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Aromatic Substitution

- 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.

Electrophilic Aromatic Substitution Reactions

- A substitution of some other group for hydrogen that is of interest.
- A substitution of silicon and mercury can be replaced by electrophile

Category of electrophiles

- 1-Those are sufficiently reactive to attack almost all aromatic compounds, even those having strongly EWG substituents.
- 2-Those react readily with benzene and derivatives having ERG substituents but are not generally reactive toward aromatic rings with EWG substituents.
- 3-Those are reactive only toward aromatic compounds that are much more reactive than benzene.

complexation of the electrophile

- 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 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.

Scheme 9.1. Electrophiles Active in Aromatic Substitution

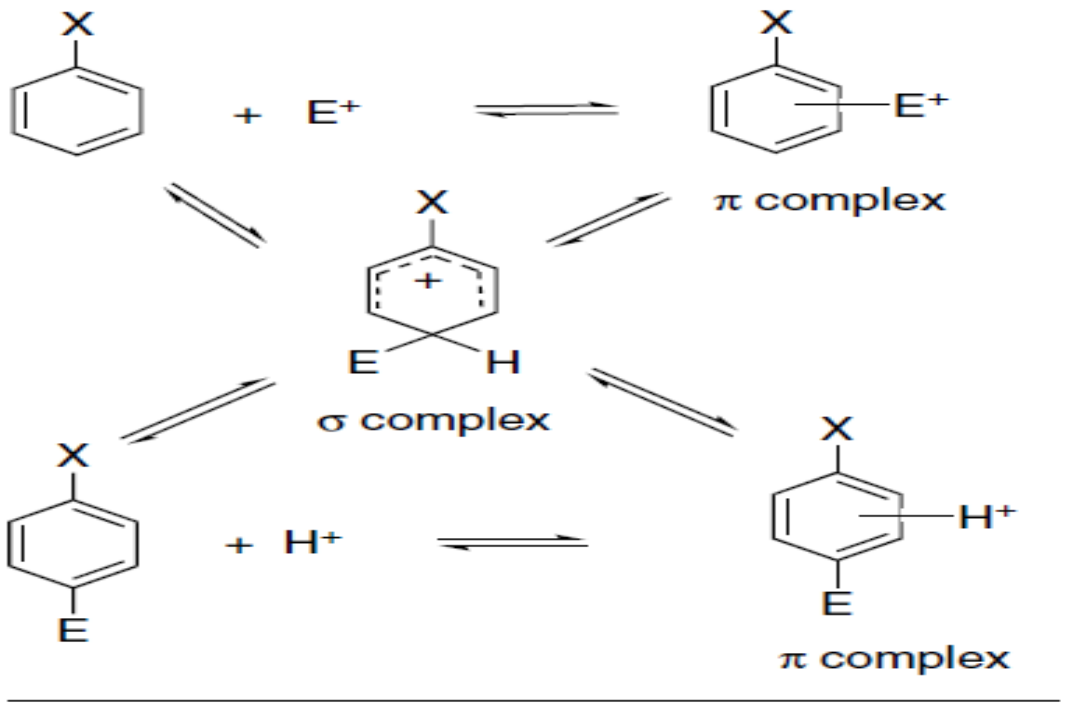
	Electrophile	Typical means of generation
A. Electrophiles capable of substituting both activated and deactivated aromatic rings		
1[a]	$O{=}N^{+}{=}O$	$2\,H_2SO_4 + HNO_3 \rightleftharpoons NO_2^{+} + 2\,HSO_4^{-} + H_3O^{+}$
2[b]	Br_2 or $Br_2{-}MX_n$	$Br_2 + MX_n \rightleftharpoons Br_2{-}MX_n$
3[b]	$BrO^{+}H_2$	$BrOH + H_3O^{+} \rightleftharpoons BrO^{+}H_2$
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[i]	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]	$ArN^+{\equiv}N$	$ArNH_2 + HONO + H^+ \rightleftharpoons ArN^+{\equiv}N + 2H_2O$

Scheme 9.2. Generalized Mechanism for Electrophilic Aromatic Substitution



- 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.

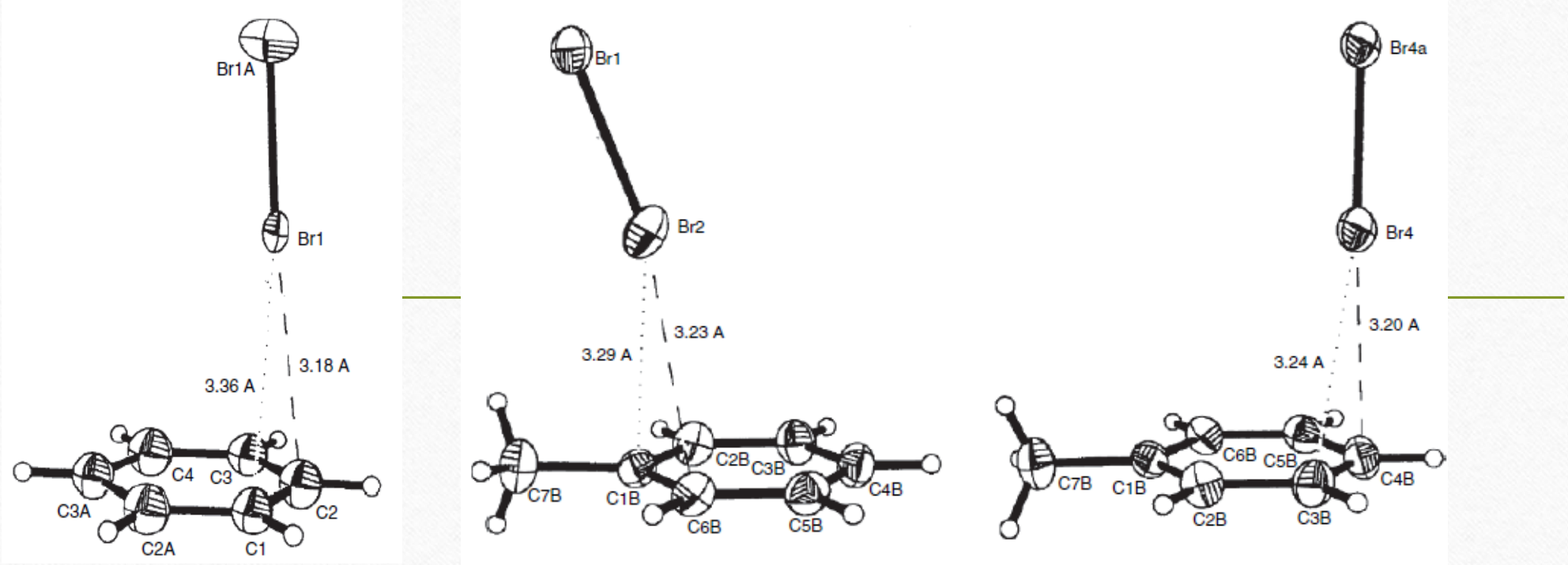


Fig. 9.1. Structures of benzene-Br_2 (top) and toluene-Br_2 (bottom) complexes. Reproduced from *Chem. Commun*, 909 (2001), by permission of the Royal Society of Chemistry.

- For toluene, there are two complexes with the Br_2 being associated with the ortho and para carbons. This is significant because these are also the preferred sites for substituation, and the structures indicate that an aspect of position selectivity is present at the complex stage.
- These structures are shown in Figure 9.1. In order for a substitution to occur, a "π complex" must be formed. The intermediate is a cyclohexadienylium cation.

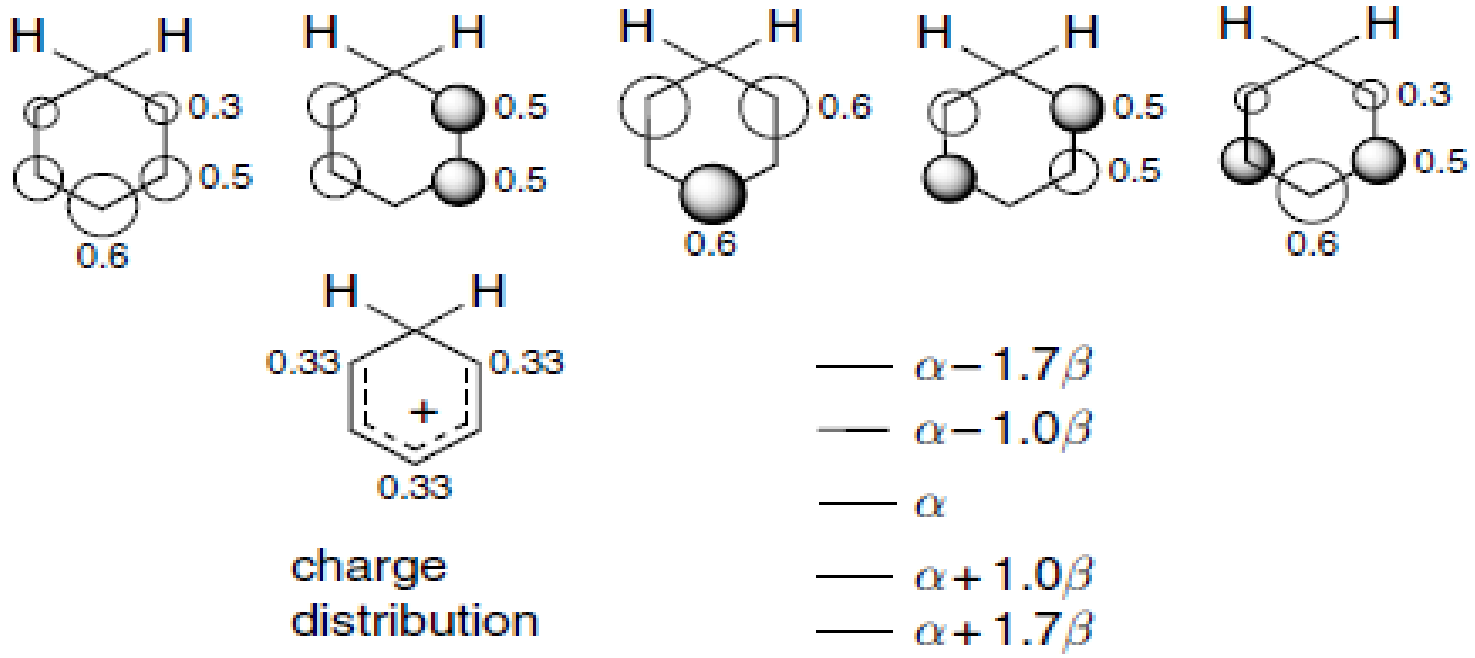
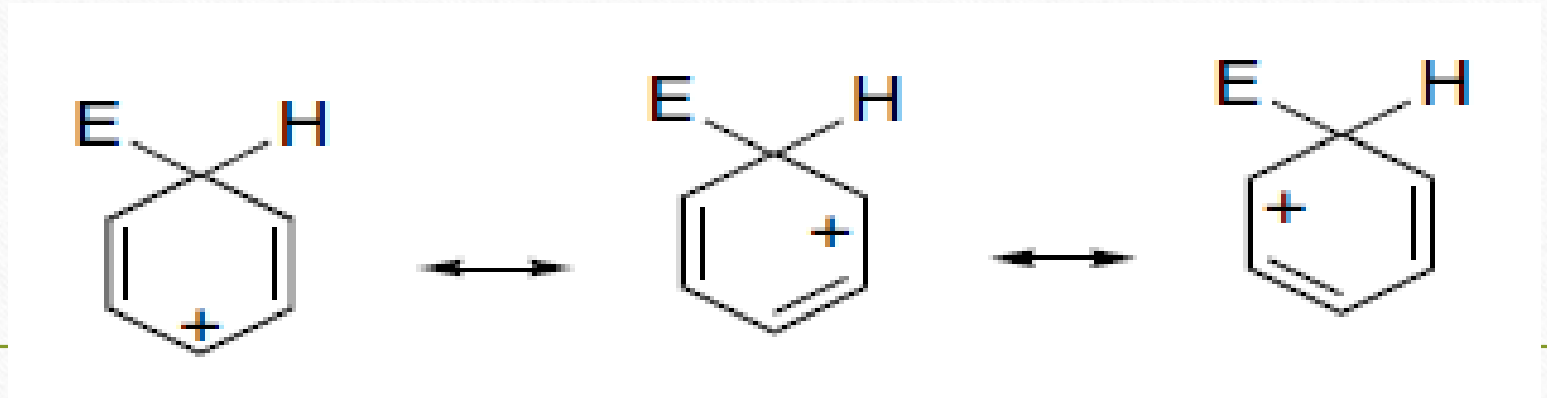
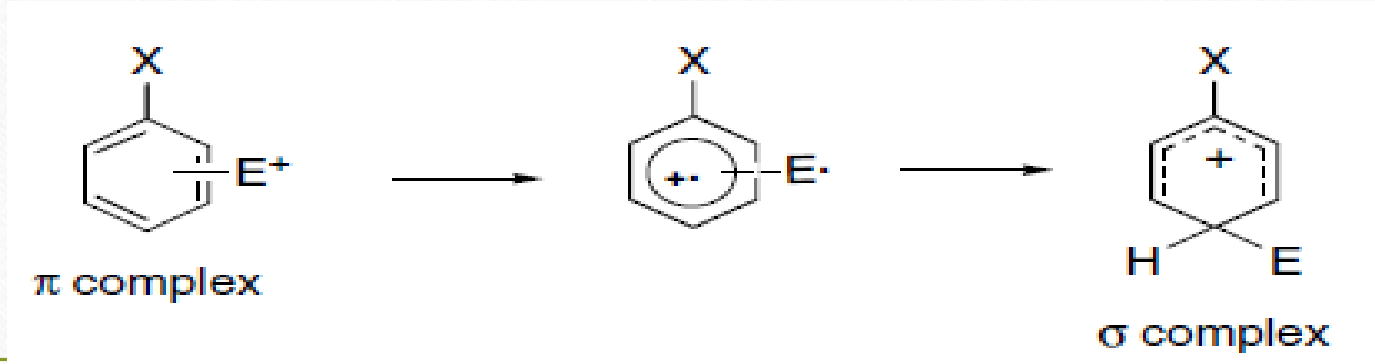


Fig. 9.2. π Molecular orbitals and energy levels for the cyclohexadienylium ion.

- 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.

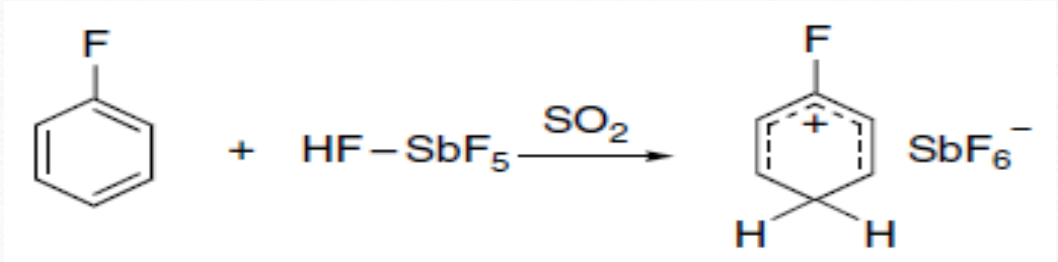


- These electronic features of the π-complex intermediate are also shown by resonance structures.
- In particular, the question arises as to whether an electron transfer occurs to yield a discrete cation radical–radical pair.
- This mechanism implies that a considerable change in the structure of the electrophile occurs prior to σ-bond formation. Moreover, this mechanism implies that the cation radical–radical pair might play a key role in determining the isomeric (ortho, meta, para) product composition.
- Formation of the σ complex can be reversible. For most electrophiles, it is easier to eliminate the proton, in which case the formation of the σ complex is essentially irreversible.



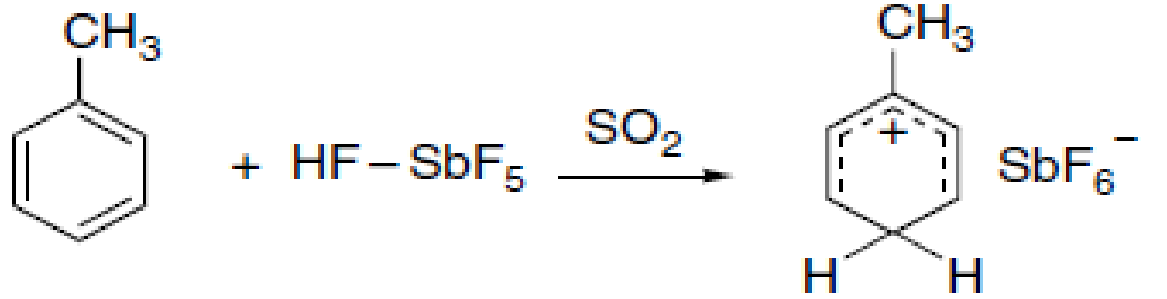
- The electrophiles in group A of Scheme 9.1 are the least likely to be reversible, whereas those in group C are most likely to undergo reversible σ-complex formation. **Formation of the σ-complex is usually, but not always, the rate-determining step in EAS.**

- 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.

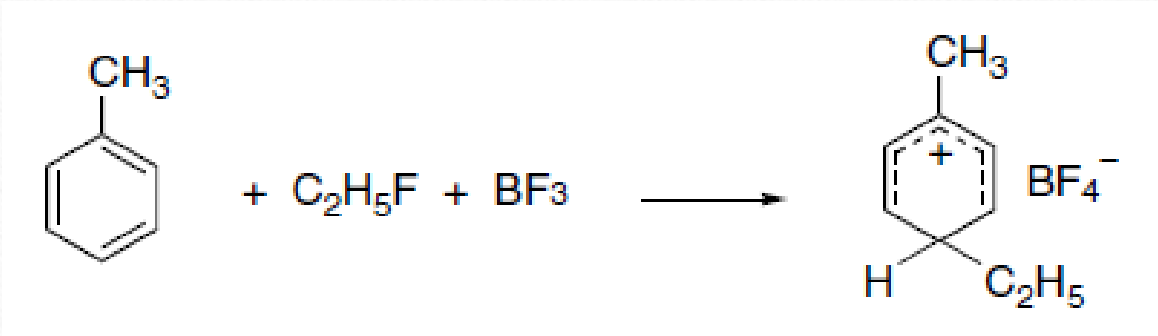


There are some electrophilic aromatic substitution reactions that show k_H/k_D values between 1 and 2 and there are a few others that are in the range indicating a primary isotope effect. The existence of these isotope effects is compatible with the general mechanism if the proton removal is rate limiting (or partially rate limiting).

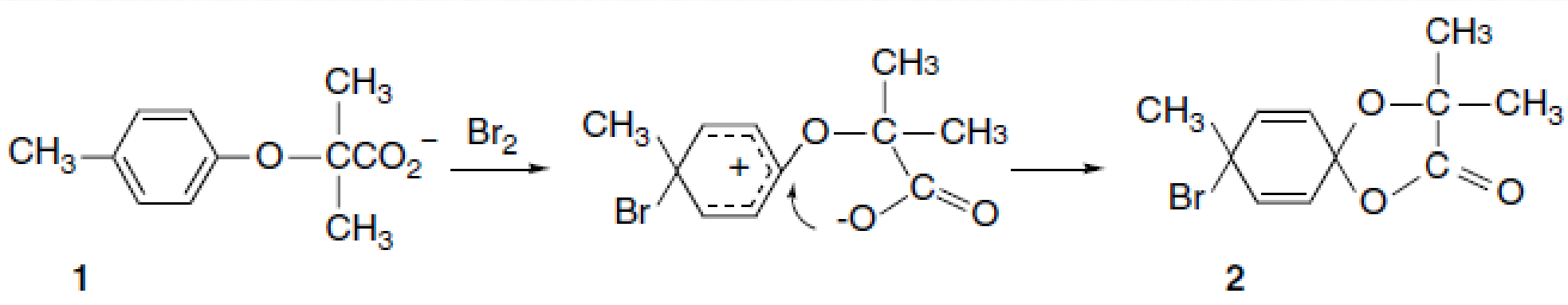
Many of the modest kinetic isotope effects ($k_H/k_D \sim 1.2 – 2.0$) have been interpreted in terms of comparable rates for formation and deprotonation of the σ-complex intermediate.



Substituted cyclohexadienylium ions can be observed by NMR under stable ion conditions. They are formed by protonation of the aromatic reactant.

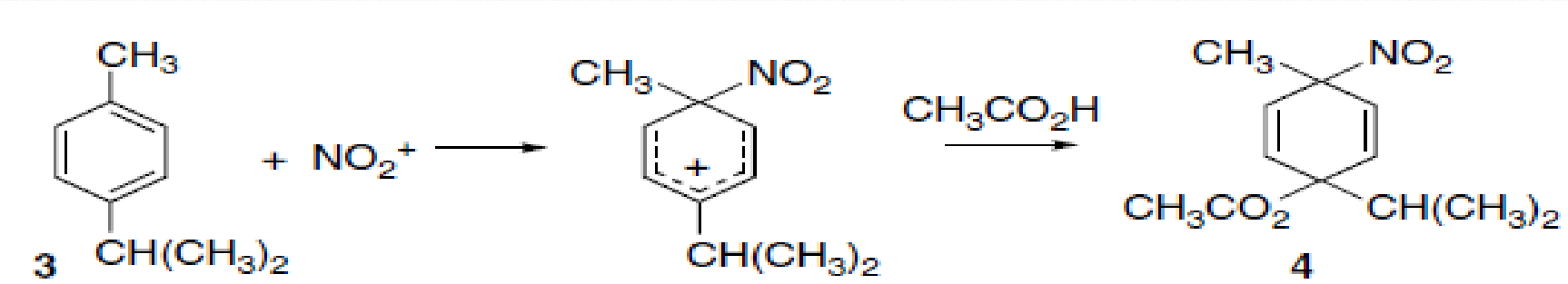


Cations formed by alkylation of benzene derivatives have also been characterized.



1 2

The existence of σ-complex intermediates can be trapped by nucleophiles. This product results from intramolecular nucleophilic capture of the σ complex by the carboxylate group.



3 4

An intramolecular nucleophilic capture of cyclohexadienylium intermediates in nitration of alkylated benzenes in acetic acid at 0 °C leads to formation of **4** with acetate serving as the nucleophile.

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 deproto-nation is then blocked. Attack at a substituted position is called ipso attack.

Addition 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.

Structure-Reactivity Relationships for Substituted Benzenes

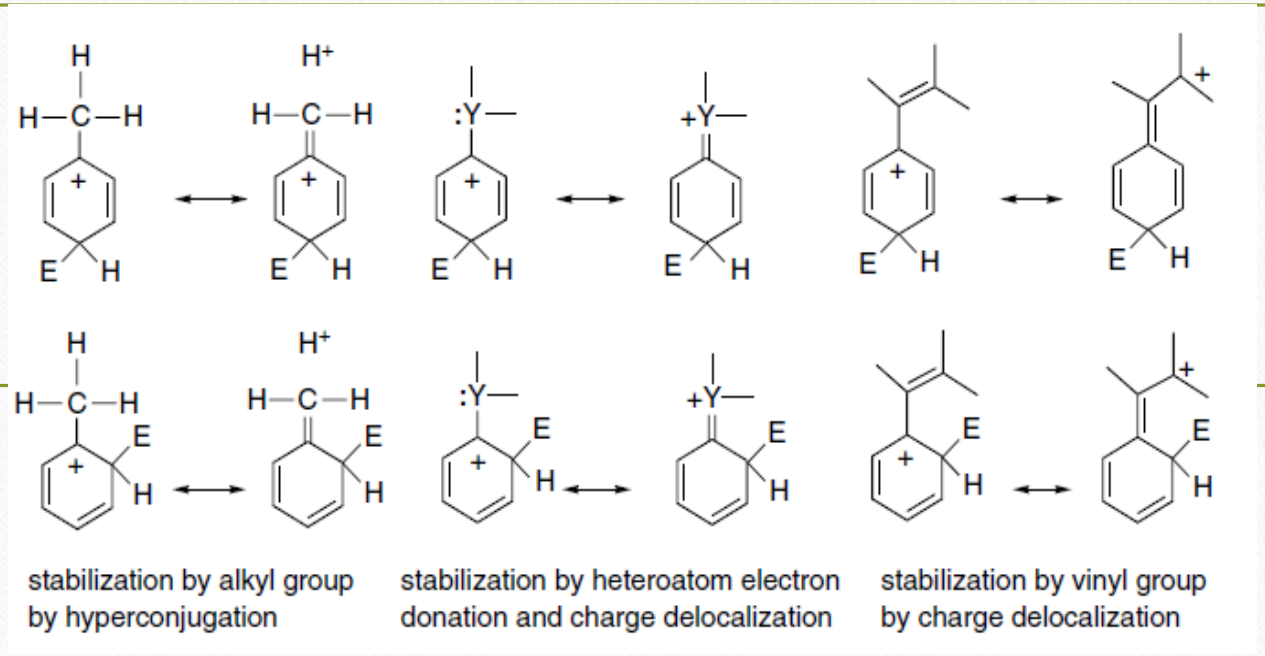
Substituent Effects on Reactivity

Activating and ortho-para directing groups:

Saturated and unsaturated hydrocarbon groups and substituents having an unshared electron pair on the atom adjacent to the ring are activating groups.

As a result the TSs for *ortho* and *para* substitution are favored over that for *meta* substitution.

Hammett equations usually correlate best with the σ +-substituent constants



Halogens are deactivating but nevertheless ortho-para directing.

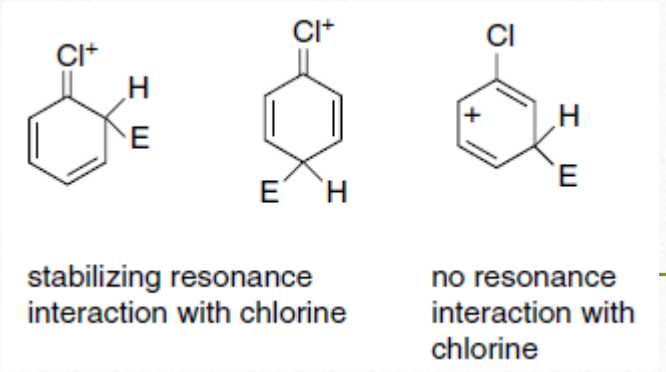
The TS should closely resemble the cyclohexadienylium intermediate.

For highly reactive electrophiles, where the Ea is low, it may be more appropriate to regard the TS as closely resembling the reactant aromatic.

- Let us examine the MO description of substituent effects from both these perspectives. The TS resembles the intermediate, a substituted cyclohexadienylium ion.

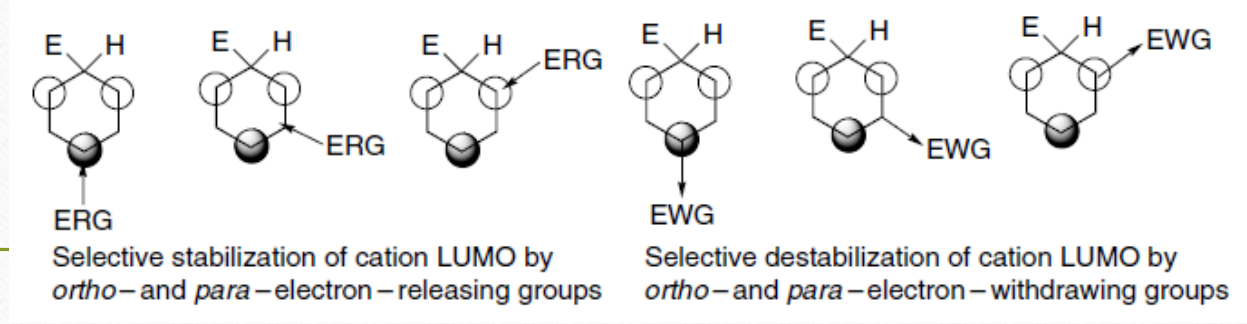
- The electrophile has localized one pair of electrons to form the new σ bond. The Hückel orbitals are the same as for the pentadienyl system, as shown in Figure 9.2. A substituent can stabilize the cation by electron donation.

- 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.



stabilizing resonance interaction with chlorine

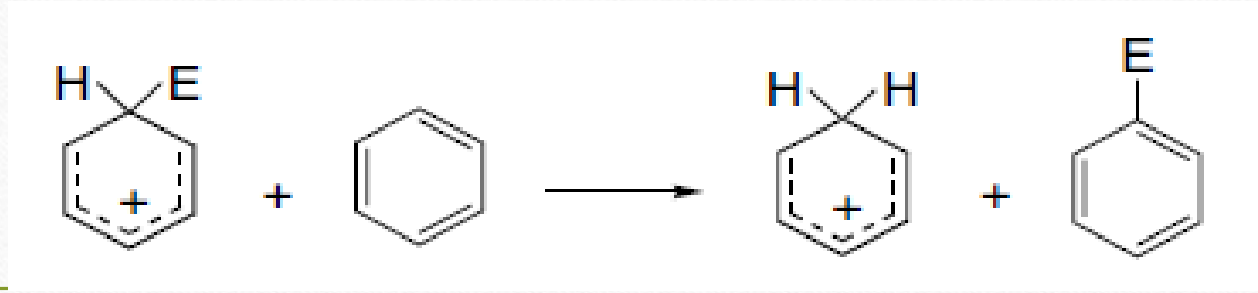
no resonance interaction with chlorine



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

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

- 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.
- 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 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.

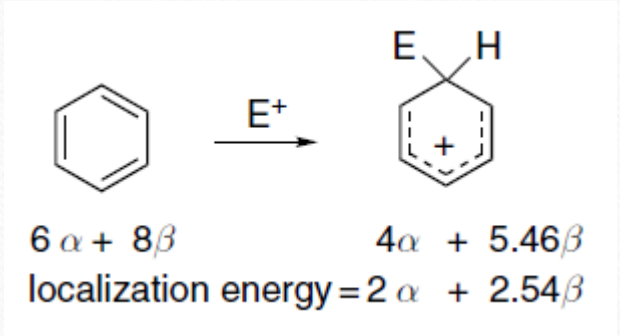
The effect of substituents was probed by MO calculations at the HF/STO-3G level. An isodesmic reaction corresponding to transfer of a proton from a substituted σ complex to an unsubstituted one indicates the stabilizing or destabilizing effect of the substituent. The results are given in Table 9.1.

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,

- Note that the numerical results parallel the conclusions from qualitative application of resonance 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 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.*
- 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.

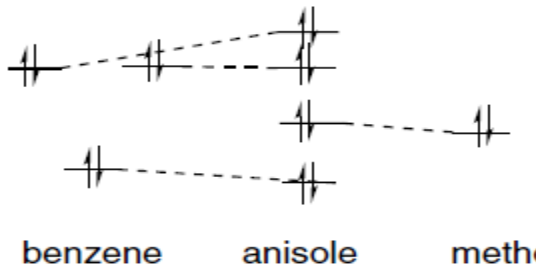


Fig. 9.3. MO diagram for anisole (methoxybenzene) showing effects of methoxy substituent.

- **With a highly reactive electrophile**, where we expect an early TS, *the charge density distribution and coefficients of the HOMO characteristic of the aromatic reactant are major factors governing the orientation of electrophilic attack.*
- The TS should resemble the reactants and according to FMO, the electrophile will attack the position with the largest coefficient of the HOMO.
- In anisole as 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.
- 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.

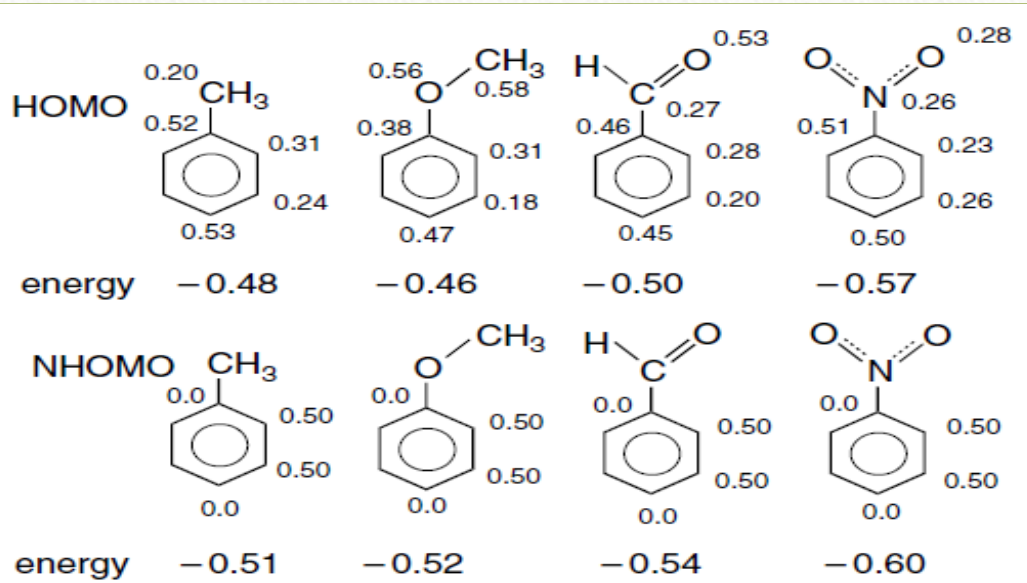


Fig. 9.4. Orbital coefficients for HOMO and next highest π MO for some substituted benzenes (from CNDO/2 calculations). The individual *ortho* and *meta* coefficients have been averaged in the case of the unsymmetrical methoxy and formyl substituents. Orbital energies are in atomic units.

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. 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.

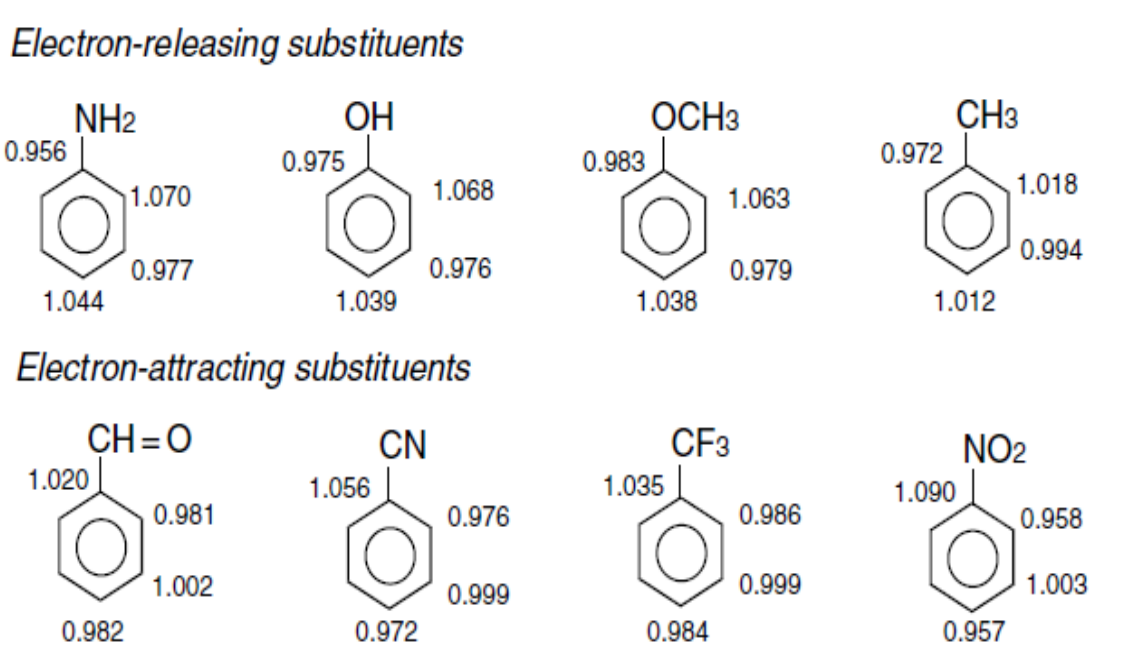


Fig. 9.5. Total π-electron density for some substituted benzenes. From HF/STO-3G calculations.

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 erroneously predicts para substitution.

Aromatic rings with EWG substituents are relatively unreactive and therefore will not have early TSs.

Figure 9.6 shows a correlation between the energy of interaction and the partial rate factors.

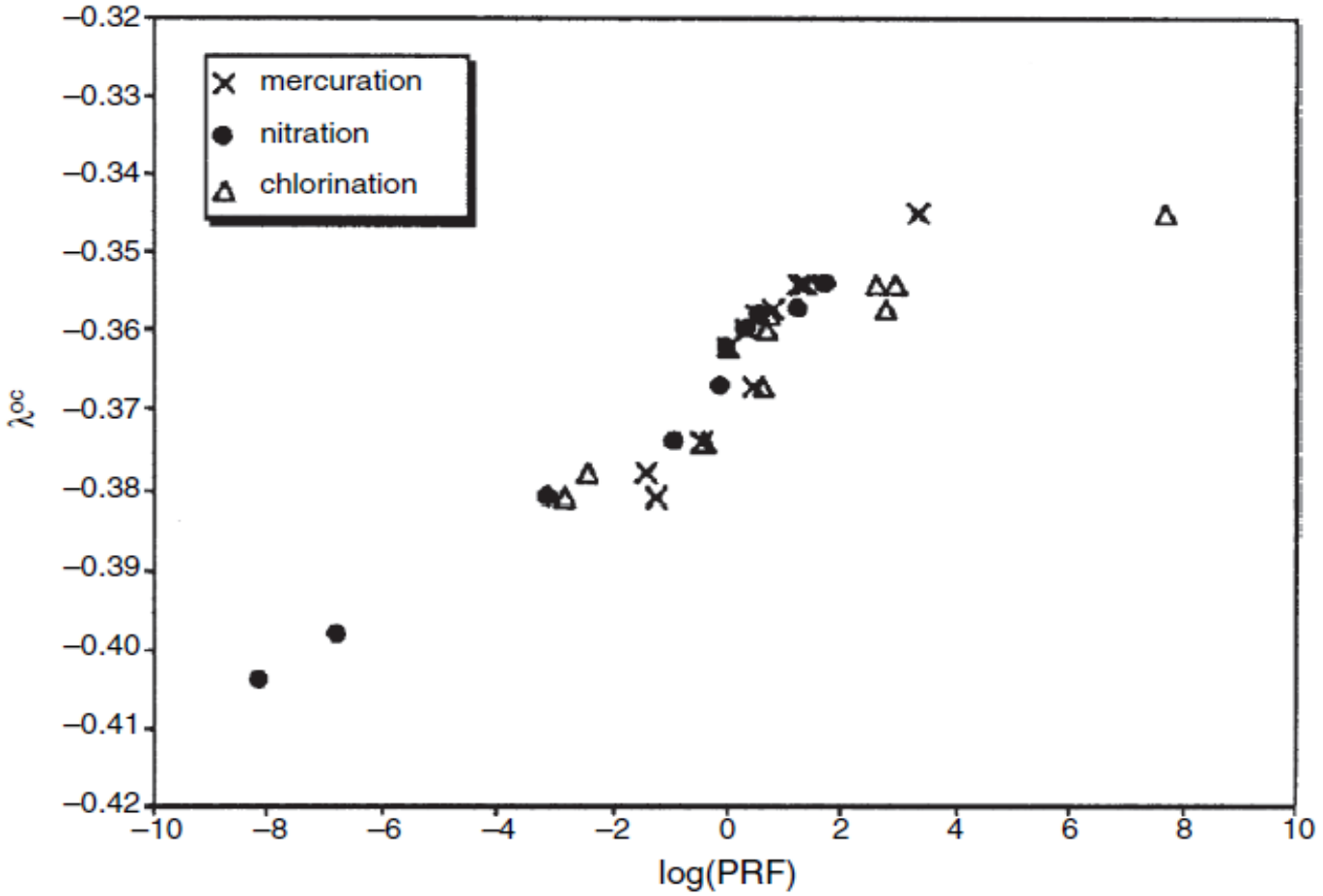
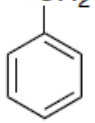
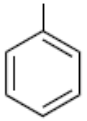
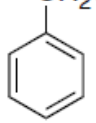
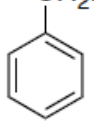
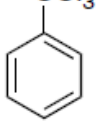
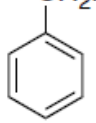


Fig. 9.6. Correlation between the interaction energy λ^{oc} and the log of partial rate factors for mercuration, nitration, and chlorination. Reproduced from *J. Phys. Chem. A*, **107**, 2875 (2003), by permission of the American Chemical Society.

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

$CH_2CO_2C_2H_5$	$CHCl_2$	CH_2CCl_3	CH_2NO_2	CCl_3	$CH_2N^+(CH_3)_3$
					
11%	34%	37%	55 %	64%	85 %

- 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:

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. 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 hydroxyl 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^+.

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 grops.

- A range of reaction conditions is represented in Table 9.3, so direct comparison is not always valid, but the trends are nevertheless clear.

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

Substituent	Product (%)		
	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

- 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.

- The halogens show o-and p–directing effects with fluorine being much less favorable to *ortho* substitution, because of the stronger C−F dipole, which results in both electrostatic and polarization effects that destabilize the *ortho* TS.

- 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-and 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 rate relative to benzene and dividing the total rate among the *ortho*, *meta*, and *para* products.

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

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.

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

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

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

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

- **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. 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

- Table 9.4 gives some data on the selectivity of some EAS reactions. The most informative data in terms of reactant is *fp*, since the partial rate factors for *ortho* substitution contain variable steric components. With *fp* as the criterion, halogenation and Friedel-Crafts acylation exhibit high selectivity, protonation and nitration are intermediate, and Friedel-Crafts alkylation shows low selectivity.

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.

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.

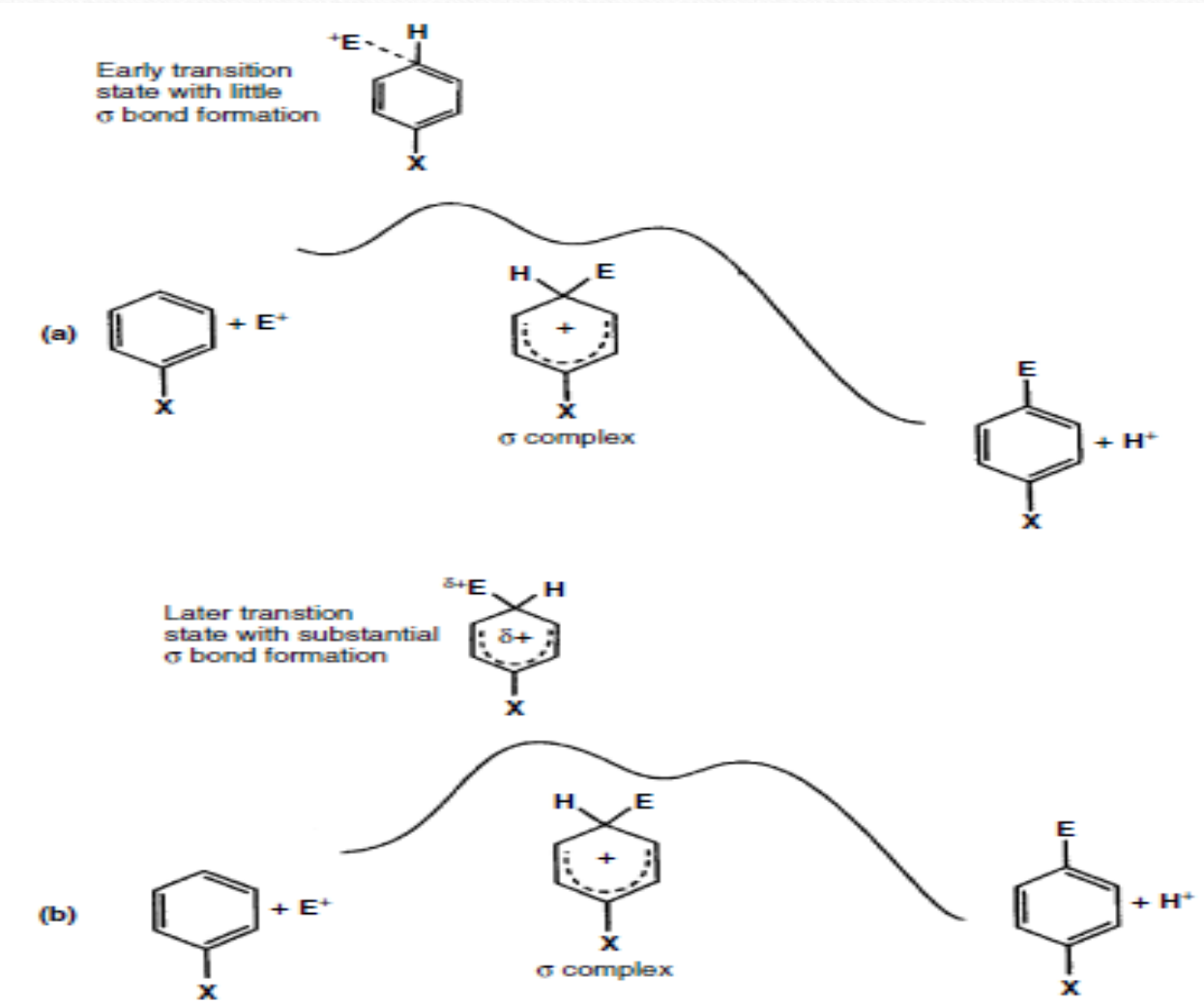


Fig. 9.7. Relation between transition state character and reaction energy profiles for highly reactive (a) and less reactive (b) electrophiles.

- 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 give better correlations. 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^+.
- 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. 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

- 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 *fp*, indicated in Table 9.4.

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

- 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 deprotonation (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.

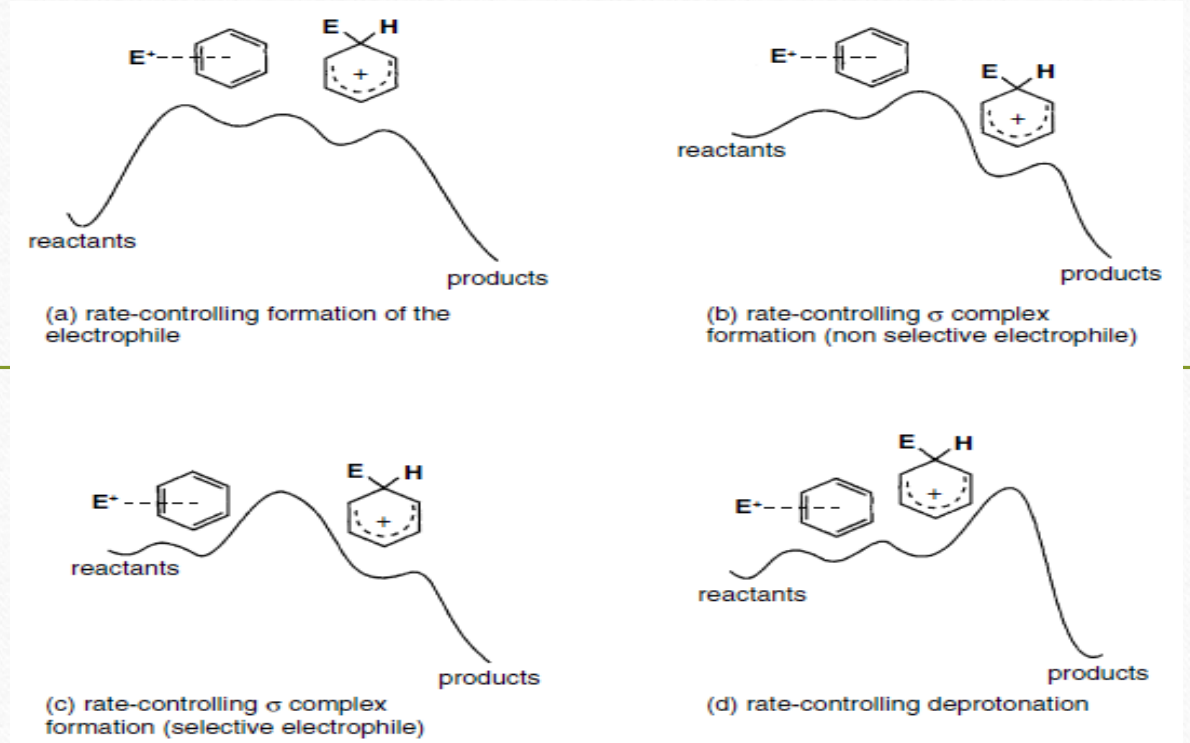


Fig. 9.8. Reaction energy profiles for electrophilic aromatic substitution showing variation in rate-determining step and electrophile selectivity.

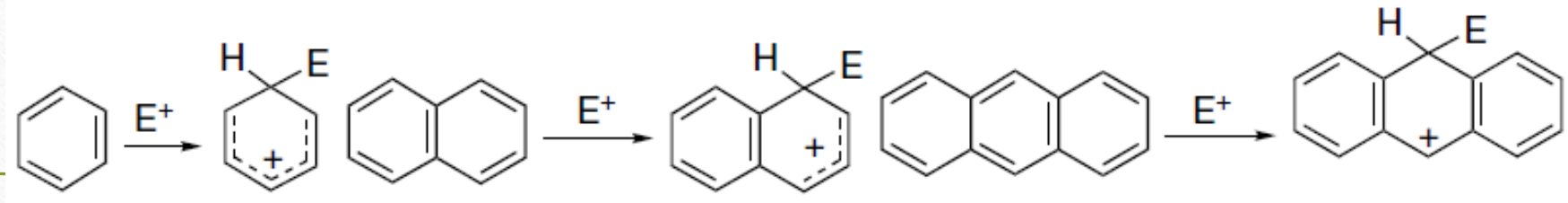
Figure 9.8 summarizes the general ideas presented in this section. At least four types of energy profiles can exist for individual EAS reactions. Case A is the rate- determining generation of the electrophile and is most readily identified by kinetics. A rate law independent of the concentration of the 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 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.

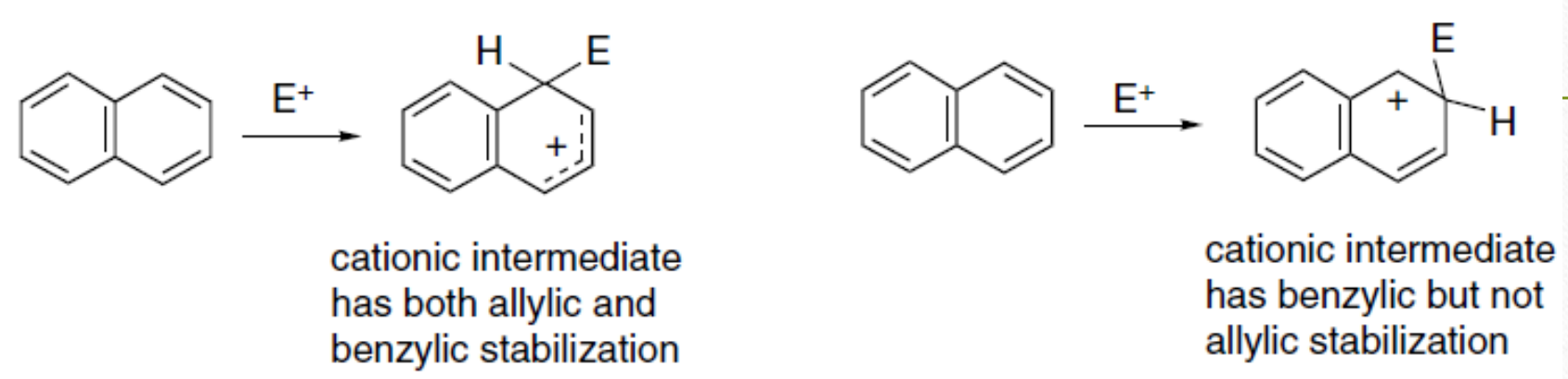
Reactivity of Polycyclic and Heteroaromatic Compounds



- 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.

- 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.

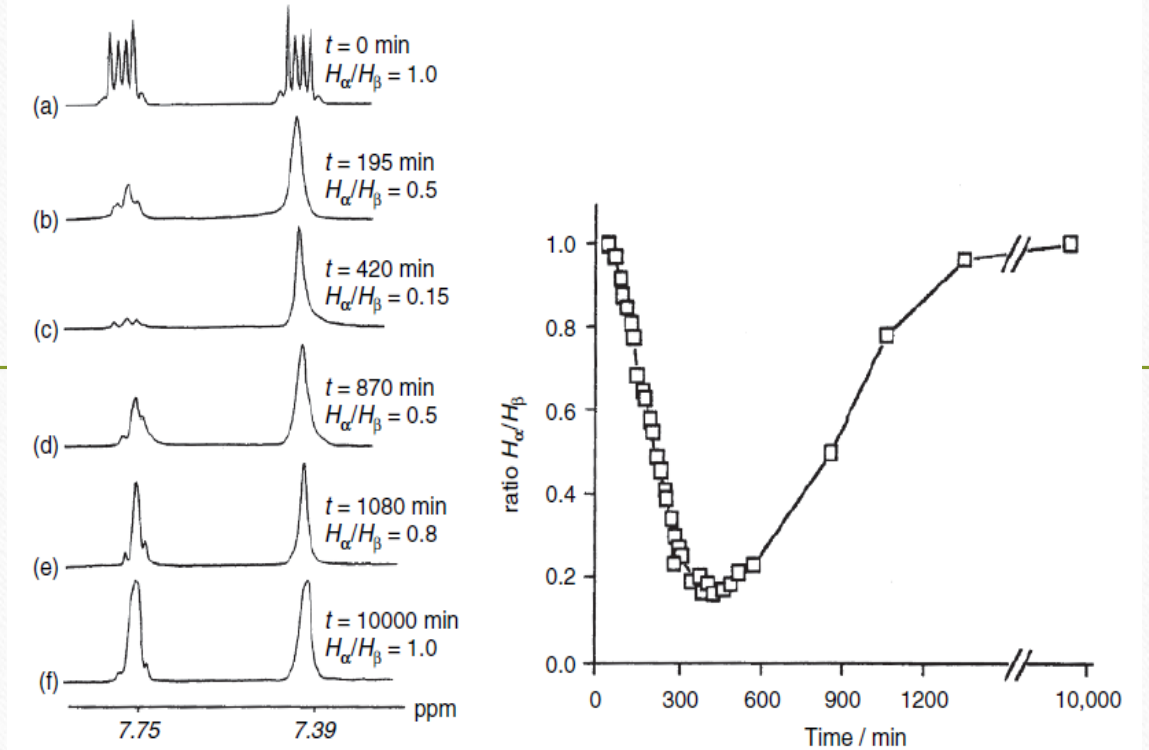
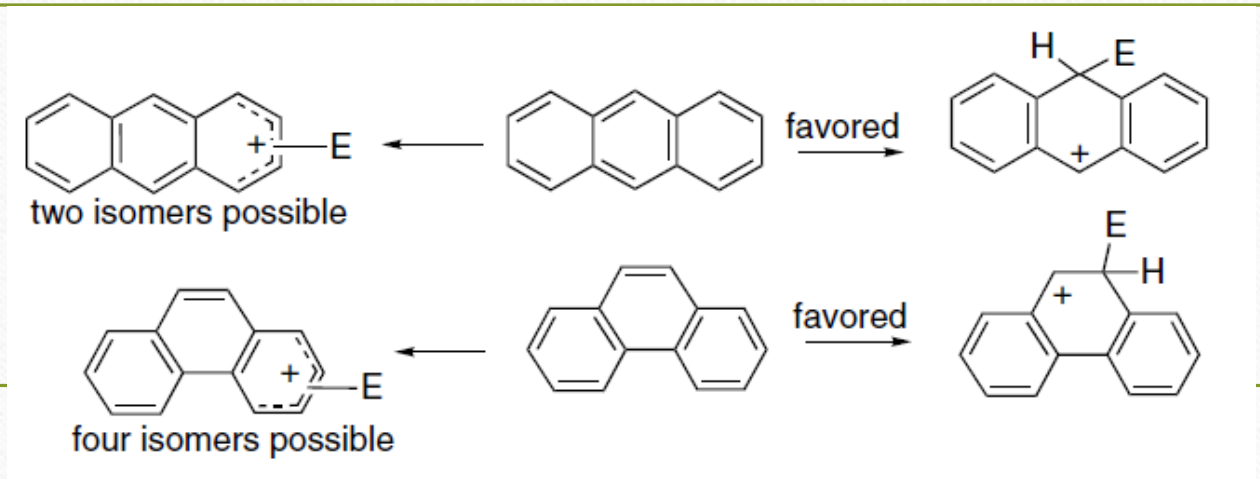


Fig. 9.9. Changes in ^{1}H-NMR spectrum of naphthalene heated with CF_3CO_2D in the presence of $(CF_3CO)_2O$ and $Al(O_2CCF_3)_3$ (left). Ratio of ^{1}H level at C(1)/C(2) (right). Reproduced from *J. Chem. Educ.*, **76**, 1246 (1999), by permission of the journal.

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.



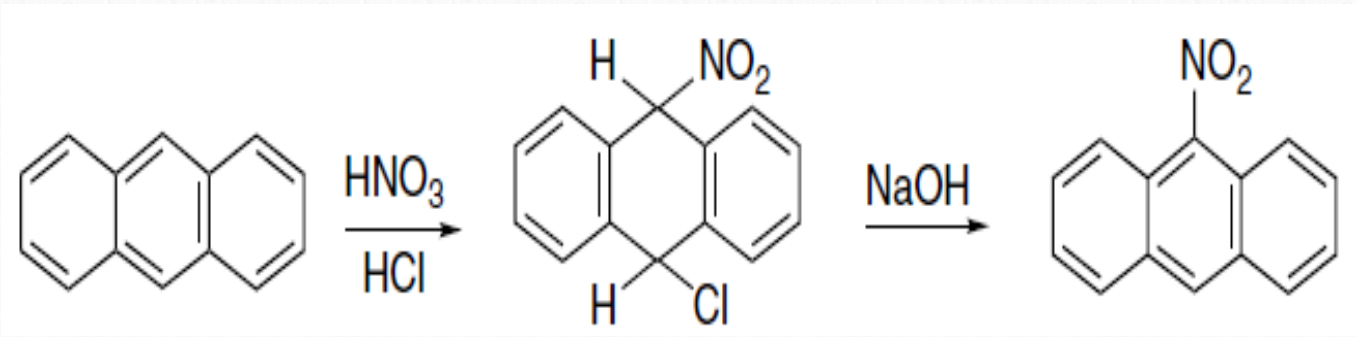
Two factors can result in substitution at the 2-position.

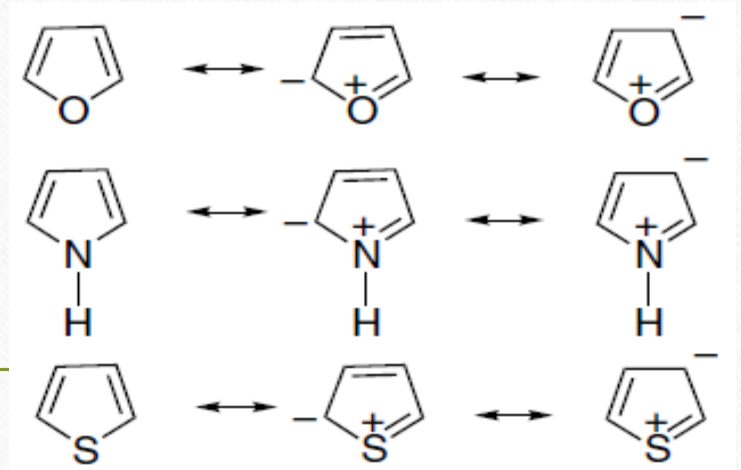
1- If the electrophile is very bulky, the hydrogen on the adjacent ring may cause a steric preference for attack at C (2).

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.

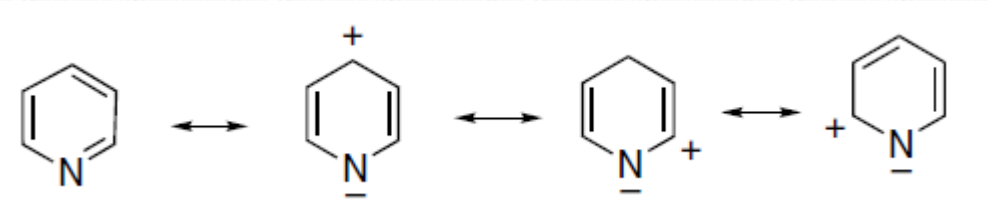
Phenanthrene and anthracene both react preferentially in the center ring. This behavior is consistent with resonance considerations. The σ complexes that result from substitution in the center ring have two intact benzene rings. The total resonance stabilization of these intermediates is larger than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





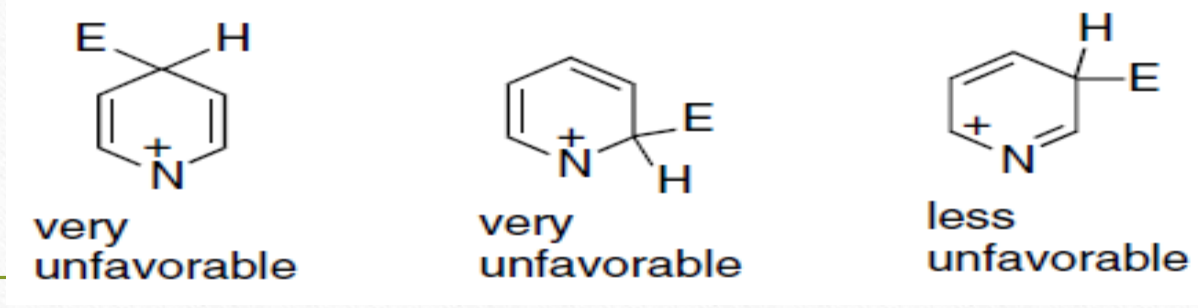
Both phenanthrene and anthracene have a tendency to undergo addition reactions under the conditions involved in certain electrophilic substitutions. For example, an addition product can be isolated in the nitration of anthracene in the presence of hydrochloric acid. This is a result of the relatively close balance in resonance stabilization to be regained by elimination.

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.



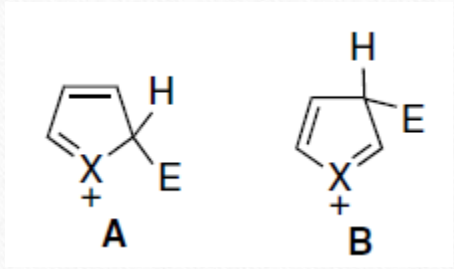
- The reactivity order is pyrrole > furan > thiophene, which indicates the order N > O > S in electron-donating capacity. The N > O order is as expected on the basis of electronegativity, and O > S probably reflects the better overlap of the oxygen 2p orbital than the sulfur 3p orbital with the carbon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

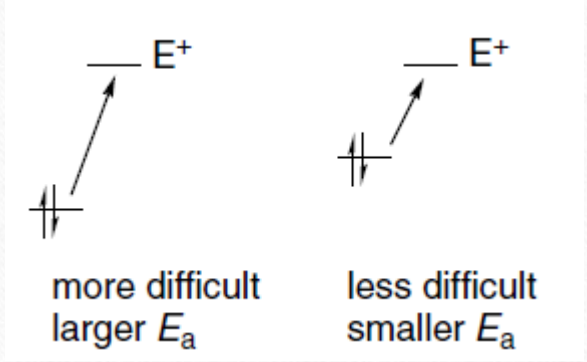


- There is another important factor in the low reactivity of pyridine derivatives toward EAS. The −N=CH− unit is basic because the electron pair on nitrogen is not part of the aromatic π system. The nitrogen is protonated or complexed with a Lewis acid under many of the conditions typical of EAS reactions. 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. 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 the LUMO and HOMO, $\eta = (\varepsilon_{LUMO} - \varepsilon_{HOMO})/2$. 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; where χ^R and χ^σ are the orbitals of the reactant and cationic intermediate.

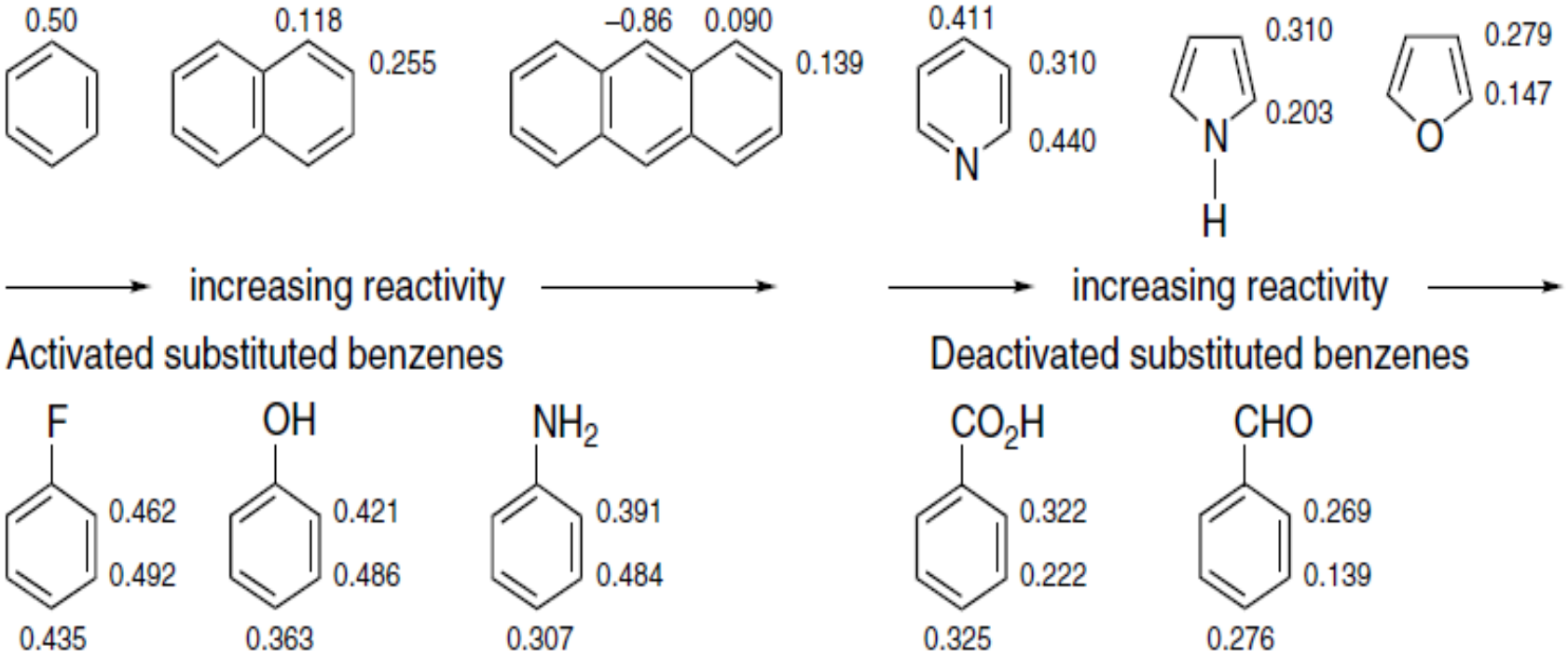
$$\Delta\eta^* = \beta[(\chi^R_{LUMO} - \chi^R_{HOMO}) - (\chi^\sigma_{LUMO} - \chi^\sigma_{HOMO})]/2$$

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]



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?

Nitration

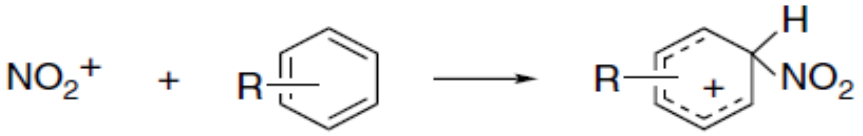
1. *Generation of the electrophile*

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

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.

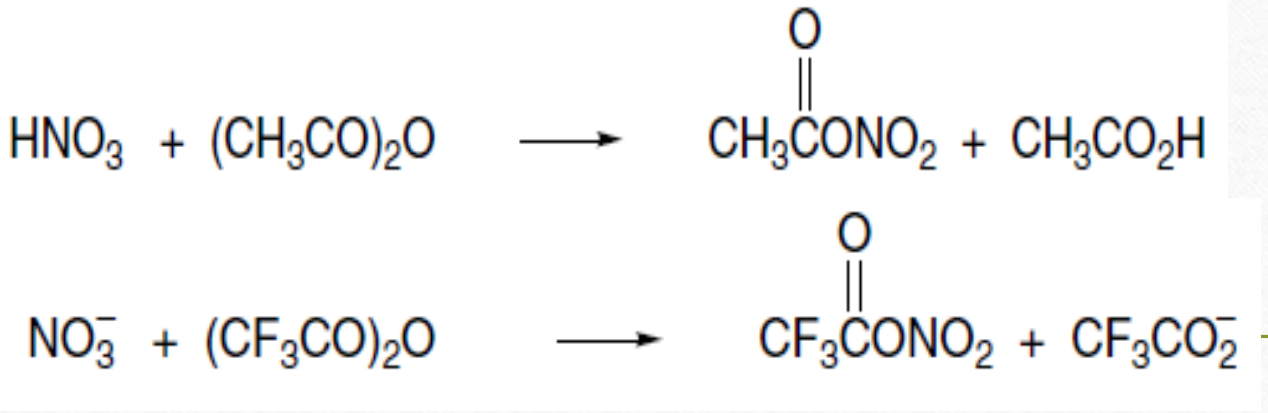
It is possible to prepare crystalline salts of nitronium ions such as nitronium tetrafluoroborate. Solutions of these salts in organic solvents nitrate aromatic compounds rapidly.

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. Under these conditions, the formation of the nitronium ion is a fast preequilibrium.

Step 2 of the nitration mechanism is rate controlling.

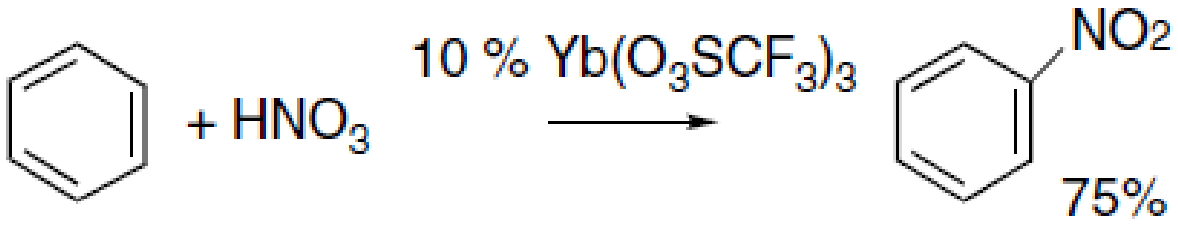
If nitration is conducted in inert organic solvents, such as nitromethane or carbon tetrachloride in the absence of a strong acid, the rate of formation of nitronium ion is slower and becomes rate limiting.



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.

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.

There are several other synthetic methods for aromatic nitration.



Benzene, toluene, and aromatics of similar reactivity can be nitrated using $Yb(O_3SCF_3)_3$ and 69% nitric acid in an inert solvent.

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.

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

A. Relative Reactivity of Some Hydrocarbons

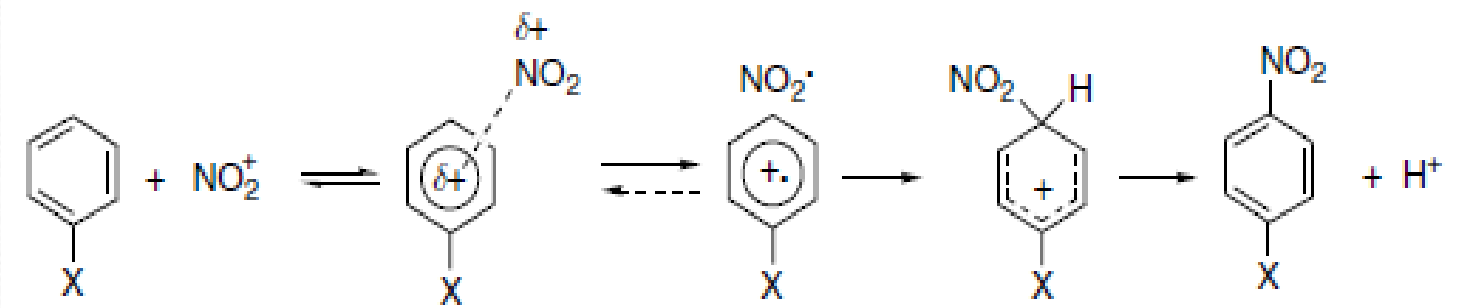
Reactant	H_2SO_4-HNO_3-H_2O[a]	HNO_3-CH_3NO_2[b]	HNO_3-$(CH_3CO)_2O$[c]
Benzene	1	1	1
Toluene	17	25	27
p-Xylene	38	139	92
m-Xylene	38	146	—
o-Xylene	38	139	—
Mesitylene	36	400	1750

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	—



In general, nitration is a relatively unselective reaction with toluene *fp* being about 50–60, as shown in 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*-nitro toluene 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.

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.

- 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.

- 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.

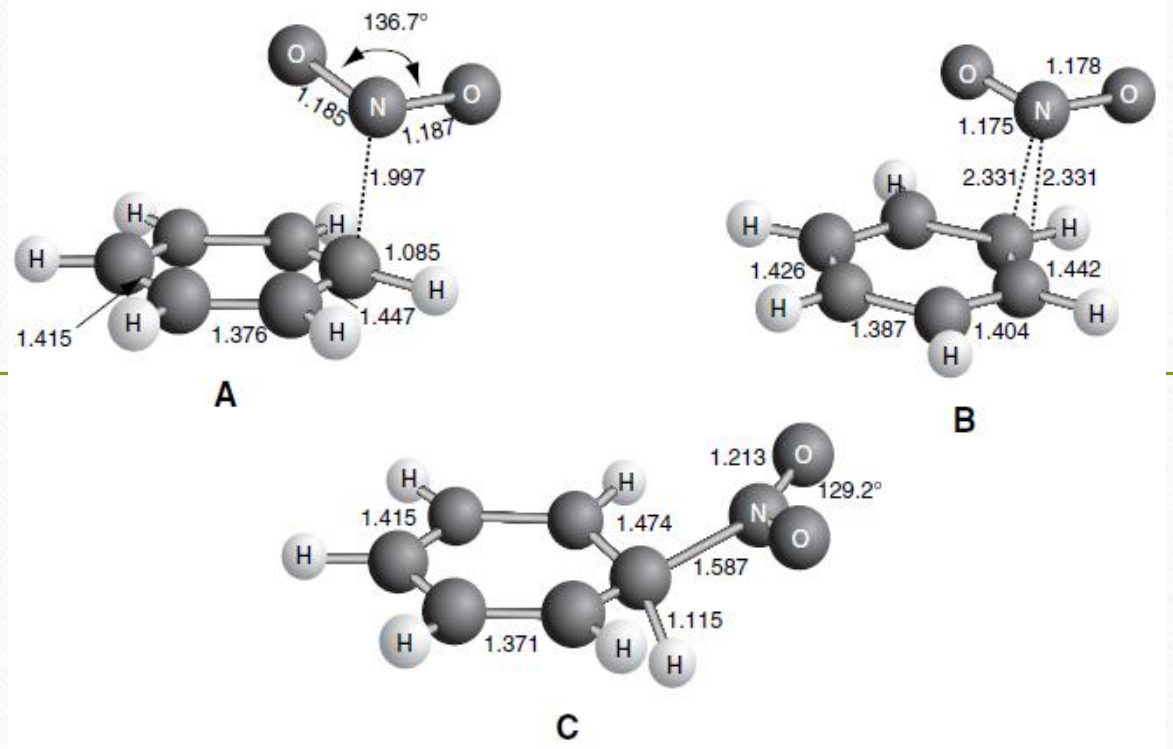


Fig. 9.10. Oriented complexes and nitrocyclohexadienylium intermediate in the nitration of benzene. Adapted from *J. Am. Chem. Soc.*, **125**, 4836 (2003), by permission of the American Chemical Society.

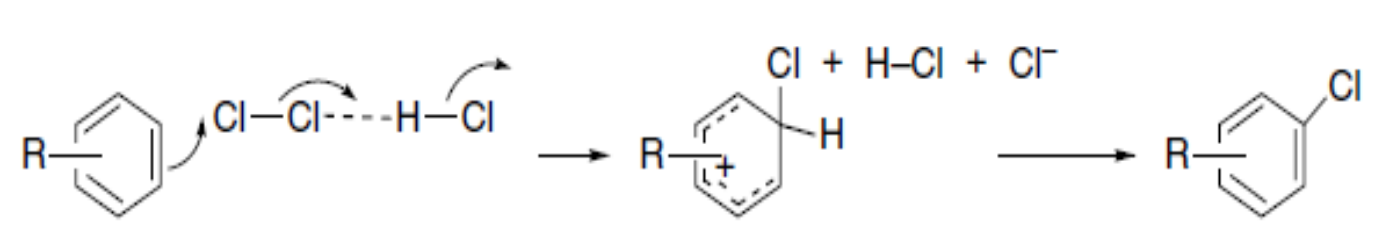
Three of the key intermediates are shown in Fig. 9.10. In structure A the NO_2 unit is associated with a single carbon atom with a C−N bond distance is 1.997 Å. This structure is only slightly more stable than B, in which the NO_2 group is located equidistant between two carbon atoms. The NO_2 group 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.

The nitration mechanism also has been modeled by B3LYP/6-311G** computations using a continuum solvent model. 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 ε >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^{+o} pair, which is followed by collapse to the nitrocyclohexadienylium intermediate. The product distribution is determined at this latter stage.

Halogenation



The order of reactivity: $I_2 < Br_2 < Cl_2 < F_2$.

Halogenation reactions occur in the presence of Lewis acids (a complex of halogen with Lewis acid is activate electrophile).

Bromine and iodine form stable complexes with the corresponding halide ions. These anionic trihalide ions are less reactive than the free halogen, but are capable of substituting highly reactive rings.

Molecular chlorine is believed to be the active electrophile in uncatalyzed chlorination of reactive aromatic compounds. Second-order kinetics are observed in acetic acid.

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.

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.

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

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^+.

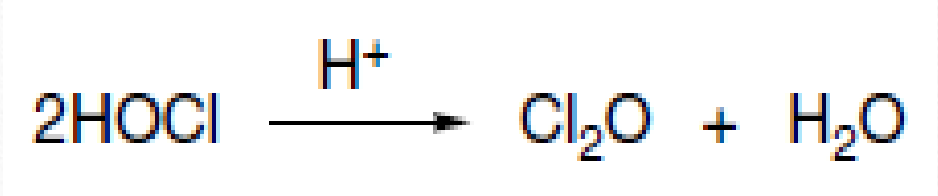
$$Cl_2 + AlCl_3 \rightleftharpoons Cl{-}Cl^{+}{-}Al^{-}Cl_3 \longrightarrow Cl^{+} + [AlCl_4]^{-}$$

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} = 160 k_{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.

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

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*.



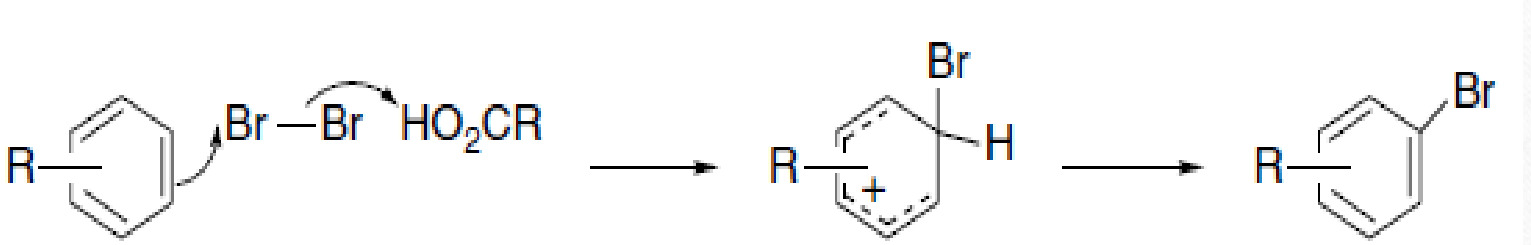
Both Cl_2O and $[H_2OCl]^+$ apparently are active electrophiles under these conditions. The terms involving Cl_2O are zero order in the aromatic reactant because formation of Cl_2O is the rate-limiting step.

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.

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, but becomes more complicated in the presence of water.

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.



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.

Kinetic studies show that the rate of disappearance 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.

Computational studies are consistent with formation of a benzene radical cation $[Br_2^{o}]^{-}$ 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.

Bromination is characterized by high reactant selectivity. The data in Table 9.4 showed that for toluene fp 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).

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.

Bromination has been shown not to exhibit a primary kinetic isotope effect in the case of benzene, bromobenzene, toluene, or methoxybenzene. There are several examples of reactants that do show significant isotope effects, including substituted anisoles, N, N-dimethylanilines, and 1, 3, 5-trialkylbenzenes.

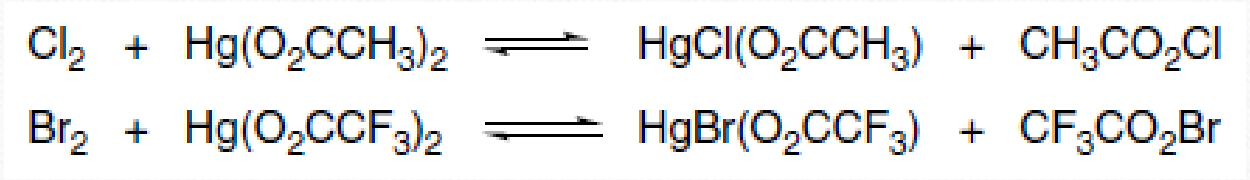
The observation of isotope effects in highly substituted systems seems to be the result of steric factors that can operate in two ways.

1-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.

2-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.

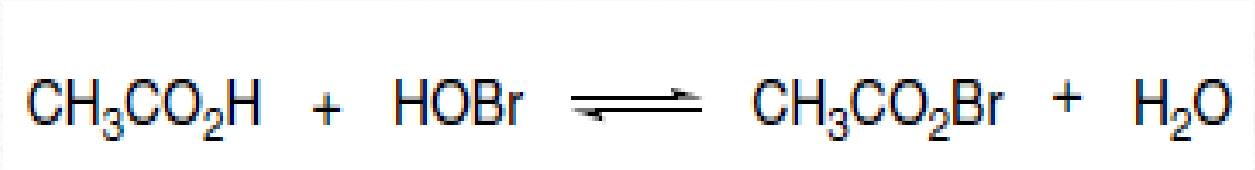
Bromination is catalyzed by Lewis acids (aluminum chloride). Toluene is found to be about 35 times more reactive than benzene under these conditions. The catalyzed reaction thus shows a good deal less substrate selectivity than the uncatalyzed reaction, because of the greater reactivity of the aluminum chloride-bromine complex.

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

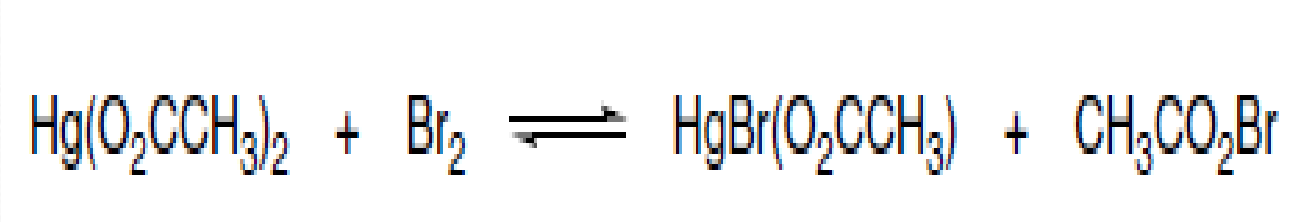


The latter is an extremely reactive species. Trifluoroacetate is a good leaving group and facilitates cleavage of the O−Br bond.

- Acetyl hypobromite is considered to be the active halogenating species in solutions of hypobromous acid in acetic acid:



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



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 $1:10^6:10^{10}$.

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 $ZnCl_2$. 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. 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 fp and fm 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.

- 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 $HOSO_2OF$.

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. 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 the aromatic ring. The intermediate σ complex is a cyclohexadienylium cation.

- Partial rate factors for exchange reaction 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 *fp* value for toluene varies somewhat, depending on the reaction medium, but is generally about 10^2. The ρ value for hydrogen exchange in H_2SO_4-CF_3CO_2H-H_2O is −8.6. A similar ρ value of −7.5 has been observed in aqueous sulfuric acid. 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.

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

Among the many experimental results pertaining to hydrogen exchange, a most important one is that general acid catalysis has been demonstrated, 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. A substantial isotope effect has also been observed for the exchange process with azulene.

Friedel-Crafts Alkylation and Related Reactions

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.

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. With aluminum bromide as the catalyst, the rate of reaction changes with time, apparently because of heterogeneity of the reaction mixture. The initial rate data fit the following kinetic expression:

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

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

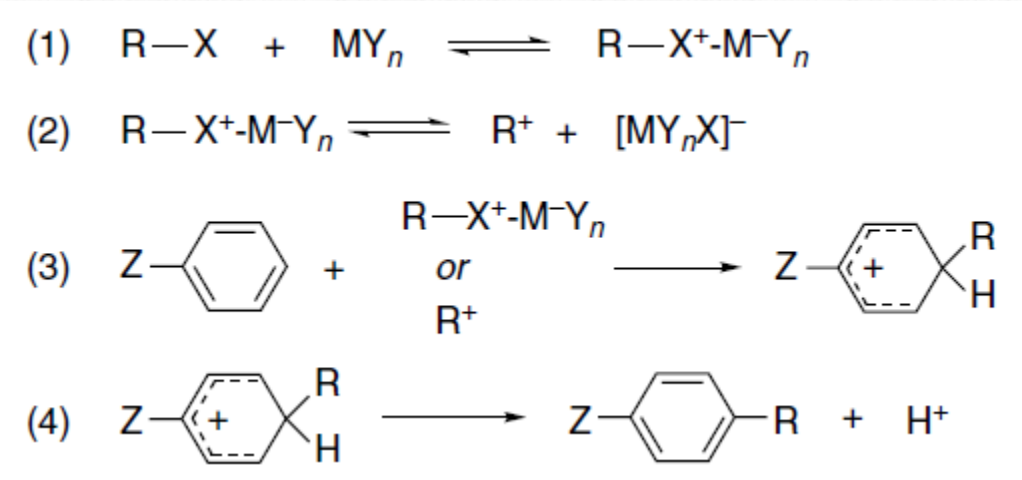
The reaction rates of toluene and benzene with i-propyl chloride or t-butyl chloride in nitromethane can be fit to a third-order rate law.

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.

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. 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:

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

(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.



- 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.

- 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.

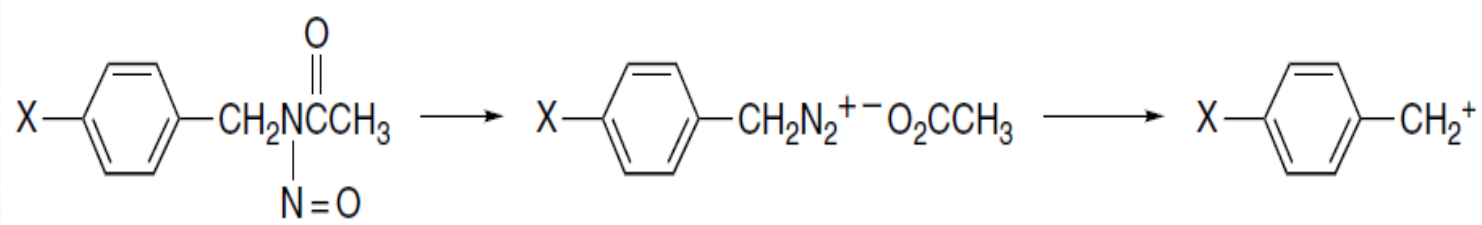
There is a clear trend within the family of substituted benzyl chlorides of increasing selectivity with the increasing ERG capacity of the benzyl substituent. The substituents on the ring undergoing substitution have a relatively weak orienting effect on the attacking electrophile. With benzylic cations 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 decreases as the size of the entering alkyl group increases along the series methyl, ethyl, *i*-propyl.

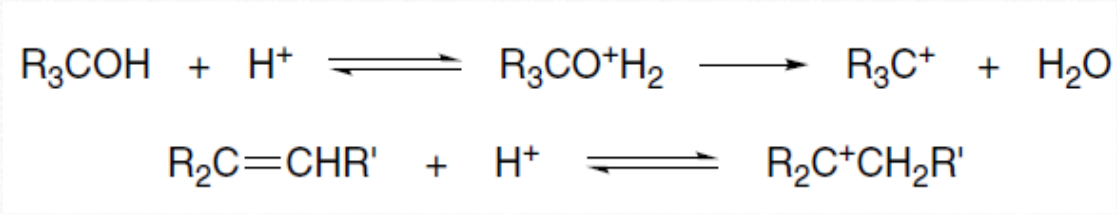
Table 9.9. Reactant and Position Selectivity in Friedel-Crafts Alkylation Reactions

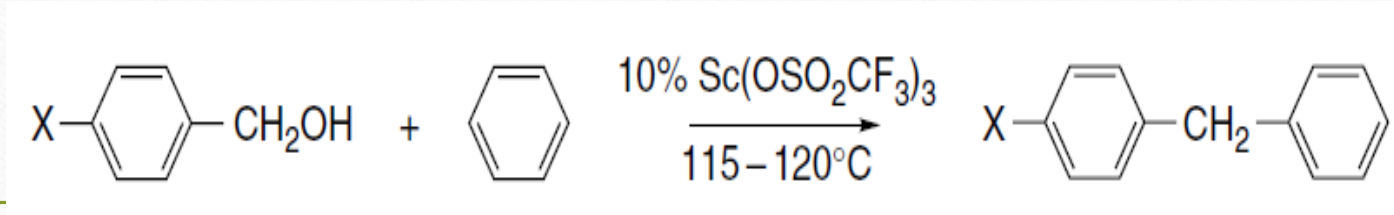
	Electrophilic reagent	k_{tol}/k_{benz}	Toluene *o*:*p* ratio
1	CH_3Br-$AlBr_3$[a]	2.5–4.1	1.9
2	C_2H_5Br-$GaBr_3$[b]	6.5	–
3	$(CH_3)_2CHBr$-$AlCl_3$[c]	1.9	1.2
4	$(CH_3)_2CHCl$-$AlCl_3$[d]	2.0	1.5
5	$(CH_3)_3CCl$-$AlCl_3$[e]	25	0
6	$(CH_3)_3CBr$-$SnCl_4$[f]	16.6	0
7	$(CH_3)_3CBr$-$AlCl_3$[f]	1.9	0
8	$PhCH_2Cl$-$AlCl_3$[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



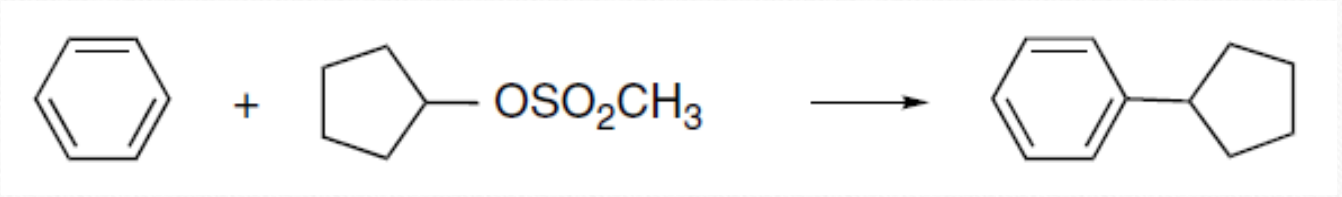
No *ortho* product is found when the entering group is t-butyl. Toluene/benzene selectivity decreases in the order X = CH_3 > H ~ Cl > NO_2 , in agreement with the expectation that the least stable (and most reactive) carbocation would be the least selective. These reactions also show low position selectivity.

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





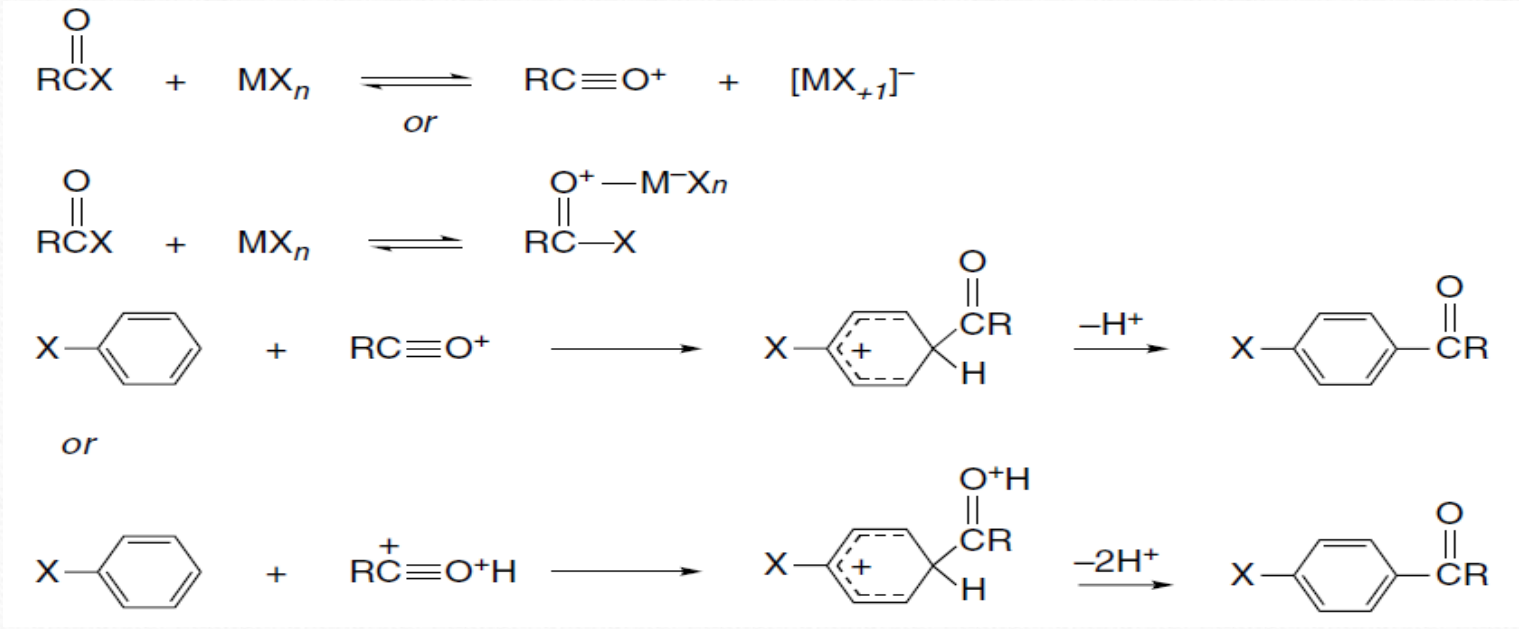
Benzyl and allyl alcohols that can generate stabilized carbocations give Friedel-Crafts alkylation products with mild Lewis acid catalysts such as $Sc(O_3SCF_3)_3$.

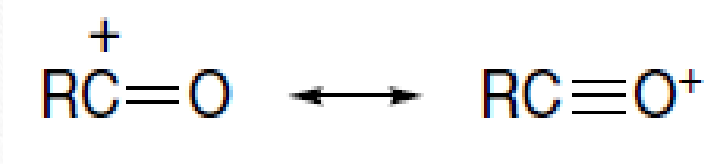


Scandium triflate, copper triflate, and lanthanide triflates catalyze alkylation by secondary methanesulfonates.

Friedel-Crafts Acylation and Related Reactions

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 forms both 1:1 and 1:2 complexes with $AlCl_3$ and acetyl chloride.

The crystal structures of $PhCOCl\text{-}SbCl_5$ and $PhCOCl\text{-}GaCl_3$ and $[PhCOCl\text{-}TiCl_4]_2$ have been determined. In all of these complexes, the Lewis acid is bound to the carbonyl oxygen.

Acylium salts are generated at slightly higher temperatures or with more reactive acyl halides. For example, both 4-methylbenzoyl chloride and 2, 4, 6-trimethylbenzoylchloride give acylium salts with $SbCl_5$.

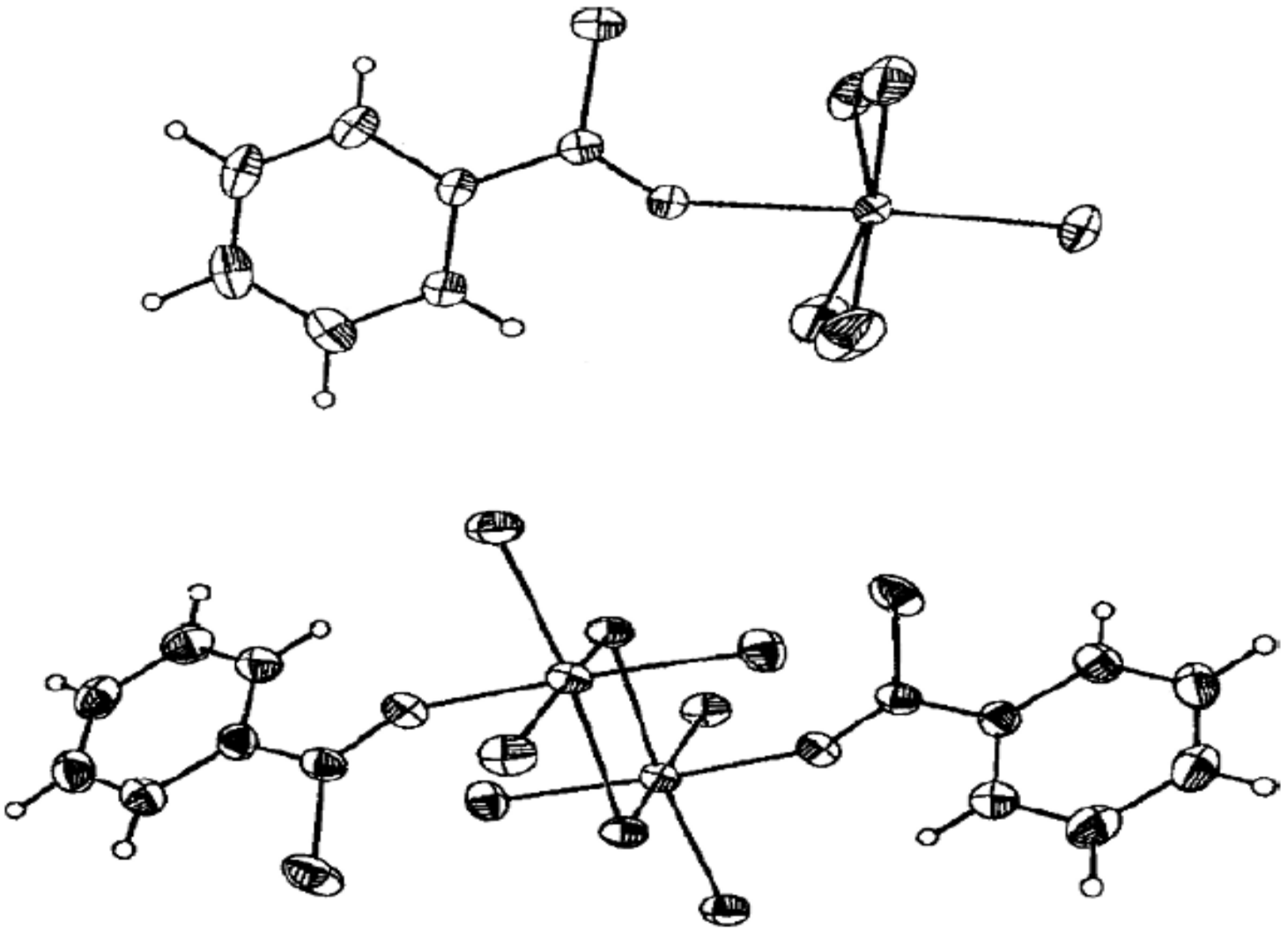
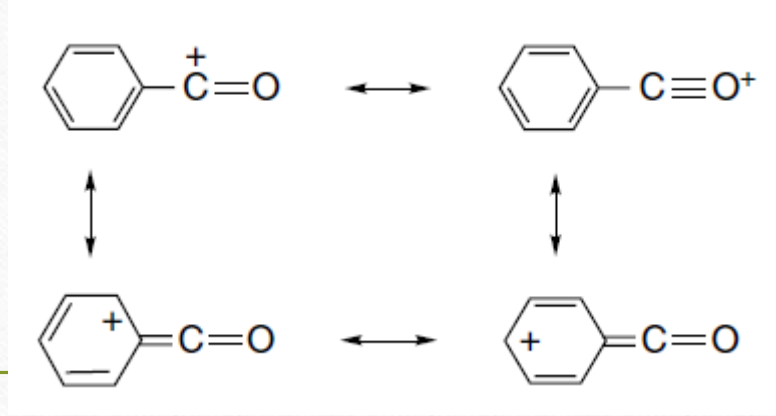
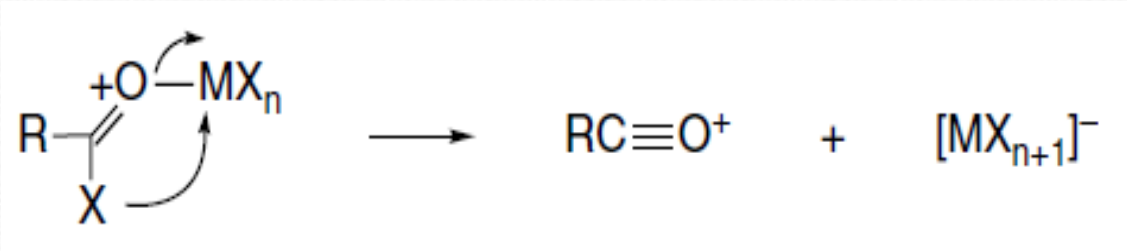


Fig. 9.11. X-Ray crystal structures of $PhCOCl\text{-}SbCl_5$ (top) and $[PhCOCl\text{-}TiCl_4]_2$ (bottom). Reproduced from *J. Org. Chem.*, **70**, 4013 (2005), by permission of



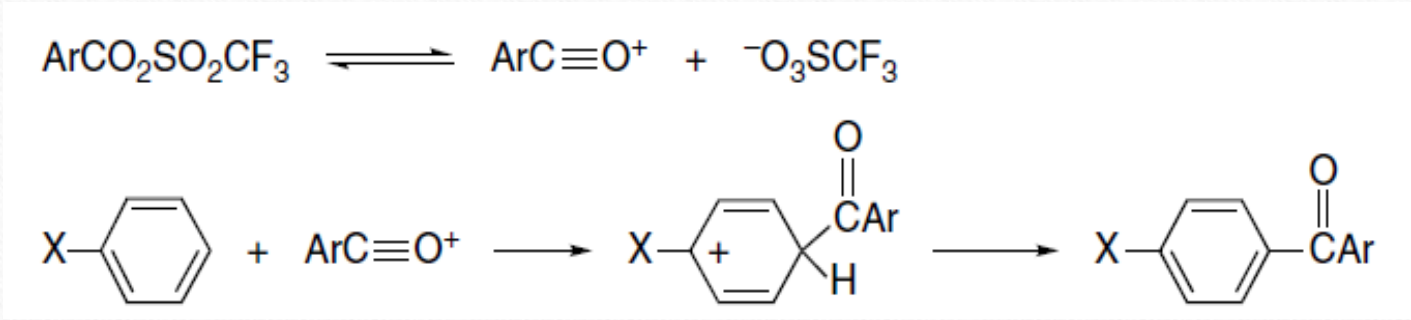
- Acylium salts are also formed from benzoyl fluoride and SbF_5.
- Aryl acylium ions are also stabilized by charge delocalization into the aromatic ring.
- The mechanisms consists of formation of the complex, ionization to an acylium ion, and substitution via a cyclohexadienylium ion intermediate.



The most likely mechanism for formation of the acylium ion is by an intramolecular transfer of the halide to the Lewis acid.

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

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



Either formation of the acylium ion or formation of the σ complex can be rate determining, depending on the reactivity of the substrate.

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. 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.

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.

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-$AlCl_3$ [a]	134	0.012
2	CH_3CH_2COCl-$AlCl_3$ [b]	106	0.033
3	$CH_3C{\equiv}O^+$ SbF_6^- [c]	125	0.014
4	HCOF-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-$AlCl_3$ [d]	153	0.09
8	*p*-Toluoyl chloride-$AlCl_3$ [d]	164	0.08
9	*p*-Methoxybenzoyl chloride-$AlCl_3$ [d]	233	0.2

Friedel-Crafts acylation sometimes shows a modest kinetic isotope effect. 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.

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

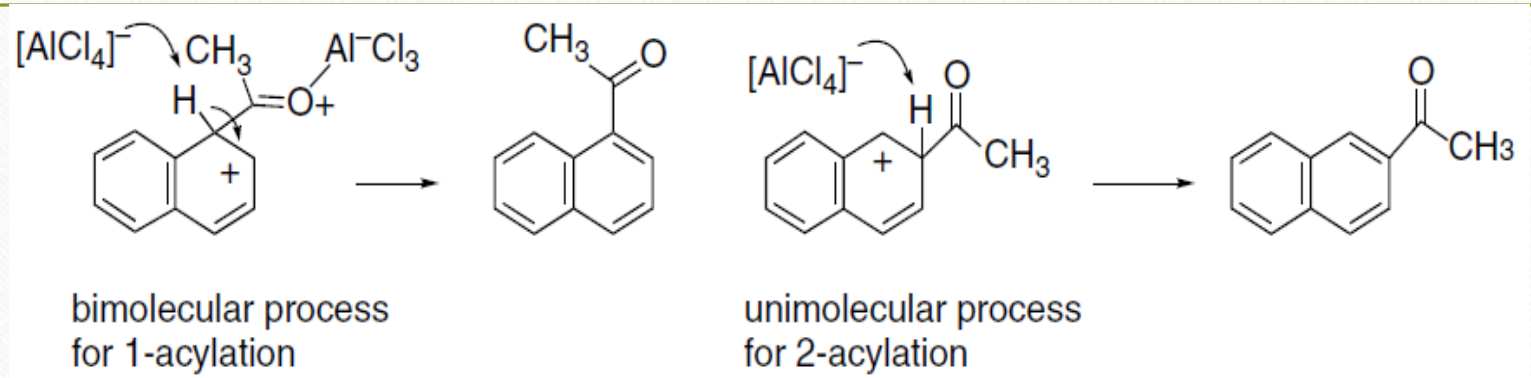
$$\text{Rate (2-acylation)} = k_2[\text{naphth}][CH_3COCl\text{-}AlCl_3]$$

- With toluene, for example, aroyl triflates give higher ratios of *ortho* product when a base, (2,4,6-tri-t-butylpyridine) is present. 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- $AlCl_3$.

- The two competing reactions show different concentration dependence, with 1-acylation being second order in acylating agent, whereas 2-acylation is first order:

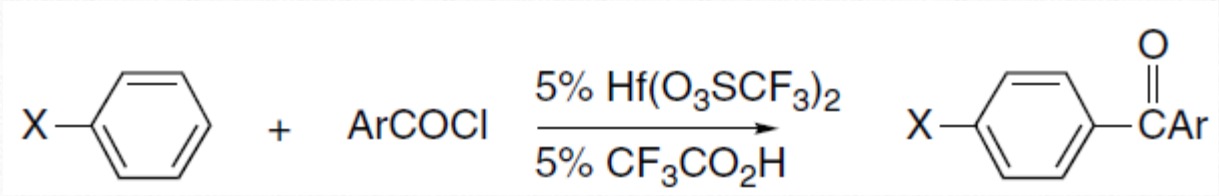
- *



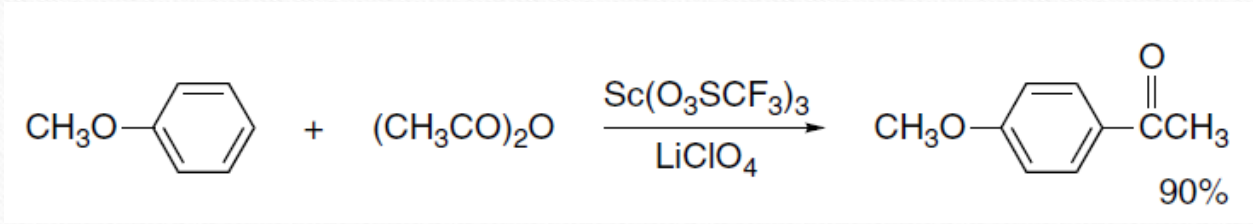
The 2-acylation also showed a much larger H/D isotope effect (~5.4 versus 1.1). The postulated mechanism suggests that breakdown of the more hindered σ complex for 1-acylation is bimolecular, whereas a unimolecular deprotonation process occurs for 2-acylation.

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.

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



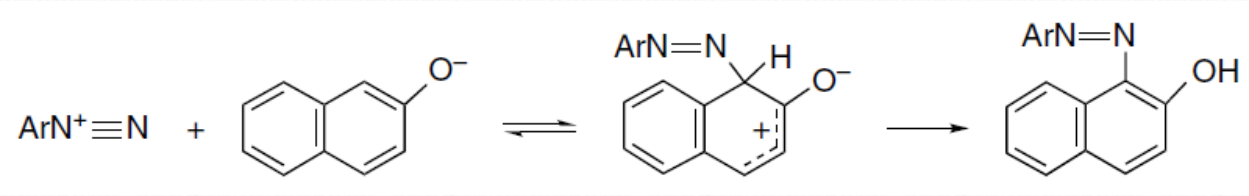
Acid anhydrides can serve as the acylating agent in place of acyl chlorides, and the carboxylic acid can be used directly, particularly in combination with strong acids. Mixtures of carboxylic acids with polyphosphoric acid in which a mixed anhydride is presumably formed in situ are reactive acylating agents.



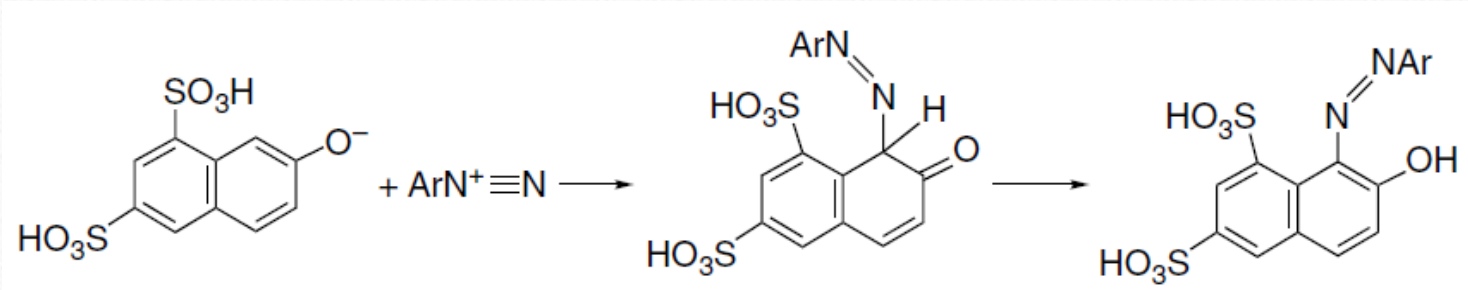
Similarly, carboxylic acids dissolved in trifluoromethanesulfonic acid can carry out Friedel- Craft acylation.

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.



Aryl diazonium ions are stable in solution only near or below room temperature. The reactivity of the diazonium ion depends on the substituent groups that are present. Reactivity is increased by EWG and decreased by ERG.



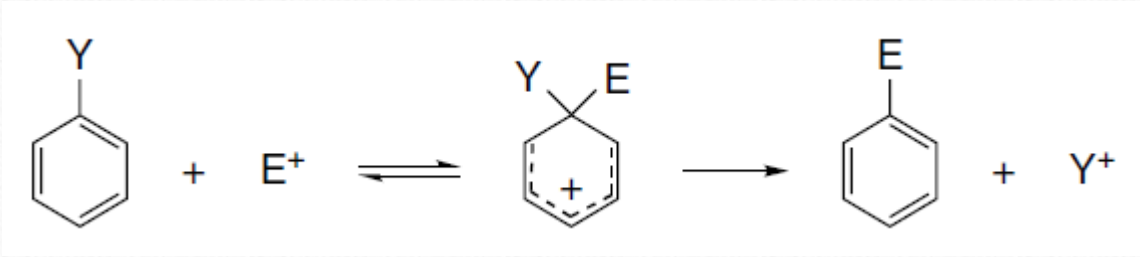
An unusual feature of the mechanism for diazonium coupling is that in some cases proton loss can be demonstrated to be the rate-determining step. This feature is revealed in two ways.

1- 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.

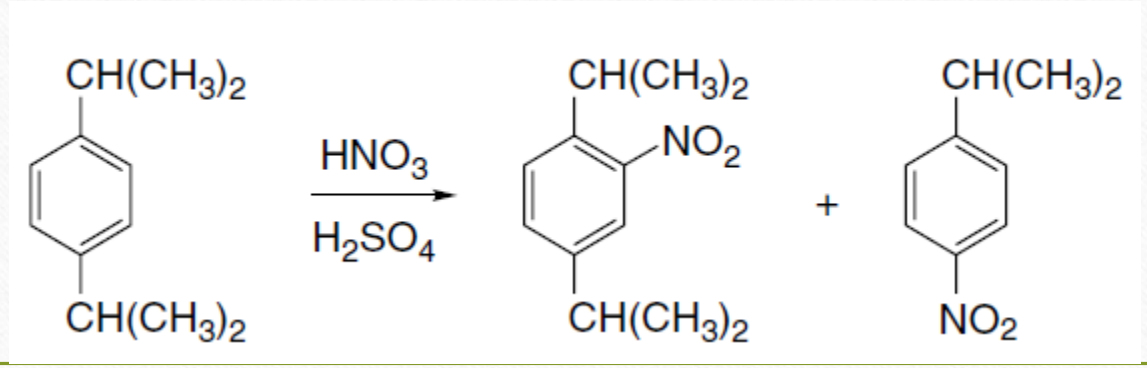
2- These reactions can also be shown to be general base catalyzed. This, too, implies that proton removal is rate determining.

Diazotization, since it involves a weak electrophile, would be expected to reveal high substrate and position selectivity.

Substitution of Groups Other than Hydrogen

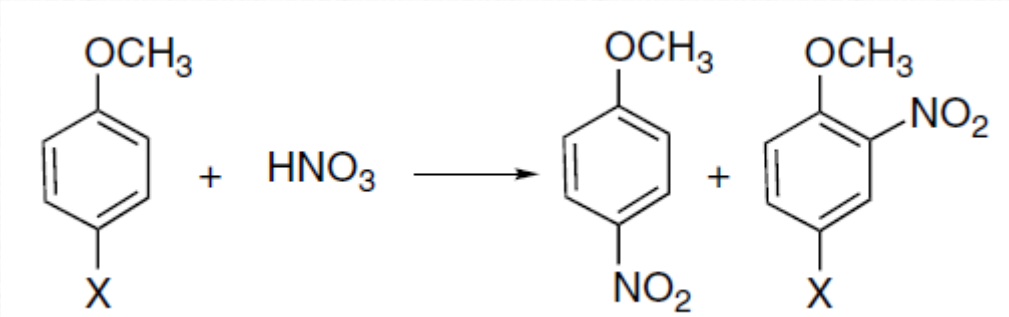


Substitution at a site already having a substituent is called *ipso* substitution and has been observed in a number of circumstances. The ease of removal of a substituent depends on its ability to accommodate a positive charge. This factor determines whether the newly attached electrophile or the substituent 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.

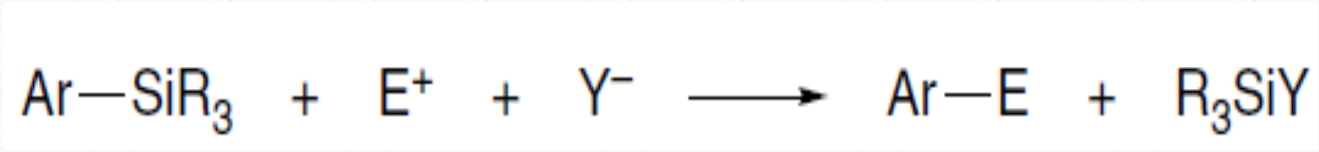
Cleavage of *t*-butyl groups has been observed in halogenation reactions. Minor amounts of dealkylated products are formed during chlorination and bromination of t-butyl-benzene. The amount of dealkylation increases greatly in the case of 1, 3, 5-tri-*t*-butylbenzene, and the principal product of bromination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



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.

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

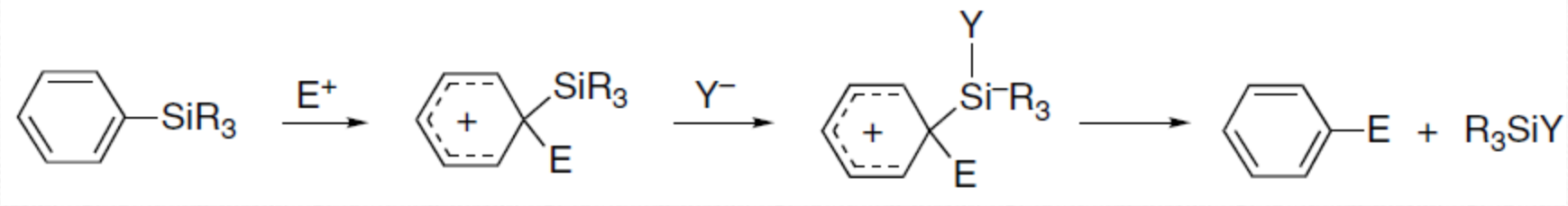
The most general type of aromatic substitution involving replacement of a substituent group in preference to a hydrogen is the electrophilic substitution of arylsilanes.



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 position is relatively electron rich.

The ability of silicon substituents to stabilize carbocation character at ß-carbon atoms also promotes ipso substitution.

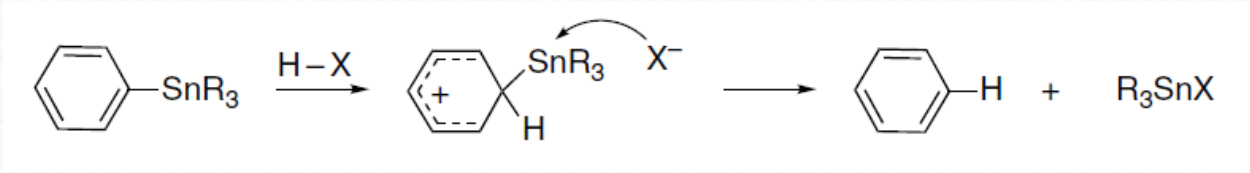
A silicon substituent is easily removed from the intermediate by reaction with a nucleophile. The desilylation step probably occurs through a pentavalent silicon species.



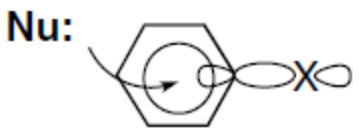
Examples of electrophiles that can effect substitution for silicon include protons and the halogens, as well as acyl, nitro, and sulfonyl groups. The fact that these reactions occur very rapidly has made them attractive for situations where substitution must be done under very mild conditions.

One example is the introduction of radioactive iodine for use in tracer studies. 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.

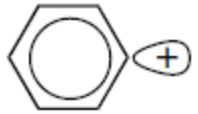
The electron density at carbon is increased, as is the stabilization of ß-carbocation character. Acidic cleavage of arylstannanes is an electrophilic aromatic substitution proceeding through an *ipso*-oriented σ -complex.



Nucleophilic Aromatic Substitution



back-side approach of the nucleophile with inversion is impossible

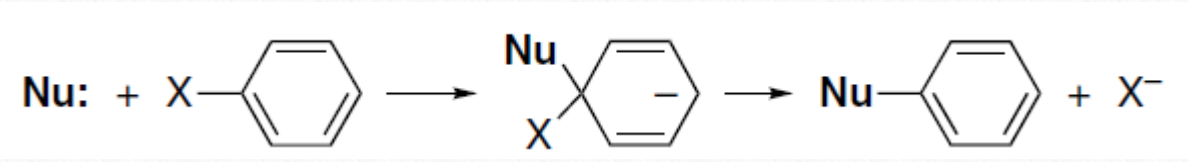


phenyl cation is a high-energy intermediate

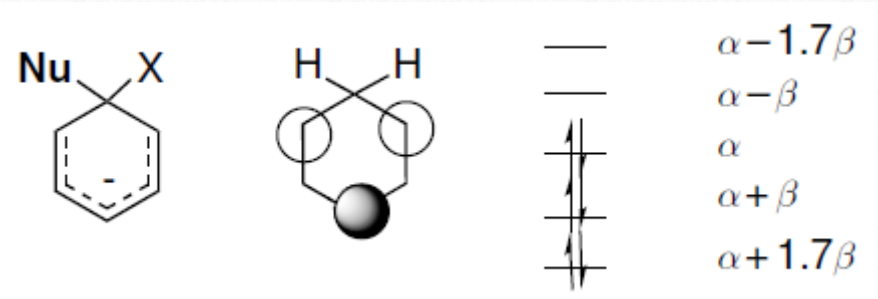
- A back-side S_N2-type reaction is precluded by the geometry of the benzene ring.
- An S_N1 mechanism is very costly in terms of energy because a cation directly on a benzene ring is very unstable.
- It is clear that a phenyl cation is less stable than even a primary carbocation, which is a consequence of the geometry and hybridization of the aromatic carbon atoms.
- An aryl carbocation is localized in a sp^2 orbital that is orthogonal to the π system so there is no stabilization available from the π electrons.

Nucleophilic Aromatic Substitution by the Addition-Elimination Mechanism

The addition-elimination mechanism 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 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 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. 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. 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.

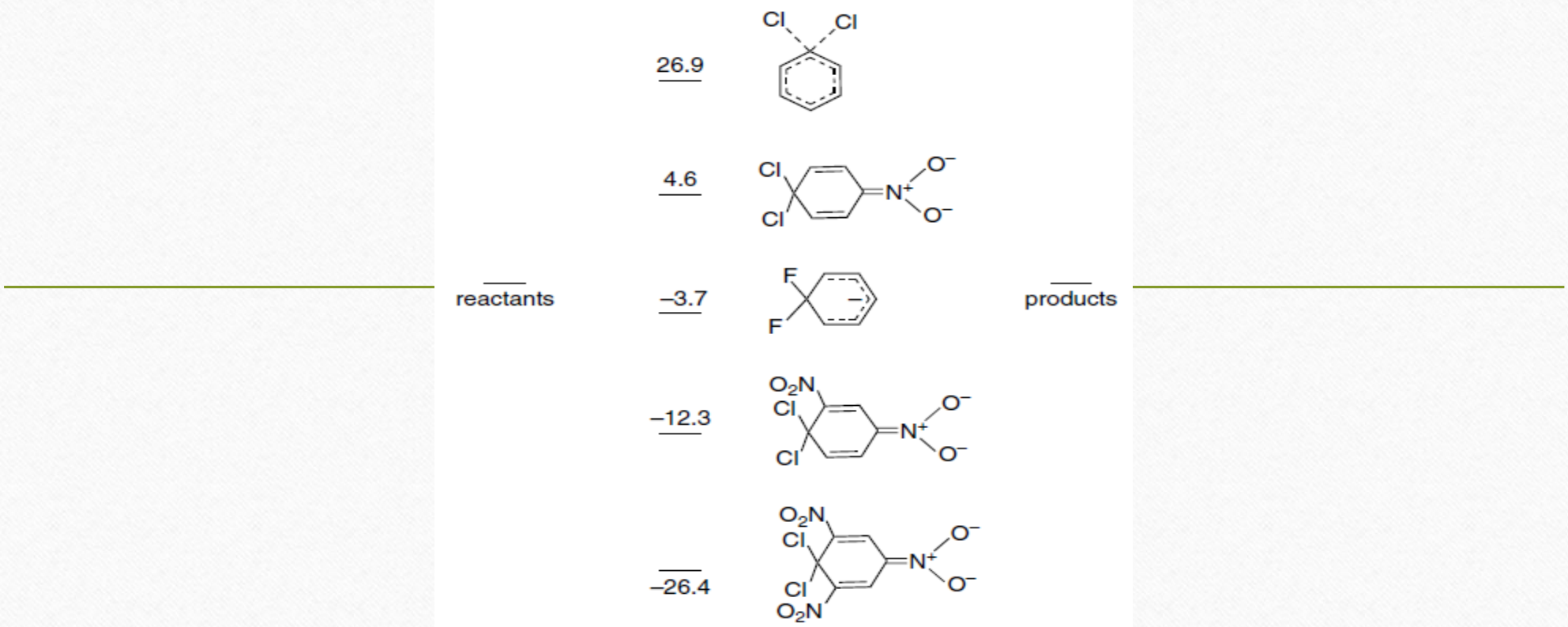
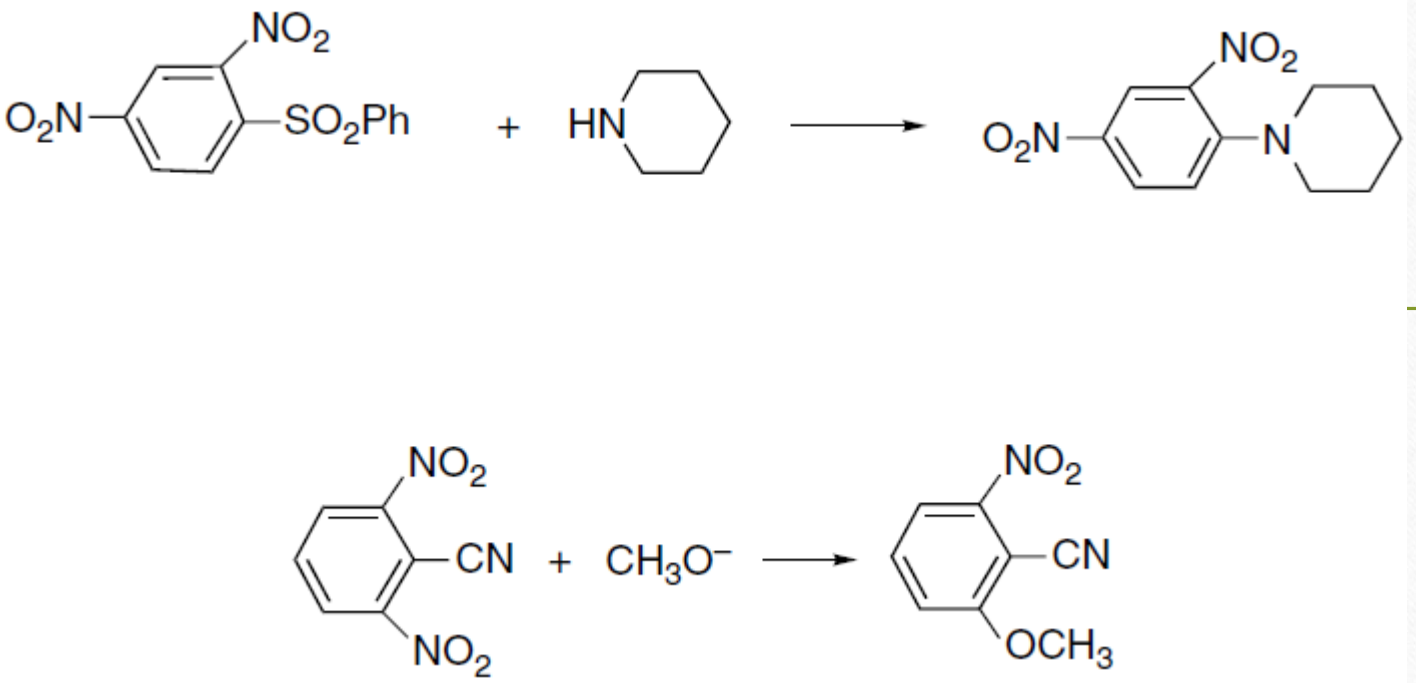
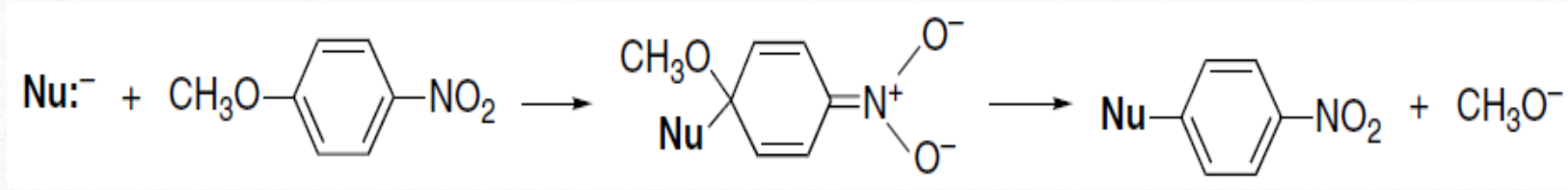


Fig. 9.12. Computed [B3LYP/6-31+G(*d*)] energy barriers for halide exchange by nucleophilic aromatic substitution. Data from *J. Org. Chem.*, **62**, 4036 (1997).

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.

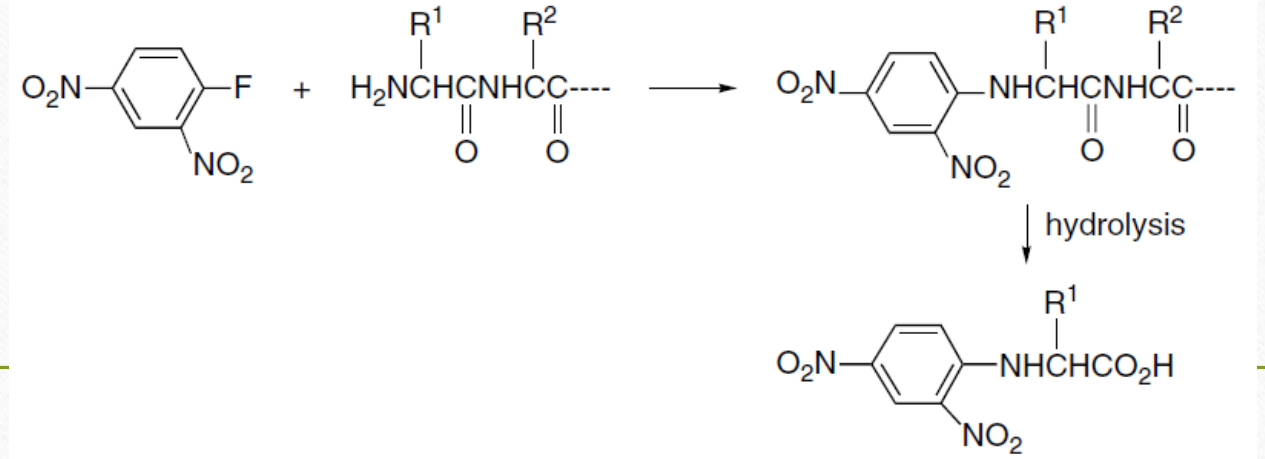


Groups other than halogen can serve as leaving groups. Alkoxy groups are very poor leaving groups in S_N2 reactions but can act as leaving groups in aromatic substitution. The reason is the same as for the inverted order of reactivity for the halogens. The rate-determining step is the addition, and the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



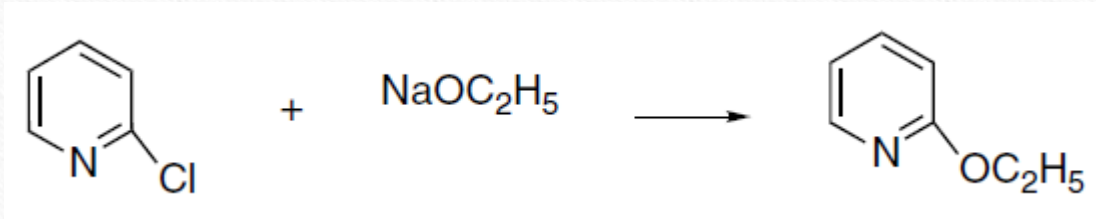
- The addition intermediates, which are known as *Meisenheimer* complexes, can often be detected spectroscopically and can sometimes be isolated. Especially in the case of adducts stabilized by nitro groups, the intermediates are often strongly colored.

- 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. Substitution by carbanions is somewhat less common. This may be because there are frequently complications resulting from electron transfer processes with nitroaromatics.

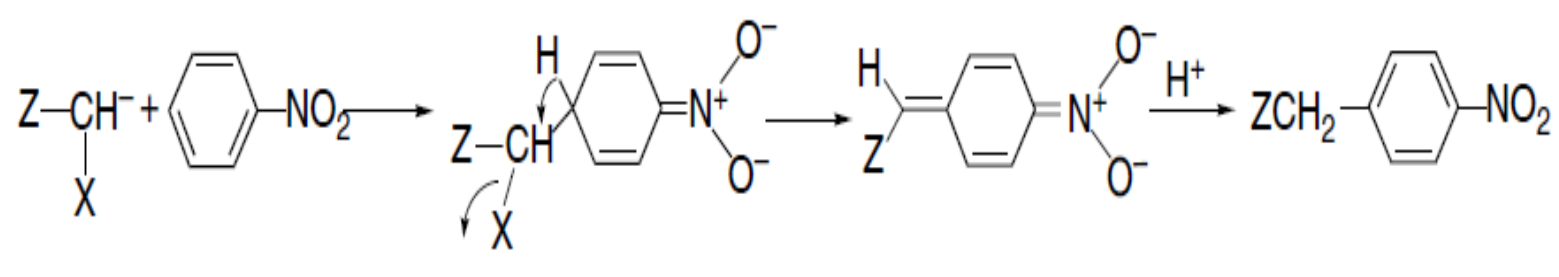


Solvent effects on nucleophilic aromatic substitutions are similar to those discussed for S_N2 reactions. Dipolar aprotic solvents, crown ethers, and phase transfer catalysts all can enhance the rate of substitution by providing the nucleophile in a reactive state with weak solvation.

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 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.

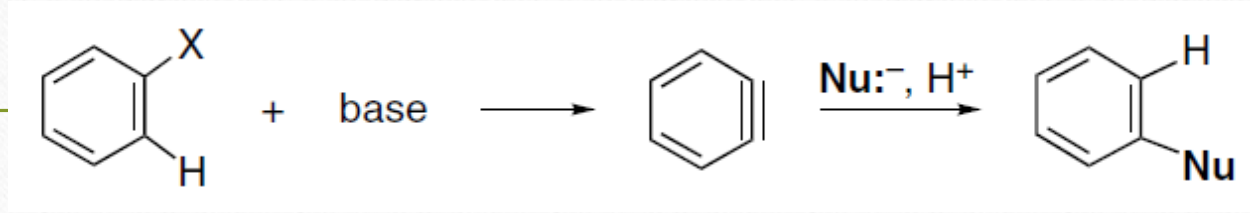


A variation of the aromatic nucleophilic substitution process in which the leaving group is part of the entering nucleophile has been developed and is known as *vicarious nucleophilic aromatic substitution*.

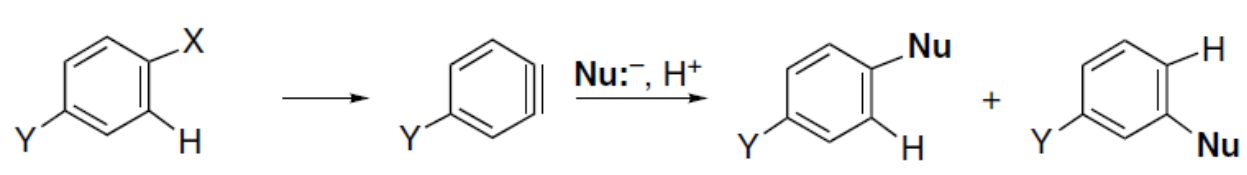
These reactions require a strong EWG substituent such as a nitro group but do not require a halide or other leaving group. The reactions proceed through addition intermediates.

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.

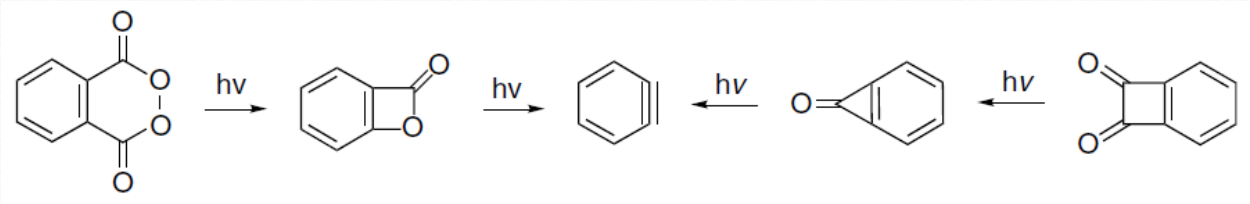
Nucleophilic Aromatic Substitution by the Elimination-Addition Mechanism

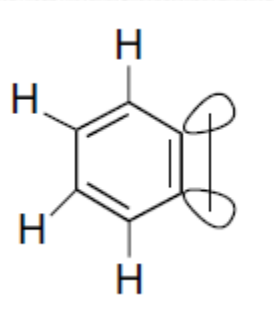


The elimination-addition mechanism involves a highly unstable intermediate, known as *dehydrobenzene* or *benzyne*.



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.



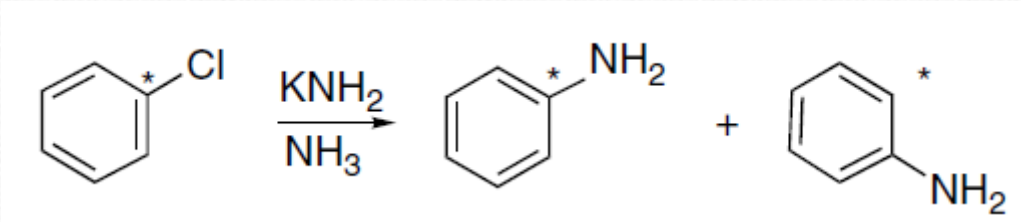


Benzyne can be observed spectroscopically in an inert matrix at very low temperatures. For these studies the molecule is generated photolytically.

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.

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

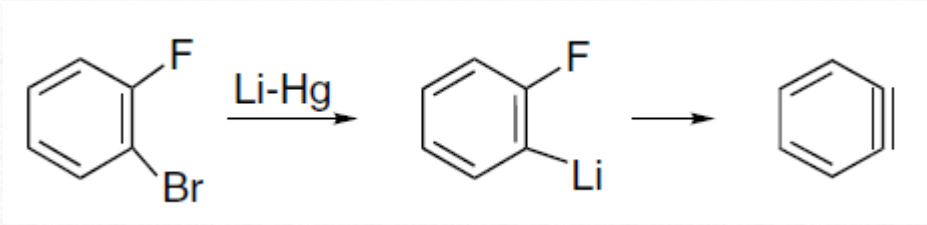
^{14}C-label in the starting material was found to be distributed between C (1) and the *ortho* position in the aniline, consistent with a benzyne intermediate.



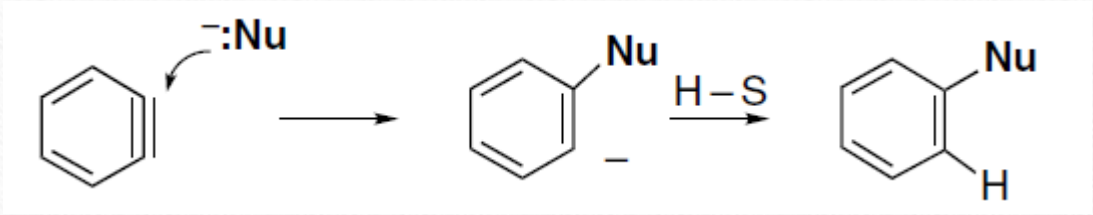
The order Br > I > Cl > F has been established in the reaction of aryl halides with KNH_2 in liquid ammonia. This order has been interpreted as representing a balance between two effects.

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.

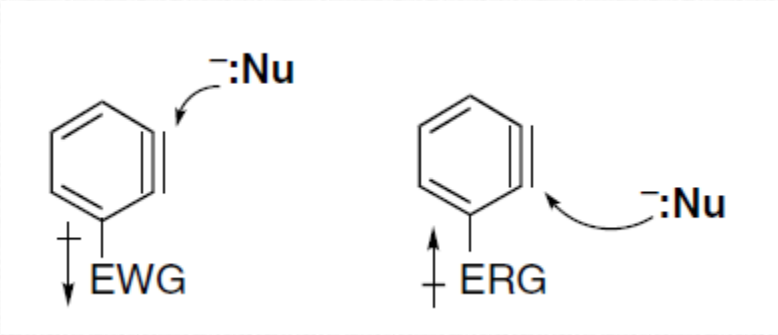
Benzyne can also be generated from *o*-dihaloaromatics.



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.

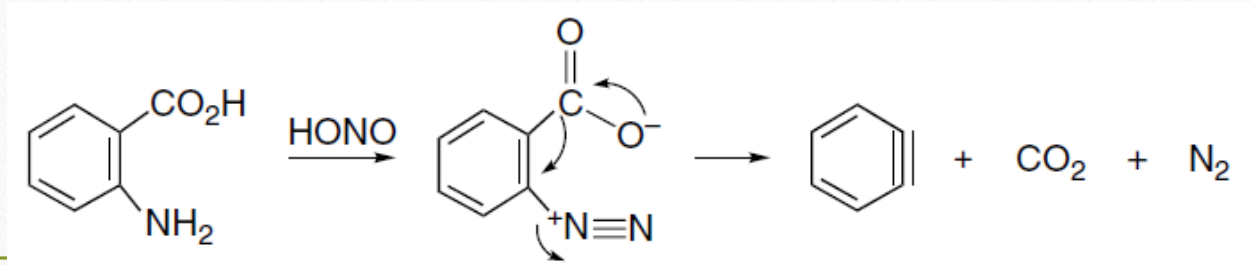


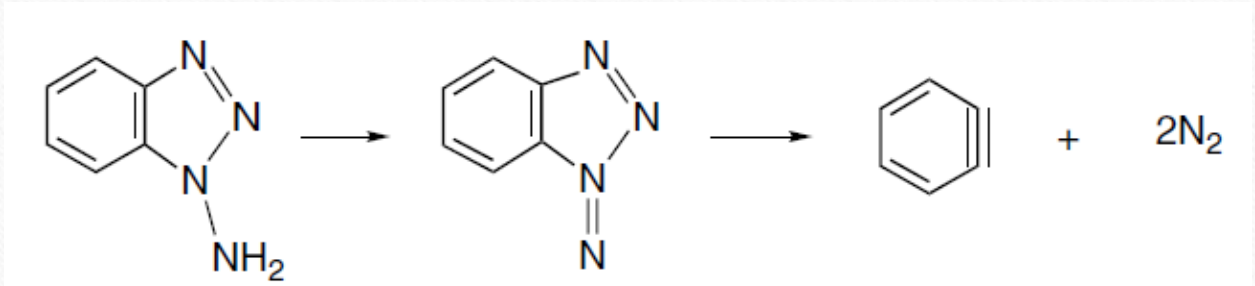
Addition of nucleophiles such as ammonia or alcohols or their conjugate bases to benzynes takes place very rapidly.



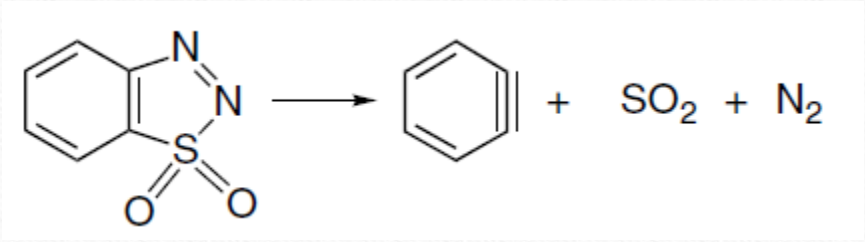
The regiochemistry of the nucleophilic addition is influenced by ring substituents. EWGs tend to favor addition of the nucleophile at the more distant end of the "triple bond," since this permits maximum stabilization of the developing negative charge. ERGs have the opposite effect.

Selectivity is usually not high, however, and formation of both possible products from monosubstituted benzynes is common. Probably the most convenient method is diazotization of *o*-aminobenzoic acids.





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.



Benzothiadiazole-1, 1-dioxide decomposes with elimination of sulfur dioxide and nitrogen.

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