example:



pent-2-ene (81%)

pent-1-ene (19%)

9.3.2 Regioselectivity

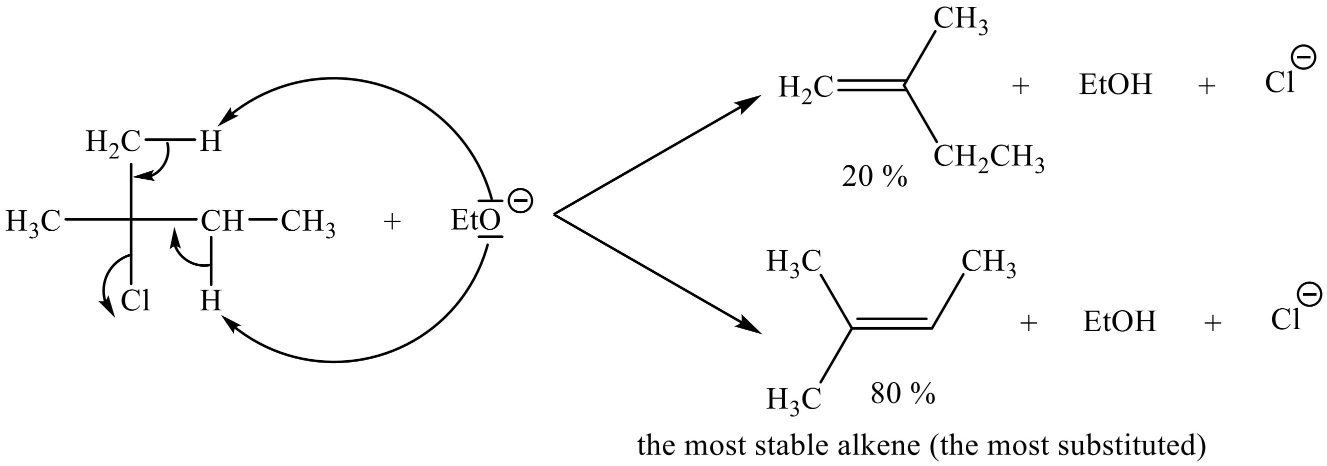
The elimination reactions are regioselective: if there are several hydrogens H carried by carbons neighboring $C-X$, only one will be preferentially attacked.

The major product formation is governed by Zaytsev rule. Hence, alkene which has the greater number of alkyl groups attached to the double bonded carbon atoms, will be the major product.

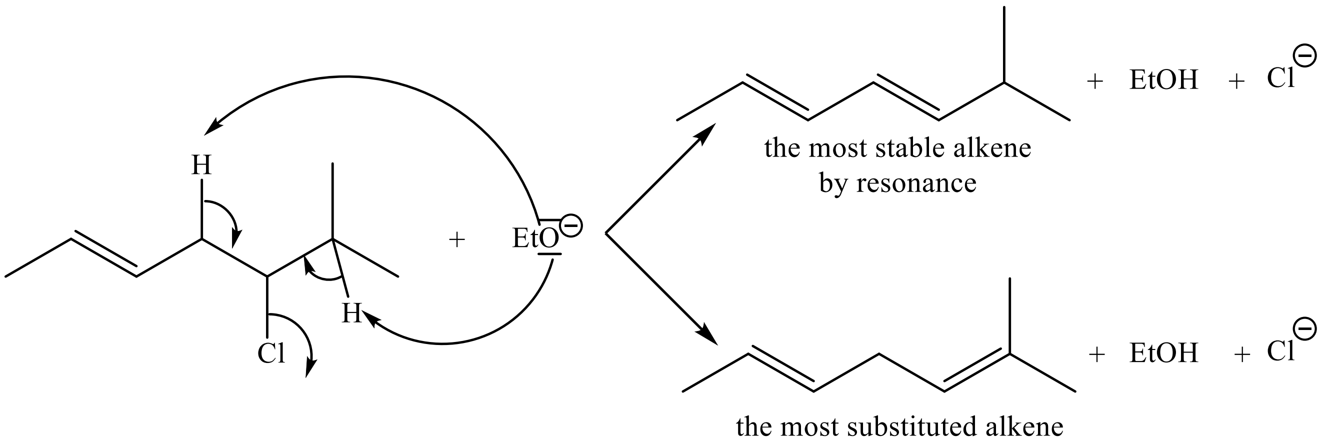
9.3.3 Zaytsev rule

An elimination reaction (E), under thermodynamic control, leads to the most stable alkene (often the most substituted alkene).

Example 1:



Example 2:



The product of the elimination reaction that presents a conjugation is the most stable product (major product) compared to the most substituted product (minor product).

Like nucleophilic substitution reactions, elimination reactions can be done in one or two steps, and this is the reason why we distinguish two possible mechanisms:

- Unimolecular eliminations noted: $E1$
- Bimolecular eliminations noted: $E2$

9.3.4 Unimolecular elimination reaction ($E1$)

This is a two-step process:

- a first slow step consisting of the departure of the nucleofugal entity from the substrate;
- a second fast step characterized by the removal of a proton located on the carbon in β of the carbocation, by a base B^-, thus allowing the formation of a double bond.

9.3.4.1 Mechanism

In the first step, a carbocation is formed by breaking the $C - X$ bond. In the second step, a Brönsted base, denoted here B^-, comes to remove a hydrogen in β position, $i.e.$ located on a carbon close to the vacant carbon (C^+). The two electrons of the $C - H$ bond form the new created π double bond.

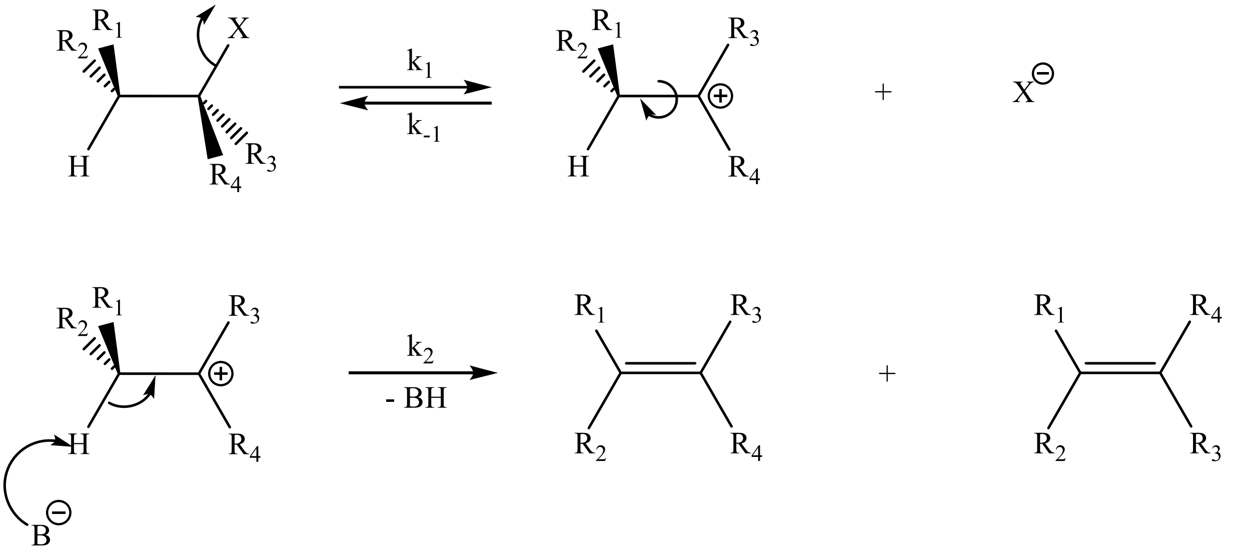


Figure 16: Mechanism of the unimolecular elimination reaction ($E1$).

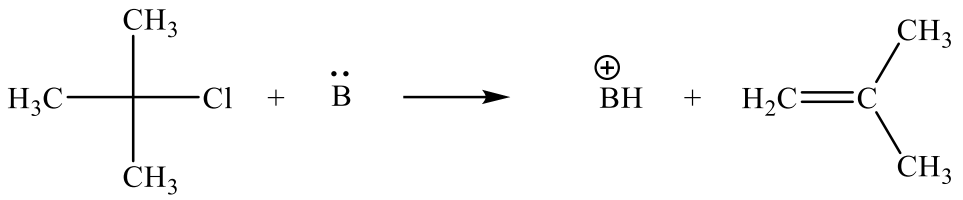
The mechanism occurs in two steps. The rate-determining step corresponds to the formation of the carbocation C^+. This rate-determining step is unimolecular, hence the name: unimolecular $E1$.

The experimental rate law corresponding to this reaction is: $v = k_1[RX]$.

Due to the free rotation around the $C - C$ bond, two possible alkenes are formed.

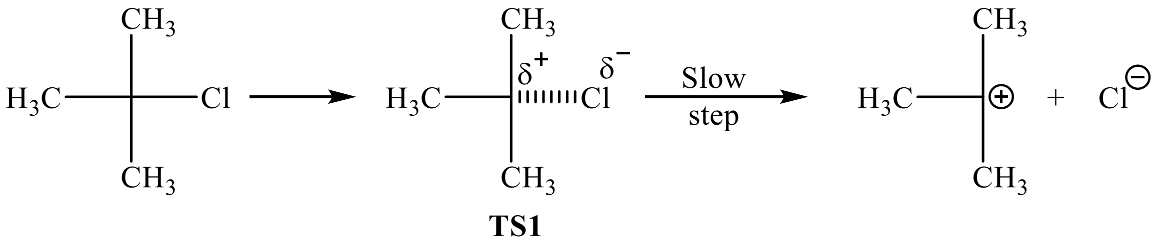
Example:

Let’s consider the following $E1$ reaction:

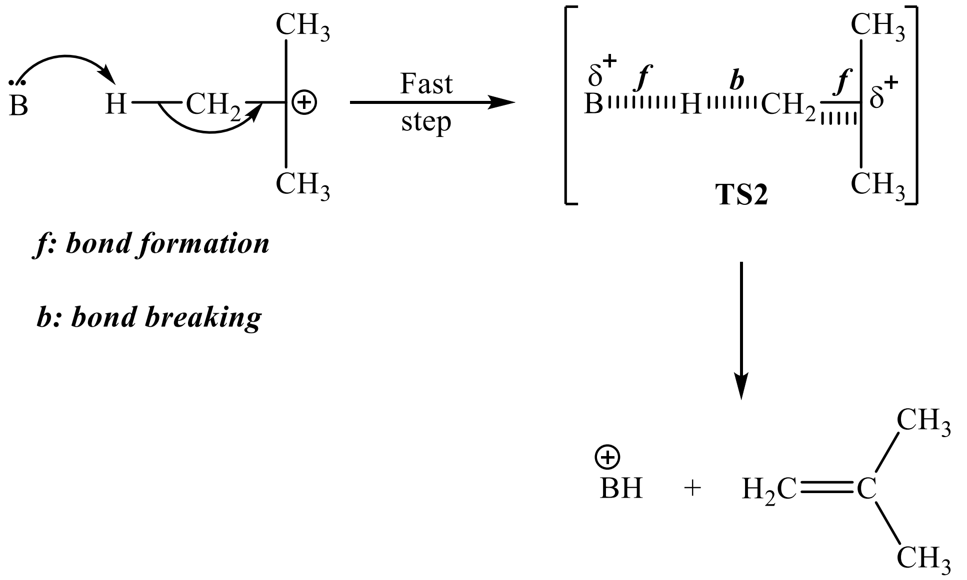


The mechanism of $E1$ elimination reaction involves the following two steps:

Step 1: formation of carbocation intermediate:



Step 2: removal of proton by a base:



f: bond formation

b: bond breaking

In the second step of this mechanism, we can see that during transition state $\boldsymbol{TS2}$ two bonds are formed corresponding to the $B - H$ bond and the newly being formed double bond $CH_2 \dashrightarrow C$; and one is being broken the one corresponding to the $C - H$ bond.

The general energy profile of $E1$ elimination reaction is given as:

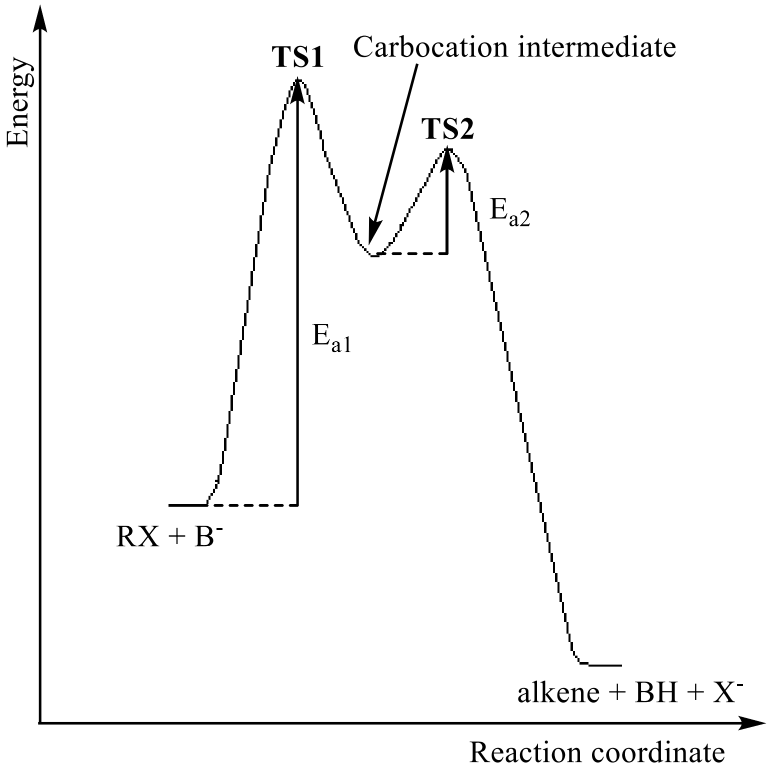
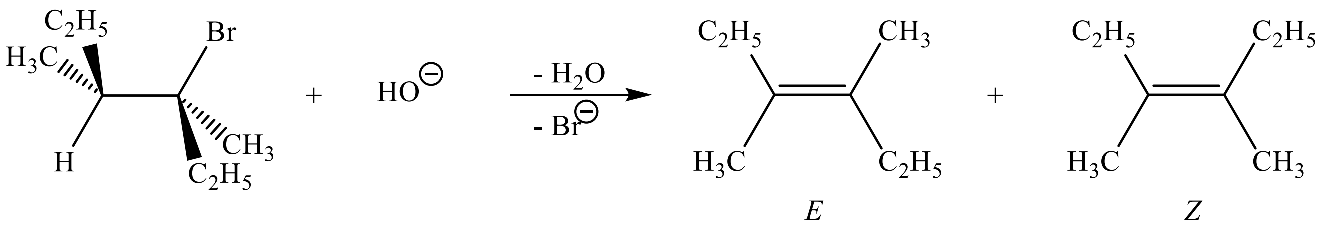


Figure 17: Energy profile of the unimolecular elimination reaction ($E1$).

9.3.4.2 Stereochemistry

The $E1$ reaction is not stereospecific: the alkenes Z and E are obtained at the end of the reaction. On the other hand, it is partially stereoselective: whatever the starting haloalkane, one of the two possible alkenes is mainly obtained (the more stable alkene E).

Example:

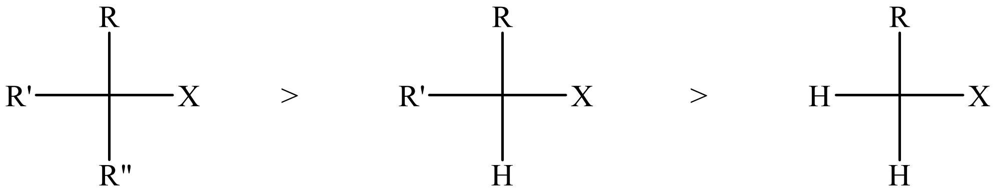


Alkene E is the major product because it is more stable.

9.3.4.3 Factors influencing $E1$ reaction

a- Influence of the carbon carrying the leaving group

As for $SN1$, during an $E1$ mechanism, the rate increases from primary halides to tertiary halides; in practice, only tertiary halides and some secondary halides react according to an $E1$ mechanism, and this only in the presence of a weak base or a weak base in low concentration.



b- Influence of the nucleofuge

The reaction strongly depends on the nature of the nucleofuge. The better the leaving group, the faster the reaction rate increases. The cleavage of the C −leaving group bond is the key step of the $E1$ mechanism. The more polarizable the $R - X$ bond is, the easier the break will be. This bond is therefore of increasing lability from fluorine to iodine: $F < Cl < Br < I$.

c- Influence of the base

The elimination reaction requires the presence of a Brönsted base able of capturing the hydrogen in β position. Therefore, the elimination is more favored when the nucleophile used is basic in the Brönsted sense.

d- Influence of the solvent

A polar solvent further stabilizes the carbocation and subsequently facilitates the first step of the reaction. The rate of the $E1$ reaction increases with the increase in the polarity of the solvent. The solvents used for $E1$ reactions are polar protic.

9.3.5 Bimolecular elimination reaction ($E2$)

This is a single-step process. The breaking of the two $C - H$ and $C - X$ bonds is synchronous (occurs at the same time). The $E2$ mechanism goes through a transition state where the bond between the base and the hydrogen ($B - H$) is not completely formed and the $C - X$ bond is not completely broken.

9.3.5.1 Mechanism

A Bronsted base removes a hydrogen in the β position concomitantly with the breaking of the $C - X$ bond. The electrons of the $C - H$ bond are relocated in the form of a π bond during the process.

The three electronic movements take place simultaneously; this is a concerted reaction.

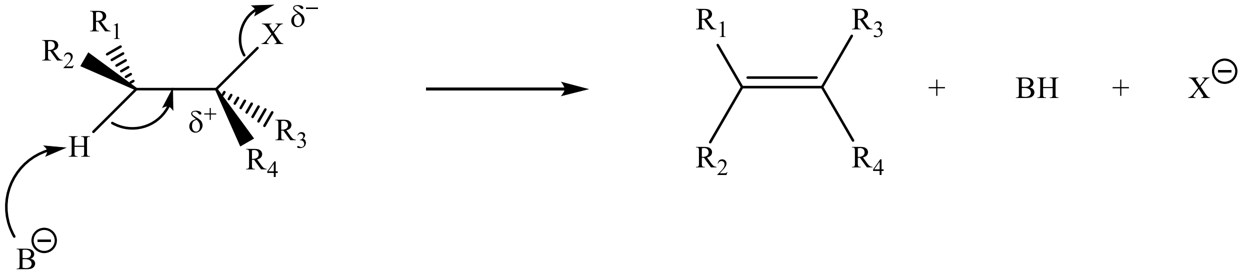


Figure 18: Mechanism of the bimolecular elimination reaction ($E2$).

Even though, a free rotation around the $C-C$ bond is possible, only the elimination reaction takes place only in this particular conformation where H and X are in anti.

This single step involves two molecules of reactants; this is the reason why it is called a bimolecular elimination reaction $E2$.

The experimental rate law that corresponds to this type of reaction is: $v = [RX][B^-]$

$[RX]$: the concentration of halogenated derivative (in $mol.L^{-1}$)

$[B^-]$: the concentration of base (in $mol.L^{-1}$)

υ: the rate of the elimination reaction (in $mol.s^{-1}$).

k: the rate constant ($L.s^{-1}.mol^{-1}$).

B^- attacks H when it is in anti of X to minimize the electrostatic repulsion between B^- and X.

The activation energy E_a of an elimination reaction $E2$ is generally higher than that of a nucleophilic substitution reaction $SN2$.

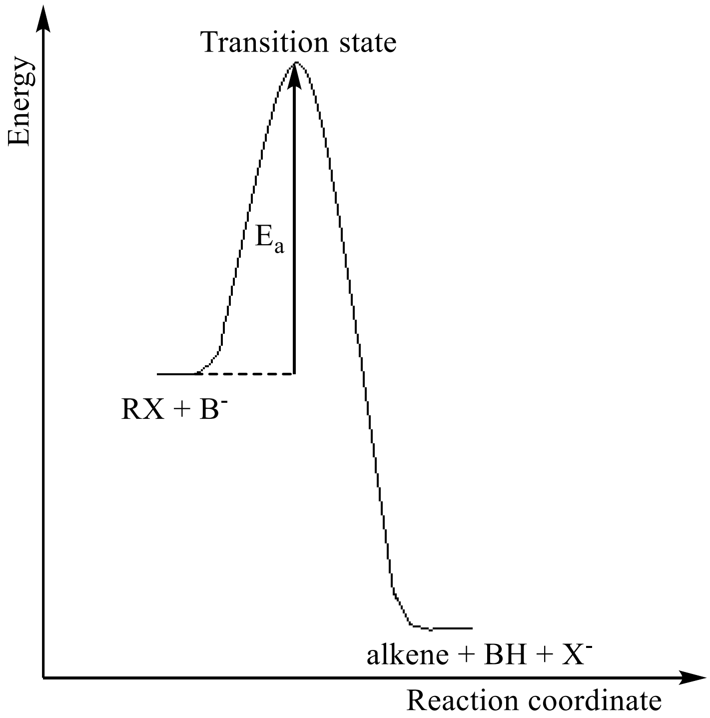


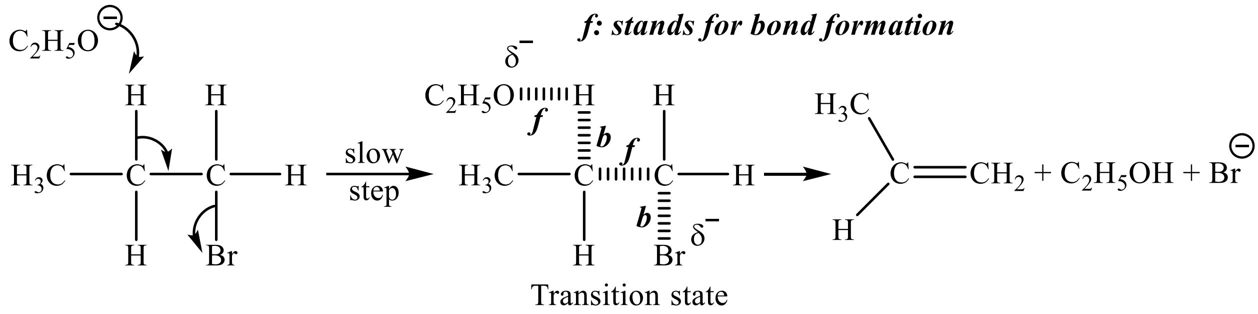
Figure 19: Energy profile of the bimolecular elimination reaction ($E2$).

Example:

Let's consider the following given reaction:

$$H_3C-CH_2-CH_2-Br + C_2H_5O^{\ominus} \longrightarrow H_3C-CH=CH_2 + C_2H_5OH + Br^{\ominus}$$

The mechanism is:



f: stands for bond formation

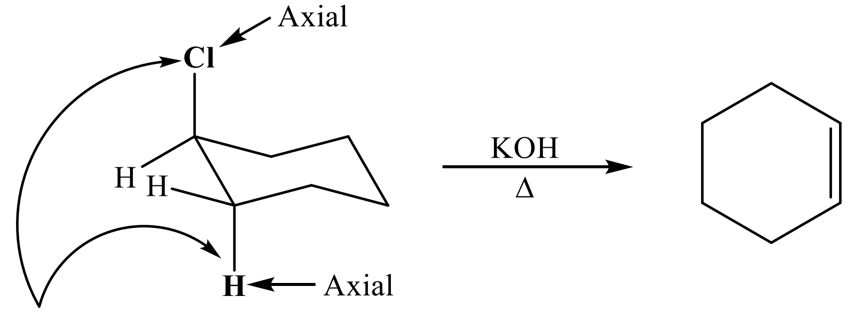
b: stands for bond breaking

(vi) In this example of $E2$ elimination reaction, it can be seen that both leaving groups $i.e.$ C_2H_5OH and Br^- are *anti*-periplanar, $i.e.$ both leaving groups are in the same plane but have anti conformation ($i.e.$ they are 180° apart from each other) $i.e.$ $E2$ mechanism is stereospecific.

(vii) In acyclic compounds, $E2$ elimination reaction is given by the most stable conformation in which both leaving groups are *anti*-periplanar.

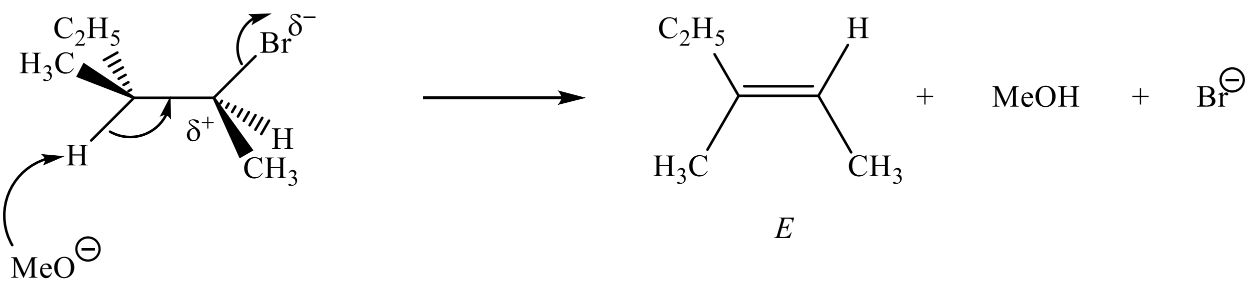
(viii) The elimination in six membered cyclic compounds (i.e., cyclohexane derivatives) proceeds best when leaving groups are diaxial (*trans* or *anti*). In this case *anti*-periplanarity is available. 1, 2-Diaxial groups are always periplanar and *anti* to each other.

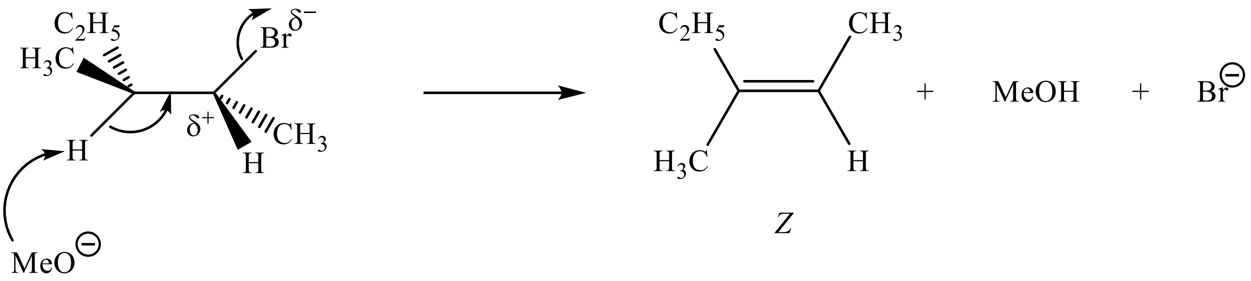
Example:



Both **Cl** and **H** are ***anti*** to each other

9.3.5.2 Stereochemistry



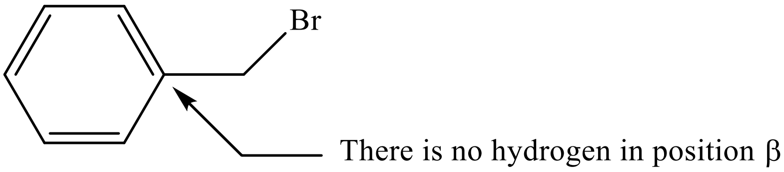


Reaction $E2$ is stereoselective and stereospecific: from a stereoisomer of given absolute configuration, only one of the two possible alkenes is obtained (*Z* or *E*).

9.3.5.3 Factors influencing $E2$ reaction

a- Presence of a hydrogen atom in the β position

For a β-elimination, it is imperative that the haloalkane has a hydrogen in the β position. Thus, bromomethylbenzene, for example, cannot undergo an elimination reaction.



b- Influence of the carbon carrying the leaving group

The ease of elimination, during an $E2$ mechanism, decreases from tertiary halogenoalkanes to primary halogenoalkanes, but the relative variation in rate remains low.

Elimination is favored if the base is hindered (bulky) or if the substrate is hindered. Indeed, in these two cases, the nucleophile can hardly reach the carbon carrying the halogen; on the other hand, it can easily reach the hydrogen in β of the carbon carrying the halogen.

c- Influence of the nucleofuge

The elimination reaction is directly linked to the ease of breaking the $C-X$ bond which must leave easily.

d- Influence of the base

The attack of the base enhances the reaction process, so a good base is necessary. Experimentally, it is observed that the rate increases with the strength of the base: NH_2^- reacts faster than EtO^- which reacts faster than HO^-.

e- Influence of the solvent

The $E2$ reactions are influenced by the polarity of the solvent in the same way as bimolecular nucleophilic substitutions.

An increase in the polarity of the solvent increases the stabilization of the initial state more than that of the transition state, therefore increasing the activation energy and reducing the rate of the reaction. The solvents used for $E2$ reactions are polar aprotic.

9.4 Competition between nucleophilic substitution and elimination

A single species can be both nucleophilic and basic (HO^-), it can therefore generate nucleophilic substitution and elimination reactions which are generally in competition. Three main factors influence this competition, namely: temperature, structure and size of the halogenated derivative, and the basicity of the reagent.

9.4.1 $SN1 - E1$ competition

These two reactions take place in the presence of a tertiary haloalkane $R - X$, with the formation of a common reaction intermediate: a tertiary carbocation.

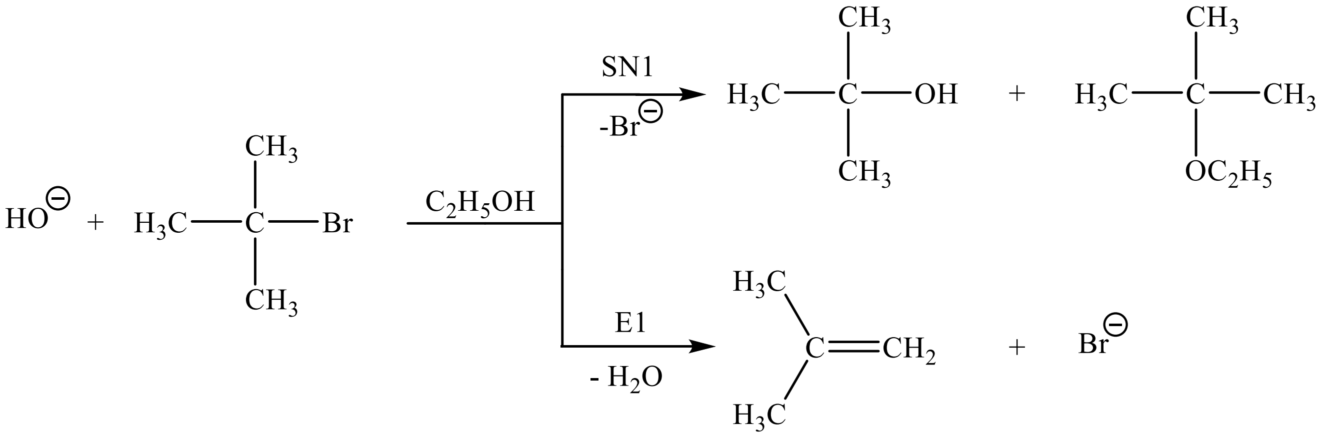


Table 2: Yields of $SN1$ and $E1$ competition products.

	$SN1$	$E1$
25 °C	83 %	17 %
80 °C	1 %	99 %

The elimination product is formed preferentially by raising the temperature. Thus, it is the temperature factor which essentially favors $E1$ to the detriment of $SN1$.

9.4.2 $SN2 - E2$ competition

The two reaction mechanisms are always competitive.

In the case where the $R - X$ is primary and in the presence of the nucleophile EtO^-: it is the $SN2$ that is favored.

$$CH_3CH_2O^{\ominus} + CH_3\text{–}CH_2\text{–}Br \xrightarrow{50\ °C} CH_3\text{–}CH_2\text{–}O\text{–}CH_2\text{–}CH_3 + CH_2{=}CH_2$$

SN2: 90 % E2: 10%

With a secondary $R - X$ and under the same conditions, it is the $E2$ reaction that is favored.

$$CH_3CH_2O^{\ominus} + CH_3\text{–}CHBr\text{–}CH_3 \xrightarrow{50\ °C} CH_3\text{–}CH(O\text{–}CH_2\text{–}CH_3)\text{–}CH_3 + CH_2{=}CH\text{–}CH_3$$

SN2: 21 % E2: 79%

To favor $E2$ over $SN2$, the temperature must be increased. Other factors affecting the ratios of products obtained by $SN2$ or $E2$ are the basicity and polarizability of the nucleophile (base):

- a strong, weakly polarizable base, such as the amide ion NH_2^- or an alkoxide ion (particularly poorly polarizable), leads to an increase in elimination products.
- a weak base, such as the chloride ion Cl^- or the ethanoate ion CH_3COO^-, or a weak, polarizable base, such as I^-, Br^- or RS^-, increase the percentage of substitution.

9.5 Addition reactions

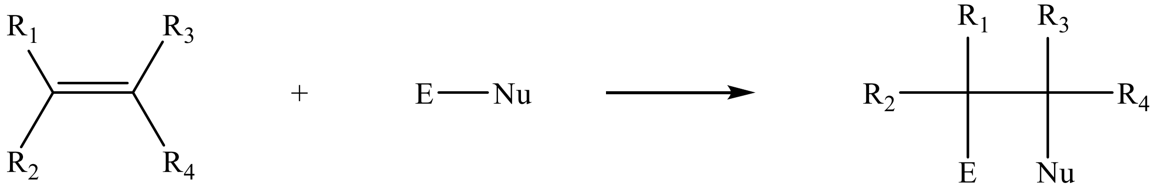
In these reactions, a nucleophilic, electrophilic or radical reagent is added to an unsaturated system, this leads to the breaking of one (or more) π bonds to form one (or two) σ bonds on each atom of the initial multiple bond. There are three main types of addition: electrophilic, nucleophilic and radical.

9.5.1 Electrophilic addition reactions

In this case, the reagent is electrophilic. This generally involves addition to unsaturated systems rich in electrons such as alkenes or alkynes.

9.5.2 Electrophilic addition reactions of alkenes ($C = C$)

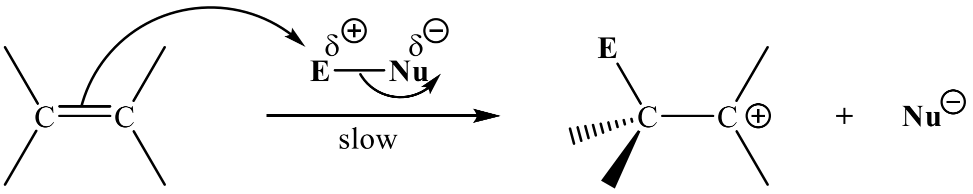
Electrophilic addition reactions are highly exothermic and almost total reactions. The general reaction of this type is:



9.5.2.1 Mechanism

The reagent $E - Nu$, which has an electrophilic part E^+ and a nucleophilic part Nu^-, adds in two steps.

Step 1:



Step 2:

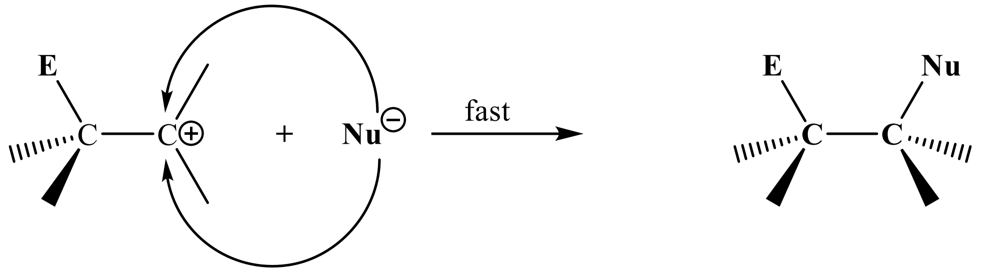
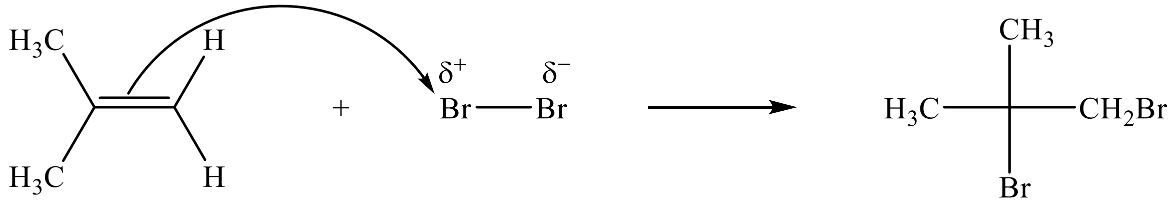


Figure 20: Mechanism of electrophilic addition of alkenes.

Example:



The energy profile of the electrophilic addition of alkenes is illustrated in the following figure 21:

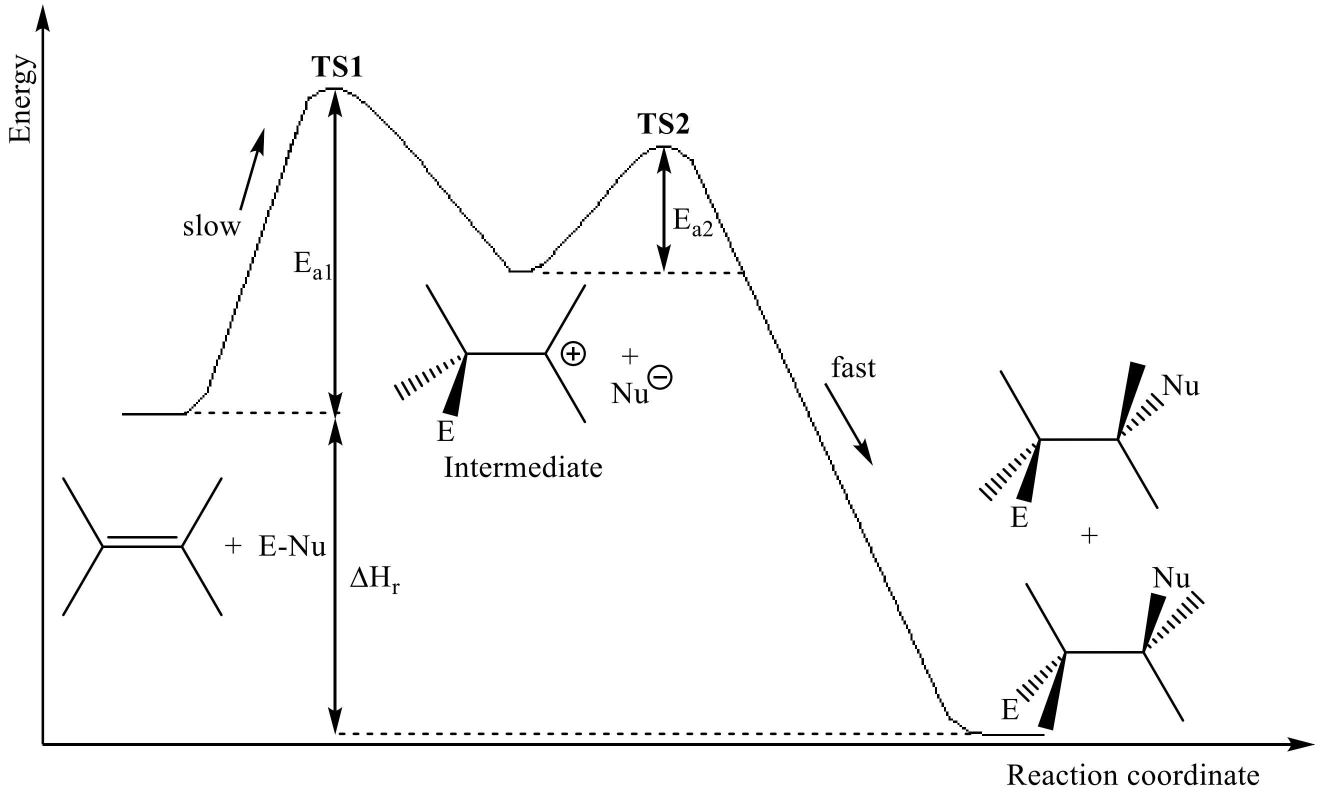
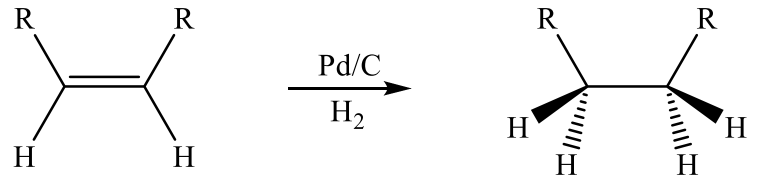


Figure 21: Energy profile of electrophilic addition reaction of alkenes.

Several cases of electrophilic addition reactions of alkenes can be cited.

9.5.2.2 Hydrogenation of alkenes

It is the reaction of addition of halogen H_2 to alkenes. The reaction leads to the formation of an alkane and must be catalyzed by metals such as Pd, Pt, Rh, and Ni. The catalytic hydrogenation with palladium on carbon (Pd/C) is a very common method.

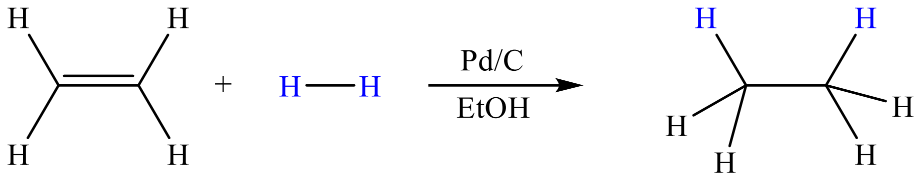


Alkene

Alkane

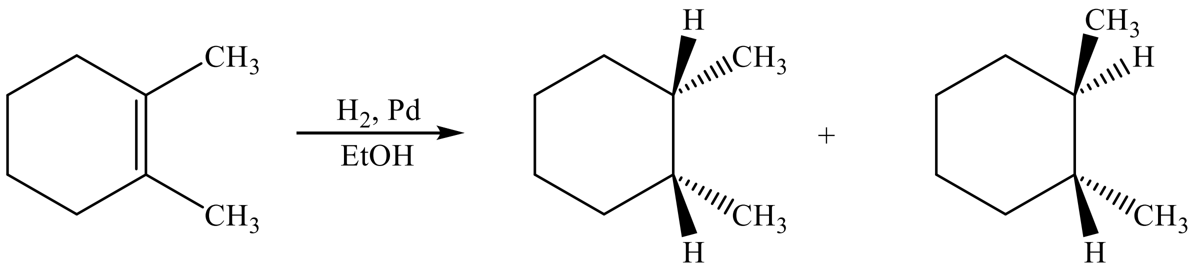
syn addition of H_2

Example:



The addition of H_2 to alkene across the π-bond is highly stereoselective and goes under syn addition, $i.e.$, it takes place from the same face of the double bond.

Example:



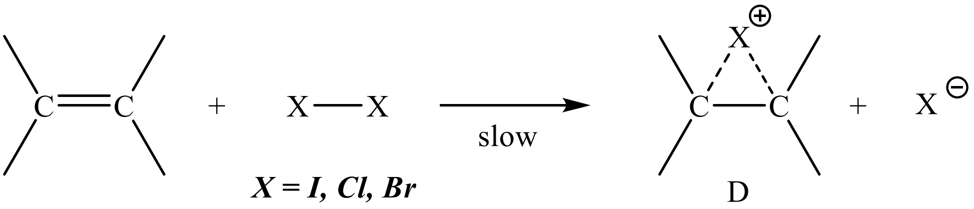
syn addition of H_2

Not observed

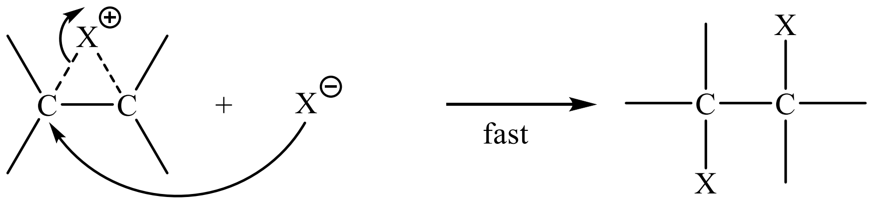
9.5.2.3 Halogenation of alkenes

It is the reaction of addition of halogen X_2 to alkenes. In the first step, the double bond $C = C$, an electron-rich center behaving as a nucleophile, attacks the positively charged atom to form a bond between one of the carbon atoms of the double bond and this atom. During this process, the $X - X$ bond is broken, and non-bonding electrons of the positively charged atom forms a bond with the other carbon of the double bond. Thus, a three-membered ring is formed, this is the bridged halonium ion (D). This step is slow and therefore it determines the overall rate of the addition reaction (rate-determining step).

a- **Mechanism**

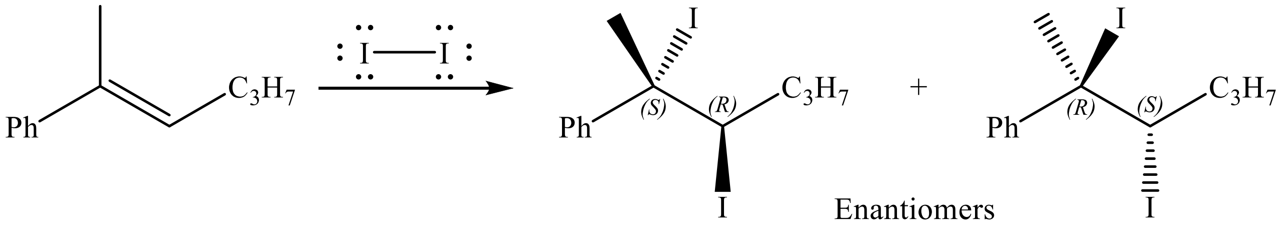


The systematic name of the bridged halonium ion (D) thus formed with the halogen is called bromonium ion in the case of bromine, iodonium in the case of iodine and chloronium ion in the case of chlorine.

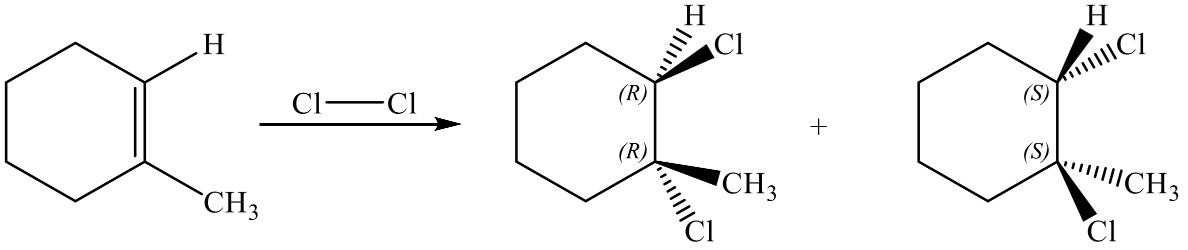


In the second step, the negatively charged liberated ion reacts as a nucleophile on one of the carbon atoms of the cycle thus formed (bridged halonium ion). The approach of the nucleophile takes place by the least hindered side, which is the side opposite the bridging halogen; the addition is therefore *anti*.

Example 1:

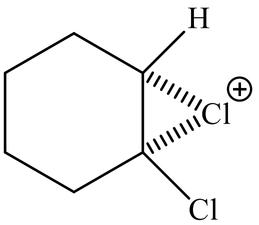


Example 2:



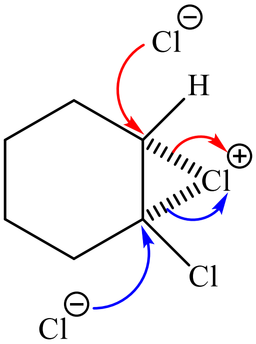
Enantiomers

The reaction, in example 2, proceeds via the chloronium intermediate:



Chloronium ion

The attack of Cl^- takes place on both sides of the three-membered ion and that is why two enantiomers are formed.



The energy profile of the halogenation of alkenes is given in Figure 22.

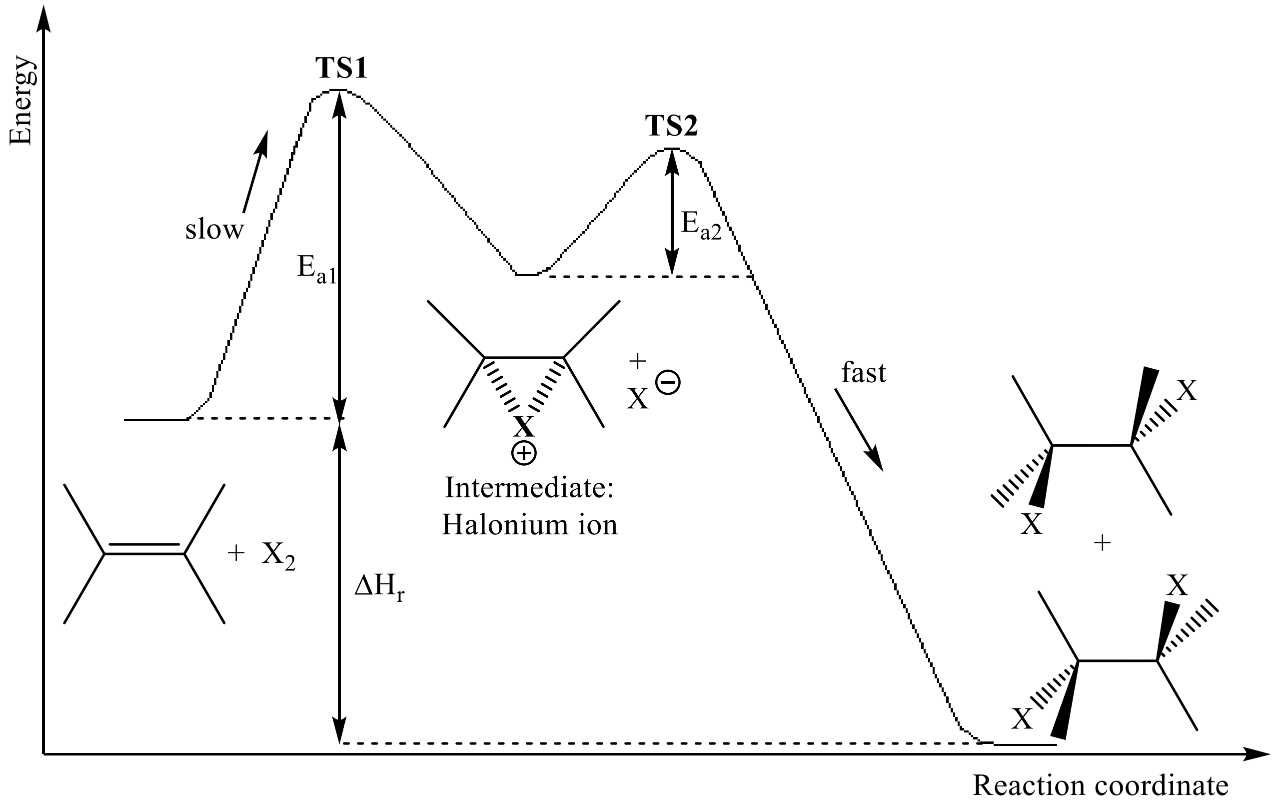
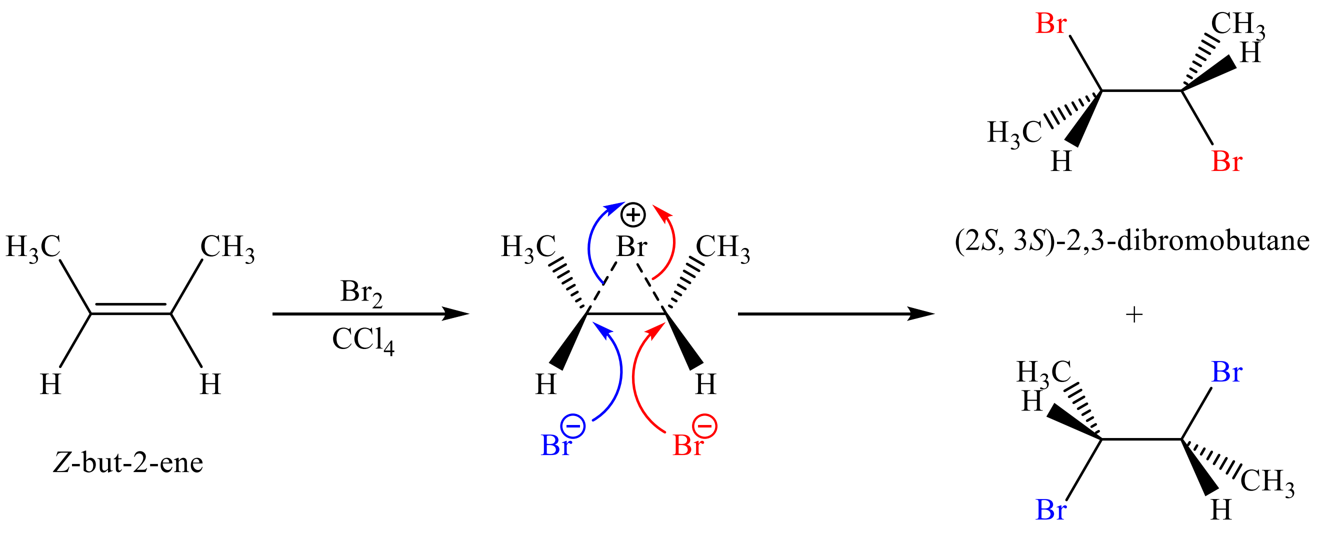


Figure 22: Energy profile of halogenation reaction of alkenes.

b- Stereochemistry

In the case of Z-but-2-ene, there are two possible ways of formation of bromonium ion on either side of the double bond. Thus, both ways give the same products. Hence, racemic mixture is obtained. Therefore, the reaction is neither stereoselective nor stereospecific.



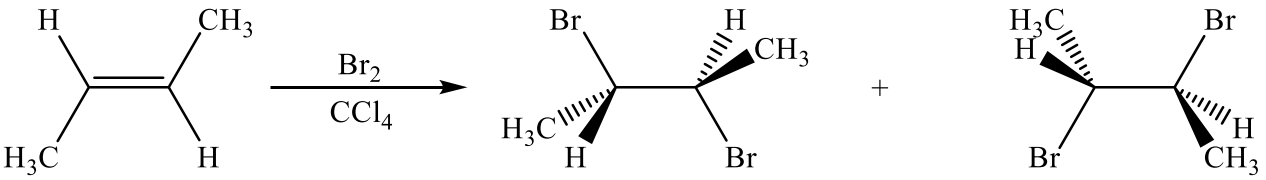
Z-but-2-ene

(2*S*, 3*S*)-2,3-dibromobutane

+

(2*R*, 3*R*)-2,3-dibromobutane

However, in the case of E-but-2-ene, only one product is obtained which is $meso$. Therefore, the reaction is stereospecific.

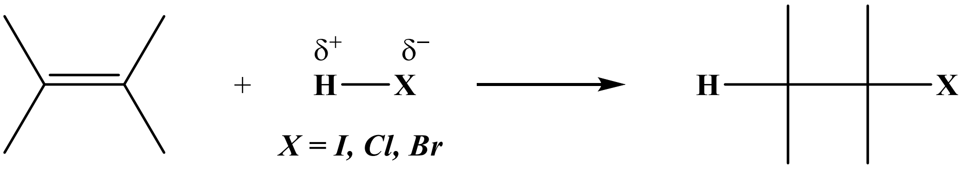


E-but-2-ene

Same compound: *meso*-2,3-dibromobutane

9.5.2.4 Hydrohalogenation of alkene

It is the reaction of addition of hydrogen halide HX to alkenes.

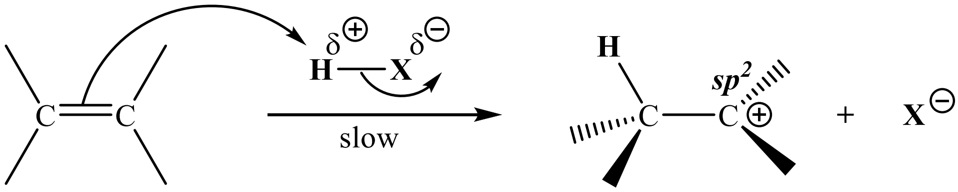


X = I, Cl, Br

The reaction proceeds via two steps. The first step corresponds to the protonation of the $C = C$ of the alkene to give the more stable carbocation intermediate. The obtained carbocation is hybridized sp^2 and hence is planar. In the second step, the nucleophile attacks the carbocation on both sides.

a- Mechanism

Step 1:



Planar carbocation

Step 2:

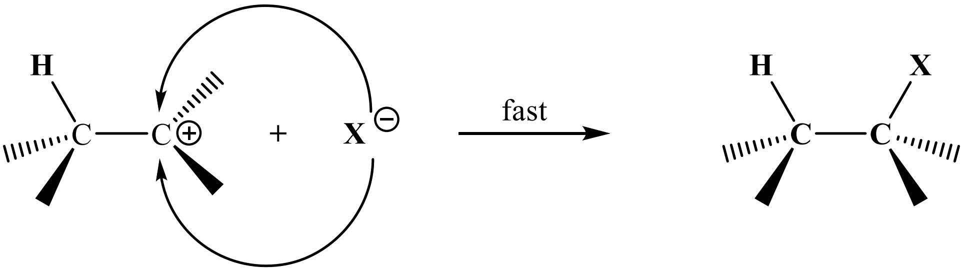
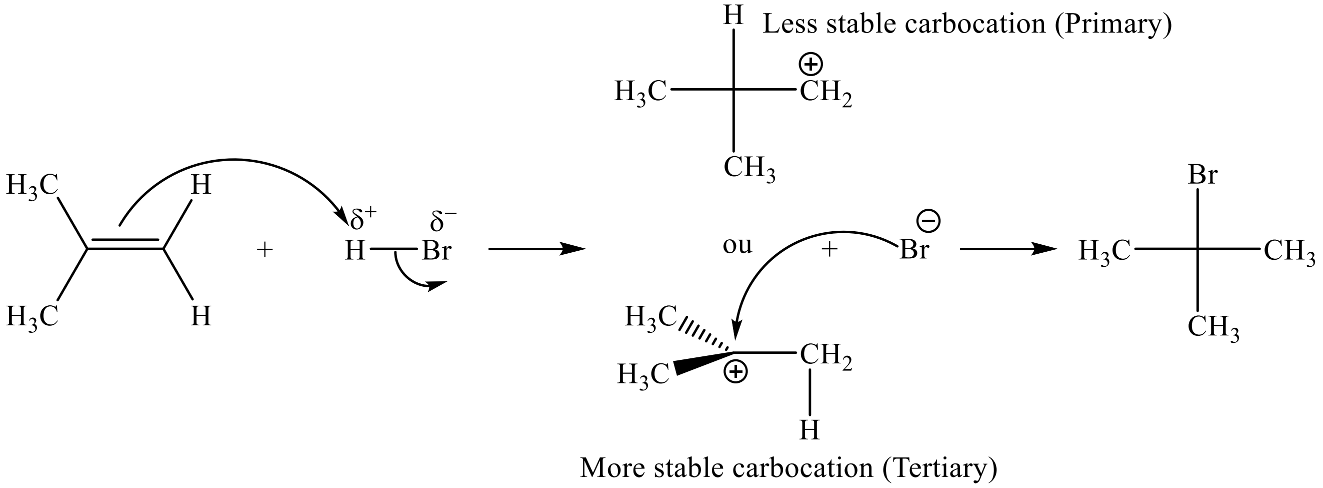


Figure 23: Mechanism of electrophilic addition of $H-X$ to alkenes.

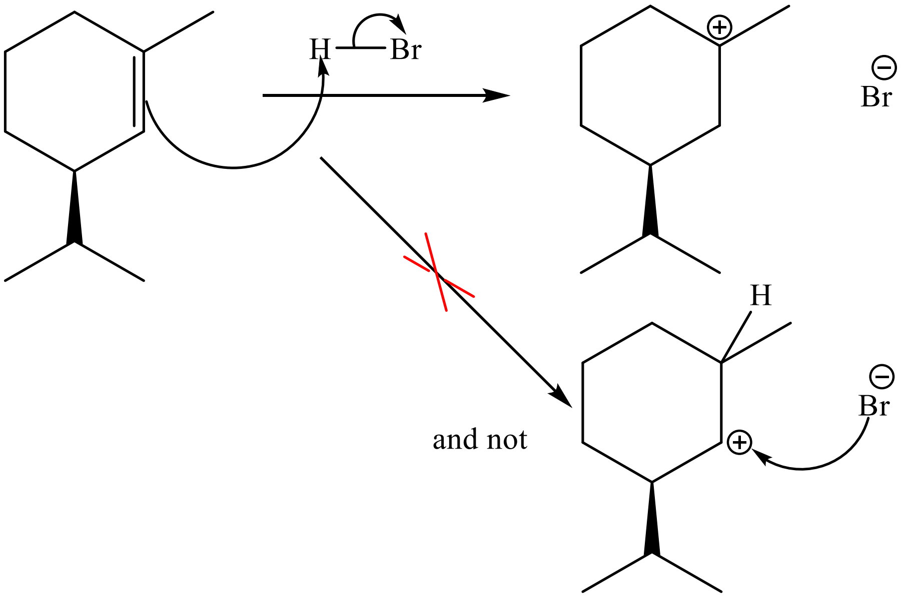
Example:

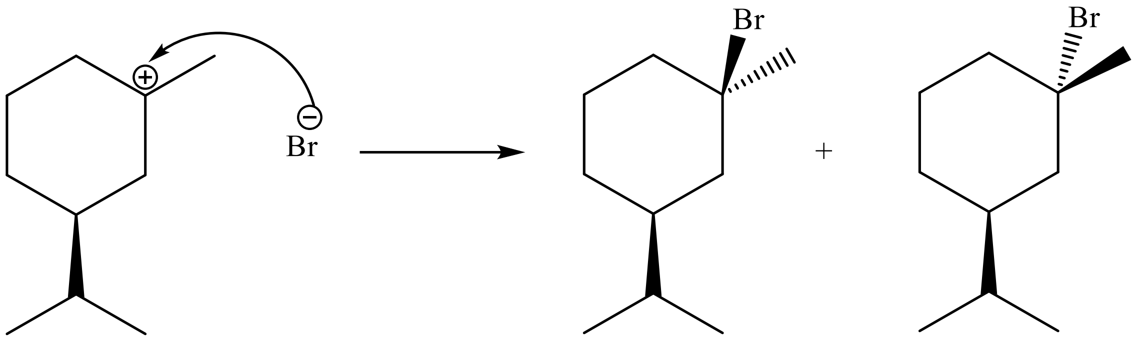


b- Stereochemistry

The electrophilic addition reaction of $H-X$ to alkenes is not stereoselective since reaction proceeds via planar carbocation (Hybridized sp^2). However, it is regioselective and goes through the most stable C^+ carbocation (Markovnikov's rule).

Example:

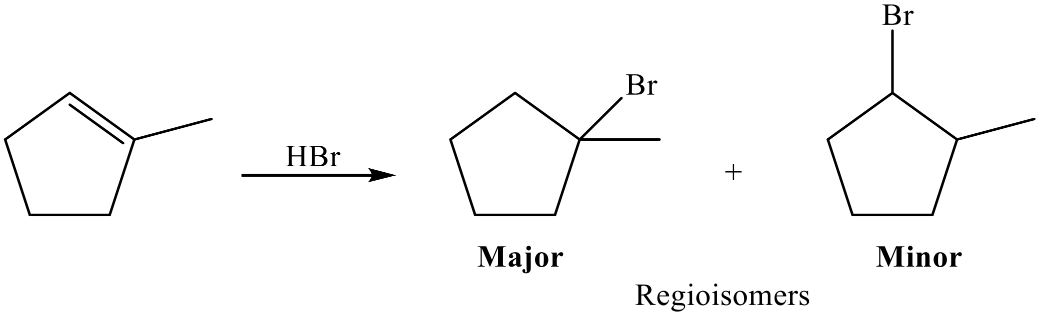


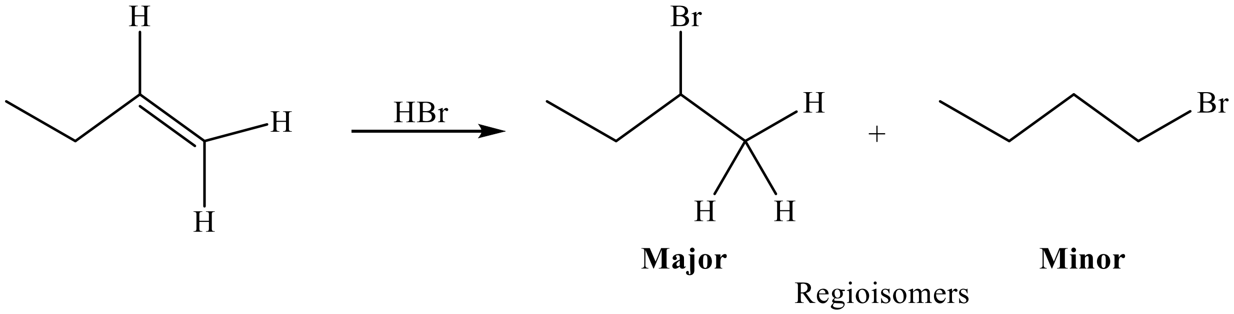


c- Markovnikov's rule

When an unsymmetrical alkene reacts with a hydrogen halide to give an alkyl halide, the hydrogen adds to the carbon of the alkene that has the greater number of hydrogen substituents, and the halogen to the carbon of the alkene with the fewer number of hydrogen substituents. In other words, the addition of HX occurs via the most stable carbocation, which is often the most substituted or the most conjugated in the case of electronic delocalization.

Example:





The major product in each reaction of the above examples corresponds to the most stable carbocation because it is more disubstituted. In the first reaction, the most stable carbocation is tertiary and the second carbocation (minor) is secondary. However, in the second reaction, the most stable carbocation is secondary (Disubstituted) while the second carbocation (Minor) is primary carbocation (Monosubstituted).

Therefore, there is a large excess of it in the reaction mixture, and in the second step, the nucleophilic attack of the bromide ion forms the major product of the most stable carbocation.

The energy profile of the hydrohalogenation of an alkene is given in Figure 24.

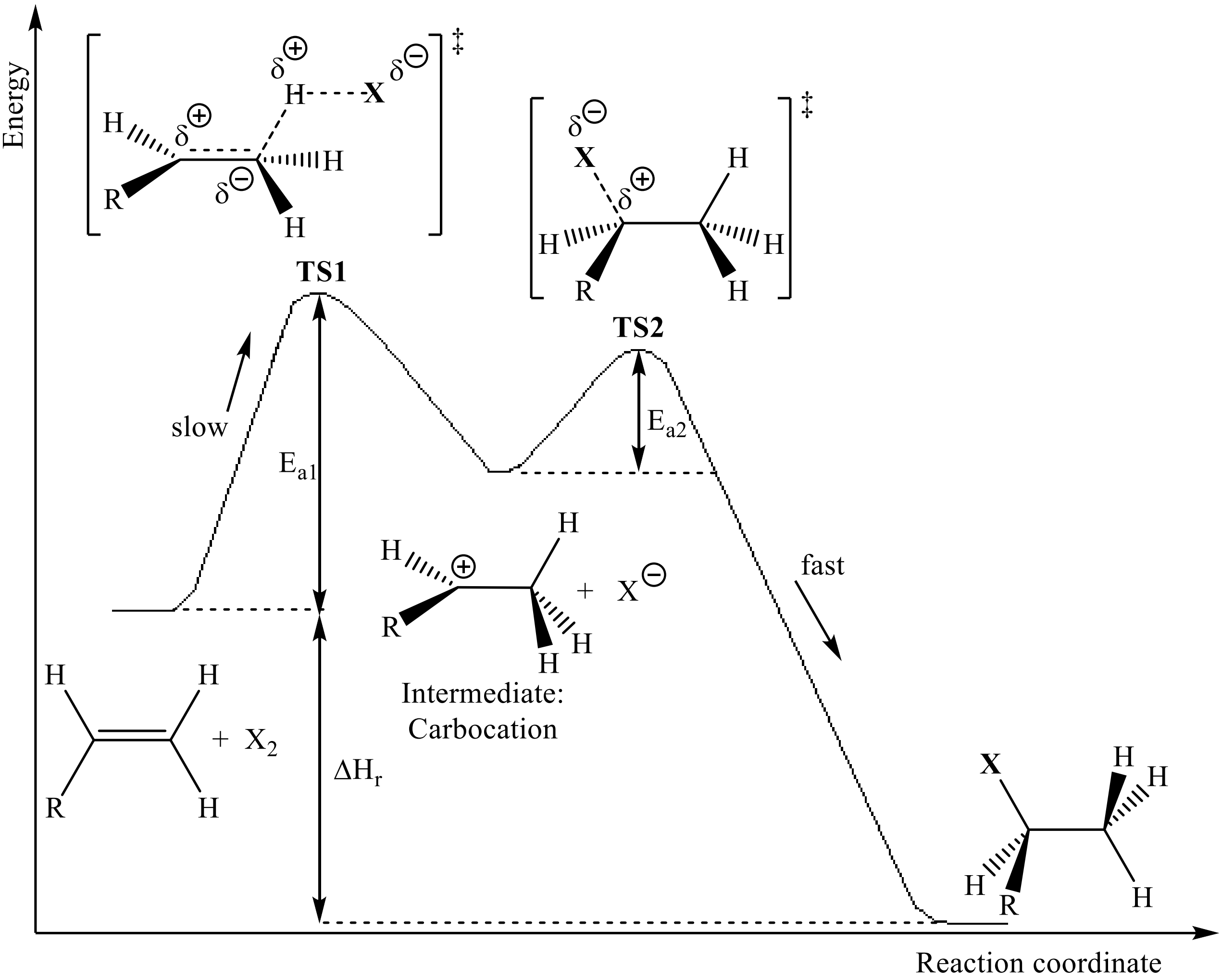


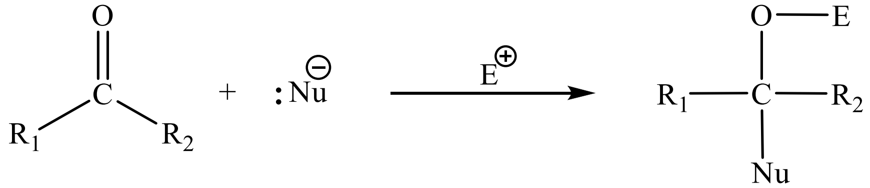
Figure 24: Energy profile of hydrohalogenation reaction of alkenes.

9.5.3 Nucleophilic addition reactions

During this type of reaction, the nucleophilic reagent adds exclusively to polar unsaturated systems deficient of electrons such as carbonyls, nitriles, imines, etc.

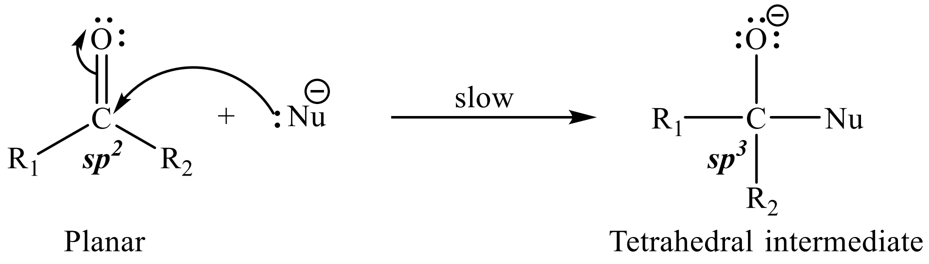
9.5.3.1 Addition reactions to carbonyls ($C = O$)

Generally speaking, the addition reaction to carbonyls is given as:



9.5.3.2 Mechanism

In the first step considered slow, the nucleophilic part of the reagent adds to the positively charged carbon to lead to a negatively charged tetrahedral intermediate.



The second step is fast. It consists of the addition of the electrophilic part of the reagent.

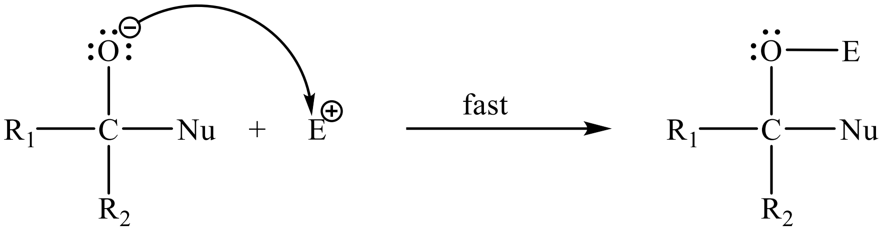


Figure 25: Mechanism of the nucleophilic addition reaction to carbonyls ($C = O$).

The slow step is the one corresponding to the attack of the nucleophile to the carbon of the carbonyl group, hence the name "nucleophilic addition". In addition, the first step is the rate-determining step. The energy profile of the nucleophilic addition to carbonyls is then given in Figure 26.

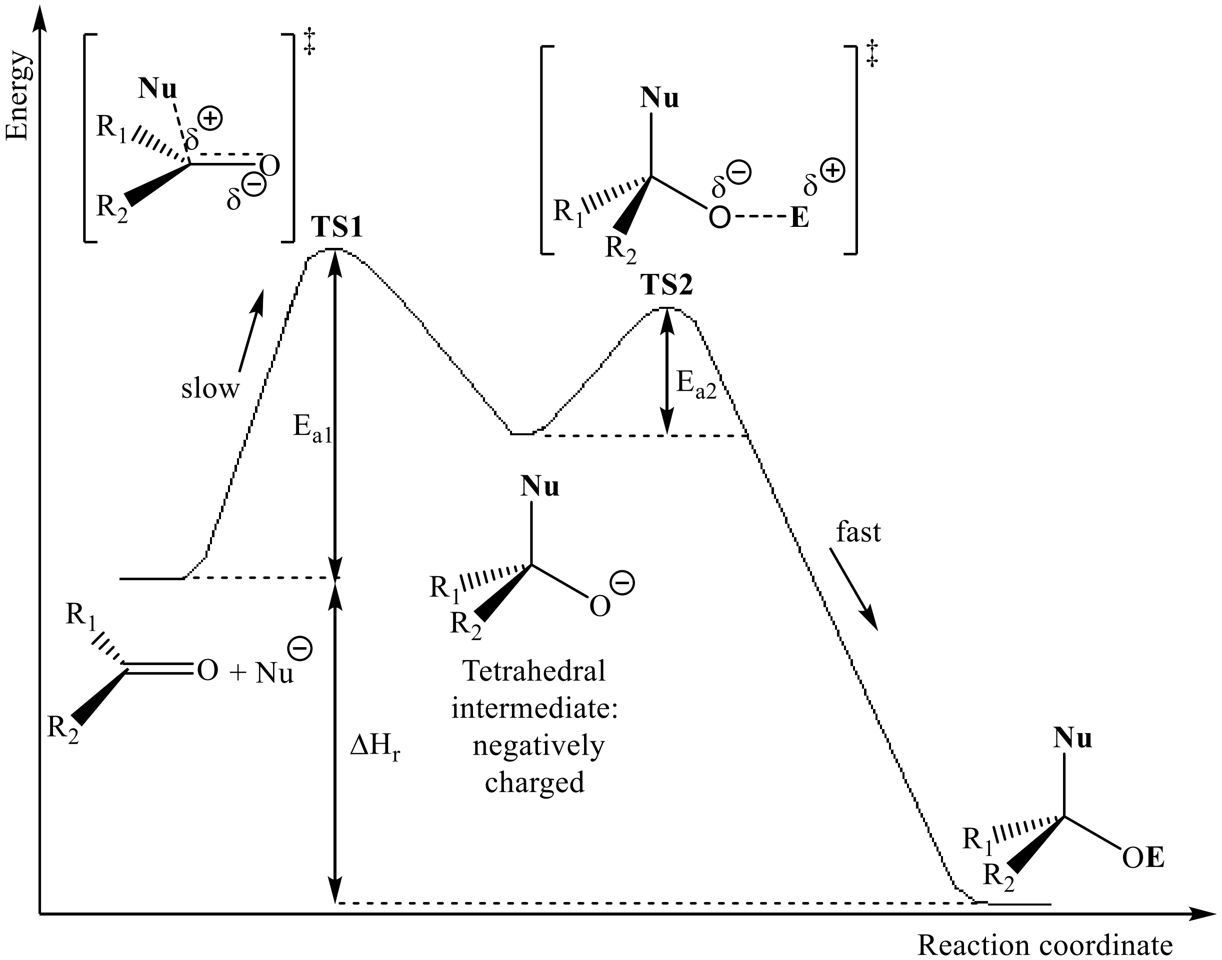
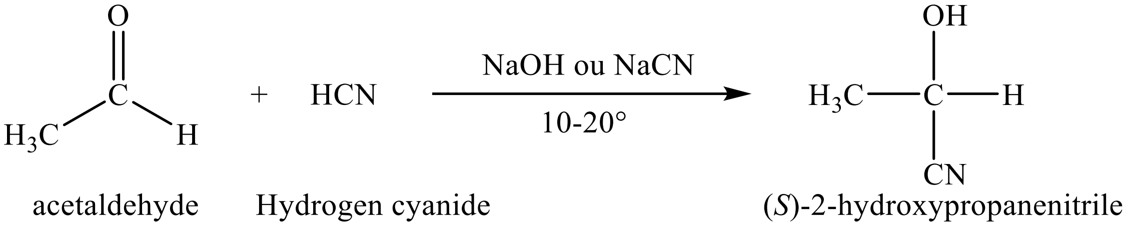


Figure 26: Energy profile of nucleophilic addition reaction of carbonyls.

Hence, the energy profile of a nucleophilic addition reaction corresponding to the attack of a nucleophile on a carbonyl group features a two-step mechanism with two peaks and two activation energies $i.e.$ one intermediate and two transition states.

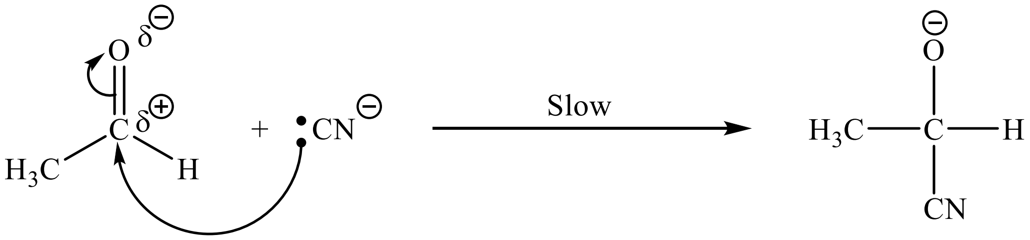
Example:



The reaction takes place in the presence of trace amounts of $NaOH$ or $NaCN$ at 10 to 20 $°C$. The mechanism of this reaction undergoes two steps.

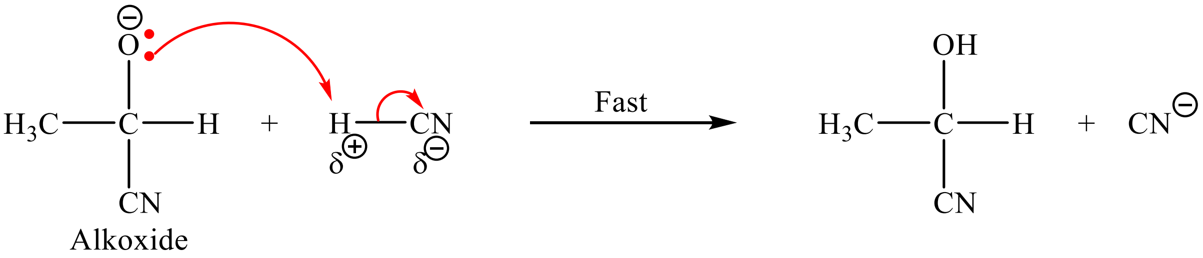
First step:

The nucleophile CN^- attacks the carbonyl carbon, and the electron pair moves to the oxygen.



Second step:

This corresponds to the protonation of the alkoxide (attack of the proton H^+) and regeneration of the CN^- catalyst.



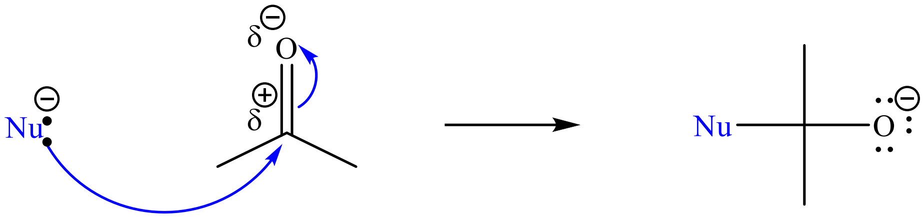
Depending on the nucleophile's reactivity, two possible cases of addition can be considered.

a- Addition of strong nucleophiles under basic conditions

Strong (anionic) nucleophiles add directly to carbonyls $C = O$ to form the intermediate alkoxide. The alkoxide is then protonated by treatment with a dilute acid to give the corresponding alcohol. This reaction proceeds in two steps.

Step 1:

The nucleophile adds to the electrophilic carbon of the polar carbonyl group and the $C = O$ electrons move towards the electronegative oxygen atom while creating a tetrahedral intermediate (alkoxide).



Step 2:

This step corresponds to a simple acid/base reaction. Protonation of the oxygen of the alkoxide yields to the corresponding alcohol from the tetrahedral intermediate.

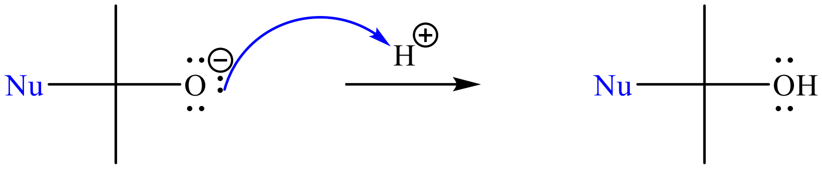


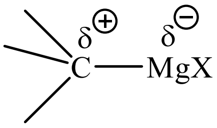
Figure 27: Nucleophilic addition under basic conditions with strong nucleophiles.

Examples of some strong nucleophiles:

Grignard reagents $RMgX$, organolithium compounds RLi, $RC \equiv CM$ ($RC \equiv CMgX$, $RC \equiv CNa$), and hydrides such as $LiAlH_4$ and $NaBH_4$.

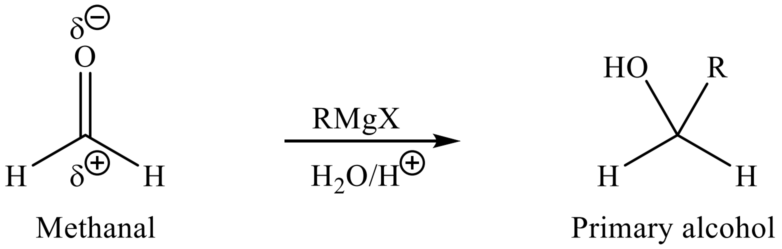
Example:

The structure of Grignard reagents $RMgX$ is:



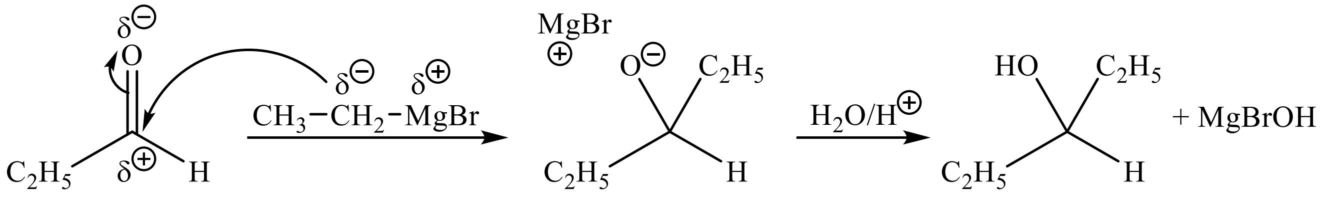
Grignard reagents react with aldehydes and ketones to form alcohols. The nature of the resulting alcohol depends on the substituents on the carbonyl group.

For example, the nucleophilic addition of methanal (formaldehyde) yields primary alcohols.



The addition of an organomagnesium compound to an aldehyde leads to a secondary alcohol.

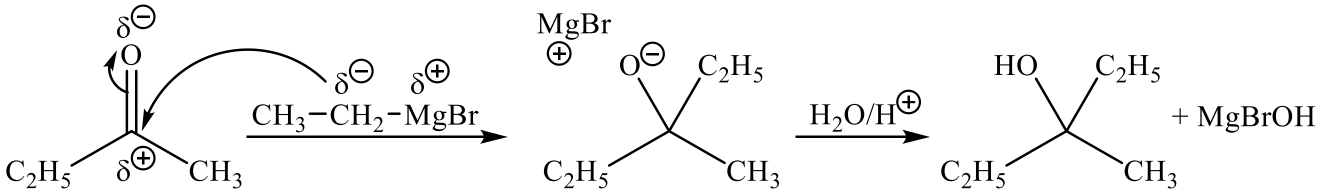
Example:



propanal pentan-3-ol

However, the addition of an organomagnesium compound to a ketone leads to a tertiary alcohol.

Example:



butan-2-one 3-methylpentan-3-ol

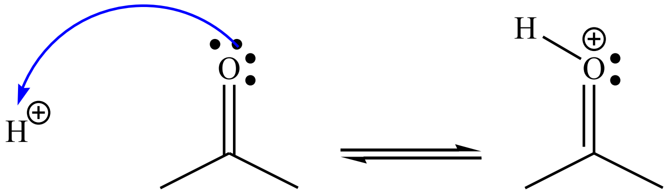
b- Addition of weak nucleophiles under acidic conditions

When the nucleophile is neutral (weak), the carbonyl group must be activated first. A carbonyl group is activated when the basic Lewis oxygen of the carbonyl group is protonated by an acidic catalyst (a proton H^+), thereby making the system more electrophilic. The neutral nucleophile then adds to the partially positive carbonyl carbon, leading to the breaking of the π bond between the carbon and oxygen. As a result, the shared electrons move to the oxygen. The oxygen is already protonated; therefore, no intermediate alkoxide is formed. The addition of the nucleophile and the breaking of the π bond lead to the formation of an alcohol after deprotonation of the nucleophile.

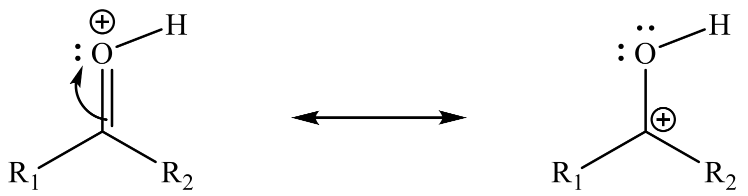
Mechanism:

Addition in acidic medium proceeds through the following steps:

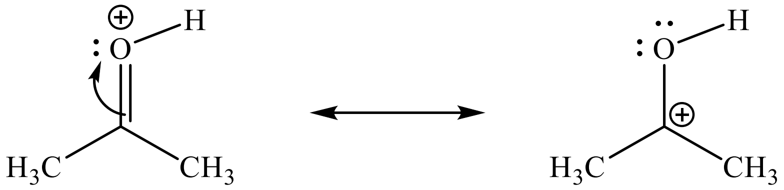
1. Protonation of the Lewis basic oxygen



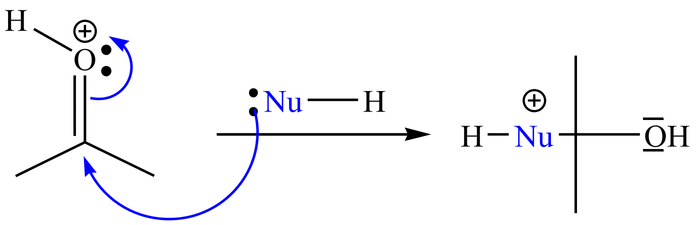
The protonation of the carbonyl group results in a structure that can be written in a different resonance form, revealing the electrophilic character of the carbocation.



Example:



2. Nucleophilic attack



3. Catalyst regeneration (H^+ acid)

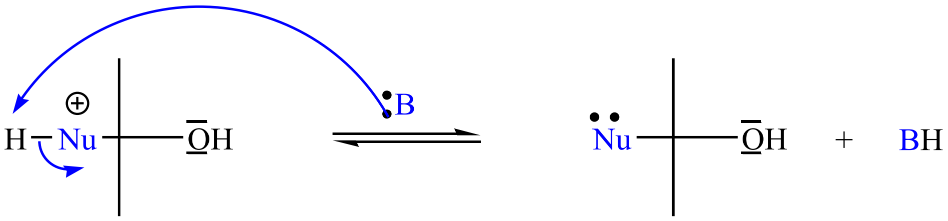
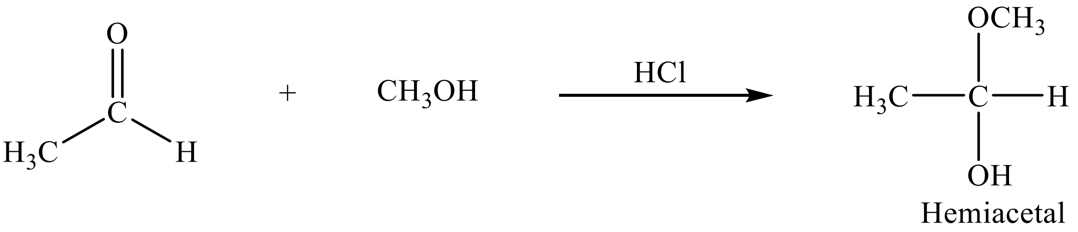


Figure 28: Nucleophilic addition of weak nucleophiles under acidic conditions.

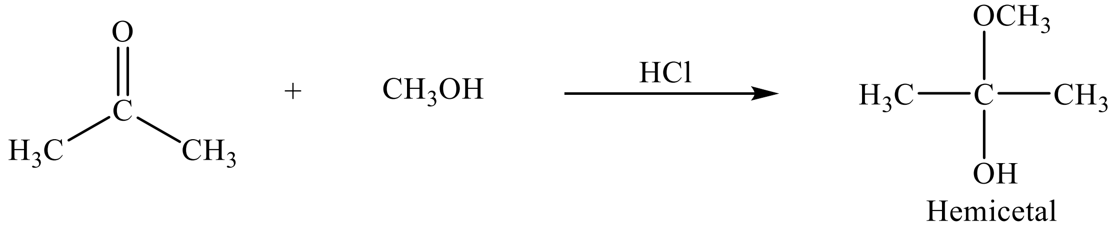
Some weak nucleophiles include water (H_2O), alcohols (ROH), and amines ($R - NH_2$).

Example:

Aldehydes react with an equivalent of monohydric alcohol in the presence of hydrogen chloride to give an alkoxyalcohol intermediate, known as hemiacetal.



Ketones react with an equivalent of monohydric alcohol in the presence of hydrogen chloride to give hemiacetal compounds.

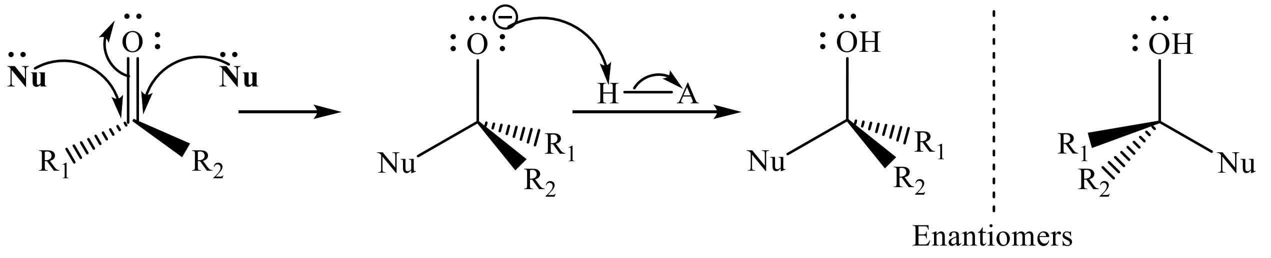


c- Stereochemistry

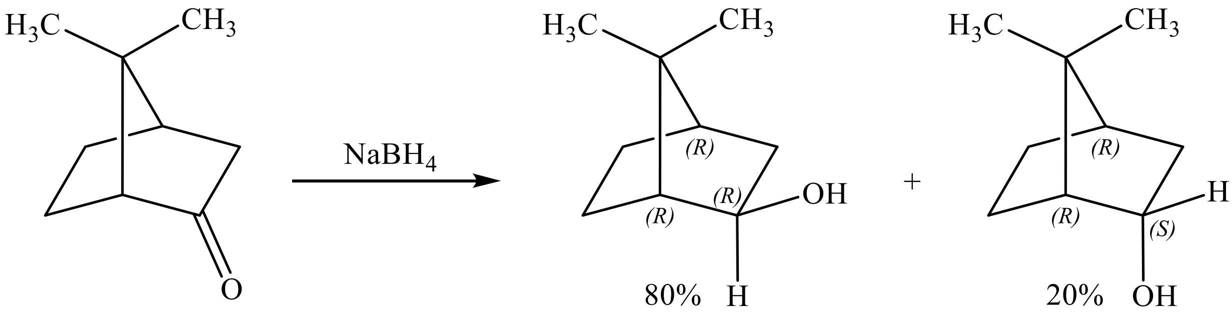
If the two alkyl groups R are not equivalent, a chiral center is created upon nucleophilic addition of the nucleophile.

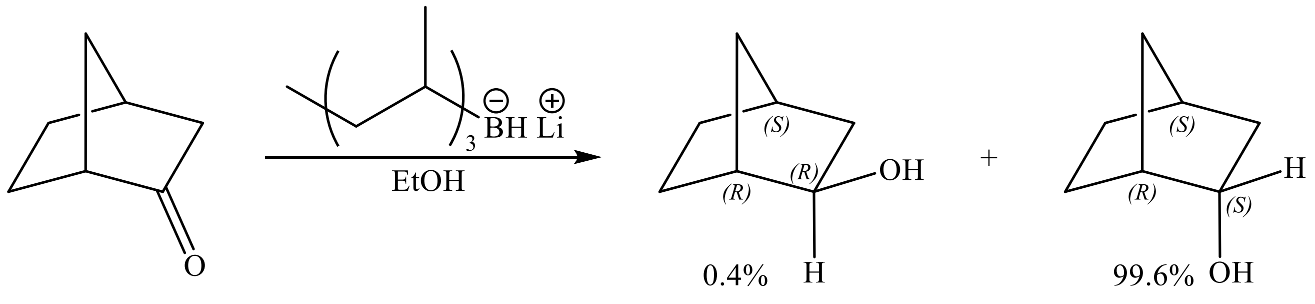
Because the carbonyl group ($C = O$) and the partially positive carbonyl carbon (C^+) are planar, there is an equal probability of nucleophile attack on either side of the plane; therefore, these reactions are not stereoselective.

Thus, the reactions of this type often result in a $50:50$ racemic mixture of stereoisomers, but it is also possible that one stereoisomer may be more abundant.



Example:





EXERCISES

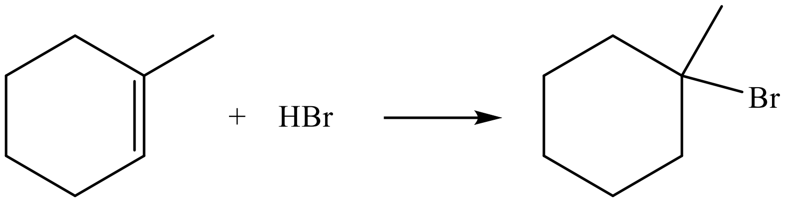
Exercise 1:

Explain the difference between a base and a nucleophile.

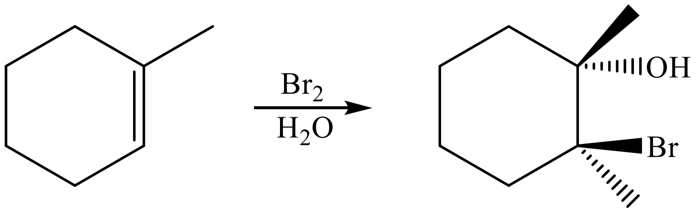
Exercise 2:

Give the detailed mechanism of the following reactions:

a) The first reaction:

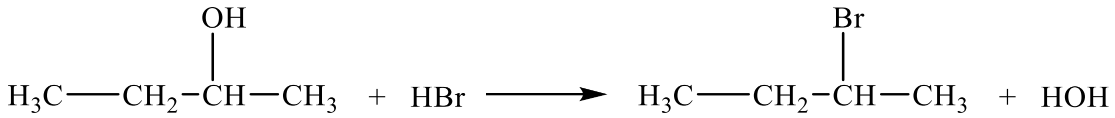


b) The second reaction:

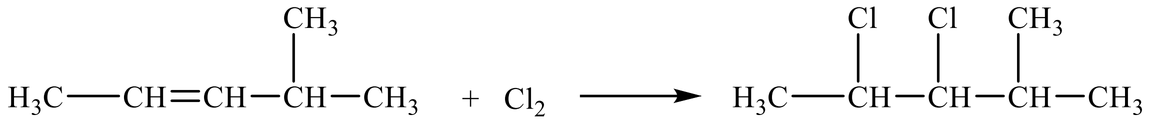


Exercise 3:

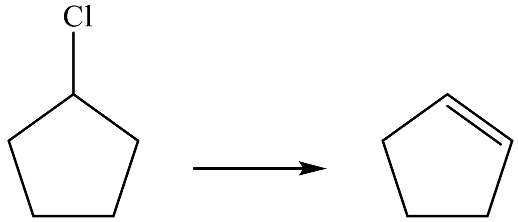
Identify each reaction as an addition, substitution, or elimination reaction.

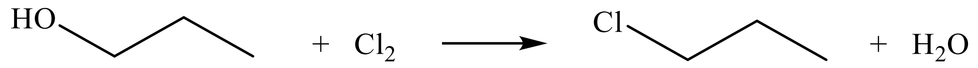
a) 

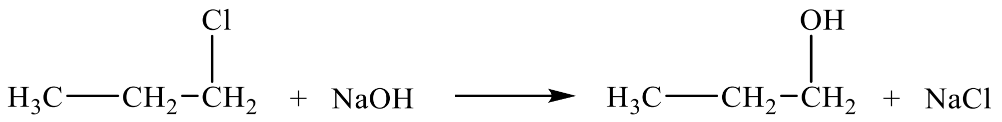
$$H_3C-CH_2-\overset{OH}{\overset{|}{CH}}-CH_3 + HBr \longrightarrow H_3C-CH_2-\overset{Br}{\overset{|}{CH}}-CH_3 + HOH$$

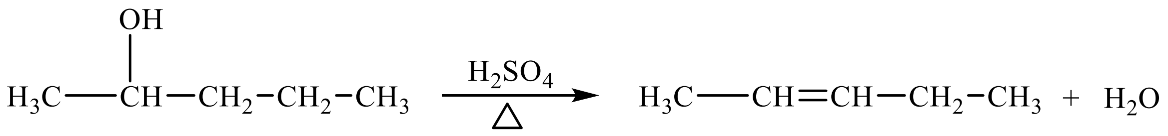
b) 

$$H_3C-CH=CH-\overset{CH_3}{\overset{|}{CH}}-CH_3 + Cl_2 \longrightarrow H_3C-\overset{Cl}{\overset{|}{CH}}-\overset{Cl}{\overset{|}{CH}}-\overset{CH_3}{\overset{|}{CH}}-CH_3$$

c) 

d) 

e) 
$H_3C-CH_2-\overset{Cl}{CH_2} + NaOH \longrightarrow H_3C-CH_2-\overset{OH}{CH_2} + NaCl$

f) 
$H_3C-\overset{OH}{CH}-CH_2-CH_2-CH_3 \xrightarrow[\Delta]{H_2SO_4} H_3C-CH=CH-CH_2-CH_3 + H_2O$

Exercise 4:

Draw the product of each of the following reactions.

a) $H_3CCH=CH_2 + Br_2 \longrightarrow$

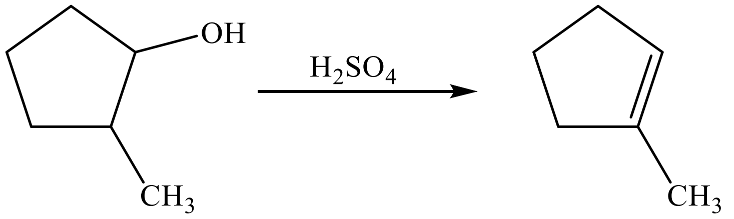
b) $H_2C=CH_2 + HOH \longrightarrow$

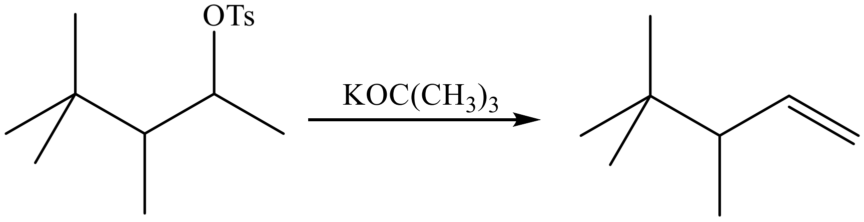
c) $H_2C=CHCH_2CH_3 + HBr \longrightarrow$

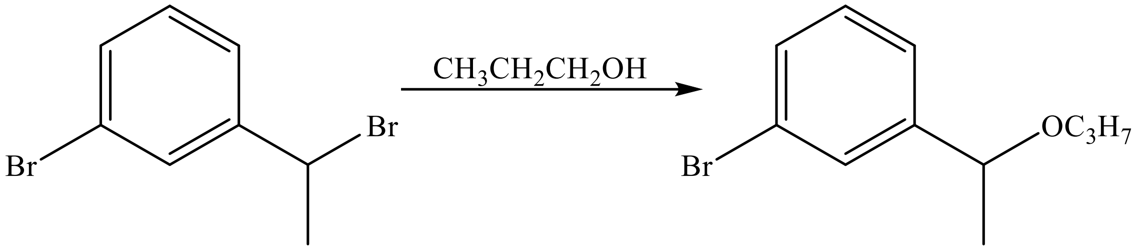
d) $(H_3C)_2C=CHCH_2CH_2CH_3 + HCl \longrightarrow$

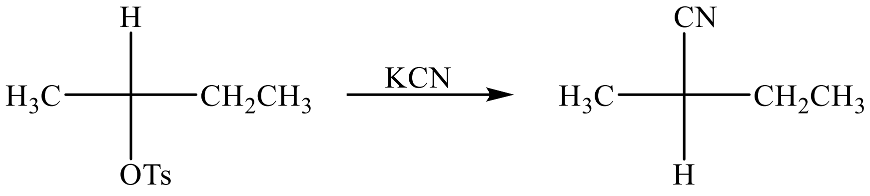
Exercise 5:

Draw the detailed mechanism for the following reactions.





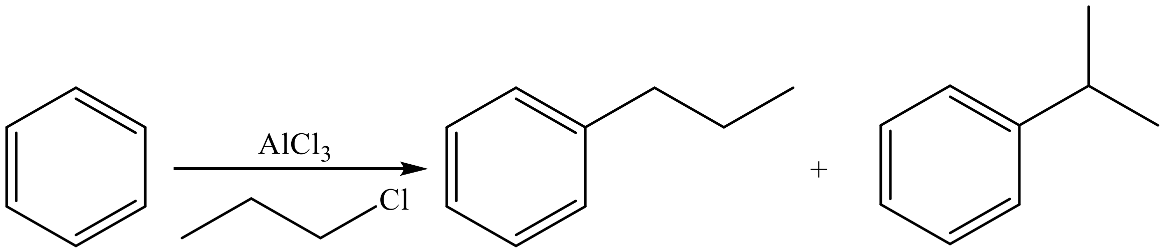




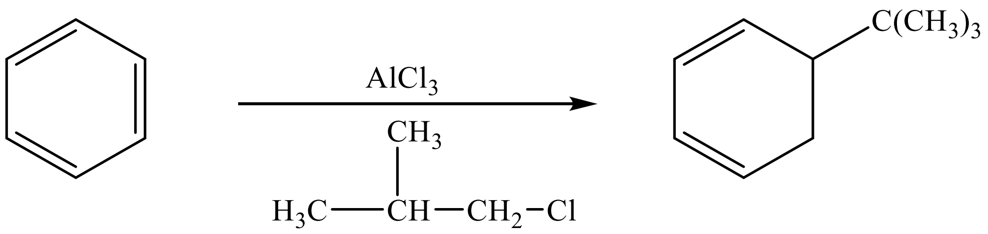
Exercise 6:

Draw the mechanism for the following reactions:

a-



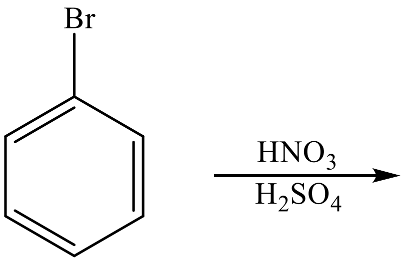
b-



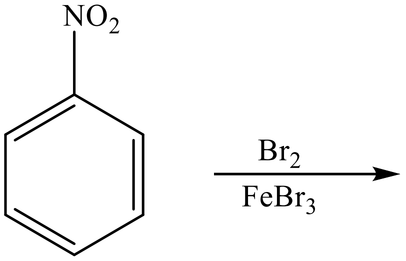
Exercise 7:

Identify the directing effect of the substituent, and draw the product.

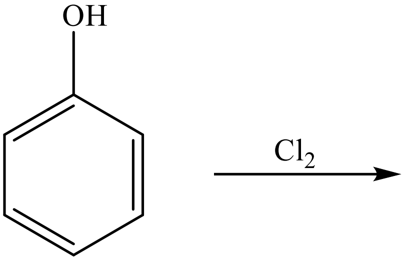
a)



b)

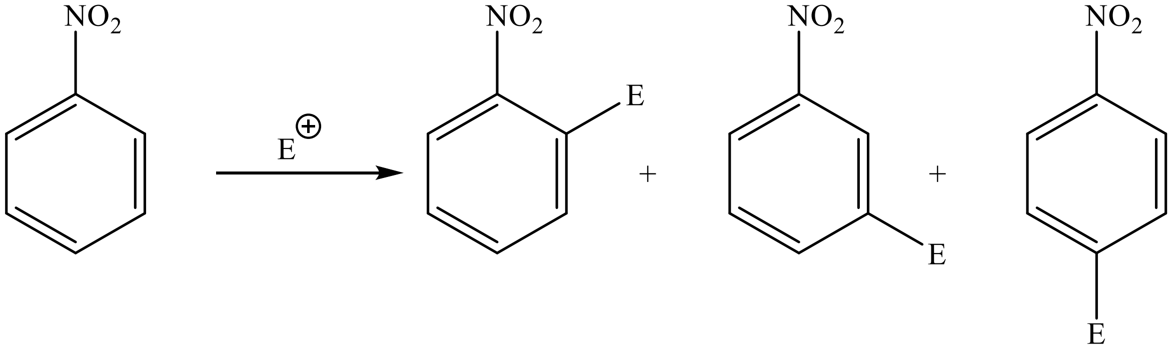


c)



Exercise 8:

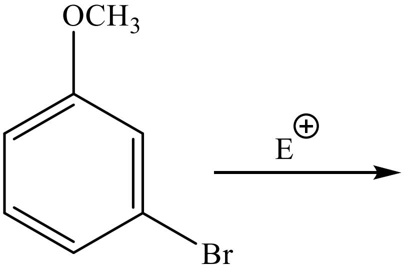
On the basis of resonance forms, identify which electrophilic attack (*ortho*, *meta* or *para*) is favored on nitrobenzene.



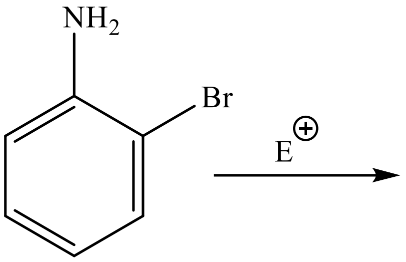
Exercise 9:

Draw the products of the EAS reactions.

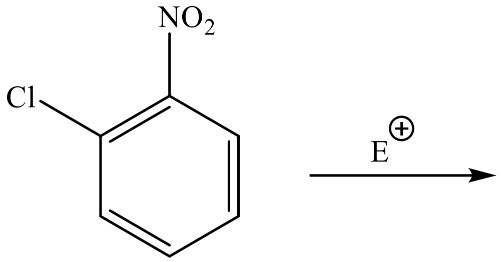
a)



b)



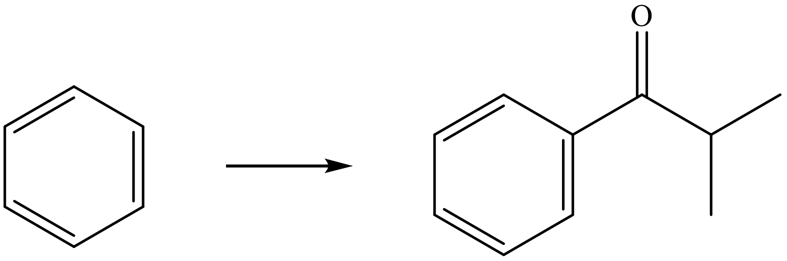
c)



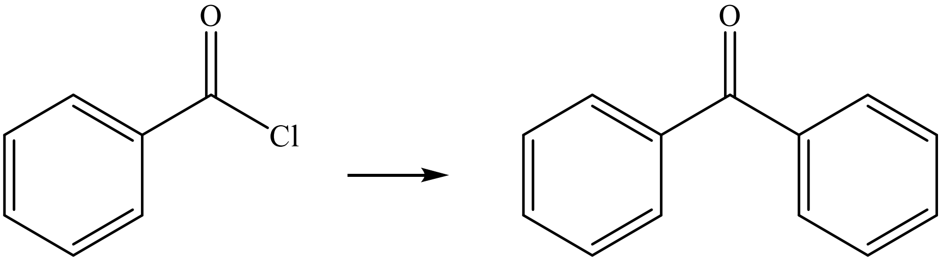
Exercise 10:

Propose a mechanism to the formation of the following product.

a)



b)



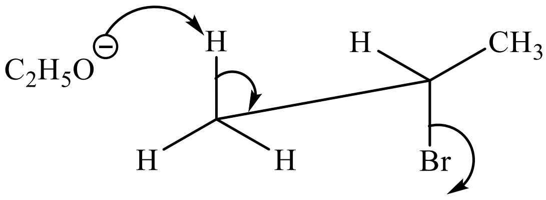
SOLUTIONS

Exercise 1:

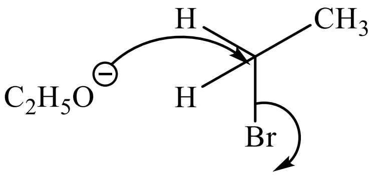
We explain the difference between a base and a nucleophile.

Both base and nucleophile are electron donors in chemical reactions. When an electron rich species uses its electron pair to form a covalent bond with a proton it is referred to as base. When the species uses its electron pair to form covalent bond with other atoms (especially carbon atom) it is referred to as nucleophile.

For example ethoxide ion can function as base as well as nucleophile under suitable conditions.



ethoxide ion acts as a base

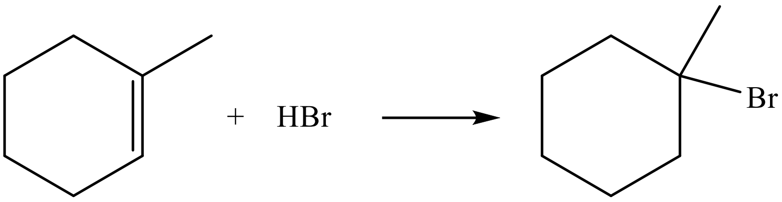


ethoxide ion acts as a nucleophile

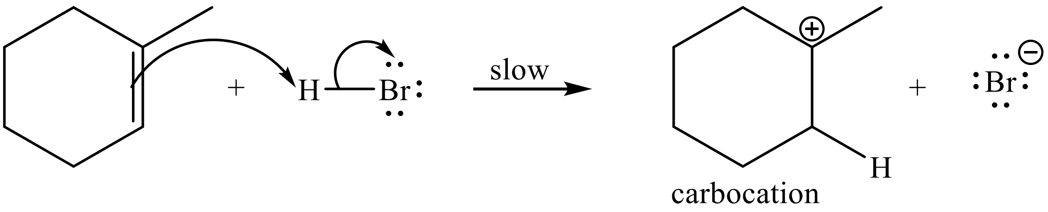
Exercise 2:

We give the detailed mechanism of the following reactions:

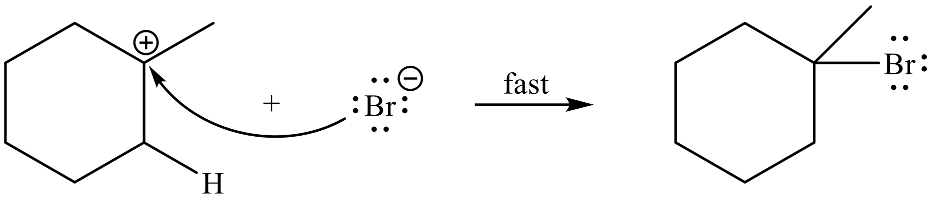
a) First reaction:



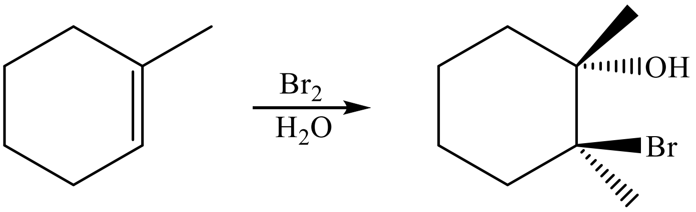
Step 1:



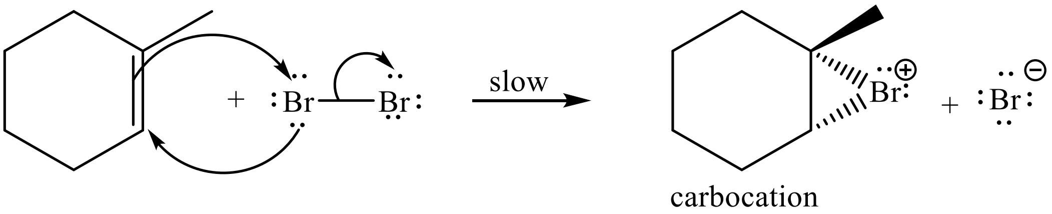
Step 2: Nucleophilic attack



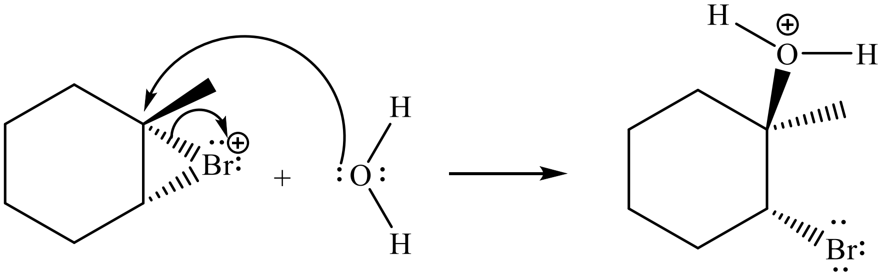
b) The detailed mechanism of the second reaction is given as:

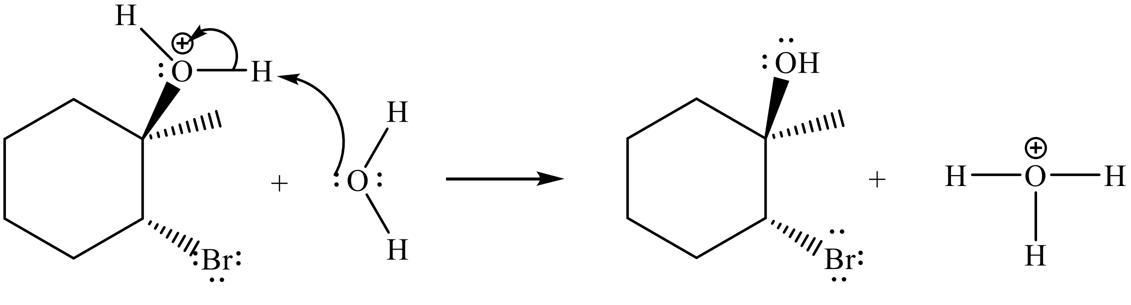


First step:



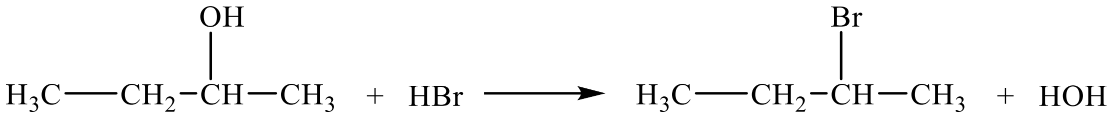
Second step:





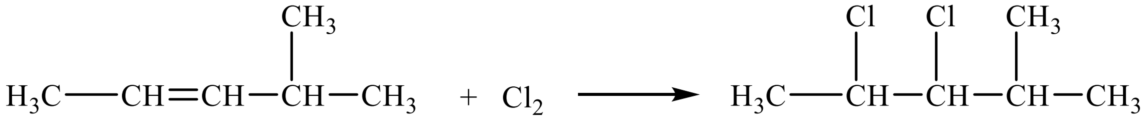
Exercise 3:

We identify each reaction as an addition, substitution, or elimination reaction.

a) 

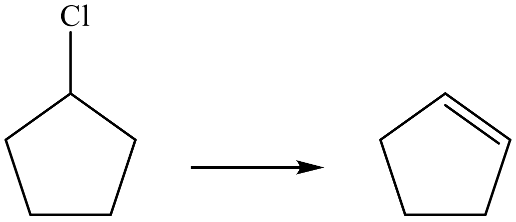
$$H_3C-CH_2-CH(OH)-CH_3 + HBr \longrightarrow H_3C-CH_2-CH(Br)-CH_3 + HOH$$

No double bond is broken or formed. Two reactants form two products. The $-OH$ group in the organic reactant is replaced with a Br atom. This is a substitution reaction.

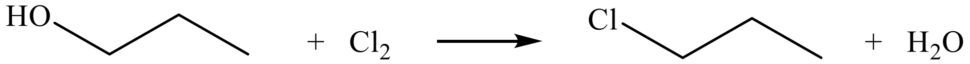
b) 

$$H_3C-CH=CH-CH(CH_3)-CH_3 + Cl_2 \longrightarrow H_3C-CH(Cl)-CH(Cl)-CH(CH_3)-CH_3$$

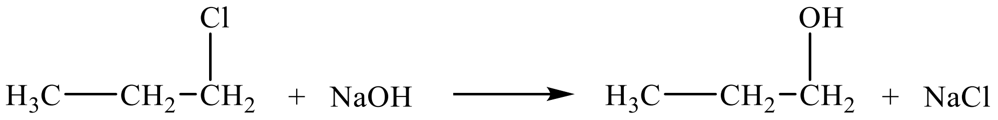
A double bond becomes a single bond. Two reactants become one product. The organic product has more non-carbon atoms bonded to carbon (14 in total) than in organic reactant (12 in total). This is an addition reaction.

c) 

A double bond is formed. One reactant forms two products (HCl is eliminated from the reactant). This is an elimination reaction.

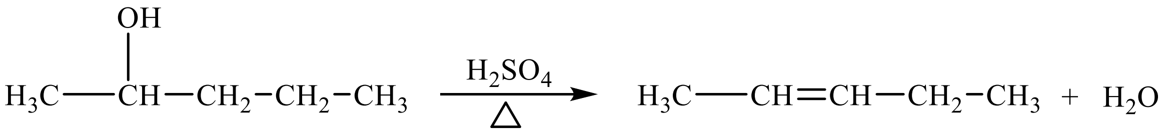
d) 

The $-OH$ group of the alcohol is replaced with a Cl atom. This is a substitution reaction.

e) 

$$H_3C-CH_2-CH_2(Cl) + NaOH \longrightarrow H_3C-CH_2-CH_2(OH) + NaCl$$

The Cl atom in 1-chloropropane is replaced with an $-OH$ group, so this is a substitution reaction.

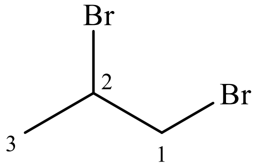
f) 

$$H_3C-CH(OH)-CH_2-CH_2-CH_3 \xrightarrow[\Delta]{H_2SO_4} H_3C-CH=CH-CH_2-CH_3 + H_2O$$

A double bond is formed by heating an alcohol in acid, so this is an elimination reaction. Water is produced as a second product.

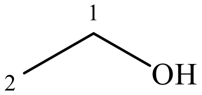
Exercise 4:

a- Only one product is possible, since one of the reactants is symmetrical. The product is 1,2-dibromopropane.



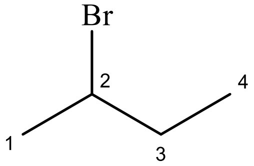
1,2-dibromopropane

b- Only one product is possible, since one of the reactants is symmetrical.



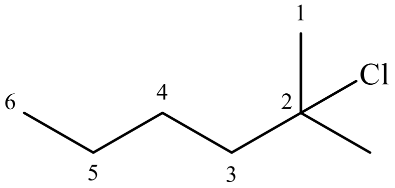
ethanol

c- Both reactants are asymmetrical, so two products are possible. The bromine atom will add to the second carbon atom, so the major product is 2-bromobutane.



2-bromobutane

d- Both reactants are asymmetrical, so two products are possible. The Cl atom will add to the second carbon atom, which has more bonds to other carbon atoms than the third carbon atom. The major product is 2-chloro-2-methylhexane.

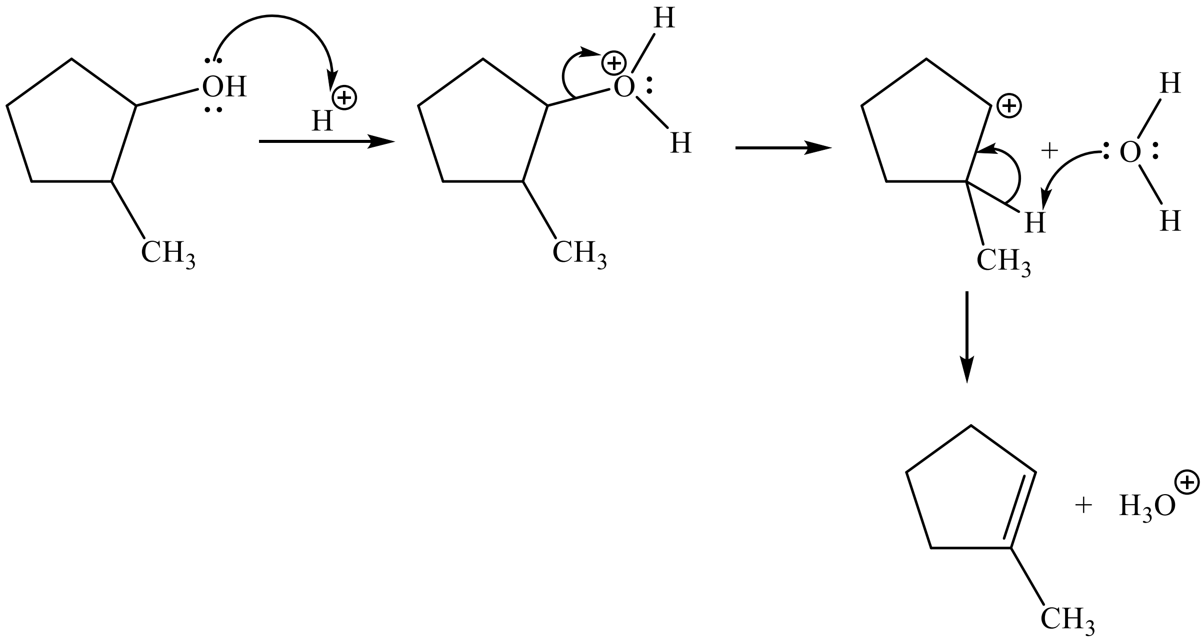


2-chloro-2-methylhexane

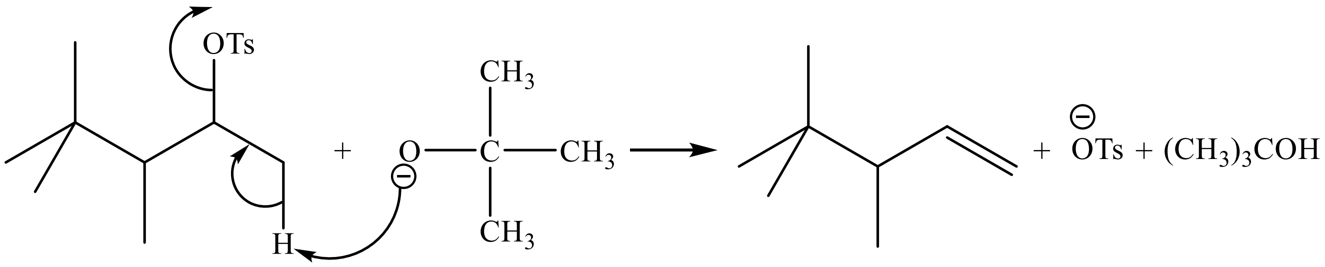
Exercise 5:

Draw the detailed mechanism for the following reactions.

a) It is a first-order elimination reaction ($E1$).



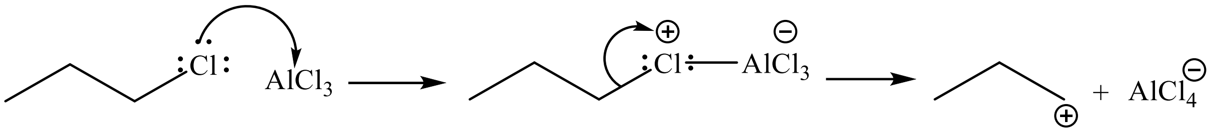
b) It is a second-order elimination reaction ($E2$).

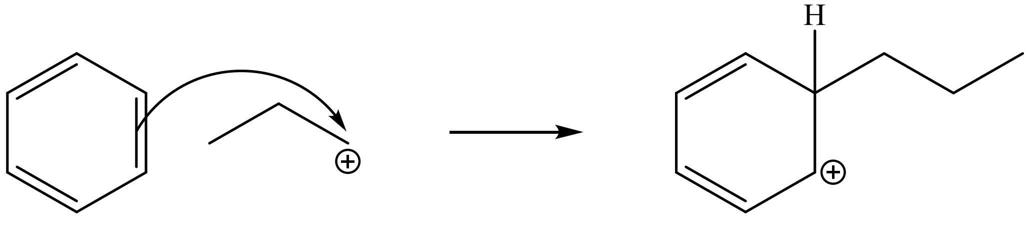


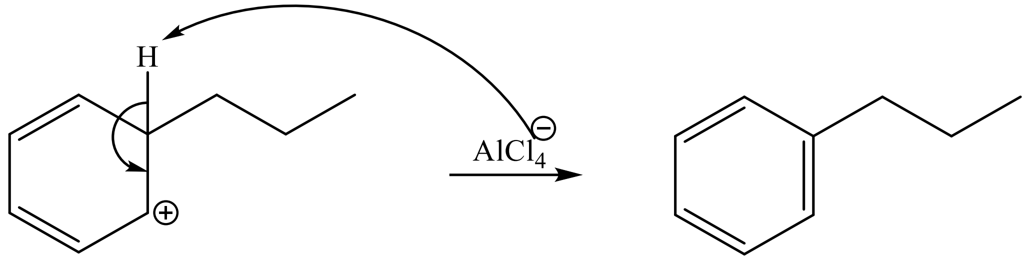
c) It is a first-order nucleophilic substitution ($SN1$).

Exercise 6:

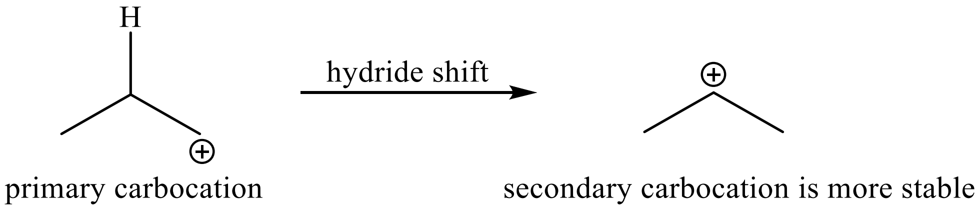
a-



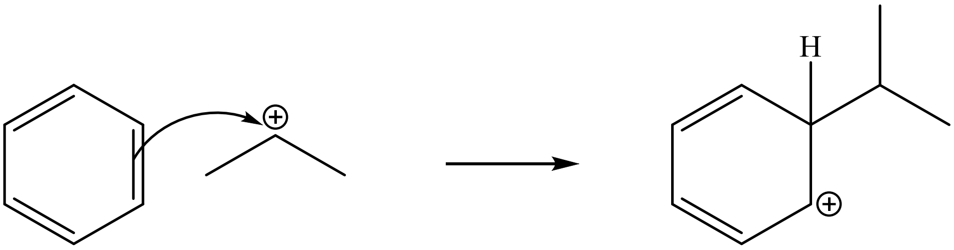


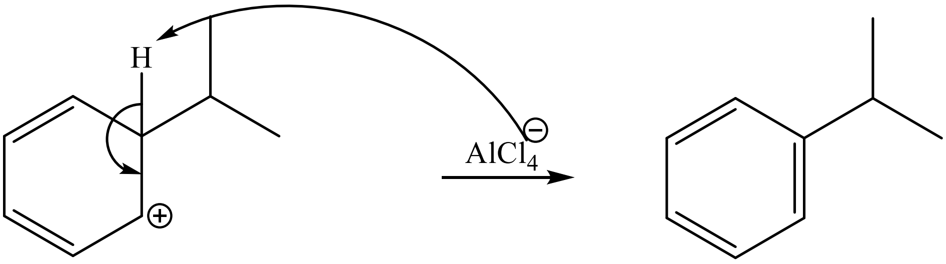


For the second product:

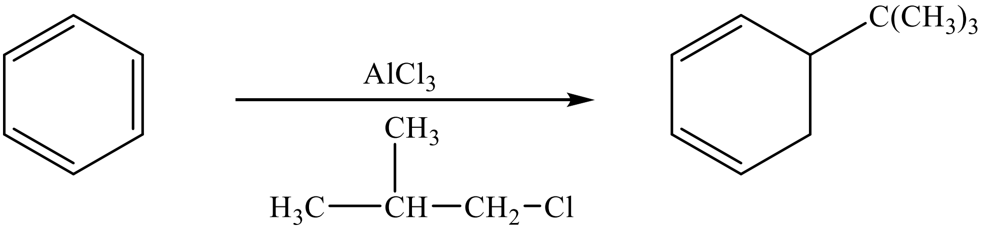


So, we get;

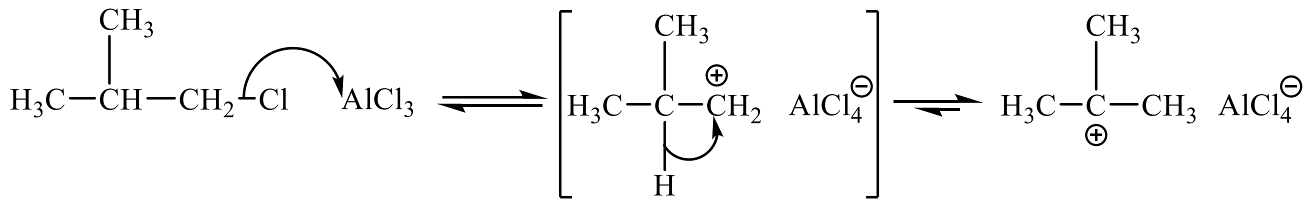




b-

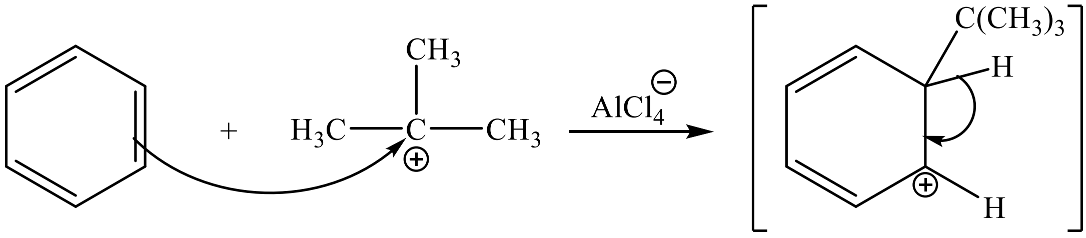


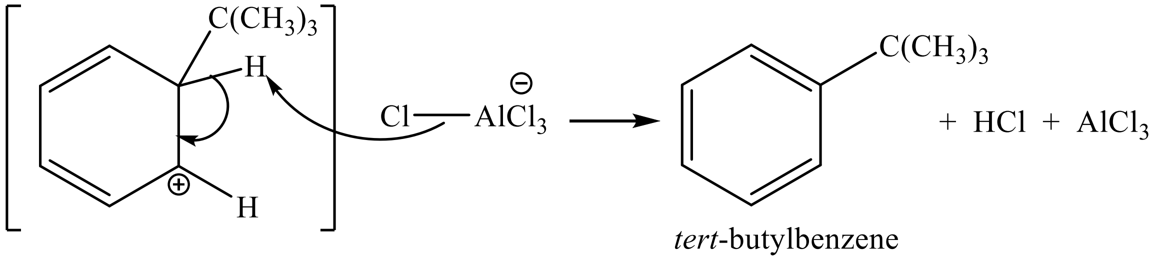
The detailed mechanism of this electrophilic aromatic substitution is:



isobutyl carbocation
(primary)

tert-butyl carbocation
(tertiary)





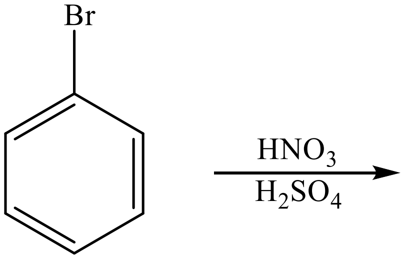
tert-butylbenzene

The isobutyl carbocation, initially formed when 1-chloro-2-methylpropane and $AlCl_3$ react, rearranges via a hydride shift to give the more stable *tert*–butyl carbocation, which can then alkylate benzene to form *tert*–butylbenzene.

Exercise 7:

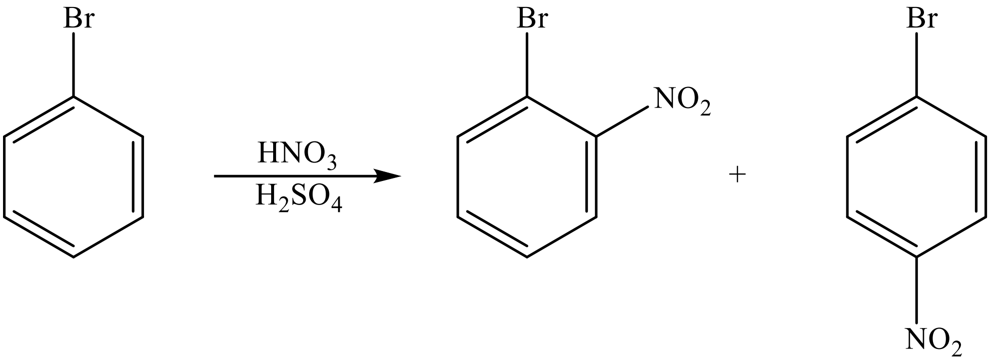
Identify the directing effect of the substituent, and draw the product.

a)

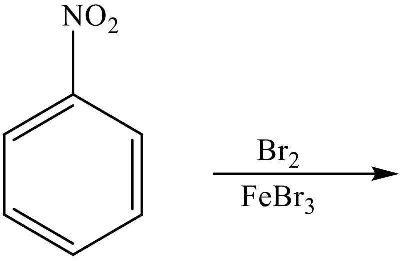


Even though bromine $(-Br)$ is a deactivator, it is an *ortho/para* director.

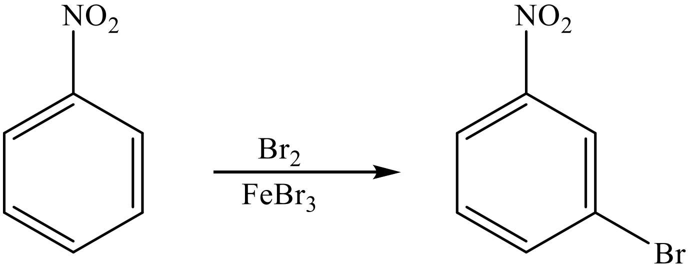
So, we get:



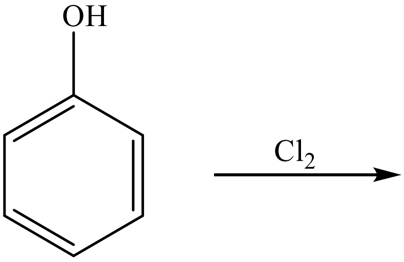
b)



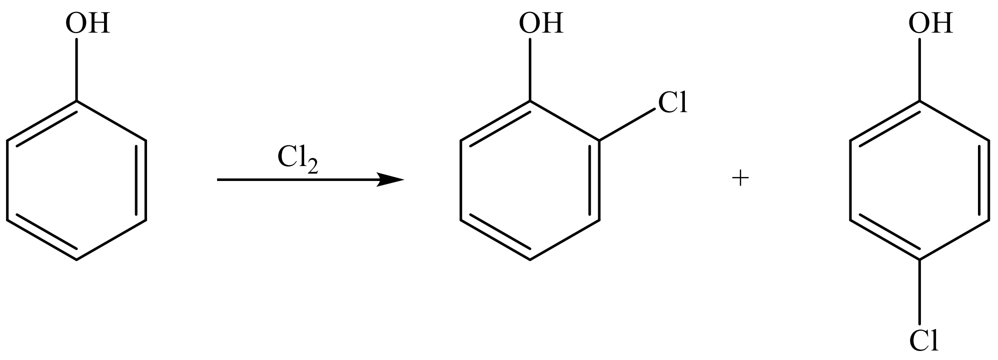
The $(-NO_2)$ group is a *meta* director. We get one product only.



c)

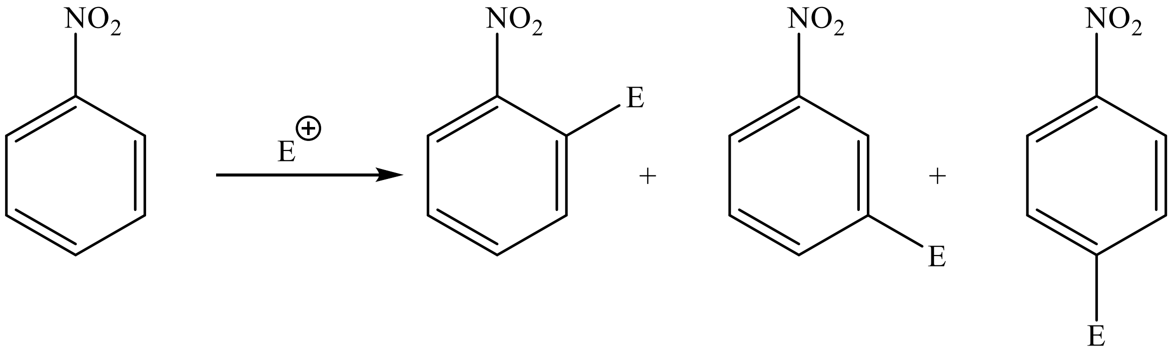


The $(-OH)$ group is an *ortho/para* director.

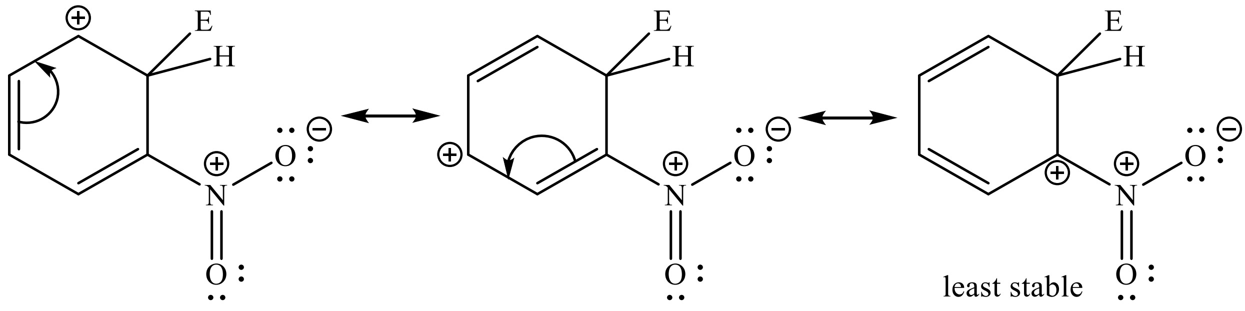


Exercise 8:

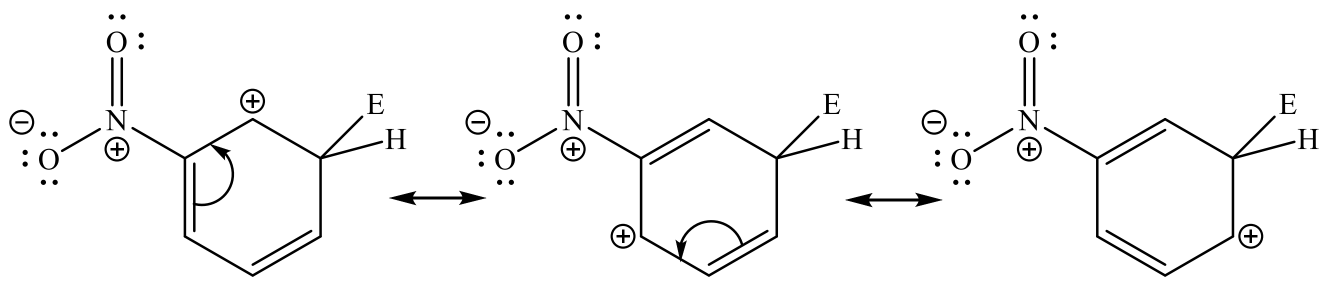
On the basis of resonance forms, we identify which electrophilic attack (*ortho*, *meta* or *para*) is favored on nitrobenzene.



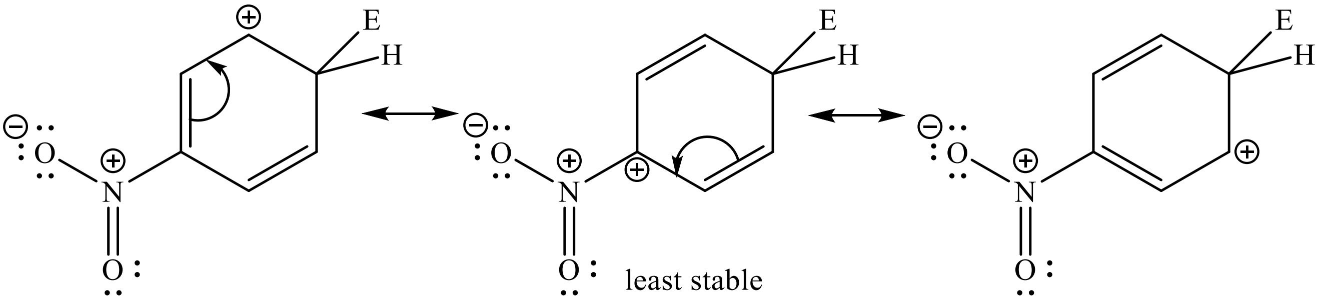
For the *ortho* attack, we get:



For the *meta* attack, we get:



For the *para* attack, we get:

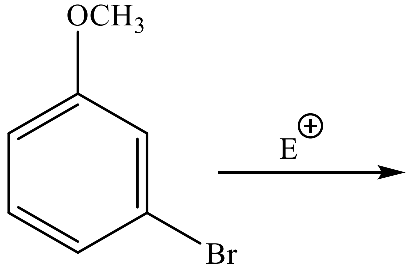


In the case of *ortho* and *para* substitution, there are resonance forms that are unfavorable, because they place two positive charges adjacent to each other. The intermediate from *meta* attack is thus favored.

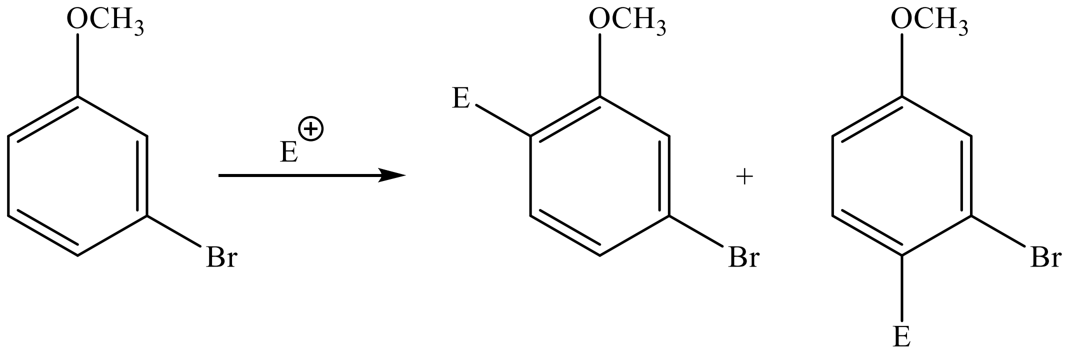
Exercise 9:

Draw the products of the EAS reactions.

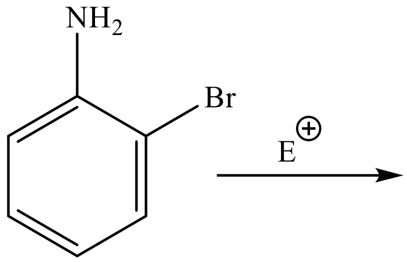
a) Both groups ($-OCH_3$ and $-Br$) are *ortho*, *para* directors and direct substitution to the same positions. Attack doesn't occur between the two groups for steric reasons.



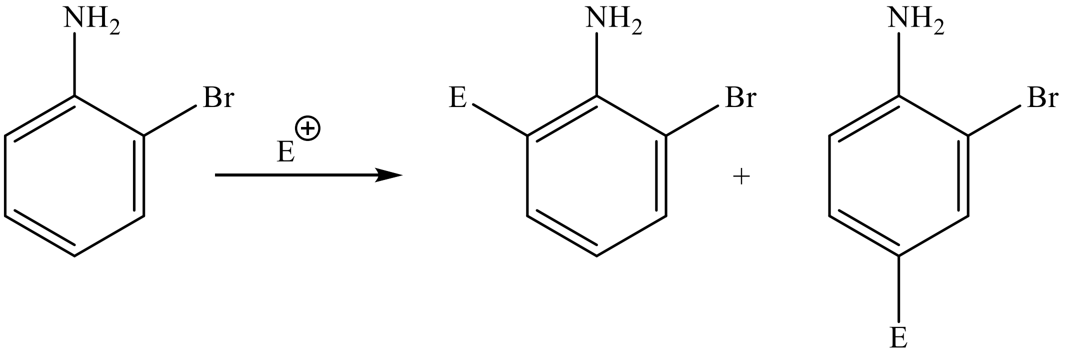
So, we can get as products:



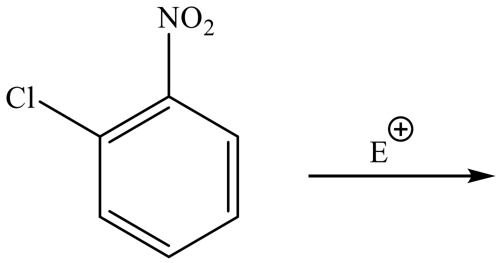
b) Both groups ($-NH_2, -Br$) are *ortho*, *para* directors, but direct to different positions. Because $-NH_2$ group is a more powerful activator, substitution occurs on *ortho* and *para* to it.



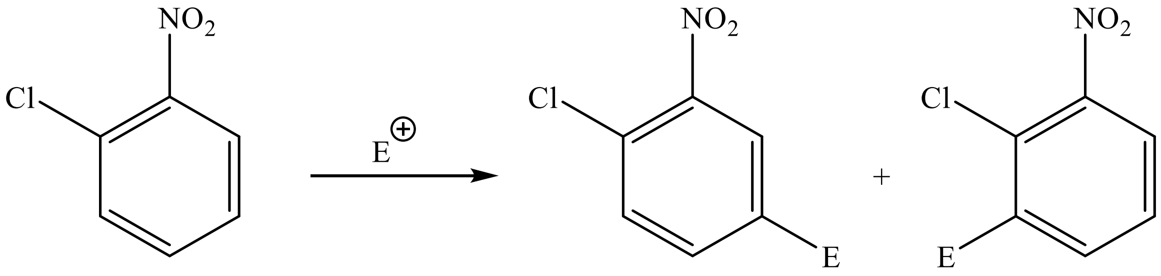
For this reason, two products are possible:



c) Both groups ($-NO_2$ and $-Cl$) are deactivating, but they orient substitution toward the same positions.



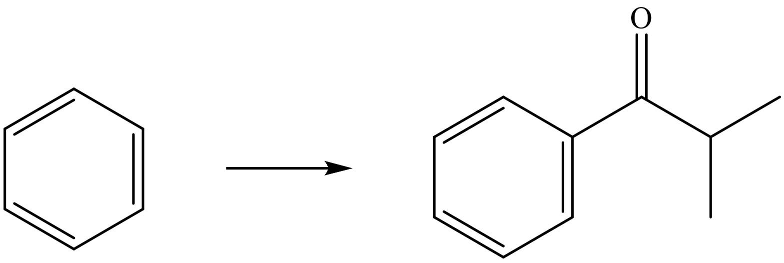
So, we get:

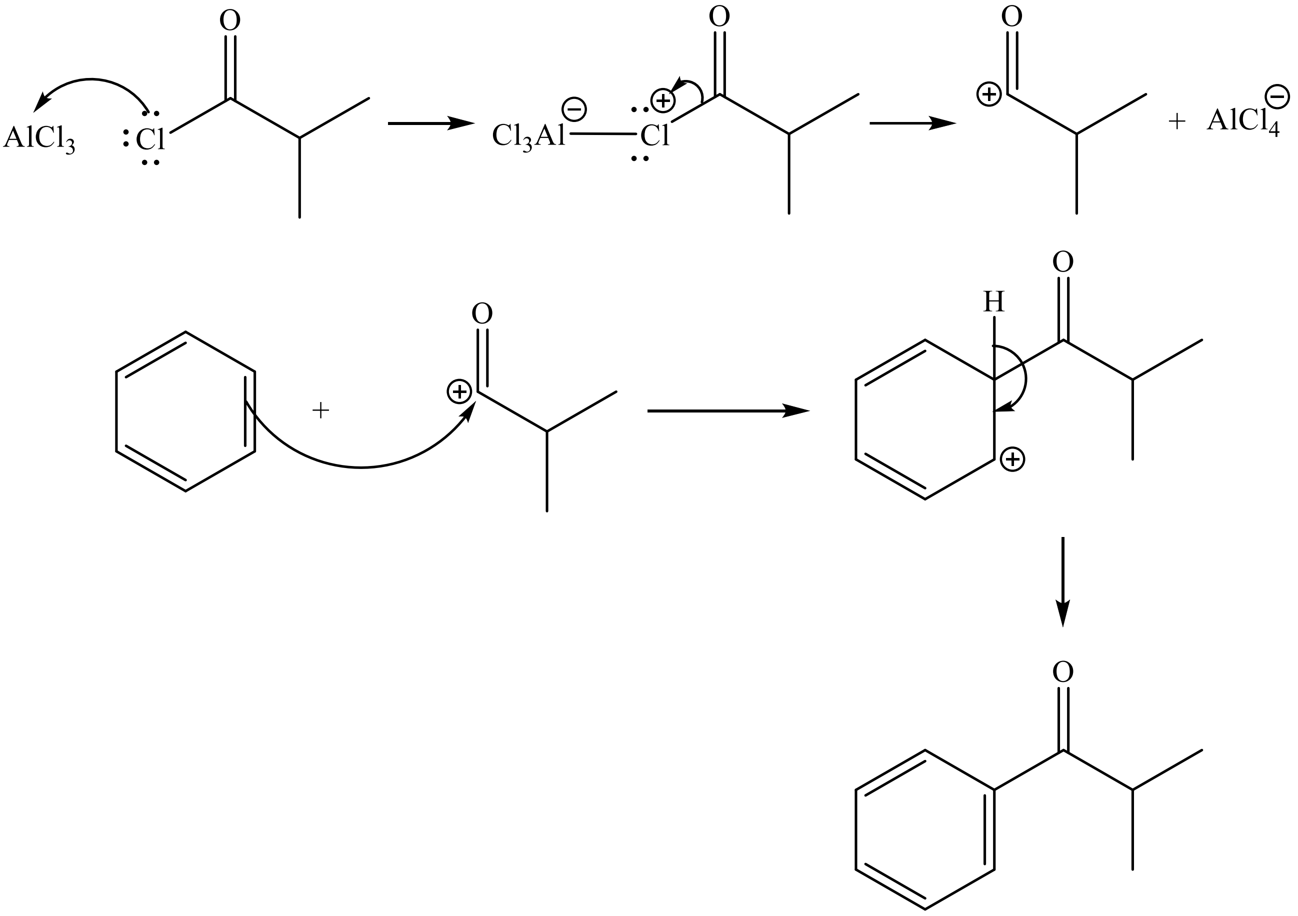


Exercise 10:

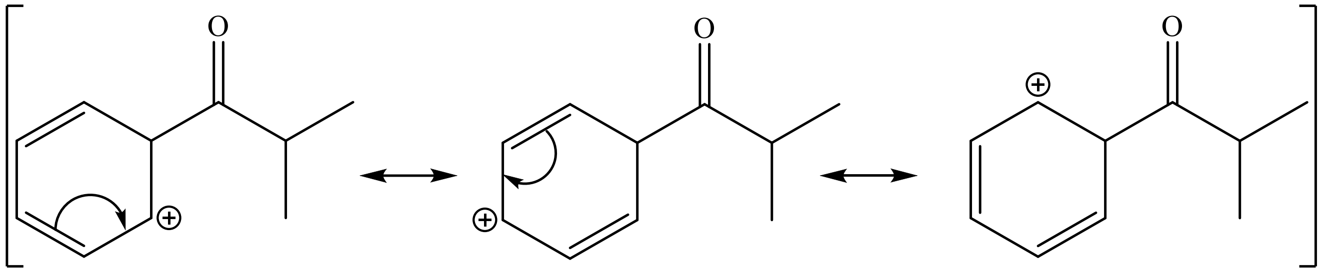
Propose a mechanism to the formation of the following product.

a) We propose a mechanism to the following reaction:

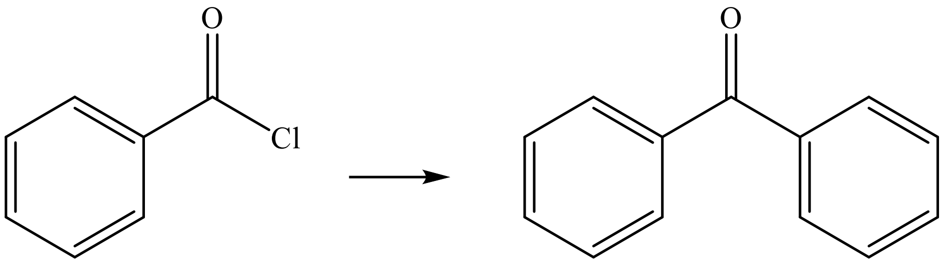




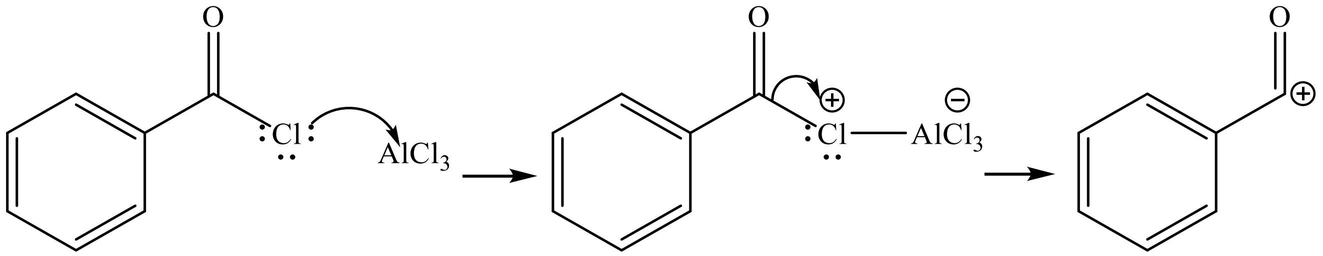
The obtained carbocation is stabilized by resonance and three resonant forms can be found.



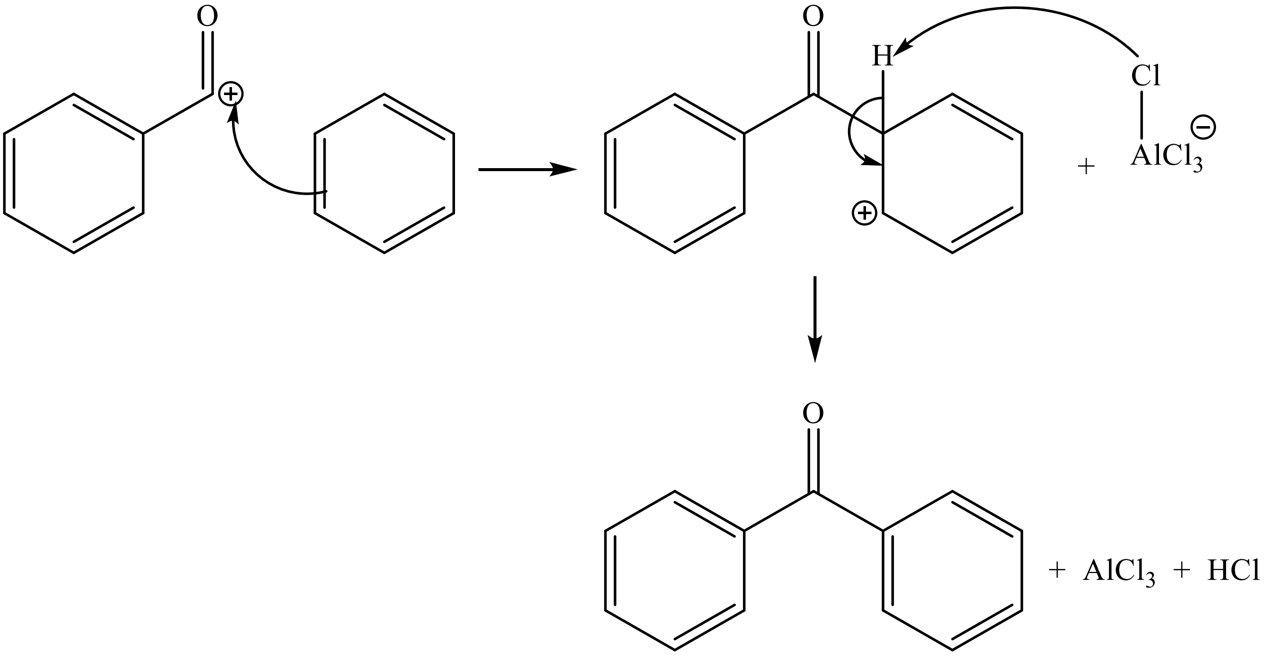
b) We propose a mechanism for the second reaction:



Firstly, the activation of the electrophile.



Secondly, the attack of the benzene ring to the electrophile.



References

REFERENCES

[1] Evelyne Chelain, Nadège Lubin-Germain, Jacques Uziel, *Maxi-fiches. Chimie organique*, 3ème Édition, Édition Dunod, 2015.

[2] Nadège-Lubin Germain, Jacques Uziel, *Chimie organique en 25 fiches*, Édition Dunod, 2008.

[3] Pierre Krausz, Rachida Benhaddou, Robert Granet, *Mini manuel de chimie organique*, 2ème Édition, Édition Dunod, 2008.

[4] Françoise Rouquérol, Gilberte Chambaud, Roland Lissillour, *Exercices résolus de chimie physique*, 3ème Édition, Édition Dunod, 2008.

[5] Paul Depovere, *Aide-mémoire de chimie organique*, Édition Dunod, 2006.

[6] Hervé Galons, *Chimie organique - Pharma essentiel du cours et exos*, 3ème Édition, Édition Masson, 2007.

[7] Jonathan Clayden, Nick Greeves, Stuart Warren, Peter Wothers, *Chimie organique*, Édition De Boeck, 2003.

[8] René Milcent, *Chimie organique, stéréochimie, entités réactives et réactions*, EDP Sciences, 2007.

[9] William A. Johnson, *Invitation à la chimie organique*, Édition De Boeck, 2002.

[10] Sylvain Robert, *Notes de cours chimie organique 1*, COR-1001, Qu'pla, Automne, 2000.

[11] André Durupthy, Odile Durupthy, Rosine Fanguet, Magali Giacino, Alain Jaubert, *Objectif prép chimie*, Édition Hachette, 2008.

[12] Karim Slama, *Chimie générale et organique*, Édition Wolters Kluwer, 2000.

[13] Richard Huot, Gérard-Yvon Roy, *Chimie organique : notions fondamentales, exercices résolus*, 5ème édition, Éditions Saint-Martin, 2011.

[14] Paul Arnaud, *Cours de chimie organique*, 14ème Édition, Édition Gauthier-Villars, 1989.

[15] Colette Ouahes, *Chimie organique, sciences biomédicales et sciences de la nature*, Office des publications universitaires (OPU), 2003.

[16] Yamina Tchoulak-Dahoun, *Principaux éléments de la nomenclature des composés chimiques*, Office des Publications Universitaires (OPU), 2004.

[17] Élise Marche, *Chimie organique-UE1*, 4ème Édition, Édition Dunod, 2013.

[18] Pierre Krausz, Rachida Benhaddou, Robert Granet, *Mini manuel de chimie organique, cours + exos*, 2ème Édition, Édition Dunod, Paris, 2012.

[19] Élise Marche, *Chimie organique-UE1, 1ère Année santé*, 3ème Édition, EdiScience, 2013.

[20] Harold Hart, Leslie E. Craine, David J. Hart, Christopher M. Hadad, *Chimie organique 1*, 12ème Édition, Édition Dunod, Paris, 2008.

[21] Élise Marche, *Fiches de révision en chimie générale, rappels de cours, QCM et QROC corrigés*, EdiScience, Édition Dunod, Paris, 2008.

[22] Adam Carter, Tiffany Culver, Robert Cichewicz, *Practice problems in biomedical organic chemistry: self-guided problems and answers for students in bioorganic and organic chemistry*, Volume I, 1st Edition, 2016.

[23] John D. Robert, Marjorie C. Caserio, *Basic principles of organic chemistry*, 2nd Edition W. A. Benjamin, Inc., Menlo Park, CA, 1977.

[24] Henri A Favre, Warren H Powell, *Nomenclature of organic chemistry: IUPAC recommendations and preferred names 2013*, IUPAC Blue Book, Royal Society of Chemistry Publishing, 2014.

[25] Anthony Nwobosi, *Introduction to organic nomenclature (IUPAC System made-easy)*, Fine Organic Limited, 2017.

[26] Ekkehard Fluck, Risto S. Laitinen, Nomenclature of inorganic chains and ring compounds (IUPAC recommendations 1997), *Pure and applied chemistry* 69.8:1659-1692, 1997.

[27] Geoffrey J. Leigh, *Principles of chemical nomenclature: a guide to IUPAC recommendations*. Royal Society of Chemistry, 2011.

[28] David R. Dalton, *Foundations of organic chemistry: unity and diversity of structures, pathways, and reactions*, 1st Edition, John Wiley & Sons, 2011.

[29] Dieter Hellwinkel, *Systematic nomenclature of organic chemistry. A directory to comprehension and applications of its basic principles*, Springer, 2001.

[30] André Durupthy, Jacques Estienne, Magali Giacino, Alain Jaubert, Claude Mesnil, *Chimie PCSI 1ère année*, Édition Hachette, 2010.

[31] Paul Arnaud, *Cours de chimie organique*, 14ème Édition, Gauthier-Villars, 1989.

[32] Christian Bellec, Jean Pierre Celerier, Gérard Lhommet, *La chimie au P.C.E.M et premier cycle universitaire*, Édition Vuibert, 1981.

[33] Simon Beaumont, *Tous les exercices de chimie MP-PSI-PT*, Édition Dunod, 2008.

[34] Pierre-Camille Lacaze, Mohamed Jouini, Jean-Christophe Lacroix, Hyacinthe Randriamahazaka, *Manuel de chimie organique, P. C. E. M, Premier cycle*, Édition Hermann, 2006.

[35] Ernest L. Eliel, Duraisamy Kandasamy, Conformational analysis. 32. Conformational energies of methyl sulfide, methyl sulfoxide, and methyl sulfone groups. *The Journal of Organic Chemistry* 41.24: 3899-3904, 1976.

[36] Manoharan, Muthiah, Ernest L. Eliel, The gauche interaction in *trans*-1, 2-dimethylcyclohexane. *Tetrahedron Letters* 24.5:453-456, 1983.

[37] Norman L. Allinger, Mary Ann Miller, Frederic A. Van Catledge, Judith A. Hirsch, Conformational analysis. LVII. The calculation of the conformational structures of hydrocarbons by the Westheimer-Hendrickson-Wiberg method. *Journal of the American Chemical Society* 89.17:4345-4357, 1967.

[38] Robert D. Stolow, Conformational Studies. VII. 1 p-Menthane-2, 5-diols and the Relative “Size” of the Isopropyl Group2. *Journal of the American Chemical Society* 86.11:2170-2173, 1964.

[39] Hans Förster, Fritz Vögtle. Steric interactions in organic chemistry: spatial requirements of substituents. *Angewandte Chemie International Edition in English* 16.7:429-441, 1977.

[40] André Collet, Jeanne Crassous, Jean-Pierre Dutasta et Laure Guy, *Molécules chirales, stéréochimie et propriétés*, EDP Sciences/CNRS Éditions, Paris, 2006.

[41] Soderberg Timothy, *Organic Chemistry with a Biological Emphasis*, Volume I, Chemistry Faculty 1, University of Minnesota Morris Digital Well, 2016.

[42] Norman L. Allinger, Tribble M. Thomas, Conformational analysis. LXXVIII. The conformation of phenylcyclohexane, and related molecules. *Tetrahedron Letters* 12.35:3259-3262, 1971.

[43] Cihang Yu, Agnes Kütt, Gerd-Volker Röschenthaler, Tomas Lebl, David B. Cordes, Alexandra M. Slawin, David O’Hagan, Janus Face All-cis 1, 2, 4, 5-tetrakis (trifluoromethyl)-and All-*cis* 1, 2, 3, 4, 5, 6-hexakis (trifluoromethyl)-Cyclohexanes. *Angewandte Chemie* 132.45:20077-20081, 2020.

[44] Gill Gurvinder, Diwakar M. Pawar, Eric A. Noe, Conformational study of cis-1, 4-di-tert-butylcyclohexane by dynamic NMR spectroscopy and computational methods. Observation of chair and twist-boat conformations. *The Journal of Organic Chemistry* 70.26:10726-10731, 2005.

[45] Adam Carter, Tiffany Culver, Robert Cichewicz, *Practice problems in biomedical organic chemistry: self-guided problems and answers for students in bioorganic and organic chemistry*, Volume I, 1st Edition, 2016.

[46] John D. Robert, Marjorie C. Caserio, *Basic principles of organic chemistry*, 2nd Edition. W. A. Benjamin, Inc. Menlo Park, CA, 1977.

[47] William Reusch, *Virtual text of organic chemistry*, Michigan State University, 1999.

[48] John Mc Murry, Eric Simanek, Chimie organique. *Les grands principes*, 2ème Édition, Édition Dunod, 2007.

[49] Arthur Winter, *Organic chemistry I for dummies*, 2nd Edition, John T. Moore Broché, 2016.

[50] Joel Karty, *Organic chemistry: principles and mechanisms*, 1st Edition, WW Norton & Company, 2014.

[51] Joel Karty, *Organic chemistry: principles and mechanisms*, 2nd Edition, WW Norton & Company, 2018.

[52] Joel Karty, *Organic chemistry: principles and mechanisms*, 3rd Edition, WW Norton & Company, 2022.

[53] Ralph H. Petrucci, F. Geoffrey Herring, Jeffry D. Madura, Carey Bissonnette, *General chemistry principles and modern applications*, 10th Edition, Édition Pearson, 2010.

[54] Ralph H. Petrucci, F. Geoffrey Herring, Jeffry D. Madura, Carey Bissonnette, *General chemistry principles and modern applications*, 11th Edition, Édition Pearson, 2017.

[55] Timothy Soderberg, *Organic chemistry with a biological emphasis*, Volume I: Chapters 1-9, Chemistry Faculty, University of Minnesota, Morris, 2010.

[56] Timothy Soderberg, *Organic chemistry with a biological emphasis*, Volume II: Chapters 10-17, Chemistry Faculty, University of Minnesota, Morris, 2010.

[57] John McMurry, *Organic chemistry with biological applications*, 2nd Edition, Publisher: Mary Finch, 2011.

[58] John McMurry, *Organic chemistry with biological applications*, 3rd Edition, Publisher: Mary Finch, 2015.

[59] Ben L. Feringa, Richard A. Van Delden, Absolute asymmetric synthesis: the origin, control, and amplification of chirality. *Angewandte Chemie International Edition* 38.23:3418-3438, 1999.

[60] Claire Ameline, Philippe Beckrich, *Physique-chimie term S*, Édition Nathan, 2017.

[61] Anil V. Karnik, Mohammed Hasan, *Stereochemistry a three-dimensional insight*, Elsevier, 2021.

[62] Dipak Kumar Mandal, *Stereochemistry and organic reactions conformation, configuration, stereoelectronic effects and asymmetric synthesis*, Academic Press, Elsevier, 2021.

[63] Vinod K. Ahluwalia, *Stereochemistry of organic compounds*, Springer, 2022.

[64] Shinsaku Fujita, *Mathematical stereochemistry*, Walter de Gruyter GmbH, 2015.

[65] Rene Milcent, *Chimie organique stéréochimie, entités réactives et réactions*, EDP Sciences, 2007.

[66] Giulio Natta, Mario Farina, *Stéréochimie molécules en 3D*, Édition Masson, 1971.

[67] Linda C. Cross, Rules for the nomenclature of organic chemistry, section E: stereochemistry. Pergamon Press, *Pure & Applied Chemistry* 45:11-30, 1976.

[68] Ernest L. Eliel, Samuel H. Wilen, *Stereochemistry of organic compounds*, Wiley, 1993.

[69] Ernest L. Eliel, Samuel H. Wilen, Michael P. Doyle, *Basic organic stereochemistry*, Wiley, 2001.

[70] James P. Snyder, Nizal S. Chandrakumar, Hirofumi Sato, David C. Lankin, The unexpected diaxial orientation of cis-3, 5-difluoropiperidine in water: a potent CF---NH charge-dipole effect. *Journal of the American Chemical Society* 122.3:544-545, 2000.

[71] Nanna Rut Jonsdottir, Ágúst Kvaran, Sigridur Jonsdottir, Ingvar Arnason, Ragnar Bjornsson, Conformational properties of 1-methyl-1-germacyclohexane: low-temperature NMR and quantum chemical calculations. *Structural Chemistry* 24:769-774, 2013.

[72] Laura B. Favero, Biagio Velino, Walther Caminati, Ingvar Arnason, Agust Kvaran, Structures and energetics of axial and equatorial 1-methyl-1-silacyclohexane. *Organometallics* 25.16:3813-3816, 2006.

[73] Golan, Oren, Zafrir Goren, Silvio E. Biali, Axial-equatorial stability reversal in all-trans-polyalkylcyclohexanes. *Journal of the American Chemical Society* 112.25:9300-9307, 1990.

[74] James R. Durig, Rachel M. Ward, Gamil A. Guirgis, Todor K. Gounev, Conformational stability from Raman spectra, r0 structural parameters, and vibrational assignment of methylcyclohexane. *Journal of Raman Spectroscopy: An International Journal for Original Work in all Aspects of Raman Spectroscopy, Including Higher Order Processes, and also Brillouin and Rayleigh Scattering* 40.12:1919-1930, 2009.

[75] James R. Durig, Ahmed M. EL Defrawy, Rachel M. Ward, Gamil A. Guirgis, Todor K. Gounev, Conformational stability of bromocyclohexane from temperature dependent FT-IR spectra of xenon solutions, r0 structural parameters and vibrational assignment. *Journal of Molecular Structure* 918.1-3:26-38, 2009.

[76] James R. Durig, Rachel M. Ward, Andrew R. Conrad, Michael J. Tubergen, Karen G. Nelson, Peter Groner, Todor K. Gounev, Microwave, Raman, and infrared spectra, r0 structural parameters, conformational stability, and vibrational assignment of cyanocyclohexane. *Journal of Molecular Structure* 967.1-3:99-111, 2010.

[77] James R. Durig, Rachel M. Ward, Andrew R. Conrad, Michael J. Tubergen, Gamil A. Guirgis, Todor K. Gounev, Microwave spectra, r0 structural parameters, and conformational stability from xenon solutions of silylcyclohexane. *Journal of Molecular Structure* 922.1-3:19-29, 2009.

[78] Michael B. Smith, Jerry March, *March's advanced organic chemistry: reactions, mechanisms, and structure*, 6th Edition, John Wiley & Sons, Inc., 2007.

[79] Xavier Deraet, Tatiana Woller, Ruben Van Lommel, Frank Proft, Guido Verniest, Mercedes Alonso, A benchmark of density functional approximations for thermochemistry and kinetics of hydride reductions of cyclohexanones, *Chemistry Open*, 8:788-806, 2019.

[80] Bruno A. Piscelli, William Sanders, Cihang Yu, Nawaf Al-Maharik, Tomas Lebl, Rodrigo A. Cormanich, David O'Hagan, Fluorine-Induced Pseudo-Anomeric Effects in Methoxycyclohexanes through Electrostatic 1, 3-Diaxial Interactions. *Chemistry–A European Journal* 26.52:11989-11994, 2020.

[81] Juaristi, Eusebio, Omar Muñoz-Muñiz, Enthalpic and entropic contributions to the conformational free energy differences in monosubstituted cyclohexanes. *Revista de la Sociedad Química de México* 45.4:218-224, 2001.

[82] Norman L. Allinger, Leslie A. Freiberg. Conformational analysis. XLVI. The conformational energies of the simple alkyl groups1-3. *The Journal of Organic Chemistry* 31.3:894-897, 1966.

[83] David R. Dalton, *Foundations of organic chemistry: unity and diversity of structures, pathways, and reactions*, John Wiley & Sons, 2020.

[84] Ernest L. Eliel, Samuel H. Wilen, *Stereochemistry of organic compounds*. John Wiley & Sons, 1994.

[85] Jerry A. Hirsch, *Table of conformational energies-1967. In Topics in Stereochemistry*, eds N.L. Allinger and E.L. Eliel, 1967.

[86] Ernest L. Eliel, Samuel H. Wilen, *Stereochemistry of organic compounds*, Wiley, 1993.

[87] Ernest L. Eliel, Samuel H. Wilen, Michael P. Doyle, *Basic organic stereochemistry*, Wiley, 2001.

[88] Robert J. Ouellette, J. David Rawn. *Organic chemistry study guide: Key concepts, problems, and solutions*, Elsevier, 2014.

[89] Claude K.W. Friedli, *Chimie générale pour ingénieur*, Édition Presses Polytechniques et Universitaires Romandes, 2010.

[90] Jean-Bernard Baudin, Frédéric Lahitète, *Chimie tout-en-un*, Bruno FOSSET, 2ème Édition, Édition Dunod, Paris, 2013.

[91] Timothy Soderberg, *Organic chemistry with a biological emphasis*, Volume I, Chemistry Faculty, 1, University of Minnesota Morris Digital Well, 2016.

[92] Timothy Soderberg, *Organic chemistry with a biological emphasis*, Volume II, Chemistry Faculty 2, University of Minnesota Morris Digital Well, 2016.

[93] Adam Carter, Tiffany Culver, Robert Cichewicz, *Practice problems in biomedical organic chemistry: self-guided problems and answers for students in bioorganic and organic chemistry*, Volume I, 1st Edition, 2016.

[94] Guy Bertrand, *Carbene chemistry: from fleeting intermediates to powerful reagents*, Copyright © Merc el Dekker, Inc, 2002.

[95] Alan D. McNaught, *Compendium of chemical terminology*, Volume 1669, Oxford: Blackwell Science, 1997.

[96] Zerong Wang, Uta Wille, Eusebio Juaristi, *Encyclopedia of physical organic chemistry*, 6 Volume Set, John Wiley & Sons, 2017.

[97] Soderberg Timothy, *Organic chemistry with a biological emphasis*, Volume I, Chemistry Publications, 2019.

[98] Xin Liu, *Organic chemistry I*, Kwantlen Polytechnic University, EBook ISBN: 978-1-989864-52-4, 2021.

[99] Riddick John Allen, William B. Bunger, Theodore K. Sakano, *Organic solvents, Physical properties and methods of purification*. A. Weissberger, Edition John Wiley&Sons, New York, 1986.

[100] Wesley L. Archer, *Industrial solvents handbook*, Marcel Dekker, New York, 1996.

[101] John W. Hill, Ralph H. Petrucci, Terry W. McCreary et Scott S. Perry, *Chimie des solutions*, 2ème Édition Pearson, 2008.

[102] Yann Verchier, Anne-Laure Valette-Delahaye, Frédéric Lemaître, Chimie *générale*, 2ème Édition Dunod, Paris, 2011.

[103] Élisabeth Bardez, *Chimie générale*, Édition Dunod, Paris, 2009.

[104] Évelyne Chelain, Nadège Lubin-Germain, Jaques Uziel, *Chimie organique*, 3ème Édition Dunod, Paris, 2015.

[105] Karim Slama, *Chimie générale et organique*, Édition Walters Kluwer, 2000.

[106] André Durupthy, Odile Durupthy, Rosine Fanguet, Magali Giacino, Alain Jaubert, *Objectif prepa chimie*, Édition Hachette, Paris, 2008.

[107] Bruno Fosset, Jean-Bernard Baudin, Frédéric Lahitète, *Chimie tout-en-un MPSI-PTSI* – 2ème Édition, Édition Dunod, Paris, 2013.

[108] Alain Demolliens, Pascal Frajman, Corinne Gauthier, Jean-Marc Urbain, *Chimie PC PC - 2ème année Tout-en-un -Classe prépa scientifique*, Nathan, 2009.

[109] Richard Huot, Gérard-Yvon Roy, *Chimie organique : Notions fondamentales*, 5ème Édition, Éditions Saint-Martin, 2011.

[110] Kirchner Barbara, *Electronic effects in organic chemistry*, Berlin, Heidelberg: Springer Berlin Heidelberg, 2014.

[111] Dakeshwar Kumar Verma, Yeestdev Dewangan, Chandrabhan Verma. *Handbook of organic name reactions: reagents, mechanism and applications*, Elsevier, 2023.

[112] Élise Marche, *Fiches de révision en chimie générale, Rappels de cours, QCM et QROC corrigés*, EdiScience, Dunod, Paris, 2008.

[113] John Robert, Marjorie Caserio, *Basic principles of organic chemistry*, 2nd Edition, W. A. Benjamin, Inc., Menlo Park, CA, 1977.

[114] Michael Smith, *Solutions manual for organic chemistry: An acid-base approach*, 2nd Edition, CRC press, 2016.

[115] John Mc Murry, Eric Simanek, *Chimie organique, Les grands principes*, 2ème Édition, DUNOD, 2007.

[116] Niels E. Henriksen, Flemming Y. Hansen, *Theories of molecular reaction dynamics: the microscopic foundation of chemical kinetics*, Oxford University Press Inc., New York, 2008.

[117] Frank Jensen, *Introduction to computational chemistry*, 1st Edition, Wiley, 1999.

[118] Frank Jensen, *Introduction to computational chemistry*, 2nd Edition, Wiley, 2007.

[119] Margaret R. Wright, *An introduction to chemical kinetics*, John Wiley & Sons, Ltd, 2004.

[120] Yu-Ran Luo, *Comprehensive handbook of chemical bond energies*, CRC Press, Boca Raton, FL, 2007.

[121] Roger L. Dekock, Harry B. Gray, *Chemical structure and bonding*, University Science Books, 1989.

[122] Marie-Virginie Speller, Erwan Guélou, Visa pour la prépa 2018-2019 - Maths-Physique-Chimie - MPSI-PCSI-PTSI-BCPST MPSI-PCSI-PTSI-BCPST, 3ème Édition, Édition Dunod, 2018.

[123] Mark Loudon, James Parise, *Organic chemistry*, 6th Edition, Roberts and Company Publishers, 2015. ISBN-10 : 1936221349, ISBN-13 : 978-1936221349

[124] Leroy G. Wade, Jan W. Simek, *Organic chemistry*, 10th Edition, 2022.

[125] Paula Yurkanis Bruice, *Essential organic chemistry*, 3rd Edition, Pearson, 2016.

[126] Richard Huot, Gérard-Yvon Roy, *Chimie organique : Notions fondamentales*, 5ème Edition, Éditions Saint-Martin, 2011.

[127] Brigitte Jamart, Jacques Bodiguel, Nicolas Brosse, *Chimie organique – Les Cours de Paul Arnaud* – 20ème Édition, Édition Dunod, 2021.

[128] Paula Yurkanis Bruice, *Chimie organique*, 2ème Édition, Pearson, 2012.

[129] Pierre Krausz, Rachida Benhaddou, Robert Granet, *Mini manuel de chimie organique*, 4ème Édition, Édition Dunod, 2020.

[130] Elise Marche, *Fiches de révision en chimie générale et organique (PCEM1)*, Édition Dunod, Paris, 2008.

[131] Stéphane Girouard, Danielle Lapierre, Claudio Marrano, *Chimie organique 1*, 2ème Édition, TC Média Livres Inc., 2019.

[132] Isabelle Paquin, Dominique Thoraval, Azélie Arpin, Alain Lachapelle, *Chimie organique 2*, Chenelière Éducation INC., 2013.

[133] Paul Arnaud, *Exercices de chimie organique*, 2ème Édition, Édition Gauthier-Villars, 1987.

[134] Nadège Lubin-Germain, Jacques Uziel, *Chimie organique en 27 fiches*, Édition Dunod, Paris, 2008.

[135] Paul Depovere, *Aide-mémoire de chimie organique : Nomenclature et réactivité*, Édition Dunod, 2006.

[136] Alain Demolliens, Pascal Frajman, Corinne Gauthier, Jean-Marc Urbain, *Chimie PC PC - 2ème année Tout-en-un -Classe prépa scientifique*, Édition Nathan, 2009.

[137] Bruno Fosset, Jean-Bernard Baudin, Frédéric Lahitète, *Chimie PCSI Tout-en-un*, 6ème Édition, Édition Dunod, 2021.