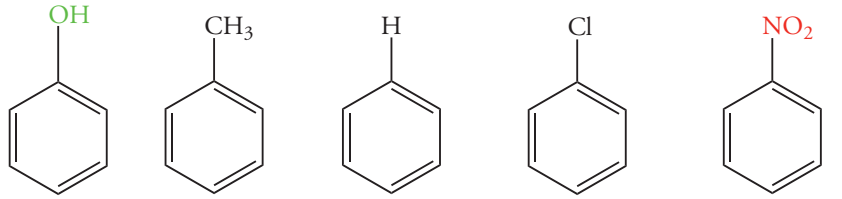
SUBSTITUENT EFFECTS IN ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS

To this point, we have discussed only electrophilic substitution reactions of benzene itself. Now we will examine the effect that a substituent already bonded to the aromatic ring has on ring attack by an electrophile to attach a second substituent. For a substitution reaction on benzene, only one product results. But if a second substituent adds to a substituted benzene, any of three possible products—the *ortho*, *meta*, and *para* isomers—can be produced. We would like to know how the original substituent affects (1) the rate of formation of these products and (2) how the substituent affects the product distribution.

Effects of Ring Substituents on Reaction Rate

To examine the effect of a substituent on the rate of electrophilic aromatic substitution, let's compare the rate of nitration of benzene to those of several substituted benzenes. The relative rate of reaction of phenol is 10^{10} faster than that of nitrobenzene. (For comparison, the speed of light is about 10^8 faster than the speed of jogging.)

Relative rates of nitration of benzene and its derivatives



	phenol	toluene	benzene	chlorobenzene	nitrobenzene
rel. rate	10^3	25	1	3×10^{-3}	10^{-7}

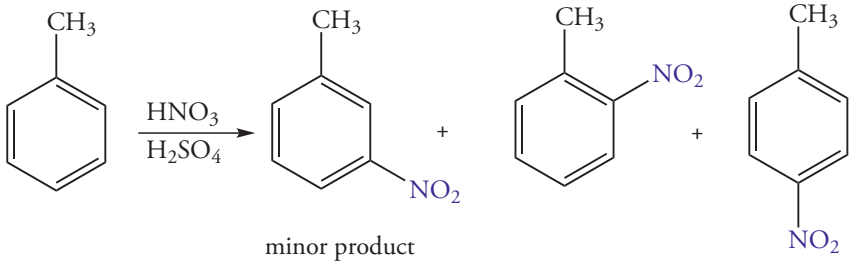
Phenol and toluene are nitrated faster than benzene, whose relative rate of reaction is set at 1. Both a hydroxyl group and a methyl group make the aromatic ring more reactive compared to benzene; they are *activating groups*. On the other hand, chlorobenzene and nitrobenzene react more slowly than benzene. The chloro and nitro groups are *deactivating groups* because they make the aromatic ring less reactive. Table 13.1 lists some common substituents and divides them into activating and deactivating groups with respect to electrophilic aromatic substitution.

Table 1
Effects of Ring Substituents on Reaction Rate

Strongly activating
—NH_2, —NHR, —NR_2, —OH, —OCH_3
Weakly activating
—CH_3, —CH_2CH_3, —R
Weakly deactivating
—F, —Cl, —Br
Strongly deactivating
—CO—R, —CO_2H, —CN
—NO_2, —CF_3, —CCl_3

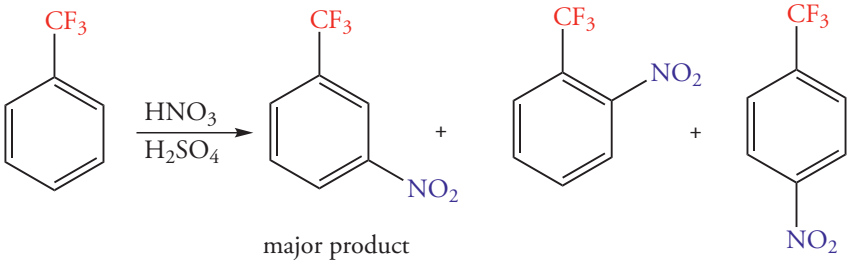
Orientation Effects of Ring Substituents

Now let's consider the distribution of products formed in the nitration of toluene. The nitro group that attacks the ring can bond at three nonequivalent sites to give *o*-, *m*-, or *p*-nitrotoluene. When we examine the product distribution, we find that the *ortho* and *para* isomers predominate, and that very little of the *meta* isomer forms. The methyl group directs or orients the incoming substituent into positions *ortho* and *para* to itself, and is therefore an **ortho, para director**. All groups that activate the aromatic ring toward further substitution are *ortho*, *para* directors. The weakly deactivating halogens also act as *ortho*, *para* directors.



minor product

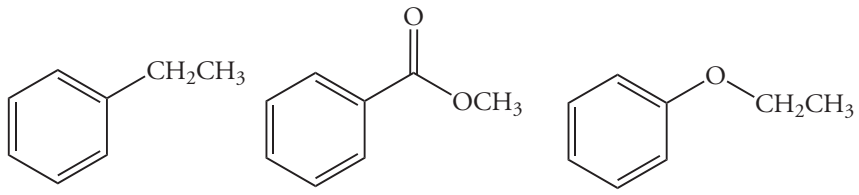
A second class of ring substituents, known as **meta directors**, direct incoming substituents into the *meta* position. These groups include nitro, trifluoromethyl, cyano, sulfonic acid, and any group with a carbonyl carbon atom bonded directly to the ring. For example, in a nitration reaction, the trifluoromethyl group orients the incoming nitro group to a position *meta* to itself. Very small amounts of the *ortho* and *para* isomers form. All deactivating groups (except halogens) are *meta*-directing groups.



major product

Problem 11

Arrange the following compounds in order of increasing rate of reaction with bromine and $FeBr_3$.



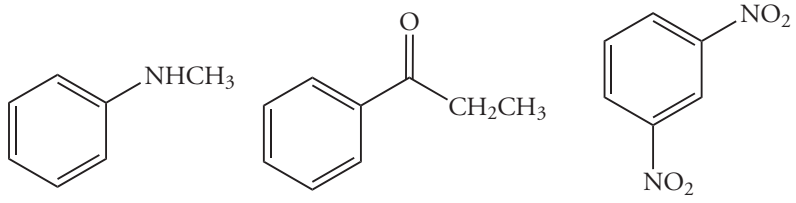
ethylbenzene methyl benzoate ethoxybenzene

Sample Solution

Ethylbenzene contains an alkyl substituent, and is slightly more reactive than benzene. Methylbenzoate has a carbonyl carbon atom bonded to the aromatic ring. As a result, its rate of bromination is significantly slower than that of benzene. Ethoxybenzene has an oxygen atom attached directly to the ring, which causes a significant rate increase over that of benzene. Thus, the order of reactivity for the bromination of benzene in an electrophilic aromatic substitution reaction is methyl benzoate < ethylbenzene < ethoxybenzene.

Problem 12

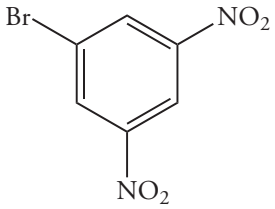
Predict the structure of the product(s) formed in the bromination of each of the following compounds.



N-methylaniline propiophenone *m*-dinitrobenzene

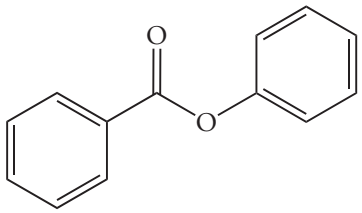
Sample Solution

N-methylaniline resembles aniline, and the bromine will be directed to the *ortho* and *para* positions. Propiophenone has a carbonyl group bonded to the benzene ring that directs the bromine to a *meta* position. The third compound has two nitro groups. Each one directs the electrophile onto the ring in positions *meta* to itself. Thus, both groups of *m*-dinitrobenzene direct the bromine into the same *meta* position. The product is 3,5-dinitrobromobenzene.



Problem 13

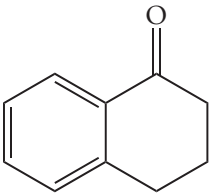
Which of the two aromatic rings of phenyl benzoate would be nitrated? Predict the structure of the product(s) formed.



phenyl benzoate

Problem 14

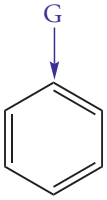
Which two of the four possible products should form in the nitration of tetralone?



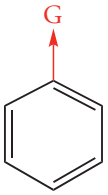
tetralone

MECHANISTIC BASIS OF SUBSTITUENT EFFECTS ON RATES OF AROMATIC SUBSTITUTION

In the preceding section, we saw that a substituent influences both the rate and distribution of products in electrophilic aromatic substitution reactions. The ability of a substituent either to donate or withdraw electron density from the aromatic ring determines both the rate of the reaction and the product distribution. Let's consider the effect of a group, G, on the electron density of the benzene ring.



If G is an electron-donating group, the ring gains electron density

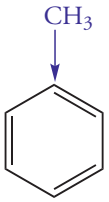


If G is a withdrawing group, the ring loses electron density

Any substituent that donates electron density to the aromatic ring makes the ring more reactive toward attack by an electrophile. A substituent that withdraws electron density from the aromatic ring decreases the electron density in the ring, and makes it less reactive toward an attacking electrophile. Therefore, all activating groups listed in Table 13.1 are electron-donating groups. The deactivating groups are electron-withdrawing groups. Substituents can donate or withdraw electron density by inductive or resonance effects.

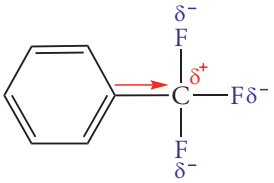
Inductive Effects of Substituents

We have seen that alkyl groups stabilize double bonds and carbocations by an inductive effect. We have also seen that an sp2-hybridized carbon is electron withdrawing with respect to an sp^3-hybridized carbon. Therefore, it follows that alkyl groups also transfer electron density to a benzene ring by an inductive effect.



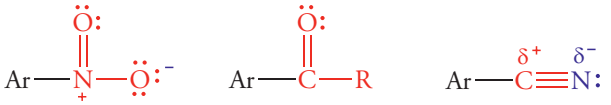
An alkyl group donates electron density to the ring by an inductive effect

The halogens are more electronegative than a benzene ring, so they withdraw electron density from a benzene ring. Any functional group with a partial positive charge on the atom bonded to the aromatic ring also withdraws electron density from the ring by an inductive effect. For example, the fluorine atoms of a trifluoromethyl group pull electrons away from the carbon atom to which they are bonded. To compensate, the carbon atom bearing the fluorine atoms withdraws electron density from the benzene ring.



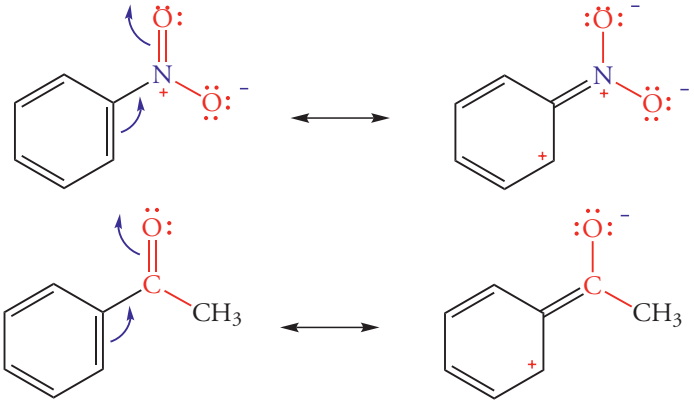
the trifluoromethyl group withdraws electron density
from the benzene ring by an inductive effect

Nitro and cyano groups and any group with a carbonyl carbon atom bonded directly to the aromatic ring are electron-withdrawing substituents. The nitrogen atom of the nitro group has a formal positive charge. The carbon atom of a carbonyl or a cyano group has a partial positive charge.

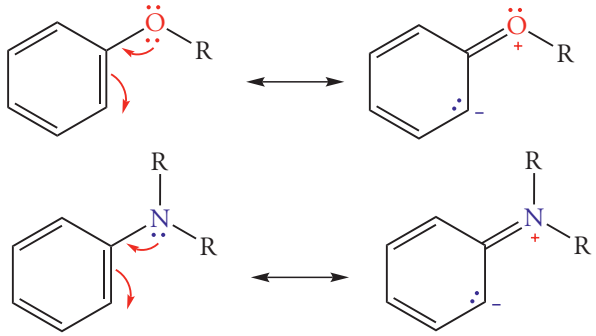


Resonance Effects of Ring Substituents

Nitro, cyano, and carbonyl-containing groups have sp or sp^2-hybridized atoms bonded directly to the benzene ring. These atoms have π orbitals conjugated with the ring. First, consider the resonance effects of the nitro group. Because the carbon atoms of the benzene ring and the nitrogen and oxygen atoms of the nitro group are all sp^2-hybridized, an extended π system is possible. Because oxygen is more electronegative than nitrogen, the electron pair in a nitrogen-oxygen double bond can be delocalized onto the oxygen atom, leaving a positive charge on the aromatic ring. Because of this positive charge, the ring is less reactive toward electrophiles. A similar effect for the acyl group also makes the ring less reactive toward electrophiles.



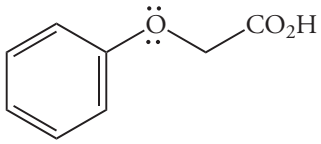
Groups with an unshared electron pair on the atom attached to the ring donate electrons to the aromatic ring by resonance. As a result, the ring develops a partial negative charge, and becomes more reactive toward electrophiles. These substituents include hydroxyl (—OH), alkoxy groups such as methoxy,(CH_3O—), and amino (—NH_2), or any substituted amino groups (—NHR, —NR_2).



Groups that can donate electrons by resonance are also electronegative. Therefore, they can also withdraw electron density from the ring by an inductive effect. These substituents take electron density from the ring by an inductive effect and give it back by resonance. A group containing a second period element bonded directly to the aromatic ring donates electrons by resonance. Examples include amino and hydroxyl groups. The 2p orbital of these second period atoms effectively overlaps with the 2p orbital of a ring carbon atom. As a result, donation of electrons by resonance is more important than inductive electron withdrawal. This situation, however, does not hold true for chlorine or bromine, which pull electrons out of the aromatic ring by an inductive effect. However, the 3p orbital of chlorine and the 4p orbital of bromine overlap poorly with the 2p orbital of carbon, so electron donation by resonance is less effective than the electron-withdrawing inductive effect.

Problem 15

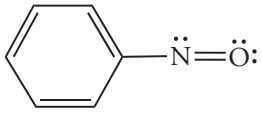
A selective herbicide that kills broad-leaf weeds is made by chlorinating phenoxyacetic acid. Is the substituent an activating or deactivating group?



phenoxyacetic acid

Problem16

Is the nitroso group (—N=O) an activating or deactivating group? Consider both inductive and res-onance interactions with the benzene ring.



nitrosobenzene

Sample Solution

At first glance one might expect the nitroso group to behave like a nitro group. Both have a nitrogen atom directly bonded to the benzene ring, and both have the electronegative oxygen atom bonded to it. However, unlike the nitro group, there is no formal charge on the nitrogen atom of the nitroso group. Thus, the nitroso group does not withdraw electrons as strongly as does the nitro group. Based only on inductive effects, the nitroso group should be less deactivating than the nitro group.

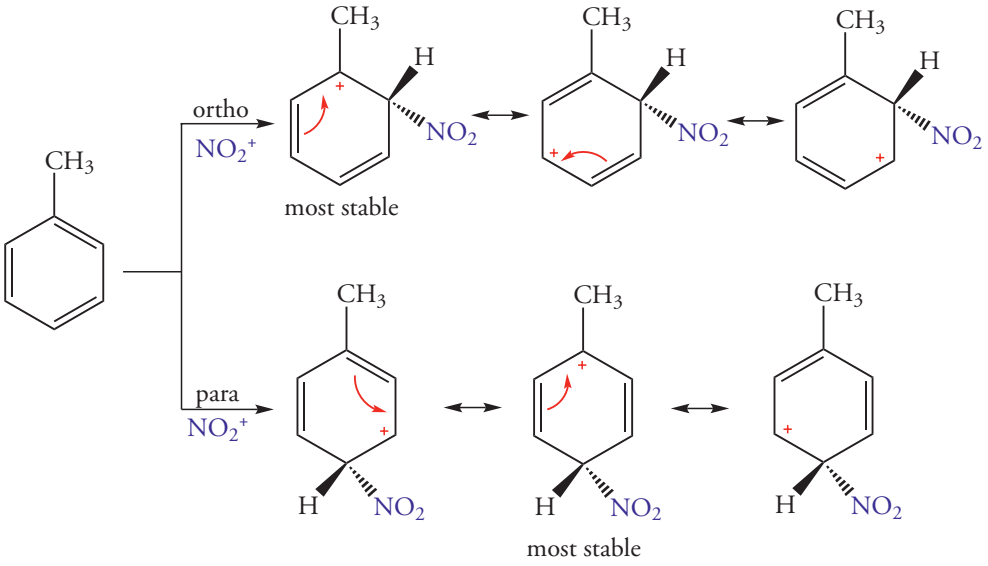
The nitroso group has a lone pair of electrons on the nitrogen atom that can be donated into the benzene ring. (The nitro group cannot donate electrons by resonance.) However, this effect is opposed by its electron-withdrawing inductive effect. Therefore, the properties of the nitroso group resemble those of the halogens. In fact, because nitrogen is a second period element, it effectively donates electrons to the ring by resonance.

---

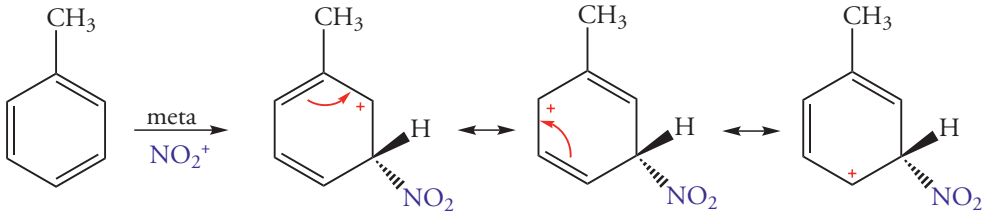
6 INTERPRETATION OF DIRECTING EFFECTS

We noted earlier that with the exception of the halogens *ortho*, *para* directors activate the ring toward electrophilic substitution by supplying electron density to the ring. But why are the *ortho* and *para* positions especially susceptible to attack? To answer this question, consider the stability of the cyclohexadienyl carbocation that forms in the first step of the electrophilic aromatic substitution mechanism. The regioselectivity of the reaction is controlled by the stability of the carbocation. To determine the stability of a cyclohexadienyl carbocation, we must compare all the possible resonance forms. Thus, we compare the stability of the intermediate carbocations resulting from attack at the *ortho* and *para* positions with those resulting when an electrophile attacks at the *meta* position.

First, we will consider the nitration of toluene at the *ortho* and *para* positions. Attack at either the *ortho* or the *para* position results in one resonance structure with a positive charge on the ring carbon atom bonded to the methyl group. This tertiary carbocation makes a major contribution to the stability of the resonance hybrid.



Now consider nitration at the *meta* position. The resonance structures show that positive charge cannot reside on the carbon atom attached to the methyl group. Only secondary carbocations are possible, and they are less stable than tertiary carbocations.



Cyclohexadienyl carbocations resulting from *ortho* or *para* substitution are more stable and form faster than the cyclohexadienyl carbocation resulting from *meta* attack. The reaction coordinate diagrams for the formation of all three cyclohexadienyl carbocations are shown in Figure 13.2. The methyl group donates electrons to the ring, making the intermediates more stable than the cyclohexadienyl carbocation derived from benzene. The formation of the *ortho*- and *para*-substituted products results from greater stabilization of the related intermediates compared to the intermediate leading to the *meta*-substituted product.

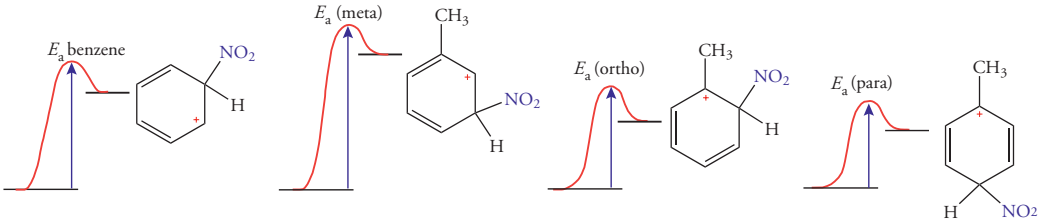
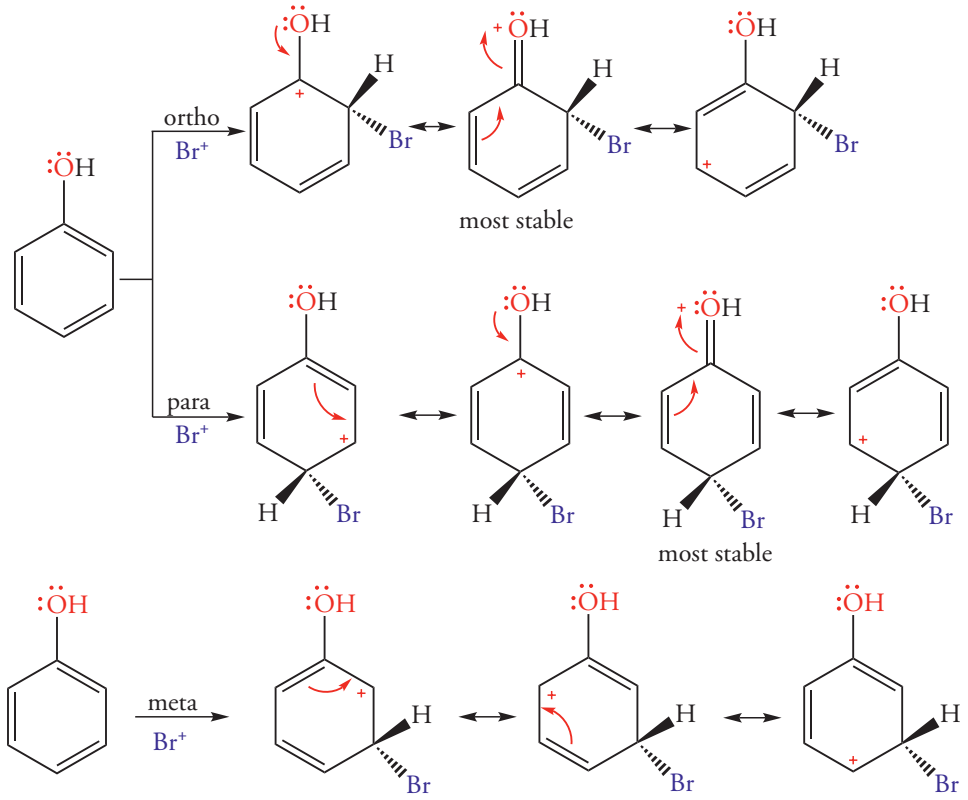


Figure2 Transition State Energies for Nitration of Toluene

Substitution at any position of toluene occurs at a faster rate than substitution of benzene. However, substitution occurs faster at the *ortho* and *para* positions than at the *meta* position.

Next, let's consider the *ortho*, *para*-directing effect of a hydroxyl group or any other group that can donate an unshared pair of electrons by resonance. An attack either *ortho* or *para* to the hydroxyl group leads to an intermediate that is resonance-stabilized by the oxygen atom. As in the case of the methyl group, a contributing structure exists in which the positive charge resides on the carbon atom bonded to the substituent. An electron pair provided by oxygen stabilizes this positive charge. No such stabilization is possible for an electrophile that attacks *meta* to the hydroxyl group. Hence, *ortho* or *para* substitution occurs instead of *meta* substitution.



We saw in Table 13.1 that some substituents strongly deactivate the ring with respect to electrophilic aromatic substitution. All the strong deactivating groups withdraw electron density from the ring and are *meta* directors. Where does the preference for attack at the meta position come from in this case? First, let's consider the possible nitration of nitrobenzene at the *ortho* and *para* positions. In one of the resonance forms for the cyclohexadienyl carbocation resulting from *ortho* or *para* substitution, a positive charge resides on a carbon atom bonded to the original nitro group. The nitrogen atom of the nitro group has a formal positive charge, and its proximity to the carbon atom bearing a positive charge makes these resonance forms unstable.