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

- Benz[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 Resonance Forms](image)

  - 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.

### Aromaticity of Naphthalene

- Naphthalene has a cyclic, conjugated π-electron system, with π 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 π electron delocalization and consequent aromaticity in naphthalene.

![Naphthalene](image)
There are many heterocyclic analogs of naphthalene
• Quinoline, isoquinoline, indole, and purine
  • Quinoline, isoquinoline, and purine all contain pyridine-like nitrogens that are part of a double bond and contribute one electron to the aromatic π system
  • Indole and purine contain pyrrole-like nitrogens that contribute two π electrons

Polycyclic Aromatic Compounds

• Adenine and guanine, two of the five heterocyclic amine bases found in nucleic acids, have rings based on purine

Polycyclic 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
Many substituents can be introduced onto an aromatic ring through electrophilic substitution reactions:
- Halogen (-Cl, -Br, -I)
- Nitro group (-NO₂)
- Sulfonic acid group (-SO₃H)
- Hydroxyl group (-OH)
- Alkyl group (-R)
- Acyl group (-COR)

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

One difference between electrophilic aromatic substitution reactions and electrophilic alkene addition reactions is that aromatic rings are less reactive toward electrophiles than alkenes are:
- Br₂ in CH₂Cl₂ 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:

- **FeBr₃** catalyst is needed for bromination of benzene to occur.
  - FeBr₃ polarizes Br₂ molecule making it more electrophilic.
  - Polarization makes FeBr₃Br⁺ species that reacts as if it were Br⁺.
  - The polarized Br₂ molecule reacts with the nucleophilic benzene ring to yield a nonaromatic carbocation intermediate which is doubly allylic and has three resonance forms.

\[
\text{BrBr} + \text{FeBr₃} \rightarrow \text{Br}⁺ \text{FeBr₄}^{-}
\]

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.

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 H⁺ from the carbocation intermediate, and the neutral substituted product forms as two electrons from the C-Br bond now 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 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)

\[
\text{Benzene} + \text{FeCl}_3 + \text{Cl}_2 \rightarrow \text{Chlorobenzene (89%)}
\]

- 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

\[
\text{I}_2 + 2 \text{Cu}^{2+} \rightarrow 2 \text{I}^+ + 2 \text{Cu}^+
\]

Reactions of Aromatic Compounds: Electrophilic Substitution

Electrophilic aromatic halogenations occur in the biosynthesis of numerous naturally occurring molecules, particularly those produced by marine organisms

- Thyroxine, synthesized in the thyroid gland in humans, is a thyroid hormone involved in regulating growth and metabolism

\[
\text{Thyroxine} \rightarrow \text{3,5-Diiodothyronine} \rightarrow \text{Thyroxine (a thyroid hormone)}
\]
### 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, \( \text{NO}_2^+ \), 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.

#### 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.

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**Equations and Diagrams:**

- **Nitration Reaction:**
  
  ![Nitration Reaction](image)

- **Sulfonation Reaction:**
  
  ![Sulfonation Reaction](image)

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**Additional Notes:**

- **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 arylamine, \( \text{ArNH}_2 \).
  - 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.

- **Aromatic Sulfonation:**
  - 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.

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**Aniline (95%)**

**Sulfanilamide (an antibiotic)**
Reactions of Aromatic Compounds: Electrophilic Substitution

- The mechanism of electrophilic sulfonation of an aromatic ring

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

- 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\(_3\))

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

Reactions of Aromatic Compounds: Electrophilic Substitution

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, \( \text{RCI} \), in the presence of \( \text{AlCl}_3 \) to generate a carboxocation electrophile, \( \text{R}^+ \)
  - Aluminum chloride catalyzes the reaction by helping the alkyl halide to dissociate
  - Loss of \( \text{H}^+ \) completes the reaction

9.7 Alkylation and Acylation of Aromatic Rings: The Friedel-Crafts Reaction
The electrophile is a carbocation, generated by AlCl₃-assisted dissociation of an alkyl halide.

Mechanism of the Friedel-Crafts alkylation reaction

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

Friedel-Crafts alkylation has several limitations:

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.

An aryl halide: ![ Aryl halide structure ]

A vinylic halide: ![ Vinylic halide structure ]

**NOT reactive**

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 (NH₂, 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.

\[
\text{Y} + \text{R}-\text{X} \xrightarrow{\text{AlCl}_3} \text{NO reaction}
\]

where Y = \(\text{~NR}_3\), \(\text{~NO}_2\), \(\text{~CN}\), \(\text{~SO}_2\text{H}\), \(\text{~CHO}\), \(\text{~COCH}_3\), \(\text{~CO}_2\text{H}\), \(\text{~CO}_2\text{CH}_3\), \(\text{~NH}_2\), \(\text{~NHR}\), \(\text{~NR}_2\).
3. It is often difficult to stop the reaction after a single substitution

- Polyalklation is observed
- High yield of monoalkylation product is obtained only when a large excess of benzene is used

![Diagram showing alkylation and acylation of aromatic rings]

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

Aromatic alkylations occur in numerous biological pathways
- The carbocation electrophile is typically formed by dissociation of an organo diphosphate
  - A diphosphate group is a common structural feature of many biological molecules
  - It can be expelled as a stable diphosphate ion
- The dissociation of an organo diphosphate in a biological reaction is typically assisted by complexation to a divalent metal cation such as $\text{Mg}^{2+}$ to help neutralize charge

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

Biosynthesis of phylloquinone, or vitamin K$_1$, the human blood-clotting factor
- The key step that joins the 20-carbon phyl side chain to the aromatic ring is an electrophilic substitution reaction

Worked Example 9.2

Predicting the Product of a Carbocation Rearrangement

The Friedel-Crafts reaction of benzene with 2-chloro-3-methylbutane in the presence of $\text{AlCl}_3$ occurs with a carbocation rearrangement. What is the structure of the product?