Reactions of Aromatic Compounds

Aromatic compounds do not react like other alkenes

A major part of the problem for this reaction is the product has lost all aromatic stabilization, thermodynamically thus the reaction is disfavored (stabilization ~ 30 Kcal/mol)

With an appropriate catalyst, however, benzene will react

The product is a substitution, not an addition, and the product is still aromatic, thermodynamically thus the reaction is favored
Electrophilic Aromatic Substitution

Aromatic compounds react through a unique substitution type reaction

Initially an electrophile reacts with the aromatic compound to generate an arenium ion (a cyclohexadienyl cation)

The arenium ion has lost aromatic stabilization (one of the carbons of the ring no longer has a conjugated p orbital)

The arenium ion can resonate the charge onto three different carbons of the ring

In a second step, a base will abstract the hydrogen to regenerate the aromatic ring

Overall, thus a substitution has occurred (Hydrogen was substituted with Electrophile)
The rate-limiting step is therefore the formation of the arenium ion.

According to Hammond postulate, the transition state for the rate-determining step will resemble the structure of the high energy intermediate.
Electrophilic Aromatic Substitution

Examples of electrophilic aromatic substitution reactions ($S_{E}Ar$)

In all $S_{E}Ar$ reactions, an electrophile reacts with the aromatic ring (which is the nucleophile in these reactions)

Start by looking at halogenation reactions

Bromine is not a strong enough electrophile for reaction to proceed

A Lewis acid is added

The Lewis acid coordinates to one bromine, thereby making the bond polarized and increasing electrophilicity of other bromine

The Arenium ion generated after this first step will be deprotonated by any base present to regain the aromatic stabilization
Electrophilic Aromatic Substitution

A chlorination reaction works quite similar to the bromination, only practical difference is the Lewis acid chosen should have chlorine instead of bromine substituents.

A variety of Lewis acids can be used, most common are FeCl$_3$ and AlCl$_3$.

The bromination and chlorination of aromatic rings is thus quite easy experimentally.

It is harder to either iodinate or fluorinate aromatic rings using these procedures (extremely difficult to generate either I$^+$ or F$^+$ electrophiles).

In order to generate either iodinated or fluorinated aromatic rings, a different procedure is required.
Electrophilic Aromatic Substitution

Another common $S_{E2}Ar$ reaction is a nitration, need a method to generate an electrophilic nitro source

Usually accomplished by adding nitric acid to a strong acid

\[
\text{HNO}_3 \xrightarrow{\text{H}_2\text{SO}_4} \text{Nitronium ion}
\]

The nitronium ion then reacts with the aromatic ring to nitrate the ring

\[
\text{HNO}_3, \text{H}_2\text{SO}_4 \xrightarrow{\text{O=N=O}} \text{Nitrobenzene}
\]

Follows same two-step mechanism with an arenium ion intermediate
Electrophilic Aromatic Substitution

Another electrophile that can be added is a sulfonate group

SO₃ is a strong enough electrophile to react itself, but sometimes sulfuric acid is added to protonate the sulfur trioxide to make an even stronger electrophile

Sulfonation is a useful reaction as many biomaterials include sulfonic groups (increased water solubility is one benefit)

Another unique advantage of the sulfonation reaction is it is reversible, the sulfonate can be removed by heating in water (often use steam)
Electrophilic Aromatic Substitution

Would be convenient to have a method to introduce new carbon-carbon bonds in aromatic compounds

In practice this is achievable if a strong carbon electrophile was available

\[
\text{Cl} + \text{AlCl}_3 \rightarrow \text{δ+Cl} - \text{AlCl}_3\ 
\]

One method to generate a carbon electrophile is to react an alkyl halide with a Lewis acid

The Lewis acid can coordinate with the halogen, or the electrons can resonate where the carbon-halogen bond is broken with a full positive charge on carbon (placement of electrons is dependent upon stability of carbocation)

The carbocation can react with aromatic ring to form arenium ion which then has a hydrogen abstracted to form the substituted aromatic compound

This reaction is called a “Friedel-Crafts” alkylation
Friedel-Crafts Alkylation

Any method that can generate a positive charge on carbon can potentially work for a Friedel-Crafts alkylation.

Other methods for this reaction:

Using alkenes

![Diagram showing the reaction of alkenes with HF to form a carbocation, which then reacts with benzene.]

Have already observed in reactions with alkenes that carbocation intermediates are formed, if the carbocation is more stable then it can react with benzene.

Using alcohols

![Diagram showing the reaction of alcohols with BF₃ to form a carbocation, which then reacts with benzene.]

Friedel-Crafts Alkylation

Limitations of Friedel-Crafts Alkylation

1) Reaction does not work with strongly deactivated aromatic rings

Friedel-Crafts alkylations do not work with nitro, sulfonic, or acyl substituents

2) Carbocation rearrangements occur

Because a carbocation is formed during this reaction, similar to any reaction involving carbocations the carbocation can rearrange to a more stable carbocation

\[ \text{CH}_3\text{Cl} \xrightarrow{\text{AlCl}_3} \text{CMe}_3^+ \rightarrow \text{CMe}_3^+ \rightarrow \text{CMe}_3^+ \rightarrow \text{Ph} \]

Can therefore never obtain n-alkyl substituents longer than 2 carbons in high yield
Friedel-Crafts Alkylation

3) Polyalkylation often occurs with Friedel-Crafts alkylation

Because an alkyl group donates electron density due to hyperconjugation, the product in a Friedel-Crafts reaction is more reactive than the starting material.

![Chemical reaction diagram]

This arenium ion is more stable than the initially formed arenium ion.

Consider what occurs if the product formed initially reacts a second time.

The rate of addition for the second reaction is faster than the initial reaction (as would the third addition be faster than the second and so on), this is not the case with any of the $S_{E}$Ar reactions studied previously.

To prevent polyreaction the starting material (benzene is this example) is used in excess.
Friedel-Crafts Acylation

Instead of adding an alkyl group this reaction adds an acyl substituent

First need to generate an acid chloride

\[
\text{O} \quad \text{Cl} \quad \text{SO} \quad \text{Cl} \quad \text{Cl} \quad \text{AlCl}_3 \quad \text{O} \quad \text{O} \quad \text{O}
\]

Thus any carboxylic acid can be converted into an acid chloride

The acid chloride can be reacted with a Lewis acid to generate an acylium ion intermediate

\[
\text{O} \quad \text{AlCl}_3 \quad \text{δ+} \quad \text{Cl} \quad \text{AlCl}_3 \quad \text{O} \quad \text{O}
\]

(which is stabilized by resonance with the carbonyl group)

The acylium ion then reacts with an aromatic ring in a typical S_EAr reaction

\[
\text{H}_2\text{O} \quad \text{H}_2\text{O}
\]

Since the Lewis acid can coordinate with the acyl group, however, a full equivalent is needed
Friedel-Crafts Acylation

Advantages of Friedel-Crafts Acylation

1) The acyl substituent is an electron withdrawing group

Therefore this reaction can be stopped easily at one addition (no polyacylation occurs – the arenium ion is less stable with the second addition)

2) No rearrangements occur

Since an isolated carbocation is not formed there is no rearrangement (due to the stability of the resonance form for the acylium ion, it will not rearrange)

Due to these two advantages, the Friedel-Crafts acylation is a much more convenient reaction than the Friedel-Crafts alkylation

-still will not react, however, with strongly deactivated aromatic rings
Friedel-Crafts Acylation

Clemmensen Reduction

The ability to reduce a carbonyl to a methylene further enhances usefulness of Friedel-Crafts acylation

In a Clemmensen reduction the conversion occurs under acidic conditions

Overall these two steps, Friedel-Crafts acylation followed by Clemmensen, allows the introduction of an n-alkyl substituent which would not be possible with a Friedel-Crafts alkylation
Another method to reduce a carbonyl to methylene is a Wolf-Kishner reduction.

Main difference is that the Wolf-Kishner occurs under basic conditions.

Both Clemmensen and Wolf-Kishner require strong conditions, Clemmensen uses acidic while Wolf-Kishner uses basic conditions.
We have seen a variety of electrophilic aromatic substitution reactions where an aromatic ring can have different substituents added. While this allows a variety of substituents, the range is far less than a chemist would ultimately desire. How can other substituents be added to an aromatic ring?
Reduction of Nitro Substituent

While only a few substituents can be added directly to aromatic ring in one step, a wide variety of substituents can be attached by chemically modifying substituents.

An easy conversion is to reduce the nitro group to an amine group.

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

A variety of conditions will allow this interconversion, two common ones include:

1. Hydrogenation with metal catalyst
2. Acidic metal catalyst (Sn is very common)

Amine groups are difficult to add directly because electrophilic amine groups are very unstable.

Amines can also easily be converted to amides by reaction with acid chlorides.
Formation of Diazonium Salts

The aromatic amine is an important substituent in addition to simply allowing an amine functionality, as the amine can be converted to a diazonium salt

\[
\text{NaNO}_2 \xrightarrow{\text{HCl}} \text{NaNO}_2 \xrightarrow{\text{HCl}} \text{N}_2\text{O}_3
\]

Sodium nitrite reacts with acid to form nitrous acid which equilibrates with dinitrogen trioxide. When dinitrogen trioxide is formed in the presence of aniline, a diazonium salt forms.
Sandmeyer Reaction

Diazonium salts are important as they can be reacted with cuprous salts to convert them into aromatic halides or cyanides, this reaction is called the Sandmeyer reaction.

\[
\begin{align*}
+ \text{N}^+ & \quad \text{N}^- \\
\text{Cl}^- & \quad \text{CuCl} & \quad \text{Cl}^{-} \\
\text{Br}^- & \quad \text{CuBr} & \quad \text{Br}^{-} \\
\text{CN}^- & \quad \text{CuCN} & \quad \text{CN}^{-}
\end{align*}
\]

Reaction generally has high yields, but need cuprous salts - common substituents are chloro, bromo or cyanide.
Diazonium Salts

Instead of using cuprous salts, however, other nucleophiles can be used to displace the good nitrogen gas leaving group.

![Chemical structures](image)

- Allows formation of other halides
- Unique method to add oxygen directly to aromatic ring
- Allows reduction to C-H bond

Otherwise very difficult to generate electrophilic oxygen to add in an electrophilic aromatic substitution reaction.
Reaction of Side Chains

In addition to allowing a variety of different substituents on an aromatic ring by reducing the nitro group to an amine and then converting the amine to different groups, another possibility is to react side chains on aromatic rings to generate different groups.

We have already observed some of these reactions on carbon based side chains.

Can further undergo any alkene reactions to add more functionality.
Aromatic Substituents

Thus while only a few substituents can be added directly to an aromatic ring, by modifying the groups on the ring a wide variety of substituents can be obtained.

**Donating**
- Reduction of nitro
- Reaction of diazonium
- Acylation of amine
- Friedel-Crafts alkylation

**Withdrawing**
- Cl or Br: direct reaction, Friedel-Crafts acylation
- F or I: diazonium
- Oxidation of alkyl
- Sandmeyer
- Direct reaction
- Direct reaction

Allows both electron donating and electron withdrawing substituents on aromatic ring.
The rate-limiting step is the formation of the arenium ion and according to the Hammond postulate, the transition state for the rate-determining step resembles the structure of the arenium ion intermediate.
SEAr Reactions on Substituted Rings

The properties of this arenium ion therefore control electrophilic aromatic substitutions (just like any reaction consider the stability of the intermediate formed in the rate limiting step)

1) The rate will be faster for anything that stabilizes the arenium ion

2) The regiochemistry will be controlled by the stability of the arenium ion

The properties of the arenium ion, therefore, will predict the outcome of electrophilic aromatic substitution chemistry on substituted rings
S_EAr Reactions on Substituted Rings

When a reaction occurs on benzene, the substituent could be placed on any of the six carbons and the same product would be obtained

When the same reaction occurs on a monosubstituted benzene, however, three different products could be obtained

How to predict which isomer is favored?
Determined by relative stability of arenium ion intermediates
S<sub>E</sub>Ar Reactions on Substituted Rings

Consider the arenium ion intermediate structures for the possible isomers

Realize that the arenium ion can resonate, thus the charge is not localized on one carbon

Only the ortho and para substitution, however, can place cation adjacent to methyl group

Since methyl group stabilizes cation by hyperconjugation, the ortho and para products are favored
SEAr Reactions on Substituted Rings

Alkyl groups are electron donating due to hyperconjugation

Therefore toluene will favor electrophilic substitution at ortho/para positions (only ortho/para substitution places carbocation adjacent to alkyl group on ring)

\[ \text{Product ratios are due to stability of arenium ion intermediates, not due to stability differences of products} \]

Often obtain more para than ortho due to sterics (even though there are twice as many ortho substitution sites)
S_EAr Reactions on Substituted Rings

In addition to orientational control, substituents affect reactivity

As the aromatic ring acquires more electron density, the arenium ion will be more stable
S_EAr Reactions on Substituted Rings

Toluene therefore reacts faster in an electrophilic aromatic substitution than benzene.

The alkyl group is called an activating group
(it activates the ring for a faster rate)

Any substituent that increases the rate for an electrophilic aromatic substitution
is called an “activating” substituent

Substituents that lower the rate for an electrophilic aromatic substitution
are called “deactivating” substituents
(nitro is one example of a deactivating group)
These are groups that lower the electron density of the aromatic ring
Factors that affect Activators/Deactivators

There are in general two mechanisms that can affect a substituent

1) Inductive

Substituents that are more electronegative than carbon
will inductively pull electron density out of the ring

Fluorine is more electronegative than carbon,
thus there is a bond dipole

2) Resonance

Substituents that have a lone pair of electrons adjacent to the ring
can donate electron density into the ring through resonance
SₐAr Reactions on Substituted Rings

Many substituents will have both inductive and resonance effects

Need to balance the effects

Electronegative atoms with lone pair of electrons have opposing effects

Alkyl substituents inductively donate, no resonance effects, therefore activators

Inductively withdrawing therefore deactivating

Resonance donating, therefore activating

- when a neutral O or N is directly bonded to a benzene ring, the resonance effect dominates and the net effect is activating
- when a halogen is bonded to a benzene ring, the inductive effect dominates and the net effect is deactivating
S_{E}Ar Reactions on Substituted Rings

Other deactivating groups

There are two other main classes of deactivating groups

1) A conjugated system where both inductive and resonance effects pull electron density from the ring

Whenever Z is more electronegative than Y as seen in structure

2) A formal positive charge is placed directly adjacent to ring
S<sub>E</sub>Ar Reactions on Substituted Rings

Activating vs. deactivating ability can be compared

The rate of a S<sub>E</sub>Ar reaction depends upon substituents and the relative rate of reaction for different substituted aromatic rings can be predicted.

![Substituents](image)

- Very fast
- fast
- slow
- Very slow
- slowest

Substituents in different categories (very fast vs. fast for example) will react with different rates.
**S$_E$Ar Reactions on Substituted Rings**

Orientational control can be predicted based on the relative rates of the compounds:

1) All activating groups favor ortho/para substitution

2) Deactivating groups with a lone pair of electrons adjacent to the ring favor ortho/para substitution
   (halogens are in this category)

3) Other deactivating groups favor meta substitution
$S_{E}Ar$ Reactions on Substituted Rings

Consider the arenium ion intermediate structures for the reaction with a meta director

Only the ortho and para substitution, however, can place cation adjacent to electron withdrawing cyano group

Placing positive charge adjacent to electron withdrawing cyano will destabilize this structure and thus the meta substitution is favored as it is the only isomer that will not place charge adjacent
Consider arenium ion structures that place carbocation adjacent to substituents.

Lone pair adjacent, O or N substituent
Alkyl substituent
Halogen adjacent
Electron withdrawing substituent adjacent

Cation adjacent is stabilized by resonance, ortho/para directing.
Cation adjacent is stabilized by hyperconjugation, ortho/para directing.
Cation adjacent is stabilized by resonance, ortho/para directing.
Cation adjacent is destabilized by $\delta^+$ charge, meta directing.

\[
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SEAr Reactions on Substituted Rings

Multiple substituents

How to determine orientation of electrophilic aromatic substitution if there is more than one substituent?

A few rules to consider:

1) The effects are cumulative

2) The stronger substituent according to the relative effects will be correspondingly more important for directing effects

3) When given a choice, a new substituent typically will not go ortho to two other substituents
$S_{E}Ar$ Reactions on Substituted Rings

Consider some examples:

- **ortho/para director**
  
  \[
  \begin{align*}
  &\text{CH}_3 \\
  &\text{CH}_3 \\
  &\text{CN} \\
  &\text{CN} \\
  \end{align*}
  \]

  meta director

  \[
  \begin{align*}
  &\text{Br}_2 \\
  &\text{FeBr}_3 \\
  \end{align*}
  \]

- **ortho/para director**
  
  \[
  \begin{align*}
  &\text{H}_3\text{C} \\
  &\text{H}_3\text{C} \\
  &\text{CN} \\
  &\text{CN} \\
  \end{align*}
  \]

  meta director

  \[
  \begin{align*}
  &\text{Br}_2 \\
  &\text{FeBr}_3 \\
  \end{align*}
  \]

- **ortho/para director**
  
  \[
  \begin{align*}
  &\text{H}_3\text{C} \\
  &\text{H}_3\text{C} \\
  &\text{OCH}_3 \\
  &\text{OCH}_3 \\
  \end{align*}
  \]

  \[
  \begin{align*}
  &\text{Br}_2 \\
  &\text{FeBr}_3 \\
  \end{align*}
  \]

  Stronger director wins

Stronger director wins
$S_{E}\text{Ar}$ Reactions on Substituted Rings

Reactivity of aromatic ring can affect amount of reaction

In reactions with strongly activated rings, polyhalogenation occurs

With either phenol or aniline, the reaction will proceed until all ortho/para positions are reacted when catalyst is used
**S<sub>E</sub>Ar Reactions on Substituted Rings**

With these highly activated ring systems, catalyst is not necessary.

Reaction will only proceed with strongly activated ring systems, still need catalyst for less activated aromatic rings, but with phenol or aniline reaction of one halogen can occur with no catalyst present.
**S_EAr Reactions**

Knowing the reactivity and directing effects of various substituents, a variety of substituted aromatic compounds can be obtained depending upon the order of reactions.

Amine can be oxidized back to nitro.

All bromines are o/p to meta director, even though Br is an o/p director.

\[ \text{NO}_2 \quad \text{Sn, HCl} \rightarrow \quad \text{NH}_2 \]

\[ \quad \text{Br}_2 \quad \text{FeBr}_3 \rightarrow \quad \text{NH}_2 \text{Br} \text{Br} \]

\[ \quad \text{CF}_3\text{CO}_3\text{H} \rightarrow \quad \text{NO}_2 \text{Br} \text{Br} \]

1) \text{NaNO}_2, \text{HCl}
2) \text{H}_3\text{PO}_2

All bromines are o/p to meta director.
S<sub>E</sub>Ar Reactions with Heteroaromatic Rings

S<sub>E</sub>Ar reactions can occur on aromatic rings besides benzene or substituted benzene derivatives

Need to consider the arenium ion intermediates for the different aromatic rings to determine directing effects for other rings

![Chemical structures](image)

Reaction at either 1, 2 or 1, 4 substitution will have one resonance form with a formal positive charge on electronegative nitrogen atom

Reaction with 1, 3 substitution does not place positive charge on nitrogen, therefore this is the preferred reaction site

Pyridine is a deactivated ring that reacts with a 1, 3 preference
S_EAr Reactions with Heteroaromatic Rings

With the 5-membered heteroaromatic rings (thiophene, pyrrole, furan) there are two possible reactions sites (called the 2-position and 3-position).

The 2-position is favored because it yields more resonance forms for the arenium ion, thus making the structure more stable.

Due to the extra electron density in the ring with the lone pair in conjugation, these ring systems react faster than benzene (activated rings).
Nucleophilic Aromatic Substitution

Another type of reaction with aromatic rings is a nucleophilic addition

Instead of adding an electrophile to form an arenium ion, a nucleophile replaces a leaving group

This is NOT a $S_N2$ or $S_N1$ reaction

Cannot react anticoplanar to C-Cl bond (requirement for $S_N2$) due to steric blocking approach

Carbocation on sp$^2$ hybridized carbon is too high in energy

Initially a carbanion is formed which subsequently loses the leaving group, unlike a $S_N2$ reaction which is a one step reaction
Nucleophilic Aromatic Substitution

Mechanism

The anion is stabilized by electron withdrawing groups ortho/para to leaving group

To regain aromatic stabilization, the chloride leaves to give the substituted product
Nucleophilic Aromatic Substitution

Unique factors for nucleophilic aromatic substitution

1) Must have EWG’s ortho/para to leaving group
   -the more EWG’s present the faster the reaction rate
     (intermediate is stabilized)

2) The leaving group ability does not parallel $S_N2$ reactions
   -bond to leaving group is not broken in rate-determining step
     (fluorine for example is a good leaving group for nucleophilic aromatic substitution
      but is a horrible leaving group for $S_N2$ reaction)

More electronegative atom has a faster rate

$F > Cl > Br > I$

(polarizability is not a factor)
Nucleophilic Aromatic Substitution

Using nucleophilic aromatic substitution for peptide determination

React 2,4-dinitrobenzene with peptide

The Sanger reagent can react with the N-terminal amine from the peptide

The resultant nucleophilic aromatic substitution product can be cleaved and thus the terminal amino acid structure determined.
Nucleophilic Aromatic Substitution

Benzyne mechanism

A second nucleophilic aromatic substitution reaction is a benzyne mechanism.

Benzyne is an extremely unstable intermediate which will react with any nucleophile present.

Need strong base at moderate temperatures, but do not need EWG’s on ring.