# Fundamentals of Theoretical Organic Chemistry

Lecture 9

2.2.2 Electrophilic substitution

The reaction which takes place between a reactant with an electronegative carbon and an electropositive reagent forming a polarized covalent bond is called electrophilic. In addition, if substitution occurs (i.e. there is a similar polarized covalent bond on the electronegative carbon, which breaks up during the reaction, so the reagent „substitutes" the „old" group or the leaving group) then this specific reaction is called electrophilic substitution. The electronegative carbon is called the reaction centre. In general, the good reactant are molecules having electronegative carbons like aromatic compounds, alkenes and other compounds containing electron-rich double bonds. These are called Lewis bases. On the contrary, good electrophilic reagents are electron poor compounds/molecule groups like acid-halides, which easily form covalent bond with an electronegative centre, thus creating a new molecule. These are often referred to as Lewis acids.

According to molecular orbital (MO) theory the driving force for the electrophilic substitution (SE) is a Lewis complex formation involving the LUMO of the Lewis Acid Reagent and the HOMO of the Lewis Base Reactant.

Reactant   Reagent

LUMO

LUMO

HOMO

Lewis base   Lewis acid

Lewis complex
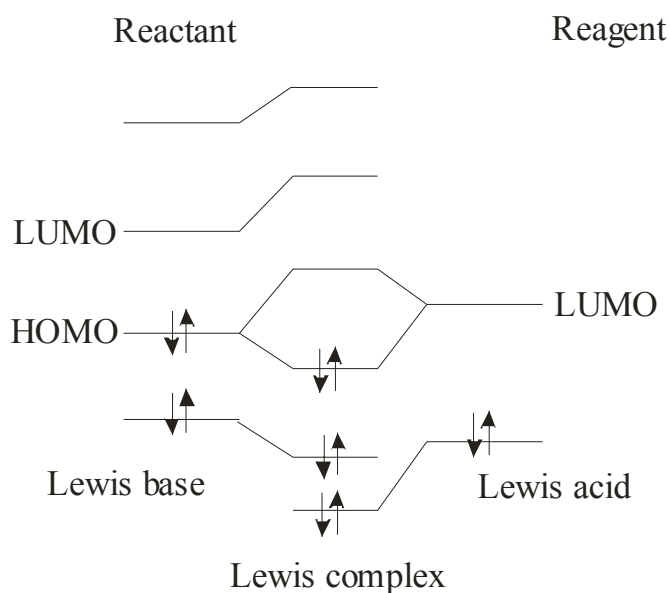
Types of reactions:

There are four types of reactions as illustrated below:

Table. 2.2.2-1.

Saturated	Aromatic
S_E1	S_E1 (Ar)
S_E2	S_E2 (Ar)

S_E reaction on saturated atom:

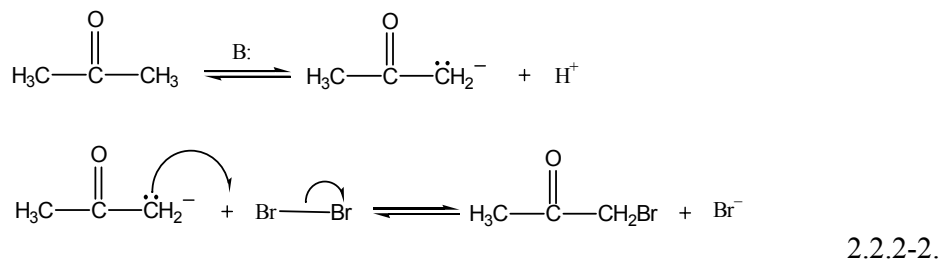**(1)Unimolecular electrophilic substitution (S_E1):**

The reaction proceeds in two steps. After the departure of the leaving group, the negatively charged reaction intermediate will combine with the reagent.


$$2.2.2\text{-}1.$$
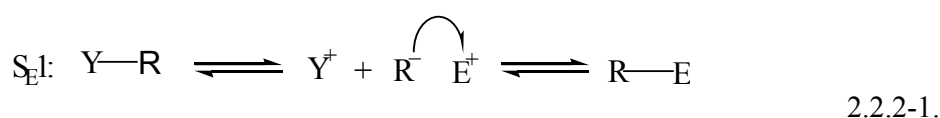
Since the reaction speed is only depending on the concentration of the reactant, the reaction follows first order kinetics.

$d[RE]/dt=k[YR]$ (first order reaction kinetics)

The basis catalysed halogenation of ketones is a classical S_E1 reaction.

$$2.2.2\text{-}2.$$

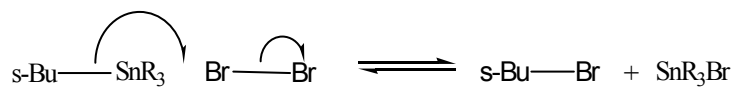**(2) Bimolecular electrophilic substitution (S_E2):**

A bimolecular reaction proceeds in one step through an intermedier complex.

$$2.2.2\text{-}3.$$
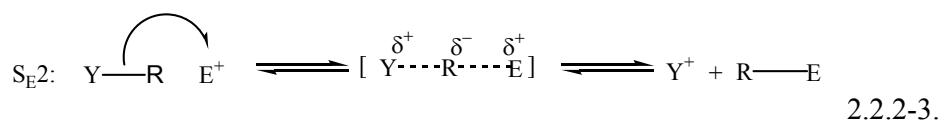
The speed of the reaction is depending on the concentration of both the reactant and the reagent, thus the reaction has second order kinetics
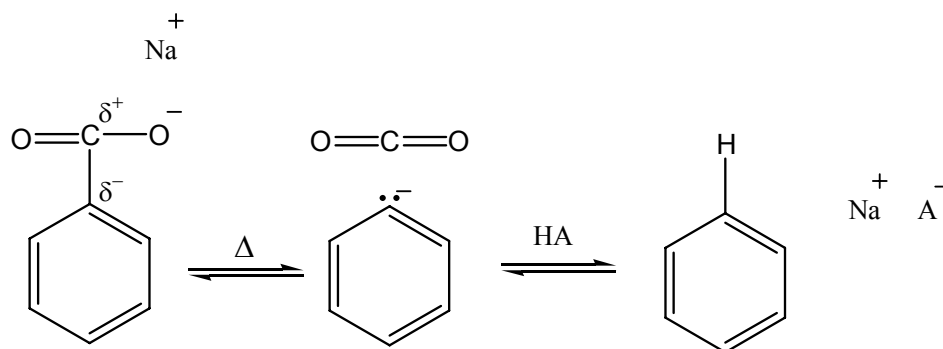
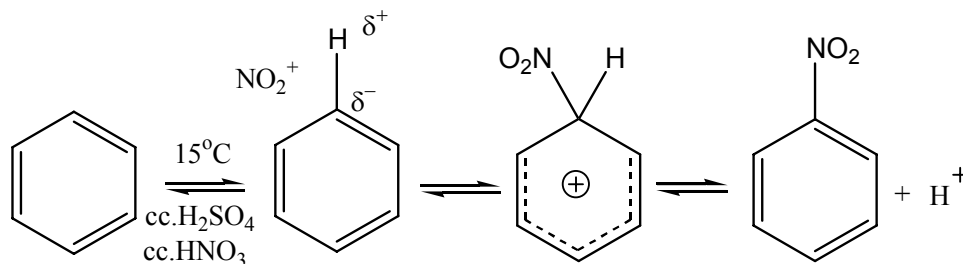$d[RE]/dt=k[YR][E+]$ (second order kinetics).

Halogenation of metal-alkilates is an S_E2 reaction

2.2.2-4.

Unsaturated/Aromatic C-atom:

Aromatic electrophilic substitution (S$_E$Ar)

There are two mechanisms of aromatic electrophilic substitution S$_E$1 and S$_E$2:

(3) S$_E$1:Thermal decrboxylation of benzoate

(4) S$_E$2: Nitration of benzene

Stereochemistry of Electrophilic Substitution.

Saturated C-atom

S$_E$1: Mechanism of the unimolecular electrophilic substition is quite similar to that of the unimolecular nucleophilic substitution. Accordingly, the S$_E$1 reaction proceeds in two steps. First, the electropositive leaving group generally catalaysed by a Lewis-acid departures from the substrate. Thus, an electronegative planar intermedier is reached, which -unlike intermediate of S$_E$2 reaction- could be detected in the reaction mixture. Second, an electropositive reagent will react with
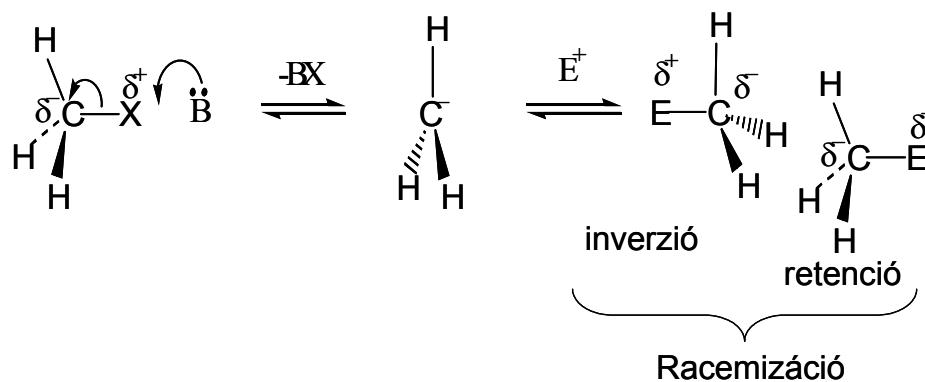
the electronegative substrate, thus forming the product. Considering the planar electronegative intermediate, the reaction could be followed by retention or inversion of the C-atom of the reaction centre.

S_E2: While bimolecular nucleophilic reaction usually proceeds with inversion due to the orientation of the bonding orbitals and lone pairs, electrophilic substitution could induce retention and inversion as well. Both reaction path is accepted by the Fukui FMO (Frontal Molecular Orbital theory). The reaction path of retention is explained by the attack of the electropositive reagent to the electronegative bonding orbital. On the contrary inversion could be favoured by a larger substituent. The simplest example is SE2 reaction of methane with different reagents (NEXT FIGURE) E.D.Jemmis, J. Chanrasekhar and P.v.R. Schleyer, JACS, 101, 527 (1979) és a benne levő referenciák. Hydrogen as a reagent is small enough to attack the bonding orbital of the reaction centre, thus forming a three centered two e− bond, which then proceeds further to the departure of the leaving group (i.e the other hydrogen) and finishing with retention. On the other hand, according to theoretical calculations the larger Li and Be-H favors the S_E2 reaction with inversion. E.D.Jemmis, J. Chanrasekhar and P.v.R. Schleyer, JACS, 101, 527 (1979)
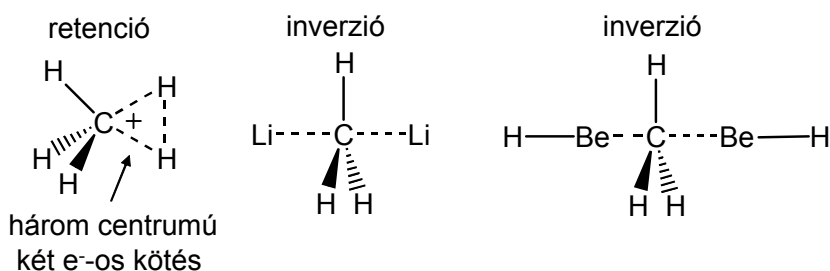

Unsaturated/Aromatic C-atom

S$_E$Ar: The only significant difference between aromatic electrophilic substitution and S$_E$2 reaction on an aliphatic C-atom is the approach of the reaction centre. In case of S$_E$Ar the electrophilic reagent approaches to the π electron cloud of the aromatic ring forming a so called π-complex, which is located approximately 3 Å-s above the aromatic ring.Proceeding along the reaction coordinate the substrate and the reagent forms a σ-complex on one of the aromatic carbons, and finally the leaving group (i.e. hydrogen) departures. When the carbon atoms of the ring could be distinguished, the reaction leadsto several isomers.

Hydrogen-Deuterium exchange in benzene- σ-complex, π-complex

When benzene is dissolved in liquid HF, a phase separation leads to a 1:1 molar mixture that poorly conducts electricity. Nevertheless, the 1:1 molar composition suggests that we are dealing with, not only a mixture, but also a stoichiometric complex. In the presence of BF$_3$ (in addition to HF), a salt-like complex $[C_6H_7]^{(+)}[BF_4]^{(-)}$ is formed which can be crystallized. The melted crystal conducts electricity very well as expected for a salt. This benzenium tetrafluoroborate has the following structure.
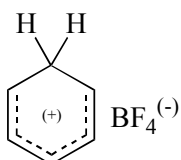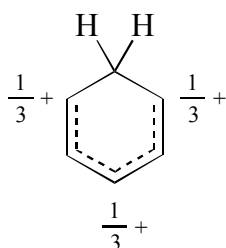

2.2.2-5.

For the cation, three resonance structures may be given [2.2.2-6] which suggest an average of +1/3 of the charge at the two ortho and para positions [2.2.2-7].
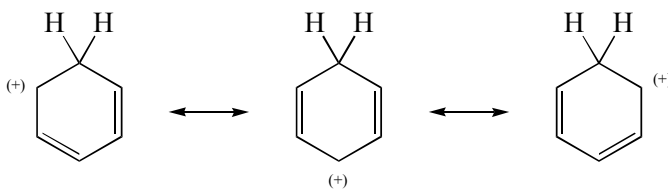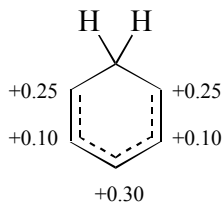

2.2.2-6.

2.2.2-7.

A slightly more sophisticated MO theory than SHMO yields a somewhat different charge distribution [2.2.2.-8]. However, the two equivalent ortho and the para positions are still the most electron deficient.
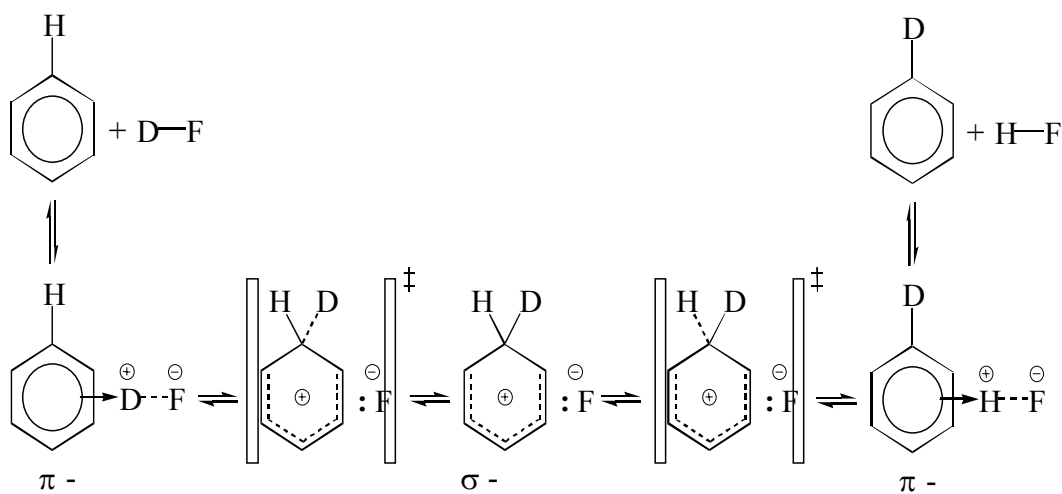

2.2.2-8.

Using DF instead of HF, one of the protons of benzene is exchanged to deuterium.

$$C_6H_6 + DF + BF_3 = [C_6H_6D]^{(+)} + HF + BF_3$$

2.2.2-9.

The H/D exchange is envisioned to occur according to the following mechanism in which a π–complex is formed first and then converted subsequently to an σ-complex.

The energy profile for this reaction is shown schematically in Figure 2.2.2-1. This energy profile is symmetrical, showing mirror image symmetry with respect to the central intermediate, the σ-complex.
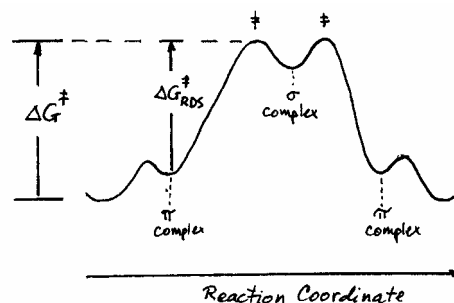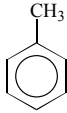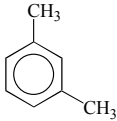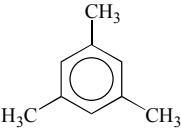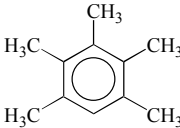
Figure 2.2.2-1. A schematic free-energy profile for the H/D exchange reaction in benzene with H[BF$_4$].

Various methylated benzenes are more basic than benzene itself and they form σ-complexes with HF. In contrast, HCl also dissolves in these hydrocarbons but only forms π–complexes. The concentration of the σ-complex and, consequently, the equilibrium constant (K) can be determined by conductivity measurements, while that of the π–complex can be determined spectroscopically since these complexes are colored.

The following table summarizes such relative stabilities as a function of methylation. These relative stabilites are presented as σ- and π-basicities.

**Table. 2.2.2-2. Sigma and pi-basicities of selected methylated benzenes.**

π-basicity	1	1.5	2.0	2.6	4.5
σ-basicity	1	790	10^6	630x10^6	2x10^9

It should be emphasized that the larger σ-basicity values, which measure relative stabilites, do not mean that the σ-complex is more stable than the π–complex. In fact, Figure 2.2.2-1 shows the opposite; the σ–complex is less stable, in the thermodynamic sense, than the π–complex. These σ– and π–basicities do give, however, relative stabilities with respect to the benzene σ– and π– complex.

It is interesting to note that the π–basicities hardly change at all, while the σ–basicities change drastically with the number of methyl groups (c.f. Table 2.2.2-2). This implies that the π–complex [2.2.2-10] formation represents only a minor perturbation on the π–aromatic sextet.

(a)   (b)
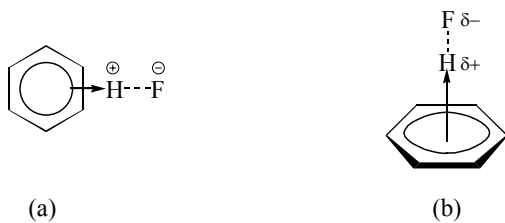
2.2.2-10.

In contrast to this in the σ–complex [2.2.2-5], the aromatic character ceases to exist and the various methyl groups stabilize the conjugated cation [2.2.2.-6] to various degrees.

15.3 Electrophilic aromatic substitution of benzene

The mechanism of electrophilic aromatic substitution in benzene with an electrophile $X^{(+)}$ can be depicted by the following stoichiometric equation:

$$C_6H_6 + X^{(+)} \rightarrow C_6H_5X + H^{(+)}$$
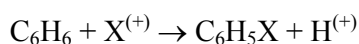
2.2.2-11.

The mechanism on Figure2.2.2-2 is envisaged to be analogous to the H/D exchange.
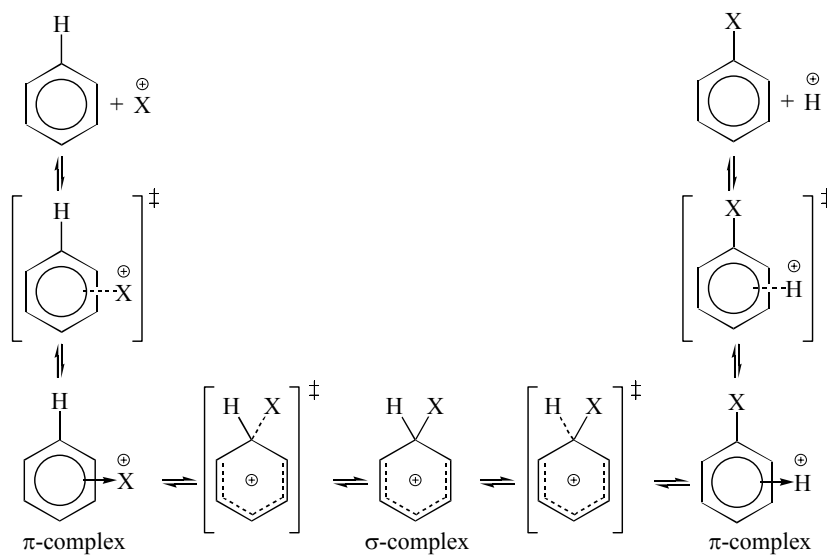
Figure 2.2.2-2.

The energy profile for an electrophilic aromatic substitution may look like the one presented in Figure 2.2.2-1, but now the two halves are not mirror images of one another. Such a schematic profile is shown in Figure 2.2.2-3.

Figure 2.2.2-3. A schematic energy profile for the general electrophilic aromatic substitution of benzene encompassing five minima and four transition states. This profile is particularly illustrative for the halogenation reactions of benzene.
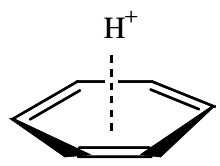

Figure 2.2.2-4. Protonation of benzene. Geometriacal and energetical parameters of π- and σ-complexes of benzene with hydroxonium and benzenium with hydrogen at MP2/6-31+G(d,p).It is interesting to see how C-C bond length is effected by H+ at different levels of theory:

H$^+$

	R(CC)
HF/6-31G(d)	1.399
HF/6-31G(d,p)	1.397
HF/6-31G(d,2p)	1.397
MP2(full)/6-31G(d,p)	1.409
MP2(fc)/6-31G(d,p)	1.408
B3-LYP/6-31G(d,p)	1.409
BzH$^+$ MP2/6-31+G(d,p)	1.400, 1.403, 1.409

Figure 2.2.2-5. BzH$^+$ indicates benzene-hidroxonium π-complex.

Glukhovtsev et al. J. CHEM. SOC. Chem. Commun. 1995 2347-2348

Kryachko et al J. Phys. Chem. A 2001, 105, 153-155

Exp:IRMPD
Theo:B3LYP/6-311++G(d,p)

IR MultiPhoton Dissociation
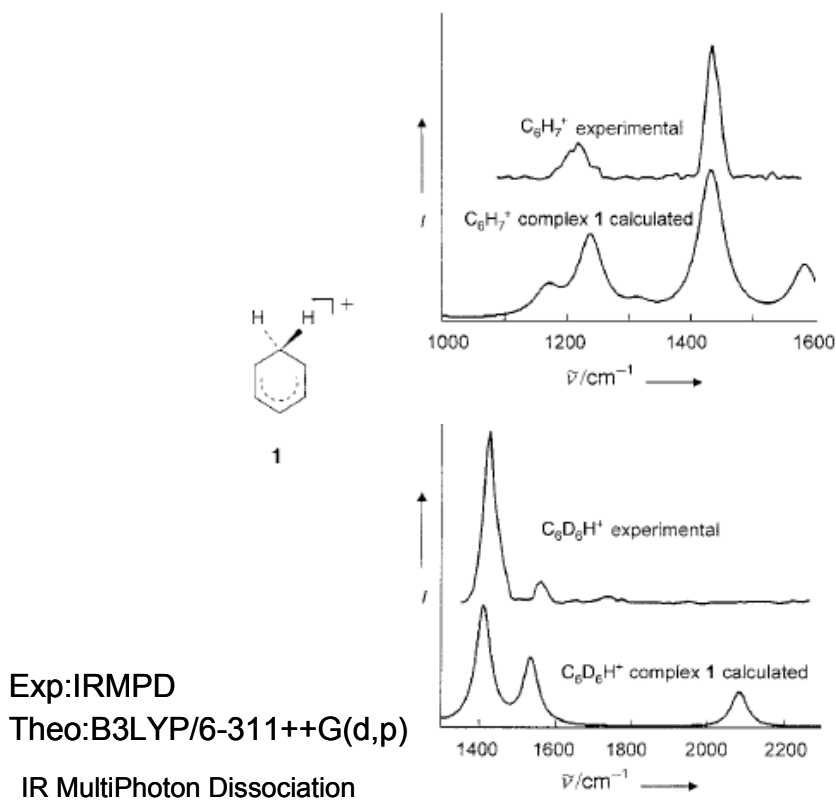
Figure 2.2.2-6. Calculated and experimental IR spectra of C$_6$H$_7^+$ C$_6$D$_6$H$^+$ for benzene:

Plíva et al. J. Mol. Spectrosc. 1991, 148, 427

Handy et al. Chem. Phys. Lett. 1992, 197, 506

And for benzenium ion, C$_6$H$_5^+$ has longer C-C bonds, according to theoretical approximations:

| cation	C_1-C_2 C_1-C_6	C_2-C_3 C_5-C_6	C_3-C_4 C_4-C_5	$C_6-C_1-C_2$
benzenium (calcd)	1.473^b 1.461^c	1.373 1.366	1.413 1.406	117.0 117.4.0
benzenium (exptl)	1.381(6) 1.391(6)	1.345(6) 1.345(6)	1.391(6) 1.381(6)	119.8(3)

b: B3LYP/6-31G(d)
c: B3P86/6-311+G(d,p)

Reed, C. etal. JACS 2003, 125, 1796-1804

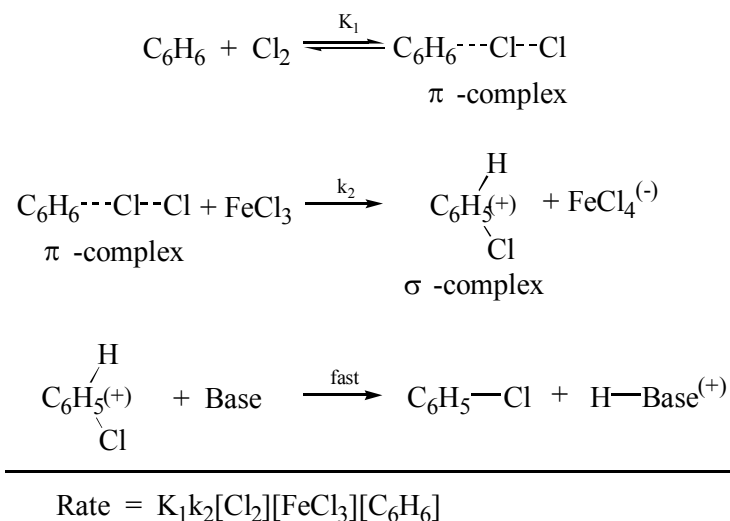## Halogenation of benzene- The spin momentum conservation rule

Halogenation usually means chlorination or bromination. The electrophilic aromatic substitution is usually enhanced by the presence of a Lewis acid such as $FeCl_3$ and $FeBr_3$ for chlorination or bromination respectively.

The kinetics of halogenation is not always simple but in many instances a third order rate equation represents the reaction rather well.

$$C_6H_6 + Cl_2 + FeCl_3 \xrightarrow{k_{obs}} C_6H_5-Cl + H^{(+)}[FeCl_4^{(-)}$$

2.2.2-12.
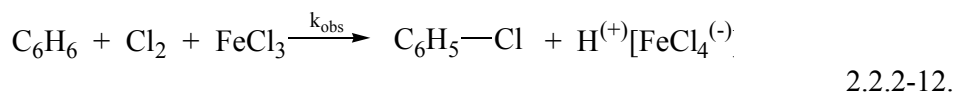
$$Rate = \frac{d[C_6H_5Cl]}{dt} = k_{obs}[C_6H_5][Cl_2][FeCl_3]$$

2.2.2-13.

This observation narrows down considerably the number of possible mechanisms that can occur. The following two alternative mechanisms (A and B) are kinetically equivalent and both of them are in agreement with the observed rate law.
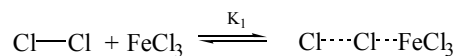
Mechanism A

$$C_6H_6 + Cl_2 \xrightarrow{K_1} C_6H_6\cdots Cl\cdots Cl$$

$$\pi \text{ -complex}$$

$$C_6H_6\cdots Cl\cdots Cl + FeCl_3 \xrightarrow{k_2} C_6H_5^{(+)}\overset{H}{\underset{Cl}{\diagup}} + FeCl_4^{(-)}$$

$$\pi \text{ -complex} \qquad\qquad \sigma \text{ -complex}$$

$$C_6H_5^{(+)}\overset{H}{\underset{Cl}{\diagup}} + Base \xrightarrow{fast} C_6H_5{-}Cl + H{-}Base^{(+)}$$

$$\text{Rate} = K_1 k_2 [Cl_2][FeCl_3][C_6H_6]$$

2.2.2-14.

In this mechanism, the benzene···halogen–complex is formed first and the Lewis acid (FeCl$_3$) is the catalytic agent that converts the π–complex to σ–complex.
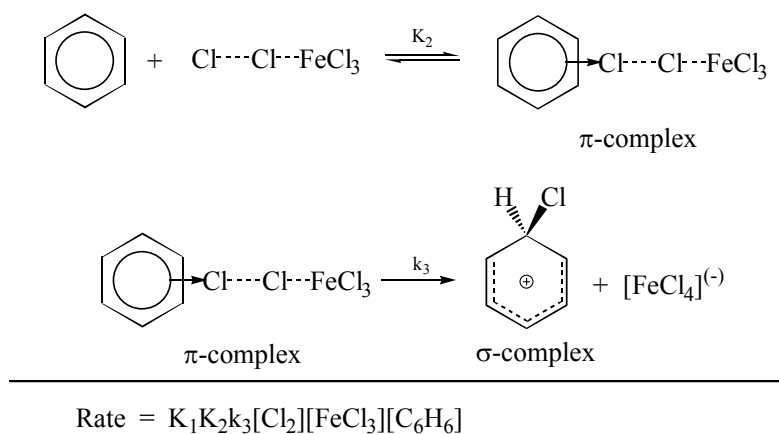
Mechanism B

In this mechanism, the first step is a complex formation between the halogen molecule and the Lewis acid.

$$Cl{-}Cl + FeCl_3 \xrightarrow{K_1} Cl\cdots Cl\cdots FeCl_3$$

2.2.2-15.

This is followed by formation of the π–complex and, subsequently, formation of the σ–complex.

$$\text{Rate} = K_1K_2k_3[Cl_2][FeCl_3][C_6H_6]$$

2.2.2-16.

Mechanism C

We can think of a third mechanism which would be kinetically equivalent to the previous two (A and B). However, this mechanism postulates the existence of a halonium ion $(X^{(+)})$ intermediate, which would be of triplet multiplicity:
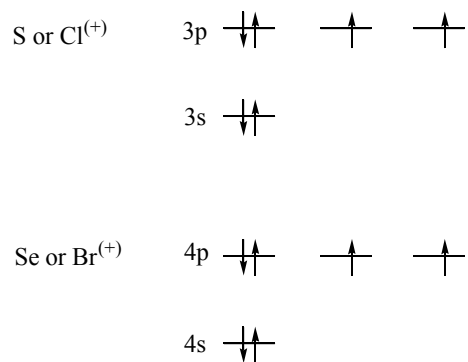
2.2.2-17.

The change of multiplicity during a chemical reaction is forbidden by the "spin momentum conservation rule". Therefore, we can eliminate Mechanism c (shown below) as a possibility.
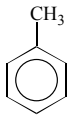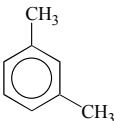
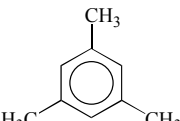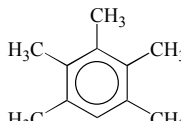$$\text{Rate} = K_1 K_2 k_3 [Cl_2][FeCl_3][C_6H_6]$$
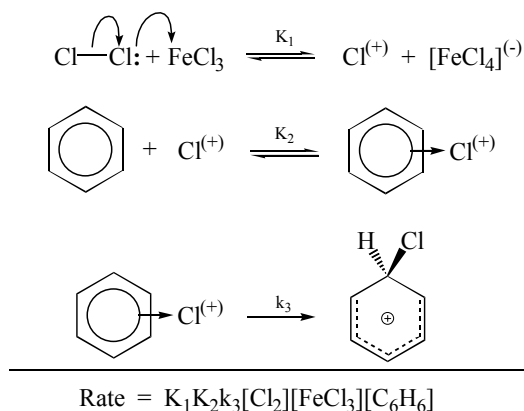
2.2.2-18.

Many textbooks use this third alternative (mechanism C) even though it involves a forbidden process, namely, the formation of $X^{(+)}$ [i.e. $Cl^{(+)}$ or $Br^{(+)}$] which is of triplet multiplicity. It should be noted that such a policy is due to the fact that using $X^{(+)}$ as reaction intermediate for halogenation makes all electrophilic aromatic substitution mechanisms match that shown in 2.2.2-2. Similar reactions may be written for bromine.

There appears to be a correlation between the σ–basicity of methylated benzenes presented in Table 2.2.2-2 and the relative rates of chlorination for the same compounds. A limited comparison is shown in Table 2.2.2-3.

Table. 2.2.2-3. A comparison of relative σ–basicities and relative chlorination rates of selected methylated benzenes.

relative σ-basicity	1	790	10^6	630×10^6	2×10^9
relative chlorination rate	1	340	1.8×10^5	30×10^6	1.34×10^8

A more extensive comparison is shown graphically in Figure 2.2.2-7.
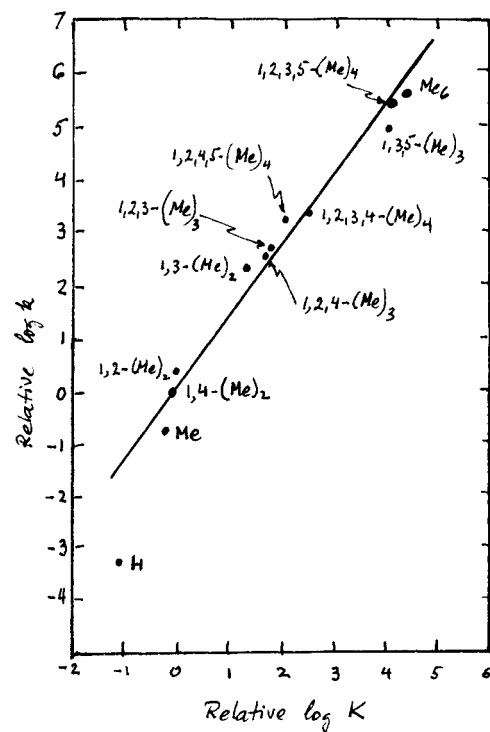
Figure 2.2.2-7. A correlation between log k of chlorination and log K of σ–protonation in HF for various methylated benzenes.

A similar correlation exists for bromination of the same family of compounds. Such a comparison is shown in Table 2.2.2-4

Table. 2.2.2-4. A comparison of log relative σ–basicity and log relative* bromination rates of polymethylated benzenes.

Methyl substituents	Relative basicities	Log (k/k_o)
None	0	0
Me	2.90	2.78
1,2-Me$_2$	2.90	2.72
1,3-Me$_2$	6.00	5.71
1,4-Me$_2$	3.51	3.40
1,2,3-Me$_3$	6.30	6.22
1,2,4-Me$_3$	6.30	6.18
1,3,5-Me$_3$	8.80	8.28
1,2,3,4-Me$_4$	7.30	7.04
1,2,3,5-Me$_4$	8.30	8.62
1,2,4,5-Me$_4$	7.00	6.45
Me$_5$	9.30	8.91

*log (k/ko) measured in 85% AcOH where ko is the rate constant for benzene.

All of these suggest that the energy of activation for the rate-determining step (RDS) is associated with the following step:

$$\pi\text{-complex} \xrightarrow{\ E_a(RDS)\ } \sigma\text{-complex}$$
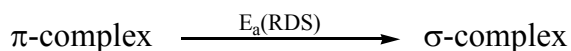
2.2.2-19.

as depicted in Figure 2.2.2-3.
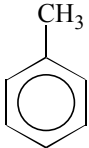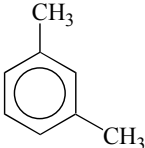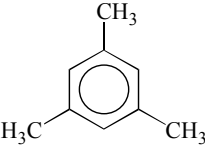
Nitration of benzene

It should be emphasized that in general, Introductory Organic Chemistry textbooks oversimplify the energy profile associated with electrophilic aromatic substitution by omitting the π–complex and emphasizing only the role of the σ–complex. In view of the reaction energy profile presented in Figure 2.2.2-3, this does not appear to be a very dramatic approximation since the barrier that leads to the π–complex is negligible compared to the

barrier that leads to the σ–complex. This approximation served us well in the halogenation reaction since the log relative rate constants (i.e. log (k/k_o)) correlated rather well with the σ–complex stability (c.f. Table 2.2.2-3, Figure 2.2.2-7 and Table 2.2.2-4).

In contrast to the above, the relative rates of nitration correlate with the π–complex stabilities as shown in Table 2.2.2-5 for polymethylated benzenes.

Table. 2.2.2-5. Comparison of relative π–basicities and relative nitration rates of selected methylated benzenes.

relative π-basicity	1	1.5	2.0	2.6
relative nitration rate	1	1.6	1.6	2.7

George Olah, long before he received a Nobel Prize in Chemistry, interpreted these results to mean that the barrier of the rate determining step (RDS) is the π–complex formation and not the σ–complex formation. This means that Figure 2.2.2-3 qualitatively depicts the halogenation reaction but not the nitration of benzene. The following figure shows an energy profile that can be associated with the nitration of benzene.
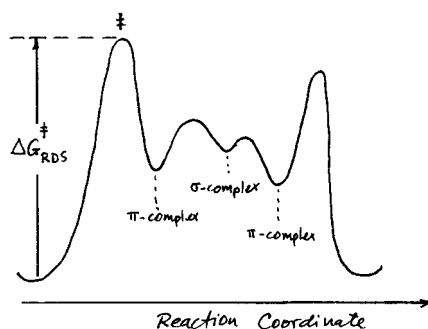

Figure 2.2.2-8. A schematic illustration of the energy profile for the nitration of benzene. (This should be compared to Figure 2.2.2-3.)

The nitrating species, i.e. the electrophile, in this case is $NO_2^{(+)}$. This ion is isoelectronic to carbon dioxide.
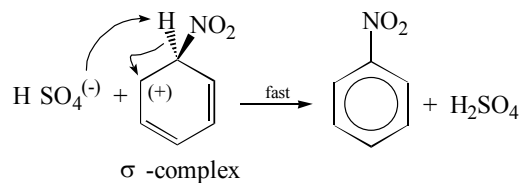
(a)   (b)

2.2.2-20.

The kinetics of nitration, of course, greatly depends on how the electrophile, NO_2^+, is generated in the reaction mixture. If $F\text{-}NO_2 + BF_3$ is used, then the mechanism and kinetics may be expected to be analogous to Mechanism B of chlorination: 2.2.2-16 with the notable exception that the π–complex formation will be the rate determining step (RDS).

$$\text{Rate} = K_1 k_2 [C_6H_6][F\text{-}NO_2][BF_3]$$
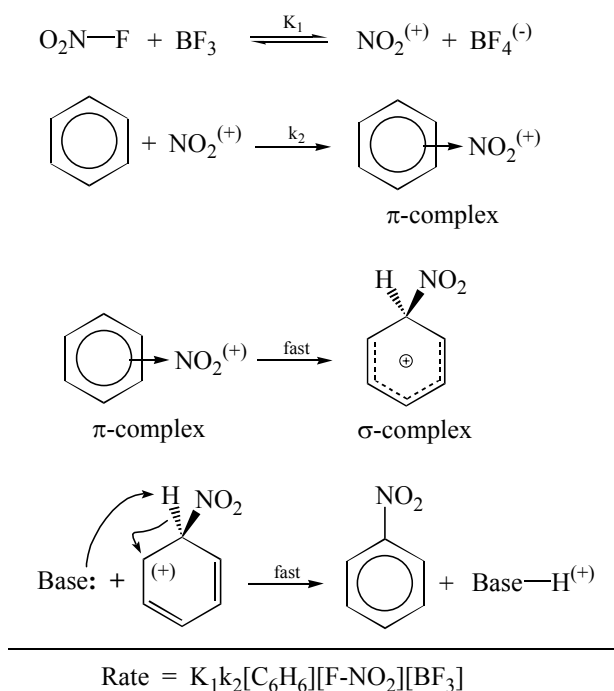
2.2.2-21.

However, if the NO_2^+ is generated from HNO_3 by using concentrated H_2SO_4, then the mechanism, as well as the kinetics, will be considerably more involved. The following mechanism may only be regarded as an oversimplified case since it is assumed that the NO_2^+ formation is achieved by a set of equilibrium processes.

$$H_2SO_4 + HONO_2 \underset{}{\overset{K_1}{\rightleftharpoons}} \; H\,SO_4^{(-)} + H_2O\!-\!NO_2^{(-)}$$

$$H_2ONO_2^{(+)} \underset{}{\overset{K_2}{\rightleftharpoons}} \; H_2O + NO_2^{(+)}$$

$$H_2SO_4 + H_2O \underset{}{\overset{K_3}{\rightleftharpoons}} \; H_3O^{(+)} + HSO_4^{(-)}$$

π -complex

π -complex   σ -complex

σ -complex
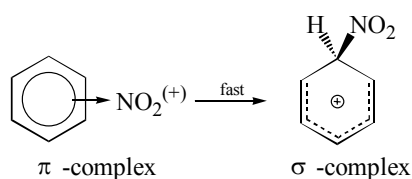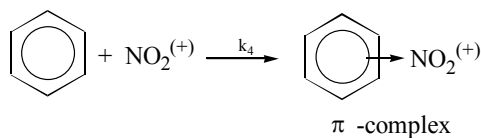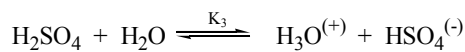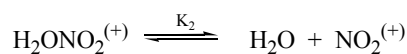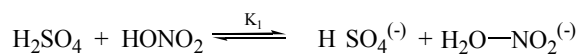
$$\text{Rate} = K_1 K_2 K_3 k_4 \frac{[H_2SO_4]^2 [HNO_3]}{[HSO_4^-]^2 [H_3O^+]} [C_6H_6]$$

2.2.2-22.

Sulfonation of benzene

The electrophile can be SO_3 in spite of the fact that the S atom has a lone electron pair since the sulfur carries a partial positive charge.
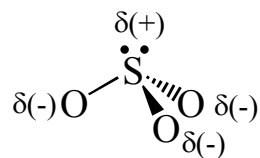
2.2.2-23.

However, when SO_3 is dissolved in 100% sulfuric acid it can be protonated at either oxygen or sulfur. The S-protonated sulfur trioxide cannot be involved in the sulfonation process thus we might say that S-protonation substantially reduces the electrophilicity of SO_3. In contrast to this, O-protonation is expected to increase the electrophilicity of SO_3. Thus, it is quite likely that in the majority of sulfonation steps, when SO_3/H_2SO_4 is used, the

electrophile is $^{(+)}SO_3H$. This electrophile may also be formed in concentrated H_2SO_4 via protonation and subsequent dehydration. This mechanism is formally analogous to the NO_2^+ formation [2.2.2-22].

$$H_2SO_4 + H_2SO_4 \xrightleftharpoons{K_1} \quad + \ H\,SO_4^{(-)}$$

<div style="text-align: right">2.2.2-24.</div>

$$\xrightleftharpoons{K_2} \quad H_2O + S\text{ }^{(+)}$$

<div style="text-align: right">2.2.2-25.</div>

$$+ SO_3H^{(+)} \xrightleftharpoons{K_3} \quad \text{—}SO_3H^{(+)}$$

π-complex

<div style="text-align: right">2.2.2-26.</div>

$$\text{—}SO_3H^{(+)} \xrightleftharpoons{K_4}$$

π-complex   σ-complex

<div style="text-align: right">2.2.2-27.</div>

$$H\,SO_4^{(-)} + \xrightleftharpoons{K_5} \quad \text{—}H^{(+)}$$

π -complex

<div style="text-align: right">2.2.2-28.</div>

$$\text{—}H^{(+)} + H\,SO_4^{(-)} \xrightleftharpoons{K_6} \quad + H_2SO_4$$
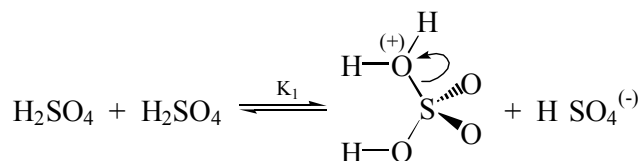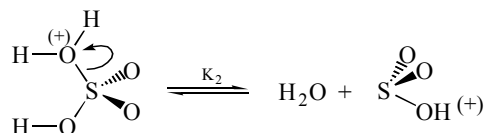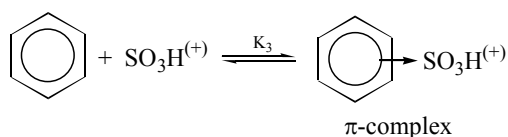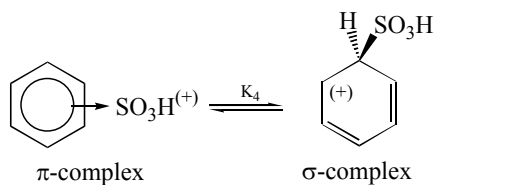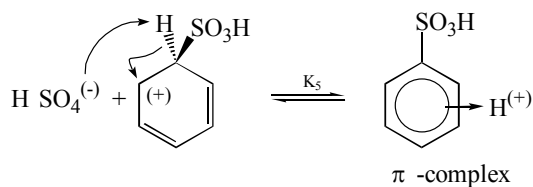
π -complex

<div style="text-align: right">2.2.2-29.</div>

The reaction is completely reversible; thus every step in the above box is marked as equilibrium. Consequently, not only sulfonation,

$$+ H_2SO_4 \longrightarrow \quad + H_2SO_4$$

<div style="text-align: right">2.2.2-30.</div>

but desulfonation
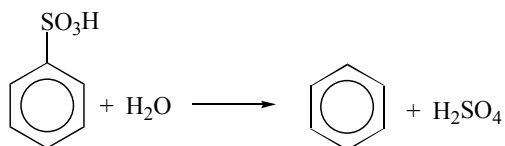
2.2.2-31.

is also possible. There is a marked difference with respect to nitration and halogenation. The implication of this is that the barrier height is accessible both ways. Although, the energy profile of the reaction may not be as symmetric as that for the protonation (c.f. Figure 2.2.2-2), it would not be as asymmetric as the potential energy curve given in Figure 2.2.2-3. Also the barrier about the Wheland intermediate would not be all that high to guarantee reversibility.
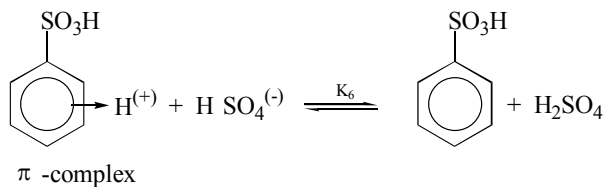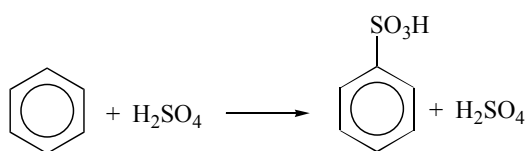

Reaction coordinate
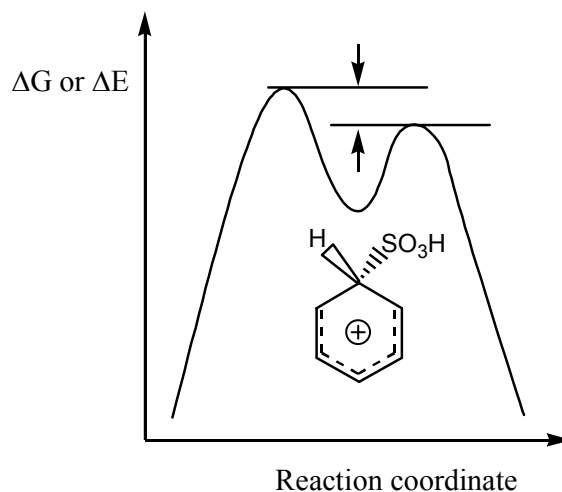
Figure 2.2.2-9. A schematic illustration of the energy profile in the vicinity of the Transition State for the sulfonation of benzene.

Orientation and Reactivity for single-substituted benzene

If the benzene ring already has a substituent (Z), then it may orient the incoming electrophile into an ortho (o-), meta (m-), or para (p-) position.
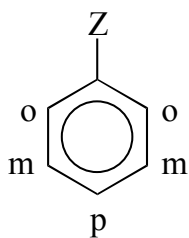
2.2.2-32.

If statistics were the only factor, which determined the product distribution, then we would always get:

o : m: p = 40: 40: 20

2.2.2-33.

In fact, in addition to the reaction conditions, the actual ratio depends, on the electronic structure at Z. The following examples are for nitration and they illustrate three general categories or types.

For Z = CH$_3$ o : m: p = 59: 4: 37

2.2.2-34.

For Z = Cl o : m: p = 30: 1: 69

2.2.2-35.

For Z = -NO$_2$ o : m: p = 6: 94: 0

2.2.2-36.

Clearly, none of these ratios are reminiscent of the statistical ratio [2.2.2-33]. This is what is called the orientation exerted on the incoming electrophile by the substituent (Z) already attached to the benzene ring.

The substituent Z also influences the reactivity of the aromatic ring. It may activate the ring, making it more susceptible to electrophilic attack, or it may deactivate the ring, making it less susceptible to electrophilic attack. In the former case, the substitution reaction will be faster and in the latter case, the substitution reaction will be slower than that of unsubstituted benzene. This rate difference translates to variations in the rate constants. Considering the relative rates of nitration we may find the following approximate relative rates for toluene, chlorobenzene and nitrobenzene.

—Z	—CH$_3$	—Cl	—NO$_2$
$k_{C_6H_5Z} / k_{C_6H_6}$	10	10^{-2}	10^{-3}

2.2.2-37.

The three compounds exemplify three types of substituents.

o, p directing with activation (e.g. –Z = –CH$_3$)

2.2.2-38.

o, p directing with deactivation (e.g. –Z = –Cl)

2.2.2-39.

m directing with deactivation (e.g. –Z = –NO$_2$)

2.2.2-40.

Various functional groups fall in these three categories.

Table. 2.2.2-6. Classification of substituents according to their effect on orientation and reactivity.

	o-, p-directing	m-directing
Activating (kC6H5Z/kC6H6) > 1	$—\ddot{\underset{\cdot\cdot}{O}}\colon^{(-)}$ $—\ddot{N}R^1R^2$ −OR −NH−COR −R −Ar −CH=CHR	No known functional group
Deactivating (kC6H5Z/kC6H5) < 1	−F −Cl −Br −I −CH₂X (halomethyl)	−CO−R −CO−OR −CO−Cl −C≡N −SO₃H −CF₃ −CCl₃ −NO₂ −NR₃⁽⁺⁾ −SR₂⁽⁺⁾

R, R1 and R2 may be H or alkyl

It is believed that inductive effects (I) of the substituents (Z) are responsible for activation or deactivation. An inductive effect denoted by +I indicates an electron push and a –I effect means an electron pull in the σ–electron network.
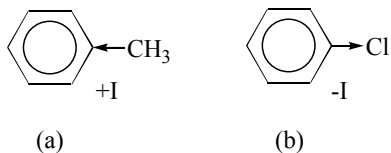
(a)   (b)

2.2.2-41.

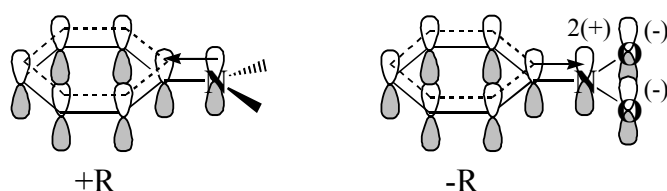If there is a σ–electron density increase, the resulting +I effect in the benzene ring will shield the positive charge of the carbon nuclei. Consequently, the π–electron density will be looser and, therefore, more readily available to react with the incoming electrophile. Hence the reaction will be faster: (kC6H5Z/kC6H6) > 1. In contrast to this, if there is a σ–electron decrease, the resulting -I effect in the benzene ring will deshield the positive charge of the carbon nuclei. Consequently, the π–electron density will be tighter and, therefore, less readily available to react with the incoming electrophile. Hence the reaction will be slower: (kC6H5Z/kC6H6) < 1. It is believed that the resonance effect R of the substituent (Z) is responsible for the orientation of the incoming electrophile.

+R   -R

2.2.2-42.

If there is a π–electron density increase, the resulting +R effect in the benzene ring will stabilize the Wheland intermediate if the incoming electrophile (E) is in the o- or p-positions, but will not stabilize the Wheland intermediate to the same extent when the incoming electrophile (E) is in the m-position.
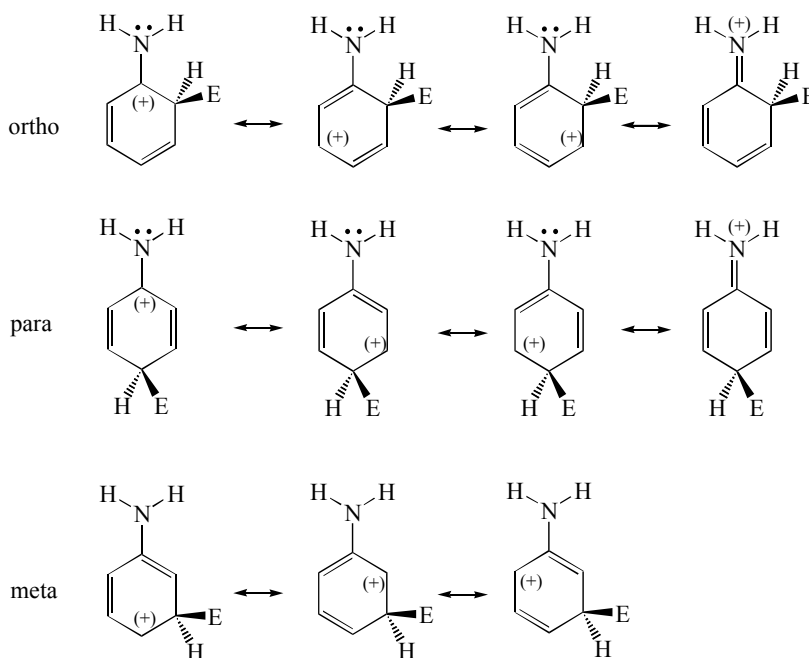

2.2.2-43.

If we were to summarize the above principles in a concise form, we would construct a 2x2 matrix analogous to the one presented in Table 2.2.2-6. The collection of the paired combinations of +I, -I, as well as +R and –R is shown in Table 2.2.2-7.

Table. 2.2.2-7. Classification of the combinations of a substituent's inductive (±I) and resonance (±R) effects to rationalize orientation and reactivity.

	o-, p-directing	m-directing
Activating	+I, +R	The combination (+I, -R) does not occur
Deactivating	-I, +R	-I, -R

For the sake of completeness we might add that the classification presented in Table 2.2.2-7 is only approximate. For example, we might say that in the phenoxide ion [2.2.2-44] we indeed have +I and +R combination. However, in phenol [2.2.2-44],

(a)   (b)
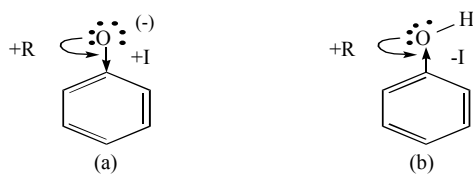
2.2.2-44.

it is likely to have the combination –I and +R since the oxygen atom is more electronegative than carbon. However, in the case of phenol [2.2.2-44] the resonance effect is overwhelming

$$\left|+R\right| \gg \left|-I\right|$$

2.2.2-45.

and it compensates in the π–network for the electron density lost in the σ–network. The net result is that the ring gains electron density with respect to benzene, therefore, the benzene ring is activated.

In connection with the in- and out- flow of π–electron density to and from the benzene ring, we might mention that alkyl groups, such as a methyl group, are regarded as π–electron donors even though it has no lone pair. It is usually envisaged as the delocalization of C-H bonding pairs to the ring via hyper-conjugation.
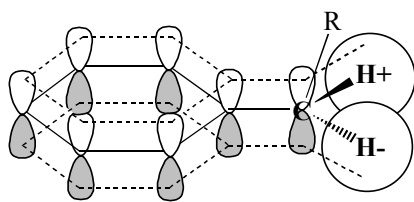
2.2.2-46.

From the overall rate constants the partial rate factors may be calculated from the o: m: p ratios . These values are usually given as a ratio with respect to benzene.
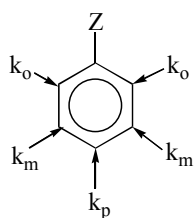
2.2.2-47.

$$k_{C_6H_5Z} = 2k_o + 2k_m + k_p$$

2.2.2-48.
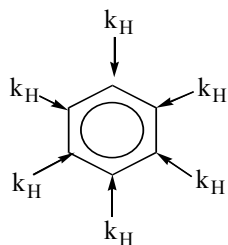
2.2.2-49.

$$k_{C_6H_6} = 6k_H$$

2.2.2-50.

The relative overall rate is

$$k_{C_6H_5Z} / k_{C_6H_6}$$

2.2.2-51.

and the relative partial rate factors are

(k_o/k_H), (k_m/k_H) and (k_p/k_H).

2.2.2-52.

The relative partial rate factors [2.2.2-52] and the relative overall nitration rates [2.2.2-51] are summarized for a few selected substituents in Table 2.2.2-8.

Table. 2.2.2-8. A comparison of Relative Partial Rate-factors and Relative Overall Rates for a few selected monosubstituted benzene derivatives.

| Relative partial rate factors	Relative overall rates	Relative partial rate factors	Relative overall rates	Relative partial rate factors	Relative overall rates
NHC(O)CH$_3$: 0.61×10^6 / 0.61×10^6, 0 / 0, 2.52×10^6	$\dfrac{3.72\times10^6}{6.0}=6.2\times10^5$	H: 1 / 1, 1 / 1, 1	$\dfrac{6.0}{6.0}=1.0$	C(O)OEt: 2.6×10^{-3} / 2.6×10^{-3}, 7.9×10^{-3} / 7.9×10^{-3}, 0.9×10^{-3}	$\dfrac{2.19\times10^{-2}}{6.0}=0.37\times10^{-3}$
CH$_3$: 38 / 38, 3 / 3, 49	$\dfrac{1.31\times10^2}{6.0}=22$	F: 0.04 / 0.04, 0 / 0, 0.77	$\dfrac{0.84}{6.0}=0.14$	CF$_3$: 4.5×10^{-6} / 4.5×10^{-6}, 67×10^{-6} / 67×10^{-6}, 4.5×10^{-6}	$\dfrac{1.48\times10^{-2}}{6.0}=2.46\times10^{-5}$
Ph	$\dfrac{1.20\times10^2}{6.0}=20$	Cl: 0.03 / 0.03, 0 / 0, 0.13	$\dfrac{0.14}{6.0}=0.032$	N$^{(+)}$Me$_3$: 4.7×10^{-8} / 4.7×10^{-8}, 0 / 0, 1.2×10^{-8}	$\dfrac{1.06\times10^{-4}}{6.0}=1.77\times10^{-8}$
CMe$_3$	$9.00\times10^1=15$	Br: 0.03 / 0.03, 0 / 0, 0.10	$\dfrac{0.16}{6.0}=0.027$		

The energy profiles for the electrophilic aromatic substitution of benzene and tri-substituted benzene: $C_6H_5–Z$ ($–Z = –CH_3, –Cl, –NO_2$) are shown in Figure 2.2.2-10.
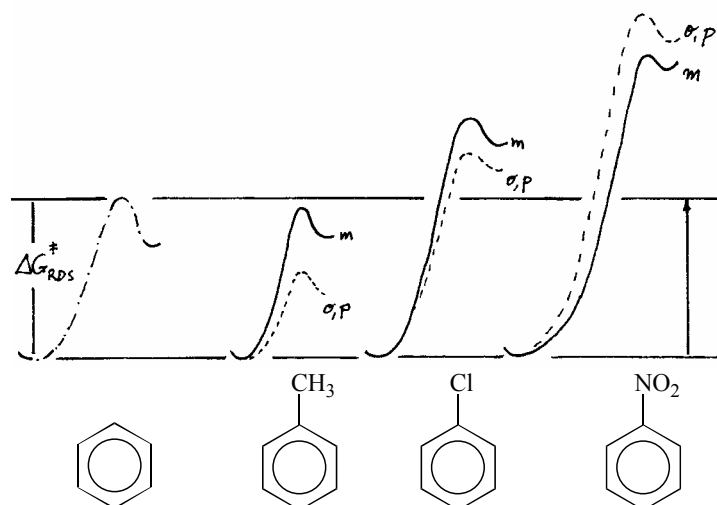
Figure 2.2.2-10. A schematic representation of the energy profiles of electrophilic aromatic substitution for four aromatic compounds: C_6H_5–Z (–Z = –H, –CH$_3$, –Cl, and –NO$_2$). For the sake of simplicity the o- and p-substituted products are shown together (denoted as o,p).

Friedel – Crafts Acylation and Alkylation

Electron-deficient carbon may also act as an electrophile in aromatic substitution. In general, acylium ions [2.2.2-53] and alkyl carbocations [2.2.2-54] are used. These became available following their original discovery by Friedel and Crafts.
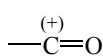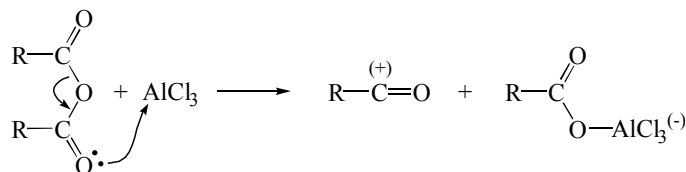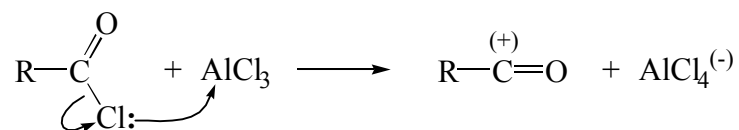

(a)   (b)

2.2.2-53.

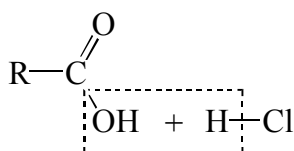Acylium ions may be generated from carboxylic acid anhydride and AlCl$_3$

2.2.2-54.

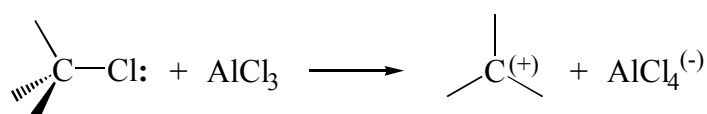but most of the time acid halide and AlCl$_3$ are used.

$$2.2.2\text{-}55.$$

Note that acylhalide can be considered, at least formally, as a mixed anhydride of a carboxylic acid and HCl.
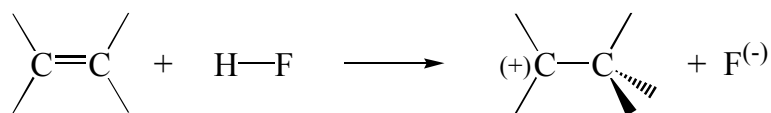

$$2.2.2\text{-}56..$$

Analogous to [2.2.2-55], carbocations (electrophile) may be generated from alkyl halides and AlCl$_3$.

$$2.2.2\text{-}57.$$

Carbocations may also be generated from alkenes [2.2.2-58] and from alcohols [2.2.1−59].
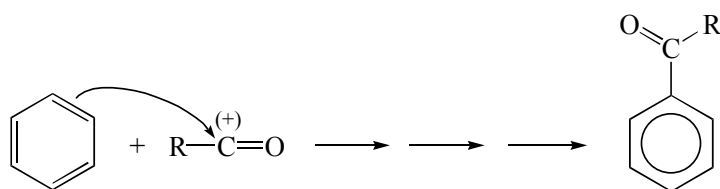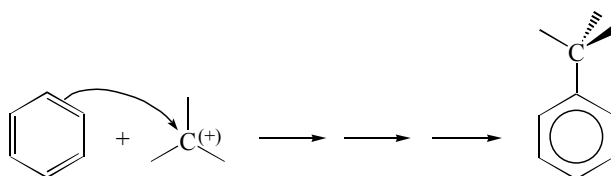

$$2.2.2\text{-}58.$$
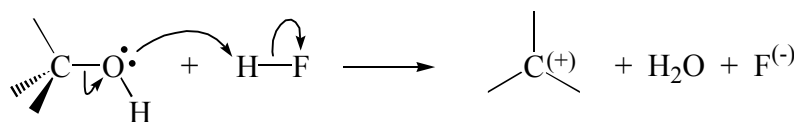
$$2.2.2\text{-}59.$$

The reaction mechanism is analogous to that presented in Figure 2.2.2-3. In the acylation, aromatic ketones [2.2.2-60] and in the alkylation, alkyl-substituted aromatic compounds [2.2.2-61] are obtained.

$$2.2.2\text{-}60.$$

2.2.2-61.

Theoretical and experimental examples

Protonation of naphthalene

Considering S_EAr reactions on a theoretical level, the simplest reaction is a proton exchange on an aromatic compound. The authors Tasi, Gy. J. Phys. Chem. A, Vol.104, No. 6, 2000, G2(MP2,SVP):[1]

decided to investigate the proton exchange of naphthalene which possesses three distinguishable C-atoms. C-atom 1 is called α, 2 is called β and 9 is called γ. The σ-complex of the α C-atom is the most stable according to G2 (MP2, SVP) combined method and applying ZPVE correction (see Appendix). Note that although there are rather high energy barriers, the position of the reagent could theoretically change through intramolecular reaction paths as well. This phenomenon is also observed, when using methyl group as a reagent. Assuming an ideal mixture, where the complexes are free to convert into each other, the product ratios could be calculated using Boltzmann's equation with and the calculated Gibbs energies:

$$x_i = \frac{\exp(-\Delta G_i^0 / kT)}{\sum_j \exp(-\Delta G_i^0 / kT)}$$

2.2.2-62.

where x_i is the ratio of the i-th cation (σ-complex) in the mixture, $\mathbf{\Delta G_i^0}$ is the difference between Gibbs energy of the i-th cation and the reference cation.

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[1] QCISD(T,FC)/6-31G(d)//MP2(FULL)/6-31G(d) energy

MP2(FC)/6-311+G(3df,2p)//MP2(FULL)/6-31G(d) energy

alkyl group	HF		MP2H		MP2		exp		MP2X		G2(MP2,SVP)		exp1	
	α	β	α	β	α	β	α	β	α	β	α	β	α	β
methyl	4.38	95.62	17.45	82.55	17.66	82.34	24.5	75.5	26.25	73.75	22.86	77.14	23.00	77.00
ethyl	0.96	99.04	7.98	92.02	9.26	90.74	9.5	90.5						
isopropyl	0.06	99.94	1.05	98.95	1.23	98.77	1.5	98.5						
tert-butyl	0	100	0	100	0	100	0	100						

As the reagent increases, the experimental product ratios and the calculated product ratios have an acceptable correlation even with lower basis sets applied.[2]

This phenomenon is explained by the dominantly increasing steric effects of the reagents, which are taken into consideration at lower levels of theory as well.

Friedel-Crafts alkylation

Current example investigation the effect of $AlCl_3$ catalyzator in Friedel-Crafts alkylations was investigated. Tarakeshwar, P. J. Phys. Chem. 1998, 102, 2253-2255 Reaction of the $AlCl_3$ and the BCl_3 catalyzators with benzene and its charge distribution was examined using different levels of theory:

	MP2/6-31+G*		MP2/6-311++G**		MP2/6-311++G(3df,2p)// MP2/6-311++G**
	BCl_3	$AlCl_3$	BCl_3	$AlCl_3$	$AlCl_3$
q(C---Y)	-0.261	-0.447	-0.215	-0.391	-0.394
q(C)	~-0.241	~-0.209	~-0.198	~-0.165	~-0.169

where q(C---Y) is the charge of the closest C-atom to $AlCl_3$/BF_3 (Mulliken charge) and q(C) is the average charge of the remaining C-atoms in the ring(Mulliken charge).

The presence of the catalyst makes the closest C-atom more electronegative, thus the catalyst is taking part both in the formation of the electrophilic reagent and in the activation of the aromatic substrate.

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[2] HF: HF/6-31G*//HF/6-31G*, MP2H: MP2(full)/6-31G*//HF/6-31G*,

MP2: MP2(full)/6-31G*//MP2(full)/6-31G*,
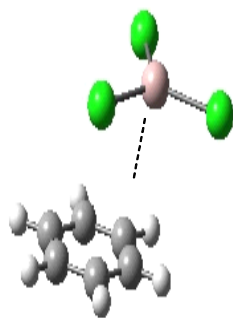
MP2X: MP2(full)/6-311++G**//MP2(full)/6-31G*

Figure 2.2.2-11.

1,8-dimetil-naftalin nitrálása:

1,8-dimetil naftalin nitrálásakor több izomer keletkezik, illetve azok eloszlása eltér a várt értéktől.Tanaka, M. J. Org. Chem. 2000, 65, 2972-2978A keletkezett orto- ill. para-termékek az irányítási szabálynak megfelelnek, ám -78 ^{o}C-on az orto/para arány 75/25, ami éles ellentétben van a 0 ^{o}C-on tapasztalt 22/78 aránnyal. A kísérleti eredmények alapján többfajta mechanizmus is elképzelhető, a megfelelő kiválasztásához az elméleti és kísérleti eredményekre egyaránt szükség van. A klasszikus elektorfil szubsztitúciós nitrálás szerint a reakcióban a pozitív töltéssel rendelkező NO_2^+ π-komplexet alakít ki a naftalin valamelyik aromás gyűrűjével. Ezután különböző arányban kialakulnak az irányítási szabálynak megfelelő σ-komplexek, majd a távozó csoportok leválnak és eljutunk a termékekhez. Lásd S$_E$2 mechanizmus.

## Nitrálás S$_E$ mechanizmussal
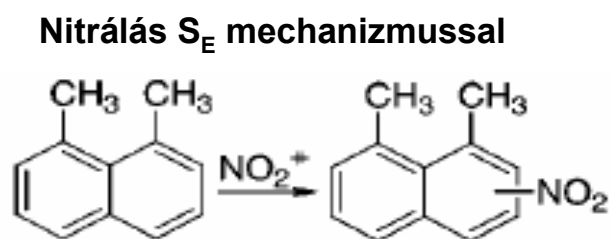
Ezzel szemben a kísérleti eredmények azt mutatták, hogy több lehetséges reakcióút is létezik.

Ezek a következőek:

Nitrálás közvetlen töltésátvitellel

Ennél a reakcióútnál a naftalin egy delokalizált elektronját átadja a pozitív töltésű NO2+-nak, majd az így kapott pozitív szubsztráton keresztül jutunk el valamely (egyenlőre ismeretlen) izomer/ekhez.

Nitrálás közvetlen töltésátvitellel
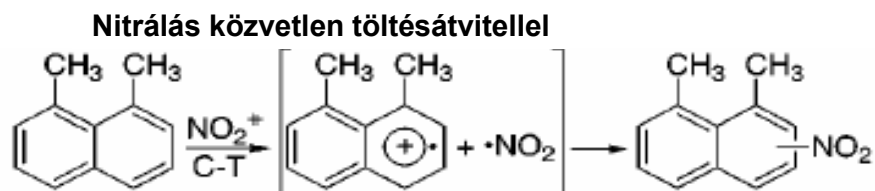
ipso-σ-komplex kialakulása:

Orto termékhez eluthatunk oly módon is, hogy a σ-komplex a metilcsoporthoz kapcsolódó szénen alakul ki, majd egy 1,2-NO_2 csoport vándorlással kapjuk az orto-σ-komplexet, ami aztán orto- termékhez vezet.
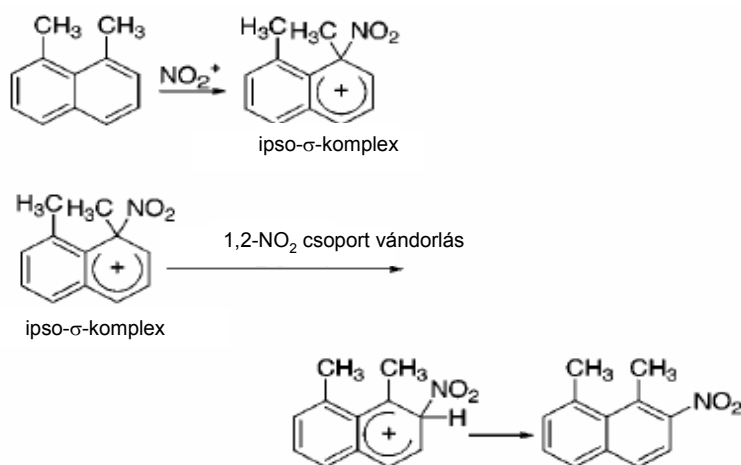

Nitrálás alternatív töltésátvitellel:

Elméletileg végbemehet a reakció ún. alternatív töltésátvitellel is, ahol az ipso-σ-komplex gyökösen bomlik és egy naftalinkationt kapunk, amelyből a közvetlen töltésátvitelhez hasonló módon különböző izomerek lehetnek a végtermékek.
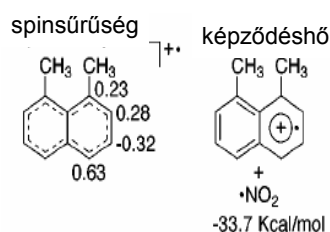
Nitrálás alternatív töltésátvitellel
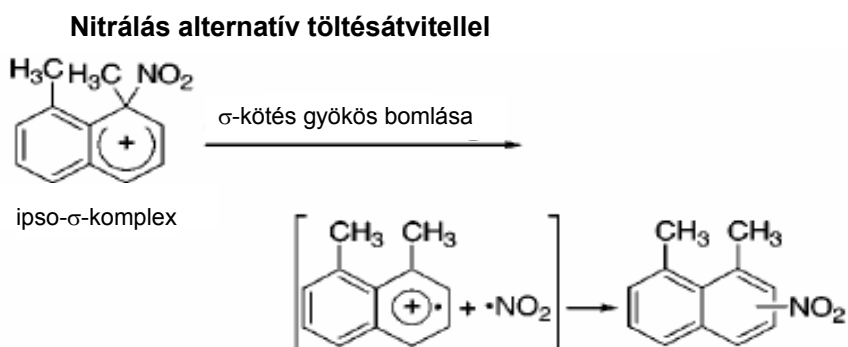
Kiértékelés:

A helyes reakcióút kiválasztásához az egyes átmeneti komplexek, ill. végtermékek energiáját szükséges kiszámolni, amik alapján már eldönthető, hogy energetikailag mely reakcióút preferált. A számolásokat a szerzők MP2/6-311G(d)//RHF/6-31G(d) szinten (a HF számolások ZPE korrekciójával) végezték el.függelékben lehetnének részletek
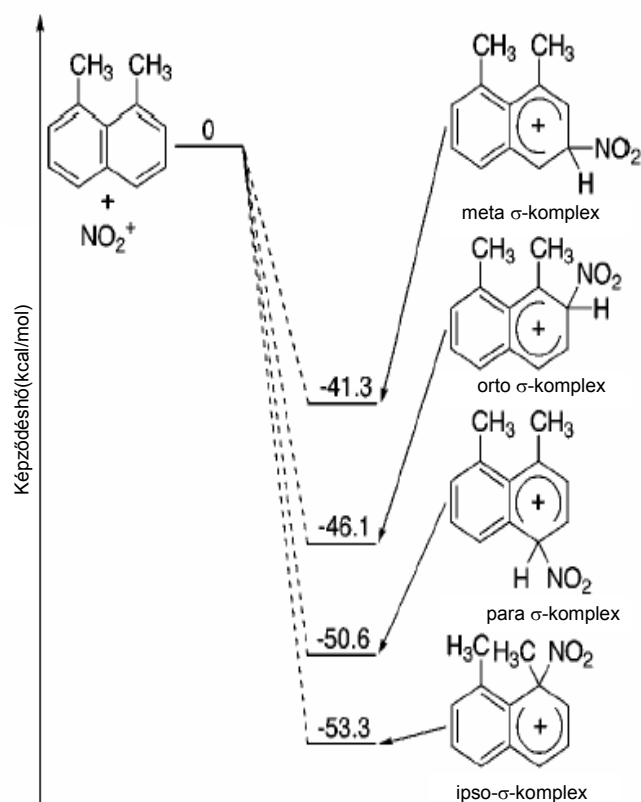

A kiindulási állapotot véve referencia pontnak (azaz 0 relatív energiájúnak) megkapjuk, hogy az egyes átmeneti állapotok mekkora energianyereséget jelentenek. Ez alapján jól látszik, hogy a klasszikus elektrofil szubsztitúción keresztül nagyrészt para,

kisebbrészt orto termékhez kellene jutnunk, látva a meta komplex viszonylag magas energiáját és feltételezve, hogy az ipso-σ-komplexből nem megy tovább reakció.

A pozitív töltésű naftalin kation relatív képződéshője -33,7 kcal.mol-1, így az alternatív töltésátvitellel végbemenő reakciót elvethetjük, hiszen 19,6 kcal.mol-1-lal nagyobb ez az energia, mint az ipso-σ-komplexé (-53,3 kcal.mol-1). Az intramolekuláris 1,2 NO_2 csoport átmenet viszont alacsony hőmérsékleten végbe mehet, mivel mindössze 5.7 kcal.mol-1-os energiagátat kell leküzdeni. Innen már könnyen kialakulhat az orto termék. A közvetlen töltésátvitellel történő nitrálás során kapott naftalin kation (-33,7 kcal.mol-1) a spinsűrűség alapján leginkább para szubsztituált terméket ad.
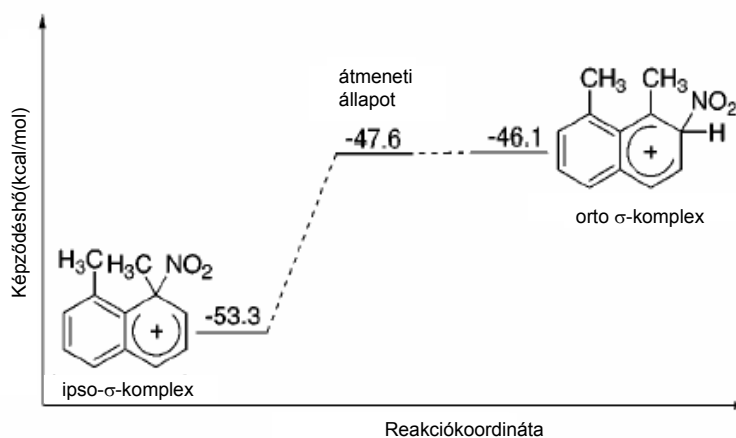
Összevetve az eredményeket arra jutunk, hogy a para termék kialakulása a klasszikus elektrofil szubsztitúció, illetve a közvetlen töltésátvitel útján megy végbe, az orto termék pedig elsősorban az ipso-σ-komplexen keresztül intramolekuláris 1,2 NO_2 vándorlással megy végbe. Az eltolt orto termék arányt pedig az ipso-σ-komplex alacsony energiája magyarázza.