Unit-1

Pharmaceutical Organic-II

UNIT- I **10 Hours**

Benzene and its derivatives

- Analytical, synthetic and other evidences in the derivation of structure of benzene, Orbital picture, resonance in benzene, aromatic characters, Huckel's rule
- Reactions of benzene - nitration, sulphonation, halogenation reactivity, Friedelcrafts alkylation-reactivity, limitations, Friedelcrafts acylation.
- Substituents, effect of substituents on reactivity and orientation of mono substituted benzene compounds towards electrophilic substitution reaction
- Structure and uses of DDT, Saccharin, BHC and Chloramine

Benzene and its derivatives

Organic Compound:

Those chemical compounds which is composed of carbon or which is derivative of carbon is called organic compound.

Eg: CH_4, CO_2, etc.

Classification of Organic Compound:

- Aliphatic Compound (Alkane, Alkene, Alkyne)
- Aromatic Compound (Benzene): Those compound which follow Huckel's rule.

Structure of Benzene:

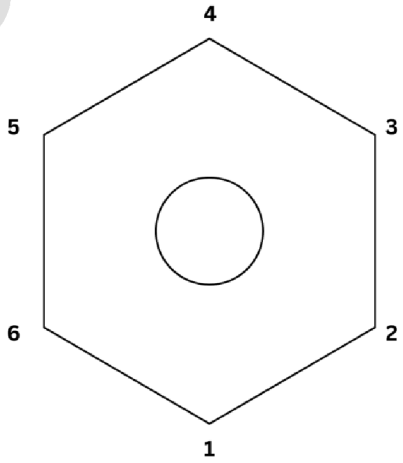
Benzene is a cyclic compound with molecular formula C_6H_6, and molecular weight is 84.

The structure of benzene can be categories into 3 types-

1. Kekule Structure
2. Chemical structure
3. Resonating structure

Kekule structure:

- Kekule explain that those compound in which 1st carbon is attached with last carbon then they form a cyclic structure.
- In the structure of benzene carbon no is attach with carbon no-6 and form a cyclic structure.

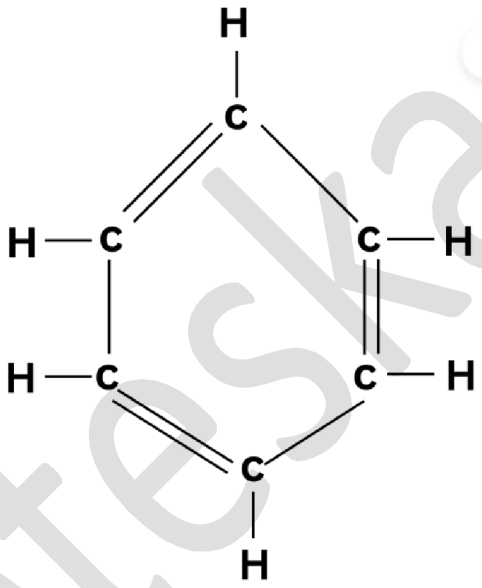


2. Chemical Structure:

- In this Chemical structure of benzene.
- Six carbon and six hydrogen is present. All hydrogen is bonded with carbon by sigma bond.
- In benzene between carbon-carbon sigma bond and Pi bond are attached in alternet position.
- Due to alternet position of sigma and Pi bond benzene show resonance.

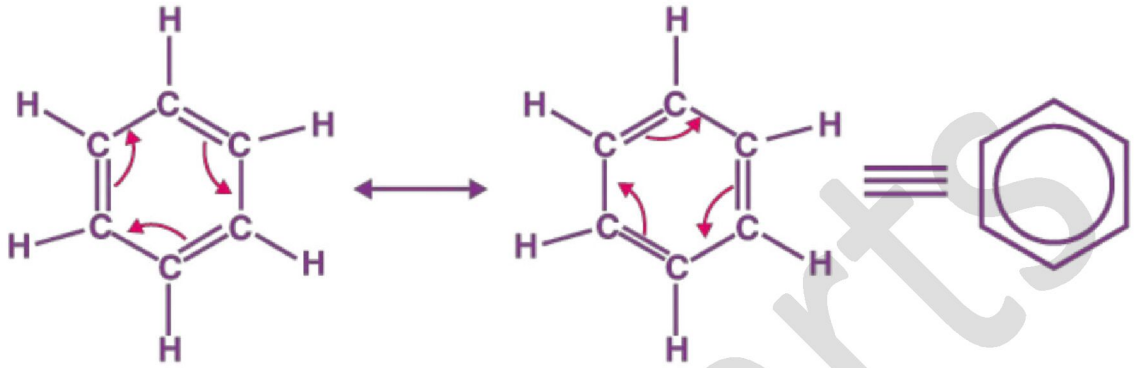
In the structure of benzene 3 type of bond of different bond length is present.

- C-H =1.54 A^o
- C-C = 1.40 A^o
- C=C = 1.34 A^o



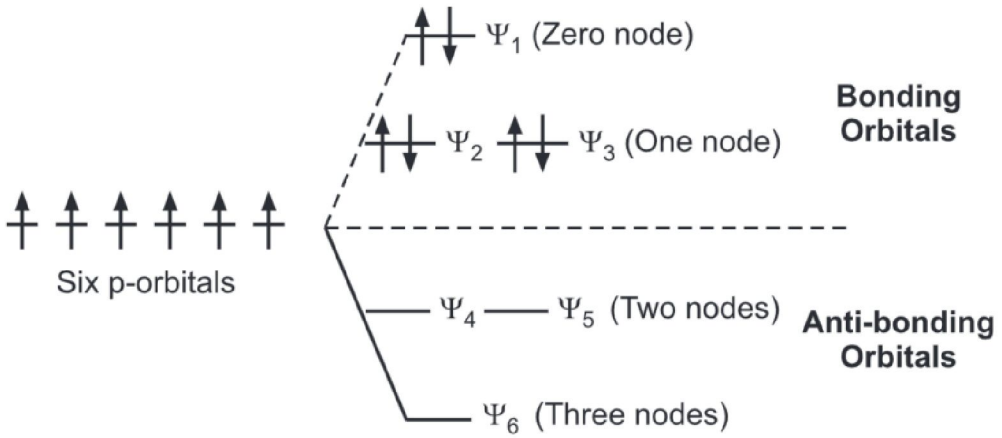
Resonating Structure (Resonance in Benzene):

In benzene there are continuously deloclisation of Pi bond, So it form resonance and also show resonance hybrid structure.

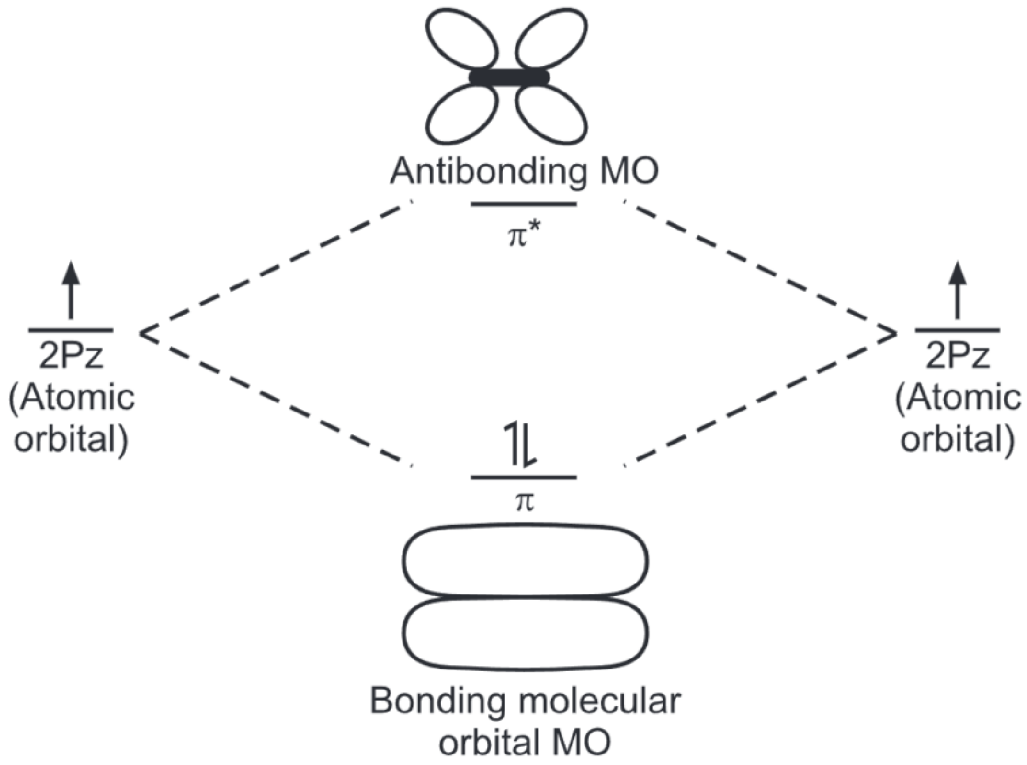


Orbital Picture of Benzene:

- The delocalization of the p-orbital carbons on the sp^2 hybridized carbons leads to the aromaticity of benzene. There are a total of six p-orbital electrons that form the stabilizing electron clouds above and below the aromatic ring.
- Benzene has a planar hexagonal structure in which all the carbon atoms are sp^2 hybridized and all the C-C bonds are equal in length.
- Each carbon has an unhybridized p-orbital perpendicular to the plane of the ring. It makes up the conjugated x-system.



- The p-orbitals (one on each carbon) linearly overlap to generate six molecular orbitals, three bonding, and three antibonding.
- It is this completely filled set of bonding orbitals or closed shell that gives the benzene ring its thermodynamic and chemical stability.
- Electrons that spend most of their time between the nuclei of two atoms are placed into the bonding orbitals, and electrons that spend most of their time outside the nuclei of two atoms are placed into antibonding orbitals. The bonding orbitals are at lower energy than the antibonding orbitals. So they are the first to fill up.



Aromaticity:

In organic chemistry "Aromaticity" is a property of cyclic (ring shaped), planar (flat) structures with a ring of resonante bonds that gives increased stability compare to other geometric or connective arrangements with the same set of atoms.

Characters of aromatic:

- The molecule is cyclic
- The molecule is planar.
- The molecule is fully conjugated (P orbitals at every atom in the ring)
- The molecules has follow Hackle's rule. $4n+2\ \pi$ Electrones[n=0 or any positive integer]

Huckel's rule:

In 1931 German Chemist and physicist "Erich Huckle" proposed a theory to his rules states that it a cyclic planar molecule has **4n+2 π electrons**.

Hückel's rule is a simple but powerful rule in organic chemistry that can be used to predict whether a planar ring molecule will exhibit aromatic properties.

It states that a planar ring molecule is aromatic if it has $4n + 2$ π electrons, where n is a non-negative integer.

Eg: Benzene (Aromatic compound)

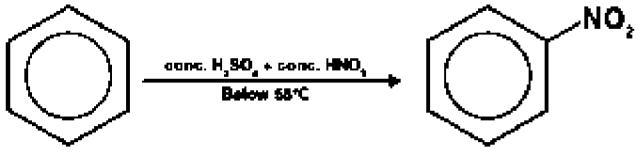
Reactions of benzene - nitration, sulphonation, halogenation reactivity, Friedelcrafts alkylation-reactivity, limitations, Friedelcrafts acylation.

Reaction of Benzene:

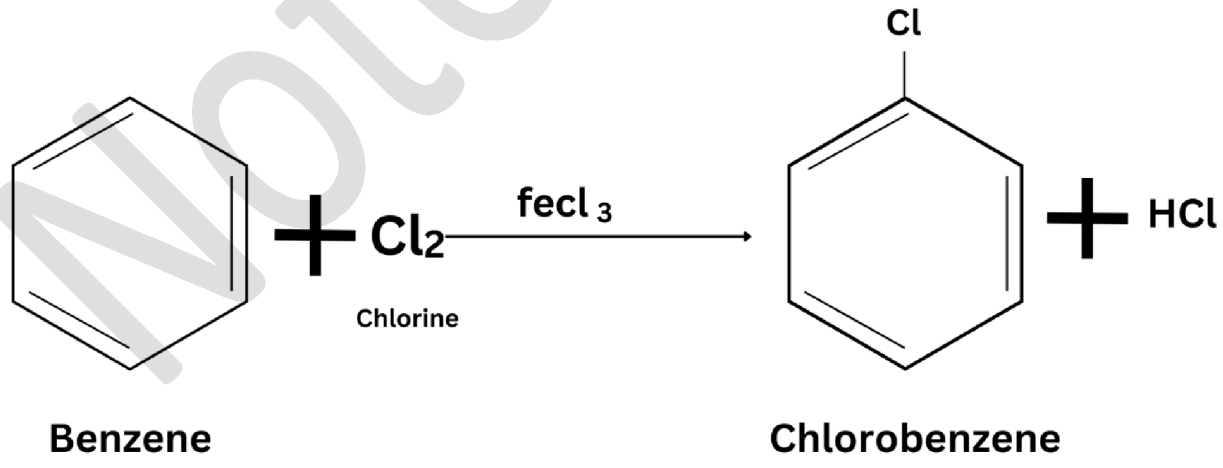
- Benzene readily undergoes a new set of reactions, all involving substitution i.e. Electrophilic Aromatic Substitution Reactions.
- It involves the reaction of an electrophile with an aromatic compound, were electrophile substitutes for a hydrogen of an aromatic compound.

Nitration of Benzene:

When benzene is treated with nitric acid it formed nitrobenzene (Nitration of Benzene)



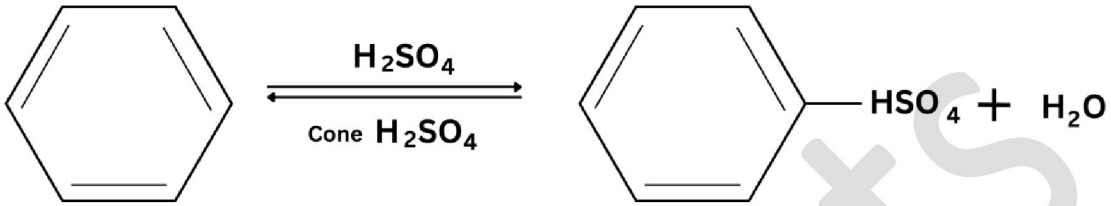
Chlorination: when benzene is treated with chlorine it formed chlorobenzene (Chlorination of benzene)



Sulphonation of Benzene:

It belong to electrophilic substitution of benzene.

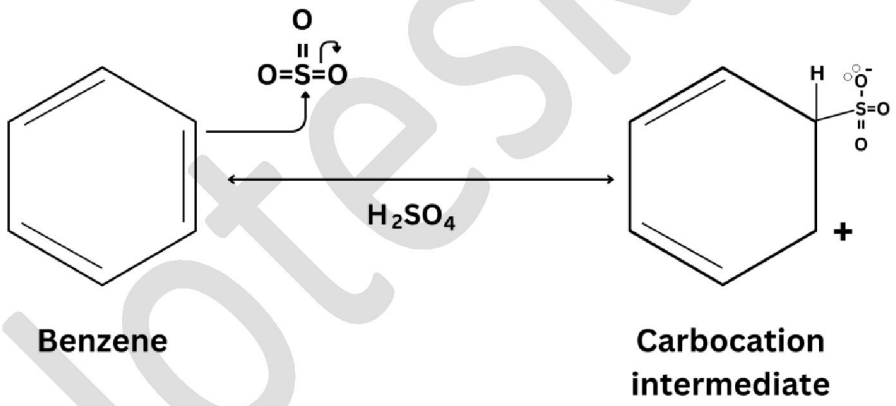
In which benzene react with H_2So_4 (Sulphuric Acid) in the presence of conc H_2So_4 it formed benzenesulfonic acid.



It is reversible reaction it forms when benzene is heated with fuming Sulphuric Acid or concentrared sulphenic acid it yield benzenesulphonic acid.

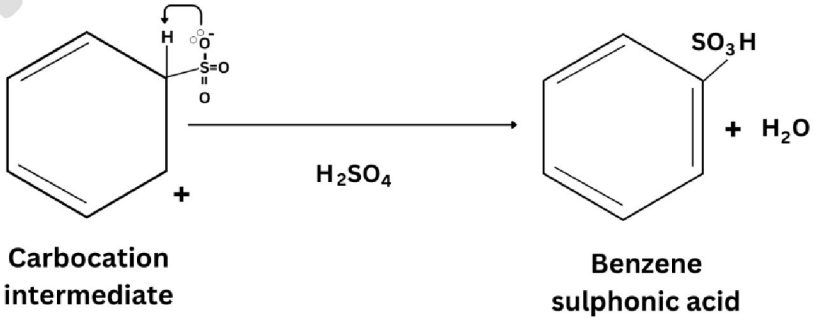
Mechanism:

Step-1:



In which carbocation formed in benzene, and SO_3 attached with benzene.

Step-2:



- Resonance stabilized carbocation intermediate
- The lone pair form a bond with hydrogen atom, releasing the electron in the hydrogen to ring bond for re-establish the electron.
- Required product obtained.

Friedal Craft Reaction:

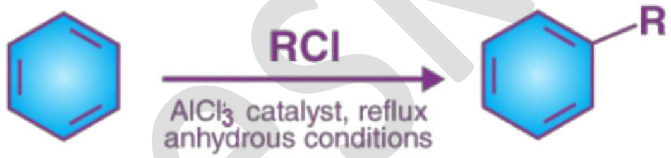
First introduced by Charles Friedel and James Crafts in 1877

Two types of Friedal Craft Reaction:

1. Alkylation
2. Acylation

1. Friedal-Craft Alkylation:

- Friedel-Crafts Alkylation refers to the replacement of an aromatic proton with an alkyl group. This is done through an electrophilic attack on the aromatic ring with the help of a carbocation.
- The Friedel-Crafts alkylation reaction is a method of generating alkylbenzenes by using alkyl halides as reactants.



A Lewis acid catalyst such as $FeCl_3$ or $AlCl_3$ is employed in this reaction in order to form a carbocation by facilitating the removal of the halide. The resulting carbocation undergoes a rearrangement before proceeding with the alkylation reaction.

Mechanism

The Friedel-Crafts alkylation reaction proceeds via a three-step mechanism.

Step 1

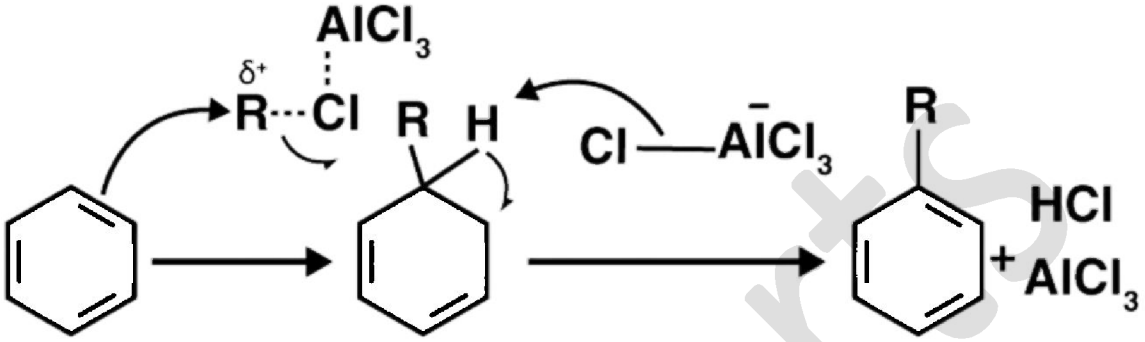
The Lewis acid catalyst ($AlCl_3$) undergoes reaction with the alkyl halide, resulting in the formation of an electrophilic carbocation.

Step 2

The carbocation proceeds to attack the aromatic ring, forming a cyclohexadienyl cation as an intermediate. The aromaticity of the arene is temporarily lost due to the breakage of the carbon-carbon double bond.

Step 3

The deprotonation of the intermediate leads to the reformation of the carbon-carbon double bond, restoring aromaticity to the compound. This proton goes on to form hydrochloric acid, regenerating the $AlCl_3$ catalyst.



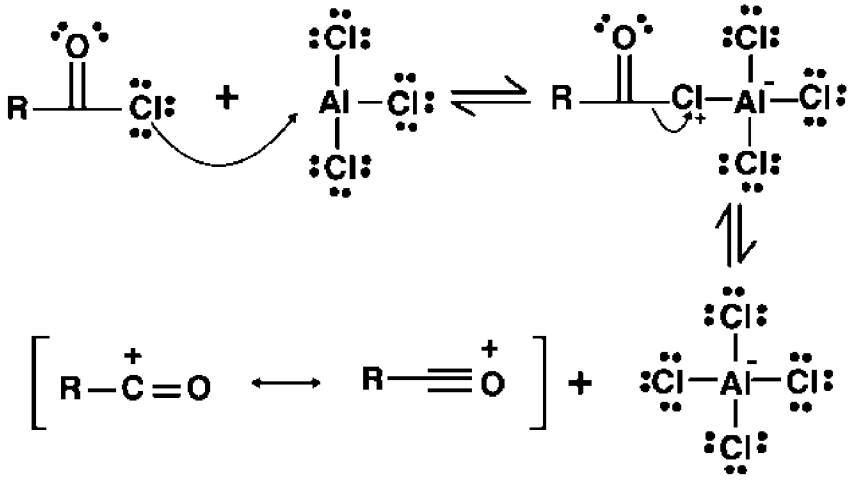
2. Friedel-Crafts Acylation:

Mechanism

Friedel-Crafts acylations proceed through a four-step mechanism.

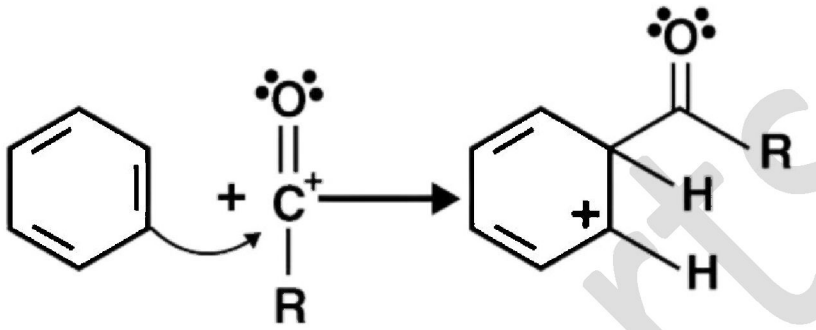
Step 1

A reaction occurs between the Lewis acid catalyst (AlCl3) and the acyl halide. A complex is formed and the acyl halide loses a halide ion, forming an acylium ion which is stabilized by resonance.



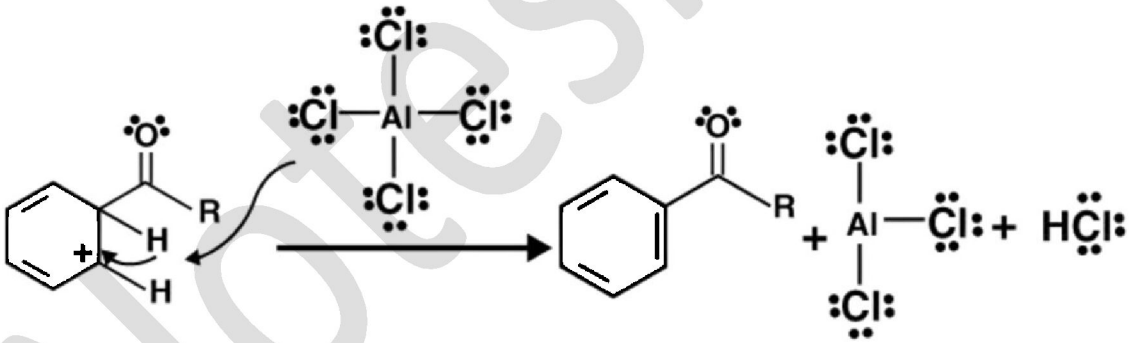
Step 2

The acylium ion (RCO+) goes on to execute an electrophilic attack on the aromatic ring. The aromaticity of the ring is temporarily lost as a complex is formed.



Step 3

The intermediate complex is now deprotonated, restoring the aromaticity to the ring. This proton attaches itself to a chloride ion (from the complexed Lewis acid), forming HCl. The AlCl3 catalyst is now regenerated.



Thus, the required acyl benzene product is obtained via the Friedel-Crafts acylation reaction.

Limitations

Despite overcoming some limitations of the related alkylation reaction (such as carbocation rearrangement and polyalkylation), the Friedel-Crafts acylation reaction has a few shortcomings.

- The acylation reaction only yields ketones. This is because formyl chloride (H(C=O)Cl) decomposes into CO and HCl when exposed to these conditions.
- The aromatic compound cannot participate in this reaction if it is less reactive than a mono-halobenzene.

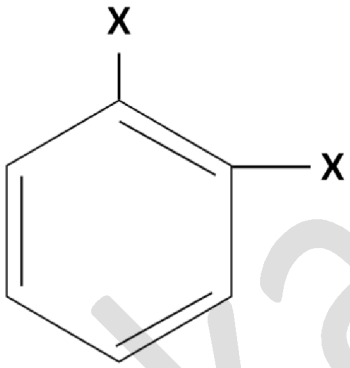
- Aryl amines cannot be used in this reaction because they form highly unreactive complexes with the Lewis acid catalyst.
- The acylations can take place on the nitrogen or oxygen atoms when amine or alcohols are used.

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

Substituents:

In organic chemistry and biochemistry a substituents is a atom or group of atom which replace one or move hydrogen atoms on the parents chain of a hydrocarbon becoming a moiety of the resultant new molecule.

A Substituent is an atom or functional group that replaces a hydrogen atom on a Hydrocarbon.

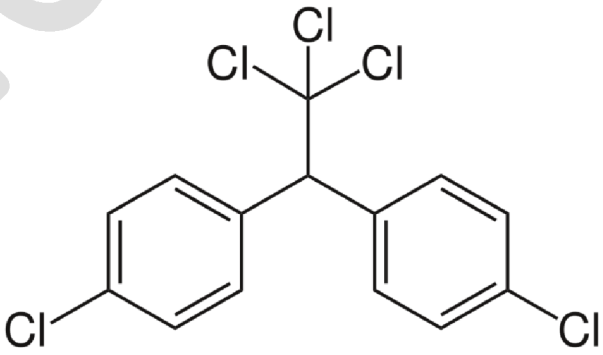


- Benzene is Parent
- X is substituent.

Structure and uses of DDT, Saccharin, BHC and Chloramine

DDT (Dichloro Diphenyl Trichloroethane):

Structure:

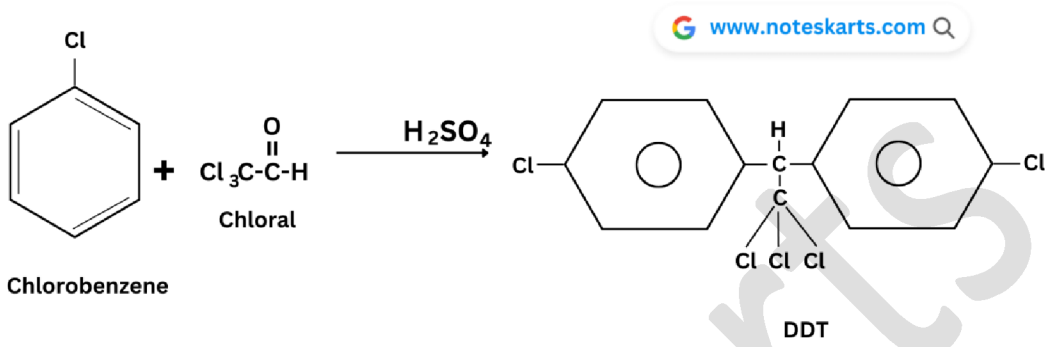


Molecular formula: $C_{14}H_9C_{15}$

Molecular weight: 354.5g/mol

Method of preparation:

It is prepared by the reaction of 2 molecule of chlorobeneze and 1 molecule of chloral in the presence of sulphuric acid.



Properties:

- DDT is an colorless white crystalline solid with melting point 109°C.
- It is water insoluble but readialy soluble in benzene ketone and acetone.

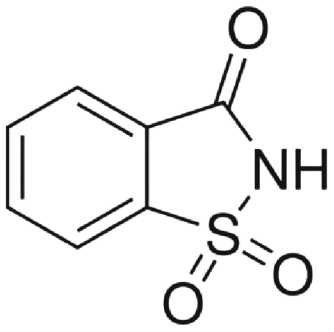
Uses:

- DDT is a powerfull insecticide which is used to kill mosquito and insect.
- DDT is non-biodegradable in nature so it accumulates inside the plant.

Saccharin:

- Saccharine is on artificial sweeteners.
- It is a non-caloric sweetner.
- Saccharine is 300-400 times more sweeter than sugar.
- It is used for the manufacturing of drinks candies, Cookies, medicine and toothpaste.

Structure of Saccharin:



Uses:

- Saccharine is used as sweetener for various vitamin supplements and medicines.
- It canbe used for the baking as a substitute of sugar.
- Saccharine has been used to sweeten foat and bevereges without catories.
- Saccharine provide products with increase stability and inprove taste low production coste and more choice for the consume.
- Saccharine is very beneficial for diabetes and ovese patient.

BHC (Benzene Hexa Chloride)

- The molecular formula of BHC is C_6Cl_6 and mol. Weight 285.
- BHC is the substitution product of benzene.
- BHC is a white or choclate colour powder.
- It is irritating to eye, nose and skin.

Use:

- It is used to kill insects by direct contact and it gives residual action for short diuration.

Chloramine:

- It is used as disinfectant in water treatment use to purified the drinking water.