9

Aromatic Substitution

Introduction

The introduction or replacement of substituents on aromatic rings by substitution reactions is one of the most fundamental transformations in organic chemistry. On the basis of the reaction mechanism, these substitution reactions can be divided into (a) electrophilic, (b) nucleophilic, (c) radical, and (d) transition metal catalyzed. In this chapter we consider the electrophilic and nucleophilic substitution mechanisms. Radical substitutions are dealt with in Chapter 11 and transition metal-catalyzed reactions are discussed in Chapter 9 of Part B.

9.1. Electrophilic Aromatic Substitution Reactions

Electrophilic aromatic substitution (abbreviated EAS in this chapter) reactions are important for synthetic purposes and are also among the most thoroughly studied classes of organic reactions from a mechanistic point of view. The synthetic aspects of these reactions are considered in Chapter 9 of Part B. This section focuses on the mechanisms of several of the most completely studied reactions. These mechanistic ideas are the foundation for the structure-reactivity relationships in aromatic electrophilic substitution that are discussed in Section 9.2.

A wide variety of electrophiles can effect aromatic substitution. Usually, it is a substitution of some other group for hydrogen that is of interest, but this is not always the case. For example, both silicon and mercury substituents can be replaced by electrophiles. Scheme 9.1 lists some of the specific electrophiles that are capable of carrying out substitution of hydrogen. Some indication of the relative reactivity of the electrophiles is given as well. Many of these electrophiles are not treated in detail until Part B. Nevertheless, it is important to recognize the very broad scope of electrophilic aromatic substitution.

The reactivity of a particular electrophile determines which aromatic compounds can be successfully substituted. The electrophiles grouped in the first category are sufficiently reactive to attack almost all aromatic compounds, even those having strongly

EWG substituents. Those in the second group react readily with benzene and derivatives having ERG substituents but are not generally reactive toward aromatic rings with EWG substituents. Those classified in the third group are reactive only toward aromatic compounds that are much more reactive than benzene. These groupings can provide a general guide to the feasibility of a given EAS reaction.

Despite the wide range of electrophilic species and aromatic ring systems that can undergo substitution, a single broad mechanistic picture encompasses most EAS reactions. The identity of the rate-determining step and the shape of the reaction energy profile are specific to individual reactions, but the sequence of steps and the nature of the intermediates are very similar across a wide range of reactivity. This permits discussion of EAS reactions in terms of the general mechanism that is outlined in Scheme 9.2.

A complexation of the electrophile with the π electron system of the aromatic ring is the first step. This species, called the π complex, may or may not be involved

Scheme 9.1. Electrophiles Active in Aromatic Substitution

	Electrophile	Typical means of generation
A. Electrophiles capable of substituting both activated and deactivated aromatic rings		
1[a]	$O{=}N^{+}{=}O$	$2\ H_2SO_4 + HNO_3 \rightleftharpoons NO_2^{+} + 2\ HSO_4^{-} + H_3O^{+}$
2[b]	Br_2 or $Br_2{-}MX_n$	$Br_2 + MX_n \rightleftharpoons Br_2{-}MX_n$
3[b]	$BrO^{+}H_2$	$BrOH + H_3O^{+} \rightleftharpoons BrO^{+}H_2$
4[b]	Cl_2 or $Cl_2{-}MX_n$	$Cl_2 + MX_n \rightleftharpoons Cl_2{-}MX_n$
5[b]	$ClO^{+}H_2$	$ClOH + H_3O^{+} \rightleftharpoons ClO^{+}H_2$
6[c]	SO_3 or $SO_2O^{+}H$	$H_2S_2O_7 \rightleftharpoons HSO_4^{-} + SO_2O^{+}H$
7[d]	RSO_2^{+}	$RSO_2Cl + AlCl_3 \rightleftharpoons RSO_2^{+} + AlCl_4^{-}$
B. Electrophiles capable of substituting activated but not deactivated aromatic rings		
8[e]	R_3C^{+}	$R_3CX + MX_n \rightleftharpoons R_3C^{+} + [MX_{n+1}]^{-}$
9[f]	R_3C^{+}	$R_3COH + H^{+} \rightleftharpoons R_3C^{+} + H_2O$
10[g]	$R_2C^{+}CHR'_2$	$R_2C{=}CR'_2 + H^{+} \rightleftharpoons R_2C^{+}CHR'_2$
11[e]	$RCH_2X{-}MX_n$	$RCH_2X + MX_n \rightleftharpoons RCH_2X{-}MX_n$
12[h]	$RC{\equiv}O^{+}$	$RCOX + MX_n \rightleftharpoons RC{\equiv}O^{+} + [MX_{n+1}]^{-}$
13[h]	$RCOX{-}MX_n$	$RCOX + MX_n \rightleftharpoons RCOX{-}MX_n$
14[i]	$RC^{+}{=}O^{+}H$	$RCOX + MX_n + H^{+} \rightleftharpoons RC^{+}{=}O^{+}H + [MX_{n+1}]^{-}$
15[j]	H^{+}	$HX \rightleftharpoons H^{+} + X^{-}$
16[k]	$R_2C{=}O^{+}H$	$R_2C{=}O + H^{+} \rightleftharpoons R_2C{=}O^{+}H$
17[k]	$R_2C{=}O^{+}{-}M^{-}X_n$	$R_2C{=}O + MX_n \rightleftharpoons R_2C{=}O^{+}{-}M^{-}X_n$
18[i]	$HC^{+}{=}N^{+}H_2$	$HC{\equiv}N + 2H^{+} \rightleftharpoons HC^{+}{=}N^{+}H_2$

Scheme 9.1. *(continued)*

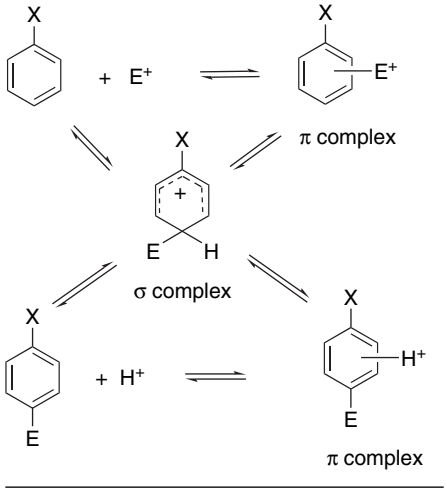
C. Electrophiles capable of substitution only strongly activated aromatic rings

19[l]	$HC{\equiv}N^+H$	$HC{\equiv}N + HX \rightleftharpoons HC{\equiv}N^+H + X^-$
20[m]	$N{\equiv}O^+$	$HONO + H^+ \rightleftharpoons N{\equiv}O^+ + H_2O$
21[n]	$ArN^+{\equiv}N$	$ArNH_2 + HONO + H^+ \rightleftharpoons ArN^+{\equiv}N + 2H_2O$

a. G. A. Olah and S. J. Kuhn, in *Friedel-Crafts and Related Reactions*, Vol. III, G. A. Olah, ed., Interscience, New York, 1964, Chapter XLIII.
b. H. P. Braendlin and E. T. McBee, in *Friedel-Crafts and Related Reactions*, Vol. III, G. A. Olah, ed., Interscience, New York, 1964, Chapter XLVI.
c. K. L. Nelson, in *Friedel-Crafts and Related Reactions*, Vol. III, G. A. Olah, ed., Interscience, New York, 1964, Chapter, XLVII.
d. F. R. Jensen and G. Goldman, in *Friedel-Crafts and Related Reactions*, Vol. III, G. A. Olah, ed., Interscience, New York, 1964, Chapter XL.
e. F. A. Drahowzal, in *Friedel-Crafts and Related Reactions*, Vol. II, G. A. Olah, ed., Interscience, New York, 1964, Chapter XVII.
f. A. Schreisheim, in *Friedel-Crafts and Related Reactions*, Vol. II, G. A. Olah, ed., Interscience, New York, 1964, Chapter XVIII.
g. S. H. Patinkin and B. S. Friedman, in *Friedel-Crafts and Related Reactions*, Vol. II, G. A. Olah, ed., Interscience, New York, 1964, Chapter XIV.
h. P. H. Gore, in *Friedel-Crafts and Related Reactions*, Vol III, G. A. Olah, ed., Interscience, New York, 1964, Chapter XXXI.
i. Y. Sato, M. Yato, T. Ohwada, S. Saito, and K. Shudo, *J. Am. Chem. Soc.*, **117**, 3037 (1995).
j. R. O. C. Norman and R. Taylor, *Electrophilic Substitution in Benzenoid Compounds*, Elsevier, New York, 1965, Chapter 8.
k. J. E. Hofmann and A. Schreisheim, in *Friedel-Crafts and Related Reactions*, Vol. II, G. A. Olah, ed., Interscience, New York, 1964, Chapter XIX.
l. W. Ruske, in *Friedel-Crafts and Related Reactions*, Vol. III, G. A. Olah, ed., Interscience, New York, 1964, Chapter XXXII.
m. B. C. Challis, R. J. Higgins, and A. J. Lawson, *J. Chem. Soc., Perkin Trans.*, **2**, 1831 (1972).
n. H. Zollinger, *Azo and Diazo Chemistry*, transl. H. E. Nursten, Interscience, New York, 1961, Chapter 10.

directly in the substitution mechanism. π Complex formation is, in general, rapidly reversible and in many cases the equilibrium constant is small. The π complex is a donor-acceptor type of complex with the π electrons of the aromatic ring donating electron density to the electrophile. Although these complexes are readily observed by spectroscopic measurements, they generally are of only modest stability. Only recently

Scheme 9.2. Generalized Mechanism for Electrophilic Aromatic Substitution



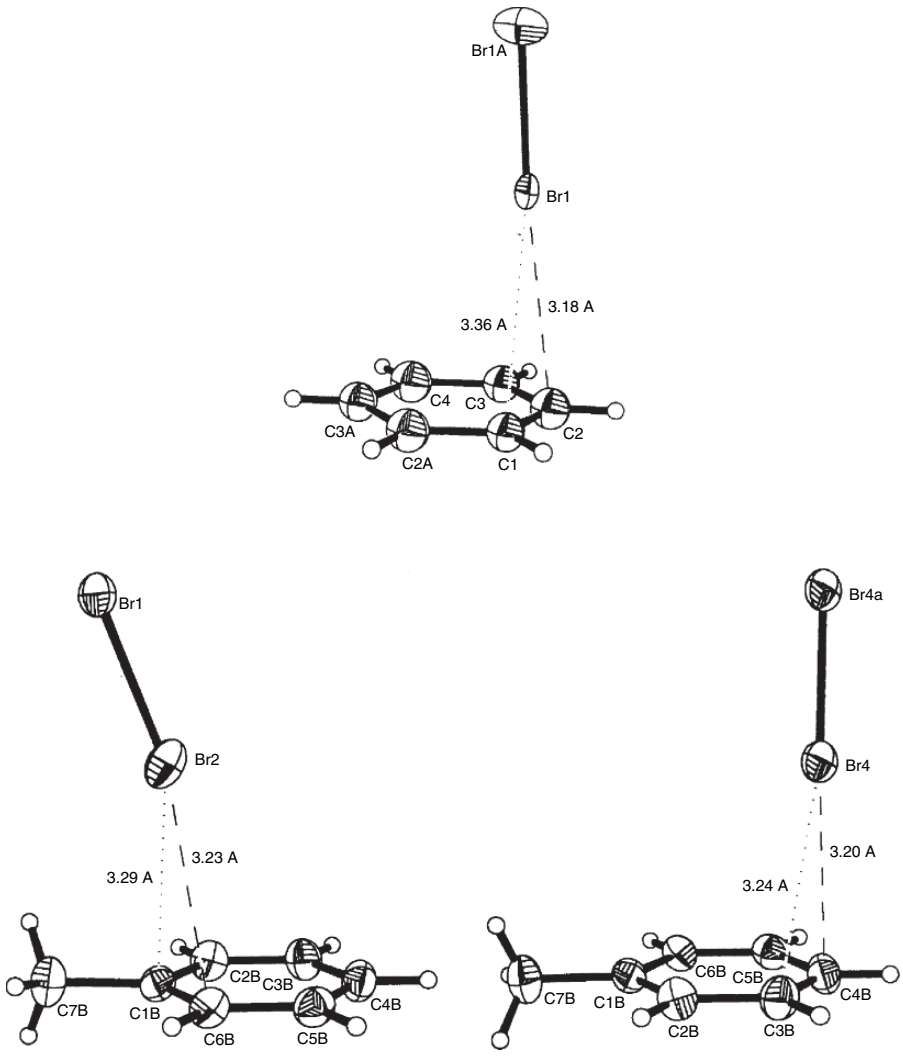


Fig. 9.1. Structures of benzene-Br_2 (top) and toluene-Br_2 (bottom) complexes. Reproduced from *Chem. Commun*, 909 (2001), by permission of the Royal Society of Chemistry.

has structural data become available. The structures of the Br_2 complexes with benzene and toluene have been examined by X-ray crystallography at low temperature. The Br_2 molecule is nearly perpendicular to the ring and located between two specific carbons, as opposed to being associated with the delocalized π electron density. For toluene, there are two complexes with the Br_2 being associated with the *ortho* and *para* carbons.[1] This is significant because these are also the preferred sites for substitution, and the structures indicate that an aspect of position selectivity is present at the π complex stage. These structures are shown in Figure 9.1.

Structural information is also available on the complex between mesitylene and the nitrosonium ion, NO^+.[2] In this case there appears to be a high degree of charge transfer and the complex is essentially between the aromatic radical cation and the NO

[1.] A. V. Vasilyev, S. V. Lindeman, and J. K. Kochi, *Chem. Commun.*, 909 (2001); S. V. Rosokha and J. K. Kochi, *J. Org. Chem.*, **67**, 1727 (2002).
[2.] E. K. Kim and J. K. Kochi, *J. Am. Chem. Soc.*, **113**, 4962 (1991).

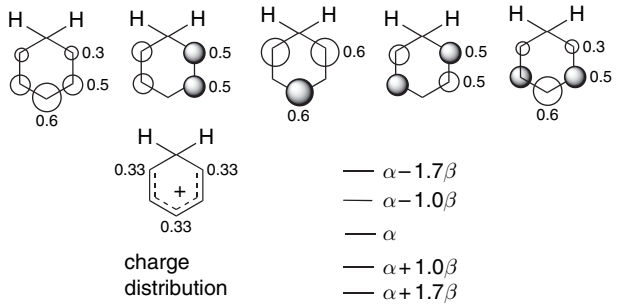
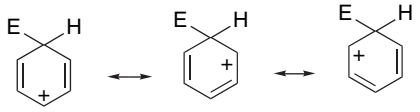


Fig. 9.2. π Molecular orbitals and energy levels for the cyclohexadienylium ion.

molecule, which is located centrally with respect to the aromatic ring. The N−O bond distance is 1.07 Å and the C−C bond distances are similar to those observed for the radical cation.[3] There are probably similar complexes in other EAS reactions. Recent computational studies of the nitration of benzene describe the earliest energy minimum as NO_2^+ approaches benzene (in the gas phase) as being directed at the midpoint of a particular C−C bond, as opposed to the center of the ring.[4]

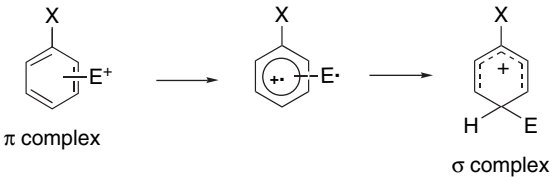
In order for a substitution to occur, a "σ complex" must be formed. The term σ *complex* is used to describe a *cationic intermediate* in which the carbon at the site of substitution is bonded to both the electrophile and the hydrogen that is being displaced. As the term implies, a σ bond is formed at the site of substitution. The intermediate is a *cyclohexadienylium cation*. Its fundamental electronic characteristics can be described in simple MO terms, as shown in Figure 9.2. The intermediate is a 4π electron delocalized system that is electronically equivalent to a pentadienyl cation. There is no longer cyclic conjugation. The LUMO has nodes at C(2) and C(4) of the pentadienyl structure and these correspond to the positions *meta* to the site of substitution on the aromatic ring. As a result, the positive charge of the cation is located at the positions *ortho* and *para* to the site of substitution. These electronic features of the σ-complex intermediate are also shown by resonance structures.



As we will see in Section 9.2, this pattern of charge distribution leads to the *o*,*p*- or *m*-directing characteristics of various ring substituents.

There is considerable interest in the mechanism for conversion of the π complex into the σ complex. In particular, the question arises as to whether an electron transfer occurs to yield a discrete cation radical–radical pair.

3. S. V. Rosokha and J. K. Kochi, *J. Am. Chem. Soc.*, **123**, 8985 (2001).
4. H. Xiao, L. Chen, X. Ju, and G. Li, *Science in China B*, **46**, 453 (2003); P. M. Esteves, J. W. de Carneiro, S. P. Cardoso, A. G. H. Barbosa, K. K. Laali, G. Rasul, G. K. S. Prakash, and G. A. Olah, *J. Am. Chem. Soc.*, **125**, 4836 (2003).



This mechanism implies that a considerable change in the structure of the electrophile occurs prior to σ-bond formation. These structural changes could account in large part for the energy barrier to formation of the σ complex.[5] Moreover, this mechanism implies that the cation radical–radical pair might play a key role in determining the isomeric (*ortho*, *meta*, *para*) product composition. These issues have been investigated most closely for nitration and bromination and are consider further when those reactions are discussed.

Formation of the σ complex can be reversible. The partitioning of the σ complex forward to product or back to reactants depends on the ease with which the electrophile can be eliminated, relative to a proton. For most electrophiles, it is easier to eliminate the proton, in which case the formation of the σ complex is essentially irreversible. The electrophiles in group A of Scheme 9.1 are the least likely to be reversible, whereas those in group C are most likely to undergo reversible σ-complex formation. Formation of the σ complex is usually, but not always, the rate-determining step in EAS. There may also be a π complex involving the aromatic ring and the departing electrophile. This would be expected on the basis of the principle of microscopic reversibility, but there is little direct evidence on this point.[6]

Let us now consider some of the evidence for this general mechanism. Such evidence has, of course, been gathered by study of specific reaction mechanisms. Only some of the most clear-cut cases are cited here. Additional evidence is mentioned when individual mechanisms are discussed in Section 9.4. A good example of studies that have focused on the identity and mode of generation of the electrophile is aromatic nitration. Primarily on the basis of kinetic studies, it has been shown that the active electrophile in nitration is often the nitronium ion, NO_2^+, which is formed by the reaction of nitric acid with concentrated sulfuric. Several other lines of evidence support the role of the nitronium ion. It can be detected spectroscopically and the freezing-point depression of the solution is consistent with the following equation:

$$2H_2SO_4 + HNO_3 \rightleftharpoons NO_2^+ + H_3O^+ + 2HSO_4^-$$

Solid salts in which the nitronium ion is the cation can be prepared with unreactive anion such as for $NO_2^+BF_4^-$ and $NO_2^+PF_6^-$. These salts act as nitrating reagents.

Two types of rate expressions have been found to describe the kinetics of many aromatic nitration reactions. With relatively unreactive substrates, second-order kinetics, first order in the nitrating reagent and first order in the aromatic, are observed. This second-order relationship corresponds to rate-limiting attack of the electrophile on the aromatic reactant. With more reactive aromatics, this step can be faster than formation of the active electrophile. In these cases, the generation of the electrophile

5. S. V. Rosokha and J. K. Kochi, *J. Org. Chem.*, **67**, 1727 (2002).
6. For additional discussion of the role of σ and π complexes in aromatic substitution, see G. A. Olah, *Acc. Chem. Res.*, **4**, 240 (1971); J. H. Ridd, *Acc. Chem. Res.*, **4**, 248 (1971).

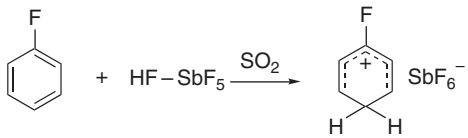
is the rate-determining step. When formation of the active electrophile is the rate-determining step, the concentration of the aromatic reactant no longer appears in the observed rate expression. Under these conditions, different aromatic substrates undergo nitration at the same rate, corresponding to the rate of formation of the active electrophile.

An important general point to be drawn from the specific case of nitration is that the active electrophile is usually some species that is more reactive than the added reagents. The active electrophile is formed from the reagents by a subsequent reaction, often involving a Brønsted or Lewis acid. One goal of mechanistic study is to determine the identity of the active electrophile, the formation of which may or may not be the rate-determining step. Scheme 9.1 indicates the structure of some of the electrophilic species that are involved in EAS processes and the reactions involved in their formation.

There are several lines of evidence pointing to formation of σ complexes as intermediates in EAS. One approach involves measurement of isotope effects on the rate of substitution. If removal of the proton at the site of substitution is concerted with the introduction of the electrophile, a primary isotope effect is expected when electrophilic attack on the ring is rate determining. This is not the case for nitration. Nitration of aromatic substrates partially labeled by tritium shows no selectivity between protium- and tritium-substituted sites.[7] Similarly, the rate of nitration of nitrobenzene is identical to that of penta-deuterio-nitrobenzene.[8]

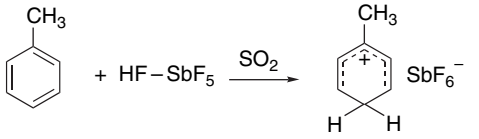
The lack of a primary isotope effect indicates that the proton is lost in a fast step following the rate-determining step, which means that proton loss must occur from some intermediate that is formed before the cleavage of the C−H bond begins. The σ-complex intermediate fits this requirement. There are some electrophilic aromatic substitution reactions that show k_H/k_D values between 1 and 2 and there are a few others that are in the range indicating a primary isotope effect.[9] The existence of these isotope effects is compatible with the general mechanism if the proton removal is rate limiting (or partially rate limiting). Many of the modest kinetic isotope effects ($k_H/k_D \sim 1.2-2.0$) have been interpreted in terms of comparable rates for formation and deprotonation of the σ-complex intermediate.

The case for the cyclohexadienylium ion intermediates is further strengthened by numerous studies showing that such cations can exist as stable entities under suitable conditions. Substituted cyclohexadienylium ions can be observed by NMR under stable ion conditions. They are formed by protonation of the aromatic reactant.[10]



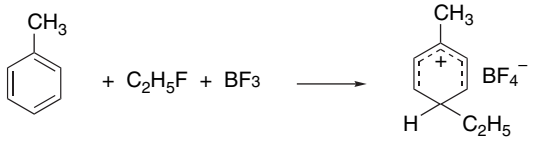
Ref. 11

7. L. Melander, *Acta Chem. Scand.*, **3**, 95 (1949); *Arkiv Kemi.*, **2,** 211 (1950).
8. T. G. Bonner, F. Bower, and G. Williams, *J. Chem. Soc.*, 2650 (1953).
9. H. Zollinger, *Adv. Phys. Org. Chem.*, **2**, 163 (1964).
10. G. A. Olah, R. H. Schlosberg, R. D. Porter, Y. K. Mo, D. P. Kelly, and G. Mateescu, *J. Am. Chem. Soc.*, **94**, 2034 (1972).
11. G. A. Olah and T. E. Kiovsky, *J. Am. Chem. Soc.*, **89,** 5692 (1967).



Ref. 12

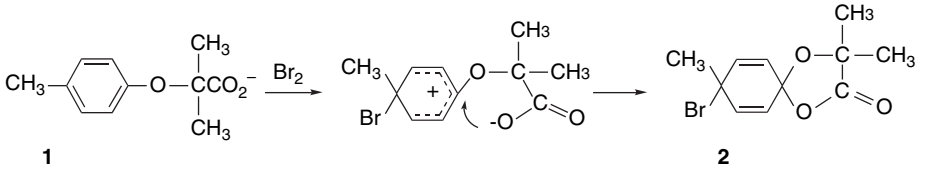
Cations formed by alkylation of benzene derivatives have also been characterized.



Ref. 13

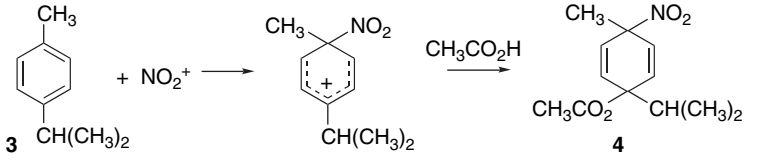
Under normal conditions of electrophilic substitution, these cyclohexadienylium ions are short-lived intermediates. The fact that the structures are stable in nonnucleophilic media clearly demonstrates the feasibility of such intermediates.

The existence of σ-complex intermediates can be inferred from experiments in which they are trapped by nucleophiles in special circumstances. For example, treatment of the acid **1** with bromine gives the cyclohexadienyl lactone **2**. This product results from intramolecular nucleophilic capture of the σ complex by the carboxylate group.



Ref. 14

A number of examples of intramolecular nucleophilic capture of cyclohexadienylium intermediates have also been uncovered in the study of nitration of alkylated benzenes in acetic acid. For example, nitration of **3** at 0°C leads to formation of **4** with acetate serving as the nucleophile.[15]



This type of addition process is particularly likely to be observed when the electrophile attacks a position that is already substituted, since facile rearomatization by deprotonation is then blocked. Attack at a substituted position is called *ipso* attack. Addition

12. G. A. Olah, *J. Am. Chem. Soc.*, **87**, 1103 (1965).
13. G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, **80**, 6541 (1958).
14. E. J. Corey, S. Barcza, and G. Klotmann, *J. Am. Chem. Soc.*, **91**, 4782 (1969).
15. R. C. Hahn and D. L. Strack, *J. Am. Chem. Soc.*, **96**, 4335 (1974).

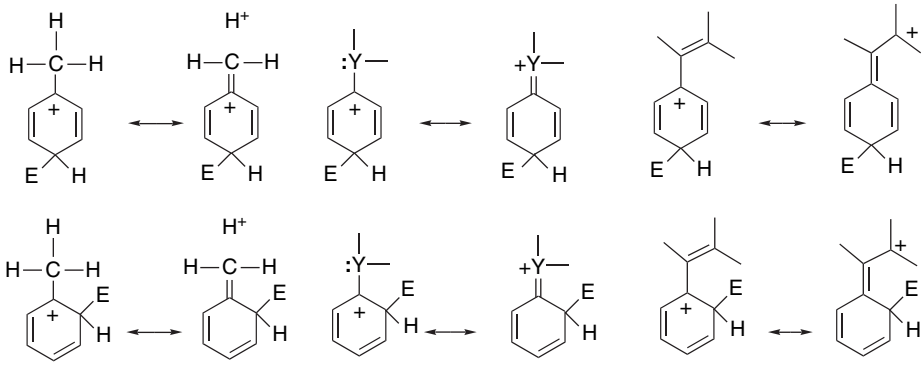
products have also been isolated when initial electrophilic attack has occurred at an unsubstituted position. The extent of addition in competition with substitution increases on going to naphthalene and the larger polycyclic aromatic ring systems.[16]

The general mechanistic framework outlined in this section can be elaborated by other details to more fully describe the mechanisms of the individual electrophilic substitutions. The question of the identity of the active electrophile in each reaction is important. We have discussed the case of nitration in which, under many circumstances, the electrophile is the nitronium ion. Similar questions about the structure of the active electrophile arise in most of the other substitution processes. Another issue that is important is the ability of the electrophile to select among the alternative positions on a substituted aromatic ring (*position selectivity*). The relative reactivity and selectivity of substituted benzenes toward various electrophiles is important in developing a firm understanding of EAS. The next section considers some of the structure-reactivity relationships that have proven to be informative.

9.2. Structure-Reactivity Relationships for Substituted Benzenes

9.2.1. Substituent Effects on Reactivity

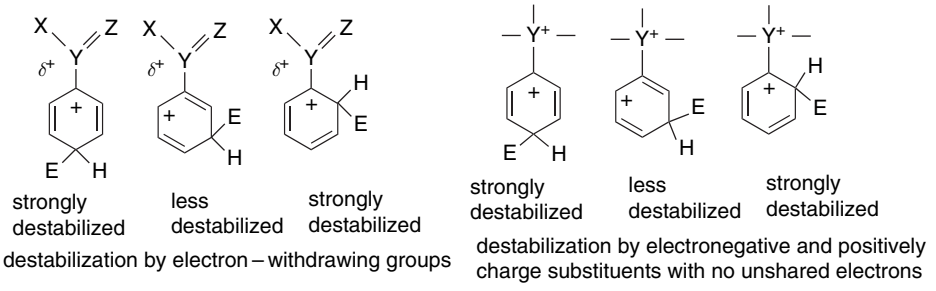
The effect that existing substituents have on EAS reactions has been studied since about 1870. The classification of substituents as *activating* and *ortho-para* directing or *deactivating* and *meta* directing became clear from these early studies. An understanding of the origin of these substituent effects became possible when ideas about electronic interactions and resonance theory were developed. Activating, *ortho-para*–directing substituents are those that can serve as electron donors and stabilize the TS leading to σ-complex formation. Saturated and unsaturated hydrocarbon groups and substituents having an unshared electron pair on the atom adjacent to the ring fall into this group. The stabilizing effects of these types of substituents can be expressed in terms of resonance and hyperconjugation. Direct resonance stabilization is only possible when the substituent is *ortho* or *para* to the incoming electrophile. As a result the TSs for *ortho* and *para* substitution are favored over that for *meta* substitution.



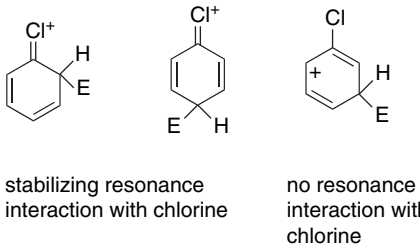
[16] P. B. de la Mare, *Acc. Chem. Res.*, **7**, 361 (1974).

As the substituent groups have a direct resonance interaction with the charge that develops in the σ complex, quantitative substituent effects exhibit a high-resonance component. Hammett equations usually correlate best with the σ^+-substituent constants (see Section 3.5).[17]

EWGs retard electrophilic substitution. The classification of specific substituents given in Scheme 3.1 (p. 299) indicates the ones that are electron attracting. Substituents in this group include those in which a carbonyl group is directly attached to the ring and substituents containing electronegative elements that do not have an unshared pair on an atom adjacent to the ring. Owing to the greater destabilization at the *ortho* and *para* positions, electrophilic attack occurs primarily at the *meta* position, which is *less deactivated* than the *ortho* and *para* positions.



A few substituents, most notably the halogens, decrease the rate of reaction, but nevertheless direct incoming electrophiles to the *ortho* and *para* positions. This is the result of the opposing influence of polar and resonance effects for these substituents. The halogens are more electronegative than carbon, and the carbon-halogen bond dipole opposes the development of positive charge in the ring. Overall reactivity toward electrophiles is therefore reduced. However, the unshared electron pairs on the halogen can preferentially stabilize the *ortho* and *para* TSs by resonance. As a result the substituents are deactivating but nevertheless *ortho-para* directing.

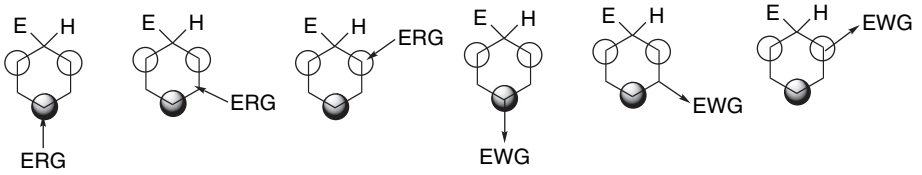


The *o*,*p*-directing and activating versus *m*-directing and deactivating effect of substituents can also be described in MO terminology. The discussion can focus either on the σ complex or on the aromatic reactant. According to the Hammond postulate, it would be most appropriate to focus on the intermediate in the case of reactions that have relatively high E_a and a late TS. In such cases, the TS should closely resemble the cyclohexadienylium intermediate. For highly reactive electrophiles, where the E_a is low, it may be more appropriate to regard the TS as closely resembling the

[17] H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).

reactant aromatic. Let us examine the MO description of substituent effects from both these perspectives.

The TS resembles the intermediate, a substituted cyclohexadienylium ion. The electrophile has localized one pair of electrons to form the new σ bond. The Hückel orbitals are the same as for the pentadienyl system, as shown in Figure 9.2. A substituent can stabilize the cation by electron donation. The LUMO is ψ_3. This orbital has its highest coefficients at carbons 1, 3, and 5 of the pentadienyl system, which are the positions that are *ortho* and *para* to the position occupied by the electrophile. EWG substituents at the 2 and 4 (*meta*) positions stabilize the system much less, because of the nodes at these carbons in the LUMO. If we consider a π-acceptor substituent, we see that such a substituent strongly destabilizes the system when it occupies the 1, 3, or 5 position on the pentadienyl cation. The destabilizing effect is less at the 2 or 4 position. The conclusions drawn by this MO interpretation are the same as from resonance arguments. ERG substituents will be *most stabilizing* in the TS leading to *ortho-para* substitution. EWG substituents will be *least destabilizing* in the TS leading to *meta* substitution.

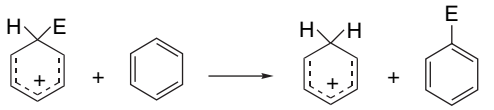


Selective stabilization of cation LUMO by *ortho*– and *para*–electron–releasing groups

Selective destabilization of cation LUMO by *ortho*– and *para*–electron–withdrawing groups

The effect of the bond dipole associated with EWG groups can also be expressed in terms of its interaction with the cationic σ complex. The atoms with the highest coefficient of the LUMO ψ_3 are the most positive. The unfavorable interaction of the bond dipole will therefore be greatest at these positions. This effect operates with substituents such as carbonyl, cyano, and nitro. With alkoxy and amino substituents, the unfavorable dipole interaction is outweighed by the stabilizing delocalization effect of the electron pair donation.

The effect of substituents was probed by MO calculations at the HF/STO-3G level.[18] An isodesmic reaction corresponding to transfer of a proton from a substituted σ complex to an unsubstituted one indicates the stabilizing or destabilizing effect of the substituent. The results are given in Table 9.1.



The calculated energy differences give a good correlation with Hammett σ^+ values. The ρ parameter ($\rho = -17$) is considerably larger than that observed experimentally for proton exchange ($\rho \sim -8$). A physical interpretation of this difference is that the computational results pertain to the gas phase, where substituents are at a maximum because of the absence of any leveling effect owing to solvation. Note that the numerical results parallel the conclusions from qualitative application of resonance

[18] J. M. McKelvey, S. Alexandratos, A. Streitwieser, Jr., J.-L. M. Abboud, and W. J. Hehre, *J. Am. Chem. Soc.*, **98**, 244 (1976).

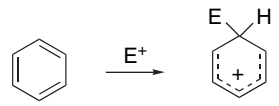
Table 9.1. Energy Changes for Isodesmic Proton-Transfer Reactions of Substituted Benzenes[a]

	ΔE(kcal/mol)	
Substituent	*meta*	*para*
NO_2	−17.9	−22.1
CN	−14.0	−13.8
CF_3	−7.5	−8.4
F	−7.5	3.7
CH_3	2.0	8.5
OCH_3		15.7
OH	−5.3	16.0
NH_2	0.6	27.2

a. From HF/STO-3G calculations reported by J. M. McKelvey, S. Alexandratos, A. Streitwieser, Jr., J.-L. M. Abboud, and W. H. Hehre, *J. Am. Chem. Soc.*, **98**, 244 (1976).

and MO arguments. Strong EWGs are more destabilizing at the *ortho* and *para* position than at the *meta* position. Methyl is stabilizing at both positions, but more so at *para*. Methoxy and amino are very stabilizing at the *para* position. Fluoro is slightly stabilizing at the *para* position, but strongly destabilizing at the *meta* position, in agreement with its competing resonance and polar effects.

Both HMO calculations and more elaborate MO methods can be applied to the issue of the position selectivity in EAS. The most direct approach is to calculate the *localization energy*, which is the energy difference between the aromatic molecule and the cyclohexadienylium intermediate. In simple HMO calculations, the localization energy is just the difference between the energy calculated for the initial π system and that remaining after two electrons and the carbon atom at the site of substitution are removed from the conjugated system.



$6\alpha + 8\beta$ $\qquad$ $4\alpha + 5.46\beta$

localization energy $= 2\alpha + 2.54\beta$

Comparison of localization energies has been applied to prediction of the relative positional reactivity in polycyclic aromatic hydrocarbons. Simple HMO calculations are only marginally success; CNDO/2 and SCF calculations give results that show good correlation with experimental data on the rate of proton exchange.[19]

Now let us turn to the case of a highly reactive electrophile, where we expect an early TS. In this case the charge density distribution and coefficients of the HOMO characteristic of the aromatic reactant are expected to be major factors governing the orientation of electrophilic attack. The TS should resemble the reactants and, according to frontier orbital theory, the electrophile will attack the position with the largest coefficient of the HOMO. The case of methoxybenzene (anisole) can be taken as an example of a reactive molecule. MO calculations place the lone-pair oxygen orbital lower in energy than the ψ_2 and ψ_3 orbitals, leading to the MO diagram in Figure 9.3.

19. A. Streitwieser, Jr., P. C. Mowery, R. G. Jesaitis, and A. Lewis, *J. Am. Chem. Soc.*, **92**, 6529 (1970).

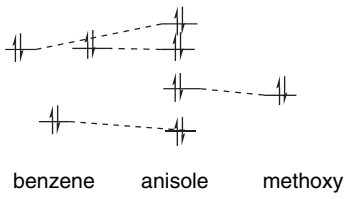


Fig. 9.3. MO diagram for anisole (methoxybenzene) showing effects of methoxy substituent.

The degeneracy of the two highest-lying occupied π orbitals is broken because the methoxy group interacts preferentially with one of them. The other has a node at the site of methoxy substitution.

Figure 9.4 gives the coefficients for the two highest-occupied π orbitals, as calculated by the CNDO method. We see that the HOMO has its highest coefficients at the *ipso*, *ortho*, and *para* positions. As indicated in Figure 9.3, the energy of this orbital is raised by its interaction with the electron donor substituent. Figure 9.5 shows the distribution of π electrons from all the orbitals, based on HF/STO-3G calculations.[20] The ERG substituents show increased electron density at the *ortho* and *para* positions. Both the HOMO coefficients and the total charge distribution predict preferential attack by the electrophile *ortho* and *para* to donor substituents.

Figures 9.4 and 9.5 also show some examples of EWG substituents, which, as expected, lower the energies of the π orbitals, but the HOMO distribution remains highest at the *para* position. The total charge distribution shows greater depletion at the *ortho* and *para* position than at the *meta* position. The lower energy of the HOMO is consistent with decreased reactivity for rings with an EWG substituent. However, if frontier orbital theory is used, the distribution of the HOMO in Figure 9.4

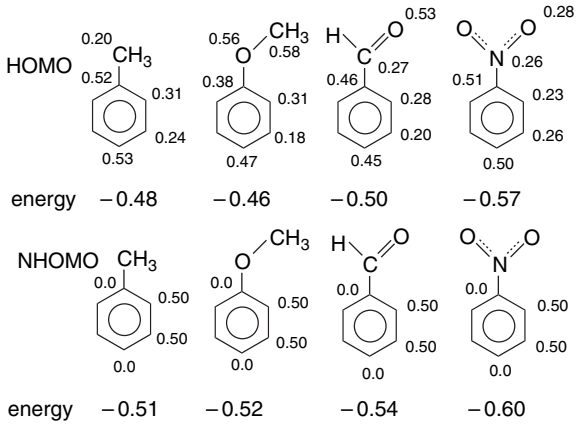


Fig. 9.4. Orbital coefficients for HOMO and next highest π MO for some substituted benzenes (from CNDO/2 calculations). The individual *ortho* and *meta* coefficients have been averaged in the case of the unsymmetrical methoxy and formyl substituents. Orbital energies are in atomic units.

[20] W. J. Hehre, L. Radom, and J. A. Pople, *J. Am. Chem. Soc.*, **94**, 1496 (1972).

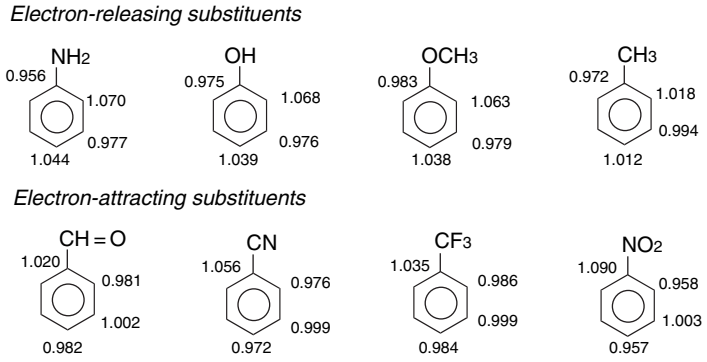


Fig. 9.5. Total π-electron density for some substituted benzenes. From HF/STO-3G calculations.

erroneously predicts *para* substitution.. Aromatic rings with EWG substituents are relatively unreactive and therefore will not have early TSs. For such compounds, considerations of the stability of the cyclohexadienylium intermediate, which correctly predict *meta* substitution, are more appropriate.

Prediction of reactivity toward EAS on the basis of MO computations can be improved by considering hybrid MOs rather than the conventional aromatic MOs. Orbitals called *reactive hybrid orbitals* can be defined to combine the contributions of all MOs to the reactivity at each site. The properties of these orbitals can be computed on the basis of the extent of electron transfer to a proton located 1.5 Å above each ring position.[21] The properties of these orbitals correlate well not only with the position selectivity of the substituents, but also with relative reactivity. Figure 9.6 shows a correlation between the energy of interaction and the partial rate factors (a measure of relative reactivity; see p. 786–787) for several reactions.

Substituents that are not directly bound to the aromatic ring also influence the course of EAS. Several alkyl groups bearing EWG substituents are *meta* directing and deactivating. Some examples are given in Table 9.2. In these molecules, stabilization of the *ortho* and *para* σ complex by electron release from the alkyl group is opposed by the polar effect of the electronegative substituent. Both the reduced electron density at the alkyl substituent and the bond dipoles in the substituent reduce electron donation by the methylene group. From the examples in Table 9.2 we see that $CH_2CO_2C_2H_5$, $CHCl_2$, and CH_2CCl_3 remain *o-p* directing, but with reduced selectivity. The stronger EWGs, CH_2NO_2, CCl_3, and $CH_2N^+(CH_3)_3$, lead to predominantly *meta* substitution.

The relationships between substituents and the typical electrophilic substitution reactions, such as those listed in Scheme 9.1, can be summarized as follows:

1. The hydroxy and amino groups are highly activating *ortho-para* directing. Such compounds are attacked by all the electrophilic reagents tabulated in Scheme 9.1 (p. 772). With some electrophilic reagents, all available *ortho* and *para* positions are rapidly substituted.
2. The alkyl, amido, and alkoxy groups are activating and *ortho-para* directing, but not as strongly so as hydroxy or amino groups. Synthetically useful conditions for selective substitution are available for essentially all the electrophiles in Scheme 9.1 except for very weak electrophiles such as NO^+ or PhN_2^+.

[21] H. Hirao and T. Ohwada, *J. Phys. Chem. A*, **107**, 2875 (2003).

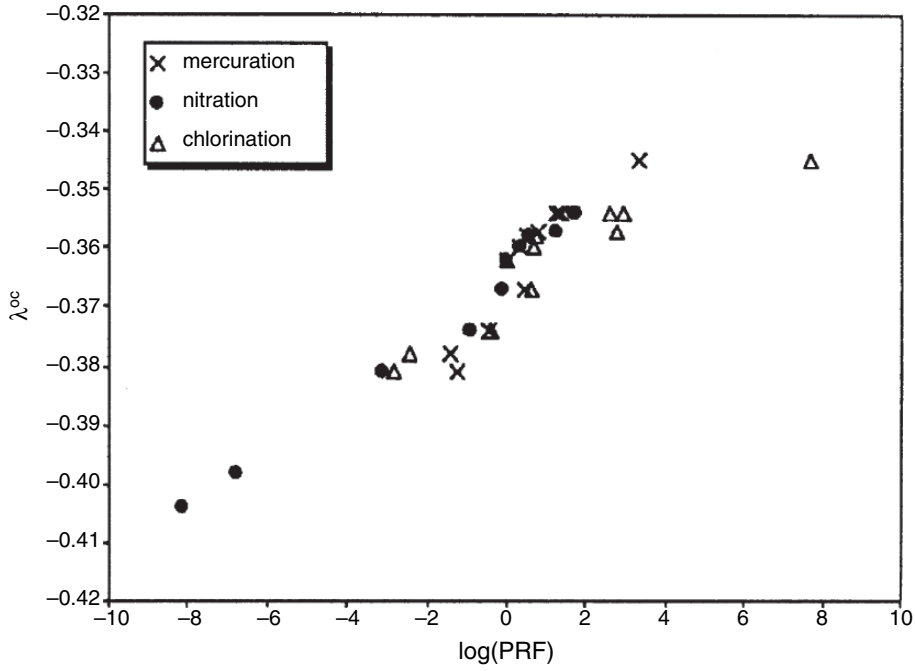


Fig. 9.6. Correlation between the interaction energy λ^{oc} and the log of partial rate factors for mercuration, nitration, and chlorination. Reproduced from *J. Phys. Chem. A*, **107**, 2875 (2003), by permission of the American Chemical Society.

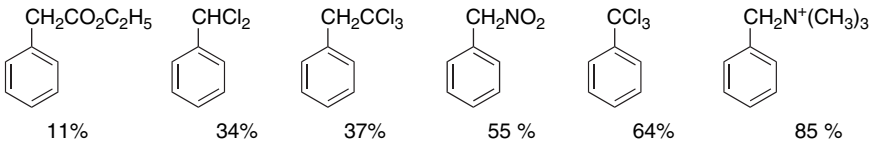
3. The halobenzenes, are unusual substituents, being deactivating but *ortho-para* directing. In general, halogenated aromatics react successfully with electrophiles listed in categories A and B.
4. The carbonyl group in aldehydes, ketones, acids, esters, and carboxamides is deactivating and *meta* directing. There are limitations on the type of substitution reactions that are satisfactory for these deactivating substituents. In general, only those electrophiles in category A in Scheme 9.1 react readily.
5. The cyano, nitro, and quaternary ammonium groups are strongly deactivating and *meta* directing. Electrophilic substitutions of compounds with these substituents require vigorous conditions, and fail completely with the less reactive electrophiles.

Nitration has been studied over a wide variety of aromatic compounds, which makes it a useful reaction for illustrating the directing effect of substituent groups. Table 9.3 presents some of the data. A range of reaction conditions is represented, so direct comparison is not always valid, but the trends are nevertheless clear. It is important to remember that other electrophiles, while following the same qualitative trends, show large quantitative differences in position selectivity.

The groups in the top half of the table are *meta* directing. Note that the carbonyl and cyano groups give rise to relatively high ratios of *ortho* product. This may be due to intramolecular process in which the nitronium ion initially bonds at the functional group.[22] The halogens show *o*,*p*–directing effects with fluorine being much less favorable to *ortho* substitution, because of the stronger C−F dipole, which results

[22] G. S. Hammond, F. J. Modic, and R. M. Hedges, *J. Am. Chem. Soc.*, **75**, 1388 (1953); P. Kovacic and J. J. Hillier, Jr., *J. Org. Chem.*, **30**, 2871 (1985).

Table 9.2. Percent *meta* Nitration for Some Alkyl Groups with Electron-Withdrawing Substituents[a]



a. From C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, 2nd Edition, Cornell University Press, Ithaca, 1969, pp. 275, 281; F. De Sarlo, A. Rici, and J. H. Ridd, *J. Chem. Soc. B*, 719 (1971).

in both electrostatic and polarization effects that destabilize the *ortho* TS.[23] The trichloromethyl and trifluoromethyl groups are *meta* directing. Similarly to some of the groups in Scheme 9.2, the CH_2CN and CH_2NO_2 groups are also *meta* directing. The alkyl and methoxy groups are strongly *o-p* directing.

The effect of substituents on electrophilic substitution can be placed on a quantitative basis by use of *partial rate factors*. The reactivity of each position in a substituted aromatic compound can be compared with benzene by measuring the overall

Table 9.3. Isomer Proportions in the Nitration of Some Substituted Benzenes[a]

	Product (%)		
Substituent	*ortho*	*meta*	*para*
N^+H_3	3–5	35–50	50–60
$N^+(CH_3)_3$	0	89	11
$CH_2N^+(CH_3)_3$	0	85	15
$S^+(CH_3)_2$	4	90	6
NO_2	5–8	91–93	0–2
CO_2H	15–20	75–85	~1
CN	15–17	81–83	~2
$CO_2C_2H_5$	24–28	66–73	1–6
$COCH_3$	26	72	0–2
F	9–13	0–1	86–91
Cl	30–35	~1	64–70
Br	36–43	1	56–62
I	38–45	1–2	54–60
CCl_3	7	64	29
CF_3	6	91	3
CH_2CN	24	20	56
CH_2NO_2	22	55	23
CH_2OCH_3	51	7	42
CH_3	56–63	2–4	34–41
CH_2CH_3	46–59	2–4	46–51
OCH_3	30–40	0–2	60–70

a. Data are from Tables 9.1, 9.2, 9.3, 9.4, 9.5, and 9.6 in J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, 1971.

23. P. Laszlo and P. Pennetreau, *J. Org. Chem.*, **52**, 2407 (1987); J. Rosenthal and D. I. Schuster, *J. Chem. Educ.*, **80**, 679 (2003).

rate relative to benzene and dividing the total rate among the *ortho*, *meta*, and *para* products. Correction for the statistical factor arising from the relative number of available positions permits the partial rate factors to provide comparisons at positions on a substituted ring with a single position on benzene.

$$\text{Partial rate factor} = f = \frac{6(k_{\text{subs}})(\text{Fraction of product})}{y(k_{\text{benz}})} \tag{9.1}$$

where y is the number of equivalent positions. A partial rate factor calculation for nitration of toluene is given in Example 9.1.

Example 9.1. The nitration of toluene is 23 times as fast as for benzene in nitric acid–acetic anhydride. The product ratio is 63% *ortho*, 34% *para*, and 3% *meta.* Calculate the partial rate factor at each position.

$$f_o = \frac{6}{2} \times \frac{23}{1} \times 0.63 = 43.5$$

$$f_m = \frac{6}{2} \times \frac{23}{1} \times 0.03 = 2.1$$

$$f_p = \frac{6}{1} \times \frac{23}{1} \times 0.34 = 46.9$$

Partial rate factors give insight into two related aspects of reactivity and reveal the selectivity of a given electrophile for different *reactants*. Some electrophiles exhibit high *reactant selectivity*; that is, there are large differences in the rate of reaction depending on the identity of the ring substituent. In general, low reactant selectivity is correlated with high electrophile reactivity and vice versa. Clearly, when reactant selectivity is high, the partial rate factors for the substituted aromatic compound will be very different from unity. The partial rate factors also reveal *positional selectivity* within the substituted aromatic, which also varies for different electrophiles and provides some insight into the mechanism. In general, there is a correlation between position and reactant selectivity. High reactant selectivity is accompanied by high position selectivity. Electrophiles that show high reactant selectivity generally exhibit low *ortho*:*para* ratios and negligible amounts of *meta* substitution. Very reactive electrophiles tend to show low position and reactant selectivity. Table 9.4 gives some data on the selectivity of some EAS reactions. The most informative data in terms of reactant is f_p, since the partial rate factors for *ortho* substitution contain variable steric components. With f_p as the criterion, halogenation and Friedel-Crafts acylation exhibit high selectivity, protonation and nitration are intermediate, and Friedel-Crafts alkylation shows low selectivity.

9.2.2. Mechanistic Interpretation of the Relationship between Reactivity and Selectivity

Reactivity and selectivity are largely determined by the position of the TS on the reaction coordinate. With highly reactive electrophiles, the TS will come early on the reaction coordinate as in Figure 9.7a. The TS then resembles the reactants more closely than the intermediate. The positive charge on the ring is small, and, as a result, the interaction with the substituent group is relatively weak. However, the substituent also effects electron distribution in the reactant, which can cause position selectivity.

Table 9.4. Selectivity in Some Electrophilic Aromatic Substitution Reactions[a]

Reaction	Partial rate factors for toluene		
	f_o	f_m	f_p
Nitration			
$HNO_3(CH_3NO_2)$	38.9	1.3	45.7
Halogenation			
Cl_2 (CH_3CO_2H)	617	5	820
Br_2 (CH_3CO_2H, H_2O)	600	5.5	2420
Protonation			
H_2SO_4-H_2O	83	1.9	83
H_2SO_4, CF_3CO_2H, H_2O	350	7.2	313
Acylation			
PhCOCl ($AlCl_3$, $PhNO_2$)	32.6	5.0	831
CH_3COCl ($AlCl_3$, $ClCH_2CH_2Cl$)	4.5	4.8	749
Alkylation			
CH_3Br ($GaBr_3$)	9.5	1.7	11.8
$(CH_3)_2CHBr$ ($GaBr_3$)	1.5	1.4	5.0
$PhCH_2Cl$ ($AlCl_3$)	4.2	0.4	10.0

a. From L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, **1**, 35 (1963).

With a less reactive electrophile, the TS is reached later, as in Figure 9.7b. The bond to the electrophile is more completely formed and a substantial positive charge is present on the ring. This situation results in stronger substituent effects. These arguments follow the general lines of Hammond's postulate (Section 3.3.2.2). MO calculations at the HF/STO-3G level reproduce these qualitative expectations by revealing greater stabilization of the *ortho* and *para* positions in toluene with a closer approach of an electrophile.[24]

Hammett correlations also permit some insight into the reactivity and selectivity of electrophiles in EAS reactions. In general, the standard Hammett σ substituent constants lead to poor correlations with EAS reactions. The σ^+ values, which reflect an increased importance of direct resonance interaction (see Section 3.6) give better correlations and, indeed, were developed as a result of the poor correlations observed with σ in EAS. It has been suggested that the position of a TS on the reaction coordinate can be judged from the slope, ρ, of the correlation line between the rate of substitution and σ^+.[25] The rationale is the following: A numerically large value for ρ suggests a strong substituent effect, that is, a late TS that resembles the intermediate. A small value indicates a weak substituent effect and implies an early TS. Table 9.5 gives some of the ρ values for typical EAS reactions. The data indicate that the halogenation reactions show the characteristics of a highly selective electrophile, nitration and Friedel-Crafts acylation represent reactions of intermediate selectivity, and Friedel-Crafts alkylation is an example of low selectivity. This is in general agreement with the selectivity trend as measured by f_p, indicated in Table 9.4.

Isotope effects provide insight into other aspects of the mechanisms of individual electrophilic aromatic substitution reactions. In particular, since primary isotope effects are expected only when the deprotonation of the σ complex to product is rate determining, the observation of a substantial k_H/k_D points to a rate-determining

24. C. Santiago, K. N. Houk, and C. L. Perrin, *J. Am. Chem. Soc.*, **101**, 1337 (1979).
25. P. Rys, P. Skrabal, and H. Zollinger, *Angew. Chem. Int. Ed. Engl.*, **11**, 874 (1972).

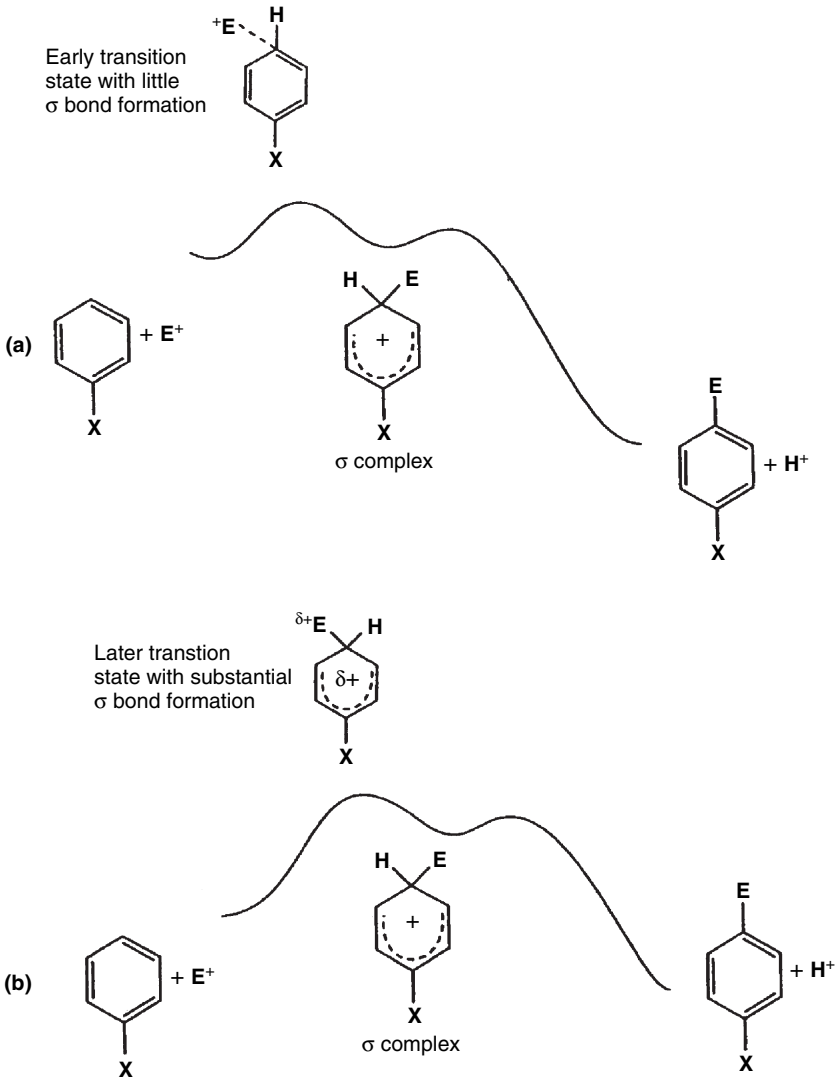


Fig. 9.7. Relation between transition state character and reaction energy profiles for highly reactive (a) and less reactive (b) electrophiles.

deprotonation. Some typical isotope effects are summarized in Table 9.6. Although isotope effects are seldom observed for nitration and halogenation, Friedel-Crafts acylation, sulfonation, nitrosation, and diazo coupling provide examples in which the rate of proton loss can affect the rate of substitution. Only in the case of the reactions involving weak electrophiles, namely nitrosation and diazo coupling, are isotope effects in the range expected for a fully rate-controlling deprotonation. Even for weak electrophiles, some factor that retards deprotonation is required for deprotonation to become rate determining. For example, in the two diazotizations cited, the steric hindrance associated with the C(8)-sulfonic acid group leads to the observation of a primary isotope effect, whereas in the unhindered four-isomer there is no isotope effect.

Table 9.5. Values of ρ for some Electrophilic Aromatic Substitution Reactions[a]

Reaction	ρ
Bromination (CH_3CO_2H)	−13.3
Chlorination (CH_3NO_2)	−13.0
Chlorination (CH_3CO_2H, H_2O)	−8.8
Protonation (H_2SO_4, CF_3CO_2H, H_2O)	−8.6
Acetylation (CH_3COCl, $AlCl_3$, $C_2H_4Cl_2$)	−8.6
Nitration (HNO_3, H_2SO_4)	−6.4
Chlorination (HOCl, H^+)	−6.1
Alkylation (C_2H_5Br, $GaBr_3$)	−2.4

a. From P. Rys, P. Skrabal, and H. Zollinger, *Angew. Chem. Intl. Ed. Engl.*, **11**, 874 (1972).

Figure 9.8 summarizes the general ideas presented in this section. At least four types of energy profiles can exist for individual EAS reactions. Case A is the rate-determining generation of the electrophile and is most readily identified by kinetics. A rate law independent of the concentration of the aromatic is diagnostic of this case. Case B represents rate-determining σ complex formation, with an electrophile of low selectivity. The rate law in such a case should have terms in both the electrophile and the aromatic. Furthermore, low selectivity, as indicated by low ρ values and low partial rate factors, is expected when this energy profile is applicable. Case C is rate-determining σ complex formation with a more selective electrophile having a

Table 9.6. Kinetic Isotope Effects for some Electrophilic Aromatic Substitution Reactions

Reaction and reactants	Reagent	k_H/k_D or k_H/k_T
Nitration		
Benzene-t[a]	HNO_3-H_2SO_4	<1.2
Toluene-t[a]	HNO_3-H_2SO_4	<1.2
Nitrobenzene-d_5[a]	HNO_3-H_2SO_4	1
Halogenation		
Benzene-d_6[a]	HOBr, $HClO_4$	1
Methoxybenzene-d[a]	Br_2	1.05
Acylation		
Benzene-d_6[b]	CH_3CO^+ SbF_6^-, CH_3NO_2	2.25
Benzene-d_6[b]	$PhCO^+$ SbF_6^-, CH_3NO_2	1.58
Sulfonation		
Benzene-d_6[c]	$ClSO_3H$, CH_3NO_2	1.7
Benzene-d_6[c]	$ClSO_3H$, CH_2Cl_2	1.6
Nitrobenzene-d_5[a]	H_2SO_4, SO_3	1.6–1.7
Nitrosation		
Benzene-d_6[d]	HNO_2, D_2SO_4	8.5
Diazo coupling		
1-Naphthol-4-sulfonic acid[a]	PhN_2^+	1.0
2-Naphthol-8-sulfonic acid[a]	PhN_2^+	6.2

a. From a more extensive compilation by H. Zollinger, *Adv. Phys. Org. Chem.*, **2**, 163 (1964).
b. G. A. Olah, J. Lukas, and E. Lukas, *J. Am. Chem. Soc.*, **91**, 5319 (1969).
c. M. P. van Albada, and H.Cerfontain, *Rec. Trav. Chim.*, **91**, 499 (1972).
d. B. C. Challis, R. J. Higgins, and A. J. Lawson, *J. Chem. Soc., Perkin Trans. 2*, 1831 (1972).

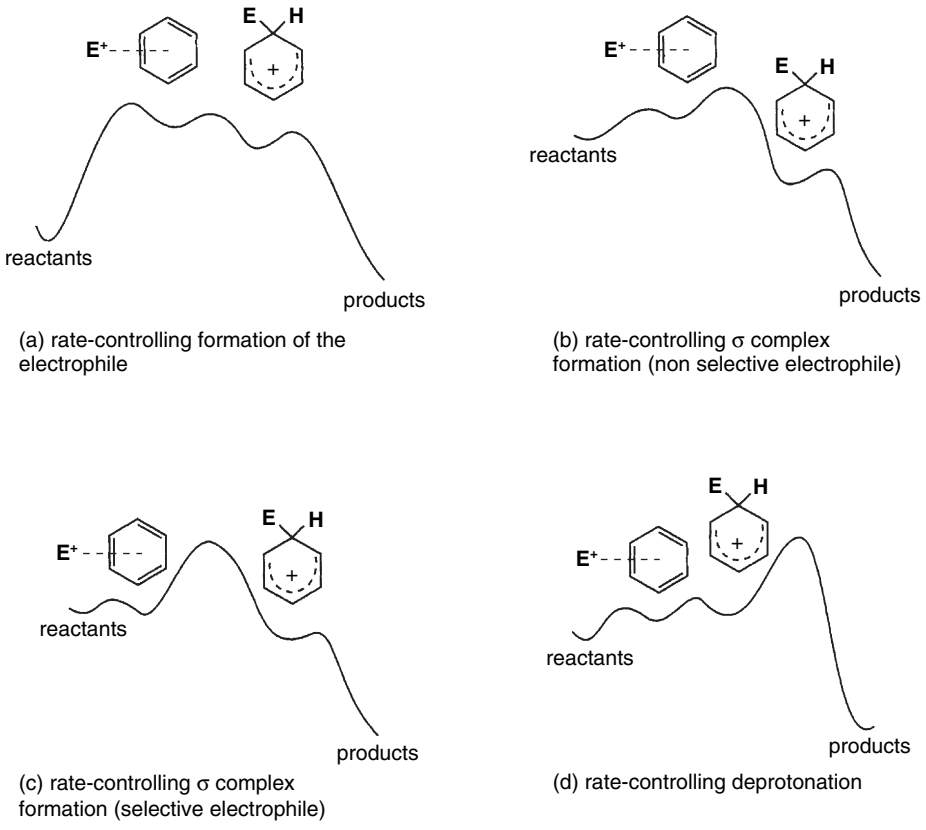
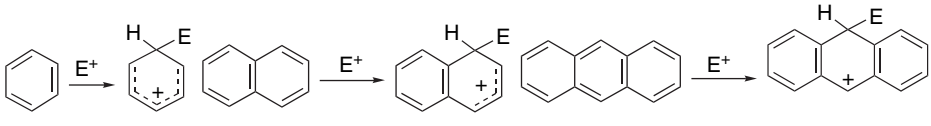


Fig. 9.8. Reaction energy profiles for electrophilic aromatic substitution showing variation in rate-determining step and electrophile selectivity.

later TS. Finally, there is case D, in which the proton removal and rearomatization are rate limiting. This case can be recognized by the observation of a primary kinetic isotope effect at the site of substitution.

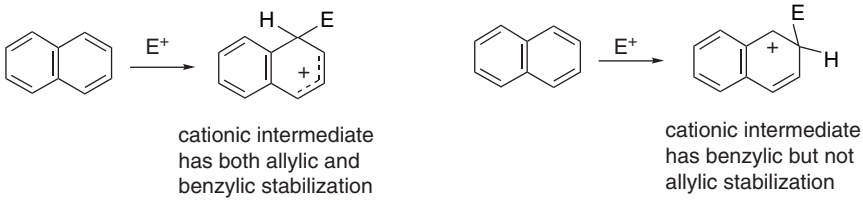
9.3. Reactivity of Polycyclic and Heteroaromatic Compounds

The polycyclic aromatic hydrocarbons such as naphthalene, anthracene, and phenanthrene undergo the various types of EAS and are generally more reactive than benzene. One reason for this is that the localization energy for formation of the cationic intermediate is lower than for benzene because more of the initial resonance stabilization is retained in intermediates that have a fused benzene ring. CNDO calculations provide estimates of the localization energies. For benzene, naphthalene, and anthracene, these are, respectively, 36.3, 15.4, and 8.3 kcal/mol.[26]



[26] A. Streitwieser, Jr., P. C. Mowery, R. G. Jesaitis, and A. Lewis, *J. Am. Chem. Soc.*, **92**, 6529 (1970).

The relative stability of the TSs determines the position of substitution under kinetically controlled conditions. For naphthalene, the preferred site for electrophilic attack is the 1-position, which is the result of the greater stability of the cationic intermediate for 1-substitution.



The more rapid substitution at C(1) of naphthalene can be demonstrated by following the incorporation of deuterium under acidic conditions. Figure 9.9 shows that the ^{1}H(C1) signal disappears more rapidly than the ^{1}H(C2) signal. As reaction continues to equilibrium, the extent of deuteration becomes the same at both positions (about 80% in this example), because there is no difference in the thermodynamic stability of the two deuterated products.[27]

Two factors can result in substitution at the 2-position. If the electrophile is very bulky, the hydrogen on the adjacent ring may cause a steric preference for attack at C(2). Under conditions of reversible substitution, where relative thermodynamic stability is the controlling factor, 2-substitution is frequently preferred. An example of this behavior is in sulfonation, where low-temperature reaction gives the 1-isomer, but at elevated temperatures the 2-isomer is formed.[28]

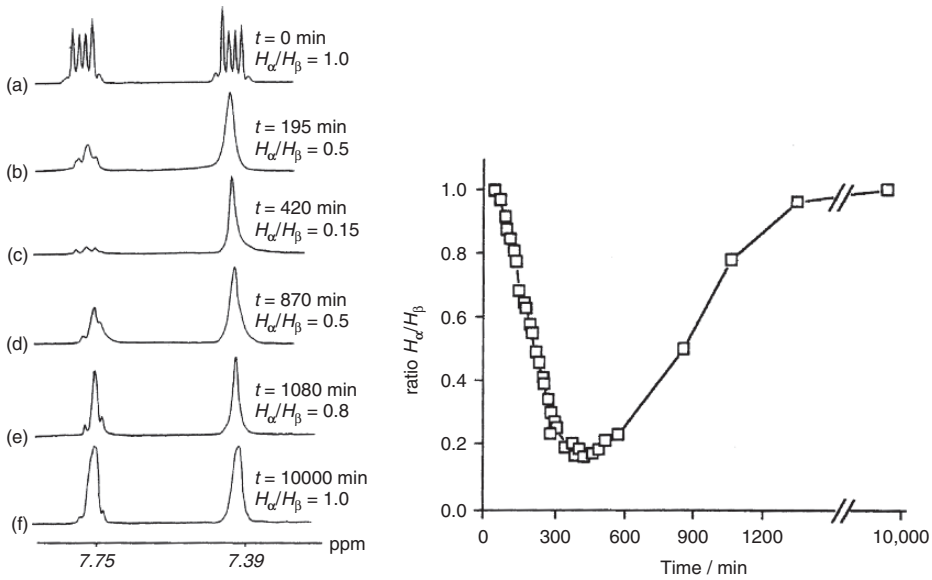
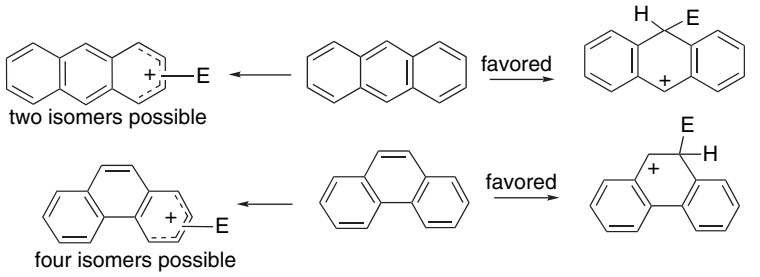


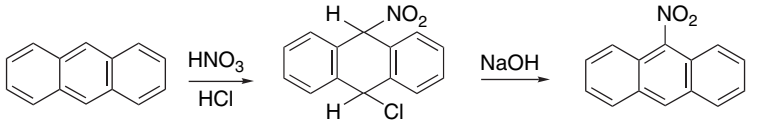
Fig. 9.9. Changes in ^{1}H-NMR spectrum of naphthalene heated with CF_3CO_2D in the presence of $(CF_3CO)_2O$ and $Al(O_2CCF_3)_3$ (left). Ratio of ^{1}H level at C(1)/C(2) (right). Reproduced from *J. Chem. Educ.*, **76**, 1246 (1999), by permission of the journal.

27. L. D. Field, S. Sternhell, and H. V. Wilton, *J. Chem. Educ.*, **76**, 1246 (1999).
28. H. Cerfontain, *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Interscience, New York, 1968, pp. 68–69.

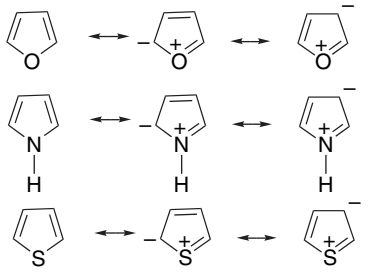
Phenanthrene and anthracene both react preferentially in the center ring. This behavior is consistent with resonance considerations. The σ complexes that result from substitution in the center ring have two intact benzene rings. The total resonance stabilization of these intermediates is larger than that of a naphthalene system that results if substitution occurs at one of the terminal rings.[29]



Both phenanthrene and anthracene have a tendency to undergo addition reactions under the conditions involved in certain electrophilic substitutions.[30] For example, an addition product can be isolated in the nitration of anthracene in the presence of hydrochloric acid.[31] This is a result of the relatively close balance in resonance stabilization to be regained by elimination (giving an anthracene ring) or addition (resulting in two benzene rings).



The heteroaromatic compounds can be divided into two broad groups, called π *excessive* and π *deficient*, depending on whether the heteroatom acts as an electron donor or electron acceptor. Furan, pyrrole, and thiophene, as well as other heterocyclics incorporating an oxygen, nitrogen, or sulfur atom that contributes two π electrons are in the π-excessive group. This classification is indicated by resonance structures and has been confirmed by various MO methods.[32]



[29] D. Z. Wang and A. Streitwieser, *Theor. Chim. Acta*, **102**, 78 (1999).

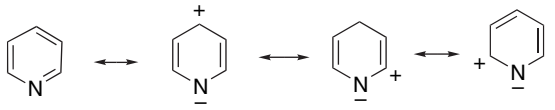
[30] P. B. D. de la Mare and J. H. Ridd, *Aromatic Substitution*, Academic Press, New York, 1959, p. 174.

[31] C. E. Braun, C. D. Cook, C. Merritt, Jr., and J. E. Rousseau, *Org. Synth.*, **IV**, 711 (1965).

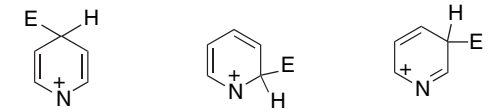
[32] N. D. Epiotis, W. P. Cherry, F. Bernardi, and W. J. Hehre, *J. Am. Chem. Soc.*, **98**, 4361 (1976); W. Adam and A. Grimison, *Theor. Chem. Acta*, **7**, 342 (1967); D. W. Genson and R. E. Christoffersen, *J. Am. Chem. Soc.*, **94**, 6904 (1972); N. Bodor, M. J. S. Dewar, and A. J. Harget, *J. Am. Chem. Soc.*, **92**, 2929 (1970).

The reactivity order is pyrrole > furan > thiophene, which indicates the order N > O > S in electron-donating capacity.[33] The N > O order is as expected on the basis of electronegativity, and O > S probably reflects the better overlap of the oxygen 2*p* orbital than the sulfur 3*p* orbital with the carbon 2*p* orbitals of the ring.

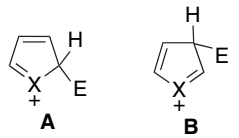
Structures such as pyridine that incorporate the −N=CH− unit are called π deficient and are deactivated to electrophilic attack. Again a resonance interpretation is evident. The nitrogen, being more electronegative than carbon, is a net acceptor of π-electron density, especially at C(2) and C(4).



There is another important factor in the low reactivity of pyridine derivatives toward EAS. The −N=CH− unit is basic because the electron pair on nitrogen is not part of the aromatic π system. The nitrogen is protonated or complexed with a Lewis acid under many of the conditions typical of EAS reactions. The formal positive charge present at nitrogen in such species further reduces the reactivity toward electrophiles. For pyridine, the reactivity toward electrophilic substitution is 3 > 4, 2. The ring nitrogen acts as a strongly destabilizing "internal" electron-withdrawing substituent in the 2- and 4- intermediates. The nitrogen also deactivates the 3-position, but less so than the 2- and 4-positions. These unfavorable effects are enhanced if the nitrogen is protonated or complexed with a Lewis acid.



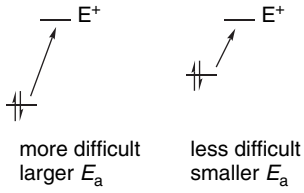
The position selectivity for electrophilic substitution in the five-membered heteroaromatic rings is usually 2 > 3, which reflects the more favorable conjugation in intermediate **A** than in intermediate **B**. In structure **A** the remaining C=C bond can delocalize the positive charge more effectively than in **B**, but substituents on the ring can override this directive influence.



Reactivity and orientation in EAS can also be related to the concept of hardness (see Section 8.1.3). Ionization potential is a major factor in determining hardness and is also intimately related to EAS. In MO terms, hardness is related to the gap between

[33] S. Clementi, F. Genel, and G. Marino, *Chem. Commun.*, 498 (1967).

the LUMO and HOMO, $\eta = (\varepsilon_{LUMO} - \varepsilon_{HOMO})/2$.[34] Thus the harder a reactant ring system is, the more difficult it is for an electrophile to complete σ-bond formation.



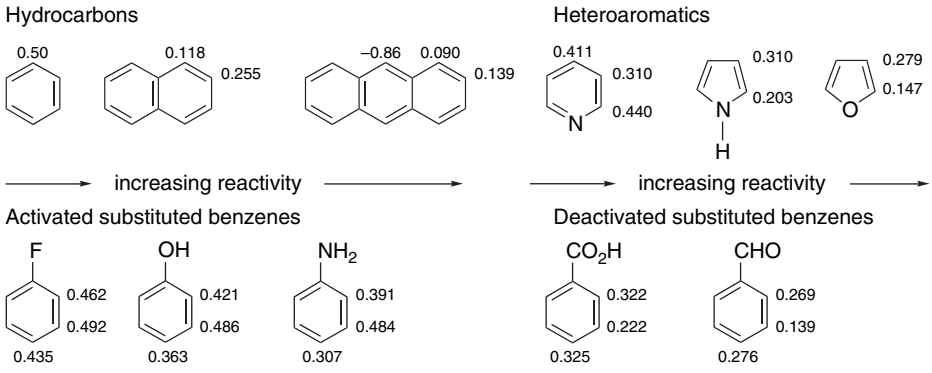
This idea can be quantitatively expressed by defining *activation hardness* as the difference in the LUMO-HOMO gap for the reactant and the cationic intermediate[35]:

$$\Delta\eta^* = \beta[(\chi^R_{LUMO} - \chi^R_{HOMO}) - (\chi^\sigma_{LUMO} - \chi^\sigma_{HOMO})]/2$$

where χ^R and χ^σ are the orbitals of the reactant and cationic intermediate.

Simple HMO theory has been used to calculate $\Delta\eta^*$ for several benzenoid hydrocarbons, substituted benzenes, and heterocycles. The resulting values are in qualitative agreement with reactivity trends. Scheme 9.3 gives some of the data. The less positive the number, the more reactive the position. Although there are some discrepancies between structural groups, within groups the $\Delta\eta^*$ values correlate well with position selectivity. The most glaring discrepancy is the smaller activation hardness for deactivated compared with activated benzenes. In particular, benzaldehyde and benzoic acid have $\Delta\eta^*$ values that are lower than that of benzene, which is counter to their relative reactivity. However, the preference for *meta* substitution of the deactivated benzenes is predicted correctly. The deactivation of pyridine, relative to benzene, is also not indicated by the $\Delta\eta^*$ value.

Scheme 9.3. Activation Hardness for Aromatic and Heteroaromatic Compounds[a]



a. Z. Zhou and R. G. Parr, *J. Am. Chem. Soc.*, **112**, 5720 (1990).

34. R. G. Pearson, *Proc. Natl. Acad. Sci. USA*, **83**, 8440 (1986).
35. Z. Zhou and R. G. Parr, *J. Am. Chem. Soc.*, **112**, 5720 (1990).

9.4. Specific Electrophilic Substitution Reactions

At this point, we focus on specific electrophilic substitution reactions. The kinds of data that have been especially pertinent in elucidating mechanistic detail include linear free-energy relationships, kinetic studies, isotope effects, and selectivity patterns. In general, the basic questions to be asked about each mechanism are: (1) What is the active electrophile? (2) Which step in the general mechanism for EAS is rate determining? (3) What are the orientation and selectivity patterns?

9.4.1. Nitration

A substantial body of data including reaction kinetics, isotope effects, and structure-reactivity relationships is available for aromatic nitration.[36] As anticipated from the general mechanism for electrophilic substitution, there are three distinct steps. Conditions under which each of the first two steps is rate determining have been recognized. The third step is usually very fast.

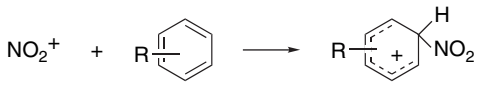
1. Generation of the electrophile

$$2H_2SO_4 + HNO_3 \rightleftharpoons NO_2^+ + 2HSO_4^- + H_3O^+$$

or

$$2HNO_3 \rightleftharpoons NO_2^+ + NO_3^- + H_2O$$

2. Attack on the aromatic ring forming the cationic intermediate



3. Deprotonation

The existence of the nitronium ion in sulfuric-nitric acid mixtures can be demonstrated by both cryoscopic measurements and spectroscopy. An increase in the strong acid concentration increases the rate of reaction by shifting the equilibrium of Step 1 to the right. Addition of a nitrate salt has the opposite effect by suppressing the preequilibrium dissociation of nitric acid. It is possible to prepare crystalline salts of nitronium ions such as nitronium tetrafluoroborate. Solutions of these salts in organic solvents nitrate aromatic compounds rapidly.[37]

There are three general types of kinetic situations that have been observed for aromatic nitration. Aromatics of modest reactivity exhibit second-order kinetics in mixtures of nitric acid with the stronger sulfuric or perchloric acid.[38] Under these

[36] J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, 1971; L. M. Stock, *Prog. Phys. Org. Chem.*, **12**, 21 (1976); G. A. Olah, R. Malhotra, and S. C. Narang, *Nitration*, VCH Publishers, New York, 1989.

[37] S. J. Kuhn and G. A. Olah, *J. Am. Chem. Soc.*, **83**, 4564 (1961); G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, **84**, 3684 (1962); C. M. Adams, C. M. Sharts, and S. A. Shackelford, *Tetrahedron Lett.*, **34**, 6669 (1993); C. L. Dwyer and C. W. Holzapfel, *Tetrahedron*, **54**, 7843 (1998).

[38] J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, *Nitration and Aromatic Reactivity*, Cambridge University Press, Cambridge, 1971, Chap. 02.

conditions, the formation of the nitronium ion is a fast preequilibrium and Step 2 of the nitration mechanism is rate controlling. If nitration is conducted in inert organic solvents, such as nitromethane or carbon tetrachloride in the absence of a strong acid, the rate of formation of nitronium ion is slower and becomes rate limiting.[39] Finally, some very reactive aromatics, including alkylbenzenes, can react so rapidly under conditions where nitronium ion concentration is high that the rate of nitration becomes governed by encounter rates. Under these circumstances mixing and diffusion control the rate of reaction and no differences are observed between the reactants.[40]

With very few exceptions, the final step in the nitration mechanism, the deprotonation of the σ complex, is fast and has no effect on the observed kinetics. The fast deprotonation can be confirmed by the absence of an isotope effect when deuterium or tritium is introduced at the substitution site. Several compounds such as benzene, toluene, bromobenzene, and fluorobenzene were subjected to this test and did not exhibit isotope effects during nitration.[41] The only case where a primary isotope effect has been seen is with 1,3,5-tri-*t*-butylbenzene, where steric hindrance evidently makes deprotonation the slow step.[42]

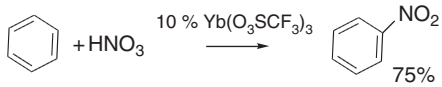
There are several other synthetic methods for aromatic nitration. Nitric acid in acetic anhydride is a potent nitrating agent and effects nitration a higher rates than nitric acid in inert organic solvents. Acetyl nitrate is formed and it is the nitrating agent.

$$HNO_3 + (CH_3CO)_2O \longrightarrow CH_3\overset{\overset{O}{\|}}{C}ONO_2 + CH_3CO_2H$$

A very convenient synthetic procedure for nitration involves the mixing of a nitrate salt with trifluoroacetic anhydride.[43] This generates trifluoroacetyl nitrate, which is even more reactive than acetyl nitrate.

$$NO_3^- + (CF_3CO)_2O \longrightarrow CF_3\overset{\overset{O}{\|}}{C}ONO_2 + CF_3CO_2^-$$

Benzene, toluene, and aromatics of similar reactivity can be nitrated using $Yb(O_3SCF_3)_3$ and 69% nitric acid in an inert solvent.[44] The catalyst remains active and can be reused. The active nitrating agent under these conditions is uncertain but must be some complex of nitrate with the oxyphilic lanthanide.



39. E. D. Hughes, C. K. Ingold, and R. I. Reed, *J. Chem. Soc.*, 2400 (1950); R. G. Coombes, *J. Chem. Soc. B*, 1256 (1969).
40. R. G. Coombes, R. B. Moodie, and K. Schofield, *J. Chem. Soc. B*, 800 (1968); H. W. Gibbs, L. Main, R. B. Moodie, and K. Schofield, *J. Chem. Soc., Perkin Trans. 2*, 848 (1981).
41. G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Am. Chem. Soc.*, **83**, 4571, 4581 (1961); H. Suhr and H. Zollinger, *Helv. Chim. Acta*, **44**, 1011 (1961); L. Melander, *Acta Chem. Scand.*, **3**, 95 (1949); *Arkiv Kemi.*, **2**, 211 (1950).
42. P. C. Myhre, M. Beug, and L. L. James, *J. Am. Chem. Soc.*, **90**, 2105 (1968).
43. J. V. Crivello, *J. Org. Chem.*, **46**, 3056 (1981).
44. F. J. Waller, A. G. M. Barrett, D. C. Braddock, and D. Ramprasad, *Chem. Commun.*, 613 (1997).

The identification of a specific nitrating species can be approached by comparing selectivity with that of nitration under conditions known to involve the nitronium ion. Examination of Part B of Table 9.7 shows that the position selectivity exhibited by acetyl nitrate toward toluene and ethylbenzene is not very different from that observed with nitronium ion. The data for *i*-propylbenzene suggest a lower *ortho*:*para* ratio for acetyl nitrate nitrations, which could indicate a larger steric factor for nitration by acetyl nitrate.

Relative reactivity data for nitration must be treated with special caution because of the possibility of encounter control. An example of this can be seen in Part A of Table 9.7, where no difference in reactivity between mesitylene and xylene is found in H_2SO_4-HNO_3 nitration, whereas in HNO_3-CH_3NO_2 the rates differ by a factor of more than 2. Encounter-control prevails in the former case. In general, nitration is a relatively unselective reaction with toluene f_p being about 50–60, as shown in

Table 9.7. Relative Reactivity and Position Selectivity for Nitration of Some Aromatic Compounds

A. Relative Reactivity of Some Hydrocarbons

Reactant	H_2SO_4-HNO_3-H_2O[a]	HNO_3-CH_3NO_2[b]	HNO_3-$(CH_3CO)_2O$[c]
Benzene	1	1	1
Toluene	17	25	27
p-Xylene	38	139	92
m-Xylene	38	146	–
o-Xylene	38	139	–
Mesitylene	36	400	1750

B. Partial Rate Factors for Some Monoalkylbenzenes

Reactant	HNO_3-H_2SO_4(sulfolane)[d]			HNO_3-CH_3NO_2[e,f]			$HNO_3(CH_3CO)_2O$[g]		
	f_o	f_m	f_p	f_o	f_m	f_p	f_o	f_m	f_p
Toluene	52.1	2.8	58.1	49	2.5	56	49.7	1.3	60.0
Ethylbenzene	36.2	2.6	66.4	32.7	1.6	67.1	31.4	2.3	69.5
i-Propylbenzene	17.9	1.9	43.3	–	–	–	14.8	2.4	71.6
t-Butylbenzene				5.5	3.7	71.4	4.5	3.0	75.5

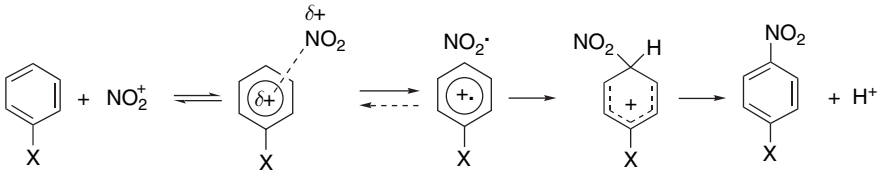
C. Relative Reactivity and Isomer Distribution for Nitrobenzene and the Nitrotoluenes[h]

Reactant	Relative reactivity	Product composition (%)		
		ortho	*meta*	*para*
Nitrobenzene	1	7	92	1
o-Nitrotoluene	545	29	1	70
m-Nitrotoluene	138	38	1	60
p–Nitrotoluene	217	100	0	–

a. R. G. Coombes, R. B. Moodie, and K. Schofield, *J. Chem. Soc. B*, 800 (1968).
b. J. G. Hoggett, R. B. Moodie, and K. Scholfield, *J. Chem. Soc. B*, 1 (1969).
c. A. R. Cooksey, K. J. Morgan, and D. P. Morrey, *Tetrahedron*, **26**, 5101 (1970).
d. G. A. Olah, S. J. Kuhn, S. H. Flood, and J. C. Evans, *J. Am. Chem. Soc.*, **84**, 3687 (1962).
e. L. M. Stock, *J. Org. Chem.*, **26**, 4120 (1961).
f. G. A. Olah and H. C. Lin, *J. Am. Chem. Soc.*, **96**, 549 (1974).
g. J. R. Knowles, R. O. C. Norman, and G. K. Radda, *J. Chem. Soc.*, 4885 (1960).
h. G. A. Olah and H. C. Lin, *J. Am. Chem. Soc.*, **96**, 549 (1974); *o*,*m*, and *p* designations for the toluenes are in relation to the methyl group.

Table 9.7. When the aromatic reactant carries an EWG, the selectivity increases, since the TS occurs later. For example, while toluene is about 20 times more reactive than benzene, *p*-nitrotoluene is about 200 times more reactive than nitrobenzene. The effect of the methyl substituent is magnified as a result of the later TS.

An aspect of aromatic nitration that has received attention is the role of charge transfer complexes and electron transfer intermediates on the path to the σ-complex intermediate. For some NO_2-X nitrating reagents, the mechanism may involve formation of a distinct electron transfer intermediate prior to the formation of the σ complex.[45]



The existence of charge transfer complexes can be demonstrated for several reaction combinations that eventually lead to nitration, but the crucial question is whether a complete electron transfer to a cation radical–radical pair occurs as a distinct step in the mechanism. This has been a matter of continuing discussion, both pro[46] and con.[47] One interesting fact that has emerged about nitration is that the product composition from toluene is virtually invariant at 4 ± 2% *meta*, 33 ± 3% *para*, and 65 ± 5% *ortho*, that is, close to a statistical *o*:*p* ratio over a wide range of nitrating species.[48] This argues for a common product-forming step, and one interpretation is that this step is a collapse of a NO_2·–cation radical pair, as in the electron transfer mechanism. If the σ-complex were formed in a single step from different NO_2-X reagents, some variation of the product composition for different X would be expected.

The mechanism of aromatic nitration has been studied by computational methods. Various structures resulting from interaction of benzene with NO_2^+ were found by B3LYP/6-311++G** computations.[49] Three of the key intermediates are shown in Fig. 9.10. In structure **A** the NO_2 unit is associated with a single carbon atom with a C−N bond distance is 1.997 Å. This structure is only slightly more stable than **B**, in which the NO_2 group is located equidistant between two carbon atoms. The NO_2 group in both structures is significantly bent and resembles the neutral NO_2 molecule, suggesting that a substantial degree of electron transfer has occurred. CHELPG charge analysis is consistent with this conclusion. Various complexes with the linear NO_2^+ ion associated more generally with the ring are at considerably higher energies. Note that these structures are similar to the Br_2-benzene and Br_2-toluene complexes described on p. 774. The nitrocyclohexadienylium ion intermediate **C** is about 1 kcal/mol more stable than these oriented complexes. These results pertain to the gas phase.

45. C. L. Perrin, *J. Am. Chem. Soc.*, **99**, 5516 (1977).
46. J. K. Kochi, *Acc. Chem. Res.*, **25**, 39 (1992); T. M. Bockman and J. K. Kochi, *J. Phys. Org. Chem.*, **7**, 325 (1994); A. Peluso and G. Del Re, *J. Phys. Chem.*, **100**, 5303 (1996); S. V. Rosokha and J. K. Kochi, *J. Org. Chem.*, **67**, 1727 (2002).
47. L. Eberson and F. Radner, *Acc. Chem. Res.*, **20**, 53 (1987); L. Eberson, M. P. Hartshorn, and F. Radner, *Acta Chem. Scand.*, **48**, 937 (1994); M. Lehnig, *J. Chem. Soc., Perkin Trans. 2*, 1943 (1996).
48. E. K. Kim, K. Y. Lee, and J. K. Kochi, *J. Am. Chem. Soc.*, **114**, 1756 (1992).
49. P. M. Esteves, J. W. de Carneiro, S. P. Cardoso, A. G. H. Barbosa, K. K. Laali, G. Rasul, G. K. S. Prakash, and G. A. Olah, *J. Am. Chem. Soc.*, **125**, 4836 (2003).

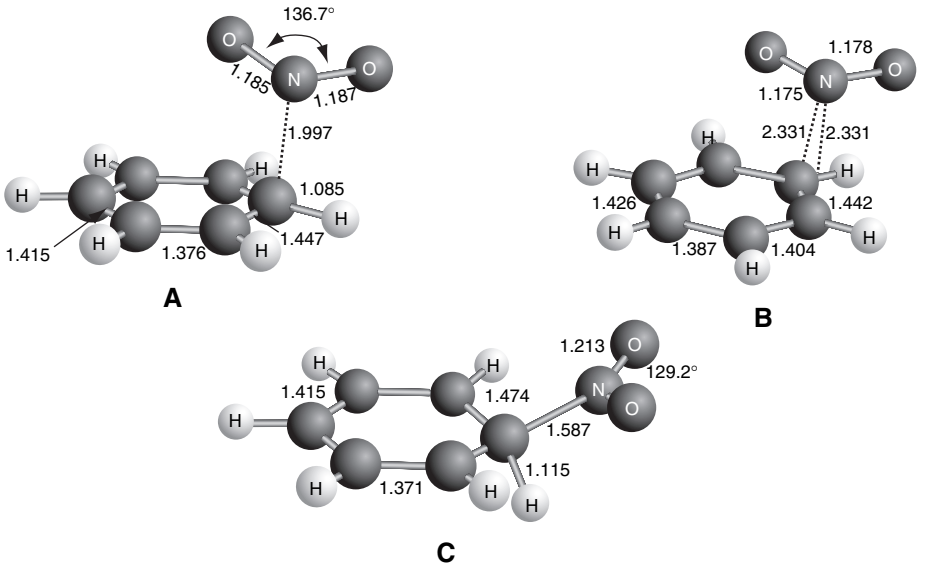


Fig. 9.10. Oriented complexes and nitrocyclohexadienylium intermediate in the nitration of benzene. Adapted from *J. Am. Chem. Soc.*, **125**, 4836 (2003), by permission of the American Chemical Society.

The nitration mechanism also has been modeled by B3LYP/6-311G** computations using a continuum solvent model.[50] Structures corresponding to an oriented π complex and the TS and σ complex intermediate were identified. Computations were done at several solvent dielectrics, ϵ, ranging from 0 (vacuum) to 78.5 (water). The barrier for σ complex formation is small and decreases as ϵ increases. The reaction is calculated to occur without a barrier at $\epsilon > 50$. These computational results are consistent with an electron transfer mechanism for nitration of benzene. The reaction occurs through a complex that allows charge transfer to form a radical cation–$NO_2\cdot$ pair, which is followed by collapse to the nitrocyclohexadienylium intermediate. The product distribution is determined at this latter stage. This feature of the mechanism explains the relatively constant position selectivity of nitration because only the NO_2 group is in intimate contact with the substrate at that point.

Visual models, additional information and exercises on Nitation of Benzene can be found in the Digital Resource available at: Springer.com/carey-sundberg.

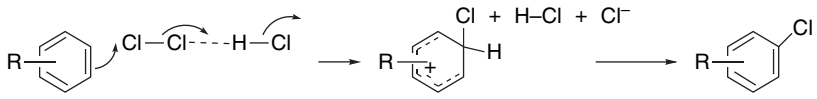
9.4.2. Halogenation

Substitution for hydrogen by halogen is a synthetically important electrophilic aromatic substitution reaction. The reactivity of the halogens increases in the order $I_2 < Br_2 < Cl_2 < F_2$. Halogenation reactions are normally run in the presence of Lewis acids, in which case a complex of the halogen with the Lewis acid is probably the active electrophile. The molecular halogens are reactive enough to halogenate activated aromatics. Bromine and iodine form stable complexes with the corresponding halide

[50] H. Xiao, L. Chen, X. Ju, and G. Ji, *Science in China B*, **46**, 453 (2003).

ions. These anionic trihalide ions are less reactive than the free halogen, but are capable of substituting highly reactive rings. This factor can complicate kinetic studies, since the concentration of halide ion increases during the course of halogenation and successively more of the halogen is present as the trihalide ion.

Molecular chlorine is believed to be the active electrophile in uncatalyzed chlorination of reactive aromatic compounds. Second-order kinetics are observed in acetic acid.[51] The reaction is much slower in nonpolar solvents such as dichloromethane and carbon tetrachloride, and chlorination in nonpolar solvents is catalyzed by added acid. The catalysis by acids is probably the result of assistance by proton transfer in the cleavage of the Cl−Cl bond.[52]



Chlorination in acetic acid is characterized by a large ρ value (~ -9 to -10) and a high partial rate factor for toluene, $f_p = 820$. Both values indicate a late TS that resembles the σ complex intermediate.

For preparative purposes, a Lewis acid such as $AlCl_3$ or $FeCl_3$ is often used to catalyze chlorination. Chlorination of benzene using $AlCl_3$ is overall third order.[53]

$$\text{Rate} = k[\text{ArH}][\text{Cl}_2][\text{AlCl}_3]$$

This rate law is consistent with formation of a Cl_2-$AlCl_3$ complex that acts as the active halogenating agent but is also consistent with a rapid equilibrium involving formation of $Cl.^+$

$$Cl_2 + AlCl_3 \rightleftharpoons Cl{-}Cl^{+}{-}Al^{-}Cl_3 \longrightarrow Cl^{+} + [AlCl_4]^{-}$$

There is, however, no direct evidence for the formation of Cl^+, and it is much more likely that the complex is the active electrophile. The substrate selectivity under catalyzed conditions ($k_{tol} = 160k_{benz}$) is lower than in uncatalyzed chlorinations, as would be expected for a more reactive electrophile. The effect of the Lewis acid is to weaken the Cl−Cl bond and lower the activation energy for σ complex formation.

Hypochlorous acid is a weak chlorinating agent. In acidic solution, it is converted to a much more active chlorinating agent. Although early mechanistic studies suggested that Cl^+ might be formed under these conditions, it was shown that this is not the case. Detailed kinetic analysis of the chlorination of methoxybenzene revealed a rather complex rate law.[54]

$$\text{Rate} = k_1[\text{HOCl}]^2 + k_2[\text{H}_3\text{O}^+][\text{HOCl}]^2 + k_3[\text{ArH}][\text{H}_3\text{O}^+][\text{HOCl}]$$

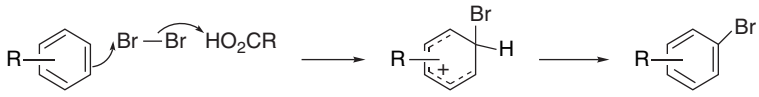
Some of the terms are independent of the concentration of the aromatic reactant. This rate law can be explained in terms of the formation of Cl_2O, the anhydride of hypochlorous acid.

$$2HOCl \xrightarrow{H^+} Cl_2O + H_2O$$

51. L. M. Stock and F. W. Baker, *J. Am. Chem. Soc.*, **84**, 1661 (1962).
52. L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, **81**, 1063 (1959); R. M. Keefer and L. J. Andrews, *J. Am. Chem. Soc.*, **82**, 4547 (1960).
53. S. Y. Caille and R. J. P. Corriu, *Tetrahedron*, **25**, 2005 (1969).
54. C. G. Swain and D. R. Crist, *J. Am. Chem. Soc.*, **94**, 3195 (1972).

Both Cl_2O and $[H_2OCl]^+$ apparently are active electrophiles under these conditions. The terms involving Cl_2O are zero order in the aromatic reactant because formation of Cl_2O is the rate-limiting step. Thermodynamic considerations argue strongly against rate-determining cleavage of $[H_2OCl]^+$ to H_2O and Cl^+. The estimated equilibrium constant for this dissociation is so small that the concentration of Cl^+ would be far too low to account for the observed reaction rate.[55]

Molecular bromine is thought to be the reactive brominating agent in uncatalyzed brominations. The bromination of benzene and toluene are first order in both bromine and the aromatic reactant in trifluoroacetic acid solution,[56] but becomes more complicated in the presence of water.[57] The bromination of benzene in aqueous acetic acid exhibits a first-order dependence on bromine concentration when bromide ion is present. The observed rate is dependent on bromide ion concentration, decreasing with increasing concentration. The acids presumably assist in the rate-determining step, as in the case of chlorination. The detailed kinetics are consistent with a rate-determining formation of the σ complex when bromide ion concentration is low, but with a shift to reversible formation of the σ complex with rate-determining deprotonation at high bromide ion concentration.[58]



The issue of involvement of an electron-transfer step in the formation of the intermediate has been investigated both experimentally and computationally. As noted in Section 9.1, discrete complexes of bromine with aromatic hydrocarbons have been characterized structurally for benzene and toluene.[59] Kinetic studies show that the rate of disapearance of the complexes is identical to the rate of formation of the bromination product, but this alone does not prove that the complex is an intermediate.[60] Computational studies are consistent with formation of a benzene radical cation–$[Br_2\cdot]^-$ radical pair as an intermediate. The calculated $\Delta H^{\ddagger}$ is about 10 kcal/mol less than for a mechanism leading directly to a cyclohexadienylium ion intermediate.[61]

Bromination is characterized by high reactant selectivity.[62] The data in Table 9.4 showed that for toluene f_p is around 2500, as compared to about 50 for nitration. The very large stabilizing effect of ERG substituents is also evident in the large negative ρ value (−12).[63] The fact that substituents can strongly influence both the rate and the orientation implies that the TS comes late in the reaction and resembles the intermediate cyclohexadienylium ion.

55. E. Berliner, *J. Chem. Ed.*, **43**, 124 (1966).
56. H. C. Brown and R. A. Wirkkala, *J. Am. Chem. Soc.*, **88**, 1447 (1966).
57. W. M. Schubert and D. F. Gurka, *J. Am. Chem. Soc.*, **91**, 1443 (1969).
58. E. Berliner and J. C. Powers, *J. Am. Chem. Soc.*, **83**, 905 (1961); W. M. Schubert and J. L. Dial, *J. Am. Chem. Soc.*, **97**, 3877 (1975).
59. A. V. Vasilyev, S. V. Lindeman, and J. K. Kochi, *Chem. Commun.*, 909 (2001); S. V. Rosokha and J. K. Kochi, *J. Org. Chem.*, **67**, 1727 (2002).
60. S. Fukuzumi and J. K. Kochi, *J. Org. Chem.*, **46**, 4116 (1981); S. Fukuzumi and J. K. Kochi, *J. Am. Chem. Soc.*, **103**, 7240 (1981).
61. W. B. Smith, *J. Phys. Org. Chem.*, **16**, 34 (2003).
62. L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, **1**, 35 (1963).
63. H. C. Brown and L. M. Stock, *J. Am. Chem. Soc.*, **79**, 1421 (1957).

Bromination has been shown not to exhibit a primary kinetic isotope effect in the case of benzene,[64] bromobenzene,[65] toluene,[66] or methoxybenzene.[67] There are several examples of reactants that do show significant isotope effects, including substituted anisoles,[46] *N*,*N*-dimethylanilines,[68] and 1,3,5-trialkylbenzenes.[69] The observation of isotope effects in highly substituted systems seems to be the result of steric factors that can operate in two ways. There may be resistance to the bromine taking up a position coplanar with adjacent substituents in the aromatization step, which would favor return of the σ complex to reactants. In addition, the steric bulk of several substituents may hinder solvent or other base from assisting in proton removal. Either factor could allow deprotonation to become rate controlling.

Bromination is catalyzed by Lewis acids, and a study of the kinetics of bromination of benzene and toluene in the presence of aluminum chloride has been reported.[70] Toluene is found to be about 35 times more reactive than benzene under these conditions. The catalyzed reaction thus shows a good deal less substrate selectivity than the uncatalyzed reaction, as would be expected on the basis of the greater reactivity of the aluminum chloride-bromine complex.

Halogenation is also effected by acyl hypohalites, such as acetyl hypochlorite and trifluoroacetyl hypobromite.[71]

$$Cl_2 + Hg(O_2CCH_3)_2 \rightleftharpoons HgCl(O_2CCH_3) + CH_3CO_2Cl$$
$$Br_2 + Hg(O_2CCF_3)_2 \rightleftharpoons HgBr(O_2CCF_3) + CF_3CO_2Br$$

The latter is an extremely reactive species. Trifluoroacetate is a good leaving group and facilitates cleavage of the O−Br bond. The acyl hypohalites are also the active halogenating species in solutions of the hypohalous acids in carboxylic acids, where they exist in equilibrium. Acetyl hypobromite is considered to be the active halogenating species in solutions of hypobromous acid in acetic acid:

$$CH_3CO_2H + HOBr \rightleftharpoons CH_3CO_2Br + H_2O$$

This reagent can also be formed by reaction of bromine with mercuric acetate:

$$Hg(O_2CCH_3)_2 + Br_2 \rightleftharpoons HgBr(O_2CCH_3) + CH_3CO_2Br$$

Both of the above equilibria lie to the left, but acetyl hypobromite is sufficiently reactive that it is the principal halogenating species in both solutions. The reactivity of the acyl hypohalites as halogenating agents increases with the ability of the carboxylate to function as a leaving group. This is, of course, correlated with the acidity of the carboxylic acid. The estimated order of reactivity of Br_2, CH_3CO_2Br, and CF_3CO_2Br is

64. P. B. D. de la Mare, T. M. Dunn, and J. T. Harvey, *J. Chem. Soc.*, 923 (1957).
65. L. Melander, *Acta Chem. Scand.*, **3**, 95 (1949); *Arkiv Kemi.*, **2**, 211 (1950).
66. R. Josephson, R. M. Keefer, and L. J. Andrews, *J. Am. Chem. Soc.*, **83**, 3562 (1961).
67. J.-J. Aaron and J.-E. Dubois, *Bull. Soc. Chim. Fr.*, 603 (1971).
68. J.-E. Dubois and R. Uzan, *Bull. Soc. Chim. Fr.*, 3534 (1968); A. Nilsson, *Acta Chem. Scand.*, **21**, 2423 (1967); A. Nilsson and K. Olsson, *Acta Chem. Scand.*, **23**, 2317 (1969).
69. P. C. Myhre, *Acta Chem. Scand.*, **14**, 219 (1969).
70. S. Y. Caille and R. J. P. Corriu, *Tetrahedron*, **25**, 2005 (1969).
71. (a) A. L. Henne and W. F. Zimmer, *J. Am. Chem. Soc.*, **73**, 1362 (1951); (b) P. B. D. de la Mare, I. C. Hilton, and S. Varma, *J. Chem. Soc.*, 4044 (1960); (c) P. B. D. de la Mare and J. L. Maxwell, *J. Chem. Soc.*, 4829 (1962); (d) Y. Hatanaka, R. M. Keefer, and L. J. Andrews, *J. Am. Chem. Soc.*, **87**, 4280 (1965); (e) J. R. Bennett, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **94**, 6129 (1972).

$1:10^6:10^{10}$.[71b,e] It is this exceptionally high reactivity of the hypobromites that permits them to be the reactive halogenating species in solutions where they are present in relatively low equilibrium concentration.

Molecular iodine is not a very powerful halogenating agent. Only very reactive aromatics such as anilines or phenolate anions are reactive toward iodine. Iodine monochloride can be used as an iodinating agent. The greater electronegativity of the chlorine makes the iodine the electrophilic entity in the substitution reaction. Iodination by iodine monochloride is catalyzed by Lewis acids, such as $ZnCl_2$.[72] Iodination can also be carried out with acetyl hypoiodite and trifluoroacetyl hypoiodite. The methods of formation of these reagents are similar to those for the hypobromites.[73]

Direct fluorination of aromatics is not a preparatively important laboratory reaction because it can occur with explosive violence. Mechanistic studies have been done at very low temperatures and with low fluorine concentrations. For toluene, the f_p and f_m values are 8.2 and 1.55, respectively, indicating that fluorine is a very unselective electrophile. The ρ value in a Hammett correlation with σ^+ is -2.45. Thus, fluorination exhibits the characteristics that would be expected for a very reactive electrophile.[74] A number of reagents in which fluorine is bound to a very electronegative group also serve as fluorinating agents, including CF_3OF, CF_3CO_2F, CH_3CO_2F, and $HOSO_2OF$.[75] The synthetic applications of these reagents are discussed in Section 11.1.2 of Part B.

9.4.3. Protonation and Hydrogen Exchange

Hydrogen exchange resulting from reversible protonation of an aromatic ring can be followed by the use of isotopic labels. Either deuterium or tritium can be used and the experiment can be designed to follow either the incorporation or the release of the isotope. The study of the mechanism of electrophilic hydrogen exchange is somewhat simplified by the fact that the proton is the active electrophile. The principle of microscopic reversibility implies that the TS occurs on a symmetrical potential energy surface, since the attacking electrophile is chemically identical to the displaced proton. The TS involves partial transfer of a proton to (or from) a solvent molecule(s) to the aromatic ring. The intermediate σ complex is a cyclohexadienylium cation.

Partial rate factors for exchange for a number of substituted aromatic compounds have been measured. They reveal activation of *ortho* and *para* positions by ERGs. Some typical data are given in Table 9.8. The k_{tol}/k_{benz} ratio of around 300 indicates considerable substrate selectivity. The f_p value for toluene varies somewhat, depending on the reaction medium, but is generally about 10^2.[76] The ρ value for hydrogen exchange in H_2SO_4-CF_3CO_2H-H_2O is -8.6.[77] A similar ρ value of -7.5 has been observed in aqueous sulfuric acid.[78] As seen for other electrophilic aromatic substitution reactions, the best correlation is with σ^+. These ρ values put protonation in the intermediate range of selectivity.

72. R. M. Keefer and L. J. Andrews, *J. Am. Chem. Soc.*, **78**, 5623 (1956).
73. E. M. Chen, R. M. Keefer, and L. J. Andrews, *J. Am. Chem. Soc.*, **89**, 428 (1967).
74. F. Cacace, P. Giacomello, and A. P. Wolff, *J. Am. Chem. Soc.*, **102**, 3511 (1980).
75. A. Haas and M. Lieb, *Chimia*, **39**, 134 (1985).
76. L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, **1**, 35 (1963).
77. P. Rys, P. Skrabal, and H. Zollinger, *Angew. Chem. Int. Ed. Engl.*, **11**, 874 (1972).
78. S. Clementi and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 2*, 1077 (1973).

Table 9.8. Partial Rate Factors for Hydrogen Exchange for Some Substituted Aromatic Compounds

Substituent	f_o	f_m	f_p
CH_3[a]	330	7.2	313
F[b]	0.136	-	1.70
Cl[b]	0.035	-	0.161
OPh[c]	6900	~0.1	31,000
Ph[d]	133	< 1	143

a. C. Eaborn and R. Taylor, *J. Chem. Soc.*, 247 (1961).
b. C. Eaborn and R. Taylor, *J. Chem. Soc.*, 2388 (1961).
c. R. Baker and C. Eaborn, *J. Chem. Soc.*, 5077 (1961).
d. C. Eaborn and R. Taylor, *J. Chem. Soc.*, 1012 (1961).

Among the many experimental results pertaining to hydrogen exchange, a most important one is that general acid catalysis has been demonstrated,[79] a finding that is in accord with a rate-limiting proton transfer step. Since proton removal is partially rate determining, hydrogen exchange exhibits an isotope effect. A series of experiments using both deuterium and tritium labels arrived at $k_H/k_D = 9.0$ for the proton-loss step for 1,3,5-trimethoxybenzene.[80] A substantial isotope effect has also been observed for the exchange process with azulene.[81]

9.4.4. Friedel-Crafts Alkylation and Related Reactions

The Friedel-Crafts reaction is a very important method for introducing alkyl substituents on an aromatic ring by generation of a carbocation or related electrophilic species. The usual method of generating these electrophiles involves reaction between an alkyl halide and a Lewis acid. The most common Friedel-Crafts catalyst for preparative work is $AlCl_3$, but other Lewis acids such as SbF_5, $TiCl_4$, $SnCl_4$, and BF_3 can also promote reaction. Alternative routes to alkylating species include reaction of alcohols or alkenes with strong acids.

There are relatively few kinetic data on the Friedel-Crafts reaction. Alkylation of benzene or toluene with methyl bromide or ethyl bromide with gallium bromide as the catalyst is first order in each reactant and in the catalyst.[82] With aluminum bromide as the catalyst, the rate of reaction changes with time, apparently because of heterogeneity of the reaction mixture.[83] The initial rate data fit the following kinetic expression:

$$\text{Rate} = k[\text{EtBr}][\text{benzene}][\text{AlBr}_3]^2$$

79. A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, **83**, 2877 (1961); A. J. Kresge, S. Slae, and D. W. Taylor, *J. Am. Chem. Soc.*, **92**, 6309 (1970).
80. A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, **89**, 4411 (1967).
81. L. C. Gruen and F. A. Long, *J. Am. Chem. Soc.*, **89**, 1287 (1967).
82. S. U. Choi and H. C. Brown, *J. Am. Chem. Soc.*, **85**, 2596 (1963).
83. B. J. Carter, W. D. Covey, and F. P. DeHaan, *J. Am. Chem. Soc.*, **97**, 4783 (1975); cf. S. U. Choi and H. C. Brown, *J. Am. Chem. Soc.*, **81**, 3315 (1959); F. P. DeHaan and H. C. Brown, *J. Am. Chem. Soc.*, **91**, 4844 (1969); H. Jungk, C. R. Smoot, and H. C. Brown, *J. Am. Chem. Soc.*, **78**, 2185 (1956).

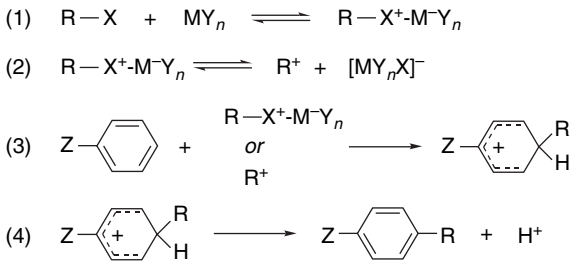
The reaction rates of toluene and benzene with *i*-propyl chloride[84] or *t*-butyl chloride[85] in nitromethane can be fit to a third-order rate law.

$$\text{Rate} = k[\text{AlCl}_3][i\text{-PrCl}][\text{ArH}]$$

Rates that are *independent* of aromatic substrate concentration have been found for reaction of benzyl chloride catalyzed by $TiCl_4$ or SbF_5 in nitromethane.[86] This can be interpreted as resulting from rate-determining formation of the electrophile, presumably a benzyl ion pair. The reaction of benzyl chloride and toluene shows a second-order dependence on the titanium chloride concentration under conditions where there is a large excess of hydrocarbon.[87] This is attributed to reaction through a 1:2 benzyl chloride-$TiCl_4$ complex, with the second $TiCl_4$ molecule assisting in the ionization reaction:

$$\text{Rate} = k[\text{PhCH}_2\text{Cl}][\text{TiCl}_4]^2$$

All these kinetic results can be accommodated by a general mechanistic scheme that incorporates the following fundamental components: (1) complexation of the alkylating agent and the Lewis acid; in some systems, there may be an ionization of the complex to yield a discrete carbocation; (2) electrophilic attack on the aromatic reactant to form the cyclohexadienylium ion intermediate; and (3) deprotonation. The formation of carbocations accounts for the fact that rearrangement of the alkyl group is observed frequently during Friedel-Crafts alkylation.



Absolute rate data for the Friedel-Craft reactions are difficult to obtain. The reaction is very sensitive to the effects of moisture and heterogeneity. For this reason, most of the structure-reactivity trends have been developed using competitive methods, rather than by direct measurements. Relative rates are established by allowing the electrophile to compete for an excess of the two reactants. The product ratio establishes

84. F. P. DeHaan, G. L. Delker, W. D. Covey, J. Ahn, R. L. Cowan, C. H. Fong, G. Y. Kim, A. Kumar, M. P. Roberts, D. M. Schubert, E. M. Stoler, Y. J. Suh, and M. Tang, *J. Org. Chem.*, **51**, 1587 (1986).
85. F. P. DeHaan, W. H. Chan, J. Chang, D. M. Ferrara, and L. A. Wamschel, *J. Org. Chem.*, **51**, 1591 (1986).
86. F. P. DeHaan, G. L. Delker, W. D. Covey, J. Ahn, M. S. Anisman, E. C. Brehm, J. Chang, R. M. Chicz, R. L. Cowan, D. M. Ferrara, C. H. Fong, J. D. Harper, C. D. Irani, J. Y. Kim, R. W. Meinhold, K. D. Miller, M. P. Roberts, E. M. Stoler, Y. J. Suh, M. Tang, and E. L. Williams, *J. Am. Chem. Soc.*, **106**, 7038 (1984); F. P. DeHaan, W. H. Chan, J. Chang, T. B. Chang, D. A. Chiriboga, M. M. Irving, C. R. Kaufmann, G. Y. Kim, A. Kumar, J. Na, T. T. Nguyen, D. T. Nguyen, B. R. Patel, N. P. Sarin, and J. H. Tidwell, *J. Am. Chem. Soc.*, **112**, 356 (1990).
87. F. P. DeHaan, W. D. Covey, R. L. Ezelle, J. E. Margetan, S. A. Pace, M. J. Sollenberger, and D. S. Wolfe, *J. Org. Chem.*, **49**, 3954 (1984).

the relative reactivity. These studies indicate low reactant and position selectivity for the Friedel-Crafts alkylation reaction.

A study of alkylations with a group of substituted benzyl halides and a range of Friedel-Crafts catalysts provided insight into the trends in selectivity and orientation that accompany changes in both the alkyl group and the catalysts.[88] There is a marked increase in selectivity on going from *p*-nitrobenzyl chloride to *p*-methoxybenzyl chloride. For example, with $TiCl_4$ as the catalyst, k_{tol}/k_{benz} increases from 2.5 to 97. This increase in reactant selectivity is accompanied by an increasing preference for *para* substitution. With *p*-nitrobenzyl chloride, the *o*:*p* ratio is close to the statistically expected 2:1 ratio, whereas with the *p*-methoxy compound, the *para* product dominates by 2.5:1. There is a clear trend within the family of substituted benzyl chlorides of increasing selectivity with the increasing ERG capacity of the benzyl substituent. All of the reactions, however, remain in a region that constitutes rather low selectivity. Therefore it seems that the TS for substitution by a benzylic cation comes quite early. The substituents on the ring undergoing substitution have a relatively weak orienting effect on the attacking electrophile. With benzylic cations stabilized by donor substituents, the TS comes later and the selectivity is somewhat higher.

Toluene-benzene reactivity ratios under a number of Friedel-Crafts conditions are recorded in Table 9.9. As would be expected on the basis of the low substrate selectivity, position selectivity is also modest. The amount of *ortho* product is often comparable to the *para* product. Steric effects play a major role in determining the *o*:*p* ratio in Friedel-Crafts alkylations. The amount of *ortho* substitution of toluene

Table 9.9. Reactant and Position Selectivity in Friedel-Crafts Alkylation Reactions

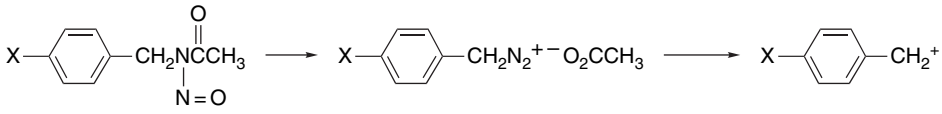
	Electrophilic reagent	k_{tol}/k_{benz}	Toluene *o*:*p* ratio
1	CH_3Br-$AlBr_3$[a]	2.5–4.1	1.9
2	C_2H_5Br-$GaBr_3$[b]	6.5	–
3	$(CH_3)_2CHBr$-$AlCl_3$[c]	1.9	1.2
4	$(CH_3)_2CHCl$-$AlCl_3$[d]	2.0	1.5
5	$(CH_3)_3CCl$-$AlCl_3$[e]	25	0
6	$(CH_3)_3CBr$-$SnCl_4$[f]	16.6	0
7	$(CH_3)_3CBr$-$AlCl_3$[f]	1.9	0
8	$PhCH_2Cl$-$AlCl_3$[g]	3.2	0.82
9	$PhCH_2Cl$-$AlCl_3$[h]	2-3	0.9
10	$PhCH_2Cl$-$TiCl_4$[i]	6.3	0.74
11	*p*-$CH_3OC_6H_4CH_2Cl$-$TiCl_4$[i]	97	0.40
12	*p*-$NO_2C_6H_4CH_2Cl$-$TiCl_4$[j]	2.5	1.7

a. H. C. Brown and H. Jungk, *J. Am. Chem. Soc.*, **77**, 5584 (1955).
b. S. U. Choi and H. C. Brown, *J. Am. Chem. Soc.*, **85**, 2596 (1963).
c. G. A. Olah, S. H. Flood, S. J. Kuhn, M. E. Moffatt, and N. A. Overchuck, *J. Am. Chem. Soc.*, **86**, 1046 (1964).
d. F. P. DeHaan, G. L. Delker, W. D. Covey, J. Ahn, R. L. Cowan, C. H. Fong, G. Y. Kim, A. Kumar, M. P. Roberts, D. M. Schubert, E. M. Stoler, Y. J. Suh, and M. Tang, *J. Org. Chem.*, **51**, 1587 (1986).
e. F. P. DeHaan, W. H. Chan, J. Chang, D. M. Ferrara, and L. A. Wainschel, *J. Org. Chem.*, **51**, 1591 (1986).
f. G. A. Olah, S. H. Flood, and M. E. Moffatt, *J. Am. Chem. Soc.*, **86**, 1060 (1964).
g. G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Am. Chem. Soc.*, **84**, 1688 (1962).
h. F. P. DeHaan, W. D. Covey, R. L. Ezelle, J. E. Margetan, S. A. Pace, M. J. Sollenberger, and D. S. Wolf, *J. Org. Chem.*, **49**, 3954 (1984).
i. G. A. Olah, S. Kobayashi, and M. Tashiro, *J. Am. Chem. Soc.*, **94**, 7448 (1972).

88. G. A. Olah, S. Kobayashi, and M. Tashiro, *J. Am. Chem. Soc.*, **94**, 7448 (1972).

decreases as the size of the entering alkyl group increases along the series methyl, ethyl, *i*-propyl.[89] No *ortho* product is found when the entering group is *t*-butyl.[90]

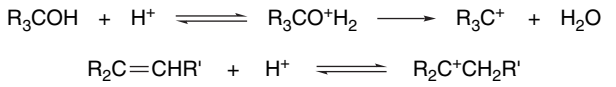
Selectivity by substituted benzyl cations has also been investigated using cations generated from benzyldiazonium ion intermediates.[91] This system removes potential complications of direct involvement of the Lewis acid in the substitution.



Toluene/benzene selectivity decreases in the order $X = CH_3 > H \sim Cl > NO_2$, in agreement with the expectation that the least stable (and most reactive) carbocation would be the least selective. These reactions also show low position selectivity.

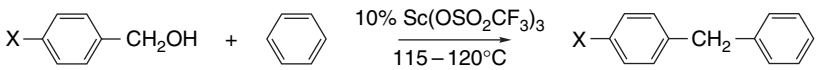
A good deal of experimental care is often required to ensure that the product mixture at the end of a Friedel-Crafts reaction is determined by *kinetic control*. The strong Lewis acid catalysts can catalyze the isomerization of alkylbenzenes and, if isomerization takes place, the product composition is not informative about the position selectivity of electrophilic attack. Isomerization increases the amount of the *meta* isomer in the case of dialkylbenzenes because this isomer is thermodynamically the most stable.[92]

Alcohols and alkenes can also serve as sources of electrophiles in Friedel-Crafts reactions in the presence of strong acids.



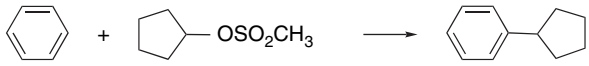
The generation of carbocations from these sources is well documented (see Section 4.4). The reaction of aromatics with alkenes in the presence of Lewis acid catalysts is the basis for the industrial production of many alkylated aromatic compounds. Styrene, for example, is prepared by dehydrogenation of ethylbenzene, which is made from benzene and ethylene.

Benzyl and allyl alcohols that can generate stabilized carbocations give Friedel-Crafts alkylation products with mild Lewis acid catalysts such as $Sc(O_3SCF_3)_3$.[93]



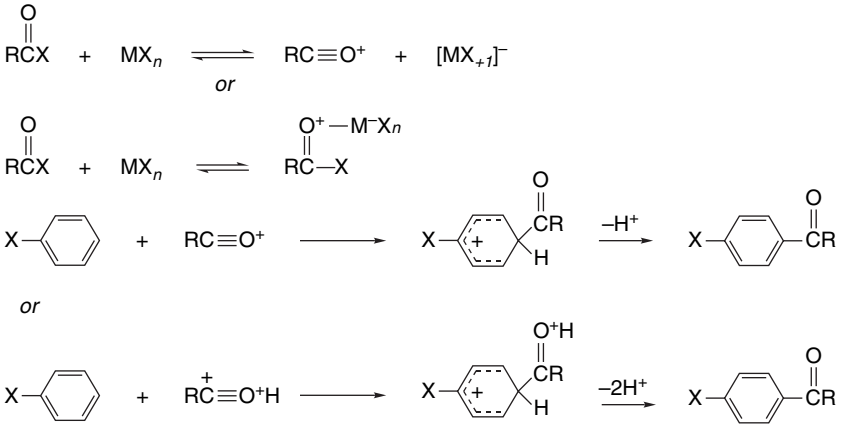
[89] R. H. Allen and L. D. Yats, *J. Am. Chem. Soc.*, **83**, 2799 (1961).
[90] G. A. Olah, S. H. Flood, and M. E. Moffatt, *J. Am. Chem. Soc.*, **86**, 1060 (1964).
[91] E. H. White, R. W. Darbeau, Y. Chen, S. Chen, and D. Chen, *J. Org. Chem.*, **61**, 7986 (1996); E. H. White, *Tetrahedron Lett.*, **38**, 7649 (1997); R. W. Darbeau and E. H. White, *J. Org. Chem.*, **65**, 1121 (2000).
[92] D. A. McCaulay and A. P. Lien, *J. Am. Chem. Soc.*, **74**, 6246 (1952).
[93] T. Tsuchimoto, K. Tobita, T. Hiyama, and S. Fukuzawa, *Synlett*, 557 (1996); T. Tsuchimoto, K. Tobita, T. Hiyama, and S. Fukuzawa, *J. Org. Chem.*, **62**, 6997 (1997).

Scandium triflate, copper triflate, and lanthanide triflates catalyze alkylation by secondary methanesulfonates.[94]



9.4.5. Friedel-Crafts Acylation and Related Reactions

Friedel-Crafts acylation usually involves the reaction of an acyl halide, a Lewis acid catalyst, and the aromatic reactant. Several species may function as the active electrophile, depending on the reactivity of the aromatic compound. For activated aromatics, the active electrophile can be a discrete positively charged acylium ion or a complex formed between the acyl halide and the Lewis acid catalyst. For benzene and less reactive aromatics, it is believed that the active electrophile is a protonated acylium ion or an acylium ion complexed by a Lewis acid.[95] Reactions using acylium salts are slow with toluene or benzene as the reactant and do not proceed with chlorobenzene. The addition of triflic acid accelerates the reactions with benzene and toluene and permits reaction with chlorobenzene. These results suggest that a protonation step must be involved.



The formation of acyl halide–Lewis acid complexes can be demonstrated readily. Acetyl chloride, for example, forms both 1:1 and 1:2 complexes with $AlCl_3$ that can be observed by NMR.[96] Several Lewis acid complexes of acyl chlorides have been characterized by low-temperature X-ray crystallography.[97] For example, the crystal structures of PhCOCl-$SbCl_5$ and PhCOCl-$GaCl_3$ and [PhCOCl-$TiCl_4$]$_2$ have been determined. In all of these complexes, the *Lewis acid is bound to the carbonyl oxygen*. Figure 9.11 shows two examples.

Acylium salts are generated at slightly higher temperatures or with more reactive acyl halides. For example, both 4-methylbenzoyl chloride and 2,4,6-trimethylbenzoyl

94. H. Kotsuki, T. Oshisi, and M. Inoue, *Synlett*, 2551 (1998); R. P. Singh, R. M. Kamble, K. L. Chandra, P. Saravanan, and V. K. Singh, *Tetrahedron*, **57**, 241 (2000).
95. M. Vol'pin, I. Akhrem, and A. Orlinkov, *New J. Chem.*, **13**, 771 (1989); Y. Sato, M.Yato, T. Ohwada, S. Sato, and K. Shudo, *J. Am. Chem. Soc.*, **117**, 3037 (1995).
96. B. Glavincevski and S. Brownstein, *J. Org. Chem.*, **47**, 1005 (1982).
97. M. G. Davlieva, S. V. Lindeman, I. S. Neretin, and J. K. Kochi, *J. Org. Chem.*, **70**, 4013 (2005).

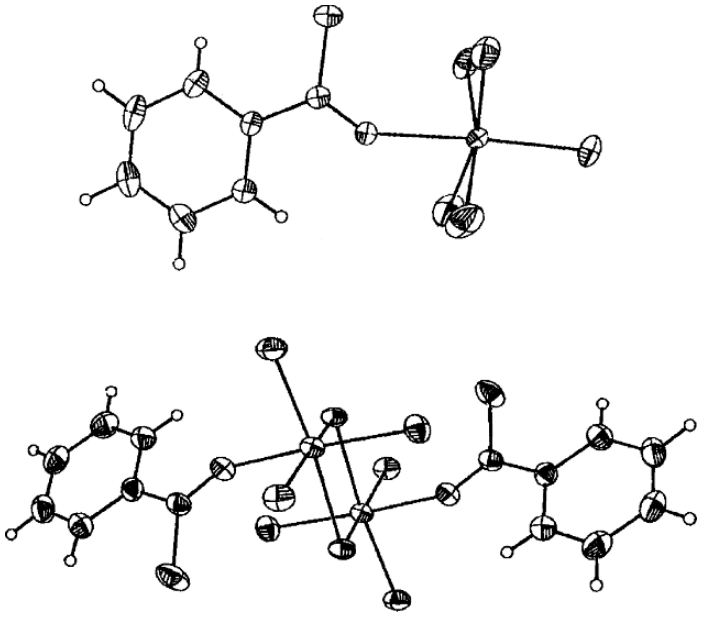
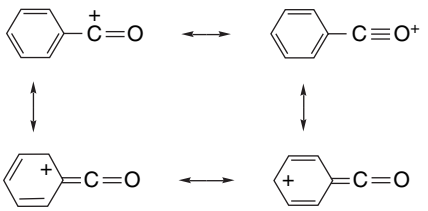


Fig. 9.11. X-Ray crystal structures of PhCOCl-$SbCl_5$ (top) and $[PhCOCl\text{-}TiCl_4]_2$ (bottom). Reproduced from *J. Org. Chem.*, **70**, 4013 (2005), by permission of the American Chemical Society.

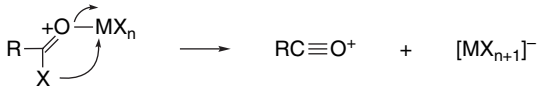
chloride give acylium salts with $SbCl_5$. Acylium salts are also formed from benzoyl fluoride and SbF_5. The structure of other acylium ions has been demonstrated by X-ray diffraction. For example, crystal structure determinations have been reported for *p*-methylphenylacylium[98] and acetylium[99] ions as SbF_6^- salts. There is also evidence from NMR measurements that demonstrates that acylium ions can exist in nonnucleophilic solvents.[100] The positive charge on acylium ions is delocalized onto the oxygen atom.[101] This delocalization is demonstrated by the short O−C bond length in acylium ions, which implies a major contribution from the structure having a triple bond.

Aryl acylium ions are also stabilized by charge delocalization into the aromatic ring.



98. B. Chevrier, J.-M. LeCarpentier, and R. Weiss, *J. Am. Chem. Soc.*, **94**, 5718 (1972).
99. F. P. Boer, *J. Am. Chem. Soc.*, **90**, 6706 (1968).
100. N. C. Deno, C. U. Pittman, Jr., and M. J. Wisotsky, *J. Am. Chem. Soc.*, **86**, 4370 (1964); G. A. Olah and M. B. Comisarow, *J. Am. Chem. Soc.*, **88**, 4442 (1966).
101. T. Xu, D. H. Barich, P. D. Torres, J. B. Nicholas, and J. F. Haw, *J. Am. Chem. Soc.*, **119**, 396 (1997).

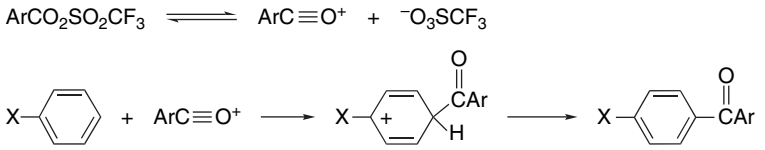
These acylium ions react rapidly with aromatic hydrocarbons such as pentamethylbenzene to give the Friedel-Crafts acylation products. Thus, the mechanisms consists of formation of the complex, ionization to an acylium ion, and substitution via a cyclohexadienylium ion intermediate.[97] The most likely mechanism for formation of the acylium ion is by an intramolecular transfer of the halide to the Lewis acid.



As is the case with Friedel-Crafts alkylations, direct kinetic measurements are difficult, and not many data are available. Rate equations of the form

$$\text{Rate} = k_1[\text{RCOCl-AlCl}_3][\text{ArH}] + k_2[\text{RCOCl-AlCl}_3]^2[\text{ArH}]$$

have been reported for the reaction of benzene and toluene with both acetyl and benzoyl chloride.[102] The available kinetic data usually do not permit unambiguous conclusions about the identity of the active electrophile. Direct kinetic evidence for acylium ions acting as electrophiles has been obtained using aroyl triflates, which can ionize without assistance from a Lewis acid.[103] Either formation of the acylium ion or formation of the σ complex can be rate determining, depending on the reactivity of the substrate.



Selectivity in Friedel-Crafts acylation with regard to both reactant selectivity and position selectivity is moderate. Some representative data are collected in Table 9.10. It can be seen that the toluene:benzene reactivity ratio is generally between 100 and 200. A progression from low substrate selectivity (Entries 5 and 6) to higher substrate selectivity (Entries 8 and 9) has been demonstrated for a series of aroyl halides.[104] EWGs on the aroyl chloride lead to low selectivity, presumably because of the increased reactivity of such electrophiles. ERGs diminish reactivity and increase selectivity. For the more selective electrophiles, the selectivity for *para* substitution is unusually high. Friedel-Crafts acylation is generally a more selective reaction than Friedel-Crafts alkylation. The implication is that acylium ions are less reactive electrophiles than the cationic intermediates involved in the alkylation process.

Steric factors clearly enter into determining the *o*:*p* ratio. The hindered 2,4,6-trimethylbenzoyl group is introduced with a 50:1 preference for the *para* position.[77] Similarly, in the benzoylation of alkylbenzenes by benzoyl chloride–aluminum chloride, the amount of *ortho* product decreases (10.3, 6.0, 3.1, and 0.6%, respectively) as the branching of the alkyl group is increased along the series methyl, ethyl, *i*-propyl, *t*-butyl.[105]

102. R. Corriu, M. Dore, and R. Thomassin, *Tetrahedron*, **27**, 5601, 5819 (1971).
103. F. Effenberger, J. K. Ebehard, and A. H. Maier, *J. Am. Chem. Soc.*, **118**, 12572 (1996).
104. G. A. Olah and S. Kobayashi, *J. Am. Chem. Soc.*, **93**, 6964 (1971).
105. G. A. Olah, J. Lukas, and E. Lukas, *J. Am. Chem. Soc.*, **91**, 5319 (1969).

Table 9.10. Reactant and Position Selectivity in Friedel-Crafts Acylation Reactions

	Electrophilic reagents	k_{tol}/k_{benz}	Toluene *o*:*p* ratio
1	$CH_3COCl\text{-}AlCl_3$[a]	134	0.012
2	$CH_3CH_2COCl\text{-}AlCl_3$[b]	106	0.033
3	$CH_3C{\equiv}O^+\ SbF_6^-$[c]	125	0.014
4	$HCOF\text{-}BF_3$[d]	35	0.82
5	2,4-Dinitrobenzoyl chloride-$AlCl_3$[d]	29	0.78
6	Pentafluorobenzoyl chloride-$AlCl_3$[d]	16	0.61
7	$PhCOCl\text{-}AlCl_3$[d]	153	0.09
8	*p*-Toluoyl chloride-$AlCl_3$[d]	164	0.08
9	*p*-Methoxybenzoyl chloride-$AlCl_3$[d]	233	0.2

a. G. A. Olah, M. E. Moffatt, S. J. Kuhn, and B. A. Hardie, *J. Am. Chem. Soc.*, **86**, 2198 (1964).
b. G. A. Olah, J. Lukas, and E. Lukas, *J. Am. Chem. Soc.*, **91**, 5139 (1969).
c. G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardi, *J. Am. Chem. Soc.*, **86**, 2203 (1964).
d. G. A. Olah and S. Kobayashi, *J. Am. Chem. Soc.*, **93**, 6964 (1972).

One other feature of the data in Table 9.10 is worthy of further comment. Note that alkyl- (acetyl- , propionyl-)substituted acylium ions exhibit a smaller *o*:*p* ratio than the various aroyl systems. If steric factors were dominating the position selectivity, one would expect the opposite result. A possible explanation for this feature of the data is that the aroyl compounds are reacting via free acylium ions, whereas the alkyl systems may involve more bulky acid-chloride catalyst complexes.

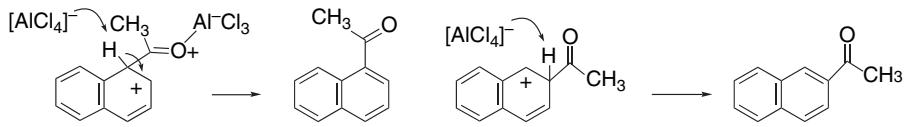
Friedel-Crafts acylation sometimes shows a modest kinetic isotope effect.[106] This observation suggests that the proton removal is not much faster than the formation of the cyclohexadienylium ion and that its formation may be reversible under some conditions. It has been shown that the *o*:*p* ratio can depend on the rates of deprotonation of the σ complex. With toluene, for example, aroyl triflates give higher ratios of *ortho* product when a base, (2,4,6-tri-*t*-butylpyridine) is present.[107] This is because in the absence of base, reversal of acylation leads to reaction through the more easily deprotonated *para* intermediate. Steric effects on deprotonation have also been surmised to be a factor in the 1- versus 2-acylation of naphthalene by acetyl chloride-$AlCl_3$.[108] The two competing reactions show different concentration dependence, with 1-acylation being second order in acylating agent, whereas 2-acylation is first order:

$$\text{Rate (1-acylation)} = k_1[\text{naphth}][CH_3COCl\text{-}AlCl_3]^2$$

$$\text{Rate (2-acylation)} = k_2[\text{naphth}][CH_3COCl\text{-}AlCl_3]$$

The 2-acylation also showed a much larger H/D isotope effect (~5.4 versus 1.1). The postulated mechanism suggests that breakdown of the more hindered σ complex for 1-acylation is bimolecular, whereas a unimolecular deprotonation process occurs for 2-acylation.

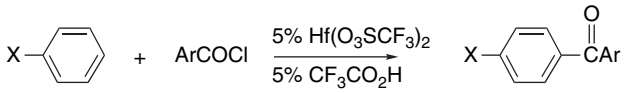
106. G. A. Olah, S. J. Kuhn, S. H. Flood, and B. A. Hardie, *J. Am. Chem. Soc.*, **86**, 2203 (1964); D. B. Denney and P. P. Klemchuk, *J. Am. Chem. Soc.*, **80**, 3285, 6014 (1958).
107. F. Effenberger and A. H. Maier, *J. Am. Chem. Soc.*, **123**, 3429 (2001).
108. D. Dowdy, P. H. Gore, and D. N. Walters, *J. Chem. Soc., Perkin Trans. 1*, 1149 (1991).



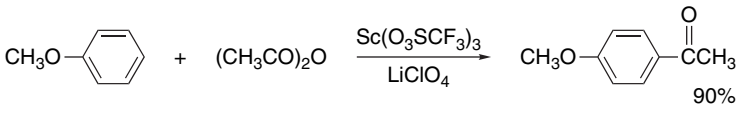
bimolecular process for 1-acylation

unimolecular process for 2-acylation

Although the Lewis acids used as co-reagents in Friedel-Crafts acylations are often referred to as "catalysts," they are in fact consumed in the reaction with the generation of strong acids. There has been interest in finding materials that could function as true catalysts.[109] Considerable success has been achieved using lanthanide triflates.[110]



These reactions are presumed to occur through aroyl triflate intermediates that dissociate to aryl acylium ions. Lithium perchlorate and scandium triflate also promote acylation.[111]



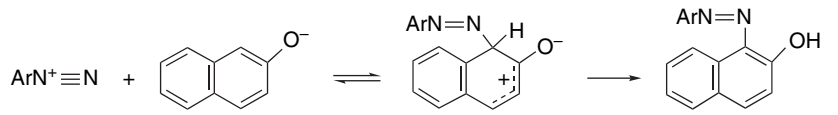
A number of variations of the Friedel-Crafts reaction conditions are possible. Acid anhydrides can serve as the acylating agent in place of acyl chlorides, and the carboxylic acid can be used directly, particularly in combination with strong acids. For example, mixtures of carboxylic acids with polyphosphoric acid in which a mixed anhydride is presumably formed in situ are reactive acylating agents.[112] Similarly, carboxylic acids dissolved in trifluoromethanesulfonic acid can carry out Friedel-Craft acylation. The reactive electrophile under these conditions is believed to be the protonated mixed anhydride.[113] In these procedures, the leaving group from the acylating agent is different, but other aspects of the reaction are similar to those under the usual conditions. Synthetic applications of Friedel-Crafts acylation are discussed further in Chapter 11 of Part B.

9.4.6. Aromatic Substitution by Diazonium Ions

Among the reagents that are classified as weak electrophiles, the best studied are the aryl diazonium ions. These reagents react only with aromatic substrates having strong ERG substituents, and the products are azo compounds. The aryl diazonium

109. K. Smith, *J. Chem. Tech. Biotech.*, **68**, 432 (1997).
110. I. Hachiya, K. Morikawa, and S. Kobayashi, *Tetrahedron Lett.*, **36**, 409 (1995); S. Kobayashi and S. Iwamoto, *Tetrahedron Lett.*, **39**, 4697 (1998).
111. A. Kawada, S. Mitamura, and S. Kobayashi, *Chem. Commun.*, 183 (1996).
112. T. Katuri and K. M. Damodaran, *Can. J. Chem.*, **47**, 1529 (1969).
113. R. M. G. Roberts and A. R. Sardi, *Tetrahedron*, **39**, 137 (1983).

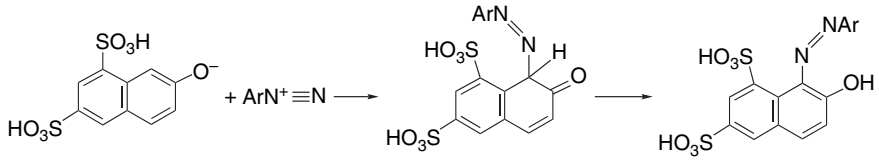
ions are usually generated by diazotization of aromatic amines. The mechanism of diazonium ion formation is discussed more completely in Section 11.2.1 of Part B.



Aryl diazonium ions are stable in solution only near or below room temperature, and this also limits the range of compounds that can be successfully substituted by diazonium ions.

Kinetic investigations revealed second-order kinetic behavior for substitution by diazonium ions in a number of instances. In the case of phenols, it is the *conjugate base* that undergoes substitution.[114] This finding is entirely reasonable, since the deprotonated oxy group is a better electron donor than the neutral hydroxy substituent. The reactivity of the diazonium ion depends on the substituent groups that are present. Reactivity is increased by EWG and decreased by ERG.[115]

An unusual feature of the mechanism for diazonium coupling is that in some cases proton loss can be demonstrated to be the rate-determining step. This feature is revealed in two ways. First, diazonium couplings of several naphthalenesulfonate ions exhibit primary isotope effects in the range 4–6 when deuterium is present at the site of substitution, clearly indicating that cleavage of the C−H bond is rate determining. Second, these reactions can also be shown to be general base catalyzed. This, too, implies that proton removal is rate determining.[116]



Because of the limited range of aromatic compounds that react with diazonium ions, selectivity data comparable to those discussed for other electrophilic substitutions are not available. Diazotization, since it involves a weak electrophile, would be expected to reveal high substrate and position selectivity.

9.4.7. Substitution of Groups Other than Hydrogen

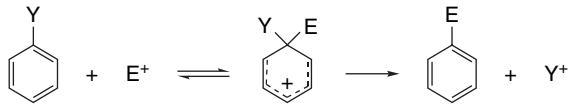
The general mechanism for EAS suggests that groups other than hydrogen could be displaced, provided that the electrophile attacked at the substituted carbon. Substitution at a site already having a substituent is called *ipso* substitution and has been observed in a number of circumstances. The ease of removal of a substituent depends on its ability to accommodate a positive charge. This factor determines whether the

[114] R. Wistar and P. D. Bartlett, *J. Am. Chem. Soc.*, **63**, 413 (1941).

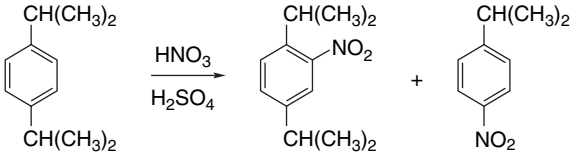
[115] A. F. Hegarty, in *The Chemistry of the Diazonium and Diazo Groups*, S. Patai, ed., John Wiley & Sons, New York, 1978, Chap. 12; H. Mayr, M. Hartnagel, and K. Grimm, *Liebigs Ann.*, 55 (1997).

[116] H. Zollinger, *Azo and Diazo Chemistry*, transl. H. E. Nursten, Interscience, New York, 1961, Chap. 10; H. Zollinger, *Adv. Phys. Org. Chem.*, **2**, 163 (1964); H. Zollinger, *Helv. Chim. Acta*, **38**, 1597 (1955).

newly attached electrophile or the substituent is eliminated from the intermediate on rearomatization.



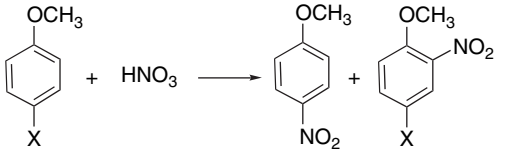
One type of substituent replacement involves cleavage of a highly branched alkyl substituent. The alkyl group is expelled as a carbocation, so substitution is most common for branched alkyl groups. The nitration 1,4-*bis*-(*i*-propyl)benzene provides an example.



Ref. 117

Cleavage of *t*-butyl groups has been observed in halogenation reactions. Minor amounts of dealkylated products are formed during chlorination and bromination of *t*-butyl-benzene.[118] The amount of dealkylation increases greatly in the case of 1,3,5-tri-*t*-butylbenzene, and the principal product of bromination is 3,5-dibromo-*t*-butylbenzene.[119]

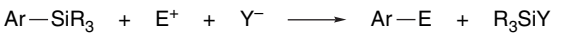
The replacement of bromine and iodine during aromatic nitration has also been observed. *p*-Bromoanisole and *p*-iodoanisole, for example, both give 30–40% of *p*-nitroanisole, a product resulting from displacement of halogen on nitration.



Ref. 120

Owing to the greater resistance to elimination of chlorine as a positively charged species, *p*-chloroanisole does not undergo dechlorination under similar conditions.

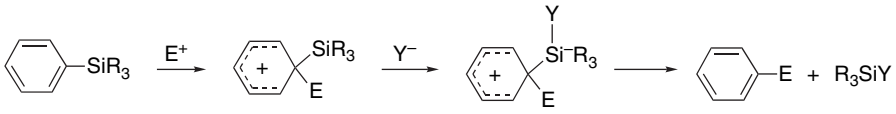
The most general type of aromatic substitution involving replacement of a substituent group in preference to a hydrogen is the electrophilic substitution of arylsilanes.



The silyl group directs electrophiles to the substituted position; that is, it is an *ipso*-directing group. Because of the polarity of the carbon-silicon bond, the substituted

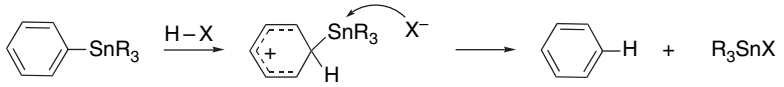
117. G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, **86**, 1067 (1964).
118. P. B. D. de la Mare and J. T. Harvey, *J. Chem. Soc.*, 131 (1957); P. B. D. de la Mare, J. T. Harvey, M. Hassan, and S. Varma, *J. Chem. Soc.*, 2756 (1958).
119. P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Am. Chem. Soc.*, **76**, 2349 (1954).
120. C. L. Perrin and G. A. Skinner, *J. Am. Chem. Soc.*, **93**, 3389 (1971).

position is relatively electron rich. The ability of silicon substituents to stabilize carbocation character at ß-carbon atoms (see Section 5.10.5, p. 564) also promotes *ipso* substitution. A silicon substituent is easily removed from the intermediate by reaction with a nucleophile. The desilylation step probably occurs through a pentavalent silicon species.



The reaction exhibits other characteristics typical of an electrophilic aromatic substitution.[121] Examples of electrophiles that can effect substitution for silicon include protons and the halogens, as well as acyl, nitro, and sulfonyl groups.[122] The fact that these reactions occur very rapidly has made them attractive for situations where substitution must be done under very mild conditions.[123] One example is the introduction of radioactive iodine for use in tracer studies.[124]

Trialkyltin substituents are also powerful *ipso*-directing groups. The overall electronic effects are similar to those in silanes but the tin substituent is more metallic and less electronegative. The electron density at carbon is increased, as is the stabilization of ß-carbocation character. Acidic cleavage of arylstannanes is an electrophilic aromatic substitution proceeding through an *ipso*-oriented σ-complex.[125]



9.5. Nucleophilic Aromatic Substitution

Neither of the major mechanisms for nucleophilic substitution in saturated compounds is accessible for substitution on aromatic rings. A back-side S_N2-type reaction is precluded by the geometry of the benzene ring. The back lobe of the sp^2 orbital is directed toward the center of the ring. An inversion mechanism is precluded by the geometry of the ring. An S_N1 mechanism is very costly in terms of energy because a cation directly on a benzene ring is very unstable. From the data in Figure 3.18 (p. 300) it is clear that a phenyl cation is less stable than even a primary carbocation, which is a consequence of the geometry and hybridization of the aromatic

121. F. B. Deans and C. Eaborn, *J. Chem. Soc.*, 2299 (1959).
122. F. B. Deans, C. Eaborn, and D. E. Webster, *J. Chem. Soc.*, 303l (1959); C. Eaborn, Z. Lasocki, and D. E. Webster, *J. Chem. Soc.*, 3034 (1959); C. Eaborn, *J. Organomet. Chem.*, **100**, 43 (1975); J. D. Austin, C. Eaborn, and J. D. Smith, *J. Chem. Soc.*, 4744 (1963); F. B. Deans and C. Eaborn, *J. Chem. Soc.*, 498 (1957); R. W. Bott, C. Eaborn, and T. Hashimoto, *J. Chem. Soc.*, 3906 (1963).
123. S. R. Wilson and L. A. Jacob, *J. Org. Chem.*, **51**, 4833 (1986).
124. E. Orstad, P. Hoff, L. Skattebol, A. Skretting, and K. Breistol, *J. Med. Chem.*, **46**, 3021 (2003).
125. C. Eaborn, I. D. Jenkins, and D. R. M. Walton, *J. Chem. Soc., Perkin Trans. 2*, 596 (1974).

carbon atoms. An aryl carbocation is localized in an sp^2 orbital that is orthogonal to the π system so there is no stabilization available from the π electrons.

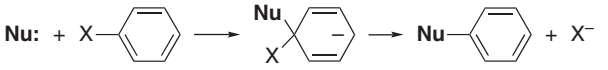
back-side approach of the nucleophile with inversion is impossible

phenyl cation is a high-energy intermediate

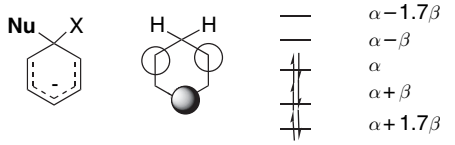
There are several mechanisms by which net nucleophilic aromatic substitution can occur. In this section we discuss the addition-elimination mechanism and the elimination-addition mechanisms. The $S_{RN}1$ mechanism, which involves radical intermediates, is discussed in Chapter 11. Substitutions via organometallic intermediates and via aryl diazonium ions are considered in Chapter 11 of Part B.

9.5.1. Nucleophilic Aromatic Substitution by the Addition-Elimination Mechanism

The addition-elimination mechanism[126] uses one of the vacant π* orbitals for bonding interaction with the nucleophile. This permits addition of the nucleophile to the aromatic ring without displacing any of the existing substituents. If attack occurs at a position occupied by a potential leaving group, net substitution can occur by a second step in which the leaving group is expelled.



The addition intermediate is isoelectronic with a pentadienyl anion.



The HOMO is ψ_3, which has its electron density primarily at the carbons *ortho* and *para* to the position of substitution. The intermediate is therefore strongly stabilized by an EWG *ortho* or *para* to the site of substitution. Such substituents activate the ring to nucleophilic substitution. The most powerful effect is exerted by a nitro group, but cyano and carbonyl groups are also favorable. Generally speaking, nucleophilic aromatic substitution is an energetically demanding reaction, even when electron-attracting substituents are present. The process disrupts the aromatic π system. Without an EWG present, nucleophilic aromatic substitution occurs only under extreme reaction conditions.

The role of the leaving group in determining the reaction rate is somewhat different from S_N2 and S_N1 substitution at alkyl groups. In those cases, the bond strength is

[126] Reviews: C. F. Bernasconi, in *MTP Int. Rev. Sci., Organic Series One*, Vol. 3, H. Zollinger, ed., Butterworths, London, 1973; J. A. Zoltewicz, *Top. Curr. Chem.*, **59**, 33 (1975); J. Miller, *Aromatic Nucleophilic Substitution*, Elsevier, Amsterdam, 1968.

usually the dominant factor, so the order of reactivity of the halogens is I > Br > Cl > F. In nucleophilic aromatic substitution, the formation of the addition intermediate is usually the rate-determining step, so the ease of C−X bond breaking does not affect the rate. When this is the case, the order of reactivity is often F > Cl > Br > I.[127] This order is the result of the polar effect of the halogen. The stronger bond dipoles associated with the more electronegative halogens favor the addition step and thus increase the overall rates of reaction.

The broad features of these experimental results, which pertain to solution reactions, are paralleled by computational results on the gas phase reactions.[128] The barriers for direct halide exchange reactions for Cl^-, Br^-, and I^- in unsubstituted rings were calculated to be 27 ± 1 kcal/mol, with little difference among the halides. These reactions are calculated to proceed through a single-stage process, without a stable addition intermediate. The situation is quite different for F^- exchange. The σ intermediate in this case is calculated to be 3.7 kcal/mol more stable than the reactants, but the barrier for F^- elimination is only 1.5 kcal/mol. The addition of one, two, or three nitro groups lowers the Cl^- exchange barrier by 22, 39, and 70 kcal/mol, so that the latter two reactions are also calculated to have negative barriers. These reactions all show addition intermediates. Figure 9.12 depicts the contrasting energy profiles for these systems. Besides indicating the important effect of EWGs, these calculations emphasize the special reactivity of the fluoride derivative.

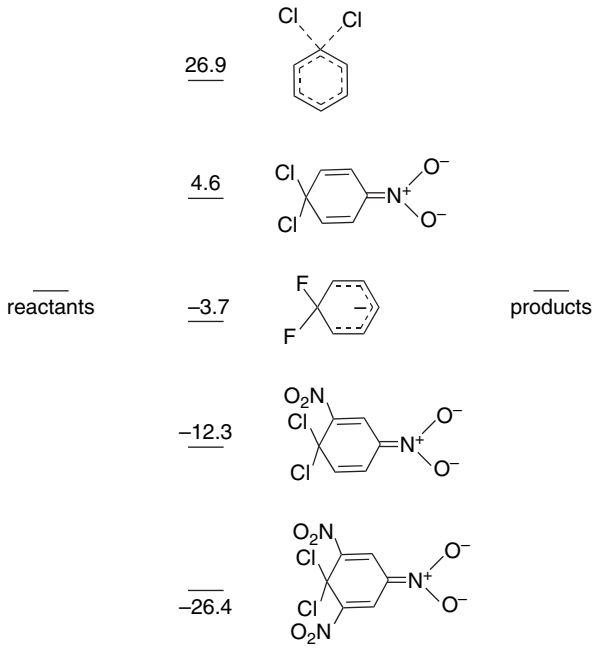
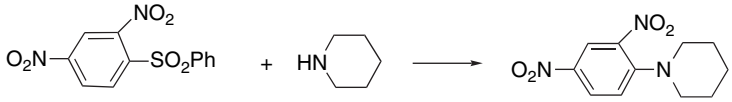


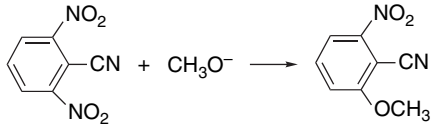
Fig. 9.12. Computed [B3LYP/6-31+G(*d*)] energy barriers for halide exchange by nucleophilic aromatic substitution. Data from *J. Org. Chem.*, **62**, 4036 (1997).

127. G. P. Briner, J. Miller, M. Liveris, and P. G. Lutz, *J. Chem. Soc.*, 1265 (1954); J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruit, *J. Am. Chem. Soc.*, **79**, 585 (1957); G. Bartoli and P. E. Todesco, *Acc. Chem. Res.*, **10**, 125 (1977).
128. M. N. Glukhovtsev, R. D. Bach, and S. Laiter, *J. Org. Chem.*, **62**, 4036 (1997).

Groups other than halogen can serve as leaving groups. Alkoxy groups are very poor leaving groups in S_N2 reactions but can act as leaving groups in aromatic substitution. The reason is the same as for the inverted order of reactivity for the halogens. The rate-determining step is the addition, and the alkoxide can be eliminated in the energetically favorable rearomatization. Nitro[129] and sulfonyl[130] groups can also be displaced.

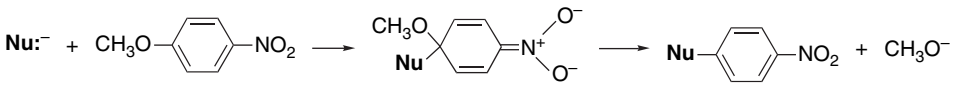


Ref. 131



Ref. 132

The addition intermediates, which are known as *Meisenheimer complexes*, can often be detected spectroscopically and can sometimes be isolated.[133] Especially in the case of adducts stabilized by nitro groups, the intermediates are often strongly colored.

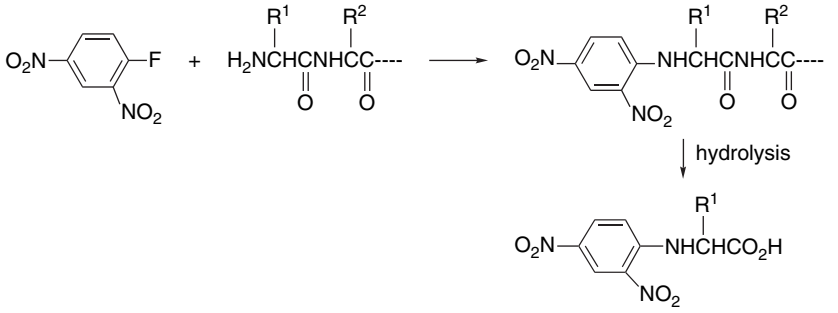


The range of nucleophiles that can participate in nucleophilic aromatic substitution is similar to the range of those that participate in S_N2 reactions and includes alkoxides,[134] phenoxides,[135] sulfides,[136] fluoride ion,[137] and amines.[138] For reaction with aromatic amines with 1-chloro-2,4-dinitrobenzene, the value of ρ is −4.0, indicting a substantial buildup of positive charge at nitrogen in the TS.[139] Substitution by carbanions is somewhat less common. This may be because there are frequently

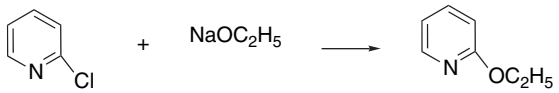
129. J. R. Beck, *Tetrahedron*, **34**, 2057 (1978).
130. A. Chisari, E. Maccarone, G. Parisi, and G. Perrini, *J. Chem. Soc., Perkin Trans. 2*, 957 (1982).
131. J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *J. Am. Chem. Soc.*, **79**, 385 (1957).
132. J. R. Beck, R. L. Sobczak, R. G. Suhr, and J. A. Vahner, *J. Org. Chem.*, **39**, 1839 (1974).
133. E. Buncel, A. R. Norris, and K. E. Russel, *Q. Rev. Chem. Soc.*, **22**, 123 (1968); M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970); C. F. Bernasconi, *Acc. Chem. Res.*, **11**, 147 (1978).
134. J. P. Idoux, M. L. Madenwald, B. S. Garcia, D. L. Chu, and J. T. Gupton, *J. Org. Chem.*, **50**, 1876 (1985).
135. R. O. Brewster and T. Groening, *Org. Synth.*, **II**, 445 (1943).
136. M. T. Bogert and A. Shull, *Org. Synth*, **I**, 220 (1941); N. Kharasch and R. B. Langford, *Org. Synth.*, **V**, 474 (1973); W. P. Reeves, T. C. Bothwell, J. A. Rudis, and J. V. McClusky, *Synth. Commun.*, **12**, 1071 (1982).
137. W. M. S. Berridge, C. Crouzel, and D. Comar, *J. Labelled Compd. Radiopharm.*, **22**, 687 (1985).
138. H. Bader, A. R. Hansen, and F. J. McCarty, *J. Org. Chem.*, **31**, 2319 (1966); F. Pietra and F. Del Cima, *J. Org. Chem.*, **33**, 1411 (1968); J. F. Pilichowski and J. C. Gramain, *Synth. Commun.*, **14**, 1247 (1984).
139. T. M. Ikramuddeen, N. Chandrasekara, K. Ramarajan, and K. S. Subramanian, *J. Indian Chem. Soc.*, **66**, 342 (1989).

complications resulting from electron transfer processes with nitroaromatics. Solvent effects on nucleophilic aromatic substitutions are similar to those discussed for S_N2 reactions (see Section 3.8). Dipolar aprotic solvents,[140] crown ethers,[141] and phase transfer catalysts[142] all can enhance the rate of substitution by providing the nucleophile in a reactive state with weak solvation.

One of the most historically significant examples of aromatic nucleophilic substitution is the reaction of amines with 2,4-dinitrofluorobenzene. This reaction was used by Sanger[143] to develop a method for identification of the N-terminal amino acid in proteins, and the process opened the way for structural characterization of proteins and other biopolymers.



2-Halopyridines and other π-deficient nitrogen heterocycles are excellent reactants for nucleophilic aromatic substitution.[144]



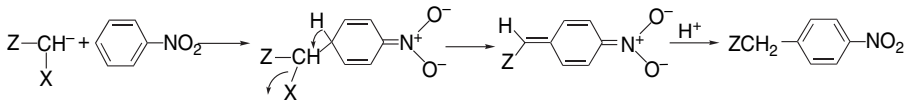
Ref. 145

Substitution reactions also occur readily for other heterocyclic systems, such as 2-haloquinolines and 1-haloisoquinolines, in which a potential leaving group is adjacent to a pyridine-type nitrogen. 4-Halopyridines and related heterocyclic compounds can also undergo substitution by addition-elimination, but are somewhat less reactive.

A variation of the aromatic nucleophilic substitution process in which the leaving group is part of the entering nucleophile has been developed and is known as *vicarious nucleophilic aromatic substitution.* These reactions require a strong EWG substituent

140. F. Del Cima, G. Biggi, and F. Pietra, *J. Chem. Soc., Perkin Trans. 2*, 55 (1973); M. Makosza, M. Jagusztyn-Grochowska, M. Ludwikow, and M. Jawdosiuk, *Tetrahedron*, **30**, 3723 (1974); M. Prato, U. Quintily, S. Salvagno, and G. Scorrano, *Gazz. Chim. Ital.*, **114**, 413 (1984).
141. J. S. Bradshaw, E. Y. Chen, R. H. Holes, and J. A. South, *J. Org. Chem.*, **37**, 2051 (1972); R. A. Abramovitch and A. Newman, Jr., *J. Org. Chem.*, **39**, 2690 (1974).
142. M. Makosza, M. Jagusztyn-Grochowska, M. Ludwikow, and M. Jawdosiuk, *Tetrahedron*, **30**, 3723 (1974).
143. F. Sanger, *Biochem. J.*, **45**, 563 (1949).
144. H. E. Mertel, in *Hetereocyclic Chemistry*, Vol 14, Part 2, E. Klingsberg, ed., Interscience, New York, 1961; M. M. Boudakian, in *Heterocyclic Compunds*, Vol 14, Part 2, Supplement, R. A. Abramovitch, ed., Wiley-Interscience, New York, 1974; B. C. Uff, in *Comprehensive Heterocyclic Chemistry*, Vol. 2A, A. J. Boulton and A. McKillop, eds., Pergamon Press, Oxford, 1984, Chap. 2.06.
145. N. Al-Awadi, J. Ballam, R. R. Hemblade, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1175 (1982).

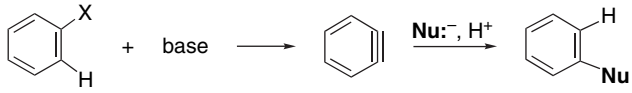
such as a nitro group but do not require a halide or other leaving group. The reactions proceed through addition intermediates.[146]



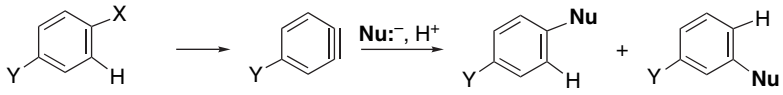
The combinations Z = CN, RSO_2, CO_2R, SR and X = F, Cl, Br, I, ArO, ArS, and $(CH_3)_2NCS_2$ are among those that have been demonstrated.[147]

9.5.2. Nucleophilic Aromatic Substitution by the Elimination-Addition Mechanism

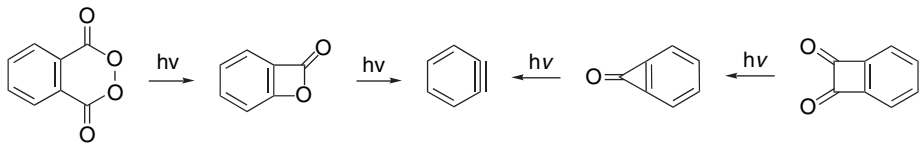
The elimination-addition mechanism involves a highly unstable intermediate, known as *dehydrobenzene or benzyne*.[148]



A characteristic feature of this mechanism is the substitution pattern in the product. The entering nucleophile need not always enter at the carbon to which the leaving group was bound, since it can add to either of the triply bound carbons.



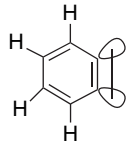
Benzyne can be observed spectroscopically in an inert matrix at very low temperatures.[149] For these studies the molecule is generated photolytically.



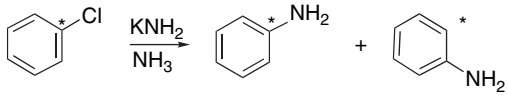
The bonding in benzyne is considered to be similar to benzene, but with an additional weak bond in the plane of the ring formed by overlap of the two sp^2 orbitals.[150]

146. M. Makosza, T. Lemek, A. Kwast, and F. Terrier, *J. Org. Chem.*, **67**, 394 (2002); M. Makosza and A. Kwast, *J. Phys. Org. Chem.*, **11**, 341 (1998).
147. M. Makosza and J. Winiarski, *J. Org. Chem.*, **45**, 1574 (1980); M. Makosza, J. Golinski, and J. Baron, *J. Org. Chem.*, **49**, 1488 (1984); M. Makosza and J. Winiarski, *J. Org. Chem.*, **49**, 1494 (1984); M. Makosza and J. Winiarski, *J. Org. Chem.*, **49**, 5272 (1984); M. Makosza and J. Winiarski, *Acc. Chem. Res.*, **20**, 282 (1987); M. Makosza and K. Wojcienchowski, *Liebigs Ann. Chem./Recueil*, 1805 (1997).
148. R. W. Hoffmann, *Dehydrobenzene and Cycloalkynes*, Academic Press, New York (1967); H. H. Wenk, M. Winkler, and W. Sander, *Angew. Chem. Int. Ed. Engl.*, **42**, 502 (2003).
149. O. L. Chapman, K. Mattes, C. L. McIntosh, J. Pacansky, G. V. Calder, and G. Orr, *J. Am. Chem. Soc.*, **95**, 6134 (1973); J. W. Laing and R.S. Berry, *J. Am. Chem. Soc.*, **98**, 660 (1976); J. G. Rasdziszewski, B. A. Hess, Jr., and R. Zahradnik, *J. Am. Chem. Soc.*, **114**, 52 (1992).
150. H. E. Simmons, *J. Am. Chem. Soc.*, **83**, 1657 (1961).

Comparison of the NMR characteristics[151] with MO calculations indicates that the π conjugation is maintained and the benzyne is a strained but aromatic molecule.[152]

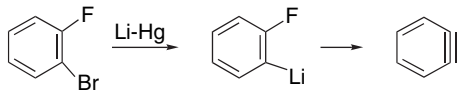


An early case in which the existence of benzyne as an intermediate was established was the reaction of chlorobenzene with potassium amide. ^{14}C-label in the starting material was found to be distributed between C(1) and the *ortho* position in the aniline, consistent with a benzyne intermediate.[153]



The elimination-addition mechanism is facilitated by structural effects that favor removal of a hydrogen from the ring by strong base. Relative reactivity also depends on the halide. The order Br > I > Cl > F has been established in the reaction of aryl halides with KNH_2 in liquid ammonia.[154] This order has been interpreted as representing a balance between two effects. The polar order favoring proton removal would be F > Cl > Br > I, but this is largely overwhelmed by the order of leaving-group ability I > Br > Cl > F, which reflects bond strengths.

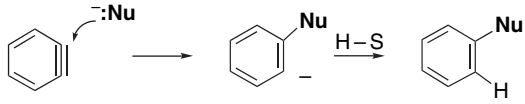
Benzyne can also be generated from *o*-dihaloaromatics. Reaction of lithium-amalgam or magnesium results in formation of a transient organometallic compound that decomposes with elimination of lithium halide. 1-Bromo-2-fluorobenzene is the usual starting material in this procedure.[155]



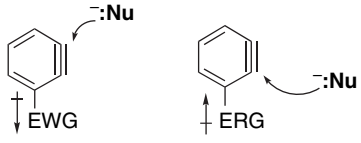
With organometallic compounds as bases in aprotic solvents, the acidity of the *ortho* hydrogen is the dominant factor and the reactivity order, owing to the bond polarity effect, is F > Cl > Br > I.[156]

151. R. Warmuth, *Angew. Chem. Int. Ed. Engl.*, **36**, 1347 (1997).
152. H. Jiao, P.v.R. Schleyer, B. R. Beno, K. N. Houk, and R. Warmuth, *Angew. Chem. Int. Ed. Engl.*, **36**, 2761 (1997).
153. J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, *J. Am. Chem. Soc.*, **78**, 601 (1956).
154. F. W. Bergstrom, R. E. Wright, C. Chandler, and W. A. Gilkey, *J. Org. Chem.*, **1**, 170 (1936).
155. G. Wittig and L. Pohmer, *Chem. Ber.*, **89**, 1334 (1956); G. Wittig, *Org. Synth.*, **IV**, 964 (1963).
156. R. Huisgen and J. Sauer, *Angew. Chem.*, **72**, 91 (1960).

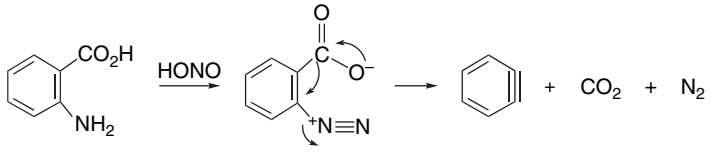
Addition of nucleophiles such as ammonia or alcohols or their conjugate bases to benzynes takes place very rapidly. These nucleophilic additions are believed to involve capture of the nucleophile, followed by protonation to give the substituted benzene.[157]



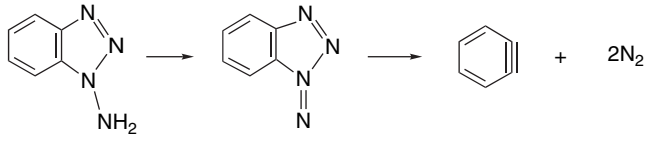
The regiochemistry of the nucleophilic addition is influenced by ring substituents. EWGs tend to favor addition of the nucleophile at the more distant end of the "triple bond," since this permits maximum stabilization of the developing negative charge. ERGs have the opposite effect. These directive effects probably arise mainly through interaction of the substituent with the electron pair that is localized on the *ortho* carbon by the addition step. Selectivity is usually not high, however, and formation of both possible products from monosubstituted benzynes is common.[158]



There are several methods for generation of benzyne in addition to base-catalyzed elimination of hydrogen halide from a halobenzene, and some of these are more generally applicable for preparative work. Probably the most convenient method is diazotization of *o*-aminobenzoic acids.[159] Concerted loss of nitrogen and carbon dioxide follows diazotization and generates benzyne, which can be formed in the presence of a variety of compounds with which it reacts rapidly.

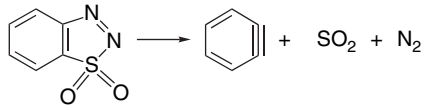


Oxidation of 1-aminobenzotriazole also serves as a source of benzyne under mild conditions. An oxidized intermediate decomposes with loss of two molecules of nitrogen.[160]

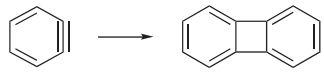


157. J. F. Bunnett, D. A. R. Happer, M. Patsch, C. Pyun, and H. Takayama, *J. Am. Chem. Soc.*, **88**, 5250 (1966); J. F. Bunnett and J. K. Kim, *J. Am. Chem. Soc.*, **95**, 2254 (1973).
158. E. R. Biehl, E. Nieh, and K. C. Hsu, *J. Org. Chem.*, **34**, 3595 (1969).
159. M. Stiles, R. G. Miller, and U. Burckhardt, *J. Am. Chem. Soc.*, **85**, 1792 (1963); L. Friedman and F. M. Longullo, *J. Org. Chem.*, **34**, 3595 (1969); P. C. Buxton, M. Fensome, F. Heaney, and K. G. Mason, *Tetrahedron*, **51**, 2959 (1995).
160. C. D. Campbell and C. W. Rees, *J. Chem. Soc. C*, 742, 745 (1969).

Another heterocyclic molecule that can serve as a benzyne precursor is benzothiadiazole-1,1-dioxide, which decomposes with elimination of sulfur dioxide and nitrogen.[161]



Benzyne dimerizes to biphenylene when generated in the absence of either a nucleophile or a reactive unsaturated compound.[162] The lifetime of benzyne is estimated to be on the order of a few seconds in solution near room temperature.[163]



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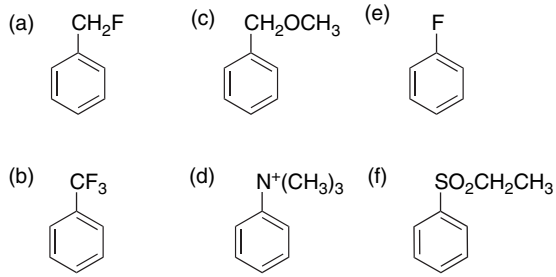
S. Patai, (ed.), *The Chemistry of Diazonium and Diazo Groups*, Wiley, New York, 1978.
R. M. Roberts and A. A. Khalaf, *Friedel-Crafts Alkylation Chemistry*, Marcel Dekker, New York, 1984.
R. Taylor, *Electrophilic Aromatic Substitution*, Wiley, Chichester, 1990.
F. Terrier, *Nucleophilic Aromatic Substitution*, VCH Publishers, New York, 1991.

Problems

(*References for these problems will be found on page 1164*)

9.1. Predict qualitatively the isomer ratio for nitration of each of the following compounds:

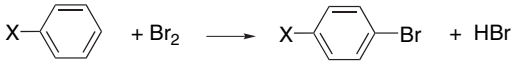


[161] G. Wittig and R. W. Hoffmann, *Org. Synth.*, **47**, 4 (1967); G. Wittig and R. W. Hoffmann, *Chem. Ber.*, **95**, 2718, 2729 (1962).
[162] F. M. Logullo, A. H. Seitz, and L. Friedman, *Org. Synth.*, **48**, 12 (1968).
[163] F. Gavina, S. V. Luis, and A. M. Costero, *Tetrahedron*, **42**, 155 (1986).

9.2. Although *N*,*N*-dimethylaniline is extremely reactive toward electrophilic aromatic substitution and is readily substituted by weak electrophiles, such as diazonium and nitrosonium ions, this reactivity is greatly diminished by introduction of an alkyl substituent in an *ortho* position. Explain.

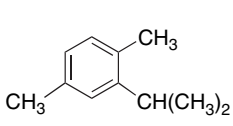
9.3. Toluene is 28 times more reactive than benzene, whereas isopropylbenzene is 14 times more reactive than benzene toward nitration in the organic solvent sulfolane. The *o*:*m*:*p* ratio for toluene is 62:3:35. For isopropylbenzene, the ratio is 43:5:52. Calculate the partial rate factors for each position in toluene and isopropylbenzene. Discuss the significance of the partial rate factors. Compare the reactivity at each position of the molecules, and explain any significant differences.

9.4. Some bromination rate constants are summarized below. Compare the correlation of the data with both σ and σ^+ substituent constants. What is the value of ρ? What information do the results provide about the mechanism of bromination?

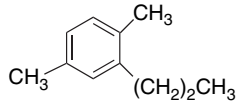


X	$k\ (M^{-1}s^{-1})$
H	2.7×10^{-6}
CH_3	1.5×10^{-2}
OCH_3	9.8×10^{3}
OH	4.0×10^{4}
$N(CH_3)_2$	2.2×10^{8}

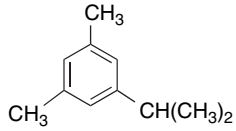
9.5. Compare the product distribution results given below for the alkylation of *p*-xylene at two different temperatures after 2 h. The ratio of aromatic reagent:halide:$AlCl_3$ was 1.0:0.5:0.1.



5-A



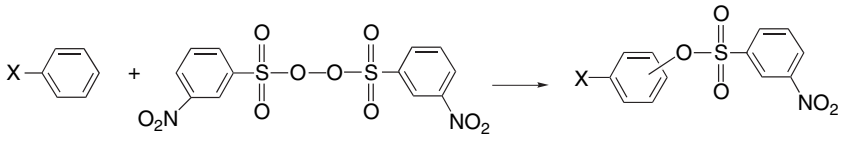
5-B



5-C

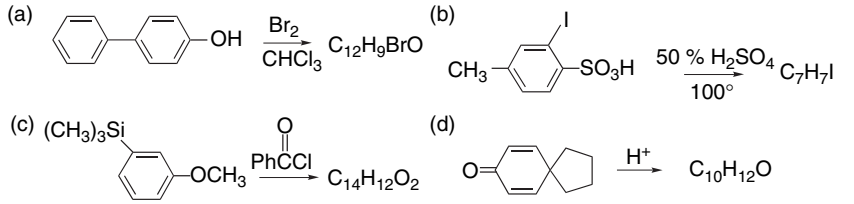
		Product Composition (%)		
alkyl chloride	temp	**5-A**	**5-B**	**5-C**
n-propyl	0°C	34	66	0
n-propyl	50°C	31	53	16
i-propyl	0°C	100	0	0
i-propyl	50°C	62	0	38

9.6. The table below gives first order-rate constants for the reaction of substituted benzenes with *m*-nitrobenzenesulfonyl peroxide. From these data, calculate the relative reactivity and partial rate factors. Does this reaction fit the pattern of an electrophilic aromatic substitution? If so, does the active electrophile exhibit low, intermediate, or high reactant and position selectivity?

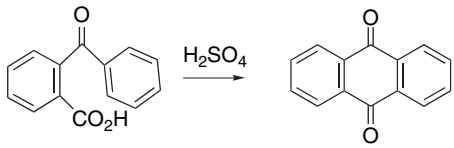


X	$k\ (s^{-1})$	product composition		
		o	*m*	*p*
H	8.6×10^{-5}	–	–	–
Br	4.8×10^{-5}	21	3	76
CH_3	1.7×10^{-3}	32	3	65
CH_3O	4.3×10^{-2}	14	0	86
CH_3O_2C	9.1×10^{-6}	24	67	9

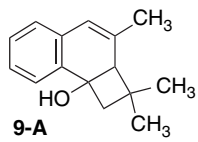
9.7. Propose a structure for the products of the following reactions:



9.8. In 100% H_2SO_4 the cyclization shown below occurs. If one of the *ortho* hydrogens is replaced by deuterium, the rate of cyclization drops from 1.56×10^{-4} to 1.38×10^{-4} s^{-1}. Calculate the kinetic isotope effect. The product from such a reaction contains 60% of the original deuterium. Write a mechanism for this reaction that is consistent with both the magnitude of the kinetic isotope effect and the deuterium retention data.



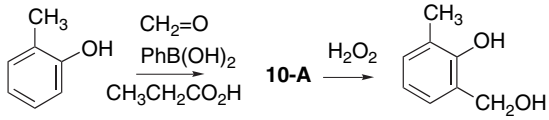
9.9. Reaction of 3,5,5-trimethylcyclohex-2-en-1-one with $NaNH_2$ (3 equiv) in THF generates an enolate. When bromobenzene is added to this solution and stirred for 4 h, a product **9-A** is isolated in 30% yield. Formulate a mechanism for this reaction.



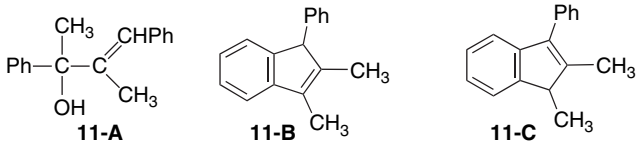
9-A

9.10. Several phenols can be selectively hydroxymethylated at the *ortho* position by heating with paraformaldehyde and phenylboronic acid in propanoic acid. An intermediate **10-A** having the formula $C_{14}H_{13}O_2B$ can be isolated in the case

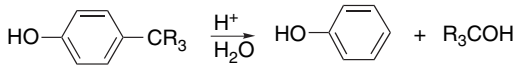
of 2-methylphenol. Propose a structure for the intermediate and indicate the role of phenylboronic acid in the reaction.



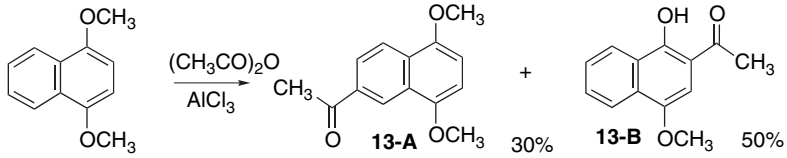
9.11. When compound **11-A** is dissolved in FSO_3H at −78°C, the NMR spectrum shows that a carbocation is formed. If the solution is then allowed to warm to −10°C, a different carbocation is formed. When the acidic solution is quenched with 15% NaOH, the first carbocation gives product **11-B**, whereas the second gives **11-C**. What are the likely structures of the two carbocations?



9.12. Alkyl groups that are *para* to strong ERG substituents such as hydroxy or methoxy can be removed from aromatic rings under acidic conditions if they can form stable carbocations. A comparison of the cases $R = CH_3$ and $R = Ph$ showed strikingly different solvent isotope effects. For $R = CH_3$ $k_H/k_D \sim 0.1$, whereas for $R = Ph$, $k_H/k_D = 4.3$. How do you account for the difference in the solvent isotope effects in the two systems? What accounts for the inverse isotope effect in the case of $R = CH_3$?

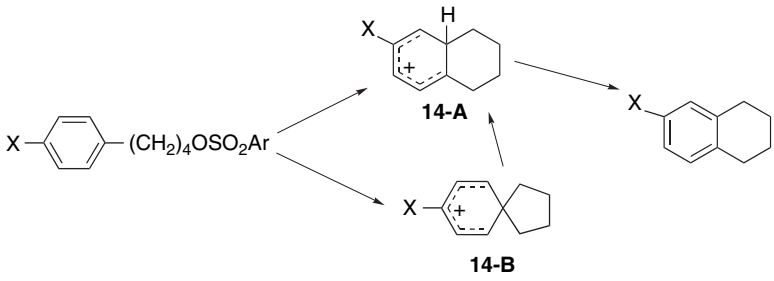


9.13. Acylation of 1,4-dimethoxynaphthalene with acetic anhydride (1.2 equiv) and $AlCl_3$ (2.2 equiv) in dichloroethane at 60°C leads to two products, as shown below. Suggest a rationalization for the formation of these two products. What might account for the demethylation observed in product **13-B**?



9.14. The solvolysis of 4-arylbutyl arenesulfonates in nonnucleophilic media leads to formation of tetralins. Two σ intermediates, **14-A** and **14-B**, are conceivable.

14-A would lead directly to product on deprotonation, whereas **14-B** would give product by rearrangement to **14-A**, followed by deprotonation.



Suggest an experiment that could determine how much of the product was formed via each of the two paths. How would you expect the relative important of the two routes to vary with the substituent group X?

9.15. The kinetic expression for chlorination of anisole by HOCl given on p. 799 becomes simpler for both less reactive and more reactive reactants. For benzene the expression is

$$\text{Rate} = k[\text{benzene}][\text{HOCl}][\text{H}^+]$$

and for 1,4-dimethoxybenzene it is

$$\text{Rate} = k[\text{HOCl}][\text{H}^+]$$

Why does the form of the rate expression depend on the reactivity of the aromatic compound? What conclusions can be drawn about the mechanism of chlorination of benzene and 1,4-dimethoxybenzene under these conditions?

9.16. Relative reactivity and product distribution data for nitration of the halobenzenes is given below. Calculate the partial rate factors for each position for each halogen. What insight into the substituent activating/directing effects of the halogens can you draw from this data?

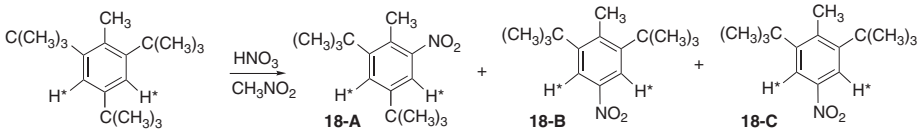
Halogen	Rel rate	*%ortho*	*%meta*	*%para*
F	0.15	13	0	87
Cl	0.033	30	1	69
Br	0.03	37	1	62
I	0.18	38	2	60

9.17. *Ipso* substitution is relatively rare in electrophilic aromatic substitution and was not explicitly covered in Section 9.2 in the discussion of substituent effects on reactivity and selectivity. Using qualitative concepts, discuss the effect of the following types of substituents on the TS and intermediate for *ipso* substitution.

a. A π-donor substituent that is more electronegative than carbon, e.g., methoxy.
b. A π-acceptor substituent that is more electronegative than carbon, e.g., cyano or nitro.

c. A very polar EWG that does not have π-conjugation capacity, e.g., $N^+(CH_3)_3$.
d. A group without strong π-conjugating capacity that is less electronegative than carbon, e.g., $Si(CH_3)_3$.

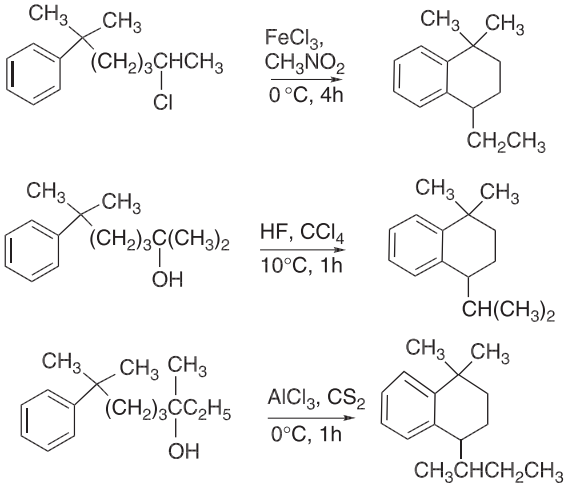
9.18. The nitration of 2,4,6-*tris*-(*t*-butyl)toluene gives rise to three products. The product distribution changes when the 3-position and the 5-position are deuterated, as shown by the data below. Indicate a mechanism for formation of each product. Show why the isotopic labeling results in a change in product composition. Calculate the isotope effect. Does this appear to be a primary isotope effect? Is an isotope effect of this magnitude consistent with your proposed mechanism?



	18-A	18-B	18-C
H	40.3	51.0	8.7
D	42.4	54.6	2.7

9.19. Analyze the results of the studies of intramolecular electrophilic substitution that are described below. Write mechanisms for each of the cyclizations and comment on the relation between ring size and the outcome of cyclization.

(a)



(b)

1) $Ph(CH_2)_3OH \xrightarrow[>\ 200°C]{H_3PO_4}$ mainly phenylpropene isomers (89%)

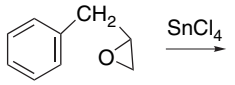
2) $PhC(CH_3)_2(CH_2)_2OH \xrightarrow[>\ 200°C]{H_3PO_4}$ mainly 2-methyl-3-phenyl-2-butene (82%) along with some 1,1-dimethylindane (18%)

3) $Ph(CH_2)_4OH \xrightarrow[>\ 200°C]{H_3PO_4}$ mainly tetralin (80%)

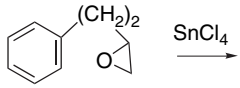
4) $Ph(CH_2)_2CH(OH)CH_3 \xrightarrow[>\ 200°C]{H_3PO_4}$ phenyl butene isomers (100%)

5) $m\text{-}CH_3C_6H_4(CH_2)_2C(OH)(CH_3)_2 \xrightarrow[>\ 200°C]{H_3PO_4}$ mainly 1,1,5-trimethylindane and 1,1,7-trimethylindane

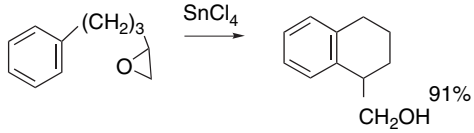
(c)

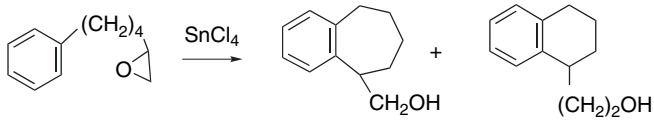
1) 

no cyclization

2) 

no cyclization

3) 

4) 

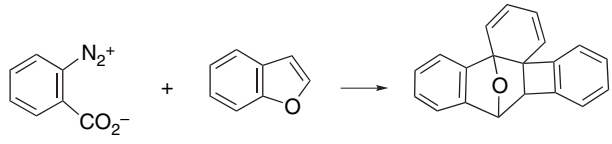
9.20. Explain the outcome of the following reactions by a mechanism showing how the product could be formed.

a. 2,6-Di-(*t*-butyl)phenoxide reacts with *o*-nitroaryl halides in NaOH/DMSO at 80°C to give 2,6-di-(*t*-butyl)-4-(2-nitrophenyl)phenol in 60–90% yield. Under similar conditions, 1,4-dinitrobenzene gives 2,6-di-(*t*-butyl)-4-(4-nitrophenyl)phenol.

b. 2-(3-Chlorophenyl)-4,4-dimethyloxazoline reacts with alkyllithium reagents to give 2-(2-alkylphenyl)-4,4-dimethyloxazolines.

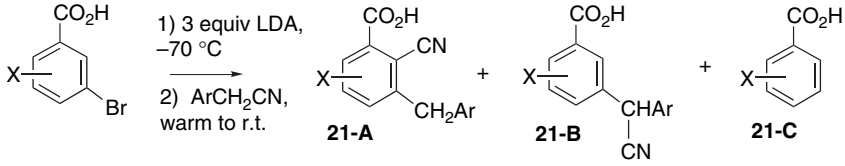
c. Nitrobenzene reacts with cyanomethyl phenyl sulfide in NaOH/DMSO to give a mixture of 2- and 4-nitrophenylacetonitrile.

d. The following transformation occurs:



e. Reaction of benzene with 3,3,3-trifluoropropene in the presence of BF_3 gives 3,3,3-trifluoropropylbenzene.
f. 3-Chloronitrobenzene reacts with 4-amino-1,2,4-triazole in $K^{+}\cdot^{-}$ O–*t*-Bu/DMSO to give 2-chloro-4-nitroaniline.
g. Good yields of tetralone can be obtained from 4-phenylbutanoic acid or the corresponding acyl chloride in the presence of the strongly acidic resin Nafion-H. With 3-phenylpropanonic acid, only the acyl chloride gives a cyclization product.

9.21. Reaction of several 3-bromobenzoic acids with excess LDA at −70°C, followed by addition of benzyl cyanide and warming, gives the product mixtures shown below. Suggest a mechanism for formation of products **21-A** and **21-B** under these conditions.



X	Ar	**21-A**	**21-B**	**21-C**
4-CH_3O	Ph	56	9	11
4-CH_3O	4-CH_3Ph	70	8	12
4-CH_3O	2-CH_3Ph	44	5	10
4-CH_3	Ph	53	<2	7
4-CH_3	4-CH_3Ph	43	<2	8