Reactions of Benzene & Its Derivatives

Chapter 22

Reactions of Benzene

The most characteristic reaction of aromatic compounds is substitution at a ring carbon:

**Halogenation:**

\[
\text{H} + \text{Cl}_2 + \text{FeCl}_3 \rightarrow \text{Cl} + \text{HCl}
\]

Chlorobenzene

**Nitration:**

\[
\text{H} + \text{HNO}_3 + \text{H}_2 \text{SO}_4 \rightarrow \text{NO}_2 + \text{H}_2 \text{O}
\]

Nitrobenzene
Reactions of Benzene

**Sulfonation:**

\[
\text{C}_6\text{H}_5\text{H} + \text{SO}_3 + \text{H}_2\text{SO}_4 \rightarrow \text{C}_6\text{H}_5\text{SO}_3\text{H}
\]

Benzenesulfonic acid

**Alkylation:**

\[
\text{C}_6\text{H}_5\text{H} + \text{RX} \xrightarrow{\text{AlI}_3} \text{C}_6\text{H}_5\text{R} + \text{HX}
\]

An alkylbenzene

**Acylation:**

\[
\text{C}_6\text{H}_5\text{H} + \text{RCX} \xrightarrow{\text{AlI}_3} \text{C}_6\text{H}_5\text{OCR} + \text{HX}
\]

An acylbenzene

---

**Carbon-Carbon Bond Formations:**

1. **Arenes** to **Halogenated arenes**

\[
\text{C}_6\text{H}_6 + \text{X}_2 \xrightarrow{\text{FeX}_3} \text{C}_6\text{H}_5\text{X}
\]

2. **Arenes** to **Nitro arenes**

\[
\text{C}_6\text{H}_6 + \text{HNO}_3 + \text{H}_2\text{SO}_4 \rightarrow \text{C}_6\text{H}_5\text{NO}_2
\]

3. **Arenes** to **Arene Sulfonic Acids**

\[
\text{C}_6\text{H}_6 + \text{SO}_3 + \text{H}_2\text{SO}_4 \rightarrow \text{C}_6\text{H}_5\text{SO}_3\text{H}
\]

---

**Arenes** to **Alkylbenzenes**

\[
\text{C}_6\text{H}_6 + \text{RCl} \xrightarrow{\text{AlCl}_3} \text{C}_6\text{H}_5\text{RC}
\]

**Arenes** to **Acylbenzenes**

\[
\text{C}_6\text{H}_6 + \text{RC} = \text{Cl} \xrightarrow{\text{AlCl}_3} \text{C}_6\text{H}_5\text{RC} = \text{O}
\]
Electrophilic Aromatic Substitution

- Electrophilic aromatic substitution: a reaction in which a hydrogen atom of an aromatic ring is replaced by an electrophile

\[
\text{aryl} + \text{E}^+ \rightarrow \text{arylE} + \text{H}^+
\]

- In this section:
  - several common types of electrophiles
  - how each is generated
  - the mechanism by which each replaces hydrogen

EAS: General Mechanism

- A general mechanism

Step 1:

- Electrophile
- Slow, rate determining
- Resonance-stabilized cation intermediate

Step 2:

- Fast

Key question: What is the electrophile and how is it generated?
Chlorination

Step 1: formation of a chloronium ion

Step 2: attack of the chloronium ion on the ring

Resonance-stabilized cation intermediate; the positive charge is delocalized onto three atoms of the ring
Chlorination

Step 3: proton transfer regenerates the aromatic character of the ring

\[
\text{Cation intermediate} ightarrow \text{Chlorobenzene}
\]

Bromination

This is the general method for Substitution of halogen onto a benzene ring (CANNOT be halogenated by Free Radical Mechanism)
Bromination - Why not addn of Br₂?

Energy

Unfavored step: addition of Br⁻

Favored step: elimination of H⁺

Regains Aromatic Energy

[Diagram showing the reaction of benzene with Br₂]

Nitration

• Generation of the nitronium ion, NO₂⁺
  – Step 1: proton transfer to nitric acid

\[
\text{HSO}_3^- + \text{H}_2\text{O} + \text{HNO}_3 \rightarrow \text{HSO}_4^- + \text{H}_2\text{O}^\cdot \text{NO}_2^+.
\]

| Sulfuric acid | pKₐ = -3 |
| Nitric acid | pKₐ = -1.4 |

– Step 2: loss of H₂O gives the nitronium ion, a very strong electrophile

[Diagram showing the reaction of nitronium ion with a molecule]
Nitration

Step 1: attack of the nitronium ion (an electrophile) on the aromatic ring (a nucleophile)

\[
\ce{+ Nitronium Ion} + \ce{Aromatic Ring} \rightarrow \ce{Resonance-stabilized Cation Intermediate}
\]

Step 2: proton transfer regenerates the aromatic ring

Nitration

- A particular value of nitration is that the nitro group can be reduced to a 1° amino group

\[
\ce{4-Nitrobenzoic Acid} + 3 \ce{H_2} \xrightarrow{\text{Ni} (3 \text{ atm})} \ce{4-Aminobenzoic Acid} + 2 \ce{H_2O}
\]
Sulfonation

- Carried out using concentrated sulfuric acid containing dissolved sulfur trioxide

\[
\text{Benzene} + \text{SO}_3 \xrightarrow{\text{H}_2\text{SO}_4} \text{Benzenesulfonic acid}
\]

(SO\(_3\) in H\(_2\)SO\(_4\) is sometimes called “fuming” sulfuric acid.)

Friedel-Crafts Alkylation

- Friedel-Crafts alkylation forms a new C-C bond between an aromatic ring and an alkyl group

\[
\text{Benzene} + \text{Cl} \xrightarrow{\text{AlCl}_3} \text{Cumene} + \text{HCl}
\]

(Benzene, 2-Chloropropane (Isopropyl chloride), Cumene (Isopropylbenzene))

The electrophilic partner is a carbocation; it will arrange to the most stable ion: allylic>3\(^{\circ}\)>2\(^{\circ}\)>1\(^{\circ}\)
Friedel-Crafts Alkylation

Step 1: formation of an alkyl cation as an ion pair

\[
\begin{align*}
R-Cl^+ + AlCl_3 &\rightarrow R-Cl^- + AlCl_4^- \\
\text{A molecular complex} &\rightarrow \text{An ion pair containing a carbocation}
\end{align*}
\]

Step 2: attack of the alkyl cation on the aromatic ring

Step 3: proton transfer regenerates the aromatic ring

There are two major limitations on Friedel-Crafts alkylations:

1. carbocation rearrangements are common:

\[
\begin{align*}
\text{Benzene} + \text{Isobutyl chloride} \xrightarrow{\text{AlCl}_3} \text{tert-Butylbenzene} + \text{HCl}
\end{align*}
\]
2. F-C alkylation fails on benzene rings bearing one or more of these strongly electron-withdrawing groups.

When Y equals any of these groups, the benzene ring does not undergo Friedel-Crafts alkylation.
The “De-activation” of Aromatic Systems

If the FG is an $e^-$ withdrawing substituent, then the ring system becomes more electron poor and is said to be "deactivated" towards electrophilic aromatic substitution. EAS occurs at a slower rate.

Note: deactivation refers to the rate of EAS

Friedel-Crafts Acylation

• Friedel-Crafts acylation forms a new C-C bond between a benzene ring and an acyl group:

\[
\text{Benzene} + \text{CH}_3\text{C}l \xrightarrow{\text{AlCl}_3} \text{Acetophenone} + \text{HCl}
\]

\[
\text{4-Phenylbutanoyl chloride} \xrightarrow{\text{AlCl}_3} \alpha\text{-Tetralone} + \text{HCl}
\]
Friedel-Crafts Acylation

- The electrophile is an acylium ion

\[
\begin{align*}
\text{An acyl chloride} & \quad + \quad \text{Aluminum chloride} \\
\text{A molecular complex} & \quad \text{with a positive charge on chlorine}
\end{align*}
\]

\[
\begin{align*}
\text{A n ion pair} & \quad \text{containing an acylium ion}
\end{align*}
\]

Friedel-Crafts Acylation

- An acylium ion is a resonance hybrid of two major contributing structures

\[
\begin{align*}
\text{complete valence shells} & \quad \text{The more important contributing structure}
\end{align*}
\]

- F-C acylations are free of a major limitation of F-C alkylations; acylium ions do not rearrange.
Friedel-Crafts Acylation

A special value of F-C acylations is preparation of **unrearranged** alkylbenzenes:

\[
\text{C}_6\text{H}_5 + \text{CH}_3\text{COCl} \xrightarrow{\text{AlCl}_3} \text{C}_6\text{H}_5\text{CH}_3\text{COCl} \\
\text{2-Methylpropanoyl chloride}
\]

\[
\text{C}_6\text{H}_5\text{CH}_2\text{CO} + \text{N}_2\text{H}_4, \text{KOH} \xrightarrow{\text{diethylene glycol}} \text{C}_6\text{H}_5\text{CH}_3
\]

2-Methyl-1-phenyl-1-propanone

Isobutylbenzene

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Di- and Polysubstitution

Ortho & Para Substituted Products

Meta Substituted Products

Only a trace
Di- and Polysubstitution

Orientation on nitration of monosubstituted benzenes:

<table>
<thead>
<tr>
<th>Substituent</th>
<th>ortho</th>
<th>meta</th>
<th>para</th>
<th>ortho + para</th>
<th>meta</th>
</tr>
</thead>
<tbody>
<tr>
<td>—OCH₃</td>
<td>44</td>
<td>-</td>
<td>55</td>
<td>99</td>
<td>trace</td>
</tr>
<tr>
<td>—CH₃</td>
<td>58</td>
<td>4</td>
<td>38</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td>—Cl</td>
<td>70</td>
<td>-</td>
<td>30</td>
<td>100</td>
<td>trace</td>
</tr>
<tr>
<td>—Br</td>
<td>37</td>
<td>1</td>
<td>62</td>
<td>99</td>
<td>1</td>
</tr>
<tr>
<td>—COOH</td>
<td>18</td>
<td>80</td>
<td>2</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>—CN</td>
<td>19</td>
<td>80</td>
<td>1</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>—NO₂</td>
<td>6.4</td>
<td>93.2</td>
<td>0.3</td>
<td>6.7</td>
<td>93.2</td>
</tr>
</tbody>
</table>

• Orientation:
  – certain substituents direct preferentially to ortho & para positions; others to meta positions
  – substituents are classified as either ortho-para directing or meta directing toward further substitution
• Rate
  – certain substituents cause the rate of a second substitution to be greater than that for benzene itself; others cause the rate to be lower
  – substituents are classified as activating or deactivating toward further substitution

If the FG is an e⁻ donating substituent, then the ring system becomes more electron rich and is said to be "activated" towards electrophilic aromatic substitution. EAS is at a faster rate.

If the FG is an e⁻ withdrawing substituent, then the ring system becomes more electron poor and is said to be "deactivated" towards electrophilic aromatic substitution. EAS occurs at a slower rate.
Di- and Polysubstitution

- **-OCH$_3$** is ortho-para directing:

  ![Reaction Scheme]

  Anisole $\rightarrow$ o-Nitroanisole (44%) $+$ p-Nitroanisole (55%)

- **-CO$_2$H** is meta directing

  ![Reaction Scheme]

  Benzoic acid $\rightarrow$ o-Nitrobenzoic acid (18%) $+$ m-Nitrobenzoic acid (80%) $+$ p-Nitrobenzoic acid (2%)

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Di- and Polysubstitution

<table>
<thead>
<tr>
<th>Ortho-para Directing</th>
<th>Meta Directing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly activating</td>
<td>O</td>
</tr>
<tr>
<td>Moderately activating</td>
<td>-NHCR</td>
</tr>
<tr>
<td>Weakly activating</td>
<td>-R</td>
</tr>
<tr>
<td>Weakly deactivating</td>
<td>-F - Cl - Br</td>
</tr>
<tr>
<td></td>
<td>-OH - OR</td>
</tr>
<tr>
<td></td>
<td>-NH2 - NHR - NR$_2$</td>
</tr>
<tr>
<td></td>
<td>-OCR - OCAr</td>
</tr>
<tr>
<td></td>
<td>-COH - COR</td>
</tr>
<tr>
<td></td>
<td>-CO$_2$H</td>
</tr>
<tr>
<td></td>
<td>-C≡N</td>
</tr>
<tr>
<td></td>
<td>-NO$_2$</td>
</tr>
<tr>
<td></td>
<td>-NH$_3$ +</td>
</tr>
<tr>
<td></td>
<td>-CF$_3$</td>
</tr>
<tr>
<td></td>
<td>-CCl$_3$</td>
</tr>
</tbody>
</table>

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Di- and Polysubstitution

the order of steps is important:

![Chemical Reaction Diagram]

Theory of Directing Effects

- The rate of EAS is limited by the slowest step in the reaction
- For almost every EAS, the rate-determining step is attack of $E^+$ on the aromatic ring to give a resonance-stabilized cation intermediate
- The more stable this cation intermediate, the faster the rate-determining step and the faster the overall reaction
Theory of Directing Effects

- For ortho-para directors, ortho-para attack forms a more stable cation than meta attack
  - ortho-para products are formed faster than meta products
- For meta directors, meta attack forms a more stable cation than ortho-para attack
  - meta products are formed faster than ortho-para products

Theory of Directing Effects

Nitration of anisole

-OCH₃; examine the meta attack:
Nitration of anisole

-\textbf{OCH}_3\textbf{: examine the ortho-para attack:}

\begin{center}
\begin{align*}
\text{OCH}_3 + \text{NO}_2^+ \xrightarrow{\text{slow}} & \quad \text{OCH}_3 \\
\text{H} \quad \text{NO}_2 & \quad \text{H} \quad \text{NO}_2 & \quad \text{H} \quad \text{NO}_2 \\
(d) & \quad (e) & \quad (f) & \quad (g)
\end{align*}
\end{center}

This resonance structure accounts for the selectivity

---

Theory of Directing Effects

Nitration of benzoic acid

-\textbf{NO}_2\textbf{: examine the meta attack:}

\begin{center}
\begin{align*}
\text{COOH} + \text{NO}_2^+ \xrightarrow{\text{slow}} & \quad \text{COOH} \\
\text{H} \quad \text{NO}_2 & \quad \text{H} \quad \text{NO}_2 & \quad \text{H} \quad \text{NO}_2 \\
(a) & \quad (b) & \quad (c) & \quad \text{COOH}
\end{align*}
\end{center}
Nitration of benzoic acid

-NO₂: assume ortho-para attack:

\[
\text{COOH} + \text{NO}_2^+ \rightarrow \text{COOHNO}_2 + \text{H}^+
\]

The most disfavored contributing structure

This resonance structure accounts for the selectivity

Activating-Deactivating

- Any resonance effect, such as that of -NH₂, -OH, and -OR, that delocalizes the positive charge on the cation intermediate lowers the activation energy for its formation, and has an activating effect toward further EAS

- Any resonance effect, such as that of -NO₂, -CN, -CO, and -SO₃H, that decreases electron density on the ring deactivates the ring toward further EAS
Activating-Deactivating

- Any inductive effect, such as that of -CH₃ or other alkyl group, that releases electron density toward the ring activates the ring toward further EAS

- Any inductive effect, such as that of halogen, -NR₃⁺, -CCl₃, or -CF₃, that decreases electron density on the ring deactivates the ring toward further EAS

Di- and Polysubstitution

- Generalizations:
  - alkyl, phenyl, and all other substituents in which the atom bonded to the ring has an unshared pair of electrons are ortho-para directing; all other substituents are meta directing
  - all ortho-para directing groups except the halogens are activating toward further substitution;
  - the halogens are weakly deactivating
**Activating-Deactivating**

- For the **halogens**, the inductive and resonance effects run counter to each other, but the former is somewhat stronger.
- The net effect is that halogens are deactivating but ortho-para directing.

$$\text{Cl} \quad + \quad E^+ \quad \rightarrow \quad \text{Cl} \quad + \quad \text{H} \quad \overset{\text{E}}{\leftarrow} \quad \text{Cl} \quad + \quad \text{H} \quad \overset{\text{E}}{\leftarrow} \quad \text{Cl} \quad + \quad \text{H} \quad \overset{\text{E}}{\leftarrow} \quad \text{Cl} \quad + \quad \text{H}$$

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**Di- and Polysubstitution**

<table>
<thead>
<tr>
<th>Ortho-para Directing</th>
<th>Strongly activating</th>
<th>-NH₂</th>
<th>-NHR</th>
<th>-NR₂</th>
<th>-OH</th>
<th>-OR</th>
</tr>
</thead>
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<tr>
<td>Moderate activating</td>
<td>-NHCR</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakly activating</td>
<td>-R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakly deactivating</td>
<td>-F</td>
<td>-Cl</td>
<td>-Br</td>
<td>-I</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Meta Directing</th>
<th>Moderately deactivating</th>
<th>-CH</th>
<th>-CR</th>
<th>-COH</th>
<th>-COR</th>
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</thead>
<tbody>
<tr>
<td>Strongly deactivating</td>
<td>-CNH₂</td>
<td>-SO₃H</td>
<td>-C≡N</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-NO₂</td>
<td>-NH₃⁺</td>
<td>-CF₃</td>
<td>-CCl₃</td>
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</tr>
</tbody>
</table>
Benzodiazepins

1) Sedative-hypnotic
2) Anticonvulsant
3) Muscle relaxant
4) Anxiolytic

Retrosynthetic Analysis

Friedel-Crafts Acylation
Short Problem Using EAS: the synthesis of p-Aminochlorobenzene

\[ \begin{align*}
\text{C}_6\text{H}_5 & \xrightarrow{\text{Cl}_2, \text{FeCl}_3} \text{C}_6\text{H}_4\text{Cl} \\
& \xrightarrow{\text{HNO}_3, \text{H}_2\text{SO}_4} \text{C}_6\text{H}_4\text{Cl} \text{NO}_2 \\
& \xrightarrow{\text{H}_2, \text{Pt or Pd}} \text{C}_6\text{H}_4\text{NH}_2
\end{align*} \]

Separate o from p

The Synthesis of the amide section:

\[ \begin{align*}
\text{C}_6\text{H}_4\text{Cl} & \xrightarrow{\text{NaH}, \text{CH}_3\text{Br}} \text{C}_6\text{H}_4\text{Cl} \\
& \xrightarrow{\text{H}_3\text{C}-\text{N} \text{C} \text{O} \text{CH}_3, \text{N}\text{Me}_2} \text{C}_6\text{H}_4\text{Cl}
\end{align*} \]
Friedel Crafts Acylation:

Amide is activating & ortho directing

1) NaOH
2) Cl

1) NaOH
2) Cl

NH₃

loss H₂O
formation of imine
The introduction (1950) of chlorpromazine into clinical use has been described as the single greatest advance in psychiatric care, dramatically improving the prognosis of patients in psychiatric hospitals worldwide, the availability of antipsychotic drugs curtailed indiscriminate use of electroconvulsive therapy and psychosurgery, and was one of the driving forces behind the deinstitutionalization movement.
Michael Reaction in Context

\[ \text{Product} \rightarrow \text{Michael addition} \rightarrow \text{Product} \]
Dieckmann Condensation in Context

1. 1) NaOH
2) H$_3$O$^+$
3) $\Delta$

Medicinal Chemistry
Haloperidol