

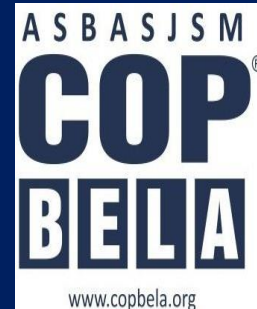


Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial

COLLEGE OF PHARMACY

(An Autonomous College)

BELA (Ropar) Punjab



Name of Unit	Stereoisomerism
Subject /Course Name	Pharmaceutical Organic Chemistry-III
Subject/Course ID	BP401T
Class: B.Pharm. Semester	IV
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Learning Outcome of Module 01

LO	Learning Outcome	Course Outcome Code
LO1	To understand about Stereoisomerism and its types.	BP402.1
LO2	To understand about Optical Isomerism, Optical Activity and Chirality.	BP402.1
LO3	To understand how to assign configuration of optical isomers.	BP402.1
LO4	To understand about Racemization and methods of resolution of racemic mixture.	BP402.1
LO5	To understand about Asymmetric synthesis.	BP402.1

Content Table

Topic
<ul style="list-style-type: none">• Isomerism• Stereoisomerism• Optical Isomerism• Optical Activity• Elements of Symmetry• Enantiomerism• Diastereoisomerism• Meso compounds• Racemization• Resolution of racemic mixture• Configuration• DL System• RS System• Reactions of Chiral molecules• Asymmetric Synthesis

INTRODUCTION OF ISOMERISM

ISOMERS: Isomers are different compounds having the same molecular formula but different physical and chemical properties. These compounds are known as isomers and this property is known as Isomerism.

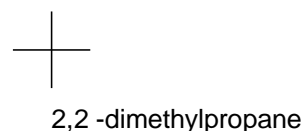
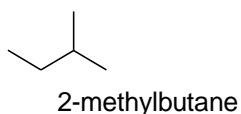
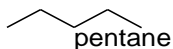
The two major classes of Isomerism are:

1. Constitutional/Structural Isomerism
2. Stereoisomerism

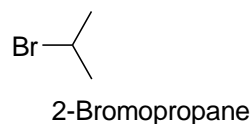
Constitutional/Structural Isomerism: These have same molecular formula but different structure and have different properties. This is further types which given below:

- Chain Isomerism
- Position Isomerism
- Functional Isomerism
- Metamerism
- Tautomerism
- Ring Chain Isomerism

Chain Isomerism: These isomers arise because of the possibility of branching in carbon chains. There are three isomers of pentane, C_5H_{12} . i.e. n-pentane, Isopentane (methylbutane) and neopentane (dimethylpropane).

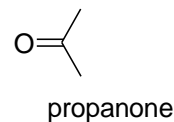
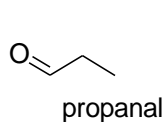


Position Isomerism: The basic carbon skeleton remains unchanged, but important groups are moved around on that skeleton. For example, there are two structural isomers with the molecular formula C_3H_7Br



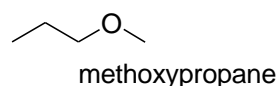
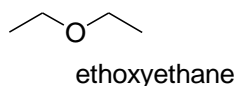
Functional group Isomerism: These isomers contain different functional groups - that is they belong to different families of compounds (different homologous series). For example, a

molecular formula C_3H_6O could be either propanal (an aldehyde) or propanone (a ketone).

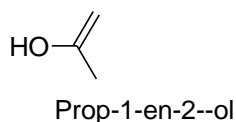
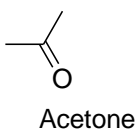


Metamerism: Compounds having the same molecular formula but different number of carbon atoms (alkyl groups) on either side of functional group are called metamers and the phenomenon is called metamerism. It is a rare type of isomerism and is generally limited to molecules that contain a divalent atom (such as sulfur or oxygen), surrounded by alkyl groups.

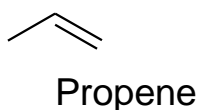
Example: $C_4H_{10}O$ can be represented as ethoxyethane ($C_2H_5OC_2H_5$) and methoxy-propane ($CH_3OC_3H_7$).



Tautomerism: Tautomers are isomers of a compound which differ only in the position of the protons and electrons. The carbon skeleton of the compound is unchanged. A reaction which involves simple proton transfer in an intramolecular fashion is called a tautomerism. For Example,



Ring Chain Isomerism: In ring-chain isomerism, one of the isomers has an open-chain structure whereas the other has a ring structure. They generally contain a different number of pi bonds. A great example of this type of isomerism can be observed in C_3H_6 . Propene and cyclopropane are the resulting isomers, as illustrated below.



STEREISOMERISM

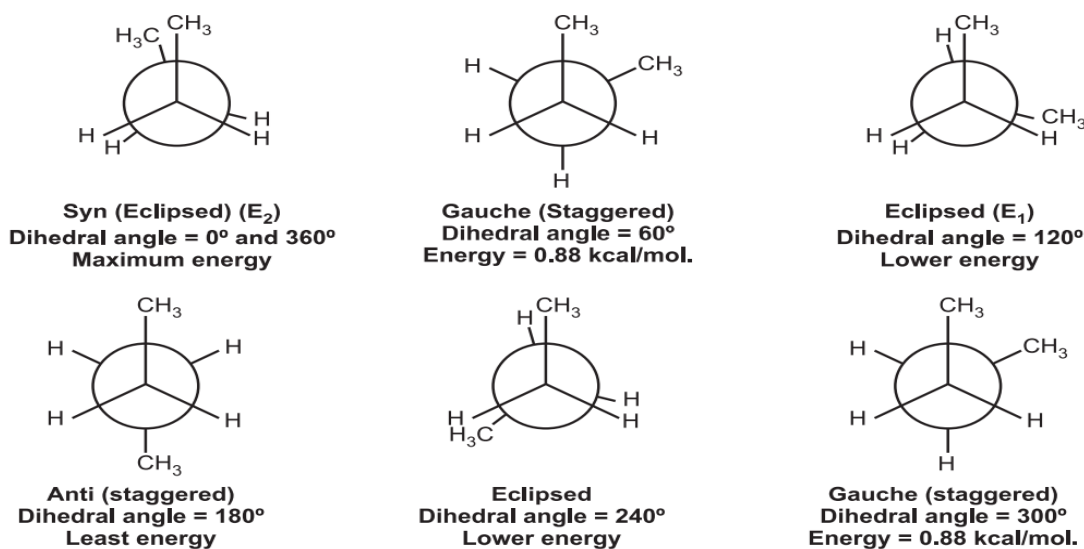
Stereoisomers have same molecular and structure formula, **same bonding sequence but differ only in the way the atoms are oriented in space**. Stereoisomers differ in configuration. This phenomenon is called Stereoisomerism.

Stereoisomerisms are two types.

Conformational Isomerism

Configurational Isomerism

Conformational Isomerism: It is a form of stereoisomerism in which the **isomers can be interconverted just by rotations about single bonds**. While any two arrangements of atoms in a molecule that differ by rotation about single bonds can be referred to as different conformations.



Configurational Isomerism: It is a form of stereoisomerism in which the isomers can be **interconverted only by breaking and remaking of covalent bonds**. These cannot be interconverted by simple rotation about single bonds.

It has two types:

Optical Isomerism

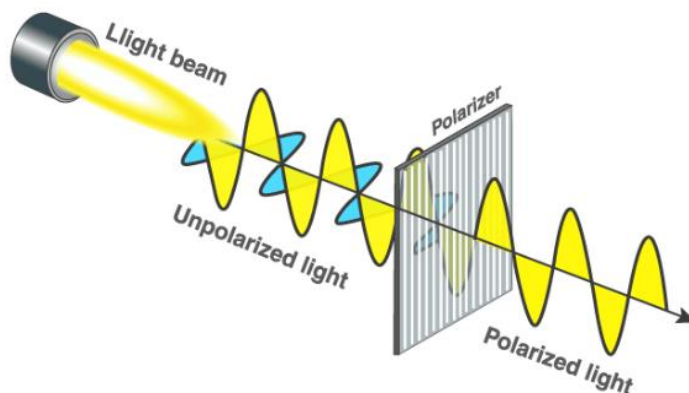
Geometrical Isomerism

Optical Isomerism:

- **Isomers** which differ only in their behavior towards plane polarized light.
- Rotates plane of polarized light towards right or left to the same extent and this phenomenon is called optical activity.
- The chemical and physical properties of two enantiomers are identical except in their interaction with chiral substances and plane polarized light.

In order to understand the phenomenon of optical isomerism and optical activity, we must know the following terms:

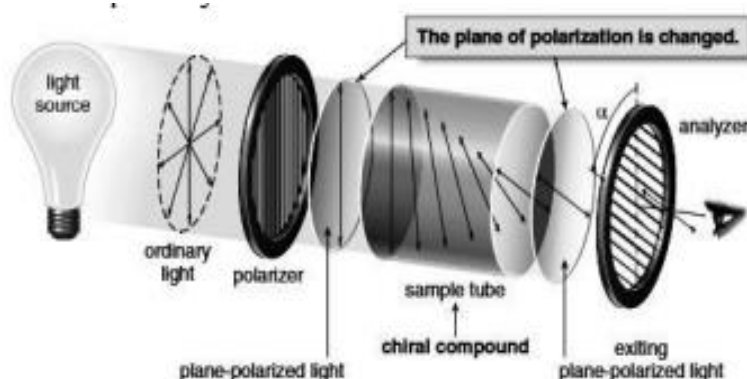
Plane Polarized Light: If by filtering the beam with specialized materials, the electric field vectors are limited to a single plane, then the light is referred to as plane or linearly polarized with respect to the propagation direction. **All waves vibrating in a single plane are referred to as plane parallel or plane-polarized.**



Optical Activity: Optical activity was first observed by **the French physicist Jean-Baptiste Biot**. He concluded that the change in direction of plane-polarized light when it passed through certain substances was actually a rotation of light, and that it had a molecular basis. His work was supported by the experimentation of **Louis Pasteur**.

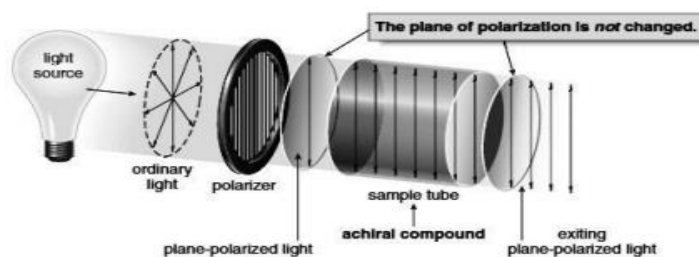
Pasteur observed the existence of two crystals that were mirror images in **tartaric acid**, an acid found in wine. Through **meticulous experimentation**, he found that one set of molecules rotated polarized light clockwise while the other rotated light counterclockwise to the same extent. He also observed that a mixture of both, a **racemic mixture (or racemic modification)**, did not rotate light because the optical activity of one molecule canceled the effects of the other molecule. **Pasteur was the first to show the existence of chiral molecule.**

Optical active compound: A chiral compound that rotates the plane of polarized light is said to be optically active.



Rotation of light: The optical active compounds can that rotates plane-polarized light in the positive direction, or clockwise, is called **dextrorotary** [(+), or **d-**], while the compounds that rotates the light in the negative direction, or counterclockwise, is called **levorotary** [(-), or **l-**]. When both d- and l- isomers are present in equal amounts, the mixture is called a racemic mixture.

Optical Inactive Compound: A achiral compound that does not change the plane of polarized light is said to be optically inactive.



Measuring Optical Activity (Angle of Rotation): Optical activity is measured by a polarimeter, and is dependent on several factors:

1. concentration of the sample,
2. temperature,
3. length of the sample tube or cell, and
- 4 wavelength of the light passing through the sample.

Rotation is given in +/- degrees, depending on whether the sample has d- (positive) or l- (negative) enantiomers. The standard measurement for rotation for a specific chemical compound is called the **specific rotation, defined as an angle measured at a path length of decimeter and a concentration of 1g/ml.**

The specific rotation of a pure substance is an intrinsic property.

In solution, the formula for **specific rotation** is:

$$[\alpha]_{\lambda}^T = \frac{\alpha}{l \cdot c}$$

where

$[\alpha]$ is the specific rotation in degrees $\text{cm}^3 \text{ dm}^{-1} \text{ g}^{-1}$.

λ is the wavelength in nanometers

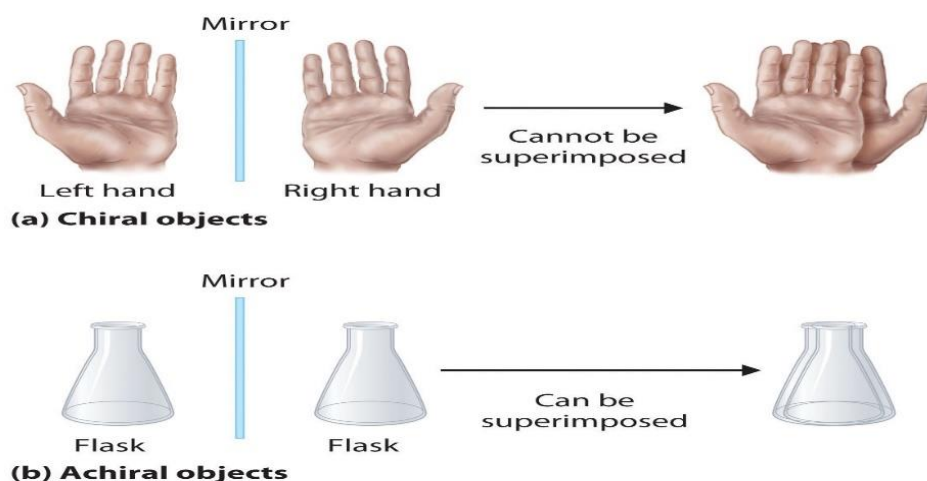
α is the measured angle of rotation of a substance,

T is the temperature in degrees,

l is the path length in decimeters

c is the concentration in g/ml

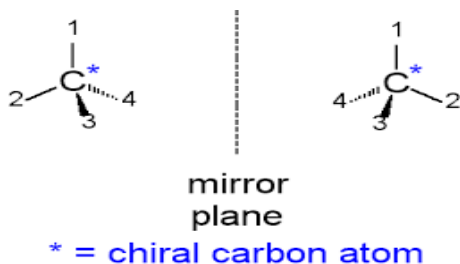
Chiral and Achiral Molecules: Chiral molecules are non-superimposable mirror images of each other. Chiral molecules are superimposable mirror images of each other. Chiral molecules are asymmetric at one or more centres. Achiral molecules are symmetric at all the centres.



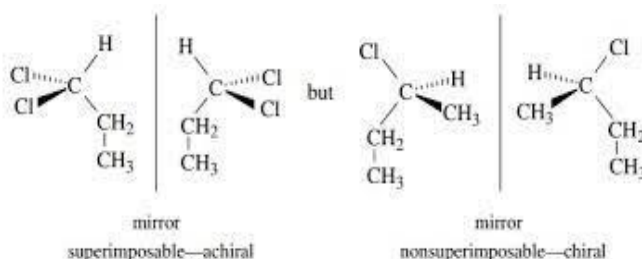
Chiral or Asymmetric Carbon: An asymmetric carbon atom (chiral carbon) is a carbon atom that is attached to four different types of atoms or groups of atoms.

Knowing the number of asymmetric carbon atoms, one can calculate the maximum possible number of stereoisomers for any given molecule as follows:

If n is the number of asymmetric carbon atoms then the maximum number of isomers = 2^n



The mirror image of such carbon is non-superimposable as shown below:



Elements of Symmetry: There are three elements of symmetry which helps in identifying the *superimpossibility* of a molecule or an object and its mirror image.

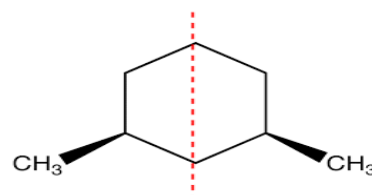
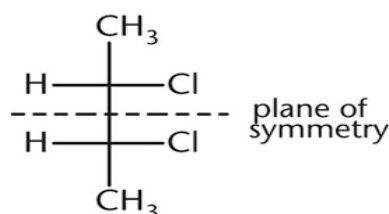
Chiral objects do not have an elements of symmetry while achiral objects have one or more elements of symmetry. The three elements of symmetry.

✚ **Plane of Symmetry**

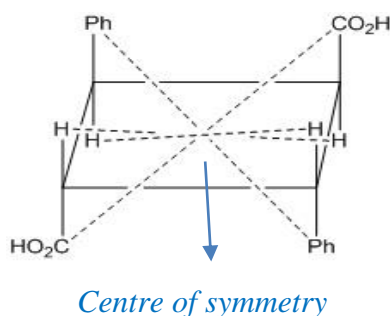
✚ **Centre of Symmetry**

✚ **Axis of Symmetry**

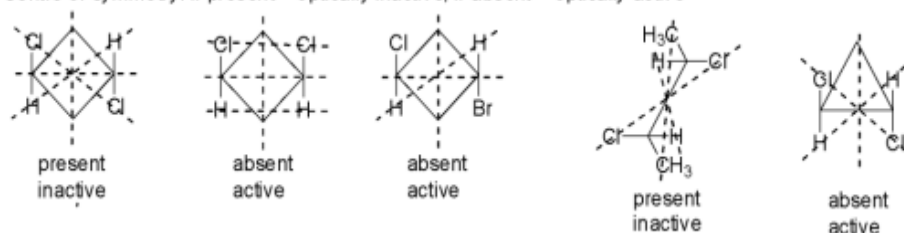
Plane of Symmetry: A plane of symmetry is **an imaginary plane that bisects a molecule into halves** that are mirror images of each other. So, Compound having plane of symmetry are optically inactive. For Examples, plane of symmetry



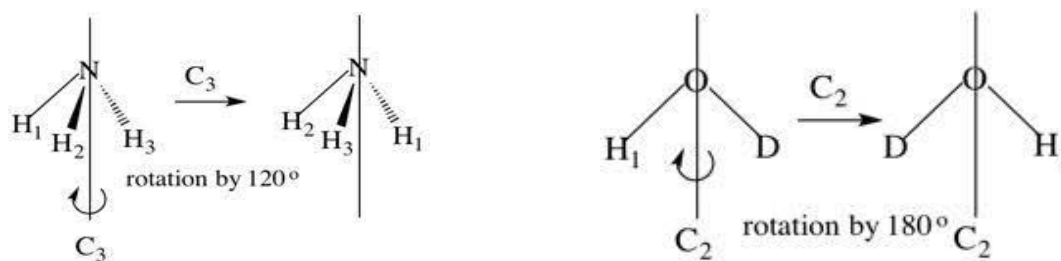
Centre of Symmetry: A centre of symmetry exists in a crystal if an imaginary line can be extended from **any point on its surface through its centre** and a similar point is present along the line equidistant from the centre. This is equivalent to i , or inversion. For Examples



Centre of symmetry; if present = optically inactive; if absent = optically active



Axis of symmetry: A molecule can have more than one symmetry axis; the one with the highest n is called the principal axis, and by convention is aligned with the z -axis in a Cartesian coordinate system. Plane of symmetry: a plane of reflection through which an identical copy of the original molecule is generated. For examples,



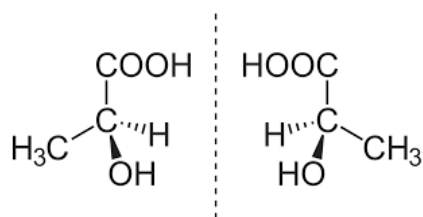
Optical Isomerism The stereoisomers which resemble each other in their chemical properties and most of the physical properties but differ only in their behaviour towards plane polarized light are called optical isomers and this phenomenon is called **optical isomerism**. It is further subdivided into **three types**:-

1. Enantiomerism

2. Diastereoisomerism

3.Meso compounds

Enantiomerism: Enantiomers are a pair of molecules that exist in two forms that are mirror images of one another but cannot be superimposed one upon the other. Enantiomers are in every other respect chemically identical. A pair of enantiomers is distinguished by the direction in which when dissolved in solution they rotate polarized light, either **dextro (d or +) or levo (l or -) rotatory**; hence the term optical isomers. For Examples,

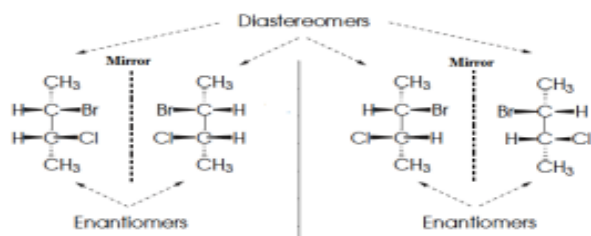


Enantiomers of Lactic Acid

Properties of Enantiomers:

1. Enantiomers generally have **identical physical properties** such as melting point, boiling point, infrared absorptions and NMR spectra.
2. It is important to realize that the melting point of one Enantiomer will be identical to that of the other Enantiomer, the melting point of a mixture of the two Enantiomers may be different.

Diastereoisomerism: Diastereomers are defined as non-mirror image, non-identical stereoisomers. Hence, they occur when two or more stereoisomers of a compound have different configurations at one or more (but not all) of the equivalent (related) **stereocenters** and are not mirror images of each other. For example



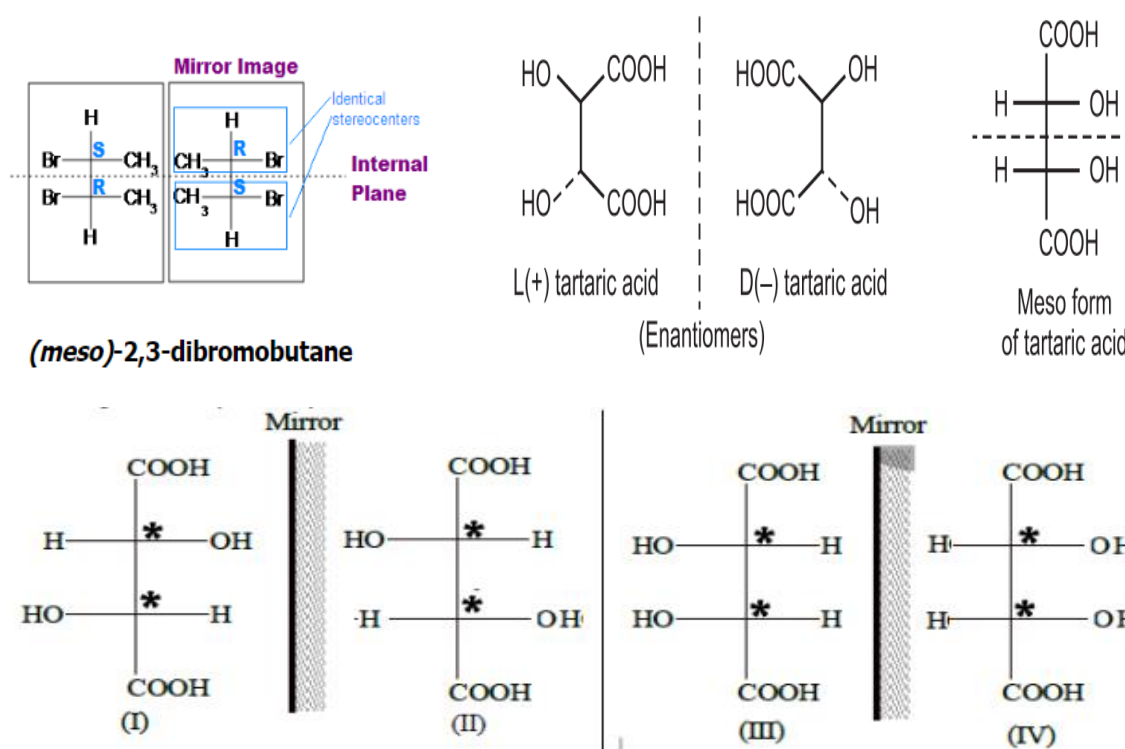
2-bromo-3-chlorobutane

Properties of Diastereoisomers:

1. Diastereomers have **different physical properties** such as melting points, boiling points, densities, solubilities, refractive indices, dielectric constants and specific rotations.

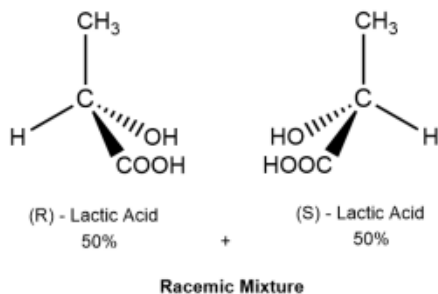
2. Diastereomers other than geometrical isomers may or may not be optically active.
3. Diastereomers show similar, but not identical chemical properties. The rates of reactions of the two diastereomers with a given reagent provided the reagent is not rapidly active.
4. On account of differences in their physical properties, diastereomers can be separated from one another through techniques like fractional crystallization, fractional distillation, chromatography etc.

Meso Compounds: An achiral compound with chiral centres is known as a meso compound. Although it has two or more stereocenters, a meso compound has an internal plane of symmetry that makes it superimposable on its mirror image and is optically inactive. For examples,



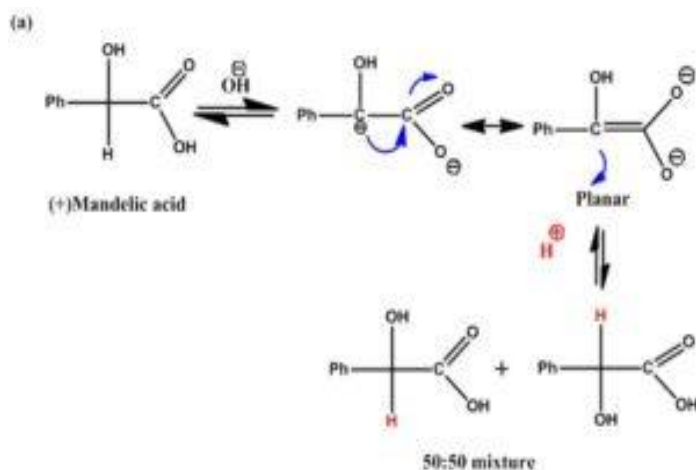
I and II are enantiomers (non-superimposable); III and IV are meso form (superimposable).

Racemization: It is a conversion, by heat or by chemical reaction, of an optically active compound into a racemic (optically inactive) form. Half of the optically active substance becomes its mirror image (enantiomer) referred as racemic mixtures (i.e. contain equal amount of (+) and (-) forms).



A solution containing equal amounts of (R)-2-butanol and (S)-2-butanol is a racemic mixture

Mechanism of Racemization: Mechanism of racemization through the carbanion formation at the chiral carbon α to a carbonyl group i.e., in the case of chiral aldehydes, ketones, carboxylic acids etc. where the chiral carbon α to the carbonyl group. This is because in such cases the carbanions undergo racemization.



Resolution of Racemic Mixture: The process of splitting a racemate into its enantiomers is known as resolution.

Various methods used for separation of a racemic mixture are given below:

1. Mechanical Separation:

This involved mechanical separation of the crystal of one enantiomers from the other in racemic mixture based on difference in their shapes. Being mirror image of each other, Crystal of the two forms have different shapes. Separated by magnifying lens and forceps.

✚ This method **first used by Pasteur (1884)** for here solution of **sodium ammonium tartarate**

which crystallize out in the form of racemic mixture below 27°C.

- ✚ This method is time consuming and every compound cannot be crystallized at room temperature

2. Biochemical Method: This method is based on the fact that when certain micro-organisms (e.g. bacteria, yeast, mould, fungi) are grown in dilute solution of racemic mixture, they assimilate one enantiomer rapidly than the others.

e.g. The mould penicillin glaucum preferentially destroys the (+) isomers of racemic ammonium tartarate and thus leaves the (-) ammonium tartarate in solution.

This method has certain **disadvantage** viz

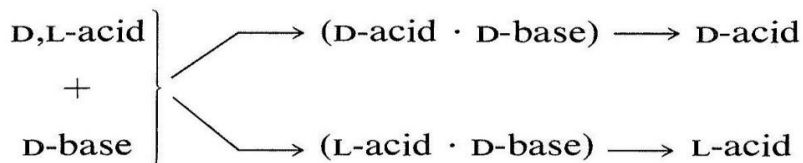
- Sometimes it is impracticable to find a microorganism (Enzyme) applicable to given racemic form.
- Sometimes the racemic modification may be toxic for the micro-organism and may destroy the enzyme or may not be attacked by either of them.

3. Chromatographic Method: The racemic mixture can be separated by chromatography on an optically active support. The diastereomeric adsorbates which are formed have different stabilities. Thus one enantiomer will be held more tightly than the other and would be eluted first. Chromatographic methods are developed for direct separation of enantiomers.

Stereoselective adsorbents prepared in the presence of a suitable reference compound of known configuration. e.g.: silica gel in the presence of quinine. **Silica gel adsorbs quinine more readily than its stereoisomer quinidine.**

Cinchonidine (configurationally related to quinine) is adsorbed more readily than its stereoisomer cinchonine (configurationally related to quinidine).

4. By Diastereomers: This method converts the enantiomers of a racemic mixture into diastereomers with the aid of a pure enantiomer of another compound. Diastereomers are non-identical, they have different physical properties and hence easily be separated into two compounds by fractional crystallization.



Configuration: The spatial arrangement of atoms in a molecule in a space which characterize a particular stereoisomer.

Two terms are quite often used while describing the configuration of different stereoisomers.

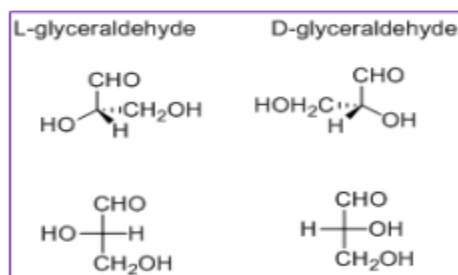
1. Absolute configuration
2. Relative configuration

Absolute configuration: Absolute configuration refers to the spatial arrangement of atoms within a chiral molecular entity (or group) and its resultant stereochemical description.

Relative configuration: The arrangement of atoms or group of atoms that is described relative to other atoms or group of atoms in the molecule.

D and L conventions

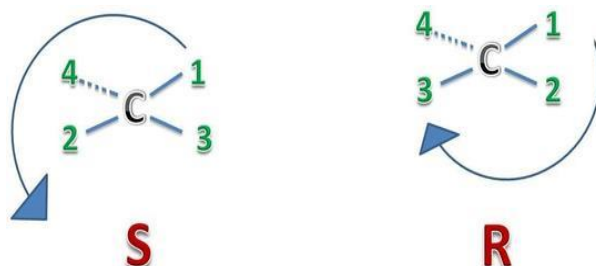
The notations D and L describe the relative configurations of organic compounds. The notations D and L are used to describe the configurations of carbohydrates and amino acids. Glyceraldehyde has been chosen as arbitrary standard for the D and L notation in sugar chemistry. Because, this has an asymmetric carbon and can exist as a pair of enantiomers.



In a Fischer projection, the carbonyl group is always placed on the top position for monosaccharide. From its structure, if the –OH group attached to the bottom-most asymmetric center (the carbon that is second from the bottom) is on the right, then, the compound is a D sugar. If the –OH group is on the left, then, the compound is a L-sugar. Almost all sugars found in nature are D-sugar.

R and S Configurational Notations: Absolute configuration uses a set of rules to describe the relative positions of each bond around the chiral center atom. The most common labeling method uses the descriptors R or S is based on the **Cahn–Ingold–Prelog priority rules**.

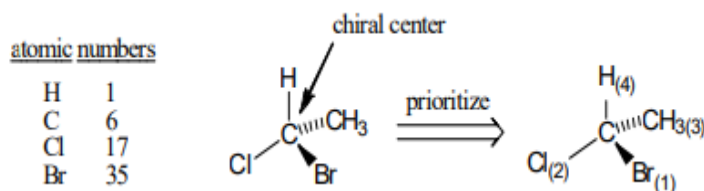
R and S refer to Rectus and Sinister, which are Latin for right and left, respectively.



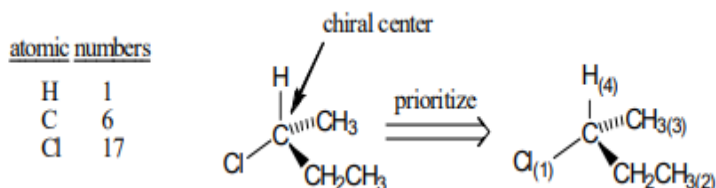
Consider the first picture: a curved arrow is drawn from the highest priority (1) substituent to the lowest priority (4) substituent. If the **arrow points in a counterclockwise direction the configuration at stereocenter considered S** ("Sinister" → Latin= "left"). If, however, **the arrow points clockwise, then the stereocenter is labeled R** ("Rectus" → Latin= "right")

Sequence Rule:

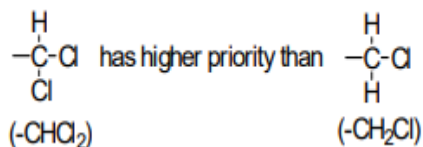
Rule1. Prioritize the four atoms, or groups of atoms, attached to the chiral center based on the atomic number of the atom that is bonded directly to the chiral center. The higher the atomic number, the higher the priority. Number the four atoms, or groups of atoms, such that "1" has the highest priority and 4" has the lowest priority.



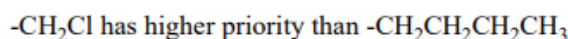
Rule 2. If two or more of the atoms that are bonded directly to the chiral center are the same, then prioritize these groups based on the next set of atoms (i.e., atoms adjacent to the directly bonded atoms). Continue until priorities can be assigned. Priority is assigned at the first point of difference.



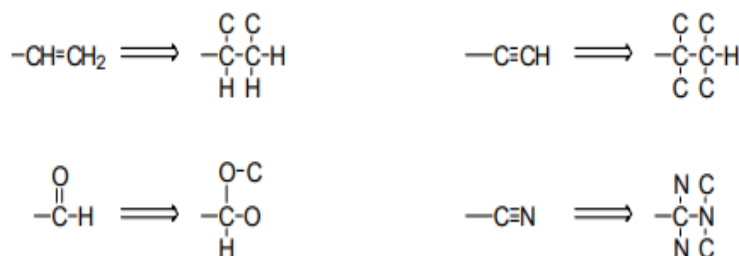
- 🌿 If two atoms have substituents of the same priority, higher priority is assigned to the atom with more of these substituents.



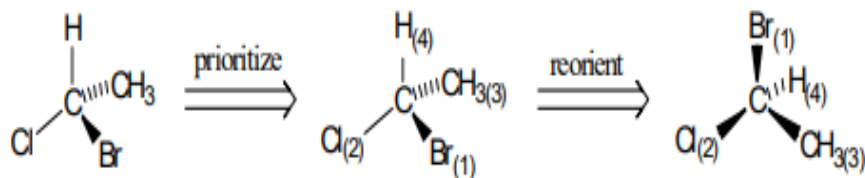
- 🌿 A larger group (i.e., more atoms) may not necessarily have a higher priority over another (smaller) group.



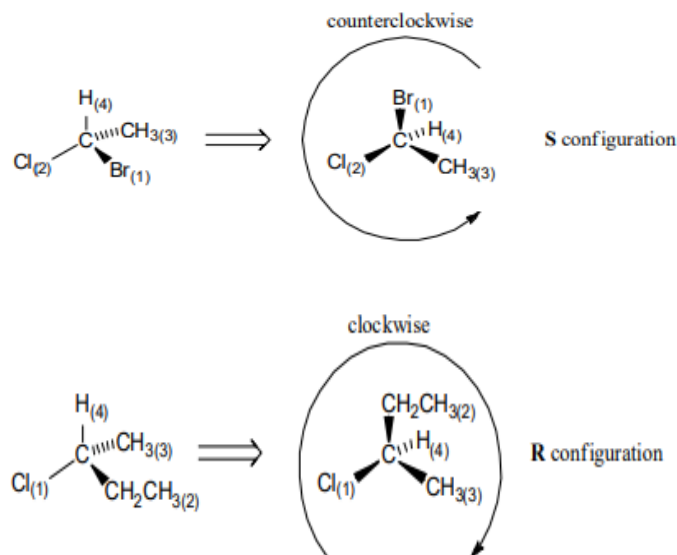
Rule 3. Atoms participating in double/triple bonds are considered to be bonded to an equivalent number of similar “phantom” atoms by single bonds. Note: “phantom” atoms are bonded to no other atoms.



Rule 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.



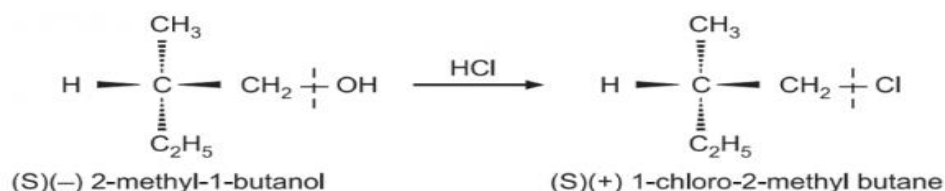
Rule 5. If the three groups projecting toward you are ordered from highest priority (#1) to lowest priority (#3) clockwise, then the configuration is “R”. If the three groups projecting toward you are ordered from highest priority (#1) to lowest priority (#3) counterclockwise, then the configuration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



REACTIONS OF CHIRAL MOLECULES: Chiral molecules react with the reagents in a variety of ways and accordingly, reactions are classified as follows:

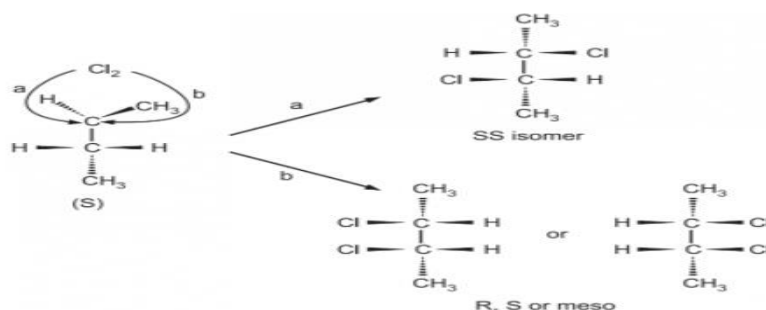
1. Reactions where bonds with the chiral center are not broken.
2. Reactions leading to generation of chiral center.
3. Reactions of chiral compounds with optically active reagents.
4. Reactions where bonds with the chiral center are broken.

1. Reactions where bonds with the chiral center are not broken: These reactions can be used to relate the configuration of one compound to that of another. Configuration is retained when the reaction does not involve the breaking of a bond to a chiral center.



Here the bond to the chiral center is not broken 'S' configuration is retained, because ' $-\text{CH}_2-\text{Cl}$ ' occupies the same relative position as that was occupied by $-\text{CH}_2\text{OH}$ in the reactant. This retention of configuration can be utilized to determine the configurational relationship between two optically active compounds by converting them into each other by reactions that do not involve the breaking of a bond to a chiral center.

2. Reactions leading to generation of chiral center: Generation of first chiral center in a compound usually yields equal amounts of enantiomers (Racemic mixture) but reactions that form second/new chiral center yield unequal amounts of diastereomers depending on the side of attack.

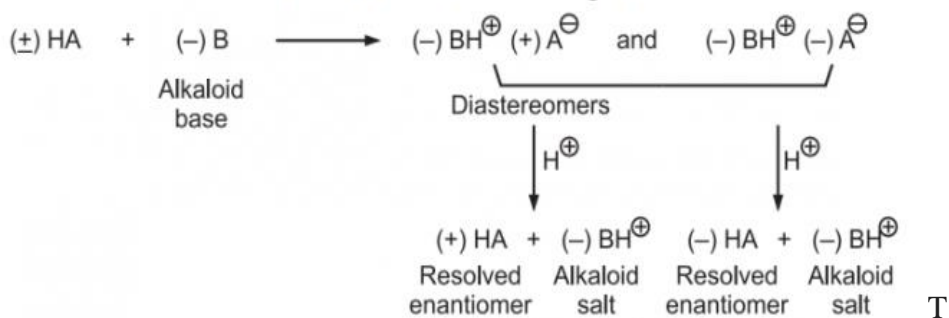


Retention of configuration(s) occurs as there is no bond breaking to the chiral center. For the new chiral center, depending on side of attack from the same or opposite side, diastereomers are formed but in unequal amounts.

3. Reactions of chiral compounds with optically active reagents: Such reactions are commonly used in the resolution or separation of a racemic mixture/modification into individual enantiomers. So to obtain pure enantiomers from racemic modification, use of optically active reagents is made. Such optically active reagent is easily obtained from natural sources or generated from naturally available reagents.

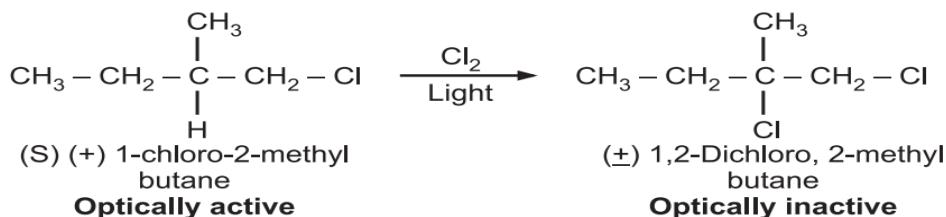
Common reactions are reactions of organic acids and bases to form salts.

e.g. Reaction of racemic acid (+) HA with alkaloid reagent (–) B.

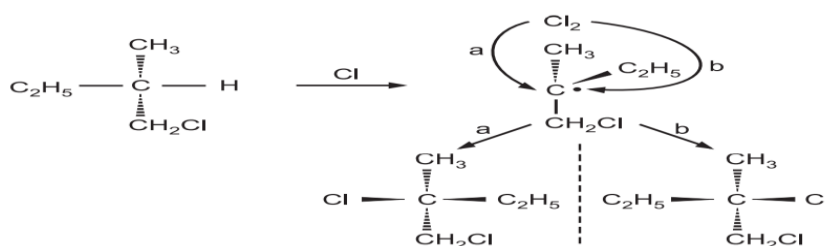


Alkaloid bases commonly used are (–) brucine, (–) quinine, (–) strychnine, etc.

4. Reactions where bonds with the chiral center are broken: The stereochemistry of such reactions depends on the mechanism of the reaction. Hence, stereochemistry can be helpful to give evidence of a particular mechanism. e.g.

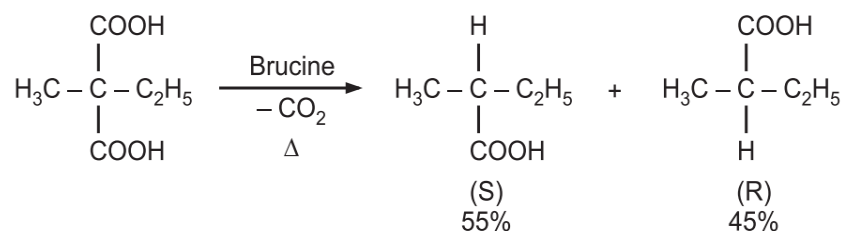


As the product is optically inactive and a racemic mixture, it implies second chlorine can be attached from either face of the intermediate, which can be a free alkyl radical with loss of chirality.



ASYMMETRIC SYNTHESIS: De novo synthesis of a chiral substance from an achiral precursor such that one enantiomer predominates over the other is called **asymmetric synthesis**. For reactions where molecules already contain a chiral element and synthesis introduces a new chiral element, synthesis is referred to as **'stereoselective or enantioselective' synthesis or diastereoselective synthesis**.

Decarboxylation of ethyl methylmalonic acid to give α methyl butyric acid is one of the first recorded asymmetric syntheses.



- Generally, **chiral reagents** are used to carry out the reaction, if they are not available, chirality is acquired upon chelation, solvation, etc.
- Reactants are adsorbed onto **chiral surfaces** or within **chiral crystals**.

🌿 **Chiral adjuvant or chiral auxiliary** is temporarily attached to the achiral substrate which is cleaved after the synthesis by hydrolysis to recycle the adjuvant.

🌿 When a **new stereogenic center** is created in an achiral molecule we get a racemic mixture while in diastereoselective synthesis, the formation of any one of the desired diastereomers is preferred over the other.

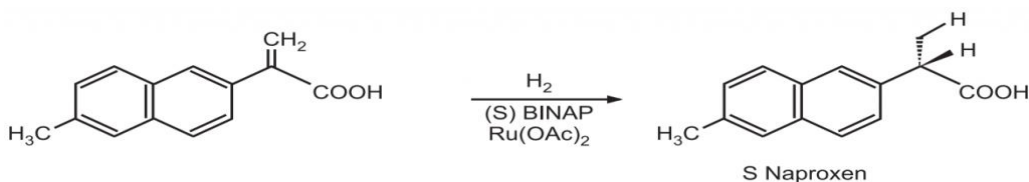
Typical Asymmetric Synthesis Include

🌿 **Asymmetric hydrogenation**

🌿 **Asymmetric epoxidation**

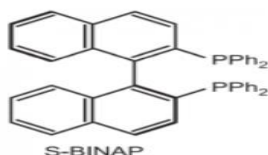
Asymmetric dihydroxylation: The partial term was used when optically active compounds are prepared from achiral compounds by intermediate use of optically active compounds as reagent without the necessity of resolution, contrary to the ‘absolute’ asymmetric synthesis where physical reagent like circularly polarised light was used.

Asymmetric hydrogenation: It is used for the asymmetric synthesis of the analgesic drug Naproxen.

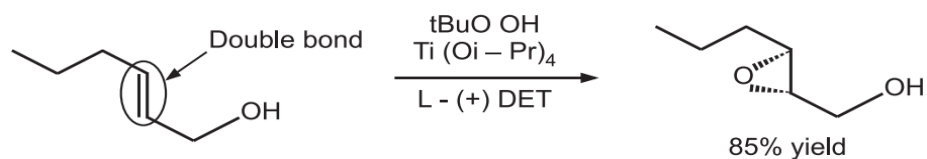


The reaction is carried out in presence of a chiral catalyst to hydrogenate a double bond. The catalyst selects a single enantiotopic face of the double bond and adds hydrogens across it.

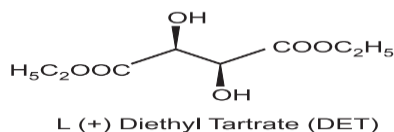
BINAP is a chelating diphosphine. Chirality is due to the restricted rotation of the bond joining two naphthalene ring systems. Along with Ruthenium, it acts as an excellent catalyst for hydrogenation.



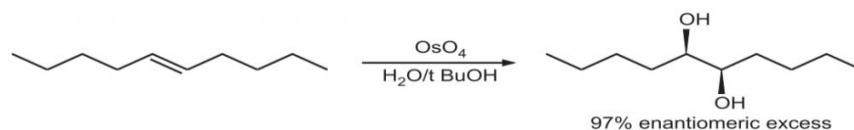
Asymmetric Epoxidation: Oxidation of alkenes by asymmetric epoxidation is one of the popular Sharpless reactions.



Catalyst is a transition metal, Titanium tetra isopropoxide with tertiary butyl hydroperoxide. The ligand is diethyl tartrate which is chiral and imparts selectivity to the reaction.



Asymmetric dihydroxylation: Dihydroxylation of alkenes by osmium tetroxide in catalytic amount is carried out.



Difference Between Diastereomer and Enantiomers

DIASTEREOMER	ENANTIOMERS
Diastereomers are stereoisomers that aren't a mirror image of each other	Enantiomers are stereoisomers that are mirror images of each other
Distinct physical properties	Have identical physical properties except for the ability to rotate plane-polarized light
Present in pairs	There can be several molecules
Different molecular shape	Similar molecular shape

Very Short Answer Type Question (2marks)

1. Define Optical activity.
2. Define Optical Isomerism.
3. Define Chiral and Achiral molecules.
4. Define Enantiomerism.
5. Define Diastereoisomerism.
6. Define Racemic mixture.
7. Define Meso Compounds.
8. Disymmetry is the essential condition for optical activity? Explain.
9. Define Racemic modification.
10. Meso compounds are optically inactive. Comment.
11. What is the difference between d,l and D,L notations?
12. What is the condition for a compound to be chiral?
13. What is the resolution of racemic mixture?
14. What are chiral and achiral molecules?
15. Difference between D and L.

Short Answer Type Question (5 marks)

1. What are Enantiomers? Write down their main characteristics.
2. Write a short note on asymmetric synthesis.
3. Explain resolution of optical isomers with suitable examples.
4. Explain the term meso compound with suitable examples.
5. Write a short note on sequence rule.
6. Differentiate between terms absolute configuration and relative configuration.
7. Draw the stereochemical formulas for all the possible stereoisomer of the 2,3 dichlorobutane. Label pairs of enantiomers, diastereomers and meso compounds.
8. Discuss in detail about partial and absolute asymmetric synthesis.
9. Give brief note on elements of symmetry.

Long Answer Type Questions (10 Marks)

1. Define the term enantiomers, diastereomers and meso compounds giving examples for each one of them.
2. Discuss in detail DL and RS system of nomenclature of optical isomers.