Nucleophilic reactions I:

Overview

Nucleophiles & nucleophilic substitution

- **Nucleophiles: species that like nucleus**
  - Can donate a pair of electrons to form a new covalent bond
  - Electron-rich (e.g., negatively charged ions)
  - Large abundance of nucleophiles in the environment (water itself is a nucleophile)

- **Nucleophilic substitution**
  - Nucleophiles may form a bond with the electron-deficient atom in an organic molecule
  - As a consequence of a new bond formation, another bond has to be broken

$$Nu\!: + R - L \;\; \Rightarrow \;\; R - Nu + L\!:$$

  - S_N2 & S_N1 mechanisms

Nucleophiles & hydrolysis

- **Important nucleophiles in the environment**
  - High abundance of water (and OH^- for high pH)
  - Water is usually the most significant among the environmental nucleophiles

- **Hydrolysis**
  - A reaction in which a water molecule (or OH^- ion) substitutes for another atom or group of atoms present in an organic molecule

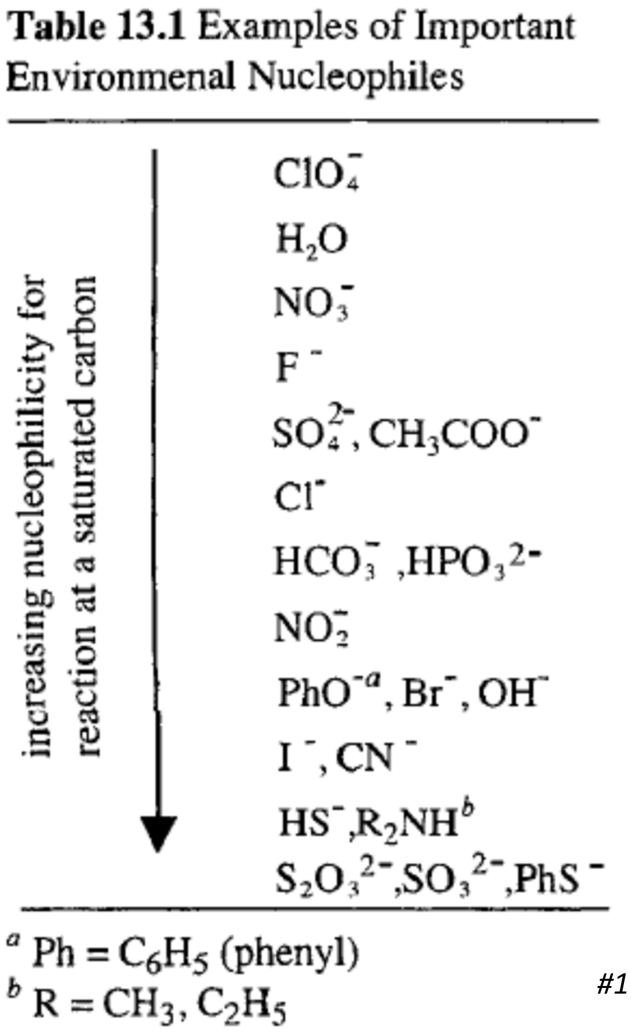

Table 13.1 Examples of Important Environmenal Nucleophiles

increasing nucleophilicity for reaction at a saturated carbon

ClO_4^-
H_2O
NO_3^-
F^-
SO_4^{2-}, CH_3COO^-
Cl^-
HCO_3^-, HPO_3^{2-}
NO_2^-
PhO^{-a}, Br^-, OH^-
I^-, CN^-
HS^-, R_2NH^b
$S_2O_3^{2-}$, SO_3^{2-}, PhS^-

[a] Ph = C_6H_5 (phenyl)
[b] R = CH_3, C_2H_5

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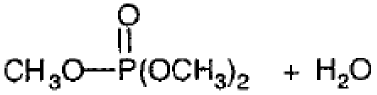
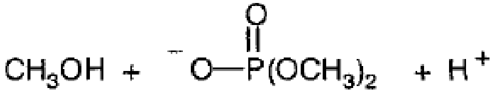
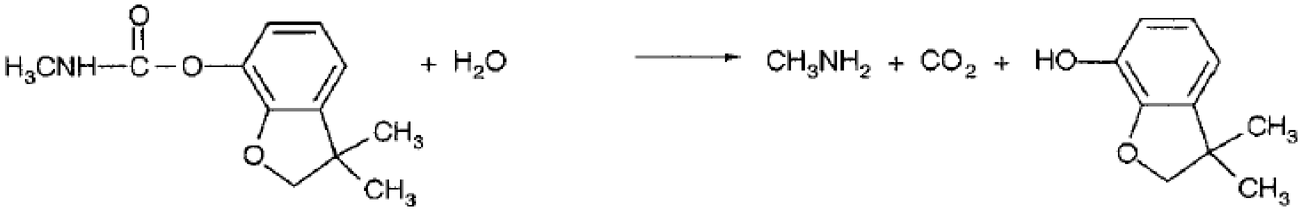
Table 13.2 Examples of Environmentally Relevant Chemical Reactions Involving Nucleophiles and/or Bases

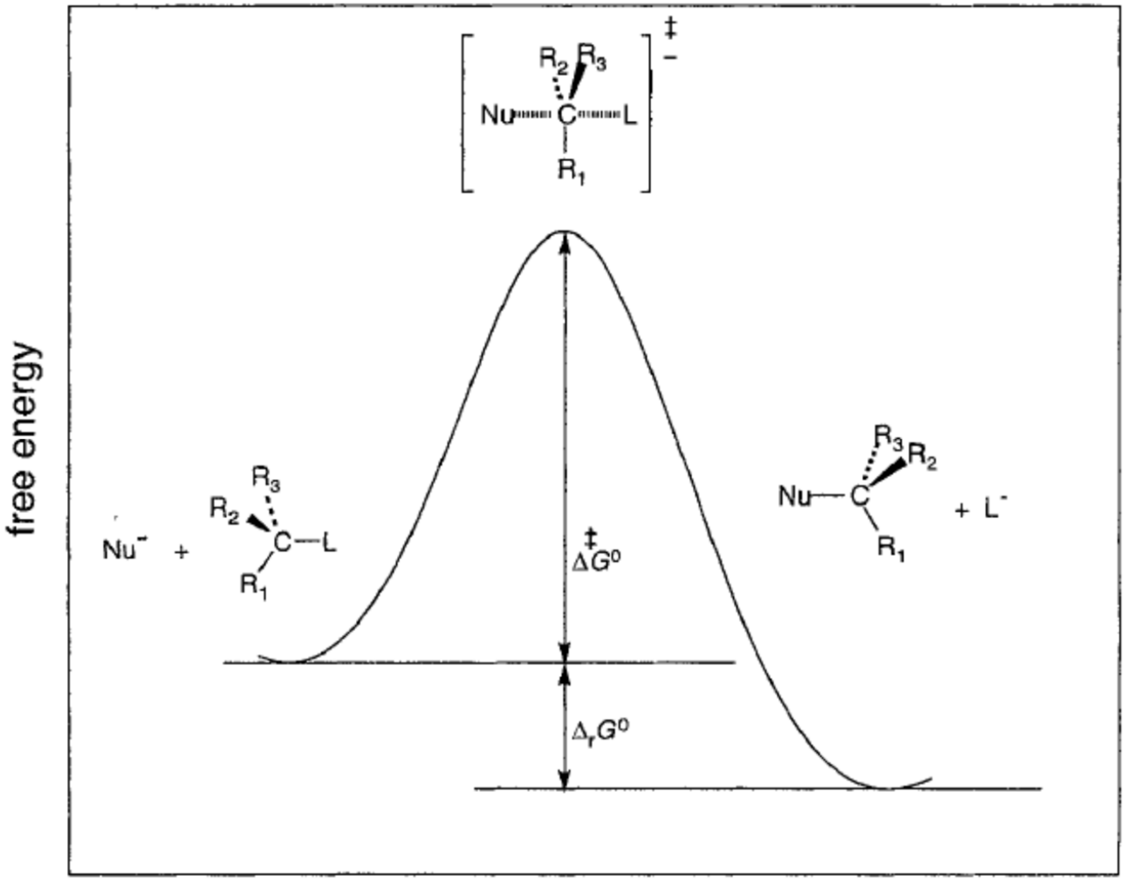
Reactants		Products	Reaction Number
		Nucleophilic Substitutions at Saturated Carbon Atoms	
$CH_3Br + H_2O$ Methyl bromide	$\longrightarrow$	$CH_3OH + H^+ + Br^-$ Methanol	(1)
$CH_3Cl + HS^-$ Methyl chloride	$\longrightarrow$	$CH_3SH + Cl^-$ Methane thiol (Methyl mercaptan)	(2)
 $CH_3O{-}\overset{\overset{\displaystyle O}{\|}}{P}(OCH_3)_2 + H_2O$ Trimethylphosphate	$\longrightarrow$	 $CH_3OH + {}^-O{-}\overset{\overset{\displaystyle O}{\|}}{P}(OCH_3)_2 + H^+$ Methanol Dimethylphosphate	(3)
		β-Elimination	
$Cl_2HC{-}CHCl_2 + HO^-$ 1,1,2,2-Tetrachloroethane	$\longrightarrow$	$Cl_2C{=}CHCl + Cl^- + H_2O$ Trichloroethene	(4)

Reactants	Products	Reaction Number
Ester Hydrolysis		
 $H_3C-\overset{O}{\overset{\|\|}{C}}-OCH_2CH_3 + H_2O \longrightarrow H_3C-\overset{O}{\overset{\|\|}{C}}-O^- + HO-CH_2CH_3 + H^+$ Ethyl acetate (Acetic acid ethylester)	Acetate Ethanol	(5)
 Parathion	O,O-Diethyl-thiophosphoric acid 4-Nitrophenol	(6)
Carbamate Hydrolysis		
 Carbofuran	Methylamine 2,3-Dihydro-3,3-dimethyl-7-benzofuranol	(7)

#2

Nucleophilic substitution at saturated carbon atoms

- **S_N2 mechanism**



#3

Nucleophilic substitution at saturated carbon atoms

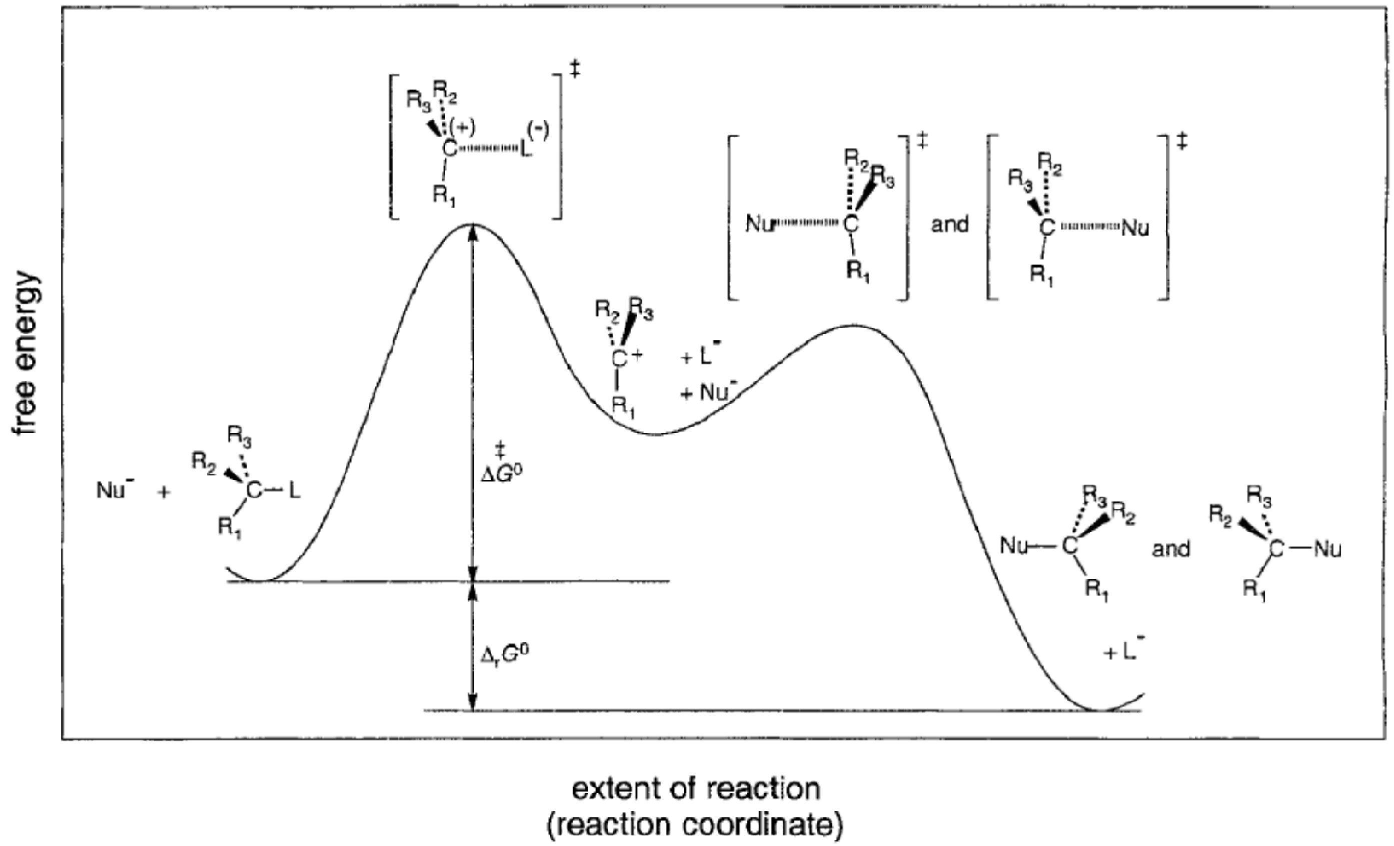
- **S_N2 mechanism**
  - Substitution, nucleophilic, bimolecular
  - The standard free energy of activation $\Delta^{\ddagger}G^0$ (which controls the reaction rate) depends strongly on both <u>the capability of the nucleophile to initiate a substitution reaction</u> and <u>the willingness of the organic molecule to undergo that reaction</u>
  - Follows a second-order kinetic rate law:

$$\frac{d[R_1R_2R_3C-L]}{dt} = -k[Nu^-][R_1R_2R_3C-L]$$

k = 2nd order rate constant (L/mole-s)

Nucleophilic substitution at saturated carbon atoms

- **S_N1 mechanism**



#4

Nucleophilic substitution at saturated carbon atoms

- **S_N1 mechanism**
  - Substitution, nucleophilic, unimolecular
  - The reaction rate depends solely on how easily the leaving group dissociates from the parent molecule
  - The structure of the activated complex is assumed to be similar to the carbon-cation complex
  - $\Delta^{\ddagger}G^0$ depends on the stability of the cation
  - Follows a first-order kinetic rate law:

$$\frac{d[R_1R_2R_3C-L]}{dt} = -k[R_1R_2R_3C-L]$$

k = 1st order rate constant (s^{-1})

References

#1-#4) Schwarzenbach, R., Gschwend, P. M., Imboden, D. M. (2003) Environmental Organic Chemistry, 2nd ed., John Wiley & Sons, p. 491; p. 492; p. 495; p. 496.

Nucleophilic reactions II:

Kinetics

S_N2: Relative nucleophilicity

- **Study of nucleophilic substitution of methyl halides for various nucleophiles:**
  - Methyl halides (CH_3X) have similar relative reactivity toward different nucleophiles
  - Swain & Scott (1953):

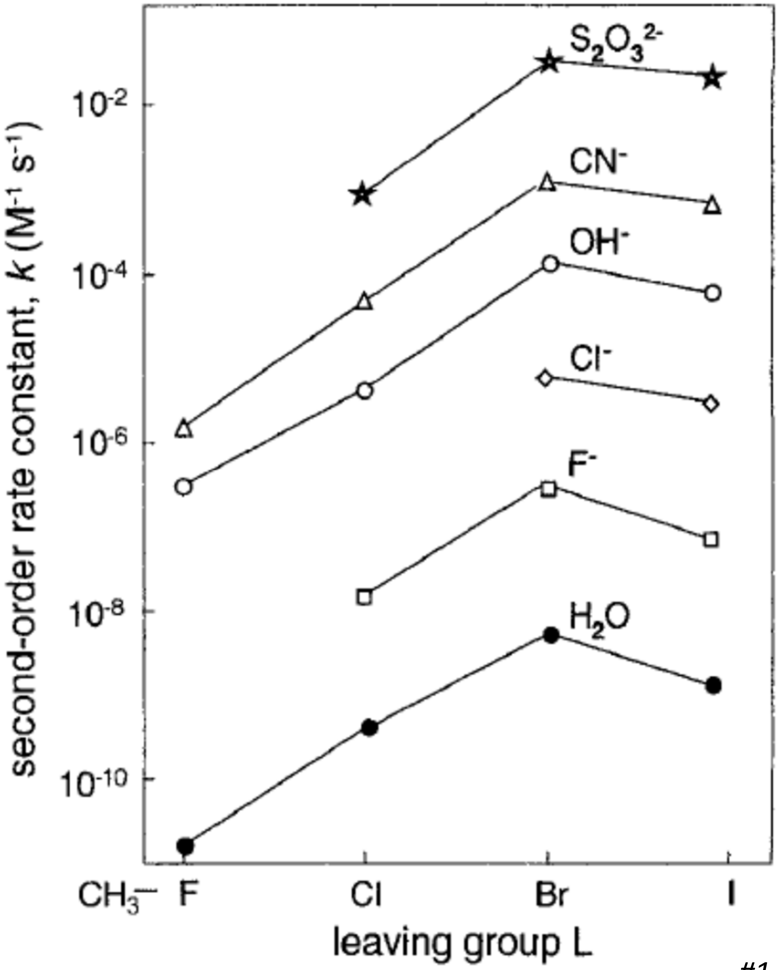
$$log\left(\frac{k_{Nu}}{k_{H_2O}}\right) = s \cdot n_{Nu,CH_3Br}$$

k_{Nu} = 2nd-order rate const. for a nucleophile of interest

k_{H_2O} = 2nd order rate const. for H_2O

n_{Nu,CH_3Br} = a measure of the nucleophilicity of the nucleophile of interest

s = sensitivity of the organic molecule to nucleophilic attack



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n_{Nu,CH_3Br}---?

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- Set CH_3Br as a reference compound to measure the nucleophilicity
- Set H_2O as a reference nucleophile
- By observing a nucleophilic substitution reaction between CH_3Br and Nu, n_{Nu,CH_3Br} can be determined:

$$n_{Nu,CH_3Br} = log\left[\frac{(k_{Nu})_{CH_3Br}}{(k_{H_2O})_{CH_3Br}}\right]$$

** so, n_{H_2O,CH_3Br} = 0*

- We saw:

$$log\left(\frac{k_{Nu}}{k_{H_2O}}\right) \approx log\left[\frac{(k_{Nu})_{CH_3Br}}{(k_{H_2O})_{CH_3Br}}\right] = n_{Nu,CH_3Br}$$

- But there is some error, so use "*s*" for modification

** **s** is not substantially different from 1*

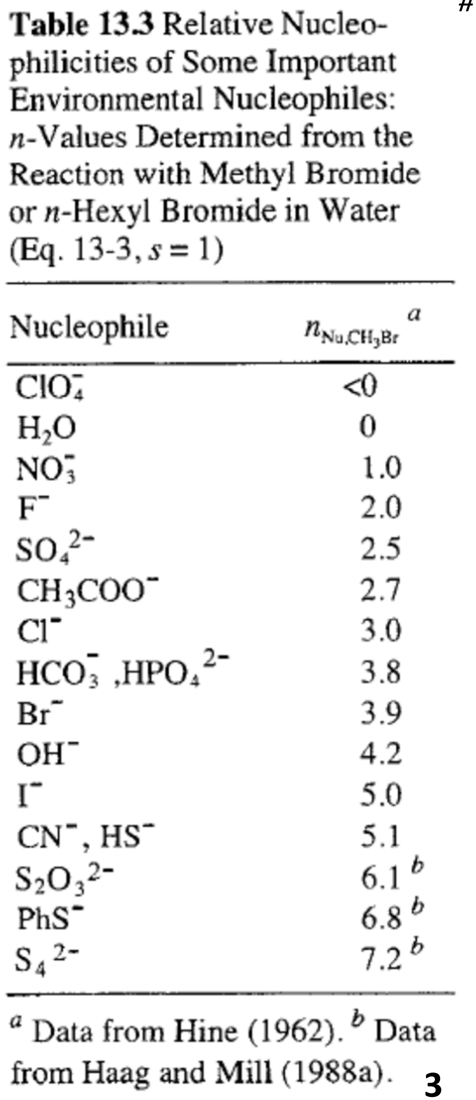

Table 13.3 Relative Nucleophilicities of Some Important Environmental Nucleophiles: *n*-Values Determined from the Reaction with Methyl Bromide or *n*-Hexyl Bromide in Water (Eq. 13-3, *s* = 1)

Nucleophile	n_{Nu,CH_3Br} [a]
ClO_4^-	<0
H_2O	0
NO_3^-	1.0
F^-	2.0
SO_4^{2-}	2.5
CH_3COO^-	2.7
Cl^-	3.0
HCO_3^-, HPO_4^{2-}	3.8
Br^-	3.9
OH^-	4.2
I^-	5.0
CN^-, HS^-	5.1
$S_2O_3^{2-}$	6.1 [b]
PhS^-	6.8 [b]
S_4^{2-}	7.2 [b]

[a] Data from Hine (1962). [b] Data from Haag and Mill (1988a).

S_N2: Competition of nucleophiles

- **Competition with hydrolysis:**
  - Reaction rate of Nu depends on *k* & [Nu]

$$\frac{d[R_1R_2R_3C-L]}{dt} = -k[Nu][R_1R_2R_3C-L]$$

  - H_2O is abundant ($[H_2O]\uparrow$), so a nucleophile should compete with hydrolysis
  - Define $[\mathrm{Nu}]_{50\%}$ as the nucleophile concentration that satisfies:

$$[Nu]_{50\%}k_{Nu} = [H_2O]k_{H_2O}$$

1st order rate of Nu reaction *1st order rate of hydrolysis*

assuming s=1, $k_{Nu} = k_{H_2O} \times 10^{n_{Nu,CH_3Br}}$

$$\Rightarrow \quad [Nu]_{50\%} = 55.3 \times 10^{-n_{Nu,CH_3Br}}$$

55.3 = molar concentration of water (M) @ 25 °C

S_N2: Determining significance

- **Use $[Nu]_{50\%}$ to determine whether a nucleophile is significant**

- **Freshwater vs. saline water**
    - Freshwater $[Cl^-] \sim 10^{-4}$ M → Cl^- not a significant nucleophile
    - Seawater $[Cl^-] \sim 0.5$ M → Cl^- a significant nucleophile

- **pH sensitivity of hydrolysis reaction**
    - Low & neutral pH → OH^- not a significant nucleophile
    - High pH (e.g., pH>11) → OH^- a significant nucleophile

#2

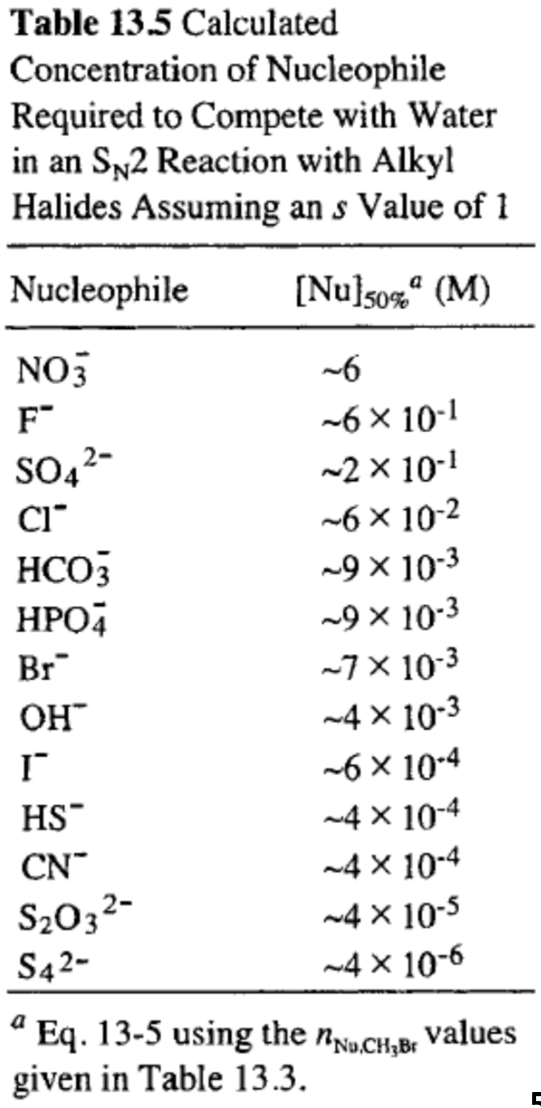

Table 13.5 Calculated Concentration of Nucleophile Required to Compete with Water in an S_N2 Reaction with Alkyl Halides Assuming an *s* Value of 1

Nucleophile	$[Nu]_{50\%}{}^a$ (M)
NO_3^-	~6
F^-	$\sim 6 \times 10^{-1}$
SO_4^{2-}	$\sim 2 \times 10^{-1}$
Cl^-	$\sim 6 \times 10^{-2}$
HCO_3^-	$\sim 9 \times 10^{-3}$
HPO_4^-	$\sim 9 \times 10^{-3}$
Br^-	$\sim 7 \times 10^{-3}$
OH^-	$\sim 4 \times 10^{-3}$
I^-	$\sim 6 \times 10^{-4}$
HS^-	$\sim 4 \times 10^{-4}$
CN^-	$\sim 4 \times 10^{-4}$
$S_2O_3^{2-}$	$\sim 4 \times 10^{-5}$
S_4^{2-}	$\sim 4 \times 10^{-6}$

[a] Eq. 13-5 using the n_{Nu,CH_3Br} values given in Table 13.3.

S_N1 & S_N2: Leaving groups

- Reaction rates for methyl halides: $CH_3Br \sim CH_3I > CH_3Cl > CH_3F$

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- **What makes one a good leaving group??**

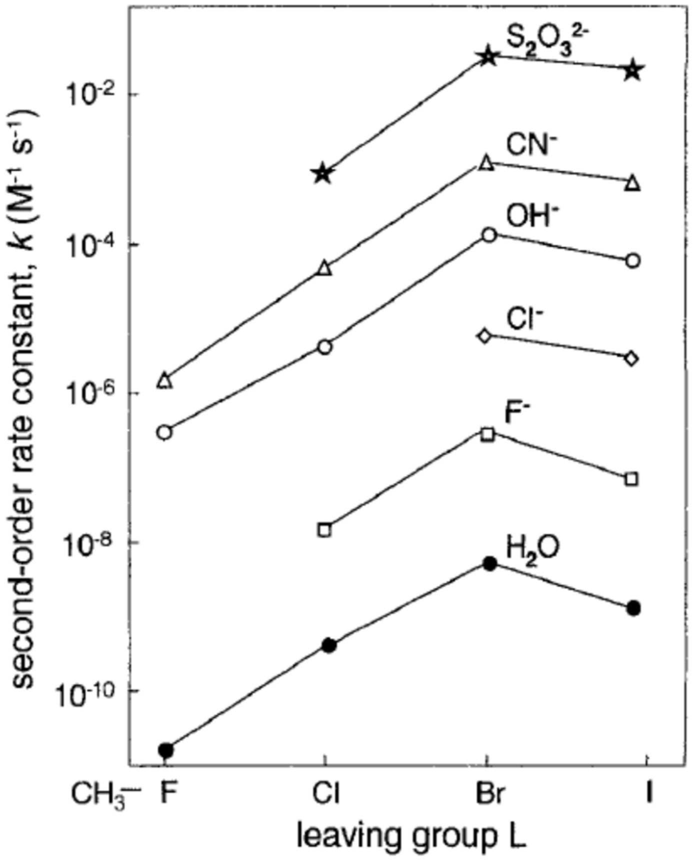
1) The one with smaller n_{Nu,CH_3Br} (a weaker nucleophile)

but n_{Nu,CH_3Br} is in the order of:
$F^- < Cl^- < Br^- < I^-$

2) The one bound weakly to carbon

C-X bond strength is in the order of:
$CH_3I < CH_3Br < CH_3Cl < CH_3F$

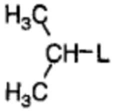
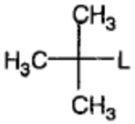
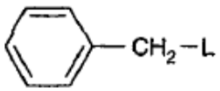
More significant!



S_N1 & S_N2: Effect of EDGs & resonance

#3

Table 13.6 Hydrolysis Half-Lives and Postulated Reaction Mechanisms at 25°C of Some Monohalogenated Hydrocarbons at Neutral pH [a]

Compound	Type of Carbon to Which L is Attached	$t_{1/2}$(Hydrolysis)				Dominant Mechanism(s) in Nucleophilic Substitution Reactions
		L = F	Cl	Br	I	
$R-CH_2-L$	primary	≈30 yr [b]	340 d [b]	20–40 d [c]	50–110 d [d]	S_N2
	secondary		38 d	2 d	3 d	S_N2… S_N1
	tertiary	50 d	23 s			S_N1
$CH_2=CH-CH_2-L$	allyl		69 d	0.5 d	2 d	S_N2… S_N1
	benzyl		15 h	0.4 h		S_N2… S_N1

[a] Data taken from Robertson (1969) and Mabey and Mill (1978). [b] R = H. [c] R = H, C_1 to C_5-*n*-alkyl. [d] R = H, CH_3.

References

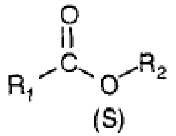
#1-#3) Schwarzenbach, R., Gschwend, P. M., Imboden, D. M. (2003) Environmental Organic Chemistry, 2nd ed., John Wiley & Sons, p. 498; p. 501; p. 505

Nucleophilic reactions III:

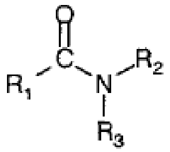
Hydrolysis of esters, etc.

Hydrolysis of carboxylic & carbonic acid derivatives

- Carboxylic acid derivatives

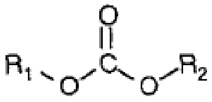


ester (thioester)

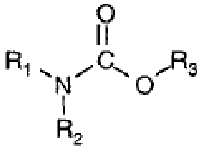


amide

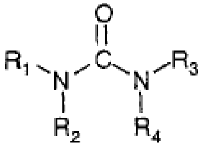
- Carbonic acid derivatives



carbonate

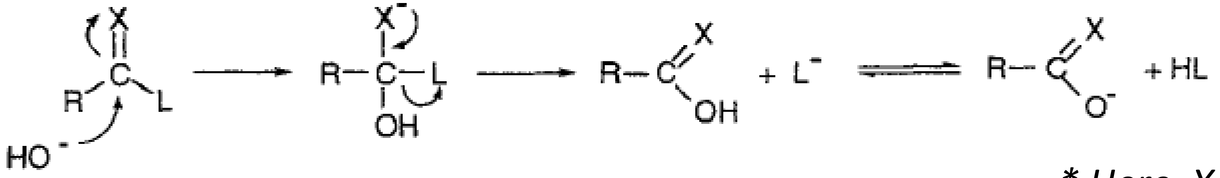


carbamate



urea

- **Unsaturated, electron-deficient C**
- **Reacts predominantly with H_2O & OH^- (hydrolysis)**
- **General reaction mechanism**



** Here, X = O, S, or NR*

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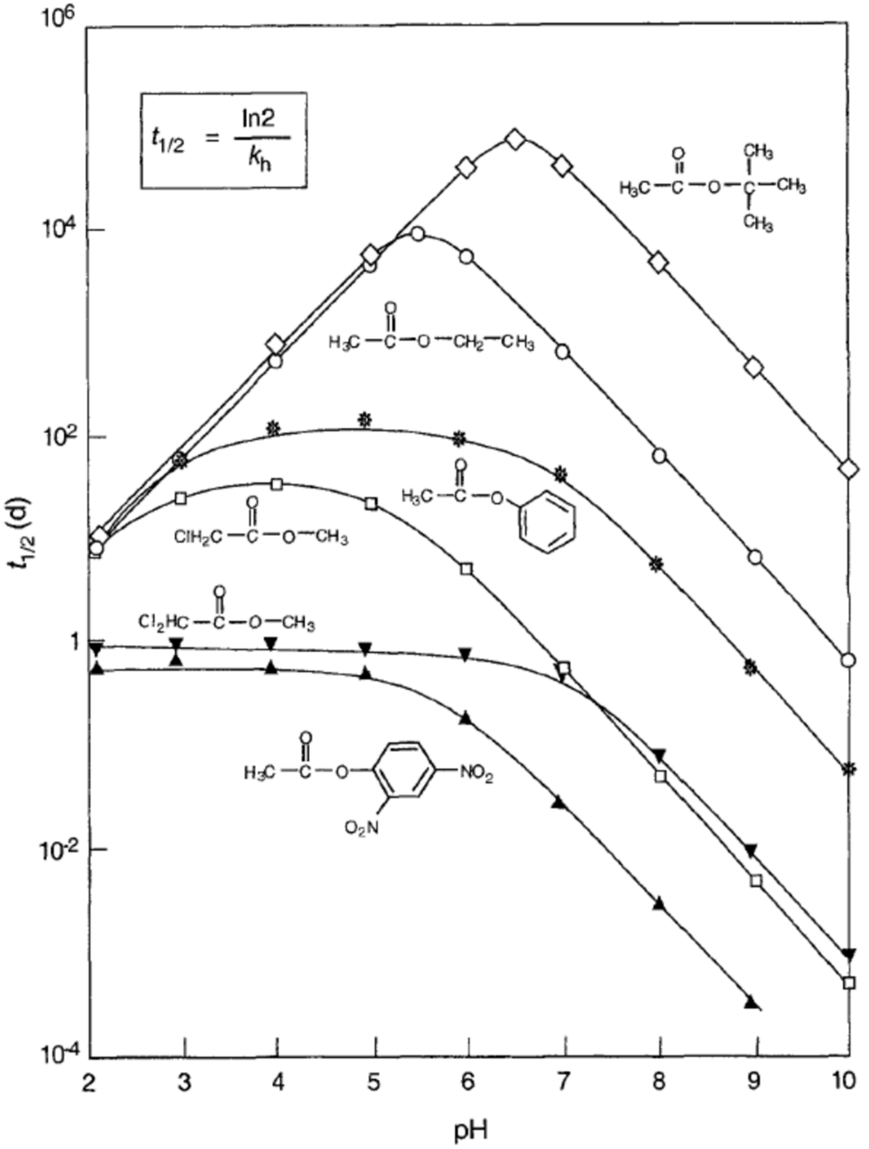
Hydrolysis of Esters

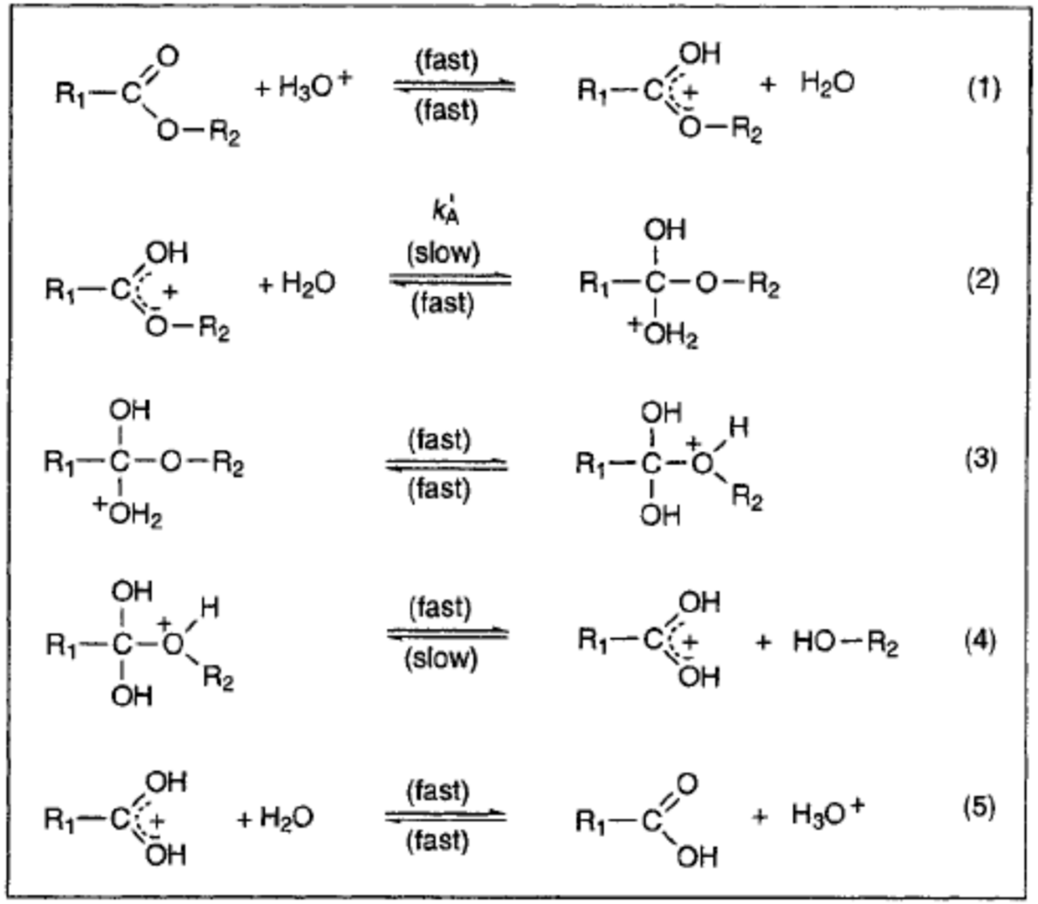
- Three mechanisms:
  1) acid-catalyzed
  2) neutral
  3) base-catalyzed

- Importance of each reaction depends on the structure of the reactant



Ester hydrolysis: acid-catalyzed

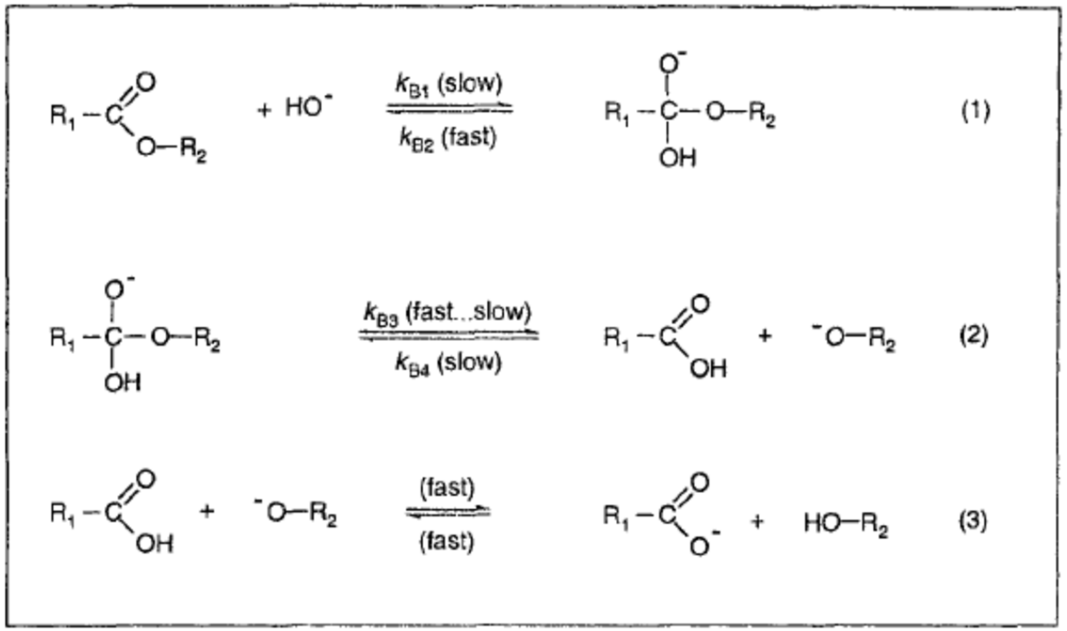
- Ester carbon is protonated → enhanced depletion of electrons near the carbon → ester carbon gets more susceptible to H_2O attack
- Reaction (2) is rate limiting
- Reaction rate depends on:
  - **k_A'**
  - **K_a of the protonated ester**
  - **[H^+]**



#3

Ester hydrolysis: base-catalyzed

- (1) only or both (1) & (2) can be rate-limiting



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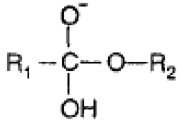
- Rate depends on **[OH$^-$]** and in addition:

  If only (1) is rate-limiting:

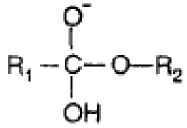
  – Depends on the formation of



$R_1-\overset{O^-}{\underset{OH}{C}}-O-R_2$

  If both (1) & (2) are rate-limiting:

  – Depends on the formation of

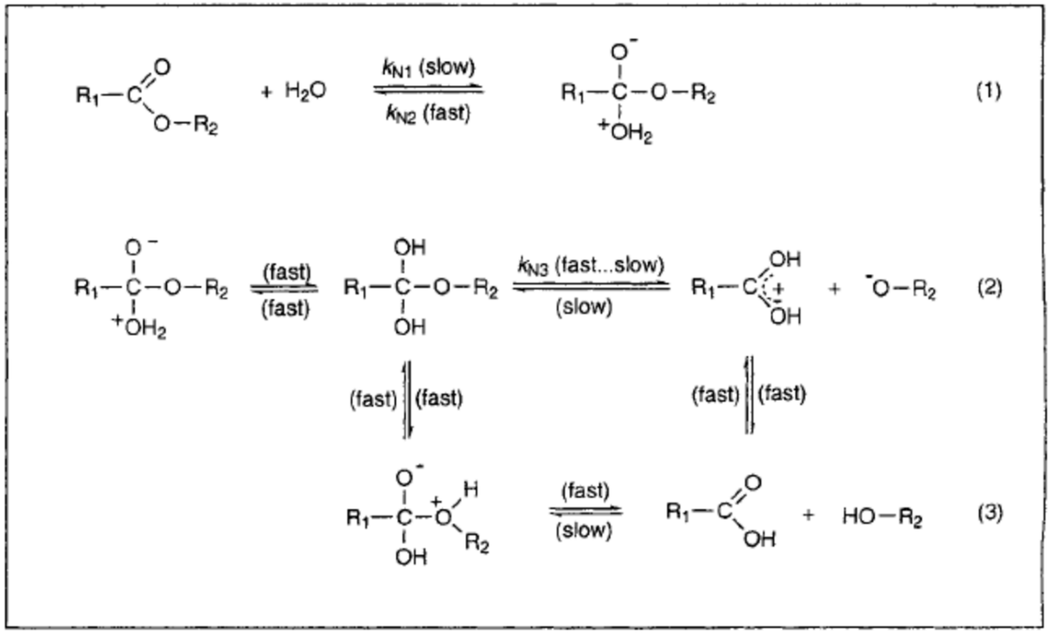


$R_1-\overset{O^-}{\underset{OH}{C}}-O-R_2$

& the property of the leaving group

Ester hydrolysis: neutral

- Similar to base-catalyzed
- The property of the leaving group is more important for H_2O (weaker nucleophile) than OH^-



#5

Ester hydrolysis kinetics

- ***k_h*: pseudo-first-order hydrolysis rate constant (s^{-1}), f(pH)**

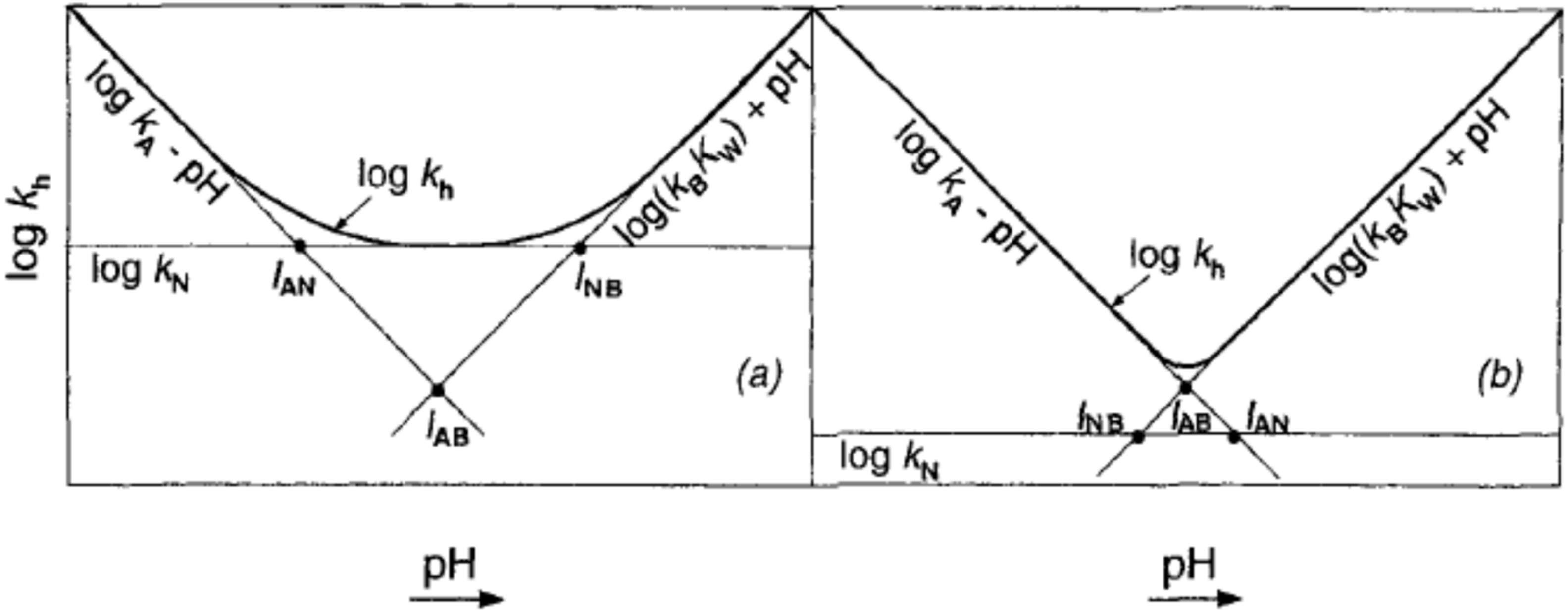
$$k_h = k_A[H^+] + k_{H_2O}[H_2O] + k_B[OH^-]$$

$$= k_A[H^+] + k_N + k_B[OH^-]$$

- **Hydrolysis half-life** *(at certain pH)*

$$t_{1/2\ (hydroysis)} = \frac{ln\ 2}{k_h}$$

Ester hydrolysis: *I* values



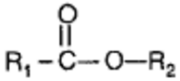
#6

I_{IJ} = the pH value at which the rates for I and J reactions are the same

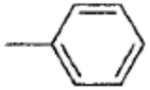
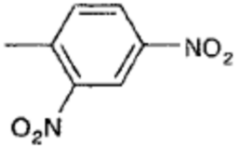
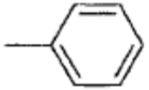
I, J: A (acid-catalyzed); N (neutral); B (base-catalyzed)

Table 13.8 Rate Constants k_A, k_N, and k_B, Half-Lives at pH 7, and I Values for Hydrolysis of Some Carboxylic Acid Esters at 25°C [a]

Compound



$R_1-C(=O)-O-R_2$

R_1	R_2	k_A ($M^{-1}\,s^{-1}$)	k_N (s^{-1})	k_B ($M^{-1}\,s^{-1}$)	$t_{1/2}$ (pH 7)	I_{AN} [b,c,e]	I_{AB} [c,e]	I_{NB} [d,e]
CH_3-	$-CH_2CH_3$	1.1×10^{-4}	1.5×10^{-10}	1.1×10^{-1}	2 yr	(5.9)	5.5	(5.1)
CH_3-	$-C(CH_3)_3$	1.3×10^{-4}		1.5×10^{-3}	140 yr		6.5	
H–	$-C(CH_3)_3$	2.7×10^{-3}	1.0×10^{-6}	1.7×10^{0}	7 d	2.6	5.6	7.8
CH_3-	$-CH=CH_2$	1.4×10^{-4}	1.1×10^{-7}	1.0×10^{1}	7 d	3.1	(4.6)	6.0
CH_3-		7.8×10^{-5}	6.6×10^{-8}	1.4×10^{0}	38 d	3.1	(4.8)	6.7
CH_3-			1.1×10^{-5}	9.4×10^{1}	10 h			7.1
CH_2Cl-	$-CH_3$	8.5×10^{-5}	2.1×10^{-7}	1.4×10^{2}	14 h	2.6	(3.9)	5.2
$CHCl_2-$	$-CH_3$	2.3×10^{-4}	1.5×10^{-5}	2.8×10^{3}	40 min	1.2	(3.5)	5.7
$CHCl_2-$			1.8×10^{-3}	1.3×10^{4}	4 min			7.1

[a] Data from Mabey and Mill (1978) except for *tert*-butyl formate ($R_1 = H$, $R_2 = C(CH_3)_3$; Church et al., 1999). [b] $I_{AN} = \log (k_A/k_N)$. [c] $I_{AB} = 1/2 \log (k_A/k_B K_w)$. [d] $I_{NB} = \log (k_N/k_B K_w)$. [e] Parentheses indicate that one or both of the processes is too slow to contribute significantly to the overall rate.

References

#1-#7) Schwarzenbach, R., Gschwend, P. M., Imboden, D. M. (2003) Environmental Organic Chemistry, 2nd ed., John Wiley & Sons, p. 513; p. 514; p. 521; p. 523; p. 524; p. 515; p. 520.

Nucleophilic reactions:
Exercise

S_N2: Relative nucleophilicity

Q: Estimate the half-life (in days) of CH_3Br present at low concentration (i.e., < 0.01mM) in a homogeneous aqueous solution (pH=7.0, T=25°C) containing 100 mM Cl^-, 2 mM NO_3^-, 1 mM HCO_3^-, and 0.1 mM CN^-. In pure water at pH 7.0 and 25°C, the half-life of CH_3Br is about 20 days.

S_N2: Relative nucleophilicity

Nucleophile concentrations are all in excess compared to CH_3Br concentration

➡ *The nucleophilic substitution reaction can be assumed to be in pseudo-1st order*

$$r = -\frac{d[CH_3Br]}{dt} = \left\{\sum_j k_{Nu_j}[Nu_j]\right\} \cdot [CH_3Br]$$

recall "reactions in parallel"

$$= k_{obs} \cdot [CH_3Br]$$

k_{obs} = pseudo-1st order rate constant by reaction of CH_3Br will all nucleophiles

For a nucleophile with a concentration much lower than $[Nu]_{50\%}$, we can neglect its contribution (it should contribute much less than H_2O)

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$[Cl^-] = 0.1$; $[NO_3^-] = 2 \times 10^{-3}$; $[HCO_3^-] = 10^{-3}$;
$[CN^-] = 10^{-4}$; $[OH^-] = 10^{-7}$ (units in M)

➡ *NO_3^- & OH^- can be neglected.*

$$log\left(\frac{k_{Nu}}{k_{H_2O}}\right) = s \cdot n_{Nu,CH_3Br} = n_{Nu,CH_3Br}$$

s=1 for CH_3Br

➡ $$k_{Nu} = 10^{n_{Nu,CH_3Br}} \cdot k_{H_2O}$$

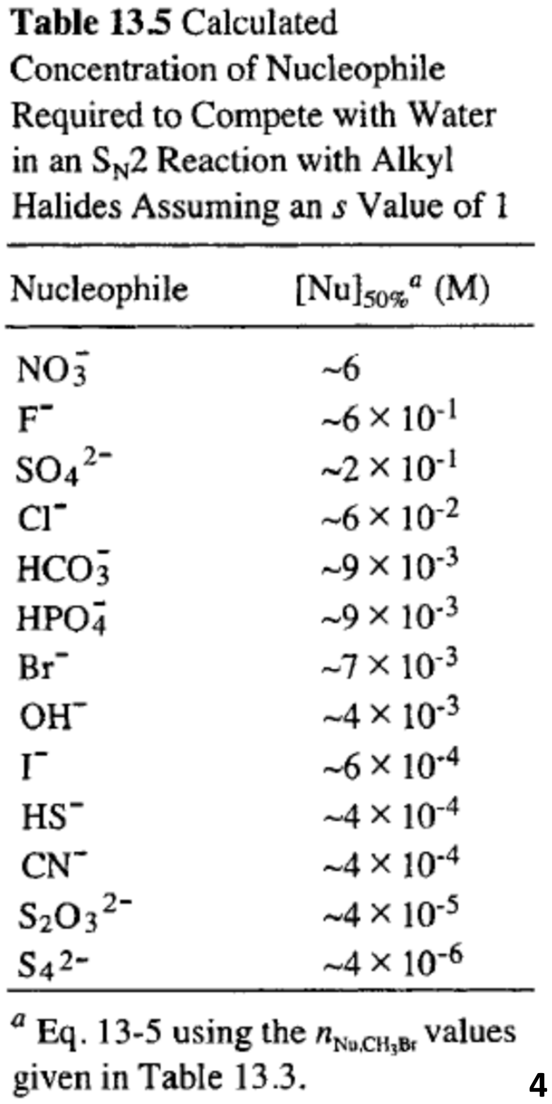

Table 13.5 Calculated Concentration of Nucleophile Required to Compete with Water in an S_N2 Reaction with Alkyl Halides Assuming an *s* Value of 1

Nucleophile	$[Nu]_{50\%}$[a] (M)
NO_3^-	~6
F^-	$\sim 6 \times 10^{-1}$
SO_4^{2-}	$\sim 2 \times 10^{-1}$
Cl^-	$\sim 6 \times 10^{-2}$
HCO_3^-	$\sim 9 \times 10^{-3}$
HPO_4^-	$\sim 9 \times 10^{-3}$
Br^-	$\sim 7 \times 10^{-3}$
OH^-	$\sim 4 \times 10^{-3}$
I^-	$\sim 6 \times 10^{-4}$
HS^-	$\sim 4 \times 10^{-4}$
CN^-	$\sim 4 \times 10^{-4}$
$S_2O_3^{2-}$	$\sim 4 \times 10^{-5}$
S_4^{2-}	$\sim 4 \times 10^{-6}$

[a] Eq. 13-5 using the n_{Nu,CH_3Br} values given in Table 13.3.

$$k_{obs} = k_{H_2O}\{[H_2O] + 10^{3.0}[Cl^-] + 10^{3.8}[HCO_3{}^-] + 10^{5.1}[CN^-]\}$$

$$= (174.2\ M) \cdot k_{H_2O}$$

Half-life for a 1st order (or pseudo-1st order) reaction is given as

$$t_{1/2} = \frac{ln2}{k}$$

In pure water, only hydrolysis reaction by H_2O occurs:

$$t_{1/2} = \frac{ln2}{k} = \frac{ln2}{k_{H_2O}[H_2O]}$$

$$k_{H_2O} = \frac{ln2}{t_{1/2}[H_2O]} = \frac{ln2}{20\ d \cdot 55.3\ M}$$

$$= 6.27 \times 10^{-4}\ M^{-1}d^{-1}$$

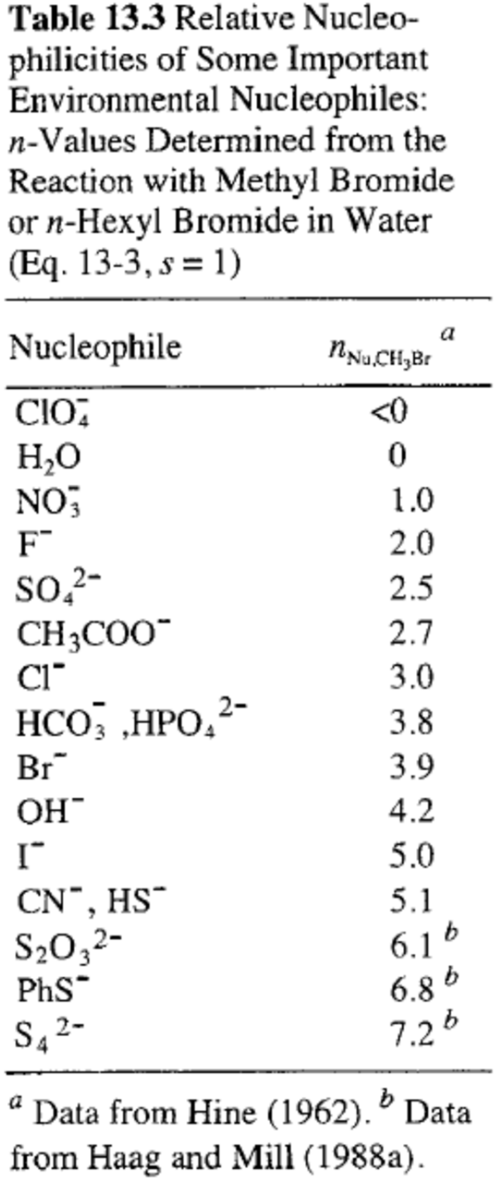

Table 13.3 Relative Nucleophilicities of Some Important Environmental Nucleophiles: *n*-Values Determined from the Reaction with Methyl Bromide or *n*-Hexyl Bromide in Water (Eq. 13-3, *s* = 1)

Nucleophile	$n_{\text{Nu,CH}_3\text{Br}}$ [a]
ClO_4^-	<0
H_2O	0
NO_3^-	1.0
F^-	2.0
$SO_4{}^{2-}$	2.5
CH_3COO^-	2.7
Cl^-	3.0
HCO_3^- ,$HPO_4{}^{2-}$	3.8
Br^-	3.9
OH^-	4.2
I^-	5.0
CN^-, HS^-	5.1
$S_2O_3{}^{2-}$	6.1 [b]
PhS^-	6.8 [b]
$S_4{}^{2-}$	7.2 [b]

[a] Data from Hine (1962). [b] Data from Haag and Mill (1988a).

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Now, we are ready to calculate the pseudo-1st order rate constant for the solution:

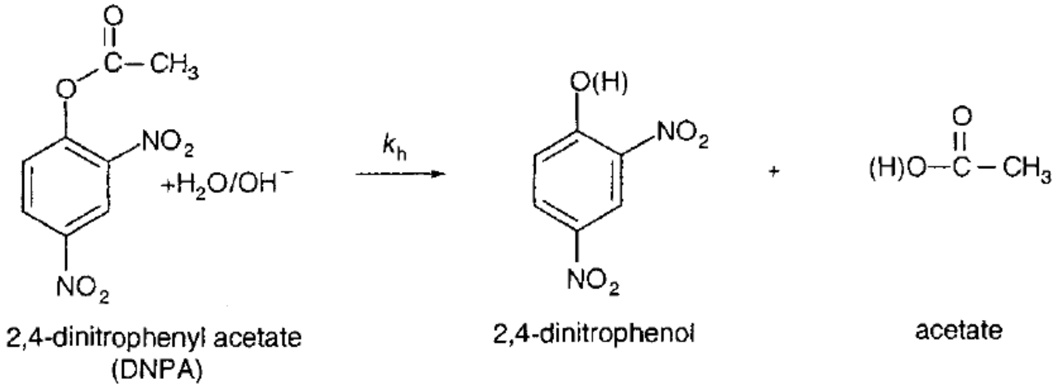
$$k_{obs} = (174.2\ M) \cdot k_{H_2O} = 0.109\ d^{-1}$$

Therefore,

$$t_{1/2} = \frac{ln2}{k_{obs}} = \frac{ln2}{0.109\ d^{-1}} = \mathbf{6.4\ d}$$

Ester hydrolysis kinetics

Q: Following pseudo-first order hydrolysis rate constants, k_h, were determined by a laboratory kinetic experiment for DNPA at 25°C. Determine the rate constants for the neutral (k_N) and base-catalyzed (k_B) hydrolysis of DNPA. Determine the I_{NB}.



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pH	**3.0**	**4.0**	**5.0**	**8.5**
k_h (s^{-1})	**4.3×10^{-5}**	**4.5×10^{-5}**	**4.4×10^{-5}**	**5.1×10^{-4}**

Ester hydrolysis kinetics

Because k_h is almost the same at pH=3.0-5.0, acid-catalyzed hydrolysis is insignificant.

As k_h is neither a function of $[H^+]$ nor $[OH^-]$ at this range, neutral hydrolysis should be dominant at pH=5.0

$$k_h(pH = 5.0) = k_N = \mathbf{4.4 \times 10^{-5}\ s^{-1}}$$

At pH=8.5, both neutral and base-catalyzed hydrolysis will occur:

$$k_h(pH = 8.5) = k_N + k_B[OH^-] = 5.1 \times 10^{-4}\ s^{-1}$$

$$[OH^-] = \frac{K_w}{[H^+]} = \frac{10^{-14}}{10^{-8.5}} = 10^{-5.5}\ M$$ (pK_w=14 @ 25^{o}C)

$$k_B = \frac{k_h - k_N}{[OH^-]} = \frac{(5.1 \times 10^{-4}\ s^{-1}) - (4.4 \times 10^{-5}\ s^{-1})}{10^{-5.5}\ M} = \mathbf{147\ M^{-1} s^{-1}}$$

At pH=I_{NB},

$$k_N = k_B[OH^-] = k_B\frac{K_w}{[H^+]}$$

$$[H^+] = k_B\frac{K_w}{k_N} = 147\ M^{-1}s^{-1} \times \frac{10^{-14}}{4.4 \times 10^{-5}\ s^{-1}} = 3.34 \times 10^{-8}\ M$$

$$pH = -log[H^+] = 7.5$$

$$\boldsymbol{I_{NB} = 7.5}$$