

1

STEREOCHEMISTRY

INTRODUCTION

Many organic compounds have same molecular formula but are different in their physical and chemical properties. These compounds are known as Isomers and this property is known as Isomerism.

Isomerism is of two types :

- a) Structural isomerism
- b) Stereoisomerism

a) Structural isomerism : In this molecules have same molecular formula but have different structures as a result of this they have different properties. Compounds having same molecular formula but different structures or structural formulae are called structural isomers and this property is known as structural isomerism. It is of 5 types :

- 1) Chain isomerism
- 2) Position isomerism
- 3) Functional isomerism
- 4) Metamerism
- 5) Tautomerism

b) Stereoisomerism : It arises due to different arrangement of atoms around the carbon in space. Molecules having the same molecular and structural formulae but different spatial arrangement of atoms are called stereoisomers and this phenomenon is known as stereoisomerism. It is of two types :

- 1) **Conformational isomerism :** Stereoisomers having different relative position of atoms within the molecule and which can be interconverted by simple rotation about sigma bonds are called conformational isomers. These interconversions do not require breaking and remaking of covalent bonds.
- 2) **Configurational isomerism :** Those stereoisomers which can be interconverted only by breaking and remaking of covalent bonds are called configurational isomers. These cannot be interconverted by simple rotation about sigma bonds. It is of two types :

✓a) Optical isomerism

✓b) Geometrical isomerism

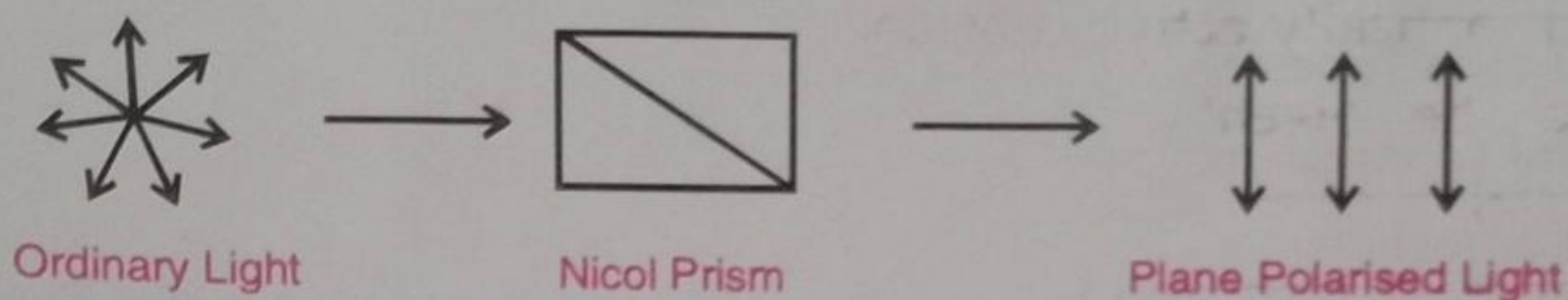
1. Optical Isomerism : Isomers which differ only in their behaviour towards plane polarised light i.e. one isomer rotates the plane of polarised light towards right and the other towards left to the same extent. Such pair of isomers are called optical isomers and the phenomenon is called optical activity.

In order to understand the phenomenon of optical isomerism and optical activity, we must know the following terms :

a) Plane polarised light : An ordinary ray of light consists of electromagnetic radiations of different wavelengths. These radiations vibrate in all planes at right angles to the direction in which it travels. Monochromatic light consists of waves of a particular (one) wavelength and these waves also vibrates in all planes.

When monochromatic light is passed through a Nicol prism (prism made from a particular crystalline form of CaCO_3 known as calcite), the light coming out of the prism has vibrations in only one plane. So, plane polarised light is defined as a beam of light having vibrations only in one plane.

The Nicol prism used to obtain plane polarized light is called a polarizer.



b) Optical activity : The optical activity was discovered by the French Chemist, Louis Pasteur in 1848. He studied that when a concentrated sodium ammonium tartrate solution was allowed to crystallize, two types of crystals separated out. Each type of crystals when dissolved in water rotated the plane of polarised light. This observation led to the discovery of optical activity.

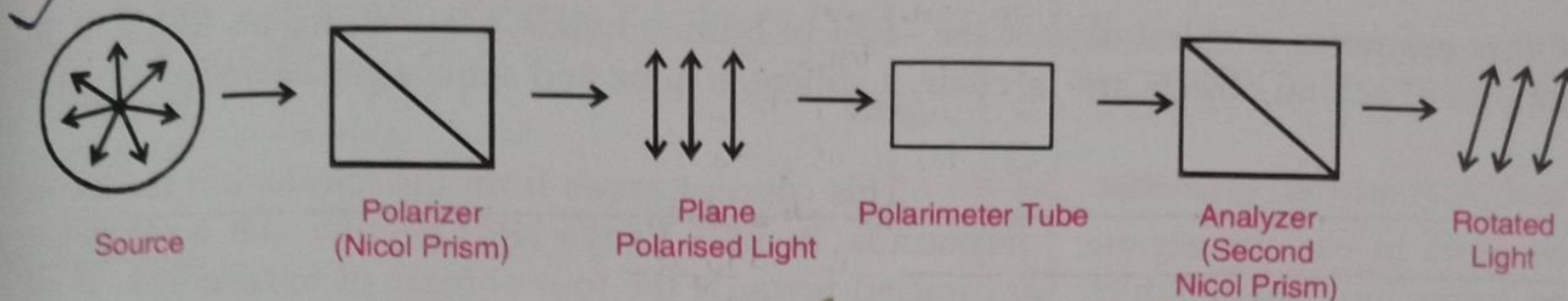
(Substances which can rotate the plane of polarised light through a certain angle are called optically active substances and this property of a substance by virtue of which the organic substances rotate the plane polarised light is called as optical activity. If the plane polarised light shows no change in angle it means that the substance is optically inactive.)

The optically active compounds can rotate the plane polarised light either towards right hand side or left hand side. The compounds which can rotate the plane of polarised light towards right side (clockwise direction) are called dextro rotatory and is represented by prefix (+) or "d" whereas the compounds which can rotate the plane of polarised light towards left side (anticlockwise direction) are called laevorotatory and is represented by prefix (-) or "l".

c) Angle of Rotation and Specific Rotation : The angle (in degrees) through which the plane polarized light is rotated by an optically active substance is called as angle of rotation. It is denoted by α . The instrument which is used for measuring the angle of rotation of the plane polarised light is known as Polarimeter.

A Polarimeter contains a light source (sodium lamp), two Nicol prisms and a polarimeter tube. The first Nicol prism which is near to the source is called polarizer and the second Nicol prism is called the analyzer. The axis of polarizer is fixed while that of analyzer can be changed. Polarimeter tube is placed between the polarizer and the analyzer, which contains the solution of optically active substance.

The arrangement of polarizer and analyzer with their axes perpendicular to each other is used to study the effect of optically active compounds towards plane polarized light. For example, the optically active compound is placed in polarimeter tube, if some light appears it indicates that compound has rotated plane polarised light through certain angle.



Schematic Representation of Polarimeter and Optical Activity

The angle of rotation depends upon various factors like :

- 1) Nature of optically active substance
- 2) Nature of the solvent
- 3) Concentration of solution
- 4) Wavelength of monochromatic light used
- 5) Length of the polarimeter tube containing the sample
- 6) Temperature of the solution

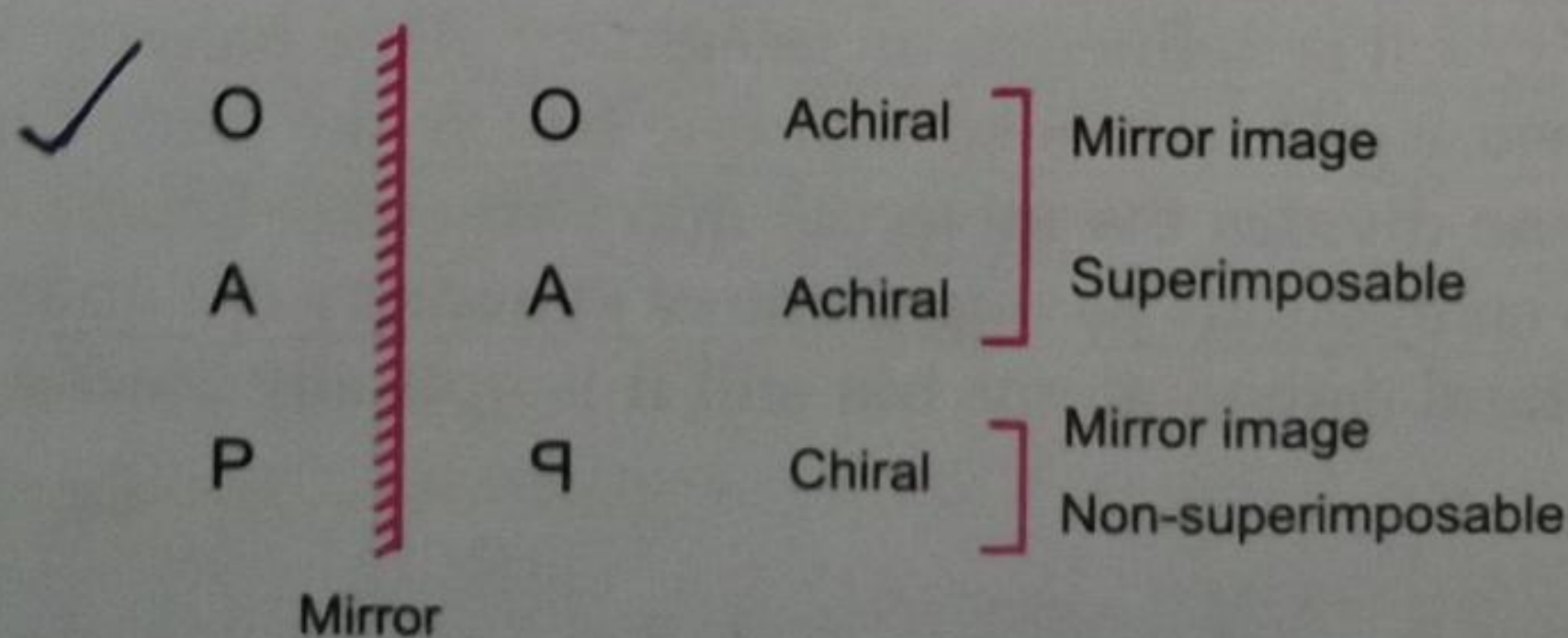
The optical activity is expressed in terms of specific rotation. Specific rotation is defined as the degree of rotation of plane polarised light produced by an optically active compound of concentration one gm/ml present in a polarimeter tube of length one decimeter at a specified temperature and wavelength. It is denoted by $[\alpha]_D^t$ where t is the temperature and D is the wavelength of light used. Generally D line of sodium vapour lamp having a wavelength of 5893\AA is used as the source of monochromatic light.

$$\checkmark \text{ Specific rotation } [\alpha]_D^t = \frac{\text{Observed angle of rotation } [\alpha]}{l \times C}$$

l = length of the polarimeter tube (dm)

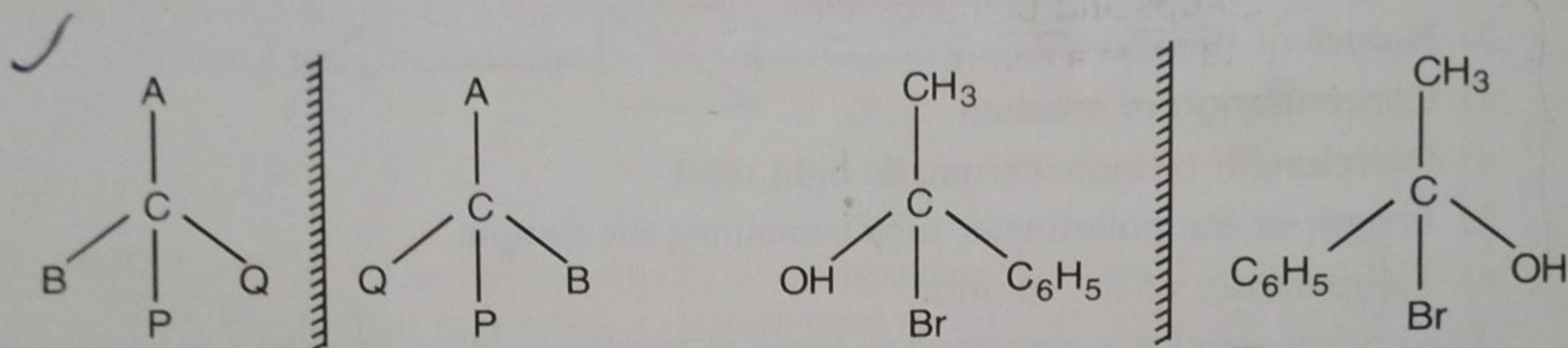
C = Concentration of optically active substance (gm/ml)

d) Chirality of molecules : It is observed that the molecular structure of all the optically active compounds is chiral (dissymmetric) in nature. A molecule is chiral or dissymmetric only if it is non super imposable on its mirror image. This property of non-super impossibility is called chirality. In contrast a molecule or an object which is superimposable on its mirror image is called achiral or symmetric for e.g. the english alphabet "O" and "A" are achiral while the alphabet "P" is chiral in nature.



Other examples of chiral objects are - Pair of human hands, some alphabets like E, P, F, J. Examples of achiral objects are- a chair, a sphere, a cube and some alphabets like "O" and "M".

e) Chiral and Asymmetric Carbon : This concept arises from the tetrahedral nature of carbon atom in various organic compounds. In 1873 Vant's Hoff assume that a saturated carbon forms four bonds which are directed towards the four corners of tetrahedron. If all the four atoms attached to the carbon are different then it will produce disymmetry. Such a carbon is known as chiral or disymmetric carbon. It can be represented as C_{ABPQ} where ABPQ are different groups. The mirror image of such carbon is non superimposable as shown below :



Non-Superimposable Mirror Images

If two atoms attached to the carbon atom are similar, the chirality is lost and the molecule becomes symmetrical. As a simple rotation through 180° about its axis will make the compound superimposable on its mirror image. For e.g. 2-chloropropane is an achiral molecule. A chiral carbon is denoted by (*) on the carbon atom. For e.g. lactic acid ($CH_3-C^*HOH-COOH$), 2,3-dihydroxy propanal ($CHOH-C^*HOH-CHO$), are chiral and are optically active.

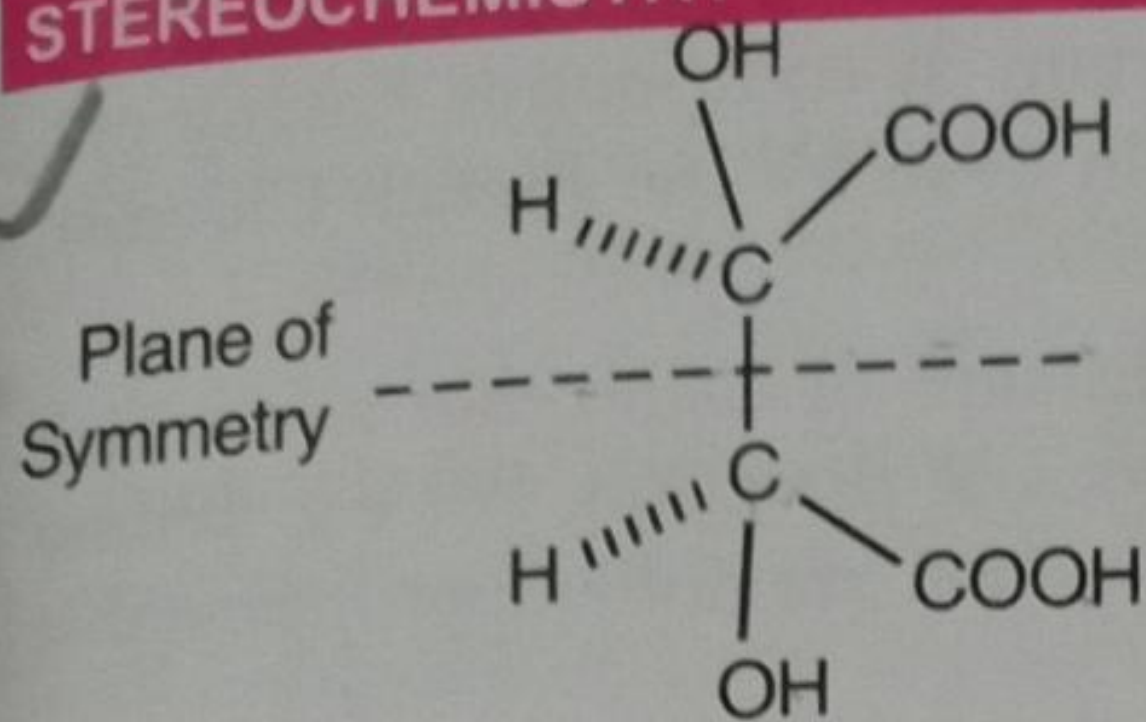
From the above examples, it is clear that the necessary and sufficient conditions for a compound to be optically active is the presence of one or more chiral carbon atoms and the chirality of the molecule as a whole.

f) Elements of Symmetry : There are three elements of symmetry which helps in identifying the superimpossibility of a molecule or an object and its mirror image. Chiral objects do not have an element of symmetry while achiral objects and molecules have one or more elements of symmetry. The three elements of symmetry are :

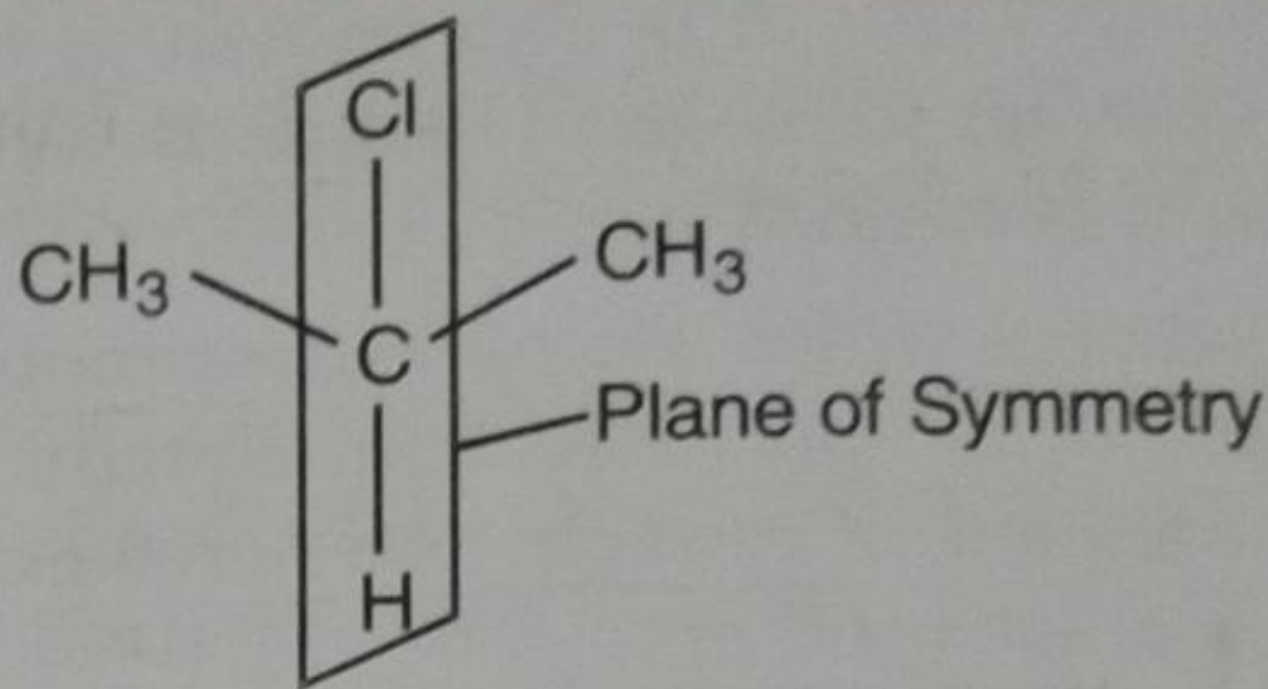
- 1) Plane of symmetry
- 2) Centre of symmetry
- 3) Axis of symmetry

1) Plane of symmetry : It is defined as an imaginary plane passing through the molecule, which divides it into two equal halves so that one half is the mirror image of the another half. The imaginary plane divides the molecule into two equal halves which are mirror images of one another. So compounds having plane of symmetry are optically inactive. For e.g. Tartaric acid has two chiral carbon atoms but still it is optically inactive as it has a plane of symmetry.

STEREOCHEMISTRY

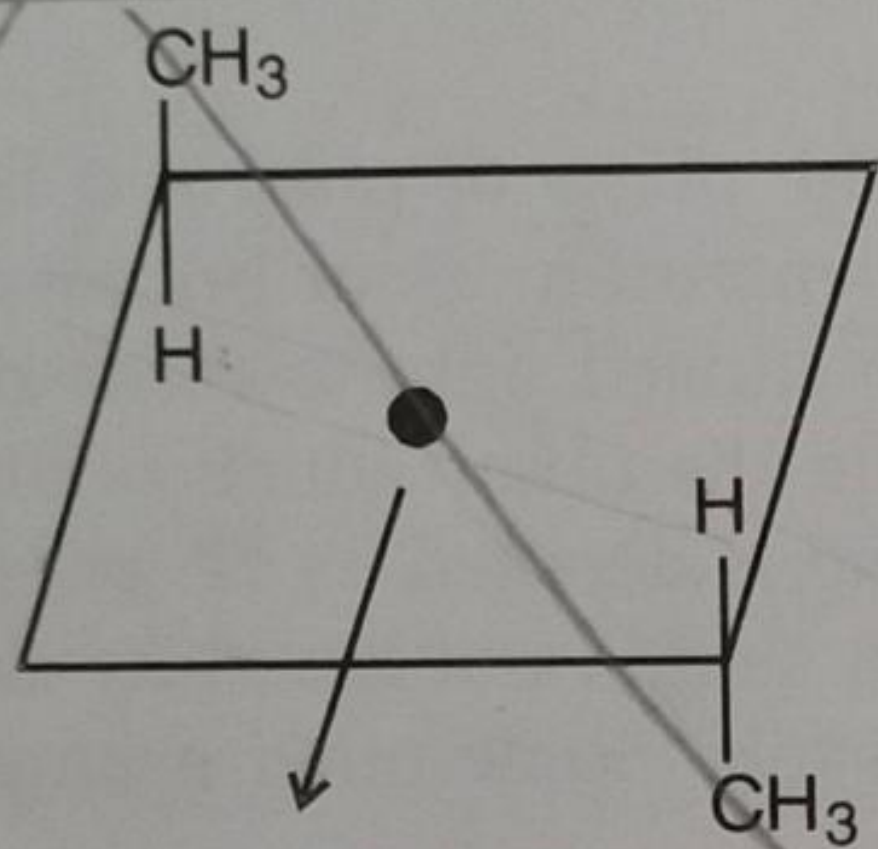


Meso-tartaric acid

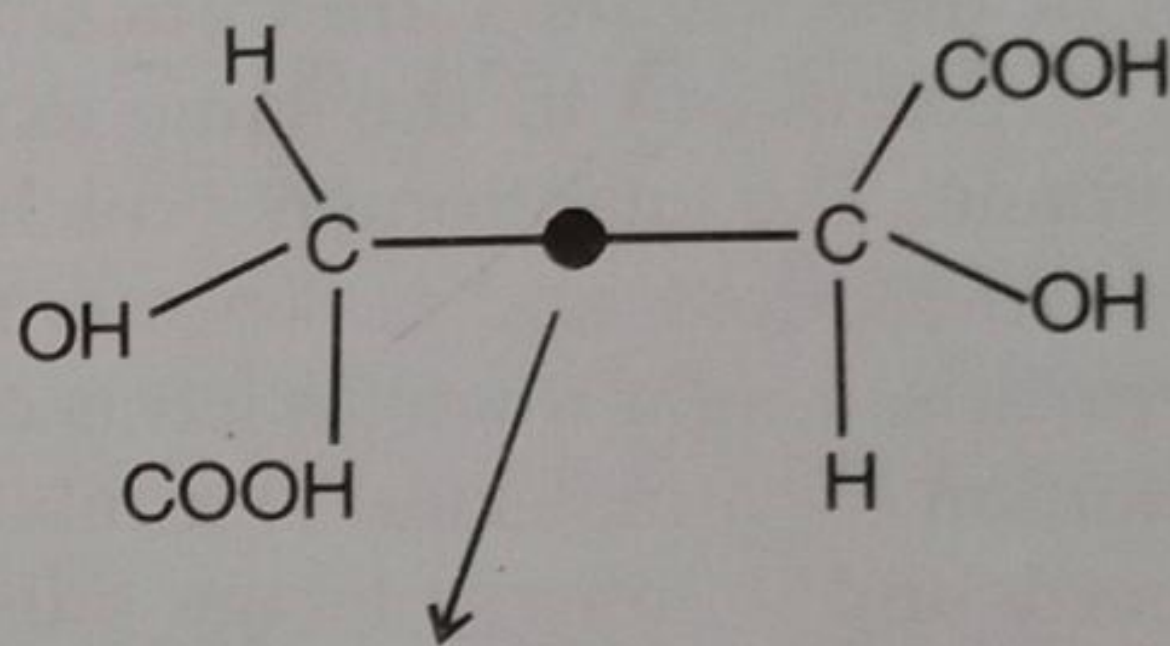


2-Chloropropane

2) Centre of symmetry : It is defined as the imaginary point in the molecule through which when lines are drawn on one side and produced an equal distance on other side, will meet identical or same groups and points on either side. For e.g. Trans-1, 3-dimethyl cyclobutane and mesotartaric acid have a centre of symmetry. So compounds having centre of symmetry are optically inactive in nature.

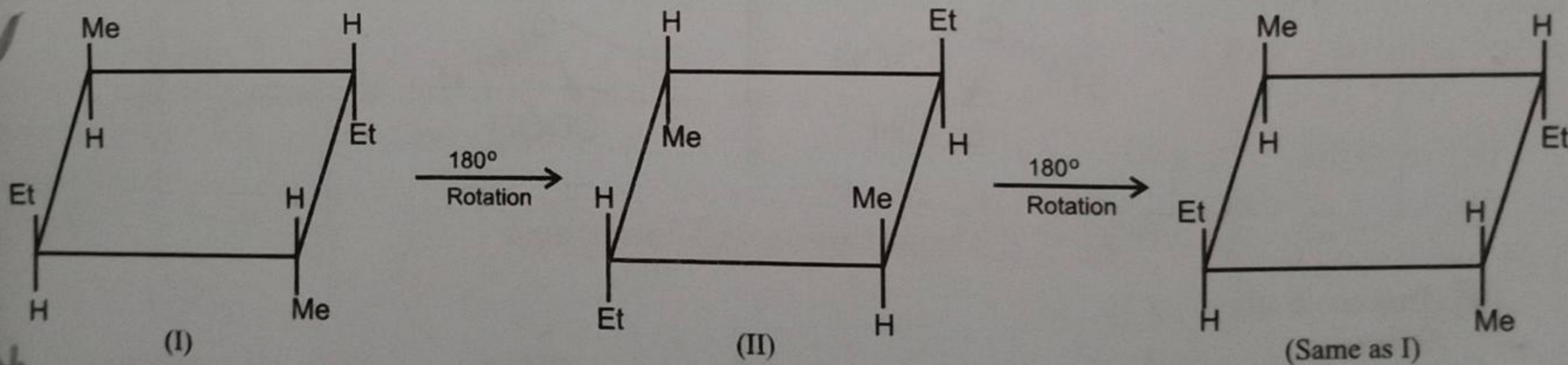


Centre of Symmetry



Centre of Symmetry

3) Axis of Symmetry : It is defined as an imaginary axis through which if a molecule is rotated through an angle of 360° it will give a molecule which is exactly similar to the original molecule. For e.g. 1,3-diethyl 2,4-dimethyl cyclobutane has an axis of symmetry and is achiral. Absence of axis of symmetry is the necessary condition for a molecule to be optically active.

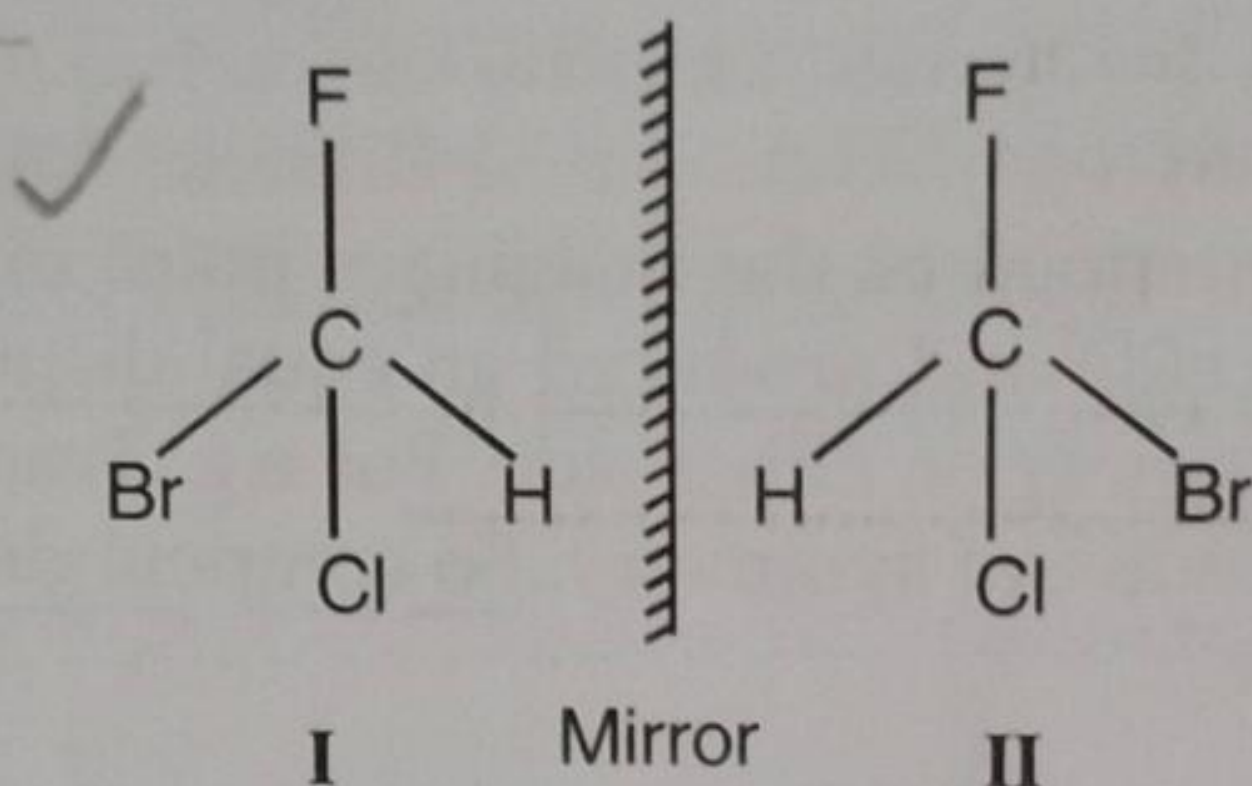


* **Optical Isomerism :** The stereoisomers which resemble each other in their chemical properties and most of the physical properties but differ only in their behaviour towards plane polarised light are called optical isomers and this phenomenon is called optical isomerism. It is further subdivided into three types :

- 1) Enantiomerism
- 2) Diastereoisomerism
- 3) Meso compounds

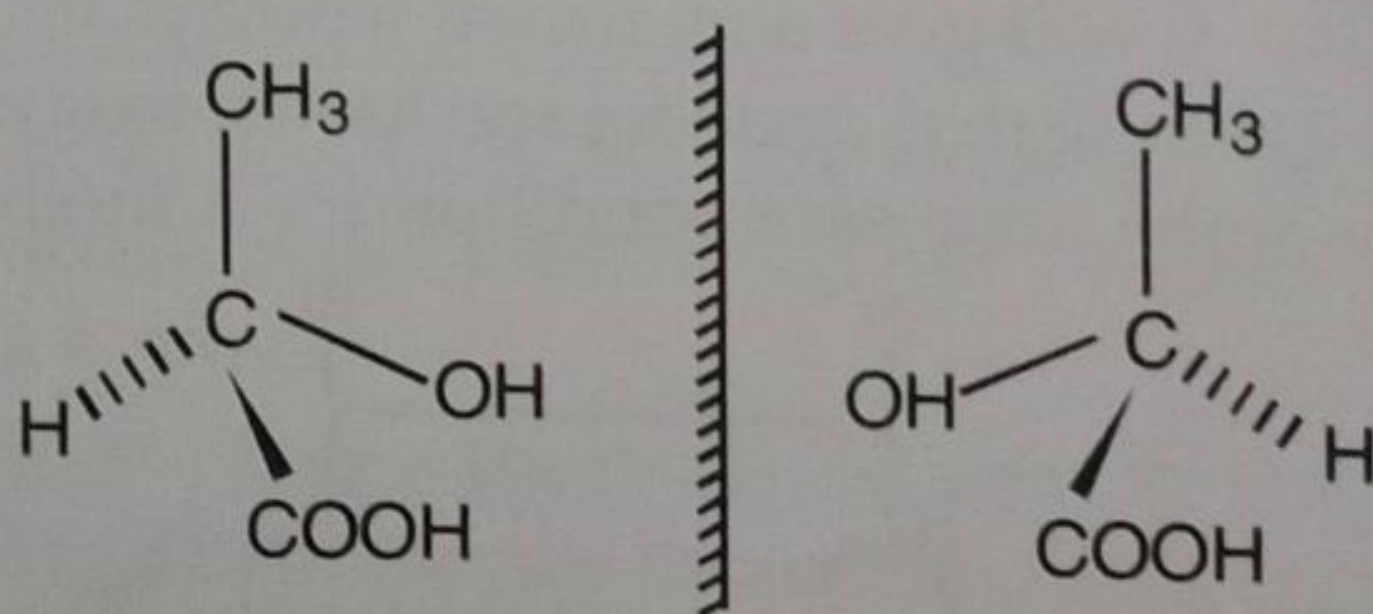
1) Enantiomerism : It is also known as optical isomerism in compounds having one chiral carbon or one stereogenic centre. It was discovered in 1848 by the French Chemist, Louis Pasteur. It is defined as :

Optical isomers which are non-superimposable mirror images of each other and which rotate the plane of the polarised light equally but in the opposite direction. For e.g. Bromo chloro fluoro methane. It exists in two stereo isomers I and II, which are non-superimposable mirror images of each other.



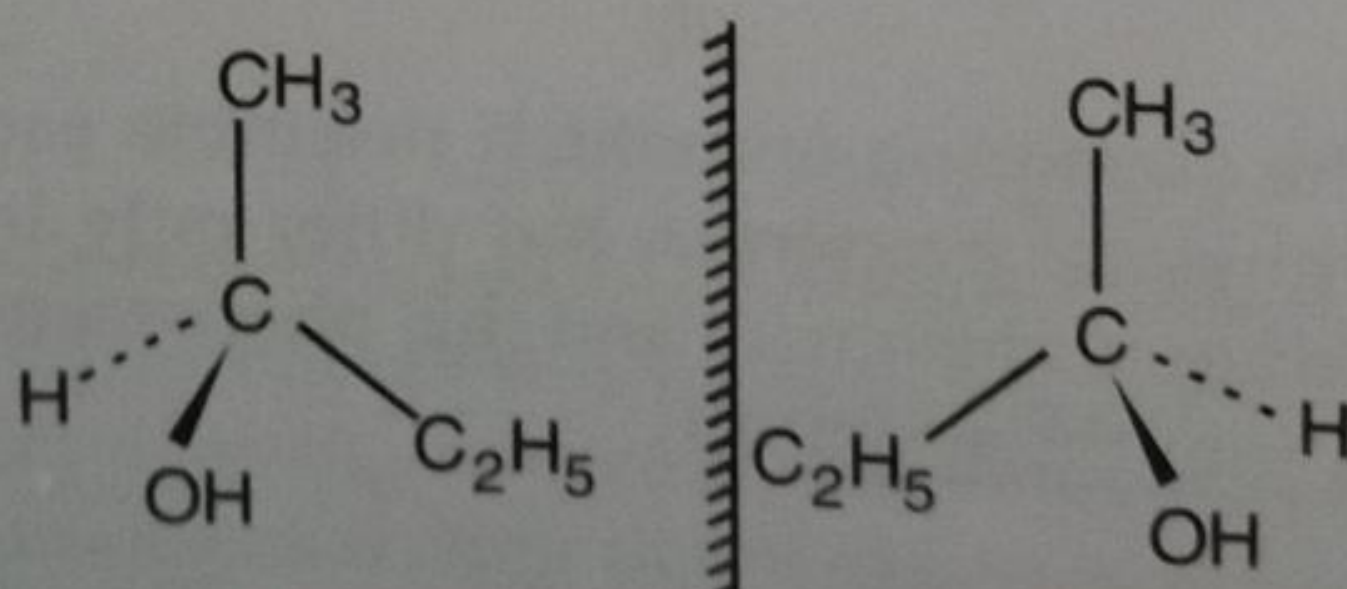
Both of these isomers are optically active and rotates the plane of polarised light in opposite direction but to the same extent. I and II are the enantiomers of bromo-chloro fluoromethane. The enantiomers which rotate the plane of polarised light towards right is called dextro-rotatory and is represented as "d" or (+) while the other which rotates the plane of polarised light towards left is called laevo rotatory and is denoted by "l" or (-). The basic condition for a molecule to exhibit enantiomerism that it should not have any element of symmetry and its mirror image must be non-superimposable. Some other examples of enantiomers are

(i) Lactic acid



Enantiomers of lactic acid

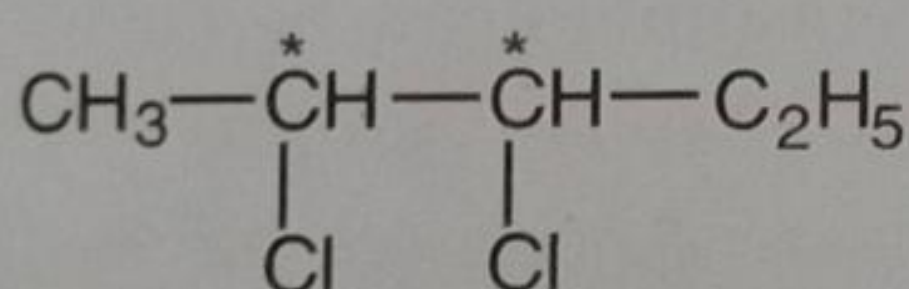
(ii) Butan-2-ol



Enantiomers of Butan-2-ol

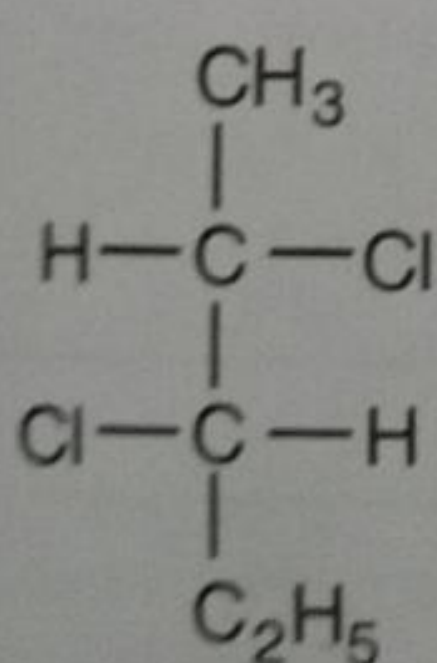
Properties of Enantiomers :

- Physical properties :** Enantiomers have similar physical properties like melting point, boiling point, solubility, dipole moment etc. They differ only in the direction of rotation of plane polarised light.
 - Chemical properties :** Enantiomers have identical chemical properties but they differ in the rate of reaction in which they react with other optically active reagent. For e.g. the reaction of enantiomers with achiral reagents like HBr, H_2SO_4 gives the same rate of reaction but if the enantiomers react with chiral reagents like lactic acid then they have different rate of reactions.
 - Biological properties :** Enantiomers have different biological properties for e.g.
 - D (+) glucose gets easily metabolised in body to produce CO_2 and H_2O but L(-) glucose is not metabolised and is excreted as such through the urine.
 - Some bacteria ferment the dextro form of a compound without affecting the laevo form.
 - (-) quinine treats the malaria fever but (+) quinine does not.
 - L(-) thyroxine is the active hormone secreted by thyroid gland and is highly active than its D(+) isomer.
- 2) **Diastereo isomerism :** It is also known as optical isomerism in compounds having two different chiral carbon atoms. It means a compound which contains two or more chiral atoms exists in more than two stereoisomeric forms. For example 2,3-dichloropentane it has two chiral carbon atoms.

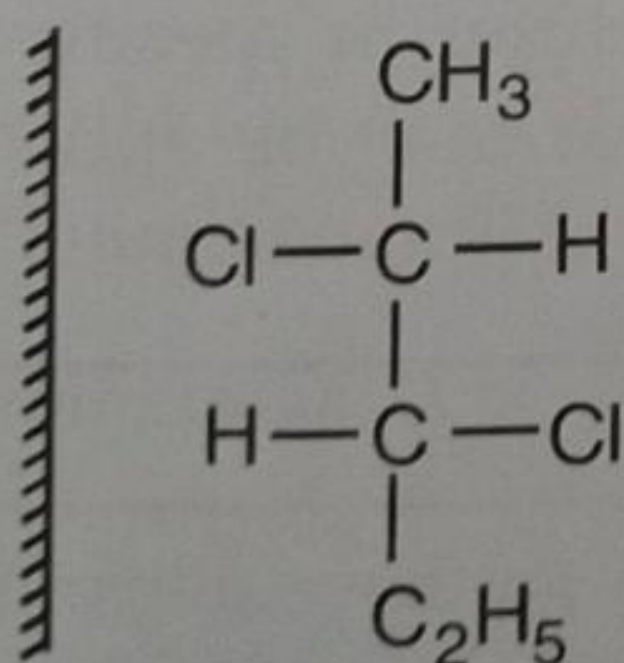


It exists in four stereoisomeric forms
i.e. I, II, III and IV

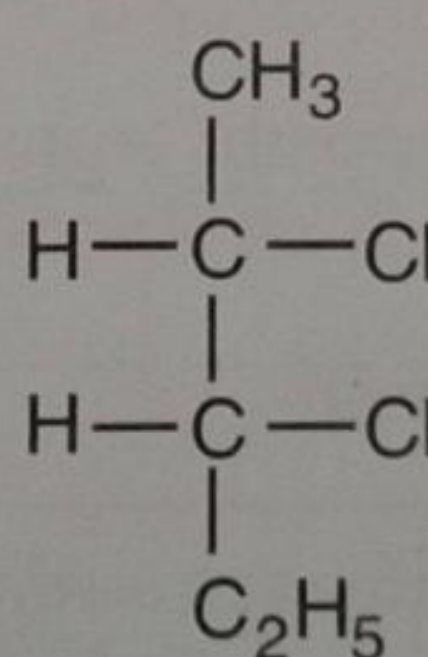
$$(2^n)$$

2,3-Dichloropentane

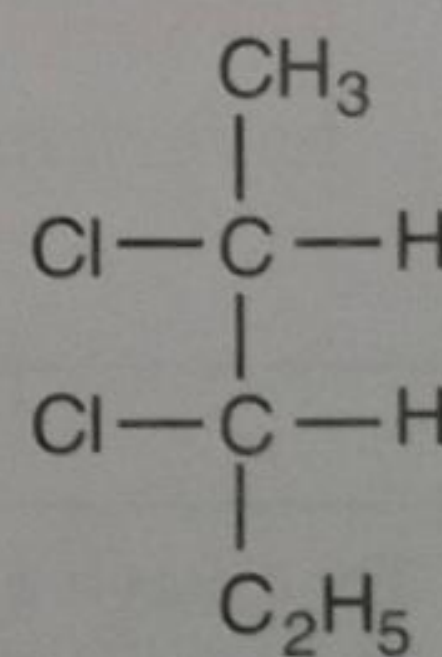
(I)



(II)



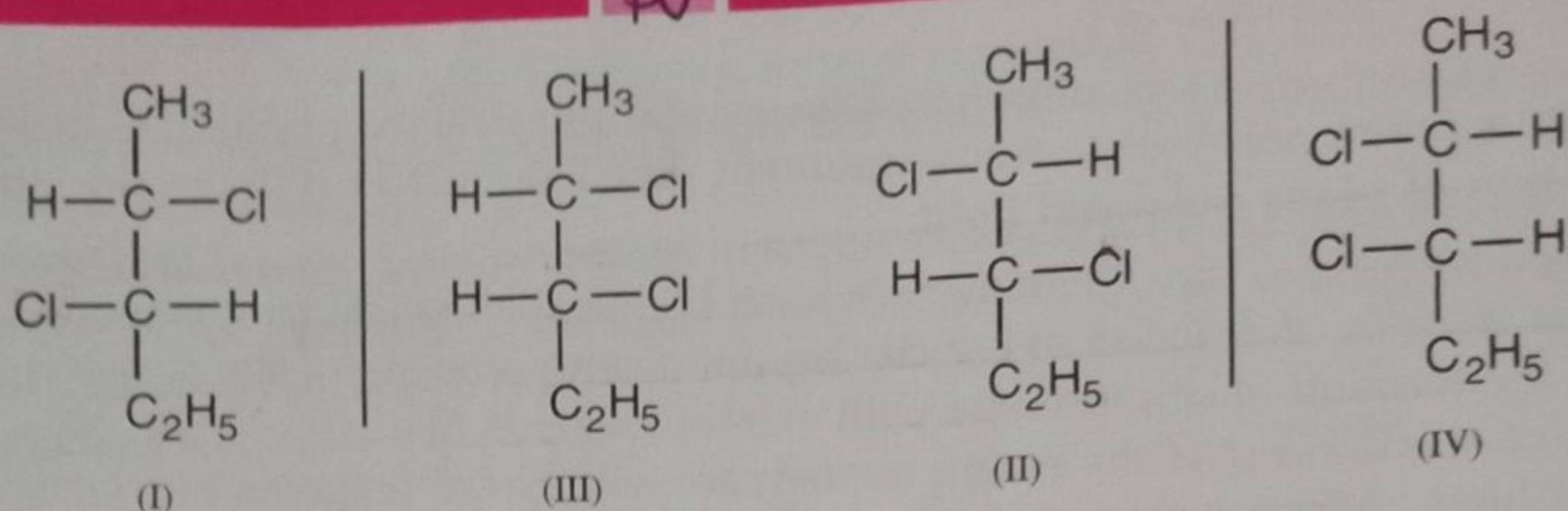
(III)



(IV)

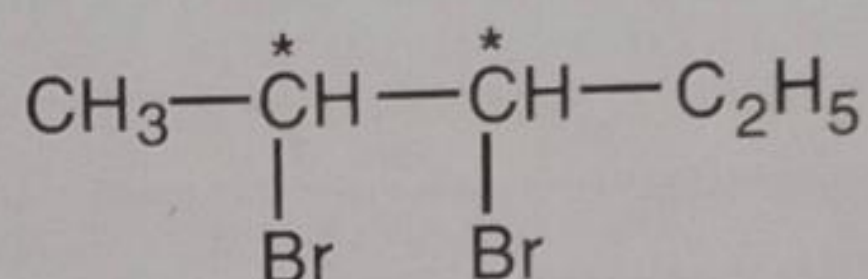
First Pair of Enantiomers**Second Pair of Enantiomers**

Out of these four pair of Enantiomers, I and II, III and IV are First and second pair of Enantiomers and are non-superimposable mirror images of each other. Stereoisomers I and III as well as II and IV are non-superimposable and also they are not mirror images of each other i.e. they do not have any mirror image relationship.



Do not have mirror image relationship

Such pair of stereoisomers that are not enantiomers are called diastereoisomers. So, diastereoisomers are defined as the pair of stereoisomers which do not have any mirror image relationship even though they have chiral centres. Another example of diastereoisomer is 2,3-dibromopentane



PROPERTIES OF DIASTEREISOMERS :

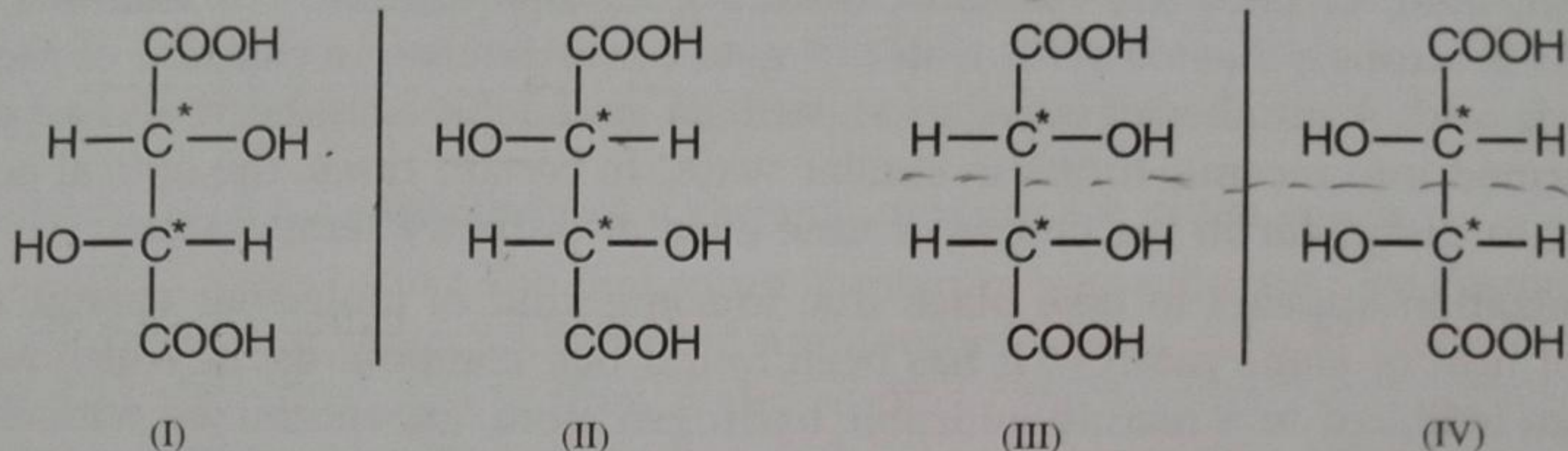
- 1) **Physical properties :** Unlike enantiomers, Diastereoisomers have different physical properties i.e. they have different boiling points, melting points, solubilities etc. Due to this difference in physical properties diastereoisomers can be easily separated by various methods like distillation, crystallisation, chromatography etc.
- 2) **Chemical Properties :** Unlike enantiomers, diastereoisomers have similar but not identical chemical properties. So, their rate of reactions also differ with respect to one another. They have different energies of activation for a particular reaction and reacts at different rates.
- 3) **Effect on plane polarised light :** Diastereoisomers differ in specific rotation, they may have same or opposite signs (+ or -) of rotation or may be optically inactive.

Difference Between Diastereoisomers and Enantiomers

Enantiomers	Diastereoisomers
<ol style="list-style-type: none"> 1. They have a mirror image relationship. 2. They have similar physical properties like melting point, boiling point etc. 3. They have identical chemical properties except rate of reaction with chiral reagents is different. 4. They cannot be separated by crystallisation, chromatography etc. 5. They are always optically active in nature. 6. It is mostly present in compounds having one chiral centre. 	<ol style="list-style-type: none"> 1. They do not have mirror image relationship. 2. They have different physical properties like melting point, boiling point, solubility etc. 3. They have similar but not identical chemical properties. 4. They can be separated by fractional distillation, chromatography etc. 5. They can be optically active or optically inactive. 6. It is present in compounds having two or more dissimilar stereogenic centre.

Optical Isomerism in Compounds containing two similar Chiral Carbon Atoms, Meso Compounds

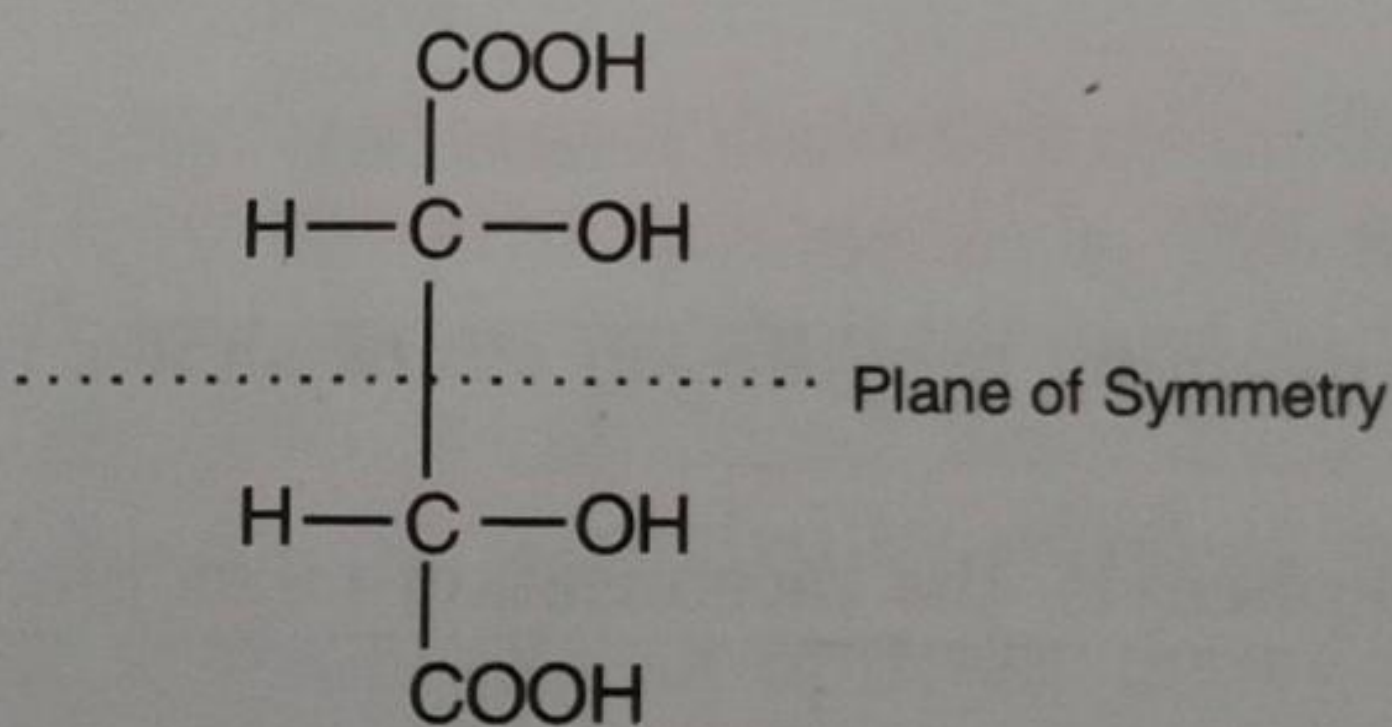
The most important example of a compound containing two similar chiral carbon atoms is tartaric acid. Because of the presence of two chiral atoms, one may expect the existence of four stereoisomers of this acid having the stereoisomeric forms I, II, III and IV.



Chiral and Achiral object

Formulae I and II are non-superimposable mirror images of each other and, therefore, represent a pair of optically active enantiomers.

Formulae IV and III again have a mirror image relationship. Close examination of these formulae, however, shows that one of these structures may be superimposed on the other just by rotating it through 180° within the plane of the paper. These two formulae, therefore, represent two superimposable mirror image molecules of the same compound. Formulae III (or IV) reveals that in spite of two chiral centres in it, the molecule is not chiral. This is because it has a plane of symmetry; one half of its molecule being mirror image of the other half. As such the compound represented by formula III (or IV) is optically inactive. Such an optically inactive compound whose molecules are superimposable on their mirror images in spite of the presence of chiral carbon is known as a **meso compound**.



Meso Tartaric Acid

Thus tartaric acid exists in three forms : (-) tartaric acid (I), (+) tartaric acid (II) and meso-tartaric acid (III or IV). Although optically inactive, the meso-tartaric acid represents a diastereomer of (-) or (+) tartaric acid. A meso compound is optically inactive because of the rotation caused by one half of the molecule is exactly cancelled by equal and opposite rotation caused by the other half of the molecule.

RACEMIZATION

Racemization is the process in which an optically active (*d*- or *l*-) compound is converted into a mixture of *d*- and *l*- forms with the result that optical activity disappears and the observed rotation drops to zero.

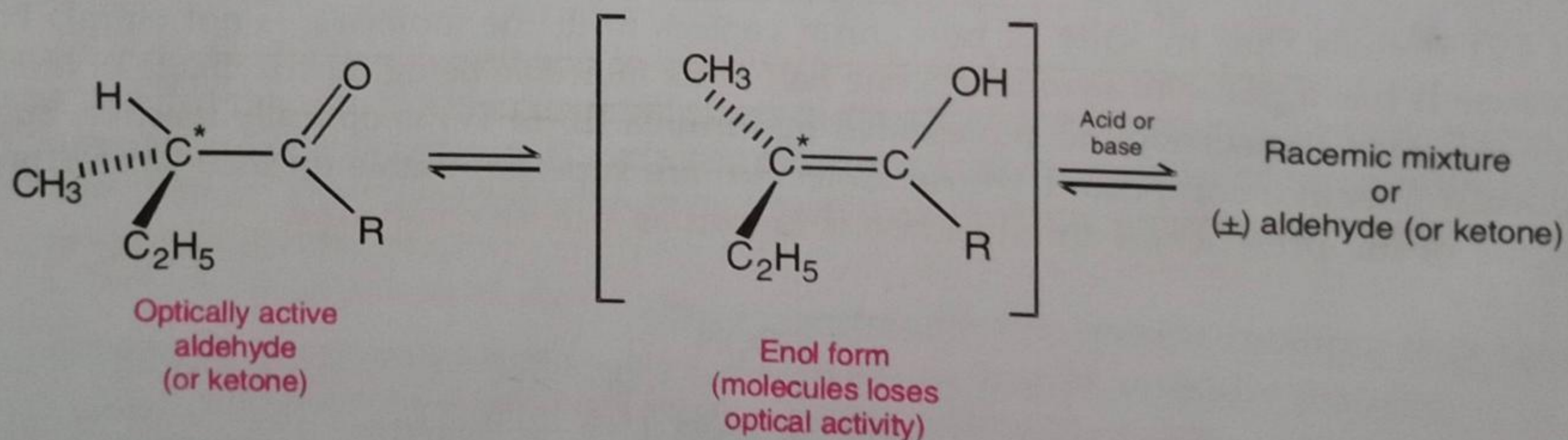
Optically active compounds become more or less completely inactive under the influence of heat, light, or chemical reagents, resulting in racemization. For example, when *d*-tartaric acid is strongly heated with water, it gets converted into a mixture of racemic and meso tartaric acid. A number of other acids, such as, mandelic, camphoric and aspartic acids are transformed into racemic forms in similar ways. In certain cases, the optical activity has been found to disappear in the course of time even at ordinary temperature.

Racemization appears to take place due to some kind of molecular change under the influence of heat or some catalyst. It has been found that compounds, in which asymmetric carbon atom is linked to a readily ionizable hydrogen atom, are racemized with ease by the action of an alkali.

Mechanism of Racemisation :

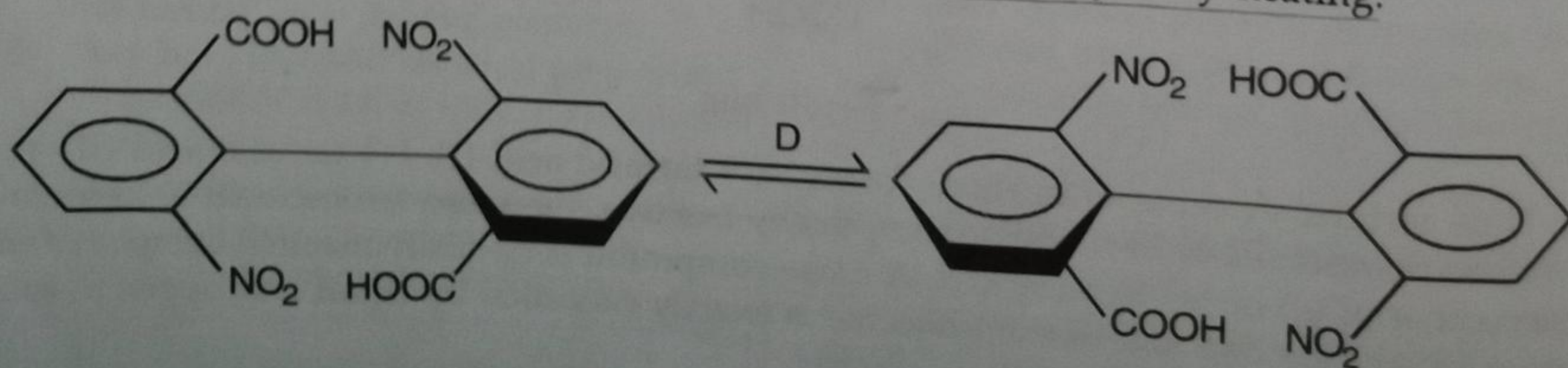
Racemisation may take place by any one of the following method :

- (I) The optically active aldehyde or ketone containing α -hydrogen always shows keto-enol tautomerism. Enol form being planar is responsible for racemisation. It is optically inactive but when it changes into a keto form by treating with an acid or a base, both the enantiomers can be formed and therefore, it gives a racemic mixture.



Similarly ketones containing α -hydrogen atoms shows racemization in the presence of an acid or a base.

- (II) In substituted Biphenyls, the racemisation takes place just by heating.



RESOLUTION OF RACEMIC MIXTURES

Racemic mixture contains equal amounts of optically active 'd' and 'l' isomers. *The process of the separation of a racemic mixture into optically active d and l isomers is known as resolution.*

The synthesis of organic compounds in the absence of a chiral reagent or chiral catalyst results in a mixture of both the enantiomers, i.e., a racemic mixture is obtained. Since *d* and *l*-isomers have identical melting points, solubilities, and all other physical properties except the direction in which they rotate the plane of polarized light, optical isomers cannot be separated by the usual methods such as distillation, crystallization, extraction etc.

Various methods used for separation of a racemic mixture are given below :

- a) **Mechanical separation** : The first racemic mixture was separated by Pasteur in 1848. He observed that when sodium and ammonium salt of racemic tartaric acid is allowed to crystallize slowly from water solution, the crystals obtained were of two shapes, which were mirror images of each other. Pasteur was able to separate these two types of crystals by sorting under microscope and found that while a solution of one type of crystals was dextro-rotatory, the solution of second type was laevo-rotatory.

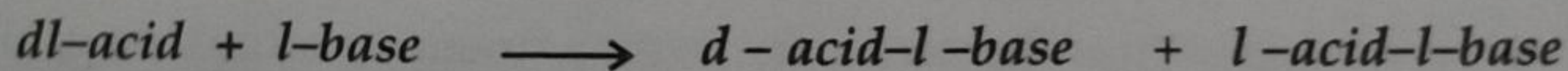
Pasteur's mechanical separation is a difficult method as most often substances do not crystallize into readily distinguishable crystals and, therefore, the separation would be difficult. Also it cannot be applied to liquid substances.

- b) **Biochemical method** : This method was also discovered by Pasteur. He found that when certain organisms such as bacteria, fungi or yeasts are allowed to grow in a solution containing racemic compound, one of the enantiomer is selectively destroyed or selectively assimilated, so that an excess of one of the active forms gets accumulated in solution. For example when penicillium galucum is allowed to grow in racemic tartaric acid or racemic ammonium tartarate, the dextro form is selectively destroyed, leaving behind laevo-tartaric acid in the solution.

This method can be applied only to a few cases because one of the enantiomers is completely destroyed in separation.

- c) **Chemical method**. This is one of the most important methods developed by Pasteur and finds greater utility than the other two methods. This method is based on the fact that when a racemic acid, for example, is allowed to react with an optically active base, two diastereoisomers are produced. Since diastereoisomers have different physical properties, they can be separated by physical methods.

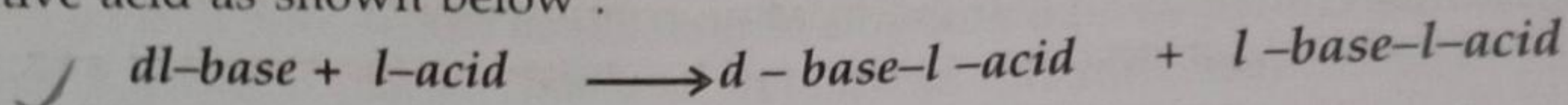
If a racemic acid is allowed to react with an optically active base, two salts will be formed.



Pair of Diastereomers

These two salts are diastereoisomers but not enantiomers and hence exhibit different physical properties. The mixture of two diastereoisomes can be separated by fractional crystallisation. The salts separated can be converted into *d*-acid and *l*-acid by treating with some acid.

In a similar manner, racemic organic base can also be resolved by treating it with some optically active acid as shown below :



Pair of Diastereomers

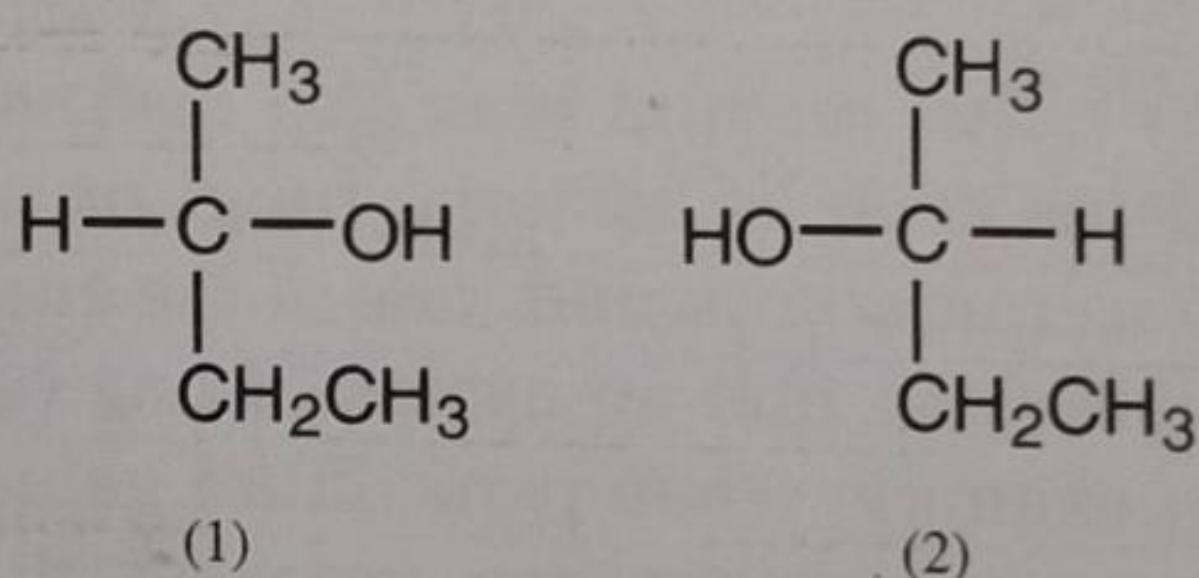
A large number of alkaloids which are found in nature are optically active bases and can be employed for separation of racemic acids. Some of the commonly used alkaloids for resolution of dl-acids are : *l*-brucine, *l*-cinchonine and *l*-quinine.

- d) **Chromatographic method.** When a racemic mixture solution is passed through an optically active adsorbent, the two enantiomers can be separated. As the adsorbates, produced by the combination of enantiomers and adsorbents, are diastereomers and as they are not equally stable, one of them will pass through the column faster than other. The two enantiomers are then obtained from the two diastereomers by careful elutions.

RELATIVE AND ABSOLUTE CONFIGURATION

Configuration : It is the actual arrangement of atoms or group of atoms present in a molecule in space which characterises a particular stereoisomer.

For example, the structures of two enantiomers of 2-butanol are given below :



These two structures differ in the arrangement of atom or groups in space and thus represent two different configurations. One of these structures represent configuration of (+)-2-butanol and the other is of (-)-2 butanol, but without any additional information it is difficult to tell which is which.

Two terms are quite often used while describing the configuration of different stereoisomers. These are absolute and relative configurations.

- a) **Absolute configuration.** It describes the actual arrangement of atoms or group of atoms in space of a particular stereoisomer of a compound. Absolute configurations were not known prior to 1951. J.M. Bijvoet in 1951 determined the absolute configuration of some compounds by using X-ray diffraction studies.
- b) **Relative configuration.** It means the arrangement of atoms or group of atoms in space of a compound relative to the atoms or groups of atoms of another compound whose absolute configuration is known. Earlier it was difficult to say as to which of the enantiomers is dextro or laevo-rotatory. In order to solve this problem, organic chemists established the relative configuration of thousands of compounds.