Benzene and aromatic compounds (McMurry Ch. 15 & 16)

C₆H₆ is an unusually stable molecule that does NOT react like alkenes do. A model was proposed by Kekule in 1865:

![Benzene resonance hybrid model](image)

The resonance hybrid model explains these properties of benzene:

- Benzene does not undergo addition reactions readily like alkenes; instead it undergoes electrophilic substitution reactions which do not disturb π bonds.

- X-ray diffraction shows all 6 bonds are equal in length (1.39 Å) and that benzene is a planar molecule.

- Hydrogenation under extreme conditions leads to cyclohexane, however the heat of hydrogenation is much less than expected for “cyclohexatriene”

Resonance hybrid model has delocalized electrons above and below the ring which lead to resonance stabilization.

Requirements for electrons to be delocalized:

1) They must be able to move toward an sp²-hybridized atom. sp³-hybridized atoms break up the delocalization "route".

2) Molecule must be (at least partly) planar, so unhybridized p orbitals can overlap.

Substituents on benzene and the “common naming system”: For monosubstituted benzene, the substituent name precedes the “benzene”. For disubstituted benzenes, the common naming system is based on positions of the substituents as follows:

Ortho = 1,2-disubstituted       Meta = 1,3-disubstituted       Para = 1,4-disubstituted
<table>
<thead>
<tr>
<th>Formula</th>
<th>Name</th>
<th>Formula</th>
<th>Name</th>
</tr>
</thead>
</table>
| \[
\begin{align*}
\text{CH}_3
\end{align*}
\] | Toluene (bp 111°C) | \[
\begin{align*}
\text{CHO}
\end{align*}
\] | Benzaldehyde (bp 178°C) |
| \[
\begin{align*}
\text{OH}
\end{align*}
\] | Phenol (mp 43°C) | \[
\begin{align*}
\text{CO}_2\text{H}
\end{align*}
\] | Benzoic acid (mp 122°C) |
| \[
\begin{align*}
\text{NH}_2
\end{align*}
\] | Aniline (bp 184°C) | \[
\begin{align*}
\text{CN}
\end{align*}
\] | Benzonitrile (bp 191°C) |
| \[
\begin{align*}
\text{C} & \text{CH}_3
\end{align*}
\] | Acetophenone (mp 21°C) | \[
\begin{align*}
\text{CH}_3
\end{align*}
\] | ortho-Xylene (bp 144°C) |
| \[
\begin{align*}
\text{CH}_3
\end{align*}
\] | Cumene (bp 152°C) | \[
\begin{align*}
\text{CH} &= \text{CH}_2
\end{align*}
\] | Styrene (bp 145°C) |

Ortho → Ortho  
Meta → Meta  
Para

Toluene → p-Bromotoluene

4-Bromo-1,2-dimethylbenzene  2-Chloro-1,4-dinitrobenzene  2,4,6-Trinitrotoluene (TNT)
Identifying whether or not compounds are aromatic: Huckel’s Rule

The term “aromatic” originally came from the fact that benzene and its derivatives had a particularly strong “aroma”…benzaldehyde (cherries, almonds), phenylpropanoids (cinnamon, cumin), substituted phenols (coves, other spices)

Compounds which fit the following criteria can be considered aromatic:

1) Cyclic and planar
2) Continuous overlap of unhybridized p-orbitals forming a delocalized $\pi$-cloud of e-
3) The number of $\pi$-electrons must be equal to $4n + 2$ (where n = 0, 1, 2…)

**Huckel’s Rule** (4n + 2 rule) relates to the way $\pi$ electrons populate MOs:

- **Aromatic** compounds: molecules with $4n+2$ $\pi$ e- have just enough to populate only the bonding MOs, leading to a very stable bonding situation

- **Anti-aromatic** compounds: in molecules containing $4n$ $\pi$ electrons, some of them will populate $\pi$ antibonding or nonbonding MOs, destabilizing the molecule

  Example: cyclobutadiene

- **Nonaromatic** molecules are those that do not fit one or more of the above criteria

**Compounds designated as aromatic based on the above rules also include:**

- Cyclic planar molecules which are ions (Ex: cyclopentadienide anion, cycloheptatrienyl cation)

- Polycyclic, fused-ring molecules (Ex: naphthalene, anthracene)

- Heterocyclic molecules in which a different atoms replaces one of the C in the ring (Ex: pyridine)
Naphthalene

Phenanthrene

Aromatic cyclopentadienyl anion with six $\pi$ electrons

Cycloheptatriene

Cycloheptatrienyl bromide

Cycloheptatrienyl cation six $\pi$ electrons

Indole

Pyridine Six $\pi$ electrons

(a) Cl-Br
(b) CH$_3$-CH$_2$CH$_2$CH$_3$
(c) NH$_2$

(d) Cl-CH$_3$
(e) O$_2$N-NO$_2$
(f) H$_3$C$_2$
Reactivity & mechanism of benzene and its derivatives:

- Because of its $\pi$ electrons, benzene is a nucleophile and is attracted to electrophiles.
- Due to the stability of aromatic $\pi$ system, addition reactions aren’t favored.
- **Electrophilic aromatic substitution** is the predominant reaction mechanism

$$
\text{benzene} + Y^+ \rightarrow \text{resonance-stabilized carbocation} \rightarrow \text{benzene-Y} + \text{HB}
$$

**Hydrogens** are easily replaced by **electrophilic substituent groups**; in fact, ease of substitution is a good test for aromaticity

**Functionalization of benzene:**
The most common **electrophilic substitutions** can also be used synthetically to provide starting points for preparation of other derivatives:

1. **Halogenation:** benzene $\rightarrow$ bromobenzene, chlorobenzene, iodobenzene
   - Grignard reagents

2. **Nitration:** benzene $\rightarrow$ nitrobenzene $\rightarrow$ anilines, diazonium salts
   - phenols, other derivs

3. **Sulfonation:** benzene $\rightarrow$ benzenesulfonic acid $\rightarrow$ phenols, Dowex resins

4. **Friedel-Crafts acylation:** benzene $\rightarrow$ acylbenzene (phenyl ketones) $\rightarrow$ alkyl benzenes

5. **Friedel-Crafts alkylation:** benzene $\rightarrow$ toluene $\rightarrow$ benzoic acid
   - alkyl derivatives, haloalkyl groups
Mechanism of halogenation by electrophilic substitution and its energy changes:

Carbocation is resonance-stabilized

Friedel-Crafts alkylations and acylations

An electron pair from the aromatic ring attacks the carbocation, forming a C–C bond and yielding a new carbocation intermediate.

Loss of a proton then gives the neutral alkylated substitution product.
1) Halogenations

FeCl₃ can be used to generate an electrophilic halogen cation from either Br₂ or Cl₂:

\[
\text{Br}_2, \text{Br} + \text{FeCl}_3 \rightarrow \text{Br}^+ + \text{FeCl}_3\text{Br}
\]

\[
\text{Cl}_2, \text{Cl} + \text{FeCl}_3 \rightarrow \text{Cl}^+ + \text{FeCl}_3\text{Cl}
\]

Iodine cation is produced by reaction with a strong oxidizer such as nitric acid or Cu²⁺:

\[
\text{I}_2 + \text{HNO}_3 \rightarrow 2\text{I}^+ + 2\text{e}^-
\]

\[
\text{I}_2 + 2\text{Cu}^{2+} \rightarrow 2\text{I}^+ + 2\text{Cu}^+
\]

2) Nitration: Electrophile is a nitronium ion generated from nitric & sulfuric acids:

\[
\text{HNO}_3 + \text{H}_2\text{SO}_4 \rightarrow \text{O}=\text{N}=\text{O} + \text{H}_2\text{O} + \text{HSO}_4^-
\]

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

3) Sulfonation/desulfonation:

The electrophile is \(^+\text{SO}_3\text{H} \), generated from fuming sulfuric acid:

\[
\text{H}_3\text{O}^+ + \text{SO}_3 \rightarrow \text{O}=\text{S}=\text{O} + \text{H}_2\text{O}
\]

\[
\text{fuming } \text{H}_2\text{SO}_4 \rightarrow \text{SO}_3\text{H}
\]

i. The overall reaction is a reversible nucleophilic attack of benzene on the \(^+\text{SO}_3\text{H} \):

ii. The reverse, desulfonation occurs under conditions of heat and dilute acid

iii. Further treatment of sulfonic acid derivative with base produces phenols
(4) & (5) Friedel-Crafts acylations and alkylations

The Friedel-Crafts reactions are used to put an **R group** or an **acyl group** on benzene.

In these reactions, the Lewis acid AlCl₃ is used to generate an electrophilic “acylium ion” from an acyl halide or alkyl halide:

\[
\text{acyl:} \quad R - C = O + AlCl_3 \rightarrow [R - C = O : \overset{\ominus}{\text{C}}] + \text{Cl}^{-} \quad -\text{AlCl}_4
\]

\[
\text{alkyl:} \quad R - \text{Cl} + AlCl_3 \rightarrow R^+ + -\text{AlCl}_4
\]

Either of these electrophilic C species can undergo a substitution with benzene.

The Friedel-Crafts **acylation** reaction:

1. Requires excess AlCl₃ due to tendency of complexation with carbonyl group
2. Requires water to hydrolyze the Al salts

\[
\text{Friedel-Crafts acylation:} \quad \text{Benzene} + \text{Acetyl chloride} + 2\text{AlCl}_3 \rightarrow \text{Acetylbenzene} + 3\text{AlCl}_3 + 3\text{HCl}
\]

The Friedel-Crafts **alkylation** process:

1. Requires excess benzene because the resulting alkylbenzene product is even more reactive than benzene & would tend to form **disubstituted** product
2. Cannot take place with **vinyl or aryl halides** due to unstable carbocations
3. May proceed with **rearrangement** of the carbocation, especially if loss of the halide produces a primary cation as in the example shown:

©2004 Thomson - Brooks/Cole
Using Reactions of Substituents in Synthesis

Reactions (1) – (5) can be starting points for obtaining other substituents by transforming the product to another group. Some of the most common examples:

Alkali fusion of benzene sulfonate produces phenol, see reaction (3)

Phenol can also be made by elimination/addition:

Reductions:
Nitrobenzene to aniline:

Wolff-Kishner reduction:

Oxidations:

KMnO₄ will oxidize any alkyl group having benzylic H to a COOH group

Amino group can be oxidized back to nitro

SN₂ reactions: Substitution at the benzylic carbon is versatile route to modify groups

1. The benzylic hydrogen is replaced by NBS in a radical substitution
2. The Br can be replaced by nucleophile in SN₂ reaction to give new substituent
Effects of substituents on the reactivity of the benzene ring:

Since benzene is a nucleophile, substituents which either donate or withdraw e-density can affect substitution reactions in 2 ways:

1) Reactivity of the ring toward electrophiles
2) Orientation (position) of substitution

Activation or Deactivation? Consider balance of inductive and resonance effects

Inductive effects:
1) Electron-rich groups donate electrons inductively through the $\sigma$ bond to the benzene ring, making the ring more reactive
   Ex: alkyl groups

2) Electron-withdrawing or positively-charged groups remove electron density through the $\sigma$ bond to make the ring less reactive
   Ex: -F, -Cl, -Br, -I
   -NO$_2$, -CN, -carbonyls, NH$_3^+$

Resonance effects:
1) Groups with nonbonding electron pairs on the attached atom donate electron density through resonance with benzene’s $\pi$ bonding system:
   Ex: -OH, -NH$_2$, -OR, -Cl and other halogens

2) Groups with $\pi$ bonds on the atom attached to the ring can withdraw electrons from the ring through resonance
   Ex: -NO$_2$, -CN, -COOH, -COOR, -CHO, -COR
Strong deactivators  Weak deactivators  Strong activators

-NO₂  -SO₃H  -COH  -CHO  -Br:  -F:  -CH₃ (alkyl)  -OCH₃  -NH₂

Meta-directing deactivators  Ortho- and para-directing deactivators  Ortho- and para-directing activators

---

**Table 16.1** Orientation of Nitration in Substituted Benzenes

Note: halogenation and other substitutions will proceed with similar orientation

<table>
<thead>
<tr>
<th>Product (%)</th>
<th><strong>Ortho</strong></th>
<th><strong>Meta</strong></th>
<th><strong>Para</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meta-directing deactivators</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−N(CH₃)₂</td>
<td>2</td>
<td>87</td>
<td>11</td>
</tr>
<tr>
<td>−NO₂</td>
<td>7</td>
<td>91</td>
<td>2</td>
</tr>
<tr>
<td>−CO₂H</td>
<td>22</td>
<td>76</td>
<td>2</td>
</tr>
<tr>
<td>−CN</td>
<td>17</td>
<td>81</td>
<td>2</td>
</tr>
<tr>
<td>−CO₂CH₃CH₃</td>
<td>28</td>
<td>66</td>
<td>6</td>
</tr>
<tr>
<td>−COCH₃</td>
<td>26</td>
<td>72</td>
<td>2</td>
</tr>
<tr>
<td>−CHO</td>
<td>19</td>
<td>72</td>
<td>9</td>
</tr>
<tr>
<td><strong>Ortho- and para-directing deactivators</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−F</td>
<td>13</td>
<td>1</td>
<td>86</td>
</tr>
<tr>
<td>−Cl</td>
<td>35</td>
<td>1</td>
<td>64</td>
</tr>
<tr>
<td>−Br</td>
<td>43</td>
<td>1</td>
<td>56</td>
</tr>
<tr>
<td>−I</td>
<td>45</td>
<td>1</td>
<td>54</td>
</tr>
<tr>
<td><strong>Ortho- and para-directing activators</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−CH₃</td>
<td>63</td>
<td>3</td>
<td>34</td>
</tr>
<tr>
<td>−OH</td>
<td>50</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>−N(HCOCH₃)</td>
<td>19</td>
<td>2</td>
<td>79</td>
</tr>
</tbody>
</table>

(a) \[ \text{Cl} \xrightarrow{\text{CH₃CH₂Cl/AlCl₃}} ? \]

(b) \[ \text{CO₂H} \xrightarrow{\text{HNO₃/H₂SO₄}} ? \]

(c) \[ \text{Cl} \xrightarrow{\text{CH₃CH₂Cl/AlCl₃}} ? \]

(d) \[ \text{N(CH₂CH₃)₂} \xrightarrow{\text{SO₃/H₂SO₄}} ? \]
Directing effects of substituents on further substitution

1) Activating groups direct further substitution to ortho and para positions

- Activating groups form resonance structures with increased e- density at ortho and para positions, encouraging electrophiles to attack at these positions.
- **Resonance-stabilized intermediates** form from substitution at ortho, para positions; meta-substituted structures are less stable.
- **Further additions** of activating groups occur easily

Example: Nitration of **phenol** (Fig. 16.15) produces 50 % ortho & 50 % para

2) Strongly deactivating groups direct substitution to meta positions

- The ring is less reactive but electrophilic attack may still occur
- Substitution at meta positions produces more stable resonance structures
- Weaker electrophiles won’t react when a deactivator is present

Example: Chlorination of benzaldehyde (Fig. 16.17) produces 72 % meta isomer

3) Weakly deactivating halogens are ortho, para directors

- Halobenzenes are less reactive than benzene, but ortho and para substitutions result in more stable resonance structures in the intermediate

Example: Nitration of chlorobenzene (Fig. 16.16) produces 64 % para, 35 % ortho (steric hindrance is a factor in the ortho/para ratio)

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Reactivity</th>
<th>Orientation</th>
<th>Inductive effect</th>
<th>Resonance effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>−CH₃</td>
<td>Activating</td>
<td>Ortho, para</td>
<td>Weak; electron-donating</td>
<td>None</td>
</tr>
<tr>
<td>−OH₃</td>
<td>Activating</td>
<td>Ortho, para</td>
<td>Weak; electron-withdrawing</td>
<td>Strong; electron-donating</td>
</tr>
<tr>
<td>−NH₂</td>
<td>Activating</td>
<td>Ortho, para</td>
<td>Weak; electron-withdrawing</td>
<td>Strong; electron-donating</td>
</tr>
<tr>
<td>−F, −Cl</td>
<td>Deactivating</td>
<td>Ortho, para</td>
<td>Strong; electron-withdrawing</td>
<td>Weak; electron-donating</td>
</tr>
<tr>
<td>−Br, −I</td>
<td>Deactivating</td>
<td>Ortho, para</td>
<td>Strong; electron-withdrawing</td>
<td>Weak; electron-donating</td>
</tr>
<tr>
<td>− Nagar</td>
<td>Deactivating</td>
<td>Meta</td>
<td>Strong; electron-withdrawing</td>
<td>None</td>
</tr>
<tr>
<td>−NO₂, −CN,</td>
<td>Deactivating</td>
<td>Meta</td>
<td>Strong; electron-withdrawing</td>
<td>None</td>
</tr>
<tr>
<td>−CHO, −CO₂H₃,</td>
<td>Deactivating</td>
<td>Meta</td>
<td>Strong; electron-withdrawing</td>
<td>Strong; electron-withdrawing</td>
</tr>
</tbody>
</table>
Properties of benzene derivatives

**Acidity**
Benzoic acid (pKₐ = 4.2) is more acidic than acetic acid due to resonance stabilization in conjugate base (benzoate ion)

Phenol is weakly acidic (pKₐ = 9.95) due to resonance-stabilized conj. base (phenoxide)

\[
\text{Phenol} + \text{NaOH} \rightarrow \text{Sodium phenoxide}
\]

Anilines are only weakly basic compared to nonaromatic amines because the non-protonated form has greater resonance-stabilization.

In general, electron-withdrawing groups on the ring lower the pKₐ of benzoic acids, phenols, and protonated amines; the stronger the deactivator, the lower the pKₐ

**Pharmacological effects:** Antiinflammatories/analgesics

**Carcinogens:** Many aromatics including benzene have been identified as carcinogens.

**Azobenzenes:** Butter yellow is an azo dye that was used to color margarine until it was found to be carcinogenic.

**Benzo[a]pyrene**
Synthesizing polysubstituted benzene derivatives:  
The order of substituent placement matters!

When making polysubstituted benzenes, consider how the first substituent affects both the **reactivity** and **orientation** of the next substitution.

**Ex:** Friedel-Crafts reaction won’t proceed when the ring contains a deactivator

\[
\text{Y} + \text{R} - \text{X} \underset{\text{AlCl}_3}{\xrightarrow{}} \text{NO reaction} \quad \text{where} \quad \text{Y} = -\text{NR}_3, -\text{NO}_2, -\text{CN}, \\
-\text{SO}_2\text{H}, -\text{CHO}, -\text{COCH}_3 \\
-\text{CO}_2\text{H}, -\text{CO}_2\text{CH}_3 \\
(=\text{NH}_2, =\text{NHR}, =\text{NR}_2)
\]

**Tips in planning synthesis:**
- When ortho or para orientation is desired, activating group goes on first
- When meta orientation is desired, the deactivating group goes on first (provided that it doesn’t completely deactivate the ring)
- Take advantage of methods to convert activating to deactivating groups afterwards, for example CH$_3$ to COOH or NH$_2$ to NO$_2$

**Example:** a multi-step synthesis of p-nitrobenzoic acid

\[
\begin{align*}
\text{CH}_3 & \xrightarrow{\text{CH}_3\text{Cl}, \text{AlCl}_3} \text{CH}_3 \\
\text{HNO}_3 & \xrightarrow{\text{H}_2\text{SO}_4} \text{O}_2\text{N} \\
\text{KMnO}_4 & \xrightarrow{\text{H}_3\text{O}^+} \text{O}_2\text{N} \text{COOH}
\end{align*}
\]

**Preparing tri-substituted benzenes**

When two substituents are already present they may have cooperating or conflicting directing effects on the third substitution. **Ex:** chlorination of these compounds:

- **p-nitrotoluene**

\[
\text{O}_2\text{N} - \text{CH}_3 \\
\text{Cl}_2, \text{FeCl}_3
\]

- **p-chlorophenol**

\[
\text{Cl}\text{O} - \text{OH}
\]

- A strong activator will be the major director over a weaker activator or a deactivator.
- Groups with equal activating ability but conflicting positions produce mixtures.