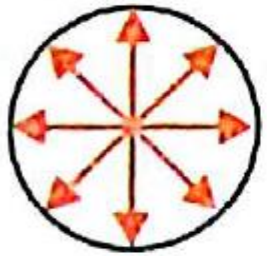
Optical Isomerism

OPTICAL ISOMERISM

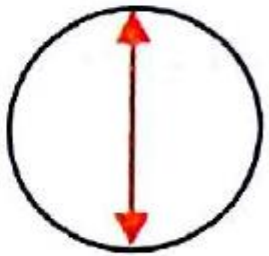
What is Optical Activity:

Optical isomerism is type of stereoisomerism. Optical isomers have the ability to rotate the plane polarized light. This property is often referred as **Optical Activity.**

A beam of ordinary light consists of electromagnetic waves that oscillate in an infinite number of planes at right angles to the direction of light travel. When a beam of ordinary light is passed through a device called a polarizer, or a Nicol prism (made of calcite or $CaCO_3$), light is found to vibrate in only one plane and is said to be plane-polarized. Light waves in all other planes are blocked out.



Ordinary Light



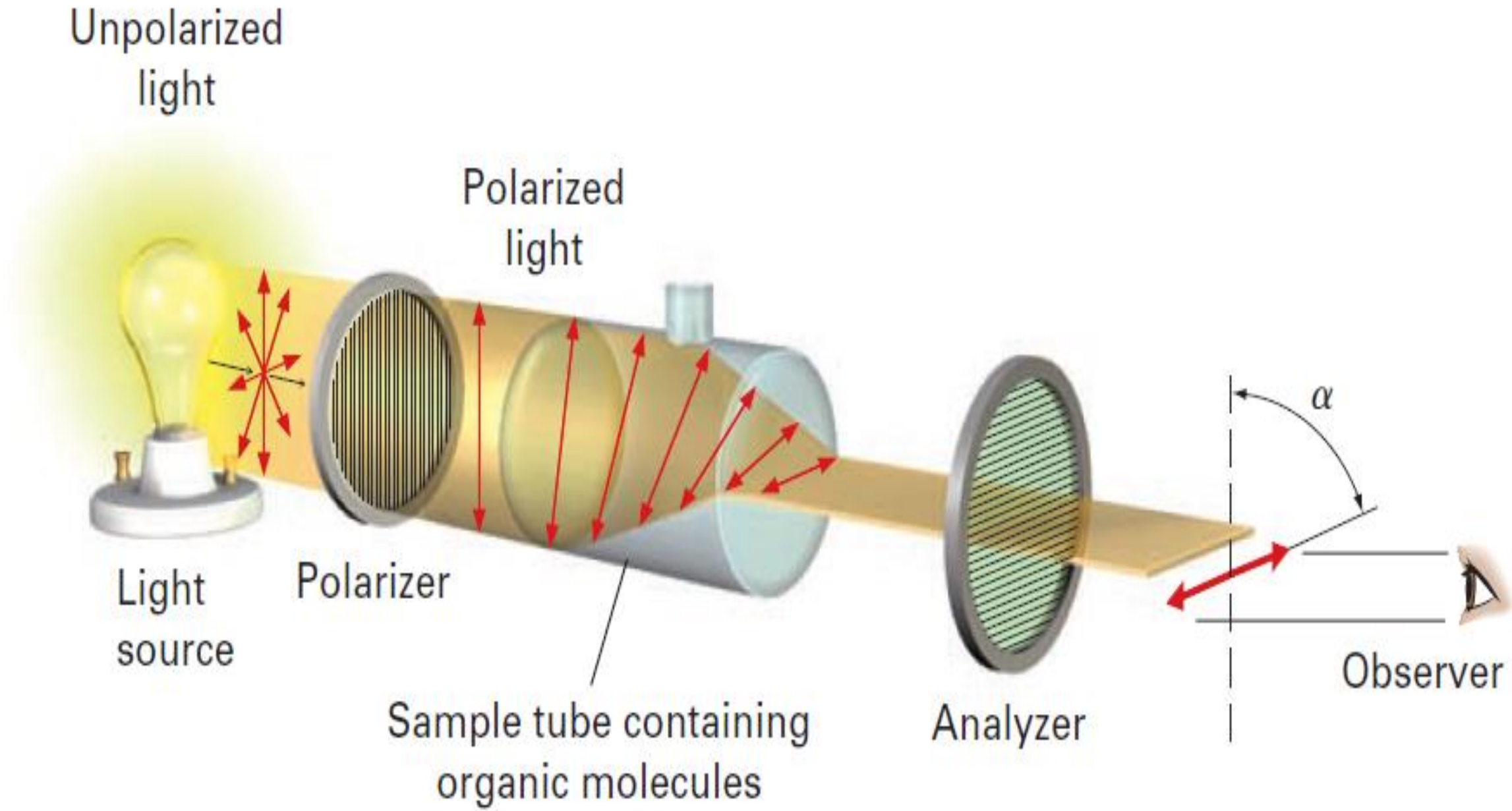
Plane-Polarized Light
(Polarised Light)

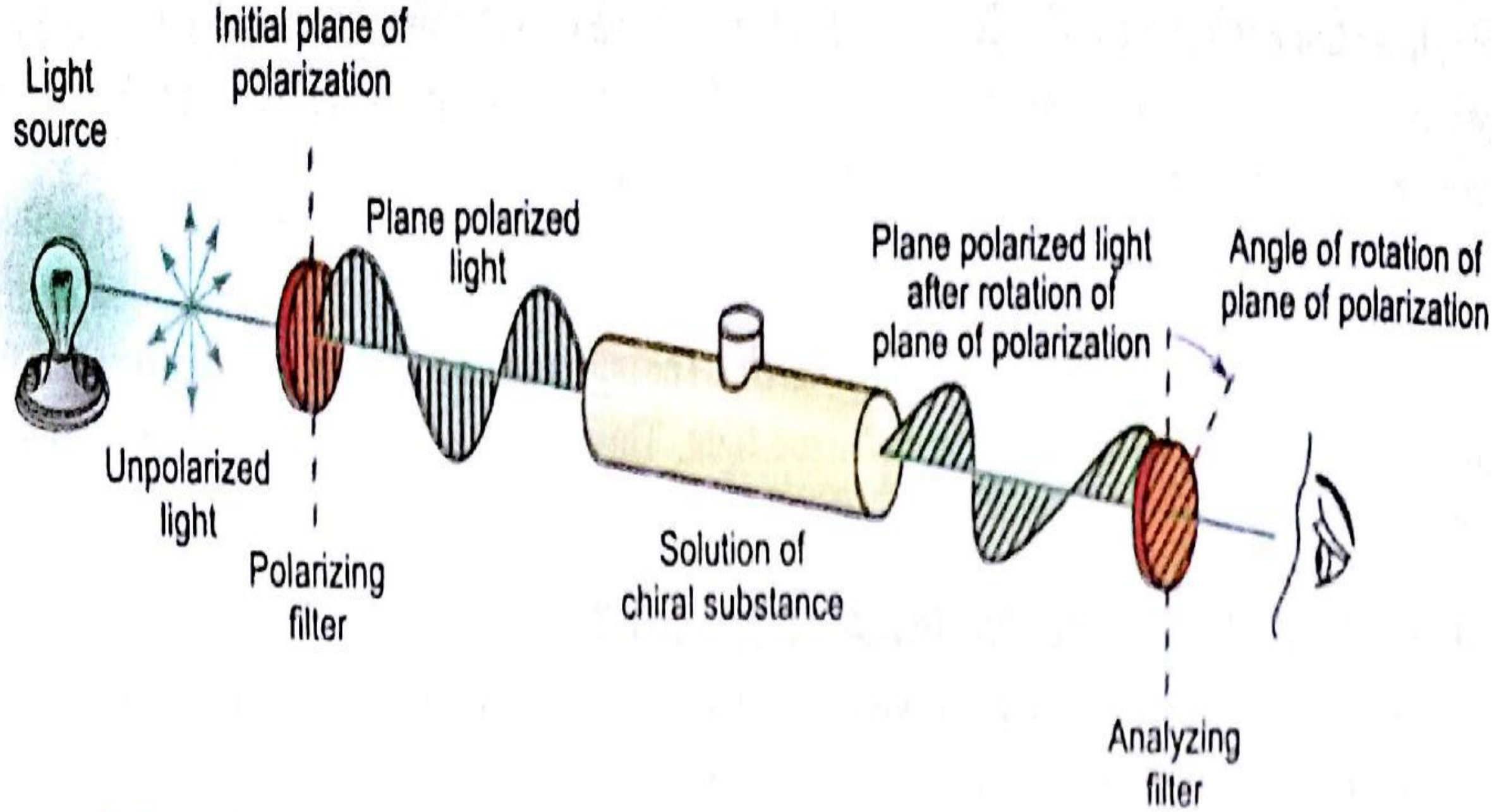
Optically Active Compounds

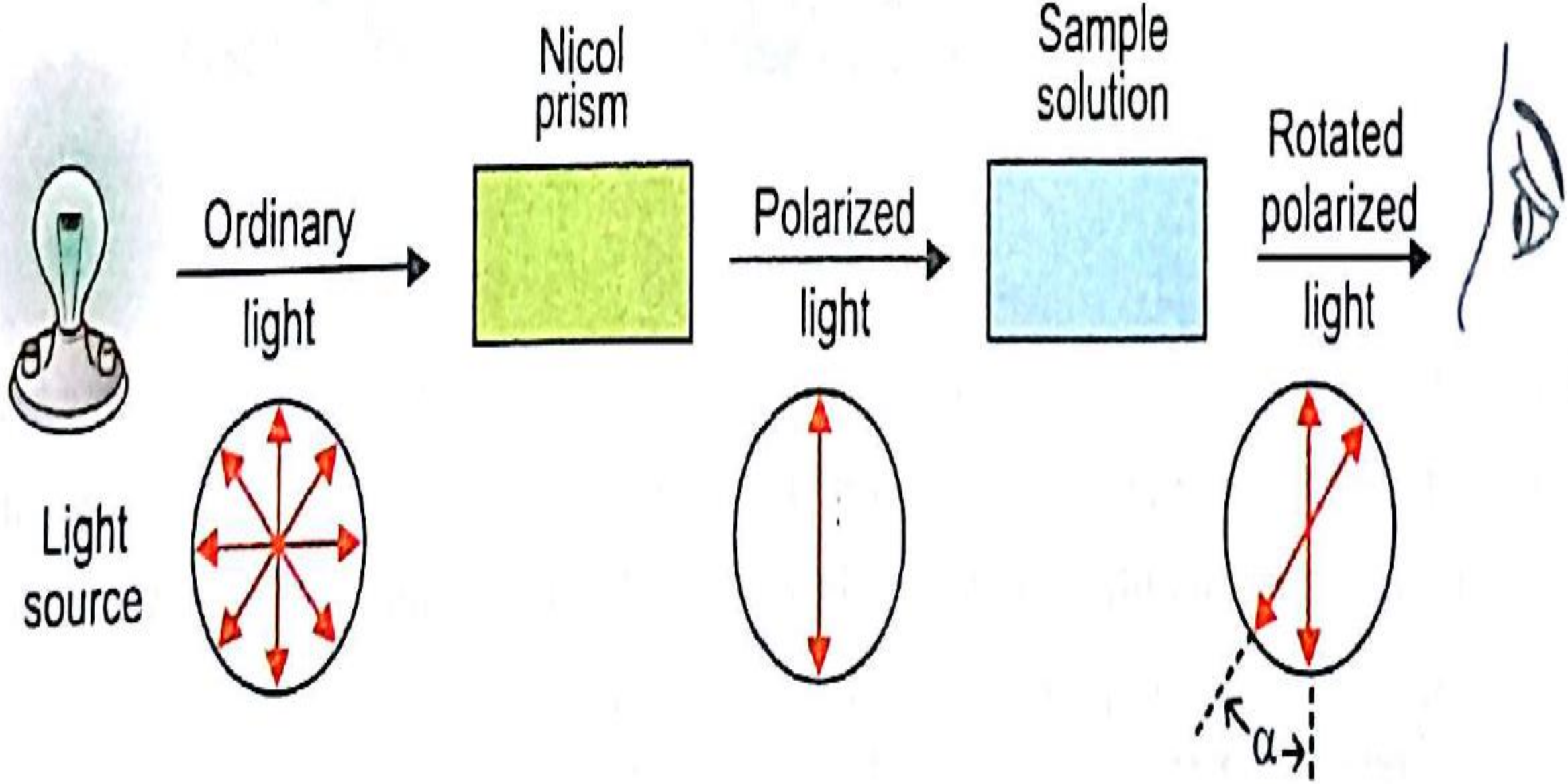
When a beam of plane polarized light passes through a solution of certain organic molecules, such as sugar or camphor, the plane of polarization is rotated through an angle **α**. Not all organic substances exhibit this property, but those that do are said to be **optically active.**

The angle of rotation can be measured with an instrument called a **polarimeter**. When a solution of known concentration of an optically active material is placed in the polarimeter, the beam of light is rotated either to the right (clockwise) or to the left (anti-clockwise). So the compounds which rotate the **plane polarized light (PPL**) to the right (clockwise) is said to be **Dextrorotatory**, and those which rotate the PPL to the left is said to be **Levorotatory.** Dextrorotatory is indicated by **+ sign,** while Levorotatory by a **minus sign (–)**

(–)-Morphine, for example, is levorotatory, and (+)-sucrose is dextrorotatory.


Unpolarized light
Polarized light
Light source
Polarizer
Sample tube containing organic molecules
Analyzer
α
Observer


Light source
Initial plane of polarization
Plane polarized light
Plane polarized light after rotation of plane of polarization
Angle of rotation of plane of polarization
Unpolarized light
Polarizing filter
Solution of chiral substance
Analyzing filter


Nicol prism
Sample solution
Ordinary light
Polarized light
Rotated polarized light
Light source
α

Specific Rotation

The extent of rotation depends on the number of optically active molecules encountered by the light beam. This number, in turn, depends on sample concentration and sample path length. If the concentration of sample is doubled, the observed rotation doubles. If the concentration is kept constant but the length of the sample tube is doubled, the observed rotation doubles. In addition, the angle of rotation depends on the wavelength of the light used.

To express optical rotations in a meaningful way so that comparisons can be made, we have to choose standard conditions. **The specific rotation**, $[\alpha]_D$, of a compound is defined as *"the observed rotation when light of **589.6 nanometer** (nm; 1 nm = 10^{-9} m) wavelength is used with a sample path length **ℓ** of **1 decimeter** (dm; 1 dm = 10 cm) and a sample concentration **c** of **1 g/cm3"**.*

$$[\alpha]_{\mathrm{D}} = \frac{\text{Observed rotation (degrees)}}{\text{Pathlength, } l \text{ (dm)} \times \text{ Concentration, } c \text{ (g/cm}^3\text{)}} = \frac{\alpha}{l \times c}$$

When optical rotation data are expressed in this standard way, the specific rotation, $[\alpha]_D$, is a physical constant characteristic of a given optically active compound. For example, (+)-lactic acid has $[\alpha]_D = +3.82$, and (–)-lactic acid has $[\alpha]_D = -3.82$. That is, the two enantiomers rotate plane-polarized light to the same extent but in opposite directions.

Specific Rotation of Some Organic Molecules

Compound	$[\alpha]_D$	Compound	$[\alpha]_D$
Penicillin V	233	Cholesterol	−31.5
Sucrose	+66.47	Morphine	−132
Camphor	+44.26	Cocaine	−16
Chloroform	0	Acetic acid	0

Three lactic acids are known.

(a) (+)-lactic °acid, *(b)* **(—)-**lactic acid, and *(c)* ± mixture.

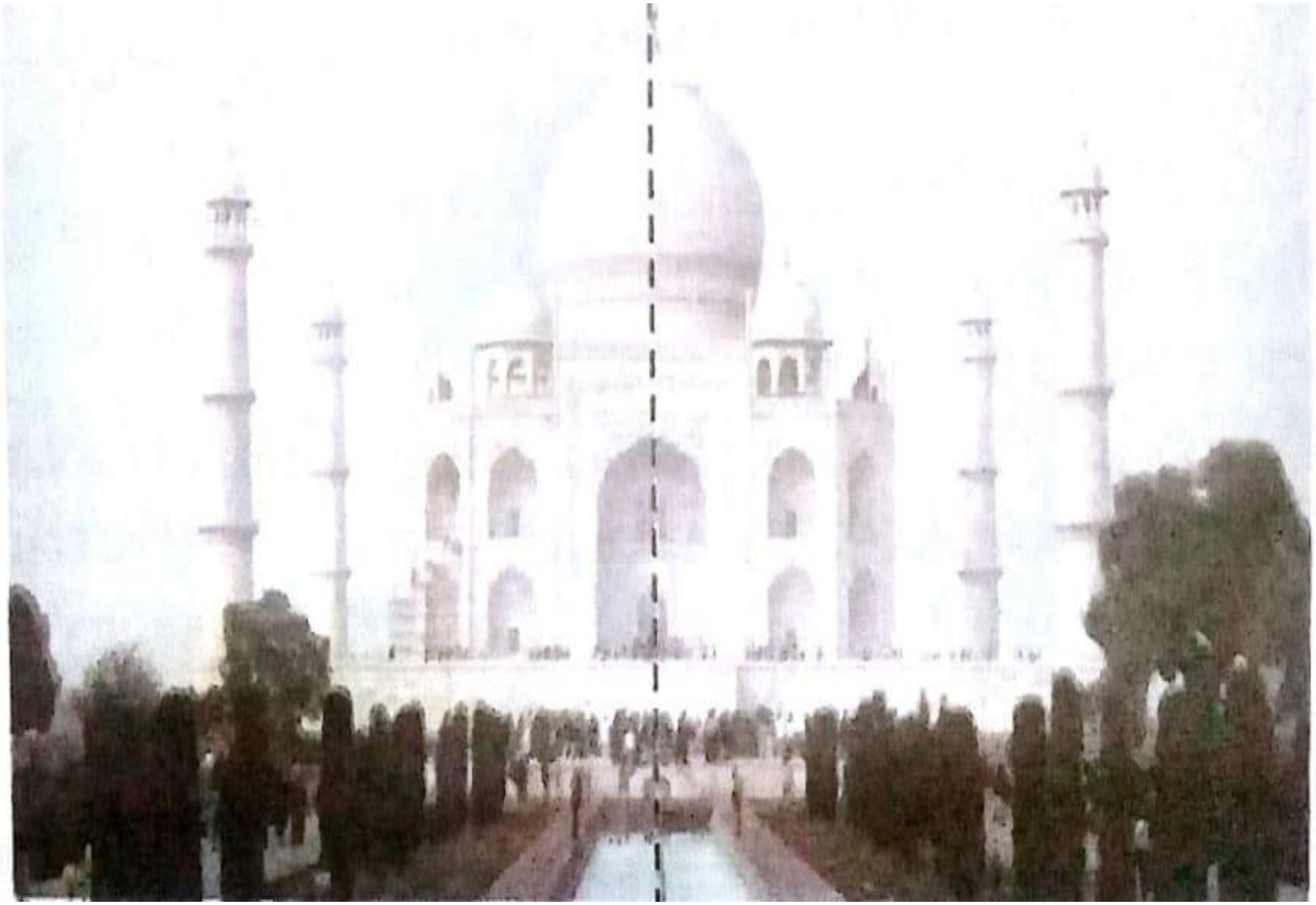
Since the (±) acid is only a mixture of (+) and **(-)-**forms, in reality lactic acid exist in two forms, the (+)-lactic acid and the **(—)-**lactic acid. These two acids are exactly identical in physical and chemical properties but differ in their action on the plane polarized light.

So such forms of the same compound which differ only in their optical properties are called **Optical isomers** and the phenomenon is termed **Optical isomerism**

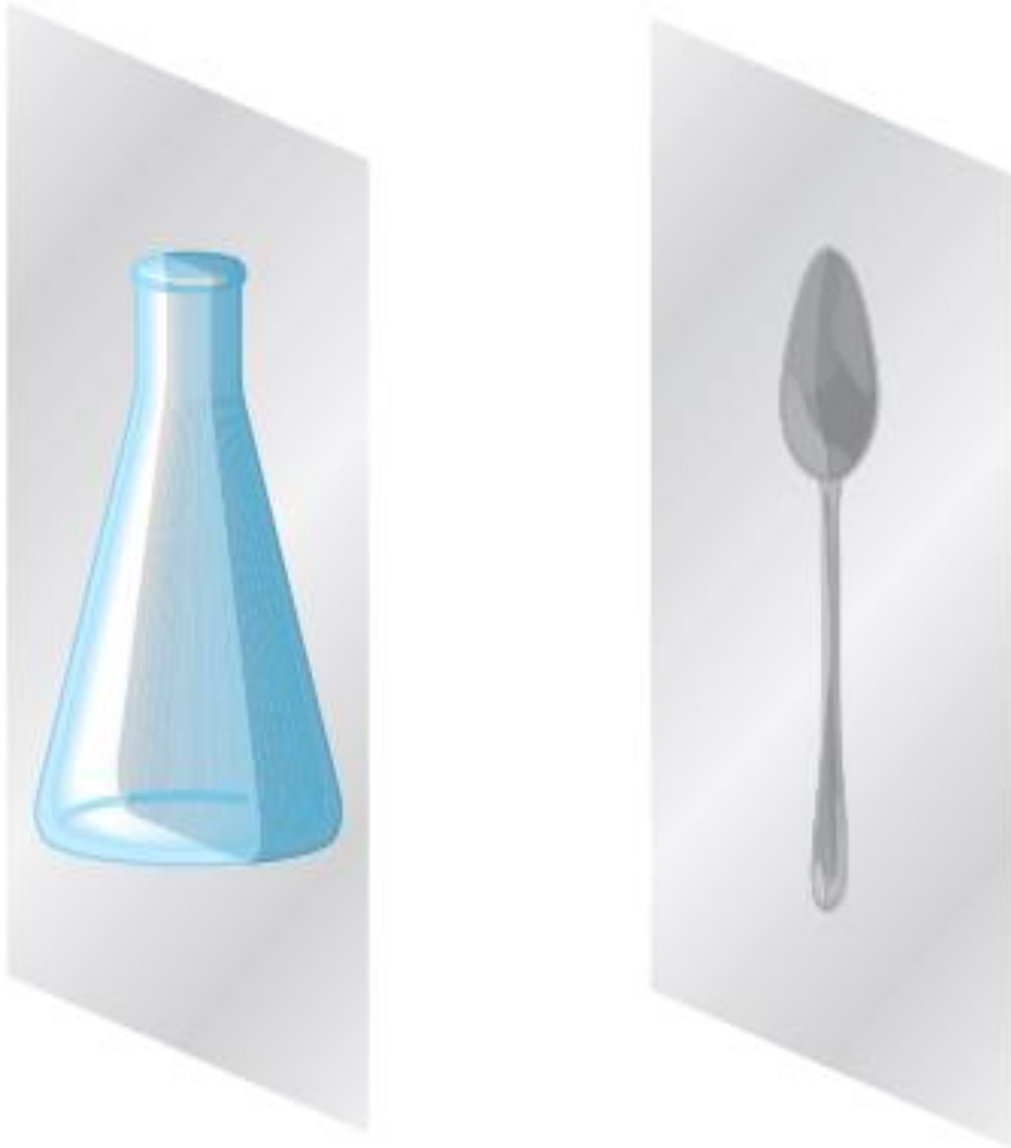
An optically active compounds exists in two isomeric forms that rotate the plane polarized light in opposite directions. The optical rotatory power of two isomers are equal in magnitude but opposite in direction.

Plane of Symmetry

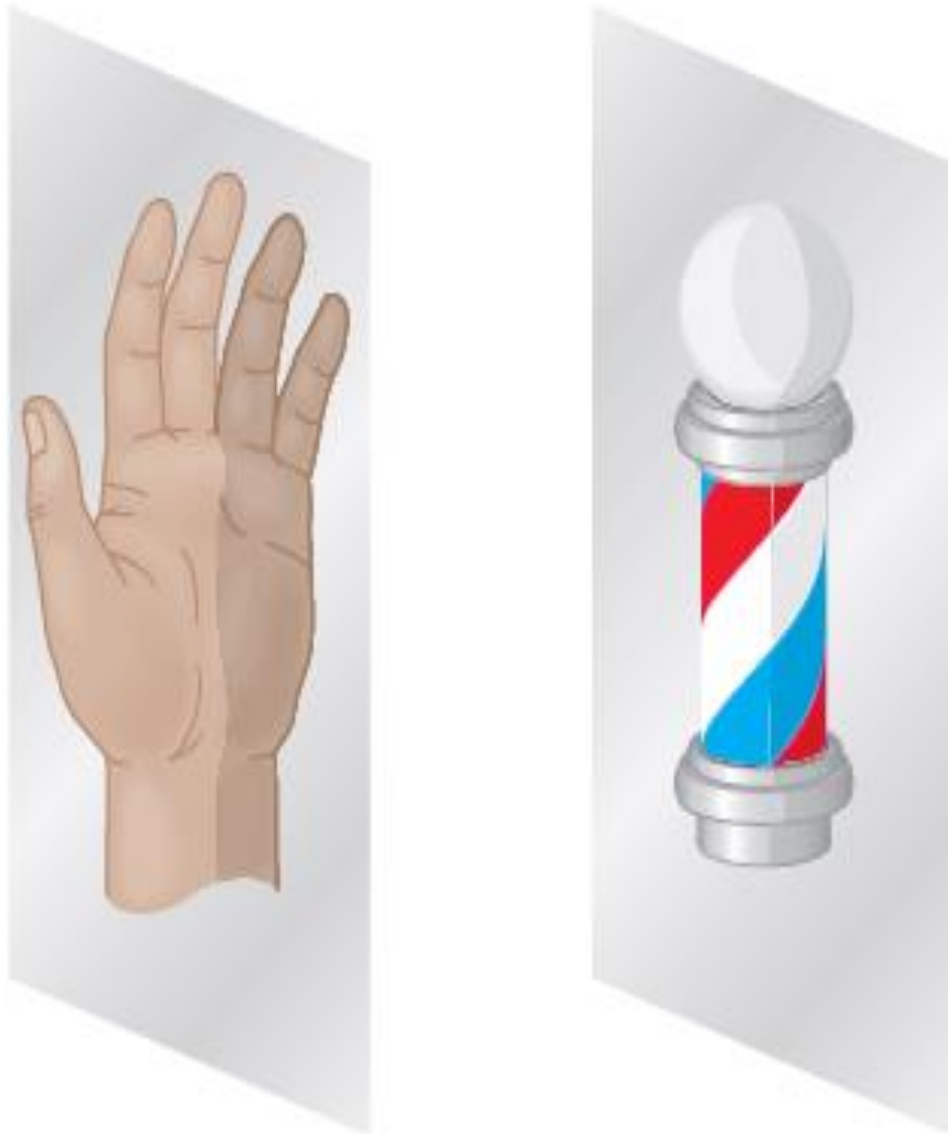
A plane which divides an object to two equal halves is said to be plane of symmetry. For example, coffee cup has a plane of symmetry in comparison with a person's hand or shoes which lack a plane of symmetry. An object lacking a plane of symmetry is called **Chiral or Dissymmetric**, while those having a plane of symmetry is referred to as **Achiral.**

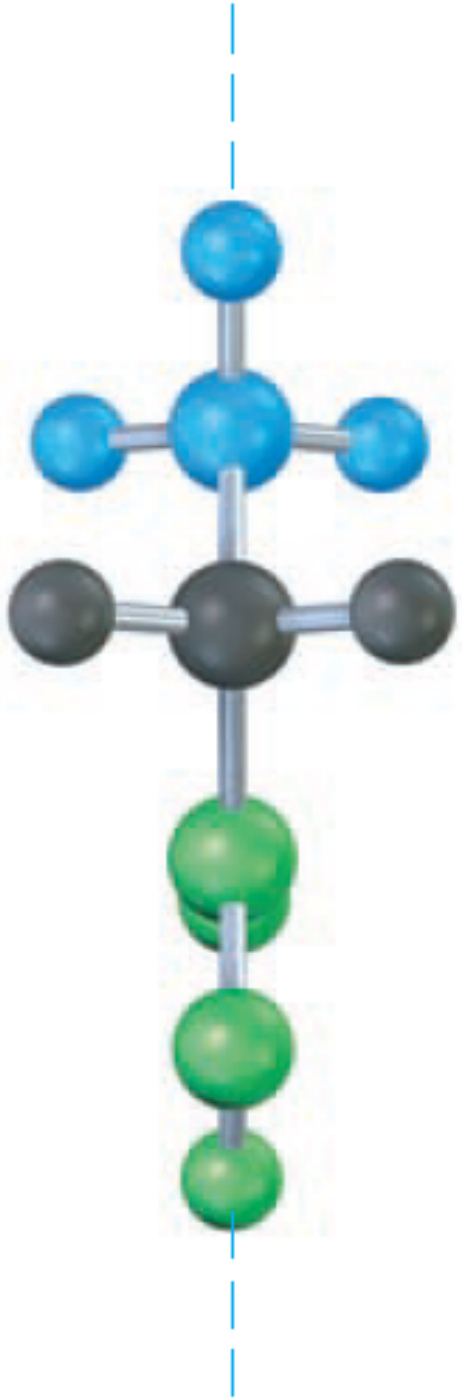


(a)

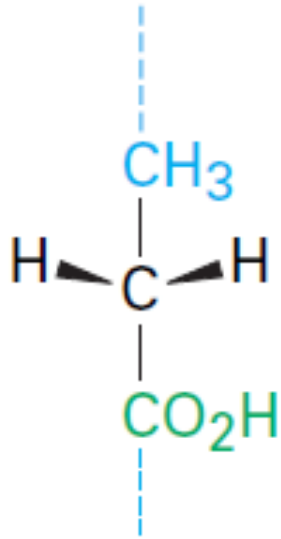


(b)





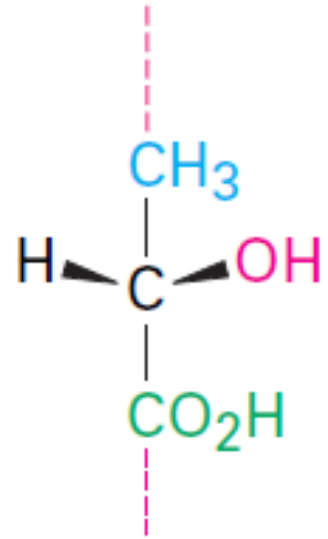
Symmetry plane

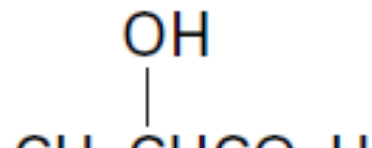


$CH_3CH_2CO_2H$

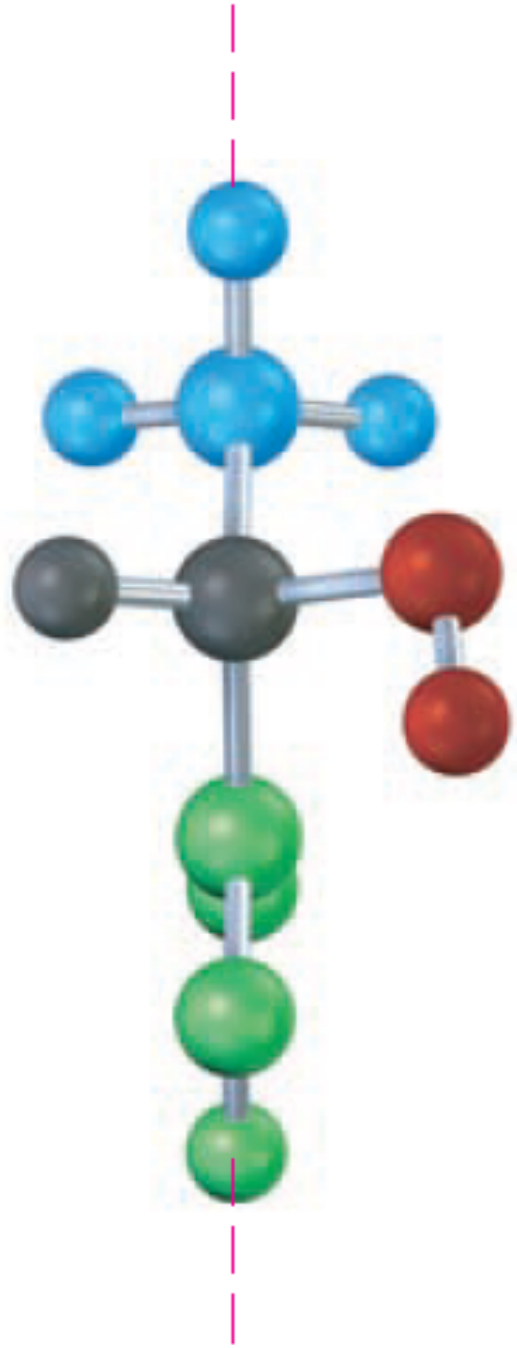
Propanoic acid (achiral)

NOT symmetry plane





Lactic acid (chiral)



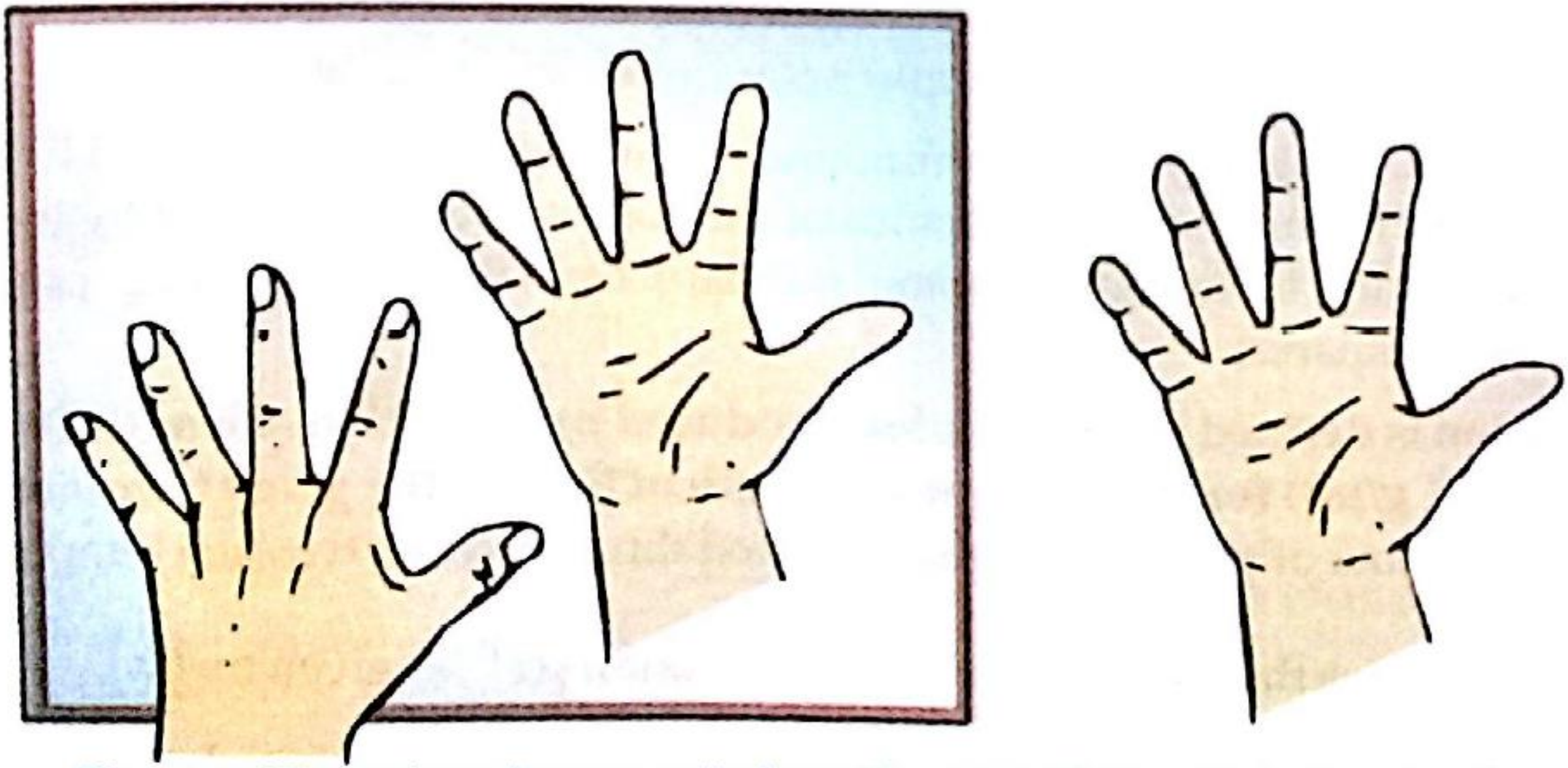


Fig. 4.4. The mirror image relationship of the left and right hands. Notice that right hand is the mirror image of the left hand.

Chiral Carbon Atom

A carbon atom which is bonded to four different groups. It is also termed as **handedness**. Chiral carbon lacks the plane of symmetry and therefore called as dissymmetric or Asymmetric.

A chiral object cannot be superimposed on its mirror image. For example, a left hand 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 and cannot be superimposed. If we lay one hand on the other, the fingers and the thumbs would clash.

Optical Isomerism

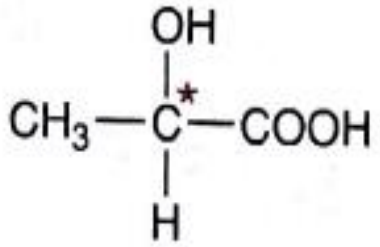
An optically active compounds exists in two isomeric forms that rotate the plane polarized light in opposite directions. They are called optical isomers and the phenomena is called optical isomerism.

The optical rotatory power of two isomers are equal in magnitude but opposite in direction. The equimolar mixture of two isomers will therefore, not rotate the PPL at all and is said to be **Racemic Mixture.**

Optical isomers have the same physical properties: Melting point, boiling point, density etc. They have the same specific rotations but with opposite signs.

Optical Isomerism of Lactic acid

It contains one chiral carbon



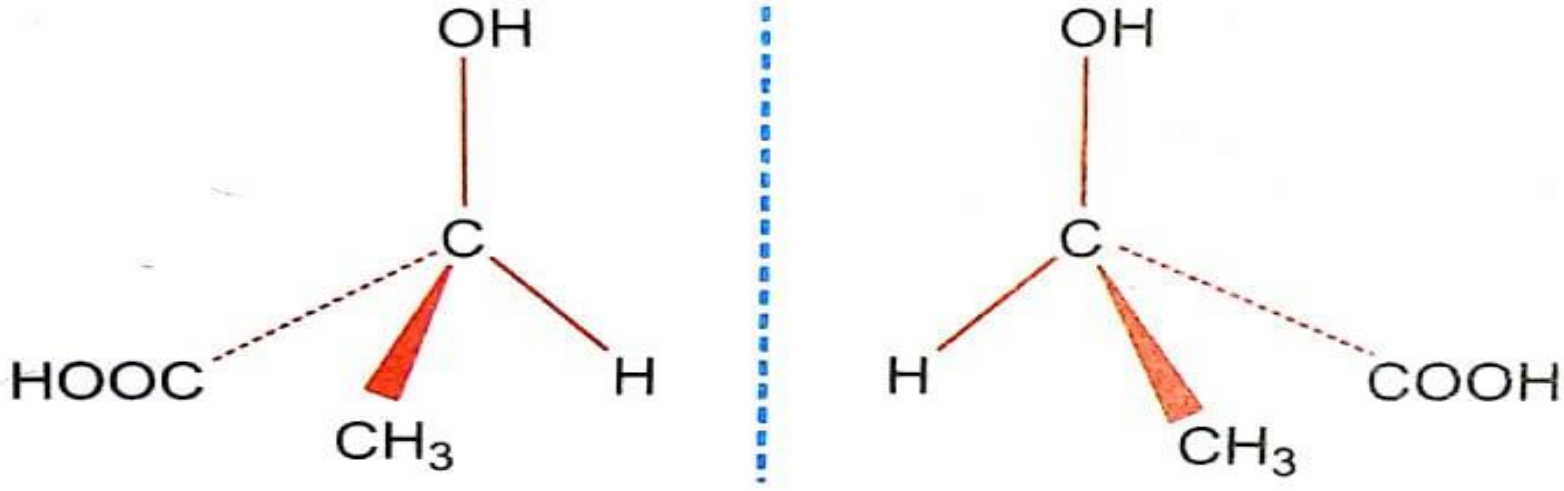
Lactic acid. The chiral carbon is shown by an asterisk.

Three forms of lactic acid are known, of which two are optically active and the third one is optically inactive.

(+)-Lactic Acid: Rotate the PPL to the right (clockwise) and is dextrorotatory

(-)-Lactic Acid: Rotate the PPL to the left (anti-clockwise) and is levorotatory.

(±)-Lactic Acid: Does not rotate PPL and is optically inactive because it is a racemic mixture of (+) and (-) forms



(+)-Acid
mp = 26°C

(–)-Acid
mp = 26°C

Optically active

Equimolar mixture of
(+)- and (–)-forms
(racemic mixture)

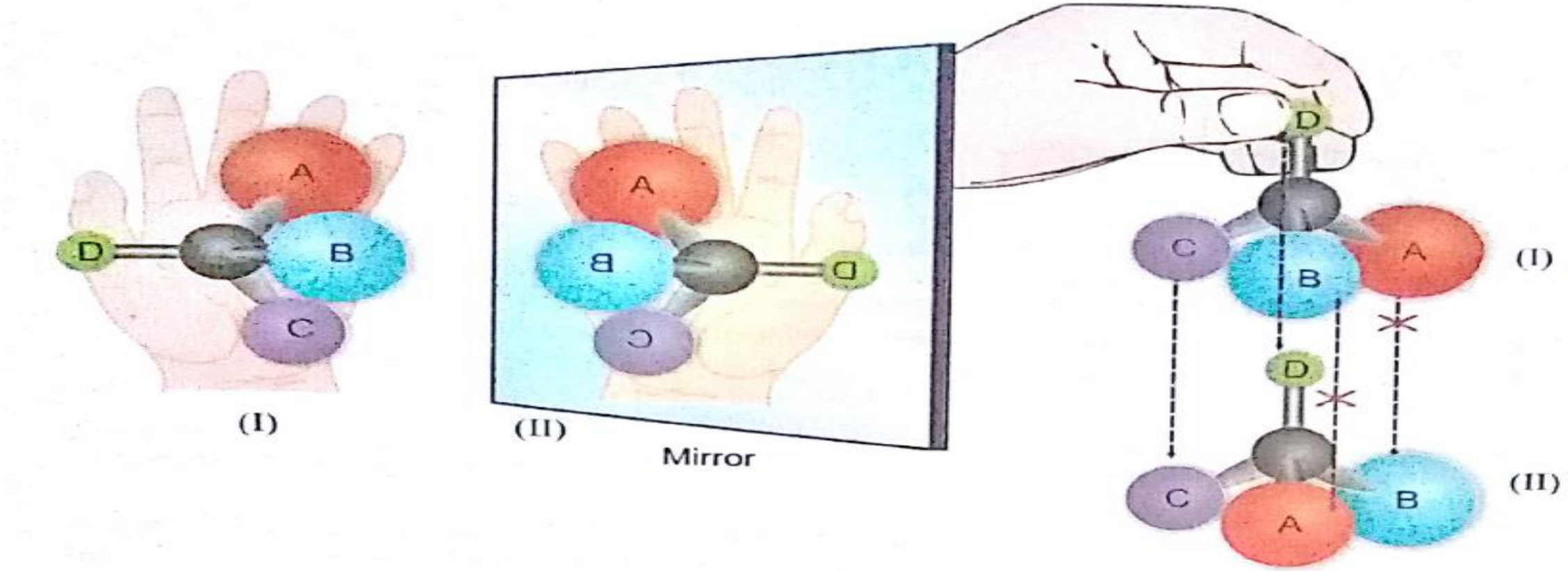
(±)-Acid
mp = 18°C

Optically inactive

Fig. 4.5. Isomers of Lactic acid. In the upper line two three-dimensional structures are shown. In the lower line a commonly used Fischer projection is given. The vertical lines represent bonds going away from the observer/reader and horizontal lines represent bonds coming toward the observer.

Conditions for Optical Isomerism

Molecule should be **dissymmetric**. That is, the molecule **should not be superimposed on its mirror image**. Simply, this dissymmetry results from the presence of a chiral carbon atom. Chiral carbon is the one, which is bonded to four different groups.



The non-superimposable mirror image forms of a chiral carbon are called **Enantiomers.** They represent two optical isomers (+), and (-). Their opposite rotatory powers are due to the opposite arrangements of groups around a chiral carbon.

Note:

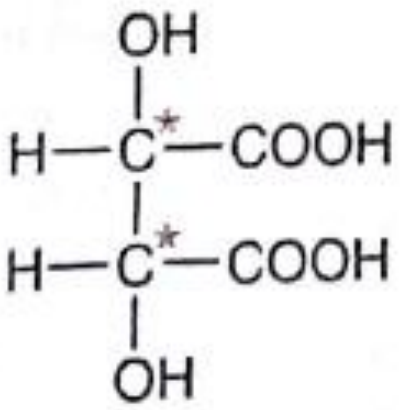
It is true that molecules containing chiral carbons are optically active, but it is not always so.

There are some compounds such as meso-tartaric acid which have chiral carbon but is not optically active.

On the other hand, there are some compounds which do not have chiral carbons but are optically active i.e., substituted allenes and biphenyls

OPTICAL ISOMERISM OF TARTARIC ACID

Tartaric acid contains two chiral carbon atoms



Tartaric acid. The two chiral carbons are shown by asterisks.

Four forms of tartaric acid are known, of which two are optically active and two are optically inactive. The two optically active forms are mirror images of each other but not superimposable, that is, they are **Enantiomers.**

Four forms of Tartaric acid

(+)-Tartaric Acid: Rotate the PPL to the right (clockwise) and is dextrorotatory

(-)-Tartaric Acid: Rotate the PPL to the left (anti-clockwise) and is levorotatory.

***meso*-Tartaric Acid:** It possesses a plane of symmetry and is optically inactive. This optically inactive form is said to be internally compensated; means optical rotation of one chiral carbon is cancelled by that of the other.

(±)-Tartaric Acid: Does not rotate PPL and is optically inactive because it is a racemic mixture of (+) and (-) forms

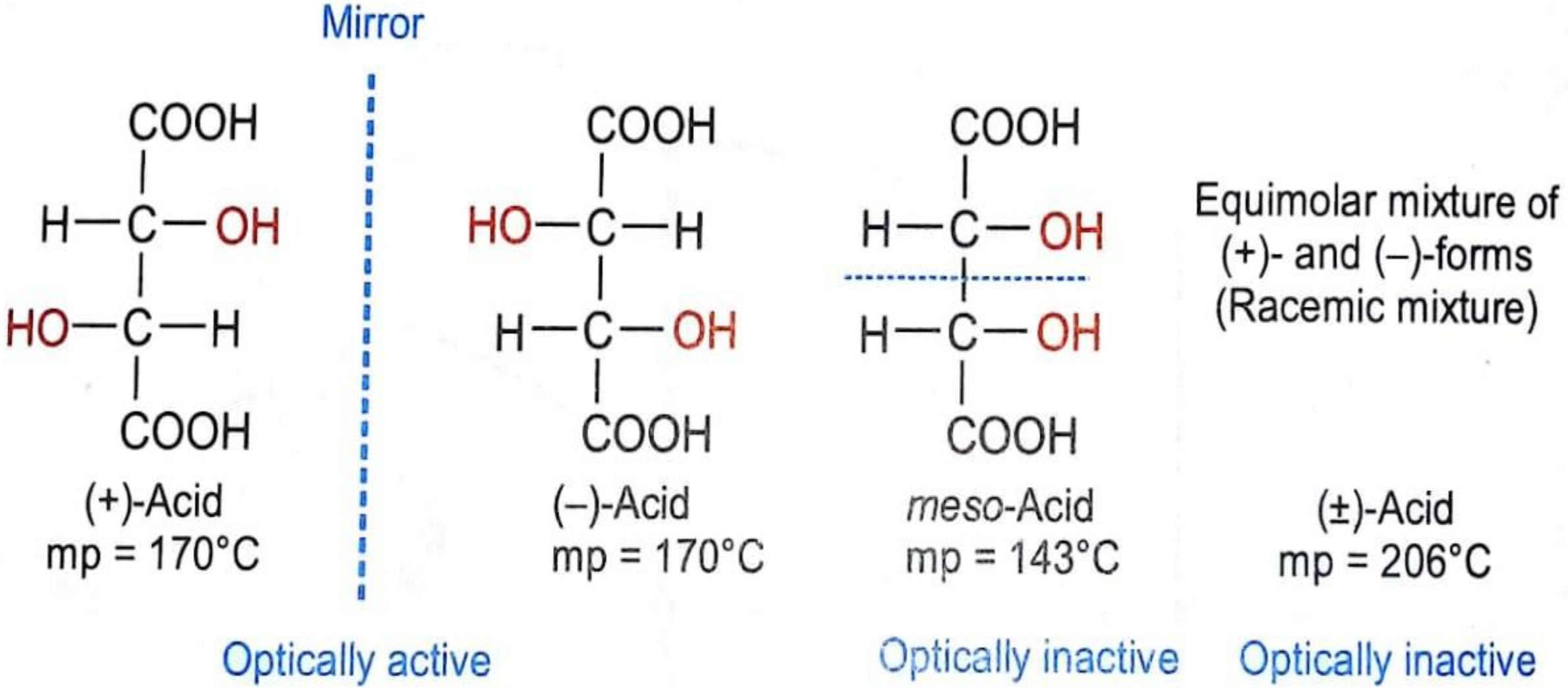


Fig. 4.7. Isomers of Tartaric acid.

Terms used to describe Optical Isomerism

Achiral molecule: Which can not be superimposed on its mirror image. It is identical to its mirror image and do not rotate the Plane polarized light.

Chiral center: For a molecule to be chiral, it must have at least one chiral center- a carbon with four nonequivalent groups. Any molecule that contain a chiral center will be chiral unless the molecule has a plane of symmetry, in which case the molecule is achiral **(meso)**

Chiral molecule: A chiral molecule is one that can not be superimposed on its mirror image. It rotate the PPL

Diastereomers: Diastereomers are stereoisomers that are not mirror images of each other. For a molecule to have a diastereomer, it must contain more than on chiral center.

Enantiomers: Mirror images of each other are enantiomers

Meso compounds: Compounds that contain a chiral center but is achiral because of plane of symmetry

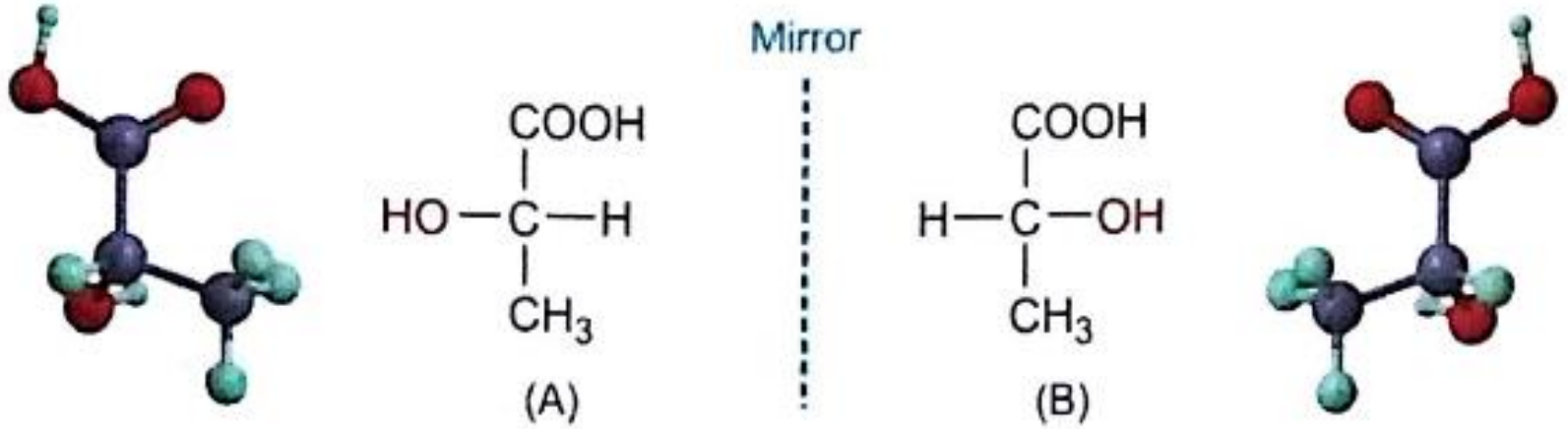
Optically active: Compounds having the ability to rotate the PPL

Racemic mixture: A racemic mixture is a 50:50 mixture of two enantiomers. Racemic mixture do not rotate PPL

PROPERTIES OF 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.



(A) Is the mirror image of (B) and are a pair of enantiomers

Enantiomers are stable, isolable compounds that differ from one another in 3-Dimentional spatial arrangements.

Enantiomers cannot be interconverted under ordinary conditions

Enantiomers have **identical properties** in all respect except in their interaction with plane polarized light.

They have same melting point, density, solubility, color, and reactivity towards acids and bases.

They differ, however, in the direction in which they rotate the PPL. Both rotate the PPL to exactly the same extent (same angle) but one rotates the plane to the right and other to the left.

A mixture of equal amounts of two enantiomers is a **racemic mixture**. Such a mixture is optically inactive because the two components rotate the PPL equally in opposite directions and cancel one other.

PROPERTIES OF DIASTEREOMERS

Diastereomers are stereoisomers that are not mirror images of each other. For a molecule to have a diastereomer, it must typically contain a chiral center.

In general, each chiral carbon atom in a molecule doubles the number of theoretically possible isomers. Hence, molecules with *n* number of chiral carbon atoms have $\mathbf{2^n}$ stereoisomers.

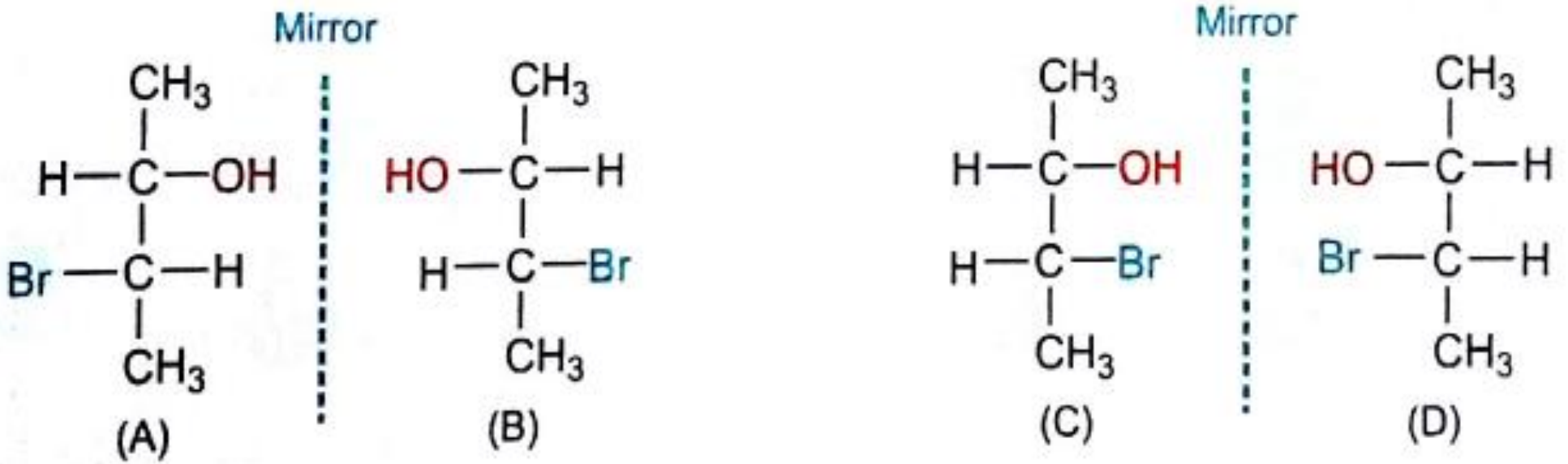
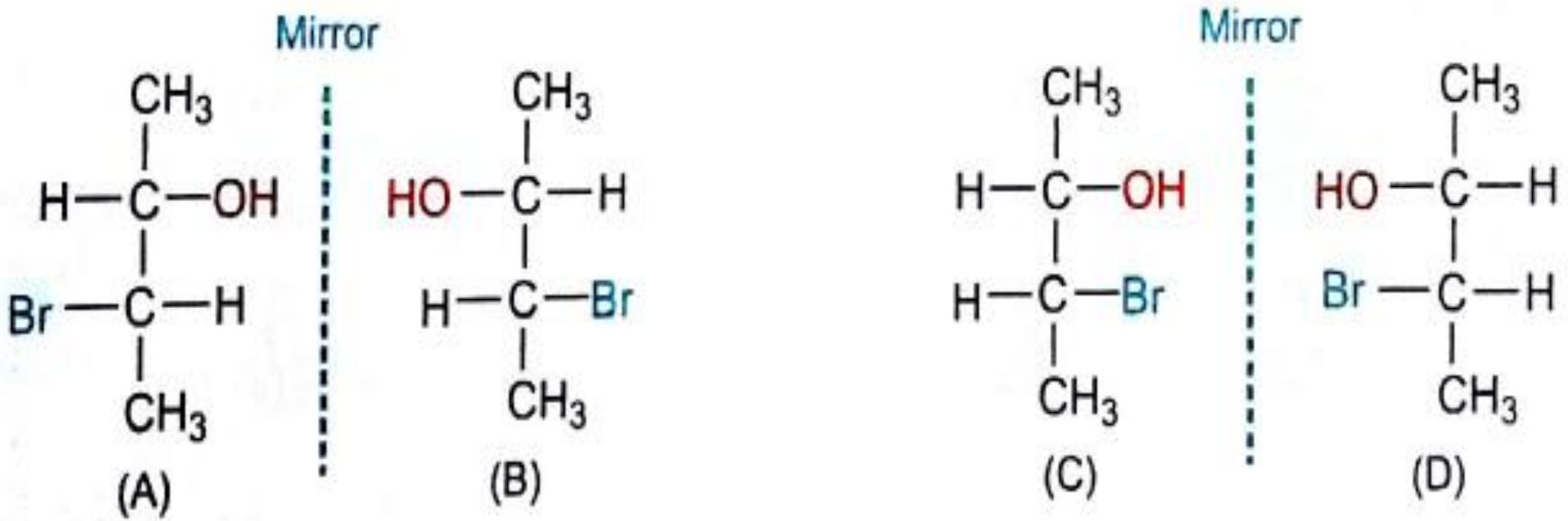


Figure shows the 4 isomers of 3-bromo-2-butanol, which has two chiral carbon atoms

Notice that (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).



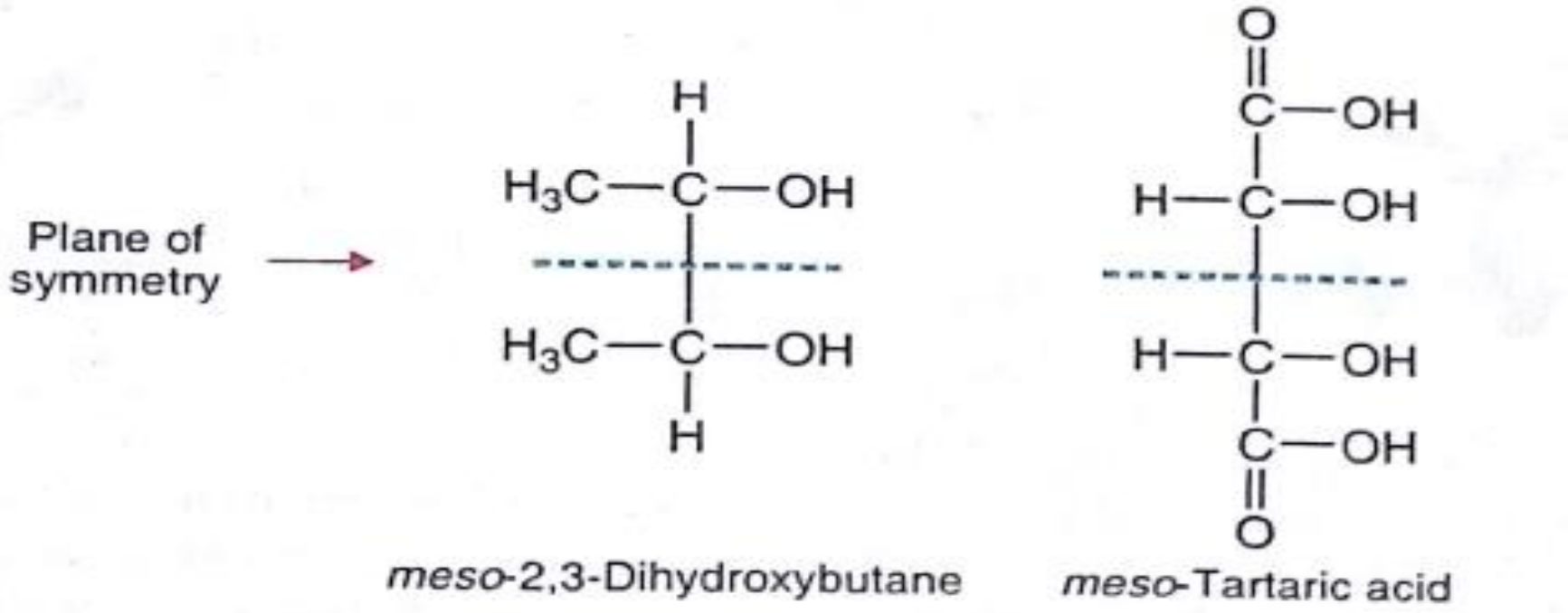
Diastereomers have different properties. Two diastereomers will have different melting points, boiling points, and solubilities. They will also have different reactivities toward most reagents

Diastereomers are stereoisomers that are not mirror images. Since we used the right-hand/left-hand analogy to describe the relationship between two enantiomers, we might extend the analogy by saying that the relationship between diastereomers is like that of hands from different people. Your hand and your friend's hand look *similar,* but they aren't identical and they aren't mirror images. **The same is true of diastereomers: they're similar, but they aren't identical and they aren't mirror images.**

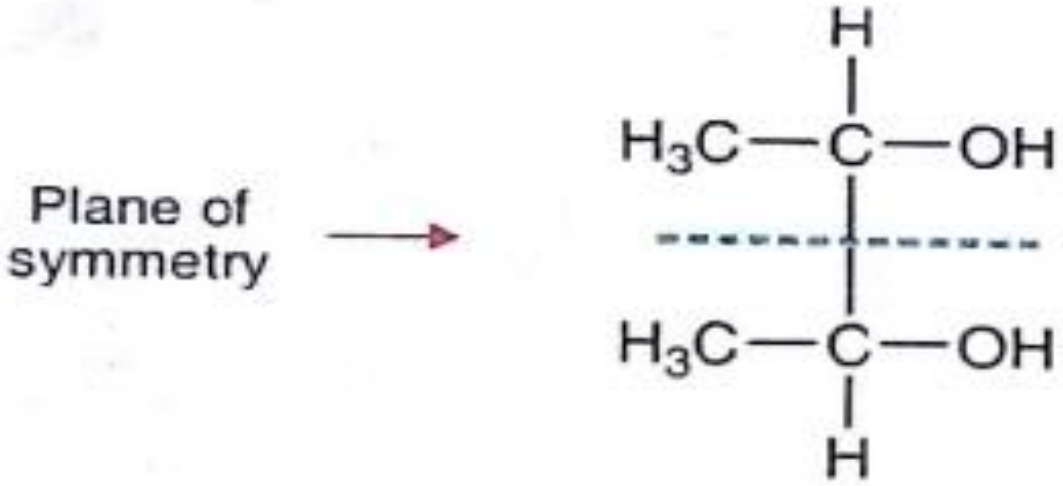
Meso Compounds

A meso compound is a molecule that contains a chiral center, but is achiral as a result of having a plane of symmetry in the molecule.

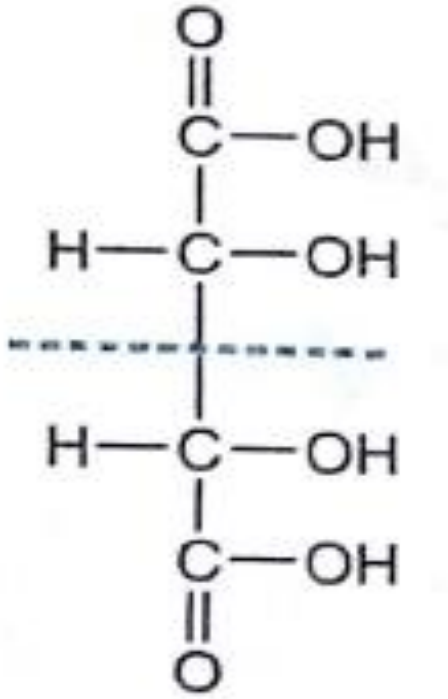
A compound with two or more chiral carbon atoms but also having a plane of symmetry is called meso compound. The molecules having plane of symmetry dividing them midway between the two chiral carbons in each.



Notice that one half of the molecule is the mirror image of the other. **Both molecules are optically inactive, even though each has two chiral centers.** Neither will rotate the PPL



meso-2,3-Dihydroxybutane



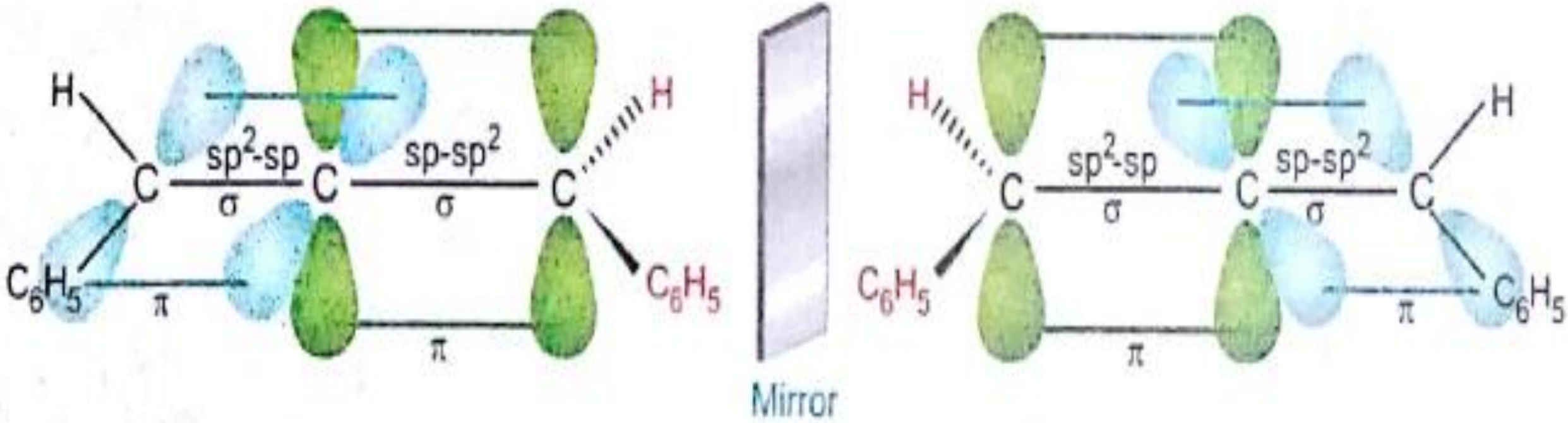
meso-Tartaric acid

OPTICAL ACTIVITY WITHOUT ASYMMETRIC CARBON

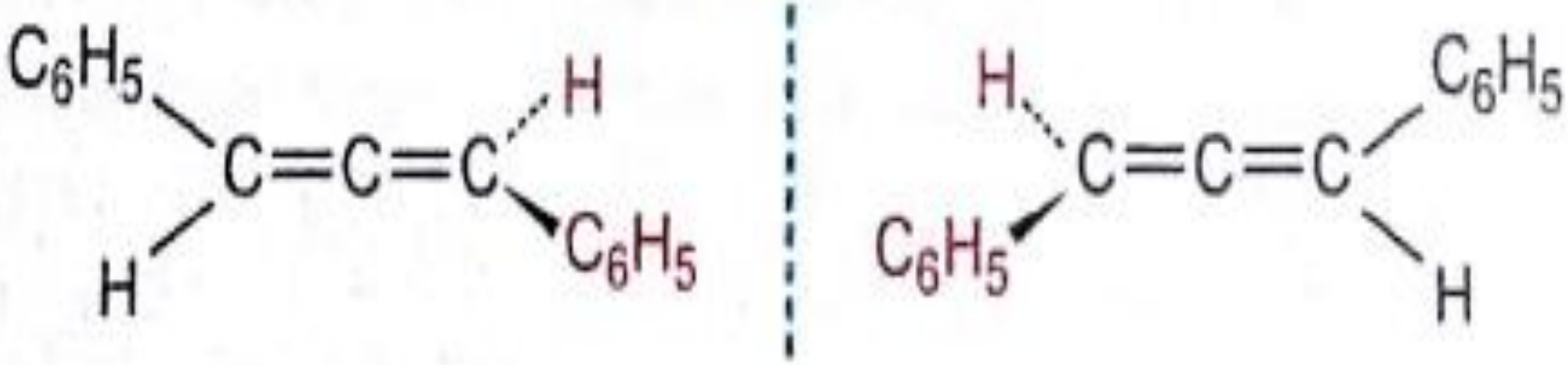
Compounds containing a chiral carbon are optically active. However, there exist some compounds which do not possess a chiral atom but are optically active provided that the molecule is dissymmetric.

ALLENE DERIVATIVES

Some derivatives of allenes **($CH_2=C=CH_2$)** exhibit optical isomerism. Example is I,3-diphenylpropadiene. In allenes, the central carbon forms **two sp-sp2 sigma bonds**. The central carbon has also **two p-orbitals** which are mutually perpendicular. These form pi-bonds with the p-orbitals on the other carbon atoms. As a result, the substituents at one end of the molecule are in plane which is perpendicular to that of the substituents at the other end, so that the compound exists in two forms which are non-superimposable mirror images and are optically active.



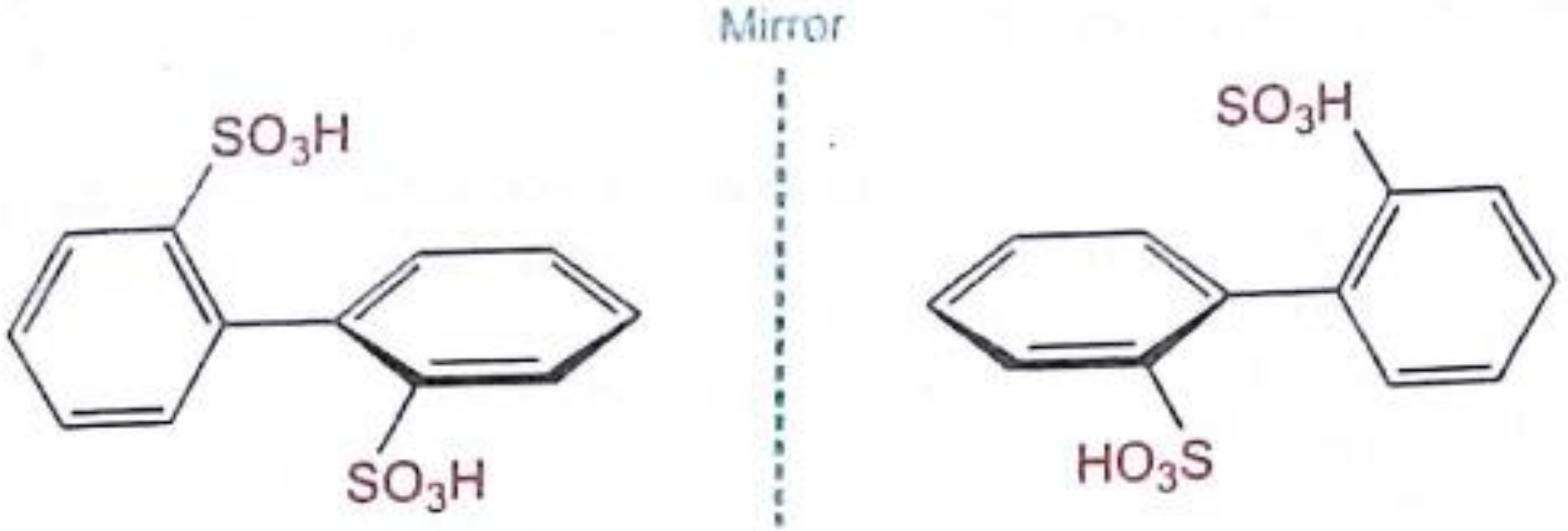
Mirror



1,3-Diphenylpropadiene

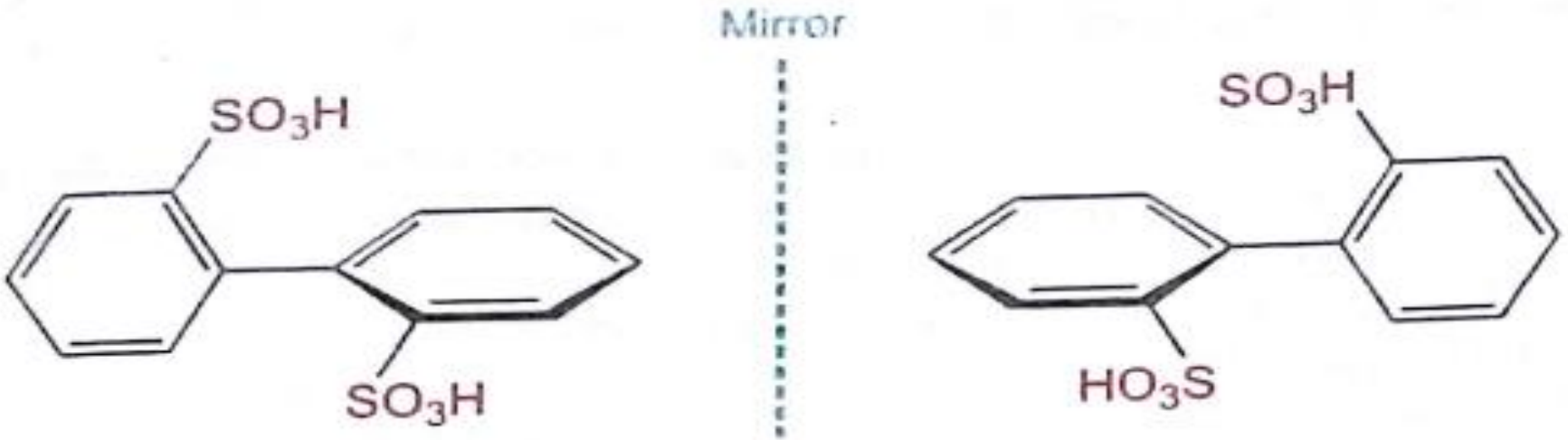
BIPHENYL DERIVATIVES

Substituted biphenyls show optical isomerism when substituents in the 2-positions are large enough to prevent rotation about the bond joining the two benzene rings. For example, biphenyl-2,2’-disulphonic acid exist in two forms.



Biphenyl-2,2'-disulfonic acid
(a Biphenyl)

These two forms are non-superimposable mirror images. They do not interconvert at room temperature because the energy required to twist one ring through 180 angle relative to the other is too high. This in turn is because, during the twisting process, the two –SO3H groups must come into very close proximity when the two benzene rings become coplanar and **strong repulsive forces** are introduced.



Biphenyl-2,2'-disulfonic acid
(a Biphenyl)

RESOLUTION OF RACEMIC MIXTURES

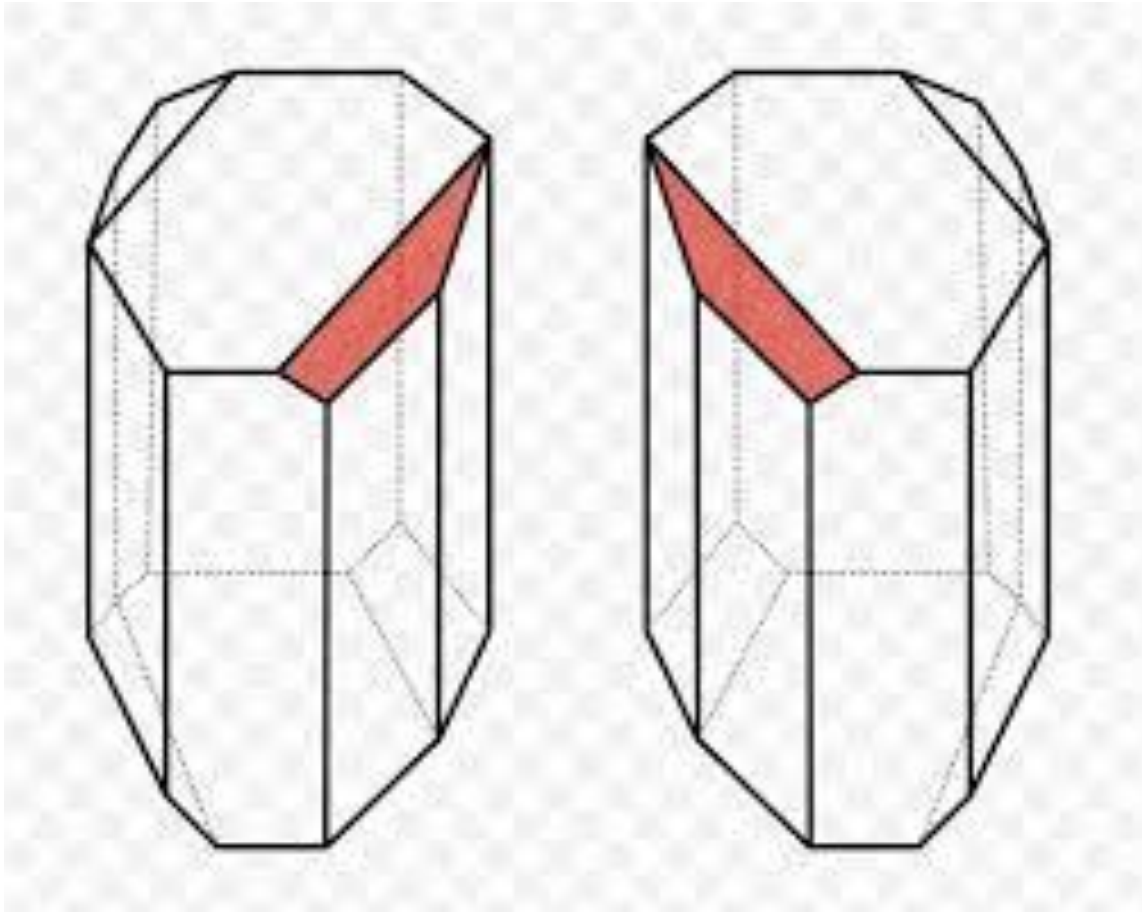
Synthesis of an optically active compound produces a mixture of + and –ve isomers in equal amounts. Recall that these isomers are non-superimposable mirror images and are called enantiomers. Such a mixture is called racemic mixture or a racemate. **The separation of a racemic mixture into its two optically active compounds (+ and – isomers) is known as Resolution.**

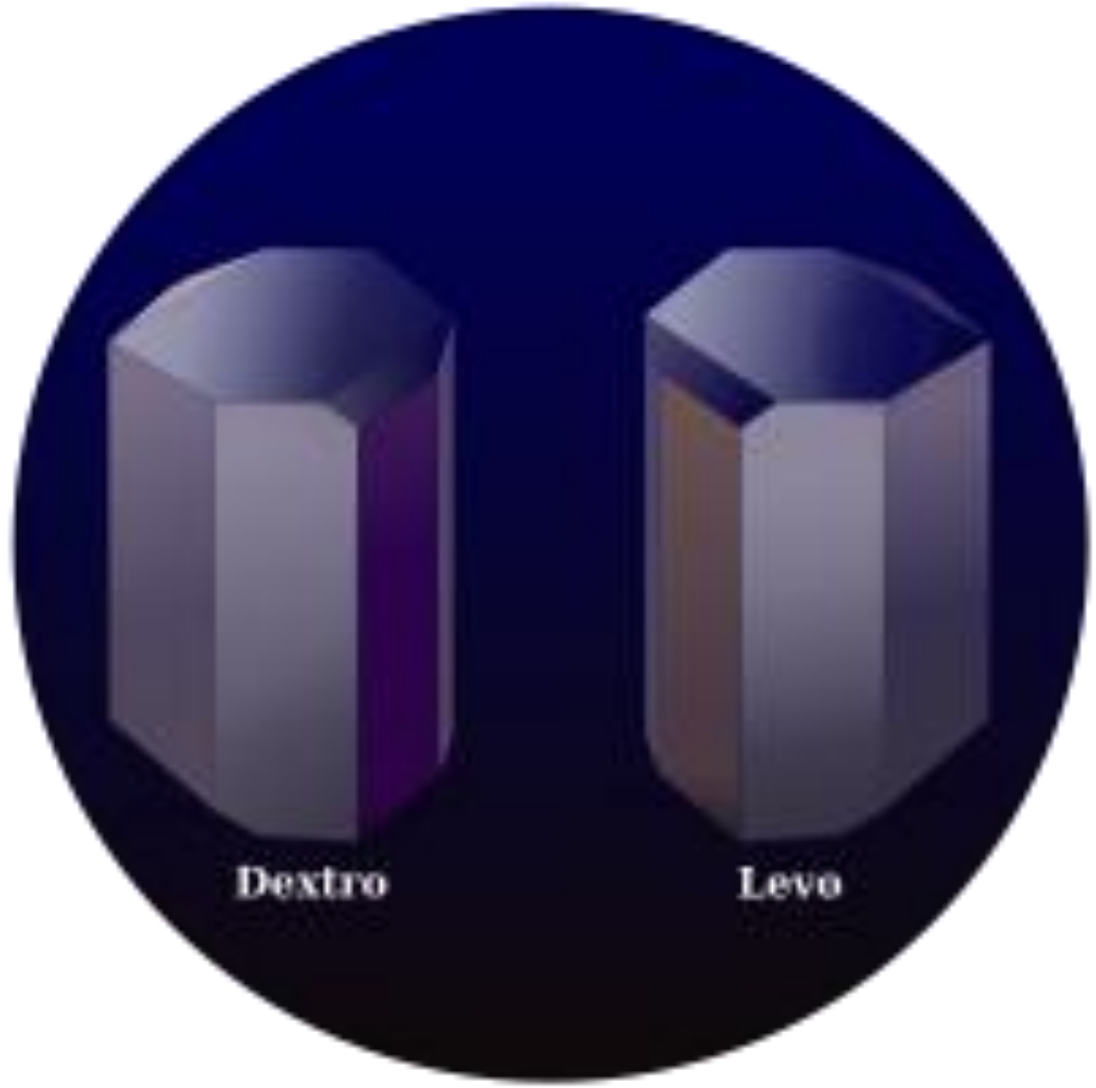
If the enantiomers are separated, the mixture is said to have been **resolved**.

MECHANICAL SEPARATION

This method is developed by L. Pasteur in 1848. It is applicable to only solid substances which form well defined crystals.

Since crystals of the two forms differ in their shapes, these can be separated mechanically with the help of a magnifying glass and tweezers (forceps). This method is too tedious for practical purposes and is now of historical interest only because it was the first method which Pasteur employed for the separation of the tartaric acids.




Dextro
Levo

CHEMICAL RESOLUTION

This method is developed by L. Pasteur in 1858. It involves the use of an optically active compound which could react easily and selectively with either of the two enantiomers to produce a mixture of two **diasteriomeric compounds**. The two compounds so formed have different physical properties and therefore can be separated by conventional method of separation e.g., crystallization. The crystals of diastereoisomers so obtained can be broken down chemically to obtain the two enantiomers separately.

Separation of racemates into their component enantiomers is a process called **resolution**.

Since enantiomers have identical physical properties, such as solubility and melting point, **therefore, resolution is extremely difficult**.

Diastereomers, on the other hand, have different physical properties, and this fact is used to achieve resolution of racemates. Reaction of a racemate with an enantiomerically pure chiral reagent gives a mixture of diastereomers, which can be separated.

For example, a solution of racemic lactic acid may be treated with an optically active base such as the alkaloid (Brucine). The resulting product will consist of two salts

(i) (+)- Acid. (—)- Base; and (ii) (—)- Acid(—)-Base

Suppose the two enantiomorphic forms of lactic acid are represented by the symbols

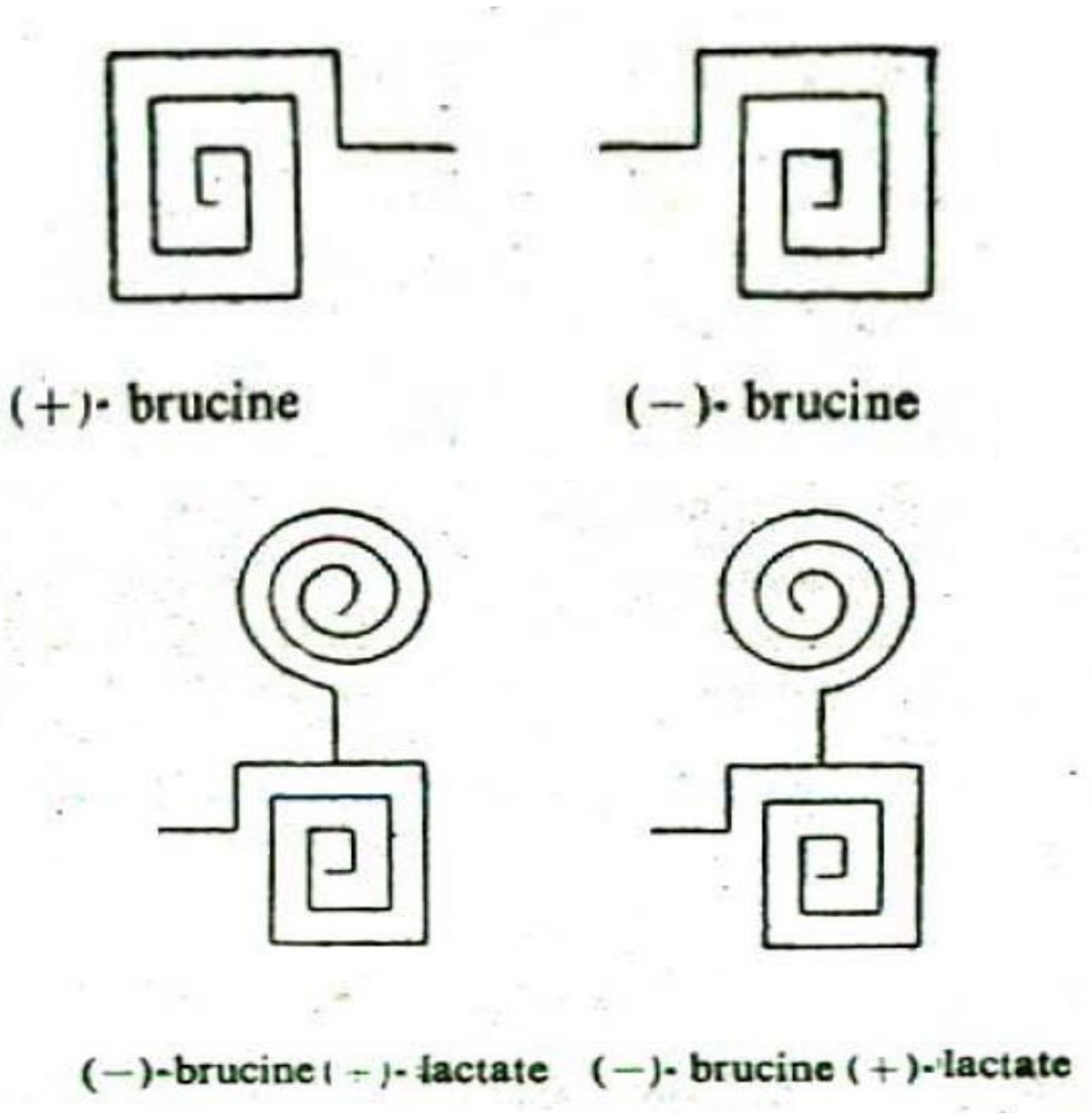
(+)-lactic acid (−)-lactic acid

And suppose the two enantiomorphic forms of brucine are represented by the symbols

Inspection of the configurations of the two salts shows that they are not enantiomorphic.

Therefore, they have different solubility in water and can be separated by fractional crystallisation.

The isolated salts are then treated with dilute sulphuric acid when the optically active acids are regenerated.



BIOCHEMICAL RESOLUTION

This method is developed by L. Pasteur in 1858. In this method, one of the enantiomers is destroyed biochemically, using a suitable microorganism such as yeast, mold or bacterium. The **microorganism utilizes** one of the enantiomers for its growth and leaves the other in the solution. The enantiomer left in the solution can be isolated by fractional crystallization.

For example: Penicilium glaucum removes Dextro form from the racemic mixture of ammonium tartrate leaving a levo ammonium tartrate

Disadvantages of biochemical resolution

Half of the material is lost.

This method can not be used if the mixture is toxic to the microorganisms.

Kinetic Method

The fact that enantiomers react with an optically active substance at different rates, is used for the separation of racemic mixtures. The procedure takes advantage of differences in reaction rates of enantiomers with chiral reagents. One enantiomer may react more rapidly, thereby leaving an excess of the other enantiomer behind.

A **disadvantage of resolutions** of this type is that the more reactive enantiomer usually is not recoverable from the reaction mixture.

Selective Adsorption/Chiral chromatography

Sometimes 'resolution' may be achieved by passing a solution of the racemate over a column of a finely powdered, optically active adsorbent such as starch, sugar or quartz. The surface of the adsorbent, adsorbs selectively one enantiomer and thus the solution emerging at the bottom is richer in the other enantiomer.

Chromatographic methods, whereby the stationary phase is a chiral reagent that adsorbs one enantiomer more strongly than the other, have been used to resolve racemic compounds.

Importance of Resolution

Majority of the drugs have many chiral centers. For example **vitamin E** has three chiral centers, therefore, 8 forms are possible. Among these 8 forms only one occurs naturally and is 100% potent. Other 7 forms have different potencies less than naturally occurring form. All forms of vitamin E has a positive impact but there are some cases where the other forms have a negative impact on the body are harmful. i.e., one enantiomer is biologically active while the other is either inactive or very harmful.

The Thalidomide Story

Thalidomide was launched on October 1, 1957 as an anti-emetic drug that had an inhibitory effect on morning sickness, that's why given to pregnant womens' to relieve morning sickness. It was later realized that while the (+)-form of the molecule was a safe and effective anti-emetic, **the (−)-form was an active teratogen**. The drug caused numerous birth abnormalities when taken in the early stages of pregnancy because it contained a mixture of the two forms. Majority of the born kids were having no legs, arms, fingers. This happens because the

Pharmaceutical company was unable to resolve the
+ **thalidomide**

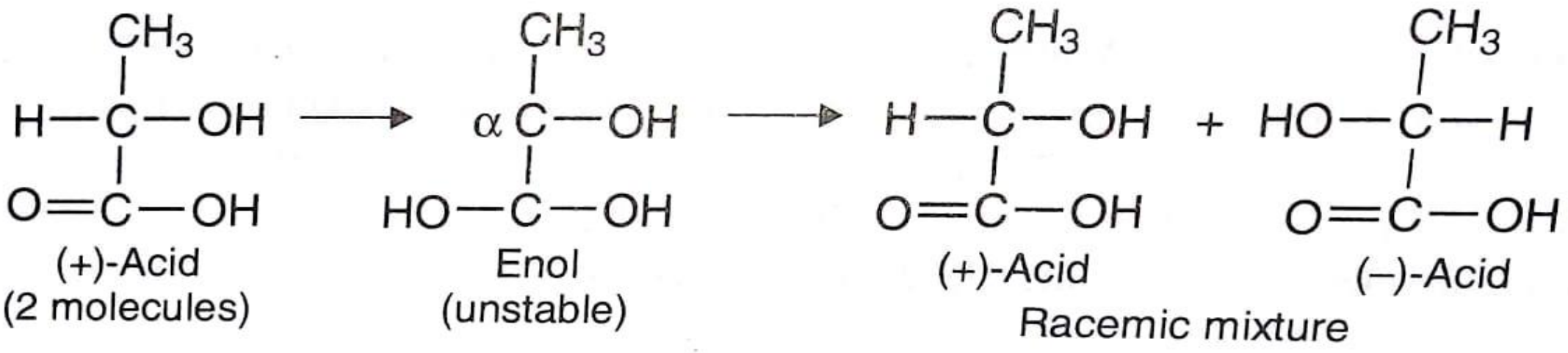
Single Enantiomer vs. Racemic Mixtures

Single enantiomer have less complex and more selective pharmacodyanamic profile as compared to racemic mixture, so have lesser adverse drug reactions, improved therapeutic profile, less chances of drug interactions than racemic mixtures. Single enantiomers seem to be more advantageous over racemic mixtures as - adverse drug reactions occurring due to one enantiomers are avoided, patients are exposed to less amount of drug so body is exposed to the lesser metabolic, renal and hepatic load of drug, there is easier therapeutic drug monitoring of the active pure active enantiomers.

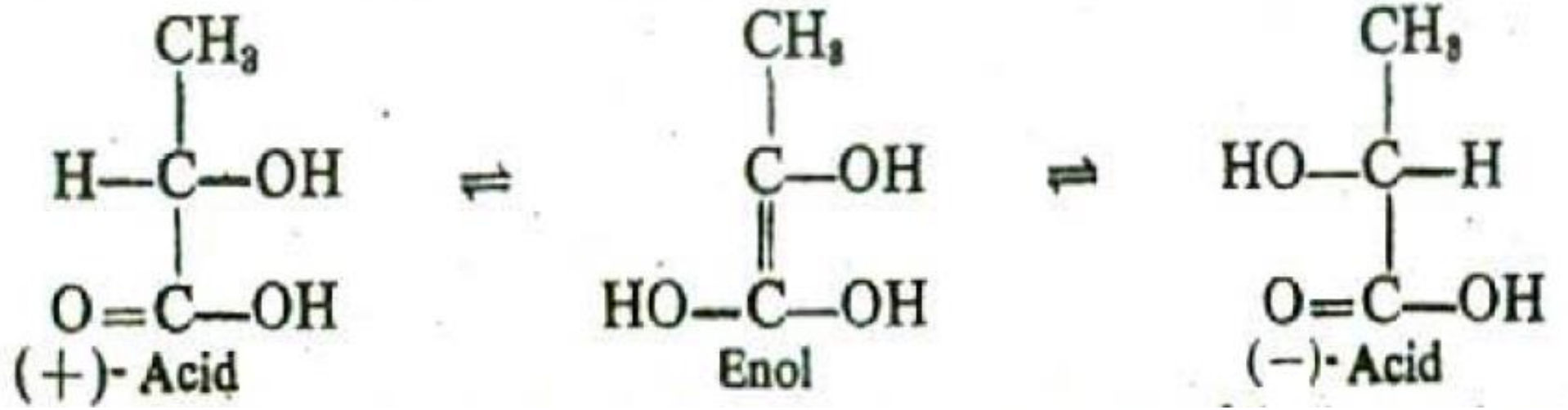
Racemization

The conversion of an optically active compound (+)- or (-)- into racemic mixture (±) is known as Racemization.

Racemization can be accomplished by the means of heat, light or by the conversion of an optically active isomers into an optically inactive intermediate which then reverts to the racemic mixture. The conversion of either of the optically active lactic acids into a racemic mixture by heating its aqueous solution may proceed through an enol intermediate.

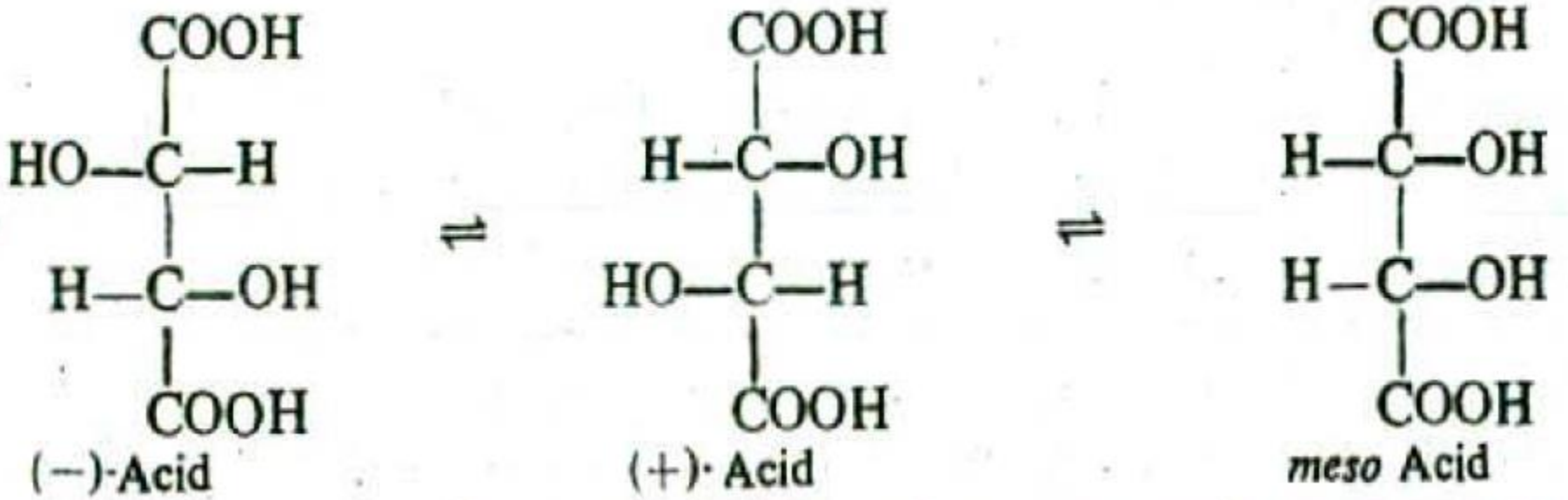


Since the enol is a planar molecule, so the possibility of frontal and rear attachment of H-atom to a carbon atom (in the enol form) is equally probable. Consequently equal number of molecules of (+)- and (-) form would result and racemic mixture would be produced. These changes are reversible and in actual practice we get an equilibrium mixture.



The equilibrium mixture thus obtained contains one molecule of (+)-Acid and one molecule of (-)-Acid i.e., the racemic mixture of the acid.

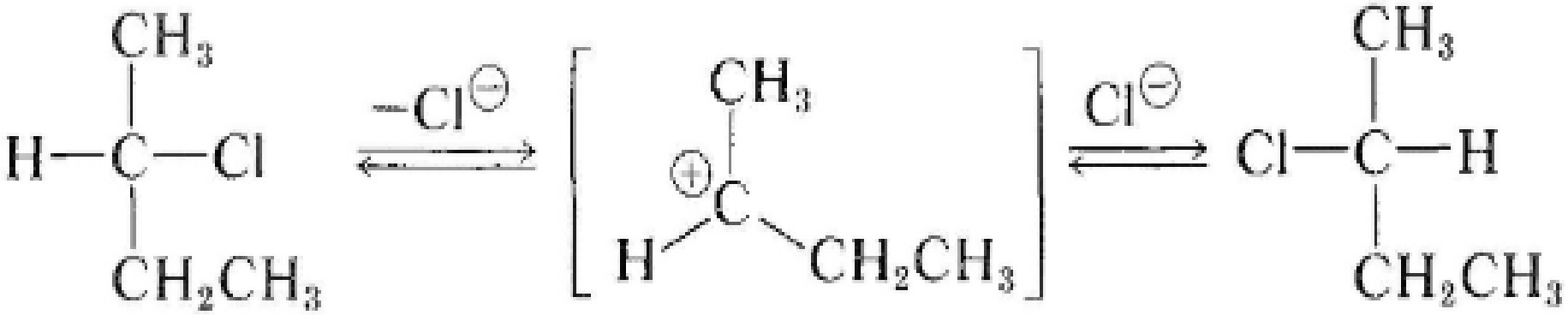
According to Pasteur, if a solution of **(+)-tartaric acid** is heated for some time at **165°C**, it loses its optical activity forming the racemic mixture and meso acid. This is due to the fact that tartaric acid having two asymmetric carbon atoms may undergo inversion of H and OH only about one carbon or both, yielding **meso or racemic form**, respectively.



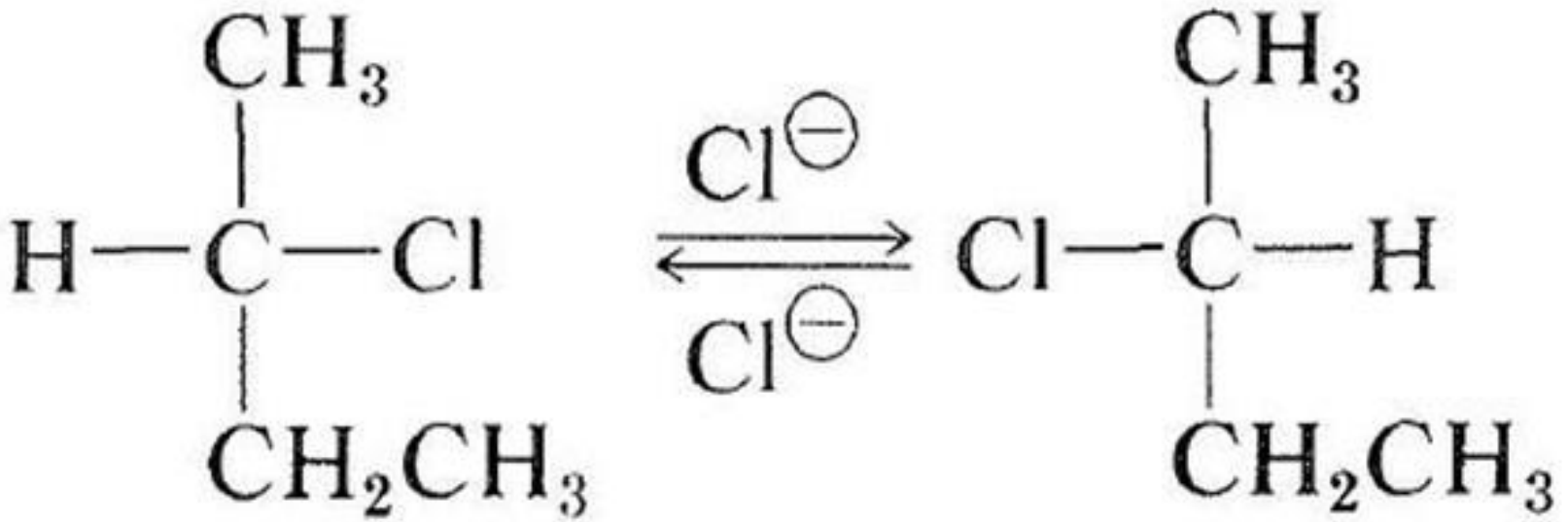
Optically active substances which cannot enolize because they have no hydrogen atom at a carbon to a carbonyl group, do not in general racemize except under conditions which bring about other chemical changes as well.

Racemization of Optically Active Halides

The racemization of optically active halides may take place either by an SN1 or SN2 mechanism depending upon the experimental conditions. In polar solvents, S-butyl chloride racemizes by SN1 mechanism. Dissociation of the compound produces planar carbonium ion which can recombine with the anion i.e., Cl yielding both S and R forms of the compound.



Optically active halides also can be racemized by an **SN2 mechanism**. A solution of active 2-chlorobutane in acetone containing dissolved lithium chloride becomes racemic. Displacement of chloride ion of the halide by chloride ion (from LiCl) inverts configuration at the carbon atom undergoing substitution. A second such substitution regenerates the original enantiomer. Eventually, this back and forth process produces equal number of R and S forms; the substance is then racemic.



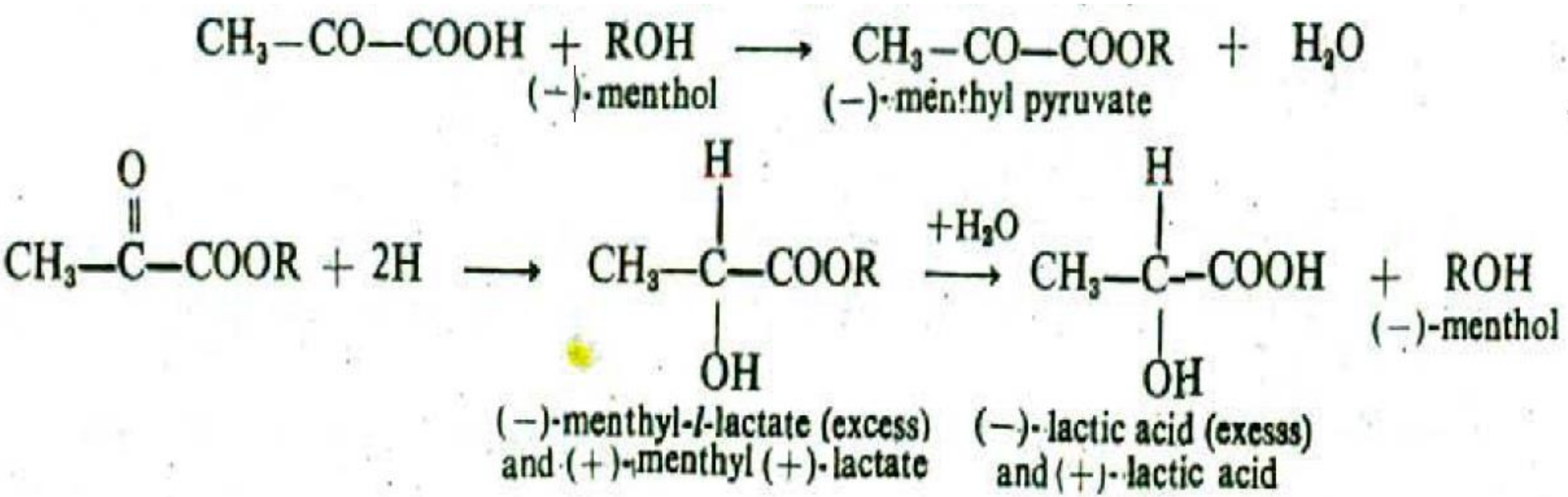
Asymmetric Synthesis

The process in which an asymmetric compound is synthesized from a symmetric compound to yield the (+)- or (-)- isomer directly, is termed Asymmetric Synthesis. **OR**

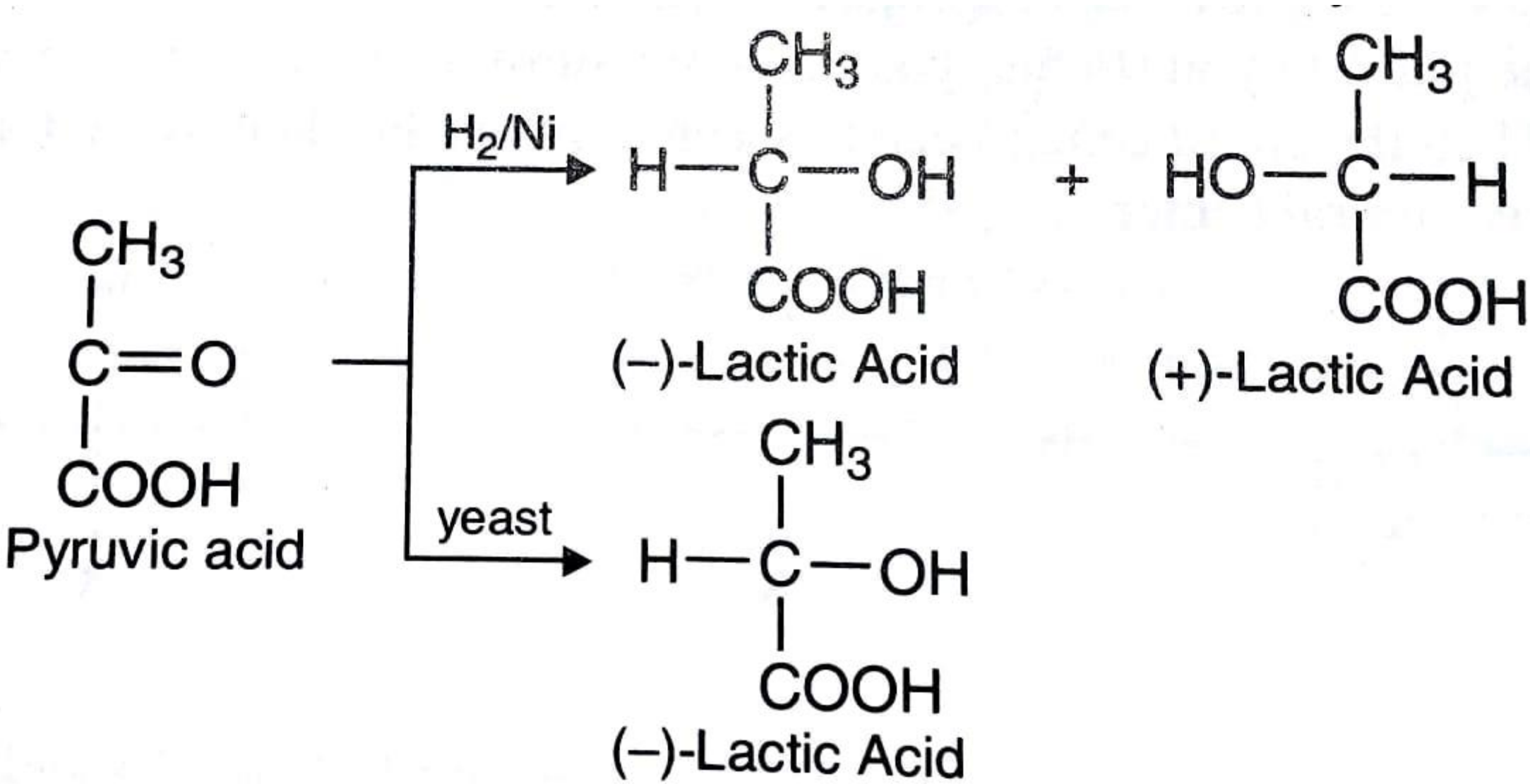
The process in which a chiral compound is synthesized from an achiral compound to yield the (+)- or (-)- isomer directly.

We have already seen that when a compound containing an asymmetric carbon atom is synthesized by ordinary laboratory methods from a symmetric compound, the product is a racemic mixture. If, however, such a synthesis is carried under the 'Asymmetric influence of a suitable optically active reagent, one of the optically active isomers, (+)-or(—)-, is produced in preference and in excess.

When pyruvic acid is reduced as such, it yields (±)- lactic acid. However, when pyruvic acid is first combined with an optically active alcohol, ROH, such as (—)-menthol* to form an ester which is then reduced, the product upon hydrolysis yields (—). lactic acid in excess.



In nature, numerous optically active substances such as terpenes, alkaloids and proteins are produced by asymmetric synthesis, under the influence of optically active enzymes. These enzymes unite with the substance available in plants and when the synthesis is complete, they separate from the product and are thus again free to combine with more of the parent inactive substance and the endless process continues.

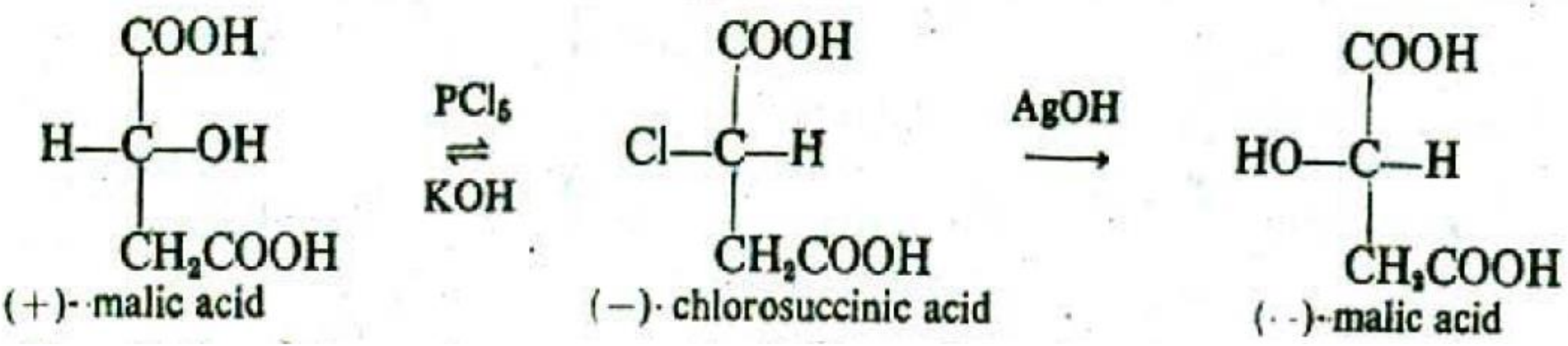

CH3
C=O
COOH
Pyruvic acid
H2/Ni
yeast
CH3
H—C—OH
COOH
(–)-Lactic Acid
+
CH3
HO—C—H
COOH
(+)-Lactic Acid
CH3
H—C—OH
COOH
(–)-Lactic Acid

Walden Inversion

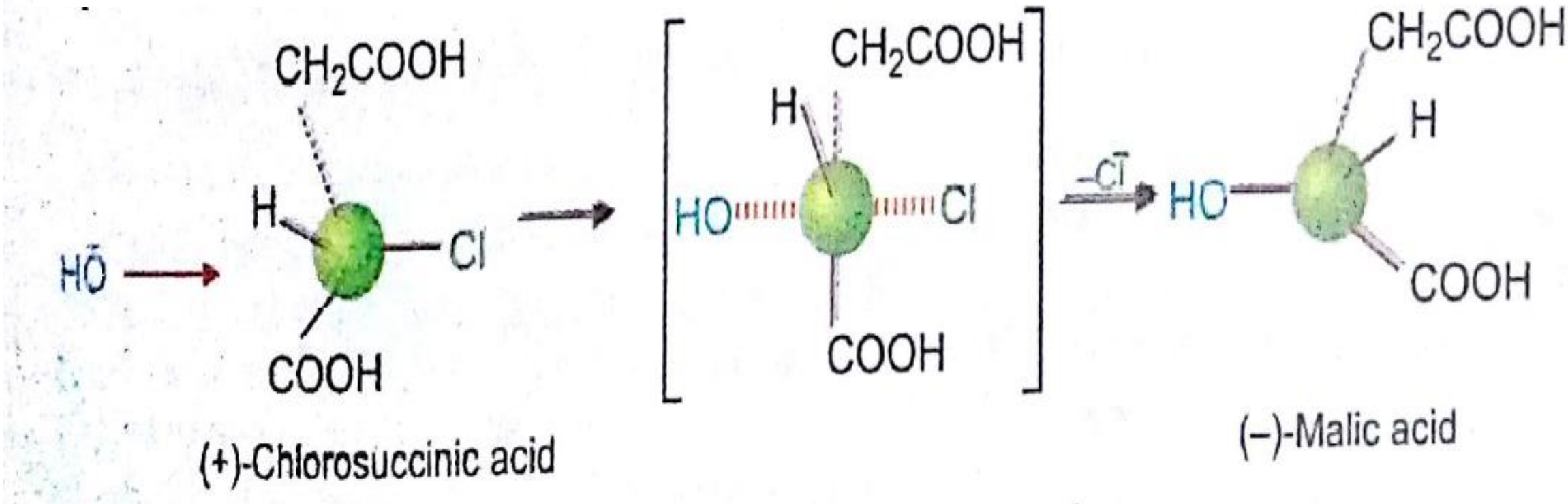
When an atom or group directly linked to chiral carbon atom is replaced, the reaction may proceed with inversion of configuration. This phenomenon was first of all observed by Walden (1895) and hence the name Walden inversion. *Walden inversion may also be defined as the conversion of the (+)-form to (—)-form or vice versa.* Thus (+)-malic acid may be converted to (—).malic acid as follows.

Walden inversion is the inversion of a chiral center in a molecule in a chemical reaction. Since a molecule can form two enantiomers around a chiral center, **the Walden inversion converts the configuration of the molecule from one enantiomeric form to the other.**

Thus (+)-malic acid may be converted to (—)-malic acid as follows.



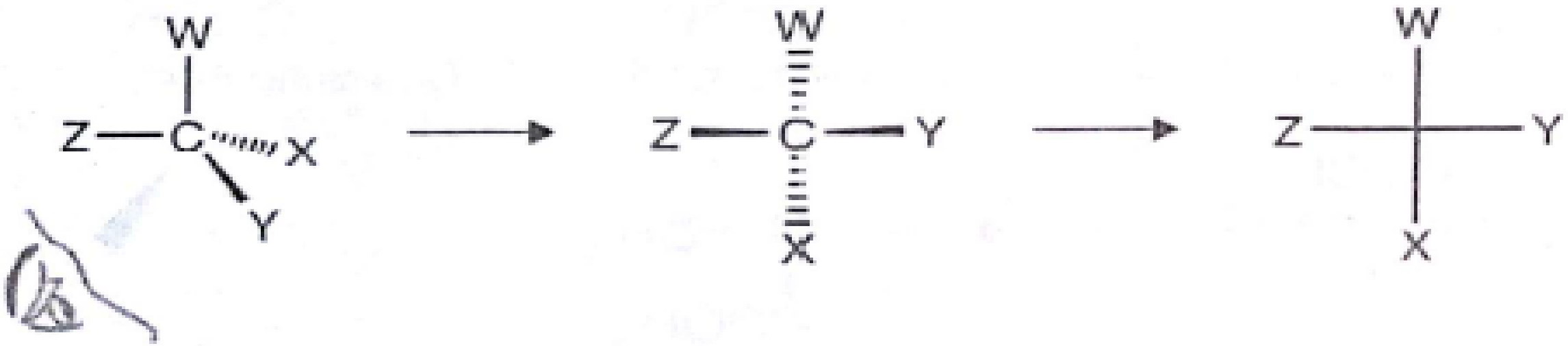
Since SN2 reactions always proceed with inversion of configuration, Walden inversion is a type of SN2 reaction


CH2COOH
H
HO
Cl
COOH
(+)-Chlorosuccinic acid
CH2COOH
H
HO
Cl
COOH
−Cl
CH2COOH
H
HO
COOH
(–)-Malic acid

FISCHER PROJECTION

When we attempt to depict configurations, we face the problem of representing three dimensional structures on a two dimensional surface. To overcome this difficulty we use the so-called **Fischer projection**. It is the most convenient way of viewing molecules with more than one chiral centers. Fischer projection is a convenient 2-D drawing that represents a 3-D molecule.

To make a Fischer projection, you view a chiral center so that two substituents are coming out of the plane at you (to hug you), and the two substituents are going back into the plane. Then the chiral center becomes a cross on the fischer projection. Every cross in Fischer Projection is a chiral center.



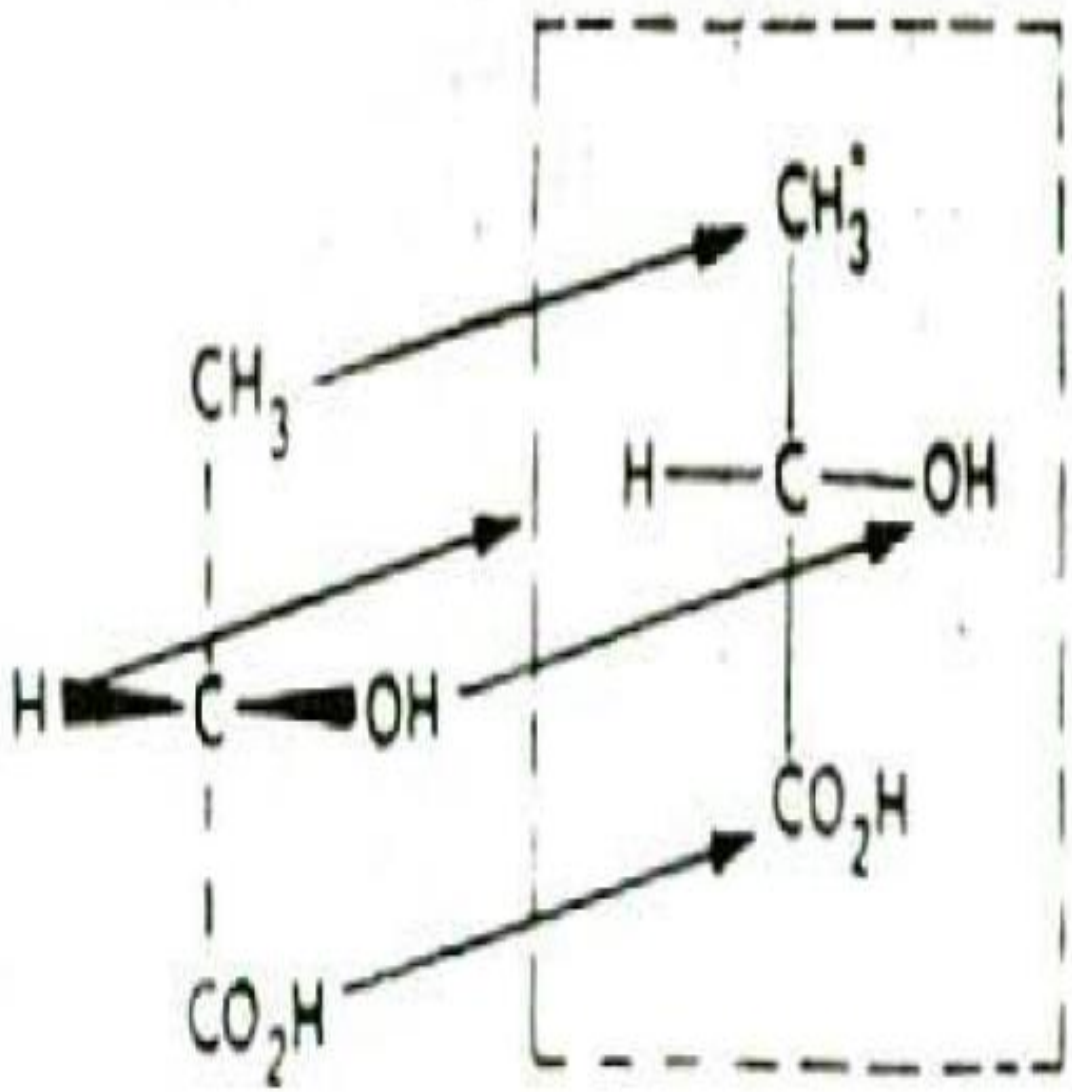
This is the structure of an asymmetric carbon atom drawn in a prescribed orientation and then projected into a planar surface.

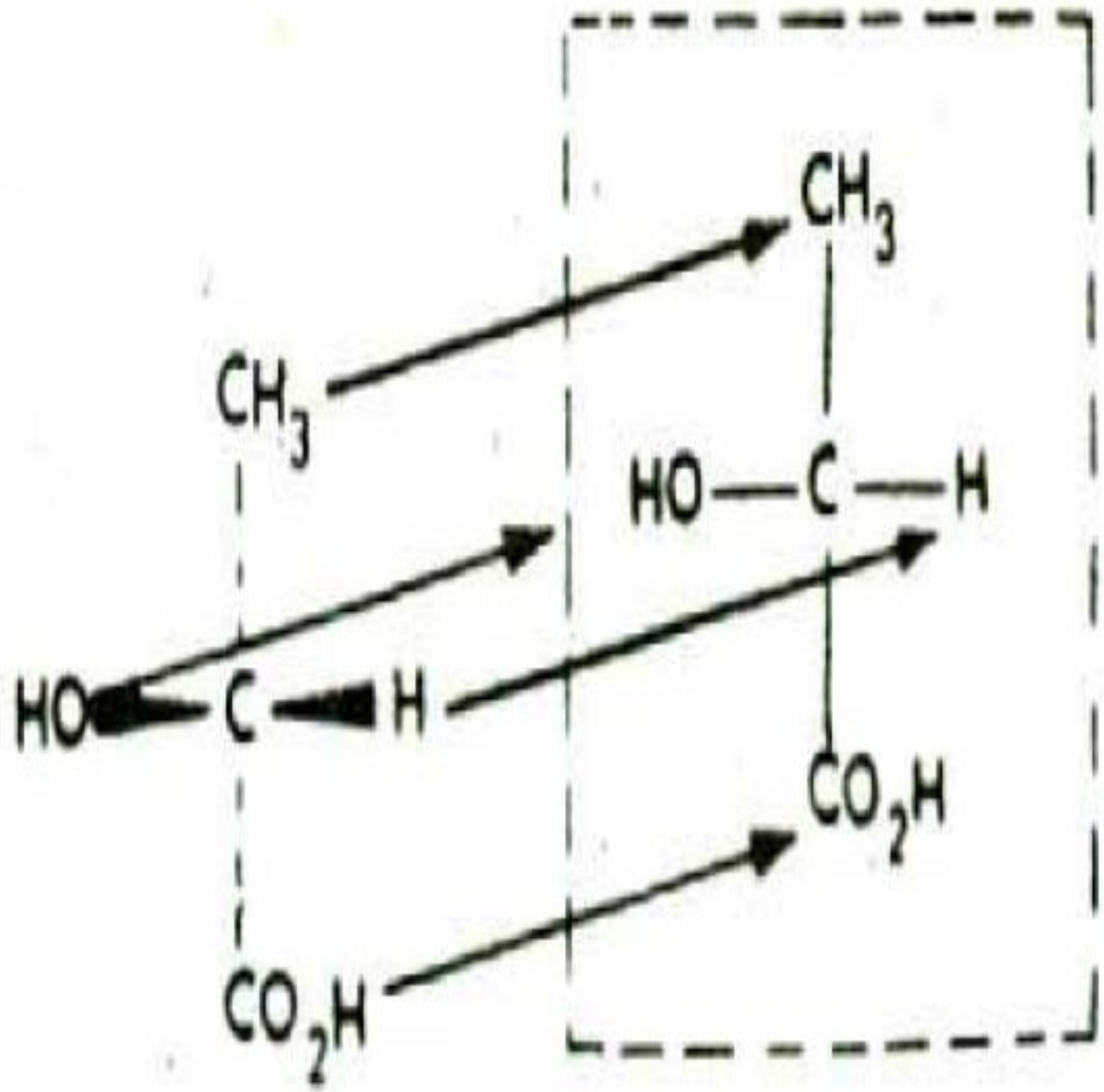
Thus planar formulas of the asymmetric carbon are obtained by placing it so that the two substituents are **horizontal** and project out towards the viewer (shown by thick wedge-like bonds), while the two other substituents are **vertical** and project away from the viewer (shown by dotted bonds).

Remember in Fischer projection molecule is oriented so that the vertical bonds at chirality center are directed away from you and horizontal are directed towards you

Planar representation of two forms of lactic acid may be given as

In these formulas the horizontal bonds i.e., C—OH and C—H project towards us out of the plane of the paper whereas the vertical bonds i.e., C—COOH and C—CH_3 project away from us. Inspection of the models shows that one interchange of a pair of substituents inverts the configuration (changes one enantiomer into) its minor image), whereas an even number of such interchanges does not. Thus interchanging of —H for —OH in **I** gives the enantiomer **II** while the interchange of CH_3 for —COOH and —H for —OH leaves the configuration unchanged.

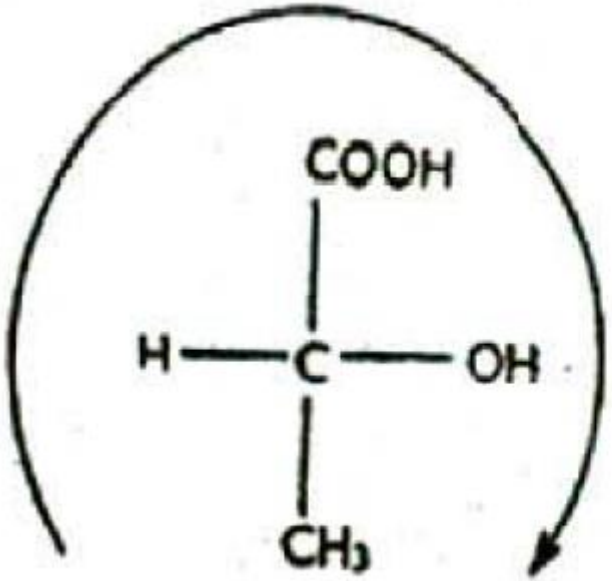

CH3
H
C
OH
CH3
H
C
OH
CO2H
CO2H


CH3
HO
C
H
CH3
HO
C
H
CO2H
CO2H

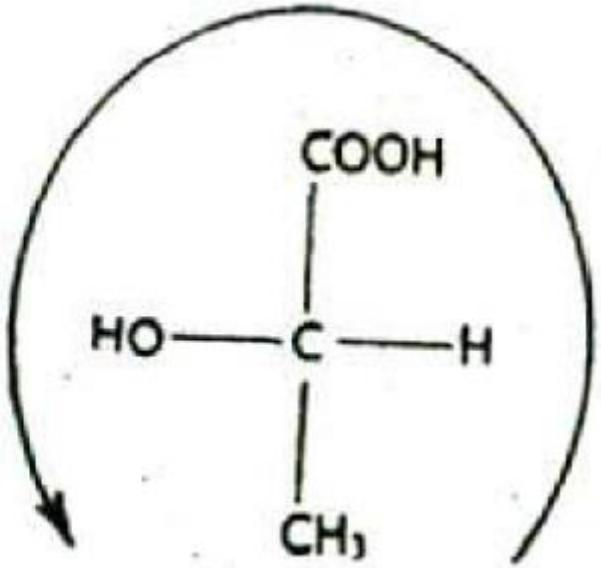
ASSIGNING CONFIGURATIONS TO CHIRAL MOLECULES

Absolute and Relative Configuration

The actual 3-D arrangement of groups in a chiral molecule is called absolute configuration. While discussing optical isomerism, we must distinguish between relative and absolute configuration (arrangement of atoms or groups) about the asymmetric carbon atom. Let us consider a pair of enantiomers, say (+)- and (-)- lactic acids.



(+)-lactic acid



(−)-lactic acid

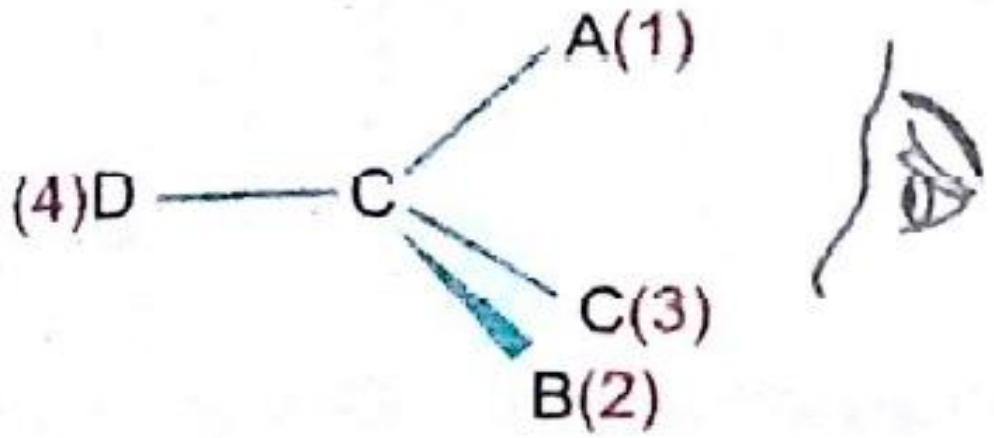
We know that they differ from one another in the direction in which they rotate the plane of polarized light. In other words, we know their relative configuration in the sense that one is of opposite configuration to the other, But we have no knowledge of the absolute configuration of the either isomer. That is, we cannot tell as to which of the two possible configurations corresponds to (+)acid and which to the (—)-acid.

R-S System

The actual 3-dimentional arrangement of groups in a chiral molecule is called absolute configuration. We can specify the configuration by using the **R-S system.**

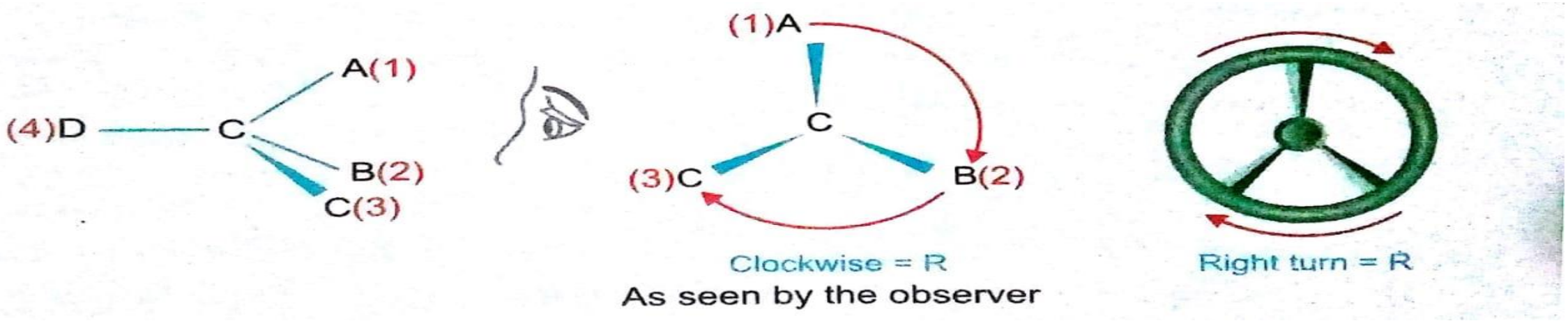
This is a newer and more systematic method of specifying absolute configuration to optically active compounds. Since it has been proposed by **R.S. Cahn, C.K. Ingold and V. Prelog,** therefore known as Cahn-Ingold Prelog system. This system of designating configuration has been used increasingly since the early 1960 and may eventually replace the DL-system.

In this system, four groups attached to the chiral carbon are arranged in decreasing order of priority (1,2,3,4) by applying priority rules. We then view the chiral carbon with the lowest priority group (4) on the side opposite the observer.

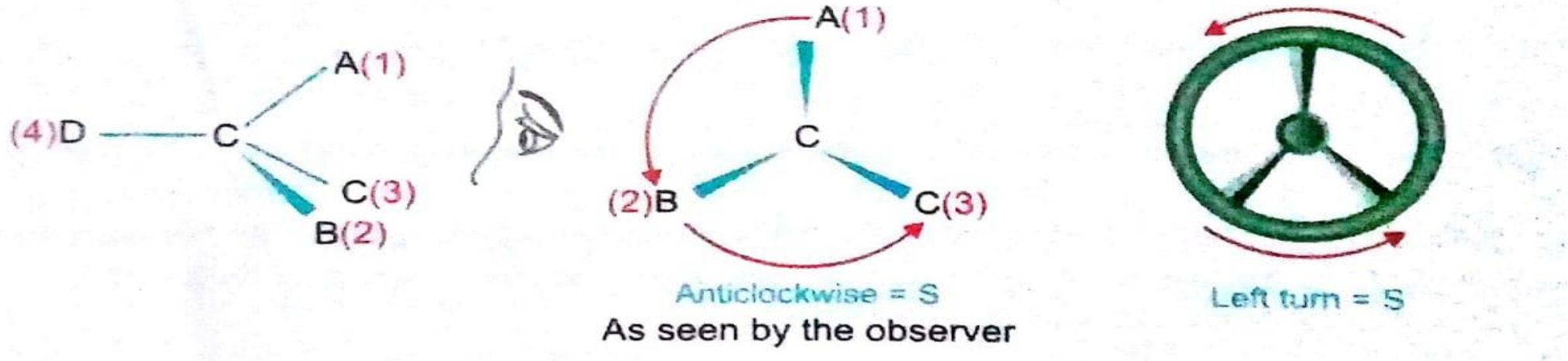


In the above example, **A** has the highest priority followed by **B** and **C,** while **D** has the lowest priority (4).

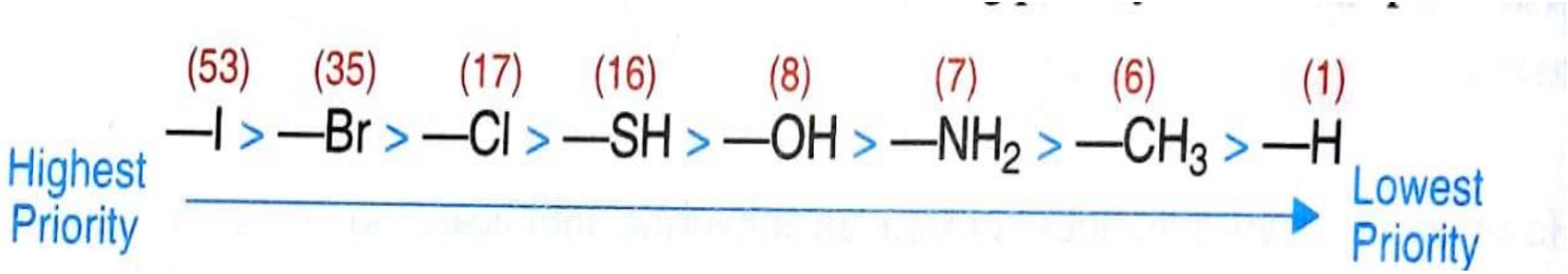
(i) If the eye while moving from 1-2-3, travels in a clockwise or right-hand direction, the configuration is designated **R (Latin, Rectus—right).**



(ii) If the eye while moving from 1-2-3 travels in counterclockwise or left-hand direction, the configuration is designated **S (Latin, Sinister= left).**

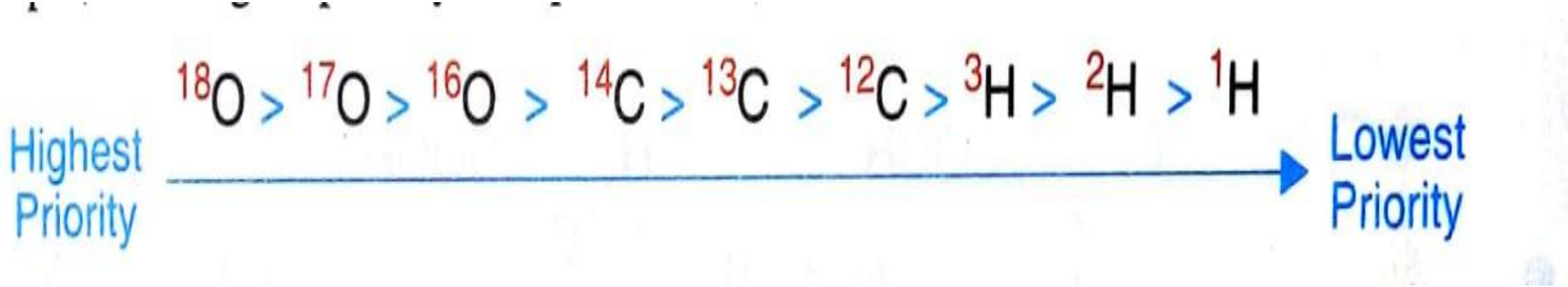


RULE 1: Look at the four atoms directly attached to the chirality center, and rank them according to atomic number. The atom with the highest atomic number has the highest ranking (first), and the atom with the lowest atomic number (usually hydrogen) has the lowest ranking (fourth).

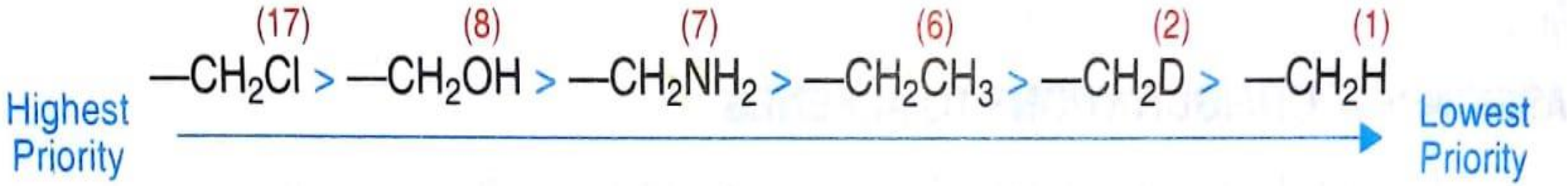


RULE 2:

For isotopes, the higher the atomic mass the higher the priority. For example, deuterium (Hydrogen-2) has higher priority than protium (Hydrogen-1)

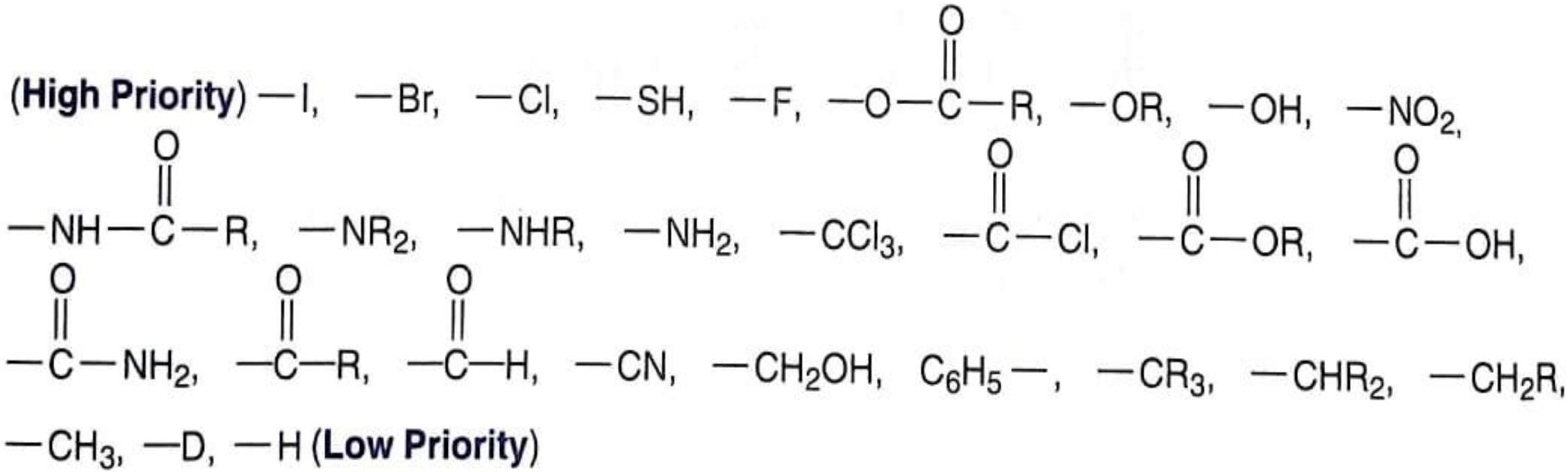


RULE 3: If a decision can't be reached by ranking the first atoms in the substituent, look at the second, third, or fourth atoms away from the chirality center until the first difference is found.



RULE 4: Multiple-bonded atoms are equivalent to the same number of single bonded atoms.

Priority sequence of common groups and atoms



Consider the following example and specify configuration by **R or S** notation = 1,1-chlorobromoethane

ClBrCHCH3

Step-1: Determine the priority of groups attached to the chiral carbon atom

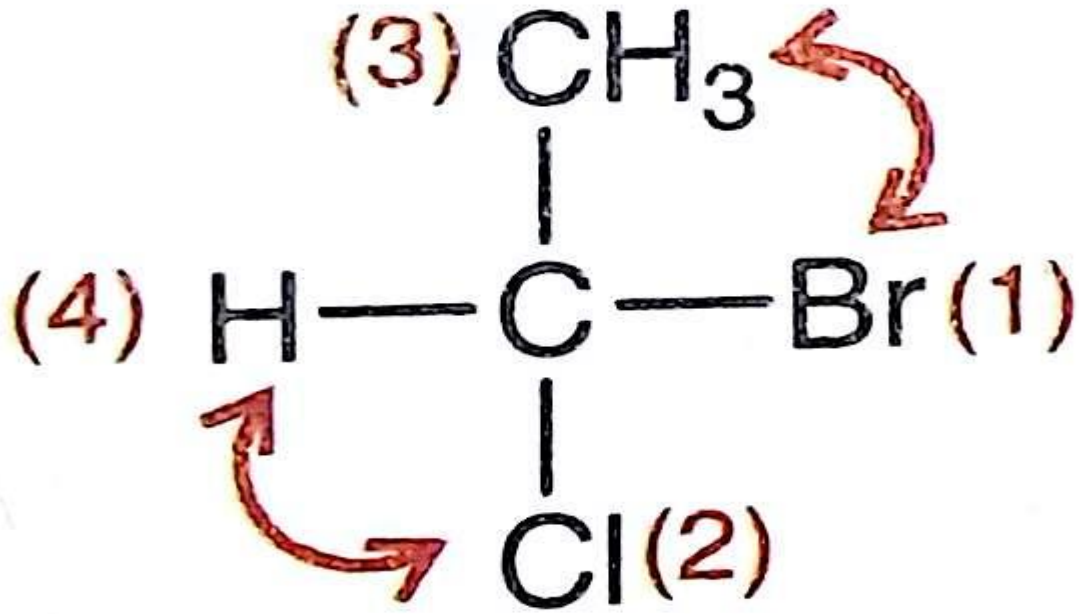
Hence the priority order is

$$Br > Cl > CH_3 > H$$

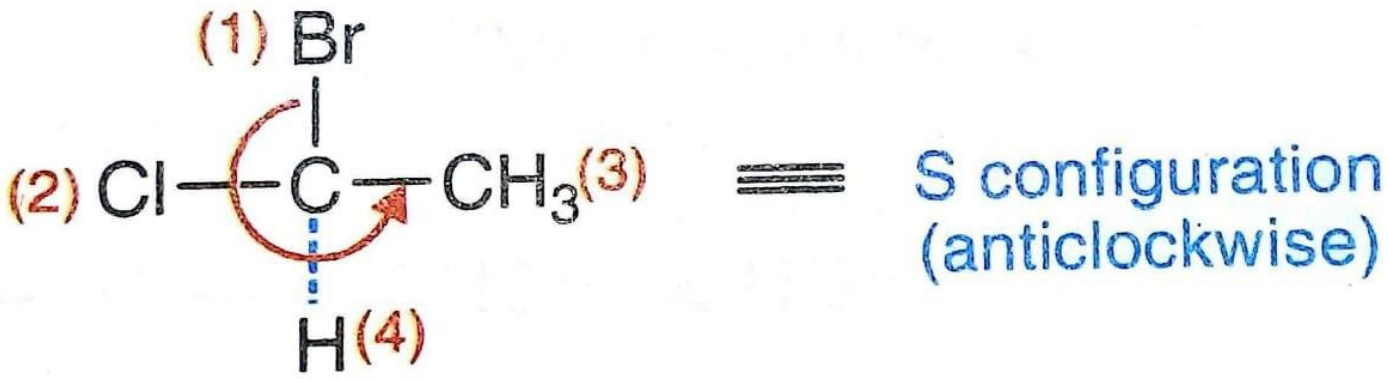
Step-2:

Position the lowest priority group down away from the observer. This is done by interchanging groups bonded to the asymmetric carbon.

Remember that interchanging any pair of groups in a fischer projection inverts the configuration. Interchanging two pairs of groups retains the original configuration. Thus, the interchange operation must always be done in pairs to avoid a configuration change.



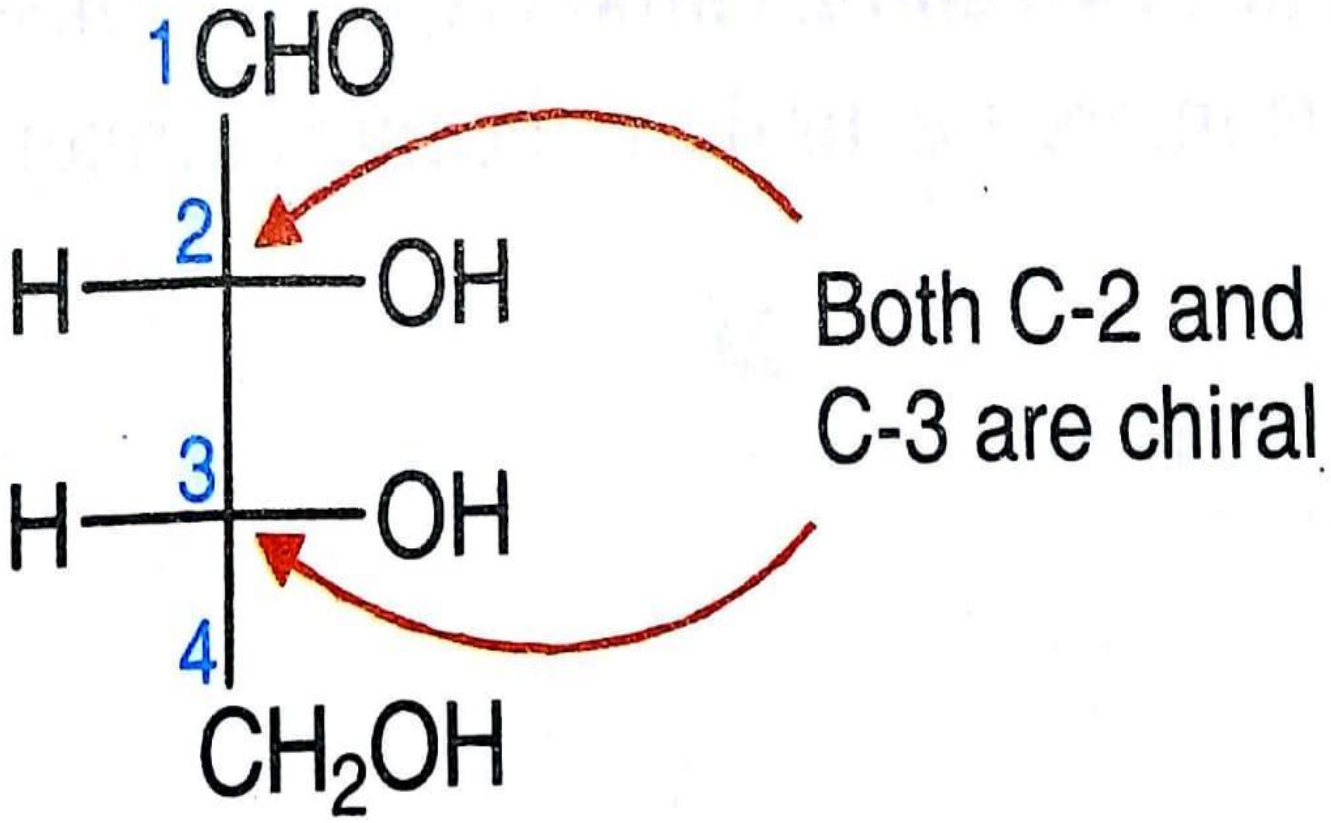
Specify the direction of decreasing priority of the three groups (1-3). Ignore the lowest priority group that is **H.** If the groups (1,2,and 3) are arranged in clockwise fashion, the configuration is **R.** If the groups occurs in anticlockwise fashion, the configuration is **S.**



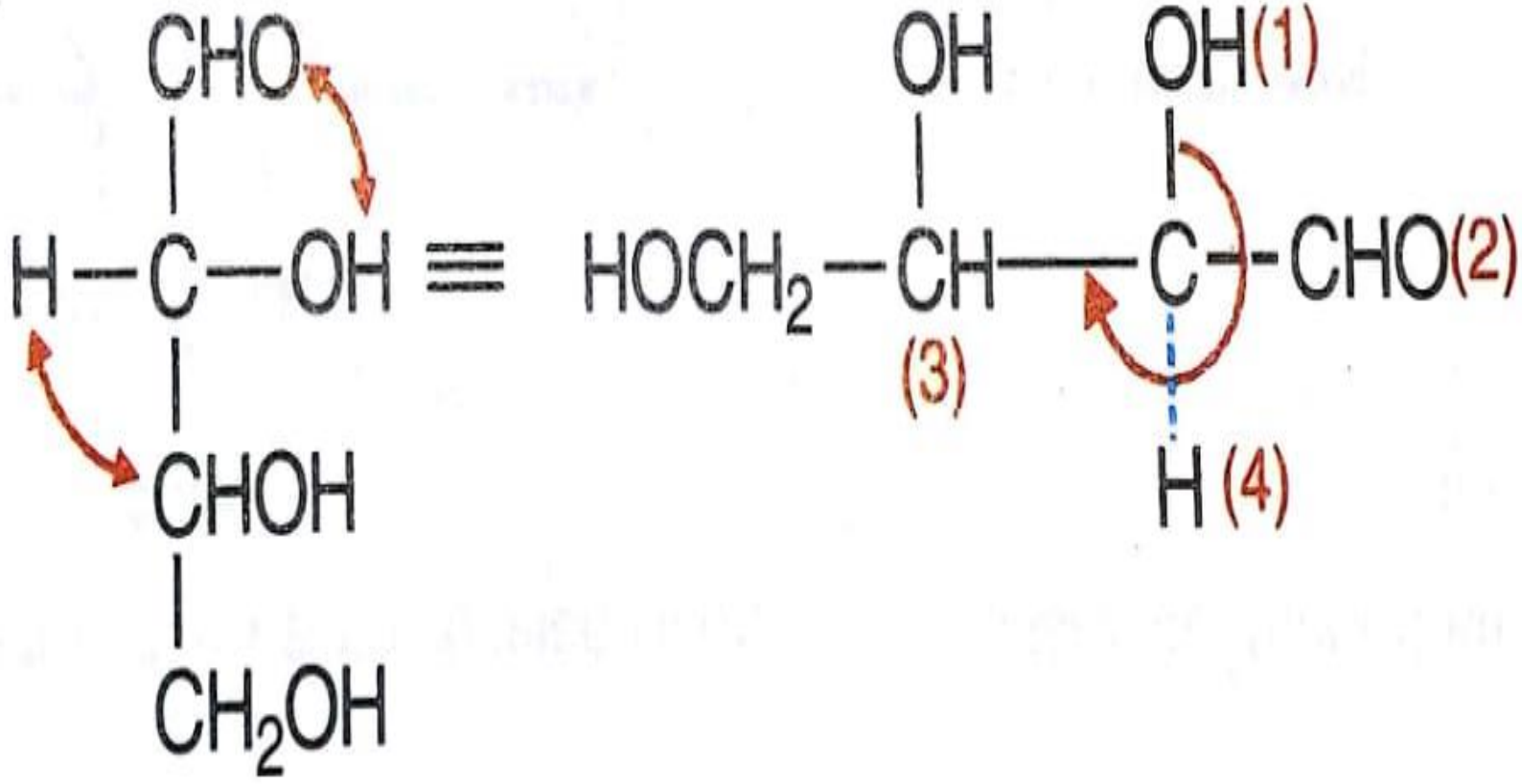
In the above example, configuration is S because groups (1,2 and 3) are arranged in anticlockwise fashion.

Configuration of compounds with more than 1 chiral center

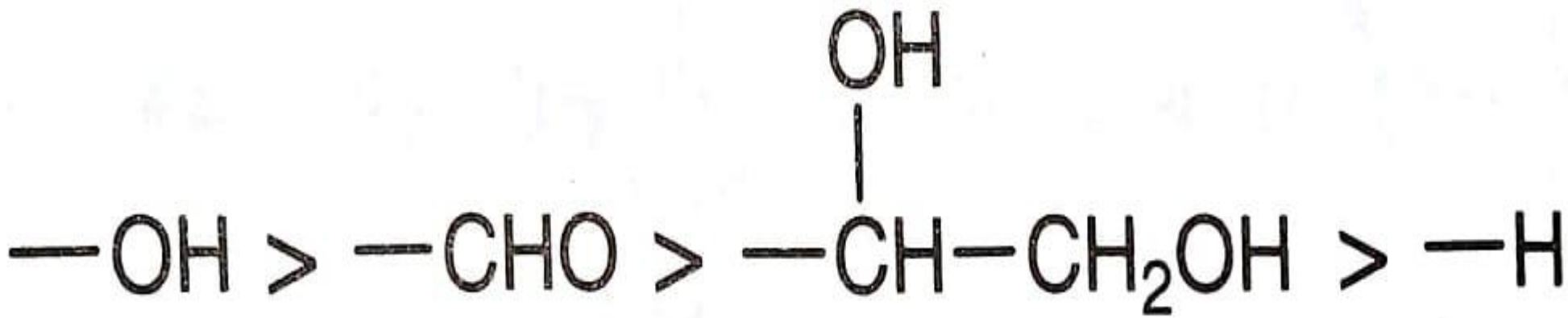
The configuration of compounds with more than one chiral center can also be specified by the R-S system. The configuration of each chiral carbon is determined individually, using the same rules as for compounds with one chiral center.



Configuration for carbon 2:

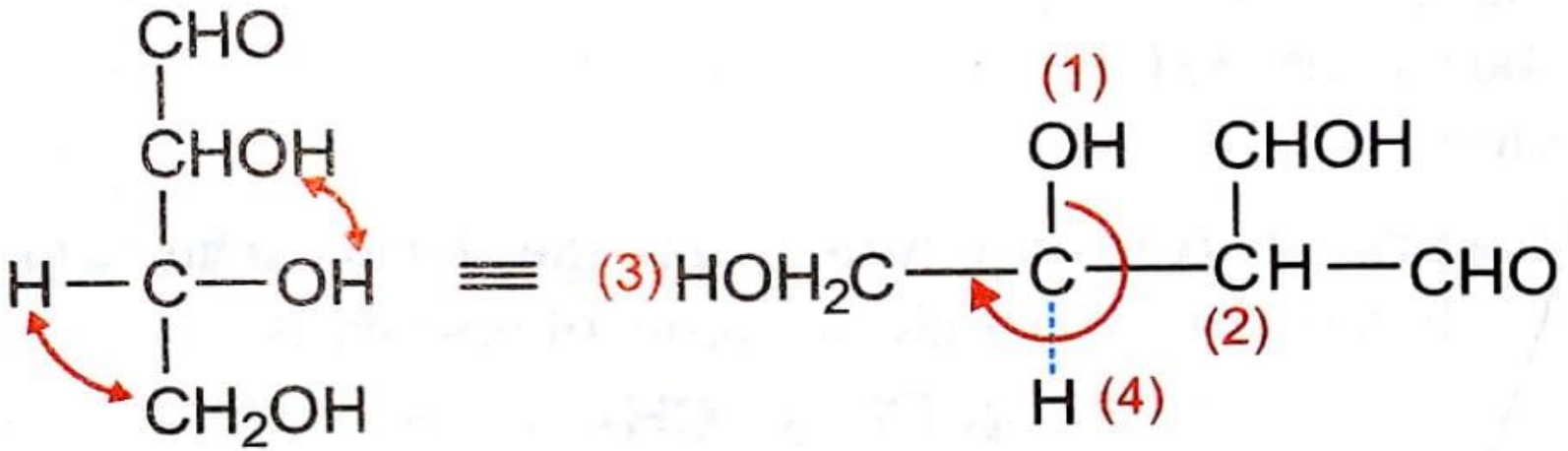


Order of priority is:

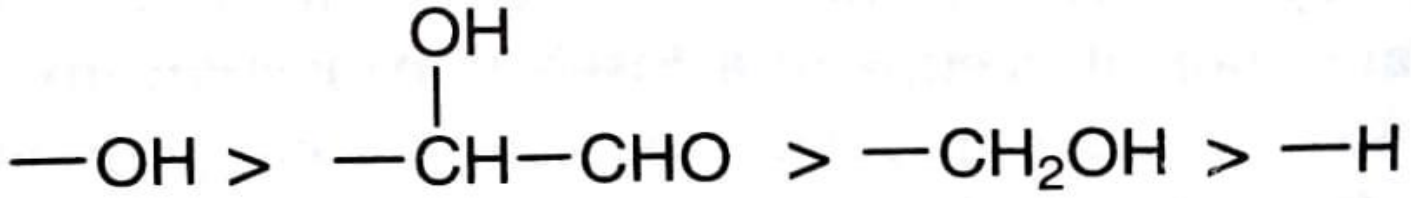


Configuration at C-2 is (2R)

Configuration for carbon 3:

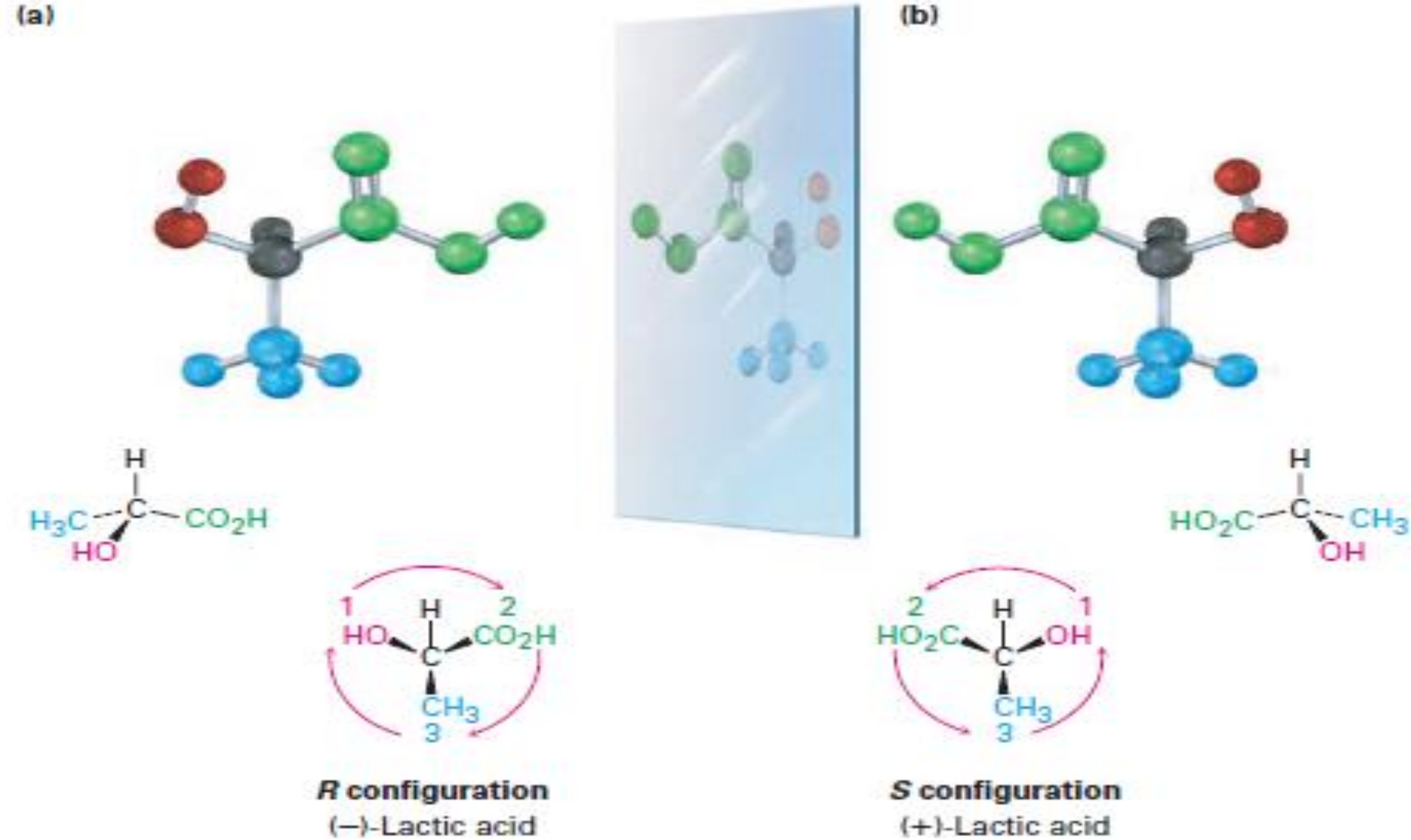


Order of priority is :



Configuration at C-3 is (3R)

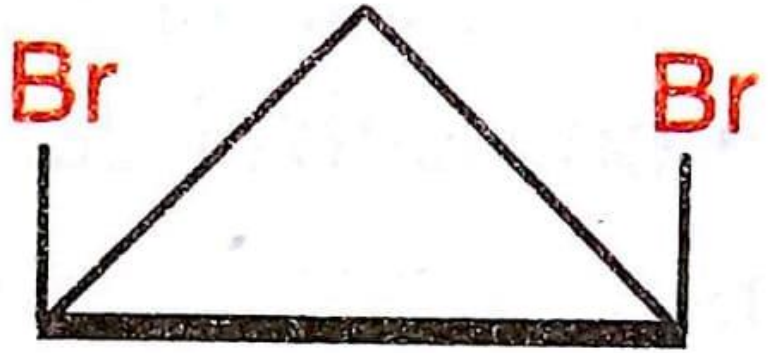
The name of compound is **(2R,3R)-**2,3,4-trihydroxybutanal


(a)
(b)
H
H3C
C
CO2H
HO
1
2
3
R configuration
(–)-Lactic acid
HO2C
OH
CH3
S configuration
(+)-Lactic acid

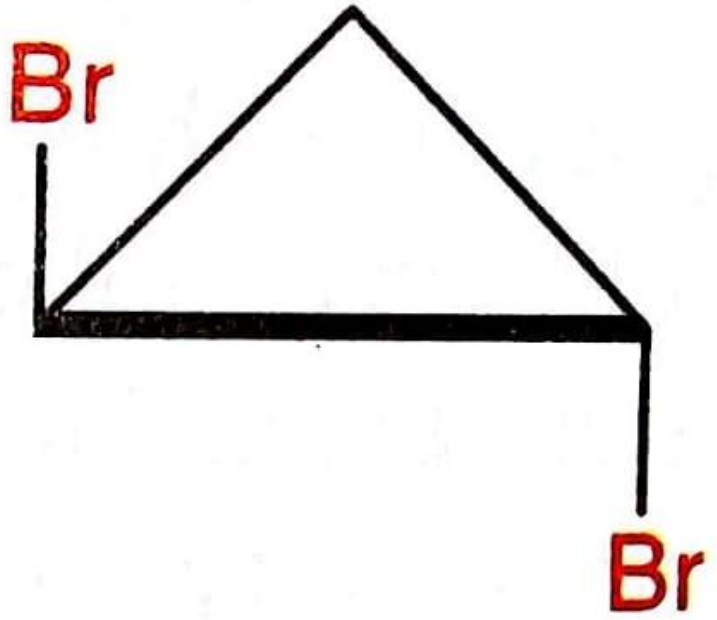
Look at (-)-lactic acid for an example of how to assign configuration. Sequence rule 1 says that OH is ranked 1 and H is ranked 4, but it doesn't allow us to distinguish between CH3 and CO2H because both groups have carbon as their first atom.

Sequence rule 2, however, says that CO2H ranks higher than CH3 because O (the highest second atom in CO2H) out ranks H (the highest second atom in CH3). Now, turn the molecule so that the fourth-ranked group (H) is oriented toward the rear, away from the observer. Since a curved arrow from 1 (OH) to 2 (CO2H) to 3 (CH3) is clockwise (right turn of the steering wheel), (-)-lactic acid has the *R* configuration. Applying the same procedure to (+)-lactic acid leads to the opposite assignment.

OPTICAL ISOMERISM IN CYCLIC COMPOUNDS



cis



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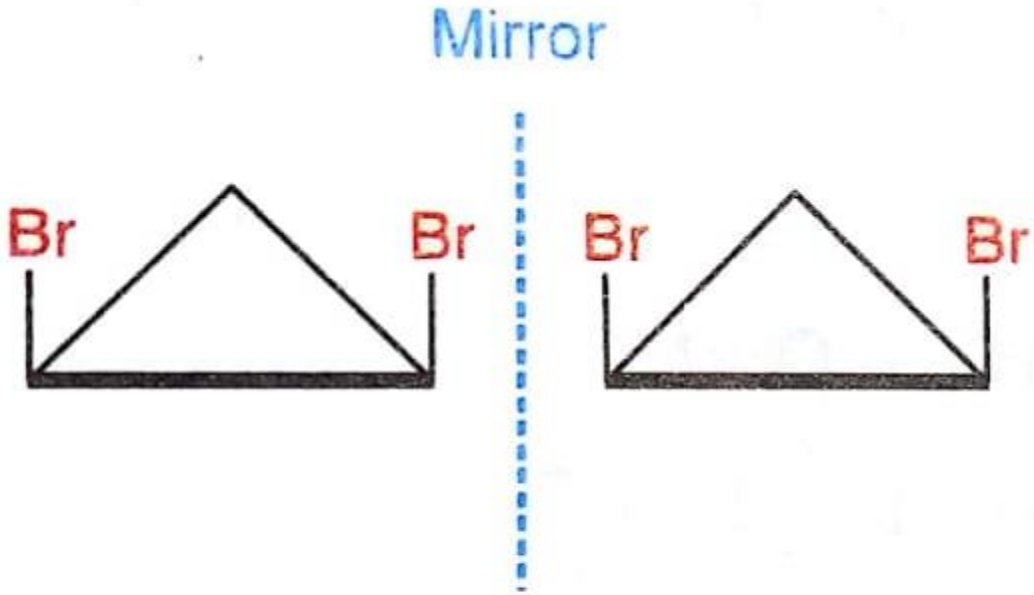
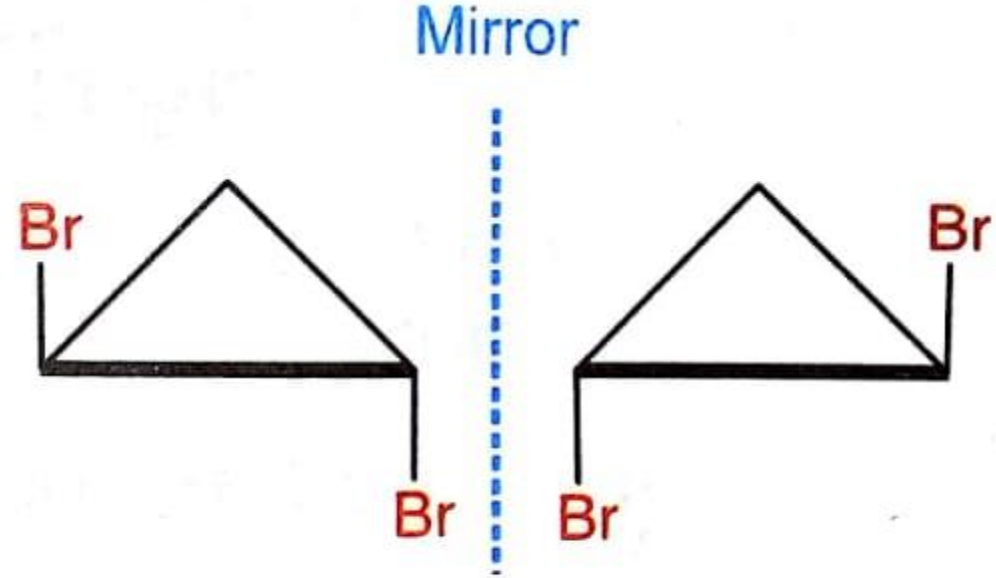


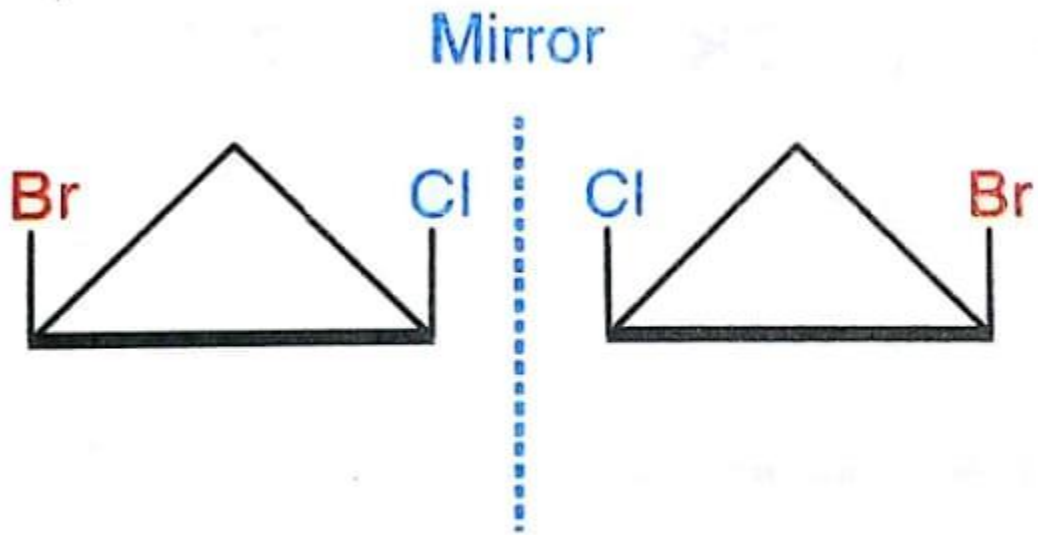
cis

Superimposable mirror images, *meso*

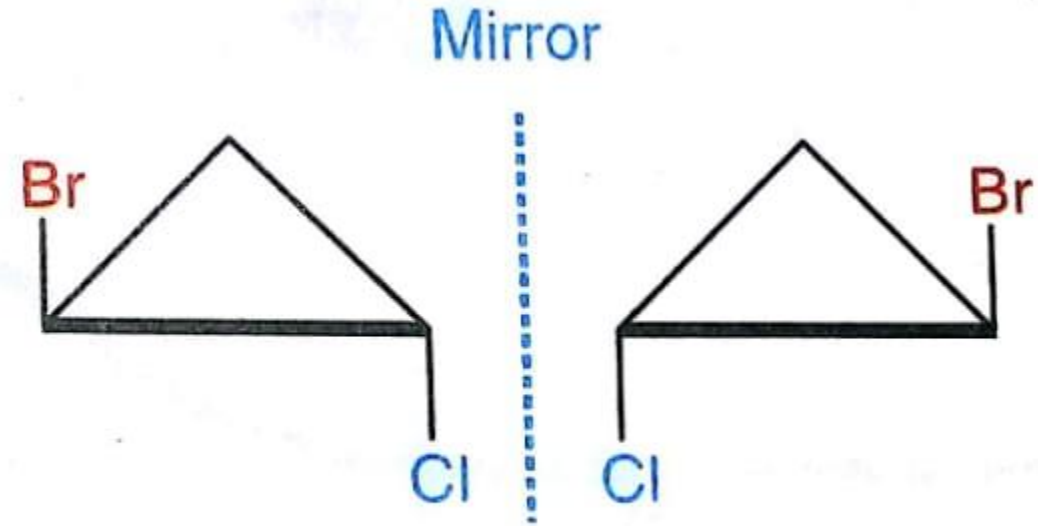


trans

Nonsuperimposable mirror images, *enantiomers*



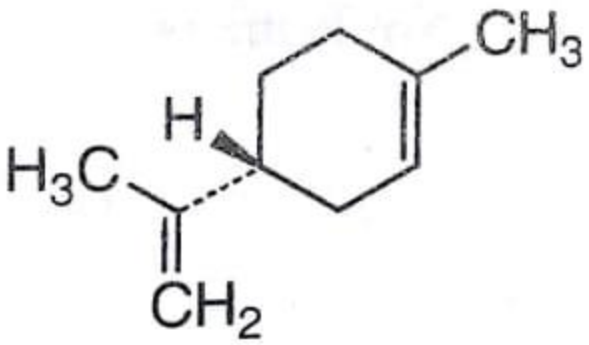
cis Enantiomers



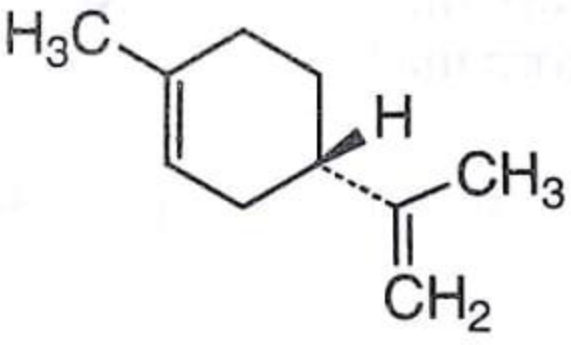
trans Enantiomers

OPTICAL ISOMERISM IN NATURE

The (+)-limonene has the odor of oranges while (-)-limonene has the odor of lemons

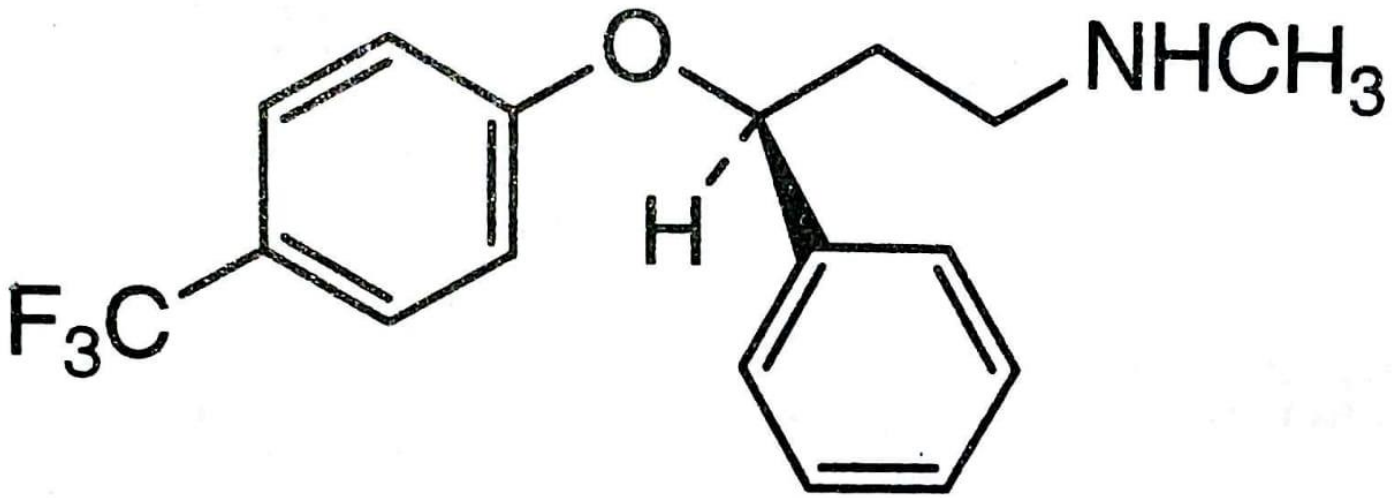


(+)-Limonene



(–)-Limonene

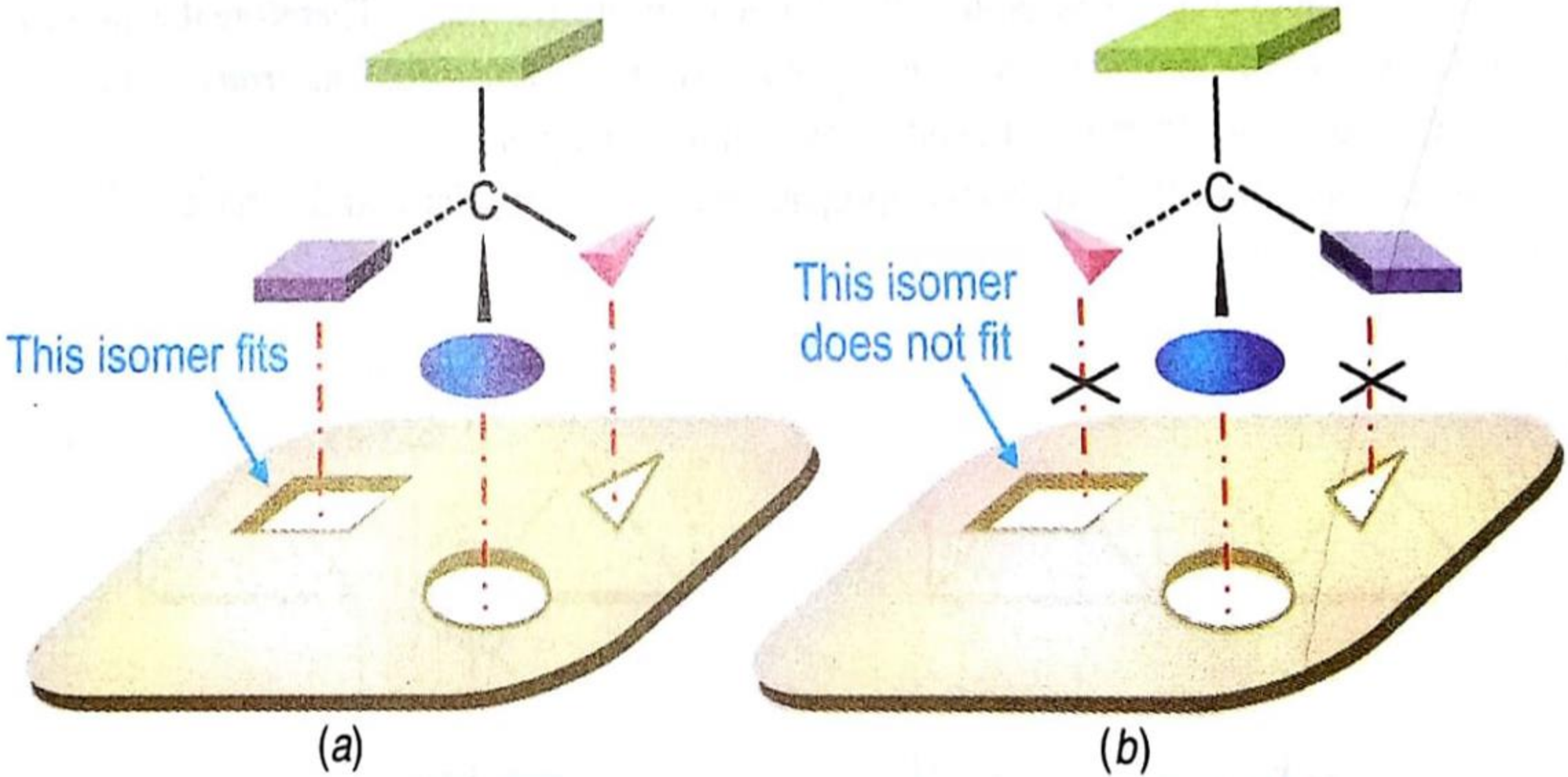
Racemic fluoxetine is an effective antidepressant but it has no activity against migraine. The pure S enantiomer, however, works remarkably well in preventing migraine



(S)-Fluoxetine
(Prevents migraine)

Why do different stereoisomers have different biological activity???

To exert its biological action, a chiral molecule must fit into a chiral receptor at a target site, much as a hand fits into a glove. But just as a right hand can fit only into a right-hand glove, so a particular stereoisomer can fit only into a receptor having the proper complementary shape. Any other stereoisomer will be a misfit like a right hand in a left-handed glove.


C
This isomer fits
(a)
C
This isomer does not fit
(b)