Pharmaceutical Organic Chemistry

UNIT-I

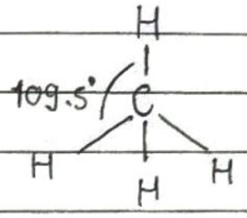
Benzene and Its Derivatives

Organic Compound - This are those chemical compounds in which carbon atom attached with other atoms or element. Most commonly used atoms are oxygen, Nitrogen, Hydrogen etc.

Example - CH_4
CO_2 etc
HCl, HCN } Inorganic Compound

118 - Compound
117 - Inorganic
1 - Carbon

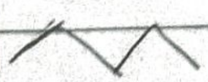
(i) CH_4



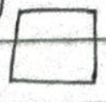
(ii) CO_2

$O=C=O$

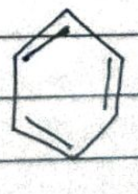
Organic Compound
- Aliphatic
  - Non cyclic



  - cyclic



- Aromatic
  Those compounds which follow Huckels Rule



Benzene

Aromatic Compound ⇒

Coined by - August Kekule
Coined form - Aroma means frugrant order

Now term Aromatic is associated with Chemical Stability.

Cyclic Compound, Where are ring atoms participate in a network gives unusual Stability.

Arenes (Aromatic Hydrocarbon)

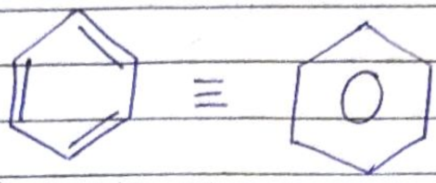
Definition - Benzene or Arene and its derivative are aromatic compounds.

The compound contains at least one Benzene or resembles benzene in Chemical Behaviour.

Aromatic Chemistry - When we are Study of Structure, property Composition reaction and application & prepration and Synthesis of these compounds is a Aromatic Chemistry.

Nomenclature of Benzene Derivatives -

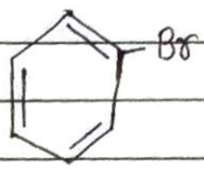
Simplest Arene is C_6H_6 = Benzene



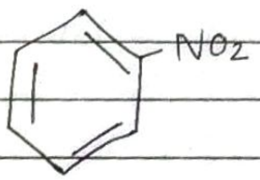
for Mono Substitution -

Mono Substituted Benzene Derivatives by placing Prefix (Name of Substituent) to the word Benzene

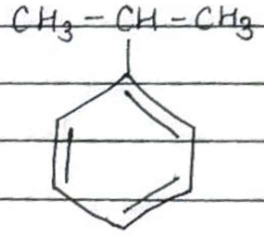
eg. -



Bromo Benzene

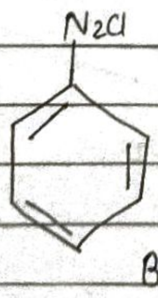


Nitro Benzene



Isopropyl Benzene

In Same Cases name of the Substituents written after Benzene



Benzene Diazonium Chloride

Benzene Sulphonic acid

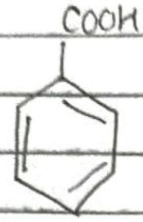
Some Derivative have Special name like-

eg.-

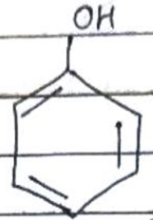
Anilene

Anisole

Toluene



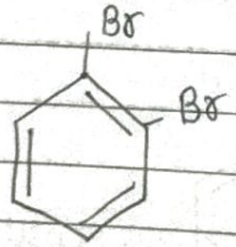
Benzoic acid



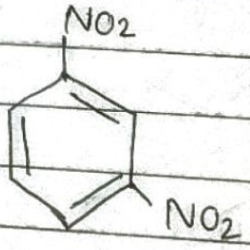
Phenol

Di Substituted Benzene -

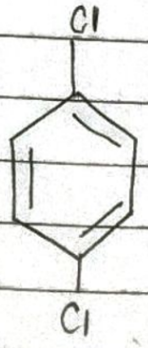
Derivatives haveing two Smiliar groups the prefix Di is added before the name of the group and the relatives position of two groups are indicated by the Symbole "O" (ortho) for 1,2 M (Meta) for 1,3 (P) (Para) for 1,4 Position respectively



1.2 Di ortho Bromo Benzene

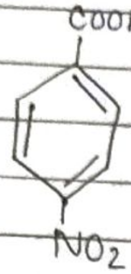


1,3 Meta Di Nitro Benzene

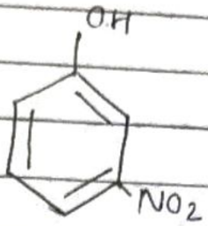


Para 1,4 Di Chloro Benzene

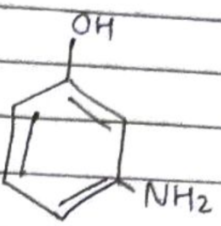
Derivatives haveing Different groups are named as a derivative of the compounds with the main functional group at position 1



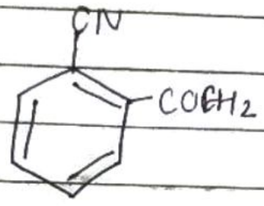
4 Nitro Benzoic Acid



3 Nitro Phenol

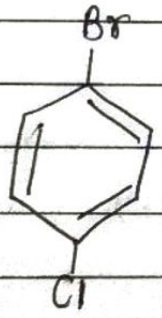


3 Amino Phenol

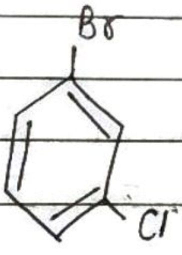


2 Actyle Benzo Nitrile

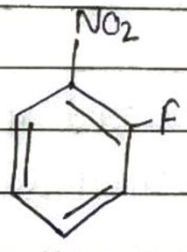
If Both the functional groups present are Substituent functional groups then they are arrange in alphabitical order.



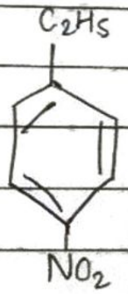
1 Bromo 4 Chloro Benzene



1 Bromo 3 Chloro Benzene



1 Floro 2 Nitro Benzene



1 Ethyle Nitro Benzene

Synthetic and other evidences in the derivation of Structure of Benzene -

The term Aromatic compound was firstly used by the Kekule (1865)

The term aromatic compounds stands for the whole series of compounds which contain one or more Benzene ring in their molecule.

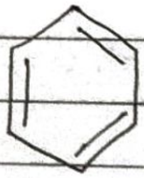
Coal as a source of aromatic compound.

Structure of Benzene -

Benzene

Molecular formula - C_6H_6
Molecular Weight - 78.11 g/mol

Molecular structure -

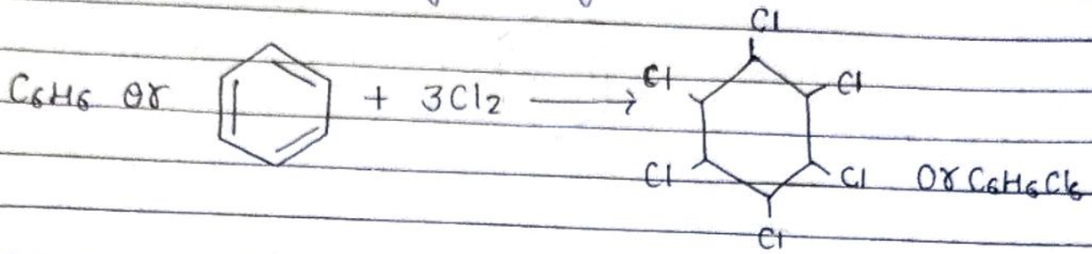


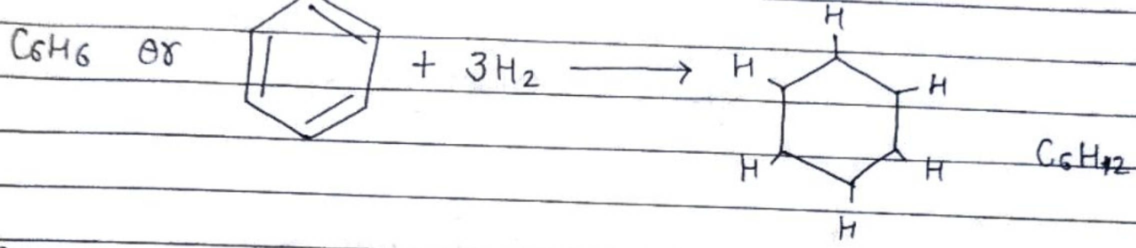
A Molecular formula -

Elemental analysis and molecular weight determination showed that Benzene had the molecular formula C_6H_6

B Unsaturated Nature -

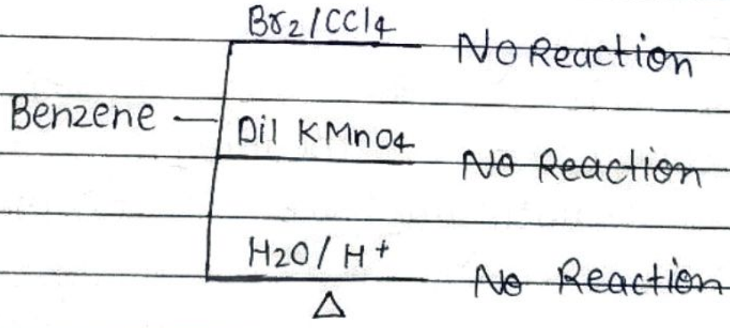
Benzene is unsaturated contain either three C=C or one C=C and C≡C. This can be explain by following reaction -





C Straight chain Structure not possible -

Benzene does not behave like alkene or alkyne because of following reasons -

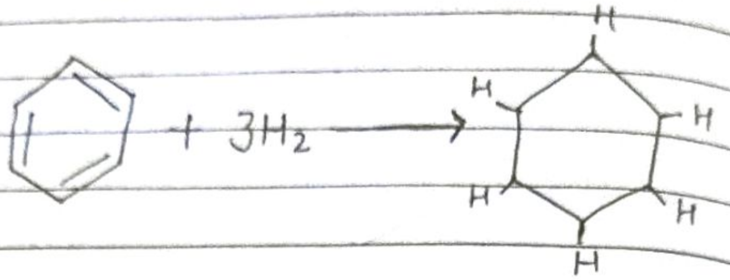


All the above reaction is characteristic reaction of open chain Alkene or Alkynes.

D Cyclic Structure of Benzene -

Benzene with When treated With hydrogen give cyclohexane (a cyclic product)

C_6H_6 or



Or

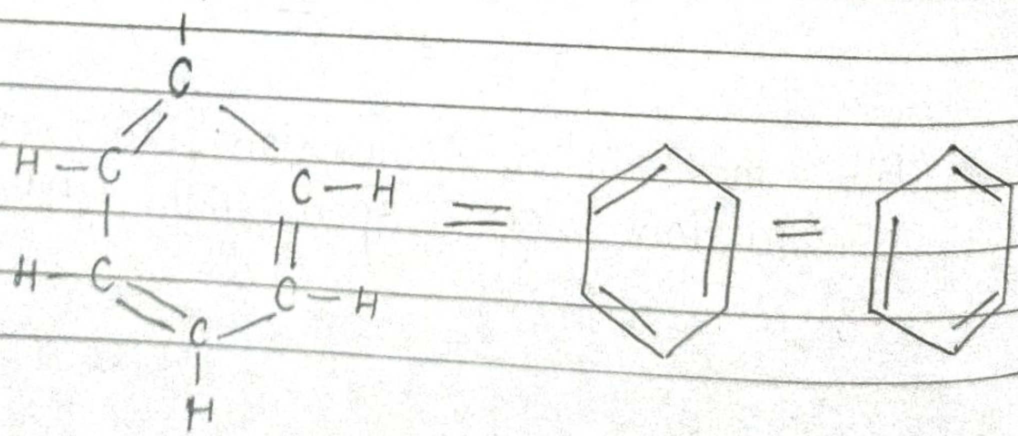
C_6H_{12}

The reaction indicates that Benzene is a Cyclic Structure.

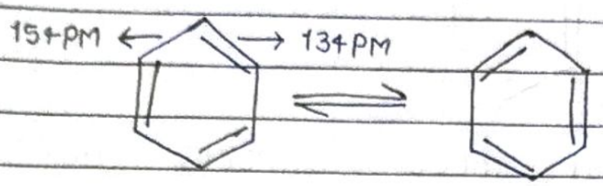
E Kekule's Structure of Benzene

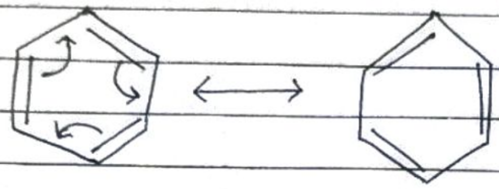
According to the Kekule each carbon atom in Benzene is join alternatively by double and single bond

A Hydrogen atom is attached to each carbon. All the Hydrogens are equivalent, meaning they are indistinguishable from each Other.



Two forms are in rapid equilibrium





All Bonds are ~ 139 pm [Intermediate between C-C and C=C]

Electron Density is distributed evenly between the six carbon.

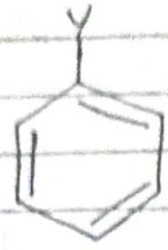
Structure is planar, Hexagonal.

C-C-C bonds angles are 120°.

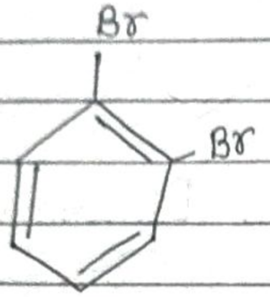
Each Carbon is SP^2 and has a p-orbital perpendicular to the plane of the six-Membered ring.

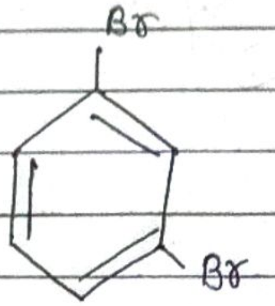
Kekule Structure for Benzene is most accepted on the Basis of following facts:

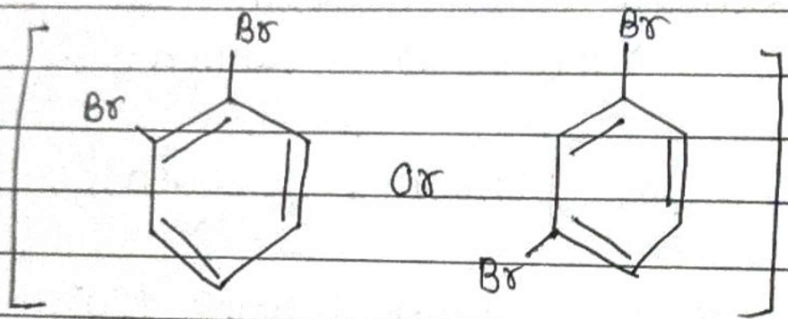
Benzene yield only one monosubstituted products i.e. C_6H_5Y



Benzene yield three isomeric disubstituted product i.e.- $C_6H_4Y_2$, C_6H_4YZ







limitation of Kekule's Structure -

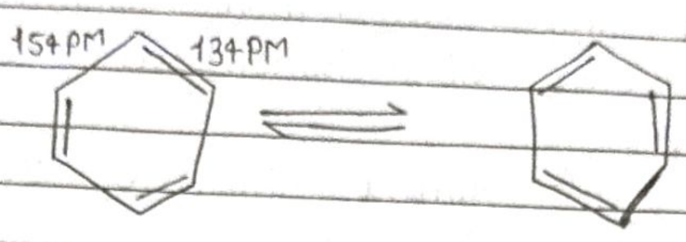
In Spite of Double bond, Benzene does not give addition reaction.

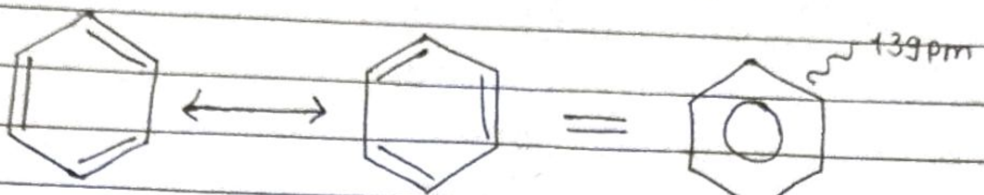
Substitution Reaction is more common in Benzene.

High Stability of Benzene Ring.

f

Resonance Model of Benzene -





Resonating Structure

Resonance Hybrid of Benzene

The Resonance model explain the following properties of Benzene -

Bond Length - All the carbon - carbon bonds in Benzene are uniform i.e. ~139 pm (intermediate between C-C and C=C)

Isomers - Benzene yield three isomeric disubstituted product i.e. - $C_6H_4Y_2$ C_6H_6YZ.

Stability - Resonance Structures more stable among two Kekule's Structure.

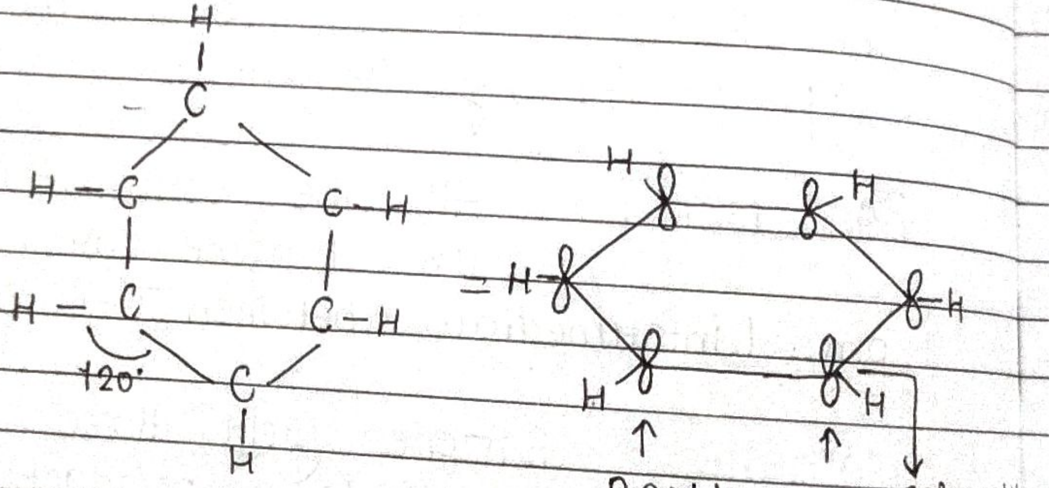
Electrophile Substitution Reaction - Electrophile Substitution does not disturb the aromaticity of the ring. Addition reaction disturbed the aromaticity.

G Molecular Orbital Structure of Benzene -

All the six carbon atoms in Benzene are SP^2- Hybridised.

The SP^2 Hybrid orbital overlap with each others and with S - Orbital of 6 Hydrogen atom form C - C and C - H sigma bond.

The p unhydridised orbital of each carbon overlap and form 3π bonds.



BENZENE = A Planer Molecule

Benzene :- [Prepration] -

Benzene was first isolated by Michael Faraday.

In 1845, August Wilhelm Hofmann and his team isolated Benzene from coal tar.

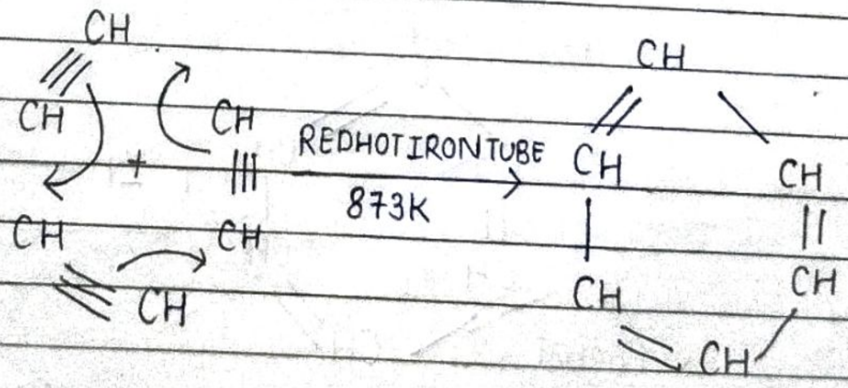
Commercially, Benzene is isolated from coal tar by subjecting it to fractional distillation.

Benzene can be prepared in the laboratory by several Method :-

1- Cyclic polymerisation of Ethyne
2- Decarboxylation of aromatic acids
3- Reduction of Phenol
4- Hydrolysis of sulphonic acid

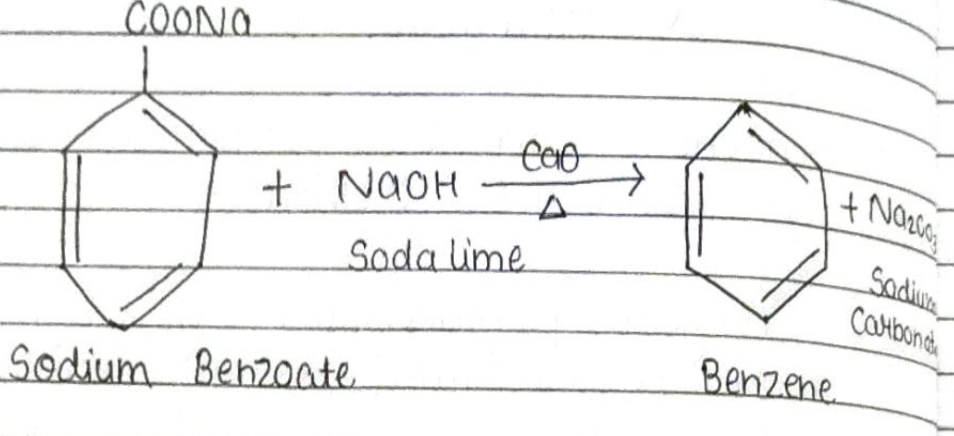
Cyclic Polymerisation -

Benzene was first isolated by Marcelin Berthelot by passing ethyne through a red hot iron tube at 873K.



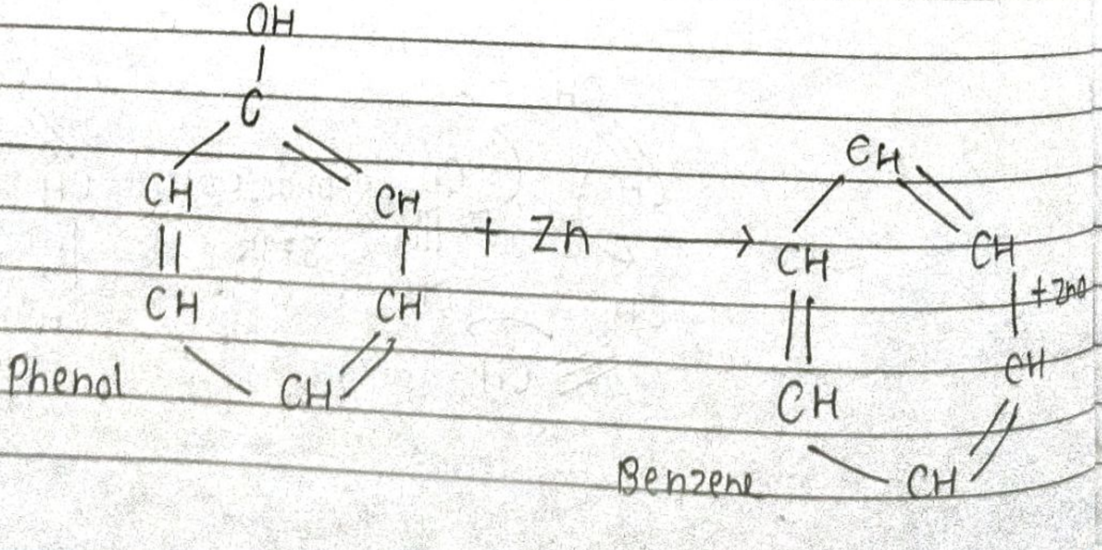
Decarboxylation of aromatic acids -

In a laboratory. Benzene can also be obtained by the decarboxylation of aromatic acid. Sodium Benzoate on heating with Soda lime loses a molecule of Carbon di oxide and forms Benzene.



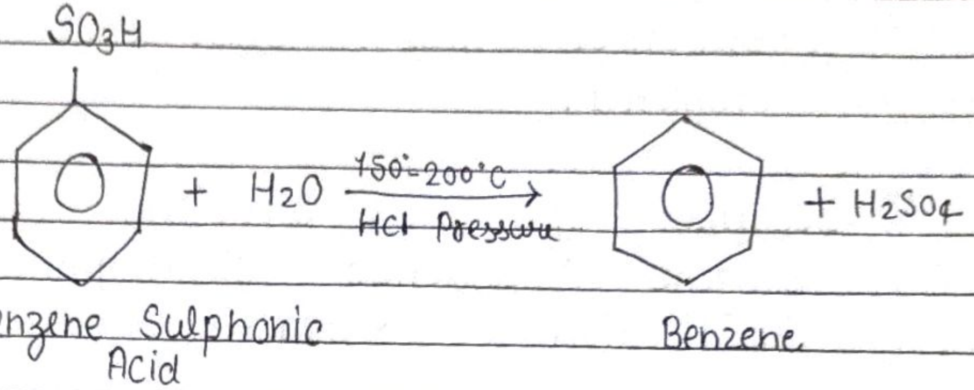
Reduction of Phenol -

Benzene can be prepared by the reduction of phenol by passing its vapours over heated Zinc dust.



Hydrolysis of Sulphonic Acid -

Benzene Sulphonic acid on Hydrolysis with Superheated Steam gives Benzene.



Properties of Benzene -

Benzene is a Colourless liquid with a Characteristic Smell.

Boiling Point of Benzene is 80°C

It is non polar in nature, thus insoluble in water but Soluble in organic Solvents Such as alcohol and ether.

Benzene is highly inflammable. It burns with a Sooty flame due to its high C to H ratio.

Electrophilic Aromatic Substitution of Benzene.-

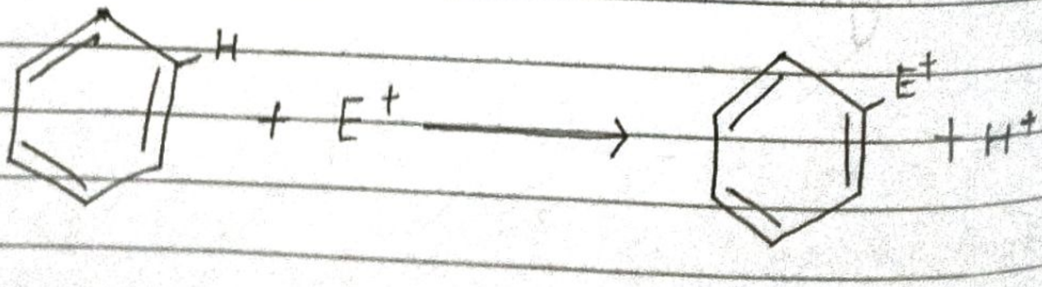
In Benzene ring there are three pi bonds which are in conjugation. Due to the Delocalization of π - electrons (Resonance) the Benzene ring is Stablized.

Because of the aromatic Stablization, Benzene undergo electrophile Substitution reaction.

Electrophilic Substitution reaction, in which a hydrogen atom of an aromatic ring is replaced by an electrophile.

As the aromaticity of Benzene is not disturbed in the reaction, these reactions are highly spontaneous in nature.

Basic examples of electrophilic substitution reaction of Benzene are Nitration, Sulfonation, Halogenation, friedel craft's alkylation and friedel crafts acylation.etc.



Aromaticity

In Organic Chemistry, the term aromaticity is used to describe a property of a cyclic, planar molecule with a ring of Resonance bonds that exhibits more stability than other.

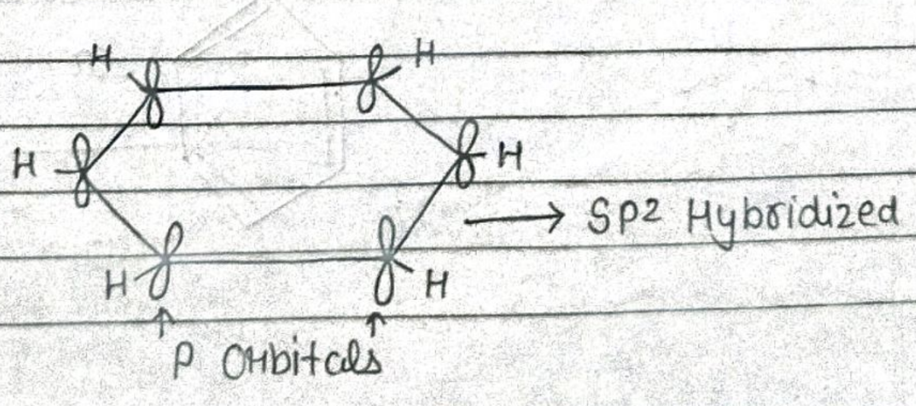
four following Conditions must be Satisfied for a compound to be an aromatic -

⇒ A Molecule must be cyclic.
To be aromatic, each p orbital must overlap with p orbitals on adjacent atom.

⇒ A Molecule must be plannar
All adjacent p orbitals must be aligned so that the π electron density can be delocalized.

⇒ A Molecule must be completely conjugated
Aromatic compounds must have a p-orbital on every atom.

⇒ A Molecule must satisfy Huckel's Rule, and contain a particular number of π e^-



Huckel's Rule

Aromatic compounds posses the property of aromaticity. Huckel's rule helps to decide whether an aromatic compound possess aromaticity or not.

Huckel's rule was given by German physicist Erich Huckel in 1931

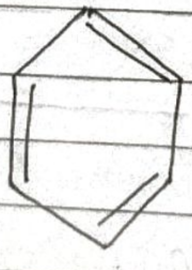
⇒ An aromatic compounds must contains $(4n+2)$ π electrons.
Where $n = 1$
$n = 2, 3, 4$ (no. of ring)

⇒ Aromatic compound may be Benzenoid (haveing Benzene ring) and non Benzenoid (Without Benzene Ring).

⇒ Heterocyclic compounds containing oxygen, Nitrogen or Sulfur can also be aromatic.

Example of Huckel's Rule -

(i) Benzene



or

Number of π bonds = 3

Number of π electrons = 6

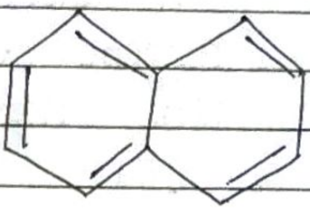
According to Huckel rule, When n=1,

$$= (4n+2)\pi$$
$$= (4\times 1 + 2)\pi$$
$$= 6\pi e^-$$

Hence no. of πe^- in the compound must be equal to 6.

Since Benzene Contains $6\pi e^-$. It is Aromatic.

Naphthalene -



Number of π bond = 5
Number of πe^- = 10

According to Huckel Rule When n=2

$$(4n+2)\pi$$
$$(4\times 2 + 2)\pi$$
$$10\pi e^-$$

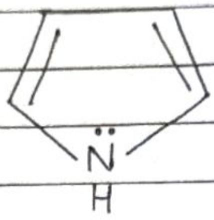
Hence Number of πe^- in the compound must be equal to 10

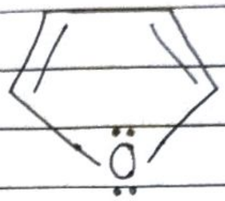
Since Naphthalene Contains $10\pi e^-$. It is Aromatic.

Heterocyclic Aromatic Compounds and Huckel's Rul

Heterocyclic Aromatic compounds, any cyclic compound that contains ring atom (s) other than carbon (N, O, S, P)


Pyridine

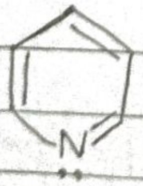

Pyrrole

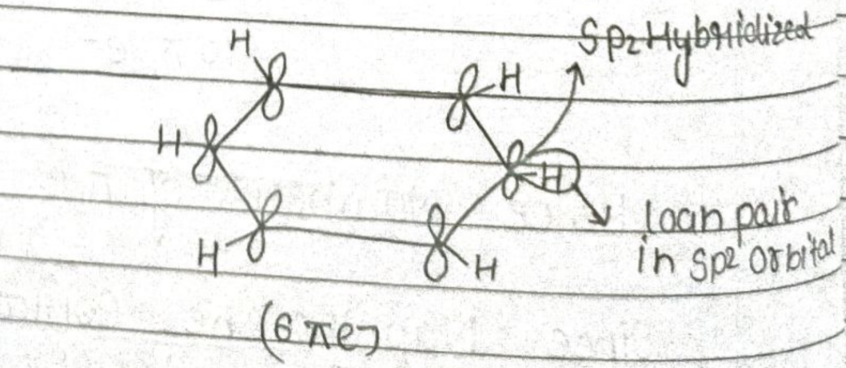

Furan


thiophene

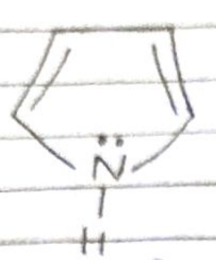
Pyridine - π - electron structure resembles Benzene (6 π- electrons). The Nitrogen lone pair elerons are not part of the aromatic system.

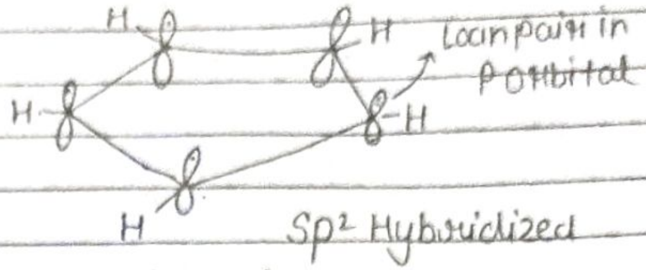
Pyrrole - There are 4 SP^2 Hybridized carbon with 4 P orbitals perpendicular to the ring and 4 π electrons and a lone pair of electrons in an unhybridized p2 orbital that is part of the aromatic sextet.


Pyridine



$(6\pi e^-)$


Pyrrole



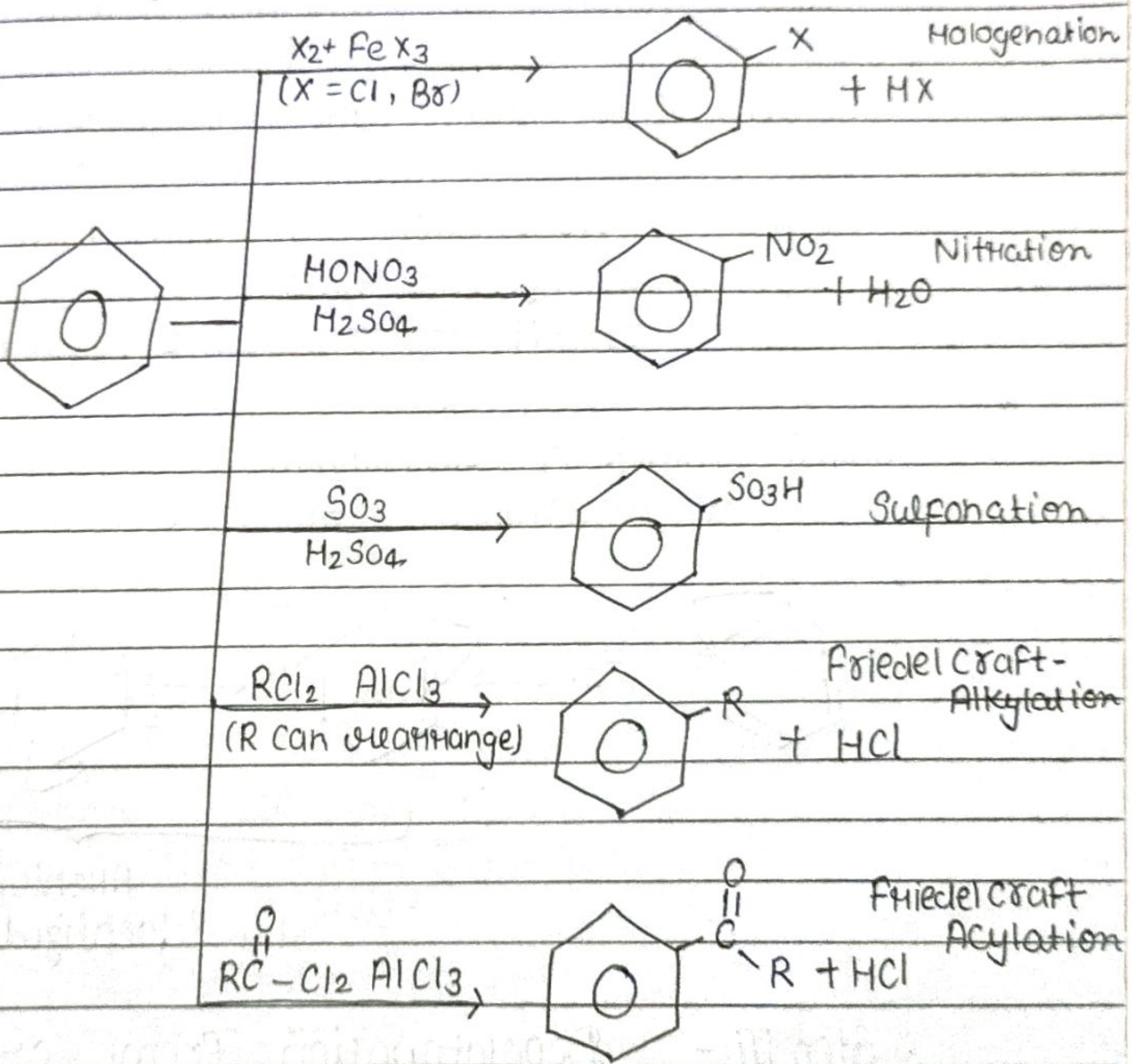
(6πe⁻)

(B)

Electrophilic Aromatic Substitution Rxn of Benzene -

[Aromaticity के आगे हैं]

Reaction of Benzene -



A General Mechanism for Electrophilic Aromatic Substitution - or Arenium Ion Intermediates Mechanism

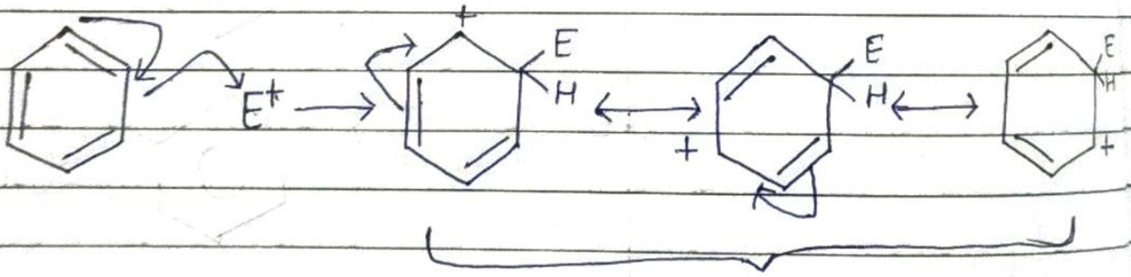
Arenium Ion Intermediates is formed when Benzene reacts with an electrophile which is resonance Stabilized.

Arenium ion is a Carbocation It is also kown as wheland intermediate or Sigma complex. (It is not aromatic, only 2 π bonds are in conjugation)

Step I - Generation of electrophile

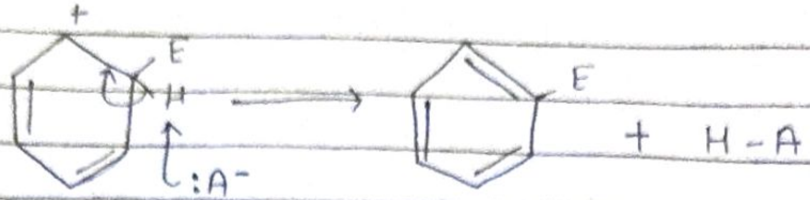
$$E - A \xrightarrow{\text{Lewis Acid}} \ddot{E}^{+} + :A^{-}$$

Step II - Attack of electrophile on Benzene ring form a resonance Stablized arenium ion



Arenium ion
(a delocalized cyclohexadienyl cation)

Step III - Deprotonation from arenium ion by a Base -

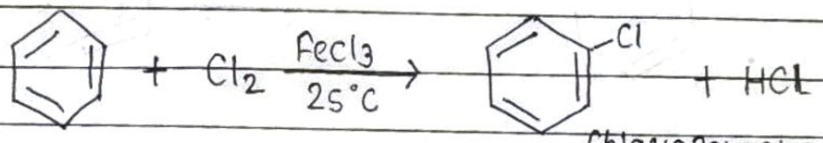


Halogenation of Benzene - (Bromination) :-

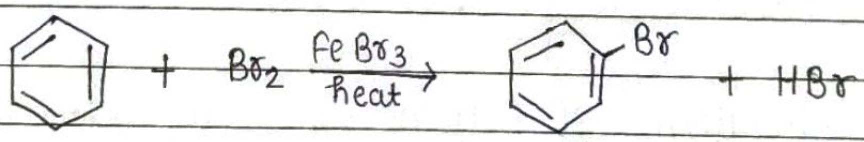
The Bromination or chlorination of Benzene requires a Lewis acid
eg. - ferric Bromide or ferric chloride.

Lewis acid is a compound that accepts a Share in a pair of electrons.

The electrophile for the reaction is Bromonium ion (Br^+).



ChloroBenzene

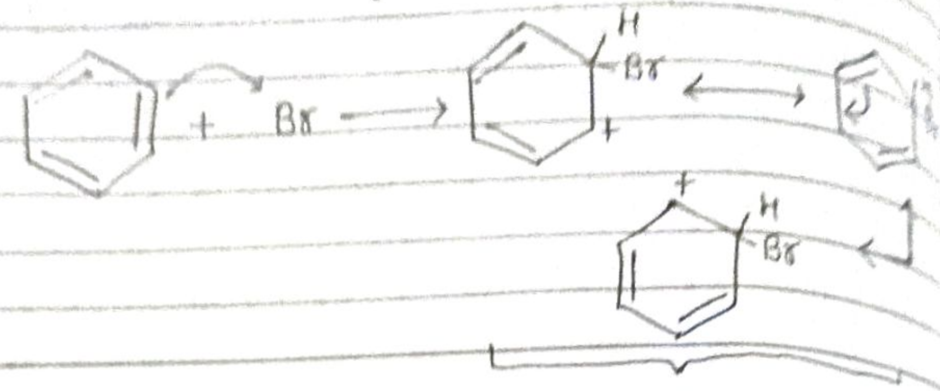


BromoBenzene

Step I - Bromine combines with $FeBr_3$ to form a Complex that dissociates to form a positive Bromine ion and $FeBr_4^-$

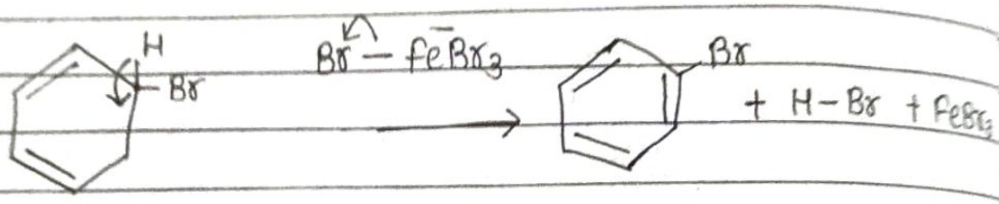
$$Br - Br + FeBr_3 \longrightarrow Br^- + FeBr_4^-$$

Step II - The positive Bromine ion attacks Benzene to form an Arenium ion.



Arenium ion

Step III - A proton is removed from the arenium ion to become BromoBenzene.

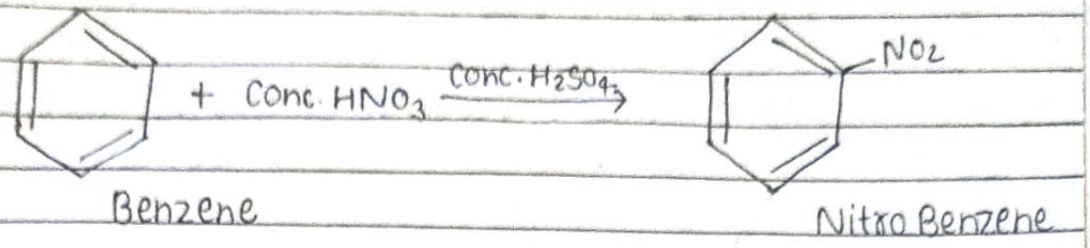


Nitration of Benzene -

Nitration of Benzene occurs with a mixture of Concentrated Nitric and Sulfuric acids.

The Electrophile for the reaction is the i.e. Nitronium ion [NO_2^+]

A Mixture Concentrated Nitric acid and Sulfuric acid is known as Nitrating Mixture.

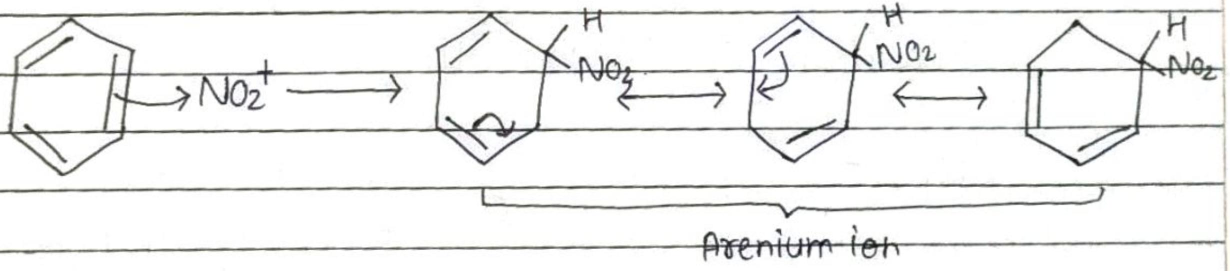


Reaction Mechanism-

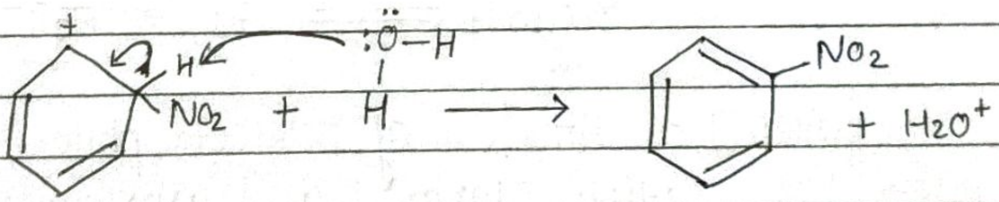
Step I - Generation of Electrophile i.e. Nitronium ion (NO_2^+)

$$H_2SO_4 + HNO_3 \longrightarrow NO_2^+ + HSO_4^-$$

Step II - Attack of electrophile on Benzene ring from a resonance Stablized arenium ion.



Step III - Deprotination from arenium ion by a Base.

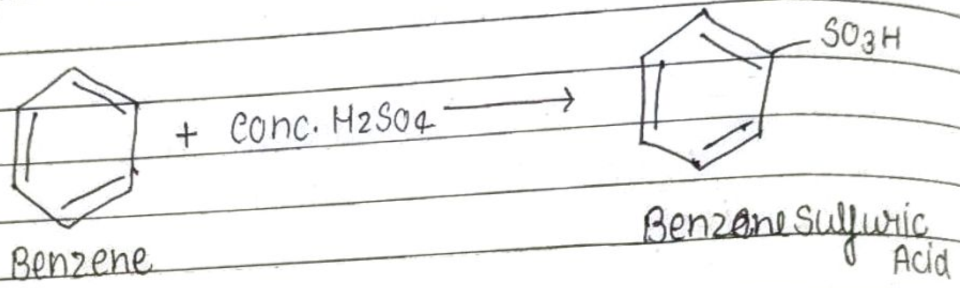


Sulphonation of Benzene -

Sulphonation occurs most rapidly using fuming sulfuric Acid (conc. H_2SO_4 that contains SO_3)

Sulphonation also occurs in conc. sulfuric acid, which contains small quantites of SO_3+

Electrophile in the reaction is SO_3 (neutral)

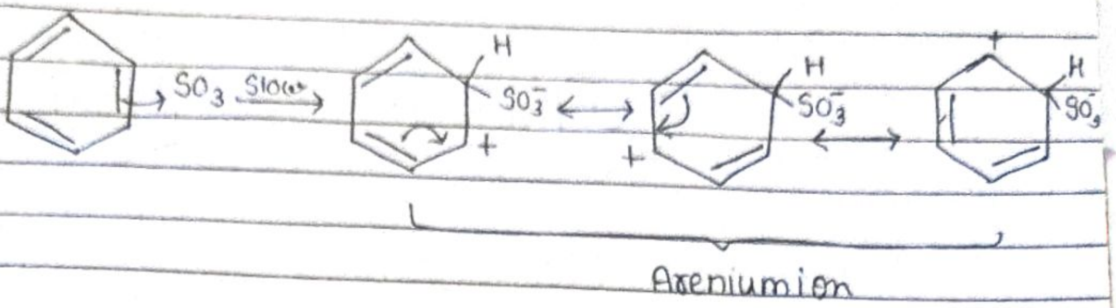


Reaction of Mechanism -

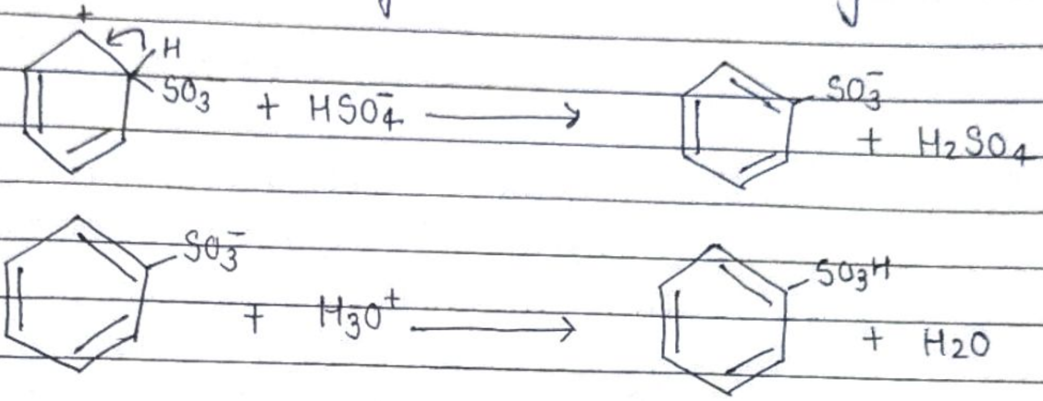
Step I - Generation of electrophile -
SO_3 is the actual electrophile that reacts with Benzene to form an arenium ion.

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

Step II - Attack of electrophile on Benzene ring form a resonance stablized arenium ion.



Step III - Deprotonation from arenium ion by a Base



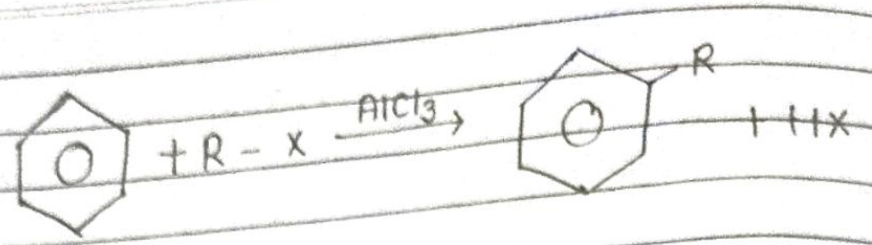
friedel Craft Alkylation -

In friedel crafts alkylation an alkyl group is interduce on a Benzene ring.

An Aromatic ring can be alkylated by an alkyl hailide in the presence of a lewis acid (The lewis acid serves to generate a carbocation electrophile).

Electrophile in the reaction is alkyl carbocation.

Re arrangement is more frequent take place in friedel - craft acylation.

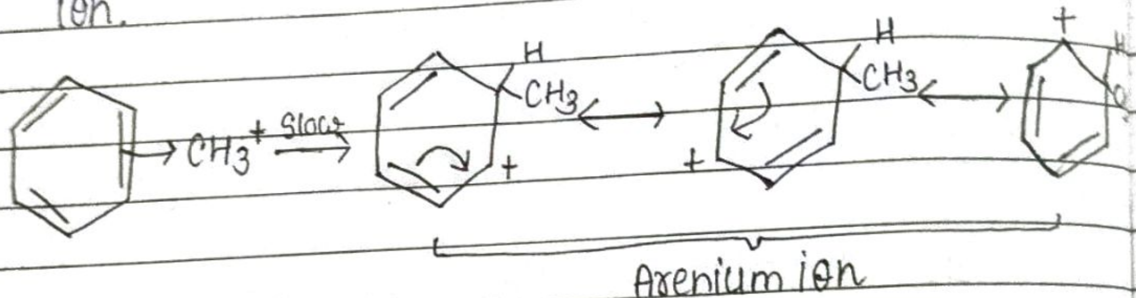


Reaction Mechanism

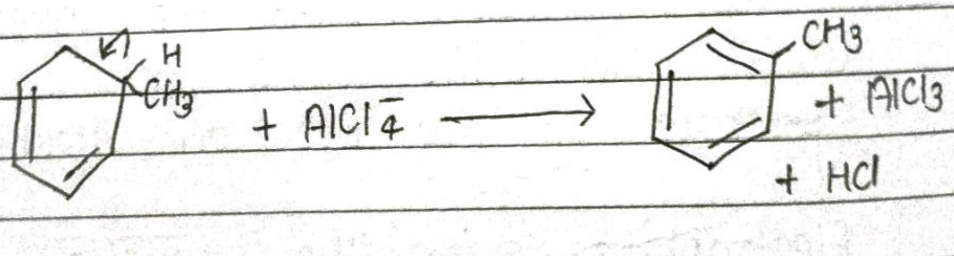
Step I - Generation of electrophile -

$$CH_3-Cl + AlCl_3 \longrightarrow CH_3^+ + AlCl_4^-$$

Step II - Attack of electrophile on Benzene ring form a resonance stablized arenium ion.



Step III - Deprotination from arenium ion by a Base.



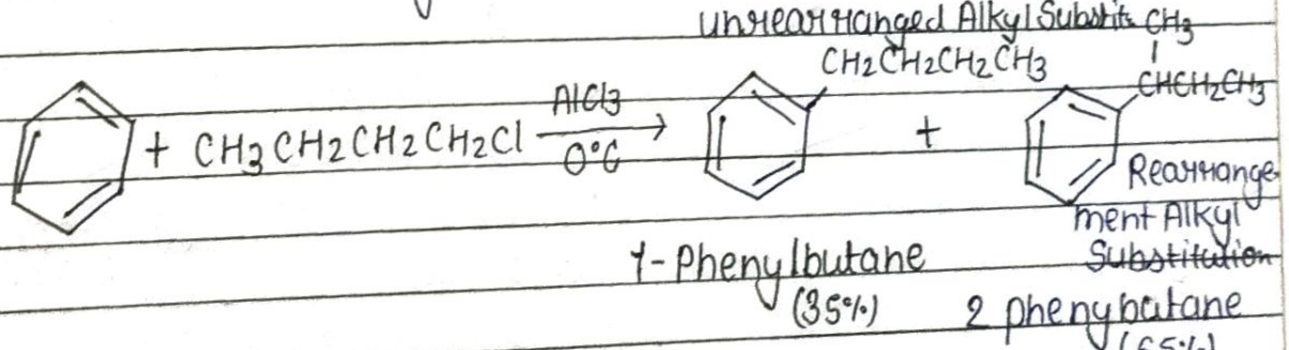
Note-

An Alkyl Substituted Benzene is more reactive than Benzene. Therefore, to prevent further alkylation of alkyl Substituted Benzene, a large excess of Benzene is used in friedel-craft alkylation.

A carbocation will rearrange if rearrangement leads to a more stable carbocation.

When the carbocation can rearrange in a friedel craft alkylation reaction, the major product will be the product with the rearranged alkyl group on the Benzene ring.

Examples- less stable primary carbocation to stable Secondary carbocation.



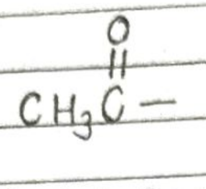
$$CH_3CH_2\underset{H}{CH}\overset{+}{C}H_2 \xrightarrow{1,2\text{ Hydride Shift}} CH_3CH_2CHCH_3$$

A primary carbocation　　　　A secondary carbocation

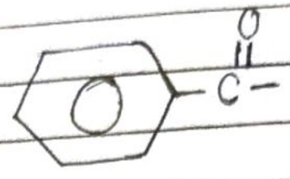
friedel Craft Acylation –

In friedel craft acylation, an acyl group is introduce on a Benzene ring

An acyl group has a carbonyl attached to Same R Group.

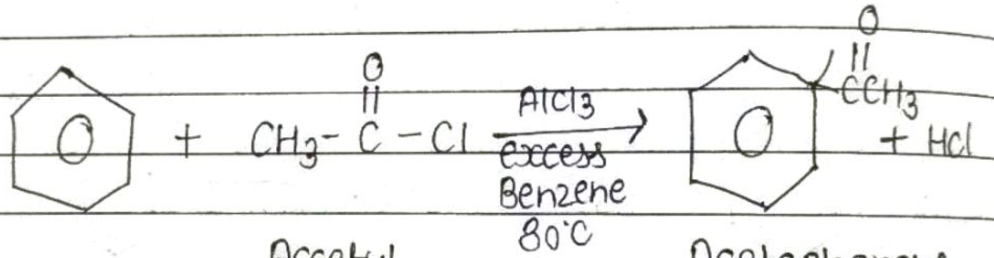


Acetyl Group
(Ethanoyl Group)



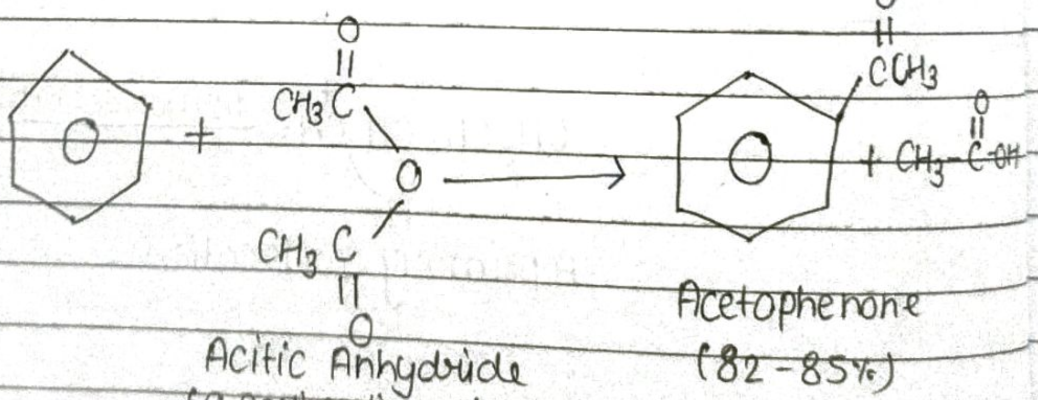
Bezyl Group

friedel Craft acylation requires reaction of an acid Chloride or acid anhydride with a lewis acid such as Aluminium Chloride.



Accetyl Chloride

Acetophenone (97%)



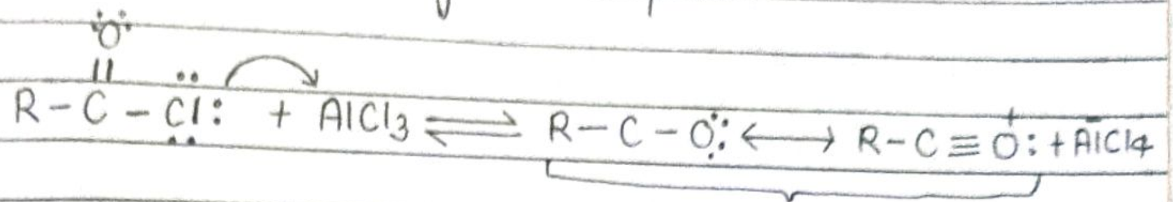
Acitic Anhydride
(a carbxylic acid anhydride)

Acetophenone
(82-85%)

Reaction Mechanism -

The Electrophile in friedel-crafts acylation is an acylium ion. The acylium ion is stablized by Resonance.

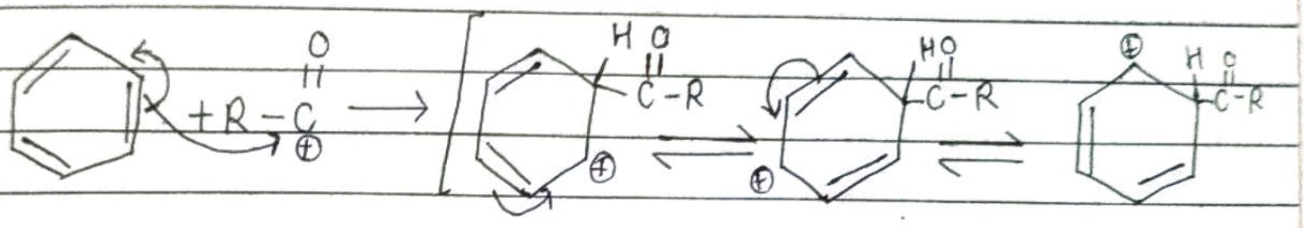
Step I - Generation of Electrophile



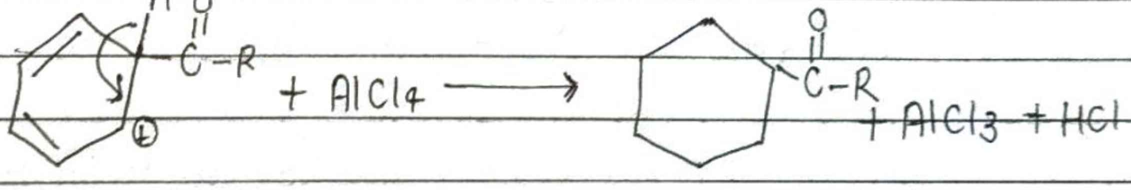
$$R-\overset{\ddot{O}}{\overset{\|}{C}}-\ddot{Cl}: + AlCl_3 \rightleftharpoons \underbrace{R-C-\ddot{O}: \longleftrightarrow R-C\equiv\overset{+}{O}:}\ + AlCl_4$$

An acylium ion electrophile

Step II - Attack of electrophile on Benzene ring form a resonance stablized arenium ion.



Step III - Deprotenation from arenium ion by a base



(C)

Substituents. Effect of Substituents on reactivity and Orientation of Mono Substituted Benzene compounds towards Electrophilic Substitution Reaction -

The Substituents - The Substituents can either increase or decrease the rate of the reaction depending on its nature.

If any Atoms or groups that provides more electrons (electron donateing groups) to the aromatic System, are called as activating (A) atoms or groups. Such Substituted Benzene ring is more active than Benzene itself.

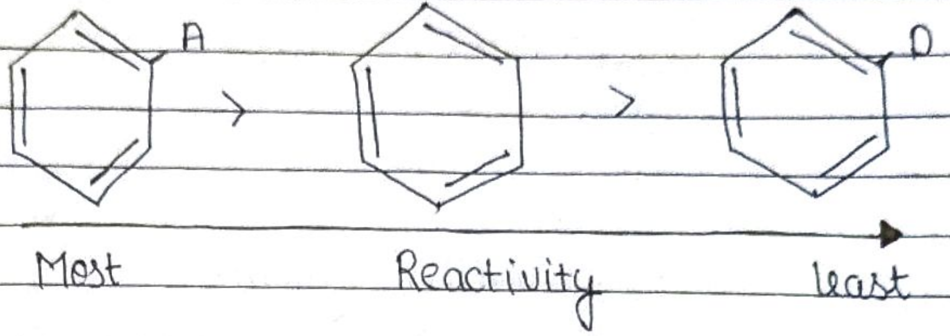
or

A Substituent (-A) is Said to be activating if the rate of electrophile aromatic Substitution of the Substituted Benzene (C_6H_6A) is faster than the Benzene.

If any atom or groups that pulls or abstract eletrons (electron withdrawing groups) form the aromatic system, are called as deactivating (D) atom or groups, Such Substituted Benzene ring is less active than benzene itself.

Or

A Substituent (-D) is said to be deactivating if the rate of electrophile aromatic substitution of the Substituted Benzene (C_6H_5D) is slower than Benzene.



The ability of substituent present in the Benzene ring to direct the position of incoming group (second substituent) is called as directive influence of the group.
On the Basis of directing influence, Substituents are classfied into three groups.

1 Activating and ortho, para directing
2 Deactivating and Meta - directing
3 Deactivating but artho, para directing

All activating groups are ortho, Para directors.

Halides are ortho, para directors but deactivating groups.

All Strong and mild deactivating groups are Meta directors.

Classification of Substituents

Strong activating groups

$-\ddot{N}H_2$, $-\ddot{N}HR$, $-\ddot{N}R_2$
$-\underset{..}{\ddot{O}}H$, $-\underset{..}{\ddot{O}}:^-$

Mild Activating group

$-\underset{..}{\ddot{N}}HCOCH_3$, $-\ddot{N}HCOR$
$-\underset{..}{\ddot{O}}CH_3$, $-\underset{..}{\ddot{O}}R$

Weak Activating Group
$-CH_3$, $-C_2H_5$, $-R$
$-C_6H_5$

Mild deactivating g

$-C\equiv N$
$-SO_3H$
$-CO_2H$, $-CO_2R$
$-CHO$, $-COR$

Strong deactivating g

$-NO_2$
$-NR_3^+$
$-CF_3$, $-CCl_3$

Deactivating: ortho, para Directors

$-\underset{..}{\ddot{F}}:$, $-\underset{..}{\ddot{Cl}}:$, $-\underset{..}{\ddot{Br}}:$, $-\underset{..}{\ddot{I}}:$

The Effect of Substituents On Orientation -

When a Subsitituted benzene undergoes an Electrophilic Substitution reaction, The Substituents already attached to the Benzene ring determine the location of the new Substituents.

The Effect of the Substituent present in the Benzene ring on its reactively and the directive influence of the Substituent can be explained using

(i) Inductive Effect
(ii) Resonance Effect

In Inductive effect, the withdrawal or release of electron takes place through σ Bonds.

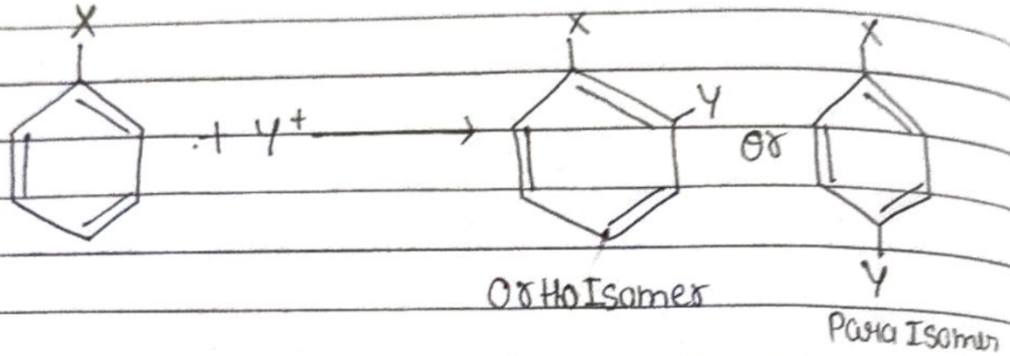
Where as in Resonance effect, the withdrawal or release of electron takes place through π Bond.

If the Group or atom attached to the Benzene ring releases the electrons into the ring +I effect + R effect.

If the group or atom attached to the Benzene ring withdraws the electrons from the ring -I effect, -R effect.

Ortho para Directors and Activators -

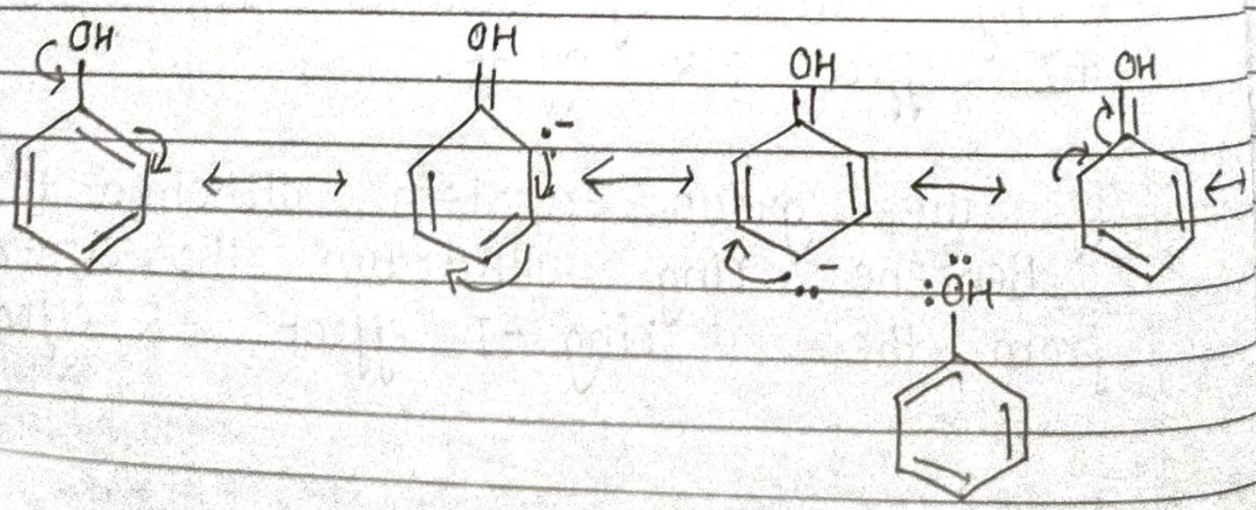
A substituent (-X) is said to be an ortho para director if it directors an incomeing electrophile to positions ortho and para to it self.



The activating groups donate electrons by resonance and withdraw electrons inductively.

The donate electrons by resonance more strongly than they withdraw electrons inductively.

for example consider an activating group Hydroxy group (-OH)



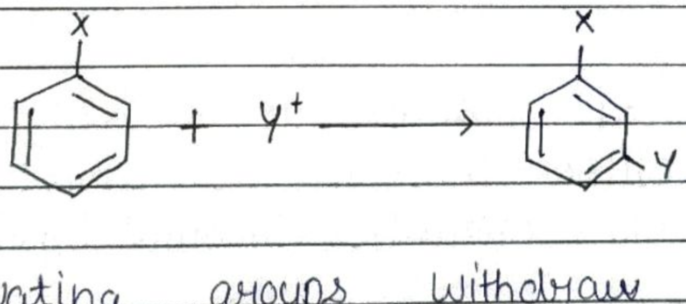
In phenol, the Hydroxy group attached to the Benzene ring releases the unsheared pair of electrons and they interact with the π electrons in the Benzene ring.

From the resonance forms it is clear that relative to Meta position, ortho and para positions have more electron Density and hence Second Substituent is directed to ortho or para position.

Hence a mixture ortho and para isomers are formed when phenol is subjected to electrophilic aromatic Substituents.

Meta Director Or Deactivaters -

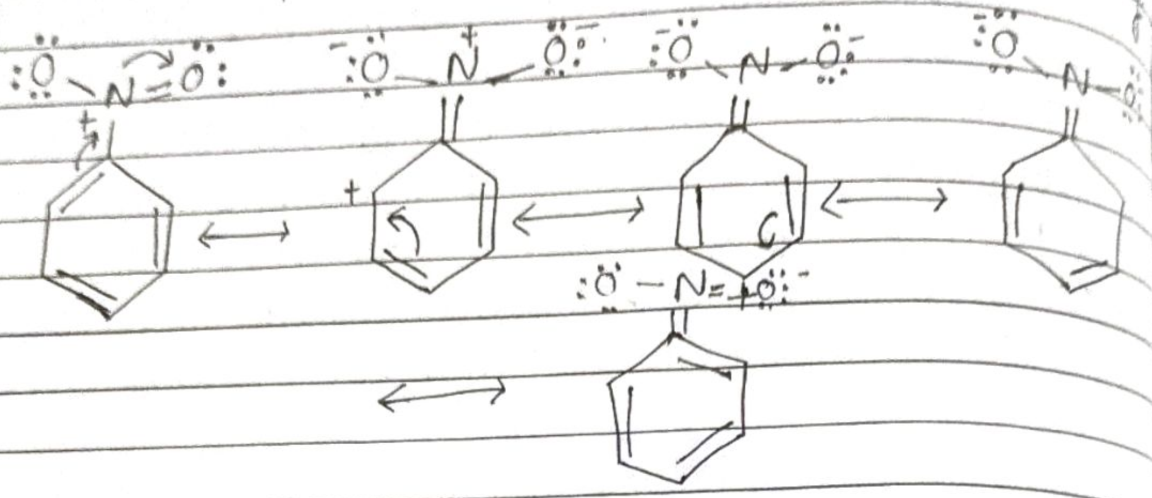
A Substituent (-X) is said to be an Meta director If it direct an incomeing electrophile to position Meta to itself.



De activating groups withdraw electrons both inductively and by resonance.

Except Halogens all ring deactivating groups are Meta direting groups and they have either a partial or full positive Charge on the atom directly attached to the aromatic ring.

for example consider an electron withdrawing



In Nitro Benzene, the Nitro group attached to the Benzene ring withdraws π-e^- in the Benzene ring.

From the resonace forms it is clear that relative to meta positions, Ortho and para positions have less electron density and hence second substituent is directed to a Meta position.

Hence Meta isomer is the major Product when Nitro Benzene is subjected to electrophilic aromatic substitution.

Halogen - Deactivating Groups And Ortho, Para Directors -

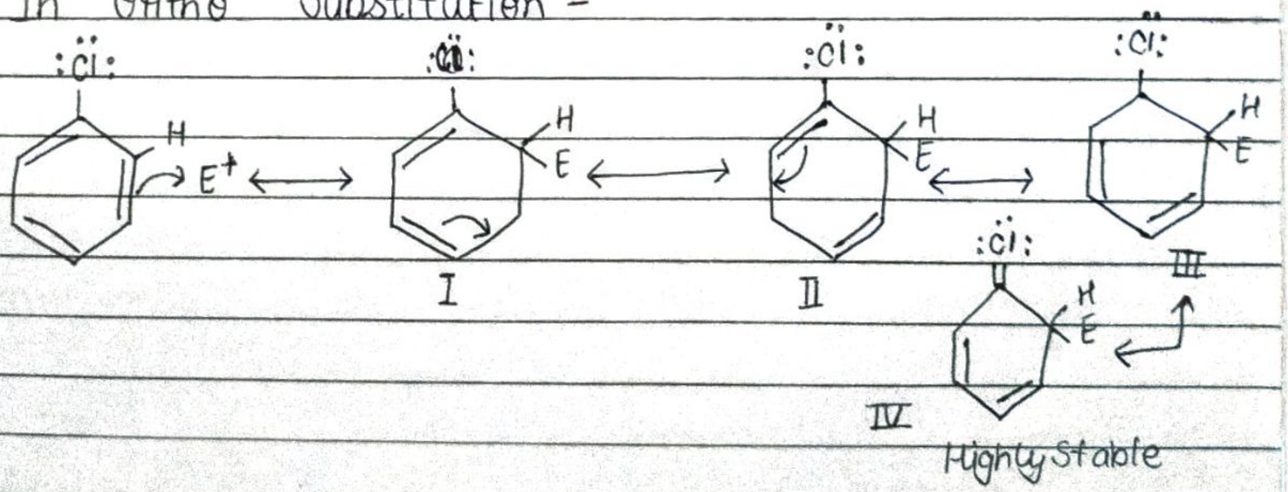
Halogen donate electrons into the ring by resonance and withdraw electron form the ring inductively.

They withdraw electrons inductively more strongly than they donate electron by resonance.

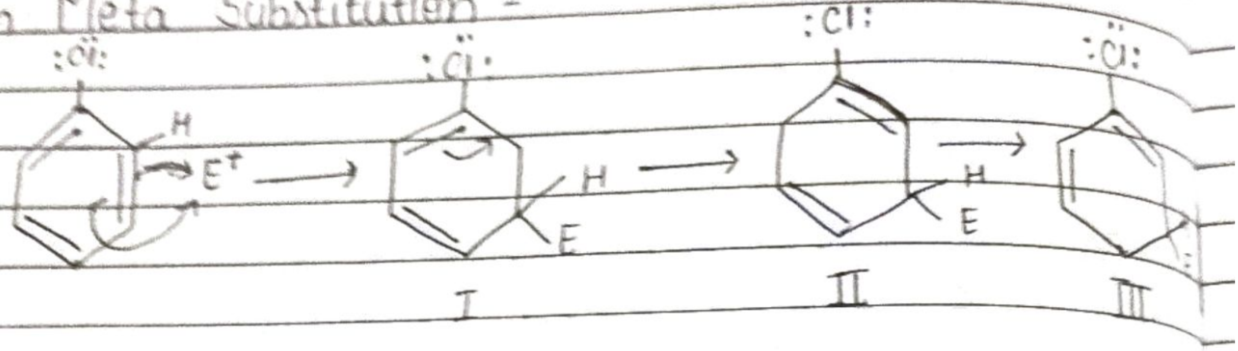
The Halogens are more electronegative than carbon and an a result of their electron withdrawal, the electron denesity in the ring is diminised and reactivity towards electrophile is reduced.

Since unsheared electrons are available, the carbecation (arenium ion) formed by the attack at the ortho and para position is Stablized by the domination of these electrons.

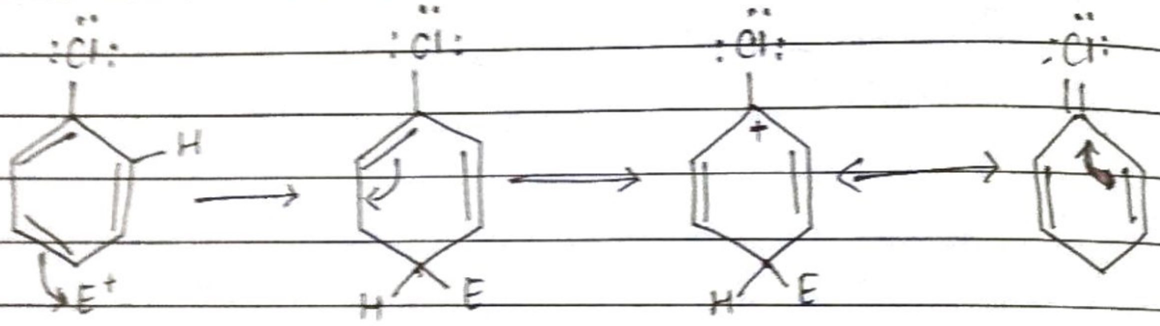
In Ortho Substitution -



In Meta Substitution -

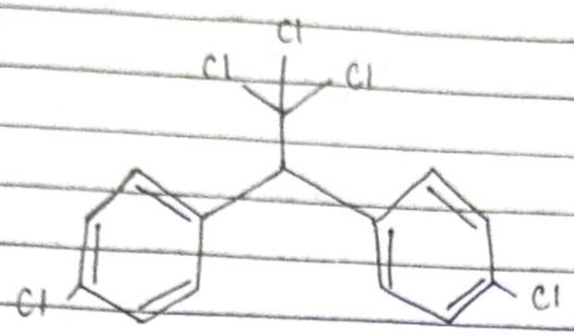


In Para Substitution -



Structure & uses of DDI Saccharin & BHC & Chloramine -

DDT [Dichloro Diphenyl Trichloro Ethane] -



DDT is Dichloro diphenyl trichloro ethane.

DDT is recognised as potent insecticidal and pesticidal chemical.

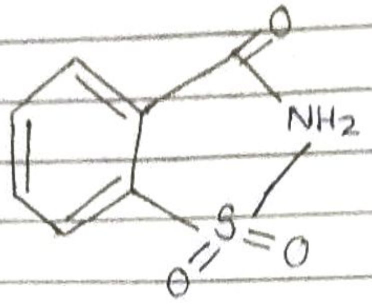
DDT is recognised as potent insectidal and pesticidal chemical.

DDT is initially used for the treatment of Malaria, typhus and other insect borne Human disease.

It is also effectively used for controlling insects in crops and livestock production, Homes and Gardens.

First time WHO (1955) recommeded DDT in prevention of transmission of Malaria.

Saccharin -



Sodium saccharine (Bezoic sulfimide) is an artificial Sweetner.

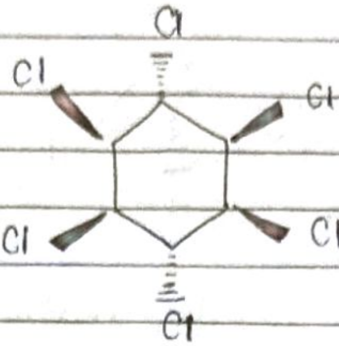
Saccharine is about 300-400 times Sweeter than SUCROSE.

Saccharine occurs as odourless white crystalline powder.

It is used as sweetening agent in products as cold drinks, candies, cookies and Medicines.

Saccharine can also used as a tabletop sweetner.

BHC [Benzene Hexachloride] -



Benzene Hexachloride (BHC) also known as Lindane, Gamma Hexachloro cyclo hexane (γ-HCCH), Gammaxene or Gamallin.

BHC is colourless to white colored, Synthetic Crystalline Solid.

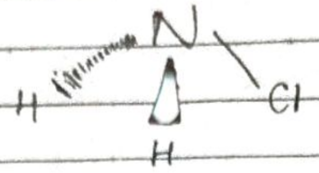
BHC is used to treat lice and Scabies but it may cause Serious Side effects.

BHC in the form of Shampoo used only for Public and head lice.

BHC lotion can be used to treat Scabies. It works by killing tiny insects and their eggs which cause Scabies.

BHC's widely used in agriculture as bug Spray and rodent control.

Chlorammine -



Based on the concentration of ammonia Chloramine is classify as Monochloramine (NH_2Cl), Dichloromines $(NHCl_2)$ and Nitrogen trichloride (NCl_3)

Monochloramine is and inorganic compound with chemical formula. NH_2Cl.

Chloramine occurs as colourless to yellow liquid.

Chloramine is generally used for the treatment of water. It is use for desinfection of drinking water.

It is also used for swimming pool disinfection.

Date
Page

UNIT-II

PHENOLS**

Phenols are molecules that have a hydroxy group (OH) Group is attached to the Carbon atom of an aromatic ring.

In Phenols, Hydroxy functional group is directaly attached to the SP^2 hybridized Carbon atom of the Benzene ring.

The C-O-H bond angle in phenol is 109°. The Carbon - Oxygen bond length (136 pm).

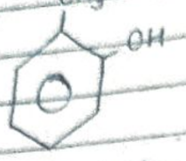
The parent compound of this group. C_6H_5OH called Simply phenol, is an important industrial chemical.

Nomenclature -

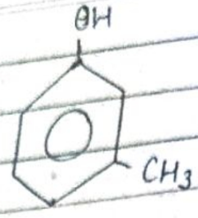
Phenols are usually named as substituted phenols.

The Methyl phenols are given the special name, coresols.

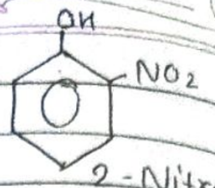
Some other phenols are named as Hydroxy compounds.



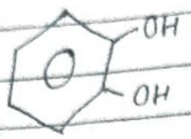
O - Coresols



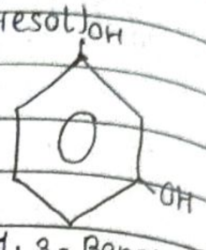
3 Methyl phenol
(m Coresol)



2 - Nitro phenol
(O Nitrophenol)

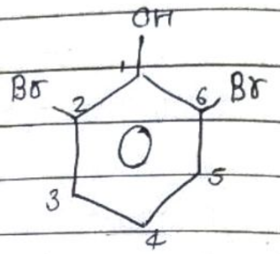


1,2 Benzenediol
(catechol)

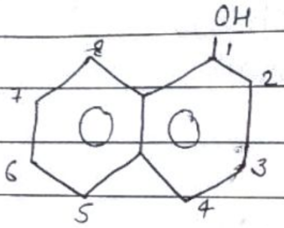


1, 3 - Benzendiol
(Resorcinol)

1,4 Benzenediole
(Hydroquinone)



2,6 Dibromophenol



1-Naphthol
(α-Naphthol)

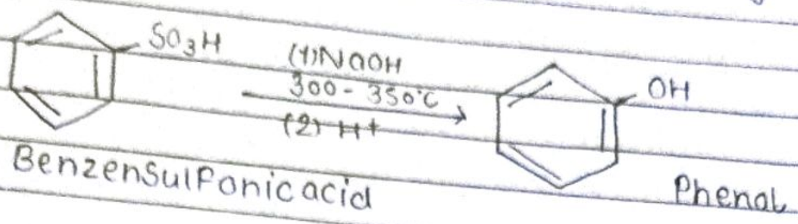
Prepration of Phenols -

Reaction of Benzensulfonic acid with Sodium Hydroxide -

This is the oldest Method for the prepration of Phenol.

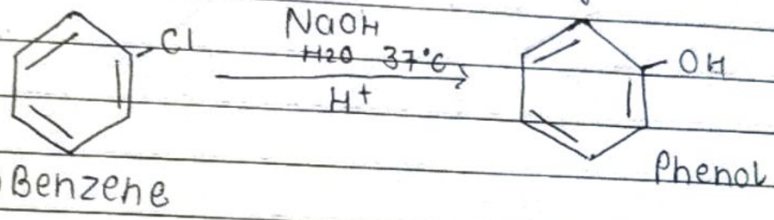
Benzene is Sulfonated and the benzensulfonic acid heated with molten Sodium Hydroxide.

Acidification of the reaction mixture gives Phenol.



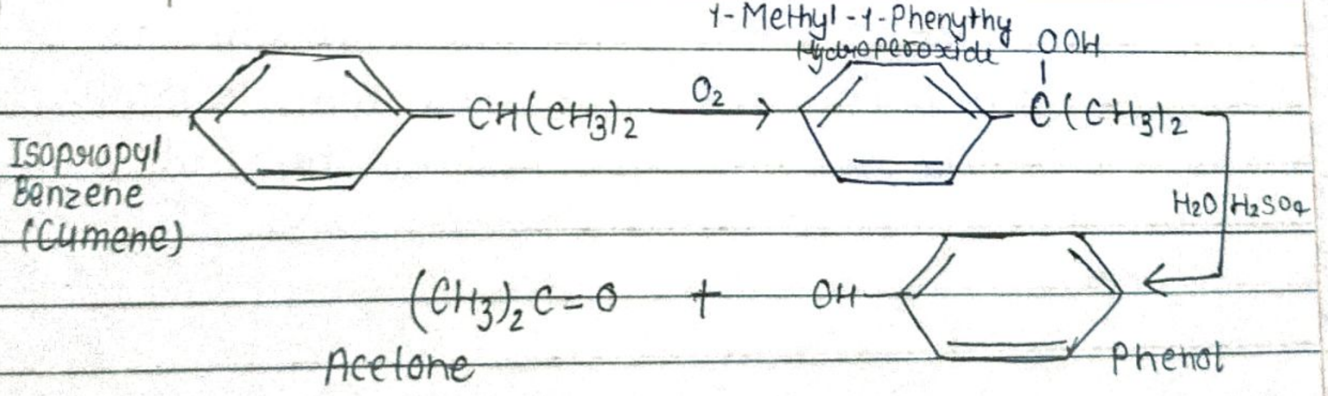
from Halo arenes -

Heating Chlorobenzene with aqueous Sodium Hydroxide at high pressure gives phenol after acidification.



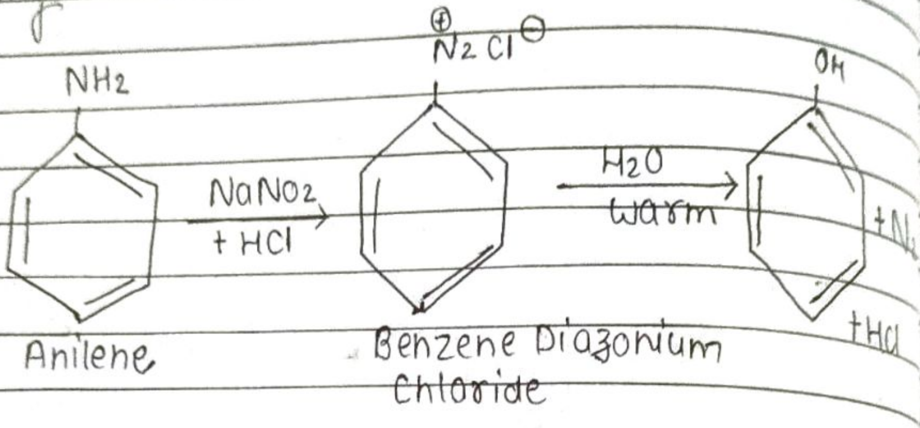
from Cumene -

oxidation of cumene takes place at the benzylic position to give a Hydroperoxide ~~its~~ on treatment with Dil H_2SO_4, this Hydroperoxide is converted to phenol and acetone.



from Diazonium Salts -

A Diazonium Salt is formed by treati an aromatic primary amine with Nitrous acid (NaNO₂ + HCl) at 273 - 278 K. Diazonium Salts are Hydrolysed to phenols by warming with Water or by treating with Dilute acids.



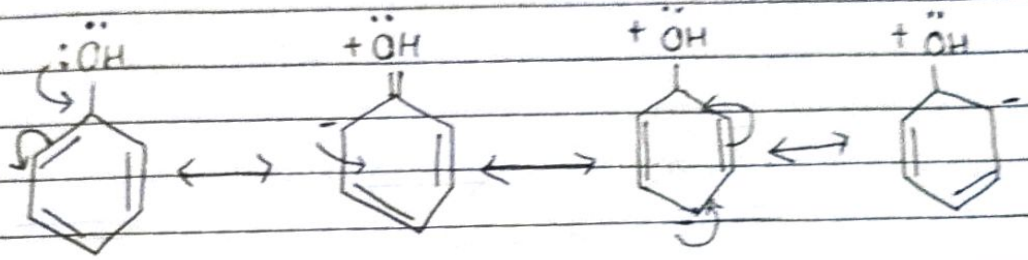
ACIDITY OF PHENOLS -

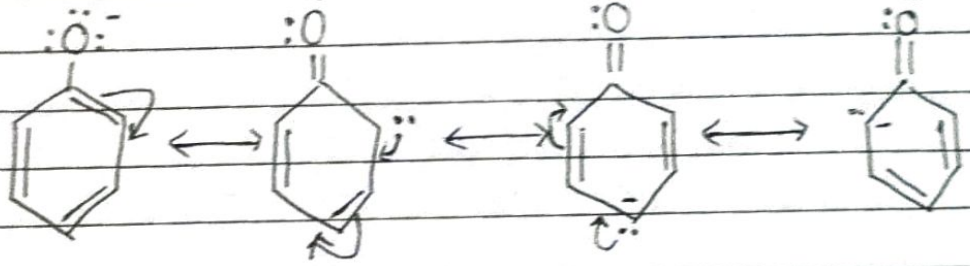
The Most characteristic property of Phenols is their acidity.

Phenols are more acidic than alcohol but less acidic than carboxylic acid. Because of ⇒acidic nature, Phenols can turn blue litmus red and react with aqueous alkali to from Phenate (Phenoxide ion). Both rxn are not Shown by alcohol.

Hydroxy group bonded to benzene ring is much more acidic than hydroxy group to alcohol. This is because of the resonance in phenol. the oxygen atom acquires a Positive charge which weakness the oxygen Hydrogen bond and facilatates the release of a proton.

e^- delocalization in phenol and Phenoxide ion is represented by resonance Str.





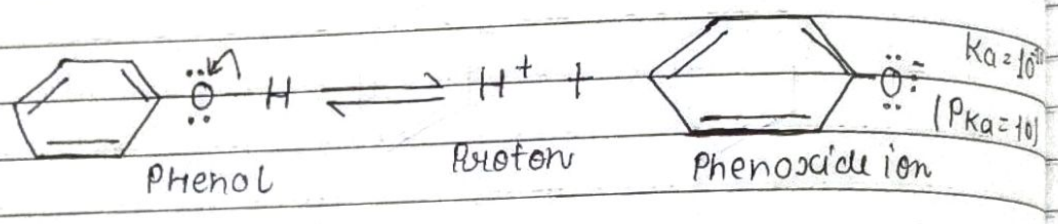
Hence Both Phenol and Phenoxide ion are stablized by resonance. Capture to phenol, Phenoxide ion is more Stable as the negative Charges gets delocalized over Benzene ring. But the resonating Structure of Phenol involves the Separation of negative & Positive Charges. Therefore ~~has~~ phenol has greater tendancy to form Phenoxide ion by releasing the proton.

To help us understand why phenols are more acidic than alcohols, let's compare the ionization equilibria for Phenol and ethanol.

⇒ Compare to alcohols. Phenol are Stronger acid as the pka value for phenol is 10 while for alcohols it's close to 16.

$$CH_3CH_2\ddot{\underset{..}{O}}-H \rightleftharpoons H^+ + CH_3CH_2\ddot{\underset{..}{O}}: \quad K_a = 10^{-16}$$

Ethanol Proton Ethoxide ion ($pK_a = 16$)

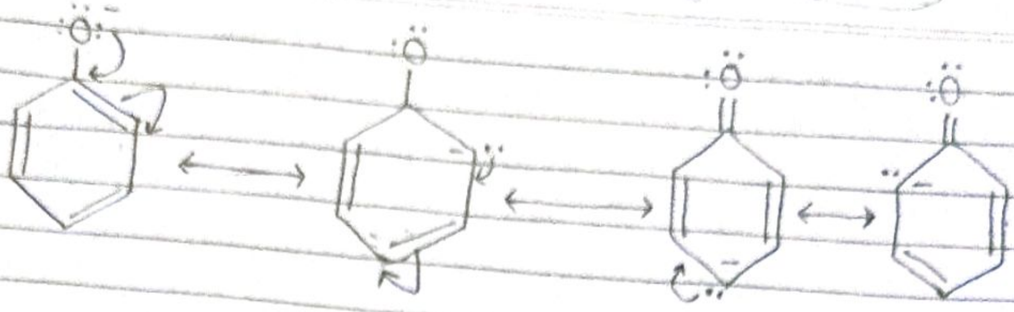


In Ethoxide, the resonance is not Possible and the +I effect of the Hydrocarbon Chain increases the e⁻ density between O and H and decreases the chances of H^+ to leave the alcohol. The more the chain is long and branched the greater the effect, the less will the alcohol be acidic.

⇒ Delocalization of its negative charge strongly Stablizes phenoxide ion.

$$CH_3CH_2\ddot{\underset{..}{O}}-H \rightleftharpoons H^+ + CH_3CH_2\ddot{O}:^-$$

Ethanol Proton Ethoxide ion



Effect of Substituent on Acidity of Phenol -

As the acidic nature of Phenol is due to the resonance Stablization of Phenoxide ion compare to phenol.

Therefore the presence of any Substituent on aromatic ring which can Stalized the phenoxide ion will tend to increases the acidity of Phenol.

While any Substituent which destablized the phenoxide ion by increasing the negative charge will decrease the acidic nature of Phenol.

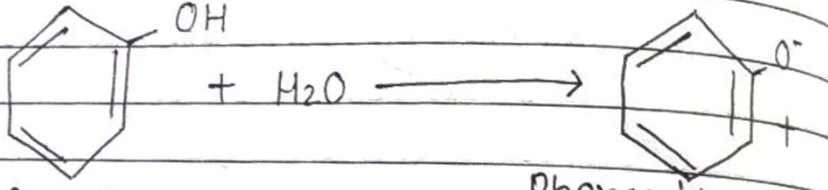
In other words, the presence of electron withdrawing group on Benzene ring in Phenol increase acidity of Phenol and electron releasing group will decrease the acidity.

for example, if there is a Nitro group It will increase the acidic nature of phenol. Hence nitrophenol will be more acidic than phenol as nitro group imparts negative mesomaric effect and negative inductive effect, hence acts as electron withdrawing group.

Qualitative test for Phenol -

litmus Test -

Phenol is a weak acid it gives red colour with litmus paper. The dissociation of Phenol in water is represented as follows -



ferric Chloride test -

Compounds with a Phenol group will form a blue, violet, Purple, green or red brown color upon addition of aqueous ferric chloride. This rxn. can be used as a test for Phenol groups.

a. Iron (III) Chloride test for Water Soluble Phenols -

Rxn

$$3ArOH + FeCl_3 \xrightarrow[\text{Pyridine}]{} FeO(Ar)_3$$

Colored Complex

Procedure - 15 mg of the unknown compound was dissolved in 0.5 ml of Water or water alcohol mixture and add 1 to 2 drops of 1% aqueous iron (III) Chloride Sol^n

Observation - A Red, ~~blue~~ blue, green or purple color observed.

Iron (III) Chloride Pyridine test for Water Insoluble Phenols. -

Procedure - A more sensitive test for Phenols consist of dissolving or Suspending 15 mg of the unknown in 0.5ml of methylene chloride and adding 3-5 drops of a 1% Sol^n ferric Chloride in methylene chloride. Add a drop of pyridine and Stir.

Observation - Addition of pyridine and Stirring will produce a color if Phenols or enols are present.

liebermann's test -

When Phenol is treated with Sodium nitr in the presence of Conc. H_2SO_4 deep blu or green colour is produced. The blu or green colour changes to red or brown colour on treatment with water. The red colour is due to the formation of indophenol.

The red colour again changes to blu or green by the addition of strong alkali The blue or green colour is due to the formation of indophenols anion.

Phthalein Dye test -

Phenol on heating with phthaleic anhydride in the presence of H_2SO_4 produces phenolphthalein, which is colourless Phenophthalein gives pink colour on treating with alkali.

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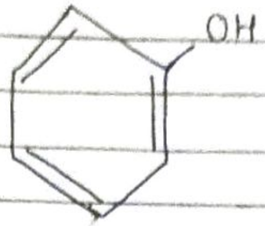
Phenol -

Structure & Uses -



The main use of Phenol is as feedstocks of Phenolic resins, bisphenol A and caprolactam (Used in manufacturing of Nylon 6).

Phenol is also used in the Study and extraction of bio-molecules.

Molecular biology finds applications of Phenol in the extraction of nucleic acids from tissue samples for Further investigation.

Phenol is also used in cosmetic industry in the manufacturing of Sunscreen Skin lightening Creams and hair coloring Soln.

Phenol is also a versalite precursor to a large collection of drugs. Most notably asprin but also many herbicide and pharmaceutical drugs.

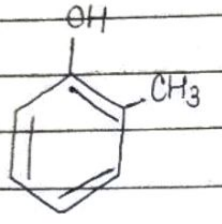
It is also used in ingrown nails in the " nail matrix phenolization Method".

Cresols - (Hydroxytoluene)-

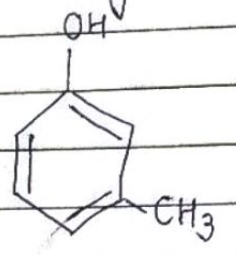
Cresols (also hydroxytoluene) are organic compounds which are methylphenols.

Cresols have a disinfectant and corrosive effect due to the degradation of Proteins.

Isomers of Cresol



O-Cresol



M-Cresol

P-Cresol

Uses of Cresols -

Mixed cresols are used to disinfactants, preservatives and wood preservatives.

O-cresol is used as a solvent, disinfactant and chemical intermediate.

M-cresol is used to produce certain herbicides, as a precursor to the pyrethroid.

insecticides, to produce antioxidants and to manufacture the explosive 2,4,6 nitro- in- cresol.

p- cresol is used largely in the formulation of antioxidants and in the fragrance and dye industries.

Uses for various Drug Synthesis-

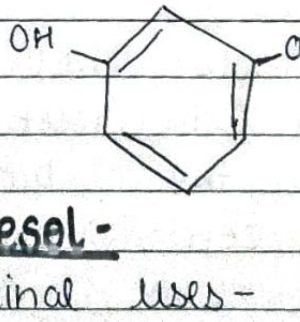
O- Cresol used for synthesis of carvacol.

m- Cresol used for synthesis of toliprolol, tolamolol etc.

p- Cresol is consumed mainly in the production of antioxidants e.g.- Butylated Hydroxy toluene. (BHT)

Resorcinol -

Resorcinol (or resorcin) is a benzenediol (m- dihydroxy Benzene).



Uses of Cresol -

Medicinal uses- It is an antiseptic and disinfactant, and is used 5 to 10% in ointment in the treatment of chronic Skin disease such as psoriasis, hidradenitis, suppurativa and eczema.

It has also been employed in the treatment of gastric ulcer in doses of 125 - 250 mg in pills, and is said to be analgesic and homeostatic (stop bleeding) in its action.

A ~~has~~ 2% ~~also~~ sol^n used to treat external vaginal itching and irritation

Resorcinol is a skin protectant and topical analgesic.

Chemical uses -

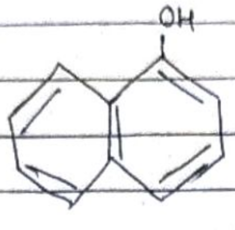
It is used in the production of diazo dyes and plasticizers and as a UV absorber in resins.

Resorcinol is an analytical reagent for the qualitative determination of Ketone (Seli won off's test).

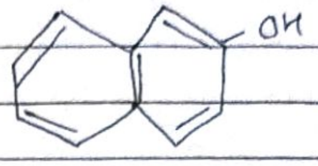
Resorcinol reacts with formaldehyde to form a thermoset resin which can form the basis of an aerogel (frozen smoke)

Naphthol -

Naphthol is a fluoroscent colorless (or occasionally yellow) crystalline solid with the formula $C_{10}H_7OH$. It has two isomer of 1- naphthol & 2 - Naphthol.



α - naphthol



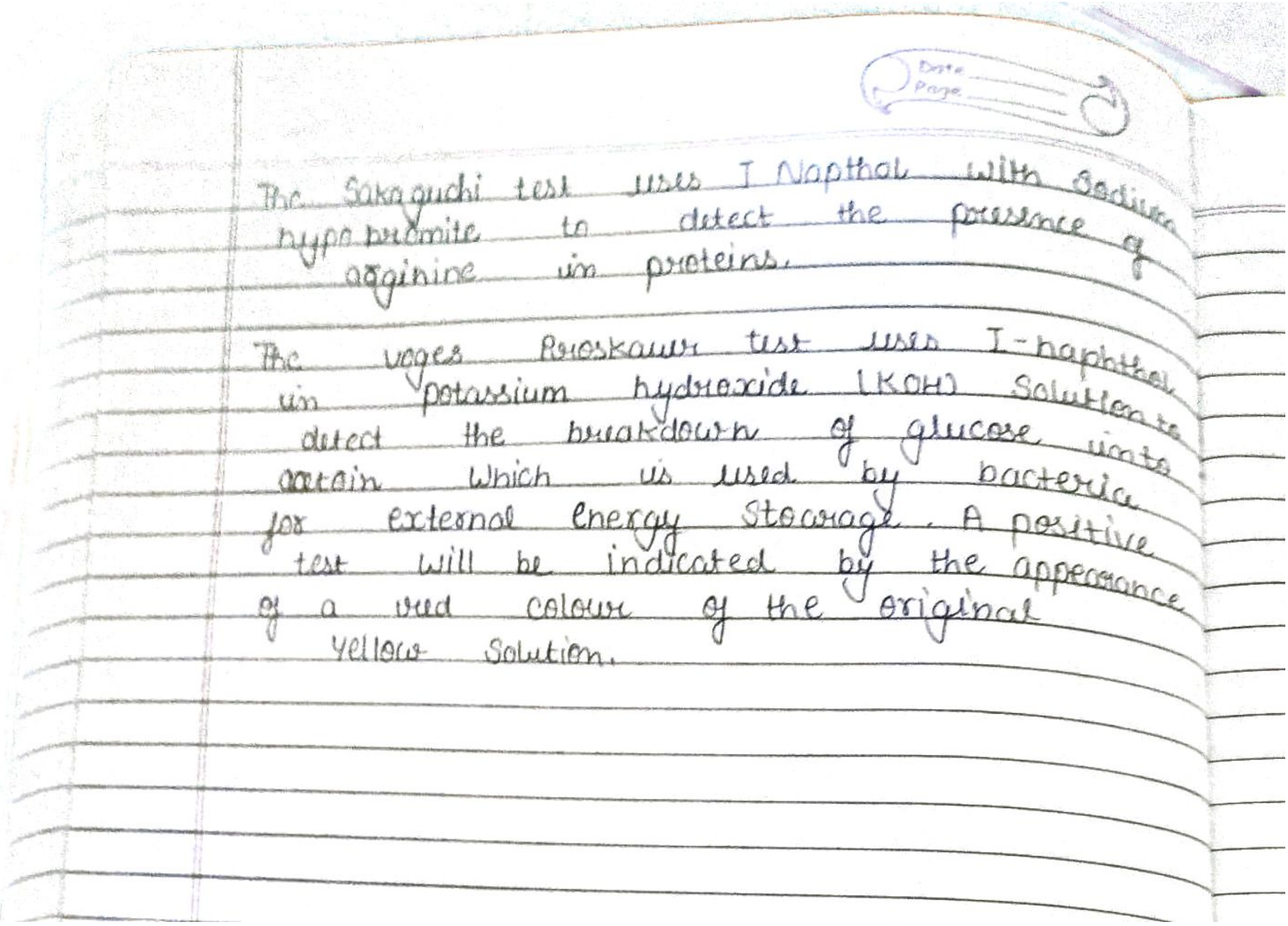
β - naphthol

Uses of Napthol-

Naphthols (both 1 & 2 isomers) are used as biomarkers for livestock & Humans exposed to polycylic aromatic hydrocarbon.

1 - Naphthol is a precursor to a variety of insecticides including carbaryl and pharmaceuticals including nadolol. It undergoes azo coupling to give various azo dyes but these are generally less useful than those derived from 2 naphthol.

In Molisch's test 1 - Naphthol dissolved in ethanol, Known as molisch's reagent is used as reagent for detecting the presence of carbohydrate.



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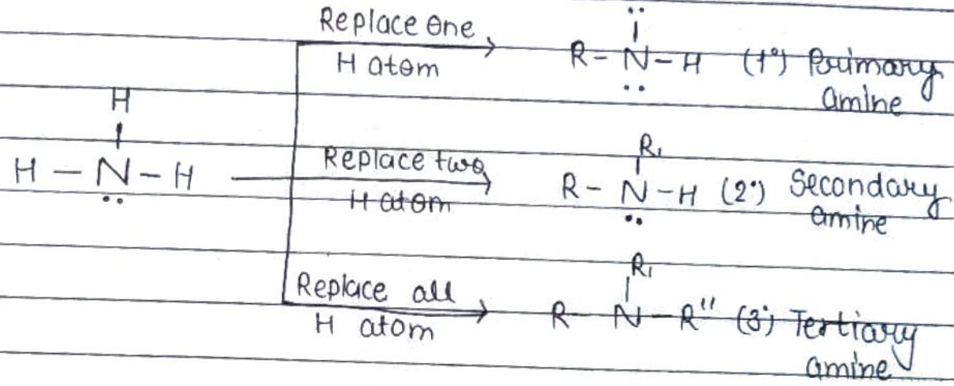
The Sakaguchi test uses I Napthal with Sodium hypobromite to detect the presence of arginine in proteins.

The voges Proskauer test uses I-naphthol in potassium hydroxide (KOH) Solution to detect the breakdown of glucose into actoin which is used by bacteria for external energy Stoarage. A positive test will be indicated by the appearance of a red colour of the original yellow Solution.

Aromatic Amines

Amines are regarded as derivatives of ammonia in which one, two or all three hydrogen atoms are replaced by alkyl or aryl group.

Classification of amines -



Preparation of Amines -

By Reduction of Nitro compound - Nitro compound can be catalytically ~~replaced~~ reduced by passing Hydrogen gas in presence of Raney Ni, Finely divided Pt or Pd as catalyst at room temp.

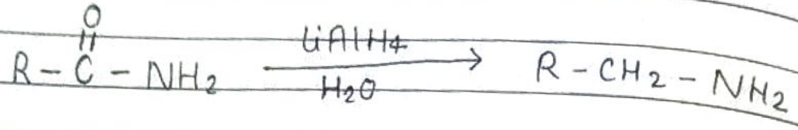
$$Ar-NO_2 + 3H_2 \xrightarrow{Ni, Pt\ or\ Pd} Ar-NH_2 + 2H_2O$$

Nitro compounds can also be reduced with active metals such as Fe, Sn, Zn etc with Conc. HCl.

$$Ar-NO_2 + 3H_2 \xrightarrow[Or\ Fe/HCl]{Sn/HCl} Ar-NH_2 + 2H_2O$$

By reduction of Amides -

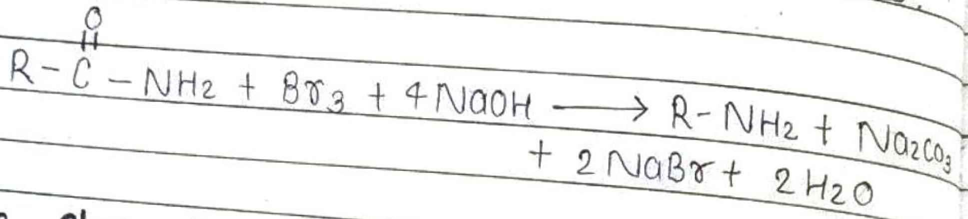
Amides are reduced to corresponding amines by Li.Al.H₄



$$R-\overset{O}{\overset{\|}{C}}-NH_2 \xrightarrow[H_2O]{LiAlH_4} R-CH_2-NH_2$$

By Hoffmann Bromaide degradation Rxn -

Primary amines can be prepared from amides by treatment with Br_2 and KOH. Amine contains one carbon atom less than the parent amides.



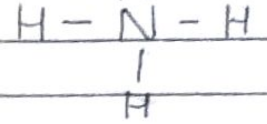
$$R-\overset{O}{\overset{\|}{C}}-NH_2 + Br_3 + 4NaOH \longrightarrow R-NH_2 + Na_2CO_3 + 2NaBr + 2H_2O$$

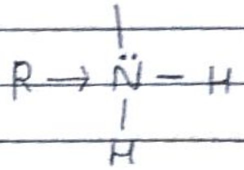
Basic Character of Amines -

Amines have an unsheared pair of electron on Nitrogen atom due to which they behave as Lewis Base.

Comprarisen of Basic Strength of Aliphatic amines & Ammonia -

Aliphatic amines are Stronger bases than ammonia due to +I effect of alkyl groups leading to high e^- density on the nitrogen atom.

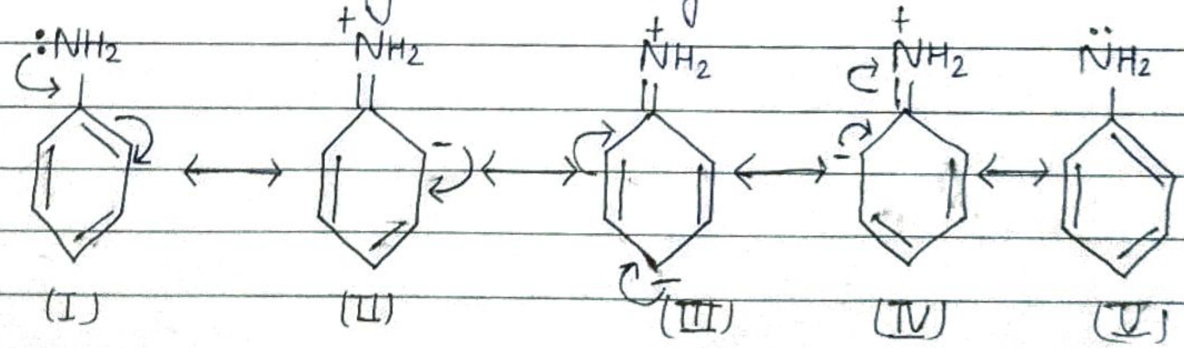

[Lone pair less Avalible]


lone pair more avaliable

Comparison of basic Strength of Aryl Amines & Alkonamines -

Generaly aryl amines are considerably less basic than alkyl amines. Takeing an example of anilene and ethylamine it is observed that ethyl amine is more basic than anilene. In anilene $-NH_2$ group is directaly attached to Benzene ring.

Hence unshared pair of electron on nitrogen is less available for Protonation because of resonance. Below mentioned are resonating str. of anilene.



In the above resonating structure there is a positive charge on Nitrogen atom makeing the lone pair less available for Protonation. Hence anilene is less basic than ethyl amine which has no resonating structure.

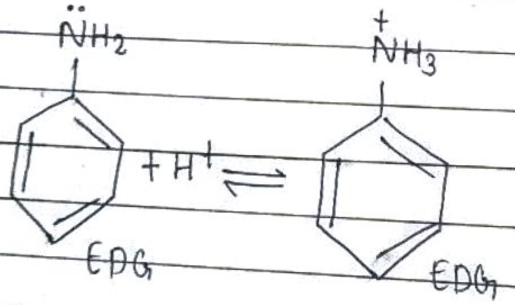
Effect of Basis Substituent on Basic Characters of Amines-

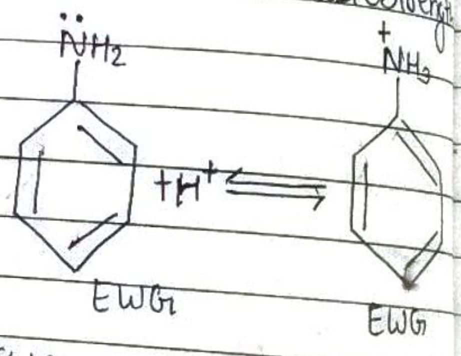
Electron donating or electron releasing group (EDG) increases Basic Strength.

Electron withdrawing group (EWG) decreases Basic Strength.

EDG releases electrons, stablizes the cation, and increases Basic strength

EWG: withdraws electrons destablizes the cation and decreases basic strength





EDG = $-CH_3$, $-OCH_3$, $-NH_2$

EWG = $-NO_2$, $-CN$, $-X$ (Halogen)

✓ Aryl Diazenium Salts -

Prepration - Reaction of Primary arylamines with nitrous acid results in the formation of relatively stable arenediazonium salts - The reaction occurs through the intermediacy of an N- nitrosoamine.
The Nitroso amine is converted to a diazonium ion.

(Arenediazonium Salt (stable if kept 5°C))

$$\underset{\text{Primary Anilene}}{Ar-NH_2} + NaNO_2 + 2HX \longrightarrow Ar-\overset{+}{N}\equiv N:\overset{-}{X} + NaX + 2H_2O$$

Synthetic Uses of aryl diazenium Salts -

$$Ar\overset{+}{N_2}\overset{-}{Cl}$$

$\xrightarrow{CuCl/HCl} ArCl + N_2$

$\xrightarrow{CuBr/HBr} ArBr + N_2$

$\xrightarrow{CuCN/KCN} ArCN + N_2$

$\xrightarrow{Cu/HCl} Ar{\cdot}Cl + N_2 + CuCl$

$\xrightarrow{KI} Ar{-}I + KCl + N_2$

$\xrightarrow{Cu/HBr} Ar{-}Br + N_2 + CuCl$

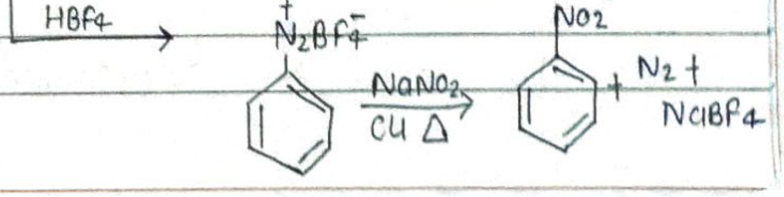
$\xrightarrow{HBF_4} Ar-\overset{+}{N_2}\,\overset{-}{BF_4} \xrightarrow{\Delta} Ar-F + BF_3 + N_2$

$\xrightarrow{H_3PO_3 + H_2O} ArH + N_2 + H_3PO_3 + HCl$

$\xrightarrow{H_2O} ArOH + N_2 + HCl$

$\xrightarrow{CH_3CH_2OH} ArH + N_2 + CH_3CHO + HCl$

$\xrightarrow{HBF_4}$



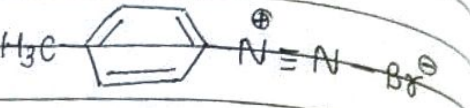
Aryl Diazonium Salts -

Aromatic diazonium Salt represented by -

$$Ar-\overset{\oplus}{N}\equiv N-\overset{\ominus}{X} \quad (\because X = Cl^-, Br^-, NO_2^-, HSO_4^- \text{ etc})$$

eg. -

Benzene Diazonium
Chloride Salt



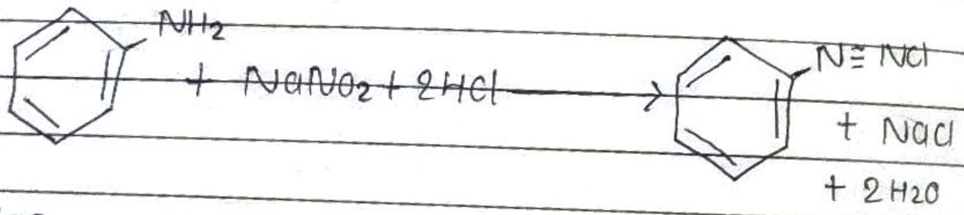
P - toluene diazonium
bromide

Properties & Prepration of Aryl Diazonium Salt ($Ar\overset{+}{N}_2X^-$)

Prepration -

It is proposed by the intraction of primary aromatic amine, Sodium nitrite and an acid at low temp (0°C)
Thus reaction is called diazotization

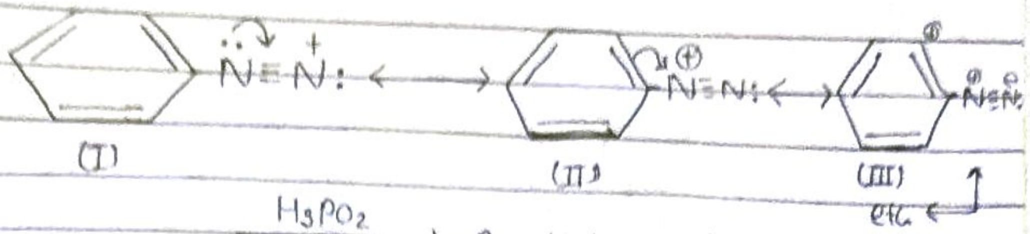
$$ArNH_2 + NaNO_2 + 2HX \xrightarrow{(0-5^\circ C)} ArN_2X + NaX + 2H_2O$$



Properties -

Aryl diazonium salt is more Stable than aliphatic diazonium Salt

The Stability of diazonium Salt is due to its resonance -



Synthetic Application of Aryl Diazonium Salt

ArN_2Cl (Aryl diazonium Salt)

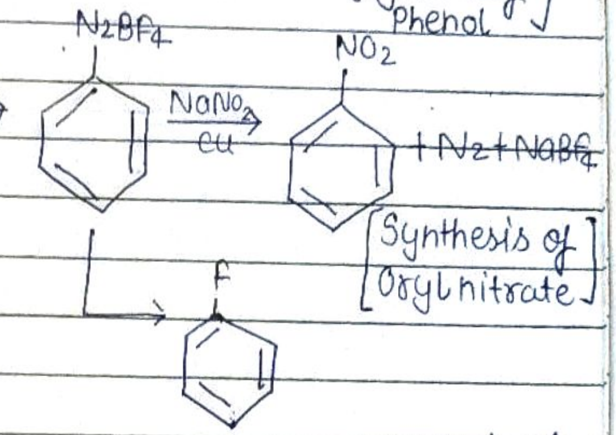
$\xrightarrow[H_2O/Cu^{\oplus}]{H_3PO_2} Ar-H + N_2 + HX + H_3PO_3$

$\xrightarrow[CuBr]{CuCl \text{ or}} Ar-Cl \,/\, Ar-Br + N_2 + CuX$ (Synthesis of oryl Halide)

$\xrightarrow[-N_2]{CuCN} Ar-CN \xrightarrow[H^+]{H_2O} Ar-COOH$ [Sythesis of oryl carboxylic acid]

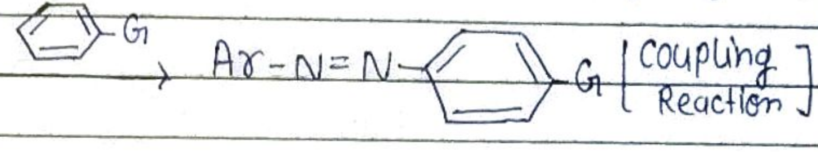
$\xrightarrow{H_2O/H^+} Ar-OH + N_2 + HX$ [Synthesis of Phenol]

$\xrightarrow{HBF_4}$



[Synthesis of Oryl nitrate]

$\xrightarrow{Ar-H} Ar-N=N-Ar^- + HX$ [Synthesis of Azo-Dyene]



[Coupling Reaction]

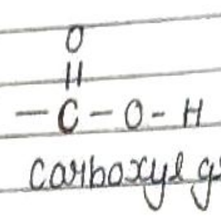
$\xrightarrow{R-OH} Ar-O-R + N_2 + HX$ [Synthesis of Ether]

$\xrightarrow{C_6H_6/NaOH} Ar-C_6H_5 + N_2 + HCl$

[Synthesis of Bi-phenil]

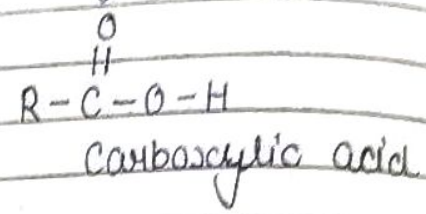
Carboxylic Acid :-

The combination of a carbonyl group and a Hydroxy on the same carbon atom is called a carboxylic group. Compounds containing the carboxyl group are distinctly acidic and are called carboxylic acids. The carboxyl group is one of the most widely occurring functional groups in Chemistry & Biochemistry.



$-\overset{\overset{O}{\|}}{C}-O-H$

carboxyl group



$R-\overset{\overset{O}{\|}}{C}-O-H$

Carboxylic acid

Depending on whether an R or Ar. residue is attached to the carboxyl group carboxylic acids are classified as alphatic or aromatic

Aliphatic carboxylic Acids

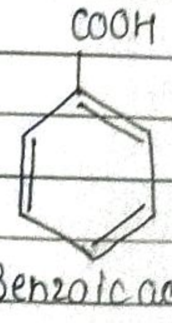
R- COOH R = H or alkyl CH_3-COOH

Aliphatic acid Acetic acid

Aromatic Carboxylic Acids

Ar- COOH R = C_6H_5-

Aromatic acid

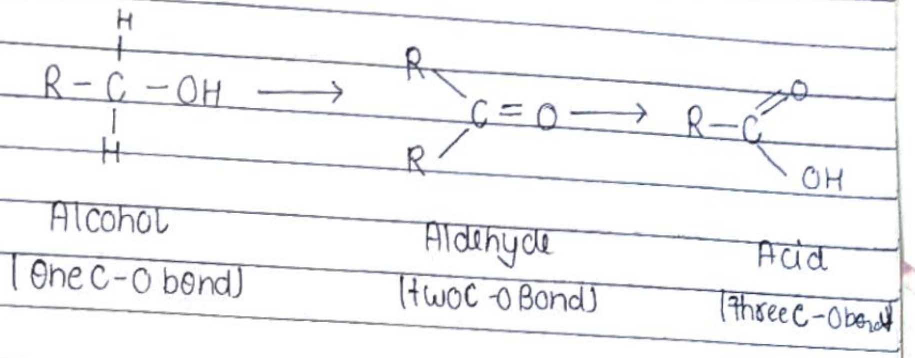


Benzoic acid

Prepration-

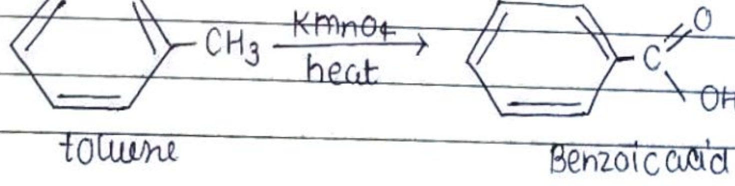
Oxidation of Primary Alcohol & Aldehyde -

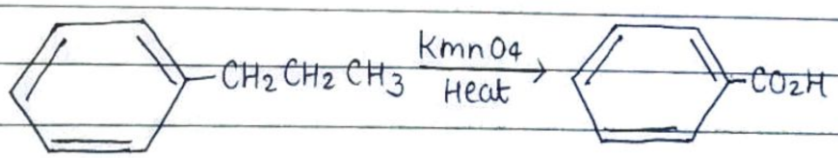
Primary alcohols are oxidized to carboxylic acid by $KmnO_4$ or by a mixture of $K_2Cr_2O_7$ and H_2SO_4.



Oxidation of Alkyl Benzene -

Aromatic acid can be prepared by oxidizing an alkyl side chain on an aromatic ring.



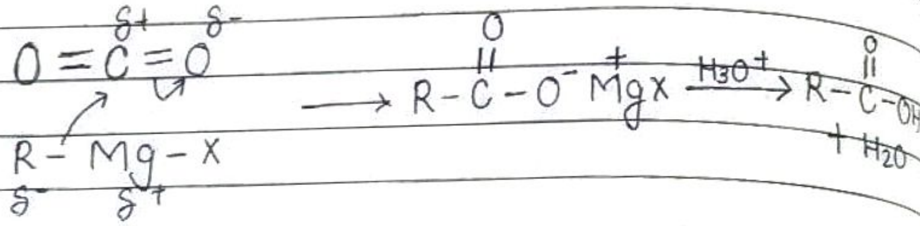


Reaction with Grignard Reagents with CO_2:

– (Carbonation of Grignard Reagent) –

Grignard reagent add to the carbonyl group of carbon di oxide to give acids. After protonation of the intermediate carboxylate salts with a mineral acid like aqueous HCl

The acid obtained has one or more carbon atom (the reaction provides a way to increase the length of a chain)

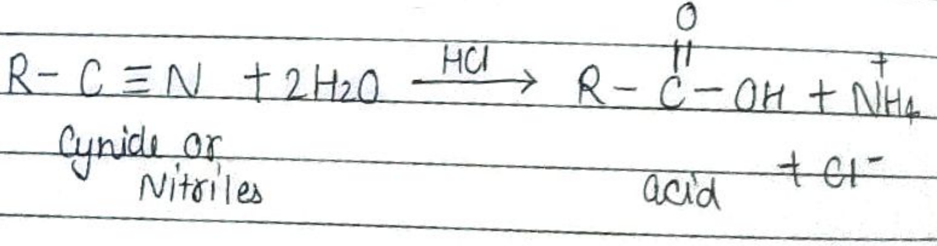


$$\overset{\delta-}{R}-\overset{\delta+}{Mg}-X + O=\overset{\delta+}{C}=\overset{\delta-}{O} \longrightarrow R-\overset{O}{\overset{\|}{C}}-O^{-}\overset{+}{Mg}X \xrightarrow{H_3O^+} R-\overset{O}{\overset{\|}{C}}-OH + H_2O$$

Hydrolysis of Cyanides (Nitriles) -

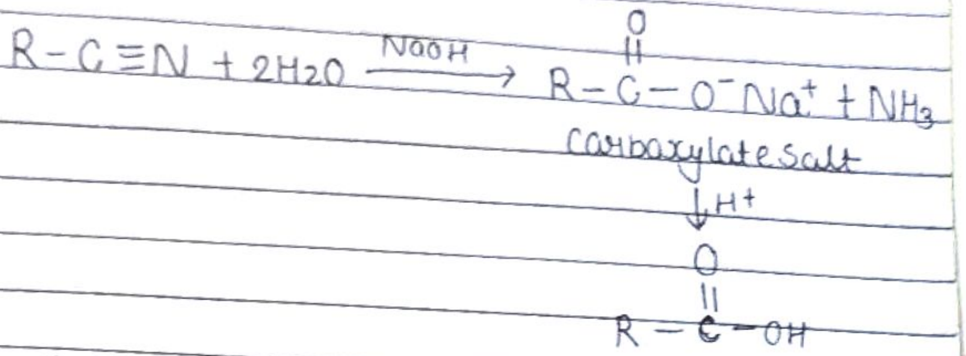
The reaction requires either acid or Base.

In acid, the nitrogen atom of the cyanide is converted to an ammonium ion.



$$R-C\equiv N + 2H_2O \xrightarrow{HCl} R-\overset{O}{\overset{\|}{C}}-OH + \overset{+}{N}H_4 + Cl^-$$

In Base, the nitrogen atom is converted to ammonia and the organic product is the carboxylate salt, Which must be naturalized in a separate step to give the acid.



$$R-C\equiv N + 2H_2O \xrightarrow{NaOH} R-\overset{O}{\overset{\|}{C}}-O^-Na^+ + NH_3$$

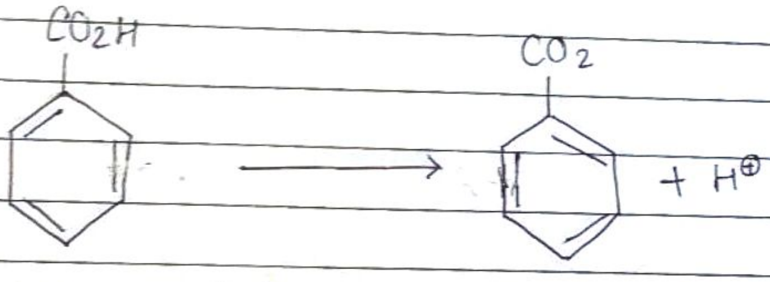
Carboxylate salt

$$\downarrow H^+$$

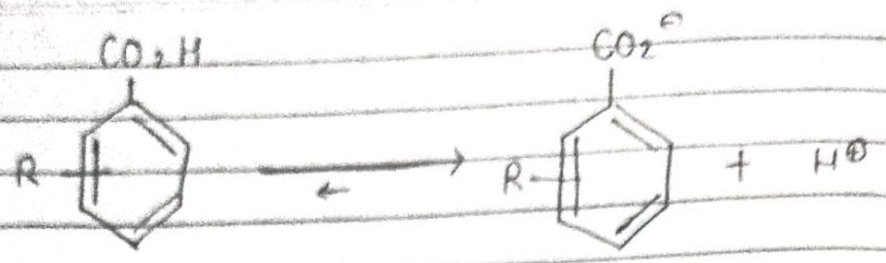
$$R-\overset{O}{\overset{\|}{C}}-OH$$

Acidity of Aromatic carboxylic acid-

Benzoic acid is the simplest of aromatic carboxylic acid.



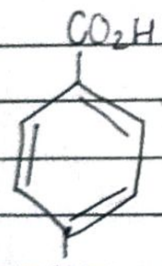
Two factor influence the acidity of Substituted aromatic carboxylic acids The resonance effect and the inductive effect. Where as the inductive effect only operates through σ bonds the resonances effect operates by e⁻ or charge delocalization through π Bonds.



Acidity of Aromatic Carboxylic Acid :-

Inductive Effect-

When an aromatic carboxylic acid has a Substituent that does not have lone pairs of electrons or charge that can be delocalized in the aromatic nucleus, then, only the inductive effect can be invoked in explaining its degree of acidity.

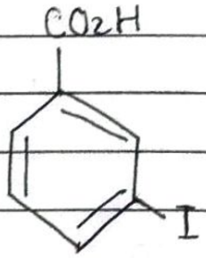


4 MethylBenzoicacid

Pka = 4.4

Benzoic acid

Pka = 4.2



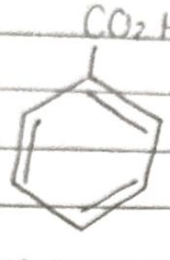
3-Iodobenzoicacid

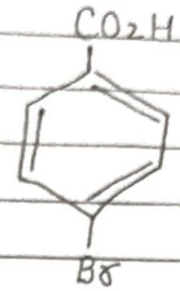
Pka = 3.8

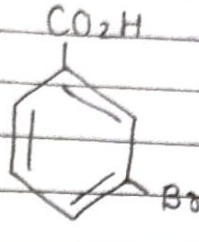
Electron donation via inductive effect

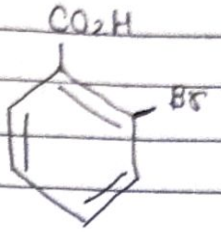
Electron Withdrawal via inductive Effect

Where as e^- donating groups suppress the acidity of Benzoic acids. e^- withdrawing groups enhance the acidity.


Benzoic acid
PKa = 4.2


4-Bromobenzoic Acid
PKa = 4.0


3 Bromobenzoic acid
PKa = 3.8


2 BromoBenzoic Acid
PKa = 2.9

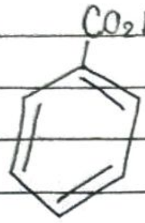
Halides (F, Cl, Br & I) are usually considered as weakly ring deactivating through the inductive effect. The Halobenzoate anions are more stablized than benzoate anions, hence the higher acidity of all isomeric halobenzoic acids relative to unsubstituted benzoic acid.

The 2 halobenzoic acids are more acidic than 3 halobenzoic acids, which are more acidic than the 4 - halobenzoic acid derivatives.

Acidity of Aromatic Carboxylic Acids :-

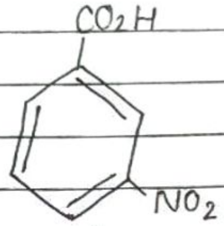
The Resonance Effect -

When both resonance and inductive effects apply in a specified Substrate. The resonance effect dominates the inductive effect and thus determines the order of acidity among isomeric carboxylic acids.



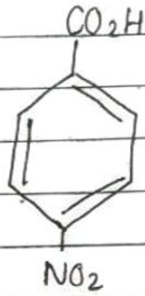
Benzoicacid

Pka = 4.2



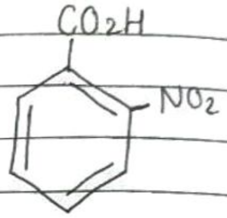
m-Nitro ~~Benzoic acid~~

Pka = 3.5



P-Nitro benzoic acid

Pka = 3.4



O-Nitro Benzoic ~~acid~~

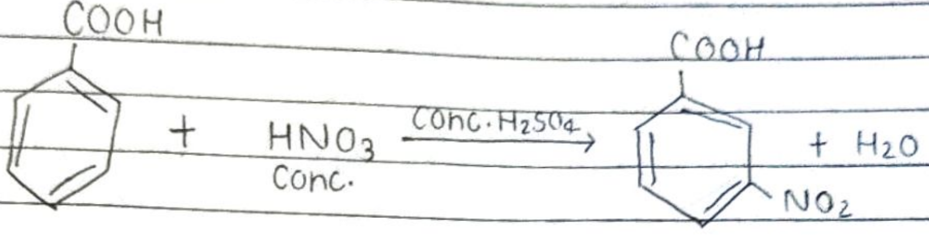
Pka = 2.2

The carboxylate anion obtained in the ionization of aromatic carboxylic acids is best Stablized when there are electron withdrawing Substituents attached to the aromatic nucleus.

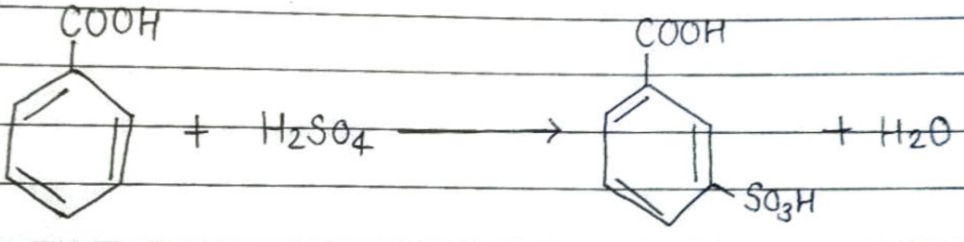
It is for this reason that the nitro benzoic acid derivatives, with the highly electron withdrawing nitro group, are stronger acids than Benzoic acid.

Electrophilic Substitution Rxn of Benzoic Acid-

Aromatic carboxylic acids undergo different type of electrophilic Substitution reaction like nitration. Sulphonation and Halogination. Carboxyl group (-COOH) is electron withdrawing group. Thus, the reaction will occur at the meta position. The carboxyl group deactivates. Therefore, The reaction will only occur under vigorous condition.



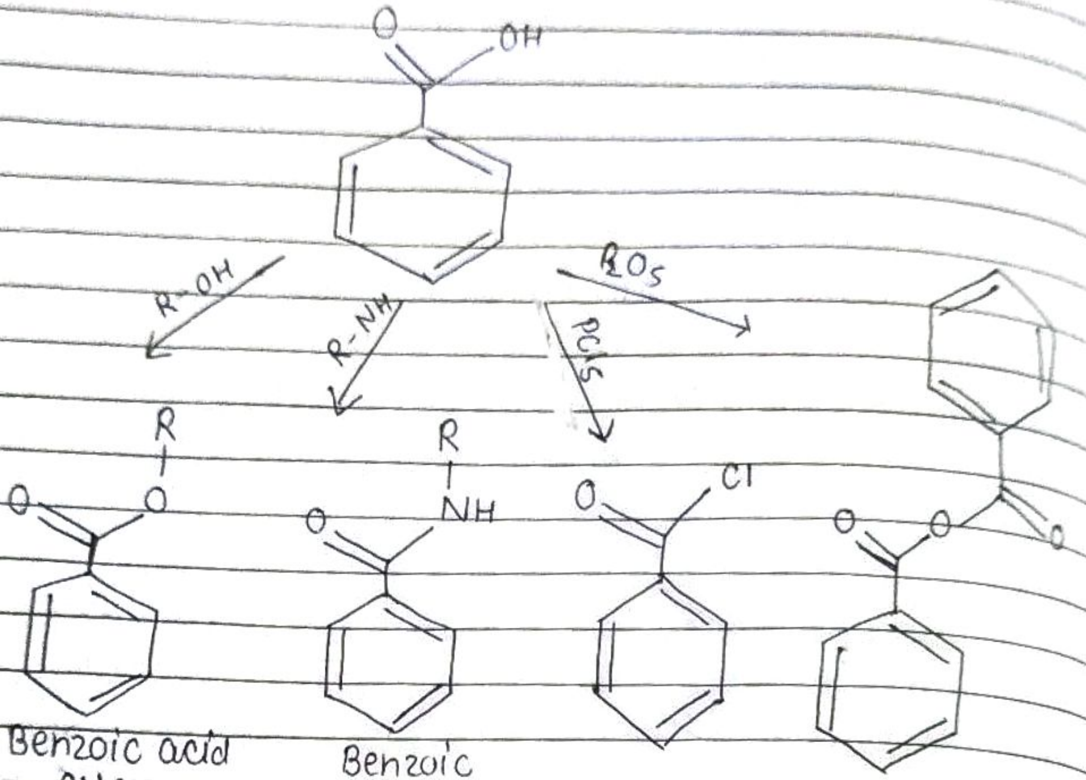
Nitration of Aromatic Carboxylic compounds



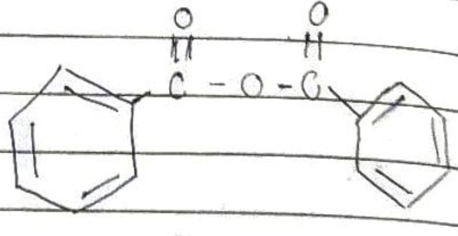
Sulphonation of Aromatic carboxylic compounds

Note - Aromatic carboxylic acids will not undergo friedel crafts Reaction because the carboxyl group is strong electron attracting group. Thus, Benzene ring will be deactivated. Hence, it will not undergo alkylation and acylation.

Other Important reaction of Benzoic Acid



Or



Anhydride