Chap. 8 Substitution Reactions

$$Y \; + \; R—X \longrightarrow \underline{R'—Y} \; + \; X$$

not necessarily the same as R

Nucleophilic：

Electrophilic：

S_N1 $(CH_3)_3CCl \xrightarrow[\text{CH}_3\text{CH}_2\text{OH}]{\text{slow}} (CH_3)_3C^+ \; + \; Cl^- \underset{\text{CH}_3\text{CH}_2\text{OH}}{\overrightarrow{}} (CH_3)_3C \overset{+}{-}OCH_2CH_3$

$\overset{|}{H}$

$$rate = \frac{-d[(CH_3)_3CCl]}{dt} = k[(CH_3)_3CCl]$$

$(CH_3)_3C—OCH_2CH_3$

S_N2 $CH_3O^- + CH_3—Br \xrightarrow{CH_3OH} H_3C—O—CH_3 \; + \; Br^-$

nucleophile   nucleofuge
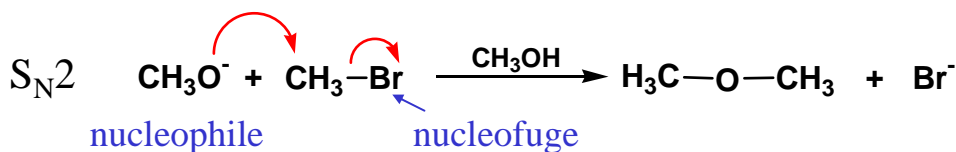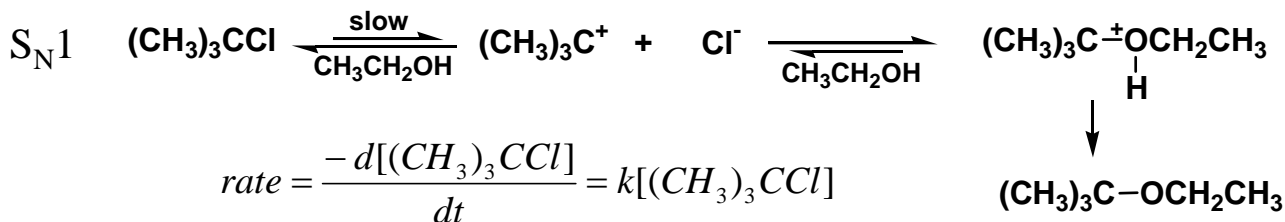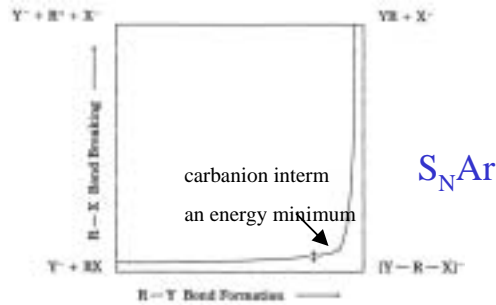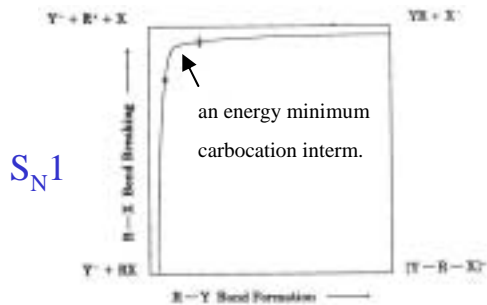
$$rate = \frac{-d[CH_3Br]}{dt} = k[CH_3Br][CH_3O^-]$$

The rxn mechanism encompasses a wide spectrum
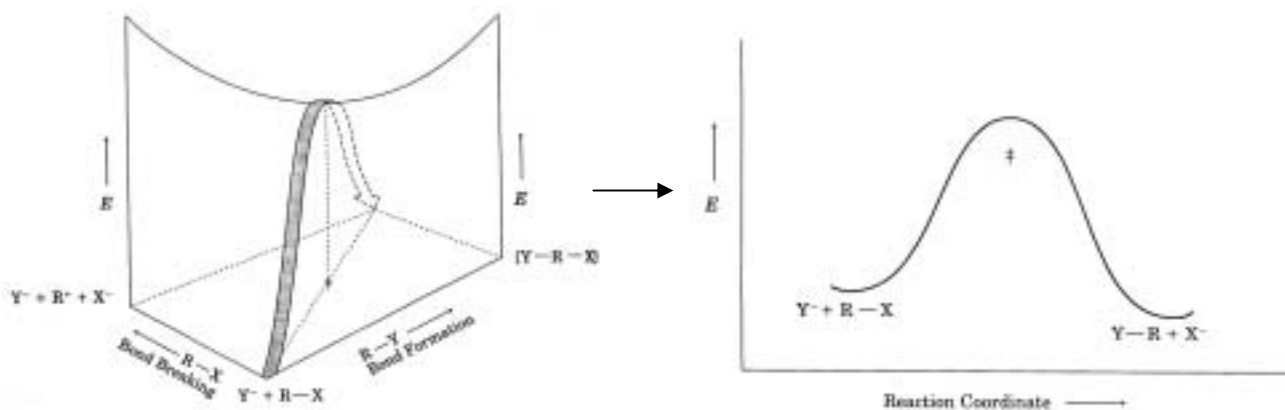two-dimensional rxn coordinate diagram for S_N2
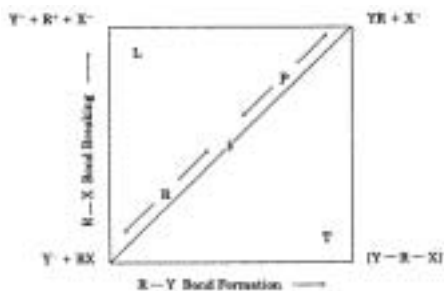
L：loose transition state
T：tight transition state
P：product-like TS (late)
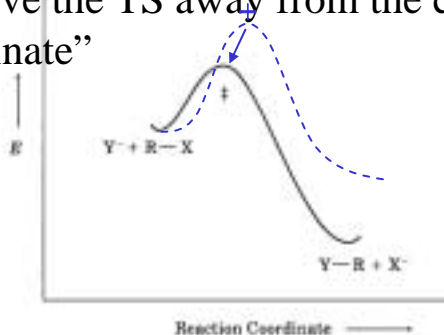R：reactant-like TS (early)

extreme of
loose TS

extreme of
tight TS

S_N1

an energy minimum

carbocation interm.

carbanion interm

an energy minimum

S_NAr

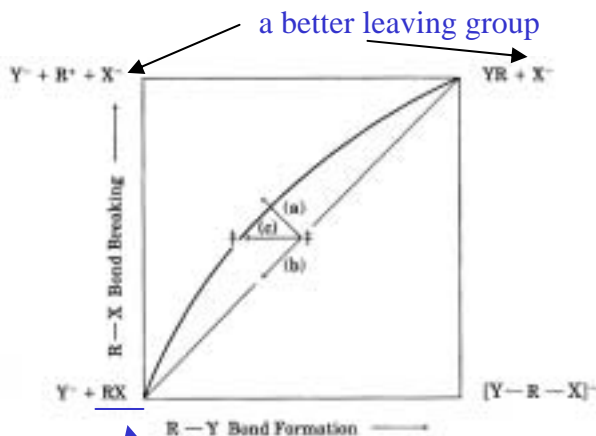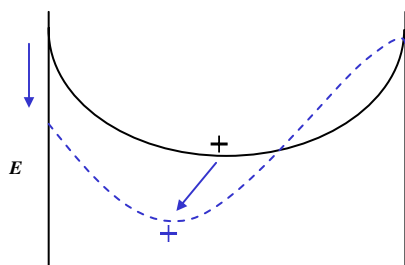# Three dimensional rxn coordinate with E as third axis

Effect of moving down (stabilizing) the energy of a corner (species)

$\rightarrow$ move the TS away from the corner "along the rxn coordinate"
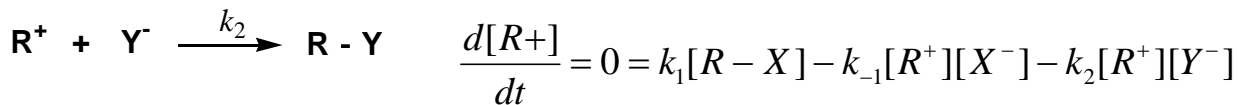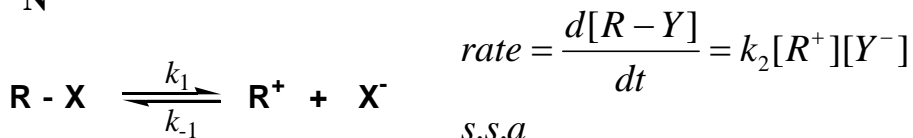

Effect of moving down (stabilizing) the energy of a corner (species) perpendicular to the rxn coordinate, shift the TS toward the corner.

The effect of nucleophile, substrate, leaving group, solvent on the geometry and energy of TS can be analyzed based on these principles

a better leaving group

with better leaving group, the TS shift toward the left.

S_N1 Reaction

$$R \quad X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R^+ + X^-$$

$$rate = \frac{d[R-Y]}{dt} = k_2[R^+][Y^-]$$

s.s.a

$$R^+ + Y^- \xrightarrow{k_2} R \quad Y$$

$$\frac{d[R+]}{dt} = 0 = k_1[R-X] - k_{-1}[R^+][X^-] - k_2[R^+][Y^-]$$

$$[R+] = \frac{k_1[R-X]}{k_{-1}[X^-] + k_2[Y^-]}$$

$$Rate = \frac{k_1 k_2[R-X][Y^-]}{k_{-1}[X^-] + k_2[Y^-]}$$

if [X⁻] very small (early stage) $k_{-1}[X^-] << k_2[Y^-]$

$$\text{Rate} = k_1[R-X]$$

if [X⁻] increases, rate decreases (common ion effect)

Effect of Structure on S_N1 reaction：
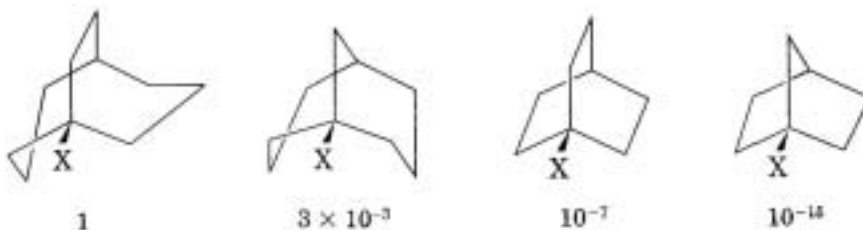
rate of solvolysis：$3° > 2° > 1° >$ methyl

parallel the stability of carbocation

size of R_1, R_2, R_3 in R_1, R_2, R_3 C-X

rate of solvolysis for $R(CH_3)_2CCl$, rel.rate   1   for Me

rate of bridgehead system：   1.67   Et

rel reactivity   1.58   Pr

| 1 | 3×10^{-3} | 10^{-7} | 10^{-14} |

Effect of Solvent：

Grunwald-Winstein eq

m：sensitivity of the substrate to solvent ionizing power

$$\log(k/k_0) = mY$$

Y：ionizing power

where $Y = \log(k_{\text{t-BuCl, solvent}}, k_{\text{t-BuCl, methanol}})$

Schleyer's eq

rate in a given solvent

$$\log(k/k_0) = l\, N_{OTs} + m\, Y_{OTs}$$

rate in reference solvent, 80% ethanol

N_{OTs} : solvent nucleophilicity

l : sensitivity to solvent nucleophilicity

Y_{OTs} : ionizing power

m : sensitivity to ionizing power

$$Y_{OTs} = \log (k/k_0) \qquad \text{for 2-Adamantyl tosylate}$$
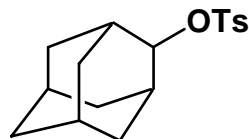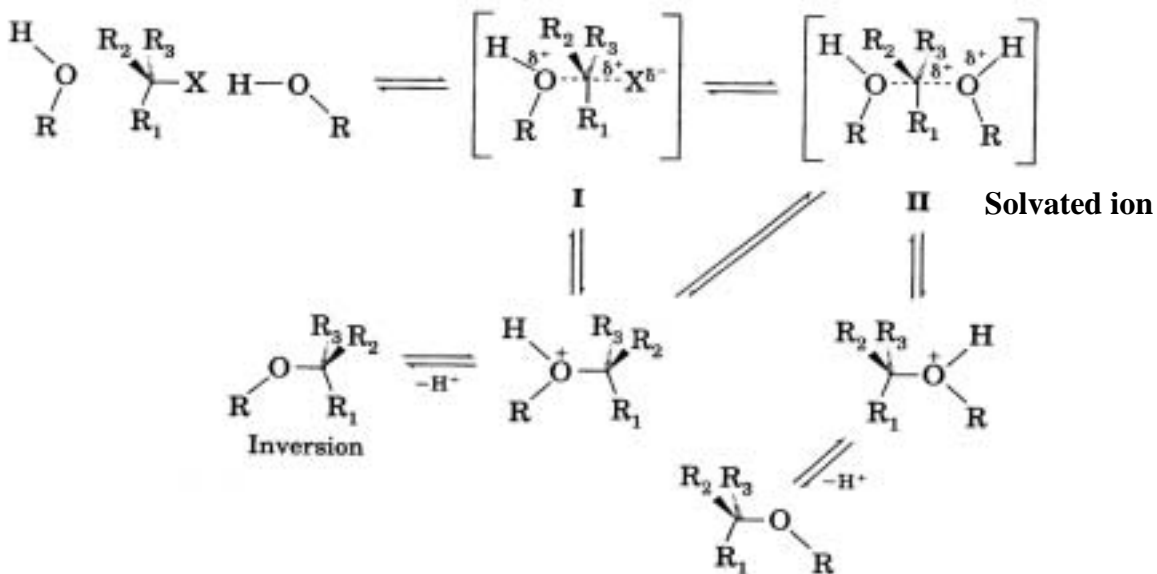

no nucleophilic rxn possible

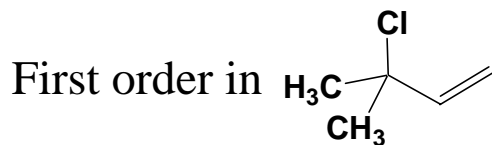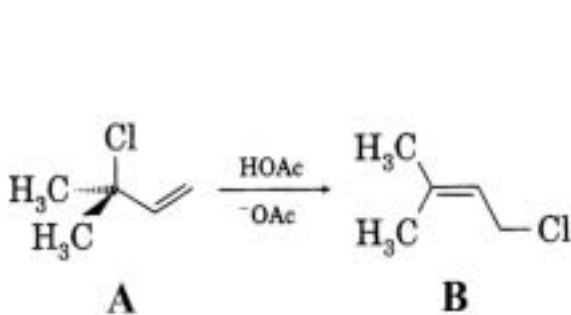$$N_{OTs} = \log (k/k_0) - 0.3 Y_{OTs} \qquad \underline{\text{for } CH_3OTs}$$

both nucleophilic rxn and ionizing rxn possible

S_N1 rxn is first order rxn in substrate

if sp^2-hybridized intermediate is formed
$\rightarrow$ racemization for chiral S.M.

Sometimes partial inversion is observed (characteristic of S_N2)
$\rightarrow$ Solvated ions and ion pairs

I

II   Solvated ion

Inversion

$$A \xrightarrow[\text{-OAc}]{\text{HOAc}} B$$

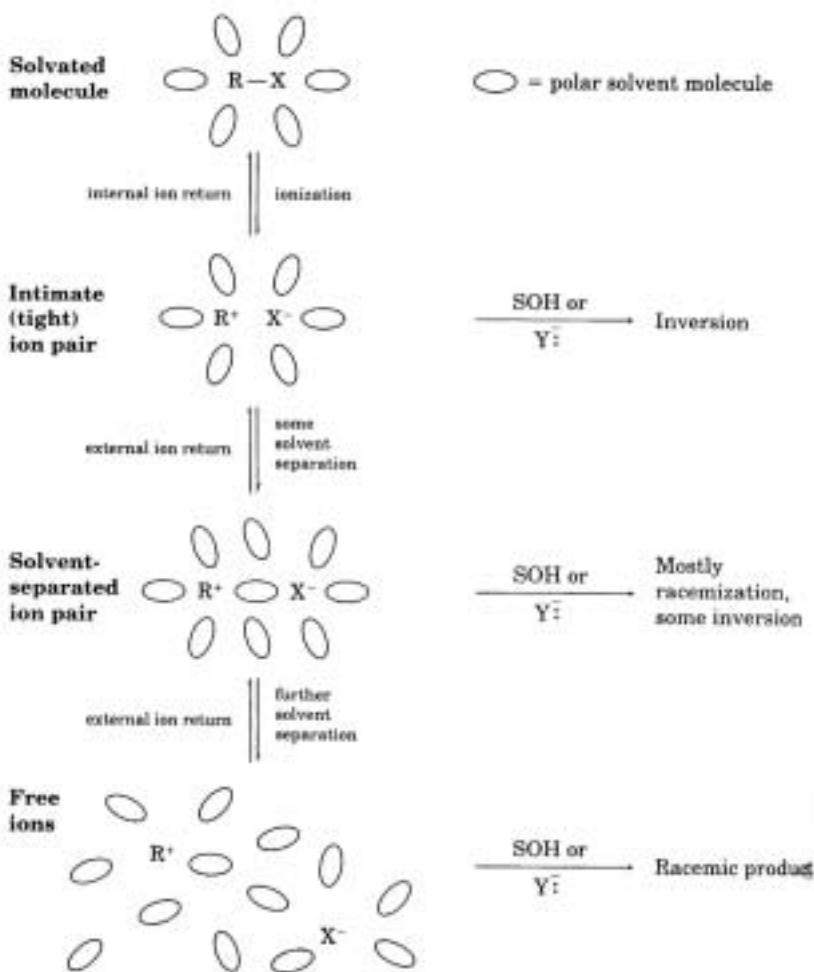First order in $H_3C\overset{\overset{\displaystyle Cl}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}$ —

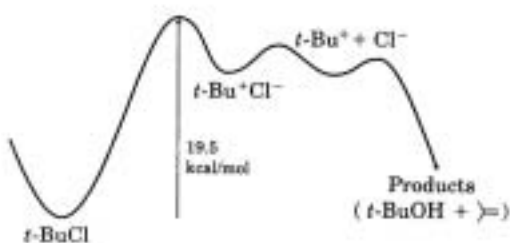independent of added Cl⁻
→ no common ion effect

chloride in B may come from
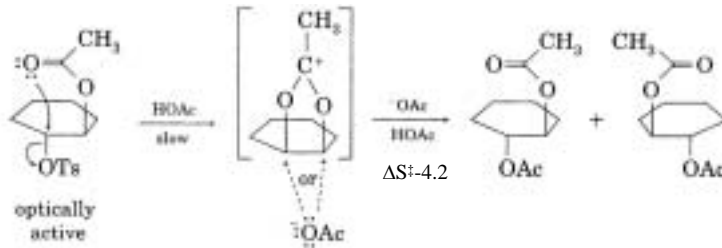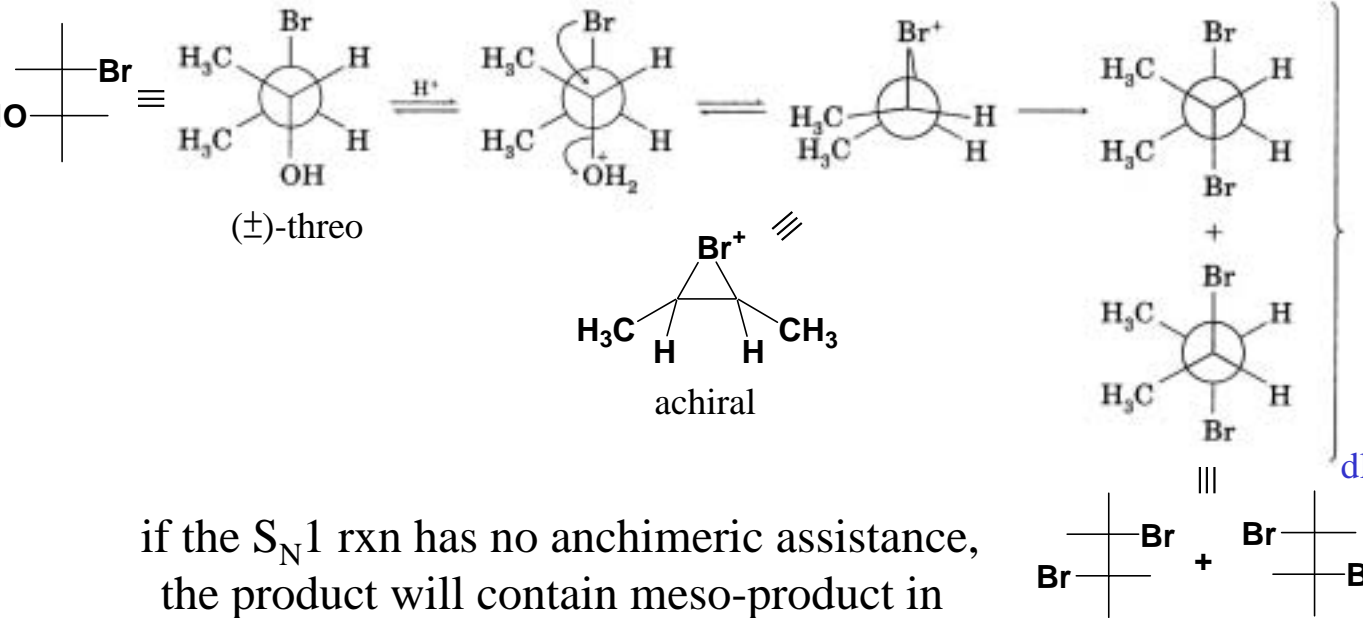the molecule itself
→ ion-pair mechanism

Figure 8.18
Species proposed
as intermediates in
solvolysis reactions.

Figure 8.19
Schematic diagram
of a possible
reaction profile for
the solvolysis of
t-butyl chloride in
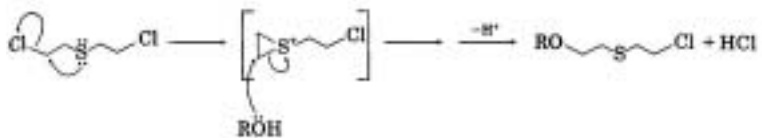water. (Adapted
from reference 53.)

Anchimeric assistance (Neighboring group participation)

(±)-threo

Br⁺
achiral

if the S_N1 rxn has no anchimeric assistance, the product will contain meso-product in addition to the racemic 2,3-dibromobutane

Br + Br

trans-tosylate
optically active

HOAc slow

$\Delta S^\ddagger$-4.2

rate of acetolysis for *trans*-tosylate ： *cis*-tosylate
10^3 ： 1

Evidence of anchimeric assistance
1. stereochem.
2. rate

OTs   OTs
5   1

OBs
Y

RÖH

phenyl group participation through π
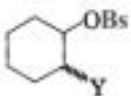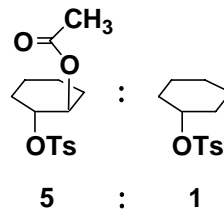
Y	$k_{(rel)}$	$\Delta S^\ddagger$ (e.u.)
H	1.00	+1.5
trans-OAc	0.24	−4.2
cis-OAc	3.8×10^{-4}	−3.5
trans-Br	0.1	+0.8
trans-OCH₃	0.06	−3.4
trans-Cl	4.6×10^{-4}	+2.7
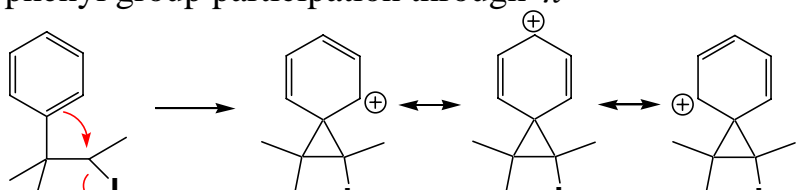
S$_N$2 reaction

backside attack with inversion at carbon

$$*I^- + H\overset{CH_3}{\underset{R}{\diagup}}I \longrightarrow \left[*I^{\delta-}\overset{CH_3}{\underset{H\ R}{\diagup}}I^{\delta-} \right]^{\ddagger} \longrightarrow *I\overset{CH_3}{\underset{R}{\diagup}}H + I^-$$
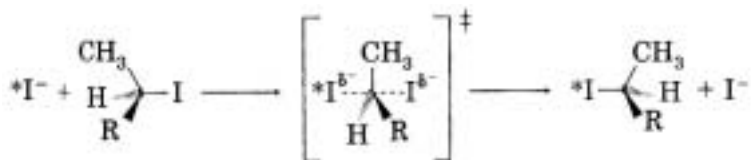
from chiral iodide, the rate of racemization is
twice the rate of incorporation of radioactive *I

Solvent effect

depend on solvation energy of reactants and transition state

1. negative nucleophile + neutral substrate

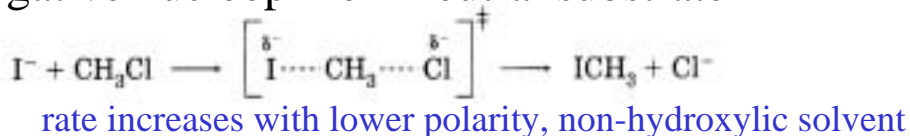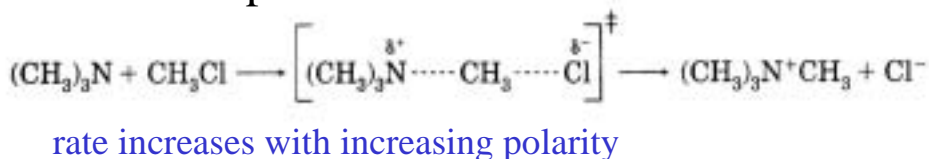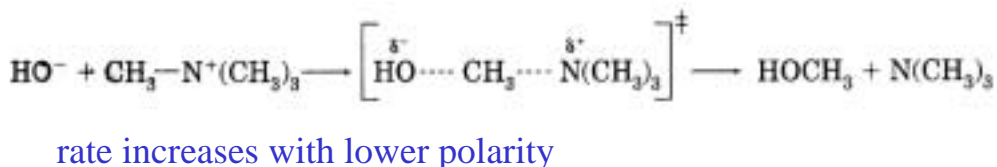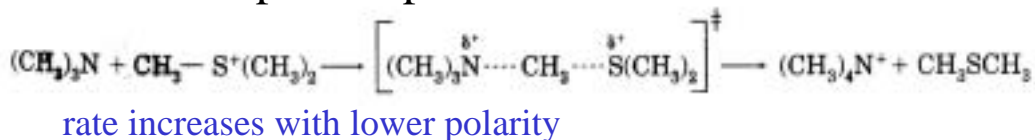$$I^- + CH_3Cl \longrightarrow \left[\overset{\delta-}{I}\cdots CH_3\cdots \overset{\delta-}{Cl} \right]^{\ddagger} \longrightarrow ICH_3 + Cl^-$$

rate increases with lower polarity, non-hydroxylic solvent

2. neutral nucleophile + neutral substrate

$$(CH_3)_3N + CH_3Cl \longrightarrow \left[(CH_3)_3\overset{\delta+}{N}\cdots CH_3\cdots \overset{\delta-}{Cl} \right]^{\ddagger} \longrightarrow (CH_3)_3N^+CH_3 + Cl^-$$

rate increases with increasing polarity

3. negative nucleophile + positive substrate

$$HO^- + CH_3-N^+(CH_3)_3 \longrightarrow \left[\overset{\delta-}{HO}\cdots CH_3\cdots \overset{\delta+}{N(CH_3)_3} \right]^{\ddagger} \longrightarrow HOCH_3 + N(CH_3)_3$$

rate increases with lower polarity

4. neutral nucleophile + positive substrate

$$(CH_3)_3N + CH_3-S^+(CH_3)_2 \longrightarrow \left[(CH_3)_3\overset{\delta+}{N}\cdots CH_3\cdots \overset{\delta+}{S(CH_3)_2} \right]^{\ddagger} \longrightarrow (CH_3)_4N^+ + CH_3SCH_3$$

rate increases with lower polarity

Polar solvent can increase solubility of ionic nucleophile, less polar solvent increase the rate. → use crown ether or special solvent to increase solubility / reactivity of nucleophile

$$CH_3I + Cl^- \rightarrow CH_3Cl + I^-$$
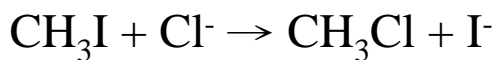
E	Solvent	k (rel.)	
32.7	CH_3OH	0.9	protic
78.4	H_2O	1.0	
111	$HCONH_2$	14.1	
35.9	CH_3NO_2	14,100	aprotic
35.9	CH_3CN	35,800	
36.7	DMF	708,000	
20.6	Acetone	1,410,000	

the nucleophilicity can change dramatically in different solvent
in protic solvent
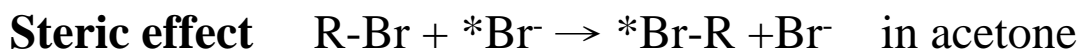$$I^- > Br^- > \underline{Cl^-}$$
in aprotic solvent strongly solvate
$$Cl^- > Br^- > I^-$$
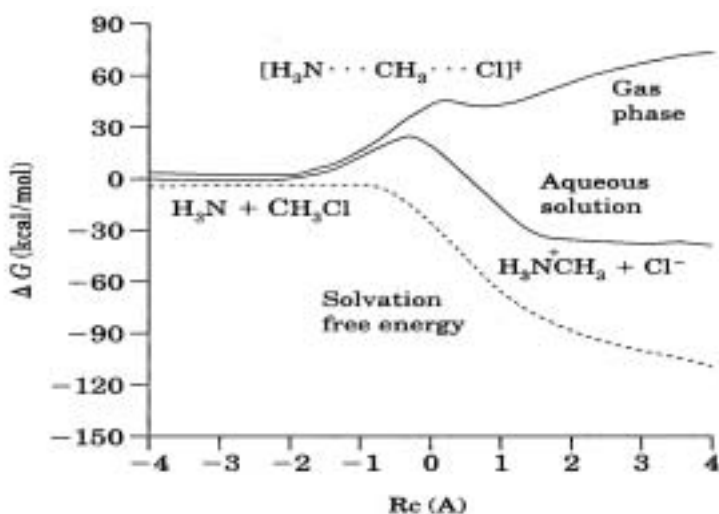
in solvents with polarity lower than H_2O, the activation energy lies between that of gas phase and H_2O

Substrate Effect

Steric effect $R\text{-}Br + {}^*Br^- \rightarrow {}^*Br\text{-}R + Br^-$ in acetone

R	k (rel.)	E_a (kcal/mol)	log A
CH_3	76	15.8	10.7
CH_3CH_2	1.0	17.5	10.1
$CH_3CH_2CH_2$	0.65	17.5	9.8
$(CH_3)_2CH$	0.011	19.7	9.7
$(CH_3)_2CHCH_2$	0.033	18.9	9.6
$(CH_3)_3C$	0.003	21.8	10.7
$(CH_3)_3CCH_2$	0.000015	22.0	8.6

Increasing Steric hindrance

Electronic effect   R-Cl + *I$^-$ → R-I + Cl$^-$ in acetone

R	k (rel.)
n-butyl	1.0
n-C$_7$H$_{15}$	1.30[98(b)]
cyclohexyl	<0.0001[98(b)]
C$_6$H$_5$COOCH$_2$	59.1[98(d)]
C$_6$H$_5$COCH$_2$	105,000
allyl	79
benzyl	195[98(c)]
H$_2$NCOCH$_2$	99
NCCH$_2$	3,070
EtO$_2$COCH$_2$	1,720

dual attraction
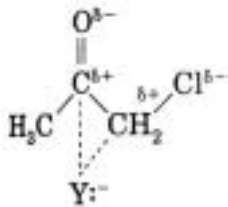
or
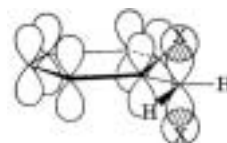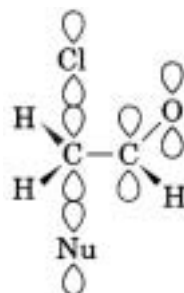
stabilization of TS
via π -system

Nucleophilicity :   relate to polarizability

Nucleophilicity: $Y{:}^- + R{-}X \xrightarrow{k_2} Y{-}R + X{:}^-$ kinetic
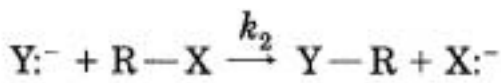
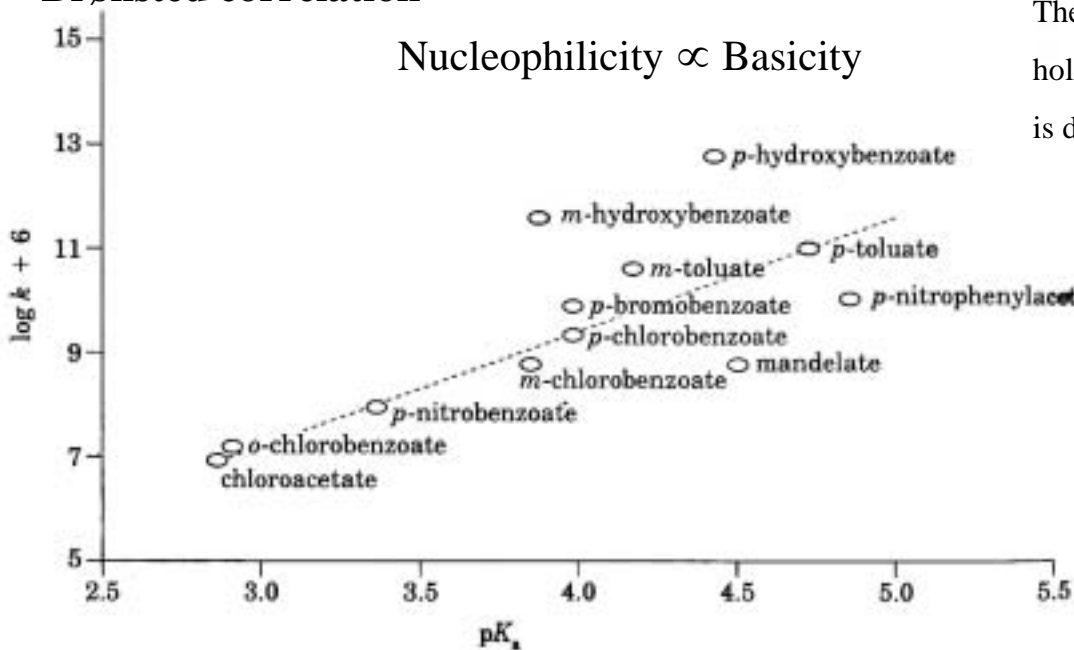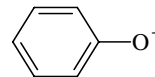Basicity: $Y{:}^- + H{-}X \xrightleftharpoons{K} Y{-}H + X{:}^-$ equilibrium

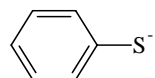Nucleophilicity and Basicity are related but not necessarily

Brønsted correlation

Nucleophilicity ∝ Basicity

The correlation does not
hold if the attacking atom
is different, e.g.

10^3 mroe basic

10^4 more nucleophilic

Swain-Scott equation

$$\log(k_n/k_0) = s\, n$$

n：nucleophilicity of a nucleophile

s：sensitivity of substrate to the nuclephile

Edward's equation

$$\log(k_n/k_0) = \alpha\, Eu + \beta\, H$$

$H = pka + 1.74$ relate to basicity

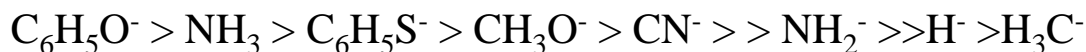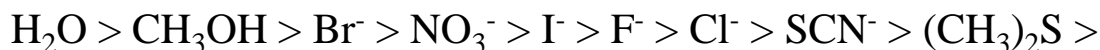$Eu = E_0 + 2.60$ relate to oxidization potent

$$\log(k_n/k_0) = A\, P + B\, H$$

B：basicity (from pK)

P：polarizability (from mole refractivity)

Leaving group Effect：

The more stable the detached leaving group, the more stable the product system

→ Leaving group ability (Nucleofugality)

$H_2O > CH_3OH > Br^- > NO_3^- > I^- > F^- > Cl^- > SCN^- > (CH_3)_2S >$
$C_6H_5O^- > NH_3 > C_6H_5S^- > CH_3O^- > CN^- >> NH_2^- >> H^- > H_3C^-$

Compare the basicity of the leaving group

(or the acidity of the conjugate acid)

Different solvent can change the leaving gp ability

			$\log [k(CH_3X)/k(CH_3I)$			
Y^-	Solvent	$X = Cl$	Br	I	OTs	Me_2S^-
N_3^-	CH_3OH	−2.0	−0.2	0.0	+0.8	−3.3
	DMF	−3.3	−0.9	0.0	−1.8	−4.8
Cl^-	CH_3OH		+0.3	0.0	+0.4	
	DMF		−0.8	0.0	−1.7	

Electrophilic Aromatic Substitution $S_E Ar$

Basic step

$$E^+ + Ar-H \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [Ar{<}^H_E]^+$$

$$[Ar{<}^H_E]^+ \xrightarrow{k_2} Ar-E + H^+$$
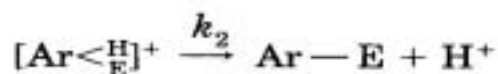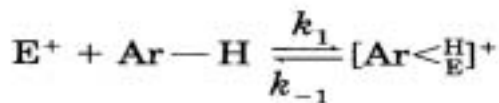
General Mech.

1. generation of attacking species

strong $\begin{cases} NO_2^+ \\ Br_2 \text{ or } Br_2\text{-}MX_n \end{cases}$

$$2\,H_2SO_4 + HNO_3 \longrightarrow NO_2^+ + 2\,HSO_4^- + H_3O^+$$
$$Br_2 + MX_n \rightleftharpoons Br_2\text{-}MX_n$$

medium $\begin{cases} R_3C^+ \\ \\ RC{\equiv}O^+ \end{cases}$

$$R_3CX + MX_n \rightleftharpoons R_3C^+ + [MX_{n+1}]^-$$

$$\underset{\overset{\|}{}}{R}-\overset{O}{C}X + MX_n \rightleftharpoons RC{\equiv}O^+ + [MX_{n+1}]^-$$

weak $\longrightarrow NO^+$

$$HNO_2 + H^+ \longrightarrow N{\equiv}O^+ + H_2O$$
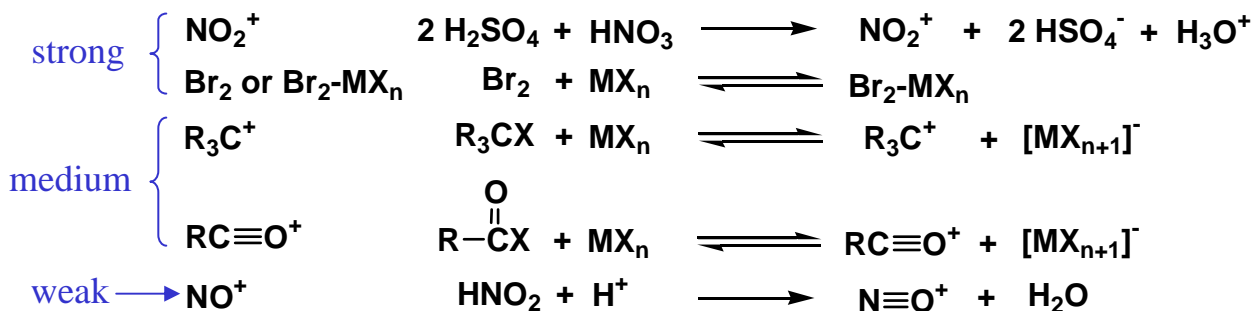
2. Formation of encounter complex (π-complex)

encounter complex
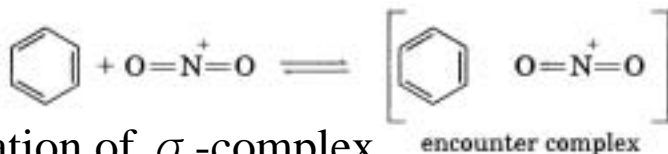
3. Formation of σ-complex

sigma complex
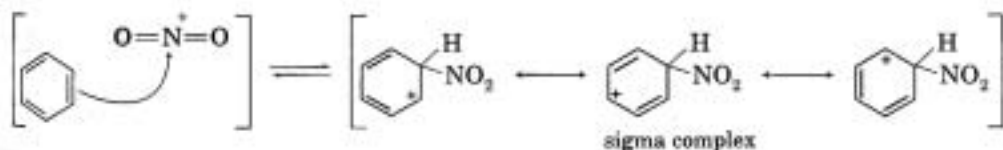
4. Loss of proton
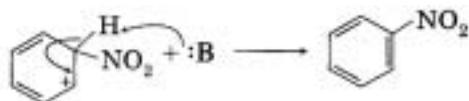
Depending on the electrophile & substrate, rate-determining step can be either of these.

Kinetic evidence for the mechanism
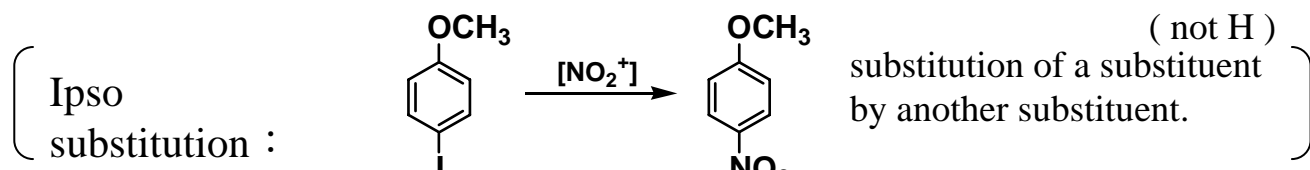
　　reaction rate,

　　kinetic isotope effect,

$$\left[\begin{array}{l} \text{Ipso} \\ \text{substitution :} \end{array} \right.$$

(not H)
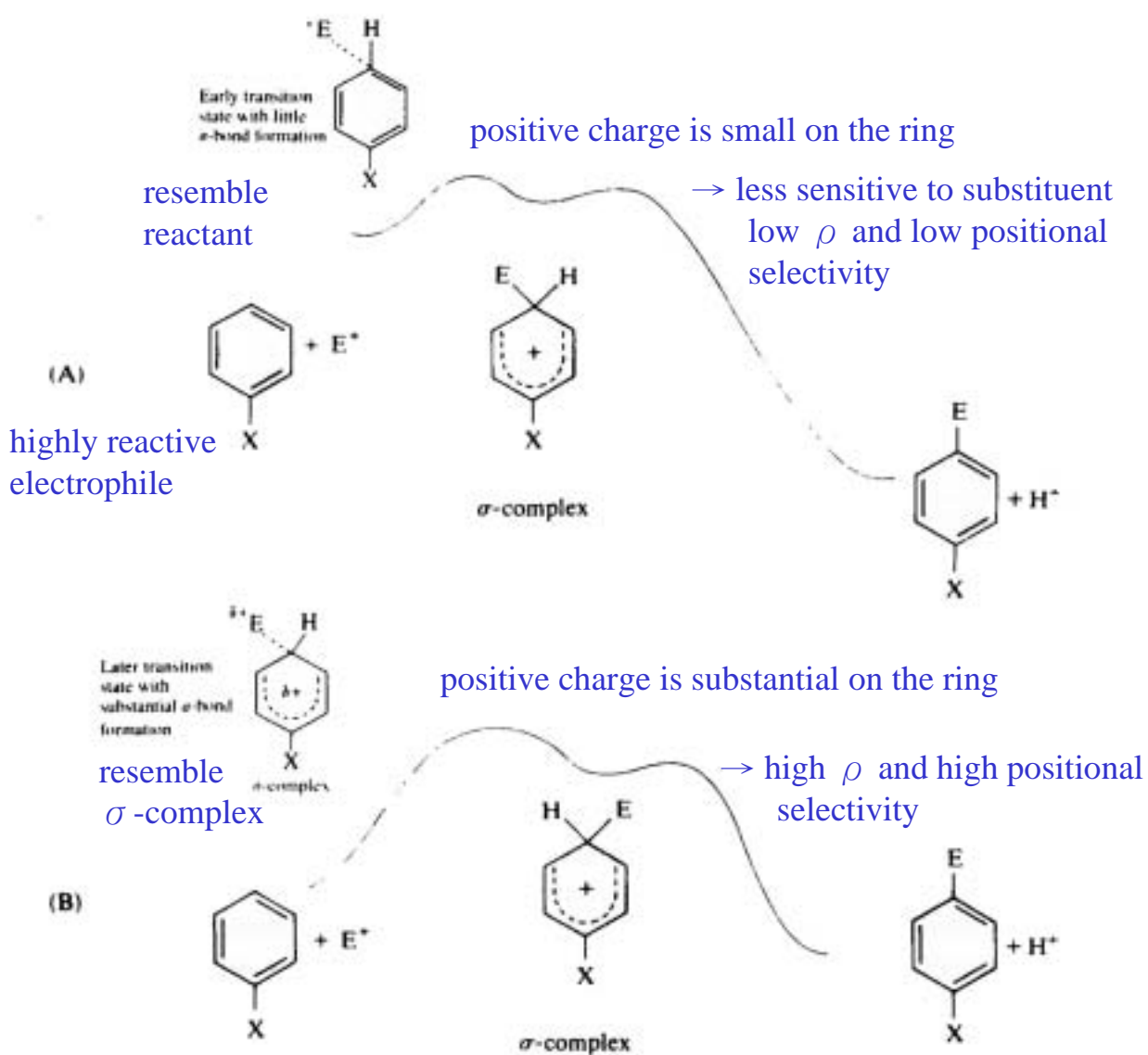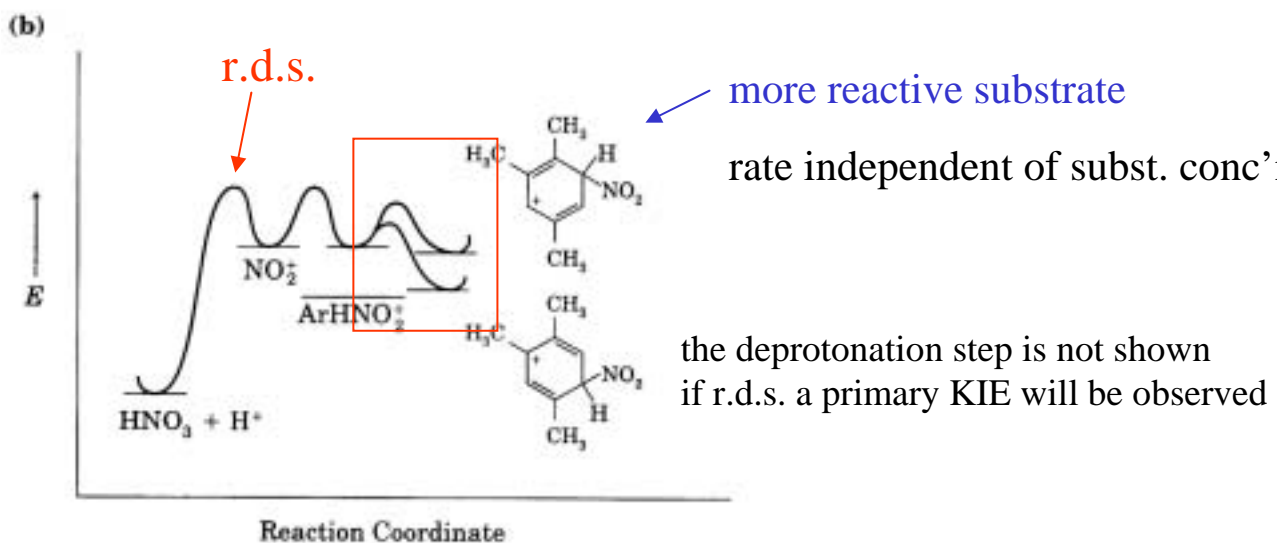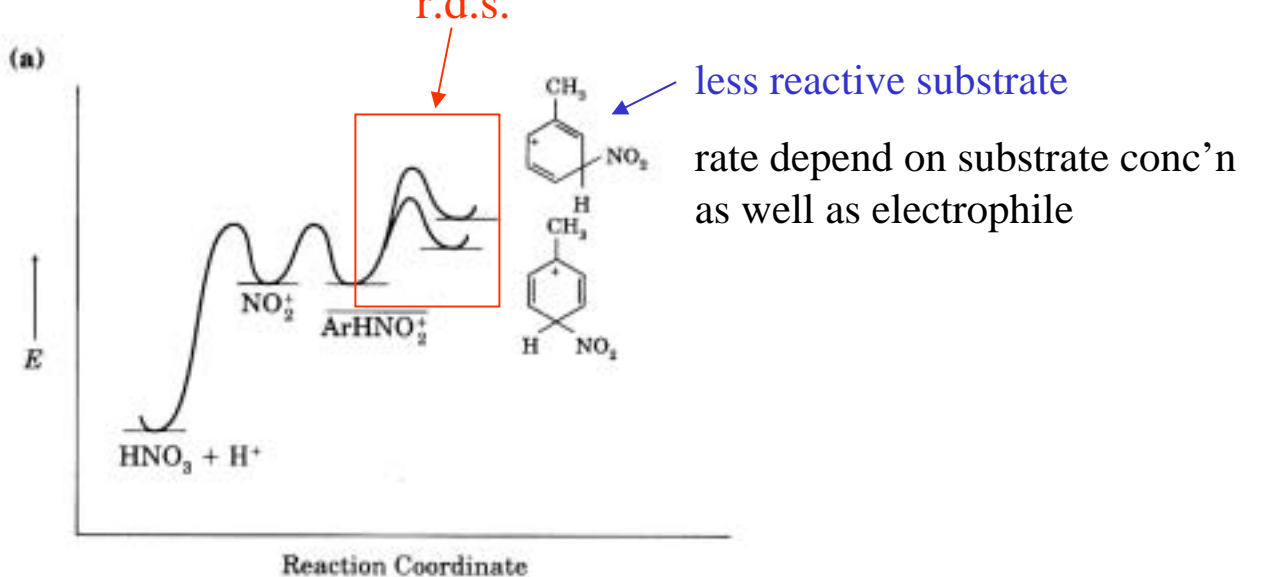substitution of a substituent by another substituent. $\Big]$

Fig. 9.7. Transition states for highly reactive (A) and less reactive (B) electrophiles.

In the figure (A):

'E H
Early transition state with little σ-bond formation
resemble reactant

positive charge is small on the ring
→ less sensitive to substituent low ρ and low positional selectivity

$+ E^+$

(A)

highly reactive electrophile X

E H
σ-complex
X
(+)

E
$+ H^+$
X

In the figure (B):

$\overset{\delta+}{E}$ H
Later transition state with substantial σ-bond formation
resemble σ-complex
σ-complex

positive charge is substantial on the ring
→ high ρ and high positional selectivity

$+ E^+$

(B)

X

H E
σ-complex
X
(+)

E
$+ H^+$
X

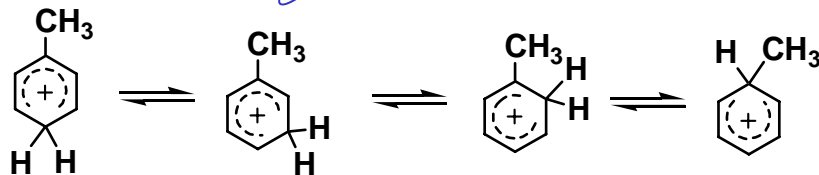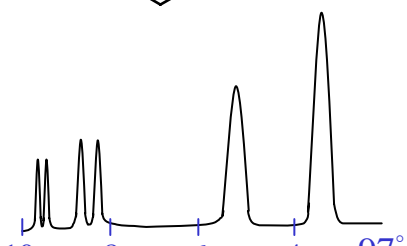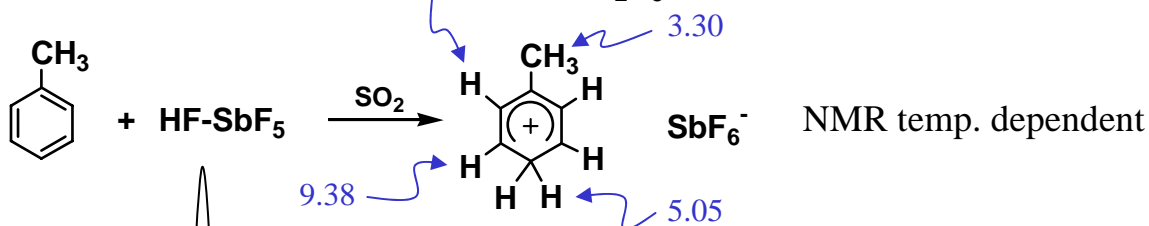Table 9.6. Values of ρ for Some Electrophilic Aromatic Substitution Reactions[a]

Reaction	ρ	relative to σ^+
Bromination (CH_3CO_2H)	−13.1	← late transition state
Chlorination (CH_3NO_2)	−13.0	
Chlorination ($CH_3CO_2H-H_2O$)	−8.8	
Proton exchange ($H_2SO_4-CF_3CO_2H-H_2O$)	−8.6	middle T.S.
Acetylation (CH_3COCl, $AlCl_3$, $C_2H_4Cl_2$)	−8.6	
Nitration ($H_2SO_4-HNO_3$)	−6.4	
Chlorination ($HOCl$, H^+)	−6.1	
Alkylation (C_2H_5Br, $GaBr_3$)	−2.4	← early transition state

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

(a)

less reactive substrate

rate depend on substrate conc'n
as well as electrophile

NO_2^+

$ArHNO_2^+$

$HNO_3 + H^+$

Reaction Coordinate

(b)

r.d.s.

more reactive substrate

rate independent of subst. conc'n

NO_2^+

$ArHNO_2^+$

$HNO_3 + H^+$

the deprotonation step is not shown
if r.d.s. a primary KIE will be observed

Reaction Coordinate

Evidence of σ -complex

salt isolated at low temp.
m.p.(dec.) -70°,
          elem. anal.

CH_3 + C_2H_3F + BF_3 ⟶ ($+$) BF_4^- H C_2H_5

8.40

3.30

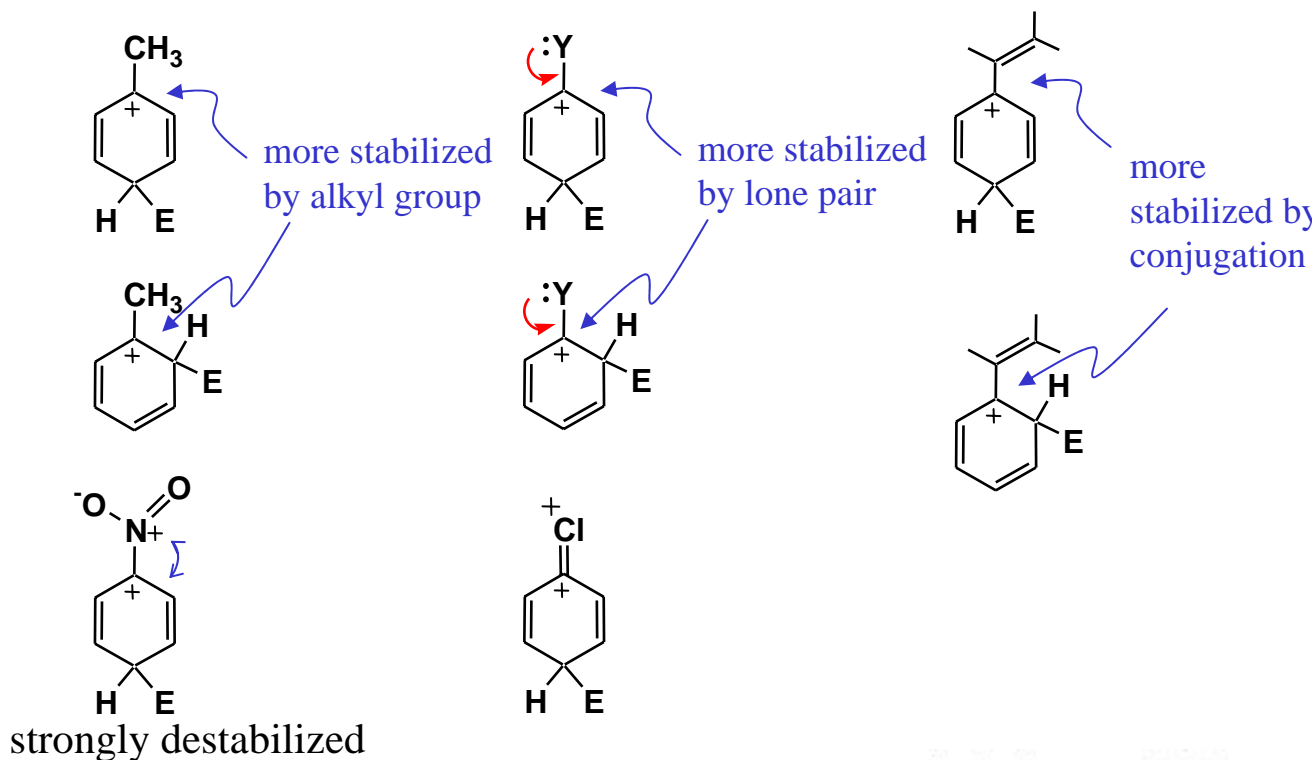CH_3 + HF-SbF$_5$ $\xrightarrow{SO_2}$ H   CH$_3$ H ($+$) H   H H H   SbF$_6^-$ NMR temp. dependent

9.38

5.05

For Substituted aromatics, the reaction sites are non-equivalent.

→ activating & ortho, para-directing gp：alkyl, OCH$_3$, -NR, $\diagup\hspace{-0.5em}=\hspace{-0.8em}\diagdown$

→ deactivating & meta-directing gp：-NO$_2$, -$^+$NR$_3$

→ deactivating & ortho, para-directing gp：Cl, Br

CH$_3$ — more stabilized by alkyl group

:Y — more stabilized by lone pair

— more stabilized by conjugation

strongly destabilized

Partial Rate factors

bromination   nitration

$$f_o^Z = [(k'/2)/(k/6)] \times (\text{percent ortho product}/100)$$

$$f_m^Z = [(k'/2)/(k/6)] \times (\text{percent meta product}/100)$$

$$f_p^Z = [(k'/1)/(k/6)] \times (\text{percent para product}/100)$$
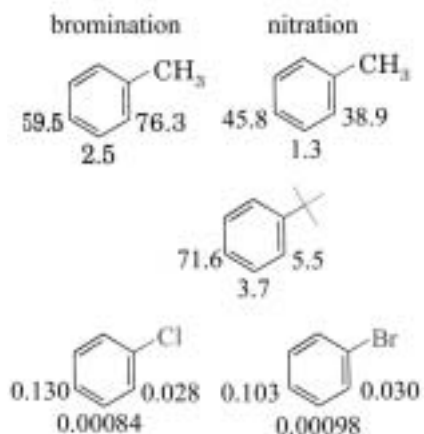
CH$_3$ (bromination): 59.5, 76.3, 2.5
CH$_3$ (nitration): 45.8, 38.9, 1.3
tert-butyl: 71.6, 5.5, 3.7
Cl: 0.130, 0.028, 0.00084
Br: 0.103, 0.030, 0.00098

k'：rate for the rxn of substituted derivative
k：rate for the rxn of benzene

if $f^Z > 0$：activating ; $f^Z < 0$：deactivating

$$f_o^Z, f_p^Z > f_m^Z \qquad o, p - \text{directing}$$

$$f_m^Z > f_o^Z, f_p^Z \qquad m - \text{directing}$$

Partial rate factors relate 1. substrate selectivity
                             2. positional selectivity

   high substrate selectivity → large differences in rate of rxn
                             → low reactivity of electrophile
   low substrate selectivity → high reactivity of electrophile

positional selectivity relates to substrate selectivity

In general：

  Electrophilie with high substrate selectivity will have
         low ortho：para ratio and negligible meta

  Electrophiles of low substrate selectivity → low position selectivity

    Selectivity factor $S_f = \log \dfrac{f_P \ \text{for toluene}}{f_m \ \text{for toluene}}$ strongly correlate with f_P

  high substrate selective → high positional selective

Table 9.5. Selectivity in Some Electrophilic Aromatic Substitution Reactions[a]

Reaction	Partial rate factors for toluene		
	f_o	f_m	f_p
Nitration			
HNO₃(CH₃NO₂)	38.9	1.3	45.7
Halogenation			
Cl₂(CH₃CO₂H)	617	5	820
Br₂(CH₃CO₂H–H₂O)	600	5.5	2420
Protonation			
H₂O–H₂SO₄	83	1.9	83
H₂O–CF₃CO₂H–H₂SO₄	330	7.2	313
Acylation			
PhCOCl(AlCl₃, PhNO₂)	32.6	5.0	831
CH₃COCl(AlCl₃, ClCH₂CH₂Cl)	4.5	4.8	749
Alkylation			
CH₃Br(GaBr₃)	9.5	1.7	11.8
(CH₃)₂CHBr(GaBr₃)	1.5	1.4	5.0
PhCH₂Cl(AlCl₃)	4.2	0.4	10.0

intermediate (Nitration)

highly selective (Halogenation, Protonation, Acylation)

← low selective (Alkylation)

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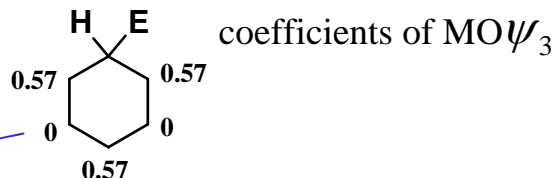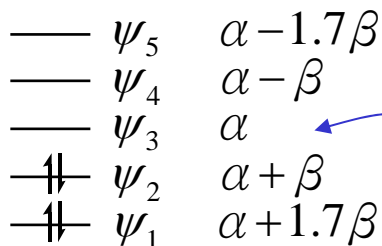
PMO Theory of directing effect

if the T.S. is similar to the intermediate σ-complex (late T.S.)

a pentadienyl cation with 4e⁻

$$\underline{\qquad} \quad \psi_5 \quad \alpha - 1.7\beta$$
$$\underline{\qquad} \quad \psi_4 \quad \alpha - \beta$$
$$\underline{\qquad} \quad \psi_3 \quad \alpha$$
$$\underline{\text{⇈}} \quad \psi_2 \quad \alpha + \beta$$
$$\underline{\text{⇈}} \quad \psi_1 \quad \alpha + 1.7\beta$$

coefficients of MO ψ_3

a substituent will have little effect if at meta-position, since it's a node there

The cation charge is on C_1, C_3, C_5 for a substituent with positive charge on atom directly bond to the ring, there will be electrostatic repulsion. → meta-directing for $>C=O$, $C \equiv N$, $-NO_2$
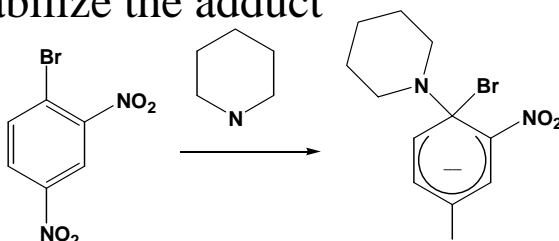
Nucleophilic Aromatic Substitution S_NAr

First order

$\ddot{N}u^-$

N_2 → Driving force

Second order   good leaving gp

$+ X^-$
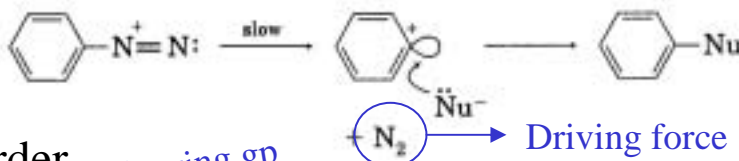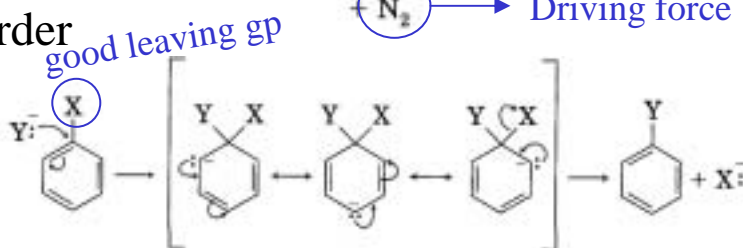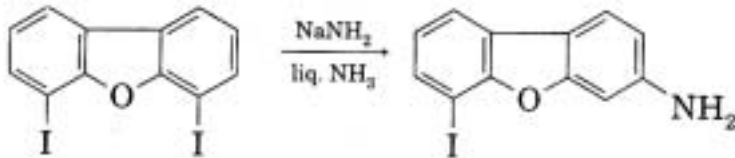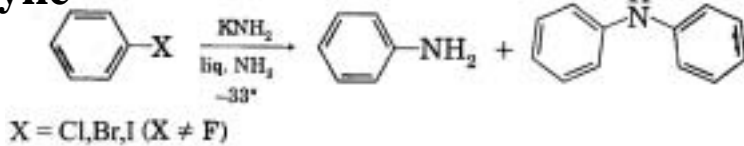
1. The site of reaction is the leaving group position, as H is not a good leaving group → no isomeric mixture formation.
2. a strong e⁻-withdrawing $-NO_2$, -CN at ortho, para-position is needed to stabilize the adduct

Benzyne

$X = Cl, Br, I \ (X \neq F)$
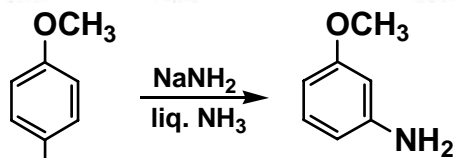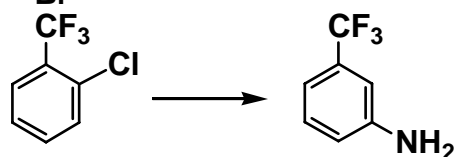

amino is at the site of leaving gp or one carbon away

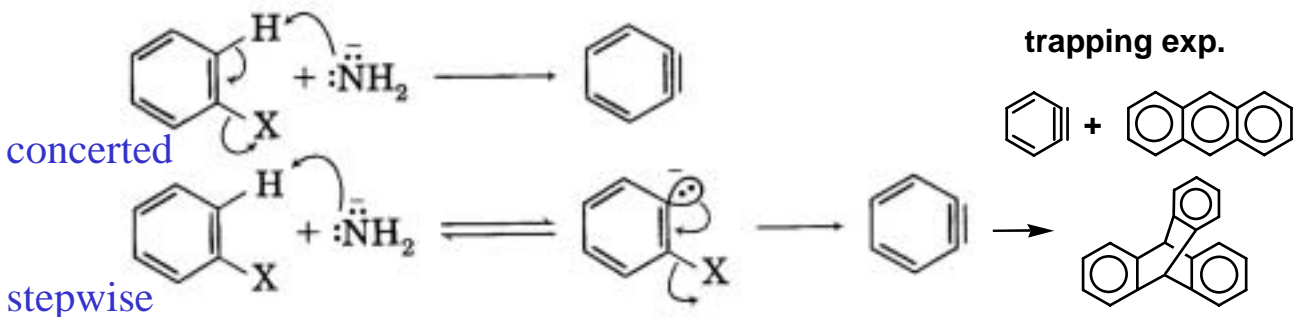the S.M. or product does not isomerize under same rxn condition
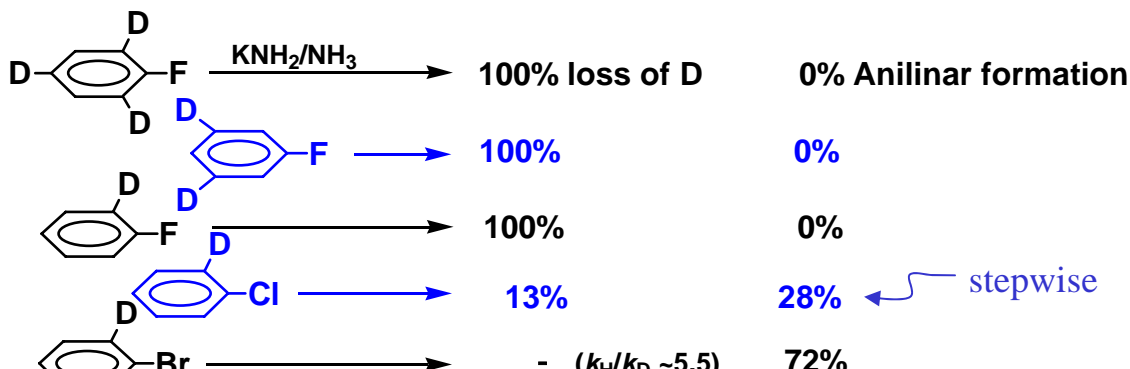
reactivity：$Br > I > Cl \gg F$

*C-labeling expt.

| X = I | 46% | 52% |
| X = Cl | 43% | 53% |
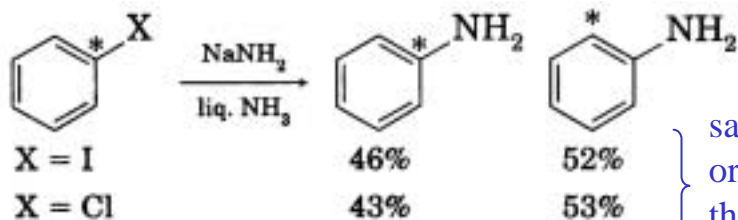
same intermediate or mechanism for the formation of both product

proposed rxn mech.

trapping exp.

concerted

stepwise

D-labeling expt.

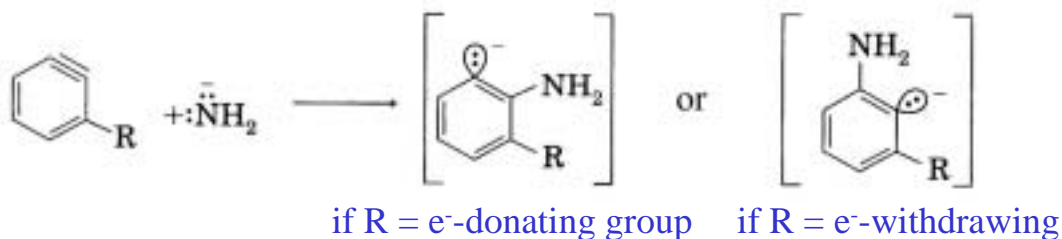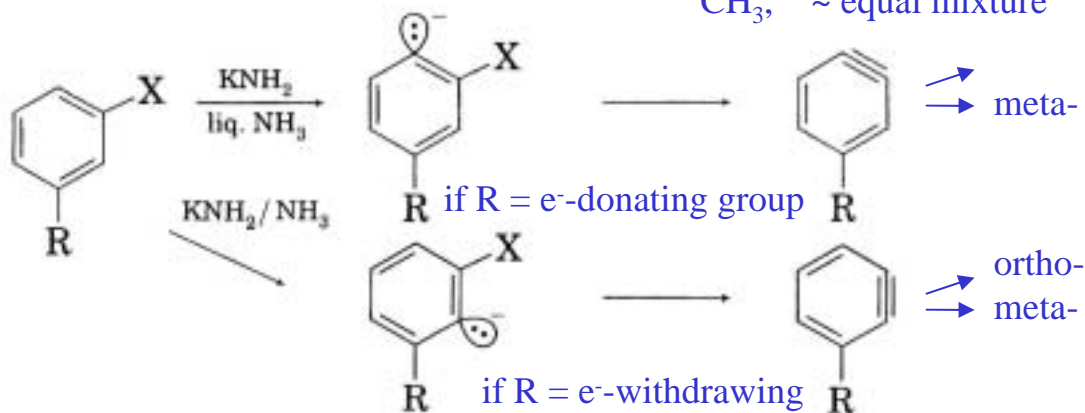| | KNH$_2$/NH$_3$ | 100% loss of D | 0% Anilinar formation |
		100%	0%
		100%	0%
		13%	28% ← stepwise
		(k_H/k_D ~5.5)	72%

Product Distribution in Benzyne Rxns
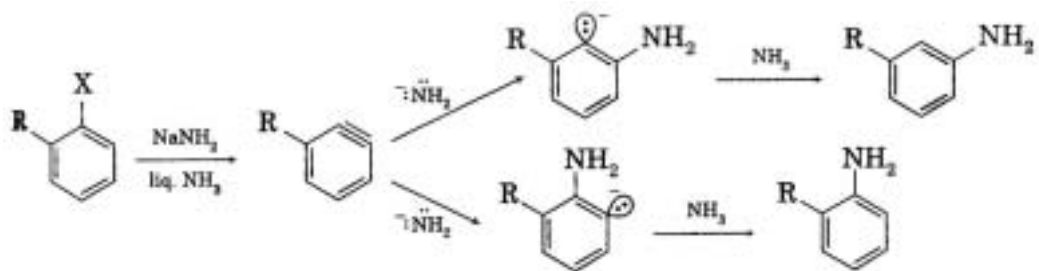
relative stability determines the prod. distribution

R = CF$_3$,   m-product favored

CH$_3$,   ~ equal mixture

if R = e$^-$-donating group   meta-

if R = e$^-$-withdrawing   ortho-
meta-

if R = e$^-$-donating group   if R = e$^-$-withdrawing

Table 8.19 Product distributions for reaction of substituted halobenzenes with amide in liquid ammonia.

R	X	Yield (%)	% Ortho	% Meta	% Para
o-CF$_3$	Cl	28		100	
o-CH$_3$	Cl	66	45	55	
o-CH$_3$	Br	64	48.4	51.5	
o-OCH$_3$	Br	33		100	
p-CF$_3$	Cl	25		50	50
p-CH$_3$	Cl	35		62	38
p-OCH$_3$	Br	31		49	51
m-CF$_3$	Cl	16		100	
m-CH$_3$	Cl	66	40	52	8
m-CH$_3$	Br	61	22	56	22
m-OCH$_3$	Br	59		100	

considered as e-withdrawing since the anion is in sp^2, orthogonal to the π -system