Chemistry of Benzene: Electrophilic Aromatic Substitution

Part B

B. Pharm. Semester-1
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Learning Outcomes

- **At the end of this lesson students will be able to**
  - **Substituent Effects in Substituted Aromatic Ring**
  - **Activating Group and examples**
  - **Deactivating Group and examples**
  - **Ortho/Para-Directing Activators**
  - **Meta-Directing Deactivators**
  - **Ortho, Para-Directing Deactivators: Halogens**
  - **Inductive Effect (Electron-withdrawing)**
  - **Resonance Effect (Electron-donating)**
  - **Case study**
  - **Electrophilic aromatic substitutions on disubstituted benzene**

Objective

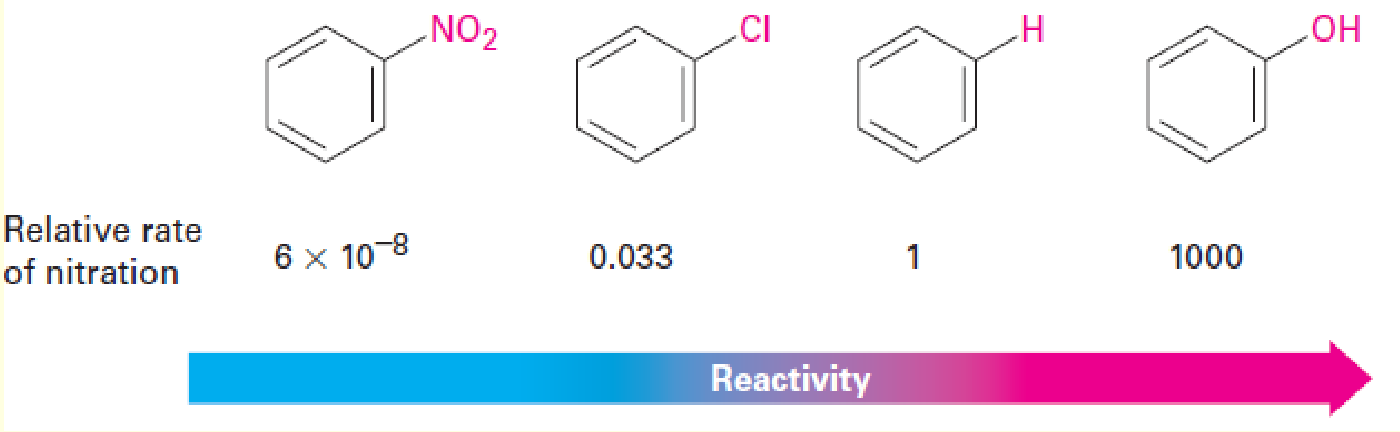
The objective of this course is to give to the students of pharmacy the basic knowledge about the organic chemistry.

Substituent Effects in Substituted Aromatic Ring

Substituents affect **the reactivity** of the aromatic ring and the **orientation** of the reaction.

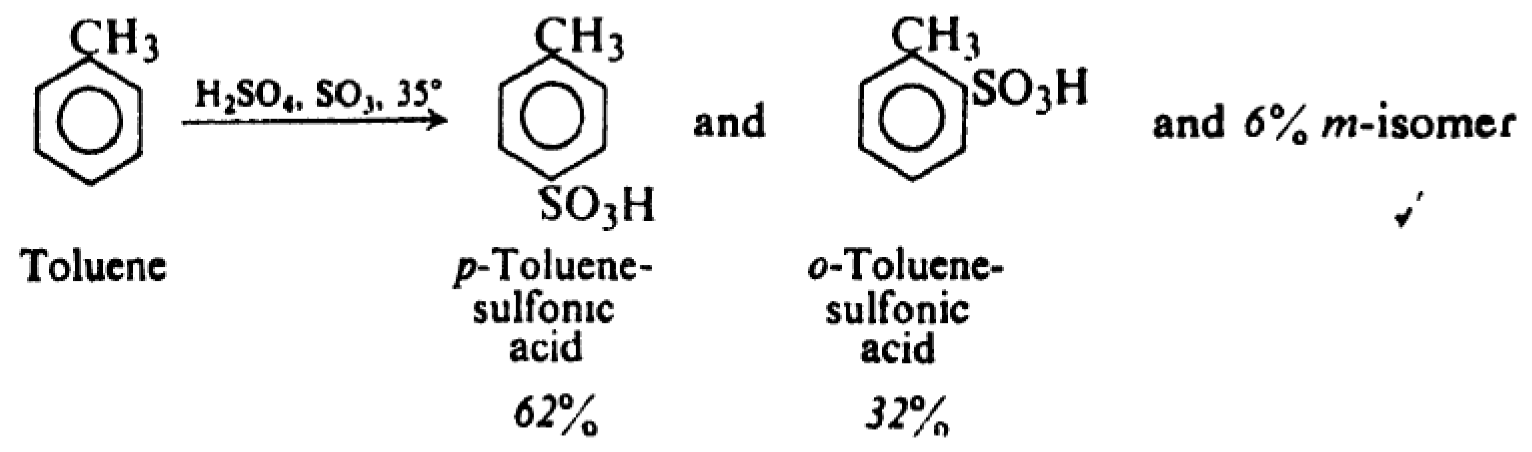
Some substituents **activate** the ring, making it more reactive than benzene, and some **deactivate the ring**, making it less reactive than benzene.

Example: Effect on reactivity



Substituent Effects in Substituted Aromatic Ring

- ✓ Like Benzene, Toluene undergoes Electrophilic aromatic substitution like sulfonation reaction.
- ✓ 3 Sulfonated products (ortho, meta and para sulfonated) are possible, but only two (ortho and para sulfonated compounds are formed in different ratio).



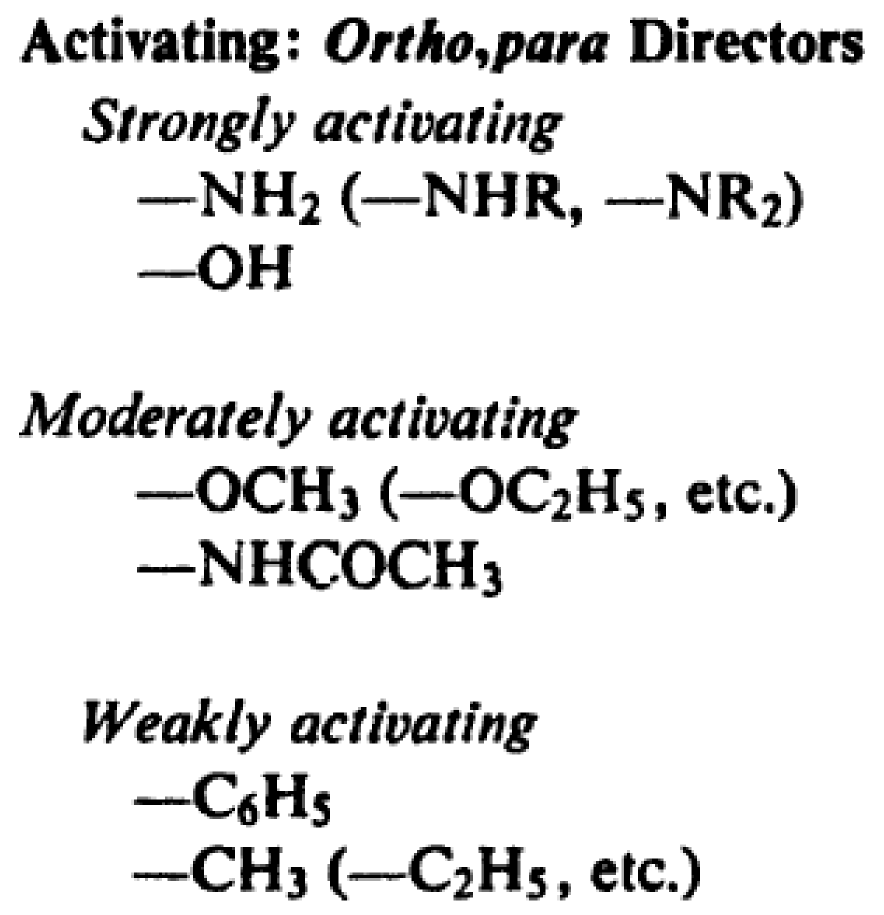
Substituent Effects in Substituted Aromatic Ring: Activating Group (Category-1)

- ✓ Any group attached with benzene ring affects the Electrophilic aromatic substitution reaction and determines the orientation of the substitution.
- ✓ **Activating Groups**: A group that make **the ring more reactive** than benzene, that influences the **incoming electrophile to attach -ortho and -para positions** only, so they are called as **-ortho, -para directors.**

  They are 3 types: Strongly activating group
  Moderately activating group
  Weakly activating group

Activating Groups: Examples

The electron releasing groups are mostly activating groups that stabilize the carbocation intermediate.



Activating: *Ortho,para* Directors

Strongly activating

$-NH_2$ ($-NHR$, $-NR_2$)

$-OH$

Moderately activating

$-OCH_3$ ($-OC_2H_5$, etc.)

$-NHCOCH_3$

Weakly activating

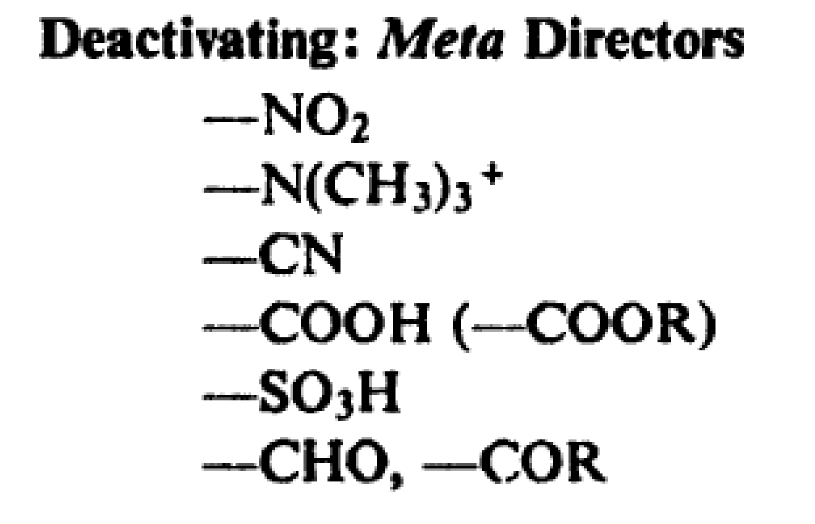
$-C_6H_5$

$-CH_3$ ($-C_2H_5$, etc.)

Substituent Effects in Substituted Aromatic Ring: Deactivating Group (Category-2)

Deactivating Groups: A group that make **the ring less reactive** than benzene, that influences the **incoming electrophile to attach –meta position only,** so they are called as **-meta directors.**

They are mostly electron -withdrawing groups, that destabilize the carbocation intermediate.



Deactivating: *Meta* Directors

—NO_2

—$N(CH_3)_3^+$

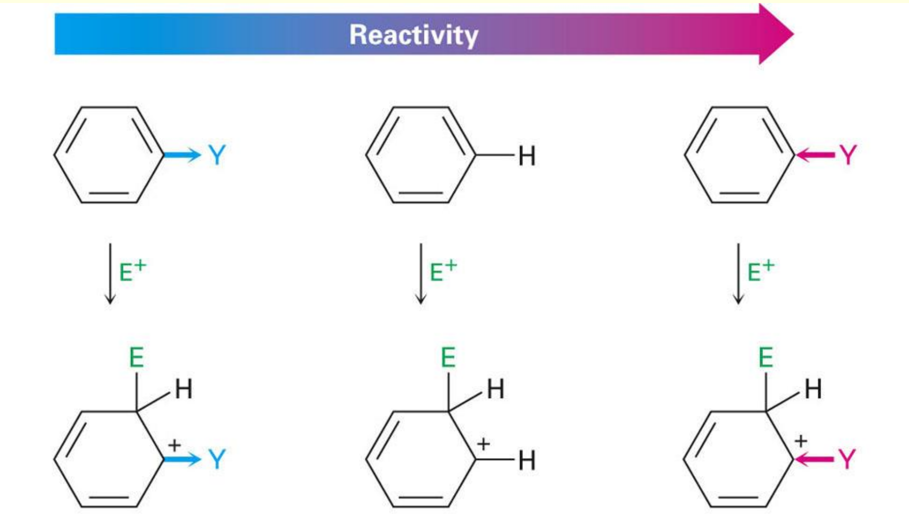
—CN

—COOH (—COOR)

—SO_3H

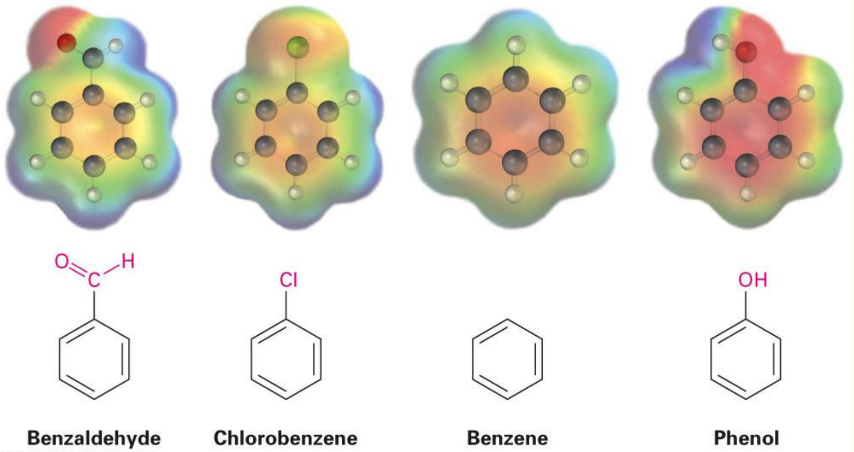
—CHO, —COR

Substituent Effects in Substituted Aromatic Ring: Explanation



Y withdraws electrons; carbocation intermediate is less stable, and ring is less reactive.

Y donates electrons; carbocation intermediate is more stable, and ring is more reactive.



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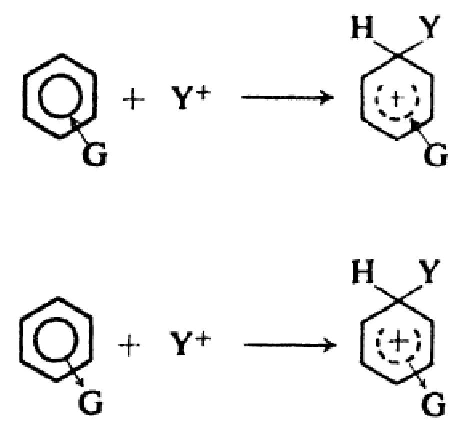
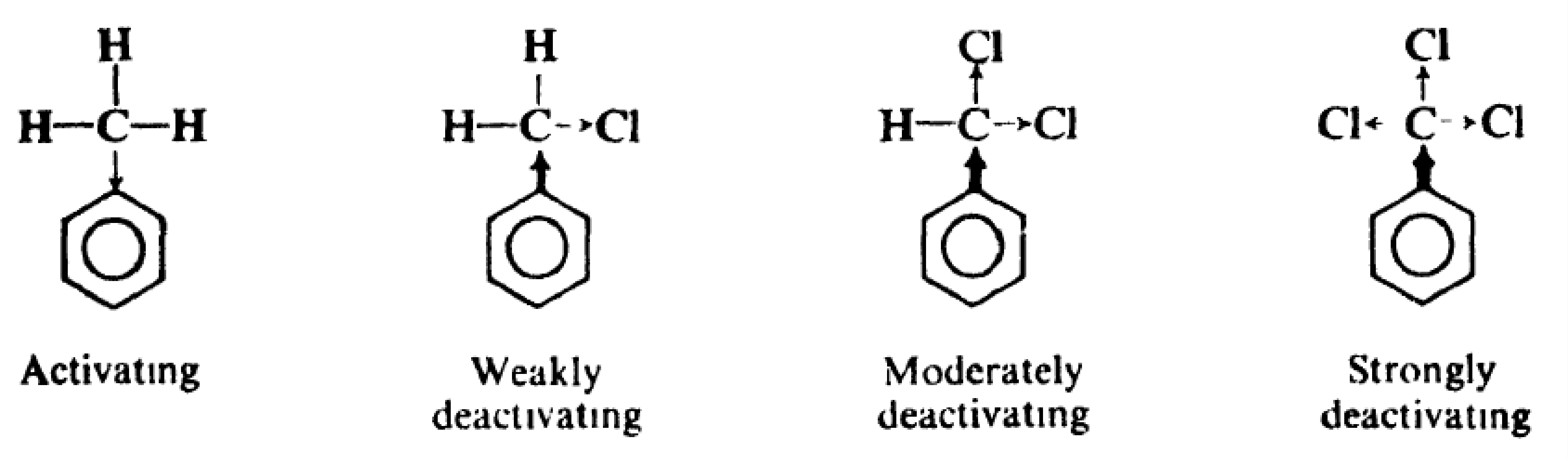


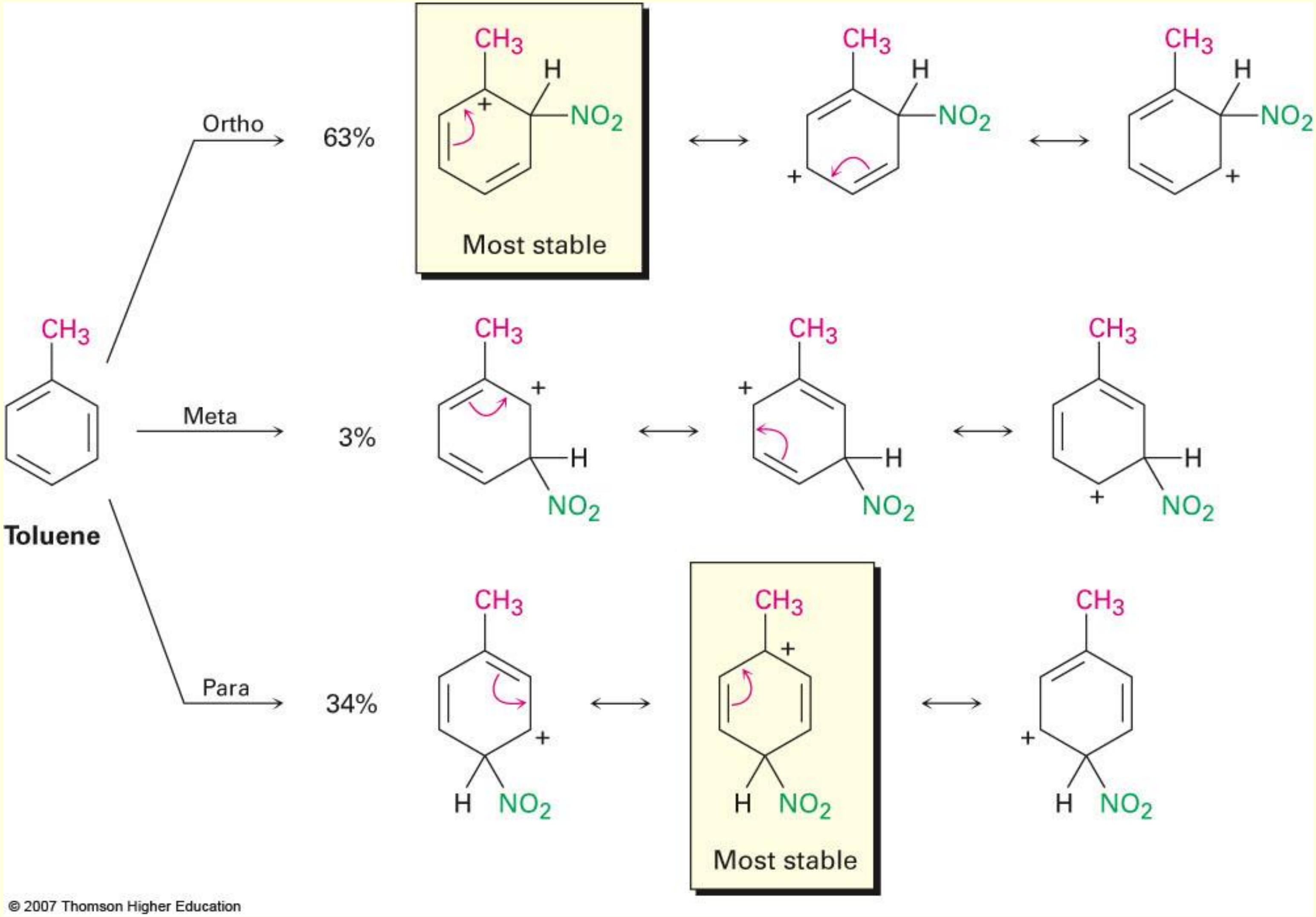
Substituent Effects in Substituted Aromatic Ring: Deactivating Halogens (Category-3)

Halogens (-F, Cl, Br, I) are **Deactivating Groups,** but they influences the **incoming electrophile to attach –ortho and –para positions.**

They have electron-withdrawing properties.



Ortho/Para-Directing Activators: Alkyl Groups: Nitration of Toluene (**Example-1**)



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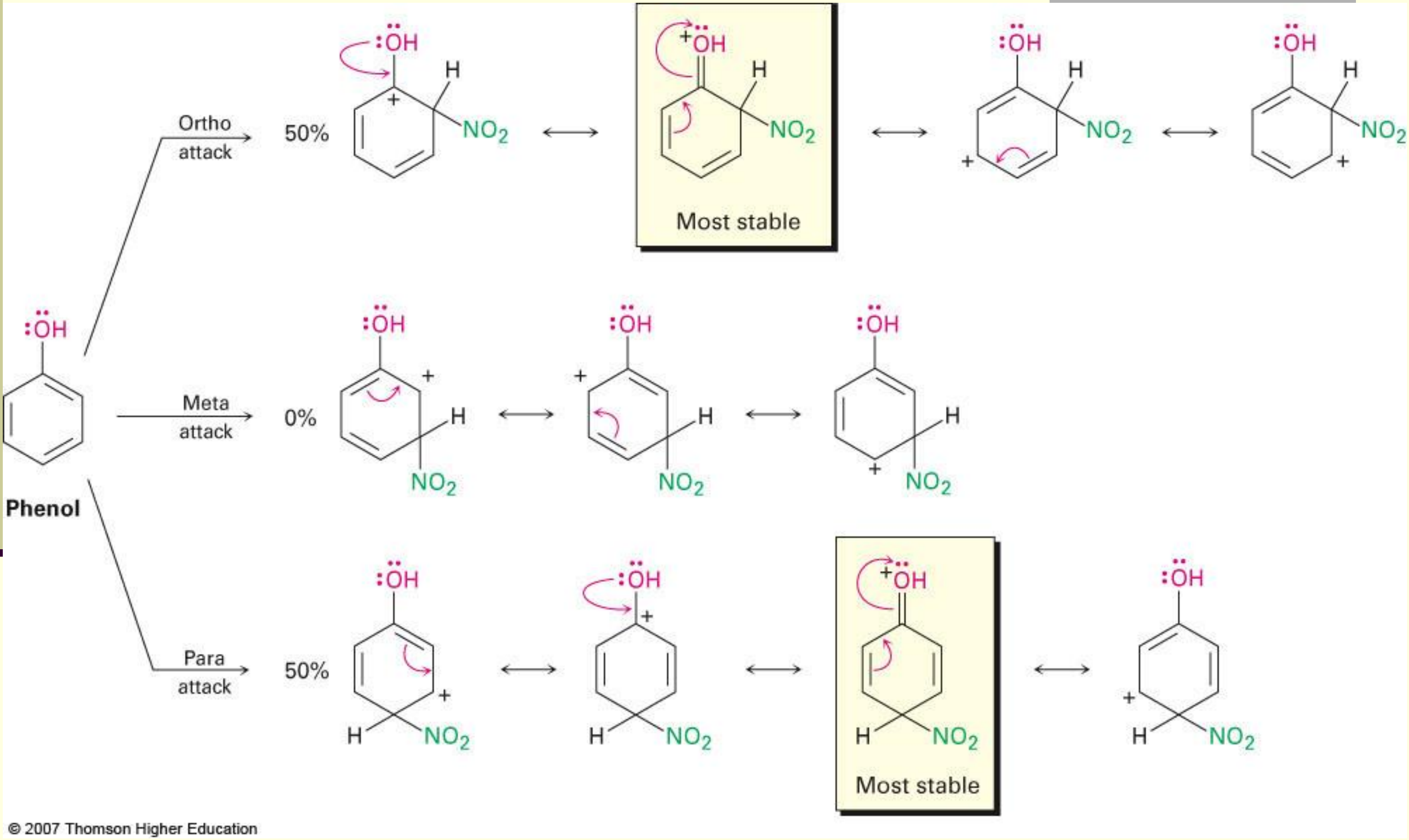
Ortho/Para-Directing Activators: -OH: Nitration of Phenol (**Example-2**)



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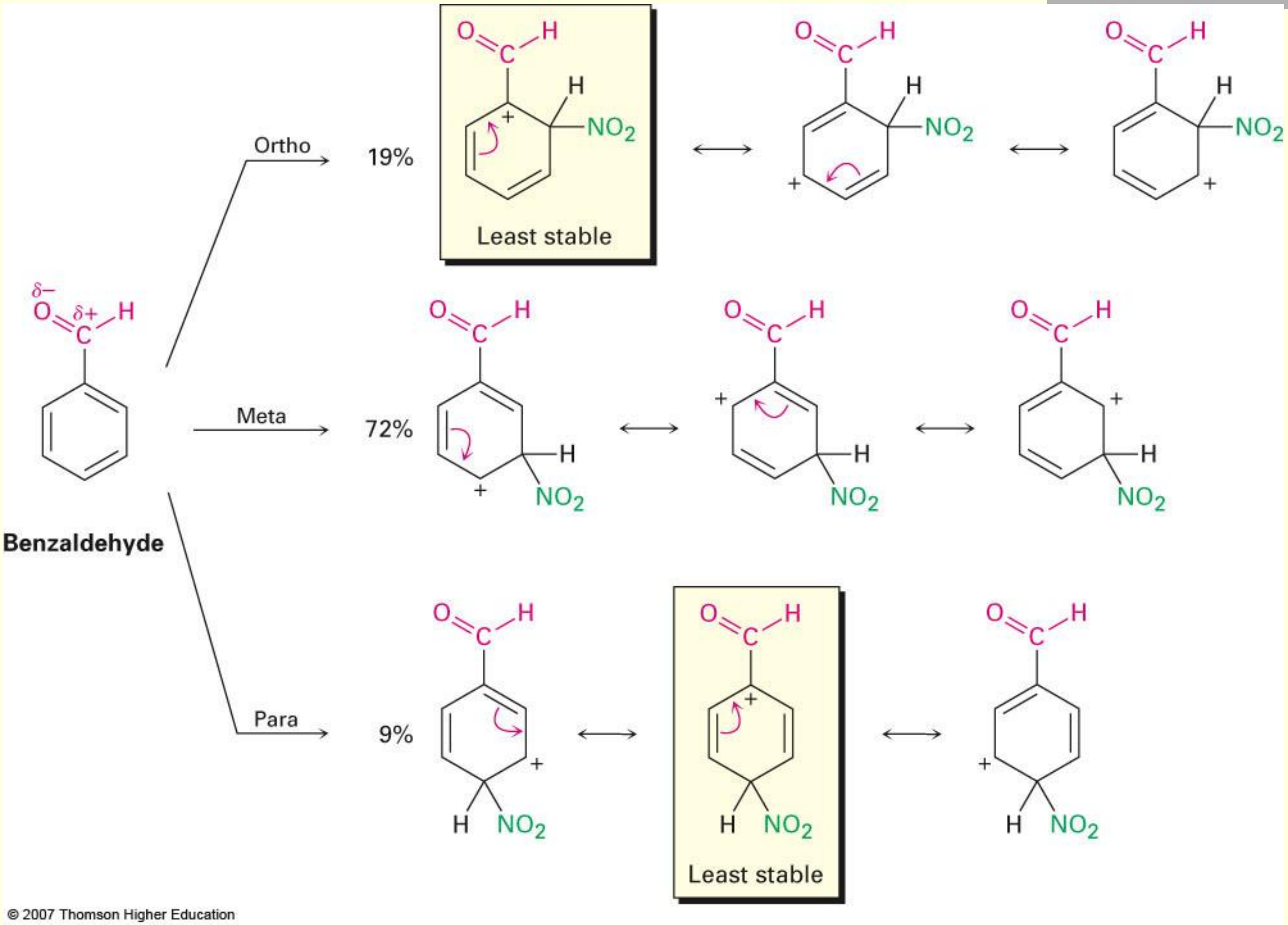
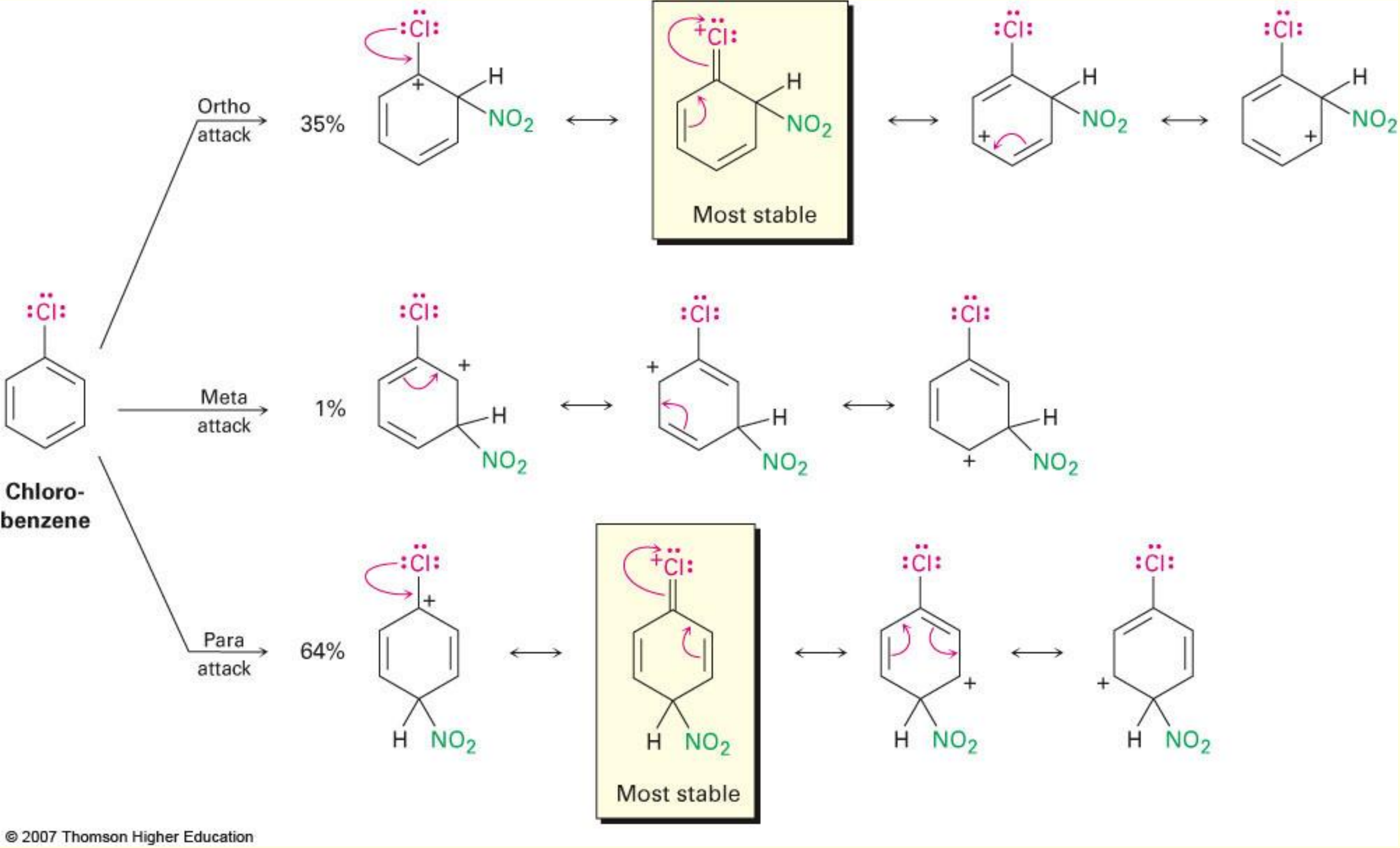
Meta-Directing Deactivators: -CHO: Nitration of Benzaldehyde



Ortho, Para-Directing Deactivators: Halogens: Nitration of Chlorobenzene



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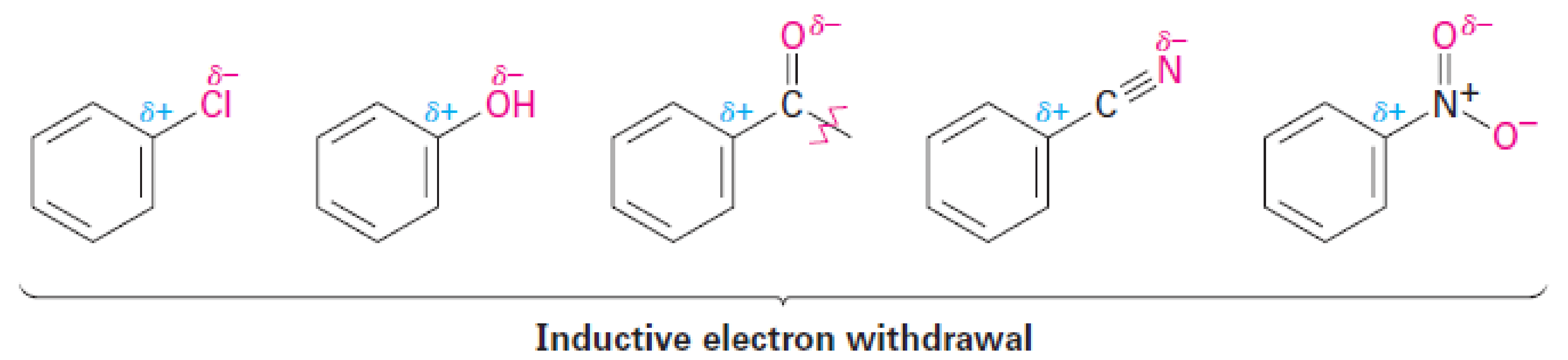
Effect of Halogen on Electrophilic Aromatic Substitution Reactions

Halogens (-F, Cl, Br, I) are **Deactivating Groups,** but **ortho** and **para positions directors.**
The deactivation is the characteristic property of electron-withdrawing process, but ortho, para orientation is the characteristic property of electron-releasing process.

Do Halogens (-F, Cl, Br, I) withdraw electrons and release electrons?
Answer: YES, Halogens have **dual** properties.
Halogens (-F, Cl, Br, I) withdraw electrons through their Inductive effect.
Halogens (-F, Cl, Br, I) release electrons through their Resonance effect.

Inductive Effect (Electron-withdrawing)

- Inductive effect is controlled by electronegativity and the polarity of bonds in functional groups
- Halogens, C=O, CN, and NO_2 *withdraw* electrons through σ bond connected to ring.
- Withdrawal electrons ***through a σ bond.***
- Electron-withdrawing inductive effect of halogens is because of the electronegativity of halogens.

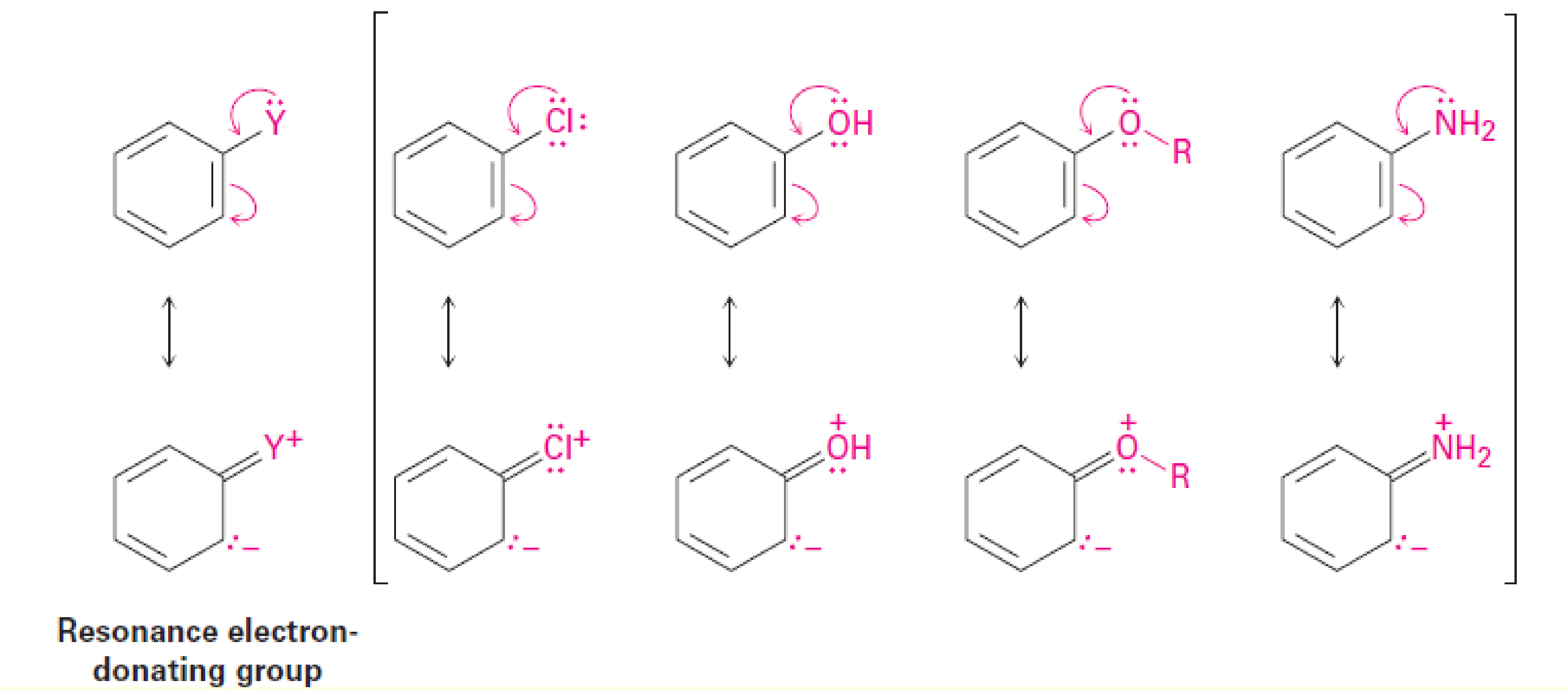


Resonance Effect (Electron-donating)

- C=O, CN, NO_2 substituents withdraw electrons from the aromatic ring by resonance.
- π-electrons flow from the rings to the substituents, leaving ring system a positive charge.
- Resonance effect happens through π–bond due to the overlap of a p orbital on the substituent with a p orbital on the aromatic ring.
- The electron donating resonance effect of halogen is mainly because of the availability of lone pair of electrons on halogens.

Resonance Effect (Electron-donating)

- Halogens, hydroxyl, alkoxyl, and amino substituents donate electrons to the aromatic ring by resonance.
- Effect is greatest at ortho and para positions.



Summary Table: Effect of Substituents

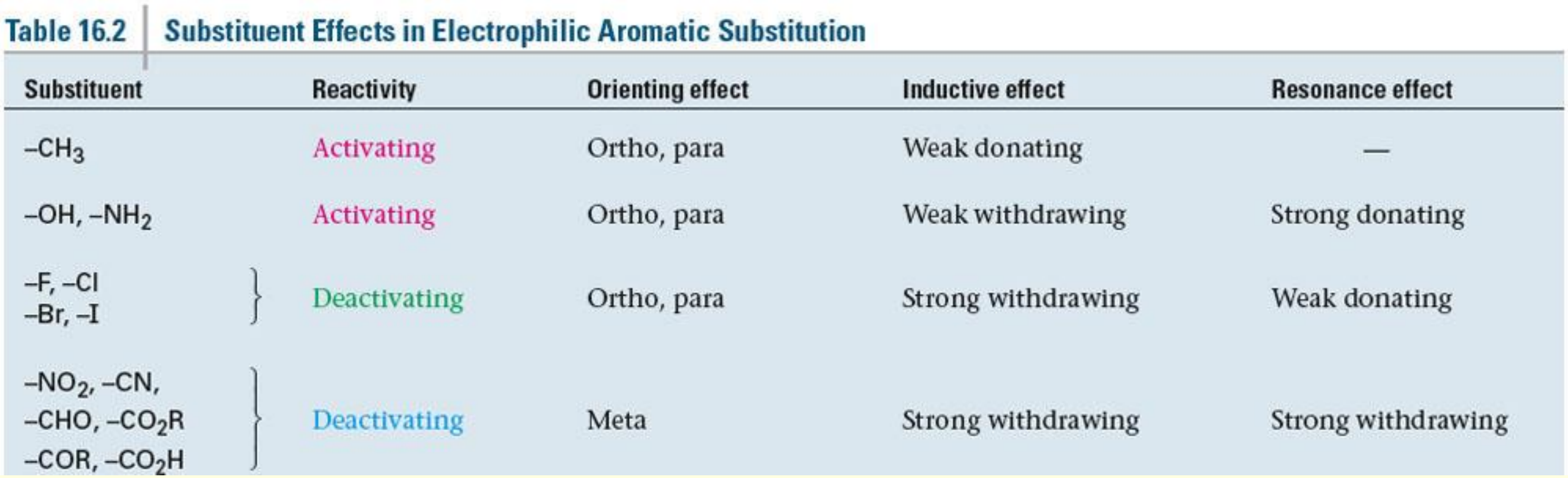
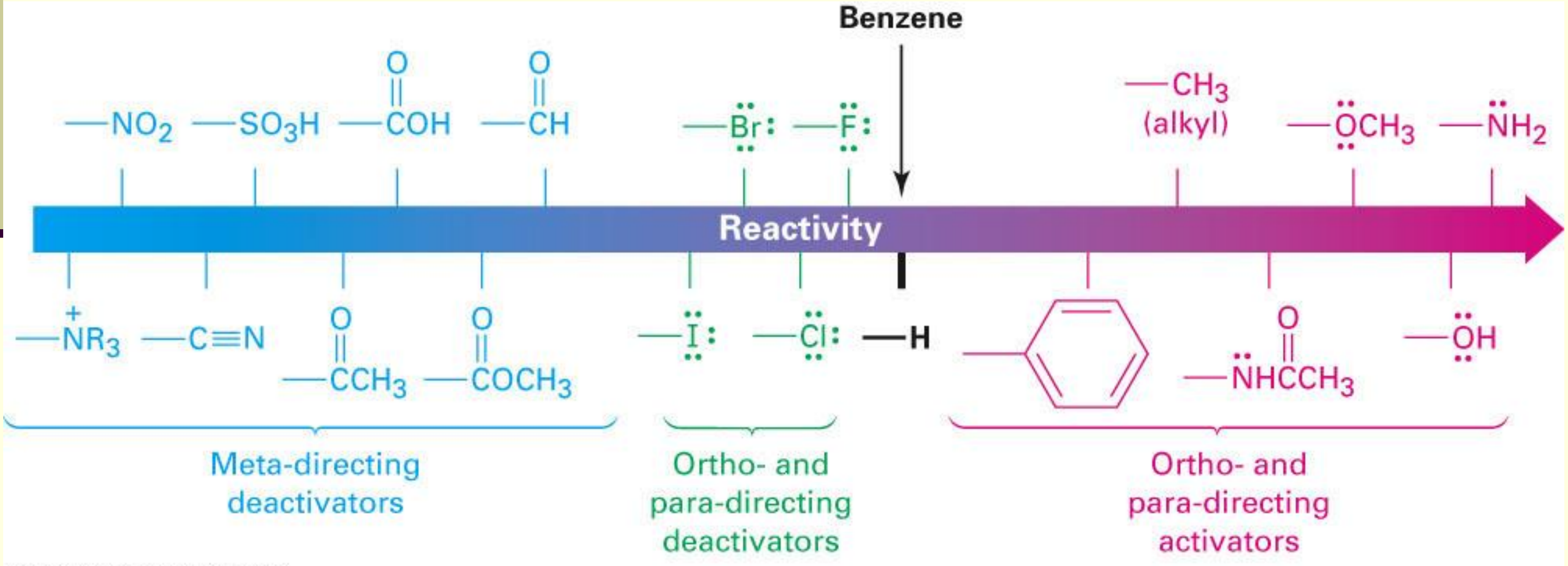
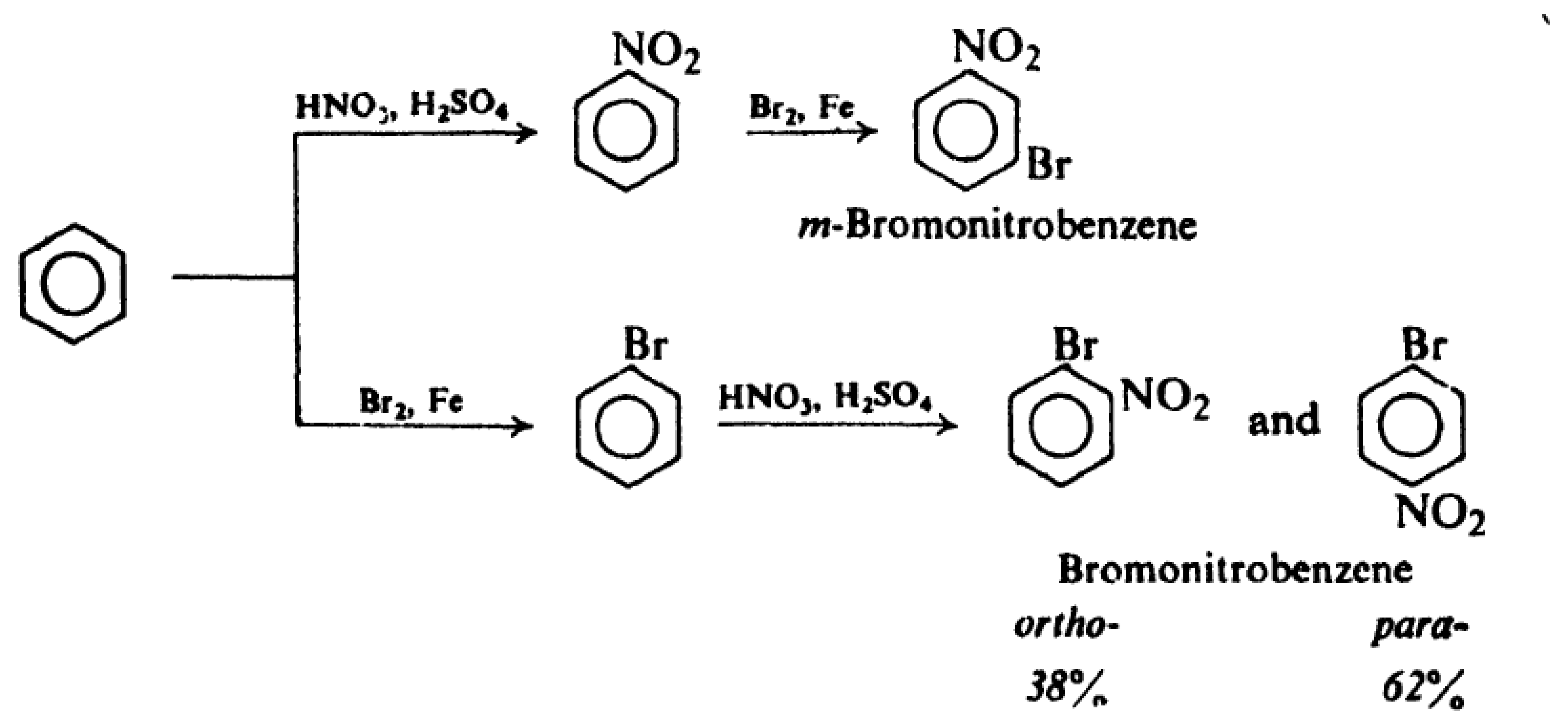


Table 16.2 **Substituent Effects in Electrophilic Aromatic Substitution**

Substituent	Reactivity	Orienting effect	Inductive effect	Resonance effect
$-CH_3$	Activating	Ortho, para	Weak donating	—
$-OH$, $-NH_2$	Activating	Ortho, para	Weak withdrawing	Strong donating
$-F$, $-Cl$ $-Br$, $-I$	Deactivating	Ortho, para	Strong withdrawing	Weak donating
$-NO_2$, $-CN$, $-CHO$, $-CO_2R$ $-COR$, $-CO_2H$	Deactivating	Meta	Strong withdrawing	Strong withdrawing



Case study: Electrophilic Aromatic Substitution Reactions



Electrophilic Aromatic Substitution Reactions of a disubstituted benzene

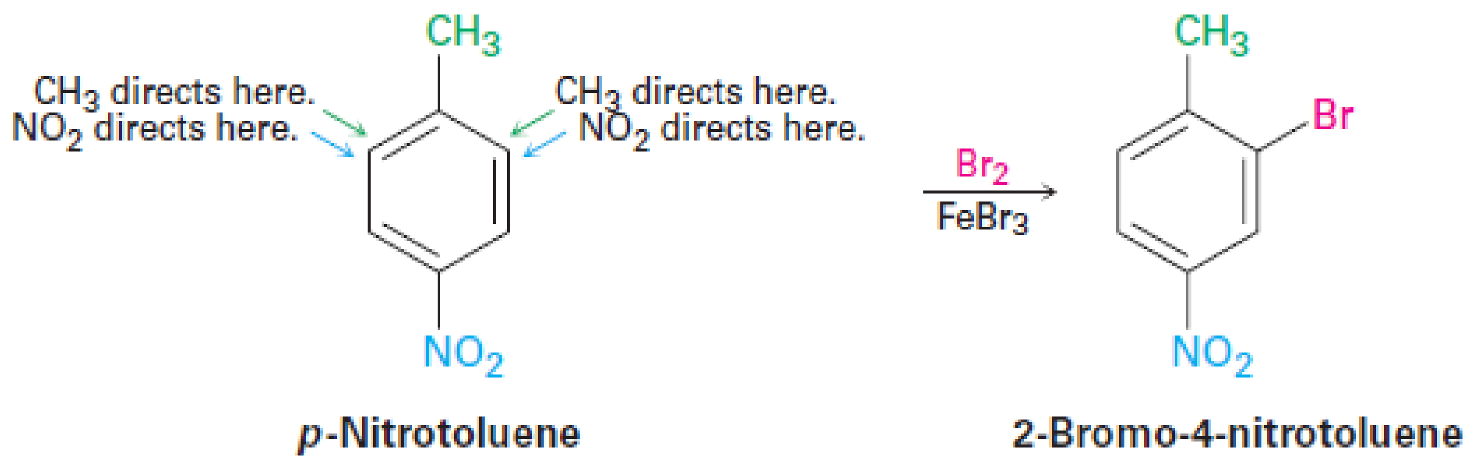
Electrophilic substitution of a disubstituted benzene ring to give tri-substituted benzene ring is governed by the same resonance and inductive effects that affect monosubstituted rings.

The only difference is that it’s necessary to consider the additive effects of two different groups.

Three rules are applicable in this type of reaction

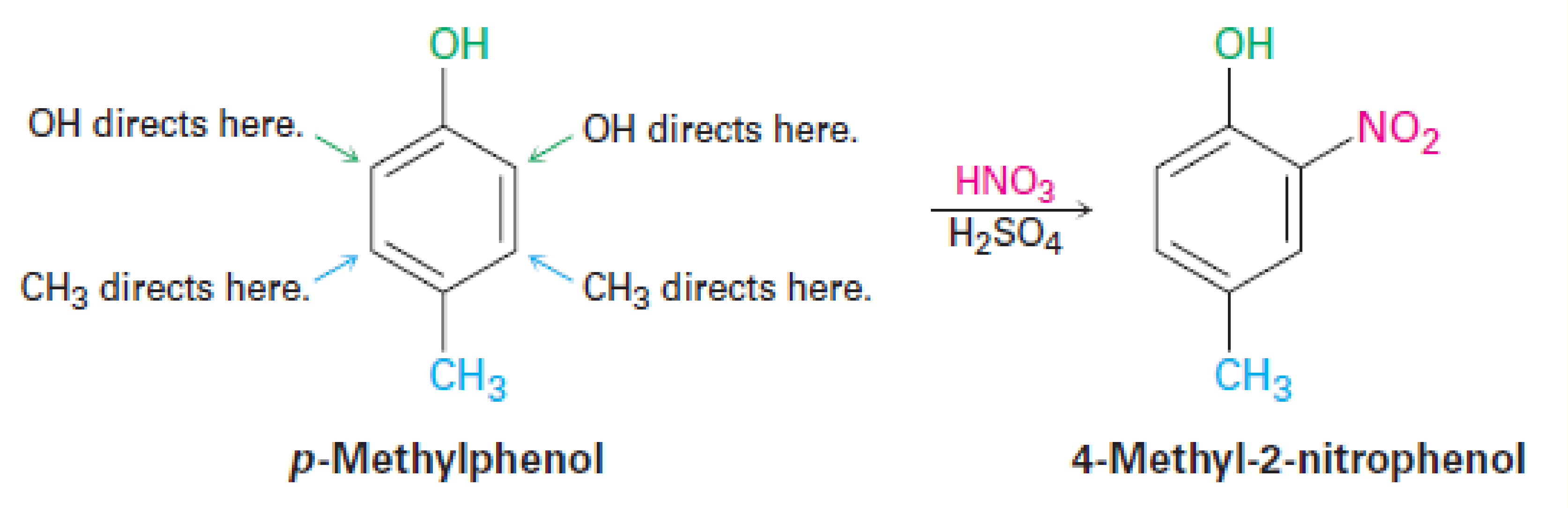
Rule-1 for the reactions of a disubstituted benzene

- If the directing effects of the two groups reinforce each other, the situation is straightforward.
- In *p*-nitrotoluene, for example, both the methyl and the nitro group direct further substitution to the same position (ortho to the **methyl,** 5-**meta** to the nitro).
- A single product is thus formed.



Rule-2 for the reactions of a disubstituted benzene

- If the directing effects of the two groups oppose each other, the more **powerful activating group** has the dominant influence, but mixtures of products are formed.
- For example, bromination of *p*-methylphenol gives 2-bromo-4-methylphenol because -OH is a more powerful activator than -CH_3.

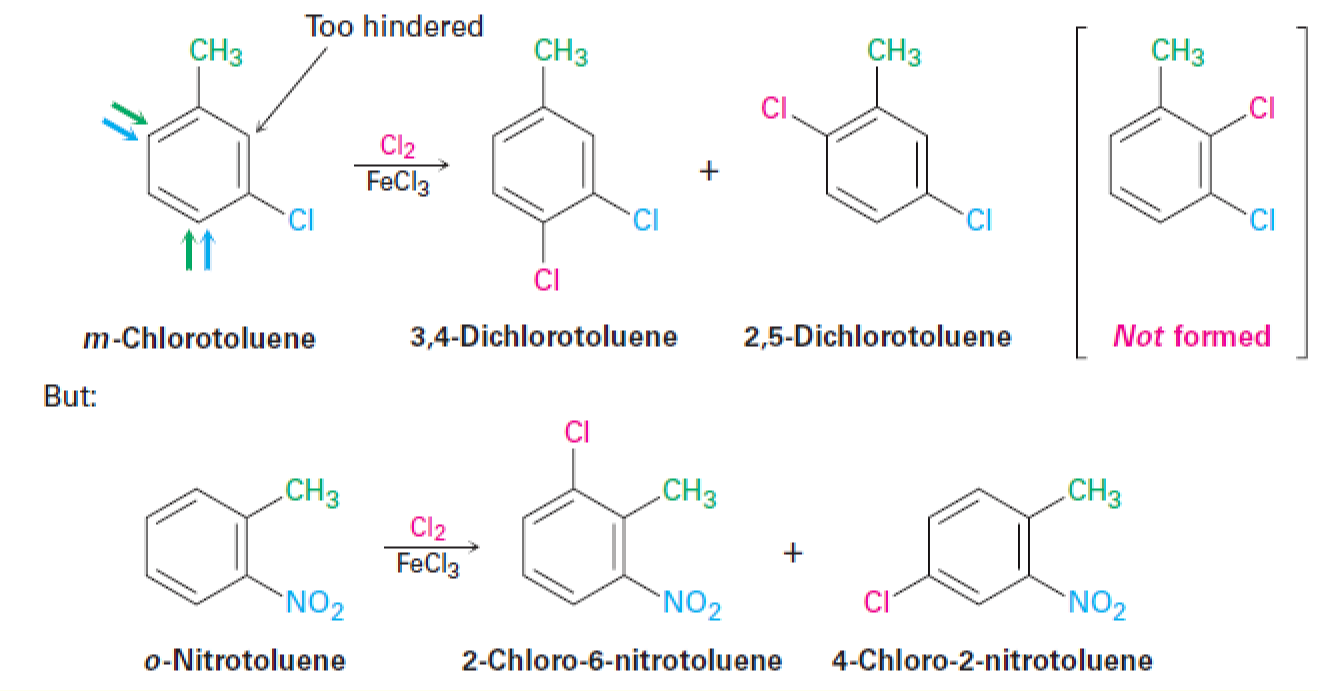


p-Methylphenol

4-Methyl-2-nitrophenol

Rule-3 for the reactions of meta-disubstituted benzene

- The substitution rarely occurs between the two groups in meta-disubstituted compound because this site is too hindered.
- So, alternate route is followed to get the product: substitution of an ortho-disubstituted compound



m-Chlorotoluene → 3,4-Dichlorotoluene + 2,5-Dichlorotoluene [Not formed]

o-Nitrotoluene → 2-Chloro-6-nitrotoluene + 4-Chloro-2-nitrotoluene

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3. **Textbook of Organic Chemistry, 22nd Edition, 2022, Authors: Arun Bahl & B S Bahl, Publisher: S Chand, ISBN: 978-9352531967.**

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