

Nucleophilic reactions

Nucleophiles

- **Nucleophiles: nucleus-liking species**
 - 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 Environmental Nucleophiles

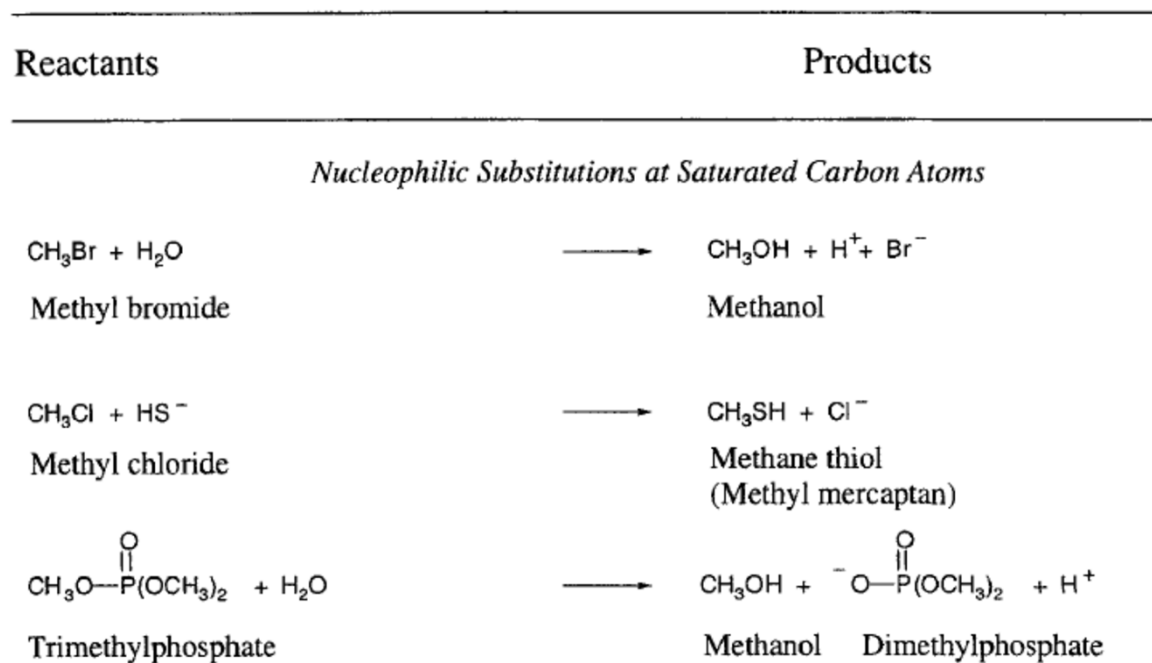
increasing nucleophilicity for reaction at a saturated carbon	ClO ₄ ⁻
	H ₂ O
	NO ₃ ⁻
	F ⁻
	SO ₄ ²⁻ , CH ₃ COO ⁻
	Cl ⁻
	HCO ₃ ⁻ , HPO ₃ ²⁻
	NO ₂ ⁻
	PhO ^{-a} , Br ⁻ , OH ⁻
	I ⁻ , CN ⁻
	HS ⁻ , R ₂ NH ^b
	S ₂ O ₃ ²⁻ , SO ₃ ²⁻ , PhS ⁻

^a Ph = C₆H₅ (phenyl)

^b R = CH₃, C₂H₅

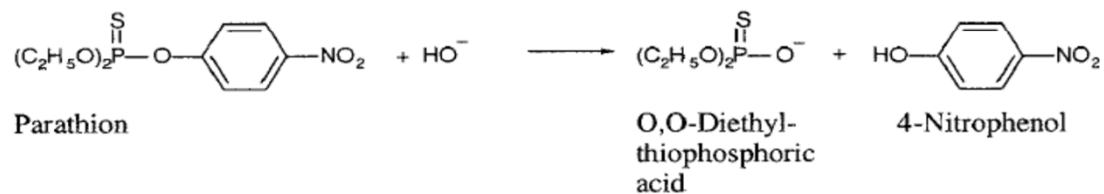
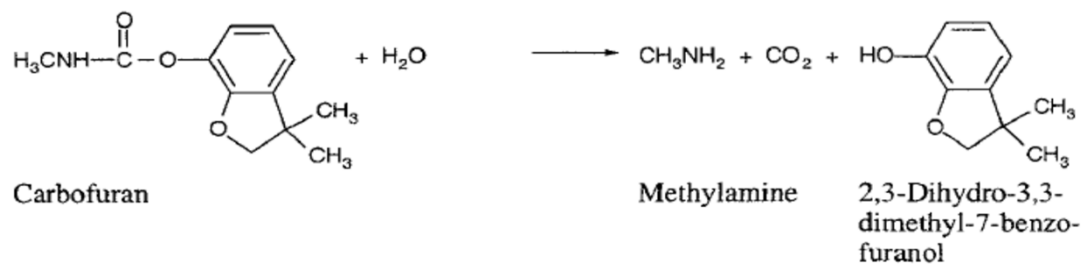
Nucleophilic reactions

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



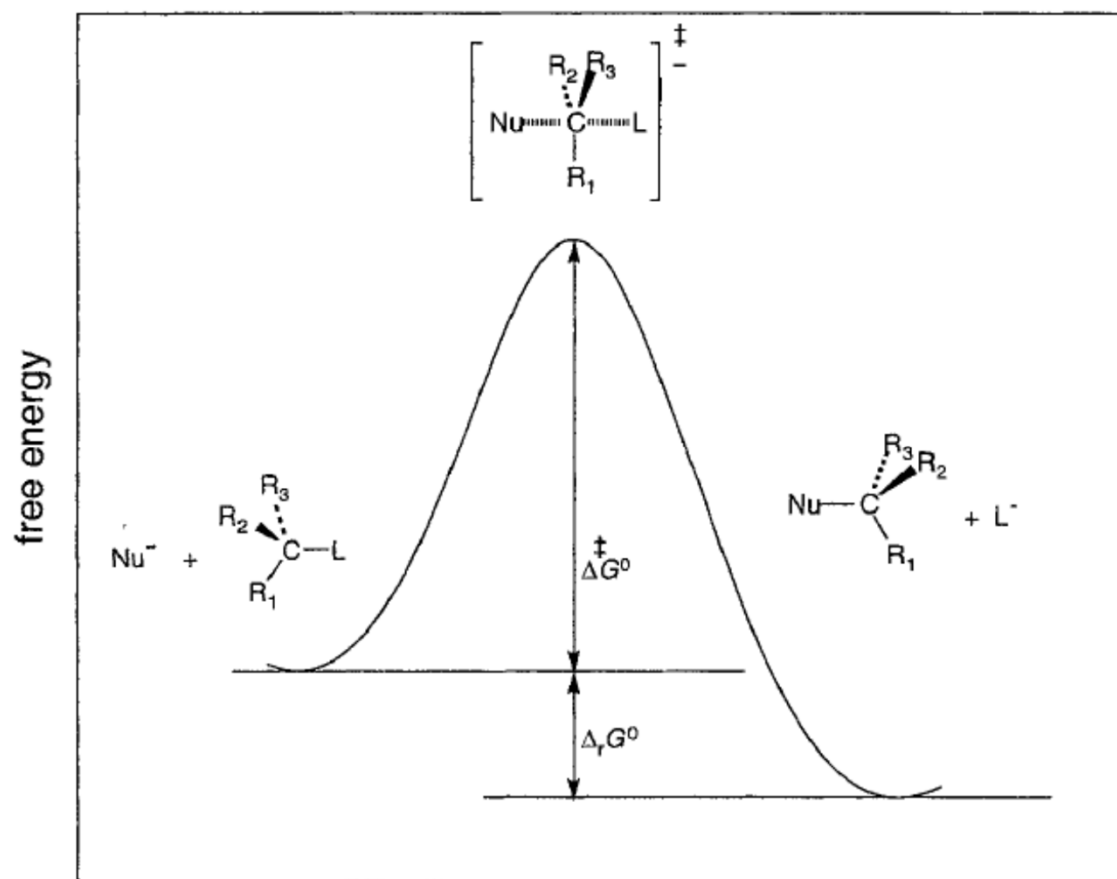
Reactants

Products

 β -Elimination*Ester Hydrolysis**Carbamate Hydrolysis*

Nucleophilic substitution at saturated carbon atoms

- S_N2 mechanism



Nucleophilic substitution at saturated carbon atoms

- **S_N2 mechanism**

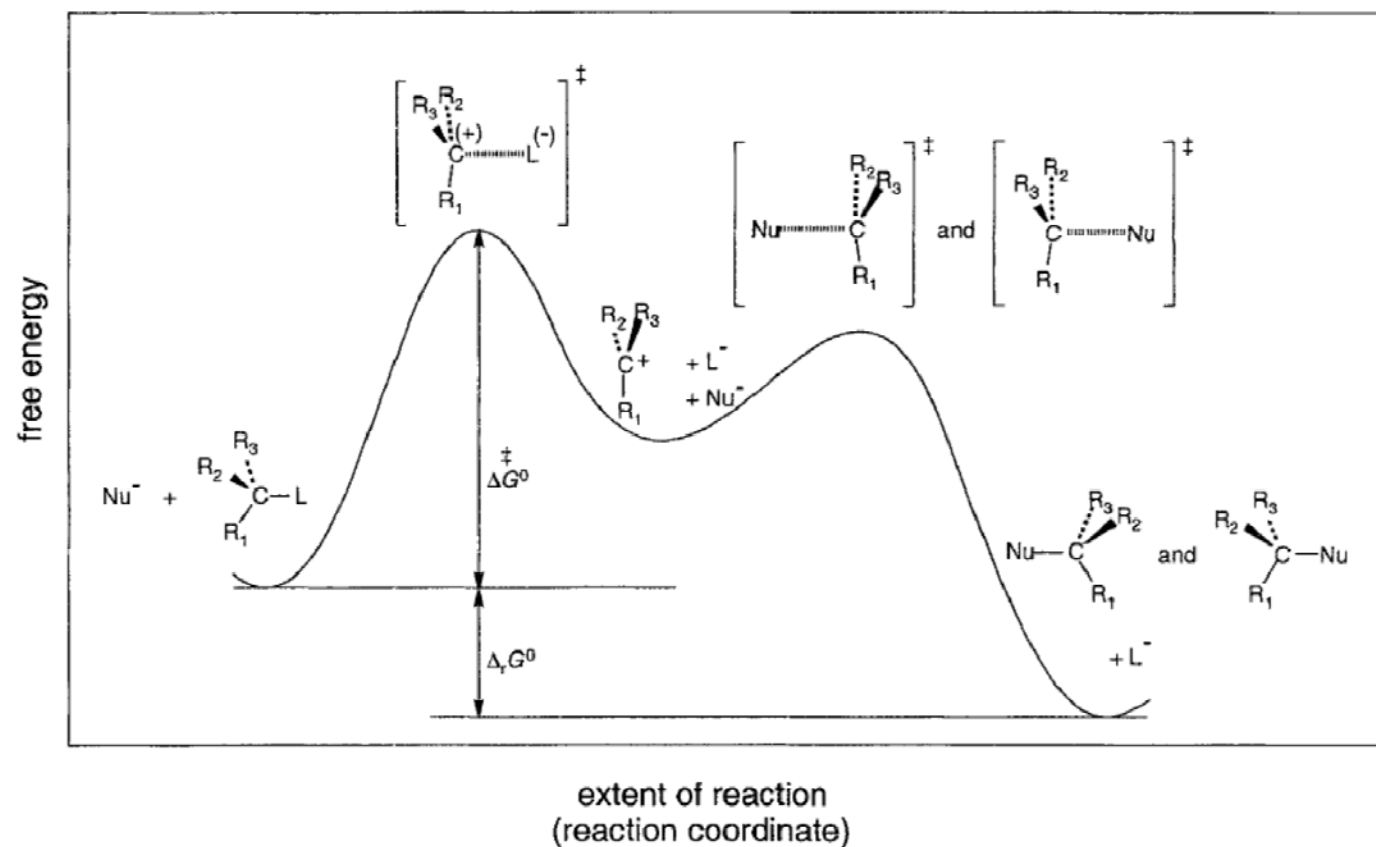
- Substitution, nucleophilic, bimolecular
- The standard free energy of activation $\Delta^\ddagger G^0$ (which controls the reaction rate) depends strongly on both the capability of the nucleophile to initiate a substitution reaction and the willingness of the organic molecule to undergo that reaction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

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

$k = 2^{\text{nd}}$ 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 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:

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

$k = 1^{\text{st}}$ 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):

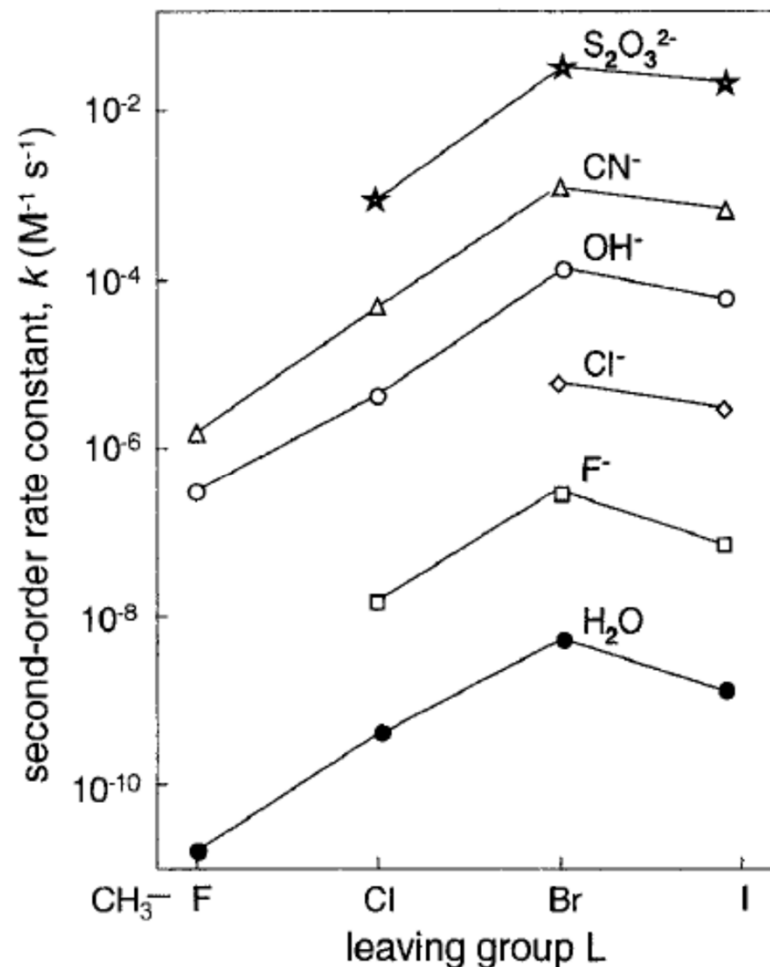
$$\log \left(\frac{k_{Nu}}{k_{H_2O}} \right) = s \cdot n_{Nu,CH_3Br}$$

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:

$$n_{Nu,CH_3Br} = \log \left[\frac{(k_{Nu})_{CH_3Br}}{(k_{H_2O})_{CH_3Br}} \right] \quad * \text{ so, } n_{H_2O,CH_3Br} = 0$$

- 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 & $[Nu]$

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

- H₂O abundant ($[H_2O] \uparrow$), so a nucleophile should compete with hydrolysis
- For a reaction to have the same rate as hydrolysis:

$$[Nu]k_{Nu} = [H_2O]k_{H_2O}$$

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

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

$[Nu]_{50\%} = [Nu]$ to get the same rate as the hydrolysis rate by H₂O

55.3 = molar concentration of water (M)

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 ⁻	~6 × 10 ⁻¹
SO ₄ ²⁻	~2 × 10 ⁻¹
Cl ⁻	~6 × 10 ⁻²
HCO ₃ ⁻	~9 × 10 ⁻³
HPO ₄ ⁻	~9 × 10 ⁻³
Br ⁻	~7 × 10 ⁻³
OH ⁻	~4 × 10 ⁻³
I ⁻	~6 × 10 ⁻⁴
HS ⁻	~4 × 10 ⁻⁴
CN ⁻	~4 × 10 ⁻⁴
S ₂ O ₃ ²⁻	~4 × 10 ⁻⁵
S ₄ ²⁻	~4 × 10 ⁻⁶

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

S_N2 : competition of nucleophiles

- **Freshwater vs. saline water**
 - Freshwater $[Cl^-] \sim 10^{-4} \text{ M} \rightarrow Cl^-$ not a significant nucleophile
 - Seawater $[Cl^-] \sim 0.5 \text{ M} \rightarrow Cl^-$ a significant nucleophile
- **pH sensitivity of hydrolysis reaction**
 - Low & neutral pH $\rightarrow OH^-$ not a significant nucleophile
 - High pH (e.g., pH>11) $\rightarrow OH^-$ 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., $< 0.01\text{mM}$) in a homogeneous aqueous solution ($\text{pH}=7.0$, $T=25^\circ\text{C}$) containing 100 mM Cl^- , 2 mM NO_3^- , 1 mM HCO_3^- , and 0.1 mM CN^- . In pure water at $\text{pH } 7.0$ and 25°C , the half-life of CH_3Br is about 20 days.

S_N1 & S_N2 : Leaving groups

- Reaction rates for methyl halides: $\text{CH}_3\text{Br} \sim \text{CH}_3\text{I} > \text{CH}_3\text{Cl} > \text{CH}_3\text{F}$

- What makes one a good leaving group??

1) The one having smaller $n_{\text{Nu},\text{CH}_3\text{Br}}$ (a weaker nucleophile)

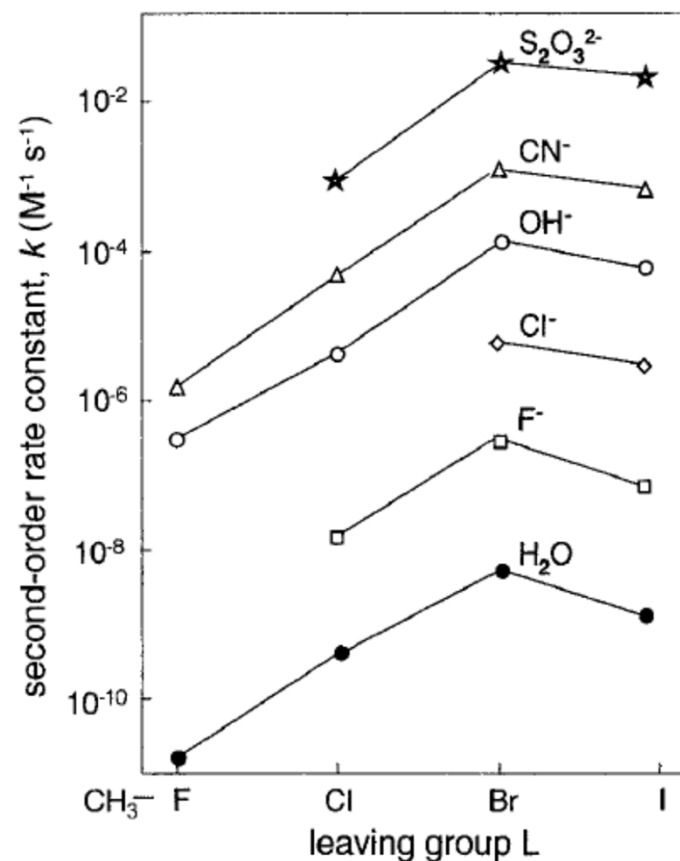
but $n_{\text{Nu},\text{CH}_3\text{Br}}$ is in the order of:

$\text{F}^- < \text{Cl}^- < \text{Br}^- < \text{I}^-$

2) The one bonded weakly to carbon

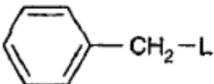
C-X bond strength is in the order of:

$\text{CH}_3\text{I} < \text{CH}_3\text{Br} < \text{CH}_3\text{Cl} < \text{CH}_3\text{F}$



S_N1 & S_N2 : Effect of EDGs & resonance

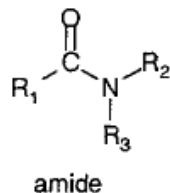
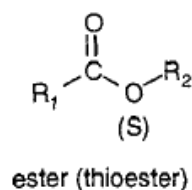
Table 13.6 Hydrolysis Half-Lives and Postulated Reaction Mechanisms at 25°C of Some Monohalogenated Hydrocarbons at Neutral pH ^a

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
$\begin{array}{c} H_3C \\ \\ CH-L \\ \\ H_3C \end{array}$	secondary		38 d	2 d	3 d	$S_N2 \dots S_N1$
$\begin{array}{c} CH_3 \\ \\ H_3C-C-L \\ \\ CH_3 \end{array}$	tertiary	50 d	23 s			S_N1
$CH_2=CH-CH_2-L$	allyl		69 d	0.5 d	2 d	$S_N2 \dots S_N1$
	benzyl		15 h	0.4 h		$S_N2 \dots S_N1$

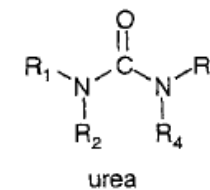
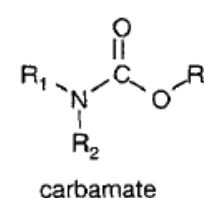
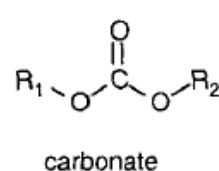
^a Data taken from Robertson (1969) and Mabey and Mill (1978). ^b R = H. ^c R = H, C₁ to C₅-*n*-alkyl. ^d R = H, CH₃.

Hydrolysis of carboxylic & carbonic acid derivatives

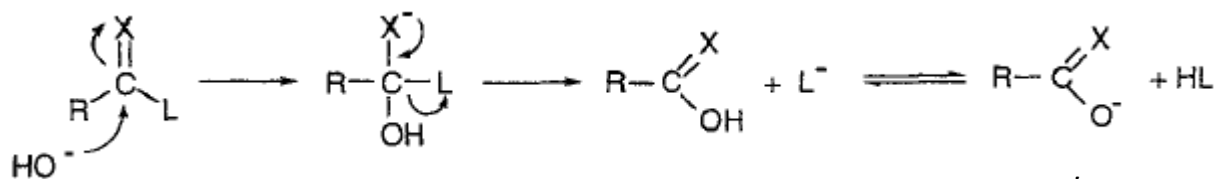
- Carboxylic acid derivatives



- Carbonic acid derivatives



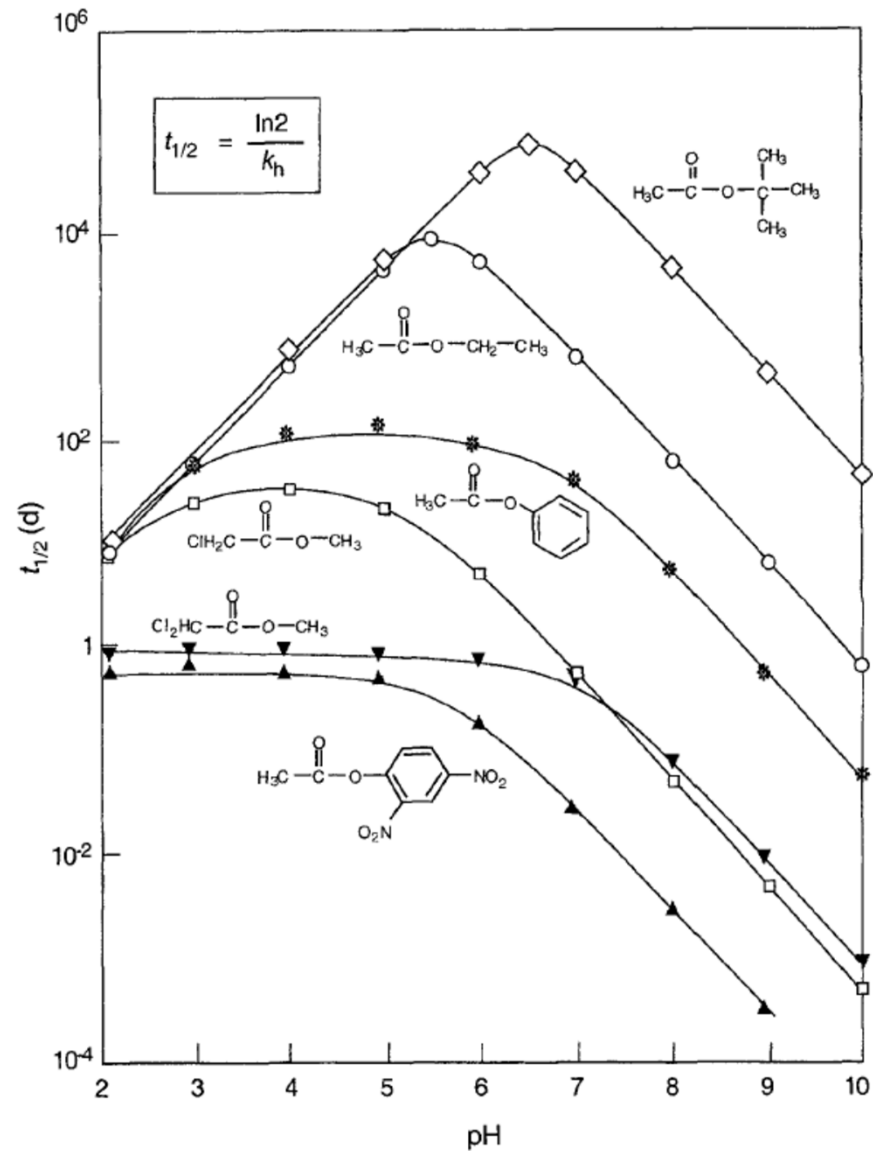
- Unsaturated, electron-deficient C
- Reacts predominantly with H_2O & OH^- (hydrolysis)
- General reaction mechanism



* Here, X = O, S, or NR

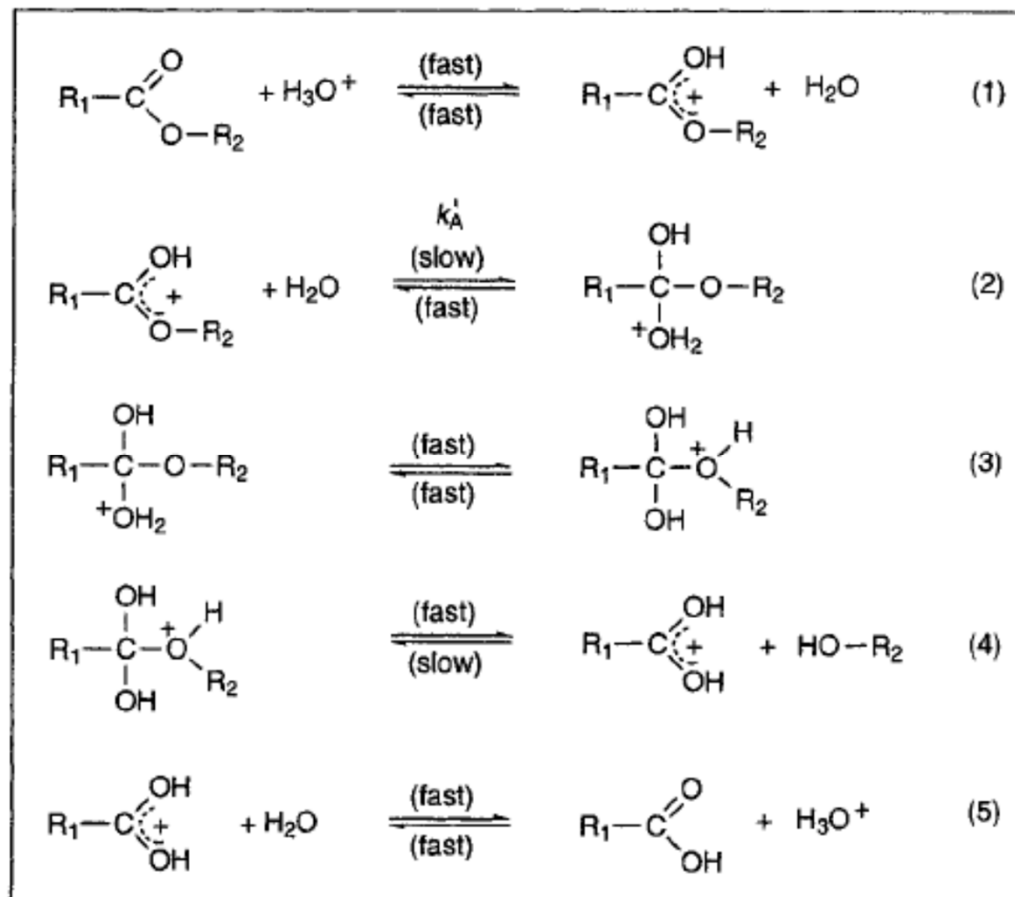
Hydrolysis of Esters

- Three mechanisms:
 - 1) acid-catalyzed
 - 2) neutral
 - 3) base-catalyzed
- Importance of each reaction depends on the structure of the reactant



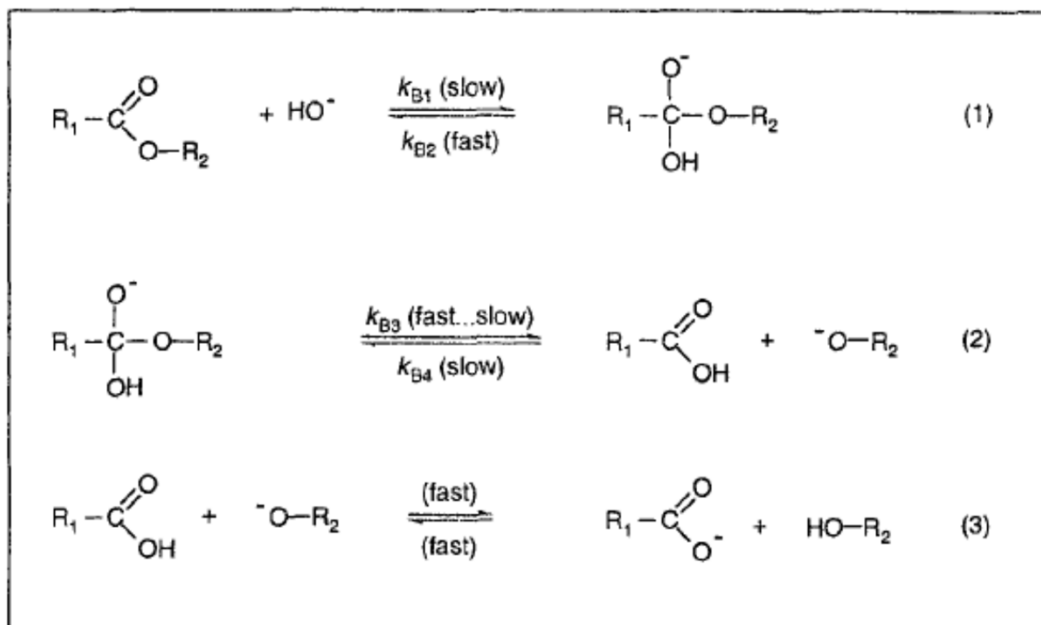
Ester hydrolysis: acid-catalyzed

- Ester carbon is protonated
 → enhanced depletion of electrons near the carbon
 → ester carbon gets more susceptible to H₂O attack
- Reaction (2) is rate limiting
- Reaction rate depends on:
 - k_A'
 - K_a of the protonated ester
 - $[H^+]$



Ester hydrolysis: base-catalyzed

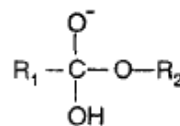
- (1) only or both (1) & (2) can be rate-limiting



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

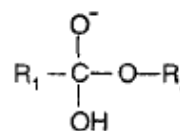
If only (1) is rate-limiting:

– Depends on the formation of



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

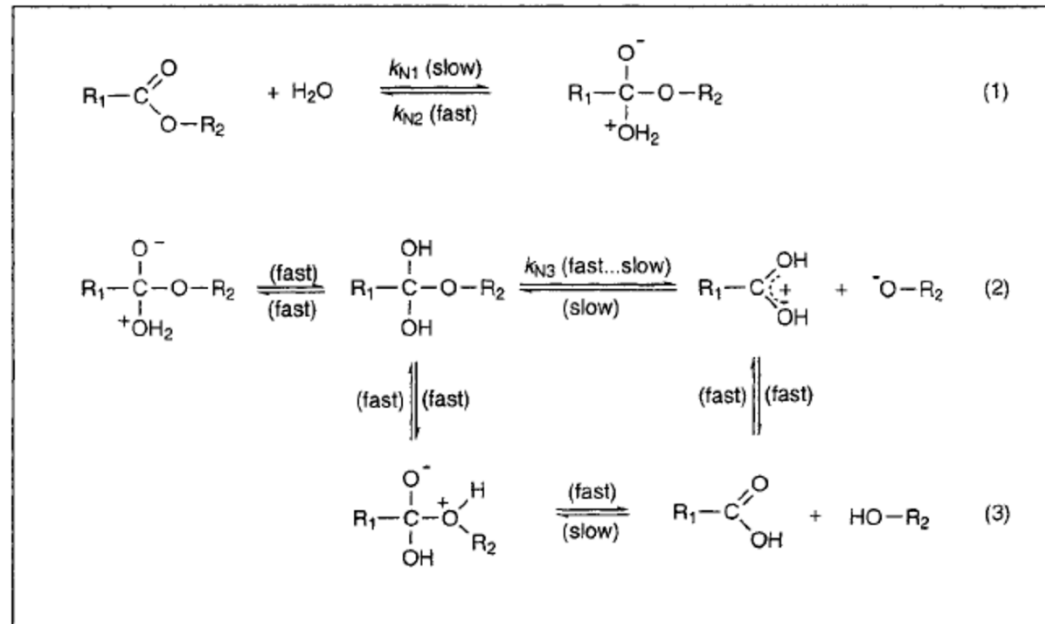
– Depends on the formation of



& the property of the leaving group

Ester hydrolysis: neutral

- Similar to base-catalyzed
- The property of the leaving group is more important for H₂O (weaker nucleophile) than OH⁻



Ester hydrolysis kinetics

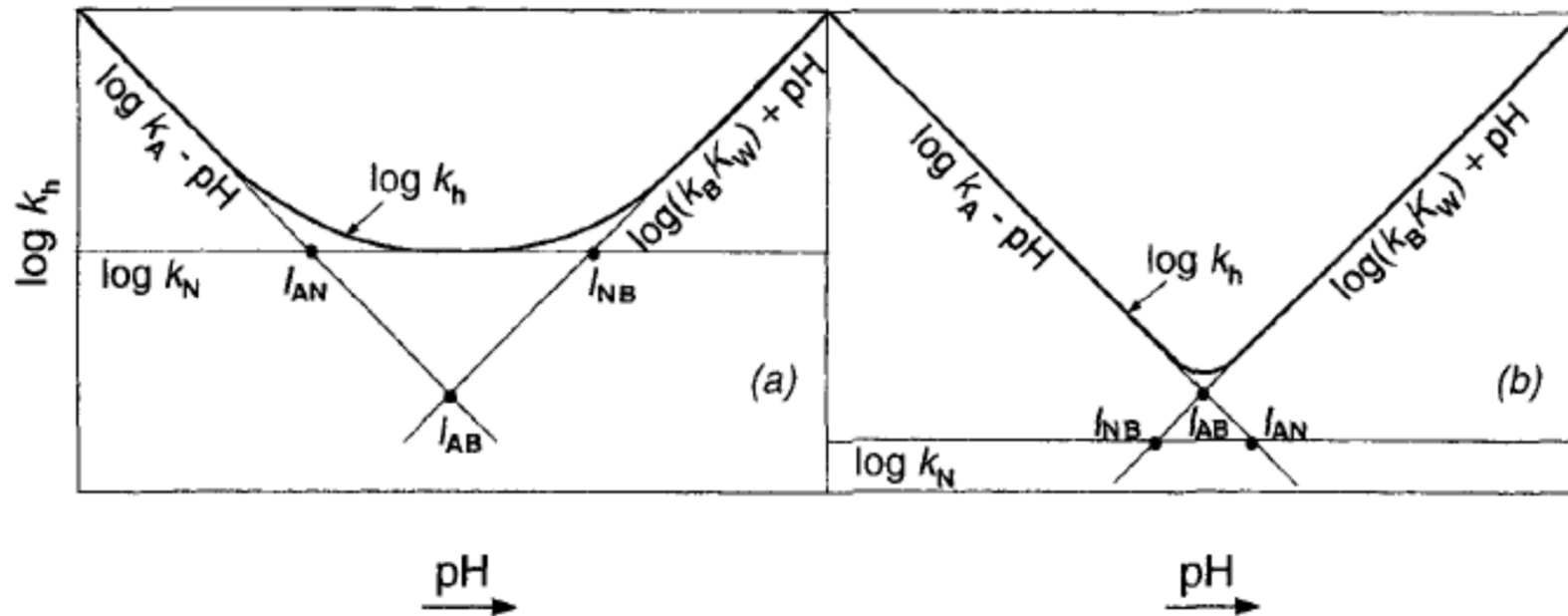
- k_h : pseudo-first-order hydrolysis rate constant (s^{-1}), f(pH)

$$\begin{aligned}k_h &= k_A[H^+] + k_{H_2O}[H_2O] + k_B[OH^-] \\ &= k_A[H^+] + k_N + k_B[OH^-]\end{aligned}$$

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

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

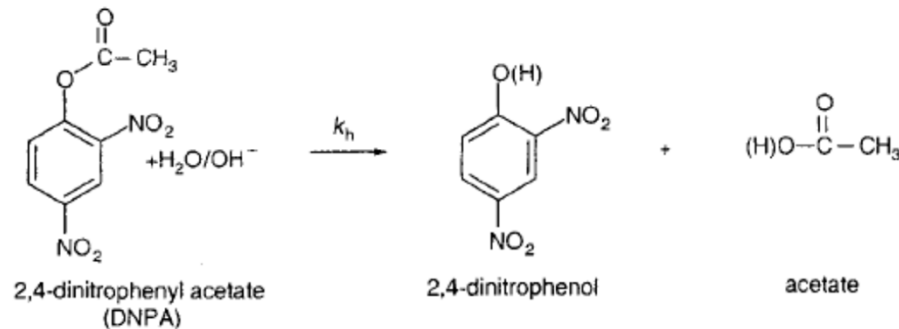
Ester hydrolysis kinetics



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°C. 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}