Nucleophilic reactions

Nucleophiles

- **Nucleophiles: nucleus-liking species**
  - Electron-rich
  - Possesses negative charge or non-bonded valence electrons
  - 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

$$Nu\colon + R - L \;\Rightarrow\; R - Nu + L\colon$$

  - S_N2 & S_N1 mechanisms

Nucleophiles

- **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 of group of atoms present in an organic molecule

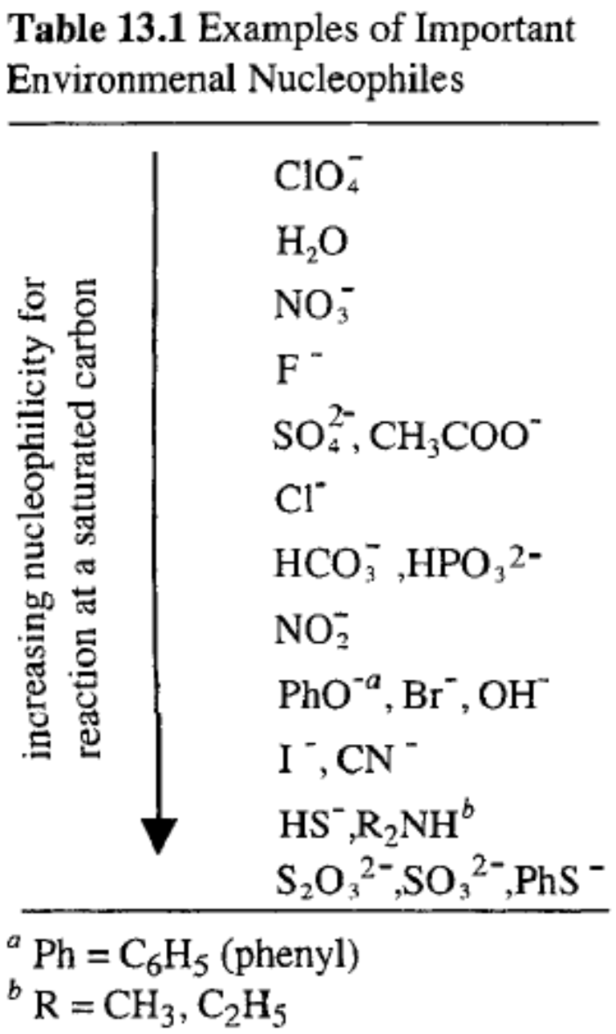


Table 13.1 Examples of Important Environmenal Nucleophiles

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

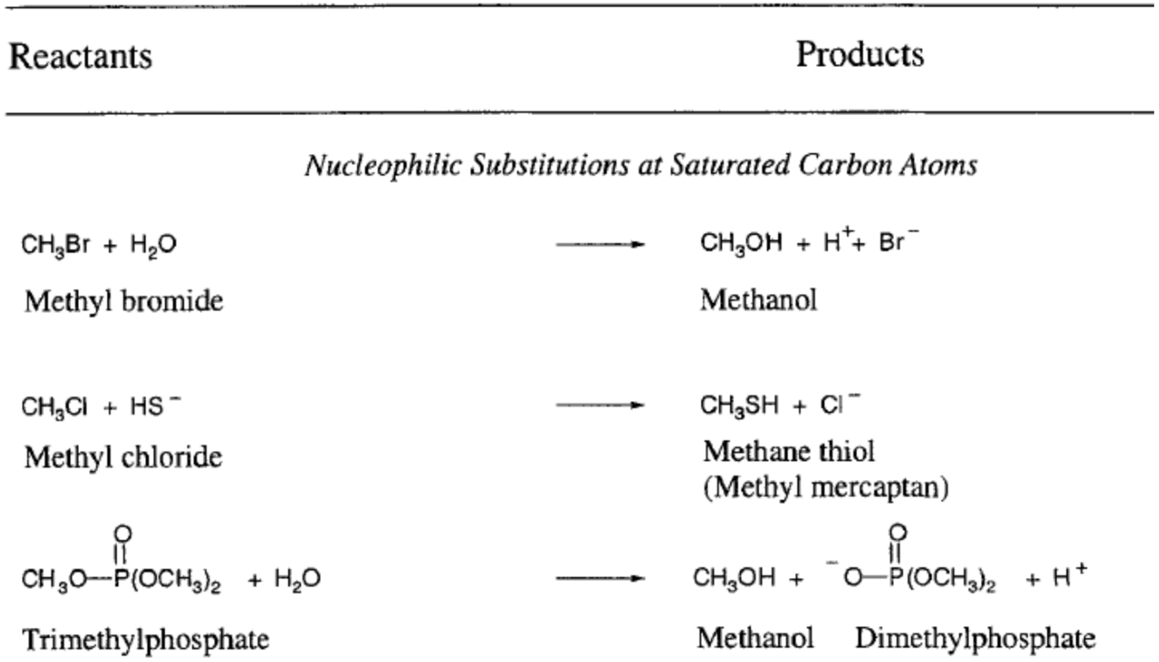
$S_2O_3{}^{2-}$,$SO_3{}^{2-}$,PhS^-

[a] Ph = C_6H_5 (phenyl)

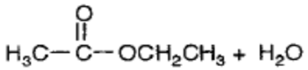
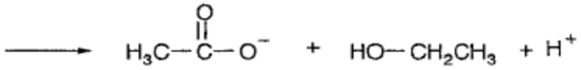
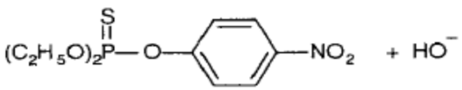
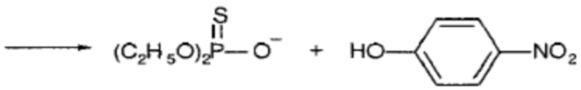
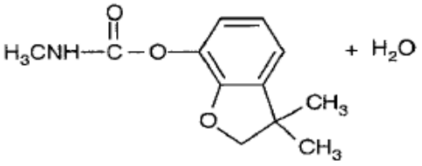
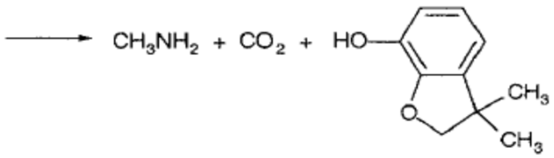
[b] R = CH_3, C_2H_5

Nucleophilic reactions

- Examples of environmentally relevant chemical reactions involving nucleophiles and/or bases

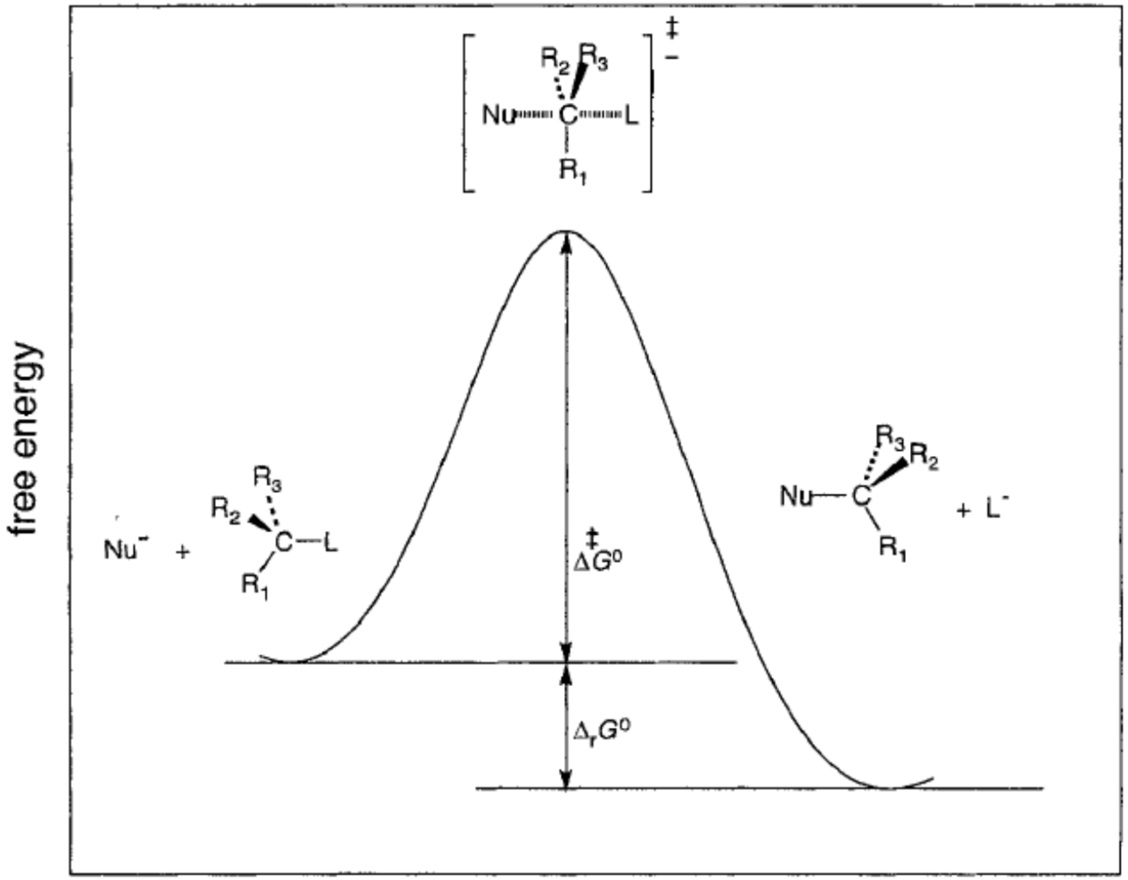


Reactants		Products
	Nucleophilic Substitutions at Saturated Carbon Atoms	
$CH_3Br + H_2O$ Methyl bromide	$\longrightarrow$	$CH_3OH + H^+ + Br^-$ Methanol
$CH_3Cl + HS^-$ Methyl chloride	$\longrightarrow$	$CH_3SH + Cl^-$ Methane thiol (Methyl mercaptan)
$CH_3O{-}\overset{O}{\overset{\parallel}{P}}(OCH_3)_2 + H_2O$ Trimethylphosphate	$\longrightarrow$	$CH_3OH + {}^{-}O{-}\overset{O}{\overset{\parallel}{P}}(OCH_3)_2 + H^+$ Methanol Dimethylphosphate

Reactants	Products
β-Elimination	
$Cl_2HC-CHCl_2 + HO^-$ 1,1,2,2-Tetrachloroethane	$\longrightarrow Cl_2C=CHCl + Cl^- + H_2O$ Trichloroethene
Ester Hydrolysis	
 $H_3C-\overset{O}{\overset{\|}{C}}-OCH_2CH_3 + H_2O$ Ethyl acetate (Acetic acid ethylester)	 $\longrightarrow H_3C-\overset{O}{\overset{\|}{C}}-O^- + HO-CH_2CH_3 + H^+$ Acetate Ethanol
 Parathion	 O,O-Diethyl-thiophosphoric acid 4-Nitrophenol
Carbamate Hydrolysis	
 Carbofuran	 Methylamine 2,3-Dihydro-3,3-dimethyl-7-benzofuranol

Nucleophilic substitution at saturated carbon atoms

- **S_N2 mechanism**



Nucleophilic substitution at saturated carbon atoms

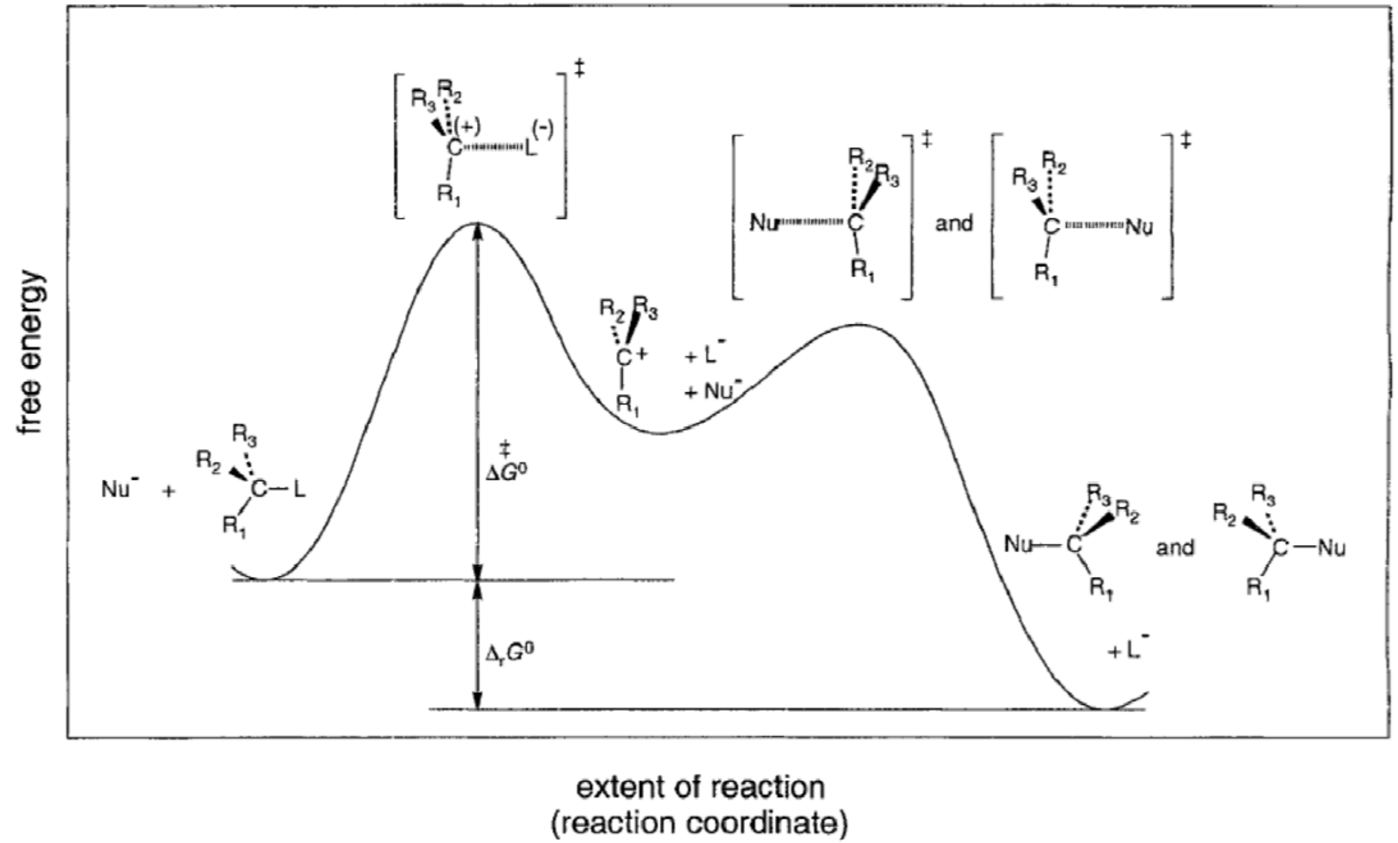
- **S_N2 mechanism**
  - The standard free energy of activation $\Delta^{\ddagger}G^0$ (which controls the reaction rate) depends strongly on both <u>the capability of the nucleophile to initiate a substitution reaction</u> and <u>the willingness of the organic molecule to undergo that reaction</u>
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



Nucleophilic substitution at saturated carbon atoms

- **S_N1 mechanism**
  - 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
  - Substitution, nucleophilic, unimolecular
  - 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})

S_N2: Relative nucleophilicity

- **Study of nucleophilic substitution of methyl halides for various nucleophiles:**
  - A methyl halide has the same relative reactivity toward the different nucleophiles as the other methyl halides
  - Swain & Scott (1953):

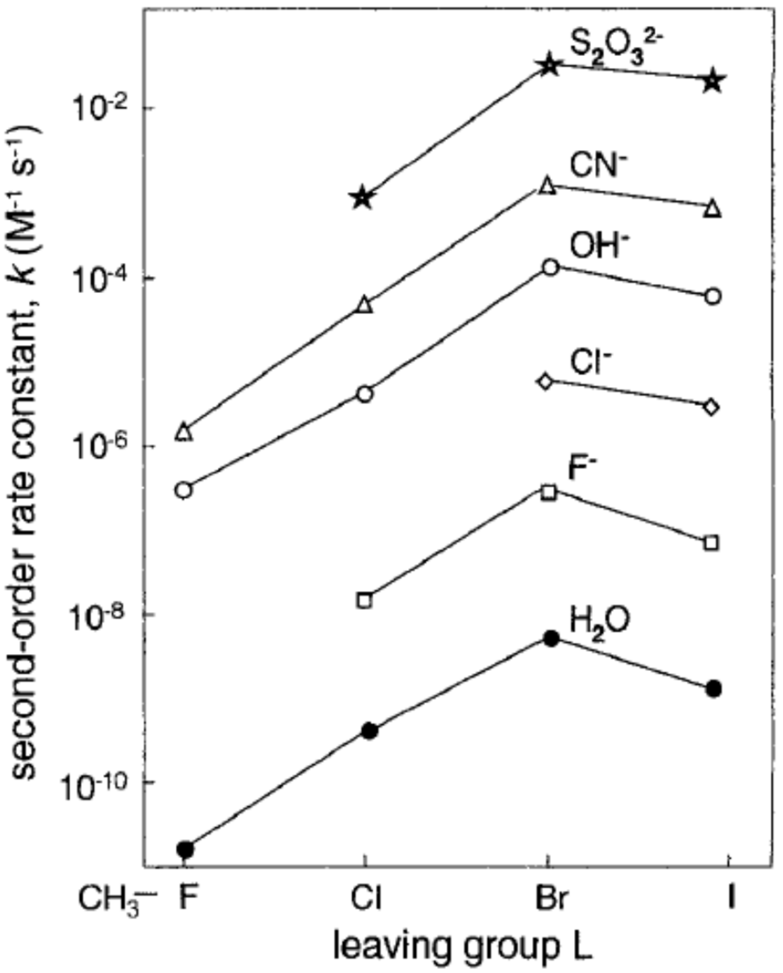
$$log\left(\frac{k_{Nu}}{k_{H_2O}}\right) = s \cdot n_{Nu,CH_3Br}$$

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, measured by the nucleophilic substitution reaction with CH_3Br in water

s = sensitivity of the organic molecule to nucleophilic attack



S_N2: Relative nucleophilicity

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

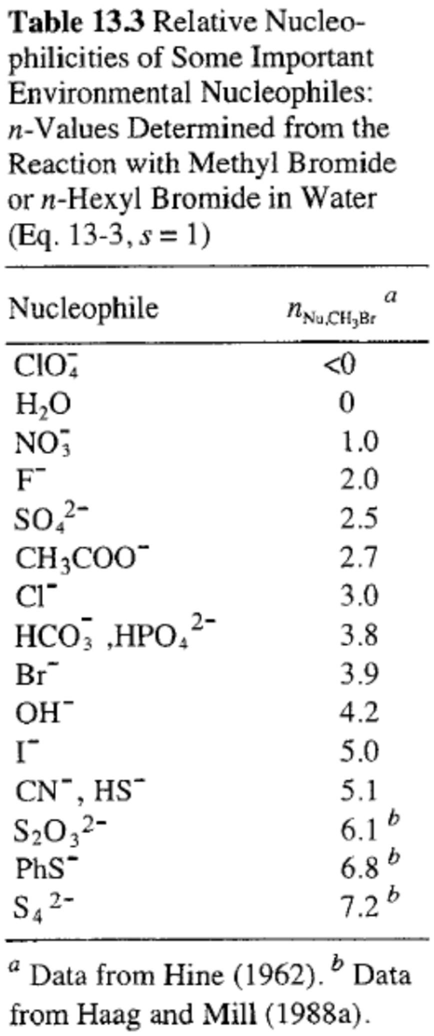


Table 13.3 Relative Nucleophilicities of Some Important Environmental Nucleophiles: *n*-Values Determined from the Reaction with Methyl Bromide or *n*-Hexyl Bromide in Water (Eq. 13-3, *s* = 1)

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).

$$log\left(\frac{k_{Nu}}{k_{CH_3OH}}\right) = s' \cdot n_{Nu,CH_3I}$$

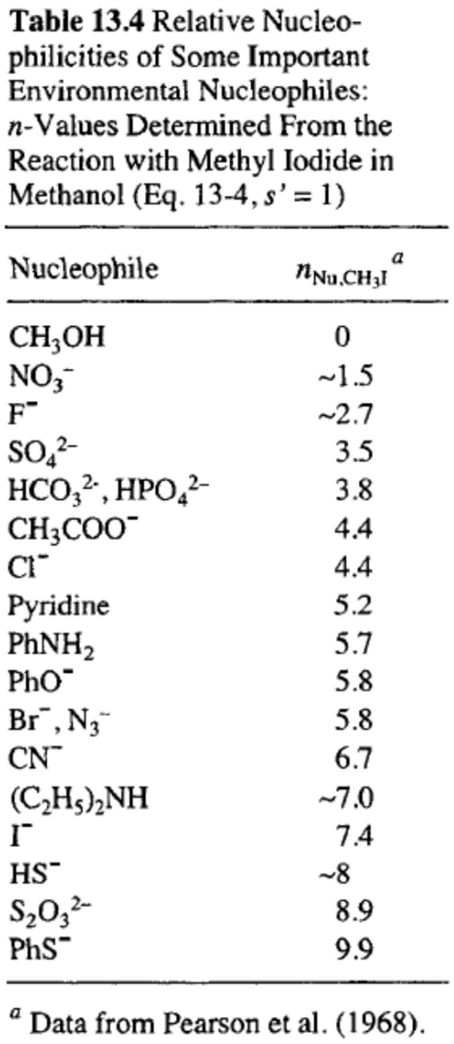


Table 13.4 Relative Nucleophilicities of Some Important Environmental Nucleophiles: *n*-Values Determined From the Reaction with Methyl Iodide in Methanol (Eq. 13-4, *s'* = 1)

Nucleophile	n_{Nu,CH_3I} [a]
CH_3OH	0
NO_3^-	~1.5
F^-	~2.7
SO_4^{2-}	3.5
HCO_3^{2-}, HPO_4^{2-}	3.8
CH_3COO^-	4.4
Cl^-	4.4
Pyridine	5.2
$PhNH_2$	5.7
PhO^-	5.8
Br^-, N_3^-	5.8
CN^-	6.7
$(C_2H_5)_2NH$	~7.0
I^-	7.4
HS^-	~8
$S_2O_3^{2-}$	8.9
PhS^-	9.9

[a] Data from Pearson et al. (1968).

S_N2: Relative nucleophilicity

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

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

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

$[Nu]_{50\%}$ = [Nu] to get the same rate as the hydrolysis rate by H_2O

- **Freshwater vs. saline water**

- **pH sensitivity of hydrolysis reaction (H_2O vs. OH^-)**

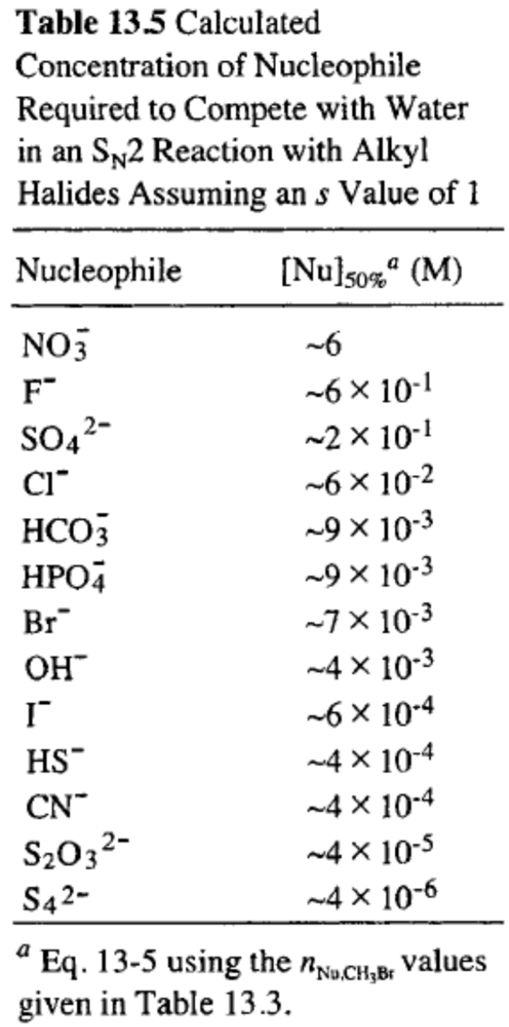


Table 13.5 Calculated Concentration of Nucleophile Required to Compete with Water in an S_N2 Reaction with Alkyl Halides Assuming an *s* Value of 1

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_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_N1 & S_N2: Leaving groups

- **Reaction rates for methyl halides**
  - Reaction rate in the order of: CH_3Br ~ $CH_3I > CH_3Cl > CH_3F$
  - A plausible hypothesis: the weaker a nucleophile, the better leaving group it should be

    But n_{Nu,CH_3Br} is in the order of: $F^- < Cl^- < Br^- < I^-$ → hypothesis NOT supported
  - Why?? C-X bond strength is in the order of: $CH_3I < CH_3Br < CH_3Cl < CH_3F$

- The likeliness of being a leaving group depends mainly on the **bond strength**

S_N1 & S_N2: Effect of EDGs & resonance

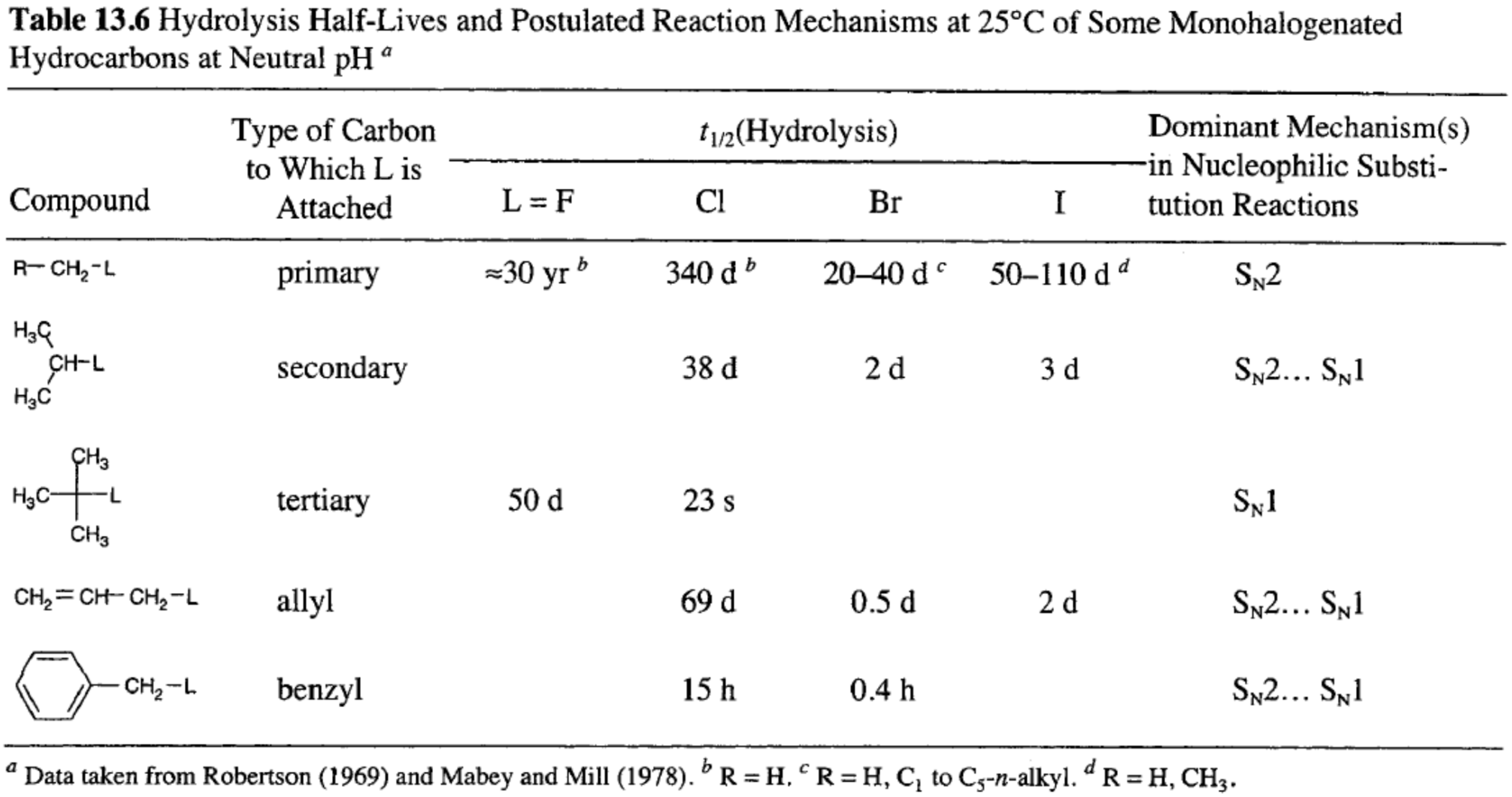


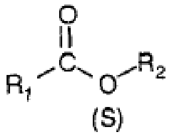
Table 13.6 Hydrolysis Half-Lives and Postulated Reaction Mechanisms at 25°C of Some Monohalogenated Hydrocarbons at Neutral pH [a]

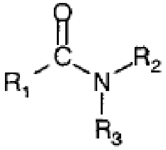
Compound	Type of Carbon to Which L is Attached	$t_{1/2}$(Hydrolysis)				Dominant Mechanism(s) in Nucleophilic Substitution Reactions
		L = F	Cl	Br	I	
$R-CH_2-L$	primary	≈30 yr [b]	340 d [b]	20–40 d [c]	50–110 d [d]	S_N2
H_3C $CH-L$ H_3C	secondary		38 d	2 d	3 d	$S_N2 \ldots S_N1$
CH_3 H_3C-C-L CH_3	tertiary	50 d	23 s			S_N1
$CH_2=CH-CH_2-L$	allyl		69 d	0.5 d	2 d	$S_N2 \ldots S_N1$
$-CH_2-L$	benzyl		15 h	0.4 h		$S_N2 \ldots S_N1$

[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.

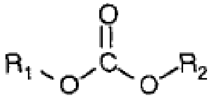
Hydrolysis of carboxylic & carbonic acid derivatives

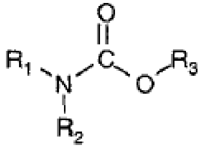
- Carboxylic acid derivatives

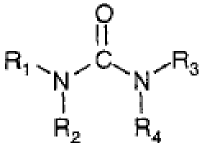

ester (thioester)


amide

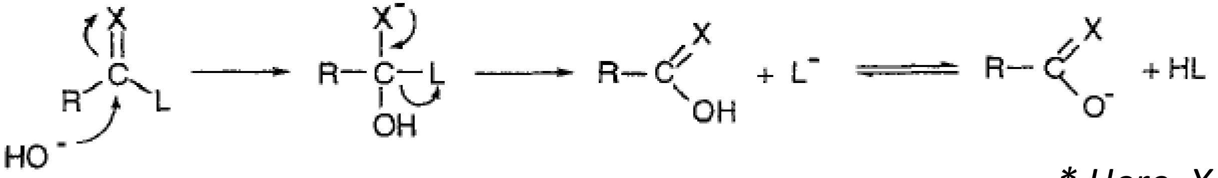
- Carbonic acid derivatives


carbonate


carbamate


urea

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

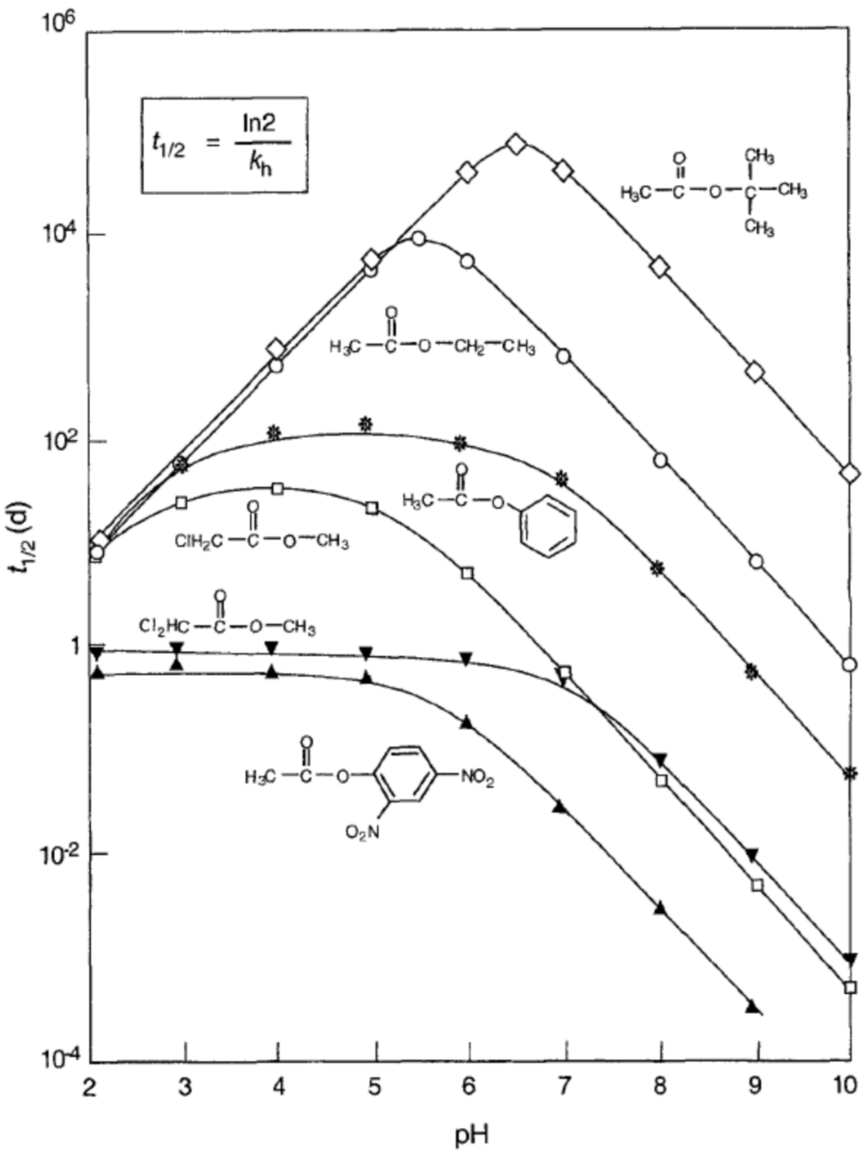


** Here, X = O, S, or NR*

Hydrolysis of Esters

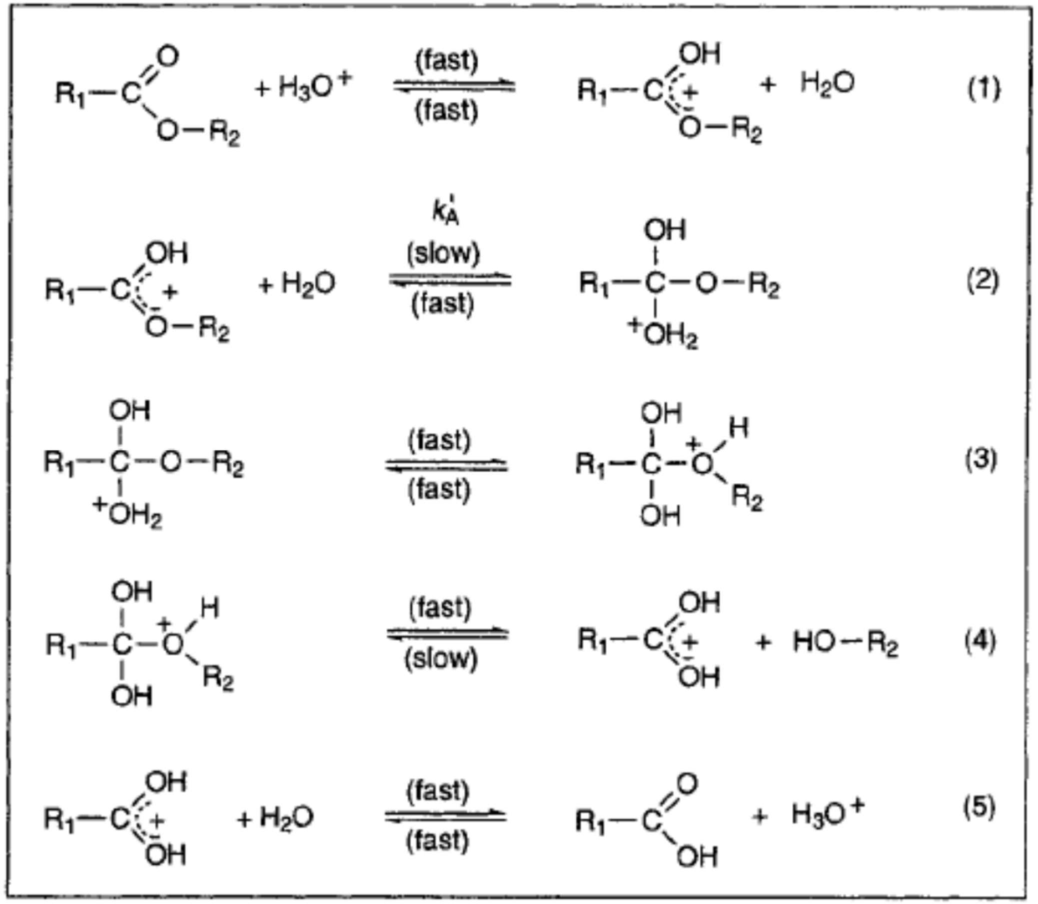
- Three mechanisms:
  - **1) acid-catalyzed**
  - **2) neutral**
  - **3) base-catalyzed**

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

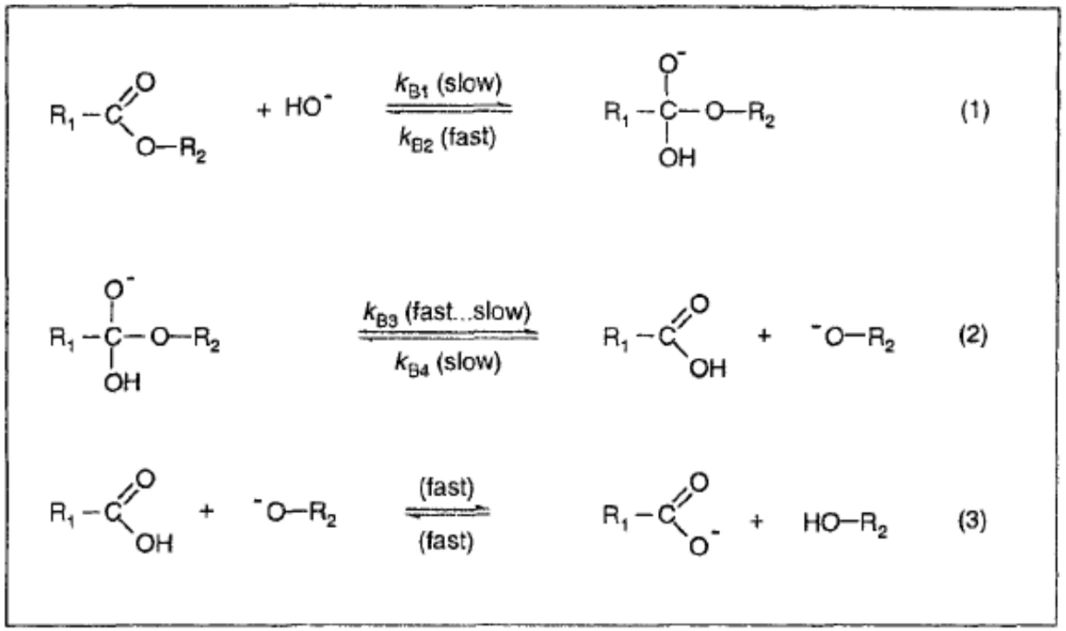


Hydrolysis of Esters

- **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**
    - **$[H^+]$**

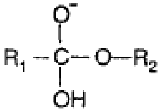


Hydrolysis of Esters

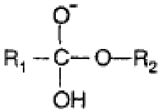


- **Base-catalyzed**
  - Only (1) or both (1) & (2) can be rate-limiting
  - Rate depends on **[OH$^-$]** and in addition:

If only (1) is rate-limiting:

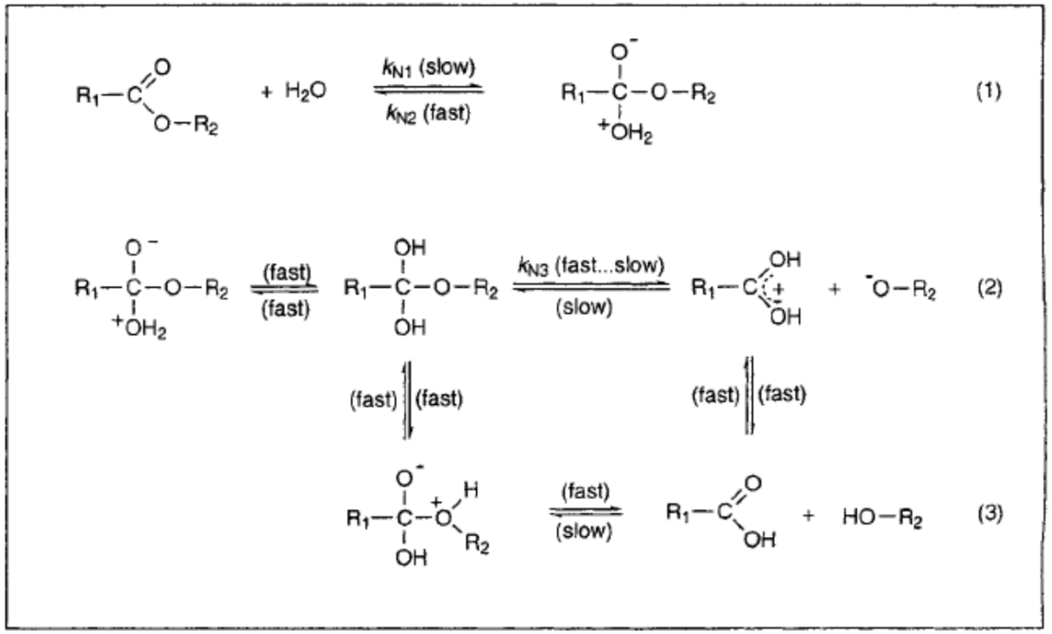
- Depends on the formation of 

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

- Depends on the formation of  & the property of the leaving group

Hydrolysis of Esters

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



Hydrolysis of Esters

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

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

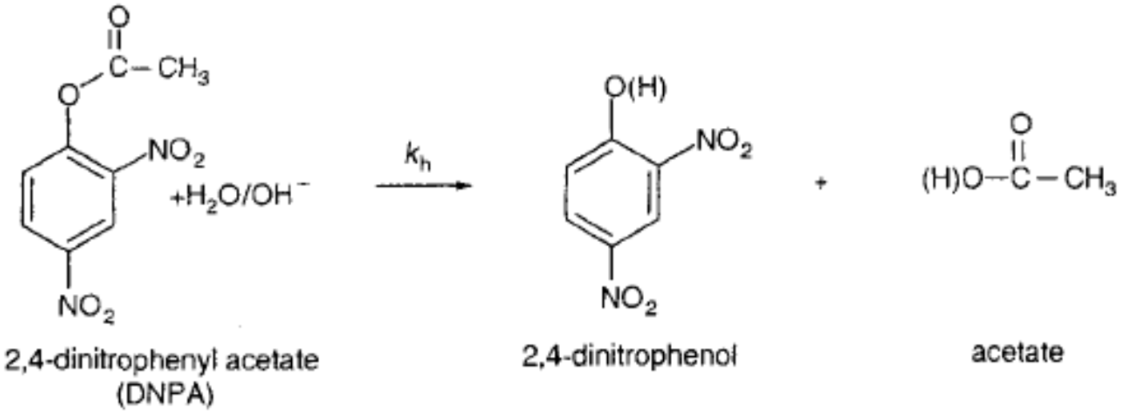
$$= k_A[H^+] + k_N + k_B[OH^-]$$

  - **Hydrolysis half-life**

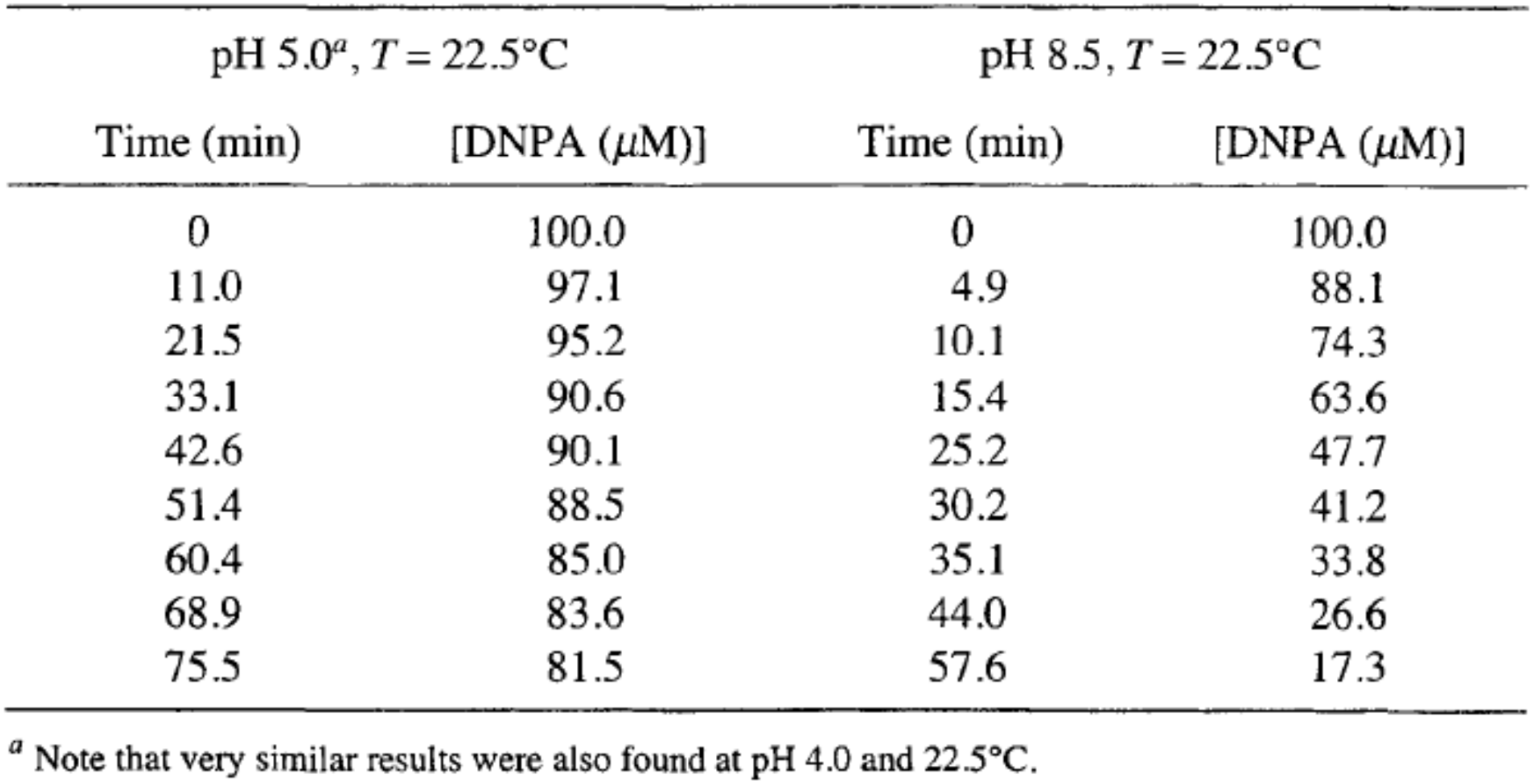
$$t_{1/2\ (hydroysis)} = \frac{ln\ 2}{k_h}$$

Hydrolysis of Esters

Q: Determine the pseudo-first order hydrolysis rate constant, k_h, for the following reaction at pH 5.0 and 8.5 at 22.5°C using the data sets given in the next slide.



Hydrolysis of Esters



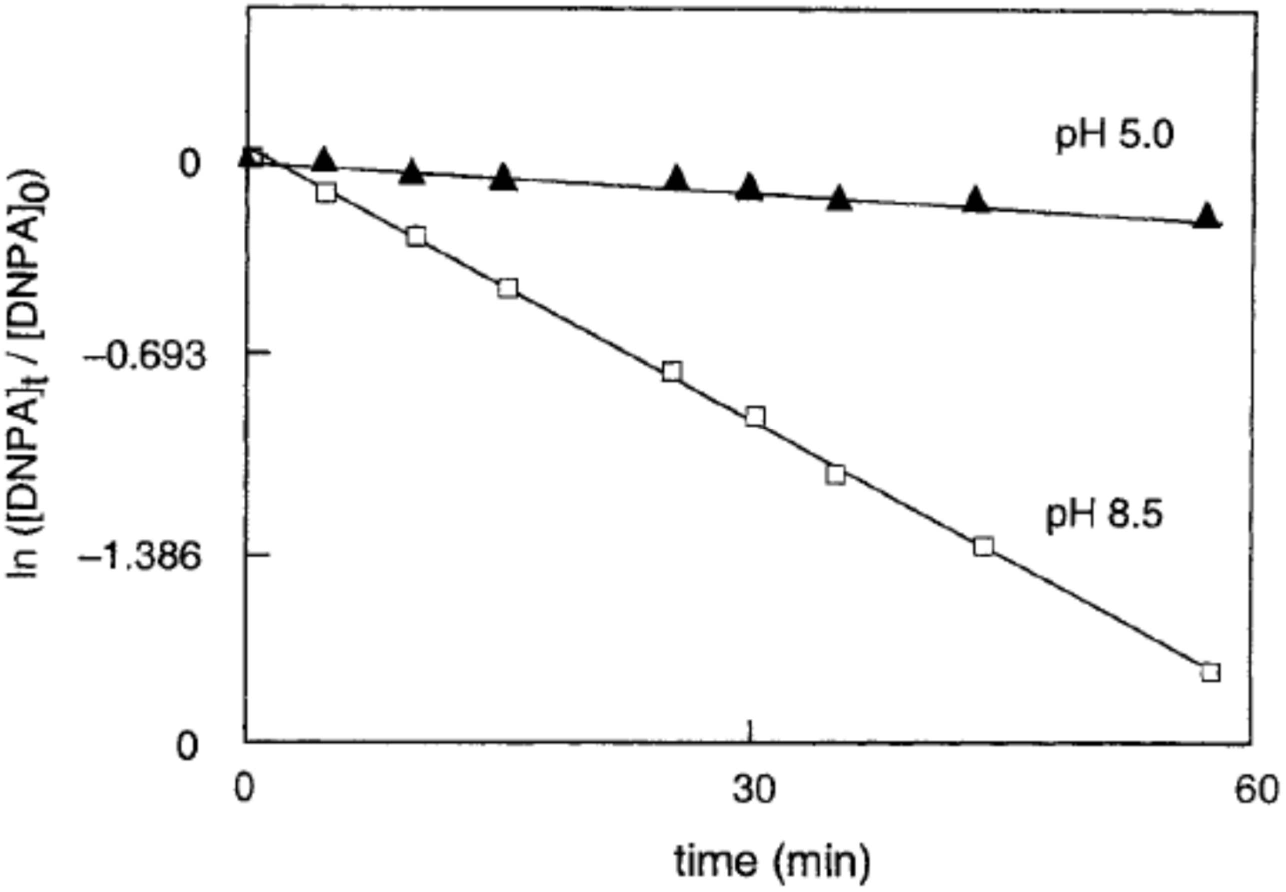
pH 5.0[a], $T = 22.5°C$		pH 8.5, $T = 22.5°C$	
Time (min)	[DNPA (μM)]	Time (min)	[DNPA (μM)]
0	100.0	0	100.0
11.0	97.1	4.9	88.1
21.5	95.2	10.1	74.3
33.1	90.6	15.4	63.6
42.6	90.1	25.2	47.7
51.4	88.5	30.2	41.2
60.4	85.0	35.1	33.8
68.9	83.6	44.0	26.6
75.5	81.5	57.6	17.3

[a] Note that very similar results were also found at pH 4.0 and 22.5°C.

Hydrolysis of Esters

Q: For the previous question, derive the rate constants for the neutral (k_N) and base-catalyzed (k_B) hydrolysis of DNPA at 22.5°C. Note that the acid-catalyzed hydrolysis is relatively unimportant at pH>2. At what pH are the two reactions equally important?

Hydrolysis of Esters



pH 5.0:

$$k_h = 4.4 \times 10^{-5}\ s^{-1}$$

pH 8.5:

$$k_h = 5.1 \times 10^{-4}\ s^{-1}$$

Hydrolysis of Esters