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Chemistry and Significance of Phenols

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ABSTRACT: Phenol is an aromatic compound. The chemical formula of this organic compound is C_6H_6O . Phenol is also known as Carbolic acid.

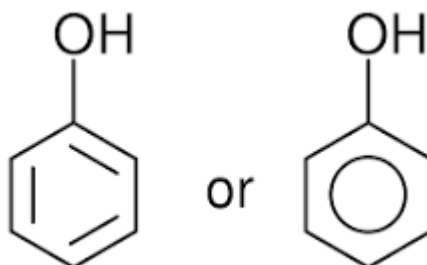
It consists of a hydroxyl group and a phenyl group attached to each other. It considerably dissolves in water. Earlier it was used as carbolic soap. It is mildly acidic and is corrosive to the respiratory tract, eyes, and skin.[1,2,3]

Phenol is a crystalline solid white in colour and needs to be handled with care as it can cause chemical burns. Friedlieb Ferdinand Runge discovered Phenol in the year 1834. It was extracted from coal tar. It is also known as phenolic acid. If a compound is consisting of a six-membered aromatic ring and bonded to a hydroxyl group directly, then it can be referred to as phenol.

KEYWORDS- chemistry, phenols, organic, significance, aromatic

I. INTRODUCTION

Properties of Phenol (Carbolic acid)- C_6H_6O



C_6H_6O	Phenol
Molecular Weight/ Molar Mass	94.11 g/mol
Density	1.07 g/cm ³
Melting Point	40.5 °C
Boiling Point	181.7 °C

Natural Sources of Phenol (Carbolic acid)- C_6H_6O

- Phenol is a constituent of coal tar and is formed during the decomposition of organic materials. Increased environmental levels of phenol may result from forest fires. It has been detected among the volatile components from liquid manure.[3,4,5]
- Industrial sources of phenols and other related aromatics from a petroleum refinery, petrochemicals, basic organic chemical manufacture, coal refining, pharmaceuticals, tannery and pulp, and paper mills.

Nomenclature of Phenol (Carbolic acid)- C₆H₆O

Phenols are organic compounds containing at least one -OH group directly attached to the benzene ring. Depending upon the number of hydroxyl groups attached to the benzene ring, phenols can be classified as monohydric, dihydric and trihydric phenols.

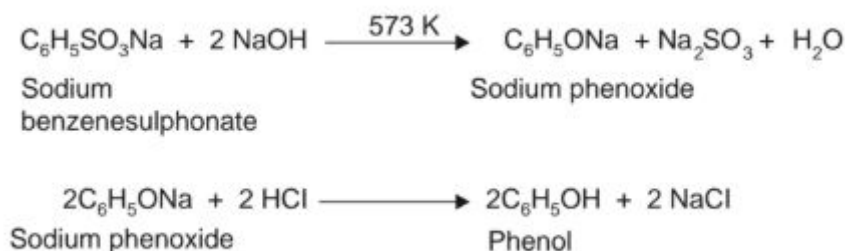
1. Monohydric phenols – The simplest member of the series is hydroxybenzene, commonly known as phenol, while others are named substituted phenols. The three isomeric hydroxyl toluenes are known as cresols.
2. Dihydric phenols – The three isomeric dihydroxy benzenes namely catechol, resorcinol, and quinol are better known by their common names.
3. Trihydric phenols – Trihydroxy phenols are known by the common names called pyrogallol, hydroxyquinol and phloroglucinol.

Synthesis of Phenol (Carbolic acid)- C₆H₆O

Phenols can be synthesized by the following methods.

1. From sulphonic acids (by alkali fusion of sodium benzenesulphonate)

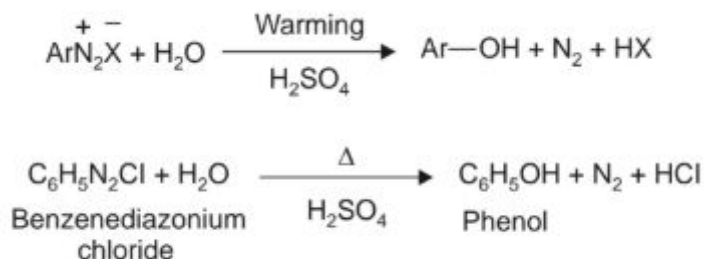
The first commercial process for the synthesis of phenol. Sodium benzenesulphonate is fused with sodium hydroxide at 573K to produce sodium phenoxide, which upon acidification yields phenol.



Synthesis of Phenols From Sulphonic Acids

2. From diazonium salts (by the hydrolysis of diazonium salt – laboratory method)[6,7,8]

When a diazonium salt solution is steam distilled or is added to boiling dil.H₂SO₄, it forms phenol.



Synthesis of Phenols From Diazonium Salts

Chemical Reactions of Phenol (Carbolic acid)- C₆H₆O

A hydroxyl group is attached to an aromatic ring and it is strongly activating ortho/para director, phenols possess considerable reactivity at their ortho and para carbons toward electrophilic aromatic substitution.

1. Reactions of the Aromatic Ring

The -OH group in phenol is ortho and para directing because it increases electron density at ortho and para positions due to resonance. Thus phenol undergoes electrophilic substitution reactions.

2. Halogenation

Like -NH₂ group, -OH group is so much activating that it is rather difficult to prevent poly substitution.

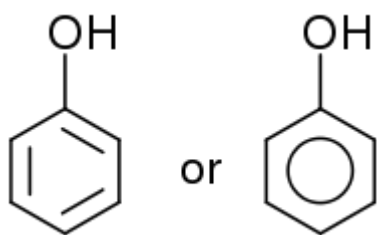
If it is required to arrest the reaction at the mono substitution stage, the reaction should be carried out in non-polar solvents like CCl₄ and CS₂ and at lower temperatures.

Uses of Phenol (Carbolic acid)- C₆H₆O

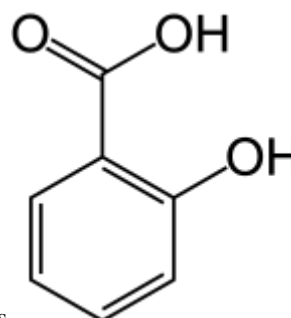
- It is used as a precursor in drugs
- It is used as an antiseptic
- It is used in the production of nylon
- It is used to preserve vaccines
- It is used in oral analgesics
- Derivatives of phenol are used in beauty products like hair colour and sunscreen
- It is used in the synthesis of plastics
- It is used to produce detergents and carbonates[8,9,10]

II. DISCUSSION

In organic chemistry, phenols, sometimes called phenolics, are a class of chemical compounds consisting of one or more hydroxyl groups (-OH) bonded directly to an aromatic hydrocarbon group.^[1] The simplest is phenol, C₆H₅OH. Phenolic compounds are classified as simple phenols or polyphenols based on the number of phenol units in the molecule.



Phenol – the simplest of the phenols



Chemical

structure of salicylic acid, the active metabolite of aspirin

Phenols are both synthesized industrially and produced by plants and microorganisms.^[2]

Properties

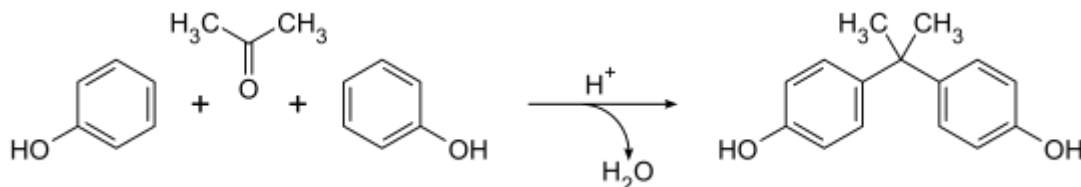
Acidity

Phenols are more acidic than typical alcohols. The acidity of the hydroxyl group in phenols is commonly intermediate between that of aliphatic alcohols and carboxylic acids (their pK_a is usually between 10 and 12). Deprotonation of a phenol forms a corresponding negative phenolate ion or phenoxide ion, and the corresponding salts are called phenolates or phenoxides (aryloxides according to the IUPAC Gold Book).[10,11,12]

Condensation with aldehydes and ketones

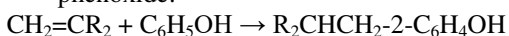
Phenols are susceptible to Electrophilic aromatic substitutions. Condensation with formaldehyde gives resinous materials, famously Bakelite.

Another industrial-scale electrophilic aromatic substitution is the production of bisphenol A, which is produced by the condensation with acetone.^[3]



C-Alkylation with alkenes

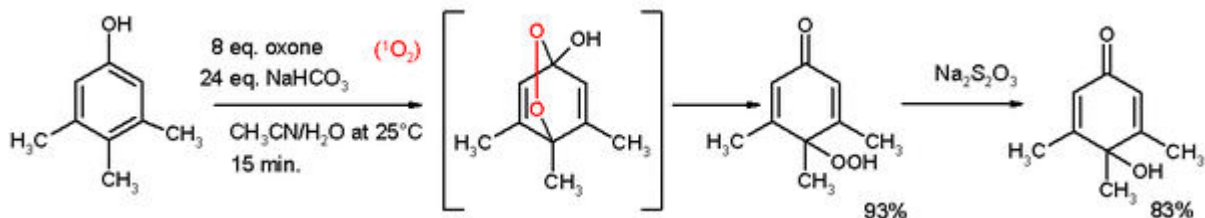
Phenol is readily alkylated at the ortho positions using alkenes in the presence of a Lewis acid such as aluminium phenoxide:



More than 100,000 tons of tert-butyl phenols are produced annually (year: 2000) in this way, using isobutylene ($\text{CH}_2=\text{CMe}_2$) as the alkylating agent. Especially important is 2,6-ditert-butylphenol, a versatile antioxidant.^[3]

Other reactions

Phenols undergo esterification. Phenol esters are active esters, being prone to hydrolysis. Phenols are reactive species toward oxidation. Oxidative cleavage, for instance cleavage of 1,2-dihydroxybenzene to the monomethylester of 2,4-hexadienedioic acid with oxygen, copper chloride in pyridine^[4] Oxidative de-aromatization to quinones also known as the Teuber reaction.^[5] and oxone.^[6] In reaction depicted below 3,4,5-trimethylphenol reacts with singlet oxygen generated from oxone/sodium carbonate in an acetonitrile/water mixture to a para-peroxyquinole. This hydroperoxide is reduced to the quinole with sodium thiosulfate.



Phenols are oxidized to hydroquinones in the Elbs persulfate oxidation.

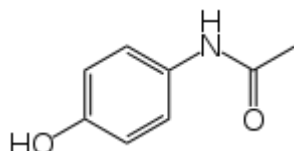
Reaction of naphthols and hydrazines and sodium bisulfite in the Bucherer carbazole synthesis.

Synthesis

Many phenols of commercial interest are prepared by elaboration of phenol or cresols. They are typically produced by the alkylation [11,12,13] of benzene/toluene with propylene to form cumene then O_2 is added with H_2SO_4 to form phenol (Hock process). In addition to the reactions above, many other more specialized reactions produce phenols:

- rearrangement of esters in the Fries rearrangement^{[7][8]}
- rearrangement of N-phenylhydroxylamines in the Bamberger rearrangement^{[9][10]}
- dealkylation of phenolic ethers
- reduction of quinones
- replacement of an aromatic amine by an hydroxyl group with water and sodium bisulfide in the Bucherer reaction^[11]
- thermal decomposition of aryl diazonium salts, the salts are converted to phenol^[12]
- by the oxidation of aryl silanes—an aromatic variation of the Fleming-Tamao oxidation^[13]
- catalytic synthesis from aryl bromides and iodides using nitrous oxide^[14]

Classification



The best-selling drug in the U.S. is Acetaminophen, also known as Paracetamol is a phenol.[12,13,14]

There are various classification schemes.^{[15]:2} A commonly used scheme is based on the number of carbons and was devised by Jeffrey Harborne and Simmonds in 1964 and published in 1980.^{[15]:2[16]}

Phenol	the parent compound, used as a disinfectant and for chemical synthesis
Bisphenol A	and other bisphenols produced from ketones and phenol / cresol
BHT	(butylated hydroxytoluene) - a fat-soluble antioxidant and food additive
4-Nonylphenol	a breakdown product of detergents and nonoxynol-9
Orthophenyl phenol	a fungicide used for waxing citrus fruits
Picric acid	(trinitrophenol) - an explosive material
Phenolphthalein	pH indicator
Xylenol	used in antiseptics & disinfectants

Drugs and bioactive natural products

More than 371 drugs approved by the FDA between the years of 1951 and 2020 contain either a phenol or a phenolic ether (a phenol with an alkyl), with nearly every class of small molecule drugs being represented, and natural products making up a large portion of this list.^[17]

tyrosine	one of the 20 standard amino acids
L-DOPA	dopamine prodrug used to treat Parkinson's disease
propofol	short-acting intravenous anesthetic agent
vitamin K hydroquinone	blood-clotting agent that converts
levothyroxine (L-thyroxine)	Top-selling drug to treat thyroid hormone deficiency.
amoxicillin	Top-selling antibiotic
estradiol	the major female sex hormone

III. RESULTS

Phenol will undergo biotransformation to oxidation and conjugated products. Phenol and phenolic compounds can be oxidized by peroxidase-dependent prostaglandin H synthase to phenoxyl radicals. It is a reactive intermediate in the P450 oxidation of benzene to hydroquinone. Phenol that is not oxidized will undergo conjugation to etheral, sulfate, or glucuronate species. This is especially true of phenol introduced to the gastrointestinal tract. Conjugates appear less toxic than the parent compound and are subsequently excreted through the kidneys. A smaller amount may be eliminated through the lungs, as detected by an aromatic odor to the breath. Absorption of phenol occurs fairly rapidly via inhalation. Rapid absorption and severe systemic toxicity can occur after any route of exposure, including skin. Death and severe toxicity are usually due to effects on the central nervous system (CNS), heart, blood vessels, lungs, and kidneys. Toxicity in animals is similar to that of humans, although additional effects have been observed. The LD₅₀ values in animals range from 250 to 500 mg kg⁻¹, differing slightly with the type of contact or species. Other toxic effects include irritation of skin and eyes in rabbits, induction of skin tumors in mice, reproductive effects in rats, and mutagenicity with Salmonella, Escherichia coli, and Drosophila. Phenol is metabolized and excreted principally by the kidneys as sulfate or glucuronide conjugates, although some phenol may be excreted unchanged, especially at high doses. Liver, gut, lung, and kidney are places where phenol is metabolized. Phenols are compounds that possess a hydroxyl group directly attached to an aromatic carbocyclic nucleus. Phenol is the trivial name for

monohydroxybenzene. The o-, m-, and p-cresols are monohydroxytoluenes ($\text{CH}_3\text{C}_6\text{H}_4\text{OH}$) and are distinct in their properties and reactions from the isomeric side-chain hydroxy compound, benzyl alcohol ($\text{C}_6\text{H}_5\text{CH}_2\text{OH}$), which is a typical aromatic alcohol. Simple monohydric phenols are either corrosive liquids or low melting solids. The dihydric and trihydric phenols are solids. The mono-hydroxy compounds are only slightly soluble in water but are miscible with organic solvents. Water solubility increases and solubility in organic solvents decreases with the introduction of additional hydroxyl groups. They are all characterized by, and distinguished from, the aliphatic or aromatic alcohols by their ready solubility in aqueous alkali. Phenols and the cresols are widely used as antiseptics and disinfectants; the cresols are contained in the wood preserving fluid, creosote. Many phenols have wide application in the industrial production of plastics, dyestuffs, insecticides, selective weedkillers, and germicides. Phenols have unique properties and are not classified as alcohols. They have higher acidities due to the aromatic ring's tight coupling with the oxygen and a relatively loose bond between the oxygen and hydrogen. This chapter opens up with the discussion of general conditions for separation of phenols and dowertherm impurities. It discusses gas chromatography separation of derivatized phenols and dihydroxybenzenes. The peaks are very intense in phenol, methylphenol, and dimethylphenol, as would be predicted for aromatic compounds. The regioisomers of dimethylphenol cannot be determined using only mass spectrometry. Differentiating these regioisomers in a GC/MS analysis may be possible using retention indices. An important point about the mass spectra of substituted phenols is the ortho effect. When the position of certain substituents is ortho to a group with labile hydrogen, a rearrangement fragmentation will occur with the loss of a molecule and the formation of an odd-electron ion. The study compares the mass spectra of 2,6-dichlorophenol and 4,5-dichlorophenol.

Phenols, particularly chlorophenols, are toxic at concentrations of a few $\mu\text{g L}^{-1}$ and are also persistent. Determining trace amounts of phenols is not easy for real samples that consist of extremely complex matrices. Methods for monitoring trace amount of phenols in real samples must be sensitive and selective, and should be rapid and simple. A mixture can be separated by GC into its individual components and, at the same time, the amount of each compound present can be determined. Furthermore, analysis can be performed with various detectors at a moderate cost. The applications presented here demonstrate the effectiveness of GC to analyse quantitatively trace levels of phenols in complex mixtures. Although various GC methods for phenol analysis have been widely used, novel techniques and sample pretreatment methods are continually being introduced. Simple retention times are not very reproducible and linking with a mass spectrometer as a detector is desirable for unambiguous identification. This approach has the merits of speed, sensitivity and selectivity. The MS-MS technique will become less expensive in the future and, eventually, the preferred means of analysing phenols when coupled to GC. Currently GC-MS-MS is more expensive than GC-MS but offers an extra separation stage to resolve the problem of analysing mixtures not amenable to GC-MS.[14,15,16]

IV. CONCLUSION

Phenol is a highly toxic compound causing protein degradation and tissue erosion. Occupational and environmental exposure to phenol is largely restricted to source-dominated areas. Ambient levels of phenol are quite low compared to the threshold limit value (TLV) of 5 p.p.m. The US Occupational Safety and Health Administration (OSHA) time-weighted average (TWA) (on skin) is 5 p.p.m. The human oral LD_{50} (lethal dose low) value is 140 mg kg^{-1} . Odor-recognition threshold of phenol is 0.05 p.p.m., far below levels of toxic effects. Upon skin contact, skin becomes white with a subsequent red blister-like appearance and an accompanying burning sensation. Solid or liquid phenol is rapidly absorbed by the skin and results in very severe tissue damage.

Exposure to large amounts of phenol results in death due to paralysis of the central nervous system. Minor ingestion causes damage mainly to the kidneys, liver and pancreas. If phenol is inhaled or swallowed, local cauterization occurs with headaches, dizziness, vomiting, irregular breathing, respiratory arrest and heart failure.[17]

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