Chapter 14 - 4th ed.

CHEM 322 Organic Chemistry II - Professor Kathleen V. Kilway
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Chapter 14 Homework: 1, 2, 5, 7, 13, 19, 20, 23, 26, 27, 28, 30, 31, 34, 35, 36, 41, 46, 54, 55, 56, 57, 58, 60.

CHAPTER 14 Substitution Reactions of Aromatic Compounds

Section 14.1

I. Preview

A- Aromatic compounds are stable
1- So it takes energy to destroy the aromaticity and is relatively easy to regain it.
2- Therefore, these compounds have high energy barriers for reactions.
3- In this chapter, we will learn the how and why of reaction on aromatic compounds.
4- In the general reaction of aromatic compounds, an electrophile, a "lover of electrons" (or Lewis Acid), substitutes for one of the hydrogens on a benzene ring.
5- The general reaction is given below. Note that the aromatic sextet is retained.

\[
\text{E}^+\text{B}^- + \text{C}_6\text{H}_6 \rightarrow \text{E}\text{C}_6\text{H}_5\text{B}^- + \text{BH}
\]

Figure 1. General reaction for electrophilic aromatic substitution.

B- Essential Skills and Details

1- The overall product of these reactions are substituted arenes (aromatic compounds).
2- All of these reactions follow a similar mechanism: generation of electrophile, attack of one of the \(\pi\) bonds of the aromatic ring with the electrophile forming a resonance-stabilized cyclohexadienyl intermediate, then regeneration of the aromatic system (6 \(\pi\) electrons).
3- Some substituents direct the next reactants to the ortho/para or meta positions.
4- It is important to understand where the positive charge resides in the cyclohexadienyl intermediate - only on three carbons of the ring - not all six.
5- Nitrobenzene and aminobenzene (aniline) are important intermediates in synthesis.
6- Carbon-carbon bonds are made in both the Friedel-Crafts alkylation and acylation.
Section 14.2

II. Hydrogenation of Aromatic Compounds

A- Benzene is both thermodynamically and kinetically very stable.

1- Only high temperature, pressure and/or a very active catalyst such as rhodium, ruthenium or platinum oxide. See Figure 14.6b on page 627.

![Figure 2. Hydrogenation of benzene.](attachment:image)

Figure 2. Hydrogenation of benzene.

Section 14.3

III. Diels-Alder Reactions

A- Diels-Alder reactions do not normally occur with benzene.

1- It contains a conjugated π system.

2- The activation energy for this reaction with benzene (or any other aromatic compound) is very high.

3- Resonance energies of some aromatic compounds are as follows: benzene 33 kcal/mol; thiophene 29 kcal/mol; pyridine 23 kcal/mol; and furan 13 kcal/mol (Table 14.1, p. 629).

4- This activation energy can be overcome with harsh conditions (high temperatures) and very reactive dienophiles or dienes (Fig 3).

![Figure 3. Conditions required for Diels-Alder reactions of aromatic compounds.](attachment:image)
Section 14.4
IV. Substitution Reactions of Aromatic Compounds

1- The addition of HBr to benzene logically should give a cyclohexadienyl bromide.
2- Although this is not the case, the speculation of how this reaction would occur shows which carbons share the delocalized positive charge generated by the hypothetical proton or halide.

![Figure 4. Issue of loss of aromaticity under normal H-Br addition to a double bond.]

B- Electrophilic Deuteration of Benzene
1- The way benzene and other aromatic systems do react is by preserving the aromatic sextet.
2- Benzene does not react by addition.
   a- It would destroy the aromatic stabilization.
   b- Aromatic compounds react by substitution reactions.
   c- These preserve the stability of the aromatic sextet (i.e., overall it remains aromatic).
3- Previous example is the reaction of benzene with D₂SO₄.

![Figure 5. General Reaction for deuteration of benzene.]

a- The exchange reaction of benzene in deuterated acid is one of the simplest examples.
b- The electrophile, E⁺ is the deuterated acid.
c- The D is substituted for a hydrogen on the ring.
d- This type of a reaction is called **electrophilic aromatic substitution**.
e- The σ system of the benzene ring acts as the nucleophile, and as in the exchange reaction of D for H.
f- The reaction is completed by the removal of a proton from the intermediate cyclohexadienyl cation by a base, regenerating the aromatic benzene ring.
C- Other Electrophilic Substitution Reactions of Benzene: The General Reaction (Figure 6)

Figure 6. General Reaction for addition of an electrophile.

1- The general 3-step process occurs as follows:
   a- Generate the electrophile if it is not already present.
   b- Attack of the nucleophile (π bond of aromatic ring).

![Figure 7. Addition of the electrophile.](image)

![Figure 8. Regeneration of aromatic ring.](image)
D- Sulfonation

1- Benzene can be treated with a very concentrated sulfuric acid to give benzenesulfonic acid in a reversible reaction.

2- Overall reaction

\[ \text{C}_{6}\text{H}_{6} + 99\% \text{H}_2\text{SO}_4 \rightarrow \text{C}_{6}\text{H}_{4}\text{SO}_3\text{H} \]

Figure 9. General Reaction for sulfonation of benzene.

3- Mechanism

  a- Step 1 - electrophile is generated
  b- Step 2 - nucleophilic attack

\[ \text{C}_{6}\text{H}_{4}\text{SO}_3\text{H} \rightarrow \text{C}_{6}\text{H}_{4}\text{SO}_3\text{H} \]

Figure 10. Nucleophilic attack.

  c- Step 3 - regeneration of aromatic system

\[ \text{C}_{6}\text{H}_{4}\text{SO}_3\text{H} \rightarrow \text{C}_{6}\text{H}_{4}\text{SO}_2\text{H} \]

Figure 11. Regeneration of aromatic ring.

4- This reaction is reversible.

\[ \text{C}_{6}\text{H}_{4}\text{SO}_3\text{H} \xrightarrow{\text{H}_2\text{O}^{+} + \text{heat}} \text{C}_{6}\text{H}_{6} + \text{H}_2\text{SO}_4 \]

Figure 12. Reversible sulfonation reaction.
E- Nitrations

1- Benzene can be treated with a nitric acid to give nitrobenzene.

2- Overall reaction

\[
\text{C}_6\text{H}_6 + \text{HNO}_3 + \text{H}_2\text{SO}_4 \rightarrow \text{C}_6\text{H}_5\text{NO}_2 + 80-90\% \text{ yield}
\]

Figure 13. General Reaction for nitration of benzene.

3- Mechanism

a- Step 1 - generation of electrophile

\[
\text{H}_2\text{O} + \text{HNO}_2 \rightarrow \text{H}_2\text{O} + \text{NO}_2^-
\]

Figure 14. Generation of electrophile \(\text{NO}_2^\cdot\).

b- Step 2- nucleophilic attack

Figure 15. Nucleophilic attack.

c- Step 3 - regeneration of aromatic system.

Figure 16. Regeneration of the aromatic ring.

d- Other conditions where the electrophile is generated.
F- Halogenation

1- Benzene can be reacted with $X_2$ and a Lewis acid to give halobenzene.
2- Reaction requires a Lewis acid usually where the $X$ of the acid ($MX_3$) is the same as the $X_2$.
3- This works because $X_2$ is a weak acid. The Lewis acid converts the $X_2$ to a more active acid (electrophile) which reacts with benzene.
4- Overall reaction

![Figure 18](image)

Figure 18. General reaction of chlorination of benzene.

5- Mechanism
   a- Step 1 - generation of electrophile

![Figure 19](image)

Figure 19. Generation of the electrophile.

b- Step 2 - nucleophilic attack.

![Figure 20](image)

Figure 20. Nucleophilic attack.

c- Step 3 - regeneration of the aromatic system.

![Figure 21](image)

Figure 21. Regeneration of the aromatic system for the chlorination reaction.
Section 14.5
V. The Friedel-Crafts Alkylation Reaction

A- Benzene can be alkylated with a variety of alkyl halides, including methyl-, ethyl-, isopropyl-, and tert-butyl chlorides and bromides.

1- Requires a complex (formed from the alkylhalide and a Lewis acid catalyst).
2- Typically examples of LA catalysts are FeCl₃ or FeBr₃ and the corresponding Al versions.
3- A catalytic amount of the Lewis acid is needed because it is regenerated in the final step.

B- Overall Reaction

\[ \text{C}_{6}H_{6} + \text{Br} \rightleftharpoons \text{AlBr}_{3} \rightarrow \text{C}_{6}H_{6} - \text{alkyl} \text{100\% yield} \]

Figure 21. Overall alkylation reaction.

C- Mechanism

a- Step 1 - generation of electrophile

\[ \text{Br} + \text{AlBr}_{3} \rightleftharpoons \text{Br-AlBr}_{3} \leftrightarrow \text{Br-AlBr}_{3} \]

Figure 22. Generation of the electrophile.

b- Step 2 - nucleophilic attack

\[ \text{AlBr}_{3} \rightarrow \text{H} \]

Figure 23. Nucleophilic attack.

c- Step 3 - regeneration of aromatic system.
D- The electrophile can exist as a cation (see below).

Figure 25. Reaction forming tert-butylbenzene using cation as electrophile.

E- Problems with this reaction

1- Linear alkyl halides may produce multiple products (see below).

Figure 26. General reaction where rearrangements occur.

2- The problem is in the generation of the electrophile.
Section 14.6

VI. Friedel-Crafts Acylation

A- A reaction related to Freidel-Crafts Alkylation uses a functional group known as an acyl group (RC=O) and acyl chloride (RCOCl), also known as an acid chloride.

\[
\text{acyl group}
\]

1- Acid chlorides can be synthesized by reacting carboxylic acids, RCOOH, with thionyl chloride (SOCl₂).

\[
\begin{align*}
\text{carboxylic acid} & \quad \xrightarrow{\text{Cl}_2\text{SO}} \quad \text{acid chloride} \\
\text{RCOOH} + \text{Cl}_2\text{SO} & \quad \rightarrow \quad \text{RCOCl} + \text{SO}_2
\end{align*}
\]

Figure 28. Reaction conditions to form acyl chloride.

B- Overall Reaction

\[
\begin{align*}
\text{benzene} & \quad \xrightarrow{1 \text{HCl} + \text{AlCl₃}} \quad \text{benzil} \\
\text{C₆H₆} & \quad \xrightarrow{\text{AlCl₃} + \text{H₂O}} \quad \text{C₆H₆Cl}
\end{align*}
\]

Figure 29. Overall reaction for the acylation reaction.

C- Mechanism

\[
\begin{align*}
\text{Step 1} & \quad \text{generation of electrophile (acylum ion)}
\end{align*}
\]
Figure 30. Generation of the electrophile.

b- Step 2 - nucleophilic attack

Figure 31. Nucleophilic attack.

c- Step 3 - regeneration of aromatic system

Figure 32. Generation of aromatic ring.

D- These reactions are not complicated by hydride shifts.

Figure 33. Two step reaction to synthesize alkylated aromatic compounds.
1- Acylates once.

2- The reduce the carbonyl by either a Clemmensen or Wolff-Kishner reduction (reagents: NH₂NH₂, NaOH or KOH, glyme or diethylene glycol, heat.

3- No rearrangements.
Section 14.7

VII. Summary of Simple Aromatic Substitutions: What We Can Do So Far

A- In total, there are six EAS that you know. They are summarized below:

![Diagram of aromatic substitution reactions]

Figure 34. Overall summary of reactions so far.
B- Sandmeyer Reaction

1- An aromatic nitro group can be reduced to the amine.
2- Nitrobenzene can be reduced to aniline either by hydrogenation (H₂/Pd/C in ethanol) or metal catalyst (Sn/HCl followed by basic workup)

\[
\text{NO}_2 + \text{H}_2 + \text{Pd} + \text{C} + \text{EtOH} \rightarrow \text{NH}_2
\]

or

1) Sn / HCl
2) OH, H₂O

Figure 35. Reduction of nitro group to amine.

3- The amino group can be treated with nitrous acid (HONO) or its sodium salt (NaONO) and HCl to give a diazonium ion (or salt).

\[
\text{NH}_2 + \text{NaONO} + \text{HCl} \rightarrow \text{N}_2^+ \text{Cl}^-
\]

Figure 36. Reaction to form the diazonium salt.

4- The diazonium ion is a critical intermediate, which can be converted into many other groups in the Sandmeyer reaction.
Figure 37. Reaction of the diazonium salt to other substituents.

5. Exact mechanism not known.
Section 14.8
IX. Electrophilic Aromatic Substitution of Heteroaromatic Compounds

A- Reactions of Pyridine and Pyrrole.

1- The reaction products are different with heteroaromatic compounds than with benzene.

![Generic substitution pattern for pyridine and pyrrole](image)

Figure 38. Generic substitution pattern for pyridine and pyrrole.

2- The possible products are depicted in Figure 38.

3- For pyridine, substitution at position 3 is the only product observed because there is no resonance structure which places a positive charge on the nitrogen (Fig 39)

![Example of preference in pyridine](image)

Figure 39. Example of preference in pyridine.

4- In pyrrole, substitution at position 2 is favored but substitution at position 3 is also observed (Fig 40).

![Example of preference in pyrrole](image)

Figure 40. Example of preference in pyrrole.
B- Reactions of Furan and Thiophene

1- These compounds react similarly to pyrrole.
2- Substitution occurs first at the 2 position followed by a small amount of substitution at the 3 position (Fig 41)

\[ \text{AcCl} \xrightarrow{\text{AlCl}_3} \text{AcOCCH}_3 \]

Figure 41. Example of substitution in thiophene.

Section 14.9

IX. Disubstituted Benzenes: Ortho, Meta, and Para Substitution

A- Three kinds of disubstitution patterns of benzene: ortho (1,2), meta (1,3), and para (1,4).
1- Nature of the groups influence where the second group will add.
2- Substituted benzenes that give mainly ortho or para products usually react faster than those alone.
3- Those that give mainly meta products react more slowly than benzene.

B- Electron donating groups (EDG)
1- EDG stabilize the system inductively or donate electrons (which can be used to stabilize the cation).
2- Overall will give another (4th) resonance structure.
3- They will give ortho and/or para products.
4- Examples are: NR\textsubscript{2}, NH\textsubscript{2}, OH, OR, alkyl, NHOR, and halides.
5- Example below with resonance.

Ortho substitution with an electron donating group

Figure 42. Resulting stability when electrophile is added to the ortho position in anisole.
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Figure 43. Resulting stability when electrophile is added to the para position in anisole.

6- Does not go meta because meta addition does not generate the 4th resonance structure.

But Meta substitution with an electron donating group

Figure 44. EDG and resulting intermediates from meta addition.

Figure 45. Specific example of the bromination of anisole (methoxybenzene).
7- Example below EDG with inductive stabilization:

Ortho substitution with an electron donating group

Para substitution with an electron donating group

But Meta substitution with an electron donating group

Figure 46. Stabilization of cation with an alkyl group when electrophile adds either ortho or para.

Figure 47. EDG as a methyl group and resulting intermediates with addition meta.
**C- Electron Withdrawing Groups**

1. EWG destabilize 1,2 or 1,4 addition because the have either positive or partial positive charge on the atom attached to the ring.
2. Therefore, the second addition will go meta to the first group.
3. Examples are: COR, SO$_2$OH, NO$_2$, CN, and NR$_3$

![Ortho substitution with an electron withdrawing group](image1)

![Para substitution with an electron withdrawing group](image2)

Figure 48. Addition of an electrophile to the ortho and para positions for an aromatic compound containing an EWG.

4. **Goes meta:**

**But** Meta substitution with an electron withdrawing group

![Meta substitution with an electron withdrawing group](image3)

Figure 49. Meta substitution with an electron withdrawing group for an ammonium group.
D- General Guidelines

1- Ortho substitution is often less favorable than para.
2- Halides withdraw inductively but donate electrons through resonance.

![Figure 50. Example of halide as a directing group.](image)

Section 14.10
X. Inductive Effects in Aromatic Substitution

A- Decreasing Reactivity - Slow reaction

1- EWGs such as NR₃ and NO₂ are strongly deactivating and polarized through the σ bond.
2- This makes introduction of a positive charge into the ring difficult.
3- Overall, slows down reaction.

B- Halogens and others - the competition between resonance and inductivity

1- The σ bond of electron donating groups is also polarized which makes introduction of a positive charge into the ring difficult.
2- But the extra resonance form available outweighs the inductive effect, and the rate of reaction is very fast.
3- Halogens help stabilize the intermediate for ortho/para substitution through a fourth resonance form.
4- However, the inductive withdrawing of electrons by the halogen makes substitution slow relative to benzene.
Section 14.11
XI. Synthesis of Polysubstituted Benzenes

A- After distribution

1- It is dependent on pre-existing groups.
2- Two meta directors in the 1,3 position will direct substitution to the remaining meta position.

![Meta directing groups](image)

Figure 51. *Meta* directing groups.

3- Specific example is depicted below.

![Nitro directing groups](image)

Figure 52. Nitro directing groups for persubstitution - nitrate last.

4- Whereas, *ortho/para* would direct it to remaining *ortho/para*.
5- The third substitution would like to follow these rules as much as possible.

![Persubstitution preference](image)

Figure 53. Persubstitution preference.

6- A specific example of this preference.

![Example of preference](image)

Figure 54. Example of preference for persubstitution - directing groups.
7- Electronic effects are dominant.

B- Specially activated aromatic systems - Aniline and Phenol

Figure 55. Structures of phenol and aniline.

1- Phenol is very activated so it can undergo EAS without a Lewis Acid.
2- It persubstitutes.
3- Example is depicted below.

Figure 56. Reactivity of phenol for electrophilic aromatic substitution.

4- Aniline also persubstitutes.

Figure 57. Reactivity of aniline - reactivity.
C- Steric vs Electronics
1- Large EDG block addition ortho to that group.
2- See examples below

Figure 58. Example of sterics used to form one product.

D- Monosubstitution of Aniline
1- Acylation of amine blocks ortho position.
2- Can remove the group (deprotect) with base to regenerate amine.
Figure 59. Substitution of aniline.

3- Example of use in synthesis.

Figure 60. Use of blocking agents in synthesis - acyl group.
Section 14.12

XII. Nucleophilic Aromatic Substitution

A- Normally, alkenes and arenes do not undergo nucleophilic substitution but under special conditions, they do.

1- There are exceptions to the rule. 2,4-Dinitrochlorobenzene and para-nitrochlorobenzene will undergo this type of substitution.

Figure 61. General reaction of nucleophilic aromatic substitution.

2- The mechanism is neither SN2 nor SN1.

a- The first step is to add the alkoxide to the carbon bonded to the chloro group.
b- This then generates a Meisenheimer complex, which is a resonance stabilized anionic intermediate.
c- The nitro groups stabilize the negative charge so as to enable the reaction to proceed. This only occurs when the nitro group is ortho and para to the halogen. If the nitro group is meta to the halogen, then there is no resonance stabilization. The reaction does not occur.
d- The resulting anion pushes the leaving group off (Cl').
e- Fluorine groups will also allow the reaction occur.

Figure 62. Generation mechanism for nucleophilic aromatic substitution.
B- Nucleophilic Additions to Heteroaromatics.

1- Pyridine is even more attractive than the other compounds because of the resonance stabilization. An example of this substitution is the Chichibabin reaction, which is the addition of amide to pyridine (Fig 59).

\[ \text{Pyridine} \xrightarrow{1. \text{KNH}_2, 105-130^\circ C} \text{Pyridine-NH}_2 \xrightarrow{2. \text{H}_2\text{O}} \]

Figure 63. Addition of amide to pyridine.

2- Another example of nucleophilic substitution is the addition of an alkyl lithium reagent to pyridine.

3- Another example is the addition-elimination reaction of pyridine.

\[ \text{Pyridine} \xrightarrow{1. \text{R-Li, } -78^\circ C} \text{Pyridine-R} \xrightarrow{2. \text{H}_2\text{O}} \]

Figure 64. Alkylation of pyridine and nucleophilic substitution of a substituted pyridine.
Section 14.13
XIII. Skip Special Topic: Stable Carbocations in "Superacid"

Section 14.14
XIV. Special Topic: Benzyne

A- Benzyne is essentially a bent acetylene.

1- Halides on benzene can be eliminated to form the alkyne.

2- Amide is a strong base which can act as a nucleophile to add to the benzyne.

B- General Reaction:

\[
\begin{align*}
\text{Cl} & \quad \xrightarrow{\text{KNH}_2} \quad \text{NH}_2 \\
\text{NH}_3, -33 ^\circ C & \quad \\
\end{align*}
\]

Figure 65. General reaction.

3- Isotopically labelled experiments:

\[
\begin{align*}
\text{Cl} & \quad \xrightarrow{\text{KNH}_2} \quad \text{NH}_2 \\
\text{NH}_3, -33 ^\circ C & \quad \\
\end{align*}
\]

Figure 66. Overall reaction using isotopically labeled carbons (\(^{13}\text{C}\) are ones indicated by spheres).

C- Mechanism:

\[
\begin{align*}
\text{Cl} & \quad \xrightarrow{\text{NH}_2} \quad \text{NH}_2 \\
\text{H} & \quad \xrightarrow{\text{H}^-} \quad \text{NH}_2 \\
\text{NH}_3 & \quad \xrightarrow{\text{NH}_2} \quad \text{NH}_2 \\
\end{align*}
\]

1) Deprotonation; followed by elimination of the chloride.
2) Nucleophilic attack of the amide
3) Protonation.

Figure 66. Reaction mechanism using the benzyne intermediate.

Section 14.15
XV. Special Topic: Biological Synthesis of Aromatic Rings; Phenylalanine