

S-14: Representation of three dimensional structures (Fisher, sawhorse and Newmann projections with example each)

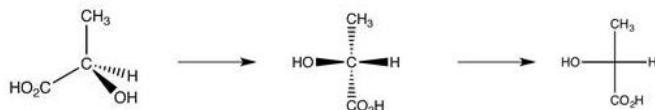
Structural isomers (definition, types- chain, position, functional isomers and metamers with one example each,Fisher, sawhorse and Newmann proections with example each)

Stereo isomers (enantiomers, diastereoisomers, definition with example)

Fisher Projection:

- A Fischer projection is a convention used to depict a three dimensional structure in two dimension without destroying the stereochemical information, i.e., absolute configuration, at chiral centers.
- In a Fischer projection, the longest chain is drawn vertically.
- The four bonds to a chiral carbon make a cross, with the carbon atom at the intersection of the horizontal and vertical lines.
- The two horizontal bonds are pointing toward the viewer.
- The two vertical bonds are directed away from the viewer.

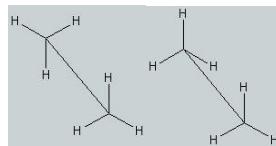
eg: (*R*)-Lactic acid



Sawhorse Projection:

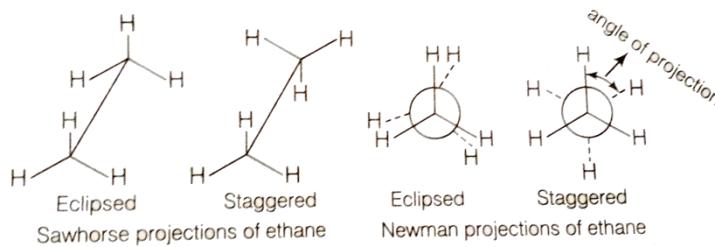
- **Sawhorse Projections** are very similar to Newman Projections, but are used more often because the carbon-carbon bond that is compressed in a Newman Projection is fully drawn out in a **Sawhorse Projection**.
- When properly laid-out, **Sawhorse Projections** are useful for determining enantiomeric or diasteromeric relationships between two molecules, because the mirror image or superimposibility relationships are clearer.
- **Sawhorse Projection** is a view of a molecule down a particular carbon-carbon bond, and groups connected to both the front and back carbons are drawn using sticks at 120 degree angles.

- **Sawhorse Projections** can also be drawn so that the groups on the front carbon are **staggered** (60 degrees apart) or **eclipsed** (directly overlapping) with the groups on the back carbon.
- Below are two **Sawhorse Projections** of ethane. The structure on the left is staggered, and the structure on the right is eclipsed.
- These are the simplest **Sawhorse Projections** because they have only two carbons, and all of the groups on the front and back carbons are identical.

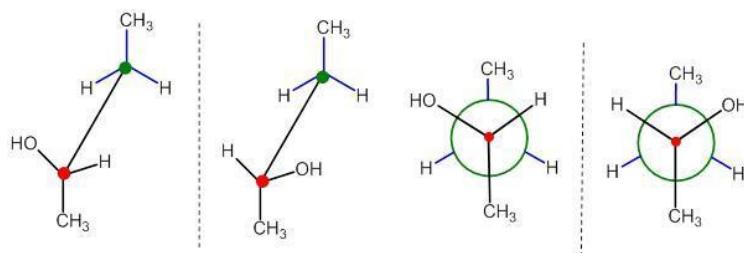


Newmann Projection:

- In a Newmann projection, we look along a carbon-carbon bond.
- The front carbon is represented as a dot and the back carbon as a circle.
- The substituents attached to the front carbon all have bonds starting from the dot while the substituents attached to the back carbon have bonds starting from the circle.
- If you look at a Newmann projection, you can see that it is a 'compact' version of the sawhorse projection.



- As an example, see below how the 2 enantiomers of 2- Butanol are represented using the Sawhorse and Newman projections:



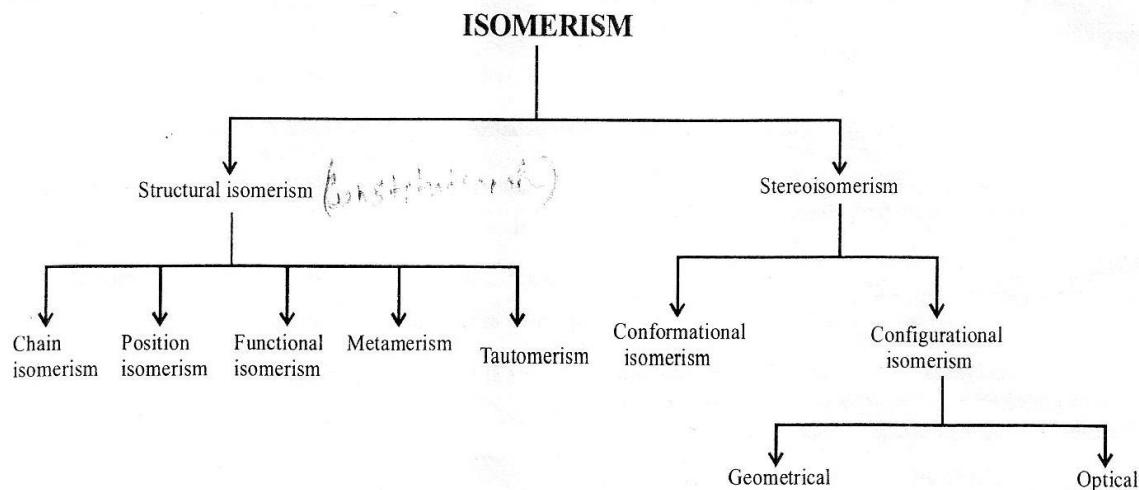
Sawhorse and Newman representations for the 2 enantiomers of 2-Butanol

ISOMERISM

Isomer word was first given by Berzelius. Compounds possessing the same molecular formula but differing in physical or chemical properties are called isomers and the phenomenon is termed as isomerism.



CLASSIFICATION OR TYPES OF ISOMERISM



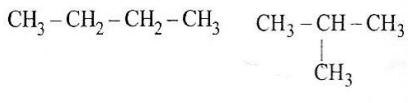
I. STRUCTURAL ISOMERISM

Structural isomers possess the same molecular formula but different structures; however, the term constitutional isomerism is a more modern term of structural isomerism. It arises because of the difference in the sequence of covalently bonded atoms in the molecule without reference to space. It is sub-classified into following types.

(a) Chain Isomerism (Skeleton or Nuclear Isomerism) :

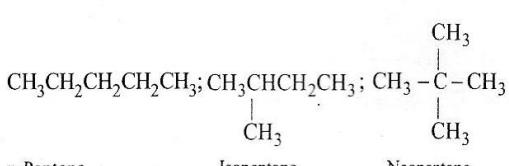
The different arrangement of carbon atoms gives rise to chain isomerism. Chain isomers possess different lengths of carbon chains (straight or branched). Such isomerism is shown by each and every family of organic compounds.

(i) Butane : C_4H_{10}



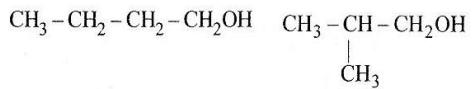
n-Butane has the chain of four carbons, while isobutane has three. Hence they are chain isomers.

(ii) Pentane : C_5H_{12}



n-Pentane, isopentane and neopentane possess the chain of five, four and three carbons, respectively. Hence they are chain isomers.

(iii) Butyl alcohol : C_4H_9OH

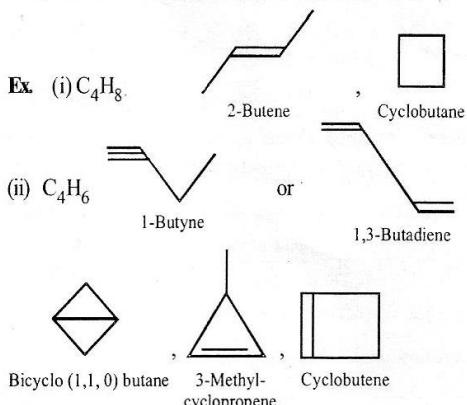


n-Butyl alcohol Isobutyl alcohol

These two butyl alcohols are chain isomers.

Ring chain isomerism :

They can also be considered as functional isomers.

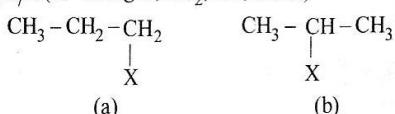
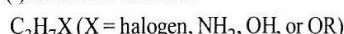


(b) Position Isomerism :

Position isomerism is shown by the compounds in which there is difference in the position of functional group, multiple bond or substituent along the same chain length of carbon atoms.

Ex.

(i) Molecular formula :



(a)

(b)

In these structures, three carbon atoms form a chain, and X is joined at the end in (a), while at the middle carbon in (b).

(a) $\text{CH}_3 - \text{CH}_2 - \text{CH}_2\text{OH}$ & $\text{CH}_3 - \text{CH} - \text{CH}_3$: Position isomers

1-Propanol

2-Propanol

(b) $\text{CH}_3 - \text{CH}_2 - \text{CH}_2 - \text{NH}_2$ & $\text{CH}_3 - \text{CH} - \text{CH}_3$: Position isomers

$\begin{matrix} \text{NH}_2 \\ | \\ \text{NH}_2 \end{matrix}$

n-Propylamine

Isopropylamine

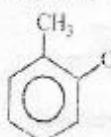
(ii) Molecular formula : C_4H_8

$\text{CH}_3 - \text{CH}_2 - \text{CH} = \text{CH}_2$ and $\text{CH}_3 - \text{CH} = \text{CH} - \text{CH}_3$:

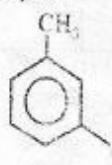
1-Butene

2-Butene

(iii) Chlorotoluene, $\text{C}_6\text{H}_5(\text{CH}_3)\text{Cl}$ exists in three isomeric forms : ortho, meta and para.



o-Chlorotoluene



m-Chlorotoluene



p-Chlorotoluene

(c) Functional Isomerism :

These isomers possess same molecular formula but different functional groups. Such compounds are called functional isomers. The following pairs of families show this isomerism.

- Monohydric alcohols and ethers
- Aldehydes and ketones
- Acids and esters
- Cyanides and isocyanides
- Nitroalkanes and alkyl nitrites
- Oximes, amides and many more
- Alkenes and cycloalkanes
- Alkynes, alkadienes and cycloalkenes

Ex.

(i) Molecular formula : $\text{C}_2\text{H}_6\text{O}$

$\text{CH}_3 - \text{CH}_2 - \text{OH}$ and $\text{CH}_3 - \text{O} - \text{CH}_3$

Ethyl alcohol
(Alcohol)

Dimethyl ether
(Ether)

(ii) Molecular formula : $\text{C}_3\text{H}_6\text{O}$

$\text{CH}_3 - \text{CH}_2 - \overset{\text{O}}{\underset{\parallel}{\text{C}}} - \text{H}$ and $\text{CH}_3 - \overset{\text{O}}{\underset{\parallel}{\text{C}}} - \text{CH}_3$

Propanal
(Aldehyde)

Propanone
(Ketone)

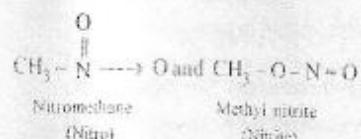
(iii) Molecular formula : $\text{C}_3\text{H}_6\text{O}_2$

$\text{CH}_3 - \text{CH}_2 - \text{COOH}$ and $\text{CH}_3 - \overset{\text{O}}{\underset{\parallel}{\text{C}}} - \text{O} - \text{CH}_3$

Propanoic acid
(Acid)

Methyl acetate
(Ester)

(iv) Molecular formula : CH_3NO_2

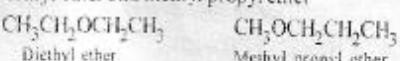


(d) Metamerism :

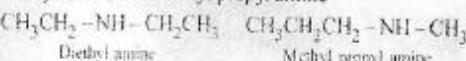
This type of isomerism is due to unequal distribution of substituents on either side of the polyvalent functional group. Members belong to the same homologous series.

Ex.

(i) Diethyl ether and methyl propyl ether



(ii) Diethyl amine and methyl propyl amine



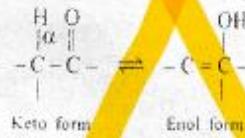
(e) Tautomerism :

Tautomerism is a special type of functional group isomerism which arises due to the migration of H-atom as proton from a polyvalent atom to other polyvalent atom with reshuffling of π bond.

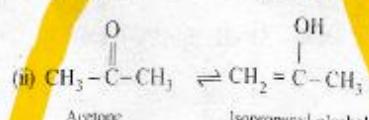
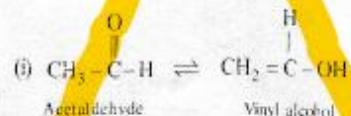
- Such isomers are directly and readily interconvertible under ordinary conditions, and the isomers are called tautomers.
- Tautomers exist in dynamic equilibrium.
- They have no separate existence under ordinary conditions like other isomers mentioned above.
- The other names of tautomerism are 'desmotropism' or 'prototropy'.

Keto-enol tautomerism :

- When the tautomers exist in the two forms viz keto & enol. Such type of tautomerism is called keto-enol tautomerism.
- It was discovered by the scientist 'Knorr' in 1911 in acetoacetic ester.
- Keto means the compound has a keto group $>\text{C}=\text{O}$, and the enol form has both double bond and OH (hydroxy) group joined to the same carbon.



Ex.



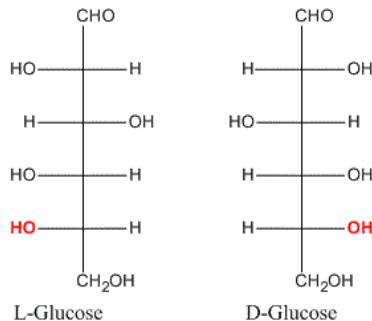
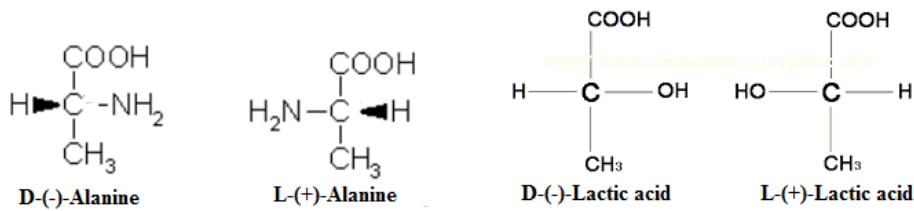
S-15: Configurations and symmetry and chirality (configuration-relative and absolute with example, Symmetry: elements of symmetry- plane of symmetry, centre of symmetry, principal axis or rotational axis of symmetry, alternating axis of symmetry, chirality-definition with examples)

Enantiomers and diastereomers

(definition with example each)

Relative configuration/ D-L configuration

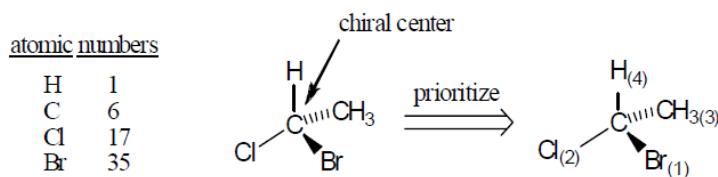
- D-L system (also called Fischer–Rosanoff convention) is mainly used for naming **α-amino acids and sugars**. It compares the relative configurations of molecules to the enantiomers of glyceraldehyde. This convention is still in common use today.
- Rosanoff in 1906 selected the **enantiomeric glyceraldehydes as the point of reference**; any sugar derivable by chain lengthening from what is now known as (+)-glyceraldehyde (or named D-glyceraldehyde) belongs to the D series.
- In other words, we used a D to designate the sugars that degrade to (+)-glyceraldehyde and an L for those that degrade to (-)-glyceraldehyde.
- In assigning the D and L configurations of sugars, we could directly **look for the OH group of the bottom asymmetric carbon in the Fischer projection**. If it's located on the right, we designate it with D, and vice versa, since they would have the same relative configurations with glyceraldehyde for the bottom asymmetric carbon.
- According to this convention, the prefix **D- and L- refer to the configuration of the lowest numbered chirality centre** of α-hydroxy or α-amino acids in the Fischer projection formula. If the α-OH or α-NH₂ group is on the right-hand side (of the viewer), the prefix D- is used, whereas if these groups are on the left-hand side, the prefix L- is used.



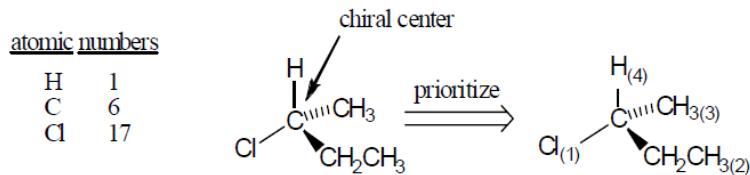
Absolute Configuration/R-S configuration/Cahn Ingold Prelog configuration

Priority Rules for Naming Chiral Centers - The R,S System

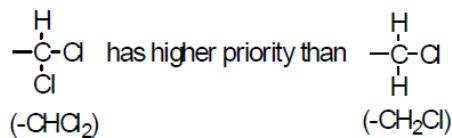
- Prioritize the four atoms, or groups of atoms, attached to the chiral center based on the atomic number of the atom that is bonded directly to the chiral center. The higher the atomic number, the higher the priority.
 - Number the four atoms, or groups of atoms, such that “1” has the highest priority and “4” has the lowest priority.



- If two or more of the atoms that are bonded directly to the chiral center are the same, then prioritize these groups based on the next set of atoms (i.e., atoms *adjacent* to the directly-bonded atoms). Continue until priorities can be assigned. Priority is assigned at the first point of difference.



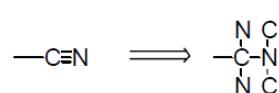
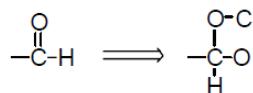
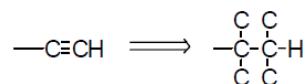
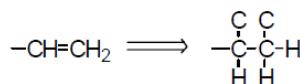
- If two atoms have substituents of the same priority, higher priority is assigned to the atom with *more* of these substituents.



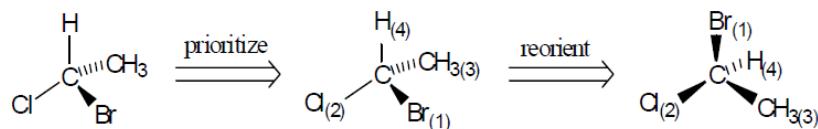
- A larger group (i.e., more atoms) may not necessarily have a higher priority over another (smaller) group.

-CH₂Cl has higher priority than -CH₂CH₂CH₂CH₃

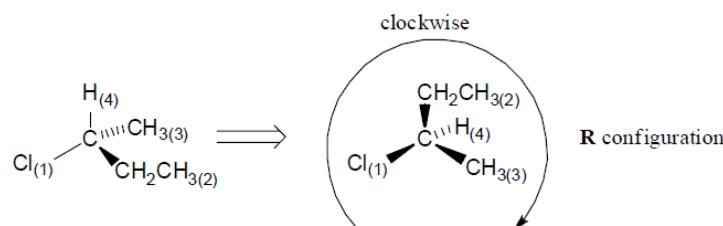
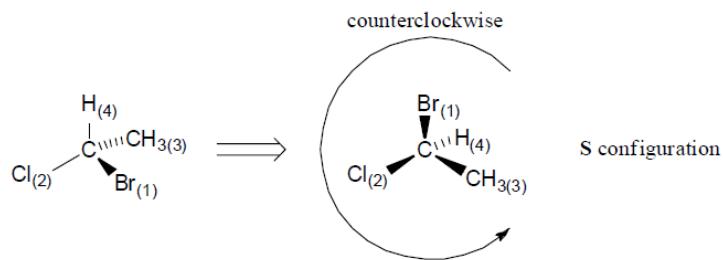
3. Atoms participating in double/triple bonds are considered to be bonded to an equivalent number of similar “phantom” atoms by single bonds. *Note: “phantom” atoms are bonded to no other atoms.*



4. Orient the molecule in space so that the lowest priority group (#4) is directed away from you. The three remaining groups then project toward you.



5. If the three groups projecting toward you are ordered from highest priority (#1) to lowest priority (#3) *clockwise*, then the configuration is “R”. If the three groups projecting toward you are ordered from highest priority (#1) to lowest priority (#3) *counterclockwise*, then the configuration is “S”.



Conversion of Saw horse to Fisher projection

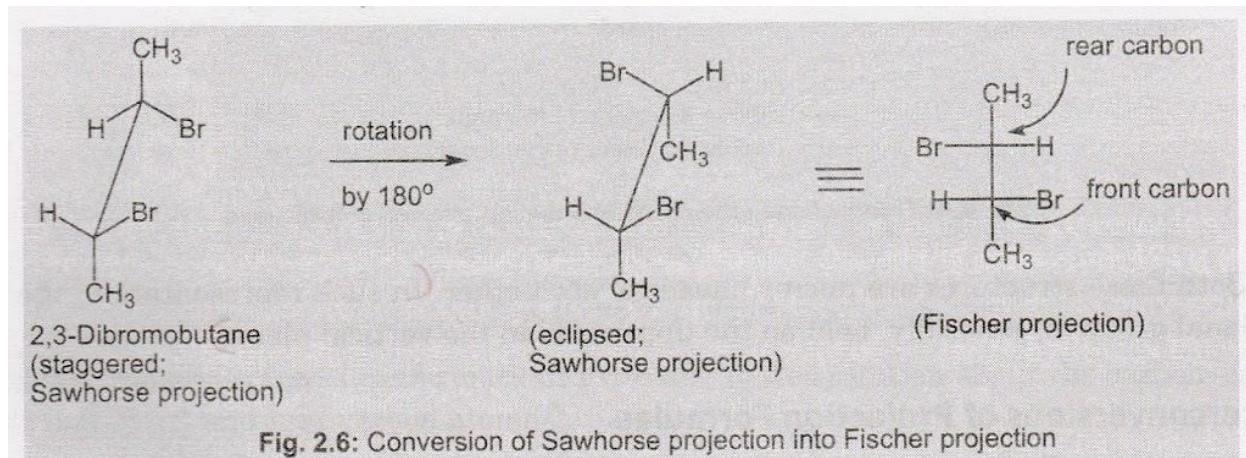
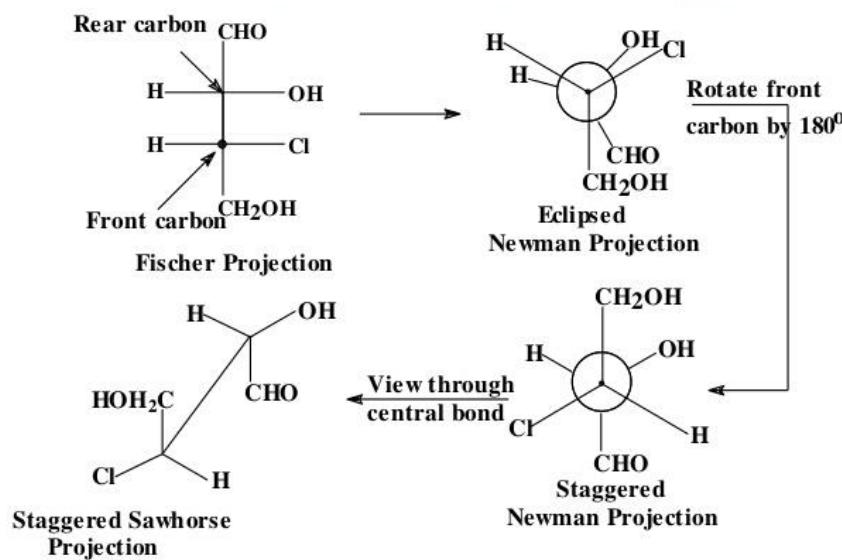


Fig. 2.6: Conversion of Sawhorse projection into Fischer projection

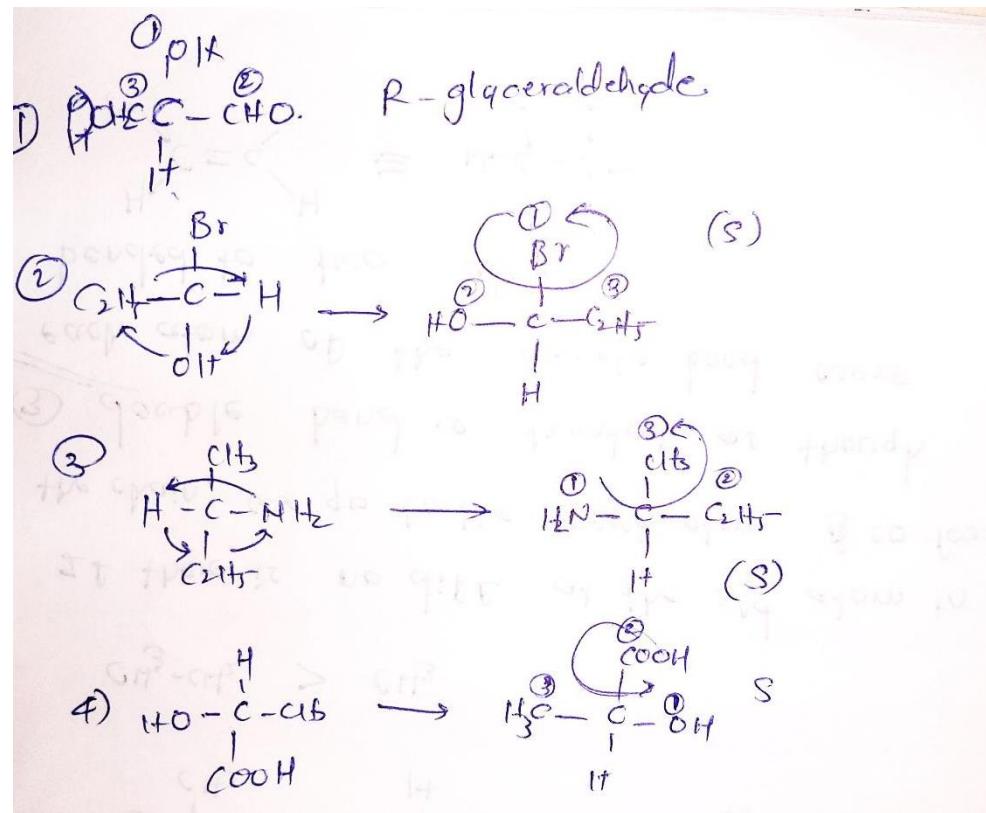
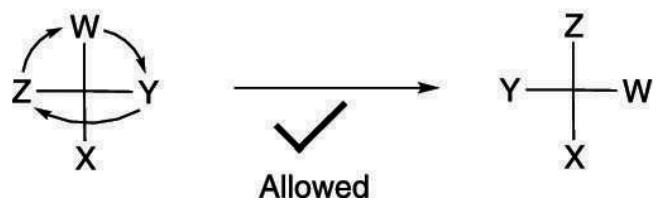
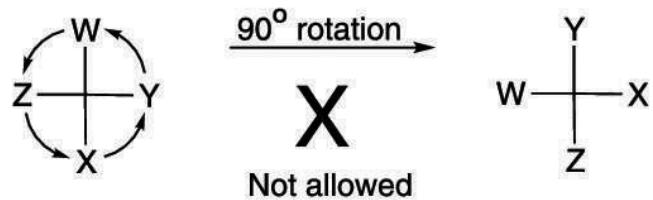
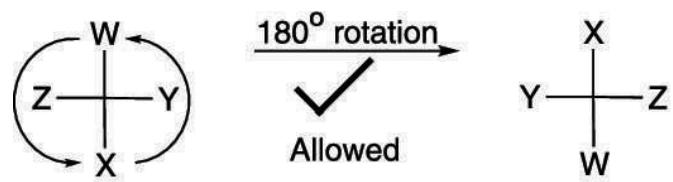
Conversion of Fisher to Newman to Sawhorse

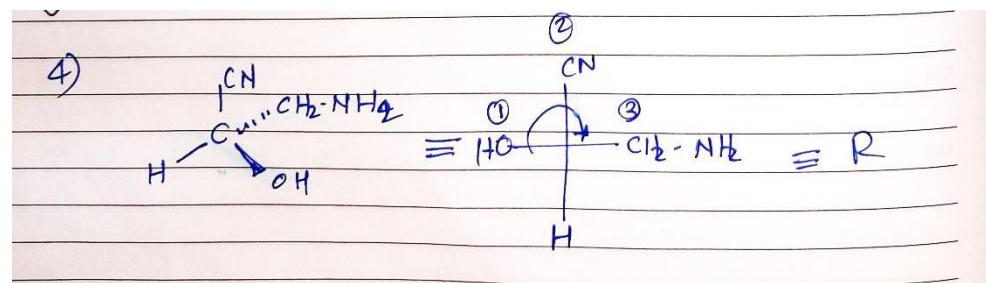
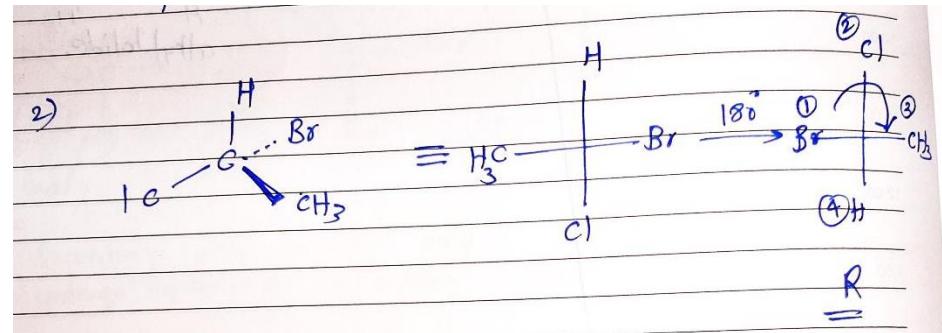
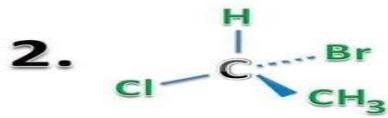
Conversion of Fischer to Newman to Sawhorse Projection



How to determine R/S configuration video link

<https://www.youtube.com/watch?v=Fod-YI4OzH0>





Symmetry Elements

A symmetry operation is carried out about an axis, plane or a point. These geometrical entities such as a line, a plane or a point about which one can perform operation of rotation, reflection or inversion are known as symmetry elements.

During any symmetry operation, at least one point in the molecule should remain unchanged. This point is centre of gravity of molecule. It means during the symmetry operation, there should not be actual displacement of the molecule/object as the movement of the molecule will only be around the centre of gravity.

There are five basic operations in nature that will leave centre of gravity of a molecule unchanged. These symmetry operations and the corresponding symmetry elements are listed in Table I

TABLE I

	Symmetry Element	Symmetry Operation
1	Identity (E)	Doing nothing
2	Mirror plane or plane of symmetry (σ)	Reflection about the plane
3	Inversion centre or centre of symmetry (i)	Inversion of all atoms in the molecule through the inversion centre
4	Proper rotation axis (C _n)	Rotation about an axis through some angle
5	Improper rotation axis (S _n)	Rotation about an axis through some angle followed by reflection in a plane perpendicular to the rotation axis

1) Identity (E)

The Identity element is obtained by an operation called “Identity Operation”. This is a “do nothing” operation. The situation can be visualized by two ways:

i) Either we do not do anything on the molecule

OR

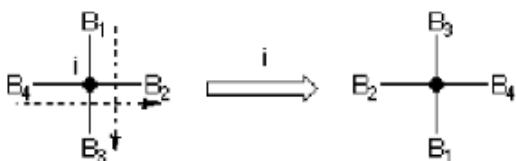
ii) We rotate the molecule by an angle of 360° .

All molecules have this element of symmetry. Identity has the same importance as the number 1 does in multiplication. There are some molecules that contain no other symmetry other than Identity e.g. CHFCIBr, SOClBr etc.

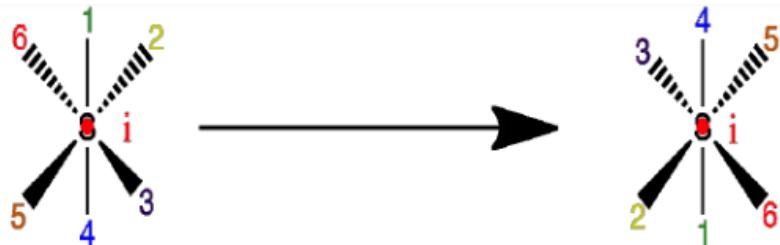
2) Inversion Centre or Centre of symmetry (i)

A molecule is said to possess a centre of symmetry if an imaginary line drawn from each atom through the centre of molecule encounters an equivalent atom in the direction and these atoms are equidistant from the centre. In this operation every atom in the molecule is moved in a straight line through the inversion centre to the opposite side of the molecule.

An atom may or may not be located at the centre of inversion and if present only one atom can be at the centre.



From the above it would be seen that atoms B1 & B3 are at equidistance from the inversion (i) and similarly atoms B2 & B4 are also at equidistance from inversion. The concept of inversion can be further explained with the help of the following example of SF_6 molecule:



3) Proper rotation axis or n-fold rotation: C_n , where n is an integer

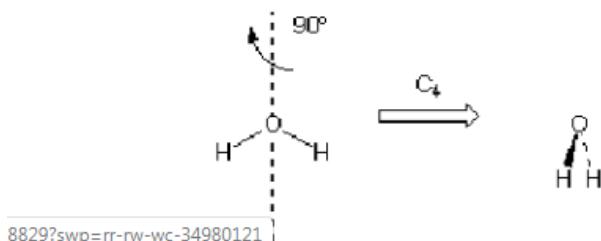
If the rotation of a molecule about an axis through some angle results in a configuration which is indistinguishable from the original, then the molecule is said to have proper rotational axis. It is denoted by symbol C_n which is called n-fold rotation with n being the order of the axis.

$$n = 360^\circ/\theta \text{ where } \theta \text{ is the angle through which the molecule is rotated.}$$

In another way we can say that the rotation by $360^\circ/n$ about a particular axis is defined as the n-fold rotation axis.

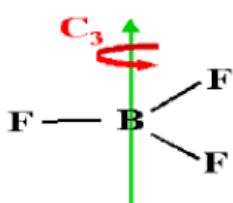
Let us take an example of water molecule which possess two fold axis of symmetry.

Here $C_2 = 180^\circ (360/2)$, i.e. two times rotation at 180° will bring the water molecule back to its original configuration. However, rotation by 90° about the same axis does not give back the identical molecule. Therefore H_2O does not possess a C_4 symmetry axis.

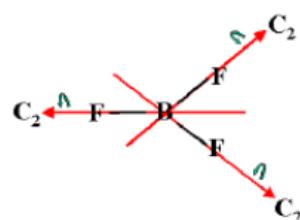


Similarly we can take boron trifluoride BF_3 as an example for C_3 axis of symmetry.

Here $C_3 = 120^\circ$ i.e three times rotation at 120° will bring back the molecule to its original form.



(A)



(B)

The figure A shows C_3 axis passes through the B atom and perpendicular to the plane of the molecule whereas Figure B shows that each C_2 axis passes through the B atom and one of the F atoms. The three C_2 axes are in the molecular plane.

Thus BF_3 molecule has one C_3 axis and three C_2 axes. The higher order C_3 axis is called the principle axis(the axis having highest value of order n is called principal axis).

The following table shows the different axes (one fold, two fold etc.) of symmetry.

TABLE 2

Angle in degree θ	$n=360^\circ/\theta$	Axis of rotation	Examples
360	1	C_1	Each molecule
180	2	C_2	H_2O
120	3	C_3	NH_3
90	4	C_4	$PtCl_4^{2-}$
72	5	C_5	$C_5H_5^-$
60	6	C_6	C_6H_6

4. Mirror plane or plane of symmetry(σ)

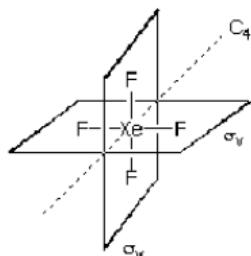
A mirror plane is an imaginary plane which divides a molecule into two equal halves such that one half is the exact mirror image of the other. Reflection in the plane leaves the molecule looking the same.

If plane contains the principle rotation axis (i.e., parallel), it is a vertical plane (σ_v).

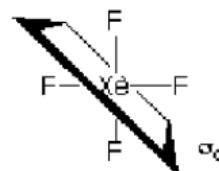
If plane is perpendicular to the principle rotation axis, it is a horizontal plane (σ_h).

If plane is parallel to the principle rotation axis, but bisects angle between 2 C_2 axes, it is a diagonal plane (σ_d).

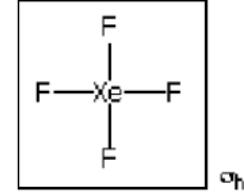
This can be further explained with the help of xenon tetrafluoride as shown below:



(A)



(B)



(C)

Fig A shows that XeF_4 has two planes of symmetry parallel to the principle rotation axis: σ_v

Fig B shows that XeF_4 has two planes of symmetry parallel to the principle rotation axis and bisecting the angle between 2 C_2 axes : σ_d

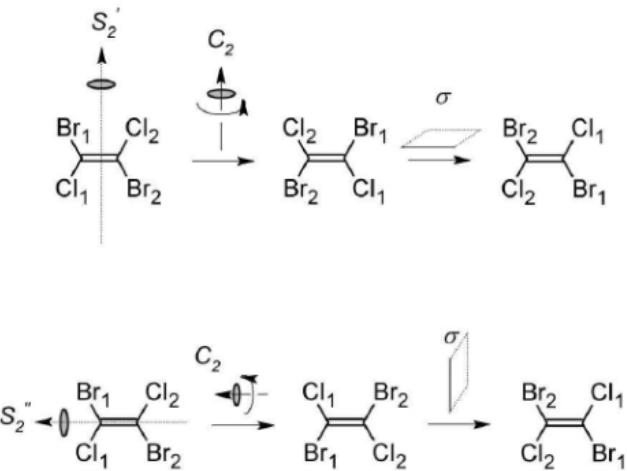
Fig C shows that XeF_4 has one plane of symmetry perpendicular to the principle rotation axis: σ_h

5) Improper Rotational Axis (S_n)

In this operation, molecule is rotated by n-fold rotation followed by reflection through the mirror plane perpendicular to the rotation axis. Thus, it is a combination of two operations; rotation(C_n) and reflection(σ)

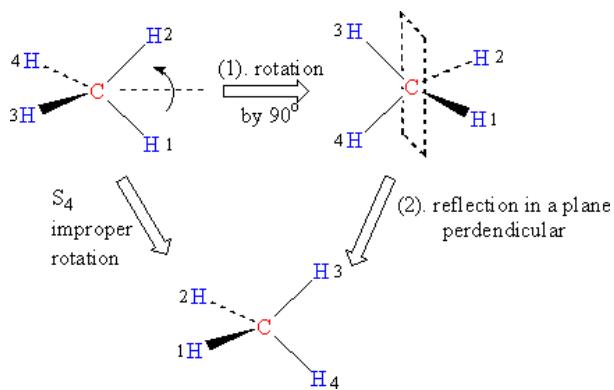
$$S_n = C_n \cdot \sigma h$$

The improper rotation can also be explained with the help of the molecule: 1,2-dibromo-1,2-dichloroethylene as shown below:



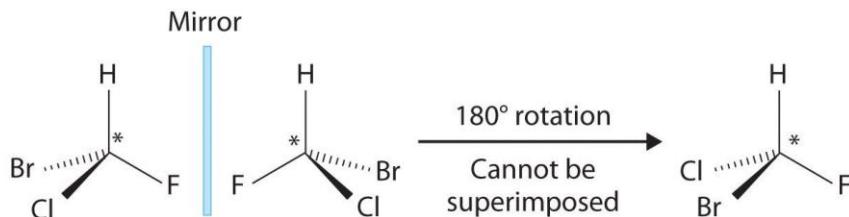
It can be seen from the figures that the configurations are not equivalent when we rotate the molecule by 180° , however, when this rotation is followed by reflection perpendicular to C_2 , then the resulting configurations become equivalent to the original configurations.

S_4 improper axis of rotation

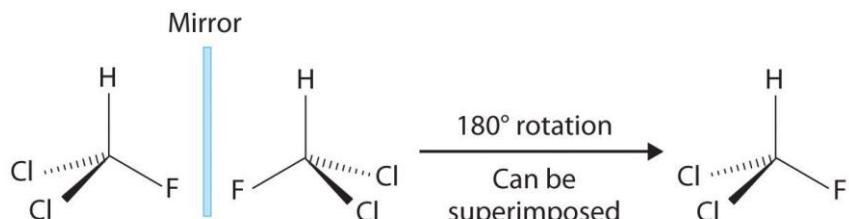


Definition of Chirality

- In chemistry, a molecule or ion is called **chiral** if it cannot be superposed on its **mirror image** by any combination of **rotations** and **translations**. This geometric property is called **chirality**. The terms are derived from Ancient Greek χείρ (cheir), meaning "hand"; which is the canonical example of an object with this property.
- Most **chiral** molecules can be identified by their lack of a *plane of symmetry* or a *center of symmetry*. Your hand is a chiral object, as it does not have either of these types of symmetry.
- A chiral molecule or ion exists in two **stereoisomers** that are mirror images of each other, called **enantiomers**; they are often distinguished as either "right-handed" or "left-handed" by their **absolute configuration** or some other criterion.
- The two enantiomers have the same **chemical properties**, except when reacting with other chiral compounds.
- They also have the same **physical properties**, except that they often have opposite **optical activities**.
- A homogeneous mixture of the two enantiomers in equal parts is said to be **racemic**, and it usually differs chemically and physically from the pure enantiomers.
- A chiral molecule or ion must have at least one **chiral center or stereocenter**.



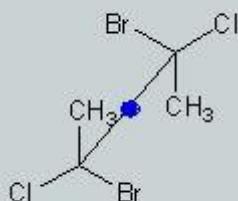
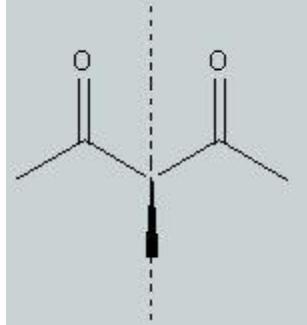
(a) Bromochlorofluoromethane



(b) Dichlorofluoromethane

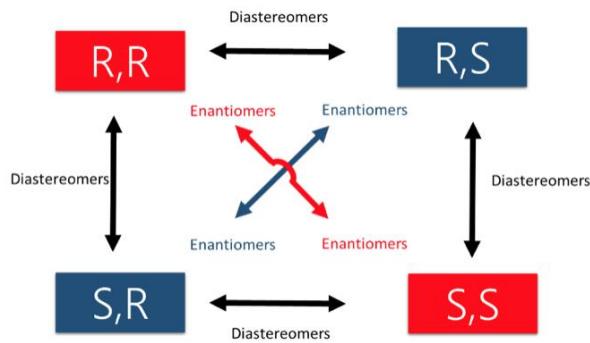
The molecule on the left below has a *plane of symmetry* through the center carbon. This is a *mirror plane*; in other words, one half of the molecule is a perfect reflection of the other half of the molecule. This molecule is not chiral because of its *mirror plane*.

The molecule on the right has a *center of symmetry*, or an *inversion center*. An *inversion center* is a point in the molecule - not necessarily on an atom - through which all other atoms can be reflected 180 degrees into another, identical, atom. (In more accurate symmetry terms, an *inversion through a center* is equivalent to rotating groups by 180 degrees and then reflecting the groups through a plane perpendicular to the rotation axis i.e. S₂ symmetry element)



-
-
-
- There are **two types of STEREOISOMERS**, enantiomers and diastereomers.
 - Enantiomers contain chiral centers that are non-superimposable & mirror images. They only come in pairs!
 - Diastereomers contain chiral centers are non-superimposable but are NOT mirror images. There can be many more than 2 depending on the number of stereocenters.

An easy way to remember enantiomers from diastereomers is to memorize the picture below. In the case of 2 chiral centers, 4 stereoisomers are possible. **Only the exact opposites (diagonal arrows) are enantiomers** and they therefore have a mirror image that is not superimposable. The molecules with **only one stereocenter that differs (parallel arrows)** are **diastereomers**.

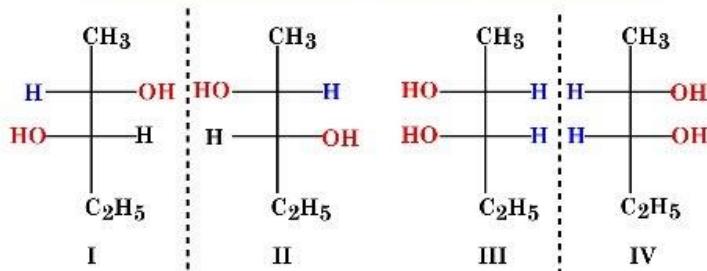


A biological example of this is saccharide (or sugar) chemistry and below is the enantiomers and diastereomers of threose.

S.No.	Enantiomers	Diastereoisomers
1.	The Chiral compounds (stereoisomers) having non-superimposable mirror image relationship are called enantiomers or enantiomorphs and this phenomenon is called as enantiomerism .	Stereoisomers having no mirror images relationship are called Diastereoisomers or Diastereoisomorphs and this phenomenon is called as diastereoisomerism .
2.	Enantiomers (both d or l-forms) have identical physical properties (like melting point, boiling point, densities, refractive indices, solubility, etc.) Hence, it cannot be separated by Fractional distillation or Crystallization.	Diastereoisomers have different physical properties (like melting point, boiling point, densities, refractive indices, solubility, etc.) Hence, they can be separated by Fractional distillation or Crystallization.
3.	Enantiomers (both d or l-forms) have one or more asymmetric (Chiral) C-atoms.	Diastereoisomers may or may not have asymmetric (Chiral) C-atoms.
4.	Enantiomers are optically active (Chiral).	Diastereoisomers may or may not be optically active (Chiral or Achiral).
5.	Enantiomers have identical chemical properties	Diastereoisomers have similar, but not identical chemical properties.
6.	They are stereoisomers that are mirror images.	They are stereoisomers that are not mirror images .

7. Examples:

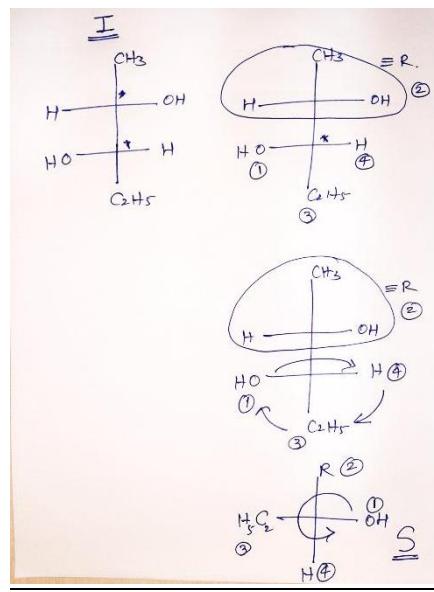
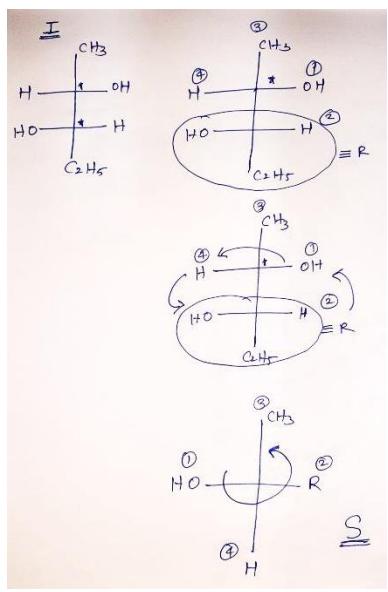
Stereochemistry - Diastereomers



Compounds I and II
are **enantiomers** of
each other.

Compounds III and IV
are **enantiomers** of
each other.

Compounds I and III are **diastereomers**.
Compounds I and IV are **diastereomers**.
Compounds II and III are **diastereomers**.
Compounds II and IV are **diastereomers**.



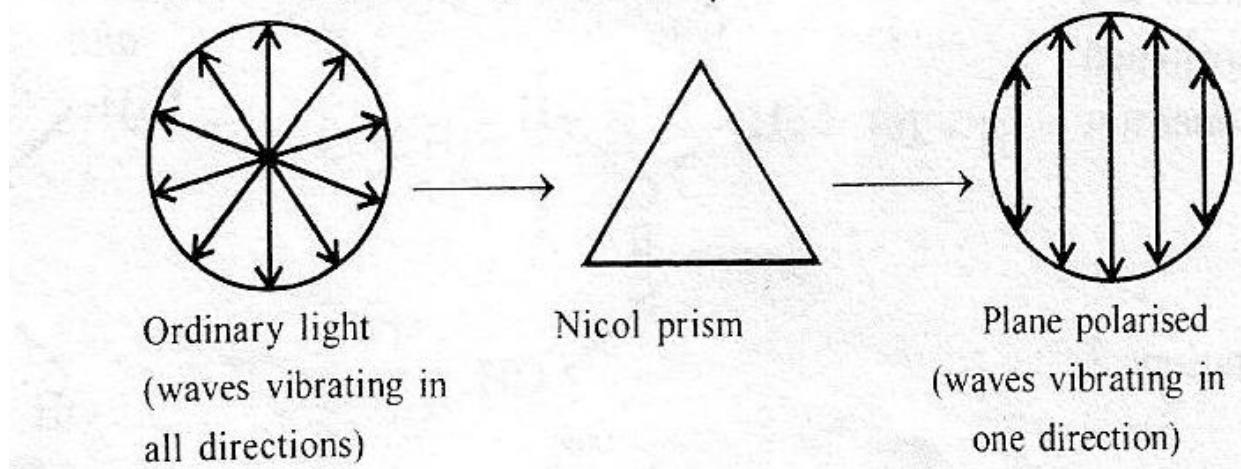
S-1: Optical activity and absolute configuration (Introduction, types-racemic, mesomers, dextro and laevo isomers, Absolute configuration-determination (R/S), Cahn-Ingold-Prelog rules)

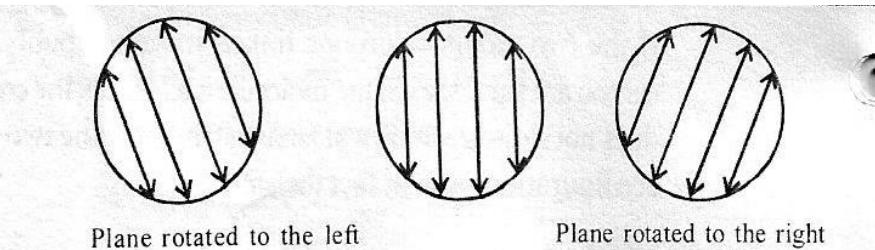
Conformational analysis: (conformations of n-butane)

Introduction:

Optical activity :

- (i) Plane polarised light can be obtained by passing ordinary light through Nicol prism.

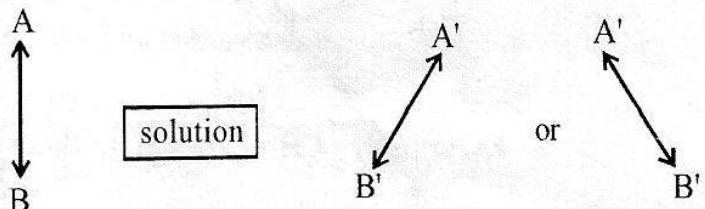




Plane rotated to the left

Plane rotated to the right

- (ii) When certain organic compounds in their solutions are placed in the path of a plane polarized light, they show the remarkable property of rotating its plane through a certain angle which may be either to the left or to the right. If the polarized light has its vibrations in the plane AB before entering such a solution, the direction on leaving it will be changed to say A' or B', the plane have been rotated through the angle as in the (fig.).



- (iii) This property of a substance of rotating the plane polarized light is called optical activity and the substance possessing it is said to be optically active.

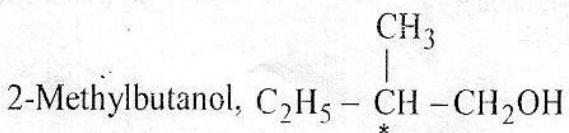
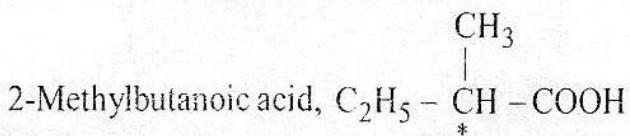
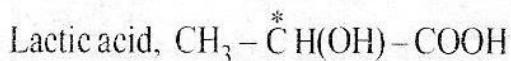
- (A) The observed rotation of the plane of polarised light produced by a solution depends on
- Nature of the substance
 - Solvent used
 - Concentration of solution
 - Length of polarimeter tube
 - Temperature of the experiment (t).
 - Wavelength of the incident light used (λ).

For the measurement of optical rotations, a term specific rotation is introduced.

- (i) Specific rotation is a physical constant characteristic of a substance as much as the melting point, boiling point, density or its refractive index.

• **Definition and examples of optical isomerism :**

The simple organic compounds which show optical activity are :



All these substances are known to exist in two forms.

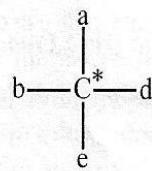
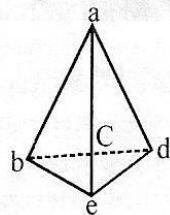
- (i) One rotating the plane of polarised light to the left. This form is named as laevorotatory.
(Latin, *laevo* = left) or direction (-) form
- (2) One rotating the plane of polarized light exactly to the same extent but to the right is named dextrorotatory (Latin, *dexter* - right) or direction (+) – form.
- (3) An inactive form which does not rotate the plane of polarized light at all. This is a mixture of equal amounts of (+) and (-) — forms and hence it is **optically inactive**.
It is named (\pm) - mixture or racemic mixture.
(Latin, racemic - mixture of equal compounds)

Note : Thus three lactic acids are known, they are :

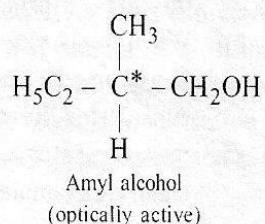
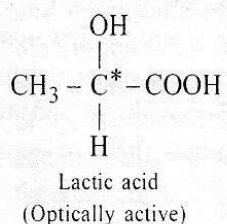
(a) (+) - lactic acid, **(b)** (-) - lactic acid and **(c)** (\pm) mixture, since (\pm) acid is simply a mixture of (+) - and (-) forms, in reality, lactic acid exists in two forms.

- (a) These two acids are exactly identical in physical and chemical properties but differ in their action on the plane polarized light as they have different sign of specific rotation.
- (b) Such forms of the same compound which differ only in their optical properties are called **optical isomers** and phenomenon is termed **optical isomerism**.

Asymmetric carbon atom :



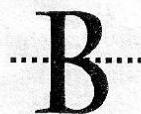
- (i) A carbon atom is described as being asymmetric when four different atoms or groups are bonded to it. An asymmetric carbon in formulas is usually indicated by an asterisk (*) placed on it.
- (ii) All organic compounds containing one asymmetric carbon atom (lactic acid, amyl alcohol etc.) are optically active.



Elements of Symmetry :

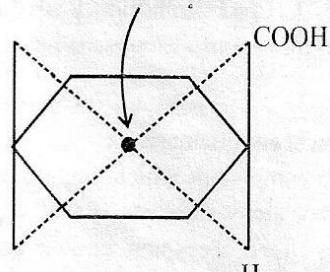
A molecule as a whole is asymmetric, if it does not possess any element of symmetry such as

- (i) Plane of symmetry (ii) Centre of symmetry
- (i) **Plane of symmetry or mirror plane :** An imaginary plane which bisects a molecule in such a way that one half of the molecule is exactly the mirror image of the other half.



- (ii) **Centre of symmetry :** An imaginary point in a molecule which divides the structure of molecule into two identical parts.

Centre of symmetry



trans-Cyclohexane-1, 4-dicarboxylic acid

Symmetrical molecule is always optically inactive.

Chirality :

This term has been recently used to describe such molecules which have no element of symmetry, thus asymmetric molecules are also called chiral molecules and optical activity is attributed to certain chiral centres in them. An asymmetric carbon is a chiral centre.

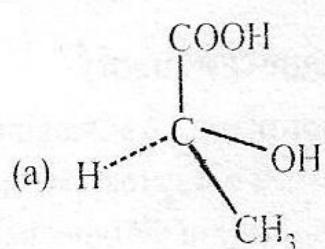
An asymmetric object cannot be superimposed on its mirror image.

Note : Chirality is lost when the two atoms bonded to an asymmetric carbon become similar, thus while lactic acid is optically active, while propionic acid is not.

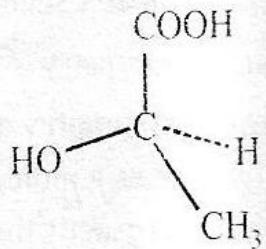
Chirality or molecular dissymmetry (Cause of Optical Isomerism):

- (i) The necessary condition for a molecule to exhibit optical isomerism is dissymmetry or chirality.
- (ii) Thus all organic compounds which contain asymmetric carbon ($C^* abde$) are chiral and exist in two tetrahedral forms.
- (iii) Although the two forms (I and II) have the same structure, they have different arrangements of groups a , b , d and e about the asymmetric carbon, in fact, they represent asymmetric molecules. They do not have a plane of symmetry, they are related to each other as an object to its mirror image and are non-superimposable.
- (iv) The two models or structures (I and II) actually stand for dextro or (+) and laevo or (-) isomers. Since they are related to each other as mirror images, they are commonly called **enantiomorphs** (Gr, enantio = opposite, morph - form) or **enantiomers**. Thus optical isomerism is now often referred to as an **enatiomerism**.
- (v) Optical isomers or enantiomers due to the presence of an asymmetric carbon atom in a compound differ only in the arrangement or configuration of groups of tetrahedral perspective.

(vi) Examples of compounds which exist as (+) and (-) enantiomers.

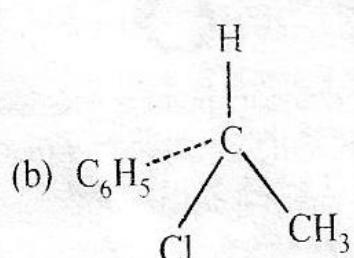


(I)

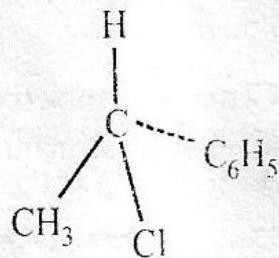


(II)

∴ (+) and (-) Lactic acid



(I)

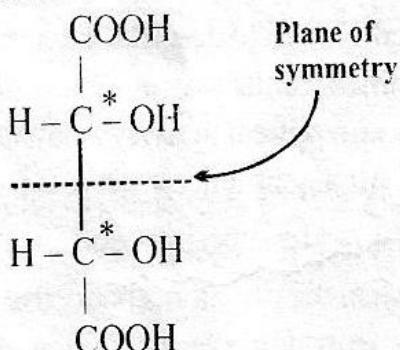


(II)

(+) and (-) -1-Chloro-1-phenylethane

Criterion of enantiomerism :

- The compounds which contain one or more asymmetric carbon atoms show enantiomerism.
- But there are some known compounds which have asymmetric carbon but due to presence of plane of symmetry do not show enantiomerism.
- meso*-Tartaric acid has two asymmetric carbons but is optically inactive.



meso-Tartaric acid

R, S – Configuration (Absolute Configuration)

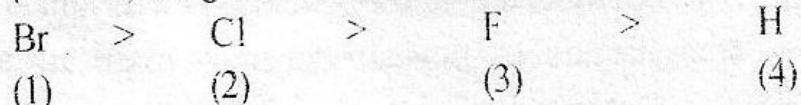
- (a) This is a newer and more systematic method of specifying absolute configuration of optically active compounds. This totally depends on sequence rule or CIP-system (sequence rule proposed by R.S. Cahn, C.K. Ingold and V.Prelog).
- (b) This system of designating configuration has been used increasingly since the early 1960's and may eventually replace the D, L-system.
- (c) In this system, the configuration of a stereoisomer is designated by using prefix R derived from Greek word rectus (means-right) and S derived from Greek word sinister (means-left). The procedure involves two main steps as described below.

Step 1 : Rank the groups (or atoms) which are bonded to the chirality centre in order of priority. The criterion of priority is based on certain set of rules known as sequence rules or Cahn-Ingold-Prelog (CIP) priority rules given as under.

The sequence rules or CIP-Priority rules :

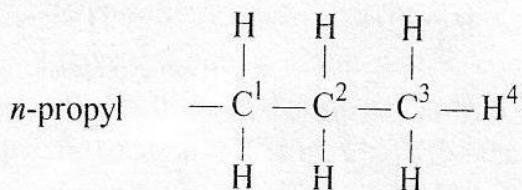
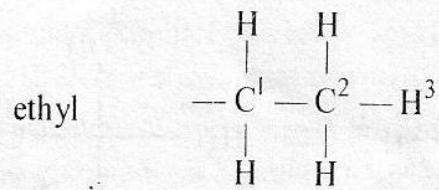
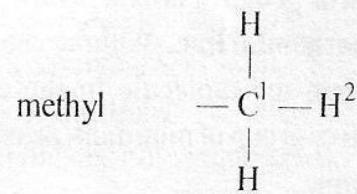
- (i) The atoms or groups directly bonded to the asymmetric carbon are arranged in order of decreasing atomic number and assigned priority 1, 2, 3, 4, accordingly.

Thus in chlorobromofluoromethane (CHClBrF), the substituent Br (at no = 35), Cl (at no = 17), F (at no = 9) and H (at no 1) are given the order of priorities as :



- (ii) When two or more groups have identical first atoms attached to asymmetric carbon, the priority order is determined by considering the atomic numbers of the second atoms; and if the second atoms are also identical, the third atoms along the chain are examined.

Let us consider the three groups

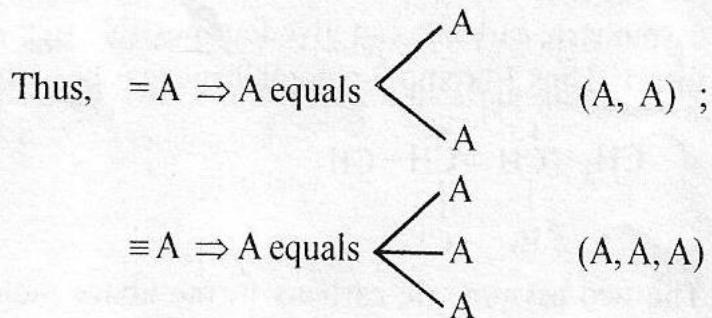


In methyl and ethyl, the first atom is carbon and therefore, atomic numbers of the second atoms H (at no 1) and C (at no 6) decide the priority order, ethyl > methyl. While considering ethyl and *n*-propyl the second atom is also identical (carbon) and hence the third atoms (H, C) give the priority order *n*-propyl > ethyl.

- (iii) If the first atoms of the two groups have same substituents of higher atomic number, the one with more substituents takes priority.

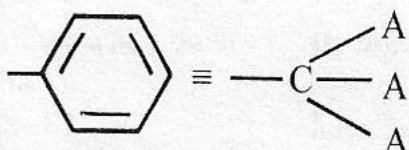
Thus —CHCl₂ has a higher priority than —CH₂Cl

- (iv) A doubly or triply bonded atom 'A' present in a group appended to asymmetric carbon, is considered equivalent to two or three singly bonded 'A' s, respectively.



Hence between groups $-C=O(O, O, H)$ and

$-CH_2OH(O, H, H)$, the former will have higher priority. A phenyl group is handled as if it had one of the Kekule structures.



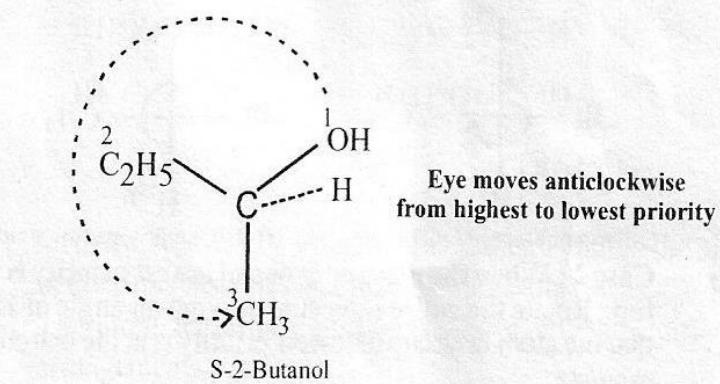
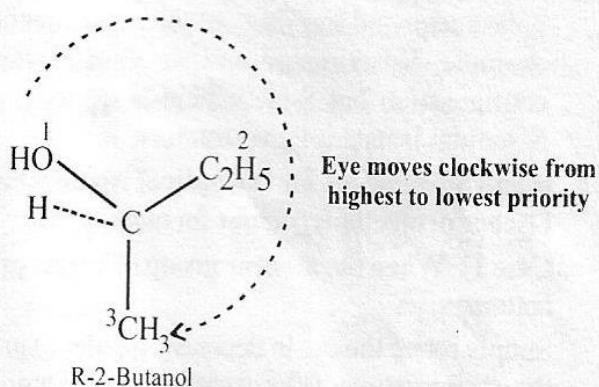
Note : It may be noted that R and S system is merely a nomenclature device and has nothing to do with the sign and magnitude of optical activity. Thus the complete description of an optically active compound must include both the direction of rotation (+ or -) and the configuration of the compound (R or S). A racemic modification is an equimolecular mixture of the two enantiomers and is given the prefix (RS).

Step 2. After deciding the priorities of atoms or groups around the chirality centre, the molecule is visualised in such a way that atom or group with lowest priority is directed away from the eye. Now, observe the remaining atoms or groups in decreasing order of priorities, i.e., from 1 to 2 to 3. In doing so, if movement of eye occurs in clockwise direction the configuration is specified as R. On the other hand, if eye moves in anticlockwise direction, the configuration is specified as S.

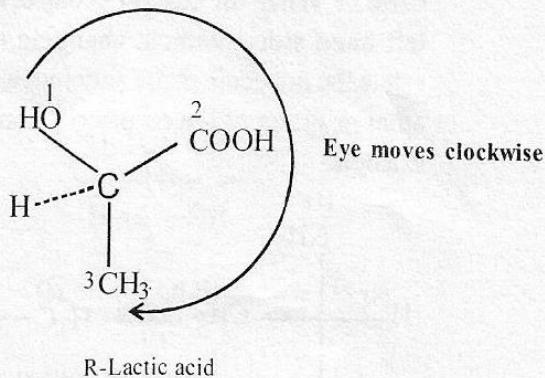
Let us now use step 1 and step 2 to specify the configurations of enantiomers of (i) 2-butanol and (ii) lactic acid.

- (i) 2-Butanol ($\text{CH}_3-\overset{*}{\text{CH}}-\text{C}_2\text{H}_5$). The sequence of priority of
- $$\begin{array}{c} * \\ | \\ \text{OH} \end{array}$$

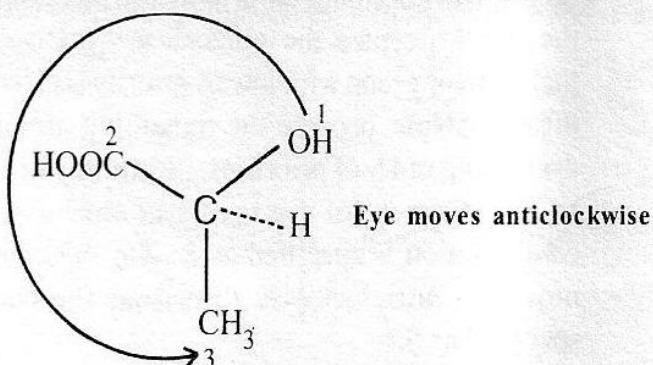
groups around the chirality centre is OH(1), C_2H_5 (2), CH_3 (3), H(4). Visualising the enantiomeric forms with H directed away from the eye.



(ii) Lactic acid ($\text{CH}_3-\overset{*}{\text{CH}}-\text{COOH}$). The sequence of priority of groups around the chirality centre is $\text{OH}(1)$, $\text{COOH}(2)$, $\text{CH}_3(3)$, $\text{H}(4)$. Visualising the formulae with H directed away from eye.



Eye moves clockwise



Eye moves anticlockwise

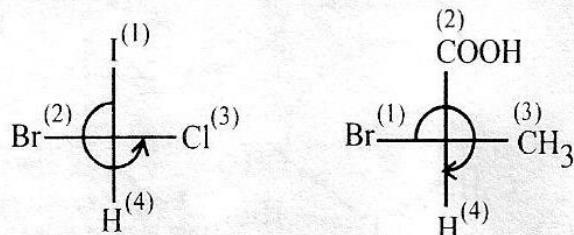
.. S-Lactic acid

It may be noted that the knowledge of R and S configuration does not tell us the direction in which the compound rotates the plane of polarised light because some compounds with R-configuration rotate the plane towards right whereas some compounds with R-configuration rotate the plane towards left. This implies that movement of eye towards left or right has no relationship with rotation of plane of polarised light towards left or right. The dextro or laevo rotatory nature of the compound can be judged by putting the compound in polarimeter and carrying out the experimental studies. For example, S-lactic acid and S-sodium lactate have same configuration but S-lactic acid is dextrorotatory whereas S-sodium lactate is laevo-rotatory.

R and S Notations for the optical isomers represented by Fischer projections (planar formulae).

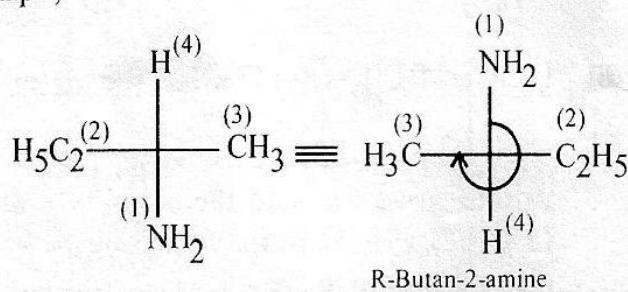
Case 1 : When the atom or group of lowest priority is at the bottom :

Simply rotate the eye in decreasing order of priority and find the configuration of chiral carbon. For example,



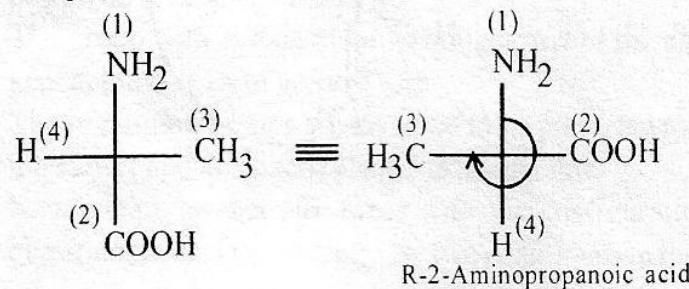
S-Bromochloroiodomethane R-2-Bromopropanoic acid

Case 2 : When the atom or group of lowest priority is at the top. Rotate the entire molecule through an angle of 180° so that the atom or group of lowest priority is at the bottom. For example,

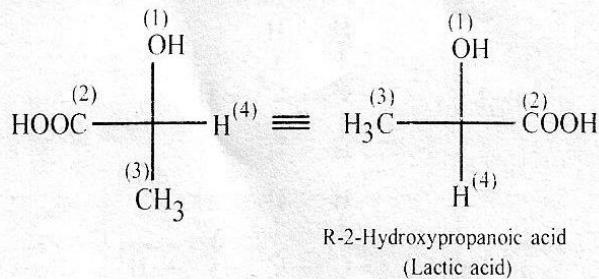


R-Butan-2-amine

Case 3 : When the atom or group of lowest priority is on the left hand side. Without changing the position at the top, rotate the molecule in the anticlockwise direction so that the atom or group of lowest priority comes to the bottom. For example,



Case 4 : When the atom or group of lowest priority is on the right hand side of the horizontal line. Without changing the position at the top, rotate the molecule in the clockwise direction so that the atom or group of minimum priority comes to the bottom. For example,



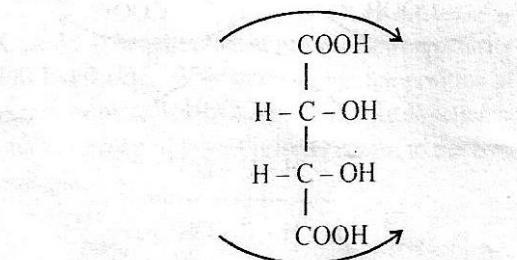
 **Note :**

R and S configurations of the stereoisomers are not linked with their dextro (+) and laevo (-) nature. This means that the stereoisomer with notation R need not be dextro and the isomer with notation S need not be laevo. However, one of them is dextro while the other is laevo.

External and internal compensation

- (i) If equimolar amounts of *d*-and *l*-isomers are mixed in a solvent, the solution is inactive.
The rotation of each isomer is balanced or compensated by the equal but opposite rotation of the other. Optical inactivity having this origin is described as due to **external compensation**. Such mixtures of (+) and (-) isomers (**racemic mixture**) can be separated into the active components.

- (ii) In *meso*-tartaric acid, the inactivity is due to effects within the molecule and not external. The force of rotation due to one half of the molecule is balanced by the opposite and equal force due to the other half. The optical inactivity so produced is said to be due to **internal compensation**. It occurs whenever a compound containing two or more chiral carbon atoms has plane or point of symmetry. Since the optical inactivity of such a compound arises within the molecule, the question of **separating into active components does not arise**.



Inactivity of *meso*-tartaric acid by internal compensation

Conformation

- (i) Molecules which differ from one another, only by rotation about carbon–carbon single bond.
- (ii) For example, in ethane ($\text{H}_3\text{C}-\text{CH}_3$), if one CH_3 group is kept constant and other CH_3 group is rotated through C – C bond axis, an infinite no. of atomic arrangements are possible, which are called conformations.

(iii) Structure of conformers including bond length & bond angle in same configuration is also same.

(iv) Configuration is also same.

(v) Conformers cannot be separated, so they are not isomers, they are only different forms of the same molecule.

Ethane is the best example of conformational isomerism. In ethane molecule, there is free rotation around the carbon–carbon single bond. The two orientations are :

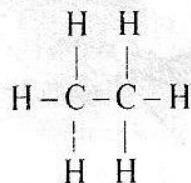
(a) **Eclipsed conformation** : In this orientation, hydrogen atoms of one carbon are exactly eclipsing the hydrogen atoms on the other. There is minimum distance between the various hydrogen atoms. The eclipsed form has greater energy content due to maximum repulsive interactions (less stable).

(b) **Staggered conformation** : In this orientation, the hydrogen atoms of one carbon are at maximum possible distance from one another. The staggered form has less energy content due to minimum repulsive interaction (more stable).

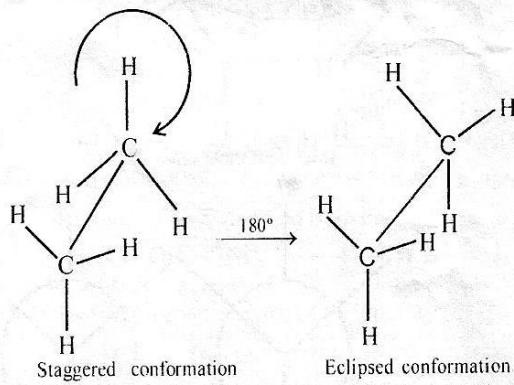
$$E_{\text{ec.}} - E_{\text{st.}} = 3 \text{ kcal/mole}$$

The two forms of ethane are rapidly interconvertible at room temperature and are thus not separable.

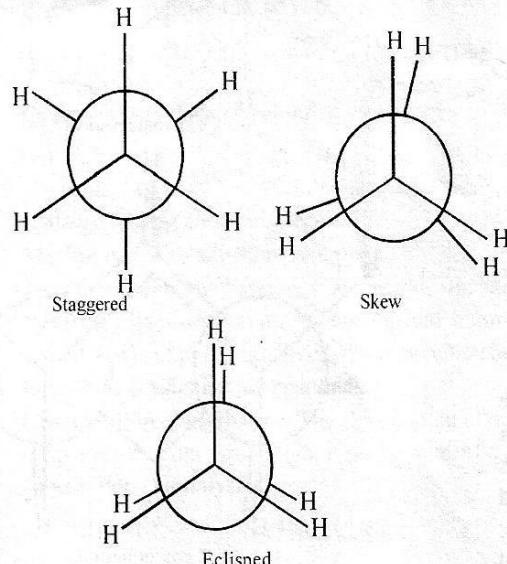
Conformers of ethane :



(i) Sawhorse projection formulae : (3D Presentation)



(ii) Newman projection formulae : (2 D Presentation)

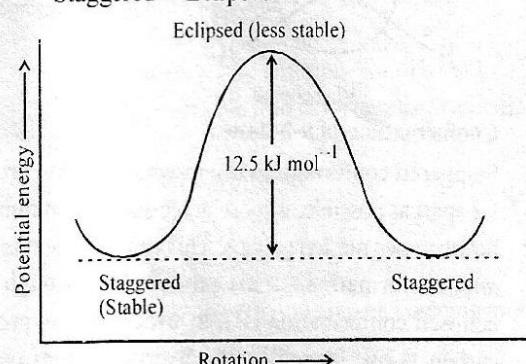


Note : (a) It may be noted that one conformation of ethane

can be converted into other by the rotation of 60° about the bond. The infinite number of other possible conformations of ethane lying between the two extremes are called **skew conformations**.

(b) Stability order & energy diagram -

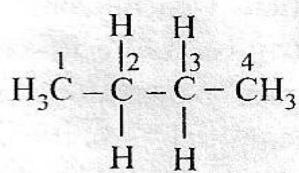
Staggered > Eclipsed



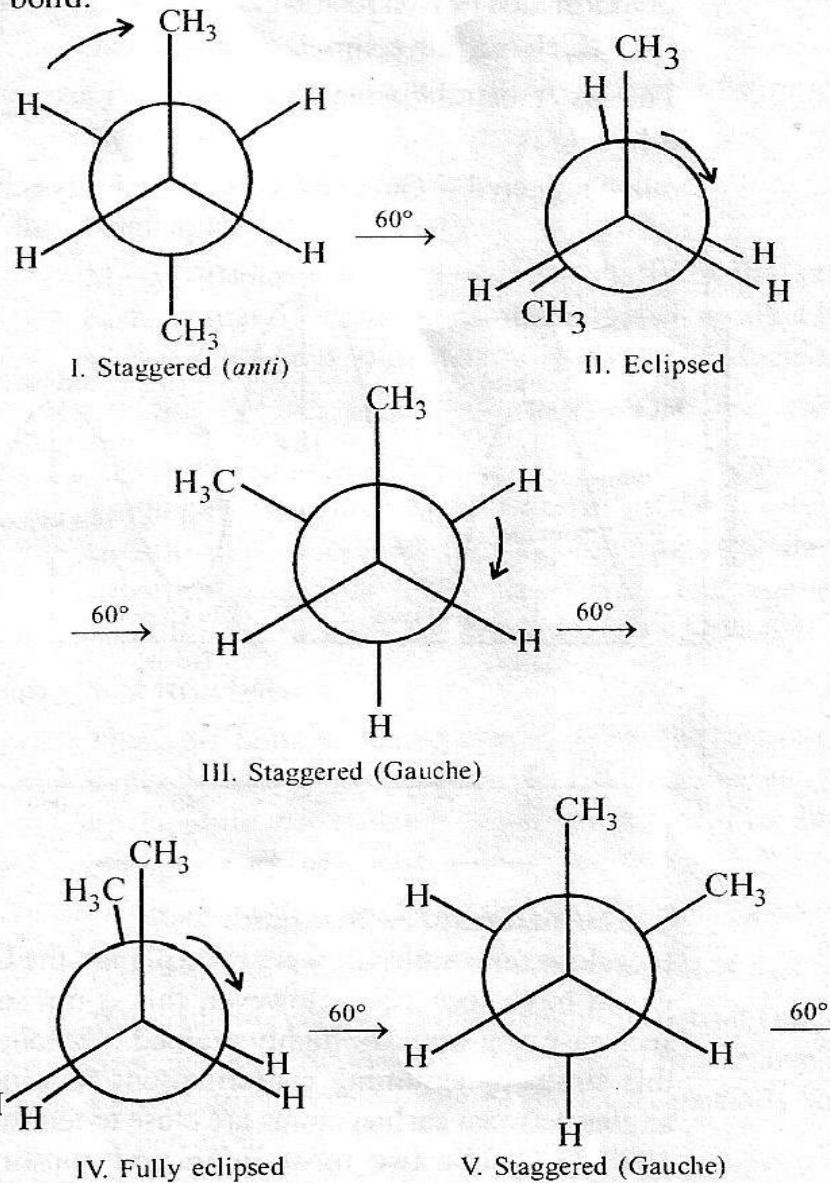
Changes in energy during rotation about C – C bond in ethane.

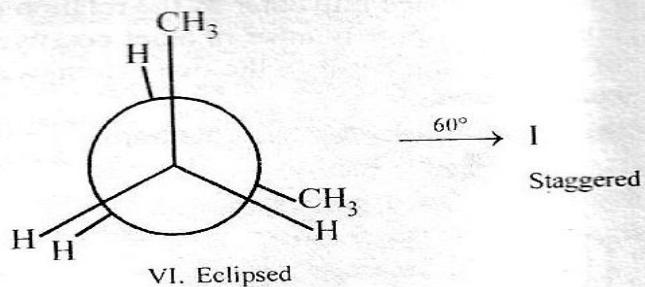
Conformations of *n*-butane :

Butane molecule can be represented as derivative of ethane, as given below.



Although, there are infinite number of conformations, obtained by infinite rotations, six conformations are important, each obtained by rotation of 60° angle around C-2 and C-3 bond.



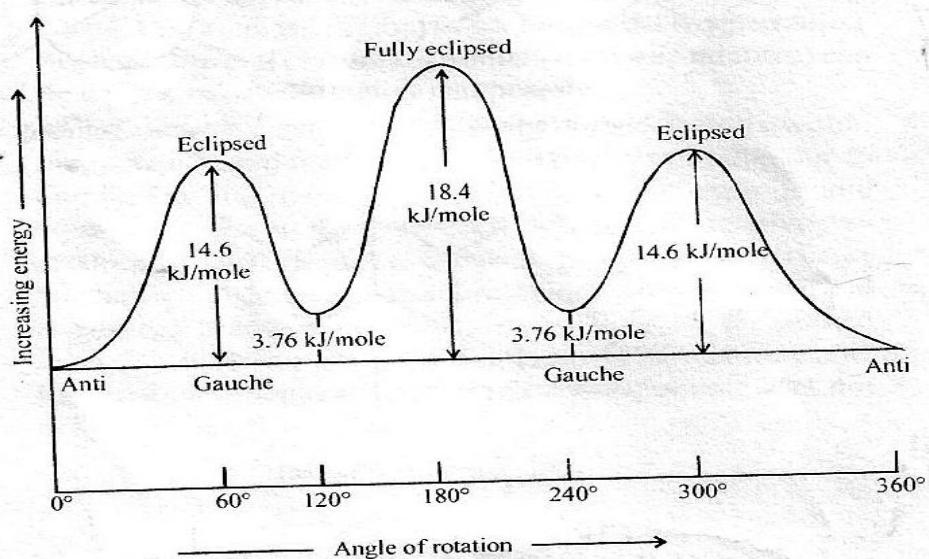


Conformations of *n*-butane :

Staggered conformation (I), in which methyl groups are as far apart as possible, is most stable due to minimum repulsion between two methyl groups. This conformation is also called *anti* conformation. This on rotation through 60° gives eclipsed conformation (II), in which methyl group on one carbon is overlapped by the hydrogen atom on the other carbon. Further rotation through 60° gives another staggered conformation (III) in which methyl groups on two carbons are 60° apart. This conformation is also called *gauche* conformation. Gauche conformation on further rotation through 60° gives fully eclipsed conformation (IV) in which methyl groups on two carbons are just opposite to each other (overlap completely). In this conformation steric strain is maximum hence this conformation is most unstable. Further rotation through 60° gives again gauche conformation (V) which is mirror image of gauche conformation (III). Conformation (V), on rotation through 60° gives conformation (VI) which is again eclipsed conformation.

The order of relative stabilities of various conformers of *n*-butane is

anti-Staggered > Gauche > Eclipsed > Fully eclipsed



S-3: Introduction to reactions involving substitution (brief account on nucleophilic and electrophilic substitution reactions with example of each, mechanism for SN1 and SN2)

Addition reactions: (brief account on nucleophilic, electrophilic and free radical addition reactions with example of each, mechanism for free radical addition reaction)

TYPES OF ORGANIC REACTIONS

The reactions of organic compounds can be classified into four main types.

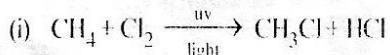
- (1) Substitution or displacement reactions
- (2) Addition reactions
- (3) Elimination reactions
- (4) Rearrangement reactions

1. Substitution or Displacement Reactions :

Substitution or displacement reactions are those reactions in which an atom or group of atoms attached to a carbon atom in a substrate molecule is replaced by another atom or group of atoms.

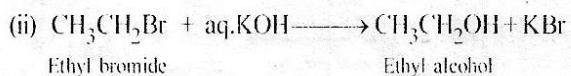
- (a) Free radical substitution reactions
- (b) Nucleophilic substitution reactions
- (c) Electrophilic substitution reactions

Some of the examples of substitution reactions are :



Methane

Hydrogen atom is replaced by chlorine



Ethyl bromide

Ethyl alcohol

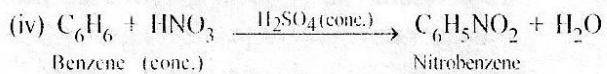
Bromine atom is replaced by hydroxyl group



Methyl alcohol

Methyl bromide

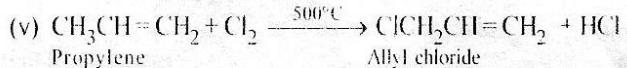
Hydroxyl group is replaced by bromine



Benzene (cone.)

Nitrobenzene

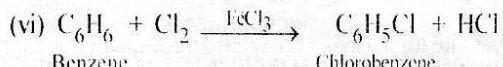
Hydrogen is replaced by NO_2 group



Propylene

Allyl chloride

Hydrogen is replaced by chlorine



Benzene

Chlorobenzene

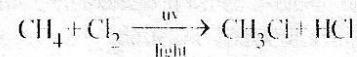
Hydrogen is replaced by chlorine

Mechanism of substitution reactions :

These reactions may follow free radical, nucleophilic or electrophilic mechanism. Some typical examples are considered to explain the three types of mechanism.

(a) Free radical substitution reactions :

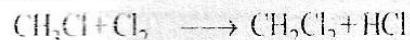
Chlorination of methane : The chlorination of methane in the presence of ultraviolet light is an example of free radical substitution (**homolysis**).



Methane

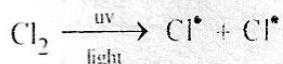
Methyl chloride

The reaction does not stop with the formation of methyl chloride (CH_3Cl) but the remaining hydrogen atoms are replaced one by one with chlorine atoms to give rise to chain reaction.



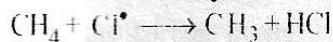
Mechanism : The reaction is initiated by the breaking of chlorine molecule into chlorine-free radicals in presence of UV light.

I Step : Chain initiation

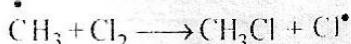


II Step : Chain propagation

The chlorine free radical attacks methane molecule.

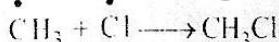
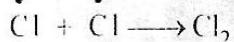


Each of the methyl free radical, in turn, reacts with chlorine molecule to form methyl chloride and at the same time chlorine free radical is produced.



III Step : Chain termination

The chain of reactions initiated and propagated as shown above may be terminated if free radicals combine amongst themselves without giving rise to any new radicals.

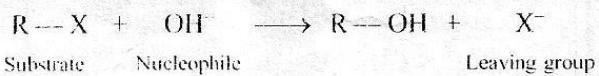


Reactivity of the halogen for free radical substitution is in the order :



(b) Nucleophilic substitution :

Many substitution reactions, especially at the saturated carbon atom in aliphatic compounds such as alkyl halides are brought about by nucleophilic reagent or nucleophiles.



Such substitution reactions are called nucleophilic substitution reactions, i.e., S_N reactions (S stands for substitution and N for nucleophile). The nucleophilic substitution reactions are divided into two classes.

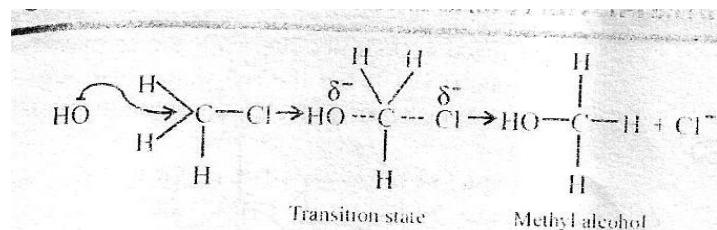
(i) S_N2 Reactions :

These are bimolecular reactions. When the rate of reaction depends on the concentration of both substrate and the nucleophile, the reaction is said to be S_N2 , i.e., 2nd order change.

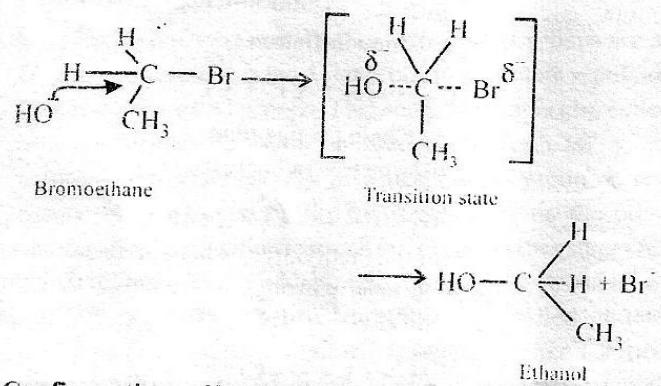
$$\text{Rate} \propto [\text{Substrate}] [\text{Nucleophile}]$$

Hydrolysis of methyl chloride is an example of S_N2 reaction

When methyl chloride is attacked by OH^- , strong nucleophile from the opposite side of the chlorine atom, a transition state (TS) results in which both OH and Cl are partially bonded to carbon atom.



When bromoethane is allowed to react with sodium hydroxide under conditions where second order kinetics are followed, ethanol is obtained.



Configuration : Hence, an S_N2 reaction proceeds with complete stereochemical inversion. This is also known Walden inversion.

Relative reactivity towards S_N2 reaction:

Methyl > ethyl > isopropyl > ter-butyl > allyl > benzyl halides

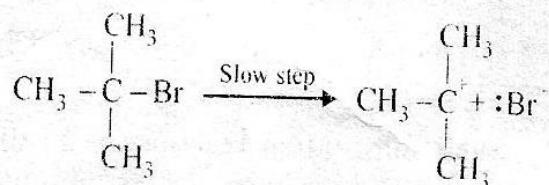
Nucleophilic Substitution Reactions

(ii) **S_N1 Reactions :** S_N1 stands for unimolecular reaction. When the rate of nucleophilic substitution reaction depends only on the concentration of the substrate, the reaction is of first order and is represented as S_N1 .

$$\text{Rate} \propto [\text{Substrate}]$$

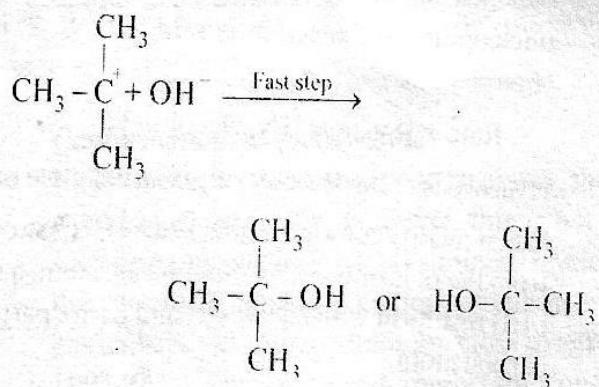
The hydrolysis of *tert*-butyl bromide is an example of S_N1 reaction. The reaction consists of two steps.

Step 1. The substrate undergoes heterolytic fission forming a carbocation. This is a slow process and rate determining step.



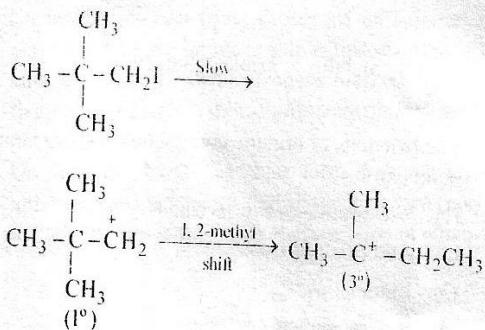
The carbocation is planar as the central positively charged carbon atom is sp^2 – hybridized.

Step 2. The nucleophile (OH^-) can attack the planar carbocation ion from either side to form *tert*-butyl alcohol and the low concentration of OH^- favours S_N1 reaction.

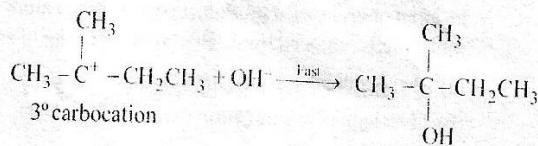


In another example, the carbocation formed (in Step I) can undergo rearrangement to give more stable carbocation.

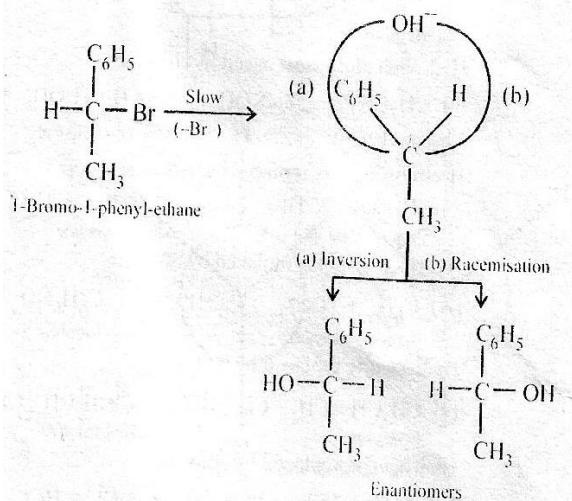
Step 1.



Step 2.

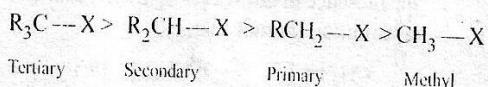


As a result of $\text{S}_{\text{N}}1$ reaction, there can be racemization and inversion. In other words, $\text{S}_{\text{N}}1$ reactions involve racemization plus inversion.



The nucleophilic reagent attacks both the back side and the front side of the carbocation. Back side attack predominates. The two enantiomers constitute the racemic modification. Thus, in $\text{S}_{\text{N}}1$ reaction, racemization as well as inversion is observed, while in case of $\text{S}_{\text{N}}2$ complete inversion takes place (where chiral carbon exists).

$\text{S}_{\text{N}}1$ reaction is favoured by heavy (bulky) groups on the carbon atom attached to halogens; i.e.,

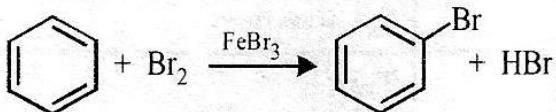


Distinction between S _N 2 Reactions and S _N 1 Reactions			
S. No.	Factors	S _N 2 Reactions	S _N 1 Reactions
1.	Number of steps	One : $R : L + : Nu^- \longrightarrow R : Nu + : L^-$	Two: (i) $R : L \xrightarrow{\text{Slow}} R^+ + : L^-$ (ii) $R^+ + : Nu^- \xrightarrow{\text{Fast}} R : Nu$
2.	Reaction rate and order	Second order : Rate \propto [Substrate][Attacking species] Rate = $K[RL][: Nu^-]$	First order : Rate \propto [Substrate] or Rate = $K[RL]$
3.	Molecularity	Bimolecular	Unimolecular
4.	Reacting nucleophile	The nucleophile attacks the carbon of the substrate exclusively from the back side.	The nucleophile can attack the carbon of the substrate both on the back and front sides, although the back side attack predominates.
5.	Stereochemistry	Complete inversion of configuration takes place.	Racemisation takes place.
6.	Reactivity order of alkyl halides	Methyl > 1° > 2° > 3° halides	3° > 2° > 1° > methyl halides
7.	Reaction rate determining factor	By steric hindrance.	By electronic factor (stability of R ⁺).
8.	Catalysis	Not catalysed by any catalyst (phase transfer).	Catalysed by Lewis and Bronsted acids, e.g., Ag ⁺ , AlCl ₃ , ZnCl ₂ and strong HA.

(C) Electrophilic substitution :

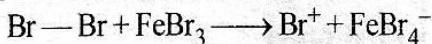
Electrophilic substitution involves the attack by an electrophile. It is represented as S_E (S stands for substitution and E stands for electrophile). If the order of reaction is 1, it is written as S_E1 (unimolecular) and if the order is 2, it is S_E2 (bimolecular).

Ex. : The bromination of benzene in the presence of FeBr_3 is an example of electrophilic substitution.

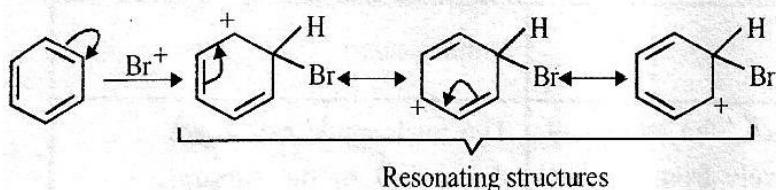


Mechanism :

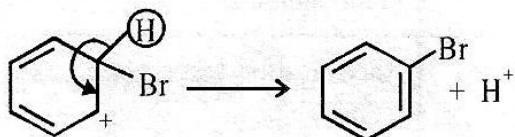
Step 1. Formation of electrophile.



Step 2. The electrophile (Br^+) attacks the benzene ring to form a resonance stabilized carbocation.

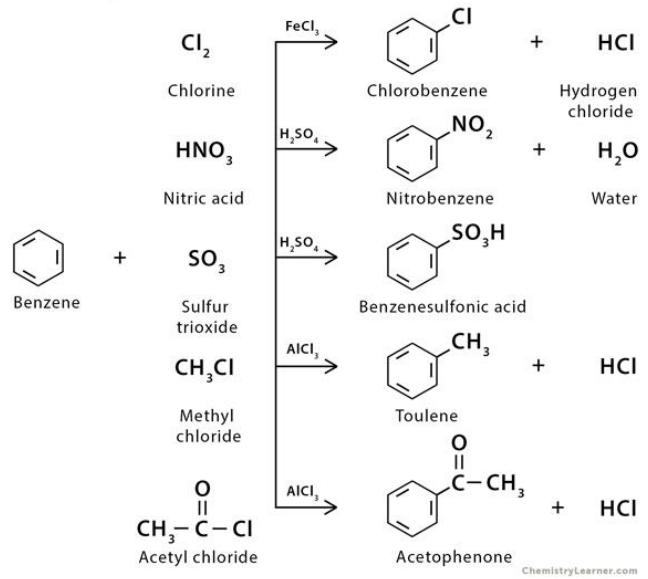


Step 3. Elimination of proton occurs and the substitution product is formed.



Similarly, nitration, sulphonation and Friedel–Crafts reaction etc., in benzene nucleus are other examples of electrophilic substitution.

Electrophilic Aromatic Substitution of Benzene



ChemistryLearner.com

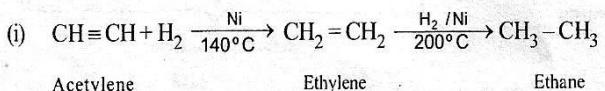
(2) Addition Reactions :

Addition reactions are those in which the attacking reagent adds up to the substrate molecule. Such reactions are given by those compounds which possess double or triple bonds. In the process, a triple bond may be converted into double bond or single bonds and a double bond is converted into single bonds. For each π -bond of the molecule two sigma bonds are formed and the hybridization state of carbon atoms changes from sp to sp^2 and sp^2 to sp^3 .

Like substitution reactions, addition reactions are also of three types.

- (a) Electrophilic addition reactions
- (b) Nucleophilic addition reactions
- (c) Free radical addition reactions

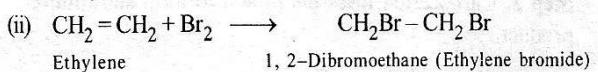
Some of the examples of addition reactions are :



Acetylene

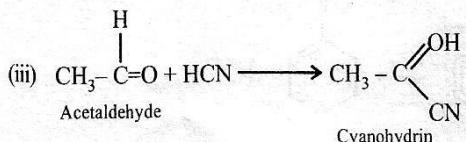
Ethylene

Ethane

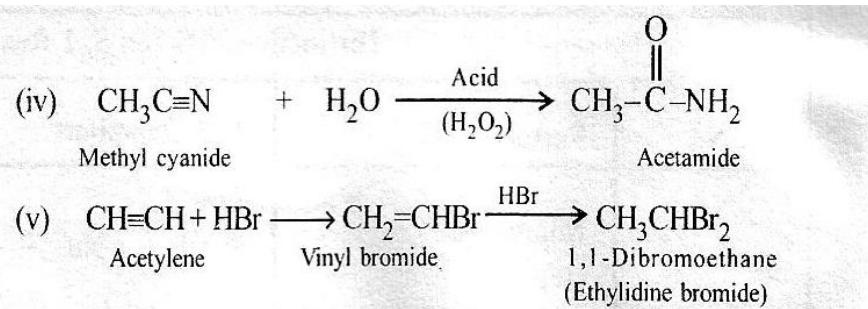


Ethylene

1, 2-Dibromoethane (Ethylene bromide)



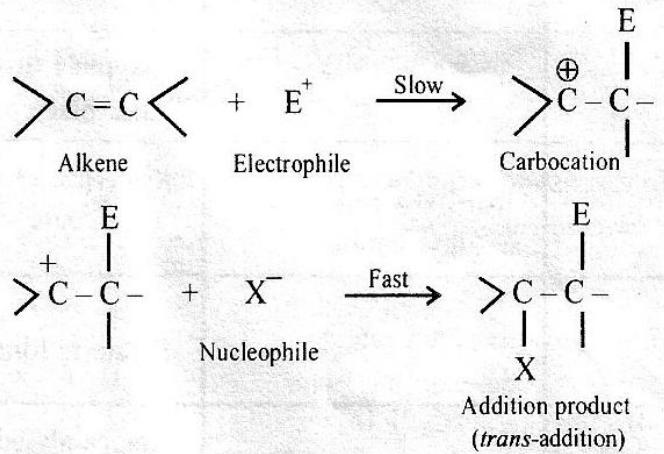
Cyanohydrin



Mechanism of addition reactions :

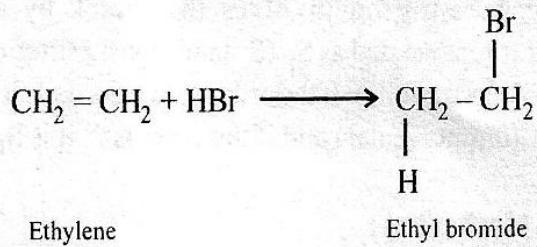
The addition reactions are the reactions of the double or triple bonds. These reactions may be initiated by electrophiles, nucleophiles or free radicals. The molecules having $>\text{C}=\text{C}<$ or $-\text{C}\equiv\text{C}-$ are readily attacked by electrophilic reagents, while molecules having $>\text{C}=\text{O}$ or $-\text{C}\equiv\text{N}$ are readily attacked by nucleophilic reagents.

- (a) **Electrophilic addition reactions :** In electrophilic addition reactions, an electrophile approaches the double or triple bond and in the first step forms a covalent bond with one of the carbon atoms resulting in the formation of carbocation which then takes up a nucleophile to form addition product.



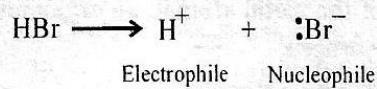
Polar molecule attacks the double bond of alkene, then π electron of double bond shifts to one of carbon atoms due to electromeric effect.

The addition of HBr on ethylene is an example of electrophilic addition. Ethylene is a symmetrical olefin.

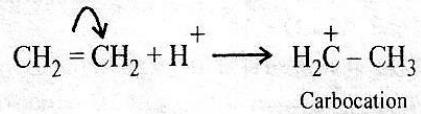


Mechanism:

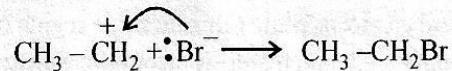
Step 1. Hydrogen bromide gives a proton and bromide ion.



Step 2. The electrophile attacks the double bond to form a carbocation.



Step 3. The nucleophile (Br^- ion) now attacks the carbocation to form the addition product.



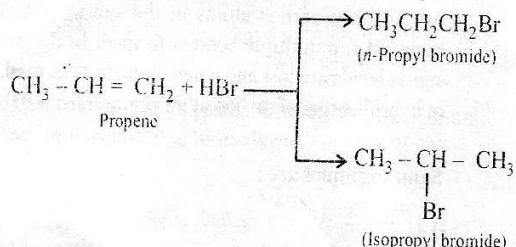
This clearly indicates that the reaction proceeds in two steps:

- (a) Formation of carbocation (more stable) and
- (b) Attack of nucleophile on the carbocation.

Stability of carbocation is in order :

Benzyllic $\sim 3^\circ >$ allylic $\sim 2^\circ > 1^\circ >$ methyl

In case, both alkene and the adding reagent are unsymmetrical, two products are expected.

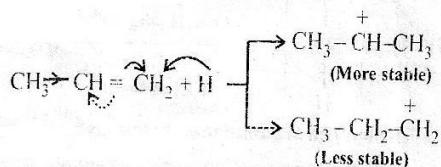


Experimentally, it is observed that isopropyl bromide is the major product. This can be explained on the basis of following mechanism. Consider the addition of HBr to propene which is unsymmetrical in nature.

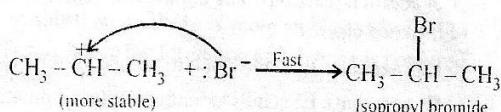
Step 1. Hydrogen bromide gives a proton (H^+) and a bromide ion (Br^-).



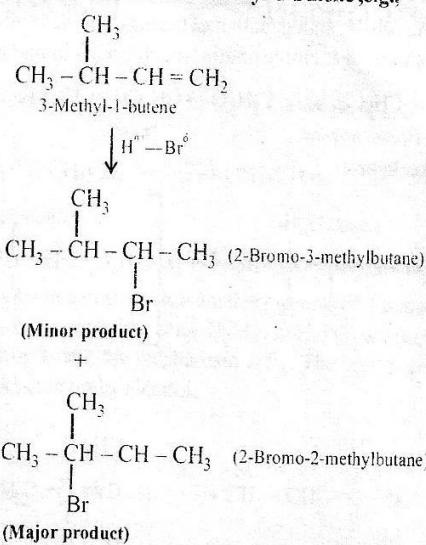
Step 2. The proton (H^+) attacks the π -bond to give a stable carbocation.



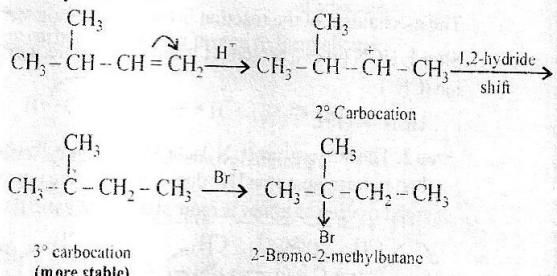
Step 3. The nucleophile bromide ion attacks the more stable carbocation to give isopropyl bromide (**major product**).



Addition of HBr on 3-methyl-1-butene, e.g.,



Formation of 2-bromo-2-methylbutane (**major product**) can be explained on the basis of rearrangement of the less stable 2° carbocation to the more stable 3° carbocation by 1,2-hydride shift.

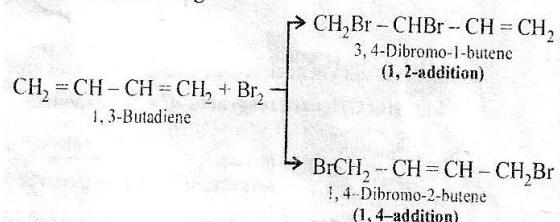


Addition reactions on alkadiene:

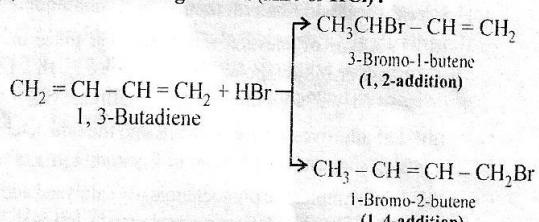
Conjugated alkadienes (1,3-butadiene) reacts with halogens, halogen acids, hydrogen and water, etc. to yield a mixture of 1,2- and 1,4-addition products.

Some of the important examples are :

(i) Addition of halogens :

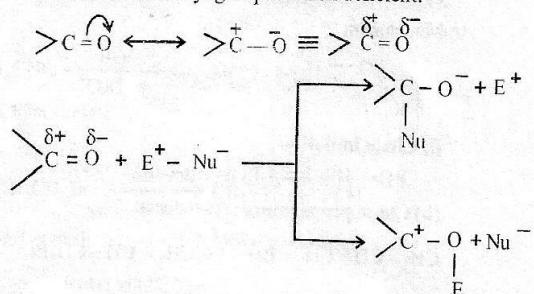


(ii) Addition of halogen acids (HBr or HCl) :

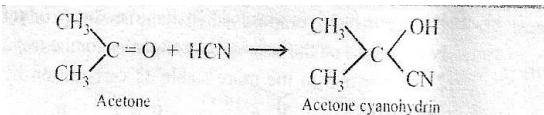


(b) Nucleophilic addition reactions :

When the addition reaction occurs on account of the initial attack of nucleophile, the reaction is said to be a nucleophilic addition reaction. Due to presence of strongly electronegative oxygen atom, the π -electrons of the carbon–oxygen double bond in carbonyl group ($>\text{C}=\text{O}$) get shifted towards the oxygen atom and thereby such bond is highly polarised. This makes carbon atom of the carbonyl group electron deficient.

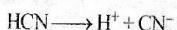


The addition of HCN to acetone ($>\text{C}=\text{O}$ compounds) is an example of nucleophilic addition.

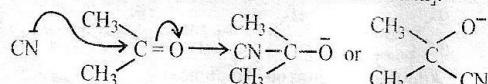


The mechanism of the reaction involves following steps.

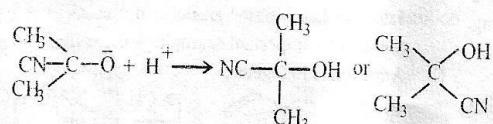
Step 1. HCN gives a proton (H^+) and nucleophile, a cyanide ion (CN^-).



Step 2. The nucleophile (CN^-) attacks the positively charged carbon to form an anion [H^+ does not attack the negatively charged oxygen as anion is more stable than cation].

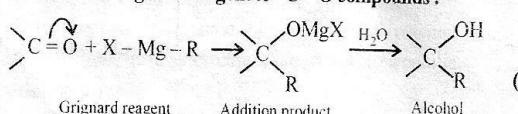


Step 3. The proton (H^+) combines with anion to form the addition product.



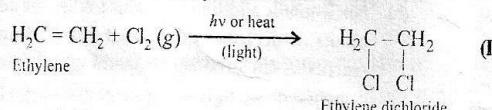
Other examples of nucleophilic addition reactions are :

Addition of Grignard reagent to $>\text{C}=\text{O}$ compounds :

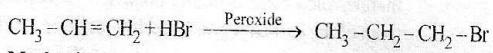


c) **Free radical addition reactions :**

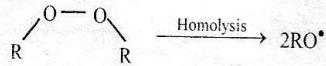
- (i) This type of addition reactions takes place in vapour phase or in non-polar solvents (i.e., Cl_2 , Br_2 , H_2 , CO_2 and CH_4 ... etc.) in presence of sunlight.
- (ii) The additives are free radicals and the rate determining step suggests for addition of free radicals.
- (iii) For example, the photochemically catalysed addition of chlorine to ethylene may be shown as follows.



- (iv) Addition of HBr on unsymmetric alkene in presence of peroxide is as follows.



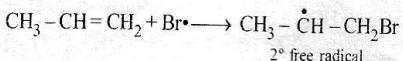
Mechanism :



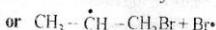
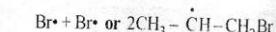
(i) **Chain initiation :**



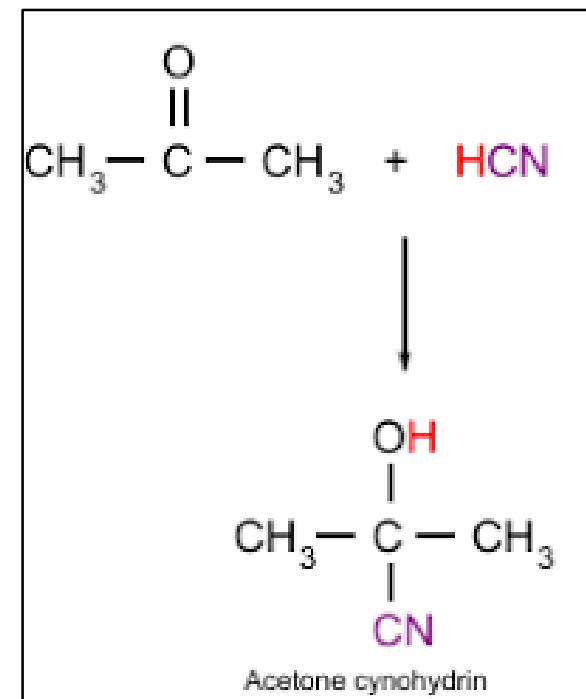
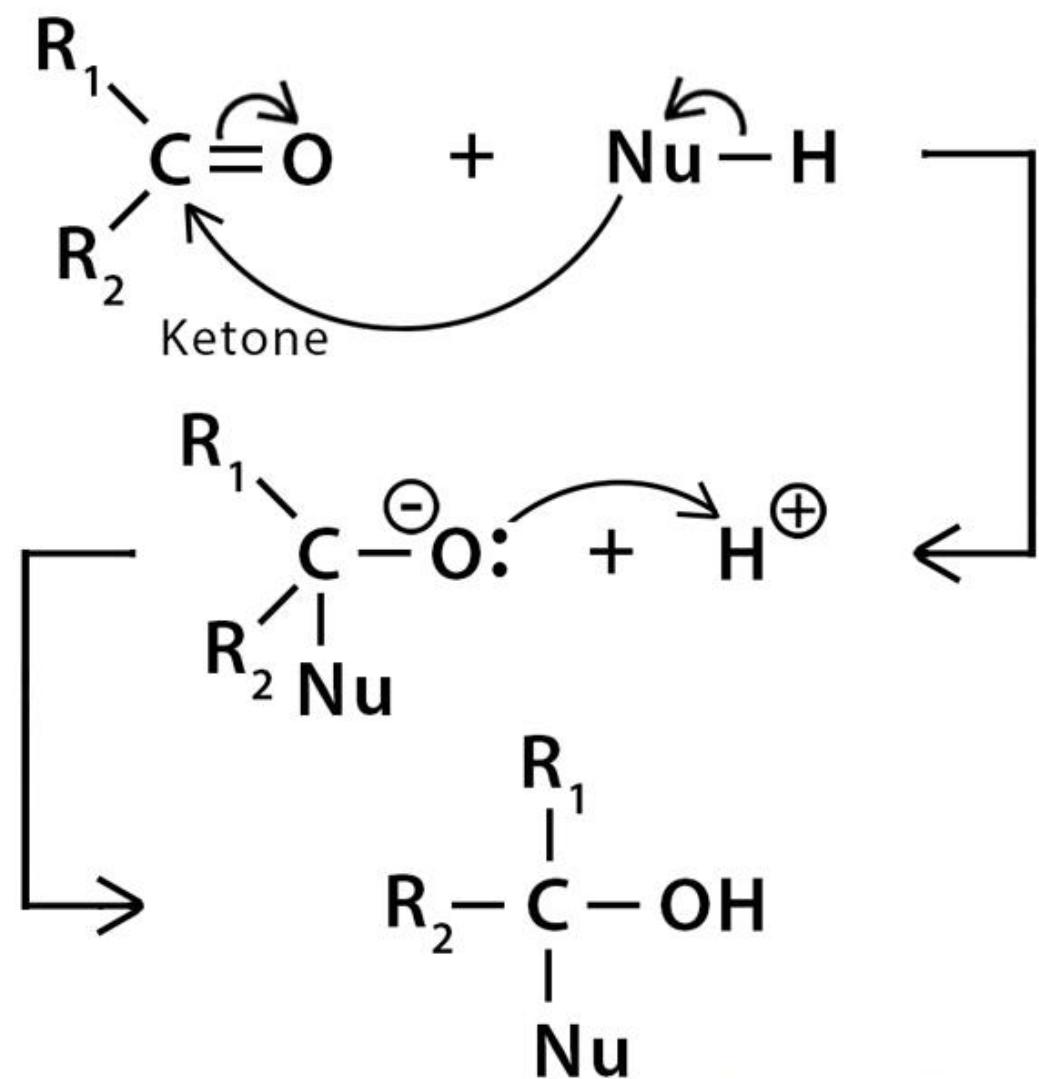
(ii) **Chain propagation : (two steps)**



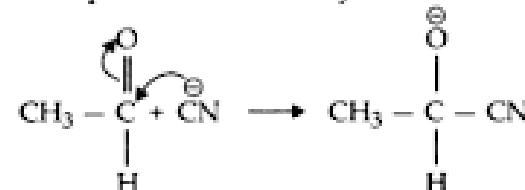
(iii) **Chain termination :**



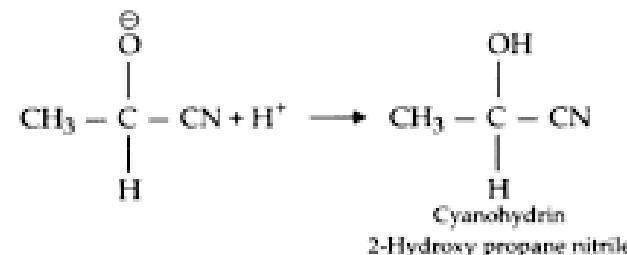
Mechanism of Nucleophilic Addition Reaction



Step I: Attack of nucleophile CN^- on carbonyl carbon.

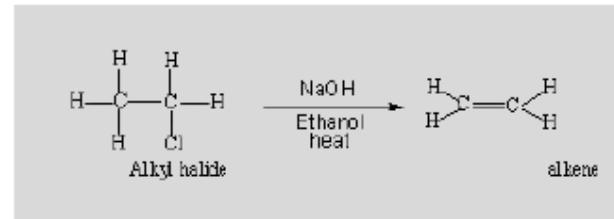


Step II: Addition of H^+



What is Elimination Reaction?

- Elimination reactions are **reverse** of addition reactions.
- It involves **loss of atoms or groups from adjacent carbon atoms** resulting in the formation of a π bond between these carbon atoms.
- Elimination reaction is a type of reaction is mainly **used to transform saturated compounds** (organic compounds which contain single carbon-carbon bonds) **to unsaturated compounds** (compounds which feature double or triple carbon-carbon bonds).
- Besides, it is an important method for the **preparation of alkenes**.



- An elimination reaction is a type of a chemical reaction where several atoms either in pairs or groups are removed from a molecule. The ***removal usually takes place due to the action of acids and bases or action of metals***. It can also happen through the process of **heating** at high temperatures.
- Normally, elimination reactions are distinguished by the kind of atoms or groups of atoms that leave the molecule. Due to this, there are two main methods involved in this type of reaction;

- *Dehydration*
- *Dehydrohalogenation*
- In the **dehydration** method, there is the **elimination** of a **water molecule** mostly from compounds such as alcohol.
- On the other hand, in **dehydrohalogenation**, there is a removal of a **hydrogen atom** and a **halogen atom**.

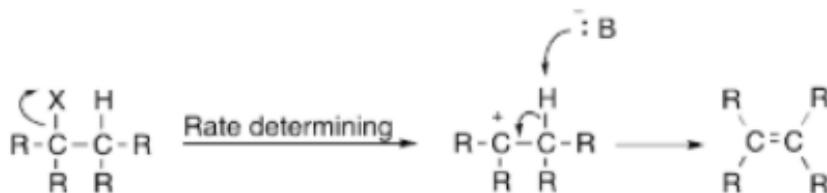
Mechanism of Elimination Reaction

The elimination reaction consists of three fundamental events and they are;

1. *Proton removal.*
 2. *C-C pi bond is formed.*
 3. *There is a breakage in the bond of the leaving group.*
-
- Depending on the reaction kinetics, elimination reactions can occur mostly by two mechanisms namely:
 - E1: unimolecular elimination
 - E2: bimolecular elimination

E1 Reaction

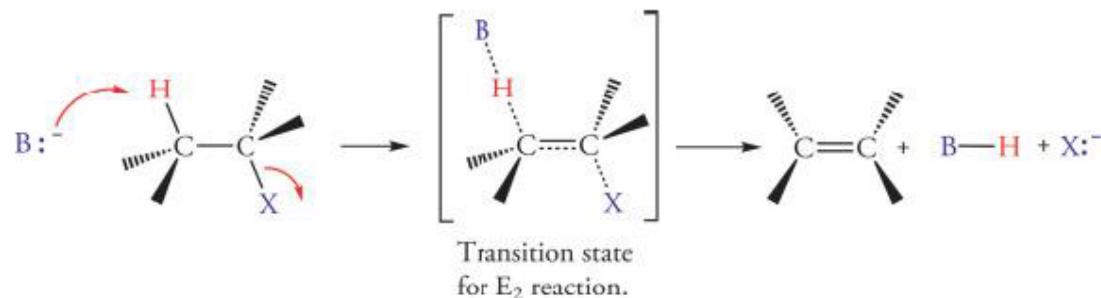
- In the E1 mechanism which is also **known as unimolecular elimination**, there are usually two steps involved – ionization and deprotonation.
- During ionization, there is a formation of **carbocation as an intermediate**. In deprotonation, a proton is lost by the carbocation.
- This happens **in the presence of a base** which further leads to the formation of a **pi-bond** in the molecule.
- In E1, the reaction rate is also proportional to the **concentration of the substance** to be transformed. **Rate = $k[RX]$**
- It exhibits **first-order kinetics**.



- E1 mechanism shares the **features of the SN1 reaction**. The initial step is the **formation of a carbocation intermediate through the loss of the leaving group**. This **slow step becomes the rate-determining step** for the whole reaction.

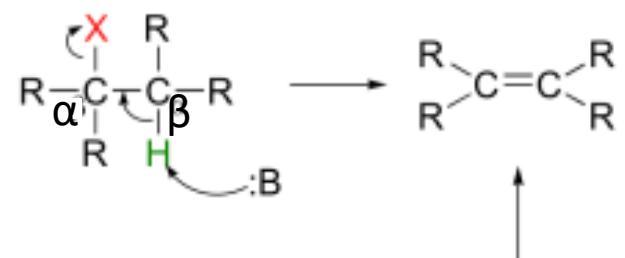
E2 Reaction

- In an E2 mechanism which refers to **bimolecular elimination** is basically a **one-step** mechanism.
- Here, the carbon-hydrogen and carbon-halogen bonds mostly break off to form a new double bond.
- However, in the E2 mechanism, a base is part of the rate determining step and it has a huge influence on the mechanism.
- The reaction rate is mostly proportional to the concentrations of both the eliminating agent and the substrate.
- It exhibits **second-order kinetics**. The rate of the E2 reaction is **Rate = $k[RX][Base]$**
- The E2 mechanism can generally be represented as below. In the below-mentioned representation, B stands for base and X stands for the halogen.

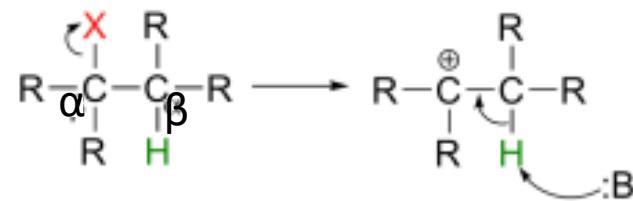


- So the reaction rate depends on both the substrate (RX) and the base involved. In the elimination reaction, the **major product formed is the most stable alkene**.

concerted (E2) elimination

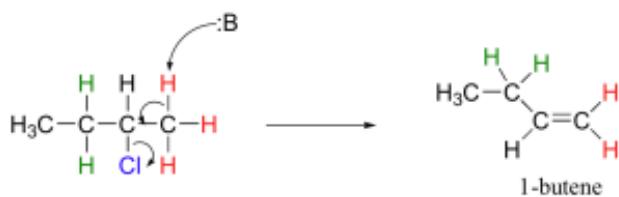
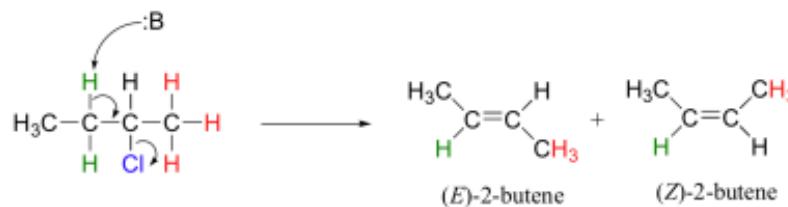


carbocation (E1) elimination



The Zaitsev (Saytseff) Rule

- When alkyl halides have two or more different β carbons, more than one alkene product is formed. In such cases, the **major product** is the more stable product—the **one with the more substituted double bond**.
- This phenomenon is called the Zaitsev rule. The Zaitsev product or the more substituted alkene product is more stable than the less substituted product.
- The stability of the more substituted alkene is a result of number of different contributing factors, including **hyperconjugation**. Each alkyl group that can involve in hyperconjugation with the double bond stabilizes it by approximately 6 kcal/mol



- This reaction is both **regiospecific** and **stereospecific**. In general, **more substituted alkenes are more stable**, and as a result, the product mixture will contain **less 1-butene than 2-butene** (this is the regiochemical aspect of the outcome, and is often referred to as **Zaitsev's rule**). In addition, we already know that *trans* (*E*) alkenes are generally more stable than *cis* (*Z*) alkenes, so we can predict that **more of the *E* product will form compared to the *Z* product**.

Characteristics	E1 elimination	E2 Elimination
Kinetics	First order	Second order
Mechanism	Two steps	Single step
Identity of R group	More substituted halides react faster	More substituted halides react faster
Rate	$R_3CX > R_2CHX > RCH_2X$	$R_3CX > R_2CHX > RCH_2X$
Strength of the base	Favored by weaker bases such as H_2O and ROH	Stronger bases favor the reaction
Leaving group	Better leaving group leads to faster reaction rates. Just as in $SN1$ reactions, the rate determining step involves the C—X bond cleavage	Better leaving group leads to faster
Type of solvent	favoured by polar protic solvents, which can stabilize the ionic intermediates	favoured by polar aprotic solvents
Potential energy diagram	<p>rate-limiting transition state</p> <p>$E1 \text{ rate} = k_r[R - X]$</p>	<p>transition state</p> <p>E_a</p>
		E2 reactions are stereoselective, resulting in the formation of trans-double bonds preferably.

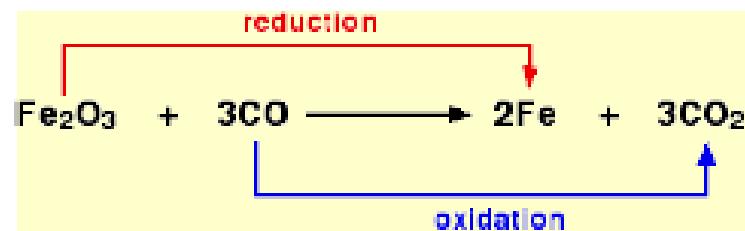
DEFINITIONS OF OXIDATION AND REDUCTION (REDOX)

Oxidation and reduction in terms of oxygen transfer

Definitions

- Oxidation is gain of oxygen.
- Reduction is loss of oxygen.

For example, in the extraction of iron from its ore:

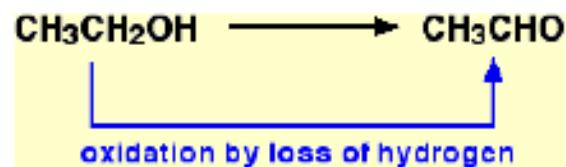


Oxidation and reduction in terms of hydrogen transfer

Definitions

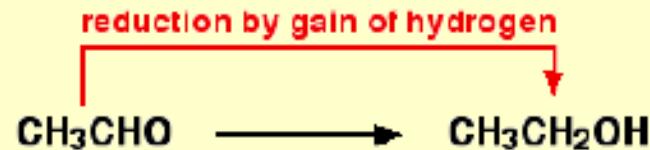
- Oxidation is loss of hydrogen.
- Reduction is gain of hydrogen.

For example, ethanol can be oxidised to ethanal:



You would need to use an oxidising agent to remove the hydrogen from the ethanol. A commonly used oxidising agent is potassium dichromate(VI) solution acidified with dilute sulphuric acid.

Ethanal can also be reduced back to ethanol again by adding hydrogen to it. A possible reducing agent is sodium tetrahydridoborate, NaBH_4 . Again the equation is too complicated to be worth bothering about at this point.



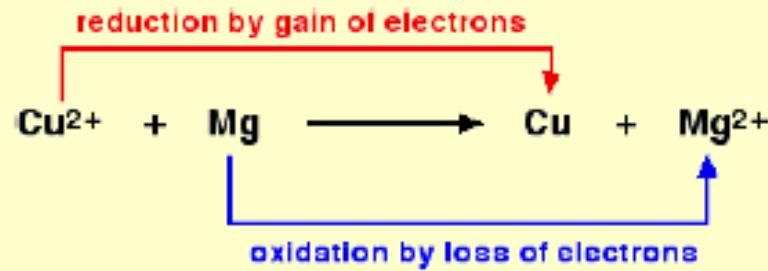
Oxidation and reduction in terms of electron transfer

Definitions

- **Oxidation is loss of electrons.**
- **Reduction is gain of electrons.**

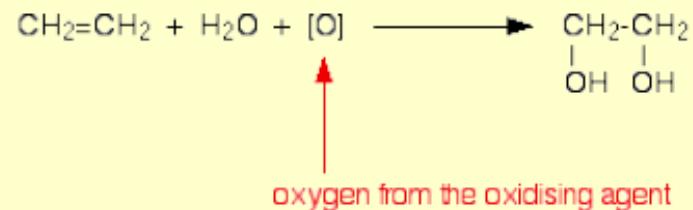
A simple example

- The equation shows a simple redox reaction which can obviously be described in terms of oxygen transfer.
- $\text{CuO} + \text{Mg} \longrightarrow \text{Cu} + \text{MgO}$
- Copper(II) oxide and magnesium oxide are both ionic. The metals obviously aren't. If you rewrite this as an ionic equation, it turns out that the oxide ions are spectator ions and you are left with:



Oxidation of alkenes with cold dilute potassium manganate(VII) solution

Manganate(VII) ions are a strong oxidising agent, and in the first instance oxidise ethene to ethane-1,2-diol (old name: ethylene glycol).



Oxidation of alkenes with hot concentrated acidified potassium manganate(VII) solution

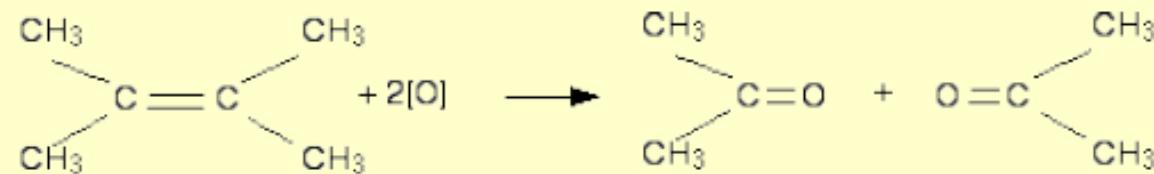
The acidified potassium manganate(VII) solution oxidises the alkene by breaking the carbon-carbon double bond and replacing it with two carbon-oxygen double bonds.



The products are known as **carbonyl compounds** because they contain the carbonyl group, C=O. Carbonyl compounds can also react with potassium manganate(VII), but how they react depends on what is attached to the carbon-oxygen double bond.

If both attached R groups in the products are alkyl groups

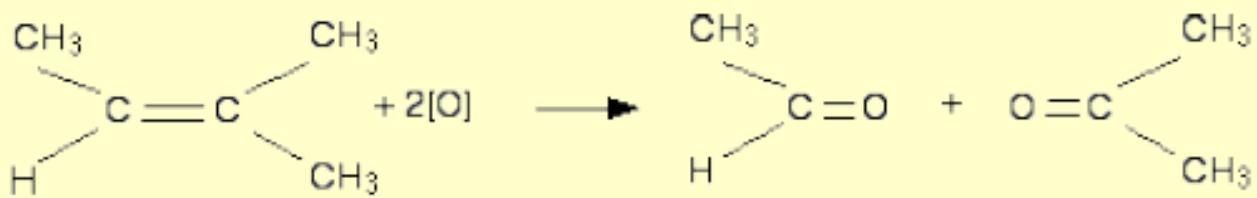
For example:



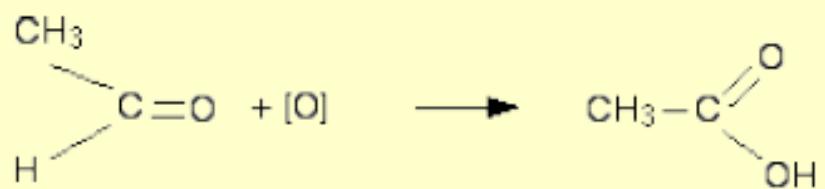
In this case, you would end up with two identical molecules called propanone. On the other hand, if one of the methyl groups in the original molecule was replaced by an ethyl group, you would get a mixture of two different ketones - propanone and butanone.

If a product has one hydrocarbon group and one hydrogen

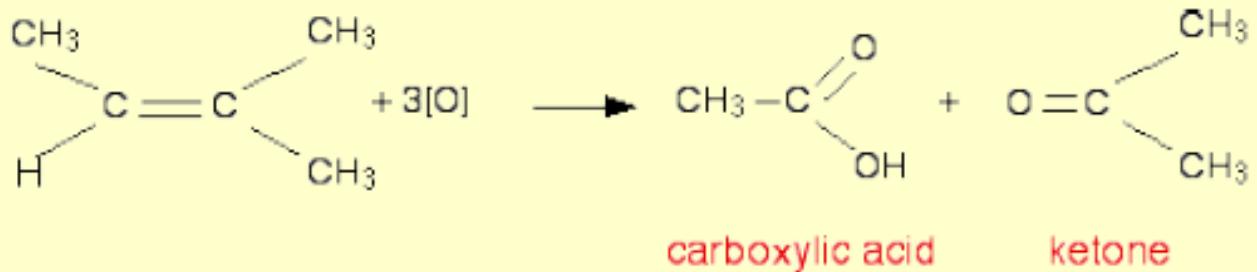
For example, suppose the first stage of the reaction was:



Aldehydes are readily oxidised to give carboxylic acids, containing the $-\text{COOH}$ group. So this time, the reaction will go on a further step to give ethanoic acid, CH_3COOH .

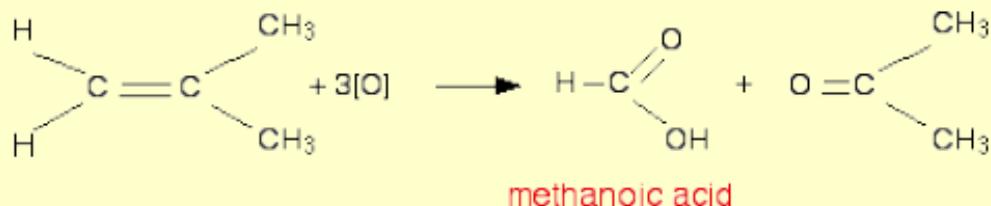


The overall effect of the potassium manganate(VII) on this kind of alkene is therefore:



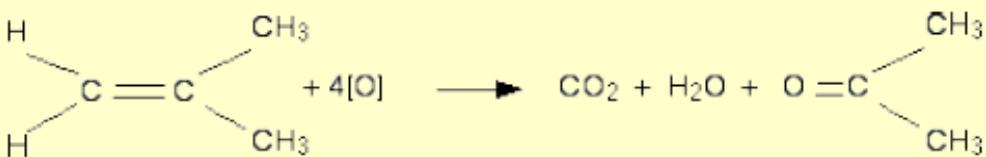
If a product has two hydrogens but no hydrocarbon group

You might have expected that this would produce methanoic acid, as in the equation:



But it doesn't! That's because methanoic acid is also easily oxidised by potassium manganate(VII) solution. In fact, it oxidises it all the way to carbon dioxide and water.

So the equation in a case like this might be, for example:

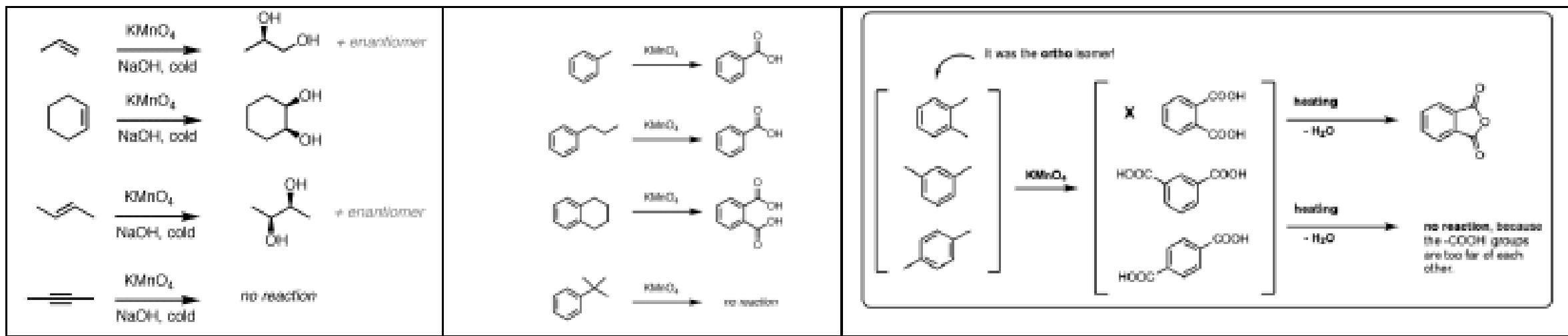


Summary

Think about both ends of the carbon-carbon double bond separately, and then combine the results afterwards.

- If there are two alkyl groups at one end of the bond, that part of the molecule will give a ketone.
- If there is one alkyl group and one hydrogen at one end of the bond, that part of the molecule will give a carboxylic acid.
- If there are two hydrogens at one end of the bond, that part of the molecule will give carbon dioxide and water.

Few more examples:



Oxidation with $K_2Cr_2O_7$ /Chromic acid

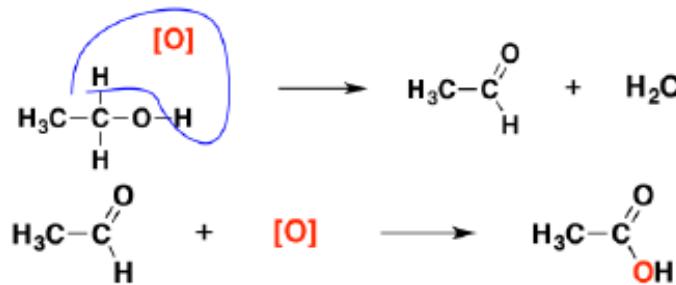
Oxidizing agent

- $K_2Cr_2O_7$ potassium dichromate
- CrO_3 Chromium Trioxide

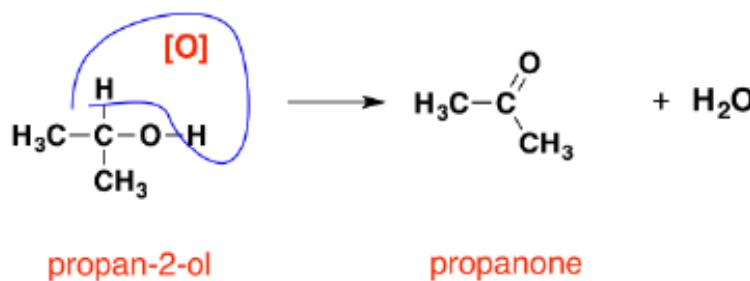
Both of these are used along with H_2SO_4 , H_2O

- 1° alcohol → Carboxylic acid
- 2° alcohol → Ketone
- 3° alcohol → No reaction

Primary alcohols



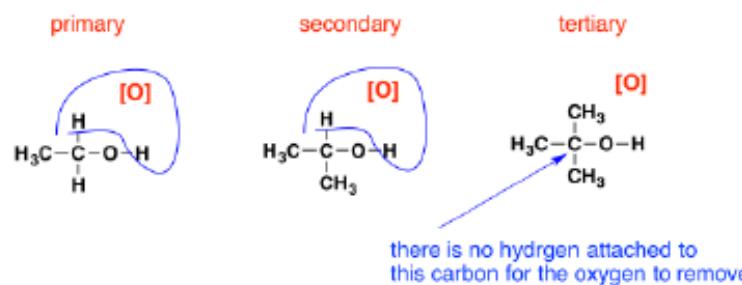
Secondary alcohols



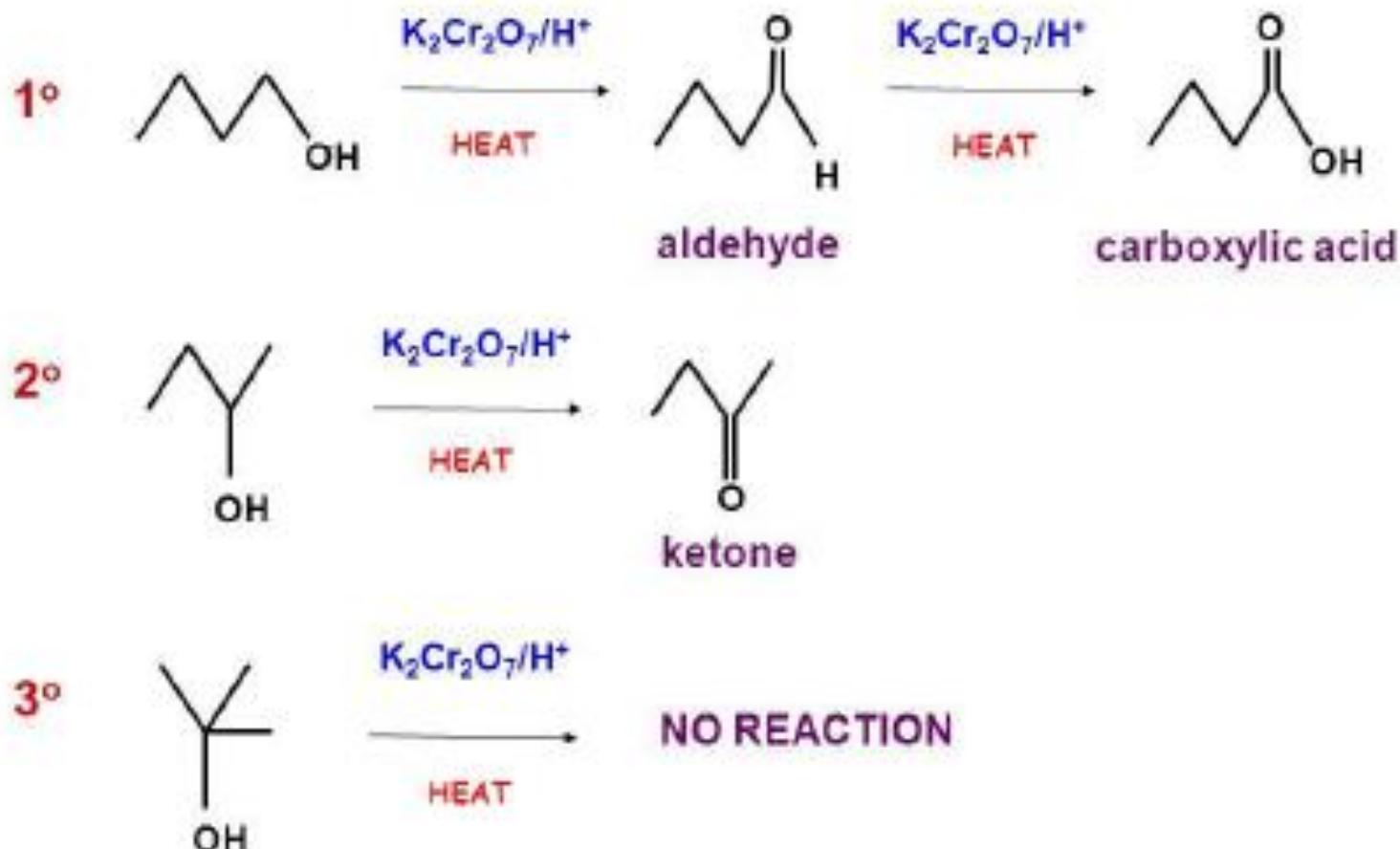
propan-2-ol

propanone

Tertiary alcohols



Acidified potassium dichromate(VI) and alcohols

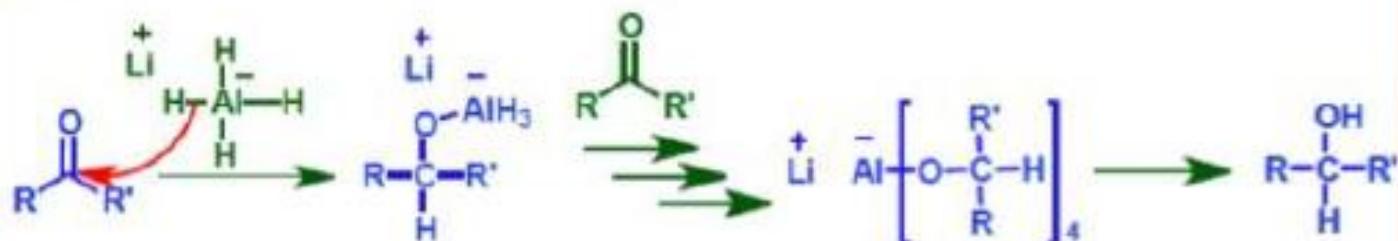


Reduction reactions using LiAlH₄

➤ LITHIUM ALUMINUM HYDRIDE (LiAlH₄)

- Very powerful reducing reagent
- Available as either powder or pellet
- Used as a suspension in ether or THF
- Reacts violently with water, alcohol
- Reduces carbonyl, carboxylic acid & ester
- Reduces nitrile, amide & aryl nitro group to amine
- Reduces acetylene to olefin
- Reduces C-X bond, opens epoxide
- LiAlH₄ is a stronger reducing agent than NaBH₄ due to weaker Al-H bond
- LiAlH₄ is used to reduce compounds that are nonreactive toward NaBH₄

○ Mechanism:



Functional group conversion

Aldehydes, ketones -----> Alcohols

Carboxylic acids -----> Alcohols

Esters, acid halides -----> Alcohols

Amides -----> amines

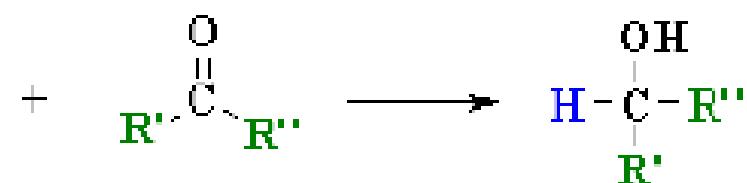
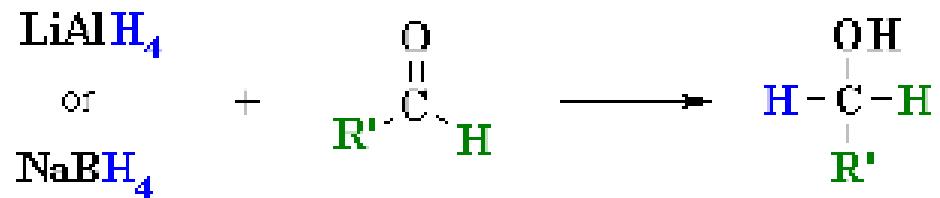
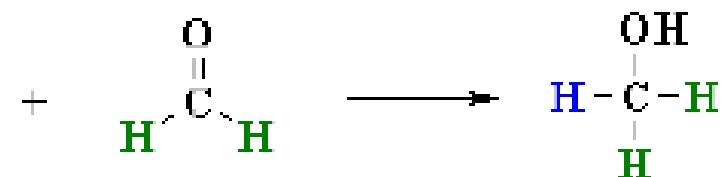
Nitriles -----> amines

oxiranes (epoxides) -----> alcohols

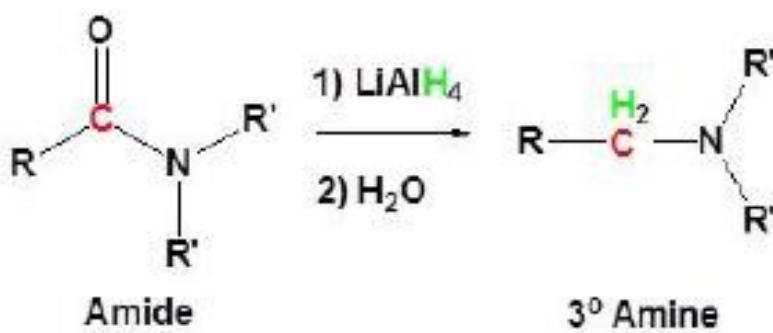
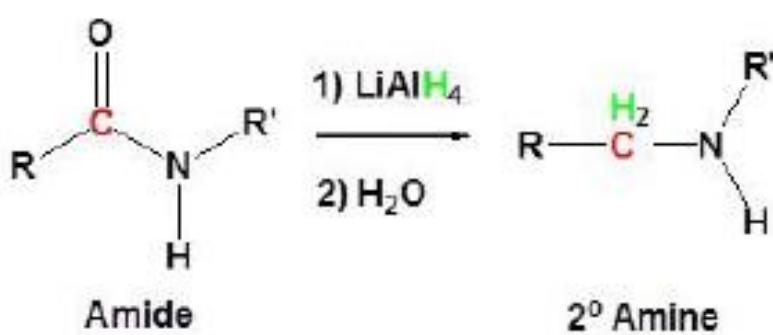
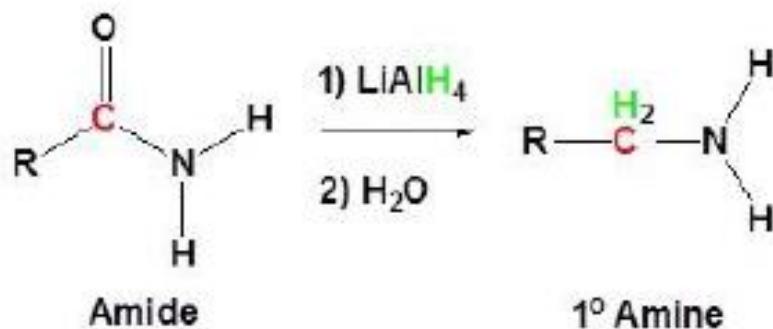
lactones -----> diols

haloalkanes, haloarenes -----> alkanes,
arenes

(1) Reduction of Aldehydes or Ketones to 1^0 or 2^0 alcohols:

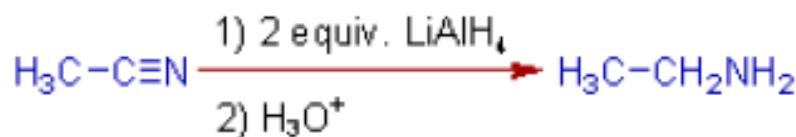


(2) Reduction of Amides to amines:

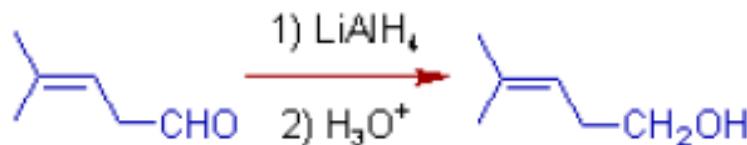


(3) The nitriles are reduced to primary amines by LiAlH₄.

E.g. Acetonitrile is reduced to ethyl amine by LiAlH₄.

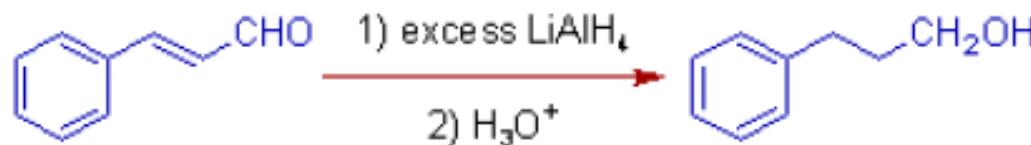


(3) LiAlH₄ does not affect the isolated carbon-carbon double or triple bonds.



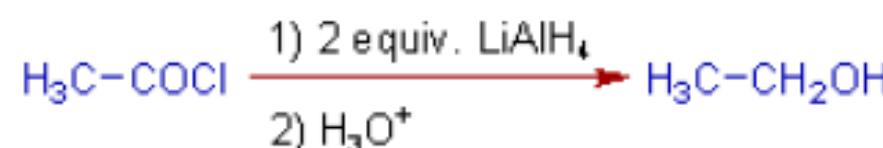
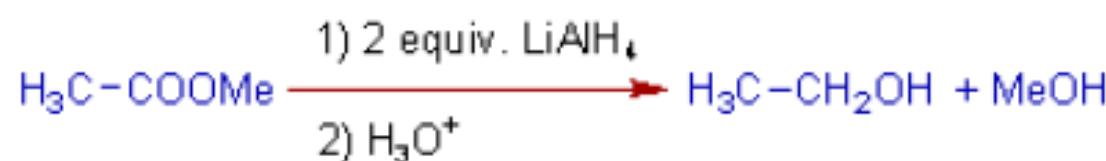
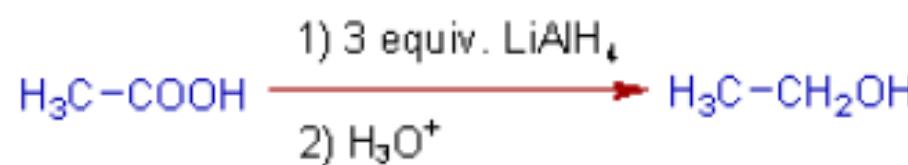
*However, the double bonds in conjugation at α,β positions of carbonyl group may also be reduced by Lithium aluminium hydride depending on the reaction conditions.

E.g. Cinnamaldehyde is reduced to Hydrocinnamyl alcohol when reduced with excess of LiAlH₄ (roughly more than 2 equivalents) by normal addition method. In this method, a solution of cinnamaldehyde is added to the solution of lithium aluminium hydride. Both the double bond and carbonyl group are reduced.



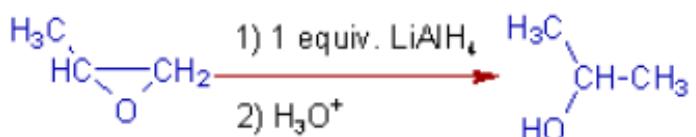
(6) The **carboxylic acids, esters and acid halides** are reduced to corresponding primary alcohols by Lithium aluminium hydride.

E.g. The reduction of Acetic acid, methyl acetate and acetyl chloride by LiAlH₄ furnish the same ethyl alcohol.



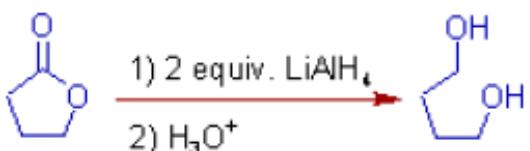
(7) Lithium aluminium hydride reduces the oxiranes (epoxides) to alcohols. The hydride attack occurs at less hindered side of the epoxide.

E.g. 2-methyloxirane gives 2-propanol predominantly.

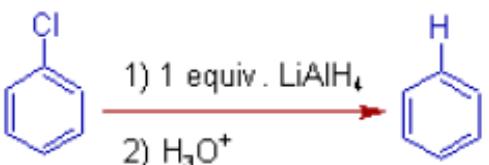
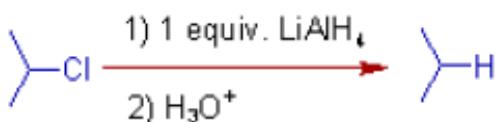


(8) The lactones are reduced to α,ω -diols by LiAlH₄.

E.g.



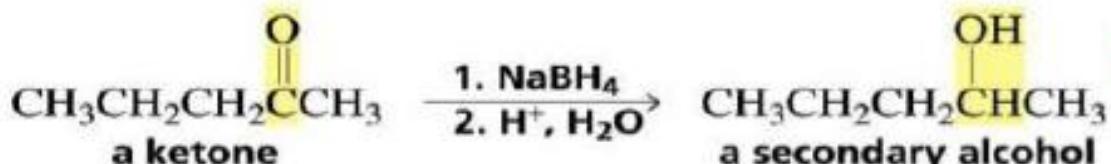
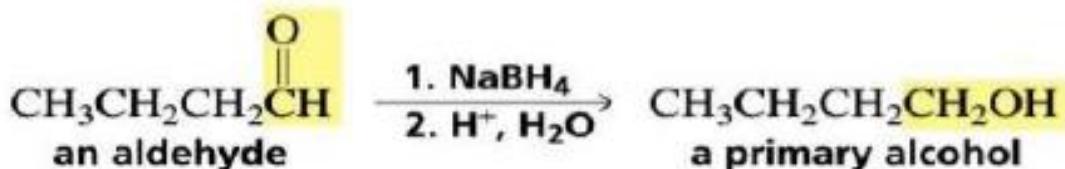
(9) The haloalkanes and haloarenes are reduced to corresponding hydrocarbons by Lithium aluminium hydride.



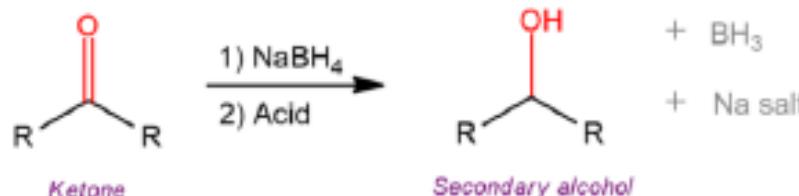
Reduction reactions using NaBH₄

➤ SODIUM BOROHYDRIDE - NaBH₄

- Sodium borohydride was first prepared by reaction of sodium hydride (NaH) with trimethylborate, B(OMe)₃.
- NaBH₄ is less reactive than LiAlH₄.
- It is only powerful enough to reduce aldehydes, ketones and acid chlorides to alcohols.
- Esters, amides, acids and nitriles are largely untouched.
- An aldehyde is reduced to 1° & ketone to a 2° alcohol respectively.
- Selective (chemoselectivity) reagent

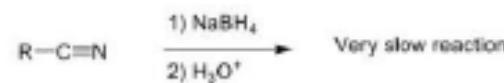
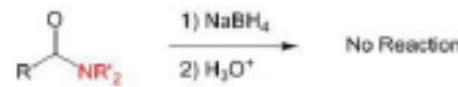
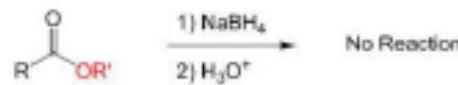
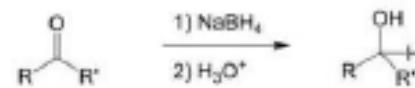
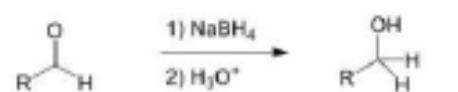


- Addition of **sodium borohydride** (NaBH_4) to **ketones** gives **secondary alcohols** (after addition of **acid**).



www.chemistryscore.com

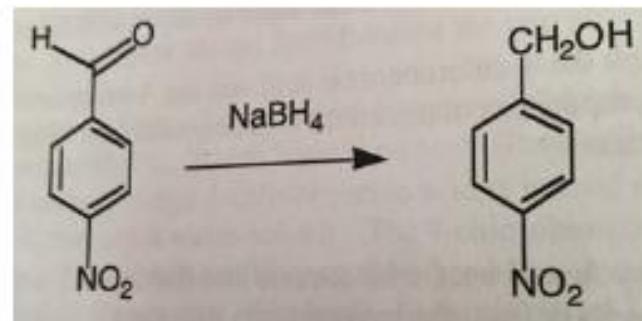
NaBH_4 is less reactive than LiAlH_4 and does not reduce esters or amides



Selective reduction: If a compound contains some functional group besides the carbonyl group, then only the latter is reduced.

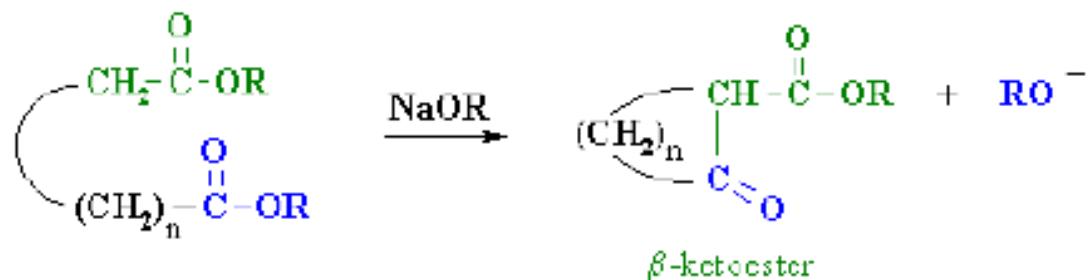


3)

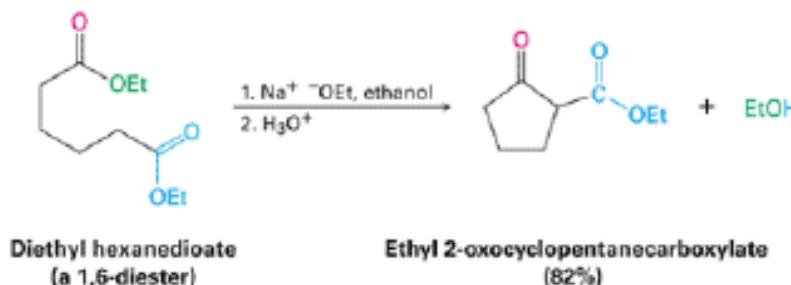


Cyclization: (Dieckmann condensation)

- It is base catalysed intramolecular condensation of a diester.
- It works well to produce 5/6 membered cyclic β keto ester.
- Usually effected with sodium alkoxide in alcoholic solvent.

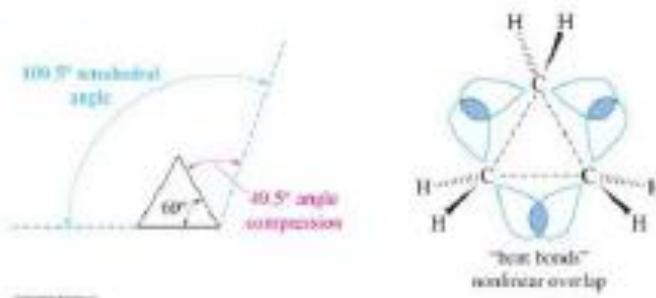


- e.g. when an ester of adipic acid (diethyl hexanedioate) treated with Na or Na ethoxide, intramolecular change produces cyclic β keto ester (ethyl 2-oxocyclopentanecarboxylate).



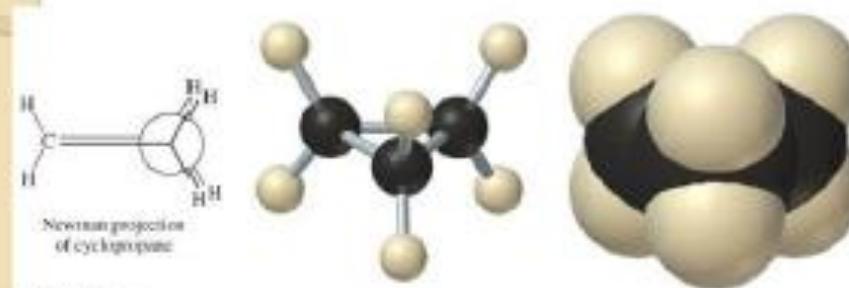
Ring Opening reactions: (Addition of Cl₂/Br₂/HI/H₂SO₄/H₂ to cyclopropane)

Angle Strain in Cyclopropane



- The bond angles are compressed to 60° from the usual 109.5° bond angle of sp^3 hybridized carbon atoms.
- This severe angle strain leads to nonlinear overlap of the sp^3 orbitals and "bent bonds."

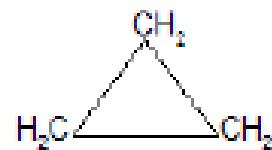
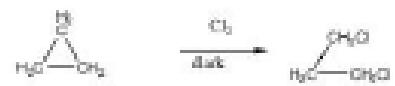
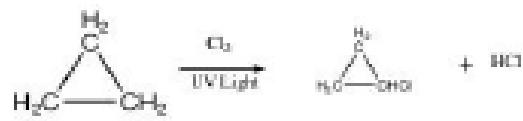
Torsional Strain in Cyclopropane



All the C—C bonds are eclipsed, generating torsional strain that contributes to the total ring strain.

Reactions of cycloalkanes.

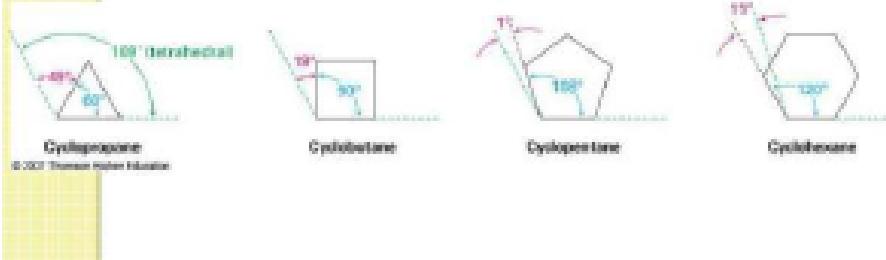
1. Addition of Cl_2 and Br_2 : Cyclopropane reacts with Cl_2 and Br_2 at room temperature and in the absence of diffused sunlight to produce 1,3-dichlorocyclopropane and 1,3-dibromocyclopropane respectively



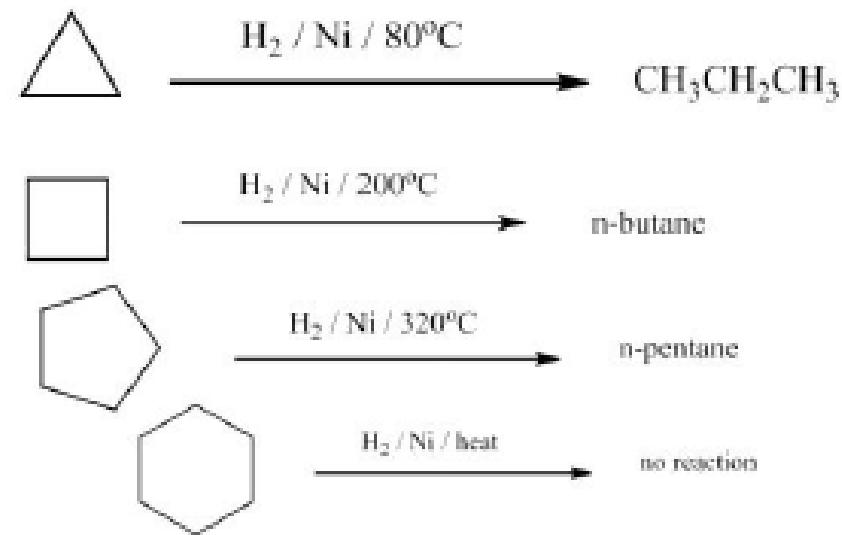
$\text{Cl}_2 / \text{Dark}$	$\rightarrow \text{Cl}(\text{CH}_2)_2\text{Cl}$ Addition reaction
$+ \text{Br}_2$	$\rightarrow \text{Br}(\text{CH}_2)_2\text{Br}$ 1,3-dibromo propane
$+ \text{HBr}$	$\rightarrow \text{CH}_3 - \text{CH}_2 - \text{CH}_2\text{Br}$ 1-bromopropane
$+ \text{Ni}, \text{H}_2$	$\rightarrow \text{CH}_3 - \text{CH}_2 - \text{CH}_3$ Propane
120°C	
$+ \text{H}_2\text{SO}_4$	$\rightarrow \text{CH}_3 - \text{CH}_2 - \text{CH}_2\text{HSO}_4$
$+ \text{KMnO}_4$	No reaction
HI	$\rightarrow \text{CH}_3 - \text{CH}_2 - \text{CH}_2 - \text{I}$

4.3 Stability of Cycloalkanes: Ring Strain

- Rings larger than 3 atoms are not flat
- Cyclic molecules can assume nonplanar conformations to minimize angle strain and torsional strain by ring-puckering
- Larger rings have many more possible conformations than smaller rings and are more difficult to analyze



α -Catalytic hydrogenation: Depends on the ring size,



- Cycloalkanes are saturated compounds like alanes and therefore exhibit substitution reactions. But cycloalkanes having ring of 3 or 4 carbon atoms are unstable and tend to form open chain aliphatic compounds by the addition of reagent.
- Thus they exhibit chemical properties of both alkanes and alkenes.
- **Reaction with halogen (Substitution with Cl_2 and Br_2):**
 - ✓ Generally cycloalkanes undergo free radical **substitution** with halogens at high temperature or in presence of light.
 - ✓ Whereas in case of cyclopropane, Cl_2 and Br_2 break the ring system and give open chain addition products in dark.
 - ✓ **Cyclobutane and higher members** do not give this reaction.
- **Reaction with halogen acids (HX):**
 - ✓ Cyclopropane add on halogen acids to give **open chain alkyl halides**.
 - ✓ Cyclobutane and higher alkanes **do not give** this reaction.
- **Reaction with hydrogen (H_2):**
 - ✓ When heated with H_2 in presence of Ni catalyst, **cyclopropane and cyclobutane** give addition products
 - ✓ whereas **higher members** do not give this reaction.
- Hence it may be pointed out that **cyclopropane is the most reactive** cycloalkane as it exhibits many addition reactions accompanied by ring cleavage. Then comes **cyclobutane** which shows some addition reactions. The **rest of the cycloalkanes** do not form addition products.

DRUGS-Introduction

Introduction to pharmacology

- The study of **drugs or chemicals** and the **effects they have on living animals** is called pharmacology.
- **Pharmacology** explains **what drugs** are, what they do **to body functions** and what the body does to them.
- Pharmacology also explains why a person may experience **side effects** when they take drugs and why there is such a **wide spectrum of differences** between drug actions in different people.

What is a drug?

- A drug is a **chemical that interacts with proteins** in the body to affect a physiological function. This is the general idea behind all **medicine**.
- Once these chemicals are absorbed into the systemic circulation they bind with certain proteins and this **changes the functioning of the cell slightly**.
- For example, **anticancer drugs** bind to proteins on the surface of cancer cells this stimulates the cells to die. In this case **cell death is the physiological action** of the drug.
- **No drugs are specific to interacting with just one type of cell** or one type of protein and this is what causes side effects. Again using an anticancer drug as an example, the medication **works by binding to very rapidly dividing cells**, such as cancer cells, however hair cells are also rapidly dividing and that is why one of the side effects of anticancer drugs is hair loss.

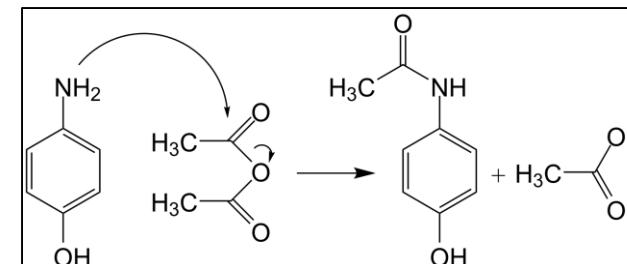
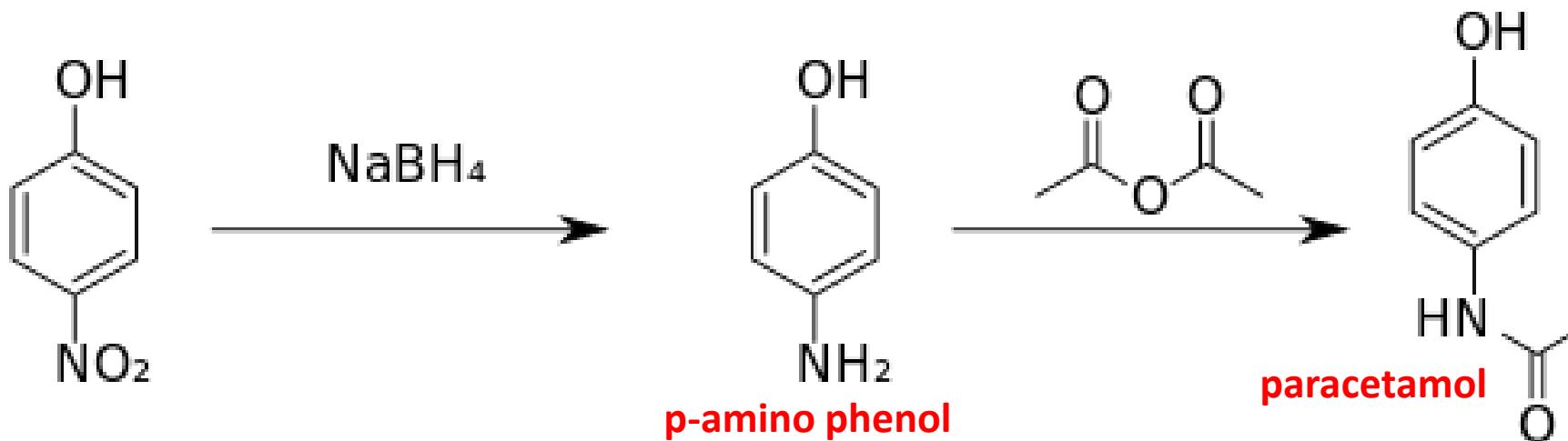
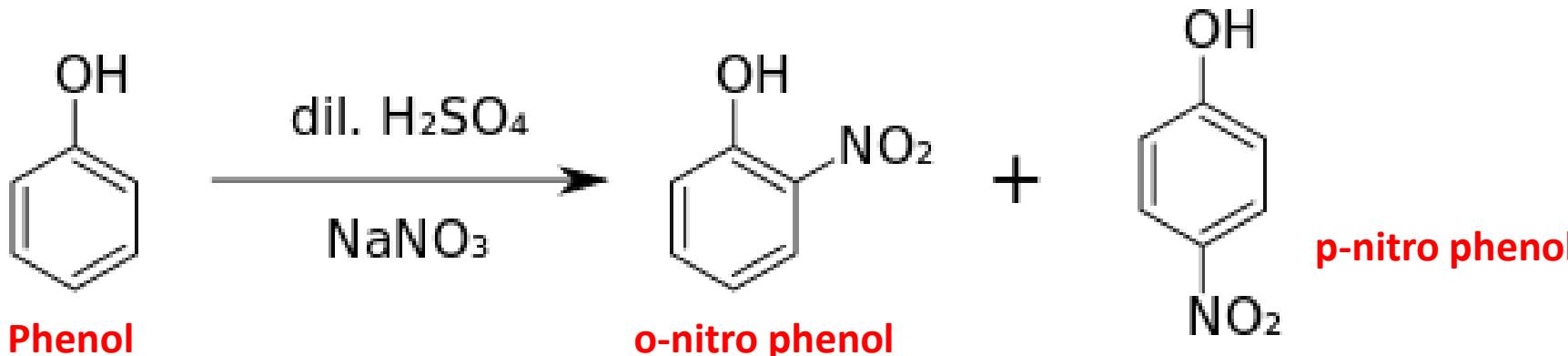
What is in a drug?

- The **chemical** in the drug that **affects physiological functioning** is the active ingredient of the drug.
- For most drugs, the amount of chemical needed to cause an effect is very small, often as small as 5 **micrograms**; this is 0.005% of a gram! As you can imagine this is too small to package and handle, these ingredients are **very expensive** and giving out little amounts like that will cause most of the drug to be lost and wasted. Therefore most of the drugs that we take are also comprised of inactive ingredients that work to fill out the drug. Inactive ingredients are, as the name suggests, ingredients that have no effect on the functioning of cells, namely lactose, dyes and gluten. If the drug needs to be taken orally, the inactive ingredients also work to **bind the drug** together and **lubricate** the drug so it is easy to swallow.
- So the inactive ingredients are the fillers, binders and lubricants of the drug whereas the active ingredient is the very small amount of chemical that reacts with the body to produce an effect.

How do drugs work?

- Our bodies are largely controlled by proteins. Proteins exist in many different forms in the body and have many different functions. Each protein has a specific function and is quite specific to the cell type that it acts on. For example, there are specific types of proteins called [receptors](#).
- Receptors are embedded on the cell surfaces, there are different receptors for different types of cells. A liver cell will have different receptors than a cardiac cell. The receptor binds to other proteins and chemicals on the outside of the cell and this in turn creates a change in the functioning of the cell.
- Proteins also **act as drug targets**. In order for a drug to exert an effect it needs to be bound to a protein. This can be thought of as a lock and key system; where the drugs are the key and the protein is the lock. Once the drug is bound in this **lock and key mechanism** it can have one of two main influences over the cell. It can produce a change in response or it can stop a normal response of the cell.
- Drugs that produce a change in the cell functioning are called [agonists](#). Drugs that stop a normal function of the cell are called [antagonists](#).

PARACETAMOL (Acetaminophen)-Synthesis



PARACETAMOL USES

1. Fever

It is widely prescribed to relieve fever in person of all ages. Paracetamol is prescribed in children if temperature is greater than 38.5 Celsius or 101.3 Fahrenheit.

2. Pain

It is also prescribed to relieve mild to moderate pain.

3. Osteoarthritis

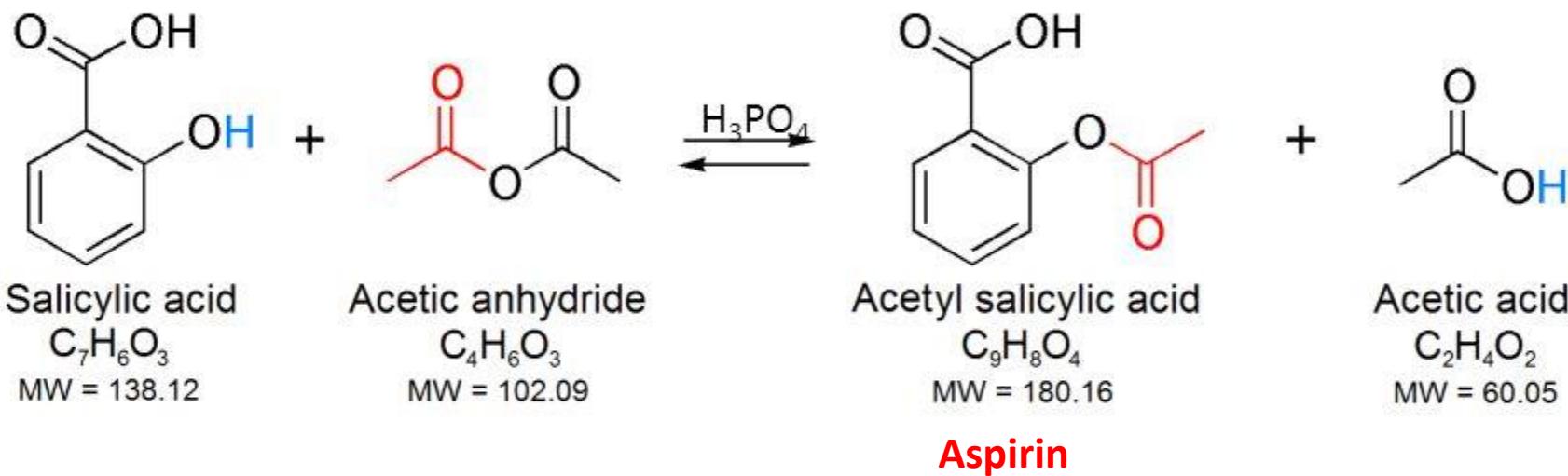
Some studies state that paracetamol is also used to treat arthritis pain of knee, hand or hips.

4. Lower Back Pain

It is first line treatment of lower back pain.

- Other names are panadol & tylenol in US

Aspirin: *synthesis*



- Place 1.5g of salicylic acid in a 125 mL Erlenmeyer flask
- In the fume hood, add 4 mL of acetic anhydride and 4 drops of 85% H3PO4
- Stir and place in a boiling water bath for 5 mins
- Remove the flask, and immediately stir in 3 mL of water stir for 2 mins then add another 30 mL
- Aspirin should start to precipitate
- Place flask in ice bath to complete precipitation

Uses

- Aspirin is a non-steroidal anti-inflammatory drug (NSAID).
- Aspirin is used primarily to reduce inflammation, to alleviate fevers, and to alleviate mild aches and pains.
- For treatment of post-surgery pain, Ibuprofen has been shown to be more effective than aspirin.
- Aspirin is the primary drug used to treat migraines.
- Aspirin, taken over a long period of time and in low doses, significantly reduces the risk of heart attack and stroke.
- Additionally, low doses of aspirin taken over a long period of time have recently been shown to dramatically reduce the mortality rate in cancer patients.