Unit - 1

Structure

1.0 Objectives of the unit

After studying this unit you are able to

- Explain the phenomenon of isomerism
- Identify the different isomerism exhibited by organic molecule
- Recognize the *cis* and *trans* isomers in alkenes
- Differentiate *E* and *Z* isomers in alkene
- Explain the isomerism in oximes
- Explain the isomerism in diazocompounds

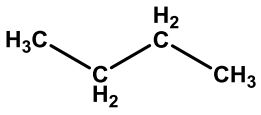
1.1 Introduction

Organic chemistry is mainly the chemistry of compounds of carbon, hydrogen and few heteroatoms like oxygen, nitrogen, sulphur etc…. To understand the nature of organic chemistry it is very important to know the structure of carbon, hydrogen and other atoms (such as sulphur, nitrogen, halogen, oxygen, phosphorus etc..) commonly encountered in organic compounds. In order to find the structure of an organic compound,

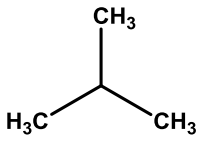
a) First it is important to know the empirical formula of the compound and it is defined as the simplest formula of a substance capable of expressing percentage composition of different elements present in it. For example, CH_2O is the empirical formula of glucose and from it we can calculate its percentage composition. It gives us the simple ratio between atoms of the various elements present as C: H: O ∷ 1: 2: 1.

b) Secondly we should know the molecular formula of the compound and it is defined as the formula which gives the actual number of atoms of various elements presents in the molecule of the substance. Some time it can be same as the empirical formula of the substance or a simple multiple of it

A molecular formula is not the last word about an organic compound. Just as a number of entirely different words can be write with the same set of alphabets, the same set of atoms can be arranged in a number of ways to give more than one organic compounds for example, C_4H_{10} is the molecular formula for butane, However, the 4, carbon atoms can be arranged in two different ways i.e., in a straight or branched chain as shown below



n-butane



Isobutane

Thus C_4H_{10} is the molecular formula of two different compounds, n-butane and isobutene.

The studies of arrangement of atoms or molecules around the central atom (usually carbon in organic chemistry) constitute a different branch in organic chemistry and it is called as stereochemistry. Thus Stereochemistry is an important fact of chemistry and it involves the study of stereochemical structures spans the entire range of organic, inorganic, biological, and supramolecules. It gives an idea why different types of products are formed during a chemical reaction.

1.2 Isomerisms

The compounds with the same molecular formulae but that are structurally different in some way are called Isomers. It is important to be able to recognize isomers because they can have different chemical, physical and biological properties.

Compounds that have the same molecular formula but different chemical structures are called *isomers.* Remember isomerism is a property between a pair (or more) of molecules, *i.e.* a molecule is an isomer of *another* molecule. A similar relationship is that of brother or sister... you can only be a brother or sister to *someone else*.

Depending on the nature of the difference between the structures, it is possible to classify isomers into various sub-types.

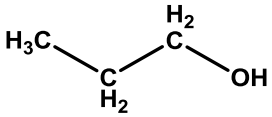
There are two common types of isomerism they are

A) Constitutional isomerism and

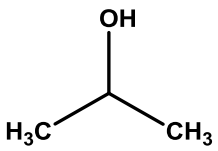
B) Steroisomerism.

A) Constitutional Isomer or Structural isomer

When two or more compounds possess the identical molecular formula but different structural formula are called structural isomers and the phenomenon is called structural isomerisum. For example; n-propyl alcohol and isopropyl alcohol are structural isomers, they differ structurally in which the –OH group linked to different carbon atom in a chain. Structural isomers do not exhibit the same chemical properties.



n-propanol



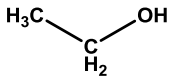
Isopropanol

In constitutional isomers, isomers are differing in "connectivity". The latter term means that the difference is in the sequence in which atoms are attached to one another. In the example of consitutional isomers pairs

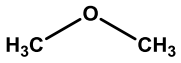
1) n-butane and methyl propane (i.e., isobutene) which are different in that butane has a sequence of four carbon atoms in a row, but isobutane has a three carbon chain with a branch methyl group.

2) Similarly dimethyl ether and ethanol--the former has a C-O-C chain, while the latter has a C-C-O chain

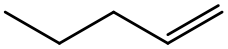
3) 1-pentene and cyclopentane--the former has an acylic chain of 5 carbons, while the latter has a 5-memb



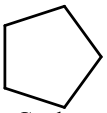
Ethanol



Dimethyl ether



1-pentene



Cyclopentane

Some more examples of structural isomers are shown below;

(i) $CH_3CH_2CH_2CH_3$ and $H_3C—\underset{\displaystyle CH_3}{\underset{|}{CH}}—CH_3$

n-butane iso butane

(ii) $CH_3CH_2CH_2CH_2CH_3$ and $H_3C—\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}—CH_3$

n-pentane iso pentane

(iii) $CH_3CH_2CH_2CH=CH_2$ and $H_3C—\underset{\displaystyle CH_3}{\underset{|}{CH}}—CH=CH_2$

n-pentene iso pentene

(iv) $CH_3CH_2CH\text{-}C\equiv CH$ and $H_3C—\underset{\displaystyle CH_3}{\underset{|}{CH}}—C\equiv CH_3$

n-pentyne iso pentyne

Depending on the nature of constitutional difference in isomeric compounds, constitutional isomerism is further classified as

a) Chain isomerism

b) Functional isomerism

c) Positional isomerism

a) Chain isomerism

Isomeric substances that differ only in the arrangement of atoms forming the base chain are known as chain isomerism and the phenomenon of their existence is said to be chain isomerism. Butane and methyl propane structure shown above are the example of chain isomerism.

b) Positional isomerism

Positional isomerism is an example of structural isomerism, occurs when functional groups are in different positions on the same carbon chain. For example see positional isomers of alcohols and alkenes and in aromatic compounds.

It is due to the difference in the position of the substituent atom or group or an unsaturated linkage in the same carbon chain. Examples are

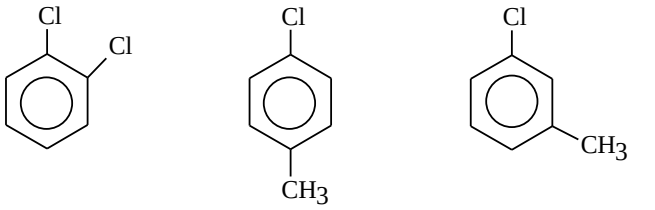
(i) CH_3CH_2-CH=CH_2 and CH_3-CH=CH-CH_3

1-butene 2-butene

(ii) CH_3CH_2 -C≡CH and CH_3-C≡C-CH_3

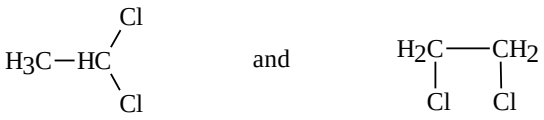
1-butyne 2-butyne

(iii)



1,2-dichloro benzene 1,4-dichloro benzene 1,3-dichloro benzene

(iv)



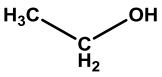
1,1-dichloro ethane 1,2-dichloro ethane

c) Functional isomer

Functional isomerism is an example of structural isomerism occurs due to the same molecular formula but different functional groups. The two examples of functional group isomers are:

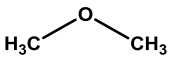
a) Alcohols and ethers b) Aldehydes and ketones

This type of isomerism is due to difference in the nature of functional group present in the two isomers.



Ethyl alcohol

(note the alcoholic group)

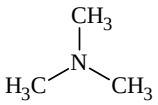


Dimethyl ether

(note the ether group)

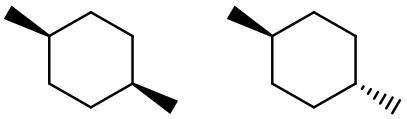
C_3H_6O	CH_3CH_2CHO	$CH_3.CO.CH_3$	$CH_2=CH-CH_2OH$
	Propanal	Acetone	Allyl alcohol

(note the different functional groups in 3 isomers)

C_3H_9N	$CH_3CH_2CH_2NH_2$	$CH_3-NH-C_2H_5$	
	n-Propylamine	Ethyl methyl amine	Trimethyl amine
	(a primary amine)	(a secondary amine)	(a tertiary amine)

B) Stereo isomers

The isomers exhibited by some compounds (example, Lactic acid, 2-butene etc…) have the identical molecular and structural formula and yet show isomerism. Theses isomers are differs only by different atoms present in the molecule occupy different positions in space. Isomers with same molecular and structural formula but different special arrangement of atoms or groups are called stereo isomers and phenomenon is called stereo isomerism. Hence *stereo isomers have the same connectivity but different arrangement of atoms in space***.** Thus all isomers are either constitutional or stereo isomers. Stereoisomerism is a more subtle kind of isomerism in which the isomers differ only in their spatial arrangement, not in their connectivity. Cis- and Trans-1,4-dimethylcyclohexane are a good example of a pair of stereo isomers.

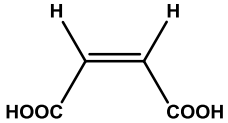


Cis Trans

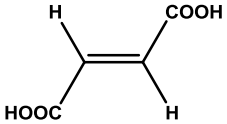
In nature butenedioic acid (HOOC-CH=CH-COOH) exists in two forms.

i) In which the two H-atoms are on the same side of the C=C double bond and two –COOH groups are on the other side of the C=C double bond. This form is called maleic acid.

ii) in which the two H- atoms are lie on the opposite sides of the C=C double bond and two-COOH groups also lie similarly. This form is called as fumaric acid.



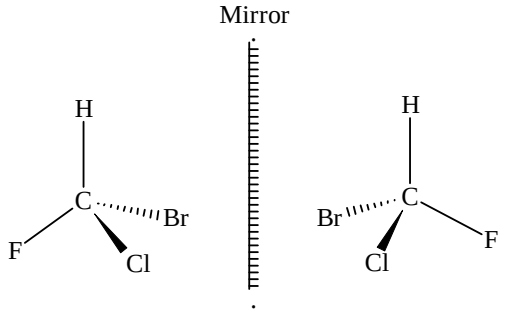
maleic acid



fumaric acid

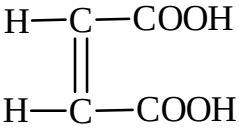
1.3 Optical isomer

Stereoisomerism in which isomers differ in the arrangement of substituents at one or more asymmetric carbon atoms, thus some (but not necessarily all) are optical isomers. The following is a good example of optical isomer.

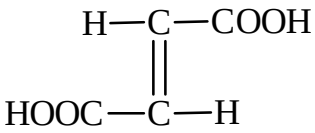


1.4 Geometric isomer

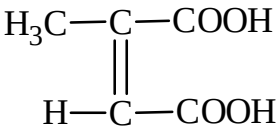
Stereoisomerism in which isomers differ in the arrangement of substituents in a rigid structure, such as double bonded carbon atoms or a ring containing carbon atoms. Eg:



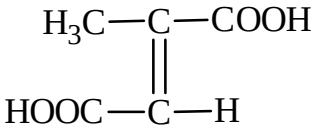
Maleic acid (*cis*)



Fumaric acid (*trans*)

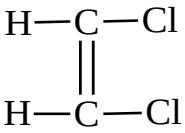


Citraconite acid (*cis* isomer)

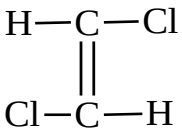


Mesaconic acid (*trans* isomer)

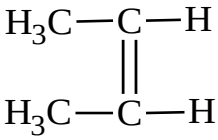
The isomers which possess the same structural formula but differ in the spatial arrangement of the groups around the double bond are known as geometrical isomers and the phenomenon is known as *geometrical isomerism*. This isomerism is shown by alkenes or their derivatives. When similar groups lie on the same side, it is the *cis*-isomer; while when the similar groups lie on opposite sides, the isomer is *trans.*



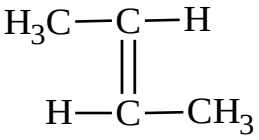
cis-1,2-Dichloroethylene



trans-1,2-Dichloroethylene



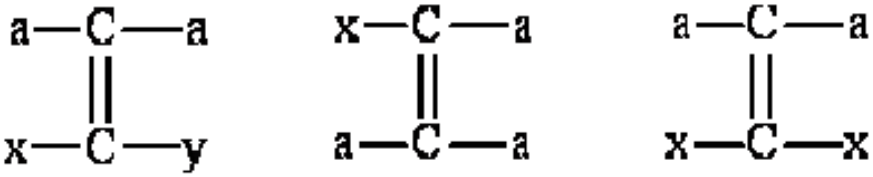
cis-2-Butene



trans-2-Butene

This also arises with cycloalkanes and compounds containing a double bond other than alkenes like azo compounds, oximes,

It is important to remember that geometrical isomerism is possible only when each of the doubly bonded carbon atom has two different groups. Therefore compounds of the following type will not show geometrical isomerism.



The similar atoms (groups) are on the one or both of the carbon atoms

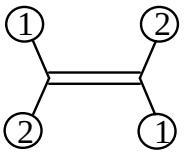
1.5 Distinction between *cis* -and *trans*- isomers

(a) Generally, the *cis*-isomer (e.g. maleic acid) cyclises on heating to form the corresponding anhydride while the *trans*-isomer does not form its anhydride at all.

(b) The *cis*-isomer of a symmetrical alkene (alkenes in which both the carbon atoms have similar groups) has a definite dipole moment, while the trans-isomer has zero dipole moment. For example, 1, 2-dichloroethylene and 2-butene. In *trans*-isomer of the symmetrical alkenes, the effect produced in one half of the molecule is cancelled by that in the other half of the molecule. In case of unsymmetrical alkenes, the *cis*-isomer has higher dipole moment than the corresponding *trans*-isomer. For example,

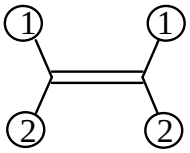
1.6 Classification of Geometric Isomers: the E-Z System

1. Apply the sequence rules to assign priorities to the two group or atom attached to each of the doubly bonded carbon atoms.
2. If the two group or atom of highest priority are on opposite sides of the double bond, the isomer is E (**entgegen, across**).
3. When the highest priority groups or atoms are on the same side of the double bond, the isomer is Z (**zusammen, together**).



E-isomer

(Top priority atom or groups on opposite sides of the pi bond)

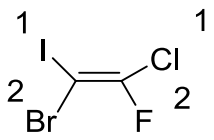


Z-isomer

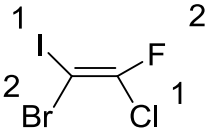
(Top priority atom or group on same side of the pi bond)

For example; an alkene in which one of the doubly bonded carbon atoms has Bromine (Br) and Iodine (I) and the other has Florine (F) and Chlorine (Cl).

Since I has a higher atomic number than Br, it is assigned higher priority (1); similarly Cl is of higher priority than F on the second olefinic carbon atom. Thus the *E* and *Z* configuration of the two isomers of 1-bromo-2-chloro-2-fluoro-1-iodoethene are assigned as shown below.

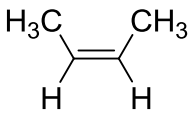


Z cis isomer



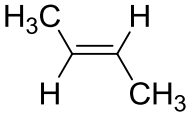
E trans isomer

Thus the *cis*- and *trans*-isomers of 2-butene become *Z*-and *E*-2-butenes respectively.



Z isomer of 2- butene

cis-2-butene

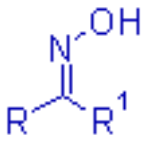


E isomer of 2- butene

trans-2-butene

1.7 Geometrical isomerism in Oximes

The oximes are formed when carbonyl compounds are treated with hydroxyl amine. These are represented as



oxime

Where R & R^1 are hydrogens or alkyl or aryl groups.

There are two types of oximes are exists, they are

1) Aldoximes: These are derived from aldehydes. In this case, at least either R or R^1 is hydrogen and

2) Ketoximes: These are derived from ketones. In this case, both R or $R^1$are alkyl or aryl groups only.

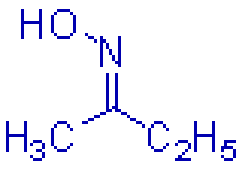
The oximes show geometrical isomerism due to restricted rotation of C=N bond. Two geometrical forms are possible for the oximes as shown below.

The descriptors, *syn* and *anti* are used to distinguish them.

In case of aldoximes, the *syn* form is the one in which both the hydrogen and the hydroxyl (-OH) group are on the same side of the C=N whereas in the *anti* form, they are on the opposite side. E.g. the syn and anti forms of acetaldoxime are shown below.

syn oxime anti oxime

However with ketoximes, the *syn* and *anti* descriptors indicate the spatial relationship between the first group cited in the name and the hydroxyl group. For example, the following ketoxime of butanone can be named as either syn methyl ethyl ketoxime or anti ethyl methyl ketoxime.

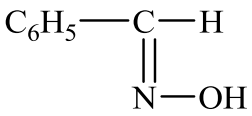


i) E-Z notation of oximes

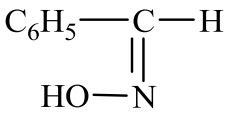
The geometrical isomers are better differentiated by using E-Z notations. The Z oxime has hydroxyl group and the group with higher priority on the same side of C=N. However in the E oxime, they are arranged on the opposite sides of the C=N.

E.g. The syn acetaldoxime is named as (E)-acetaldoxime, since the hydroxy group and the group with higher priority i.e., methyl group are on the different sides of the C=N. Whereas the anti form is named as (Z)-acetaldoxime.

Aromatic aldoximes and aromatic ketoximes also show geometrical isomerism. In aldoximes, when H and OH groups are on the same side, the isomer is known as syn (analogous to cis)



syn-Benzaldoxime



Anti-Benzaldoxime

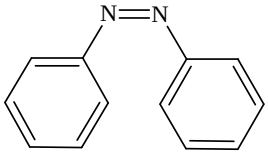
and when these groups are on the opposite sides, the isomer is known as *anti* (analogous to *trans).*

In ketoximes the prefixes syn and anti indicate which group of ketoxime is syn (on the same side) or anti (on the opposite sides) to the OH group. For example,

However, remember that all aromatic ketoximes do not show geometrical isomerism e.g., $(C_6H_5)_2C$ = NOH, (benzophenone oxime) having two similar aryl groups does not show geometrical isomerism.

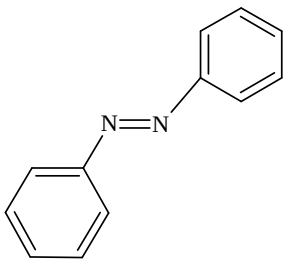
1.8 Geometrical isomerism in diazo benzene

diazo compounds are organic molecules in which two benzene rings (known as phenyl groups) are linked by two nitrogen atoms, In diazo benzene syn is one in which the two phenyl groups are on the same side and anti is one in which two phenyl groups are on opposite side.



(*Z*)-diphenyldiazene

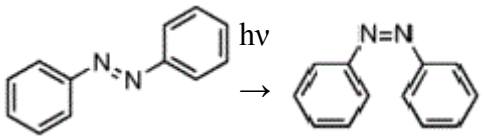
syn isomer



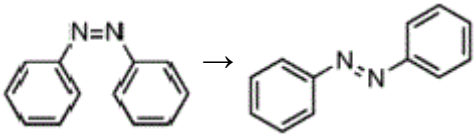
(E)-diphenyldiazene

anti isomer

The cis isomer is less stable than the trans isomer. In the presence of light (hν) , the trans isomer will convert to the cis isomer:



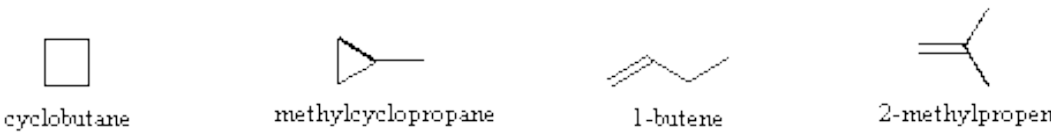
but because the cis isomer is less stable, it will relax back to the trans isomer over time:



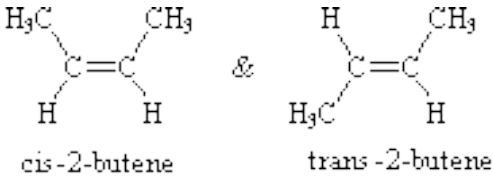
Cis-azobenzene is more polar than trans-azobenzene so cis-azobenzene is more water soluble than trans-azobenzene.

1.9 Summary of the unit

Isomers are different compounds that have the same molecular formula. When the groups of atoms that make up the molecules of different isomers are bonded together in fundamentally different ways, we refer such compounds as *constitutional isomers*. For example, in the case of the C_4H_8 hydrocarbons, most of the isomers are constitutional.



The twelve atoms that make up these isomers are connected or bonded in very different ways. Furthermore, the molecular formula provides information about some of the structural features that must be present in the isomers. Since the formula C_4H_8 has two fewer hydrogens than the four-carbon alkane butane (C_4H_{10}), all the isomers having this composition must incorporate either a ring or a double bond. A fifth possible isomer of formula C_4H_8 is $CH_3CH=CHCH_3$. This would be named 2-butene according to the IUPAC rules; however, a close inspection of this molecule indicates it has two possible structures. These isomers may be isolated as distinct compounds, having characteristic and different properties. They are designated as *cis* and *trans*.



Optical isomers are isomers in octahedral and tetrahedral geometry that do not exhibit symmetry and do not have identical mirror images. Optical isomers are difficult to understand because one must be able to visualize them in a 3D manner.

1.10 Key words

Isomers; Constitutional Isomer; Chain isomerism; Positional isomerism; Functional isomer; Optical isomer; Geometric isomer; *cis* -and *trans*- isomers; Oximes; Diazo benzene.

1.11 References for further study

1) Stereochemistry of Organic Compounds: Principles and Applications**;** D. Narsipuri, *New Age International*; **1994**.

2) Stereochemistry; Devid G. Morris, *Royal Society of Chemistry*, **2001**.

3) Stereochemistry Conformation and Mechanism; P. S. Kalsi, *New Age International*, **2005**.

4) Stereochemistry of Organic Compounds; Ernest Ludwig Eliel, Samuel H. Wilen. *John Wiley & Sons*, **2008**.

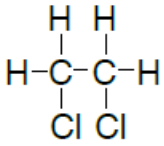
5) Dynamic Stereochemistry of Chiral Compounds; Christian Wolf, *Royal Society of Chemistry*, **2013**.

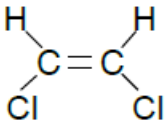
6) Organic Mechanisms: Reactions, Stereochemistry and Synthesis; Reinhard Bruckner, *Springer*, **2010**

1.12 Questions for self understanding

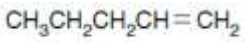
1. Give the molecular formula for cis-azobenzene and trans-azobenzene.
2. Explain why azobenzene displays cis-trans (geometric) isomerism.
3. If the N=N bond in azobenzene was replaced with N-N, would the resulting molecule display cis-trans (geometric) isomerism? Explain your answer.
4. On a drawing of the structural formula of trans-azobenzene, circle a phenyl group.
5. Diazene (diimine) has the molecular formula $(NH)_2$. It contains the same N=N bond as azobenzene or diphenyldiazene. Diazene also displays cis-trans (geometric) isomerism. Draw both cis-diazene and trans-diazene.
6. Hydrazine has the molecular formula N_2H_4. Draw a possible structural formula for hydrazine.
7. Do you expect hydrazine to display cis-trans (geometric) isomerism? Explain your answer.
8. Draw the molecular formula for the molecule trans-dibutyldiazene.
9. Dibutyldiazene undergoes an addition reaction with hydrogen gas. Draw the structural formula for the product of this reaction.
10. There are five structural isomers for hexane, C_6H_{14}. Draw the five structures using simplified structural formulae. For example, one of the isomers of butane, C_4H_{10}, could be drawn as $CH_3CH_2CH_2CH_3$. Use the same sort of format for the other questions on this page.

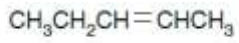
11. Draw as many structural isomers as possible for C_3H_8O.
12. Draw as many structural isomers as you can for C_8H_{10} containing a benzene ring.
13. Draw as many structural isomers as you can for $C_4H_8O_2$ containing the group carboxylate.
14. One of these molecules has geometric isomers and the other one doesn't. Explain the difference.

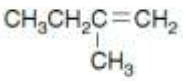


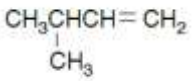


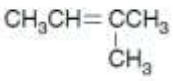
15. The following are all isomers of pentene, C5H10. Pick out any of these which have geometric isomers, and draw the isomers











16. Draw all the isomers (including structural and geometric isomers) of C2H2Br2 which contain a carbon-carbon double bond.
17. Explain why the boiling point of cis-1,2-dichloroethene is higher than that of the trans isomer.
18. Explain why the melting point of cis-1,2-dichloroethene is lower than that of the trans isomer.

Unit - 2

Structure

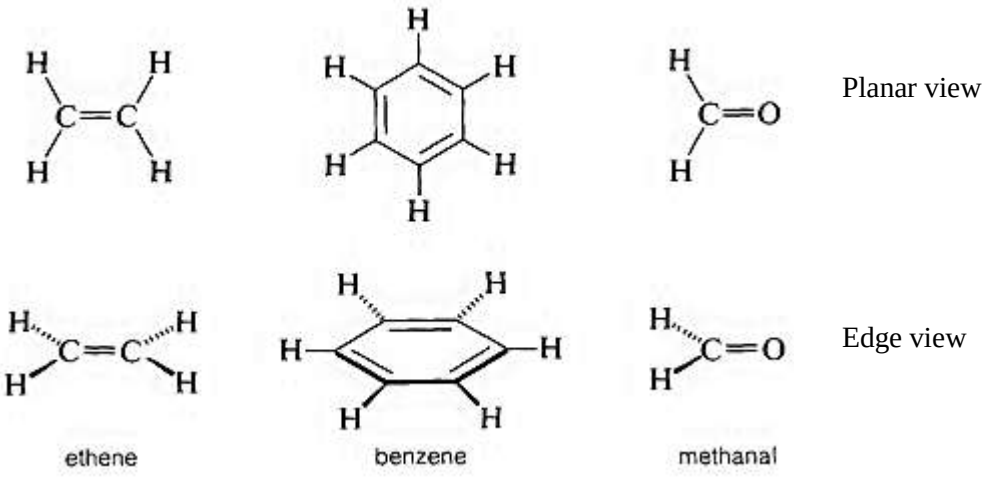
2.0 Objectives of the unit

After studying this unit you are able to

- Explain what is conformation of molecule
- Draw the different conformations of molecule
- Recognize the most stable conformation of a given molecule
- Draw the different conformations of butane
- Draw the stable conformation structure of different disubstituted cyclohexane
- Explain stable conformation of cyclic compounds
- Explain stable conformation of bicyclic compounds

2.1 Introduction

Methane (CH_4) is a simplest organic molecule and has a perfect tetrahedron structure. There is no isomerism is possible for methane molecule, however, the constantly vibrate and bending of carbon-hydrogen atoms in methane make an appearance of different methane molecule having C-H atoms orient at different position (isomer) to exist. But these structures are has almost equal energy minima, and so they do not considered as isomers. As complexity increases (ie, from methane to ethane.), isomers induced by rotations about bonds becomes a bigger factor. For example, in ethane (CH_3CH_3) molecule, both carbons are approximately tetrahedral. Thus, there are many rotational isomers are possible to write, among them, two isomers are considered as important with respect to the energy concern. One rotational isomer in which all the carbon-hydrogen bonds are as far apart as possible and the molecule has minimum energy. Another isomer in which all the C-H bonds are as close as possible and the molecule has maximum energy. Therefore these two structures are certainly not the same. These structured are best viewed with the help of projection formula.



The Planar structure is a one-dimensional representation of any structures. Molecules such as benzene, ethene, formaldehyde, etc…., are Planar and easily drawn in the plane of the paper with bond angles of about 120°. If one can try to draw their edge view structure with proper perspective (out of plane) as shown in above picture, then the forward bonds should be drawn with slightly heavier lines. The wide ends (thick bonds) are considered pointing toward the viewer and the narrow ends (dashed bond) are considered as away from the viewer. Hence representation of three dimensional structure in a two dimensional paper is called projection formula. There are different kind of projection formulas are available for effective representation of conformers, each has their own advantages. In this unit we will study the different types of conformational representation and study of conformational analysis in details.

2.2 Conformation and conformational analysis

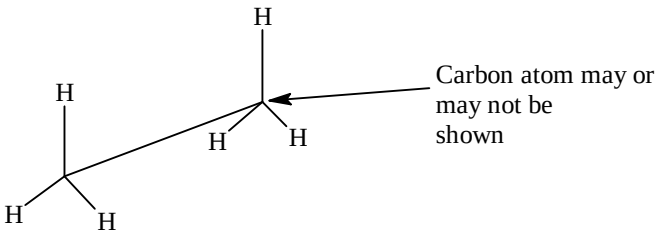
Free rotation is possible about the carbon-carbon single bond in a molecule. This rotation makes the atoms in a molecule assume different spatial positions with respect to each other. *The different spatial arrangements of the atoms which result from rotations of groups about a single (sigma) bond is called the conformations of a molecule. A study of the energy changes which accompany these rotations is called conformational analysis*.

In case of simple molecules the magnitude of energy associated with the torsional strain due to free rotation of single bond is very small and it is less than 5 kcal/mole. Thermal energy is sufficient to overcome this energy so that inter-conversation between the isomers is rapid. As the number of carbon chain length increases, more and more number of isomers are exits and the energy barrier between these isomers are large.

2.3 Projection formulae

Projection formulae is conventions for showing three-dimensional structures in to two dimensional on the paper

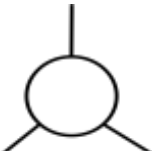
There are various methods to show the three dimensional molecule on a two dimensional paper. The conformation of a molecule containing two tetrahedral atoms linked together can be represented by a "*Newman***"** or "*sawhorse*" projections. In the Newman projection the molecule is viewed along the axis of a rotatable bond.



2.4 Newman Projections

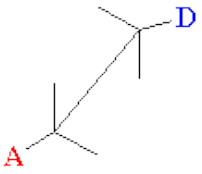
A convenient representation of a molecule viewed along one of its carbon-carbon axes is the Newman projection.

Bonds on the front carbon atoms are shown as 

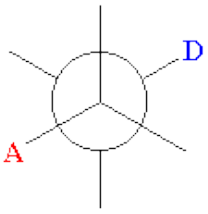
And those on the rear carbon atom as 

2.5 Sawhorse Formulae

Sawhorse Projections are very similar to Newman Projections, but are used more often because the carbon-carbon bond that is compressed in a Newman Projection is fully drawn out in a Sawhorse Projection. When properly laid-out, Sawhorse Projections are useful for determining enantiomeric or diasteromeric relationships between two molecules, because the mirror image or superimposibility relationships are clearer.

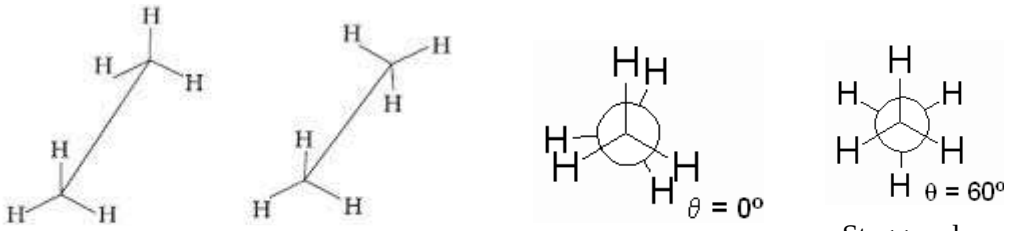


Sawhorse projection



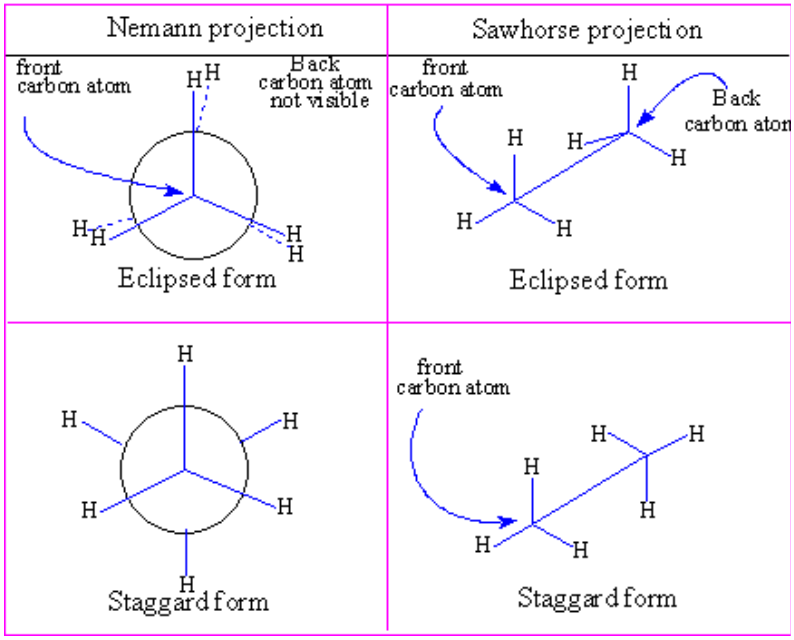
Newman projection

Interconversions of conformers are proceeds by an infinite number of intermediate conformers. The number of such conformations (conformers) depends on the number of energy minima on the energy profile. For example, in the case of ethane molecule three energy minima conformers are obtained during 360^{o} rotation. The minima on the energy potential correspond to "*staggered*" conformers, in which the hydrogen atoms on the two carbons are apart from maximum distance (have a dihedral angle of 60^{0}). The maxima on the energy potential correspond to "*eclipsed*" conformations in which the hydrogen atoms on each carbon atoms have a dihedral angle of 0^{o}. In the staggered conformation, two largest substituents in the system are corresponds to *anti-peri-planar* orientation (conformation). Unless influenced by factors other than steric size the anti-peri-planar conformers are the most stable for all molecules.



Eclipsed *Staggered* *Eclipsed* Staggered

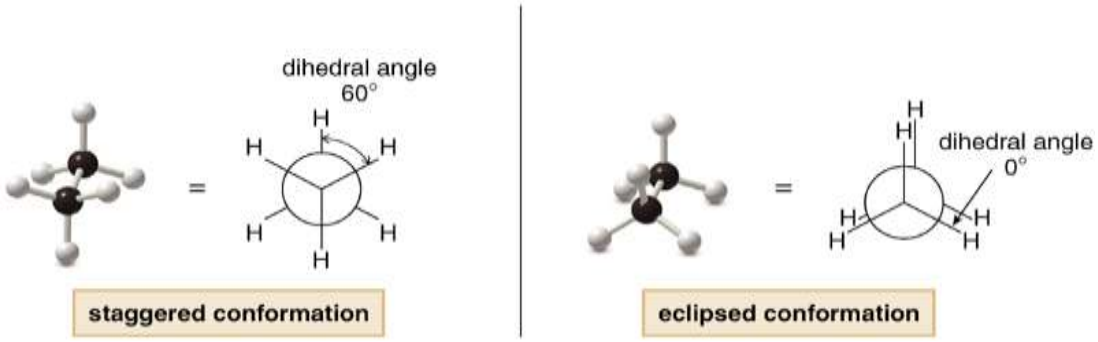
Sawhorse projections of ethane Newman Projections of ethane



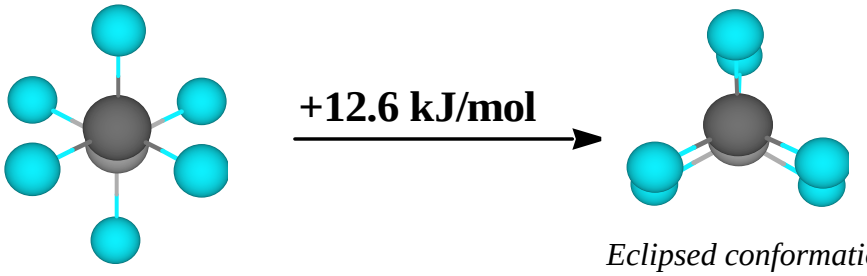
Like with Newman Projections, a Sawhorse Projection is a view of a molecule down a particular carbon-carbon bond, and groups connected to both the front and back carbons are drawn using *sticks* at 120^0 angles. Sawhorse Projections can also be drawn so that the groups on the front carbon are *staggered* (60 degrees apart) or *eclipsed* (directly overlapping) with the groups on the back carbon. Above are two Sawhorse Projections of ethane. The structure on the left is staggered, and the structure on the right is eclipsed. These are the simplest Sawhorse Projections because they have only two carbons and all of the groups on the front Sawhorse Projections slightly more complicated. It is important to notice that, it is much easier to determine the number of carbons in the longest chain using Sawhorse Projections than it is for Newman Projections because the carbon-carbon bond between the second and third carbons is drawn out.

Staggered conformation: a conformation about a carbon-carbon single bond in which the atoms or groups on one carbon are as far apart as possible from the atoms or groups on an adjacent carbon

Eclipsed conformation: a conformation about a carbon-carbon single bond in which the atoms or groups of atoms on one carbon are as close as possible to the atoms or groups of atoms on an adjacent carbon



Torsional strain: it is also called eclipsed interaction strain. The strain arises when non-bonded atoms separated by three bonds are forced from a staggered conformation to an eclipsed conformation. The torsional strain between eclipsed and staggered ethane is approximately 12.6 kJ (3.0 kcal)/mol



Staggered conformation

Eclipsed conformation

Stability of conformer

Stability of conformers depends on the four factors.

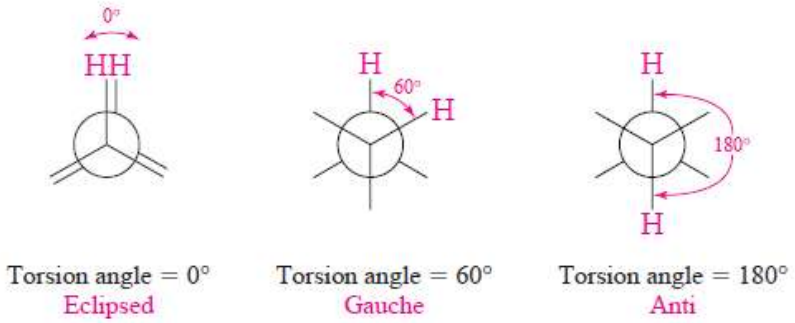
1. Non-bonded group interaction or steric strain
2. Torsional strain
3. Electrostatic force of repulsion.
4. Hydrogen bonding.

Torsional strain is the bonded pair electron repulsion while non bonded group interaction is the interaction due to bulky groups.

2.6 Conformation of ethane

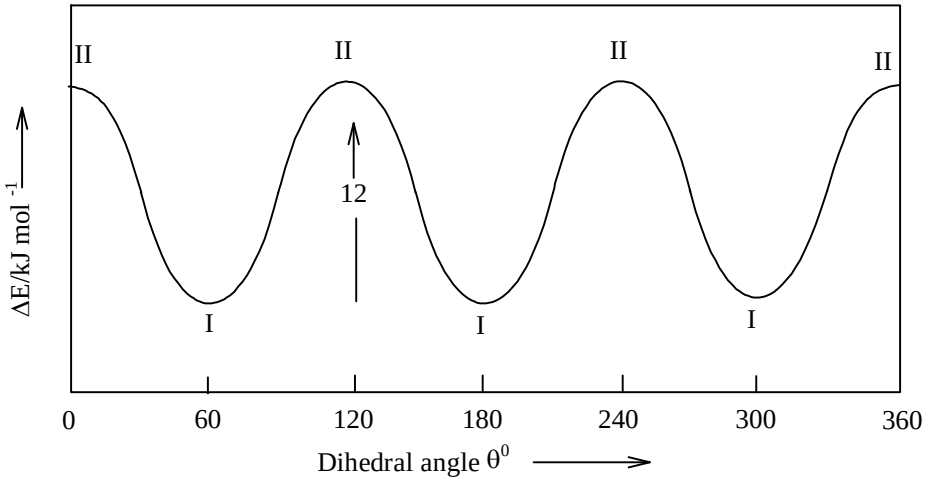
Ethane is the simplest hydrocarbon that can have distinct conformations. In ethane torsional strain plays an important role. Each H-C-C-H unit in ethane is characterized by a *torsion angle* or *dihedral angle*, which is the angle between the H-C-C plane and the C-C-H plane. The torsion angle is easily seen in a Newman projection of ethane as the angle between C-H

bonds of adjacent carbons. In principle there are an infinite number of conformations of ethane, differing by only tiny increments in their torsion angles. In the staggered (or anti) conformation, the H atoms are as far apart as possible, and electrostatic repulsion between the C-H bonding electron pairs is at a minimum. In the least stable eclipsed conformation, electron pair repulsion is maximum.



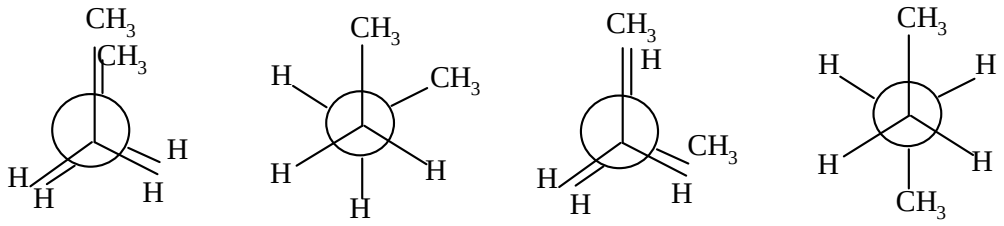
In eclipsed conformation bonds are characterized by a torsion angle of 0°. In *gauche* conformation the torsion angle is approximately 60°, and when the bond angle is 180° the conformation is called *anti***.** For ethane, staggered conformations is either gauche or anti (both are same for ethane) relationships. The staggered conformation is more stable than the eclipsed and the measured potential energy difference between them is 12 kJ/mol (2.9 kcal/mol). This is because in the staggered conformation, the electron pairs in the C-H bonds of one carbon is away from the electron pairs in the C-H bonds of the other while in the eclipsed conformation the electron pairs are closer therefore electron repulsion is more in this conformation. This electron-pair repulsion on adjacent carbons is responsible for the relative stability of staggered and eclipsed conformations.

The changes in internal (potential) energy which accompany rotation about the carbon-carbon bond in ethane are shown diagrammatically in below figure



Variation of internal energy of the ethane with rotation about C-C bond. Number I and II referrers Staggerd and eclipsed conformations respectively

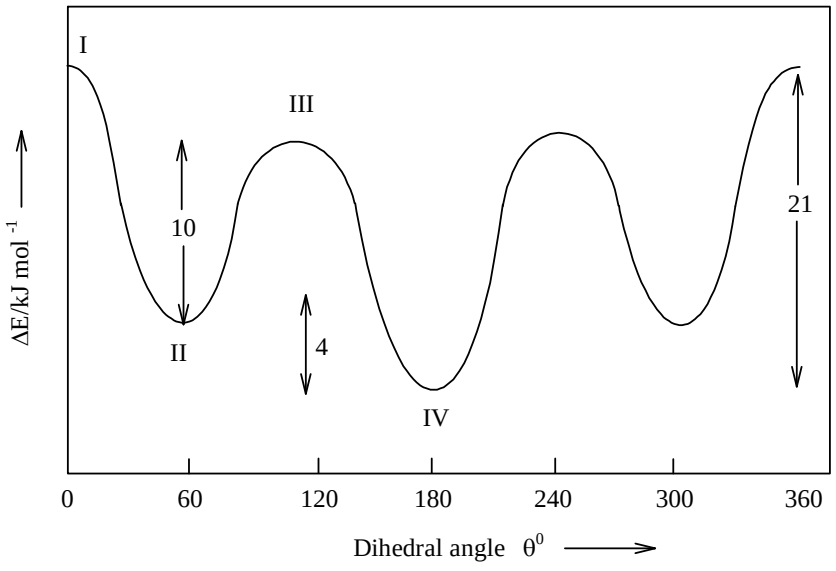
2.7 Conformations of Butane



Synperiplanar (I) Synclinal (II) Anticlinal (III) Antiperiplanar (IV)

Principal conformations of butane

Newman projections (along the C_2-C_3 axis) for the principal conformations of butane are shown in above diagram. On rotating the C-C bond between at 2nd and 3rd carbons at 60° intervals, two eclipsed confermers [(I) and (III), one staggered conformer (IV) and one gauche conformer (II) are obtained. Among the two eclipsed conformations, structure I referred as *synperiplanar* and structure III referred as *anti clinal*. Structure **I** is the least stable because of additional steric strain due to the close proximity of the two bulky methyl groups. Similarly, the staggered conformer **IV** is referred as *antiperiplanar* and is more stable than gauche conformer II which is referred as *synclinal***.** Energy differences for the various conformations are shown in below.



Variation in internal (potential) energy of butane with rotation about the C2-C3 carbon-carbon bond. Numbers I-IV relate to conformers.

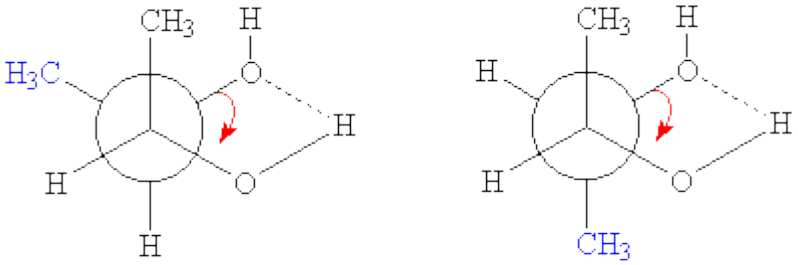
The proportions of the different conformations present and energy differences between them may be determined by various spectroscopic methods (Raman, IR, NMR and microwave

spectroscopy). At room temperature about 70% of butane molecules are antiperiplanar, which is said to be the preferred conformation. These terms refer to the relative positions of the two methyl groups. syn = together, anti = opposite, periplanar = about planar, and clinal = inclined.

Higher alkanes of unbranched carbon chains are most stable in their all-anti conformations (like butane). The energy difference between gauche and anti conformations is similar to that of butane, and appreciable quantities of the gauche conformation are present in liquid alkanes at 25°C. To depict the conformations of higher alkanes, it is often more helpful to look at them from the side rather than end-on as in a Newman projection.

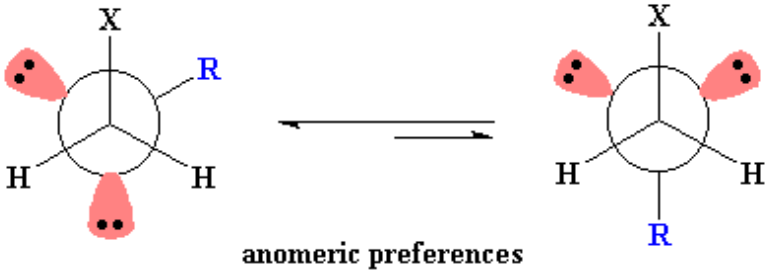
2.8 Effect of hydrogen bonding

Hydrogen bonds have a locking effect on the conformation about the C-C bonds. For example, the most stable conformer of both *meso*- and *dl*-butane-2,3-diol is sc, since it enables formation of the hydrogen bond between the hydroxyl group. In *meso*-compound this hydrogen bonding overrides two unfavorable *synclinal*-interactions: one between methyl groups and one between oxygen atoms.



2.9 Anomeric effect

In the case when two heteroatoms (usually oxygen, sulfur and hologenides) are bonded to the same carbon atom the preferred conformation is different that the one predicted on the steric effect grounds. This conformational bias is called *anomeric effect* (based on analogy to sugar carbon atom C-1). In this case the determining factor is the interaction of the nonbonding electron pair of the heteroatom with the electron deficient orbital of C-heteroatom bond. The effect is that the synclinal conformer is more stable than the antiperiplanar conformer. The typical illustration of such effect is greater stability of alpha-anomers of sugars than beta-anomers.



anomeric preferences

2.10 Conformations of Cycloalkanes

During the nineteenth century it was widely believed that cycloalkane rings are planar. Baeyer connected how closely the angles of planar rings match the tetrahedral value of 109.5°. For example, the 60° bond angle of cyclopropane and the 90° bond angles of a planar cyclobutane ring are much smaller than the tetrahedral angle of 109.5°. Baeyer suggested that three- and four-membered rings suffer from what we now call angle strain. *Angle strain* is the strain a molecule has because one or more of its bond angles deviate from the ideal value, in the case of alkanes the ideal value is 109.5°. According to Baeyer, cyclopentane should be the most stable of all the cycloalkanes because the ring angles of a planar pentagon, 108°, are closer to the tetrahedral angle than those of any other cycloalkane. A prediction of the *Baeyer strain theory* is that the cycloalkanes beyond cyclopentane should become increasingly strained and correspondingly less stable. The angles of a regular hexagon are 120°, and the angles of larger polygons deviate more and more from the ideal tetrahedral angle. The Baeyer strain theory is useful to identifying angle strain as a destabilizing effect. Its fundamental failure is its assumption that the rings of cycloalkanes are planar. *With the exception of cyclopropane, cycloalkanes are nonplanar.*

e) Conformation of cylopropane

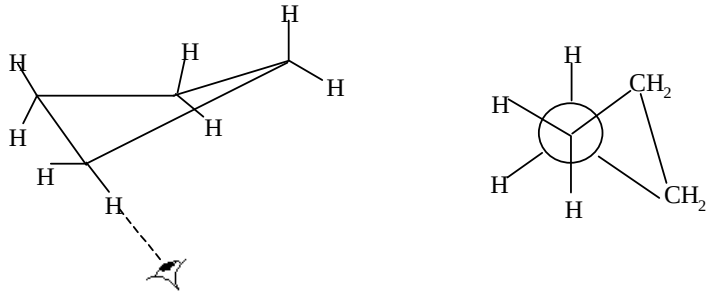
Cyclopropane's three carbon atoms are, coplanar, and rotation about its carbon-carbon bonds is impossible. Strong sp^3 -sp^3 s bonds are not possible for cyclopropane, because the 60° bond angles of the ring do not permit the orbitals to be properly aligned for effective overlap. The less effective overlap leads to "bent" bonds. The electron density in the carbon-carbon bonds of cyclopropane does not lie along the internuclear axis but is distributed along an arc between the two carbon atoms. The ring bonds of cyclopropane are weaker than other carbon-carbon σ bonds

Cyclopropane is relatively unstable because it has both ring strain from a shortening of the C-C-C bond angle (109.5° down to 60°), and torsional (Pitzer) strain due to eclipsing of the hydrogen atoms.

All adjacent pairs of bonds are eclipsed

f) Conformation of cylobutane

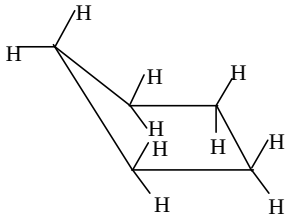
Cyclobutane has less angle strain than cyclopropane and can reduce the torsional strain that goes with a planar geometry by adopting the nonplanar "puckered" conformations. In cyclobutane there is butterfly effect because of the variation on bond angle at four corners due to conformational change.



The preferred 'butterfly' conformation of cyclobutane

g) Conformation of cyclopentane

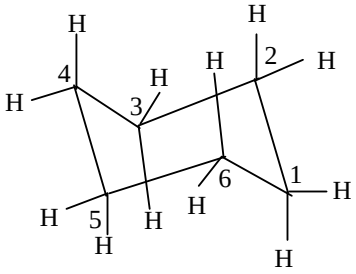
Angle strain in the planar conformation of cyclopentane is relatively small because the 108° angles of a regular pentagon are not much different from the normal 109.5° bond angles of sp^3 hybridized carbon. The torsional strain, however, is substantial, since five bonds are eclipsed on the top face of the ring, and another set of five are eclipsed on the bottom face. This torsional strain is relieved in nonplanar conformations. Cyclopentane is a flexible molecule with rapidly interchanging conformations, called the **envelope** and the **half-chair** are of similar energy. The most stable ('preferred conformation') of these is the 'envelope' in which torsional strain is minimised by having one carbon atom above (or below) the plane of the other four.



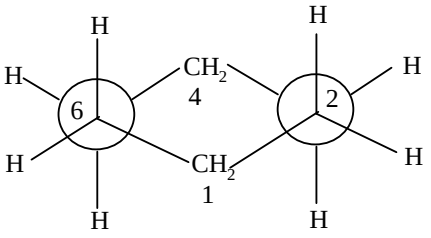
The preferred 'envelope' conformation of cyclopentane

h) Conformation of cyclohexane

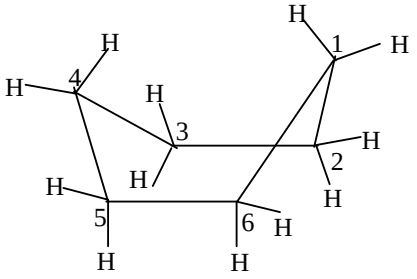
Two important conformations of cyclohexane are the semi-rigid chair form which is free of both ring strain and torsional strain and the flexible boat form, which, although free of ring strain, has both torsional strain and Vander-Vaals repulsion ('flagpole interaction') between H atoms on carbons 1 and 4.



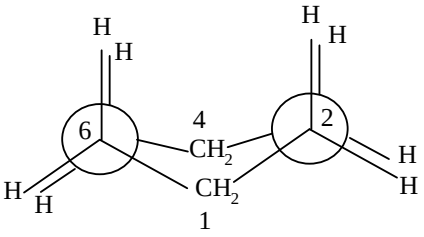
(I)



(III)

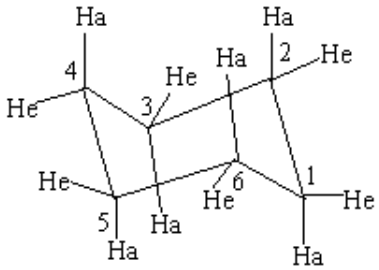


(II)

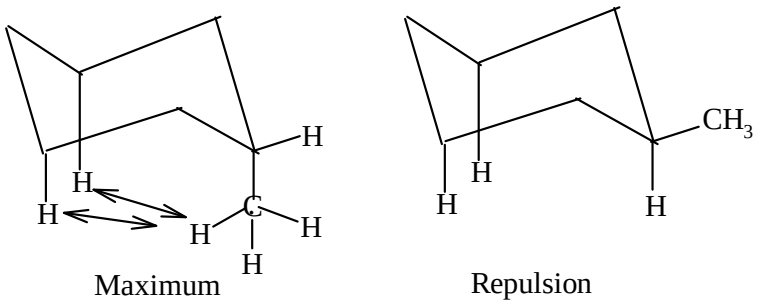


(IV)

In the chair form of cyc1ohexane, six hydrogen atoms, one on each carbon atom, lie in the ring plane and are called *equatorial hydrogen* represented by $\mathbf{H_e}$. The other six are at right angles to this plane and are called *axial hydrogen* represented by $\mathbf{H_a}$.



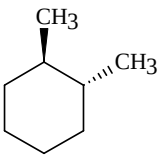
At normal temperatures the cyc1ohexane ring rapidly flips between *two* equivalent chair conformations via boat conformation and in the process the axial hydrogen become equatorial and vice versa.When a substituent such as a methyl group is present (Carbon 1) Vander Vaals repulsion between it and axial H atoms on carbons 3 and 5 ('steric crowding' or 'non-bonded interaction') is minimised if the substituent is in an equatorial position.

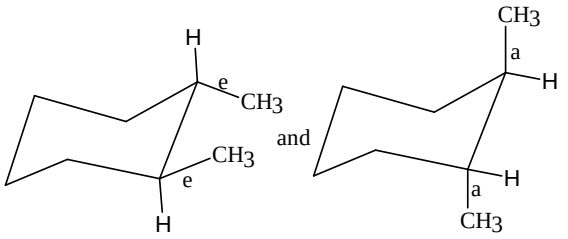


1,3-diaxial interaction in methyl cyclohexane (only relevent H atoms are shown)

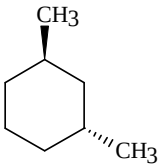
The following examples demonstrate the configuration structures of cyclohexane derivatives can be converted into conformation structures and illustrated how substituents occupies equatorial and axial positions with respect to configuration structure..

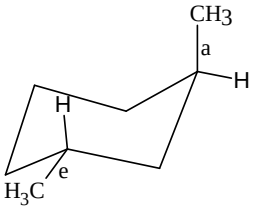
Configuration Structures Conformation Structures



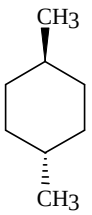


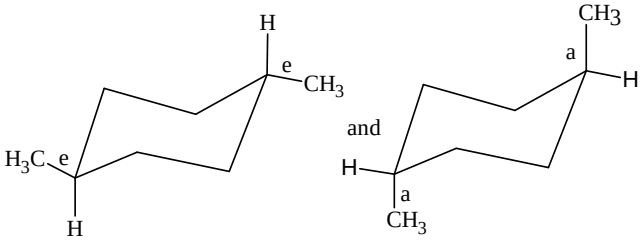
trans-1,2-Dimethylcyclohexane





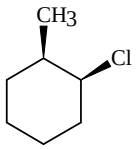
trans-1,3-Dimethylcyclohexane

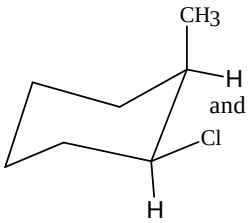


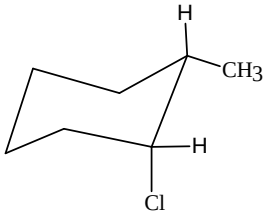


trans-1,4-Dimethylcyclohexane

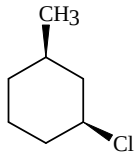
Configuration Structures Conformation Structures

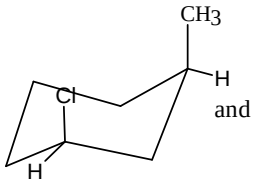


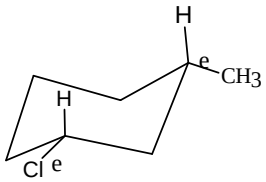




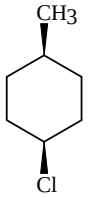
cis-1-chloro-2-methylcyclohexane

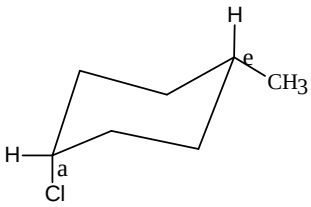






cis-1-chloro-3-methylcyclohexane



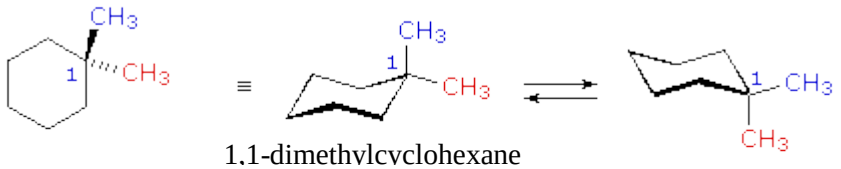


cis-1-chloro-4-methylcyclohexane

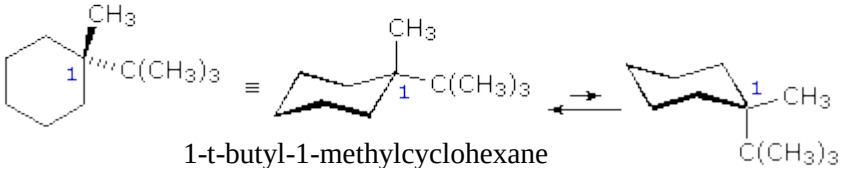
Conformations of di-substituted cyclohexanes are summarised in Table given below.

Equatorial (e) and axial (a) position of substituents in chair conformations of *cis* and *trans* disubstituted cyclohexanes

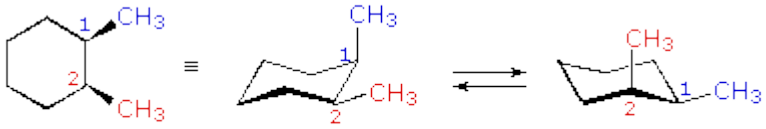
Isomer	Cis or trans	Position of Substituents
1,2-dimethylcyclohexane		
	cis	ea and ae
	trans	ee and aa
1, 3-dimethyl Cyclohexane		
	cis	ee and aa
	trans	ea and ae
1, 4-dimethyl Cyclohexane		
	cis	ea and ae
	trans	ee and aa



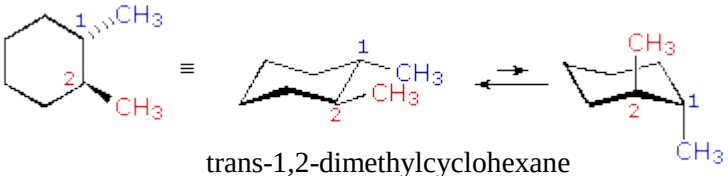
1,1-dimethylcyclohexane



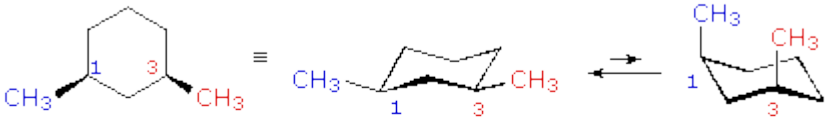
1-t-butyl-1-methylcyclohexane



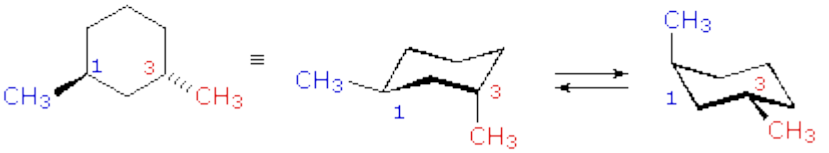
cis-1,2-dimethylcyclohexane



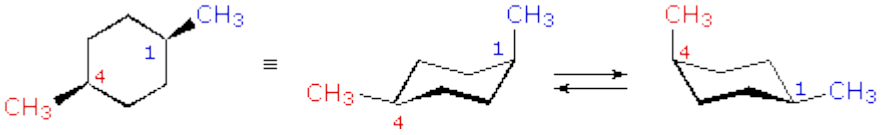
trans-1,2-dimethylcyclohexane



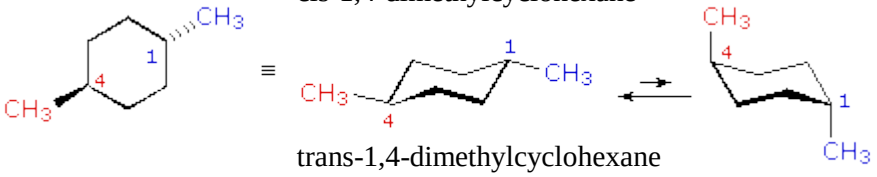
cis-1,3-dimethylcyclohexane



trans-1,3-dimethylcyclohexane



cis-1,4-dimethylcyclohexane



trans-1,4-dimethylcyclohexane

2.11 Conformations of Decalins

Decalins are the most important members of group of molecules called fused rings. The name, as it might suggest, applies to molecules which have two adjacent rings, which have two atoms in common. Decalins are two fused cyclohexane rings, and can occur in two isomers: cis and trans:

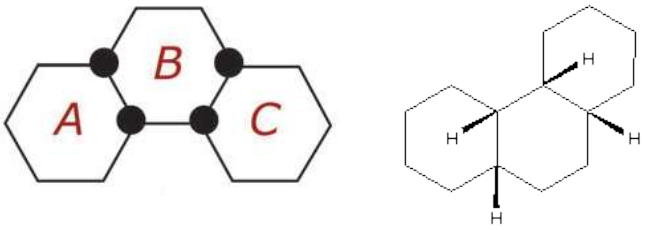
trans cis

The two isomeric forms get their names from the relative position of the two hydrogen atoms indicated in either case (i.e. they are trans, or on opposite sides, in the first case, and cis, or on the same side, in the second case.)

The cis isomer is fused by an axial and an equatorial bond, however, the trans isomer is fused by two equatorial bonds. According to the earlier discussion ofcyclohexane, we would expect that the trans isomer, with its two equatorial bonds would be the more stable of the two isomers. The trans isomer is conformationally rigid, that is, it cannot undergo ring-flipping, but the cis form (depending on its substituents) can undergo rapid ring-flipping. The trans form has a centre of symmetry, and is therefore optically inactive, whereas the cis form has no centre of symmetry in either of its two forms, and has non-superimposable mirror-images, so is optically active.

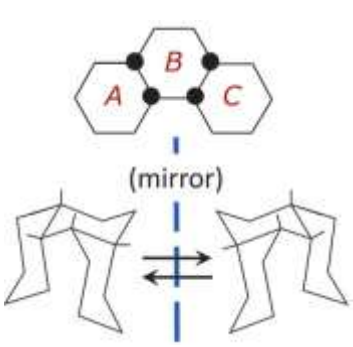
Determining relative stabilities of substituted decalins is more difficult than with cyclohexane

2.12 Conformations ofPerhydro Phenanthrenes

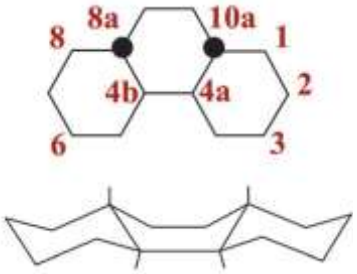


The conformation analysis of Fused tricyclic systems are done by considering two viewpoints, namely the relationship between two adjacent (fused) rings, and the steric relationship between the two non-adjacent (external) rings. Perhydrophenanthrene is an interesting model compound of great stereochemical richness. Four stereogenic centers are apparent (4a, 4b, 8a, 10a, i.e., the C-atoms involved in ring fusion) and the molecule occurs as ten stereoisomers (two meso-forms and four pairs of enantiomers). The fusion of rings A and B, and that of rings B and C, are described by the same cis-trans notation ship discussed above in the case of decalins. The relation between rings A and C is described by considering the relative position of the H-atoms at C(4a) and C(4b). The prefixes syn and anti are used

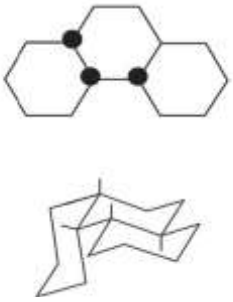
when these H-atoms are on the same or opposite side, respectively. The terms cisoid and transoid, respectively, are also allowed. The two meso-forms are the cis-syn-cis and trans-syn-trans-isomers, since a plane of symmetry is present. The four other forms are chiral, and only one enantiomer per pair being shown below.



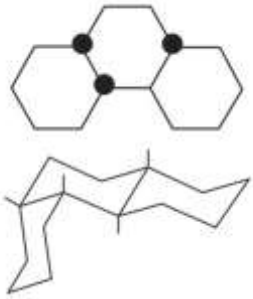
cis-syn-cis



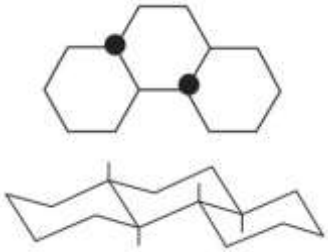
trans-syn-trans



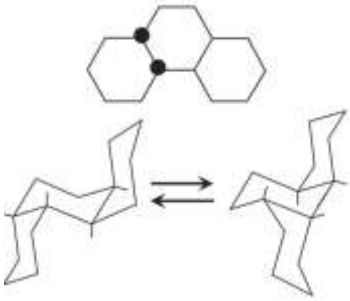
cis-syn-trans



cis-anti-trans



Trans-anti-trans



cis-anti-cis

The relative energy of perhydrophenanthrene stereoisomers is discussed by considering the preferred conformations and their number of equatorial and axial bonds at the C-atoms engaged in ring fusion. The lowest energy isomer is the *trans-anti-trans* form since it has four equatorial bonds. The higher energy (ca.12 kJ/mol) isomers are the *cis-syn-cis* and cis *anti-trans* form. Each has three equatorial and one axial bond). The two isomers *cis-syn-cis* and *cis-anti-cis* have two equatorial and two axial bonds while the isomer of highest energy isomer is the *trans-syn-trans* form in which the central ring is forced to a boat conformation.

The isomers of perhydrophenanthrene having no or just one cis-junction are conformationally rigid and two cis-junctions render the molecule flexible. As a result, the *cis-syn-cis* form is a mixture of two enantiomeric conformers, while the *cis-anti-cis* form undergoes isomerization between two diastereoisomeric conformers.

2.13 Summary of the unit

The concept of conformational isomerism was created by Derek H. R. Barton and Odd Hassel. As defined by Barton, the word conformation is used to denote differing strainless arrangements in space of a set of bonded atoms. This definition applies to free rotation

around single bonds. The IUPAC (International Union of Pure and Applied Chemistry) has accepted the following definition for conformers: The spatial arrangement of the atoms affording distinction between stereoisomers which can be interconverted by rotations about single bonds. The energy difference between rotational isomers, rotamers, are relatively small, i.e., on the order of a few to several kJ/mol. For a ethane molecule (simplest one) an infinite number of rotational isomers are conceivable by rotation around single bonds. But two are remarkable, namely the eclipsed and staggered ones, where the torsion angle has a value of 0^0 and 60^0, respectively. The molecule of n-butane provides a more complex example. Despite the fact that this molecule has three strainlessly rotating C - C bonds, only the central C - C bond is considered. The molecule presents three eclipsed and three staggered conformations. The staggered conformers are the low-energy ones. Cyclic molecules will obviously tend to adopt the conformation(s) minimizing all strain contributions. In these energy minima, the remaining strain is optimally distributed between the various contributions (bond-length and bond-angle deviations, Pitzer strain, and other nonbonded interactions). Cyclic systems usually exhibit several possible conformations whose interconversion can occur by two distinct processes, i.e., cycle reversal and pseudorotation. Ring reversal (sometimes inadequately called inversion) involves a relatively high-energy transition state (some kJ/mol) occurring with modification of bond angles and all other strains. Pseudorotation is a lower-energy process which does not involve bond-angle variations but only changes in Pitzer strain and other nonbonded interactions. Conformers which can be transformed by pseudorotation are called flexible, those which can only undergo reversal are called rigid.

2.14 Key Words

Conformation; Projection formula; Newman Projections; Staggered conformation; Eclipsed conformation; Hydrogen bonding; Anomeric effect; cycloalkanes; decalins; PerhydroPhenanthrenes.

2.15 References for study

1) Stereochemistry of Organic Compounds: Principles and Applications**;** D. Narsipuri, *New Age International*; **1994**.

2) Stereochemistry; Devid G. Morris, *Royal Society of Chemistry*, **2001**.

3) Stereochemistry Conformation and Mechanism; P. S. Kalsi, *New Age International*, **2005**.

4) Stereochemistry of Organic Compounds; Ernest Ludwig Eliel, Samuel H. Wilen. *John Wiley & Sons*, **2008**.

5) Dynamic Stereochemistry of Chiral Compounds; Christian Wolf, *Royal Society of Chemistry*, **2013**.

6) Organic Mechanisms: Reactions, Stereochemistry and Synthesis; Reinhard Bruckner, *Springer*, **2010.**

2.16 Questions for self understanding

1) Define the term conformation.

2) Draw a Newman projection of the most stable conformation of 2-methylpropane

3) Provide a representation of the gauche conformer of butane

4) View a butane molecule along the C2-C3 bond and provide a Newman projection of the lowest energy conformer

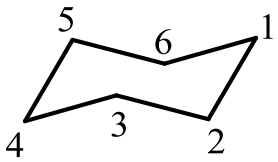
5) Draw the most stable conformation of trans-1,2-dimethylcyclohexane.

6) Draw the most stable conformation of cis-1,2-dimethylcyclohexane.

7) Using both a wedge-and-dash representation and a Newman projection, draw the eclipsed conformation of ethane

8) Draw a chair conformation of a cyclohexane ring with bromine axial on the ring.

9) Consider the chair conformation of the cyclohexane ring shown below, and answer the following questions. (Note: "Up" and "down" are relative to how the structure is drawn.)



a) Is a methyl group that is "up" at C5 axial or equatorial?

b) Is a tert-butyl group that is "down" at C1 more or less stable than one that is "down" at C4?

c) Which is more stable, a methyl group that is "down" at C3 or one that is "down" at C6?

10) Draw both chair conformations of cis-1,4-dimethylcyclohexane. Determine which chair conformation is most stable.

11) Draw the two conformations of cis-1-ethyl-2-methylcyclohexane. Determine which is more stable

12) Write the structural formula for the more stable conformation of each of the following compounds.

a) trans-1-Fluoro-3-methylcyclohexane

b) cis-1-Iodo-4-methylcyclohexane

c) cis-1-tert-Butyl-4-methylcyclohexane

d) cis-1,3,5-Trimethylcyclohexane

13) Write a note on

a) *Conformation of cylopropane*

b) *Conformation of cylobutane*

c) *Conformation of cyclopentane*

d) *Conformation of cyclohexane*

14) Explain the effect of hydrogen bonding on conformation?

15) What is anomeric effect?

Unit - 3

Structure

3.0 Objectives of the unit

After studying this unit you are able to

- Explain and identify chiral molecule
- Interpret and draw the three dimensional representation of organic compounds
- Identify enantiomers
- Draw the Flying-Wedge and Fischer Projections for given chiral molecule
- Write the R and S configuration of given chiral molecule
- Distinguish symmetrical and asymmetrical molecule

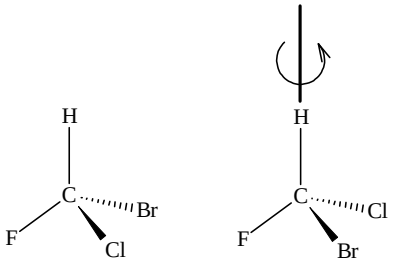
3.1 Introduction

As we study in first and second units isomers are molecules that have the same molecular formula but have a different arrangement of atoms in space. This definition excludes any different arrangements which are simply due to the molecule rotating as a whole or rotating about particular bonds. In some cases molecules have the same constitution, but different disposition of groups in space i.e, the atoms are connected to each other in the same way but only differ with respect to relative orientation in three dimensional space. Stereoisomers are molecules that have the same molecular formula and the same connectivity of atoms, but differ only in the three-dimensional arrangement of those atoms in space. Two general forms of stereoisomerism are geometric isomers which we studied in first unit and optical isomers. Optical isomerism is an example of stereo-isomerism and occurs when substances have the same molecular and structural formulae, but one cannot be superimposed on the other. Simply, they are mirror images of each other. Any tetrahedral carbon atom that has four different substituents is a chiral center and there are two different ways to place these four different substituents in a tetrahedral arrangement. Looking for four different substituents on a single carbon atom is one of the easiest ways to identify a chiral centre. Chiral center is a special type of situation called a stereocenter. A stereocenter is any atom in a molecule for which exchanging two groups creates a different stereoisomer. All chiral centers are stereocenters, however, not all stereocenters are chiral centers. As a consequence of simple geometry, there are only two different ways to place four substituents around a chiral center, and resulting two different molecules are mirror images of each other. They are non-superimposable mirror images of each other.

3.2 Chirality

In 1874 Jacobus Van't Hoff and Joseph Le Bel recognized that a compound that contains a single tetrahedral carbon atom with four different substituents could exist in two forms that were mirror images of each other.

For example, Consider the CHFClBr molecule, for example, which contains four different substituent's on a tetrahedral carbon atom. If we rotate the molecule on the right by 180 around the C — H bond we get the structure as shown below.

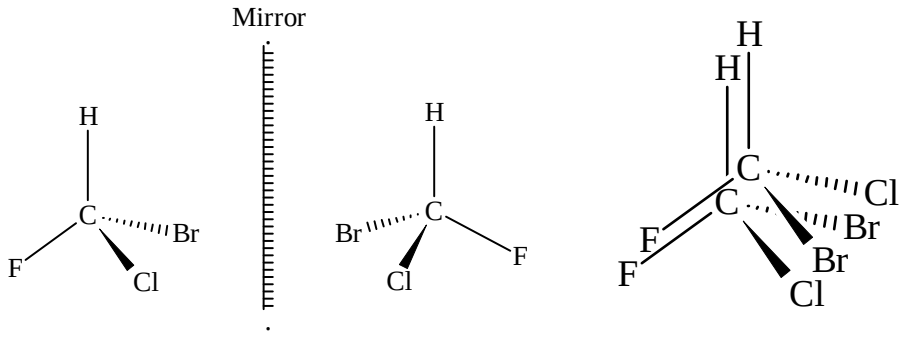


These structures are different because they cannot be superimposed on each other, as shown in the figure below

3.3 Enantiomers

Carbon atom that has four non-identical substituents around it is called chiral centre and molecule which has at least one chiral centre is called chiral molecule. All chiral molecules have nonsuperimposable mirror images. These supermiposable mirrorimages are called enentiomers. Therefore *pair of molecules which are nonsuperimposable mirror images to each other are called eantiomers*. And the phenomenon is described as enantiomerism. Molecules which have supermiposable on the mirror image are not chiral and they called achiral molecule. Many molecules are achiral, but many are chiral, especially complex molecules such as are found in biological systems.

The figure below shows one possible arrangement of four different substituents and the mirror image of its structure. By convention, solid lines are used to represent bonds that lie in the plane of the paper. Wedges are used for bonds that come out of the plane of the paper toward the viewer; dashed lines describe bonds that go behind the paper.



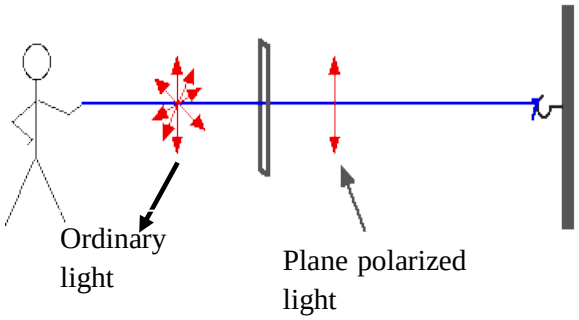
Thus CHFClBr is therefore a chiral molecule that exists in the form of a pair of stereoisomers that are mirror images of each other. *As a rule, any tetrahedral atom that carries four different substituents is a stereocenter, or a stereogenic atom.* However, the only criterion for chirality is the nonsuperimposable nature of the object.

Enantiomers resemble each other in their physical properties except that they rotate the plane-polarized light in opposite directions and a chemical property except another chiral molecule is involved.

3.4 Optical activity

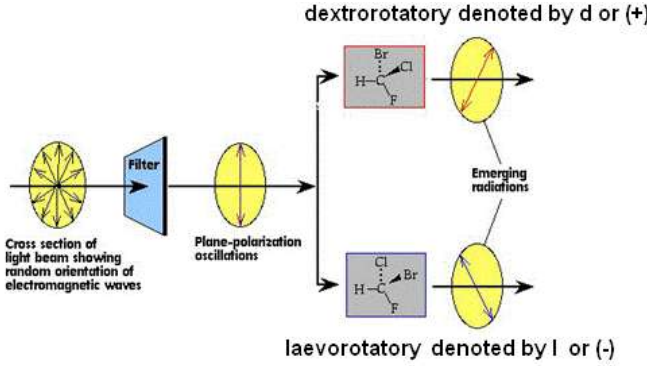
The ability of a substance to rotate plane-polarized light is called *optical activity***.** When an optically active compound is placed in the path of plane polarized light, it rotates the plane polarized light to either right or left directions

The ordinary light that we observe is not plane polarized because it travels in all possible directions. Suppose if we pass this light through a polarizer, the polarizer make the light to travels only in one direction and it called plane polarized.



If the plane polarized light is rotated in a clockwise direction when viewed through a polarimeter, then the optically active compound is called *dextrorotatory* and denoted by (+) or (*d*) { **do not confuse with D**}

If the plane polarized light is rotated in a counter-clockwise direction when viewed through a polarimeter, then the optically active compound is called *levorotatory* and denoted by (-) or (*l*) {**do not confuse with** L}



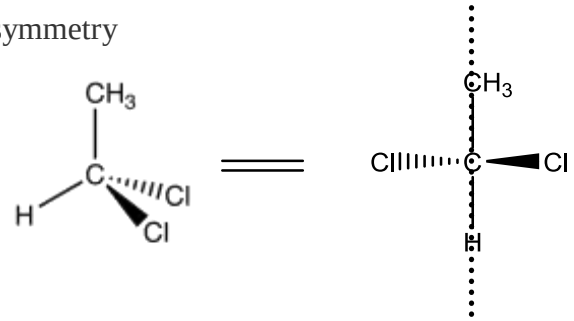
3.5 Condition for optical activity

Chiral molecules are obtical active i.e., compounds with one chiral centre will show optical activity and compound without chiral centre donot normally show optical activity. However having chirality is not the only criteria for a molecule to be optical active. Compounds with more than one chiral centre may or may not show optical activity depending on whether or not they are non-super imposable on their mirror image. Therefore if molecule has more than one stereogenic center, it may be either chiral or achiral. The presence of chirality in such compounds is determined by use of *symmetry elements***.** If the molecule or object has either a plane of symmetry or a center of symmetry then is an achiral molecule, even though it has more than one stereogenic centers.

a) Plane of symmetry

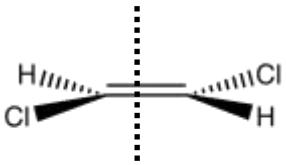
A plane of symmetry is an imaginary plane that bisects a molecule into halves that are mirror images of each other. If reflection through a plane leaves an identical copy of the original molecule it has a plane of symmetry

Eg. 1:



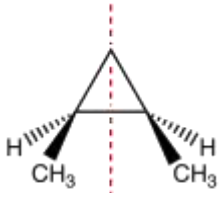
In the above compound a vertical plane that bisects the methyl group, the carbon atom, and the hydrogen atom, the molecule into two halves that are mirror images of each other. Therefore, it is a plane of symmetry.

Eg. 2



In the above compound the horizontal plane that bisects all six atoms in the molecule into two halves that are mirror images of each other. Therefore, it is a plane of symmetry.

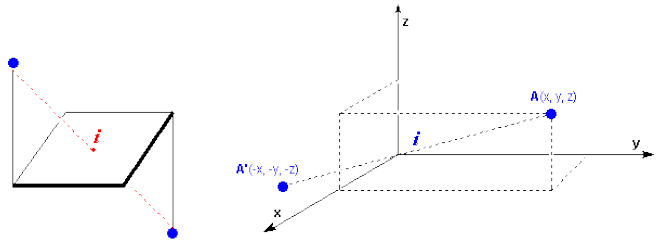
Eg. 3



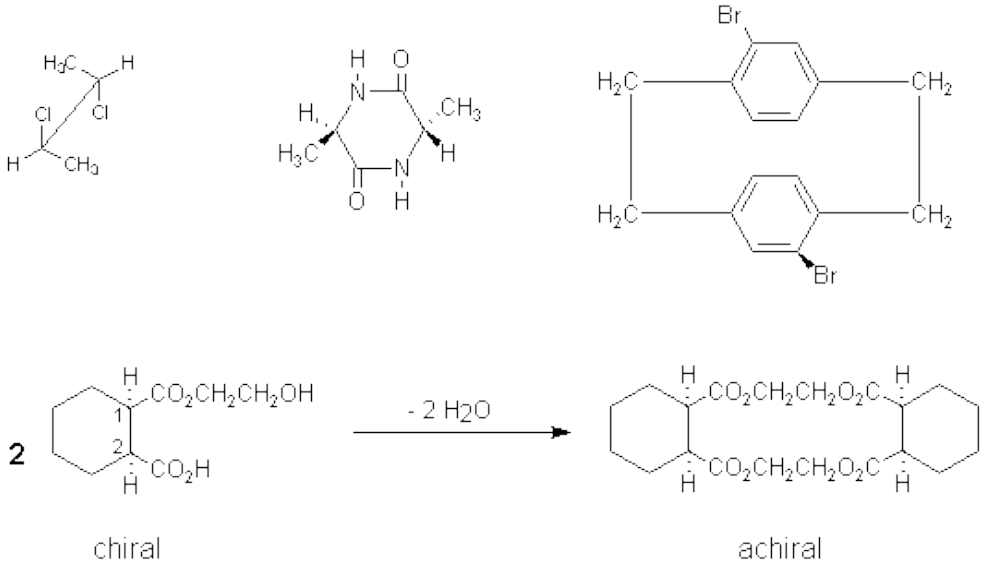
In above compound, the vertical plane that passes through the plane of the cyclopropane ring bisects the molecule into two halves that are mirror images of each other. Therefore, it is a plane of symmetry.

b) Centre of symmetry

This is a point such that any line drawn through it meets the same atom at equal distances in opposite directions. A molecule has a center of symmetry when for any atom in the molecule an identical atom can be found when it moves in a straight through this center an equal distance on the other side. All homo-nuclear diatomic molecules possess the centre of symmetry.



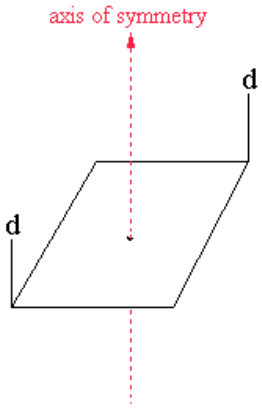
Examples:



chiral achiral

c) Axis of Symmetry

It is also called Alternating axis symmetry. Symmetry axis C_n, (or n-fold axis) is an axis which rotates the object (molecule) around by $360^{o}/n$, such that the new position of an object is superimposable with the original one.



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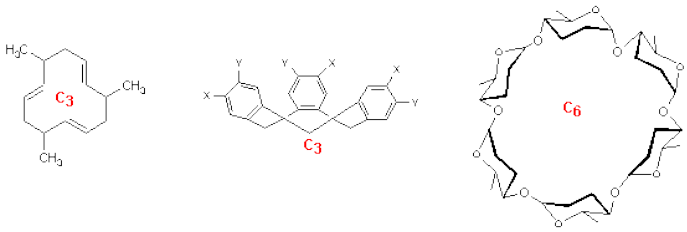
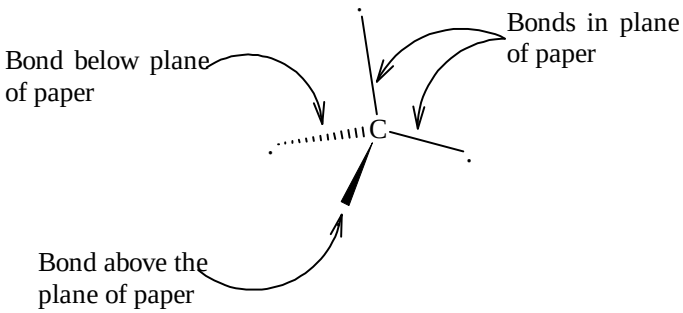


3.6 Asymmetric molecules

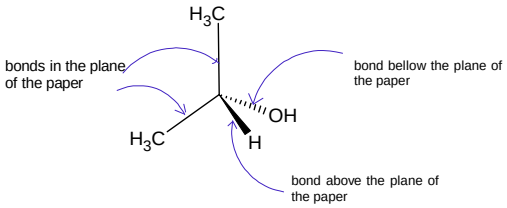
A term asymmetric denotes the absence of any symmetry. An object or molecule is asymmetric if it has no elements of symmetry i.e., Plane of symmetry, centre of symmetry and axis symmetry. All asymmetric molecules are chiral, however chiral molecule may not be necessarily an asymmetric.

3.7 Flying-Wedge or Wedge-Dash projection

The Flying-Wedge projection is the most common three-dimensional representation of a three dimensional molecule on a two dimensional surface (paper). This kind of representation is usually done for molecules containing chiral centre. In this representation, the ordinary lines represent bonds in the plane of the paper. A solid Wedge ( ) represents a bond above the plane of the paper and a dashed wedge ( ) or a broken line ( ) represents a bond below the plane of the paper.



The Flying-Wedge projection formula of (R)- Lactic acid , for example, can be shown as follows

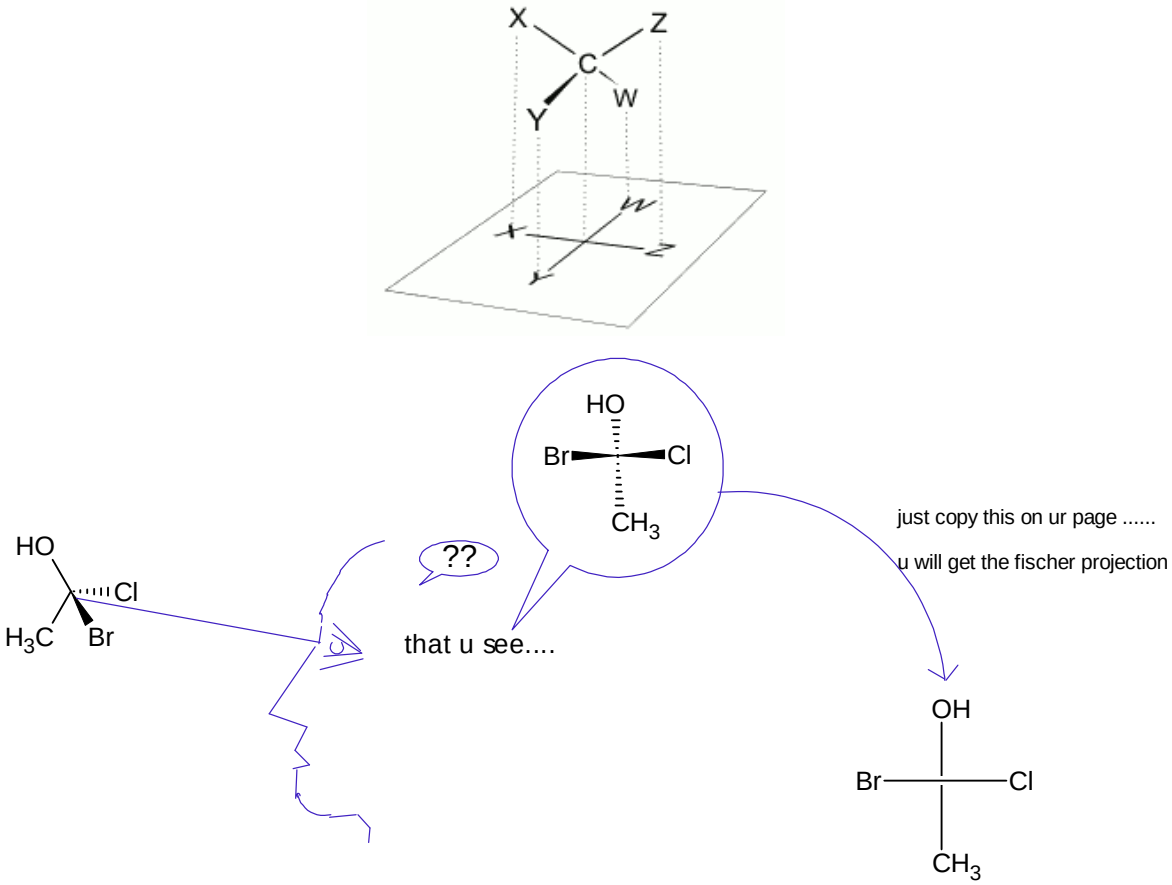


(R) - Lactic acid

3.8 Fischer Projections

The wedge and dash representations of stereochemistry can often become cumbersome, especially for large molecules which contain a number of stereocenters. An alternative way to represent stereochemistry is the Fischer Projection

The Fischer projection was, devised by Hermann Emil Fischer in 1891, it is a two dimensional representation of a three-dimensional organic molecule by projection. Fischer projections were originally proposed for the depiction of carbohydrates and used by chemists, particularly in organic chemistry and biochemistry. In a Fischer Projection, each place where the horizontal and vertical lines cross represents a carbon. The vertical lines are actually oriented away from you (similar to *dashes* in the Wedge-Dash Notation) and the horizontal lines are oriented toward you (similar to *wedges* in the Wedge-Dash Notation).



3.9 Manipulations of Fischer Projections

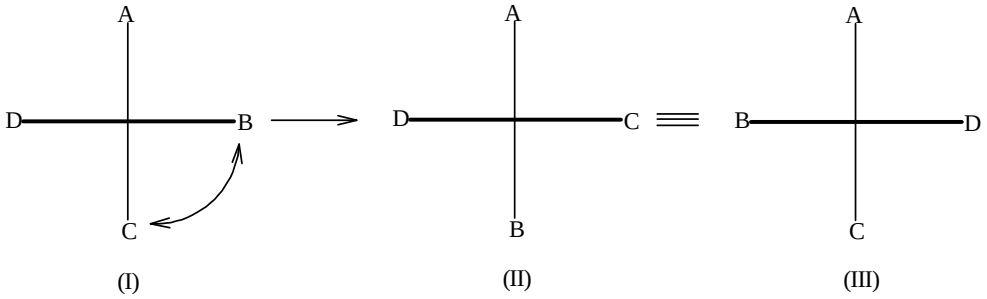
When working with Fischer Projections, keep in mind the following rules:

1. Because the "up" and "down" aspects of the bonds don't change, a Fischer projection may be rotated by 180 degrees without changing its meaning.

2. A Fischer projection may not be rotated by 90 degrees. Such a rotation typically changes the configuration to the enantiomer.

3. To find the enantiomer of a molecule drawn as a Fischer projection, simply exchange the right and left horizontal bonds.

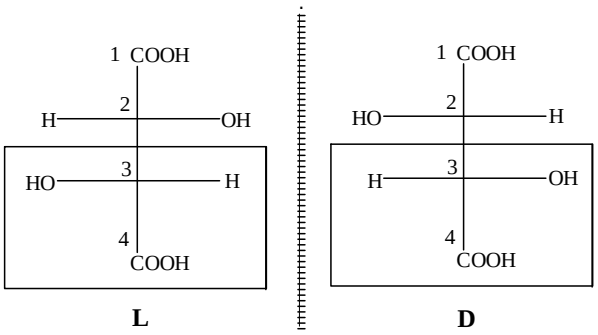
4. To determine whether the molecule in Fischer projection is a meso compound, draw a horizontal line through the center of the molecule and determine whether the molecule is symmetric about that line.



Interconversion of Fischer Projection formulae. Projections I and III are mirror images and represent an enantiomeric pair of molecules

3.10 Nomenclature of Enantiomers: the R-S System

In 1951 dextrorotatory (+)-2,3-dihydroxybutanedioic acid [(+)-tartaric acid] was shown by X-ray diffraction to have an absolute (i.e. actual) configuration with the 3-hydroxyl group on the left as seen in the Fischer projection



This is described as the **L-configuration** and the mirror image (with the OH group on the right) is the **D-configuration**. Subsequently, the absolute configuration of other chiral molecules has been established by chemical interconversions using reactions of known stereochemistry. The arrangement of atoms in an optically active molecule, based on chemical interconversion, is a *relative configuration.*

The absolute configuration at a chiral center in a molecule is a time-independent and unambiguous symbolic description of the spatial arrangement of ligands around it. Therefore tt is required a way to name the individual steroisomers of a compound so that one can easily realize which steroisomer is talking about. i.e, a system of nomenclature that indicates the configutration of atoms or groups about the asymmetric carbon is needed. Generally R and S letters are used to indicate the configuration of an asymmetric carbon. Any pair of

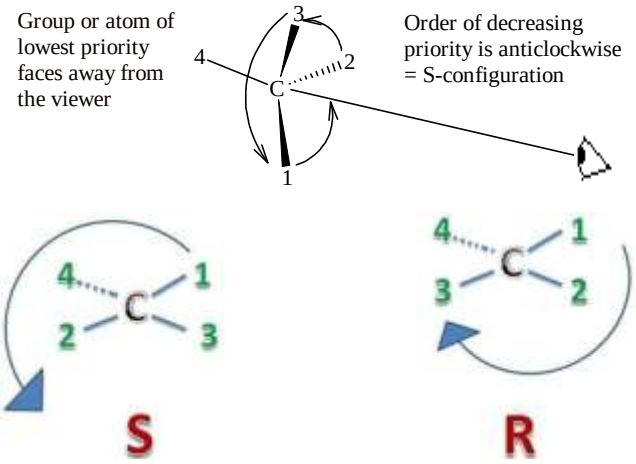
enantiomers with one asymmetric carbon, if one will have R configuration then other must have S configuration.

The steps are

1. Assign an order of priority to each ligand on the chiral carbon atom by the Sequence Rules.

2. Orient the drawing or projection of the molecule so that the ligand of lowest priority faces away from the viewer. When using Fischer projections this means manipulating the formula so that the ligand of lowest priority is at the top or bottom of the projection.

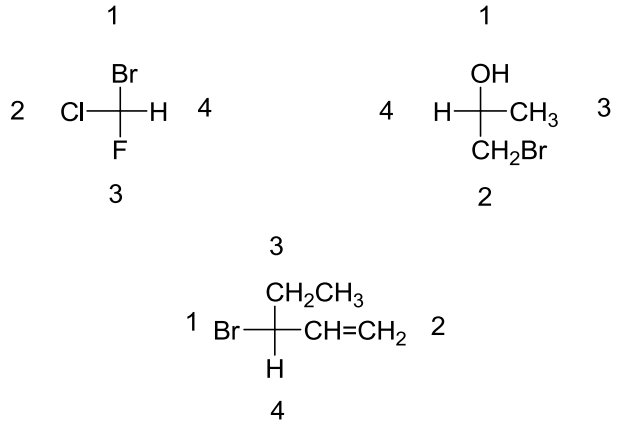
3. Observe the order of decreasing priority of the other three atom or group : if this is clockwise, the configuration is R (rectus); if it is antic1ockwise the configuration is S (sinister).



3.11 The Sequence Rules (Cahn-Ingold-Prelog Rules)

1. Atoms directly attached to the chiral carbon atom are arranged in order of *decreasing atomic number* (lower atomic number, lower priority)

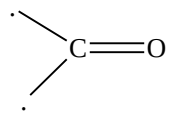
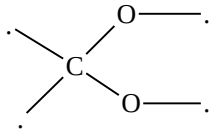
For example

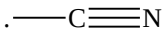
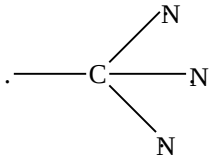


2. Isotopes when present are arranged in decreasing *mass number*.

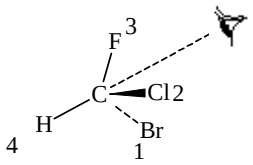
3. For atom or group attached by the same kind of atom (e.g. methyl and ethyl groups are both attached by a carbon atom), the next atoms are considered and the process continued until a decision can be made. Thus ethyl, with C-C has priority over methyl with C-H.

4. Doubly or triply bonded atoms are treated as though both atoms were duplicated or triplicated.

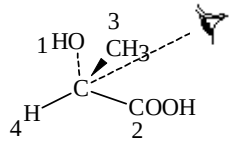
For example  Is regarded as 

 Is regarded as 

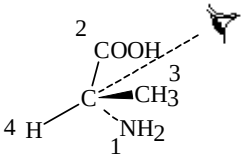
Examples



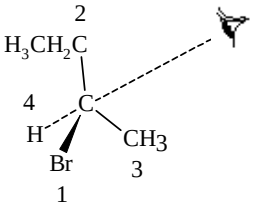
(*R*)-bromo(chloro)fluoromethane
R-Configuration



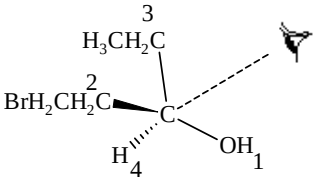
(2*R*)-2-hydroxypropanoic acid
R-Configuration



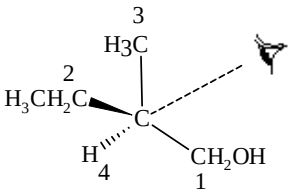
(2*S*)-2-aminopropanoic acid
S-Configuration



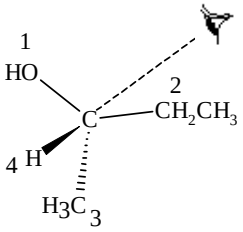
(2*R*)-2-bromobutane
R-Configuration



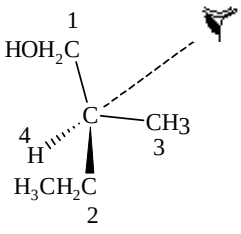
(3*R*)-1-bromopentan-3-ol
R-Configuration



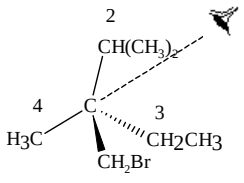
(2*R*)-2-methylbutan-1-ol
R-Configuration



(2S)-butan-2-ol
S-Configuration

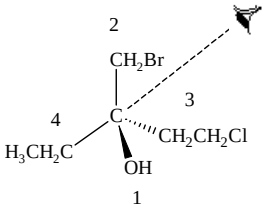


(2*S*)-2-methylbutan-1-ol
S-Configuration



(3*R*)-3-(bromomethyl)-2,3-dimethylpentane

R-Configuration

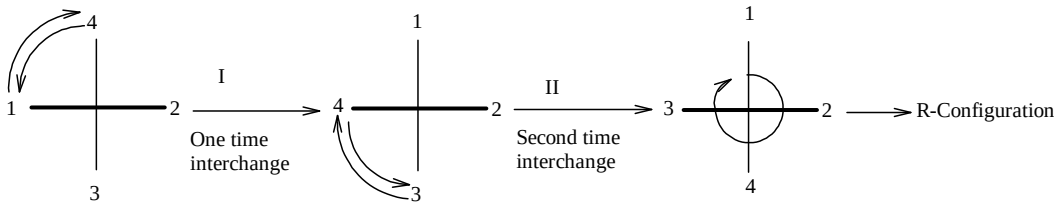


(3*R*)-3-(bromomethyl)-1-chloropentan-3-ol

R-Configuration

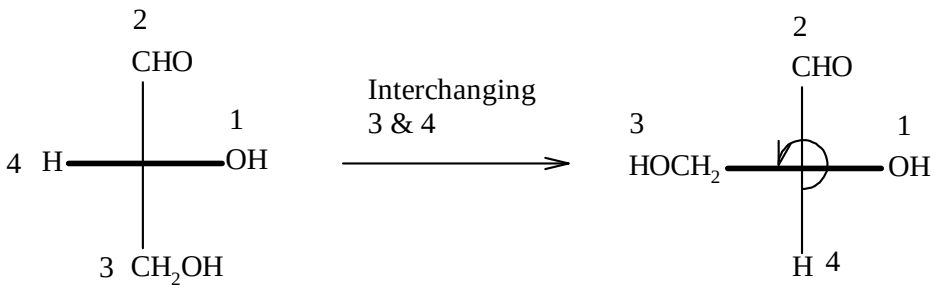
Similarly, in another case, when the compound is written in the Fischer projection, the configuration can easily be determined without constructing the model. If the lowest priority group is either at the top or the left or right side of the Fischer structure, we should have to bring the lowest ranking group, at the bottom by simply interchange it twice with the other groups respectively. Bearing in mind that in so doing, one is inverting the configuration, hence if add no of interchange, the opposite configuration should be considered and in case of even number of interchange same configuration should be considered. For example see the following illustration.

The lower priority substitution present at the top of the Fischer structure. Hence it should bring at the bottom and then if the other three groups are in descending order are said to be clockwise (R), for example, the order of priority in the given example is as follows.



Order of decreasing priority is clockwise = R-Configuration

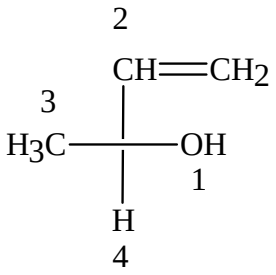
(Even number of interchange, to maintain the configuration)

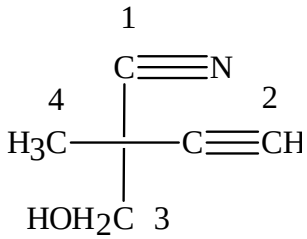


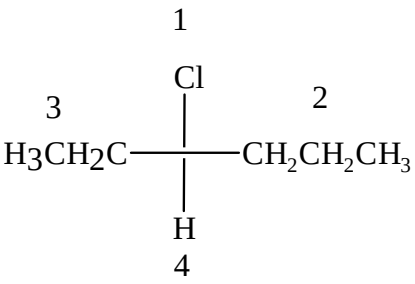
(R)-Glyceraldehyde

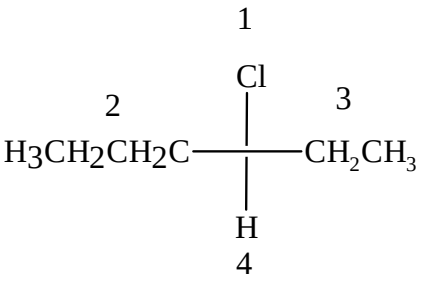
(S)-Glyceraldehyde

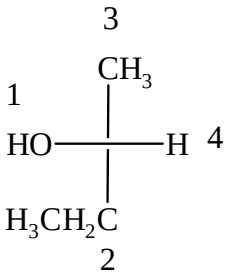
Worked Example: Solve the following problems

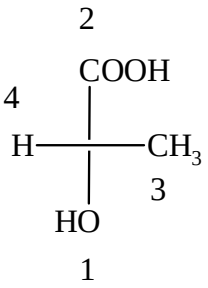


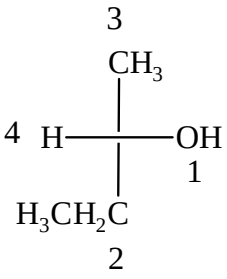


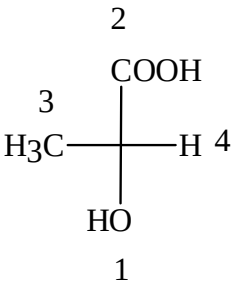








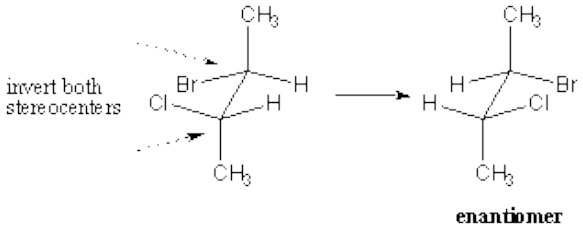




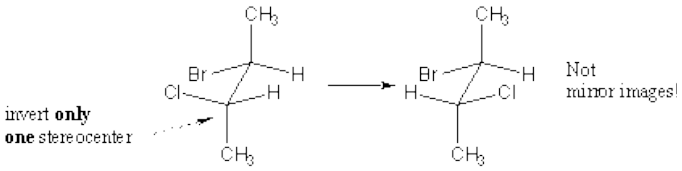
3.12 Diastereomers [Diastereoisomers].

So for we have deal with the compounds those contain only a single stereogenic center. For these compounds, we can produce the enantiomer by changing the configuration at that stereocenter. i.e., the enantiomers differ only in their spatial arrangements at the stereocenter. Suppose what happens if we have molecules with more than one stereo center?

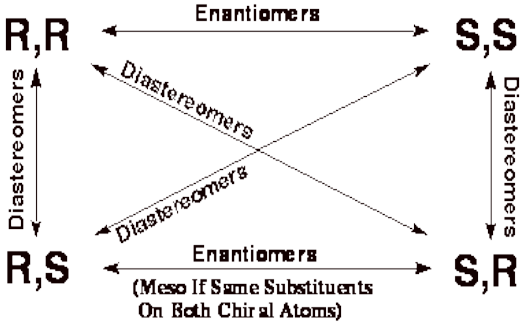
The mirror image of such a molecule has all its stereocenters inverted. Hence the enantiomer of such molecule has precisely the opposite configuration at every stereo center. i.e., every (R) configuration becomes (S), and vice versa.

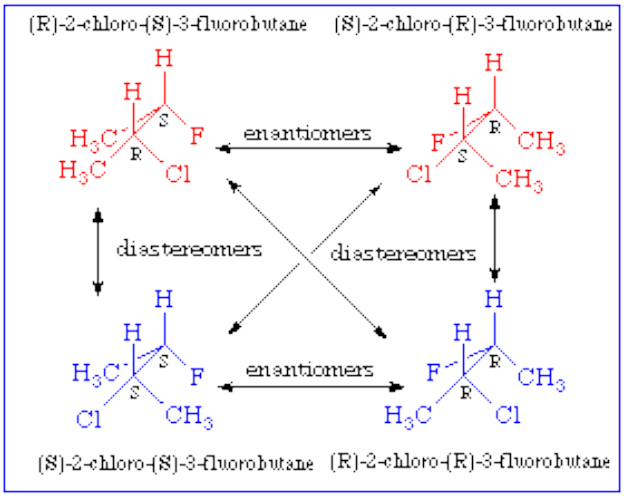


However, interesting case occurs when only *one* of the stereocenters is inverted. Stereoisomers that differ at some stereocenters but not at others are not mirror images, so they are not enantiomers.



They are called diastereomers. *Hence a diastereomer is simply any stereoisomer that is not an enantiomer*. Technically,*cis-trans* isomers are diastereomers. However, typically the term is reserved for stereoisomers that differ at some but not all stereocenters.





3.13 Racemic mixtures

A racemic mixture (or racemate) is one that has equal amounts of left and right-handed enantiomers of a chiral molecule.

A solution in which both enantiomers of a compound are present in equal amounts is called a racemic mixture, or racemate.

Racemic mixtures can be symbolized by a (d/l)- or (±)- prefix in front of the substance's name. Since enantiomers have equal and opposite specific rotations, a racemic mixture exhibits no optical activity. Therefore it is impossible to tell a racemic mixture apart from an achiral substance using polarimetry alone. It would be incorrect to say that a racemic mixture is achiral. Chirality is a property of individual molecules. Optical activity is a property of solutions. A racemic mixture consists of chiral molecules, but it has no net optical activity.

The process by which a racemic mixture is formed from chiral materials is called racemization. One way to do this is to mix equal amounts of enantiomeric substances. Racemic mixtures are often formed when achiral substances are converted into chiral ones. This is due to the fact that chirality can only be distinguished in a chiral environment. An achiral substance in an achiral environment has no preference to form one enantiomer over another.

3.14 Resolution of Racemates

The separation of enantiomers poses a special problem for chemists. Enantiomers have the same boiling points, melting points, solubilities, etc., so many of the techniques used to separate other compounds don't work on racemic mixtures. Racemic mixtures can be separated, or resolved, into their pure enantiomers by three methods.

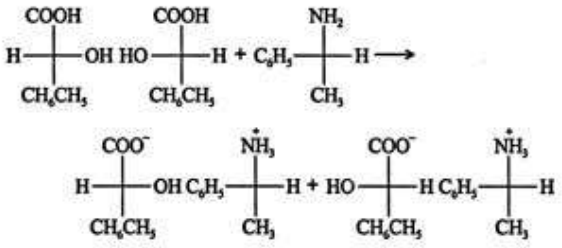
The first method is to mechanically separate the crystals in such a mixture based on differences in their shapes. This was the method first used by Pasteur, and it is mainly of historical interest.

The second resolution method employs enzymes. *Enzymes* are stereospecific chiral protein molecules that act as catalysts. Because of their chirality, these molecules react with only one enantiomer in a racemic mixture. The enantiomer that momentarily bonds to an enzyme undergoes reaction, while the enantiomer that does not bond remains unchanged. The unreacted enantiomer can then be removed from the reaction mix by ordinary separation methods, such as distillation or recrystallization.

The third method involves converting the enantiomers of a racemic mixture into diastereomers and then resolving that mixture with ordinary separation techniques. The

separated diastereomers are then treated with appropriate reagents to regenerate the original enantiomers. The one way to solve this problem is to separatee nantiomers in a chiral environment, where they interact differently. i.e.,chiral resolving agent. This technique relies on the fact that while enantiomers have identical physical properties, diastereomers generally have different properties.

For example, suppose we wanted to separate the enantiomers of 2-hydroxylpropionic acid. we need to add the resolving agent enantiomerically pure amount of (R)-2-phenyl-ethylamine. The two enantiomers interact with (R)-2-phenyl-ethylamine to form two distinct salt species that are diastereomers of each other. The diastereomers can then be crystallized separately.



In this example, the diastereomer salts are separated by recrystallization, and the original acids are regenerated by the addition of a hydrochloric acid solution

Another technique is to use chiral chromatography. In this process, the racemate is run through a column that is filled with a chiral substance. The enantiomers will interact differently with the substance and will then elute (or filter through the substance) at different rates. These techniques are also applied to mixtures of enantiomers beside racemic mixtures, for example to purify a species from small amounts of its enantiomer.

3.15 Summary of the unit

A molecule or object which is not identical to (i.e., non-superimposable upon) its mirror image molecule or object is said to be chiral. This means it resembles a human hand in that the left and right hands are not superimposabile but can be readily distinguished. A molecule or any object is said to be achiral if it is identical to (superimposable upon) its mirror image molecule or object. Many molecules are achiral, but many are chiral, especially complex molecules such as are found in biological systems.

2-butanol is a chiral molecule and therefore has two enantiomers, the very similar molecule 2-propanol is achiral and does not exist as an enantiomeric pair. Many simple molecules are of this kind. One of the simple ways to distinguish thw chiral and achiral molecule is to use the concept of a stereogenic center. If a molecule has a single stereogenic center it will

necessarily be chiral. The most common kind of stereogenic center is a carbon which has four different atoms or groups directly attached to it. We can see that the central carbon of 2-butanol is a stereogenic center, having H,OH,methyl, and ethyl groups attached. Since it has just a single stereogenic center, it must be chiral. On the other hand, 2-propanol has no stereogenic center and is achiral. The corresponding carbon atom of 2-propanol has an OH, H, and two methyl groups are attached. The second method which is especially useful when there is more than one stereogenic center is the use of symmetry elements. If the molecule or object has either a plane of symmetry or a center of symmetry it is achiral. The plane of symmetry is relatively easy to find and is the most common one to look for, but one other element of symmetry also guarantees an achiral molecule, and that is the center of symmetry.

3.16 Key words

Chirality; Enantiomers; Optical activity; Plane of symmetry; Centre of symmetry; Axis of Symmetry; Asymmetric molecules; Wedge-Dash projection; Fischer Projections; Diastereomers; Racemic mixture; Resolution.

3.17 References for further study

1) Stereochemistry of Organic Compounds: Principles and Applications**;** D. Narsipuri, *New Age International*; **1994**.

2) Stereochemistry; Devid G. Morris, *Royal Society of Chemistry*, **2001**.

3) Stereochemistry Conformation and Mechanism; P. S. Kalsi, *New Age International*, **2005**.

4) Stereochemistry of Organic Compounds; Ernest Ludwig Eliel, Samuel H. Wilen. *John Wiley & Sons*, **2008**.

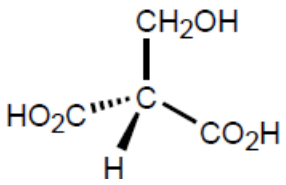
5) Dynamic Stereochemistry of Chiral Compounds; Christian Wolf, *Royal Society of Chemistry*, **2013**.

6) Organic Mechanisms: Reactions, Stereochemistry and Synthesis; Reinhard Bruckner, *Springer*, **2010.**

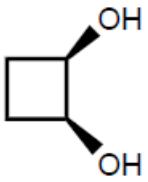
3.18 Questions for self understanding

1) What is chirality?

2) Is the molecule shown below chiral or achiral?



3) Is the molecule shown below chiral or achiral?

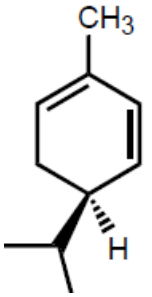


4) Draw the structure of (2*R*,3*S*)-2,3-dichloropentane. Take particular care to indicate three dimensional stereochemical details properly.

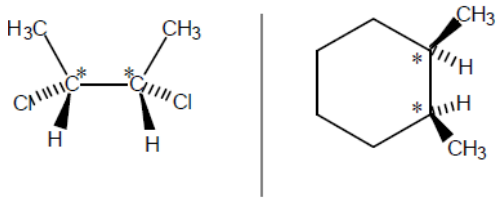
5) Draw the structure of (*S*)-1-bromo-1-chloropropane. Take particular care to indicate three dimensional stereochemical details properly.

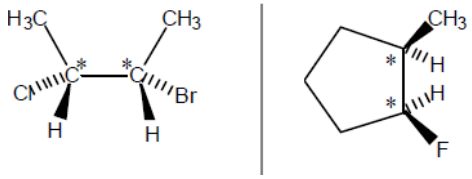
6) Draw the structure of a meso form of 1,3-dichlorocyclopentane. Take particular care to indicate three-dimensional stereochemical detail properly.

7) How many asymmetric carbons are present in the compound below?

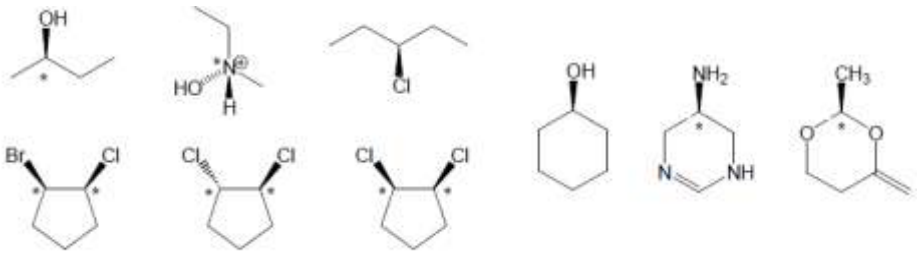


8) Draw the mirror image of each molecule mentioned below and identify the structures that are not chiral and explain the reason

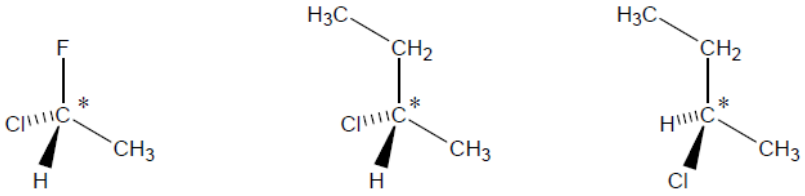




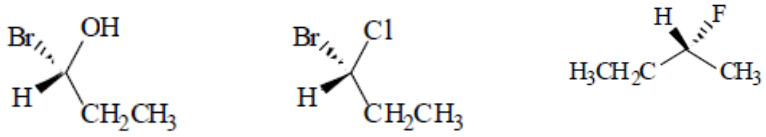
9) Determine the absolute configuration (R or S) of each chiral centers in each below structures.



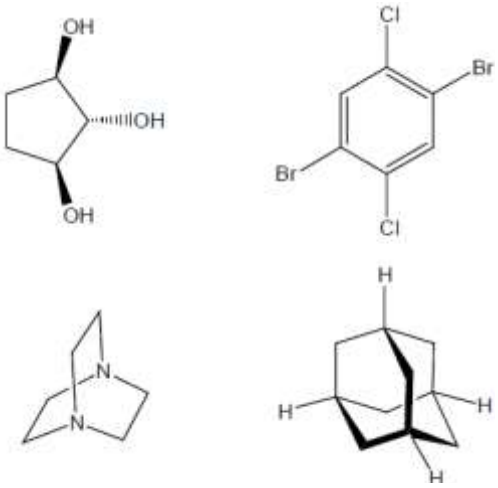
10) Determine the absolute configuration of each chiral center in the following structures and identify the enantiomers



11) Draw a Fischer Projection for the following chiral, tetrahedral carbon



12) How many *planes of symmetry* does each of the following molecules possess?



13) With examples write a note on

a) Plane of symmetry

b) Centre of symmetry

c) Axis of Symmetry

14) Write a note on asymmetric compound

15) What are diastereomers? Give two examples

16) What is meant by optically active compounds?

17) What you mean by dextro and levo rotator?

18) What is recemic mixture? Discuss the optical activity of recemic mixture

19) Discuss the resolution of recemic mixture.

Unit - 4

Structure

4.0 Objectives of the unit

After studying this unit you are able to

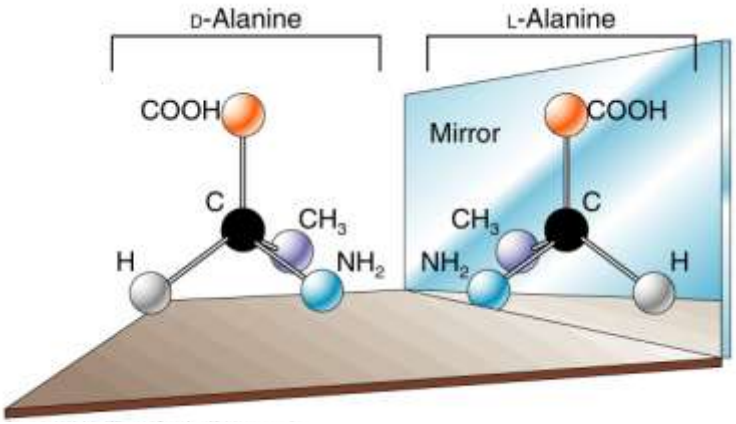
- Explain the optical isomerism in Allenes
- Explain the optical isomerism in Biphenyls
- Explain the optical isomerism in Spiranes
- Explain the reason for optical isomerism in Helicenes
- Identify the stereoselective reactions
- Differentiate between stereospecific and diastereoselctive reactions

4.1 Introduction

The stereogenic center need not be carbon. It can be a quaternary nitrogen atom the nitrogen of an ammonium salt, if there are four different groups attached to the nitrogen. Most chiral compound have at least one chiral (carbon) atom. However some molecules are chiral without having any asymmetric (carbon) atoms their chirality is due to their shape. Certain molecules are so bulky or strained that they cannot easily convert from one chiral conformation to its mirror image conformation (the opposite of cis-1,2-dibromocyclohexane). Molecules can become 'locked' or stuck in one conformation which cannot equilibrate. This is more common for strained ring systems and /or bulky substituents.

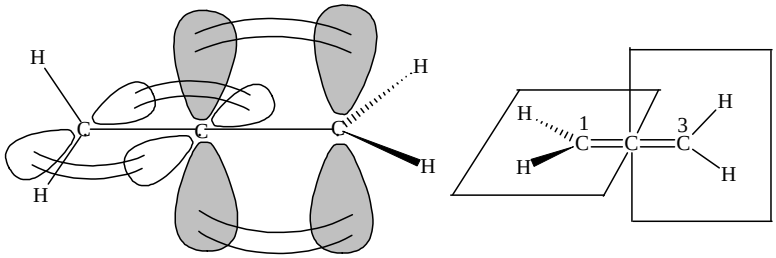
4.2 Optical isomerism

When four separate groups are attached to a carbon atom it is possible to have a non-superimposible mirror image of the molecule. This is called optical isomerism. Each of the mirror images is called an enantiomer. Optical isomers have identical physical properties (except for polarised light) and identical chemical properties (unless reacting with other optical isomers)



4.3 Optical Isomerism in allenes

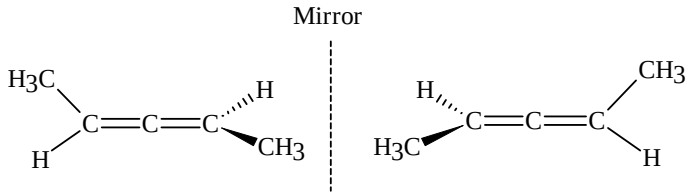
Allenes are compounds, having the structure deC=C=Cab. In an allene, middle carbon atom of the cumulative double bond is sp hybridized and so it is linear, and the two outer carbon atoms are sp^2 hybridized and trigonal. The central, sp hybrid carbon atom must therefore use different p orbitals to form the pi bonds with the two outer carbon atoms. The two unhybridized p orbitals on a sp hybrid carbon atom are perpendicular so the two pi bonds must also be perpendicular as follows.



In allene (1,2-propadiene) planes defined by H(C1) H and H (C3) H are mutually perpendicular. Allene is achiral, it has two planes of symmetry.

In the spatial arrangement of the cumulative double bonds of allene, the four substituents of the allene grouping are situated at the apexes of an imaginary tetrahedron. In order to produce molecular dissymmetry it is not necessary for all of the substituents to be different. It is sufficient to have each terminal substituents should be different.

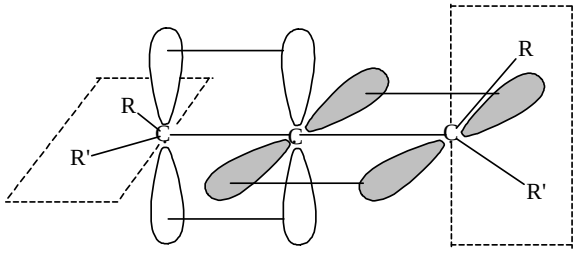
Therefore, allene of the type ABC = C = CAB (A ≠ B) as in 2,3-pentadiene is chiral, (not superimposable on its mirror image) and exist as enantiomers despite the absence of a asymmetric center. Thus, in allenes there is restricted rotation giving rise to perpendicular dissymmetric planes.

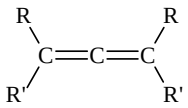


2,3-Pentadiene

Chiral allene 2,3-pentadiene have a C_2 axis. The interchange of groups at either end reverses the chirality results in an enantiomer

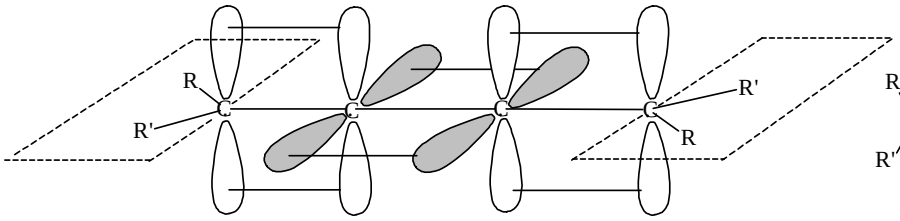
Hence allene itself is achiral and when different substituents are present at each end, the substituted allene becomes chiral. Thus the cumulated bonding systems (compounds with two or more successive double bonds) with an even number of double bonds do not have a plane of symmetry or a centre of symmetry and therefore, must show optical isomerism and can be resolvable into enantiomers.

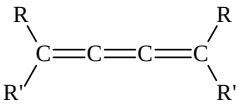




(I)

A cumulene (even number of double bonds) shows enantiomerism if R ≠ R'





(II)

A cumulene (odd number of double bonds) shows geometrical isomerism

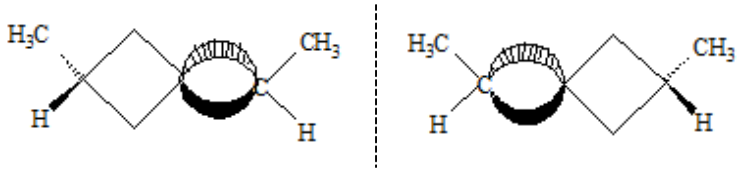
Interestingly the compounds with odd number of cumulated double bonds display Z-E (geometrical) isomerism and do not show enantiomerism. When the allene chain of compound I, is extended by one more double bond (introduction of another sp-hybridized carbon atom) then gets a system II, in which the substituted groups at the two ends of the cumulated chain now lie in the same plane and geometrical isomerism is shown.

4.4 Optical isomerism of Spiranes

The name *"spirane"* is derived from the Latin *spira* meaning twist or whorl, implies that spiranes are not planar; it is because of their nonplanarity that gives rise to their chirality.

When one or both of the double bonds in allenes are replaced by one and two rings, the resulting systems are respectively known as alkylidene, cycloalkanes and spiranes as shown below.

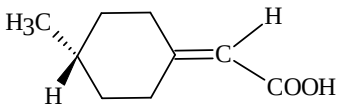
Mirror



1-Ethylidene-3-methyl cyclobutane

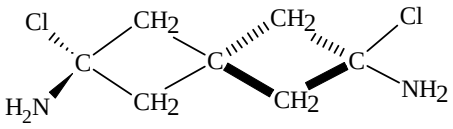
(I)

Alkylidenecycloalkanes (a distinct class) are also chiral (like allenes), if the pair of geminal substituents are non equivalent due to the presence of stereoaxis these can have C_2 axes as the sole symmetry element.



1-Methyl cyclo hexylidene-4-acetic acid
(Alkylidene cycloalkane)

or

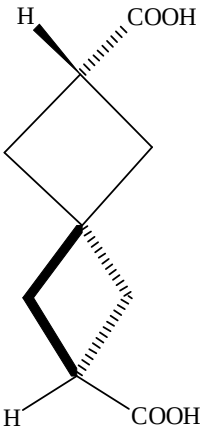


Spiranes

The replacements of one double bond in an allene by a ring gives alkylidene cycloalkanes (sometimes referred to an hemispiranes) does not alter the basic geometry of the system of allenes and suitably substituted compounds, therefore, exist in optically active forms Related compounds in which sp^2-carbon are replaced by nitrogen, e.g., compound has also been obtained as Enantiomers.

Among the chiral spiranes one may find three types

1) **A**, which definitely displays axial chirality similar to that of allenes and alkylidenecycloalkanes:

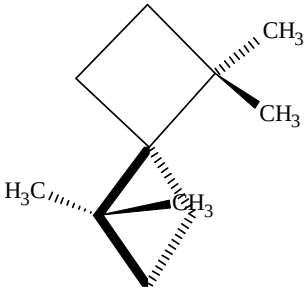


Spirane Type **A**

(S)-Spiro[3,3]heptane-2,6-
dicarboxylic acid

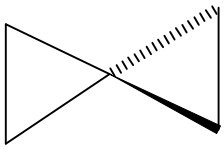
2) **B**, which displays central rather than axial chirality

3) **C**, which contains chiral center according to Cahn-Ingold-Prelog Priority rules (CIP)



Spirane Type **C**

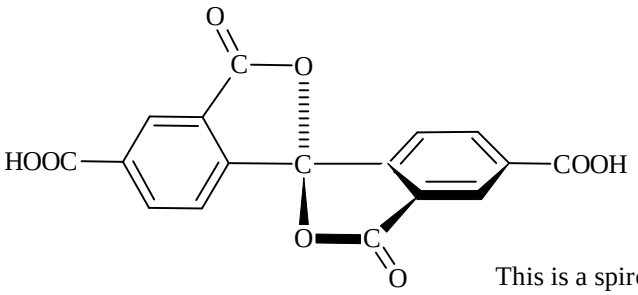
(R)-1,1,5,5-tetramethylspiro
[3,3]heptane



Spiro[2,2]pentane

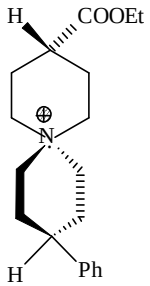
The most strained saturated spirane, spiro[2,2]pentane, was first synthesized in 1896 by Gustavson

Chirality of spiranes was demonstrated by Mills and Nodder (1920) by resolution of the following **spirodicarboxylic acid.**



This is a spiro type **C**

A spiro type A was resolved 5 years later by Mills and Warren.

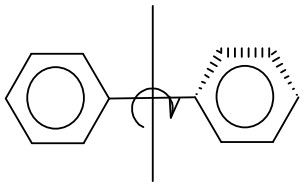


This is a Spiro type **A**

Please notice that the spiro center in this compound is a quaternary nitrogen rather than a carbon atom.

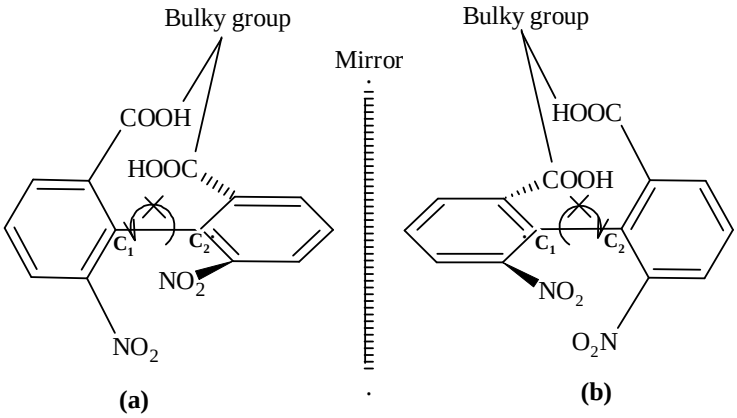
4.5 Optical isomerism in biphenyls (Atropisomerism)

Biphenyl is optically inactive the reason is molecules show plane of symmetry and there is free rotation along C-C bond of two phenyl groups.

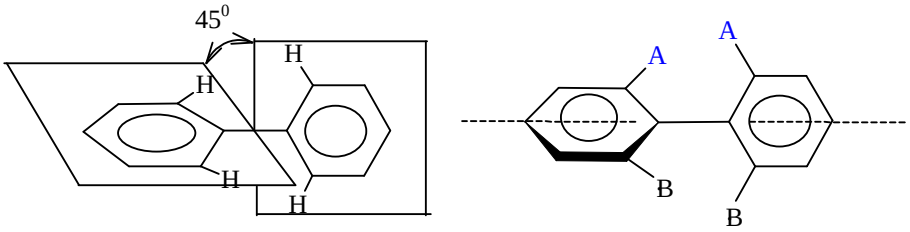


At ortho-ortho positions, if there is a bulky group then the free rotation is restricted along C_1-C_2. This type of enantiomerism was first discovered by Christie and Kenner (1922) in the case

of 6,6'-dinitro-2,2'-diphenic acid, which they were able to resolve: Hence the isomer (a) is not super imposable on (b). Hence (a) and (b) are enantiomers.



In solution two rings of biphenyl are twisted (450) due to repulsion of O-hydrogens ths repulsion enhances with larger O-substituents which arrests the rotation. Chirality in biphenylsis generated due to two different bulky ortho-substituents in each rings (A≠B)due to restricted rotation. The two enetiomers (atropisomers) can exist provided the rings display dissymmetric planes.



Suitably substituted biphenyl (diphenyl) compounds are also devoid of individual chiral carbon atom, but the molecules are chiral due to restricted rotation around the single bond between the two benzene nuclei and hence they must exist as two non–superimposible mirror images of each other. *Such type of stereoisomerism which is due to restricted rotation about single bond, is known as atropisomerism* and the stereoisomers are known as atropisomers. atropoisomerism

a = not

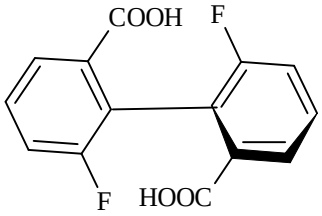
tropus = turn

The followings makes the biphenyls are optically active.

a) The restricted rotation about the bond linking the two phenyl rings due to steric hindrance between the bulky ortho substituents makes the biphenyl compounds dissymmetric.

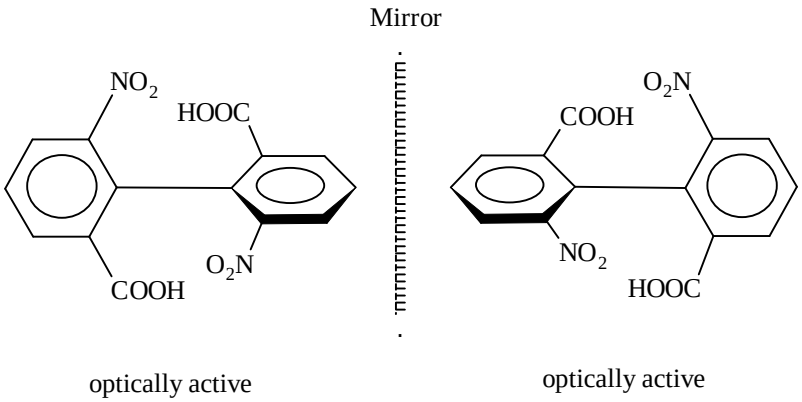
b) The two rings lie in different planes which may or may not be exactly perpendicular to each other

Eg:- *O,O'*- difluorodiphenic acid.



c) Isolable stereoisomers resulting from restricted rotation about single bonds are called atropisomers, while rotamers are stereoisomers obtained by rotation about a single bond.

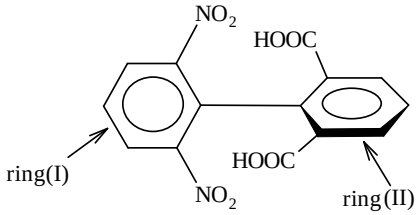
The, 6,6'-dinitrobiphenyl-2,2'-dicarboxylic acid can be resolved into its enantiomers and each enantiomer is stable. The nitro and carboxylic groups are so bulky that the two rings lie in different planes which are perpendicular to each other. Hence, the molecule does not have symmetry and will be optically active.



optically active optically active

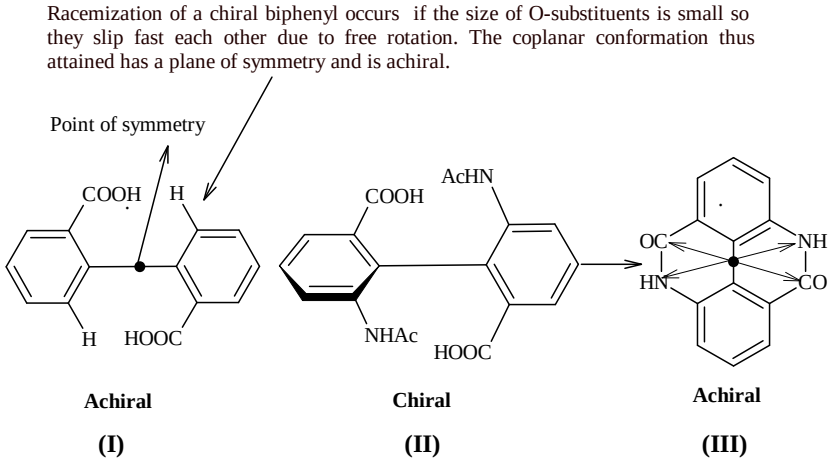
The minimal conditions for optical activity in biphenyls are

a) None of the rings should be symmetrically substituted, so that the molecule cannot have a plane of symmetry. Thus, the biphenyl is chiral (A ≠ B in either pair, COOH ≠ NO_2 of the ortho substituents. The compound 2,6-dinitro 2',6'-dicarboxylic biphenyl is, however, achiral. In this case e.g., ring is symmetrically substituted (A = B = NO_2) as well ring II (A=B = COOH). A plane drawn perpendicular to ring contains all the atoms and groups of ring in it, hence it is a plane of symmetry and since it bisects the plane of ring B into two equal halves, thus the biphenyl is achiral. In both the rings all the atom are in a single plane. So each plane cuts the other plane into equal halves. Hence plane of symmetry exists so that the molecule becomes optically inactive.



Achiral

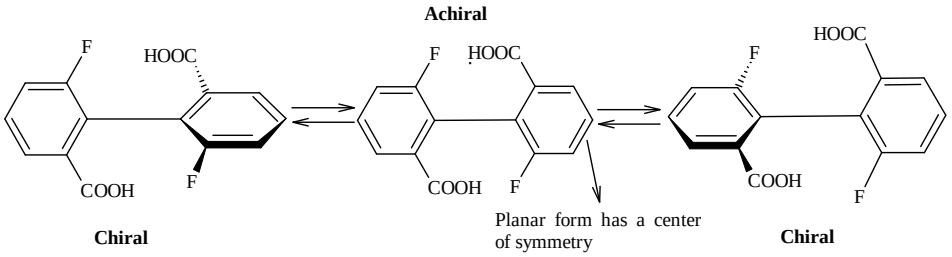
b) In order to display optical activity the substituents in the ortho position must be large enough to prevent the two rings from becoming coplanar (the rotational energy barrier must be high enough so that interconversions of enantiomeric conformers does not occur). Thus all attempts to resolve diphenic acid I into its enantiomers have failed. The process of slipping small hydrogen past the carboxylic acid group is very facile so that racemization of enantiomers occurs very rapidly through the planar form at room temperature. In the planar form the center of symmetry is clearly seen. Interestingly the diamide dicarboxylic biphenyl II is optically active and is resolvable since there is no free rotation along the C-C bond of biphenyl due to the large substituents. The optical activity is lost on hydrolysis and lactumisation since the resulting dilactum III is forced to be planar and a point of symmetry is observed in it.



Achiral **Chiral** **Achiral**

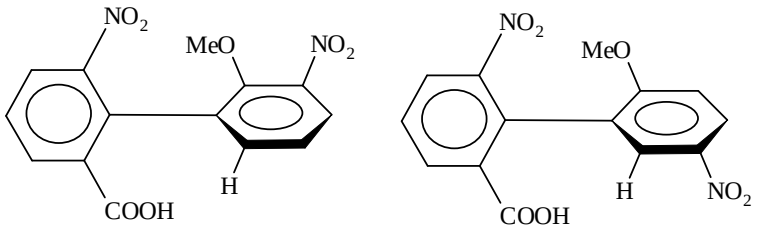
(I) **(II)** **(III)**

When the bulky nitro groups are replaced by the smaller fluorine atoms the resulting compound, 6,6'-difluorobiphenyl-2,2'-dicarboxylic acid can still display optical activity (Figure 48). However, the compound racemizes readily, i.e., the Enantiomers are readily interconverted. The process involves squeezing fluorine past the adjacent carboxyl groups via the planar conformation. Once they reach the planar conformation the Chirality is lost and racemization results. This transition state is congested and requires the bending of bonds. The process takes energy and is measurably slow.



c) In the second case the benzene ring that is unsubstituted in the ortho-positions must have a substituent in a meta-position.

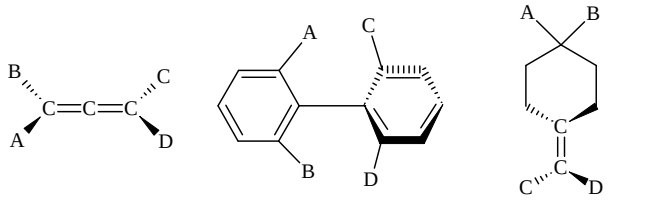
d) In addition to the bulk of the ortho substituents, the substituents in the meta-position tend to enhance racemization barriers by what is called as "buttersing effect", i.e., by preventing the outward bending of an ortho substituent, which otherwise occur in the transition state (coplanar conformation) for racemization. This bending would allow the ortho substituents to slip past each other more readily. Thus the rate of racemization of the 3-nitroderivative (structure I,) is much lower compared with the 5'-nitroderivative (Structure II,)



(I) a "buttressing effect" (II)

4.6 The (R) and (S) nomenclature system of Allenes & Biphenyls

The Cahn-Ingold-Prelog system has also been extended to chiral compounds that do not contain stereogenic centers, but have a chiral axis. Compounds having a chiral axis include unsymmetrical allenes, biaryls, alkylidene cyclohexane derivatives that exhibit atropisomerism,. A series of rules have been proposed to address the few cases where the rules can be ambiguous, as in cyclophanes and other system. Thus the (R) and (S) nomenclature system can also be used for structures with an axis or plane of Chirality. The dissymmetry is factorized into stereogenic units with the following order of priority: centers, axis, and planes are as follows.



Allenes Biaryls Alkylidenecyclohexanes

The application of additional rule with examples

Allenic compound

In an allenic compound, Glutinic acid (a)

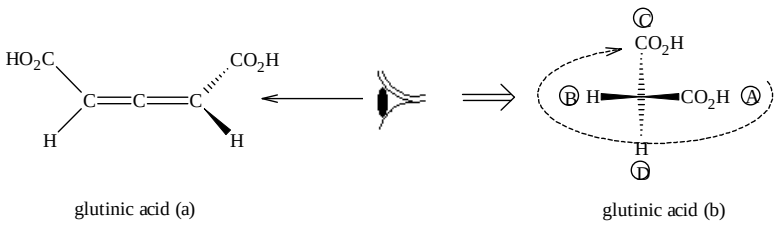
1. Viewing the structures along the C=C=C axis from the right of the drawing (as indicated by the eye symbol) would produce the image **(b)**.

2.Using the rule that near groups precede the far groups in priority.

3. We first assign highest priority (A) to the COOH group and second priority (B) to the hydrogen on the near carbon atom.

4. The COOH group on the far carbon atom is third priority (C), and the hydrogen on that carbon atom is lowest in priority (D).

5. Now we determine the configuration as we would do for a chiral carbon having the same substituents with priorities A,B,C and D bonded to it. Thus, the structure 'a' has R configuration.

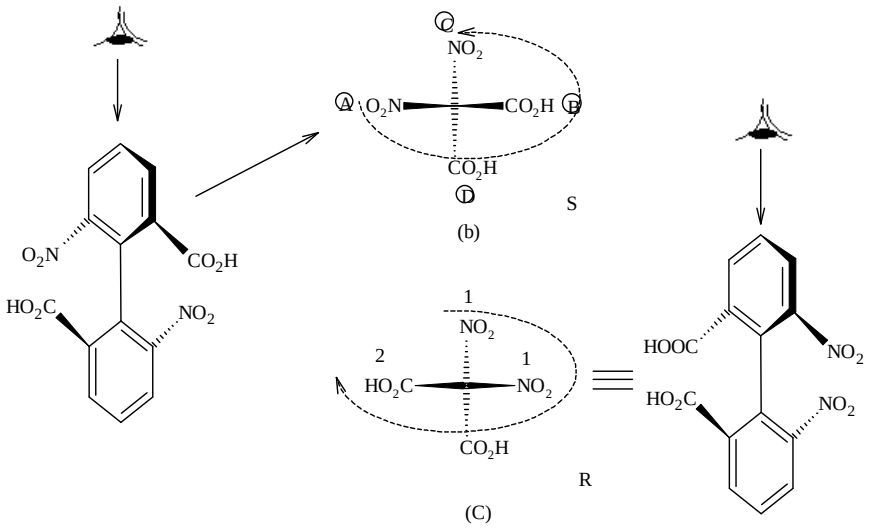


glutinic acid (a) glutinic acid (b)

R-Configuration

Biphenyl compound

1. Viewing the three-dimensional representation from the perspective indicated by the top eye symbol would produce the image.
2. Again assigning the two near groups higher priority than the two far ones, the structure is found to be (S).



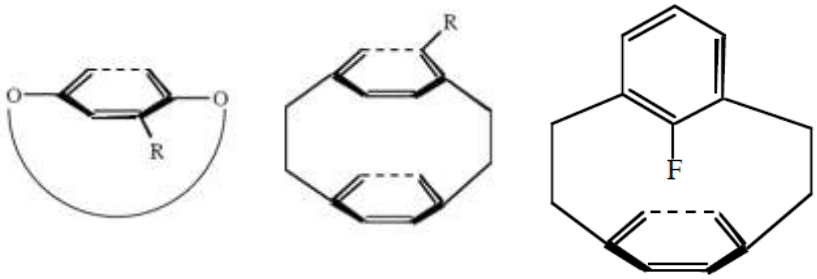
Determination of (R) or (S) designation for an atropisomer

4.7 Cyclophanes

Cyclophanes are compounds having two *p*-phenylene groups held face to face by $–[CH_2]_n–$ bridges. They are also called Paracyclophanes. They consist of a parasubstituted aromatic ring whose substituents are bound together forming an aliphatic bridge above the plane of the ring. If the bridge is small enough, or if the aromatic ring carries an additional third substituent, the rotation of the aromatic ring through the aliphatic ring may be restricted. In this case, the paracyclophane is optically active because the enantiomers cannot rapidly interconvert. Due to their handle-like aliphatic ring above the plane of the aromatic ring, cyclophanes are also called ansa compounds (from the Latin *ansa*, handle).

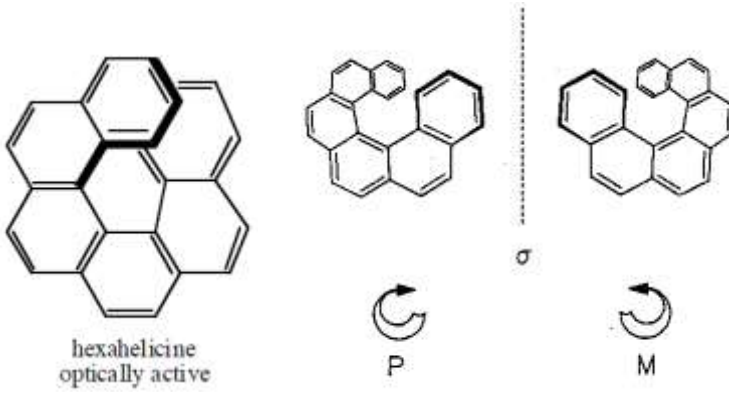
Restrictricted rotation in the compounds below also give rise to dissymetric planes of symmetry, and chiral isomers can be resolved.

The cyclophane below shows much more restricted rotation when the R is a fluorine atom than when the R is a hydrogen atom. Ring flipping in the hydrogencompound occurs 10^{11} times faster than in the fluorine compound. This also shows that Fis larger than H.



4.8 Helicenes

Helicenes are ortho-condensed polycyclic aromatic compounds in which benzene rings or other aromatics are angularly annulated to give helically-shaped molecules, Helicines are chiral and can be resolved into enantiomers that show optical activity. The chirality in the molecule occurs because the rings are distorted to avoid bumping into each other. The computerized structure on the right shows the shape of the molecule.



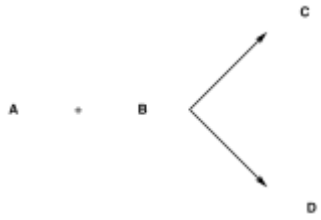
hexahelicine
optically active

4.9 Stereoselective reactions

If more than one reaction could occur between a set of reactants under the same conditions giving products that are stereoisomers and if one product forms in greater amounts than the others, the overall reaction is said to be stereoselective.

A reaction that yields predominately one stereoisomer (or one pair of enantiomers) of several diastereomers is called a stereoselective reaction.

Suppose two reactions could occur between the hypothetical reactants **A** and **B** under the same conditions giving the stereoisomeric products **C** and **D**.



There are two possibilities:

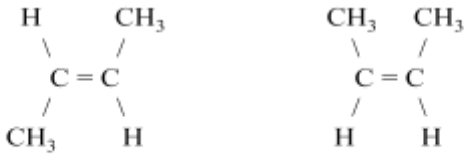
1. The two products form in equal amounts, i.e., the relative yield of each product is 50%. Then the overall reaction between **A** and **B** is not stereoselective reaction.

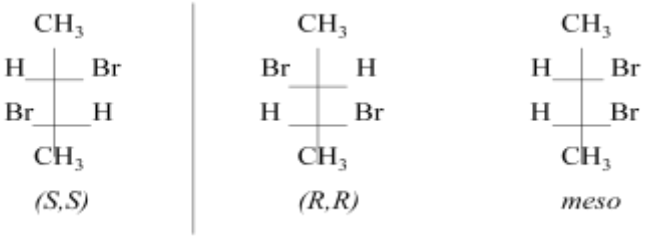
2. One product forms in greater amounts than the other. Say, for example, the relative yields of **C** and **D** are 95% and 5%, respectively. The overall reaction between **A** and **B** is stereoselective.

For example; consider the following reaction

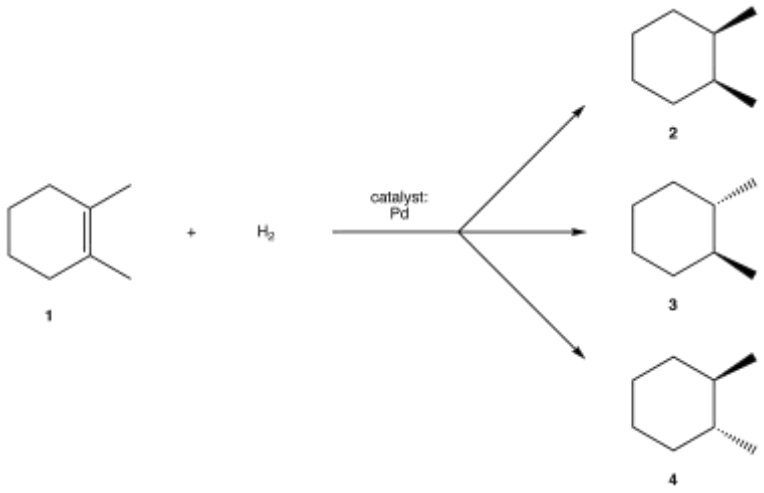
$$CH_3CH{=}CHCH_3 + Br_2 \rightarrow CH_3C^*HC^*HCH_3 \quad (Br\ Br)$$

The starting material 2-butene exists in two geometrical isomers called Cis andtrans 2-butene. There are there products are possible to form in this reactions they are (R,R); (S,S) and (R,S)-2,3-dibromobutane as shown below. The (R,S)-2,3-dibromobutane is *meso* compound





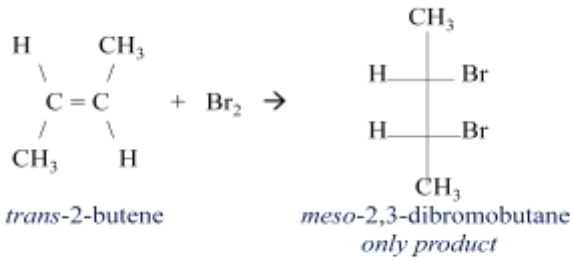
Example 2



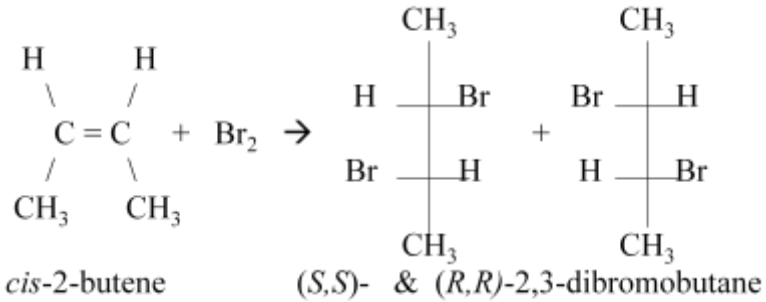
In the above hydrogenation reaction, eventhough there are 3 prodcuts are possible to form, **2** is the major product. Thus, the overall reaction between **1** and H_2 is stereoselective toward **2**.

4.10 Stereospecific reactions

A reaction in which stereochemically different molecules react differently is called a stereospecific reaction. In the above reaction *cis*- and *trans*- stereoisomers give different products as shown below.



In this case the *meso*- product is produced and not the other two diastereomers

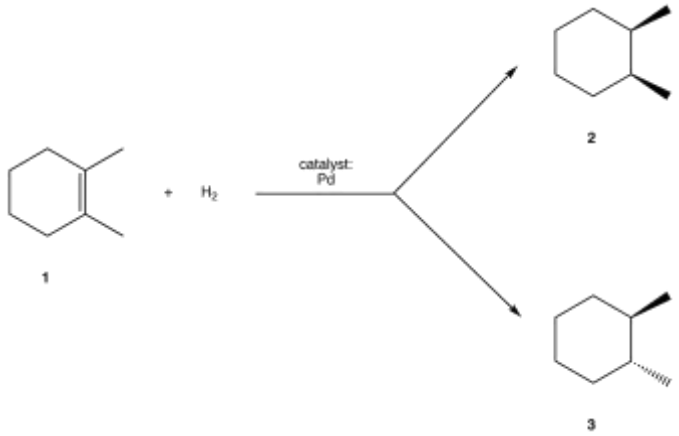


Addition of halogens to alkenes is both stereoselective and stereospecific. This provides us information about the stereochemistry of the addition and the mechanismof the reaction.

4.11 Diastereoselective

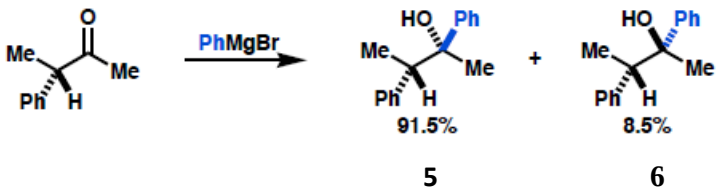
A stereoselective reaction in which the possible products are diastereomers is said to be diastereoselective. In this type of reactions a stereogenic centre is introduced into a product molecule in such a way that diastereoisomers are produced in unequal amounts.

Example 1:



In the above reaction **2** is the major product; **3** is the minor product. Since **2** and **3** are diastereomers, the overall reaction between **1** and H_2 is diastereoselective.

Example 2:



5 **6**

In the above reaction **5** is the major product and **6** is the minor product. Since **5** and **6** are diastereoselective, the overall reaction is diastereoselective selective.

diastereoselective reactions are very common. In contrast, enantioselective reactions are rare becuase they require special chiral reagents or catalysts. Therefore, the term stereoselective is casually used to mean diastereoselective.

4.12 Summary of the unit

The basic requirement for a compound to be optically active is its non-superimposability of its mirror image. Although the largest numbers of known optically active compounds are optically active due to the presence of chiral carbon, some compounds are also known which do not possess any chiral carbon atom, but on the whole their molecules are chiral. Hence they are optically active. Such molecules were earlier called dissymmetric. In certain ring compounds, molecular distortions cause ring systems to lose their symmetry and show chirality. Hence ring systems need not have to contain a chiral center to be chiral. Unsymmetrically substituted cumulenes with even number of double bonds are chiral while with odd number show geometric (E-Z) isomerism and they show achirality.

4.13 Key words

Optical isomerism; allenes; Spiranes; biphenyls; Cyclophanes; Helicenes; Stereoselective reactions; Stereospecific reactions; Diastereoselective reactions

4.14 Reference for the further study

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4.15 Questions for self learning

1) What is optical isomerism?

2) What are allenes why they show optical isomerism?

3) Explain the conditions for allenes to display optical isomerism

4) Discuss optical isomerism in biphenyls

5) What are spirans? Explain their optical isomerism

6) Write a note on optical isomerism in helicenes

7) Discuss the optical isomerism properties in Cyclopanes.

8) What is steroselctive reaction? Give two examples

9) What is stereoselective reaction? Give two examples

10 Write a note on diasteroselective reaction.

Unit - 5

Structure

5.0 Objectives of the unit

After studying this unit you are able to

- Expalin arromaticity
- Identify the conditions required for aromaticity
- Explain Hückel (4n + 2) rule
- Test the different compounds to obey Hückel (4n + 2) rule
- Explain non aromaticity and anti-aromaticity
- Explain alternant and non alternant compounds

5.1 Introduction

Benzene, first isolated by Michael Faraday in 1825 is the simplest and the ideal molecule to illustrate electron delocalization, resonance and aromaticity. Important milestones during structure elucidation of benzene include

a) Friedrich Kekule's (1866) proposal of cyclic equilibrating structures which partially explained the existence of three isomers (instead of four) for disubstituted benzene. If benzene is just a cyclo-triene, replacement of two hydrogen atoms by two bromines in principle should give four compounds. In realty, we will get only three, corresponding to 1, 2; 1, 3- and 1, 4- substitutions. Kekule assumed that the two 1,2-disubstituted benzenes (III and IV) interconvert too rapidly to be distinguished. disubstituted benzenes (III and IV) interconvert too rapidly to be distinguished. Debate over the structure of benzene came to an end in 1930s when X-ray and electron diffraction studies confirmed that it is a planar, regular hexagon in which all the carbon-carbon bond lengths are 1.39 Å, which is shorter than C-C single bond (1.54 Å), but slightly longer than C-C double bond (1.33 Å). Such a structure is possible only if all the carbon atoms have the same electron density, with π electrons delocalized over the entire skeleton of ring carbons. Now we know that all carbon atoms in benzene are sp^2 hybridized. Each carbon atom uses two of these hybrid orbitals to form two sigma bonds with neighboring carbons and use the third orbital to form a sigma bond with 1s orbital of hydrogen. Each carbon atom has in addition a p orbital right angle to the sp^2orbitals and planarity of the molecule allows these orbitals to overlap sideways leading to delocalization. It is now clear that benzene doesn't contains any double bonds and the exact structure is a resonance hybrid of two possible kekule structures, with delocalized electrons.

5.2 Aromaticity

Although the name 'aromatic' was originated from the characteristic odor or 'aroma' of benzene-like compounds, chemists now have a completely different method of deciding

whether a compound is aromatic or not. Based on the analysis of a number of compounds with unusual resonance stabilization energies, the following characteristics have been accepted as criteria for aromaticity.

Aromaticity is special stability provided to a molecule upon possessing four specific quapities mentioned below. To determine if a molecule is aromatic

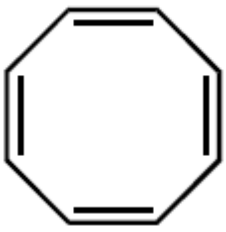
1) Molecule must be cyclic structre
2) Pi bonds must lie within cyclic structure
3) Each atom in the cycle must have p orbital forming orbital loop below and above the plane the molecule
4) All p orbital loop must overlap
5) orbital arrangement must result in a lowering of energy, and contains (4n + 2) pi electrons (n is an integer: 0, 1, 2, 3, etc…) in the loop

Aromaticity is also defined as the ability of compound to sustain an induced ring current and this type of compounds are called as diatropic. There are several methods available for determining whether a compound can sustain a ring current among them the most important one is based on NMR chemical shift. Every atom in the ring must have a p orbital and the delocalization should result in an uninterrupted cyclic cloud of π electrons above and below the plain of the ring.

The German

Chemist Erich Hückel was the first one to recognize that an aromatic compound must have an odd number of pairs of electrons, which can mathematically be written as 4n+2 (n = 0,1,2,3 etc). Molecules which obey these rules are classified as aromatic and those which partially follow these rules are categorized as anti-aromatic and non aromatic compounds. Delocalization is possible only if atoms sharing the electrons lie in or close to the same plane so that their p orbitals can overlap efficiently.

For example, cyclooctatetraene despite having alternate single and double bonds do not show the extended overlap of p orbitals and delocalization as it is tub shaped.



cyclooctatetraene

Dlocalization of electrons and resonance can significantly affect the properties of chemical compounds. Delocalization means possibility of new orbital overlap and additional stabilization of the system. The extra stability (in terms of energy) gained through delocalization is called delocalization energy or resonance energy. If delocalization was not possible, benzene should behave as a cyclohexatriene.

2. 3 Conditions for romaticity

For a compound to be aromatic one looks for diamagnetic ring current, equal or approximately equal bond distances, planarity, chemical stability and the ability to undergo aromatic substitution reactions.

1. The structure must be cyclic.
2. The ring must be planar.
3. Each of the rings must be sp^2 hybridized (or occasionally sp hybridized) and have an unhybridized p-orbital.
4. The total number of p electrons in the molecule or ion should be (4n + 2) where n = 0,1,2,3,.....
5. The unhybridized p-orbital must overlap to give a continuous ring of parallel orbital (the condition of planarity is for effective overlap).
6. This delocalization of p electrons over the ring result in the lowering of the electronic energy

2. 4 Hückel (4n + 2) rule for aromaticity

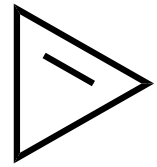
Huckel carried out molecular orbital calculation on monocyclic systems C_nH_n containing n number of p electrons and each carbon atom providing one p electrons and as a result connected aromatic stability (high delocalization energy or high resonance energy) with the presence of (4n + 2) π electrons in a closed shell. To be aromatic, a molecule must have 2(n = 0), 6(n =1), 10(n = 2)…….. p electrons. In this description of aromaticity no mention is made of the number of carbon atom in the ring. The essential requirement is the presence of (4n + 2) p electrons. Another requirement, for Aromaticity is planarity of the ring. If the ring is not planar, overlap of the p-orbital is diminished or absent. Thus if a molecule is a monocyclic planar system and contains (4n+2) p electrons that molecule will exhibit aromatic character (i.e.) will have unusual stability.

To apply the 4n+2 rule, first count the number of π electrons in the molecule. Then, set this number equal to 4n+2 and solve for n. If is 0 or any positive integer (1, 2, 3,...), the rule has been met. For example, benzene has six π electrons:

$$4n + 2 = 6$$
$$4n = 4$$
$$n = 1$$

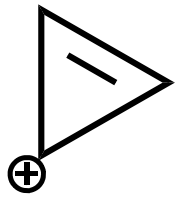
For benzene, we find that n=1, which is a positive integer, so the rule is met.

1) Cyclopropene

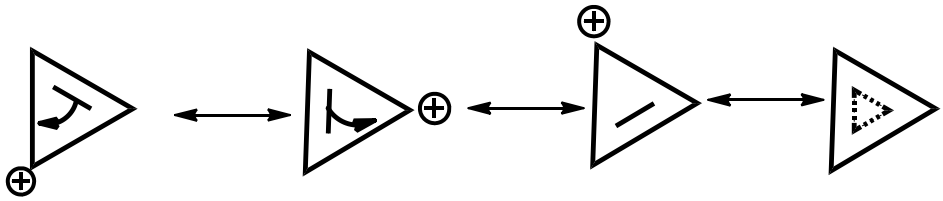


It has 2 electrons (4n + 2; n = 0); the delocalization is inturrupted due to sp^3 methylene hence non *Nonaromatic*

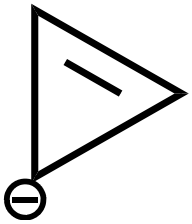
2) Cyclopropenyl cation



It also has 2 electrons (4n+2; n = 0), the delocalization of 2 electrons is possible through the empty p orbital hence the compound is *Aromatic*



3) Cyclopropenyl anion



It has 4 electron (even number of pairs) 4n +2; n = 1); *Theoretically it is antiaromatic compound and not stable*

2.5 Non aromatic compounds

As the name implies, these compounds are not aromatic due to reasons such as lack of planarity or disruption of delocalization. They may contain 4n or 4n+2 π electrons.

2.6 Antiaromatic compounds

These compounds are planar, cyclic, conjugated systems with an even number of pairs of electrons. Such compounds satisfy the first three criteria for aromaticity.

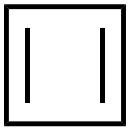
i.e. they are planar, cyclic with an uninterrupted ring of p orbital. But they have an even number of pairs of π electrons (4n, n = 1, 2, 3 etc).

It should be noted that an aromatic compound is more stable compared to an analogous cyclic compound with localized electrons, where as an antiaromatic compound is less stable compared to an analogous cyclic compound with localized electrons (*in 4n+2 systems delocalization increases the stability where as in 4n systems, delocalization decreases stability*)

2.7 Annulenes

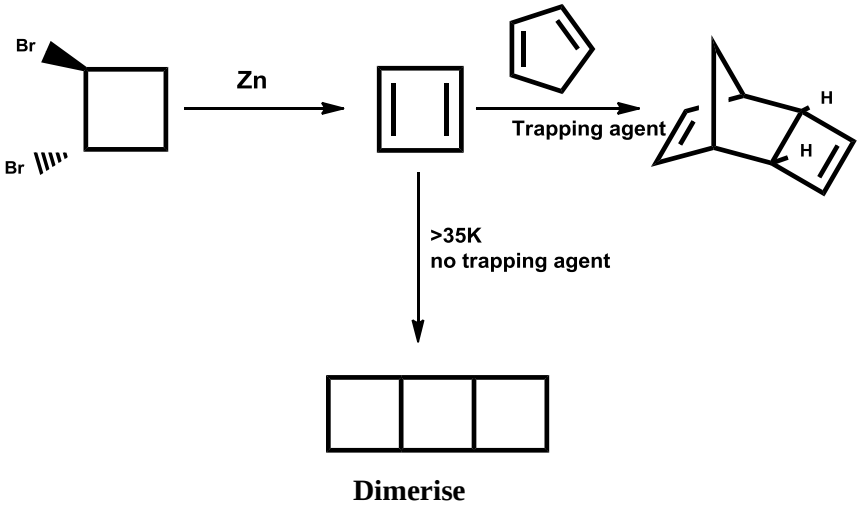
Monocyclic hydrocarbons with alternating single and double bonds are called annulenes. A prefix in brackets denotes the number of carbons in the ring.

a) *Cyclobutadiene or [4]-annulene*

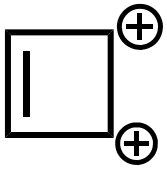


It has 4 electrons. It is a Cyclic, planar and has uninterrupted ring of p orbital (i.e., conjugation). It has even number of pairs (4n, n = 1) hence antiaromatic.

Being antiaromatic, cyclobutadiene is unstable. It can be isolated only under controlled conditions such as in Argon matrix or using trapping agents such as dienes. Studies show that it has a rectangular structure rather than a square, with C-C bond length of 1.567 Å and C=C bond length of 1.346 Å.

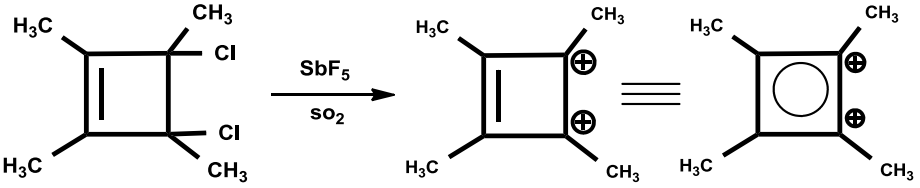


b) Cyclobutadienyl dication

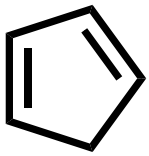


It has 2 electrons (4n+2; n = 0). The delocalization of 2 electrons is possible through the empty p orbitals. Hence it is *Aromatic*

e.g. Ionization of 3,4-dichloro- 1,2,3,4-tetramethylcyclobutene in SbF5/SO2 at -75^{o}C leads to a dication whose formation and special stability is attributable to aromaticity.

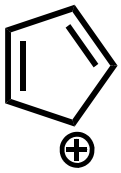


c) Cyclopentadiene or [5] annulene



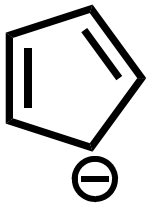
It has 4 electron system and does not have an uninterrupted ring of p orbital i.e.,(conjugation) hence *Nonaromatic* and also has even number of pairs

d) Cyclopentadienyl cation



It has 4 electrons. It is a cyclic and planar molecule. It also has uninterrupted ring of p orbital (conjugation). But it has even number of pairs; 4n, n = 1; hence it is *antiaromatic compound.*

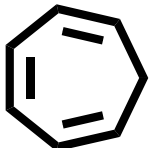
e) Cyclopentadienyl anion



It is a 6 electron system (4n+2, n = 1), and cyclic as well as planar molecule with conjugation. Hence it is *Aromatic*

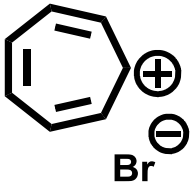
The pKa of cyclopentadiene is 15, which is extraordinary for hydrogen bonded to a sp^3 carbon. The reason for this low pKa is its high tendency to become aromatic by releasing a proton.

f) Cycloheptatriene or [7] annulene



Although it is a 6π electrom system, one of the atoms in the cyclic structure cannot contribute a p orbital for conjugation. Hence it is *Nonaromatic*

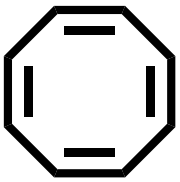
g) Cyclopentatienyl cation



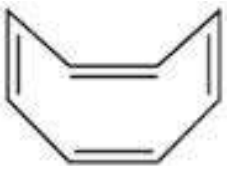
It is also a 6π electron system, Cyclic, planar and conjugated, and has 4n+2 p electrons. Hence it is *Aromatic*

Alkyl halides such as cyclopentyl chloride are nonpolar and dissolve in non-polar solvents and remain insoluble in water. Surprisingly, cycloheptatrienyl bromide is an exception. It is insoluble in nonpolar solvents, but dissolves in water! It turns out that cycloheptatrienyl bromide is an ionic compound, since its cation (known as tropylium cation) is aromatic. In the covalent form, there is no continuity in p orbital overlap as one of the carbon atoms is sp^3 hybridized.

h) *Cyclooctatetraene or [8]-annulene*



It is an 8 π electron system. If completely planar, this molecule will become antiaromatic. The bond angle for planar structrure = 135^o which can give considerable angle strain in a cyclic structure involving sp^2 carbon atoms. The molecule is actually boat shaped and *nonaromatic.* Nonaromatic form is more stable than an antiaromatic form.

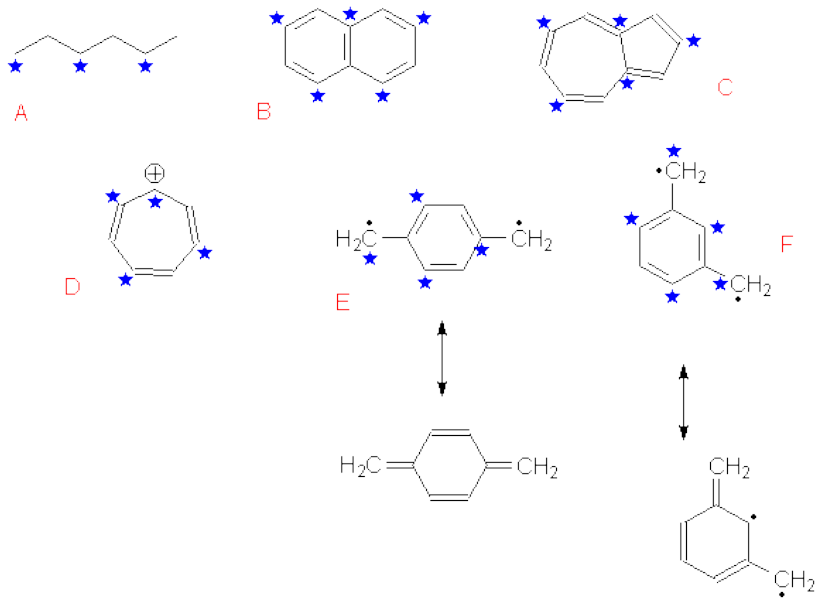


2.8 Alternant and non alternant hydrocarbons

A convenient way of describing conjugated hydrocarbon systems that is helpful in predicting properties is the alternant/nonalternant classification. A conjugated hydrocarbon is alternant if stars (asterisks) can be placed on alternating p-centers with no two stars adjacent. It is nonalternant if the two or more adjacent centers receive stars.

Alternant systems can be further subclassified as *even* alternant if equal numbers of starred and unstarred carbons occur and *odd* alternant if the numbers in the two sets are not equal. Since we always maximize the number of stars, this means that odd alternant systems will have more starred than unstarred atoms.

In the below diagram, A, like all linear systems, is an alternant hydrocarbon. The ones with even numbers of atoms are *even* alternant, with odd numbers are *odd* alternant.



Structure B, naphthalene, is an even alternant species, having five starred and five unstarred carbons. Azulene (C) is a nonalternant, any way of placing stars on alternate carbons eventually leads to two adjacent stars. In this case, starring was started at the top bridgehead. Tropylium, (D) is also nonalternant, as are all odd rings. In alternant species, no carbons in the same set (starred or unstarred) have overlapping p orbitals. Therefore, in the Huckel theory description, all H_{ii} = a integrals and all H_{ij} = b integrals are the same. The consequence of this is that all charge densities are zero. Nonalternants, like azulene, have nonzero charges

on some atoms. Even alternant molecules have equal numbers of bonding and antibonding orbitals, symmetrically distributed and no nonbonding orbital.

2.9 Summary of the unit

Although the name 'aromatic' was originated from the characteristic odor or 'aroma' of benzene-like compounds, chemists now have a completely different method of deciding whether a compound is aromatic or not. Based on the analysis of a number of compounds with unusual resonance stabilization energies, the following characteristics have been accepted as criteria for aromaticity.

1. *The molecule must be cyclic, planar with uninterrupted cloud of π electrons above and below the plane of the ring.*
2. *It should have 4n+2 π electrons.*

Every atom in the ring must have a p orbital and the delocalization should result in an uninterrupted cyclic cloud of π electrons above and below the plain of the ring. The German Chemist Erich Hückel was the first one to recognize that an aromatic compound must have an odd number of pairs of electrons, which can mathematically be written as 4n+2 (n = 0,1,2,3 etc). Molecules which obey these rules are aromatic and those which follow these rules partially fall in the category of anti-aromatic and non aromatic compounds.

2.10 Key words

Aromaticity; Hückel (4n + 2) rule; Non aromatic compound; Antiaromatic compound; Annulenes; Alternant and non alternant hydrocarbons.

2.11 References for further study

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2.12 Questions for self understanding

1) What is aromaticity?
2) Explain the condition for aromaticty

3) What is Hückel (4n + 2) rule for aromaticity?
4) Discuss the arromaticity of following compounds
    a) Cyclopropene
    b) Cyclobutadiene
    c) Cyclopentadiene
    d) Cycloheptatriene
    e) cyclooctatetraene
5) What are non aromatic compounds? Give two examples
6) What are anti-aromatic compounds? Give two examples
7) Write a note on alternant and non alternant hydrocarbons

Unit - 6

Structure

6.0 Objectives of the unit

After studying this unit you are able to

- Explain the stability of conjugated dienes
- Explain the stability of benzene
- Draw the energy level diagram for pi molecular orbital
- Explain the molecular orbital description of aromaticity and anti-aromaticity

6.1 Introduction

Geometry is one of the primary and most direct indicators of aromaticity and antiaromaticity. a regular structure with delocalized double bonds (e.g., benzene) is symptomatic of aromaticity, whereas a distorted geometry with localized double bonds (e.g., 1,3-cyclobutadiene) is characteristic of antiaromaticity. A molecular-orbital (MO) model of aromaticity explains, simple orbital-overlap arguments. MO model is based on accurate Kohn-Sham DFT analyses of the bonding in benzene, 1,3-cyclobutadiene, cyclohexane, and cyclobutane, and how the bonding mechanism is affected if these molecules undergo geometrical deformations between regular, delocalized ring structures, and distorted ones with localized double bonds. The propensity of the pi electrons is always, that is, in both the aromatic and antiaromatic molecules, to localize the double bonds, against the delocalizing force of the sigma electrons. More importantly, it shows that the pi electrons nevertheless decide about the localization or delocalization of the double bonds.

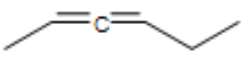
6.2 Stability of conjugated dienes

Conjugated dienes are two double bonds separated by a single bond where as Nonconjugated (Isolated) Dienes are two double bonds are separated by more than one single bond.

3,5-octadiene

2,5-heptadiene

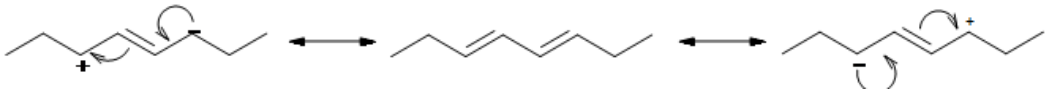
There is another type of dine called cumulated dienes are also exist in which two double bond connected to a similar (i.e., single carbon) atom.



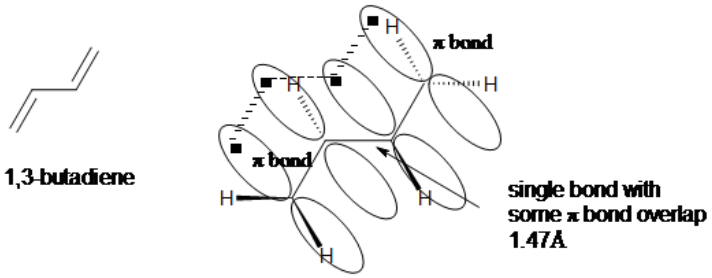
2,3-hexadiene

Conjugated dienes are more stable than both isolated and cumulated dienes due to the delocalization of charge through resonance and hybridization energy. This will explain why allylic carbocations are much more stable than secondary or even tertiary carbocations. The

positioning of the pi orbitals provides ability for overlap and strengthen the single bond between the two double bonds. The resonance structure shown below gives a good understanding of how the charge is delocalized across the four carbons in this conjugated diene. This delocalization of charges is responsible for the stabilization of the conjugated diene



Along with resonance, hybridization energy effect the stability of the compound. For example unlike in nonconjugated dienes where the single bonded carbons atoms are sp^3 hybridized, carbons with the single bond are sp^2 hybridized in 1,3-butadiene. Therefore C-atoms in conjugated dienes have more 's' character and draw more of the pi electrons, thus making the single bond stronger and shorter than an ordinary alkane C-C bond (1.54Å).

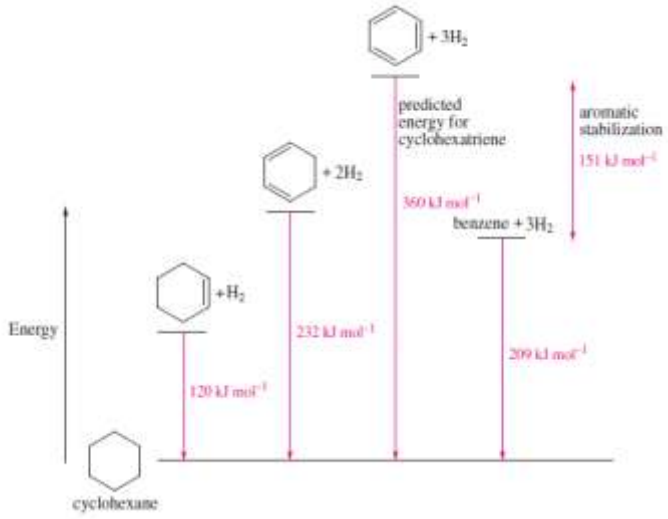


The heats of hydrogenation of different arrangements of double bonds provide the useful information about their stability. The higher the heat of hydrogenation, the compound is less stable. Form experiments it is shown that conjugated dienes (~54 kcal) have a lower heat of hydrogenation than their isolated (~60 kcal) and cumulated (~70 kcal) diene isomers. This difference energy is a measure of the extra stability of the conjugated system compared to the corresponding isolated double system and it is called *resonance energy*.

6.3 Stability of benzene ring

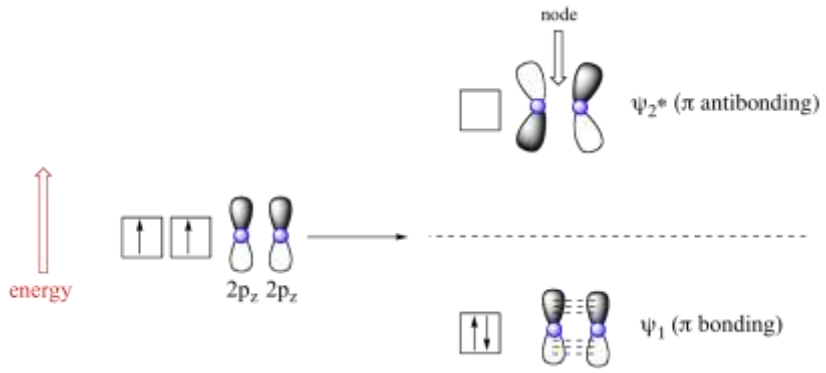
If delocalization is not possible in benzene, then it will behave as a cyclohexatriene. Experimentally determined heat of hydrogenation of cyclohexene is to be 28.6 kcal/mol. suppose we consider C_6H_6 as just a cyclohexatriene, the heat of hydrogenation of benzene should be 3 x 28.6 kcal/mol = 85.8 kcal/mol. However, when the heat of hydrogenation of benzene is experimentally determined it is found to be 49.8 kcal/mol. The hydrogenation of cyclohexatriene and benzene both lead to cyclohexane, therefore reason for the difference in

their heat of hydrogenation is due to the difference in their stabilities. From this study, it is clear that benzene is 36 kcal/mol (ie. 85.8-49.8 kcal/mol) more stable than cyclohexatriene. (i.e. benzene with six delocalized π electrons is 36 kcal/mol more stable than 'cyclohexatriene' with six localized π electrons). Hence 36 kcal/mol is the resonance energy of benzene (*Heat of hydrogenation is the quantity of heat released when one mole of an unsaturated compound is hydrogenated*).



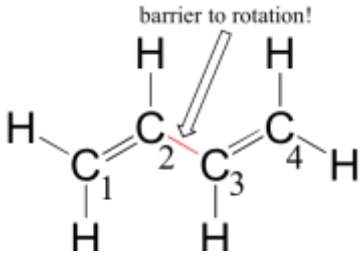
6.4 Energy level pi molecular orbital and concept of aromaticity

The advantage of MO theory becomes more apparent to think about pi bonds, especially in those situations where two or more pi bonds are able to interact with one another. For example, consider the pi bond in ethene from an MO theory standpoint, According to MO theory, the two atomic $2p_z$ orbitals combine to form two **pi (π) molecular orbitals**, one a low-energy π bonding orbital and one a high-energy **π-star (π*) antibonding molecular orbital**. These are denoted, in MO diagrams shown below, with the Greek letter psi (Ψ) instead of π.



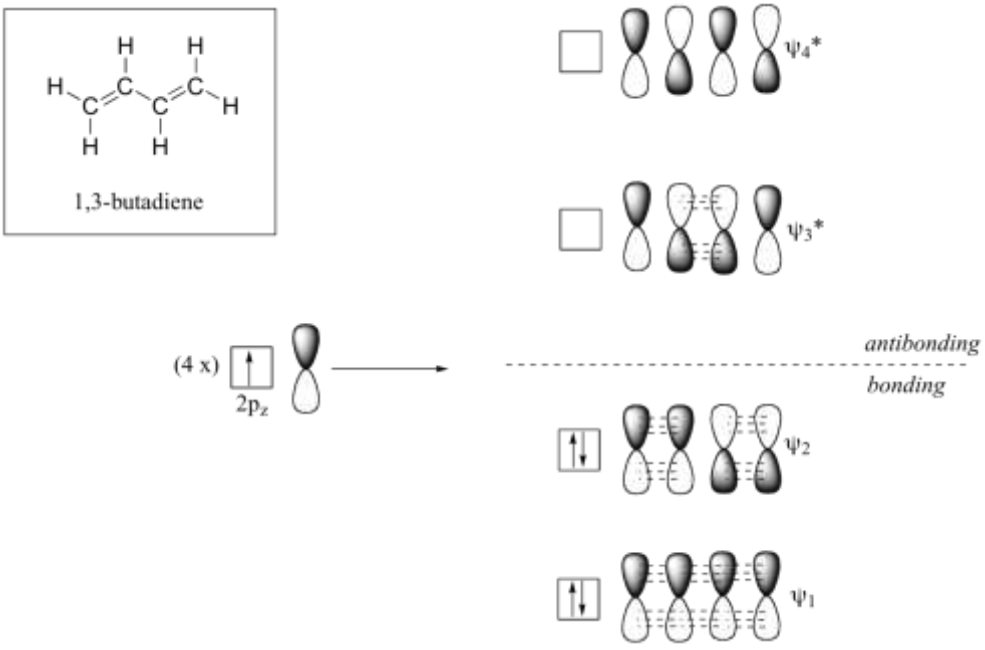
In the bonding Ψ_1 orbital, the two shaded lobes of the $2p_z$ orbitals interact constructively with each other therefore there is increased electron density between the nuclei in the molecular orbital. Hence it is a bonding orbital. In the antibonding Ψ_2* orbital, the shaded lobe of one $2p_z$ orbital interacts destructively with the unshaded lobe of the second $2p_z$ orbital, leading to a node between the two nuclei and overall repulsion. Therefore there is decreased electron density (even obscene) between the nuclei in the molecular orbital. Hence it is a anti-bonding orbital. By the *aufbau* principle, the two electrons from the two atomic orbitals will be paired in the lower-energy $\Psi_1$orbital when the molecule is in the ground state.

Consider the higher alonogue 1,3-butadiene molecule. From valence orbital theory we might expect that the C_2-C_3 bond in this molecule would be able to rotate freely (because it is a sigma bond).



Experimentally, however, it is found that there are significant barriers to rotation about this bond (as well as about the C_1-C_2 and C_3-C_4 double bonds), and that the entire molecule is planar. It is also observed that the C_2-C_3 bond, while longer than the C_1-C_2 and C_3-C_4 double bonds, is significantly shorter than a typical carbon-carbon single bond.

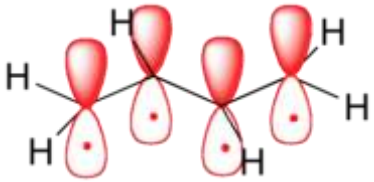
Molecular orbital theory accounts for these observations with the concept of delocalized π bonds**.**



In this picture, the four $2p_z$ orbitals are all parallel to each other (and perpendicular to the plane of the sigma bonds), and thus there is π-overlap not just between C_1 and C_2 and C_3 and C_4, but between C_2 and C_3 as well. The four atomic ($2p_z$) orbitals have combined to form four π molecular orbitals.

The lowest energy molecular orbital, Ψ_1, has zero nodes, and is a bonding MO. Slightly higher in energy, but still lower than the isolated *p* orbitals, is the Ψ_2 orbital. This orbital has one node between C_2 and C_3, but is still a bonding orbital due to the two constructive interactions between C_1-C_2 and C_3-C_4. The two higher-energy MO's are denoted Ψ_3* and Ψ_4*, and are antibonding orbitals. Notice that Ψ_3* has two nodes and one constructive interaction, while Ψ_4* has three nodes and zero constructive interactions. The energy of both of these antibonding molecular orbitals is higher than that of the $2p_z$ atomic orbitals of which they are composed.

By the *aufbau* principle, the four electrons from the isolated $2p_z$ atomic orbitals are placed in the bonding $\Psi_1$and Ψ_2 MO's. Since $\Psi_1$includes constructive interaction between C_2 and C_3, there is some short of π-bonding interaction between these two carbons, which accounts for the shorter length and the barrier to rotation. The simple Lewis structure picture of 1,3-butadiene shows the two π bonds as being isolated from one another, with each pair of π electrons 'stuck' in its own π bond. However, molecular orbital theory predicts (accurately) that the four π electrons are to some extent delocalized, or 'spread out', over the whole π system.

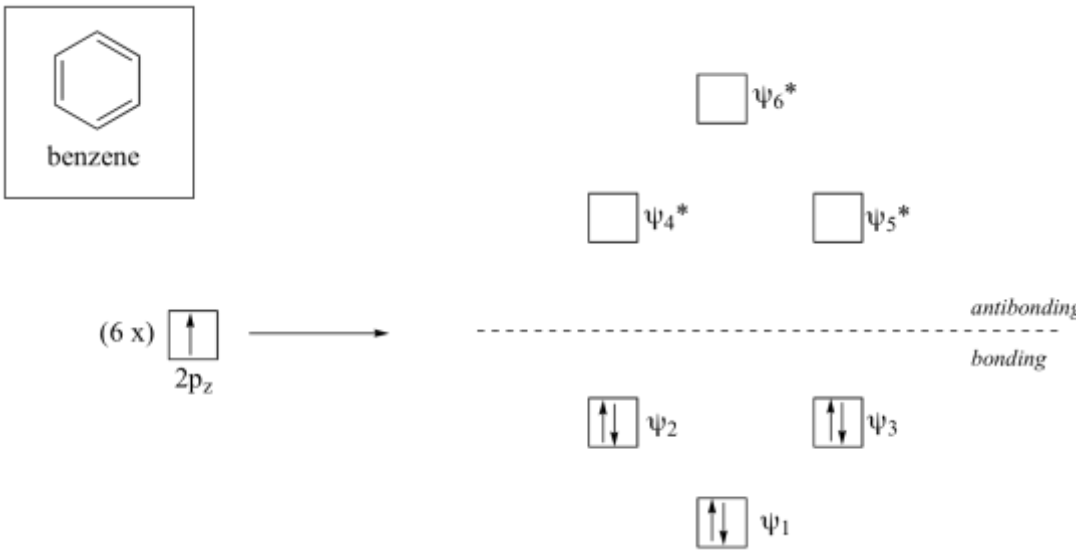


6.5 Molecular orbital description of aromaticity and anti-aromaticity

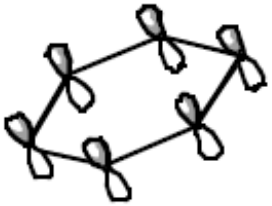
Our current understanding on the structure of benzene is based on molecular orbital theory. As mentioned earlier, all the six sp^2 carbon atoms are arranged in such a way that each uses two of its hybridized orbitals to bond to adjacent carbon atoms and the third one to bond with the 1s orbital of hydrogen. The un-hybridized p orbital associated with each carbon atom contain one electron and lie perpendicular to the plane of the ring. According to molecular orbital theory, these six p orbitals combine to form six molecular orbitals, three of which are bonding and three, anti-bonding. Six π electrons occupy the bonding orbitals, which are lower in energy compared to the un-hybridized p orbitals (atomic orbitals).

Molecular orbital theory is especially helpful in explaining the unique properties of Benzene, a simplest example of an aromatic compound. Clearly it takes something more to be aromatic, and this can best be explained with molecular orbital theory. Let's look at an energy diagram for the molecular orbitals containing the π electrons in benzene.

Quantum mechanical calculations conclude that the six molecular orbitals in benzene, formed from six atomic $2p_z$ orbitals, occupy four separate energy levels. Ψ_1 and Ψ_6* have unique energy levels, while the Ψ_2- Ψ_3 and Ψ_4*-Ψ_5* pairs are **degenerate** (more than one orbital at the same energy level). When we use the aufbau principle to fill up these orbitals with the six π electrons in benzene, we see that the bonding orbitals are completely filled, and the antibonding orbitals are empty. This gives us a good clue to the source of the special stability of benzene: a full set of bonding MO's is similar in many ways to the 'full shell' of electrons possessed by the very stable noble gases like helium, neon, and argon.

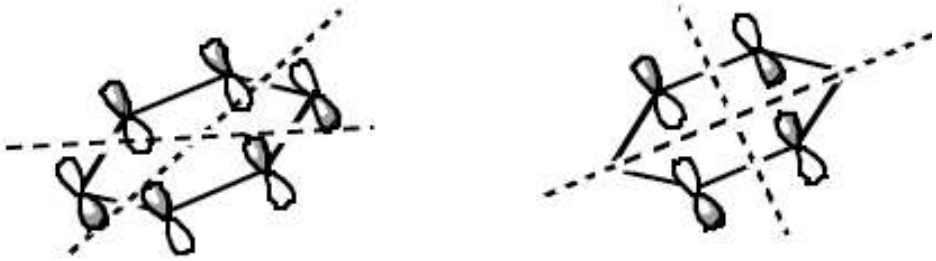


In drawing M.O. diagrams for benzene, it is possible to draw a diagram where there are no nodes

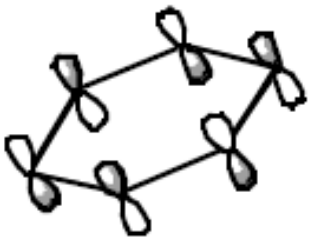


However, it is not possible to draw a diagram where there is only one node. This restriction against having an odd number of nodes is due to the cyclic nature of benzene, and the high degree of symmetry involved. To make up for this, there are two representatives of the 2-node system

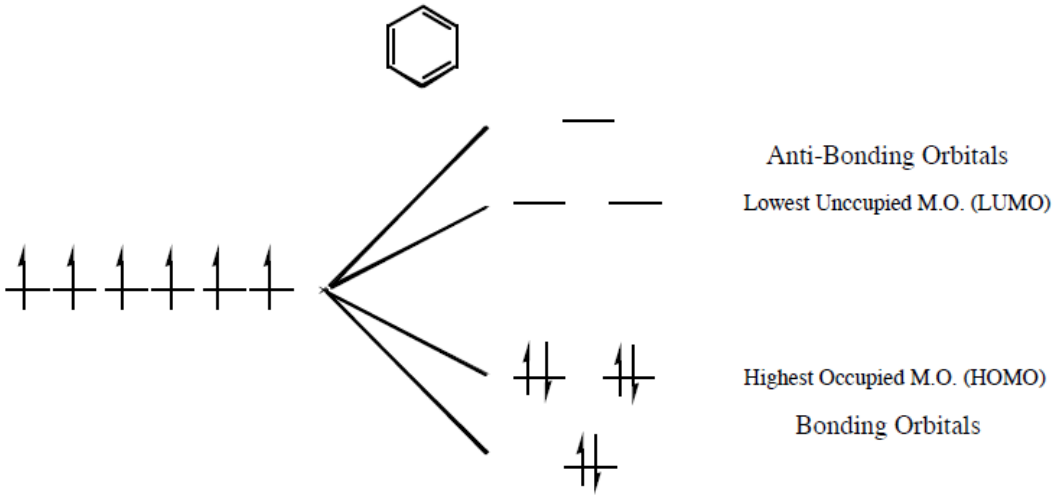
Although it is possible to draw an M.O. level for benzene with 3 nodes, it is not possible to use it due to symmetry considerations. Thus it will be looking at levels with 4 nodes, of which again there are two

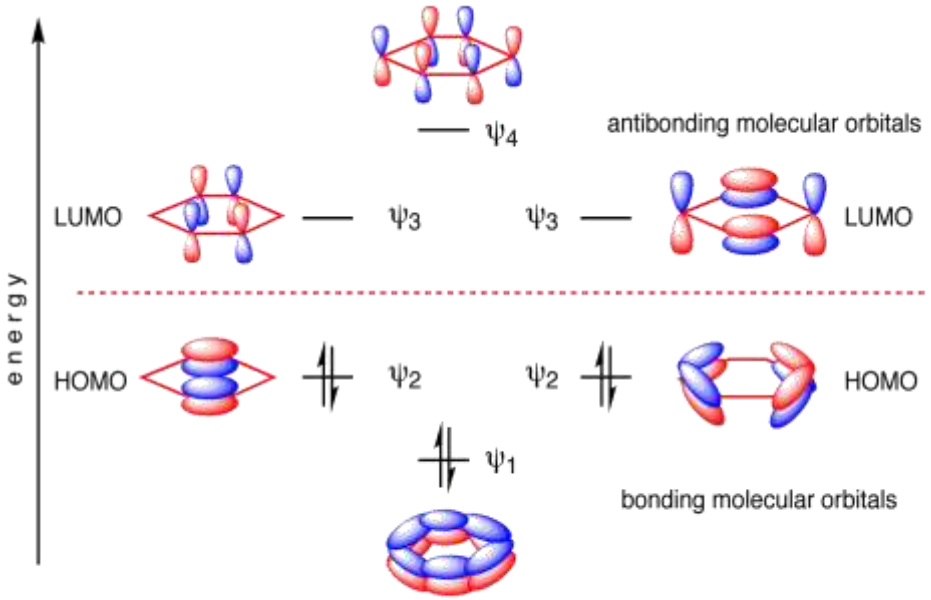


And, it is possible to draw a one diagram where 6 nodes



Therefore the energy level diagram of benzene is comprised of two HOMO orbitals of equal energy. These are called degenerate orbitals. There are also two degenerate (but unfilled) orbitals of LUMO.





the π molecular orbitals for benzene. The dashed line represents the energy of an isolated p orbital – all orbitals below this line are bonding, all above it are antibonding. Benzene has six electrons in its π system so all the bonding MOs are fully occupied

The relative energies of p molecular orbitals in planar cyclic conjugated systems can be determined by a simplified approach developed by A. A. frost in 1953. This involves the following steps:

1) Draw a circle

2) Place the ring (polygon representing the compound of interest) in the circle with one of its vertices pointing down. Each point where the polygon touches the circle represents an energy level.

3) Place the correct number of electrons in the orbitals, starting with the lowest energy orbital first, in accordance with Hund's rule.

If the polygon touches the circle at a horizontal diameter, that point would represent a nonbonding orbital. Energy levels below this line indicate bonding MOs and those above are anti-bonding.

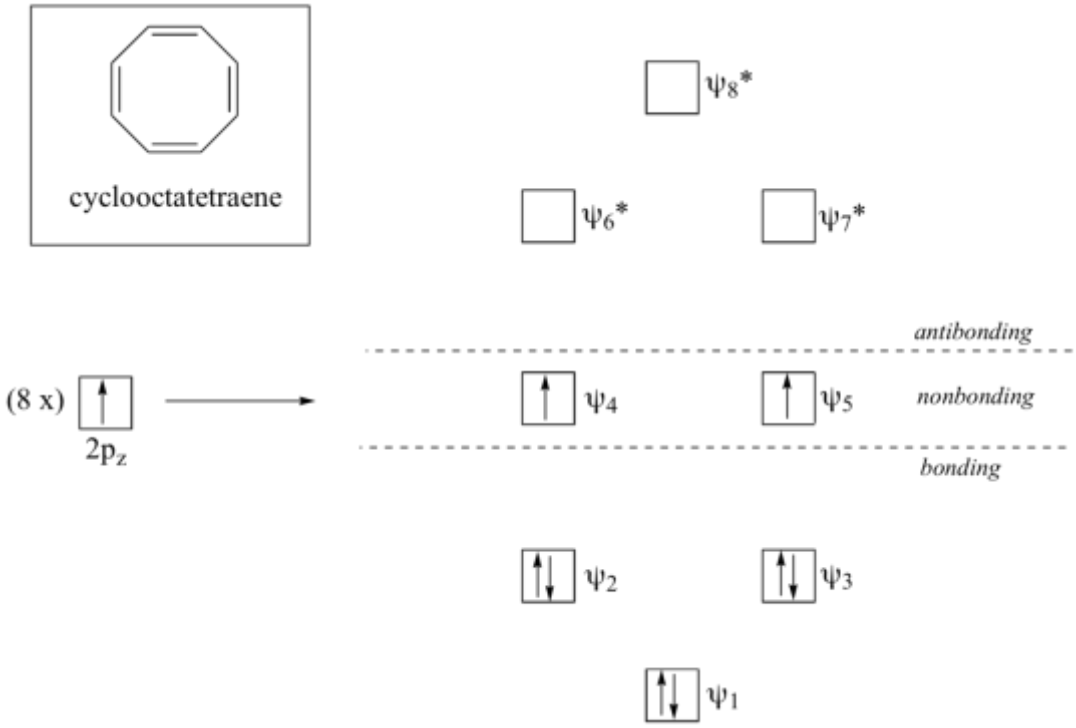
6.6 Frost diagrams - Illustrative examples

Points to remember while making predictions on aromaticity using Frost's circle

i) Aromatic compounds will have all occupied molecular orbitals completely filled where as antiaromatic compounds would have incompletely filled orbitals.

ii) If an antiaromatic system (4n electrons) has the freedom to undergo conformational change and become nonaromatic that would do so. Remember that antiaromatic state is less stable than aromatic and nonaromatic forms. A comparison of molecular orbitals in aromatic and antiaromatic systems is presented in below figures .

1) Using Frost diagrams, predict the aromatic/antiaromatic/non aromatic nature of i) cyclopropenyl cation, ii) cyclopentadienyl cation, iii) cyclobutadienyl dication, and iv) cyclooctatetraenyl dianion



The result of molecular orbital calculations tells us that the lowest and highest energy MOs (Ψ_1 and Ψ_8*) have unique energy levels, while the other six come in degenerate pairs. Notice that $\psi_4$and $\psi_5$are at the same energy level as the isolated $2p_z$ atomic orbitals: these are therefore neither bonding nor antibonding, rather they are referred to as nonbonding MOs. Filling up the MOs with the eight π electrons in the molecule, we find that the last two electrons are unpaired and fall into the two degenerate nonbonding orbitals. Because we don't have a perfect filled shell of bonding MOs, our molecule is not aromatic. As a consequence, each of the double bonds in cyclooctatetraene acts more like an *isolated* double bond.

6.7 Summary of the unit

Conjugated dienes are two double bonds separated by a single bond where as Nonconjugated (Isolated) Dienes are two double bonds are separated by more than one single bond. Conjugated dienes are more stable than both isolated and cumulated dienes due to the delocalization of charge through resonance and hybridization energy. This will explain why allylic carbocations are much more stable than secondary or even tertiary carbocations. The positioning of the pi orbitals provides ability for overlap and strengthen the single bond between the two double bonds. If delocalization is not possible in benzene, then it will behave

as a cyclohexatriene. Experimentally determined heat of hydrogenation of cyclohexene is to be 28.6 kcal/mol. suppose we consider C_6H_6 as just a cyclohexatriene, the heat of hydrogenation of benzene should be 3 x 28.6 kcal/mol = 85.8 kcal/mol. The advantage of MO theory becomes more apparent to think about pi bonds, especially in those situations where two or more pi bonds are able to interact with one another. For example, consider the pi bond in ethene from an MO theory standpoint, According to MO theory, the two atomic $2p_z$ orbitals combine to form two pi (π) molecular orbitals**,** one a low-energy π bonding orbital and one a high-energy π-star (π*) antibonding molecular orbital**.**

6.8 Key words

Conjugated dienes; Pi molecular orbital; Frost diagrams.

6.9 References for further study

1) Aromatic Organic Chemistry, Amit Arora, *Discovery Publishing House*, **2006**.
2) Aromatic character and aromaticity, *CUP Archive*
3) Organic Chemistry, Volume 2, Roger S. Macomber, *University Science Books*, **1996**.
4) Textbook of Organic Chemistry, Volume 1, V. K. Ahluwalia, *Ane Books Pvt Ltd*, **2010**.
5) March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Michael B. Smith, Jerry March, *John Wiley & Sons*, **2007**.
6) Molecular Structure: Understanding Steric and Electronic Effects from Molecular Mechanics, Norman L. Allinger, *John Wiley & Sons*, **2010.**

6.10 Questions for self understanding

1) Write a note on stability of conguated dienes
2) Discus the stability of benzene
3) Explain energy level of pi molecular orbital and concept of resonance.
4) Explain aromaticity and antiaromaticity o the basis of molecular orbital description
5) Write a note on symmetry of pi orbitals and their energy levels in benzene
6) Explain Frost diagrams with example.

Unit - 7

Structure

7.0 Objectives of the unit

After studying this unit you are able to

- Explain the aromaticity in higher annulenes
- Identify the Homoaromatic compounds
- Explain the aromaticity in heterocyclic compounds
- Explain the aromaticity in fused ring compounds
- Explain the aromaticity in tropone
- Explain the structure of Fullerene C-60

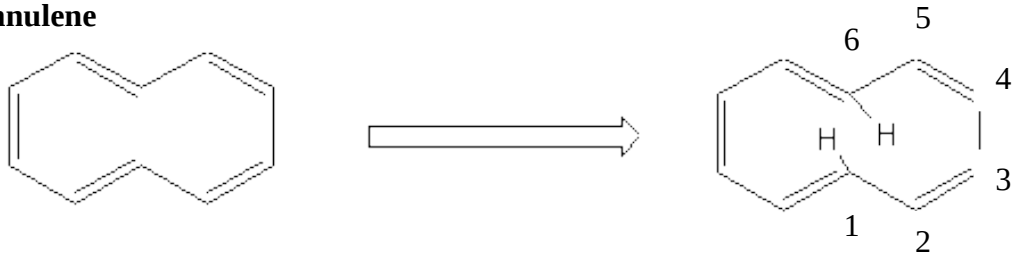
7.1 Introduction

The criteria for aromaticity that we discussed earlier can also be applied to higher annulenes as well. However, maintain planarity is a difficult for many larger rings due to potential steric clashes or angle strains. If the ring (with 4n+2 π electrons) is sufficiently large such that planarity does not cause steric or angle strains, then the system would adopt that conformation, and stabilized through electron delocalization hence become aromatic. Larger annulenes with 4nπ electrons are not antiaromatic because they are flexible enough to become non-planar and become non-aromatic.

7.2 Aromaticity in higher Annulenes

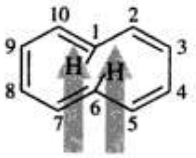
Completely conjugated monocyclic hydrocarbons are called annulenes. Examples, [4] Annulene [6] Annulene [8] Annulene [10] Annulene.

[10]-annulene



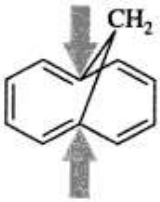
In [10]-annulene, the molecule experiences considerable steric interaction between hydrogens at 1 and 6 positions. Further, a planar form (regular decagon) requires an angle of 144^{o} between carbon atoms which is too large to accommodate in a sp^2 framework. The system prefers a nonplanar conformation and is not aromatic. In general the angle strain need not always be a problem in achieving planarity as it is evident from examples such as cyclooctatetraenyldianion, which is stable and aromatic. Bridging between C1 and C6 in [10]-annulene leads to reasonably planar with all the bond distances in the range of 1.37-1.42Å and show aromaticity.

Structure-I



These two hydrogens cause the steric hindrance which makes molecule non-planar. Thus, it **does not exhibit aromatic character**.

Structure-II

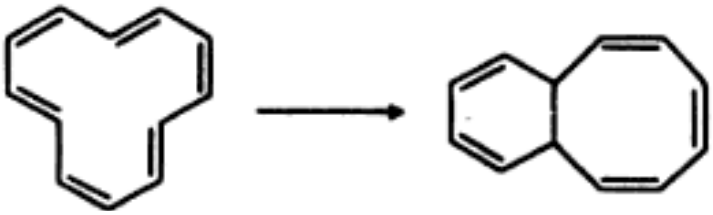


In the bridged structure hydrogens are removed which relieves the molecule from steric hindrance and delocalization occurs effectively. Thus, it exhibits **aromatic character**.

In NMR, outer protons are found at 6.9-7.3 δ and the bridgehead methylene at -5.0 δ.

7.3 [12]-annulene

[12]-annulene (4n, n = 3) is an antiaromatic and hence is not stable above -50^{o} C. Its dianion (4n+2, n = 3) is however stable up to 30^{o} C and is aromatic.

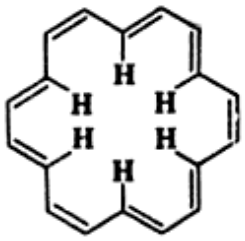


A B

In solution this molecule undergoes rapid conformational mobility. At -150^{o} C all protons are magnetically equivalent. At -170^{o} C the mobility is greatly slow down and three inner protons are found around δ 8, while the nine outer protons are at about δ 6. The structure A suffers from hydrogen interference and is certainly not plamar. Hence it is very unstable and above -50^{o} C rearranges to structure B.

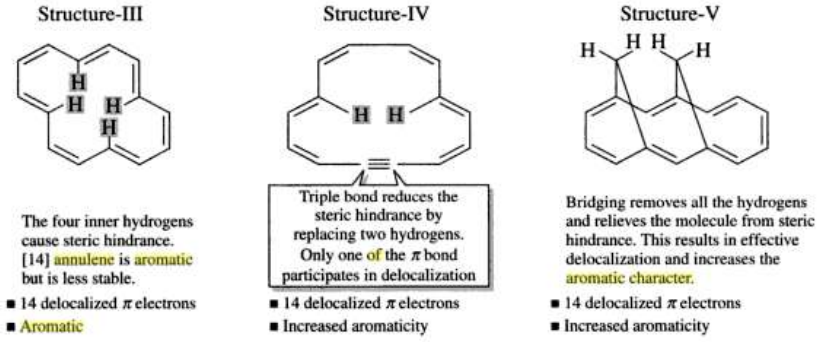
7.4 [14]-annulene

Bond lengths in [14]-annulene range from 1.35-1.41Å but do not show the alternating pattern of localized polyenes. It is aromatic (except for the isomers that are not planar). NMR shows that it is in conformational equilibrium.

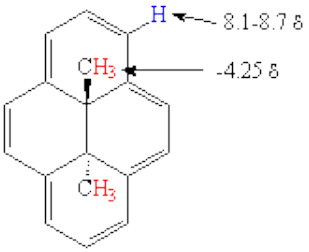


Molecule undergoes aromatic substitution and diatropic. The outer protons are found at 8.14 to 8.67δ. The steric interactions associated with internal hydrogens can be minimized if C3, C6, C10 and C13 positions are locked using suitable bridging units. Thus *trans*-15,16-

dimethyldihydropyrene and its diethyl and dipropyl homologs are aromatic with C-C bond distances between 1.39-1.40 Å.

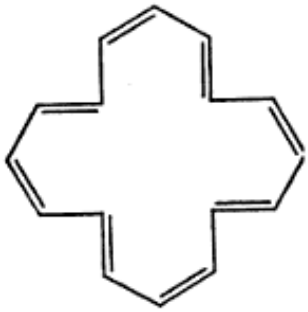


Conformational flexibility in [14]-annulene can be restricted by inserting triple bond in place of one of the more double bonds. Here, the triple bond contributes only two electrons for delocalization leaving the other two localized. The bridged [14]annulene is much more stable than [14]annulene itself because the Hs that cause the steric strain are not present. It has many characteristics of an aromatic compound, including an aromatic ring current. The blue H's appear at 8.1-8.7 delta in its NMR spectrum, whereas the H's of the methyl groups (red), which sit over the inside of the ring, appear at the extremely high field position of -4.25 delta.



7.5 [16]-annulene

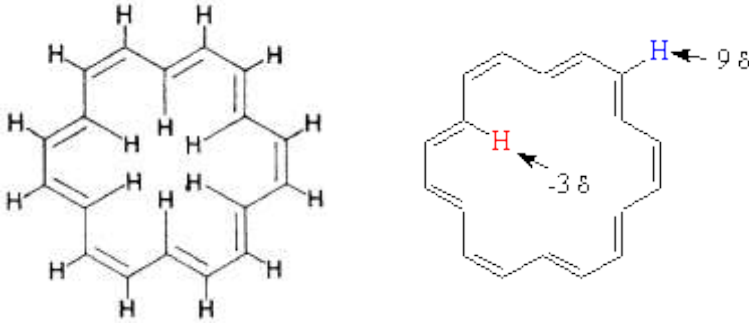
This compound has 16πelectrons and does not conform to Huckel's rule. Therefore it should be non aromatic. [16]-annulene shows significant bond alteration, characteristic of a polyene structure (C-C, 1.46Å; C=C, 1.34 Å). It is nonplanar. Its dianion shows aromatic character (4n+2 systems).



7.6 [18]-annulene

[18]-Annulene is predicted to be aromatic by the Hückel rule ($4n + 2 = 18$ when $n = 4$). The structure shown has a shape that makes it free of angle strain and is large enough so that

repulsive forces between hydrogen atoms in the interior are minimal. Thermochemical measurements indicate resonance energy of roughly 100 kilocalories per mole, and structural studies reveal that the molecule is planar with all its bond distances falling in the range 1.37-1.43 angstroms.



In terms of its chemical reactivity, however, [18]-annulene resembles an alkene more than it resembles benzene. The cavity in [18]-annulene is sufficiently large and hence the steric interaction involving internal hydrogens is at minimum. The molecule is free of any significant angle strain, nearly planar, and show aromaticity. Its estimated resonance energy is 37 kcal/mol, which is in the range as that of benzene.

7.7 Homoaromaticity

In 1959 Winstein introduced the term homoaromatic to describe compounds that display aromaticity despite one or saturated linkages interputting the formal cyclic conjugation. If a stabilized cyclic conjugated system of (4n+2) elecrons can be formed by bypassing one saturated atom that leads to homoaromaticity. i. e., homoaromatic is a term used to describe system in a stabilized cyclic system is formed by bypassing one saturated atom. The saturated unit is generally a CH_2 group but it can be a larger alkyl residue or even a heteroatomic moiety. Compared to true aromatic systems, the net stabilization here may be low due to poorer overlap of orbitals.

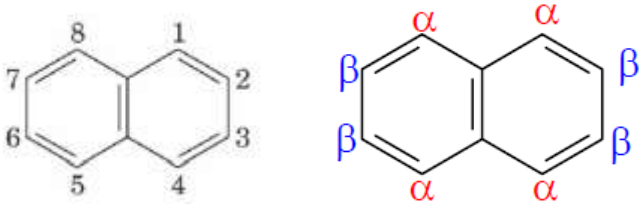
Homoaromaticity is well established in cationic systems where delocalization of charge provides an additional driving force for homoaromaticity. Cyclooctatrienyl cation (homotropylium ion) formed when cyclooctatetraene is dissolved in concentrated sulfuric acid is the best example to demonstrate homoaromaticity. Here, six electrons are spread over seven carbon atoms as in Tropylium cation.

7.8 Aromaticity in fused rings

The criteria for aromaticity in mono cyclic hydrocarbons can aslo be applied for polycyclic hydrocarbons as well. Following are some of the well known examples for this class of compounds.

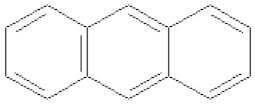
a) Naphthalene

Naphthalene is the simplest example of a polycyclic aromatic hydrocarbon, a compound which has a number of benzene rings fused together. The carbons of these compounds are all sp^2 hybridized with trigonal planar geometry. As a result, the compounds are planar and highly conjugated. Huckel's rule does not apply to such fused systems. However, if the individual rings that are fused to form the polycyclic compound are aromatic, then the fused compound is also considered to be aromatic. Naphthalene has two fused benzene rings, so it is aromatic. Its resonance energy has been calculated to be 61 kcal/mol (255 kJ/mol), a value that is larger than that of benzene (36 kcal/mol [151 kJ/mol]), although not twice as large.

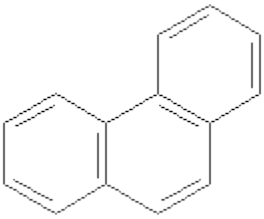


b) Anthracene and Phenanthrene

Anthracene has three benzene rings fused in a linear manner, so it is also expected to be aromatic. Its resonance energy has been calculated to be 84 kcal/mol (352 kJ/mol). Phenanthrene has three benzene rings fused in a bent manner, so it is also expected to be aromatic. Its resonance energy has been calculated to be 92 kcal/mol (385 kJ/mol).



Anthracene



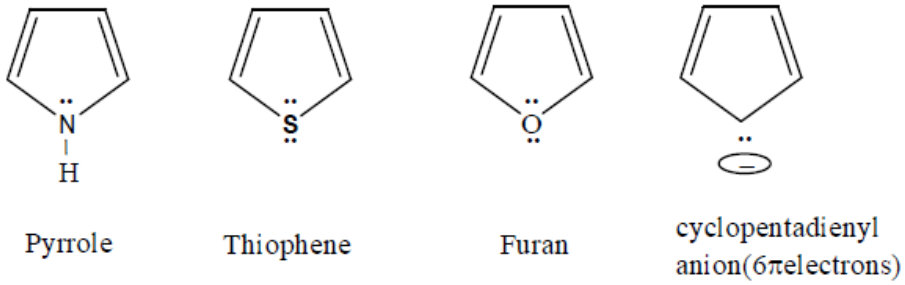
Phenanthrene

As the number of aromatic rings increases, the resonance energy per π electron decreases. As a result, larger polynuclear aromatic hydrocarbons have a tendency to undergo addition reaction to an internal ring to give more stable compounds.

7.9 Aromatic heterocyclic compounds

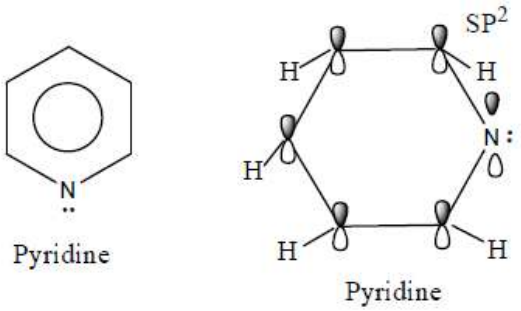
Heterocyclic compounds can also be aromatic since for the application of Huckel's rule what one needs is a ring of atoms, all with unhybridized 'p' orbital in a planar arrangement in order that the 'p' orbital overlaps in a continuous ring. Thus the heterocyclic compounds are all aromatic.

Pyrrole, furan and thiophene in fact represent 1-hetero 2, 4-cyclopentadiene and a butadiene unit bridged by a hetero atom bearing lone pairs. In electronic structure these three compounds are similar to cyclopentadienyl anion.



a) Pyridine

Both benzene and pyridine have a similar Kekule structure. Pyridine with resonance energy of 27*KCal* (113*KJ*) per mole shows typical characters of aromatic compound. The nitrogen atom in pyridine is sp^2 hybridized nitrogen donates one electron to the π system and this along with one each from the five carbon atoms give pyridine a sextet of π electrons similar



to that in benzene. The non-bonding electrons of nitrogen are in an sp^2 orbital which lies in the plane of the ring and these electrons do not interact with the π system of the ring. The unshared pair of non-bonding electrons confers on pyridine the properties of a weak base. Thus pyridine protonates to yield the pyridinium ion which retains its aromatic character since the process does not disturb the electrons of the aromatic sextet.

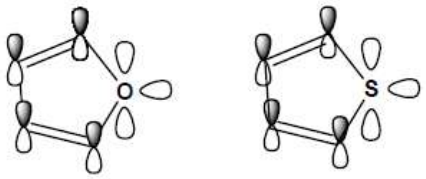
b) Pyrrole

In pyrrole only four π electrons are contributed by the carbon atoms of the ring. To make an aromatic sextet the SP_2 hybridized nitrogen then contributes two electrons. Pyrrole is far less

basic than pyridine because these apparently unshared electrons are in the aromatic π cloud. These are not readily available for bonding with proton (protonation).

c) Furan and thiophene

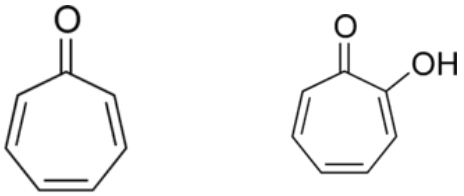
Both furan and thiophene have two pairs of electrons on the hetero atoms and therefore, combine the structural features of pyrrole and pyridine. One pair of electrons is in the sixelectron π system and other lies in the plane of the ring.



Furan Thiophene

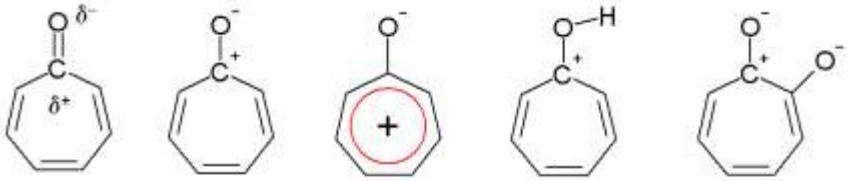
7.10 Tropone and Tropolone

It is a non-benzenoid aromatic compound. This compound consists of a ring of seven carbon atoms with three conjugated double bonds groups and a ketone group. Dewar in 1945 proposed that tropones have aromatic properties. The carbony group in tropones is polarized with a partial positive charge on the carbon atom and a partial negative charge on oxygen.



Tropone Tropolone

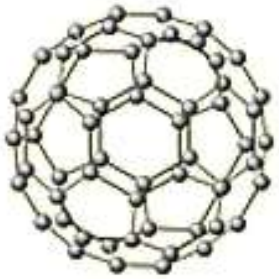
In an extreme case the carbon atom has a full positive charge and forming atropylium ion ring which is an aromatic 6 electron system.



According to huckel's rule tropone and tropolone must be anti-aromatic because they contain 8π electrons. But they are having aromatic character. The reason for this is electrogegative oxygen in this case pulls the pi-electrons towards itself and produces tropylium cation structure. This is why tropolone exhibits aromatic character and undergoes electrophillic substitution.

7.11 Fullerene C -60

Fullerenes consist of 20 hexagonal and 12 pentagonal rings as the basis of an icosohedral symmetry closed cage structure. Each carbon atom is bonded to three others and is sp^2 hybridised. The C60 molecule has two bond lengths - the 6:6 ring bonds can be considered "double bonds" and are shorter than the 6:5 bonds.C60 is not "superaromatic" as it tends to avoid double bonds in the pentagonal rings, resulting in poor electron delocalisation. As a result, C60 behaves like an electron deficient alkene, and reacts readily with electron rich species. The geodesic and electronic bonding factors in the structure account for the stability of the molecule. In theory, an infinite number of fullerenes can exist, their structure based on pentagonal and hexagonal rings, constructed according to rules for making icosahedra.



Fullerenes are highly stable chemically and have a variety of unusual properties. Chemists have been able to add branches of other molecules to them, place atoms inside of them, and stretch them into rods and tubes. Fullerenes can be made to be magnetic, act as superconductors, serve as a lubricant, or absorb light. Fullerenes are not "aromatic aromatic compounds and they are electron- deficient molecules. They form multiple-charged anions with electron donating species.

7.12 Summary of the unit

Completely conjugated monocyclic hydrocarbons are called annulenes. [10]-annulene molecule experiences considerable steric interaction between hydrogens at 1 and 6 positions. Further, a planar form (regular decagon) requires an angle of 144^o between carbon atoms which is too large to accommodate in a sp^2 framework. [12]-annulene (4n, n = 3) is an antiaromatic compound. Bond lengths in [14]-annulene range from 1.35-1.41Å but do not show the alternating pattern of localized polyenes. It is aromatic (except for the isomers that are not planar). NMR shows that it is in conformational equilibrium. [16]-annulene compound has 16πelectrons and does not conform to Huckel's rule. Therefore it should be non aromatic. [16]-annulene shows significant bond alteration, characteristic of a polyene structure (C-C, 1.46Å; C=C, 1.34 Å). It is nonplanar. Its dianion shows aromatic character

(4n+2 systems). Homoaromaticity is well established in cationic systems where delocalization of charge provides an additional driving force for homoaromaticity. Naphthalene is the simplest example of a polycyclic aromatic hydrocarbon, a compound which has a number of benzene rings fused together. The carbons of these compounds are all sp^2 hybridized with trigonal planar geometry. As a result, the compounds are planar and highly conjugated. Huckel's rule does not apply to such fused systems. Anthracene has three benzene rings fused in a linear manner, so it is also expected to be aromatic. Its resonance energy has been calculated to be 84 kcal/mol (352 kJ/mol). Phenanthrene has three benzene rings fused in a bent manner, so it is also expected to be aromatic. Heterocyclic compounds can also be aromatic since for the application of Huckel's rule what one needs is a ring of atoms, all with unhybridized 'p' orbital in a planar arrangement in order that the 'p' orbital overlaps in a continuous ring. Thus the heterocyclic compounds are all aromatic. Fullerenes consist of 20 hexagonal and 12 pentagonal rings as the basis of an icosohedral symmetry closed cage structure. Each carbon atom is bonded to three others and is sp^2 hybridised.

7.13 Key words

Annulenes; Homoaromaticity; Fused rings; Heterocyclic compounds; Tropone; Tropolone; Fullerene C -60.

7.14 References for further study

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7.15 Questions for self understanding

1) Explain the aromaticity in [10] annulenes.
2) Explain the aromaticity in [12]-annulene
3) Explain the aromaticity in [14]-annulene
4) Explain the aromaticity in [16]-annulene
5) Explain the aromaticity in [18]-annulene
6) What are homoaromatic compounds? Give one example
7) Write a note aromaticity Pyrrole, Pyridine, furan and thophene.

8) Explain the aromaticity in naphthalene and anthrcene.
9) Write a note on aromaticity in tropone
10) Explain the structure of Fullerene C-60,
11) Is fullerene is aromatic? Give the reason.
12) What types of reactions are observed in Fullerene

Unit - 8

Structure

8.0 Objectives of the unit

After studying this unit you are able to

- Explain the structure of azulenes
- Explain the structure of Ferocene
- Explain the structure of tropylium salt
- Explain the structure of crown ethers
- Explain the structure of catenanes
- Explain the structure of cryptands
- Explain the structure of cyclodextreins

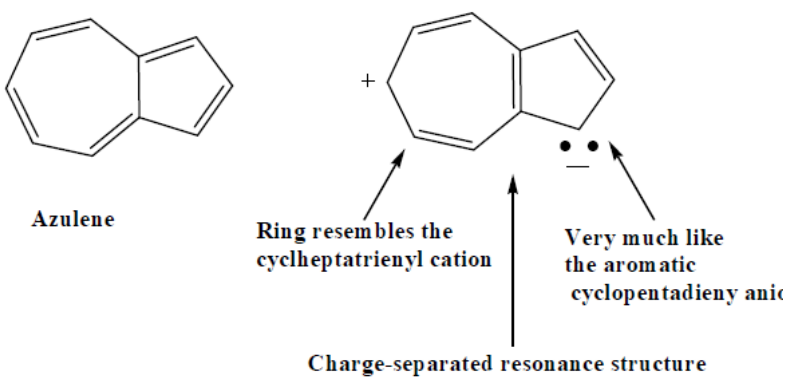
8.1 Introduction

Like aromatic compounds, many molecules have very interesting structural features and properties. In this unit we will study such types of compounds and their properties.

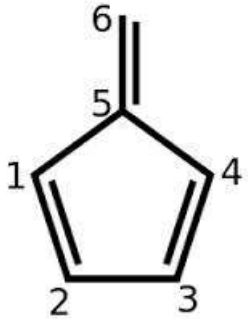
8.2 Azulenes

Azulene is one of the few completely conjugated non-benzenoid hydrocarbons that appear to have appreciable aromatic stabilization. The parent hydrocarbon and many of its derivatives have been well characterized and are stable compounds. The structure of azulene itself has been determined by both X-ray and electron-diffraction measurements. The peripheral bond lengths are in the aromatic range and show no regular alteration. The bond shared by the two rings is significantly longer, indicating dominant single-bond character.

Azulene has resonance energy of 49 kcal/mol. It has a substantial dipole moment (1.0 D) while the dipole moment of the isomeric compound naphthalene is 0. That presence of dipole moment in azulene suggests that charge separation exists in the molecule and that each ring approximates to six π-electron system. Azulene may be regarded as a combination of aromatic cyclopentadienyl anion and aromatic cycloheptatrienyl cation. Thus in valence bond terms, the ionic structure of azulene (a non-benzenoid aromatic compound) is an important contributor to the resonance bond.



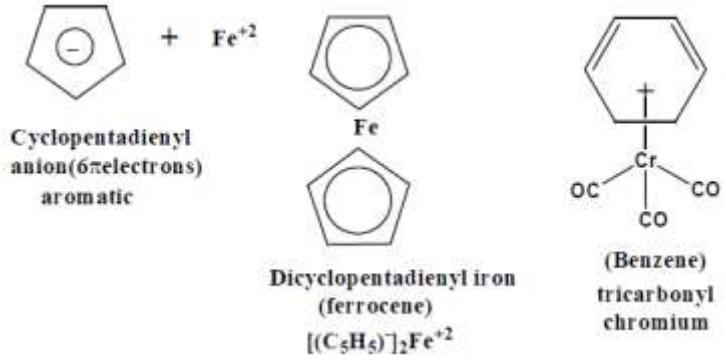
8.3 Fulvene



Fulvene is an isomer of benzene first prepared by Thiele in his quest for new aromatic compounds. In order to be aromatic, a molecule must first be planar, and possess a cyclic, conjugated double bond system. In the fulvene molecule, all the carbon atoms are sp^2 hybridized, and the molecule is planar. The molecule consists of alternating single and double bonds hence it is conjugated, but the molecule does not have the linear conjugation required for aromaticity it is cross-conjugated instead. Consequently, we expect that fulvene will be neither aromatic nor antiaromatic; it is non-aromatic.

8.4 Ferrocene

Ferrocene is an aromatic compound (non-benzenoid) which is highly stable and undergoes a number of electrophilic aromatic substitutions. The carbon-carbon bond distances are also 1.40 Å and carbon-iron bond distances are all 2.04 Å. Due to these structural features the compounds like Ferrocene they are called "Sandwich" compounds. The carbon iron bonding in Ferrocene may be looked upon as a result from overlap between the inner lobes of the '*p*' orbital of the cyclopentadienyl anions and 3d orbital of the iron atoms. A noteworthy feature of many organic derivatives of transition metals is that the organic group is bonded to the metal through the π system rather than by a 'σ'bond as in (benzene/tricarbonyl chromium).



The two cyclopentadienyl (Cp) rings of ferrocene may be orientated in the two extremes of either an eclipsed or staggered conformation. The energy of rotation about the Fe-Cp axis is

very small (~ 4kJmol^{-1}) hence the ground state structures of ferrocene may show either of these conformations. There is also very little difference in electronic states between the *eclipsed* and *staggered* symmetries however the *staggered* representations are used here in the description of the electronic structure of ferrocene as they simplify the symmetry matching of ligand molecular orbitals and metal atomic orbitals.

The primary orbital interactions that form the metal-ligand bonds in ferrocene occur between the Fe orbitals and the π-orbitals of the Cp ligand. If *staggered* symmetry is assumed, so that there is a centre of symmetry in the ferrocene molecule.

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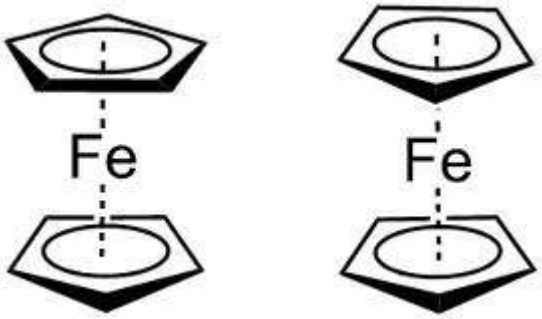


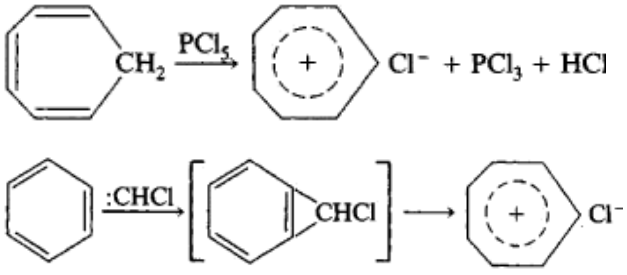
Staggered Eclipsed

8.5 Ttropylium salts

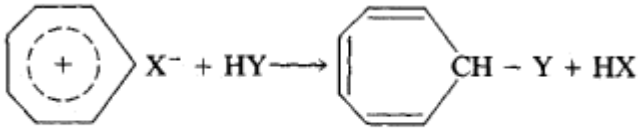
The tropylium cation is an aromatic nonbenzenoid carbonium ion whose charge is delocalized among all the carbon atoms of the seven-carbon ring.

Salts

Tropylium Cation forms salts with strong acids. Methods for the preparation of these salts are based on the reaction of cyclohepta-triene with phosphorus pentahalides or of benzene with halocarbenes as shown below.



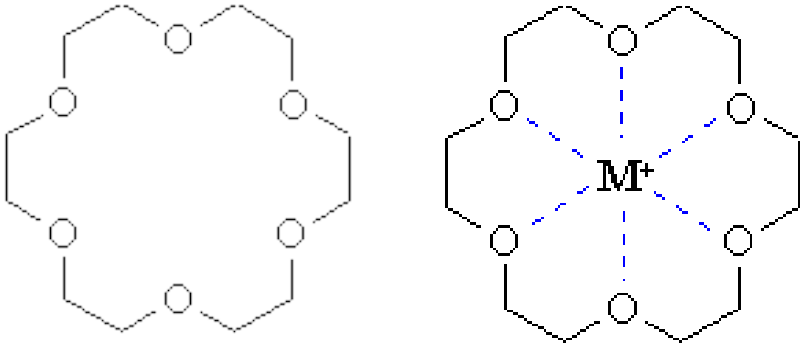
Tropylium salts are generally solids and are soluble in polar solvents. The melting points of tropylium chloride, bromide, and iodide are 102°, 203°, and 136°C, respectively. The resonance energy of tropylium cation is 84 kilojoules per mole (kJ/mole), i.e., 20 kilocalories per mole (kcal/mole); therefore the salts formed are stable. Unlike other aromatic compounds, tropylium salts do not react with electro-philic reagents. Nucleophiles, including weak acids, convert tropylium salts into substituted cycloheptatrienes with covalent structure.



(Y = OOCR, OR, NHR, and so on)

8.6 Crown ethers

Crown ethers are macrocyclic compounds containing equally spaced linkages in a large ring system. They readily form complexes with metal salts or ammonium salts. Crown ether contains hydrogen, carbon and oxygen atoms. These ethers are called "crown ethers" due to their shape. Each oxygen atom is bound between two of the carbon atoms and arranged in a ring. Oxygen atoms are capable of acting as Lewis bases due to the presence of the lone pairs.



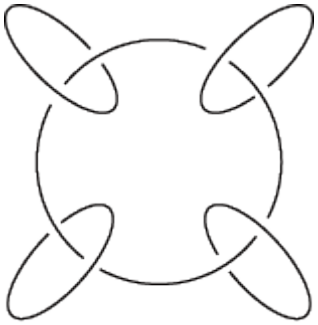
Crown ethers are named as x-crown-y where x denotes the total number of atoms in the cyclic backbone and y denotes the number of oxygen atoms. Depending on size, number and type of heteroatom, crown ethers can exhibit selectivity toward specific metal cation. For example, 12-crown-4 prefers to form complex with Li^+, where as 18-crown-6 prefers K^+. These crown-metal complexes are referred to as hos-guest chemistry where the crown ether is the host and the metal cation is the guest. Hence crown ether are used to separate cations, dissolve inorganic salts in to organic covalent to perform naked anion chemistry, serve as phase transfer catalyst and chiral crown ethers have been used to resolve recemic mixtures or separate isomers by chiral chromatography.

8.7 Catenanes

Compounds of interlocking macrocycles are called catenanes. The interlocking rings are said to be mechanically rather than chemically bound. Catenanes are named according to the number of interlocking rings. The simplest catenane containing two interlocking rings, is called [2]-catenane. The most common catenanes consist of a linear arrangement of interlocking rings, so [2]-catenane is the first member of this series.

Molecular catenanes are synthetic compounds. However, natural deoxyribonucleic acid (DNA) macromolecules were shown to assemble into catenated structures under certain conditions. The rings of the catenanes may be purely organic macrocycles or metallomacrocycles, that is, macrocycles including transition-metal ions in their bond sequences. Actually, the chemical nature of the ring is dictated by the method of synthesis.

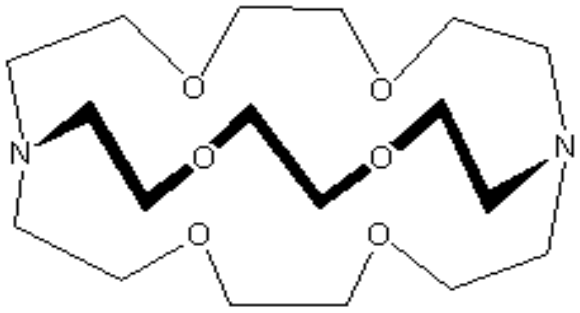
Linear catenanes



Necklace catenanes

8.8 Cryptands

Cryptands are a family of synthetic bi- and polycyclic multidentate ligands for a variety of cations. These molecules are three dimensional analogues of crown ethers but are more selective and complex the guest ions more strongly. The resulting complexes are lipophilic.



Structure

The most common and most important cryptand is $N[CH_2CH_2OCH_2CH_2OCH_2CH_2]_3N$; the formal name for this compound is 1,10-diaza-4,7,13,16,21,24 hexaoxabicyclo [8.8.8] hexacosane. So it is easy to see why the common name of "cryptand" was preferable. This compound is termed **[2.2.2]cryptand**, where the numbers indicate the number of ether

oxygen atoms (and hence binding sites) in each of the three bridges between the amine nitrogen "caps". Many cryptands are commercially available under the tradename "Kryptofix." All-amine cryptands exhibit particularly high affinity for alkali metal cations, which has allowed the isolation of salts of K^-.

Properties

The three-dimensional interior cavity of a cryptand provides a binding site - or nook - for "guest" ions. The complex between the cationic guest and the cryptand is called a cryptate. Cryptands form complexes with many "hard cations" including NH_4^+, lanthanides, alkali metals, and alkaline earth metals. In contrast to typical crown ethers, cryptands bind the guest ions using both nitrogen and oxygen donors. Their three-dimensional encapsulation mode confers some size-selectivity, enabling discrimination among alkali metal cations (e.g. Na^+ vs. K^+).

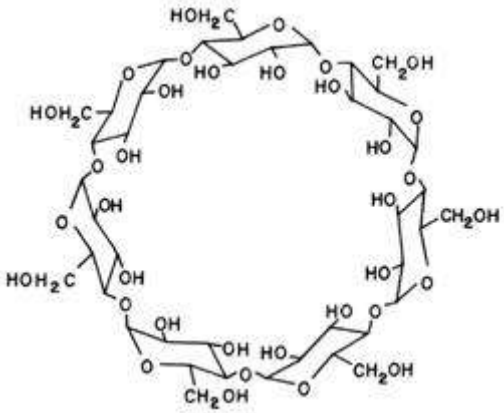
Uses

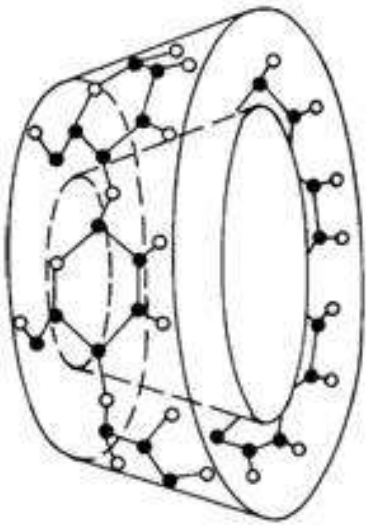
Cryptands although they are more expensive and more difficult to prepare offer much better selectivity and strength of binding than other complexants for alkali metals, such as crown ether they are able to extract otherwise insoluble salts into organic solvents. Cryptands increase the reactivity of anions in salts since they effectively break up ion-pairs. They can be also be used as phase transfer catalysts by transferring ions from one phase to another cryptands enabled the synthesis of alkalides and.

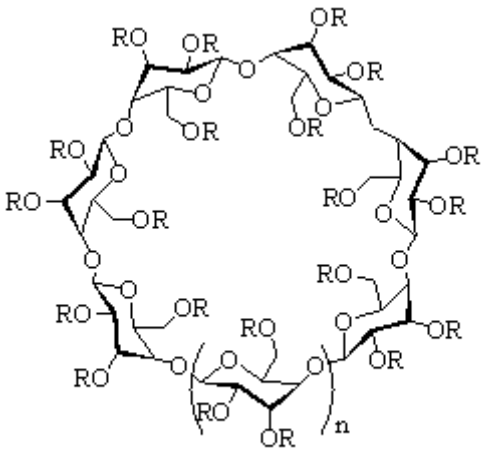
8.9 Cyclodextrin

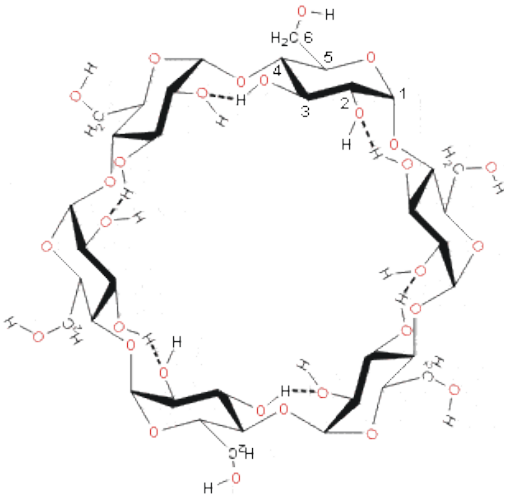
Cyclodextrins are a group of structurally related natural products formed during bacterial digestion of cellulose. These cyclic oligosaccharides consist of (α-1,4)-linked α-D-glucopyranose units and contain a somewhat lipophilic central cavity and a hydrophilic outer surface. Due to the chair conformation of the glucopyranose units, the cyclodextrins are shaped like a truncated cone rather than perfect cylinders. The hydroxyl functions are orientated to the cone exterior with the primary hydroxyl groups of the sugar residues at the narrow edge of the cone and the secondary hydroxyl groups at the wider edge. The central cavity is lined by the skeletal carbons and ethereal oxygens of the glucose residues, which gives it a lipophilic character. The polarity of the cavity has been estimated to be similar to that of an aqueous ethanolic solution. The natural α-, β- and γ-cyclodextrin consist of six, seven, and eight glucopyranose units, respectively. The natural cyclodextrins, in particular β-cyclodextrin, are of limited aqueous solubility meaning that complexes resulting from interaction of lipophiles with these cyclodextrin can be of limited solubility resulting in

precipitation of solid cyclodextrin complexes from water and other aqueous systems. In fact, the aqueous solubility of the natural cyclodextrins is much lower than that of comparable acyclic saccharides. This is thought to be due to relatively strong intermolecular hydrogen bonding in the crystal state. Substitution of any of the hydrogen bond forming hydroxyl groups, even by lipophilic methoxy functions, results in dramatic improvement in their aqueous solubility. Cyclodextrin derivatives of pharmaceutical interest include the hydroxypropyl derivatives of β- and γ-cyclodextrin, the randomly methylated β-cyclodextrin, sulfobutylether β-cyclodextrin, and the so-called branched cyclodextrins such as glucosyl-β-cyclodextrin.









8.10 Summary of the unit

The structure of azulene itself has been determined by both X-ray and electron-diffraction measurements. The peripheral bond lengths are in the aromatic range and show no regular alteration. The bond shared by the two rings is significantly longer, indicating dominant single-bond character. Fulvene is an isomer of benzene first prepared by Thiele in his quest for new aromatic compounds. In order to be aromatic, a molecule must first be planar, and

possess a cyclic, conjugated double bond system. Ferrocene is an aromatic compound (non-benzenoid) which is highly stable and undergoes a number of electrophilic aromatic substitutions. The tropylium cation is an aromatic nonbenzenoid carbonium ion whose charge is delocalized among all the carbon atoms of the seven-carbon ring. Crown ethers are macrocyclic compounds containing equally spaced linkages in a large ring system. They readily form complexes with metal salts or ammonium salts. Crown ether contains hydrogen, carbon and oxygen atoms. These ethers are called "crown ethers" due to their shape. Compounds of interlocking macrocycles are called catenanes. The interlocking rings are said to be mechanically rather than chemically bound. Catenanes are named according to the number of interlocking rings. The simplest catenane containing two interlocking rings, is called [2]-catenane. The most common catenanes consist of a linear arrangement of interlocking rings, so [2]-catenane is the first member of this series. Cryptands are a family of synthetic bi- and polycyclic multidentate ligands for a variety of cations. Cyclodextrins are a group of structurally related natural products formed during bacterial digestion of cellulose. These cyclic oligosaccharides consist of (α-1,4)-linked α-D-glucopyranose units and contain a somewhat lipophilic central cavity and a hydrophilic outer surface

8.11 Key words

Azulenes; Ferrocene; Tropylium salts; Crown ethers; Catenanes; Cryptands; Cyclodextrin.

8.12 References for further study

13) Aromatic Organic Chemistry, Amit Arora, *Discovery Publishing House*, **2006**.
14) Aromatic character and aromaticity, *CUP Archive*
15) Organic Chemistry, Volume 2, Roger S. Macomber, *University Science Books*, **1996**.
16) Textbook of Organic Chemistry, Volume 1, V. K. Ahluwalia, *Ane Books Pvt Ltd*, **2010**.
17) March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Michael B. Smith, Jerry March, *John Wiley & Sons*, **2007**.
18) Molecular Structure: Understanding Steric and Electronic Effects from Molecular Mechanics, Norman L. Allinger, *John Wiley & Sons*, **2010.**

8.13 Questions for self understanding

1) Discuss the structure and arromaticity in Azulenes
2) Write a note on structure of Ferrocene
3) Why Tropylium salts are soluble in non polar solvent?
4) Discuss the arromaticity of Tropylium cation
5) What are Crown ethers?

6) What are the uses of crown ethers?
7) Discuss the structure of Catenanes
8) What are Cryptands? Write a note on their structure
9) Write a note on Cyclodextrin.

Unit – 9

Structure

9.0 Objectives of the unit

After studying this unit you are able to

- Identify the different reaction intermediates involved in organic reactions
- Explain the synthesis of different reaction intermediates
- Determine their stereochemistry and stability
- Write the mechanisms of reactions involved in these intermediates
- Identify the products with each intermediates reacts in organic reactions
- Explain the methods for detection of these intermediates

9.1 Introduction

Electronegativity of the atoms has a great role in deciding the type of organicreactions shown by the any compound. On the basis of this electronegativitydifference between two atoms forming the covalent bonds in a compound thenature of organic reactions & nature of attacking reagents are decided.On the basis of electronegativity difference only, a covalent bond of organiccompound is broken by two different ways to generate different types of shortlived species which are commonly called as reaction intermediates.

First ways

When electronegativity between two bonding atom is same or nearly same, then on breaking of bond, one electron of the bonding pair goes with each of the leaving atom. Such type of bond breaking is called as homolytic breaking, hemolytic cleavage, homolytic fission or homolysis. Ex

$A - B \rightarrow A^{\cdot} + B^{\cdot}$

Homolysis always give rise to free radicals. If carbon acquires such arrangement then it is called as carbon free radical .Homolysis in organic chemistry is mainly seen in alkanes where electronegativity of carbon-carbon bond is same and that of carbon-hydrogenbond is nearly same. Such species are very reactive and the reactions which proceed through hemolytic fission are known as free radical reactions. These free radicals are transitory and react with other radicals or molecules by gaining one or more electron to restore the stable bonding pair. This homolytic fission generally takes place either in presence of light, heat or in presence of peroxides.

Second ways

When electronegativity between the two bonding atoms is not same, then on breaking of bond both the bonding electron goes to one of the atom. Such breaking is called as heterolytic breaking, heterolytic cleavage, heterolytic fission or heterolysis. Ex

$A - B \rightarrow A^{+} + B^{-}$

Or

$A - B \rightarrow A^- + B^+$

Heterolysis always gives anion & cation. If carbon acquires positive charge then it is called as carbocation & if carbon acquires negative charge then it is called as carbanion. The species free radicals, carbocations ans carbanions are called as reaction intermediates, they are exists for short periods during the course of reaction. Like it is possible to generate reaction intermediates like carbenes, nitrenes, arynes tec…. Each reaction intermediates undergo characteristic reactions hence it is possible to predict the reaction mechanism. Reaction intermediates are studied by, traping intermediates, analysing product, cross product experiments, spectroscopy techniques and various other methods. In this unit we are going to study the preparation properties and reactions of organic intermediates and their analysis.

9.2 Reaction intermediates

A reaction intermediate or an intermediate is a molecular entity that is formed from the reactants (or proceeding intermediates) and reacts further to give the directly observed products of a chemical reaction. Most chemical reactions are stepwise, that is they take more than one elementary step to complete. An intermediate is the reaction product of each of these steps, except for the last one, which forms the final product. Reactive intermediates are usually short lived and are very seldom isolated. Also, owing to the short lifetime, they do not remain in the product mixture.

For example, consider this hypothetical stepwise reaction:

$A + B \rightarrow C + D$

The reaction includes these elementary steps:

$A + B \rightarrow X^*$

$X^* \rightarrow C + D$

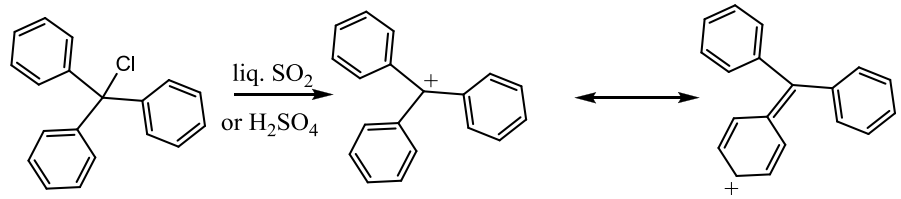
The chemical species X* is an intermediate

When their existence is indicated, reactive intermediates can help explain how a chemical reaction takes place. A reactive intermediate differs from a reactant or product or a simple reaction intermediate only in that it cannot usually be isolated, but is sometimes observable only through fast spectroscopy methods. When a reactive intermediate is not an observable, its existence must be inferred through experimentation. This usually involves changing reaction conditions such as temperature or concentration and applying the techniques of chemical kinetics, chemical thermodynamics or spectroscopy. Reactive intermediates based on carbon are radicals, carbebes, carbocations, carbanions arynes and carbynes.

9.3 Carbocations

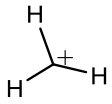
Species containing trivalent, positively charged carbon are implicated as intermediates in a wide variety of reactions and some stable forms have been known since the beginning of this century. The more stable carbocation have been prepared in solutions and in a few cases even as solid state. In solutions, carbocation ion may be free or many exist as ion pair.

The formation of deep yellow colour on solutions of Ph_3CX in certain solvents was reported in 1902 by Gamberg and Norris. They attributed this reversible change to what today is called "ionic dissociation", the ions being intensely coloured.

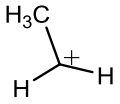


a) Classification

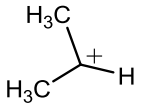
They are classified as classical and nonclassical carbocations. Classical carbocations are further classified as primary, secondary and tertiary carbocations.



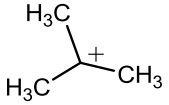
Methyl C^+ ion



Ethyl C^+ ion



Isopropyl C^+ ion



Mt-butyl C^+ ion

b) Methods of formation

i. Dissociation of alkyl halides: For ionization to occur, a highly solvating solvating medium is necessary.

$$Me_3CCl \longrightarrow Me_3C^+ + Cl^-$$

$$PhCH_2Cl \longrightarrow PhCH_2^+ + Cl^-$$

$$H_2C{=}CHCH_2Cl \longrightarrow H_2C{=}CHCH_2^+ + Cl^-$$

$$CH_3OCH_2Cl \longrightarrow CH_3OCH_2^+ + Cl^-$$

ii. From amines: Through the formation of diazonium salt.

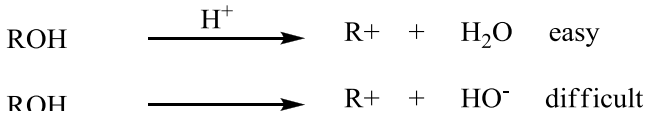
$$RNH_2 \xrightarrow[HCl]{HNO_2} R\text{-}N_2^+\,Cl^- \longrightarrow R^+$$

iii. From aromatic substitution:

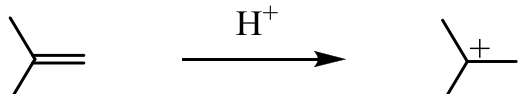
These species are believed to be transcient intermediate in aromatic electrophilic substitution. The existence of intermediate is inferred from the lack of kinetic isotopic effect on the reaction

iv. From alcohols:

The carbocation is formed by dissociation of protonated alcohol involves a separation of charged particle from a neutral species water.

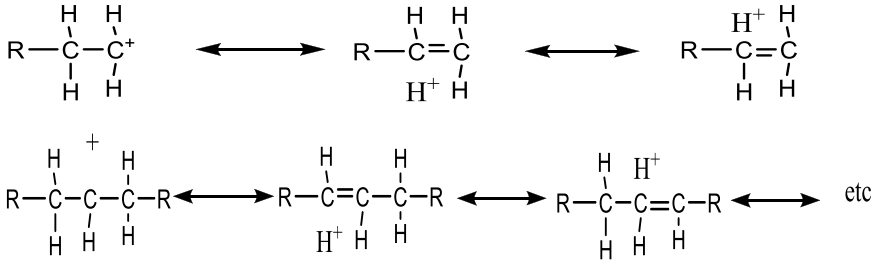


v. Protonation of alkenes: Addition of hydrogen ion to alkenes to form the carbocation.



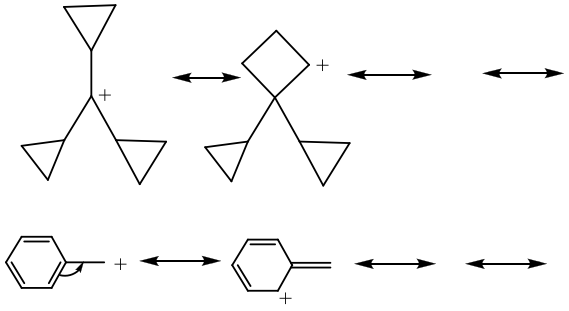
c) Stability of carbocation

The inductive effect explanation is that alkyl group attached to electron deficient carbon of carbocation tends to release electron to that carbon and thus reduce its positive charge. Thus a tertiary carbocations with three alkyl group is more stable than a secondary with two alkyl groups in turn is more stable than a primary ion with only one. The stability order may also be explained by hyperconjugation. If we compare a primary carbocation with tertiary, it is seen that there are many more canonical form possible for the latter.



Another factor responsible for the greater stability of tertiary carbocation is β-strain. If the halide is tertiary, and the three alkyl groups are large enough, they will be pushed together by the enforced` tetrahedral angle resulting in strain. This type of strain is called β-strain.

Tricyclopropyl methyl carbocations are more stable than triphenyl methyl carbocation.

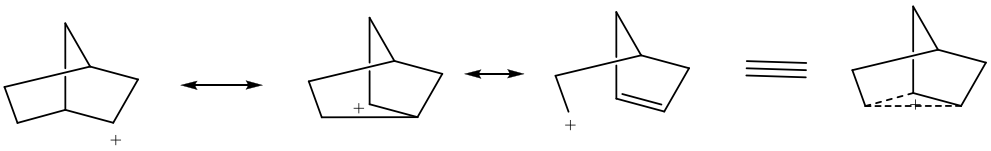


d) Non-classical carbocations (brigded carbocation)

Thre are two types of non classical carbocations are present, they are

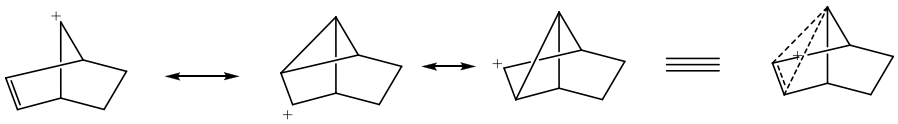
1. Electron defficient non-classical carbocation

Canonical forms may be drawn which involve unsaturation which is not on the adjacent atom.



2. Electron sufficient non-classical carbocation

We may draw canonical form which donot involve unsaturation at all. These canonical forms involve overlap with the σ- orbitals of C-C single bond.



9.4 Stereochemistry of carbocation

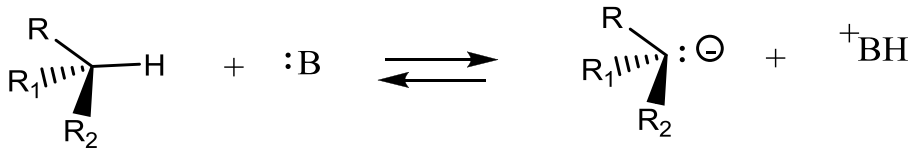
When six bonding electrons are arranged about a carbon atom, thus most stable electronic configuration is such that they part of the maximum amount of s character in their orbitals. Therefore the orbitals in a carbocation $RR_1R_2C^+$have sp2 hybridized and the ion in a planar with valence angle of 120^o. Carbocations which have substituents capable of conjugative delocalization of the electron pair will perforce be planar in order to allow the maximum overlap of the p-orbitals with those of the substituent (eg. allyl carbocation).

9.5 Carbanions

A carbanion is an anion in which carbon has an unshared pair of electrons and bears a negative charge usually with three substituents for a total of eight velence electrons.. The carbanion exists in a trigonal pyramidal geometry. Formally, a carbanion is the conjugate base of a carbon acid, where B stands for the base. A carbanion is one of several reactive intermediates in organic chemistry

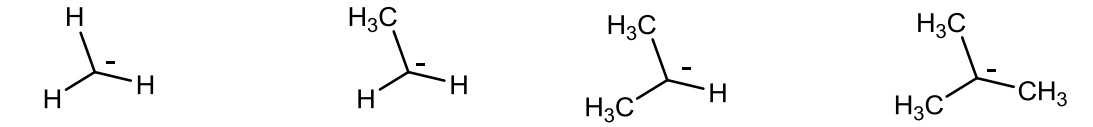
$R_3C\text{-}H + B^- \rightarrow \mathbf{R_3C^-} + H\text{-}B$

Many organic reactions appear to depend upon the ability of C-H bond to break heterolytically under appropriate conditions and give up a proton to a base. What remains is a speies containing a trivalent carbon atom with lone pair of elctron pair isoelectronic with an amine and known as carbanions.



c) **Classification**

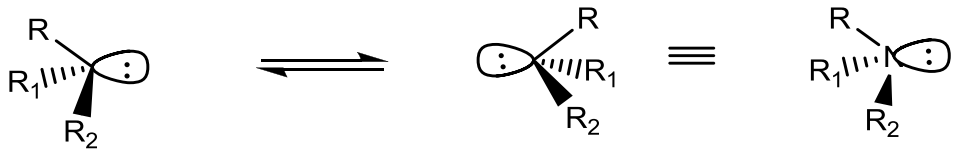
They are classified as as primary, secondary and tertiary carbocations.



Methyl C^- ion Ethyl C^- ion Isopropyl C^- ion Mt-butyl C^- ion

Primary Secondary tertiary

The geometry of carbanions may be described in terms of a pyramidal model in which carbon uses sp3-hybridized orbitals and readily undergoes inversions like an amine. Thus it has proved impossible to establish substantial retention of configuration in RR_1R_2C groups in reactions in which the carbanion intermediate are known to be involved. Positive evidence in support of a preferred sp3 configuration is provided by the observation that RR_1R_2C reaction takes place readily at bridgehead carbon, where the corresponding RR_1R_2C reaction fail.



Carbanions which have substituents capable of conjugative delocalization of the electron pair will perforce be planar in order to allow the maximum overlap of the p-orbitals with those of the substituent.

d) **Stability**

A carbanion is a nucleophile. The stability of a carbanion therefore may be appliedwith its basicity and hence the acidity of the corresponding carbon acids. The order of stability in carbanions is reverse to that of carbocation ions, ie., prim> sec> ter. The order is well documented in metal alkyls. For instance, CH_3Li is stable in ether while t-butyl lithium decomposes to give ethylene. The carbanion can be stabilized largely by electron withdrawing substitution unlike the carbocations which are stabilized by conjugation and inductive effects. The main features that serve to stabilize carbanions are

i. increase in s character at the carbon atom

ii. Electron withdrawing inductive effects

iii. Conjugation of the carbanion lone pair with multiple bond and

iv. Through aromatization.

9.6 Free radicals

A free **radical** (more precisely, a **free radical**) may be defined as a specis that contain one or more unpaired valence electrons. Example: methyl radical, triphenyl methyl radical, chlorine atom (Cl.), the nitric oxide .NO etc., each of which has a single unshared electron. The majority are electricllay neutral (some e free radical ions are known). All possess addition properties andare extreemly reactive, when a free radical is stabl its stability is believed due to resonance. Free radicals are paramagnetic, ie., it possessa small permanent magnetic moment due to the presence of odd (unpaired) electrons. The property is used to detect the presence of free radicals. Free radicals can therefore be detected by magnetic suceptibility measurements but for this technique a relatively high concentration of radicals is required. A much more important technique is electron spin resonance.

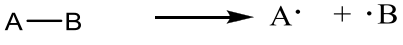
Radical alkyl intermediates are stabilized by similar physical processes to carbocations: as a general rule, the more substituted the radical center is, the more stable it is. This directs their reactions. Thus, formation of a tertiary radical ($R_3C\cdot$) is favored over secondary ($R_2HC\cdot$), which is favored over primary ($RH_2C\cdot$). Likewise, radicals next to functional groups such as carbonyl, nitrile, and ether are more stable than tertiary alkyl radicals.

c) **Configuration of free radicals**

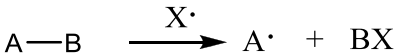
There are two possible structures for simple alkyl radicals. They might have sp^2 bonding, in which case the structure would be planar, with the odd electron in a p orbital, or the bonding might be sp^3, which would make the structure pyrimidal and place the odd electron in an sp^3 orbital. ESR spectra of methyl radical and other simple alkyl radicals as well as the other evidence indicate that these radicals have planar structure. This is in accordance with the known loss of optical activity when a free radical is generated at an assymmetric carbon. In addition, electronic spectra of CH_3 and CD_3 radicals (generated by flash photolysis) in the gas phase has definitely established that under these conditions the radicals are planar or near planar. IR spectra of CH3 radical trapped in solid argon led to a similar conclusion.

Free radicals are formed in two general ways:

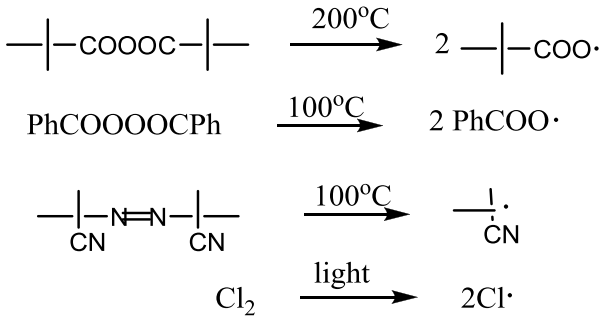
i. Through homolytic cleavage of bonds



ii. By reaction of molecules with other free radicals

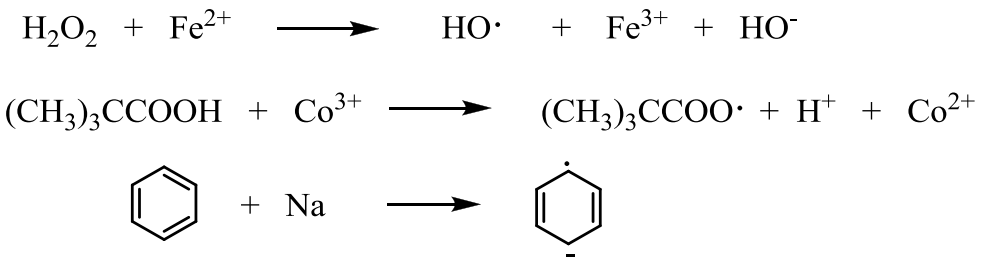


The formation of radicals may involve breaking of covalent bonds homolytically, a process that requires significant amounts of energy. For example, splitting H_2 into 2H· has a $\Delta H°$ of +435 kJ/mol, and Cl_2 into 2Cl· has a $\Delta H°$ of +243 kJ/mol. This is known as the homolytic bond dissociation energy, and is usually abbreviated as the symbol *DH*°. The bond energy between two covalently bonded atoms is affected by the structure of the molecule as a whole, not just the identity of the two atoms. Likewise, radicals requiring more energy to form are less stable than those requiring less energy. Homolytic bond cleavage most often happens between two atoms of similar electronegativity.



Free radicals formed in this ways are most often the generation of other free radicals. For instance,

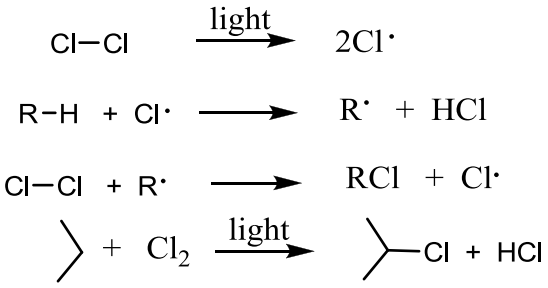
Free radicals may also be generated by various oxidation reduction processess. Transfer of electrons from metal atoms and ions is a common method for initiating radical reactions. Electrochemical oxidation-reduction also is gaining importance in organic chemical process.



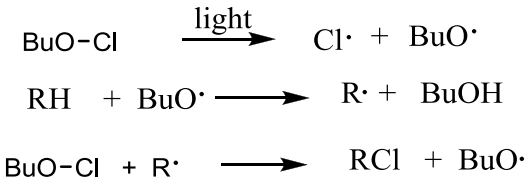
d) **Reactions of free radicals**

Saturated hydrocarbons and aromatic side chains undergo substitution by chlorine in a typical radical chain processess. The reaction is catalyzed by light, peroxides and other radical sources and is inhibited by oxygen, thiols, hydroquinone etc. Free radicals also take part in radical addition and radical substitution as reactive intermediates. Chain reactions involving

free radicals can usually be divided into three distinct processes. These are *initiation*, *propagation*, and *termination*.



In these examples there is preferred order of attack at ter > sec > pri and benyllic > non-benzyllic carbons which is consistent with the formation of the most stable radical.

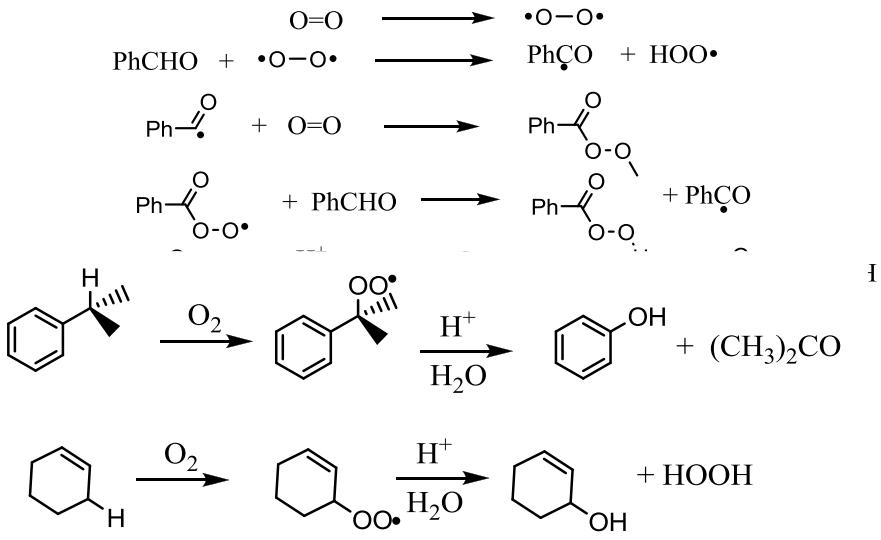


i) Autooxidation

The direct reaction of oxygen with organic compounds is termed autooxidation, the primary product being peroxy compounds which are often isolable.

$$RH + O_2 \dashrightarrow ROOH$$

This reaction is of great practical importance: useful auto oxidation include the dying of oils in paints and varnishes, while on the debit side the deteriotion of rubber and spoilage of food in air occurs by this type of reaction. Auto oxidation are fairly selective and are especially prone to occur when a tertiary, allylic or benzyllic hydrogen is available for abstraction. The auto oxidation of benzaldehyde has been studied in detail and emphasizes the characteristic of many auto oxidation.



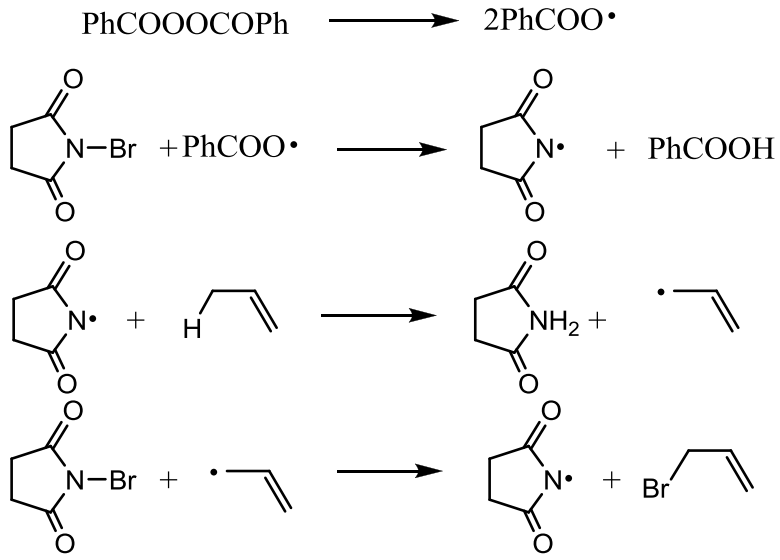
The formation of linear polymers from certain ethylenic compounds by a radical chain mechanism is one of the most typical of such reactions, on account of the practical importance of the products as plastic materials.

ii) **Halogenation**

In contrast to electrophilic halogenation by chlorine or bromine promoted by Lewis acids, radical halogenation leads to addition with the ultimate formation of a substituted product. Thus benzene reacts with chlorine when irradiated with UV or sunlight to produce a mixture of isomeric hexachlorocyclohexanes [one of which (gammexane) has been used as the insecticide].

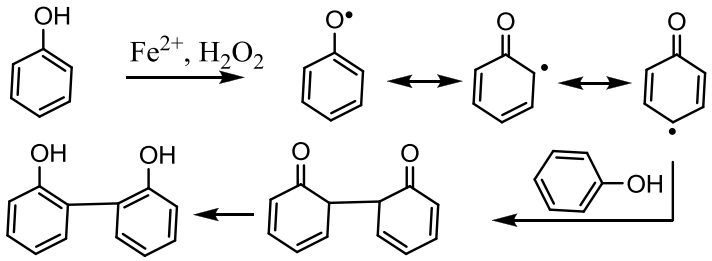
iii) **Allylic halogen substitution**

N-Bromosuccinimide has been found to be very useful reagent for the introduction of bromine into the allylic position, is adjacent to a double bond. The reaction is accelerated by added peroxides and by light and is retarded by the common radical inhibition. The bormination is best carried out in CCl_4, a solvent in which NBS is insoluble. The use of solvents in which the reagent is soluble leads to greatly reduced yields.It is believed that the radical process occur at the surface of the crystal rather than in solution.



iv) **Phenol coupling**

Phenol coupling is a very important process in the biological synthesis of many natural products and can be induced in vitro by the enzyme peroxidase in the presence of H_2O_2.



9.7 The Hunsedecker reaction

Treatment of the silver slat of a carboxylic acid with bromine results in the formation of alkyl bromide and loss of CO_2. The reaction has the characteristic of a radical process. The initial step is the formation of an acyl hypochlorite which may be detected in solution and which is decomposed by a chain mechanism. The reaction is often accomplished by at least partial racemization of an asymmetric group R.

$$RCOOAg + Br\text{-}Br \longrightarrow RCOOBr + AgBr$$

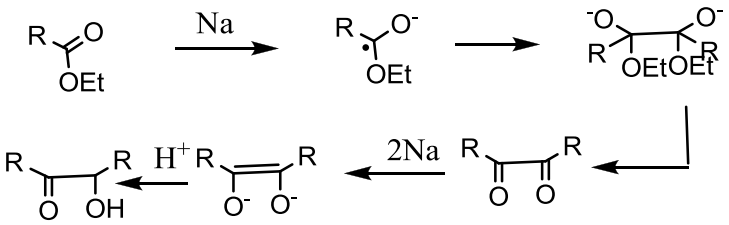
$$RCOOBrH \longrightarrow RCOO\bullet + Br\bullet$$

$$RCCO\bullet \longrightarrow R\bullet + CO_2$$

$$RCOOBr + R\bullet \longrightarrow RBr + RCOO\bullet$$

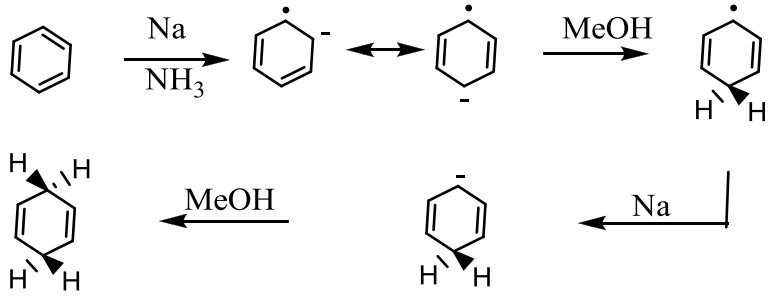
9.8 Acyloin synthesis

The treatment of carboxylic ester with liquid sodium in an inert solvent such as boiling xylene results in the formation of dimeric ketol.



9.9 Birch reduction

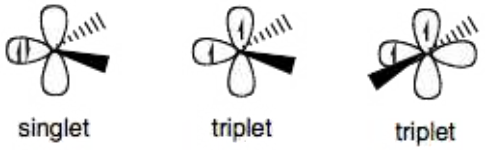
When sodium dissolved in liquid ammonia, a blue solution results, which is paramagnetic and contain solvated electron. The solvated electrons are capable of coordinating to an aromatic system to form the hexadiene radical, which in the presence of acid, accepts proton. The resulting radical is reduced to 1,4-dihydrobenzene.



9.10 Carbenes

In chemistry, a carbene is a molecule containing a neutral carbon atom with a valence of two and two unshared valence electrons. The general formula is R-(C:)-R' or R=C:. The term "carbene" may also refer to the specific compound H_2C:, also called methylene. Carbenes are classified as either singlets or triplets depending upon their electronic structure. Singlet carbenes are spin-paired. Triplet carbenes have two unpaired electrons. Most carbenes are very short lived, although persistent carbenes are known. One well studied carbene is Cl_2C: or dichlorocarbene, which can be generated *in situ* from chloroform and a strong base

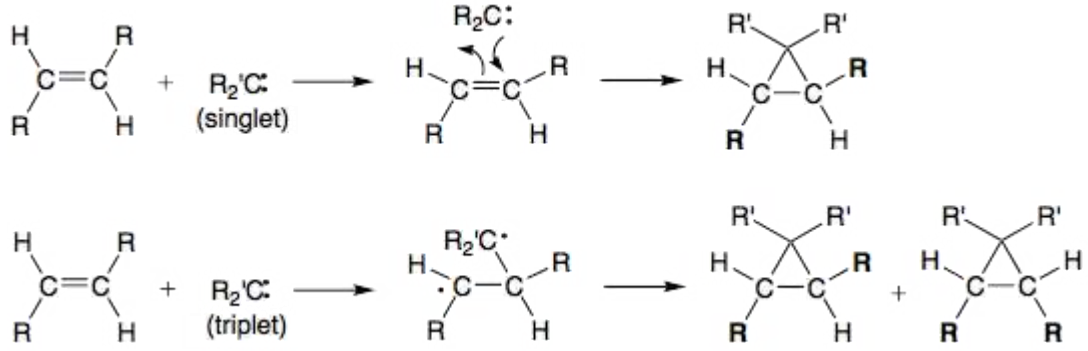
f) Structure and bonding



g) Singlet and triplet carbenes

Carbenes are called singlet or triplet depending on the electronic spins they possess. Triplet carbenes are paramagnetic and may be observed by electron spin resonance spectroscopy if they persist long enough. The total spin of singlet carbenes is zero while that of triplet carbenes is one (in units of $\hbar$). Bond angles are 125-140° for triplet methylene and 102° for singlet methylene (as determined by EPR). Triplet carbenes are generally stable in the gaseous state, while singlet carbenes occur more often in aqueous media.

Singlet and triplet carbenes exhibit divergent reactivity. Singlet carbenes generally participate in cheletropic reactions as either electrophiles or nucleophiles. Singlet carbenes with unfilled p-orbital should be electrophilic. Triplet carbenes can be considered to be diradicals, and participate in stepwise radical additions. Triplet carbenes have to go through an intermediate with two unpaired electrons whereas singlet carbene can react in a single concerted step.

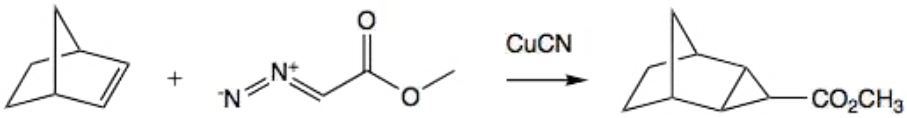


Due to these two modes of reactivity, reactions of singlet methylene are stereospecific whereas those of triplet methylene are stereoselective. This difference can be used to probe

the nature of a carbene. For example, the reaction of methylene generated from photolysis of diazomethane with *cis*-2-butene or with *trans*-2-butene each give a single diastereomer of the 1,2-dimethylcyclopropane product: *cis* from *cis* and *trans* from *trans*, which proves that the methylene is a singlet. If the methylene were a triplet, one would not expect the product to depend upon the starting alkene geometry, but rather a nearly identical mixture in each case.

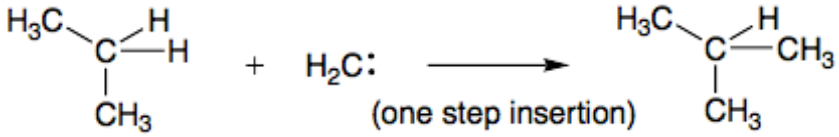
Reactivity of a particular carbene depends on the substituent groups. Their reactivity can be affected by metals. Some of the reactions carbenes can do are insertions into C-H bonds, skeletal rearrangements, and additions to double bonds. Carbenes can be classified as nucleophilic, electrophilic, or ambiphilic. For example, if a substituent is able to donate a pair of electrons, most likely carbene will not be electrophilic. Alkyl carbenes insert much more selectively than methylene, which does not differentiate between primary, secondary, and tertiary C-H bonds.

h) Cyclopropanation



Carbenes add to double bonds to form cyclopropanes. A concerted mechanism is available for singlet carbenes. Triplet carbenes do not retain stereochemistry in the product molecule. Addition reactions are commonly very fast and exothermic. The slow step in most instances is generation of carbene. A well-known reagent employed for alkene-to-cyclopropane reactions is Simmons-Smith reagent. This reagent is a system of copper, zinc, and iodine, where the active reagent is believed to be iodomethylzinc iodide. Reagent is complexed by hydroxy groups such that addition commonly happens syn to such group.

i) C—H insertion

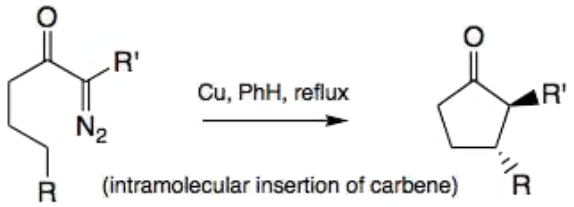


Carbene insertion

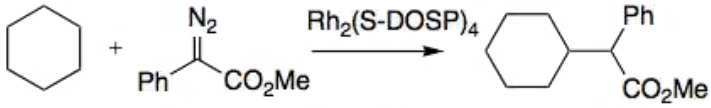
Insertions are another common type of carbene reactions. The carbene basically interposes itself into an existing bond. The order of preference is commonly

1. X–H bonds where X is not carbon
2. C–H bond
3. C–C bond.

Insertions may or may not occur in single step. Intramolecular insertion reactions present new synthetic solutions. Generally, rigid structures favor such insertions to happen. When an intramolecular insertion is possible, no intermolecular insertions are seen. In flexible structures, five-membered ring formation is preferred to six-membered ring formation. Both inter- and intramolecular insertions are amendable to asymmetric induction by choosing chiral ligands on metal centers.



Carbene intramolecular reaction



j) Generation of carbenes

A method that is broadly applicable to organic synthesis is induced elimination of halides from gem-dihalides employing organolithium reagents. It remains uncertain if under these conditions free carbenes are formed or metal-carbene complex. Nevertheless, these metallocarbenes (or carbenoids) give the expected organic products.

$R_2CBr_2 + BuLi \rightarrow R_2CLi(Br) + BuBr$

$R_2CLi(Br) \rightarrow R_2C + LiBr$

For cyclopropanations, zinc is employed in the Simmons–Smith reaction. In a specialized but instructive case, alpha-halomercury compounds can be isolated and separately thermolyzed. For example, the "Seyferth reagent" releases CCl_2 upon heating.

$C_6H_5HgCCl_3 \rightarrow CCl_2 + C_6H_5HgCl$

Most commonly, carbenes are generated from diazoalkanes, via photolytic, thermal, or transition metal-catalyzed routes. Catalysts typically feature rhodium and copper. The Bamford-Stevens reaction gives carbenes in aprotic solvents and carbenium ions in protic solvents. Base-induced elimination HX from haloforms (CHX_3) with under phase-transfer conditions.

Photolysis of diazirines and epoxides can also be employed. Diazirines are cyclic forms of diazoalkanes. The strain of the small ring makes photoexcitation easy. Photolysis of epoxides

gives carbonyl compounds as side products. With asymmetric epoxides, two different carbonyl compounds can potentially form. The nature of substituents usually favors formation of one over the other. One of the C-O bonds will have a greater double bond character and thus will be stronger and less likely to break. Resonance structures can be drawn to determine which part will contribute more to the formation of carbonyl. When one substituent is alkyl and another aryl, the aryl-substituted carbon is usually released as a carbene fragment. Carbenes are intermediates in the Wolff rearrangement

9.11 Nitrenes

The high energy neutral species containing electron sextets are called nitrene (R-N:), where R may be any of the following groups: H, COCH3, Ph, alkyl, sulphonyl etc. These species are isoelectronic with carbenes and names like azines, imines and imidazen have also been assigned to them. Nitrenes are too reactive for isolation under ordinary conditions. Alkyl nitrenes have been isolated by traping in matrics at 4K while aryl nitrenes which are less reactive, can be traped at 77K.

In the most simple nitrene, the linear imidogen (:N-H), two of the 6 available electrons form a covalent bond with hydrogen, two other create a free electron pair and the two remaining electrons occupy two degenerate p orbitals. Consistent with Hund's rule the low energy form of imidogen is a triplet with one electron in each of the p orbitals and the high energy form is the singlet state with an electron pair filling one p orbital and the other one vacant.

a) Formation

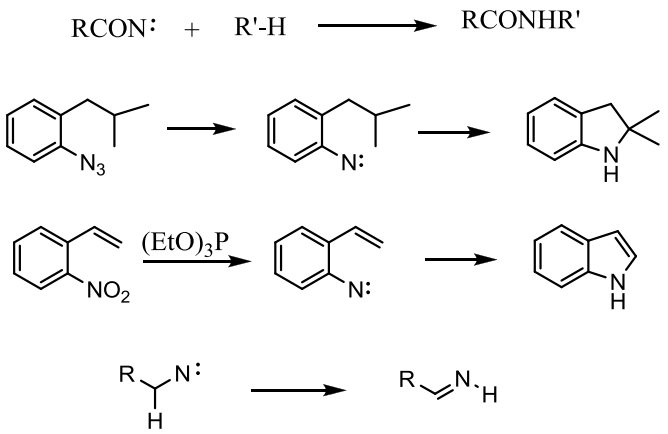
Because nitrenes are so reactive, they are not isolated. Instead, they are formed as reactive intermediates during a reaction. There are two common ways to generate nitrenes: i. from azides by thermolysis or photolysis, with expulsion of nitrogen gas. This method is analogous to the formation of carbenes from diazo compounds; ii. from isocyanates, with expulsion of carbon monoxide. This method is analogous to the formation of carbenes from ketenes.

Since nitrenes are univalent nitrogen derivatives they can be generated from trivalent nitrogen by some elimination or by reduction process.

b)Reactions

Chemically nitrenes behaves similar to carbene, ie., it adds to double bond, insert into C-H single bonds. In addition, they isomerize to imines, abstract hydrogen atom to form amino groups and effect ring closures. Nitrenes also exist in two electronic states, the singlet and the

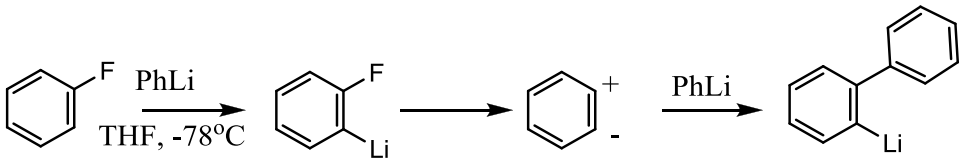
triplet. The singlet nitrene adds to C=C bonds stereospecifically while the triplet nitrenes add to give both cis and trans aziridines.



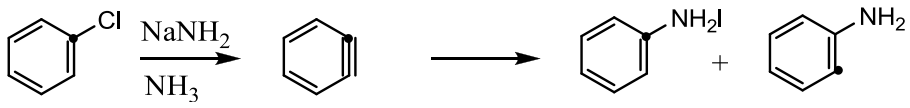
Arynes or benzynes are highly reactive species derived from an aromatic ring by removal of two ortho substituents. Arynes usually best described as having a strained triple bond; however, they possess some biradical character as well.

Arynes were first postulated by Georg Wittig in 1940 and by Roberts in 1953 The discovery of benzyne led to rapid developments in synthetic methodologies to make this highly reactive intermediate useful for organic synthesis. To date, a variety of natural products have been prepared using arynes as intermediates. Examples of such natural products are Cryptaustoline, (+)-Liphagal, Dehydroaltenuene B, Herbindole A, Taxodione, Melleine and many others. Perhaps one of the most famous reactions of arynes is Bergman cyclization, which lies in the core of mechanism of action of enediyne cytostatics.

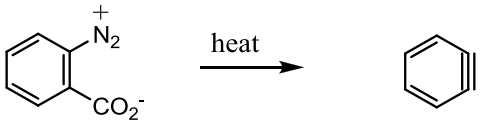
Wittig and coworkers were studying the formation of biphenyl via reactions of fluorobenzene and phenyllithium. They proposed that the reaction proceeded via a zwitterionic intermediate.



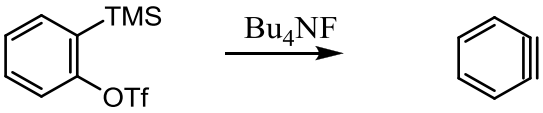
In 1953 John D. Roberts performed the classic ^{14}C labeling experiment, which provided strong support for benzyne. Roberts and his students performed the reaction of chlorobenzene-1-^{14}C with potassium amide, and analyzed the ^{14}C-label incorporation into the resulting aniline: equal amounts of aniline with ^{14}C incorporation at C-1 and C-2 were observed. This result necessitated a symmetrical intermediate – now known as benzyne.



Arenediazonium-2-carboxylates can serve as precursors to benzynes. The main drawback of this method is the explosive nature of diazonium compounds.

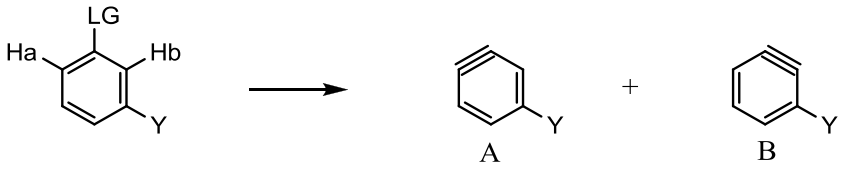


Milder methods for benzyne generation have been developed. Aryl triflates have been widely used in synthesis. Fluoride displacement of the trimethylsilyl group, as shown below, allows for generation of benzyne under mild conditions.



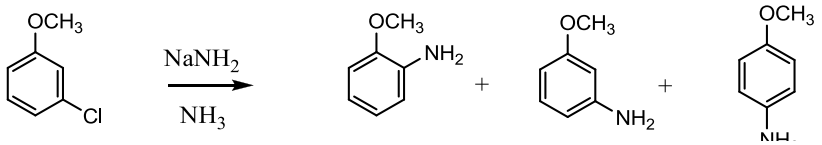
c) Regiochemistry of the triple bond formation

When leaving group (LG) and substituent (Y) are mutually ortho or para, only one benzyne intermediate is possible. However, when LG is meta to Y, then regiochemical outcomes (A and B) are possible. If Y is electron withdrawing, then Hb is more acidic than Ha resulting in regioisomer B being generated. Analogously, if Y is electron donating, regioisomer A is generated, since now Ha is the more acidic proton.



d) Regiochemistry of the addition of nucleophile to the triple bond

There are two possible regioisomers of benzyne with substituent (Y): triple bond can be positioned between C2 and C3 or between C3 and C4. Substituents ortho to the leaving group will lead to the triple bond between C2 and C3. Para Y and LG will lead to regioisomer with triple bond between C3 and C4. Meta substituent can afford both regioisomers as described above. In case of triple bond located between C2 and C3, electron withdrawing substituents (EWG) will direct the nucleophile addition to place carbanion as close as possible to EWG. However, electron donating substituents (EDG) will provide little selectivity between products. In the regioisomer where triple bond is located between C3 and C4 the effect of substituent on nucleophile addition is diminished, and mixtures of para and meta products are often obtained.



9.12 Nitrile oxide

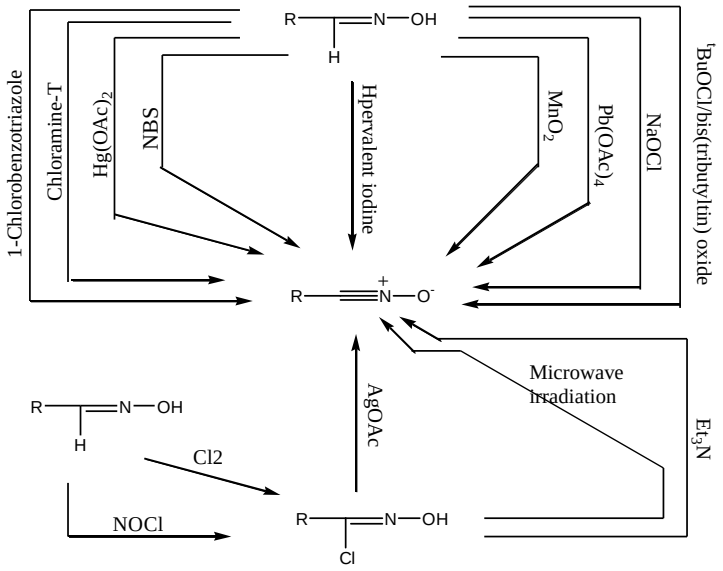
a) Generation of nitrile oxides

All known methods for the synthesis of nitrile oxides start with organic system already containing -C-N-O sequence of the nitrile oxide structure. Many methods are reported to generate nitrile oxide. The usual synthetic methods of nitrile oxides involve the oxidative dehydrogenation of aldoximes, the dehydration of primary nitro compounds with aryl isocyanate and the dehydrohalogenation of hydroxyiminoyl halides. Hydroximoyl chlorides are generated from oximes by chlorination with chlorine, N-chlorosuccinimide, nitrosyl chloride, sodium hypochlorite or tert-butyl hypochlorite. Tokunaga et al utilized silver acetate for the generation of nitrile oxide starting from hydroxyimoyl halides. Loupy *et al* developed a new method for the generation of nitrile oxides by microwave irradiation of hydroximoyl chlorides in the presence of dipolarophiles. Nitrile oxides are generated from *O*-trimethylsilylhydroximoyl chlorides by treatment with potassium fluoride in acetonitrile at ~20^{o}C or from hydroximoyl chlorides using molecular sieves (3-5Å) in CH_2Cl_2.

A few oxidative dehydrogenation methods of aldoximes using oxidants such as lead tetraacetate, alkali hypohalite, N-bromosuccinimide in dimethyl formamide followed by base treatment, 1-chlorobenzotriazole, chloramine-T mercuric acetate are reported. *In situ* generation of nitrile oxide from aldoxime by potassium fericycanide require aqueous medium while that of ceric ammonium nitrate can be used only for aromatic aldoximes. Radhakrishna *et al* reported the use of hypervalent iodine compounds as a oxidizing agent for the *in situ* conversion of aldoximes to nitrile oxides. Since the workup require alkaline condition, this method is limited to alkaline resistant compounds. Moreya *et al* reported the *insitu* generation of nitrile oxides by the reaction of aldoximes with tertiary butyl hypochlorite and bis (tributyltin) oxide. The reaction proceeded efficiently under mild condition in which O-stannylated aldoximes are thought to be the intermediate (Scheme 1)

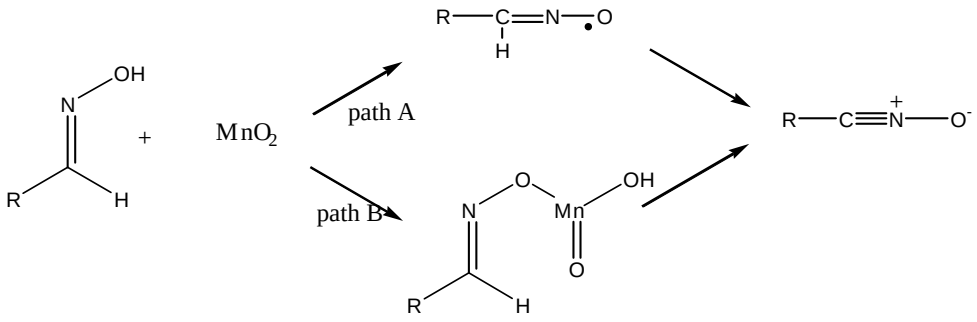
Rai and Hassner's method not only allows *in situ* generation but also allows the isolation of nitrile oxides from aldoximes using chloramine-T as dehydrogenating reagent. This reaction is usually carried out by heating a mixture of aldoxime and an alkene in ethanol in the presence of chloramine-T. By employing this method, we have isolated and characterized the nitrile oxide, of which some are liquids and some are solids. The unstable compound

identified by NMR spectrometry slowly dimerizes on standing it alone or in presence of added vinyl sulfone, undergo cycloaddition to yield isoxazoline in good yield.



Scheme 1

Manganese(IV) oxide (MnO_2) was found effective for the *in situ* generation nitrile oxide from aldoximes. Keigiel *et al* proposed the following mechanism for the oxidation of aldoxime to nitrile oxide (path B), analogous to the oxidation of aldoximes to nitrile oxide by lead tetraacetate (Scheme 2).



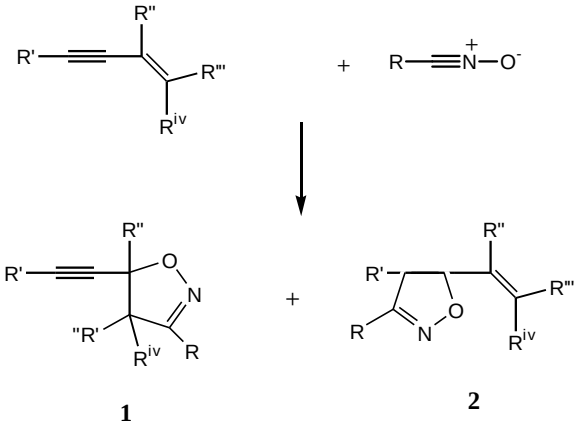
Scheme 2

The exomethylene pyrolidine system undergoes a highly regioselective 1,3-dipolar cycloaddtion reaction with nitrile oxide generated from the corresponding aldoxime afforded spiro isoxazoline protein based aminoacids in good yields and with 1:4 *cis-trans* diastereoselectivity.

b) Reactions of nitrile oxides

Nitrile oxides undergo 1,3-dipolar cycloaddition reactions with various dipolarophiles. Alkenes and alkynes serve as an excellent dipolarophiles. Cycloaddition of nitrile oxides to

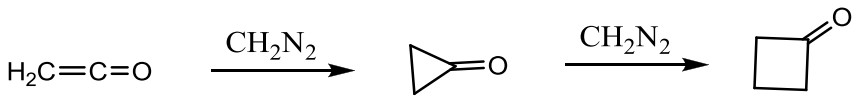
olefins yield isoxazolines while addition of nitrile oxide to alkyne yield isoxazole directly. If the dipolarophile posses more than one set of unsaturation as in an en-yne, addition to either (or both) site(s) may occur. Indeed with nitrile oxides as dipole and 1,3-en-yne as substrate, the chemoselectivity is very sensitve to the substitution pattern of the en-yne, either product (**1**) or (**2**) may predominate (Scheme 3).



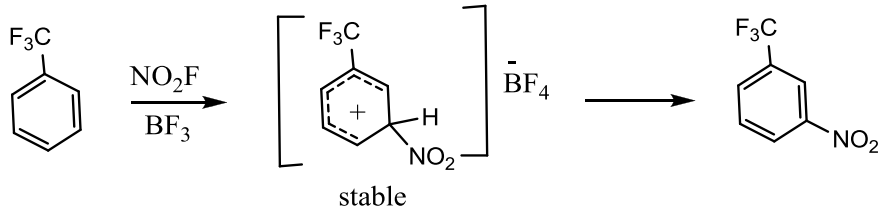
Scheme 3

9.13 Identification of reactive intermediates by trapping of intermediates

Many chemical reactions proceed with intervension of one or more intermediates which vary in their stabilities. A stable intermediate lies in a deep trough on the energy profile diagram. Though the existence of a reaction intermediate is generally inferred from kinetic measurements, this type of evidence is never conclusive. It is therefore desirable to obtain positive evidence for reaction intermediate from additional chemical experimentation. In ideal case it is desired that the intermediate may be isolable or alternatively synthesized and then treated under the conditions of the experiment to determine if it yield the same product as the reaction. This has proved possible in many cases. For instance, the formation cyclobutanone from ketene and CH_2N_2 at low temperature has been known for a long time. Roberts et al have demonstrated by 13C labeled diazomethane, cyclopropane is the most likelyintermediate. Recently direct evidence for its formation has been provided by its independent synthesis and further demonstration that it reacts with CH_2N_2 to yield cyclobutanaone.

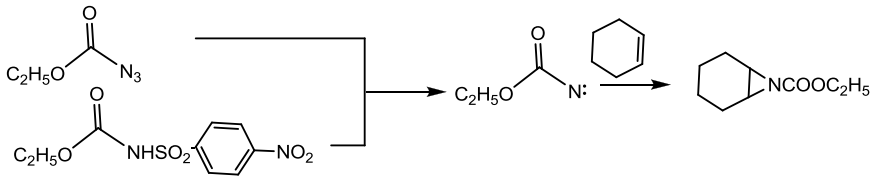


Another interesting case is the electrophilic substitution on aromatic rings. From kinetic measurements, the stepwise mechanism been accepted to involve cyclohexadienate cation (Olah isolated this intermediate)



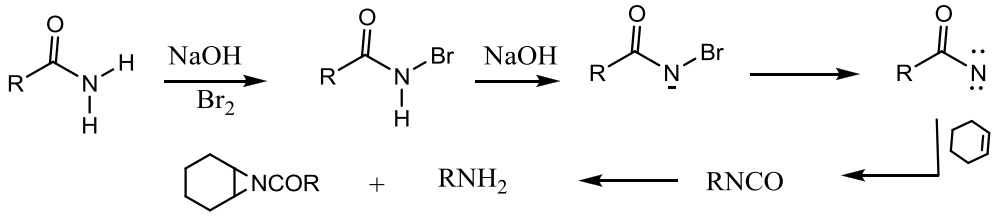
It is not always easy to synthesize or isolate an intermediate, particularly when it is highly reactive. In such cases, the likely intermediate can be trapped with some other suitable reagent and the product examined. Moreover if the same intermediate can be generated from a different precursor, then te structure of the intermediate can be established.

In the photolysis of ethylazidoformate, carbethoxy nitrene was suspected to be the intermediate. All attempts to isolate the intermediate fails. Nitrene being vary reactive, can be trapped by olefinic compound.

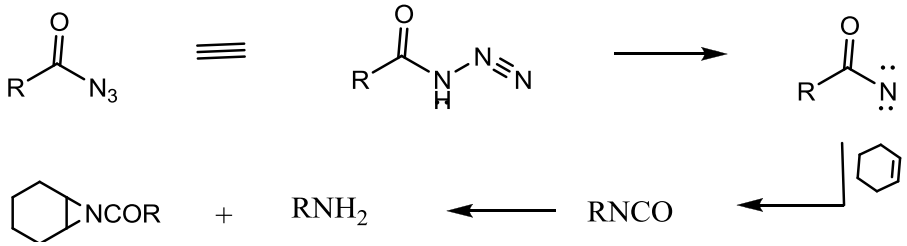


During Hoffmann, Losen and Curtius rearrangement, acyl nitrene was suspected to be the reactive intermediate. Inorder to identify the nitrene intermediate, during the reaction one has to add small amount of cyclohexene as trapping agent. After the reaction and usual work up, fused aziridine was isoled as one of as the product besides the required amine. Formation of the fused N-acyl aziridine implies that during the reaction, the reactive intermediate formed was nitrene. On the basis of this we can write the mechanism for the above said reactions as-

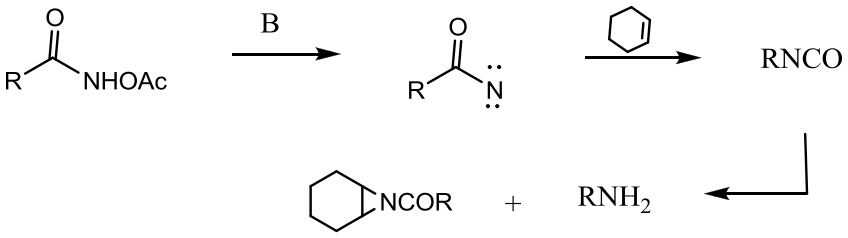
Hoffmann rearrangement:



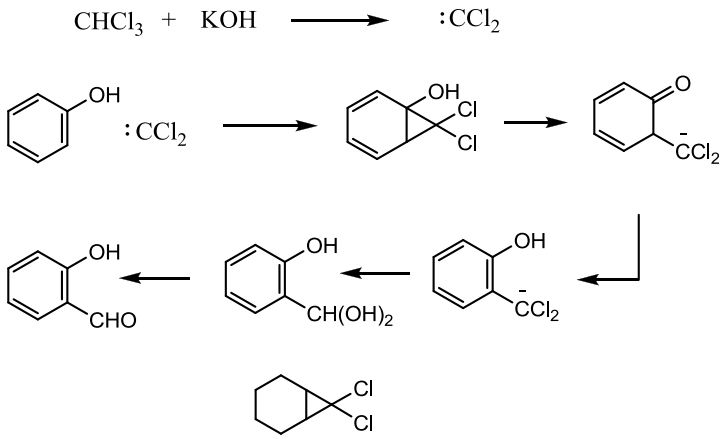
Curtius rearrrangment:



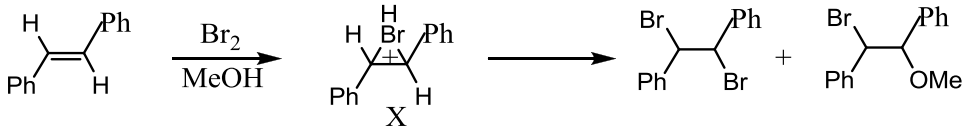
Lossen rearrangement:



During Rreimer-Tieman reaction, dichlorocarbene was suspected to be the reactive intermediate. In order to identify the carbene intermediate, during the reaction one has to add small amount of cyclohexene as trapping agent. After the reaction and usual work up, fused aziridine was isoled as one of as the product besides salicyladehyde. Formation of the fused N-acyl aziridine implies that during the reaction, the reactive intermediate formed was carbene. On the basis of this we can write the mechanism for the above said reactions as



The addition of bromine to many olefins in polar solvents proceeds through an intermediate which we will represent (X). In simple addition, this cyclic bromonium ion is thought to react with Br^- present in solution to form the observed dibromide. Strong evidence for such an intermediate is that it can be diverted from its ordinary reaction course by the presence of basic reagents other than Br^-. For example when bromine is added to stilbine in methanol, the bromoether may be isolated from the mixture.



9.14 Isotopic labeling

Eventhough the mechanism for any particular reaction is proven correct by kinetic data or by identification products, or by identification of reactive intermediates, some time these datas

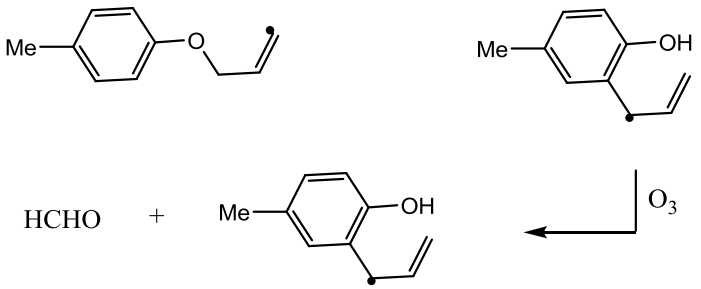
are not sufficient to confirm the mechanism. In such cases isotopic labeling studies will help. By using isotopes many information about reaction mechanism can be obtained; some of them are gieven below:

i. Whether a particular bond breaks in the rate determining step breaks or not
ii. Whether exchange of an atom (or a group) takes palce or not
iii. Whether a reaction is reversible or no

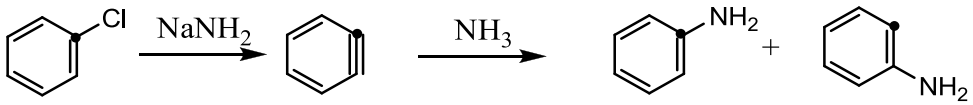
For instance, consider the Claissen rearrangement reaction of allyloxy phenyl ether or the aminolysis of chlorobenzene.

The Claissen rearrangement has been carried out using allyloxy phenl labeled with C^{14}at the γ position. When the resulting allyl cresol ether was subjected to oxidative degradation, the end carbon on the chain was eliminated as formaldehyde. Since none of

the radioactive carbon was lost, itfollows that the γ-carbon in the original ether does not become the end carbon in the rearrangement product.since it is very difficult to conceive of a reaction path in which the β-carbon becomes attached to the ring during rearrangement, we may then conclude that during rearrangement, γ-carbon becomes attached to the benzene ring.

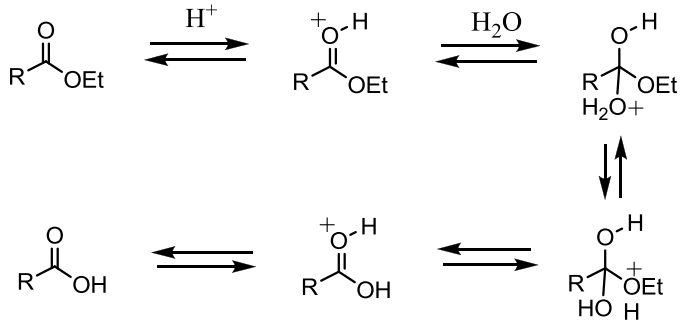


Let us consider the reaction of chlorobenzene with sodamide in presence of ammonia. The reaction goes via elimination-addition reaction with the generation of benzyne intermediate. This can be easily proved by isotopic labeling studies. Before the reaction, chlorine bearing carbon in chlorobnzene is isotopically labeled. After the reaction one can isolate mixture of two, in which one containing the NH_2 group is attached to the carbon from which the chlorine departed and the other one containing the NH_2 group is attached to the ortho carbon labeled to the carbon.



Let us consider the reaction involving hydrolysis of ester either by acid or base catalyzed. There are two C-O σ-bonds in an ester molecule, one is acyl-O bond and the other is alkyl-O

bond. Based on these facts, the hydrolysis of esters can be classified into several classes. They are : i. BAc1, ii. BAc2, iii. AAc1, iv. AAc^2, v. Bal1, vi. BAl^2, vii. AAl^1 & viii. AAl^2. These can be easily desided by isotopic labelling studies. For instance let us consider the hydrolysis of ester involving AAc^2/BAc^2 mechanism. When the hydrolysis is carried out in the presence of $H_2{}^{18}O$, the alcohol formed does not contain ^{18}O. This clearly indicates the breakage of acyl oxygen bond breakage. If the alcohol contains labeled oxygen, then the reaction involves the breakage of alkyl oxygen bond breakage.



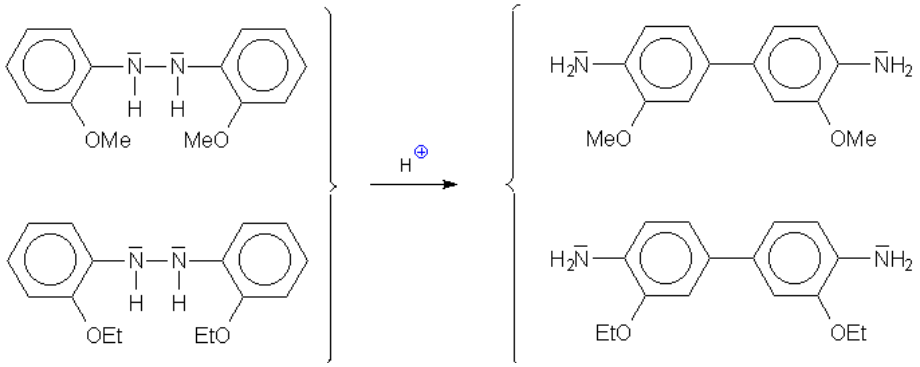
Whether a reaction is reversible ornot can be determined by isotope exchange reaction. When a compound having active –CH2- group is treated with NaOEt in the presence of EtOD, deuterium is exchanged.

9.15 Crossover Experiments

Crossover experiments are particularly useful in studying the reaction mechanisms of many molecular rearrangements. This method is useful to find out whether the reorganization of the carbon skeleton occurs during the intramolecular displacement, and an intermolecular exchange of atoms or a group of atoms. In crossover experiments a mixture of starting products that differ from each other only in one characteristic group is applied. The structure of the products is analyzed to know whether or not an intermolecular exchange of atoms or a group of atoms has occurred.

The principles of crossover experiments are illustrated below

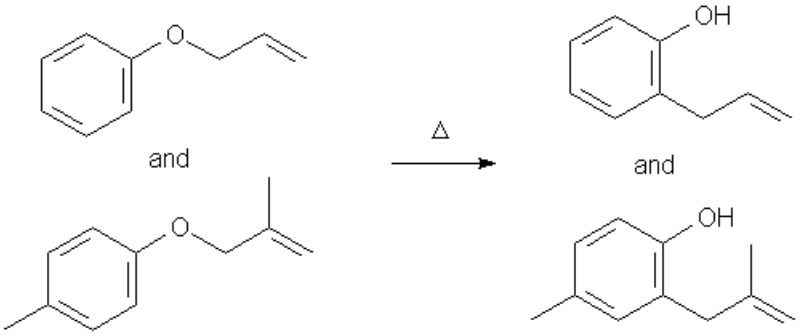
Benzidine rearrangement carried out with a mixture of starting materials containing 2,2'-dimethoxyhydrazobenzene and 2,2'-diethoxyhydrazobenzene. After the reaction is completed, a product mixture that consists of two symmetrically substituted benzidines is obtained. This explains that the reaction takes an intramolecular course.



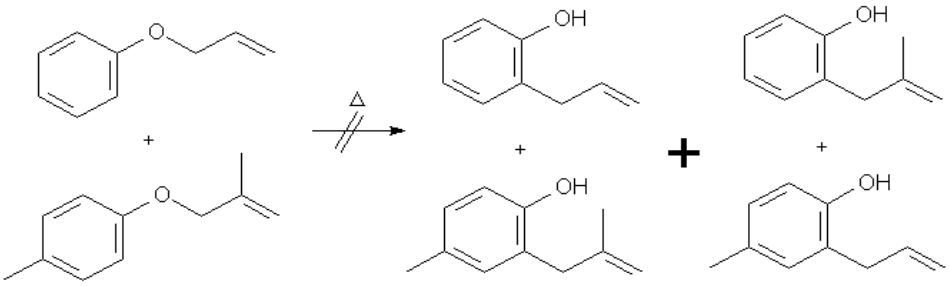
Otherwise unsymmetrically substituted benzidines must also be formed.

Claisen rearrangement

The Claisen rearrangement of allyl phenyl ether yields 2-allylphenol. If a starting compounds consists a mixture of allyl phenyl ether and 2-methylallyl 4-methylphenyl ether is allowed react, an intermolecular and an intramolecular mechanism ought to yield different product mixtures



The intramolecular mechanism of the Claisen rearrangement would only yield 2-allylphenol and 4-methyl-2-(2-methylallyl)-phenol. In contrast, an intermolecular mechanism would additionally result in 2-(2-methylallyl)-phenol and 2-allyl-4-methylphenol. The Claisen rearrangement must obviously be an intramolecular reaction, since no crossover products are obtained



9.16 Summary of the unit

Organic reaction intermediates are very short lived species and are tries to convert themselves quickly into stable molecule. They are differing in their stabilities, half life times and

reactivities. Their half lives range from fractions of seconds to several minutes. Their existence can be proved by spectroscopy which is a modern method to find out the existence of any molecules. They can be generally isolated during the course of reaction from reaction container. They are the reaction intermediates which are observed in many organic reactions such as of alkyl halide, alcohol, ether, alkenes, alkynes, aromatic compounds, carbonyl compounds, carboxylic acid and its derivatives, carbohydrates, amino acids etc. Reactions which involve heterolytic fission are called as polar or ionic reactions**.** Those reactions in which carbanion is formed as an intermediate are said to proceed with carbanionic mechanism and similarly those reactions in which carbocation is formed as an intermediate are said to proceed with carbocationic mechanism. Organic reaction intermediates are mainly of six types they are

1. Carbocations
2. Carbanions
3. Carbon free radicals
4. Carbenes
5. Nitrenes
6. Benzynes

9.17 Key words

Carbocation; Carbanion; Hunsedecker reaction; Free radicals; Auto oxidation; Birch reduction; Carbenes; Nitrenes; Nitrile oxide; Isotopic labeling.

9.18 Books for further references

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2) MTG Reaction Mechanisms in Organic Chemistry, Mukul C. Ray, *MTG Learning Media*, 2009.

3) The Art of Writing Reasonable Organic Reaction Mechanisms, **Grossman**, Robert B., *Springer-Verlag New York, Inc*. 2nd ed. 2003.

4) Organic Reactions: Mechanism with problems, Rajpal tyagi, *Discovery Publishing House*, 2005.

5) Writing Reaction Mechanisms in Organic Chemistry, Audrey Miller, Philippa H. Solomon, *Academic Press*, 2000.

6) Organic Reactions Stereochemistry and Mechanism (Through Solved Problems), By P. S. Kalsi, *New Age International*, 2007.

9.19 Questions for self understanding

1. What are non-classical carbocations? How they are classified? Give example for each class
2. Discuss the structure and stability of carbocations.
3. Write any two methods of generating carbocation
4. Among triphenyl methyl carbocations and tricyclopropyl methyl carbocations which one is more stable and why?
5. How carbanions are generated? Discuss their stability.
6. Discusss the geometry of cabanions.
7. What are free radicals? How they are generated and identified?
8. Discuss the geometry of free radicals?
9. Name the reactions which involve radical intermediates. Write the structure of singlet and triplet carbene. Explain how they may be differentiated with one example.

Unit - 10

Structure

10.0 Objectives of the unit

After studying this unit you are able to

- Explain the aromatic electrophilic substitution reaction
- Predict the Ortho-para product ratio
- Write the mechanism of nitration of benzene
- Explain the sulfonation and desulphonation reaction of benzene.
- Predict he product formed in Friedel-Craft reaction
- Explain the advantage of Friedel–Crafts acylation reaction.
- Write the mechanism of Diazo coupling reaction
- Explain the mechanism of Chloromethylation reaction
- Write the mechanism of Vilsmeier–Haack reaction
- Explain the Ipso substitution reactions

10.1 Introduction

Just like an alkene, benzene has clouds of π electrons above and below its sigma bond framework. Although the π electrons in a aromatic system are stable, they are still available for reaction with strong electrophiles. This generates a carbocation which is resonance stabilized (but not aromatic). This cation is called a sigma complex because the electrophile is joined to the benzene ring through a new sigma bond. The sigma complex (also called an arenium ion) is not aromatic since it contains an sp^3 carbon (which disrupts the required loop of p orbitals). The loss of aromaticity required to form the sigma complex explains the highly endothermic nature of the first step. (That is why we require strong electrophiles for reaction). The sigma complex wishes to regain its aromaticity, and it may do so by either by a reversal of the first step (i.e. regenerate the starting material) or by loss of the proton on the sp^3 carbon (leading to a substitution product). When a reaction proceeds this way, it is electrophilic aromatic substitution. There are a wide variety of electrophiles that can be introduced into a benzene ring in this way, and so electrophilic aromatic substitution is a very important method for the synthesis of substituted aromatic compounds.

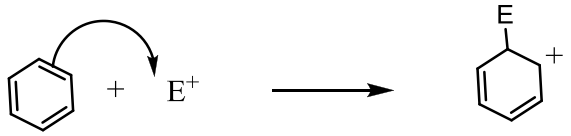
10.2 Aromatic electrophilic substitution reaction

Benzene molecule contains three double bonds. All the three bonds are involved in resonance and hence it does not easily undergo addition reactions. On the other hand the delocalized electron cloud of benzene attracts the electrophile and hence it undergoes electrophiliuc substitution reactions. Electrophilic aromatic substitution is an organic reaction in which an atom that is attached to an aromatic system (usually hydrogen) is replaced by an electrophile.

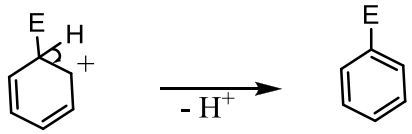
Some of the most important electrophilic aromatic substitutions are aromatic nitration, aromatic halogenation, aromatic sulfonation, and acylation and alkylating Friedel-Crafts reactions.

The electrophilic substitution reaction of benzene involve three steps.

1. Generation of electrophile
2. Attack by the electrophike on the π electrons of benzene



3. Elimination of proton.

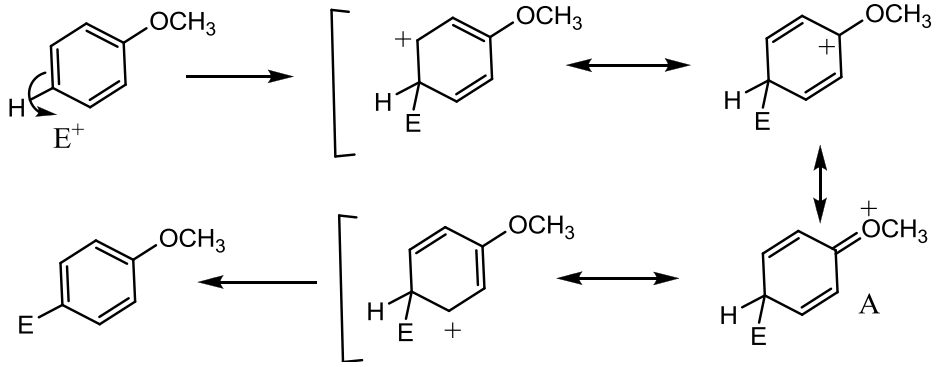


10.3 Effect of substituent groups

Both the regioselectivity and the speed of an electrophilic aromatic substitution are affected by the substituents already attached to the benzene ring. In terms of regioselectivity, some groups promote substitution at the ortho or para positions, while other groups increase substitution at the meta position. These groups are called either ortho-para directing or meta directing. In addition, some groups will increase the rate of reaction (activating) while others will decrease the rate (deactivating). While the patterns of regioselectivity can be explained with resonance structures, the influence on kinetics can be explained by both resonance structures and the inductive effect.

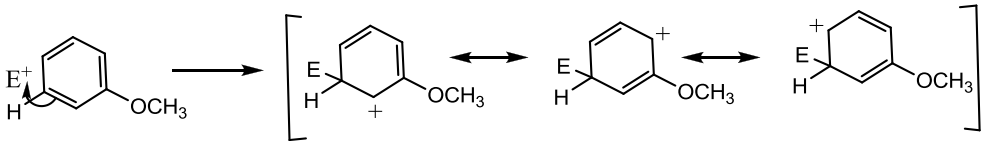
Substituents can generally be divided into two classes regarding electrophilic substitution: activating and deactivating towards the aromatic ring. Activating substituents or activating groups stabilize the cationic intermediate formed during the substitution by donating electrons into the ring system, by either inductive effect or resonance effects. Examples of activated aromatic rings are toluene, aniline and phenol. The extra electron density delivered into the ring by the substituent is not equally divided over the entire ring, but is concentrated on atoms 2, 4 and 6 (the ortho and para positions). These positions are thus the most reactive towards an electron-poor electrophile. The highest electron density is located on both ortho and para positions, though this increased reactivity might be offset by steric hindrance between substituent and electrophile. The final result of the elecrophilic aromatic substitution might thus be hard to predict, and it is usually only established by doing the reaction and determining the ratio of ortho versus para substitution. For instance, let us consider the attack

of anisole on a general electrophile E+, first at the para position then ate the meta position to see whether we can understand the reason for the directig effect of methoxy (OCH_3) group.



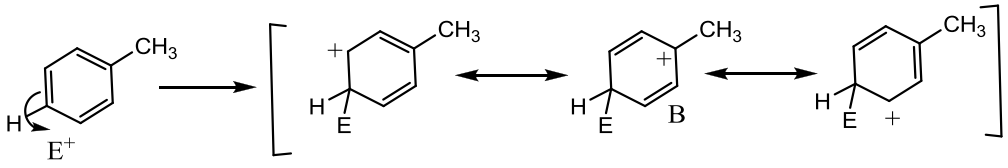
Notice that there are four important resonance structures for the carbocation intermediate formed by the attack on the electrophile at the para position. The structure (A) shows that the substituent can delocalize the positive charge with its unshared electron pair. This is an important structure because it contains more formal bonds than the others and every atom in it has an octet.

If the electrophile is attacked by anisole at the meta position, the carbocation intermediate formed has fewer resonance structures than the para attack. In particular the charge cannot be delocalized onto the $–OCH_3$ group when reaction occurs ate meta position. In otherwords there is no structure corresponding to (A).

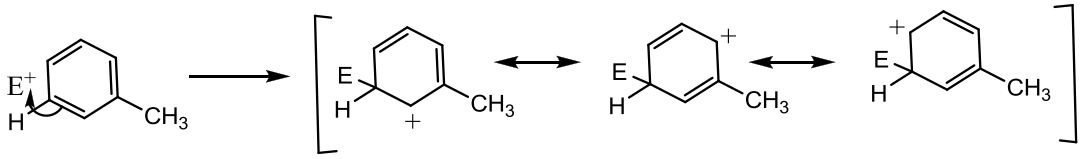


Thus, reaction of an electrophile at either an ortho or para position of anisole gives a carbocation with more resonance structures – amore stable carbocations. This why the $–OCH_3$ group is an ortho-para directing group. An exactly analogous argument explains the ortho-para directing effects of other groups with unshared electrons in a similar arrangements.

Alkyl groups such as a methyl group have no unshared electrons, but the explanation of the directing group of these is quite similar. Reaction at a position ortho or para to an alkyl group yields an ion (B) that has one tertiary carbocation resonance structure.

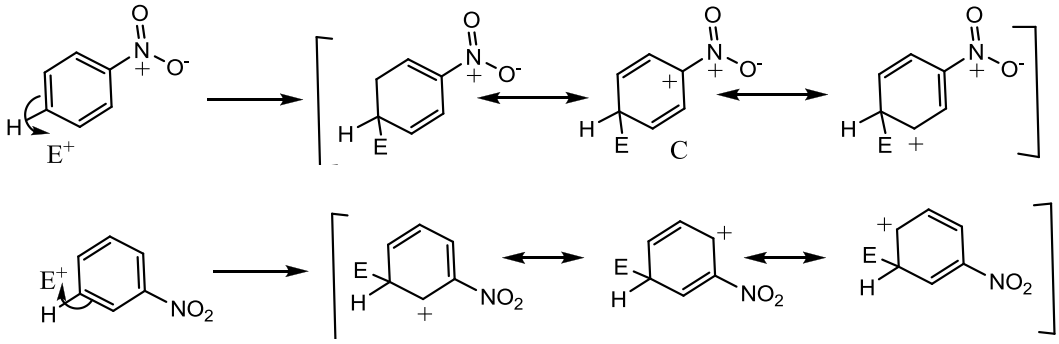


Reaction of the electrophile at the ring position meta to the alkyl group also yields an ion with three resonance structures. But in this case all resonance forms are secondary carbocations. Since reactions at the ortho or para positions give the more stable ions – ions with some structure carbocation character – alkyl groups are o, p- directing groups.



On the other hand, deactivating substituents destabilize the intermediate cation and thus decrease the reaction rate. They do so by withdrawing electron density from the aromatic ring, though the positions most affected are again the ortho and para ones. This means that the most reactive positions (or, least unreactive) are the meta ones (atoms 3 and 5). Examples of deactivated aromatic rings are nitrobenzene, benzaldehyde and trifluoromethylbenzene. The deactivation of the aromatic system also means that generally harsher conditions are required to drive the reaction to completion. An example of this is the nitration of toluene during the production of trinitrotoluene (TNT). While the first nitration, on the activated toluene ring, can be done at room temperature and with dilute acid, the second one, on the deactivated nitrotoluene ring, already needs prolonged heating and more concentrated acid, and the third one, on very strongly deactivated dinitrotoluene, has to be done in boiling concentrated sulfuric acid.

Functional groups thus usually tend to favor one or two of these positions above the others; that is, they *direct* the electrophile to specific positions. A functional group that tends to direct attacking electrophiles to the *meta* position, for example, is said to be meta-directing. Non-halogen groups with atoms that are more electronegative than carbon, such as a carboxylic acid group (CO_2H) draw substantial electron density from the *pi* system. These groups are strongly deactivating groups. Additionally, since the substituted carbon is already electron-poor, the resonance contributor with a positive charge on this carbon (produced by *ortho/para* attack) is less stable than the others. Therefore, these electron-withdrawing groups are *meta* directing. Let us try to understand the directing effect of these groups by considering as an example the reactions of a general electrophile E^+ with nitrobenzene at the meta and para positions.



Both reactions give carbocations that are characterized by three resonance structures. However, attack at the para position gives an ion with one particularly unfavorable looking structure (C). In this structure there are positive charges on two adjacent atoms. For this reason, reaction at the meta position, which gives an ion with two positive charges separated by one atom, is favoured energetically over reaction at the para position, which gives an ion with positive charges located on two adjacent atoms.

10.4 Ortho-para ratio

When electrophilic substitution reactions are carried out on a benzene derivative containing an ortho-para directing group, the ratio of the yield of the ortho- product to that of the para-product is found to vary from reaction to reaction and substrate to substrate. Since there are two o-positions and one p-position relative to the substituent in mono substituted benzene, it may seem that the o/p ratio will be 2:1 in all reactions irrespective of any substituent, but this is not true. The products never form corresponding to that ratio. Several factors need to consideration for explain of the o/p ratios observed in aromatic substitution reactions. The factors are

i. steric effect

ii. Electronic effects of the substituent already present in the benzene ring

iii. Interaction between the substituent and the attacking electrophile

iv. Effect of temperature and

v. solvation effect.

Ortho-positions being very near to the substituent, the attacking electrophile experience a special congestion when it approaches the o-positions; but it does not experience the same when it attacks the p-postion since this is far from the substituent. The larger the volume of the substituent or that of the attacking electrophile, the greater is the spatial congestion at the o-position and consequently the lower is the o/p ratio; this means with increasing spatial congestion at the o-position the yield of o-product decreases and that of the p-product increases. Let us discuss some examples to substantiate the steric effect on o/p ratio. For

instance, when alkylbenzenes are treated under the same set of conditions, the o/p ratio is found to be the highest in the case of toluene and the lowest in the case of t-butyl benzene as shown below

Substituents	% of o-product	% of p-product	o/p ratio
Me	58	37	1.57
Et	45	49	0.92
i-Pr	30	62	0.48
t-Bu	16	73	022

10.5 Electronic effects of the substituent already present in the benzene ring

When halobenzenes are treated under the same conditions, the yield of o-product increase and that of p-product decrease despite the increase in size of the substituents, F to I as shown below

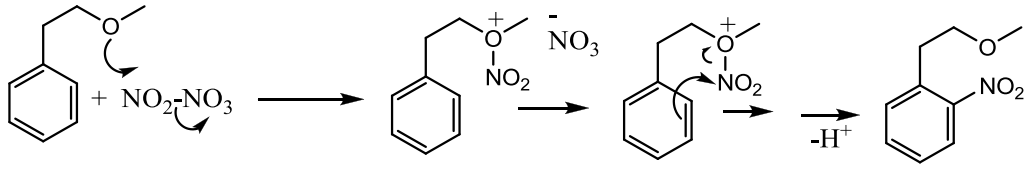
Substituents	% of o-product	% of p-product	o/p ratio
F	12	88	0.14
Cl	30	69	0.44
Br	37	62	0.60
I	38	60	0.63

-I effect of the halogen groups is supposed to be responsible for the observed o/p ratios. The –I effect decreases on going from F to I as the electronegativity of the group decreases. The –I effect deactivates the o-, m- and p-positions but the effect is highest on the o-positions and it is practically nil on the p-position. In flurobenzene the o-positions being highly deactivated by the strong –I effect of the F atom, the attacking electrophile, nitronium ion, attacks the p-position preferentially and p-nitroflurobenzene forms in large excess over the o-isomer; while in the case of iodobenzene the –I effect of the I atom being very, small, it deactivates the o-position to a minimal extent and consequently an appreciable amount of o-product forms; if there were no steric hinderance owing to the large volume of the I atom, the failed of o-product would have still higher than the observed yield. Thus the o/p ratio increases on going from flurobenzene to iodobenzene in the nitration of halobenzenes though the steric congestion increase on going down the series.

10.6 Interaction between the substituent and the attacking electrophile

When the attacking reagent undergoes some sort of interaction with the substituent before attacking the ring, usually the o-attack is the predominant one and the o/p-ratio increase. For example, when methylethyl ether is nitrated with N_2O_5 in methyl cyanide, 69% o-product and

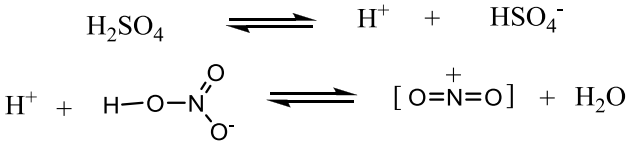
28% p-product form: while nitration of the same compound by the common nitrating agent gives 32% o-product and 59% p-product. It is argued that the interaction between the O atom of the ether linkage and the N_2O_5 group occurs in the first stage and then a $^+NO_2$ ion develops which attacks the ring perhaps in a concerted step; the distance between the developing nitronium ion and the o-position being small, the $^+NO_2$ ion attacks the o-position preferentially.



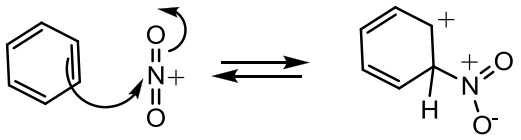
Solvents can also influence the o/p-ratios of ArSe reactions. If a solvent through salvation brings extra stability to the T.S. for the o-attack relative to the T.S for the p-attack, the o/p-ratio will increase; on the other hand if the salvation stabilizes the T.S for the p-attack more than the T.S of the o-attack, the ratio will decrease. In the halogenations of toluene without a Lewis catalyst the solvents are found to play this role and the o/p-ratio varies from 1.57 to 0.67 with the change of the solvent and keeping other conditions of the reaction identical.

10.7 Nitration

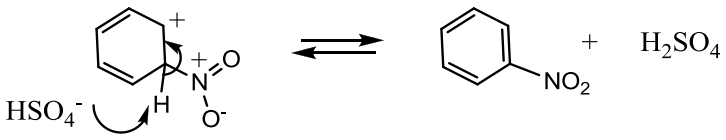
Displacement of an H atom of an aromatic nucleus by a nitro group is called aromatic nitration process. First step involves the generation of an electrophile ($^+NO_2$) from the nitrating mixture. This ion is formed by the acid-catalyzed removal of water from HNO_3. Here H_2SO_4 behaves as acid and HNO_3 as base.



In the second step, the nitronium ion then attacks a nuclear carbon as a n electrophile to form a resonance stabilized σ-complex.



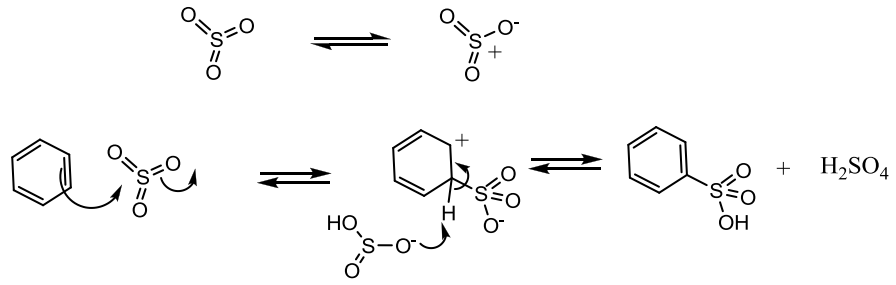
In the final step, the σ-complex then gives up a proton to a base and gets aromatized to a nitrobenzene.



10.8 Sulfonation

The process of introducing $–SO_3H$ group into an aromatic compound react with a solution of sulfur trioxide in H_2SO_4 to yield benzene sulfonic acid to yield benzenic nucleusane, pyridine etc) or chlorosulhonic acid in carbon tetrachloride on aromatic compounds is called aromatic sulfonation. In sulfonation, the electrophile is the neutral compound sulfur trioxide (SO_3). Sulfur trioxide is fuming liquid that react violently with water to give H_2SO_4. The source of SO_3 for sulfonation is usually a solution of 10-30% SO_3 in conc. H_2SO_4 called fuming sulfuric acid or oleum. The octet structure shows that in SO_3, sulfur has substantial positive charge.

Attack of benzene on SO_3 and the completion of the substitution reaction occur by a mechanism similar to those of nitration.

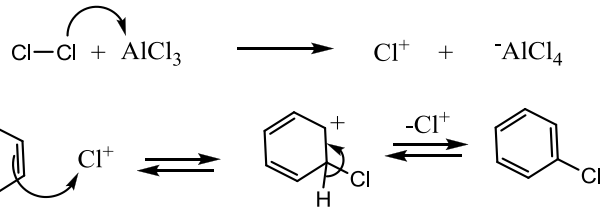


Aromatic sulphonation is reversible reaction. At low temperatures, the reaction is practically irreversible since the reaction, known as desulphonation reaction is very slow. Sesulphonation is usually done by heating the sulphonic acid derivatives with 60% sulphuric acid media at an elevated temperature.

10.8 Halogenation

Replacement of an H atom from an aromatic ring by a halogen atom is called halogenation reaction. Fluorination and iodination procedures differ from chlorination and bromination procedures.

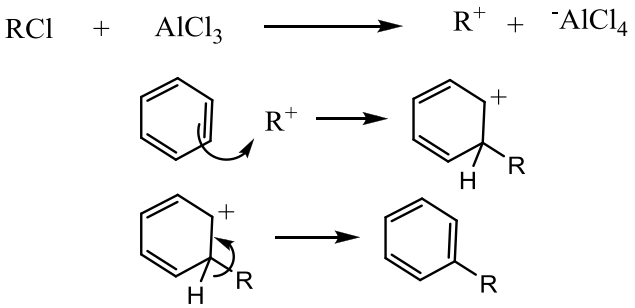
Chlorination and bromination of aromatic rings may be carried out at ordinary temperature by allowing the compound to react with molecular chorine or bromine in the presence of Fe, or a Lewis acid, e.g., $AlCl_3$, $AlBr_3$, $SnCl_4$, $SbCl_5$, etc. Activated compounds react with molecular chlorine or bromine even in the absence of Lewis acid for eg.ols, amines etc.; a solution of the reagent in water or in an organic solvent.



10.9 Friedal-Craft's Alkylation reaction

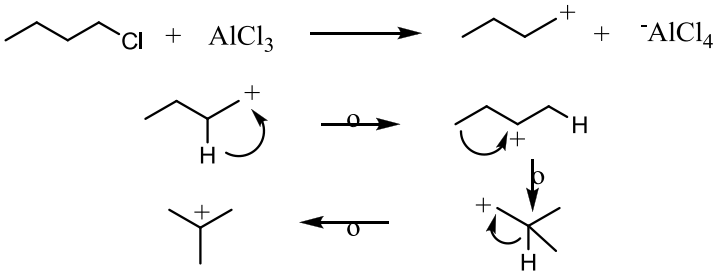
The Friedel–Crafts reactions are a set of reactions developed by Charles Friedel and James Crafts in 1877 to attach substituents to an aromatic ring. There are two main types of Friedel–Crafts reactions: alkylation reactions and acylation reactions both proceeded by electrophilic aromatic substitution.

Friedel–Crafts alkylation involves the alkylation of an aromatic ring with an alkyl halide using a strong Lewis acid catalyst. The general mechanism is shown below.



Alkylations are not limited to alkyl halides: Friedel–Crafts reactions are possible with any carbocationic intermediate such as those derived from alkenes and a protic acid, Lewis acid, enones, and epoxides.

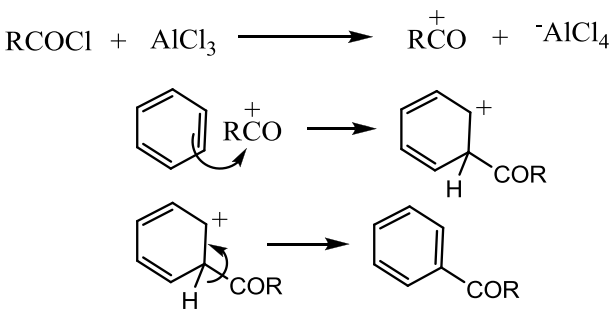
This reaction has one big disadvantage, namely that the product is more nucleophilic than the reactant due to the electron donating alkyl-chain. Therefore, hydrogen is substituted with an alkyl-chain, which leads to over alkylation of the molecule. Also, if the chloride is not on a tertiary carbon or secondary carbon, carbocation rearrangement reaction will occur. This reactivity is due to the relative stability of the tertiary and secondary carbocation over the primary carbocations.



Thus alkylation of benzene with n-butyl chloride in presence of $AlCl_3$ gave tert.butyl benzene as the sole product. This implies that here Fridel-Craft's alkylation reaction fails.

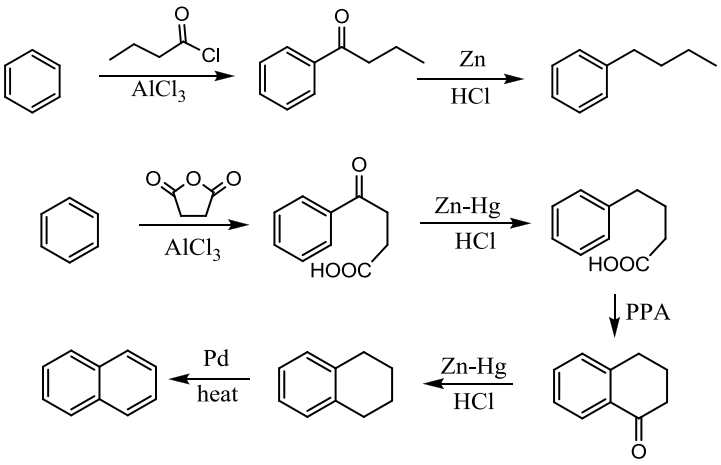
10.10 Friedel–Crafts acylation

Friedel–Crafts acylation is the acylation of aromatic rings with an acyl chloride using a strong Lewis acid catalyst. Friedel–Crafts acylation is also possible with acid anhydrides. Reaction conditions are similar to the Friedel–Crafts alkylation mentioned above. This reaction has several advantages over the alkylation reaction. Due to the electron-withdrawing effect of the carbonyl group, the ketone product is always less reactive than the original molecule, so multiple acylations do not occur. Also, there are no carbocation rearrangements, as the carbonium ion is stabilized by a resonance structure in which the positive charge is on the oxygen.



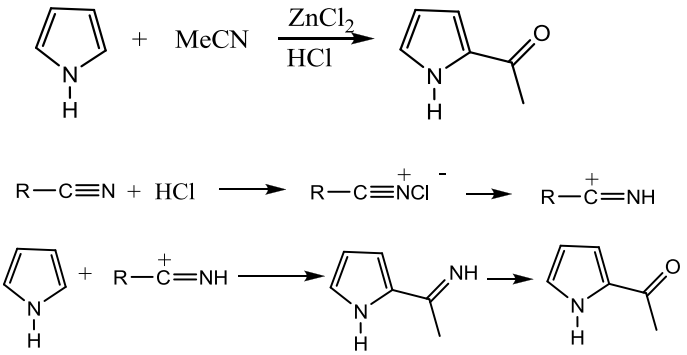
The reagents of the reaction are usually acid halides, acid anhydrides and carboxylic acids. The viability of the Friedel–Crafts acylation depends on the stability of the acyl chloride reagent. Formyl chloride, for example, is too unstable to be isolated. Thus, synthesis of benzaldehyde via the Friedel–Crafts pathway requires that formyl chloride be synthesized *in situ*. This is accomplished via the Gattermann-Koch reaction, accomplished by treating benzene with carbon monoxide and hydrogen chloride under high pressure, catalyzed by a mixture of aluminium chloride and cuprous chloride.

The usual solvents are nitrobenzene, carbon disulfide and tetra chloroethylene. However, it has been found in some cases that orientation of acyl group changes with the change of solvent. For instance, when naphthalene is treated with acetyl chloride-aluminium chloride in nitrobenzene gives predominantly β-acetyl naphthalene while in tetrachloroethylene gives



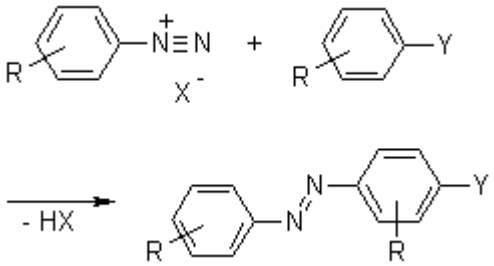
predominantly α-acetyl naphthalene. The reaction has good synthetic and preparative value. The Friedel–Crafts acylation has a number of advantages over the Friedel–Crafts alkylation. Heterocycles and polynuclear hydrocarbons can be acylated and via acylation they can be converted to alkyl derivatives using the Clemenson or the Wolf-Kishner reduction.

The Friedel–Crafts acylation on aromatic compounds may be carried out with a nitrile and HCl in the presence of a Lewis acid as catalyst; the widely used catalyst is anhydrous $ZnCl_2$ and the reaction is known as Houben-Hoesch reaction. Phenols, phenolic ethers and reactive heterocycles such as pyrroles undergo the reaction. The mechanism is not certain, however, this may be represented as follows:



10.11 Diazo coupling reactions

An azo coupling is an organic reaction between a diazonium compound and another aromatic compound that produces an azo compound. In this electrophilic aromatic substitution reaction, the aryldiazonium cation is the electrophile and the activated arene is a nucleophile.

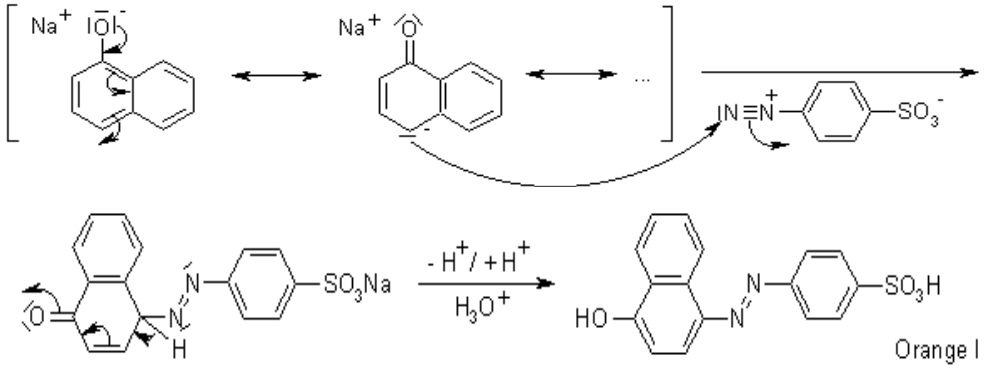


The treatment of aniline with nitrous acid produces a diazonium salt, in a reaction called diazotization. Diazonium salts are important synthetic intermediates that can undergo coupling reactions to form azo dyes and substitution reaction to affect the functional group present on aromatic rings.

The product will absorb longer wavelengths of light (specifically they absorb in the visible region) than the reactants because of increased conjugation. Consequently, aromatic azo compounds tend to be brightly colored due to the extended conjugated systems. Important

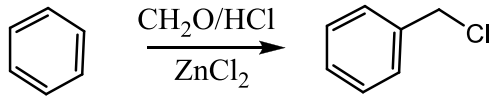
azo dyes include methyl red and pigment red 170. Azo coupling is also used to produce prontosil and other sulfa drugs.

Mechanism of Azo Coupling

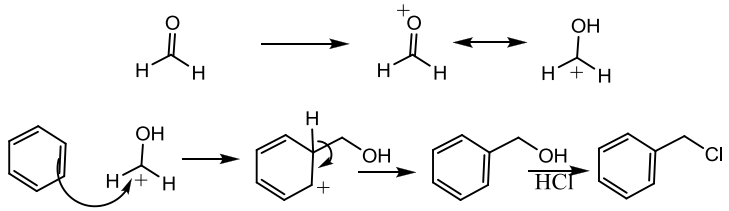


10.12 Chloromethylation reaction

The Blanc chloromethylation is the chemical reaction of aromatic rings with formaldehyde and hydrogen chloride catalyzed by zinc chloride to form chloromethyl arenes. The reaction should be performed with care, as (like most chloromethylation reactions) it produces highly carcinogenic bis(chloromethyl) ether as a by-product.



Mechanism

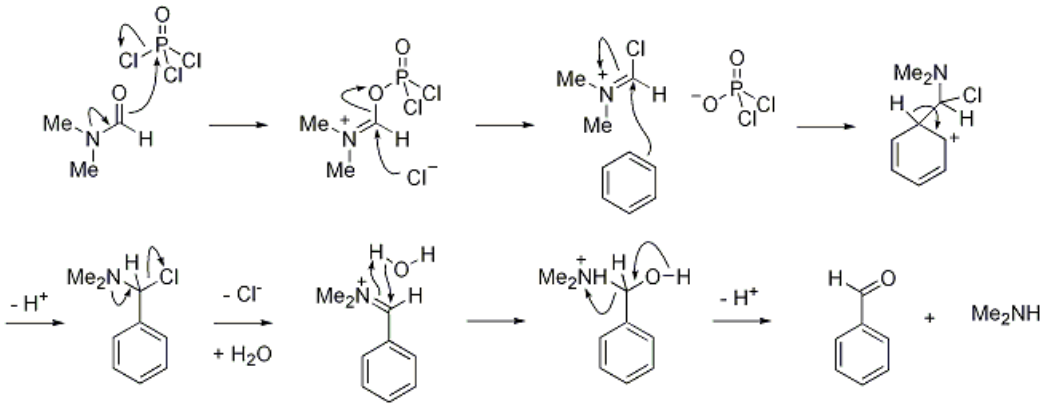


10.13 Vilsmeier–Haack reaction

The Vilsmeier–Haack reaction (also called the Vilsmeier reaction) is the chemical reaction of a substituted amide with phosphorus oxychloride and an electron-rich arene (3) to produce an aryl aldehyde or ketone. The reaction is named after Anton Vilsmeier and Albrecht Haack. The reaction of a substituted amide with phosphorus oxychloride gives a substituted chloroiminium ion, also called the Vilsmeier reagent. The initial product is an iminium ion, which is hydrolyzed to the corresponding aromatic ketone or aldehyde during workup.

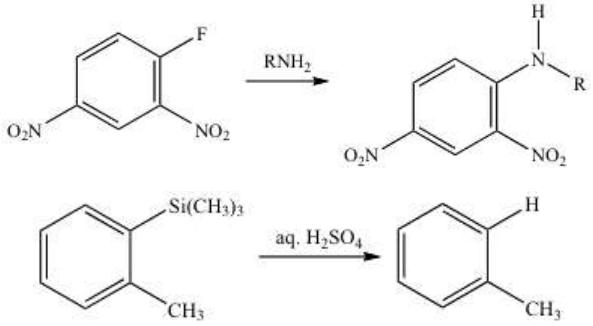
Reaction mechanism

The reaction of the amide with phosphorus oxychloride produces an electrophilic iminium cation. The subsequent electrophilic aromatic substitution produces an iminium ion intermediate, which is hydrolyzed to give the desired aryl ketone or aryl aldehyde.

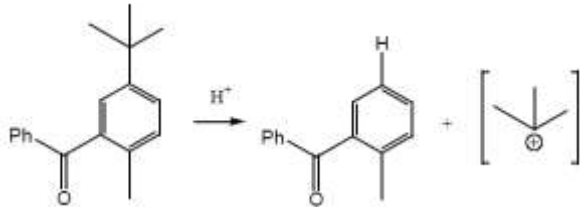


10.14 Ipso substitution

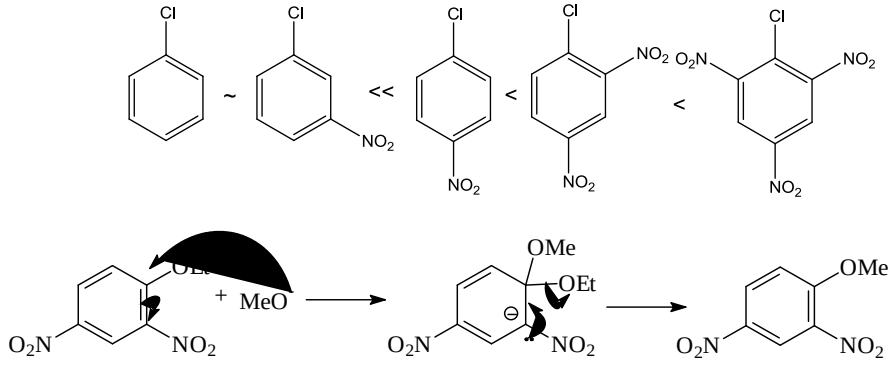
Ipso substitution is a special case of electrophilic aromatic substitution where the leaving group is not hydrogen. A classic example is the reaction of salicylic acid with a mixture of nitric and sulfuric acid to form picric acid. The nitration of the 2 position involves the loss of CO_2 as the leaving group. In aromatics substituted by silicon, the silicon reacts by ipso substitution.



Ipso-substitution usually occurs either with tert – alkyl substituents which can form stable carbocations after attack by the electrophile or in reversible electrophilic substitution reactions such as sulphonation



Ortho/para electron withdrawing groups activate ipso substitution, because o/p electron withdrawing groups most effectively accept the charge. Hence the orders of the reactivity of different aromatic compounds are as follows



10.15 Summary of the unit

The benzene ring is noted for the stability it gains from its aromaticity. However, aromatic compounds can participate in a variety of chemical reactions, including a range of substitution, coupling, and hydrogenation reactions. The electrons in the π system of the benzene ring are responsible to the reactivity observed. While aromatic compounds are best represented by a continuous electron density evenly distributed around the aromatic core, the alternating single and double bonds that are commonly drawn are very useful when predicting the reactivity of aromatic compounds. Many reactions common to alkenes (carbon-carbon double bonds) also function in a similar fashion with the "alkenes" in aromatic compounds, though generally the activation barrier is higher due to the stabilizing force of aromaticity (ca. 36 kcal/mol).

In an electrophilic aromatic substitution reaction, a substituent on an aromatic ring is displaced by an electrophile. These reactions include aromatic nitration, aromatic halogenation, aromatic sulfonation, Friedel-Crafts acylations and alkylations. These reactions can involve a resonance-stabilized carbocation intermediate known as a sigma complex. The reactivity can be thought of in terms of an alkene attacking a cationic species, such as the first step in an acid-catalyzed hydration of an alkene.

A number of patterns have been observed regarding the reaction of substituted benzene rings. These observations have been generalized to provide a predictive rule for electrophilic aromatic substitutions. It states that an electron-donating substituent generally accelerates substitution and directs reactivity toward the positions that are ortho and para to it on the ring, while an electron-withdrawing substituent will slow reaction progress and favor the meta position on the ring.

10.16 Key words

Aromatic compounds; Electrophilic substitution reaction; Ortho-para ratio; Nitration; Sulfonation; Halogenation; Friedel–Crafts acylation; Diazo coupling; Chloromethylation; Vilsmeier–Haack reaction; Ipso substitution

10.17 References for further studies

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10.8 Questions for self understanding

1) Write a note on aromatic electrophilic substitution reaction
2) What is Ortho-para ratio? Discuss the ration ortho and para product obtained in nitration reaction with toluene, aniline, ethylbenzoate and clhlorobenzene
3) Write a note on nitration of benzene?
4) Discuss Sulfonation and desulphonation of benzene.
5) Why $FeCl_3$ is used in Halogenation of aromatic compounds?
6) What is Friedel-Craft reaction?
7) Write demerits of Friedel-Craft reaction?
8) Write a note on Friedel–Crafts acylation reaction.
9) What is Diazo coupling reaction discuss its mechanism?
10) Explain the mechanism of Chloromethylation reaction.
11) What is Vilsmeier–Haack reaction?
12) Write a note on Ipso substitution

Unit - 11

Structure

11.0 Objectives of the unit

After studying this unit you are able to

- Explain the differences between aromatic nucleophilc and electrophilic substituion reactions
- Identify the aromatic compounds prone to exhibit nucleophilc substitution reactions
- Describe addition-Elimination mechanism.
- Explain the Elimination- Addition mechanism.
- Explain the preparation of benzyne intermediate
- Describe the structure of aryne
- Explain the aryne reaction patterns

11.1 Introduction

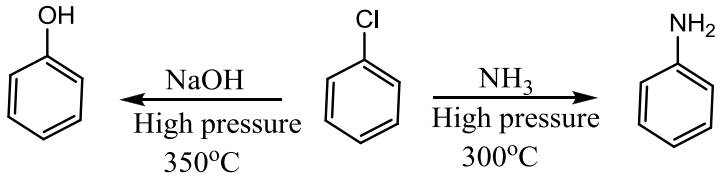
Although most reactions of aromatic compounds occur by way of electrophilic aromatic substitution, aryl halides undergo a limited number of substitution reactions with strong nucleophiles. In a nucleophilic aromatic substitution reaction, a nucleophile displaces a substituent on an aromatic ring. The replaced moiety is typically a good leaving group, for example, nitrogen gas or a halide ion. The presence of an electron-withdrawing group on the ring can speed up the progress of this class of reactions. Chemically, this is similar to an addition reaction to a michael acceptor or other electron-deficient unsaturated system, followed by an elimination reaction.

These aromatic nucleophilic substitution reactions *cannot* occur by an SN1 or SN2 mechanism, which take place only at *sp*3 hybridized carbons. Instead, two different mechanisms are proposed to explain the results those are *addition–elimination* and *elimination–addition.* Nucleophilic aromatic substitution occurs with a variety of strong nucleophiles, including –OH, –OR, –NH2, –SR, and in some cases, neutral nucleophiles such as NH3 and RNH2. The mechanism of these reactions has two steps, addition of the nucleophile to form a resonance-stabilized carbanion, followed by elimination of the halogen leaving group. Nucleophilic aromatic substitution by an elimination–addition mechanism affords substitution on the carbon directly bonded to the leaving group and the carbon adjacent to it.

11.2 Aromatic nucleophilic substitution reactions

Even though the electophilic substitution is by far the most common mode of substitution in aromatic systems, the nucleophilic substitution is indeed possible and is a useful tool in

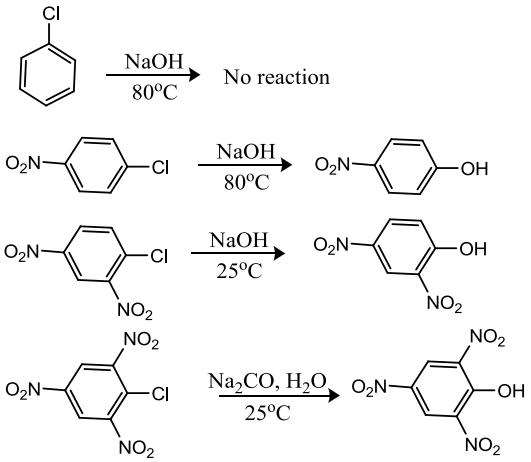
certain cases. The early industrial syntheses of phenols and anilines in fact were based on the nucleophilic aromatic substitution reaction.



If we try and draw parallels between nucleophilic substitution in aliphatic systems and that in aromatic systems, we would quickly realize that the typical S_N1 and S_N2 mechanisms are not feasible in aromatic systems. One of the major reasons is that the p electrons in aromatic systems are in conjugation. Moreover, back side attack (as in S_N2) and inversion is precluded by the geometry of the ring. On the other hand, S_N1 type of substitution would require formation of the phenyl cation which is less stable than a primary carbocation. Obviously, the reaction has to proceed with a totally different type of mechanisms. There are two mechanisms which are possible and they are:

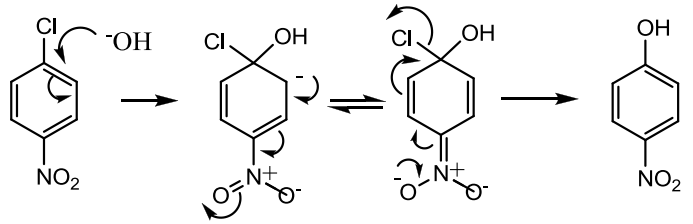
11.3 Addition-Elimination Mechanism

Consider the reaction of an amine with chlorobenzene or nitro-substituted chlorobenzenes. Here, the reaction takes place with substituted chlorobenzene readily whereas under similar conditions, the chlorobenzene itself is unreactive. The nitro group clearly influences the rate of the reaction. In a similar manner, it was observed that the electron withdrawing groups such as –CN, -CO- etc. facilitated the substitution reaction.

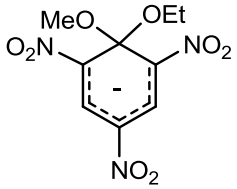


These observations suggest that electron withdrawing groups lower the energy of activation by stabilizing the negative charge developed as the nucleophile adds to aromatic ring. One can write a series of resonating structures for the cyclohexadienyl anion generated after the addition of the nucleophile to the aromatic system. Finally, loss of chlorine completes the

substitution process. This mechanism is parallel to the one which we studied for the electrophilic aromatic substitution reaction.



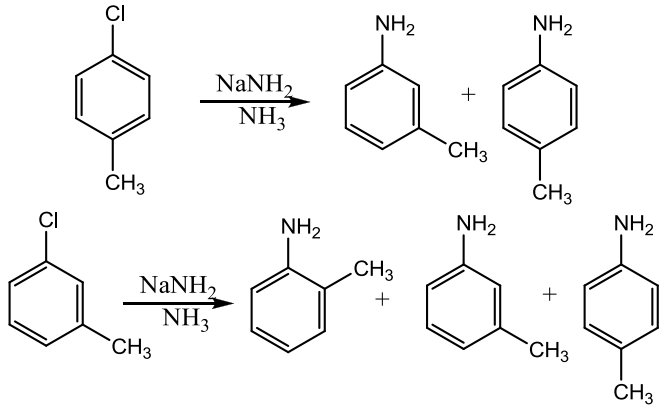
Kinetic studies demonstrate that these reactions are second-order – first order in nucleophile and first-order in the aromatic substrate. The formation of the addition intermediate is the rate determining step (r.d.s.) in these reactions. A further proof for this argument comes from the fact that the order of reactivity for halogens is F > Cl > Br > I (and not the reverse of this i.e. I > Br > Cl > F based on their leaving group ability). This order clearly suggests that stronger bond dipoles associated with the more electronegative atom favor the addition step thus lowering the energy of activation of the nucleophilic addition step (which is r.d.s.). The most convincing evidence that nucleophilic addition is a reasonable initial step was provided by the isolation of a stable adduct from potassium ethoxide and the methyl ether of 2,4,6-trinitrophenol (picric acid) which is called as Meisenheimer complex.



One of the most important applications of the nucleophilic aromatic susbstitution could be seen in Sanger's method for determining the primary structure of protein – particularly determination of the N-terminal amino acid in proteins. In Sanger's protocol, the 2,4-dinitrofluorobenzene is treated with the protein of interest under mild alkaline conditions (this doesn't cause cleavage of peptide bonds). The 2,4-dinitrofluorobenzene – protein adduct is then subjected to acid hydrolysis which leads to the cleavage of peptide bonds, leaving the N-terminal residue in the form of its 2,4-dinitrofluorobenzene – derivative. This derivative can be then be identified by chromatographic methods. This method was introduced in 1945 and used in the structural elucidation of insulin, reported in 1955. Sanger was awarded Nobel prize for chemistry in 1958 for those contributions.

11.4 Elimination-Addition Mechanism – Benzyne

As we have seen earlier, substituted halobenzenes on treatment with strong bases under harsh conditions lead to products formed by nuclephilic aromatic substitution reaction. But products could spring some surprises i.e. position of substitution does not necessarily correspond to the carbon atom from which the leaving group departs. In other words, in cases, we see formation of regioisomeric products. These reactions cannot be adequately explained by addition-elimination mechanism. After several studies, it was proposed that these reactions involve initial elimination of HX by the strong base. The intermediate thus formed contains a triple bond within the benzene and is called benzyne. This is a very unstable intermediate and readil undergoes addition of nucleophile (base) in a second step. This addition can take place at either end of the triple bond and after subsequent protonation, leads to product mixtures observed.

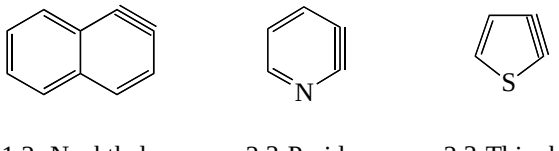


Even though, the formation of benzyne seems quite surprising, there is strong evidence for its formation apart from the product distribution that we have seen above. Unlike addition-elimination, the order of halogen reactivity in these reactions is I > Br > Cl > F. This is in line with what we would expect if elimination was to be the rate controlling step. Another evidence for this mechanism is reaction of 2,6-dimethylchlorobenzene with sodium amide in liquid ammonia. No substitution is observed in this reaction – obviously because there are no hydrogen atoms betas to the chlorine for the initial elimination step. Further support was obtained by trapping the benzyne intermediate in a Diels-Alder reaction.

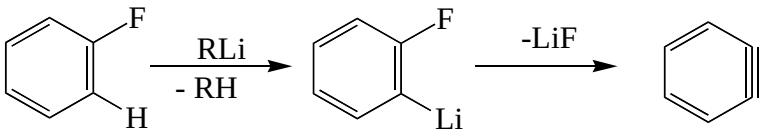
11.5 Benzyne

Benzyne is an example of an *aryne* (a reactive intermediate) and tends to undergo addition reactions. The compound C_6H_4 which we have been referring to as 'benzyne' is formally derived from benzene by removal of a pair of adjacent H atoms and the formation of a triple bond. More accurately it should be called *ortho*-benzyne since *meta*- and *para*- isomers are

also known. The latter, however have quite different structures to the *ortho*-isomer. Benzyne is just one of a general class of reactive intermediates known collectively as *'arynes*'. Arynes derived from aromatic species other than benzene are also known such as

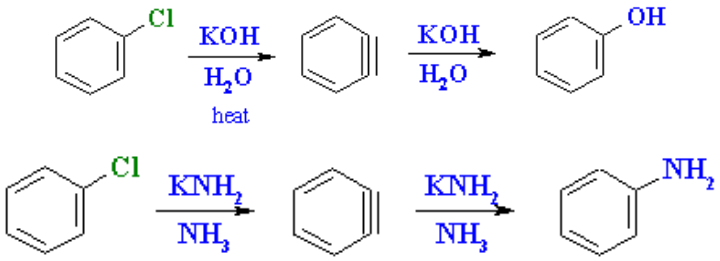


1,2- Naphthalyne 2,3-Pyridyne 2,3-Thiophyne

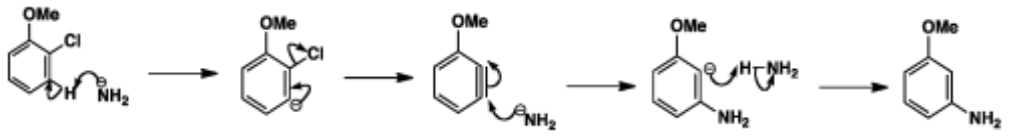


The triple bond is not an ordinary triple bond, because the second p interaction results from a weak interaction of sp^2 hybrid orbitals lying in the plane of the ring. Also the triple bond is non-linear due to the constraints of the 6-membered ring, as a result of the non-linear triple bond, benzyne is highly reactive.

Formation of Benzyne

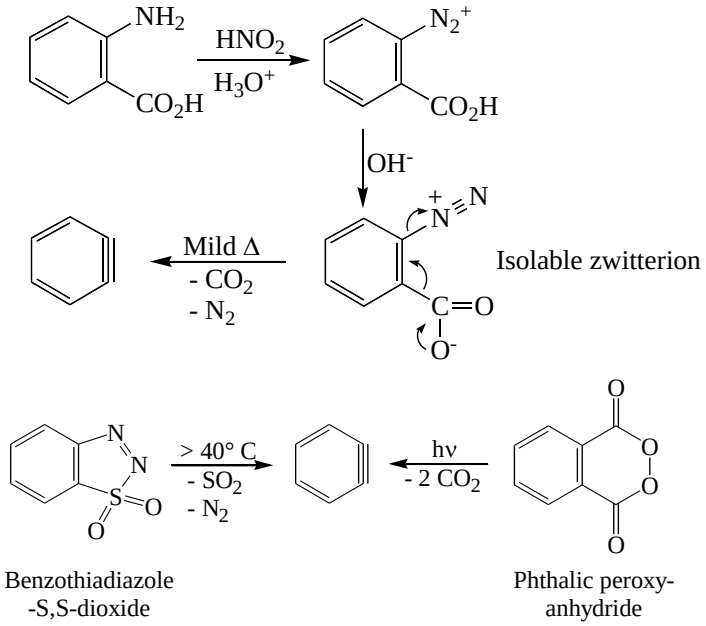


The strained triple bond in benzyne makes it reactive towards addition reactions. Additions of H_2O and NH_3 are commonly encountered are a result of the methods of formation (see above). Substituted benzynes can also be formed, where the subsequent addition reaction typically gives mixtures of products. For example, in the reaction of ochloro anisol with sodamide, the reaction begins with the removal of a proton *ortho* to the leaving group by a strong base e.g. sodium amide (sodamide). The next step is the loss of the leaving group in an elimination reaction resulting in a benzyne intermediate. The benzyne is a very unstable intermediate which is attacked by nucleophiles followed by protonation to give the final product.The benzyne intermediate can be attacked at either end so the characteristic loss of regiochemistry in the substitution can result



The reaction conditions that we looked at so far involved the use of strong bases which could also act as nucleophiles and add to benzyne to form substitution products. One can generate benzynes without having to resort to strong bases. This allows us to use nonbasic nucleophile to be added to the intermediate benzyne. E.g. the thermal decomposition of the diazonium salt derived from 2-aminobenzoic acid (anthranilic acid) leads to the formation of benzyne which undergoes addition of methanol to form anisole. In this reaction pentyl nitrite (amyl nitrite) is used to prepare the diazonium salt.

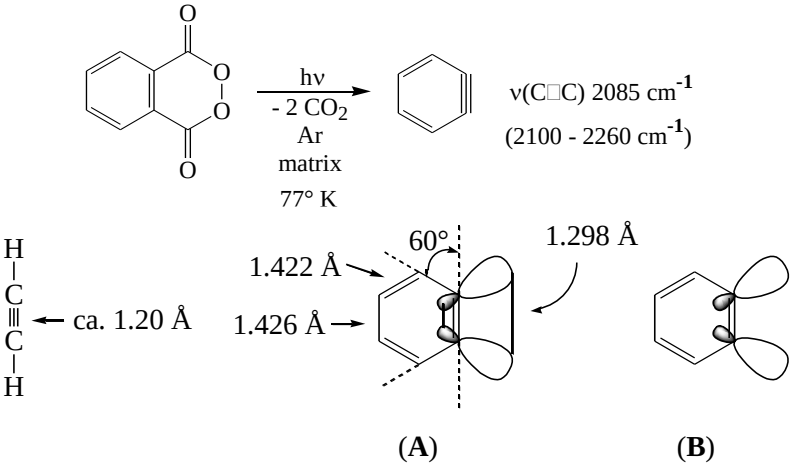
For many synthetic applications of arynes it is necessary to generate the labile intermediate under mild conditions that don't require highly basic reactive organolithium reagents



11.6 Properties of benzyne

Free benzyne is very reactive and rapidly dimerises as shown below. The lifetime of benzyne in the gas phase has been estimated to be at least 20 nanoseconds (2×10^{-8} seconds).

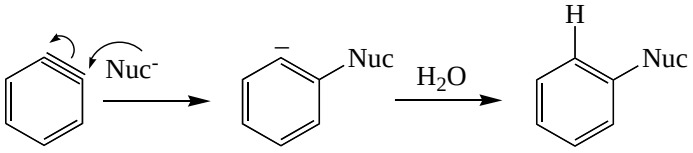
Some spectroscopic properties of benzyne have been determined by Orville Chapman using Matrix Isolation techniques. The theoretical calculations suggest that strained 'bent alkyne' form of benzyne is lower in energy than the alternative structure of di-radical species.



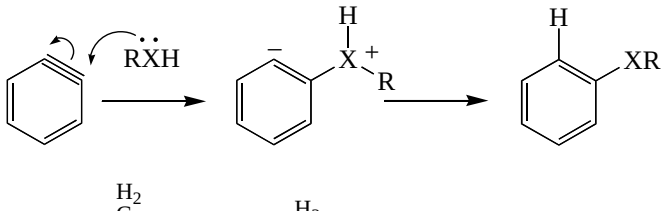
The calculations also suggest that the π-overlap in the strained π bond is weaker and the π* component of the bond (*i.e.* the LUMO) is at lower energy than normal triple bond. Hence *arynes behave as powerful electrophiles*.

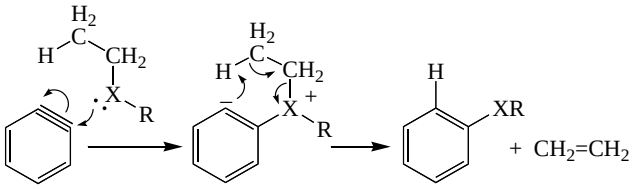
11.7 Aryne reaction patterns

1) Addition of nucleophiles to the triple bond.

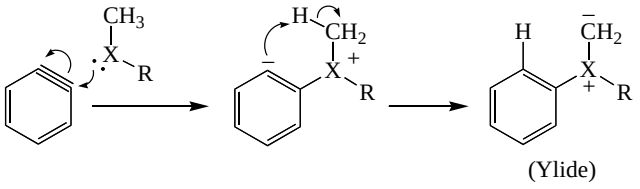


Nuc = Ph-C≡C$^-$ (30%), $[(EtO_2C)_2CH]^-$ (51%) etc.





X = S, NR, PR

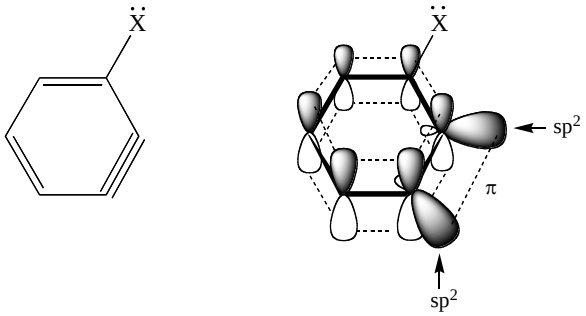


X = S, NR, PR

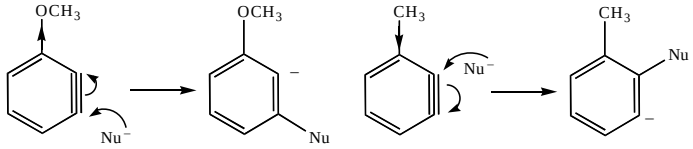
Substituent effects on the addition of nucleophiles to arenes

The π and π*molecular orbitals of the reactive 'extra' π-bond in benzyne lie at right angles to

the aromatic π-cloud as shown in below figure and cannot interact with it. Therefore the 'extra' π-bond is insulated from the *resonance* effects of substituents because these are transmitted via the π-cloud. On the other hand addition of nucleophiles to the low-energy aryne π* molecular orbital is affected by the *inductive* effect of neighbouring substituents

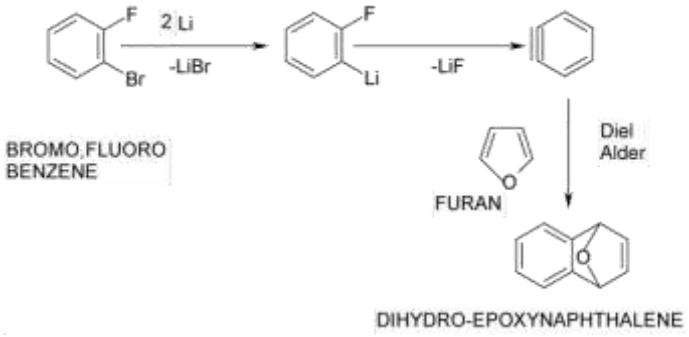


Inductively electron-withdrawing substituents are *meta*-directing and inductively electron-releasing substituents are *ortho*-directing.

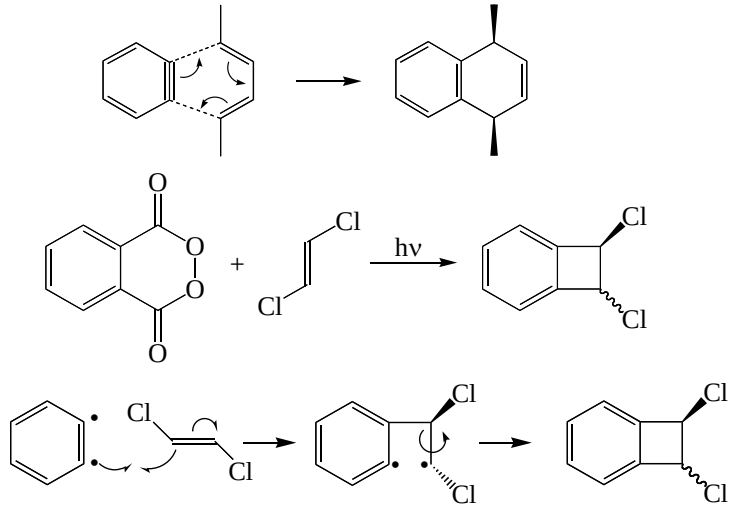


2) Cycloaddition reactions to the aryne triple bond.

Diels-Alder reactions of benzyne with 1,3-dienes in which the aryne triple bond behaves as dienophile are very common and an example involving furan as the diene has been isolated and very well characterized



The stereochemistry of the product in the following thermally promoted Diels-Alder reaction with 2,4-hexadiene demonstrates the concerted nature of the addition.

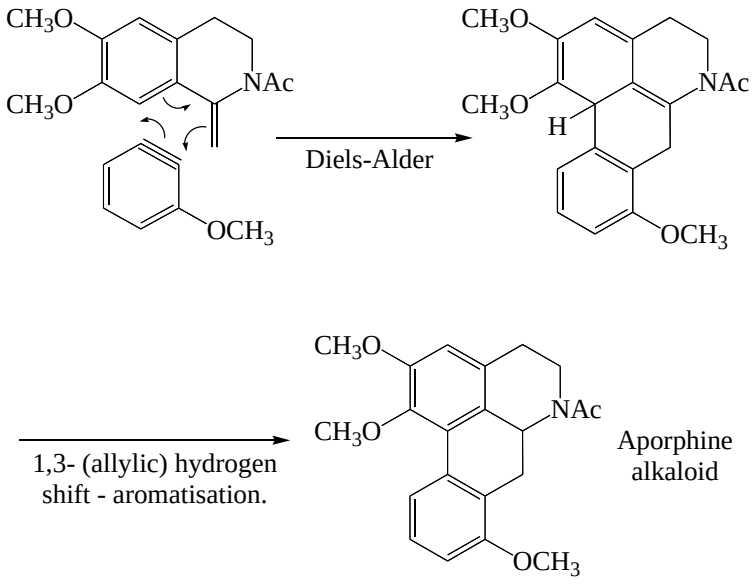


Arynes also undergo formal [2+2] additions to alkenes but many of these are stepwise rather than concerted processes. The loss of the alkene *trans*-stereochemistry in the product of the photochemically mediated cycloaddition illustrated above suggests that it proceeds via a photochemically generated diradical excited state of benzyne rather than by a concerted mechanism.

11.8 Application of arene intermediate in organic synthesis

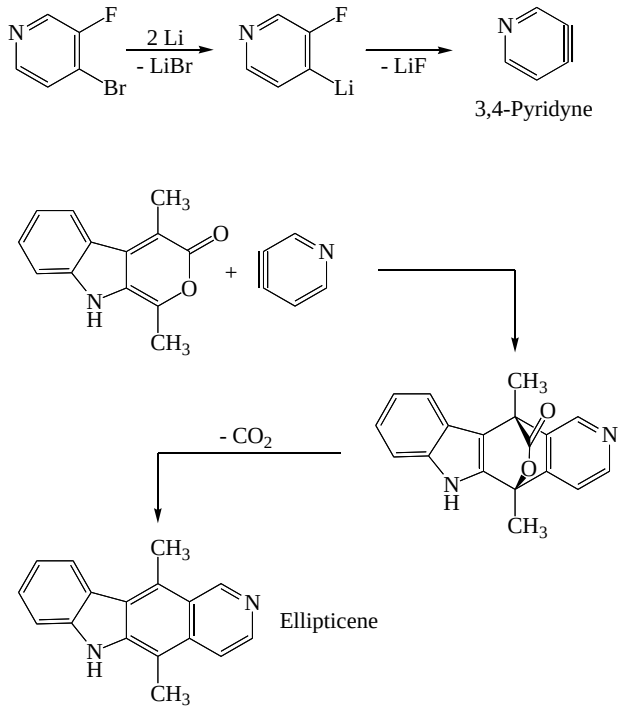
Arynes have not been exploited in organic synthesis to the same extent as free radicals or carbenes but there are still many examples of the use of arenes in natural product synthesis. Some of the examples are listed below.

1) Synthesis of an Aporphine alkaloid

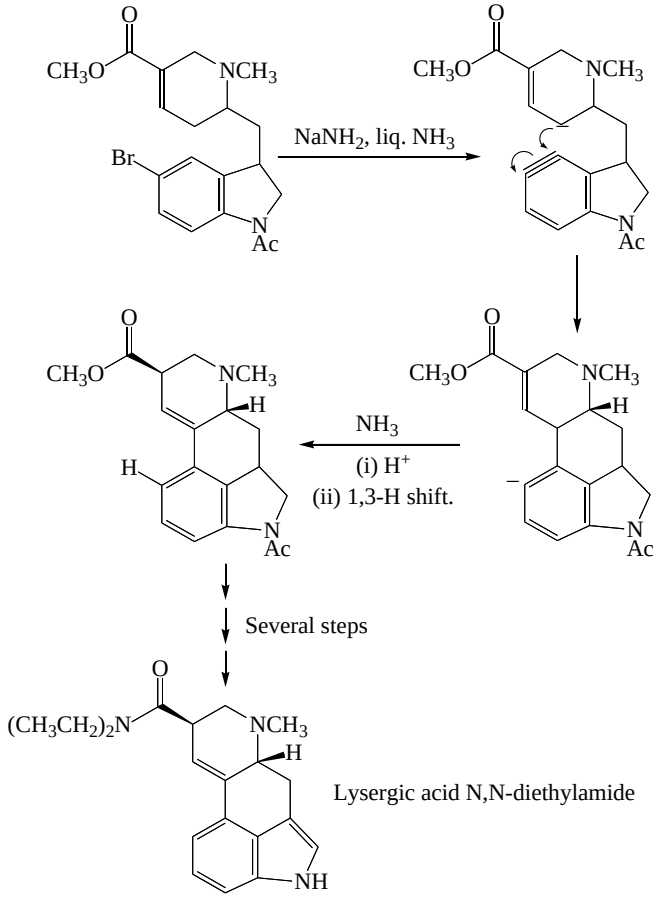


It involves the unusual incorporation of a benzene double bond as part of the 'diene' component of the Diels-Alder reaction.

2) 3,4-Pyridyne in the synthesis of Ellipticene, an anti-cancer alkaloid



3) Benzyne in a synthesis of a Lysergic Acid N,N-Diethylamide (*i.e.* LSD) precursor



11.9 Summary of the unit

Nuleophilic aromatic substitution is much rarer than electrophilic substitution because the aromatic ring is relatively electron rich and will therefore tend to repel the electron rich nucleophilic reagent. Two mechanisms are possible for aromatic nucleophilc substitution reactions they are, the SNAr mechanism and the benzyne mechanism.

The mechanism occurs in those aromatic rings which bear powerfully electronwithdrawing groups which can

(i) Attract the nucleophile by withdrawing electron density from the ring and

(ii) Stabilize the intermediate (which looks like the anionic equivalent of the Wheland intermediate). An example of this is the displacement of halide from 2,4-dinitro – halobenzenes

11.10 Key words

Aromatic nucleophilic substitution; Addition-Elimination; Elimination-Addition; Benzyne; Aryne.

11.11 References for further study

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2) I. L. Finar, Organic Chemistry, ELBS Longmann, Vol. I & II, 1984.

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4) S. K. Ghosh, Advanced General Organic Chemistry, Book and Alleied (P) Ltd, 1998.

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6) Clayden, Greeves, Warren and Wother , Organic chemistry, Oxford University Press, 2001.

11.12 Questions for self understanding

1) Why aromatic nucleophilc substitution reactions are very rare compared to aromatic electrophilic substitution reactions?

2) Which types of aromatic compound prone to exhibit nucleophilc substitution reactions?

3) Whit two examples describe addition-Elimination mechanism.

4) Write a note on Elimination- Addition mechanism.

5) Write two methods for preparation of benzyne

a) Using strong base

b) Using neutral condition

6) Discuss the structure of aryne

7) Why aryne triple bond is more reactive than normal triple bond?

8) Discuss the aryne reaction patterns

Unit - 12

Structure

12.0 Objectives of the unit

After studying this unit you are able to

- Explain the reactions underwent in alkene molecules
- Predict the regioselectivity in alkene addition reaction
- Reasoning the rearrangement occurs in addition reactions
- Explain the steroselctivity in addition reactions
- Identify the product formed in hydroboration reaction
- Recognize the difference between hydroboration and oxymercuration reactions
- Explain the conditions to obtain Markovnikoff and anti- Markovnikoff products

12.1 Introduction

Alkenes have at least one double bond. This double bond contains one σ and one π bonds. Since σ bonds are stronger than π bonds, double bonds tend to react and convert the double bond into σ bonds by addition reactions. Therefore addition reactions are typically exothermic. The π bond is localized above and below the C-C σ bond. The π electrons are relatively far away from the nuclei and are therefore they loosely bound. An electrophile will attract those π electrons, and can pull them away to form a new bond. This leaves one carbon with only 3 bonds and a +ve charge (carbocation), thereby the double bond acts as a nucleophile (attacks the electrophile). In most cases, the cation produced will react with another nucleophile to produce the final overall electrophilic addition product. Electrophilic addition is probably the most common reaction of alkenes.

12.2 Addition reactions of alkenes

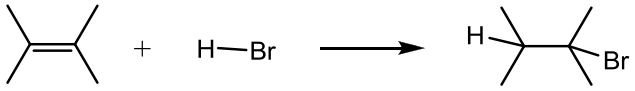
In alkenes two double bonded C atoms and four other atoms bonded to the C's of C=C moiety lie in a plane. The π-orbital with its weekly held electron pair remains perpendicular to the plane of σ-bond. One lobe of the π-orbital lies above the plane of σ-bond and the other lobe lie below it. Thus the two double-bonded C atoms become sandwitched between negative clouds. These in turn, shield the C atoms from attack by nucleophiles and make them react readily with electrophiles.

In fact, electrophilic addition to the C-C double bond is the most common type of reactions. A large number of reagents, both inorganic and organic, have been found to add to this double bond, and in this section we shall review many of these reactions. A majority of these reactions are exothermic, due to the fact that the C-C pi-bond is relatively weak (ca. 63 kcal/mole) compare to the sigma-bonds formed to the atoms or groups of the reagent. Remember, the bond energies of a molecule are the energies required to break

(homolytically) all the covalent bonds in the molecule. Consequently, if the bond energies of the product molecules are greater than the bond energies of the reactants, the reaction will be exothermic. The following calculations for the addition of H-Br are typical. Note that by convention exoth

Bonds broken: C=C (63) & H-Br (87.5) Sum = 150.5 Kcal/mol

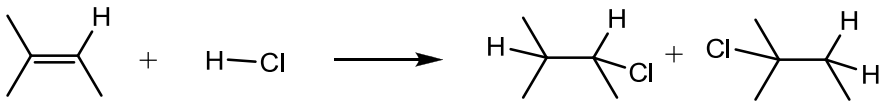
Bonds formed: H-C (99) & Br-C (68) Sum = 167.o Kcal/mol



As illustrated by t Heat of reaction = 150.5-167.0 = -16.5 kcal/mole such as HCl, HBr, HI & H_2SO_4, rapidly add to the C=C functional group of alkenes to give products in which new covalent bonds are formed to hydrogen and to the conjugate base of the acid. Weak Brønsted acids such as water (pK_a = 15.7) and acetic acid (pK_a = 4.75) do not normally add to alkenes. However, the addition of a strong acid serves to catalyze the addition of water, and in this way alcohols may be prepared from alkenes. For example, if sulfuric acid is dissolved in water it is completely ionized to the hydronium ion, $H_3O^{(+)}$, and this strongly acidic (pK_a = -1.74) species effects hydration of ethene and other alkenes.

The importance of choosing an appropriate solvent for these addition reactions should now be clear. If the addition of HCl, HBr or HI is desired, water and alcohols should not be used. These strong acids will ionize in such solvents to give $ROH_2^{(+)}$ and the nucleophilic oxygen of the solvent will compete with the halide anions in the final step, giving alcohol and ether products. By using inert solvents such as hexane, benzene and methylene chloride, these competing solvent additions are avoided. Because these additions proceed by way of polar or ionic intermediates, the rate of reaction is greater in polar solvents, such as nitromethane and acetonitrile, than in non-polar solvents, such as cyclohexane and carbon tetrachloride.

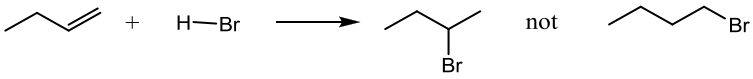
Only one product is possible from the addition of these strong acids to symmetrical alkenes such as ethene and cyclohexene. However, if the double bond carbon atoms are not structurally equivalent, as in molecules of 1-butene, 2-methyl-2-butene and 1-methylcyclohexene, the reagent conceivably may add in two different ways.



12.3 Regio selectivity in electrophilc alkene addition

Addition of non-symmetrical reagent to a non-symmetrical alkene, then two isomeric products that are constitutional isomers can be obtained. For example, the reaction of H-Br

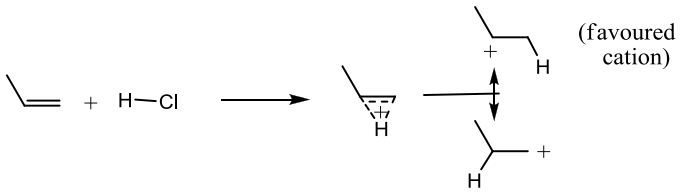
with propene gives 1-Brompropane and 2-bromopropane. When addition reactions to such unsymmetrical alkenes are carried out, we find that one of the two possible constitutionally isomeric products is formed preferentially. Selectivity of this sort is termed *regioselectivity*. In the above example, 2-chloro-2-methylbutane is nearly the exclusive product. Similarly, 1-butene forms 2-bromobutane as the predominant product on treatment with HBr.



After studying many addition reactions of this kind, the Russian chemist Vladimir Markovnikov noticed a trend in the structure of the favored addition product. He formulated this trend as an empirical rule we now call The *Markovnikov Rule*:

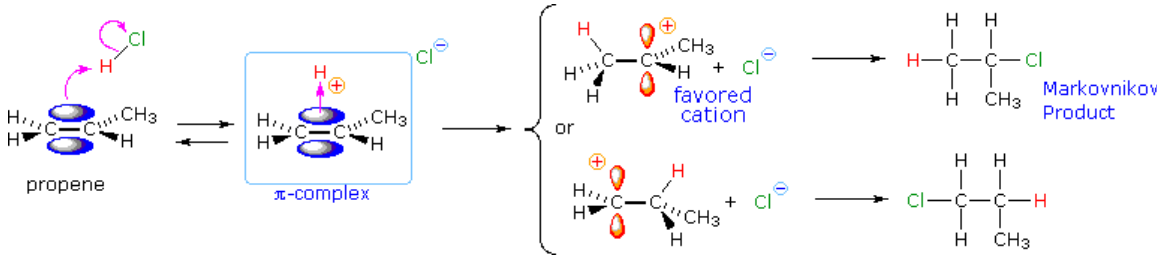
This rules state that *when a Brønsted acid, HX, adds to an unsymmetrically substituted double bond, the acidic hydrogen of the acid bonds to that carbon of the double bond that has the greater number of hydrogen atoms already attached to it*.

When an unsymmetrically substituted double bond is protonated, we expect the more stable carbocation intermediate to be formed faster than the less stable alternative, because the activation energy of the path to the former is the lower of the two possibilities. This is illustrated by the following equation for the addition of hydrogen chloride to propene. Note that the initial acid-base equilibrium leads to a pi-complex which immediately reorganizes to a sigma-bonded carbocation intermediate. The more stable 2º-carbocation is formed preferentially, and the conjugate base of the Brønsted acid (chloride anion in the example shown below) then rapidly bonds to this electrophilic intermediate to form the final product.



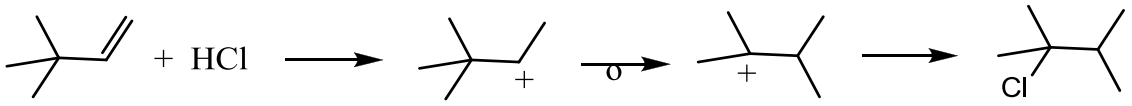
The stability of the carbocation follows the order as shown below

$$CH_3^{(+)} < CH_3CH_2^{(+)} < (CH_3)_2CH^{(+)} \approx CH_2{=}CH\text{-}CH_2^{(+)} < C_6H_5CH_2^{(+)} \approx (CH_3)_3C^{(+)}$$

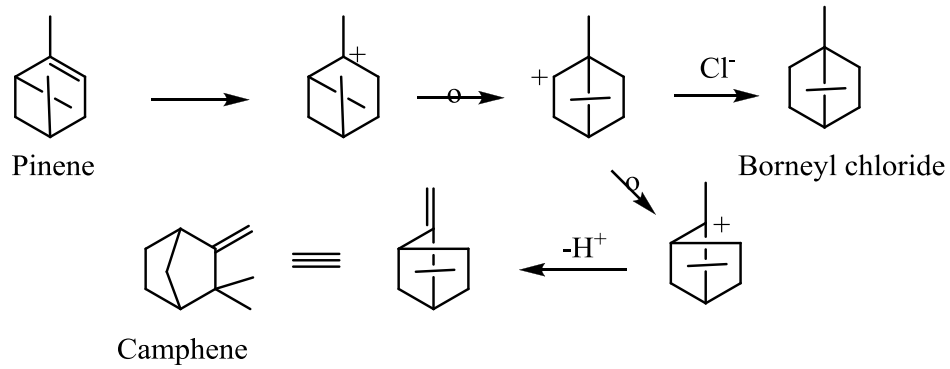


12.4 Rearrangement of carbocations while addition reaction

The formation of carbocations is sometimes accompanied by a structural rearrangement. Such rearrangements take place by a shift of a neighboring alkyl group or hydrogen, and are favored when the rearranged carbocation is more stable than the initial cation. The addition of HCl to 3,3-dimethyl-1-butene, for example, leads to an unexpected product, 2-chloro-2,3-dimethylbutane, in somewhat greater yield than 3-chloro-2,2-dimethylbutane, the expected Markovnikov product. This surprising result may be explained by a carbocation rearrangement of the initially formed 2º-carbocation to a 3º-carbocation by a 1,2-shift of a methyl group.



Another factor that may induce rearrangement of carbocation intermediates is strain. The addition of HCl to α-pinene, the major hydrocarbon component of turpentine, gives the rearranged product, bornyl chloride, in high yield. As shown in the following equation, this rearrangement converts a 3º-carbocation to a 2º-carbocation, a transformation that is normally unfavorable. However, the rearrangement also expands a strained four-membered ring to a much less-strained five-membered ring, and this relief of strain provides a driving force for the rearrangement.

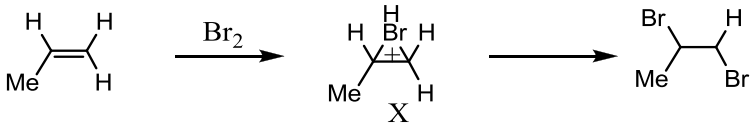


12.5 Addition of Lewis Acids (Electrophilic Reagents)

The proton is not the only electrophilic species that initiates addition reactions to the double bond. Lewis acids like the halogens, boron hydrides and certain transition metal ions are able to bond to the alkene pi-electrons, and the resulting complexes rearrange or are attacked by nucleophiles to give addition products. The electrophilic character of the halogens is well known. Although fluorine is uncontrollably reactivity, chlorine, bromine and iodine react selectively with the double bond of alkenes. The addition of chlorine and bromine to alkenes,

as shown in the following general equation, proceeds by an initial electrophilic attack on the pi-electrons of the double bond. Iodine adds reversibly to double bonds, but the equilibrium does not normally favor the addition product, so it is not a useful preparative method. Dihalo-compounds in which the halogens are juxtaposed in the manner shown are called vicinal, from the Latin *vicinalis*, meaning neighboring.

For instance, the addition of bromine to many olefins in polar solvents proceeds through an intermediate which we will represent (X). In simple addition, this cyclic bromonium ion is thought to react with Br^- present in solution to form the observed dibromide.

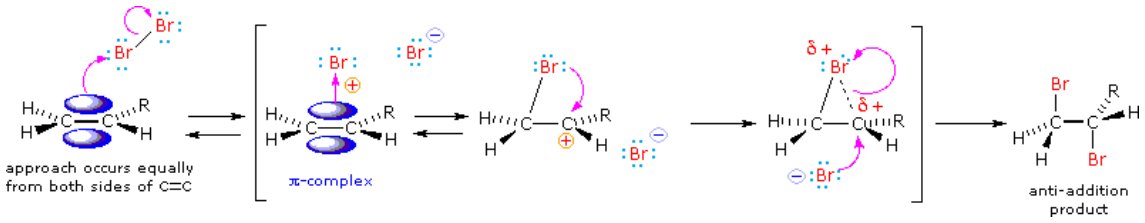


Other halogen containing reagents which add to double bonds include hypohalous acids, HOX, and sulfenyl chlorides, RSCl. These reagents are unsymmetrical, so their addition to unsymmetrical double bonds may in principle take place in two ways. In practice, these addition reactions are regioselective, with one of the two possible constitutionally isomeric products being favored. The electrophilic moiety of these reagents is the halogen.

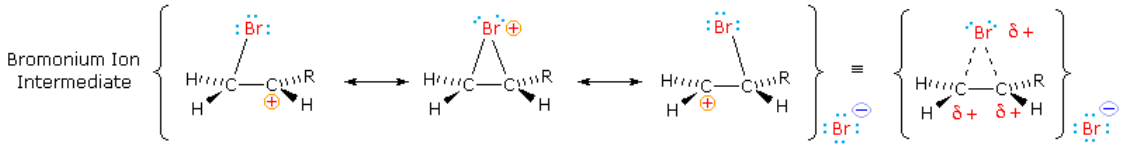
The regioselectivity of the above reactions may be explained by the same mechanism we used to rationalize the Markovnikov rule. Thus, bonding of an electrophilic species to the double bond of an alkene should result in preferential formation of the more stable (more highly substituted) carbocation, and this intermediate should then combine rapidly with a nucleophilic species to produce the addition product.

12.6 Stereoselectivity in addition Reactions to double bonds

When an alkene undergoes addition, two new σ-bonds form. If we think of an alkene as having two faces, then the two new s bonds can either on the same face, which we call *syn* addition, or they can be formed on different faces which we call *anti* addition.



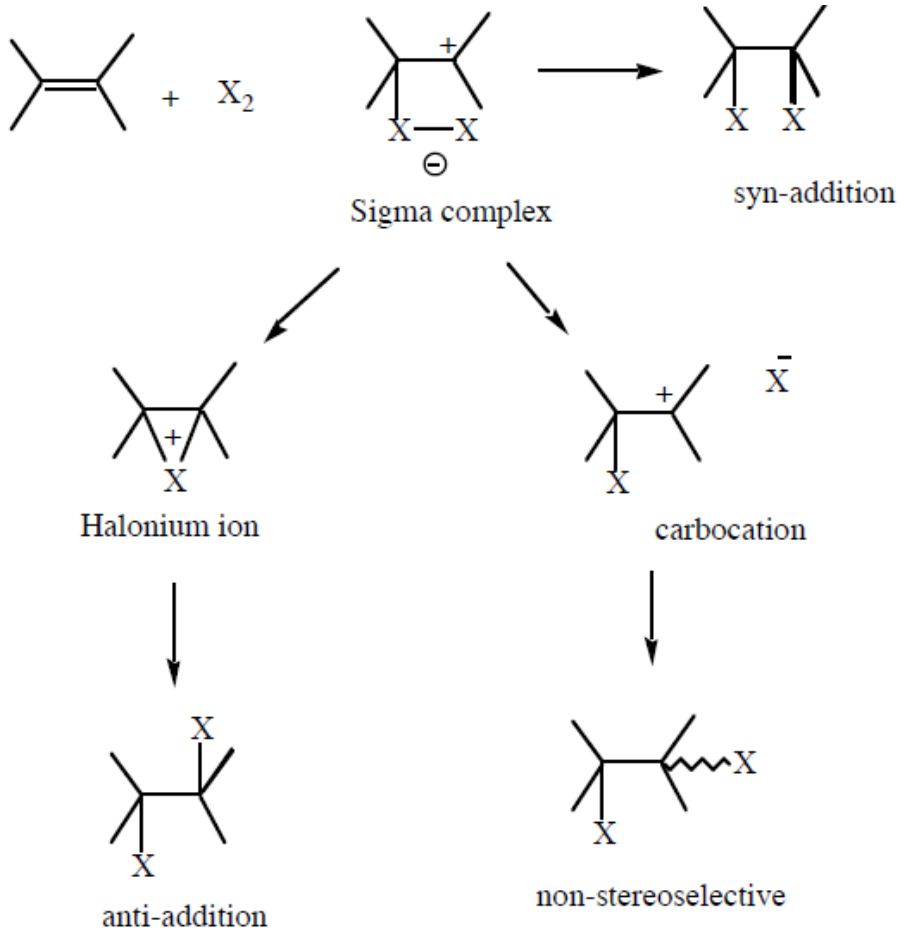
Since initial electrophilic attack on the double bond occur equally well from side, the second step (or stage) of the reaction (bonding of the nucleophile) imposed the stereoselectivity.

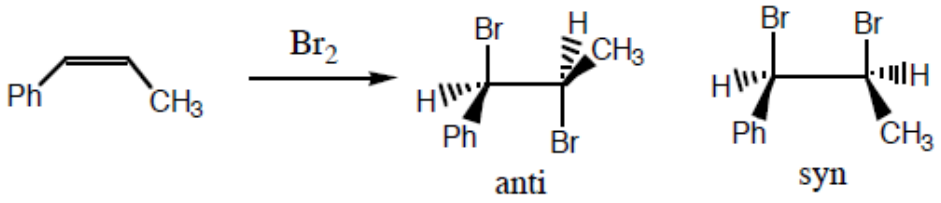


If the two-step mechanism described above is correct, and if the carbocation intermediate is

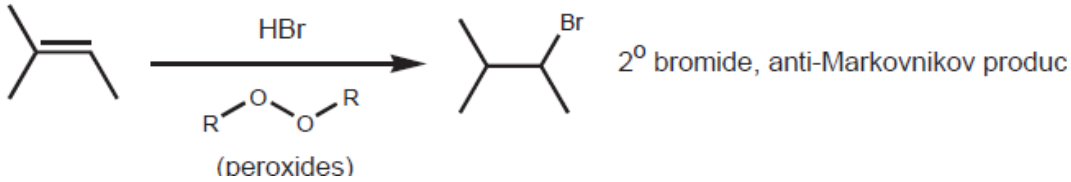
Reagent	H-X	X_2	HO-X	RS-Cl	$Hg(OAc)_2$	BH_3
Streoselectivity	mixed	anti	anti	anti	anti	syn

sufficiently long-lived to freely-rotate about the sigma-bond component of the original double bond, we would expect to find random or non-stereoselective addition in the products. On the other hand, if the intermediate is short-lived and factors such as steric hindrance or neighboring group interactions favor one side in the second step, then stereoselectivity in product formation is likely. The following table summarizes the results obtained from many studies, the formula HX refers to all the strong Brønsted acids. The interesting differences in stereoselectivity noted here provide further insight into the mechanisms of these addition reactions.





Ionic mechanisms favor formation of the Markovnikov product through formation of the most stable carbocation. However, it is possible to manipulate conditions to favor formation another product with opposite orientation, called the anti-Markovnikov product. The anti-Markovnikov product form through a different mechanism in the *presence of peroxides*. Peroxides are well known *free radical initiators*. This promotes a reaction where the reactants add by formation of the most stable free radical.



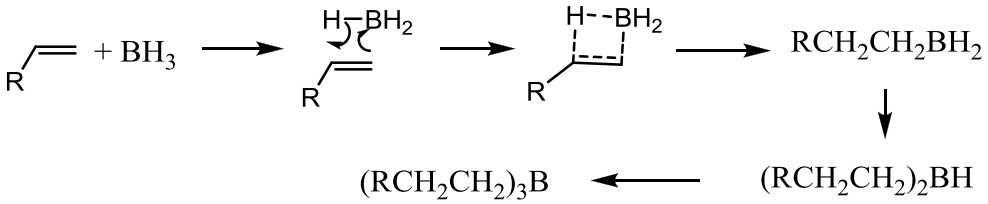
12.7 Hydroboration reactions

In chemistry, hydroboration refers to the addition of a hydrogen-boron bond to C-C, C-N, and C-O double bonds, as well as C-C triple bonds. This chemical reaction is useful in the organic synthesis of organic compounds. The development of this technology and the underlying concepts were recognized by the Nobel Prize in Chemistry to Herbert C. Brown. He shared the Noble prize in chemistry with Georg Wittig in 1979 for his pioneering research on organoboranes as important synthetic intermediates.

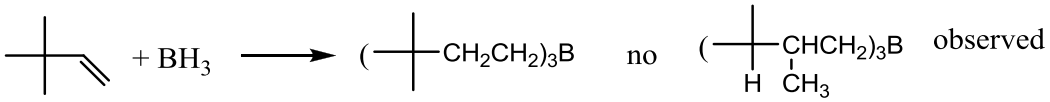
Hydroboration produces organoborane compounds that react with a variety of reagents to produce useful compounds, such as alcohols, amines, alkyl halides. The most widely known reaction of the organoboranes is oxidation to produce alcohols typically by hydrogen peroxide. This type of reaction has promoted research on hydroboration because of its mild condition and a wide scope of olefins tolerated.

Hydroboration proceeds via a four-membered transition state: the hydrogen and the boron atoms added on the same face of the double bond. Granted that the mechanism is concerted, the formation of the C-B bond proceeds slightly faster than the formation of the C-H bond. As a result, in the transition state, boron develops a partially negative charge while the more substituted carbon bears a partially positive charge. This partial positive charge is better

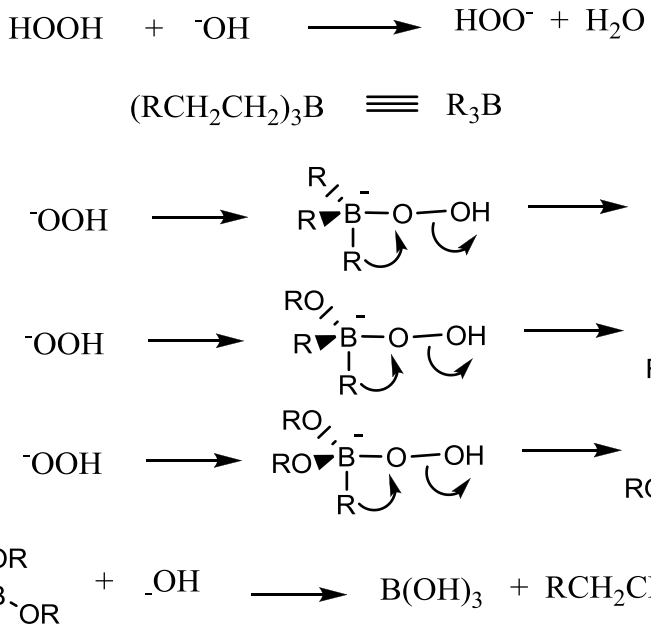
supported by the more substituted carbon. The reaction is an electrophikic additiuon because the electron defficient BH_3 is initially attracted to the electrons of the π-bond.



The addition of borane to an alkene also follows Markovnikov rule. In BH_3, the hydrogen is the negative end and the boron is the positive end of the dipole. Although hydroboration follows Markovnikov rule, the reaction does not appear to involve carbocation intermediates. One piece of evidence is that rearrangements are not oserved in hydroboration.

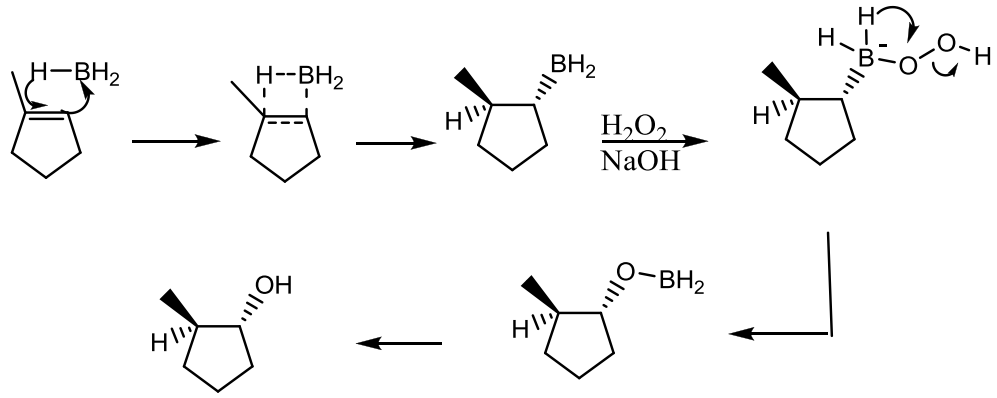


The C-B bonds generated by hydroboration are reactive with various reagents, the most common one being hydrogen peroxide and aqueous base. Because the addition of H-B to olefins is stereospecific, this oxidation reaction will be diastereoselective when the alkene is tri-substituted. Hydroboration-oxidation is thus an excellent way of producing alcohols in a stereospecific and anti-Markovnikov fashion. The mechanism for the oxidation stage involves the following steps.



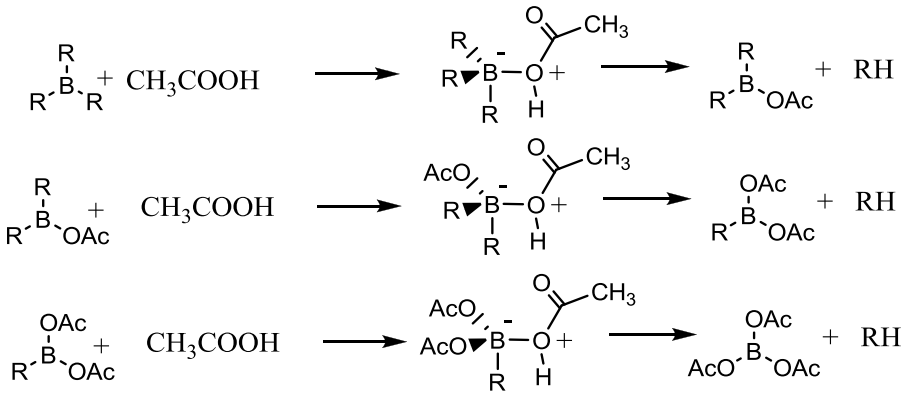
Since the boron atom attaches itself to the less substituted double bonded or tripple bonded C atom, the method provides a means for hydrating a double bond or tripple bond anti-

Markovnikoffically. Hydroboration has the advantage that stereochemistry is created in the hydroboration step. In drawing the mechanism, it is usually best to darw it as a simple concerted four-centre mechanism wherein the regiochemistry is controlled by the initial interaction between the nucleophilic end of the alkene and the empty p orbital on boron.



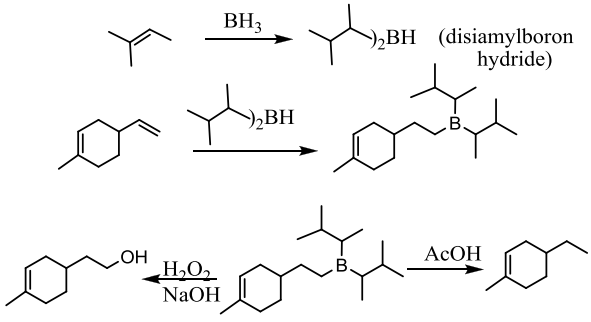
12.8 Non-catalytic hydrogenation of alkenes and alkynes

When alkylboranes and vinylboranes are treated with protic aicds, alkanes and cis-alkenes are produced respectively. Acetic acid may be used for the purpose.

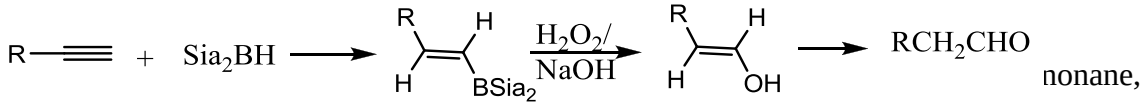


12.9 Selective reduction and hydration by bis-3-methyl-2-butylboran [$(Si\alpha)_2BH$: disiamyl boron hydride]

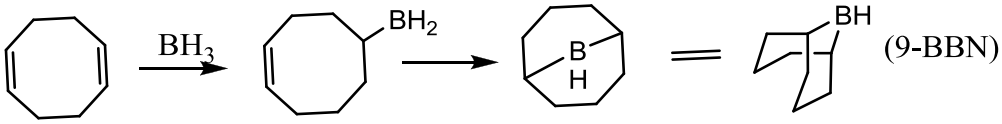
When 2-methyl-2-butene is treated with diborane by bis-3-methyl-2-butylborane results. This can hydroboronate selectively a less hindered double bond. From the product of hydroboration desired alcohol and alkane can be prepared as usual.



Hydroboration is not restricted ot restricted to alkenes; alkynes also react well to give vinylboranes. These may be used directly synthesis or oxidized to the corresponding enol, which immediately tautomerizes to the aldehyde.



nonane, commonly abbreviated as 9-BBN. Relative to disiamylborane, 9-BBN is more sensitive to electronic influences. Additionally, 9-BBN allows shorter reaction time and higher regioselectivity.



Although oxidation to the alcohol is the most common reaction of organoboranes in organic synthesis, the reaction with ⁻O-OH is just one example of a general reaction with a nuceophile of the type ⁻X-Y where the nucleophilic atom X can be O, N or even C, and Y is a leaving group. If X is nitrogen then a direct method of amination results. The required reagent is chloramine or O-hydroxylaminesulfonic acid (HSA) and the leaving group is chloride or sulfonate. The overall process of hydroboration-amination corresponds to a regioselective syn addition of ammonia across the alkene.

Carbon-carbon bonds can also be made with alkyl boranes. The requirement for a carbon nuceophile that bears a suitable leaving group is met by α-halo carbonyl compounds. The halogen makes enolization of the carbonyl compound easier and then departs in the rearrangement step. The product is boron enolate with the boron bound to carbon. Under the basic conditions of the reaction, hydrolysis to the corresponding carbonyl compound is rapid. In this example it is important which group migrates from boron to carbon as that is the group that forms the new C-C bond in the product. In the Baeyer-Villeger reaction (migration from carbon to oxygen) the more highly substituted carbon atom migrates best so the order is t-alkyl > s-alkyl > n-alkyl > methyl. In organoborane rearrangements it is the reverse order: n-alkyl > s-alkyl > t-alkyl. Methyl doesnot feature as you cannot make a B-Me bond by hydroboration.

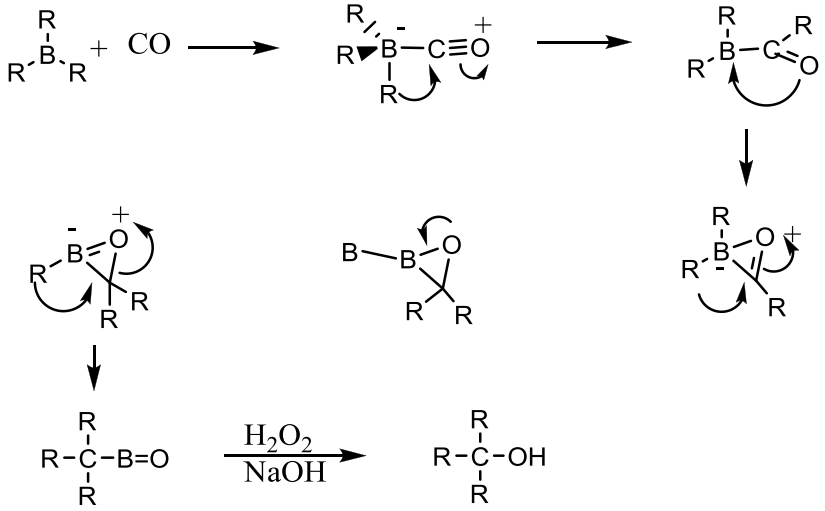
The transition state for the Baeyer-Villeger rearrangement has a positive charge in the important area. Anything that can help to stabilize the positive charge, such as a tertiary migrating group stabilizes the transition state and make the reaction go better. In the boron rearrangements, by contrast, the whole transition state has a negative charge. Alkyl groups

stabilize rather than stabilize negative charges, but primary alkyl groups destabilize them less than secondary ones do, and so on.

Terminal olefins are converted to the corresponding alkyl bromides and alkyl iodides by treating the organoborane intermediates with bromine or iodine. Of the many hydroborating reagents available, borane (BH_3) is commercially available as THF solutions wherein it exists as the adduct BH_3(THF). Long term storage of BH_3/THF requires stabilization by a small amount of sodium borohydride and storage at 0 °C. The concentration of BH_3 usually cannot exceed 2M. The related borane dimethylsulfide complex $BH_3S(CH_3)_2$ (BMS) is comparatively more convenient because it is more stable and it can be obtained in highly concentrated forms. Less volatile sulfides have also been developed for odor control. This borane sulfide adducts are stable at room temperature and soluble in ethers and dichloromethane.

12.10 Carbonylation reactions

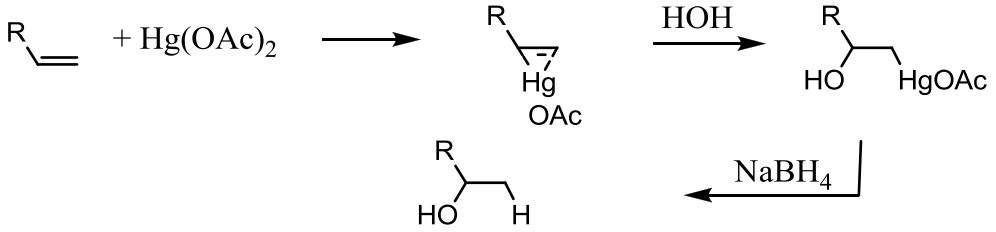
At low temperature, carbon monoxide reacts with trialkylboranes yielding intermediates which on oxidative hydrolysis with alkaline hydrogen peroxide give tertiary alcohols. Probable mechanism for this reaction is as shown below



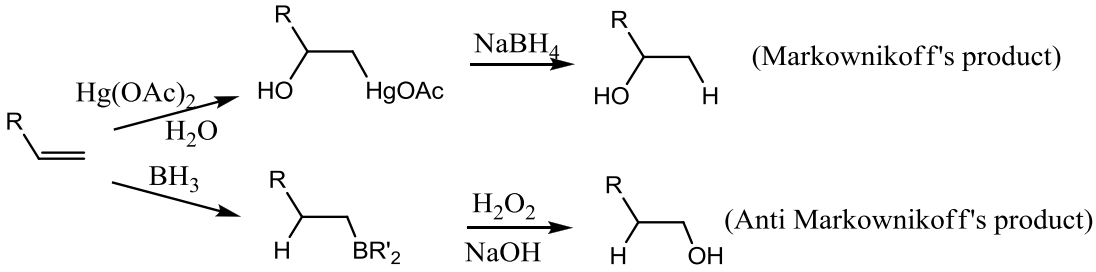
12.11 Oxymercuration reactions

When alkenes are treated with mercuric acetate in acetic acid we get 1-acetoxy-2-mercuriacetate derivatives. This reaction takes place in two stages. A hydroxyalkyl mercury or an alkoxyalkyl mercury compound forms in the oximercuration step. It is a rapid step. The positive charge resides mostly on the Hg in step I and mercuriacetate cation may attack the double bond carbons either from hindered or from the unhindered side of the double bond. However, the nucleophilic solvent water or ROH attacks that carbon which better

accommodates the δ_1^+ or δ_2^+ charge; the attack occurs from the less hindered side of the double bond. In fact the more alkyl group substituted C atom holds more positive charge than the less substituted C atom and hence the oxymercuration step follows the markownikoff's addition.



The addition products formed in reactions of alkenes with mercuric acetate and boron hydrides (compounds shown at the bottom of of the reagent list) are normally not isolated, but instead are converted to alcohols by a substitution reaction. The oxymercuration reaction gives the product predicted by Markovnikov's rule; hydroboration on the other hand gives the "anti-Markovnikov" product. Complementary reactions such as these are important because they allow us to direct a molecular transformation whichever way is desired. Mercury and boron are removed from the organic substrate in the second step of oxymercuration and hydroboration respectively. It is worth noting that the mercury moiety is reduced to metallic mercury by borohydride (probably by way of radical intermediates), and boron is oxidized to borate by the alkaline peroxide. Addition of hydroperoxide anion to the electrophilic borane generates a tetra-coordinate boron peroxide, having the general formula $R_3B\text{-}O\text{-}OH^{(-)}$. This undergoes successive intramolecular shifts of alkyl groups from boron to oxygen, accompanied in each event by additional peroxide addition to electron deficient boron. The retention of configuration of the migrating alkyl group is attributed to the intramolecular nature of the rearrangement.



12.12 Radical addition reactions

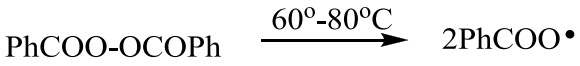
The most important type of radical reactions which deserve special mention is the radical addition to C-C double bonds. These reactions occur either in the gas phase or in inert non-

polar solvents in the presence of light, heat or catalytic amount of radical initiators such as organic peroxides, labile azo compounds etc. The mode of addituon reaction involves the general steps for radical reactions, i.e. initiation, chain propagation and termination.

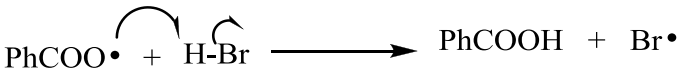
The radical addition of HBr to a C-C double bond occurs in the presence of UV light or a small amount of radical initiators such as dibenzoyl peroxides. HF, HCl and HI do not undergo the reaction because it is not energetically favourable for them. Kharasch in 1932 studied extensively the radical addition of HBr across a C-C double bond and found that it occur anti-Markownikoffically with unsymmetrical alkenes in the presence of organic peroxides. Thus HBr adds to the propene in the presence of dibenzoyl peroxide at a temperature 60o-80oC to give 1-bromopropane instead of 2-bromopropane. According to Kharasch the change in orientation is due to the presence of organic peroxide and so the change in orientation is said to be peroxide effect and the principle of addition is called Kharasch principle.

The mechanistic steps for the reaction are

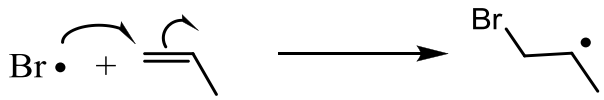
Step 1: Thermolysis of dibenzoyl peroxide to benzoylperoxy radical



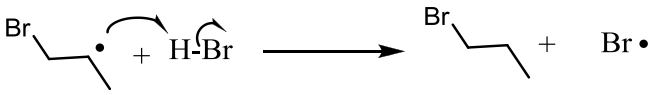
Step 2: Generation of bromine radical from HBr



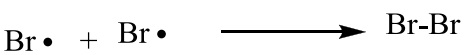
Step 3: Electrophilic addition of bromine radical to a double bonded C- atom which generates the more stable carbocation.

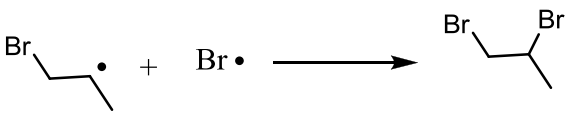


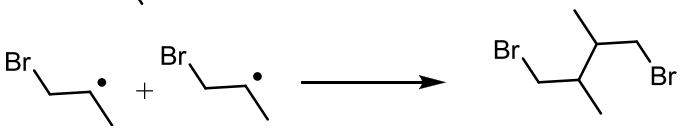
Step 4: Abstraction of a hydrogen radical form another molecule of HBr to give 1-bromopropane and bromine radical.



Step 5: Termination



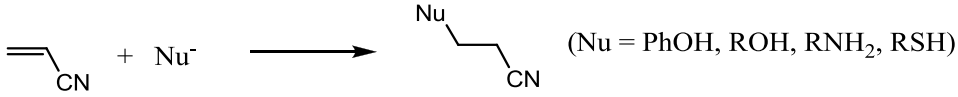




Thus we see that bromine and hydrogen atoms add to the double bond and a carbon radical is an intermediate in the addition of HBr in the presence of a peroxide to a C=C. It is the bromine radical and not the hydrogen radical starts the propagation step. Since the stability order of the alkyl radicals is $3^o > 2^o > 1^o$, the Br. Radical attaches itself to the least sunbstituted double bonded C atom and thereby generates 2^o or 3^o carbon radical and consequently anti-Markownikoff's addition occurs through the abstraction of H. radical from HBr by the incipient carbon radical in the next propagation step.

12.13 Nucleophilic addition to C=C:

Since the two double bonded C atoms being sanwitched between negative charge clouds, the nucleophiles cannot attack them easily. However, favourable structural changes on the C=C moiety can make it to undergo nucleophilic addition reaction. Thus if electron withdrawing substituents are present on the multiple bonded C atoms, they will decrease electron density on the involved Cs. And thereby nucleophilic addition will be facilitated. Simple alkenes or alkenes with electron releasing substituents do not undergo nucleophilic addition. Polyhalo, polycyano alkenes or alkenes with strong electron withdrawing substituents such as –CHO, -COR, $-NO_2$ etc undergo nucleophilic addition reaction.



12.14 Summary of the unit

In many addition reactions the attacking reagent (unlike H_2) is a polar molecule. Hydrogen halides are among the simplest examples of polar substances that add to alkenes. Addition occurs rapidly in a variety of solvents, including nonpolar solvent like pentane, benzene, dichloromethane, chloroform, and polar solvent like acetic acid, etc... It involves two steps. The first is an acid–base reaction in which the hydrogen halide donates a proton to the alkene, forming a carbocation. Unlike other acid–base reactions that we have seen in which a proton is rapidly transferred to oxygen, proton transfer to carbon is almost always slow. Among the hydrogen halides, reactivity parallels acid strength. Hydrogen iodide reacts with alkenes at the fastest rate, hydrogen fluoride at the slowest.

The characteristic chemical *property* of a C=C *structural* unit is susceptibility to attack by electrophiles. Generally electrons flow from the π component of the double bond toward the electrophile and resulting in the formation of a covalent bond. Hydrogen halide adds to an unsymmetrical alkene in either of two directions. In practice, addition is so highly regioselective and considered as regiospecific.

In 1870, Vladimir Markovnikov, at the University of Kazan, noticed a pattern in the hydrogen halide addition to alkenes and organized his observations into a simple statement. Later it was called Markovnikov's rule, which states that *when an unsymmetrically substituted alkene reacts with a hydrogen halide, the hydrogen adds to the carbon that has the greater number of hydrogens, and the halogen adds to the carbon having fewer hydrogens.* In general, alkyl substituents increase the reactivity of a double bond toward electrophilic addition because alkyl groups are electron-releasing, and the more *electron-rich* a double bond, the better it can share its π electrons with an electrophile. Along with the observed regioselectivity of addition, this supports the idea that carbocation formation, rather than carbocation capture, is rate-determining step. An addition occurred opposite to Markovnikov's rule when peroxides were present in the reaction mixture.

12.15 Key words

Electrophilic addition; Regioselectivity; Markovnikoff's rule; anti- Markovnikoff's addition; Steroselctivity; Hydroboration; Oxymercuration.

12.16 References for further study

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3. F. A. Carrey and Sundberg, Advanced Organic Chemistry – Part A & B, 3rd edition, Plenum Press, New York, 1990.

4. S. K. Ghosh, Advanced General Organic Chemistry, Book and Alleied (P) Ltd, 1998.

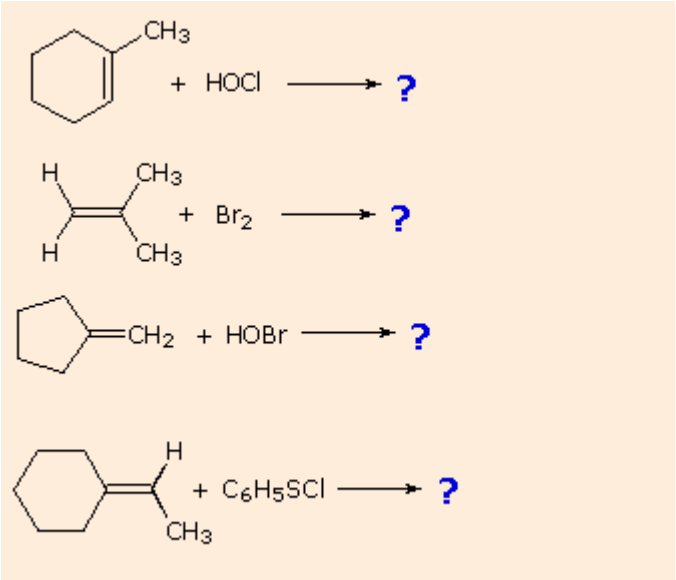
5. J. March, Advanced Organic Chemistry, Wiley Interscience, 1994.

6. Clayden, Greeves, Warren and Wother, Organic chemistry, Oxford University Press, 2001.

12.17 questions for self understanding

1) What is electrophilic addition reaction?
2) Which type of reaction generally aklenes shows? Give three examples.
3) Discuss the regioselectivity observed in electrophilic substitution reactions of alkenes.
4) What is Markovnikoff's rule? Explain with example.
5) In the presence of per acids, alkenes exhibit anti- Markovnikoff's addition products. Give the reason and discuss the mechanism with example.
6) With an example discuss the rearrangement occurs in alkenes addition reactions
7) Explain the steroselctivity in addition reactions
8) What is hydroboration reaction? Discuss its mechanism

9) What is Oxymercuration reaction? What is the difference between product formed in hydroboration reaction and Oxymercuration reaction?
10) Discuss aradical addition reactions to alkenes.
11) Write a note on nucleophilic addition to alkenes double bond.
12) Explain the conditions to obtain Markovnikoff and anti- Markovnikoff products
13) Write the products formed in these reactions



Unit- 13

Structure

13.0 Objectives of the unit

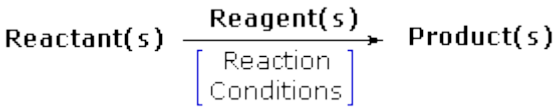
After studying this unit we are able to learn

- Way of writing the reactions
- Distinguish different types of organic reactions
- Classifying Neuclophiles and Electrophiles
- Writing the mechanism of different Neucleophilic substitution reactions.
- Predicting stereochemical outcome of different Neucleophilic substitution reactions.

13.1 Introduction

All most all organic compounds contain one or more atoms or groups of atoms that determine the reactive, structural, or other functional characteristics of a molecule and they are called *Functional Groups***.** Understanding the behavior of these functional groups in different conditions is the way of learning organic chemistry**.**

A transformation which involves change of composition, constitution and/or configuration of a compound is called *Chemical Reaction***.** The chemical reaction has at least three basic components. The organic compound undergoing change in a chemical reaction is called *Reactant or Substrate*. The second component is a common partner of the reactant in the chemical reactions and is called *Reagent*. The final form taken by the reactant in the reaction is called *Product*. The chei



The main factor which has direct influence on the chemical reaction is *Reaction Conditions* such as reagents, temperature, pressure, & solvent, under which a reaction progresses optimally. In the first three blocks we have discussed on structural features of organic molecules. Now in this unit we will briefly defining some of the basic reactions those will be used frequently in the organic chemistry.

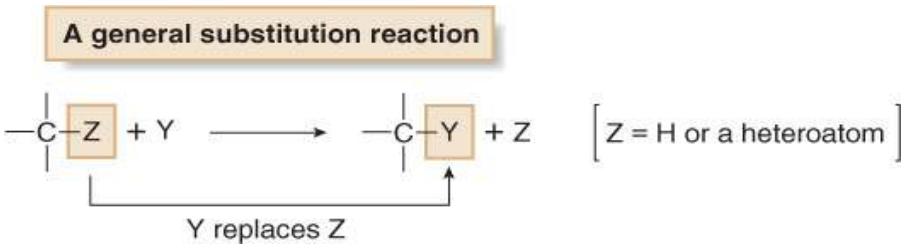
13.2 Reaction Classification

As already mention most of the reactions occur at special sites of reactivity known as functional groups. Reactions of Organic compounds are mainly classified in to four types. They are

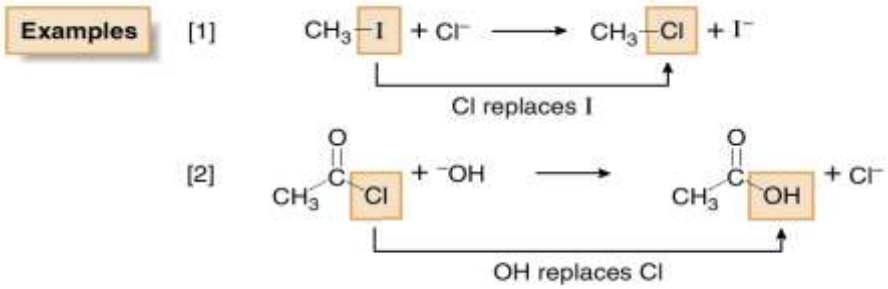
1) Substitution reaction
2) Elimination reaction
3) Addition reaction and
4) Rearrangement reaction

i) Substitution Reactions

A substitution is a reaction in which an atom or a group of atoms is replaced by another atom or group of atoms.



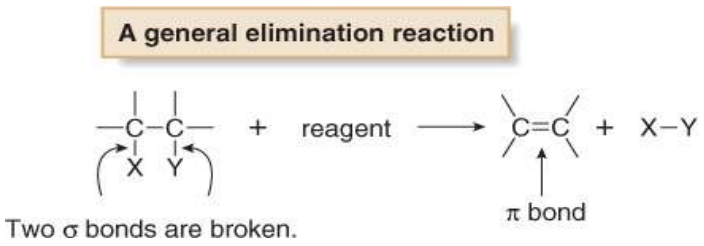
In the above reaction Y replaces Z on a carbon atom. Generally substitution reactions involve breaking one σ bond and forming another at the same carbon atom.



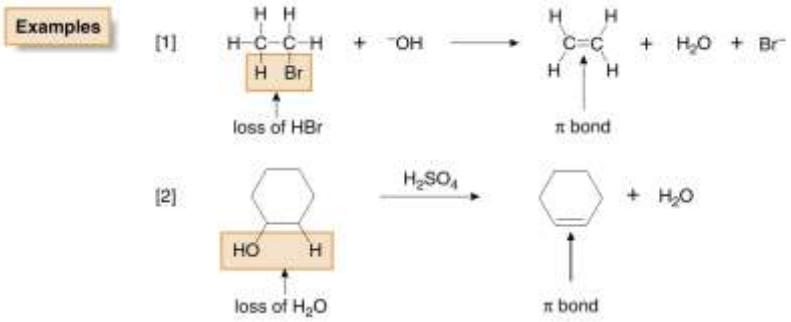
Substitution reactions, as the name implies, are characterized by replacement of an atom or group (Y) by another atom or group (Z). Aside from these groups, the number of bonds does not change

ii) Elimination Reactions

Elimination reactions are those which involve the removal atoms or groups of atoms from two adjacent atoms in the substrate molecule to form a multiple bond. In the elimination reaction elements of the starting material are "lost" and a π bond is formed in the product.

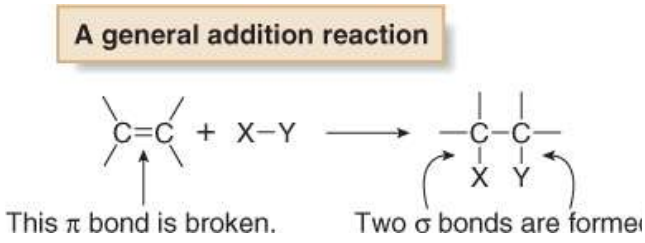


In general two σ bonds are broken, and a π bond is formed between adjacent atoms. The most common examples of elimination occur when X = H and Y is a heteroatom more electronegative than carbon like Cl, Br, I etc….

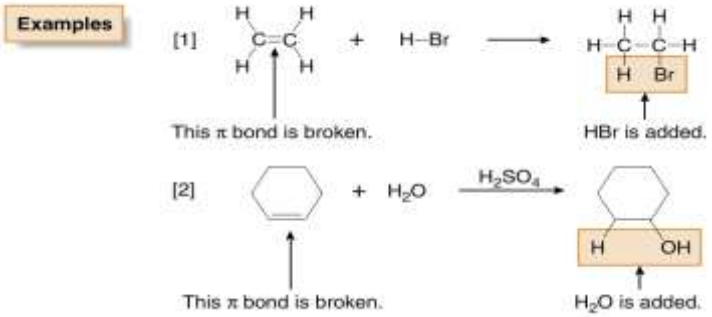


iii) Addition Reactions

An addition reaction is a type of organic reaction in which atoms or group of atoms are simply added to a double or triple bond without the elimination of atom. In addition reaction a 'Pi' bond (π) is broken and two 'sigma' bonds (σ) are formed. The substrate of an addition reaction must have double or triple bond.



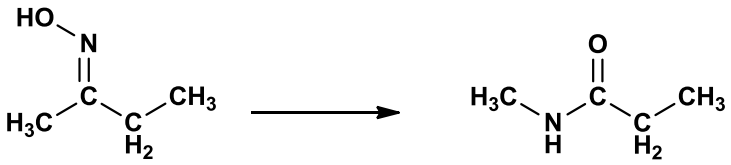
In the addition reaction, two new groups X and Y are added to the starting material across the multiple bonds. Consequently a π bond is broken and two σ bonds are formed. The number of σ bonds in the substrate molecule increases at the expense of one or more π-bonds.



The reverse of addition reaction is true for elimination reactions, *i.e*, the number of σ-bonds in the substrate decreases, and new π-bonds are often formed.

iv) Rearrangement Reaction

A rearrangement reaction involves the migration of an atom or group of atoms from one site to another within the same molecule. The number of bonds normally does not change in this reaction. The product is always the structural isomer of the original compound.



13.3 Mechanisms of Organic Reactions

A detailed description of the changes in structure and bonding that take place in the course of a reaction, and the sequence of such events is called the **reaction mechanism**. A reaction mechanism should include a representation of plausible electron reorganization, as well as the identification of any intermediate species that may be formed as the reaction progresses. These features are elaborated in the following sections.

Organic reagents are broadly classified in to two types, they are

i) Nucleophiles or Nucleophilic reagents

ii) Electrophiles or Electrophilic reagents

i) Nucleophiles

The name nucleophile means "nucleous-loving' indicate that they are electron rich species. *A reagent which can donate an electron pair in a reaction is called nucleophile.* Nucleophiles attacks low electron density region (Positive charge centre) of the substrate. Nucleophiles may be negative ions or neutral molecules with free electron pairs. Nucleophiles are represented by a general symbol $Nu:^-$

Ex: OH^-,$R\text{-}O^-$, $R\text{-}CH^-_2$,Cl^-, Br^-, I^-, CN^-,$\text{-}N_3^-$,H_2O,R-OH,NH_3,R-SH.

ii) Electrophiles

Electrophile means "electron-loving" indicate that they are electron deficient species. *A reagent which can accept an electron pair in a reaction is called an electrophile.* Electronphile attacks high electron density region (negative charge centre) of the substrate. Electrophile may be positive ions or neutral molecules with electron deficient centre.

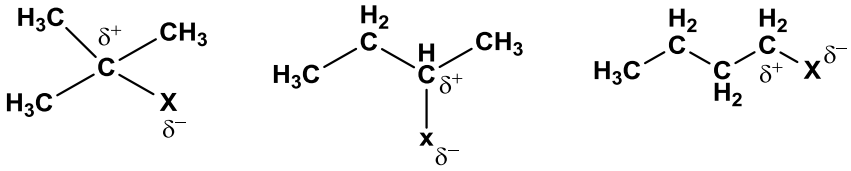
Ex: H^+, $R\text{-}CH_2^+\text{-}R$, $R_3\text{-}C^+$, SO_3H^+, $AlCl_3$, BF_3, NO^+, NO_2^+ , etc….

13.4 Nucleophilic substitution reaction

*A reaction in which a nucleophile displaces another nucleophile and takes its position is called a nucleophilic substitution reaction***.** Nucleophilic substitution reactions are represented by the symbol "$\mathbf{S_N}$".

Consider an alkyl halide, since the C-atom is attached to a highly electro-negative halogen atom, the C-X bond is polar. Hence in alkyl halides carbon atom has partial positive charge

and has electrophilic character. Similarly halogen has atom has partial negative charge and has nucleophilic character.



X = Cl, Br, I, OTs, OMs

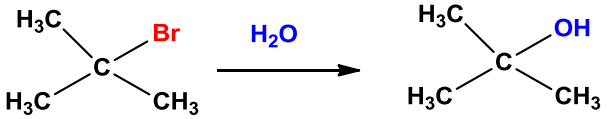
Alkyl halides are converted in to the corresponding alconols by queous alkali. Study of reactions with different alkyl halides revealed two fundamentally different types of behavior. In the kinetic study of the hydrolysis of n-and t-butyl chlorides, the primary halides was found to be second order, while the tertiary halide was first order. Thissuggest that the neucleophilic substitution reactions are of two types with respect to kinetic mechanism they follow and they are S_N1 and S_N2 reactions.

13.5 S_N1 reaction

S_N1 stands for Substitution Neucleophilic Unimolecular reaction. The rate of a nucleophilic substitution reaction depends only on the concentration of the alkyl halide, such reaction is of first order and is called S_N1 reaction

Rate α [substrate]

Ex: the hydrolysis of t-butyl bromide.



i) Mechanism of S_N1 reaction

The S_N1 reaction proceeds in two steps

Step1. An alkylhalide undergo ionization to give a carbonium ion (carbocation). This step proceeds slowly hence is the rate determining step.

Step2. The neucleophile attack the carbocation to give a alchol. This step proceeds very fast

ii) Stereochemistry of S_N1 reaction

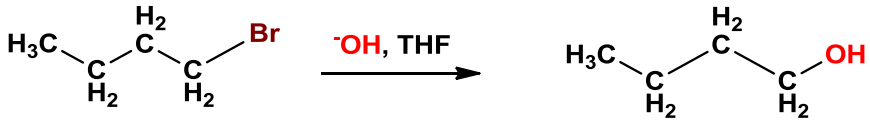
The carbocation formed in the first step is a planar geometry because the central positive charged carbon atom in the carbocation is sp^2 hybridized. The neucleophile attack in the second step can approach either side of carbocation resulting recemic mixture.

13.6 S_N2 reaction

S_N2 stands for Substitution Neucleophilic bimolecular reaction. The rate of a nucleophilic substitution reaction depends both on the concentration of the substrate and the nucleophile, such reaction is of second order and is called S_N2 reaction

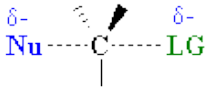
Rate α [substrate] [nucleophile]

Ex: Hydrolysis of n-butyl bromide.

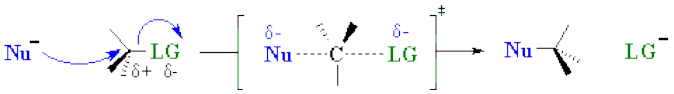


i) Mechanism of S_N2 reaction

The S_N2 reaction proceeds in single step without formation of intermediate. The nucleophile approaches the carbon atom from the opposite side of the leaving group. This is because both nucleophile and leaving group are electron rich.As S_N2 proceeds there is simultaneous formation of the carbon-nucleophile bond and breaking of the carbon-leaving group bond occurs. This transition state has 5 groups around the central C atom.



The nucleophile attacks on the opposite side to leaving group. Therefore the reaction will proceed with an **inversion of configuration**.



ii) Stereochemistry of S_N1 reaction

In the course of SN2 reaction the configuration of central carbon atom is inverted like an umbrella blown inside out. The change in configuration is called **Walden Inversion**.

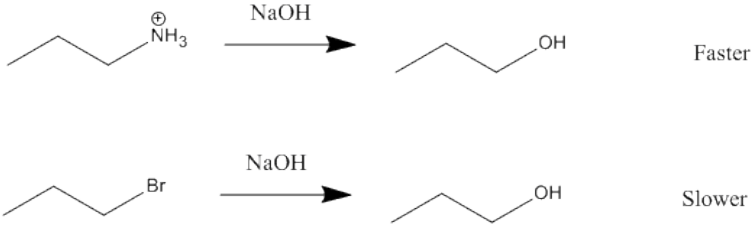
13.7 Factors affecting the S_N1 and S_N2 reactions

The following factors have greater effect on reaction kinetics and mechanism of both S_N1 and S_N2 reactions.

a) Nature of leaving group
b) Nature of solvent
c) Nature of nucleophile
d) Nature of substrate.

i) Nature of leaving group

An S_N1 reaction speeds up with a good leaving group. This is because the leaving group is involved in the rate-determining step. A good leaving group is one that breaks the C-L group bond faster. For S_N1 reaction leaving group should be, ideally a very weak nucleophile to carbon because it will allow the reaction to occur more readily. Chloride, bromide and iodide are good leaving groups for S_N1 reaction in the order I > Br > Cl > F. A number of sulphonate groups particularly those with electron-withdrawing groups are also much better leaving groups.



The two reactions mentioned above are the same reaction done with two different leaving groups. First one is significantly faster than the second reaction due to the better leaving group leaves faster and thus the reaction can proceed faster. The table 1describe the relative nature of leaving groups for S_N1 reaction.

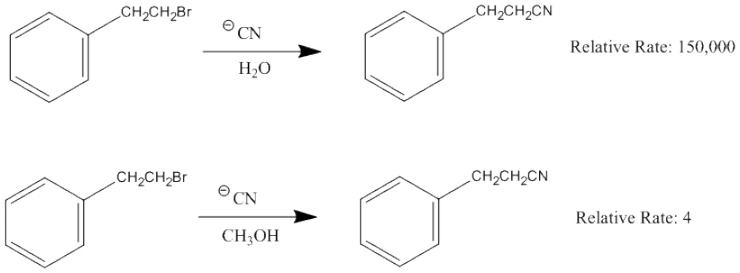
Nature	Nuclophile
Very poor	-OH, $-NH_2$
poor	-F
fair	-Cl
good	-Br
Very good	-I, $-O^+H_2$
excellent	-OTs, $-N^+H_3$

In case of S_N2 reaction, the C-LG bond is broken in the rate determining step therefore the rate does depend on the nature of the leaving group. However, if a leaving group is too good, then an SN1 reaction may result

ii) Effect of solvent on S_N1 reaction

Since the hydrogen atom in a polar protic solvent is highly positively charged, it can interact with the anionic nucleophile which would negatively affect an S_N2. Solvation of nucleophiles by polar protic solvents also inhibits the nucleophile's ability to take part in an S_N2 reaction, so S_N2 reactions are much slower in polar protic solvents. But it does not affect an S_N1

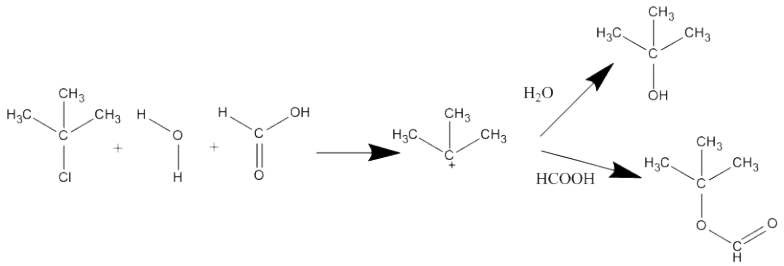
reaction because the nucleophile is not a part of the rate-determining step. Polar protic solvents speed up the rate of the S_N1 reaction because the large dipole moment of the solvent helps to stabilize the transition state. Below is the example of reaction S_N1 conducted in two different solvents and their relative rate.



iii) Nature of Nucleophile

In general the nucleophile strength does not affect the $S_N1$reaction rate. This is because the nucleophile is not involved in the rate determining step. However, if we carry out a reaction with more than one nucleophile competing to bond to the carbocation, the strengths and concentrations of the nucleophiles affects the distribution of products

Ex: in the reaction $(CH_3)_3CCl$ reacting in water and formic acid where the water and formic acid are competing nucleophiles, wewill get two different products: $(CH_3)_3COH$ and $(CH_3)_3COCOH$



The relative yields of these products depend on the concentrations and relative reactivities of the nucleophiles. Because the nucleophile is involved in the rate-determining step in S_N2 reactions, stronger nucleophiles react faster.

iv) Nature of substrate

Steric accessibility of the substrate (electrophilic center) is the most important factor that determines if a nucleophilic substitution reaction will follow an S_N1 or an S_N2 mechanism. The substrates which are sterically hindered are not preferred to undergo S_N2 reactions. Generally S_N2 reactions are sensitive to steric factors and they are greatly retarded by steric hindrance (crowding) at the site of reaction. The order of reactivity of alkyl halides to S_N2 reactions is: methyl > 1° > 2°. The 3° alkyl halides are so crowded that they do not react by an S_N2 mechanism. They easily form stable cabocation hence they undergo S_N1 reaction.

Substrate they can either dissociate into very stable carbocations or stabilize the carbocation by resonance stabilization prefers to undergo S_N1 reaction.

13.8 Comparison of S_N1 and S_N2 reaction

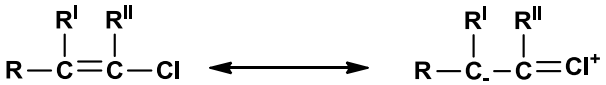
In both S_N1 and S_N2 substitution reactions occur when an alkyl halide reacts with a nucleophile in a way that the nucleophile replaces the halogen attached to the carbon atom. They have considerable differences in the reaction mechanism. The comparison of S_N1 and S_N2 reactions is given below

	S_N2	**S_N1**
Rate of reaction	Second order	First order
Nucleophile strength	Stronger or Moderate	Irrelevant (Weak)
Nucleophile concentration	Affects on the rate of reaction	Not affect on the rate of reaction
Stereochemistry	Stereo specific (Inversion)	Non stereo specific (Recemization)
Best solvent	Aprotic, Polar	Protic, Polar
Favored structure	Methyl $>1^0>2^0$	3^0

13.9 Special cases

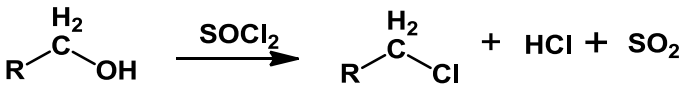
Nucleophilc substitution reactions do not proceeds well with Vinylic, allylic, Acetylenic and Aryl substrate. This is because most of the leaving groups have one or more unshared electron pairs, therefore the carbon-leaving group bond is greatly strengthened in the molecule through resonance stabilization. As a result the leaving group has little tendency to depart. Due to this reason S_N1 reaction is fail to undergo. The reason for the inertness of these substrates towards S_N2 reaction may be traced to the difference in hybridization of carbon atom undergoing displacement. Sp and Sp^2 carbon are more electronegative, therefore they have greater hold on the bonding electrons than Sp^3 carbon atom. Hence they are reluctant to

lose the leaving group (along with bonding electron pair) in a direct displacement mechanism.



13.10 SNi Mechanism

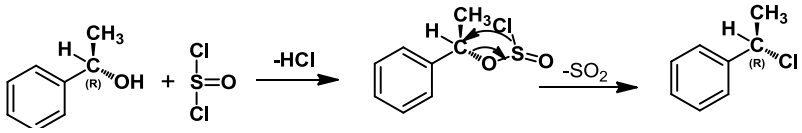
An alcohol react with thionyl chloride gave chlosulphate which subsequently decomposes to alkyl halide.



The overall reaction is a neucleophilc displacement reaction. Like SN2 reaction, this reaction also found to be second order and the rate of a reaction is depends on concentrations of both substrate (alcohol) and reactant ($SOCl_2$).

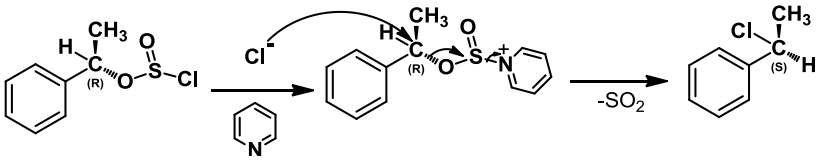
Rate α [substrate] [Reactent]

If alcohol is optically active, inconstant to S_N2 reaction, the resulting alkyl halide have been found to have the same configuration as the starting alcohol ie, retention of configuration in the final compound is observed. Therefore the stereochemistry of the reaction is inconsistent with the rules formulated for either S_N2 or S_N1 reaction. This different reaction path is termed as SNi reaction and SNi stand for ***Substitution nucleophilic internal***. Generally SNi reaction is carried out in the absence of solvent or in ether

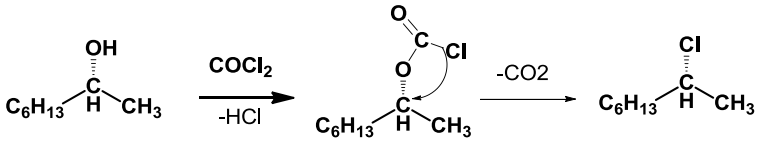


The SNi reaction mechanism consist an internal transformation through a cyclic transition state in which chlorine ion attack only from the front side leading to the retention of configuration.

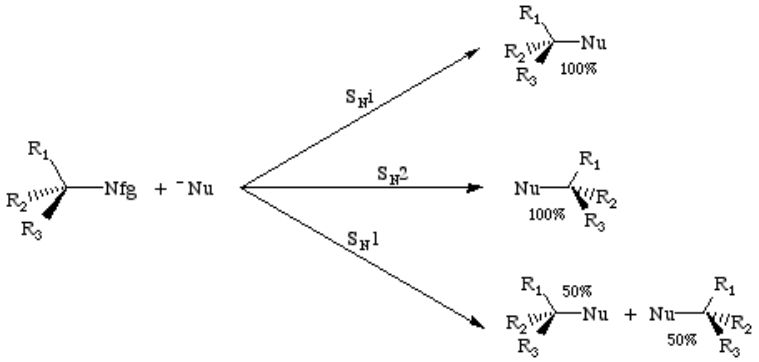
Evidence for SNi reaction mechanism comes from the observation that the addition of pyridine to the reaction mixture leads to the formation of alkyl chloride with inverted configuration. This is because the free chloride ion attacks from the rear side like in the normal S_N2 reaction leading to inversion of configuration.



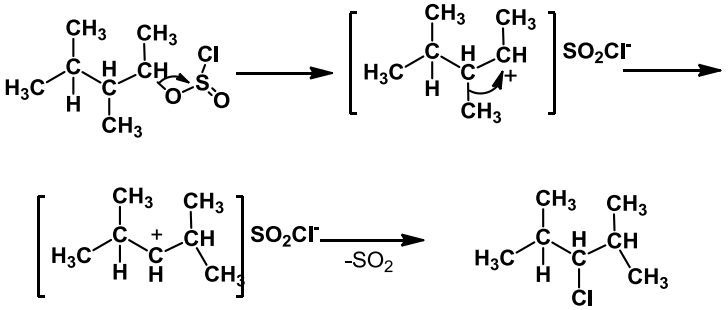
The SNi mechanism is rarely encountered. Another example is the reaction of 2-octyl alcohol with phosgene that proceeds with retention of configuration.



The stereochemistry outcome of the different neucleophilc substitution reactions is summarized in the bellow diagram.



However recent studies pointed out that the decomposition of chlorosulphite begins (like in the typical SN1 reaction) with the formation of an ion pair. A part of the leaving group (chloride ion) then attacks from the front side, since it unable to get in to rare side. Observation of formation of rearrangement product in the below mentioned reaction support this fact. Rearrangement in the carbonium ion before the nucleophlic attack may lead to the rearrangement product.



13.11 summary

Nucleophiles are chemical species that react with centers of positive ionic character. When the center is an aliphatic carbon, the process is called aliphatic nucleophilic substitution. Chemical reactions of this type are extremely important for the synthesis of new compounds and for understanding the mechanisms in organic chemistry. All nucleophilic substitution reactions may take several reaction courses, but all have similar appearances at the outset. All reactions have an attacking species, a nucleophile (Nu) that bears a pair of electrons either as an anion or as a neutral compound. The organic compound known as the substrate has a structure that greatly influences the outcome of the reaction and it contains the leaving group (L) that is lost in the reaction. The conditions of the reaction, especially solvent and

temperature are also important contributors to the process. In order to understand the products of the reaction and how they are formed, the reaction is studied from a mechanistic point of view. The S_N2 reaction occurs when a nucleophile attack a primary substrate and sometimes a secondary substrate. The reaction of a secondary substrate depends on the nucleophile and the leaving group. Tertiary substrates do not undergo reactions by the S_N2 mechanism. The overall rate of the reaction depends of the concentration of the nucleophile and the concentration of the substrate, thus it is called second-order. In an S_N1 there is loss of the leaving group generates an intermediate carbocation which is then undergoes a rapid reaction with the nucleophile. The rate determining step is the loss of the leaving group to form the intermediate carbocation. The more stable the carbocation is, the easier it is to form, and the faster the S_N1 reaction will be.

13.12 Key words

Neucleophile; electrophile; substitution reaction; elimination reaction; addition reaction; rearrangement reaction; S_N1, S_N2, SNi,

13.13 References for further study

1) Advanced Organic Chemistry: Reactions, Mechanisms, and Structure by Jerry March, John *Wiley and Sons* 4th ed. 2007.

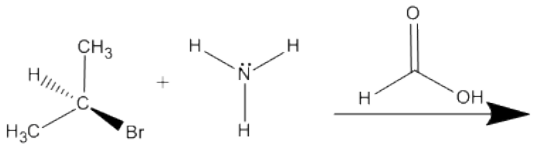
2) Organic Chemistry by Clayden, Greeves, Warren, and Wothers, *Oxford university press*, 2001.

3) Organic Chemistry by J. G. Smith, *Tata McGraw-Hill Priv, Litd* 2nd ed, 2008.

4) Organic chemistry by Bhupinder Mehta, Manju Metha. PHI Learning Pvt. Ltd. 2005

4.14 questions for self understanding

1. Which solvent would an S_N1 reaction occur faster in? H_2O or CH_3CN Explain the reason.
2. What kind of conditions disfavor S_N1 reactions?
3. What are the products of the following reaction and does it proceed via S_N1 or S_N2?

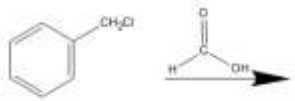


4. How could you change the reactants in the problem 3 to favor the other substitution reaction?
5. Discus the mechanism and stereochemistry outcome of SNi reaction.
6. Write a note on S_N1 and S_N2 reaction and discuss the effect of leaving group, nucleophile, solvent and substrate structure on the reaction rate.

7. What are electrophile and nucleophile? and give five examples for each.

8. Write a note on substitution reaction, elimination reaction, addition reaction and rearrangement reaction.

9. Indicate the expected product and list why it occurs through S_N1 instead of S_N2?



Unit- 14

Structure:

14.0 Objectives of the unit

After studying this unit you are able to learn:

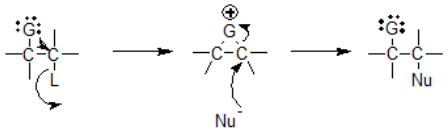
- What is mean by neighbouring group participation
- Effect of neighbouring group participation on S_N2 reaction
- Which groups are participating in neighbouring group effect.
- Differences between Electrophilic and nucleophilc substitution reactions.
- Types of electrophilic substitution reactions.
- Mechanism and stereochemical outcome of electrophilic substitution reaction.

14.1 Introduction

In some cases of nucleophilic substitution reactions, the substitution occurs with complete retention of configuration (though these reactions are not proceeds through SNi mechanism), also the rate of reaction is greater than expected. ie, reaction occurs much faster. This type of unusual results are common when substrate molecule having a second functional group with a pair of electrons situated at a favorable distance from the carbon atom undergoing the displacement reaction. This type of effect is called neighbouring group participation.

14.2 Neighbouring Group Participation (NGP)

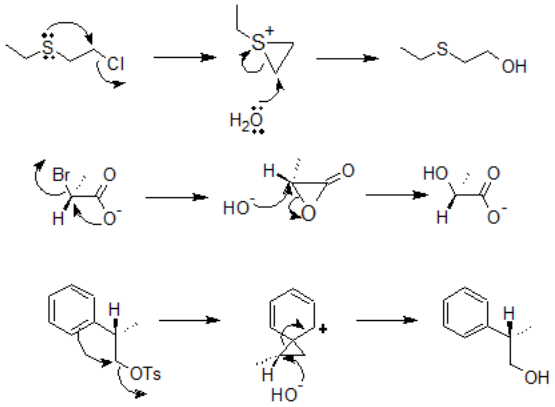
Neighbouring Group Participation (NGP) is observed in nucleophilic substitution reactions, where a neighbouring group helps in the departure of the leaving group to form a reactive intermediate that leads to the formation of the product. Increase in the reaction rate and unexpected stereo chemical outcomes are associated in NGP reactions. *An atom having an unshared pair of electrons and also present at least beta to the leaving group can act as a neighbouring group*. Also, NGP is mostly observed on solvolysis reactions where the solvent acts as the nucleophile. A typical reaction involving NGP is shown below.



G = Neighbouring Group L = Leaving Group Nu^- = Nucleophile

During NGP, the neighbouring group (G) attacks the electrophilic centre to eliminate the leaving group (L). This leads to the formation of a cyclic intermediate which is very reactive. This phenomenon is called anchimeric assistance from the neighbouring group or simply *anchimeric effect*. The nucleophile (Nu^-) then attacks this intermediate to form the product. If the leaving group attached carbon atom is chairal then the configuration will be retained in the product because the configuration at that carbon will be inverted twice during the reaction

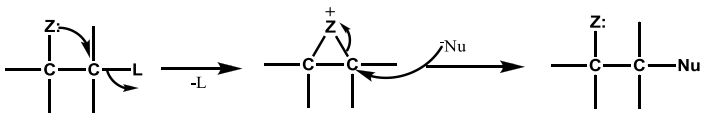
due to NGP. Groups like halides, hydroxides, ethers, thio ethers, amino groups, carboxylates, phenyl group, pi-bonds etc. have been indentified to act as neighbouring groups in many reactions. Some more examples of reaction involving NGP are shown below.



The involvement of a functional group with a reaction centre on a molecule leading to reaction via cyclic intermediate is known as neighbouring group participation. If such participation results in an increase in the rate of the reaction, the phenomenon is described as anchimeric assistance.

Neighbouring group participation is a useful tool for synthetic chemists. In contrary to S_N2 reactions, retention of configuration in the reaction centre is obtained. If the neighbouring group helps to stabilize the intermediate produced in the rate determining step, acceleration in the rate of the reaction occurs. Generally use of polar solvents help to stabilize the cyclic cation intermediate and, the strength of the nucleophile was found to affect the reaction outcome. When strong nucleophiles were used, only direct substitution (S_N2) was observed.

From the mechanistic point of view, a bridged ion was suggested as an intermediate in this type of reaction. The group Z becomes partially bonded to both C_1 and C_2 simultaneously and positive charge is delocalized over both the carbon atoms, unlike in classical ion in which the positive charge is localized on a single carbon atom. An attack of the external neucleophile at front side of the the carbon atoms can leads to product



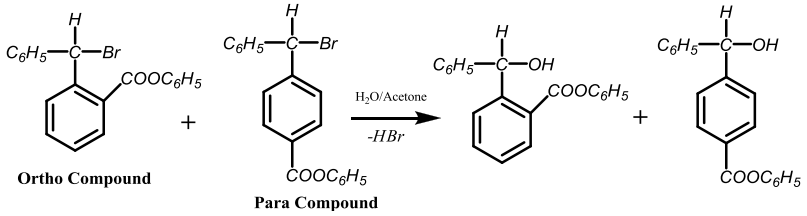
14. 3 Methods for studying the neighbouring group participation

Many experimental studies such as kinetic measurement, product isolation, stereochemical evidence have been adopted to demonstrate the involvement of a neighbouring group in a given reaction. Some of them are discussed below.

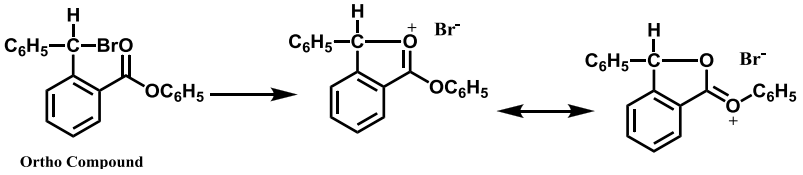
a) Kinetic measurement

Kinetic investigation is probably the best to evaluate the effect of participation by a neighbouring group. In this method the compounds under examination are subjected to kinetic measurement under identical experimental conditions. The magnitude of the anchimeric assistance obtained by the comparing the rates of neighbouring group participation reaction with the rate expected in the absence of participation.

Ex: In the hydrolysis reaction of ortho and para cabophenoxybenzhydrylbromide reaction, the ortho compound was found to be 90 times more reactive compared to para compound.

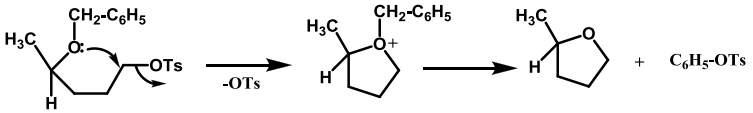


This high reactivity for the ortho compound cannot be explained on the basis of steric or inductive effects which should rather operate in the opposite direction to decrease rate because of close proximity of the carbophenoxy group to the reaction site. The observed high rate has been explained by an intramolecular participation of the carbophenoxy group in the rate controlling step with the stabilization of the C-Br bond by releasing electrons to the p-orbital being vacant at the place of displacement. Such participation of carbophenoxy group is not possible in the p action centre.



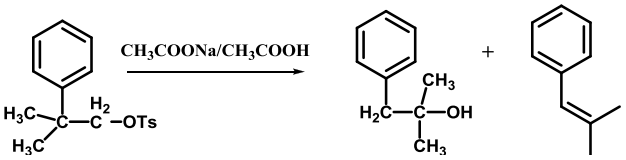
b) Product isolation

A care full analysis of products provides considerable information about the involvement of a neighbouring group in the reaction. The products so obtained are often cyclic or rearranged. Below example of reaction illustrate the cyclic product formation by 4-O-benzyl-1-O-tosyl

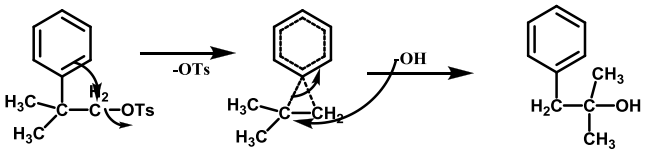


pentane in ethanol. In this cyclization reaction it is argued that the bezyloxy group participate to form intermediate cyclic oxonium ion.

The formation of 1,1-dimethylphenylcarbinol in the solvolysis reaction of neophenyl-para-bromobezenesulphonate is an another example for the detection of neighbouring group participation through product isolation method.



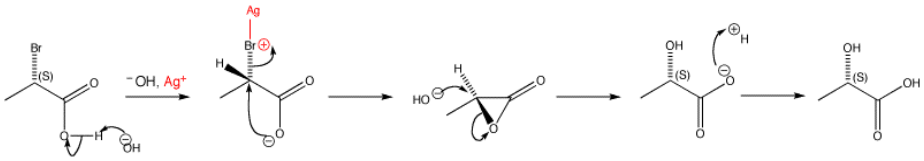
Analysis of the products showed that in the resulting alcohol the phenyl group had migrated from C_β to C_α. There is also a formation of β,β-dimethylstyrene and the absence of any un rearranged solvolytic product. This ruled out a classical cationic intermediate but strongly support the participation of the phenyl group to form a phenonium ion.



c) Stereochemical evidence

Increased rate of a reaction is good evidence for the participation by a neighbouring group. But this alone fails to provide any information about the structure of the intermediate involved. Kinetic measurements are also incapable of differentiating between classical and non classical information because rate comparisons represents only differences in activation energies and provides no information about the analysis of stereochemical results of the products and the reactants. Reactions involving neighbouring group participation are generally stereospecific. These reactions yields the producats with retention of configuration as compared to recemization and inversion of the reaction centre resulting in SN1 and SN2 reactions respectively.

Ex: In the reaction of hydrolysis of α-bromopropinoate, the formation of the lactone is postulated as an intermediate in the reaction. Isolation of this intermediate is not possible but there considerable evidences for its existence.



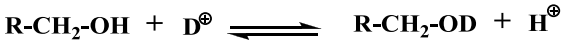
From the mechanistic stand point, neighbouring group participation consists essentially of two SN2 displacements each causing an inversion. Hence the net result is the retention of configuration. In the above reaction the carboxylate ion acts as an internal nucleophile and from a lactone by displacing bromine atom. Hydroxide ion then opens up the lactone to yields the product.

14.4 Electrophilic aliphatic substitution

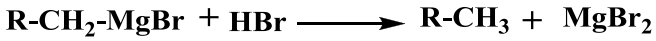
An organic reaction in which an electrophile is substituted by leaving group is called electrophilic substitution reaction. Electrophiles are stronger when they are more positive charge hence strong electrophiles are react quickly with neucleophile. By use of a strong acid it is possible to convert weak electrophile in to a stronger one. The mechanism of aliphatic electrophilic substitution reactions is not completely well defined. In electrophilic substitution reactions both the entering group and the leaving group are electrophiles, ie, lewis acid. The electron pair of the breaking bond remains with the substrate when the formation of the new bond with the entering lectrophile.

A few examples of aliphatic electrophilc substitution reactions are known. Some of the important examples are mentioned below

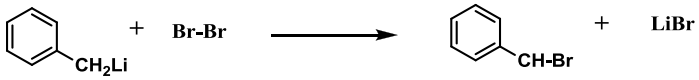
i) Isotopic exchange of hydrogen for deuterium or tritium.



ii) Replacement of metal in organometallic compound by hydrogen.



iii) Replacement of a metal by halogen.

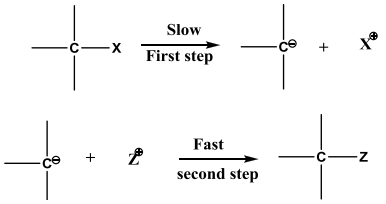


In an electrophilic substitution of aliphatic compounds, an electrophile displaces a functional group. This reaction is similar to nucleophilic substitution reactions. Like Neucleophilc substitution reactions, aliphatic electrophilic substitution reactions are distinguished as unimolecular S_E1 and bimolecular S_E2. These two types of electrophilic reactions follow very similar to S_N1 and S_N2 reactions with respect to mechanism**.**

14.5 S_E1 reaction

S_E1 stands for substitution electrophilic unimolecular

The S_E1 reaction proceeds in two steps, ie, electrophilic interchange with bond braking (the rate limiting step) followed by bond making. In the S_E1 action the substrate first ionizes into a carbanion. The carbanion then quickly recombines with the electrophile. The reaction is first order with respect to substrate and zero order with respect to attacking electrophile. The electrophilic substitution reaction occurs only in case that the leaving group is more electropositive than carbon.



The examples of aliphatic electrophilic substitution reactions are

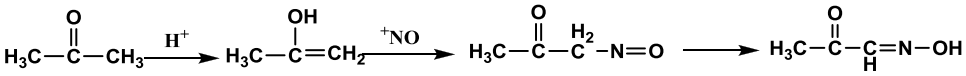
a) Nitosation reaction

b) Ketohalogenation reaction

c) Aliphatic diazonium coupling reaction.

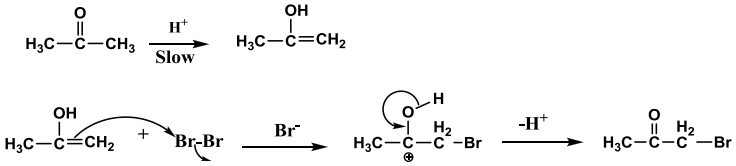
Nirosation reaction:

The nitrosation reaction consist the replacement of a hydrogen atom by the nitroso group with the formation of a nitroso or oximo derivative. The replacement of hydrogen on an aliphatic carbon atom requires the presence of electron-attracting groups adjacent to the carbon to be nitrosated. Acyl, aroyl, carbonyl, carboxy, carbalkoxyl, nitro, cyano, imino, and aryl groups may serve as activators. Monoketones are readily converted into alpha-oximino ketones, whereas monoesters containing no other activating groups do not undergo the reaction.



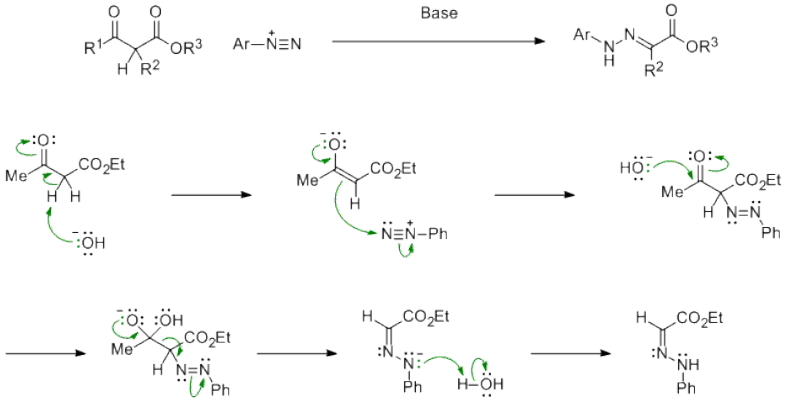
Ketohalogenation reaction

The process of acid catalyzed keto-enol tautomerism allows aldehydes and ketones with α-hydrogens to react with electrophiles. α-halogenation is a typical reaction of this type. In this reaction, the π electrons between the vinylic carbons of an enol form of the aldehyde or ketone are subject to electrophilic attack, leading to a new bond between the α-carbon and halogen.

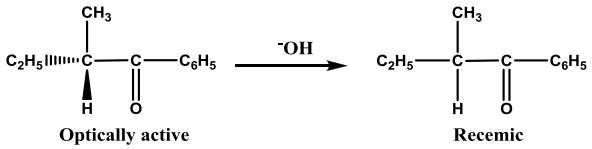


Aliphatic diazonium coupling reaction

The reaction of beta-keto esters or acids with aryldiazonium salts in the presence of base in aqueous medium to form hydrazones is an example of electrophilc aliphatic substitution reaction. This reaction is also called Japp-Klingemann reaction.



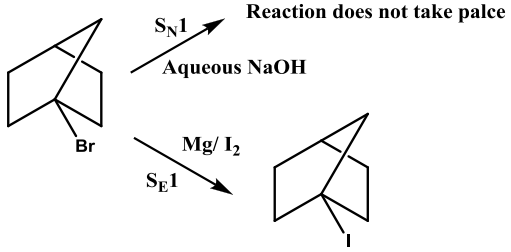
The evidence of the S_E1 mechanism is the base catalyzed tutomerisation of optically active phenyl sec-butyl ketone with NaOH which is resulted with recemization.



The cabanion formed as an intermideate is flat due to enol form in which the former stereo centre is planar and achiral. Thus in an optically active compound chirality is due to a stereogenic carbon α to carbonyl group is reacted with a base resulting racemization.

Special case:

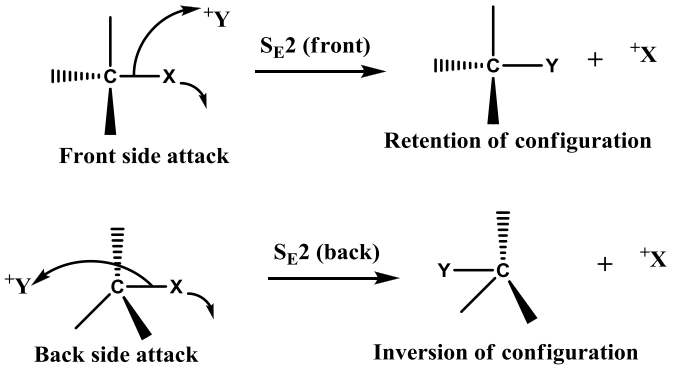
Though S_N1 and S_E1 reactions are similar with respect to mechanistic point of view, S_N1 reaction does not occur at bridgehead carbon in bicyclic system. This is because planar carbocation cannot form at this carbon. The carbanion is not stabilized by resonance, therefore they need not be planar. Hence the S_E1 reaction occurs at bridgehead carbon centre also



14.6 S_E2 Reaction

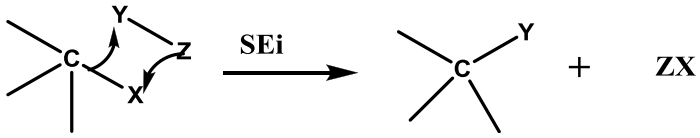
S_E2 stands for substitution electrophilic bimolecular

S_E2 reaction taking place in single step, ie, new bond forms at the same time old bond is broken. The S_N2 and S_E2 reactions follow similar kind of mechanism with respect to reaction rate but the very different in the approach of attacking group toward the reaction site. In S_N2 reaction the attacking group brings with pair of electrons and the leaving group takes away its electrons hence attacking group approaches from the backside of leaving group resulting to inversion of configuration. In case of S_E2 reaction the attacking group is an electrophile, this brings only empty orbital towards the substrate. Therefore it is difficult to predict from which side the electrophile attack taking place. There are two possibilities, one is attack from the front side which is called S_E2 (front), another is attack from the rear side which is called S_E2 (back). These can be represented as shown in below figure. S_E2 (front) reaction mechanism ended up with retention of configuration in the product, while S_E2 (back) reaction mechanism results in inversion of configuration in product.



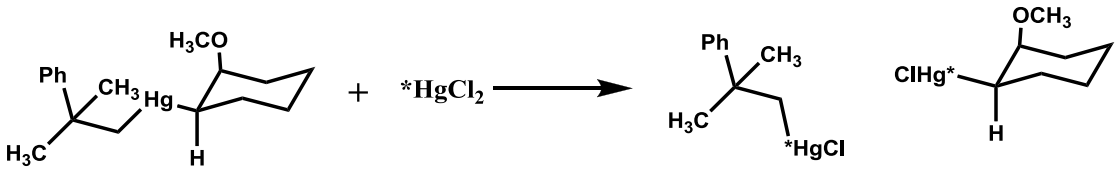
14.7 SEi Mechanism

When an electrophile attacks from the front side, there is a possibility for a portion of the electrophile to assist in the removal of leaving group by forming a bond with it and at the same time a new C-Y bond is formed as shown in below figure. These types of reactions follow second order kinetics and results in retention of configuration and are referred as SEi reactions.



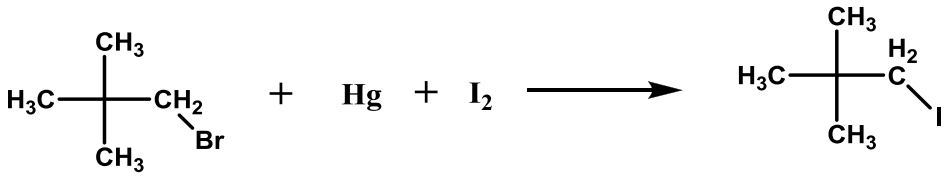
The S_E2 (back) S_E2 (front) and SEi mechanisms are not easy to distinguish. All there are follows second order kinetics, the S_E2 (front) and SEi results in retention of configuration. Therefore the study of configuration of the product gives little idea about the reaction mechanism.

The majority of electrophilic substitution reactions results the retention of configuration due to the front side attack of the electrophile following wither S_E2 (front) or SEi mechanism. For ex: in the below reaction, when the cis-isomer of the compound was treated with labled mercury the product was found to 100% retention of configuration ie, cis-isomer.

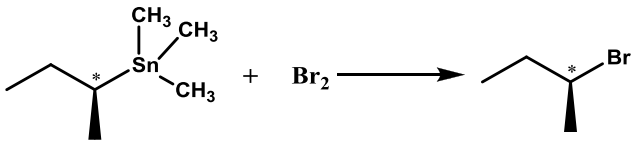


This indicates that the bond between the Hg atom and the ring on the same side and the carbon (Hg-C) on the other side hace been broken. Which facilitate the front attack of the electrophile on the substrate carbon to produce the cis-isomer.

Another indication of front attack is the second order electrophilic substitution reactions proceeds very easily at the bridgehead carbons. Although back side attack is impossible for these centre.



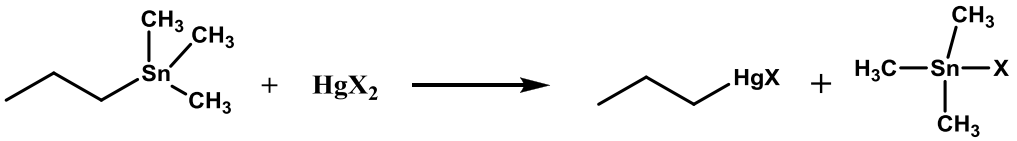
Neopentyl substrate is another example where S_N2 reactions are extremely slow because attack from the rear side is blocked by t-butlyl group. But the neopentyl system mentioned bellow undergoes electrophilic substitutions slightly faster due to the front side attack of the electrophile.



The stereo chemical investigation cannot distinguish between the S_E2 (front) and SEi mechanism. The reaction with the neutral starting molecule acquires charge in the transition state and aided by an increase in concentration of added common ion salt. Hence S_E2 mechanism would be more influenced by salt then SEi mechanism, which acquire no charge in the transition state. On the basis of above criteria Abraham and co-worker studied the many reactions and concluded that following kind of reactions undergo by S_E2 (front) mechanism.

However inversion of the configuration has been observed for few cases in electrophilic substitution reaction indicating that S_E2 (back) mechanism can also taking place.

For ex: the reaction of optically Sec-butyltrimethyltin with bromine gives sec-butylbromide with inverted configuration. A number of argano-metalic compounds have also been shown to give inversion when treated with halogens and conforming the S_E2 (back) mechanism.



14.8 Factors affecting the reactivity of aliphatic electrophilic substitution reactions

1) *Effect of substrate structure*.

For S_E1 reaction electron donating group decreases and electron withdrawing groups increases the rates of the reactions. This is because the formation of the carbanion in the rate

determining step. The effect of substrate (the alkyl group) for S_E2 (back) reaction and S_N2 reaction discussed in previous units are same. Since both involves backside attacks and are effected by steric hindrance and follows this order, Me > Et > Pr > iso-Pr > neopentyl. In case of S_E2 (front), the rate is increased by substrate structure having α-branching. This is due to electron donating effect of alkyl groups which stabilizes the electron deficient transition state. In other hand β- Branching decreases the rate of the reaction due to steric hindrance. The below table explains the effect of α and β branching of the substrate on the rate of S_E2 (front) reaction.

Substrate	**Rate**
Me	1
Et	10.8
iso-Pr	780
Tert-Butyl	3370
Iso-Butyl	1.24
neopentyl	0.713

2) Effect of leaving group

The more polar nature of the C-X bond, the easier to cleave, ie, it is easy for the electofuge (leave with the out electron pair) For ex: in the organo-mercurial compound RHgW, as the electronegative of the W increases, then it decreases the polarity og C-Hg bond and resulting in a less stable $HgW^{(+)}$ therefore electrofugal ability of HgW decreases with increasing the electro negativity of W. Thus HgR is a better leaving group and increase the rate of reaction comparing to HgCl in case of S_E1, S_E2 and SEi reactions.

3) *Effect of solvent.*

The increase in solvent polarity increases the possibility of an ionizing mechanism ie, S_E1 mechanism. The S_E2 (front or back) mechanism should also favored by an increasing in solvent polarity, while SEi mechanism is much less affected by solvents.

14.9 summary

In Electrophilic Subsititution, most of leaving groups are those that can best exist with an outer shell that is deficient in a pair of electrons. In case of Aromatic Systems, the most common leaving group is the proton, whereas in aliphatic system, organo-Metallic compounds are susceptible to undergo electrophilic substitution reaction. So far, aliphatic electrophilic substitution can in four major mechanisms e.g. S_E1, S_E2, (front) S_E2 (Back) and SEi. The SE_1 is unimolecular and others are bimolecular mechanism and these aliphatic electrophilic substitutions are analogous to S_N2 mechanism in that the new bond forms, as the

old one breaks. In the S_N2 the incoming group brings with it a pair of electrons and this orbital can over-lap with the central carbon only to the extent that the leaving group takes away it electrons, otherwise 'C' would have more than eight electrons at one in its outer shell, since electron cloud repel this means also the incoming group attacks backside from the leaving group resulting in inversion of configuration. In certain cases stereochemical investigation cannot distinguish between S_E2 (front) and SE_i reaction.In S_E1 mechanism is analogous to the S_N1. It involves two steps – a slow ionization and a fast combination. The base catalysed tantomerization in S_E1 was obtained. Thus inversion occurs without exchange and known as isoinversion. When ES is carried out at an allylic substrate, the product may be rearranged. This process is analogous to the nucleophilic allylic rearrangements. There are two pathways, first is analogous to S_E1 mechanism in that the leaving group is first removed, giving a resonance-stabilized allylic carbonion and then the electrophilie attacks and in other pathway the Y group first attacks, giving a carbocataion, which then loses X. In electrophilic allylic rearrangements involve H_2 as the leaving group but Metallic leaving groups are also observed other mechanism in this are addition, elimination and cyclic mechanism are also seen. In the case of reactivity aliphatic nucleophilic substitution and aromatic electrophilic substitution are not reliable. The effect of substrate is effect of leaving group and effect of solvent in S_E1 and S_E2 are rate determining steps.

14.10 Key words

Neighboring group; electrophile; substitution reaction, anchimeric assistant; S_E1,S_E2 and SEi reactions.

14.11 References for further study

1) Organic chemistry by Bhupinder Mehta, Manju Metha. PHI Learning Pvt. Ltd. 2005.

2) Organic synthesis by Michael. B. Smith. 3rd ed. Academic press, 2011.

3) Organic reaction mechanism. By Raj. K. Bansal, 3rd ed. Tata McGraw-Hill Education. 1998.

14.12 Questions for self study

1) What is anchimeric effect?

2) What are the methods available for studying neighboring group participation in nucleophilic substitution reaction? Discuss with example.

3) What are the consequences of neighboring group assistance?

4) Write two differences and similarities between Nucleophilc substitution and electrophilc substitution reactions.

5) Discuss S_E1 and S_E2 reaction mechanism and give 2 examples for each reaction?

6) Discuss the stereochemical outcome of S_E2 reaction in brief.

7) How do you recognize the electrophilic substitution reaction follows S_E1 or S_E2 mechanism?

8) Write a note on SEi reaction mechanism.

9) Why S_N1 reaction does not takes place at bridgehead carbon while S_E1 reaction easily takes place?

10) Discuss in brief the factors affecting the reactivity of electrophilc substitution reactions.

Unit- 15

Structure:

15.0 Objective of the unit

After studying this unit you will be able to learn about:

- ❖ Be able to write E1 and E2 mechanisms
- ❖ Recognize the stereochemistry required for the substrate to react via an E1 or E2 mechanism
- ❖ Know the regiochemistry of the product of an elimination reaction
- ❖ Know how to predict whether a substitution or elimination reaction will occur with a particular substrate and set of reaction conditions
- ❖ Predict the products of elimination reactions involving organohalides, alcohols, and vicinal diols.
- ❖ Recognize the regiochemistry of the Hofmann elimination reaction.
- ❖ Know the elimination reaction involving alcohols that form carbonyl compounds.

15.1 Introduction

The Elimination reactions are important in organic chemistry since this reaction provides method for the preparation of alkenes and alkynes. The term "***elimination***" describes the fact that a small molecule is lost during the process. A **1,2-elimination** also called β-elimination is commonly absorbed in most of elimination reaction. The 1,2-elimination indicates that the atoms that are lost come from adjacent C atoms. The two most important methods are:

- Dehydration (- H_2O) of alcohols, and
- Dehydrohalogenation (- HX) of alkyl halides.

Followings are the three fundamental events in the elimination reactions:

1. removal of a proton
2. formation of the carbon carbon π bond
3. breaking of the bond to the leaving group

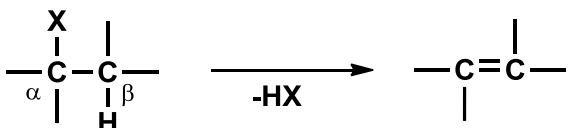
Depending on the relative timing of these events, different mechanisms are possible: They are

- ✓ Loss of the **LG** to form a carbocation then removal of H^+ with formation of **C=C** bond (two steps like $S_N1$reaction)
- ✓ Simultaneous H^+ removal, **C=C** bond formation and loss of the **LG** (one step like S_N2 reaction)
- ✓ Removal of H^+ to form a carbanion then formation of **C=C** bond with loss of the **LG** (two steps) wich is called E1cb reaction

In the first two units we discussed about substitution reaction and their mechanisms. In the substitutions reactions the outgoing leaving group and incoming nucluophile group are simply exchange each other and none of the groups are lost from the starting material ie, number of sigma bonds in the starting material and product are same. In contrast to substitution reaction, elimination reaction involves the removal of two substituents, from adjacent atoms in a molecule (starting material), without being replaced by other atoms or groups. As a result of the removal, unsaturation is introduced in the product obtained at the end of the reaction. The most common products of elimination reaction are alkene, alkyne and their hetroatom variations such as carbonyl and cyano groups. There are three pathways that differ in the timing of the proton is pulled off and when the leaving group L falls off from the intermediate. The different elimination paths often produce different alkene constitutional isomers as products (Regiochemistry). One type of elimination reaction favours the formation of the more substituted alkene because reversible protonation of the double bond occurs and creates an equilibrium mixture that favours the more stable product. Another type of elimination reaction yields the alkene with minimum steric interactions. The size of the base is important in this type because one proton may be more accessible than another. In addition to the formation of different regioisomers, elimination reactions can produce different stereoisomers also, for example, *cis* and *trans* alkenes. Since the *trans* isomer is usually of lower energy because of steric reasons, it usually predominates over the *cis* isomer in the product mixture. The same factors that determined the regiochemistry also influence stereochemistry.

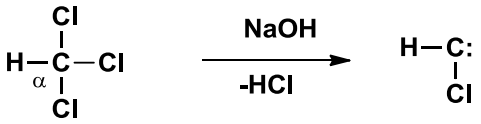
15.2 Elimination Reaction

The reaction in which two atoms or groups are removed from a molecule to yield unsaturated compound is called elimination reaction. Usually in elimination reaction the loss of two substituents from vicinal atoms or groups resulting in the formation of double or triple bond. Generally a proton is lost from one carbon whereas nucleophile is lost from adjacent carbon. These two carbon atoms are called -β and – α carbons, respectively.



This type of elimination reactions are called β-elimination reactions or a 1,2-elimination reactions. Examples for elimination reactions are dehydration of alcohols under acidic condition, dehydrohalogination of alkyl halides and the Hofmann degradation of quaternary

ammonium hydroxides. In some case of elimination reactions the both groups are lost from the same carbon atom. These are referred as α-elimination reactions or 1,1-elimination reactions. The most common examples of this type of elimination reaction occurs in the generation of dichlorocarbene from ch

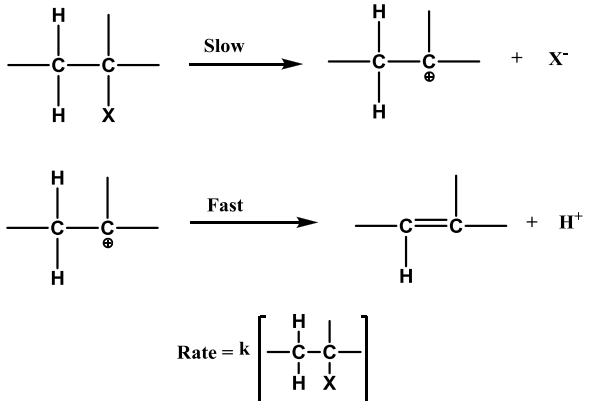


Elimination reaction occurs in the presence of strong base. The formation of ethylene on the treatment of ethylbromide with sodium ethoxide is an example of elimination reaction. On the basis of reaction mechanism, the elimination reactions are of two types they are E_1reaction and E_2 reaction.

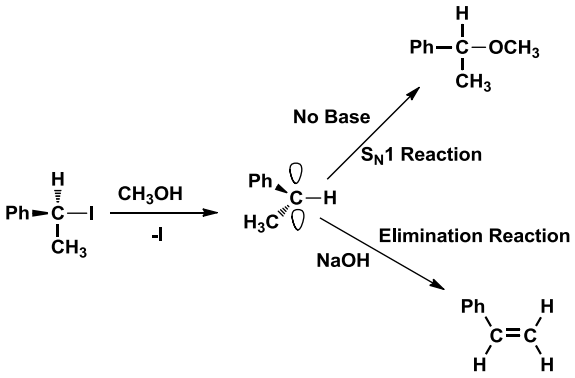
15.3 E_1 elimination reaction

E_1 stands for Unimolecular elimination reaction. The E_1 reaction mechanism takes place in two steps. In the first step leaving group breaks away along with the bonding electrons to form a carboniumion. The resultant carboniumion loses a proton to the solvent or to the some other proton acceptor to yield alkene.

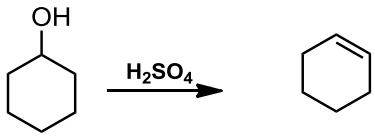
The first step is the slow step hence the rate determining step. Therefore the rate of the reaction



is depends only on the concentration of the reactant. This reaction mechanism is very similar to the S_N1 reaction. In the E_1 reaction a proton is eliminated from the carbon adjacent to the positive (electron deficient) carbon and the pair of electrons formerly shared by this hydrogen atom is available for the formation of a π-bond. Since carbonium ion is common intermediate for the S_N1 and E_1 reactions, substitution is favored by the presence of a good nucleophile whereas elimination is favored by the presence of strong base.



The acid catalyzed dehydration of alcohols generally yields an alkene because the medium does not contain effective nucleophile but the acid medium can cause further reactions of the alkene is an example for E_1 reaction.



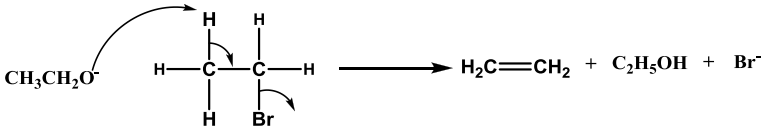
15.4 E_2 elimination reaction

E_2 stands for bimolecular elimination reaction. In the reaction of ethylbromide with sodium ethoxide to yield ethylene, the rate is proportional to the concentration of ethylbromide as well as that of sodium ethoxide.

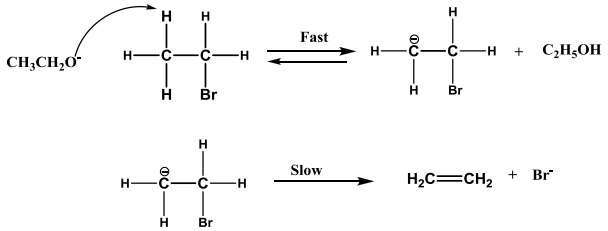
CH_3-CH_2-Br + C_2H_5ONa ⟶ CH2 = CH2 + C_2H_5OH + NaBr

ie, Rate = k [CH_3CH_2Br] [C_2H_5ONa]

Two different mechanisms can be proposed for this reaction. In the first mechanism, the base abstracts a proton from the β-carbon and simultaneously the leaving group departs from the α-carbon along with the pair of bonding electron.



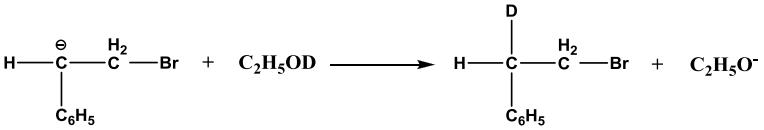
In the second mechanism, the base first removes proton from the β-carbon resulting in the formation of carbanion, then lose of leaving group in a rate determining step to yield alkene.



Since the elimination reaction is base catalyzed it does not allow the formation of an unstabilized carbanion. Therefore second mechanism is ruled out. Hence E_2 reactions are taking place in one step and follow the first mechanism.

The second mechanism is also observed in some cases of elimination reaction. In those reactions the overall rate is limited to that of the slower second step and depends only on the concentration of the conjugate base of the reactant. This mechanism is called as $E_{1C}B$ and it stands for elimination unimolecular conjugate base.

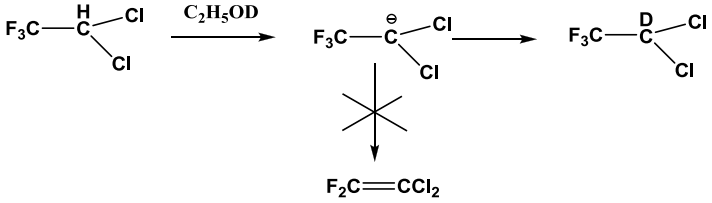
Distinguish between E_2 and $E_{1C}B$ mechanism can be made very easily by means of labeling experiments. The first step in the E1CB mechanism is reversible and hence when the reaction is carried out in C_2H_5OD instead of C_2H_5OH the intermediate carbocation should pickup deuterium as



Therefore if the reaction follows $E_{1C}B$ mechanism we should able to recover labeled 2-phenylethylbromide. On the other hand if reaction follows an E_2 mechanism there should be no incorporation of deuterium atom is observed.

In the above reaction it has shown that there is no deuterium atom incorporation to the product hence reaction follows E_2 mechanism.

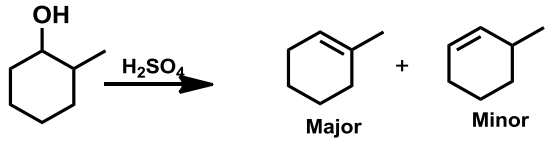
In case of elimination reaction of 1,1,1-trifluoro-2,2-dichloroethane the exchange of β-hydrogen atom with solvent was observed.



This indicates that the above reaction follows $E_{1C}B$ mechanism. Because a strong Carbon-Fluorine bond and the electron withdrawing effect of the two chlorines favors the formation of carbanion and stabilizing it.

15.5 Regio selective preferences in the elimination reaction

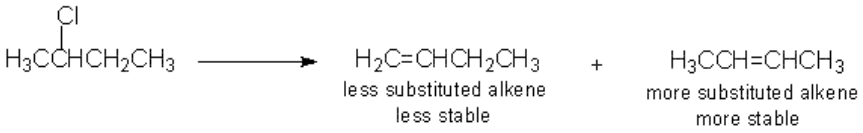
If more than one alkene can be formed from a single carbocation, the major alkene is the one with the most substituents. Substituents tend to increase alkene stability. The more substituted alkene is called the Saytzeff product.



Elimination reactions discussed above are always accompanied by and also competing with nucleophilic substitution reactions discussed in previous unit. Reaction conditions can be adjusted to make either one the (elimination or substitution) reaction could be main reaction, which we will discuss in later. Fluorine can also be eliminated as fluoride in elimination reaction. But among all the halogens, fluorine is the least reactive, because the C-F bond is very strong and not easy to break, thus for halogens the rate of elimination is as follows I>Br>Cl>F. Because of its great electronegativity fluorine, can cause the beta hydrogen to become acidic. The mechanism of elimination form many fluorinated compounds involves a carbanion.

15. 6 Saytzeff rule

The Saytzeff rule predicts the regio-selectivity of olefin formation in the elimination of secondary or tertiary alkyl halides. According to this rule, if there can be more than one adjacent carbon, the proton is eliminated preferentially from the carbon bearing the least number of protons. The regioselectivity to give a more stable olefin is referred to as the Saytzeff regiospecificity, and the corresponding olefin is known as the Saytzeff product.

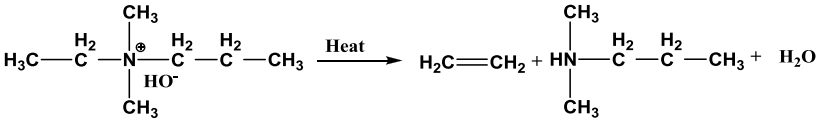


If the hydrogen at C1 is involved the result is 1-Butene, the less substituted alkene. If the hydrogen at C3 is involved the result is 2-Butene, the more substituted alkene. More substituted alkene is more stable therefore 2-butene is the major product.The unimolecular elimination such as the Chugaev reaction and the pyrolysis of esters in the liquid phase follows the Saytzeff rule. However, the Saytzeff rule does not apply in some of the cases. It has been reported that the steric effect during the elimination may also lead to the product not obeying the Saytzeff rule

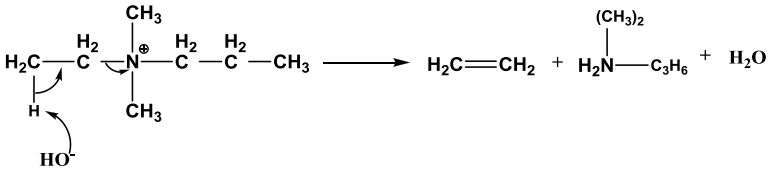
15.7 Hofmann's Rule

It states that charged substrates [quaternary ammonium and Sulphonium salts] yield predominantly the less substituted alkene.

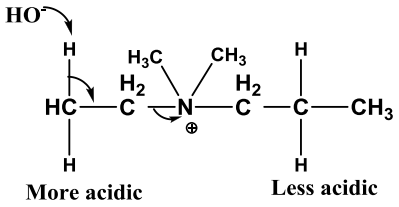
For example, N,N-dimethyl, N-ethylpropylamine hydroxide salt on heating yields an alkene and a tertiary base as shown below



First hydroxide ion abstract a proton from the β-carbon resulting in the formation of a double bond and expulsion of a tertiary amine.



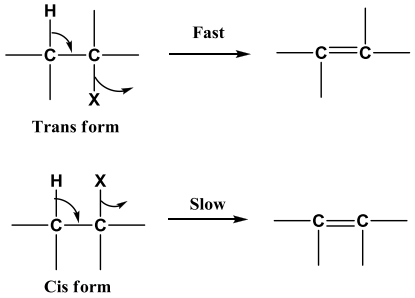
Formation of less substituted alkene can be explained on the basis of the inductive effect of the alkyl group. Due to the presence of a strong electron-attracting leaving group, a positive charge is induced on all the surrounding atoms resulting in the loosening of a β- proton which is easily abstracted by a base thus causing an E2 reaction. If an alkylgroup is attached to the β-carbon, it tends to neutralize the induced positive charge by releasing electrons due to its inductive effect. Therefore acidity of the β-proton is somewhat reduced and hence abstraction is inhibited.



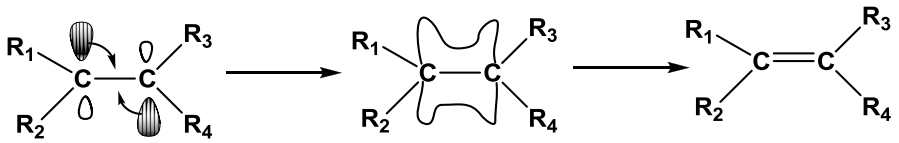
Another explanation for the less substituted alkene formation in Hofmann elimination reaction is that, the transition stae of the reaction Hofmann reaction was proceeds through carbanion formation. The carbon-nitrogen and carbon-sulphur bonds are difficult to break compare to carbon-halogen bonds. In the reaction carbanion is formed before the loss of leaving group. Therefore stability of the carbanion formed plays an important role. As we know due to the +ve inductive effect of alkylgroups, primary carbanions are more stable than secondary and tertiary carbanion. The proton is loss from the β-carbon which generate more stable carbanion and hence the less substituted alkene formed.

15.8 Stereo chemical preference in elimination reactions

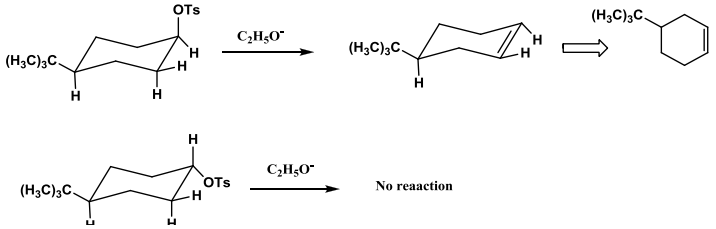
E_2 reactions are stereo specific and proceeds very easily when the departing groups are trans configuration then they are in cis configuration. The reason for trans configuration favoring is that, a p-orbitals are produces form the bonds of leaving group and the hydrogen while an elimination reaction occurs.



In order to achieve maximum overlap of these p-orbitals in the transition state, they should be co-planar and for the minimum energy of the transition state the two eliminated groups must be antiparallel to each other



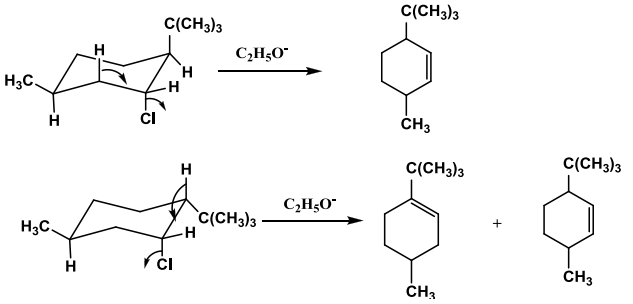
Elimination reactions of cyclic compounds have benn studied in detail to understand the stero chemical requirement of E_2 reaction, because rotation about carbon-carbon single bond is restricted in cyclic compounds. It has been found that cis isomer of 4-t-butylcyclohexyl-p-toluenesulphonate is readily undergoes E_2 reacton, on the other hand the trans isomer does not undergo E_2 reaction under same conditions.



In the cis isomer the t-butyl group preferred equatorial position. This make the leaving group (OTs) to place in axial position, and the flipping of the cyclohexane ring is restricted by bulky t-butyl group. Therefore the leaving group is situated anti-parallel to the hydrogen and makes E2 reaction undergo very easy. On the other hand in trans isomer the leaving group is situated at equatorial position and due to lack of geometrical requirement E_2 reaction does not take place.

Another example to prove requirement of trans configuration in the elimination reactions of cyclohexane derivatives is provided by methyl chlorides.

Although methyl chloride exists predominantly in the morestable conformation in which all the three substituents are in the equatorial position, a conformational flip may makes these bonds to occupy axial position. It undergoes an E2 elimination reaction which sodium ethoxide in ethanol to yiled 2-methene which is an anti Saytzeff product. This illustrating the importance of the trans arrangement of the hydrogen and chlorine situated on carbon atoms 2 and 3 position respec

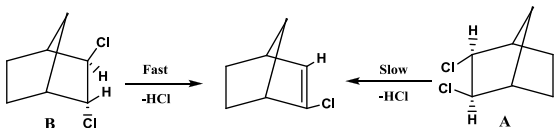


A similar reaction with neomethylchloride yields 3-methane in addition to 2-methane. Because a trans coplanar arrangement is possible for axial chlorine with the axial hydrogen situated on 2 and 4 poitions. As would be expected the saytzeff product predominates over the anti saytzeff product.

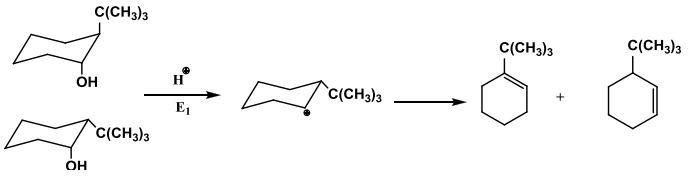
15.9 Cis-elimination in E_2 reactions

Open chain system involves the trans elimination reactions in the majority of cases due to free rotation around carbon-carbon single bond which produces the trans periplanar conformation. Though certain cyclic compounds violate the trans rule. In such cases, the necessary orbital overlap for an E_2 reaction can also be achieved if two groups that are being eliminated are cis coplanar. A dihedral angle of 0^0 serves the same purpose as that of 180^0 and is actually preferred to a trans elimination with a dihedral angle of 120^0.

For example in 2,3-dichloronorborane series, where a cis elimination from compound B faster than trans elimination from compound A due to the geometric rigidity of the norborane system, co-planarity in these cases can only be achieved in the transition state leading to cis rather than trans eliminati



In contrast to E_2 reactions, E_1 reactions are not stereo specific. The reason is the planarity of the intermediate carbonium ion. Cis and trans orientation in the substrate produces the same carboniumion in the initial step of the E_1 reaction and therefore the product composition remains the same.



15.10 Orientation in elimination reaction

The elimination reactions of the unsymmetrical substrates yield mixtures of all possible products. Two empirical rules are governing the orientation in these reactions. E_1 reactions predominantly follows Saytzeff rule and most of the E_2 reactions are also follows this rule. The preferential formation of more substituted alkenes in the elimination reactions can be correlated with the relative stability of various alkenes. Calculations from heats of combustion and hydrogenation established that the stability of the double bond is increased by alkyl substitution on the double bonded carbon atoms. The greater stability of the more

substituted alkene is also explained on the basis of hyperconjugation effects. The stability of alkene follows the order

$R_2C=CR_2 > RCH=CR_2 > RCH= CHR > RCH=CH_2 > CH_2=CH_2$

Elimination Vs Substitution reaction:

S_N1 and E_1 similarly S_N2 and E_2 reactions are occur simultaneously. As already explained, if the attacking reagent is a good base it abstracts the β-proton and causes elimination reaction, in other hand the attacking reagent is good nucleophile then it attacks on the α-carbon causing substitution reaction.

In addition to nature of attacking reagent many other factors also influences the elimination or substitution reactions, they are

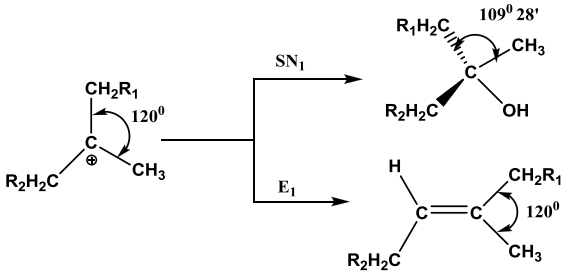
1) Structure of reagents

2) Nature of solvent/base

3) Effect of temperature

Structure of reagents:

Elimination and substitution reaction are compete reactions. The proportion of elimination product increases with increasing chain branching of the reagent. The reason for this preference is that the greater stability of highly substituted alkenes formed from the substrate having more branches. Another reason is due to steric factor and it is applicable only for an E_1 and S_N1 reactions where carboniumions are common intermediates. As carbonium ions are planar structure, their bond angle is about 120^0. Increasing in branching show more resistance to the decrease in band angle ($120^0 \rightarrow 109^0$-28') to brought about the substitution reaction. On the other hand elimination reaction will be preferred as it does not involve any change in the bond angles.



Nature of solvent/ Base.

As already explained a good nucleophile may not necessarily be a good base or vice versa. This can be demonstrated by comparing the nucleophilic and basic properties of some common reagents, the basisity of these reagents are found to be in the order $H_2O < I^- < Cl^- < CH_3COO^- < SH^- < OH^-$, where as nucleophilicities of the same reagents follows a different order H_2O < CH3COO$^-$< Cl$^-$<OH$^-$< I-<SH$^-$. The extent of elimination/substitution ratio

depends upon the nature of the base involved, in bimolecular reaction weaker base are stronger nucleophilic, therefore substitution reaction is favored, where as stronger base are weaker nucleophile and favors elimination reaction. In addition, increasing the concentration of base tends unimolecular reaction to bimolecular reaction.

A change in the polarity of the solvent also effect the course of reaction.in bimolecular reaction E_2/S_N2 ratio depends on how well the solvent is able to solvet the transition state of the reactant. Usually bimolecular reactions are favored by a decrease in polarity of the solvent. This effect is more pronounced in E2 reaction. Thus a less polar solvent not only favors bimolecular reaction but also the E_2 reaction compare to S_N2 reaction.

Effect of temperature:

Elimination reactions usually have higher activation energy than the accompanying substitution reactions. Therefore increase in the temperature of the reaction mixture increases the extent of elimination reaction.

15.11 summary

C=C and C≡C bonds are formed in elimination reactions by removing atoms or groups of atoms are from two adjacent carbons that are bonded together. Reactants for elimination reactions can include haloalkanes, alcohols, or amines. Most elimination reactions follow either E_1 or E_2 mechanisms that are analogous to $S_N1$and S_N2 mechanisms. The E_1 mechanism is a two-step reaction with an intermediate carbocation, while the E_2 mechanism is a single step process. Nucleophilic substitution (SN) reactions are always competing with elimination reactions. The carbon skeletons of intermediate carbocations formed during E_1 reactions sometimes rearrange.

15.12 Key words

1,2 and 1,3 elimination reaction; E_1, E_2 and $E_{1C}B$ mechanism; Saytzeff's rule; Hofmann's rule, conjugate base, nucleophile, electrophile, Cis and trans elimination;

15.13 References for further study

1) Organic reaction mechanisms by V.K. Ahluwalia, Rakesh Kumar Parasha. *Alpha Science International,***2007**.
2) Mechanisms in Organic Reactions, Volume 23 of Tutorial chemistry texts, by Richard A. Jackson. *Royal Society of Chemistry,***2004**.
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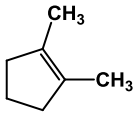
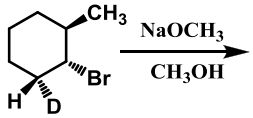
4) Organic Reaction Mechanisms: A Step by Step Approach, Michael Edenborough. *Taylor & Francis*, **1999**.

15.14 Questions for self understanding

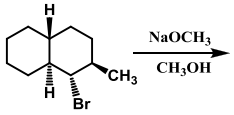
1) One of the products that results when 1-bromo-2,2-dimethylcyclopentane is heated in ethanol is shown below. Give a mechanism by which it is formed and give the name of this mechanism.



2) Provide the structure of the major organic product in the following reaction.

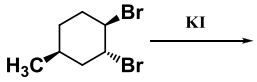


3) Provide the structure of the major organic product from following reaction.



4) Which diastereomer of 1-bromo-4-*t*-butylcyclohexane, the *cis* or the *trans*, undergoes elimination more rapidly when treated with sodium ethoxide? Explain your answer.

5) Provide the structure of the major organic product from the following reaction.

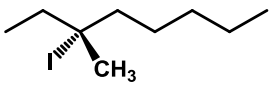


6) When 1-iodo-1-methylcyclohexane is treated with $NaOCH_2CH_3$ as the base, the more highly substituted alkene product predominates. When $KOC(CH_3)_3$ is used as the base, the less highly substituted alkene predominates. Give the structures of the two products and offer an explanation.

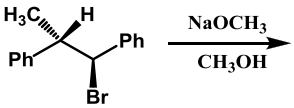
7) What is Saytzeff's rule?

8) What major product results when 2-bromo-2-methylbutane is treated with sodium ethoxide.

9) How many *distinct* alkenes can result from E_2 elimination of the compound below?



10) Give the major product and the mechanism of the following reaction.



11) Which compound produces only one alkene when treated with sodium methoxide?

A) 2-chloro-2-methylpentane

B) 3-chloro-3-ethylpentane

C) 3-chloro-2-methylpentane

D) 2-chloro-4-methylpentane

E) 2-chloro-3-ethylpentane

11) Based on Saytzeff's rule, select the most stable alkene.

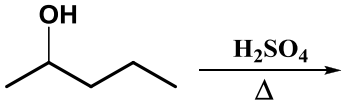
A) 1-methylcyclohexene

B) 3-methylcyclohexene

C) 4-methylcyclohexene

D) They are all of equal stability

13) Draw all likely products of the following reaction and circle the product you expect to predominate.



Unit- 16

Structure

16.0 Objectives of the unit

After studying this unit you are able to learn

- Understand the various methods which are used in elucidating reaction mechanisms.
- Factor influencing the organic reaction mechanism
- Be able to interpret the results of kinetic, labelling, and other mechanistic studies.
- Solvent effect on organic reaction mechanism.
- Isotope effect in elucidating organic reaction mechanism.
- Effect of substituent, steric and Ionic strength on organic reaction mechanism.
- Linear free energy relationships (LFER).
- Hammett and Taft treatment.
- Understand the meaning of linear free energy relationships, and know the meaning of the parameters σ and ρ

16.1 Introduction

During the course of a reaction the molecules comes closer, atoms changes their position and electrons shifts take place and as a result new compounds are formed. Complete description of such path is called reaction mechanism. The physical and chemical properties of a molecule are predicted from knowledge of reaction studies in which they are involved. Chemical bonds are usually referred to as ionic or covalent. The same types of bonds presumably display the same kind of properties in different molecules. Elucidation of reaction mechanism is one of the most fascinating subjects in organic chemistry. New mechanisms are being discovered or old ones are reexamined with the help of modern analytical instruments. Various experimental techniques are available now a day to study the reaction mechanism. The choice of particular methods is actually a matter of chemical intuition. Number of factors can influence the reactivity a molecule in a given situation. One can obtain useful information by studying the reaction by varying those factors. In this unit we discussed the factors influencing the reaction mechanism and elucidating the organic reaction mechanism using those factors.

16.2 Factors affecting the organic reaction mechanism

The following factors have considerable impact on organic reaction mechanism

a) Reaction media ie, solvent
b) Structure of reactant.
c) Ionic strength.
d) Isotopic substitution

e) Substitution around the reaction center.

16.3 Solvent effect on reaction mechanism

Organic reactions are classified in to three classes depending on the character of the activated complex through which these reactions can proceed. They are dipolar, isopolar, and free-radical transition-state reactions. Reactions proceeds through ionization (S_N1 and E1), displacement (S_N2), elimination (E2 and EICb) involves dipolar transition-state. Charge separation or charge distribution in dipolar activated complexes large compare to the initial reactants, these reactions exhibit large solvent effects.

i) *The Hughes–Ingold Rules*

Hughes and Ingold extensively studied the effect of solvent on aliphatic nucleophilic substitution and elimination reactions. Based on result they made the following assumptions

(a) Increase in magnitude of charge will increase solvation;

(b) Increase in dispersal of charge will decrease solvation; and

(c) Destruction of charge will decrease solvation more than dispersal of charge,

The gross effect of the solvent on reactions of different charge types can be summarized as follows:

(a) An increase in solvent polarity results in an increase in the rates of those reactions in which the charge density is greater in the activated complex than in the initial reactant molecule(s).

(b) An increase in solvent polarity results in a decrease in the rates of those reactions in which the charge density is lower in the activated complex than in the initial reactant molecule(s).

(c) A change in solvent polarity will have a negligible e¤ect on the rates of those reactions that involve little or no change in the charge density on going from reactant(s) to the activated complex.

ii) *Solvent Effects on S_N1 reactions*

The transition state of the rate determining step in the S_N1 reaction is a carbocation and it has *ionic character*. Since ions are stabilized greatly from solvation in the polar solvents, therefore an *increase in the solvent polarity will yield an increased stabilization of the transition state* thereby greatly increasing the rate. Thus, *S_N1 reactions occur especially rapidly in polar solvents* like water, methanol, ethanol, or acetic acid.

iii) *Solvent Effect on S_N2 Reactions*

The solvent effect on S_N2 reactions is more complex. In the S_N2 reaction the nucleophile is negatively charged therefore in a polar solvent nucleophile is solvated and greatly slowdown the reaction rate. However, the transition state (TS) is also anionic, and is stabilized by a polar solvent. But the direction of slowing down the reaction due to salvation of nucleophile is more significant in a more polar solvent ie, the nucleophile is more stabilized by the solvent than is the TS. This is because the TS is a much larger in size and charges are more dispersed, therefore less efficiently solvated.

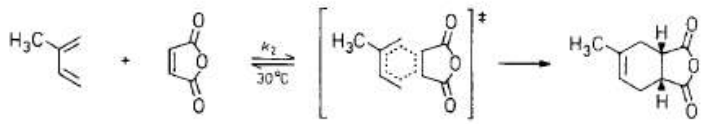
A change in solvent not only affects the reaction rate, but also the reaction mechanism. The reaction mechanism for some haloalkanes can changes from S_N1 to S_N2 or vise versa when the solvent is changed. For example, the reaction of iodomethane, which proceed in aqueous ethanol by an S_N2 mechanism, can become S_N1 in formic acid.

The mechanisms of nucleophilic substitution and elimination reactions are very similar with regard to the rate-determining step. The two unimolecular reactions S_N1 and E1 have a common rate-controlling step ie, formation of carbanion. Similarly two bimolecular reactions S_N2 and E2, have similarity in the electron transfers from the reagent to the leaving group. However, E2 reactions pass through a larger chain of carbon atoms than S_N2 reactions. Therefore, similar rules for solvent effects for monomolecular, and bimolecular, β-elimination reactions of different charge-type have been observed.

iv) Solvent Effects on isopolar transition State reactions

Reactions involving isopolar activated complexes (neither dipolar nor radical in nature), normally exhibit only small solvent rate effects. This is because there is much charge distribution occurs in the activated complexes and the reactants. Electrocyclic, sigmatropic, cheletropic, or cycloaddition reactions precede through isopolar transition states. All of these reactions are representative of concerted reactions known as ‘‘pericyclic reactions’’. Woodward and Hoffmann have suggested that these reactions are controlled by the molecular orbitals symmetry of the reactants and products. Hence changing either the substituent or the medium has least effect on the rates of the reactions.

The cycloaddition of isoprene and maleic anhydride yields cyclopentadiene through dimerization as shown below is the examples for the reaction proceeds through isopolar transition state. This shows little effect on the rate of a reaction with respect to solvent change.



(5-42)

Solvent	$(i\text{-}C_3H_7)_2O$	C_6H_6	C_6H_5Cl	CH_3NO_2	$C_6H_5NO_2$	*o*-Dichlorobenzene
k_2^{rel}	1	3.5	5.0	6.6	11	13

v) *Solvent effects on free-radical transition state reactions*

Generally the free radical-forming reactions are not very sensitive to medium effects, because activated complexes which produce radicals normally exhibit no charge separation. This behaviour is typical for reactions involving isopolar transition states.

16.4 Isotope effect on reaction mechanism

The difference in physical and chemical properties of atom or molecules brought about by isotope substitution is called isotope effect.

Examples of isotope effect are

i) The reaction of organic compounds can be slowdown substantially by replacing the C-H bond by C-D bond if the C-H bond is broken during the reaction.

ii) The diffusion rate of ^{36}Ar isotope is higher than that of heavier argon isotope ^{40}Ar.

iii) The equally charged ions of ^{63}Cu and ^{65}Cu are accelerated to different velocities by the same electric potential.

iv) The infrared spectrum of methane (CH_4) is different from that of deuteromethane (CD_4).

Isotope substitution is a useful technique for the probing of reaction mechanisms. The change of an isotope may affect the reaction rate in a number of ways and provide use full information about mechanism of the reaction. The main advantage of isotopic substitution is that there is no difference in chemical behaviour of different isotopes and hence the chemical properties of the compounds are same when an isotope is substituted for an atom. However the rate of a chemical reaction can be varied by isotopic substitution. Therefore *the variation in the rate of a chemical reaction due to the difference in the isotope present in the molecule is called kinetic isotope effect*.

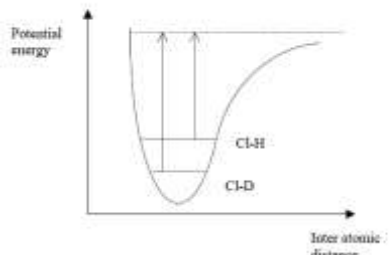
Kinetic isotope effects are of two types

i) The isotope substitution is made with an atom at which the cleavage of bond is the rate determining step. In such case the isotope effect is relatively large and is called primary kinetic isotope effect.

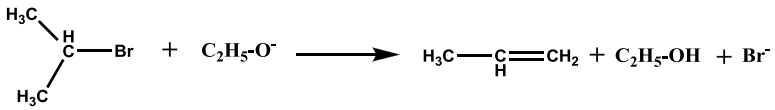
ii) If the isotope substitution is made with an atom that does not directly participate in the reaction, a *secondary kinetic* isotope effect. Each effect can give different mechanistic information.

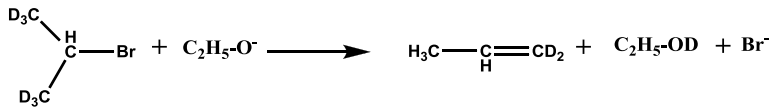
16.5 Cause of Primary kinetic isotope effect

Any C-H bond has characteristic vibrations which import some energy to the molecule in its normal state and this energy is called zero-point energy (ZPE). The energy associated with these vibrations is related to the mass of the vibrating atoms. Since deuterium has greater mass, the vibrations associated with C-D bond contribute less to ZPE than corresponding C-H bond. Hence substitution of D lowers the ZPE of the molecule. For a reaction involving cleavage of C-H bond (or C-D bond) a vibrational degree of freedom in the normal molecule (C-H) is converted in to a translational degree of freedom by passing through the transition state. The energy difference due to this vibration disappears at the transition state since the transition sate has the same energy for the C-H and C-D spices. Because of the deuterated molecule had the lower ZPE, it requires higher activation energy to reach the transition state.

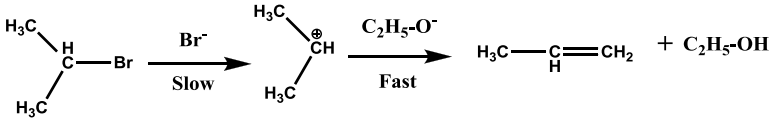


The primary kinetic isotope effect has been found to be powerful toll in the elucidation of mechanism of many reactions. For example, the substitution of hydrogen by deuterium in the methyl group of isopropylbromide considerably slows down the rate of its reaction with the ethoxide ion.

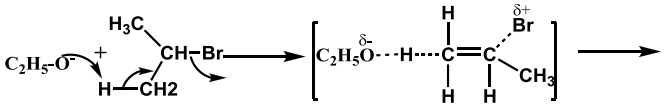


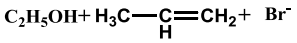


The observed large isotope effect ($\frac{k_H}{k_D} = \frac{\quad}{0.15} = 6.66$) indicate that C-H bond cleavage by ehtoxide ion is the rate determining step for this reaction, and ruled out the mechanism involving carbocation formation as mentioned bellow.

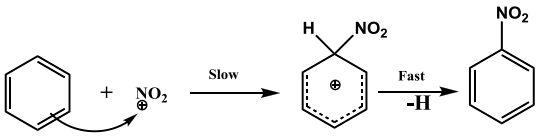


The correct mechanism for this reaction is



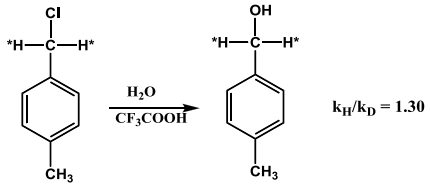


The nitration reaction benzene does not show any isotope effect. In the nitration of deuterated benzene, deuterium atoms are replaced at the same rate as hydrogen atoms. Thus rate determining step of the reaction does not involve breaking of the C-H (or C-D) bond. The mechanism of aromatic ring is visualized as follows. Attack of the nitronium ion to the aromatic ring is the slow step followed by loss proton from the intermediate. This is a fast step because product is stabilized by regaining aromaticity.



Secondary isotope effect are smaller than primary ones and are usually in the range of $\frac{k_H}{k_D} =$ 0.7-1.5. The secondary kinetic isotope effects may be normal ie, $\frac{k_H}{k_D} = 1$ or inverse ie, $\frac{k_H}{k_D} < 1$. The secondary kinetic isotope effects are further classified as α, β,etc….depending on weather the isotopic substitution is on the reacting carbon, or farther away. The secondary kinetic isotope effects are result from a tightening or loosening of the C-Hbond at the transition state. The change in the strength of the bond is due to hybridization change or a change in hyperconjugation.

Ex: If sp3-hybridized carbon is converted in to sp2 as reaction occurs, a hydrogen bond to the carbon will experience decreased resistance to C-H bending. Since C-H bond is slightly longer than C-D bond, C-H bond has longer amplitude for vibration. Therefore replacements of C-D will resist bending. This will result in an isotope effect. The below reaction is an example for such effect since it proceeds through a carbocation intermediate.



An inverse isotope effect will occur if coordination at the reaction centre increases in the transition state. The bending will become more restricted. In the below reaction which involving conversion of a tri-coordinate carbonyl group to a tetravalent cyanohydrin. In this reaction the secondary kinetic isotope effect (0.73) is observed.

Secondary kinetic isotope effects at the β-position have been thoroughly studied in nucleophilc substitution reactions. When carbocation are involved as intermediates, substantial isotope effects are observed. This is because the hyperconjugative stabilization by the β-hydrogen weakens the C-H bond.

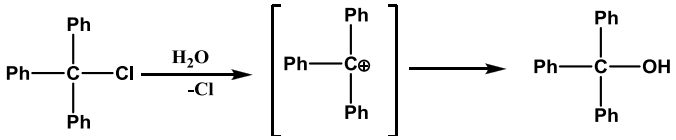
16.6 Salt effect on reaction mechanism

The rate equation for an S_N1 mechanism is

$$\text{Rate} = \frac{d[RY]}{dt} = \frac{kk_1[RX][Y^-]}{k_{-1}[X^-] + k[Y^-]}$$

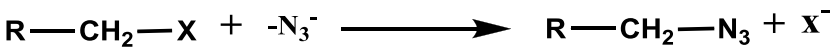
The dissociation of alkylhalide produces the carbocation R^+ and halide ion X^-. From the above equation it is clear that the rate of the reaction will decrease as increase in the concentration of the halide ion. The first step in the S_N1 reaction involves the dissociation and it is reversible, the carbocation will combine with halide ion to regenerate alkylhalide R-X if the concentration of X is high in reaction media thereby decreases the rate of reaction. Hence addition of slat with common ions ie, an anion identical with that given by the alkylhalide compound decrease the rate of the reaction.

For ex: in the sovolysis reaction of triphenylmethylchloride which form a stable carbocation. The rate is decreased four times on the addition of 0.01M NaCl.



On the other hand the addition of non-common ion salt ie, salt with a different ion than the alkylhalide, increases the rate of the reaction. The addition of 0.05M of LiBr, NaN_3 or $(CH3)_4N^+NO_3^-$ salt to the above reaction the rate of the reaction increases correspondingly 1.46, 1.50 and 1.53.

In case of S_N2 reaction (bimolecular reaction), which take place in single step with irreversible manner, the addition common ion salt has no effect on the kinetics of the reaction. However addition of non common reaction (such as azide ion) markedly accelerate the rate of the reaction. This is because the azide ion is strong nucleophile than the halide ion and provides an additional mode to attack on the alkyl derivates.



Thus effect of adding salt on the rate of a solvolysis reaction has been employed as a technique to elucidate mechanism in solvolysis reaction. The absence of any decrease in the reaction rate on the addition of a common ion salt has been taken as proff for the absence of carbocation formation.

16.7 Solvent Kinetic isotope effect on the reaction mechanism

The physical properties of solvents such as viscosity, dielectric constant, specific heat, etc…. are isotopes sensitive and these differences must be taken in to account in the interpretation of solvent kinetic isotope effect data. In spite of some difficulties, the solvent kinetic isotpe effect provides valuable information about reaction mechanism.

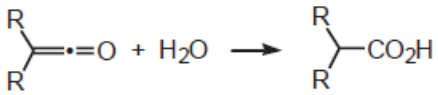
Reaction rates often changes when the solvent is changed from H_2O to D_2O, or R-OH to R-OD. The changes in the rate may be due to any of the following reasons.

i) The solvent may be a reagent in some cases. Hence if –O-H bond of the solvent is broken in the rate determining step, which will represent the primary isotope effect

ii) Substrate molecule may become labelled with deuterium by rapid hydrogen exchange and then the newly labelled molecule may become cleaved in the rate determining step.

iii) The extent of nature of solvent-solute interactions may be different in the deuterated and nondeuterated solvents. This may change in the energies of the transition state and hence the activation energy of the reaction.

For example, solvent isotope effects on hydration of ketenes to form carboxylic acids catalyzed by the hydronium ion have proved to be useful in elucidating the mechanisms.

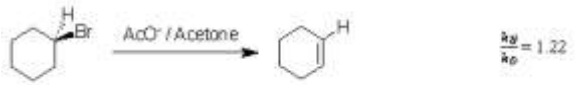


The ketenes are reacts more rapidly in D_2O than in H_2O solutions of sodium hydroxide, and gives an inverse (kH/kD < 1) isotope effect. This proves that hydroxide ion is participating in the reaction and attack of hydroxide ion on ketene is the rate limiting step. The observed solvent kinetic isotope effect is due to, the hydroxide ion in aqueous solution is strongly solvated by three water molecules whose solvating O—H bonds are looser than the O—H bonds of bulk water. When such a hydroxide ion is consumed by reaction with a substrate, the solvating water molecules are transformed into bulk solvent, and they consequently move

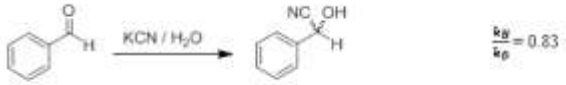
from a more loosely bound state to a more tightly bound state, thus producing an inverse isotope effect.

Another example is, the hydrogen bonds play an important role in maintaining the conformational stability of protein structure, measuring the stability of protein structure in D_2O and H_2O solvent it is possible to measure the contribution of H-bonding effect on protein stability and what are the amide bond participating in hydrogen bonding.

Following are few examples that exemplify secondary kinetic isotope effect.

1. 

Here, the reaction center changes from sp^3 to sp^2, hence it is normal secondary isotope effect.

2. 

Here, we observed inverse kinetic isotope effect as there occurs a change in the hybridization from sp^2 to sp^3. Both examples above are instances of α-secondary kinetic isotope effect. The β-secondary kinetic isotope effect in most of the cases deals with hyperconjugation and this hyperconjugation is likely to become less effective as a stabilization factor with each successive replacement of hydrogen by the heavier deuterium. This is because C-H bond, being weaker, participates in hyperconjugation to a greater extent than the C-D bond resulting in decrease of the energy gap between the two species in the TS as compared to that in the ground state. In some cases, this hyperconjugation depends on the conformation of the molecule under investigation as can be seen in the following example:

k_H/k_D = 1.19 k_H/k_D = 1.03

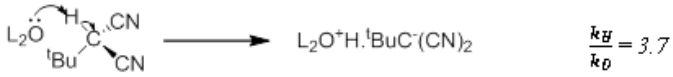
The above experimental values of k_H/k_D can be explained by analyzing the conformations in the transition state. The solvolysis reaction proceeds via loss of brosylate group to generate the intermediate carbocation. Now, the overlap of the C-H/D σ-bond with the developing p orbital in the TS is dependent on the dihedral angle that the C-H/D bond makes with respect to the p-orbital. The maximum secondary kinetic isotope effect is observed when the isotopic β C-H bond is parallel to the developing p-orbital and minimum when it is orthogonal. So, a better overlap can take place in the first case due to lesser dihedral angle than that in the second one leading to a higher k_H/k_D value.

16.8 Solvent Isotope effect

Rate or equilibrium of a chemical reaction may alter upon changing the solvent to the one that is isotopically subsituted, e.g., H_2O to D_2O or ROH to ROD. The change observed as a consequence of solvent effects over the equilibria or rates is called as *solvent isotope effect*, which may arise due to any of the three factors or combination of all of them. The solvent may be a reactant. If the O-H bond of a solvent is broken in the rate-limiting step, there will be primary kinetic isotopic effect. However, it is relatively rare for proton transfer from a solvent to be rate determining, as this is usually a very fast process. Far more common is the equilibrium proton transfer, the initial step in any acid or base catalyzed reaction.

$$A\text{-}H + B \underset{}{\overset{slow}{\rightleftharpoons}} A^- + BH^+ \xrightarrow{fast} products$$

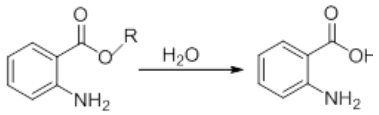
Smaller secondary effects may result from changes in the vibrational frequencies, even if no cleavage occurs, e.g., if solvent water is acting as a base as shown below.



The substrate may undergo rapid hydrogen exchange with the solvent which is faster than the rate of reaction. In this case also isotope effect can be observed upon changing the solvent to its duterated analog. The extent or the nature of the solvent-solute interaction may be different in deuterated and non-deuterated solvents, this change may influence the energy of transition state as a consequence of difference in stabilization via solvation.

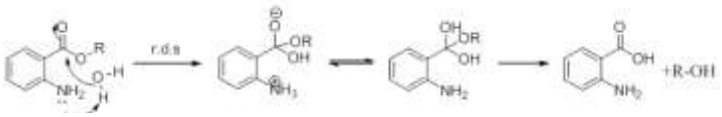
In the following are given examples of solvent kinetic isotope effects.

1. The hydrolysis of 2-aminobenzoate esters is found to be independent in the pH region of 4-8.5.



R = C_6H_5, p-NO_2 C_6H_4, CH_2CF_3

In this pH region, the reaction shows solvent isotope effect (k_{H_2O} / k_{D_2O}= 2). The reaction could then be regarded as a case of intramolecular general base catalysis by the neighboring amino group with the involvement of solvent in which O-H bond is cleaved.

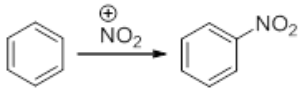


Below pH 4, the reaction follows the normal $A_{AC}2$ pathway and at a pH higher than 8.5, the reaction follows the normal $B_{AC}2$ pathway.

16.9 Mechanistic insights using Isotope effects

Kinetic Isotope Effect is a handy tool that has been widely used in determining reaction mechanism. Let us consider a few examples.

1. Nitration of benzene:

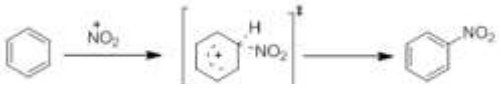


The C-H bond of the benzene molecule must clearly be broken at some stage in the overall nitration and the idealized rate law is:

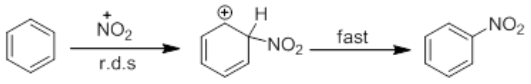
$$\text{Rate of the reaction} = k\,[C_6H_6]\,[NO_2^{+}]$$

The above idealized rate law indicates that both the species should be involved in the rate limiting step of the reaction. Thus, we have the following probable pathways for the nitration of benzene:

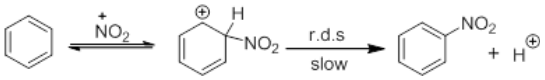
Pathway 1:



Pathway 2:



Pathway 3:

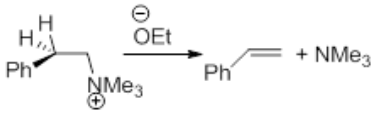


When the nitration is carried out on benzene and hexadeuterated benzene, the observed

$$k_H/k_D = 1.0$$

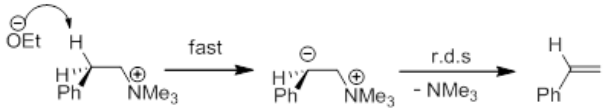
Thus, the C-H bond is not broken in the rate limiting step of the overall reaction, and the pathway 1 and pathway 3 in which elimination of proton is rate limiting cannot clearly be operating. It is, however, important to emphasize that this does not necessarily provide unambiguous proof in favor of pathway 2.

2. Elimination Reaction:

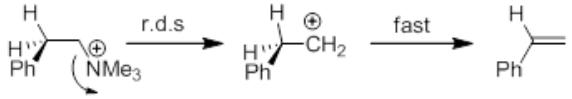


There can be three probable mechanisms possible for this elimination reaction:

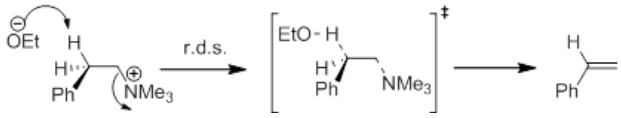
Mechanism 1 (E1cB):



Mechanism 2 (E_1):



Mechanism 3 (E_2):

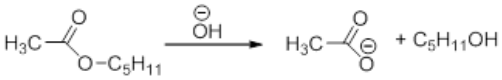


For the above reaction, we have following information obtained from isotopic labeling experiment, k_H/k_D = 4.6 and $k_N{}^{14}/k_N{}^{15}$ = 1.009. The value for k_H/k_D suggests that β C-H bond breaks in the rate limiting step and hence E_1 mechanism cannot be operating. Also, the $k_N{}^{14}/k_N{}^{15}$ value indicates that the heavy atom (N) primary kinetic isotope effect is operative here. So, C-N bond is also cleaved in the r d s, which implies that $E_{1C}B$ cannot be an acceptable mechanism. Thus, E_2 mechanism involving the cleavage of both C-H and C-N bonds in the r.d.s is consistent with the available information based on isotope effect.

16.10 Non kinetic isotope effect

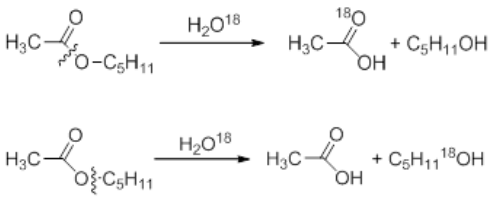
Isotopes that are not involved in the kinetic effect may in many cases be used to derive a reaction mechanism. The isotopes such as D, O^{18}, N^{15}, S^{35}, etc. have wide applications in this regard. Let us consider one example to exemplify the use of non-kinetic isotope effects.

For the following ester hydrolysis:



The reaction may proceed either via acyl-oxygen cleavage.

In this case, no kinetic measurements will enable us to distinguish between them. However, if the reaction is carried out in water enriched in O^{18}, then the O^{18} label will be found in the product acetic acid if acyl-oxygen cleavage occurs or in the amyl alcohol if alkyl-oxygen cleavage operates.



Thus, when the hydrolysis reaction was followed in H_2O^{18} medium, no O^{18} label was found to be present in amyl alcohol. Therefore, the hydrolysis, under these conditions, must proceed entirely via acyl-oxygen bond cleavage.

16.11 Linear Free energy relationship

Organic functional groups exert characteristic electronic effects upon other groups to which tey are attached. The quantitative expression of such effects by means of linear free energy relationship provides some very useful correlations of chemical results.

According to transition theory the logarithm of rate constant (log k) is proportional to the standard free energy of activation and the logarithm of equilibrium constant is proportional to change in the standard free energy of reaction. ie,

$$\Delta G^o \alpha \text{ lnk or}$$

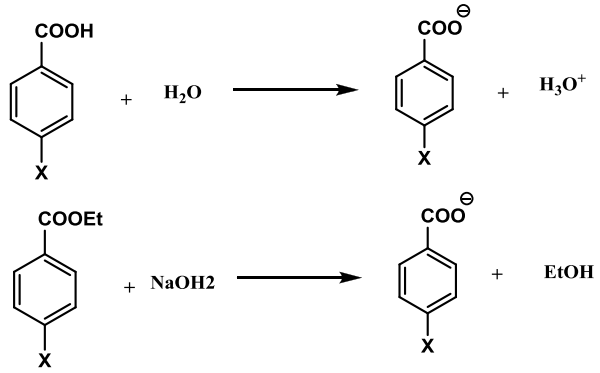
$$\Delta G^o = -RT \text{ In } K_{(eq)}$$

$$\therefore \Delta G^o = -2.303 \text{ RT log } K_{(eq)} \text{ ------ (1)}$$

Hence if there is a linear relationship between two sets of logarithm of rate or equilibrium constant, this is equivalent to a linear relation between standard free energy changes ie, the correlation is a linear free-energy relationship. And is defined as *a linear correlation between the logarithms of a rate constant or equilibrium constant for a one series of reactions and the logarithm of rate constant equilibrium constant for a related series of reactions*. Or *the change in ΔG^0 on introduction of a series of substituent groups is directly proportional to the change in the ΔG of ionization caused by the same series of substituents on benzoic acid. The correlations arising from such direct proportionality in free-energy changes are called linear free-energy relationships.* Typical example of such relations is the Bronsted relation and the Hammett equation.

The best known linear free energy relationship is the Hammett equation which deals with the transitions of electronic effects across a benzene or other aromatic ring. It is important to know effects of substituents on chemical properties. Since this contributes to understanding reaction mechanisms and to predicting rate constants and equilibrium constants.

There is a relationship between the acid strengths of substituted benzoic acids and the rates of many other chemical reactions, for example, the rates of hydrolysis of substituted ethyl benzoates.



Suppose k_o : rate constant for hydrolysis of ethyl benzoate

k : rate constants for hydrolysis of substituted esters

K_o : acid dissociation constant of benzoic acid (X = H)

K : acid dissociation constant of substituted acids (X = substituents)

If ΔG^o_x is the free energy change for the dissociation of substituted benzoic acid, then it is equal to the combination of free energy change of unsubstituted benzoic acid ΔG^o_H and the influence due to the substituent and let denote this influence by σ and called as substituent constant.

$$\therefore \Delta G^o_x = \Delta G^o_H + \sigma \text{ ----- (2)}$$

From equation 1 we have $\Delta G^o = -2.303RT \log K$

Then equation 2 becomes

$$-2.303RT \log K_X = -2.303RT \log K_H + \sigma$$

$$\text{or } \log K_X = \log K_H - \sigma$$

$$\log K_H - \log K_X = \sigma$$

$$[\ log_b(^m/_n) = log_b(m) - log_b(n)\ ]$$

$$\therefore \log \left(\frac{K_H}{K_X} \right) = \sigma \text{ ----- (3)}$$

The Hammett equation relates observed changes in equilibrium or rate constants to systematic changes in substituents of electron donating or withdrawing ability.

Hammett analyze the effect of substituents on any reaction by defining an empirical electronic substituent parameter (σ), which is derived from the acidity constant K_a of substituted benzoic acids. The Hammett Equation relates the relative magnitude of the equilibrium constants to a *reaction constant* ρ and a *substituent constant* σ.

$$\log (K_H / K_X) = \rho\, \sigma$$

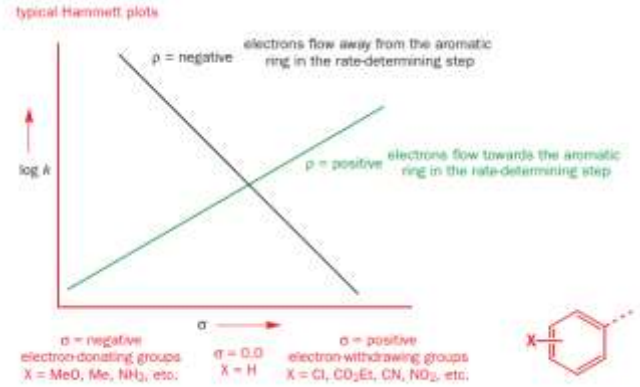
$$\text{or } pK_H - pK_X = \rho\, \sigma$$

For the ionization of benzoic acid in pure water at 25°C (the reference reaction), the constant ρ is defined as 1.00. Thus, the electronic substituent parameter (σ) is defined as

$$\sigma = \log (K_H / K_X)$$

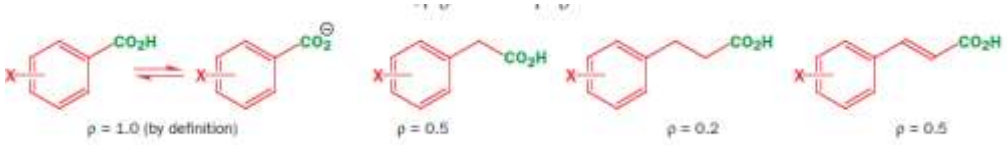
The reaction constant is a measure of how sensitive a particular reaction is to changes in electronic effects of substituent groups.

The reaction constant depends on the nature of the chemical reaction as well as the reaction conditions (solvent, temperature, etc). Both the sign and magnitude of the reaction constant are indicative of the extent of charge build up during the reaction progress. Reactions with ρ > 0 are favoured by electron withdrawing groups (i.e., the stabilization of negative charge). Those with ρ < 0 are favoured by electron donating groups (i.e., the stabilization of positive charge). The greater the magnitude of ρ, the more sensitive the reaction is to electronic substituent effects



16.12 Equilibria with positive Hammett ρ values

Equilibria of a reaction can be compared directly with the ionization of benzoic acids. As the distance between the carboxylic acid group and benzene ring increases, the ρ value for ionization decreases. The ρ value has no effect on the reaction if there are two saturated carbons between the benzene ring and the carboxylic acid. Therefore in order to use the aromatic ring as a probe for a reaction mechanism, carboxylic acid should not be placed too far away from the reaction centre. However, if there is a conjugation with double bond, then electronic communications with benzene ring will be possible and the ρ value has considerable effect on the equilibrium of the reaction

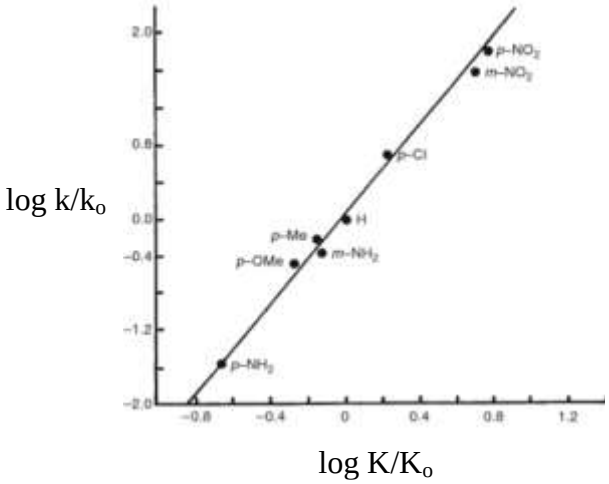


In case of substituted phenols, the negative charge on the oxygen anion delocalized round the ring, the value of ρ increases. The larger effect is observed for the ionization of anilinium

salts, because the acid ($ArNH_3^+$) form does not have a delocalized lone pair electron on nitrogen atom but the conjugate base ($ArNH_2$) does.

16.13 Mechanistic implication of LFER

If a plot of log k/k_0 against an appropriate set of σ give a linear line, the LFER is valid and the slope of the plot is ρ (the reaction constant).



Correlation of dissociation constant of benzoic acids with rates of basic hydrolysis of ethyl benzoates.

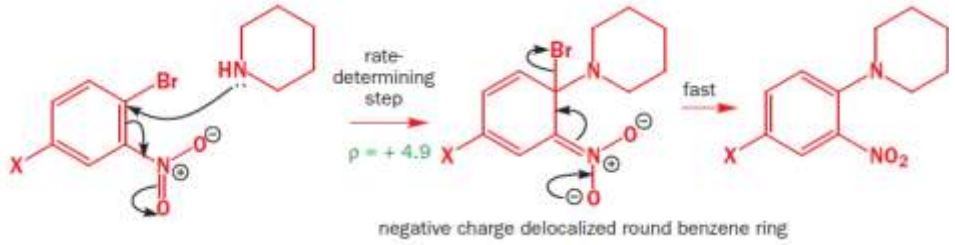
i) The linear line obtained from the plot indicates that the reaction mechanism and the coordination of the transition states do not change upon the variation of the substituent.

ii) The ρ values can be used to give information about the structures of the transition states

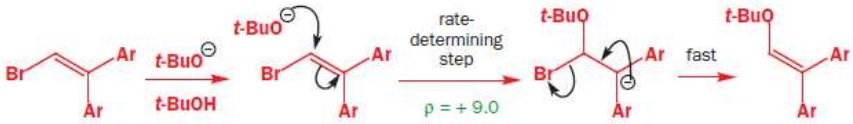
iii) A *positive* ρ indicates that the reaction center in the transition state becomes more *negative* comparing to the starting material. The reaction under study is more sensitive to substituents than benzoic acid, and negative charge is building during the reaction. Therefore an electron withdrawing group stabilizes the developed negative charge.

The large positive ρ values usually indicate extra electrons in the transition state delocalized into the ring itself.

Example 1: A classic example is a nucleophilic aromatic substitution which follows the addition–elimination mechanism. The value of ρ is +4.9 for the below mentioned reaction. This large value does not support the formation of complete anion on the benzene ring. Because the nitro group present in takes most of the negative charge. Therefore the substituent X merely helps. The full value of ρ can be obtained when there are no nitro groups to take the brunt of the negative charge.



Example 2: The vinylic substitution reaction mentioned below has a ρ value of +9.0. This reaction cannot proceeds through an S_N2 reaction mechanism. Otherwise it would have a small ρ value due to charge distribution in transition state. Also it cannot follow an S_N1 reaction mechanism. In such case it would have a negative ρ value due to fewer electrons in the transition state. Therefore it must be an addition- elimination mechanism through a benzylic anion delocalized round both benzene rings.

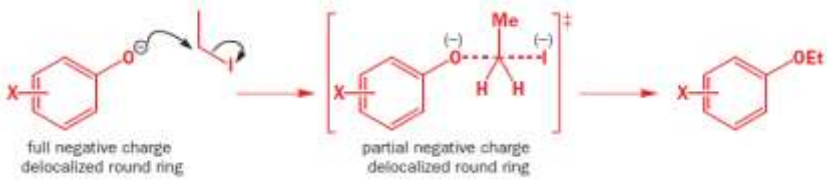


iv) When $0 < \rho < 1$, the reaction is less sensitive to substituents than benzoic acid, but negative charge is still building. And when ρ is equal to or close to 0, the reaction shows no substituent effects

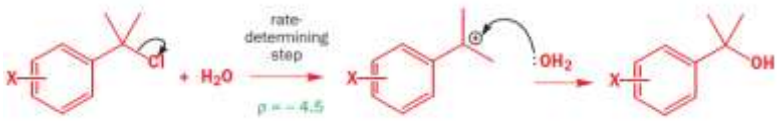
v) A *negative ρ* indicates that the reaction center in the transition state becomes more *positive* comparing to the starting material. The reaction is creating positive charge. Therefore electron donating groups increases in rates.

Negative ρ values mean electrons flowing away from the ring

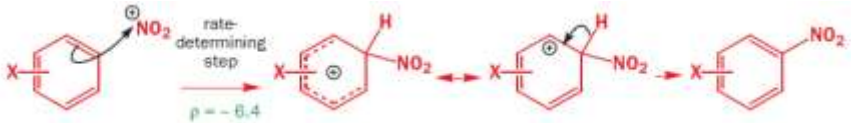
Example 1: The S_N2 displacement of iodide from Ethyliodide by phenoxide anions. This reaction has a ρ value of –1.0. Though the transition state in this reaction has a negative charge, which is decreasing on the aromatic ring compared starting material when it approaches the tr



Example 2: An S_N1 reaction on the carbon atom next to the ring has a large negative ρ value. In the below mentioned reaction, the intermediate tertiary benzylic cation formation is the rate-determining step. The cation is next to the ring and delocalized the electron in the benzene ring round it. Therefore the ρ value is decreases and is equal to –4.5.



Example 3: The largest negative ρ values observed for electrophilic aromatic substitution where the electrons of the ring are used in the reaction leaving a positive charge on the ring itself in the intermediate. The simple nitration reaction has ρ = – 6.4 and ρ values for electrophilic aromatic substitution are usually in the range –5 to –9.



vi) lρl large: much positive or negative charge separation

16.14 summary

When the part of the molecule that we vary is a discrete atom or molecular fragment, we call it a substituent. Substituent effects are the changes on a reaction or property in the unchanged part of the molecule resulting from *substituent variation*. Effects of substituents on known reactions or properties of molecules tell us about the steric and electronic characteristics of *substituents*. We can then use these substituents to influence chemical reactions and properties in predictable ways. Alternatively, we can use substituent effects to understand chemical reactions with unknown mechanisms or features. The electronic effect of the substituents, which directly influences the mechanism and rate of a reaction, is known as *substituent effect*. This substituent effect can be considered as an electronic perturbation that allows a system (reaction) to respond in certain ways. It should be emphasized at the very beginning that the substituent effects can be drastically different for two completely different reactions. In other words, although substituent is the same, the effect that it exerts on two different reactions may be vastly different. The application of the concept of substituent effect is not straightforward. For example, if a substituent is located near the reaction center, then steric considerations come into picture; this steric effect could be so dominant that it may completely mask the electronic effect. On the other hand, if the substituent is located far away from the reaction center, then the electronic effect may be severely attenuated, although there will be no such steric constraints.

16.15 Key words

Isotopic effect; primary isotopic effect; secondary isotopic effect; solvent isotopic effect; salt effect; Hammett equation, Linear free energy relationship; substituent constant; reaction constant.

16.16 References for further study

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16.17 Questions for self understanding

1) What are the factors affecting the reaction mechanism?

2) Discuss in brief the solvent effect on the reaction mechanism.

3) What is Isotope effect?

4) Write a note on primary and secondary isotope effects. And with example explain how these effects are helpful to deduce reaction mechanism?

5) Discuss the cause of primary isotope effect.

6) Discuss solvent kinetic isotope effect on the reaction mechanism.

7) Write a note on solvent isotope effect.

8) Taking nitration of benzene as an example, explain the mechanistic insight using isotope effect.

9) Derive Hammett equation.

10) What are the significance of σ (reaction constant) and ρ (substituent constant)?

11) What is meant by linear free energy relationship?

12) With example explain how ρ can useful to deduce reaction mechanism.