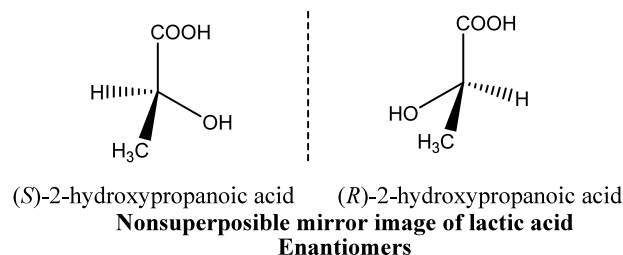


Stereochemistry

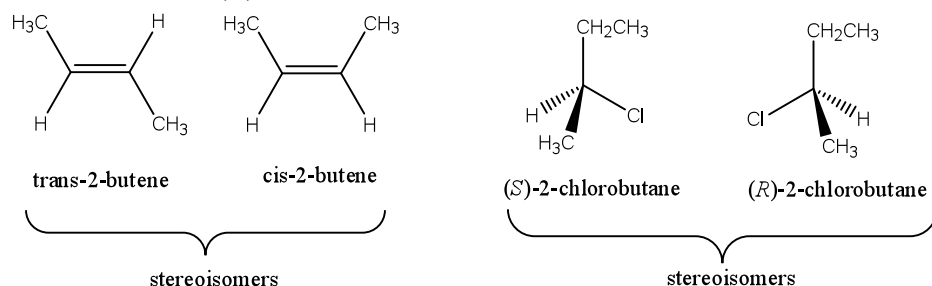
After the completion of this chapter the students should be familiar with stereoisomers, know how to differentiate between E and Z geometrical isomers, know the differences between enantiomers and diastereomers. The students should understand basic concepts like chirality, plane polarized light, specific rotation, stereocenters, maximum number of stereoisomers related to the number of chiral centers, racemic mixture, meso compound, and ways to separate enantiomers from their racemic mixture, etc.

Compounds having stereocenters (stereogenic carbons) have two or more stereoisomers. Many pharmaceuticals (drugs) are chiral compounds and consist of only one particular stereoisomer. In many cases the use of other isomers instead of a particular one is either less effective or even toxic. In other words: one of the stereoisomer might be biologically active whereas the other form(s) might not. Before 1963, racemic Thalidomide was used for the cure of morning sickness and later it was found to be the cause of several birth defects. Careful investigation highlighted that (*R*)-Thalidomide was the active agent for curing morning sickness but (*S*)-Thalidomide was responsible for serious birth defects. Similarly, (*S*)-Penicillamine is used in the treatment of arthritis, whereas (*R*)-Penicillamine is toxic; and (*S*)-Ibuprofen is active anti-inflammatory agent, whereas (*R*)-Ibuprofen is ineffective.



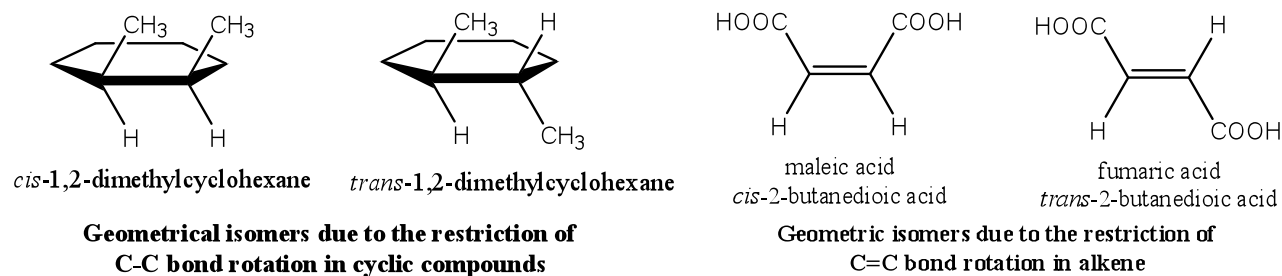
1. Stereoisomers

Compounds having same molecular formula and atomic connectivity but different arrangement of atoms or groups in space are called stereoisomers. For example: *cis*-2-butene & *trans*-2-butene and (*S*)-2-chlorobutane & (*R*)-2-chlorobutane are stereoisomers.



2.1 Geometric isomers

Compounds having same molecular formula and atomic connectivity but different arrangement of atoms or groups in space due to the restriction of C-C bond rotation in cyclic compounds or C=C bond in alkenes are called geometric isomers. Geometric Isomers are also called *cis*- and *trans*- isomers or *E* and *Z* isomers. Example:



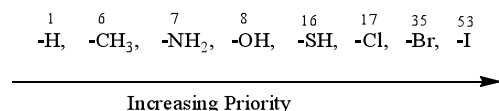
2.2 *E* and *Z* system for naming geometric isomers

When all the groups attached to the doubly bonded carbon are different it is almost impossible to name them as either *cis*- or *trans*- alkene. In such case *E* and *Z* system of nomenclature is used. *E* and *Z* system was introduced by Cahn and Ingold from England and Prelog from Switzerland. In this method the groups attached to the double bonds are assigned priority order based on the sequence rule and are named as *E* or *Z* as following.

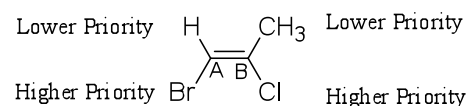
If the groups of higher priority on the double bonded carbons are on the same side then the compound is designated as *Z* (from German word *zusammen*; meaning together) and if the groups of higher priority on the double bonded carbons are on the opposite side then the compound is designated as *E* (from German word *entgegen*; meaning opposite).

Sequence rule

1. The atom directly attached to the doubly bonded carbon with higher atomic number has higher priority.

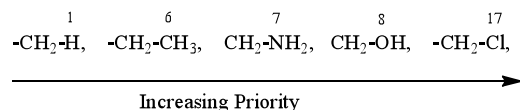


For example: In 1-bromo-2-chloroprop-1-ene, Bromine (atomic number 35) and Hydrogen (atomic number 1) are attached to carbon designated as A and Carbon (atomic number 6) and Chlorine (atomic number 17) are attached to the carbon designated as B. Bromine has higher priority than hydrogen and chlorine has higher priority than carbon (of methyl group). In this case the atoms or groups with higher priority are in the same side; therefore, the compound is named by prefixing *Z* in parenthesis.

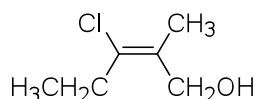


(*Z*)-1-bromo-2-chloroprop-1-ene

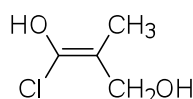
2. If two or more than two atoms directly attached to the doubly bonded carbon are same, then atomic number of the next atom is considered. This process is continued till the priority order of the groups is assigned.



For example:

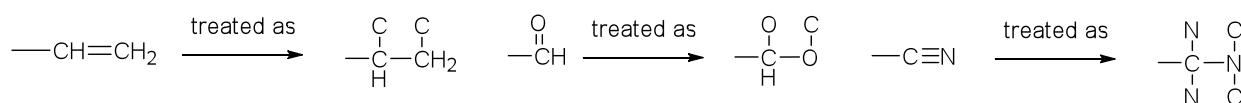


(*E*)-3-chloro-2-methylpent-2-en-1-ol

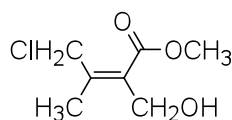


(*Z*)-1-chloro-2-methylprop-1-ene-1,3-diol

3. Atoms participating in a double bond are considered as duplicated and triple bonds are triplicated.



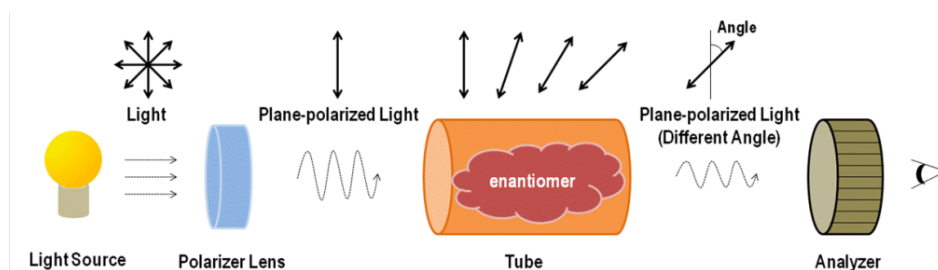
For example:



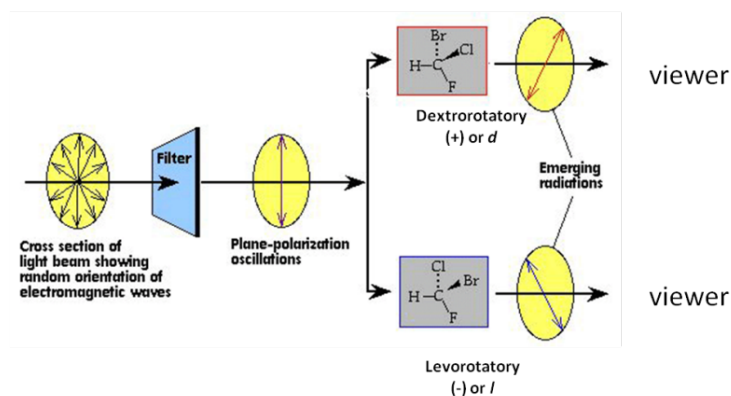
(*Z*)-methyl 4-chloro-2-(hydroxymethyl)-3-methylbut-2-enoate

3.1 Optical Activity and Chirality

Compounds that can rotate the plane polarized light are called optically active compounds. Many drugs both natural and synthetic are optically active. Light is an electromagnetic radiation. The electric and magnetic vectors are perpendicular to each other. In a normal light the electric vector oscillates in all planes perpendicular to the direction of its propagation. However, when such light is allowed to pass through a polarizer like Nicol Prism (crystalline calcium carbonate), the emerging light has the electric vector oscillating only in one plane. Such light is called plane polarized light.



In this case the enantiomer is dextrorotatory and is designated as (+) or *d*



Any object or compound whose mirror image is not superposable to itself is chiral (ki-ral) compounds. For example, our hand is chiral because the mirror image of right hand is a left hand and is not superposable to each other. On other hand, any object or compound whose mirror image is superposable to itself is called achiral objects or compounds. For example, a perfect sphere is achiral. Chiral substances lack plane of symmetry; whereas, achiral substances have a plane of symmetry. Chiral substances are optically active and exist as a pair of enantiomers. If a compound rotates plane-polarized light in the clockwise direction (right) it is said to be dextrorotatory (Latin; *dexter*, right) and is denoted by adding (+)- or *d*- in front of the name of the compound. Similarly, if a compound rotates plane-polarized light in the anticlockwise direction (left) it is said to be levorotatory (Latin; *laevus*, left).

3.2 Specific rotation

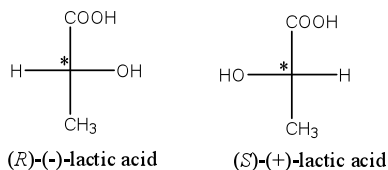
The degree of rotation (α) of plane polarized light depends on the nature of the substance, temperature, wave length of light used, length of the sample tube, and concentration of the sample (or density of the sample). In order to express measured rotation on standard basis, chemists calculate a quantity called the specific rotation, $[\alpha]$.

$$\text{Specific rotation } [\alpha]_{\lambda}^t = \alpha c \times l \text{ (solvent)}$$

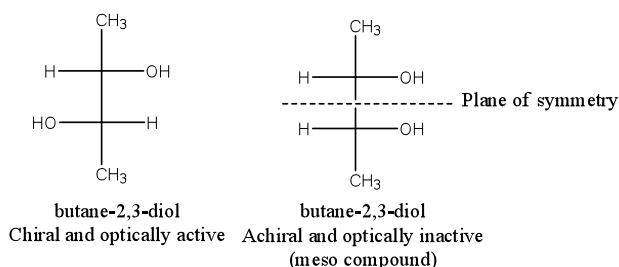
Where, α = the observed rotation; t = temperature in degrees Celsius; λ = wavelength of light used (generally 589.6 nm; D line of sodium light), c = concentration of solutions in grams per milliliter (or density in g mL^{-1} for neat liquids), and l = length of the sample tube in decimeters (1 dm = 10 cm).

3.3 Stereocenter or stereogenic carbon

Carbon connected to four different groups is called stereocenter or asymmetric carbon or stereogenic center or chiral carbon and is denoted by asterisk (*). Compound having one stereocenter is always chiral and exists as a pair of enantiomers. Compounds having more than one stereocenters (asymmetric or chiral carbon) may or may not be chiral. Chiral compounds are optically active and achiral compounds are not.



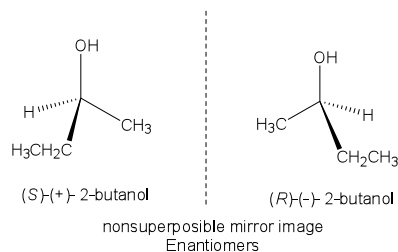
Lactic acid exists in two enantiomeric forms because of the presence of one stereoisomers



4. Enantiomers (Optical isomer)

Enantiomers are stereoisomers that are nonsuperposable mirror image of each other. Enantiomers have same physical properties except they differ in the interaction with plane polarized light. Enantiomers rotate plane polarized light in opposite directions but with same magnitude. For example, specific rotation, $[\alpha]_{\text{D}(589.6 \text{ nm})}^{25}$ of (S)-2-Butanol is +13.52 (+ indicates dextrorotatory) and $[\alpha]_{\text{D}(589.6 \text{ nm})}^{25}$ of (R)-2-

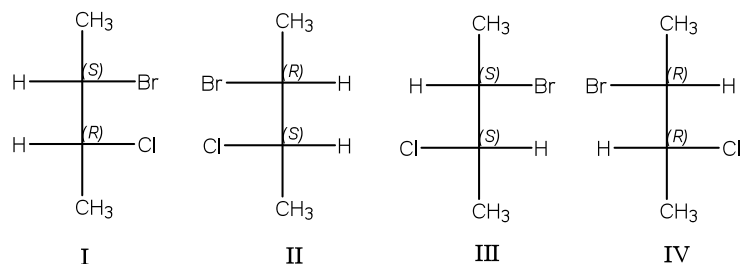
Butanol is -13.52 (- indicates levorotatory). Similarly, (*R*)-(-)-lactic acid and (*S*)-(+)-lactic acid have specific rotation, $[\alpha]^{25}_{D(589.6\text{ nm})}$, of -3.33 and $+3.33$ respectively.



Chemical properties of enantiomers depend on the reaction condition. In achiral reaction condition (chemicals like reagents, catalyst, solvent, etc. are achiral) enantiomers have identical chemical properties; however, under chiral condition (if one or more of the chemicals used are chiral) then the enantiomers differ in chemical reactivity. Many enantiomers behave differently in organism. Few examples are given below:

1. Enzymes in our body can only act on L-amino acids
2. (*R*)-Thalidomide is useful in curing morning sickness in pregnant women; whereas, (*S*)-Thalidomide is found responsible in birth defects.
3. Enzyme called lactic acid dehydrogenase oxidizes (*S*)-(+)-lactic acid but has no effect on (*R*)-(-)-lactic acid.
4. (*S*)-Penicillamine is used in the treatment of arthritis; whereas, (*R*)-Penicillamine is toxic.
5. (-)-Adrenalin is cardiac stimulant; whereas, (+)-adrenalin has no effect.
6. (*S*)-Ibuprofen is active as anti-inflammatory agent; whereas, (*R*)-Ibuprofen has no effect.

Similarly, in 2-bromo-3-chlorobutane, compound I & II and compound III & IV are enantiomers because they are nonsuperposable mirror image of each other. They are chiral and are optically active. The structures of all stereoisomers are highlighted in the section



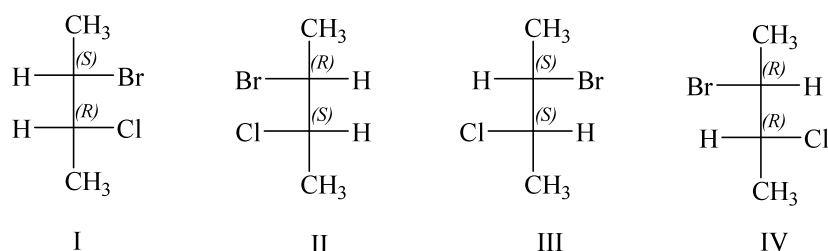
5. Racemic mixture

A mixture containing equimolar amount of pair of enantiomers is called racemic mixture or racemic modification. For example 1: 1 molar mixture of (*R*)-2-butanol and (*S*)-2-butanol will form a racemic

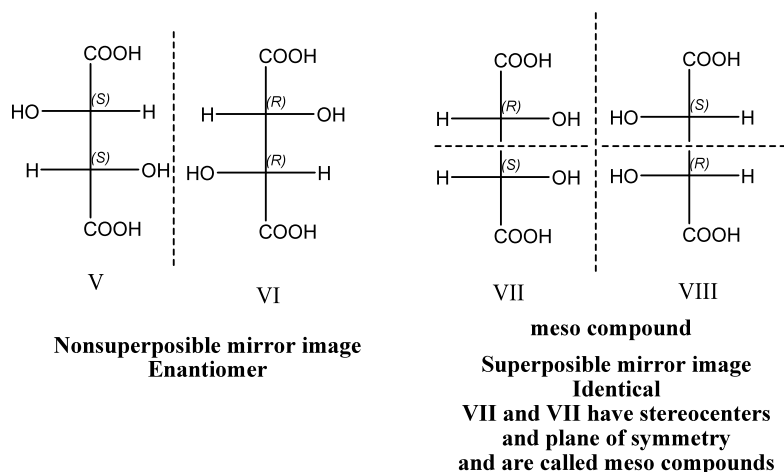
mixture and is represented as (\pm)-2-butanol or (*dl*)-2-butanol. A racemic mixture is optically inactive due to external compensation because the degrees of plane polarized light rotated by one enantiomer is cancelled by the other. A method of separating enantiomers from their mixture is called racemic modification and will be discussed later in this chapter. The process of converting one pure enantiomer to a racemic mixture is known as racemization.

6. Stereoisomerism in compound having two stereogenic center (asymmetric carbon or stereocenters)

The maximum number of stereoisomers for a compound having n number of stereocenter is given by 2^n rule. Compounds having one stereocenter ($n=1$) will always exist as a pair of enantiomers. As discussed earlier lactic acid has one stereocenter and exists as a pair of enantiomers. For compound having 2 stereocenters, the maximum number of stereoisomers possible is 4. For example 2-bromo-3-chlorobutane exists in the form of 4 stereoisomers.



Structures I, II, III, and IV are all the four stereoisomers possible for 2-bromo-3-chlorobutane. Structures I & II and structures III & IV are nonsuperposable mirror image of each other and are enantiomers (I & II are enantiomers and III & IV are enantiomers). Structures I & III are not the mirror image of each other but are stereoisomers. Stereoisomers which are not the mirror image of each other are called as diastereomers. Similarly, structures I & IV, structures II & III, and II & IV are diastereomers. Diastereomers have different physical properties. As enantiomers the chemical properties of diastereomers depends on the nature of the reagent. For chiral reagent their chemical properties are different but for achiral reagent they are same. They can be easily separated by physical methods like crystallization, fractional distillation, chromatography, etc. Similarly, let us also analyze all the stereoisomers of tartaric acid (2,3-dihydroxybutanedioic acid).



Compound V and VIII or compound VI and VIII are not mirror image but are stereoisomers called diastereomers.

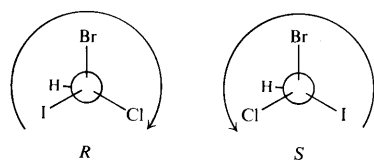
Structures V & VI are nonsuperposable image of each other, hence are enantiomers. Structure VII & VIII are mirror image but are superposable; therefore, are identical because of the plane of symmetry which dissects the molecule into two identical halves. Thus tartaric acid only has three stereoisomers. Compound V & VIII and compound VI & VIII are diastereomers because they are stereoisomers but not the mirror image of each other. Compound VII or VIII have a plane of symmetry so are achiral and optically inactive so are called meso compound. Meso compound are optically inactive due to internal compensation, i.e, the degree of plane polarized light rotated by one half is cancelled by the rotation of plane polarized light by the other half.

7. Sequence rule for assigning *R* or *S* configuration to the stereocenters

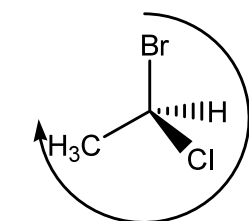
This rule was developed by Cahn, Ingold, and Prelog to assign *R* and *S* configuration to the stereocenters. This system of nomenclature is also known as *R, S*-system or Cahn-Ingold-Prelog system and has been a part of IUPAC system.

1. All the four groups are assigned priority by the sequence rule discussed earlier in this chapter.
2. The group with the least priority is then directed away from the observer. If the path traced by the groups from higher priority to lower priority follows clockwise direction then the stereocenter is assigned (*R*) configuration (*R* derived from Latin word *rectus* meaning right). If the path traced by the groups from higher priority to lower priority follows anticlockwise direction then the stereocenter is assigned (*S*) configuration (*S* derived from Latin word *sinister* meaning left).

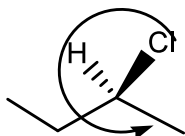
For example:



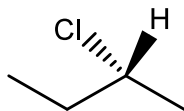
Few more examples:



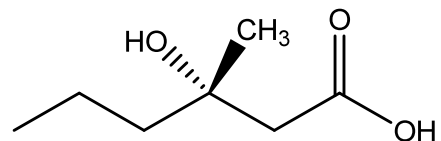
(*R*)-1-bromo-1-chloroethane



(*S*)-2-chlorobutane

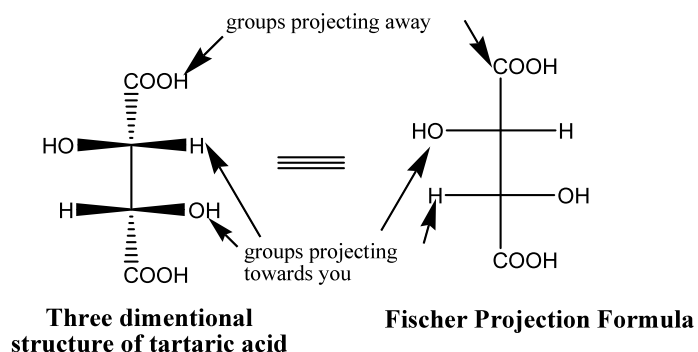


(*R*)-2-chlorobutane
(find how?)

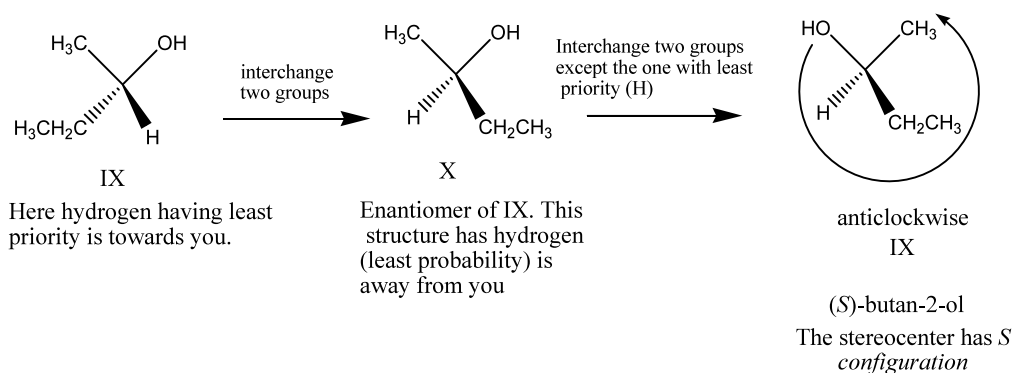


(*S*)-3-hydroxy-3-methylhexanoic acid
(find how?)

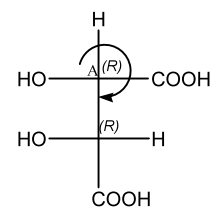
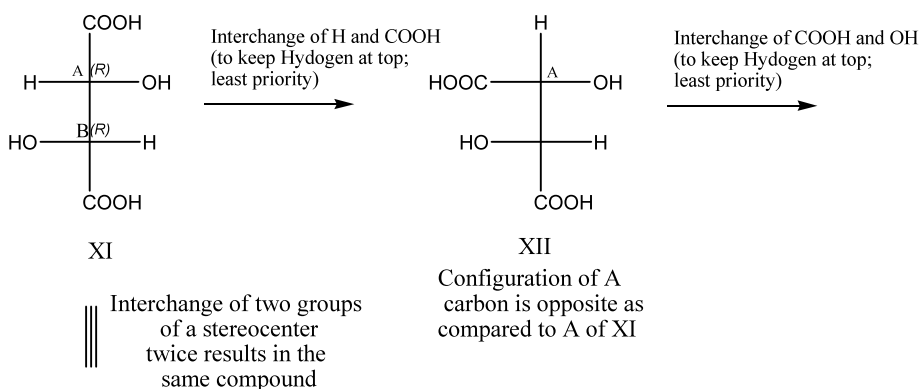
In Fischer projection formula, the groups represented on the vertical line are directed away from the observer and the groups represented on the horizontal line are directed towards the observer.



When assigning *R* and *S* configuration make sure to keep the group with lower priority away from you. Interchanging two groups twice and keeping the atom or group with least priority on top or bottom (vertical) in Fischer projection formula (two dimension) or away from you in a three dimensional formula results in identical structure.



The compound IX has one stereocenter and has S configuration. Note: interchange of two groups twice results in the same compound. Interchange of two groups once results in enantiomer.



Similarly, the configuration of B carbon of XI can be determined as has R configuration

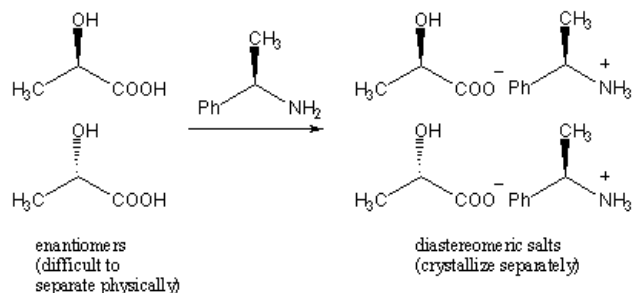
8. Resolution of enantiomers from racemic mixture (racemic modification)

Separation of enantiomers from their racemic mixture is known as resolution of enantiomers. The separation of enantiomers has always been a big problem for chemists. Enantiomers have same physical properties so many of the techniques used to separate other compounds don't work to separate enantiomers from racemic mixtures. Some methods for the resolution of enantiomers from their racemic mixture are as follows:

Chemical Method

One technique frequently used is to convert the enantiomers to diastereomers by reacting the racemic mixture with a pure chiral reagent (*R* or *S* enantiomer of other substance). Since the diastereomers have

different physical properties so can be separated by methods like crystallization, fractional distillation, etc. For example, if we want to separate the enantiomers of 2-hydroxypropionic acid, we add an enantiomerically pure (*R*)-2-phenyl-ethylamine as a resolving agent. The two enantiomers interact with (*R*)-2-phenyl-ethylamine to form two distinct salt species that are diastereomers of each other. The diastereomers can then be crystallized separately. After the separation of diastereomers, the added optically active pure reagent is removed to get pure enantiomers.



Mechanical Method

This method was first used by Lewis Pasteur for separating the enantiomers of ammonium tartarate. When the racemic mixture is crystallized, two types of crystals are formed, which are mirror image of one another. With great care, the two different crystals can be separated using a pair of tweezers and a powerful lens. This type of separation is followed only when the enantiomers form good and distinguishable crystals.

Biochemical separation

Certain microorganism or enzymes when added to racemic mixture will consume one enantiomers leaving the other unaffected. For example, when penicillium (fungi) is allowed to grow in a racemic mixture (\pm) of tartaric acid, the (+) tartaric acid is consumed leaving (-) tartaric acid.