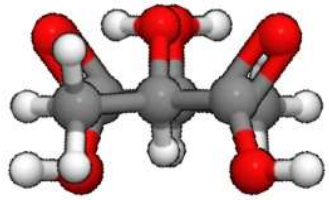


UNIT 2

STEREOISOMERISM OF MOLECULES WITH CHIRAL CENTRES

Structure

2.1 INTRODUCTION

In the first unit of this course we recapitulated some concepts that you have read in your undergraduate classes. These were related to the classification of stereoisomerism and the concept of optical activity. We discussed various ways of structural representation of three dimensional molecules in two dimensions as it becomes necessary to explain the stereochemistry of the molecule. You also learnt the interconversion of one type of projection into another. It was learnt that a carbon atom with four different groups is called a chiral carbon and a molecule containing such a carbon atom, has a non-superimposable mirror image. The two isomers are called enantiomers. We discussed the types of symmetry elements and their role in explaining the existence of enantiomerism and optical activity of organic molecules.

In the second unit we would explain stereoisomerism in the molecules with one, two, three or more chiral centres. You would learn the process of racemisation and separation of two isomers from a racemic mixture. This would be followed by the concept of optical purity. In the first unit you have read that stereoisomers are mainly of two types viz., the configurational and conformational isomers. The next unit deals with conformational isomerism and conformational isomers.

Expected Learning Outcomes

After studying this unit you should be able to:

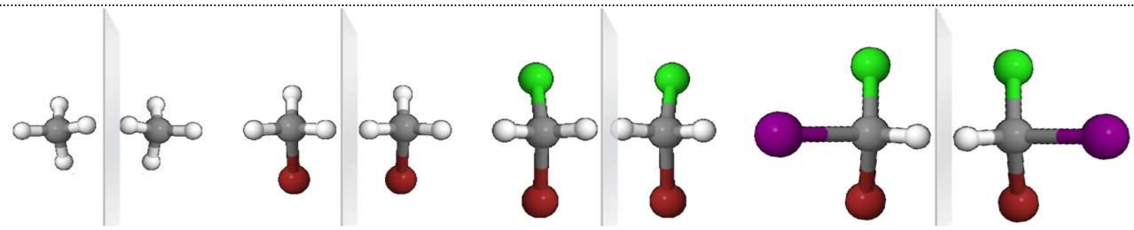
- explain the stereoisomerism in molecules with one, two, three or more chiral centres;
- define and differentiate among the enantiomers, diastereomers and meso compounds;
- define racemic mixtures and explain their formation and properties;
- list and describe the methods of separating racemic mixtures;
- identify a pseudo asymmetric centre; and
- explain the criteria of optical purity in the context of optical isomers.

2.2 MOLECULES WITH ONE CHIRAL CENTRE

In the previous unit we have discussed about asymmetry and chirality. You would recall that asymmetric carbon atom has four different groups attached to it. If one such carbon atom is present in a molecule then the molecule becomes chiral and this carbon atom is called a **chiral centre.** Due to this stereoisomerism is generated in the molecule hence it is also called the **stereogenic centre** . However, it is not correct to use the term chiral carbon atom because it is the overall molecule which is chiral. The term chiral carbon is sometimes used when we have to differentiate this carbon atom from other atoms like nitrogen or phosphorus etc. present in a molecule.

A carbon atom carrying four different groups is known is **asymmetric** carbon atom or a **stereogenic** centre or a **chiral centre**.

Let us now apply the concept of chirality to a simple molecule like methane with four hydrogen atoms tetrahedrally attached to a carbon atom. You will be able to visualise that the molecule of methane and its mirror image would be superimposable, Fig. 2.1(a). We find the similar situation in case of bromomethane, Fig. 2.1 (b) and bromochloromethane, Fig. 2.1(c). These molecules are achiral and do not show optical isomerism. Let us consider the molecule of bromochloroiodomethane. Here we would observe that this molecule and its mirror image are not identical as these are non-superimposable mirror images, Fig. 2.1 (d), hence this is a chiral molecule. The two mirror images in (d) differ only in the arrangement of atoms in space that is in their spatial arrangement. In other words, these possess different configuration. This molecule has one carbon atom which is attached to four different groups whereas in case of methane, bromomethane and bromochloromethane, all the four groups are not different.

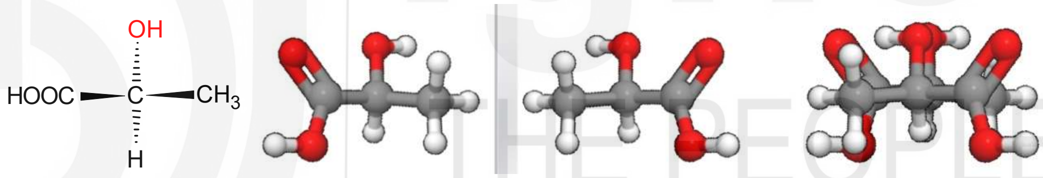


(a) (b) (c) (d)

Fig. 2.1: Nonchiral molecules (a) Methane (b) Bromomethane (c) Bromochloromethane Chiral molecule (d) Bromochloroiodomethane.

We have already studied that if a molecule contains one asymmetric carbon atom then it gives rise to a pair of isomers called **enantiomers**. Both of these isomers are optically active and rotate the plane polarised light in opposite direction with the same magnitude. The isomer which rotates the plane of plane polarised light towards right side is called **dextrorotatory** and is represented by a (+) sign or prefixed by the letter (*d*) before its name. Similarly the isomer which rotates the plane of plane polarised towards left side is called **laevorotatory** and is represented by a (-) sign or prefixed by the letter (*l*) before its name.

Lactic acid was the first compound which was studied in connection with optical isomerism. It contains one asymmetric carbon atom and so it exhibits optical activity. The enantiomers of lactic acid and the non-superimposable molecule are shown in Fig. 2.2.

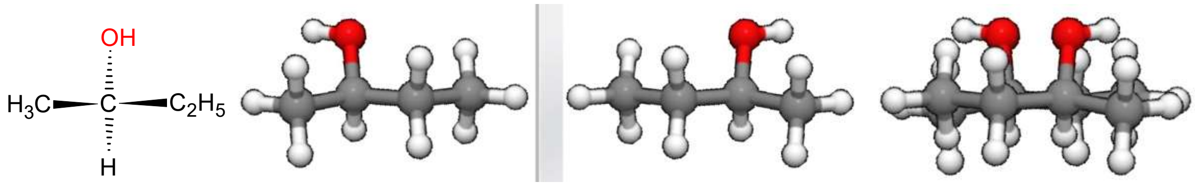


L- lactic acid **Enantiomers** **Non-superimposable**

Fig 2.2: Enantiomers and the non-superimposable molecule of L- lactic acid.

In lactic acid, the central carbon atom is attached to four different substituents, viz., H, CH_3, OH and COOH which are arranged tetrahedrally around the carbon. These isomers being non-superimposable mirror images of each other hence are called enantiomers. It should be noted that this molecule as a whole is chiral rather than possessing one chiral carbon atom. It has been suggested that it is more appropriate to call carbon atom of this type as stereogenic centre as mentioned earlier also.

According to IUPAC rules, the term chiral centre is used for stereochemical notation. The enantiomers of butan-2-ol are represented as shown in Fig. 2.3. It can be seen that the two are nonsuperimposable.



Butan-2-ol **Enantiomers** **Non-superimposable**

Fig. 2.3: Enantiomers and the non-superimposable molecule of butan-2-ol.

Some more examples of compounds containing one asymmetric carbon atom are given in Fig. 2.4. It should be noted that usually the asymmetric carbon atom or the chiral centre is shown by an asterisk mark. Molecules containing a single chiral centre are always chiral and lead to a pair of enantiomers. A carbon atom forming a double bond cannot be a chiral centre since it cannot have four different substituents.

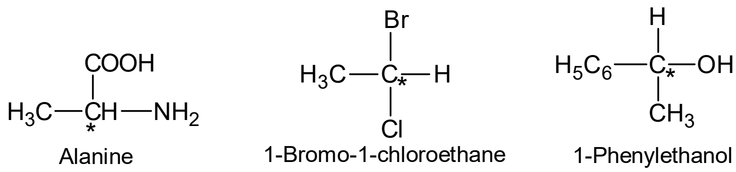


Fig. 2.4: Molecules with one stereogenic centre

You know from your previous classes that the absolute configuration of enantiomers is designated by the letters *R* and *S*. You would recall that for assigning the configuration, four groups attached to the asymmetric carbon atom are given the priorities according to CIP rules. The molecule is viewed from a direction that is opposite to the group getting the fourth priority. If the sequence of other three groups from 1→2→3 is clockwise then it is assigned *R*- configuration and if the sequence is anticlockwise then it is assigned *S*- configuration. For example, the two enantiomers of lactic acid are shown in Fig.2.5 where the priorities to different substituents are depicted along with the configuration of each enantiomer.

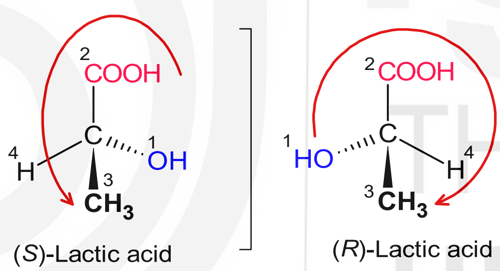


Fig. 2.5: Absolute configuration of enantiomers of lactic acid.

In the next section we will discuss the molecules containing two chiral centres. You should proceed after trying to answer the following SAQ.

SAQ 1

Write the structures of the following molecules and indicate the asymmetric carbon(s) in these.

i) 3-Methyl-1-pentene ii) Glyceraldehyde

2.3 MOLECULES WITH TWO CHIRAL CENTRES

The stereoisomers with two chiral centres exist not only in the form of enantiomers as observed in molecules with one chiral centre but also show another type of stereoisomers called the diastereoisomers. You have prior knowledge regarding the later type also. We would recall and discuss these two in this subsection. These stereoisomers broadly fall into two categories. These are:

- Isomers with dissimilar stereogenic centres
- Isomers with similar stereogenic centres

How do we find out the number of isomers in these? In the following subsection we would understand the way stereoisomers are identified in these molecules and study the stereoisomerism in case of molecules with dissimilar stereogenic centres.

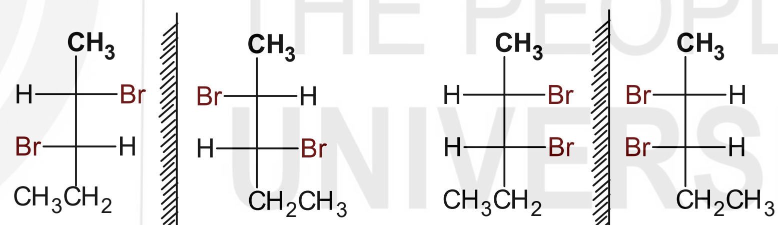
2.3.1 Enantiomers and Diastereoisomers: Dissimilar Stereogenic Centres

There is a general rule by which the number of stereoisomers which can be shown by a molecule with two or more stereogenic centres can be determined. According to it,

In compounds where the stereoisomerism is due to chiral centres, the total number of stereoisomers will not exceed 2^n, where n is equal to the number of chiral centres.

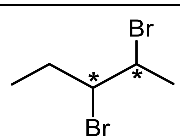
Let us understand it with the help of an example viz., 2, 3-dibromopentane. As can be seen by a two-dimensional bond-line structure, this molecule contains two asymmetric carbon atoms therefore; the number of possible stereoisomers should be equal to 4. These isomers are written in Fischer projection as can be seen in Fig 2.6.

The pairs of enantiomers are drawn by drawing an imaginary mirror between the two structures as was shown while studying optical isomers.



I II III IV

Fig. 2.6: Stereoisomers of 2,3-dibromopentane.



2,3-Dibromopentane

First we draw a configuration I and then its mirror image II. It is observed that the two structures I and II are non-superimposable, hence they represent a pair of enantiomers and both of these will be optically active. If we interchange the bromine and hydrogen at second carbon i.e., invert the configuration, we get a structure that is different from I and II and shown as structure III. Then we write a structure that is a non-superimposable mirror image of III, shown as structure IV. As can be seen, structure IV is also different from I and II. You can say that the compounds represented by structures I – IV are all optically active compounds. The compounds represented by structures I, II and III,IV are pairs of **enantiomers**.

But what is the isomeric relationship between the compounds represented by I and III? We can answer this question by observing that I and III are **stereoisomers** and that they do not have a mirror image relationship with each other. Such isomers are called **diastereoisomers or diastereomers.** Thus, diastereomers can be defined as the pair of stereoisomers which do not have mirror image relationship with each other. The properties of diastereoisomers are listed below:

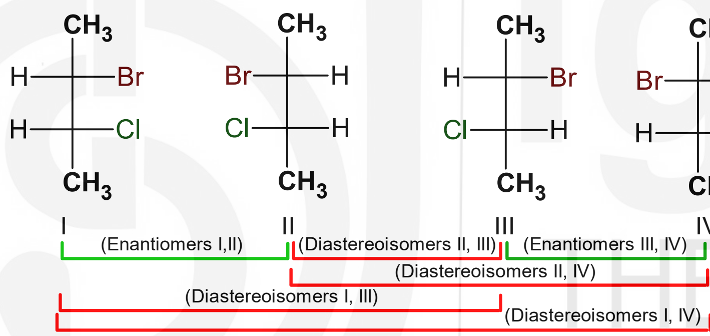
1. Diastereoisomers may or may not be optically active and if optically active, these have different values for specific rotation.

2. These possess different physical properties such as m.p., solubility, etc.

3. Due to the difference in their physical properties, these may be separated by fractional crystallisation, fractional distillation or by chromatographic techniques.

4. Diastereoisomers differ in some chemical properties also. These may differ in the rate of reaction with the same reagent.

Another example that can be looked into is 2-bromo-3-chlorobutane. As can be seen by the structure given in Fig. 2.7, it contains two asymmetric carbon atoms. Therefore, the number of possible stereoisomers is $2^2 = 4$. These can be represented by four Fischer projection structures as given below.



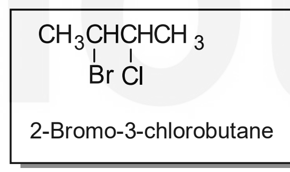
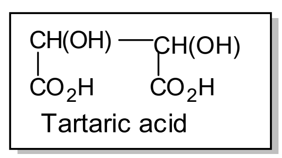


Fig. 2.7: Enantiomers and Diastereoisomers in 2-bromo-3-chlorobutane.

You can practice drawing the enantiomers and diastereoisomers of some other molecules. One such example is given as SAQ 2 at the end of next subsection. In the following subsection you would study to identify the isomers in case of molecules that have similar stereogenic centres.

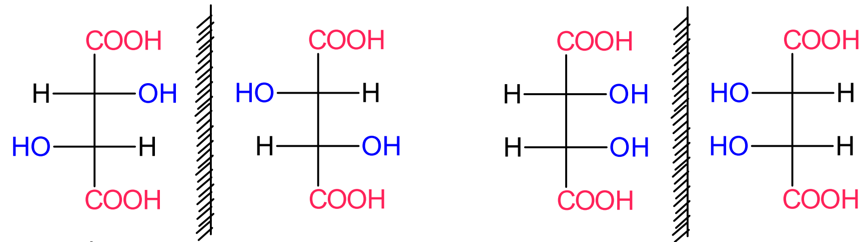
2.3.2 Meso Compounds: Similar Stereogenic Centres

We consider molecules with two stereogenic centres which carry an identical set of substituents at each asymmetric carbon atom. Look at the structure of tartaric acid i.e., 2,3-dihydroxybutanedioic acid. You know that it has two chiral centres. How is this structure different from the structures of molecules considered above in subsection 2.3.1?



Let us understand it by drawing the various possible stereoisomers for tartaric acid. You can see from Fig. 2.8 that of the possible isomers, I and II represent a pair of enantiomers and III and IV represent another pair of enantiomers. When you look more closely at structures III and IV, you can see that these are identical because these are superimposable over each other. Therefore, we can say that the structure III is achiral despite containing two stereogenic centres.

Some molecules are achiral even though these contain more than one chiral centre.

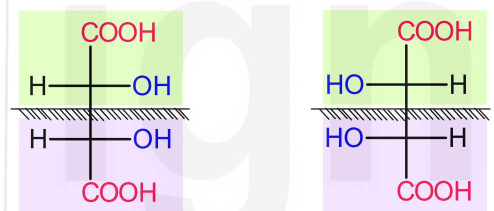


I II III IV

Fig. 2.8: Stereoisomers of tartaric acid.

Let us explain the above-mentioned observation.

The structure III possesses a plane of symmetry which is half-way along the C2-C3 bond, such that $-CO_2H$ reflects on to $-CO_2H$, -OH on to -OH, and -H on to –H as can be observed from the structures III and IV given below. This reveals the opposite configuration of C2 and C3 carbon atoms. You have read in Unit 1 that if a molecule possesses a plane of symmetry, it is not chiral. The same can also be shown for structure IV although these are identical.



III IV

Stereoisomers of tartaric acid showing plane of symmetry

The *meso* compounds are optically inactive due to internal compensation which means internally one half of the molecule is compensating the effect caused by the other half.

Thus, we can conclude that structures I and II are the enantiomers and will show optical activity. The structures I and III, II and III are diastereoisomers of each other. As regards optical activity of III, the effect of C2 cancels the effect of C3 because the stereogenic centres have opposite configuration so it is optically inactive. As is evident, the rotation due to one half of the molecule is compensated by the rotation of the second half, causing the molecule to become optically inactive. Such compounds were previously called to be **'internally compensated'**. It is well known to you that now such compounds are given the prefix ***meso***. The *meso* compounds are always achiral i.e., optically inactive even though they have two or more stereogenic centres.

You would observe that in case of tartaric acid only three stereoisomers are possible. Out of these, two isomers form a pair of enantiomers and are optically active whereas the third isomer is *meso* and in optically inactive. The compounds with two similar stereogenic centres have 3 stereoisomers instead of the expected 4 stereoisomers.

In this subsection you have read that a compound with two chiral centres may show optical inactivity due to the cancellation of optical activity of one half of the molecule with that of the other half. You might have studied another situation leading to optical inactivity when a pair of enantiomers is present in equal ratio as a mixture. In the following section let us recall and understand this concept. Before proceeding, try to answer the following SAQ.

SAQ 2

Draw all the possible enantiomers and diastereoisomers of 3-chloro-2-butanol.How many of these are optically active?

2.4 RACEMIC MODIFICATIONS

You might have come across reactions where an achiral reactant may end up forming chiral products. If there is absence of a factor that might lead to the formation of a product in major amount, an equimolar mixture of products is formed. For example, the nickel-catalysed hydrogenation of butanone results in the formation of 2-butanol. As butanone is achiral, the trigonal planar carbonyl group interacts with hydrogen with equal probability to be added from either side which produces chiral products in equal amounts. As is clear from the reaction given in Fig. 2.9, mixture of the two enantiomers, (-)-2-butanol and (+)-2-butanol is obtained.

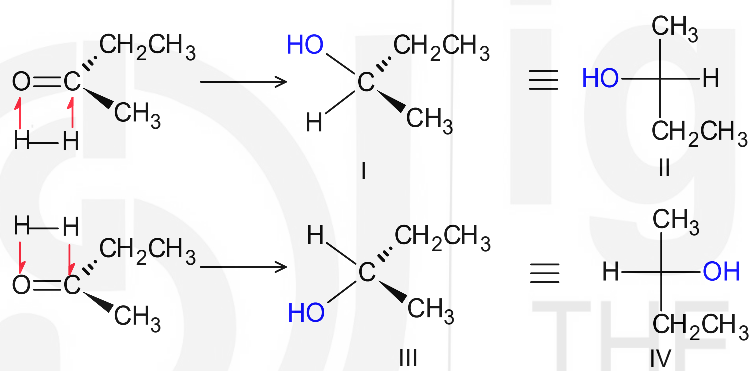


Fig. 2.9: Hydrogenation of butanone forming enantiomers of 2-butanol.

If both the (+) and (-) enantiomers are present in equal amounts, each of them rotates the plane of plane polarised light in opposite direction. Such a mixture becomes optically inactive because the rotation caused by one isomer would be exactly cancelled by the other isomer present. Such a mixture is named the **racemic mixture or racemate or racemic form**. The term used to explain the cause of optical inactivity of racemic mixtures is **"external compensation"** (*cf*. the ***meso*** compounds that are optically inactive **due to internal compensation).** We can say that a racemic mixture causes no net rotation of plane-polarised light. It is also written as ***dl*** mixture and **±** sign is written before the name. For example, a racemic mixture of (-)-2-butanol and (+)-2-butanol can be written as (±)-2-butanol **or** (±)-$CH_3CH_2CHOHCH_3$.

> Tartaric acid is obtained from grapes, so it was also called racemic acid (*racemus*is Latin for "a bunch of grapes"). When Pasteur found that tartaric acid was actually a mixture of enantiomers, he called it a "racemic mixture."

You have read that an optically active molecule rotates the plane of a plane polarised light when it is passed through its solution. The mixture obtained in above reaction will show no net optical rotation, can be explained as shown in Fig. 2.10. As can be seen, first a beam of plane-polarised light encounters a molecule of one isomer of 2-butanol, a chiral molecule, Fig. 2.10 (a). This causes a slight rotation of the plane of polarisation Fig. 2.10 (b). This rotation gets cancelled when the light interacts with a molecule of another enantiomer of 2-butanol Fig. 2.10 (c), and no net rotation is observed, Fig. 2.10 (d). If the mixture of two isomers is in unequal amounts, a net rotation of the plane of plane polarised light would be observed as shown in Fig. 2.10 (e).

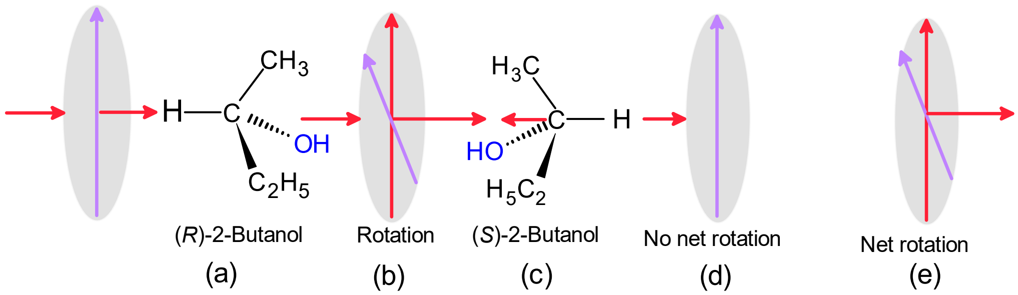


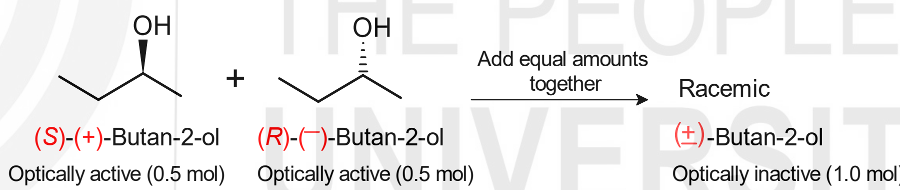
Fig. 2.10: Rotation of plane polarised light by a mixture of isomers of 2-butanol.

Although several methods are now prevalent for the preparation of enantiomerically pure products yet large number of such compounds are still obtained by resolution of racemates. Let us first learn how racemates are formed after which we would focus on their resolution. These are explained in the next subsection.

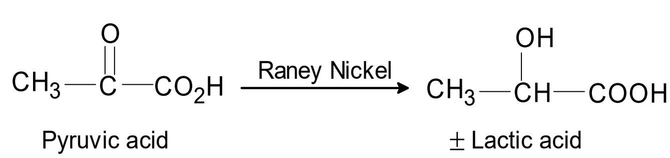
2.4.1 Formation of Racemic Mixtures

A racemic mixture is formed by any of the following methods:

(i) **By mixing a pair of enantiomers in equimolar ratio i.e., equal number of moles of the enantiomers:** If we take 0.5 moles of (+)-butan-2-ol and 0.5 moles of (-)-butan-2-ol,1.0 mole of a racemic mixture of butan-2-ol is obtained. The process can be depicted as follows.

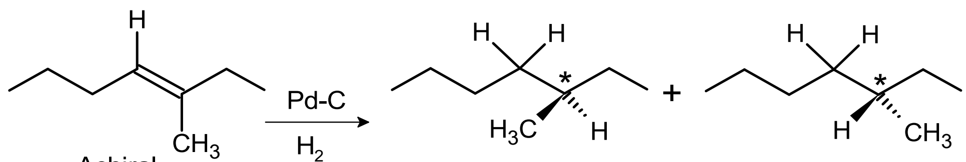


(ii) **Production of a chiral centre from an achiral compound**
One example of this type of reaction has been discussed above and explained in Fig.2.9 which involves the reduction of butanone. Another similar example can be taken as the catalytic reduction of 2−oxopropanoic acid (pyruvic acid) in which two isomers of lactic acid are produced in 50:50 ratio. In this rection hydrogen is added across the carbon-oxygen double bond and this carbon atom now becomes asymmetric carbon atom. Since there is equal probability of addition of hydrogen from any side of the plane of carbonyl group, a mixture of two enantiomers is produced in equal ratio which is a racemic mixture. The reaction is given below.



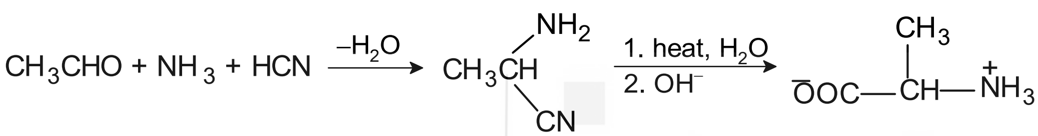
Some more examples involving such reactions are given below.

Hydrogenation of alkenes: An achiral alkene on catalytic hydrogenation also gives the mixture of two enantiomers or can be said that a racemic mixture is obtained as shown in the following equation.



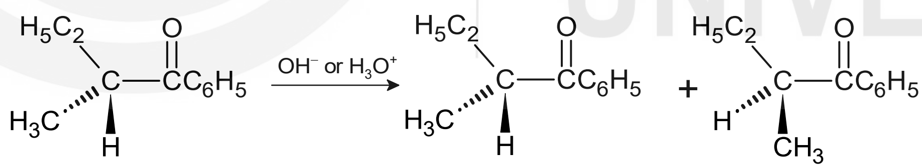
(*R*) (*S*)

Synthesis of α-amino acids: Strecker method, which is used for the synthesis of α-amino acids, produces a racemic mixture. It involves the reaction of an aldehyde (e.g., acetaldehyde) with ammonia and hydrogen cyanide to give 2-aminopropanenitrile which on hydrolysis gives (±) alanine.



Acetaldehyde (±) 2-Aminopropanenitrile (±)-Alanine

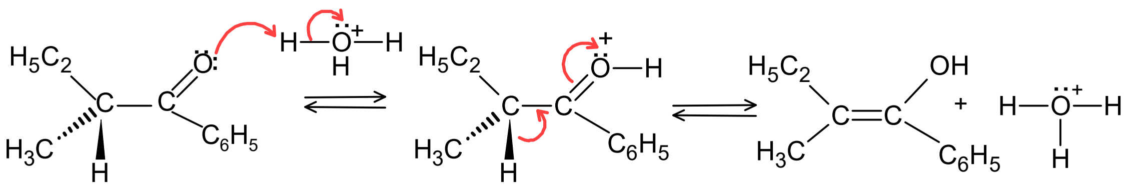
(iii) Racemisation: Racemic mixture is also formed by the process of racemisation which involves the conversion of an optically active compound into a pair of enantiomers by using heat, light or a chemical reagent. A compound can be racemised under a given set of conditions or by some specific reagent, which depends upon the nature of the compound. For example, racemisation may occur by **enolization** in those compounds which have a carbonyl function attached to a chiral carbon. As can be seen, the treatment of a solution of one isomer, say (+)-*sec* butylphenyl ketone in aqueous ethanol with acid or base leads to the compound that loses its optical activity showing that the compound has racemised as given below.



(*R*)-(+)-*sec*-Butylphenyl ketone (±)-*sec*-Butylphenyl ketone

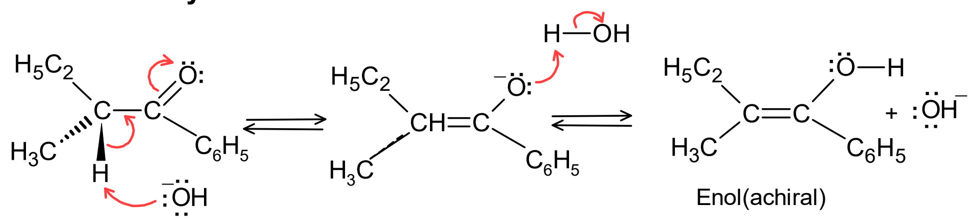
This is explained by the formation of enolic structure in the first step. The enol on reverting back to the keto form gives equal amounts of the two enantiomers. The mechanism of acid and base catalysed enolisation can be shown as given in Fig. 2.11.

Acid Catalysed Enolisation



Enol(achiral)

Base Catalysed Enolisation



Conversion of Enol form back into the Keto form

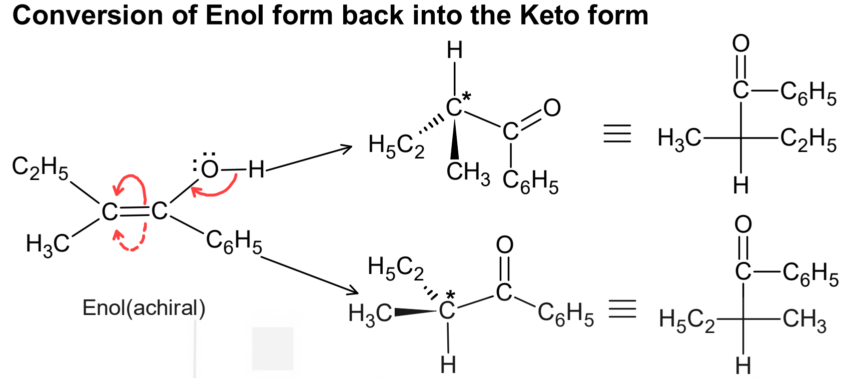
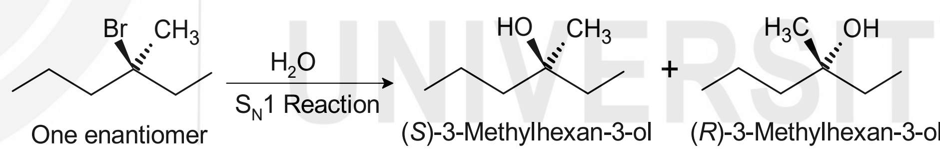


Fig. 2.11: Mechanism of acid and base catalysed enolisation.

We can also end up with a racemic mixture in a chemical reaction even if the starting material is optically active. For example, substitution reaction of a tertiary alkyl halide which follows SN^1 pathway leads to the formation of a racemic mixture. Why? You have studied that in this pathway, the product is formed through a planar intermediate, the carbocation. A carbocation can be attacked by a nucleophile from back as well as front. Many other reactions following S_N1 mechanism also produce racemic mixtures. An example is shown in the following reaction.



Racemisation is not a desired process when we aim to synthesise a particular enantiomer. As you are aware, most of the natural products, foodstuffs, drugs, flavouring agents, perfumes and other biologically active materials usually show their desirable or beneficial effects in one enantiomeric form only. If in any reaction a racemic mixture is obtained then It becomes essential to separate the two enantiomers. The process involving separation of enantiomers is called **resolution.** Before discussing the methods of resolution, it is worthwhile to study some important properties of racemic mixtures. These are briefly explained in the following subsection.

2.4.2 Properties of Racemic Mixtures

The enantiomers depict both, scalar (only magnitude) and nonscalar (magnitude as well as direction) properties. The scalar properties like, melting point, boiling point, solubility in achiral solvents, density, refractive index, infrared (IR)spectra, Raman spectra, ultraviolet-visible spectra, Nuclear Magnetic Resonance (NMR), nonresonant X-ray diffraction pattern, etc., are found to be the same for enantiomers. Nonscalar properties such as chiroptical properties, interaction with other chiral species and biological activities differ in most of the cases and are dealt in the second block of this course. We will briefly discuss the nature of the racemates in three phases viz., the gaseous phase, the liquid phase and the solid phase in the following paragraphs.

Melting point: There are three types of racemic modifications in crystalline state. The melting point varies depending upon the type:

1. **Conglomerates** of homochiral species with enantiomers at 50:50 composition have lower melting points than the individual enantiomers.

2. Racemic Compounds with each unit crystal having **equal numbers** of (+) and (-) molecules, the melting point of racemic modification has higher melting point than the individual enantiomers.

3. **Pseudoracemates** or solid solution forms have the unit crystals in any proportion of (+) and (-) forms. The melting point of the pseudoracemates is almost similar to the individual enantiomers.

Crystal Shape/Morphology: The crystals may belong to 'centrosymmetric' or 'non-centrosymmetric' space groups with or without an inversion centre between atoms, respectively. The enantiomerically pure compounds form disymmetric crystals or non-centrosymmetric crystals while the racemic compounds crystallise in centrosymmetric space groups. X-ray diffraction studies can differentiate between these two types.

Density in solid state: You know that a closer packing of molecules can be expected to exhibit higher density. Therefore, the racemic compounds can be expected to exhibit higher density than the enantiomers.

Solubility behaviour: The solubility of racemates is twice in comparison to solubility of enantiomers. This generalisation is not applicable to all types of racemic modifications and is primarily applicable to neutral organic compounds i.e. the ones which lack polar groups.

Spectroscopy: The IR and NMR spectra of racemic mixtures and that of any single enantiomer are found to be significantly different. You will study about this in the unit on spectroscopy.

The term **'Homochiral'** describes a sample with isomeric molecules e.g., all the molecules with *S* or with *R* configuration in a given sample. **Heterochiral** is a sample containing isomers with opposite configuration.

Chromatographic behaviour: Enantiomers show different chromatographic behaviour when the adsorbent used is chiral. It is difficult to separate the enantiomers by the use of achiral stationary and mobile phases. However, the predominant enantiomer can be separated from the racemic heterochiral associates under achiral chromatography conditions.

In the following section let us study the methods by which enantiomers can be separated from their racemic mixtures. You should proceed after answering the following SAQ.

SAQ 3

Which of the following statements is incorrect regarding the racemic mixture of a compound?

a) Racemic mixture of a compound is optically inactive due to external compensation of rotation of the plane polarised light.

b) Racemic mixtures can be obtained during the production of a chiral centre from an achiral compound.

c) Racemic mixtures can be separated by the formation of diastereoisomeric salts.

d) Racemisation of a compound is independent of its nature or the reagent used.

2.5 SEPARATION OF RACEMIC MIXTURES: RESOLUTION

The process of separating a racemic mixture into its components i.e., its enantiomers viz., (+) and (–) forms is known as **resolution**. It is very significant to get the individual enantiomers in pure state as these have varied characteristic properties and biological reactions. A pair of enantiomers has identical physical and chemical properties (except towards optically active reagents) so their separation is not possible by the usual techniques such as fractional crystallisation, fractional distillation or chromatography. Various methods have been developed for resolution, but the selection of a particular method depends upon the chemical nature of the compound under consideration.

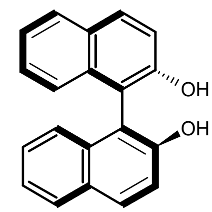
> The shape of a crystal depends upon the translational repetition of a basic structural pattern, described as the unit cell that involves a number of forces. Unit cell may contain one or several molecules, the arrangement of which reflects the overall symmetry of the crystal structure.

2.5.1 Mechanical Separation

This method is applicable for those mixtures only, where the enantiomers form different crystals which themselves are **enantiomorphous**. The crystals of racemic modification contain two types of crystals, which are mirror image of each other. Such crystals can be separated mechanically by using a magnifying lens and a pair of tweezers. This method was introduced by Pasteur when he separated the crystals of sodium ammonium tartrate. Separation of the isomers became possible in this case because the two types of crystals were hemihedric and possessed different orientations. This method is of very limited use and quite cumbersome also. Moreover, all the compounds do not form asymmetric crystals to permit separation mechanically.

A more useful variation of mechanical separation is the method of inoculation, originally discovered by Gernez. If a saturated solution of a racemic mixture is carefully inoculated with a pure crystal of one of the enantiomers, the crystal will grow and an appreciable amount of that enantiomer shall be deposited, hence separated from the racemic mixture. For example, (+)- sodium ammonium tartrate can be crystallised from a solution of the racemic modification not only by inoculation with a crystal of the (+) salt but also by inoculation with (-)- asparagine, $H_2NCOCH_2CH(NH_2)CO_2H$.

Inclusion Complex Procedure: An inclusion complex is formed by the treatment of one component called the **host** which has a cavity or space in the crystal lattice with a second compound called the **guest**. In inclusion complex, the guest fits into the cavity of the host. The guest and host molecules are held by van der Waals forces and there is no covalent bonding. Chiral phenols like 1,1-bi (2-naphthol) which are optically active, act as good hosts for the separation of racemic mixtures. In such separations, solvents like benzene or hexane are used.



Structure of
1, 1-bi(2-naphthol)

The procedure used for separation consists in keeping the racemic mixture (guest) and the host molecule e.g., 1,1-bi(2-naphthol) in a solvent (benzene or hexane) for 5-10 hrs. During this process crystals of inclusion complex separate out, which are filtered. The mother liquor is used for the isolation of the second isomer. The inclusion complex is formed in the 1:1 or 1:2 host-guest ratio and is recrystallised from the same solvent (benzene or hexane).

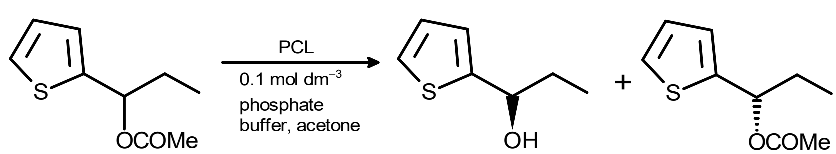
2.5.2 Biochemical Resolution

Certain bacteria or fungi consume one enantiomer selectively when these grow in the presence of a racemic mixture, while the other remains intact and can be recovered later. The separation by this method is almost quantitative. The enantiomer that is left in solution is isolated by fractional crystallisation. For example, a solution of (±) tartaric acid is treated with an ordinary mould '*Penicillium glaucum*' to achieve resolution. The mould selectively utilises *dextro* tartaric acid and leaves *laevo* tartaric acid. This method has some disadvantages as listed below.

- The growth of such microorganisms occurs in very dilute solutions therefore, compound is obtained in small amounts only.
- One enantiomer is always destroyed as a result only one enantiomer is obtained during resolution.
- A suitable microorganism is also required for the purpose of resolution.It is very difficult to find an appropriate microorganism for a particular substrate.

Resolution with Enzymes

All enzymes are catalysts, chiral and stereoselective in their natural aqueous environment. Some enzymes are highly selective whereas others are broadly receptive. For example, formation of one enantiomer of a chiral insect pheromone, was achieved by enantioselective hydrolysis of its racemic mixture (Fig.2.12a) by *Pseudomonas cepacia* lipase (PCL), the enzyme of choice, to produce alcohol (Fig. 2.12b).



(±)- Insect pheromene

(a) **(b)** **(c)**

Fig. 2.12: Resolution of racemic pheromone with PCL.

After the reaction is complete, the resolved alcohol is separated from its enantiomeric acetate Fig. 2.12 (c) which is left unchanged. Similarly, racemic 2-hydroxy-4-phenylbutanoic acid was reacted with lipase PS (LPS) and vinyl acetate (VA, ethynyl ethanoate) in *t*-butyl methyl ether (2-methoxy-2-methylpropane) to give its acetate in 35% yield and 99% *ee*. The unreacted alcohol was found to have 99% *ee* with *R* configuration, Fig. 2.13.

You will study about enantiomeric excess(*ee*) in Sec. 2.6.

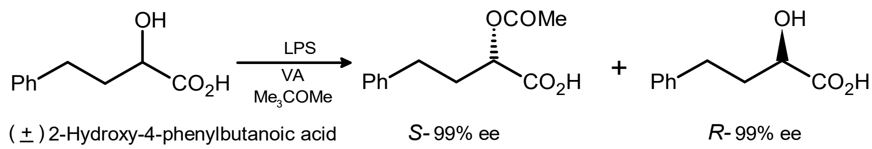


Fig. 2.13: Resolution of substituted butanoic acid with LPS.

2.5.3 Chemical Methods

These methods involve treatment of the racemic mixture with an appropriate optically active compound called the **resolving agent** to form a pair of diastereoisomers. The basis of separation of racemic mixtures in this method is that the diastereoisomers have different physical properties whereas enantiomers have identical physical properties. If a mixture of enantiomers is converted into a pair of diastereoisomers, these can be separated by using conventional methods such as crystallisation, distillation or chromatography, etc. The pure diastereoisomers are then treated with a suitable reagent to give a pure enantiomer. According to Wilen (1971), the desirable characteristics of a good resolving agent are:

- Stability in use and in storage
- Ease of preparation, recovery, reuse thus cost-effective
- Low molecular weight and low toxicity
- Availability in high enantiomeric purity and availability of both the enantiomers
- Reasonable solubility

In one of the ways, chemical resolution can be achieved by the formation of diastereoisomeric salts as explained below.

Formation of diastereoisomeric salts:

This method is most suitable for the resolution of carboxylic acids or amines because they can easily form diastereoisomeric salts. For example, a racemic mixture of acids can form two salts on treatment with an optically active base. The two salts will be diastereoisomers of each other which can be separated by fractional crystallisation. Each of the separated diastereomeric salt will give an enantiomer on treatment with a mineral acid e.g., sulphuric acid or hydrochloric acid. The resolution process can be shown with the help of a flow chart given in Fig. 2.14.

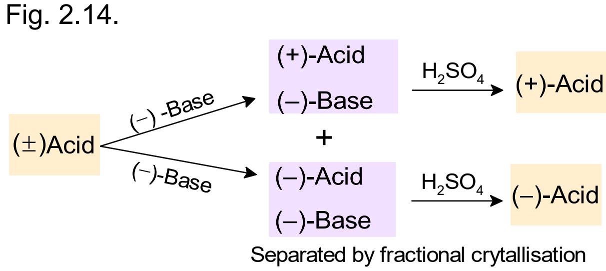


Fig. 2.14: Flow chart showing resolution by formation of diastereomeric salts.

An example of separation of a racemic mixture (acid) using a chiral base is given in Fig. 2.15. One of the asymmetric carbon atoms in the *R*,*S*-salt is identical to an asymmetric carbon atom in the *S*,*S*-salt, and the other asymmetric carbon atom in the *R*,*S*-salt is the mirror image of an asymmetric carbon atom in the *S*,*S*-salt. Therefore, the salts are diastereomers so have different physical properties and can be separated. After separation, they can be converted back to the carboxylic acids by adding a strong acid such as HCl. The chiral base can be separated from the carboxylic acid and used again.

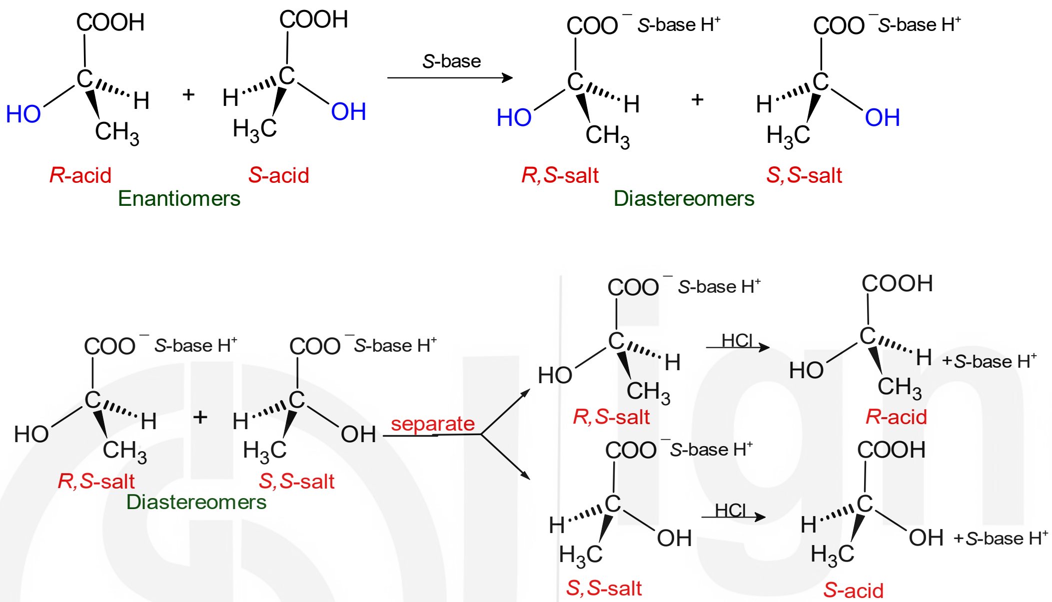


Fig. 2.15: Resolution of a racemic acid by formation of diastereomeric salts.

The above method can also be used for the separation of racemic mixture of bases by treating with one enantiomer of a suitable acid. The most commonly used bases for the separation of enantiomers of acids are (+)-strychnine, (–)-brucine, (–)-quinine, (–)-ephedrine, (–) menthylamine, and β-picolene etc. The acids generally used for the separation of basic compounds are (+)-alanine or any amino acid, (+)-10-camphor sulphonic acid, tartaric acid, malic acid, etc. Structures of some resolving agents are given in Fig. 2.16.

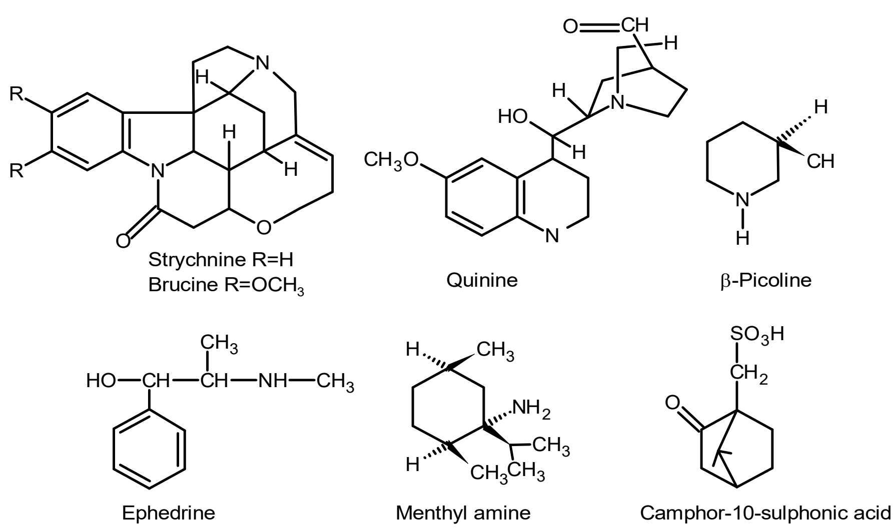


Fig. 2.16: Structures of some resolving agents.

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2.5.4 Chromatographic Separation

You are familiar with the principle of chromatographic separation where the components of a mixture of compounds get separated on the basis of their distribution between the stationary and the mobile phase. If an optically active adsorbent is taken as the stationary phase in the chromatography column, the adsorption for two different enantiomers will be different during elution. The two would get separated after the process is over. Some adsorbents used for this purpose are lactose, quinine, silica gel, etc.

The chromatographic method of resolution of racemic mixtures is carried out generally under three different conditions:

(i) **Direct resolution of the racemic mixture using chiral adsorbent materials:** The naturally occurring polysaccharides and their derivatives provide useful chiral stationary phase materials. The microcrystalline triacetyl cellulose (MCTC) forms a versatile column on which a number of compounds, e.g., racemic olefins, biphenyls, ketones, alcohols, esters, acids and salts have been resolved.

(ii) **Direct resolution on an achiral solid phase using a mobile chiral liquid phase:** Many cationic chelated metal complexes, e.g., tris(diamino)metal complex have been resolved on a column of cation-exchange sephadex (dextran cross-linked with epichlorohydrin) by elution with an aqueous solution of (+)- tartarate.

(iii) **Direct resolution using an achiral solid stationary phase modified by chiral reagents:** An ordinary adsorbent like silica gel is made stereoselective by special treatment with optically active substances, e.g., (+)-tartaric acid and (+)-camphor sulphonic acids which are later removed by elution with solvent.

Gas chromatography has also been extensively used for analysis as well as separation of enantiomers working on the above principles. The trifluoroacetyl derivatives of optically active amino acids have been used for gas chromatographic resolution of racemic alcohols via the corresponding esters. Paper chromatography can also affect partial resolution; the paper (cellulose material) itself can act as chiral adsorbent or it may be impregnated with solution of optically active compound such as camphor sulphonic acids.

2.5.5 Kinetic Methods

This method is based on the principle that sometimes the rate of reaction of enantiomers with a particular reagent is different i.e., k_R is not equal to k_S. This is possible because the activation energy of the diastereomeric transition states in the reaction of the racemate with a chiral reagent are different and so the two enantiomers react at different rates. For example, (−) menthol reacts with (+) mendelic acid at a faster rate than that with (−) isomer. If (±) mendelic acid is esterified with insufficient quantity of (−) menthol (chiral alchohol), the resulting mixture will have (−) menthyl (+) mendelate formed at a faster rate and in larger amounts. The unreacted mendelic acid will be rich in the (−) enantiomer. These are separated and repetition of the process may lead to almost full separation. (+)Mandelic acid can be obtained by the hydrolysis of the ester obtained.

You have learnt that it is important to separate a desired isomer from a mixture of isomers because of a specific utility of one over the other. When separated from a racemic mixture, it is essential to check the extent of purity of the isolated isomer. In the following section we will discuss what are the criteria of purity of the isolated isomers.

2.6 CRITERIA OF OPTICAL PURITY

You know that racemic mixture has a composition of 50:50 enantiomers of both the types. The composition of non-racemic mixture has enantiomer composition different from 50:50. If only one enantiomer is present, it may be called '**enantiopure**' or '**enantiomerically pure'**. The term, '**enantiomeric excess'** (*ee*) is defined in simple percentage terms as follows:

$$\text{enantiomer ic excess} = \frac{\text{excess of a single enantiomer}}{\text{entire mixture}} \times 100\ \%$$

When we consider the number of moles of the enantiomers involved the above expression can be modified as follows:

$$\%\ \text{Enantiomeric excess} = \frac{\text{moles of one enantiomer} - \text{moles of other enantiomer}}{\text{total moles of both enantiomers}} \times 100$$

The terms in the numerator arise because what the polarimeter registers is a measure of the difference in population of the enantiomers in a sample. An enantiomeric excess of 50% signifies that the sample contains75% of the enantiomer with, say, *(+ or d)* optical rotation and 25% of *(- or l)*, that is 50% of a 1 : 1 mixture and 50% of the (+ or *d*) enantiomer. The enantiomeric excess can be calculated from optical rotations by the following formula.

$$\%\text{Enantiomeric excess}^{*} = \frac{\text{observed specific rotation}}{\text{specific rotation of the pure enantiomers}} \times 100$$

The enantiomeric purity is expressed as optical purity also and can be given as follows.

$$\textit{Optical purity or op} = [\alpha]_{obs.} / [\alpha]_{max} \times 100\%$$

A crystalline enantiomer is often considered optically pure when its melting point and rotation are unchanged by further crystallization. However, this criteria of calculating or getting an idea of the optical purity fails when the racemic modification forms a solid solution, since in that case even a partially resolved enantiomer may not change in either rotation or melting point by further recrystallization. Apart from sample purity, the optical rotation is affected by solvent polarity, moisture content in the solvent, temperature, wavelength employed, and the possibility of human error. Thus the determination of enantiomer composition by use of equation given above can give a rough estimate of the enantiomer composition.

In a solution of a chemically (not enantiomerically) pure compound, the values of optical purity and enantiomeric excess are identical. If the solution does not contain any other compound (except for the solvent) and the specific rotation

The enantiomeric excess of 50%means that 50%of the mixture consists of the (+) enantiomer (the excess) and the other 50% consists of the racemic form. Since for the 50% that is racemic the optical rotations cancel one another, only the 50% of the mixture that consists of the (+) enantiomer contributes to the observed optical rotation. The observed rotation is, therefore, 50% (or one-half) of what it would have been if the mixture had consisted only of the (+) enantiomer. As long as the compound is chemically pure, enantiomeric excess and optical purity will be the same.

of the pure enantiomer is known, the enantiomeric excess may be determined by measuring the optical rotation of a solution of a two-enantiomer mixture. In order for the optical purity and the enantiomeric excess to be calculated, the specific rotation of the pure enantiomer must first be noted. Therefore, a mixture showing a specific rotation of one of the enantiomers is said to have an enantiomeric excess of 100%.

For example, an enantiomerically pure sample of (*S*)-(+)-2-butanol shows a specific rotation of + 13.52 ($[\alpha]_D^{25} = +13.52$). On the other hand, a sample of (*S*)-(+)-2-butanol that contains less than an equimolar amount of (*R*)-(-)-2-butanol will show a specific rotation that is less than +13.52 but greater than zero. Such a sample is said to have an enantiomeric excess less than 100%.

If a mixture of the enantiomers of 2-butanol shows a specific rotation of +6.76, the enantiomeric excess of the (*S*)-(+)-2-butanol can be calculated as:

$$\text{Enantiomeric excess} = \frac{+6.76}{+13.52} \times 100 = 50\%$$

On the basis of the above calculations, it can be said that of the total mixture, 50% consists of racemic form (which contains equal number of the two enantiomers). So, half of 50% (or 25%) is the (–) enantiomers and 25% is the (+) enantiomer. The remaining 50% of the mixture is also the (+) enantiomer. So, the mixture is 75% (+) enantiomer and 25% (–) enantiomer.

After answering the following SAQs, you may proceed to study about molecules with three or more chiral centres.

SAQ 4

Calculate the enantiomeric excess of the mixture containing,

12.8 mol of *R*-isomer and 3.2 mol of *S*-isomer of 2-chlorobutane

2.7 MOLECULES WITH THREE OR MORE CHIRAL CENTRES

You have learnt the general formula that is applied to find out the number of stereoisomers in a chiral molecule. By using the formula 2^n we can say that a compound with three stereocentres (n=3) can have 8 stereoisomers. As the number of stereocentres in a molecule increases, the stereochemical situation might become more complex. Let us understand the case of molecules that have three stereocentres by taking 3-bromo-4-chloro-2-pentanol as an example. We can draw eight possible configurations (I-VIII) for this compound as shown in Fig.2.17. These are drawn in such a way that for one structure its mirror image is shown next. For example II is the mirror image of I where a hypothetical mirror is shown in between. Similarly, other pairs are III and IV, V and VI, VII and VIII. Since none of the mirror image is superimposable, so there are four pairs of enantiomers and all the eight isomers will be optically active.

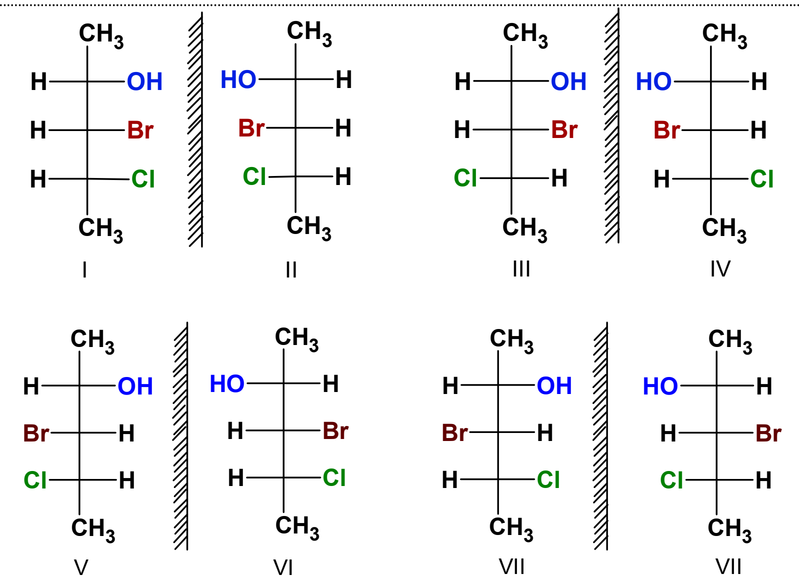

Fig. 2.17: stereoisomers of 3-bromo-4-chloro-2-pentanol

You will learn another term here that is related to the absolute configuration of molecules with three setereocentres. The term is called **pseudoasymmetry** about which you will study in the following subsection.

2.7.1 Pseudoasymmetry

Certain molecules may contain tetrahedral carbon atom that is joined to two constitutionally identical chiral groups and two other different achiral groups. The chiral groups may or may not have the same absolute configuration. Let us take the example of trihydroxyglutaric acid. The possible stereoisomers of this molecule are given in Fig. 2.18 (**I-VIII).** It has three stereocentres as depicted by the numbers 2, 3 and 4.

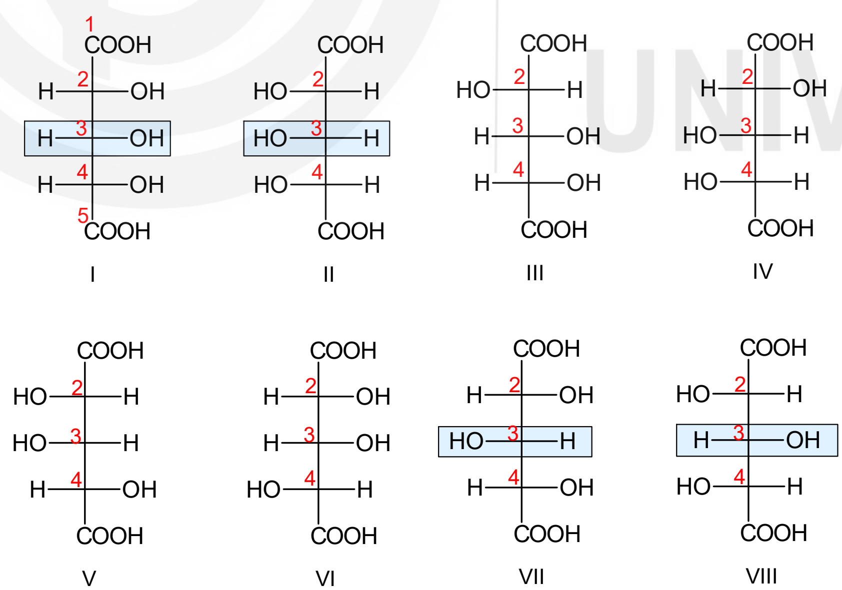

Fig. 2.18: Stereoisomers of 2,3,4-trihydroxyglutaric acid.

If we look at these structures carefully, it can be seen that structures **I** and **II** are identical as these can be interconverted by a 180° rotation in the plane of the paper and that they represent a *meso* structure. The central carbon atom (C3) in structure I or II is a stereocentre as four different groups are attached

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to it. Although the two groups vertically attached to C3 as drawn contain the same functional groups. These have opposite absolute configurations which are responsible to make C3 a stereocentre. The stereocentre C3 in structure **I** is the **pseudoasymmetric centre**. The existence of a pseudoasymmetric centre in a molecule can be called pseudoasymmetry. The *R*/*S* nomenclature system can be applied to pseudoasymmetric centres, through lower case letters *r* and *s* are used to represent their configuration. Same is true for the pair represented by structures VII and VIII. These do not represent a chiral species because these are also superimposable on their mirror images. As in the case of the *meso* compound represented by structure I, the central carbon atom, C3 in compound VII or VIII is also a pseudoasymmetric centre.

> When odd number of chiral centres is present in constitutionally symmetric molecules, the total number of stereoisomers possible is given by $2^{(n-1)}$. Such molecules produce chiral and (meso) achiral stereoisomers.

Structures III and IV represent a pair of enantiomers, as these differ in the absolute configuration at each of their stereocentres. In these two compounds, the central carbon atom C3 is not a stereocentre, as the two groups vertically attached to it are identical both in the functionality contained and in their stereochemistry. Thus, in this pair of stereoisomers, C3 has only three different groups attached to it and the compounds contain only two stereocentres. Structures V and VI do not represent new species, as these can be superimposed on structures III and IV respectively by a 180° rotation about a horizontal axis through C3. Thus, there are just four stereoisomers of trihydroxyglutaric acid, a pair of enantiomers represented by structures III and IV, and two *meso* isomers represented by structures I (or II) and VII (or VIII). The meso forms are diastereomers of each other and of the pair of enantiomers. Hence, due to the symmetrical nature of trihydroxyglutaric acid, there are considerably fewer than the maximum eight possible stereoisomers. It exists in four stereoisomeric forms, two of which are optically active (III and IV) while the other two (I and VII) are optically inactive because they are meso forms. In all it contains two asymmetric and one pseudoasymmetric carbon atoms.

Let us again look into the molecule of trihydroxyglutaric acid to understand it from the point of view of configuration at different stereocentres. The possible stereoisomers of this molecule are given in Fig. 2.18 (**I-VIII).** It has three stereocentres as depicted by the numbers 2, 3 and 4. Table 2.1 shows the absolute configuration at each stereocentre for each of the eight structures.

Table 2.1: Absolute configurations of 2,3,4-trihydroxyglutaric acid structures

Stereocentre	Compound No. (I-VIII)							
	I	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**
2	*R*	*S*	*S*	*R*	*S*	*R*	*R*	*S*
3	*r*	*r*	*I*	*I*	*I*	*I*	*s*	*s*
4	*S*	*R*	*S*	*R*	*S*	*R*	*S*	*R*

I = Not a stereocentre since two of the groups are identical.
r, s = Pseudoasymmetric centre

If we analyse the structures and the absolute configuration given in the above table, it can be seen that structures **I** and **II** are identical (they can be interconverted by a 180° rotation in the plane of the paper) and that they represent a *meso* structure.

In general, a molecule can have one pseudoasymmetric centre only when the number of constitutionally alike chiral centres is (n-1) and the value of *n* is even and the minimum value is four. For example, 2, 3, 4-trihydroxyglutaric acids can have a pseudoasymmetric centre but 2,3,4,5-tetrahydroxyadipic acid has no possibility of having a pseudoasymmetric centre.

You can check your understanding regarding pseudoasymmetric centre by answering the following SAQ.

SAQ 5

Draw the meso isomers of 2,3,4-trichloropentane and indicate the configuration (*r* or *s*) pseudoasymmetric centre in the isomers.

2.8 SUMMARY

Let us summarise the key concepts studied in this unit.

A carbon atom with four different groups attached to it becomes chiral and hence called a chiral centre and generates chirality in the molecule**.** This generates stereoisomerism in the molecule. The chirality in the case of molecules with one, two and three chiral centres has been discussed in this unit.

The molecules like, methane and bromomethane have their mirror images superimposable upon each other therefore contain an achiral carbon and do not show optical activity. While the molecules with one chiral centre like, bromochlorofluoromethane has a non-superimposable mirror image and shows optical activity. The isomers obtained are called the enantiomers. Some other molecules belonging to this category are, lactic acid, glyceraldehyde, alanine, etc.

The stereoisomers with two chiral centres are not only in the form of enantiomers as observed in molecules with one chiral centre but also form another type of stereoisomers called the diastereoisomers or diastereomers. The diastereoisomers can be defined as the pair of stereoisomers which do not have mirror image relationship with each other. The stereoisomers with more than one chiral centre broadly fall into two categories. These are: isomers with dissimilar stereogenic centres and isomers with similar stereogenic centres. The number of stereoisomers is calculated by the formula 2^n, where n is the number of chiral centres.

For example, 2, 3-dibromopentane molecule contains two asymmetric carbon atoms therefore; the number of possible stereoisomers should be equal to 4. The enantiomers and diastereomers of the molecule 2, 3-dibromopentane can be drawn in Fischer projection. Another molecule of this type considered is 2-bromo-3-chlorobutane. Tartaric acid is the example of a molecule having similar stereogenic centres. One of the isomers here is prefixed as meso which is optically inactive as the rotation of one half of the molecule is compensated by the rotation of the second half.

In some cases the (+) and (-) enantiomers are present in equal amounts in a mixture as a result there would be no net rotation of the plane of polarised light. Such a mixture becomes optically inactive because the rotation caused by one isomer would be exactly cancelled by the other isomer present. Such a mixture is named the racemic mixture or racemate or racemic form. There are a number of ways of formation of a racemic mixture, e.g., mixing a pair of enantiomers, racemisation, hydrogenation of alkenes, etc.

The process of separating a racemic mixture into its components i.e., its enantiomers viz., (+) and (–) forms is known as resolution. The methods employed here are mechanical separation, biochemical resolution, resolution with enzymes, chemical methods, chromatographic separation and kinetic methods.

The extent of purity of the isolated isomer from a racemic mixture can be found out by calculating the enantiomeric excess. The enantiomeric excess of 50%means that 50%of the mixture consists of the (+) enantiomer (the excess) and the other 50% consists of the racemic form. Since for the 50% that is racemic the optical rotations cancel one another, only the 50% of the mixture that consists of the (+) enantiomer contributes to the observed optical rotation. The observed rotation is, therefore, 50% (or one-half) of what it would have been if the mixture had consisted only of the (+) enantiomer. As long as the compound is chemically pure, enantiomeric excess and optical purity will be the same.

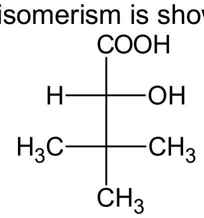
A compound with three stereocentres (n = 3) can have 8 stereoisomers. As the number of stereocentres in a molecule increases, the stereochemical situation might become more complex. For example, 3-bromo-4-chloro-2-pentanol can be depicted by 8 isomers. Certain molecules may contain tetrahedral carbon atom that is joined to two constitutionally identical chiral groups and two other different achiral groups. The chiral groups may or may not have the same absolute configuration e.g., trihydroxyglutaric acid. In such cases the number of isomers would be less than the expected 8 isomers and are considered to have a pseudoasymmetric centre.

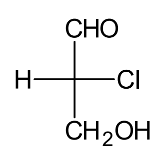
2.9 TERMINAL QUESTIONS

1. What is meant by pseudoasymmetry? Give example of a molecule with the presence of a pseudo-asymmetric centre.

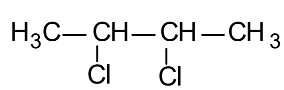
2. What is meant by enantiomeric excess? How is it expressed if number of moles of the two enantiomers or their specific rotations are given?

3. What type of isomerism is shown by the following compounds?

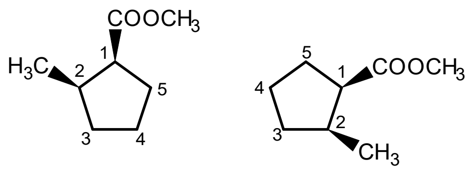




4. Draw all the possible stereoisomers for the following compound in Fisher projection. How many of these are optically active. Is there any optically inactive isomer?



5. What type of isomerism is shown by the following compounds? Assign *R/S* configuration to the stereogenic centres.



6. How many chiral carbon atoms are generated when bromine is added to *cis* 2-butene. Draw the isomers obtained in Fischer projection and assign *R/S* configuration to each chiral carbon atom. (Note: Addition of Br_2 is anti addition).

7. Explain with the help of an example that the following statement is not always true.

   "All molecules with stereogenic centres are chiral".

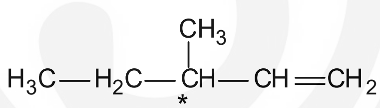
8. Draw all the possible stereoisomers for the following compounds. Identify the optically active and meso isomers amongst these.

   (i) $CH_3 - CH(OH) - CH(OH) - CH(OH) - CH_3$

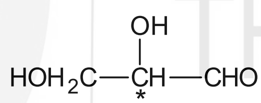
   (ii) $CH_3 - CHBr - CHBr - CH_2\ Br$

2.10 ANSWERS

Self Assessment Questions

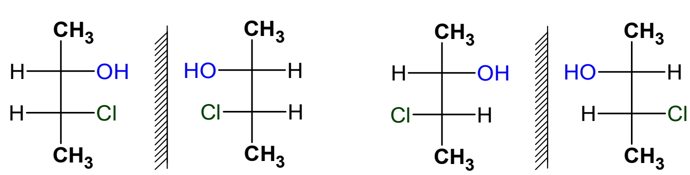
1. 

3-Methyl-1-pentene



Glyceraldehyde

2. As can be seen from the Fischer projections, structures (I and II), and (III and IV) are enantiomers. The structures (I and III), (I and IV), (II and III) and (II and IV) constitute a pair of diastereomers. All the four stereoisomers will be optically active.



(I) (II) (III) (IV)

Pair of enantiomers (non-superimposable) Pair of enantiomers (non-superimposable)

3. d)

4. $$\% ee(R) = \frac{9.6\,\text{mol}}{12.8\,\text{mol} + 3.2\,\text{mol}} \times 100\% = 60\%$$

   ee = moles (*R*) – moles (*S*) = 12.8 – 3.2 = 9.6 moles

   % *ee* (*R*) = enantiomer *R* – enantiomer *S* = 80% – 20% = 60%

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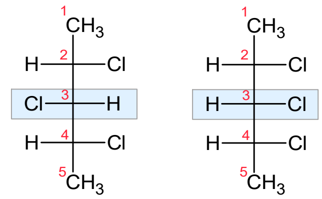
5. These are the meso stereoisomers with pseudo-asymmetric centre, with *r* and *s* notations.



2*S*, 3*r*, 4*R* 2*S*, 3s, 4*R*

Terminal Questions

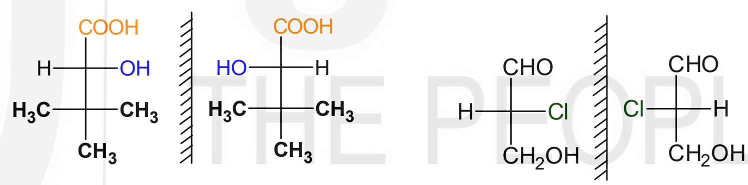
1. Refer to subsection 2.7.1 for definition and example.

2. Enantiomeric excess tells us how much more of one enantiomer is present in the mixture. It is expressed in percentage and the percent ee can be calculated by dividing the excess of the one enantiomer by the total number of moles for both the enantiomers. In terms of moles and specific rotations, it can be calculated by the following formulae.

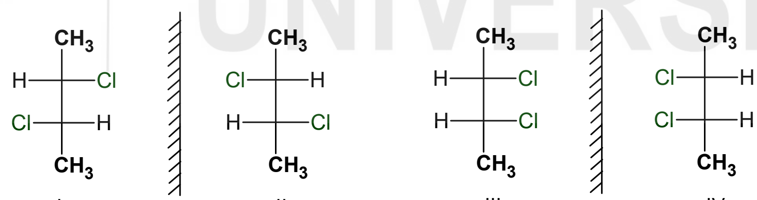
$$\%\text{Enantiomeric excess} = \frac{\text{moles of one enantiomer} - \text{moles of other enantiomer}}{\text{total moles of both enantiomers}} \times 100$$

$$\textit{Optical purity or op} = [\alpha]_{obs.} / [\alpha]_{max} \times 100\%$$

3. Both these compounds show optical isomerism. Each compound contains are chiral centre so a pair of enantiomers is possible in each case.



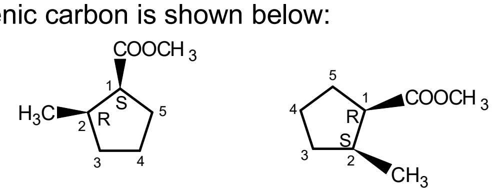
4. Theoretically four possible configurations (I-IV) can be written because there are two chiral centres present in this molecule.



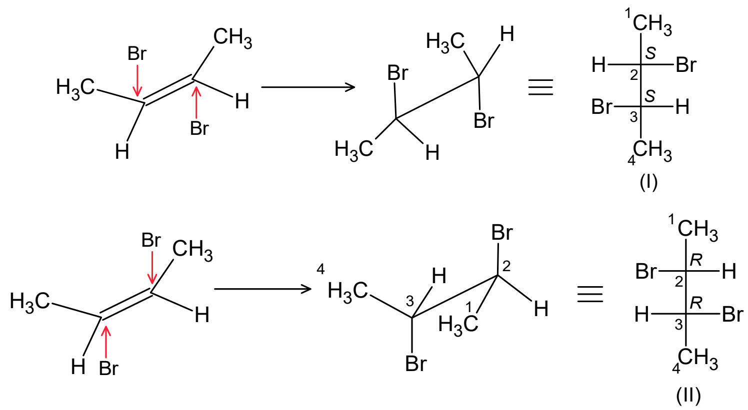
I II III IV

Structures I and II are nonsuperimposable mirror images of each other so both of these will be optically active. Structures III and IV are superimposable mirror images and contain a plane of symmetry so they are identical molecules and represent a meso structure which will be optically inactive.

5. The two given structures are enantiomers because they are non-superimposable mirror image of each other. The absolute configuration for each stereogenic carbon is shown below:



6. The anti addition of bromine to cis 2-butene can be shown as given below. Two chiral centres are generated. The two products formed (I and II) in this reaction are enantiomers.



7. Compounds containing one stereogenic centre are always chiral but some molecules containing more than one stereogenic centre may not be chiral. Refer to isomers of tartaric acid in subsection 2.3.2.

8. (i) This compound contains three chiral centres, hence the maximum number of possible isomers is $2^3 = 8$. Draw all the eight configurations as in Fig. 2.18 for 2,3,4-trihydroxyglutaric acid. You will find that only two of the stereoisomers are optically active and two are meso compounds.

   (ii) This compound contains two chiral centres which are differently substituted so four stereoisomers are possible. They form two pairs of enantiomers and all are optically active.