# 1

ELECTROPHILIC AROMATIC SUBSTITUTION: MECHANISM

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1.1 INTRODUCTION

Electrophilic aromatic substitution (S_EAr) is one of the most important synthetic organic reactions [1]. Since its discovery in the 1870s by Charles Friedel and James Crafts [2], it has become a general route to functionalized aromatic compounds. The chemistry is used extensively in the chemical industry, providing millions of tons of aromatic products annually for chemical feed-stock, commodity chemicals, and consumer applications. For example, detergents (i.e., **1**, Scheme 1.1) are commonly prepared using two S_EAr reactions: alkylation and sulfonation. The antibacterial agent *sulfadiazine* (**2**) is prepared using nitration and chlorosulfonation reactions during the course of its synthesis, while the disperse dye (**3**) is prepared using an azo coupling reaction. Several important polymers, such as thermosetting phenol-formaldehyde resins, are also prepared via S_EAr reaction steps. In other applications, the chemistry is commonly used in natural product and target-directed syntheses [1].
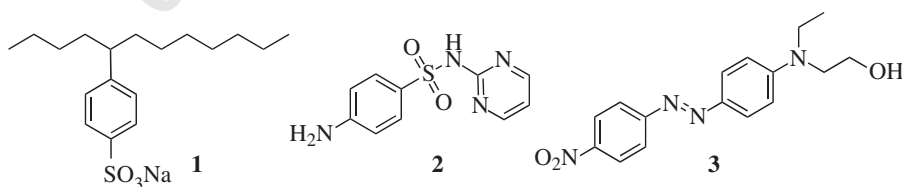

SCHEME 1.1 Products from S_EAr reactions.

In addition to its application in synthetic chemistry, $S_E Ar$ has one of the most thoroughly studied mechanisms among organic reactions. These studies have paralleled the development of chemistry itself—from the understanding of ions in chemistry and aromaticity in π-systems to the development of high-level theoretical calculations and ultrafast spectroscopic methods. Our understanding of these mechanisms has evolved steadily since the time when the chemistry was first described. This area continues to be an active area of research, and these studies provide new insights into the mechanisms of these valuable organic transformations. The importance of this mechanistic understanding cannot be overstated. Because the chemistry has significant economic value, mechanistic understanding is crucial for chemists to maximize reaction yields, reduce costs, and minimize the environmental impacts of these synthetic processes. In the following chapter, I will provide an overview of the $S_E Ar$ reaction mechanism, discussing the salient features of these processes and efforts to understand them.

1.2   GENERAL ASPECTS

The $S_E Ar$ reactions involve more than 20 distinctly different types of substitutions, yet these transformations have similar overall mechanisms. The commonly proposed mechanism involves interaction of an electrophilic species with the π-system of an arene (Scheme 1.2) [3]. The electrophile (E+) itself is often a cationic species (*vide infra*), but $S_E Ar$ reactions may also be initiated by dipolar
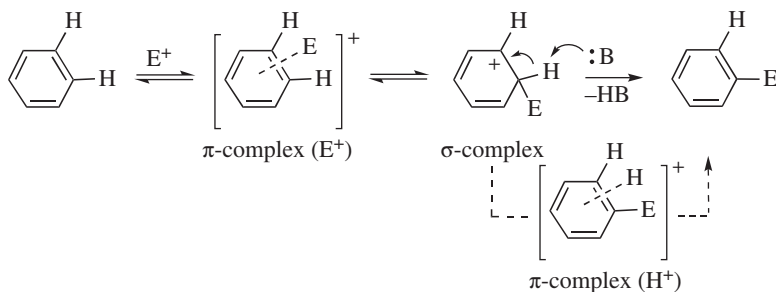

SCHEME 1.2   Proposed mechanism for the $S_E Ar$ reaction.

groups or molecules. The initial interaction may lead to the formation of a π-complex or an encounter complex. The π-complex often forms the σ-complex intermediate, also known as the Wheland complex. In the final step, a base removes the *ipso* proton and the substitution product is obtained. This mechanistic interpretation also allows for the formation of a second π-complex from the σ-complex intermediate, where the proton is loosely bound to the π-system. With the regeneration of the aromatic π-system, product stability typically leads to a fast reaction in the final step.

There are several variations of this mechanism. For example, in nitrations, there is considerable evidence to suggest single electron transfer between the nitronium cation (NO_2^+) and the arene (*vide infra*), followed by coupling of the product radicals to give a σ-complex intermediate [4]. There are also examples known involving addition of radical species into the arene (such as $\cdot NO_2$) as a route to substitution products [5]. Moreover, there are examples of $S_E Ar$ reactions in which (cationic) groups other than H^+ leave the final reaction step [6].
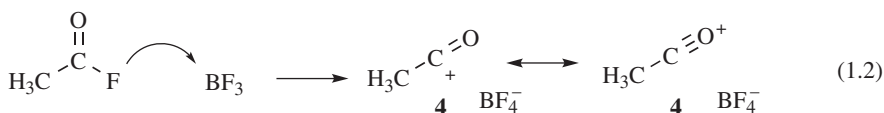
1.3   ELECTROPHILES

The electrophiles in $S_E Ar$ reactions may be divided into two basic categories: those with fully formed cationic charge centers and those having reactive, polarized bonds. For example, Friedel–Crafts alkylation often occurs through the involvement of discrete carbocation intermediates (see Chapter 2).

$$\text{(1.1)}$$
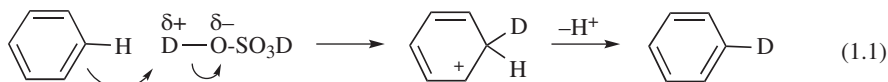
This may be contrasted with the D_2SO_4-promoted hydrogen–deuterium exchange at an arene (Eq. 1.1). In this case, the electrophilic chemistry occurs at the polarized deuterium–oxygen bond, where the deuterium atom carries a significant positive charge. Although the various S_EAr synthetic reactions do share a common basic mechanism (Scheme 1.2), they often differ considerably in the means or mechanisms by which the electrophiles are generated. Several of the common mechanistic types are described below.

Many electrophilic species are generated by the action of Lewis acid catalysts. For example, Friedel–Crafts acylation may occur through the involvement of the acylium ion (i.e., 4) often generated by Lewis acid-promoted halide abstraction (Eq. 1.2) [7]. Similar Lewis acid-promoted reactions may be used to give carbocationic species from alkyl halides, carboxonium ions from acetals and related precursors, iminium ions from α-haloalkylamines, and others.

$$\text{(1.2)}$$

While discrete cationic species may be formed by Lewis acid reactions, highly polarized species may also be the active electrophiles in the transformations. In the case of brominations (Scheme 1.3), Br_2 itself may develop a small dipole (5) with approach to an electron-rich arene (such as phenol). Interaction with the Lewis acid may increase the degree of polarization (6) or, in the limiting case, give the bromonium ion (7). The exact nature of the reacting electrophile depends on several factors, including the reactivity of the arene nucleophile, temperature, strength of the Lewis acid, or solvent ionizing power.
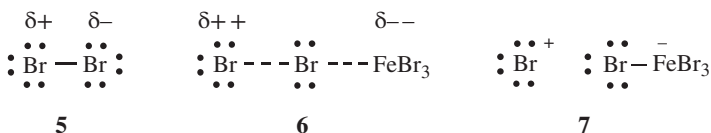
SCHEME 1.3 The development of cationic charge on bromine.

In the case of Brønsted acid catalysts, cationic electrophiles may be generated by the direct protonation of a functional group (Fig. 1.1). This type of chemistry is especially important in the S_EAr reactions of carbonyl compounds and olefins. The carboxonium ions (8 and 9) and nitrilium ion (10) are formed by protonation at a nonbonding electron pair, while protonation at the olefinic π-bond gives the carbocation (11). Both solid (i.e., zeolites) and liquid Brønsted acids may generate electrophiles by this chemistry.

In many types of S_EAr reactions, cationic electrophile formation requires one or more steps after functional group protonation or activation (Fig. 1.2). Alcohols and related functional groups are protonated, and with subsequent cleavage of C—O bond, the carbocation electrophile (11) is formed. In a similar respect, a common method of nitration involves the use of HNO_3 with H_2SO_4. The nitronium ion electrophile (NO_2^+, 12) is formed by protonation of nitric acid and subsequent loss of water by cleavage of the N—O bond [8]. The nitrosonium ion electrophile (NO^+) may be generated by an analogous transformation from nitrous acid, HNO_2 [9]. Likewise, N-acyliminium ion electrophiles (i.e., 13) may be formed by ionization of N-hydroxymethylamides [10].
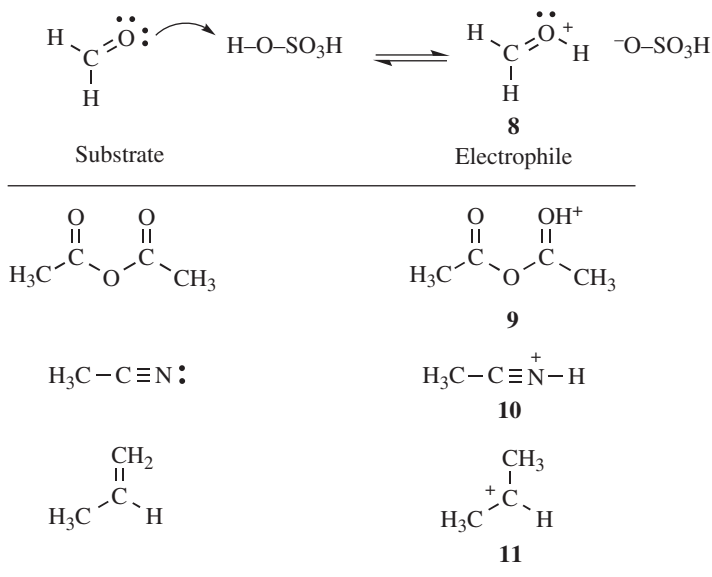
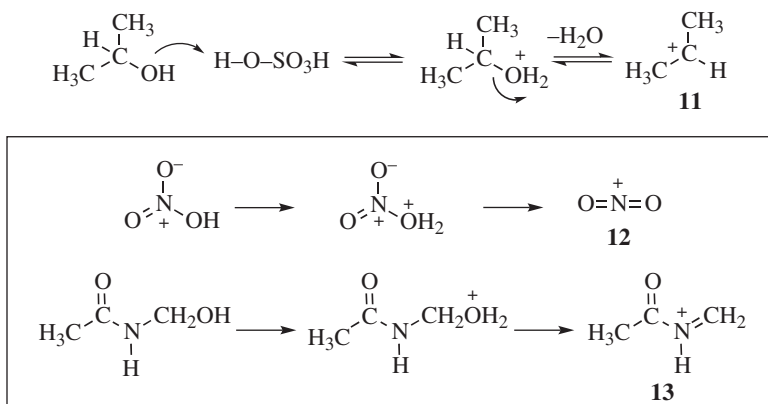**FIGURE 1.1**   Examples of electrophiles formed by direct protonation.

FIGURE 1.2   Electrophiles generated from Brønsted acids.

There are many examples of Brønsted acid-promoted reactions where highly polarized functional groups are the active electrophiles. For example, Olah and coworkers reported *N*-chlorosuccinimide to be a powerful chlorinating agent with superacidic BF_3–H_2O [11]. The active electrophile is likely the diprotonated (**14**) or triprotonated species (**15**, Eq. 1.3),
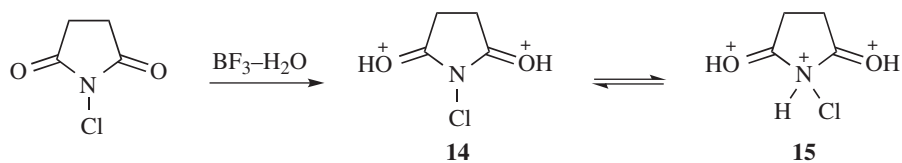

$$(1.3)$$

which transfers Cl[+] directly to the arene nucleophile. This system is capable of chlorinating nitrobenzene—a strongly deactivated arene—in 69% yield. In S_EAr reactions with epoxides, the C—O bond may undergo nucleophilic ring opening following protonation or strong hydrogen bonding at the oxygen. Thus, the epoxide substrate (**16**) provides the cyclialkylation product (**17**) in quantitative yield by the action of 1,1,1,3,3,3-hexafluoroisopropanol (Scheme 1.4) [12]. It is suggested that the epoxide is protonated (or coordinated through hydrogen bonding), leading to a nucleophilic ring opening of the epoxide.
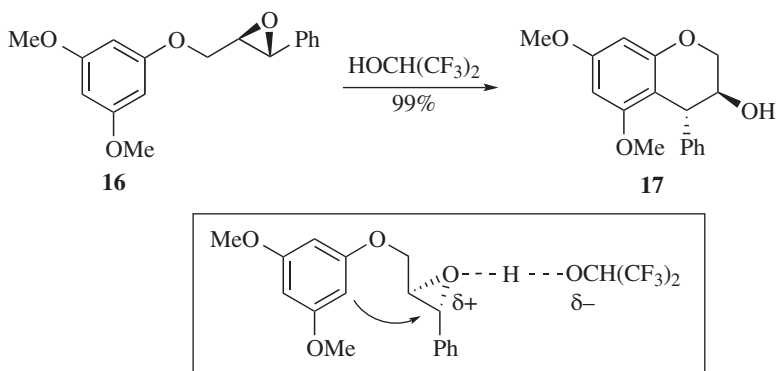

SCHEME 1.4 An intramolecular S_EAr reaction with epoxide **16**.

There are numerous multistep processes that generate electrophiles. As examples of these types of reactions, we will consider the diazotization of anilines and the formation of chloroiminium ions in the Vilsmeier–Haack reaction. Aryl diazonium ions are useful in the modification of arenes by the Sandmeyer reaction and as electrophilic intermediates in diazonium coupling reactions for the synthesis of dyes and pigments. Several types of synthetic methods have been developed for this chemistry, and the mechanism varies depending on the methodology [13]. Under some conditions, the nitrosonium ion (**18**) initiates the process (Scheme 1.5). N_2O_5 and NOCl have also been proposed as intermediates in diazotization—both are considered as nitrosonium ion carriers. The aniline reacts
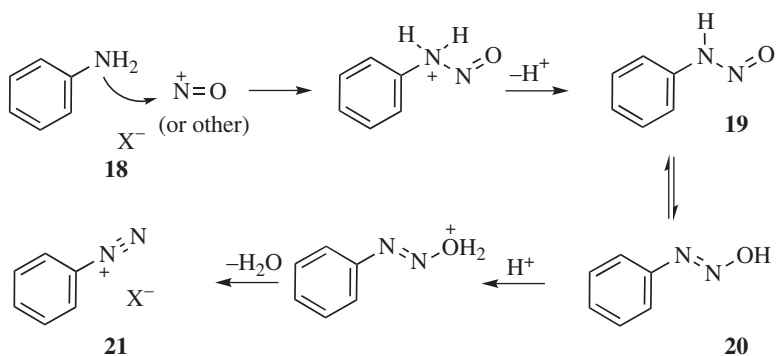
SCHEME 1.5 Proposed mechanism for a diazotization of aniline.

to provide the *N*-nitrosamine (**19**). Tautomerization gives **20**, which upon protonation cleaves off water to give the diazonium ion electrophile (**21**). In the Vilsmeier–Haack reaction, a chloroiminium ion is the electrophile [14]. The electrophilic intermediate is usually generated by the reaction of a formamide with POCl$_3$ (Scheme 1.6). Thus, phosphorous oxychloride reacts at the carbonyl group to provide the addition compound **22**. Cleavage of the C—O bond then provides the electrophilic chloroiminium ion (**23**). Following the S_EAr reaction, hydrolysis gives the formyl group.
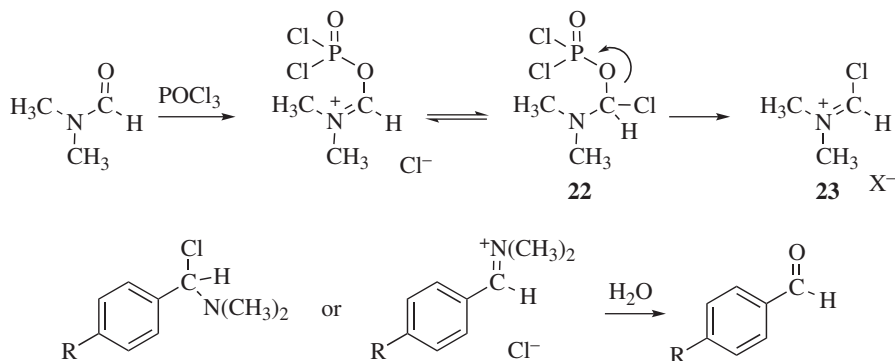
SCHEME 1.6   Proposed mechanism for the Vilsmeier–Haack reaction.

A number of S_EAr reactions have also been developed in which the electrophile is generated by an oxidative process. For example, She and coworkers recently used a (diacetoxyiodo)benzene-promoted phenol oxidation to generate the cationic species (**24**) that undergoes cyclization to the natural product—gymnothelignan N (**25**, Scheme 1.7) [15]. Other oxidative synthetic methods have been developed for electrophilic halogenation [16], aminations [17], and nitrations [18].
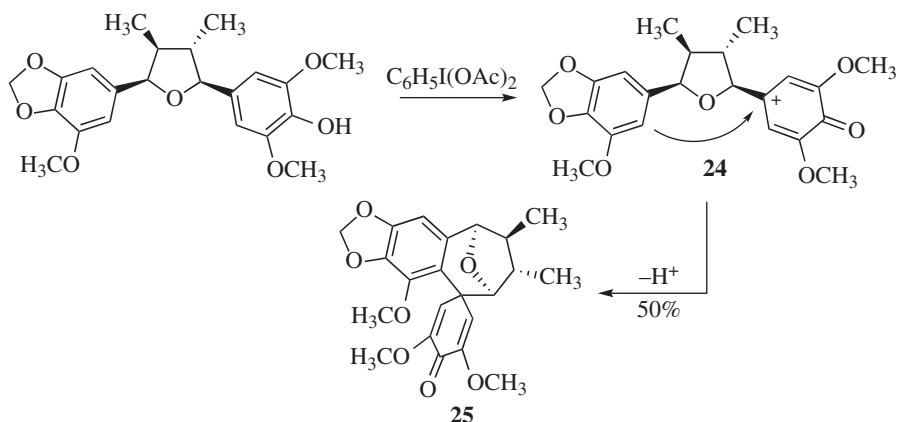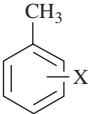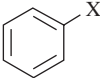

SCHEME 1.7   Oxidative route to electrophile and the cyclization to gymnothelignan N (**25**).

In addition to the mechanisms of electrophile formation, another critical consideration relates to electrophile strength. There has been a vast amount of work done to characterize electrophile strengths [19]. Although much of the work relates to chemistry with n-type nucleophiles and nonaromatic π-nucleophiles, some studies have sought to estimate electrophile strengths in S_EAr reactions. Relative electrophile strengths became apparent as the synthetic S_EAr reactions were developed. While the nitronium ion (NO_2^+) salts react with benzene under mild conditions, carboxonium ions such as protonated formaldehyde ($CH_2{=}OH^+$) are weaker electrophiles and consequently do not react with benzene.

Among the methods for evaluating electrophile strength, a useful approach involves comparing relative reaction rates with benzene and toluene [20]. More reactive electrophiles are expected to be less selective in competition reactions between the two arenes. As noted by Stock and Brown [21],

TABLE 1.1   Relative Yields and k_T/k_B for Competitive S_EAr Reactions with Toluene and Benzene

			k_T/k_B
NO_2BF_4 sulfolane, 25°C	62.5%	37.5%	1.67
		$(X = NO_2)$	
Cl_2, CH_3CN, 25°C	99.9%	0.1%	1650
Cl_2, CH_3CO_2H, 24°C	99.7%	0.3%	353
Cl_2, CH_3NO_2, 25°C $FeCl_3$	93.1%	6.9%	13.5
		$(X = Cl)$	

an exceptionally reactive electrophile should exhibit no selectivity and give relative rates, k_T/k_B, of approaching 5/6 (reflecting the number of arene C—H positions) or 0.833. Conversely, less reactive electrophiles are expected to be more selective in the reaction with toluene (the more nucleophilic arene) and provide larger values for k_T/k_B. Many electrophilic systems have been studied using this approach, and the data is generally consistent with observations from synthetic chemistry. For example, nitronium tetrafluoroborate is considered a very strong electrophilic system, and it gives nitration products with k_T/k_B of 1.67 (Table 1.1) [22].

Without a Lewis acid catalyst, molecular chlorine is a rather weak electrophile, and this is reflected in its highly selective reaction with toluene (k_T/k_B 1650) [21]. When the reaction is done in acetic acid (a strong hydrogen bonding solvent and Brønsted acid catalyst), the chlorine is somewhat polarized. The more reactive Cl_2 electrophile exhibits slightly lower selectivity with k_T/k_B 353. With the use of a strong Lewis acid, a highly electrophilic system is formed and the chlorination shows only modest selectivity with k_T/k_B of 13.5. Extensive studies of k_T/k_B rates have been presented in the literature [21].

Other approaches of evaluating electrophile strengths have been developed, including comparisons of the regioselectivities of electrophilic attacks. The assumption is that more reactive electrophiles should exhibit less positional selectivity in chemistry with substituted arenes. In a method developed by Brown and associates [21], electrophiles were compared by the relative reactivities of the *meta* and *para* positions of toluene, where more reactive electrophiles give increasing proportions of *meta* substitution. While this approach has some general applicability, problematic cases are known. For example, Olah has described a series of very reactive electrophiles exhibiting low substrate selectivity but high positional selectivity [23]. To explain this, it was suggested that the highest-energy transition state resembles the σ-complex in some S_EAr reactions and the π-complex in other S_EAr reactions (*vide infra*). Correlating electrophilic reactivities with positional regioselectivity seems to work best in the former case.

The Mayr group has applied Equation 1.4 to determine the electrophilicity parameters [19b], E, in reactions between electrophiles and nucleophiles, where N is the

$$\log k(20°C) = s(N + E) \tag{1.4}$$

nucleophilicity parameter and s is the nucleophile-dependent slope parameter. By analyzing pseudo-first-order rate constants from reactions with various types of nucleophiles, the electrophilicities of numerous cationic species have been established. Several of the characterized

electrophiles are known to be involved in $S_E Ar$ reactions [24], such as carbocations **26** and **27**, the iminium ion **28**, and carboxonium ion **29** (Scheme 1.8). For comparison, toluene and anisole have

	26	**27**	**28**	**29**
E parameter:	8.02	5.73	−5.77	2.97
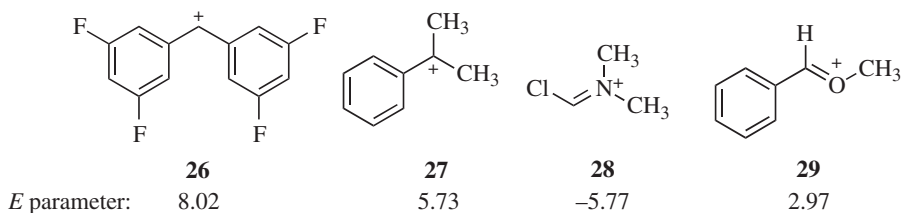
SCHEME 1.8   Electrophilicity parameters, *E*, for electrophiles **26–29**.

respective nucleophilicity parameters, *N*, of −4.67 (S_N 1.77) and −1.18 (S_N 1.20). Recently, this approach was used to predict the rate constant for the $S_E Ar$ reactions involving iminium ion salts and pyrroles (for the rate-determining C—C bond-forming step) [25].

Among the most reactive electrophiles, an informal benchmark of reactivity has been often cited—the $S_E Ar$ reaction with nitrobenzene. As a strongly deactivated arene (*vide infra*), nitrobenzene only reacts with the most active electrophiles. Moreover, since many $S_E Ar$ reactions are done in highly acidic media, the nitro group may itself be completely protonated (pK_a −11.3), thereby enhancing the deactivation of the aromatic ring. Examples of electrophiles capable of reacting with nitrobenzene are iodine (I) trifluoromethane sulfonate **30** [26], nitronium salts **31** and **32**, and the carboxonium ions **33** and **34** (Scheme 1.9) [27–29]. Dications **32–34** are examples of superelectrophilic species, a class of reactive intermediates usually formed by (multi-)protonation equilibria or multidentate Lewis acid
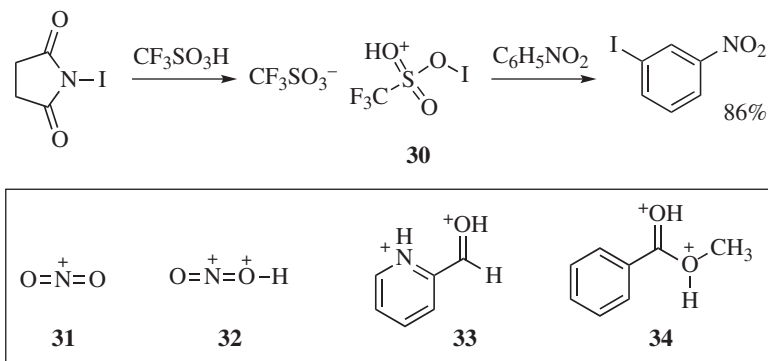
SCHEME 1.9   Examples of electrophiles shown to react with nitrobenzene.

interactions. Superelectrophiles are often capable of reacting with the weakest nucleophiles [30]. For example, the protio-nitronium dication (**32**) has been shown to nitrate even 1,3-dinitrobenzene.

A very active area of research in $S_E Ar$ chemistry is in the field of asymmetric synthesis. This chemistry involves a unique set of electrophiles—those in which a chiral environment must exist near the electrophilic reaction site. In most cases, these asymmetric synthetic reactions are accomplished with a chiral electrophile or a chiral catalyst (or counterion) in tight coordination to the electrophile. For example, Stadler and Bach used a chiral electrophile (**36**) in an $S_E Ar$ reaction leading to the natural product (−)-podophyllotoxin **38** (Scheme 1.10) [31]. With planar sp^2 carbocation centers, facial selectivity may be controlled by neighboring groups, in this case the adjacent vinyl group on the lactone **36**. The Friedel–Crafts chemistry provides intermediate **37**, which is then converted to (−)-podophyllotoxin (**38**) as a single enantiomer.
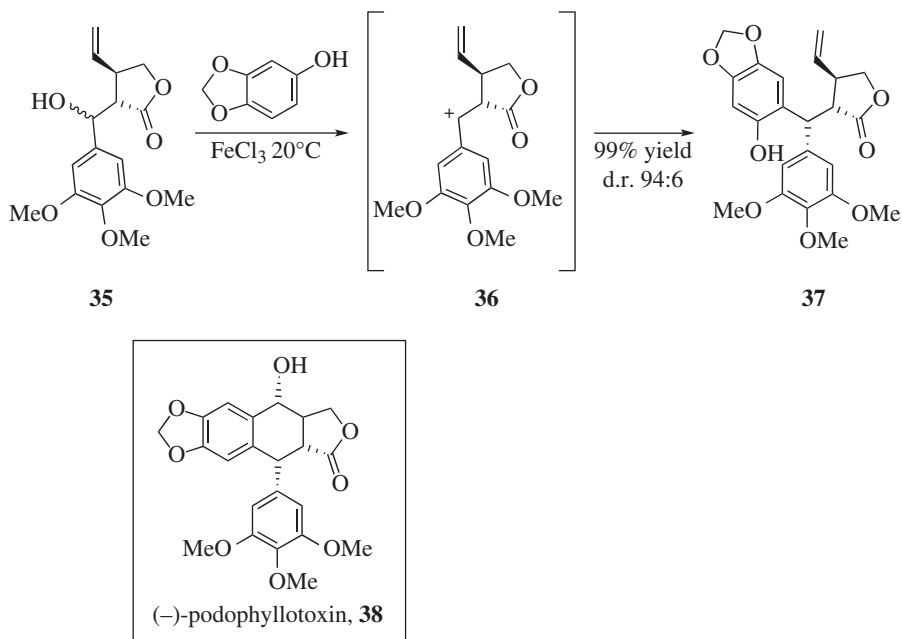
SCHEME 1.10 S_EAr reaction with a chiral electrophile.
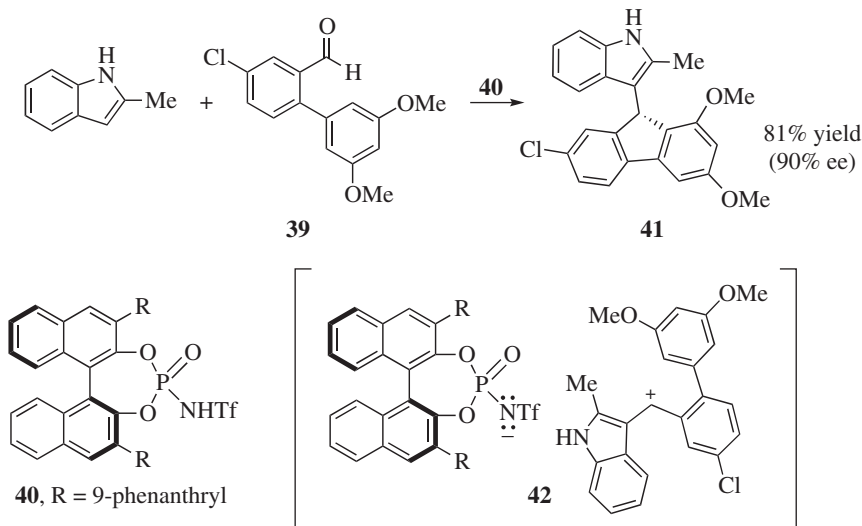
SCHEME 1.11 S_EAr reaction with a chiral catalyst.

Both chiral Brønsted and Lewis acids have been useful in asymmetric Friedel–Crafts reactions. For example, the chiral Brønsted acid **40** was used in the asymmetric synthesis of chiral fluorenes from an achiral indole and the biarylaldehyde **39** (Scheme 1.11) [32]. Initial steps in the conversion lead to the ion pair **42**. Through ion pairing with the electrophilic carbocation, the chiral anion

directs ring closure to provide the S_EAr product **41** in reasonable enantioselectivity. Owing to the value of this type of synthetic methodology, asymmetric S_EAr reactions have been the subject of several recent reviews [33].

1.4 ARENE NUCLEOPHILES

As described earlier, the S_EAr involves the reaction of an electrophilic species with an arene nucleophile. There are several types of arenes common to the S_EAr reactions: substituted benzenes, polycyclic aromatic compounds, and heterocyclic compounds. Substituent effects largely control the chemistry of substituted benzenes and related compounds. This includes both activating and directing effects of substituents on the S_EAr reaction.

Functionalized arenes are generally compared to benzene with respect to their relative reactivities. Substituents are described as activating groups if they increase the S_EAr reaction rates compared to benzene, and they are described as deactivating groups if they decrease the relative reaction rate. These substituent effects may be understood in terms of the Hammond postulate. In many cases, the σ-complex is the highest-energy intermediate in the S_EAr reaction, and the transition state leading to it resembles the σ-complex. Any substituent capable of stabilizing the cationic σ-complex should also stabilize the corresponding transition state, lowering the energy barrier and increasing the relative reaction rate (Fig. 1.3). Thus, σ-complex **43** may be stabilized by an electron-donating group (i.e., EDG = −OCH$_3$), while benzene or a derivative with a deactivating group (i.e., EWG = − CF$_3$) leads to the less stable σ-complex **44.** The respective transition states (‡$_1$ and ‡$_2$) are raised or lowered accordingly, and this affects the relative reactivities or reaction rates.

As a carbocationic species, the σ-complex is stabilized by electron-donating groups. These interactions may involve resonance and/or inductive effects. With substituents such as the methoxy group, σ-complex stabilization may occur through resonance interaction with the *n*-electrons (Eq. 1.5). Hyperconjugation is also an important stabilizing effect for σ-complexes (Eq. 1.6), an interaction that explains the activating effects of alkyl groups. Similar interactions are important
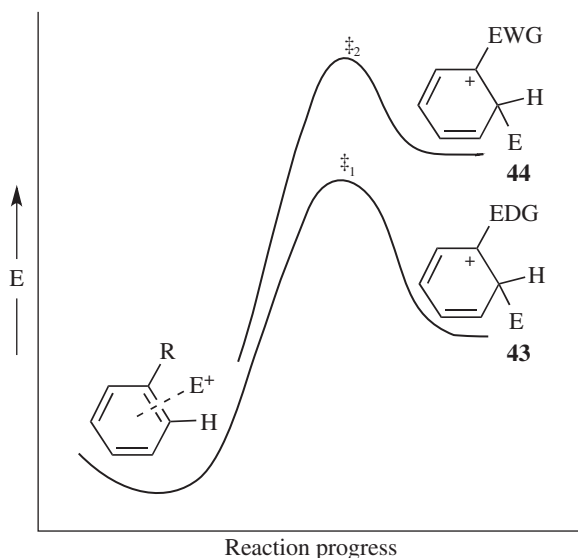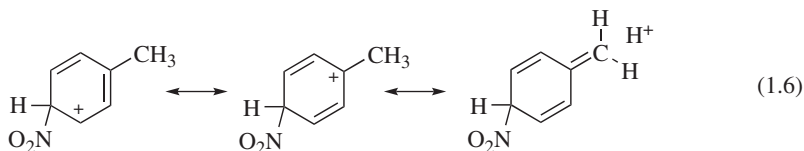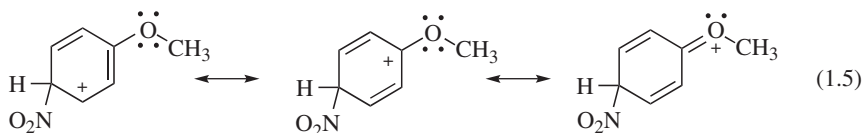
FIGURE 1.3   The effects of substituents on σ-complex stability and energy barriers. EDG, electron-donating group; EWG, electron-withdrawing group.

$$(1.5)$$

$$(1.6)$$

with *para* attack and σ-complex formation. In contrast to the stabilizing effects of electron-donating groups, the σ-complex is destabilized by electron-withdrawing groups (Scheme 1.12). Among these structure types, there are groups that destabilize the σ-complex primarily by inductive effects (**45**) and by unfavorable charge–charge repulsive interactions (**46** and **47**). The electron-withdrawing groups are deactivating in S_EAr reactions.
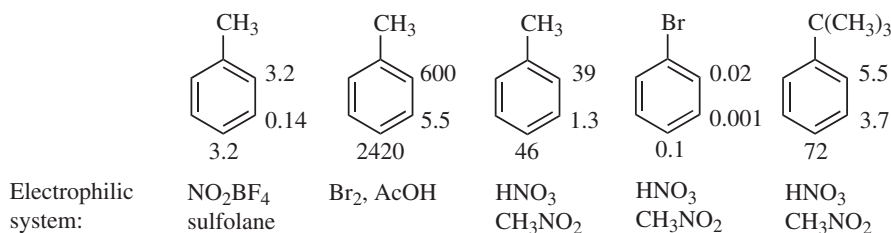

45   **46**   **47**
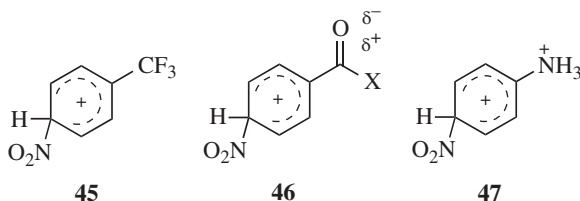
SCHEME 1.12   Destabilized σ-complexes.

The activating or deactivated effects of the substituents may be quantitatively described through the use of partial rate factors [34]. These values estimate the reactivities of positions on an arene relative to the carbons of benzene. For example, partial rate factors may be calculated for a monosubstituted benzene (Ar) at the *ortho*, *meta*, and *para* positions. For a given electrophilic system, the partial rate factor, f, is calculated using the relative rates of reactions ($k_{benzene}$ and k_{Ar}) and the fraction or percent of each regioisomer (Eq. 1.7). The first term is a statistical factor that accounts for the

$$\text{Partial rate factor at the } ortho \text{ position of arene Ar} \qquad f_o^{Ar} = \left(\frac{6}{2}\right)\left(\frac{k_{Ar}}{k_{benzene}}\right)\left(\frac{\% \ ortho}{isomer}\right) \qquad (1.7)$$

number of reactive positions on benzene versus those on the substituted arene—6/2 for the *ortho* and *meta* and 6/1 for the *para*. The second term describes the ratio of the overall rate difference between reactions at the arene (k_{Ar}) and benzene ($k_{benzene}$). For sulfonation (H_2SO_4–H_2O, 25°C) of toluene, the $k_{toluene}/k_{benzene}$ ratio is found to be 31.0 and the product sulfonic acids are formed in an isomer ratio 36:5:59 (*ortho:meta:para*) [21]. Solving for the partial rate factor at the *ortho* position, $f = (6/2)(31.0)(0.36) = 34.0$. For the sulfonation, partial rate factors at the *meta* and *para* positions are, respectively, 4.3 and 112. These values not only reflect the relative reactivity of toluene compared to benzene—large values indicate a substantially more reactive arene—but they also indicate the relative reactivities of the positions on the substituted arene. The higher reactivities of the *ortho* and *para* positions of toluene are clearly apparent by the respective partial rate factors.

As expected from the previous discussion on $k_{toluene}/k_{benzene}$, the partial rate factors are quite sensitive to the nature of the electrophilic system [35]. For toluene, strong electrophiles (i.e., NO_2BF_4) have $k_{toluene}/k_{benzene}$ approaching unity, while weaker electrophiles (i.e., Br_2) show more selectivity. These trends are seen in the partial rate factors for the reactions (Scheme 1.13). The less reactive nitrating system (HNO_3) shows increasing $k_{toluene}/k_{benzene}$ selectivity, compared to the nitronium salt, and the partial rate factors are correspondingly higher.

CH_3	CH_3	CH_3	Br	$C(CH_3)_3$
3.2	600	39	0.02	5.5
0.14	5.5	1.3	0.001	3.7
3.2	2420	46	0.1	72

| Electrophilic system: | NO_2BF_4 sulfolane | Br_2, AcOH | HNO_3 CH_3NO_2 | HNO_3 CH_3NO_2 | HNO_3 CH_3NO_2 |

SCHEME 1.13   Partial rate factors for S_EAr reactions.

Partial rate factors are also strongly influenced by the nature of substituents on the arene, where electronic and steric effects are both found to be significant. Thus, halogens are found to be deactivating substituents, as seen in the low values for the partial rate factors in nitration. With *tert*-butylbenzene, the partial rate factor for the *ortho* position is significantly lower than the *ortho* partial rate factor for toluene. This results from the steric effects from the *tert*-butyl group.

Several research groups have also used theoretical methods in an effort to understand the activating and deactivating effects of the substituents in S_EAr reactions. For example, Galabov and coworkers have developed a computational approach for determining *electrophile affinity*, Eα, as a measure to determine arene reactivity and positional selectivity in S_EAr reactions [36]. Other recent approaches to this problem include the development of reactive hybrid orbital analysis [37], the topological analysis of electron localization function [38], the calculations of electrostatic potentials at the arene carbons [39], and several other methods. A comprehensive summary of this area is beyond the scope of this chapter; however, the interested reader may consult one of the recent reviews of this topic [40].

A critically important consideration also involves the directing effects of the arene substituents. As seen in the calculation of partial rate factors (*vide supra*), arene substituents may tend to favor, or direct, reactions at specific sites on the ring. Among the substituents that activate the arenes toward S_EAr reactions, many of these are *ortho/para* directing groups (Table 1.2). Deactivating substituents are often *meta* directing groups.

The halogens are an exception to this trend, as they are mildly deactivating but *ortho/para* directing. Alkyl groups tend to be activating and *ortho/para* directing; however, electronegative atoms/groups on the alkyl group may change this. For example, the trifluoromethyl group is deactivating and *meta* directing, due to the inductive effects of the fluorine atoms. Nitration of α,α,α-trifluorotoluene provides the *meta* substitution product in good yield (Eq. 1.8) [41].

TABLE 1.2   Relative Activating and Directing Effects of Substituents

	Activating Groups	Deactivating Groups
Ortho/para directing	Amino, hydroxy (strongly) alkyl, alkoxy, amido, aryl (weakly)	Halogens
Meta directing	None	Nitro, ammonium, sulfonium (strongly) aldehydes, ketones, acids, (weakly) esters, carboxamides

$$(1.8)$$

94%
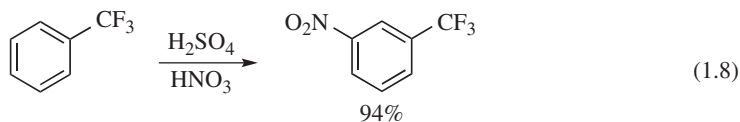
The directing effects may again be understood by a stabilization or destabilization of the σ-complex. Since most S_EAr reactions are kinetically controlled processes, product distributions are generally controlled by the relative stabilities of the transition states leading to the σ-complex. As noted earlier, any substituent that stabilizes or destabilizes the σ-complex will likely have a similar effect on the transition state. The σ-complex, and to some extent the preceding transition state, is an example of the cyclohexadienyl cation-type structure (Scheme 1.14). Using resonance structures, the cyclohexadienyl cation is characterized by positive charge centers at the *ortho* and *para*
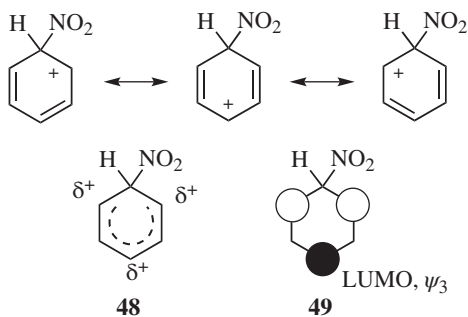

SCHEME 1.14   Charge distribution in a σ-complex and the orbital coefficients for the LUMO, ψ_3.

positions to the attacking electrophile. This means that the most significant positive charge is located at the *ortho* and *para* positions (**48**). In considering the Hückel-type molecular orbitals of this system, the lowest unoccupied molecular orbital (LUMO, ψ_3) has large coefficients at the *ortho* and *para* positions (**49**). Thus, electron-donating substituents stabilize the σ-complex most effectively when they are *ortho* and *para* to the position of electrophilic attack. This also tends to lower the energies of the transition states leading to the *ortho* and *para* σ-complex intermediates and increases the relative rates of these reaction paths.

As an example of these directing effects, Qin and coworkers utilized Friedel–Crafts chemistry to generate functionalized pyrroloindolines [43], a class of structures known for their biological activities (Scheme 1.15). The benzylic carbocation **50** was generated by silver-promoted halide abstraction, and this species was reacted with toluene. The *ortho* and *para* directing effect of the alkyl group is apparent in resonance structure **51b** where the cationic charge center is adjacent to the methyl group. As noted previously, the σ-complex is stabilized by the hyperconjugative resonance with the methyl group. Following rearomatization of the tolyl group, the functionalized pyrroloindoline (**52**) is obtained in good stereoselectivity and yield.

Electron-donating groups at the *meta* position of the σ-complex have a much smaller effect on the stability of the σ-complex, as these groups are unable to directly interact with the cationic charge center (alternatively, the *meta* position is a nodal point in the LUMO, ψ_3, and this prevents the groups from donating electron density into the LUMO). This is seen, example, in the σ-complex resulting from bromination of anisole (Eq. 1.9). With less stable σ-complex intermediates, *meta* attack tends to be disfavored in these types of systems.
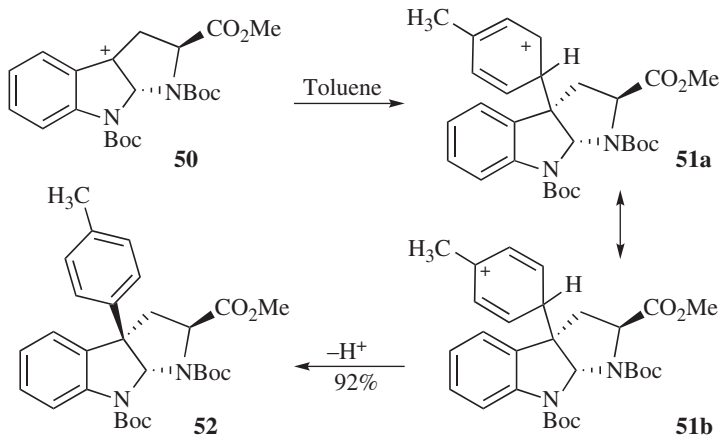
SCHEME 1.15   *Ortho* and *para* directing effect with toluene.

$$(1.9)$$
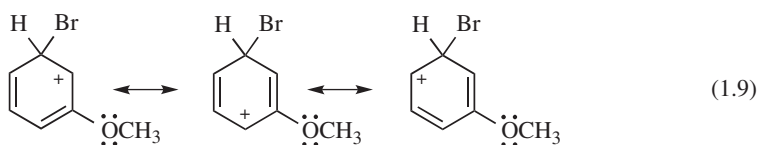
In order to explain the *meta* directing effects of electron-withdrawing groups, it is also useful to consider the position of the cationic charge center in the σ-complex (Scheme 1.16). Nitration of aniline has been accomplished in acidic media to give *meta* nitroaniline as the major product with the *para* isomer as a minor product. Comparing the respective σ-complexes, *para* attack leads to **54** and *meta* attack leads to **56**. Intermediate **54** is destabilized by unfavorable electrostatic interactions, as the ammonium cation is adjacent to a charge center in the σ-complex. Moreover, the ammonium cation—an electron-withdrawing group—is bonded to a ring carbon having a
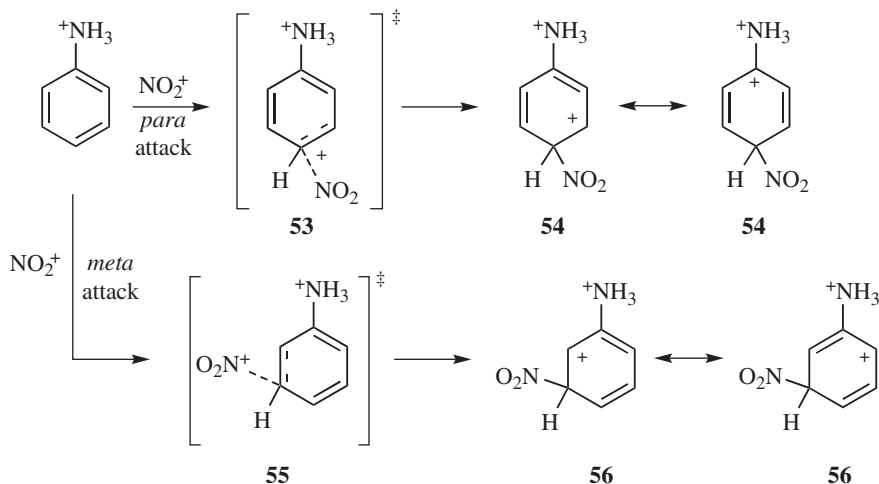
SCHEME 1.16   Transition states (**53** and **55**) and σ-complexes (**54** and **56**) for nitration of the anilinium ion.

large LUMO coefficient. In the case of **56**, the cyclohexadienyl cation system does not generate a positive charge center adjacent to the ammonium cation, and this gives the σ-complex **56** a small measure of stability. The respective transition states (**53** and **55**) are also affected by the destabilizing/stabilizing interactions. This leads to more rapid formation of the *meta* regioisomeric product.

An approach has also examined directing effects from the perspective of the arene starting material. For example, theoretical calculations have been used to estimate the electron densities at the ring carbons of substituted benzenes [46]. Electron-donating groups such as the ethyl, hydroxyl, and amine groups all exhibit greatest π-electron populations at the *ortho* and *para* positions (Scheme 1.17). Conversely, electron-withdrawing groups exhibit the greatest π-electron populations at the *meta* position. These observations are consistent with the general
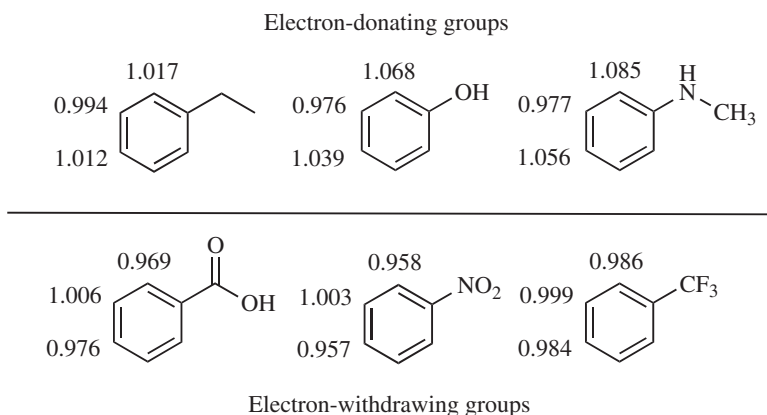
SCHEME 1.17 Calculated (HF/STO-3G level) π-electron populations at ring positions of substituted benzenes.
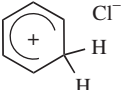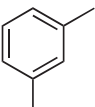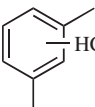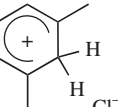
directing effects of substituents, but the electronic structure of the arene starting material may also be more important in cases where an early transition occurs (i.e., with highly reactive electrophiles).

1.5   π-COMPLEX INTERMEDIATES

In the initial stages of an S_EAr reaction, a π-complex often forms between the electrophile and the arene. Similar donor–acceptor complexes have been long known from solution-phase studies. These complexes were observed to be nonconducting, colored solutions formed from mixing an aromatic compound with a π-acceptor, such as HCl, Ag salts, or I_2.

The involvement of π-complexes in S_EAr reactions was first proposed by Dewar to explain relative reaction rates for some conversions [48]. For example, the relative stabilities of arene π-complexes (with HCl) have been shown to correlate with the relative rates of nitration (Table 1.3) [49]. The π-complex for *m*-xylene is estimated to be only about twice as stable as that for benzene. The relative rates of nitration for these two arenes are similar, suggesting a role of the π-complex in the rate-determining step of the nitration. In contrast, chlorination exhibits a markedly greater rate of reaction with *m*-xylene compared to benzene. This suggests that the rate-determining step for chlorination involves a transition state resembling the σ-complex. Thus, the importance of π-complexes varies among different S_EAr reactions.

TABLE 1.3   Relative Stabilities of HCl–Arene π- and σ-Complexes and Relative Rates of Reactions

	Relative stabilities			Relative reaction rates	
	π-complex	σ-complex		Nitration	Chlorination
	0.61	0.09	Benzene	0.51	0.0005
	1.26	26	m-Xylene	0.84	200

FIGURE 1.4   X-ray crystal structures of the [Br_2, C_6H_6] π-complex (**57**) and the [Br_2, $C_6H_5CH_3$] π-complexes (**58** and **59**). From Vasilyev *et al.* [42]—Reproduced with permission from the Royal Society of Chemistry.

The Kochi group has conducted several comprehensive studies of π-complexes in S_EAr reactions [50]. Most notably, this group has obtained accurate structural parameters of several π-complexes from low-temperature X-ray diffraction studies of stable π-complex crystals (Fig. 1.4). When Br_2 and C_6H_6 are sealed in a capillary and cooled to −150°C, the π-complex (**57**) is obtained [42]. This structure confirms the prediction from previous theoretical calculations showing that η^2 hapticity is favored over η^1 or η^6 with the [Br_2, C_6H_6] π-complex [51]. The ring-Br_2 bond distance is found to be less than the van der Waals radii, consistent with a weak donor–acceptor interaction within the π-complex. Analysis also shows there is little Br—Br bond elongation observed and the C—H bonds remain within the ring plane. Upon warming the π-complex crystals to −78°C, HBr is released and bromobenzene is formed quantitatively [42].

A similar π-complex was obtained with Br_2 and toluene at −150°C [42]. Two structures were observed from the crystalline products: a π-complex with Br_2 located near the *ortho* carbon (**58**) and a π-complex with Br_2 located near the *para* carbon (**59**). Both structures show the Br_2 perpendicular to the plane of the ring with η^2 hapticity. Interestingly, electrophiles tend to react at the *ortho* and *para* positions of toluene, and these π-complexes are consistent with the observed regiochemistry. This is

also consistent with calculated electron densities and charges at the ring carbons [23, 51], where the *ortho* and *para* carbons are shown to have the highest degree of electron density. As an activated arene, toluene is considered a better electron donor compared to benzene. This is seen in the respective π-complexes, as Br_2 is located slightly closer to the aromatic ring with toluene compared to benzene.

Another study by Kochi *et al.* examined the chemistry of nitrosation [52]. Several [NO, arene]$^+$ π-complexes were characterized by UV–visible, NMR, and IR spectroscopy. X-ray quality crystals were also obtained at −78°C with mesitylene, hexamethylbenzene, and other arenes. The highly colored nitroso π-complexes were prepared directly from nitrosonium salts (i.e., NO$^+$ SbCl$_6^-$) and the aromatic compound. Structural studies revealed the distance between the ring and the electrophile is roughly 1 Å less than the sum of the van der Waals radii and the N—O bond length is significantly lengthened as a result of strong donor–acceptor interaction.

In the [NO, hexamethylbenzene]$^+$ complex, the N—O bond length is measured as 1.108 Å, increasing from 1.06 Å found in the uncomplexed nitrosonium ion (NO$^+$) [53]. The effects of inner-sphere electron donation are also observed in the infrared N—O stretching frequencies. With the uncomplexed nitrosonium ion, N—O stretch is observed at 2272 cm^{-1}, while the [NO, hexamethylbenzene]$^+$ π-complex exhibits a stretch at 1885 cm^{-1} [52]. For comparison, nitric oxide (·NO) has an estimated bond length of 1.15 Å and an N—O stretch frequency of 1876 cm^{-1}. These data indicate a significant degree of electron transfer in the π-complex; however, the complexes are ESR silent, suggesting the nitric oxide and hexamethylbenzene radical cation are not fully formed species.

The [NO, hexamethylbenzene]$^+$ π-complex has also been studied by UV–Vis and NMR spectroscopy [54]. In ^{13}C NMR spectroscopy, hexamethylbenzene exhibits two resonances at δ, 17.0 and 133.2, while the [NO, hexamethylbenzene]$^+$ π-complex shows signals at δ, 17.8 and 150.8. The significant downfield shift of the ring carbons is consistent with charge transfer in the donor–acceptor complex. The same π-complex exhibits UV–Vis absorption bands at 337 nm (strong) and 500 nm (weak). The low-energy absorption band has been shown to be closely related to the E_{ox}° (electron donor strength) of the arene.

Several π-complexes have also been characterized using theoretical methods [55]. For example, the potential energy surfaces of the nitrosonium ion/benzene and nitronium ion/benzene reactions have been studied using ab initio molecular orbital calculations (Scheme 1.18) [53]. The first minimum for nitrosation is the π-complex (**60**), which is found to be 36 kcal/mol below the starting materials. Calculations indicate there is no barrier to formation of the π-complex. The subsequently formed σ-complex is characterized as a transition state structure (**61**), a stationary point that is located at a saddle point (+23 kcal/mol). Rearomatization of the ring leads to the final *N*-protonated product in a deep potential energy minimum (−42 kcal/mol).
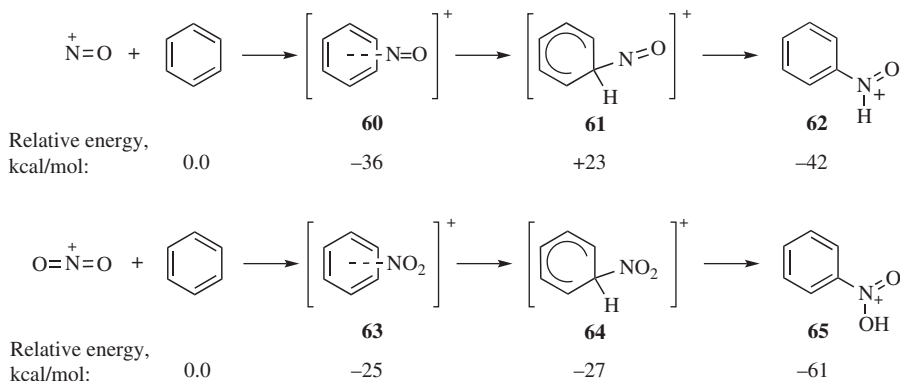
SCHEME 1.18 Molecular-orbital calculated energies for energy minima for the nitrosation and nitration of benzene (CCSD(T)/6-31G** level).
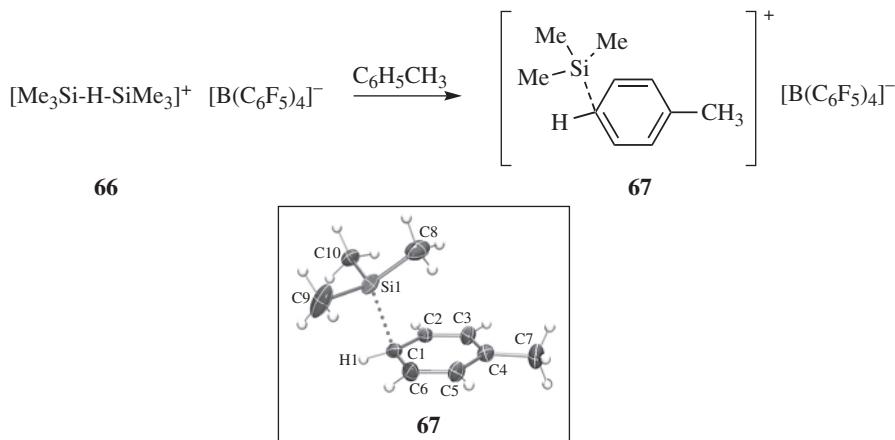
FIGURE 1.5   Preparation of silylium ion complex **67** and its crystal structure. Adapted with permission from Ibad *et al*. [44]. © (2011) American Chemical Society.

In the nitration, both π-complex (**63**) and σ-complex (**64**) are located at energy minima. The π-complex is located 25 kcal/mol below the starting materials, and it is characterized by a significant degree of bending of the nitronium ion and donor–acceptor bonding above the rim of the benzene ring. Despite the obvious transfer of π-electron density toward NO_2^+, there is little distortion of the C—H bond angle. Formation of the σ-complex (**64**, −27 kcal/mol) is followed by rearomatization and product formation. These results confirmed the earlier suggestion by Olah and coworkers [23] that the σ-complex is not necessarily associated with the highest-energy species on the reaction coordinate. As such, the π-complex is expected (in some cases) to strongly influence positional selectivity in S_EAr reactions. Interestingly, the molecular orbital calculated energy profiles of nitrosation and nitration have been shown to coincide with a theoretical treatment using Marcus–Hush theory [53].

Although not commonly involved in S_EAr reactions, there has been extensive work related to π-complexes and σ-complexes involving silylium ions (R_3Si^+) and arene donors. Several crystal structures have been obtained for these donor–acceptor complexes, beginning with Lambert's $[Et_3Si]^+$ $[B(C_6F_5)_4]^-$· $C_6H_5CH_3$ isolated in 1993 [56]. A recent study examined several complexes of trimethylsilylium cations with arenes [44], some of which were isolated as crystalline solids (Fig. 1.5). For example, a relatively stable silylium ion donor–acceptor complex (**67**) was prepared from the hydride-bridged silane adduct cation (**66**). Complex **67** is found to be stable to 80°C, but at higher temperatures, the crystalline material decomposes. A major product of the decomposition is Me_3SiF, suggesting fluoride abstraction from the borate anion is favored over the S_EAr reaction. Similar crystalline solids were isolated from benzene, ethylbenzene, *n*-propyl and *i*-propylbenzene, xylenes, and trimethylbenzenes. Each was characterized by Raman and IR spectroscopy as well as X-ray crystallography.

Analysis of the structural parameters reveals some interesting trends. As can be seen in structure **67**, the geometry around silicon atom deviates considerably from the planar structure expected from the uncomplexed silylium ion. The sum of the C—Si—C bond angles in **67** is found to be about 341°, compared to 360° for the silylium cation (Me_3Si^+) and 328.4° for a tetrahedral structure. The coordination is also clearly a η^1-type interaction. This raises an obvious question: is it a π-complex or a σ-complex? There is no definitive point at which a structure becomes a σ-complex. As noted by Sidorkin, the ideal π-complex has a 90° angle between the ring and the electrophilic center [57], while the ideal σ-complex has a bonding angle of about 125° (Scheme 1.19). A continuum of structures is also suggested, which includes a mixed π/σ-type complex. In complex **67**, the α-bond angle is 102.4°. The measured C_1—Si bond length in **67** is 2.135 Å. This is longer than the sum of the C–Si covalent radii (1.91 Å) but much shorter than the sum of the van der Waals radii (3.8 Å). These data suggest a structure of mixed π/σ type for the $[Me_3Si]^+$ $[B(C_6F_5)_4]^-$ ·$C_6H_5CH_3$ complex (**67**).
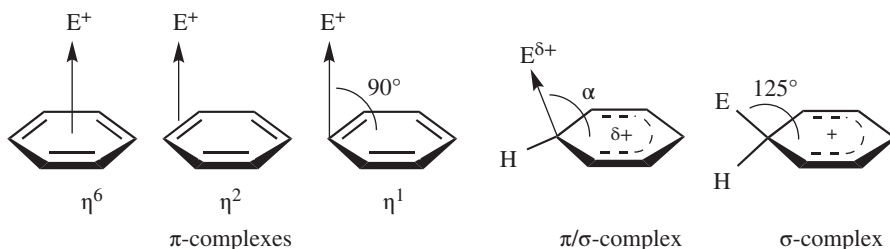
SCHEME 1.19   Structure types for intermediates in the S_EAr reaction.
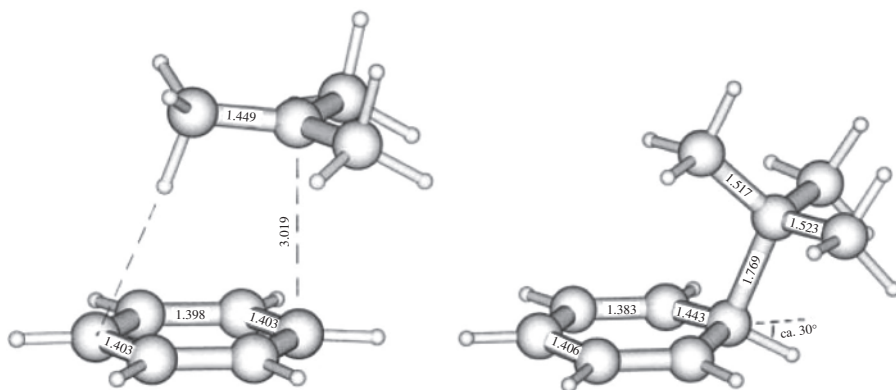
FIGURE 1.6   MP2/6-31+G**(fc) calculated π-complex and σ-complex for the alkylation of benzene. From Heidrich [45]—Reproduced with permission from WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Notably, the progression from a π-complex to a π/σ-complex to a σ-complex involves an increasing amount of charge transfer from the arene to the electrophile. A fully formed σ-complex thus has a cyclohexadienyl cation structure. Based on the data from crystallographic studies, the extent of σ-complex formation depends on the nature of both electrophile and arene. The silylium cation studies showed that increasing the nucleophilic character of the arene leads to increasing amounts of σ-complex character. This was evident from measurement of the α-bond angles and C_1—Si bond lengths.

Similar trends were observed in recent computational study that examined the potential energy surface for the Friedel–Crafts alkylation of benzene [45]. The MP2/6-31+G**(fc) calculations studied the reactions of benzene with the methyl cation, the isopropyl cation, and the *tert*-butyl cation. A stable π-complex was only found in the case of the *tert*-butyl cation reacting with benzene (Fig. 1.6). Both the η^1 and η^2 hapticity π-complex structures were found to be comparable in energy and about 10 kcal/mol more stable than the gas-phase starting materials. The planar structure of the *tert*-butyl cation suggests only a minimal amount of electron density has been transferred from benzene. The stable σ-complex was also located, and it was estimated to be approximately 4 kcal/mol more stable than the π-complex. Interestingly, the π-complexes could not be located for either the reaction of isopropyl cation or the methyl cation, but the reaction proceeds directly to the σ-complex. This reflects an increasing electron demand at the 2° isopropyl cation and methyl cation centers. It is also a further indication that the π-complex intermediate may not be involved, or have a much diminished lifetime, in some S_EAr reactions.

Gas-phase ion chemistry has also been used as an interesting approach in the study of π- and σ-complexes. For example, an isotopically labeled sample of *sec*-butylbenzene was subjected to chemical ionization with the CD_5^+ ion and studied by collisionally activated dissociation and metastable

dissociations using tandem mass spectroscopy (MS/MS) [58]. The chemical ionization with methane is thought to be a clean method of preparing gas-phase arenium ions (Scheme 1.20). Examination of the fragments suggests that isomerization of alkyl group takes place in the gas phase. This occurs through
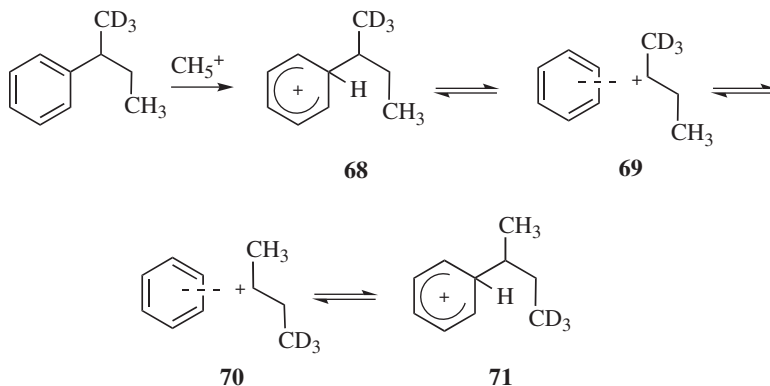
SCHEME 1.20   Gas-phase isomerization via π-complex.

an equilibrium between the initially formed σ-complex (**68**) and a subsequently formed π-complex (**69**). 1,2-Hydride shift gives the isomeric π-complex (**70**), and this leads to the σ-complex (**71**). The study also found evidence that larger alkyl groups had a greater probability of isomerizing through the π-complex route, likely reflecting the increasing stability of the alkyl carbocation species.

1.6   σ-COMPLEX OR WHELAND INTERMEDIATES

As described earlier, the S_EAr reaction mechanism generally involves the formation of a σ-complex intermediate. This species is formally a cyclohexadienyl cation, and it has also been called the Wheland intermediate, Pfeiffer–Wizinger complex, arenium ion, benzonium ion, and benzenium ion. Since it was first proposed as an intermediate in Friedel–Crafts reactions, there has been a considerable amount of evidence for its involvement in the reactions. As described previously, the involvement of the σ-complex provides a good basis for the understanding of some activating and directing effects in S_EAr reactions.

Early studies of acid–base chemistry suggested a role of cyclohexadienyl cations in S_EAr reactions. While arenes and HCl provide nonconducting solution, use of the Brønsted–Lewis acid conjugate HCl–$AlCl_3$ leads to colored solutions that conduct electric current [59]. This was interpreted as formation of the cyclohexadienyl cation and $AlCl_4^-$ ion pair, as the HCl–$AlCl_3$ is an exceptionally strong proton donor. Thus, the proton serves as the electrophile to generate the cyclohexadienyl cation. Brown and associates conducted a number of studies demonstrating a linear relationship between σ-complex stability (determined by protonation equilibria) and the rates of a variety of S_EAr reactions [21, 60]. These results are considered strong evidence for the σ-complex as the key intermediate in these reactions.

The final step in the S_EAr reaction mechanism involves deprotonation of the σ-complex intermediate to regenerate the aromatic π-system, and this is expected to be a very fast step. Since the C—H bond is not being broken in a rate-determining step, there is usually little or no detectable kinetic isotope effect (KIE) for S_EAr reactions [61]. Thus, studies of KIEs are also consistent with the involvement of the σ-complex. Larger KIEs have been observed in conversions involving weak electrophiles, such as nitrosations and diazonium coupling reactions [61c].

Several examples have been reported of S_EAr reactions providing different products under thermodynamic and kinetic control. For example, sulfonation of naphthalene at 80°C gives predominantly the α-isomer (the kinetic product), while reaction at an elevated temperature provides the β-isomer (the

more stable thermodynamic product) as the major product (Scheme 1.21) [62, 63]. These results may be understood by considering the stabilities of the respective σ-complex intermediates. The σ-complex-α is a more stable intermediate than σ-complex-β, as it benefits from favorable resonance stabilization. This
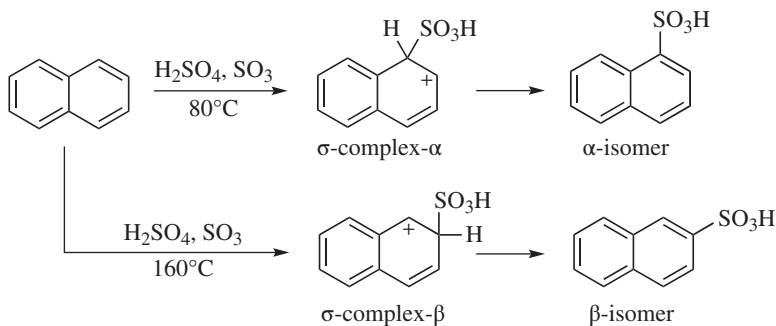
SCHEME 1.21   Sulfonation of naphthalene.

leads to formation of the α-isomer under kinetically controlled conditions. However, the α-isomer itself is less stable than the β-isomer, due to steric effects involving the sulfonic acid group and the peri position hydrogen. Under thermodynamic control, the reversible S_EAr reaction gives the more stable β-isomer.

Numerous studies have sought to directly observe σ-complexes using spectroscopic methods. This has not been an easy task, as rapid deprotonation of the σ-complex often limits the lifetime of this reactive intermediate. Under normal S_EAr reaction conditions, even rapid spectroscopic methods—such as time-resolved UV–visible spectroscopy—generally do not detect the σ-complexes. A common method of stabilizing and observing the σ-complex species has been through the use of hexamethylbenzene (and other hexa-substituted benzenes). This arene produces a σ-complex that cannot undergo deprotonation to give a stable aromatic substitution product. Doering and Saunders first used this method in 1958 to characterize the methylation of σ-complex intermediate using ^{1}H NMR (Eq. 1.10) [64]. As expected, the resulting σ-complex (**72**) gives four ^{1}H signals in a 3:6:6:6 ratio.

(1.10)

72
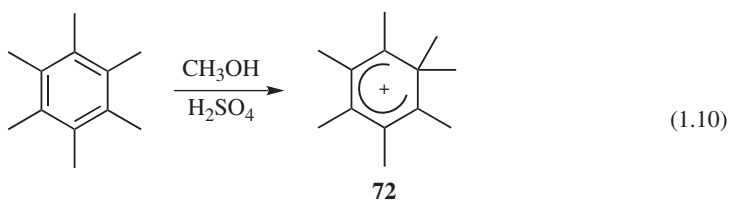
Subsequent studies have provided detailed structural information related to these σ-complexes [50, 65], including species from halogenation, nitration, sulfonation, acylation, alkylation, and other methods (Table 1.4). Importantly, the NMR characterizations of these structures showed clear differences from the related π-complexes. For example, nitrosonium cation (NO$^+$) salts provide the π-complex with hexamethylbenzene giving rise to a ^{13}C spectrum with two signals (*vide supra*) [50]. Nitronium cation (NO$_2$$^+$) salts provide the stable σ-complex (**74**), giving a ^{13}C spectrum with eight signals (four ring carbons and four methyl carbons). The ring carbons are observed at δ, 98.4 (C_1), 141.8 ($C_{3,5}$), 181.5 ($C_{2,6}$), and 204.7 (C_4) [50]. The downfield signals at the $C_{2,6}$ and C_4 are consistent with the cyclohexadienyl cation structure.

Several σ-complex structures have also been studied using X-ray crystallography. The crystalline adducts **73**, **75**, **76**, **81**, and **83** from hexamethylbenzene have all been characterized by X-ray diffraction [65f–j]. In complex **75**, the C—Cl bond distance is measured to be 1.81 Å, a value typical

TABLE 1.4　Observed σ-Complexes from Hexamethylbenzene

73[a,b,c]　　　75[a,b,c]　　　77[a]　　　79[c]　　　81[b]　　　83[b]

74[a,c]　　　76[a,b,c]　　　78[c] R = Me, Ph　　　80[c]　　　82[a,d] X = S, Se
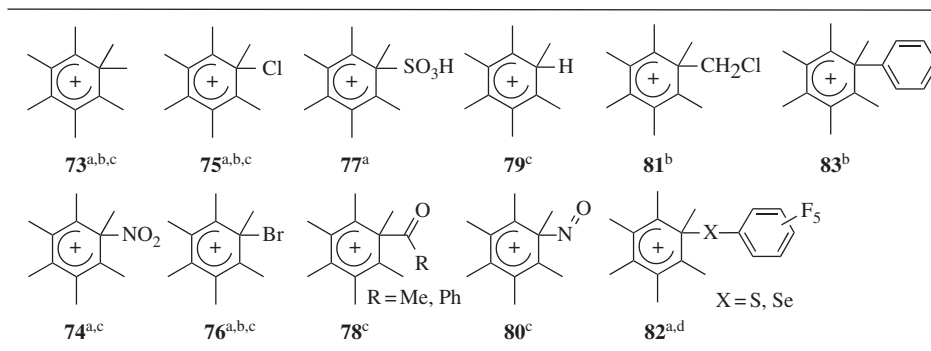
(a) ^{1}H and ^{13}C NMR　(b) X-ray crystal structure　(c) UV–vis　(d) ^{19}F NMR
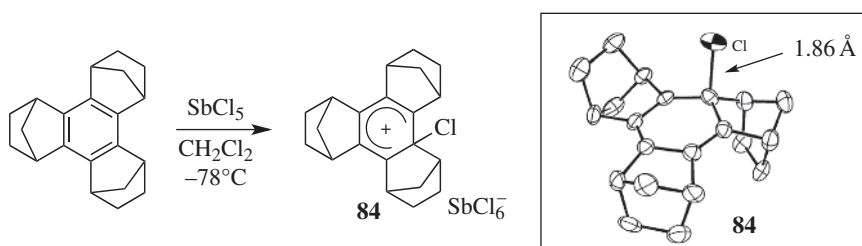
FIGURE 1.7　Preparation of σ-complex **84**. Adapted with permission from Rathore *et al.* [47]. © (1994) American Chemical Society.

for a C—Cl single bond [65j]. The C_2—C_1—Cl bond is about 106°, which is near the expected value for an sp^3 carbon center. Kochi and coworkers have used the sterically crowded aromatic donor to prepare the relatively stable σ-complex **84** from electrophilic chlorination (Fig. 1.7) [47]. Analysis of the crystal structure reveals the C—Cl bond distance to be 1.86 Å. Reed *et al.* have also used low-coordinating anion chemistry to prepare several σ-complexes as protonated arenes [66], for example, obtaining X-ray crystal structures of protonated *m*-xylene, mesitylene, pentamethylbenzene, and hexamethylbenzene. Both steric and electronic stabilizing effects may be used to stabilize σ-complexes, as the crystalline salt **85** was isolated from 1,3,5-pyrrolidinobenzene (Scheme 1.22) [67]. The electron-donating properties of the pyrrolidine nitrogens are clearly apparent by shortening of the C—N bonds to the cyclohexadienyl ring upon formation of the σ-complex.

　　Another valuable method of studying the σ-complexes involves the use of superacidic and stable ion conditions pioneered by Olah and colleagues [68]. These solutions are nonnucleophilic and

85
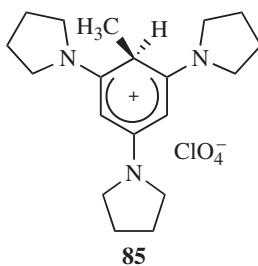
SCHEME 1.22　Stable σ-complex **85**.

nonbasic, enabling cationic species to be long-lived (at low temperature) and amenable for study. For example, this chemistry has been used to generate the parent σ-complex, the benzenium ion (**86**) from protonation of benzene in solutions of $HF-SbF_5$, FSO_3H-SbF_5, and carborane superacid (Scheme 1.23) [68]. Many other aromatic hydrocarbons have been studied using this technique, leading to stable σ-complexes such as **87** and **88** [68, 69]. Although the cationic species such as **86–88** possess very high acidity, the superacidic solution prevents deprotonation equilibria.
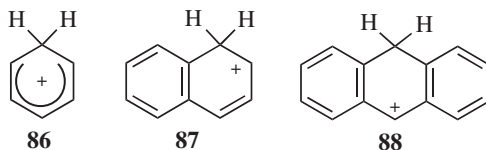
SCHEME 1.23   Protonated aromatic hydrocarbons.

Conventional Friedel–Crafts σ-complexes have likewise been generated under stable ion conditions. Olah and Kuhn generated alkylation and formylation of σ-complexes [70], both isolated as solids with well-defined ionic character (conductance studies), and heating of the solids produced the S_EAr products (Scheme 1.24). A subsequent NMR study involving the low-temperature ethylation of 1,3,5-triethylbenzene also revealed the presence of σ-complex intermediates [65a]; however, isomeric species were formed rapidly by hydride/alkyl shifts. Indeed, this aspect of cyclohexadienyl cation chemistry has made the study of σ-complexes difficult, as the barrier for isomerization is often quite low.
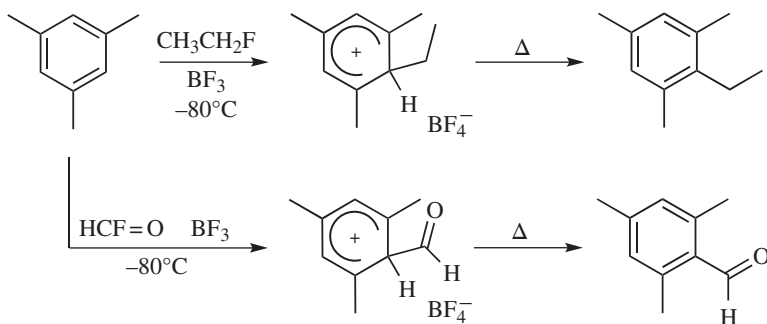
SCHEME 1.24   Intermediate σ-complexes and the conversion to Friedel–Crafts products.

Likewise, the isomerization of the σ-complex **83** was observed in solution phase [71]. While the crystalline complex **83** is stable to 70°C, dissolving the salt in solvent leads to rapid isomerization at 25°C (Eq. 1.11). Moreover, the rates of isomerization have been shown to vary with differing counterions, such as $AlCl_4^-$ and BPh_4^-. Regarding σ-complex isomerization, it has also been shown that an

(1.11)

Al_2O_3 surface can accelerate alkyl group migrations in some σ-complexes [72]. The 1,2-alkyl shifts are also known to retain their configuration at the migrating carbon [73], in accordance with Woodward–Hoffmann rules for the sigmatropic rearrangement.

The isomerization of σ-complexes does have significant commercial importance. For example, this chemistry is used to prepare isomeric xylenes—important feedstock chemicals for aromatic dicarboxylic acids [74]. The proportion of xylene isomers depends on the conditions used, as strongly acidic conditions (i.e., HF—BF₃) are employed to favor the *meta* isomer and shape-selective zeolites are used to favor the *para* isomer (the isomer with the smallest cross-sectional area). The thermodynamically most stable σ-complex for the protonated xylenes is the arenium ion **89**, which leads to the *meta* xylene product (Scheme 1.25).

SCHEME 1.25   Isomerization of *p*-xylene to *m*-xylene.

The chemistry of the σ-complex is also important in transalkylations and related reactions. For example, monoalkylbenzenes undergo disproportionation reactions by transalkylation, which in the case of cumene provides diisopropylbenzene and benzene (Eq. 1.12) [75]. In this case, cumene serves as a nucleophile, while the isopropyl cation is the likely electrophile. Shape-selective zeolite catalysts

(1.12)

may be used to preferentially give the *para* isomer [75b]. The tendency for groups to undergo transalkylation follows the well-known trends of carbocation stability (isopropyl > ethyl > methyl) [76]. Transacylation was demonstrated with acetylmesitylene [77], where the acetyl cation is transferred from the incipient σ-complex (**90**) to the arene nucleophile (Eq. 1.13). Other examples of deformylation, desilation, dealkylation, and similar reactions of the σ-complex intermediates are known [78].

(1.13)

Several examples of dearylation reactions have also been reported [79]. These are thought to proceed through *ipso* protonation of aryl groups [80], with formation of a σ-complex (**91**) and

cleavage of the aryl group (Scheme 1.26). This chemistry has been utilized as a general route to aza-polycyclic aromatic compounds [81]. A similar reaction pathway has been proposed for the acid-promoted depolymerization of coals [82].

SCHEME 1.26 Dearylation through *ipso* protonation.

1.7 SUMMARY AND OUTLOOK

Mechanistic considerations of the S_EAr reaction began shortly after Friedel and Crafts reported their interesting conversions. These studies have continued for nearly 140 years, as chemists investigated the mechanisms of these valuable reactions. The studies have involved—and in some cases contributed to the development of—major areas of organic chemistry including the theory of aromaticity, the role of reactive ionic intermediates, the concept of resonance interactions, linear free energy relationships, the transition state theory, and reaction kinetics. The S_EAr reaction mechanism has been studied by most spectroscopic methods, and recently, intermediates have been examined by X-ray crystallography. Theoretical approaches have also provided many useful insights. With these considerations, the S_EAr may be the most thoroughly studied reaction mechanism in organic chemistry.

Despite the extensive mechanistic studies, there continues to be the need for more work. Many questions remain to be answered. For example, how do asymmetric environments affect the S_EAr reaction? What factors provide the highest regioselectivity in S_EAr reaction? When does the π-complex form and how does it affect the S_EAr reaction? How does σ-complex stability affect the outcome of these synthetic conversions? Can electrophiles be generated that show unusual reactivities? How do environmentally friendly catalysts affect the S_EAr reaction mechanism? These and other questions will certainly be addressed by research chemists in the decades ahead.

ABBREVIATIONS

Å   Ångströms
B   Base
E   Electrophilicity parameter
E+   Electrophile

EDG	Electron-donating group
ESR	Electron spin resonance
EWG	Electron-withdrawing group
IR	Infrared
k	Rate constant
KIE	Kinetic isotope effect
k_T/k_B	Relative rates of reaction with toluene (k_T) and benzene (k_B)
LUMO	Lowest unoccupied molecular orbital
MS	Mass spectroscopy
N	Nucleophilicity parameter
NMR	Nuclear magnetic resonance
OMe	Methoxy
Ph	Phenyl
S_EAr	Electrophilic aromatic substitution
UV	Ultraviolet

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