BP401T. PHARMACEUTICAL ORGANIC CHEMISTRY III (THEORY)

UNIT- I

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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 andabsolute

STEREOISOMERISM

Compounds have the same molecular formula but differ from each other in physical or chemical properties, and are called Isomers and the phenomenon is called isomerism. There are two main types of isomerism,

(1) Constitutional/ Structural Isomerism

(2) Stereoisomerism

Constitutional Isomerism. When the isomerism is due to difference in the arrangement of atoms within the molecule, without any reference to space, the phenomenon is called Constitutional isomerism. Constitutional isomers are compounds that have the same molecular formula but different structural formulas. Constitutional isomerism is of five types

(a) Chain Isomerism

(b) Position Isomerism

(c) Functional Isomerism

(d) Metamerism

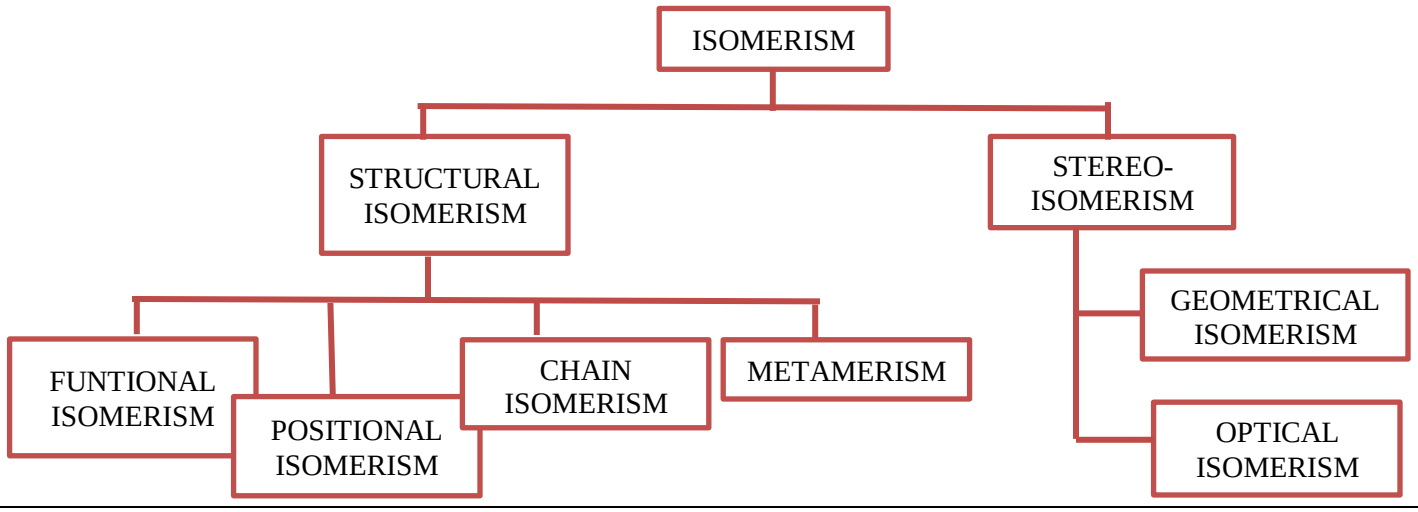
(e) Tautomerism

Stereoisomerism. When isomerism is caused by the different arrangements of atoms or groups in space, the phenomenon is called Stereoisomerism. The stereoisomers have the same structural formulas but differ in arrangement of atoms in space. In other words, stereoisomerism is exhibited by such compounds which have the same structural formula but differ in configuration.

Stereoisomerism is of two types :

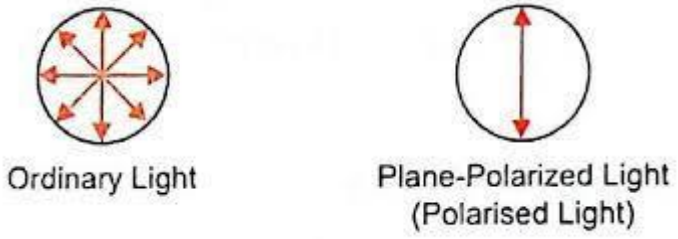
(a) Geometrical or Cis-Trans Isomerism

(b) Optical Isomerism



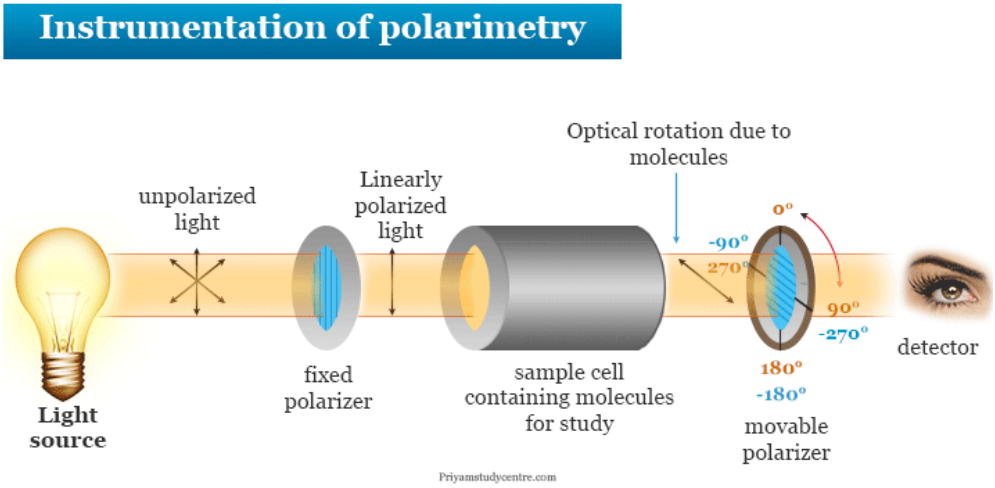
OPTICAL ISOMERISM

- Optical isomerism is a type of stereoisomerism.
- The outstanding feature of optical isomers is that they have the ability to rotate plane-polarized light.
- Most compounds do not rotate the plane of polarized light.
- Light possesses certain properties that are best understood by considering it to be a wave phenomenon in which the vibrations occur at right angles to the direction in which the light travels. There are an infinite number of planes passing through the line of propagation, and ordinary light is vibrating in all these planes.
- Plane-polarized light is light whose vibrations take place in only one of these possible planes. Ordinary light is turned into plane-polarized light by passing it through a lens made of the material known as Polaroid or more traditionally through pieces of calcite (a particular crystalline form of CaCO3) so arranged as to constitute what is called a Nicol prism.
- An optically active substance is one that rotates the plane of polarized light.
- When polarized light, vibrating in a certain plane, is passed through an optically active substance, it emerges vibrating in a different plane.



POLARIMETER

- When a beam of polarized light passes through an individual molecule, in nearly every instance its plane is rotated a tiny amount by interaction with the charged particles of the molecule; the direction and extent of rotation varies with the orientation of the particular molecule in the beam.
- Optical activity in a compound is detected and measured by means of a polarimeter.
- When a solution of a known concentration of an optically active material is placed in the polarimeter, the beam of polarized light is rotated through a certain number of degrees, either to the right (clockwise) or to the left (anti-clockwise).
- The compound which rotates the plane of polarized light to the right (clockwise) is said to be dextrorotatory. It is indicated by the sign (+).
- The compound which rotates the plane of polarized light to the left (anticlockwise) is said to levorotatory. It is indicated by the sign (-).



Monochromatic (single wavelength) light, is polarized by a fixed polarizer next to the light source. A sample cell holder is located in line with the light beam, followed by a movable polarizer (the analyzer) and an eyepiece through which the light intensity can be observed. In modern instruments an electronic light detector takes the place of the human eye. In the absence of a sample, the light intensity at the detector is at a maximum when the second (movable) polarizer is set parallel to the first polarizer ($\alpha = 0^o$). If the analyzer is turned 90^o to the plane of initial polarization, all the light will be blocked from reaching the detector.

SPECIFIC ROTATION

- Specific rotation is defined as the rotation produced by a solution of length 10 centimeters and unit concentration (1 g/ml) for the given wavelength of light at the given temperature.

- Specific rotation is the number of degrees of rotation observed if a 1 -decimeter tube is used, and the compound being examined is present to the extent of Ig cc. This is usually calculated from observations with tubes of other lengths and at different concentrations by means of the equation where d represents density for a pure liquid or concentration for a solution.

$$\text{specific rotation} = \frac{\text{observed rotation (degrees)}}{\text{length (dm)} \times \text{g/cc}}$$

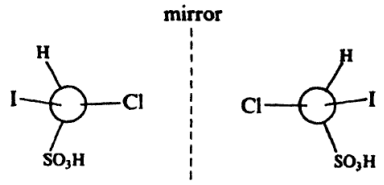
- The specific rotation is as much a property of a compound as its melting point, boiling point, density, or refractive index. Thus the specific rotation of the 2-methyl-l-butanol obtained from fusel oil is $[\alpha]_D^{20} = -5.756°$

$[\alpha] = \alpha / (l * d)$

ENANTIOMERS

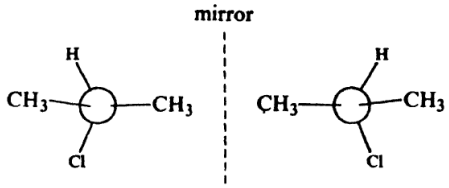
Optical isomers that are mirror images are called Enantiomers.

- The non-superimposability of mirror images that brings about the existence of enantiomers, gives them their optical activity, and hence enantiomers are often referred to as (one kind of) optical isomers.
- Molecules that are not superimposahle on their mirror images are chiral. Chirality is the necessary and sufficient condition for the existence of enantiomers. That is to say: a compound \\hose molecules are chiral can exist as enantiomers; a compound whose molecules are achiral (vMthout chirality) cannot exist as enantiomers.



Chloroiodomethanesulfonic acid
Not superimposable: enantiomers

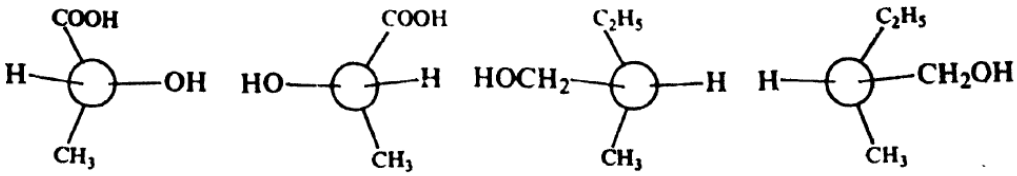
These molecules are chiral, and we know that chloroiodomethanesulfonic acid can exist as enantiomers, which have the structures we have just made or drawn. Others, we find, are superimposable, like these:



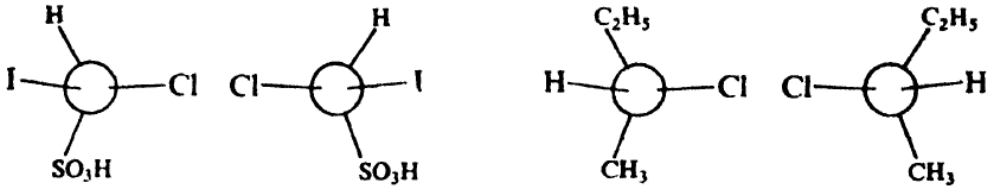
Isopropyl chloride
Superimposable: no enantiomers

These molecules are achiral, and so we know that isopropyl chloride cannot exist as enantiomers.

- For example, two isomeric lactic acids and two 2-methyl-l-butanols, two chloroiodomethanesulfonic acids and two sec-butyl chlorides. the structures of each pair are mirror images; the structures of each pair are not superimposable and therefore represent Enantiomers.

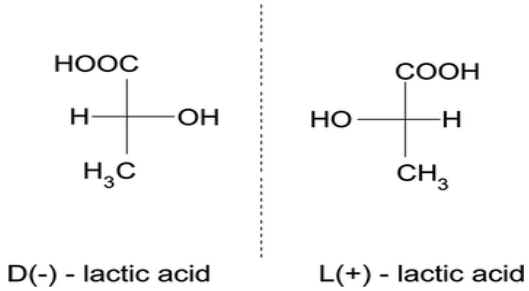


Lactic acid 2-Methyl-1-butanol



Chloroiodomethanesulfonic acid *sec*-Butyl chloride

These always exist as discrete pairs. For example, there are two optical isomers of lactic acid. They are apair of enantiomers.



D(-) - lactic acid L(+) - lactic acid

- Enantiomers have identical physical properties, except for the direction of rotation of the plane ofpolarized light.
- It is reasonable that these molecules, being so similar, can rotate light by the same amount.
- The molecules are mirror images, and so are their properties: the mirror image of a clockwiserotation is a counterclockwise rotation and of exactly the same magnitude.
- Enantiomers have identical properties in all respects except in their interaction with plane ofpolarized light.
- Enantiomers have the same melting point density, solubility, color, and reactivity toward acidsand bases.
- They differ, however, in the direction in which they rotate the plane of polarized light.
- Both rotate the plane of polarized light to exactly the same extent (same angle) but one rotates theplane to the right (clockwise : called dextrorotatory), while the other rotates the plane to the left (anticlockwise called levorotatory).
- The two 2-methyl-l-butanols, for example, have identical melting points, boiling points, densities, refractive indices, and any other physical constant one might measure, except for this: one rotates planepolarized light to the right, the other to tire left. This fact is not surprising, since the interactions of both kinds of molecule with their fellows should be the same. Only the direction of rotation is different; the amount of rotation is the same, the specific rotation of one being + 5.756, the other - 5.756.
- Enantiomers have identical chemical properties except toward optically active reagents. The two lactic acids are not only acids, but acids of exactly the same strength; that is, dissolved in water at the same concentration, bo'h ionize to exactly the same degree.
- The influences exerted on the reagent are not identical in the attack on the two enantiomers, and reaction rates will be different so different, in some cases, that reaction with one isomer does not take place at all.
- For example, The sugar (+)-glucose plays a unique role in animal metabolism and is the basis of a multimillion-dollar fermentation industry; yet (-)-glucose is neither metabolized by animals nor fermented by yeasts. When the mold Penicillium glaucum feeds on a mixture of enantiomeric tartaric acids, it consumes only the (+)-enantiomer and leaves (-)-tartaric acid behind.
  The hormonal activity of (-)-adrenaline is many times that of its enantiomer.

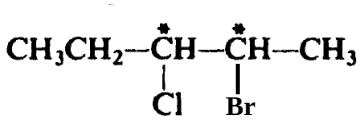
A mixture of equal parts of enantiomers is called a *racemic modification*.
A racemic modification is optically inactive when enantiomers are mixed together, the rotation caused by a molecule of one isomer is exactly canceled by an equal and opposite rotation caused by a molecule ofits enantiomer.
The prefix is used to specify the racemic nature of the particular sample, as, for example,(±)-lactic acid or (±)- 2-methyl-l-butanol.

DIASTEREOMERS

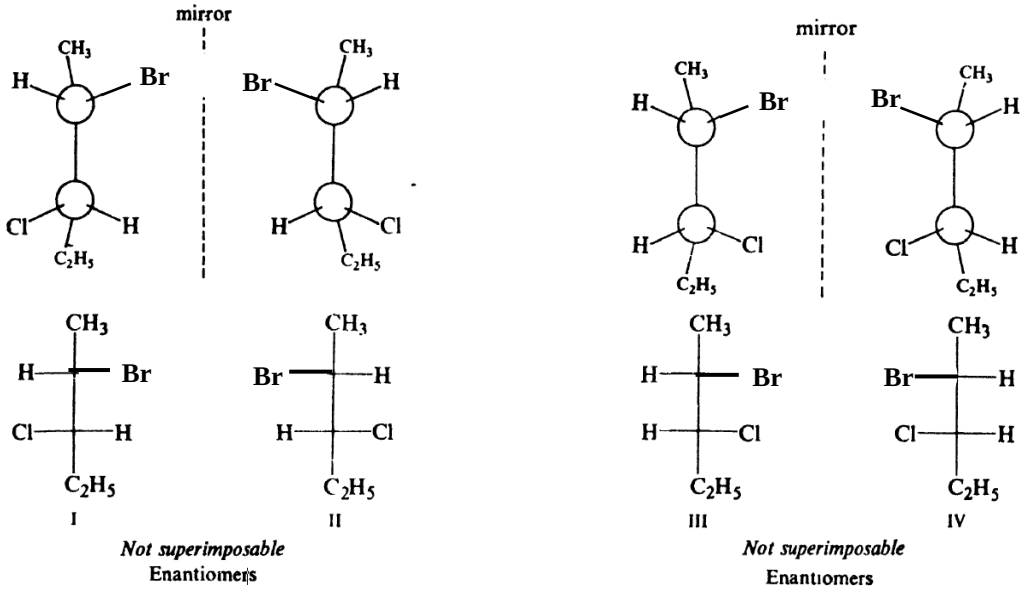
Stereoisomers that are not mirror images of each other and non-superimposable; these are called diastereomers.

Molecules contain, not just one, but more than one chiral centre.

Example 1: 2-Bromo-3-chloropentane



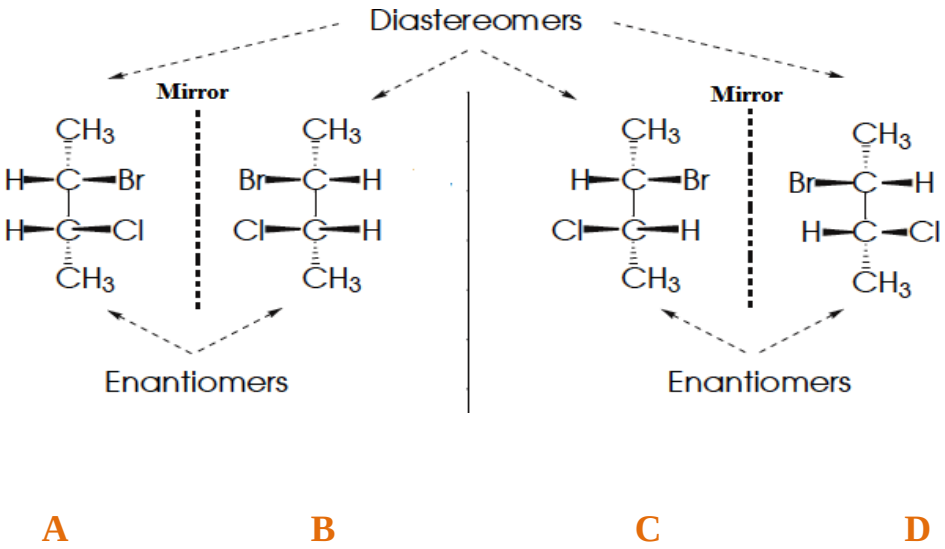
This compound contains two chiral centers, C-2 and C-3.



- Structure I and its mirror image II, are non-superimposable, and hence must be enantiomer.
- Interconvert I and II by rotations about carbon-carbon bonds. We get structures III and IV.
- Structure III and IV are mirror image, are non-superimposable, and hence must be enantiomer. Thus, Structures III and IV represent a second pair of enantiomers.
- Structure III, which we find to be non-superimposable on either I or II: it is not, of course, the mirror image of either.
- Isomer (III and I) are stereoisomer but not enantiomer, also (IV and II) are stereoisomer but not enantiomer
- Compound III is a diastereomer of I and similarly of II.
- Compound IV is diastereomer of I and II.

Example 2:

(A) is the mirror image of (B): (C) is the mirror image of (D). Thus, the four isomers are two pairs ofenantiomers. Now compare (A) with (C). They are neither superimposable nor are they mirror images.They are called diastereomers. (A) and (D) are also diastereomers, as are (B) and (C), and (B) and (D). Stereoisomers that are not mirror images of each other are called *Diastereomers.*

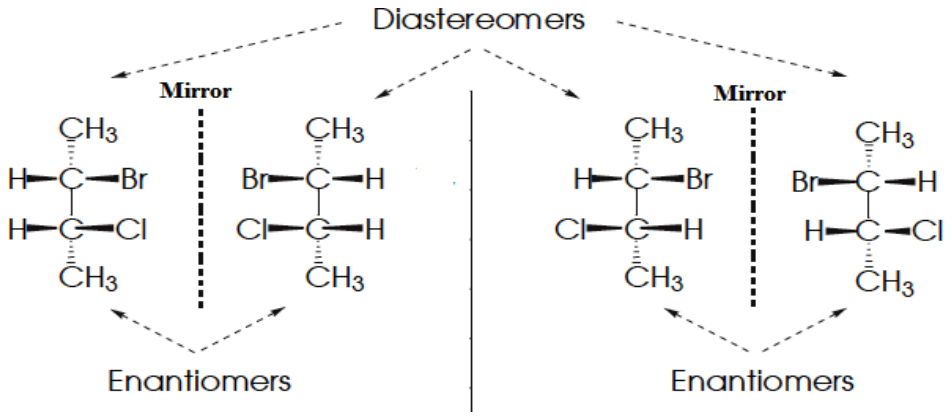


Diastereomers have different properties. Two diastereomers will have different melting points, boiling points, and solubilities. They will have different chemical reactivities toward most reagents.

Diastereomers have different chemical properties: Their chemical properties are not identical, however. In the reaction of two diastereomers with a given reagent, will not be of equal energies. E_{aft} 's will be different and so will the rates of reaction.

Diastereomers have different physical properties: different melting points, boiling points, solubilities in a given solvent, densities, refractive indexes, and so on. Diastereomers differ in specific rotation; they may have the same or opposite signs of rotation, or some may be inactive.
As a result of their differences in boiling point and in solubility, they can, in principle at least, be separated from each other by fractional distillation or fractional crystallization; as a result of differences in molecular shape and polarity, they differ in adsorption, and can be separated by chromatography.
Given a mixture of all four stereoisomeric 2,3-dichloropentanes, we could separate it, by distillation, for example, into two fractions but no further. One fraction would be the racemic modification of I plus II; the other fraction would be the racemic modification of HI plus IV. Further separation would require resolution of the racemic modifications by use of optically active reagents

Enantiomers	**Diastereomers**
An enantiomer is one of two stereoisomers that are non-superimposable complete mirror images of eachother.	Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers (non-superimposable non-mirror images of each other).
Molecules must contain atleast one chiral centers.	Molecules must contain more than one chiral center.
Enantiomers have, when present in a symmetric environment, identical chemical and physicalproperties except for their ability to rotate planepolarized light by equal amounts but in opposite directions.	Diastereomers can have different physical properties and different reactivity. In another definition diastereomers are pairs of isomers that have opposite configurations at one or more of the chiral centers but are not mirror images of each other.
A mixture of equal parts of an optically active isomerand its enantiomer is termed Racemic and has a net rotation of plane polarized light of zero.	Racemic mixture is not possible.



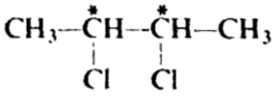
2-bromo-3-chlorobutane

- Thus, the presence of two chiral centers can lead to the existence of as many as four stereoisomers.
- For compounds containing three chiral centers, there could be as many as eight stereoisomers; for compounds containing four chiral centers, there could be as many as sixteen stereoisomers, and so on.
- The maximum number of stereoisomers that can exist is equal to 2", where n is the number of chiral centers. (In any case where meso compounds exist, there will be fewer than this maximum number.)

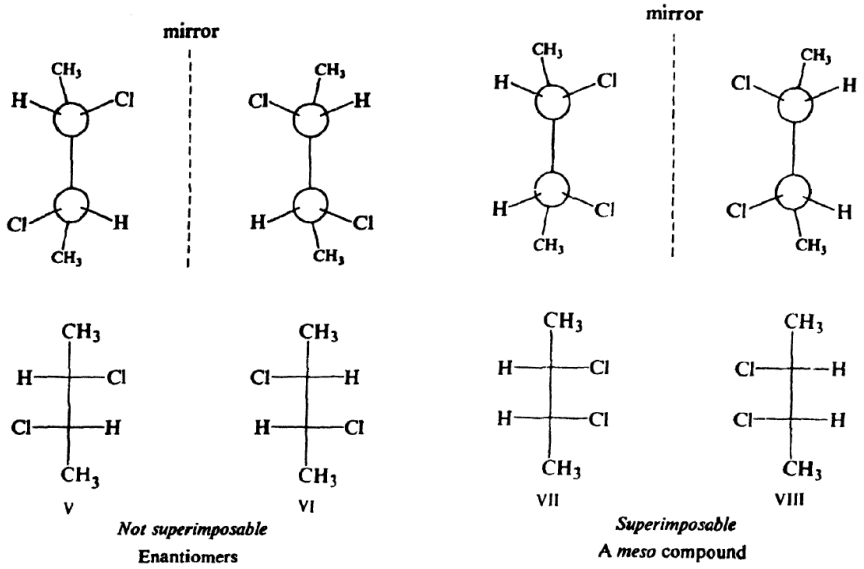
MESO COMPOUNDS- A meso compound is one whose molecules are superimposable on their mirror images even though they contain chiral centers**.**

A compound with two or more chiral carbon atoms, but also having a plane of symmetry is called a meso compound.

Look at 2,3-dichlorobutane, which also has two chiral centers.



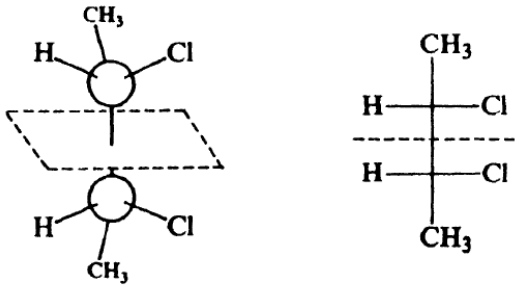
2,3-Dichlorobutane



- Structures V and VI: These are mirror images that are not superimposable or interconvertible; they are therefore enantiomers, and each should be capable of optical activity.
- Structure VII: diastereomer of V and of VI.
- We now have three stereoisomers; is there a fourth? No.
- If we make VIII, the mirror image of VII, we find the two to be superimposable; turned end-for-end, VII coincides in every respect with VIII. In spite of its chiral centers, VII is not chiral. It cannot exist in two enantiomeric forms, and it cannot be optically active. It is called a meso compound.

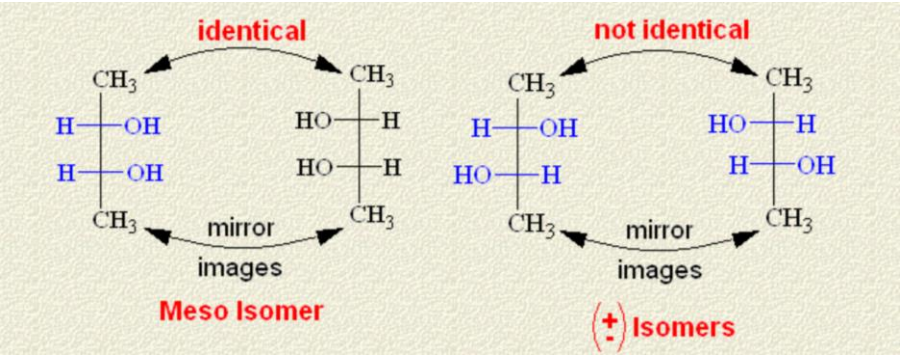
A meso compound is optically inactive for the same reason as any other compound whose molecules are achiral: the rotation caused by any one molecule is cancelled by an equal and opposite rotation caused by another molecule that is the mirror image of the first.

We can often recognize a meso structure on sight by the fact that (in at least one of its conformations) one half of the molecule is the mirror image of the other half. This can be seen for meso-2,3-dichlorobutane by imagining the molecule to be cut by a plane lying where the dotted line is drawn. The molecule has a plane of symmetry, and cannot be chiral.



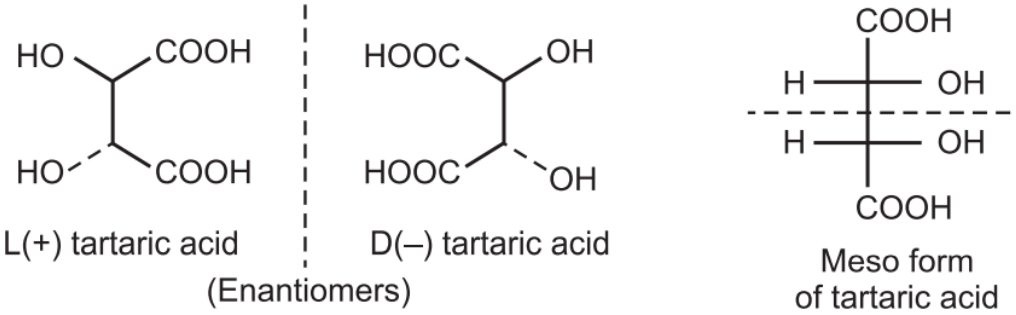
A molecule may contain several chiral carbons and still be identical with its mirror image; we call such isomers meso, and of course they do not rotate the plane of polarized light. Since only symmetrical objects are identical with their mirror images, meso isomers must contain some internal symmetry despite the presence of chiral centers. Usually, this is a **plane of symmetry**, some imaginary plane which divides the molecule into two halves such that one half is the mirror image of the other. For simplicity consider the isomers of 2,3-butanediol. Because there are two chiral carbons, we might expect four stereoisomers, two pairs of enantiomers. Instead, only three isomers exist; one stereoisomer is identical with its mirror image. This **meso** isomer can be written in such a way that it is divided by an internal plane of symmetry; the two chiral carbons that it contains are mirror images of one another.

2,3-butanediol

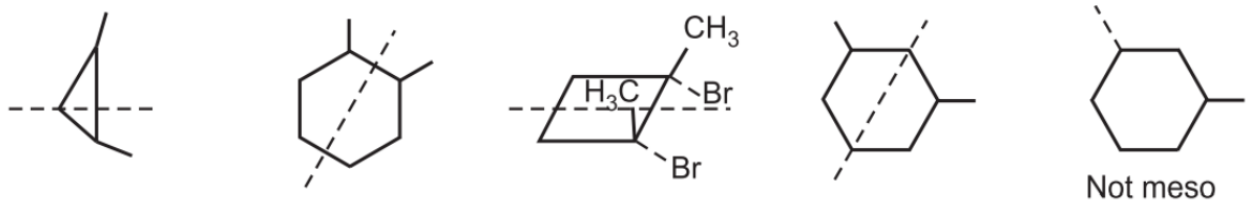


Meso Compounds in Stereoisomerism: When multiple stereocenters present in a molecule create an internal plane of symmetry, it leads to meso compounds. Tartaric acid contains two asymmetric centers which give rise to four configurations. But there are only three stereoisomers of tartaric acid: a pair of chiral molecules (enantiomers of each other) and the achiral meso compound. In the meso compound, we have an internal mirror plane that splits the molecule into two symmetrical sides, the stereochemistry of both left and right sides should be opposite to each other. This leads to auto cancellation of stereo activity of each other resulting in optical inactivity. Hence, meso compounds cannot 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 to be a meso compound. These stereocenters must also have different absolute configurations. Due to internal symmetry, the 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 pairs (D-and L-form).



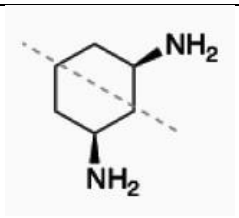
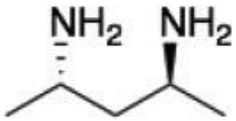
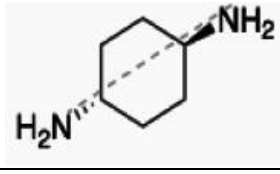
The melting point of both enantiomers of tartaric acid is about 170°C while the mesotartaric acid has a melting point of 145°C. A meso compound is 'superimposable' on its mirror image. Examples in cyclic meso compounds include.



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

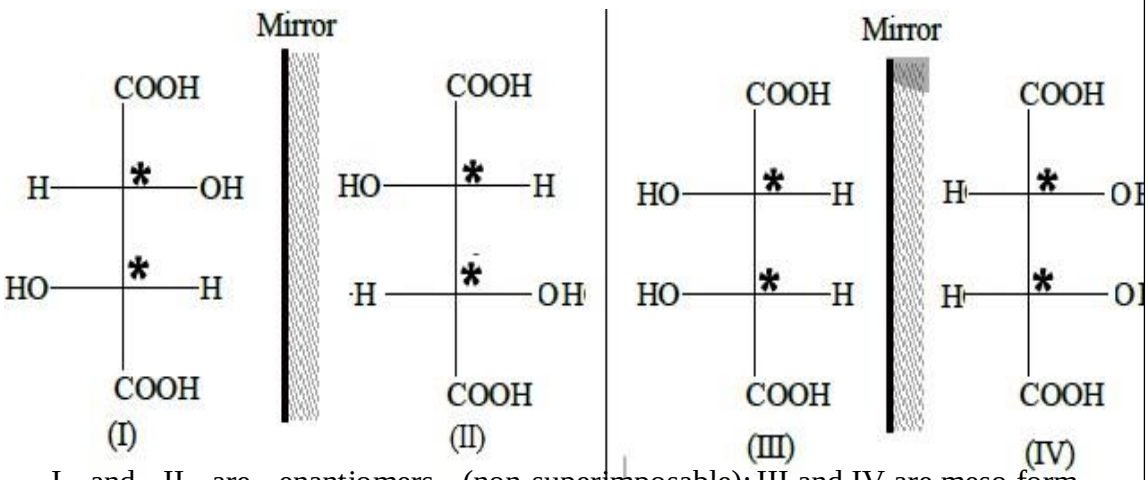
These molecules have planes of symmetry dividing them midway between the two chiral carbon atoms in each. Notice that one half of the molecule is the mirror image of the other, both the molecules m e s o 2,3-butanediol and meso tartaric acid are optically inactive even though which have two chiral centres neither will rotate the plane polarized light.

	A person is meso (NOT CHIRAL) even though they have chiral elements (hands and feet). There is a plane of symmetry down the middle of a person, which makes a person the same as their mirror image.

	This molecule is meso (NOT CHIRAL). It has two chiral centersand a plane of symmetry.
	This molecule is not meso (CHIRAL). It has two chiral centersbut no plane of symmetry.
	This molecule is not meso (NOT CHIRAL). It has a plane of symmetry but no chiral centers. The carbons attached to the NH2 groups may look like chiral centers but they are not.

In Tartaric acid:

The molecule contains two chiral carbons and the number of optical isomers should be $2^n = 2^2 = 4$ but number of optical isomer is reduced to 3 because one molecule has a plane of symmetry. The stereoisomers of tartaric acid are,



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

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

Sr. 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

Table.1: Difference between enantiomer and diastereomers

Enantiomers: Mirror images, Non-superimposable, Chiral
Diastereomers: Non-Mirror images, Non-superimposable, Chiral
Meso compounds: Mirror images, Superimposable, Achiral

ELEMENTS OF SYMMETRY

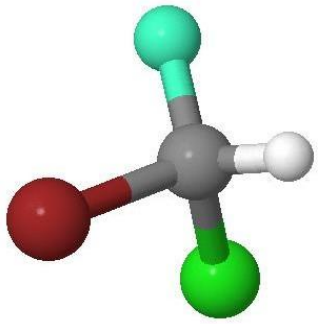
A symmetry element is a point of reference about which symmetry can take place. In particular elements can be identities, mirror planes, axis of rotation and centres of inversion.

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, the 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.

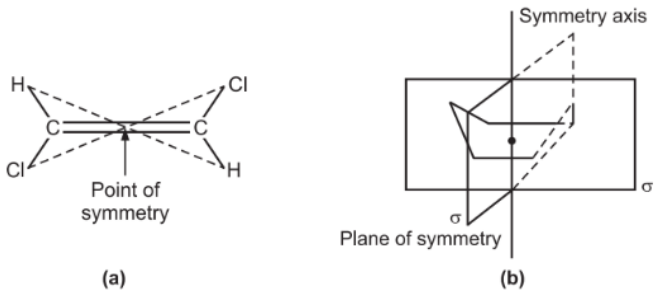
1. The identity symmetry

The identity operation consists of doing nothing, and the corresponding symmetry element is the entire molecule. Every molecule has at least this element. For example, the CHFClBr molecule. The identify symmetry is not indicated since all molecule exhibit this symmetry.



2. Point of symmetry:

In a chiral molecule, (E)-1,2,-dichloroethene, two lines drawn passing through the point of symmetry ensure the same structural features at the opposite lines. Similarly, the boat conformation of cyclohexane has two intersecting planes of symmetry (σ). 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 side 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.

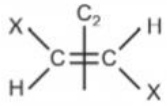
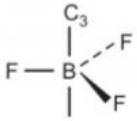
Type	n	Angle Rotation	Example
C_2	2	180°	E isomers 
C_3	3	120°	Boron trifluoride 
C_4	4	90°	Cyclobutane 
C_5	5	72°	Cyclopentane 
C_6	6	60°	Benzene 
C_∞	∞	0-360°	Linear molecules O = C = C e.g. CO_2, Acetylene HC ≡ CH

Table.1: Examples of rotational axis (360°/n) in the molecules

Sr. No.	Terms	Symbol
1.	Plane of symmetry	δ
2.	Center or point of symmetry	i
3.	Rotational axis where the degrees of rotation that restore the object is 360/n (C_2 = 180° rotation; C_3 = 120° rotation; C_4 = 90° rotation; C_5 = 72° rotation; At C_1 = (i.e. 360° rotation), the molecule returns to its original orientation	C_n
4.	Only a single plane of symmetry	C_s
5.	Only a single point of symmetry	C_i
6.	Vertical plan Horizontal plan Diagonal plane	v h d

Table.2: Terms commonly used

Examples:

(1) Methane: It is an example of a high symmetry molecule having 4 C_3 axes, 3 C_2 axes, and 6 σ (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 the C_2 axis at their intersection. It is achiral.

(3) Trans-1,2-dichloroethane: This structure has a plane of symmetry, an orthogonal C_2 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 dissymmetric and chiral.

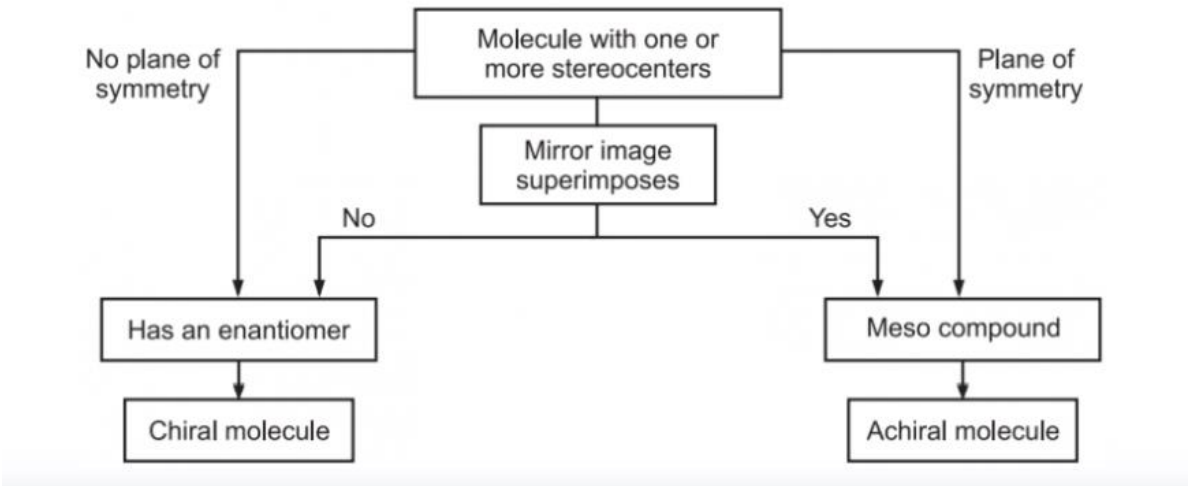
(5) Cyclohexane (boat conformation): It has a C_2 axis and two planes of symmetry. It is achiral.

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

3. PLANE OF SYMMETRY

A plane which divides an object into two symmetrical halves, is said to be plane of symmetry. The plane that cuts the molecule in half to get the same things on both sides is known as the 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.

- For example, a person or a hat has a plane of symmetry. An object lacking plane of symmetry is called Chiral (pronounced as Ki-ral) er Dyssymmetric. A symmetric object is referred to as Achiral. Achiral object cannot be superimposed on its mirror image. A left hand, for example, does not possess a plane of symmetry, and its mirror image is not another left hand but a right hand. The two are not identical, because they cannot be superimposed. If we were to lay one hand on top of the other the fingers and the thumbs would clash.



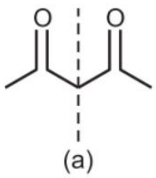
4. ROTATIONAL SYMMETRY/RADIAL SYMMETRY (C_n)

Rotating an object about its centre point and seeing how many times it looks exactly like the original one. Rotation is by 360^0. Some shape have an order of symmetry 'n'.
(https://youtu.be/s4tS-ZmpJfw)

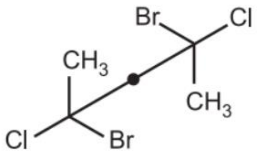
5. INVERSION SYMMETRY

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 be converted through 180° into another identical part. The molecule is achiral because of the inversion center.



(a)



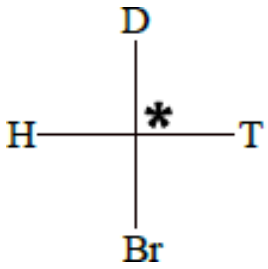
(b)

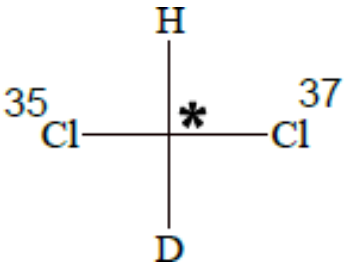
6. Sn5+: an n -fold axis of improper rotation Symmetry.

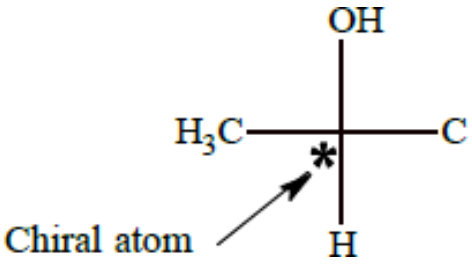
The identity symmetry and rotation symmetry are symmetry operations that could actually be carried outon a molecule. For these reasons they are called proper symmetry operations.

CHIRAL AND ACHIRAL MOLECULES

- A molecule (or an object) is said to be chiral or dissymmetric, if it is not superimposable on its mirror image and the property of non-superimposability is called chirality.
- On the other hand, a molecule (or an object) which is superimposable on its mirror image is called achiral (non- dissymmetric or unsymmetrical).
- Chiral carbon atom (chiral centre/stereo centre). Carbon atom bonded to four different atoms or groups is called an asymmetric carbon atom or a chiral atom. A chiral atom is indicated by an asterisk (*).
- **Note:** Isotopes of a particular atom behave as different groups in stereoisomerism





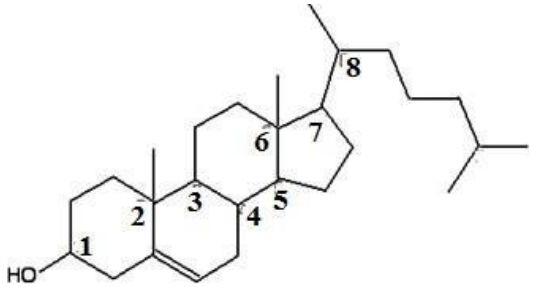


If a molecule contains only one chiral centre/atom, then the molecule has to be optically

active (i.e. non superimposable on its mirror image) as it will not contain any element of symmetry. Molecules containing two or more chiral centers may or may not be chiral (optically active).

It is necessary to distinguish chiral and chiral centre. The word chiral is used for molecule as a whole which is optically active, whereas chiral centre is for an atom which is attached to form different atoms/groups.

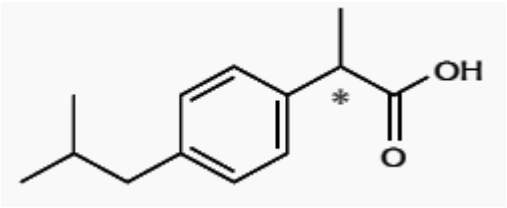
Cholesterol has eight chiral centres



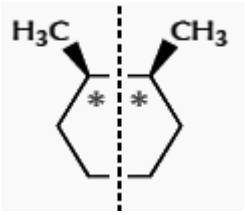
Relationships between **Chiral Centers** and **Chiral Molecules**

- The term **chiral center** refers to an atom in the molecular structure. The term **chiral molecule** refers to the entire molecule.
- The presence of one chiral center renders the entire molecule chiral. The presence of two ormore chiral centers may or may not result in the molecule being chiral. In the examples given below the chiral centers are indicated with an asterisk. The vertical broken line represents a plane of symmetry.

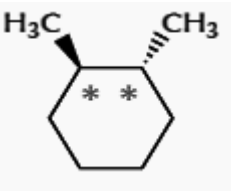
Ibuprofen: One chiral center renders the molecule chiral



***cis*-1,2 dimethylcyclohexane** is an **achiral molecule**



***trans*-1,2 dimethylcyclohexane** is a chiral molecule



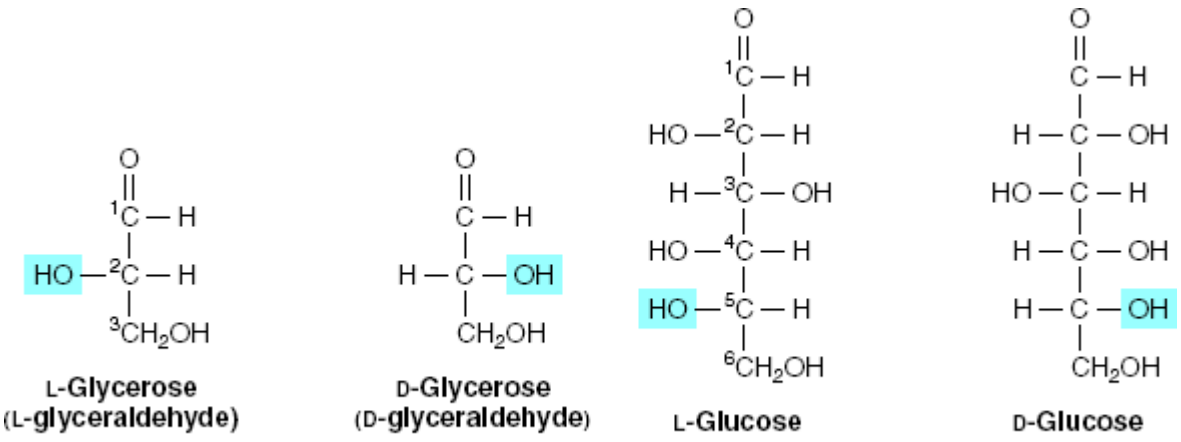
What is Chirality?

The property of **nonsuperimposability** of an object on its mirror image is called **chirality**. Such molecule has nosymmetry elements of the second kind. If the molecule is superposable on its mirror image, it is **ACHIRAL**.

D & L-SYSTEM

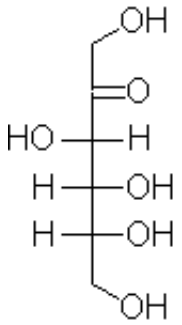
- The **D** & **L** convention, not to be confused with the **d** (**dextro**) and **l** (**levo**) descriptors used to designate the direction of specific rotation of chiral compounds, is a convention used to distinguish between enantiomers of chiral monosaccharides and chiral alpha-amino acids, based on the molecule drawn as a ***Fischer projection*** in a specific orientation.
- The **L** and **D** forms of the sugar depends on the orientation of the **-H** and **-OH** groups around thecarbon atom adjacent to the **terminal primary alcohol carbon** (carbon 5 in glucose) determines whether the sugar belongs to the **D** or **L** series.

- The **D-** and **L- notation** is based on **glyceraldehyde**.
- When the **-OH** group on this carbon is on the **right**, then sugar is the ***D-isomer***; when it is on the **left**, then it is the
  L-isomer.

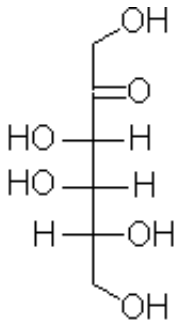


D- and L-isomerism of glycerose and glucose

- Most of the monosaccharide occurring in mammals is **D sugars**, and the enzymes responsible for their metabolism are specific for this configuration. In solution, glucose is dextrorotatory- hence the alternative name **dextrose.**
- The presence of asymmetric carbon atoms also confers **optical activity** on the compound. When a beam of plane- polarized light is passed through a solution of an **optical isomer,** it will be rotated either to the right, dextrorotatory (+); or to the left, levorotatory (-). The direction of rotation is independent of the stereochemistry of the sugar, so it may be designated D (-), D (+), L (-), or L (+). For example, the naturally occurring formof fructose is the D (-) isomer.



D (-) fructose



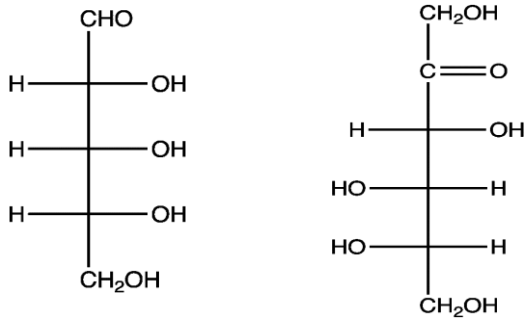
D (-) Tagatose

D-Tagatose is an epimer of D-fructose inverted at C-4

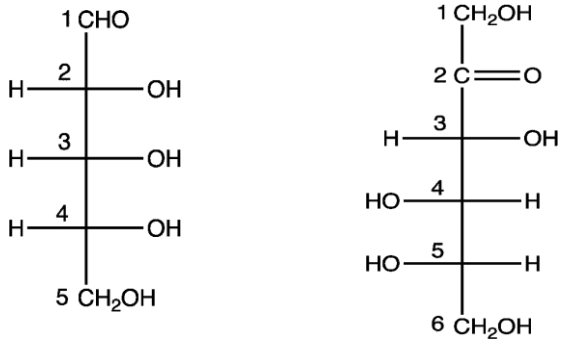
Application of D,L convention to monosaccharides:

- One enantiomer of a chiral monosaccharide is labeled **D** and the other **L**. To determine whethera given enantiomer of a chiral monosaccharide is **D** or **L**, use the following procedure.

✓ **Step 1:** Make sure the acyclic form of the molecule is drawn as a Fischer projection. If the monosaccharide is an aldose, the aldehyde group must be on top; if it is a ketose, thecarbonyl carbon must be the second carbon from the top.

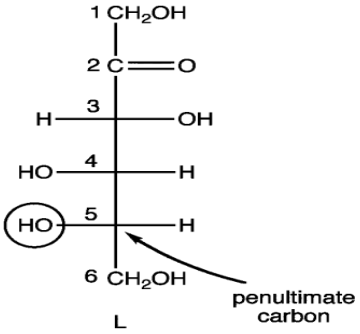


✓ **Step 2:** Number the carbon atoms starting at the top.



Aldose Sugar (Glucose) ***Ketose Sugar (Fructose)***

✓ **Step 3:** Locate the carbon atom that bears the second highest number, which is known as the **penultimate carbon**. If the **hydroxy group** on the **penultimate carbon** is on the right of the carbon chain, assign the label **D** to the compound; if it is on the left of the carbon chain, assign the label **L**.

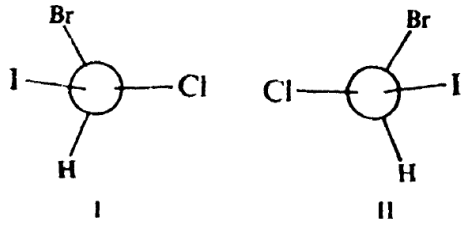


D-Glucose

L

SPECIFICATION OF CONFIGURATION: R AND S

How can we specify a particular configuration in some simpler, more convenient way than by always having to draw its picture? The most generally useful way yet suggested is the use of the prefixes R and S.



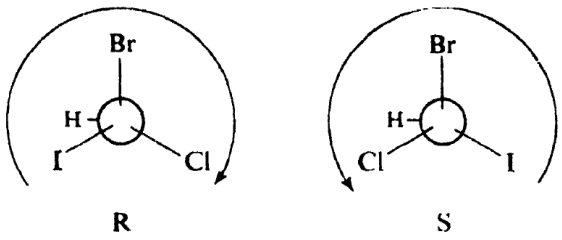
I II

Bromochloroiodomethane

- **Step 1**. Following a set of sequence rules, we assign a sequence of priority to the four atoms or groups of atoms attached to the chiral center. In the case of CHClBrI, for example, the four atoms attached to the chiral center are all different and priority depends simply on atomic number, the atom of higher number having higher priority. Thus I, Br, CI, H.

- **Step 2.** in proceeding from the group of highest priority group to the group of second priority and then to third, our eye travels in a clockwise direction, the configuration is specified R (Catinl rectus, right); if counter clockwise, the configuration is specified S (Latin: sinister, left).

- Thus, configurations I and II are viewed like this: and are specified R and S, respectively.



R S

A complete name for an optically active compound reveals-if they are known both configuration and direction of rotation, as, for example, (S)-(+)-sec butyl chloride. A racemic modification can be specified by the prefix RS, as, for example, (RS)-sec-butyl chloride.

We must not, of course, confuse the direction of optical rotation of a compound a physical property of a real substance, like melting point or boiling point-with the direction in which our eye happens to travel when we imagine a molecule held in an arbitrary manner.

So far as we are concerned, unless we happen to know what has been established experimentally for a specific compound, we have no idea whether (+) or (-) rotation is associated with the R or the S configuration.

To establish the group priorities we use the following **Sequence Rules**:

Rule 1.

Of the atoms attached directly to the chiral carbon atom, the one atomic number has the highest priority.For example,

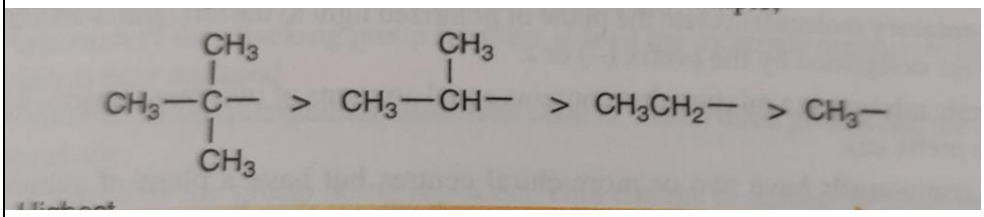
I > Br > C > F > 0 > N > C > H.

Highest ---------- >Lowest

Rule 2.

Of the atoms attached to the chiral carbon atom are the same, we determine priority by going to the nextatom away from the chiral carbon atom. For example,

$-CH_2CH_2CH_3 > -CH_2CH_3 > -CH_3 > -H$

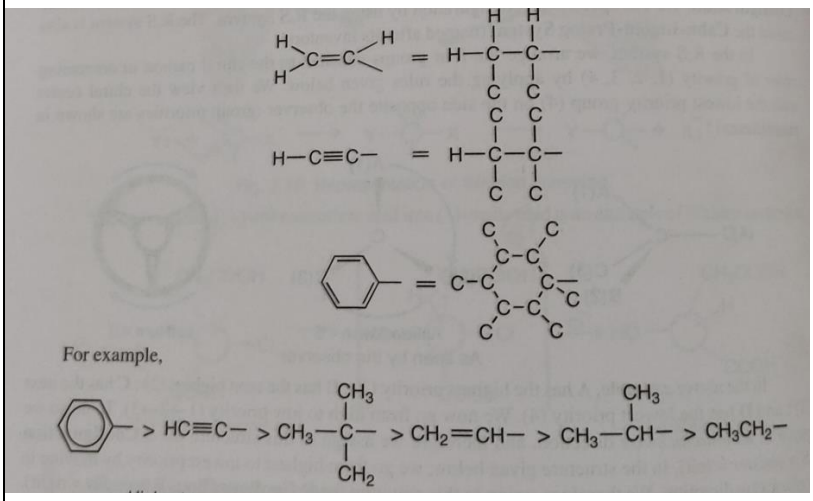


Highest ---------- >Lowest

Ethyl has a higher priority than methyl because the ethyl group has (CHH attached to the fir carbon, whereas the methyl carbon has only hydrogens (HHH), and C has priority over, Isopropyl is of higher priority than ethyl because it has two carbons attached to the first carbon and ethyl has only one. If thereis no difference at the second atom in the chain, we go to the next atom and so forth .

Rule 3.

A double bond is treated as though each atom of the double bond were bonded to two atoms



Highest ----------> Lowest

The **R** and **S** notations can be used as part of the IUPAC name of a chiral molecule to provide a complete structural description, including configuration. The **R** and **S** designations precede the remainder of the name, separated from it with a hyphen.

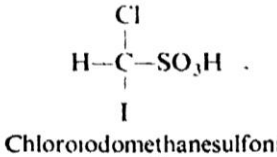
The configuration of compounds with more than one chiral center can also be specified by the R.S system. The configuration of each chiral center carbon is determined individually, using the same rules as for compounds with one chiral carbon. The configuration of all chiral centers are then specified before thename of the compound, identifying each chiral carbon by a number before the symbol **R** or **S.** For example, the compound 2R,3S-3-chloro-2-pentanol has the **R** configuration at carbon 2 and the S configuration at carbon 3.

SEQUENCE RULES

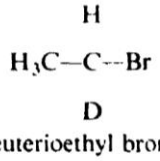
Sequence Rule 1.

If the four atoms attached to the chiral center are all different priority depends on atomic number, with theatom of higher atomic number getting higher priority. If two atoms are **isotopes** of the same element, the atom of highest mass number has the higher priority.

For example, in chloroiodomethanesulfonic acid the sequence is I, Cl, S, H;. in α-deuterioethyl bromide it is Br, C,D, H.



Chloroiodomethanesulfonic acid

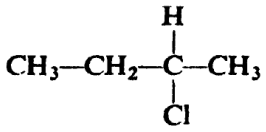


α-Deuterioethyl bromide

Sequence Rule 2.

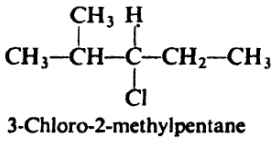
If the relative priority of two groups cannot be decided by Rule 1, it shall be determined by a similar comparison of the next atoms in the groups (and so on, if necessary, working outward from the chiral center). That is to say, if two atoms attached to the chiral center are the same, we compare the atoms attached to each of these first atoms.

For example, take sec-butyl chloride, in which two of the atoms attached to the chiral center are themselves carbon. In CH_3, the second atoms are H, H, H in C_2H_5 they are C, H, H. Since carbon has a higher atomic number than hydrogen, C_2H_5 has the higher priority. A complete sequence of priority for sec-butyl chloride is there fore Cl, C_2H_5 CH_3 H.

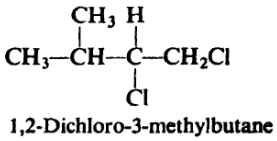


sec-Butyl chloride

- In 3-chloro-2-methylpentane the C, C, H of isopropyl takes priority over the C, H, H of ethyl, and the complete sequence of priority is Cl, isopropyl, ethyl, H. In l,2-dichloro-3-methylbutane the Cl, H, H of CH2C1 takes priority over the C, C, H of isopropyl. Chlorine has a higher atomic number than carbon, and the fact that there are two C's and only one Cl does not matter. (One higher number is worth more than two or three of a lower number.)



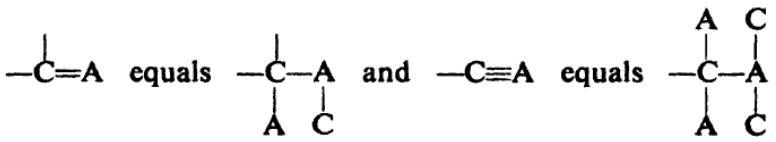
3-Chloro-2-methylpentane



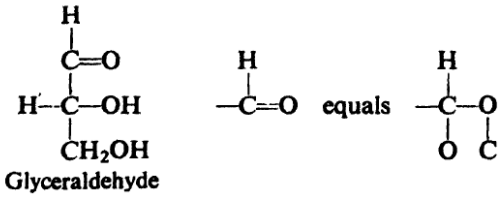
1,2-Dichloro-3-methylbutane

Sequence Rule 3.

(The student should defer study of this rule until he needs it.) Where there is a double or triple bond, both atoms are considered to be duplicated or triplicated. Thus,

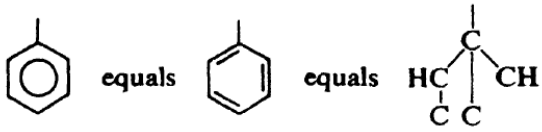


For example, in glyceraldehyde the OH group has the highest priority of all,

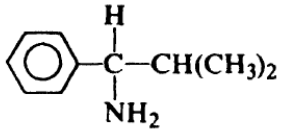


and the O, O, H of —CHO takes priority over the O, H, H of $—CH_2OH$. The complete sequence is then —OH, —CHO, $—CH_2OH$, —H.

The phenyl group, $C_6H_5—$ is handled as though it had one of the Kekulé structures:

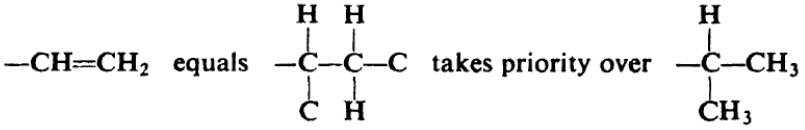


In 1-amino-2-methyl-1-phenylpropane, for example, the C, C, C, of phenyl takes



priority over the C, C, H of isopropyl, but not over N, which has a higher atomic number. The entire sequence is then NH_2, C_6H_5, C_3H_7, H.

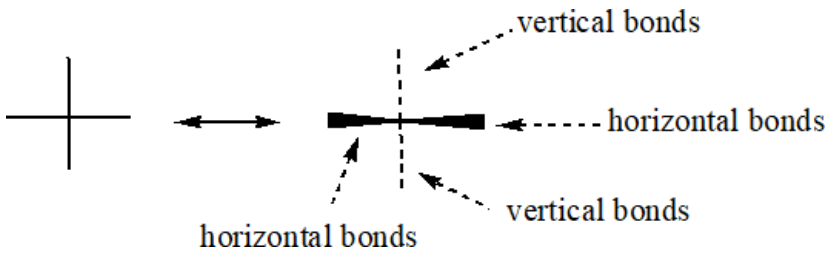
The vinyl group, $CH_2=CH—$, takes priority over isopropyl.



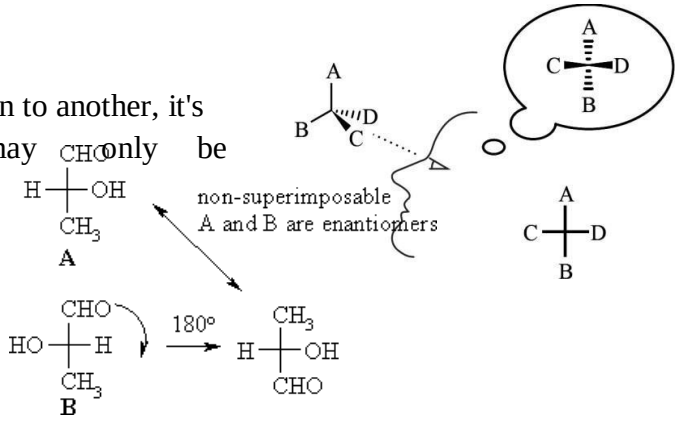
Following the "senior" branch. $—CH_2—C$, we arrive at C in vinyl as compared with H in the $—CH_2—H$ of isopropyl.

Fischer Projection

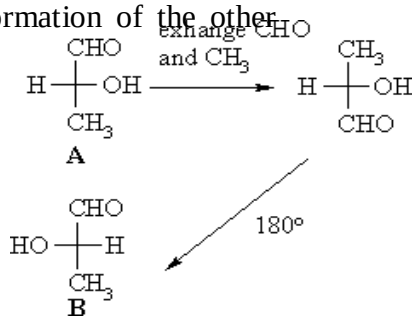
- Fischer Projections are abbreviated structural forms that allow one to convey valuable stereochemical information.
- The definition is that every carbon is specified completely by a cross designating the carbon (at the center) and the four bonds to that carbon. The stereochemistry of the bonds is defined (now) as the **horizontal bonds** are in **front of the plane** (coming toward you, the viewer); the **vertical bonds** are **behind the plane** (going away from you).


vertical bonds
horizontal bonds
vertical bonds
horizontal bonds

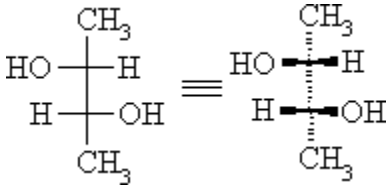
- When relating one Fischer projection to another, it's importantto realised that it may only be manipulated within the 2D plane



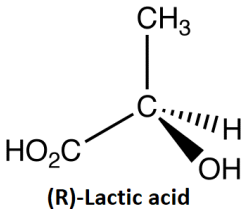
- **Why we can't rotate 90^0?** A 90^0 rotation is equivalent to breaking bonds and exchanging twogroups, which would result in the formation of the other enantiomer.



- Fischer projections a can also be used to represent molecules with **more than one chirality center**



A **Fischer projection** or **Fischer projection formula** is a convention used to depict a stereo-formula in two dimensionswith out destroying the Stereochemical information, i.e., absolute configuration, at chiral centers.



(R)-Lactic acid

- ***To convert this stereoformula into a Fischer projection use the following procedure***

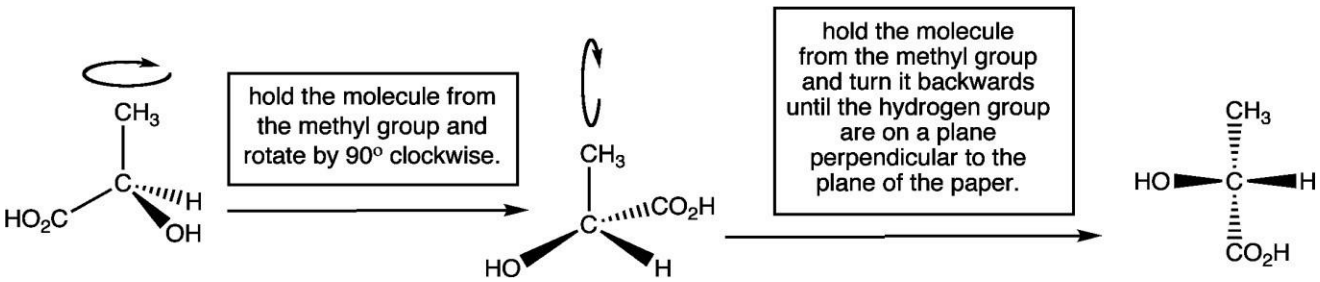
[Fischer Projection of (R)-Lactic acid]

Step 1: *Hold the molecule so that*

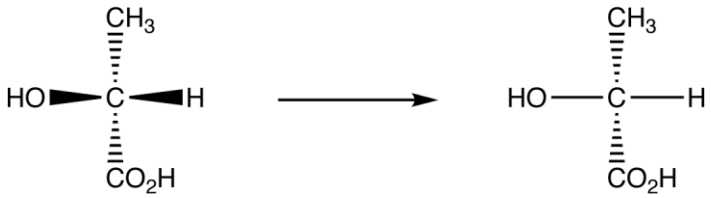
(i) The chiral center is on the plane of the paper,

(ii) Two bonds are coming out of the plane of the paper and are on a horizontal plane,

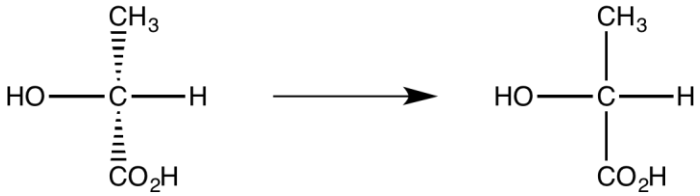
(iii) The two remaining bonds are going into the plane of the paper and are on a vertical plane.



Step 2: *Push the two bonds coming out of the plane of the paper onto the plane of the paper.*



Step 3: *Pull the two bonds going into the plane of the paper onto the plane of the paper.*



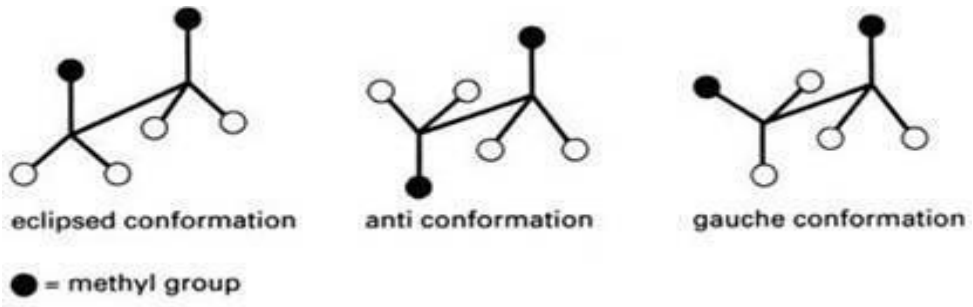
Step 4: *Omit the chiral atom symbol for convenience.*

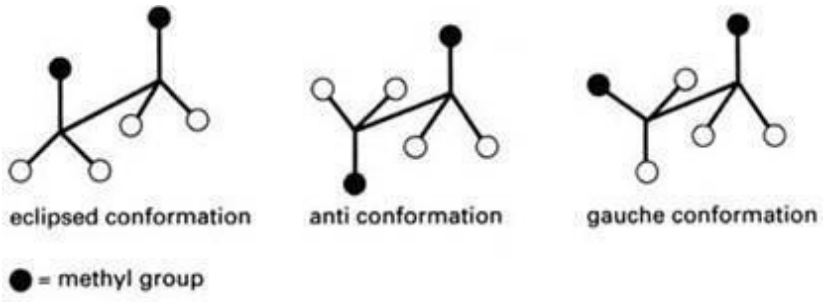
SAWHORSE FORMULA

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

Anti conformation

eclipsed conformation





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

REACTIONS INVOLVING STEREOISOMERS:

Now let us look at stereoisomers involvement in chemical reactions: reactions in which stereoisomers are formed, and reactions in which stereoisomers are consumed', Reactions in which the reagent is of the ordinary (that is, optically inactive) kind and those in which the reagent is optically active. We shall take up:

(a) the conversion of an achiral molecule into a chiral molecule, with the generation of a chiral center:

(b) reactions of chiral molecules in which bonds to the chiral center are not broken, and see how such reactions can be used to relate the configuration of one compound to that of another

(c) reactions of the kind in (b) in which a second chiral center is generated

(d) reactions of chiral compounds with optically active reagents.

(e) a reaction of a chiral compound in which a bond to a chiral center is broken.

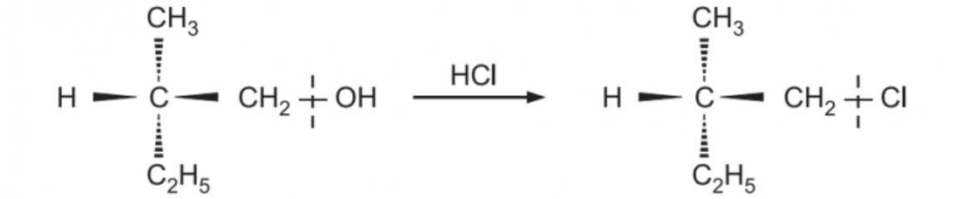
(f) a reaction of an achiral compound in which two chiral centers are generated at the same time.

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

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

1. Reactions where bonds with the chiral center are not broken:

These reactions can be used to relate the configuration of one compound to that of another. Configuration is retained when the reaction does not involve the breaking of a bond to a chiral center.



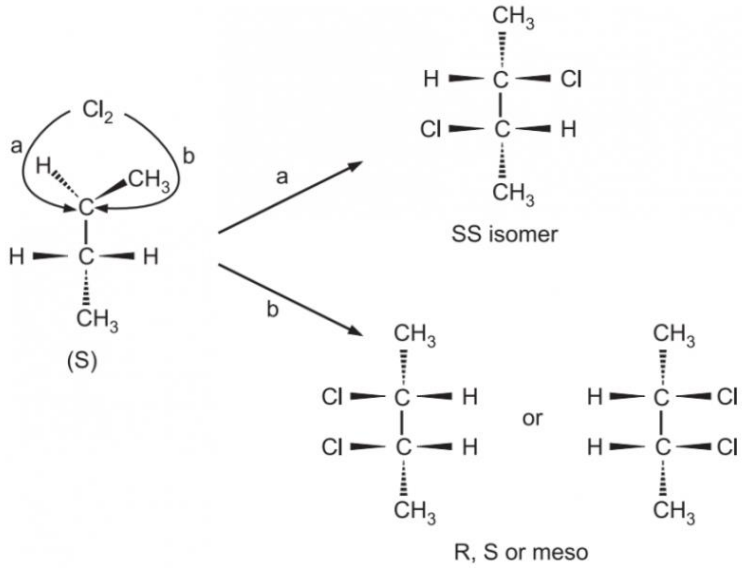
(S)(–) 2-methyl-1-butanol (S)(+) 1-chloro-2-methyl butane

- Here is the bond to the chiral center is not broken 'S' configuration is retained, because '–CH_2–Cl' occupies the same relative position as that was occupied by –CH_2OH in the reactant. This retention of configuration can be utilized to determine the configurational relationship between two optically active compounds by converting them into each other by reactions that do not involve the breaking of a bond to a chiral center. 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 a specific rotation of –5.90° and is optically pure. Upon treatment with hydrogen chloride, 1-chloro 2-methyl butane has a specific rotation of +1.67°. So if a sample has rotation equal to this value, the compound is said to be pure. If rotation is about + 0.8º, the 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 yield unequal amounts of diastereomers depending on the side of attack.



- Retention of configuration(s) occurs as there is no bond breaking to the chiral center. For the new chiral center, depending on side of attack from the same or opposite side, diastereomers are formed but in unequal amounts. 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 the ratio of 29:71.

- In some reactions, both configurations may not be generated but probability exists. Similarly, the R isomer would yield RR and meso compound in the ratio of 29:71. If the reactant is optically inactive, it yields optically inactive products.

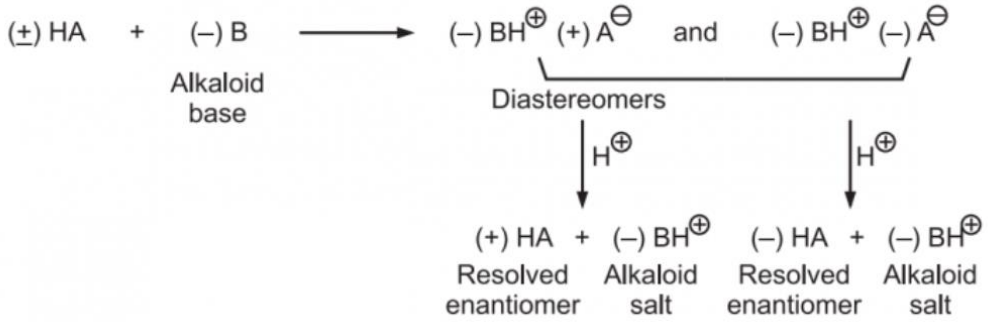
3. Reactions of chiral compounds with optically active reagents

- Such reactions are commonly used in the 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.

- So to obtain pure enantiomers from racemic modification, use of optically active reagents is made. Such optically active reagent is easily obtained from natural sources or generated from naturally available reagents.

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

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



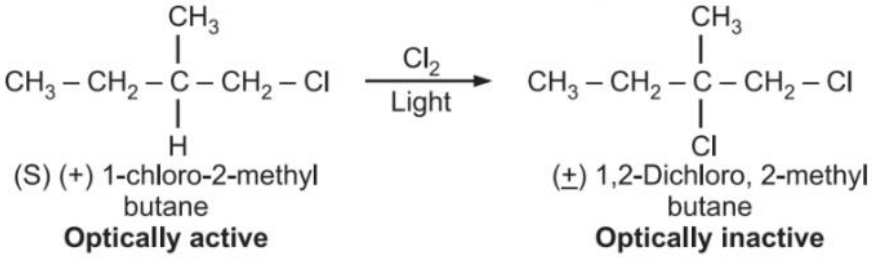
- Formed diastereomers have different physical properties and can be easily separated by fractional distillation or crystallization. Further by the addition of mineral acid resolved enantiomers can be recovered from the solution.

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

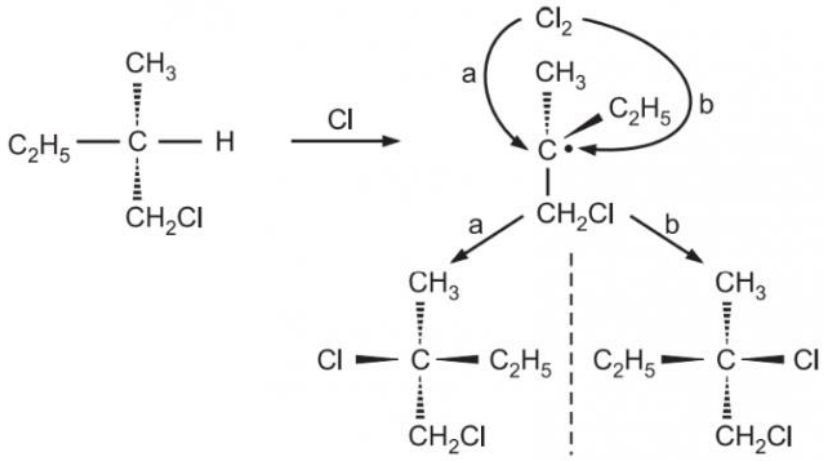
- Similarly, racemic bases can be separated with acid reagents e.g. (–) malic acid. Compounds other than acids, bases can also be resolved. Alcohols are weakly ionized and are not appreciably acidic or basic so their resolution is facilitated by attaching them with an acidic handle which can be removed later.

4. Reactions where bonds with the chiral center are broken:

The stereochemistry of such reactions depends on the mechanism of the reaction. Hence, stereochemistry can be helpful to give evidence of a particular mechanism. e.g.



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



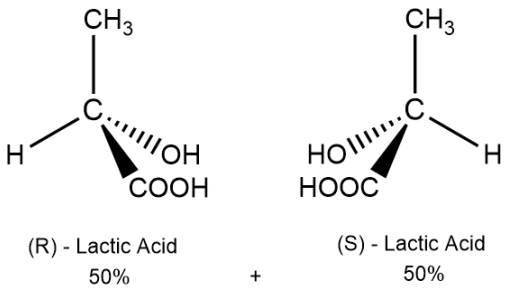
If there is a simultaneous attack of chlorine while the displacement of hydrogen, only the product from backside attack of chlorine would have been obtained instead of optically inactive product, so the mechanism involving free alkyl radicals is correct.

- 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.

Racemic Mixture & Racemization

RACEMIC MIXTURE

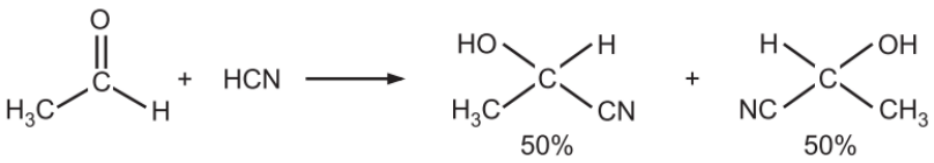
- A racemic mixture is a 1:1 mix of two enantiomers (Each of a pair of molecules that are mirror images of eachother).
- No matter how many molecules are in a mixture, it is racemic if there are equal numbers of the two enantiomers.
- The racemic mixture produces a net optical rotation - of plane polarized light - of zero degrees. This is because themixture contains equal amounts - **equimolar mixture** - of both enantiomers that have opposite rotations.
- A **racemic mixture** is a solution containing equal amounts of **a pair of enantiomers**.



Racemic Mixture

Racemic Modification: A racemic modification or racemate is a 1:1 mixture of (+) and (–) enantiomers. When enantiomers are mixed in equal amounts, 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 the 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 materials is chiral, the product of the reaction will always be formed as a racemate in the absence of a chiral catalyst.



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

Methods of Racemic Modification

(a) Mixing: A racemic modification may be achieved by intimate mixing of exactly equal amounts of Dextro (+) and Levo (–) isomers.

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

RESOLUTION OF RACEMIC MIXTURES

- The separation of a racemic mixture into the individual enantiomerically pure enantiomers is called resolution.
- Since enantiomers have identical physical properties, such as solubility, boiling point and melting point, they cannot be resolved by common physical techniques such as direct crystallization, distillation or basic chromatography.
- The main difficulty in a process of resolution is that **d** or (+) and **l** or (–) forms have identical physical and chemical properties, so they cannot be separated by ordinary methods. However, the following methods can be used for this purpose.

(i) Mechanical separation:

- If the **d** or (+) and **l** or (–) forms of a substance exits in well-defined crystalline forms, the separation can bedone by hand picking with the help of magnifying lens and a pair of tweezers.
- For example, the d and l forms of sodium ammonium tartarate can be separated by this method.
- The method has very limited application and applies to only few crystalline constituents having differentshape.

(ii) Biochemical separation:

- In this method, the resolution is done by the use of microorganisms.
- When certain **bacteria** or **moulds** are added to a solution of a racemic mixture, they decompose one of theoptically active forms more rapidly than the other.
- 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 the racemic mixture, it selectively destroys the dextro isomer leaving pure Levo isomer behind.

- For example, when the **mould**, **racemic ammonium tartarate**, the mould completely decomposes the **d** form while **l** form is left practically unaffected. The main drawback of the method is that half of the material is destroyed during resolution. The process is very slow and only small amounts of the materials can be separated.

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^{++} 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
Tranylcypromine	Antidepressant	(–)
	Improvement in performance	(+)
Sotalol	Antihypertensive	(–)
	Antiarrhythmic	(+)

(iii) Chemical separation:

- This is probably the best method of resolution. The racemic mixture is made to combine with another optically active compound and the resulting solubility in various solvents.
- By fractional crystallization from a suitable solvent, they can be separated.
- 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 differences 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.

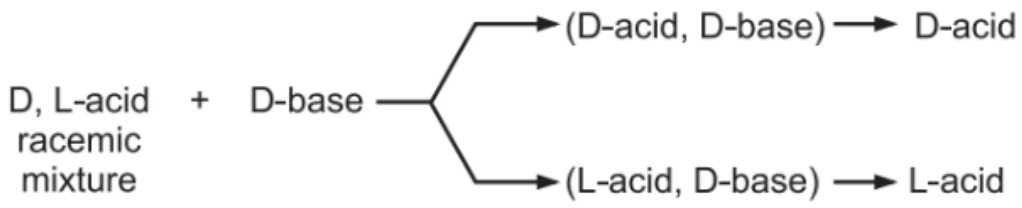
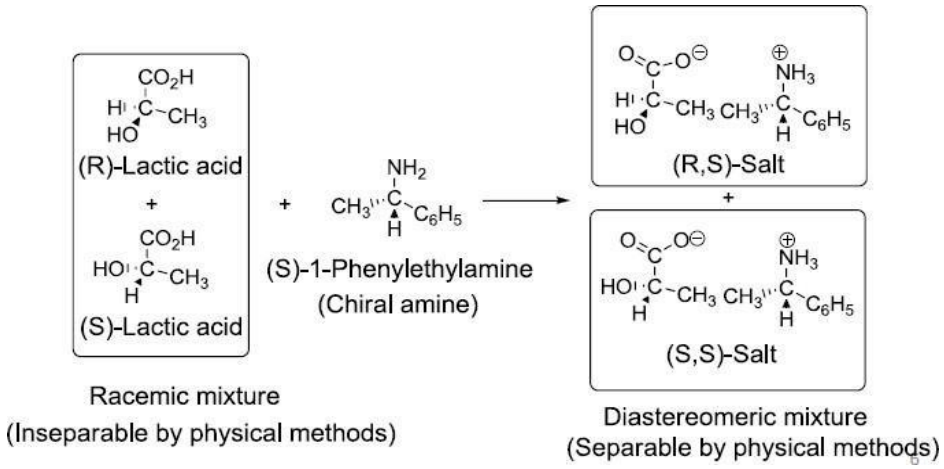


Fig. 1: Resolution of a racemic mixture

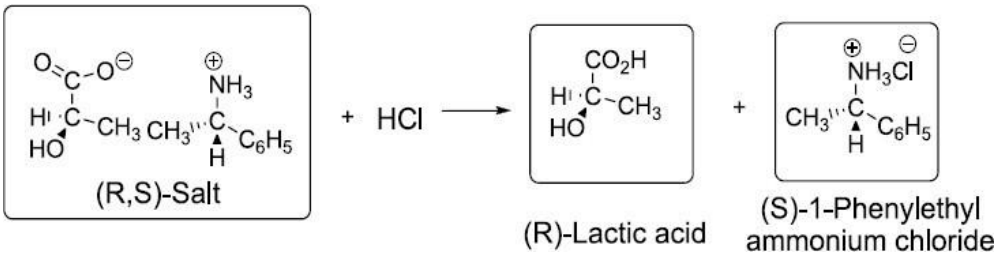
- Racemic acids may be resolved using commercially available chiral bases like brucine, strychnine, l-phenyl ethanamine. Similarly, racemic bases may be resolved using chiral acids such as (+) tartaric acid, (–) malic acid, (–) mandelic acid, and (+) camphoric acid.
- For example, the racemic mixture of lactic acid is allowed to combine with the optically active base (-) strychnine or (+) brucine.

- ***Example of Resolution of Racemic Mixtures***

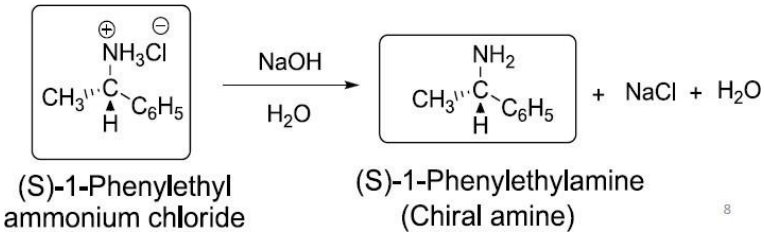
(i) ***(S)-1-Phenylethylamine*** combines with a racemic mixture of lactic acid to form **diastereomeric salts**. The diastereomers are separated by fractional crystallization.



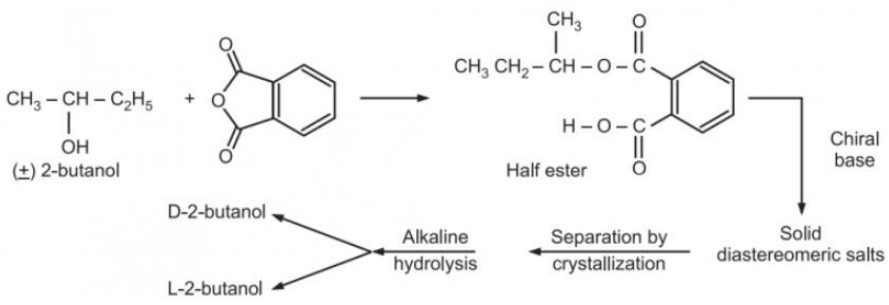
- After the separation process, each of the diastereomers is subsequently treated with a strong acid such as hydrochloric acid to regenerate the corresponding enantiomer of lactic acid



- Note that the lactic acid would be soluble in the organic layer, while the ammonium salt would be in the water layer.
- Since enantiomerically pure compounds are very expensive, it is usually necessary to recover and reuse the chiral amine. This is achieved by treating the (S)-1-phenylethyl ammonium chloride salt with a base such as sodium hydroxide to regenerate and recover the chiral amine.



ii) Racemic alcohol may be resolved by converting the racemate into a mixture of diastereomeric esters using a chiral acid. The separation of these diastereomeric esters becomes difficult if they are liquid. In such cases, instead of full ester, the 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.



Advantages of Resolution:

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

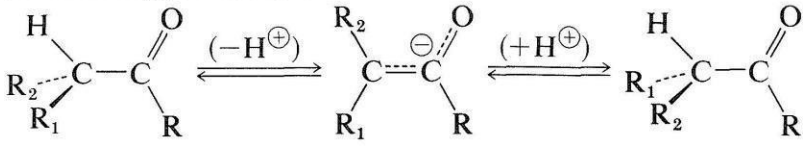
(ii) Reduction in the therapeutic dose and hence the cost of treatment.

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

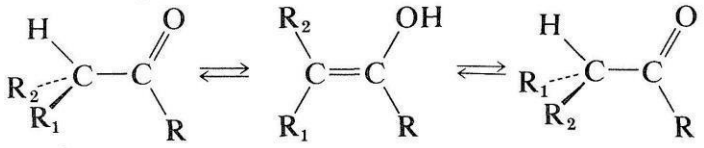
● RACEMIZATION

- **Racemization** is the conversion of an enantiomerically pure mixture (one where only one enantiomer is present) into a mixture where more than one of the enantiomers are present. (Or) Conversion of an optically active substance to a raceme.
- Optically active carbonyl compounds of the type **−CHC=O** , in which the **alpha** carbon is asymmetric, are racemized by both acids and bases

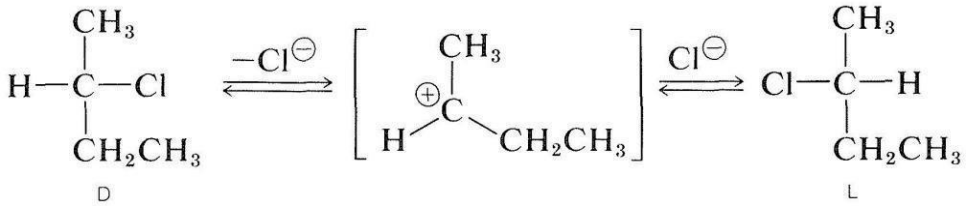
Base-catalyzed enolization



Acid-catalyzed enolization



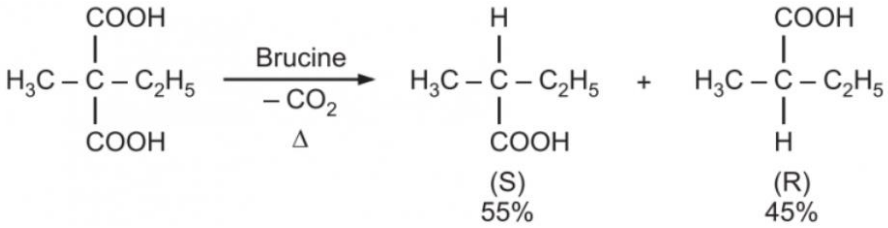
- The racemization of an optically active secondary halide with the chiral carbon carrying the halogen (e.g., 2- chlorobutane) may occur in the solution and, usually, the more polar and better ionizing the solvent is, the more readily the substance is racemized. Ionization of the halide by an **SN^1** process probably is responsible, and this certainly would be promoted by polar solvents. All indications are that an alkyl carbocation once dissociated from its accompanying anion is planar; and, when such an ion recombines with the anion, it has equal probability of forming the **D** and **L** enantiomers:



ASYMMETRIC SYNTHESIS (PARTIAL AND ABSOLUTE)

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

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



- Generally, chiral reagents are used to carry out the reaction, if they are not available, chirality is acquired upon chelation, solvation, etc.
- Reactants are adsorbed onto chiral surfaces or within chiral crystals.
- Chiral adjuvant or chiral auxiliary is temporarily attached to the achiral substrate which is cleaved after the synthesis by hydrolysis to recycle the adjuvant.
- When a new stereogenic center is created in an achiral molecule we get a racemic mixture while in diastereoselective synthesis, the formation of any one of the desired diastereomers is preferred over the other.

For example: If one could prepare 2-hydroxypropanenitrile from ethanal and hydrogen cyanide in the absence of any chiral reagent and produce an excess of one enantiomer over the other, this would constitute an absolute asymmetric synthesis - that is, creation of preferential chirality (optical activity) in a symmetrical environment from symmetrical reagents:

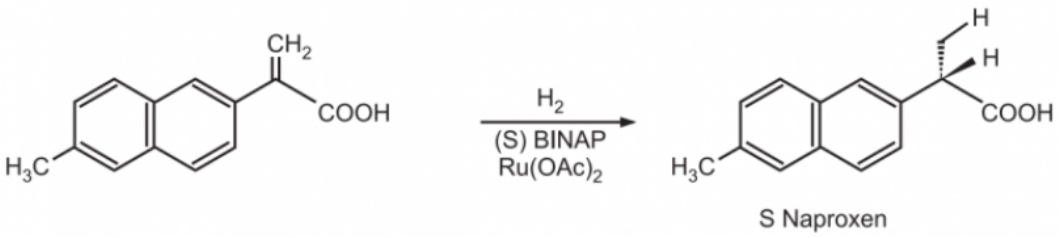
Typical asymmetric syntheses include:

- Asymmetric hydrogenation
- Asymmetric epoxidation
- Asymmetric dihydroxylation

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

1. **Asymmetric Hydrogenation (Reduction):**

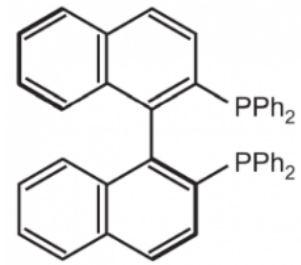
It is used for the asymmetric synthesis of the analgesic drug Naproxen.



S Naproxen

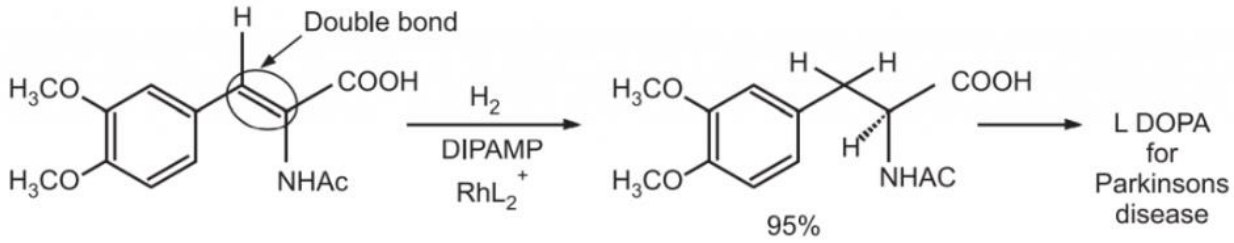
The reaction is carried out in presence of a chiral catalyst to hydrogenate a double bond. The catalyst selects a single enantiotopic face of the double bond and adds hydrogens across it.

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

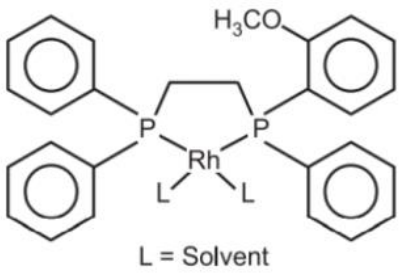


S-BINAP

For double bonds bearing amino groups, better catalysts are based on rhodium.



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

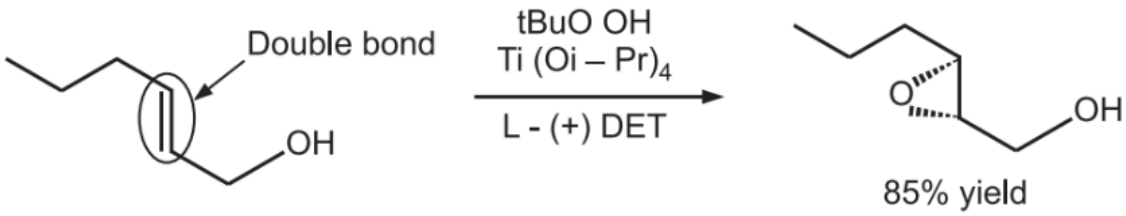


L = Solvent

An important application of asymmetric hydrogenation is in the synthesis of L menthol from (R) citronellal.

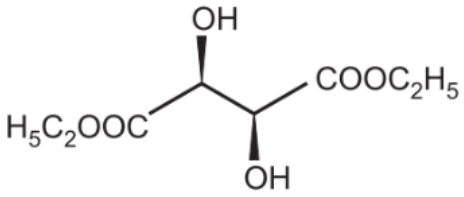
2. Asymmetric epoxidation:

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



85% yield

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)

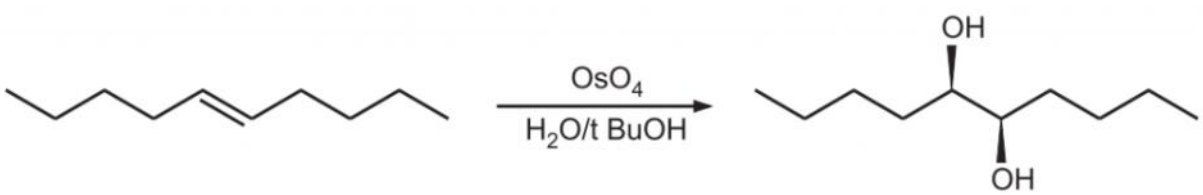
- Such metal-catalyzed epoxidation works only on allylic alcohols. Initially, the active complex is formed from two titanium atoms bridged by two tartrate ligands. Each titanium atom retains two of its isopropoxide ligands and is co-ordinated to one of the carbonyl groups of the tartrate ligand. When oxidizing agent tBuOOH is added, it displaces one of the remaining isopropoxide ligands and one of the tartrate carbonyl groups. Further allylic alcohol is coordinated with the titanium displacing another isopropoxide ligand.

- Because of the shape of the complex of the reactive oxygen atom of the bound hydroperoxide has to be delivered to the lower face of alkene and epoxide is formed in high enantiomeric excess.

- Epoxides easily react with many nucleophiles to give 1,2, disubstituted products and thus used in the synthesis of drugs e.g. Propranolol- used as β blocker.

3. Asymmetric dihydroxylation:

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



97% enantiomeric excess

- Osmium (VIII) acts as an oxidizing agent and $K_3Fe(CN)_6$ is commonly used to reoxidize the osmium after each catalytic reaction.
- To increase the rate of reaction K_2CO_3 and methanesulfonamide are added.
- Chiral ligands are usually alkaloids dihydro quinidine and hydroquinone based which must be attached to aromatic rings e.g. Phthalazine.
- Trans alkenes dihydroxylates more selectively than other alkenes because of the alignment of ligand and catalyst.
- The reaction has been successfully used for the synthesis of antibiotic chloramphenicol in few steps.

Energy Profile diagrams for asymmetric synthesis

Energy Profile diagrams for asymmetric synthesis

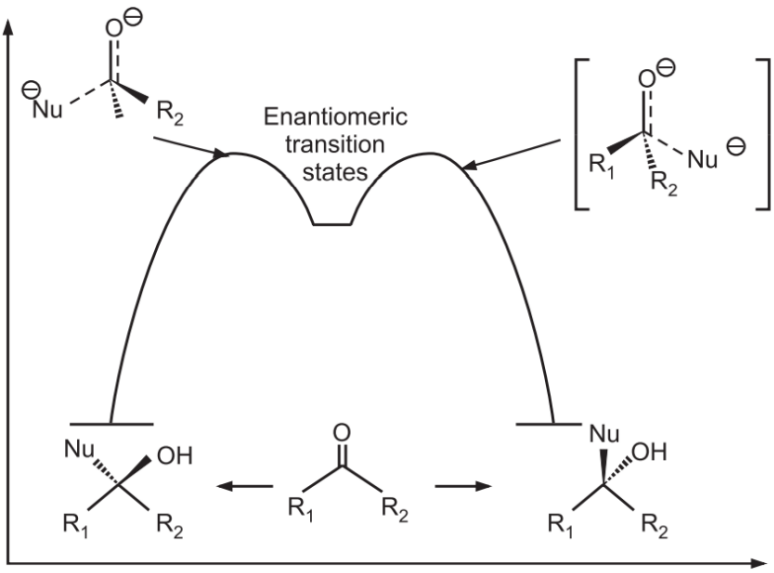


Fig.1: Nucleophilic attack on ketone in an achiral environment where enantiomeric products are produced in exactly equal amounts.

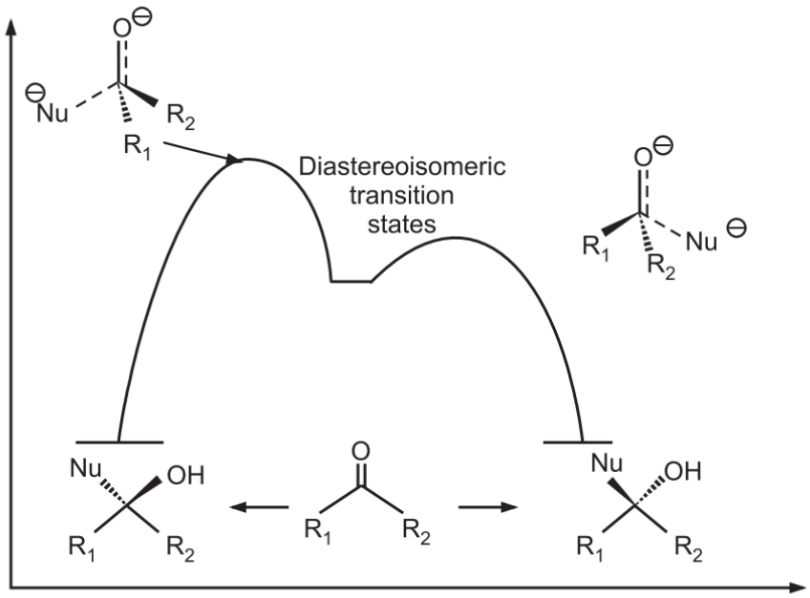


Fig.1: Nucleophilic attack on a ketone in a chiral environment where enantiomeric products are produced in unequal amounts.

Partial vs Absolute Asymmetric Synthesis

	Partial Asymmetric Synthesis	Absolute Asymmetric Synthesis
DEFINITION	Partial asymmetric synthesis is the creation of less favorable chirality in symmetrical molecules	Absolute asymmetric synthesis is the chemical reaction that includes the creation of preferential chirality in a symmetrical environment from symmetric reagent
THEORY	Produce equal amounts of both enantiomers	Produce one enantiomer over the other
CONVERSION	Not all the possible centers are converted to chiral centers	Usually all possible centers are converted to chiral centers
EXAMPLE	Reaction of optically active styrene oxide with triethyl alpha-phosphonopropionate which gives 2-phenyl-1-methylcyclopropanecarboxylate which is chiral	If we can prepare 2-hydroxypropanenitrile from ethanal and hydrogen cyanide in the absence of other chiral reagents, it gives an excess of one enantiomer over the other