The regioselectivity of substitution in pyrrole and thiophene is like that of furan and for similar reasons.

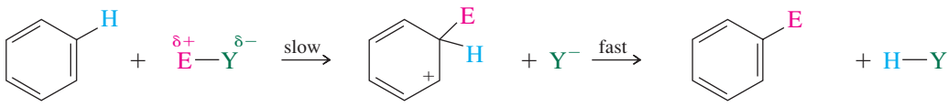
PROBLEM 12.23

When benzene is prepared from coal tar, it is contaminated with thiophene, from which it cannot be separated by distillation because of very similar boiling points. Shaking a mixture of benzene and thiophene with sulfuric acid causes sulfonation of the thiophene ring but leaves benzene untouched. The sulfonation product of thiophene dissolves in the sulfuric acid layer, from which the benzene layer is separated; the benzene layer is then washed with water and distilled. Give the structure of the sulfonation product of thiophene.

12.19 SUMMARY

Section 12.1 On reaction with electrophilic reagents, compounds that contain a benzene ring undergo **electrophilic aromatic substitution.** Table 12.1 in Section 12.1 and Table 12.3 in this summary give examples.

Section 12.2 The mechanism of electrophilic aromatic substitution involves two stages: bonding of the electrophile by the π electrons of the ring (slow, rate-determining), followed by rapid loss of a proton to restore the aromaticity of the ring.

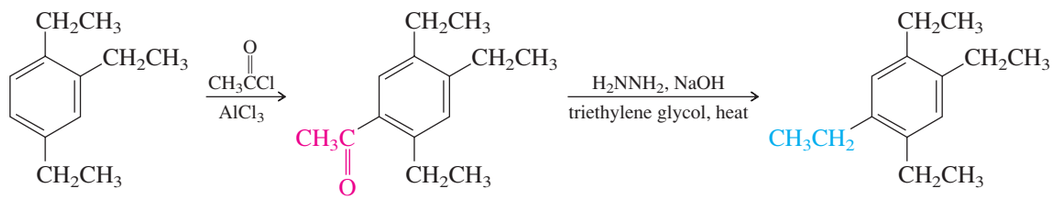


Benzene | Electrophilic reagent | Cyclohexadienyl cation intermediate | Product of electrophilic aromatic substitution

Sections 12.3–12.5 See Table 12.3

Sections 12.6–12.7 See Tables 12.3 and 12.4.

Section 12.8 Friedel–Crafts acylation, followed by Clemmensen or Wolff–Kishner reduction is a standard sequence used to introduce a primary alkyl group onto an aromatic ring.



1,2,4-Triethylbenzene | 2,4,5-Triethylacetophenone (80%) | 1,2,4,5-Tetraethylbenzene (73%)

Section 12.9 Substituents on an aromatic ring can influence both the *rate* and *regioselectivity* of electrophilic aromatic substitution. Substituents are classified as *activating* or *deactivating* according to whether they cause electrophilic aromatic substitution to occur more rapidly or less rapidly than

TABLE 12.3 Representative Electrophilic Aromatic Substitution Reactions

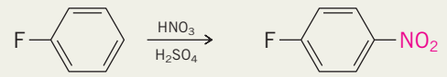
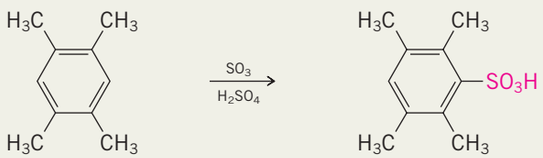
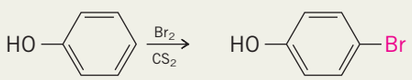
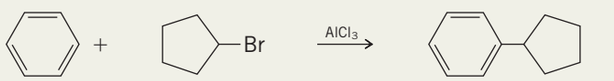
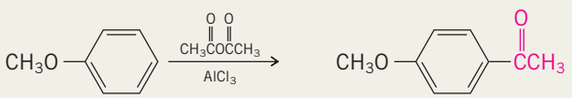
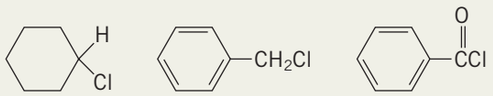
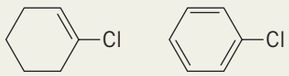
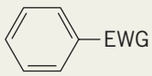
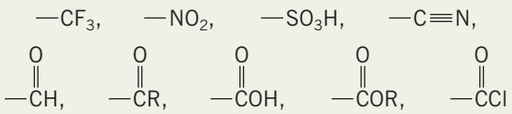
Reaction (section) and comments	General equation and specific example
Nitration (Section 12.3) The active electrophile in the nitration of benzene and its derivatives is nitronium cation ($:\ddot{O}{=}\overset{+}{N}{=}\ddot{O}:$). It is generated by reaction of nitric acid and sulfuric acid. Very reactive arenes—those that bear strongly activating substituents—undergo nitration in nitric acid alone.	$ArH + HNO_3 \xrightarrow{H_2SO_4} ArNO_2 + H_2O$ Arene · Nitric acid · Nitroarene · Water  Fluorobenzene · *p*-Fluoronitrobenzene (80%)
Sulfonation (Section 12.4) Sulfonic acids are formed when aromatic compounds are treated with sources of sulfur trioxide. These sources can be concentrated sulfuric acid (for very reactive arenes) or solutions of sulfur trioxide in sulfuric acid (for benzene and arenes less reactive than benzene).	$ArH + SO_3 \longrightarrow ArSO_3H$ Arene · Sulfur trioxide · Arenesulfonic acid  1,2,4,5-Tetramethylbenzene · 2,3,5,6-Tetramethylbenzenesulfonic acid (94%)
Halogenation (Section 12.5) Chlorination and bromination of arenes are carried out by treatment with the appropriate halogen in the presence of a Lewis acid catalyst. Very reactive arenes undergo halogenation in the absence of a catalyst.	$ArH + X_2 \xrightarrow{FeX_3} ArX + HX$ Arene · Halogen · Aryl halide · Hydrogen halide  Phenol · *p*-Bromophenol (80–84%)
Friedel–Crafts alkylation (Section 12.6) Carbocations, usually generated from an alkyl halide and aluminum chloride, alkylate the aromatic ring. The arene must be at least as reactive as a halobenzene. Carbocation rearrangements can occur, especially with primary alkyl halides.	$ArH + RX \xrightarrow{AlCl_3} ArR + HX$ Arene · Alkyl halide · Alkylarene · Hydrogen halide  Benzene · Cyclopentyl bromide · Cyclopentylbenzene (54%)
Friedel–Crafts acylation (Section 12.7) Acyl cations (acylium ions) generated by treating an acyl chloride or acid anhydride with aluminum chloride acylate aromatic rings to yield ketones. The arene must be at least as reactive as a halobenzene. Acyl cations are relatively stable, and do not rearrange.	$ArH + RCCl \xrightarrow{AlCl_3} ArCR + HCl$ Arene · Acyl chloride · Ketone · Hydrogen chloride $ArH + RCOCR \xrightarrow{AlCl_3} ArCR + RCOH$ Arene · Acid anhydride · Ketone · Carboxylic acid  Anisole · *p*-Methoxyacetophenone (90–94%)

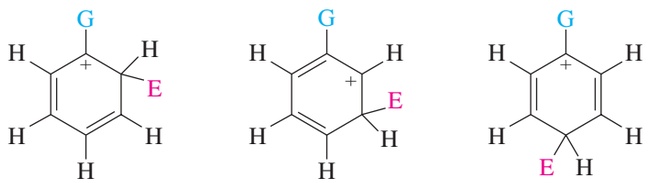
TABLE 12.4 Limitations on Friedel–Crafts Reactions

1. The organic halide that reacts with the arene must be an alkyl halide (Section 12.6) or an acyl halide (Section 12.7).	*These will react with benzene under Friedel–Crafts conditions:*  Alkyl halide; Benzylic halide; Acyl halide
Vinylic halides and aryl halides do not form carbocations under conditions of the Friedel–Crafts reaction and so cannot be used in place of an alkyl halide or an acyl halide.	*These will not react with benzene under Friedel–Crafts conditions:*  Vinylic halide; Aryl halide
2. Rearrangement of alkyl groups can occur (Section 12.6).	Rearrangement is especially prevalent with primary alkyl halides of the type RCH_2CH_2X and R_2CHCH_2X. Aluminum chloride induces ionization with rearrangement to give a more stable carbocation. Benzylic halides and acyl halides do not rearrange.
3. Strongly deactivated aromatic rings do not undergo Friedel–Crafts alkylation or acylation (Section 12.16). Friedel–Crafts alkylations and acylations fail when applied to compounds of the following type, where EWG is a strongly electron-withdrawing group: 	*EWG:* 
4. It is sometimes difficult to limit Friedel–Crafts alkylation to monoalkylation. Only monoacylation occurs during Friedel–Crafts acylation.	The first *alkyl* group that goes on makes the ring more reactive toward further substitution because alkyl groups are activating substituents. Monoacylation is possible because the first *acyl* group to go on is strongly electron-withdrawing and deactivates the ring toward further substitution.

benzene. With respect to regioselectivity, substituents are either *ortho, para-directing* or *meta-directing*. A methyl group is activating and ortho, para-directing. A trifluoromethyl group is deactivating and meta-directing.

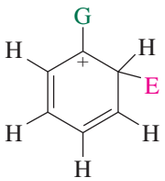
Sections 12.10–12.14

How substituents control rate and regioselectivity in electrophilic aromatic substitution results from their effect on carbocation stability. An electron-releasing substituent stabilizes the cyclohexadienyl cation intermediates leading to ortho and para substitution more than meta.

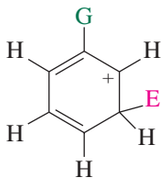


Stabilized when G is electron-releasing; Less stabilized when G is electron-releasing; Stabilized when G is electron-releasing

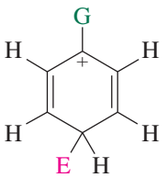
Conversely, an electron-withdrawing substituent destabilizes the cyclohexadienyl cations leading to ortho and para substitution more than meta. Thus, meta substitution predominates.



Destabilized when G is electron-withdrawing



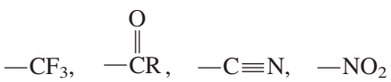
Less destabilized when G is electron-withdrawing



Destabilized when G is electron-withdrawing

Substituents can be arranged into three major categories:

1. **Activating and ortho, para-directing:** These substituents stabilize the cyclohexadienyl cation formed in the rate-determining step. They include $-\ddot{N}R_2$, $-\ddot{O}R$, —R, —Ar, and related species. The most strongly activating members of this group are bonded to the ring by a nitrogen or oxygen atom that bears an unshared pair of electrons.
2. **Deactivating and ortho, para-directing:** The halogens are the most prominent members of this class. They withdraw electron density from all the ring positions by an inductive effect, making halobenzenes less reactive than benzene. Lone-pair electron donation stabilizes the cyclohexadienyl cation intermediates for ortho and para substitution more than those for meta substitution.
3. **Deactivating and meta-directing:** These substituents are strongly electron-withdrawing and destabilize carbocations. They include



and related species. All the ring positions are deactivated, but because the *meta* positions are deactivated less than the ortho and para, meta substitution is favored.

Section 12.15 When two or more substituents are present on a ring, the regioselectivity of electrophilic aromatic substitution is generally controlled by the directing effect of the more powerful *activating* substituent.

Section 12.16 The order in which substituents are introduced onto a benzene ring needs to be considered in order to prepare the desired isomer in a multistep synthesis.

Section 12.17 Polycyclic aromatic hydrocarbons undergo the same kind of electrophilic aromatic substitution reactions as benzene.

Section 12.18 Heterocyclic aromatic compounds may be more reactive or less reactive than benzene. Pyridine is much less reactive than benzene, but pyrrole, furan, and thiophene are more reactive.

PROBLEMS

12.24 Give reagents suitable for carrying out each of the following reactions, and write the major organic products. If an ortho, para mixture is expected, show both. If the meta isomer is the expected major product, write only that isomer.

(a) Nitration of benzene

(b) Nitration of the product of part (a)

(c) Bromination of toluene

(d) Bromination of (trifluoromethyl)benzene

(e) Sulfonation of anisole

(f) Sulfonation of acetanilide ($C_6H_5NHCCH_3$, O above C)