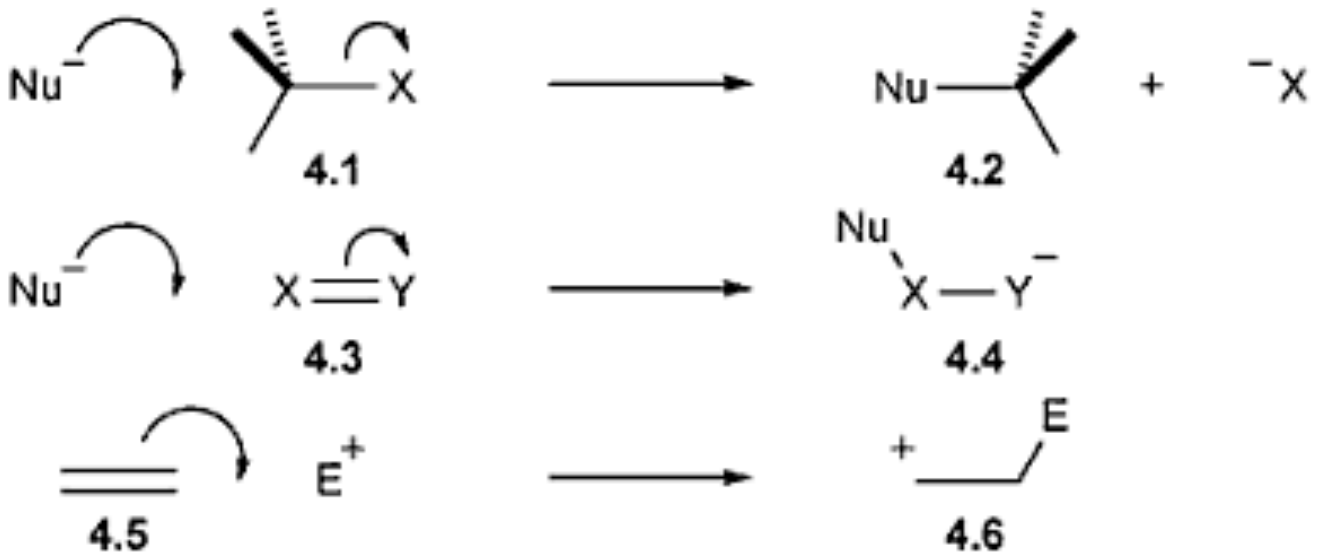
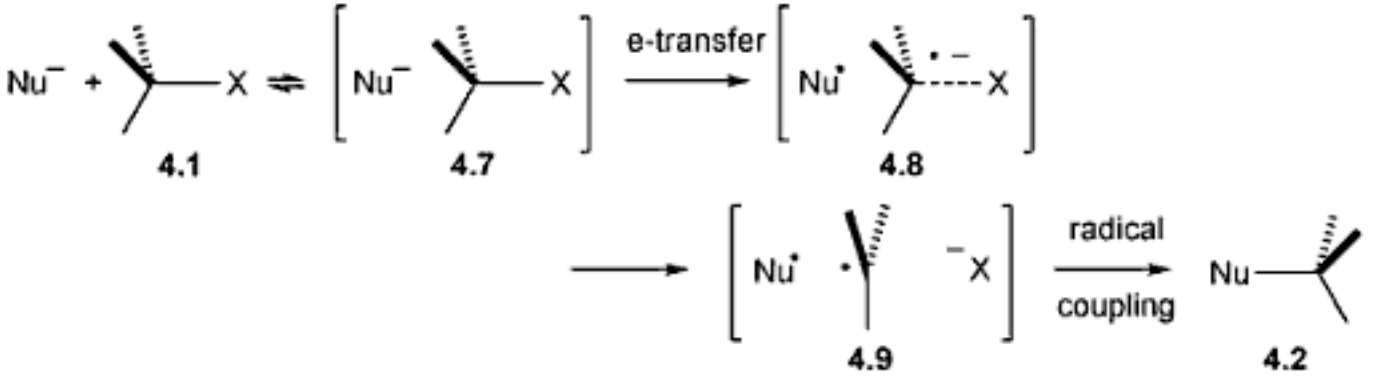
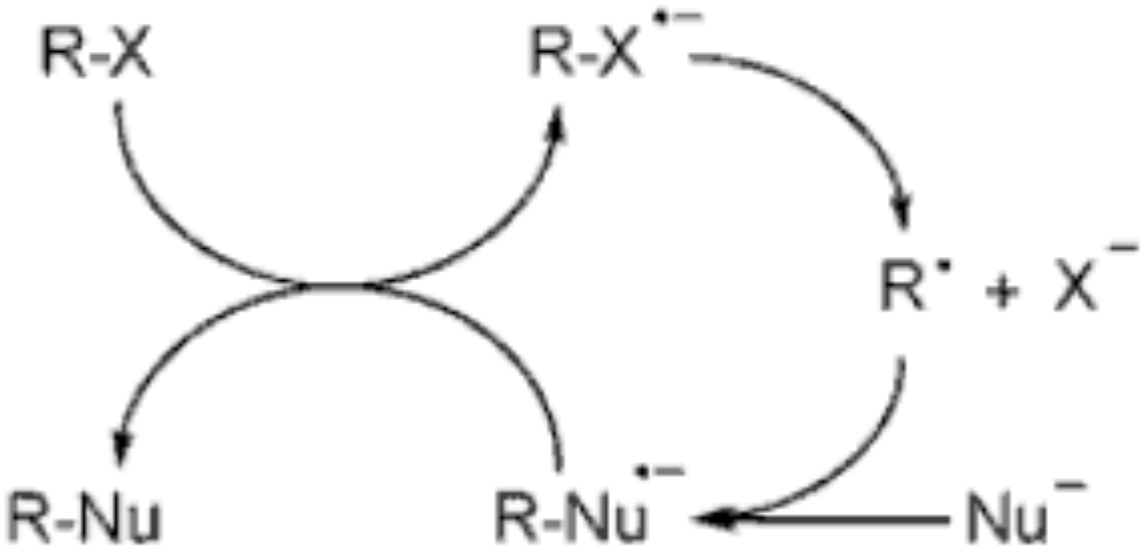
Substituição Nucleofílica

Tipos

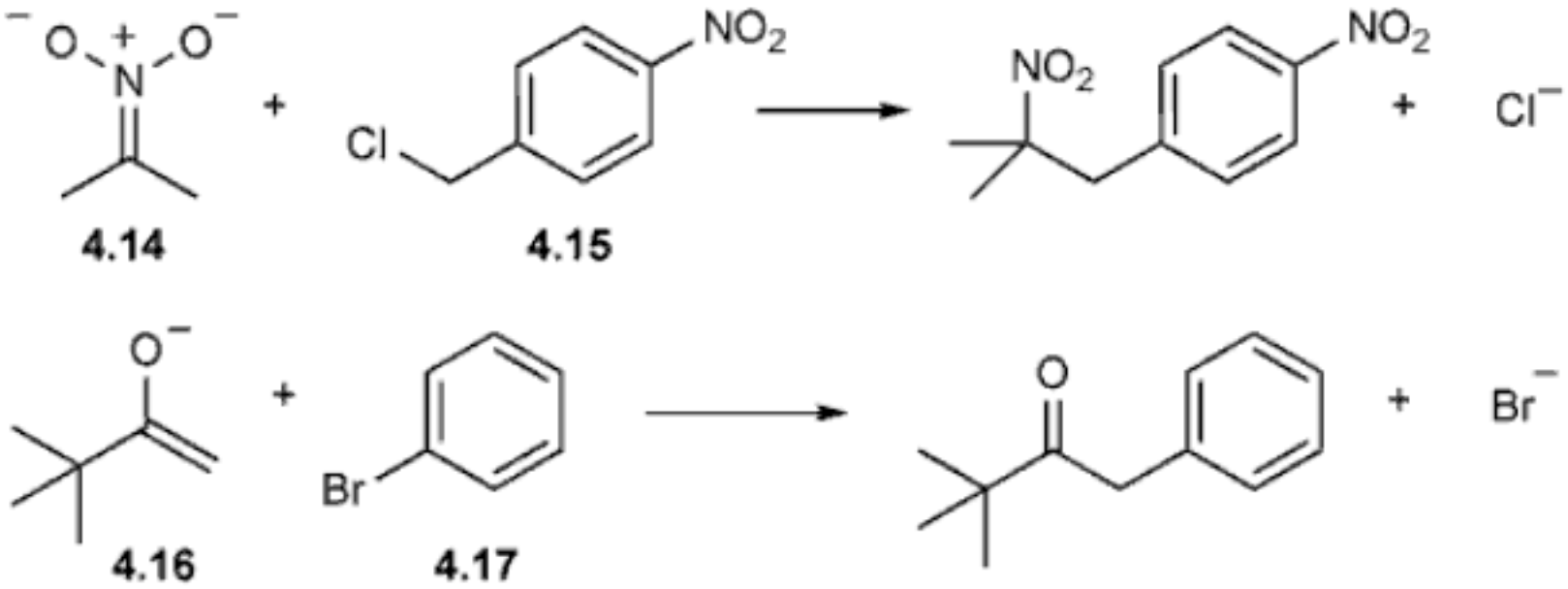



Nu⁻ + X
4.1
Nu⁻ X
4.7
e-transfer
Nu• X
4.8
Nu• X
4.9
radical
coupling
Nu
4.2
Nu⁻ + X=Y
4.3
Nu⁻ X=Y
4.10
e-transfer
Nu• X=Y
4.11
radical
coupling
Nu
X—Y⁻
4.4
+ E⁺
4.5
E⁺
4.12
e-transfer
E•
4.13
radical
coupling
+ E
4.6

$S_{RN}1$

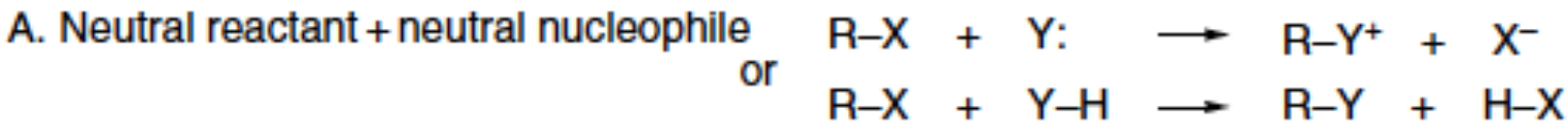


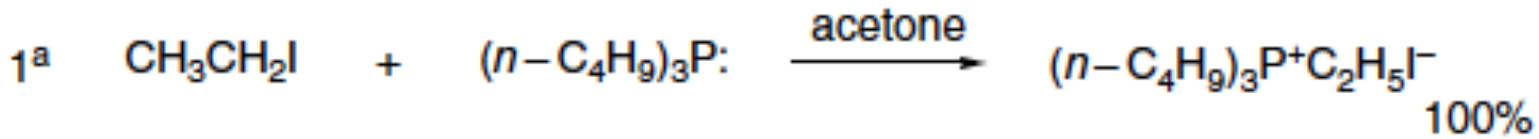
The $S_{RN}1$ reaction

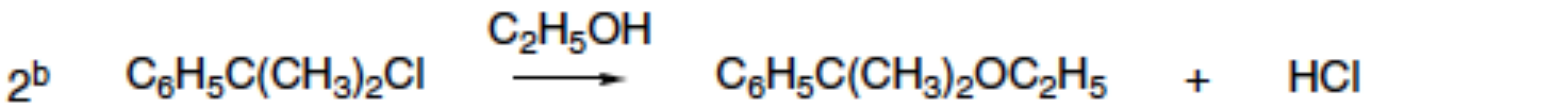

O
N
O
NO2
Cl
NO2
NO2
Cl−
4.14
4.15
O
Br
O
Br−
4.16
4.17

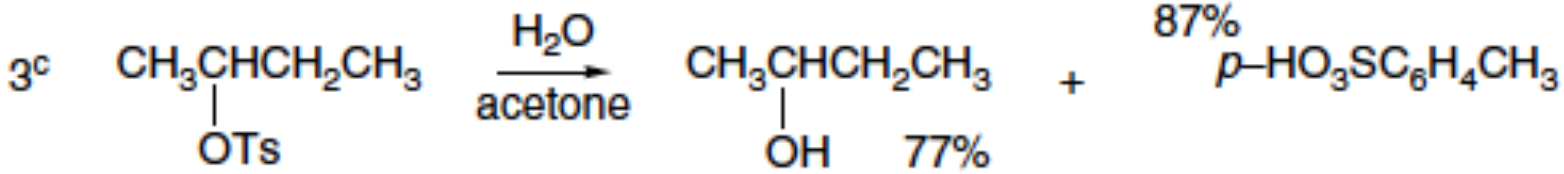
Scheme 4.1. Representative Nucleophilic Substitution Reactions

A. Neutral reactant + neutral nucleophile

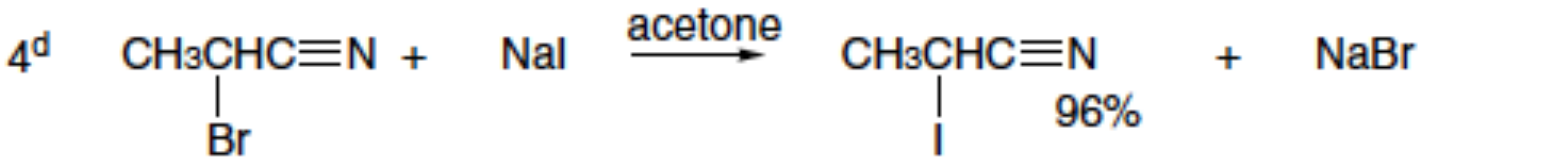


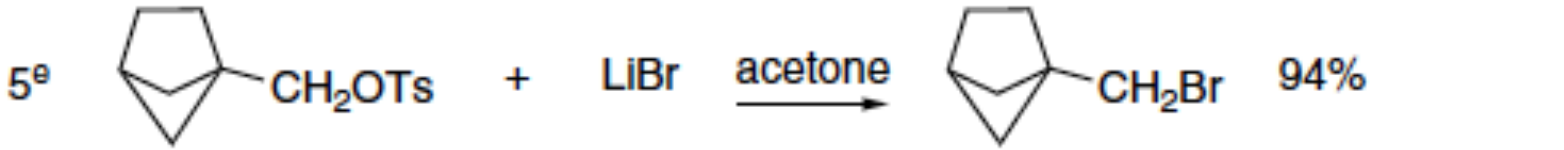
1[a] 

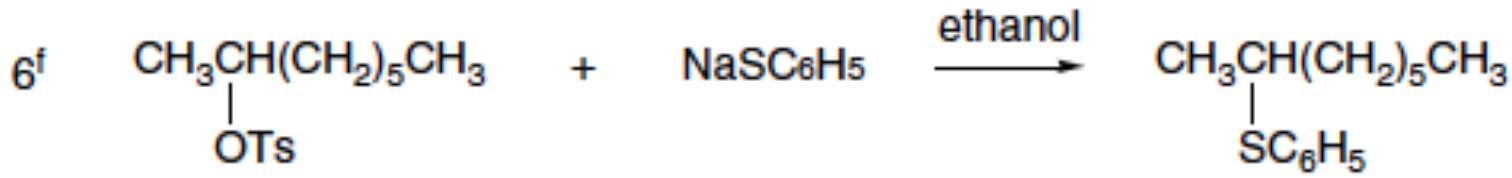
2[b] 

3[c] 

B. Neutral reactant + anionic nucleophile 

4[d] 

5[e] 

6[f] 

C. Cationic reactant and neutral nuclophile $R{-}X^+ + Y: \longrightarrow R{-}Y^+ + X$

7[g] $C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}HS^+(CH_3)_2 + (H_2N)_2C{=}S \xrightarrow{\text{acetonitrile}} [C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}H{-}S{-}C(NH_2)_2]^+$

8[h] $(C_6H_5)_2C{=}N^+{=}N^- + TsOH \longrightarrow (C_6H_5)_2CH{-}N^+{\equiv}N \xrightarrow{C_2H_5OH} (C_6H_5)_2CHOC_2H_5 + N_2$

D. Cationic reactant and anionic nucleophile $R - X^+ + Y: \longrightarrow R - Y + X:$

9[i] $(C_2H_5)_3O^+{}^-BF_4 + Na^+{}^-O_2CC(CH_3)_3 \longrightarrow (CH_3)_3CCO_2C_2H_5 + O(C_2H_5)_2$

90%

10[j] $CH_2{=}CHCH_2CH_2S^+(CH_3)C_6H_5 \xrightarrow[DMF]{NaI} CH_2{=}CHCH_2CH_2I + CH_3SC_6H_5$

52%

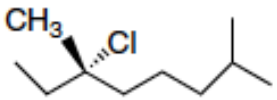
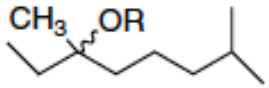
---

a. S. A. Buckler and W. A. Henderson, *J. Am. Chem. Soc.*, **82**, 5795 (1960).
b. R. L. Buckson and S. G. Smith, *J. Org. Chem.*, **32**, 634 (1967).
c. J. D. Roberts, W. Bennett, R. E. McMahon, and E. W. Holroyd, *J. Am. Chem. Soc.*, **74**, 4283 (1952).
d. M. S. Newman and R. D. Closson, *J. Am. Chem. Soc.*, **66**, 1553 (1944).
e. K. B. Wiberg and B. R. Lowry, *J. Am. Chem. Soc.*, **85**, 3188 (1963).
f. H. L. Goering, D. L. Towns, and B. Dittmar, *J. Org. Chem.*, **27**, 736 (1962).
g. H. M. R. Hoffmann and E. D. Hughes, *J. Chem. Soc.*, 1259 (1964).
h. J. D. Roberts and W. Watanabe, *J. Am. Chem. Soc.*, **72**, 4869 (1950).
i. D. J. Raber and P. Gariano, *Tetrahedron Lett.*, 4741 (1971).
j. E. J. Corey and M. Jautelat, *Tetrahedron Lett.*, 5787 (1968).

Estereoquímica

Scheme 4.2. Stereochemistry of Nucleophilic Substitution Reactions

	Reactant[a]	Conditions	Product	Sterechemistry
1[b]	$CH_3CH_2CH_2CHDOBs$	HCO_2H 99° C	$CH_3CH_2CH_2CHDO_2CH$	99 ± 6% inv.
2[c]	$C_6H_5CHDOTs$	CH_3CO_2H 25° C	$C_6H_5CHDO_2CCH_3$	82 ± 1% inv.
3[c]	$CH_3CH(CH_2)_5CH_3$ OTs	$Et_4N^+{-}O_2CCH_3$ acetone, 56° C	$CH_3CH(CH_2)_5CH_3$ O_2CCH_3	100% inv.
4[d]	$CH_3CH(CH_2)_5CH_3$ OTs	75 % aq. dioxane 65° C	$CH_3CH(CH_2)_5CH_3$ OH	77% inv.
		75 % aq. dioxane 0.06 *M* NaN_3, 65° C	$CH_3CH(CH_2)_5CH_3$ OH 22%	100% inv.
			$CH_3CH(CH_2)_5CH_3$ N_3 78%	100% inv.

5[e]				
			CH_3OH, DTBP, 25° C	78% inv.
			C_2H_5OH, DTBP, 40° C	55% inv.
			HCO_2H, DTBP, 0° C	42% inv.
			CF_3CH_2OH, DTBP, 25° C	13% ret.
			t-BuOH, 20% H_2O, 25° C	49% inv.
			dioxane, 20% H_2O, 25° C	98% inv.
6[f]	$C_6H_5CHCH_3$ | Cl	$K^+{-}O_2CCH_3$, CH_3CO_2H, 50° C	$C_6H_5CHCH_3$ | O_2CCH_3	15% inv.
		$Et_4N^+{-}O_2CCH_3$ 50% acetone	$C_6H_5CHCH_3$ | O_2CCH_3	65% inv.
7[f]	CH_3 | $C_6H_5CC_2H_5$ | OPNB	$K^+{-}O_2CCH_3$, CH_3CO_2H, 23° C	CH_3 | $C_6H_5CC_2H_5$ | $O_2CH_2CH_3$	5 ± 2% inv.
		NaN_3 in CH_3OH, 65° C	CH_3 | $C_6H_5CC_2H_5$ | N_3	56 ± 1% inv.
			CH_3 | $C_6H_5CC_2H_5$ | OCH_3	14% inv.
		90% aq, acetone	CH_3 | $C_6H_5CC_2H_5$ | OH	38% ret.

Mecanismos Casos Limitantes: S_N2

$$R\text{–}X + Y\text{:}^- \xrightarrow{k} R\text{–}Y + X\text{:}^-$$

$$\text{rate} = -\frac{d[R\text{–}X]}{dt} = -\frac{d[Y\text{:}^-]}{dt} = k[R\text{–}X][Y\text{:}^-]$$

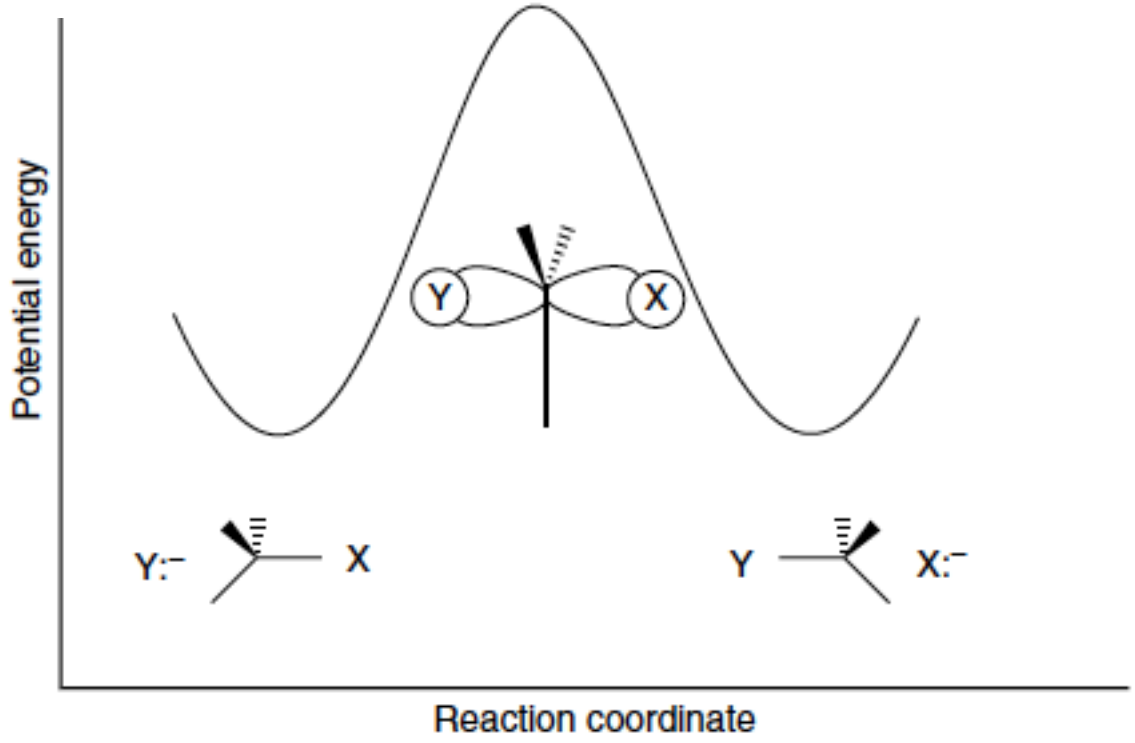
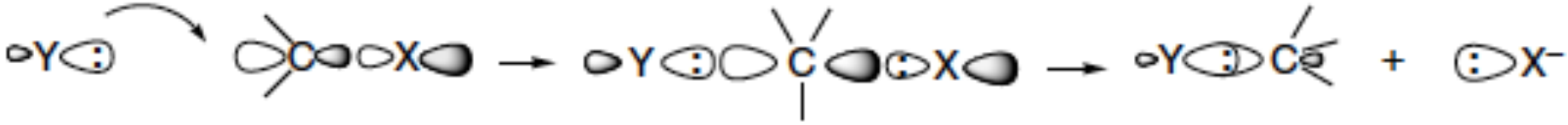
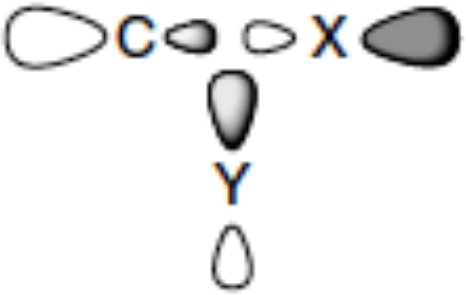


Fig. 4.3. Reaction energy profile for nucleophilic substitution by the direct displacement (S_N2) mechanism.

- Favorecido



- Desfavorecido



(a) Inversion of configuration

(b) Retention of configuration

Fig. 5.1 Frontier orbitals for the S_E2 reaction

Mecanismos Casos Limitantes: S_N1

$$R\text{–}X \xrightarrow[\text{slow}]{k_1} R^+ + X^-$$

$$R^+ + Y^- \xrightarrow[\text{fast}]{k_2} R\text{–}Y$$

$$\text{rate} = k_1[R\text{–}X]$$

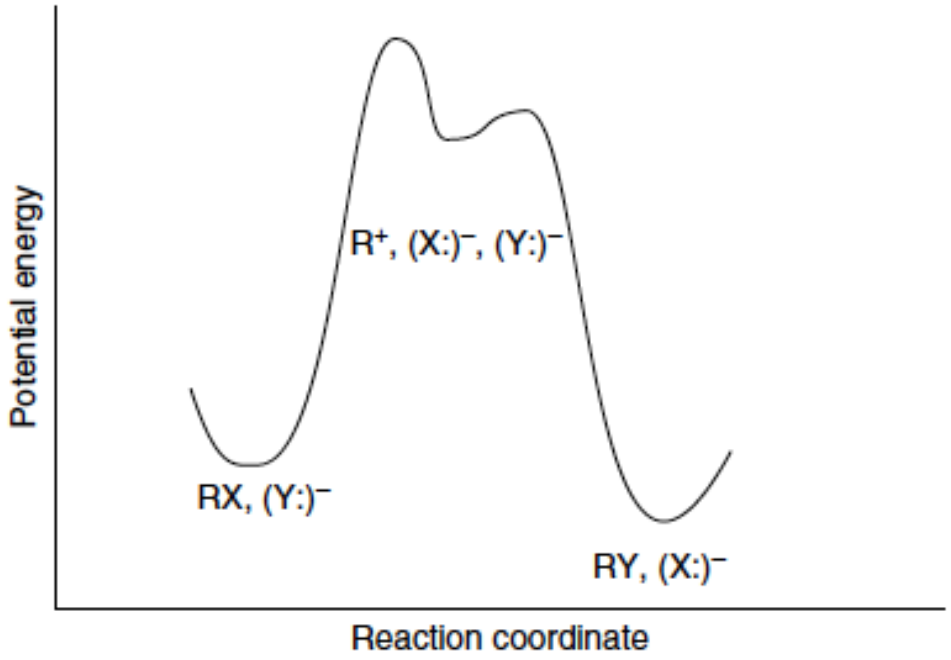
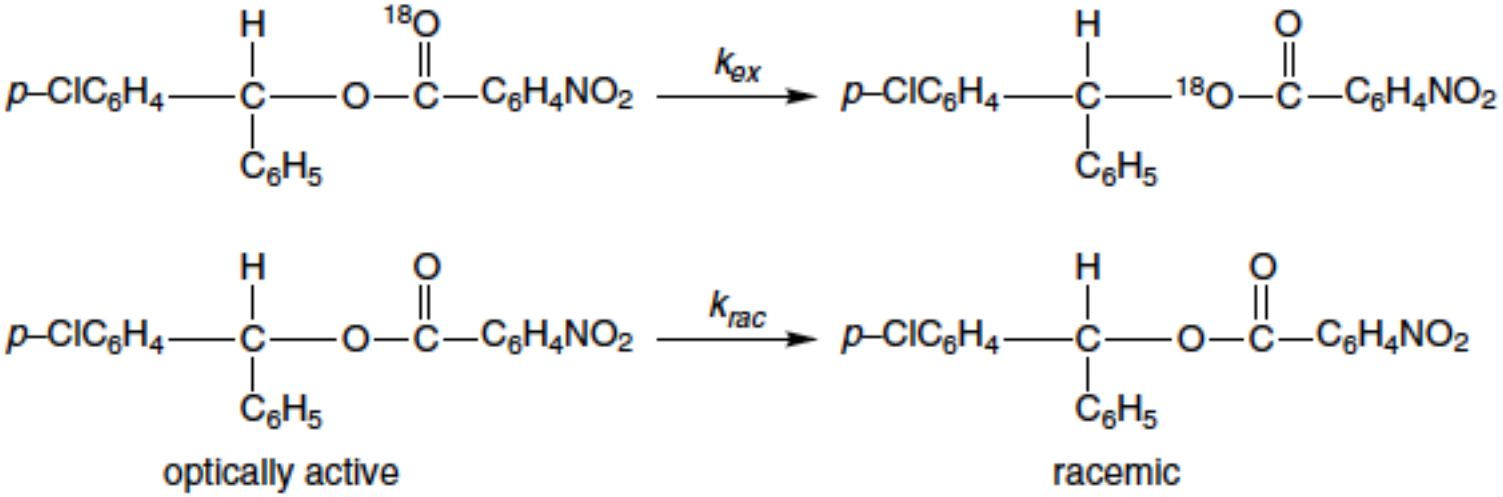


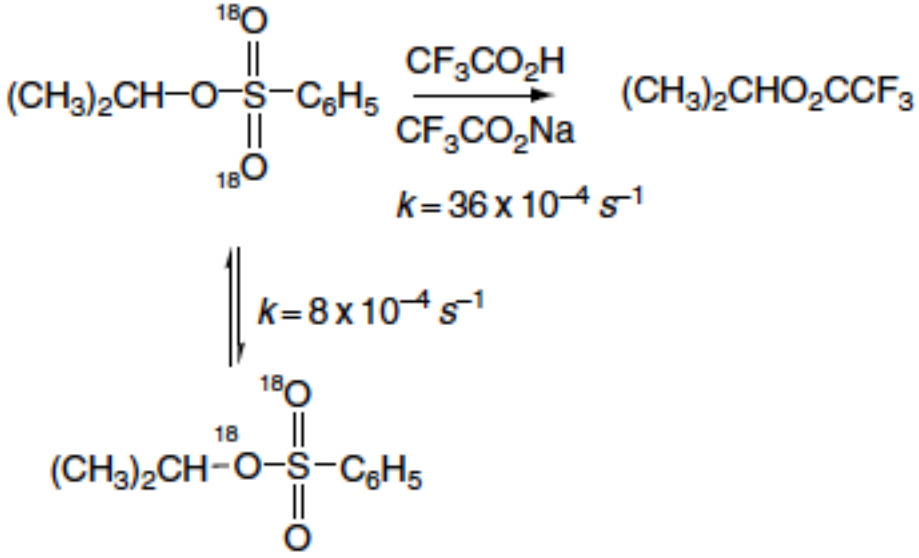
Fig. 4.1. Reaction energy profile for nucleophilic substitution by the ionization (S_N1) mechanism.

Retorno interno



$k_{ex}/k_{rac} = 2.3$

H. L. Goering and J. F. Levy, *J. Am. Chem. Soc.*, ***86, 120 (1964).***


18O
(CH3)2CH–O–S–C6H5
18O
CF3CO2H
CF3CO2Na
(CH3)2CHO2CCF3
k = 36 x 10−4 s−1
k = 8 x 10−4 s−1
18O
18
(CH3)2CH–O–S–C6H5
O

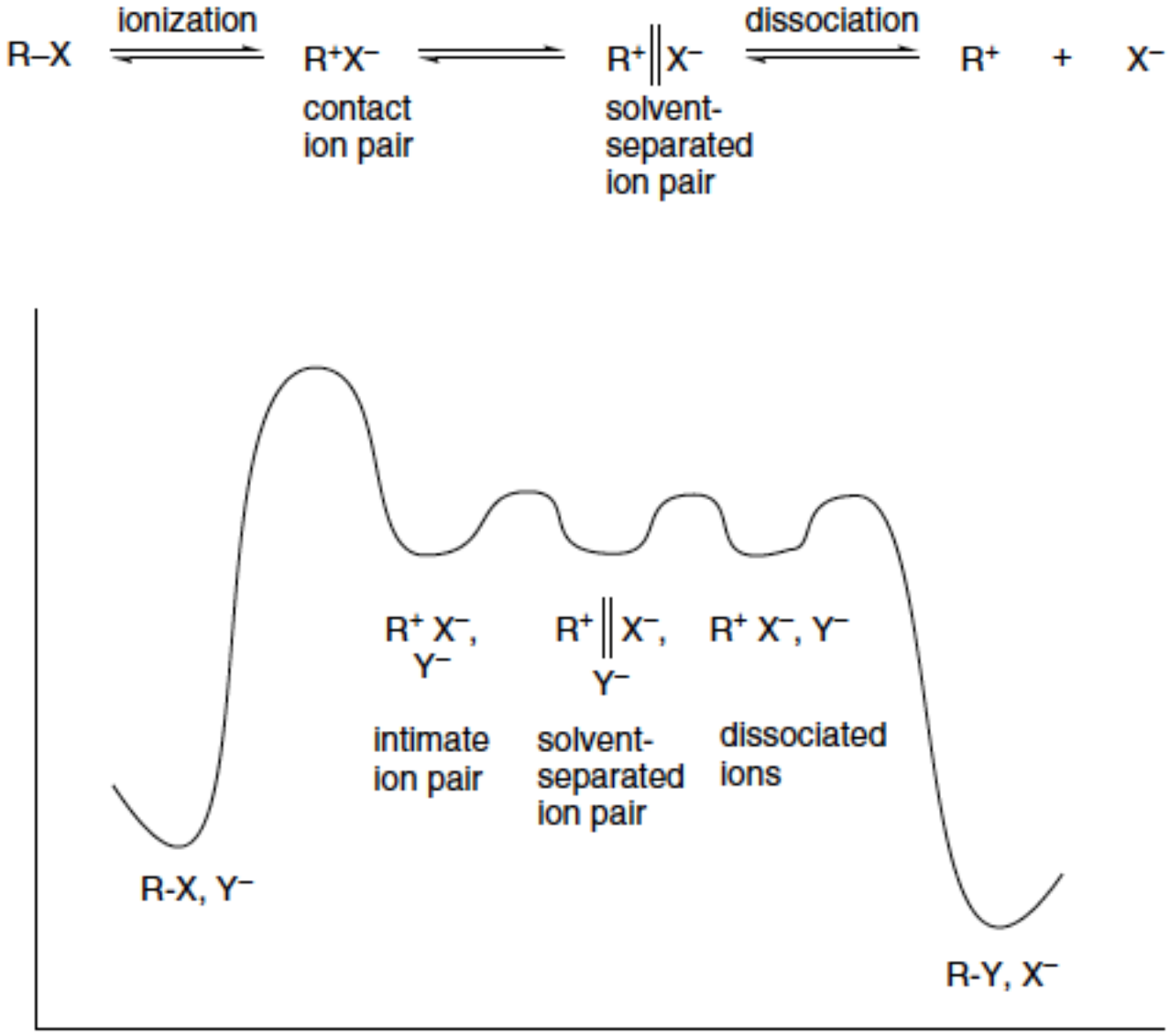


Fig. 4.4. Schematic relationship between reactants, ion pairs, and products in substitution proceeding through ion pairs.

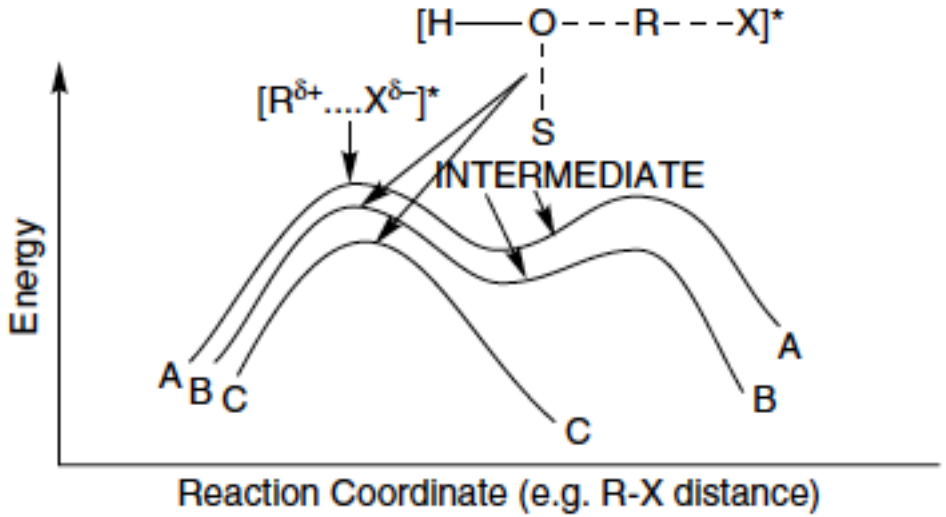


Fig. 4.5. Reaction energy profiles for substitution mechanisms. A is the S_N1 mechanism. B is the S_N2 mechanism with an intermediate ion pair or pentacoordinate species. C is the classical S_N2 mechanism. Reproduced from T. W. Bentley and P. v. R. Schleyer, *Adv. Phys. Org. Chem.*, **14,** 1 (1977), by permission of Academic Press.

Gráficos de O'Ferrall-Jencks

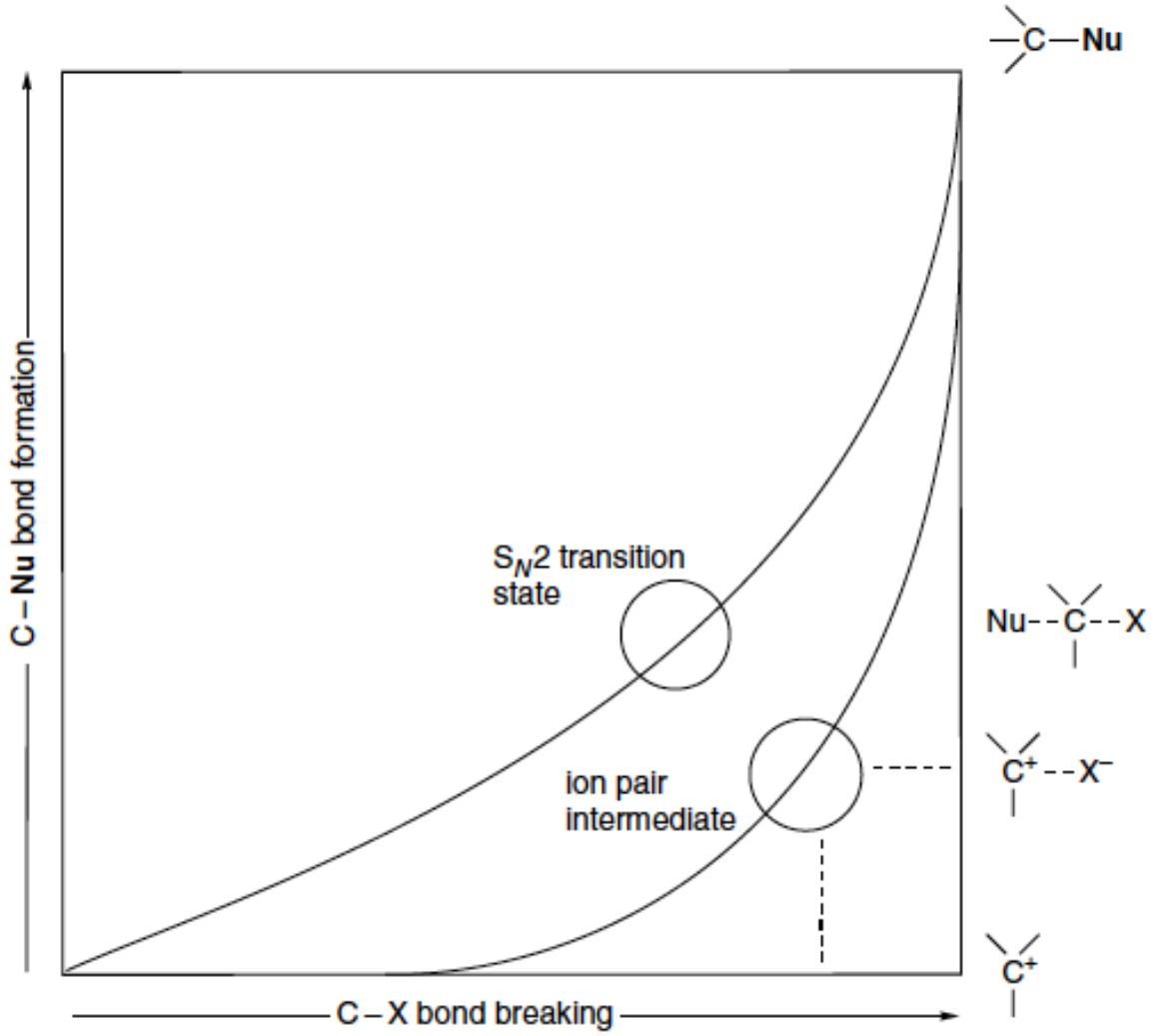


Fig. 4.7. Two-dimensional reaction energy diagram showing concerted, ion pair intermediate, and stepwise mechanisms for nucleophilic substitution.

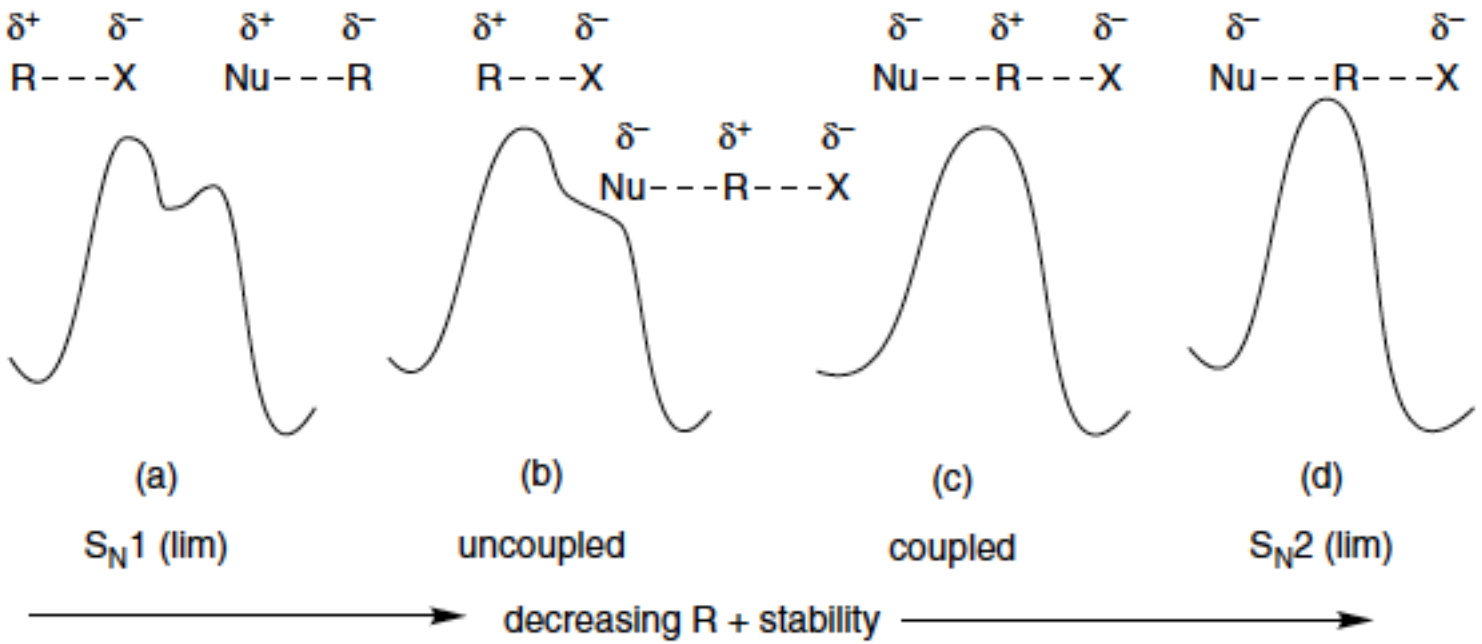
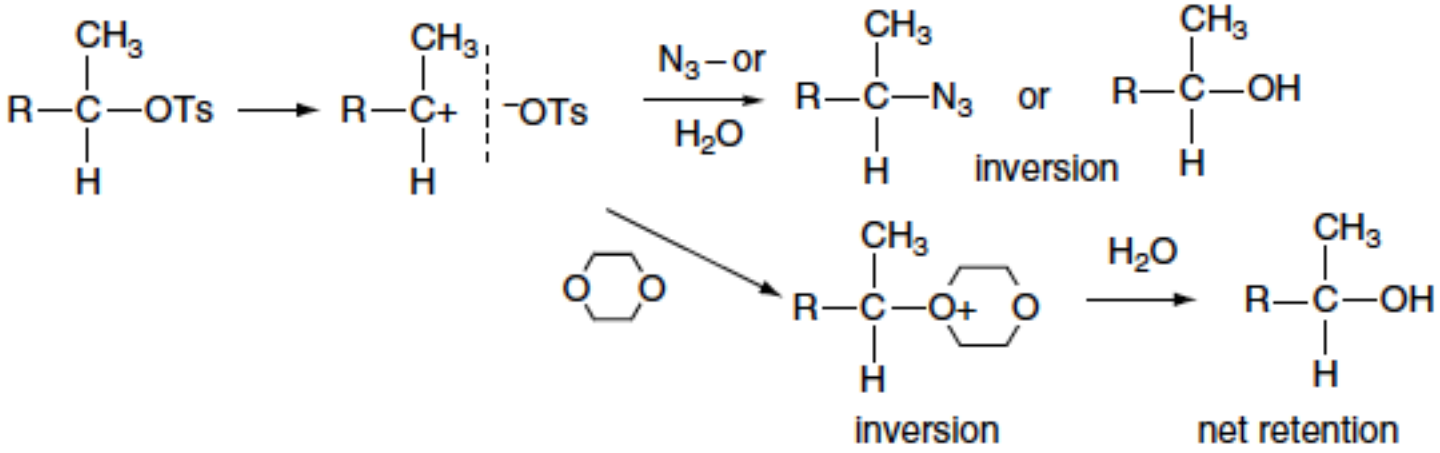


Fig. 4.6. Reaction energy profiles showing decreasing carbocation stability in change from S_N1(lim) to S_N2(lim) mechanisms.

Estereoquímica: Explicação



Escalas de nucleofilicidade

- Swain-Scott $n_{CH_3I} = \log(k_{nucl}/k_{CH_3OH})$ in CH_3OH, 2

Table 4.3. Nucleophilicity Constants for Various Nucleophiles[a]

Nucleophile	n_{CH_3I}	Conjugate acid pK_a
CH_3OH	0.0	−1.7
NO_3^-	1.5	−1.3
F^-	2.7	3.45
$CH_3CO_2^-$	4.3	4.8
Cl^-	4.4	−5.7
$(CH_3)_2S$	5.3	
NH_3	5.5	9.25
N_3^-	5.8	4.74
$C_6H_5O^-$	5.8	9.89
Br^-	5.8	−7.7
CH_3O^-	6.3	15.7
HO^-	6.5	15.7
NH_2OH	6.6	5.8
NH_2NH_2	6.6	7.9
$(CH_3CH_2)_3N$	6.7	10.7
CN^-	6.7	9.3
$(CH_3CH_2)_3As$	7.1	
I^-	7.4	−10.7
HO_2^-	7.8	
$(CH_3CH_2)_3P$	8.7	8.7
$C_6H_5S^-$	9.9	6.5
$C_6H_5Se^-$	10.7	
$(C_6H_5)_3Sn^-$	11.5	

a. Data from R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.*, **89**, 1827 (1967); R. G. Pearson, H. Sobel, and J. Songstad, *J. Am. Chem. Soc.*, **90**, 319 (1968); P. L. Bock and G. M Whitesides, *J. Am. Chem. Soc.*, **96**, 2826 (1974).

Scheme 4.3. Examples of Competition between Nucleophilicity and Basicity

S_N1 Substitution *versus*	**Y:**$^-$ acts as a nucleophile	**Y:**$^-$ + $R_2C^+CHR'_2 \longrightarrow R_2CCHR'_2$ (Y)
E1 Elimination	**Y:**$^-$ acts as a base	**Y:**$^-$ + $R_2C^+CHR'_2 \longrightarrow R_2C{=}CR'_2 + H{-}\mathbf{Y}$
S_N2 Substitution *versus*	**Y:**$^-$ acts as a nucleophile	**Y:**$^-$ + $RCH_2CH_2X \longrightarrow RCH_2CH_2\mathbf{Y} + X^-$
E2 Elimination	**Y:**$^-$ acts as a base	**Y:**$^-$ + $RCH_2CH_2X \longrightarrow RCH{=}CH_2 + H{-}\mathbf{Y}$
Nucleophilic addition to a carbonyl group	**Y:**$^-$ acts as a nucleophile	**Y:**$^-$ + $RCH_2C(=O)R' \longrightarrow RCH_2C(O^-)(\mathbf{Y})R'$
Enolate formation	**Y:**$^-$ acts as a base	**Y:**$^-$ + $RCH_2C(=O)R' \longrightarrow RCH{=}C(O^-)R' + H{-}\mathbf{Y}$

Table 4.4. Hardness and Softness of Some Common Ions and Molecules

	Bases (Nucleophiles)	Acids (Electrophiles)
Soft	RSH, RS^-, I^-, R_3P	I_2, Br_2, RS—X, RSe—X, RCH_2—X
	$^-C{\equiv}N$, $^-{:}C{\equiv}O^+$, RCH=CHR	Cu(I), Ag(I), Pd(II), Pt(II), Hg(II)
	benzene	zero-valent metal complexes
Intermediate	Br^-, N_3^-, $ArNH_2$	Cu(II), Zn (II), Sn,(II)
	pyridine	R_3C^+, R_3B
Hard	NH_3, RNH_2	H—X, Li^+, Na^+, R_3Si—X
	H_2O, HO^-, ROH, RO^-, RCO_2^-, Cl^-	Mg(II), Ca(II), Al(III), Sn(IV), Ti(IV)
	F^-, NO_3^-	H^+

- Winstein-Grunwald

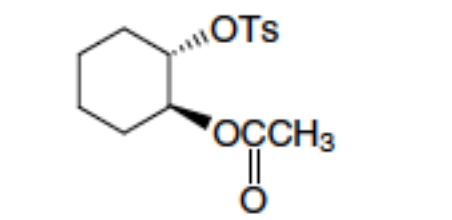
$$\text{Log}(k/k_0) = lN + mY$$

Table 4.5. Solvent Nucleophilicity and Ionization Parameters[a]

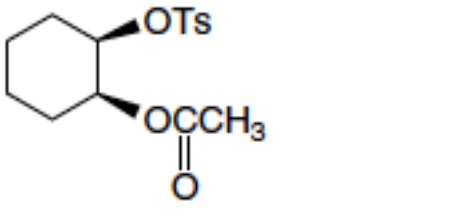
Solvent	*t*-Butyl chloride		2-Adamantyl tosylate	
	N	Y	N_{Tos}	Y_{Tos}
Ethanol	+0.09	−2.03	0.00	−1.75
Methanol	+0.01	−1.09	−0.04	−0.92
50% Aqueousethanol	−0.20	1.66	−0.09	1.29
Water	−0.26	3.49		
Acetic acid	−2.05	−1.64	−2.35	−0.61
Formic acid	−2.05	2.05	−2.35	3.04
Trifluoroethanol	−2.78	1.05	−3.0	1.80
97% $(CF_3)_2CHOH$-H_2O	−3.93	2.46	−4.27	3.61
Trifluoroacetic acid	−4.74	1.84	−5.56	4.57

a. From F. L. Schadt, T. W. Bentley, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **98**, 7667 (1976).

Ajuda Anquimérica



$k = 1.9 \times 10^{-4}\, s^{-1}$ (100° C)



$k = 2.9 \times 10^{-7}\, s^{-1}$ (100° C)

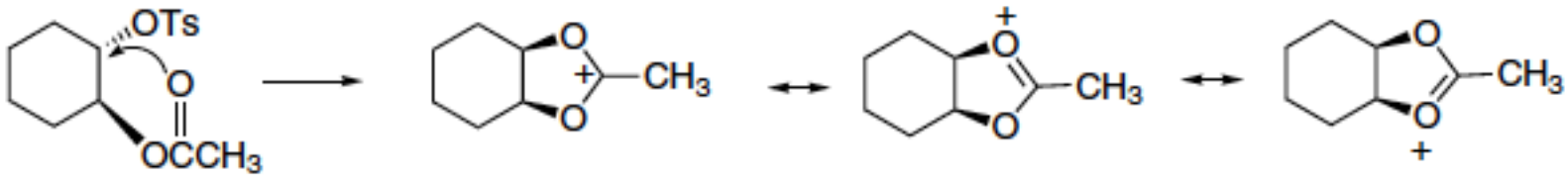


Table 4.11. Solvolysis Rates of ω-Chloro Alcohols[a]

ω-Chloro alcohol	Approximate relative rate
$Cl(CH_2)_2OH$	2000
$Cl(CH_2)_3OH$	1
$Cl(CH_2)_4OH$	5700
$Cl(CH_2)_5OH$	20

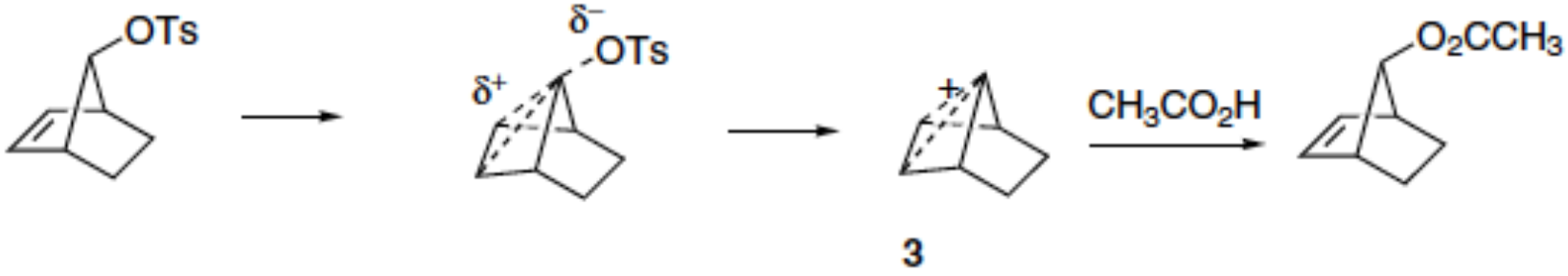
a. B. Capon, *Q. Rev. Chem. Soc.*, **18**, 45 (1964); W. H. Richardson, C. M. Golino, R. H. Wachs, and M. B. Yelvington, *J. Org. Chem.*, **36**, 943 (1971).

Table 4.13. Relative Rates of Cyclization as a Function of Ring Size

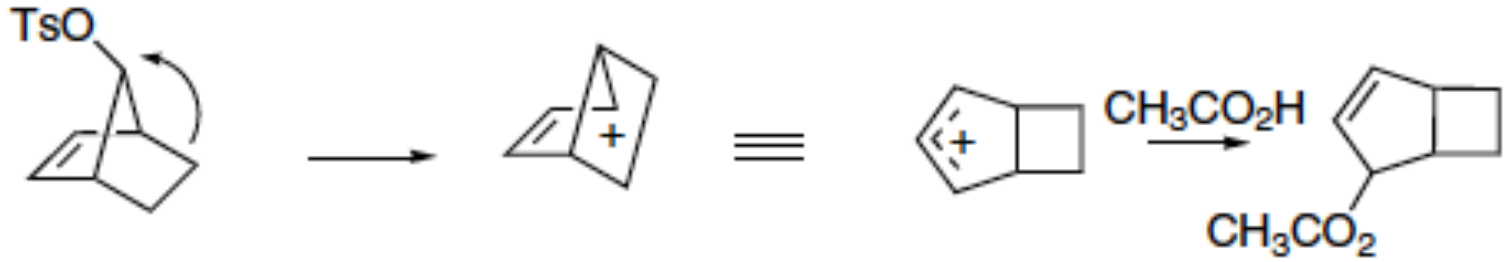
Ring size	Lactonization of ω-bromo carboxylates[a]	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)	Cyclization of ω-bromoalkylmalonates[b]
3	8.2×10^{-4}	22.0	−2.5	
4	0.92	17.7	−5.0	0.58
5	108	15.9	−5.5	833
6	1.00	17.2	−4.1	1.00
7	3.7×10^{-3}	17.4	−13.5	8.7×10^{-3}
8	3.8×10^{-5}	21.7	−9.2	1.5×10^{-4}
9	4.3×10^{-5}	20.3	−14.0	1.7×10^{-5}
10	1.3×10^{-4}	17.3	−20.7	1.4×10^{-6}
11	3.3×10^{-4}	16.4	−22.3	2.9×10^{-6}
12	4.1×10^{-4}	17.6	−18.0	4.0×10^{-4}
13	1.2×10^{-3}	15.3	−23.0	7.4×10^{-4}
17				2.9×10^{-3}
18	2.0×10^{-3}	15.2	−21.8	
21				4.3×10^{-3}
23	2.3×10^{-3}	14.5	−22.3	

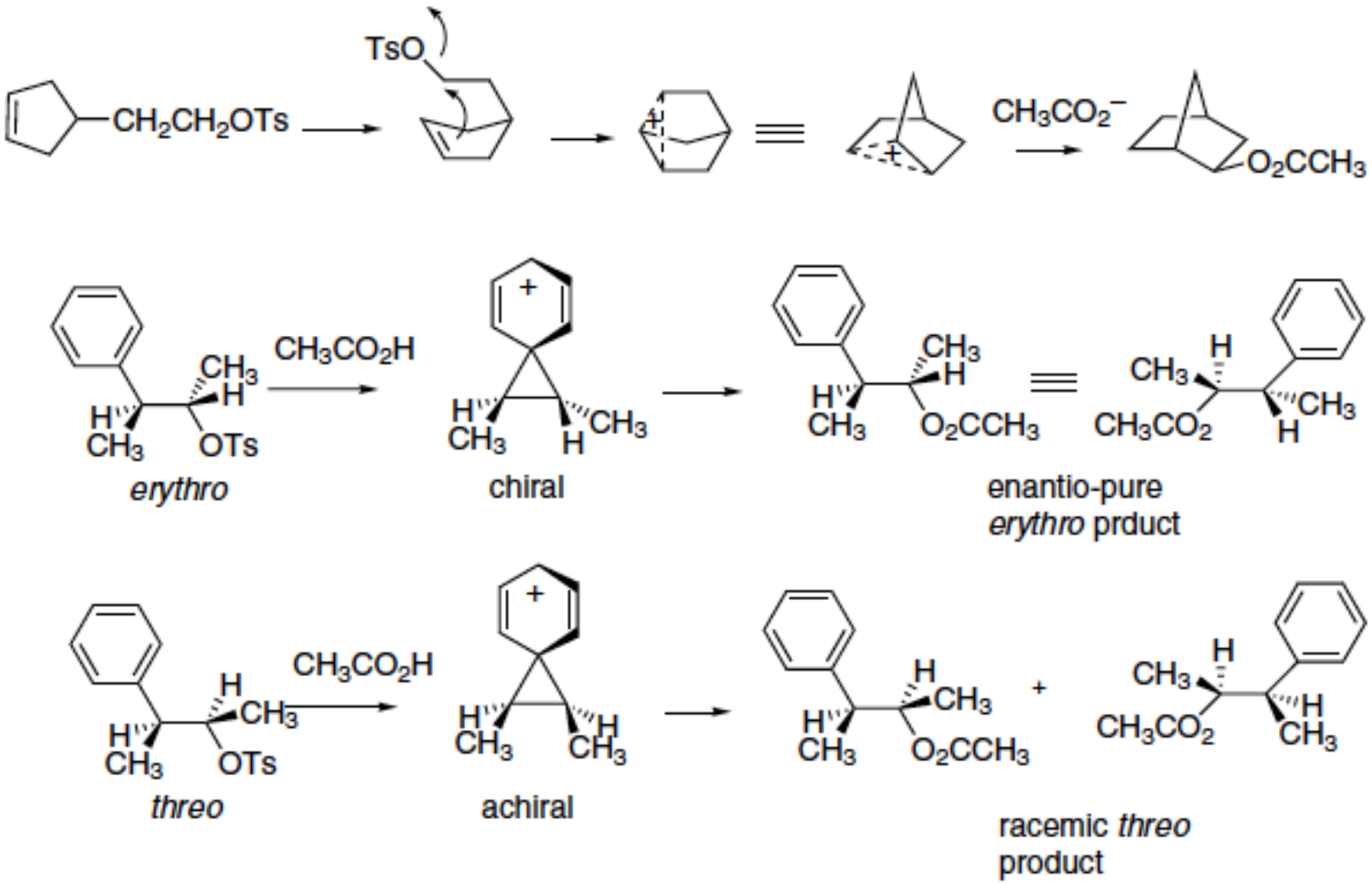
a. C. Galli, G. Illuminati, L. Mandolini, and P. Tamborra, *J. Am. Chem. Soc.***99**, 2591 (1977); L. Mandolini, *J. Am. Chem. Soc.*, **100**, 550 (1978).
b. M. A. Casadei, C. Galli, and L. Mandolini, *J. Am. Chem. Soc.*, **106**, 1051 (1984).

Solvólise da 7-tosilnorbornenila *anti* é 10^7 vezes mais rápido do que o *syn*



3




TsO
CH2CH2OTs
CH3CO2−
O2CCH3
CH3CO2H
erythro
chiral
enantio-pure
erythro prduct
threo
achiral
racemic threo
product

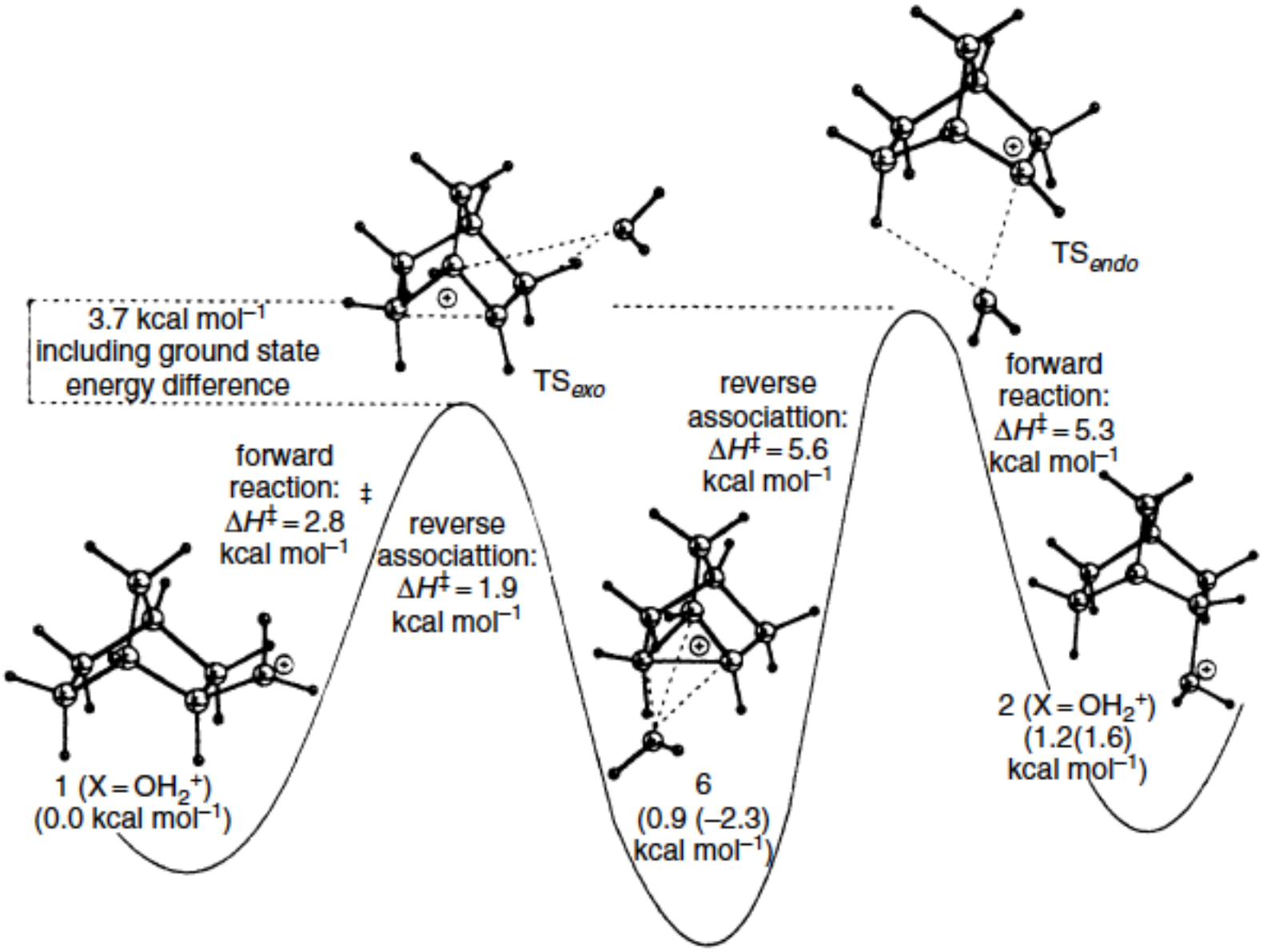


Fig. 4.14. Computational energy diagram (B3LYP)/6-311+G*) for intermediates and transition states in ionization and rearrangement of protonated 2-norbornanol. Reproduced from *J. Org. Chem.*, **62**, 4216 (1997), by permission of the American Chemical Society.