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 and absolute

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 isomeris. There are two main types of isomerism,

(1) Constitutional 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

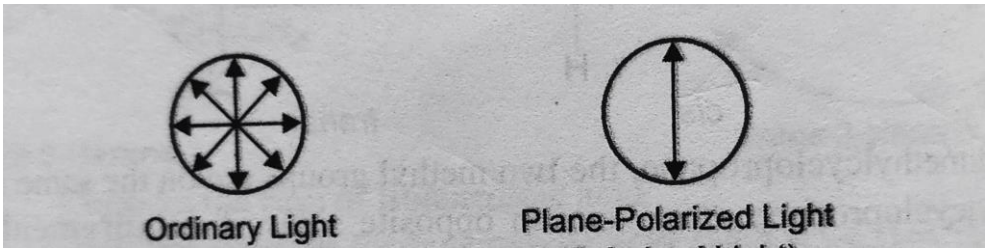
(b) Optical Isomerism

OPTICAL ISOMERISM

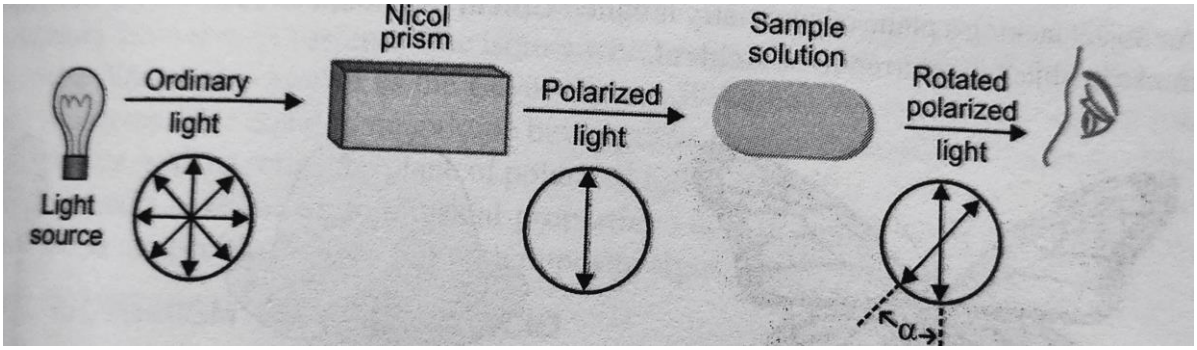
Optical isomerism is a type of stereoisomerism.

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.



- 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. ENANTIOMERS

Optical isomers that are mirror images are called Enantiomers.

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

D(–) – lactic acid L(+) – lactic acid

- Enantiomers have identical physical properties, except for the direction of rotation of the plane of polarized 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 clockwise rotation is a counterclockwise rotation and of exactly the same magnitude.
- Enantiomers have identical properties in all respects except in their interaction with plane of polarized light.
- Enantiomers have the same melting point density, solubility, color, and reactivity toward acids and 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 the plane to the right (clockwise : called dextrorotatory), while the other rotates the plane to the left (anticlockwise called levorotatory).

A mixture of equal parts of enantiomers is called a *racemic modification*.

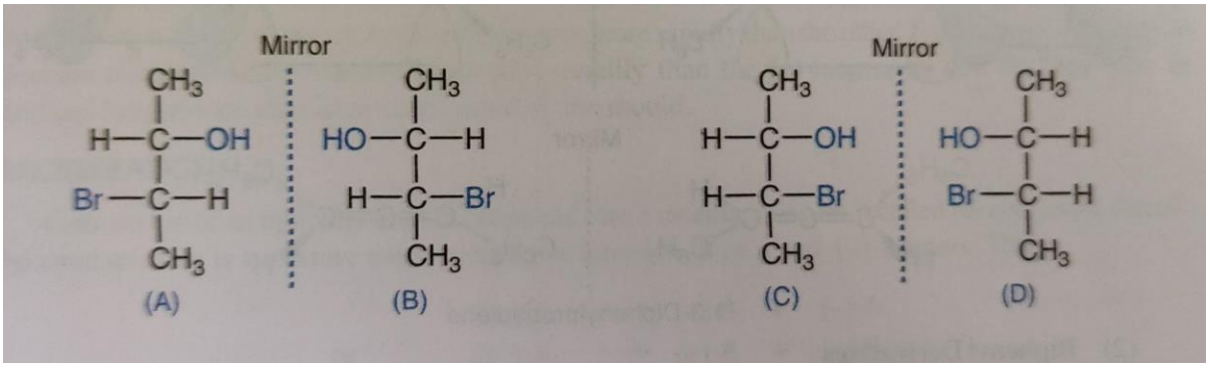
A racemic modification is optically inactive when enantiomers are mixed together, the rotation caused by a molecule of one isomer is exactly canceled by an equal and opposite rotation caused by a molecule of its enantiomer.

DIASTEREOMERS

Each chiral carbon atom in a molecule doubles the number of theoretically pos isomers. Hence, molecule with n chiral carbon atoms should have 2 stereoisomers.

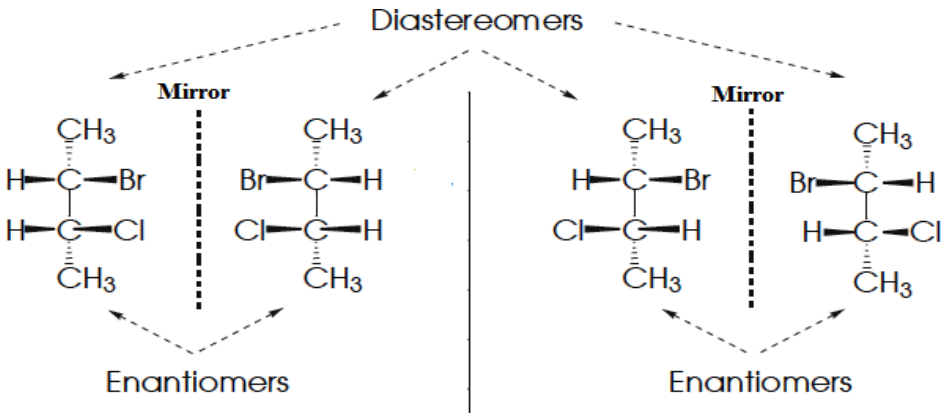
Diastereomers have different properties. Two diastereomers will have different melting points,

boiling points, and solubilities. They will have different chemical reactivities toward most reagents.



(A) is the mirror image of (B): (C) is the mirror image of (D). Thus the four isomers are two pairs of enantiomers. 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.*

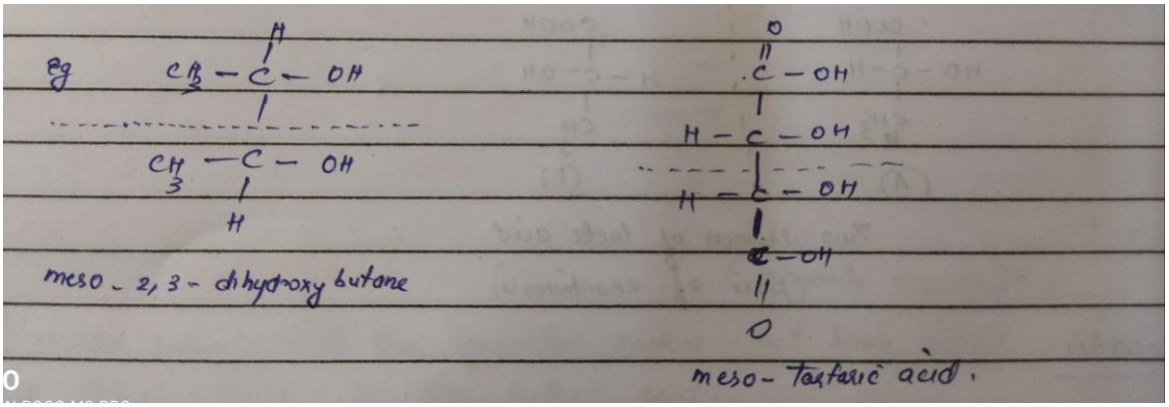
Enantiomers	**Diastereomers**
An enantiomer is one of two stereoisomers that are non-superimposable complete mirror images of each other.	Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers (non-superimposable mirror images of each other).
Molecules must contain atleast one chiral centers.	Molecules must contain more than one chiral center.
Enantiomers have, when present in a symmetric environment, identical chemical and physical properties except for their ability to rotate plane polarized 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 isomer and its enantiomer is termed Racemic and has a net rotation of plane polarized light of zero.	Racemic mixture is not possible.



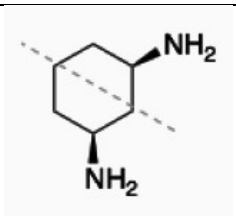
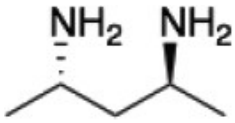
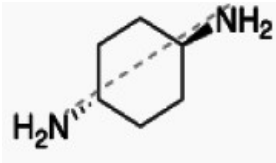
2-bromo-3-chlorobutane

Meso compounds

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

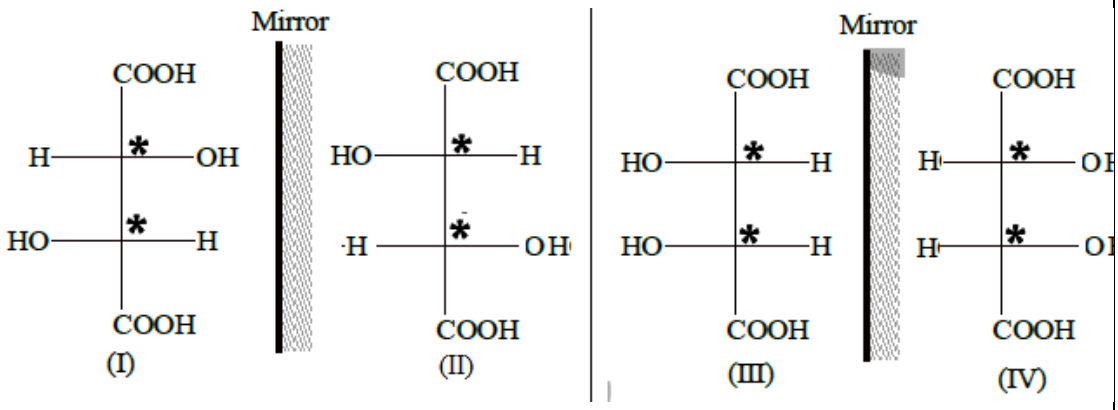


These molecule have planes of symmetry dividing them midway between the two chiral carbon atoms in each. Notice that one half of the molecule is the mirror image of the other, both the molecules are optically inactive even though which have two chiral centres neither will rotate the plane polarized light.

	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 centers and a plane of symmetry.
	This molecule is not meso (CHIRAL). It has two chiral centers but 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 NH_2 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,



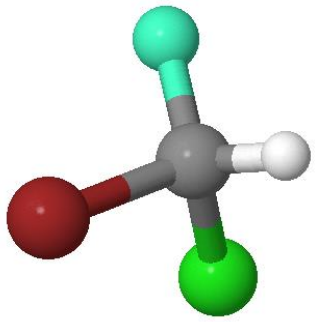
I and II are enantiomers (non-superimposable); III and IV are meso form (superimposable).

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.

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.PLANE OF SYMMETRY

A plane which divides an object into two symmetrical halves, is said to be plane of symmetry. For example, a person or a hat has a plane of symmetry. An object lacking a 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 posses 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.

3.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)

The other elements of symmetry includes,

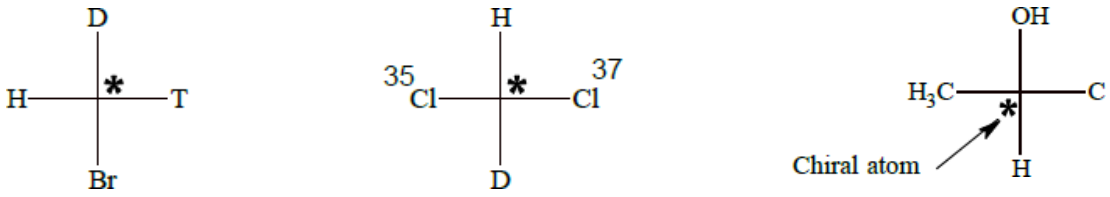
4. Center of Inversion symmetry (*i*)

5. Sn : an n -fold axis of improper rotation Symmetry.

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

CHIRAL AND ACHIRAL MOLECULES

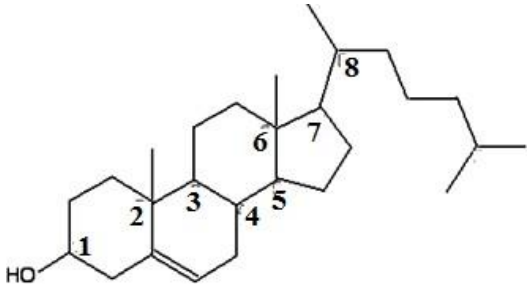
- A molecule (or an object) is said to be chiral or dissymmetric, if it is not superimposable on its mirror image and the property of non-superimposability is called chirality.
- On the other hand, a molecule (or an object) which is superimposable on its mirror image is called achiral (non- dissymmetric 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.

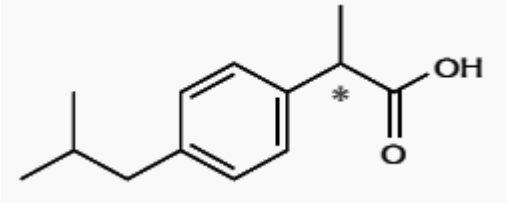
  Cholesterol has eight chiral centres



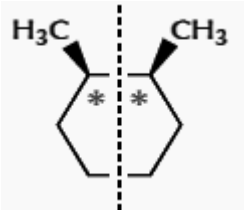
Relationships between **Chiral Centers** and **Chiral Molecules**

- 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 or more 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.

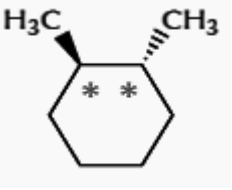
Ibuprofen: One chiral center renders the molecule chiral



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



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



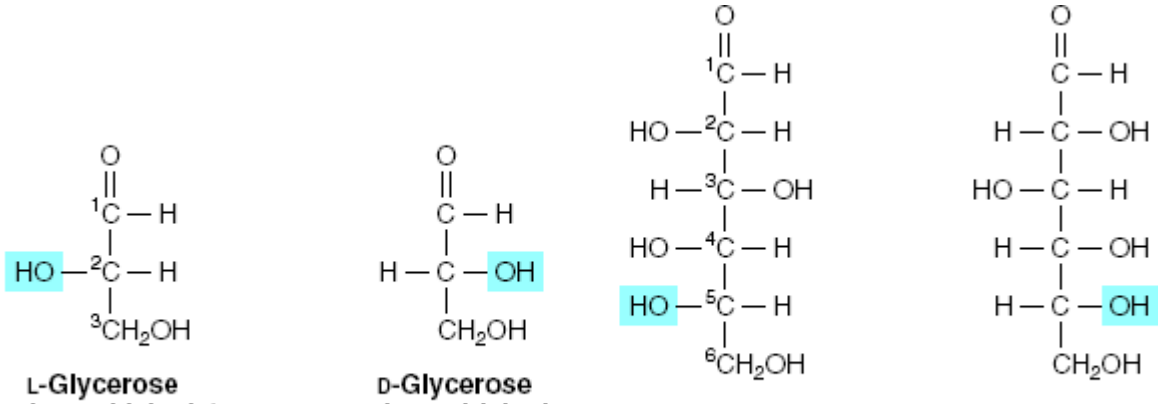
What is Chirality?

The property of **nonsuperimposability** of an object on its mirror image is called **chirality**. Such molecule has no symmetry elements of the second kind. If the molecule is superposable on its mirror image, it is **ACHIRAL**.

D & L-SYSTEM

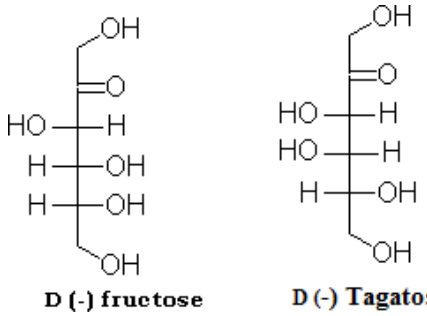
- The **D** & **L** convention, not to be confused with the **d** (**dextro**) and **l** (**levo**) descriptors used to designate the direction of specific rotation of chiral compounds, is a convention used to distinguish between enantiomers of chiral monosaccharides and chiral alpha-amino acids, based 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 the carbon 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

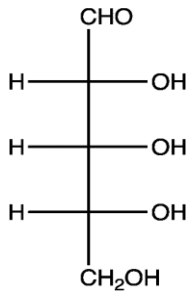
- Most of the monosaccharide occurring in mammals is **D sugars**, and the enzymes responsible for their metabolism are specific for this configuration. In solution, glucose is dextrorotatory- hence the alternative name **dextrose.**
- The presence of asymmetric carbon atoms also confers **optical activity** 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.

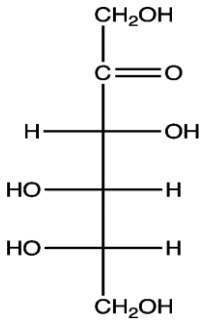


D-Tagatose is an epimer of D-fructose inverted at C-4

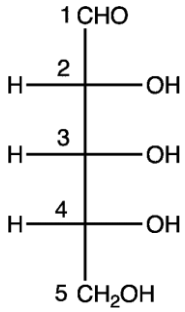
Application of D,L convention to monosaccharides:

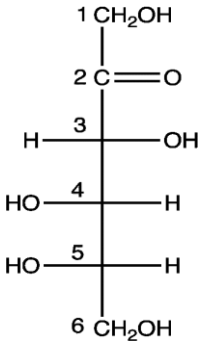
- One enantiomer of a chiral monosaccharide is labeled **D** and the other **L**. To determine whether a given enantiomer of a chiral monosaccharide is **D** or **L**, use the following procedure.
  - ✓ **Step 1:** Make sure the acyclic form of the molecule is drawn as a Fischer projection. If the monosaccharide is an aldose, the aldehyde group must be on top; if it is a ketose, the carbonyl carbon must be the second carbon from the top.





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

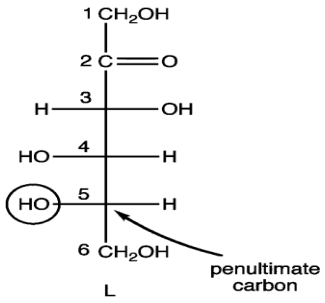




Aldose Sugar (Glucose) ***Ketose Sugar (Fructose)***

  - ✓ **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

he compound; if it is on the left of the carbon chain, assign the label **L**.

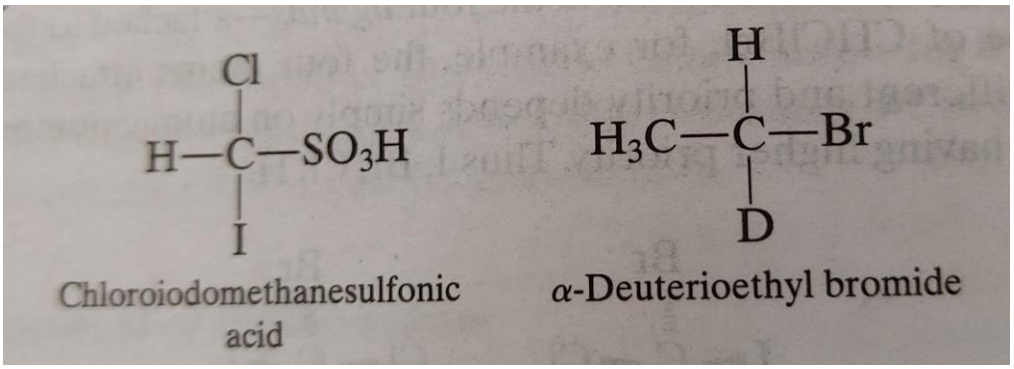


D-Glucose

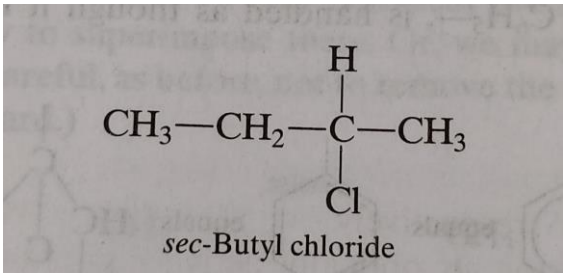
SEQUENCE RULES

Sequence Rule 1.
If the four atoms attached to the chiral center are all different priority depends on atomic number, with the atom of higher atomic number getting higher priority. If two atoms are isotopes of the same element, the atom of highet mass number has the higher priority.

For example, in chloroiodomethanesulfonic acid the sequence is I. CI, a-deuterioethyl bromide it is Br, C, D, H.



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, 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.



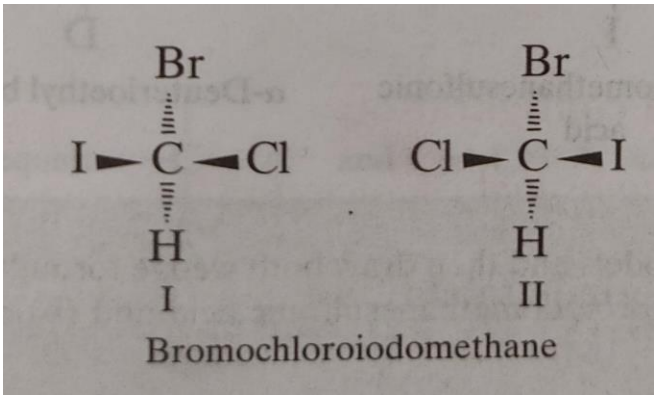
Specification of configuration: R and S

Now, a further problem arises. 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. According to a procedure proposed by R. S. Cahn, Sir Christopher Ingold, and V. Prelog, two steps are involved.

Step 1.

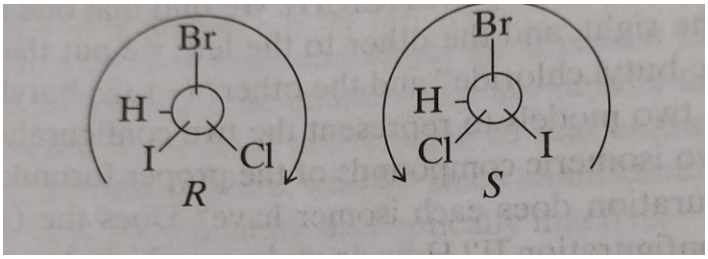
Following a set of sequence rules, we assign a sequence of priority to the four atoms or groups of atoms that is, the four ligands-attached to the chiral center. In the case of CHCIBrl, for example, the four atoms attached to the chiral center are all different and priority depends simply on atomic number,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



Step 2.

We visualize the molecule oriented so that the ligand of lowest priority is directed away from us, and observe the arrangement of the remaining ligands. It in proceeding from the ligand of highest priority to the ligand of second priority and thence to the third, our eye travels in a clockwise direction, the configuration specified R (Latin: rectus, right); if counterclockwise, the configuration is specified S (Latin: sinister left).

Thus configurations I and II are viewed like this:



and are specified R and S, respectively.

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.

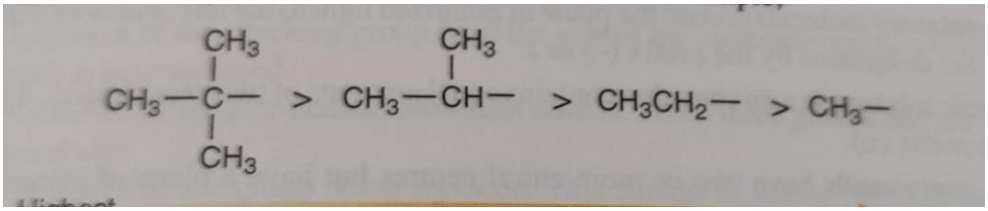
Of the atoms attached directly to the chiral carbon atom, the one atomic number has the highest priority. For example,

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 next atom away from the chiral carbon atom. For example,

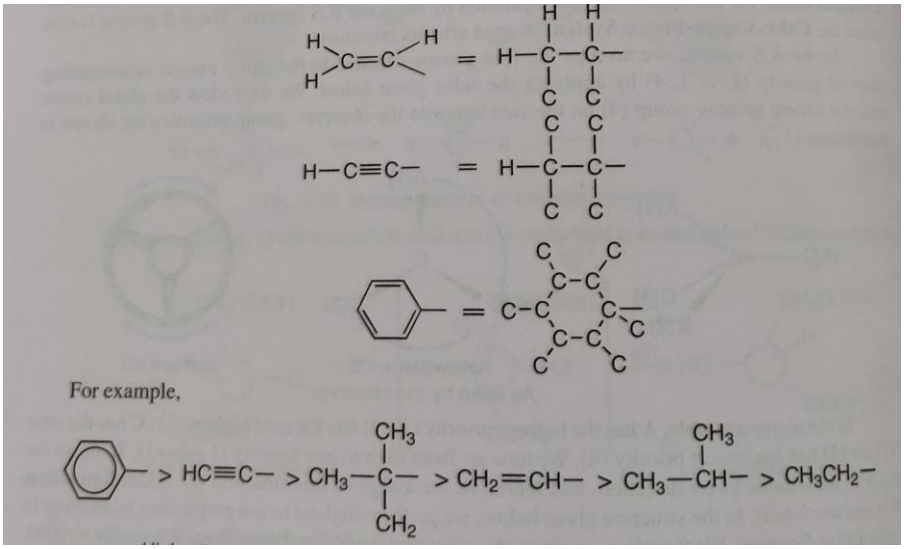


Highest---------->Lowest

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 there is 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



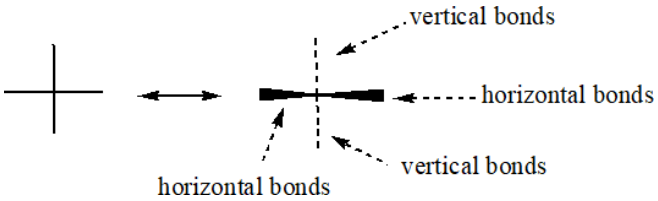
Highest----------->Lowest

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.

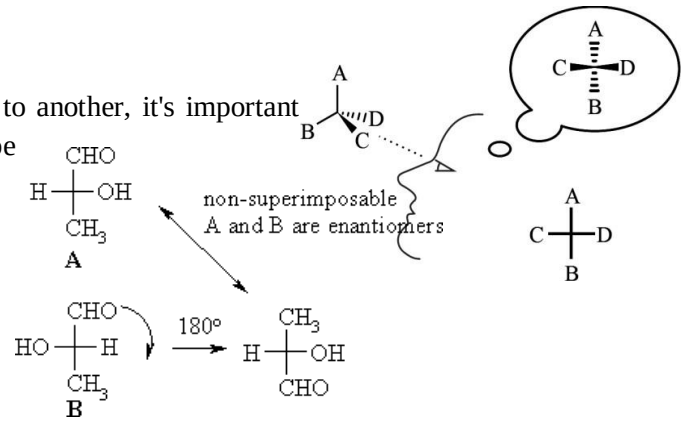
The configuration of compounds with more than one chiral center can also be specified by the R.S system. The configuration of each chiral center carbon is determined individually, using the same rules as for compounds with one chiral carbon. The configuration of all chiral centers are then specified before the name 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.

Fischer Projection

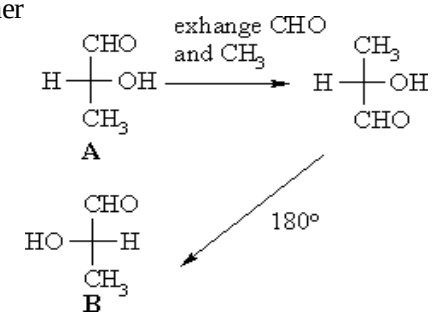
- Fischer Projections are abbreviated structural forms that allow one to convey valuable stereochemical information.
- The definition is that every carbon is specified completely by a cross designating the carbon (at the center) and the four bonds to that carbon. The stereochemistry of the bonds is defined (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).



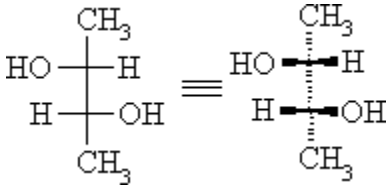
- When relating one Fischer projection to another, it's important to realised that it may only be manipulated within the 2D plane



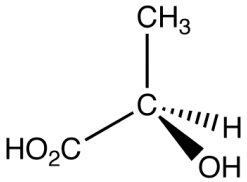
- **Why we can't rotate 90^0?** A 90^0 rotation is equivalent to breaking bonds and exchanging two groups, which would result in the formation of the other enantiomer.



- 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 dimensions with 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***

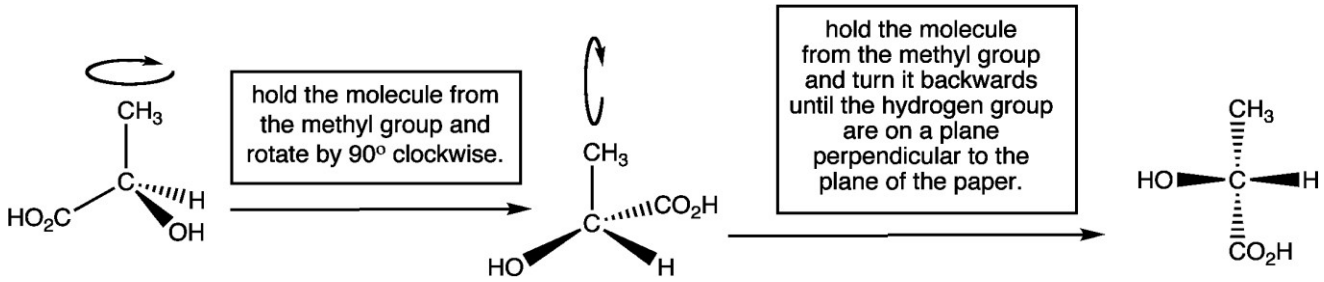
[Fischer Projection of (R)-Lactic acid]

Step 1: *Hold the molecule so that*

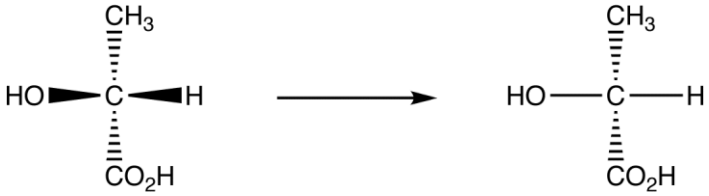
(i) The chiral center is on the plane of the paper,

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

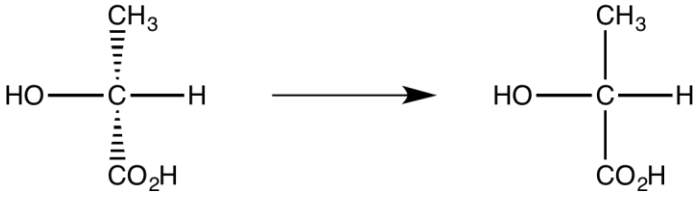
(iii) The two remaining bonds are going into the plane of the paper and are on a vertical plane.



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



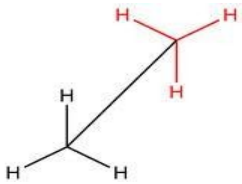
Step 3: *Pull the two bonds going into the plane of the paper onto the plane of the paper.*



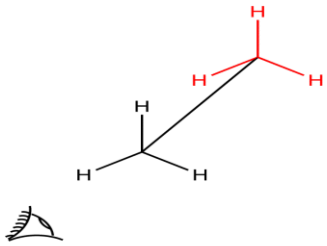
Step 4: *Omit the chiral atom symbol for convenience.*

SAWHORSE FORMULA

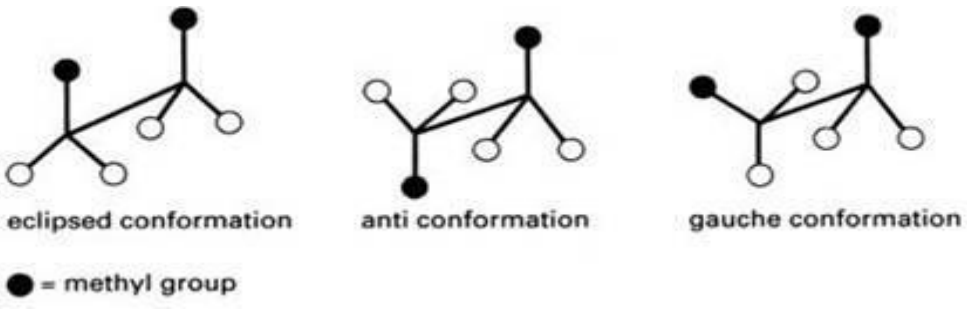
The sawhorse formula indicates the arrangement of all the atoms or groups on two adjacent carbon atoms. The bonds between the two carbon atoms are drawn diagonally and of relatively greater length for the sake of clarity. The lower left hand carbon is taken as the front carbon or towards the observer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

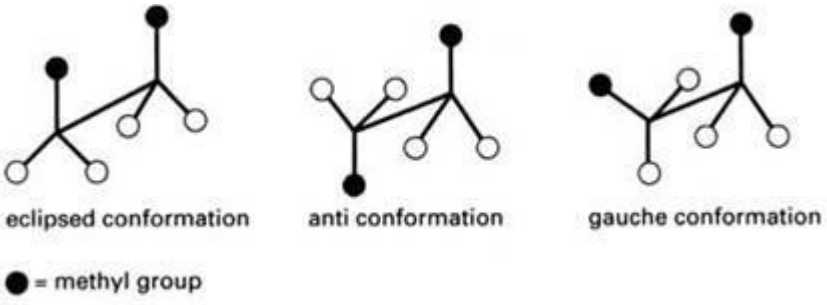


Anti conformation



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 :

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

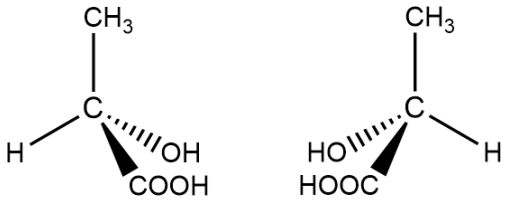
(d) reactions of chiral compounds with optically active reagents.

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

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 each other).
- 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 the mixture 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**.



(R) - Lactic Acid 50% + (S) - Lactic Acid 50%

Racemic Mixture

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 be done 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 different shape.

(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 the optically active forms more rapidly than the other.

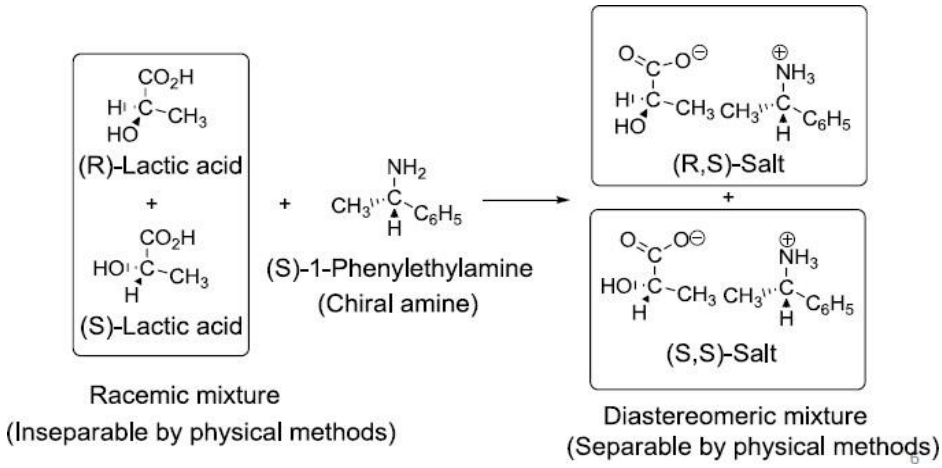
- For example, when the **mould**, **racemic ammonium tartarate**, the mould completely decomposes the **d** form white **l** form is left practically unaffected. The main drawback of the method is that half of the material is destroyed during resolution. The process is very slow and only small amounts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

(iii) ***Chemical separation:***

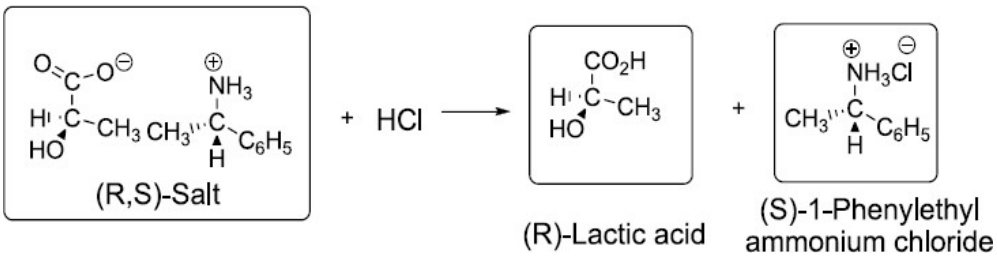
- This is probably the best method of resolution. The racemic mixture is made to combine with another optically active compound and the resulting solubility in various solvents.
- By fractional crystallization from a suitable solvent, they can be separated.
- For example, the racemic mixture of lactic acid is allowed to combine with the optically active base (-) strachnine or (+) brucine.

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

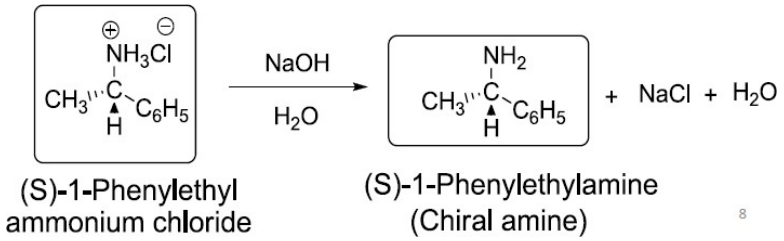
(i) ***(S)-1-Phenylethylamine*** combines with a racemic mixture of lactic acid to form **diastereomeric salts**. The diastereomers are separated by fractional crystallization.



- 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



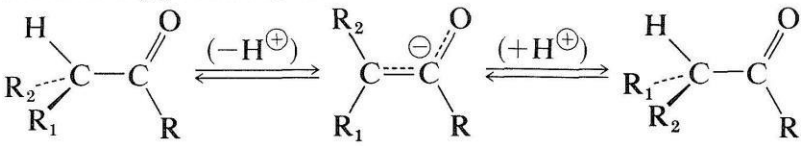
- Note that the lactic acid would be soluble in the organic layer, while the ammonium salt would be in the water layer.
- Since enantiomerically pure compounds are very expensive, it is usually necessary to recover and reuse the chiral amine. This is achieved by treating the (S)-1-phenylethyl ammonium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



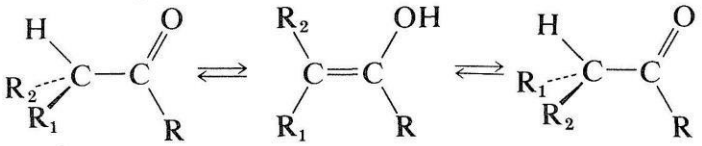
● RACEMIZATION

- **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

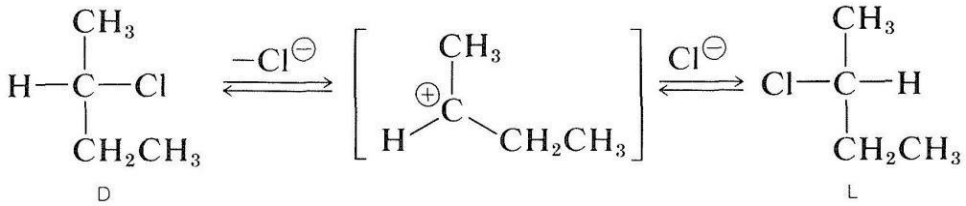
Base-catalyzed enolization



Acid-catalyzed enolization

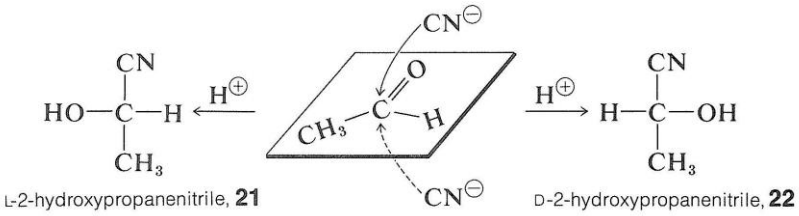


- The racemization of an optically active secondary halide with the chiral carbon carrying the halogen (e.g., 2- chlorobutane) may occur in the solution and, usually, the more polar and better ionizing the solvent is, the more readily the substance is racemized. Ionization of the halide by an **SN^1** 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:



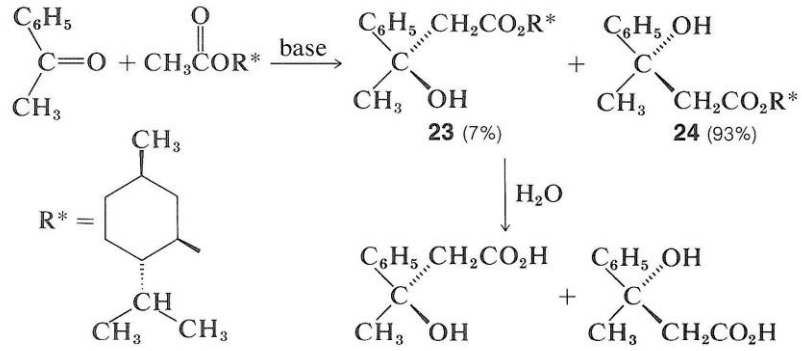
Asymmetric Synthesis

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:



L-2-hydroxypropanenitrile, **21** D-2-hydroxypropanenitrile, **22**

This obviously is unlikely for the given example because there is no reason for cyanide ion to have anything other than an exactly equal chance of attacking above or below the plane of the ethanal molecule, producing equal numbers of molecules of the enantiomers, 21 and 22 . However, when a chiral center is created through reaction with a dissymmetric (chiral) reagent, we should not expect an exactly 1:1 mixture of the two possible isomers. For example, in an aldol-type addition (Section 18-8E) of a chiral ester to a prochiral ketone the two configurations at the new chiral center in the products 23 and 24 are not equally favored. That is to say, asymmetric synthesis is achieved by the influence of one chiral center (R∗) on the development of the second:



You will notice that the reaction products 23 and 24 are diastereomers, not enantiomers. Asymmetric synthesis can be achieved only when the possible transition states for reaction are diastereomeric because they then will have different energies and will lead to products at different rates. The larger the energy difference between diastereomeric transition states, the more stereochemical preference there will be for one chirality over the other.

The degree of stereochemical control displayed by the first chiral center usually depends on how close it is to the second - the more widely separated they are, the less steric control there is. Another factor is the degree of electronic control. If all the groups are very much the same electrically and sterically, not much stereochemical control is to be expected. Even when the chiral centers are close neighbors, asymmetric induction is seldom 100% efficient in simple molecules. In biochemical systems, however, asymmetric

synthesis is highly efficient. The stereospecificity of living organisms is imperative to their efficiency.