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Class : Semester-2

Paper: C4T: Organic Chemistry

Topic : Stereochemistry II

(Chirality arising out of stereoaxis: stereoisomerism of substituted cumulenes with even and odd number of double bonds; chiral axis in allenes, spiro compounds, alkylidenecycloalkanes and biphenyls; related configurational descriptors (*Ra/Sa* and *P/M); Atropisomerism;* racemisation of chiral biphenyls; *buttressing effect.*

Comments: Read the notes thoroughly. This part is very important for final examination.

References:

Basic Stereochemistry of Organic Molecules by Prof. Subrata Sen Gupta

Stereoisomerism of substituted allenes :

Allene itself does not exhibit enantiomerism because it has two σ planes, three C_2 simple axes and one S_4 axis. Its point group is D_{2d}.
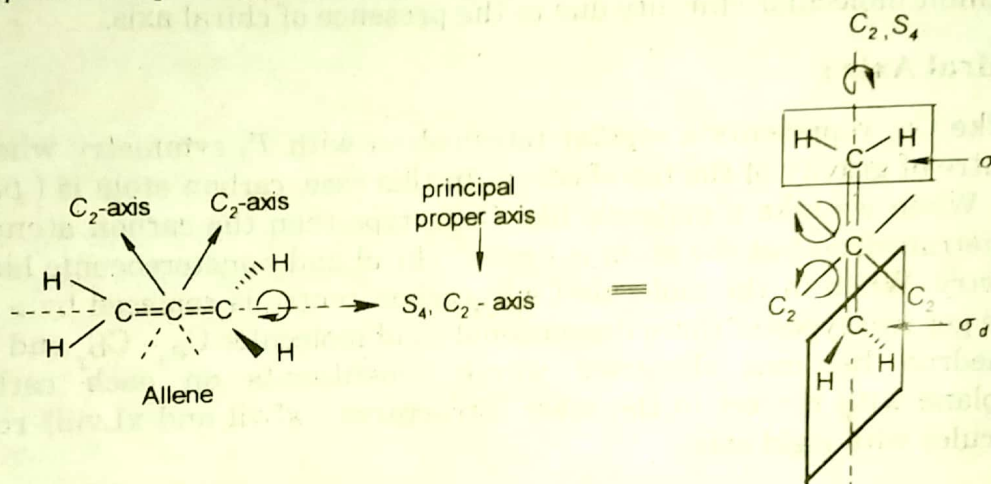

Fig. 3.144

When a molecule contains several C_n axes with same value of n then one which involves maximum number of atoms is the principal proper axis. In case of allene, there are three C_2 axes but the axis passing through the three carbon atoms is the *principal* proper axis.
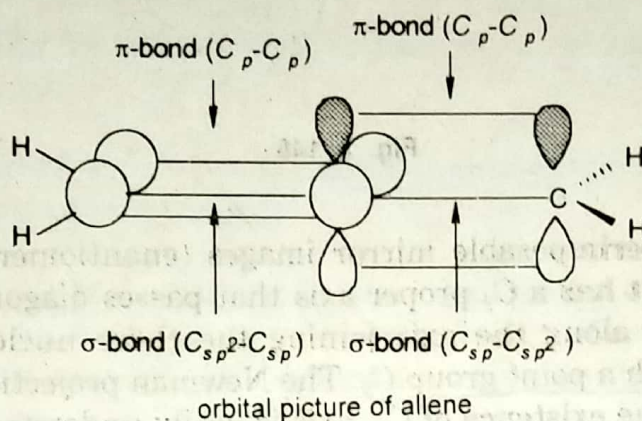
Orbital picture of allene is shown below.

π-bond (C_p-C_p) π-bond (C_p-C_p)

σ-bond (C_{sp^2}-C_{sp}) σ-bond (C_{sp}-C_{sp^2})

orbital picture of allene

Fig. 3. 145

There are several possibilities of differently substituted allenes. They are (xLix), (L), (Li) and (Lii). The point group of these are C_{2v}, C_s, C_2 and C_1 respectively.
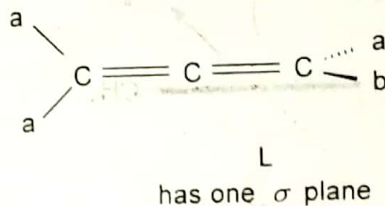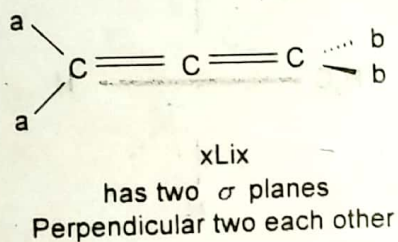
xLix

has two σ planes
Perpendicular two each other

L

has one σ plane

Fig. 3. 146

Li

only C_2 - axis

Lii

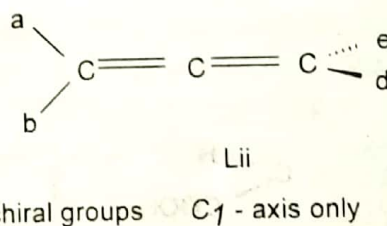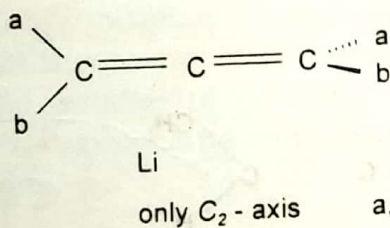a,b,e,d are atoms or achiral groups C_1 - axis only

Fig. 3. 147

Of these four types (xLix) and (L) are achiral because both of them have σ planes and, therefore, they do not exist as enantiomers. But (Li) and (Lii) are chiral molecules having no σ, i and S_n $(n>1)$. Structure (Li) has a C_2 simple axis and, therefore, represents a dissymmetric molecule. In structure (Lii), even the C_n $(n>1)$ axis is absent and its point group is C_1. Therefore, allenes of the type (Lii) are asymmetric allenes. Allenes of the type (Li) and (Lii) are optically active and exist as a pair of enantiomers.

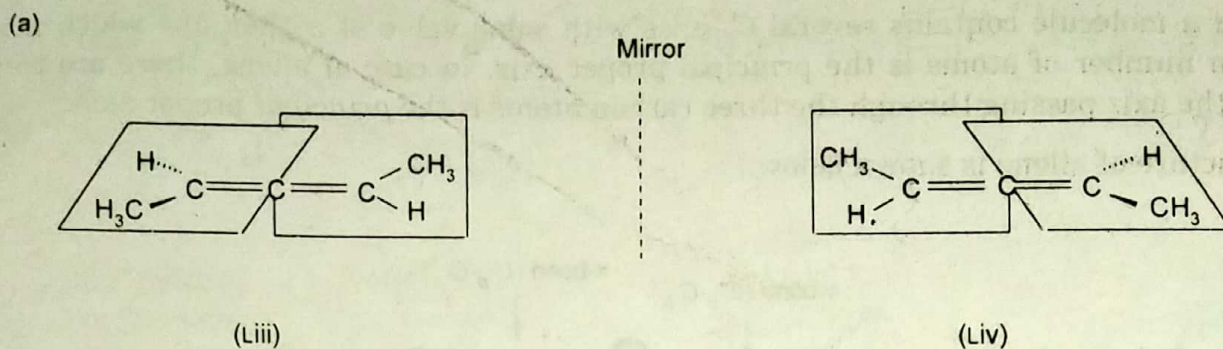A few examples of dissymmetric and asymmetric allenes are given below.

(a)

Fig. 3. 148

Liii and Liv are nonsuperimposable mirror images (enantiomers) of 1,3-dimethyl allene (IUPAC : Penta-2-3-diene). It has a C_2 proper axis that passes diagonally through the central sp-carbon. Its chiral-axis is along the axis joining the three nuclei of carbon atoms. The molecule is dissymmetric with a point group C_2. The Newman projections of Liii and Liv can be represented as follows and the existence of C_2 axis is easily understood. A model will be more helpful. This axis bisects the angle between the two perpendicular planes passing through the carbon atoms.
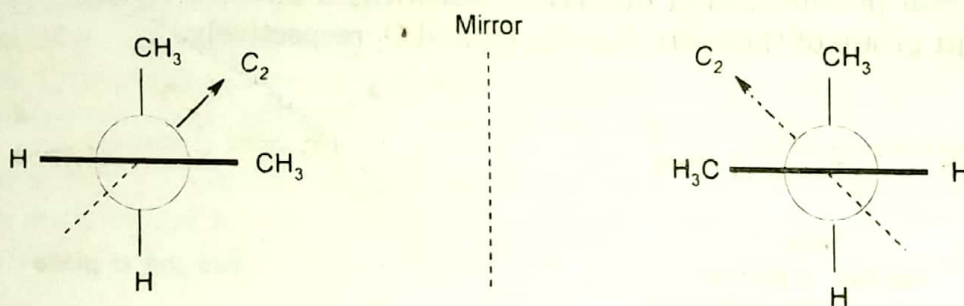

Fig. 3. 149

(b)

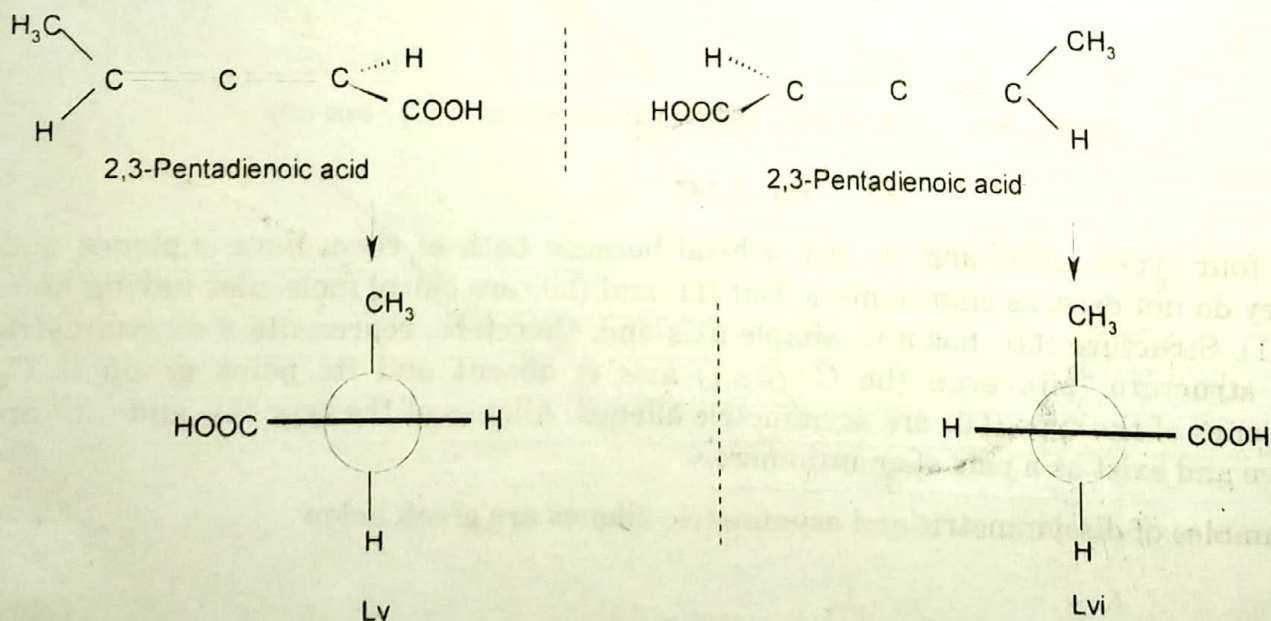2,3-Pentadienoic acid   2,3-Pentadienoic acid

Lv   Lvi

Fig. 3. 150

(Lv) and (Lvi) are enantiomers of penta-2,3-dienoic acid. Since it is an allene of the type, (Lii), it is an asymmetric allene, and, therefore, has no C_n $(n>1)$ proper axis (evident from Newman projections).

A few important facts are to be remembered in case of stereoisomerism of substituted cumulenes.

1. Cumulenes with even number of double bonds exhibit enantiomerism if each of the terminal carbon atoms contains non-identical substituents

2. Cumulenes with even number of double bonds can not exhibit cis-trans isomerism when the substituents are incapable in doing so, because interchange of groups on any terminal carbon does not produce a diastereoisomer with different relative positions and dihedral angles among the substituents. For example, following allenes are not cis-trans diastereoisomers but enantiomers.
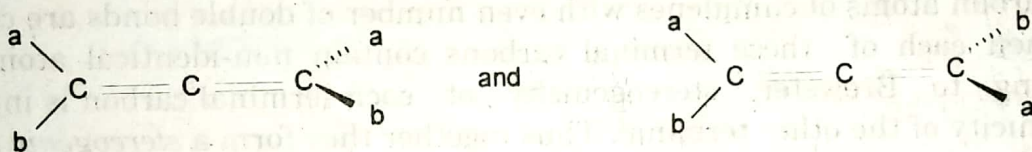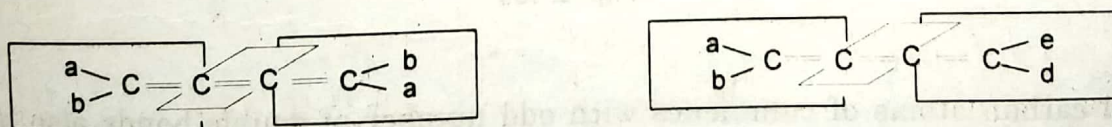

Fig. 3. 151

3. Cumulenes with odd number of double bonds never exhibit enantiomerism irrespective of the nature of substituents on the terminal carbons. This is because of the fact that in cumulenes with odd number of double bonds, the terminal carbon atoms along with their substituents lie in the same plane and such cumulenes have always σ plane irrespective of the nature of substituents.
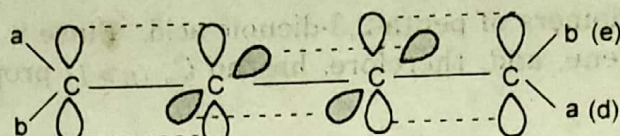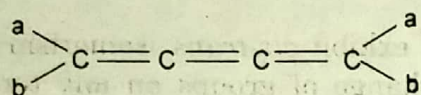

Lvii   Lviii

Fig. 3. 152

Both Lvii and Lviii are achiral because they possess plane of symmetry. The orbital picture of such a cumulene (Lviia) is shown below.
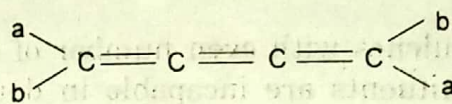
Lviia

Fig. 3. 153

However, cumulenes with odd number of double bonds show *cis - trans* isomerism. For example, Lix and Lx are geometric isomers (diastereoisomers).

Lix

cis-isomer

Lx

trans-isomer

Fig. 3. 154

4. Terminal carbon atoms of cumulenes with even number of double bonds are chirotopic and stereogenic, when each of these terminal carbons contain non-identical atoms or achiral groups. According to Brewster, stereogenicity of each terminal carbon is interdependent on the stereogenicity of the other terminal. Thus together they form a *stereogenic dyad* system. In C-1 and C-5 are stereogenic dyad and *chirotopic.*
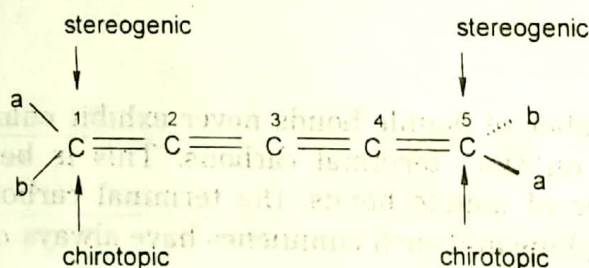

Fig. 3. 155

5. Terminal carbon atoms of cumulenes with odd number of double bonds also belong to a *stereogenic dyad* system but they are *achirotopic.*

Configurational nomenclature of substituted allenes : *R, S* system :

To apply CIP method to determine absolute configuration of allenes having chiral axis, it is necessary to use the rule 0 (written below in italics) already mentioned earlier. The structure of allene is regarded as an elongated tetrahedron and viewed along the axis (Fig : 3.156). It is immaterial from which end it is viewed. The four substituents (two on each terminal carbon) giving rise to chirality are projected onto a plane at right angles to the chiral axis. The resultant projection is now regarded as representing a chiral carbon with the proviso that the *near groups always take precedence over the far and the bonds between the near groups and the*

imaginary chiral carbon are always above the plane of projection. These bonds are shown by thick lines. This is called the standard subrule 0 in CIP system(see Chapter Three).

The method is explained by the following example.

(i)

Projected from side Y

(4) (2) H\   /Cl (1) (3)

(4) (2) H   Cl (1) (3)

Projected from side X

priority of groups on each terminal carbon, Cl > H

Absolute configuration of the allene is (R) because the path traced by movement from 1 → 2 → 3 is clockwise
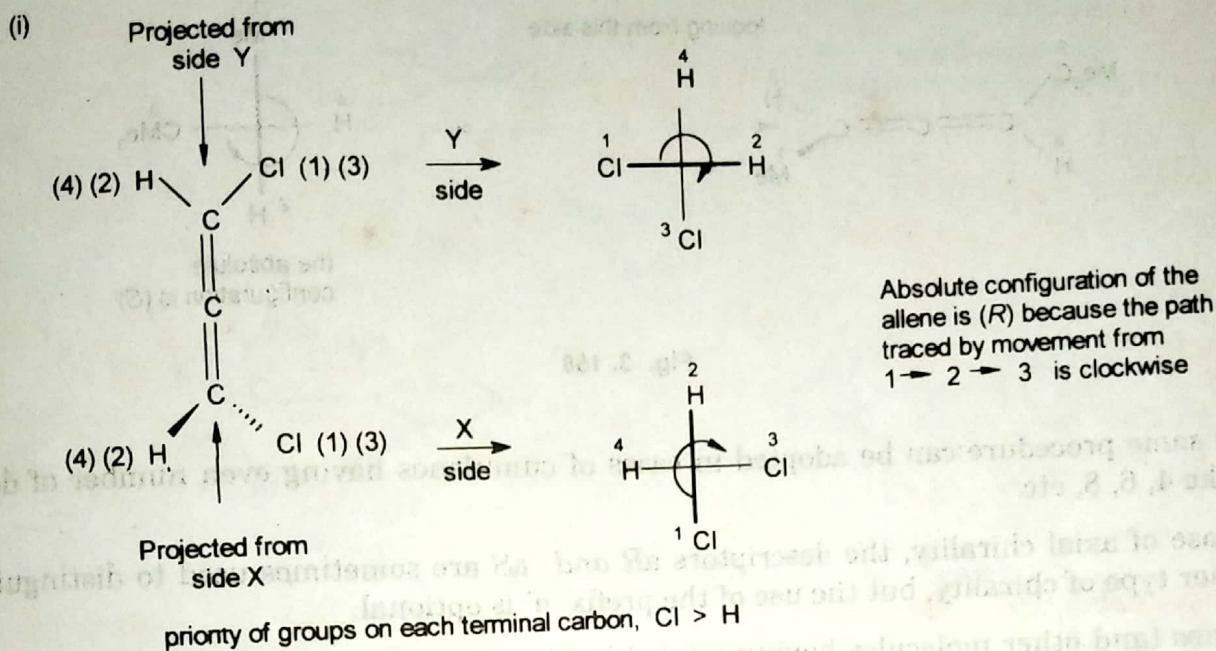
In the example, (Fig. 3.156) looking from Y side nearer groups Cl and H get the number (1) and (2) and the far Cl and H get priority (3) and (4) respectively. Similarly looking from X side Cl, H of the nearer C- atom get the preference in the numbering. If the resulting Fischer-projection lowest priority group (4) remains in the horizontal bond, *interchanges of groups need not be done to put it into any vertical bond*, before tracing a path from 1→ 2 → 3. Clockwise path indicates R configuration and anticlockwise path indicates S configuration. Usually projection is done from any one side along the chiral axis.
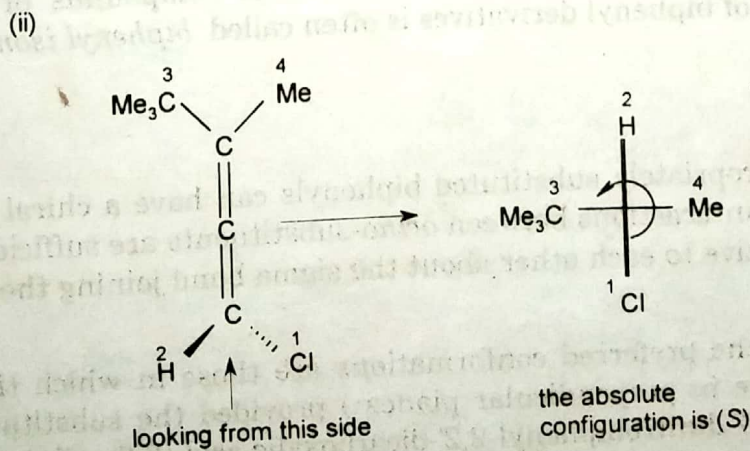
(ii)

3   4
Me₃C\   /Me
      C

2   1
H   Cl

looking from this side

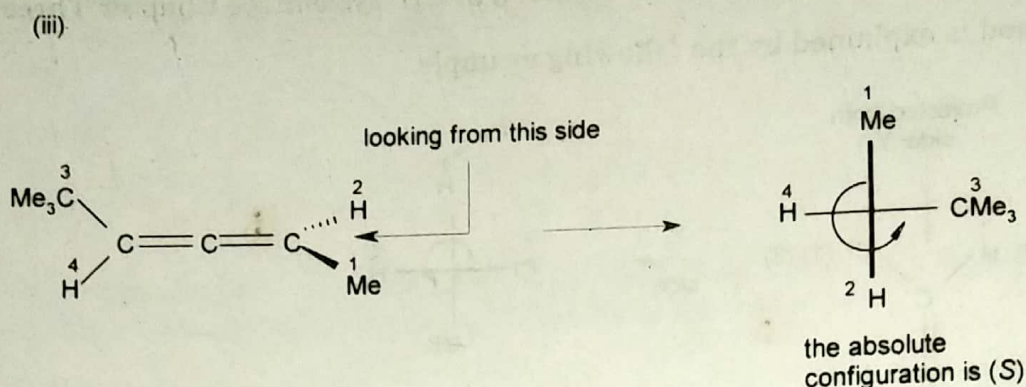the absolute configuration is (S)

Fig. 3.157

(iii)

Fig. 3. 158

The same procedure can be adopted in cases of cumulenes having even number of double bonds like 4, 6, 8, etc.

In case of axial chirality, the descriptors a*R* and a*S* are sometimes used to distinguish it from other type of chirality, but the use of the prefix 'a' is optional.

Allenes (and other molecules having axial chirality) may alternatively be viewed as *helices* and their configuration may be denoted as *P* or *M* in a manner similar to that of conformational isomers. This has been discussed in Chapter Five .

Absolute configurations of substituted biphenyls, spiranes and alkylidenecycloalkanes are also assigned by similar procedure. These have been discussed in appropriate part of the book.

Atropisomerism : Conformational Chirality:

The term *atropisomerism* (taken from the German literature - meaning *no rotation*) includes cases of stereoisomerism due to restricted rotation about single bond where the isomers can actually be isolated under usual experimental conditions. Optical isomerism (enantiomerism) of this type was first detected in compounds of biphenyl series. This rotational isomerism of biphenyl derivatives is often called *biphenyl isomerism.*

Biphenyl isomerism :

A number of appropriately substituted biphenyls can have a chiral axis when steric (van der Waals repulsive) interactions between *ortho*-substituents are sufficient to prevent rotation of aromatic rings relative to each other about the sigma bond joining them. This σ bond is also called pivotal bond.

In this situation the preferred conformations are those in which the aromatic rings are almost orthogonal (lie in perpendicular planes) provided the substitution is of the type in structure (Lxi), e.g. 6,6'-dinitrobiphenyl-2,2'-dicarboxylic acid (6,6' - dinitrodiphenic acid), then the minimum energy conformations (conformers) are enantiomeric, and the isomers can be isolated under usual experimental conditions.

This type of isomerism (enantiomers) which owes its existence due to inhibited rotation around a *single bond* is called *atropisomerism* and the isolable enantiomers are called *atropisomers*. Atropisomers are also known as *torsional* isomers about single bonds.
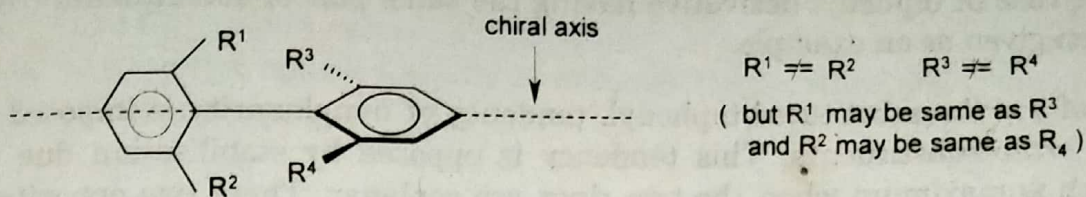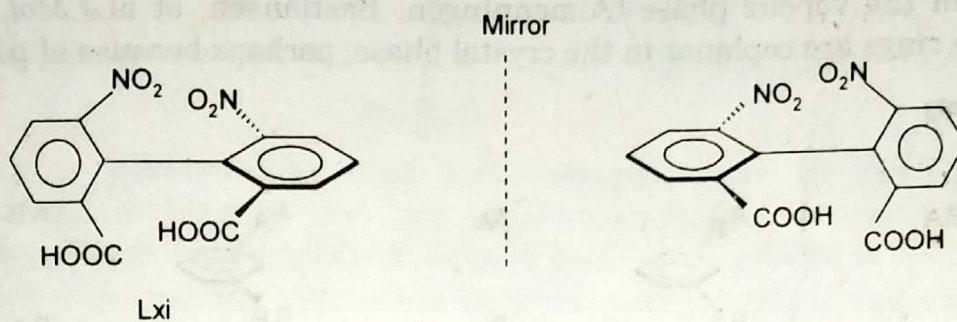

R¹ ≠ R²   R³ ≠ R⁴

(but R¹ may be same as R³
and R² may be same as R₄)

Fig. 3. 159

enantiomers of 6,6'-Dinitrodiphenic acid (atropisomers)

Fig. 3. 160

Recemisation of either enantiomer occurs by rotation through 180° about the bond between the aromatic rings and the ease of racemisation depends on the steric compression of the *ortho*-substituents in the conformation in which the aromatic rings are co-planar.

Even certain tetrasubstituted biphenyl like 2,2′,6,6′-tetrasubstituted biphenyl may be nonresolvable because steric inhibition is not large enough to prevent free rotation about the sp^2-sp^2 sigma bond. For example, difluorodimethoxy derivative is nonresolvable. On the other hand, biphenyl-2,2′-disulphonic acid having only two *ortho*-substituents is resolvable because of much higher bulk of sulphonic acid group.

2,2'-Difluoro-6,6'-dimethoxybiphenyl

nonresolvable
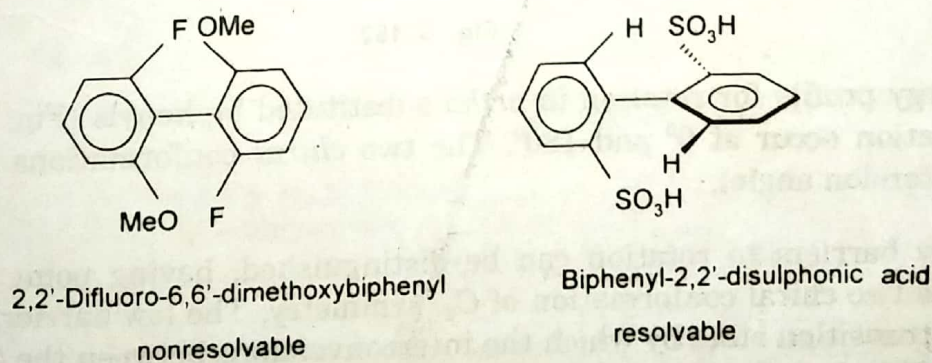
Biphenyl-2,2'-disulphonic acid

resolvable

Fig. 3. 161

Atropisomers can be resolved at room temperature when the energy barrier to rotation is of the order of 80 to 100 kJmol⁻¹ or more. The variation in energy accompanying rotation of a

phenyl group around the bond joining the two rings is shown qualitatively in the following energy profile diagram of an *ortho*-substituted biphenyl derivative.

The simple case of biphenyl derivative having the same pair of substituents (A, B) in each ring, has been given as an example.

In case of a *ortho*-substituted biphenyl, tendency of nonplanarity is imposed by the steric demands of *ortho*-substituents. This tendency is opposed by stabilisation due to π-electron overlap which is maximum when the two rings are coplanar. These two opposite forces make the two rings in a substituted biphenyl neither coplanar nor orthogonal in the lowest energy conformation. Even biphenyl itself is nonplanar in the ground state. The inter-ring *torsion angle* being 44^0 in the vapour phase (Almenningen, Bastiansen, et al,*J.Mol.Struct*, **128**, 59, 1985), though the rings are coplanar in the crystal phase, perhaps because of packing forces.
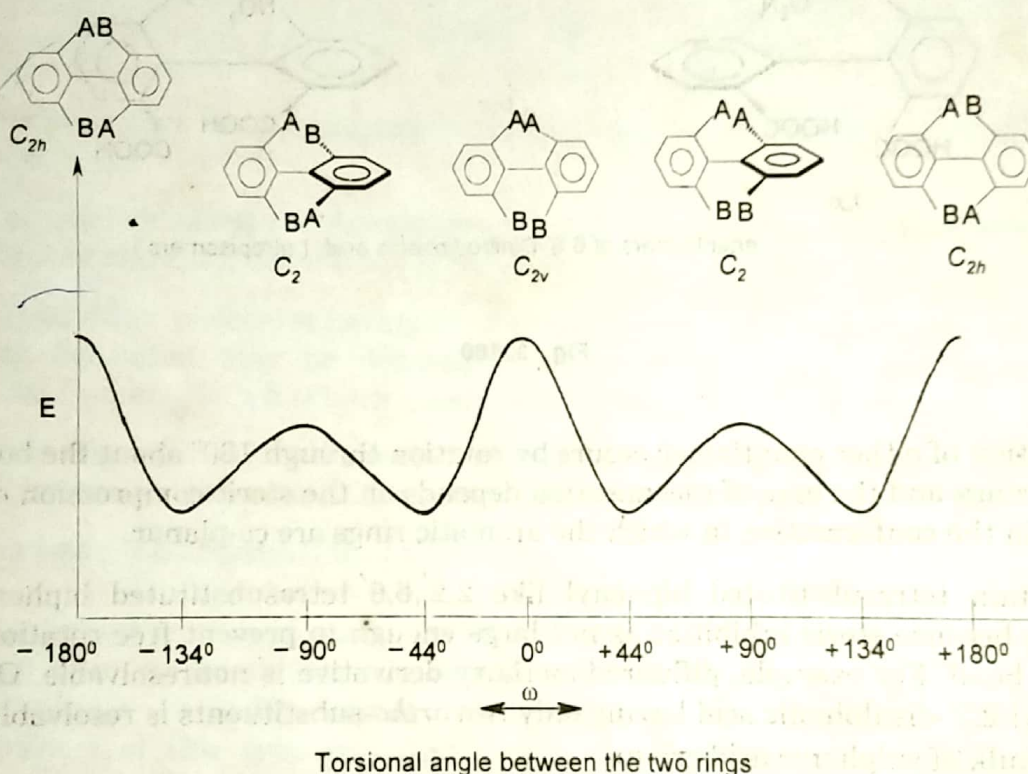

Torsional angle between the two rings

Fig. 3. 162

In the energy profile for rotation in *ortho* substituted biphenyls (Fig. 3.153), the maxima barriers to rotation occur at 0^0 and 180^0. The two *chiral* conformations occurs at $+90^0$ and -90^0 (based on torsion angle).

Two energy barriers to rotation can be distinguished, having point groups C_{2v} and C_{2h} which separates two chiral conformation of C_2 symmetry. The low barrier, C_{2h}, represents the more probable transition state by which the interconversions between the C_2 enantiomers take place. The two chiral conformations are flanked by two minima (in each case). This is because of the fact that when the rings are perfectly orthogonal then π-electron overlap stability is minimum. The two minima before and after the each chiral conformation due to compromise between the steric interaction and π-electron overlapping. The conformation C_{2h} has greater stability than the conformation C_{2v}, because A/A and B/B in-plane interaction is greater than that of A/B and A/B interaction. On the same reasoning it can be concluded that two minima

near $\pm 44^0$ and $\pm 134^0$ will not be exactly equienergetic. For biphenyl itself and biphenyls without ortho substituents ; the energy barriers at 0^0 to 90^0 is around 6-8 kjmol^{-1}.

To avoid appreciable racemisation at room temperature, it is necessary that the lower rotational barrier , C_2 to C_{2v} , should exceed 80- 90 kJmol^{-1}. In practice, examples are known of compounds having very fugitive optical stability at ordinary temperature and complete optical stability even at high temperature.

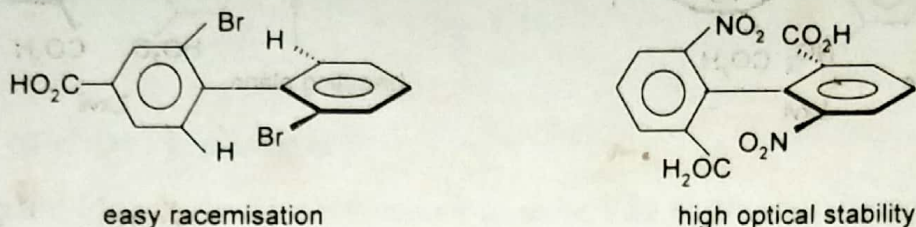easy racemisation   high optical stability

Fig. 3. 163

It is interesting to observe here that atropisomerism may be described both as configurational isomers, (as long as they are isolable) since they are enantiomeric, and conformational isomers, since they are interconverted by rotation around a C-C single bond. This further demonstrates that the distinction between configurational and conformational isomerism is not always very sharp.

Ortho substituted biphenyls can be of different types , as shown below .

Lxii (inactive)   Lxiii (inactive)
C_{2v} C_s

Lxiv (active)   Lxv (active)
C_2 C_1
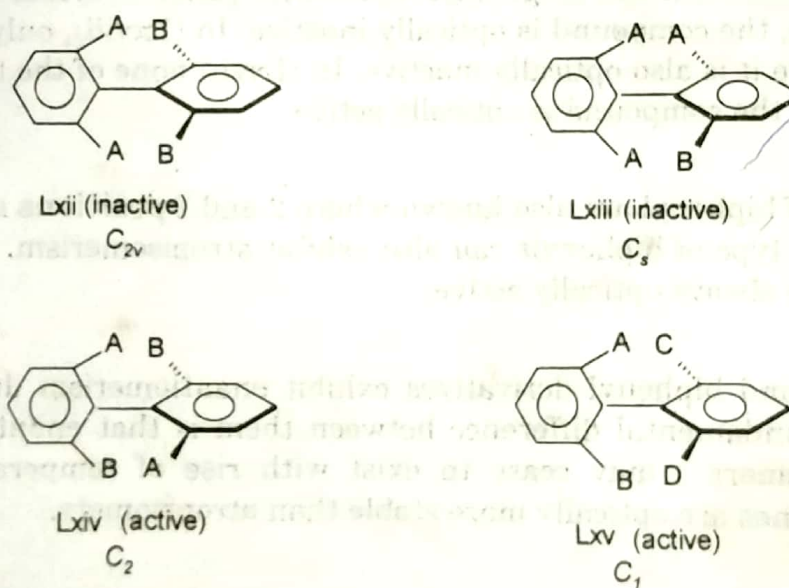
A,B,C,D are bulky atoms
or achiral groups

Fig. 3. 164

Of these, Lxii and Lxiii are optically inactive because of their point group , C_{2v} and C_s respectively. Biphenyls of the type Lxiv, which is optically active , is dissymmetric (point group C_2). Biphenyls of the type Lxiv represents asymmetric molecule with no C_n $(n > 1)$ axis also. It has point group C_1 and is optically active.

In fact, if a substituted biphenyl is divided into two halves by passing a horizontal plane along the σ bond joining the two phenyl rings and if any one of the rings shows a symmetry about that plane then that biphenyl derivative is optically inactive.
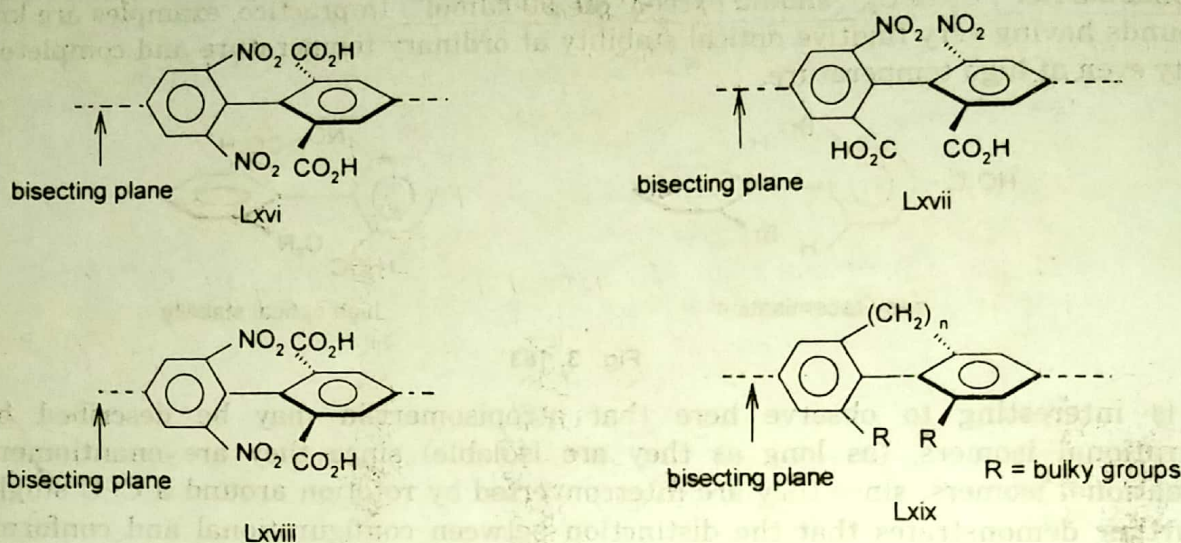

Fig. 3. 165

In the case of (Lxvi) both the rings have horizontal plane of symmetry (as drawn in two dimensions) therefore, the compound is optically inactive. In (Lxviii), only one ring has a plane of symmetry, therefore it is also optically inactive. In (Lxvii) none of the two rings has plane of symmetry. Therefore, the compound is optically active.

A large number of biphenyl are also known where 2 and 2'positions are bridged with rings of various size. These type of biphenyls can also exhibit atropisomerism. Biphenyls of the type (Lxix) where n > 2, are always optically active.

Both cumulenes and biphenyl derivatives exhibit enantiomerism due to the presence of chiral axis but one fundamental difference between them is that enantiomerism of biphenyl derivatives (atropisomers) may cease to exist with rise of temperature due to thermal racemisation. Cumulenes are optically more stable than atropisomers.

Like substituted cumulenes with even number of double bonds , biphenyl derivatives having perpendicular rings do not exhibit geometrical isomerism, because interchange of positions of substituents in any ring does not change the relative distances between the substituents in the rings. (Lxix) and (Lxx) in Fig 3.110 represents a pair of enantiomers and not a pair of E - Z geometric isomers.
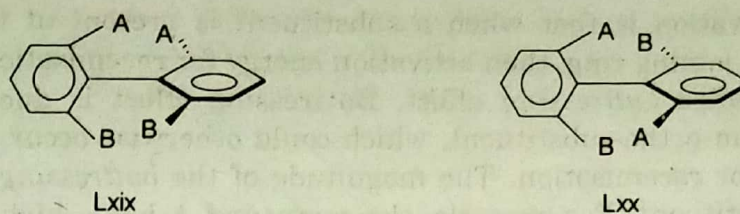
Lxix   Lxx

Fig. 3. 166

Recemisation of chiral biphenyls :

In case of chiral biphenyl, chirality comes to exist due to the restricted rotation about the sp^2-sp^2 σ bond joining the two phenyl rings. If free rotation of the two rings is allowed then we get equimolecular amount of nonseparable d- and l- isomers. This is called recemisation biphenyls. That ortho-substituent interfere in the transition state for racemisation. That this interference is steric in origin has been conclusively proved by the elegant works of Westheimer and co-workers [(F. H. Westhrimer and G. E. Mayer, J. Chem. Phys., 14, 744 (1946) ; F. H. Westthrimer , ibid., 15, 1947)]. These investigations correctly calculated the enthalpy of activation for racemisation of different di-ortho-substituted biphenyls from known data on van der Waals radii and stretching and bending force constants of various bonds. Investigation have also confirmed that undeformed planar transition state for racemisation is not the actual case because of the severe van der Waals interpenetration- energy between the ortho-substituents and ortho-Hydrogen atoms as shown in the following figure.
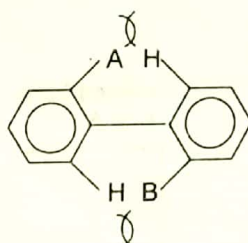

Fig. 3. 167

Therefore, conclusion has been drawn that interference for free rotation can be minimised by following manners :

    (i) bending the ortho-Hydrogens and other substituents (A and B) away from each other,

    (ii) compressing of C—H (ortho-bonds),

    (iii) stretching the interannular bonds.

    (iv) deforming the angle between the benzene and interannular bonds and

    (v) deforming the benzene ring themselves.

When all these factors are considered then theoretical values are found to be in close agreement with the experimental values of the activation energy of racemisation. A decreasing order of the capacity of the certain ortho-substituent with the passage to the so called planar transition state is $I > Br >> CH_3 > Cl > NO_2 > COOH > OCH_3 > F > H$. It might be noted that there is no parallel between group-interference (steric in origin) and polar properties. This order roughly parallels van der Waals radii ($I > Br > C > Cl > N > O > F > H$).

A striking observation is that when a substituent is present at the *meta*-position with respect to the σ bond joining ring, then activation energy for racemisation of chiral biphenyls is enhanced. This is called *buttressing* effect. Buttressing effect is due to prevention of the outward bending of an ortho-substituent, which could otherwise occur in co-planar transition state conformation for racemisation. The magnitude of the *buttressing* effect depends on the size of the *meta*-substituent. For example, the compound A has a higher activation energy of racemisation of about 21 kcalmol^{-1} than the compound B.
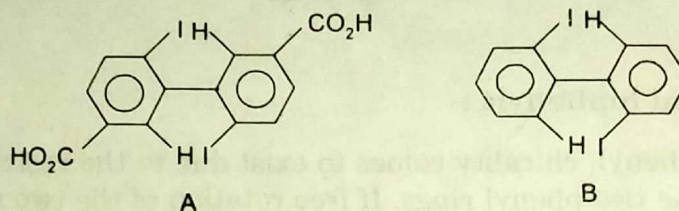

Fig. 3. 168

Configurational Nomenclature of active biphenyl derivatives :

R, S - descriptors to atropisomers of biphenyl derivatives can also be assigned by the same method as in the cases of allenes with chiral axis. In this method four atoms C-2, C-6, C-2', C-6' which correspond to four vertices of an elongated tetrahedron are taken into considerations for the application of sequence rule according to CIP conventions.

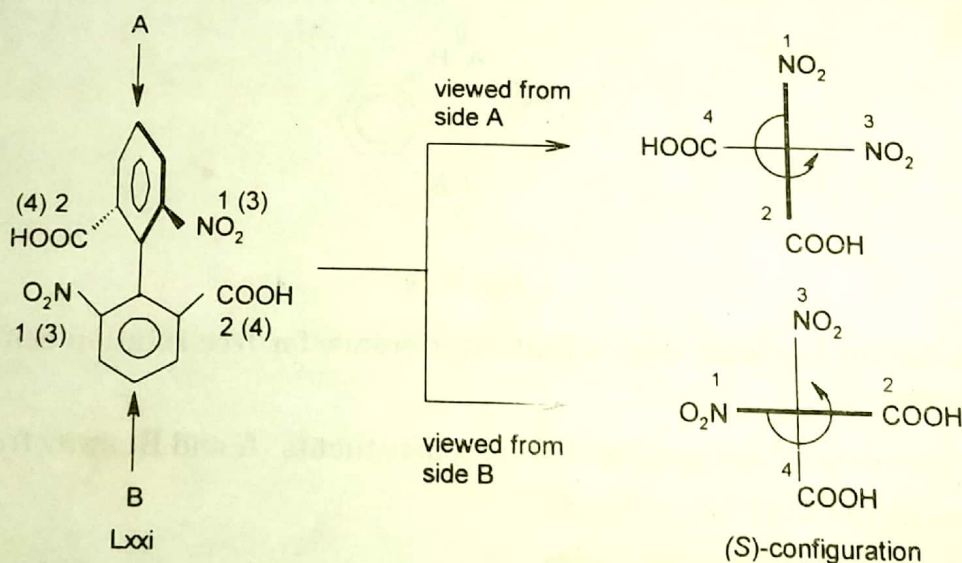The method is illustrated using a few examples.

Fig. 3. 169

In the above case (6, 6'- dinitrodiphenic acid), the substituents giving rise to chirality are viewed along the chiral axis and are then projected on to a plane at right angle to the chiral axis. The resultant projection is now regarded as representing a chiral carbon with the proviso that the near groups from the side of observation take precedence over the far groups according to sequence rule and the bonds between the near groups and the imaginary chiral centre are always above the plane of the projection. A path is then drawn from 1 → 2 → 3 irrespective of the location of lowest priority group (4) i.e., whether it is in vertical bond or

horizontal bond in the Fischer-like projection. If the traced path from $1 \to 2 \to 3$ is clockwise then the configuration is (R) and the anticlockwise path represents (S) configuration. In this modern method when the molecule is viewed from either side leads to the same (R or S) configurational designation.

Same conclusion is achieved when the *ortho*-substituents are shown as an elongated tetrahedron. An example is given below.
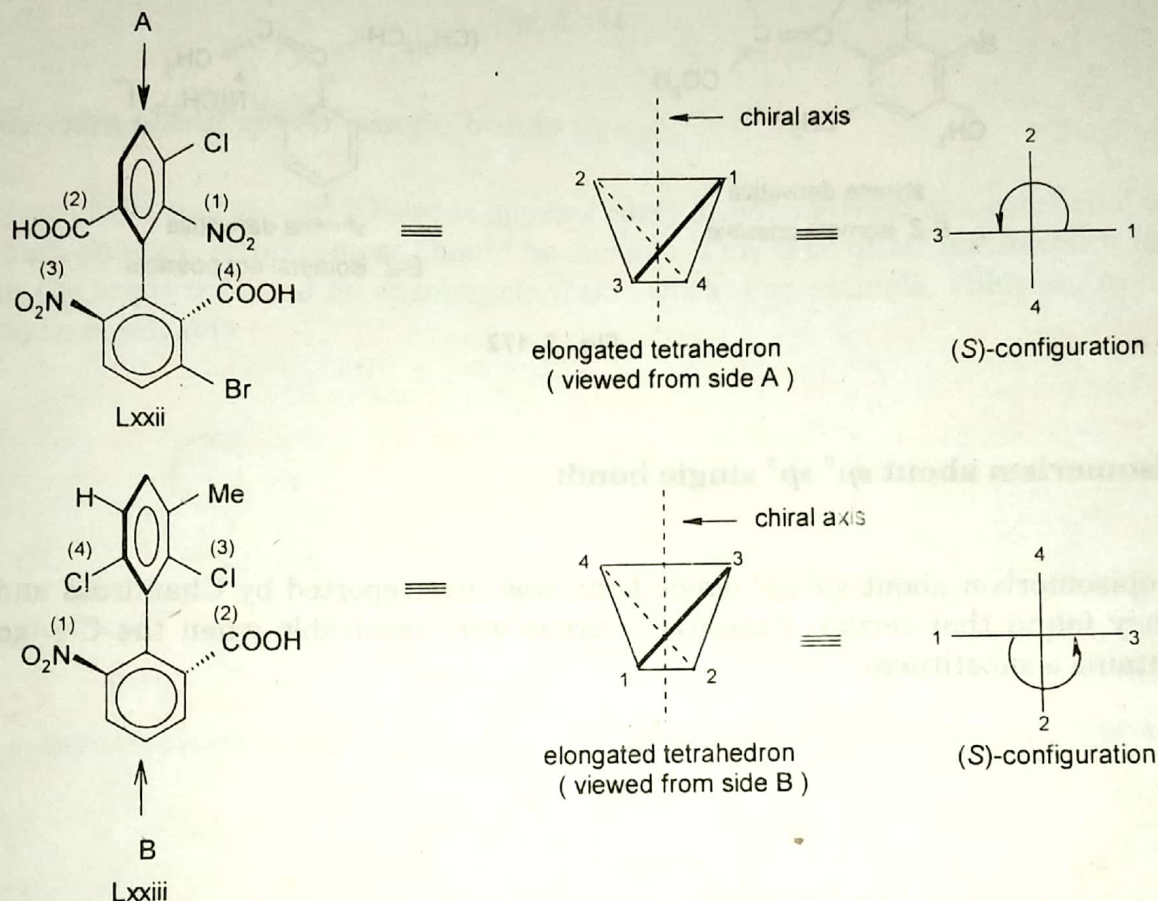

elongated tetrahedron
(viewed from side A)

(S)-configuration

elongated tetrahedron
(viewed from side B)

(S)-configuration

Fig. 3. 170

In the example (Lxxiii), since the upper ring has Cl in both the ortho-positions, groups H (at C-5) and Me (at C-3) are, therefore, selected for sequencing of groups in that ring.

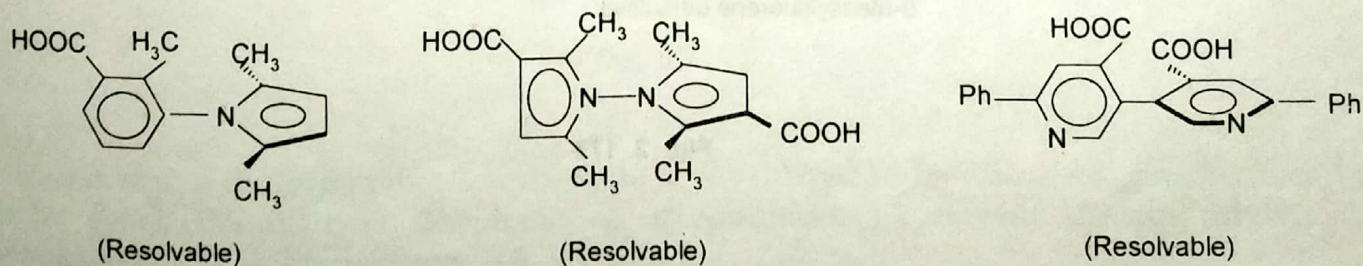**Other examples of atropisomerism around sp^2- sp^2 sigma bond without biphenyl system :**

(Resolvable)

(Resolvable)

(Resolvable)

Fig. 3. 171