PHARMACEUTICAL ORGANIC CHEMISTRY II

(THIRD SEMESTER B. PHARM.)

Course Content:

General methods of preparation and reactions of compounds superscripted with asterisk (*) to be explained

To emphasize on definition, types, classification, principles/mechanisms, applications, examples and differences

UNIT I **10 Hours**

- **Benzene and its derivatives**

A. Analytical, synthetic and other evidences in the derivation of structure of benzene, Orbital picture, resonance in benzene, aromatic characters, Huckel's rule

B. Reactions of benzene - nitration, sulphonation, halogenation- reactivity, Friedelcrafts alkylation- reactivity, limitations, Friedelcrafts acylation.

C. Substituents, effect of substituents on reactivity and orientation of mono substituted benzene compounds towards electrophilic substitution reaction

D. Structure and uses of DDT, Saccharin, BHC and Chloramine

BENZENE AND ITS DERIVATIVES

Aliphatic and aromatic compounds

Chemists have found it useful to divide all organic compounds into two broad classes: aliphatic compounds and aromatic compounds. The original meanings of the words "aliphatic" (*fatty*) and "aromatic" (*fragrant*) no longer have any significance.

Aliphatic compounds are open-chain compounds and those cyclic compounds that resemble the open-chain compounds. The families we have studied so far—alkanes, alkenes, alkynes, and their cyclic analogs—are all members of the aliphatic class.

Aromatic compounds *are benzene and compounds that resemble benzene in chemical behavior*. Aromatic properties are those properties of benzene that distinguish it from aliphatic hydrocarbons. Some compounds that possess aromatic properties have structures that seem to differ considerably from the structure of benzene: actually, however, there is a basic similarity in electronic configuration

Benzene and all other aromatic hydrocarbons which are structurally related to benzene, are now designated as **Arenes**. These are further subdivided into *monocyclic*, *bicyclic* and *tricyclic arenes* according to the number of six-carbon benzene structural units present in their molecules. In this chapter we will discuss the **Monocyclic Arenes** or benzene and its homologues.

Aliphatic hydrocarbons, as we have seen, undergo chiefly addition and free-radical substitution; addition occurs at multiple bonds, and free-radical substitution occurs at other points along the aliphatic chain. In contrast, we shall find that *aromatic hydrocarbons are characterized by a tendency to undergo ionic substitution.* We shall find this contrast maintained in other families of compounds (i.e., acids, amines, aldehydes, etc.); the hydrocarbon parts of their molecules undergo reactions characteristic of either aliphatic or aromatic hydrocarbons.

It is important not to attach undue weight to the division between aliphatic and aromatic compounds. Although extremely useful, it is often less important than some other classification. For example, the similarities between aliphatic and aromatic acids, or between aliphatic and aromatic amines, are more important than the differences.

Structure of benzene

It is obvious from our definition of aromatic compounds that any study of their chemistry must begin with a study of benzene. Benzene has been known since 1825; its chemical and physical properties are perhaps better known than those of any other single organic compound. In spite of this, no satisfactory structure for benzene had been advanced until about 1931, and it was ten to fifteen years before this structure was generally used by organic chemists.

The difficulty was not the complexity of the benzene molecule, but rather the limitations of the structural theory as it had so far developed. Since an understanding of the structure of benzene is important both in our study of aromatic compounds and in extending our knowledge of the structural theory, we shall examine in some detail the facts upon which this structure of benzene is built.

(*a*) *Benzene has the molecular formula* C_6H_6. From its elemental composition and molecular weight, benzene was known to contain six carbon atoms and six hydrogen atoms.

the

pure material was first isolated in 1825 by Michael Faraday. He found that the vapour density of benzene was 39 so that its molecular formula was established to be C_6H_6.

(1) The molecular formula of benzene C_6H_6 as compared to that of hexane (C_6H_{14}), at once suggests that it is a highly unsaturated compound. The obvious conclusion was that the

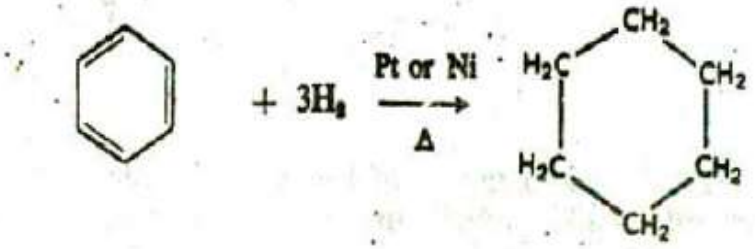
six carbon atoms in benzene were linked by double or triple bonds so as to form a straight chain or a closed ring as proposed by Kekule.

(2) Open-Chain Structure untenable. The possible open-chain structures for benzene could be as

$H_2C=CH-C\equiv C-CH=CH_2$ (I) $HC\equiv C-CH_2-CH_2-C\equiv CH$ (II) $H_3C-C\equiv C-C\equiv C-CH_3$ (III)

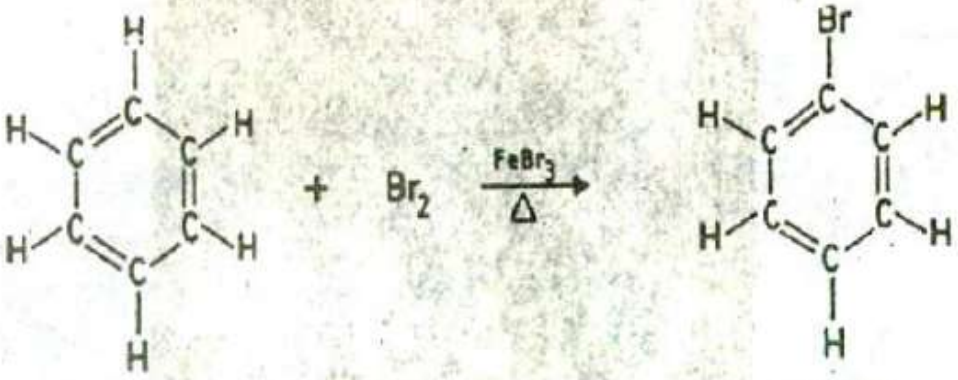
All these structures were ruled out because benzene did not give the usual reactions of alkenes and alkynes. For example, benzene does not react with aqueous potassium permanganate by oxidation, or with bromine in carbon tetrachloride to form the addition products. All known straight-chain structures as I, II or III, containing double or triple bonds, react with these reagents readily at room temperature.

(3) Evidence in Favour of Ring Structure. (*a*) Catalytic hydrogenation of benzene yielded cyclohexane,



Since hydrogenation cannot bring about any major structural change in the carbon frame work, the above reaction demonstrated the presence of a closed ring of six carbon atoms in benzene molecule.

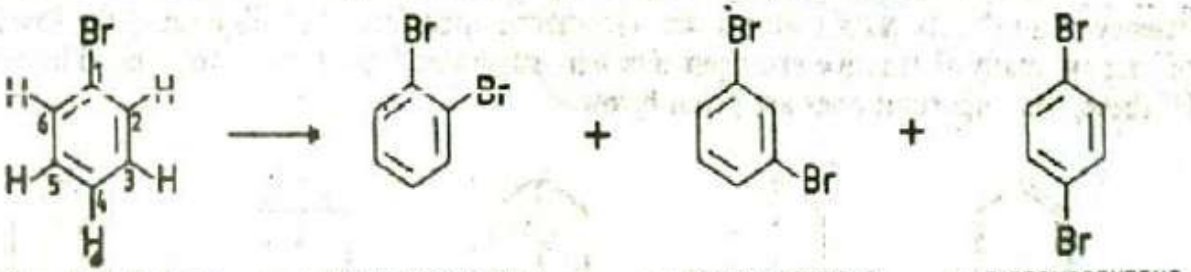
(*b*) It was noted that benzene gave substitution reactions to form one and only one monosubstitution product. Thus when heated to its boiling point in the presence of ferric bromide, benzene gives C_6H_5Br, when just one hydrogen atom is replaced by Br. This could be possible only if the six carbons in benzene are joined to each other to form a closed ring, and that one hydrogen atom is attached to each carbon.



ALL H ATOMS IN BENZENE ARE EQUIVALENT

ONLY ONE MONOBROMOBENZENE IS POSSIBLE

(*c*) Benzene forms three *di*- and three *tri*-substitution products, which were again explained on the basis of the ring structure of its molecule. Thus,



Positions 2,3,5,6 are similar; therefore only three dibromobenzenes are possible

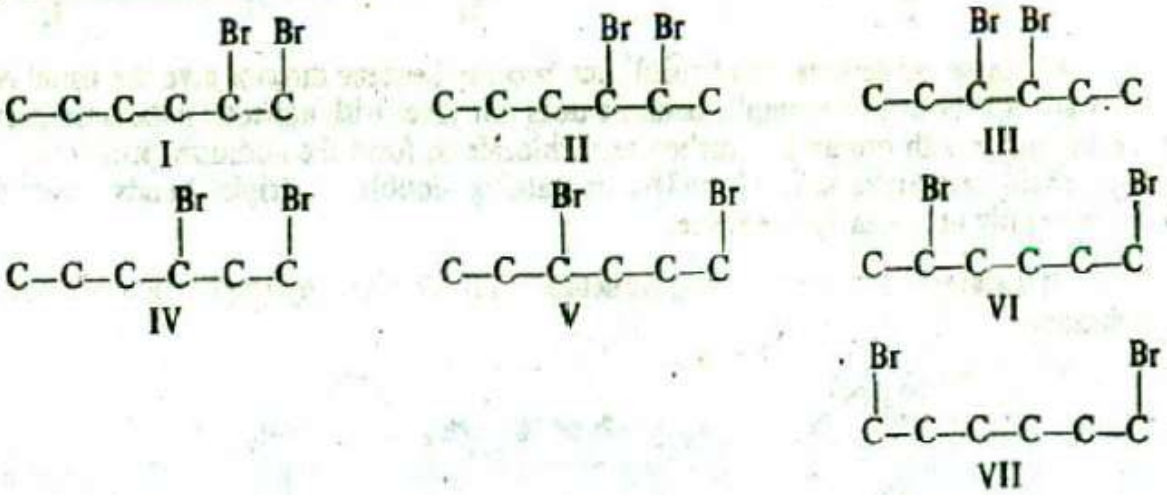
o-DIBROMOBENZENE

m-DIBROMOBENZENE

p-DIBROMOBENZENE

Proceeding similarly it can be shown that if a th..d bromine atom be introduced in the above dibromobenzenes, only three trisubstitution products would be obtained.

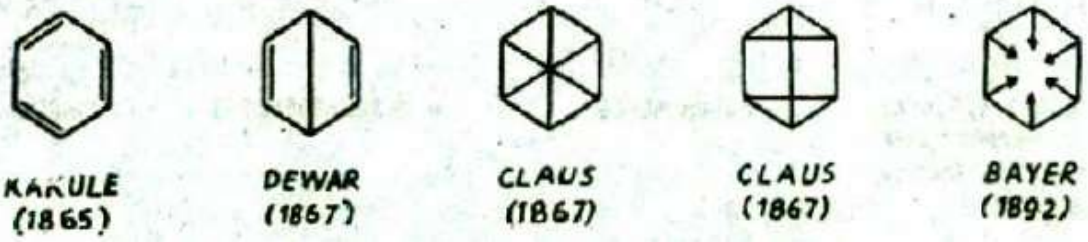
The formation of three *di*- and three *tri*-substitution products is possible if benzene has a ring formula. A straight-chain of six carbons, each carrying one hydrogen atom, would give as many as seven dibromo derivatives.



(*d*) Lonsdale (1929) took 'photographs' of hexamethylbenzene with the help of X-ray *diffraction camera* and provided a 'visible proof' that benzene ring indeed consisted of a planar ring of six carbon atoms.

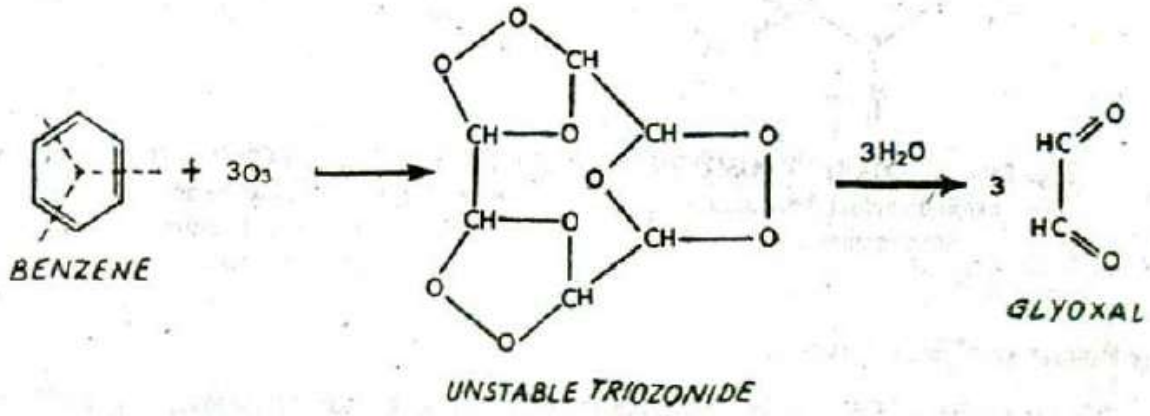
Fig. 35·2. X-ray Diffraction photograph of hexamethylbenzene, showing that benzene ring is made of six carbon atoms (black spots), while the outer spots represent the carbons of the six methyl groups attached to these carbon atoms.

(4) **Bond Structure of Benzene.** In the ring formula of benzene discussed above, the fourth valency of all the six carbon atoms was left unaccounted for. For disposal of the fourth valency of carbon, many alternative arrangements were suggested from time to time by different workers. Of these, the important ones are given below.



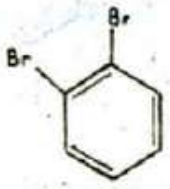
The most important of these formulae was that put forth by Kekule which, in fact, formed the basis of the modern structure of benzene. All the other formulae were dropped for one reason or the other.

(5) Under suitable conditions benzene combined with three molecules of hydrogen and chlorine to form respectively cyclohexane, C_6H_{12}, and benzene hexachloride $C_6H_6Cl_6$. This proved the presence of three double bonds in the benzene ring. Further, on ozonolysis benzene formed three molecules of glyoxal and this showed that the three double bonds in benzene are present in alternate positions.

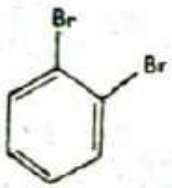


B. Objections to Kekule's Formula

(1) It admits the formation of two ortho disubstitution products for similar substituents. Thus the two *o*-dibromobenzenes possible would be :

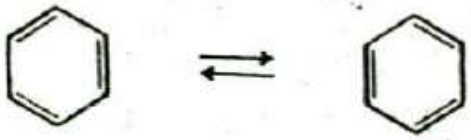


I. (two Br atoms are attached to carbons containing a single bond)



II. (two Br atoms are attached to carbons containing a double bond)

However, actually only one *o*-dibromobenzene is known. Kekule himself replied to this objection by proposing that the double bonds in benzene ring were continuously oscillating back and forth between two adjacent positions.



Since the positions of the double bonds were not fixed, the question of formation of two dibromobenzenes did not arise.

(2) The X-ray diffraction measurements have shown that benzene ring indeed consists of a planar ring of six carbon atoms, and also that the ring carbon-carbon bonds are equal in length. These dimensions are now accurately known. The bond angles of benzene are 120°, the carbon-carbon distances are all 1·40 Å and carbon-hydrogen distances are 1·09 Å. The carbon-carbon distances in benzene are different from the normal carbon-carbon length in alkanes (1·54 Å) and the normal carbon-carbon double-bond length in alkenes (1·34 Å). These findings depict the actual position as in Fig 35·3 A, while the position if Kekule formula were correct in Fig. 35·3 B.

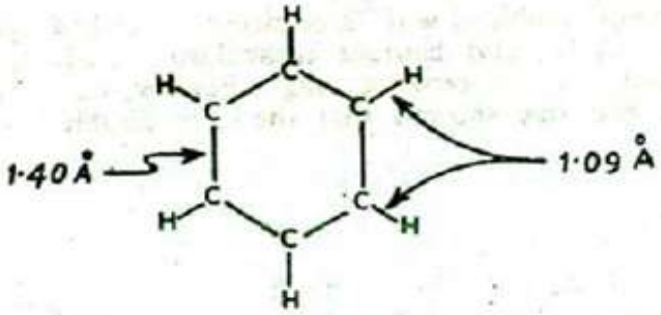


Fig. 35·3 A. CORRECT POSITION based on actual diffraction measurements.

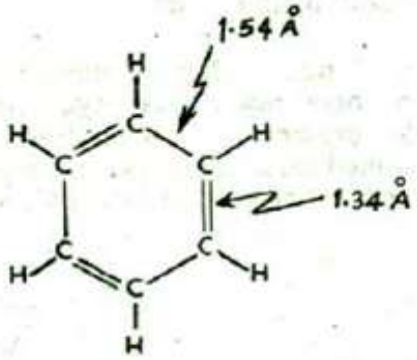
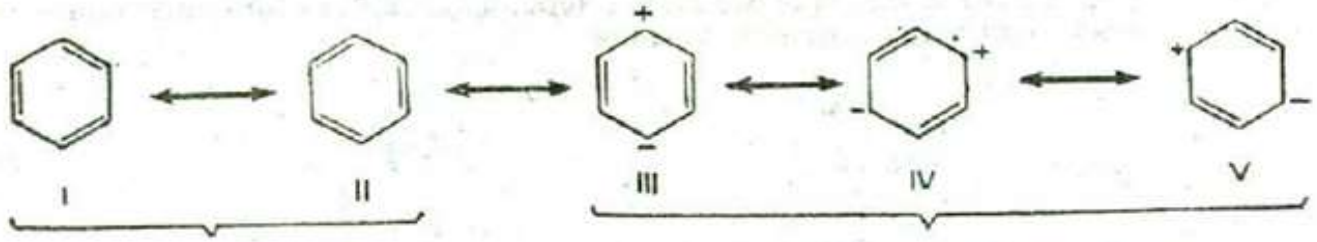


Fig. 35·3 B. INCORRECT POSITION presuming benzene to be cyclo-hexatriene which is disproved by diffraction measurements.

C. The Resonance Hybird Structure

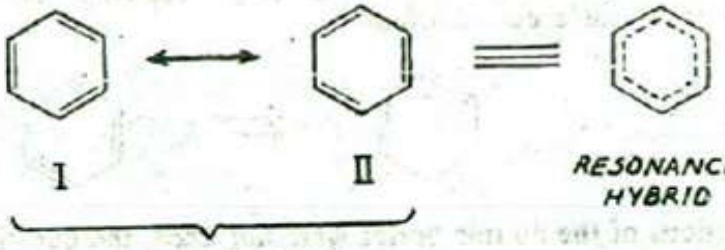
We get to the true picture of the structure of benzene by the application of the theory of resonance which was proposed in 1933. According to this theory, benzene is a resonance hybird of the following canonical forms.



Kekule Structures (most important contributors)

Charge-separated Dewar's Structures (least important contributors)

Since forms I and II are most important contributors, for simplyfying, benzene is represented as a hybrid structure of these canonical forms.



It would not be incorrect to say that the resonance between Kekule forms described above, was, in fact, brilliantly conceived some fifty years earlier. It was to explain the existence of one dibromobenzene only, that he had proposed the oscillation of single and double bonds between adjacent positions on the ring. However, the concept of resonance is imaginary and the canonical forms mentioned above actually do not exist. It is the resonance hybrid structure which is a reality. Since the π electrons are delocalised in the hybrid structure, each of the carbon-carbon bonds in benzene ring has a character intermediate between that of a σ bond and π bond.

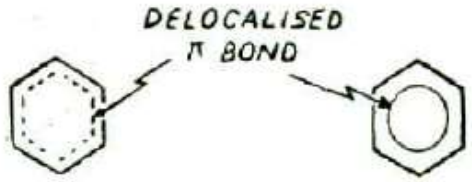
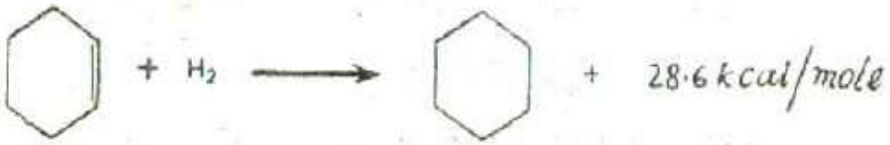


Fig. 35·4. Resonance hybrid of benzene which truly depicts the structure of benzene.

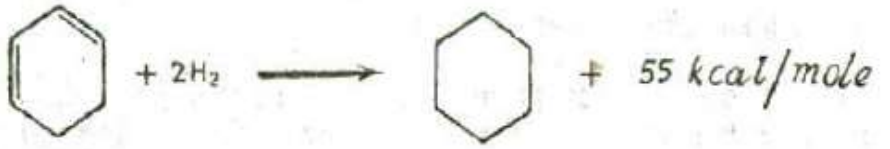
(*a*) RESONANCE HYBRID STRUCTURE CONFORMS TO X-RAY DIFFRACTION RESULTS. The fact that benzene is a resonance hybrid of the two Kekule forms, is in conformity with the results of X-ray diffraction experiments : (*i*) the carbon-sextet is flat ; and (*ii*) all the carbon-carbon bond lengths are equal (1·40Å) and are intermediate between those of an ordinary σ bond (1·54Å) and double bond (1·34°).

(*b*) RESONANCE THEORY EXPLAINS ELEGANTLY THE STABILITY OF BENZENE RING. The resonance hybrid structure of benzene, explained admirably the unusual stability of the benzene ring, a problem that had baffled the chemists for over half-a-century. The resonance stabilisation energy or 'resonance energy' which is really responsible for the unusual stability of benzene, could be calculated indirectly from the measurements of heat of combustion or heat of hydrogenation as follows.

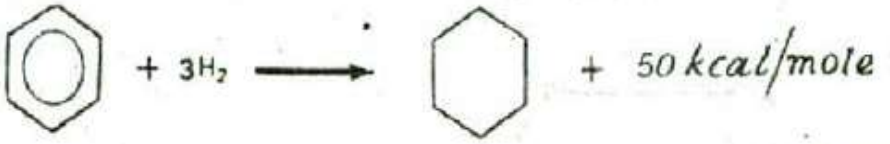
The addition of hydrogen to a double bond is an exothermic reaction. Since heat is given out on hydrogenation, it implies that for the product in each case listed below, the energy is lower (more stable) than the original compound.



CYCLOHEXENE CYCLOHEXANE



CYCLOHEXADIENE



BENZENE

The heat of hydrogenation of one double bond in cyclohexene is 28·6 kcal/mole, which is nearly twice that of cyclohexadiene (55·0 kcal/mole) as here two double bonds are hydrogenated. Taking for granted that Kekule structure of benzene with three double bonds is correct, its heat of hydrogenation would be expected to be $3 \times 28{\cdot}6 = 85{\cdot}8$ kcal/mole. But when benzene is actually hydrogenated, only 50 kcal/mole are evolved. Thus thermodynamically benzene is more stable than the imaginary Kekule structures could predict. The difference, $(85{\cdot}8 - 50) = 35{\cdot}8$ kcal/mole, between the calculated and observed values is the resonance stabilisation energy of real benzene (resonance hybrid). These data are summarised in Fig. 35·5. The hydrogenation results prove clearly that benzene is correctly represented by the hybrid structure, and that Kekule formula is incorrect.

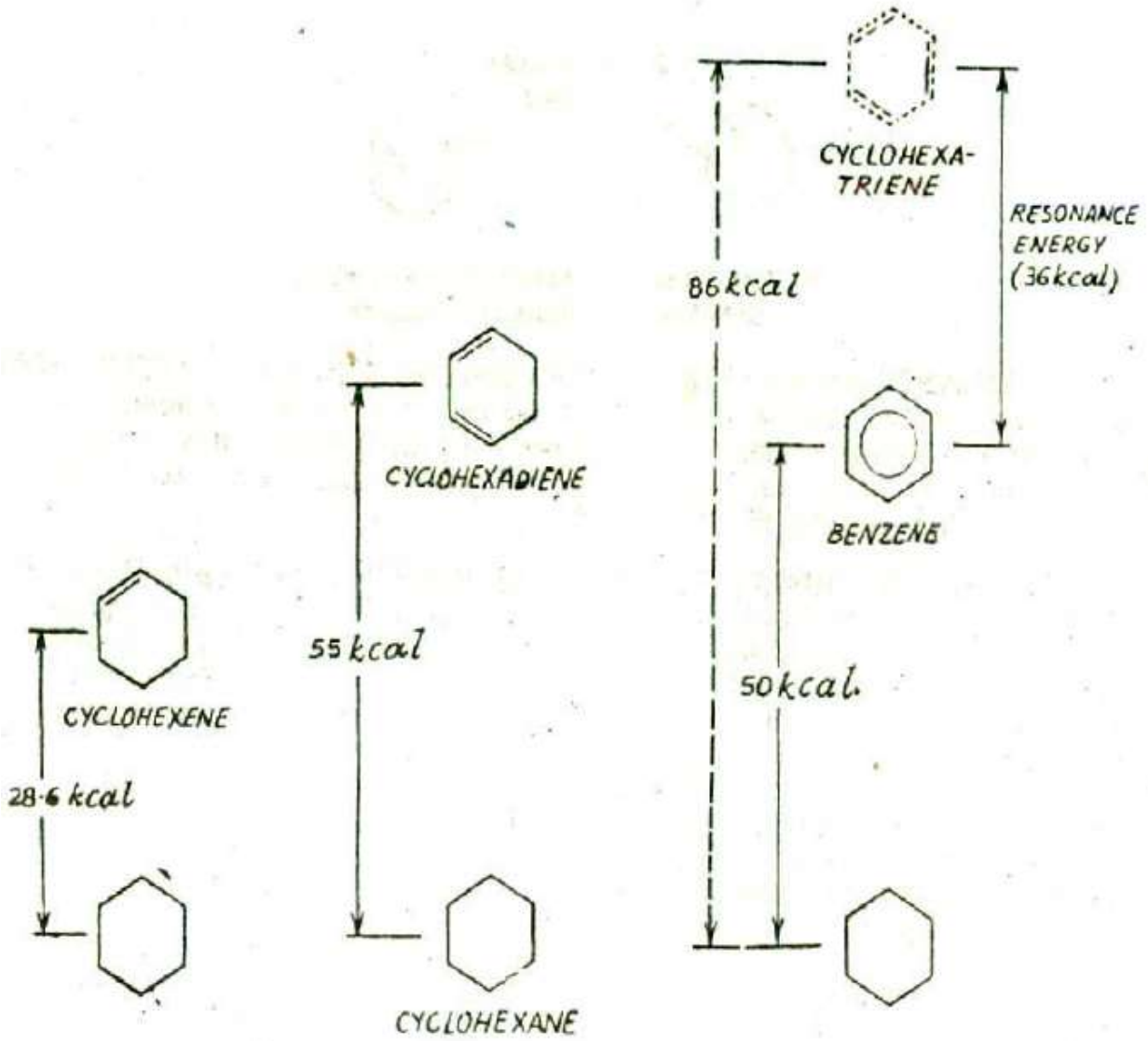
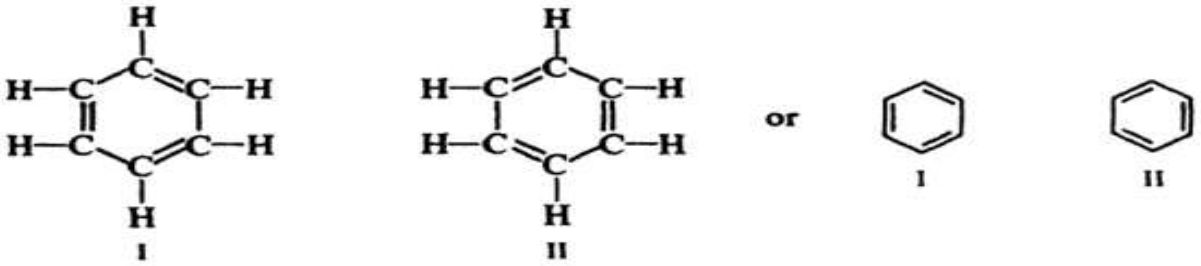


Fig. 35·5. Heats of hydrogenation of cyclohexene, cyclohexadiene, as also of hypothetical Kekule structure (cyclohexatriene), and real benzene (hybrid structure). Here are depicted beautifully the relative energies of these compounds, as also the resonance energy of benzene.

Resonance structure of benzene

The Kekulé structure of benzene, while admittedly unsatisfactory, was generally used by chemists as late as 1945. The currently accepted structure did not arise from the discovery of new facts about benzene, but is the result of an extension or modification of the structural theory; this extension is the concept of *resonance* (Sec. 6.23).

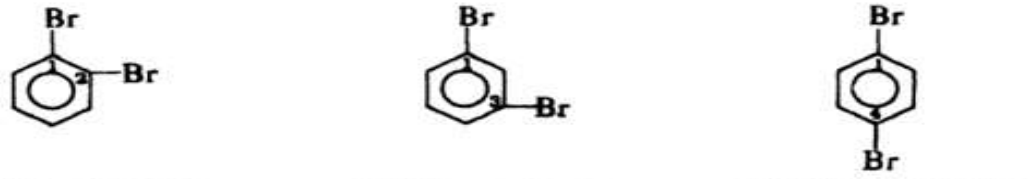


I II

The Kekulé structures I and II, we now immediately recognize, meet the conditions for resonance: *structures that differ only in the arrangement of electrons*. Benzene is a *hybrid* of I and II. Since I and II are exactly equivalent, and hence of exactly the same stability, they make equal contributions to the hybrid. And, also since I and II are exactly equivalent, stabilization due to resonance should be large.

The puzzling aspects of benzene's properties now fall into place. The six bond lengths are identical because the six bonds are identical: they are one-and-a-half bonds and their length, 1.39 A, is intermediate between the lengths of single and double bonds.

When it is realized that all carbon–carbon bonds in benzene are equivalent, there is no longer any difficulty in accounting for the number of isomeric disubstitution products. It is clear that there should be just three, in agreement with experiment:



1,2-Dibromobenzene 1,3-Dibromobenzene 1,4-Dibromobenzene

Finally, the "unusual" stability of benzene is not unusual at all: it is what one would expect of a hybrid of equivalent structures. The 36 kcal of energy that benzene does not contain—compared with cyclohexatriene—is resonance energy. It is the 36 kcal of resonance energy that is responsible for the new set of properties we call *aromatic properties*.

Addition reactions convert an alkene into a more stable saturated compound. Hydrogenation of cyclohexene, for example, is accompanied by the evolution of 28.6 kcal; the product lies 28.6 kcal lower than the reactants on the energy scale (Fig. 10.1).

But addition would convert benzene into a *less* stable product by destroying the resonance-stabilized benzene ring system; for example, according to Fig. 10.1 the first stage of hydrogenation of benzene requires 5.6 kcal to convert benzene into the less stable cyclohexadiene. As a consequence, it is easier for reactions of benzene to take an entirely different course, one in which the ring system is retained: *substitution*.

The Molecular Orbital Structure of Benzene

The stucture of benzene can probably be best described by using the molecular-orbital approach. We have already studied with the help of X-ray diffraction measurements that benzene consists of a planar hexagon of six-carbon atoms, having all carbon-carbon bonds equal in length (1·40 Å) and C—C—C bond angles of 120°. each. Therefore, it stands to reason that each of

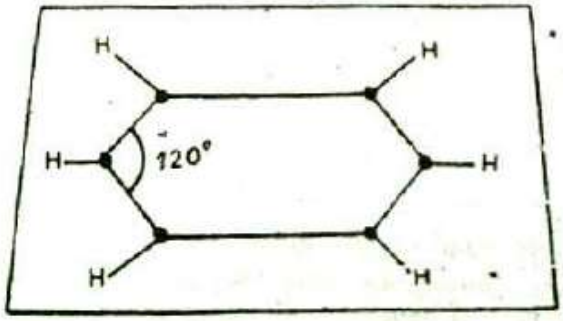


Fig. 35·6. Planar framework of benzene shown by X-ray diffraction measurements, having all C—C bonds of 1·4 Å and bond angles of 120°.

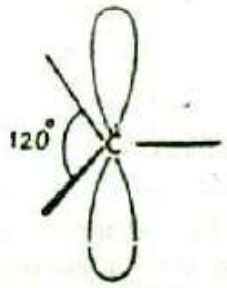


Fig. 35·7. An sp^2 hybridised carbon with sp^2 orbitals shown by lines in one plane and unused half-filled p orbital standing at right angle to the plane.

the six crabon atoms in benzene ring is in a state of sp^2 hybridisation (trigonal hybridisation) as shown in Fig. 35·6. Evidently the ring system is constructed from six sp^2 hybridised carbons,

by the overlapping of the two hybrid orbitals, each to each, to from a σ bond structure. This is a planar hexagon as visualised in Fig. 35·8 given blow.

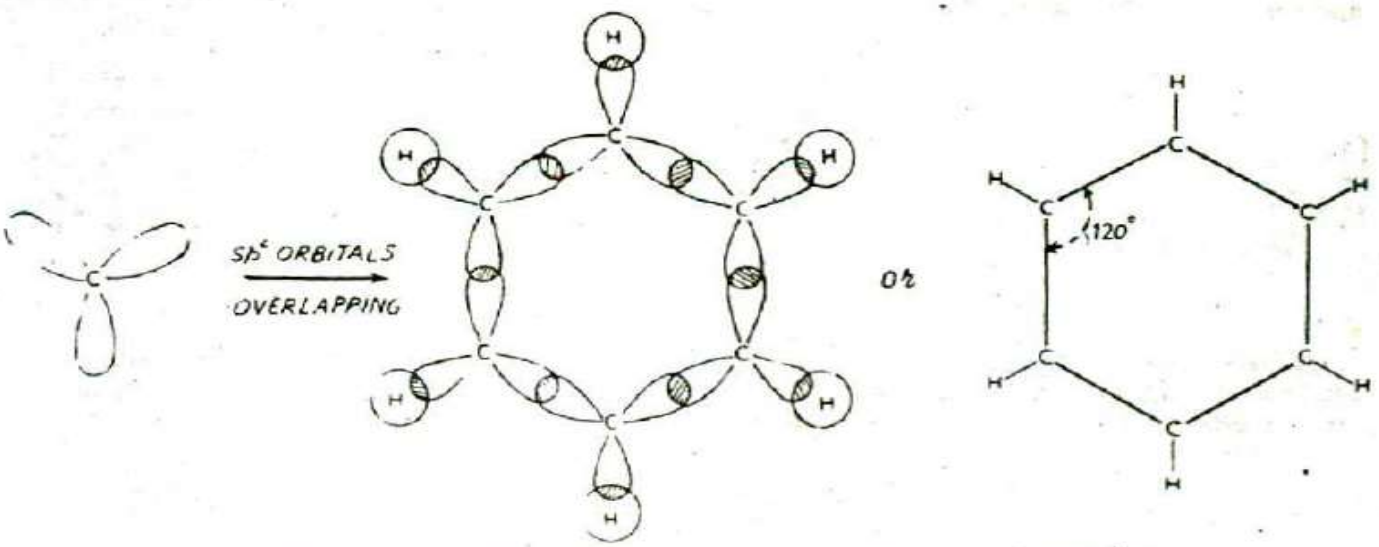


Fig. 35·8. σ-bond structure of benzene, constructed from six sp^2 hybridised carbon atoms ; the in-plane sp^2 orbitals interlocking to form a planar hexagon; the third hybrid orbital of each carbon forming a σ bond with a hydrogen atom.

As shown in Fig. 35·8 each carbon of the planar hexagon will have an unused *p* orbital disposed at right angle to the plane of the hexagon. The *p* orbitals on the six carbon atoms are perfectly aligned for side-side overlap. Since the system is completely symmetrical, the *p* orbitals can overlap equally well with either neighbour to give two molecular orbitals (*a*) and (*b*) analogous to the two classical Kekule structures.

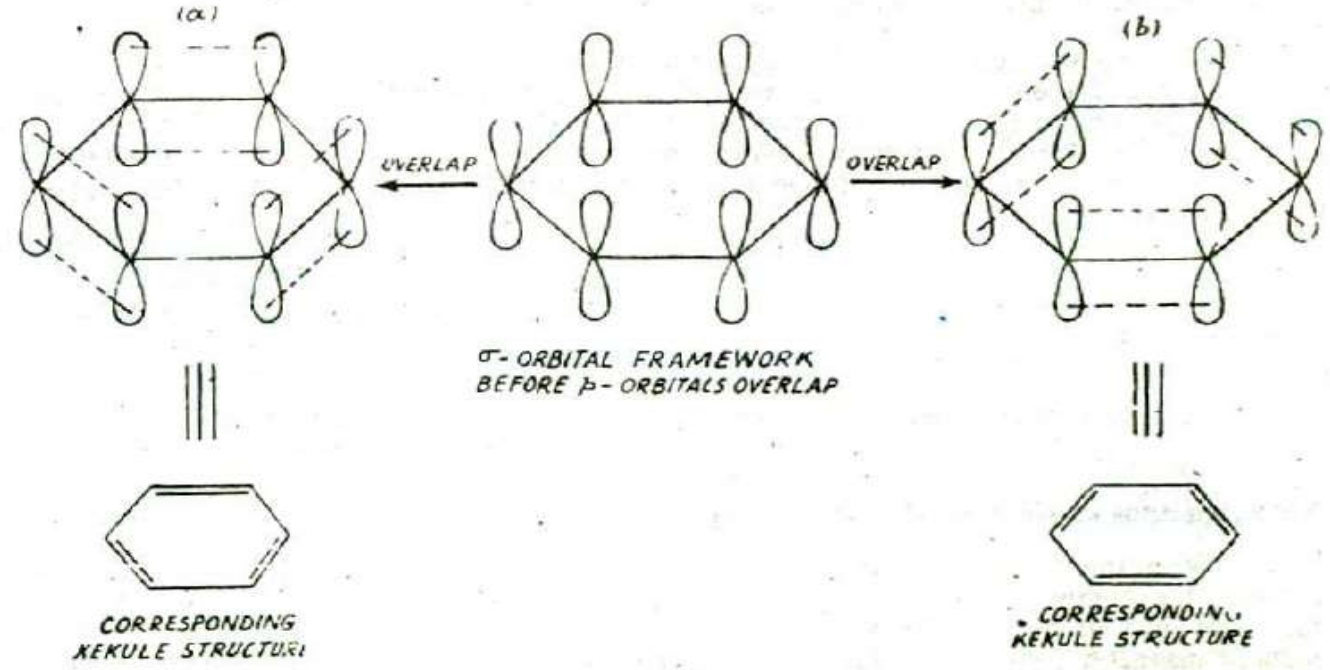
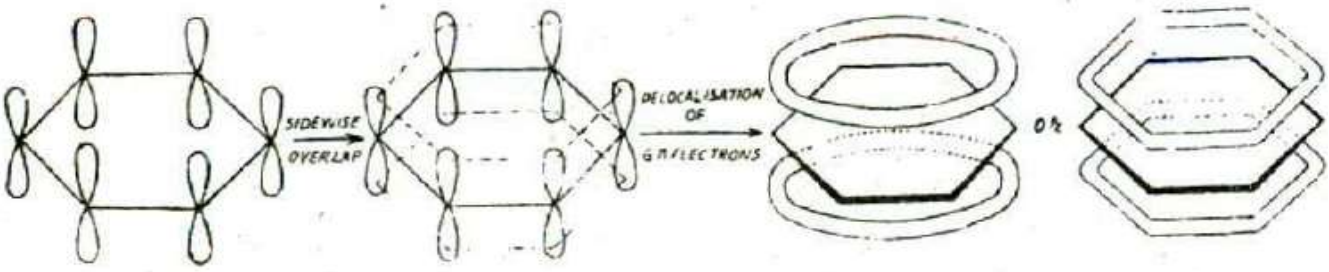


Fig. 35·9

As visualised above, the two Kekule structures correspond to localised π bond formation in one of the two ways as shown in Fig. 35·9. Since internuclear distances between the carbon atoms of the hexagon are equal, there appears to be no good reason why any one particular *p* orbital should overlap in one direction specifically rather than in both directions

Thus each of *p* orbital on the six carbons can overlap on either side with adjacent *p* orbital. There results a molecular orbital which is actually made of two continuous rings, one ring above and one below the plane of hexagon (Fig. 35·10).



Separate *p* orbitals on benzene ring may overlap on either side

The six *p* orbitals are delocalised, the lobes above and below the ring separately.

π molecular orbitals of benzene having a continuous annular cloud, one above and one below the carbon sextet.

Fig.35·10. Formation of continuous π electron annular clouds in benzene molecule.

The π electrons are now said to be completely delocalised and can freely move about the six positive carbon nuclei instead of any two as in Kekule structure. The amount of energy by which the total energy of the system is less than that of the arrangement corresponding to Kekule formula, called the delocalisation or resonance energy, actually accounts for the stability of the benzene ring.

The aromatic hydrocarbons resist addition and oxidation reactions since these destroy the extensive overlap and the stability of the system. The negative π electron clouds of benzene impart to it nucleophilic character. Thus benzene mainly gives electrophilic substitution reactions in which process the aromatic system remains intact.

The ring-like molecular orbital structure or resonance hybrid structure, both give the correct picture of the structure of benzene. Thus benzene is generally represented in a simple way by a regular hexagon with an inscribed circle that symbolises the three delocalised π orbitals or 6π electrons. This is the representation of benzene, which we shall adopt in this text. However, for the purpose of clarity in showing reaction mechanisms Kekule formula is still used.

I. Simplified representation of benzene

Kekule structure equivalent to structure I ; the two canonical forms

AROMATICITY

We have already observed that benzene and numerous other structually related compounds exhibit distinctly different physical and chemical properties as compared to aliphatic compounds. These benzenoid compounds even though highly unsaturated and possessing π bonds, resist addition and oxidation reactions, and instead undergo substitution reactions. While the benzene ring shows unusual stability, a substituent such as Cl, OH or NH_2 directly attached to the ring behaves very differently than the counterparts in the aliphatic series. Thus the term 'aromatic character' or **Aromaticity** was adopted to signify the characteristic physical and chemical behaviour of benzene and the related compounds.

Originally the aromatic character was attributed to the presence of a planar, cyclic conjugated π bond system as in benzene. Thus cyclic polyenes possessing alternate double and single bonds, with a planar carbon skeleton were shown to have aromatic character.

It was Robinson who first pointed out that the presence of alternate double and single bonds conferred *aromaticity* on the benzene ring owing to delocalisation of the six π electrons over the carbon-sextet. Thus the *aromaticity* of benzene was attributed to the six carbon planar hexagon having a sextet of π electrons in a continuous cloud above and below it.

Modern Theory of Aromaticity. The modern theory of aromaticity was advanced by Eric Huckel in 1931. He based it on molecular orbital calculations, extending the scope of the theory to larger or smaller rings than of benzene. The modern theory of aromaticity embraces polynuclear compounds, cyclic ions, and heterocyclic ring systems. The fundamental concepts of this theory are :

I. *The complete delocalisation of π electrons of the ring systems makes them wholly aromatic in character.* As seen in case of benzene, the delocalisation of π electrons is caused by side-side overlapping of available *p* orbitals (each containing one electron) present on the carbons constituting the ring.

II. *The ample delocalisation of the π electrons is possible only if the ring is flat or coplanar, so as to allow cyclic overlap of p orbitals.*

Thus benzene having a coplanar ring is aromatic, while 1, 3, 5, 7-cyclooctatetrene being nonpolar lacks aromaticity.

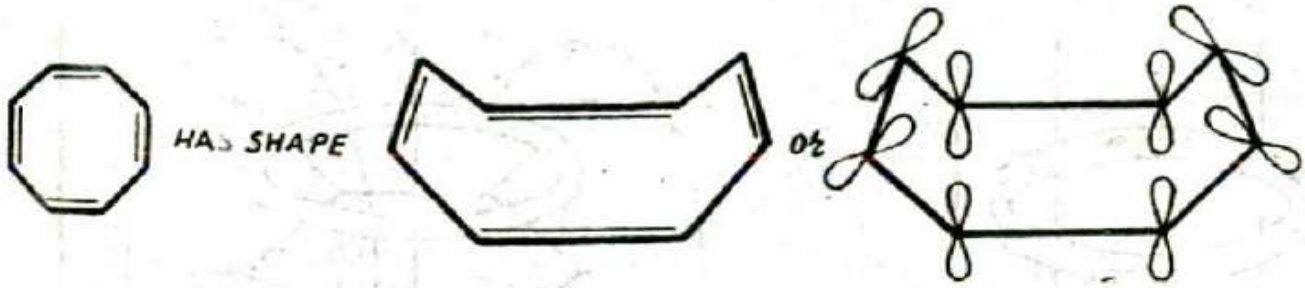
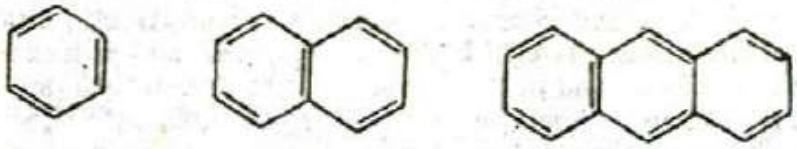


Fig.35·13. Cyclooctatetrene is nonpolar and hence complete side-side overlap is not possible, which makes it non-aromatic

In general five, six and seven carbon-rings being flat show aromatic character.

III. *The bonding orbitals in the conjutated ring system should be completely filled.* This requirement can be predicted by **Huckel Rule** or **4n+2 Rule.** According to this rule, in a cyclic system of overlapping *p* orbitals if the number of π electrons is $4n+2$, the system will have aromatic character, otherwise not. Here $n=0, 1, 2, 3$ etc. Thus :

(*a*) benzene, naphthalene and anthracene containing 6, 10 and 14 π electrons respectively satisfy Huckel Rule and are aromatic.

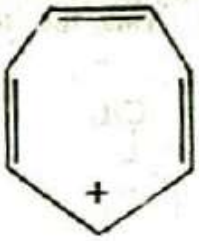


benzene	naphthalene	anthracene
6 π electrons	10π electrons	14π electrons
(n=1 ; 4×1+2=6)	(n=2 ; 4×2+2=10)	(n=3 ; 4×3+2=14)
4n+2 rule satisfied	4n+2 rule satisfied	4n+2 rule satisfied
AROMATIC	AROMATIC	AROMATIC

(*b*) 1, 3-cyclobutadiene and 1, 3, 5, 7-cyclooctatetrene containing 4π electrons and 8π electrons respectively do not satisfy Huckel Rule and are nonaromatic.

1, 3-cyclobutadiene	1, 3, 5, 7-cyclooctatetrene
4π electrons	8π electrons
(4n+2 rule not satisfied)	(4n+2 rule not satisfied)
NONAROMATIC	NONAROMATIC

IV. *The cyclic systems formed by loss of a proton, which are ionic in character that obey Huckel Rule also exhibit aromaticity.* Thus cycloheptatrienyl (tropylium) cation, and cyclopentadienyl anion, both having 6π electrons ($n=1$), are aromatic. Even the cyclopropenyl cation which has 2π electrons ($n=0$) displays armoaticity.



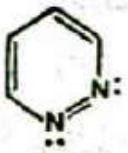
cycloheptatrienyl cation
6π electrons
(n=1 ; 4×1+2=6)
AROMATIC

cyclopentadienyl anion
6π electrons
(n=1 ; 4×1+2=6)
AROMATIC

cyclopropenyl cation
2π electrons
(n=0 ; 4×0+2=2)
AROMATIC

V. Huckel enlarged the scope of his rule so as to embrace the heterocyclic ring systems as well. Thus for pyridine and pyridiazine, $n=1$. They have six π electrons each and satisfy Huckel rule and are aromatic.

pyridine
(6π electrons)
AROMATIC



pyridiazine
(6π electrons)
AROMATIC

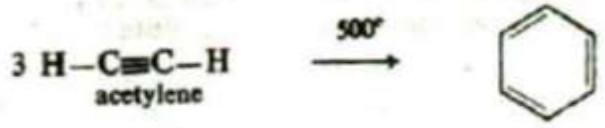
VI. Huckel extended the application of his rule to non-benzenoid heterocyclic aromatic systems also with some modification. Thus for furan, thiophene and pyrrole, $n=1$. Here, the hetero atoms contribute the nonbonded p orbital pair of electrons lying inside the ring which is counted towards deciding the aromaticity of these compounds.

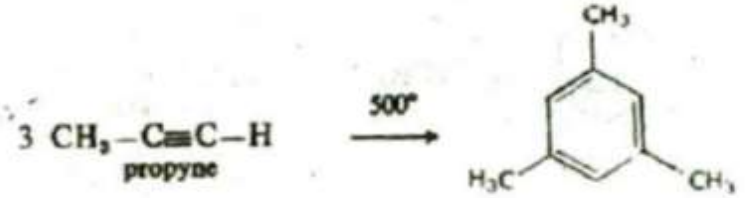
It may be noted that in each of above compounds there are four π electrons and two p electrons on the hetero atom inside the ring. Therefore here the aromaticity is shown by compounds in which π-electron system remains unchanged.

GENERAL SYNTHETIC METHODS OF PREPARATION

While benzene and its homologues are mostly obtained by distillation of coal-tar or from the petroleum fraction, the general methods for their synthesis are listed below. However, these methods are not widely used.

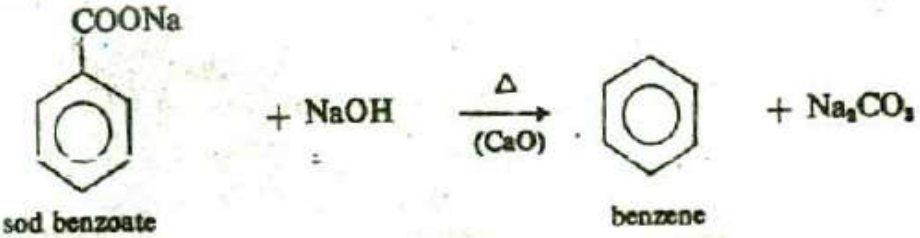
(1) **From Alkynes.** Benzene and many of its homologues can be prepared by polymerisation of appropriate alkynes. Acetylenes will polymerise at high temperature to yield arenes. Thus,



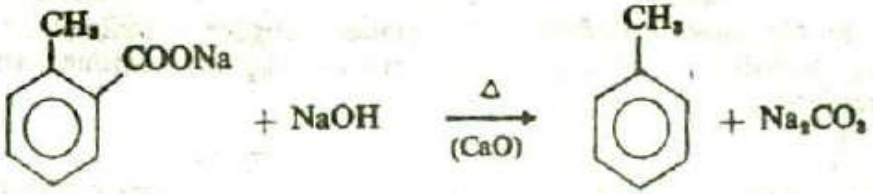


mesitylene

(2) **Decarboxylation of Aromatic acids.** Arenes can be prepared by heating aromatic acids or their sodium salts with sodalime.

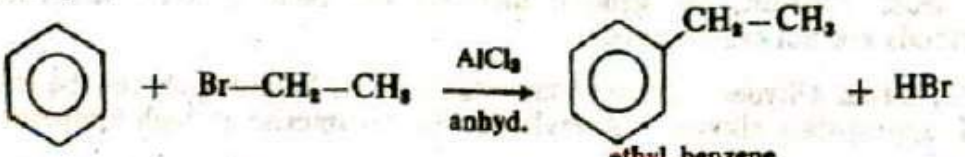


sod benzoate — benzene



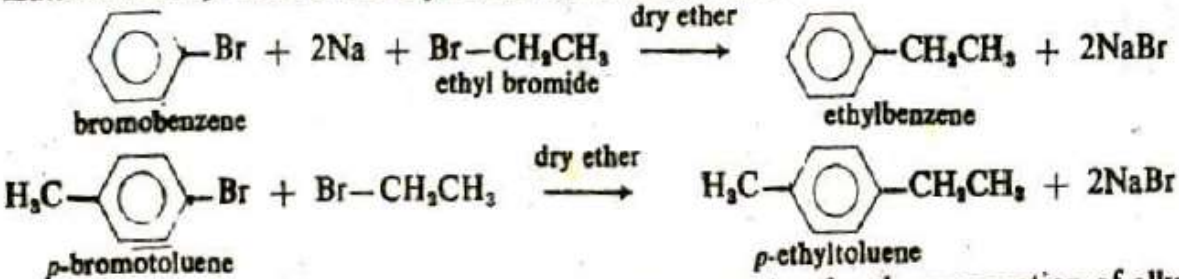
sod toluate — toluene

(3) **By Friedel-Crafts Reaction.** Alkylbenzenes can be best prepared by the action of alkyl halides on benzene and its homologues in the presence of anhydrous aluminium chloride as catalyst. For example,



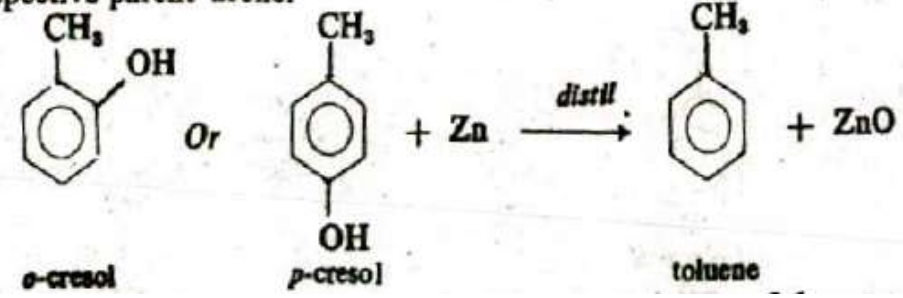
ethyl benzene

(4) **By Wurtz-Fitting Reaction.** Arenes con be obtained by the action of sodium metal on a mixture of alkyl halide and aryl halide in ether solution.



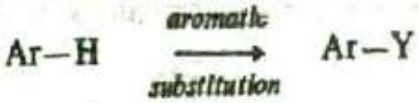
This method is, in fact, an extension of Wurtz reaction for the preparation of alkanes. It may be noted that in the reaction cited above from bromobenzene, diphenyl ($C_6H_5—C_6H_5$), and *n*-butane ($CH_3CH_2CH_2CH_3$) are also formed, but these can be easily separated by distillation because of their widely different boiling points.

(5) **By Deoxygenation of Phenols.** When distilled with zinc dust, phenols are deoxygenated to yield the respective parent arene.

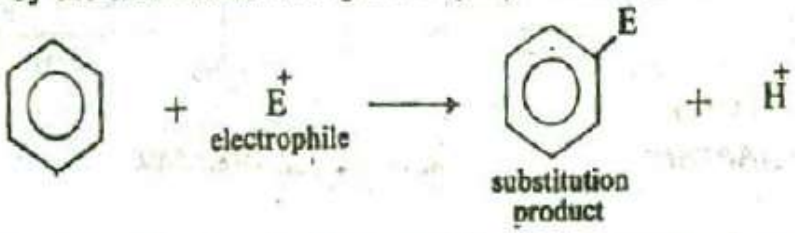


REACTIONS OF BENZENE

By far the most characteristic and useful reactions of arenes are those in which a hydrogen of the aromatic ring is substituted by an atom or group Y.



Such aromatic substitution reactions are, in fact, initiated by the attack of an electrophile (E^+) on the ring followed by the elimination of a proton (H^+). Thus,



The substitution reactions of aromatic ring caused by the presence of an active spieces, the electrophile (E^+), are commonly referred to as the **Electrophilic Substitution Reactions.**

GENERAL MECHANISM OF ELECTROPHILIC SUBSTITUTION

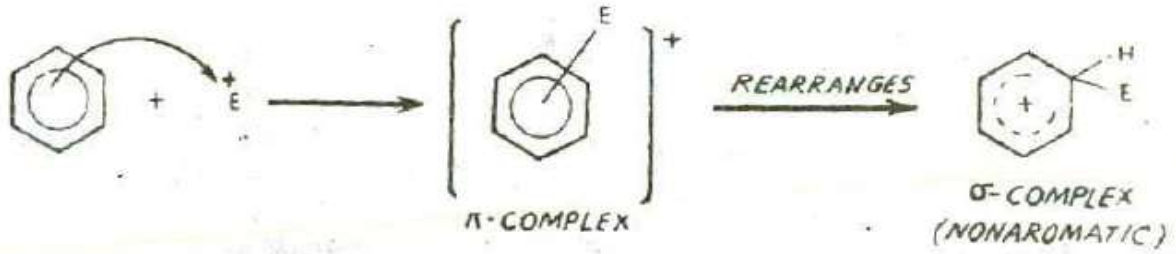
The benzene ring with its π electrons behaves as an electron-rich system. The electrons in the π clouds are readily available to form new bonds with electron-deficient spieces, the electrophile (E^+). The various electrophilic substitution reactions follow the same mechanistic pathway.

STEP 1. Generation of electrophiles either by *spontaneous dissociation* of the reagent (E—Nu) or by *acid-catalysed dissociation.*

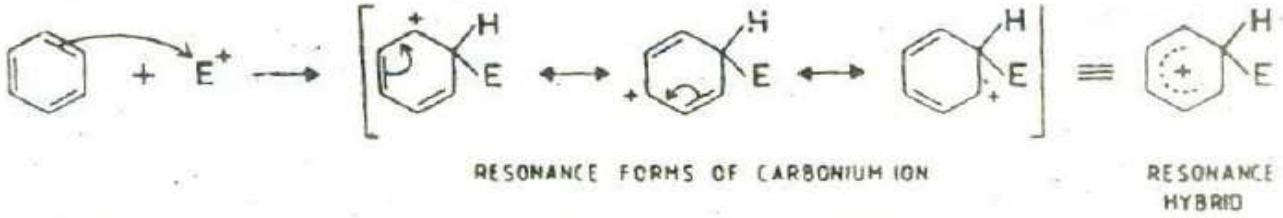
$$E{-}Nu \rightleftharpoons E^+ + Nu^- \qquad \text{(spontaneous dissociation)}$$

$$E{-}Nu + \underset{\text{(Lewis acid)}}{A} \rightleftharpoons E{-}\overset{+}{N}u{-}\bar{A} \rightleftharpoons E^+ + Nu{-}\bar{A} \qquad \text{(acid-catalysed dissociation)}$$

STEP 2. Formation of π-complex due to a loose association of the electrophile (E^+) with the aromatic ring. In this π-complex, the electrophile is not attached to any specific position of the ring, but later arranges to give the σ-complex.

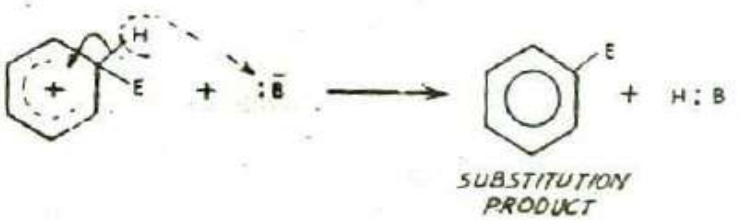


In fact the σ-complex is a resonance-stabilised carbonium ion produced by the attack of the electrophile on the benzene ring.

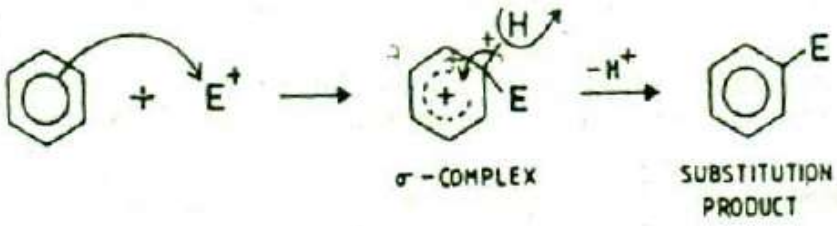


In the mechanism of the reactions that we will consider in this chapter, formation of the π-complex will be omitted for brevity. We will, therefore, write this step as

STEP 3. A proton (H^+) is then eliminated from the σ-complex by a base ($:\bar{B}$) to yield the final substitution product.

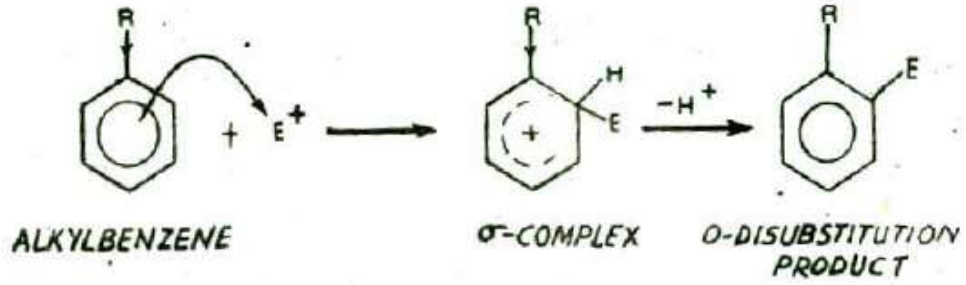


The *Overall Mechanism* of aromatic electrophilic substitution, putting the steps (2) and (3) together may be stated as

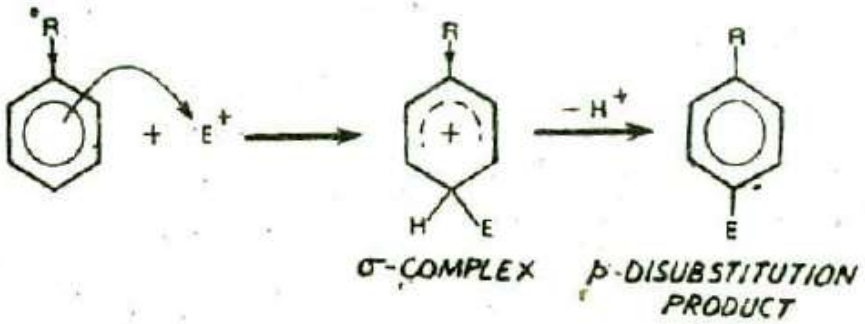


Alkyl benzenes, like benzene, undergo typical electrophilic substitution reactions. As the alkyl groups are electron-pumping in nature, the electron density of π ring system increases in ortho and para positions. Thus the substitution reactions in alkylbenzenes proceed more readily than in benzene itself, and in ortho and para positions. The reaction mechanism is the same as already described for benzene.

Ortho-attack by E^+:

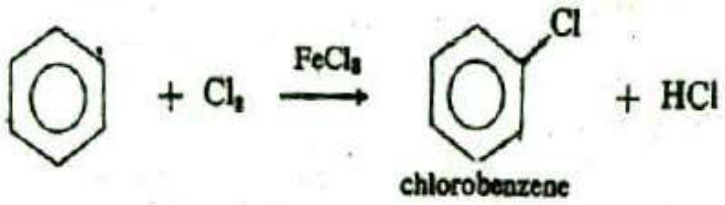


Para-attack by E^+:

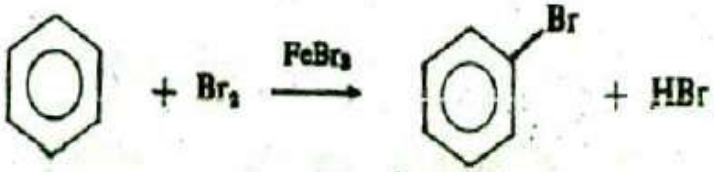


A. ELECTROPHILIC SUBSTITUTION REACTIONS OF ARENES

(1) **Halogenation.** (*a*) Benzene reacts with chlorine or bromine in the presence of a Lewis acid catalyst such as $AlCl_3$, $FeCl_3$ or $FeBr_3$ when substitution in the ring takes place, a proton being lost as HCl or HBr.

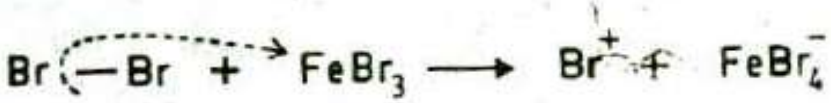


chlorobenzene



bromobenzene

MECHANISM. (*i*) Generation of the electrophile Br^+



(*ii*) Formation of σ-complex

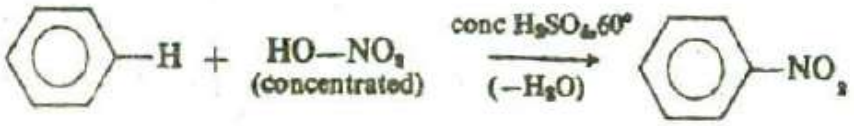
σ-COMPLEX

(*iii*) Elimination of a proton

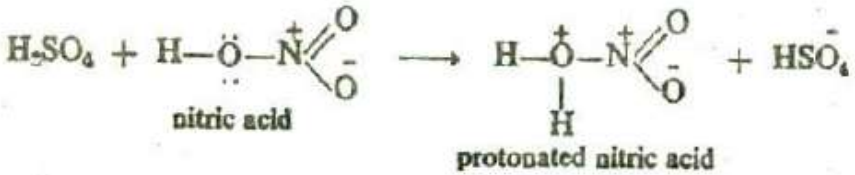
σ-COMPLEX

BROMOBENZENE

(2) **Nitration.** (*a*) Benzene reacts with nitric acid in presence of sulphuric acid to form nitrobenzene



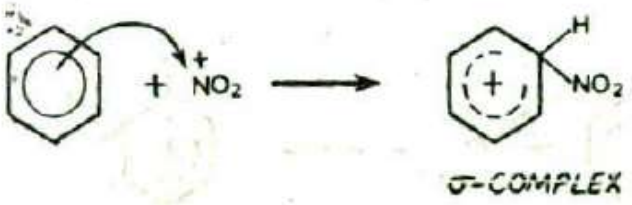
MECHANISM. (*i*) Generation of the electrophile nitronium ion by the protonation of concentrated nitric acid by sulphuric acid.



The overall reaction is :

$$HNO_3 + H_2SO_4 \longrightarrow \underset{\text{electrophile}}{NO_2^+} + HSO_4^- + H_2O$$

(*ii*) **Formation of σ-complex or stable resonance hybrid.**

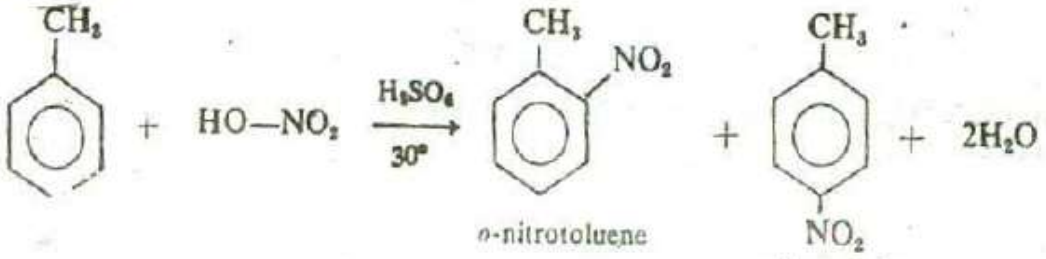


(iii) Elimination of proton from σ-complex

NITROBENZENE

On prolonged treatment with nitrating mixture and at higher temperatures di- and trinitrobenzene can be obtained. The mechanism of the reaction remains the same as described above and the incoming nitro group occupies the meta position relative to the previous one.

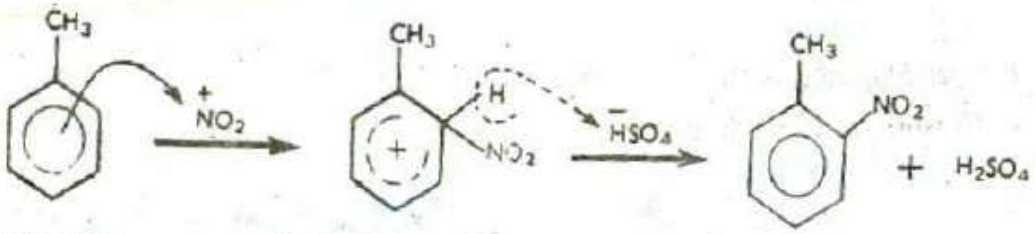
(*b*) Toluene when treated with concentrated nitric acid and sulphuric acid gives *o*- and *p*-nitrotoluene.



o-nitrotoluene

p-nitrotoluene

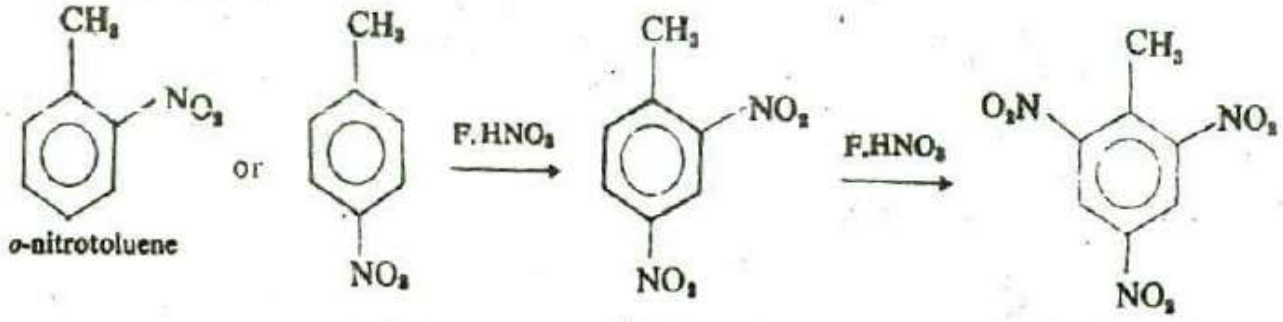
The *Mechanism* of the reaction remains the same as for benzene, except that the electrophile is attached to electron-rich sites (ortho and para).



TOLUENE σ- COMPLEX O-NITROTOLUENE

Nitration of toluene is easier than that of benzene, because CH_3 is an electron-releasing group and makes the π ring system electron-rich

Further nitration of toluene in the presence of fuming nitric acid yields 2, 4, 6-trinitrotoluene (TNT).



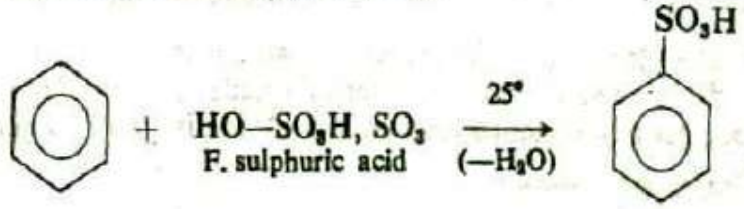
o-nitrotoluene

p-nitrotoluene

2, 4-dinitrotoluene

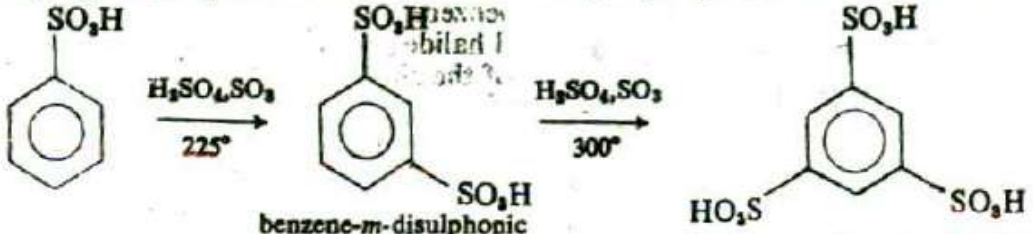
2, 4, 6-trinitrotoluene

(3) **Suiphonation.** (*a*) Benzene may be sulphonated by treating it with concentrated sulphuric acid or fuming sulphuric acid (H_2SO_4,SO_3).



benzenesulphonic acid

By using higher temperatures two or three $-SO_3H$ groups can be introduced in the ring.



benzene-*m*-disulphonic acid

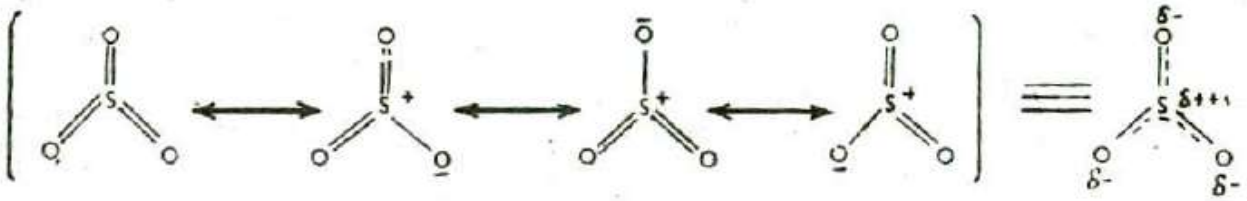
benzene-1, 3, 5-trisulphonic acid

MECHANISM. Sulphonation of benzene to give benzenesulphonic acid follows the steps :

(*i*) Generation of the electrophile

$$2H_2SO_4 \rightleftharpoons H_3O^+ + HSO_4^- + SO_3$$

Although SO_3 is a neutral molecule, its sulphur atom carries a positive charge due to resonance of the molecule.

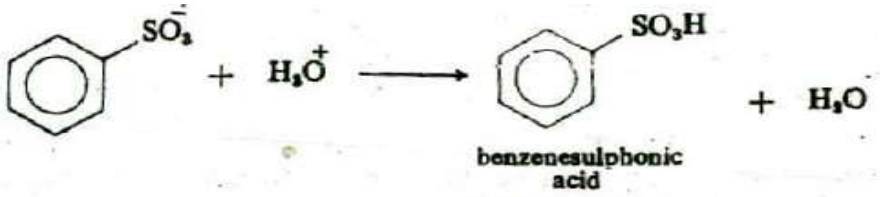


Therefore SO_3 acts as an electrophile.

(*ii*) Formation of σ-complex

σ—Complex

(*iii*) Elimination of proton (H^+)



benzenesulphonic acid

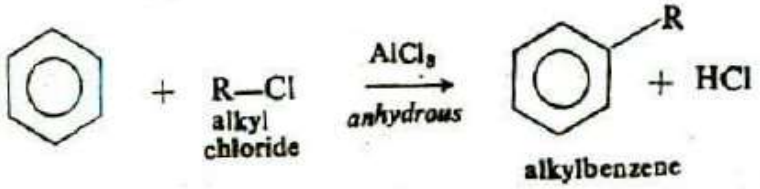
The similar mechanisms apply to *di-* and *tri-*sulphonation.

(4) Friedel-Crafts Reaction. This reaction, which now occupies prestigious positic organic synthesis, was discovered in 1877 by Charles Friedel and M. Crafts. Since then the of the reaction has been greatly widened and we can divide it into two general types

(*a*) *Friedel-Crafts Alkylation* ;

and (*b*) *Friedel-Crafts Acylation*.

Friedel-Crafts Alkylation. This reaction involves the introduction of an alkyl group in the benzene ring for the synthesis of alkylbenzenes which are not ordinarily available. For illustration, when benzene reacts with an alkyl halide (RCl or RBr) in the presence of anhydrous $AlCl_3$ as catalyst, one of the hydrogen atoms of the ring is substituted by the alkyl group R.



alkyl chloride

alkylbenzene

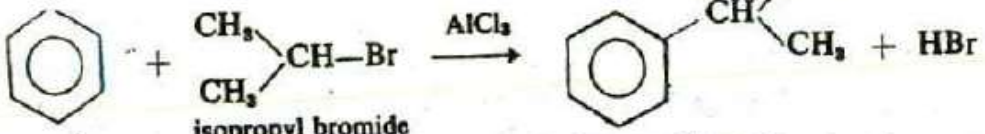
The alkylating agent used in Friedel-Crafts alkylation is an alkyl halide. The catalyst employed is a Lewis acid which may be $AlCl_3$, BF_3, $FeCl_3$, HF etc. Some examples illustrating the reaction to form arenes are :

(*i*)

ethyl chloride

ethylbenzene

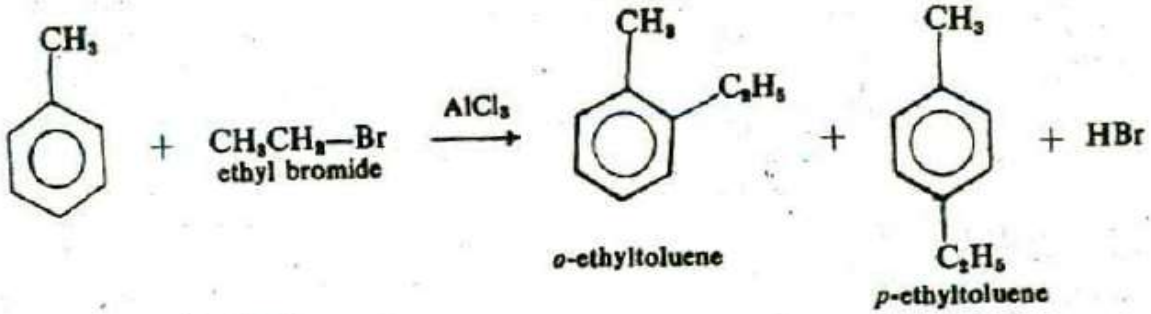
(*ii*)



isopropyl bromide

isopropylbenzene

(*iii*)

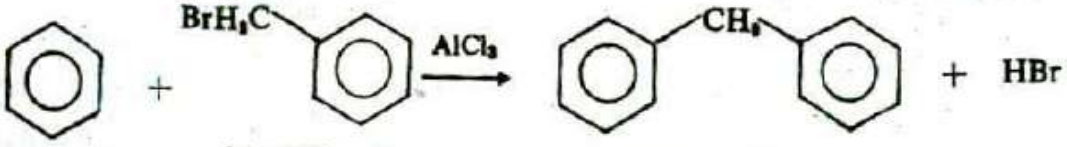


ethyl bromide

o-ethyltoluene

p-ethyltoluene

(*iv*)

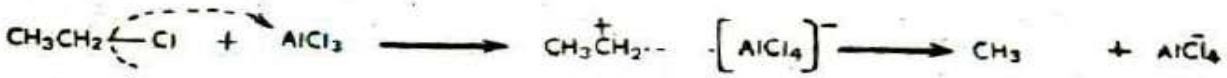


benzyl bromide

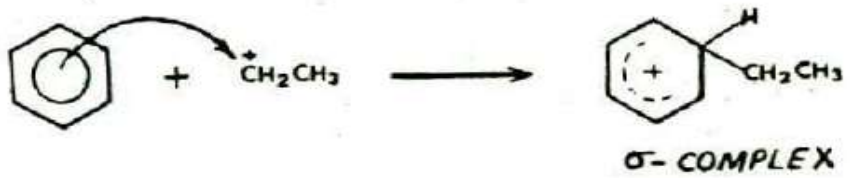
diphenylmethane

MECHANISM. Friedel-Crafts alkylation is an electrophilic substitution reaction and proceeds by the following steps.

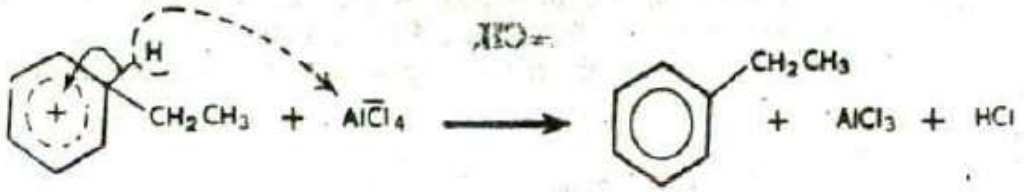
(*i*) Generation of the electrophile which in this case is a carbonium :



(*ii*) Formation of the σ-complex



(*iii*) Elimination of proton (H^+) from σ-complex

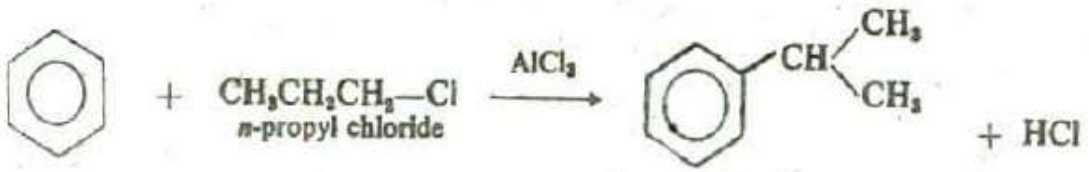


ethylbenzene

Drawbacks of Friedel-Crafts Alkylation

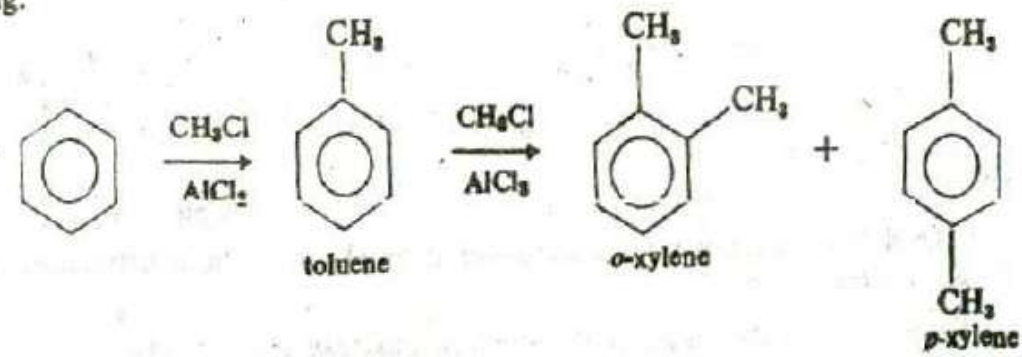
Although, the Friedel-Crafts alkylation reaction is very advantageous for attaching an alkyl group to an aromatic ring, it suffers from the following limitations.

(*i*) *Rearrangement of the Alkyl group.* It is difficult to introduce an alkyl group higher than CH_3CH_2— group as it tends to undergo skeletal rearrangement. For example, alkylation of benzene with *n*-propyl chloride gives isopropylbenzene, and not *n*-propylbenzene.



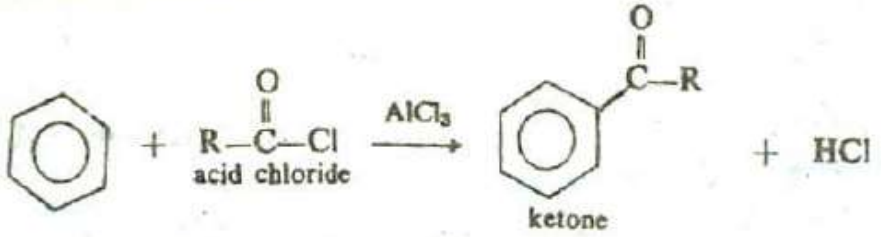
This is due to the fact that *n*-propylcarbonium that results from interaction with $AlCl_3$, undergoes rearrangement to give more stable isopropyl carbonium ion, which electrophile then attacks benzene as usual to form isopropylbenzene.

(*ii*) *Polyalkylation.* The introduction of an alkyl group in benzene activates the ring for further electrophilic substitution. Thus more than one alkyl groups get attached to the aromatic ring.

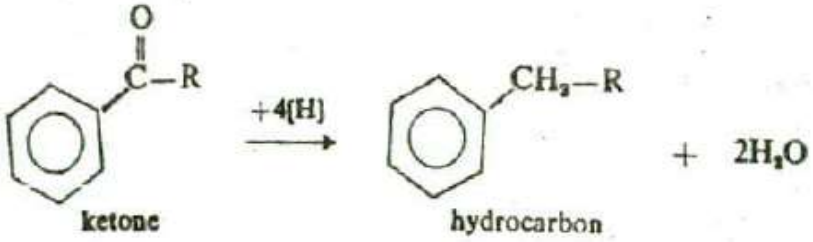


(*iii*) *Hindrance due to meta orienting groups.* The presence of a meta-orienting group in the aromatic ring hinders the Friedel-Crafts alkylation as such a group lowers the electron-density in the ring. Thus nitrobenzene does not respond to Friedel-Crafts reaction.

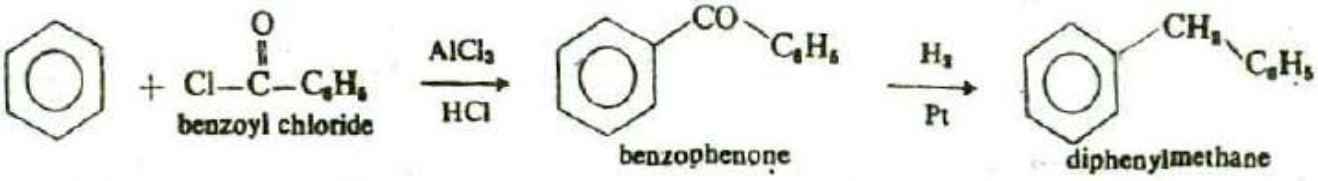
Friedel-Crafts Acylation. This reaction involves the introduction of an acyl group (RCO—) in the aromatic ring in the presence of anhydrous $AlCl_3$ (or other Lewis acid catalysts : BF_3, $FeCl_3$, $ZnCl_2$). The acylating agents employed are acid chlorides, acid anhydrides and esters.



Friedel-Crafts Acylation reaction can be used in preference to the Friedel-Crafts alkylation as it is free from the two chief drawbacks of the latter : skeletal rearrangement and poly-substitution. The ketone obtained can be conveniently reduced to give the required hydrocarbon.

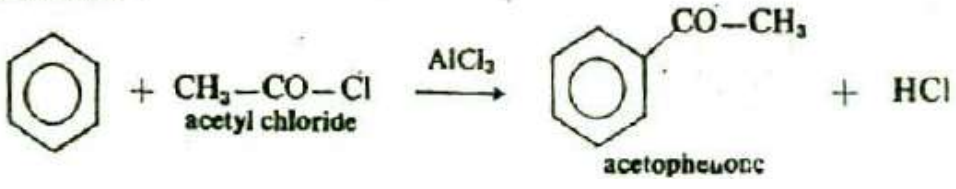


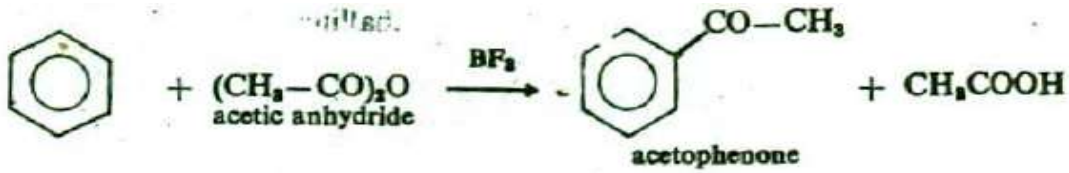
For example,



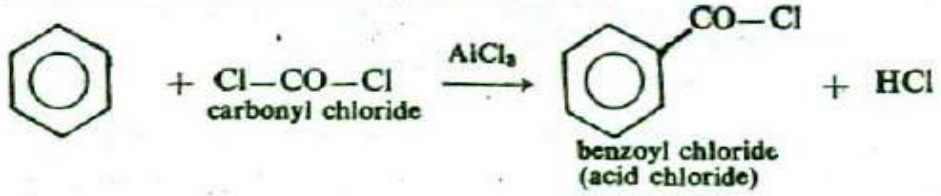
Some examples indicating the synthetic applications of Fridel-Crafts Acylation reaction are listed below.

(*i*) ***Synthesis of Ketones*** :





(*ii*) ***Synthesis of Acid chlorides and Carboxylic acids.***

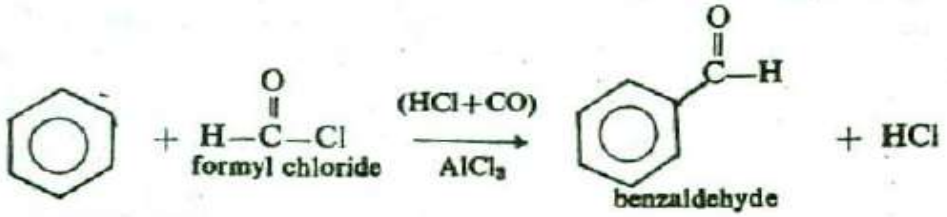


The acid chloride upon hydrolysis would yield the corresponding carboxylic acid.

$$\underset{\text{benzoyl chloride}}{C_6H_5—CO—Cl} + H_2O \longrightarrow \underset{\text{benzoic acid}}{C_6H_5—CO—OH} + HCl$$

(*iii*) *Synthesis of* ***Aldehydes*** (***Formylation***)

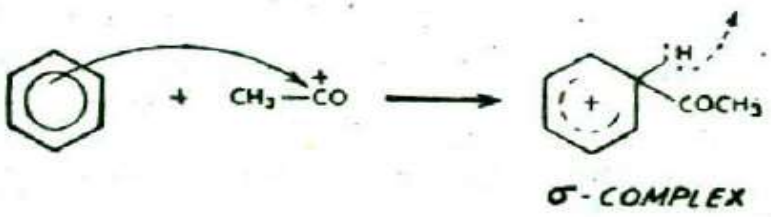
Here the arene is treated with hydrogen chloride and carbon monoxide in the presence of $AlCl_3$, when formylation occurs.



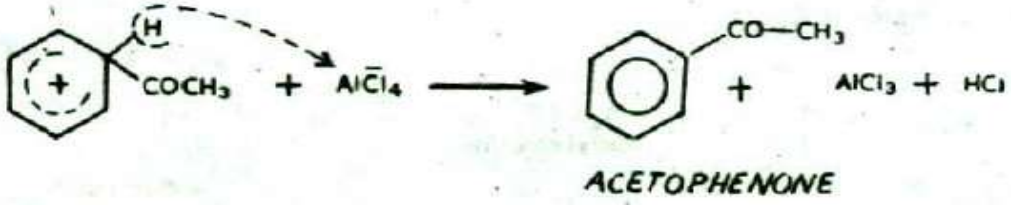
MECHANISM. Friedel-Crafts acylation is an electrophilic substitution reaction and follows the pathway sketched below.

(*i*) Generation of electrophile which is an acylium ion

(*ii*) Formation of σ-complex

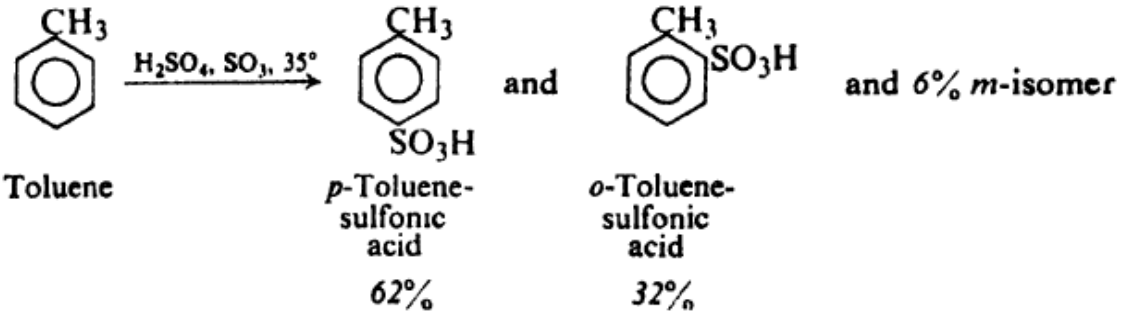


(*iii*) Elimination of proton ($\overset{+}{H}$)



Effect of substituent groups

Like benzene, toluene undergoes electrophilic aromatic substitution: sulfonation, for example. Although there are three possible monosulfonation products, this reaction actually yields appreciable amounts of only two of them: the *o*- and *p*-isomers.



Benzene and toluene are insoluble in sulfuric acid, whereas the sulfonic acids are readily soluble; completion of reaction is indicated simply by disappearance of the hydrocarbon layer. When shaken with fuming sulfuric acid at room temperature, benzene reacts completely within 20 to 30 minutes, whereas toluene is found to react within only a minute or two.

Studies of nitration, halogenation, and Friedel-Crafts alkylation of toluene give analogous results. In some way the methyl group makes the ring more reactive than unsubstituted benzene, and *directs* the attacking reagent to the *ortho* and *para* positions of the ring.

On the other hand, nitrobenzene, to take a different example, has been found to undergo substitution more slowly than benzene, and to yield chiefly the *meta isomer*.

Like methyl or nitro, any group attached to a benzene ring affects the **reactivity** of the ring and determines the **orientation** of substitution. When an electrophilic reagent attacks an aromatic ring, it is the group already attached to the ring that determines *how readily* the attack occurs and *where* it occurs.

A group that makes the ring more reactive than benzene is called an **activating group.** A group that makes the ring less reactive than benzene is called a **deactivating group.**

A group that causes attack to occur chiefly at positions **ortho** and **para** to it is called an **ortho,para director.** A group that causes attack to occur chiefly at positions **meta** to it is called a **meta director.**

In this chapter we shall examine the methods that are used to measure these effects on reactivity and orientation, the results of these measurements, and a theory that accounts for these results. The theory is, of course, based on the most likely mechanism for electrophilic aromatic substitution; we shall see what this mechanism is, and some of the evidence supporting it. First let us look at the facts.

Determination of orientation

To determine the effect of a group on orientation is, in principle, quite simple: the compound containing this group attached to benzene is allowed to undergo substitution and the product is analyzed for the proportions of the three isomers. Identification of each isomer as *ortho*, *meta*, or *para* generally involves comparison with an authentic sample of that isomer prepared by some other method from a compound whose structure is known. In the last analysis, of course, all these identifications go back to absolute determinations of the Körner type (Problem 10.8, p. 332).

In this way it has been found that every group can be put into one of two classes: *ortho,para* directors or *meta* directors. Table 11.1 summarizes the orientation of nitration in a number of substituted benzenes. Of the five positions open to attack, three (60%) are *ortho* and *para* to the substituent group, and two (40%) are *meta* to the group; if there were no selectivity in the substitution reaction, we

Table 11.1 ORIENTATION OF NITRATION OF C_6H_5Y

Y	*Ortho*	*Para*	*Ortho* plus *para*	*Meta*
—OH	50–55	45–50	100	trace
—$NHCOCH_3$	19	79	98	2
—CH_3	58	38	96	4
—F	12	88	100	trace
—Cl	30	70	100	trace
—Br	37	62	99	1
—I	38	60	98	2
—NO_2	6.4	0.3	6.7	93.3
—$N(CH_3)_3^+$	0	11	11	89
—CN	—	—	19	81
—COOH	19	1	20	80
—SO_3H	21	7	28	72
—CHO	—	—	28	72

would expect the *ortho* and *para* isomers to make up 60% of the product, and the *meta* isomer to make up 40%. We see that seven of the groups direct 96–100% of nitration to the *ortho* and *para* positions; the other six direct 72–94% to the *meta* positions.

A given group causes the same general kind of orientation—predominantly *ortho,para* or predominantly *meta*—whatever the electrophilic reagent involved. The actual distribution of isomers may vary, however, from reaction to reaction. In Table 11.2, for example, compare the distribution of isomers obtained from toluene by sulfonation or bromination with that obtained by nitration.

Table 11.2 ORIENTATION OF SUBSTITUTION IN TOLUENE

	Ortho	*Meta*	*Para*
Nitration	58	4	38
Sulfonation	32	6	62
Bromination	33	—	67

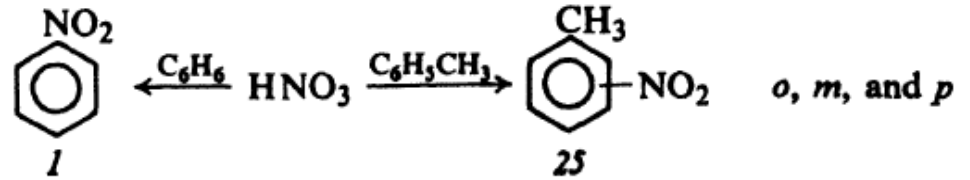
Determination of relative reactivity

A group is classified as *activating* if the ring it is attached to is more reactive than benzene, and is classified as *deactivating* if the ring it is attached to is less reactive than benzene. The reactivities of benzene and a substituted benzene are compared in one of the following ways.

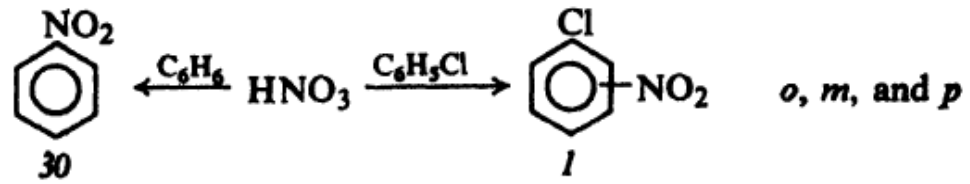
The **time required** for reactions to occur under identical conditions can be measured. Thus, as we just saw, toluene is found to react with fuming sulfuric acid in about one-tenth to one-twentieth the time required by benzene. Toluene is more reactive than benzene, and $-CH_3$ is therefore an activating group.

The **severity of conditions** required for comparable reaction to occur within the same period of time can be observed. For example, benzene is nitrated in less than an hour at 60° by a mixture of concentrated sulfuric acid and concentrated nitric acid; comparable nitration of nitrobenzene requires treatment at 90° with fuming nitric acid and concentrated sulfuric acid. Nitrobenzene is evidently less reactive than benzene, and the nitro group, $-NO_2$, is a deactivating group.

For an exact, quantitative comparison under identical reaction conditions, **competitive reactions** can be carried out, in which the compounds to be compared are allowed to compete for a limited amount of a reagent (Sec. 3.22). For example, if equimolar amounts of benzene and toluene are treated with a small amount of nitric acid (in a solvent like nitromethane or acetic acid, which will dissolve both



1 *25*



30 *1*

organic and inorganic reactants), about 25 times as much nitrotoluene as nitrobenzene is obtained, showing that toluene is 25 times as reactive as benzene. On the other hand, a mixture of benzene and chlorobenzene yields a product in which nitrobenzene exceeds the nitrochlorobenzenes by 30:1, showing that chlorobenzene is only one-thirtieth as reactive as benzene. The chloro group is therefore classified as deactivating, the methyl group as activating. The activation or deactivation caused by some groups is extremely powerful: aniline, $C_6H_5NH_2$, is roughly one million times as reactive as benzene, and nitrobenzene, $C_6H_5NO_2$, is roughly one-millionth as reactive as benzene.

Classification of substituent groups

The methods described in the last two sections have been used to determine the effects of a great number of groups on electrophilic substitution. As shown in Table 11.3, nearly all groups fall into one of two classes: activating and *ortho,para*-directing, or deactivating and *meta*-directing. The halogens are in a class by themselves, being deactivating but *ortho,para*-directing.

Table 11.3 EFFECT OF GROUPS ON ELECTROPHILIC AROMATIC SUBSTITUTION

Activating: *Ortho,para* Directors	**Deactivating: *Meta* Directors**
Strongly activating	$-NO_2$
$-NH_2$ ($-NHR$, $-NR_2$)	$-N(CH_3)_3^+$
$-OH$	$-CN$
	$-COOH$ ($-COOR$)
Moderately activating	$-SO_3H$
$-OCH_3$ ($-OC_2H_5$, etc.)	$-CHO$, $-COR$
$-NHCOCH_3$	
	Deactivating: *Ortho,para* Directors
Weakly activating	$-F$, $-Cl$, $-Br$, $-I$
$-C_6H_5$	
$-CH_3$ ($-C_2H_5$, etc.)	

Just by knowing the effects summarized in these short lists, we can now predict fairly accurately the course of hundreds of aromatic substitution reactions. We now know, for example, that bromination of nitrobenzene will yield chiefly the *m*-isomer and that the reaction will go more slowly than the bromination of benzene itself; indeed, it will probably require severe conditions to go at all. We now know that nitration of $C_6H_5NHCOCH_3$ (*acetanilide*) will yield chiefly the *o*- and *p*-isomers and will take place more rapidly than nitration of benzene.

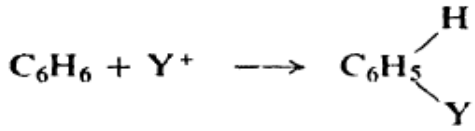
Although, as we shall see, it is possible to account for these effects in a reasonable way, it is necessary for the student to memorize the classifications in Table 11.3 so that he may deal rapidly with synthetic problems involving aromatic compounds.

Reactivity and orientation

We have seen that certain groups activate the benzene ring and direct substitution to *ortho* and *para* positions, and that other groups deactivate the ring and (except halogens) direct substitution to *meta* positions. Let us see if we can account for these effects on the basis of principles we have already learned.

First of all, we must remember that reactivity and orientation are both matters of relative rates of reaction. Methyl is said to activate the ring because it makes the ring react *faster* than benzene; it causes *ortho,para* orientation because it makes the *ortho* and *para* positions react *faster* than the *meta* positions.

Now, we know that, whatever the specific reagent involved, the rate of electrophilic aromatic substitution is determined by the same slow step –attack of the electrophile on the ring to form a carbonium ion:

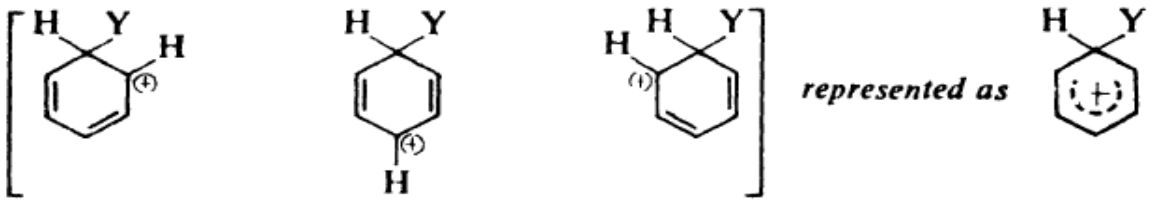


Slow: *rate-determining*

Any differences in rate of substitution must therefore be due to differences in the rate of this step.

For closely related reactions, a difference in rate of formation of carbonium ions is largely determined by a difference in E_{act}, that is, by a difference in stability of transition states. As with other carbonium ion reactions we have studied, factors that stabilize the ion by dispersing the positive charge should for the same reason stabilize the incipient carbonium ion of the transition state. Here again we expect the more stable carbonium ion to be formed more rapidly. We shall therefore concentrate on the relative stabilities of the carbonium ions.

In electrophilic aromatic substitution the intermediate carbonium ion is a hybrid of structures I, II, and III, in which the positive charge is distributed about the ring, being strongest as the positions *ortho* and *para* to the carbon atom being attacked.

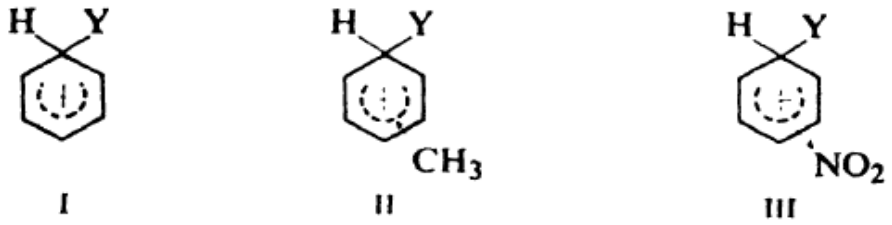


I II III IV

A group already attached to the benzene ring should affect the stability of the carbonium ion by dispersing or intensifying the positive charge, depending upon its electron-releasing or electron-withdrawing nature. It is evident from the structure of the ion (I–III) that this stabilizing or destabilizing effect should be especially important when the group is attached *ortho* or *para* to the carbon being attacked.

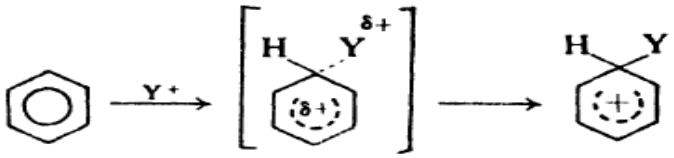
Theory of reactivity

To compare rates of substitution in benzene, toluene, and nitrobenzene, we compare the structures of the carbonium ions formed from the three compounds:



I II III

By releasing electrons, the methyl group (II) tends to neutralize the positive charge of the ring and so become more positive itself; this dispersal of the charge stabilizes the carbonium ion. In the same way the inductive effect stabilizes the developing positive charge in the transition state and thus leads to a faster reaction.



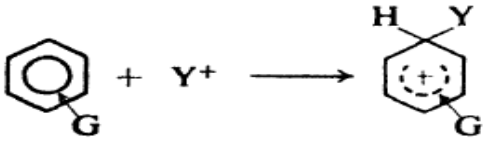
Transition state. *developing positive charge*

Carbonium ion: *full positive charge*

The $-NO_2$ group, on the other hand, has an electron-withdrawing inductive effect (III); this tends to intensify the positive charge, destabilizes the carbonium ion, and thus causes a slower reaction.

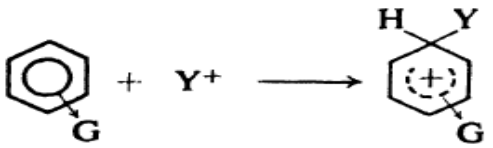
Reactivity in electrophilic aromatic substitution depends, then, upon the tendency of a substituent group to release or withdraw electrons. **A group that releases electrons activates the ring; a group that withdraws electrons deactivates the ring.**

Electrophilic Aromatic Substitution



G releases electrons, stabilizes carbonium ion, activates

G = $-NH_2$, $-OH$, $-OCH_3$, $-NHCOCH_3$, $-C_6H_5$, $-CH_3$



G withdraws electrons · destabilizes carbonium ion, deactivates

G = $-N(CH_3)_3^+$, $-NO_2$, $-CN$, $-SO_3H$, $-COOH$, $-CHO$, $-COR$, $-X$

Like $-CH_3$, other alkyl groups release electrons, and like $-CH_3$ they activate the ring. For example, *tert*-butylbenzene is 16 times as reactive as benzene toward nitration. Electron release by $-NH_2$ and $-OH$, and by their derivatives $-OCH_3$ and $-NHCOCH_3$, is due not to their inductive effect but to resonance, and is discussed later (Sec. 11.20).

We are already familiar with the electron-withdrawing effect of the halogens (Sec. 6.11). The full-fledged positive charge of the $-N(CH_3)_3^+$ group has, of course, a powerful attraction for electrons. In the other deactivating groups (e.g., $-NO_2$, $-CN$, $-COOH$), the atom next to the ring is attached by a multiple bond to oxygen or nitrogen. These electronegative atoms attract the mobile π electrons, making the atom next to the ring electron-deficient; to make up this deficiency, the atom next to the ring withdraws electrons from the ring.

We might expect replacement of hydrogen in $-CH_3$ by halogen to decrease the electron-releasing tendency of the group, and perhaps to convert it into an electron-withdrawing group. This is found to be the case. Toward nitration,

Activating | Weakly deactivating | Moderately deactivating | Strongly deactivating

toluene is 25 times as reactive as benzene; benzyl chloride is only one-third as reactive as benzene. The $-CH_2Cl$ group is thus weakly deactivating. Further replacement of hydrogen by halogen to yield the $-CHCl_2$ and the $-CCl_3$ groups results in stronger deactivation.

11.19 Theory of orientation

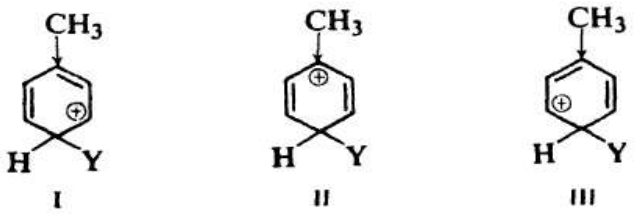
Before we try to account for orientation in electrophilic substitution, let us look more closely at the facts.

An activating group activates all positions of the benzene ring; even the positions *meta* to it are more reactive than any single position in benzene itself. It directs *ortho* and *para* simply because it activates the *ortho* and *para* positions much *more* than it does the *meta*.

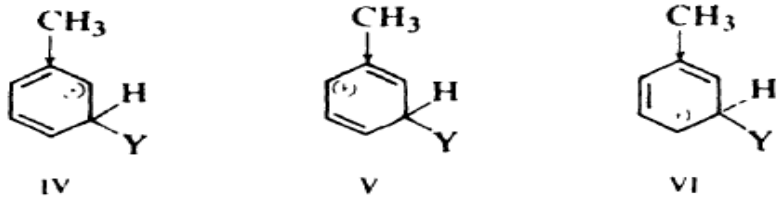
A deactivating group deactivates all positions in the ring, even the positions *meta* to it. It directs *meta* simply because it deactivates the *ortho* and *para* positions even *more* than it does the *meta*.

Thus both *ortho,para* orientation and *meta* orientation arise in the same way: **the effect of any group—whether activating or deactivating—is strongest at the *ortho* and *para* positions.**

To see if this is what we would expect, let us compare, for example, the carbonium ions formed by attack at the *para* and *meta* positions of toluene, a compound that contains an activating group. Each of these is a hybrid of three structures, I–III for *para*, IV–VI for *meta*. In one of these six structures, II, the positive charge is located on the carbon atom to which $-CH_3$ is attached. Although $-CH_3$ releases electrons to all positions of the ring, it does so most strongly to the car-

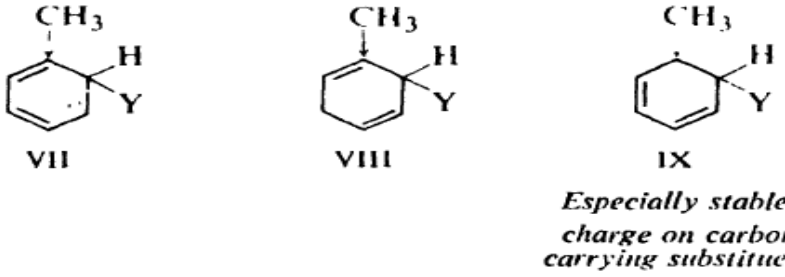


bon atom nearest it; consequently, structure II is a particularly stable one. Because of contribution from structure II, the hybrid carbonium ion resulting from



attack at the *para* position is more stable than the carbonium ion resulting from attack at a *meta* position. *Para* substitution, therefore, occurs faster than *meta* substitution.

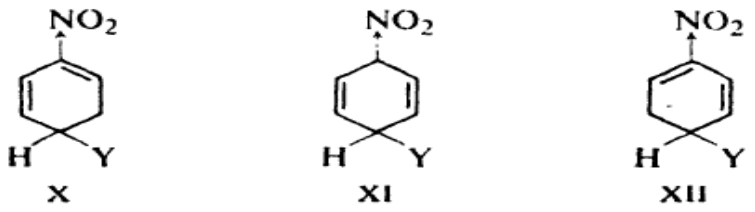
In the same way, it can be seen that attack at an *ortho* position (VII–IX)



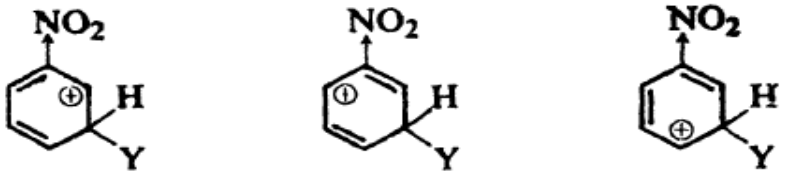
also yields a more stable carbonium ion, through contribution from IX, than attack at a *meta* position.

In toluene, *ortho,para* substitution is thus faster than *meta* substitution because electron release by $-CH_3$ is more effective during attack at the positions *ortho* and *para* to it.

Next, let us compare the carbonium ions formed by attack at the *para* and *meta* positions of nitrobenzene, a compound that contains a deactivating group. Each of these is a hybrid of three structures, X–XII for *para* attack, XIII–XV for *meta* attack. In one of the six structures, XI, the positive charge is located on the



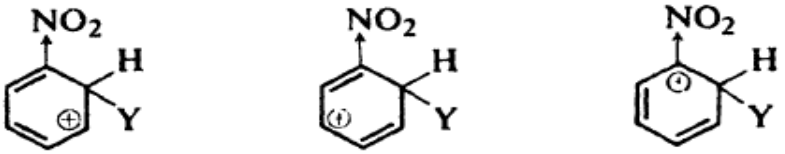
carbon atom to which $-NO_2$ is attached. Although $-NO_2$ withdraws electrons from all positions, it does so most from the carbon atom nearest it, and hence this carbon atom, already positive, has little tendency to accommodate the positive charge of the carbonium ion. Structure XI is thus a particularly unstable one and does little to help stabilize the ion resulting from attack at the *para* position. The ion for *para* attack is virtually a hybrid of only two structures, X and XII; the positive charge is mainly restricted to only *two* carbon atoms. It is less stable than the ion resulting from attack at a *meta* position, which is a hybrid of three structures, and in which the positive charge is accommodated by *three* carbon atoms. *Para* substitution, therefore, occurs more slowly than *meta* substitution.



XIII XIV XV

***Meta* attack**

In the same way it can be seen that attack at an *ortho* position (XVI–XVIII) yields a less stable carbonium ion, because of the instability of XVIII, than attack at a *meta* position.



XVI XVII XVIII

***Ortho* attack**

Especially unstable:
charge on carbon
carrying substituent

In nitrobenzene, *ortho,para* substitution is thus slower than *meta* substitution because electron withdrawal by $-NO_2$ is more effective during attack at the positions *ortho* and *para* to it.

Thus we see that both *ortho,para* orientation by activating groups and *meta* orientation by deactivating groups follow logically from the structure of the intermediate carbonium ion. The charge of the carbonium ion is strongest at the positions *ortho* and *para* to the point of attack, and hence a group attached to one of these positions can exert the strongest effect, whether activating or deactivating.

The unusual behavior of the halogens, which direct *ortho* and *para* although deactivating, results from a combination of two opposing factors, and will be taken up in Sec. 11.21.

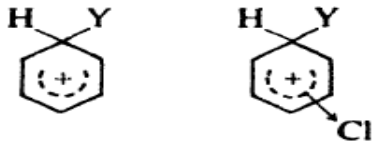
11.21 Effect of halogen on electrophilic aromatic substitution

Halogens are unusual in their effect on electrophilic aromatic substitution: they are deactivating yet *ortho,para*-directing. Deactivation is characteristic of electron withdrawal, whereas *ortho,para* orientation is characteristic of electron release. Can halogen both withdraw and release electrons?

The answer is *yes*. Halogen withdraws electrons through its inductive effect, and releases electrons through its resonance effect. So, presumably, can the $-NH_2$ and —OH groups, but there the much stronger resonance effect greatly

outweighs the other. For halogen, the two effects are more evenly balanced, and we observe the operation of both.

Let us first consider **reactivity**. Electrophilic attack on benzene yields car-

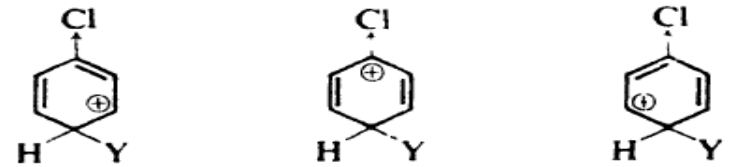


I II

— Cl withdraws electrons: destabilizes carbonium ion, deactivates ring

bonium ion I, attack on chlorobenzene yields carbonium ion II. The electron-withdrawing inductive effect of chlorine intensifies the positive charge in carbonium ion II, makes the ion less stable, and causes a slower reaction.

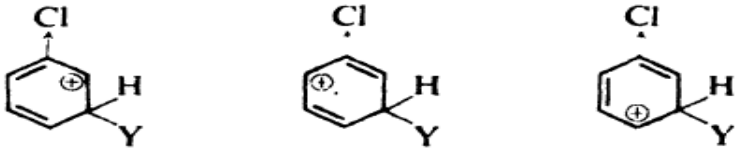
Next, to understand **orientation**, let us compare the structures of the carbonium ions formed by attack at the *para* and *meta* positions of chlorobenzene. Each of



III IV V

***Para* attack**

Especially unstable: charge on carbon bearing substituent

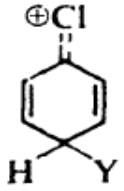


VI VII VIII

***Meta* attack**

these is a hybrid of three structures, III–V for *para*, VI–VIII for *meta*. In one of these six structures, IV, the positive charge is located on the carbon atom to which chlorine is attached. Through its inductive effect chlorine withdraws electrons most from the carbon to which it is joined, and thus makes structure IV especially unstable. As before, we expect IV to make little contribution to the hybrid, which should therefore be less stable than the hybrid ion resulting from attack at the *meta* positions. If only the inductive effect were involved, then, we would expect not only deactivation but also *meta* orientation.

But the existence of halonium ions (Sec. 7.12) has shown us that halogen can share more than a pair of electrons and can accommodate a positive charge. If we apply that idea to the present problem, what do we find? The ion resulting from *para* attack is a hybrid not only of structures III–V, but also of structure IX, in which chlorine bears a positive charge and is joined to the ring by a double bond. This structure should be comparatively stable, since in it every atom (except hydrogen, of course) has a *complete octet of electrons*. (Structure IX is exactly analogous to those proposed to account for activation and *ortho,para* direction by $-NH_2$ and $-OH$.) No such structure is possible for the ion resulting from *meta* attack. To the extent that structure IX contributes to the hybrid, it makes the ion resulting from *para* attack more stable than the ion resulting from *meta* attack.



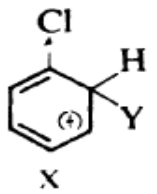
IX

Comparatively stable: every atom has octet

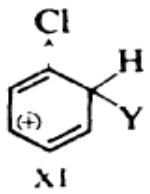
***Para* attack**

Although we could not have predicted the relative importance of the two factors — the instability of IV and the stabilization by IX —the result indicates that the contribution from IX is the more important.

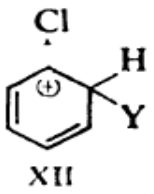
In the same way it can be seen that attack at an *ortho* position also yields an ion (X–XIII) that can be stabilized by accommodation of the positive charge by chlorine.



X

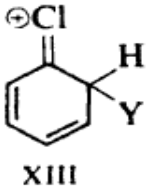


XI



XII

Especially unstable: charge on carbon bearing substituent



XIII

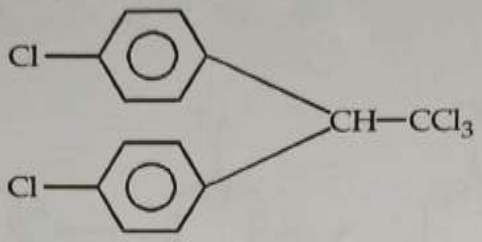
Comparatively stable: every atom has octet

***Ortho* attack**

STRUCTURE AND USES

(1) DDT (DICHLORO DIPHENYL TRICHLORO ETHANE)

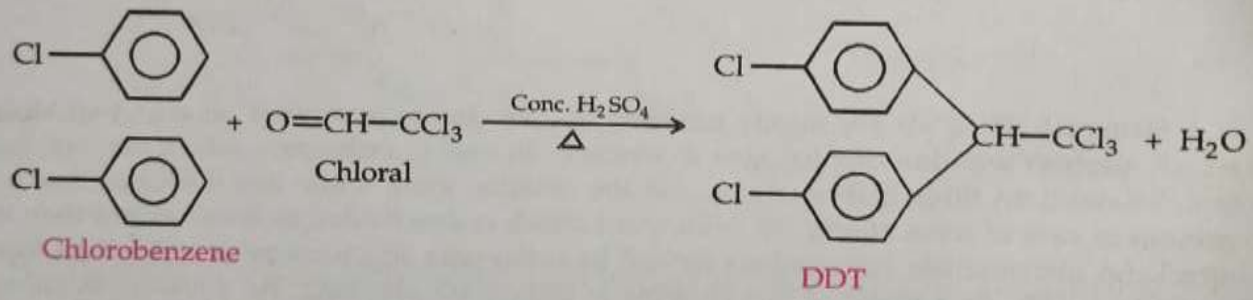
Structure



Its actual name is 2, 2 bis (4-chlorophenyl)-1, 1, 1 trichloroethane. Its molecular formulae is $C_{14}H_9Cl_5$.

Properties : DDT is a colourless, crystalline, tasteless and odourless organochlorine. It is highly hydrophobic and nearly insoluble in water but soluble in most organic solvents, fats & oils. It does not occur naturally.

Method of Preparation : DDT is prepared by heating chlorobenzene with Chloral in presence of conc. H_2SO_4.



Uses of DDT

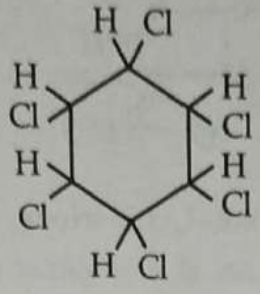
DDT is a powerful insecticide. It is generally used to kill mosquitoes and other insects. It is effective against Anopheles mosquitoes which spread malaria. It is a cheap insecticide.

Side effects

It is non-biodegradable. Its residues gets accumulated in the environment and are toxic to human beings & mammals. It is still widely used due to non-availability of any other cheaper insecticide.

(2) BHC (BENZENE HEXACHLORIDE)

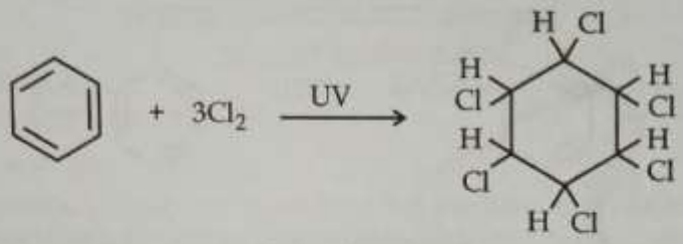
Its IUPAC name is 1, 2, 3, 4, 5, 6 – hexachlorocyclohexane. Its structure is



Its molecular formulae is C_6Cl_6.

Properties : BHC is a white, crystalline solid having no solubility in water and variable solubility in organic solvents. It is mostly soluble in halogenated solvents like chloroform, less soluble in esters and hydrocarbons and very less soluble in short chain alcohols.

Preparation : It is prepared by chlorination of benzene in presence of ultraviolet light.



It occurs in various stereoisomeric forms but γ-isomer is most effective and also known as Lindane.

Uses

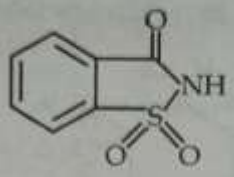
It is used as a pesticide in agriculture. It has been used to treat food crops and to forestry products, as a seed treatment, a soil treatment and to treat livestock and pets. It has also been used as pharmaceutical treatment for lice and scabies and used in the form of shampoos and lotions.

Side effects

It is an animal carcinogen and also considered to be human carcinogen. Because of its used as a fungicide it was found in all food types. It causes increased chances of liver, kidney and thyroid cancers.

3. SACCHARIN

Its structure is

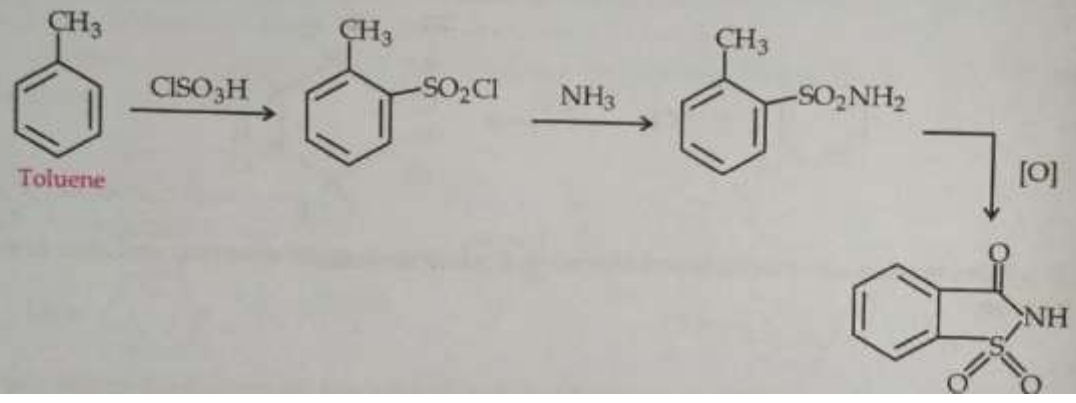


IUPAC name is 2–H, 2–Benzothiazol–1, 1,3–trione. Molecular formulae of saccharin $C_7H_5NO_3S$.

Saccharin is an artificial sweetner about 300-400 time as sweet as sucrose or table sugar. At higher concentration it has bitter or metallic after taste.

Properties : Saccharin is heat stable. It is inert in nature so it does not react chemically with other food ingredients. As such it is water insoluble but its sodium salt is water soluble.

Preparation : It is prepared from toluene.

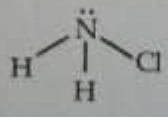


Uses

It is used to sweeten the products such as drinks, medicines, toothpastes etc. It is used in blended form with cyclamate or aspartame in diet carbonated soft drinks. It has no nutritional value it is safe to consume for persons with diabeties. It can help to reduce consumption of sugar.

4. CHLORAMINE

Its molecular formulae is NH_2Cl. It is a derivative of ammonia. Chloramine also refers to a family of organic compounds with formulae R_2NCl and $RNCl_2$. Its structure is



Properties : It is an inorganic compound with formulae NH_2Cl. It is an unstable colourless liquid and its melting point is 66°C. It is generally handled as a dilute aqueous solution. Pure chloramine decomposes violently above –40°C. It is readily soluble in water and ether but less soluble in chloroform and carbon tetrachloride.

Preparation :

It is prepared by the reaction of ammonia with sodium hypochlorite.

$$NH_3 + NaOCl \longrightarrow NH_2Cl + NaOH$$

Uses

It is used as a disinfectant for water as it is less reactive than chlorine and more stable against light than hypochlorites. It is also used as a swimming pool disinfectant. It is responsible for chlorine smell of swimming pool. But exposure to chloramine lead to asthma and other respiratory problems. It is used to improve odour & flavour of water. It can be used as a bleach and as oxidators. It is also used to resist biofouling water systems.