

Unit-2

Pharmaceutical Organic-II

UNIT- II**10 Hours**

Phenol* – Acidity of phenols, effect of substituents on acidity, qualitative tests, Structure and uses of phenol, cresols, resorcinol, naphthols

Aromatic Amines* – Basicity of amines, effect of substituents on basicity, and synthetic uses of aryl diazonium salts

Aromatic Acids* – Acidity, effect of substituents on acidity and important reactions of benzoic acid.

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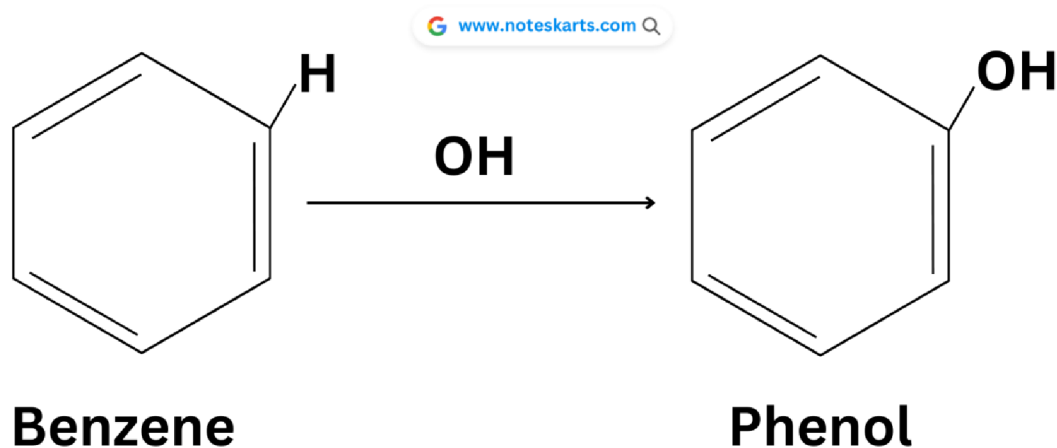


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- **Phenol*** – Acidity of phenols, effect of substituents on acidity, qualitative tests, Structure and uses of phenol, cresols, resorcinol, naphthols

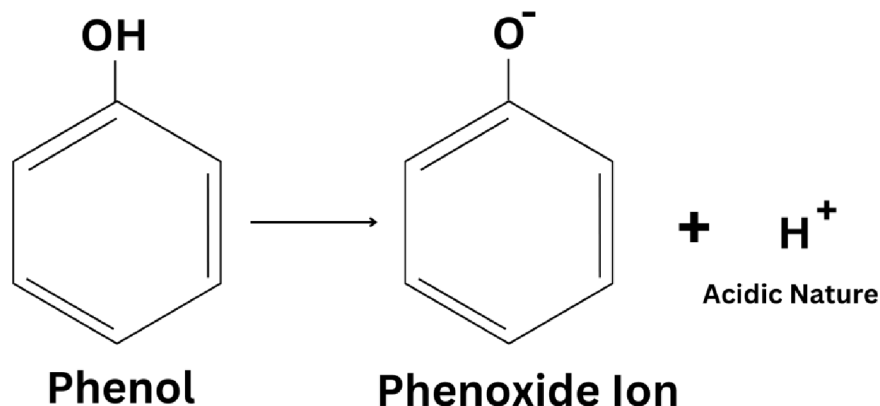
Phenols:

- Phenols are the compounds containing an OH group attached directly to a Benzene ring.
- They are mono-hydric or poly-hydric according to the number of OH groups that they contain.
- Phenol is an aromatic organic compound.



Acidity of phenols:

- When any substance dissociates into H^+ ions, it shows acidic character.



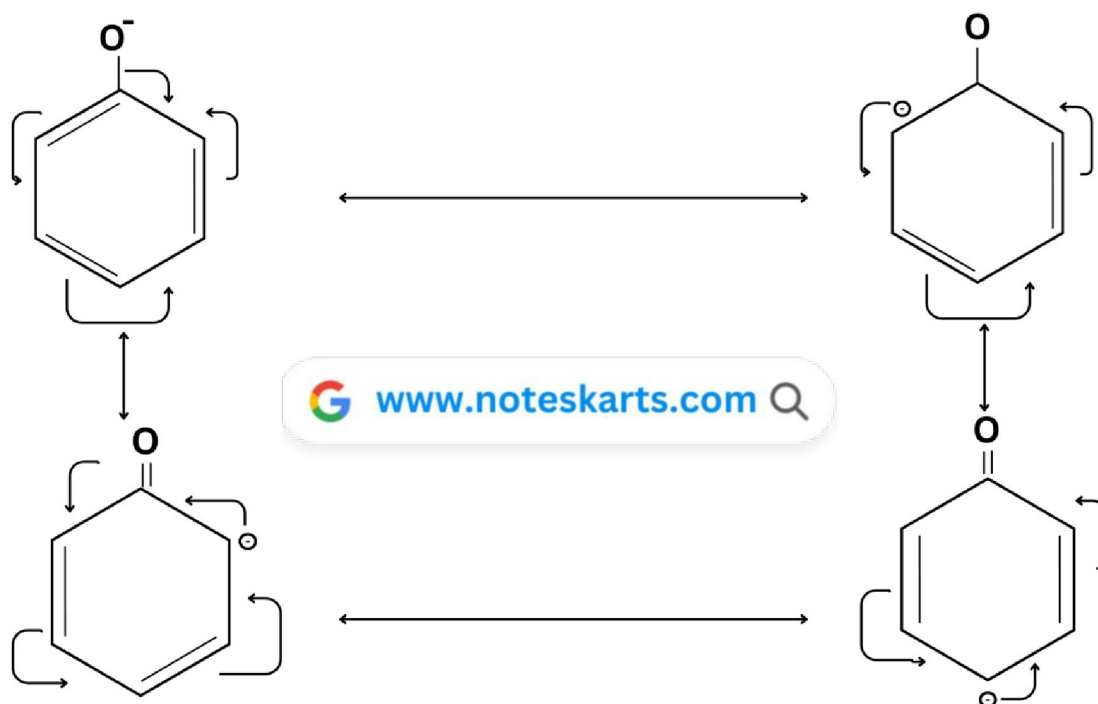
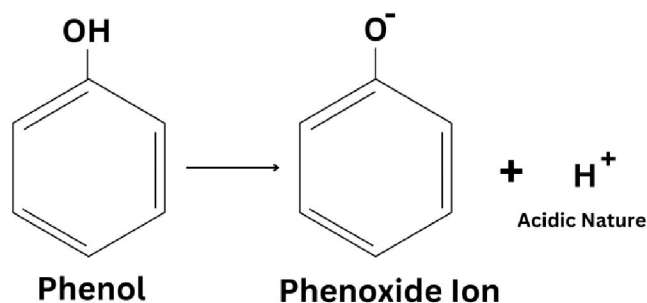
- When phenol dissociates, it breaks into two parts, one of which is H^+ . So, phenol is acidic in nature.
- The substance or compound which releases H^+ more or quickly has more acidic character.
- The substance which is more stable after the release of H^+ has more acidic character.
- Phenol is more acidic:-
- The condition or situation which shows acidity or stability is resonance and character.



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Resonance:

After Disassociation:



So phenol has resonance so it is stable due to resonance so it is Acidic in nature.

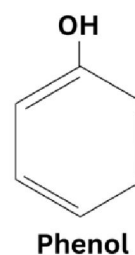
% S Character:-

Phenol has 3 sigma (σ) bond so it has sp^3 Hybridization.

In which % s character is

= 33.33%

Which is acidic more than alcohols.



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Effect of Substituent on Acidity of phenol.

There are two types of substituents (group) which will add or attached on phenol.

1. Electron donate group: which has ability to donate electrons. Eg: CH₃, Cl, OH, C₂H₅, etc.
2. Electron accept group: Which has ability to accept (gain) electrons. Eg: CN, NO₂, NH₂

Qualitative tests for Phenols:

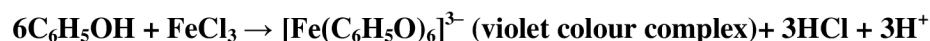
1. Litmus test
2. Ferric chloride test
3. Libermann's test
4. Bromine water test
5. Phthalein dye test

(a) Litmus Test:

- Scientists use litmus paper to test whether the given solution is acidic or basic.
- Red litmus paper turns blue while blue litmus paper remains unchanged in the presence of a base.
- Phenol turns blue litmus paper red. This shows that phenol is acidic in nature.
- Carboxylic acid also gives this test.
- Compared to carboxylic acid, phenol is weakly acidic and it does not give an effervescence with aqueous sodium carbonate.

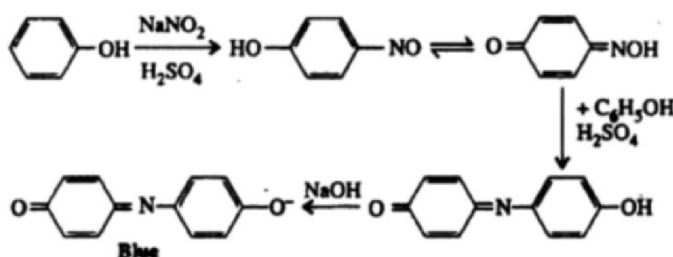
(b) Ferric Chloride Test:

- Aqueous solution of phenol reacts with freshly prepared ferric chloride solution gives coloured complex. Most phenols give dark coloured solutions.



(c) Libermann's Test:

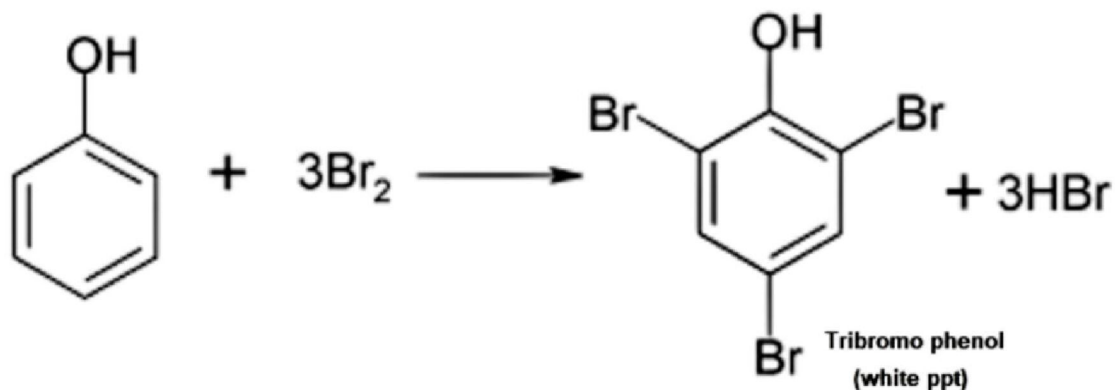
- Phenol reacts with concentrated sulfuric acid and sodium nitrite forms a yellow colour quinone monoxime complex. With excess of phenol and sulfuric acid a deep blue indophenol complex is formed.
- On dilution a red colour indophenol is formed which turns to deep blue colour sodium salt solution of indophenol on treatment with sodium hydroxide.



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(d) Bromine Water Test:

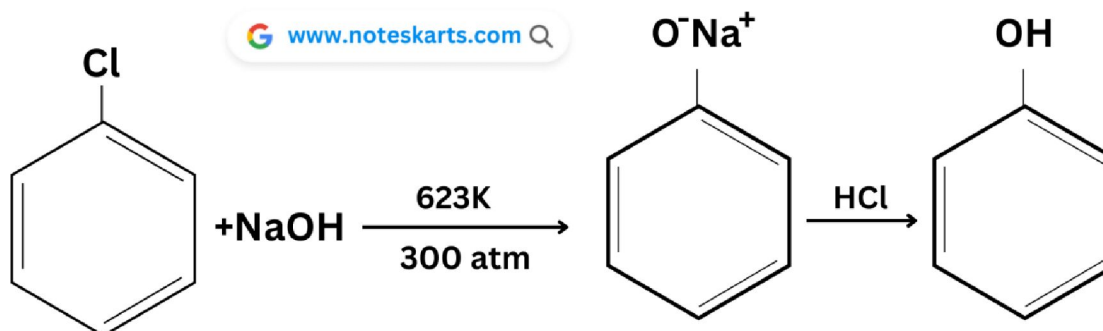
- Phenol undergoes electrophilic substitution reaction with bromine.
- When bromine water is added to aqueous solution of phenol the brown colour of bromine disappears and a white precipitate of tribromophenol is formed.



Method of Preparation of Phenol:

Preparation of Phenols from Haloarenes:

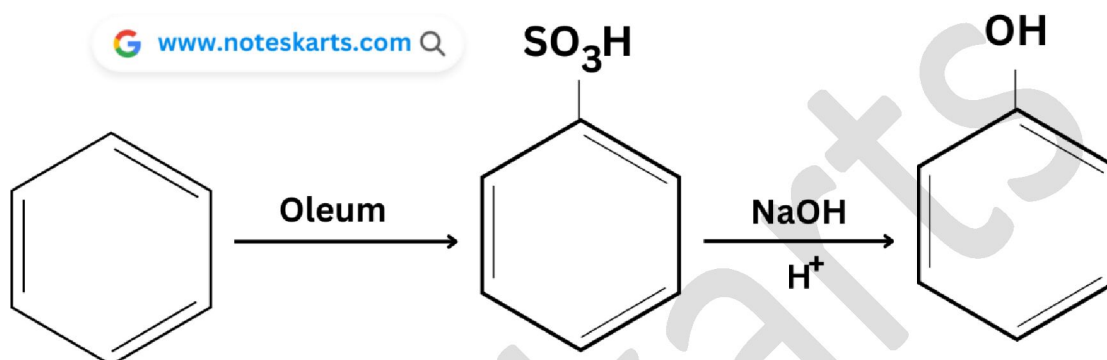
- Chlorobenzene is an example of a haloarene which is formed by the monosubstitution of the benzene ring.
- When chlorobenzene is fused with sodium hydroxide at 623K and 320 atm, sodium phenoxide is produced. Finally, sodium phenoxide on acidification gives phenol.



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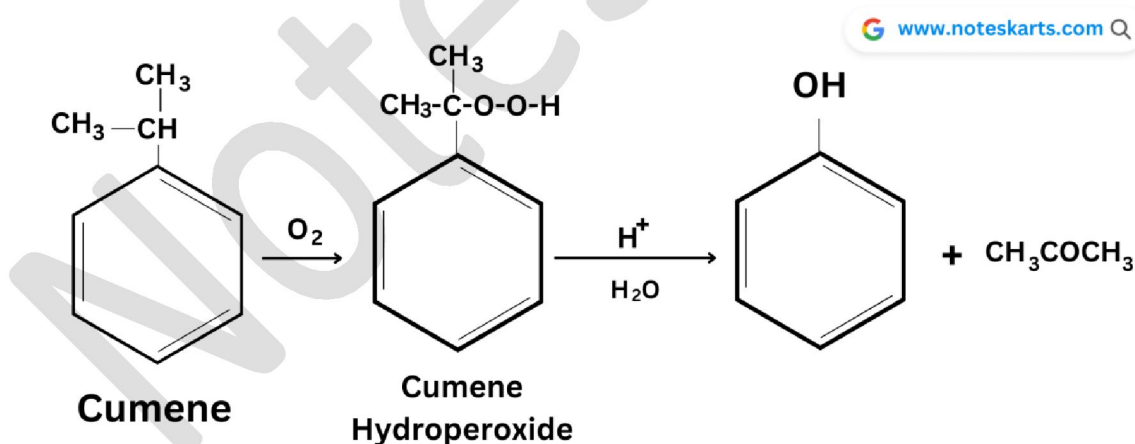
Preparation of Phenols from Benzene Sulphonic Acid:

- When sodium salts of aromatic sulphonic acids are fused with sodium hydroxide, sodium derivatives of phenol is obtained which on acidification yield phenol.



Preparation of Phenols from Cumene:

- Cumene is oxidized using air to give cumene hydroperoxide which on acidification yield phenol.



Physical properties of Phenol:

- Phenol is colorless.
- Soluble in water
- Used as disinfectants



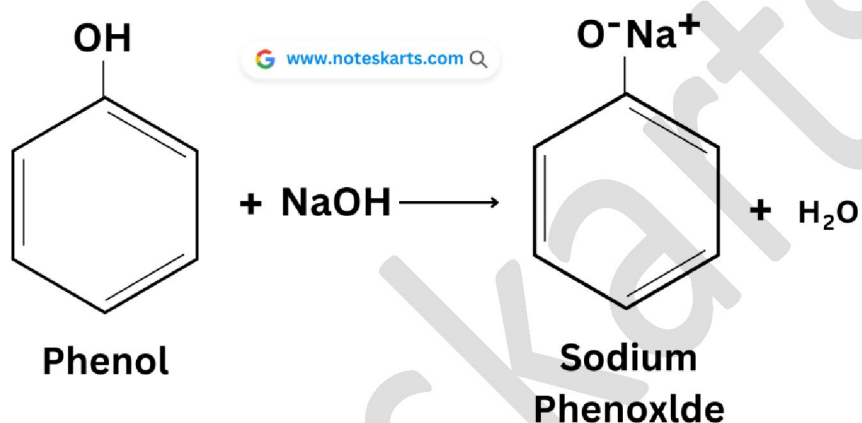
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- Melting point: 41°C
- Boiling Point: 182°C

Chemical reaction of Phenol:

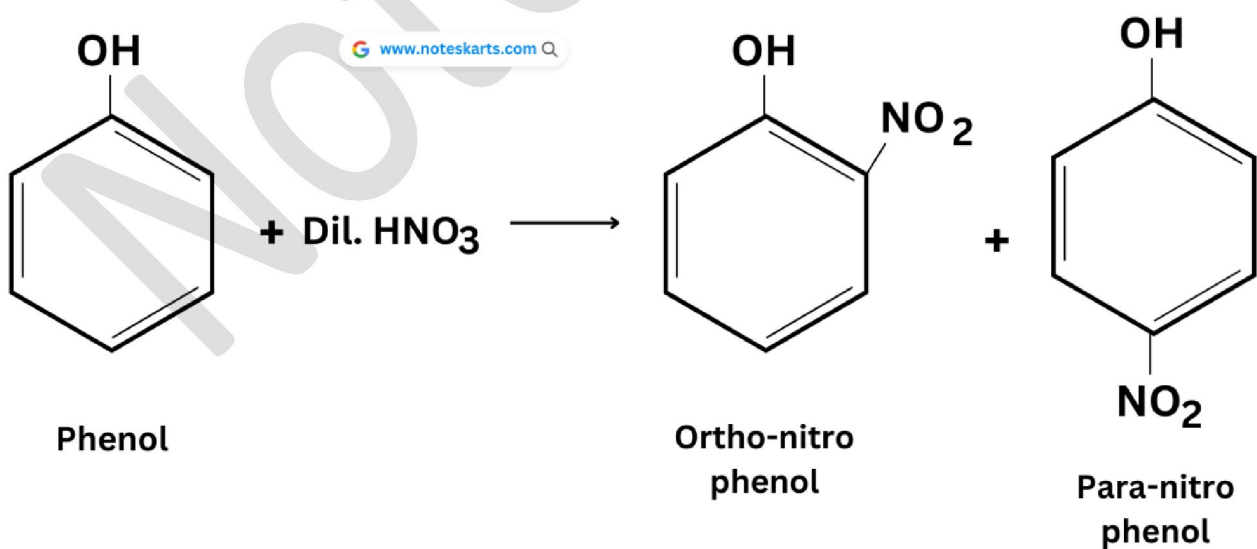
1. Formation of Salts:

Phenol react with sodium hydroxide to form salts.



2. Electrophilic Substitution Reaction (Nitration):

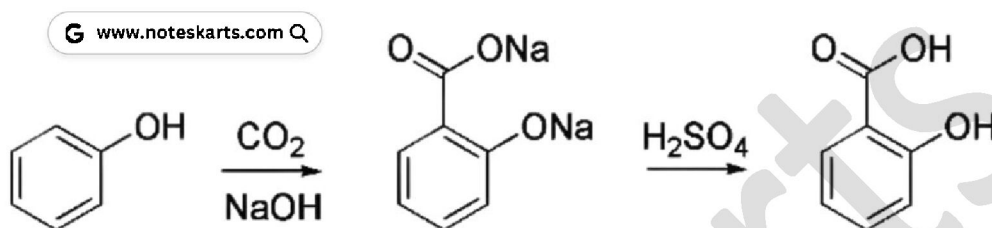
Phenol react with dil. HNO₃ to give a mixture of O-nitrophenol and P-nitrophenol.



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3. Kolbe's Reaction:

- When phenol is treated with sodium hydroxide, phenoxide ion is formed.
- This phenoxide ion formed is highly reactive towards electrophilic substitution reactions.
- Upon treatment with a weak electrophile (carbon dioxide), it undergoes electrophilic substitution reaction to form Ortho-hydroxybenzoic acid.



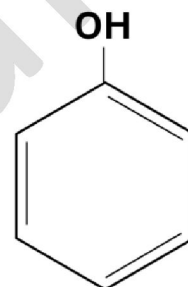
Structure and uses of phenol, cresols, resorcinol, naphthols

Phenol:

Structure:

Uses:

- Phenol is an antiseptic and disinfectant.
- Phenol is also used in the study and extraction of biomolecules.
- Phenol is also used in the cosmetic industry in the manufacturing of sunscreens, skin lightening creams and hair colouring solutions.



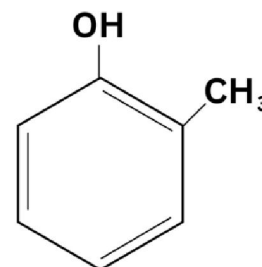
Phenol

Cresols:

Structure:

Uses:

The primary medical indications for cresols in general include being used as bactericides, pesticides, and disinfectants.



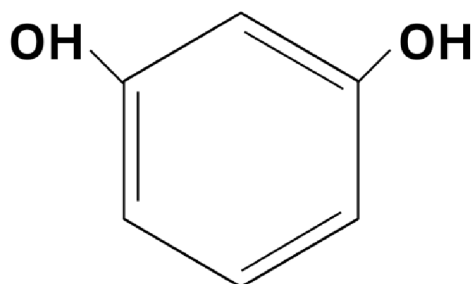
Cresols



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Resorcinol:

Structure:

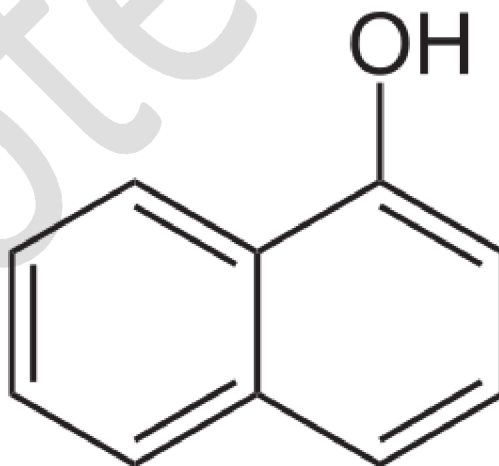


Resorcinol

Uses:

- Resorcinol is used as a disinfectant or an antiseptic in pharmaceutical products.
- It is used to treat skin infections such as seborrheic dermatitis, psoriasis, calluses, eczema, warts, and acne.
- It is used in the manufacturing of resins.
- It is an analytical reagent used to determine the quality of ketoses.

Naphthols:



Uses:

- Dyes and pigments.
- Insecticides.
- Pharmaceuticals.
- Perfumes.

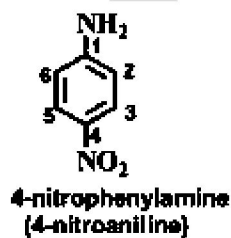
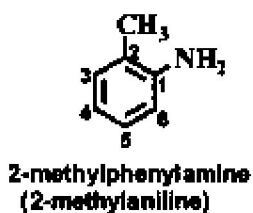
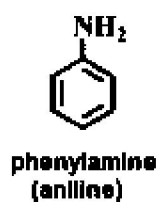


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- Antiseptics.
- Synthesis of fungicides
- **Aromatic Amines*** – Basicity of amines, effect of substituents on basicity, and synthetic uses of aryl diazonium salts

Aromatic Amines:

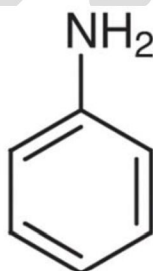
- The derivative in which hydrogen of Benzene ring has been replaced by Amine group.
- Aromatic amines have an amine group (-NH₂) attached directly to the aromatic ring.
- Aromatic amines known as arylamines. Examples,



It is also Three types:

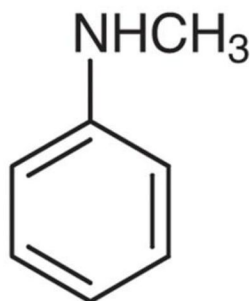
1. Primary amines:

Eg: Aniline



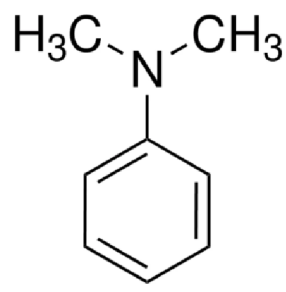
2. Secondary amines:

Eg: n-methylaniline



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3. Tertiary Amines:

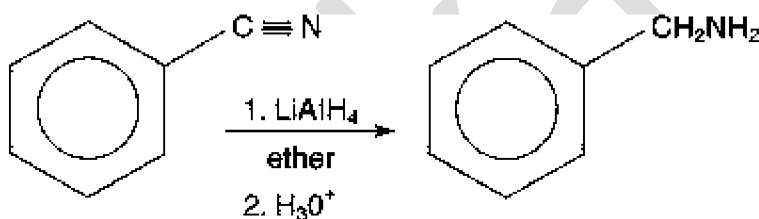


Eg: N,N-Dimethylaniline

Method of preparation of Aromatic Amines:

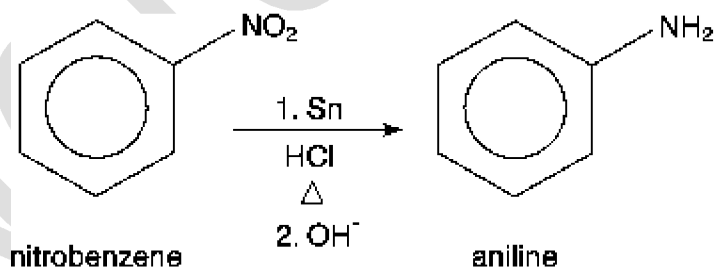
Reduction of nitriles:

Nitriles can be reduced by lithium aluminum hydride (LiAlH₄) to primary amines.



Reduction of nitrocompounds:

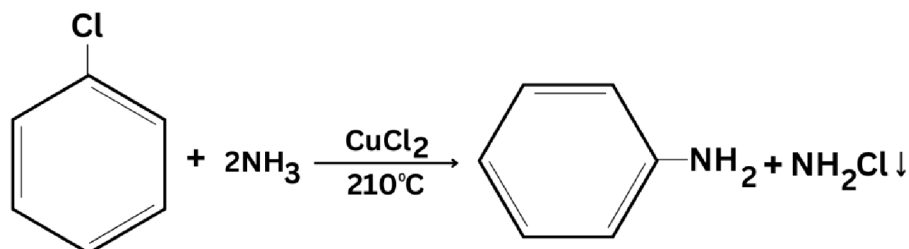
Aromatic amines are normally prepared by reduction of the corresponding aromatic nitrocompound.



By Amonolysis of Chlorobenzene:

- When Chlorobenzene undergoes analysis (react with ammonia) in the presence of copper dichloride (CuCl₂) at high temperature it produce Aromatic amine (aniline).





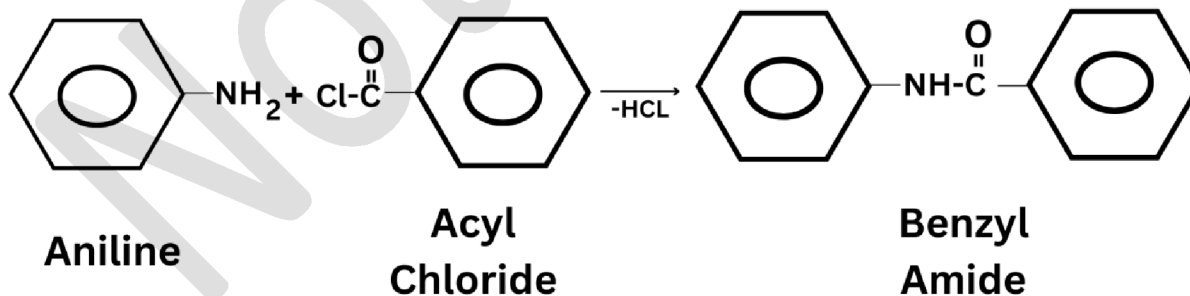
Physical Properties of Aromatic Amines:

- Aromatic amines are colourless liquids or solids with an unpleasant odour.
- The melting and boiling points of aromatic amines are greater compared to aliphatic amines of the same molecular weight.
- The melting and boiling point of aromatic amines also increases with increase in molecular weight of the compound.
- They are completely soluble in organic solvents but insoluble in water. Exception- Aniline is more soluble in water than in an organic solvent.

Chemical Reaction of Aromatic amine:

Formation of Amides:

- When aromatic amine (Aniline) react with Acyl Chloride it produced Benzyl amide with the formation of amide linkage.

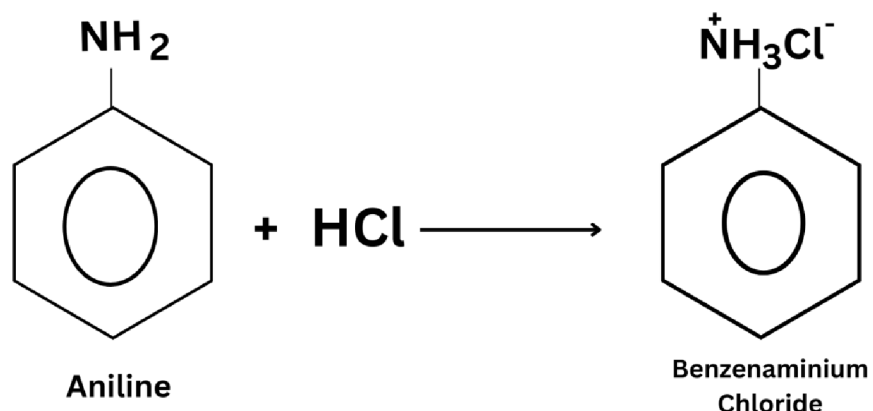


Formation of Salts:

- When aromatic amine (aniline) treated with HCl it produced Benzenaminium Chloride (amine salt)

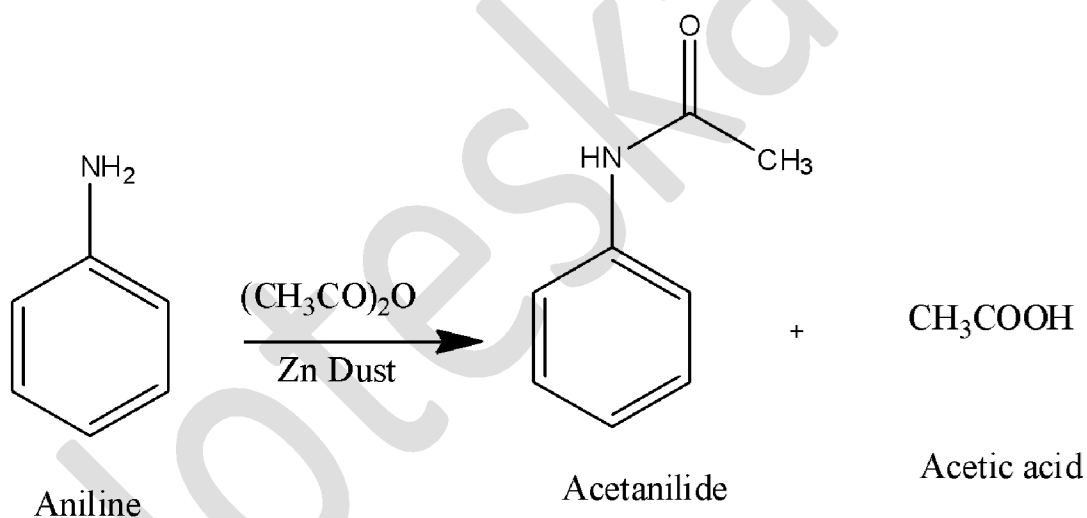


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Acetylation:

When aromatic amine (aniline) with acetic anhydride it formed acetanilide.

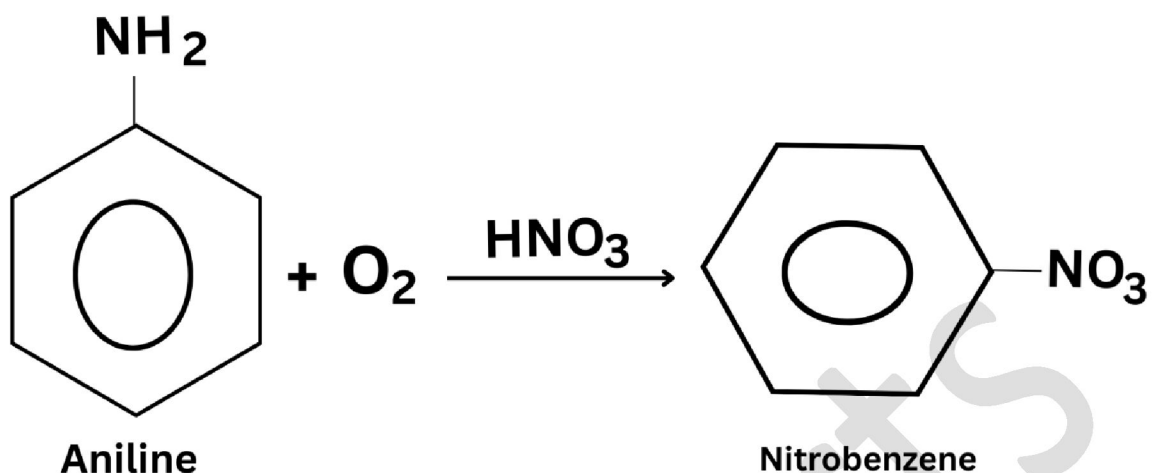


Oxidation:

When aromatic amine (aniline) undergoes oxidation in the presence nitric acid (HNO_3) it produce nitrobenzene.



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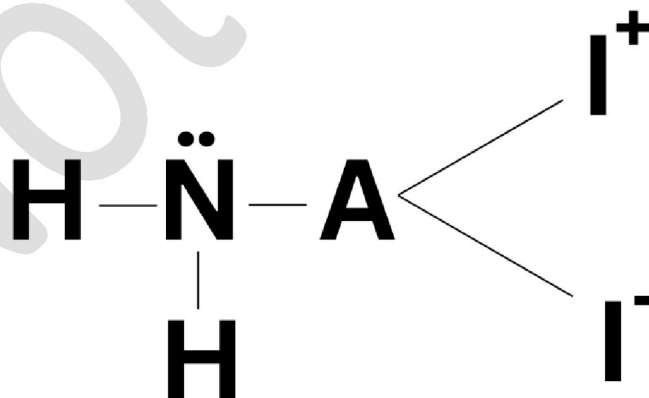


Basicity of amines:

Lewis concept: Those element which accept lone pair called Acid. And those which donate lone pair called base.



- So Ammonia contain lone paor so it is basic in nature.
- So All of their derivatives are also basic in nature.



I^+ : Electron releasing group (donating group)

E^- density $\uparrow \rightarrow$ Basicity \uparrow



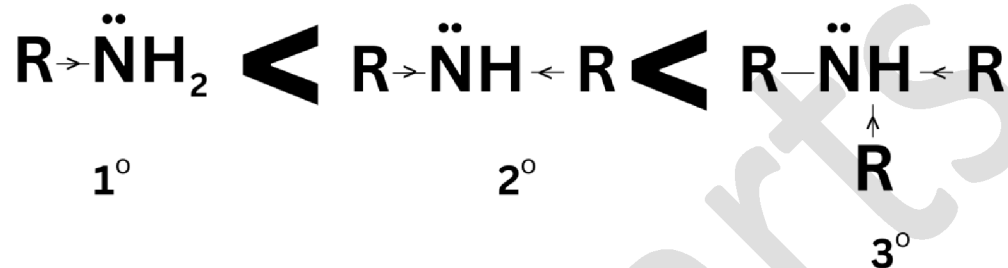
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Eg: Alkyl compound, CH₃, CH₂ etc.

I: Electron withdrawing group (accept electron)

E^- density $\downarrow \rightarrow$ Basicity \downarrow

Take an eg:

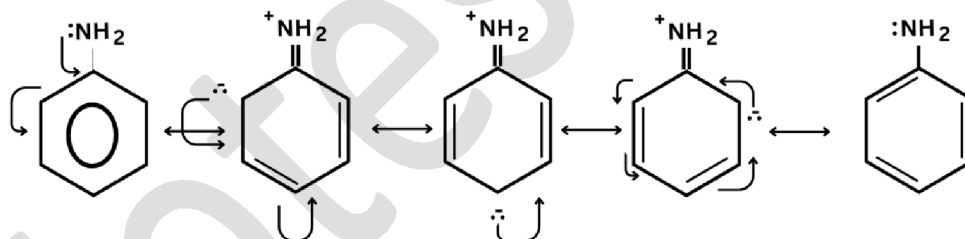


So,

$2^\circ > 3^\circ > 1^\circ$

But in Aromatic amines:

Lone pair of ammonia is delocalised in benzene ring so it can not donate lone pair.



So due to resonance electron density is decrease So basicity decrease.

So,

Basicity

Aliphatic amines > Aromatic Amines



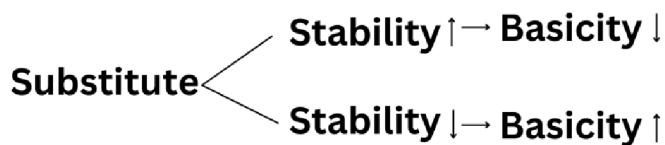
Effect of substituent on basicity of aromatic amines:

In aromatic amines, benzene has resonance So it is less basic but it is more stable.

Stability $\uparrow \rightarrow$ Acidity $\uparrow \rightarrow$ Basicity \downarrow



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Nature: Depend upon nature of substituents

- E : Donating group
- E : Withdrawing group

Electron Donating group:

- If This group attached with aromatic amines as a substituents it increase the electron density, which further increase the basicity.
- Eg: CH₃, C₂H₅ etc.

Electron withdrawing group:

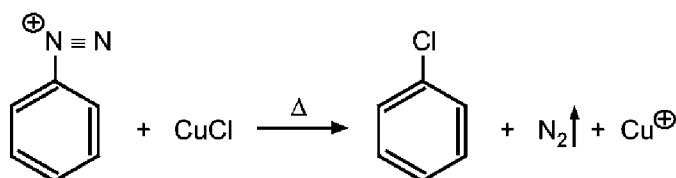
- If this group attached with aromatic amines as a substituents, it decrease the electron density which further decrease the electron density.
- Eg: Cl, Br, f, OH⁻, CN⁻

Aryl Diazonium Salts:

- Diazonium compounds, also known as diazonium salts, are organic compounds with the functional group R-N₂⁺ X⁻, where R can be any chemical group, such as an alkyl or an aryl, and X can be an inorganic or organic anion, such as a halogen.

Synthetic

(a) **Sandmeyer reaction (Aryl halides):** Benzene diazonium salt heated with cuprous chloride or cuprous bromide respectively dissolved in HCl or HBr gives chlorobenzene or bromobenzene respectively.



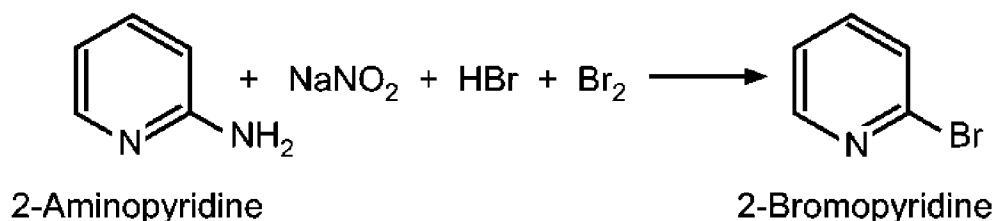
(b) **Gatterman reaction (Aryl halides):** Benzene diazonium salt is warmed with copper powder and HCl or HBr to produce chlorobenzene or bromobenzene respectively.



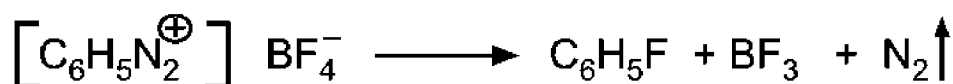
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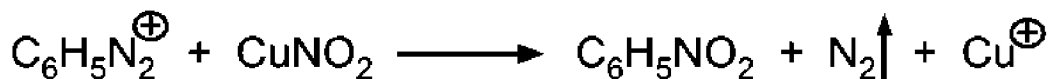
(c) **Craig method:** 2-Aminopyridine reacts with sodium nitrite, hydrobromic acid, and excess bromine to give 2-bromopyridine.



(d) **Balz-Schiemann reaction:** Fluorobenzene is produced by thermal decomposition of benzene diazonium fluoroborate.



(e) **Replacement by nitro group:** Benzene diazonium salt is treated with sodium nitrite in presence of copper to give [nitrobenzene](#).



Uses Of Diazonium Salts:

- They are useful in the synthesis of a large variety of organic compounds, especially aryl derivatives.
- They find application in the dye and pigment industries and are used to produce dyed fabrics.

Aromatic Acids* – Acidity, effect of substituents on acidity and important reactions of benzoic acid.

Aromatic Acids

They are a type of aromatic compound include in that class are substance containing an aromatic ring & an organic acid functional group.



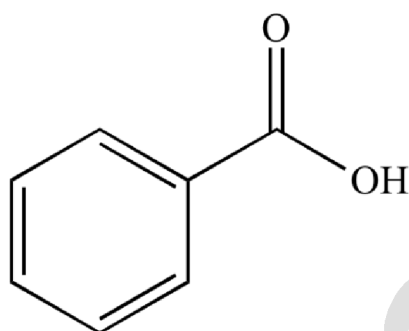
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There are two categories of aromatic acids including:

1. Phenolic Acid: Substance containing an aromatic ring organic carboxylic acid.
2. Aromatic Amino acid: Phenylalanine, Tryptophan

Benzoic Acid:

Structure:

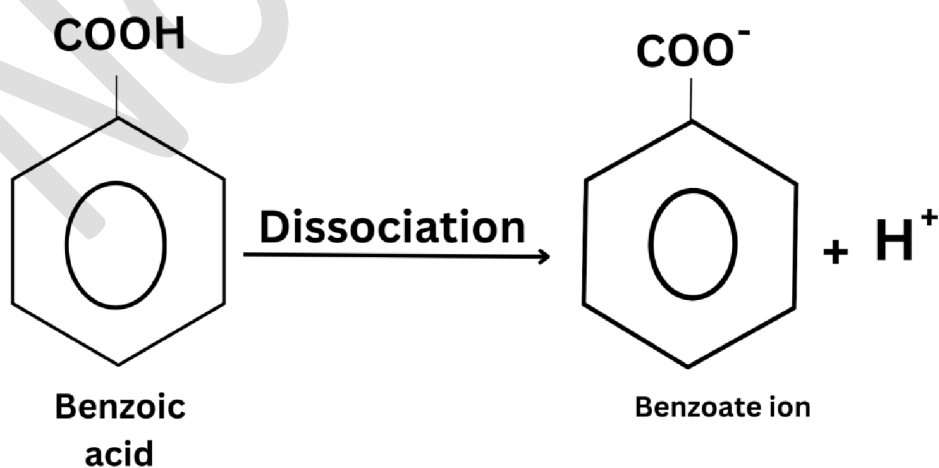


Uses:

- Benzoic acid used as topical antiseptic.
- Benzoic acid and its salts are used as food preservation.
- Benzoic acid is most widely used to produce a wide range of products such as perfumes, dyes, topical drugs and insect repellents.

Acidity of Aromatic Acids:

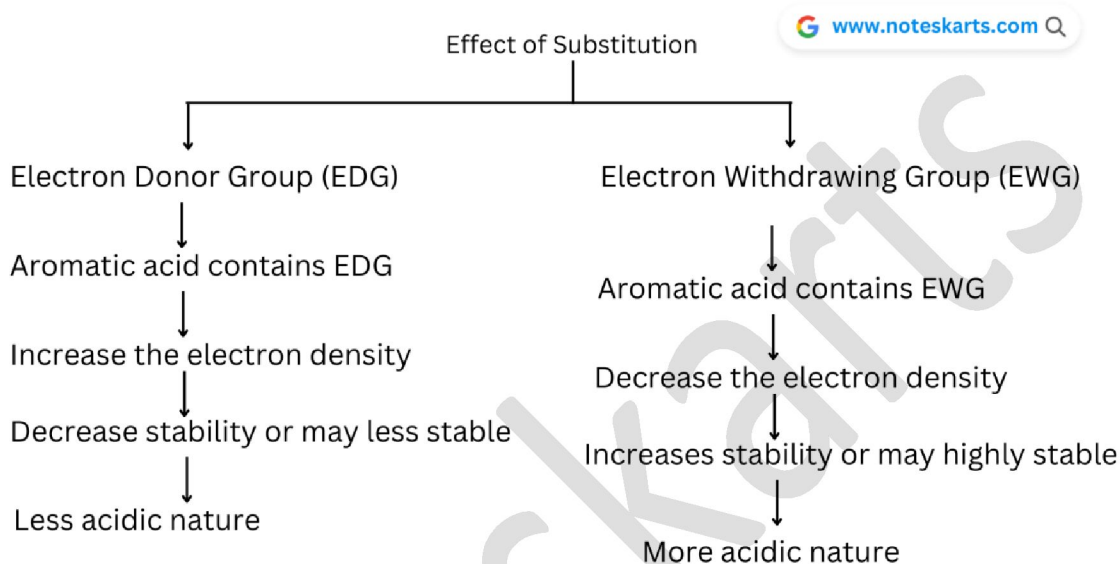
- Those compounds release H^+ which are acidic in nature.
- In aromatic acid after dissociation it release H^+ ion so they are acidic in nature.



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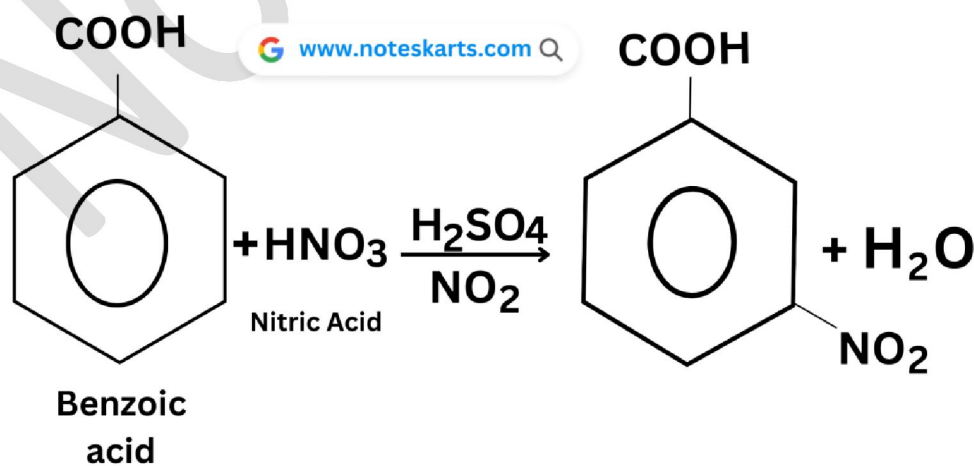
Benzoate ion is stable due to sharing of the charge so they are acidic in nature.

Effect of Substitution:



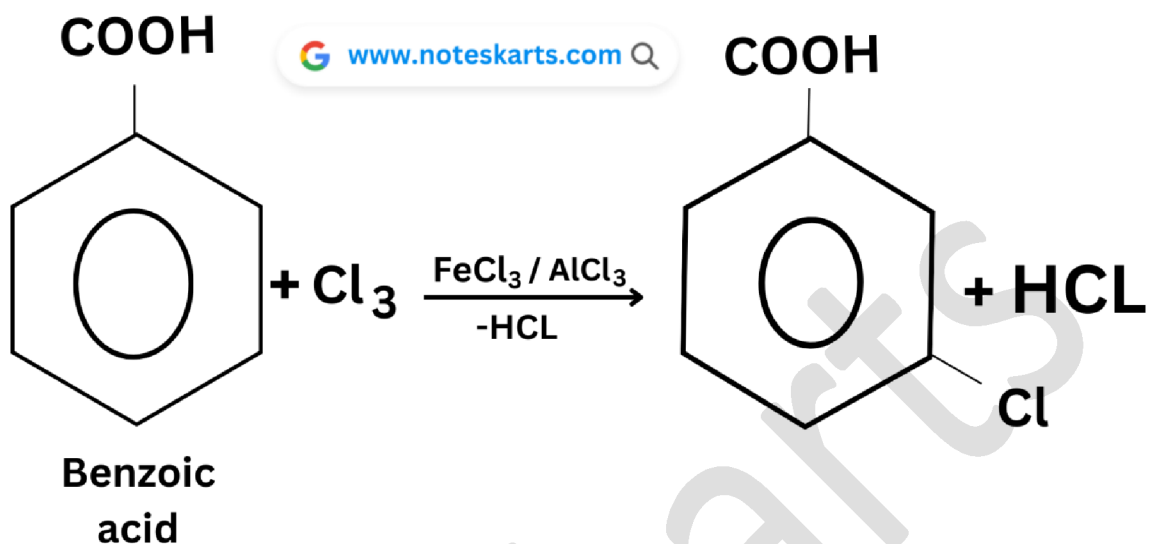
Important reaction of benzoic Acid:

Nitration:



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