UNIT 1

BASIC CONCEPTS OF STEREOCHEMISTRY

Unit Structure

1.1.   INTRODUCTION:

Stereochemistry deals with three dimensional representation of molecule in space. This has sweeping implications in biological systems. For example, most drugs are often composed of a single stereoisomer of a compound. Among stereoisomers one may have positive effects on the body and another stereoisomer may not or could even be toxic. An example of this is the drug thalidomide which was used during the 1950s to suppress the morning sickness. The drug unfortunately, was prescribed as a mixture of stereoisomers, and while one stereoisomer actively worked on controlling morning sickness, the other stereoisomer caused serious birth defects.

The study of stereochemistry focuses on stereoisomers and spans the entire spectrum of organic, inorganic, biological, physical and especially supramolecular chemistry. Stereochemistry includes method for determining and describing these relationships; the effect on the physical or biological properties.

So to have the sound knowledge of stereochemistry we should have good command over their basic concepts.

1.2.   OBJECTIVES:

- Classification of stereoisomers

- Recognize a stereogenic (chiral) center in a molecular structure

- Various representation of three dimentional molecules

- To be able to predict, identify and distinguish between enantiomers and diastereomers.

- Various nomenclature of stereoisomers to define them properly

1.3.   STEREOCHEMISTRY: DEFINITION

The branch of chemistry which deals with three dimensional structure of molecule and their effect on physical and chemical properties is known as stereochemistry. To represent molecule as three dimensional object we need at least one carbon sp3- hybridized.

Example:
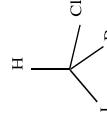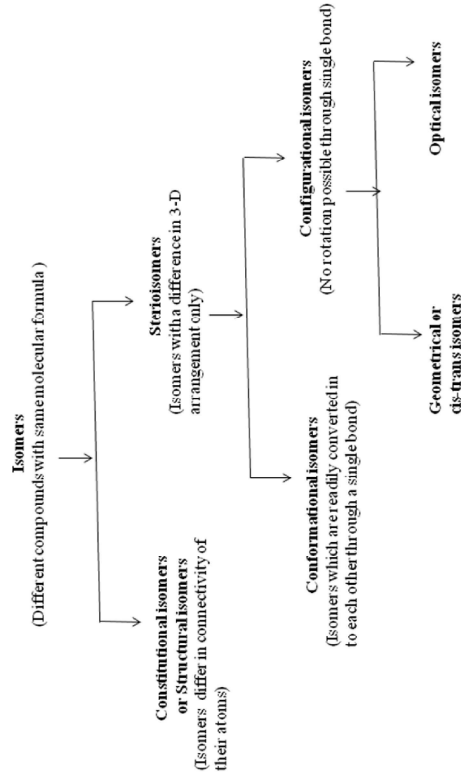

2D drawing Not appropriate for steriochemistry
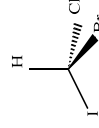
3D drawing appropriate for steriochemistry

1.4. TERMINOLOGY USED IN STEREOCHEMISTRY

A. ISOMERS AND THEIR CLASSIFICATION

You are already familiar with the concept of isomers: different compounds which have the same molecular formula. Here we will learn to make distinction between various kinds of isomers, especially the stereoisomers.

Isomers
(Different compounds with same molecular formula)

Constitutional isomers or Structural isomers
(Isomers differ in connectivity of their atoms)

Sterioisomers
(Isomers with a difference in 3-D arrangement only)

Conformational isomers
(Isomers which are readily converted in to each other through a single bond)

Configurational isomers
(No rotation possible through single bond)

Geometrical or cis-trans isomers

Optical isomers

B. OPTICAL ACTIVITY

We know that ordinary lights are composed of rays of different wavelengths vibrating in all directions perpendicular to the path of its propagation. These vibrations can be made to occur in a single plane by passing ordinary light through the polarizing Nicol prism. Such light whose vibrations occur in only one plane is called plane polarized light

polarizer

analyzer

light source

sample tube
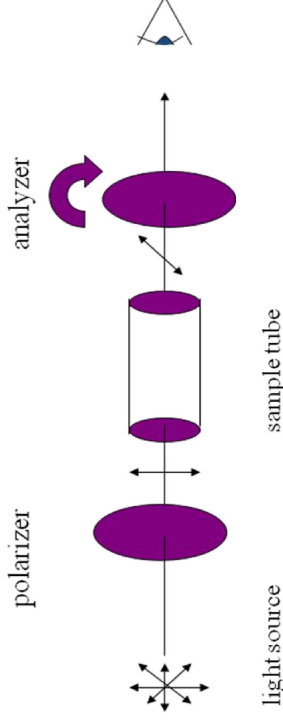
Compounds which rotate the plane of polarized light are called optically active compounds and this property is known as optical activity. Rotation of plane of polarized light can be of two types.

- **Dextrorotatory :** If the compound rotates the plane of polarization to the right(clockwise) it is said to be dextrorotatory (Latin: dexter-right) and is denoted by (+), or 'd'.

- **Laevorotatory :** If the compound rotates the plane of polarization to the left(anticlockwise) it is said to be laevorotatory (Latin: laevus-left) and is denoted by (-) or 'l'

The change in the angle of plane of polarization is known as optical rotation. The optical rotation is detected and measured by an instrument called polarimeter. The measurement of optical activity is reported in terms of specific rotation [α], which is given as,

$[\alpha]_\lambda^t = \alpha/lc$

[α]= specific rotation

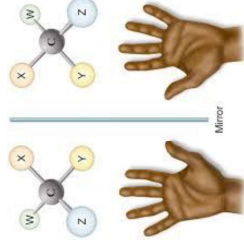t = temperature of measurement

λ=wavelength of the light used

α= observed angle of rotation

l= length of sample tube in decimeter

c=concentration of the sample in g/mL of solution

C. CHIRALITY

- **The term Chiral-** The word chiral (Greek word Chier,meaning hand) is used for those objects which have right-handed and left-handed forms, i.e., molecules which have "handedness" and the general property of "handedness" is termed chirality. An object which is not superimposable upon its mirror image is chiral.
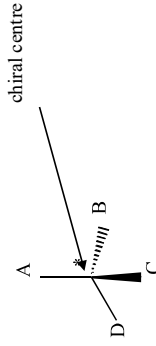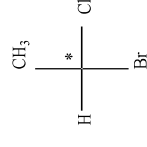
CH_3 — $\overset{*}{C}$ — with Cl, H, Br

Chiral (asymmetric) has four different atoms bonded to carbon

CH_3 — C — with H, H, Br
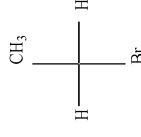
Achiral does not have four different atoms bonded to the carbon

CH_3 — $\overset{*}{C}$ — with H, CH_2CH_3, $CH_2CH_2CH_3$

Chiral has four different groups bond to the carbon

$O=C$ — with H, CH_3

Achiral only has three atoms bonded to the carbon

CHO
H — $\overset{*}{C}$ — OH
H — $\overset{*}{C}$ — OH
CH_2OH
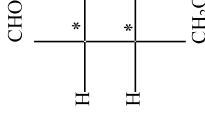
Chiral with two chiral centre

CHO
H — $\overset{*}{C}$ — OH
H — $\overset{*}{C}$ — OH
HO — $\overset{*}{C}$ — H
CH_2OH
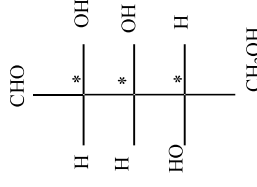
Chiral with three chiral centre

Chiral centres are shown by astrik (*)

The term Achiral-

Object and molecules which are superimposable on their mirror images is achiral. Achiral molecule has internal plane of symmetry, a hypothetical plane which bisects an object or molecule into mirror-reflactive halves. An object or molecule with an internal plane of symmetry is achiral.


The term Asymmetric center and chiral center- Three terms are used to designate, a carbon atom bonded tetrahedrally to four different substituents in a chiral molecule: Asymmetric atom, chiral center or stereocenter.
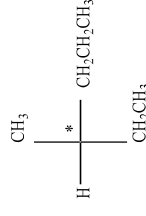

chiral centre

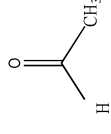Let us understand chiral and achiral center taking few more examples.

The term steregenic center or stereocenter-

A stereogenic center is defined as an atom on which an interchange of any two atoms or groups result in a new stereoisomer, When the new stereoisomers is an enantiomer ,the stereocenter is called chiral center. All stereocenters are not tetrahedral.
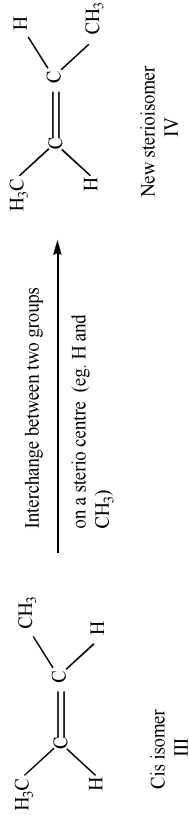
Example 1

COOH
H — C — OH
CH_3

Interchange between two groups (eg. H and OH) →

COOH
HO — C — H
CH_3

Steriocentre
I
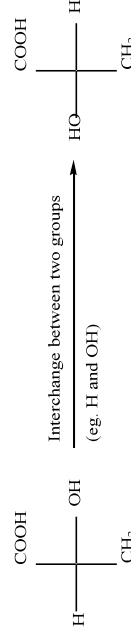
New Sterioisomer
II

First and second are enantiomers (non superimposible mirror images), Hence the steriocentre is a chiral centre

Example-2

Cis isomer
III

Interchange between two groups on a sterio centre (eg. H and CH₃)

New sterioisomer
IV

III and IV are not enantiomers . they are diasteriomers hence in this case sterio centres are not chiral centres. Also these are not tetrahedral.

Thus, all chiral centres are sterio centres but all steriocentres are not chiral centres. If a molecule contains only one chiral centres it must be chiral. Molecule containing two or more chiral centres may or may not be chiral. For example: meso tartaric acid has two chiral centres but it is achiral.
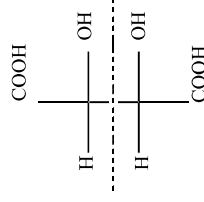

Achiral due to presence of plane of symmetry

D. STEREOISOMERS- Isomers having the same molecular formula but different spatial arrangement of their atoms are known as stereoisomer. They are of following types:

• **Enantiomers:** Stereoisomers which are non superimposable mirror images of each other are called enantiomers. Chirality is necessary and sufficient condition for existence of enantiomers. These always exist as discrete pairs.

Eg.
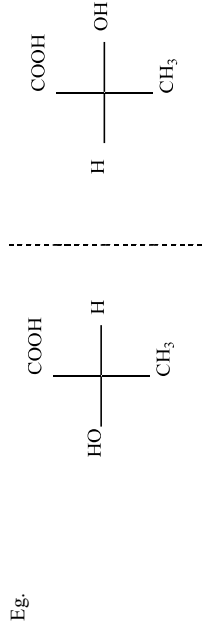
Two isomers of Lactic acid

• **Diastereomers:** Stereoisomers that are not mirror images of each other are called diastereomers.

Example.

A   B
Enantiomers

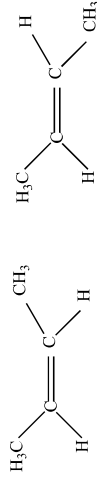C   D
Enantiomers
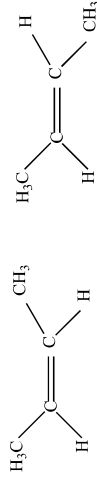
Diasteriomers
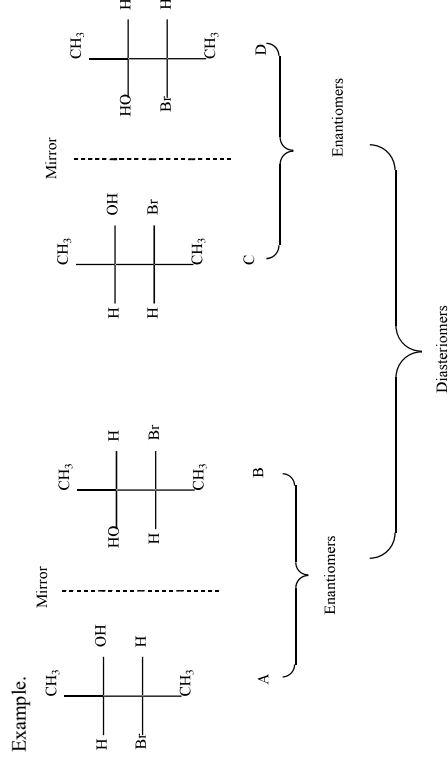
Four isomers of 3-Bromo-2-butanol

• **Geomatrical Isomers:**

Geometrical isomers occurs as a result of restricted rotation about a carbon-carbon bond. This is also called cis-trans isomerism.
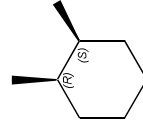
This isomerism exhibited by variety of compounds such as compound containing double bond C=C, C=N, N=N, compound containing cyclic structure or compound containing restricted rotation due to steric hindrance.

1.5. REPRESENTATION OF THREE DIMENSIONAL MOLECULES

1.5.1 FLYING-WEDGE OR WEDGE-DASH PROJECTION

The Flying-Wedge Projection is the most widely used three dimensional representation of a molecule on a two dimensional surface (paper). This kind of representation is usually done for molecule containing chiral centre. In this type of representation three types of lines are used.

- A solid wedge or thick line (———◢) - it represents bond projection towards the observer or above the plane of paper.
- A continuous line or ordinary line (———) - it represents bond in the plane of paper.
- A dashed wedge or broken line (·······|||||) - it represents bond projection away from the observer or below the plane of paper. Example:- CH₄ (methane)

"Ball and stick" model
of 3-D structure of methane

sketched 3-D structural
formula of methane

1.5.2 FISCHER PROJECTION

Fischer projection provide an easy way to draw three dimensional molecule on two dimensional paper and all the bonds are drawn as solid lines around asymmetric carbon atom.

The Fischer rules for showing the arrangement around asymmetric carbon.

- The carbon chain of the compound is projected vertically, with the most oxidized carbon at the top or place the carbon number one at the top (as defined by nomenclature rule).
- The chiral carbon atom lies in the plane of the paper and usually omitted. The intersection of cross lines represents asymmetric carbon.
- The horizontal bonds attached to the chiral carbon are considered to be above the plane of paper or point towards the observer.
- The vertical bonds attached to the chiral carbon are considered to be below the plane of paper or point away from the observer.
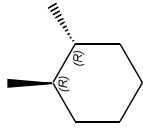

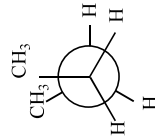Cis isomer   Trans isomer
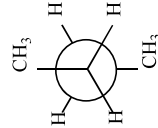
Cis isomer   Trans isomer

- **Conformational isomers:** Conformational isomers are the isomers that can be converted into one another by rotation around a single bond.
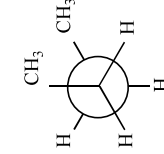
Example: eclipsed, gauche and anti butane are all conformational isomers of one another.(eclipsed means that identical groups are all directly in line with one another, gauche means that identical groups are 60 degree from one another and anti means that identical groups are 180 degree from one another.)

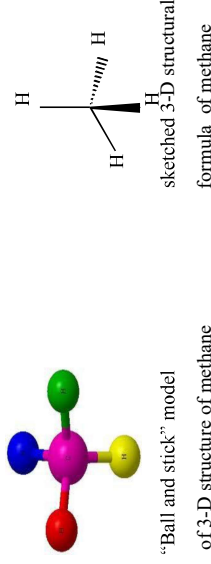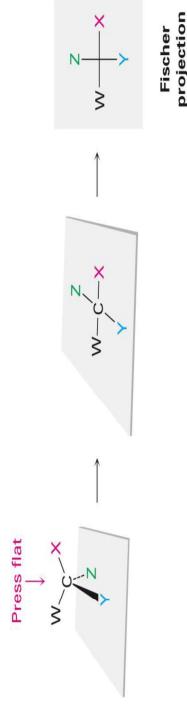Eclipsed   Anti   Gauche

These molecules can be interconverted by rotating around the central carbon-carbon single bond.

All parallel bonds in sawhorse formula are eclipsed and all anti parallel bonds are opposite or scattered. Gauche representation is that in which bulky groups are nearer to each other at 60^0 angles.

1.5.4 NEWMAN PROJECTION

Newman devised a very simple method of projecting three dimensional formulas on two dimensional paper which are known as Newman projection.

- In these formulae the molecule is viewed from the front or along the axis of a carbon-carbon bond.
- The carbon nearer to the eye is represented by a point and the carbon atom towards the rear by circle.
- The three atoms or groups on the carbon atoms are shown as being bonded to dot or circle by an angle of 120^0 to each other.
- In Newman formula all parallel bonds are eclipsed or all anti parallel or opposite bonds are staggered.


Eclipsed   Anti   Gauche
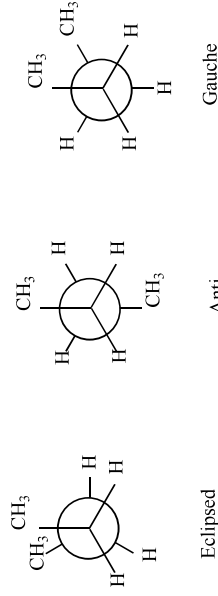
1.6 ELEMENTS OF SYMMETRY

Elements of symmetry offer a simple device to decide whether a molecule is chiral or achiral, *i.e.*, whether it is superimposable on its mirror image or not. When a molecule has no plane of symmetry, no centre of symmetry and no alternating axis of symmetry, it is non superimposable on its mirror image and is chiral (optically active).

1.6.1 PLANE OF SYMMETRY

The plane which divides a molecule in to two equal halves which are related as object and mirror image is known as plane of symmetry. For example
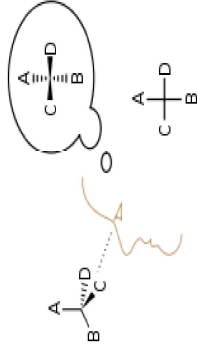
Example: glyceraldehyde
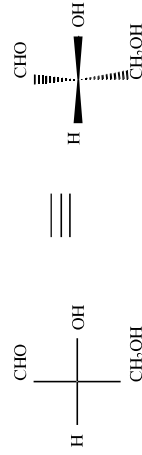
1.5.3 SAWHORSE FORMULA

The sawhorse formula indicates the arrangement of all the atoms or groups on two adjacent carbon atoms. The bonds between the two carbon atoms are drawn diagonally and of relatively greater length for the sake of clarity. The lower left hand carbon is taken as the front carbon or towards the observer and the upper right hand carbon as the back carbon or away from the observer. e.g. ethane

Anti conformation

eclipsed conformation

eclipsed conformation   anti conformation   gauche conformation

● = methyl group

CO-CO and NH-NH are symmetrical but CH₃ and H are not mirror images i.e., not symmetrical with respect to centre point.

NH-NH, CO-CO, CH₃ - CH₃ and H-H they are symmetrical with respect to centre of the molecule.

(Centre point)
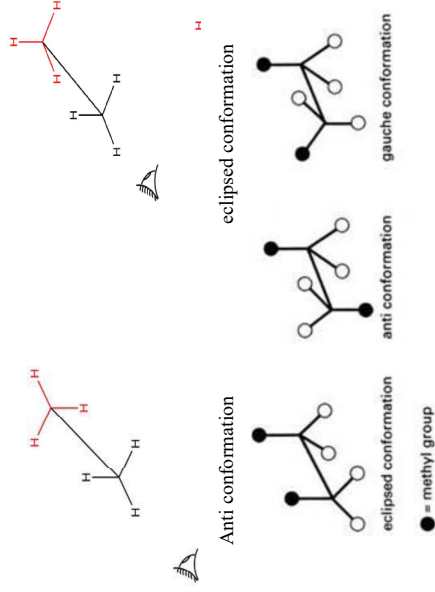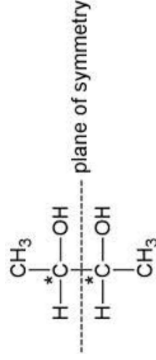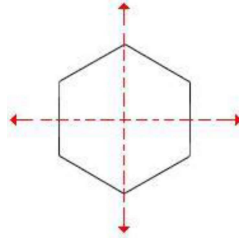
The molecules having plane of symmetry are achiral (optically inactive).

1.6.2 CENTER OF SYMMETRY

A center of symmetry in a molecule is said to exist if a line is drawn from any atom or group to this point and when extended to an equal distance beyond this point, meets the identical atom or group.

All lines are passing through this point, hence it is the center point of the molecule.

A centre of symmetry is usually present only in an even number ring. For example, the molecule of trans -2,4-dimethyl-cyclobutane –trans-1,3- dicarboxaylic acid has a center of symmetry.

(All lines are passing through this point, hence it is the center point of the molecule)
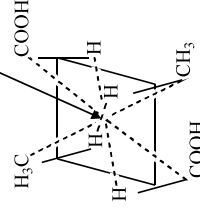
I

Another interesting example is dimethyl ketopiperizine. This has two isomers, cis and trans. The cis form has no plane of symmetry or centre of symmetry. The trans form on other hand, has a centre of symmetry.
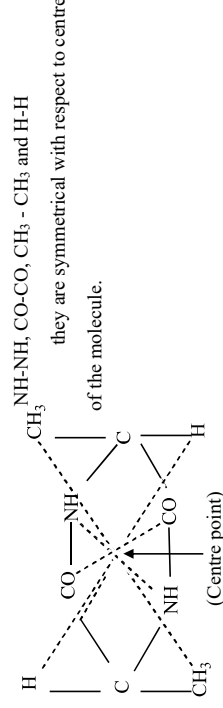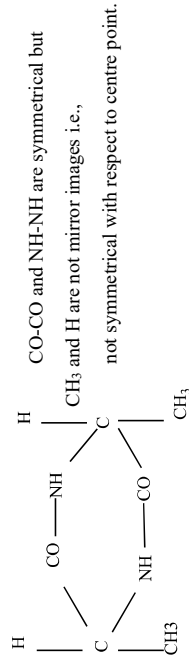
1.6.3 ALTERNATING AXIS OF SYMMETRY

A molecule possesses an alternating axis of symmetry if, when rotated through an angle $360^0/n$ about this axis and then followed by reflection in a plane perpendicular to the axis, the molecule is indistinguishable from the original molecule. Alternating axis of symmetry is rare and can be present in cyclic as well as open chain compounds.
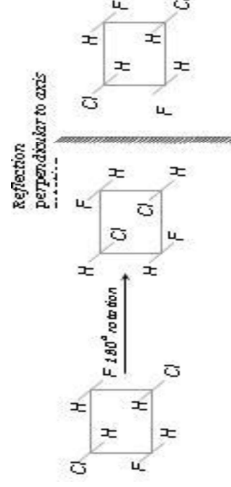
1.7 NOMENCLATURE OF OPTICAL ISOMERS

Following three nomenclatures are used for optically active compounds:

1.7.1 D, L SYSTEM OF NOMENCLATURE

This nomenclature is mainly used in sugar chemistry or optically active polyhydric carbonyl compounds. This is a relative nomenclature because all the configurations described with respect to glyceraldehydes.

All sugars whose Fischer projection formula shows the OH group on the right hand side of the chiral atom belong to the D-series.
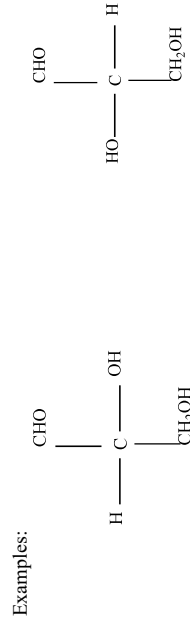
$$
\begin{array}{c}
\text{H} \longrightarrow \text{C} \longrightarrow \text{OH} \\
| \\
\text{CH}_2\text{OH}
\end{array}
$$
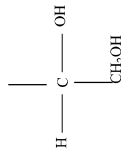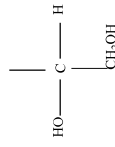
D-series.

Similarly, if OH is on the left hand side, then the sugar belongs to the L-series.

$$
\begin{array}{c}
\text{HO} \longrightarrow \text{C} \longrightarrow \text{H} \\
| \\
\text{CH}_2\text{OH}
\end{array}
$$

L-series

Examples:

$$
\begin{array}{c}
\text{CHO} \\
| \\
\text{H} \longrightarrow \text{C} \longrightarrow \text{OH} \\
| \\
\text{CH}_2\text{OH}
\end{array}
$$

D(+) glyceraldehyde

$$
\begin{array}{c}
\text{CHO} \\
| \\
\text{HO} \longrightarrow \text{C} \longrightarrow \text{H} \\
| \\
\text{CH}_2\text{OH}
\end{array}
$$

L(–) glyceraldehydes

- It must be noted that there is no relation between sign of rotation and (+, - or d,l) and configuration (D and L) of enentiomer.

- Any compound that can be prepared from, or converted in to D(+) glyceraldehydes will belong to D-series and similarly any compound that can be prepared from, or converted in to L(–) glyceraldehydes will belongs to the L-series.
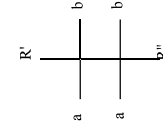
1.7.2 ERYTHRO AND THREO SYSTEM OF NOMENCLATURE

This nomenclature is mainly used only in those compounds which have only two chiral carbons and the following structures:
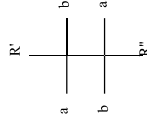
R'-Cab-Cab-R''   or   R'-Cab-Cbc-R''
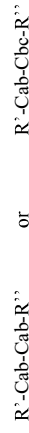
i.e. out of six substituent on two asymmetric carbons, at least one should be same in both the carbons.

When two like groups in fisher projection formula are drawn on the same side of vertical line, the isomer is called *erythro* form; if these are placed on the opposite sides the isomer is said to be *threo* form.
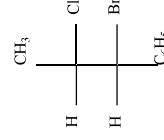
$$
\begin{array}{c}
\text{R'} \\
\text{a} \longrightarrow \longrightarrow \text{b} \\
\text{a} \longrightarrow \longrightarrow \text{b} \\
\text{R''}
\end{array}
$$

erythro form

$$
\begin{array}{c}
\text{R'} \\
\text{a} \longrightarrow \longrightarrow \text{b} \\
\text{b} \longrightarrow \longrightarrow \text{a} \\
\text{R''}
\end{array}
$$

threo form

Following are some examples of *threo* and *erythro* form.

$$
\begin{array}{c}
\text{CH}_3 \\
\text{H} \longrightarrow \longrightarrow \text{Cl} \\
\text{H} \longrightarrow \longrightarrow \text{Br} \\
\text{C}_6\text{H}_5
\end{array}
$$

erythro form

$$
\begin{array}{c}
\text{CH}_3 \\
\text{H} \longrightarrow \longrightarrow \text{Cl} \\
\text{Br} \longrightarrow \longrightarrow \text{H} \\
\text{C}_6\text{H}_5
\end{array}
$$

threo form

Rule 2: if two or more than two isotopes of the same element are present, the isotope of higher mass receives the higher priority.

$_1H^1$ $_1H^2$ $_1H^3$

increasing priority →

Rule 3: if two or more of the atoms directly bonded to the chiral carbon are identical, the atomic number of the next atom is used for priority assignment. If these atoms also have identical atoms attached to them, priority is determined at the first point of difference along the chain. The atom that has attached to it an atom of higher priority gets the higher priority.

- In the above example, the atoms connected directly to the chiral carbon are iodine and three carbons.
- Iodine has the highest priority.
- Connectivity of other three carbons are 2H and Br, 2H and C and 2H and C.
- Bromine has the highest atomic number amongst C, H, Br and thus CH_2Br has highest priority among these three groups (*i.e.* priority number 2).
- The remaining two carbon are still identical (C and 2H) connected to the second carbon of these groups are 2H and I and 2H and C. Iodine has highest priority.
- Amongst these atoms, so that CH_2-CH_2-I is next in priority list and CH_2-CH_2-CH_3 has the last priority.

Rule 4: If a double or a triple bond is linked to chiral centre, the involved electrons are duplicated or triplicated respectively.
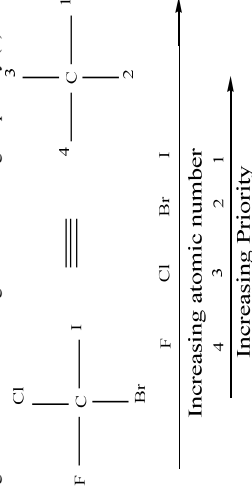
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erythro form

threo form

1.7.3 *R.S.* NOMENCLATURE

The order of rearrangement of four groups around a chiral carbon is called the absolute configuration around that atom. System which indicates absolute configuration was given by three chemists R.S. Cahn, C.K. Ingold and V. Prelog. This system is known as (*R*) and (*S*) system or the Cahn-Ingold Prelog system. The letter (*R*) comes from the Latin rectus (means right) while (*S*) comes from the Latin sinister (means left). Any Chiral carbon atoms have either an (*R*) configuration or a (*S*) configuration. Therefore one enantiomer is (*R*) and the other is (*S*). A racemic mixture may be designated as (*RS*), meaning a mixture of the two.
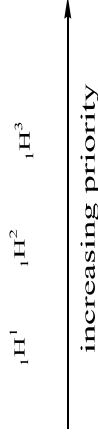
The R, S nomenclature involves two steps:

Step I: The four ligands (atom or groups) attached to the chiral centre are assigned a sequence of priority according to sequence rules.
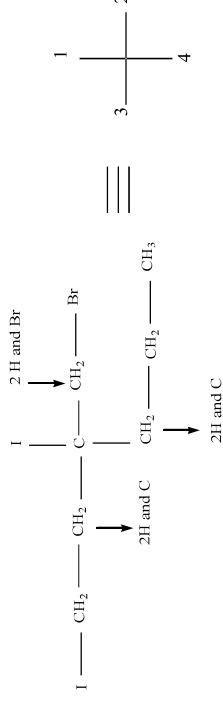
Rule 1: If all the four atoms directly attached to the chiral carbon are different, priority depends on their atomic number. The atom having highest atomic number gets the highest priority, i.e., (1).The atom with lowest atomic number is given lowest priority, i.e. (2), the group with next higher atomic number is given the next higher priority (3) and so on.
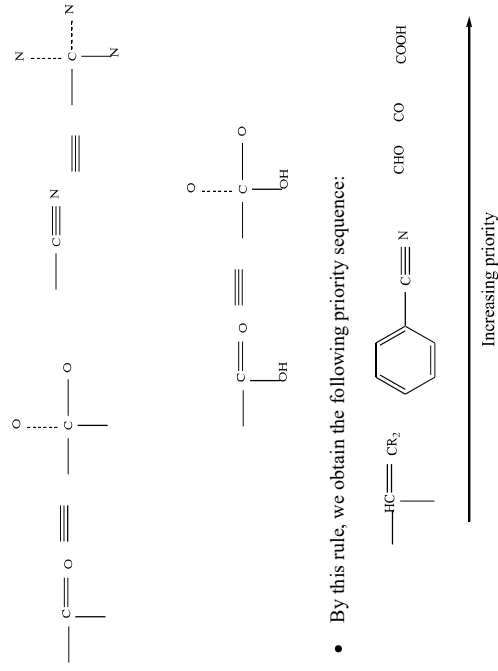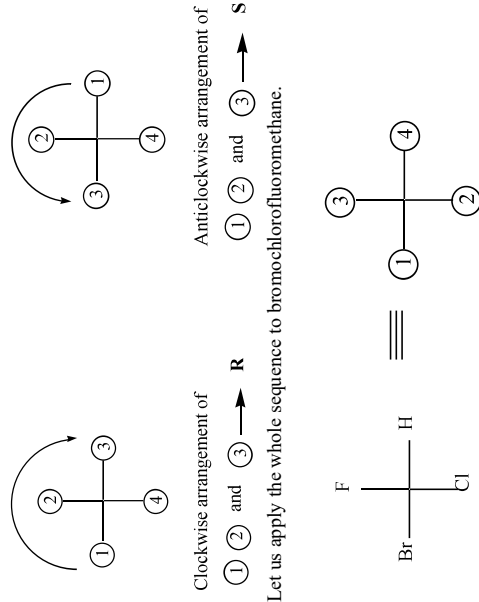
For example:

F   Cl   Br   I

4   3   2   1

Increasing atomic number

Increasing Priority →

In this Fischer projection, the least priority number is not at the bottom of the plane.

In such cases, the Fisher projection formula of the compound is converted in to another equivalent projection formula in such a manner that atom the lowest priority is placed vertically downward. This may be drawn by two interchanges between four priority numbers. The first interchange involves the two priority numbers, one is the least priority number and the other is the priority number which is present at the bottom of the plane. In the above case, first interchanges will takes place between 2 and 4.

A

First interchange
between 2 and 4

B

A second inter change creates the original molecule (i.e. A).

Second interchange between
remaining groups, i.e., 1 and 3

B

arrangement of 1,2 and 3 are
clockwise, hence
configuration is **R**

Example:-

Second interchange between
1 and 2

A

First interchange between
3 and 4

B

clockwise, hence
configuration is **R**

- By this rule, we obtain the following priority sequence:
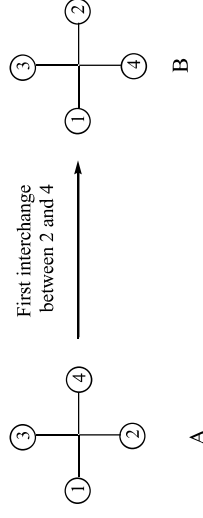
Increasing priority

STEP-II: The molecule is then visualised so that the group of lowest priority (4) is directed away from the observer (at this position the lowest priority is at the bottom of the plane). The remaining three groups are in a plane facing the observer. If the eye travels clockwise as we look from the group of highest priority to the group of second and third priority (i.e. 1→2→3 with respect to 4) the configuration is designated R. If arrangement of groups is in anticlockwise direction, the configuration is designated as S.
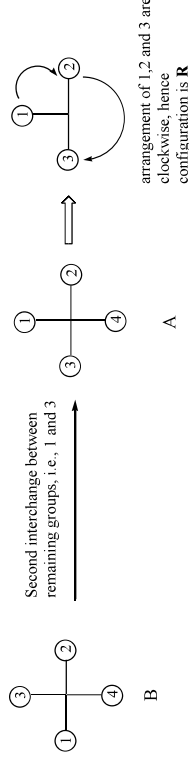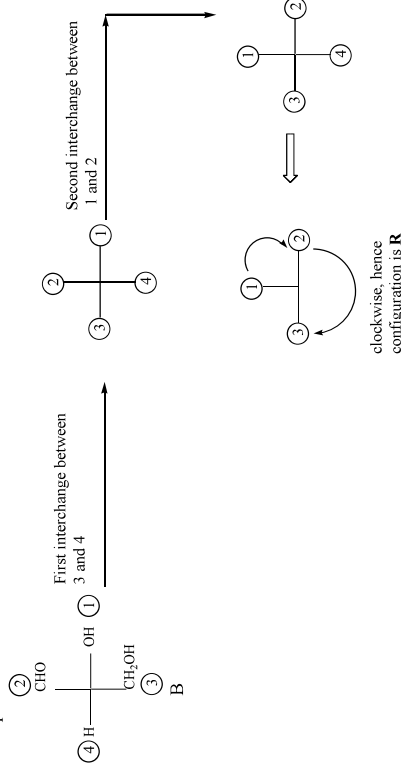
For example:

Clockwise arrangement of
①②and③ ⟶ **R**

Anticlockwise arrangement of
①②and③ ⟶ **S**

Let us apply the whole sequence to bromochlorofluoromethane.

Note:-

- An odd number of interchange of positions of groups on chiral carbon gives different compound.

- An even number of interchange of positions of groups on chiral carbon gives same compound.

An alternative, simple and most widely accepted procedure used now (Epling,1982) to assign R,S configuration in the case of Fischer projections is as followes:

Case-I: R and S nomenclature from Fischer projection formula (Golden rule): If in a Fischer projection, the group of lowest priority (4) is on a vertical line, then the assignment of configuration is R for a clockwise sequence of 1 to 2to 3 and S for anticlockwise sequence.
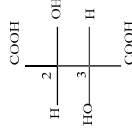
For example:

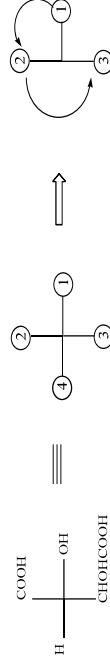Anticlockwise arrangement hence S- configuration
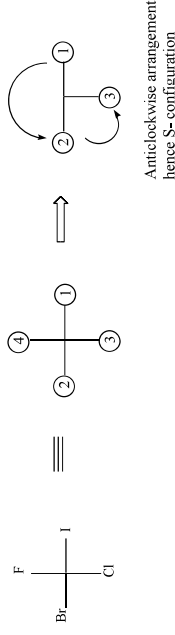
However, if the group of lowest priority is on horizontal line, then the assignment of configuration is S for a clockwise sequence of 1 to 2 to 3, and R for the anticlockwise sequence.

Anticlockwise arrangement but lowest priority at horizontal line hence R- configuration
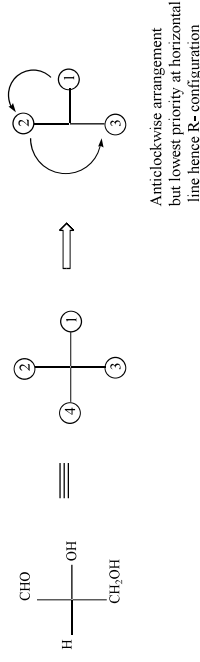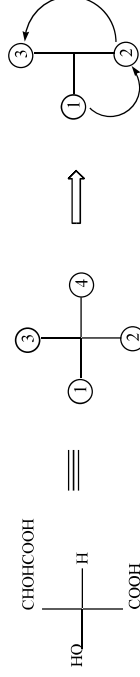
When molecule contain two or more chiral centres, each chiral centre is assigned an R or S configuration according to the sequence and conversion rules. Thus (+) tartaric acid is (2R, 3R) (+) tartaric acid.


Configuration at chiral carbon - 2.

Anticlockwise arrangement but lowest priority at horizontal line hence R- configuration

Configuration at chiral carbon - 3.

Anticlockwise arrangement but lowest priority at horizontal line hence R- configuration

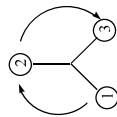**Case-II: R, S- nomenclature from flying-wedge formula.**

- If the group of the lowest priority is away from the observer (i.e., bonded by dashed line) and the priority sequence (1 → 2→ 3) is clockwise, then the configuration is assigned as R. If the priority sequence is anticlockwise then the configuration is S.

Lowest priority order is on deshed line

Clockwise arrangement thus configuration is R
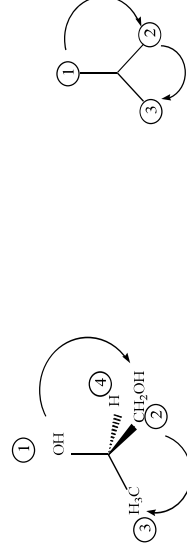
- If the group of lowest priority is not bonded by dashed line then interchange a pair of groups so that the group with the lowest priority is bonded by dashed line. Now see the sequence ($1 \rightarrow 2 \rightarrow 3$), if it is clockwise then the configuration is assigned as S and if anticlockwise R. This is because you have interchanged a pair of groups and now you are determining the configuration of enantiomer of original molecule.
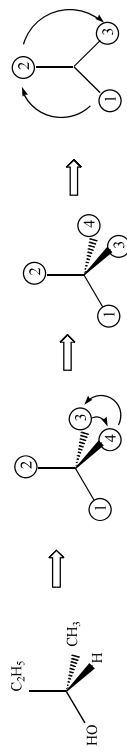
Least priority order is not bonded with deshed line , so interchange the group 3 and 4

This is R configuration, which means that the original compound has S configuration

1.8 SUMMARY

In this unit we have discussed the various basic terms used in stereochemistry and necessary conditions which are important for any molecule to show stereoisomerism. Further we studied various kinds of three dimensional representations and their nomenclature and brief description of element of symmetry.

1.9 GLOSSARY

Asymmetric carbon is a carbon atom that is bonded to four different groups. It is also called *chiral carbon.*

Diastereomers are optical isomers that are not mirror images.

Enantiomers are optical isomers that are mirror images.

Meso Compound is a compound that has more than one asymmetric carbon and that is superimposable on its mirror image. Meso compounds are optically inactive.

Optically active molecule is a molecule that cannot be superimposed on its mirror image. It is also called chiral molecule.

1.10 CHECK YOUR PROGRESS

1. Define the term 'Stereochemistry'.
2. Explain the terms 'Chirality' and 'Achirality'.
3. What do you understand by the term 'Stereogenic center'?
4. Explain 'Stereoisomers'
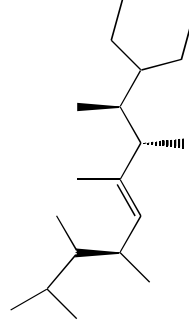5. Explain ' Element of Symmetry'.

1.11 BIBLIOGRAPHY

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Singh, J. and Yadav, L.D.S. (2013) Organic Chemistry Vol-I, A Pragati Prakashan, Meerut.

Nasipuri, D. (2012) Stereochemistry of organic Compounds, New Academic Science, UK.

Bahl, A. and Bahl, B.S. (2011) A Text Book of Organic Chemistry, S. Chand Publisher, New Delhi.

1.12 SUGGESTED READINGS

Christian Wolf (2007), Dynamic Stereochemistry of Chiral Compounds, Royal Society of Chemistry.

Eliel E.L.,Samuel H. W., Stereochemistry of Organic Compounds. Wiley.

1.13 TERMINAL QUESTIONS

1. How many chiral atoms does the following molecule have?

2. What is the steriochemical relationship between the following two molecules?

CH₃ | CH₂CH₃
Cl —|
Cl —|
H |
C₆H₅

CH₂CH₃ CH₃
H
H
Cl
Cl