Chemists prior to 1951 could not determine the absolute configurations of stereocenters, instead configurations relative to that of (+)-glyceraldehyde were determined. Thus prior to 1951 only relative configurations of compounds were known. For example, if (+)-glyceraldehyde is converted to glyceric acid using a reaction that is known to put the COOH group where the CHO was, then the two compounds have the same relative configuration (scheme 1.3c) at their stereocenters even though one may not know their absolute configuration. The oxidation reaction (scheme 1.3c) does not break a bond to the stereocenter in (+)-glyceraldehyde and proceeds with retention of configuration. Thus the product glyceric acid of this conversion though levorotatory has the same relative configuration as that of (+)-glyceraldehyde. Since now the absolute configuration of D-(+)-glyceraldehyde (X-ray diffraction) is known, the absolute configuration of glyceric acid (still a member of D-series) is also known. Following points may be noted:

- There is no simple relation between the sign of rotation (+)- or (–) (scheme 1.3c) and the absolute configuration *R* and *S*. Thus D-glyceraldehyde (*R* configuration) is dextrorotatory while D-glyceric acid (*R* configuration) is levorotatory.
- Two closely related compounds with the same relative configuration may have different descriptors (*R* or *S*, See scheme 1.28*i*).
- In summary relative configuration is the relationship between configurations of two chiral molecules. When two such molecules are chemically interconverted without breaking any bonds to the stereocenter, these are said to have the same relative configuration independent of the direction of rotation of the plane polarized light and independent of the (*R* and *S*) designation (see, scheme 1.28*j*).
- Retention of configuration is the conversion of one molecule into another with the same relative configuration.
- Inversion of configuration is the conversion of one molecule into another which has the opposite relative configuration. Inversion of configuration does not require a change in designated absolute configuration, similarly a change in designated absolute configuration does not require an inversion of configuration. The reaction (III, scheme 1.28*i*) proceeds with inversion although (*R*) reactant gives (*R*)-product.
- Relative configuration at a stereocenter is also the relation with that of any other stereocenter in the same molecule.

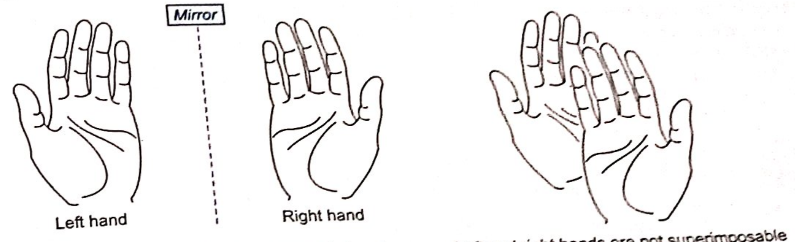
1.3 CHIRAL MOLECULES-ENANTIOMERISM (OPTICAL ISOMERISM) A SUMMARY

Enantiomers occur only with those compounds whose molecules are chiral. A chiral molecule can be defined as one that is not superposable on its mirror image.

(A) The Terms Chiral, Stereogenic Center (Stereocenter)

(i) The Term Chiral

The word chiral (Greek word Chier, meaning hand) is used for those objects which have right-handed and left-handed forms, *i.e.*, molecules which have "handedness" and the general property "handedness" is termed chirality. An object which is not superimposable upon its mirror



The mirror image of left hand is a right hand

Left and right hands are not superimposable

Fig. 1.2

image is chiral. Enantiomers occur only with those compounds whose molecules are chiral. Thus *e.g.*, 2-butanol molecule is chiral as well as *trans*-cyclooctene (scheme 1.1). Human hands are related to each other as object and its mirror image typical of enantiomers (Fig. 1.2). Thus *e.g.*, one's right hand will fit into a right glove and not into a left glove. The term chiral is used to describe molecules of enantiomers since these are related the same way that a right hand is related to a left hand. A structurally chiral system is the human body itself, the heart lies to the left of center and the liver to the right. From an evolution point of view most people are right handed. Several plants display chirality by way they wind around supporting structures and thus represent as a left-handed or a right-handed helix. All but one of the 20 amino acids, the components of proteins are chiral and left handed. The molecules of almost all natural sugars on the other hand are right handed. The enantiomers display physiological differences, one enantiomeric form of a terpenoid limonene smells like oranges while the other enantiomer smells like lemons. Ones nose is capable of distinguishing between enantiomers, *i.e.*, the receptor sites for the sense of smell are chiral (see, scheme 1.2*c*).

Generally, otherwise, enantiomers have identical properties in a symmetrical environment, enantiomers react at the same rate with achiral compounds. Their properties may however, differ in an unsymmetrical environment, and enantiomers may react at different rates with other chiral compounds (see scheme 1.2*b*). This difference is reflected in a compound being biologically active, while its enantiomer is not.

(*ii*) The Term Achiral

Objects and molecules which are superimposable on their mirror images *e.g.* a cup (Fig. 1.2*a*) is achiral. An internal plane of symmetry is a hypothetical plane which bisects an object or a molecule into mirror-reflective halves. An object or a molecule with an internal plane of symmetry is achiral (can be superposed on its mirror image). Thus a cup is achiral since it can be divided into two equal halves by its plane of symmetry. Similar is the case with *meso* tartaric acid (drawn as Fischer projection or perspective formula Fig. 1.2*a*). A hand is chiral since a plane cannot split it into two equal halves. Similarly either of the (+)- or (–)-enantiomer of tartaric acid is chiral.

(*iii*) The Terms Asymmetric Center and Chiral Center

Three terms are used to designate *e.g.*, a carbon atom bonded tetrahedrally to four different substituents in a chiral molecule: asymmetric atom, chiral center (*i.e.*, chiral atom) or stereocenter. From the time of Le Bel and vant Hoff an atom with four different substituen was called an asymmetric atom. This is indeed so, since compounds with one such atom ... truly asymmetric as they lack symmetry. There are molecules which have atoms with ... different substituents and which also have various symmetry elements, including plane ... symmetry as in *meso* tartaric acid Fig. 1.2*a*. Use of the term asymmetric atom in these type ... cases may be confusing.

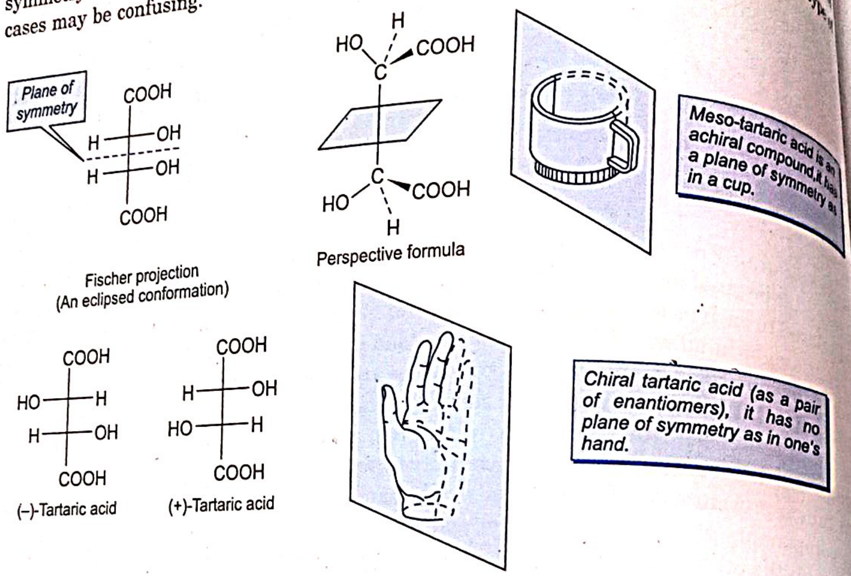


Fig. 1.2a

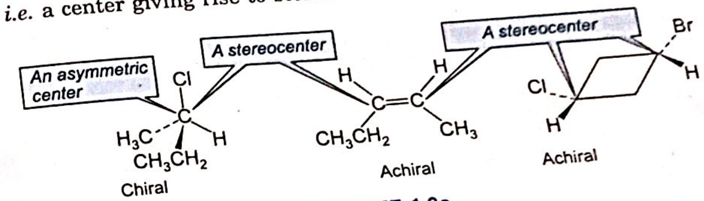
Similarly, like asymmetric atom the term chiral atom (used prior to 1984) may also cause a conceptual confusion, although these terms, particularly the use of term chiral center are well accepted in literature. Chirality is a geometric property which influences and affects all parts of a chiral molecule. All the atoms of a chiral molecule like 2-butanol (scheme 1.1) are placed in a chiral environment and are therefore chirotopic. Thus when, C-2 carbon atom in 2-butanol is termed a chiral center (or chiral carbon to distinguish it from chiral nitrogen chiral phosphorus etc.), it may cause a conceptual confusion. The more ideal term for such a center or atom is stereogenic center.

(*iv*) The Terms Stereogenic Center-Stereocenter and Chirality Center

A stereogenic center or in short a stereocenter is an atom having groups of such nature that an interchange of any two groups will produce a stereoisomer. C-2 in glyceraldehyde (see, scheme 1.2) is an example of a tetrahedral, stereocenter. It is easy to see that interchanging *e.g.*, the OH and H in the Fischer projection of glyceraldehyde (scheme 1.2) converts one enantiomer into other. A carbon atom that is a stereocenter is also called a stereogenic carbon. The carbon atom C-2 of glyceraldehyde with four different groups bonded to it (lacks the two key symmetry elements, the plane of symmetry and center of symmetry), is an example of chirality center. The term stereocenter can also be used to define the C-2 atom of glyceraldehyde, but is broader. The stereocenters involved in *cis-trans* isomerism may however, not be chirality centers (scheme 1.3*c*). All stereocenters may not be tetrahedral, thus the carbon atoms of *cis*-

and *trans*-2-butene provide an example of trigonal planar stereocenters, since an interchange of groups at either atom leads to a stereoisomer (a diastereomer).

All three alternative terms, asymmetric center, chiral center (chirality center) or stereogenic center (stereocenter) are in current use for carbon atoms which have four different substituents. The term chiral is applied to the whole molecule to mean being capable of existing as nonsuperimposable object and mirror image forms. Chirality is the property of the whole molecule and cannot be localized in a particular atom or a center. Thus the more widely used term 'chiral center' and asymmetric center should be replaced by stereogenic center or simply stereocenter *i.e.* a center giving rise to stereoisomers (scheme 1.3*c*).



SCHEME 1.3c

(B) The Chiral Molecules

(*i*) Nonsuperimposability of a Structure on Its Mirror Image

The ultimate criterion for chirality *i.e.*, existence of enantiomers in a molecule is th... nonsuperimposability of a structure and its mirror image. [*Thus enantiomers must be isome... and mirror images as well, i.e., they must not be superimposable*].

(*ii*) Elements of Symmetry and Chirality—Rotation/Reflection Axis

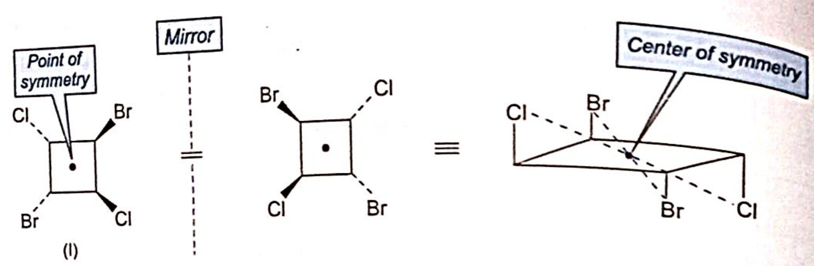
Chirality—A Necessary and Sufficient Condition

Only those molecules are chiral which do not have an alternating axis of symmetry S_n (i.e., absence of a rotation/reflection axis). The chiral molecules can, however, have an axis of rotation (C_n).

An alternative approach to decide if or not a structure is chiral *i.e.*, capable of exis... enantiomeric forms (optically active forms) is to examine the symmetry of a molecule. ... ture which lacks an alternating axis of symmetry is chiral and is not superimposabl... mirror image and therefore, can exist in optically active forms. Symmetry operations ... cussed in detail (see sec. 1.8), however, here the common practice is to look for a ... symmetry (a one fold alternating axis of symmetry S_1) and a center of symmetry ... equivalent to S_2 will be discussed while higher subscripts for S_n are rare (A molecule i... have an *n* fold alternating axis of symmetry S_n if rotation of 360°/*n* about an axis fol... reflection in a plane perpendicular to that axis brings the molecule into a position ... guishable form the original).

meso-Tartaric acid is achiral even though it has two stereocenters since it has a ... symmetry (see scheme 1.2*a* and Fig. 1.2*a*).

When one cannot detect a mirror plane of symmetry in a molecule, the molecule necessarily chiral. Thus the cyclobutane derivative (I, scheme 1.3*d*) has no internal plane of symmetry, yet the mirror image is superposable on the original molecule (when the mirror image is rotated the two structures are superposable. Unlike a three dimensional formula which does not change on rotation, the two dimensional representations of dimensional molecules like Fischer projections can only be manipulated in specified ways). fact (I, scheme 1.3*d*) has a center of symmetry *i.e.*, it contains an S_2 axis (an inversion see, scheme 1.73). A molecule is said to have a center of symmetry or an inversion center if all straight lines that can be drawn through the center of the molecule meet identical atoms (or points) at the same distance from the center. In other words inversion of all atoms (or points in the molecule through the point leads to an arrangement indistinguishable from the original. There can be only one such inversion center in the molecule.



(I)

In this achiral cyclobutane derivative no plane of symmetry is detectable. Infact the compound has a center of symmetry (point of symmetry) and the two structures are superimposable on their mirror images.

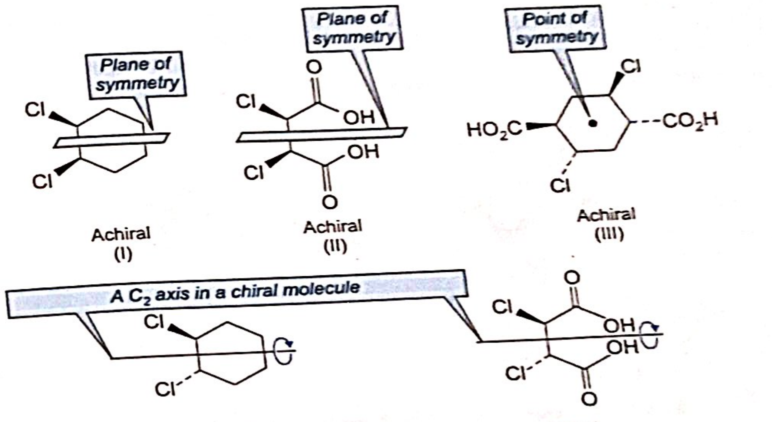
SCHEME 1.3d

Thus the most common cause of chirality in organic molecules is a tetrahedral atom (generally carbon) bonded to four different groups. A carbon atom with four different groups bonded to it lacks the two key symmetry elements, plane and center of symmetry (as well as a rotational axis of symmetry as well) and is called a chiral center (or asymmetric center) or alternatively a chirality center. The term stereocenter is also used, but it is a broader term. Thus all chirality centers are stereocenters, but all stereocenters e.g., those involved in cis-trans isomerism need not be chirality centers. Chirality centers are however, not limited to carbon, enantiomers are known with compounds having stereocenters other than carbon i.e., tetrahedral, phosphorus, nitrogen, etc. Chirality can also be present without chirality centers.

Molecules with a Plane or a Centre of Symmetry and Axis of Rotation

The mirror plane of symmetry (S_1) is the most frequently occuring rotation reflection axis in organic molecules. Examples of further compounds which have this axis are in (I and II scheme 1.3e), cis-1, 2-dichlorocyclohexane and meso-2, 3-dichlorosuccinic acid are achiral even though each has two stereocenters. Dichlorocyclohexane dicarboxylic acid (III) on the other hand is achiral even though

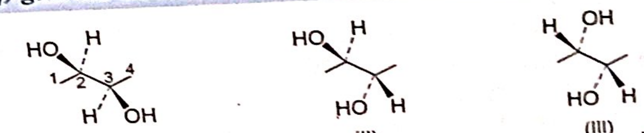
it has four stereocenters due to the presence of a point of symmetry—presence of S_2 axis which is somewhat rare in organic chemistry. A molecule can, however, be chiral if it has only an axis of rotation. Both trans-1, 2-dichlorocyclohexane and dichlorosuccinic acid (IV and V respectively, scheme 1.3e) have a two fold axis of rotation (C_2) as the only symmetry element and both are chiral.



SCHEME 1.3e

EXERCISE 1.1

From the stereorepresentations for the three stereoisomers of 2, 3-butanediol (scheme 1.3f) give the stereochemical relationships:



SCHEME 1.3f

- *Which are enantiomers?*
- *Which is the meso compound?*
- *Which are diastereomers?*

ANSWER

- *Compounds (I) and (III) are enantiomers. (Configuration reversed at every stereocenter).*