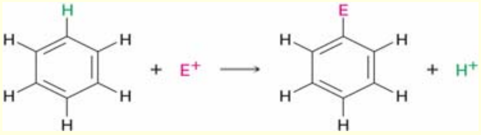
Reactions of Aromatic Compounds

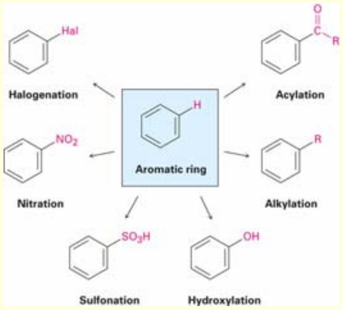
Electrophilic aromatic substitution

- A process in which an electrophile (E^+) reacts with an aromatic ring and substitutes for one of the hydrogens
- The most common reaction of aromatic compounds
- This reaction is characteristic of all aromatic rings
  - The ability of a compound to undergo electrophilic substitution is a good test of aromaticity



Reactions of Aromatic Compounds

- Many substituents can be introduced onto an aromatic ring through electrophilic substitution reactions
  - Halogen (-Cl, -Br, -I)
  - Nitro group ($-NO_2$)
  - Sulfonic acid group ($-SO_3H$)
  - Hydroxyl group (-OH)
  - Alkyl group (-R)
  - Acyl group (-COR)



Reactions of Aromatic Compounds

1. **Nitration**

   Ar-H + HNO_3, H_2SO_4 → Ar-NO_2 + H_2O

2. **Sulfonation**

   Ar-H + H_2SO_4, SO_3 → Ar-SO_3H + H_2O

3. **Halogenation**

   Ar-H + X_2, Fe → Ar-X + HX

4. **Friedel-Crafts alkylation**

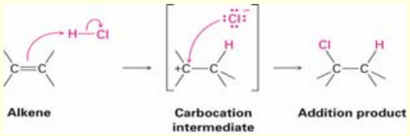
   Ar-H + R-X, $AlCl_3$ → Ar-R + HX

Ar-H = aromatic compound

Reactions of Aromatic Compounds: Electrophilic Substitution

Electrophilic alkene addition

- Addition of a reagent such as HCl to an alkene
  - The electrophilic hydrogen approaches the π electrons of the double bond and forms a bond to one carbon, leaving a positive charge at the other carbon
  - The carbocation intermediate then reacts with the nucleophilic Cl^- ion to yield the addition product



Reactions of Aromatic Compounds: Electrophilic Substitution

One difference between electrophilic aromatic substitution reactions and electrophilic alkene addition reactions is that aromatic rings are less reactive toward electrophiles than alkenes are

- Br_2 in CH_2Cl_2 solution reacts instantly with most alkenes but does not react with benzene at room temperature

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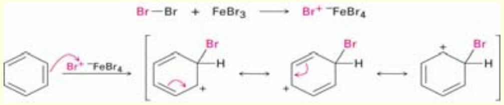
Reactions of Aromatic Compounds: Electrophilic Substitution

Electrophilic aromatic substitution reaction begins in a similar way to electrophilic alkene addition reaction

- $FeBr_3$ catalyst is needed for bromination of benzene to occur
  - $FeBr_3$ polarizes Br_2 molecule making it more electrophilic
  - Polarization makes $FeBr_4^-Br^+$ species that reacts as if it were Br^+
    - The polarized Br_2 molecule reacts with the nucleophilic benzene ring to yield a nonaromatic carbocation intermediate which is doubly allylic and has three resonance forms



Reactions of Aromatic Compounds: Electrophilic Substitution

The intermediate carbocation in electrophilic aromatic substitution is more stable than a typical alkyl carbocation because of resonance but much less stable than the starting benzene ring

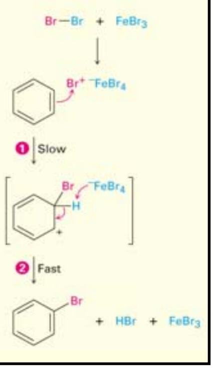
Comparison of alkene addition and aromatic substitution

- Instead of adding Br^- to give an addition product, the carbocation intermediate loses H^+ from the bromine-bearing carbon
  - If addition occurred, the 150 kJ/mol stabilization energy of the aromatic ring would be lost and the overall reaction would be endergonic
  - When substitution occurs, the stability of the aromatic ring is retained and the reaction is exergonic
- Loss of H^+ restores aromaticity to ring
- The net effect is the substitution of H^+ by Br^+

Reactions of Aromatic Compounds: Electrophilic Substitution

The mechanism of the electrophilic bromination of benzene

- The reaction occurs in two steps and involves a resonance-stabilized carbocation intermediate



❶ An electron pair from the benzene ring attacks the positively polarized bromine, forming a new C–Br bond and leaving a nonaromatic carbocation intermediate.

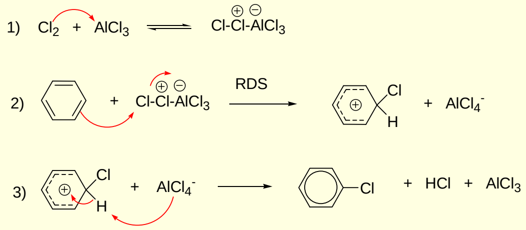
❷ A base removes H^+ from the carbocation intermediate, and the neutral substitution product forms as two electrons from the C–H bond move to re-form the aromatic ring.

Reactions of Aromatic Compounds: Electrophilic Substitution

Aromatic Halogenation

- Electrophilic substitution reactions can introduce halogens into aromatic rings
  - Aromatic rings react with Cl_2 in the presence of $FeCl_3$ catalyst to yield chlorobenzenes
    - Reaction mechanism just like Br_2 in the presence of $FeBr_3$
    - Reaction used in the synthesis of numerous pharmaceutical agents such as the antianxiety agent diazepam (Valium)

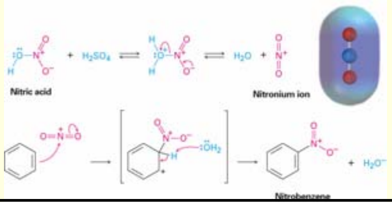
Mechanism for Halogenation



Reactions of Aromatic Compounds: Electrophilic Substitution

Aromatic Nitration

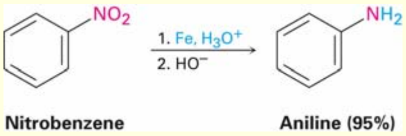
- Aromatic rings can be nitrated with a mixture of concentrated nitric and sulfuric acids
  - The electrophile is the nitronium ion, NO^{2+} which is generated from HNO_3 by protonation and loss of water
  - The nitronium ion reacts with benzene to yield a carbocation intermediate, and loss of H^+
  - The product is a neutral substitution product, nitrobenzene



Reactions of Aromatic Compounds: Electrophilic Substitution

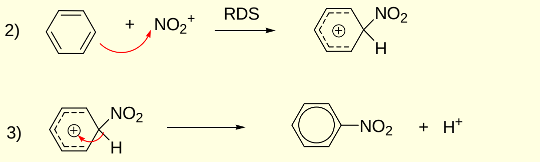
Aromatic nitration

- Does not occur naturally
- Important in the laboratory
  - The nitro-substituted product can be reduced by reagents such as iron or tin metal or to yield an *arylamine*, $ArNH_2$
  - Attachment of an amino group to an aromatic ring by the two-step nitration-reduction sequence is a key part of the industrial synthesis of many dyes and pharmaceutical agents



Mechanism for Nitration

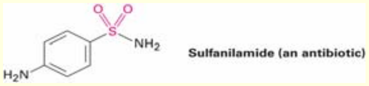
1) $HONO_2 + 2\,H_2SO_4 \rightleftharpoons H_3O^+ + 2\,HSO_4^- + NO_2^+$



Reactions of Aromatic Compounds: Electrophilic Substitution

Aromatic Sulfonation

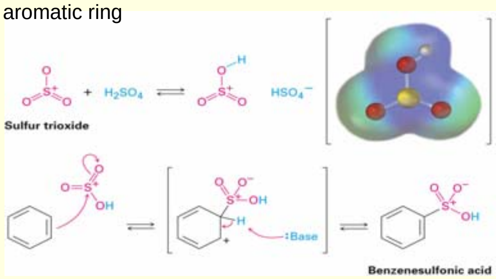
- Aromatic rings can be sulfonated in the laboratory by reaction with fuming sulfuric acid, a mixture of H_2SO_4 and SO_3
  - The reactive electrophile is either HSO_3^+ or neutral SO_3
  - Substitution occurs by the same two-step mechanism seen for bromination and nitration
- Aromatic sulfonation does not occur naturally
- Aromatic sulfonation is widely used in the preparation of dyes and pharmaceutical agents
  - The sulfa drugs, such as sulfanilamide, were among the first clinically useful antibiotics



Sulfanilamide (an antibiotic)

Reactions of Aromatic Compounds: Electrophilic Substitution

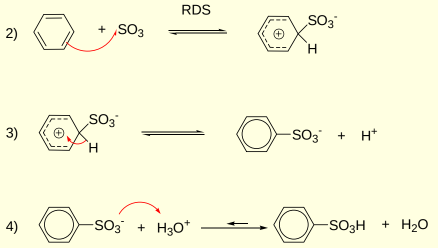
- The mechanism of electrophilic sulfonation of an aromatic ring



Benzenesulfonic acid

Mechanism for Sulfonation

1) $2\,H_2SO_4 \rightleftharpoons H_3O^+ + HSO_4^- + SO_3$



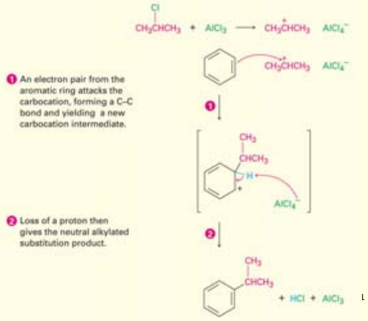
Alkylation

- The introduction of an alkyl group onto the benzene ring
- Called the ***Friedel-Crafts reaction*** after its discoverers
- Among the most useful electrophilic aromatic substitution reactions in the laboratory
- The reaction is carried out by treating the aromatic compound with an alkyl chloride, RCl, in the presence of $AlCl_3$ to generate a carbocation electrophile, R^+
  - Aluminum chloride catalyzes the reaction by helping the alkyl halide to dissociate
  - Loss of H^+ completes the reaction

Alkylation

Mechanism of the Friedel-Crafts alkylation reaction

- The electrophile is a carbocation, generated by $AlCl_3$-assisted dissociation of an alkyl halide



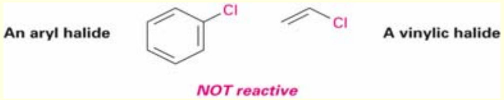
① An electron pair from the aromatic ring attacks the carbocation, forming a C–C bond and yielding a new carbocation intermediate.

② Loss of a proton then gives the neutral alkylated substitution product.

Alkylation

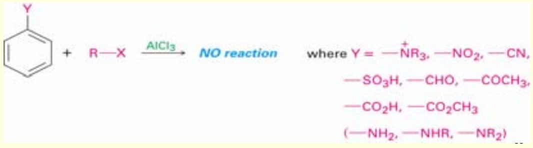
Friedel-Crafts alkylation has several limitations

1. Only *alkyl* halides can be used
   - Aromatic (aryl) halides and vinylic halides do not react because aryl and vinylic carbocations are too high in energy to form under Friedel-Crafts conditions
     - *Vinylic* means that a substituent is attached directly to a double bond, C=C-Cl

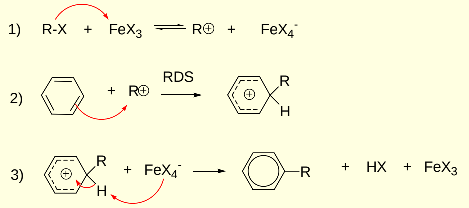


Alkylation

2. **Friedel-Crafts** reactions do not succeed on aromatic rings that are substituted either by a strongly electron-withdrawing group such as carbonyl (C=O) or by an amino group (-NH_2, NHR, -NR_2)
   - The presence of a substituent group already on a ring can have a dramatic effect on that ring's subsequent reactivity toward further electrophilic substitution



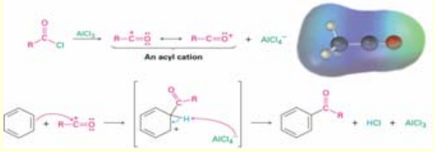
Mechanism for Friedel-Crafts Alkylation



Acylation

An aromatic ring is ***acylated*** by reaction with a carboxylic acid chloride, RCOCl, in the presence of $AlCl_3$

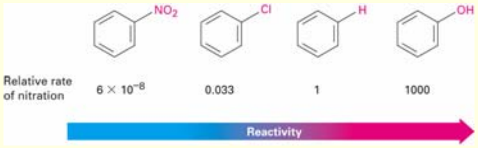
- An acyl group is substituted onto an aromatic ring
  - The reactive electrophile is a resonance-stabilized acyl cation
    - An acyl cation is stabilized by interaction of the vacant orbital on carbon with lone-pair electrons on the neighboring oxygen
  - Because of stabilization, no carbocation rearrangement occurs during acylation



Substituent Effects

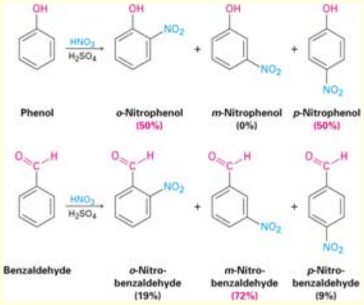
Substituent effects in the electrophilic substitution of an aromatic ring

- **Substituents affect the *reactivity* of the aromatic ring**
  - Some substituents activate the ring, making it more reactive than benzene
  - Some substituents deactivate the ring, making it less reactive than benzene
  - Relative rates of aromatic nitration



Substituent Effects

- **Substituents affect the *orientation* of the reaction**
  - The three possible disubstituted products – ortho, meta, and para – are usually not formed in equal amounts
  - The nature of the substituent on the ring determines the position of the second substitution



Substituent Effects

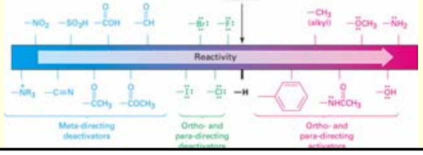
Substituents can be classified into three groups

- *ortho-* and *para-directing activators*
- *ortho-* and *para-directing deactivators*
- *meta-directing deactivators*
  - There are no meta-directing activators

All activating groups are ortho- and para- directing

All deactivating groups other than halogen are meta-directing

The halogens are unique in that they are deactivating but ortho- and para-directing



Substituent Effects

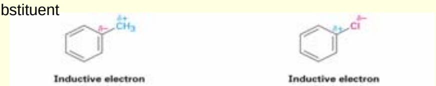
Activating and Deactivating Effects

- The common characteristic of all activating groups is that they **donate electrons** to the ring
  - Makes the ring more electron-rich
  - Stabilize the carbocation intermediate
  - Lower activation energy
- The common characteristic of all deactivating groups is that they **withdraw electrons** from the ring
  - Makes the ring more electron-poor
  - Destabilizes the carbocation intermediate
  - Raising the activation energy for its formation

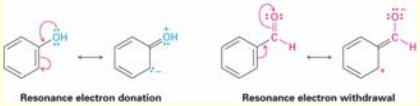
Substituent Effects

The electron donation or electron withdrawal may occur by either an *inductive effect* or a *resonance effect*

- **Inductive effect**
  - Due to an electronegativity difference between the ring and the attached substituent



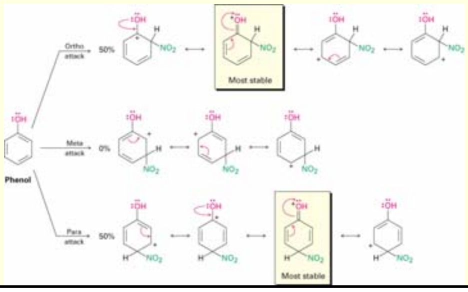
- **Resonance effect**
  - Due to overlap between a *p* orbital on the ring and an orbital on the substituent



Substituent Effects

Orienting Effects: Ortho and Para Directors

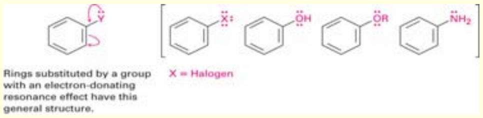
- The ortho and para intermediates are more stable than the meta intermediate because they have more resonance forms



Substituent Effects

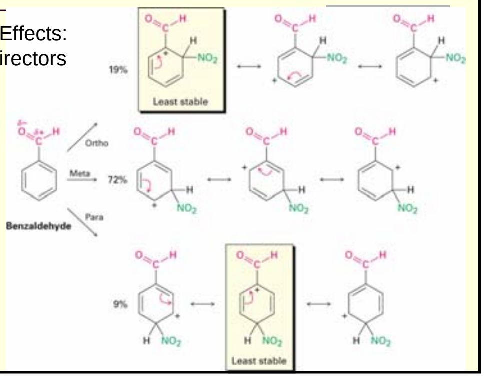
Any substituent that has a lone pair of electrons on the atom directly bonded to the aromatic ring allows an electron-donating resonance interaction to occur

- Additional electron-donating resonance interaction lowers the energy of the hybrid
- Electron-donating substituent increases electrophilicity of ortho and para positions and acts as an ortho and para director



Substituent Effects

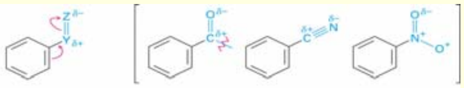
Orienting Effects:
Meta Directors



Substituent Effects

Any substituent that has a positively polarized atom ($\delta+$) directly attached to the ring increases the activation energy leading to the intermediate hybrid for ortho and para substitutions

- Substitution at ortho or para position gives a higher energy intermediate
- Meta substitution avoids higher energy intermediate and has a lower activation energy
- Approaching electrophile is directed to the meta positions



Rings substituted by a group with an electron-withdrawing resonance effect have this general structure.

Substituent Effects

A Summary of Substituent Effects in Electrophilic Substitutions

Table 8.2
Substituent Effects in Electrophilic Aromatic Substitutions

Substituent	Reactivity	Orienting effect	Inductive effect	Resonance effect
$-CH_3$	Activating	Ortho, para	Weak donating	—
$-OH$, $-NH_2$	Activating	Ortho, para	Weak withdrawing	Strong donating
$-F$, $-Cl$ $-Br$, $-I$	Deactivating	Ortho, para	Strong withdrawing	Weak donating
$-NO_2$, $-CN$, $-CHO$, $-CO_2R$ $-COR$, $-CO_2H$	Deactivating	Meta	Strong withdrawing	Strong withdrawing