Chapter 17: Reactions of Aromatic Compounds
Electrophilic aromatic substitution (17-1)

– Most common (normal) reaction of aromatics

\[
\text{HNO}_3 + \text{H}_2\text{SO}_4 \rightarrow \text{H}_2\text{O} + \text{NO}_2
\]
− Similar to alkenes, benzene (aromatics) has a cloud of \( \pi \) electrons available to attack electrophiles (the aromatic ring is nucleophilic)

− The resulting carbocation is stabilized by resonance and is called: Sigma complex

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{E} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{E} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

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The general mechanism above can be applied to the following reactions: Halogenation, nitration, sulfonation and Friedel-Crafts alkylation/acylation. The only difference will be the nature of the electrophile, and how it is formed.
**Halogenation of Benzene (17-2)**

While benzene is similar in structure to alkenes, it is much **less reactive**

- Reactions are usually endothermic because they require loss of aromaticity (stability)

\[
\begin{align*}
\text{Cyclohexene} & \xrightarrow{\text{Br}_2} \text{Hexa-1,3-diene-1,3-dibromide} \\
\text{Benzene} & \xrightarrow{\text{Br}_2} \text{no reaction}
\end{align*}
\]
The halogenation can be accomplished with chlorine, bromine and iodine. It can be achieved by using a **Lewis Acid** catalyst along with the halogen. The bormination and chlorination is done using one of the following catalysts.

**Lewis acids:** $\text{AlCl}_3$, $\text{FeBr}_3$, $\text{FeCl}_3$

![Chemical reactions diagram]
A similar process is used for chlorination, formation of a better nucleophile between Cl₂ and FeCl₃ (or AlCl₃), followed by electrophilic substitution.
For iodination, iodine is simply oxidized with nitric acid (HNO₃) to liberate the I⁺, which is then used as the electrophile.

\[ \text{H}^+ + \text{HNO}_3 + \frac{1}{2} \text{I}_2 \rightarrow \text{I}^+ + \text{NO}_2 + \text{H}_2\text{O} \]
Nitration (17-3)

\[
\text{HNO}_3 \not\text{ is not the nitrating species.}
\]

It reacts with \( \text{H}_2\text{SO}_4 \) to give the \textit{nitronium ion} (a powerful electrophile). This is the nitrating species

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Once $\text{NO}_2^+$ is present in solution, the mechanism of nitration is the same as the halogenation of aromatics.

One of the most important features of the nitro aromatic compounds, is that the nitro group can be reduced to the corresponding amino function.
Sulfonation (17-4)

$$\text{benzene} + \text{SO}_3 \xrightarrow{\text{H}_2\text{SO}_4} \text{SO}_3\text{H}$$

benzene  sulfur trioxide  sigma complex (resonance-delocalized)

$$\text{HSO}_4^- \xrightarrow{\text{sigma complex}} \text{benzenesulfonate anion} + \text{H}_2\text{SO}_4 \rightarrow \text{SO}_3\text{H}$$
Benzenesulfonic acids are important since they provide a route to the synthesis of phenols.

You do not need to know the mechanism of this reaction.

Example

1) SO$_3$/H$_2$SO$_4$
2) NaOH, Δ
3) H$_3$O$^+$
Practice Question

What is the major organic product formed in the reaction of benzene under the following reaction conditions?

(a) $\text{H}_2\text{SO}_4$, $\text{SO}_3$, heat
(b) $\text{Cl}_2$, $\text{FeCl}_3$
(c) $\text{H}_2\text{SO}_4$, $\text{HNO}_3$
Nitration of Toluene: Effect of the Alkyl Substitution (17-5)

✓ The reactions of substituted benzenes are similar to those of benzene, but can take place faster or slower than benzene depending on the substitution pattern.

✓ The substituent can either increase or decrease the rate of the reaction depending on its nature.

A is an activating group, i.e., one that provides more electrons to the aromatic system.

D is a deactivating group, i.e., one that pulls electrons away from the aromatic system.

苯 > 苯 > 苯

most reactivity least
If the rate is faster, A is an activating substituent or and activator.

If the rate is slower, D is a deactivating substituent or deactivator.

The activation or deactivation of the aromatic ring can be accomplished via the sigma bond by inductive effect.
Stabilization and destabilization can also take place via the pi system by resonance. This happens with group bearing non-bonding electrons or charges on the atom directly bonded to the ring.

**Activators**

**Groups**

\[
\begin{align*}
\text{Phenoxides} & > \text{Anilines} & \text{Phenols} & > \text{Phenyl ethers} & \text{Anilides} & > \text{Alkylbenzenes}
\end{align*}
\]

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# Deactivators

<table>
<thead>
<tr>
<th>Group</th>
<th>Resonance Forms</th>
<th>Example</th>
</tr>
</thead>
</table>
| $-\text{NO}_2$ | $\begin{array}{c}
\text{N}^+ \overset{\ddot{-}}{O}^- \\
\text{N}^+ \overset{\ddot{-}}{O}^- \\
\end{array}$ | nitrobenzene |
| $-\text{SO}_3\text{H}$ | $\begin{array}{c}
\text{S}^+ \overset{\ddot{-}}{O}^- \overset{\ddot{-}}{H} \\
\text{S}^+ \overset{\ddot{-}}{O}^- \overset{\ddot{-}}{H} \\
\text{S}^+ \overset{\ddot{-}}{O}^- \overset{\ddot{-}}{H} \\
\end{array}$ | benzenesulfonic acid |
| $-\text{C}≡\text{N}$ | $\begin{array}{c}
-\text{C}≡\text{N}^+ \\
-\text{C}≡\text{N}^+ \\
\end{array}$ | benzonitrile |
| $-\text{C}≡\text{R}$ | $\begin{array}{c}
\text{C}≡\text{R}^- \\
\text{C}≡\text{R}^- \\
\end{array}$ | acetophenone |
| $-\text{C}≡\text{O}^-$ | $\begin{array}{c}
\text{C}≡\text{O}^- \\
\text{C}≡\text{O}^- \\
\text{C}≡\text{O}^- \\
\end{array}$ | methyl benzoate |
| $-\text{NR}_3$ | $\begin{array}{c}
\text{N}≡\text{R} \overset{\ddot{-}}{R} \\
\text{N}≡\text{R} \overset{\ddot{-}}{R} \\
\end{array}$ | trimethylammonium iodide |

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The other important aspect associated with substituted aromatic is that there are three possible locations for the new substituent. The location of the new substituent does not follow a statistical pattern. For example, the nitration of toluene:
✓ Conclusion: Substituent(s) direct the incoming electrophile to a specific location.

- Activating substituents direct incoming electrophile to the ortho/para positions

\[
\text{toluene} \xrightarrow{\text{HNO}_3, \frac{\text{H}_2\text{SO}_4}{\text{H}_2\text{SO}_4}} \text{CH}_3 \quad \text{NO}_2 \quad \text{CH}_3 \quad \text{NO}_2 \quad \text{O}_2\text{N} \quad \text{CH}_3
\]

\begin{align*}
\text{o-nitrotoluene} \quad (60\%) \\
\text{m-nitrotoluene} \quad (4\%) \\
\text{p-nitrotoluene} \quad (36\%)
\end{align*}

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The reason for this observation is found in the stability of the sigma complexes of each possible reaction.

**Ortho attack**

\[
\text{CH}_3 + \text{H}^+ \text{NO}_2 \rightarrow \begin{cases} \text{CH}_3\text{NO}_2 \text{H} & \text{3° (favorable)} \\ \text{HNO}_2 \text{H} & 2° \end{cases}
\]

**Para attack**

\[
\text{CH}_3 \rightarrow \begin{cases} \text{CH}_3 \text{HNO}_2 & 2° \\ \text{HNO}_2 & 3° (favorable) \end{cases}
\]

**Meta attack**

\[
\text{CH}_3 \rightarrow \begin{cases} \text{CH}_3\text{HNO}_2 & 2° \\ \text{HNO}_2 & 2° \end{cases}
\]
The energy diagrams leading to the possible intermediate shows the tendency to form ortho and para products.
We have just seen that toluene direct new substituents ortho and para. This is true for all other alkyl group, ie they are o and p directors. However since they are larger than CH3, they usually give more para products.
With resonance stabilizing groups, the ortho para preference is even more obvious.

**Ortho attack**

**Para attack**

**Meta attack**
Deactivating, Meta-Directing Substituents

(17-7)

In the case of deactivating substituents, the meta position is preferred by default. That is the meta position is not affected, but the ortho and para positions are affected negatively (deactivated) leaving the meta sigma complex lower in energy.

\[
\text{nitrobenzene} \xrightarrow{\text{HNO}_3, 100 \, ^\circ \text{C} \, \text{H}_2\text{SO}_4} \text{dinitrobenzenes}
\]

- ortho (6%)
- meta (93%)
- para (0.7%)

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The very unstable resonance structure found in the ortho and para sigma complexes, increase the energy of the intermediate, disfavouring reactions at these positions.

*Ortho attack*

*Meta attack*
Any group attached to the ring with a positive or partial positive charge will orient the new substituent at the meta position.

**Ortho attack**

acetophenone

**Meta attack**

This sigma complex does not place the positive charge on the ring carbon bearing the carbonyl group.
# Deactivators

<table>
<thead>
<tr>
<th>Group</th>
<th>Resonance Forms</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{NO}_2$</td>
<td><img src="image" alt="Resonance Forms" /></td>
<td><img src="image" alt="Deactivator" /></td>
</tr>
<tr>
<td>nitro</td>
<td></td>
<td>nitrobenzene</td>
</tr>
<tr>
<td>$\text{SO}_3\text{H}$</td>
<td></td>
<td><img src="image" alt="Deactivator" /></td>
</tr>
<tr>
<td>sulfonic acid</td>
<td></td>
<td>benzenesulfonic acid</td>
</tr>
<tr>
<td>$\text{C≡N}$</td>
<td><img src="image" alt="Resonance Forms" /></td>
<td><img src="image" alt="Deactivator" /></td>
</tr>
<tr>
<td>cyano</td>
<td></td>
<td>benzonitrile</td>
</tr>
<tr>
<td>$\text{C\text{-}R}$</td>
<td></td>
<td><img src="image" alt="Deactivator" /></td>
</tr>
<tr>
<td>ketone or aldehyde</td>
<td></td>
<td>acetophenone</td>
</tr>
<tr>
<td>$\text{C\text{-}O}\text{-}R$</td>
<td><img src="image" alt="Resonance Forms" /></td>
<td><img src="image" alt="Deactivator" /></td>
</tr>
<tr>
<td>ester</td>
<td></td>
<td>methyl benzoate</td>
</tr>
<tr>
<td>$\text{NR}_3$</td>
<td><img src="image" alt="Resonance Forms" /></td>
<td><img src="image" alt="Deactivator" /></td>
</tr>
<tr>
<td>quaternary ammonium</td>
<td></td>
<td>trimethylanilinium iodide</td>
</tr>
</tbody>
</table>

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Halogen Substituents: Deactivating, but o/p Directing (17-8)

☑ Of course there is always an exception to all good rule. The halogens are this exception since they are deactivators (react slower than benzene) but orient new substituents at the ortho and para positions.
The inductive effect of the halogen makes it a deactivator by definition. But the resonance stabilization of the sigma complex makes them ortho/para directors.
<table>
<thead>
<tr>
<th><strong>π Donors</strong></th>
<th><strong>σ Donors</strong></th>
<th><strong>Halogens</strong></th>
<th><strong>Carbonyls</strong></th>
<th><strong>Other</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>⋯NH₂</td>
<td>⋯R alkyl</td>
<td>⋯F</td>
<td>⋯C—R</td>
<td>⋯SO₃H</td>
</tr>
<tr>
<td>⋯OH</td>
<td>⋯</td>
<td>⋯Cl</td>
<td>⋯C—OH</td>
<td>⋯C≡N</td>
</tr>
<tr>
<td>⋯OR</td>
<td>aryI (weak π donor)</td>
<td>⋯Br</td>
<td>⋯C—OR</td>
<td>⋯NO₂</td>
</tr>
<tr>
<td>⋯NHCOCH₃</td>
<td></td>
<td>⋯I</td>
<td>⋯</td>
<td>⋯NR₃</td>
</tr>
</tbody>
</table>

**Ortho, para-directing**

**Activating**

**Deactivating**

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Practice Questions

✔ Are the following groups ortho/para or meta directors?

\[
\begin{align*}
\text{Ar} & \text{– COOH} & \text{Ar} & \text{– NO}_2 \\
\text{Ar} & \text{– C\equiv C\equiv C} & \text{Ar} & \text{– CH}_2\text{OH}
\end{align*}
\]
What is the major organic product of the following reactions?
Effect of Multiple Substituents on Electrophilic Aromatic Substitution (15.8)

✔ When 2 substituents are already on the ring
  – the stronger activator usually predominates.
  – Steric factors will also play a role in determining the structure of the new product.
Each is *ortho* to one CH₃, *para* to the other.

*m*-xylene

Ortho to both CH₃’s, but hindered

HNO₃

H₂SO₄

Major product (65%)

OCH₃

Br₂

FeBr₃
Friedel-Crafts Alkylation (17-10)

In the F-C alkylation, one of the hydrogen of the aromatic ring is substituted by an alkyl group.

Friedel–Crafts alkylation

\[
\text{H} + \text{R–X} \xrightarrow{\text{Lewis acid} (\text{AlCl}_3, \text{FeBr}_3, \text{etc.})} \text{R} + \text{H–X}
\]

\[(X = \text{Cl, Br, I})\]
Mechanism of Friedel-Crafts Alkylation (1° halides)

\[
\text{CH}_3\text{CH}_2\text{Cl} + \text{AlCl}_3 \underset{\text{\textbullet\textbullet\textbullet}}{\rightleftharpoons} \text{CH}_3\text{CH}_2\text{Cl}\text{AlCl}_3 \overset{\text{\textbullet\textbullet\textbullet}}{\rightarrow} \left[\begin{array}{c}
+ \\
\text{H}
\end{array}\right] \text{CH}_2\text{CH}_3 \text{Cl}\text{AlCl}_3
\]

sigma complex

\[
\text{H} \overset{\text{\textbullet\textbullet\textbullet}}{\rightarrow} \text{CH}_2\text{CH}_3 \text{Cl}\text{AlCl}_3 \rightarrow \left[\begin{array}{c}
+ \\
\text{H}
\end{array}\right] \text{CH}_2\text{CH}_3 + \text{HCl} + \text{AlCl}_3
\]
When 2° and 3° alkyl halides are used, the electrophile is the corresponding carbocations.
Since carbocation or carbocation like species are formed, rearrangement is always a potential problem.

*Ionization with rearrangement gives isopropyl cation*

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl} + \text{AlCl}_3 \rightleftharpoons \text{CH}_3\text{C}^+\text{CH}_2\text{Cl} \rightleftharpoons \text{AlCl}_3 \rightarrow \text{CH}_3\text{C}^+\text{CH}_3 + \text{AlCl}_4^-
\]

*Reaction with benzene gives isopropylbenzene*

\[
\text{CH}_3\text{C}^+\text{CH}_3 + \text{C}_6\text{H}_5 \rightarrow \text{C}_6\text{H}_5\text{CH}^+\text{CH}_3 + \text{HCl} + \text{AlCl}_3
\]

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Any other carbocation source can be used in the presence of an aromatic ring to give Friedel-Crafts substitution products.

\[
\text{H}_2\text{C} = \text{C} - \text{CH}_3 + \text{HF} \rightleftharpoons \text{H}_3\text{C} - \text{C}^+ - \text{CH}_3 + \text{F}^- \\
\]

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There are 3 important limitations to the Friedel-Crafts Alkylation:

1. Works only with benzene and activated derivatives (no reaction when deactivators are present).
2. Rearrangements of carbocations or carbocation-like species is common.
3. Poly-alkylation is often the result since the alkylation product is more reactive than the original compound.
Friedel-Craft Acylation (17-11)

F-C acylation can be done either with an acid chloride or anhydride since both possess the acyl group within their structure. The end result is the formation of an aromatic ketone.

Friedel–Crafts acylation

\[
\text{benzene} + R\text{-C-Cl} \xrightleftharpoons{\text{AlCl}_3} \text{an acylbenzene (a phenyl ketone)} + \text{HCl}
\]

Example

\[
\text{benzene} + \text{CH}_3\text{-C-Cl} \xrightleftharpoons{\text{AlCl}_3} \text{acetylbenzene (95%) (acetophenone)} + \text{HCl}
\]
Mechanism of Friedel-Crafts Acylation

$$\text{acyl chloride} \quad \xleftrightarrow{} \quad \text{complex} \quad \xleftrightarrow{} \quad \text{acylium ion}$$

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Practice Question

✓ Propose a mechanism for the following reaction.

\[
\text{Ph-CH₂-CH₂-Cl} \xrightarrow{1) \text{AlCl}_3 \quad 2) \text{H}_2\text{O}} \text{2,3-Oxindole}
\]
We have just seen that Friedel-Crafts alkylation rarely provides a straight chain alkyl function on the aromatic (due to rearrangement)

Ionization with rearrangement gives isopropyl cation

\[
\text{CH}_3\text{—CH}_2\text{—CH}_2\text{—Cl} + \text{AlCl}_3 \overset{\text{δ+}}{\rightleftharpoons} \text{CH}_3\text{—C—CH}_2\text{—Cl—AlCl}_3 \overset{\text{δ—}}{\rightarrow} \text{CH}_3\text{—C—CH}_3 + \text{AlCl}_4
\]

Reaction with benzene gives isopropylbenzene

\[
\text{CH}_3\text{—C—CH}_3 + \text{H} + \text{AlCl} \rightarrow \text{CH}_3\text{—C—CH}_3 + \text{HCl} + \text{AlCl}_3
\]

To avoid this problem, one can use either of the Clemmensen reduction of acyl benzene to form the desired alkylated aromatic.
The Clemmensen reduction is a series of 2 reaction, (1) Friedel-Crafts Acylation, (2) decarbonylation of the resulting ketone.
Nucleophilic aromatic substitution

(15.12)

- This process usually follows an addition/elimination pathway because it is not possible for an aromatic halide to be substituted directly.
- Strong Electron Withdrawing Groups must be present ortho/para to the carbon bearing the halide.

\[
\begin{align*}
\text{Cl} & \quad \text{NO}_2 \\
\text{NO}_2 & \\
\text{2,4-dinitrochlorobenzene} & + & 2 \text{NH}_3 & \xrightarrow{\text{(heat, pressure)}} & \text{NH}_2 & \text{NO}_2 \\
& & & & \text{NO}_2 & \\
& & & & \text{2,4-dinitroaniline} \ (90\%) & + & \text{NH}_4^+ \text{Cl}^-
\end{align*}
\]
Mechanism of Nucleophilic Aromatic Substitution.

[Chemical reaction diagram showing the mechanism of nucleophilic aromatic substitution.]
Side-Chain Reactions of Benzene Derivatives (14.19)

- The benzylic position of any alkyl chain can be transformed into the corresponding bromide as long as there is at least one hydrogen located on the benzylic carbon.
- This is an important reaction since the benzylic bromide can be substituted easily.
The reaction proceed via a radical mechanism:
Oxidation of the carbon side chain is also a common reaction. It will take place as long as at least one benzylic proton is present. The rest of the carbon chain is destroyed in the process.