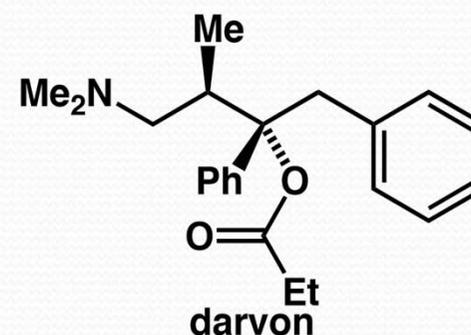
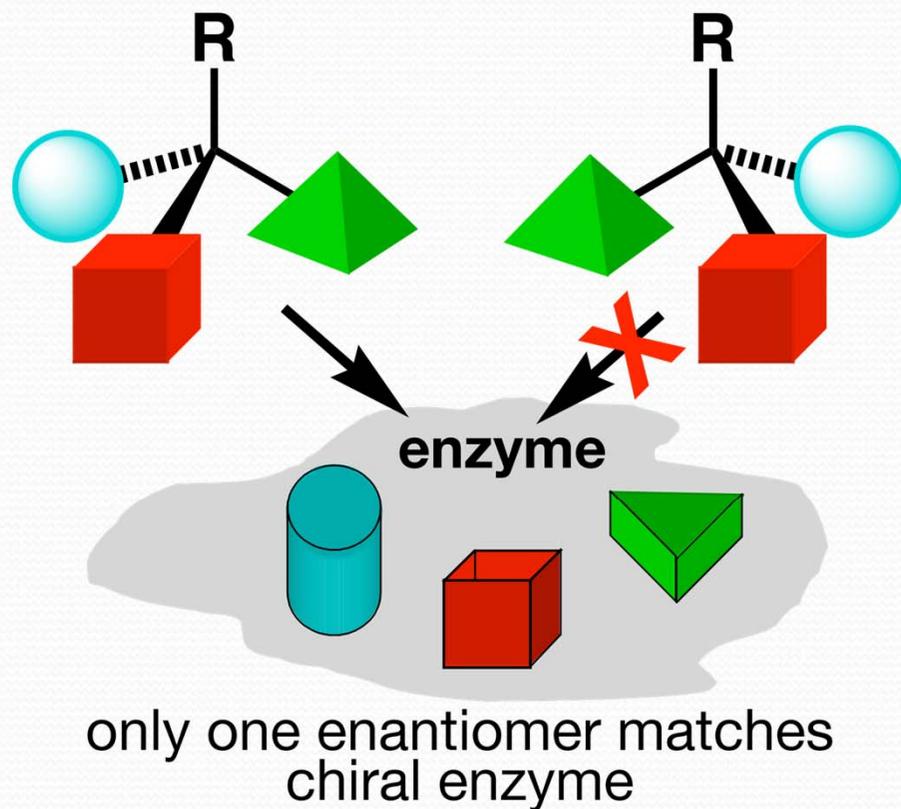


STEREOCHEMISTRY OF BIPHENYLS, ALLENES AND SPIRANS

IMPORTANCE OF STEREOCHEMISTRY

- interaction with other **chiral molecules**

Important in biology...



Darvon is a
painkiller.
Its enantiomer is an
anticough agent.

Louis Pasteur

- In 1848, Louis Pasteur noticed that a salt of racemic (\pm)-tartaric acid crystallizes into mirror-image crystals.
- Using a microscope and a pair of tweezers, he physically separated the enantiomeric crystals.
- Pasteur had accomplished the first artificial resolution of enantiomers.



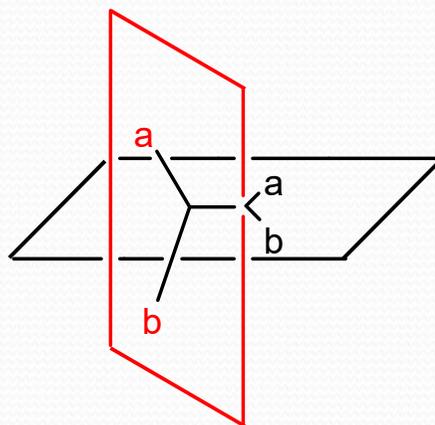
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Types of stereoisomerism

- Atropisomerism
- Cis-trans isomerism
- Conformational isomerism
- Diastereomers
- Enantiomers
- Rotamers

INTRODUCTION

- **RESTRICTED ROTATION GIVING RISE TO PERPENDICULAR DISYMMETRIC PLANES :**
- A molecule is chiral if it is *not superimposable* on its mirror image. So far, we believe that a chiral atom is must for the chirality of a molecule. Some compounds are optically active(chiral), eventhough they do not have chiral atoms. The *molecule as a whole is chiral* in such structures because they possess two perpendicular disymmetric planes, e.g.



Difference between asymmetry and dissymmetry

- A dissymmetric molecule may have one axis or more axes of symmetry (C_n). They lack i , σ or S_n symmetry element. On the other hand the chiral or dissymmetric molecules which lack even C_n axis is termed as asymmetric.

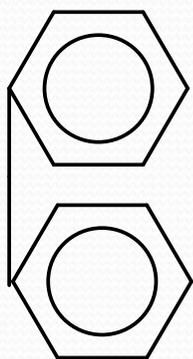
INTRODUCTION

- Neither of the plane can be dissected by a plane of symmetry. Therefore, the molecule is not superimposable and hence it is optically active. The examples of optical isomerism without a chiral center is given : **BIPHENYLS, ALLENES AND SPIRANS**. The required condition is that the molecule should not have of either σ , i or S_n symmetry element to be present.

BIPHENYL ISOMERISM

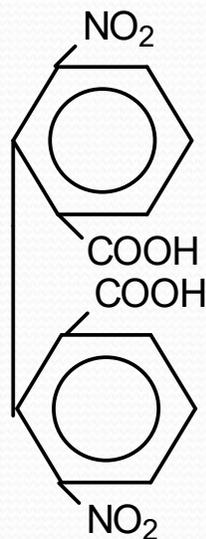
- In 1907, Kaufler proposed the “*BUTTERFLY*” formula (I) for biphenyl compounds. Later, this argument was found to be erroneous. Schultz prepared an acid, for which Schmidt et. al. gave the name 6,6'-dinitrodiphenic acid (II). They continued with the same structure proposed by Kaufler. In 1921, Kenner et. al. prepared 6,6'-dinitrodiphenic acid, for which he proposed **co-axial** structure (III). If it has butterfly formula, $\mu \neq 0$ for 4,4'-dinitrodiphenic acid. That is measured actually zero which is only possible if it has co-axial structure.

Introduction of Biphenyls



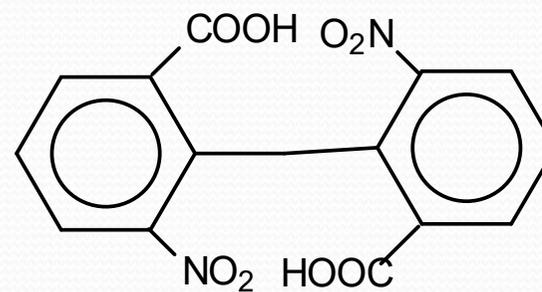
(I)

**Butterfly
Kaufler**



(II)

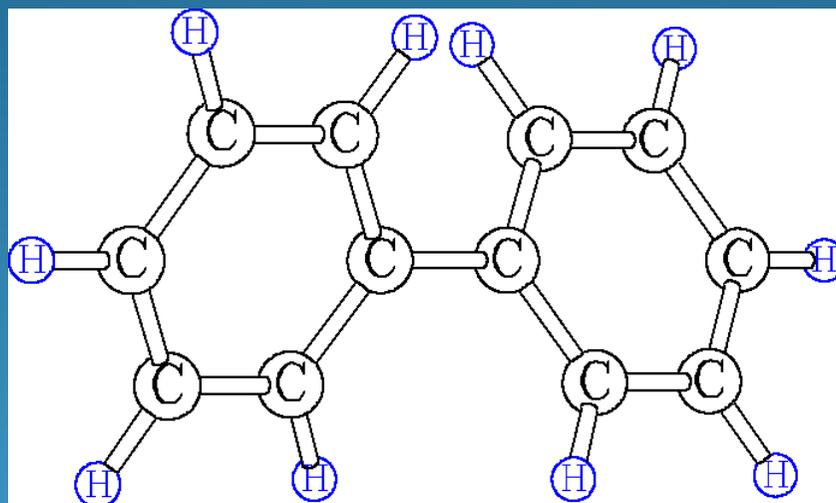
**Butterfly
Scultz et al**



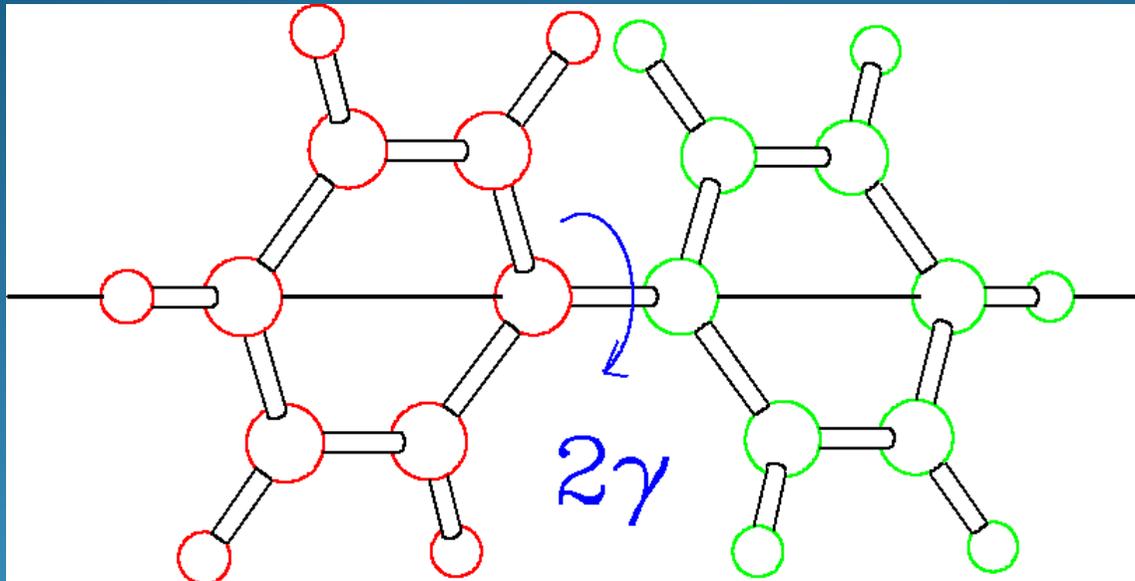
(III)

**Co-axial
Kenner**

biphenyls



Biphenyl is a non-rigid molecule



1. Merer and Watson, *J. Mol. Spec.* **47**, 499 (1973)

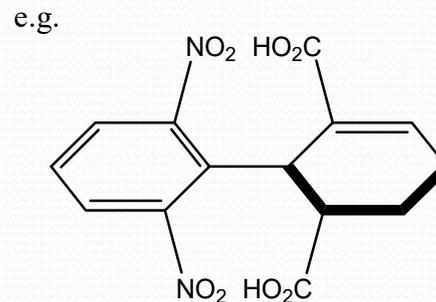
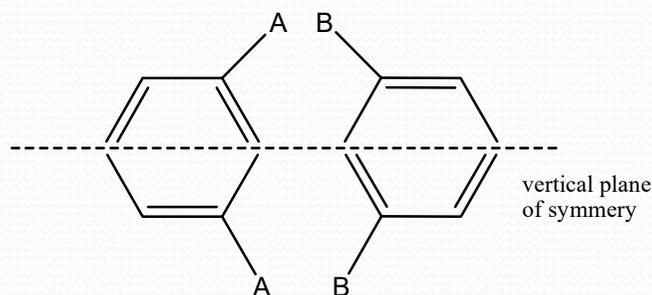
Biphenyls

- Acid II & III have different melting points and Kenner claimed that these two acids were distereoisomers. Further, III was resolved because of the absence of the any kind of symmetry. It was pointed out that the optical activity is due to the co-axial structure (III). Here, **two benzene rings do not lie in one plane and rotation about the single bond is restricted.**
- If the biphenyl derivatives have at least THREE ortho-positions, occupied by certain functional groups, then such compounds can be resolved. The two conditions for the optical activity in biphenyl compounds have been given :

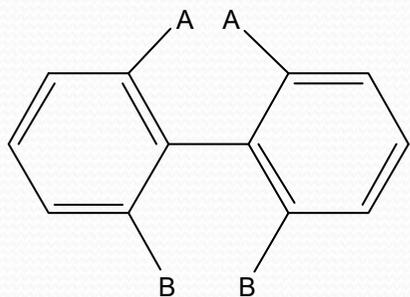
Biphenyls

- (1) Absence of a vertical plane of symmetry :

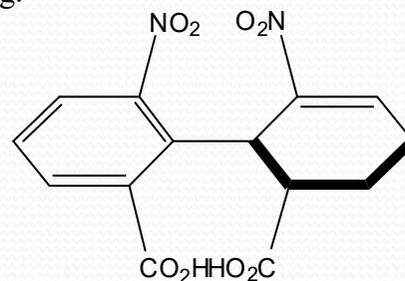
- Although, the large groups are present in ortho-positions, the compound may not be optically active. The important condition is the absence of the plane of symmetry, Consider the following example, which is nonresolvable and inactive because both the rings have a vertical plane of symmetry. Thus, the plane of symmetry is present. e.g.



Biphenyls

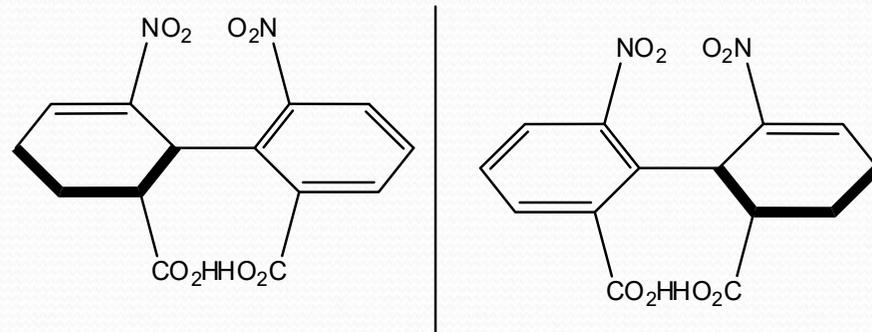


e.g.

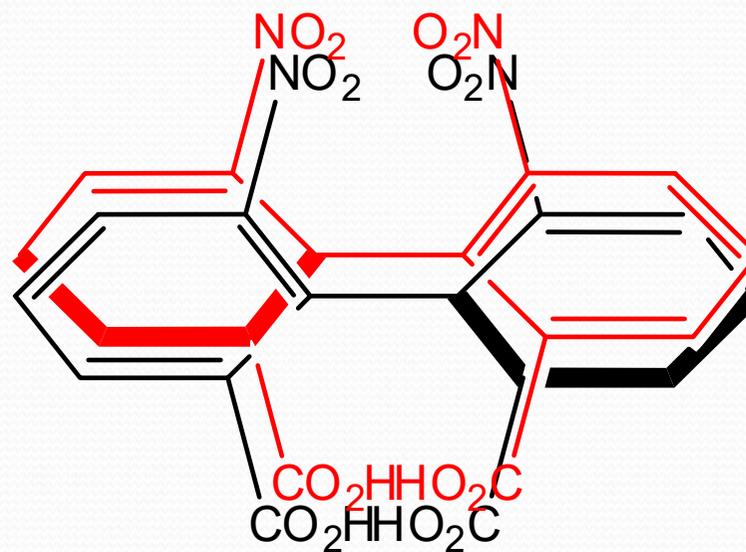


- But 6,6'-dinitrodiphenic acid can exist as non superimposable mirror images and are resolvable because of the absence of the plane of symmetry.

Biohenyl



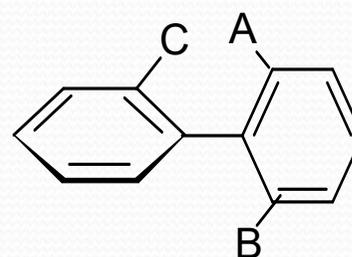
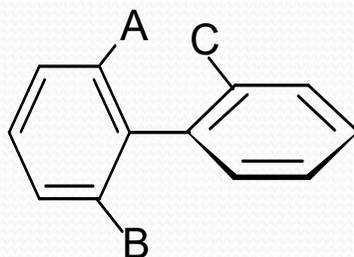
Nonsuperimposable, optically active



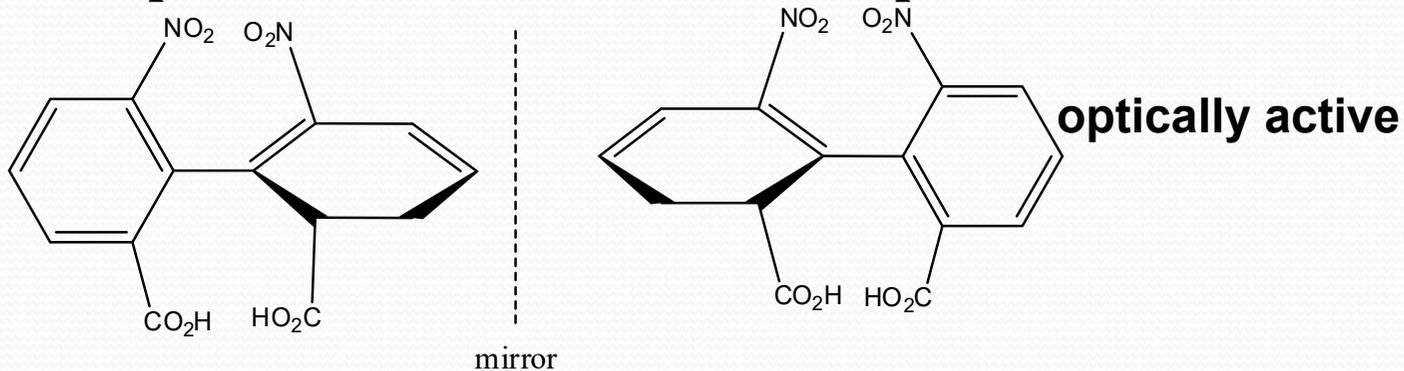
- (2) The substituents in ortho- positions should have a large size :

- When bulky groups are present at ortho- positions in biphenyl system, the molecule can not remain in planner form because of the steric hindrance. The steric effect prevents the free rotation about the C-C single bond joining two benzene rings in co-axial manner.

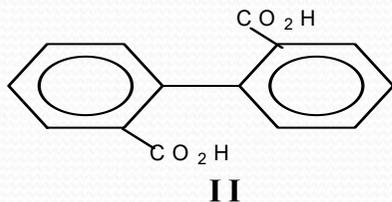
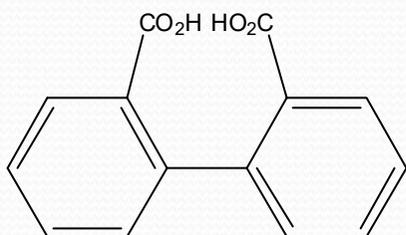
- In the following example, the free rotation is restricted due to the presence of bulky groups and hence the molecule is not planner. As a result, the compound is not superimposable and they are enantiomers without having a chiral centre. The molecule as a whole is chiral due to restricted rotation, e.g.



- Optical isomerism in 6,6'-dinitrodiphenic

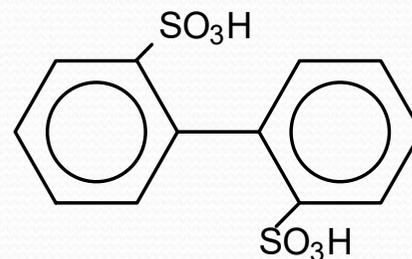
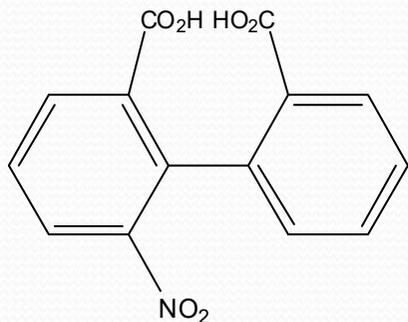


The diphenic acid is not optically active. It has a plane of symmetry.



**It has a centre of symmetry.
It cannot be resolved.**

- 6-Nitro diphenic acid with following structure is optically active.



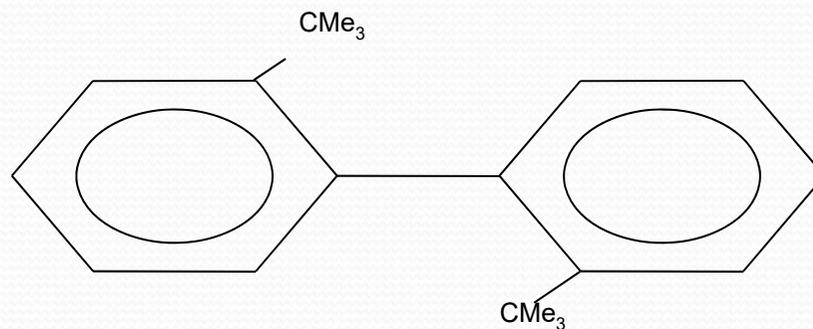
- Sometimes, only two large substituents in o-and o'- positions are sufficient to produce the restricted rotation. For example, biphenyl-2,2'-disulphonic acid was resolved by Lesslie and Turner, e.g.
- Here, sulphonic acid group is large enough to collide with H-atoms at ortho positions. The molecule is racemised on heating.

3D Structure of biphenyl



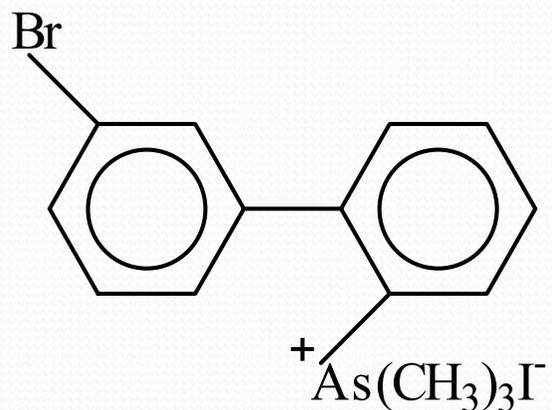
Biphenyls

- Lesslie et. al.(1962) prepared enantiomers of 2,2'-di-*t*-butylbiphenyl, which was highly optically stable. The stability was due to bulky *t*- butyl group.



Biphenyls

- Another example of only two functionality is 3'-bromobiphenyl-2-trimethylarsonium iodide. Here, the bulky trimethylarsonium group is too large and capable of restricted rotation. Moreover, bromine at *m*-position gives asymmetry to ring. It is optically active but easily racimized.

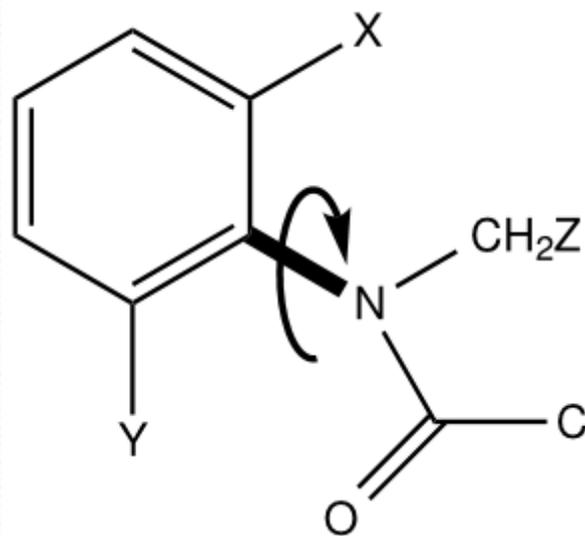


Atropisomerism

- In biphenyl, due to steric hindrance, the two isomers are separable due to restricted rotation about single bond. Such isomers are called “*atropisomers*” and the property is call “*atropisomerism*”.

Other examples

- Atropisomerism in aryl amides
- Rotation is restricted about single bond where $X=H$ and $Y= C, N, O, Cl$



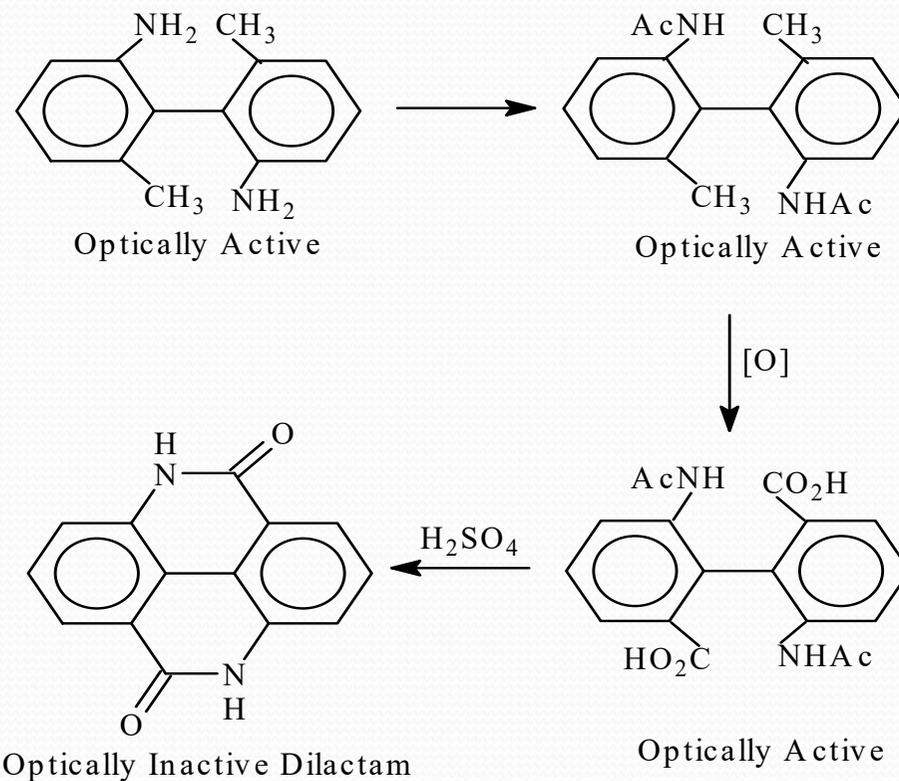
Obstacle theory

Evidence for obstacle theory :

- Evidence for obstacle theory provides the information about the interference of groups and its non co-planar in nature.
- A chemical proof for non co-planar nature was given by Meisenheimer et al. The “**obstacle groups**” in optically active biphenyls were united to give cyclic compounds, 2,2'-diamino-6,6'-dimethyl biphenyl was resolved and carried out the following reaction.

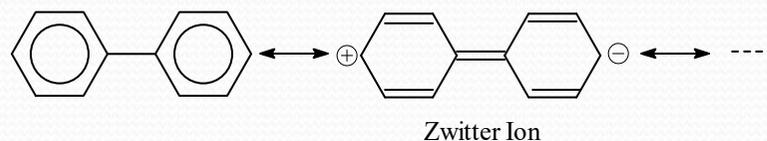
Obstacle theory

6,6'-Dimethyldiphenylamine



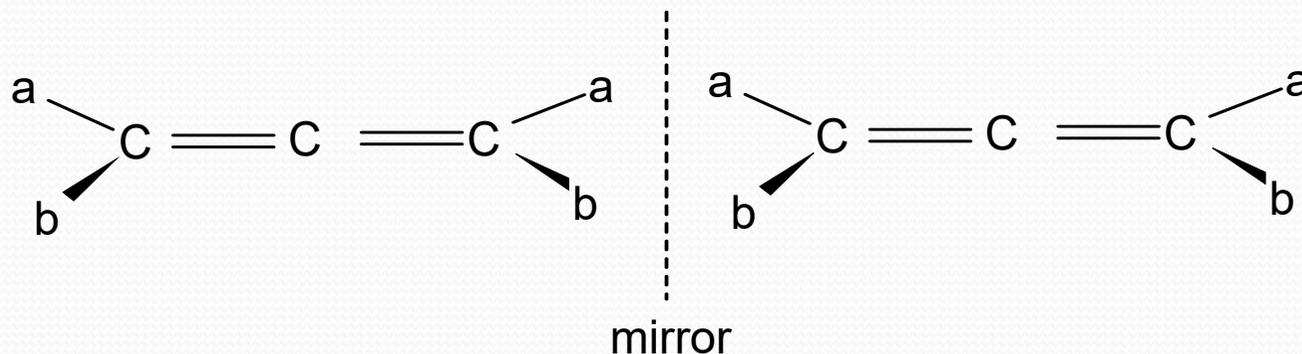
x-ray, UV and ESR analysis

- The dilactam is not active and hence it must be planner. This can be explained in terms of resonance.
- On the basis of that, it is proved that the non-planarity is the result of steric repulsion with o-hydrogen atoms.
- UV measurements show that biphenyls with o-substitutions are not co-planer. The λ_{max} of biphenyl = 248(19,000) nm: while benzene has 198(8,000) nm. This is due to resonance hybrid. e.g.
- Wheland et al. studied such compounds by means of ESR.

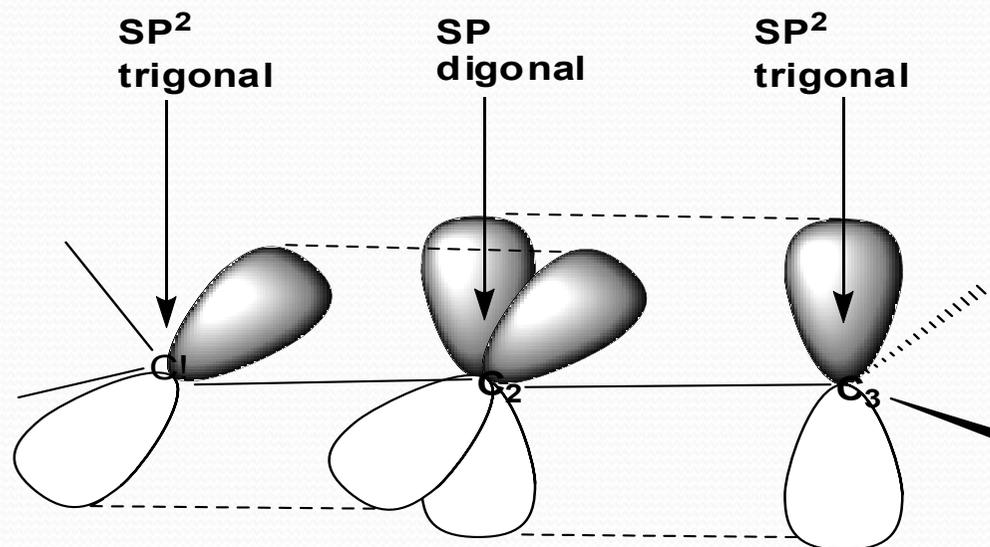


● 2. STEREOCHEMISTRY OF ALLENES:

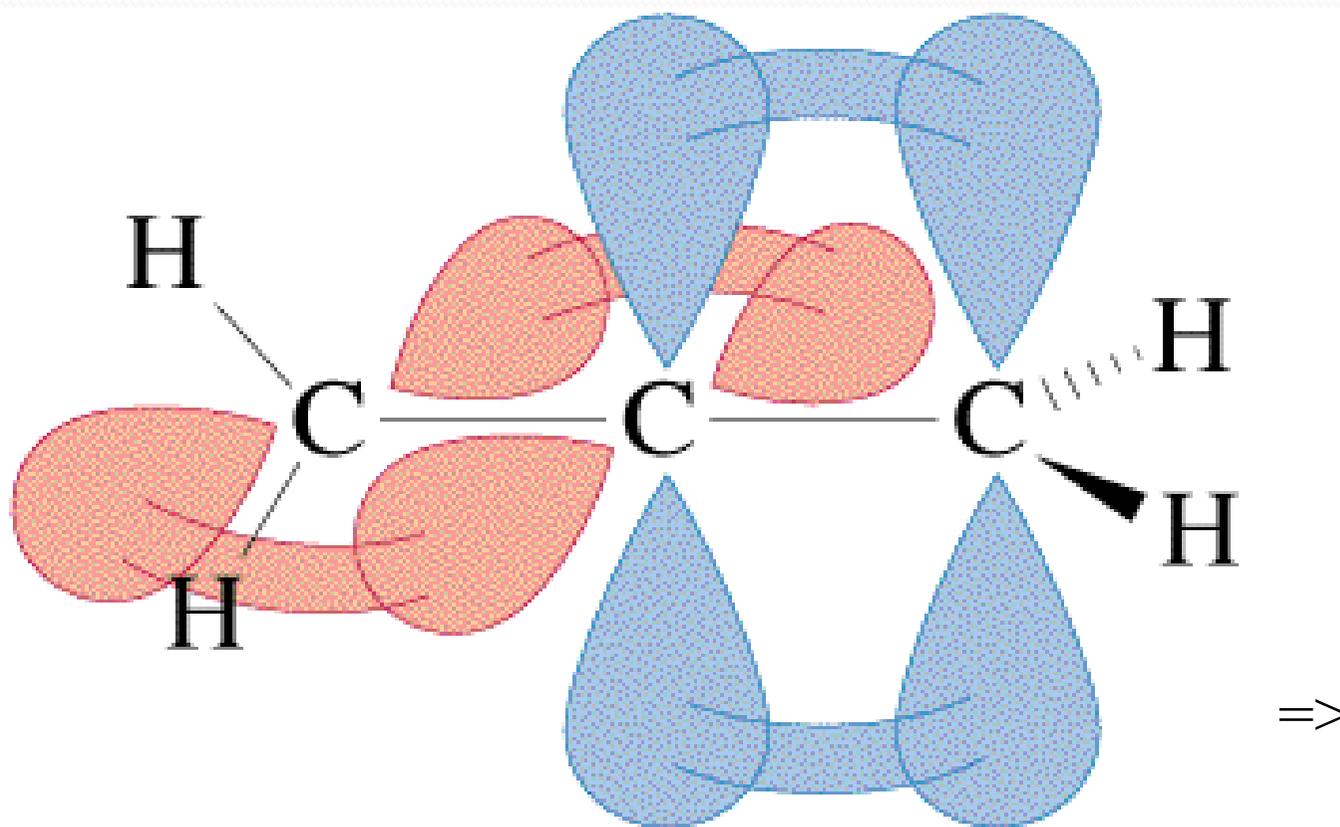
- Van't Hoff, as early as in 1875 suggested that an unsymmetrically substituted allene should exist in two enantiomeric forms. e.g. $abC=C=Cab$; where: $a \neq b$. *The molecule and its mirror image are not superimposable. The groups a and b are in perpendicular planes.*



- In allenes, the two end carbon atoms are in a state of trigonal hybridization. The center carbon atom is in a state of diagonal hybridization. So, the central carbon forms two π bonds, which are perpendicular to each other. In allenes, C-1 and C-3 are sp^2 and central C-2 is sp hybridized. Thus, two end groups are non-planar. e.g.

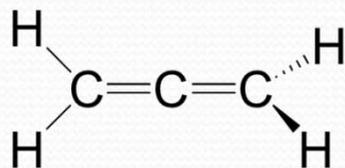
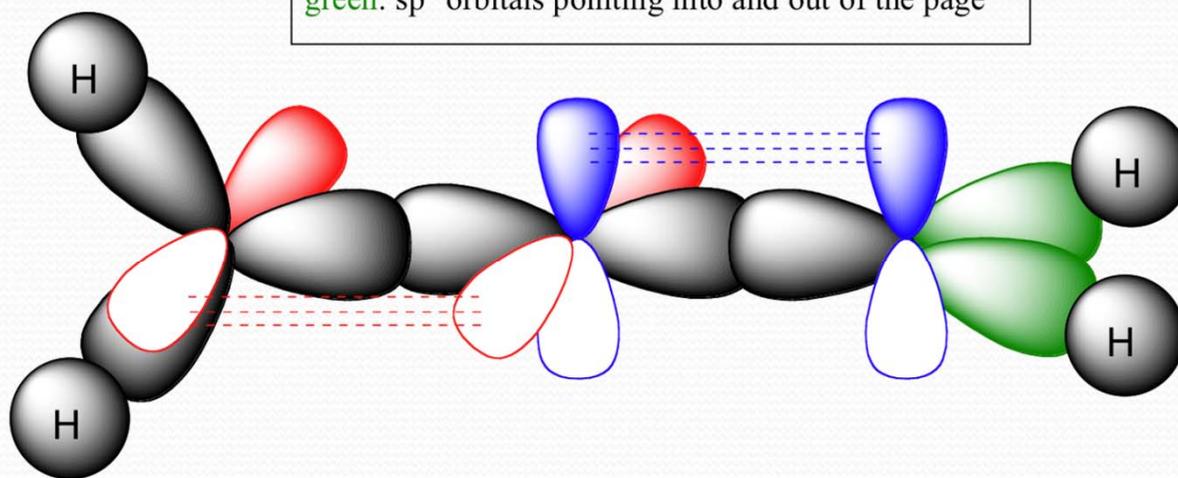


M O Picture of allene, pi bonds are in different planes

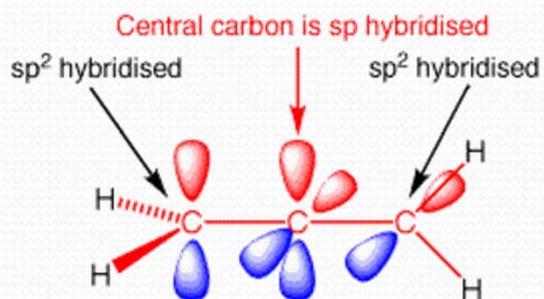


Molecular orbital picture

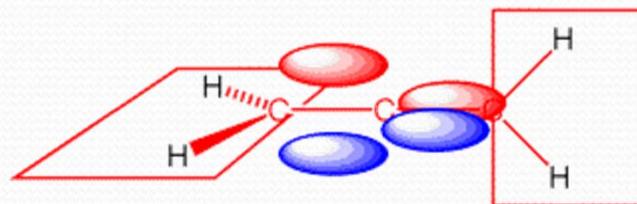
red: 2p orbitals perpendicular to page
blue: 2p orbitals in plane of page
green: sp^2 orbitals pointing into and out of the page



End groups in different planes



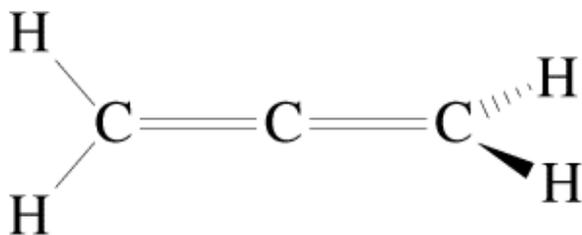
The π bonds formed as a result of the overlap of the p-orbitals must be at right angles to each other.



Not only are the two π bonds perpendicular, but the two methylene groups are too.

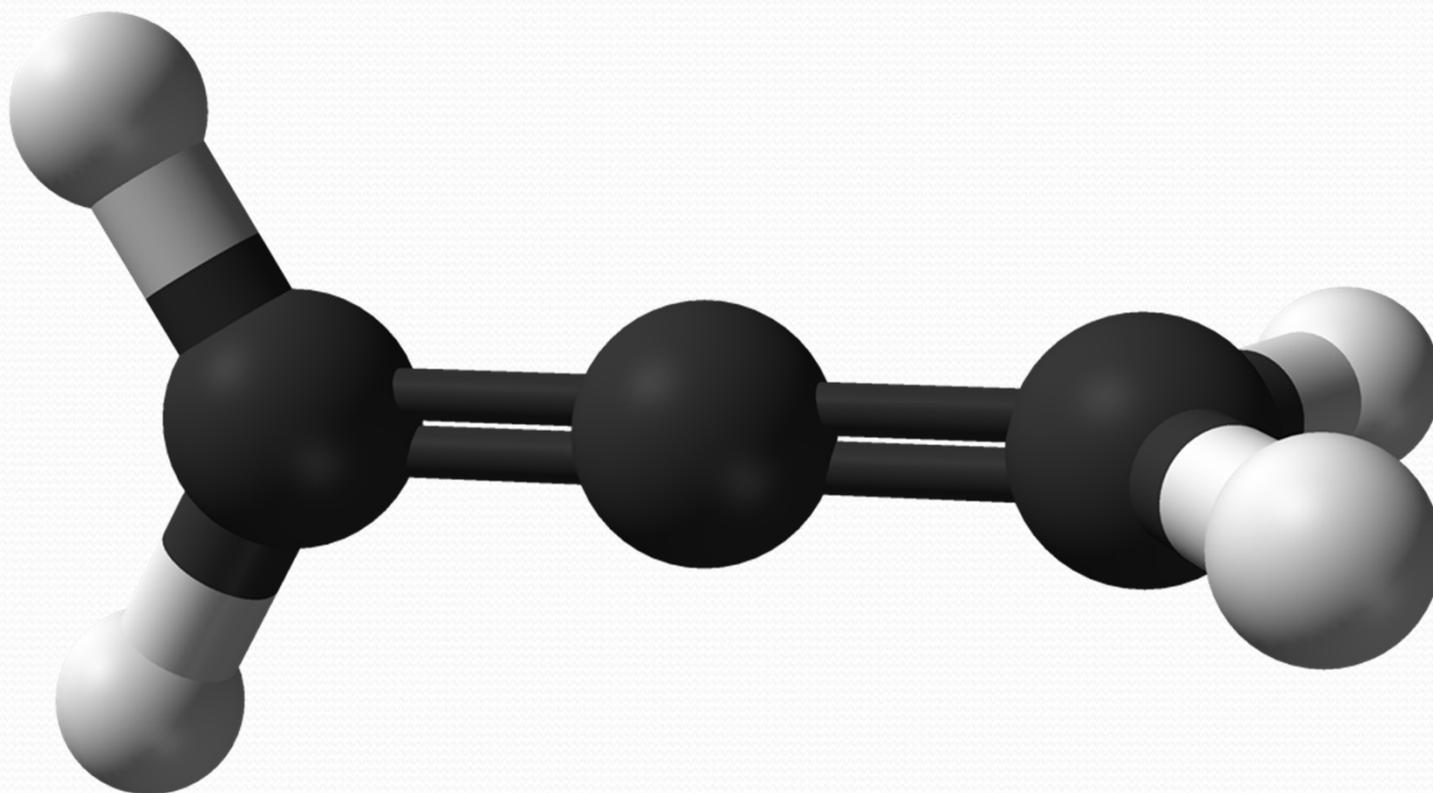
Allenes

- **Chiral compounds** with no chiral carbon
- Contains *sp* hybridized carbon with adjacent double bonds: $>C=C=C<$, which are perpendicular.
- End carbons must have different groups.

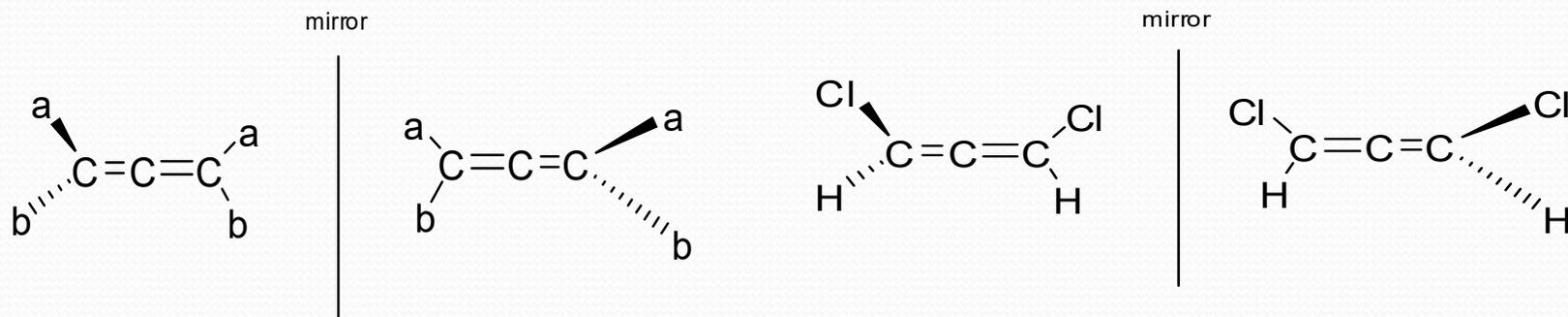


Allene is achiral.

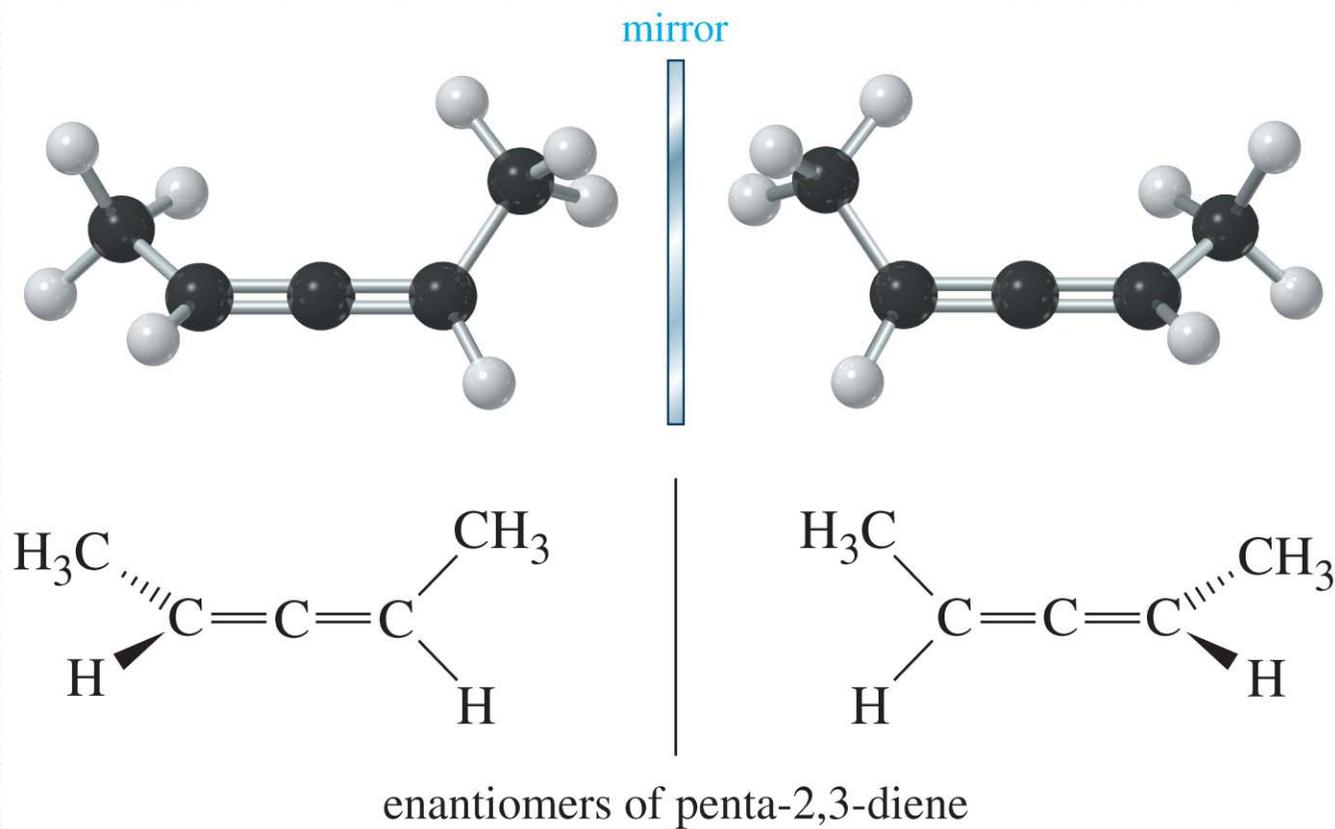
3D ball and stick model of allene



- If a is not equal to b like (or the four groups are different as in $abC=C=Cde$), the C_2 axis disappears and molecule is not symmetric. (C_2 point group). In trigonal state, the π -bond is perpendicular to the plane having three σ -bonds. Thus, the molecule can not have a plane or centre of symmetry. Therefore, it is resolvable. Let us consider following cases.
- In case-3, two perpendicular planes are present and therefore optical active enantiomers are possible.
- Enantiomers of 1,3-dichloroallene are as under, where $a=Cl$ and $b=H$:
- where $a \neq b$

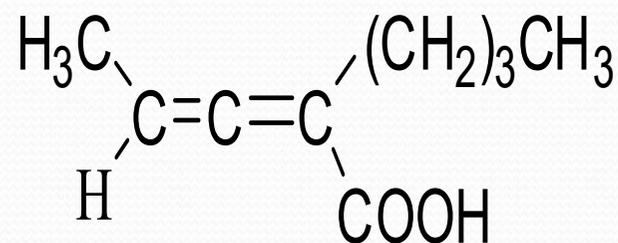
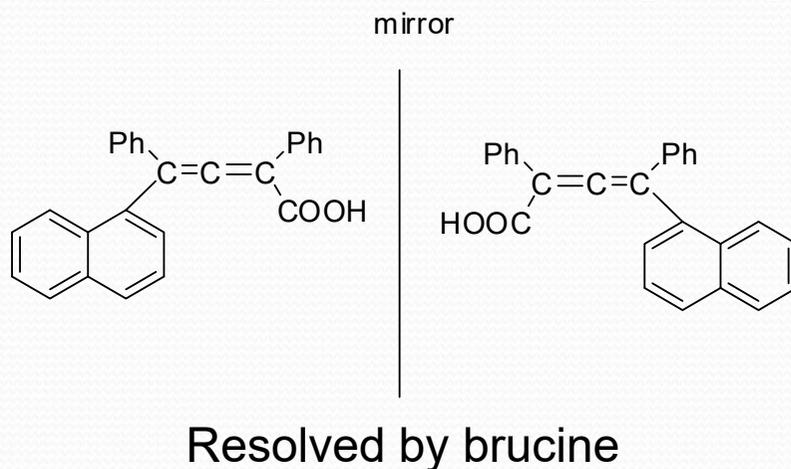


Penta-2,3-diene Is Chiral

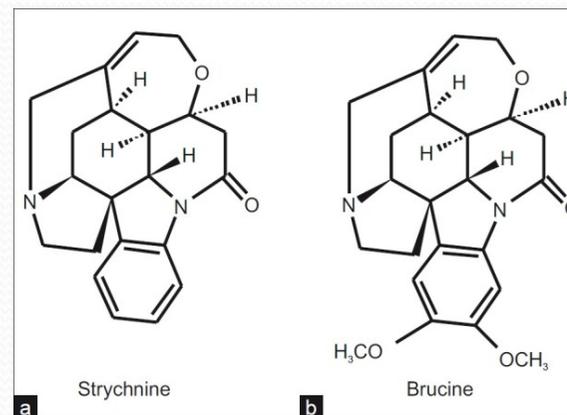


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- The first successful resolution of an allene was carried out by Kohler et al (1935) i.e. 3- α -naphthyl-1,3-diphenylallene-1-carboxylic acid through its glycolate with brucine. And other allene carboxylic acid was resolved by Wotiz using strychnine.

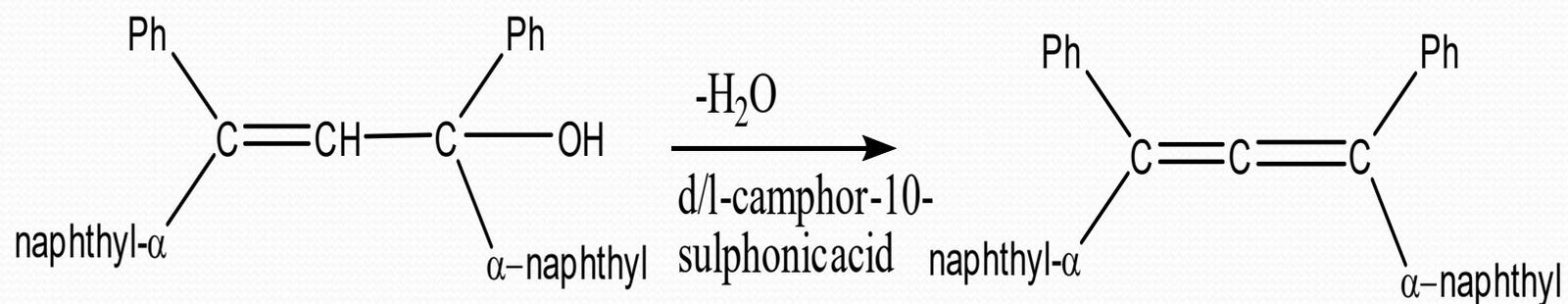


Resolved by strychnine

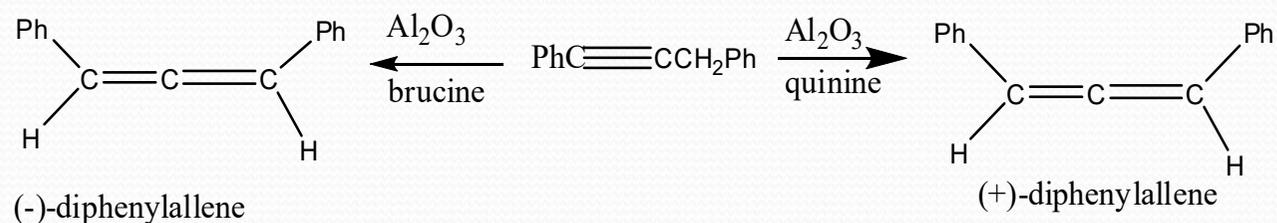


Synthesis

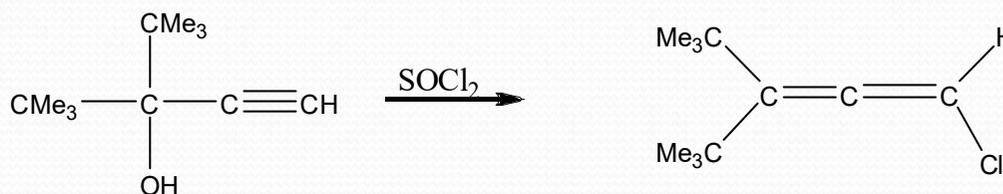
- Mills and Maitland provided the experimental proof to the prediction of Van't Hoff. They performed catalytic asymmetric dehydration of 1,3-dinaphthyl-1,3-diphenylprop-2-enol to give dinaphthyldiphenyl allene.



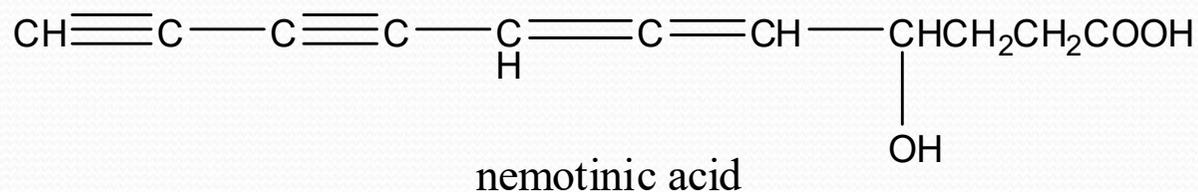
- Reaction with boiling 1% benzene solution of (+)-camphorsulphonic acid gives a dextro rotatory and (-)-camphorsulphonic acid gives laevorotatory allene.
- 1,3-Diphenylpropyne is rearranged over alumina impregnated with quinine or brucine, to get active 1,3-diphenylallene. Quinine gives (+)-allene while brucine gives (-)-allene.



- **Linder synthesized (1959) (+)-1-chloro-3,4,4-trimethylpenta-1,2-diene using SOCl_2 .**



- The naturally occurring **antibiotics nemotinic acid** also contains allene grouping.

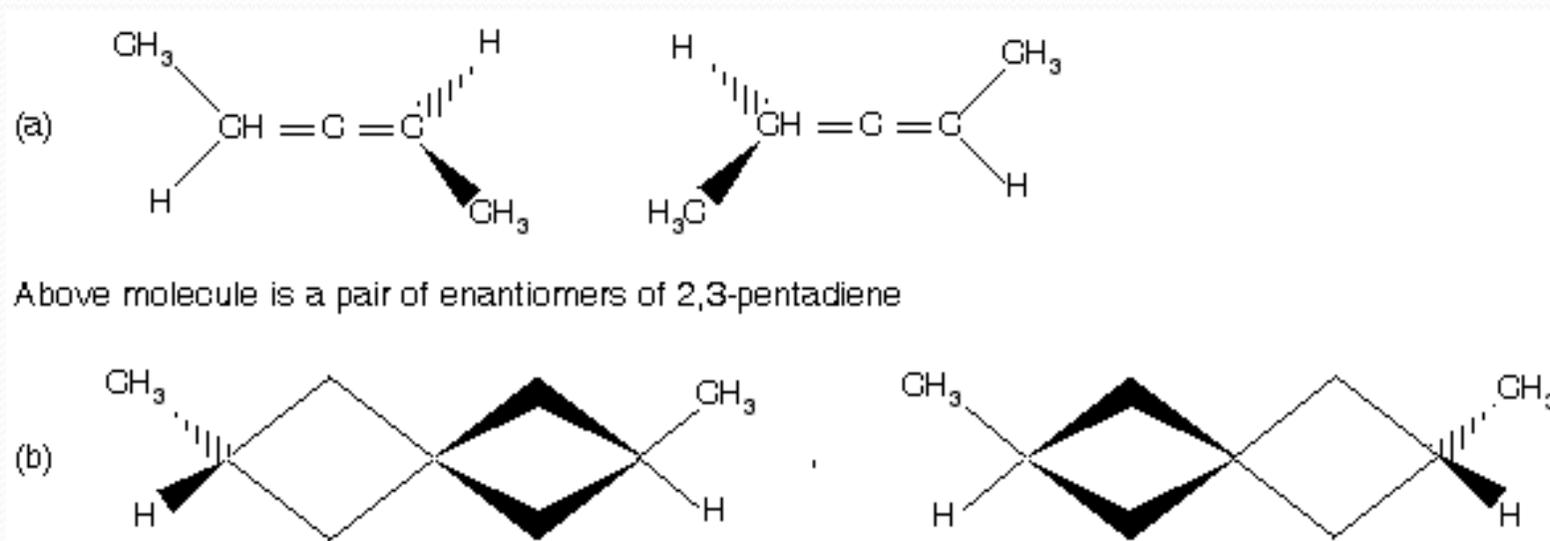


STEREOCHEMISTRY OF SPIRANS



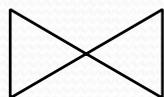
- When both the double bonds in allene structure are replaced by ring systems, the molecule is known as spiran. Spirans as a whole is asymmetric and shows enantiomerism.
- Like allene, in spirans, the groups lie in perpendicular planes and hence they are optically active. Let us consider a following spiran:

Spirans

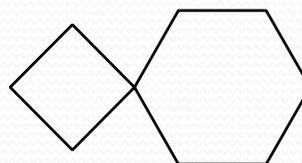


Nomenclature in spirans

- Carry out nomenclature as a parent chain of alkane as per total no of carbon atoms present in ring
- Write number of carbon atoms in each ring except central atom in big bracket giving priority to higher number before the parent name
- Add prefix spiro to the name of compound
- E.g.



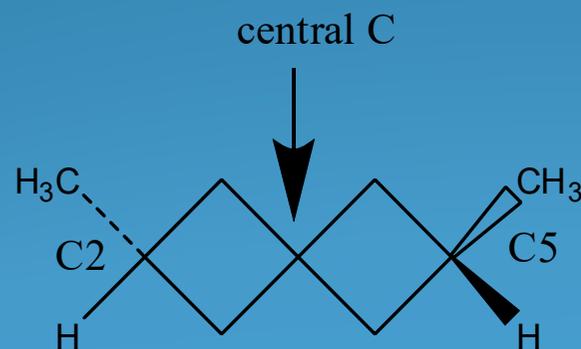
spiro-[2,2]pentane



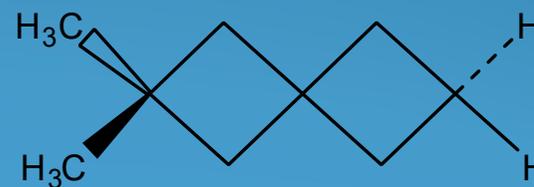
spiro-[5,3]nonane

SPIRANS

Spiro [3,3] heptane is the basic structure, in which a & b are the substituents. C₂ and C₅ are perpendicular to each other. The absence of symmetry is observed, which makes the molecule as a whole asymmetric. Therefore, two optical isomers are possible. Here, a,b and C₂, C₅ are also in different planes. Thus, plane of symmetry is absent. e.g. 2,5-Dimethyl spiro[3,3] heptane.

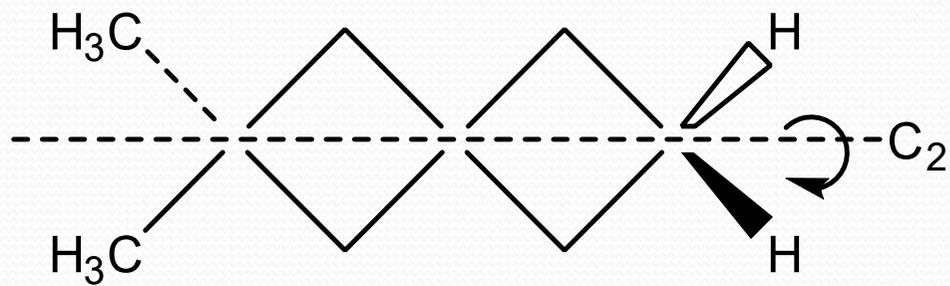


Optically active



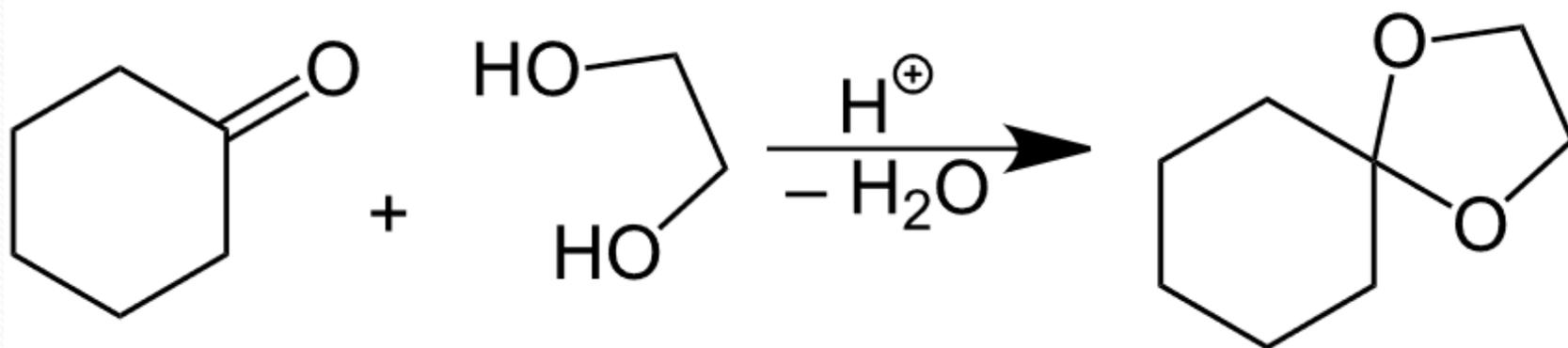
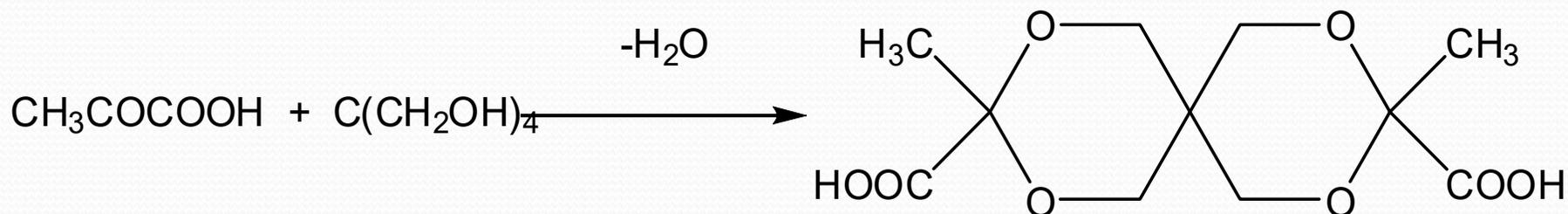
Optically inactive

The plane of symmetry in 2,2-dimethyl spiro [3,3] heptane is responsible for its inactive nature.

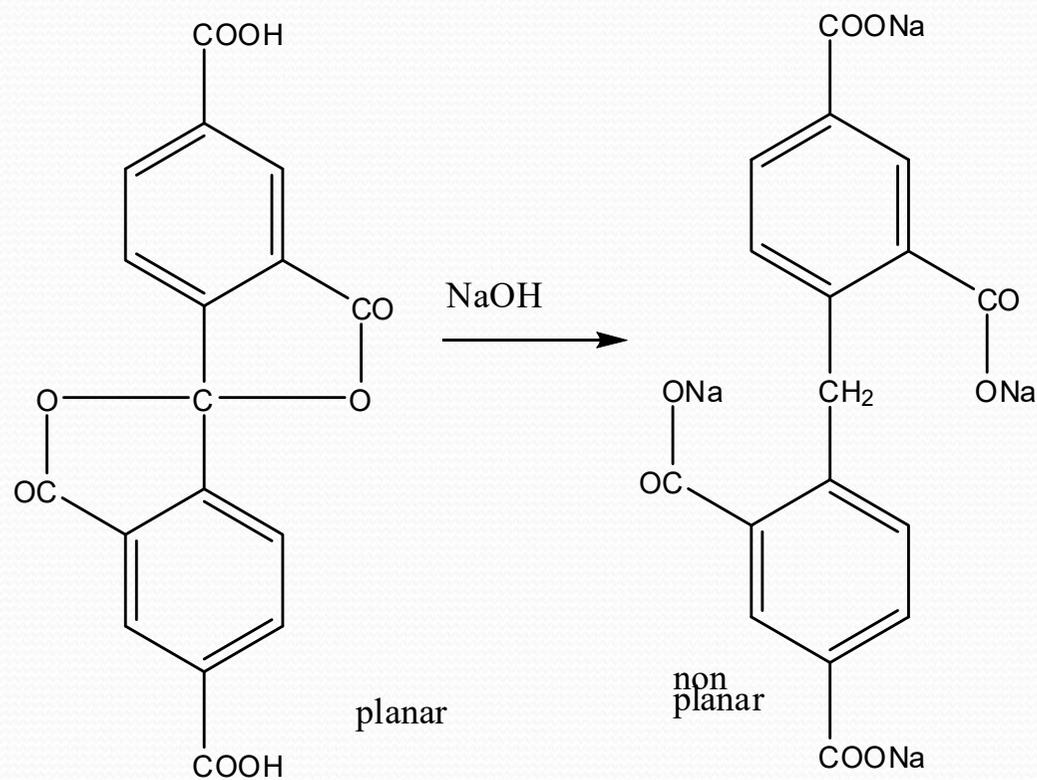


SPIRANS

When penta-erythritol is condensed with pyruvic acid, a spiro compound is obtained. This compound is resolvable. Other synthesis is from cyclohexanone and glycol.

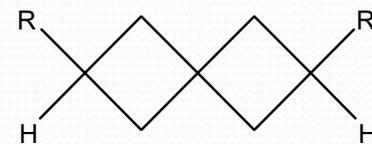
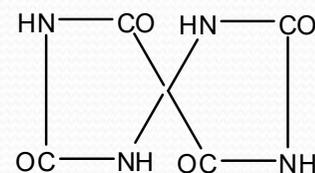


Optically active Dilactam of 2,2',4,4'-benzophenone tetracarboxylic acid hydrolyzed to inactive 2,2',4,4'-benzophenone tetracarboxylic acid



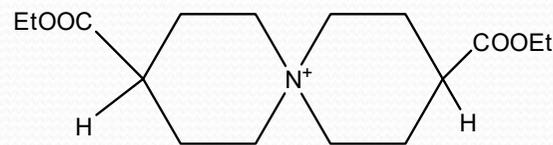
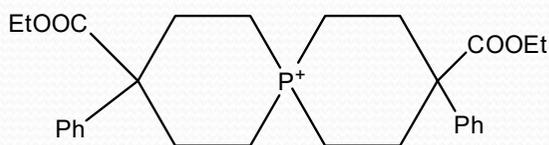
Spiro-hydantoin and other spirans

- Spiro-hydantoin with following formula can also be resolved. Phenatoin, one of the epilepsy drug has hydention functionality
- Other spiro[3,3]heptane are given bellow



R=NH₂ or COOH

- Other examples of optically active spirans are phosphonium and ammonium spiro compounds are as follows.



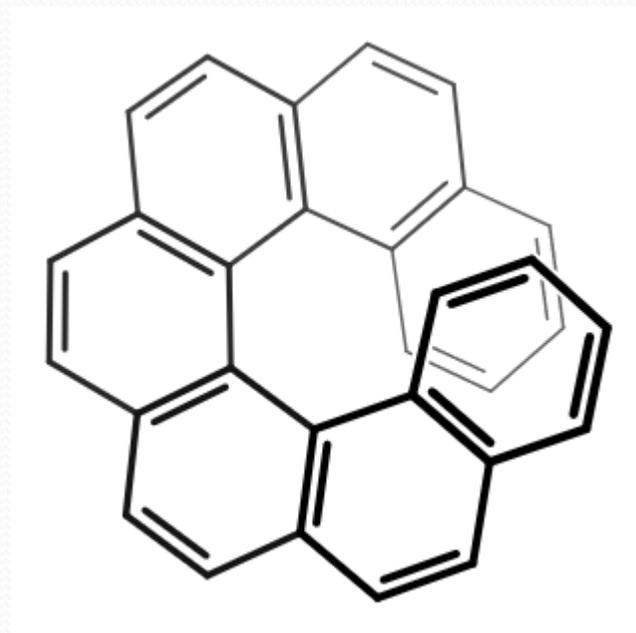
SPIRANS

- As above discussed optical activity of spirans is due to the asymmetry of the molecules as a whole and one pair of enantiomers is found. If spiro compound contains asymmetric carbon atoms, then the number of isomers will be more than two.
- **CHIRAL AXIES**
- Axial chirality refers to stereoisomerism resulting from the non- planar arrangement of four groups in pairs about a **chiral axis**.

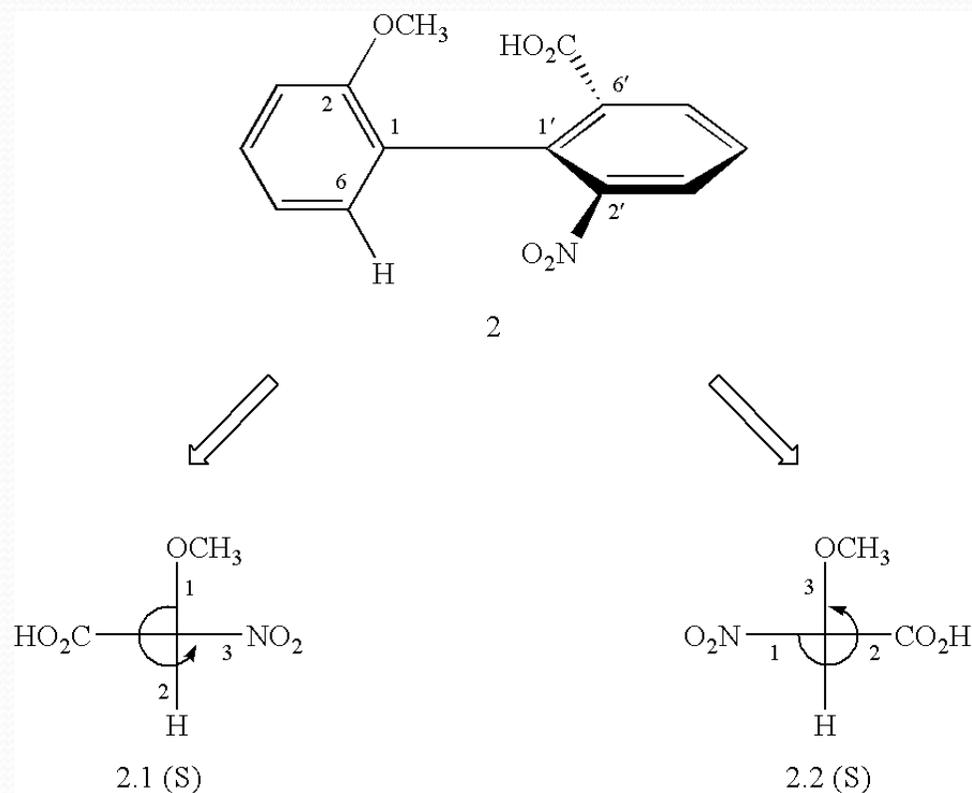
HELICITY

- This property can also be called helicity, since the axis of the structure has a helical, propeller, or screw-shaped geometry. P (plus) or Δ is a right-handed helix, where M (minus) or Λ is a left-handed helix.^{[3][4]} The P/M or Δ/Λ terminology is used particularly for molecules that actually resemble a helix, such as hexahelicene. It can also be applied to other structures having axial chirality by considering the helical orientation of the "front" vs "back" Cahn–Ingold–Prelog rankings.

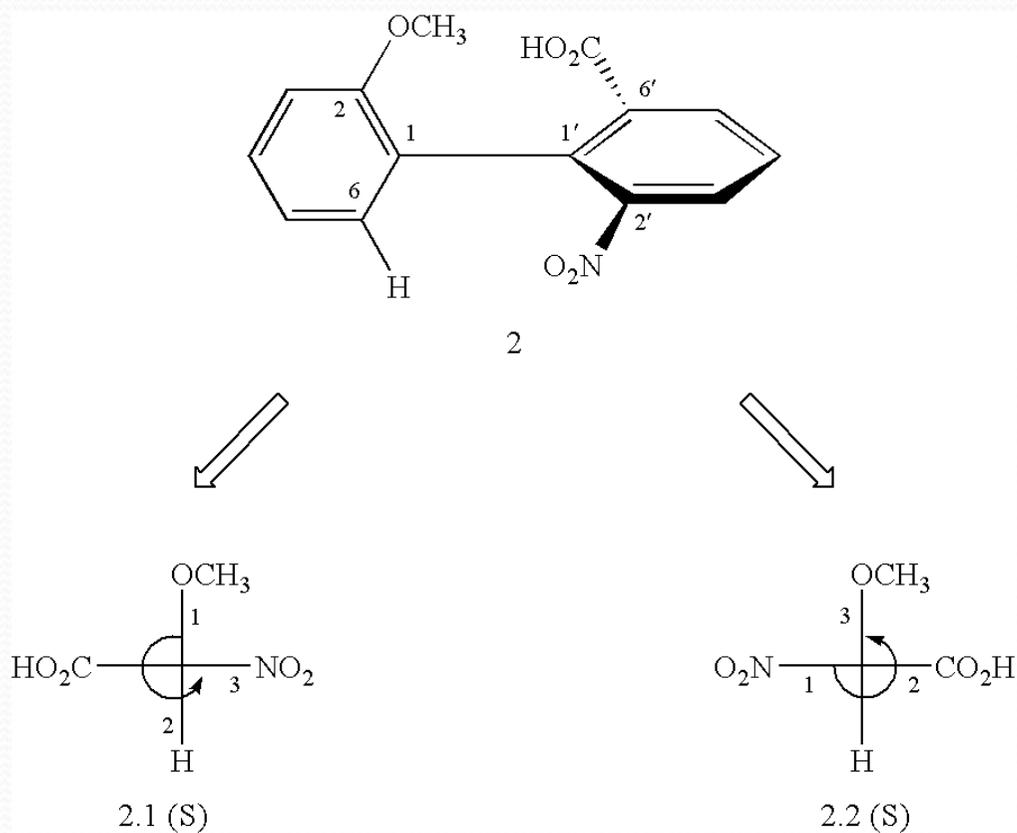
HELICITY



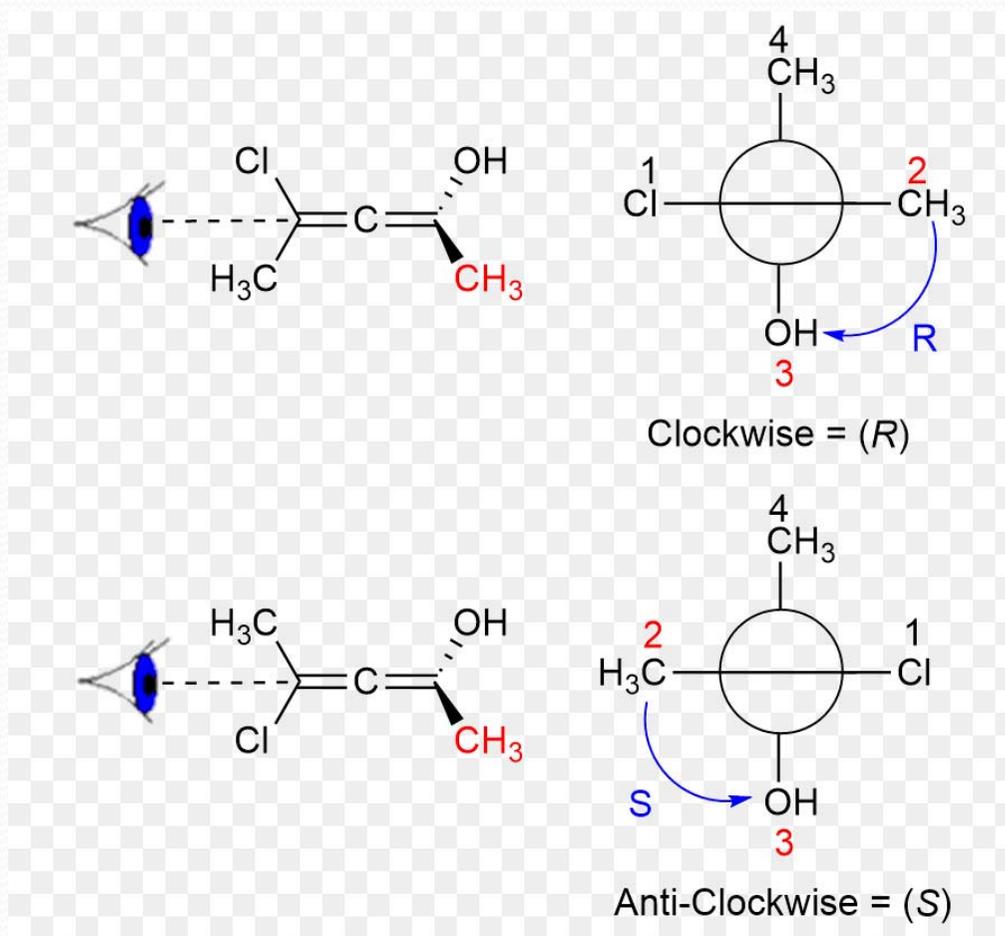
CHIRAL AXIES IN BIPHENYLS



Assignment of configuration in biphenyls



Assignment of configuration in allenes



CHIRAL AXIES IN SPIRANS

