Chemistry of Benzene: Electrophilic Aromatic Substitution

Part A

B. Pharm. Semester-1
Course Code: 0510210; Session: 2022-2023

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Learning Outcomes

- At the end of this lesson students will be able to
  - Electrophilic aromatic substitution
  - Understand why this chapter is important
  - Halogenation: Bromination with mechanism
  - Other halogenation: Chlorination, Iodination
  - Nitration with mechanism
  - Sulfonation with mechanism
  - Friedel–Crafts Reactions: Alkylation and Acylation of Aromatic Rings with mechanisms and limitations

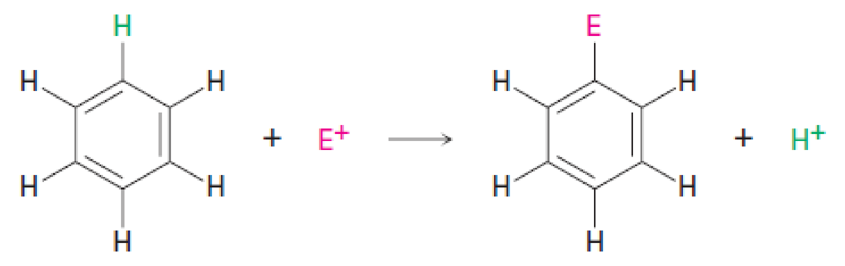
Objective

The objective of this course is to give to the students of pharmacy the basic knowledge about the organic chemistry.

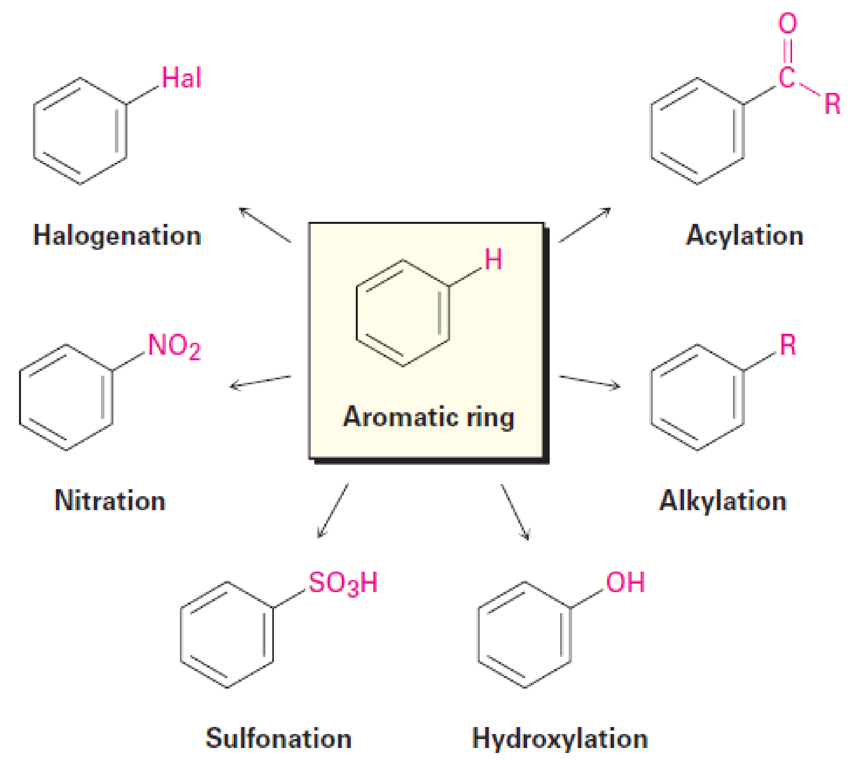
Electrophilic Aromatic Substitution Reactions

- The most common reaction of aromatic compounds is electrophilic aromatic substitution, in which an electrophile (E^+) reacts with an aromatic ring and substitutes for one of the hydrogens.
- The reaction is characteristic of all aromatic rings, not just benzene and substituted benzenes.
- In fact, the ability of a compound to undergo electrophilic substitution is a good test of aromaticity.

Electrophilic Aromatic Substitution Reactions

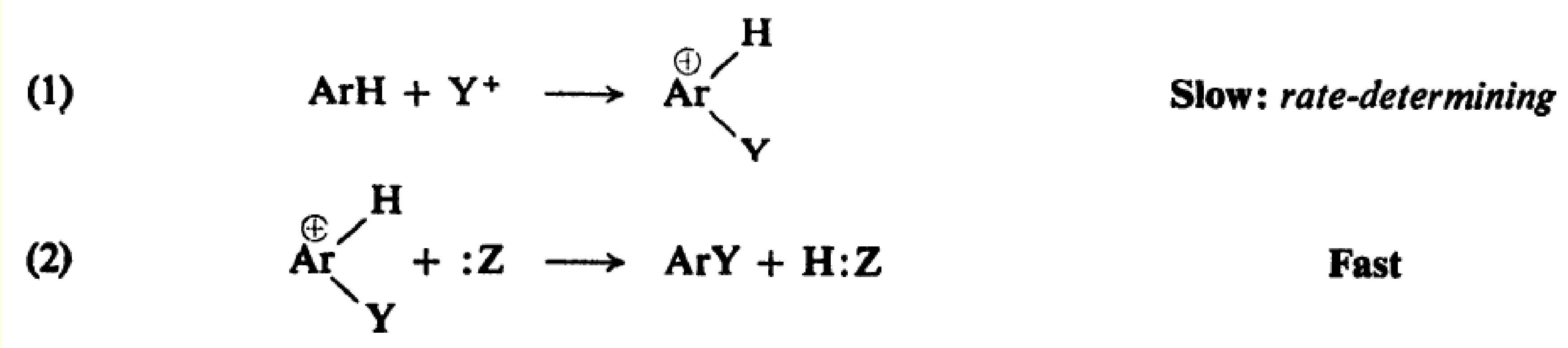


Benzene ring is a source of electrons due to π electron cloud, like a base.



An aromatic ring can be substituted by a halogen (-Cl, -Br, -I), a nitro group (-NO2), a sulfonic acid group (-SO_3H), a hydroxyl group (-OH), an alkyl group (-R), or an acyl group (-COR).

Electrophilic Aromatic Substitution Reactions: General Mechanism



$$\text{(1)}\quad ArH + Y^+ \longrightarrow \overset{\oplus}{Ar}\begin{matrix} H \\ Y \end{matrix} \qquad \text{Slow: rate-determining}$$

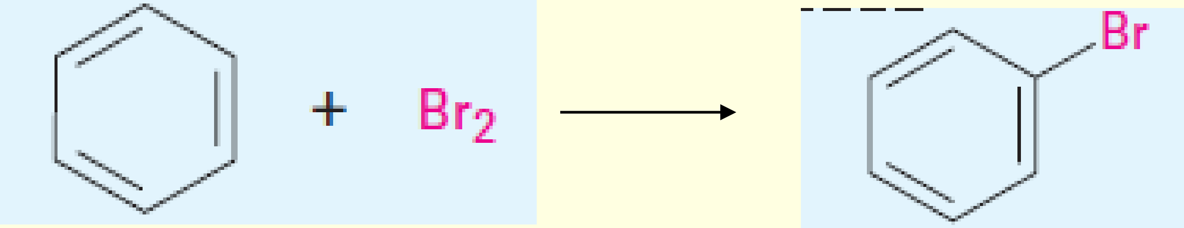
$$\text{(2)}\quad \overset{\oplus}{Ar}\begin{matrix} H \\ Y \end{matrix} + :Z \longrightarrow ArY + H{:}Z \qquad \text{Fast}$$

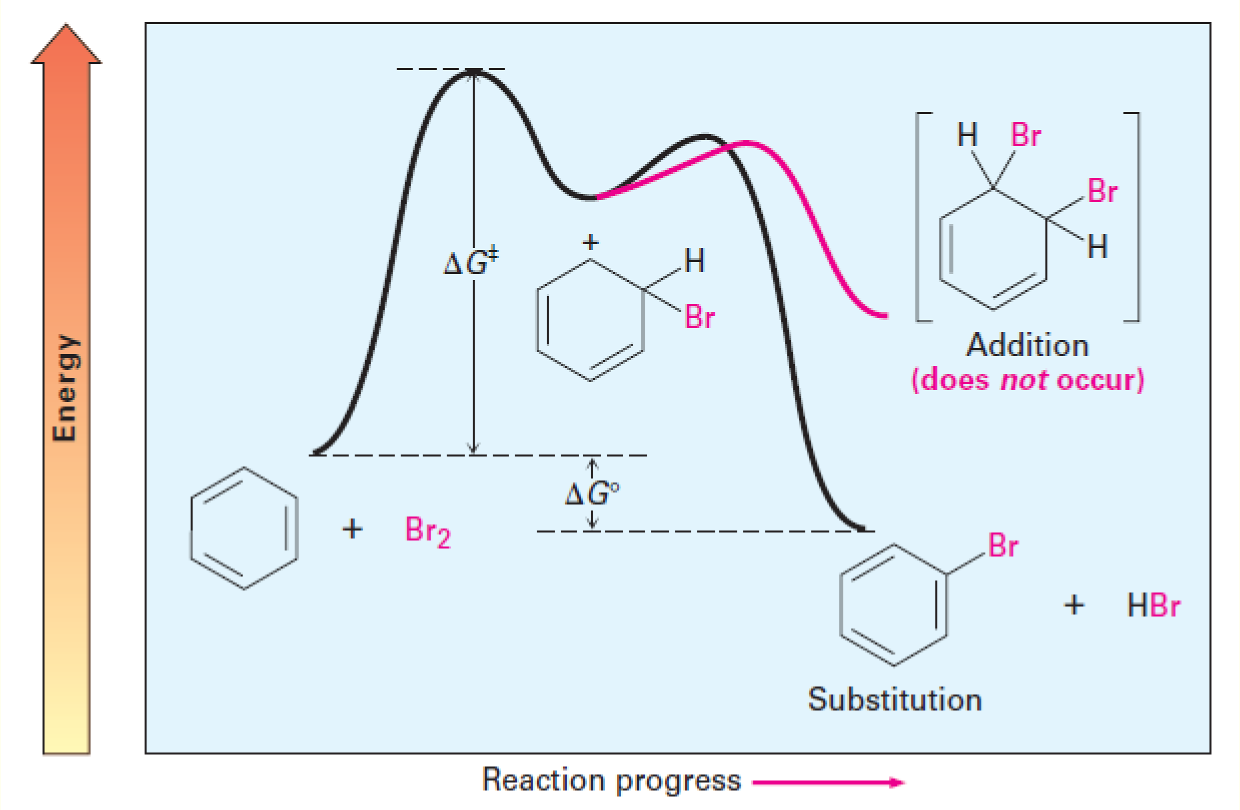
- Two important steps involved in the mechanism of electrophilic aromatic substitution reactions:-
- Step-1: Attack of an electrophilic reagent to benzene to produce carbonium ion or carbocation. It is slow process.
- Step-2: Abstraction of Hydrogen ion from this carbonium ion by some base. It is fast process.
- In some mechanisms, the production of electrophile will be the first step followed by other 2 steps as mentioned above.

Why this Chapter?

- This chapter continues the coverage of aromatic compounds in preceding chapter…we focus to understanding reactions, examining relationship between aromatic structure and reactivity.
- This relationship is critical to understanding of how biological molecules/pharmaceutical agents are synthesized.

Halogenation: Bromination

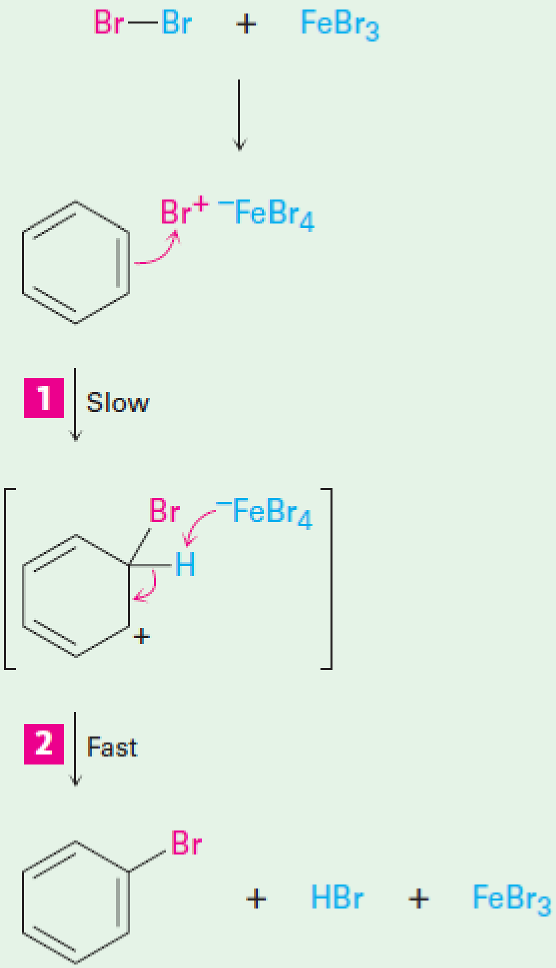




Energy diagram for bromination

Bromination: Mechanism

$FeBr_3$ is added as a catalyst to polarize the bromine reagent



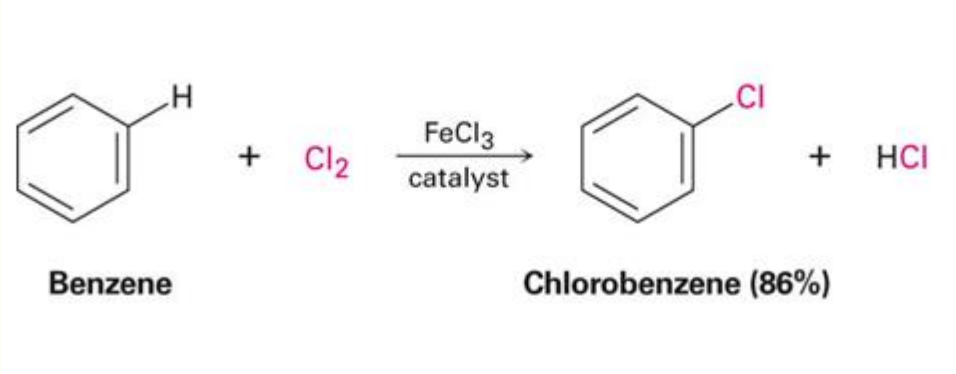
1 An electron pair from the benzene ring attacks the positively polarized bromine, forming a new C–Br bond and leaving a nonaromatic carbocation intermediate.

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

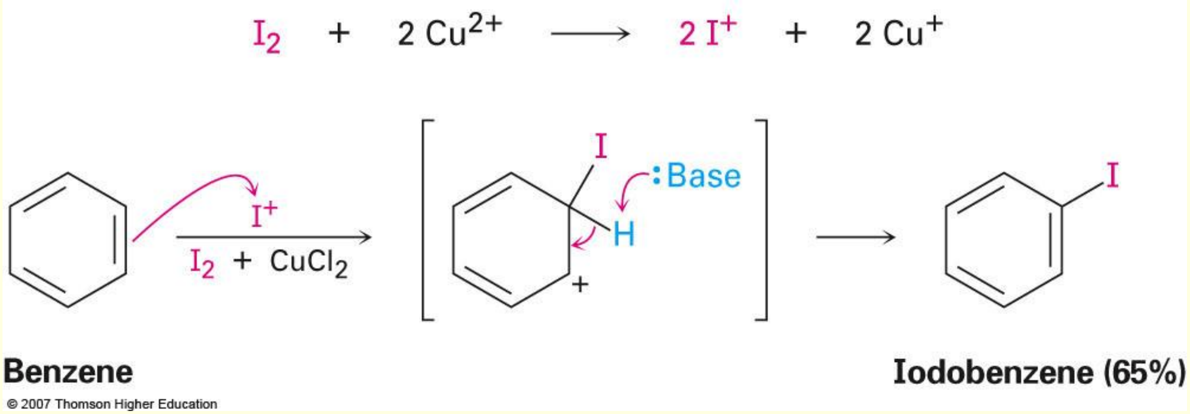
Other Aromatic halogenations

Chlorination

Chlorination requires $FeCl_3$

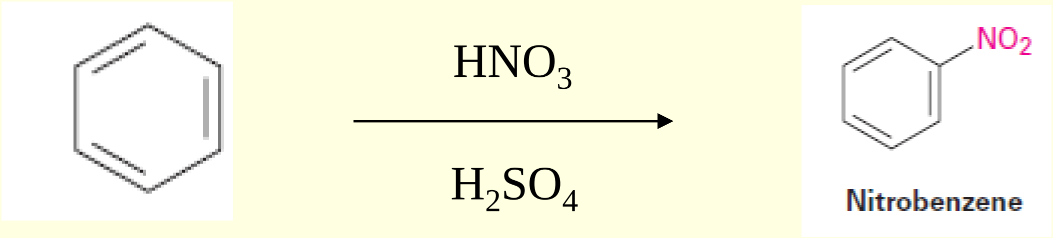


Iodination



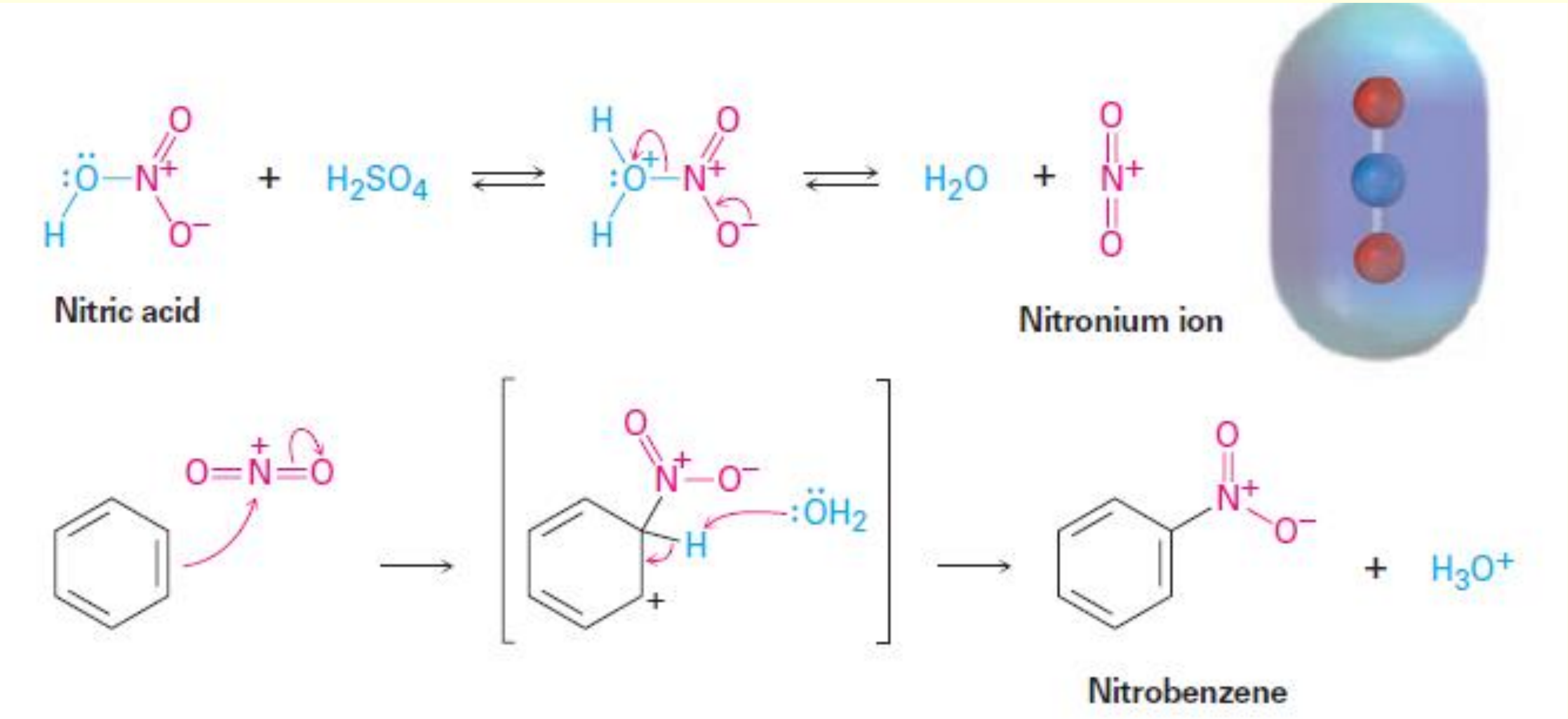
Iodine must be oxidized to form a more powerful I^+ species (with Cu^{2+} from $CuCl_2$)

Aromatic Nitration

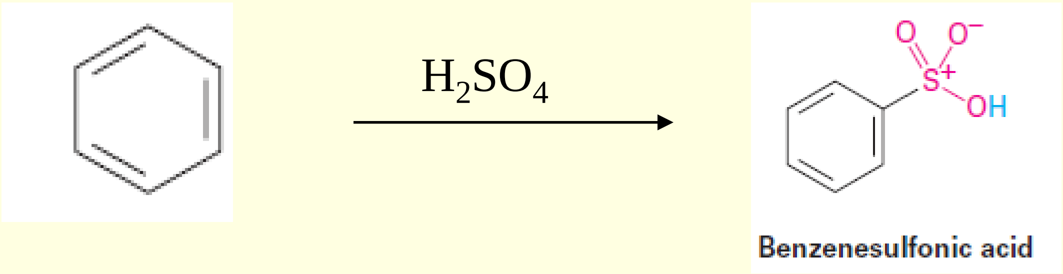


- Aromatic rings are nitrated by reaction with a mixture of concentrated nitric and sulfuric acids.
- The electrophile is the nitronium ion, NO_2^+, which is formed from HNO_3 by protonation and loss of water.
- The nitronium ion reacts with benzene to yield a carbocation intermediate, and loss of H^+ from this intermediate gives the neutral substitution product, nitrobenzene.

Aromatic Nitration: Mechanism

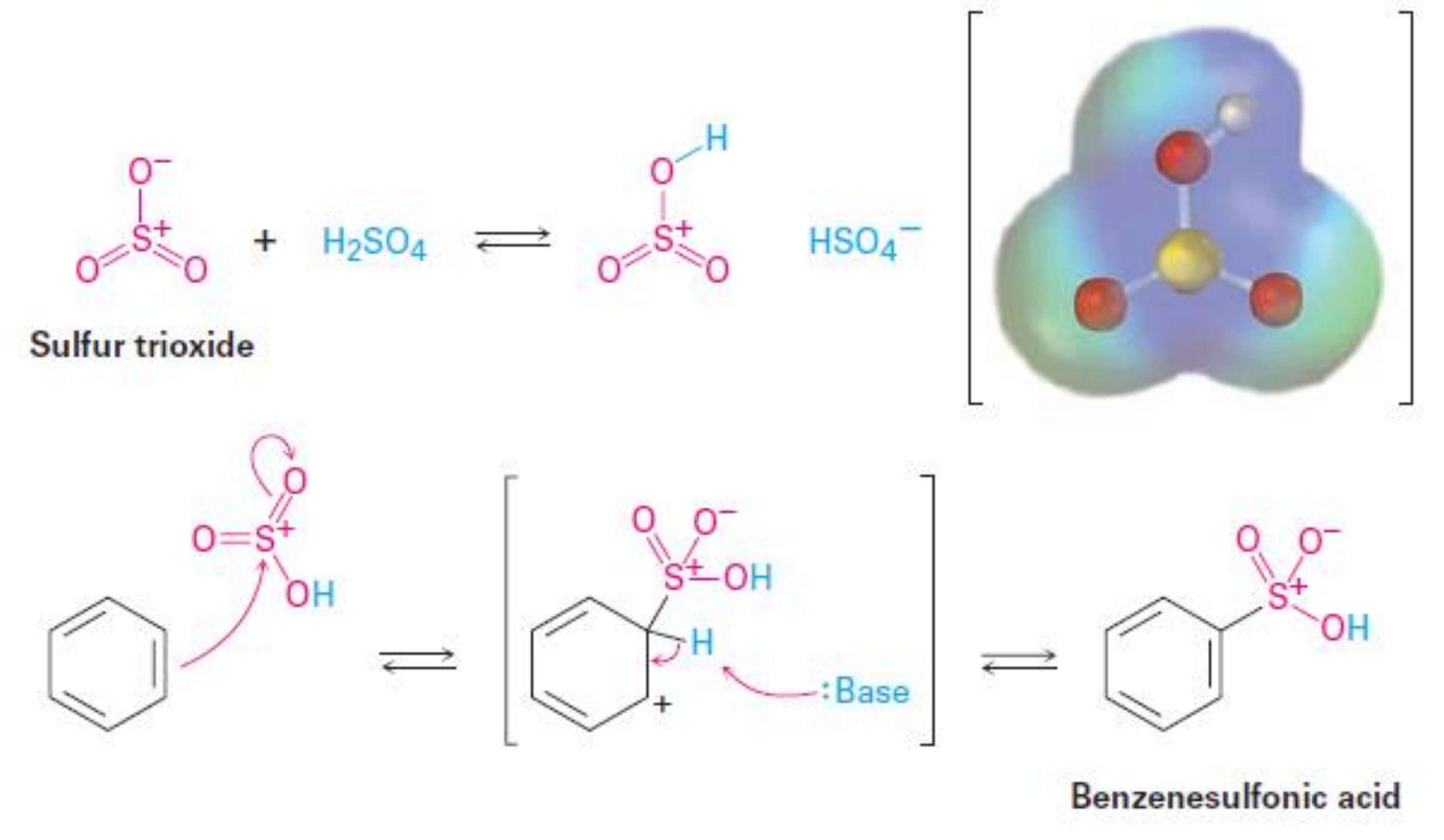


Aromatic Sulfonation



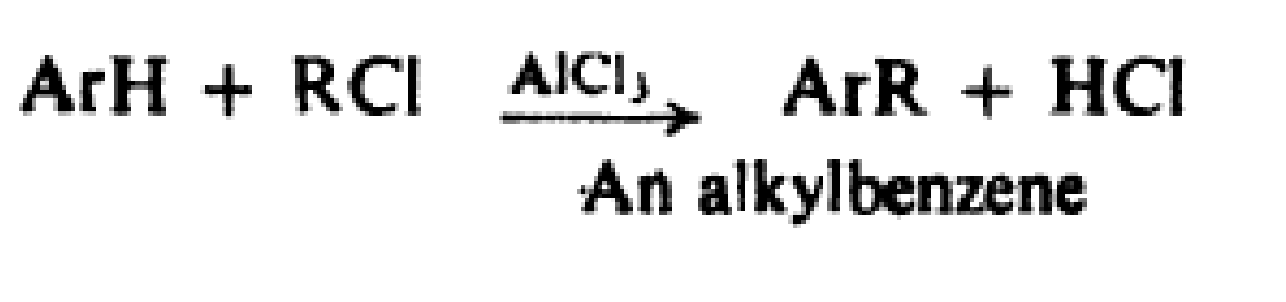
- Substitution of H by SO_3 (sulfonation)
- Reaction with a mixture of sulfuric acid and SO3 (“Fuming H2SO4)
- Reactive species is sulfur trioxide or its conjugate acid

Aromatic Sulfonation: Mechanism



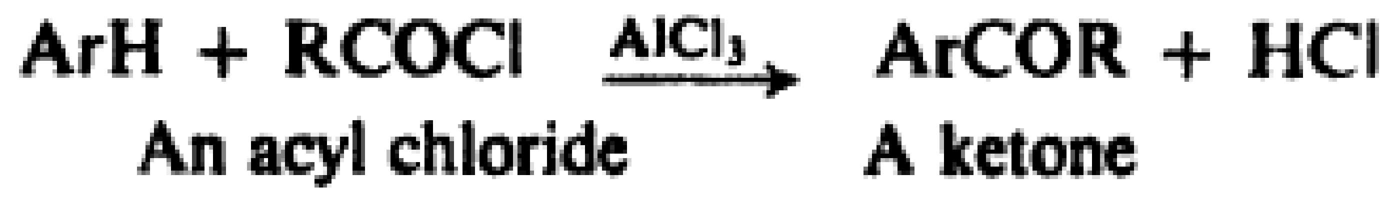
Friedel–Crafts Reactions: Alkylation and Acylation of Aromatic Rings

Friedel–Crafts Reactions: Alkylation



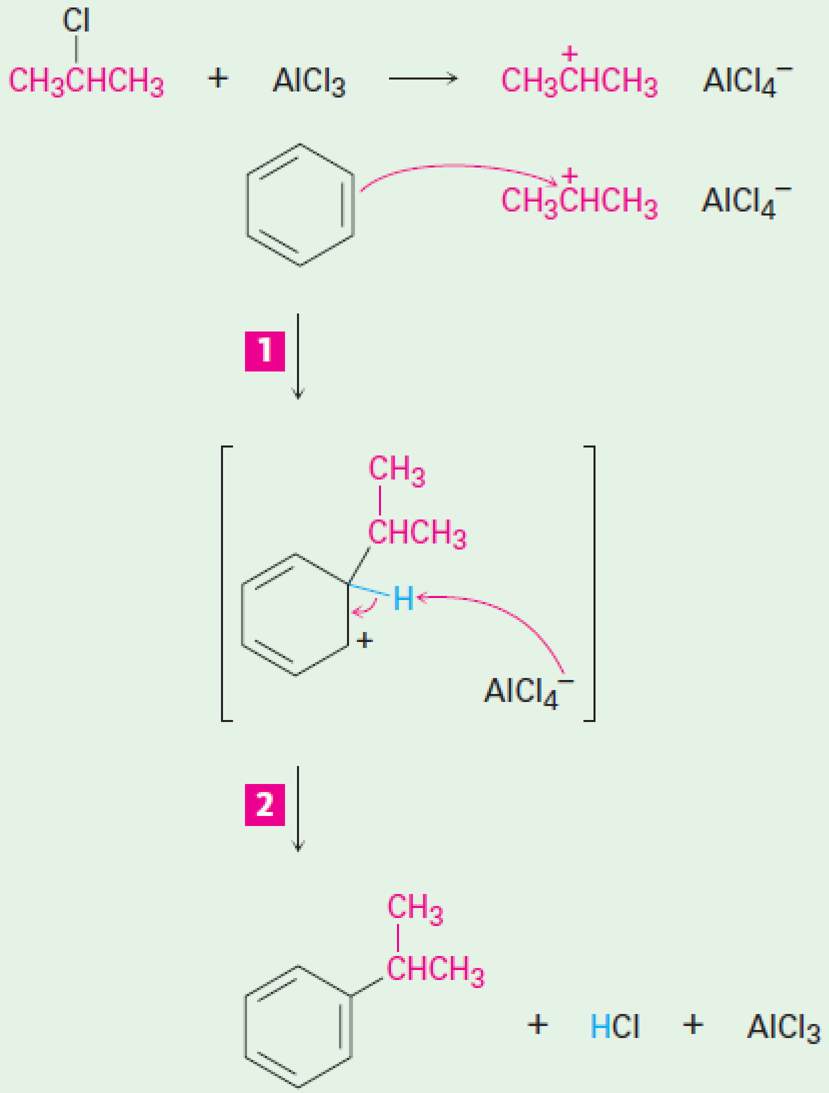
$$\mathrm{ArH + RCl \xrightarrow{AlCl_3} \underbrace{ArR}_{\text{An alkylbenzene}} + HCl}$$

Friedel–Crafts Reactions: Acylation



$$\mathrm{ArH + \underbrace{RCOCl}_{\text{An acyl chloride}} \xrightarrow{AlCl_3} \underbrace{ArCOR}_{\text{A ketone}} + HCl}$$

Friedel–Crafts Reactions: Mechanism of Alkylation

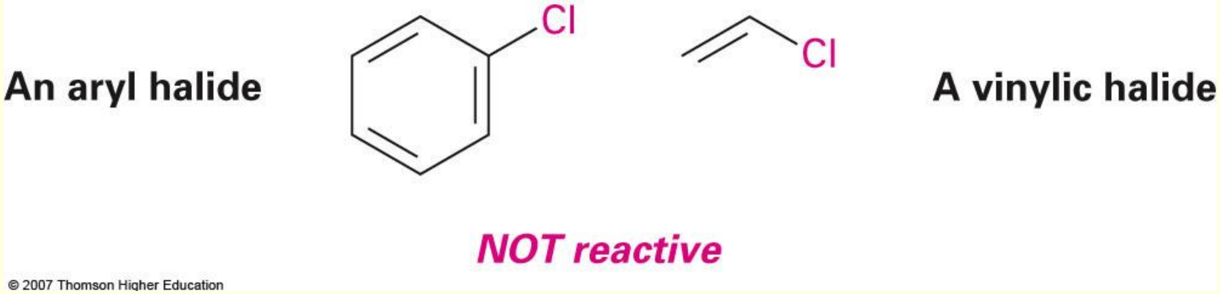


1 An electron pair from the aromatic ring attacks the carbocation, forming a C–C bond and yielding a new carbocation intermediate.

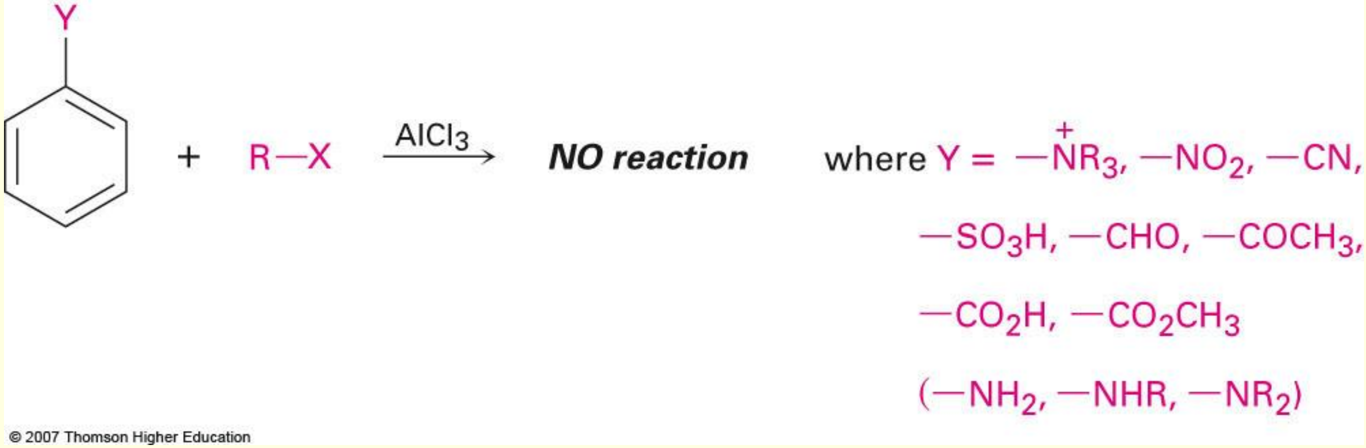
2 Loss of a proton then gives the neutral alkylated substitution product.

Limitations of Friedel–Crafts Alkylation

- Only *alkyl* halides can be used (F, Cl, I, Br)
- *Aryl* halides and *vinylic* halides do not react (their carbocations are too hard to form)



Will not work with rings containing a strongly electron-withdrawing group like carbonyl group (C=O)

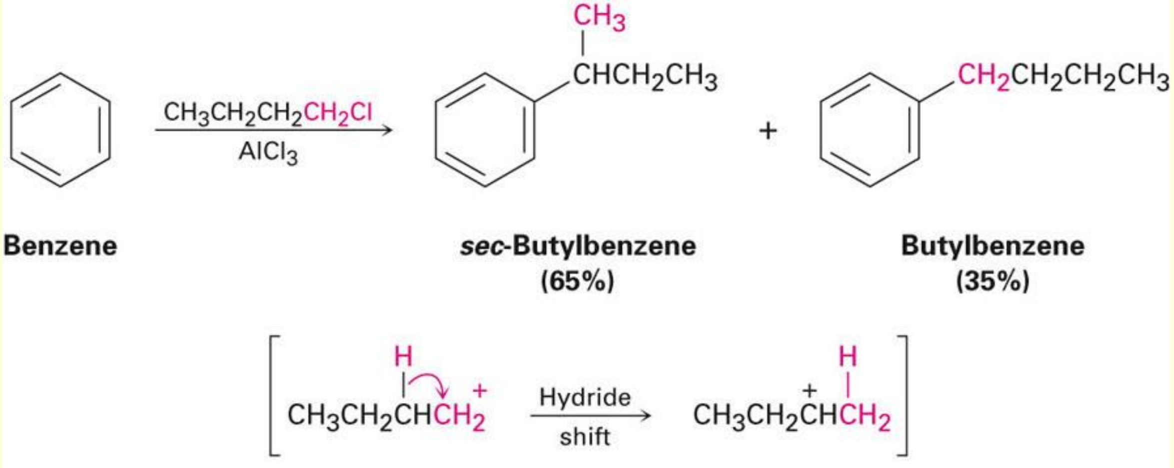


Limitations of Friedel–Crafts Alkylation

It is difficult to stop the reaction after a single substitution, so multiple alkylations can occur because first alkylation is activating the ring

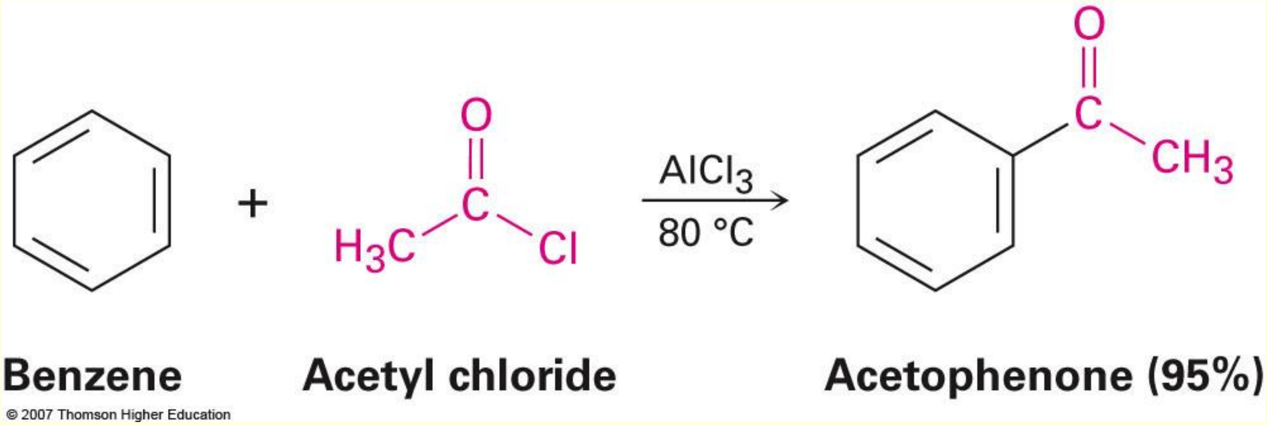
Limitations of Friedel–Crafts Alkylation

- Final limitation to the Friedel–Crafts reaction is that a skeletal rearrangement of the alkyl carbocation electrophile sometimes occurs during reaction, particularly when a primary alkyl halide is used.
- Treatment of benzene with 1-chlorobutane at 0 °C, for instance, gives an approximately 2;1 ratio of rearranged (sec-butyl) to unrearranged (butyl) products.



Friedel–Crafts Reactions: Acylation

- Reaction of an acid chloride (RCOCl) and an aromatic ring in the presence of $AlCl_3$ introduces **acyl group**, —COR
  - Benzene with acetyl chloride yields acetophenone



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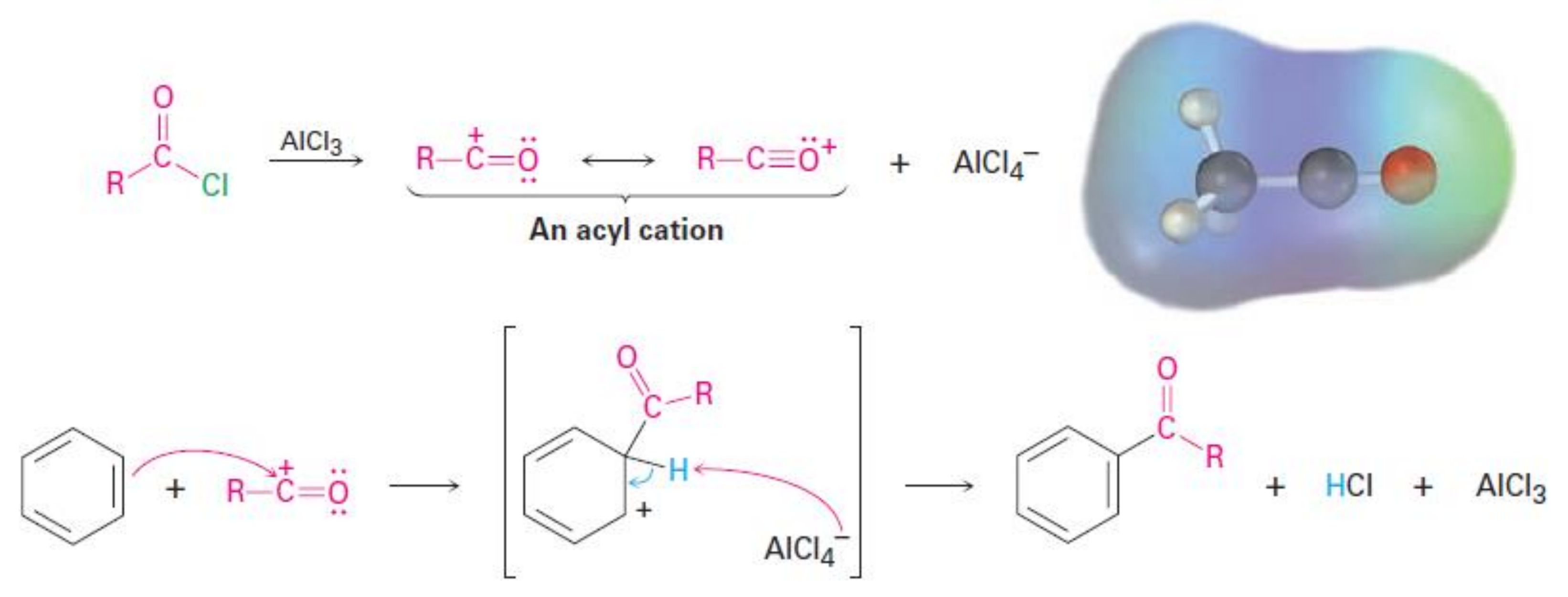
- Avoids many of the problems of alkylation
  - Only substitutes once, because acyl group is deactivating
  - No rearrangement because of resonance stabilized cation

Friedel–Crafts Reactions: Mechanism of Acylation

The mechanism of the Friedel–Crafts acylation reaction is similar to that of Friedel–Crafts alkylation.

Reactive electrophile: resonance-stabilized acyl cation

An acyl cation does not rearrange, so acylations never occur more than once on a ring



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