BP204T · B.PHARM THEORY

BP204T Pharmaceutical Organic Chemistry

Unit IV — Benzene & Its Derivatives

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From-zero teaching standard: every technical term is defined before use.

Syllabus coverage: Unit IV (12 hours).

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CHAPTER 12 — Structure of Benzene, Aromaticity, Hückel's Rule, and Nomenclature

Learning objectives

- Describe the structure of benzene: Kekulé structures, bond lengths, planarity.
- Explain resonance and the molecular orbital (MO) picture of benzene.
- State the resonance energy of benzene and what it means.
- Define aromaticity and apply Hückel's rule (4n+2).
- Classify compounds as aromatic, anti-aromatic, or non-aromatic with examples.
- Name mono- and di-substituted benzene derivatives using IUPAC rules.

12.1 Definitions

- **Benzene:** A hydrocarbon with molecular formula C_6H_6 — a six-membered ring of carbon atoms with alternating single and double bonds (in the classical picture).
- **Kekulé structures:** The two alternating double-bond drawings of benzene (proposed by Kekulé). The real benzene is a hybrid — neither structure alone is correct; the truth is an average of both.
- **Resonance:** The idea that a molecule's true structure is a blend (hybrid) of two or more Lewis drawings. The real molecule is MORE stable than any single drawing suggests.
- **Resonance energy:** The extra stability gained by resonance — the difference between the actual energy of the molecule and the energy of its most stable single Lewis drawing. For benzene it is about 150 kJ/mol (36 kcal/mol).
- **Delocalisation:** Spreading of electrons over several atoms instead of being fixed between two atoms. Benzene's six π electrons are delocalised over the whole ring.
- **Aromaticity:** The special stability (and characteristic reactivity) of cyclic, planar, fully conjugated systems with (4n+2) π electrons.

12.2 Terminology alert — learn these first

- **π (pi) electrons:** Electrons in the sideways-overlapping p-orbitals above and below the ring plane — the electrons of the double bonds. (σ electrons are the ones in the direct head-on bonds forming the skeleton.)
- **Molecular orbital (MO) picture:** A model in which electrons occupy orbitals spread over the whole molecule, not fixed between two atoms. In benzene, six p-orbitals (one on each carbon) merge sideways into a continuous ring-shaped cloud of π electrons — like a doughnut above and below the ring.
- **Planar:** Flat — all atoms lying in one plane. Benzene is perfectly flat, which allows the p-orbitals to overlap all around the ring.
- **Conjugated system:** Alternating single and double bonds (...–C=C–C=C–...), allowing π electrons to spread over the whole chain or ring.
- **Anti-aromatic:** A cyclic, planar, conjugated system with 4n π electrons (e.g., 4, 8) — unusually UNSTABLE, the opposite of aromatic.
- **Ortho / meta / para:** Positions on a disubstituted benzene ring relative to the first substituent: ortho = adjacent (1,2), meta = one carbon between (1,3), para = opposite (1,4).

12.3 The structure of benzene — what experiments show

1. **Molecular formula C_6H_6:** Highly unsaturated (an alkane with 6 carbons would be C_6H_{14}), yet benzene does NOT behave like an alkene — it does not decolourise bromine water or react easily with typical addition reagents.
2. **All C–C bonds are equal:** Measured bond length is 139 pm — between a single bond (154 pm) and a double bond (134 pm). If Kekulé's alternating structure were literally true, we would see two different lengths.
3. **Planar hexagon:** All six carbons and six hydrogens lie in one flat plane, with 120° bond angles (sp^2 hybridised carbons).
4. **Unusual stability:** Benzene resists addition reactions that alkenes undergo readily; instead it undergoes substitution, keeping its π system intact. Its resonance energy (~150 kJ/mol) measures this extra stability.

The MO picture in words: Each carbon contributes one p-orbital sticking up and down from the ring plane. All six p-orbitals overlap sideways into one continuous ring-shaped electron cloud — three filled molecular orbitals holding 6 π electrons, spread evenly over all six carbons. This is why all bonds are identical.

Key takeaway: Benzene is a flat ring with 6 delocalised π electrons; it is far more stable than three isolated double bonds would be, and it prefers substitution over addition.

12.4 Hückel's rule and aromaticity

Hückel's rule: A compound is aromatic if it is (1) cyclic, (2) planar, (3) fully conjugated (every atom has a p-orbital), and (4) has (4n+2) π electrons, where n = 0, 1, 2, ... (i.e., 2, 6, 10, 14 ... π electrons).

> **Worked examples:**

- **Benzene:** cyclic ✓, planar ✓, conjugated ✓, 6 π electrons = 4(1)+2 ✓ → aromatic.
- **Cyclobutadiene (C_4H_4):** cyclic ✓, planar ✓, conjugated ✓, but 4 π electrons = 4n (n=1) ✗ → anti-aromatic (very unstable, exists only at very low temperatures).
- **Cyclooctatetraene (C_8H_8):** 8 π electrons = 4n ✗, and it twists out of planarity to avoid anti-aromaticity → non-aromatic (behaves like four ordinary double bonds).
- **Cyclopentadiene (C_5H_6):** has one sp^3 carbon breaking conjugation → non-aromatic (but its anion, $C_5H_5^-$, with 6 π electrons, IS aromatic — a famous result).

Key takeaway: Count the π electrons and check the four conditions. 4n+2 = aromatic (stable); 4n planar = anti-aromatic (unstable); anything breaking the ring/planarity/conjugation = non-aromatic.

12.5 IUPAC nomenclature of benzene derivatives

Mono-substituted: Name the substituent as a prefix + "benzene": chlorobenzene, nitrobenzene, methylbenzene. Some have special retained names you must know:

- Methylbenzene = **toluene**
- Hydroxybenzene = **phenol**
- Aminobenzene = **aniline**
- Carboxybenzene = **benzoic acid**
- Formylbenzene = **benzaldehyde**
- Acetylbenzene = **acetophenone**

Di-substituted: Use ortho (1,2), meta (1,3), para (1,4) — or numbers:

- 1,2-dimethylbenzene = ortho-xylene (o-xylene)
- 1,3-dinitrobenzene = meta-dinitrobenzene
- 1,4-dichlorobenzene = para-dichlorobenzene

Numbering rule: give the lowest set of numbers; the first substituent gets position 1.

> **Worked example:** A benzene ring with $-NO_2$ at position 1 and –Br at position 3 → 1-bromo-3-nitrobenzene, or meta-bromonitrobenzene.

Key takeaway: Learn the six special names (toluene, phenol, aniline, benzoic acid, benzaldehyde, acetophenone); use o/m/p or 1,2-/1,3-/1,4- for disubstituted rings.

12.6 Pharmacy relevance

The benzene ring is the single most common structural unit in drugs — from paracetamol and aspirin to antibiotics and antihistamines. A pharmacist who can name substituted benzenes correctly can read any drug structure or label without confusion.

12.7 India context

Many Indian-manufactured drugs (paracetamol, ibuprofen intermediates, sulfa drugs) are benzene derivatives made by the electrophilic substitution reactions of Chapter 13. India's bulk-drug industry grew partly on mastery of this aromatic chemistry.

12.8 Common confusions

1. **Aromatic vs fragrant:** In chemistry, "aromatic" means Hückel-rule stability, not smell. Many aromatic compounds do have odours, but the word is technical.
2. **Resonance structures are not real:** Benzene does not flip between two Kekulé forms; the real structure is a single hybrid, always the same.
3. **Cyclooctatetraene is not anti-aromatic:** It escapes by becoming non-planar (tub-shaped). Anti-aromatic requires planarity.
4. **ortho/meta/para vs 1,2-/1,3-/1,4-:** Same thing — o = 1,2; m = 1,3; p = 1,4.

12.9 Common mistakes

1. Counting σ electrons in Hückel's rule — count only π electrons.
2. Forgetting the planarity requirement when judging aromaticity.
3. Naming $C_6H_5–CH_3$ as "methylbenzene" is correct, but "toluene" is the expected common name in pharmacy — know both.
4. Drawing benzene with fixed alternating double bonds and then treating one double bond as an ordinary alkene in mechanisms.

12.10 Mnemonics

- **"4n+2, aromatic true":** chant the Hückel numbers — 2, 6, 10, 14.
- **"OMP — Oh My Positions":** Ortho = adjacent (1,2), Meta = middle gap (1,3), Para = opposite (1,4).

12.11 One-minute revision

- Benzene: C_6H_6, planar hexagon, all C–C bonds 139 pm (equal).
- Resonance energy ≈ 150 kJ/mol (36 kcal/mol) — extra stability.
- MO picture: 6 p-orbitals merge into a ring-shaped π cloud (6 delocalised electrons).
- Hückel's rule: cyclic + planar + conjugated + (4n+2) π electrons → aromatic.
- Benzene (6 π) = aromatic; cyclobutadiene (4 π) = anti-aromatic; cyclooctatetraene (8 π, non-planar) = non-aromatic.
- Benzene prefers substitution over addition (keeps aromaticity).
- Special names: toluene, phenol, aniline, benzoic acid, benzaldehyde, acetophenone.
- o/m/p = 1,2- / 1,3- / 1,4-.

12.12 Practice questions

MCQs

1. The C–C bond length in benzene is:

a) 154 pm b) 134 pm c) 139 pm d) 120 pm

1. Which compound is aromatic by Hückel's rule?

a) cyclobutadiene b) cyclooctatetraene c) benzene d) cyclopentadiene

1. The resonance energy of benzene is approximately:

a) 15 kJ/mol b) 150 kJ/mol c) 1500 kJ/mol d) 36 J/mol

1. 1,4-dichlorobenzene is also called:

a) ortho-dichlorobenzene b) meta-dichlorobenzene c) para-dichlorobenzene d) sym-dichlorobenzene

1. Hydroxybenzene is commonly known as:

a) aniline b) phenol c) toluene d) anisole

Short-answer

1. State Hückel's rule and use it to classify benzene, cyclobutadiene, and cyclooctatetraene.
2. Give the common names of: $C_6H_5–CH_3$, $C_6H_5–NH_2$, $C_6H_5–COOH$.
3. Why are all C–C bonds in benzene equal in length?

Long-answer

1. Describe the structure of benzene using the Kekulé, resonance, and molecular orbital pictures. Include bond lengths, planarity, and resonance energy.
2. Explain the term aromaticity. How does Hückel's rule distinguish aromatic, anti-aromatic, and non-aromatic compounds? Give one example of each.

Mechanism-writing

1. (Conceptual) Draw in words the two Kekulé structures of benzene and explain why neither alone represents the true molecule.

Application-based

1. A student counts 8 π electrons in a flat, cyclic, conjugated compound and calls it aromatic. Is she right? Explain.

Viva

1. What is resonance energy, and what does benzene's value tell us?
2. Why does benzene undergo substitution rather than addition?

Answer key (MCQs): 1-c, 2-c, 3-b, 4-c, 5-b.

References

- Morrison, R.T., Boyd, R.N. and Bhattacharjee, S.K., *Organic Chemistry* (Pearson Education India).
- Finar, I.L., *Organic Chemistry*, Vol. I (Pearson).
- Bahl, B.S. and Bahl, A., *Textbook of Organic Chemistry* (S. Chand).

CHAPTER 13 — Electrophilic Aromatic Substitution: Nitration, Halogenation, Friedel–Crafts, Sulphonation

Learning objectives

- Describe the general mechanism of electrophilic aromatic substitution (EAS) in three steps.
- Identify the electrophile in nitration, halogenation, sulphonation, and Friedel–Crafts reactions.
- Write reaction equations with reagents and conditions for each named EAS reaction.
- List the four limitations of Friedel–Crafts alkylation.
- Explain why Friedel–Crafts acylation avoids rearrangement and poly-substitution.
- Explain sulphonation and its reversal (desulphonation) as a blocking-group strategy.

13.1 Definitions

- **Electrophilic aromatic substitution (EAS):** A reaction in which an electrophile replaces a hydrogen atom on a benzene ring. The aromatic π system is restored at the end — this is why substitution wins over addition.
- **Arenium ion (σ-complex):** The positively charged intermediate formed when the electrophile bonds to the ring carbon. The positive charge is delocalised over the ring by resonance (it can be drawn in three resonance forms). It is NOT aromatic — aromaticity is temporarily lost.
- **Electrophile (in EAS):** The electron-poor species that attacks the ring — e.g., NO_2^+, Br^+, R^+, RCO^+, SO_3.
- **Lewis acid catalyst:** A substance that accepts an electron pair — e.g., $AlCl_3$, $FeBr_3$, $FeCl_3$. Used to generate the electrophile.

13.2 Terminology alert — learn these first

- **Nitrating mixture:** Concentrated HNO_3 + concentrated H_2SO_4 — the classic reagent pair for nitration.
- **Oleum:** Fuming sulphuric acid (H_2SO_4 with extra dissolved SO_3) — a stronger sulphonating agent than conc. H_2SO_4.
- **Aqueous work-up:** Treating the reaction mixture with water (or dilute acid) at the end to release the final product from its complex with the catalyst.
- **Blocking group:** A substituent put on the ring temporarily to block a position from reacting, then removed later. The $–SO_3H$ group is the classic example.
- **Polyalkylation:** Formation of di-, tri- (multiple) alkylated products because the first alkyl group activates the ring toward further attack.

13.3 The general EAS mechanism (learn once, apply everywhere)

Step 1 — Attack of the electrophile: The benzene π electrons attack the electrophile (E^+). One C–H carbon forms a new C–E bond; the ring's aromaticity is broken, giving the resonance-stabilised arenium ion (positive charge spread over ortho and para positions).

Step 2 — Loss of proton: A base (often HSO_4^- or the solvent) removes the hydrogen from the same carbon that gained E. The electron pair flows back into the ring.

Step 3 — Restoration of aromaticity: The π system is fully restored; the product is the substituted benzene + H^+.

In words as an equation: $C_6H_6 + E^+ \rightarrow$ [arenium ion]$^+ \rightarrow C_6H_5–E + H^+$

Key takeaway: EAS always follows attack → arenium ion → deprotonation. The electrophile differs per reaction; the pattern never changes.

13.4 Nitration

Reagents and conditions: Concentrated HNO_3 + concentrated H_2SO_4 ("nitrating mixture"), typically at 50–60 °C for benzene. **Electrophile:** Nitronium ion, NO_2^+ (formed by: $HNO_3 + 2H_2SO_4 \rightarrow NO_2^+ + H_3O^+ + 2HSO_4^-$). **Equation:** C_6H_6 + conc. HNO_3 / conc. $H_2SO_4 \rightarrow C_6H_5–NO_2$ (nitrobenzene) + H_2O.

> **Worked example:** Toluene nitrated under mild conditions gives ortho- and para-nitrotoluene (the methyl group directs ortho/para — Chapter 14). Vigorous conditions give 2,4,6-trinitrotoluene (TNT).

Key takeaway: Nitration needs the nitrating mixture; the electrophile is NO_2^+.

13.5 Halogenation

Reagents and conditions: Br_2 with $FeBr_3$ catalyst (or Cl_2 with $FeCl_3$); no catalyst is needed for the ring because Br_2 alone is not electrophilic enough — the Lewis acid polarises it. **Electrophile:** Br^+ (or Cl^+), generated as $Br_2 + FeBr_3 \rightarrow Br^+ + FeBr_4^-$. **Equation:** $C_6H_6 + Br_2$ / $FeBr_3 \rightarrow C_6H_5–Br$ (bromobenzene) + HBr.

> **Worked example:** Chlorination of benzene with $Cl_2/FeCl_3$ gives chlorobenzene, a starting material for many syntheses.

Key takeaway: Ring halogenation needs a Lewis acid ($FeBr_3/FeCl_3$); the electrophile is Br^+ or Cl^+.

13.6 Friedel–Crafts alkylation

Reagents and conditions: Alkyl halide (R–Cl) + anhydrous $AlCl_3$ catalyst, typically in dry conditions (water destroys $AlCl_3$). **Electrophile:** A carbocation, R^+ (formed as $R–Cl + AlCl_3 \rightarrow R^+ + AlCl_4^-$). **Equation:** $C_6H_6 + CH_3–Cl$ / $AlCl_3 \rightarrow C_6H_5–CH_3$ (toluene) + HCl.

FOUR LIMITATIONS (examiners love this list):

1. **Carbocation rearrangement:** If R^+ can rearrange to a more stable carbocation, it will. Example: n-propyl chloride ($CH_3–CH_2–CH_2–Cl$) gives mainly the isopropyl product (cumene, $C_6H_5–CH(CH_3)_2$), because the primary carbocation shifts a hydride to become secondary.
2. **Fails on strongly deactivated rings:** Rings carrying strong electron-withdrawing groups (e.g., nitrobenzene) do not react — the ring is too electron-poor to attack.
3. **Polyalkylation:** The alkyl group added is activating, so the product reacts FASTER than benzene — mixtures of mono-, di-, and tri-alkyl products form.
4. **Amino groups interfere:** $–NH_2$ coordinates with $AlCl_3$ (forming $–NH_2 \rightarrow AlCl_3$), turning the group deactivating and stopping the reaction.

> **Worked example:** Benzene + n-propyl chloride / $AlCl_3$ → mainly cumene (isopropylbenzene), NOT n-propylbenzene — the classic rearrangement proof.

Key takeaway: F–C alkylation attaches R via a carbocation — so expect rearrangement, polyalkylation, and failure on deactivated rings.

13.7 Friedel–Crafts acylation

Reagents and conditions: Acid chloride (R–COCl) + anhydrous $AlCl_3$, followed by aqueous work-up (water/dilute acid) to free the ketone. **Electrophile:** Acylium ion, $R–C^+=O$ (resonance-stabilised: $R–C\equiv O^+$). **Equation:** $C_6H_6 + CH_3–COCl / AlCl_3 \rightarrow$ (aqueous work-up) $\rightarrow C_6H_5–CO–CH_3$ (acetophenone, methyl phenyl ketone) + HCl.

Why acylation is better behaved:

1. **No rearrangement:** The acylium ion is resonance-stabilised and does not rearrange.
2. **No polyacylation:** The product is a ketone — the –COR group is deactivating, so the ring becomes LESS reactive after the first acylation and stops.
3. Still needs anhydrous conditions and still fails on strongly deactivated rings.

> **Worked example:** Benzene + benzoyl chloride ($C_6H_5–COCl$) / $AlCl_3 \rightarrow$ benzophenone ($C_6H_5–CO–C_6H_5$) after work-up. (Benzophenone-type structures appear in sunscreens and in ketoprofen's chemistry — Chapter 18.)

Key takeaway: F–C acylation gives aryl ketones cleanly — no rearrangement, no poly-reaction — but needs aqueous work-up at the end.

13.8 Sulphonation and desulphonation

Reagents and conditions: Concentrated H_2SO_4 (or oleum for difficult cases), with heating. **Electrophile:** SO_3 (or HSO_3^+). **Equation:** C_6H_6 + conc. H_2SO_4 (heat) $\rightarrow C_6H_5–SO_3H$ (benzenesulphonic acid) + H_2O.

Reversibility — desulphonation: Unlike other EAS reactions, sulphonation is REVERSIBLE. Heating benzenesulphonic acid with superheated steam or dilute acid removes the $–SO_3H$ group: $C_6H_5–SO_3H$ + steam (heat) $\rightarrow C_6H_6 + H_2SO_4$.

Use as a blocking group (worked example): Want para-bromoaniline but $–NH_2$ directs ortho/para (mixture)? Sulphonate first (blocks para), brominate (goes ortho), then desulphonate with steam — the $–SO_3H$ leaves and you keep the product you wanted. This "block, react, unblock" trick is a standard synthesis strategy.

Key takeaway: Sulphonation is the only easily reversible EAS — the $–SO_3H$ group is installed and removed at will, making it a perfect temporary blocking group.

13.9 Pharmacy relevance

Nitration, halogenation, and Friedel–Crafts reactions build the substituted benzene cores of countless drugs — sulfa antibiotics come from sulphonation chemistry, and many NSAIDs and antihistamines are assembled via F–C acylation/alkylation steps.

13.10 India context

Sulphonation plants and nitration units are core infrastructure in India's bulk-drug and dye industries (dyes like azo dyes are built on nitrated anilines). Safe handling of the nitrating mixture and oleum is standard training for Indian production chemists.

13.11 Common confusions

1. **F–C alkylation vs acylation:** Alkylation adds R– (rearranges, poly-reacts); acylation adds R–CO– (clean, stops at one). Know which is which.
2. **Why acylation needs work-up:** The ketone product complexes with $AlCl_3$; water releases it. Alkylation products do not complex, so no work-up is needed.
3. **Desulphonation conditions:** Superheated steam or dilute aqueous acid with heat — NOT just standing in air.
4. **The electrophile is not the reagent:** The reagent is $Br_2/FeBr_3$; the electrophile is Br^+. Examiners ask for the electrophile specifically.

13.12 Common mistakes

1. Writing F–C alkylation with n-propyl chloride giving n-propylbenzene — it rearranges to the isopropyl product.
2. Forgetting anhydrous conditions for Friedel–Crafts (water kills $AlCl_3$).
3. Drawing addition products on benzene — EAS always restores the ring.
4. Confusing sulphonation (reversible) with nitration (not reversible).

13.13 Mnemonics

- **"No-Ha-FA-FA-Su"** — the five EAS reactions in order: Nitration, Halogenation, F–C Alkylation, F–C Acylation, Sulphonation.
- **"RAPP"** — the four alkylation limitations: Rearrangement, deActivated rings fail, Polyalkylation, amino-group Poisoning (coordinates $AlCl_3$).

13.14 One-minute revision

- EAS mechanism: electrophile attacks → arenium ion → proton lost → aromaticity restored.
- Nitration: conc. HNO_3 + conc. H_2SO_4; electrophile NO_2^+.
- Halogenation: $Br_2/FeBr_3$ or $Cl_2/FeCl_3$; electrophile Br^+/Cl^+.
- F–C alkylation: R–Cl + $AlCl_3$ (anhydrous); electrophile R^+; limitations RAPP.
- n-propyl chloride → isopropyl product (rearrangement proof).
- F–C acylation: R–COCl + $AlCl_3$, then aqueous work-up; electrophile RCO^+; no rearrangement, no polyacylation.
- Sulphonation: conc. H_2SO_4/oleum, heat; electrophile SO_3; reversible by steam → blocking group.
- The electrophile is the attacking species, not the whole reagent bottle.

13.15 Practice questions

MCQs

1. The electrophile in nitration is:

a) NO_3^- b) NO_2^+ c) HNO_3 d) HSO_4^-

1. Friedel–Crafts alkylation of benzene with n-propyl chloride gives mainly:

a) n-propylbenzene b) isopropylbenzene c) toluene d) no reaction

1. Which EAS reaction is reversible?

a) nitration b) halogenation c) sulphonation d) F–C acylation

1. F–C acylation requires, after the main step:

a) cooling b) aqueous work-up c) distillation d) nothing

1. The catalyst in Friedel–Crafts reactions is:

a) $FeBr_3$ b) $AlCl_3$ c) H_2SO_4 d) Pt

Short-answer

1. Write the general three-step mechanism of electrophilic aromatic substitution.
2. List the four limitations of Friedel–Crafts alkylation with one example for rearrangement.
3. Why is Friedel–Crafts acylation free from rearrangement and poly-substitution?

Long-answer

1. Describe nitration, halogenation, Friedel–Crafts alkylation, Friedel–Crafts acylation, and sulphonation of benzene, giving reagents, conditions, electrophiles, and equations in each case.
2. Explain sulphonation and desulphonation. How is the $-SO_3H$ group used as a blocking group in synthesis? Give an example.

Mechanism-writing

1. Write the step-by-step EAS mechanism for the nitration of benzene, showing the formation of NO_2^+, the arenium ion (describe its resonance in words), and the final deprotonation.

Application-based

1. A synthesis needs para-bromoaniline without ortho contamination. Outline how sulphonation/desulphonation can be used as a blocking strategy.

Viva

1. Why must Friedel–Crafts reactions be carried out under anhydrous conditions?
2. Name the electrophiles in the five EAS reactions.

Answer key (MCQs): 1-b, 2-b, 3-c, 4-b, 5-b.

References

- Morrison, R.T., Boyd, R.N. and Bhattacharjee, S.K., *Organic Chemistry* (Pearson Education India).
- Finar, I.L., *Organic Chemistry*, Vol. I (Pearson).
- Bahl, B.S. and Bahl, A., *Textbook of Organic Chemistry* (S. Chand).

CHAPTER 14 — Effect of Substituents: Activating vs Deactivating, Ortho/Para vs Meta Directors

Learning objectives

- Classify common substituents as activating or deactivating.
- Classify substituents as ortho/para or meta directors, and state the rule linking the two.
- Explain, using the arenium ion, why –OH/–NH_2 direct ortho/para and –NO_2 directs meta.
- Explain why halogens are deactivating yet ortho/para directing.
- Predict the major product of EAS on a substituted benzene.

14.1 Definitions

- **Activating group:** A substituent that makes the benzene ring MORE reactive toward electrophilic substitution than benzene itself (donates electrons into the ring).
- **Deactivating group:** A substituent that makes the ring LESS reactive than benzene (withdraws electrons from the ring).
- **Ortho/para director:** A group that directs the incoming electrophile to the ortho (1,2) and para (1,4) positions.
- **Meta director:** A group that directs the incoming electrophile to the meta (1,3) position.
- **Inductive effect:** Electron withdrawal or donation through σ bonds due to electronegativity differences (falls off quickly with distance).
- **Resonance (mesomeric) effect:** Electron donation or withdrawal through π bonds / lone pairs overlapping with the ring's π system.

14.2 Terminology alert — learn these first

- **Lone pair:** A pair of valence electrons not involved in bonding (e.g., on –OH oxygen or –NH_2 nitrogen). Lone pairs next to the ring can be donated into it by resonance.
- **Electron-withdrawing group (EWG):** Pulls electrons away from the ring (e.g., –NO_2, –CHO, –COOH).
- **Electron-donating group (EDG):** Pushes electrons into the ring (e.g., –OH, –NH_2, –CH_3).
- **The master rule:** ALL activating groups are ortho/para directors; ALL deactivating groups are meta directors — EXCEPT the halogens, which are deactivating but ortho/para directing.

14.3 The two families

Activating, ortho/para directors (electron donors): –OH, –NH_2, –OR (e.g., –OCH_3), –NHCOR, and alkyl groups like –CH_3. Reason: the lone pair on O or N is donated into the ring by resonance, increasing electron density — especially at ortho and para positions (the arenium ion for ortho/para attack has an extra resonance form with the positive charge on the substituent atom, which is extra stable).

Deactivating, meta directors (electron withdrawers): –NO_2, –CHO, –COR, –COOH, –CN, –SO_3H, –$N^+(CH_3)_3$. Reason: these pull electrons out of the ring, making it electron-poor and slow to react; attack at ortho/para would place the positive charge next to the electron-withdrawing group (very unstable), so the electrophile goes meta, where the charge avoids the substituent.

The halogen exception: –F, –Cl, –Br, –I are DEACTIVATING (their strong inductive withdrawal outweighs everything, so the ring reacts slower than benzene) but ORTHO/PARA directing (their lone pairs still donate by resonance, stabilising the ortho/para arenium ion). Both effects operate; induction wins on rate, resonance wins on direction.

> **Worked example 1 — phenol bromination:** Phenol (–OH, strongly activating) with bromine water gives 2,4,6-tribromophenol (white precipitate) instantly — ortho and para positions all brominated. This reaction is so fast it is used as a test for phenol.

> **Worked example 2 — nitrobenzene nitration:** Nitrobenzene (–NO_2, deactivating meta director) on further nitration gives meta-dinitrobenzene as the major product.

> **Worked example 3 — toluene nitration:** Toluene (–CH_3, activating ortho/para) gives ortho- and para-nitrotoluene (para predominates slightly for steric reasons — the ortho positions are crowded).

Key takeaway: Donors activate and go o/p; withdrawers deactivate and go meta; halogens are the exception — deactivating but o/p.

14.4 Why direction works — the arenium ion argument (in words)

When the electrophile attacks ortho or para to a donor group (–OH), one resonance form of the arenium ion places the positive charge ON the oxygen/nitrogen atom, with every atom having a full octet — an especially stable arrangement. Attack at the meta position cannot do this. So o/p attack is faster. With a withdrawer (–NO_2), attack at ortho/para places the positive charge on the ring carbon directly attached to the electron-withdrawing group — two positive centres side by side, highly unstable. Meta attack avoids this. So meta attack wins.

14.5 Comparison table: substituent effects

Group	Example	Activating/Deactivating	Direction	Reason (short)
–OH, –NH_2	phenol, aniline	Strongly activating	o/p	Lone-pair resonance donation
–OR, –NHCOR	anisole, acetanilide	Activating	o/p	Lone-pair donation (weaker)
–CH_3 (alkyl)	toluene	Activating	o/p	Hyperconjugation + inductive donation
–F, –Cl, –Br, –I	chlorobenzene	Deactivating	o/p (exception!)	Inductive withdrawal > resonance donation
–NO_2, –CN, –CHO, –COR, –COOH, –SO_3H	nitrobenzene	Deactivating	meta	Electron withdrawal by resonance/induction

14.6 Predicting products — worked method

1. Identify the substituent already on the ring.
2. Classify it: activating or deactivating? o/p or meta director?
3. Place the new group at the directed positions; if several, remember: para usually beats ortho when both are free (less crowding), and with two substituents already present, the stronger director controls.

> **Worked example:** Nitration of benzoic acid (–COOH, deactivating meta director) → meta-nitrobenzoic acid as major product.

14.7 Pharmacy relevance

Drug molecules often carry several ring substituents (e.g., paracetamol has –OH and –$NHCOCH_3$). Predicting where the next substitution goes is exactly the skill used in designing drug syntheses and in understanding drug metabolism (the body often hydroxylates aromatic rings at activated positions).

14.8 India context

The manufacture of dyes, sulfa drugs, and many generics in India depends on getting substitution at the right ring position — a wrong isomer can be inactive or toxic. Orientation rules are therefore not just exam theory; they are quality-control logic on the plant.

14.9 Common confusions

1. **"Deactivating means no reaction":** No — it means SLOWER than benzene. Nitrobenzene can still be nitrated, just under vigorous conditions.
2. **Halogens:** The single biggest confusion — deactivating (rate) but o/p directing (position). Learn it as the exception.
3. **–NHCOR vs –NH_2:** Both o/p directors, but –NHCOR (acetamido) is less activating because the carbonyl pulls the lone pair away.
4. **Alkyl groups are weak activators:** –CH_3 directs o/p but only mildly — do not expect tribromination like phenol.

14.10 Common mistakes

1. Calling –NO_2 an o/p director.
2. Forgetting that a second substitution on toluene still follows o/p direction from the methyl group.
3. Mixing up "activating" (speed) with "directing" (position) — they usually go together, but halogens split them.
4. In di-substituted rings, ignoring which of the two groups is the stronger director.

14.11 Mnemonics

- **"DONORS DO o/p, WITHDRAWERS WANT meta":** donors = activating o/p; withdrawers = deactivating meta.
- **"Halogens Have it Half":** halogens are HALF-exceptional — deactivating rate, o/p direction.

14.12 One-minute revision

- Activating = faster than benzene; deactivating = slower.
- Activating groups are o/p directors (–OH, –NH_2, –OR, –NHCOR, –CH_3).
- Deactivating groups are meta directors (–NO_2, –CHO, –COR, –COOH, –CN, –SO_3H).
- Halogens: deactivating BUT o/p directing (the exception).
- Donation by lone-pair resonance → o/p; withdrawal → meta.
- Phenol + Br_2 water → 2,4,6-tribromophenol (white ppt) — instant test.
- Nitrobenzene nitration → meta-dinitrobenzene.
- Para usually beats ortho (less crowding); stronger director wins in di-substituted rings.

14.13 Practice questions

MCQs

1. Which group is a meta director?

a) –OH b) $–NH_2$ c) $–NO_2$ d) $–CH_3$

1. Chlorine on a benzene ring is:

a) activating, o/p director b) deactivating, o/p director c) deactivating, meta director d) activating, meta director

1. Nitration of toluene gives mainly:

a) meta-nitrotoluene b) ortho- and para-nitrotoluene c) 2,4,6-trinitrotoluene (mild conditions) d) no reaction

1. Which is the strongest activating group?

a) $–CH_3$ b) –Cl c) $–NH_2$ d) –COOH

1. Phenol with bromine water gives:

a) monobromophenol b) 2,4,6-tribromophenol c) meta-bromophenol d) no reaction

Short-answer

1. State the master rule linking activation and direction, and name the exception.
2. Why is $–NO_2$ a meta director? Explain using the arenium ion.
3. Why are halogens deactivating yet ortho/para directing?

Long-answer

1. Classify the following substituents as activating/deactivating and o/p-/meta-directing, with reasons: –OH, $–OCH_3$, $–CH_3$, –Cl, $–NO_2$, –COOH, $–NH_2$.
2. Explain how the stability of the arenium ion intermediate decides orientation in EAS. Illustrate with a donor group and a withdrawer group.

Mechanism-writing

1. Describe in words the three resonance forms of the arenium ion formed by ortho attack on phenol, and explain why one of them is especially stable.

Application-based

1. Predict the major product of the nitration of (i) anisole ($C_6H_5–OCH_3$) and (ii) benzoic acid, giving reasons.

Viva

1. What is the difference between an activating group and an ortho/para director?
2. Give two examples each of activating and deactivating groups.

Answer key (MCQs): 1-c, 2-b, 3-b, 4-c, 5-b.

References

- Morrison, R.T., Boyd, R.N. and Bhattacharjee, S.K., *Organic Chemistry* (Pearson Education India).
- Finar, I.L., *Organic Chemistry*, Vol. I (Pearson).
- Bahl, B.S. and Bahl, A., *Textbook of Organic Chemistry* (S. Chand).