ELECTROPHILIC AROMATIC SUBSTITUTION

- Above and below the plane of the benzene ring there is a cloud of π electrons. Because of resonance.

- It is not surprising that in its typical reactions the benzene ring serves as a source of electrons, that is, as a base. The compounds with which it reacts are deficient in electrons, that is, are electrophilic reagents or acids. Just as the typical reactions of the alkenes are electrophilic addition reactions, so the typical reactions of the benzene ring are electrophilic substitution reactions.

- These reactions are characteristic not only of benzene itself, but of the benzene ring wherever it is found and, indeed, of many aromatic rings, benzenoid and non-benzenoid.
Electrophilic Aromatic Substitution Reactions

Ar = ary1, any aromatic group with attachment directly to ring carbon

1. Nitration. \[ \text{ArH} + \text{HONO}_2 \xrightarrow{\text{H}_2\text{SO}_4} \text{ArNO}_2 + \text{H}_2\text{O} \]
   A nitro compound

2. Sulfonation
   \[ \text{ArH} + \text{HOSO}_3\text{H} \xrightarrow{\text{SO}_3} \text{ArSO}_3\text{H} + \text{H}_2\text{O} \]
   A sulfonic acid

3. Halogenation
   \[ \text{ArH} + \text{Cl}_2 \xrightarrow{\text{Fe}} \text{ArCl} + \text{HCl} \]
   An aryl chloride
   \[ \text{ArH} + \text{Br}_2 \xrightarrow{\text{Fe}} \text{ArBr} + \text{HBr} \]
   An aryl bromide

4. Friedel-Crafts alkylation
   \[ \text{ArH} + \text{RCl} \xrightarrow{\text{AlCl}_3} \text{ArR} + \text{HCl} \]
   An alkylbenzene
5. Nitrosation

ArH + HONO $\rightarrow$ ArN=O + H₂O

A nitroso compound

Only for highly reactive ArH

6. Diazo coupling

ArH + Ar′N₂ +X⁻ $\rightarrow$ ArN=NAr′ + HX

A diazonium salt An azo compound

Only for highly reactive ArH
Effect of substituent groups

- Like benzene, toluene undergoes electrophilic aromatic substitution: sulfonation

- There are three possible monosulfonation products, this reaction actually yields appreciable amounts of only two of them: the \( o \)- and \( p \)-isomers

\[
\text{Toluene} \xrightarrow{\text{H}_2\text{SO}_4, \text{SO}_3, 35^\circ} \begin{align*}
\text{CH}_3 \text{SO}_3\text{H} & \quad \text{and} \quad \text{CH}_3 \text{SO}_3\text{H} \\
62\% & \quad \text{and} \quad 32\%
\end{align*}
\]

- A group that makes the ring more reactive than benzene is called an **activating group**. A group that makes the ring less reactive than benzene is called a **deactivating group**
A group that causes attack to occur chiefly at positions ortho and para to it is called an ortho, para director. A group that causes attack to occur chiefly at positions meta to it is called a meta director.
Classification of substituent groups

- All groups fall into one of two classes: activating and ortho, para directing, or deactivating and meta-directing. The halogens are in a class by themselves, being deactivating but ortho, para-directing.

Effect of groups on electrophilic aromatic substitution:

**Activating: Ortho,para Directors**
- *Strongly activating*
  - $\text{NH}_2$ (—NHR, —NR$_2$)
  - $\text{OH}$
  - $\text{OCH}_3$ (—OC$_2$H$_5$ etc.)
  - $\text{NCOCH}_3$

- *Moderately activating*
  - $\text{COOH}$ (—COOR)
  - $\text{CN}$
  - $\text{SO}_3\text{H}$

- *Weakly activating*
  - $\text{C}_6\text{H}_5$
  - $\text{CH}_3$ (—C$_2$H$_5$, etc.)

**Deactivating: Meta Directors**
- $\text{NO}_2$
- $\text{N(CH}_3)_3^+$
- $\text{CN}$
- $\text{COOH}$ (—COOR)
- $\text{SO}_3\text{H}$
- $\text{CHO}$, $\text{COR}$

**Deactivating: Ortho,para Directors**
- $\text{F}$, $\text{Cl}$, $\text{Br}$, $\text{I}$
Orientation in disubstituted benzenes

- The two substituents may be located so that the directive influence of one *reinforces* that of the other; for example, in I, II, and III the orientation clearly must be that indicated by the arrows.

- When the directive effect of one group *opposes* that of the other, it may be difficult to predict the major product; in such cases complicated mixtures of several products are often obtained.
(a) Strongly activating groups generally win out over deactivating or weakly activating groups. The differences in directive power in the sequence

\[-\text{NH}_2, -\text{OH} > -\text{OCH}_3, -\text{NHCOCH}_3 > -\text{C}_6\text{H}_5, -\text{CH}_3 > \text{meta directors}\]
There must be, however, a fairly large difference in the effects of the two groups for clear-cut results; otherwise one gets results like these:

(b) There is often little substitution between two groups that are meta to each other.
Orientation and synthesis

- A laboratory synthesis is generally aimed at obtaining a single, pure compound.
- A goal of aromatic synthesis is control of orientation: the preparation, at will and from the same substrate, of a pure ortho, a pure meta, or a pure para isomer.
- First of all, we must consider the order in which we introduce these various substituents into the ring. In the preparation of the bromonitrobenzenes, for example:
If our synthesis involves conversion of one group into another, For example, oxidation of a methyl group yields a carboxyl group.

\[
\begin{align*}
\text{CH}_3 \quad \text{Toluene} \\
\text{KMnO}_4 \quad \rightarrow \\
\text{NO}_2 \quad \text{COOH} \\
\text{HNO}_3, \text{H}_2\text{SO}_4 \\
\text{COOH} \\
\text{CH}_3 \quad \text{NO}_2 \\
\text{K}_2\text{Cr}_2\text{O}_7 \\
\text{COOH} \\
\text{NO}_2 \\
\text{K}_2\text{Cr}_2\text{O}_7 \\
\text{p-Nitrobenzoic acid} \\
\text{CH}_3 \\
\text{NO}_2 \\
\text{O-Nitrobenzoic acid} \\
\end{align*}
\]
Substitution Reactions of Benzene and Its Derivatives

- Benzene is aromatic: a cyclic conjugated compound with 6 $\pi$ electrons
- Reactions of benzene lead to the retention of the aromatic core

Diagram:
- Halogenation
- Nitration
- Sulfonation
- Acylation
- Alkylation
- Hydroxylation
Mechanism of nitration

- The combination of nitric acid and sulfuric acid produces \( \text{NO}_2^+ \) (nitronium ion)
- The reaction with benzene produces nitrobenzene

\[
\begin{align*}
\text{Nitric acid} \quad & \quad \text{Nitronium ion} \\
\begin{array}{c}
\text{H}_3\text{O}^+ - \text{OH}^- \\
\text{H}_2\text{O} \\
\text{H}_2\text{O} + \text{NO}^+
\end{array}
\end{align*}
\]

- Just what is the structure of this carbonium ion? We find that we can represent
- It by three structures (I, II, and III) that differ from each other only in position of double bonds and positive charge.
The Nitro group can be reduced to an Amino group if needed

Substitution of H by SO$_3$ (sulfonation)

Reaction with a mixture of sulfuric acid and SO$_3$ (“Fuming H$_2$SO$_4$”)

Reactive species is sulfur trioxide or its conjugate acid
Mechanism of Friedel-Crafts alkylation

- Friedel-Crafts alkylation is an electrophilic aromatic substitution in cation acts as the electrophile which an alkyl
Step 1: Formation of a carbocation.

\[
\text{CH}_3\text{C-Cl}^+: \text{Al-Cl} \rightleftharpoons \text{CH}_3\text{C}^+ \text{AlCl}_3
\]

\text{t-butyl chloride}

\text{t-butyl cation}

Step 2: Electrophilic attack forms a sigma complex.

\[
\begin{align*}
\text{CH}_3\text{C-CH}_3 + \text{C}^+ & \rightarrow \text{CH}_3\text{C}^+\text{CH}_3
\end{align*}
\]

\text{sigma complex}

Step 3: Loss of a proton regenerates the aromatic ring and gives the alkylated product.

\[
\begin{align*}
\text{CH}_3\text{C-CH}_3 + \text{AlCl}_3 & \rightarrow \text{CH}_3\text{C-CH}_3
\end{align*}
\]

\text{CH}_3\text{C-CH}_3 + \text{AlCl}_3 + \text{HCl}

\text{alkylated product}
In certain cases, there is no free carbonium ion involved. Instead, the alkyl group is transferred -without a pair of electrons- directly to the aromatic ring from the polar complex, I, between AlCl$_3$ and the alkyl halide:
Mechanism of halogenation

- The bromination or chlorination of benzene requires a Lewis acid such as ferric bromide or ferric chloride.

In the first step of the bromination reaction, bromine donates a lone pair to the Lewis acid. This weakens the Br-Br bond, thereby providing the electrophile necessary for electrophilic aromatic substitution.
In the last step of the reaction, a base from the reaction mixture removes a proton from the carbocation intermediate. The following equation shows that the catalyst is regenerated:
Mechanism of Friedel-Crafts Acylation

- Similar to alkylation
- Reactive electrophile: resonance-stabilized acyl cation
- An acyl cation does not rearrange

Can reduce carbonyl to get alkyl product
Reactivity and orientation

- We have seen that certain groups activate the benzene ring and direct substitution to ortho and para positions, and that
- Other groups deactivate the ring and (except halogens) direct substitution to meta positions.
- Methyl is said to activate the ring because it makes the ring react faster than benzene; it causes ortho, para orientation because it makes the ortho and para positions react faster than the meta positions.
- ***The rate of electrophilic aromatic substitution is determined by the same slow step-attack of the electrophile on the ring to form a carbonium ion:
****Any differences in rate of substitution must therefore be due to differences in the rate of this step.

In electrophilic aromatic substitution the intermediate carbonium ion is a hybrid of structures I, II, and III, in which the positive charge is distributed about the ring, being strongest as the positions ortho and para to the carbon atom being attacked.

***A group already attached to the benzene ring should affect the stability of the carbonium ion by dispersing or intensifying the positive charge, depending upon its electron-releasing (activating) or electron-withdrawing nature (deactivating).
Theory of reactivity

To compare rates of substitution in benzene, toluene, and nitrobenzene, we compare the structures of the carbonium ions formed from the three compounds:

- By releasing electrons, the methyl group (II) tends to neutralize the positive charge of the ring and so become more positive itself; this dispersal of the charge stabilizes the carbonium ion. In the same way the inductive effect stabilizes the developing positive charge in the transition state and thus leads to a faster reaction.
The -NO₂ group, on the other hand, has an electron-withdrawing inductive effect (III); this tends to intensify the positive charge, destabilizes the carbonium ion, and thus causes a slower reaction.
Reactivity in electrophilic aromatic substitution depends, then, upon the tendency of a substituent group to release or withdraw electrons. A group that releases electrons activates the ring; a group that withdraws electrons deactivates the ring.

Electrophilic Aromatic Substitution

\[
\begin{align*}
\text{G releases electrons:} & \quad \text{stabilizes carbonium ion, activates} \\
+ & \\
\text{G withdraws electrons:} & \quad \text{destabilizes carbonium ion, deactivates}
\end{align*}
\]

- \( G = \text{--NH}_2 \)
- \( \text{--OH} \)
- \( \text{--OCH}_3 \)
- \( \text{--NHCOCH}_3 \)
- \( \text{--C}_6\text{H}_5 \)
- \( \text{--CH}_3 \)
- \( \text{--N(CH}_3)_3^+ \)
- \( \text{--NO}_2 \)
- \( \text{--CN} \)
- \( \text{--SO}_3\text{H} \)
- \( \text{--COOH} \)
- \( \text{--CHO} \)
- \( \text{--COR} \)
- \( \text{--COR} \)
- \( \text{--X} \)
We might expect replacement of hydrogen in -CH₃ by halogen to decrease the electron-releasing tendency of the group, and perhaps to convert it into an electron-withdrawing group.
Theory of orientation

- An activating group activates all positions of the benzene ring; even the positions meta to it are more reactive than any single position in benzene itself. It directs ortho and para simply because it activates the ortho and para positions much more than it does the meta.

- A deactivating group deactivates all positions in the ring, even the positions meta to it. It directs meta simply because it deactivates the ortho and para positions even more than it does the meta.

- Thus both ortho, para orientation and meta orientation arise in the same way: the effect of any group whether activating or deactivating is strongest at the ortho and para positions.
Para attack

Especially stable:
charge on carbon carrying substituent

Meta attack

Ortho attack

Especially stable:
charge on carbon carrying substituent
compare the carbonium ions formed by attack at the *para* and *meta* positions of nitrobenzene

Each of these is a hybrid of three structures, X-XII for *para* attack, XI-XV for *meta* attack. In one of the six structures, XI, the positive charge is located on the

 Especially unstable:
charge on carbon carrying substituent

*Para attack*

*Meta attack*
In nitrobenzene, *ortho*-*para* substitution is thus slower than *meta* substitution because electron withdrawal by -NO$_2$ is more effective during attack at the positions *ortho* and *para* to it.

**Electron release via resonance**

Groups (-NH$_2$ and -OH, and their derivatives) act as powerful activators toward electrophilic aromatic substitution, even though they contain electronegative atoms and can be shown in other ways to have electron-withdrawing inductive effects.
They are believed to do this by a resonance effect.

That nitrogen and oxygen can share more than a pair of electrons with the ring and can accommodate a positive charge.

Para attack

Especially stable:
every atom has octet

Meta attack
Examination of the corresponding structures (VIII-XI) shows that *ortho* attack is much like *para* attack:

- Thus substitution in aniline occurs faster than substitution in benzene, and occurs predominantly at the positions ortho and para to $-\text{NH}_2$.

- In the same way activation and *ortho*, *para* orientation by the $-\text{OH}$ group is accounted for by contribution of structures like XII and XIII, in which every atom has a complete octet of electrons:
The similar effects of the derivatives of -NH₂ and -OH are accounted for by similar structures (shown only for para attack):
Effect of halogen on electrophilic aromatic substitution

- Halogens are unusual in their effect on electrophilic aromatic substitution: they are deactivating yet ortho, para-directing

- Can halogen both withdraw and release electrons?

- Halogen withdraws electrons through its inductive effect, and releases electrons through its resonance effect.

- but there the much stronger resonance effect greatly outweighs the other.

![Diagram](image_url)
The electron withdrawing inductive effect of chlorine intensifies the positive charge in carbonium ion II, makes the ion less stable, and causes a slower reaction.

To understand orientation, we compare the structures of the carbonium ions formed by attack at the para and meta positions of chlorobenzene.

- **Para attack**
  - Especially unstable: charge on carbon bearing substituent

- **Meta attack**
the existence of halonium ions has shown us that halogen can share more than a pair of electrons and can accommodate a positive charge.

This structure should be comparatively stable, since in it every atom (except hydrogen, of course) has a complete octet of electrons.
In the same way it can be seen that attack at an ortho position also yields an ion (X-X1II) that can be stabilized by accommodation of the positive charge by chlorine.

\[ \text{Ortho attack} \]

- Especially unstable:
  - charge on carbon bearing substituent

- Comparatively stable:
  - every atom has octet
Arenes

- Aliphatic-aromatic hydrocarbons
  - Important compounds are contain both aliphatic and aromatic units; hydrocarbons of this kind are known collectively as arenes for example:

    ![Ethylbenzene](image1)

    - The ring of ethylbenzene should undergo the electrophilic substitution characteristic of benzene, and the side chain should undergo the free radical substitution characteristic of ethane

    ![Chemical reactions](image2)

    - More readily than for benzene

    Chief products:
    - o-Nitroethylbenzene
    - p-Nitroethylbenzene
Thus each portion of the molecule affects the reactivity of the other portion and determines the orientation of attack.

Structure and nomenclature

The simplest of the alkylbenzenes, methylbenzene, is given the special name of toluene.
Compounds containing longer side chains are named by prefixing the name of the alkyl group to the word - *benzene*

- Toluene
- Ethylbenzene
- *n*-Propylbenzene
- Isobutylbenzene

The simplest of the dialkylbenzenes, the dimethylbenzenes, are given the special names of *xylenes*

- *α*-Xylene
- *m*-Xylene
- *p*-Xylene
Dialkylbenzenes containing one methyl group are named as derivatives of toluene.

Others are named by prefixing the names of both alkyl groups to the word -benzene.

A compound containing a very complicated side chain might be named as a phenylalkane ($C_6H_5 = \text{phenyl}$).
Compounds containing more than one benzene ring are nearly always named as derivatives of alkanes.

The simplest alkenylbenzene has the special name styrene. Others are generally named as substituted alkenes, occasionally as substituted benzenes. Alkynylbenzenes are named as substituted alkynes.
Physical properties

- As compounds of low polarity, the alkylbenzenes possess physical properties that are essentially the same as those of the hydrocarbons.

- They are insoluble in water, but quite soluble in non-polar solvents like ether, carbon tetrachloride.

- They are almost always less dense than water.

- Boiling points rise with increasing molecular weight, the boiling point increment being the usual 20-30° for each carbon atom.
Preparation of alkylbenzenes

1. Attachment of alkyl group: Friedel-Crafts alkylation.

\[
\text{Ar} + RX \xrightarrow{\text{Lewis acid}} \text{Ar}^+X^- + HX \quad \text{R may rearrange}
\]

Lewis acid: \(\text{AlCl}_3, \text{BF}_3, \text{HF}, \text{etc.}\)
\(\text{Ar}-X\) cannot be used in place of \(R-X\)

polyhalogenated alkanes it is possible to prepare compounds containing more than one aromatic ring

\[
2\text{C}_6\text{H}_6 + \text{CH}_2\text{Cl}_2 \xrightarrow{\text{AlCl}_3} \text{C}_6\text{H}_5\text{CH}_2\text{C}_6\text{H}_5 + 2\text{HCl} \\
\text{Diphenylmethane}
\]

\[
2\text{C}_6\text{H}_6 + \text{ClCH}_2\text{CH}_2\text{Cl} \xrightarrow{\text{AlCl}_3} \text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5 + 2\text{HCl} \\
1,2-\text{Diphenylethane}
\]
mechanism for Friedel-Crafts alkylation involves the following steps

1. $\text{RCI} + \text{AlCl}_3 \rightleftharpoons \text{AlCl}_4^- + \text{R} \cdot \omega$

2. $\text{R} \cdot \omega + \text{C}_6\text{H}_6 \rightleftharpoons \text{C}_6\text{H}_5^-$

3. $\text{C}_6\text{H}_5^- + \text{AlCl}_4^- \rightleftharpoons \text{C}_6\text{H}_5\text{R} + \text{HCl} + \text{AlCl}_3$
We might expect the benzene ring to be attacked by carbonium ions generated in other ways: by the action of acid on alcohols and on alkenes.

$$\text{ROH} + \text{H}^+ \rightleftharpoons \text{ROH}^+ \rightleftharpoons \text{R}^+ + \text{H}_2\text{O}$$

Carbonium ions from alcohols and from alkenes

$$\text{C}_6\text{H}_6 + (\text{CH}_3)_3\text{COH} \xrightarrow{\text{H}_2\text{SO}_4} \text{C}_6\text{H}_5-\text{C}(\text{CH}_3)_3$$

*tert*-Butyl alcohol

$$\text{C}_6\text{H}_6 + (\text{CH}_3)_2\text{C}=\text{CH}_2 \xrightarrow{\text{H}_2\text{SO}_4} \text{C}_6\text{H}_5-\text{C}(\text{CH}_3)_3$$

Isobutylene

*tert*-Butylbenzene
We might expect Friedel-Crafts alkylation to be accompanied by the kind of rearrangement that is characteristic of carbonium ion reactions.
2. Conversion of side chain.

Clemmensen or Wolff-kishner reaction

Reactions of alkylbenzenes

1. Hydrogenation
2. Oxidation.

- This reaction is used for two purposes:
- Synthesis of carboxylic acids

- Ethylbenzene
- $\text{CH}_2\text{CH}_3 \xrightarrow{\text{KMnO}_4} \text{COOH} \quad (+\text{CO}_2)$
- Benzoic acid
- $n$-Butylbenzene
- $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \xrightarrow{\text{hot KMnO}_4} \text{COOH} \quad \text{and CO}_2$
- Benzoic acid

- $p$-Xylene
- $\text{CH}_3 \xrightarrow{\text{KMnO}_4} \text{COOH}$
- Terephthalic acid
- (1,4-Benzenedicarboxylic acid)
- $p$-Nitrotoluene
- $\text{NO}_2 \xrightarrow{\text{Cr}_2\text{O}_7^{2-}, \text{H}^+} \text{COOH}$
- $p$-Nitrobenzoic acid
Identification of alkylbenzenes

- $\text{o-Xylene (b.p. 144^\circ)}$ → Phthalic acid, m.p. 231$^\circ$

- $\text{p-Xylene (b.p. 138^\circ)}$ → Terephthalic acid, m.p. 300$^\circ$ subl.

- $\text{m-Xylene (b.p. 139^\circ)}$ → Isophthalic acid, m.p. 348$^\circ$

- Ethylbenzene (b.p. 136 ) → Benzoic acid, m.p. 122$^\circ$

- The ring and the side chain. We can control the position of attack simply by choosing the proper reaction conditions.