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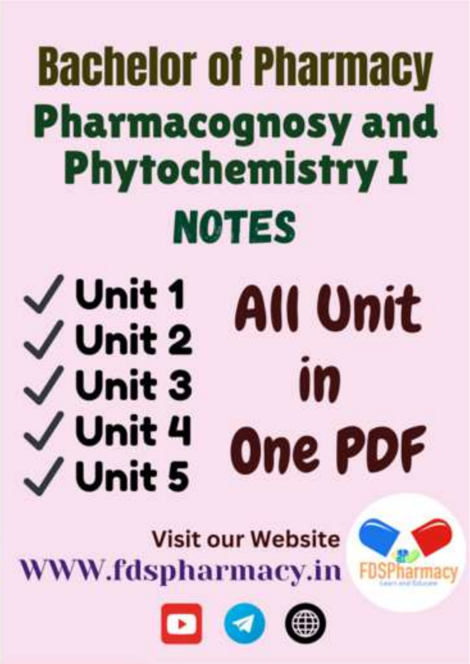

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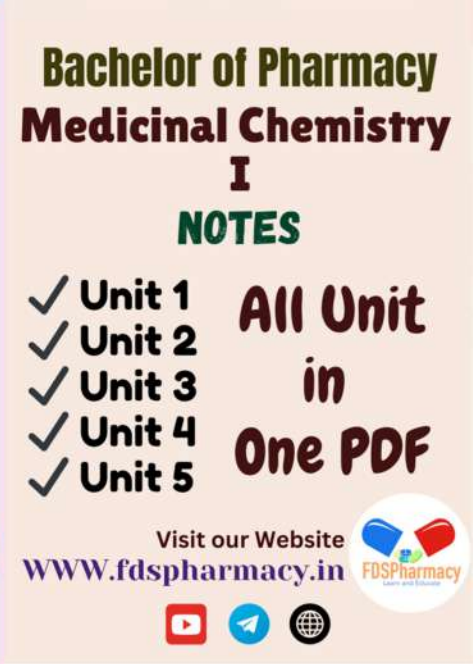

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PHARMACEUTICAL ORGANIC CHEMISTRY – III

UNIT 1

TOPIC :

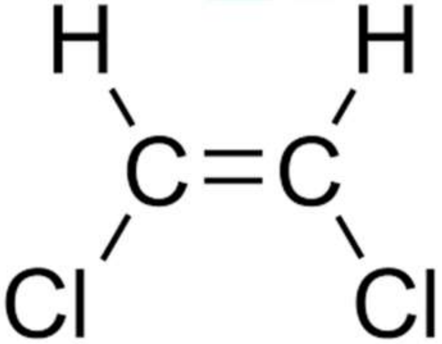
- **Stereo isomerism**
  Optical isomerism
  Optical activity, enantiomerism, diastereoisomerism, meso compounds
  Elements of symmetry, chiral and achiral molecules
  DL system of nomenclature of optical isomers, sequence rules,
  RS system of nomenclature of optical isomers
  Reactions of chiral molecules
  Racemic modification and resolution of racemic mixture.
  Asymmetric synthesis: partial and absolute

Stereoisomerism

- The branch of chemistry that deals with the three-dimensional structure of molecules is known as Stereochemistry.
- The phenomenon of isomerism that arises due to the different spatial arrangement of atoms or groups in space, without any difference in connectivity of atoms, is called Stereoisomerism.
- Compounds exhibiting this property are called Stereoisomers.
- These molecules have the same molecular formula and the same structural formula, but they differ in the arrangement of atoms in three-dimensional space.

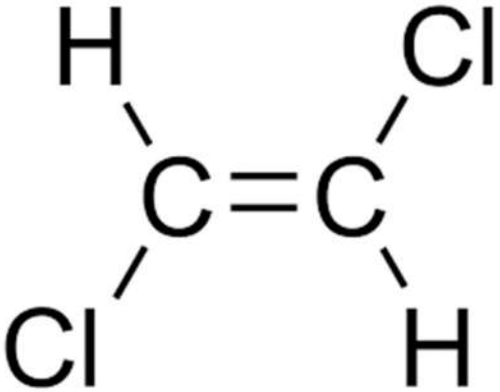
Examples

1. **cis-1,2-dichloroethene**
    - Both chlorine atoms are on the same side of the double bond.



2. **trans-1,2-dichloroethene**

- The two chlorine atoms are on opposite sides of the double bond.



Types of Stereoisomerism

Stereoisomerism can be classified into two main categories:

1. Conformational Isomerism

- Isomerism that arises due to the rotation around single (σ) bonds.
- Conformations are different spatial arrangements of atoms that can be interconverted by rotation about a single bond.
- Example:
    - Ethane shows conformations such as staggered and eclipsed forms.
    - Cyclohexane shows chair, boat, twist-boat, and half-chair conformations.
- These isomers usually do not require bond breaking for interconversion.

2. Configurational Isomerism

- Definition: Isomerism in which molecules cannot be interconverted without breaking bonds.
- It is further divided into:

(a) Geometrical Isomerism (cis–trans or E/Z isomerism)

- Occurs due to restricted rotation around a double bond (C=C) or in cyclic structures.
- Example:
    - cis- and trans-butenes
    - cis- and trans-1,2-dichloroethene
- cis-isomers: Similar groups on the same side.
- trans-isomers: Similar groups on opposite sides.

(b) Optical Isomerism

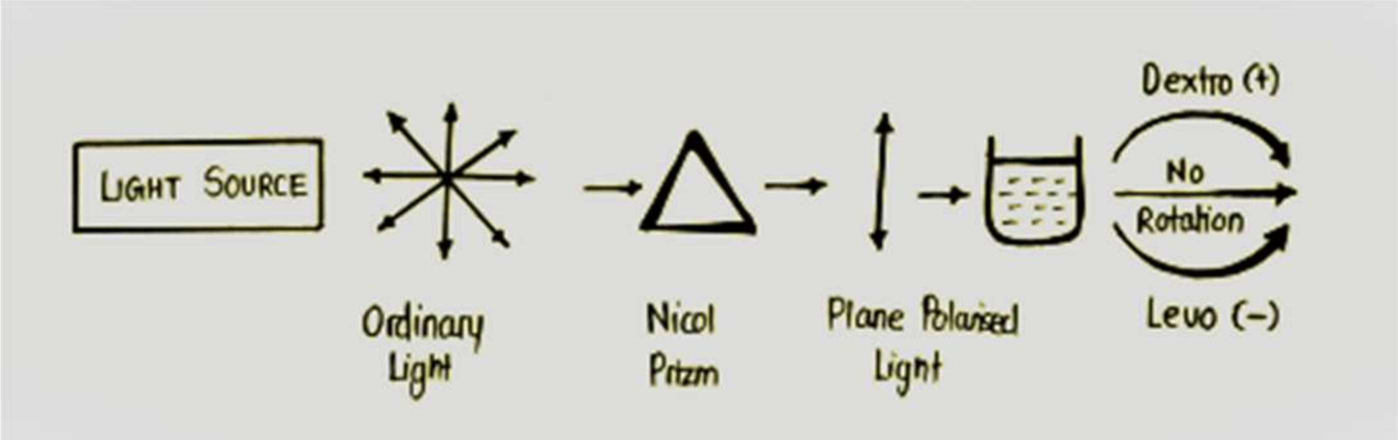
- Occurs when a molecule contains an asymmetric carbon atom (chiral center).
- Such molecules rotate plane-polarized light either to the right (dextrorotatory, +) or to the left (levorotatory, –).
- Optical isomers are non-superimposable mirror images, also called enantiomers.
- Examples:
    - Lactic acid, tartaric acid, amino acids, glucose.
- Sub-types:
    - Enantiomers – mirror image pairs.
    - Diastereomers – stereoisomers which are not mirror images.
    - Meso compounds – optically inactive due to internal plane of symmetry.

Optical Activity

- Optical activity is the property of certain compounds to rotate the plane of plane-polarized light when it passes through them.
- This phenomenon is known as Optical Rotation.
- Compounds which exhibit this property are called Optically Active Compounds.

Principle

1. Ordinary light consists of waves vibrating in all possible planes perpendicular to the direction of propagation.
2. When this ordinary light is passed through a Nicol prism (polarizer), it becomes plane-polarized light (vibrates in only one plane).
3. When this plane-polarized light passes through an optically active substance, the plane of vibration is rotated either clockwise or anticlockwise.
4. The extent of rotation depends on:
    - Nature of the compound.
    - Concentration of solution.
    - Length of the path of light through the substance.
    - Wavelength of light used (usually sodium D-line, 589 nm).



Types of Optical Rotation

1. **Dextrorotatory compounds (+ or d-form)**
    - Rotate the plane of polarized light to the right (clockwise).
    - Example: D-(+)-Glucose.
2. **Levorotatory compounds (– or l-form)**
    - Rotate the plane of polarized light to the left (anticlockwise).
    - Example: L-(–)-Glucose.
3. **Optically Inactive compounds**
    - Do not rotate plane-polarized light.
    - Examples: Achiral compounds (like methane, benzene).

Representation

- **(+)/d** → Clockwise rotation.
- **(–)/l** → Anticlockwise rotation.
- Note: D/L system (based on glyceraldehyde reference) is not the same as +/– rotation. A D-compound can be either dextrorotatory or levorotatory.

Examples of Optically Active Compounds

- Naturally occurring sugars (Glucose, Fructose).
- Amino acids (except Glycine).
- Lactic acid, Tartaric acid.

Enantiomerism

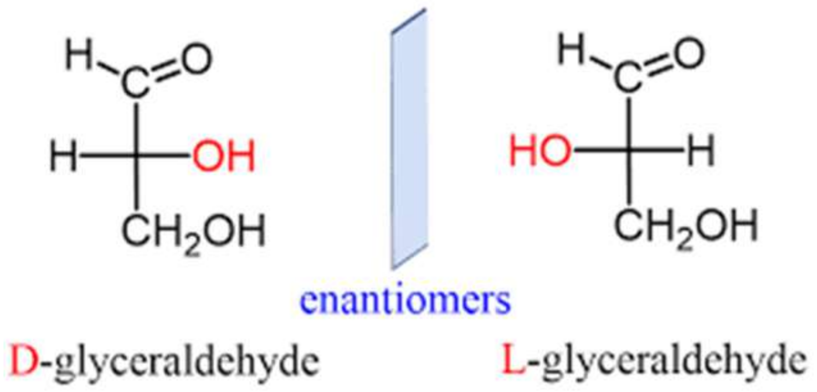
- Enantiomerism (also called Optical Isomerism) is a type of stereoisomerism in which molecules exist as non-superimposable mirror images of each other.
- Such mirror image forms of molecules are called Enantiomers.
- Enantiomers have the same molecular formula and same connectivity of atoms, but differ in the spatial arrangement of groups around a chiral center.

Characteristics of Enantiomers

1. They are mirror images of each other.
2. They are non-superimposable (cannot be placed one over the other completely, just like left and right hands).
3. They have identical physical properties (melting point, boiling point, density, solubility, etc.).
4. They differ only in:
    - Direction of rotation of plane-polarized light.
    - Biological activity (interaction with enzymes, receptors).
5. One enantiomer rotates plane-polarized light clockwise (dextrorotatory, +) and the other anticlockwise (levorotatory, –) by the same magnitude but opposite direction.

Examples

- **D- and L-Glyceraldehyde**:



  - **D-Glyceraldehyde**: rotates plane-polarized light clockwise (dextrorotatory, +).
  - **L-Glyceraldehyde**: rotates plane-polarized light anticlockwise (levorotatory, –).

$CHO – CHOH – CH_2OH$ (mirror images)

- **Lactic acid**, **Tartaric acid**, **Amino acids (except glycine)**, **Sugars like glucose, fructose**.

Diastereoisomerism

- Diastereoisomerism is a type of stereoisomerism where the isomers have the same molecular formula and the same connectivity of atoms, but they are:
  - Not mirror images of each other.
  - Not superimposable.

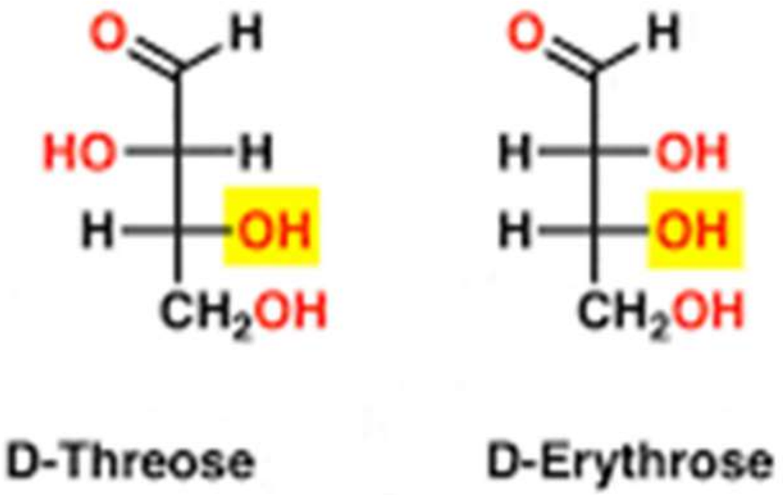
Thus, diastereomers differ in the three-dimensional arrangement of atoms around two or more chiral centers.

Characteristics of Diastereoisomers

1. They are not related as object and mirror image (unlike enantiomers).
2. They may or may not be chiral.
3. They have different physical properties such as melting point, boiling point, solubility, and refractive index.
4. They also have different chemical reactivities.
5. Their separation is comparatively easier than enantiomers (enantiomers need special methods like resolution, while diastereomers can often be separated by crystallization or distillation).

Examples

1. **Erythrose and Threose** (aldotetroses):
    - Both have the same molecular formula ($C_4H_8O_4$) and same functional groups.
    - They differ in spatial arrangement of –OH groups.
    - **Erythrose**: –OH groups on the same side.
    - **Threose**: –OH groups on opposite sides.



Difference Between Enantiomers and Diastereomers

Property	Enantiomers	Diastereomers
Mirror image relation	Non-superimposable mirror images	Not mirror images
Physical properties	Identical (except direction of optical rotation)	Different (mp, bp, solubility, etc.)
Chemical reactivity	Same in achiral environments	Different
Separation	Difficult (need resolution techniques)	Easy (simple crystallization/distillation)

Meso Compounds

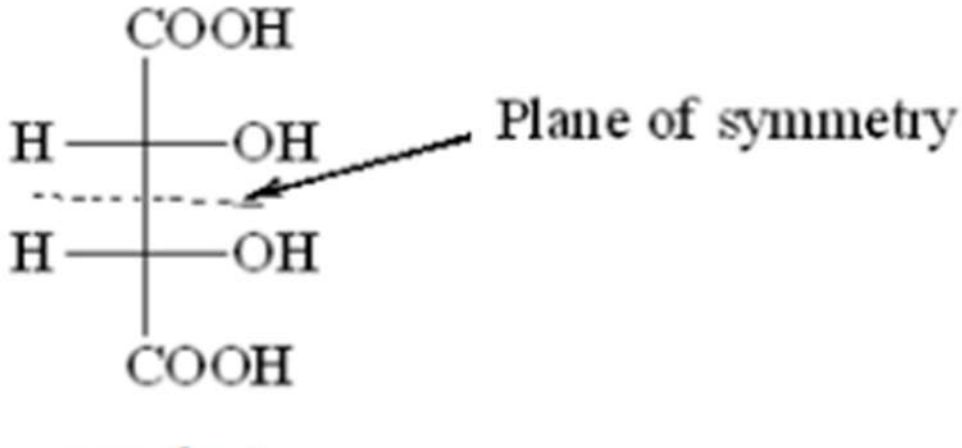
- A meso compound is a special type of stereoisomer that contains two or more chiral centers, but the molecule is optically inactive.
- The inactivity arises due to the presence of an internal plane of symmetry, which makes one half of the molecule a mirror image of the other.
- Because of this symmetry, the optical rotations of individual chiral centers cancel each other, resulting in no net optical activity.

Characteristics of Meso Compounds

1. They contain two or more chiral centers.
2. They have an internal plane of symmetry.
3. They are achiral despite the presence of stereogenic (chiral) centers.
4. They do not rotate plane-polarized light (optically inactive).
5. They belong to the class of diastereoisomers (because they are not mirror images of enantiomers).

Example: Tartaric Acid

- **Tartaric acid** (HOOC–CHOH–CHOH–COOH) has two chiral centers.
- It exists in three stereoisomeric forms:
    1. **D-(+)-tartaric acid** (optically active).
    2. **L-(–)-tartaric acid** (optically active).



meso form

Elements Of Symmetry

- Elements of symmetry refer to geometric features of a molecule that allow it to be transformed (rotated, reflected, or inverted) into a configuration indistinguishable from its original one.
- If a molecule possesses certain symmetry elements, it cannot show optical isomerism, because chirality requires the absence of symmetry.
- Therefore, for a molecule to be chiral and optically active, it must lack a plane of symmetry, center of symmetry, and certain symmetry axes.

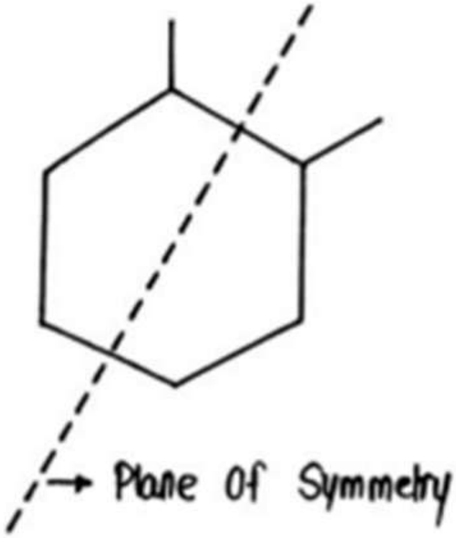
Key Symmetry Elements

1. Plane of Symmetry (σ)

- **A** plane of symmetry is an imaginary flat plane that divides a molecule into two equal halves that are mirror images of each other.
- If you fold the molecule along this plane, both sides will overlap perfectly.
- Molecules with a plane of symmetry are achiral (optically inactive).

Example:

- **Meso-tartaric acid** has a plane of symmetry and is optically inactive.

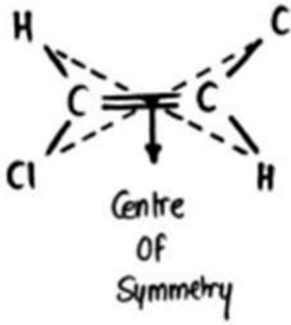


2. Centre of Symmetry (i)

- A center of symmetry (also called point of symmetry) is a point in the molecule such that for any group present at a certain distance in one direction, there exists an identical group at the same distance in the opposite direction.
- If a molecule has a center of symmetry, it cannot be chiral.

Example:

- **trans-1,2-dichloroethene** has a center of symmetry.

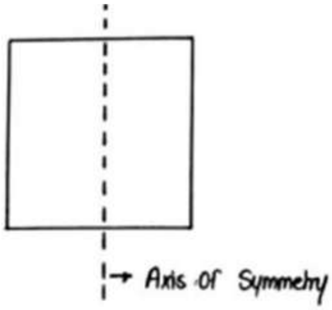


3. Axis of Symmetry (Cn)

- An axis of symmetry is an imaginary line passing through a molecule, around which the molecule can be rotated by a certain angle (360°/n), and it looks identical after rotation.
- If such an axis exists, the molecule may be achiral.
- A common type is the proper rotation axis (Cn), where n is the order of rotation.

Example:

- A benzene molecule has a C6 axis of symmetry (rotation by 60° gives the same appearance).



Chiral And Achiral Molecules

Chiral Molecules

- A molecule is chiral if it cannot be superimposed on its mirror image, similar to how the left and right hands are mirror images but not identical.
- These molecules lack a plane of symmetry and usually have a chiral center — typically a carbon atom bonded to four different groups.
- Chiral molecules are generally optically active, meaning they can rotate plane-polarized light.

Characteristics

1. Absence of plane of symmetry or center of symmetry.
2. Presence of at least one chiral center.
3. Exhibit optical activity (+ or – rotation).
4. Exist as enantiomers (non-superimposable mirror images).

Example

- **Lactic acid** (CH_3–CHOH–COOH) – carbon bonded to four different groups.
- **D- and L-Glyceraldehyde** – classical example of chirality.

Achiral Molecules

- A molecule is achiral if it can be superimposed on its mirror image.
- These molecules are optically inactive, meaning they do not rotate plane-polarized light.

Characteristics

1. Possess a plane of symmetry **or** center of symmetry.
2. May include meso compounds or molecules without chiral centers.
3. **Do** not exhibit optical activity.

Example

- **Meso-tartaric acid** – has two chiral centers but a plane of symmetry, making it achiral.
- **Ethane, benzene** – simple molecules without chiral centers.

D/L System of Nomenclature

- The D/L system is used to designate the configuration of chiral molecules, particularly amino acids and sugars, based on their structural similarity to the reference molecule D- or L-glyceraldehyde.
- This system refers to the relative configuration of molecules, not their optical activity.

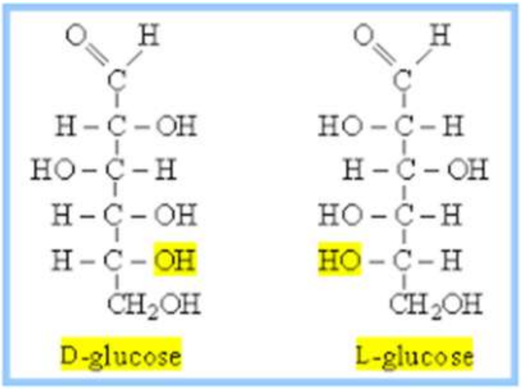
Rules for D/L System

1. Draw the Fischer projection of the given molecule.
2. Arrange the molecule so that the most oxidized group (usually –CHO for sugars) is at the top.
3. Locate the last chiral carbon (the chiral center farthest from the top group).
4. Determine the position of the –OH or $-NH_2$ group on this last chiral carbon:
    - Right side → D-configuration
    - Left side → L-configuration

Examples

1. Glucose

- **D-Glucose**
    - Fischer projection shows –OH on the **last chiral carbon on the right** → D-form.
- **L-Glucose**
    - –OH on the **last chiral carbon on the left** → L-form.



Key Features

1. The D/L notation does NOT indicate optical rotation (+ or −).
2. Some D-compounds are dextrorotatory (+), while others are levorotatory (−).
    - Example:
        - D-Glucose → dextrorotatory (+)
        - D-Fructose → levorotatory (−)
3. D/L system indicates relative configuration compared to D- or L-glyceraldehyde.
4. Widely used for sugars and amino acids, but in modern chemistry, it is often replaced by the R/S system for absolute configuration.

R/S System Of Nomenclature

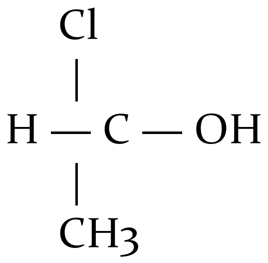
- The R/S system is a modern and systematic method to assign the absolute configuration of chiral molecules based on the three-dimensional spatial arrangement of atoms around a chiral center.
- Developed by Cahn, Ingold, and Prelog, it is applicable to all chiral compounds, unlike the D/L system, which is mainly for sugars and amino acids.

Rules for R/S System

1. Identify the chiral center (carbon with four different substituents).
2. Assign priorities to the four groups attached to the chiral center based on atomic number:
    - Higher atomic number → higher priority (1 = highest, 4 = lowest).
    - Example: Br (35) > Cl (17) > C (6) > H (1).
3. If two atoms directly attached are identical, move along the chain until a difference is found.
4. Multiple bonds: double or triple bonds are treated as if the atoms are duplicated or triplicated.
5. Orient the molecule so that the lowest priority group (4) points away from you along the vertical axis.
6. Draw a curved arrow from priority 1 → 2 → 3:
    - Clockwise → R-configuration (Rectus)
    - Anticlockwise → S-configuration (Sinister)

Example

R-2-Chlorobutanol



$$\begin{array}{ccc} & \text{Cl} & \\ & | & \\ \text{H} — & \text{C} & — \text{OH} \\ & | & \\ & \text{CH}_3 & \end{array}$$

- Assign priorities: $Cl > OH > CH_3 > H$
- Orient H (lowest priority) away, draw arrow from Cl → OH → CH_3
- Arrow moves clockwise → R-configuration

Special Cases

- If the lowest priority group lies on a horizontal bond (toward the viewer):
  - Reverse the configuration obtained from the arrow.
  - Example: If arrow clockwise → assign S, if arrow anticlockwise → assign R.
- Multiple chiral centers: apply R/S rules independently to each center.

Importance of R/S System

1. Universal system: applies to all chiral molecules, not just sugars and amino acids.
2. Provides absolute configuration rather than relative configuration (like D/L system).
3. Standard system in organic chemistry, medicinal chemistry, and drug nomenclature.
4. Helps in predicting stereochemistry-dependent biological activity.

Reactions of Chiral Molecules

Chiral molecules contain **stereogenic centers** and can undergo chemical reactions that affect their **stereochemistry**. These reactions are important in **drug synthesis and pharmaceutical chemistry**, as the biological activity of drugs often depends on the **chirality** of molecules.

Chiral molecules generally undergo **three main types of reactions**:

1. **Retention of configuration**
2. **Inversion of configuration**
3. **Racemization (Racemic modification)**

1. Retention of Configuration

- A reaction in which the configuration (R or S) of the chiral center remains unchanged.
- The stereochemistry of the molecule is retained after the reaction.

Example

R-2-Chlorobutane → R-2-Chlorobutane derivative

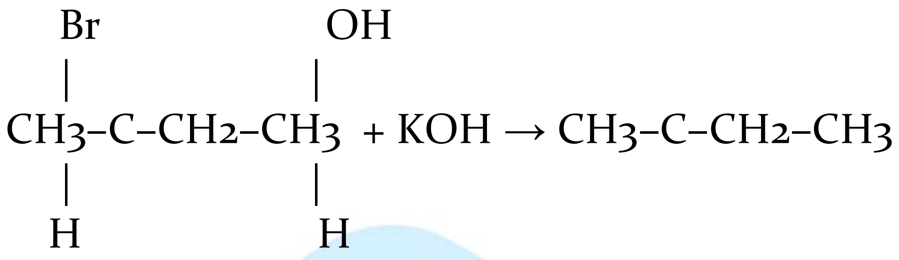
- No change in configuration at the chiral center.

2. Inversion of Configuration

- A reaction in which the **configuration of the chiral center is reversed** (R ↔ S).
- Also called **Walden inversion**, commonly observed in **SN2 nucleophilic substitution reactions**.

Example

R-2-Bromobutane + KOH → S-2-Butanol



$$CH_3{-}\overset{\displaystyle Br}{\underset{\displaystyle H}{C}}{-}CH_2{-}CH_3 + KOH \rightarrow CH_3{-}\overset{\displaystyle OH}{\underset{\displaystyle H}{C}}{-}CH_2{-}CH_3$$

- The nucleophile attacks from the opposite side of the leaving group → inversion of configuration.

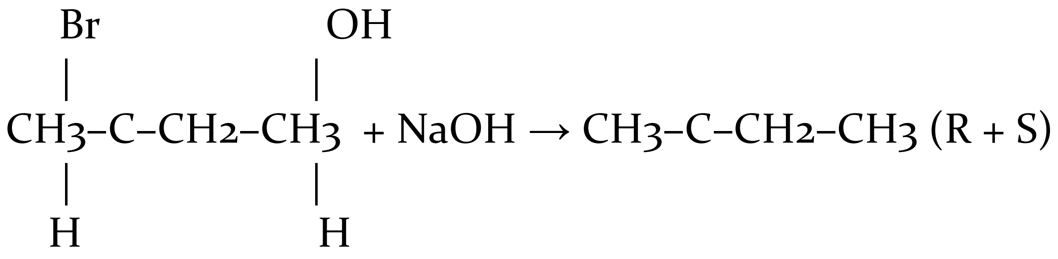
3. Racemization / Racemic Modification

- Racemization is the process where an optically active compound is converted into a racemic mixture, containing equal amounts of both enantiomers.
- Since the enantiomers rotate light in opposite directions, the net optical activity becomes zero.

Example

R-2-Bromobutane + NaOH → Racemic 2-Butanol

- Products: 50% R-2-Butanol + 50% S-2-Butanol → **optically inactive**



$$CH_3{-}\overset{\displaystyle Br}{\underset{\displaystyle H}{C}}{-}CH_2{-}CH_3 + NaOH \rightarrow CH_3{-}\overset{\displaystyle OH}{\underset{\displaystyle H}{C}}{-}CH_2{-}CH_3\ (R + S)$$

Resolution of Racemic Mixtures

- Resolution refers to the process of separating a racemic mixture (50:50 mixture of enantiomers) into its individual optically active components.
- This is important in pharmaceutical chemistry, as often only one enantiomer is biologically active, while the other may be inactive or toxic.

Methods of Resolution

1. Mechanical Separation

- Earliest method used to separate enantiomers based on crystal shape differences.

Process:

1. The racemic mixture is allowed to crystallize slowly under controlled conditions.
2. Crystals are examined under a microscope.
3. Individual enantiomer crystals are picked using a fine needle or tweezers.

Limitation:

- Labor-intensive and suitable only for few racemic mixtures with large crystal differences.

2. Chemical Separation

- Most commonly used method.
- Involves converting enantiomers into diastereomers using a chiral resolving agent.
- Diastereomers have different physical properties, allowing separation by crystallization or chromatography.
- After separation, the resolving agent is removed to obtain pure enantiomers.

Example:

- Conversion of racemic tartaric acid into diastereomeric salts with chiral amines.

3. Enzymatic Separation

- Uses enzymes, which are biological catalysts.
- Enzymes often react selectively with only one enantiomer, leaving the other unchanged.
- Highly selective and mild, making it suitable for sensitive pharmaceutical compounds.

Example:

- Lipases selectively hydrolyze one enantiomer of a chiral ester.

4. Chromatographic Separation

- Uses chiral stationary phases in High-Performance Liquid Chromatography (HPLC) or other chromatographic techniques.
- One enantiomer binds more strongly to the chiral stationary phase, while the other elutes faster.
- Allows rapid and high-resolution separation of enantiomers.

Example:

- Chiral HPLC separation of racemic ibuprofen.

Asymmetric Synthesis

- Asymmetric synthesis is the conversion of an achiral (or symmetric) compound into a chiral compound in such a way that one enantiomer is produced preferentially over the other.
- This process is crucial in pharmaceutical chemistry, as often only one enantiomer of a drug is therapeutically active.

Types of Asymmetric Synthesis

1. **Partial Asymmetric Synthesis**
2. **Absolute Asymmetric Synthesis**

1. Partial Asymmetric Synthesis

- Produces a chiral product with an excess of one enantiomer, but both enantiomers are formed.
- The product is not enantiomerically pure, but one enantiomer predominates.

Example

Ethyl Methyl Malonic Acid + Chiral Reagent (e.g., Brucine) → Predominantly one enantiomer

COOH
 |
H–C–GHS + Chiral reagent → H–C–COOM (mixture with excess R or S)
 |
COOH

- R/S ratio is not 100%, e.g., 55% R : 45% S.
- One enantiomer is more abundant, but both are present.

2. Absolute Asymmetric Synthesis

- Produces only one specific enantiomer directly from an achiral starting material.
- The product is enantiomerically pure.

Example

Lactic Acid Formation using Yeast or Lactic Acid Dehydrogenase

ACHIRAL SUBSTRATE → (Enzyme) → L-Lactic Acid (single enantiomer)

- Enzymes act as chiral catalysts, producing a single optically active enantiomer.
- Important in the industrial synthesis of pharmaceuticals.

Key Points

1. Partial asymmetric synthesis: mixture of enantiomers, one predominates.
2. Absolute asymmetric synthesis: only one enantiomer formed, 100% stereoselective.
3. Chiral reagents or enzymes are commonly used to control stereochemistry.
4. Critical in drug synthesis, as biological activity is often enantiomer-specific.