Chapter 16: Reactions of Substituted Benzenes

Learning Objectives:

1. Be able to recognize and utilize the oxidative and reductive reactions involving the substituents on benzene.
2. Recognize whether a substituent on a benzene ring is activating or deactivating toward electrophilic aromatic substitution reaction, and why it is so.
3. Predict the effect a substituent will have on the regioselectivity of an electrophilic substitution reaction.
4. Predict the effect a substituent will have on $pK_a$.
5. Be able to design the synthesis of a multisubstituted benzene.
6. Be able to recognize and utilize the reactions involving arenediazonium salts.
7. Recognize and be able to write the mechanism of nucleophilic aromatic substitution.
8. Recognize the structure of benzyne, be able to explain how it is formed, and how it reacts.

Sections:

16.1 Nomenclature of Disubstituted and Polysubstituted Benzenes
16.2 Reactions of Substituents on Benzene
16.3 The Effect of Substituents on Reactivity*
16.4 The Effect of Substituents on Orientation (Regioselectivity)*
16.5 The Effect Substituent on $pK_a$
16.6 The Ortho-para ratio
16.7 Additional Considerations Regarding Substituent Effects
16.8 Designing a Synthesis III: Synthesis of monosubstituted and Disubstituted Benzenes*
16.9 Synthesis of Trisubstituted Benzenes
16.10 Synthesis of Substituted Benzenes Using Arenediazonium Salts*
16.11 The Arenediazonium Ion as an Electrophile*
16.12 Mechanism for the Reaction of Amines with Nitrous Acid*
16.13 Nucleophilic Aromatic Substitution Reactions*
16.14 Benzyne
16.15 Polycyclic Benzenoid Hydrocarbons#
16.16 Electrophilic Substitution Reactions of Naphthalene and Substituted Naphthalene#

* Sections that will be focused
# Sections that will be skipped

Recommended additional problems

16.36 – 6.41, 6.43 – 6.55, 6.57 – 6.60, 6.62 – 6.68
Class Note

16.1 Nomenclature of Disubstituted and Polysubstituted Benzenes

\[
\begin{align*}
&\text{Br} \quad \text{Br} \\
&\text{Br} \quad \text{NO}_2 \\
&\text{Br} \quad \text{OH} \\
&\text{Br} \quad \text{CH}_3 \\
&\text{Cl} \quad \text{Br} \\
&\text{Cl} \quad \text{Br} \\
&\text{Cl} \quad \text{Br} \\
&\text{Cl} \quad \text{Br} \\
&\text{Cl} \quad \text{Br} \\
&\text{Cl} \quad \text{Br} \\
&\text{Cl} \quad \text{Br} \\
&\text{Cl} \quad \text{Br} \\
\end{align*}
\]
16.2 Reactions of Substituents on Benzene

A. Reactions of Alkyl Substituents
B. Oxidations of Alkyl Substituents

1. KMnO$_4$, heat (reflux)

2. H$^+$

$\text{Na}_2\text{Cr}_2\text{O}_7$, H$^+$, heat
\[
\text{Na}_2\text{Cr}_2\text{O}_7, \text{H}^+, \text{heat}
\]

\[
\text{Na}_2\text{Cr}_2\text{O}_7, \text{H}^+, \text{heat}
\]

\[
\text{Na}_2\text{Cr}_2\text{O}_7, \text{H}^+, \text{heat}
\]

\[
\text{MnO}_2 \\
\text{(no heating needed)}
\]

\[
\text{Na}_2\text{Cr}_2\text{O}_7, \text{H}^+, \text{heat}
\]
C. Reduction of Nitro Group

\[
\text{H}_2, \text{Pt} \quad \text{Sn, HCl} \quad \text{Fe, HCl}
\]

16.3 The Effect of Substituents on Reactivity and 16.4 The Effect of Substituents on Orientation (Regioselectivity)

electron donation group (EDG)

electron withdrawing group (EWG)
A. Relative rate of electrophilic aromatic substitution

Examples:

- Rate-determining step (r.d.s)
- Resonance effect and inductive effect
B. Relative reactivity and regioselectivity of substituted benzenes

Strong activating groups (substituents)

Moderate activating groups (substituents)
Weak activating groups (substituents)

\[ R \]

Weak deactivating groups (substituents)

\[ F \]
\[ Cl \]
\[ Br \]
\[ I \]
Moderate deactivating groups (substituents)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{R} \\
\text{O} & \quad \text{OR} \\
\text{O} & \quad \text{HNR} \\
\end{align*}
\]
Strong deactivating groups (substituents)

- $\text{SO}_3\text{H}$
- $\text{NO}_2$
- $\text{CN}$
- $\text{NR}_3^+$
C. Examples (combined with 16.6 The Ortho-para ratio and 16.7 Additional Considerations Regarding Substituent Effects)

(i)

\[
\begin{align*}
\text{CH}_3 & \quad \text{Br}_2, \text{FeCl}_3 \\
& \quad \text{HNO}_3, \text{H}_2\text{SO}_4
\end{align*}
\]

(ii)

\[
\begin{align*}
\text{CH}_3 & \quad \text{HNO}_3, \text{H}_2\text{SO}_4 \\
\text{CH}_2\text{CH}_3 & \quad \text{HNO}_3, \text{H}_2\text{SO}_4 \\
\text{C(CH}_3)_3 & \quad \text{HNO}_3, \text{H}_2\text{SO}_4
\end{align*}
\]
(iii) 

\[ \text{Br} \quad \text{Cl}_2, \text{FeCl}_3 \]

(iv) 

\[ \text{Br}_2 \text{ (1 equivalent)} \quad \text{FeCl}_3 \]

\[ \text{Br}_2 \text{ (excess)} \quad \text{FeCl}_3 \]
(vii) Synthesis of trinitrotoluene

\[
\text{CH}_3 \quad \xrightarrow{\text{HNO}_3, \text{H}_2\text{SO}_4} \quad \text{H}_2\text{SO}_4
\]
16.5 The Effect Substituent on pKa
16.8 Designing a Synthesis III: Synthesis of monosubstituted and Disubstituted Benzenes and 16.9 Synthesis of Trisubstituted Benzenes

**Design multiple-step synthesis:**

* Selectivity: chemoselectivity, regioselectivity, and stereoselectivity
* Retrosynthetic analysis: breaking and formation of chemical bonds
A. Examples

(i)

\chem{\text{from}} \quad \text{from} \quad \text{from}
(ii) 

\[
\text{CH}_3\text{O} \quad \text{from} \quad \text{C}_6\text{H}_6
\]

(iii) 

\[
\text{NO}_2 \quad \text{from} \quad \text{C}_6\text{H}_6
\]
A. Formation of diazonium salt

\[
\text{NaNO}_2, \text{HCl} \quad 0^\circ \text{C} \quad R\text{NH}_2 \rightarrow R\text{N}^+\text{N}^-\text{Cl}^- \quad \text{diazonium salt}
\]

Mechanism:
B. Reaction of arenediazonium salt with nucleophiles

**Sandmeyer reaction (CuBr, CuCl, and CuCN)**

Reaction with KI, HBF$_4$, H$_3$O$^+$, and H$_3$PO$_2$
16.11  The Arenediazonium Ion as an Electrophile

* Nucleophile better be bulky
* Terminal nitrogen reacts with nucleophile
16.13 Nucleophilic Aromatic Substitution ($S_{\text{Ar}}$) Reactions

A. Comparison of $S_{\text{Ar}}$, $S_{\text{N1}}$, and $S_{\text{N2}}$

B. General mechanism
C. Examples

(i)

\[
\begin{align*}
\text{Cl} \quad \text{NO}_2 & \quad \xrightarrow{\Theta OH} \quad \text{OH} \\
\text{NO}_2 & \\
\text{Cl} \quad \text{NO}_2 & \quad \xrightarrow{\Theta OH} \quad \text{OH} \\
\text{NO}_2 & \\
\text{O}_2 & \\
\text{NO}_2 & \quad \xrightarrow{\Theta OH} \quad \text{OH} \\
\text{NO}_2 & \quad \xrightarrow{\Theta OH} \quad \text{OH} \\
\end{align*}
\]

(ii)

\[
\begin{align*}
\text{Br} \quad \text{NO}_2 & \quad \xrightarrow{\text{CH}_3\text{CH}_2\text{NH}_2} \quad \xrightarrow{\Theta OH} \quad \text{NHCH}_2\text{CH}_3 \\
\text{NO}_2 & \\
\end{align*}
\]
16.14 Benzyne