STEREOCHEMSITRY - II

(CCF , SEMESTER – 2)

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TOPICS

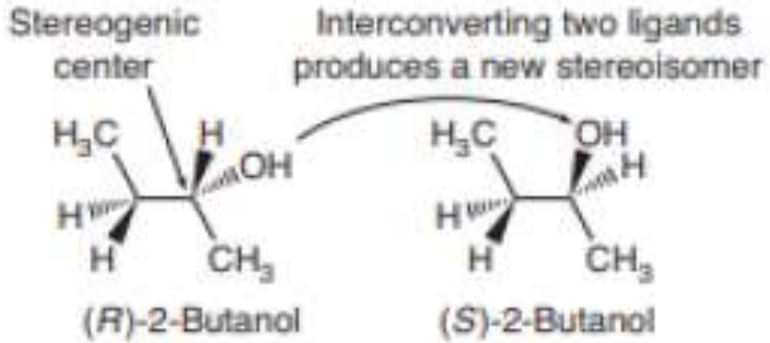
- 1. Chirotopicity and its relationship with stereogenicity
- 2. Pseudoasymmetry in ABA-type systems
- 3. Relative and absolute configuration, including R/S descriptors
- 4. Erythro/threo and meso nomenclature
- 5. E/Z descriptors for alkenes (C=C)
- 6. Optical activity of chiral compounds, including optical rotation and specific rotation
- 7. Racemic compounds and racemization
- 8. Resolution of acids and bases via diastereomeric salt formation
- 9. Optical purity and enantiomeric excess

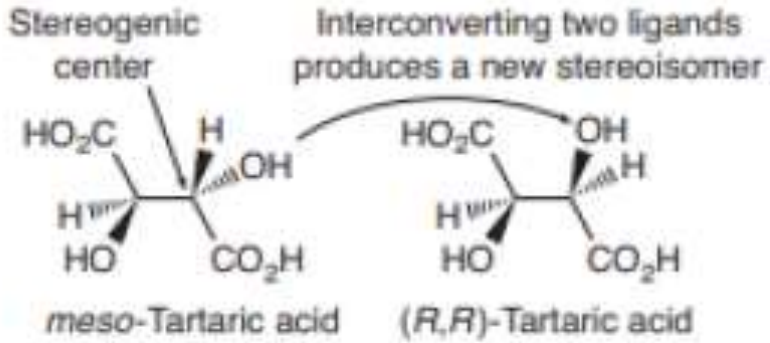
Topic 1
Chirotopicity and its relationship with stereogenicity

- In stereochemistry, a chirotopic atom (or center) is a atom that lacks a symmetry element (like a plane or axis) and thus can give rise to chirality.
- Stereogenicity, on the other hand, refers to the ability of an atom (usually a carbon) to give rise to stereoisomers

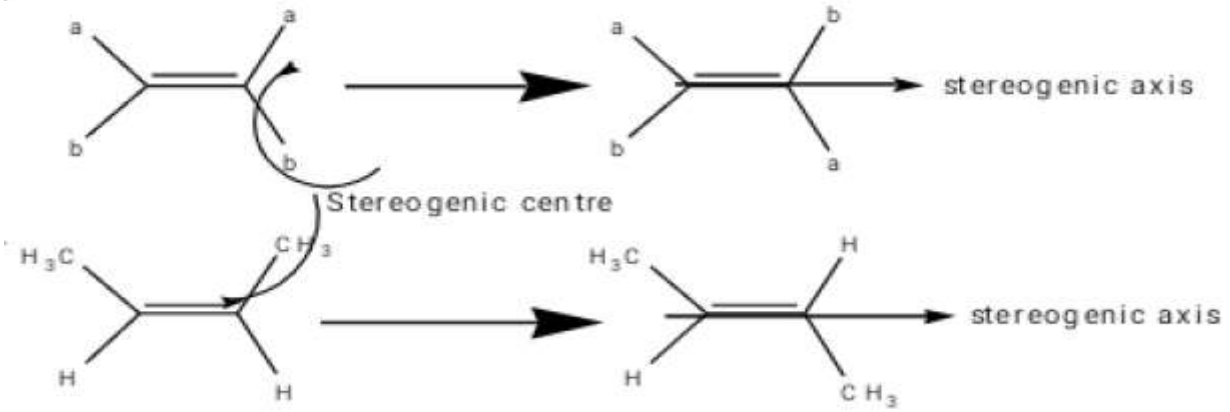
- *Both terms are very similar and often lead to confusion*
- *Much of the confusion that can be generated with the terms given above was eliminated with the introduction of the stereogenic center (or equivalently ,stereocenter)*
- *An atom or a group of atoms,is Considered to be a stereogenic center if the interchange of two ligands attached to it can produce a new stereoisomer.*
- *Not all interchanges have to give a new stereoisomer,But if one does,then the center is stereogenic.The center therefore ‘‘generates’’ stereochemistry .*
- *A non-stereogenic center is one in which exchange of any pair of Ligands does not produce a stereoisomer .*
- *The term ‘‘ stereogenic center’’ is ,in a sense , broader than the term ‘‘ chiral center’’. It implies nothing about the molecule being chiral,only that stereoisomerism is possible .*

two non equivalent configuration of Cabcd

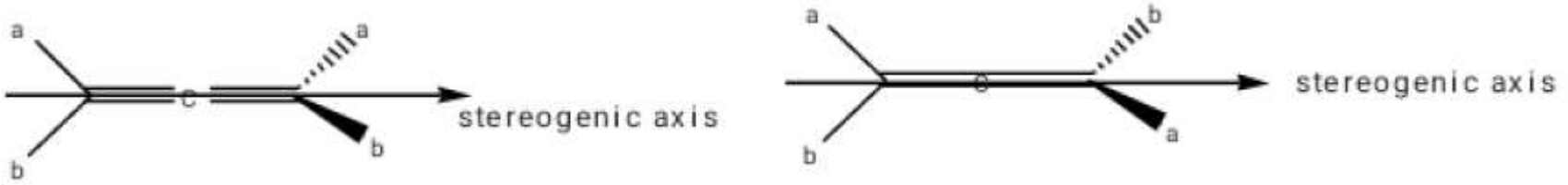




- *Stereogenicity is also associated with double bonds .*
- *If you Interchange the position of methyl and hydrogen attached to one carbon of cis-2-butene, You will get trans-2-butene, which are stereoisomers*
- *But they are not mirror images .So they are Diastereomers*
- *In case of alkenes like Cab=Cab or Cab=Cac or Cab=Ccd , the axis joining two carbon atoms is called stereogenic axis, because stereoisomerism generate through this axis*



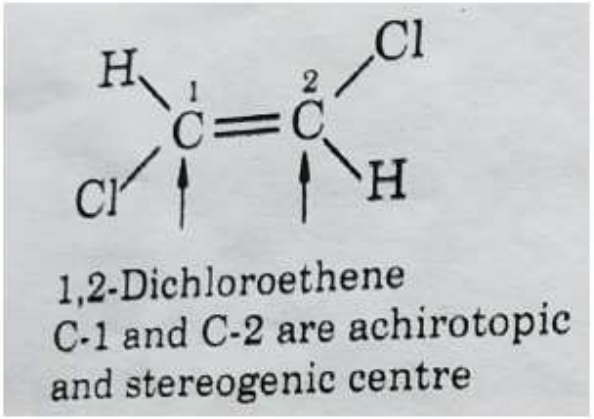
- *In case of allenes same process will be applied*



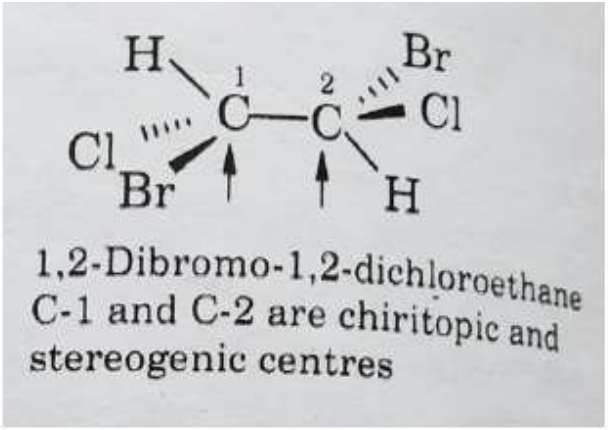
- *An atom within a molecular framework is said to be chirotopic if its site symmetry is chiral , i.e., the atom resides in a chiral environment. Molecule(s) bearing chirotopic centre need not be as a whole chiral.*
- *An atom within a molecular framework is said to be achirotopic if its site symmetry is achiral*

* In stereochemistry, **site symmetry** refers to the symmetry elements present at a specific atom or center within a molecule. It describes the local symmetry at that particular site, ignoring the rest of the molecule.Site symmetry is important in determining the chirotopicity of an atom and the overall symmetry of the molecule.

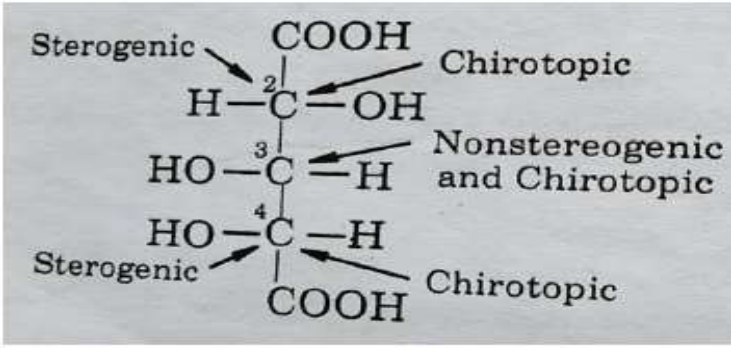
examples



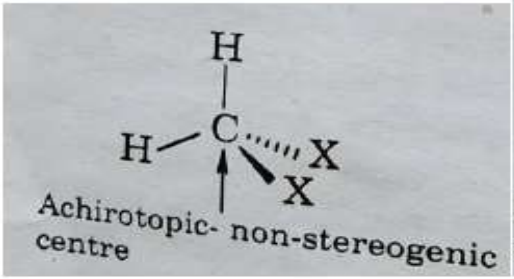
1,2-Dichloroethene
C-1 and C-2 are achirotopic and stereogenic centre

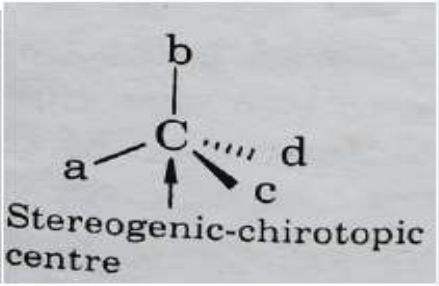


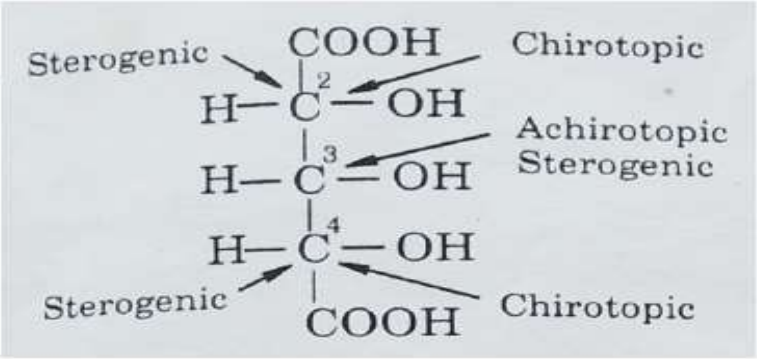
1,2-Dibromo-1,2-dichloroethane
C-1 and C-2 are chiritopic and stereogenic centres



2,3,4-Trihydroxyglutaric acid
C-2 and C-4 are streogenic-chirotopic centres but C-3 is non-stereogenic-chirotopic centre. Mutual exchange of positions of H and OH on C-3 followed by 180° in plane rotation gives back the same structure

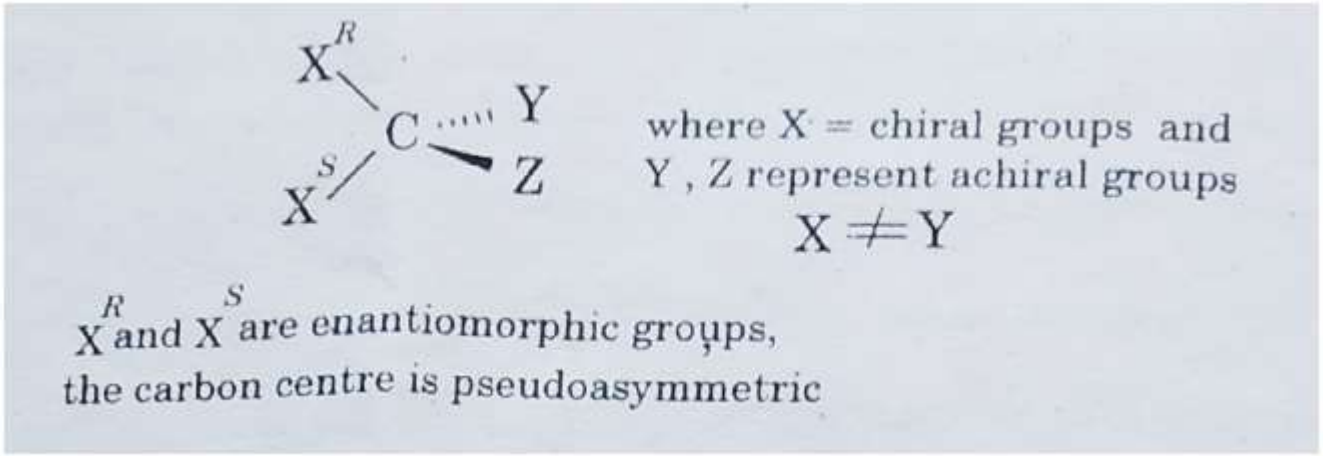






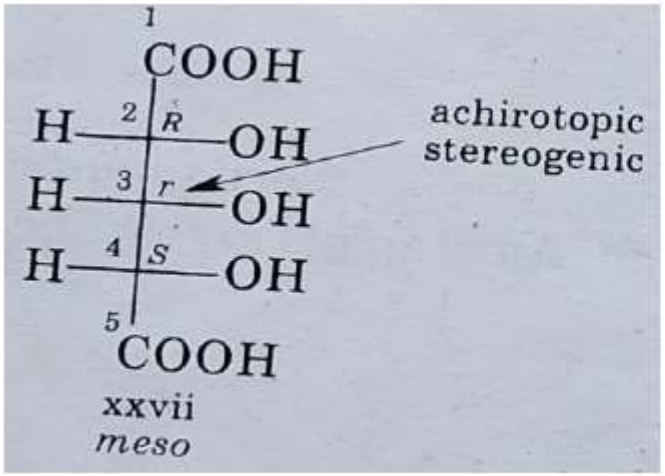
TOPIC -2
Pseudoasymmetry in ABA-type systems

- A pseudo-asymmetric centre is found in a *meso* molecule where a plane of symmetry runs through a stereogenic centre and that stereogenic centre's two substituents are constitutionally the same (same atoms connected by the same type of bonds) but configurationally different (one *R* , another *S*).
- In this situation, the carbon atom is achirotopic but stereogenic .

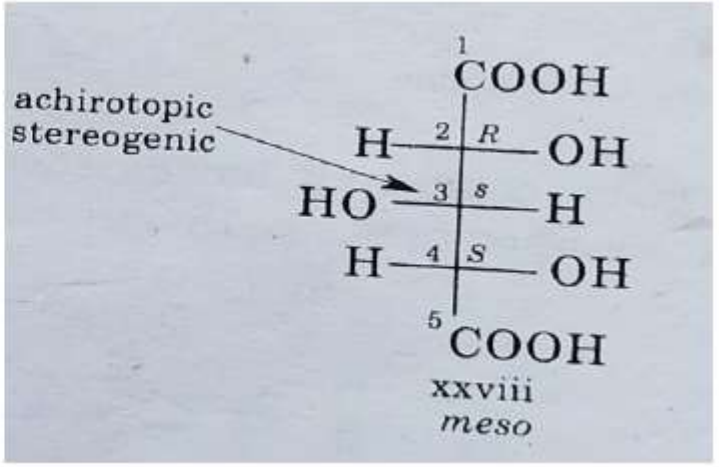


the psuedo-asymmetric centre is designated r/s , following CIP rules.

examples



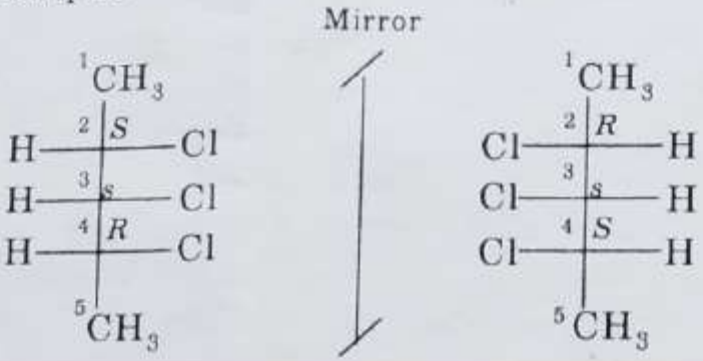
xxvii
meso



xxviii
meso

The complete stereochemical nomenclatures of (xxvii) and (xxviii) are (2*R*,3*r*,4*S*)-2,3,4-tryhydroxypentanedioic acid and (2*R*,3*s*,4*S*)- 2,3,4-tryhydroxypentanedioic acid respectively.

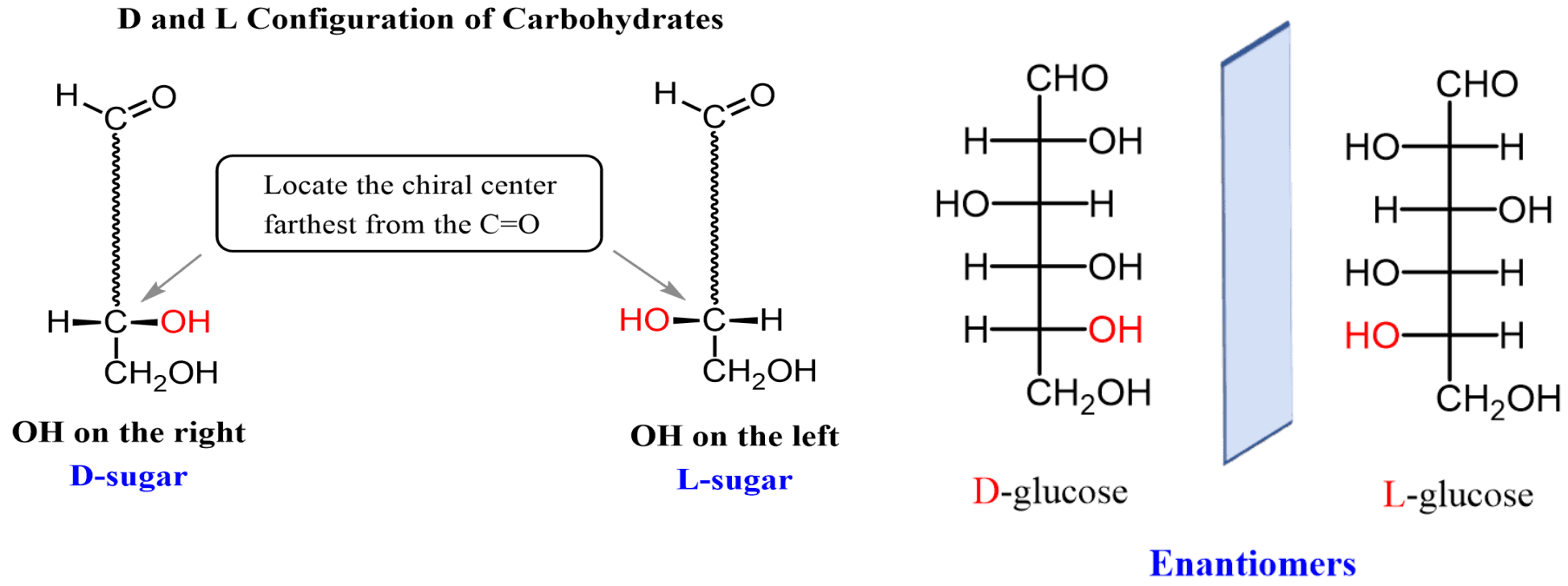
The sterechemical descriptor of a pseudoasymmetric centre is reflection invarient. This can be shown by the following example.



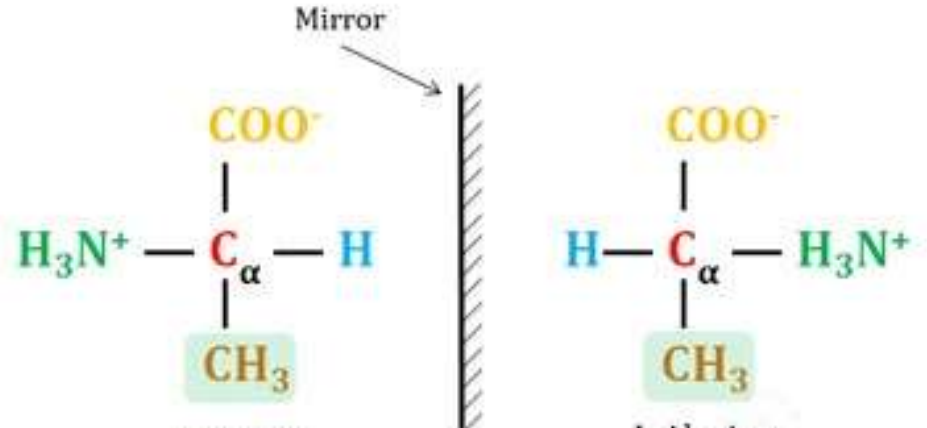
TOPIC -3
Relative and absolute configuration, including R/S descriptors

- Relative configuration refers to the arrangement of atoms in a molecule compared to a reference molecule. It describes the spatial relationship between atoms or groups in a molecule, without considering the absolute arrangement in space.
- EXAMPLE -
- D/L configuration : It is a way to describe the relative configuration of a molecule, especially sugars and amino acids. It's based on the orientation of hydroxyl (-OH) group attached to the last chiral carbon atom in case of carbohydrates and amino (-NH2) group attached at the asymmetric carbon atom in case of amino acids.

- D-carbohydrates: The hydroxyl group is on the right side (dexter) when viewing the molecule in fisher projection with the main chain vertical and the asymmetric carbons at the center.
- Most naturally occurring carbohydrates, like glucose, fructose, and galactose, are D-carbohydrates.
- L-carbohydrates: The hydroxyl group is on the left side (laevus) when viewing the molecule in the same orientation.
- Less common in nature, but still found in some bacteria and other organisms.



- L-amino acids: The amino group is on the left side (laevus) when viewing the molecule with the main chain vertical and the asymmetric carbon at the center.
- Most naturally occurring amino acids, like alanine, valine, and serine, are L-amino acids.
- L-amino acids are the building blocks of proteins and are biologically active.
- D-amino acids: The amino group is on the right side (dexter) when viewing the molecule in the same orientation.
- Less common in nature, but found in some antibiotics, like gramicidin, and in bacterial cell walls.



- Absolute configuration refers to the actual three-dimensional arrangement of atoms in a molecule, considering the handedness (chirality) of the molecule.
- Example :
- (d/l) or (+/-) configaration
- (R/S) configaration

(d/l) or (+/-) configaration

- When solution of a optically active compound is placed inside a polarimeter instrument and a “plane polarised light” is passed through it , then it rotates the plane of the plane polarised light .
- If the rotation is clockwise the molecule is designated as (d) or (+)
- If the rotation is anti-clockwise the molecule is designated as (l) or (-)
- (d): dextrorotatory ; (l) : levorotatory
- It is an absolute configration , it is experimentally determined

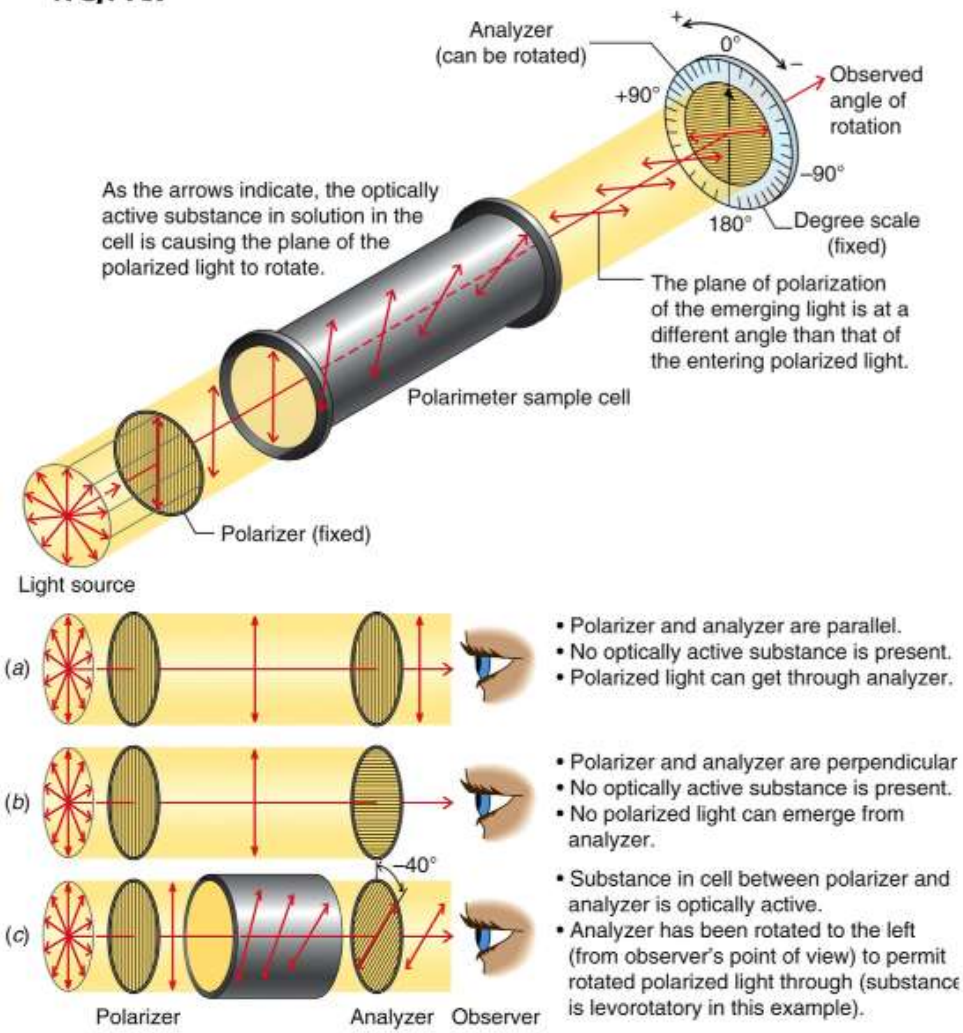
- **POLARIMETER INSTRUMENT**

OPTICAL ACTIVITY & OPTICAL ROTATION

- The moleclues which can rotate the plane of the *Palne polarised light* are called **Optically active molecules or Chiral molecules**
- The rotation of plane polarised light by an optically active molecule is called **optical rotation**.
- The property due to which specific molecules are able to show optical rotation is called **optical activity**

The Polarimeter

A polarimeter is used to measure the rotation of the plane-polarized light.



Rotation clockwise is called **dextrorotatory** (+), and counterclockwise is called **levarotatory** (–).

The maximum amount of light will pass through the polarimeter if the polarization of the incoming light matches the polarization of the detector.

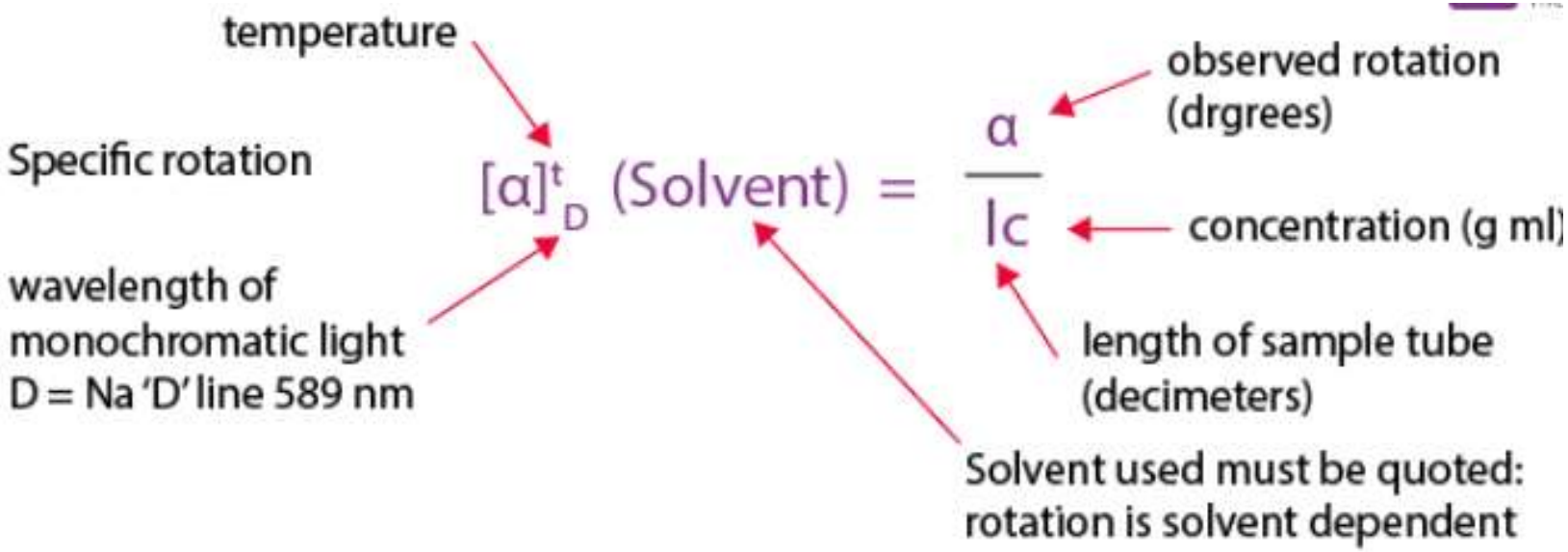
Rotation of the plane of polarized light results in needing to rotate the detecting polarizer to achieve maximum light passing through the polarimeter.

Factors influencing Optical rotation

- Optical rotation value is calculated in degree(°)
- Value of optical rotation depends on
  - 1 . Substance's concentration
  - 2. Wavelength of the light sourse
  - 3. Solvent used
  - 4.Temperature
  - 5.Path length (length of polarimeter tube)
  - 6. molecular structure

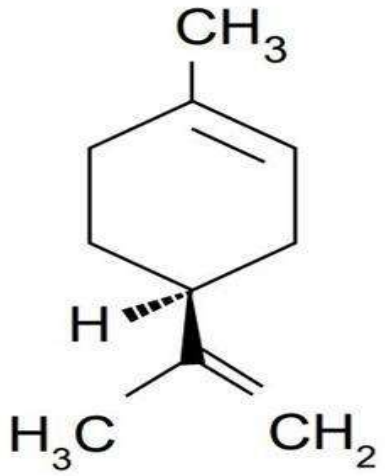
SPECIFIC ROTATION

- Value of optical rotation is influenced by molecular structure which is an intrinsic property of a molecule and external factors (temperature , solvent , path length of tube , wavelength of light , concentration)
- To compare the values of optical rotation of different molecules , the influences of external factors are needed to be cancelled out
- A normalised value of optical rotation is obtained at a specific temperature (usually 20°C) , using a light of specific wavelength (usually 589 nm , the Sodium D line) , with 1g/mL solution concentration and 10 cm (1dm) long polarimeter tube . This normalised value of optical Rotation is called Specific Rotation

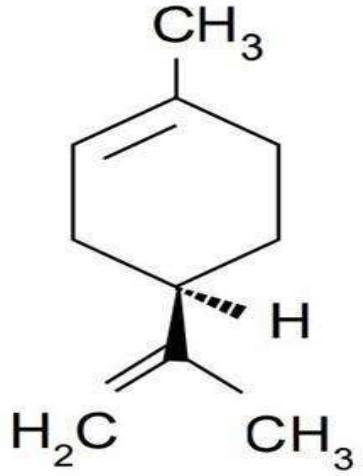


Application of Optical Rotation

1. Pharmaceuticals: To distinguish between enantiomers (mirror-image molecules) of drugs, which can have different biological effects.
2. Food industry: To detect sugars, amino acids, and other optically active compounds in food samples.
3. Chemical synthesis: To monitor the progress of chemical reactions and detect the presence of optically active intermediates.
4. Biotechnology: To analyze biomolecules like proteins, DNA, and polysaccharides.
5. Quality control: To verify the authenticity and purity of optically active compounds.
6. Medical research: To study the properties of biomolecules and their interactions.
7. Materials science: To investigate the properties of optically active materials.
8. Environmental monitoring: To detect and analyze optically active pollutants in water and air.
9. Academic research: To study the fundamental principles of optical activity and its applications.



(*R*) - (+) - Limonene



(*S*) - (-) - Limonene

R/S configaration

- It is chiral centre specific configraion
- every chiral carbon atom is surrounded by four diffrernt groups.
- These groups are arranged according to priority following CIP sequence rule
- Lowest priority group (4^{th}) on back side;

  1 →2→3 : clockwise rotation : R

  1 →2→3 : anti-clockwise rotation : S

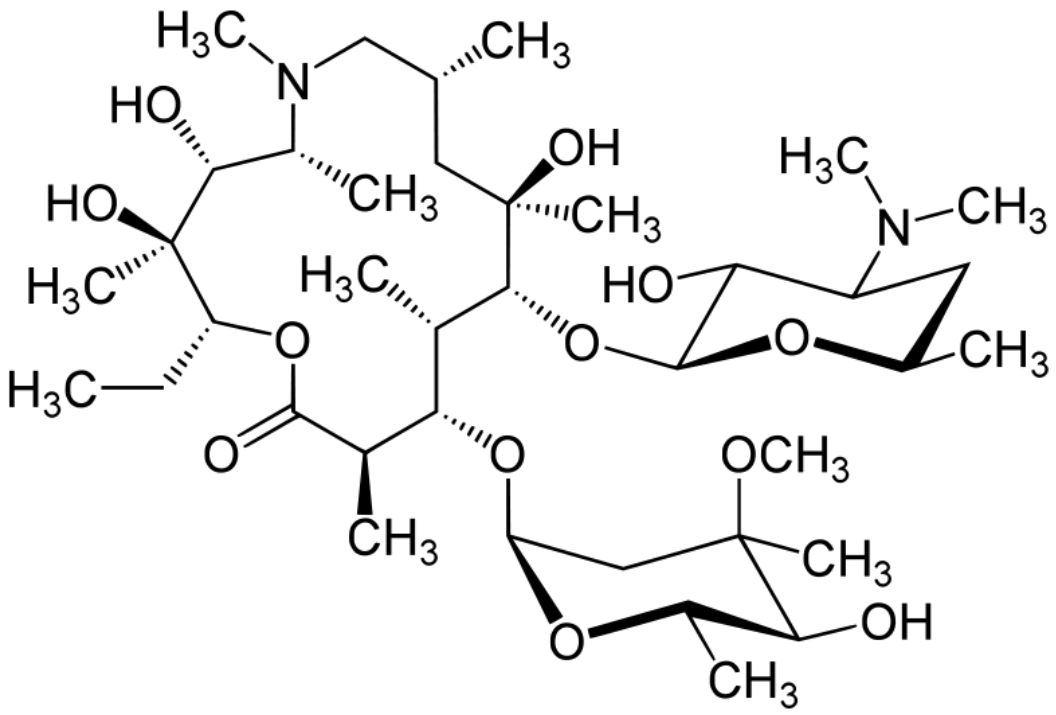
  Lowest priority group (4^{th}) on front side ;

  1 →2→3 : clockwise rotation : S

  1 →2→3 : anti-clockwise rotation : R

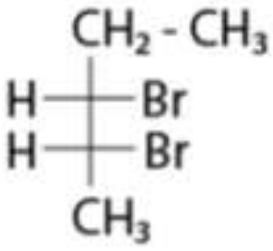
AZITHROMYCIN

(2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-15-oxo- 11-{[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy}-1-oxa-6-azacyclopentadec-13-yl 2,6-dideoxy-3*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranoside

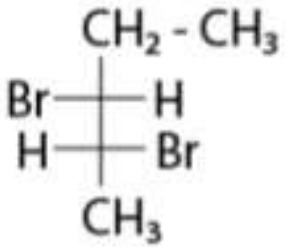


Erythro and Threo Diastereomers

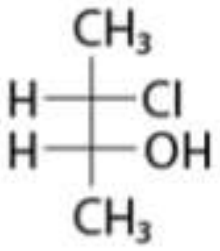
- A Diastereomer is called erythro if its Fischer projection shows similar groups on the same side of the molecule. It is called threo if similar groups are on the opposite sides of the Fischers projection.



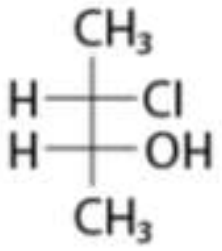
Erythro



Threo



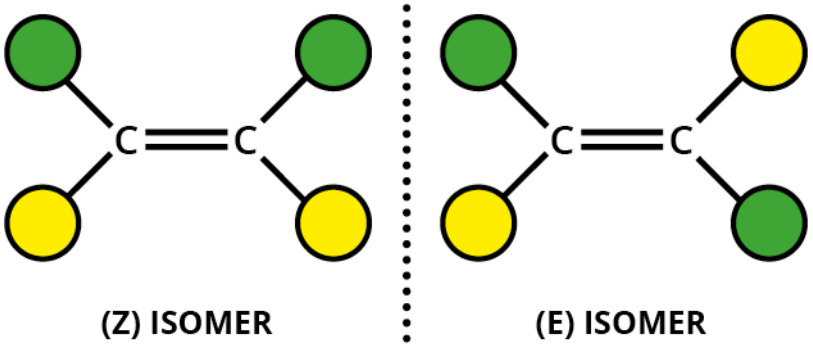
Erythro

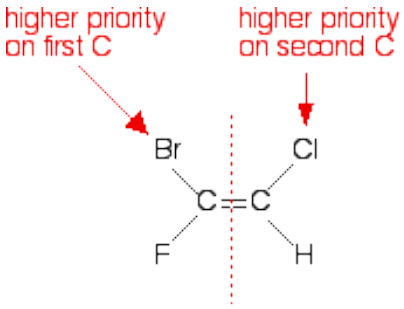


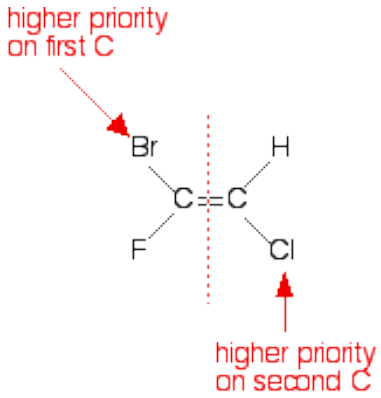
Threo

E/Z isomers of Alkenes

- If similar priority groups are on the same side of a alkene double bond then it is designated as Z- isomer ; if same priority groups are on opposite side of the double bond then it is designated as E-isomer .
- Priority is assigned according to CIP rule





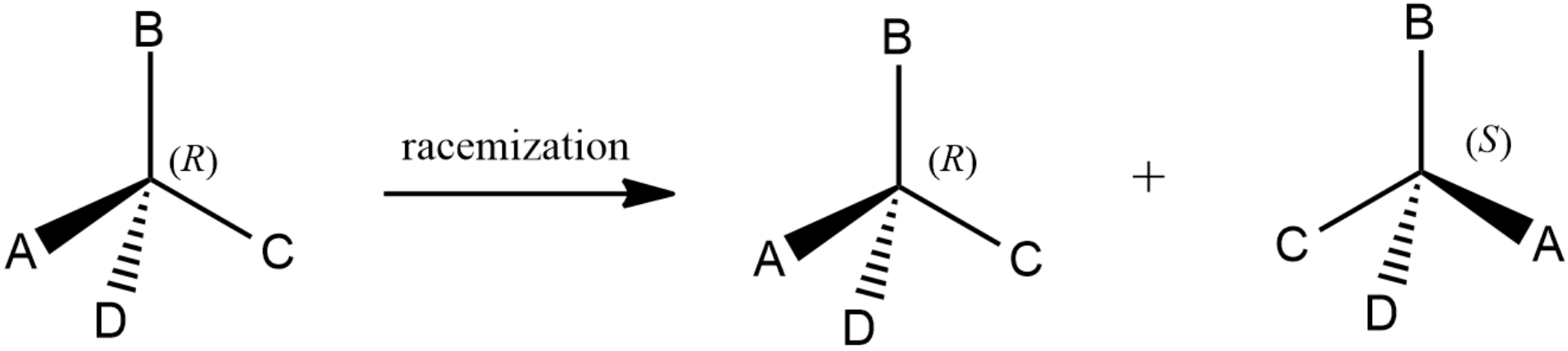


Racemic mixture

- A racemic mixture is a mixture of two enantiomers (R and S stereoisomers) in equal proportions, containing 50% of each.
- The mixture has no net optical activity, as the effects of the two enantiomers cancel each other out.
- In a racemic mixture:- The + and - isomers are present in a 1:1 ratio.
- The physical and chemical properties of the mixture are identical to those of the individual enantiomers, except for optical activity.

RACEMIZATION

- Racemization is a process in which a single enantiomer (R or S) is converted into a racemic mixture, containing equal amounts of both R and S stereoisomers.
- This means that the optical activity of the original enantiomer is lost, and the mixture becomes optically inactive

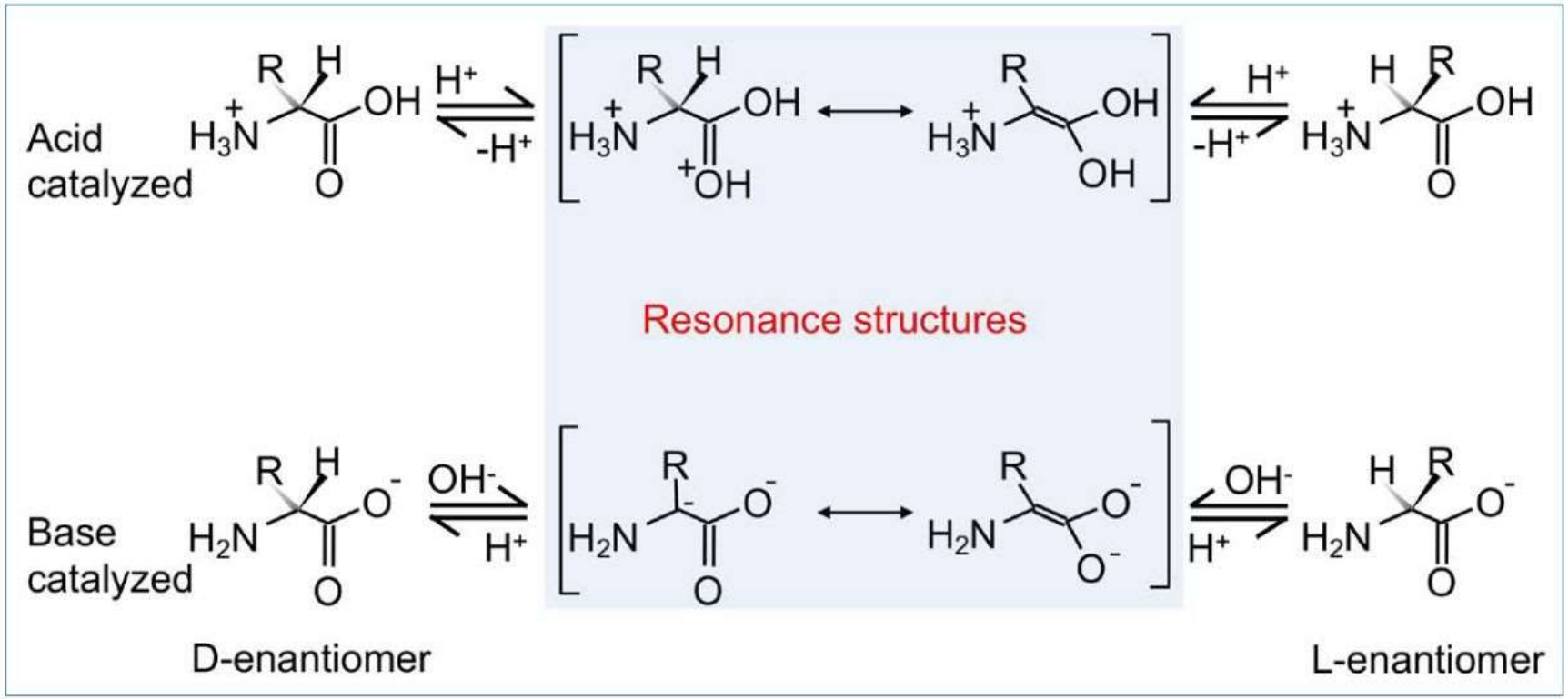


A > B > C > D

50 : 50

- Racemization can occur through various mechanisms, such as:
- 1. Thermal racemization: Heat can cause the molecules to interconvert between R and S forms.
- 2. Acid-catalyzed racemization: Certain acids can facilitate the interconversion of R and S forms.
- 3. Base-catalyzed racemization: Certain bases can also facilitate the interconversion of R and S forms.
- 4. Enzymatic racemization: Certain enzymes can catalyze the interconversion of R and S forms.

Racemization of amino acids



CONSEQUENCES OF RACEMIZATION

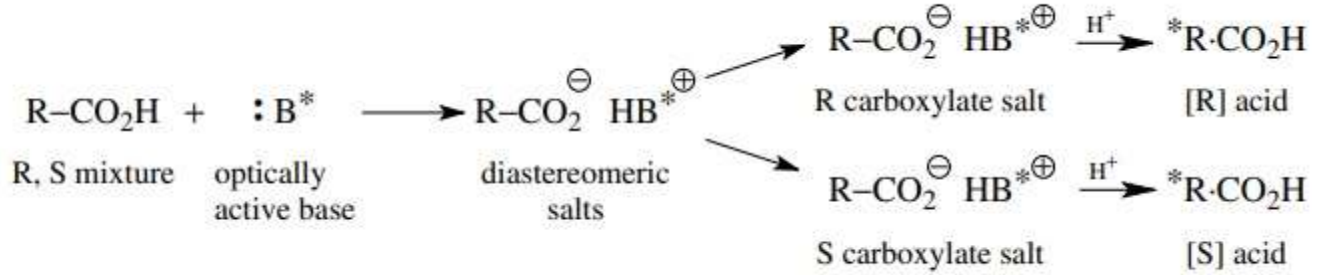
1. Pharmaceuticals: Racemization can affect the efficacy, safety, and potency of drugs. Different enantiomers can have different biological activities, and the wrong enantiomer can be toxic or less effective.
2. Food industry: Racemization can affect the flavor, aroma, and nutritional value of food molecules. For example, racemization of amino acids can lead to a loss of nutritional value.
3. Organic synthesis: Racemization can result in the loss of stereochemical information, making it challenging to synthesize complex molecules with specific stereochemistry.
4. Biological systems: Racemization can affect the biological activity of molecules, leading to changes in protein function, enzyme activity, and receptor binding.
5. Quality control: Racemization can affect the quality of products, leading to variations in their performance, stability, and shelf life.

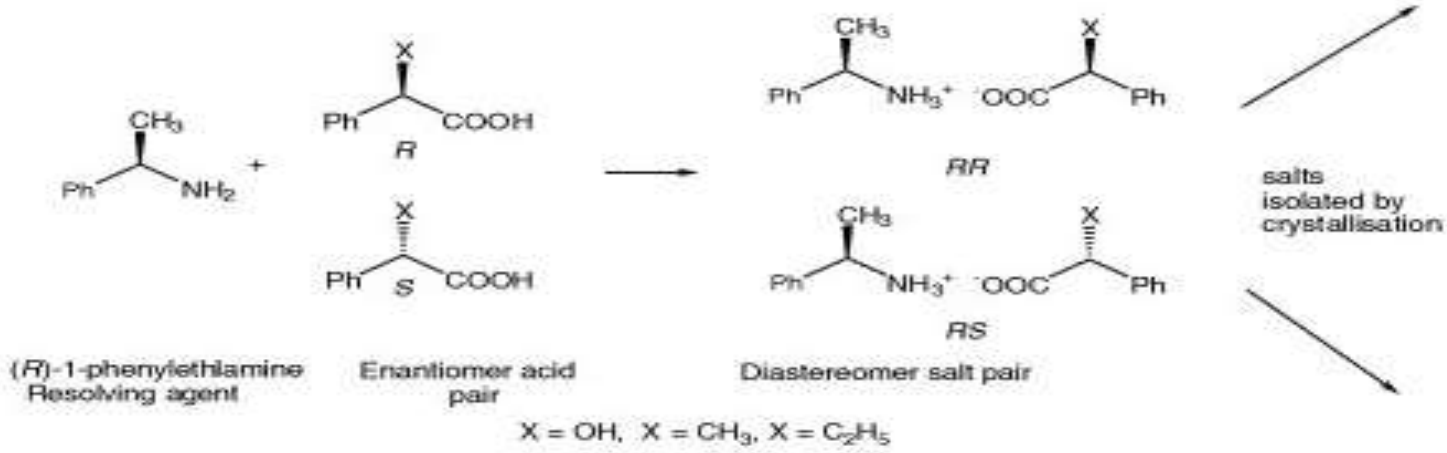
Resolution

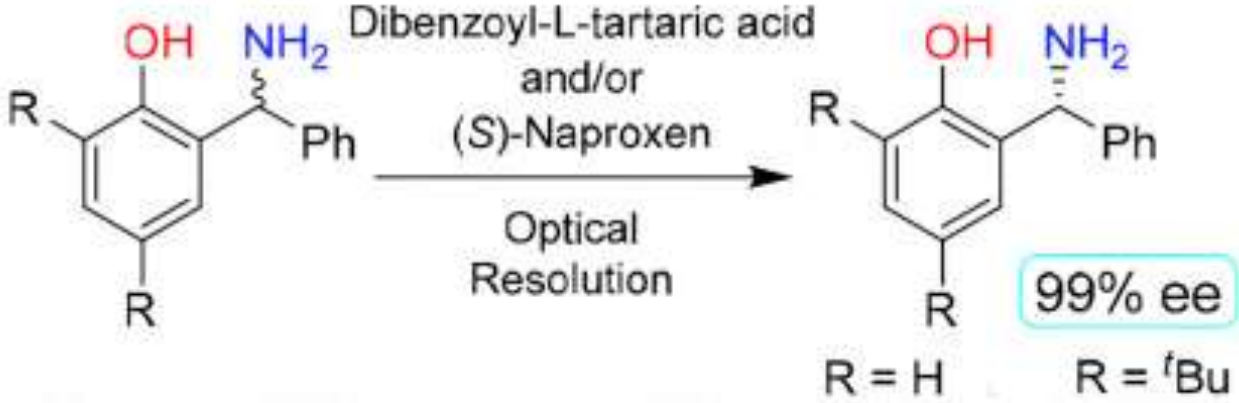
- In organic chemistry, "resolution" refers to the process of separating a racemic mixture
- Racemic mixture (50% R + 50% S) → Pure R + Pure S
- Some common methods used for resolution in organic chemistry include
- :1. Diastereomeric salt formation
- 2. Chromatography (Chiral HPLC)
- 3. Crystallization
- 4. Enzymatic resolution
- 5. Chemical resolution (using chiral reagents or catalysts)

Resolution via diastereomeric salt formation

- Diastereomeric salt crystallization is a classical, widely applicable chiral resolution technique
- Procedure :
- **1. Formation of diastereomeric salts:** A chiral acid (R or S) is reacted with a chiral base (R' or S') to form a pair of diastereomeric salts (R-R' and S-R' or R-S' and S-S').
- **2. Separation of diastereomeric salts:** The diastereomeric salts have different physical properties (e.g., solubility, melting points), allowing them to be separated through techniques like crystallization, chromatography, or solubility differences.
- **3. Isolation of individual enantiomers:** Once the diastereomeric salts are separated, the individual enantiomers can be isolated by treating the salts with a suitable acid or base.
- **4. Recovery of the chiral acid or base:** The isolated enantiomers can be converted back to the original chiral acid or base through acid-base reactions.


R–CO2H + :B*
R, S mixture
optically active base
R–CO2⊖ HB*⊕
diastereomeric salts
R–CO2⊖ HB*⊕ H+ *R·CO2H
R carboxylate salt
[R] acid
R–CO2⊖ HB*⊕ H+ *R·CO2H
S carboxylate salt
[S] acid


(R)-1-phenylethlamine
Resolving agent
Enantiomer acid pair
Diastereomer salt pair
RR
RS
salts isolated by crystallisation
X = OH, X = CH3, X = C2H5


Dibenzoyl-L-tartaric acid
and/or
(S)-Naproxen
Optical Resolution
99% ee
R = H
R = tBu

Enantiomeric excess & optical purity

- Enantiomeric excess (ee) is a measure of the excess of one enantiomer over the other in a mixture of two enantiomers.
- ee is defined as the difference in concentration between the two enantiomers, divided by the total concentration of both enantiomers, expressed as a percentage.
- ee (%) = ([S] - [R]) / ([S] + [R]) x 100
- Where [S] and [R] are the concentrations of the S and R enantiomers, respectively.

- Optical purity, on the other hand, is a term that is sometimes used interchangeably with enantiomeric excess, but it is more closely related to the specific rotation of the sample.
- Optical purity is defined as the ratio of the observed specific rotation to the maximum possible specific rotation for a pure enantiomer.
- It is usually expressed as a percentage and can be calculated using the following formula:
- Optical purity (%) = (Observed specific rotation / Maximum possible specific rotation) x 100

- NUMERICAL PROBLEMS

- A sample of a chiral compound contains 85% S enantiomer and 15% R enantiomer. What is the ee of the sample?

A sample of a chiral compound contains 85% S enantiomer and 15% R enantiomer. What is the ee of the sample?

- Solution:
- ee (%) = ([S] - [R]) / ([S] + [R]) x 100
- ee (%) = (85 - 15) / (85 + 15) x 100
- ee (%) = 70 / 100 x 100
- ee (%) = 70%

- A mixture of two enantiomers contains 46 g of the S enantiomer and 4 g of the R enantiomer. What is the ee of the mixture?

A mixture of two enantiomers contains 46 g of the S enantiomer and 4 g of the R enantiomer. What is the ee of the mixture?

- Solution:
- Total weight = 46 g + 4 g = 50 g
- ee (%) = ([S] - [R]) / ([S] + [R]) x 100
- ee (%) = (46 - 4) / 50 x 100
- ee (%) = 42 / 50 x 100
- ee (%) = 84%.

- A sample of a chiral compound has a specific rotation of +20°. The maximum possible specific rotation for a pure enantiomer of this compound is +40°. What is the optical purity of the sample?

A sample of a chiral compound has a specific rotation of +20°. The maximum possible specific rotation for a pure enantiomer of this compound is +40°. What is the optical purity of the sample?

- Solution:
- Optical purity (%) = (Observed specific rotation / Maximum possible specific rotation) x 100
- Optical purity (%) = (+20° / +40°) x 100
- Optical purity (%) = 50%

- A sample of a chiral compound has a specific rotation of -12°. The maximum possible specific rotation for a pure enantiomer of this compound is -30°. What is the optical purity of the sample?

A sample of a chiral compound has a specific rotation of -12°. The maximum possible specific rotation for a pure enantiomer of this compound is -30°. What is the optical purity of the sample?

- Solution:
- Optical purity (%) = (-12° / -30°) x 100
- Optical purity (%) = 40%

ENANTIOPURE DRUG

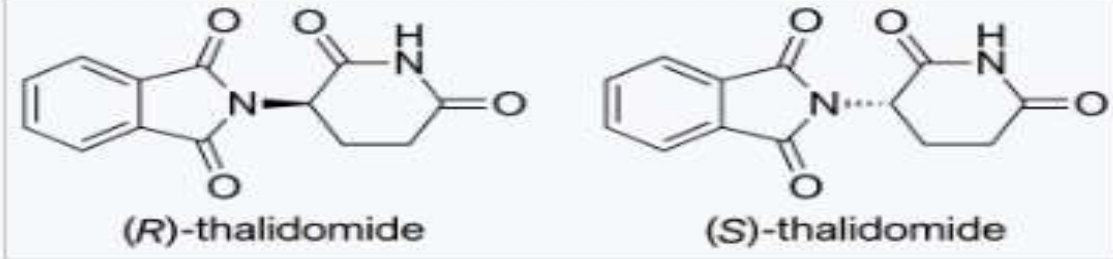
- An **enantiopure drug** is a pharmaceutical that is available in one specific enantiomeric form.
- The formation of an enantiopure drug results from the separation of the enantiomers of a chiral drug.
- This separation was prompted when it was found that each enantiomer of a molecule can have different effects when used in drugs.
- This is because the body is very chiral selective reacting to each enantiomer differently and therefore producing different pharmaceutical effects.
- The use of a drug with a single enantiomer makes the drug more effective.
- Before a drug of a pure enantiomer can be formed, the two enantiomers must first be separated and tested.

Drugs which are available in Racemic form as well as single-enantiomer

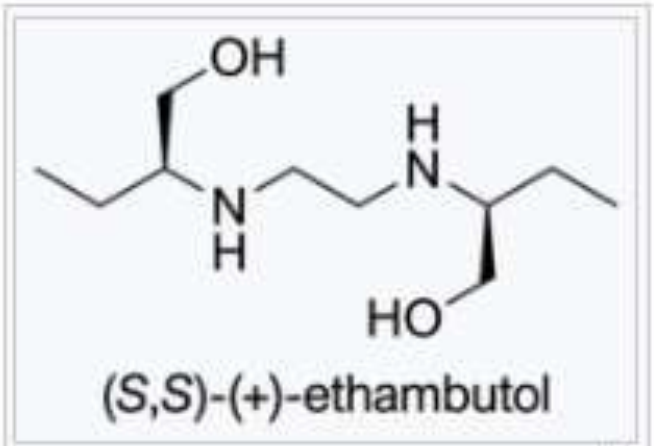
Racemic mixture	Single-enantiomer
Amlodipine (Norvasc)	Levamlodipine (Conjupri)
Amphetamine (Benzedrine)	Dextroamphetamine (Dexedrine)
Bupivacaine (Marcain)	Levobupivacaine (Chirocaine)
Cetirizine (Zyrtec / Reactine)	Levocetirizine (Xyzal)
Chlorphenamine (INN) Chlorpheniramine (USAN) (Chlor-Trimeton)	Dexchlorpheniramine (Polaramine)
Citalopram (Celexa / Cipramil)	Escitalopram (Lexapro / Cipralex)
Fenfluramine (Pondimin)	Dexfenfluramine (Redux)
Formoterol (Foradil)	Arformoterol (Brovana)
Ibuprofen (Advil / Motrin)	Dexibuprofen (Seractil)
Ketamine (Ketalar)	Esketamine (Ketanest S)
Ketoprofen (Actron)	Dexketoprofen (Keral)
Methylphenidate (Ritalin)	Dexmethylphenidate (Focalin)
Milnacipran (Ixel / Savella)	Levomilnacipran (Fetzima)
Modafinil (Provigil)	Armodafinil (Nuvigil)
Ofloxacin (Floxin)	Levofloxacin (Levaquin)
Omeprazole (Prilosec)	Esomeprazole (Nexium)
Salbutamol (Ventolin)	Levalbuterol (Xopenex)

Thalidomide

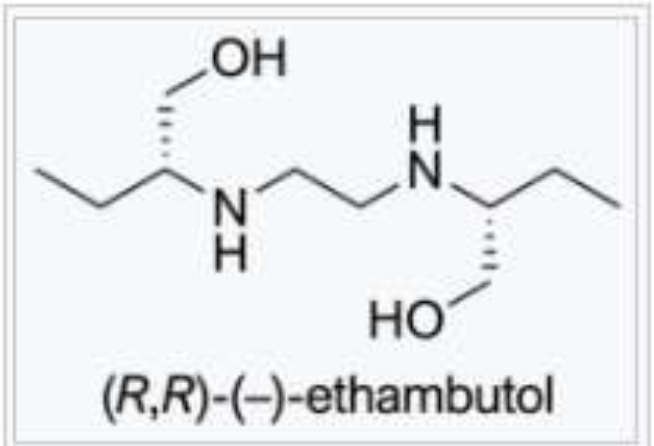
- Thalidomide is racemic.
- One enantiomer is effective against morning sickness, whereas the other is teratogenic
- However, the enantiomers are converted into each other *in vivo*.
- As a result, dosing with a single-enantiomer form of the drug will still lead to both the enantiomers eventually being present in the patient's serum and thus would not prevent adverse effects—at best, it might reduce them if the rate of *in vivo* conversion can be slowed.



The *S* enantiomer causes birth defects, while the *R* enantiomer is effective against morning sickness.



Enantiomer of ethambutol used to treat tuberculosis

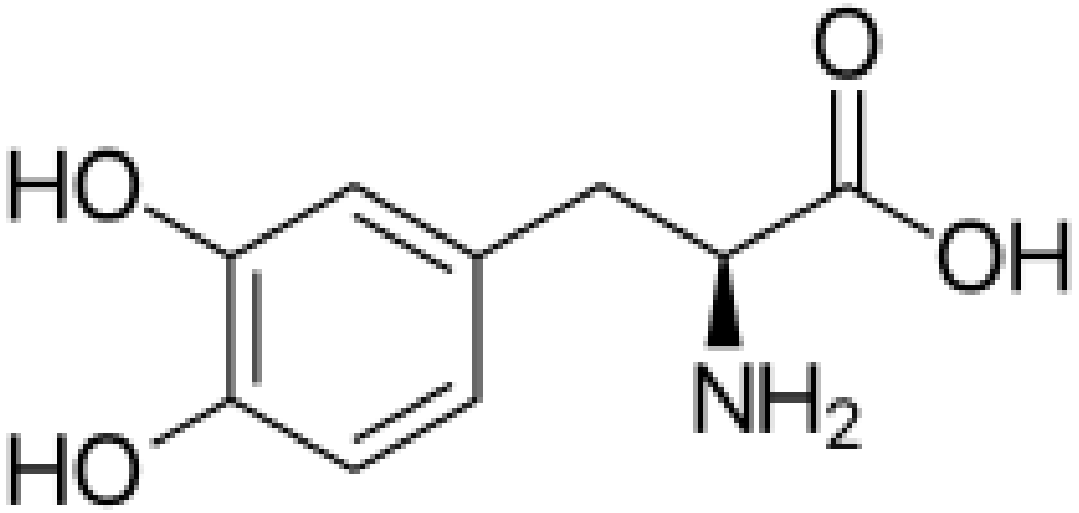


Enantiomer of ethambutol that causes blindness

- Ethambutol:
- (*S*,*S*)-(+)-enantiomer is used to treat tuberculosis
- (*R*,*R*)-(–)-ethambutol may cause blindness.

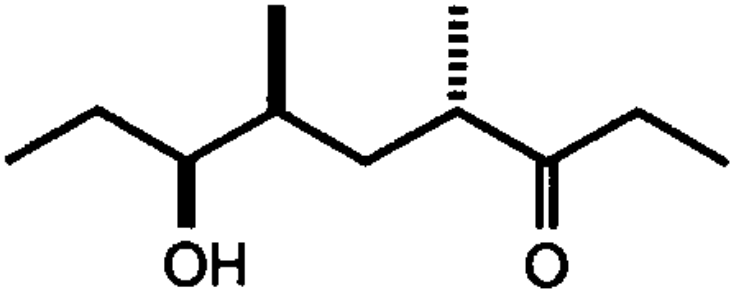
Dihydroxy-3, 4 phenylalanine (Dopa):

- L-Dopa, is used as a treatment for Parkinson's Disease
- D-Dopa is considered to be toxic. D-Dopa can cause headaches, abdominal pains, nausea, vomiting, and dizziness



Lasioderma serricorne, more commonly referred to as the **cigarette beetle**, **cigar beetle**, or **tobacco beetle**

Tobacco and its related products can be infested by *Lasioderma serricorne*



Serricornin

sex pheromone released by female cigarette beetle

(1.5 mg isolated from 65,000 females)

Lasioderma serricorne

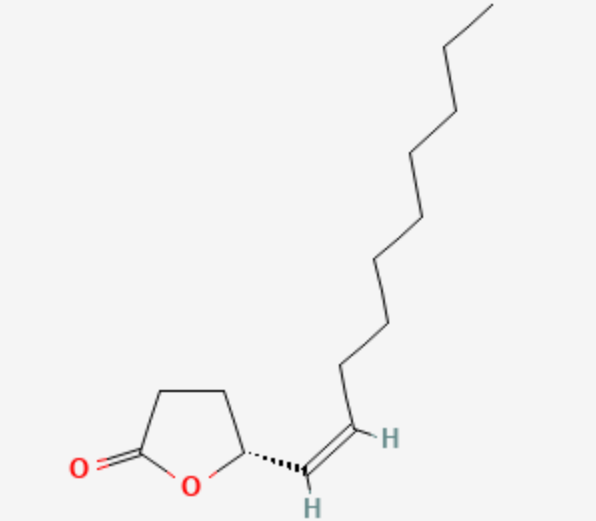
Scientific classification

Domain:	Eukaryota
Kingdom:	Animalia
Phylum:	Arthropoda
Class:	Insecta
Order:	Coleoptera
Family:	Ptinidae
Genus:	*Lasioderma*
Species:	***L. serricorne***

The **Japanese beetle** (***Popillia japonica***) is a species of scarab beetle. Due to the presence of natural predators, the Japanese beetle is not considered a pest in its native Japan, but in North America and some regions of Europe, it is a noted pest to roughly 300 species of plants. Some of these plants include rose bushes, grapes, canna ,birch trees and others.

Japonilure

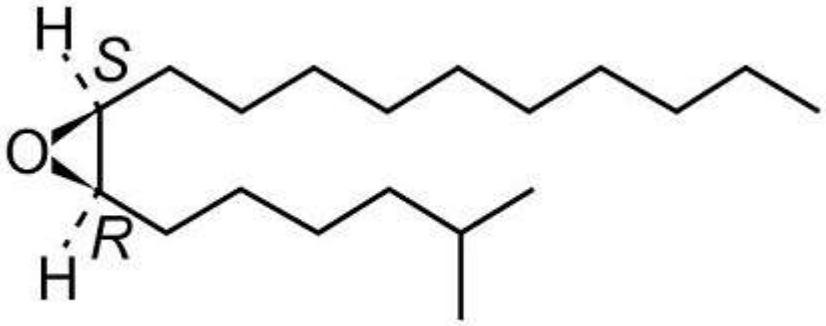
sex pheromone released by female japanese beetle (5 micro-gram is enough to attract one male!)



Japanese beetle

Scientific classification

Domain:	Eukaryota
Kingdom:	Animalia
Phylum:	Arthropoda
Class:	Insecta
Order:	Coleoptera
Family:	Scarabaeidae
Genus:	*Popillia*
Species:	***P. japonica***



Disparlure is sex pheromone produced by female gypsy moths.

Disparlure has two enantiomers, referred to by (+) and (−).

The (+)-enantiomer is typically used to attract the males by the females, while the (−)-enantiomer inhibits attractions and turns the males away from females.

Lymantria dispar

Mounted *Lymantria dispar dispar* male

Mounted *Lymantria dispar dispar* female

Scientific classification

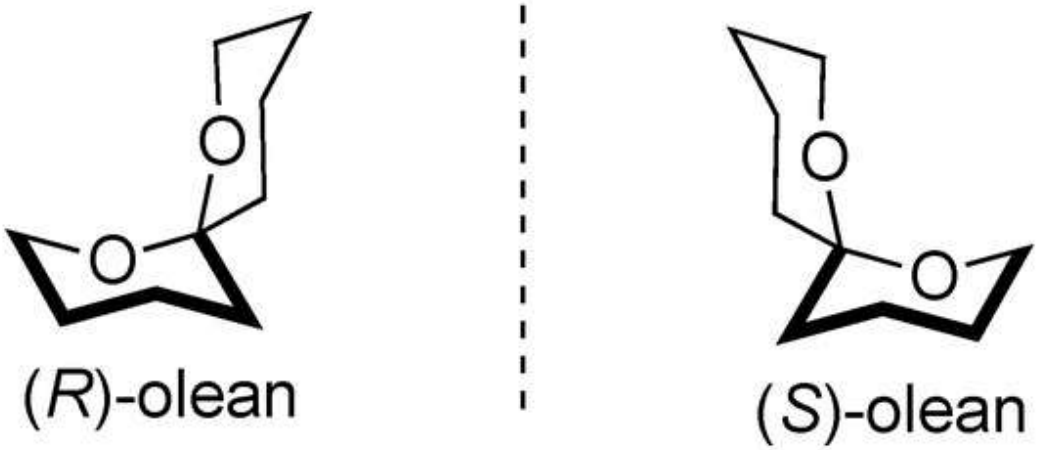
Domain:	Eukaryota
Kingdom:	Animalia
Phylum:	Arthropoda
Class:	Insecta
Order:	Lepidoptera
Superfamily:	Noctuoidea
Family:	Erebidae
Genus:	*Lymantria*
Species:	***L. dispar***

Binomial name

Lymantria dispar

In Olive Fruit Fly , the Pheromone released by Females to attract males is (R)-olean whereas the Pheromone released by males to attract the females is (S)-Olean .

They are enantiomers to each other!



The Pheromone **Frontalin** is released by male elephants . The interesting fact is , the pheromone released by Young male elephants and Old male elephants are Mirror image (enantiomer) to each other !