Nucleophilic reactions

Nucleophiles

- **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

- **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

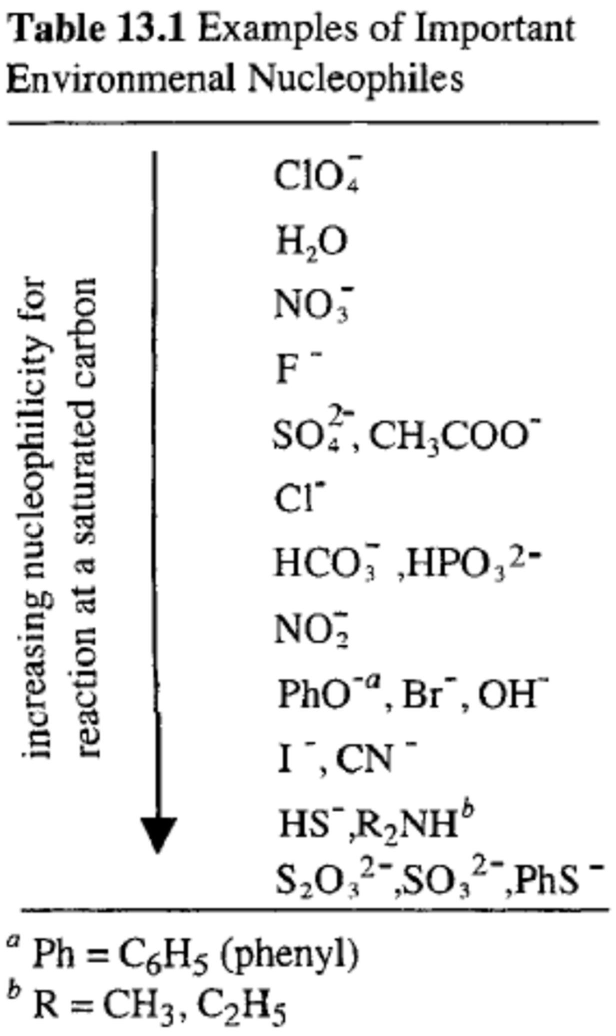


Table 13.1 Examples of Important Environmenal Nucleophiles

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

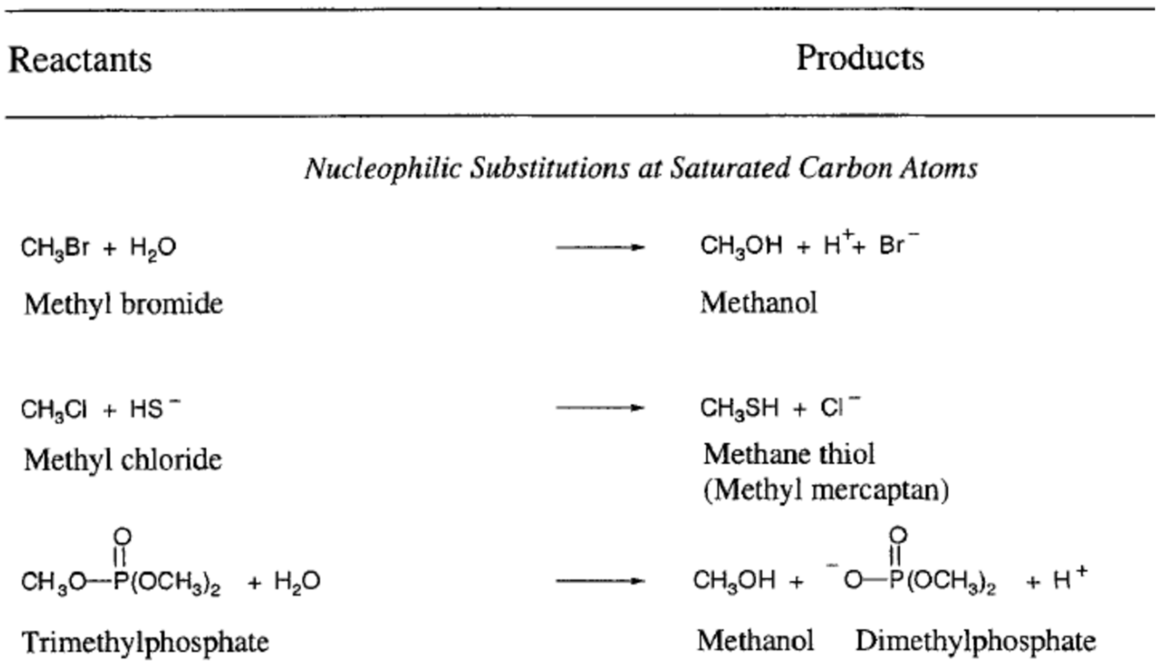
$S_2O_3^{2-}$,SO_3^{2-},PhS^-

[a] Ph = C_6H_5 (phenyl)

[b] R = CH_3, C_2H_5

Nucleophilic reactions

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

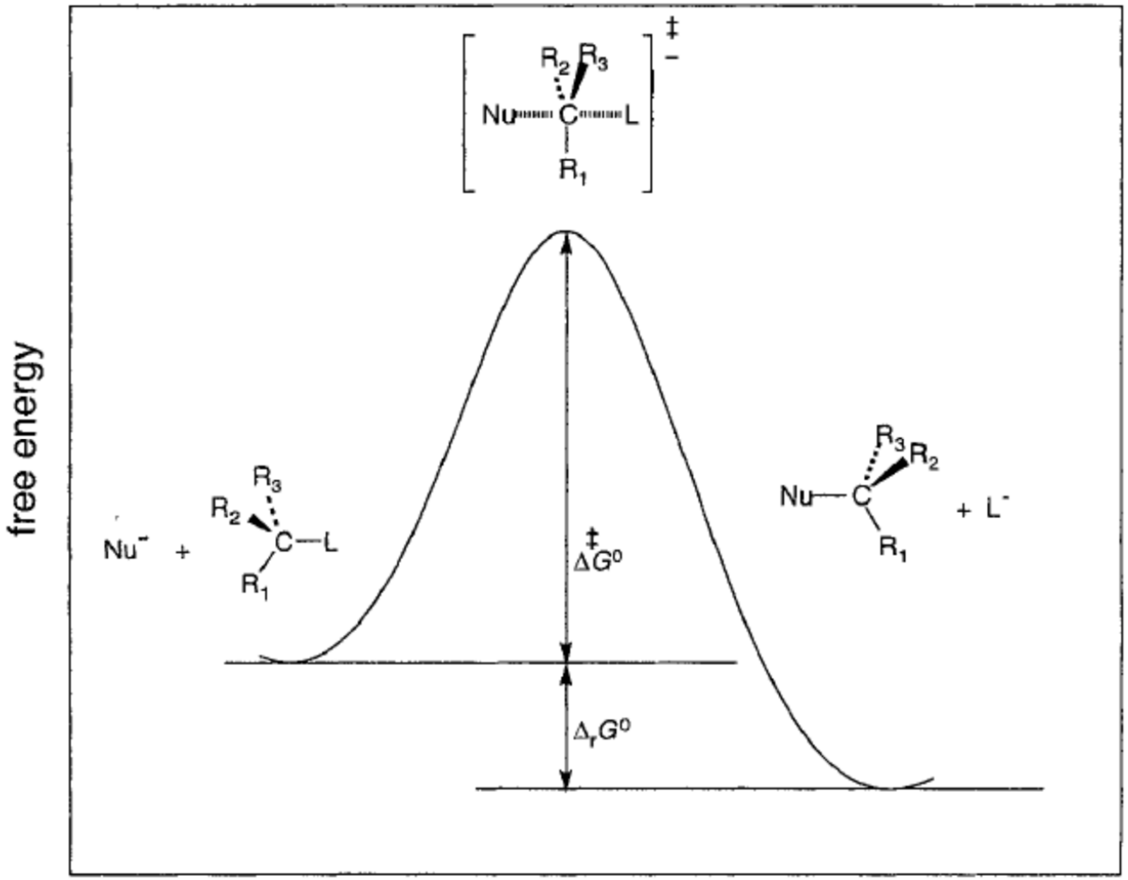


Reactants		Products
Nucleophilic Substitutions at Saturated Carbon Atoms		
$CH_3Br + H_2O$ Methyl bromide	$\longrightarrow$	$CH_3OH + H^+ + Br^-$ Methanol
$CH_3Cl + HS^-$ Methyl chloride	$\longrightarrow$	$CH_3SH + Cl^-$ Methane thiol (Methyl mercaptan)
$CH_3O{-}\overset{O}{\overset{\parallel}{P}}(OCH_3)_2 + H_2O$ 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	
 $H_3C-C(=O)-OCH_2CH_3 + H_2O$ Ethyl acetate (Acetic acid ethylester)	$\longrightarrow H_3C-C(=O)-O^- + HO-CH_2CH_3 + H^+$ Acetate Ethanol
 Parathion	O,O-Diethylthiophosphoric 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

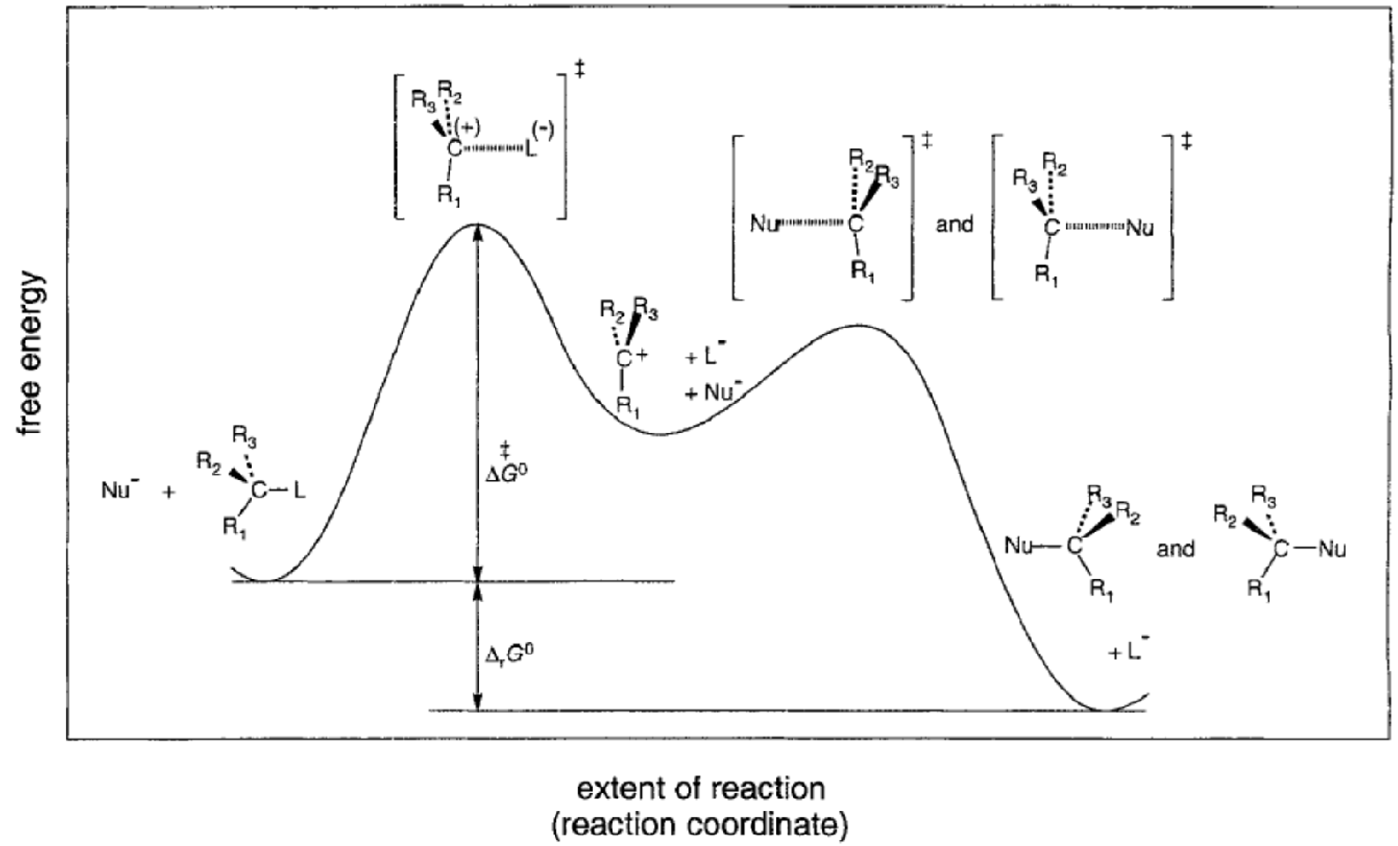
- **S_N2 mechanism**
  - Substitution, nucleophilic, bimolecular
  - The standard free energy of activation $\Delta^{\ddagger}G^{0}$ (which controls the reaction rate) depends strongly on both the capability of the nucleophile to initiate a substitution reaction and the willingness of the organic molecule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

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

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

Nucleophilic substitution at saturated carbon atoms

- **S_N1 mechanism**



Nucleophilic substitution at saturated carbon atoms

- **S_N1 mechanism**
  - Substitution, nucleophilic, unimolecular
  - The reaction rate depends solely on <u>how easily the leaving group dissociates</u> 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})

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):

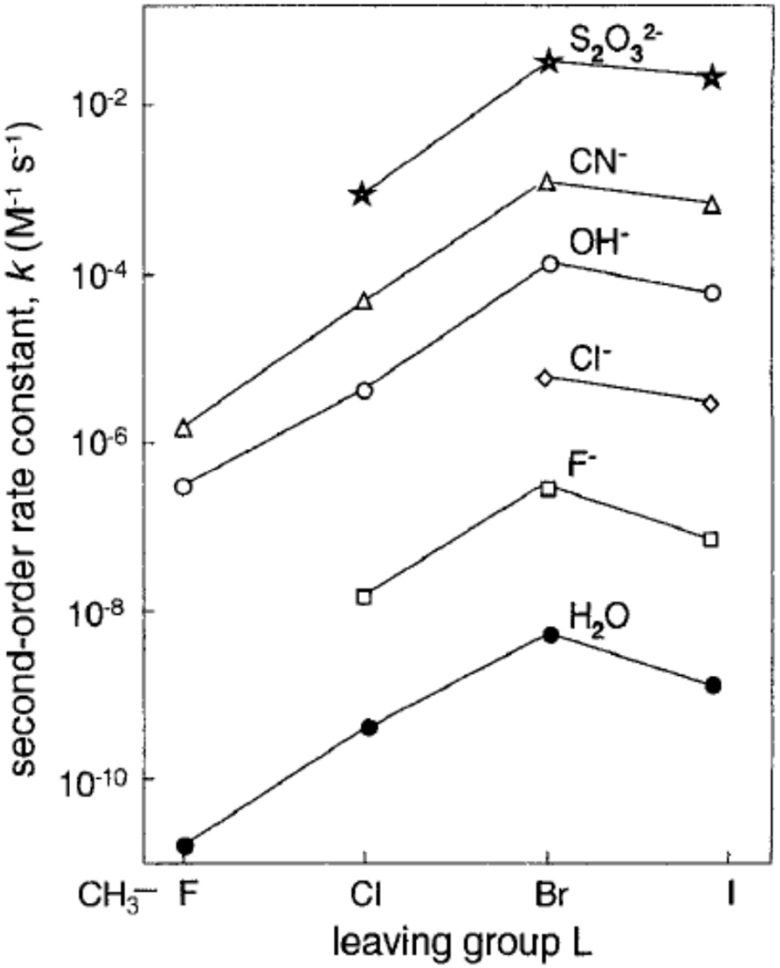
$$log\left(\frac{k_{Nu}}{k_{H_2O}}\right) = s \cdot n_{Nu,CH_3Br}$$

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



n_{Nu,CH_3Br}---?

- 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*

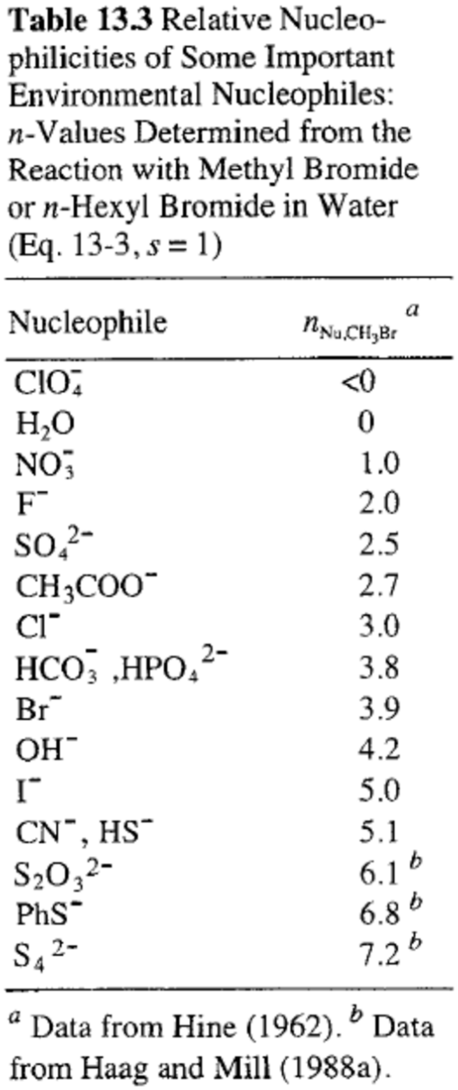


Table 13.3 Relative Nucleophilicities of Some Important Environmental Nucleophiles: *n*-Values Determined from the Reaction with Methyl Bromide or *n*-Hexyl Bromide in Water (Eq. 13-3, *s* = 1)

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

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

55.3 = molar concentration of water (M)

S_N2: competition of nucleophiles

- **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

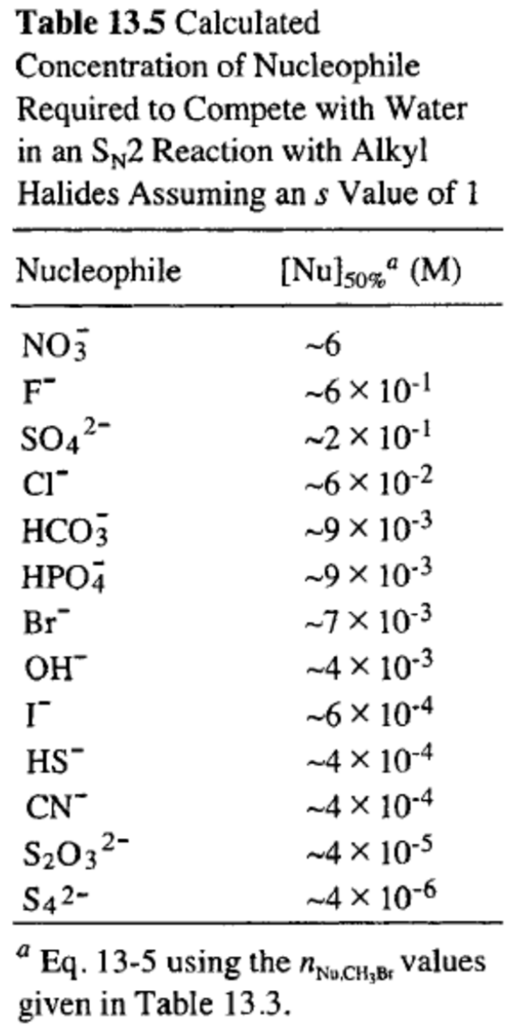


Table 13.5 Calculated Concentration of Nucleophile Required to Compete with Water in an S_N2 Reaction with Alkyl Halides Assuming an *s* Value of 1

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: CH_3Br ~ CH_3I > CH_3Cl > CH_3F

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

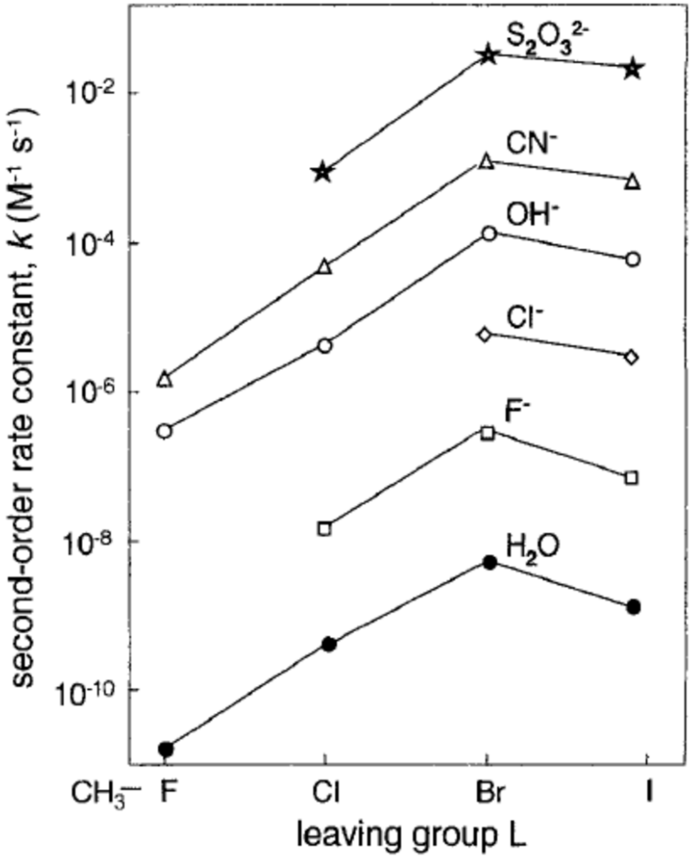
1) The one with smaller n_{Nu,CH_3Br}
(a weaker nucleophile)

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

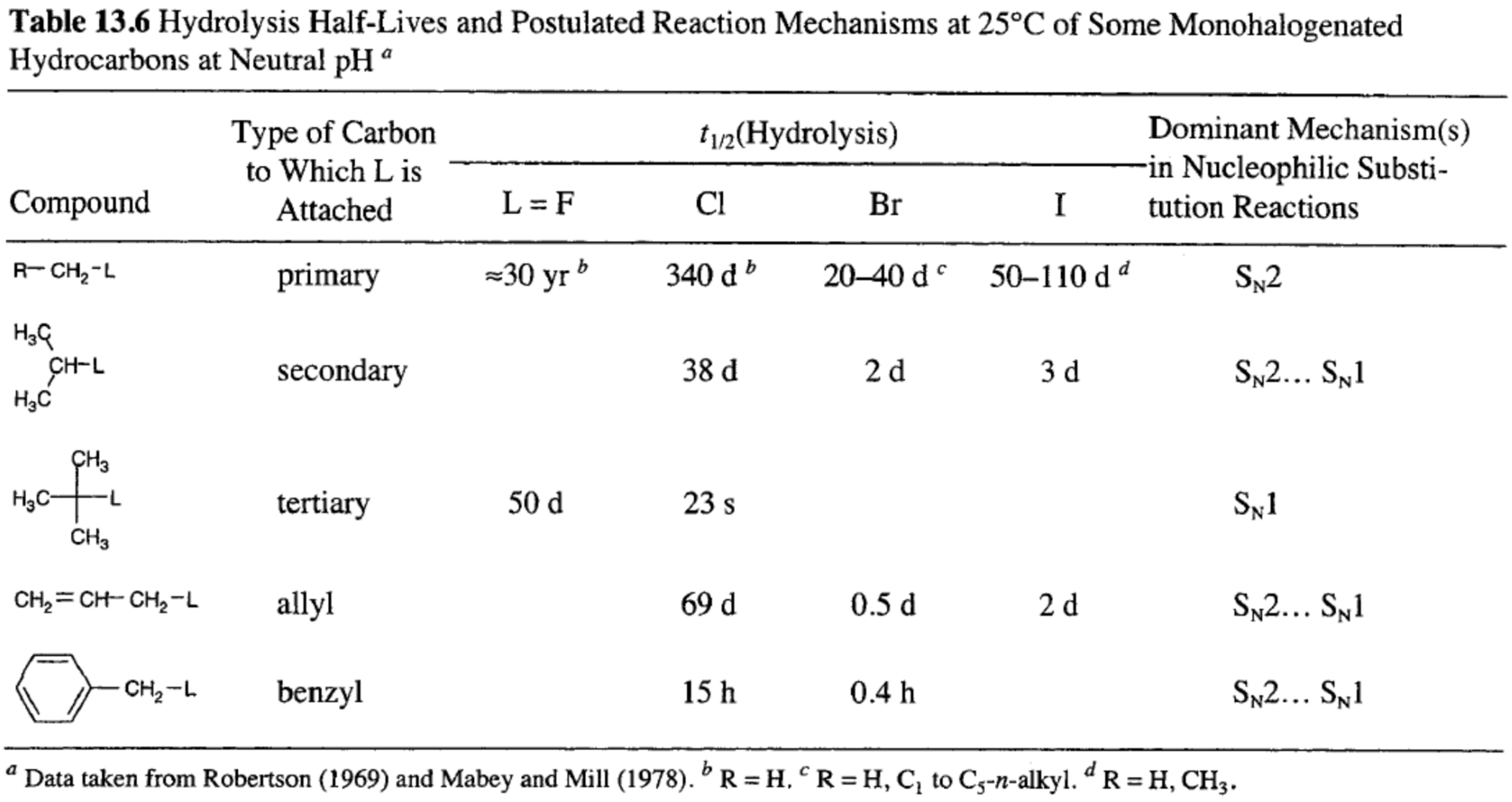


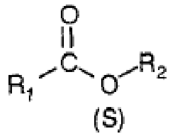
Table 13.6 Hydrolysis Half-Lives and Postulated Reaction Mechanisms at 25°C of Some Monohalogenated Hydrocarbons at Neutral pH [a]

Compound	Type of Carbon to Which L is Attached	$t_{1/2}$(Hydrolysis) L = F	Cl	Br	I	Dominant Mechanism(s) in Nucleophilic Substitution Reactions
$R-CH_2-L$	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- $-L$ 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		$S_N2 \ldots S_N1$

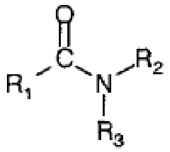
[a] Data taken from Robertson (1969) and Mabey and Mill (1978). [b] R = H. [c] R = H, C_1 to C_5-n-alkyl. [d] R = H, CH_3.

Hydrolysis of carboxylic & carbonic acid derivatives

- Carboxylic acid derivatives

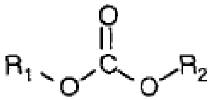


ester (thioester)

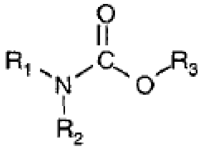


amide

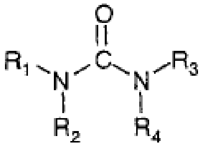
- Carbonic acid derivatives



carbonate

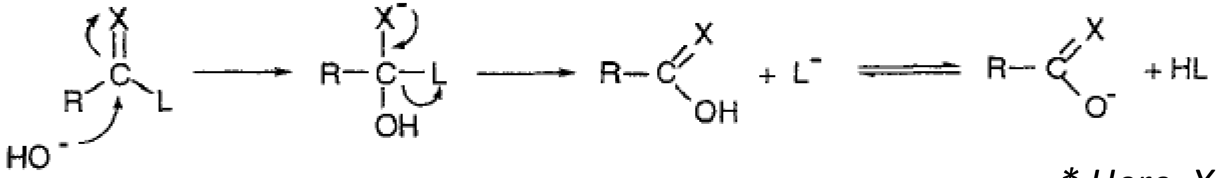


carbamate



urea

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

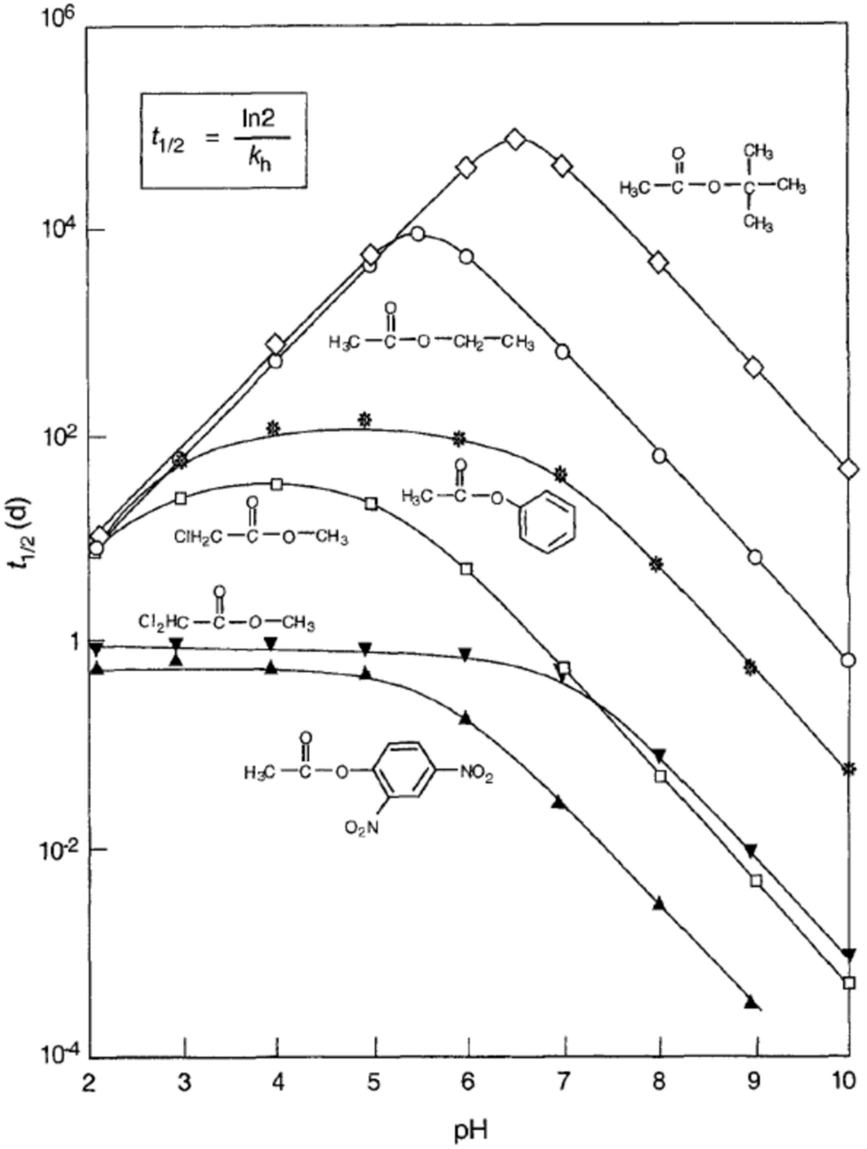


** Here, X = O, S, or NR*

Hydrolysis of Esters

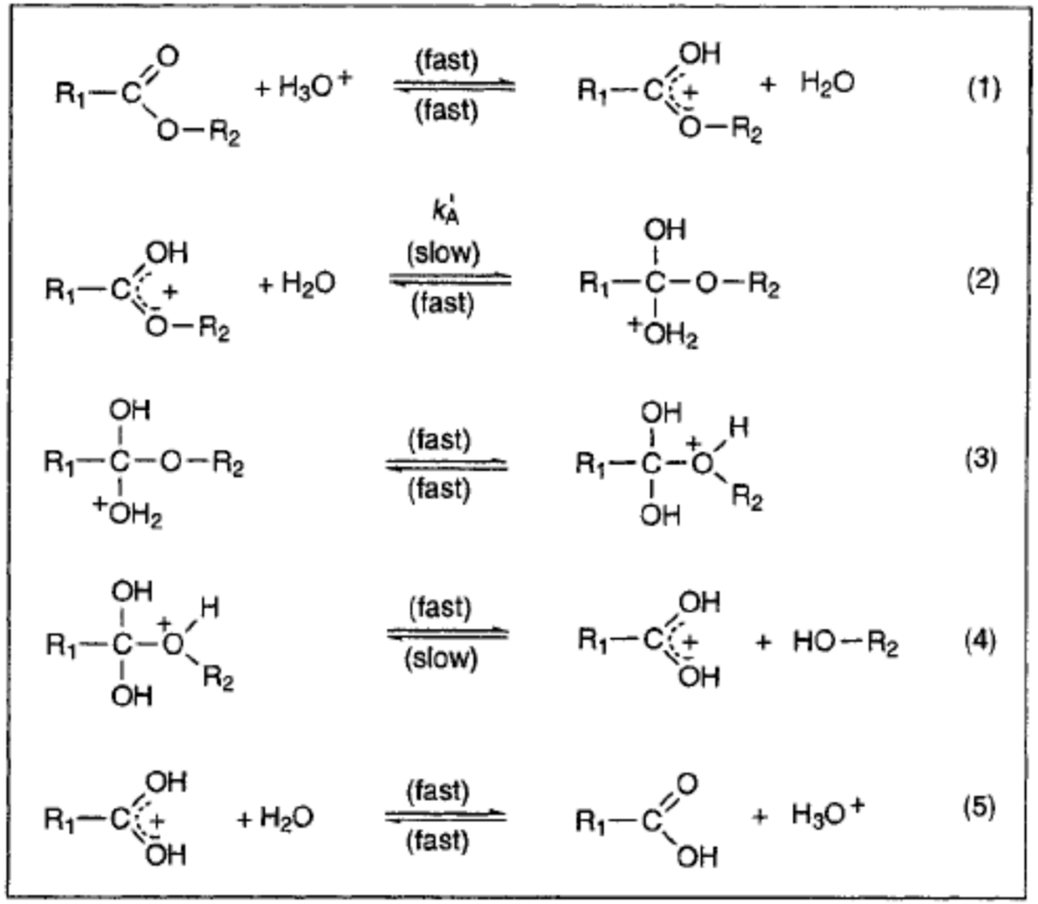
- Three mechanisms:
  - **1) acid-catalyzed**
  - **2) neutral**
  - **3) base-catalyzed**

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



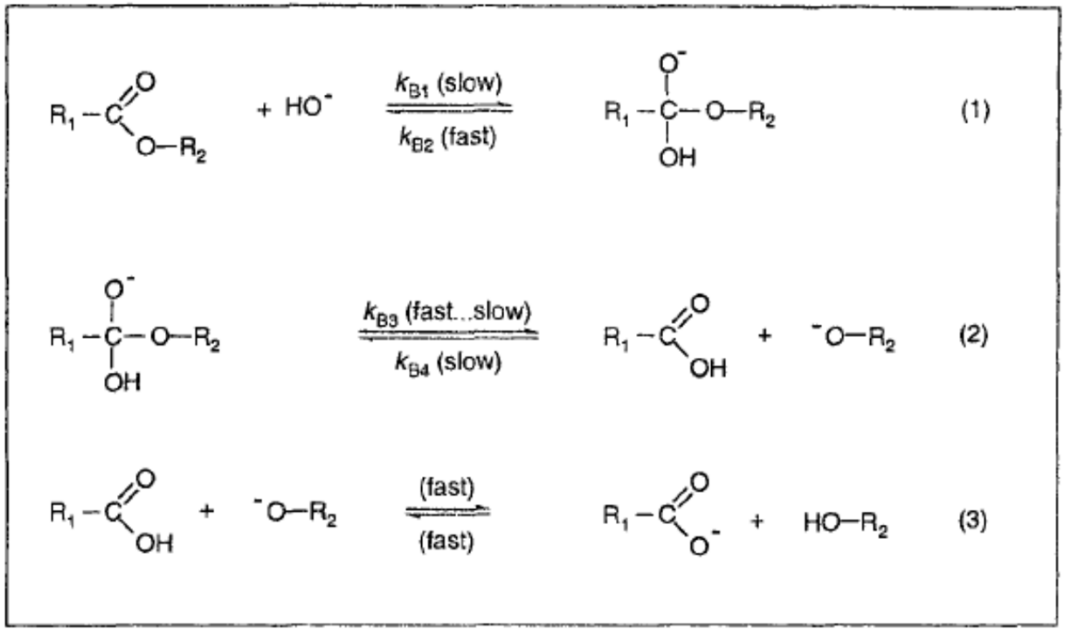
Ester hydrolysis: acid-catalyzed

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



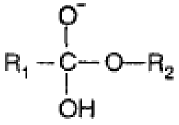
Ester hydrolysis: base-catalyzed

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

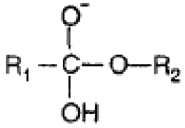


- Rate depends on **$[OH^-]$** and in addition:

  If only (1) is rate-limiting:

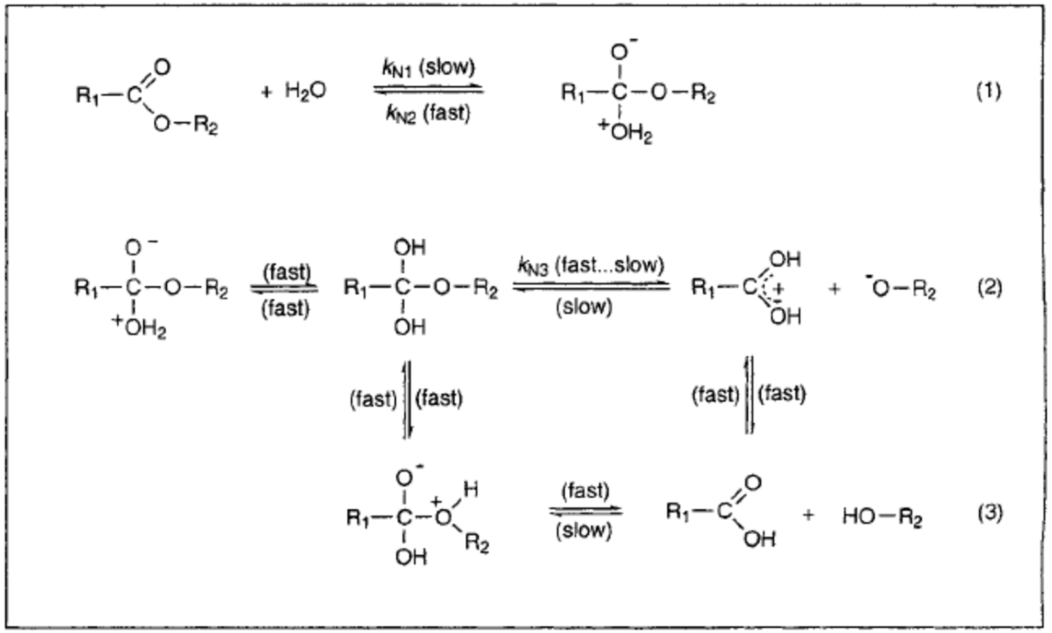
  – Depends on the formation of  $R_1-C(O^-)(OH)-O-R_2$

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

  – Depends on the formation of  $R_1-C(O^-)(OH)-O-R_2$ & 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^-



Ester hydrolysis kinetics

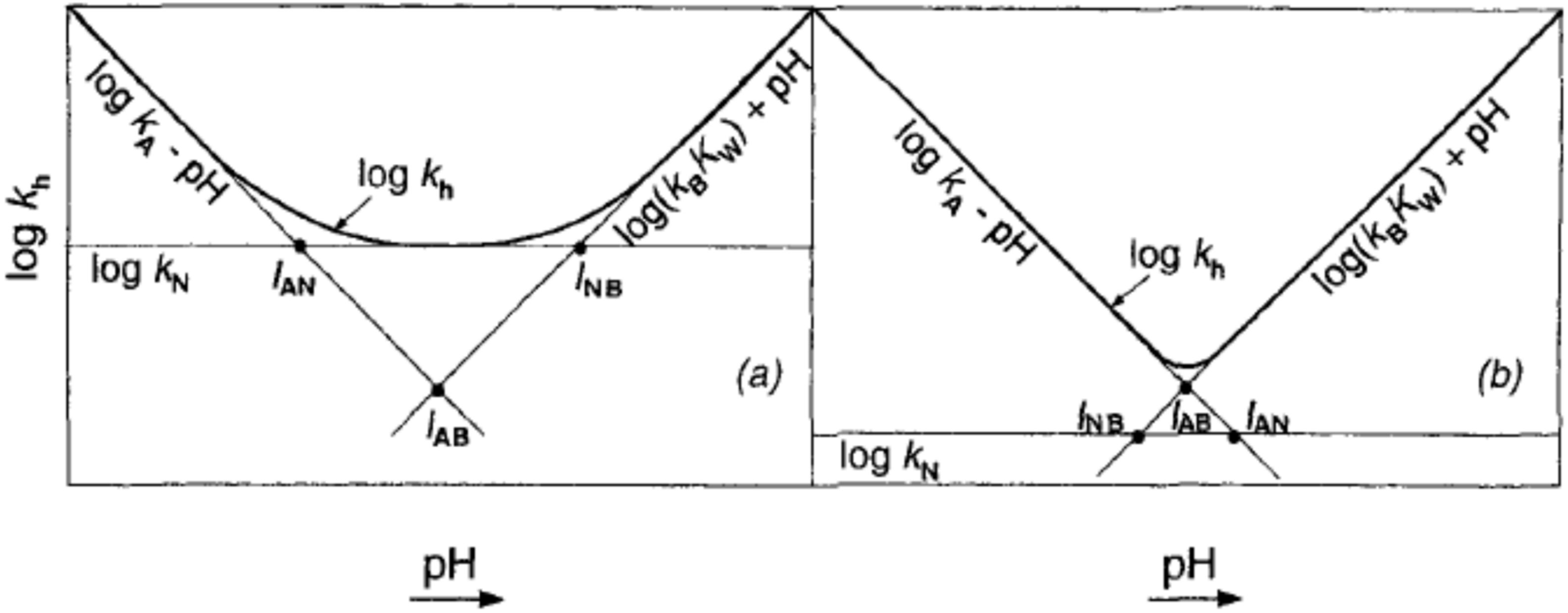
- ***k_h*: pseudo-first-order hydrolysis rate constant (s^{-1}), f(pH)**

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

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

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

Ester hydrolysis kinetics

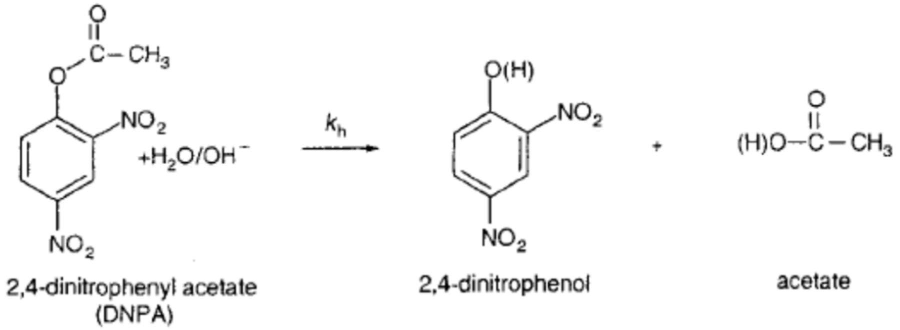


I_{IJ} = the pH value at which the rates for I and J reactions are the same

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

Ester hydrolysis kinetics

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



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}