The general concept of aromaticity can be extended to include polycyclic aromatic compounds.

- Benzo[a]pyrene is one of the cancer-causing substances found in tobacco smoke.

Polycyclic Aromatic Compounds

- All polycyclic aromatic hydrocarbons can be represented by a number of different resonance forms.
  - Naphthalene has three resonance forms.
  

Naphthalene shows many of the chemical properties associated with aromaticity.

- Heat of hydrogenation measurements show an aromatic stabilization energy of approximately 250 kJ/mol (60 kcal/mol).
- Naphthalene reacts slowly with electrophiles to give substitution products rather than double-bond addition products.

Polycyclic Aromatic Compounds

Aromaticity of Naphthalene

- Naphthalene has a cyclic, conjugated \( \pi \) electron system, with \( \rho \) orbital overlap both around the ten-carbon periphery of the molecule and across the central bond.
- \( 10 \) is a Hückel number (\( 4n + 2 \) when \( n = 2 \)) so there is \( \pi \) electron delocalization and consequent aromaticity in naphthalene.
9.6 Reactions of Aromatic Compounds: Electrophilic Substitution

**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

![Diagram of electrophilic aromatic substitution](image)

Reactions of Aromatic Compounds: Electrophilic Substitution

- 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$_3$H)
  - Hydroxyl group (-OH)
  - Alkyl group (-R)
  - Acyl group (-COR)

![Diagram of various substituents](image)

**Electrophilic alkene addition**
- Addition of a reagent such as HCl to an alkene
  - The electrophilic hydrogen approaches the $\pi$ 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

![Diagram of electrophilic alkene addition](image)
One difference between electrophilic aromatic substitution reactions and electrophilic alkene addition reactions is that aromatic rings are less reactive toward electrophiles than alkenes are.

- \( \text{Br}_2 \) in \( \text{CH}_2\text{Cl}_2 \) solution reacts instantly with most alkenes but does not react with benzene at room temperature.

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

- \( \text{FeBr}_3 \) catalyst is needed for bromination of benzene to occur.
- Polarization makes \( \text{FeBr}_3 \) molecule making it more electrophilic.
- The polarized \( \text{Br}_2 \) molecule reacts with the nucleophilic benzene ring to yield a nonaromatic carbocation intermediate which is doubly allylic and has three resonance forms.

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 \( \text{Br}^- \) to give an addition product, the carbocation intermediate loses \( \text{H}^+ \) 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 \( \text{H}^+ \) restores aromaticity to ring.
- The net effect is the substitution of \( \text{H}^+ \) by \( \text{Br}^- \).
The mechanism of the electrophilic bromination of benzene

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

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

2. A base removes an H⁺ from the carbocation intermediate, and the neutral substitution product forms by an 1,2-addition from the C-Br bond to reform the aromatic ring.

Reactions of Aromatic Compounds: Electrophilic Substitution

Aromatic Halogenation

- Electrophilic substitution reactions can introduce halogens into aromatic rings.
  - Aromatic rings react with Cl₂ in the presence of FeCl₃ catalyst to yield chlorobenzenes.
    - Reaction mechanism just like Br₂ in the presence of FeBr₃.
    - Reaction used in the synthesis of numerous pharmaceutical agents such as the antianxiety agent diazepam (Valium).

Reactions of Aromatic Compounds: Electrophilic Substitution

Fluorine is too reactive to give mono-fluorinated products. Iodine itself is unreactive toward aromatic rings.

- An oxidizing agent such as hydrogen peroxide or a copper salt such as CuCl₂ must be added to the reaction.
  - These substances oxidize I₂ to a more powerful electrophilic species that reacts as if it were I⁺.
- The aromatic ring reacts with the I⁺ to yield a substitution product.
Aromatic Nitration

- Aromatic rings can be nitrated with a mixture of concentrated nitric and sulfuric acids
- The electrophile is the nitronium ion, $\text{NO}_2^+$ which is generated from $\text{HNO}_3$ by protonation and loss of water
- The nitronium ion reacts with benzene to yield a carbocation intermediate, and loss of $\text{H}^+$
- The product is a neutral substitution product, nitrobenzene

Reactions of Aromatic Compounds: Electrophilic Substitution

Aromatic Nitration

- Does not occur in nature
- Important in the laboratory
  - The nitro-substituted product can be reduced by reagents such as iron or tin metal or to yield an aniline, $\text{ArNH}_2$
  - 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

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 $\text{H}_2\text{SO}_4$ and $\text{SO}_3$
- The reactive electrophile is either $\text{HSO}_3^+$ or neutral $\text{SO}_3$
- 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

Reactions of Aromatic Compounds: Electrophilic Substitution

Aromatic Sulfonation
Reactions of Aromatic Compounds: Electrophilic Substitution

- The mechanism of electrophilic sulfonation of an aromatic ring

\[ \text{Sulfur trioxide} + \text{H}_2\text{SO}_4 \rightarrow \text{HSO}_3^- + \text{H}_3\text{O}^+ \]

Benzene sulfonic acid

Reactions of Aromatic Compounds: Electrophilic Substitution

Aromatic Hydroxylation
- Direct hydroxylation of an aromatic ring to yield a hydroxybenzene (a phenol)
  - Difficult and rarely done in the laboratory
  - Occurs much more freely in biological pathways
    - Hydroxylation of p-hydroxyphenyl acetate to give 3,4-dihydroxyphenyl acetate
    - The reaction is catalyzed by p-hydroxyphenylacetate-3-hydroxylase and requires molecular O\(_2\) plus the coenzyme reduced flavin adenine dinucleotide (FADH\(_3\))

\[ \text{p-Hydroxyphenylacetate} + \text{O}_2 \rightarrow \text{3,4-Dihydroxyphenylacetate} \]

9.7 Alkylation and Acylation of Aromatic Rings: The Friedel-Crafts Reaction

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
The electrophile is a carbocation, generated by AlCl₃-assisted dissociation of an alkyl halide.

Mechanism of the Friedel-Crafts alkylation reaction:

1. Only alkyl halides can be used as electrophiles.
   - 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.

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 (NHR, -NR₂).
   - 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.

Y + R-X + AlCl₃ → NO reaction where Y = -NR₂, -NO₂, -CN, -SO₂H, -CHO, -COCH₃, -CO₂H, -CO₂CH₃, (-NH₂, -NHR, -NR₂)
3. It is often difficult to stop the reaction after a single substitution
- Polyaliklation is observed
- High yield of monoalkylation product is obtained only when a large excess of benzene is used

![Chemical reaction diagram]

Alkylation and Acylation of Aromatic Rings: The Friedel-Crafts Reaction

- A skeletal rearrangement of the alkyl carbocation electrophile sometimes occurs during a Friedel-Crafts reaction, particularly when a primary alkyl halide is used
- Carbocation rearrangements occur either by hydride shift or alkyl shift
  - Alkylation of benzene with 1-chloro-2,2-dimethylpropane yields (1,1-dimethylpropyl)benzene

Alkylation and Acylation of Aromatic Rings: The Friedel-Crafts Reaction

An aromatic ring is acylated by reaction with a carboxylic acid chloride, RCOCl, in the presence of AlCl₃
- An acyl group, -COR, 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

![Chemical reaction diagram]
The Friedel-Crafts reaction of benzene with 2-chloro-3-methylbutane in the presence of AlCl₃ occurs with a carbocation rearrangement. What is the structure of the product?