UNIT-1

Stereo Isomerism (Optical isomerism)

Points to be covered in this topic

- ❖ Stereoisomerism
- ❖ 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

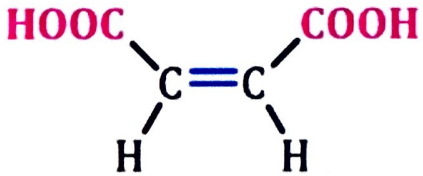
Stereo Isomerism

❑ INTRODUCTION

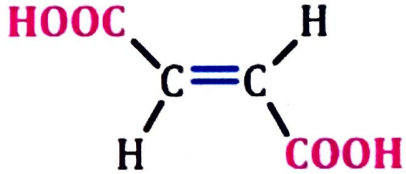
- Stereochemistry helps to define the **structure of a molecule and orientation of the atoms and functional groups** present, in **three dimensions.**
- Stereoisomers possess the same molecular and structural formulae and the same functional groups but **differ in the three dimensional spatial orientation** of these atoms or groups within the molecule.
- Due to the difference in orientation of the functional group and geometry of the molecule, stereoisomers differ in their physical, chemical, physicochemical and biochemical properties.
- Based on symmetry and energy criteria, stereoisomers are divided into three classes.
- **(a) Geometrical isomers**
- **(b) Optical isomers**
- **(c) Conformational isomers.**

❖ GEOMETRICAL ISOMERS (CIS-TRANS ISOMERISM):

- Maleic acid (m.p. 130°C) and fumaric acid (m.p. 287°C) have the **same molecular formula but differ in the arrangement of functional groups around double bond.**
- They have different physical and, to some extent, chemical properties. This type of isomerism is known as geometrical isomerism.



Maleic acid
(**cis**-butenedioic acid)

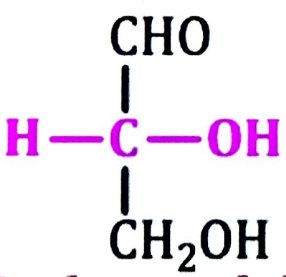


Fumaric acid
(**trans**-butenedioic acid)

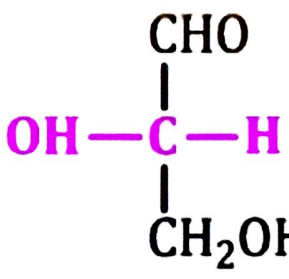
- Isomerism seen in non-cyclic, open-chain compound due to the presence of a double bond, is called as **π stereoisomerism** while when it occurs in a cyclic skeleton lacking a double bond, it is termed as **σ stereoisomerism.**

❖ OPTICAL ISOMERISM (ENANTIOMERISM):

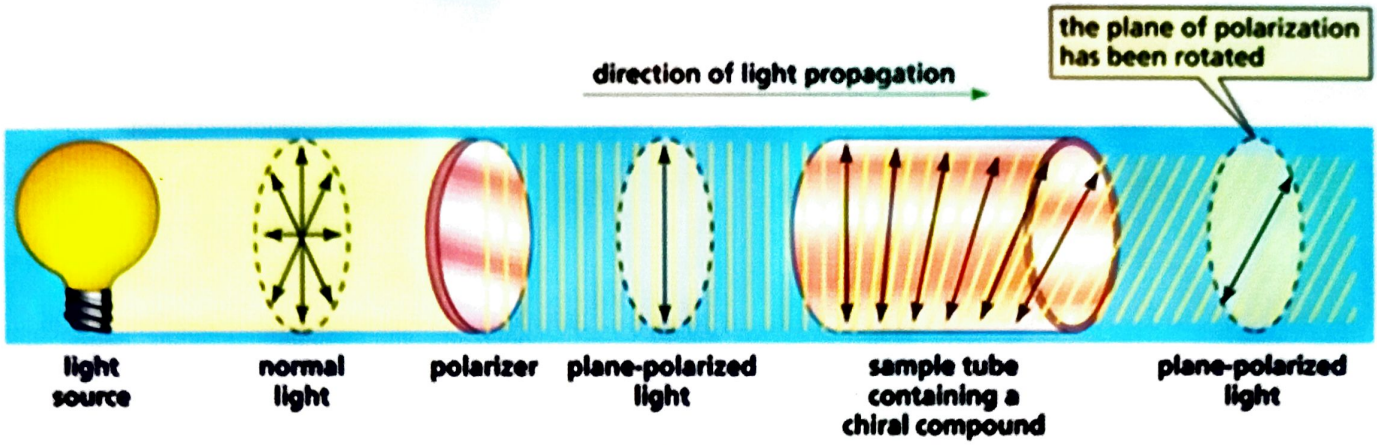
- In 1815, Biot found that a number of organic and inorganic compounds in the solution form, have the **ability to rotate the plane of polarized light in opposite directions** but in **identical amplitude,** passing through them.
- Optical isomerism is seen in compounds that can **rotate plane polarised light.**
- A carbon atom connected to **four chemically different functional** groups is known as asymmetric or **chiral carbon** and the presence of at least one asymmetric carbon atom in the structure is the prerequirement for a molecule to **show optical isomerism.**
- If there is one asymmetric carbon then two optically active isomers are possible.
- Isomer rotating **plane of polarized light to the right** is said to be **dextrorotatory (Latin, dexter : right)** while isomer showing **rotation to the left** is known as **laevorotatory (Latin, laevus : left).**
- Both isomers are **mirror images of each other yet are not superimposable. They are called as enantiomers** and the pair of enantiomers is called as enantiomorph. An enantiomer does not possess a plane or center of symmetry. For example,



D-glyceradehyde



L-glyceradehyde



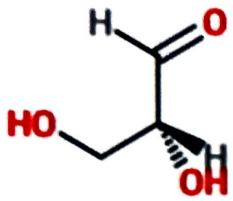
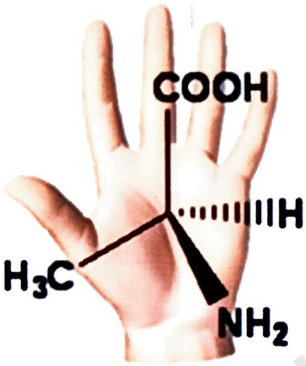


Fig 1

L-alanine



D-alanine

(+) *dextro*rotatory (S)-enantiomer

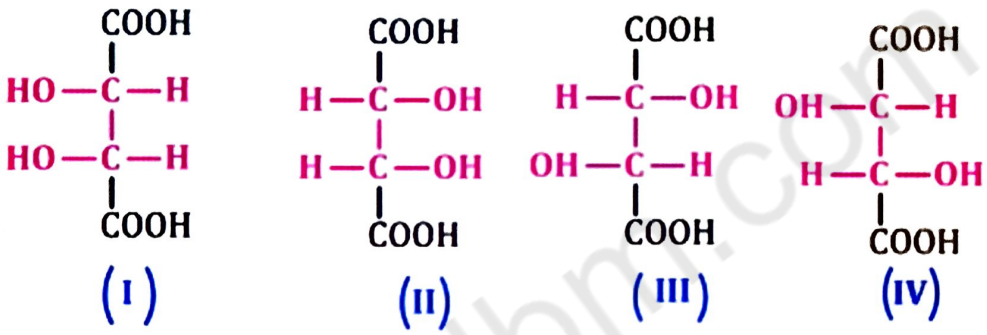
(–) *levo*rotatory (R)-enantiomer

- When the enantiomers are present together in **equal concentration**, the **rotation of plane polarized light** caused by **laevo isomer** will be **neutralized** by a **dextro rotating isomer** and the mixture will **be optically inactive.** Such mixtures are called as **racemic mixtures**.
- The conversion of an **enantiomer into a racemic** form is called as **racemization.**
- While the **separation of racemic mixture** into individual enantiomers is called as **resolution.**
- The maximum number of optically active isomers possible for a molecule having more than one asymmetric carbon atoms may be given by the **formula**

$$N = 2n$$

where,
N = Number of optically active isomers, and
n = Number of asymmetric carbon atoms.

- With the **exception of rotation of plane-polarised light,** enantiomers have identical **physical and chemical properties** like boiling point, melting point, solubility.
- Their **chemical properties are same towards** achiral reagents, solvents and conditions. **Towards chiral reagents, solvents and catalysts, enantiomers react at different rates.**
- As per the rule given above, tartaric acid will have **four optically active forms because of the presence of two asymmetric carbon atoms.**



- Forms **(I) and (II)** are **identical and symmetrical.** In these forms, the **upper half is the mirror image** of the lower half. This makes the **molecule optically inactive** through internal compensation. Such **identical and symmetrical stereoisomers** are called as **Meso isomers.**
- Forms **(III) and (IV)** are **mirror images** of each other but **are not superimposable.** They are **enantiomeric forms.**
- While if you compare (III) with (I) or (IV) with (I), these are **not enantiomeric pairs.**
- They are neither mirror images nor superimposable. Only one of the two halves of their molecules are identical while the remaining halves are mirror images. Such stereoisomers which are **not mirror images** and are **non-superimposable** are called as **diastereomers.**
- They have **different** physical and chemical properties, with **both achiral**

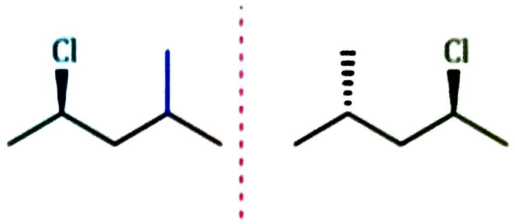
- **and chiral reagents.** The rates are different and the product may be different.

❑ IMPORTANCE OF OPTICAL ISOMERISM

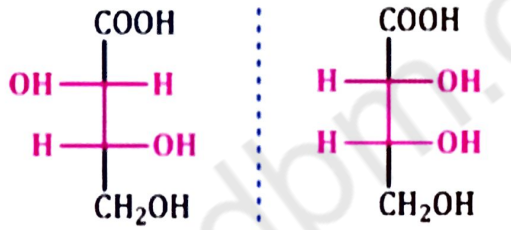
- Nearly **all naturally occurring** substances having **asymmetric carbon atoms** are in either the **d or the l form rather than as racemic mixtures.**
- In drugs and pharmaceuticals, most of the **adverse effects and low potency** may be related to the utilization of the drug in the form of its **racemic mixture.**
- Since, enantiomer in its pure form, is **more active** and selective, there is now an increasing interest to present the drug in the market in its active enantiomeric
- form instead of its racemic form. Optical isomerism has also been successfully utilized in elucidating the mechanism of many chemical reactions.
- The **enantiomer that rotates** a beam of polarised light in the **clockwise direction** is indicated by the prefix **(+), formerly d (+)** or **dextro (–),** the other enantiomer rotates light in a **counter clockwise** direction and is indicated by the prefix **(–), formerly l(–) or levo.**
- They have identical chemical and physical properties in an achiral environment but form different products when reacted with other chiral molecules and exhibit optical activity.

❑ DIASTEREOISOMERISM

- Stereoisomers with **two or more asymmetric or chiral carbons (stereocenter)** will show diastereoisomerism. The stereoisomers that are neither **mirror images** of one another **nor are superimposable, are known as diastereoisomers.**

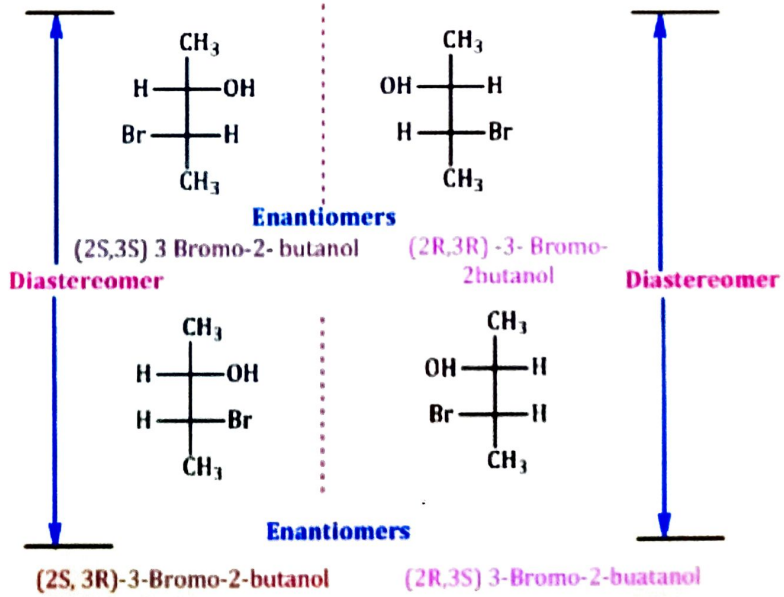


- Each stereocenter gives to **two different configurations.** It means if a molecule contains two asymmetric carbons, there are upto four possible conformations.
- When **two diastereoisomers differ from each other at only one stereocenter** they are known as epimers. **e.g., D- threose and D-erythrose** are epimers of each other. Unlike enantiomers, diastereoisomers have different physical and chemical properties.

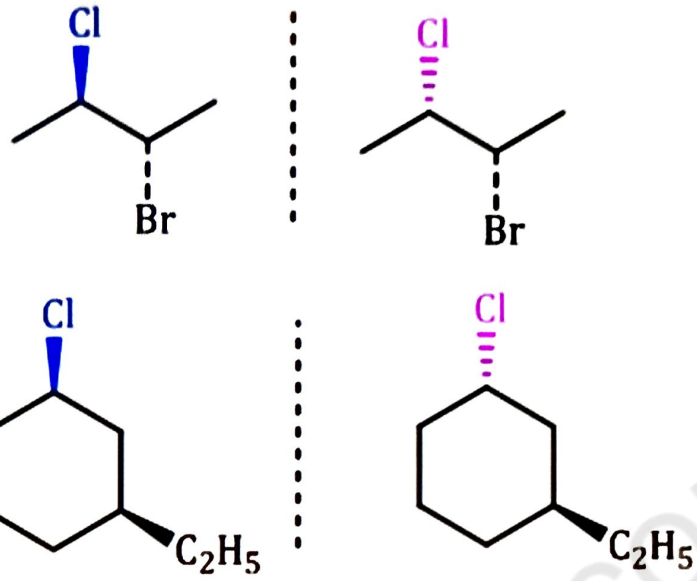


D-Threose **D-Erythrose**

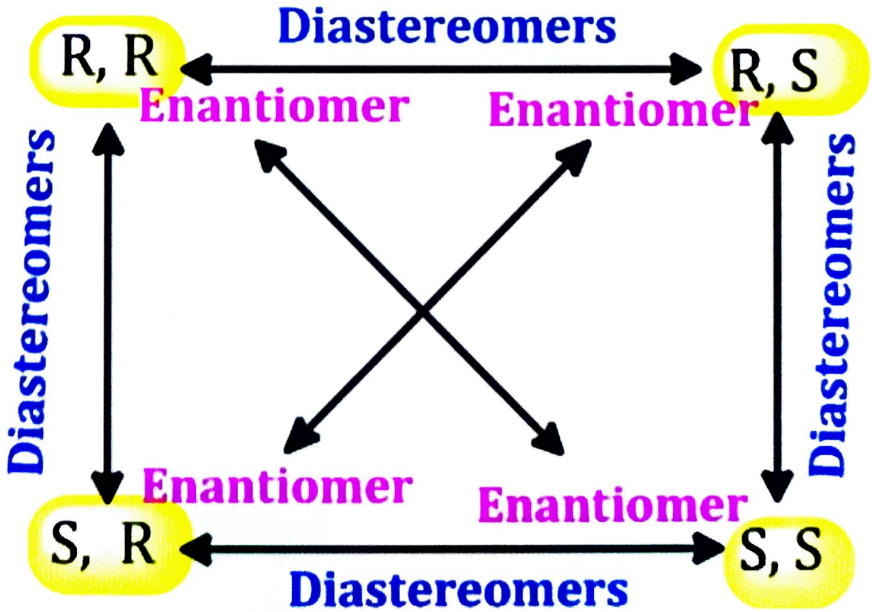
- In case of **3-bromo-2-butanol,** we have four possible combinations **as SS, RR, SR and RS.**
- Out of these, **two molecules SS and RR are enantiomers** of each other while the **configurations RS and SR are diastereomers of SS and RR configurations.**



- Thus in diastereoisomers, the chemical formula and atom connectivity remain the same but the three dimensional orientation or shape of the molecule is different e.g., 2-bromo-3-chloro ethane.



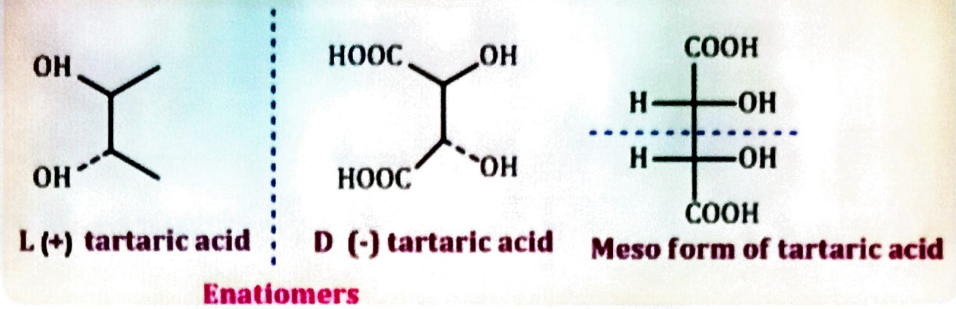
- The molecules are **different in the configuration of chlorine atoms** but same with the **bromine atoms hence they are diastereomers.** Similarly in cyclic compound **3-ethyl-1- chlorocyclohexane, ethyl groups** have same configuration but the chlorine atoms have **opposite configuration.**
- Hence, these molecules are diastereomers. Configurations **differ at some stereocenters but not at others can not create mirror images**. So they are not enantiomers, but are diastereomers.



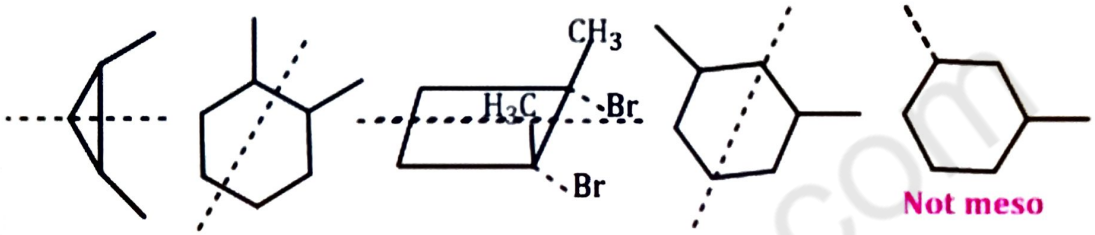
- The dihydrotestosterone molecule contains **seven stereocenters**. Applying 2^N rule, gives 128 possible configurations. Out of these, only one is enantiomeric pair while rest are diastereomers.

❑ MESO COMPOUNDS

- When **multiple stereocenters present** in a molecule create an internal plane of symmetry, it leads to **meso compounds.**
- **Tartaric acid** contains **two asymmetric centers which give rise to four configurations.**
- But there are really **only three stereoisomers** of tartaric acid: a pair of chiral molecules (enantiomers of each other) and the achiral meso compound.
- In meso compound, we have **internal mirror plane that splits** the molecule into two symmetrical sides, the **stereochemistry of both left and right side should be opposite to each other.**
- This leads to auto cancellation of stereo activity of each other resulting into optical inactivity.
- Hence, meso compounds can not be assigned with either **dextrorotatory (+) or levorotatory (–) designation.** The internal mirror plane is simply a line of symmetry that bisects the molecule. Each half is a mirror image of the other half. Each half must contain a stereocenter in order to be a meso compound.
- These stereocenters must also have **different absolute configurations.** Due to internal symmetry, they meso molecule is achiral. Hence, this configuration is not optically active. The meso form is also a type of diastereomer.
- The remaining **two isomers are enantiomeric pair (D-and L-form).**



- The melting point of both enantiomers of tartaric acid is about 170°C while the **mesotartaric acid has the melting point of 145°C.**
- A meso compound is 'superimposable' on its mirror image. Examples in cyclic meso compounds include.



- In summary a meso compound should have two or more stereocenters, an internal symmetry plane and the stereochemistry should be R and S.

✓ **Difference between enantiomer and diastereomers**

S.NO.	Parameter	Enantiomer	Diastereomer
1.	Number of stereocenters	One	Two or more
2.	Mirror images	Yes	No
3.	Superimposition	No	No
4.	Physical properties	Same	Different
5.	Chemical properties	Same	Different

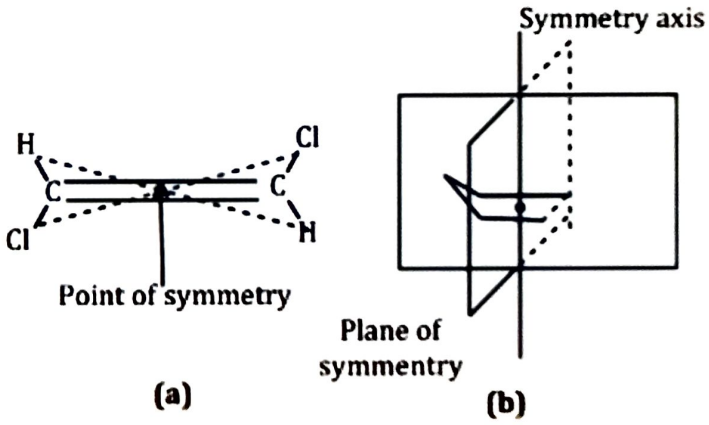
❑ ELEMENTS OF SYMMETRY

- A chiral object is not identical (i.e. non-superimposable) in all respects. An achiral object is identical (hence superimposable) with its mirror image. Chiral objects have a "handedness".
- Like gloves or shoes, chiral objects come in pairs, a right and a left. Achiral

- objects do not have a handedness just like a plain round ball. Thus, chirality of an object is related to its symmetry. Certain symmetry elements like a point, a line or a plane may be useful to check the symmetry of the molecule.
- The rotation or reflection around the symmetry element leaves the object in an orientation indistinguishable from the original.
- Reflection means the coincidence of atoms on one side of the plane with corresponding atoms on the other side, as though reflected in a mirror.

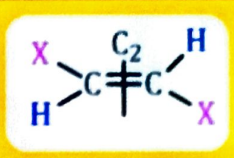
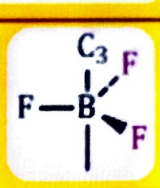
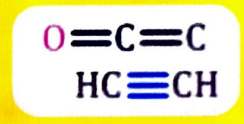
(i) Point of symmetry:

- In a **chiral molecule, (E)-1,2,-dichloroethene,** two lines drawn passing through point of symmetry ensure the same structural features at the opposite lines.
- Similarly the **boat conformation of cyclohexane** has **two intersecting planes of symmetry (s).**
- A plane of symmetry divides the object in such a way that the points on one side of the plane are equivalent to the points on the other sides by reflection through the plane.



- The existence of a **reflective symmetry (a point or plane of symmetry) indirectly proves the molecule is achiral.**
- **Chiral molecules** however may have **rotational symmetry axes and do not have any reflective symmetry elements.**

✓ Examples of rotational axis (360º/n) in the molecules

Type	n	Angle Rotation	Example
C_2	2	180°	E isomers 
C_3	3	120°	Boron trifluoride 
C_4	4	90°	Cyclobutane 
C_5	5	72°	Cyclopentane 
C_6	6	60°	Benzene 
C_∞	∞	0-360°	Linear molecules e.g. CO_2, Acetylene 

✓ Examples:

(1) Methane: It is an example of a high symmetry molecule having 4 C_3 axes, 3 C_2 axes and 6 s (planes). It belongs to the tetrahedral point group Td. It is achiral.

(2) Cis-1,2-dichloroethane: This structure has two orthogonal planes of symmetry and C_2 axis at their intersection. It is achiral.

(3) Trans-1,2-dichloroethane: This structure has a plane of symmetry, an orthogonal C2 axis and a point of symmetry at their intersection. It is achiral.

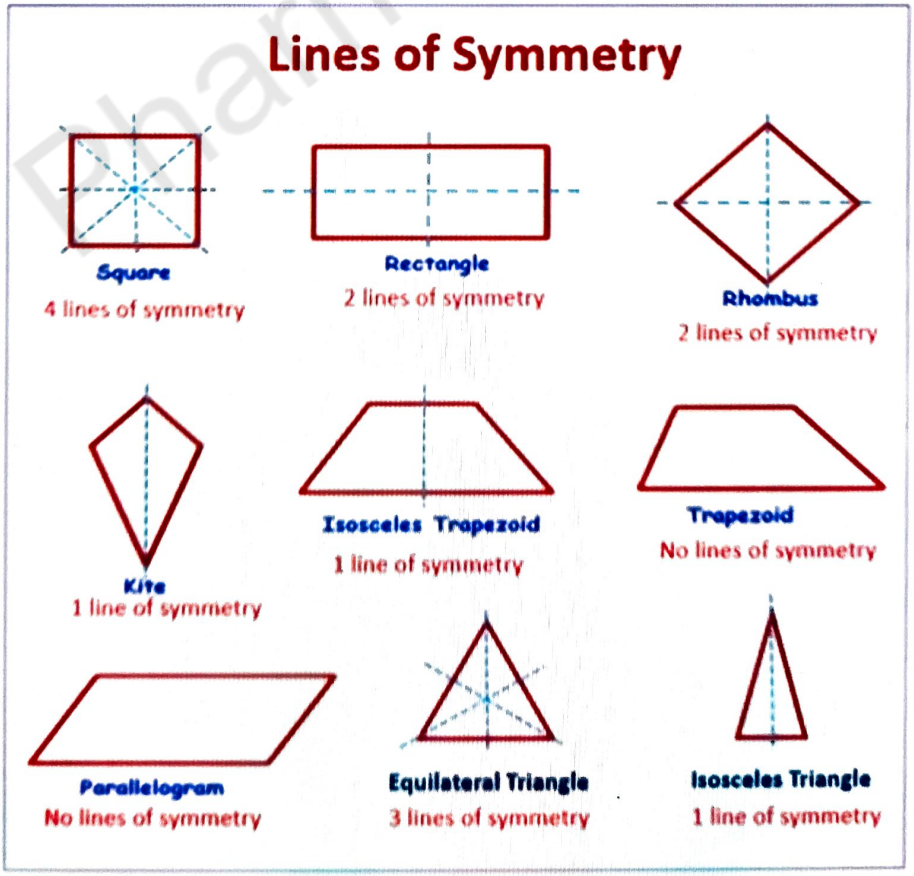
(4) Trans-1,2-dimethylcyclopropane: This structure has only a single C_2 axis. It is a dissymmetric and chiral.

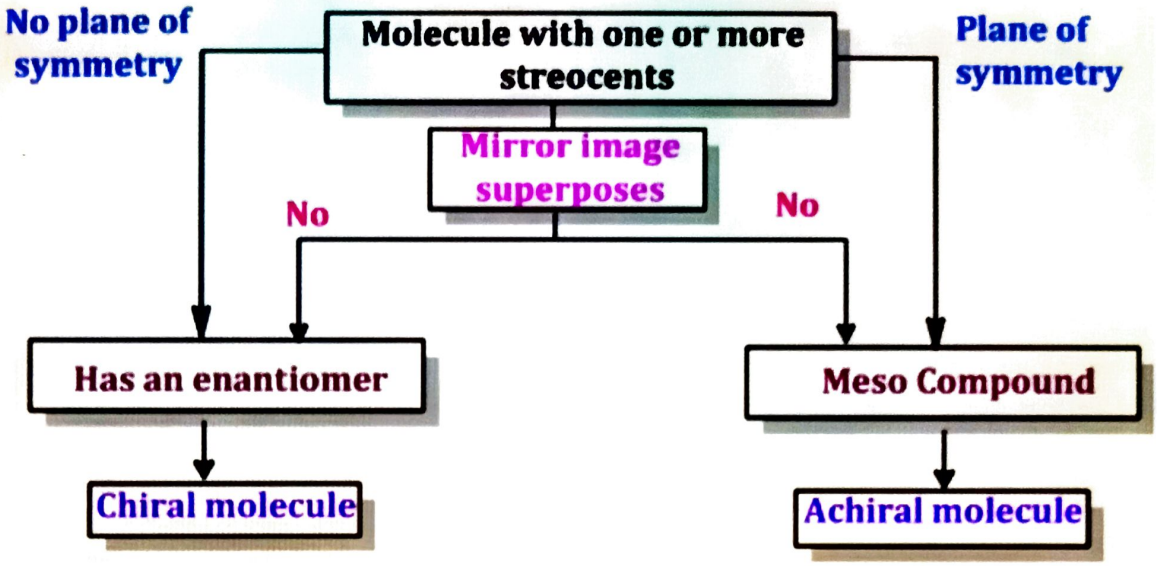
(5) Cyclohexane (boat conformation): It has a C_2 axis and two planes of symmetry. It is achiral.

(6) Cyclohexane (chair conformation): It has planes, axes and a point of symmetry. The principle axis is C_3.

(ii) Plane of symmetry:

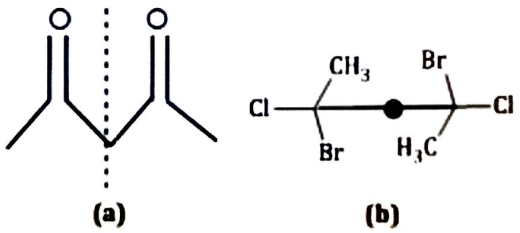
- A molecule with a **zero stereocenters is always achiral**. A molecule with odd number of **stereoisomers (1, 3, 5 etc.)** will always be chiral.
- A molecule with even number of **stereocenters may be chiral or achiral due to meso compounds.** Beside this planes of symmetry and inversion centers are the parameter to **determine chirality of a molecule.** Planes of symmetry are usually easier to identify than inversion centers.
- Plane that cuts the molecule in half to get same things on both sides is known as plane of symmetry.
- It can be either perpendicular to the plane or within the plane. A molecule having a plane of symmetry in any conformation is usually achiral.





(iii) Inversion center:

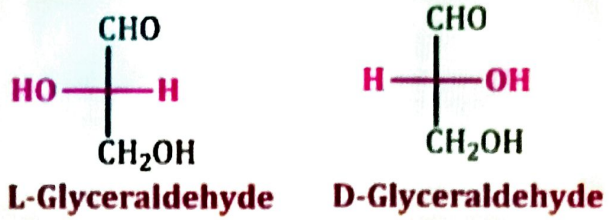
- The molecule (a) has a **plane of symmetry through the central carbon.** This is a mirror plane where **one half of the molecule is a perfect reflection of the other half of the molecule.**
- This molecule is **achiral.**
- The molecule (b) has a center of symmetry or an inversion center. An inversion center is a point in the molecule (may or may not be an atom) through which all other atoms can converted through 180° into another identical part. The molecule is achiral because of inversion center.



(a) (b)

❖ NOMENCLATURE OF OPTICAL ISOMERS

- The d/l system was developed by Fischer and Rosanoff in around 1900. Totally arbitrarily, (+) glyceraldehyde was defined as being D because the OH group attached to the C2 is on the right hand side of the molecule. While (–) glyceraldehyde was defined as L because the OH group is on the left hand side.



L-Glyceraldehyde D-Glyceraldehyde

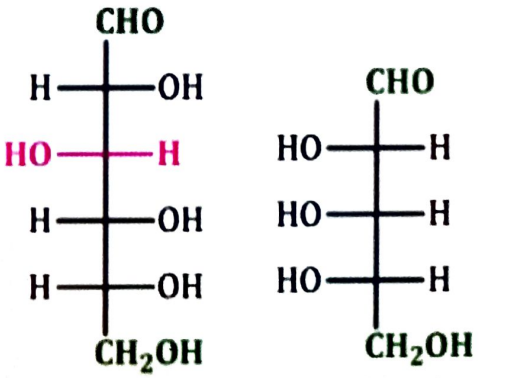
(1) The **d/l system** (named after Latin dexter and laevus, right and left) names the molecule by relating them to the molecule **glyceraldehyde**. This system of nomenclature represents an older system for **distinguishing enantiomers of amino acids and carbohydrates.** This arbitrary type of configuration (d/l system) is known as **Relative Configuration.**

(a) To name complex **amino acids and carbohydrates** in Fischer projection, take **carbonyl group (aldehyde, ketone or carboxylic acid) on the top and CH_2OH on the bottom.**

(b) The D descriptor is used when the –OH or –NH2 on the 2nd carbon (from bottom) points to the right and L is used when the –OH or –NH2 points to the left. Thus, from stereochemistry of only one stereocenter (i.e. 2nd carbon from bottom) the stereochemistry of all other stereocenters in the molecule is defined.

(c) The **d/l nomenclature does not indicate** which **enantiomer is dextrorotatory** and **which is levorotatory.** It just says that the compound's stereochemistry is related to that of dextro - or levo - enantiomer of glyceraldehyde. **For example, d-fructose is levorotatory.**

✓ Hence, it is stated that all natural amino acids are L while natural carbohydrates are D. Thus, (+) glucose has the D-configuration and (+) ribose has the L-configuration.



D (+) -glucose D (+) -ribose

❑ The Cahn Ingold Prelog (CIP) Sequence Rule

- An absolute configuration refers to the **spatial arrangement** of the atoms of the chiral molecules and its stereochemical description using **terms (R) or (S).** Cahn, Ingold and Prelog introduce Sequence Rules to assign an order of priority to the atoms or the groups directly attached to a stereocenter.

➢ **The absolute configuration of a given stereocenter is defined as either (R) or (S) by applying these rules.**

✓ **Rule 1:** Atom of **higher atomic number is given priority** over those of lower atomic number

e.g., I > Br > Cl > F >O > N > C > H.

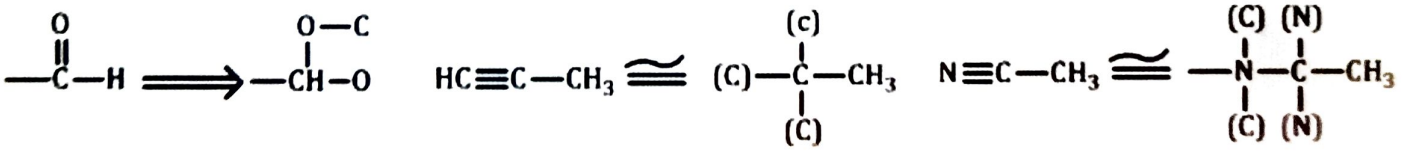
✓ **Rule 2:** Isotope of **higher atomic weight** takes precedence. e.g.,

3H (tritium) > 2H (deuterium) > 1H (hydrogen)

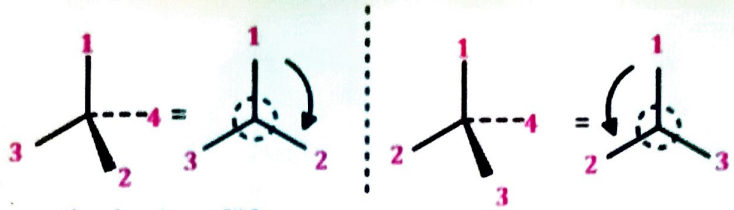
✓ **Rule 3:** When two or more atoms **directly attached to a stereocenter** are same, the order of priority depends on the next atom along the chain.

e.g., $-CO_2CH_3 > -CO_2H > CONH_2 > COCH_3 > CHO > CH_2OH$

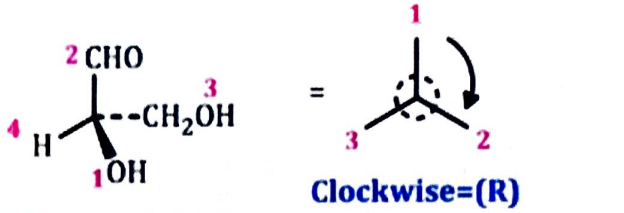
✓ **Rule 4:** If an atom is **double bonded to another atom**, treat it as if it were singly bonded to two of those atoms. If an atom is triply bonded to another atom, treat it as if it were singly bonded to three of these atoms. **Convert the unsaturated group directly attached to the stereocenter into saturated group to decide order of priority e.g.,**



- Applying above sequence rules, assign the numbers to the **functional groups as per order of priority.** Draw a generic tetrahedral center and view the molecule so that the atom/group with lowest priority should project maximum away in space.
- **A clockwise decreasing order is assigned the (R) - configuration while an anti-clockwise decreasing order is assigned the (S)-configuration.**



Clockwise=(R) Anti-Clockwise=(S)



(+) Glyceraldehyde Clockwise=(R)

(R) (+) Glyceraldehyde

As per sequence rule, the order of priority of the groups is
$OH > CHO > CH_2OH > H$

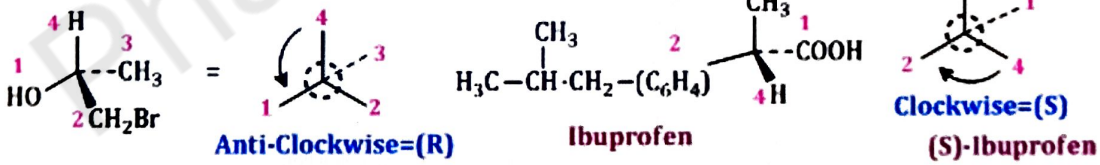
(-) Serine Anti-Clockwise=(S)

(S) (-) Serine

As per sequence rule, the order of priority of the groups is
$NH_2 > COOH > CH_2OH > H$

✓ **Rule 5:** A longer group may not necessarily have a higher priority over another smaller group. e.g. –CH2Cl has a higher priority than –CH2CH2CH2CH3.

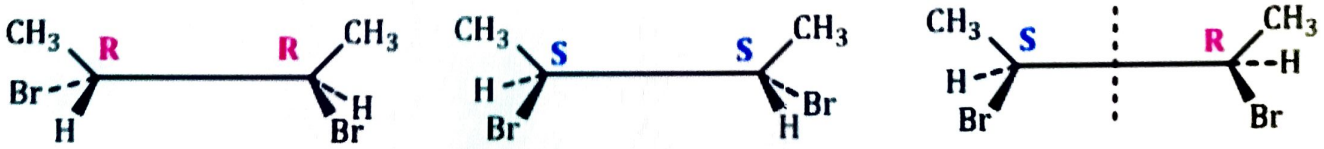
✓ **Rule 6:** If a lowest priority group is in the front of the plane of the molecule then the assignment is reversed. i.e., **clockwise is S and anticlockwise is R.**



Anti-Clockwise=(R) Ibuprofen Clockwise=(S)

(S)-Ibuprofen

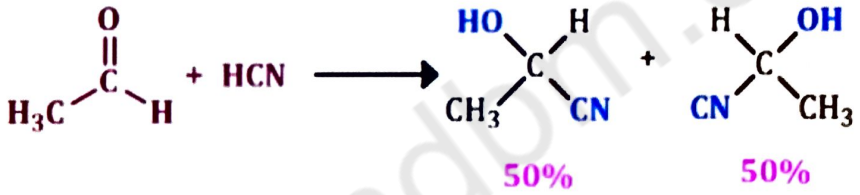
✓ **Rule 7:** If there are **multiple chiral carbons in a molecule,** the configuration of entire molecule can be defined by using number that specifies the location of the stereocenter preceding configuration e.g., (1R, 4S). e.g.,



(2R,3R) -2,3- dibromobutane (2S, 3S)2,3- dibromobutane meso-2,3-dibromobutane

❖ RACEMIC MODIFICATION

- A racemic modification or racemate is **a 1 : 1 mixture of (+) and (–) enantiomers.**
- When enantiomers are mixed together in equal amount, the rotation caused by a molecule of one isomer is exactly cancelled by an **equal and opposite rotation caused by a molecule of its enantiomer.**
- Hence, the overall optical rotation of racemate is zero. A racemic modification is thus **optically inactive. The prefix (±) is used to denote the racemic nature of the sample. e.g., (±)-2-methyl-1-butanol.**
- When one of the starting material is chiral, the product of the reaction will always be formed as a racemate in the absence of chiral catalyst.



- However, biologically active pure enantiomer can be synthesized in the presence of chiral catalysts or agents.

❑ Methods of Racemic Modification

(a) Mixing: A racemic modification may be achieved by an intimate mixing of exactly **equal amounts of dextro (+) and levo (–) isomers.**

(b) Chemical synthesis: When one of the starting material is chiral the product of reaction will always be formed as a **racemate in the absence of chiral catalyst. e.g.,** when hydrogen cyanide reacts with acetaldehyde (chiral), equal number of mole of two enantiomeric forms of **lactonitrile, $CH_3CHOHCN$ results.**

(c) Thermal racemization: Racemization may occur when an optically active material is heated. It leads to temporarily breaking one of the 4 bonds to a

- stereocenter. The atom/group separated exchanges the position and joins back to stereocenter to form another enantiomer e.g., the distillation of optically active enantiomer of α-phenethyl chloride leads to its racemization.

(d) Walden inversion: The racemization of 2-iodooctane by potassium iodide in refluxing acetone involves a process known as Walden inversion.

(e) Epimerization: It is the change in the configuration at one asymmetric carbon atom in a compound having more than one stereocenters. It thus leads to interconversion of diastereomers.

(f) Mutarotation: It is a spontaneous change with time, in the rotation of freshly prepared solutions of optically active substance till it reaches an equilibrium. Mutarotation is the result of either epimerization or a spontaneous structural change. The rate of mutarotation depends on temperature, solvent and catalyst. For example, the mutarotation of glucose is known to be acid-base catalysed.

❖ Resolution of Racemic Mixture

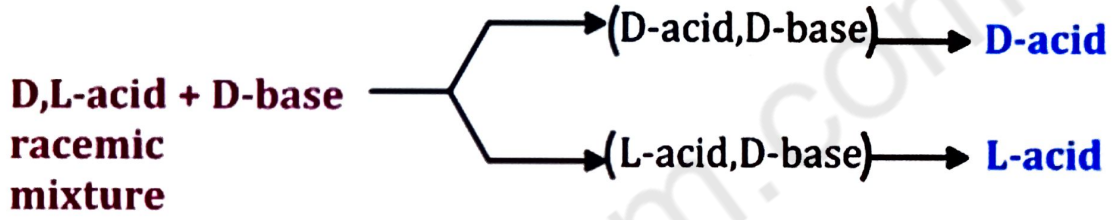
- The process of separating a racemate into pure enantiomers is known as resolution.
- Enantiomers have identical physical properties (b.p., m.p., solubility) and hence it is difficult to separate enantiomers using conventional methods. If a pair of enantiomers is converted into a pair of diastereomers, the diastereomers can be separated easily utilizing the difference in their physical properties.
- Once separated, the pure enantiomer may be regenerated back from its respective diastereomer.

For example,

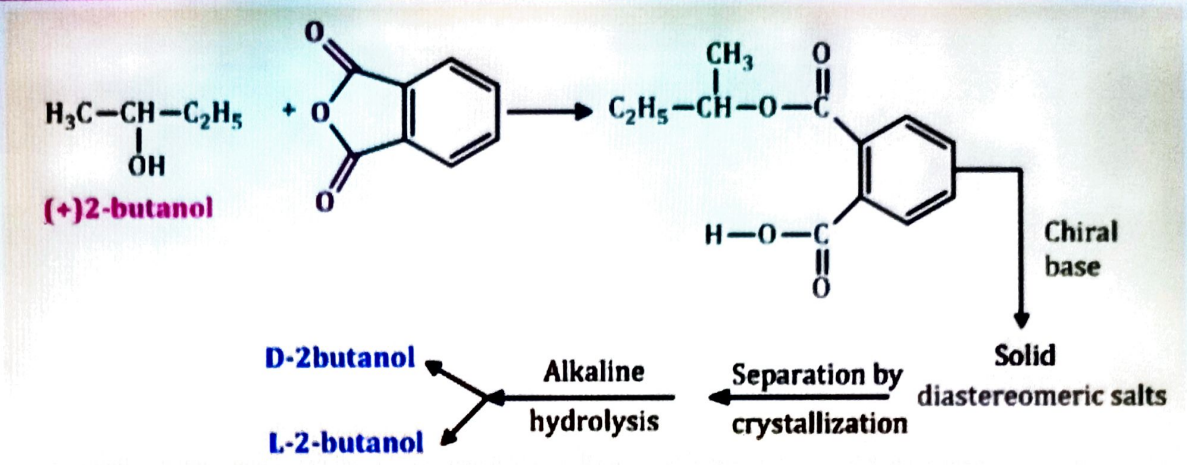
(i) A racemic mixture of enantiomers of an acid can be **converted to a salt using a chiral base having D-configuration.** The salt obtained contains a mixture of two diastereomers:

- **(D acid, D base) and (L acid, D base).** Due to difference in their physical properties, the diastereomeric salts are fully separated. Dissociation of separated diastereomeric salt leads to regeneration of D-acid and L-acid respectively.

Resolution of racemic mixture



- **Racemic acids may be resolved** using commercially available chiral bases like brucine, strychnine, l-phenyl ethanamine. Similarly racemic bases may be resolved using chiral acids such as **(+) tartaric acid, (–) malic acid, (–) mandelic acid and (+) camphoric acid.**
- A **racemic alcohol may be resolved by converting the racemate into a mixture of diastereomeric esters using a chiral acid.** The separation of these diastereomeric ester becomes difficult if they are liquid.
- In such cases, instead of full ester, half ester is synthesized containing one free carboxylic group. A chiral base, brucine then forms solid diastereomeric salts which can be later separated by crystallization.
- The pure enantiomer of 2-butanol is regenerated through hydrolysis of respective diastereomeric salt.



(ii) Resolution by biochemical means: Certain **mold, bacteria or fungi** selectively destroy one enantiomer at a faster rate than the other enantiomer. For example, the mold **Penicillium glaucum** if allowed to grow with racemic mixture, it selectively destroys the dextro isomer leaving pure levo isomer behind.

✓ Pharmacological effects of Racemic drug mixtures

Drug	Biological response	Enantiomer
Terbutaline	Trachea relaxation	(–)
Propranolol	β-blockade	(S)
Amosulalol	α-blockade	(+)
	β-blockade	(–)
Warfarin	Anticoagulation	(S)
Verapamil	Negative chronotropic	(–)
Atenolol	β-blocker	(S)
Nitrendipine	Ca^{2+} channel blocker	(S)
Zopiclone	Sedation	(R)
Terfenadine	Antihistaminic	(S)
Albuterol	Antiasthmatic	(S)
Flurbiprofen	Anti-inflammatory	(S)
Ketoprofen	Anti-inflammatory	(S)
Thalidomide	Immunosuppresive	(S)
Tetramisole	Anthelmintic	(S)-form (levamisole)
Propoxyphene	Analgesic	Dextro form
	Antitussive	Laevo form

Drug	Biological response	Enantiomer
Tranylcypromine	Antidepressant	(–)
	Improvement in performance	(+)
Sotalol	Antihypertensive	(–)
	Antiarrhythmic	(+)

✓ Advantages of Resolution:

(i) To avoid side effects of unwanted enantiomer leading to improved therapeutic profile and less chances of drug interaction.

(ii) Reduction in the therapeutic dose and hence the cost of treatment.

(iii) Lesser metabolic, renal and hepatic load of a drug on the body as the dose (for a pure enantiomer) reduces to the half of racemic mixture.

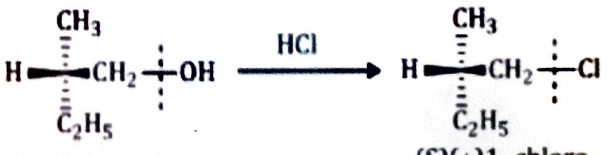
❖ REACTIONS OF CHIRAL MOLECULES

- Chiral molecules react with the reagents in 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 configuration of one compound to that of another.
- Configuration is retained when reaction does not involve breaking of a bond to a chiral center.



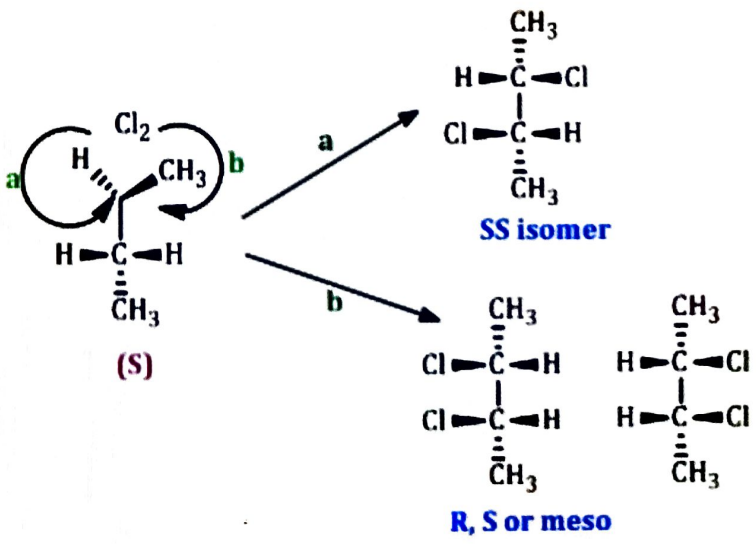
(S)(-) 2- methly - 1 butanol

(S)(+)1- chloro-2methyl butane

- Here as the bond to the chiral center is not broken **'S' configuration** is retained, **because $-CH_2-Cl$ occupies** same relative position as that was occupied by $-CH_2OH$ in the reactant.
- This retention of configuration can be utilized to **determine configurational relationship between two optically active** compounds by converting them into each other by reactions that do not involve breaking of a bond to a chiral center. Only relative configuration can be assigned than absolute configuration.
- Such reactions are used to get specific rotations of optically pure compounds.
- **e.g. 2-methyl-1-butanol from fusel oil has specific rotation of –5.90° and is optically pure.**
- Upon treatment with **hydrogen chloride, 1-chloro 2-methyl butane has specific rotation of +1.67°.** So if a sample has rotation equal to this value, compound is said to be pure. If rotation is about + 0.8º, compound is said to be only 50% optically pure.

2. Reactions leading to generation of chiral center:

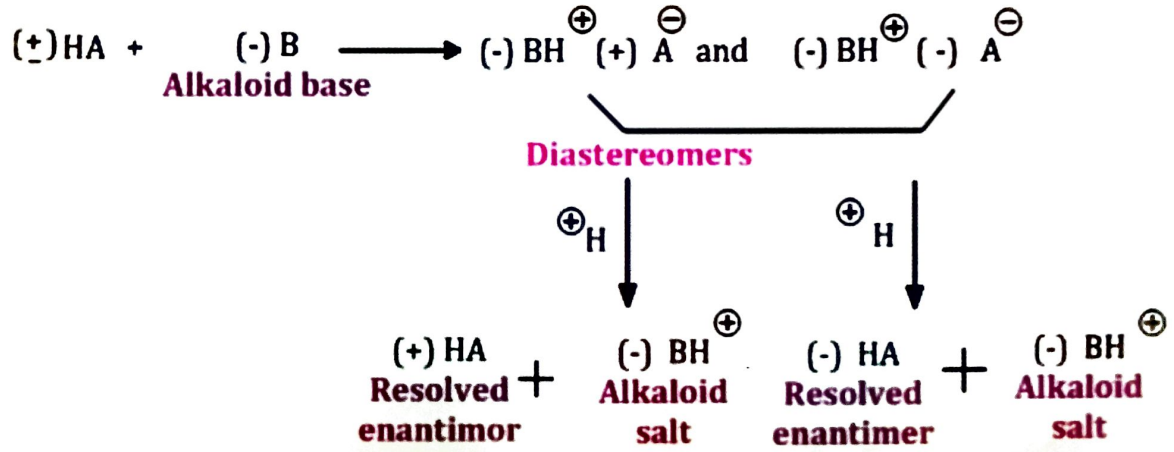
- Generation of first chiral center in a compound usually yields **equal amounts of enantiomers (Racemic mixture)** but reactions that form **second/new chiral center yields unequal amounts of diastereomers depending on the side of attack.**



- Retention of configuration(s) occurs as there is no bond breaking to the chiral center. For new chiral center, depending on side of attack from the same or opposite side, diastereomers are formed but in unequal amounts.
- This is because the intermediate 3-chloro-2-butyl radical contains a chiral center and it lacks symmetry. So two faces of the molecule for attack are not equal to each other. Here S isomer would yield the SS and meso compound in ratio of 29 : 71.
- In some reactions both configurations may not be actually generated but probability exists. Similarly R isomer would yield RR and meso compound in ratio of 29 : 71. If the reactant is optically inactive, it yields optically inactive products.

3. Reactions of chiral compounds with optically active reagents

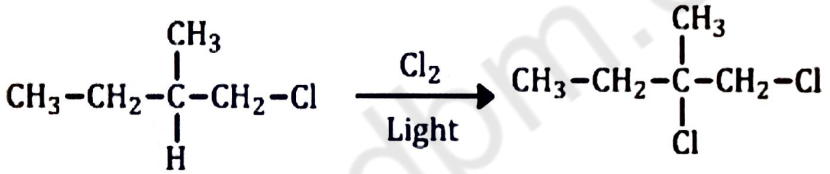
- Such reactions are commonly used in resolution or separation of a racemic mixture/modification into individual enantiomers. Because enantiomers have similar physical properties (except optical rotation) they are not separated by usual methods of fractional distillation or crystallization.
- Common 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. Similarly, racemic bases can be separated with acid reagents e.g. (–) malic acid.
- Compounds other than acids, bases can also be resolved. Alcohols are weakly ionized and are not appreciably acidic or basic so their resolution is facilitated by attaching them with acidic handle which can be removed later.

4. Reactions where bonds with chiral center are broken

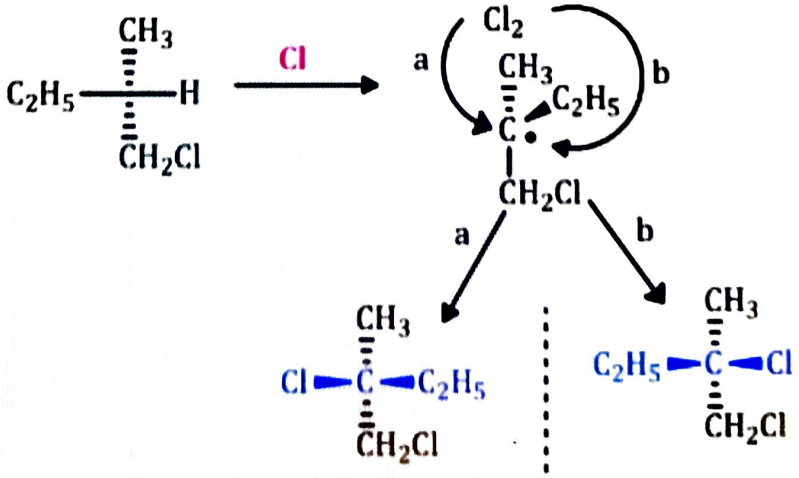
- Stereochemistry of such **reactions depend on the mechanism of the reaction.** Hence, stereochemistry can be **helpful to give evidence of a particular mechanism.**
- **e.g.**



(S)(+) 1- chloro - 2-methyl butane
Opticaly active

(±) 1,2 -Dichloro, 2-methyl butane
Optically inactive

- 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.



- If there is simultaneous attack of chlorine while displacement of hydrogen, only the product from backside attack of chlorine would have been obtained instead of optically inactive product, so mechanism involving free alkyl radicals is correct.

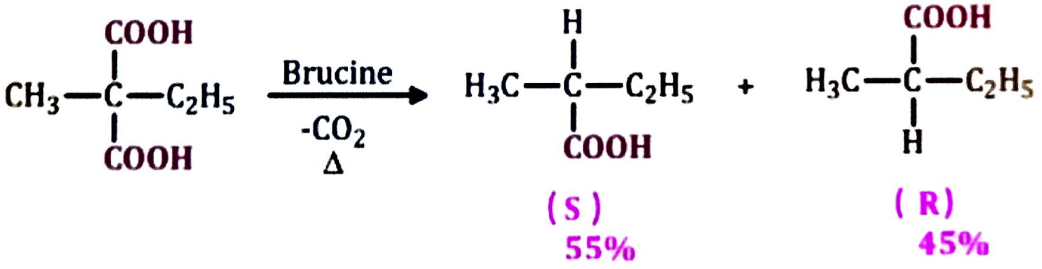
✓ A reaction is stereospecific when reactants exist as stereoisomers and each isomeric reactant gives a **different stereoisomeric product.**

✓ A reaction is stereoselective when reactant irrespective of any stereoisomerism produces predominantly or exclusively one stereoisomeric form of **the product than other possible forms.**

❖ ASYMMETRIC SYNTHESIS (PARTIAL AND ABSOLUTE)

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

✓ Decarboxylation of ethyl methyl malonic acid to give a methylbutyric acid is one of the first recorded asymmetric synthesis.

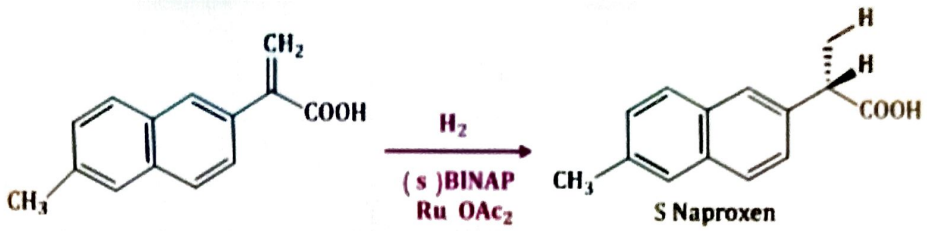


➢ Typical asymmetric syntheses include

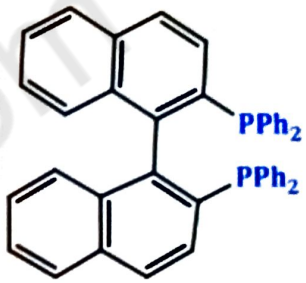
- **Asymmetric hydrogenation**
- **Asymmetric epoxidation**
- **Asymmetric dihydroxylation**

1. Asymmetric Hydrogenation (Reduction):

- It is used for asymmetric synthesis of analgesic drug Naproxen.

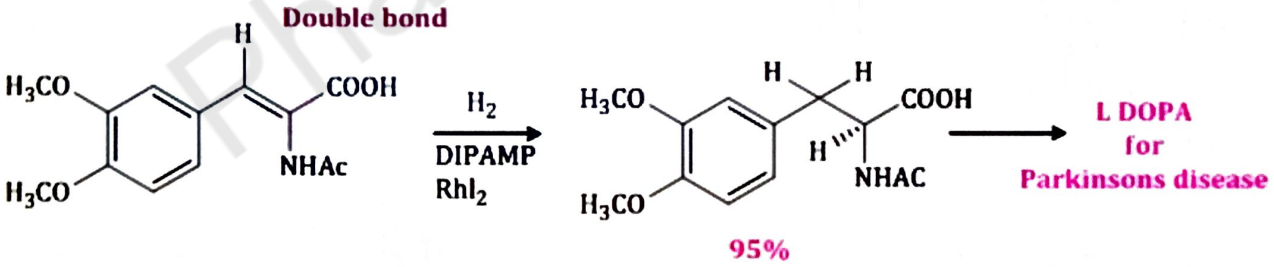


- Reaction is carried out in presence of chiral catalyst **to hydrogenate double bond.**
- The catalyst selects a **single enantiotopic face of the double bond** and adds hydrogens across it.
- **BINAP is a chelating diphosphine.** Chirality is due to restricted rotation of the bond joining two naphthalene ring systems. Along with Ruthenium it acts as excellent catalyst for hydrogenation.

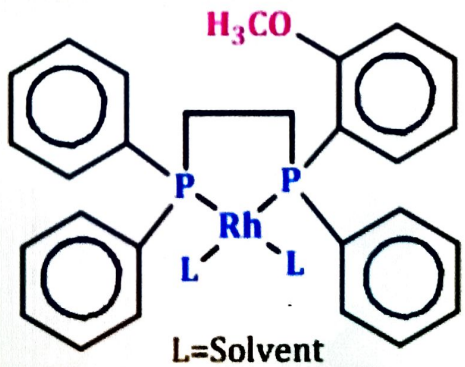


S-BINAP

- For **double bonds** bearing amino group, better catalysts are based on rhodium.



- The catalyst is a **cationic complex of rhodium with another diphosphine DI PAMP.**

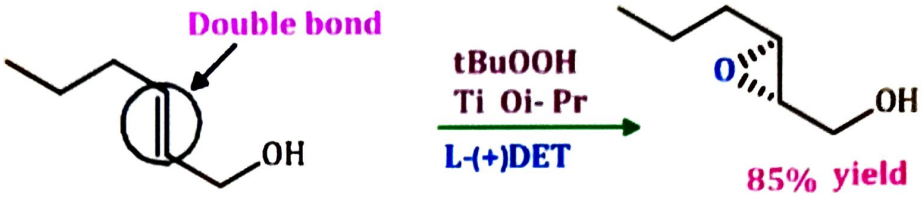


L=Solvent

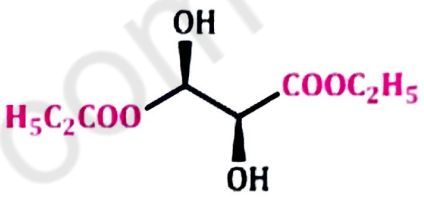
- Important application of asymmetric hydrogenation is in synthesis of L menthol from (R) citronellal.

2. Asymmetric epoxidation:

- Oxidation of alkenes by **asymmetric epoxidation** is one of the **popular sharpless reaction.**



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

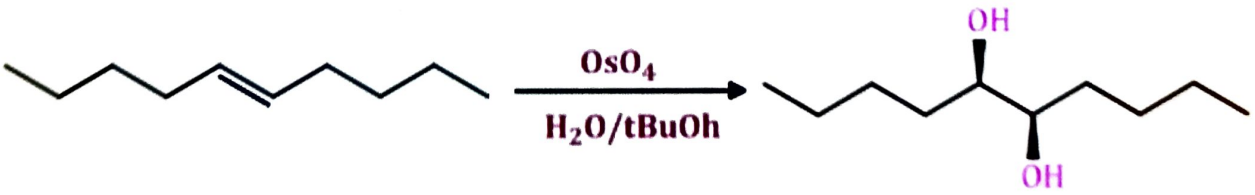


L (+) Diethyl Tartrate (DET)

- Such metal catalysed **epoxidation works only on allylic alcohols.** Initially active complex is formed from **two titanium atoms bridged by two tartrate ligands.**

3. Asymmetric dihydroxylation:

- Dihydroxylation of alkenes by **osmium tetroxide** in catalytic amount is carried out.



- Osmium (VIII) act as oxidizing agent and K3Fe (CN)6 is commonly used to reoxidize the osmium after each catalytic reaction.

✓ To increase rate of reaction K2CO3 and methanesulfonamide are added.

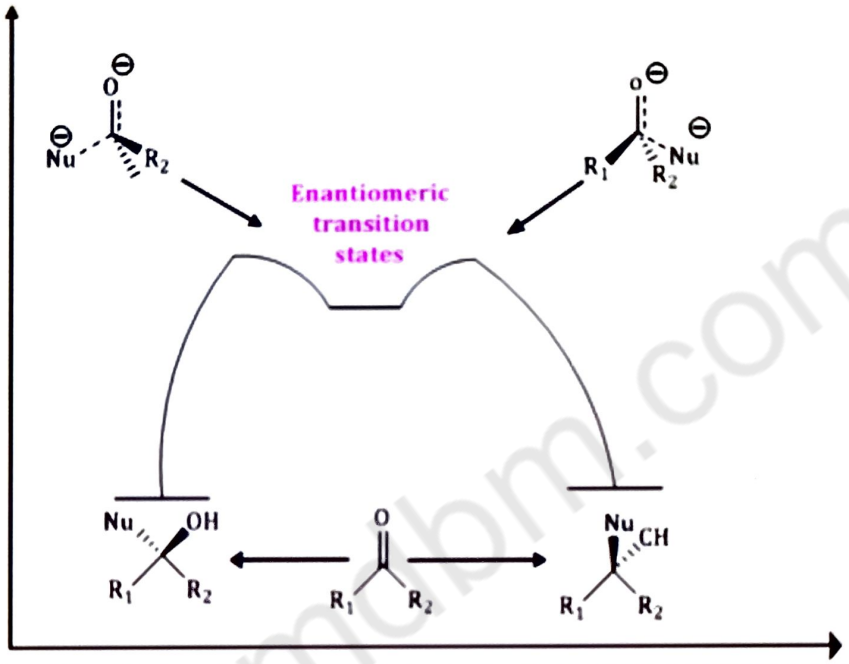
✓ Chiral ligands are usually alkaloids dihydroquinidine and dihydroquinine

- Based which must be attached to aromatic ring **e.g. Phthalazine.**

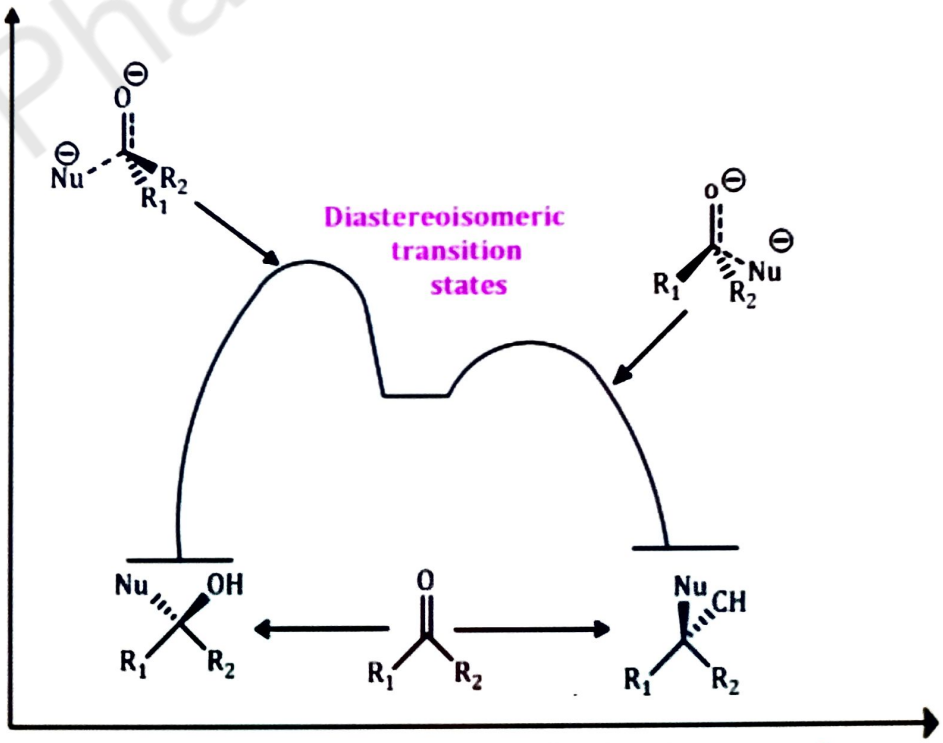
✓ Trans alkenes dihydroxylation more selectively than other alkenes **because of alignment of ligand and catalyst.**

✓ Reaction has been **successfully used for synthesis of antibiotic chloramphenicol in few steps.**

- Energy Profile diagrams for asymmetric synthesis



Nucleophilic attack on ketone in achiral environment where enatiomeric products are produced in exactly equal amounts



Nucleophilic attack on a ketone in chiral environment where enantiomeric products are produced in unequal amounts.