

Pharmaceutical Organic Chemistry II | BP-301T

Theory Sessional Examination ST1 Solution

Section A — Answer all questions

1(a). Give two limitations of the Kekulé structure of benzene. [2 marks]

Unequal bonds predicted: A fixed Kekulé structure contains three C–C single bonds and three C=C double bonds, so it predicts two different bond lengths. Experimentally, all six carbon–carbon bonds are equivalent, approximately 1.39 Å (139 pm), intermediate between ordinary single and double bonds.

Stability and reactivity unexplained: Three localized double bonds suggest alkene-like addition and a much larger heat of hydrogenation. Benzene instead strongly favors substitution under usual electrophilic conditions and has extra stabilization due to delocalization of six π electrons.

1(b). Define electrophile. Give two examples involved in benzene reactions. [2 marks]

An electrophile is an electron-pair acceptor that attacks an electron-rich site, such as the π -electron cloud of benzene, to form a covalent bond.

Examples: NO_2^+ (nitronium ion), the electrophile in nitration; and RCO^+ (acylium ion, for example CH_3CO^+), the electrophile in Friedel–Crafts acylation.



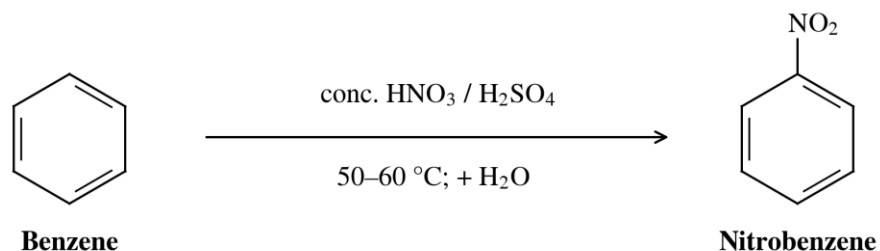
1(c). Write the nitration reaction of benzene. [2 marks]



Conditions: Concentrated HNO_3 and concentrated H_2SO_4 ; controlled warming at approximately 50–60 °C (323–333 K). The product is nitrobenzene.



Sulfuric acid helps generate NO_2^+ . The nitronium ion replaces one hydrogen on the benzene ring by electrophilic aromatic substitution.



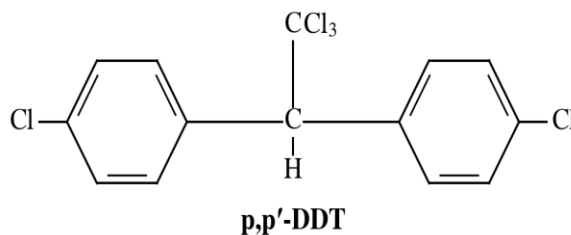
1(d). Write the structure and uses of DDT. [2 marks]

DDT stands for dichlorodiphenyltrichloroethane. The principal insecticidal isomer is p,p'-DDT, named 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane.

Condensed structure: $(\text{p-Cl-C}_6\text{H}_4)_2\text{CH-CCl}_3$

Molecular formula: $\text{C}_{14}\text{H}_9\text{Cl}_5$

Uses: It was used as a contact insecticide against agricultural pests and against disease vectors, including mosquitoes associated with malaria and lice associated with typhus. Its environmental persistence and bioaccumulation led to severe restrictions; these are historical/regulated uses, not a recommendation for routine use.

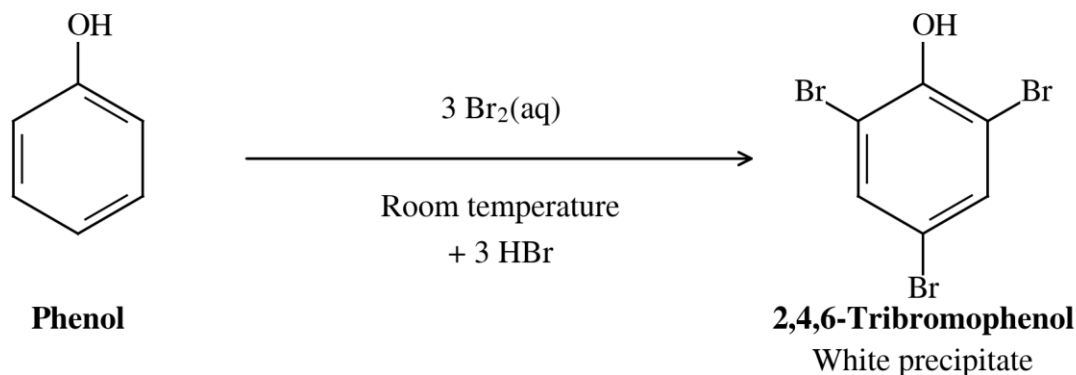


1(e). What happens when phenol reacts with bromine water? [2 marks]

Phenol rapidly decolorizes bromine water and forms a white precipitate of 2,4,6-tribromophenol. The $-\text{OH}$ group activates the ring and directs substitution to both ortho positions and the para position.



Conditions: Aqueous bromine at room temperature, approximately $20-25\text{ }^{\circ}\text{C}$ ($293-298\text{ K}$); no Lewis acid catalyst is required.



Section B — Answer any one question

2(a). Discuss the structure of benzene using analytical and experimental evidence supporting its cyclic and aromatic structure. [10 marks]

Analytical evidence and molecular formula

Benzene is a hydrocarbon with molecular formula C_6H_6 and molar mass approximately 78 g mol^{-1} . Its carbon-to-hydrogen ratio gives the empirical formula CH. Analytical composition and molar mass establish the formula, but do not alone prove a cyclic structure.

Carbon percentage = $(72/78) \times 100 = 92.31\%$

Hydrogen percentage = $(6/78) \times 100 = 7.69\%$

Empirical-formula mass of CH = 13; **multiplier** = $78/13 = 6$

Molecular formula = $(\text{CH})_6 = \text{C}_6\text{H}_6$

Degree of unsaturation: worked calculation

For a neutral organic compound with normal valences, degree of unsaturation (DU), also called double-bond equivalents, is calculated as follows. C, H, N and X represent the numbers of carbon, hydrogen, nitrogen and halogen atoms; oxygen does not enter the expression.

DU = $(2C + 2 + N - H - X)/2$

For C_6H_6 : **DU** = $[2(6) + 2 - 6]/2 = 8/2 = 4$

Four units of unsaturation are consistent with one ring and three double-bond equivalents. This is supporting evidence, not proof of benzene's exact bonding arrangement.

Evidence for a symmetrical six-membered carbon ring

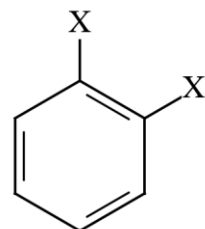
Monosubstitution: Benzene gives only one monosubstituted product of a given type, such as chlorobenzene. Thus all six hydrogen positions are equivalent.

Disubstitution: For two identical substituents, benzene gives only three positional isomers: 1,2- (ortho), 1,3- (meta) and 1,4- (para). This supports a symmetrical hexagonal arrangement. A fixed alternating-bond model would incorrectly distinguish two kinds of adjacent positions.

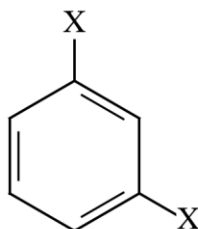
Catalytic hydrogenation: Benzene consumes three moles of hydrogen per mole to form cyclohexane, supporting a six-carbon ring and three π -bond equivalents.



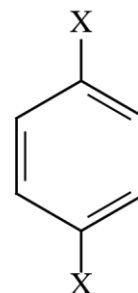
Conditions: Ni, Pt or Pd catalyst, with heat and hydrogen pressure as required. Product: cyclohexane.



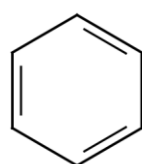
1,2 Ortho



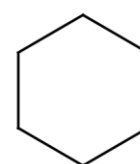
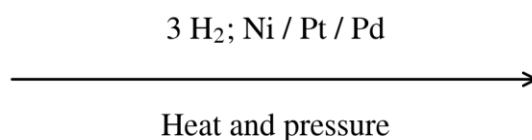
1,3 Meta



1,4 Para



Benzene



Cyclohexane

Chemical evidence for unsaturation and unusual stability

Ozonolysis: Ozone addition followed by reductive work-up gives glyoxal (ethanedial, $\text{OHC}-\text{CHO}$), conventionally represented as three glyoxal molecules per benzene molecule. This supports the unsaturation pattern, although the reaction alone does not establish aromaticity.



Conditions: O_3 , followed by reductive work-up such as $\text{Zn}/\text{H}_2\text{O}$. The equation above is a transformation scheme, not a complete reagent-balanced equation.

Substitution preference: Unlike ordinary alkenes, benzene does not rapidly decolorize bromine water under normal test conditions. With $\text{Br}_2/\text{FeBr}_3$ it undergoes substitution, retaining its aromatic ring. This behavior is not explained by three isolated double bonds.



Conditions: FeBr_3 catalyst; electrophilic aromatic substitution.

Thermochemical evidence: resonance stabilization

Hydrogenation of one cyclohexene double bond releases approximately 120 kJ mol^{-1} . A hypothetical ring with three isolated double bonds would therefore be expected to release approximately 360 kJ mol^{-1} . Actual benzene hydrogenation releases only about 208 kJ mol^{-1} .

$$\text{Expected } \Delta H \approx 3 \times (-120) = -360 \text{ kJ mol}^{-1}$$

$$\text{Observed } \Delta H \approx -208 \text{ kJ mol}^{-1}$$

$$\text{Estimated stabilization} \approx 360 - 208 = 152 \text{ kJ mol}^{-1}$$

Therefore benzene starts at a lower energy than the hypothetical localized-bond model. Values around $148\text{--}152 \text{ kJ mol}^{-1}$ are quoted depending on reference data and rounding; approximately 150 kJ mol^{-1} is the appropriate interpretation.

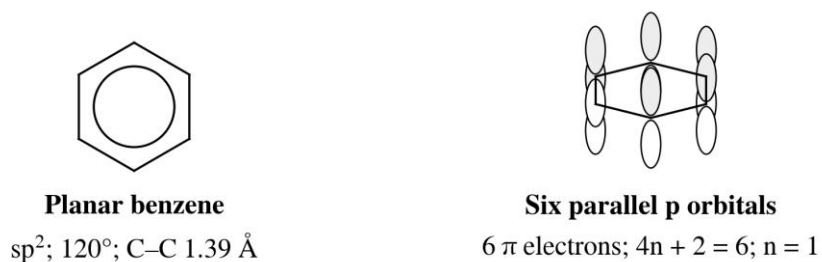
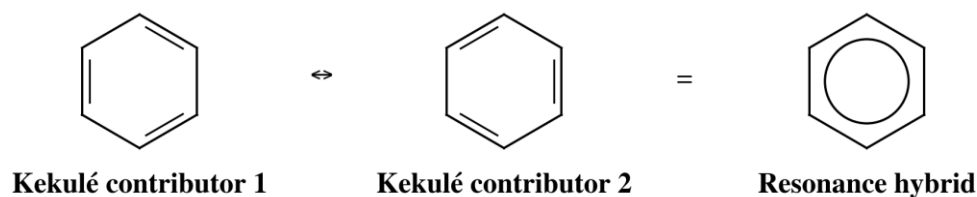
Modern orbital and aromatic structure

Diffraction studies establish a planar regular hexagon. Each carbon is sp^2 hybridized, with bond angles approximately 120° . Each carbon forms two C–C σ bonds and one C–H σ bond, leaving a perpendicular p orbital containing one electron. Continuous sideways overlap of six p orbitals produces a delocalized π system above and below the ring.

All six C–C bonds have the same length, approximately $1.39 \text{ \AA}$. The two Kekulé drawings are resonance contributors to a single resonance hybrid; benzene does not oscillate between two isolable structures.

$$\pi\text{-electron count} = 6 = 4n + 2; \text{ therefore } n = 1$$

Benzene satisfies all aromaticity requirements: it is cyclic, planar, fully conjugated and contains $4n + 2$ π electrons. Together, the analytical, chemical, thermochemical and structural evidence explain its formula, symmetry and exceptional stability.



2(b). Explain substituent effects on the reactivity and orientation of electrophilic substitution in monosubstituted benzene. [10 marks]

Meaning of reactivity and orientation

A substituent already attached to benzene influences the rate of further electrophilic aromatic substitution and the position at which it occurs. Reactivity compares the substituted ring with benzene under comparable conditions. Orientation describes whether the incoming group mainly enters the ortho (C2/C6), meta (C3/C5) or para (C4) position relative to the original substituent at C1.

The key step is formation of the positively charged σ complex (arenium ion). Groups that stabilize this intermediate generally increase the reaction rate; groups that destabilize it generally decrease the rate. Relative stabilization of intermediates determines the preferred position.

Electronic effects

Inductive effect: Electron donation (+I) or withdrawal (–I) is transmitted through σ bonds. Alkyl groups donate weakly; electronegative atoms and positively charged groups withdraw.

Resonance effect: Groups with an available lone pair, such as –OH and –OR, can donate into the ring (+M/+R). Groups such as –NO₂ and carbonyl-containing substituents withdraw by resonance (–M/–R). Alkyl groups also stabilize suitable arenium-ion contributors by hyperconjugation.

Class	Representative groups	Effect and orientation
Activating	–OH, –OR, –NH ₂ , –NHR, –NR ₂	Faster than benzene; mainly ortho/para
Moderately/weakly activating	–NHCOR; alkyl such as –CH ₃	Ortho/para directing
Deactivating	–NO ₂ , –CN, –CHO, –COR, –COOH, –COOR, –SO ₃ H, –NR ₃ ⁺	Slower than benzene; mainly meta
Halogen exception	–F, –Cl, –Br, –I	Deactivating but ortho/para directing

Activating ortho/para directors

For phenol, oxygen donates a lone pair into the aromatic system. Ortho and para attack produce σ complexes with an additional resonance contributor in which oxygen supplies electron density to the electron-deficient carbon. This stabilization is absent for the corresponding meta intermediate, so ortho/para substitution is favored.

In toluene, the methyl group donates electron density by hyperconjugation and a weak +I effect. Ortho/para attack allows a particularly stabilized contributor with positive charge at the carbon bearing –CH₃. Consequently, toluene reacts more readily than benzene and mainly gives ortho and para products.



Conditions: Concentrated HNO₃/H₂SO₄, controlled temperature. CH₃C₆H₄NO₂ represents mainly the ortho and para nitrotoluene isomers, with a smaller meta fraction.

Deactivating meta directors

The –NO₂ group withdraws electron density by both –I and –M effects. During ortho/para attack, a σ -complex contributor places positive charge on the ring carbon directly bonded to the strongly withdrawing group; this contributor is especially unfavorable. Meta attack avoids that particular destabilization. Thus nitrobenzene reacts more slowly than benzene, but its preferred nitration product is meta substituted.



Conditions: Concentrated HNO₃/H₂SO₄ and stronger heating than for benzene nitration. Major product: 1,3-dinitrobenzene. Meta directing does not mean that the meta position is activated relative to benzene.

Why halogens are exceptions

Halogens withdraw electron density strongly through the inductive effect and therefore deactivate the ring overall. Their lone pairs nevertheless donate by resonance and selectively stabilize σ complexes arising from ortho and para attack. Overall rate and preferred position reflect different comparisons; deactivation and ortho/para direction can therefore occur together.

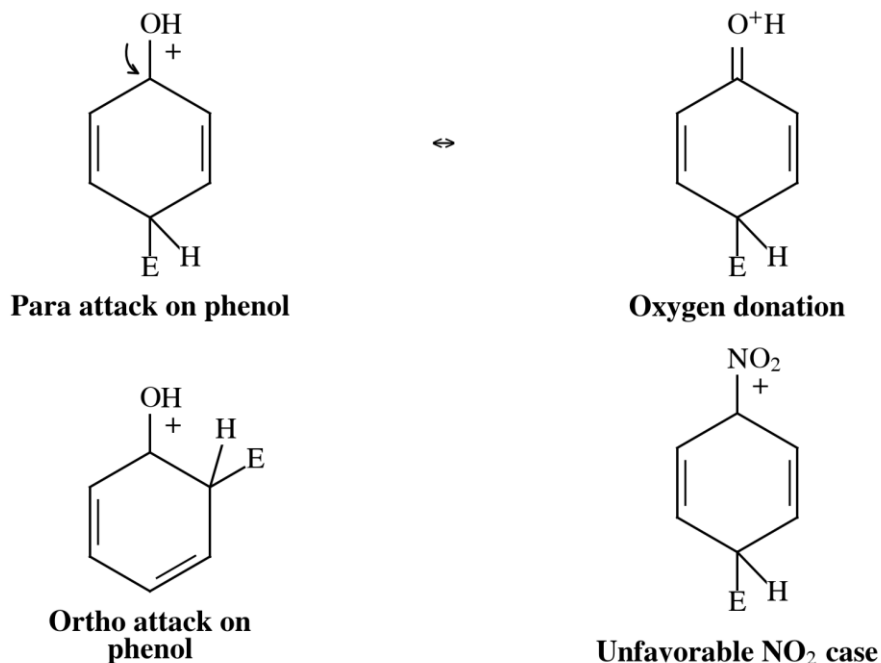


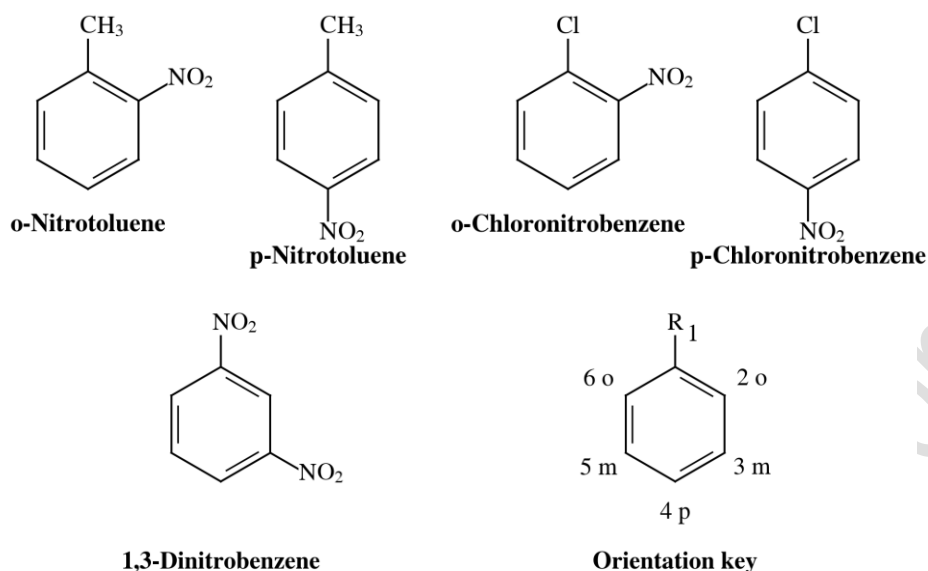
Conditions: Concentrated $\text{HNO}_3/\text{H}_2\text{SO}_4$ with warming. Products: mainly ortho- and para-chloronitrobenzene; para substitution is often favored by lower steric crowding.

Steric effects and reaction conditions

Bulky substituents or bulky incoming electrophiles can suppress ortho attack and increase the para proportion. Product ratios also depend on reagents, temperature and medium; an ortho/para director does not always give para as the major product.

The chemical form of the substituent matters. In strongly acidic medium, $-\text{NH}_2$ may become $-\text{NH}_3^+$, which is deactivating and meta directing. Therefore, simple activating-group classifications refer to the stated, unprotonated groups and should not be applied without considering the reaction medium.





Conclusion: Electron donation generally activates and directs ortho/para; electron withdrawal generally deactivates and directs meta. Halogens are the important deactivating ortho/para exception, and steric effects refine the product distribution.

Section C — Answer any two questions

3(a). State Hückel's rule for aromaticity and explain its application to benzene. [5 marks]

Hückel's rule states that a cyclic, planar, continuously conjugated ring is aromatic when it contains $(4n + 2) \pi$ electrons, where n is a non-negative integer: 0, 1, 2, 3, and so on.

Corresponding allowed counts are 2, 6, 10, 14, etc.

The electron count must be applied only after checking the structural conditions. Every ring atom must provide a p orbital so that overlap extends around the complete ring; the participating orbitals must be able to align in a planar cyclic arrangement.

Application to benzene

Cyclic: Six carbons form a closed ring. **Planar:** All carbons are sp^2 hybridized and lie in one plane, with approximately 120° bond angles. **Fully conjugated:** Every carbon has one perpendicular p orbital that overlaps with its neighbors. **Electron count:** Each carbon contributes one p electron, giving six π electrons in total.

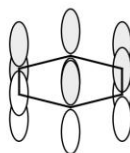
$$4n + 2 = 6 \rightarrow 4n = 4 \rightarrow n = 1$$

Because n is an allowed integer and the structural conditions are satisfied, benzene is aromatic. The six π electrons occupy three bonding π molecular orbitals, producing a stable closed-shell system. Delocalization explains equal C–C bond lengths and the preference for substitution reactions that preserve aromaticity.

A cyclic, planar, fully conjugated system with $4n$ π electrons is antiaromatic. A system that lacks planarity or continuous conjugation is nonaromatic, even if a numerical electron count appears suitable. Ordinary cyclooctatetraene, for example, avoids antiaromaticity by adopting a nonplanar shape.



Planar benzene
 sp^2 ; 120° ; C–C 1.39 Å



Six parallel p orbitals
 6 π electrons; $4n + 2 = 6$; $n = 1$

3(b). Explain the mechanism of electrophilic aromatic substitution in benzene using chlorination. [5 marks]

Overall: $C_6H_6 + Cl_2 \rightarrow C_6H_5Cl + HCl$

Conditions: Anhydrous $FeCl_3$ (or $AlCl_3$) catalyst; avoid UV light. Product: chlorobenzene. This is ring substitution, not photochemical addition.

Step 1 — Activation of chlorine (Electrophile generation)

$FeCl_3$ acts as a Lewis acid and accepts electron density from Cl_2 . Coordination strongly polarizes the Cl–Cl bond, making one chlorine atom electrophilic.

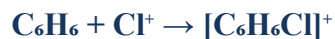


Formal shorthand: $Cl_2 + FeCl_3 \rightleftharpoons Cl^+ + FeCl_4^-$

Cl^+ is convenient mechanistic shorthand for electrophilic chlorine in the activated complex; it should not be interpreted as a freely accumulating ion in the reaction mixture.

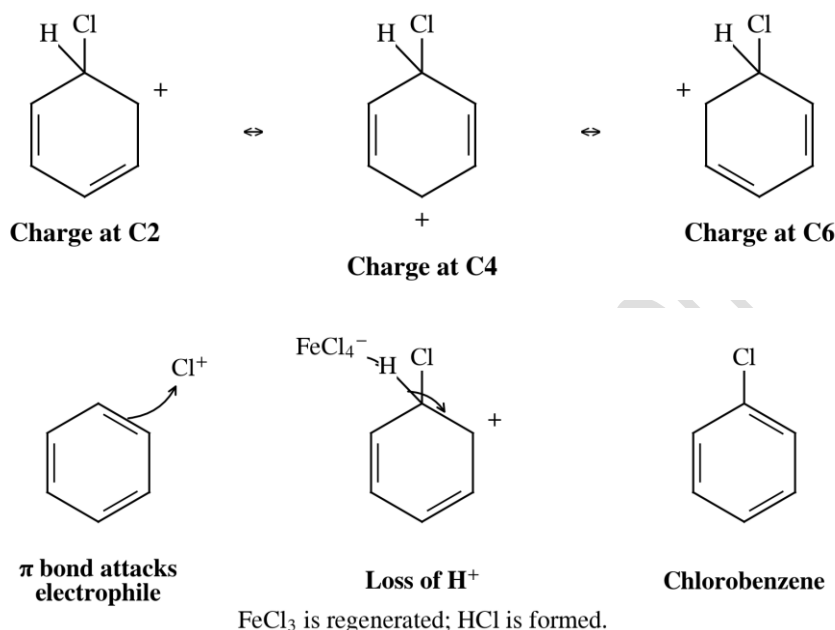
Step 2 — Formation of the σ complex intermediate (slow)

A benzene π -electron pair attacks electrophilic chlorine, forming a C–Cl σ bond. The attacked carbon temporarily bears both H and Cl and becomes approximately sp^3 hybridized. Aromaticity is lost, and the positive charge is delocalized over three ring carbons in the arenium ion. This high-energy step is normally rate determining.



Step 3 — Deprotonation and restoration of aromaticity (fast)

FeCl_4^- removes the proton from the carbon bearing chlorine. The C–H bond electron pair reforms the ring π bond, restoring aromaticity and regenerating FeCl_3 .



3(c). Discuss the acidic character of phenol and the effect of substituents on its acidity. [5 marks]

Acidic character and resonance stabilization

Phenol is a weak Bronsted acid because it can donate the hydrogen of its $-\text{OH}$ group to form the phenoxide ion. Its aqueous pK_a is approximately 10, compared with approximately 16 for ethanol, so phenol is appreciably more acidic than a typical aliphatic alcohol.



In phenoxide, the negative charge is delocalized through conjugation between oxygen and the ring, with contributors placing charge at the ortho and para positions. The oxygen-centered contributor remains important. An ethoxide ion lacks this aromatic delocalization. Preferential stabilization of the conjugate base helps explain phenol's greater acidity.

Reactions demonstrating acidity

Conditions: Aqueous sodium hydroxide. Product: sodium phenoxide.



Conditions: Sodium metal; hydrogen is evolved.

Ordinary phenol does not give appreciable CO_2 effervescence with aqueous NaHCO_3 because it is too weakly acidic to displace carbonic acid effectively. This distinguishes it from ordinary carboxylic acids; strongly electron-poor substituted phenols can behave differently.

Effect of electron-withdrawing substituents

Groups such as $-\text{NO}_2$, $-\text{CN}$ and $-\text{CHO}$ generally increase acidity by stabilizing the phenoxide ion. A nitro group at ortho or para can stabilize it by both inductive withdrawal and resonance; at meta its influence is mainly inductive/field withdrawal. Consequently, o- and p-nitrophenol are substantially more acidic than phenol, and m-nitrophenol also shows increased acidity.

Multiple nitro groups produce a stronger effect. Thus 2,4,6-trinitrophenol (picric acid) is much more acidic than phenol. Exact ortho/para comparisons also depend on solvation and intramolecular hydrogen bonding; do not assign their order solely from resonance drawings.

Effect of electron-donating substituents

Alkyl groups such as $-\text{CH}_3$ donate electron density and generally make phenoxide formation less favorable. Cresols are therefore slightly less acidic than phenol. For groups capable of both induction and resonance, such as $-\text{OCH}_3$, the net effect depends on position; avoid assuming that every substituent behaves identically at ortho, meta and para.

Typical trend: p-nitrophenol > phenol > p-cresol

Supporting calculation: interpreting pK_a

This is an explanatory calculation, not a numerical problem supplied in the paper. Taking rounded illustrative values $\text{pK}_a(\text{phenol}) \approx 10.0$ and $\text{pK}_a(\text{p-nitrophenol}) \approx 7.2$:

$$\text{K}_a = 10^{-\text{pK}_a} ; \text{K}_a(\text{phenol}) = 10^{-10}, \text{K}_a(\text{p-nitrophenol}) = 10^{-7.2},$$

$$\text{K}_a(\text{p-nitrophenol}) / \text{K}_a(\text{phenol})$$

$$= 10^{-7.2} / 10^{-10}, = 10^{2.8} \approx 631$$

Therefore, p-nitrophenol has approximately 630 times larger the acid dissociation constant of phenol under comparable aqueous conditions. Lower pK_a means greater acid strength; it does not mean a lower K_a .

