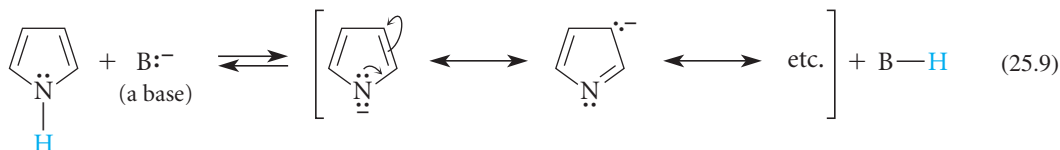


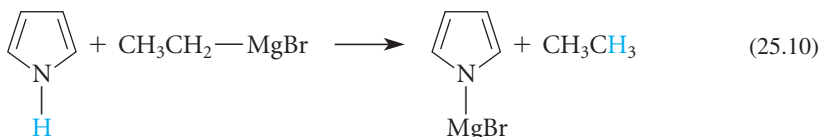
## B. Acidity of Pyrrole and Indole

Pyrrole and indole are weak acids.



**Further Exploration 25.1**  
Relative Acidities of  
1,3-Cyclopentadiene  
and Pyrrole

With  $pK_a$  values of about 17.5, pyrrole and indole are about as acidic as alcohols and about 15–17  $pK_a$  units more acidic than primary and secondary amines (Sec. 23.5D). The greater acidity of pyrroles and indoles is a consequence of the resonance stabilization of their conjugate-base anions (Eq. 25.9; draw the three missing resonance structures in this equation.) Pyrrole and indole are rapidly deprotonated by Grignard and organolithium reagents.



### PROBLEMS

- 25.6 (a) Suggest a reason why pyridine is miscible with water, whereas pyrrole has little water solubility.  
(b) Indicate whether you would expect imidazole to have high or low water solubility, and why.
- 25.7 (a) The compound 4-(dimethylamino)pyridine protonates to give a conjugate acid with a  $pK_a$  value of 9.9. This compound is thus 4.7  $pK_a$  units more basic than pyridine itself. Draw the structure of the conjugate acid of 4-(dimethylamino)pyridine, and explain why 4-(dimethylamino)pyridine is much more basic than pyridine.  
(b) What product is expected when 4-(dimethylamino)pyridine reacts with  $\text{CH}_3\text{I}$ ?
- 25.8 Protonation of aniline causes a dramatic shift of its UV spectrum to lower wavelengths, but protonation of pyridine has almost no effect on its UV spectrum. Explain the difference.

## 25.3 THE CHEMISTRY OF FURAN, PYRROLE, AND THIOPHENE

### A. Electrophilic Aromatic Substitution

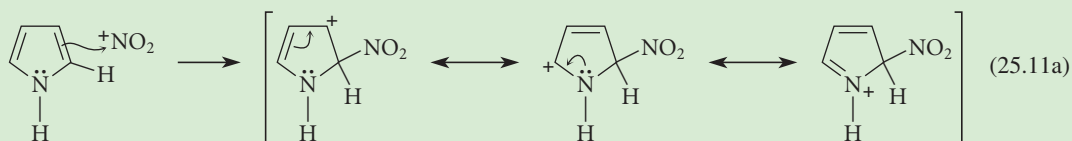
Furan, thiophene, and pyrrole, like benzene and naphthalene, undergo electrophilic aromatic substitution reactions. Let's try to predict the ring carbon at which substitution occurs in these compounds by examining the carbocation intermediates involved in the substitution reactions at the two different positions and applying Hammond's postulate.

## Study Problem 25.2

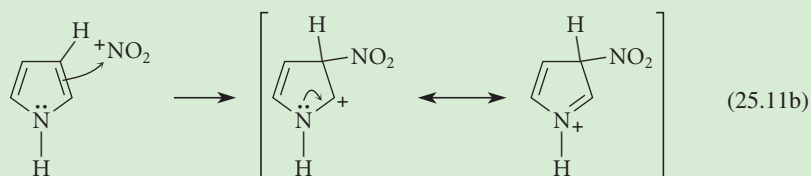
Using the nitration of pyrrole as an example, predict whether electrophilic aromatic substitution occurs predominantly at carbon-2 or carbon-3.

**Solution** Recall (p. 755) that the electrophile in nitration is the nitronium ion,  $^+\text{NO}_2$ . Substitution at the two different positions of pyrrole by the nitronium ion gives different carbocation intermediates:

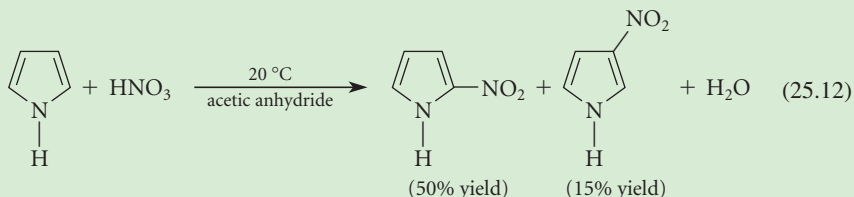
*Substitution at carbon-2:*



*Substitution at carbon-3:*

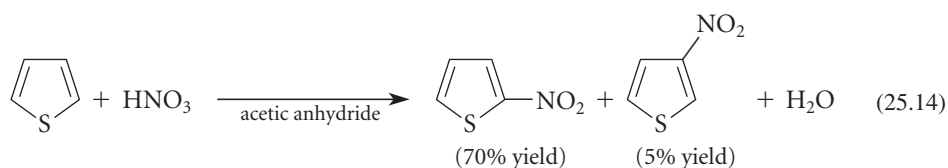
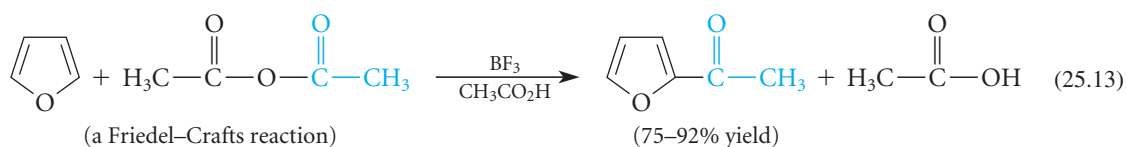


The carbocation resulting from substitution at carbon-2 has more important resonance structures and is therefore more stable than the carbocation resulting from substitution at carbon-3. Applying Hammond's postulate, we predict that the reaction involving the more stable intermediate should be the faster reaction. Consequently, nitration should occur at carbon-2. The experimental facts are as follows:

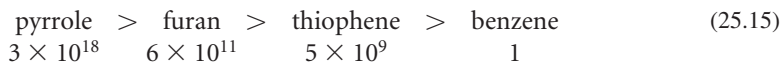


2-Nitropyrrole is the major nitration product of pyrrole, as predicted. Nothing is really wrong with substitution at carbon-3; substitution at carbon-2 is simply more favorable. As Eq. 25.12 shows, some 3-nitropyrrole is obtained in the reaction.

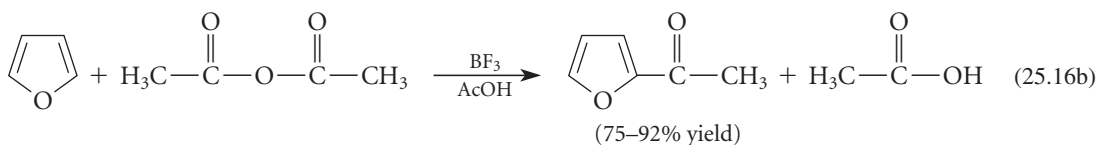
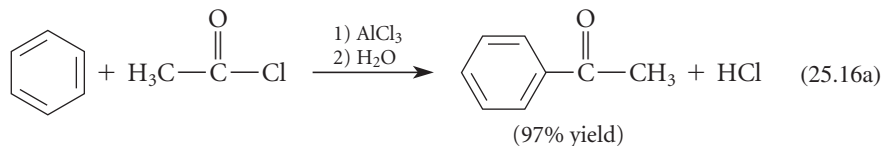
As Study Problem 25.2 suggests, electrophilic substitution of pyrrole occurs predominantly at the 2-position. Similar results are observed with furan and thiophene:



Pyrrole, furan, and thiophene are all much more reactive than benzene in electrophilic aromatic substitution. Although precise reactivity ratios depend on the particular reaction, the relative rates of bromination are typical:

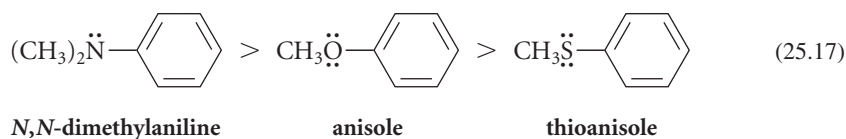


Milder reaction conditions must be used with more reactive compounds. (Reaction conditions that are too vigorous in many cases bring about so many side reactions that polymerization and tar formation occur.) For example, a less reactive acylating reagent is used in the acylation of furan than in the acylation of benzene. (Recall that anhydrides are less reactive than acid chlorides; pp. 1011–1015.)

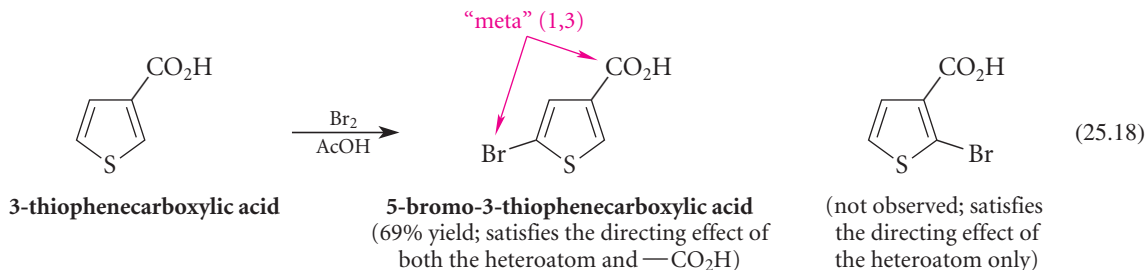


The reactivity order of the heterocycles (Eq. 25.15) is a consequence of the relative abilities of the heteroatoms to stabilize positive charge in the intermediate carbocations (as in Eq. 25.11a, for example). Both pyrrole and furan have heteroatoms from the second period of the periodic table. Because nitrogen is better than oxygen at delocalizing positive charge—nitrogen is less electronegative—pyrrole is more reactive than furan. The sulfur of thiophene is a third-period element and, although it is less electronegative than oxygen, its  $3p$  orbitals overlap less efficiently with the  $2p$  orbitals of the aromatic  $\pi$ -electron system (see Fig. 16.7, p. 771). In fact, the reactivity *order* of the heterocycles in aromatic substitution parallels the reactivity order of the correspondingly substituted benzene derivatives:

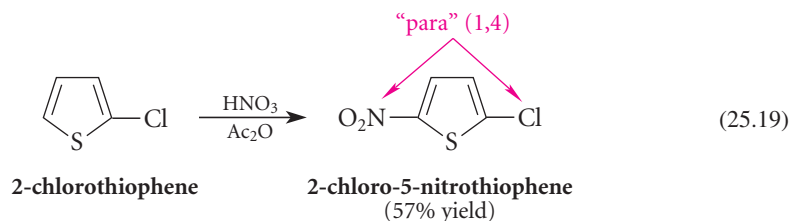
Relative reactivities:



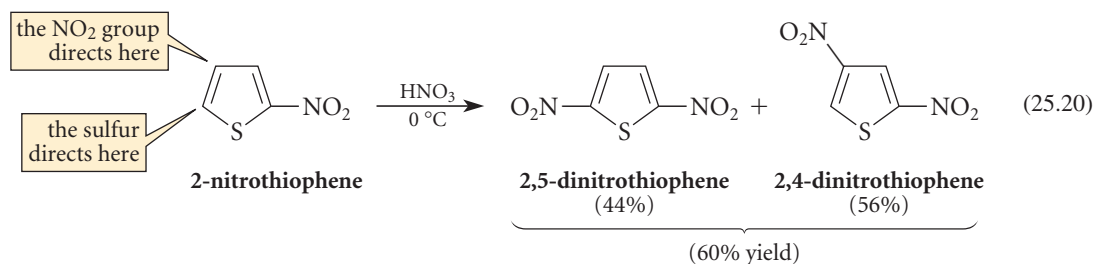
When we consider the activating and directing effects of substituents in furan, pyrrole, and thiophene rings, the usual activating and directing effects of substituents in aromatic substitution apply (see Table 16.2, p. 763). Superimposed on these effects is the normal effect of the heterocyclic atom in directing substitution to the 2-position. The following example illustrates these effects:



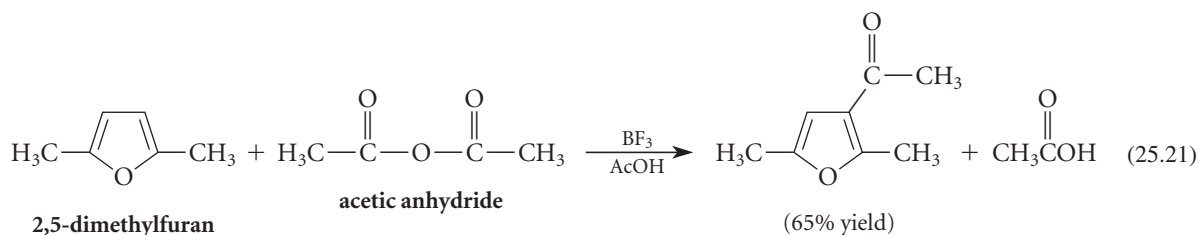
In this example, the  $-\text{CO}_2\text{H}$  group directs the second substituent into a “meta” (1,3) relationship; the thiophene ring tends to substitute at the 2-position. The observed product satisfies both of these directing effects. (Notice that we count around the *carbon* framework of the heterocyclic compound, not through the heteroatom, when using this ortho, meta, para analogy.) In the following example, the chloro group is an ortho, para-directing group. Because the position “para” to the chloro group is also a 2-position, both the sulfur of the ring and the chloro group direct the incoming nitro group to the same position.



When the directing effects of substituents and the ring compete, it is not unusual to observe mixtures of products.



Finally, if both 2-positions are occupied, 3-substitution takes place.



## B. Addition Reactions of Furan

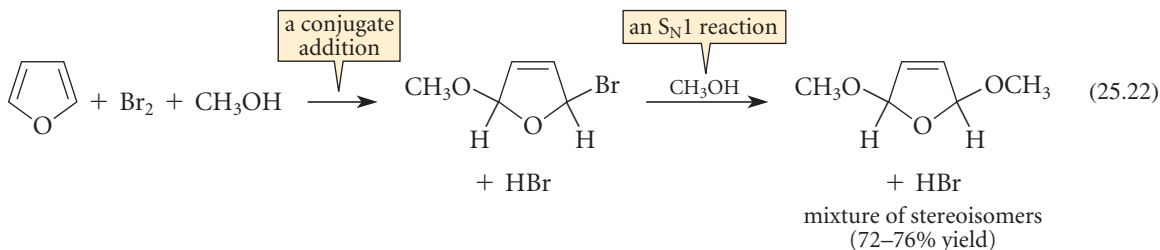
The previous sections focused on the aromatic character of furan, pyrrole, and thiophene. A furan, pyrrole, or thiophene could, however, be viewed as a 1,3-butadiene with its terminal carbons “tied down” by a heteroatom bridge.



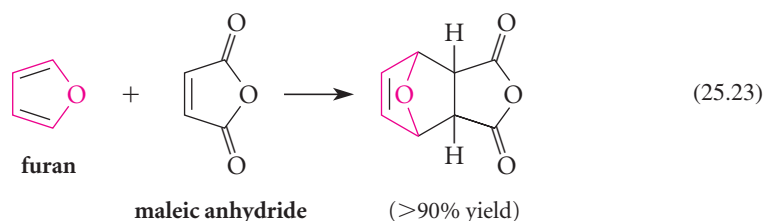
“butadiene” unit within furan

Do the heterocycles ever behave chemically as if they are conjugated dienes? Of the three heterocyclic compounds furan, pyrrole, and thiophene, furan has the least resonance energy (Table 25.1) and, by implication, the least aromatic character. Consequently, of the three compounds, furan has the greatest tendency to behave like a conjugated diene.

One characteristic reaction of conjugated dienes is *conjugate addition* (Sec. 15.4A). Indeed, furan does undergo some conjugate addition reactions. One example of such a reaction occurs in bromination. For example, furan undergoes conjugate addition of bromine and methanol in methanol solvent; the conjugate-addition product then undergoes an  $S_N1$  reaction with the methanol. (Write mechanisms for both parts of this reaction; refer to Sec. 15.4A if necessary.)

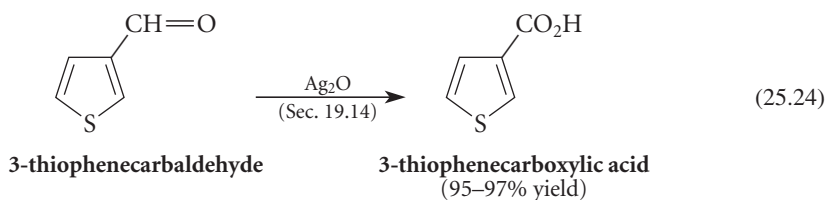


Another manifestation of the conjugated-diene character of furan is that it undergoes Diels–Alder reactions (Sec. 15.3) with reactive dienophiles such as maleic anhydride.

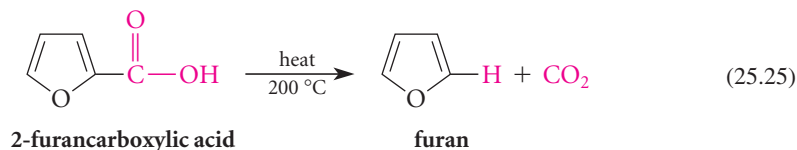


### C. Side-Chain Reactions

Many reactions occur at the side chains of heterocyclic compounds without affecting the rings, just as some reactions occur at the side chain of a substituted benzene (Secs. 17.1–17.5).

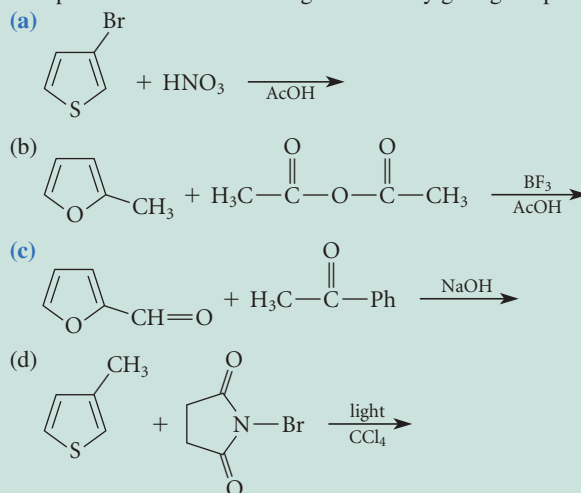


A particularly useful example of a side-chain reaction is removal of a carboxy group directly attached to the ring (*decarboxylation*). This reaction is effected by strong heating, in some cases with catalysts.

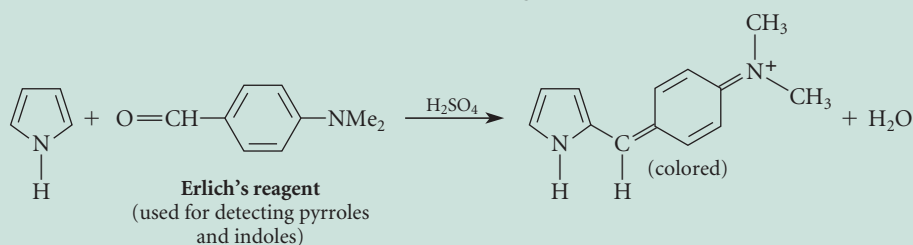


## PROBLEMS

25.9 Complete each of the following reactions by giving the principal organic product(s).



25.10 Write a curved-arrow mechanism for the following reaction.



## 25.4 THE CHEMISTRY OF PYRIDINE

## A. Electrophilic Aromatic Substitution

In general, it is difficult to prepare monosubstituted pyridines by electrophilic aromatic substitution because pyridine has a very low reactivity; it is much less reactive than benzene. An important reason for this low reactivity is that pyridine is protonated under the very acidic conditions of most electrophilic aromatic substitution reactions (Eq. 25.4, p. 1224). The resulting positive charge on nitrogen makes it difficult to form a carbocation intermediate, which would place a second positive charge within the same ring.

Fortunately, a number of monosubstituted pyridines are available from natural sources. Among these are the methylpyridines, or *picolines*:

