Chemistry of C-C $\pi$-bonds

Lectures 5-8: Aromatic Chemistry

“I was sitting writing on my textbook, but the work did not progress; my thoughts were elsewhere. I turned my chair to the fire and dozed. Again the atoms were gamobiling before my eyes. This time the smaller groups kept modestly in the background. My mental eye, rendered more acute by the repeated visions of the kind, fitted together all twining and twisting in snake-like motion. But look! What was that? One of the snakes had seized hold of its own tail, and the form whirled mockingly before my eyes. As if by a flash of lightning I awoke; and this time also I spent the rest of the night in working out the consequences of the hypothesis. Let us learn to dream, gentlemen, then perhaps we shall find the truth... But let us beware of publishing our dreams till they have been tested by waking understanding”

Handout 2

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Aromatic Chemistry

- Benzene – Preparation and general reactivity profile

  What is aromaticity?
  ‘Resonance’ and molecular orbital explanations

- Reactivity

  Typical reactivity – electrophilic aromatic substitution
  Mechanisms of electrophilic substitution – bromination as a worked example
  Nitration, Sulfonation
  Friedel Crafts Alkylation and Acylation
  Reminder: cation stability through hyperconjugation and delocalization
  Gatterman-Koch Formylation

- Monosubstituted Benzenes

  Phenol – acidity
  Benzoic acid – preparation and acidity
  Aniline – preparation and basicity

- Reactions of Monosubstituted Benzenes

  Electrophilic Aromatic substitution: ortho-, meta- and para-

  Substituent effects: 
  (i) ortho- and para- directing and ACTIVATING
  Energy Profiles and the Hammond Postulate

  (ii) ortho- and para- directing and DEACTIVATING
  inductive effects

  (iii) meta- directing and DEACTIVATING

- Reactions of Monosubstituted and Polysubstituted Arenes

  Substituents affect both rate and orientation
  Designing synthetic routes
  The ordering of synthetic steps is important
  Multiple substitutions: effects of orientation (which group dominates?)
  Transforming functional groups in aromatic chemistry

  Diazonium salts
  Generation and Stability
  The $S_N1$ reaction for aromatic compounds
Introducing Iodine (via a radical mechanism)
Introducing Fluorine (the Balz-Scheimann reaction)
The Sandmeyer reaction (introduction of CN, Cl and Br)
Replacement with H (not as pointless as it appears!)

- **Nucleophilic Aromatic Substitution**

  Mechanistic considerations
  An addition-elimination process (compare with conjugate addition-substitution)
  Evidence for anionic intermediates
  Substituent effects (which groups work and which ones don’t?).
  Real Examples:  Synthesis of Fluoxetine (Prozac)
  Synthesis of Vancomycin

**Books**

*Textbooks:*


**Comments, questions and queries welcome.**
- **Aromatic Chemistry**

  ![Benzene](image)

  - **Typical reaction: Electrophilic Aromatic *Substitution***:

  \[
  \text{Ar} + E^+ \rightarrow \text{Ar}-E + H^+
  \]

  - **Example: Halogenation**

  \[
  \text{Ar} + \text{Br-Br} \xrightarrow{\text{FeBr}_3} \text{Ar} - \text{Br} + \text{HBr}
  \]

  - **Compare reactivity of benzene with the reactivity of an isolated alkene in a bromination reaction**:

  \[
  \text{C}_{6}\text{H}_{6} + \text{Br-Br} \rightarrow \text{C}_{6}\text{H}_{5}^{+} - \text{Br} \rightarrow \text{C}_{6}\text{H}_{5}/\text{Br} + \text{Br}^{-}
  \]

  **Conclusion**: benzene is less reactive than an isolated (cyclic) alkene (why?)
Benzene contains \([4n+2]\) \(\pi\) electrons and is *aromatic*

The formation of a continuous \(\pi\) system through the overlap of 6 p-orbitals is a stabilizing interaction

**How much is this ‘aromatic’ stability worth?**

Examine hydrogenation – an exothermic reaction (as the products are thermodynamically more stable than the starting materials)

Conclusion:
Bromination gives a substitution rather than an addition product.

Mechanism?

Stabilization of the cationic intermediate by delocalization (sometimes called ‘resonance’)

Evidence for the cationic intermediate [for reference, $\delta_C$ (benzene) = 128.5]

$^{13}$C NMR: o, p- carbons very deshielded
Reminder:

An **intermediate** can be directly observed (and often isolated!)

We cannot directly look at the TS, so we make assumptions about what the TS looks like based on the **Hammond Postulate**:

“If two states, as for example a transition state and an unstable intermediate, occur consecutively during a reaction process and have nearly the same energy content, their interconversion will only involve a small reorganisation of molecular structure.”

This is an elegant way of saying:

“the transition state (probably) looks like an intermediate close to it in energy”
Other common electrophilic substitution reactions: Nitration ($E = \text{NO}_2$)

- Electrophile is $\text{NO}_2^+$

Other common electrophilic substitution reactions: Sulfonation ($E = \text{SO}_3\text{H}$)
- At high temperatures sulfonation is reversible

\[
\begin{align*}
\text{Br} & \quad \text{OH} \\
\text{SO}_3\text{H} & \quad \text{H}_2\text{SO}_4 \quad \text{H}_2\text{SO}_4 \\
\text{SO}_3\text{H} & \quad \text{Br} \\
\end{align*}
\]

200°C

- Other common electrophilic substitution reactions: Friedel Crafts Alkylation (R = alkyl)

\[
\begin{align*}
\text{R} & \quad \text{Cl} \quad \text{AlCl}_3 \quad \text{AlCl}_3 \\
\text{R} & \quad \text{Cl} \quad \text{AlCl}_3 \\
\text{R} & \quad \text{H} \\
\end{align*}
\]

- Rearrangement and polysubstitution

\[
\begin{align*}
\text{H} & \quad \text{Cl} \quad \text{AlCl}_3 \quad \text{catalytic} \\
\text{H} & \quad \text{Cl} \quad \text{AlCl}_3 \\
\text{H} & \quad \text{H} \\
\end{align*}
\]
- Alkyl groups are electron-donating through hyperconjugation (so the starting materials are more reactive than the products)

'hyperconjugation' or \( \sigma \)-conjugation -

one of the C-H bonds interacts with the \( \pi \) system
[C-H must be perpendicular to the plane of the ring for the C-H \( \sigma \)-orbital to overlap with the \( \pi \) system]

this means that alkyl groups are electron donating
and means that alkyl substituted benzenes are MORE reactive than unsubstituted benzenes

- Cation stability – a reminder

- 1. Hyperconjugation

\[
\begin{align*}
\text{Planar Structure} & \\
\text{empty } p \text{ orbital} & \\
\end{align*}
\]

- \( \pi \)-conjugation - ['resonance' is a shorthand way of describing how the molecular orbitals overlap leading to delocalization]

\[
\begin{align*}
\text{remember: the bonds are not 'moving'} & \\
\text{the cation is delocalized over these three atoms} & \\
\end{align*}
\]
- Friedel-Crafts acylation

\[
\begin{align*}
R\text{C}l & \quad \text{Cl}_2\text{AlCl}_3 \\
\text{anhydride} & \quad R\text{C}l^+ \quad \text{AlCl}_3 \\
& \quad \text{Acylium Cation} \\
\end{align*}
\]

- How to introduce alkyl groups on an aromatic ring (if FC alkylation does not work):
- *Use Friedel-Crafts acylation and reduce the ketone functional group*

**Target:**

**Problem with FC alkylation:**

\[\text{AlCl}_3 \quad \text{plus other products of rearrangement and polyalkylation}\]

\[\text{NH}_2\text{NH}_2 \quad \text{KOH, heat} \quad \text{Wolff-Kishner reaction}\]
**Gatterman-Koch formylation (a special Friedel-Crafts type reaction):**

\[
\text{AlCl}_3 + \text{C}≡\text{O} + \text{HCl} \xrightleftharpoons{\text{CuCl}} \text{H}–\text{C}≡\text{O}
\]

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>C≡O</td>
<td>H–C≡O</td>
</tr>
<tr>
<td>AlCl₃</td>
<td></td>
</tr>
<tr>
<td>HCl</td>
<td></td>
</tr>
</tbody>
</table>

**Monosubstituted Benzenes**

So far:

\[
\text{Y} = \text{H}, \text{NO}_2, \text{SO}_3\text{H}, \text{Alkyl}, \text{acyl (aldehyde, ketone)}
\]

**Phenol (Y = OH)**

Acidity: compare with non aromatic alcohol:

<table>
<thead>
<tr>
<th>Compound</th>
<th>pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenol</td>
<td></td>
</tr>
<tr>
<td>an extremely stable enol</td>
<td></td>
</tr>
</tbody>
</table>

A reminder (and brief aside): pKa is a measure of the position of the equilibrium between an acid and its conjugate base

\[
\text{AH}_{(aq)} + \text{H}_2\text{O} (l) \rightleftharpoons \text{H}_3\text{O}^+_{(aq)} + \text{A}^-_{(aq)}
\]
Most important factor in acid strength is the stability of the conjugate base $A^-$. 

So for a strong acid, the conjugate base $A^-$ is stable, the equilibrium lies over to the RHS and the pKa is low.

The stronger the acid, the lower the pKa.

A few representative examples:

<table>
<thead>
<tr>
<th>pKa</th>
<th>1</th>
<th>5</th>
<th>7</th>
<th>10</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F$_3$C-CH$_2$COOH</td>
<td>CH$_3$COOH</td>
<td>4-NO$_2$C$_6$H$_4$OH</td>
<td>OH$_2$C$_6$H$_4$OH</td>
<td>CH$_3$=C=C=CH$_2$</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>5.0</td>
<td>7.4</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>EtO$_2$C-C=OEt</td>
<td>CH$_3$OH</td>
<td>H$_2$O</td>
<td>CH$_3$CO</td>
<td>CH$_3$=C=C=CH$_2$</td>
</tr>
<tr>
<td></td>
<td>12.0</td>
<td>15.3</td>
<td>15.7</td>
<td>20.0</td>
<td>25.0</td>
</tr>
</tbody>
</table>

---

Acidity of Phenol vs cyclohexanol

Most important to consider the stabilities of the anions

1. ‘Delocalization’

The lone pair in a p-orbital on oxygen, which is perpendicular to the plane of the ring, can interact with the pi system.
1. ‘Delocalization’ (continued)

We can draw this as:

[Chemical structures showing delocalization]

[Remember – the charge is not actually moving around the ring]

2. An inductive effect

The aromatic substituent is sp² hybridized (vs sp³ hybridized in cyclohexanol) and hence has more ‘s’ character. The higher proportion of ‘s’ character means that the electrons see more effective nuclear charge [cf radial probability functions].

- Y = CO₂H (benzoic acids)

Prepared by: (i) oxidation of toluene

![Chemical structure of benzoic acid prepared by oxidation of toluene]

(ii) Grignard reaction with CO₂

![Chemical structures showing Grignard reaction with CO₂]

Prepared by: (ii) Grignard reaction with CO₂
Benzoic acid pKa = 4.2 (compare with acetic acid CH₃CO₂H, pKa 4.8)

- Y = NH₂ (anilines)

Prepared by: Reduction of nitro compounds

Basicity: Aniline is less basic than cyclohexylamine

pKaₐ = 10.7  

pKaₐ = 4.6

- Two effects:

Delocalization

Inductive effect
- Reactions – Electrophilic aromatic substitution. How do substituents affect reactivity?

The nature of Y affects both orientation (o- vs m- vs p-) and rate of reaction

1. Ortho- and para- directing, and ACTIVATING groups

Typically: Y = alkyl, NH₂, NR₂ (R = alkyl), NHCOR, OH, OR, OCOR

The OMe group is ACTIVATING (the reaction goes 10⁹ times faster than it does with benzene) – why?

[activation energy is effectively the energy required to overcome the barrier to reaction]
To predict reactivity we need to look at the nature of the TS.
We can do this using the Hammond Postulate:

“The transition state looks like an intermediate close to it in energy”

- Therefore: consider intermediates in this reaction

**Ortho**:
Meta:

Relating this to the TS energy:

Para:
Therefore: more stable intermediate formed faster, and ortho- and para- products predominate

- 2. Ortho- and para- directing, and DEACTIVATING groups

Typically: \( Y = F, Cl, Br, I \) (these groups ‘withdraw’ and ‘donate’ electrons)

Halogens withdraw electrons via an inductive effect (this affects the rate) and donate through the unsaturated system (this affects orientation and is sometimes called a ‘mesomeric’ effect).
Consider ortho-

\[ \text{Cl} \quad \text{Br-Br} \quad \text{FeBr}_3 \]

\[ \text{Cl} \quad \text{Br} \quad \text{Br} \quad \text{Cl} \]

\[ \quad \text{Cl} \quad \text{Br} \quad \text{Br} \quad \text{Cl} \quad + \]

\[ \quad \text{Cl} \quad \text{Br} \quad \text{Br} \quad \text{Cl} \quad + \]

\[ \quad \text{Cl} \quad \text{Br} \quad \text{Br} \quad \text{Cl} \quad \]

\[ \quad \text{Br} \quad \text{Cl} \quad \text{Br} \quad \text{Cl} \quad \]

\[ \quad \text{TS} \ 1 \quad \text{TS} \ 2 \quad \]

\[ \quad m\text{- higher in energy} \quad \]

\[ \quad o\-, \ p\text{- similar in energy} \quad \]

\[ \quad \text{Intermediate} \quad \text{benzene} \quad \text{lower in energy} \quad \]

\[ \quad \text{Starting materials} \quad \text{Products} \quad \]

Conclusions:
2. *Meta-* directing, and DEACTIVATING groups

Typically: NO₂, SO₃H, almost all carbonyl compounds (CO₂H, CO₂R, CHO, COR)

![Chemical structures](image)

Consider *ortho-* and *meta-*
- Designing a simple synthetic route: substituent effects are important for selectivity and efficiency

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{CO}_2\text{H} \\
\text{NO}_2 & \quad \text{NO}_2 \\
\text{NO}_2 & \quad \text{or} \\
\text{or} & \quad \text{or} \\
\end{align*}
\]

All cheap and readily available
Which is the best starting material?

- Consider monosubstituted starting materials:

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{Me group activating} \\
\text{NO}_2 & \quad \text{o, p - directing} \\
\end{align*}
\]

- Choice of starting material:

\[
\begin{align*}
\text{HNO}_3 & \quad \text{H}_2\text{SO}_4 \\
\text{NO}_2 & \quad 37\% \text{ para} - \\
\text{or} & \quad 59\% \text{ ortho} -
\end{align*}
\]
The order of reactions in a synthetic sequence can be important.

ROUTE 1: Oxidation then nitration

Conclusion:
ROUTE 2: Nitration then oxidation

Conclusion:

- What about arenes with two or more groups? Which effects dominate?

*Examine the effects of individual substituents: electronically *first*, then consider steric effect*

- (i) substituents direct to the same position
(i) substituents direct to conflicting positions

Broadly categorize substituents into 3 classes of decreasing effect

1. STRONGLY activating and ortho- & para- directing (OH, OR, NH$_2$ and NR$_2$ groups)
2. Alkyl groups and halogens
3. All other meta- directors

• If substituents are in ‘different’ classes, then the ‘higher numbered class dominates.

• If substituents are in the same class then it is to be expected that mixtures will be produced (and hence that this is maybe not a good route to the proposed compound!)

Important to remember that we can extend and modify these effects through functional group interconversion reactions:
Diazonium salts:

\[ \begin{align*}
\text{NO}_2^- + \text{H}_2, \text{Pd} \quad & \rightarrow \quad \text{NH}_2^- \\
\text{(or Sn/HCl)} \quad & \rightarrow \quad \text{NaNO}_2 \\
\text{HCl (aq), 0°C} \quad & \rightarrow \quad \text{N}_2^+ \\
\end{align*} \]

Mechanism for generation:

\[ \begin{align*}
\text{NaNO}_2 + \text{HCl} & \quad \leftrightarrow \quad \text{HNO}_2 + \text{NaCl} \\
\text{N}_2^+ + \text{H}_2\text{O} & \quad \leftrightarrow \quad \text{N}_2\text{O} + \text{H}_2\text{O}
\end{align*} \]

Effectively the S\(_{N1}\) mechanism for aromatic compounds (note: cation is not stable)

Compare with S\(_{NAr}\) reaction in the next lecture

A useful reaction – there is not a reagent for ‘HO\(^+\)’
Other substituents may be introduced in this fashion:

(i) iodine (probably a radical, rather than an ionic mechanism).

(ii) Fluorine (the Balz-Schiemann reaction)
(iii) The Sandmeyer reaction (to introduce Cl, Br CN)

\[
\begin{align*}
\text{NH}_2 & \quad \text{NaNO}_2 \quad \text{aq. HCl} \\
& \quad \text{Cu} \quad X \\
& \quad X = \text{Cl, Br, CN}
\end{align*}
\]

Mechanism – another radical reaction

\[
\begin{align*}
\text{Cu(I)} & \quad \text{Recycle - catalytic in Cu} \\
& \quad \text{Cu(II)}
\end{align*}
\]

Finally: replacement by H (not a good way to make benzene, but useful for directing other groups, though an outdated way to achieve this – better methods available)

\[
\begin{align*}
\text{NH}_2 \text{used to direct orientation of bromination}
\end{align*}
\]
Nucleophilic Aromatic Substitution: $S_{N}Ar$ (substitution nucleophilic aromatic)

Overall: substitution on an aromatic ring – what is the mechanism?

Mechanistic considerations: I. Cannot be $S_{N}2$

$S_{N}2$ requires access to $\sigma^*$ orbital of C-F bond (which is buried inside the aromatic ring)
Therefore nucleophile (HO$^-$) cannot get ‘anti’ to the requisite C-F bond

Mechanistic considerations: II. Unlikely to be $S_{N}1$ (compare with diazo compounds!)

Carbocation would be in an sp$^2$ orbital (and would not be stabilized by the aromatic ring)

*Compare with other cations we have seen:*
The Chemistry of C-C \( \pi \) bonds.

- **Mechanism:** an addition-elimination reaction

\[
\begin{align*}
&\text{HO-} &\rightarrow &\text{HO-} \\
&\text{F} &\rightarrow &\text{F} \\
&\text{N} &\rightarrow &\text{N} \\
&\text{O} &\rightarrow &\text{O} \\
&\text{O} &\rightarrow &\text{O} \\
&\text{HO-} &\rightarrow &\text{HO-}
\end{align*}
\]

- **Remember:** S\(_{N2}\) reactions at sp\(^2\) centres (including aromatic rings) are very rare

Our shorthand structures indicate that the charge is delocalized around the ring but is centred on the ‘ortho’ and ‘para’ positions – is there evidence for this?

For Anion (often called a ‘Meisenheimer’ complex)

\[
\begin{align*}
&\text{NH}_2^- &\rightarrow &\text{NH}_2^- \\
&\text{C} &\rightarrow &\text{C} \\
&\text{C} &\rightarrow &\text{C} \\
&\text{C} &\rightarrow &\text{C} \\
&\text{C} &\rightarrow &\text{C}
\end{align*}
\]

In both cases the ionic charge is localized almost exclusively to the ortho and para positions

**Implication:** groups to stabilize the anionic intermediates in S\(_{NAr}\) reactions MUST be on these carbons
- Compare with other addition-eliminations: (i) conjugate substitution of an amine

\[
\text{EtO} \quad \text{CO} \quad \text{CO} \quad \text{Et} + \begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array}
\begin{array}{c}
\text{NH} \\
\text{NH}
\end{array}
\text{ArNH}_2 \xrightarrow{\text{heat}} \begin{array}{c}
\text{EtO} \\
\text{EtO}
\end{array}
\begin{array}{c}
\text{NH} \\
\text{NH}
\end{array}
\text{Cl}
\]

Amine nucleophiles prefer 1,4 addition

Overall addition-elimination mechanism

- (ii) conjugate substitution of an alcohol

\[
\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array}
\begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array}
\xrightarrow{\text{MeOH}} \begin{array}{c}
\text{MeO} \\
\text{MeO}
\end{array}
\begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array}
\xrightarrow{-\text{HCl}}
\]

proton transfer

Overall addition-elimination mechanism
**Example of S_NAr:**

```
\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{N} & \quad \text{O} \\
\text{Cl} & \quad \text{N} \\
\end{align*}
\]

Only the *ortho* chlorine is lost – the meta one is retained

**Further confirmation: isolation of an intermediate (!)**

```
\[
\begin{align*}
\text{MeN} & \quad \text{MeN} \\
\text{HO} & \quad \text{HO} \\
\end{align*}
\]

A stable molecule (structure confirmed by X-ray crystallography)

**Which (EWG) groups can accelerate nucleophilic aromatic substitution?**

So far we have seen the NO_2 group – but other groups can also function in this regard

```
\[
\begin{align*}
\text{F} & \quad \text{Nu} \\
\text{Nu} & \quad \text{Nu} \\
\end{align*}
\]

So any group that can stabilize the negative charge in the intermediate can facilitate the reaction – so carbonyl groups are effective too
Nucleophilic aromatic substitution is generally fastest when the leaving group is fluoride.

Rate $F > Cl > Br > I$ [compare with $S_N 2$: Rate $I > Br > Cl > F$]

- The rate-determining step is attack of the nucleophile on the aromatic ring as this breaks the aromaticity.
- The second step, involving loss of the leaving group and restoration of aromaticity, is fast.

Electronegative F polarizes $\sigma$-bond and inductively withdraws electron density from the high energy anionic intermediate

Note that the reaction is bimolecular in the RDS and therefore:

Synthesis of Fluoxetine - serotonin uptake inhibitor for treatment of depression (marketed as ‘Prozac’)

$$
\begin{align*}
\text{F}_3\text{C} & & \text{Ph} & & \text{O} & & \text{NHMe} \\
\text{F} & & \text{HO} & & \text{NHMe} & & \text{NaH} & & \text{Me}_2\text{NAC} & & \text{F}_3\text{C} \\
\text{F} & & \text{Ph} & & \text{O} & & \text{NHMe} & & \text{NaH} & & \text{F}_3\text{C} \\
\end{align*}
$$
Example of $S_N$Ar in the synthesis of a complex molecule: Synthesis of Vancomycin

Regiochemistry in $S_N$Ar reaction: attacks at the centre substituted with the fluorine