# 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

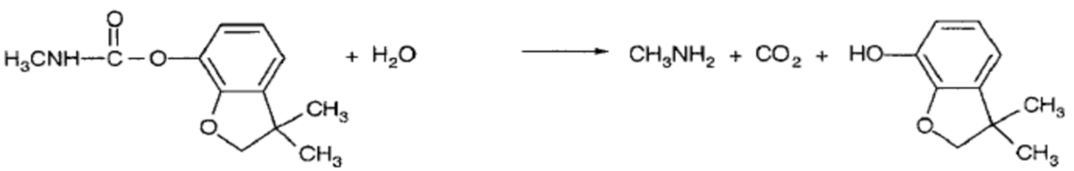
- Examples of environmentally relevant chemical reactions involving nucleophiles and/or bases

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

| Reactants | | Products |
|---|---|---|
| | ***β*-Elimination** | |
| $Cl_2HC{-}CHCl_2 + HO^-$<br>1,1,2,2-Tetrachloroethane | ⟶ | $Cl_2C{=}CHCl + Cl^- + H_2O$<br>Trichloroethene |
| | ***Ester Hydrolysis*** | |
| $H_3C{-}C({=}O){-}OCH_2CH_3 + H_2O$<br>Ethyl acetate<br>(Acetic acid ethylester) | ⟶ | $H_3C{-}C({=}O){-}O^-$ + $HO{-}CH_2CH_3$ + $H^+$<br>Acetate, Ethanol |


Parathion — O,O-Diethyl-thiophosphoric acid, 4-Nitrophenol

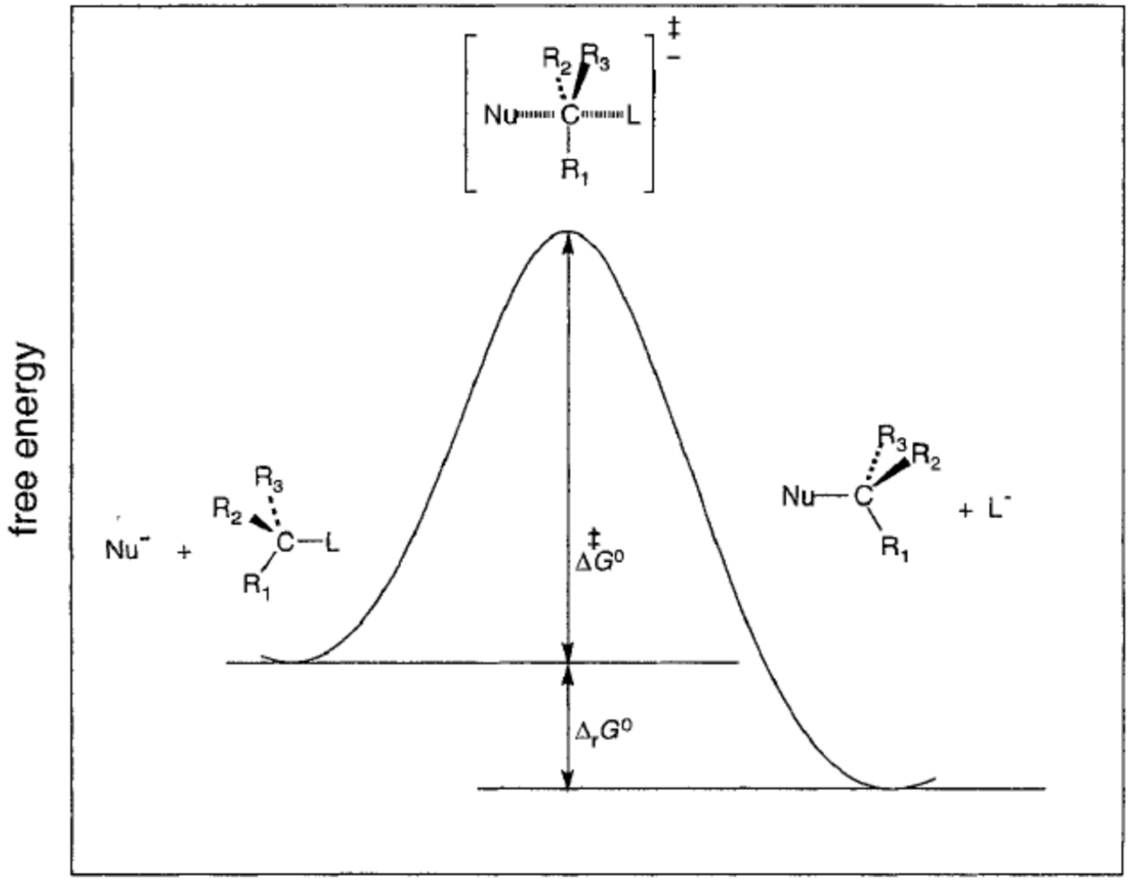
***Carbamate Hydrolysis***




Carbofuran — Methylamine, 2,3-Dihydro-3,3-dimethyl-7-benzo-furanol

# Nucleophilic substitution at saturated carbon atoms

- **$S_N2$ mechanism**



# Nucleophilic substitution at saturated carbon atoms

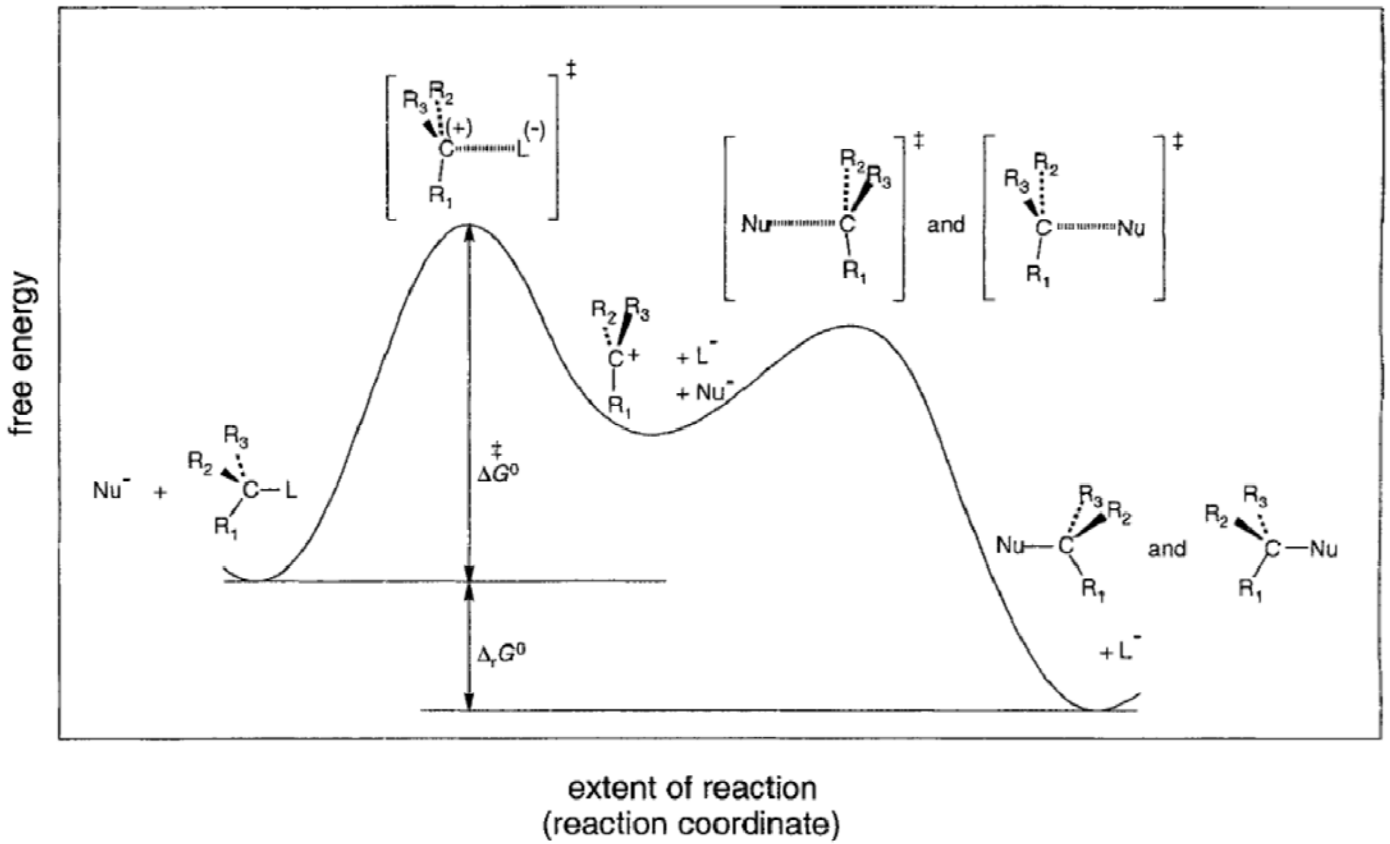
- **$S_N2$ mechanism**
  - Substitution, nucleophilic, bimolecular
  - The standard free energy of activation $\Delta^{\ddagger}G^0$ (which controls the reaction rate) depends strongly on both <u>the capability of the nucleophile to initiate a substitution reaction</u> and <u>the willingness of the organic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

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

$k$ = $2^{nd}$ 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
  - $\Delta^{‡}G^0$ 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):

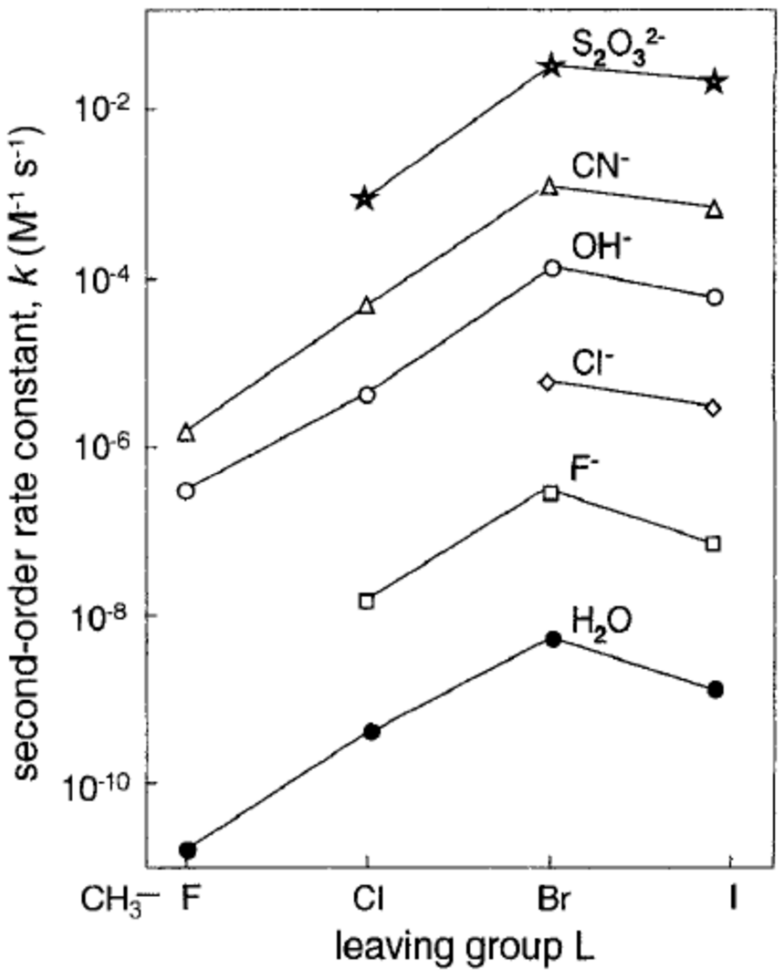
$$log\left(\frac{k_{Nu}}{k_{H_2O}}\right) = s \cdot n_{Nu,CH_3Br}$$

*$k_{Nu}$ = 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]

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

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

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

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

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 |
| $F^-$ | $\sim 6 \times 10^{-1}$ |
| $SO_4^{2-}$ | $\sim 2 \times 10^{-1}$ |
| $Cl^-$ | $\sim 6 \times 10^{-2}$ |
| $HCO_3^-$ | $\sim 9 \times 10^{-3}$ |
| $HPO_4^-$ | $\sim 9 \times 10^{-3}$ |
| $Br^-$ | $\sim 7 \times 10^{-3}$ |
| $OH^-$ | $\sim 4 \times 10^{-3}$ |
| $I^-$ | $\sim 6 \times 10^{-4}$ |
| $HS^-$ | $\sim 4 \times 10^{-4}$ |
| $CN^-$ | $\sim 4 \times 10^{-4}$ |
| $S_2O_3^{2-}$ | $\sim 4 \times 10^{-5}$ |
| $S_4^{2-}$ | $\sim 4 \times 10^{-6}$ |

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

# $S_N2$: competition of nucleophiles

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

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| $HCO_3^-$ | $\sim 9 \times 10^{-3}$ |
| $HPO_4^-$ | $\sim 9 \times 10^{-3}$ |
| $Br^-$ | $\sim 7 \times 10^{-3}$ |
| $OH^-$ | $\sim 4 \times 10^{-3}$ |
| $I^-$ | $\sim 6 \times 10^{-4}$ |
| $HS^-$ | $\sim 4 \times 10^{-4}$ |
| $CN^-$ | $\sim 4 \times 10^{-4}$ |
| $S_2O_3^{2-}$ | $\sim 4 \times 10^{-5}$ |
| $S_4^{2-}$ | $\sim 4 \times 10^{-6}$ |

[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: $CH_3Br \sim CH_3I > CH_3Cl > CH_3F$

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

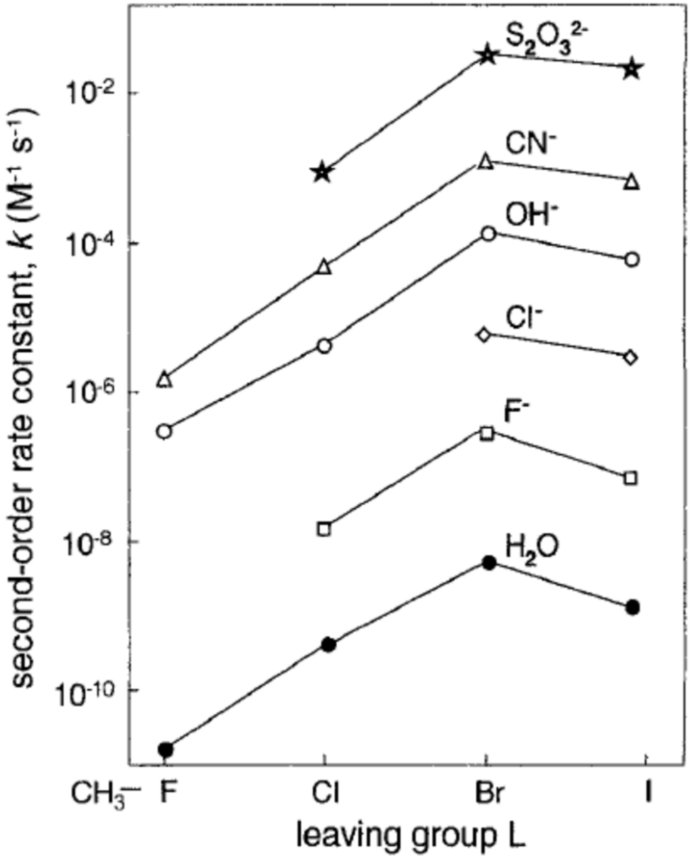
  1) The one having smaller $n_{Nu,CH_3Br}$ (a weaker nucleophile)

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

  2) The one bonded weakly to carbon

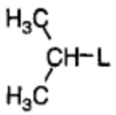
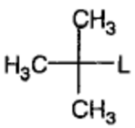
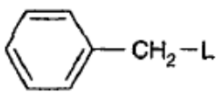
  *C-X bond strength is in the order of:*
  *$CH_3I < CH_3Br < CH_3Cl < CH_3F$*

  More significant!



# $S_N1$ & $S_N2$: Effect of EDGs & resonance

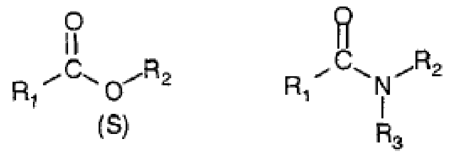
**Table 13.6** Hydrolysis Half-Lives and Postulated Reaction Mechanisms at 25°C of Some Monohalogenated Hydrocarbons at Neutral pH [a]

| 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] | $S_N2$ |
|  | secondary | | 38 d | 2 d | 3 d | $S_N2 \ldots S_N1$ |
|  | tertiary | 50 d | 23 s | | | $S_N1$ |
| $CH_2=CH-CH_2-L$ | allyl | | 69 d | 0.5 d | 2 d | $S_N2 \ldots S_N1$ |
|  | 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, $CH_3$.

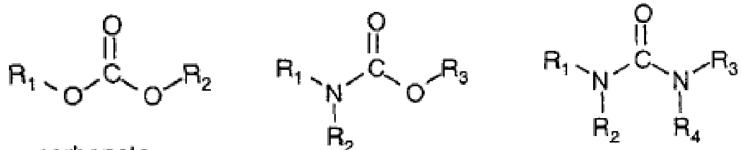
# Hydrolysis of carboxylic & carbonic acid derivatives

- Carboxylic acid derivatives



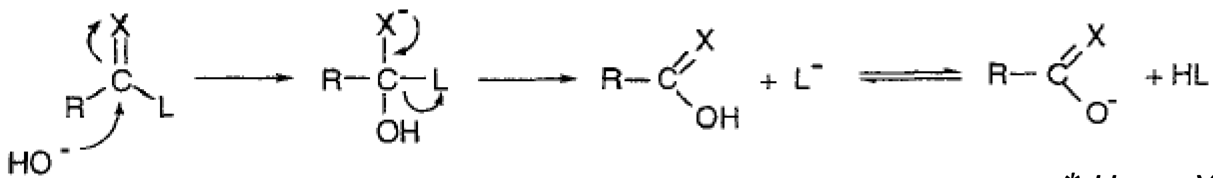

ester (thioester) amide

- Carbonic acid derivatives




carbonate carbamate urea

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

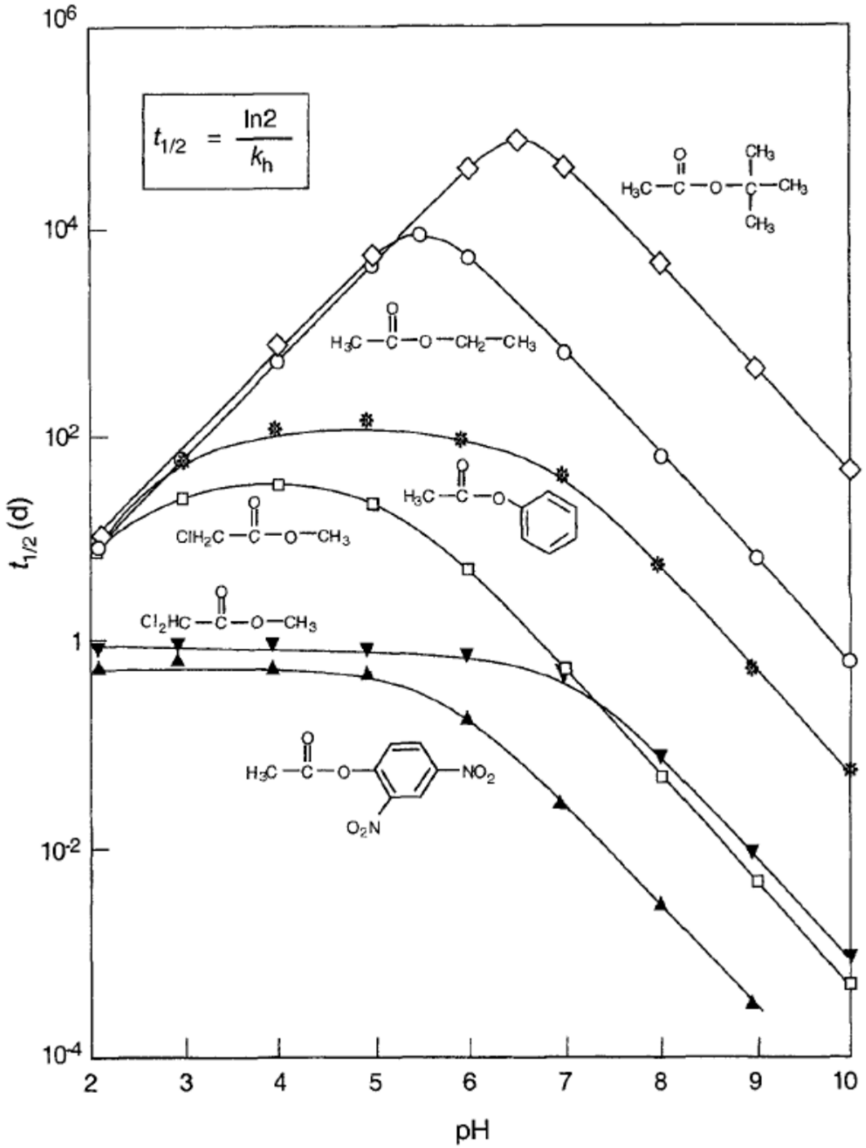



** Here, X = O, S, or NR*

# Hydrolysis of Esters

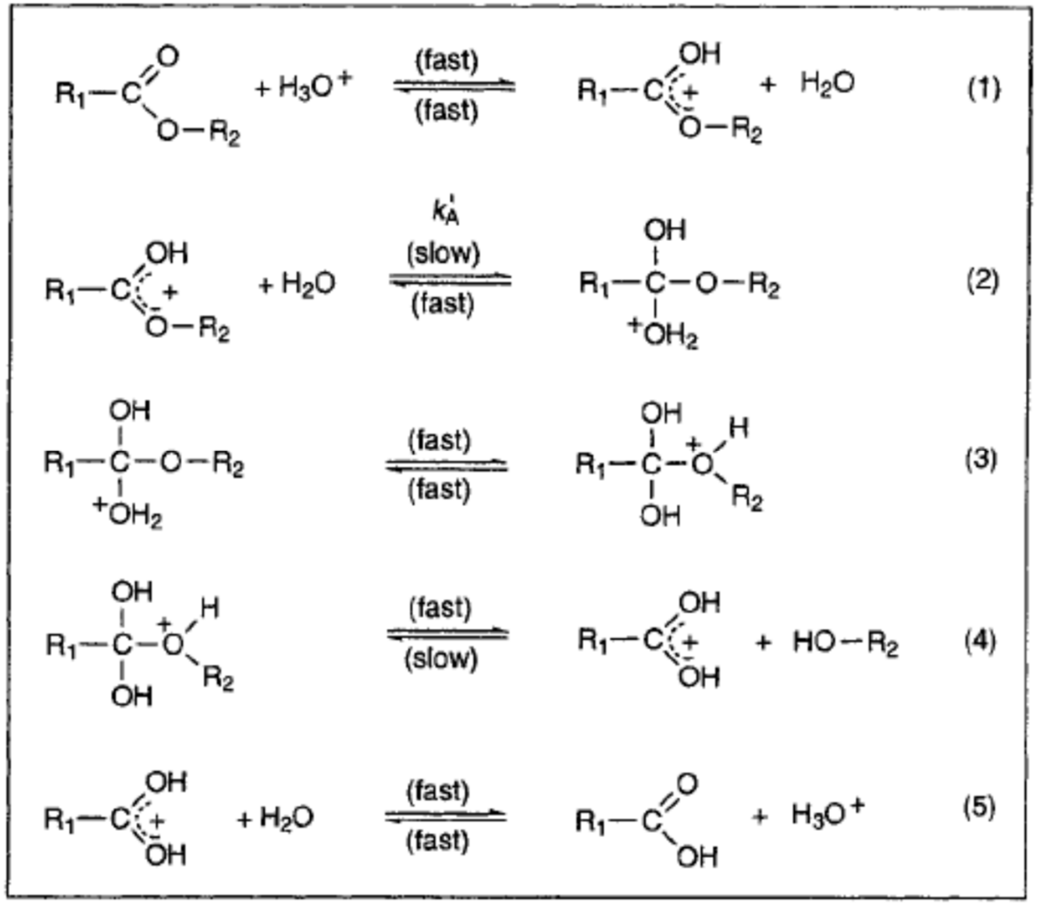
- Three mechanisms:
  1) **acid-catalyzed**
  2) **neutral**
  3) **base-catalyzed**

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



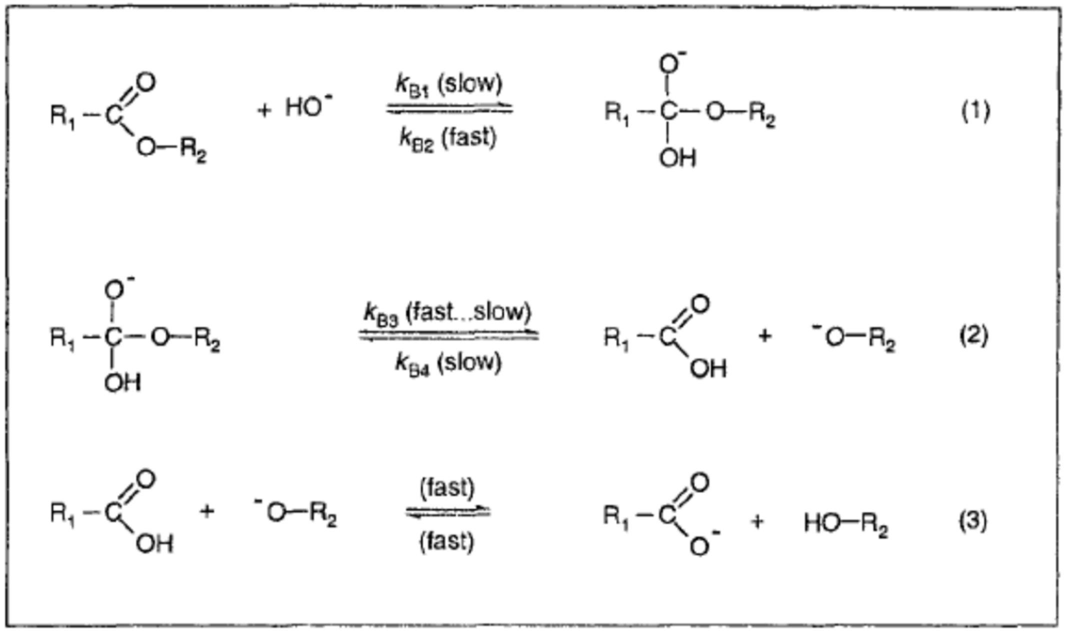
# Ester hydrolysis: acid-catalyzed

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



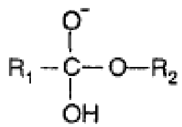
# Ester hydrolysis: base-catalyzed

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

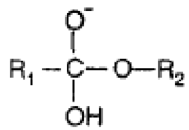



- Rate depends on **<u>[OH⁻]</u>** and in addition:

  If only (1) is rate-limiting:

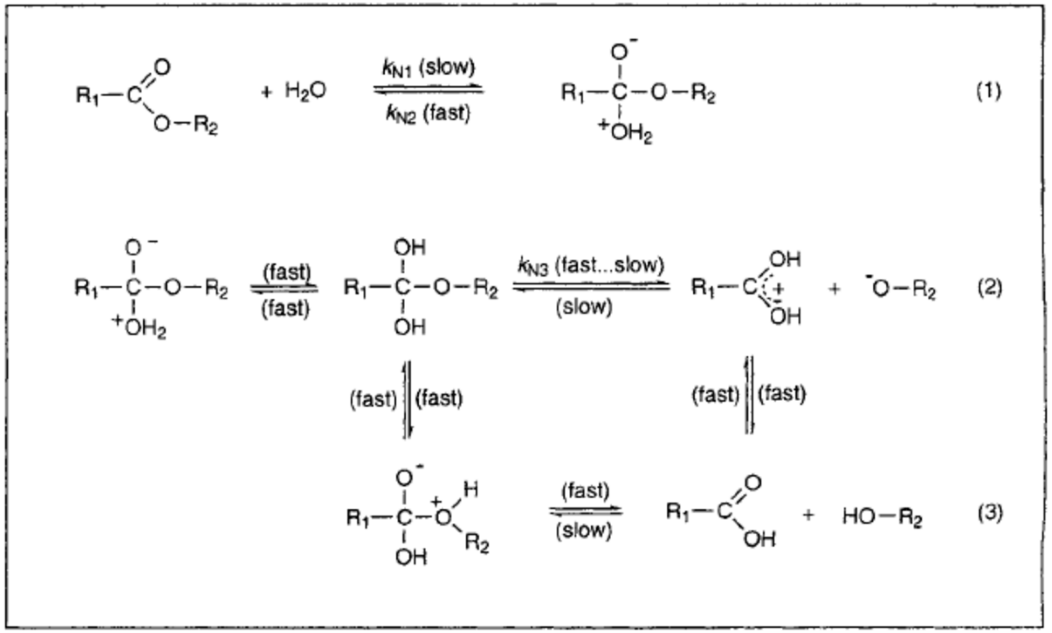
  – Depends on the formation of 

  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 $H_2O$ (weaker nucleophile) than $OH^-$



# Ester hydrolysis kinetics

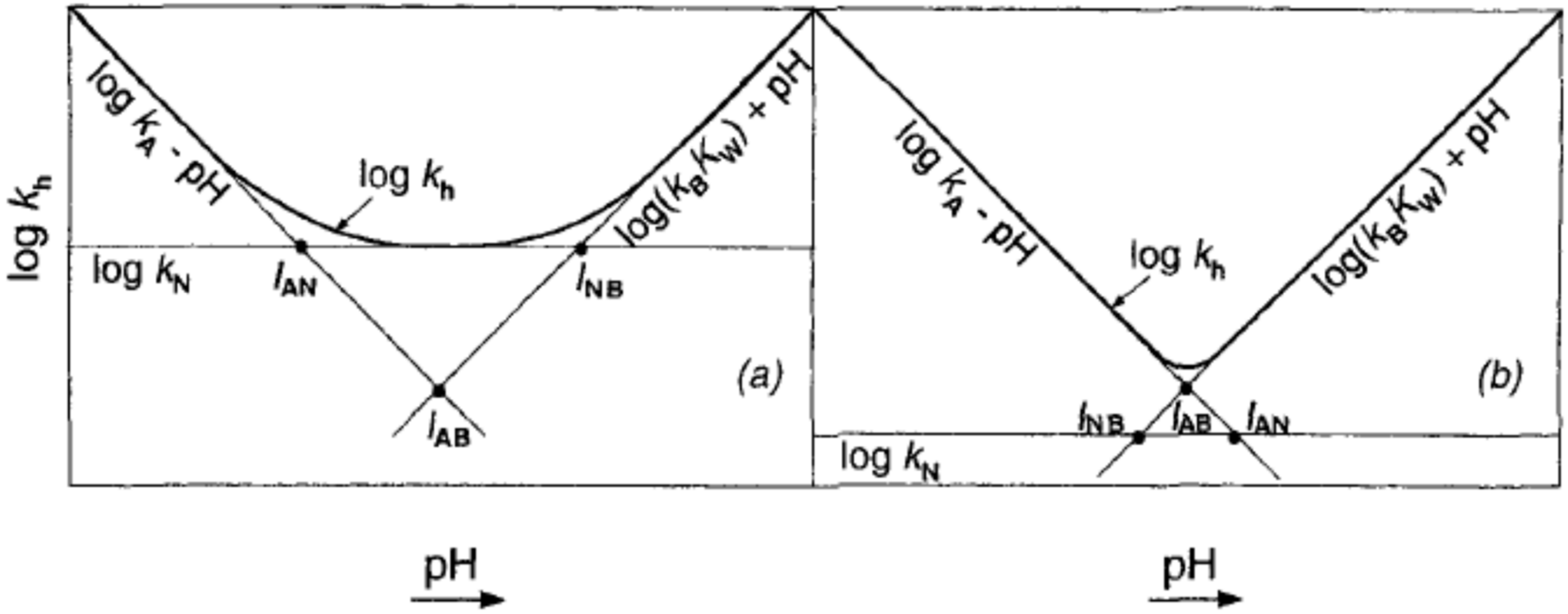
- ***$k_h$*: pseudo-first-order hydrolysis rate constant ($s^{-1}$), f(pH)**

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

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

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

# Ester hydrolysis kinetics

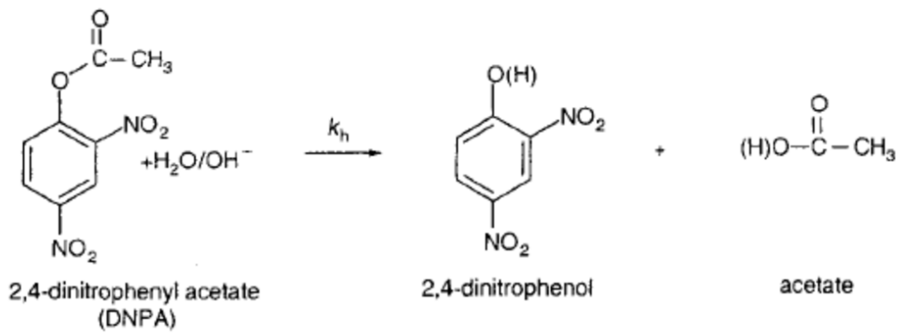



***$I_{IJ}$ = the pH value at which the rates for I and J reactions are the same***

*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$^o$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** |
|---|---|---|---|---|
| **$k_h$ ($s^{-1}$)** | **$4.3 \times 10^{-5}$** | **$4.5 \times 10^{-5}$** | **$4.4 \times 10^{-5}$** | **$5.1 \times 10^{-4}$** |