Lecture IV

Aromatic Substitution

Previously: Aromaticity
1. Theory
2. Experimental criteria
3. Special topics

Today:
1. Electrophilic aromatic substitution (EAS)
   a. Benzene
   b. Parahalogenation
   c. Heteroaromatics

1. Electrophilic aromatic substitutions are by far the most common type of aromatic substitutions.

\[
\text{\textcolor{blue}{\text{+}} + \text{E}^+ \rightarrow \leftrightharpoons \text{J-complex} \rightarrow \text{\textcolor{red}{\text{+}}} \rightarrow \text{\textcolor{green}{\text{+}}}}
\]

J-complexes, even if formed, impart no regioselectivity to the reaction.

Overall substitution of H⁺ with E⁺ other X⁺ groups can also be substituted, if they are able of handling charge:

\[
\begin{align*}
\text{I} & \rightarrow \text{I} + \text{TMS-Cl} \\
\text{Br} & \rightarrow \text{Br} + \text{Br} \\
\end{align*}
\]

I⁺ is more easily replaced than H⁺.

\[
\text{H}^+ > \text{Br}^+ > \text{I}^+
\]
Kinetics:

\[
E^+ + \text{Ph} \xrightarrow{k_1, \text{slow}} \text{Ph}_E^+ \xrightarrow{k_2} \text{Ph}^+ + \text{BH}^+
\]

Using SSA:

\[
\frac{d[\text{Ph}_E^+]}{dt} = 0 = k_1 [E^+] [\text{Ph}^+] - k_1 [\text{Ph}_E^+] - k_2 [\text{Ph}^+][\text{Ph}]
\]

\[
\frac{[\text{Ph}_E^+]}{k_1 + k_2[\text{Ph}]} = \frac{d[\text{Ph}_E^+]}{dt} = k_2 [\text{Ph}][\text{Ph}^+] = \frac{k_1 k_2 [\text{Ph}][E^+][\text{Ph}^+]}{k_1 + k_2[\text{Ph}]}
\]

Typically, \( k_1 \) is RO5, but sometimes IE's are observed, suggesting some partitioning.

Regiochemistry and relative rates

What happens in substituted benzenes? Look at the resonance structures of the \( \text{Ph}_E^+ \) complex:

Relative \( \delta \)-complex stabilities

<table>
<thead>
<tr>
<th>Substituent</th>
<th>( \delta )-Complex Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Ph} - \text{H} )</td>
<td>1</td>
</tr>
<tr>
<td>( \text{Ph} - \text{CH}_3 )</td>
<td>700</td>
</tr>
<tr>
<td>( 0 - \text{Ph} - \text{CH}_3 )</td>
<td>1,900</td>
</tr>
<tr>
<td>( m^- )</td>
<td>100,000</td>
</tr>
<tr>
<td>( p^- )</td>
<td>3200</td>
</tr>
<tr>
<td>( \text{Ph} )</td>
<td>630,000,000</td>
</tr>
</tbody>
</table>

\( \text{NH}_2 \) is an example of an activating group:

To quantify this behavior, partial rate factors are used:

\[
J^r = \left[ \frac{k_0}{k/6} \right] \quad k_0 = \text{rate of rxn in } \text{p-}\text{-position}; \quad k = \text{rate of rxn on benzene}
\]
Examples Toluene

<table>
<thead>
<tr>
<th></th>
<th>$S_{0}$</th>
<th>$S_{m}$</th>
<th>$S_{m}^{*}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>steric problem</td>
<td>4.5</td>
<td>4.8</td>
<td>74.9</td>
</tr>
<tr>
<td></td>
<td>4.2</td>
<td>0.4</td>
<td>10.0</td>
</tr>
</tbody>
</table>

We will not go into individual reactions, but here are some common electrophiles:

- React with everything: $\text{NO}_2, \text{SO}_3, \text{Br}_2, \text{Cl}_2, \text{BrOH}, \text{ClOH}_2, \text{RSO}_2$
- React only with activated rings: $\text{R}_3\text{C}^+, \text{RCO}^+, \text{H}^+, \text{HC}^-=\text{NH}_2$
- React only with strongly activated rings: $\text{HC}^+=\text{NH}, \text{N}^=\text{O}, \text{Ar} \text{N}^=\text{N}$

What happens on a PAH nucleus?

1) bulky electrophile
2) EAS is reversible in which case the more stable product forms

- Favored, substitution in the central ring
- Clar's arguments also favor central ring substitution
In heterocyclic nucleo- and ring connectivity play an important role, analogous to the substituent on the benzene ring.

**1,3-**substituted heterocycles:

\[
\begin{align*}
\text{pyrrole} & \quad \text{sulfoxide} & \quad \text{thiophene} \\
\text{N} & \quad \text{S} & \quad \text{both 2- and 3-position are activated}
\end{align*}
\]

These rings are activated relative to benzene. N is the best donor and S has the weakest orbital overlap.

In the intermediate:

\[
\begin{align*}
\text{E}^+ & \quad \text{E}^- & \quad \text{E}^+ \\
\text{in the intermediate} & \quad \text{substituent can easily change all this.}
\end{align*}
\]

2-substitution is easier, because of more resonance.

**3,4-difluorine** heterocycles

Also, \[
\begin{align*}
\text{basic, since they are not a part of aromatic circuit} & \\
\text{easily protonated under EAS conditions, which are often acidic} & \\
\text{once pyridine is protonated, EAS is even further shut down}
\end{align*}
\]

In the intermediates:

\[
\begin{align*}
\text{less bad – crowded substitution site} & \quad \text{bad} \\
\text{Next time, we will talk about nucleophile and radical aromatic substitutions.}
\end{align*}
\]

OFFICE HOURS ON FRIDAY CANCELLED. EMAIL FOR APPOINTMENT.