**Electrophilic Aromatic Substitution**  
Part 1

**Generic reaction:**

![Chemical structure](image)

Optional reading: OCATSA  Email instructor for access

---

**Introduction**

*Fact:* Alkenes undergo *electrophilic addition*  
•Addition reaction: Increases the number of groups attached to the substrate at the expense of a pi bond

Nucleophile (pi bond)

Electrophile (induced dipole)

How is the Br-Br dipole induced?

\[ \Delta EN = 0 \]  
No bond dipole  
Weak C=C/Br-Br repulsion  
Weak Br-Br polarization  
Strong Br-Br polarization
Addition to Benzene Pi Bonds?

**Question:** Benzene has pi bonds...also adds Br₂?

Why NR? What is special about benzene?

Is benzene a nucleophile?  Benzene has pi electrons → **Benzene is a nucleophile**

Is ΔG‡ too large? Benzene + Br₂ gives carbocation with resonance → ΔG‡ probably ok

So What It Up With Benzene?

**How else is benzene different from an alkene?**

• Aromaticity - worth 36 kcal mol⁻¹ of stabilization
• Loss of aromaticity = large increase in ΔG‡ = mechanism step too expensive

How to solve this problem?
• Make Br₂ more electrophilic

Electrophile = e⁻ deficient
Therefore take e⁻ away from Br

Lewis acid

More electrophilic than Br₂ alone
Reaction and Mechanism

Mechanism?

Capture a nucleophile:

Be deprotonated; form pi bond:
• Weak base adequate

Rearrangement: Does not change overall reaction product

Which carbocation fate is favored?
Reaction Name and Kinetics

Overall reaction

\[
\text{Benzene} \quad \text{Br}_2 \quad \text{FeBr}_3 \quad \rightarrow \quad \text{Bromotoluene} + \text{Br}^- + \text{FeBr}_3
\]

Electrophilic aromatic substitution (EAS)

Mechanism

- Carbocation formed
- Aromaticity lost
- Carbocation quenched
- Aromaticity restored

Reaction rate depends on:
- Nucleophilicity of benzene ring
- Arenium ion stability
- Strength of electrophile

Kinetics: Which step is rds?
- Carbocation formed
- Aromaticity lost
- Carbocation quenched
- Aromaticity restored

What If Benzene Ring Has Substituent(s)?

Benzene

\[
\text{Benzene} \quad \text{Br}_2 \quad \text{FeBr}_3 \quad \rightarrow \quad \text{Bromotoluene}
\]

Only one product possible

Toluene

\[
\text{Toluene} \quad \text{Br}_2 \quad \text{FeBr}_3 \quad \rightarrow \quad \text{2-Bromotoluene} + \text{3-Bromotoluene} + \text{4-Bromotoluene}
\]

Ortho-bromotoluene
Meta-bromotoluene
Para-bromotoluene
Which Product is Major?

Number of positions (probability)

Steric hindrance to electrophilic attack

- Ortho attack (between CH₃ and H) 
  More hindered
- Meta attack (between CH₃ and H) 
  More hindered
- Para attack (between H and H) 
  Less hindered

Product ratio conclusion:

---

Which Product is Major?

Arenium ion stability

- Ortho attack:
- Meta attack:
- Para attack:

Product ratio conclusion:
Which Product is Major?

Summary
- Number of positions: Ortho, meta > para
- Steric effects: Meta, para > ortho
- Arenium ion stability: Ortho, para > meta

Which factor dominates? Ask Mother Nature...

Conclusion: Arenium ion stability

Directing Effects

CH$_3$ is an ortho/para director
- Why? Arenium ion stability
  CH$_3$ stabilizes adjacent carbocation by electron-donating inductive effect

Extension: Any carbocation stabilizing group = ortho/para director

Ortho/para directors
- Alkyl groups (-CH$_3$, -CH$_2$CH$_3$, etc.)
- Pi bonds: Alkene, alkyne, aromatic rings
- Lone pairs (-X) -OH, -OR
  -NH$_2$, -NHR, -NR$_2$
  -F, -Cl, -Br, -I

Electron donation (resonance) outweighs electron withdrawing (induction)

In general... If it stabilizes a carbocation it is an ortho/para director.
Substituent Effects: Kinetics

Select the faster reaction:

- Rate-determining step: Electrophile + nucleophile $\rightarrow$ arenium ion
- Electrophile: Same in both cases
- Nucleophile: CH$_3$ is electron-donating group (EDG)
  H is neither EDG or EWG
- Arenium ion: CH$_3$ is electron-donating group
  H is neither EDG or EWG

Conclusion: Br$_2$/FeBr$_3$ reacts with toluene than with benzene.

Activating Effects

CH$_3$ is an EAS activator

Why? Relative to H...
• CH$_3$ enhances benzene ring nucleophilicity
• CH$_3$ increases arenium ion stability
• CH$_3$ is electron-donating group; stabilizes adjacent carbocation

Extension: Any carbocation-stabilizing group is an activator

EAS Activating Groups
• Alkyl groups (-CH$_3$, -CH$_2$CH$_3$, etc.)
• Pi bonds: Alkene, alkyne, aromatic rings
• Lone pairs (-X): -OH, -OR
  -NH$_2$, -NHR, -NR$_2$

Better electron donors = more powerful activators
Activating Effects: An Exception

Are all ortho/para directors also activators?
Yes, except F, Cl, Br, and I
Why? Balance of electron-donation versus electron-withdrawal
Does transition state look more like benzene ring or arenium ion?
Net effect: F, Cl, Br, I are ortho/para directors, but deactivators

Example:

\[
\begin{align*}
\text{Ph-OCH}_3 & \quad \text{Ph-Br} \\
\text{Ph-Br} & \quad \text{Ph-OCH}_3 \\
\text{Ph-F} & \quad \text{Ph-Br} \\
\text{Ph-Br} & \quad \text{Ph-F}
\end{align*}
\]

- OCH\(_3\) is ortho/para director
- OCH\(_3\) is activator
- Ph-OCH\(_3\) EAS faster than Ph-H EAS

- F is ortho/para director
- F is deactivator
- Ph-F is slower than Ph-H EAS

Substituent Effects: the Nitro Group (NO\(_2\))

Predict major product:

Nitro group structure?

\[
\begin{align*}
\text{Ph-NO}_2 & \quad \text{Ph-Br} \\
\text{Ph-Br} & \quad \text{Ph-NO}_2 \\
\text{Ph-N=O} & \quad \text{Ph-Br} \\
\text{Ph-Br} & \quad \text{Ph-N=O}
\end{align*}
\]
Electrophilic Aromatic Substitution
Part 2

---

Part 1 Summary

**Electrophilic aromatic substitution (EAS):** Electrophilic attack on aromatic ring leads to hydrogen atom replacement

**Example:**

```
\[ \text{ ortho } \quad \text{ meta } \quad \text{ para } \]
```

**Mechanism:**

```
\[ \text{ ortho } \quad \text{ meta } \quad \text{ para } \]
```

**Substituent effects:** CH₃ is an ortho/para director and activator
Substituent Effects: the Nitro Group (NO$_2$)

Predict major product:

Nitro group

Nitro group structure?

Substituent Effects: the Nitro Group (NO$_2$)

Arenium ion stability.

Ortho attack:

Meta attack:

Para attack:

Product ratio conclusion:
Directing Effects

NO₂ is an **meta director**

*Why? Arenium ion stability*

NO₂ destabilizes adjacent carbocation by electron-withdrawing inductive effect

**Extension:** Any carbocation destabilizing group = meta director

**Meta directors**

-NO₂
-⁻NH₃, -⁻NH₂R, -⁻NHR₂, -⁻NR₃
-C=O (ketone, aldehyde, ester, carboxylic acid, etc.)
-C=N
-CF₃
-SO₂H sulfonic acid

**Others...**

*In general: If it destabilizes a carbocation it is a meta director.*

---

Substituent Effects: Kinetics

Select the faster reaction:  

\[
\text{Br}_2/\text{FeBr}_3 \quad \text{or} \quad \text{Br}_2/\text{FeBr}_3
\]

• Rate-determining step: electrophile + nucleophile → arenium ion
• Electrophile: same in both cases

• Nucleophile: NO₂ is electron-withdrawing group (EWG)
  H is neither EDG or EWG

• Arenium ion: NO₂ is electron-withdrawing group
  H is neither EDG or EWG

**Conclusion:** Br₂/FeBr₃ reacts with nitrobenzene than with benzene.

-NO₂ is a **deactivator**
Other Electrophiles: Bromination

\[ \text{Ar-H} \rightarrow \text{Ar-Br} \]

Origin of electrophile:

\[ \begin{align*}
\text{Br} & \quad \text{Br} \quad \text{FeBr}_3 \quad \rightarrow \quad \text{Br}^+ \quad \text{FeBr}_3 \\
\text{Br} & \quad \text{Br} \quad \text{FeBr}_3 \quad \rightarrow \quad \text{Br}^+ \quad \text{FeBr}_4
\end{align*} \]

Example:

Write out the complete mechanism for yourself

Other Electrophiles: Chlorination

\[ \text{Ar-H} \rightarrow \text{Ar-Cl} \]

Origin of electrophile:

\[ \begin{align*}
\text{Cl} & \quad \text{Cl} \quad \text{AlCl}_3 \quad \rightarrow \quad \text{Cl}^+ \quad \text{AlCl}_3 \\
\text{Cl} & \quad \text{Cl} \quad \text{AlCl}_3 \quad \rightarrow \quad \text{Cl}^+ \quad \text{AlCl}_3
\end{align*} \]

Example:

Write out the complete mechanism for yourself
What is the Electrophile?

A useful pattern for remembering EAS reactions...

Bromination:

Chlorination:

General EAS:

Other Electrophiles: Nitration

\[ \text{Ar-H} \rightarrow \text{Ar-NO}_2 \]

Electrophile: \(^{\circ} \text{NO}_2 \)

Origin of electrophile:

Example:

Write out the complete mechanism for yourself
More on Directing Effects

Just Who Is In Charge Here?

Nitration of bromobenzene:

\[
\text{Bromination of nitrobenzene:} \quad \text{Br}_2 + \text{FeBr}_3 \rightarrow \text{Br} - \text{NO}_2
\]

Generic EAS reaction:

Other Electrophiles: Sulfonation

\[
\text{Ar-H} \rightarrow \text{Ar-SO}_2\text{H} \quad \text{(sulfonic acid)}
\]

Electrophile:

Origin of electrophile:

Example:

Write out the complete mechanism for yourself
Other Electrophiles: Friedel-Crafts Alkylation

\[ \text{Ar-H} \rightarrow \text{Ar-R} \quad (R = \text{alkyl group}) \]

**Electrophile:** \( R^+ \) (a carbocation)

**Origin of electrophile:**

\[ \text{R} \text{Cl} \rightarrow \text{R}^+ \text{Cl}^- \rightarrow \text{R}^+ \text{AlCl}_3 \]

*Elec when \( R^+ \) less stable*

*Elec when \( R^+ \) more stable*

*Carbocation rearrangements possible*

**Example:**

\[ \text{Example: } \]

Write out the complete mechanism for yourself

---

Other Electrophiles: Friedel-Crafts Acylation

(a ketone)

**Electrophile:** \( +C(CH_3)_3 \)

**Acylium ion**

**Origin of electrophile:**

\[ \text{Acid chloride} \rightarrow \rightarrow \text{Acylium ion} \]

**Example:**

\[ \text{Example: } \]

Write out the complete mechanism for yourself
Other Electrophiles: Azo Coupling

Electrophile: \( \text{Ar} \rightarrow \text{Ar} \hspace{1cm} \text{N} \rightarrow \text{N} \rightarrow \text{Ar} \)

Origin of electrophile: \( \text{Ar} \rightarrow \text{Ar} + \text{H} \rightarrow \text{H}_2 \hspace{1cm} \text{N} \rightarrow \text{N} \rightarrow \text{O} \rightarrow \text{O} \rightarrow \text{H}_2 \)

Example:

Write out the complete mechanism for yourself

EAS Application Example:
Synthesis of Allura Red AC

\( \text{Ar-N=N-Ar} \) suggests synthesis via azo coupling

• Allura Red AC (an azo dye)
• Color due to extensive conjugation
• Many dyes are azo compounds

Strawberry soda colored with Allura Red AC
Synthesis of Allura Red AC

Electrophile

Azo coupling (EAS)