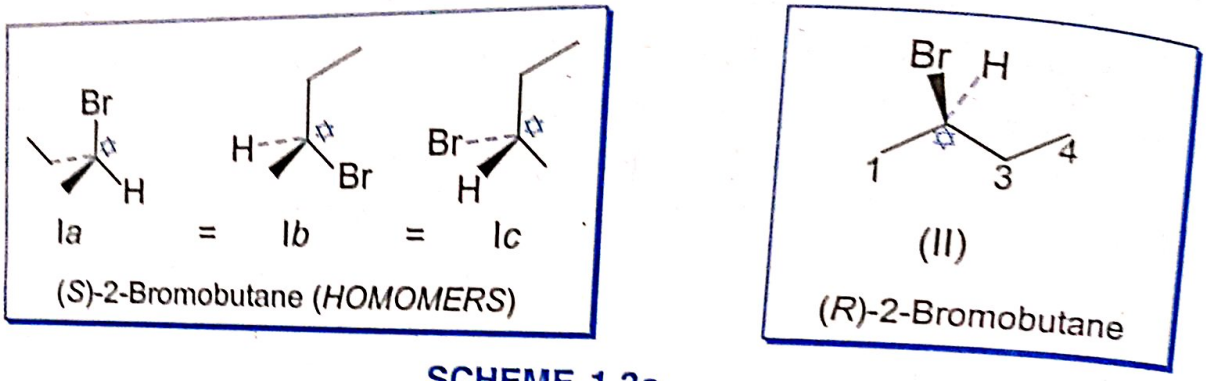
due to self-cancelling [illegible] with two or more stereocenters are termed [illegible] plane of symmetry. Compounds also exist in cyclic structures (See scheme 1.66).

6. Homomers

A molecule may be written in two or more orientations which infact represent the same [illegible] but at first sight look different. Such different orientations of the same compound (which superimpossable) are called homomeric. For example, for (*S*)-2-bromobutane one can write many equivalent orientations, three of which are presented (Ia-Ic, scheme 1.3*a*). These structures are thus homomeric (one may note that one gets S-2-bromobutane by exchanging any two substituents of the (*R*)-configuration (II, scheme 1.3*a*).



SCHEME 1.3a

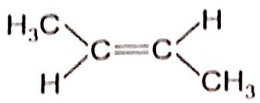
7. Homochiral Molecules

When the molecules have the same sense of chirality, they are called homochiral, e.g., right hands of a group of people are homochiral (Kelvin 1904). However, recently, in violation of the original definition the term has been used to depict enantiomeric purity, when one it to refer to such a compound as homochiral. In the original sense *e.g.*, the hog-kidney acylase hydrolyzes the natural L-enantiomers of *N*-acylamino acids, no matter what the structure the *R* group is, *N*-acyl-L-amino acids thus are homochiral molecules (see scheme 1.86).

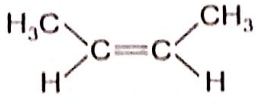
8. Configuration and Conformation—Residual Stereoisomers

The actual three-dimensional arrangement of groups around a stereocenter is termed configuration and the term configurational isomers is synonymous with stereoisomers. Other way to designate the configuration of geometrical isomers is to use the terms *cis* or *trans* (better *E*, *Z* nomenclature).

The term conformations (conformational isomers, conformers or rotamers) refers to various shapes that a molecule can adopt by rotation about single bonds *e.g.*, an eclipsed or staggered conformation of ethane and different conformations of chlorocyclohexane (see scheme 1.1). Unless it is held rigid by a small ring or double bonds, a molecule could have an infinite number of conformations, however, only one configuration. Thus, 2-butanol has two stable enantiomers (*R*)-2-butanol and (*S*)-2-butanol (see, scheme 1.1) each exists as a dynamic mixture of conformations *e.g.*, in the ethyl group. Thus normally 2-butanol is considered to exist in only two enantiomeric forms (scheme 1.1) as again shown in the planar projection formula (scheme 1.3*b*). In doing so, one ignores the otherwise important conformational details. Using the concept of residual stereoisomerism, 2-butanol is considered to have only two residual stereoisomers (the two enantiomers) since fast rotation at room temperature reduces the number of isolable species. In case with amine invertomers as well *e.g.*, in *N*-methyl-1-phenylethyl amine (scheme 1.3*b*) although there are two stereocenters at carbon and nitrogen, it has only two residual stereoisomers (residual enantiomers with different configuration only at the benzylic carbon).



(*E*)-2-Butene
(*trans*-2-Butene)



(Z)-2-Butene
(*cis*-2-Butene)

cis- and *trans*-2-Butenes are stereoisomers, which are not mirror images, therefore, these are diastereomers. The isomeric 2-butenes each have trigonal planar stereocenters.

SCHEME 1.3

4. Properties of Diastereomers

Diastereomers have a major advantage over enantiomers from a practical point of view. Diastereomers have different physical properties like m.p., b.p., solubility, retention times and R_f values and have different rates of reactions (chemical properties) even in achiral environments. Standard techniques like crystallization distillation or chromatography can therefore, be used to separate diastereomeric mixtures. For example, *meso* tartaric acid (specific rotation = 0) melts at 140°C as against either of the enantiomers (m.p. 171°C) and has different value of pK_a. Use of this difference in properties of diastereomers is made in the resolution of racemic mixture (See scheme 1.82). Another example is of erythroses and threoses (See scheme 1.32).

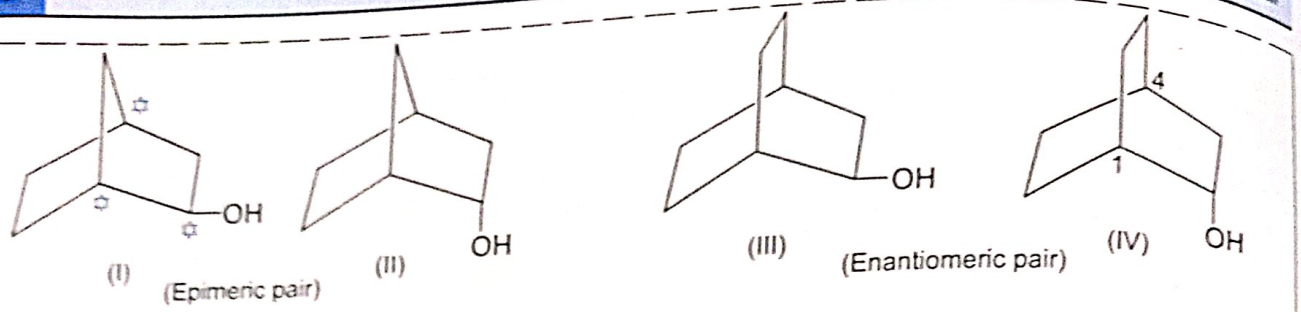
Enantiomers and Diastereomers

One may note the following points :

- *Enantiomers (mirror images of each other) are related by symmetry elements of the second kind, i.e., σ plane, i, and S_n axis while diastereomers are not related by any such symmetry element.*
- *Since a molecule (or an object) can have only one mirror image, enantiomers can exist only in pairs. On the other hand, structural conditions permitting, a molecule can have any number of diastereomers, e.g., meso tartaric acid has two diastereomers (diastereomeric relationship with either of the enantiomers).*
- *Two stereoisomers can not be enantiomers and diastereomers at the same time, i.e., enantiomeric and diastereomeric relationships are mutually exclusive.*
- *Diastereomers may be (or may not be) chiral in which case each of the diastereomer will show enantiomerism. Thus cholesterol with 8 stereocenters has 256 stereoisomers. Cholesterol is one of these and the second is its mirror image (enantiomer). Cholesterol is thus diastereomeric with 254 molecules.*
- *Diastereomers include all stereoisomers (but for enantiomers), optically active diastereomers, geometrical isomers and cis-trans isomers of classical stereochemistry.*
- *Enantiomeric relationship can only be specified by comparison with a chiral reference (plane polarized light). The diastereomeric relationship can be established without any external reference.*

5. Chiral, Achiral Compounds and Meso Compounds (An Introduction)

Consider the stereoisomers of tartaric acid (two stereocenters with identical set of substituents at each stereocenter, scheme 1.2*a*). The pair of enantiomers (which are non-superimposable mirror images) constitute chiral compounds whereas the *meso* stereoisomer is achiral (optically inactive) even though it has two stereocenters. The configuration of the *meso*- tartaric acid is 2*R*, 3*S* (see scheme 1.2*a*) if one draws its mirror image (2*S*, 3*R*) it is found to be superimposable with it. The *meso* compounds have two features in common : (*a*) a plane of symmetry and (*b*) two stereocenters with opposite stereodescriptors. *Meso* compounds are optically inactive



SCHEME 1.2d

(iii) Anomers

To give a pyranose structure, the OH group at C5 of open chain form of glucose attacks the aldehyde (carbon C1) to form a hemiacetal. A new stereocenters at C1 is generated and a pair of diastereomers is formed. These diastereomers (in the case of a monosaccharide) which differ in the configuration at C1 (called anomeric carbon) are called anomers (scheme 1.2*e*). Thus α-D-glucopyranose and β-D-glucopyranose are diastereomers. They are also epimers and anomers.

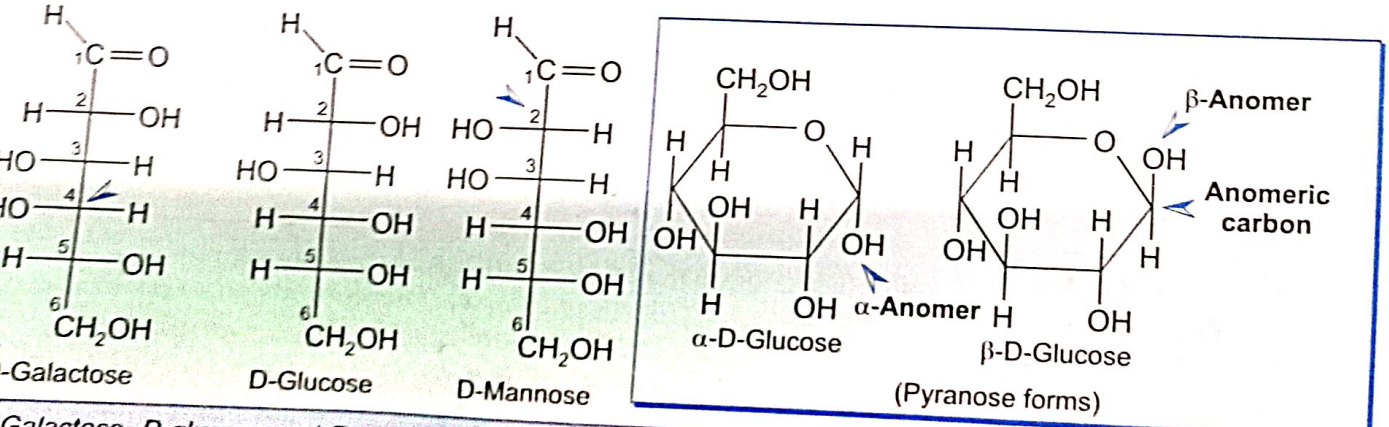
It is important to note that in general a molecule can have only one enantiomer, but it may have many diastereomers (*i.e.*, consider the case of cholesterol scheme 1.68*d*).

(iv) Trigonal planar stereocenters

A stereocenter is defined as an atom having groups of suitable nature so that an interchange of any two groups will give a stereoisomer. However, all stereocenters are not tetrahedral the unsaturated carbon atoms of *cis* and *trans*-2-butene (scheme 1.3) are examples of trigonal planar stereocenters, since an interchange of groups at these stereocenters gives a stereoisomer (a disastereomer).

cis- and *trans*-2-Butene (scheme 1.3) are not mirror images of each other, *i.e.* if a structural model of *cis*-2-butene is shown to a mirror, the arrangement which one sees in the mirror is not *trans*-2-butene. However, *cis*- and *trans*-2-butene are stereoisomers and, since they are not related to each other as an object and its mirror image, they are thus distereomers. Diastereomers are stereoisomers which are not mirror images of each other.

Although *cis*- and *trans* isomers of alkenes are diastereomers (see scheme 1.3) that are achiral, the majority of diastereomeric compounds are chiral compounds however, which have more than one stereocenter. For an example of diastereomers in alicyclic compounds (see, scheme 1.67).



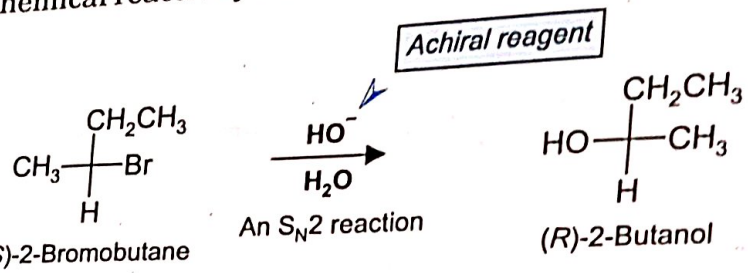
Galactose, D-glucose and D-mannose are diastereomers, D-galactose and D-glucose are C4 epimers while D-cose and D-mannose are C2 epimers. α-β-Anomers of D-glucose-are also diastereomers differing in configuration at meric carbon.

SCHEME 1.2e

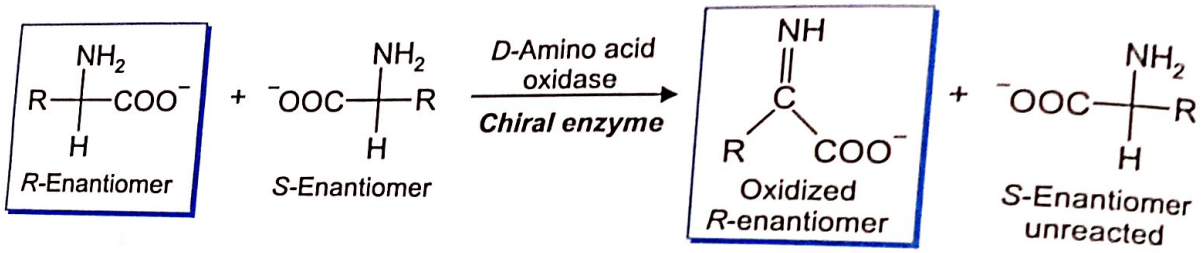
2. Properties of Enantiomers

Each enantiomer of a pair has the same physical and chemical properties in achiral environments with the important exceptions of their interactions with (*i*) plane polarized light (optical activity) and (*ii*) chiral reagents. When plane polarized light is passed through the solution of each enantiomer (in the same solvent, using the same cell and same concentration), then the plane of polarized light is rotated in opposite directions by the same amount as in glyceraldehyde enantiomers (scheme 1.2). Similarly the enantiomers of tartaric acid have *e.g.*, the same melting point (171°C), the same value of pK_a (25°C $pK_1 = 2.98$; $pK_2 = 4.34$), but different signs of specific rotation (+)-tartaric acid + 12.7 while (–)-tartaric acid – 12.7 (scheme 1.2*a*). Each enantiomer shows the same chemical reactivity with achiral reagents *i.e.*, enantiomers react with achiral reagents

Plane polarized light is in fact an equal mixture of left and right circularly polarized light which propagates through space as left handed and right handed helices respectively. Due to the chirality of the circular components of the plane polarized light the two enantiomers of a compound react with it differently.



Achiral reagents e.g. hydroxide ion react with enantiomers (reaction only with (S)-enantiomer is shown) at the same rate. Chiral reagents discriminate between them.



SCHEME 1.2b

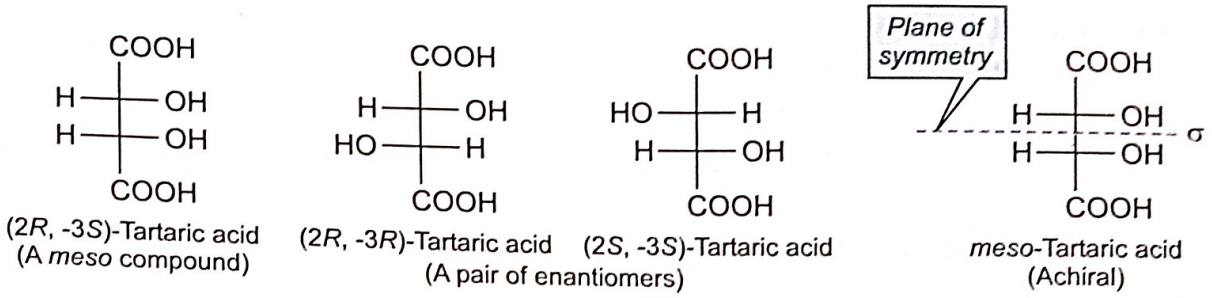
at the same rate. Thus *e.g.* (*S*)-2-bromobutane reacts with achiral hydroxide ion to give (*R*)-2-butanol (scheme 1.2*b*) by an S_N2 mechanism. The rate of this reaction is found to be the same with the enantiomeric (*R*)-2-bromobutane with hydroxide ion to give (*S*)-2-butanol. When, however, the reagent is chiral *e.g.*, an enzyme, the two enantiomers will react at different rates. Thus the enzyme D-amino acid oxidase reacts only with one of the enantiomers–the (*R*)-enantiomer, the (*S*)-enantiomer remaining unchanged (scheme 1.2*b*). Another example is found during the kinetic resolution of amino acids (See, scheme 1.86).

This is an example of stereospecificity in general and the reaction with only one nantiomer shows that the enzyme displays total enantioselectivity.

Receptors are proteins which are chiral and thus these will bind one of the enantiomers tter than the other *i.e.*, one enantiomer binds with a particular receptor whereas the other es not. Receptors located on the exterior of nerve cells in the nose are thus able to differentiate urs. The enantiomers of carvone (scheme 1.2*c*) smell different since each fits into a different ptor.

In summary chiral substances react only with substances that match their own chirality. forms the basis for an enzyme to distinguish between two enantiomers of a compound, g enzyme catalyzed reactions. The enzyme first positions a molecule at the binding site surface (via, hydrogen bonds, electrostatic attractions, dispersion forces or even covalent

Stereocenters *e.g.*, in tartaric acid stereoisomers are assigned *R* and *S* configurational descriptors, so as to specify stereochemical features of each stereoisomer. The enantiomer of (+) tartaric acid is its nonsuperimposable mirror image (–) tartaric acid and these constitute an enantiomeric pair. Notice that pairs of enantiomers (as expected) have opposite configuration at every stereocenter.



Stereoisomers of tartaric acid in Fischer projections

Physical properties of stereoisomers of tartaric acid

	Melting point, °C	$[\alpha]_D^{25°C}$	Solubility, g/100 g H_2O at 15°C
(2R, 3R)-(+)-Tartaric acid	171	+ 12.7°	139
(2S, 3S)-(–) Tartaric acid	171	– 12.7°	139
(2R, 3S)-Tartaric acid	140	0°	125
(±)-Tartaric acid	206	0°	20.6

SCHEME 1.2a

(*b*) Complex organic molecules and biomolecules

Except for few low molecular weight organic compounds, the organic substances found in living systems both animals and plants are chiral. No doubt these molecules (with several stereocenters) can theoretically exist as a number of stereoisomers, almost invariably only one stereoisomer is found in nature. Naturally occurring alkaloid brucine has several stereocenters which are located in fused ring systems, however, nature makes only one enantiomer (–)-brucine. Naturally occurring amino acids (with the exception of achiral glycine) are chiral. There are two possible enantiomers (optical isomers) for each amino acid, but only one of them (L-form) exists in the body. Enzymes are proteins which are derived from chiral amino acids, thus an enzyme is also chiral and can exist as enantiomers, however only one enantiomer exists naturally (since an amino acid exists only as one enantiomer these will construct only one mirror image form of the enzyme). Thus enzymes provide a chiral environment.

Enzymes catalyzed reactions are stereospecific and stereoselective

- *For definition of terms, stereospecific and stereoselective (see Sec. 1.13).*
- *Enzymes are chiral and enantiomerically pure.*
- *Enzymes display stereospecificity and stereoselectivity (see Sec. 2.3 D).*
- *All stereospecific reactions are necessarily stereoselective, however, the converse is not true.*

with one tetrahedral atom with four different groups attached to it is enantiomerism as it glyceraldehyde (scheme 1.2). An important property of such enantiomers (i.e., a chiral tetrahedral model) is that on interchanging any two groups at the stereocenter converts one enantiomer into another. In addition to the compounds of the type C_{abcd} with one stereocenter e.g., glyceraldehyde (scheme 1.2) and 2-butanol (scheme 1.1) which fulfill the conditions for the occurrence of enantiomeric pairs, several other structural situations may give rise to optical isomerism. These include compounds with more than one stereocenter (as in glucose, scheme 1.2), stereocenters other than carbon (sec. B, IV) and compounds which are optically active in the absence of stereocenters (scheme 1.1*e*).

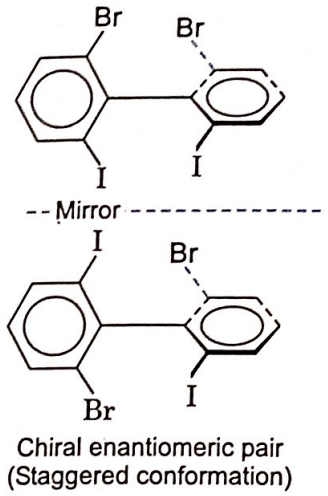
Chiral Organic Compounds

- *The presence of a stereocenter usually leads to molecular chirality.*
- *A tetrahedral atom or a pyramidal atom with three ligands (the lone pair of electrons serves as the fourth ligand) gives a stereocenter provided an interchange of any two ligands (this process reverses the chirality of the center) leads to a new stereoisomer.*
- *The presence of a stereocenter in an organic molecule is a sufficient condition for chirality, however it is not a necessary condition.*
- *Several molecules display chirality (optical isomerism) in the absence of stereocenters e.g., chiral biphenyls. Thus a compound is chiral if it is not superimposable on its mirror image.*
- *Organic stereochemistry is based on tetrahedral geometry of carbon which is absolutely central to its study. Study of stereochemistry is also based on atoms like N, P, Si and S and to a lesser extent on the trigonal geometry of sp^2 hybrid carbon and nitrogen.*

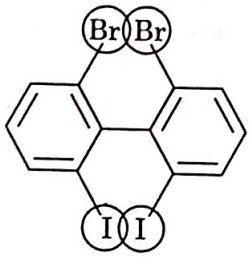
In tartaric acid (scheme 1.2*a*) one has two stereocenters. A molecule with two stereocenters can give rise to a maximum of four stereoisomers (2^n as also in 2-bromo-2-butanol, see scheme 1.33). However, if the two stereocenters carry an identical set of substituents, the number of stereoisomers is less than 2^n, since there will be a *meso* compound (scheme 1.2*a*). The *meso* tartaric acid has a plane of symmetry and is achiral (it has a mirror image which is, however, superimposable on it). The name *meso* is given to an achiral member of a set of a diastereomers which also includes at least one chiral member. Tartaric acid stereoisomers are drawn in Fischer projections (The Fischer projections are the eclipsed conformations).

Chirality and Stereocenters

- *Chirality is a necessary and sufficient condition to generate enantiomerism and requires the absence of Sn (alternating axis of symmetry of any order).*
- *The presence of a stereocenter usually imparts molecular chirality. A unique feature of such a stereocenter is that exchange of any two ligands inverts the chirality of the stereocenter to yield a new stereoisomer. When all the ligands are achiral, the exchange gives an enantiomer, however, if one or more of the ligands are chiral, a diastereomer will be formed. This is seen in the case of tartaric acid. When one interchanges the groups on one stereocenter in meso-tartaric acid (see, scheme 1.2a) an enantiomer of tartaric acid is formed and vice versa.*
- *Thus an organic molecule with one stereocenter must be chiral, however, molecules with two or more stereocenters are not all chiral.*



Chiral enantiomeric pair
(Staggered conformation)



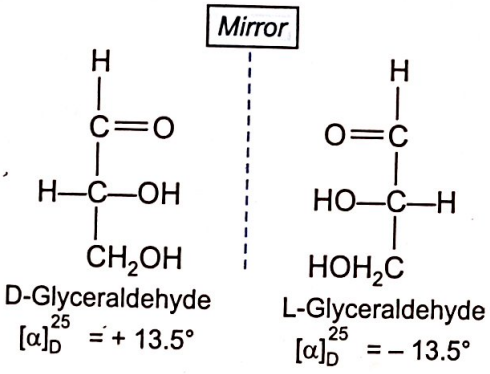
Achiral
(Eclipsed conformation)
too crowded to exist

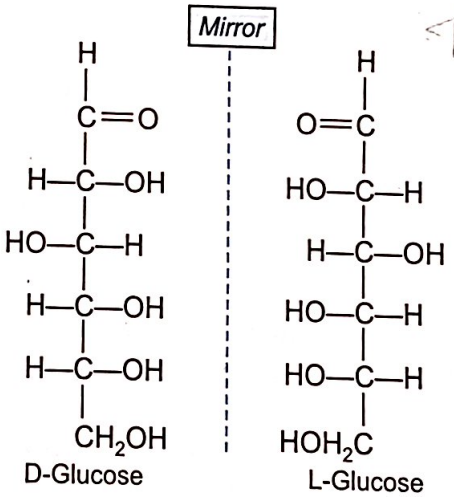
Stable conformational isomers (atropisomers) exist in compounds, e.g., biphenyls due to steric strain between the ortho substituents. These isomers become chiral when both rings are unsymmetrically substituted. The biphenyl then gets locked in one of the two chiral enantiomeric staggered conformations. This biphenyl would have been achiral if a symmetric (planar) high energy eclipsed conformation could be achieved (an impossible situation.)

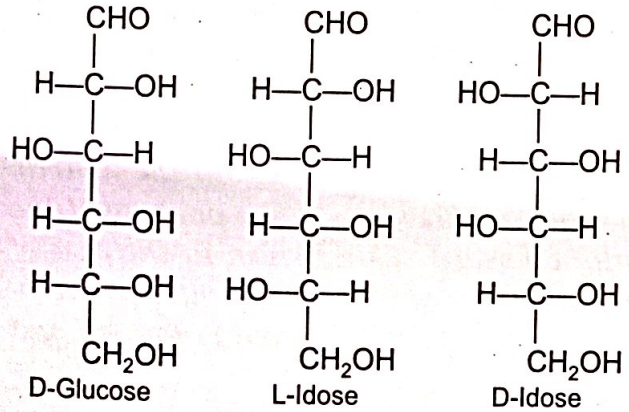
SCHEME 1.1e

Compounds can be chiral and thus exist as a pair of enantiomers in the absence of stereocenters as in *trans*-cyclooctene (scheme 1.1, further details are in schemes 1.136–1.138). Another example of compounds which are chiral in the absence of stereocenters are biphenyl derivatives (scheme 1.1*e*, further details are in Sec. 1.16, B).

Thus compounds of the type C_{abcd} exist in enantiomeric forms and are described as chiral and the carbon atom with four different achiral atoms or groups as substituents is called a stereogenic centre of simply a stereocenter. The phenomenon of enantiomers is also known as optical isomerism. An important property of compounds of type C_{abcd} *i.e.*, a molecule



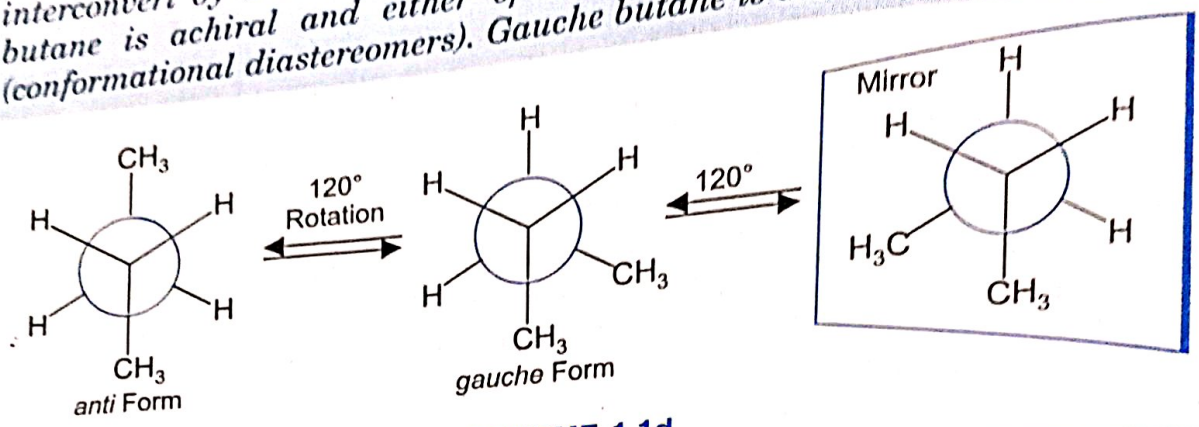




The mirror image (enantiomer) of D-glucose is L-glucose with inverted stereochemistry at every stereocenter. By simply changing the stereochemistry at only one stereocenter (bottom) of D-glucose does not, however, give L-glucose, it however, converts a D-sugar (D-glucose) into a L-sugar, which is L-idose an enantiomer of natural D-sugar D-idose.

SCHEME 1.2

The distinction between conformation and configuration is in fact subtle and not agreed upon universally. The acyclic amine inversion (scheme 1.1) has a typically low energy barrier (33.5 kJ/mol) and may be considered either a configurational or a conformational change. These invertomers are however, better considered as conformers or as conformational enantiomers. However, these arguments do not apply to chiral phosphines (scheme 1.1c) where inversion is associated with high energy (~ 150 kJ/mol) to result in configurational isomers. Rotation around a single bond may be easy to give conformational isomers e.g., in n-butane (scheme 1.1d). Gauche butane is chiral. Two enantiomers interconvert by a conformational change (conformational enantiomers). Anti butane is achiral and either of the gauche butanes is its diastereomer (conformational diastereomers). Gauche butane is an example of racemization.



SCHEME 1.1d

Similarly chlorocyclohexane (scheme 1.1) represents a pair of conformational diastereomers. In fact chlorocyclohexane shows conformational isomerism at room temperature while configurational isomerism at –150°C (see Fig. 4.2). Another interesting example of conformational enantiomers is in (scheme 4.33).

(B) Stereoisomers—An Introduction

When the isomers have the same sequence of covalent bonds, but differ in the relative disposition of their atoms in space, then the difference is stereoisomeric (scheme 1.1) (also see Fig. 1.1). Some examples are, enantiomers, diastereomers (epimers, anomers), conformational isomers (atropisomers and invertomers).

1. Enantiomers—Optical Isomerism

(a) Simple organic molecules

Consider a simple molecule *e.g.*, a compound with an sp^3 hybridized carbon with four different substituents as in 2-butanol (scheme 1.1). The molecule cannot be superimposed on its mirror image and such molecules are said to be chiral (or handed). The pair of butanol molecules are termed enantiomers (from the Greek 'enantio' meaning opposite) which are defined as pair of molecules related as non-superimposable mirror images. The enantiomers of 2-butanol are drawn (scheme 1.1) in the three dimensional projection formulas (a procedure to draw these projections is depicted in scheme 1.15). Another example of enantiomers is in D and L-glyceraldehydes and D- and L-glucose drawn now in another projection (scheme 1.2) called Fischer projection, (a procedure to draw these projections is detailed in scheme 1.17). The sugars have the OH group on the bottom stereocenter on the right in the Fischer projection. The unnatural L-series of sugars are the enantiomers of the natural D-series.