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PHARMACEUTICAL ORGANIC CHEMISTRY - II

UNIT 2

TOPIC :

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



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PHENOLS

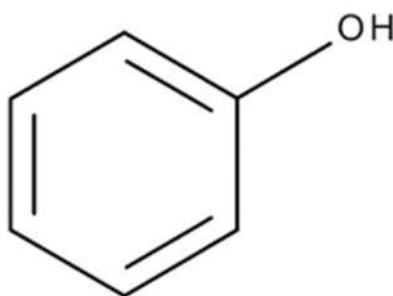
- Phenols are aromatic organic compounds containing a hydroxyl group (-OH) directly attached to a carbon atom of the benzene ring.
- Phenol is also known as Carboic Acid.
- Chemically, phenols are benzene derivatives.
- Phenols are generally white or colorless crystalline solids.
- General Chemical Formula: C_6H_5OH
- Where:
 - C_6H_5 = Phenyl group
 - OH = Hydroxyl group

Types of Phenols

→ Phenols are classified based on the number of hydroxyl (-OH) groups attached to the benzene ring:

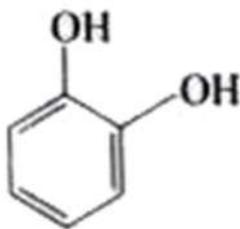
1. Monohydric Phenols:

- Contain only one hydroxyl (-OH) group.
- Example:
Phenol (C_6H_5OH)
(One -OH group directly attached to benzene ring)

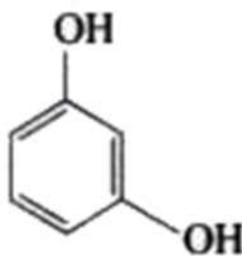


2. Dihydric Phenols:

- Contain two hydroxyl (-OH) groups on the benzene ring.
- Also known as Dihydroxybenzenes.
- Types:
 - 1,2-Dihydroxybenzene (Catechol)
 - 1,3-Dihydroxybenzene (Resorcinol)
 - 1,4-Dihydroxybenzene (Hydroquinone)



Catechol



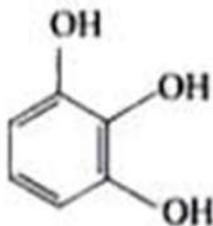
Resorcinol



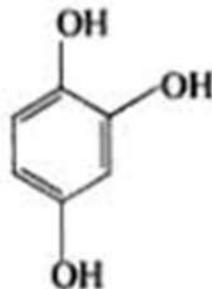
Hydroquinone

3. Trihydric Phenols:

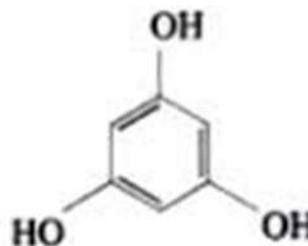
- Contain three hydroxyl (-OH) groups on the benzene ring.
- Also called Trihydroxybenzenes.
- Examples:
 - 1,2,3-Trihydroxybenzene (Pyrogallol)
 - 1,2,4-Trihydroxybenzene (Hydroxyquinol)
 - 1,3,5-Trihydroxybenzene (Phloroglucinol)



Pyrogallol



Hydroxyquinol



Phloroglucinol

Method of Preparation

→ Phenol can be prepared using several methods. The most important industrial and laboratory methods are:

1. From Haloarenes (Dow's Process)

- Reactants: Chlorobenzene and aqueous Sodium Hydroxide (NaOH)
- Conditions:
 - Temperature: 623 K ($\approx 350^\circ\text{C}$)
 - Pressure: 300 atm

Reaction:

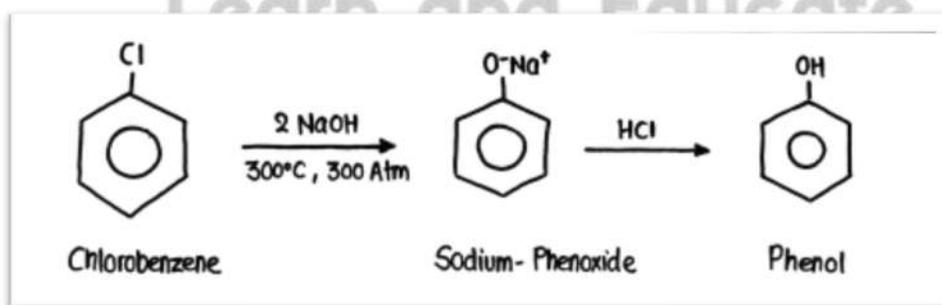
Chlorobenzene is fused with concentrated NaOH at high temperature and pressure to form Sodium Phenoxide, which is then acidified with HCl to yield Phenol.



Steps:

1. Chlorobenzene + NaOH (aq) → Sodium Phenoxide
2. Sodium Phenoxide + HCl → Phenol + NaCl

Diagram:



2. From Diazonium Salts

- Reactants : Aniline ($C_6H_5NH_2$) and Nitrous Acid (HNO_2)
- Conditions:
 - Cold conditions: around 273–278 K
 - Aqueous medium for hydrolysis

Reaction:

Aniline is first converted to a diazonium salt (benzene diazonium chloride), which on hydrolysis in warm water yields Phenol.

Step-wise Reaction:

1. Formation of Diazonium Salt:



2. Hydrolysis

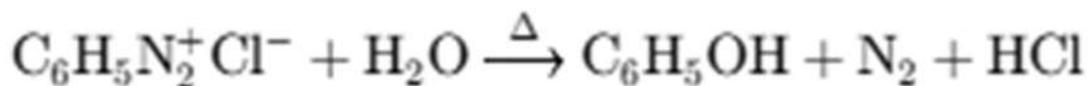
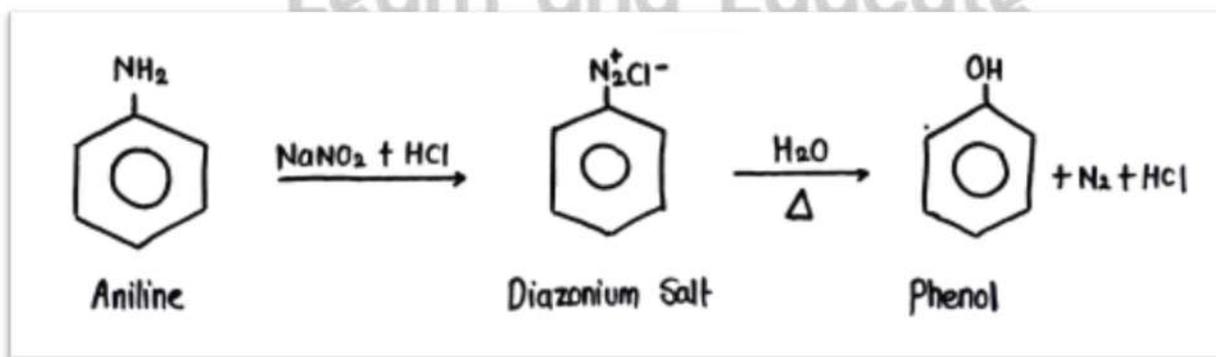


Diagram:



Acidity of Phenols

Phenols are weakly acidic in nature due to the ability of the -OH group attached to the aromatic ring to lose a proton (H^+), forming a phenoxide ion ($C_6H_5O^-$).

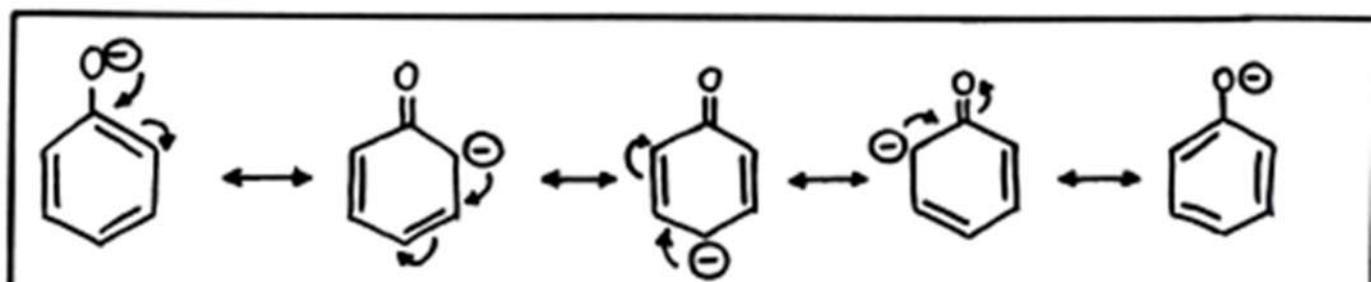


Phenoxide Ion Stability

- The acidity of phenol arises from the stability of the phenoxide ion formed after deprotonation.
- Phenoxide ion is stabilized by resonance, as the negative charge on oxygen is delocalized into the aromatic ring through conjugation.

Resonance Structures of Phenoxide Ion:

→ The phenoxide ion has multiple resonance structures that distribute the negative charge over the oxygen and the ortho- and para-positions of the benzene ring.



→ This resonance stabilization makes phenol more acidic than alcohols, where such resonance is not possible.

Effect of Substituents On Acidity Of Phenol

→ The acidity of phenol is influenced by the nature of the substituent groups attached to the benzene ring. These substituents affect the stability of the phenoxide ion formed after deprotonation, thereby increasing or decreasing the acidity of phenol.

Types of Substituent Groups:

1. Electron-Withdrawing Groups (-I or -M Effect)
2. Electron-Donating Groups (+I or +M Effect)

1. Effect of Electron-Withdrawing Groups (EWGs)

Examples: $-NO_2$, $-CN$, $-CHO$, $-COOH$, $-SO_3H$

- ❖ These groups pull electrons away from the phenol ring via inductive (-I) or mesomeric (-M) effects.
- ❖ This increases the positive character on the oxygen atom of the -OH group.
- ❖ As a result, the O-H bond weakens, and the proton (H^+) is released more easily.
- ❖ Hence, phenol becomes more acidic.

Resonance Stabilization:

- Electron-withdrawing groups stabilize the negative charge on the phenoxide ion formed after deprotonation.

Positional Effect:

- Ortho and para positions show a stronger effect than the meta position.

Conclusion:

- ✚ Electron-withdrawing groups increase the acidity of phenol.

2. Effect of Electron-Donating Groups (EDGs)

Examples: $-OH$, $-NH_2$, $-OCH_3$, $-CH_3$

- ❖ These groups donate electrons to the ring via +I (inductive) or +M (resonance) effect.
- ❖ This increases electron density on the oxygen atom of the $-OH$ group.
- ❖ As a result, the O-H bond becomes stronger, and the release of H^+ becomes more difficult.
- ❖ Hence, acidity of phenol decreases.

Positional Effect:

- Like EWGs, EDGs also have a stronger influence when present at ortho and para positions due to resonance overlap.

Conclusion:

- ✚ Electron-donating groups decrease the acidity of phenol.

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Qualitative Tests for Phenols

→ To identify the phenolic group (-OH attached to an aromatic ring) in a compound, several qualitative tests are performed. These tests rely on the acidic nature and reactivity of phenols.

1. Litmus Paper Test

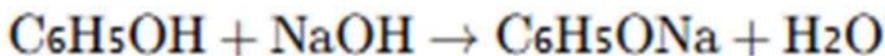
- ❖ **Basis:** Phenols are weak acids.
- ❖ **Observation:** When tested with blue litmus paper, it turns red, indicating the presence of an acidic compound.
- ❖ **Conclusion:** Change of litmus confirms acidic character of phenol.

2. Solubility Test

→ Phenols are soluble in aqueous sodium hydroxide (NaOH) due to the formation of sodium phenoxide, but insoluble in weaker bases like sodium carbonate (Na₂CO₃) or sodium bicarbonate (NaHCO₃).

Reactions:

- **With NaOH (soluble):**



- **With Na₂CO₃ / NaHCO₃ (no reaction):**

No visible change or gas evolution

Conclusion : Solubility in NaOH but not in carbonates indicates weakly acidic phenolic nature.

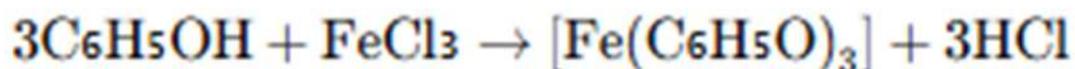
3. Ferric Chloride Test (FeCl₃ Test)

- This is a specific and sensitive test for phenols.
- When aqueous phenol is treated with neutral FeCl₃ solution, it forms colored complexes.

Observation:

- ▲ A deep color appears (can be violet, blue, green, red, or purple) depending on the phenol type.

Reaction:



(Colored complex)

Conclusion: Formation of a colored solution confirms the presence of phenolic group.

4. Liebermann's Test

- Specific for phenols like carbolic acid and naphthols.
- Involves reaction with sodium nitrite and concentrated sulfuric acid, then made alkaline.

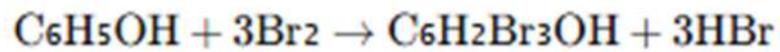
5. Bromine Water Test

- Phenols undergo electrophilic substitution with bromine water due to the activation of the ring by the -OH group.

Observation:

- When bromine water is added to phenol:
 - Reddish-brown color of bromine disappears.
 - A white precipitate of 2,4,6-tribromophenol is formed.

Reaction:



Conclusion : Decolorization of bromine and white precipitate confirm phenol.

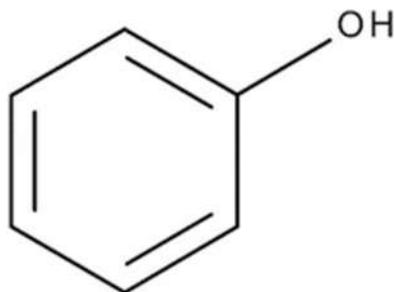


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Phenol (C_6H_5OH)

Structure:

- A hydroxyl group (-OH) is directly attached to a benzene ring.



Uses:

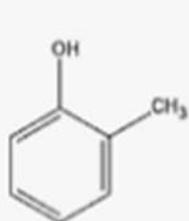
- ✓ Used as an antiseptic and disinfectant.
- ✓ Intermediate in the manufacture of plastics (Bakelite).
- ✓ Used in the preparation of dyes, drugs, perfumes, and explosives.
- ✓ Acts as a preservative in some pharmaceutical preparations.

Cresols (Methylphenols)

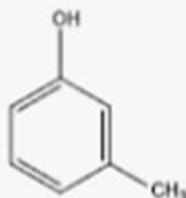
- Cresols are monomethyl derivatives of phenol.
- They have three isomers depending on the position of the $-CH_3$ group relative to the $-OH$ group.

Types & Structures:

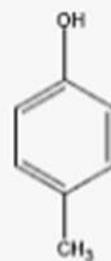
- o-Cresol (1,2-methylphenol)
- m-Cresol (1,3-methylphenol)
- p-Cresol (1,4-methylphenol)



o-Cresol



m-Cresol



p-Cresol

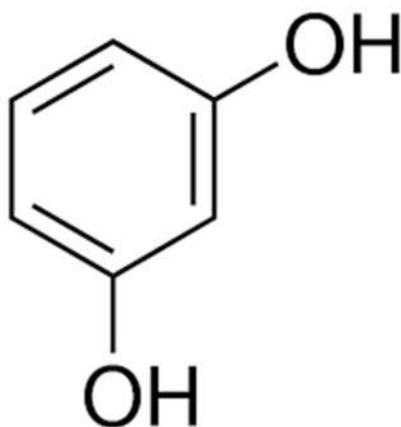
Uses:

- ✓ Used as disinfectants and antiseptics (e.g., Lysol).
- ✓ Used in phenolic resins and plastics.
- ✓ Intermediate in the manufacture of dyes, pesticides, and pharmaceuticals.

Resorcinol (1,3-Dihydroxybenzene)

Structure:

- Two hydroxyl groups at the meta positions (1 and 3) on the benzene ring.



Uses:

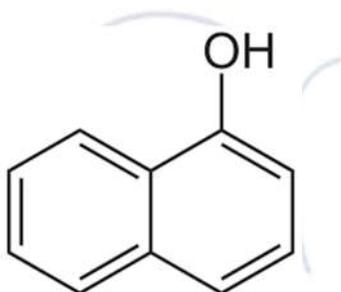
- ✓ Used in the preparation of dyes (e.g., fluorescein).
- ✓ Used in acne creams, antiseptic ointments, and skin treatments.
- ✓ Used in the production of adhesives, rubber chemicals, and resins.
- ✓ Intermediate in pharmaceutical and cosmetic products.

Naphthols (Hydroxynaphthalenes)

- Naphthols are naphthalene derivatives containing one hydroxyl group.
- Exist as two isomers: α -naphthol and β -naphthol.

Structures:

- α -Naphthol (1-Naphthol)
Hydroxyl group at position 1 of the naphthalene ring.



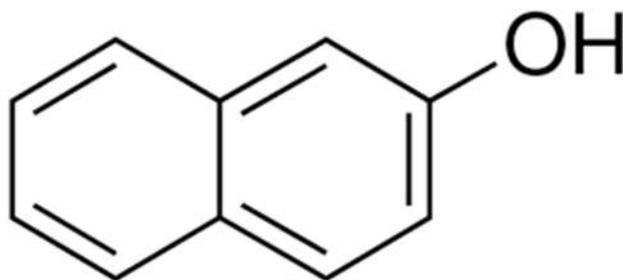
Uses:

- ✓ Used to make dyes – especially azo dyes for textiles and fabrics.
- ✓ Used in making medicines – as intermediates in drug synthesis.
- ✓ Used in agrochemicals – to make pesticides and herbicides.
- ✓ Used in rubber and plastics – as stabilizers and antioxidants.
- ✓ Used in labs – as reagents in chemical tests and organic synthesis.

β -Naphthol (2-Naphthol)

- Hydroxyl group at position 2 of the naphthalene ring.

Structures:



Uses:

- ✓ Used in the manufacture of azo dyes, antiseptics, and pharmaceuticals.
- ✓ Acts as a fungicide and antioxidant.
- ✓ Used in the preparation of β -naphthol orange and other colorants.

