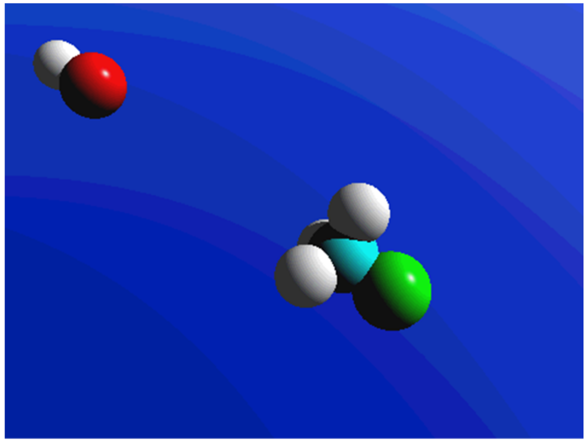
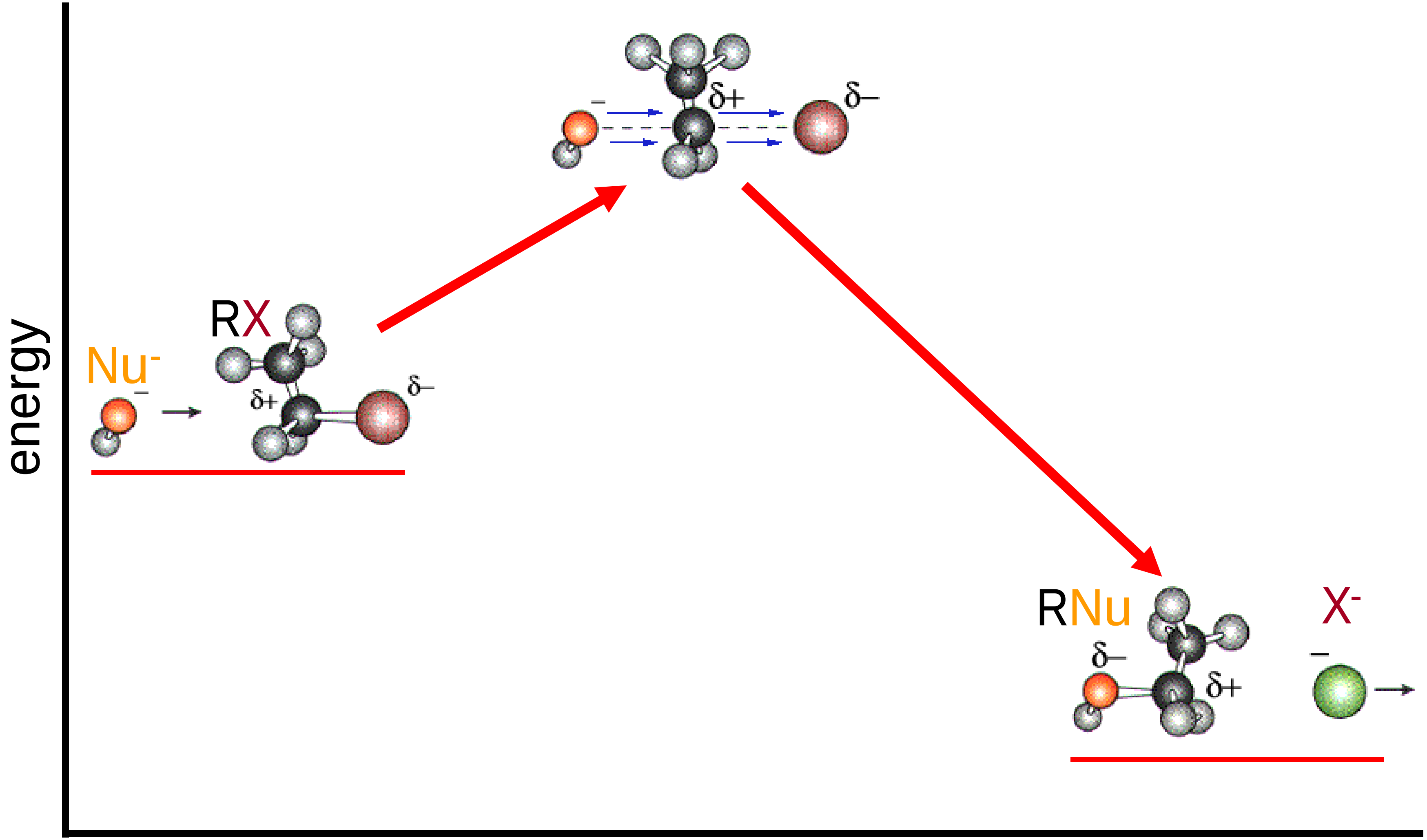
Nucleophilic Substitution



- Reaction

  RX + Nu = RNu + X
- nucleophile, Nu
  - species attracted to nucleus (δ^+ region)
  - negatively charged or non-bonded electrons
  - generally abundant in aqueous environments
- leaving group, X
  - nucleophile substitutes for leaving group
  - leaves with extra electron
  - negatively charged or non-bonded electrons
  - typically not as nucleophilic as nucleophile

Nucleophilic Substitution



Nucleophilic Substitution

- Relative nucleophilicities (***n***)
  - based on kinetics of reaction with methyl bromide

$$CH_3Br + Nu^- \rightleftarrows CH_3Nu + Br^-$$

  - *n* related to electronegativity of Nu

Nu	***n***
ClO_4^-	<0
H_2O	0.0
NO_3^-	1.0
F^-	2.0
SO_4^{2-}	2.5
CH_3COO^-	2.7
Cl^-	3.0
HCO_3^-	3.8
HPO_4^{2-}	3.8
Br^-	3.9
OH^-	4.2
CN^-	5.0
I^-	5.0
HS^-	5.1

faster

Nucleophilic Substitution

- Relative leaving group effectiveness
  - lower pK_a → better able to accommodate negative charge → better leaving group

X	pK_a
I^- (HI)	~ -11
Br^- (HBr)	~ -9
Cl^- (HCl)	~ -7
F^- (HF)	3.17

$$CH_3Br + Nu^- = CH_3Nu + Br^-$$

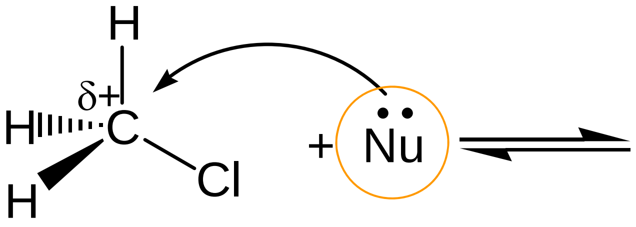
Nucleophilic Substitution

- Second order, S_N2
  - nucleophile initiates reaction
  - rate depends on nucleophile concentration

- First order, S_N1
  - leaving group initiates reaction
  - rate DOES NOT depend on nucleophile concentration

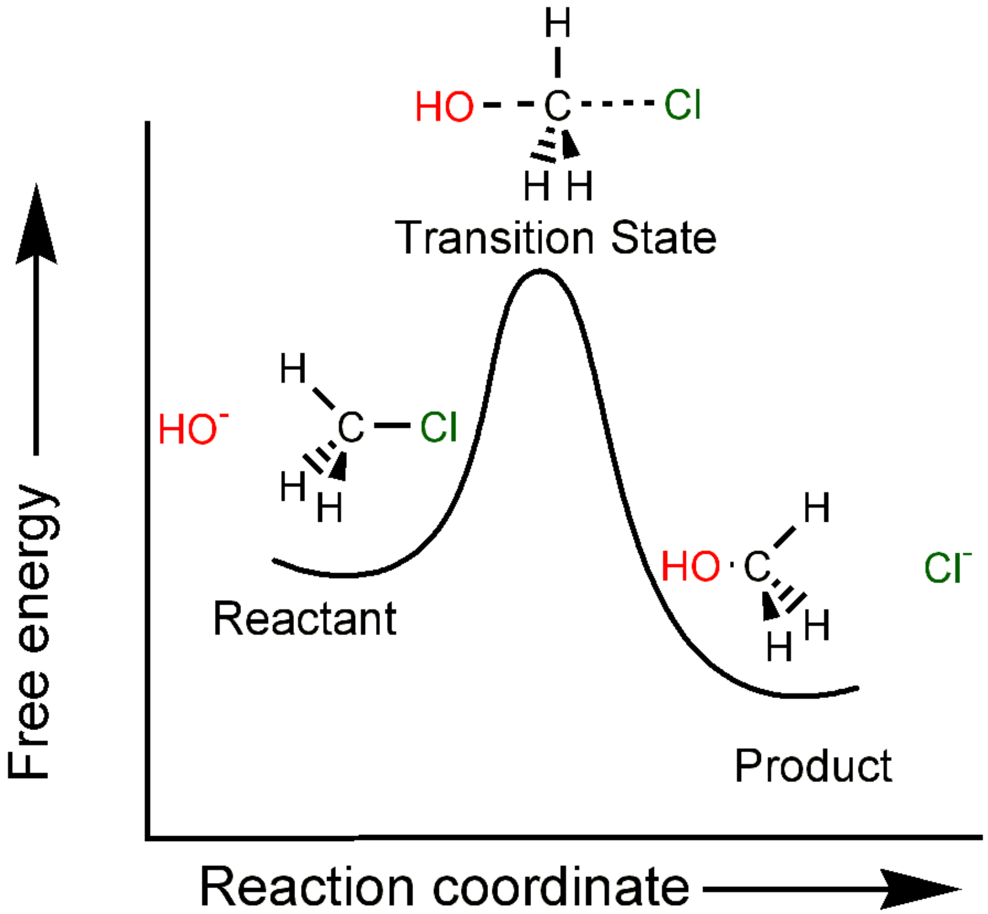
Nucleophilic Substitution

- Second order, S_N2
  - nucleophile bonds with δ^+ carbon
    - nucleophile supplies electrons for bond
    - creates high energy transition state
  - leaving group leaves δ^+ carbon
    - leaving group takes electrons from bond



Nucleophilic Substitution

- Transition state
  - both Nu and X are bonded to carbon
  - stability of transition state governs rate
    - stabile transition state = easy to form



Nucleophilic Substitution

- Second order, S_N2
  - kinetics
    - $CH_3Cl + Nu^- \rightleftarrows CH_3Nu + Cl^-$

$$\frac{d[CH_3Cl]}{dt} = -k_{S_N2}[CH_3Cl][Nu^-]$$

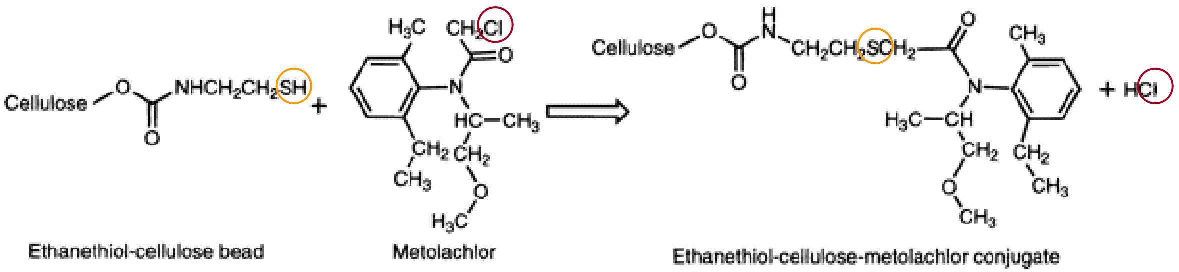
$$\frac{d[CH_3Cl]}{dt} = -k'[CH_3Cl]$$

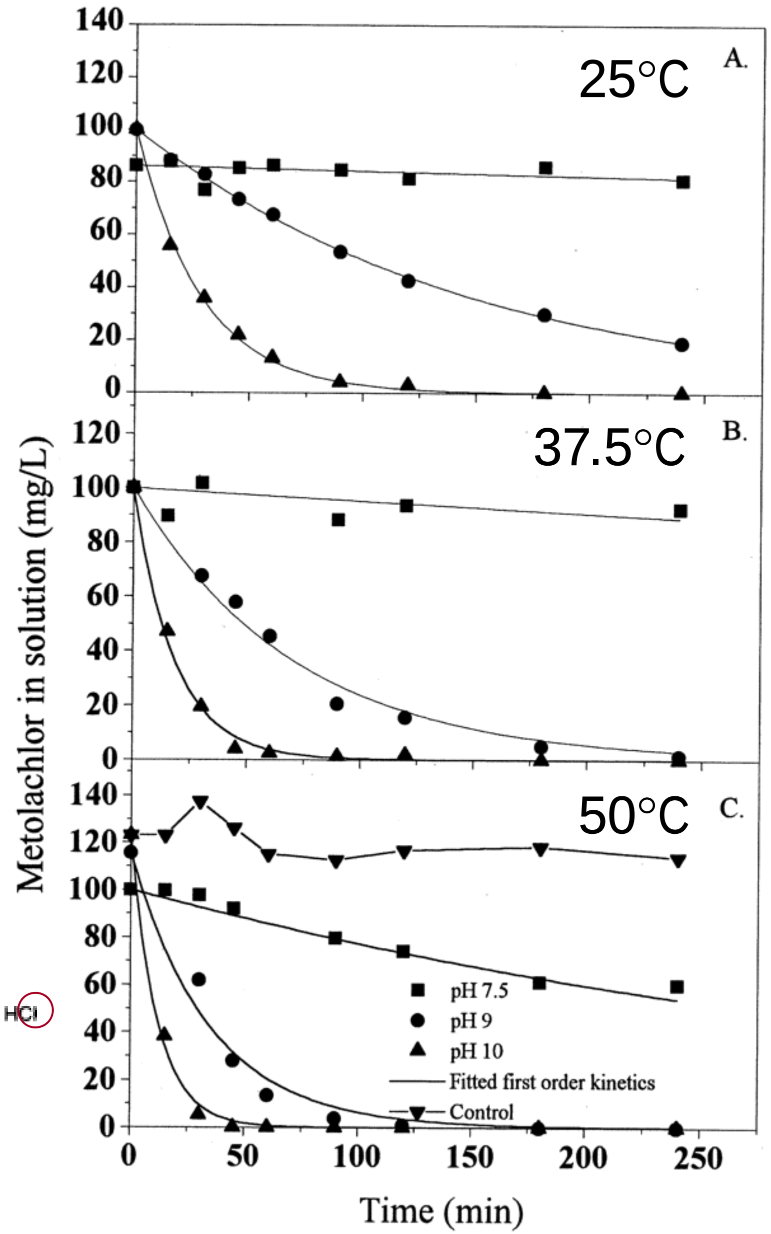
Nucleophilic Sub

- Metolachlor and thiol-derivatized beads

$$MCl + RSH \rightleftarrows M\text{-}SR + H^{+} + Cl^{-}$$

$$\frac{d[MCl]}{dt} = -k_{S_N2}[MCl][RSH] = -k^{/}[MCl]$$

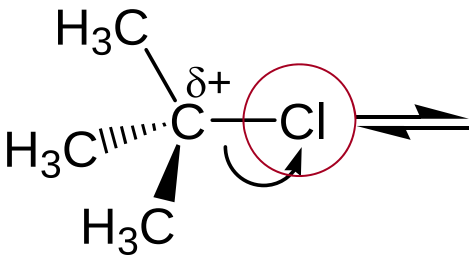




Willems et al. (1996, *ES&T* **30**, 2148-2154)

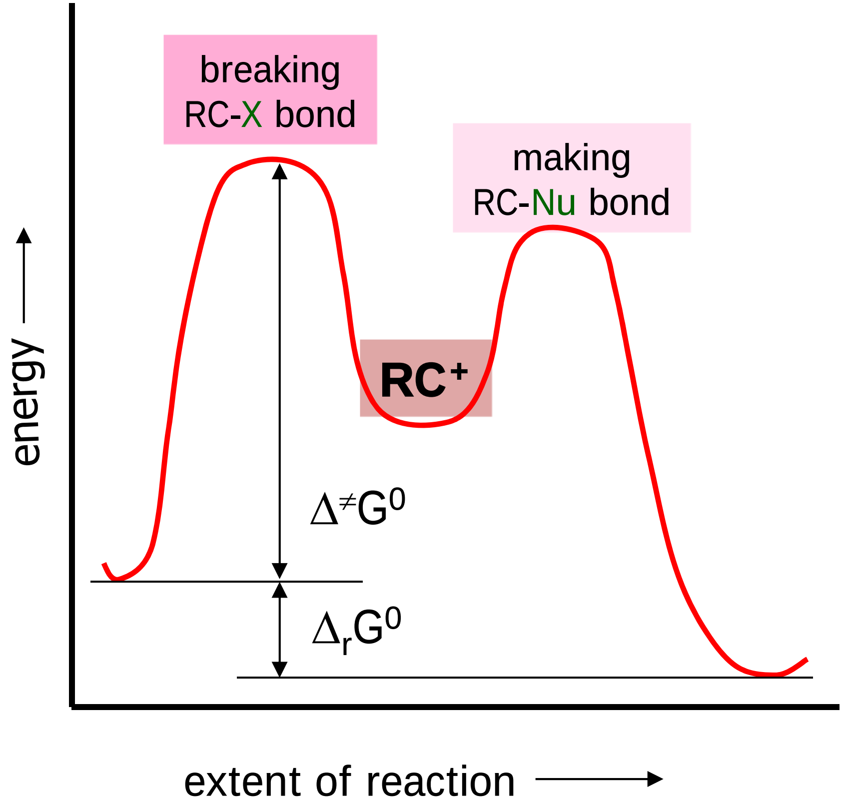
Nucleophilic Substitution

- First order, S_N1
  - leaving group leaves δ^+ carbon
    - forms “carbocation”
  - δ^+ carbon “finds” nucleophile
    - nucleophile supplies electrons for bond



Nucleophilic Substitution

- Transition state
  - rate dictated by stability of carbocation RC^+
  - S_N1 favored by bulky R
    - steric hindrance of Nu attack



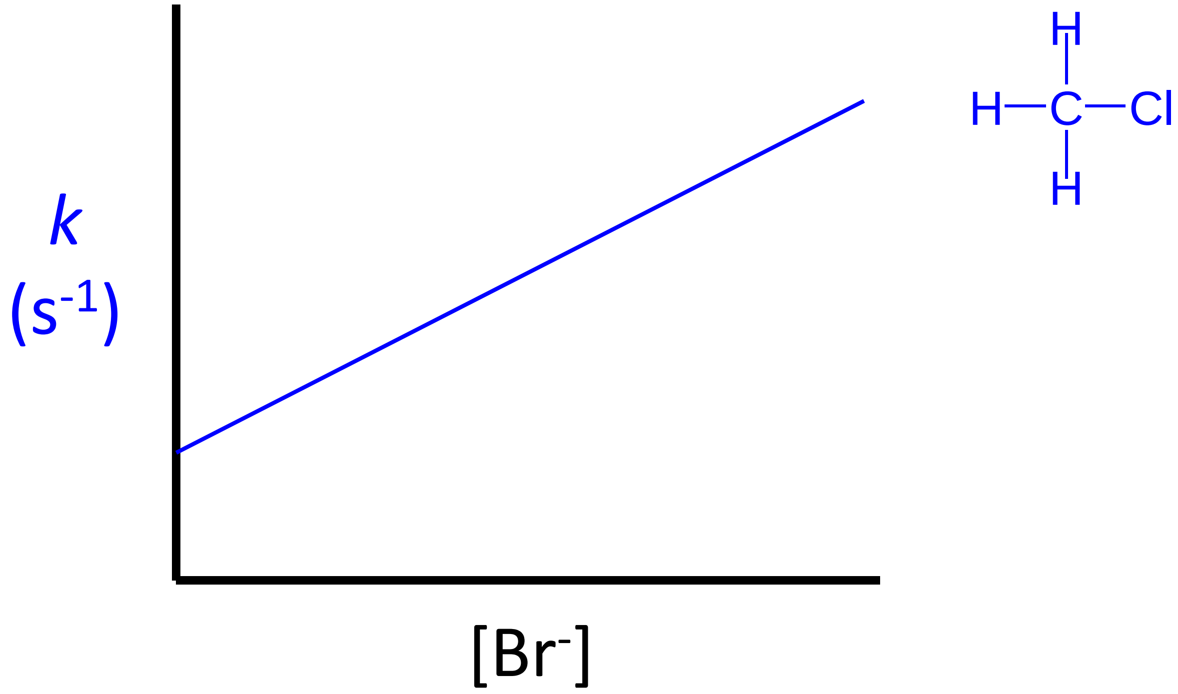
Nucleophilic Substitution

- First order, S_N1
    - kinetics
        - $(CH_3)_3CCl \rightleftarrows (CH_3)C^+ + Cl^-$
        - $(CH_3)_3C^+ + Nu^- \rightleftarrows (CH_3)CNu$

$$\frac{d[C(CH_3)_3Cl]}{dt} = -k_{S_N1}[C(CH_3)_3Cl]$$

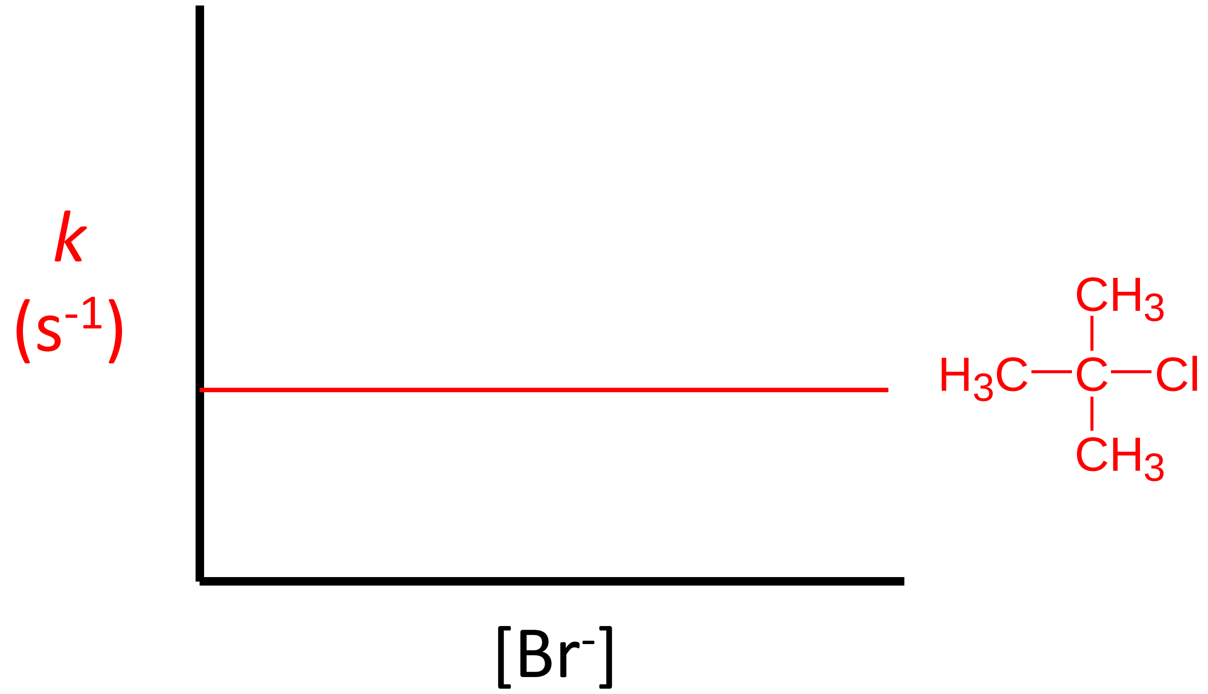
Nucleophilic Substitution

- Does chloromethane degrade by
  A. first order
  B. second order
  nucleophilic substitution?



Nucleophilic Substitution

- Does *tert*-butyl chloride degrade by
  A. first order
  B. second order
  nucleophilic substitution?

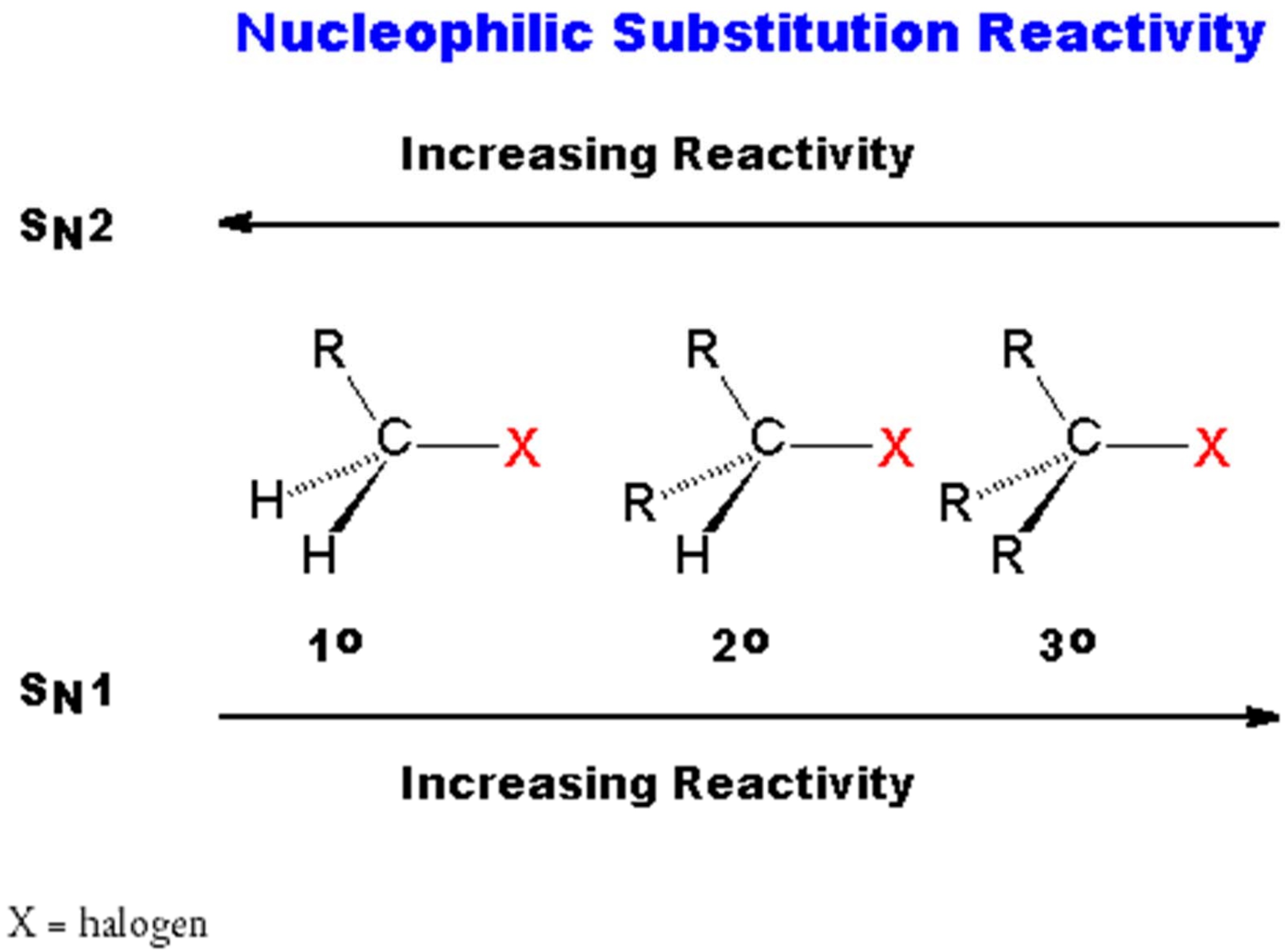


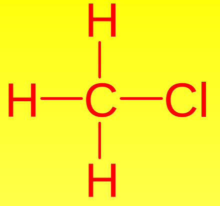
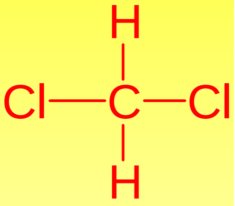
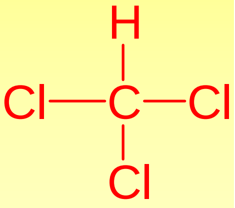
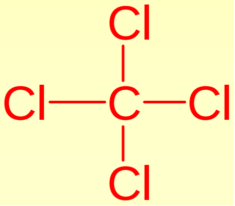
Nucleophilic Substitution

- Factors favoring S_N2:
  - δ^+ carbon
    - nearby electron-withdrawing groups (e.g., halogens)
  - no steric hindrance
    - from methyls, from halogens
- Factors favoring S_N1:
  - stabilized carbocation, RC^+
    - nearby electron-donating substituents (e.g., methyl)
    - double bond, or aromatic ring
  - steric hindrance
    - from methyls

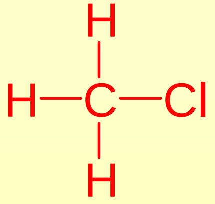
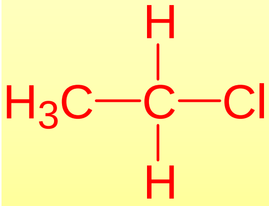
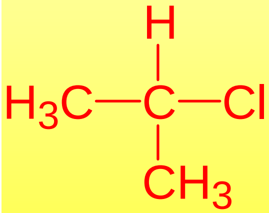
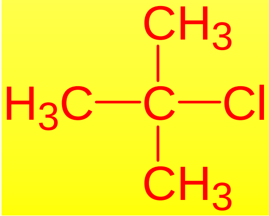
Nucleophilic Substitution

- Contrast between S_N2 and S_N1



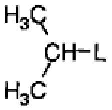
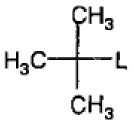
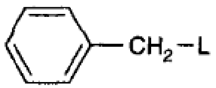
	mechanism/ half-life*
 $H-\overset{H}{\underset{H}{C}}-Cl$	S_N2 0.93 y
 $Cl-\overset{H}{\underset{H}{C}}-Cl$	S_N2 704 y
 $Cl-\overset{H}{\underset{Cl}{C}}-Cl$	S_N2 3500 y
 $Cl-\overset{Cl}{\underset{Cl}{C}}-Cl$	S_N2 7000 y

*hydrolysis
at pH 7,
25°C

	mechanism/ half-life*
 $H-\overset{H}{\underset{H}{C}}-Cl$	S_N2 340 d
 $H_3C-\overset{H}{\underset{H}{C}}-Cl$	S_N2 38 d
 $H_3C-\overset{H}{\underset{CH_3}{C}}-Cl$	$S_N2 \ldots S_N1$ 38 d
 $H_3C-\overset{CH_3}{\underset{CH_3}{C}}-Cl$	S_N1 23 s

*hydrolysis
at pH 7,
25°C

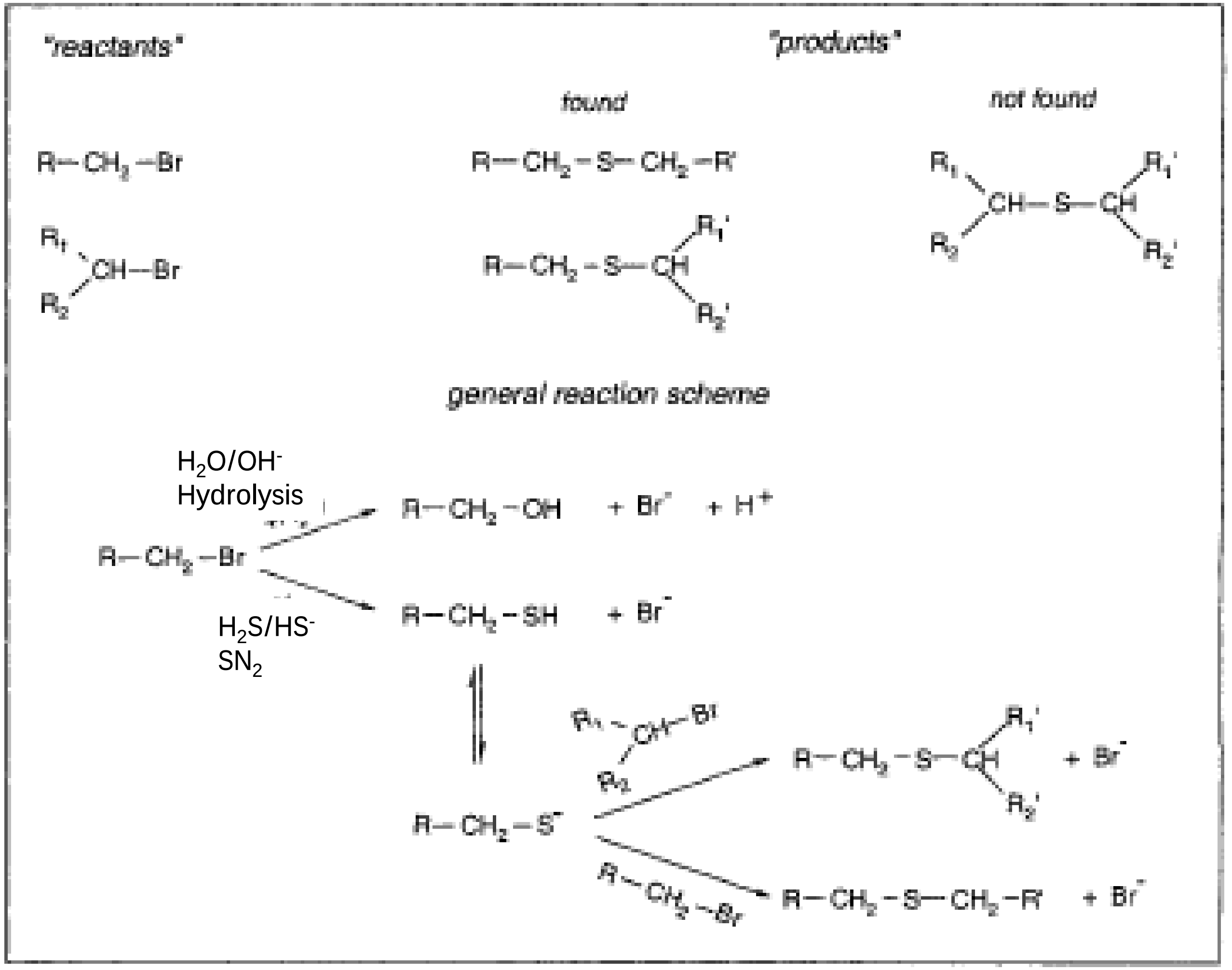
Table 13.6 Hydrolysis Half-Lives and Postulated Reaction Mechanisms at 25°C of Some Monohalogenated Hydrocarbons at Neutral pH [a]

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
 $H_3C-C(CH_3)_2-L$	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.

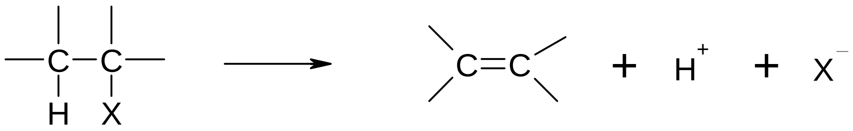
Groundwater Contamination by Volatile Halogenated Alkanes: Abiotic Formation of Volatile Sulfur Compounds under Anaerobic Conditions

Alkyl bromides leaked into groundwater and dialchyl sulfides found several years later.

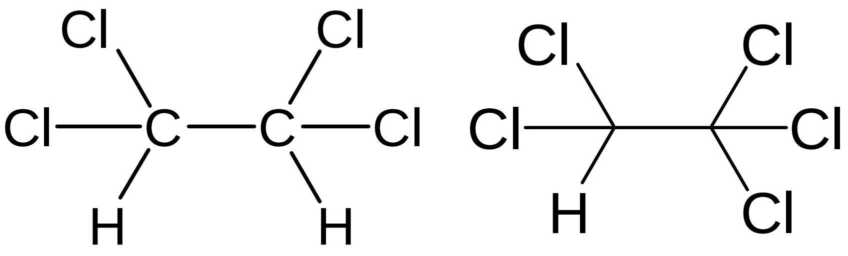


Schwarzenbach et. al, *Envronmental Science & Technology*, **19**, 322-327 (1985)

Elimination



- Elimination
  - also called
    - β-elimination
    - dehydrohalogenation
  - competes with nucleophilic substitution
  - favored by “acidic protons”
  - faster when S_N2 is sterically hindered
  - faster for polyhalogenated hydrocarbons
    - more steric hindrance
    - more acidic protons

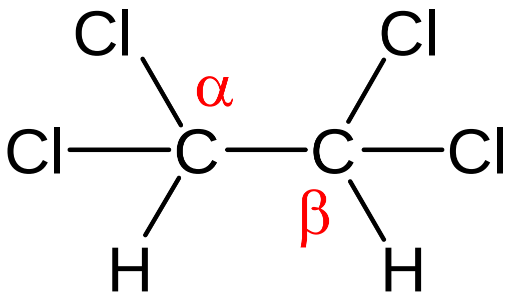


Elimination

- Elimination
  - second order, E2
    - nucleophile “abstracts” an acidic proton
    - C – C bond becomes C = C
    - leaving group on neighbor carbon departs

  - first order, $E1_{CB}$ or E1
    - acidic proton leaves on its own, $E1_{CB}$
      or
      leaving group leaves on its own, E1
    - no need for nucleophile

Elimination

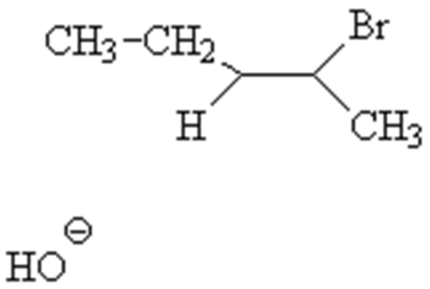


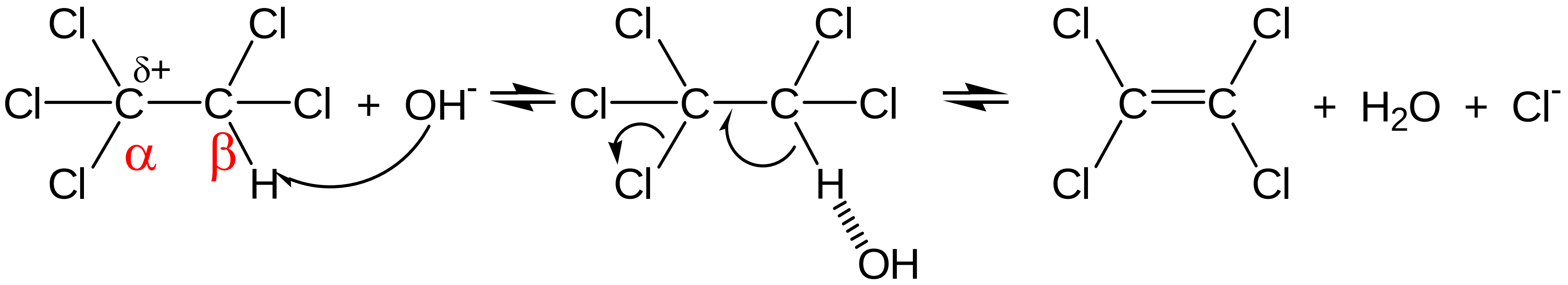
- Second order, E2
  - nucleophile “abstracts” acidic H
    - nucleophile usually OH^-
      - strong nucleophile
    - C—(H) bond mimics nucleophilic attack
      - electrons attack α carbon

  - leaving group leaves
    - leaving group on α carbon
      - takes electrons in bond
      - result of “internal” nucleophilic attack

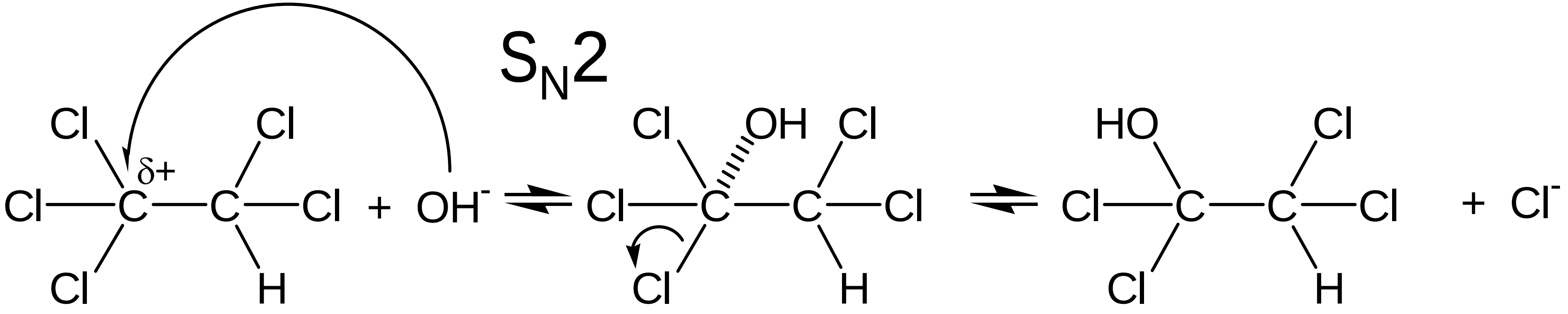
Elimination

- Second order, E2





S$_N$2

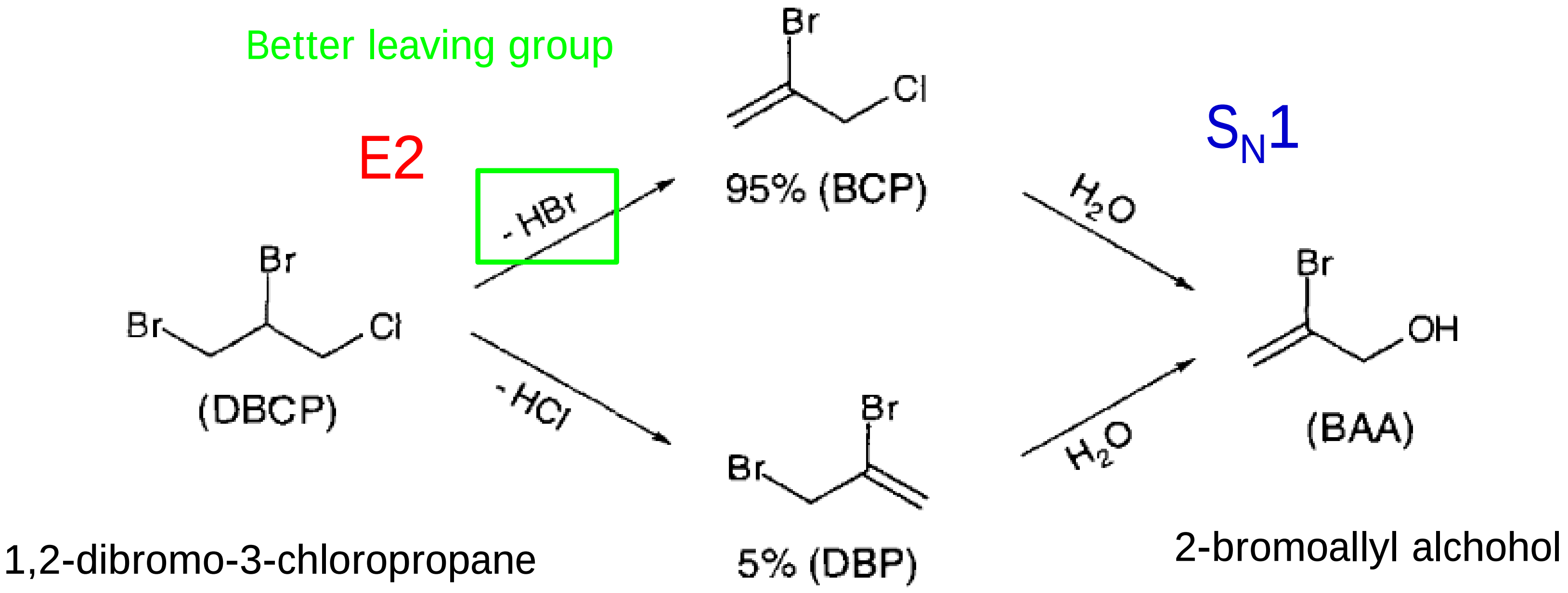


Elimination

- Second order, E2
  - kinetics
    - $Cl_3C—CHCl_2 + OH^- \rightleftarrows Cl_2C{=}CCl_2 + H_2O + Cl^-$

$$\frac{d[Cl_3CCHCl_2]}{dt} = -k_{E2}[Cl_3CCHCl_2][OH^-]$$

$$\frac{d[Cl_3CCHCl_2]}{dt} = -k^{/}[Cl_3CCHCl_2]$$



Better leaving group

E2

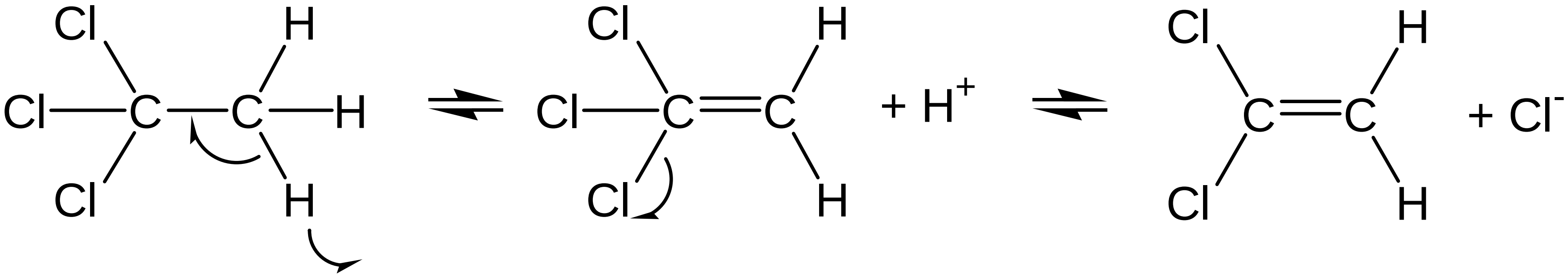
S_N1

1,2-dibromo-3-chloropropane

2-bromoallyl alchohol

Elimination

- First order, $E1_{CB}$
  - acidic H released
    - electrons from C—H bond return to C—C bond
  - leaving group on α carbon leaves
    - leaving group takes electrons in bond



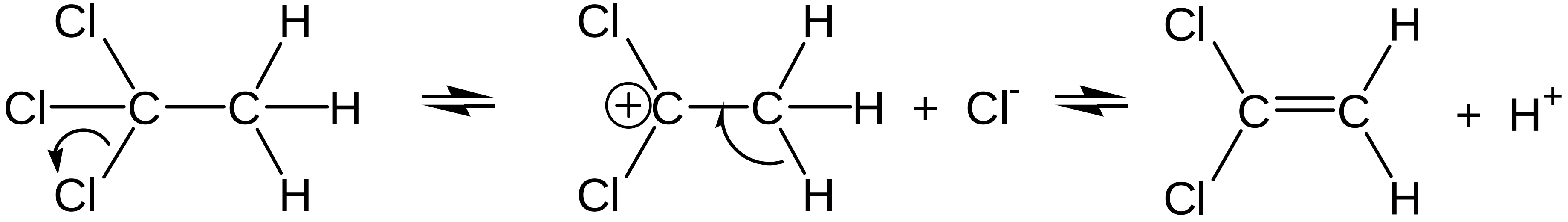
Elimination

- First order, E1$_{CB}$
  - kinetics
    - $Cl_3C—CH_3 \rightleftarrows Cl_2C{=}CH_2 + H^+ + Cl^-$

$$\frac{d[Cl_3CCH_3]}{dt} = -k_{E1_{CB}}[Cl_3CCH_3]$$

Elimination

- First order, E1
  - leaving group on α carbon leaves
    - leaving group takes electrons in bond
  - acidic H released
    - electrons from C—H bond return to C—C bond



Elimination

- First order, E1
  - kinetics

    - $Cl_3C—CH_3 \rightleftarrows Cl_2C{=}CH_2 + H^+ + Cl^-$

$$\frac{d[Cl_3CCH_3]}{dt} = -k_{E1}[Cl_3CCH_3]$$

Elimination

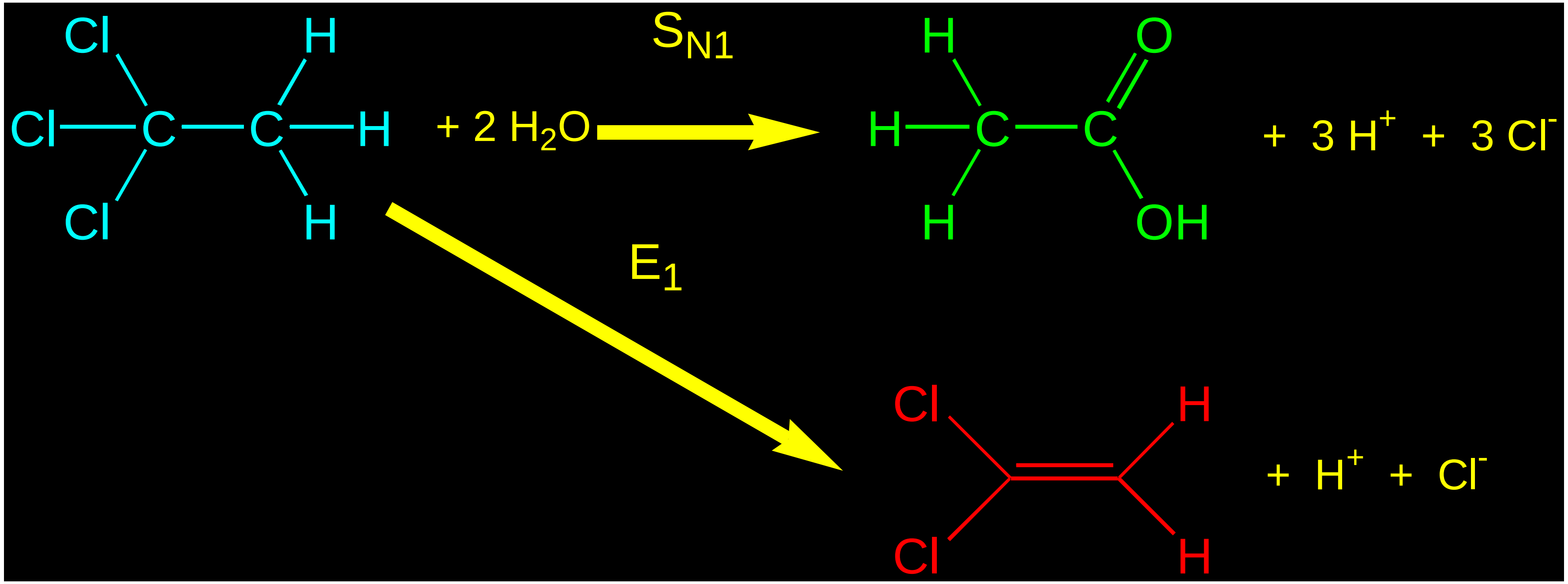
- E2 favored by
  - acidic proton vulnerable to abstraction

- $E1_{CB}$ favored by
  - very acidic proton
  - lacking good leaving groups in α

- E1 favored by
  - very good leaving group
  - carbocation can be stabilized
    - electron-donating substituents
  - less acidic proton

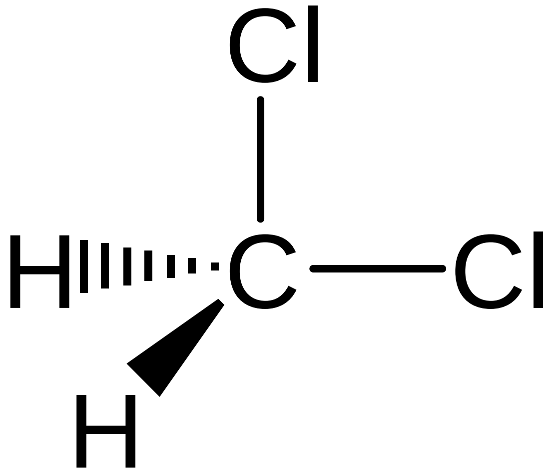
Elimination

- 1,1,1-Trichloroethane
  - substitution and elimination
    (Gerkens and Franklin, 1989, *Chemosphere* **19**, 1929)
  - S_N1 (~75-80%)
  - E1 (~20-25%)



Substitution and Elimination

- How does it react?



$t_{1/2}$ (pH 7) = 704 y

nucleophilic substitution?

A. second order?

[✓ B. first order?]

~~elimination?~~

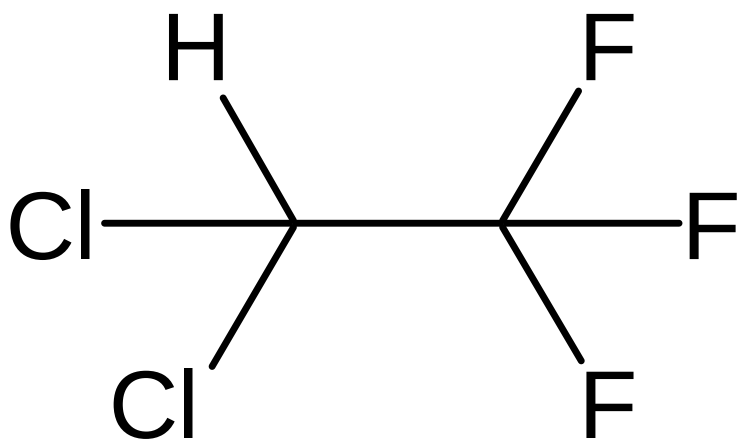
C. second order?

D. first order?

need
two C's

Substitution and Elimination

- How does it react?



~fast

nucleophilic substitution?

~~A. second order?~~

B. first order?

elimination?

C. second order?

[✓ D. first order?]

steric hindrance

$E1_{CB}$; proton goes first

Nucleophilic Substitution

- Factors favoring S_N2:
  - δ^+ carbon
    - nearby electron-withdrawing groups (e.g., halogens)
  - no steric hindrance
    - from methyls, from halogens
- Factors favoring S_N1:
  - stabilized carbocation, RC^+
    - nearby electron-donating substituents (e.g., methyl)
    - double bond, or aromatic ring
  - steric hindrance
    - from methyls

Elimination

- E2 favored by
  - acidic proton vulnerable to abstraction

- $E1_{CB}$ favored by
  - very acidic proton
  - lacking good leaving groups in α

- E1 favored by
  - very good leaving group
  - carbocation can be stabilized
    - electron-donating substituents
  - less acidic proton

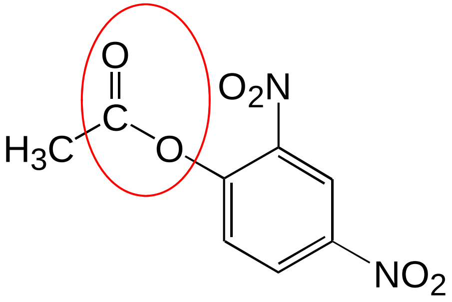
- Overall reaction kinetics

$$\frac{d[A]}{dt} = -\left\{ k_{S_N1} + \sum_i k_{S_N2}[Nu_i] + k_{E1} + k_{E1_{CB}} + \sum_i k_{E2}[Nu_i] \right\}[A]$$

- Hydrolysis
  - water and hydroxide as Nu
  - includes substitution and elimination

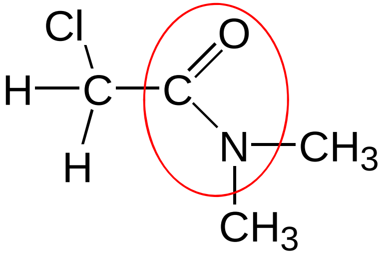
Hydrolysis of Acid Derivatives

- Examples
  - carboxylic acid esters



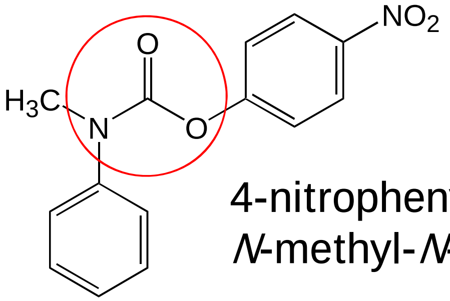
2,4-dinitrophenyl acetate

  - carboxylic acid amides



N,*N*-dimethyl chloroacetamide

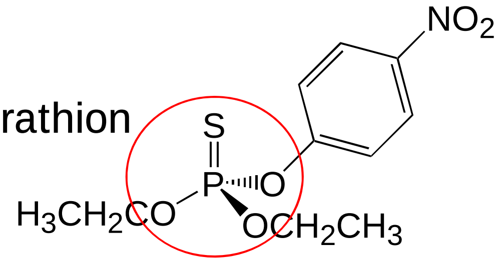
  - carbamates



4-nitrophenyl
N-methyl-*N*-phenyl carbamate

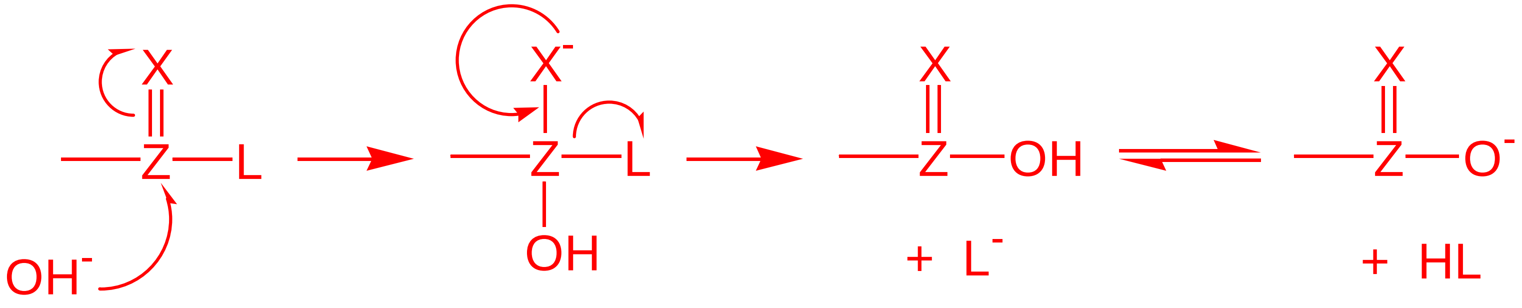
  - phospho- and thioesters

parathion



Hydrolysis of Acid Derivatives

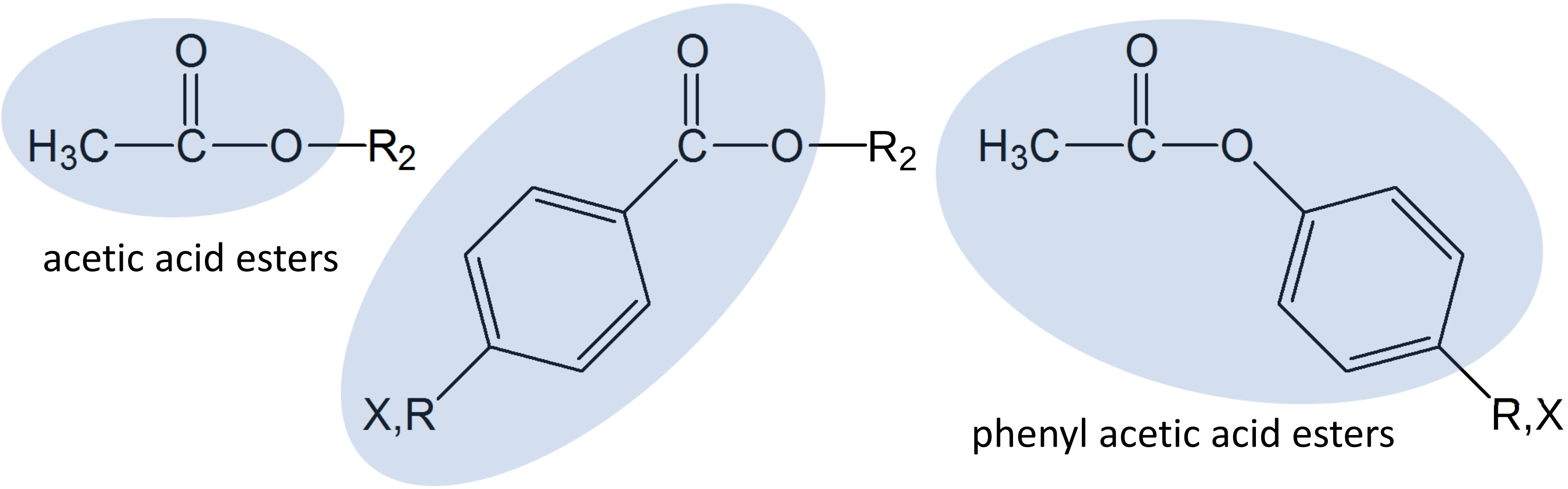
- General mechanism



  - *Z* is C, P, or S (the target of nucleophilic attack)
  - *X* is O, S, NR (heteroatoms)
  - *L* is RO^-, $R_1R_2N^-$, RS^-, Cl^-, etc. (the leaving group)

Hydrolysis of Acid Derivatives

- Nomenclature for carboxylic acid esters

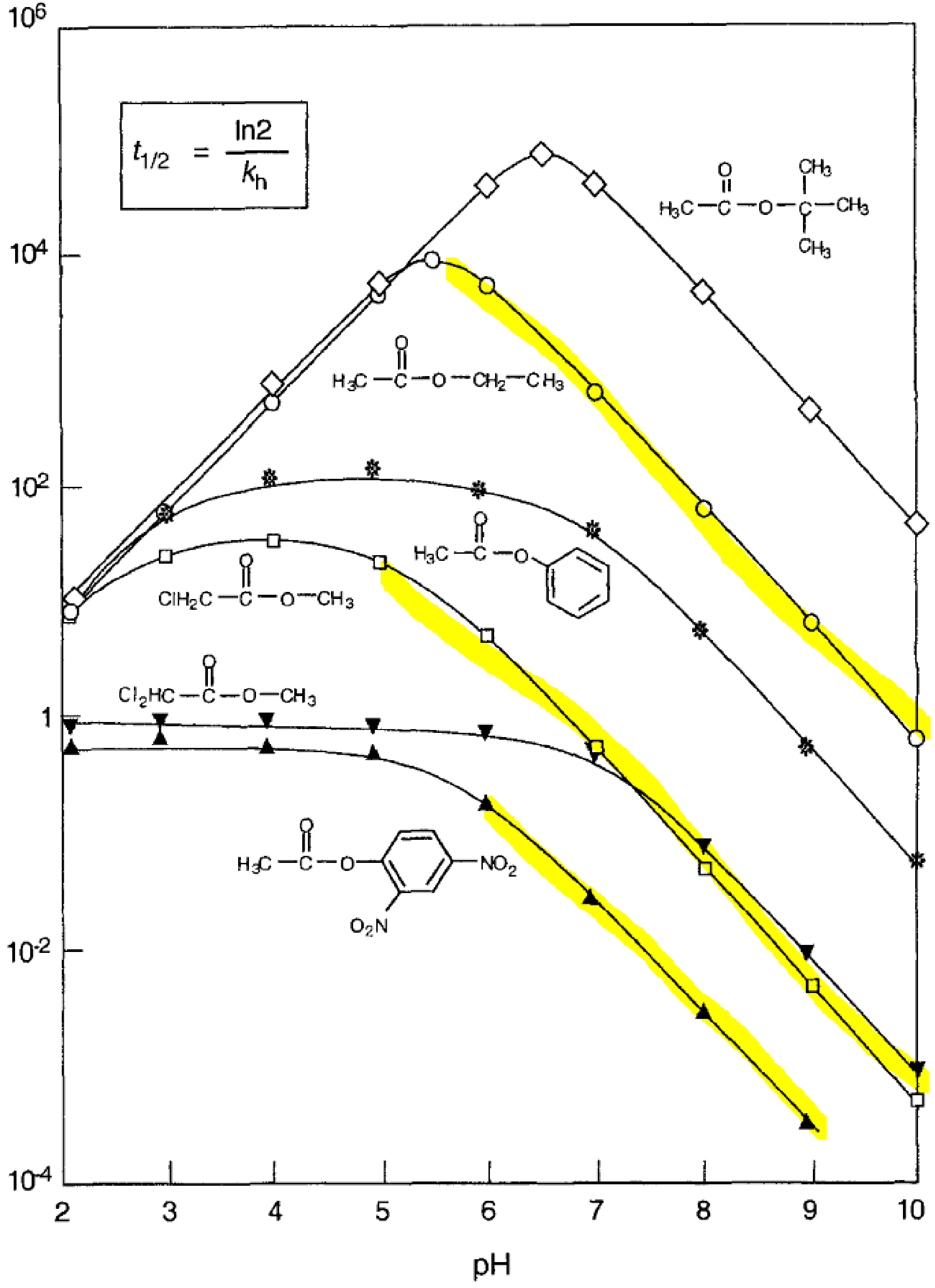


acetic acid esters

benzoic acid esters

phenyl acetic acid esters

Hydrolysis $t_{1/2}$ (d) at 25°C for several caboxylic acid esters as a function of solution pH due to changing contributions of the catalysis

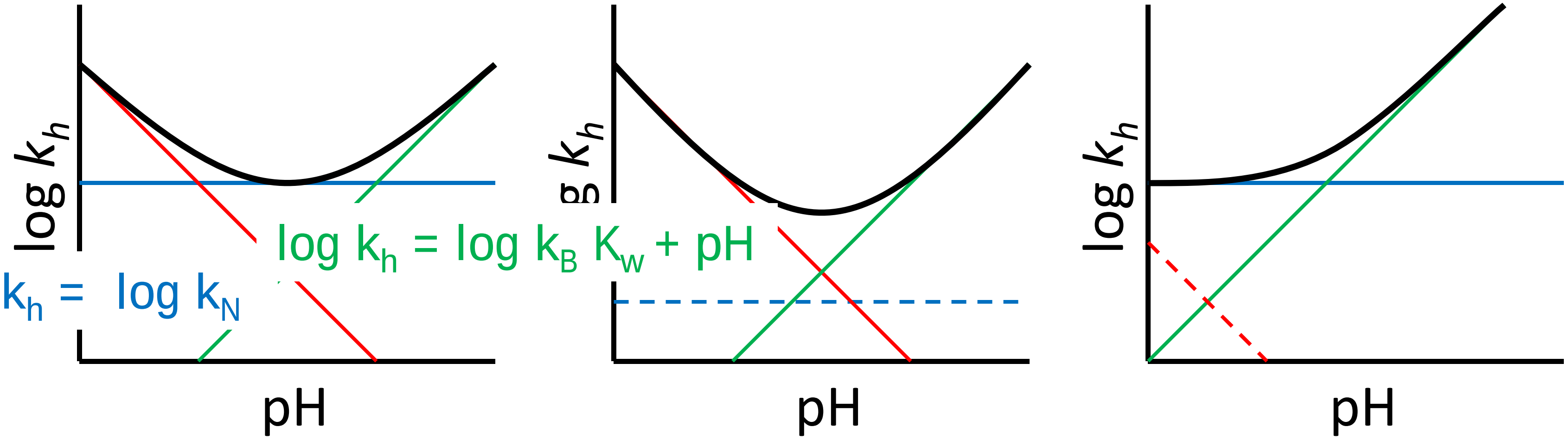


Hydrolysis of Acid Derivatives

- Hydrolysis mechanisms
  - acid-catalyzed – k_A (M^{-1} s^{-1})
    - protonation of carboxylic acid ester
    - H_2O as nucleophile
  - neutral – k_N (s^{-1})
    - H_2O as nucleophile
  - base-catalyzed – k_B (M^{-1} s^{-1})
    - OH^- as nucleophile

Hydrolysis of Acid Derivatives

- Hydrolysis mechanisms
  - effect of pH, compound



$\log k_h = \log k_A - \text{pH}$

$\log k_h = \log k_N$

$\log k_h = \log k_B K_w + \text{pH}$

$$k_h = k_A[H^+] + k_{H2O}[H_2O] + k_B[OH^-]$$

$$k_h = k_H + k_N + k_{OH}$$

Effect of pH:

$$k_h = k_A\,[\mathrm{H^+}] + k_{H2O}\,[\mathrm{H_2O}] + k_B\,[\mathrm{OH^-}]$$

$k_h = k_A\,[\mathrm{H^+}]$ $\Longrightarrow$ $\log \mathrm{k_h} = \log \mathrm{k_A} - \mathrm{pH}$

$k_h = k_{H2O}\,[\mathrm{H_2O}] = \mathrm{k_N}$ $\Longrightarrow$ $\log \mathrm{k_h} = \log \mathrm{k_N}$

$k_h = k_B\,[\mathrm{OH^-}]$ $\Longrightarrow$ $\log \mathrm{k_h} = \log \mathrm{k_B} + \log\,[\mathrm{OH^-}]$ ma $[\mathrm{OH^-}] = \dfrac{\mathrm{K_w}}{[\mathrm{H^+}]}$

$$\log \mathrm{k_h} = \log \mathrm{k_B} + \log \mathrm{K_w} - \log\,[\mathrm{H^+}]$$

$$\log \mathrm{k_h} = \log \mathrm{k_B}\,\mathrm{K_w} + \mathrm{pH}$$

Hydrolysis of Acid Derivatives

$\log k_h = \log k_A - pH$

$\log k_h = \log k_N$

$\log k_h = \log k_B K_w + pH$

- Determining I_{AN}, I_{AB}, I_{NB}
  - I_{AN} occurs at the pH at which

    $k_A [H^+] = k_N$ $\quad\quad$ $I_{NA} = \log (k_A/k_N)$

  - I_{AB} occurs at the pH at which

    $k_A [H^+] = k_B [OH^-]$ $\quad\quad$ $I_{AB} = ½ \log (k_A/k_B K_W)$

  - I_{NB} occurs at the pH at which

    $k_B [OH^-] = k_N$ $\quad\quad$ $I_{NB} = \log (k_N/k_B K_W)$

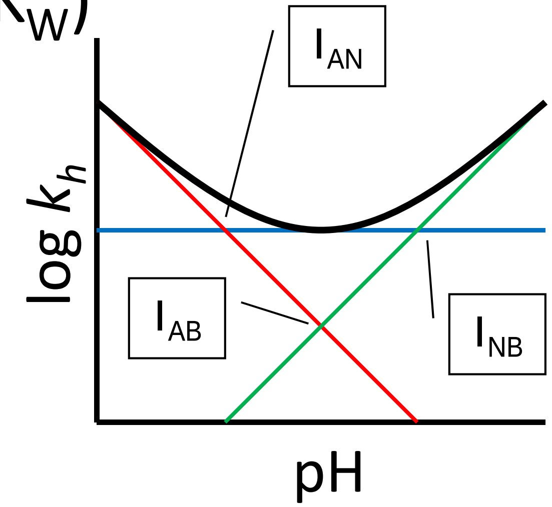
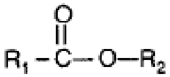
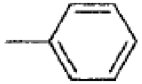
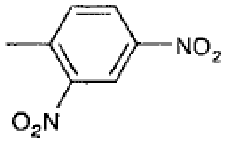
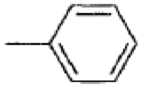


Table 13.8 Rate Constants k_A, k_N, and k_B, Half-Lives at pH 7, and I Values for Hydrolysis of Some Carboxylic Acid Esters at 25°C [a]

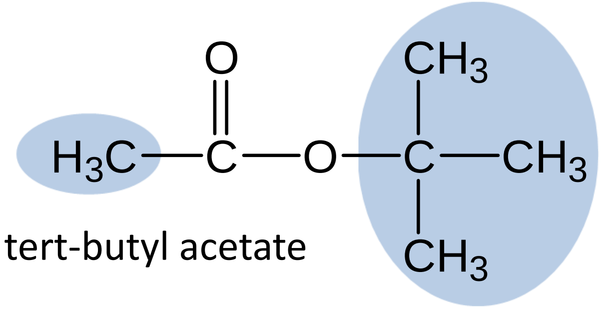
Compound  $R_1-C(=O)-O-R_2$								
R_1	R_2	k_A ($M^{-1}\ s^{-1}$)	k_N (s^{-1})	k_B ($M^{-1}\ s^{-1}$)	$t_{1/2}$ (pH 7)	I_{AN} [b,c,e]	I_{AB} [c,e]	I_{NB} [d,e]
CH_3-	$-CH_2CH_3$	1.1×10^{-4}	1.5×10^{-10}	1.1×10^{-1}	2 yr	(5.9)	5.5	(5.1)
CH_3-	$-C(CH_3)_3$	1.3×10^{-4}		1.5×10^{-3}	140 yr		6.5	
H–	$-C(CH_3)_3$	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.

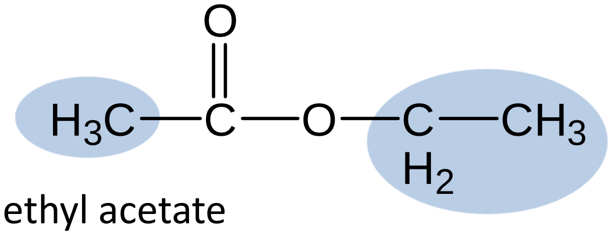
Hydrolysis of Acid Derivatives

- Acid hydrolysis important for esters with:
  - electron-donating substituents
  - poor leaving groups (high pK_a)
  - R_1 and R_2 as alkanes (methyl, ethyl, …)

$$R_1COOR_2 + H_2O + H^+ \rightleftarrows R_1COOH + R_2OH + H^+$$



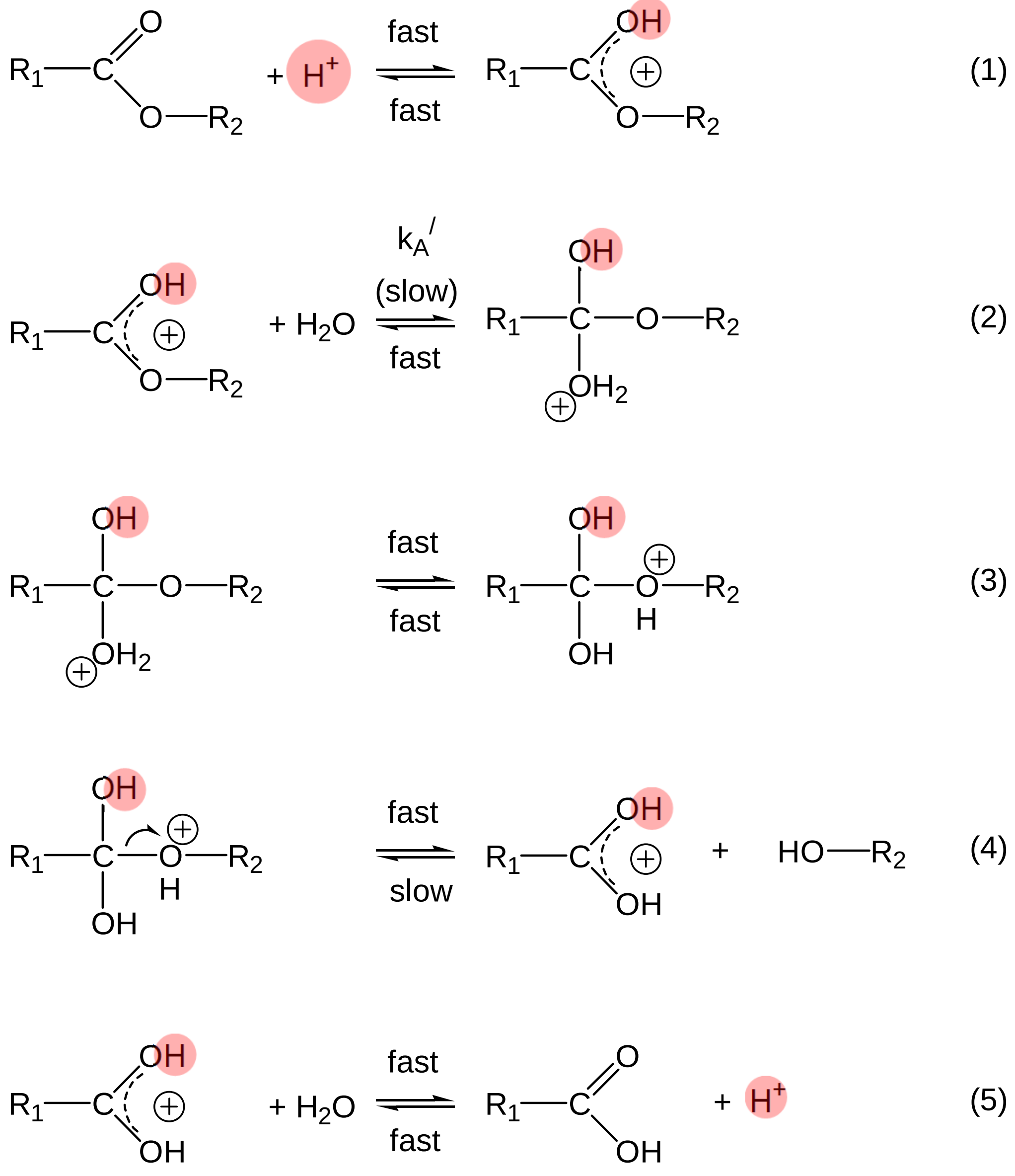
tert-butyl acetate



ethyl acetate

Hydrolysis of Acid Derivatives

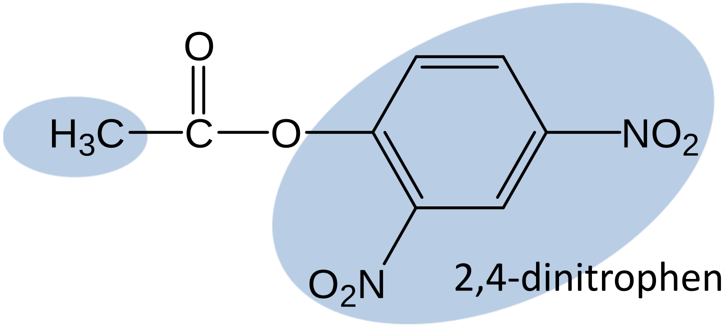
- Acid hydrolysis
  - protonation
    - makes C more δ+
    - better target for Nu
  - Nu is H_2O
  - rate-limiting step: nucleophilic attack by H_2O



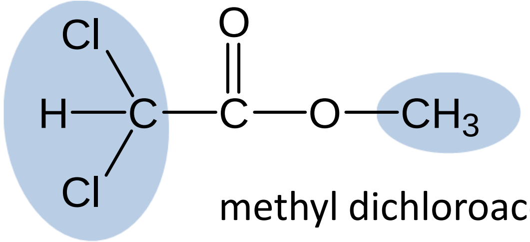
Hydrolysis of Acid Derivatives

- Base-catalyzed hydrolysis for esters with:
  - electron-withdrawing substituents
  - good leaving groups (low pK_a)
  - R_1 or R_2 as halogens, nitro-, chloro-substituted phenyls

$$R_1COOR_2 + OH^- \rightleftarrows R_1COO^- + R_2OH$$



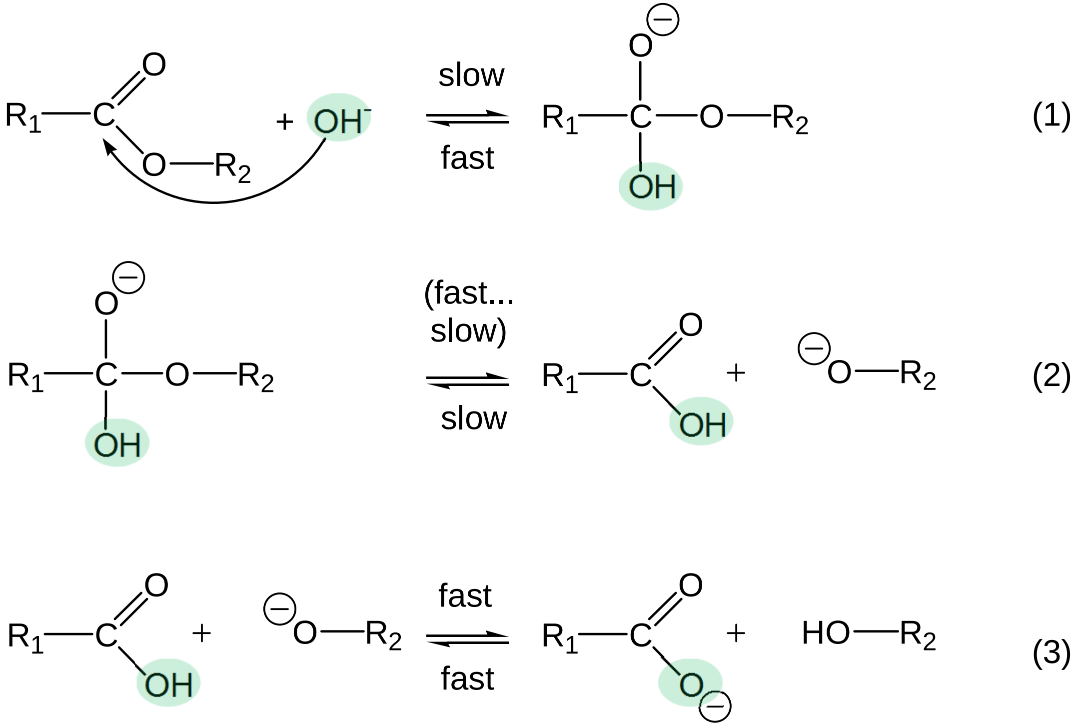
2,4-dinitrophenyl acetate



methyl dichloroacetate

Hydrolysis of Acid Derivatives

- Base-catalyzed hydrolysis
  - C already very δ+
  - rate-limiting step
    - Nu is OH^-
    - departure of leaving group (fast if pK_a is low; slow if pK_a is high)



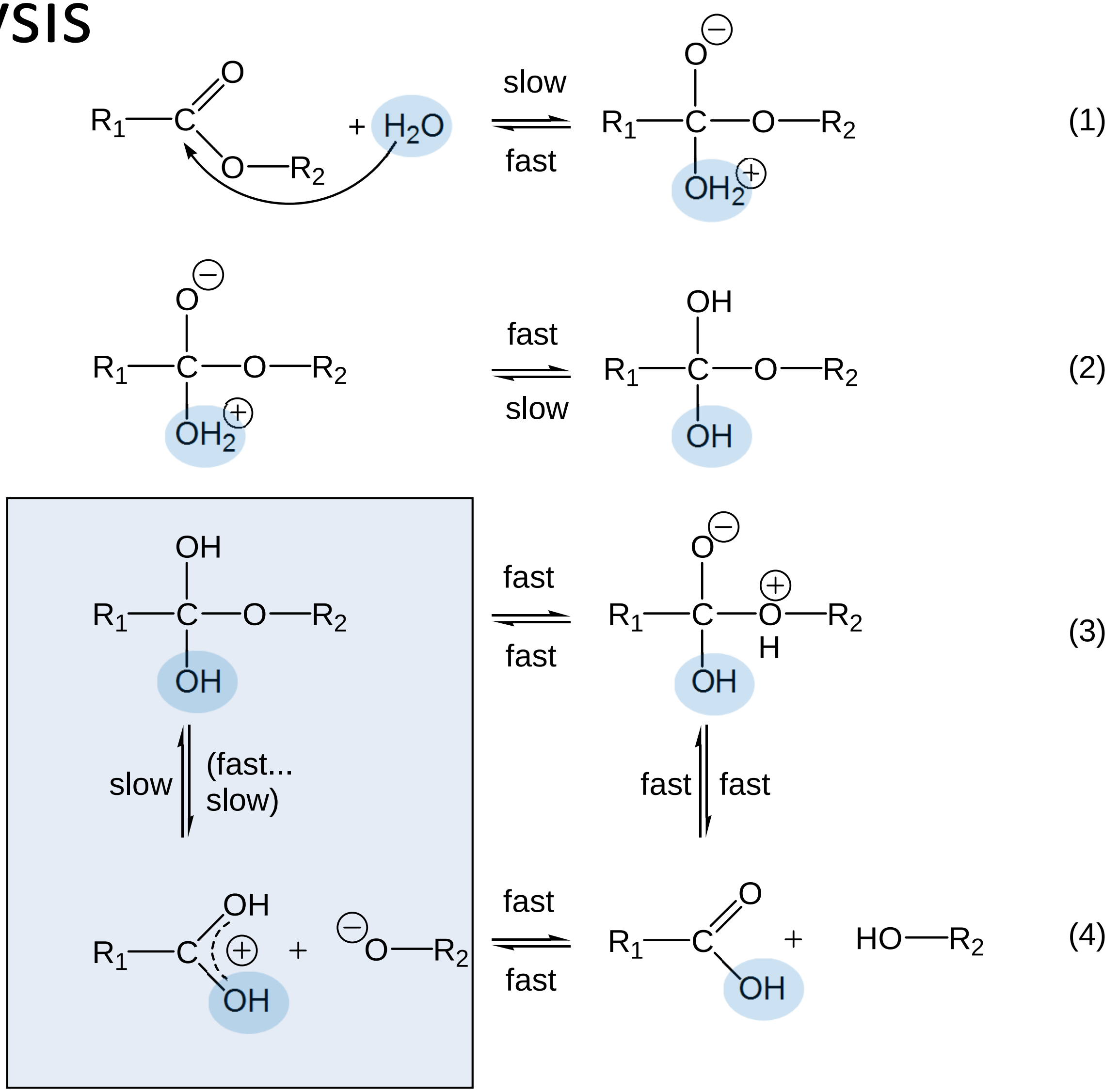
Hydrolysis of Acid Derivatives

- Neutral hydrolysis
  - H_2O is a weaker, but more abundant, nucleophile
  - electron-withdrawing substituents
  - good leaving groups (low pK_a)

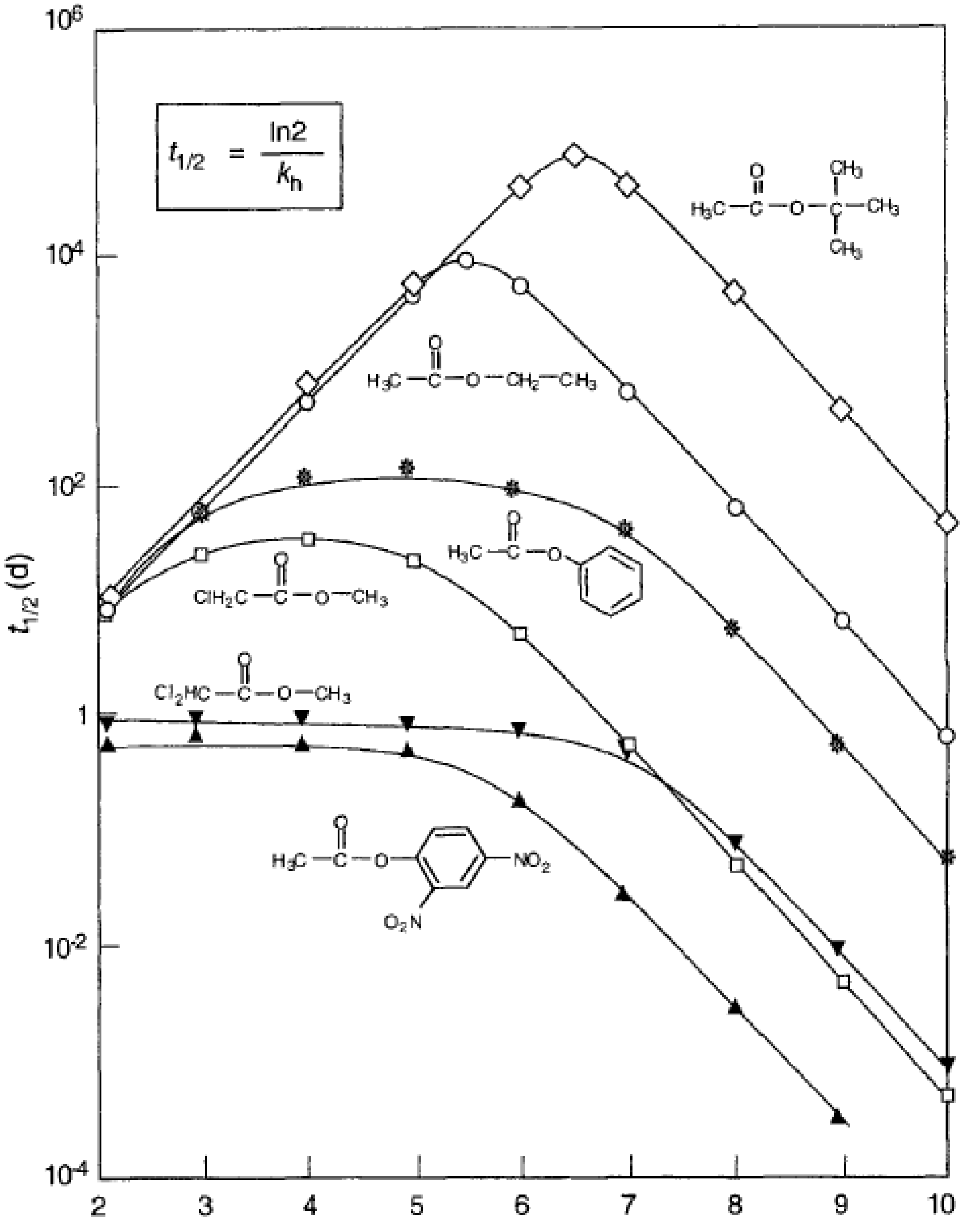
$$R_1COOR_2 + H_2O \rightleftarrows R_1COOH + R_2OH$$

Hydrolysis of Acid Derivatives

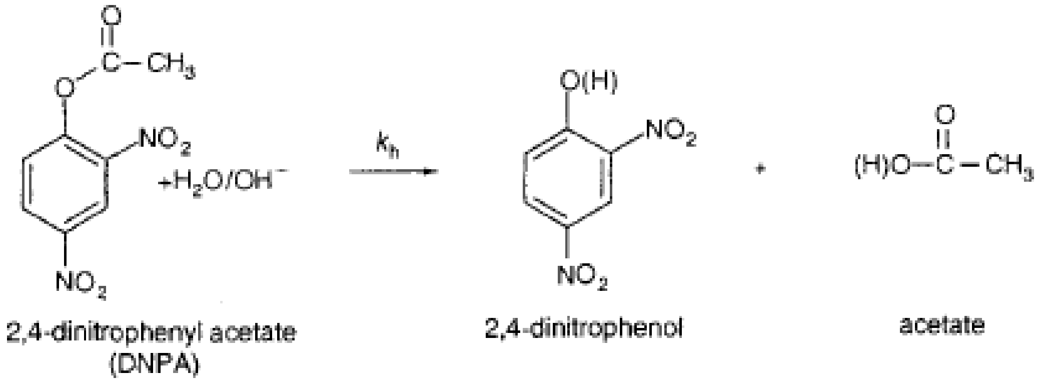
- Neutral hydrolysis
  - Nu is H_2O
  - H_2O more sensitive to
    - presence of electron-withdrawing substituents (δ+ of C)
    - pK_a of the leaving group



Hydrolysis $t_{1/2}$ at 25°C for several caboxylic acid esters as a function of solution pH due to changing contributions of the catalysis



Determine the (pseudo-)first-order reaction rate constants, k_h, for this reaction at pH 5.0 and pH 8.5 at 22.5°C using the data sets given below:



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.

Answer

Assuming a (pseudo-)first-order rate law, k_h can be determined from a least squares fit of $\ln([\mathrm{DNPA}]_t / [\mathrm{DNPA}]_0)$ versus time (see also Figure below):

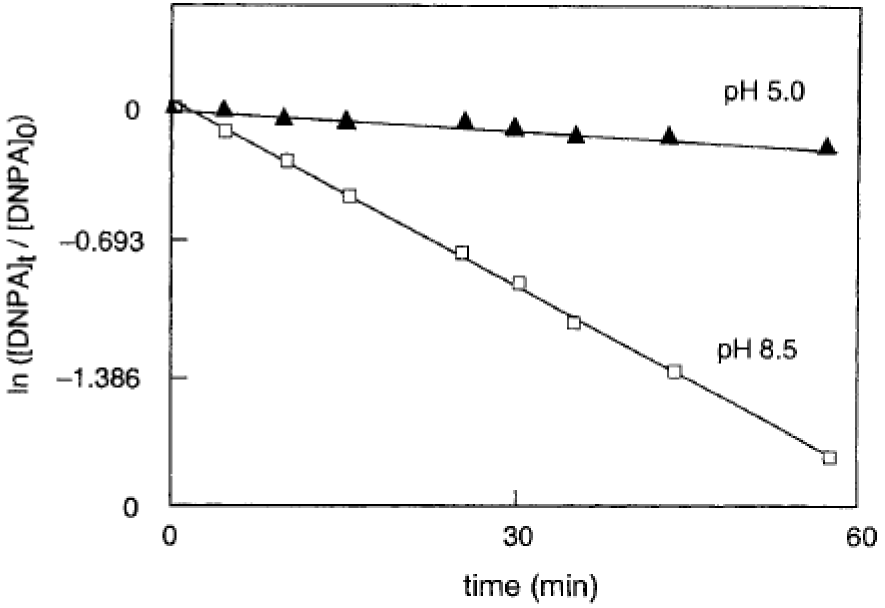
$$\ln([\mathrm{DNPA}]_t / [\mathrm{DNPA}]_0) = -k_h \cdot t \qquad (1)$$

The resulting k_h values are:

$$k_h(\mathrm{pH}\ 5.0, 22.5°\mathrm{C}) = 2.6 \times 10^{-3}\ \mathrm{min}^{-1} = 4.4 \times 10^{-5}\ \mathrm{s}^{-1}$$

$$k_h(\mathrm{pH}\ 8.5, 22.5°\mathrm{C}) = 3.1 \times 10^{-2}\ \mathrm{min}^{-1} = 5.1 \times 10^{-4}\ \mathrm{s}^{-1}$$

Note that k_h increases with increasing pH, indicating that the base-catalyzed reaction is important, at least at higher pH values.



Problem

Using the data given above, derive the rate constants for the neutral (k_N) and base-catalyzed (k_B) hydrolysis of DNPA at 22.5°C. At what pH are the two reactions equally important?

When assuming that the acid-catalyzed reaction is not important in the pH-range considered, Eq. 3-17 simplifies to:

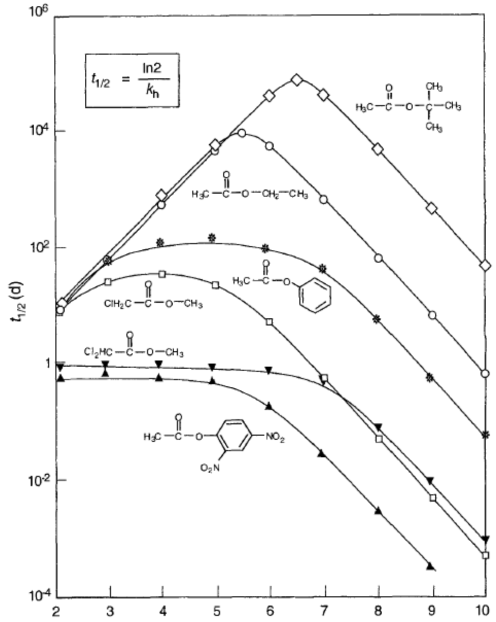
$$k_h = k_N + k_B \cdot [OH^-] \qquad (2)$$

The fact that very similar k_h values have been found at pH 4.0 and pH 5.0 indicates that up to pH 5.0, the base-catalyzed reaction can be neglected, and therefore:

$$k_N\,(22.5°C) = k_h\,(\text{pH } 5.0,\ 22.5°C) = 4.4 \times 10^{-5}\ s^{-1}$$

Using this k_N-value, k_B can be determined by rearranging Eq. 2:

$$k_B(22.5°C) = \frac{k_h(\text{pH } 8.5,\ 22.5°C) - k_N(22.5°C)}{[OH^-]}$$



with the hydroxide concentration given by (see Eq. 8-18) :

$$[\mathrm{OH}^-] = \frac{K_\mathrm{w}}{[\mathrm{H}^+]}$$

Note that the ionization constant of water, K_w, is strongly temperature dependent. At 22.5°C, $K_\mathrm{w} = 10^{-14.08}$ (Table D2 in Appendix D). Hence, at pH 8.5 (i.e., $[\mathrm{H}^+] = 10^{-8.5}$), $[\mathrm{OH}^-] = 10^{-5.58}$ and:

$$k_\mathrm{B}(22.5°\mathrm{C}) = \frac{4.7 \times 10^{-4}}{10^{-5.58}} = 180\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$$

The pH value, I_NB,

$$I_\mathrm{NB} = \log \frac{k_\mathrm{N}}{k_\mathrm{B} \cdot K_\mathrm{w}} = \log \frac{4.4 \times 10^{-5}}{180 \cdot 10^{-14.08}} = 7.5$$

Thus, at pH 8.5, the hydrolysis of DNPA is dominated by the base-catalyzed reaction.

Problem

Derive the Arrhenius activation energy, E_a, for the neutral hydrolysis of DNPA using

T (°C)	k_N / s^{-1}
17.7	3.1×10^{-5}
22.5	4.4×10^{-5}
25.0	5.2×10^{-5}
30.0	7.5×10^{-5}

$1/T$ / K^{-1}	$\ln k_N$ / s^{-1}
0.00344	– 10.38
0.00338	– 10.03
0.00335	– 9.86
0.00330	– 9.50

According to Eq. 12-29, the temperature dependence of a rate constant can be described by:

$$\ln k = -\frac{E_a}{R} \cdot \frac{1}{T} + \text{const.}$$

Note that for the temperature range considered, E_a is assumed to be constant. Convert temperatures in °C to K and calculate $1/T$ values. Also take the natural logarithms of the k_N values (see margin).

Perform a least squares fit of $\ln k_N$ versus $1/T$. The resulting slope is:

$$\text{slope} = -\frac{E_a}{R} = -6318 \text{ K}$$

and therefore:

$$E_a = -R \cdot \text{slope} = 8.31 \cdot (6318) = 52.5 \text{ kJ} \cdot \text{mol}^{-1}$$

The E_a value determined for the base-catalyzed reaction is 60.0 kJ · mol^{-1} (data not shown).

Problem

Calculate the time required to decrease the concentration of DNPA (see Illustrative Example 13.4) by hydrolysis to 50% (half-life) and to 5% of its initial concentration (a) in the epilimnion of a lake ($T = 22.5°\text{C}$, pH = 8.5), and (b) in the hypolimnion of the same lake ($T = 5°\text{C}$, pH = 7.5).

The hydrolysis half-life is calculated by:

$$t_{1/2} = \frac{\ln 2}{k_h} = \frac{0.693}{k_h}$$

By analogy, the time required to reduce the concentration to 5% (i.e., $[\text{DNPA}]_t / [\text{DNPA}]_0 = 0.05$) is given by (see Eq. 1, Illustrative Example 13.4):

$$t_{0.05} = \frac{\ln(1/0.05)}{k_h} = \frac{3}{k_h} \qquad (1)$$

(a) Calculate k_h (Eq. 2, Illustrative Example 13.4) for 22.5°C and pH 8.5 using the above derived k_N and k_B values and $[\text{OH}^-] = 10^{-5.58}$ M:

$$k_h\,(22.5°\text{C}) = (180)\,(10^{-5.58}) + 4.4 \times 10^{-5} = 5.1 \times 10^{-4}\ \text{s}^{-1}$$

Note that at pH 8.5 and 22.5°C, hydrolysis is dominated by the base-catalyzed reaction. Insertion of k_h into Eqs. 12-13 and 1 then yields:

$$t_{1/2}(22.5°\text{C}) = \frac{0.693}{5.1 \times 10^{-4}\ \text{s}^{-1}} = 1360\ \text{s} = 22.7\ \text{min}$$

$$t_{0.05}\ (22.5°\text{C}) = \frac{3}{5.1 \times 10^{-4}\ \text{s}^{-1}} = 5880\ \text{s} = 1.63\ \text{h}$$

(b) Calculate the k_N and k_B values for 5°C (278.2 K) from the corresponding rate constants derived above for 22.5°C (295.7 K) using (see Eq. 12-30):

$$k(T_1) = k(T_2) \cdot e^{(E_a/R)(1/T_2 - 1/T_1)}$$

where T_2 = 295.7 K and T_1 = 278.2 K, and E_a is the activation energy given in Illustrative Example 13.4. The results obtained are:

$$k_N\,(5°\text{C}) = 1.1 \times 10^{-5}\ \text{s}^{-1} \text{ and } k_B\,(5°\text{C}) = 38.6\ \text{M}^{-1}\,\text{s}^{-1}.$$

Since $K_w = 10^{-14.73}$ at 5°C (Table D2, Appendix D), the OH^- concentration at pH 7.5 is $10^{-7.23}$ M, resulting in a k_h-value of:

$$k_h\,(5°\text{C}) = (38.6)\,(10^{-7.23}) + 1.1 \times 10^{-5} = 1.3 \times 10^{-5}\ \text{s}^{-1}$$

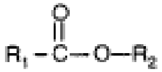
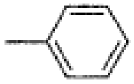
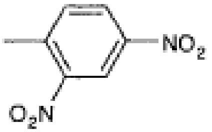
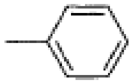
Note that in contrast to the epilimnion, in the hypolimnion the hydrolysis of DNAP is dominated by the neutral reaction. The corresponding reaction times are:

$$t_{1/2}(5°\text{C}) = \frac{0.693}{1.3 \times 10^{-5}\ \text{s}^{-1}} = 53300\ \text{s} = \mathit{14.8}\ \text{h}$$

$$t_{0.05}\,(5°\text{C}) = \frac{3}{1.3 \times 10^{-5}\ \text{s}^{-1}} = 230000\ \text{s} = \mathit{62.9}\ \text{h}$$

Hence, under the assumed conditions, DNPA hydrolyzes about 40 times faster in the epilimnion of the lake as compared to the hypolimnion.

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  $R_1-\overset{O}{\overset{\|}{C}}-O-R_2$								
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.

Hydrolysis $t_{1/2}$ at 25°C for several caboxylic acid esters as a function of solution pH due to changing contributions of the catalysis

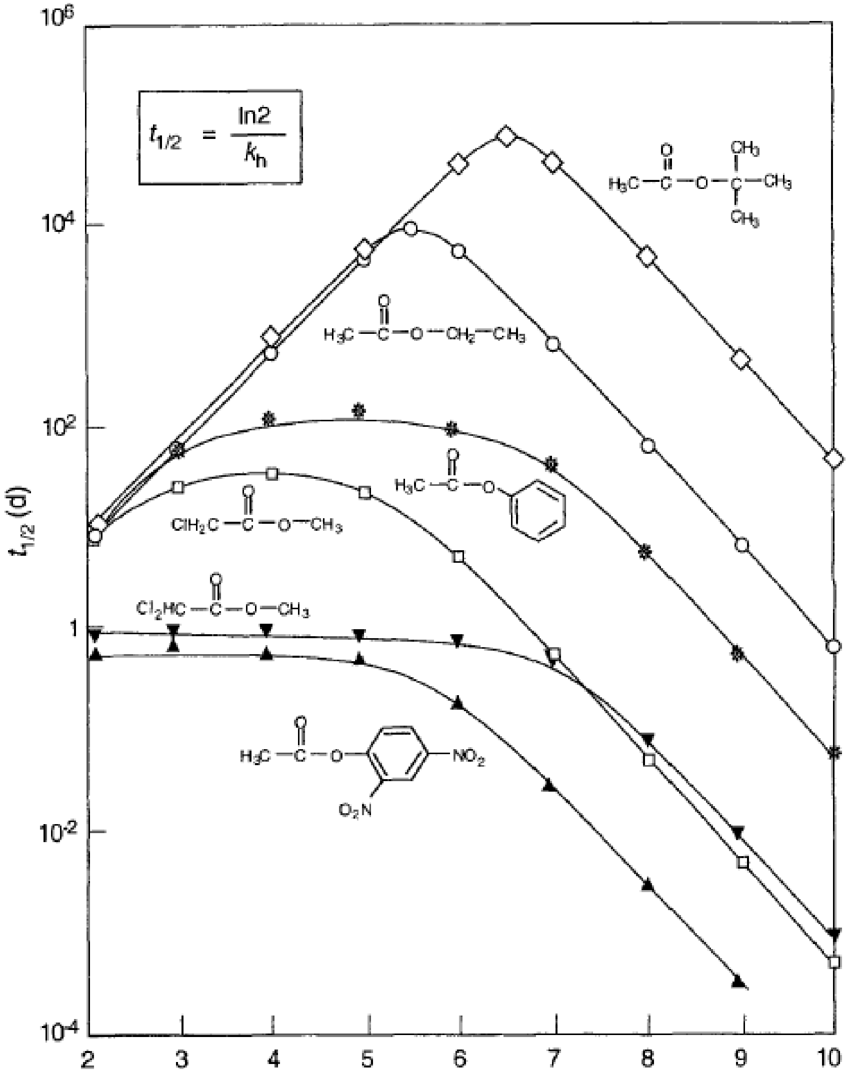
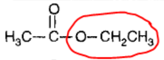
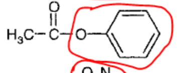
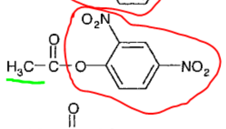
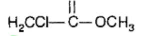
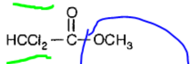
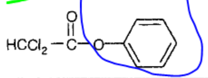
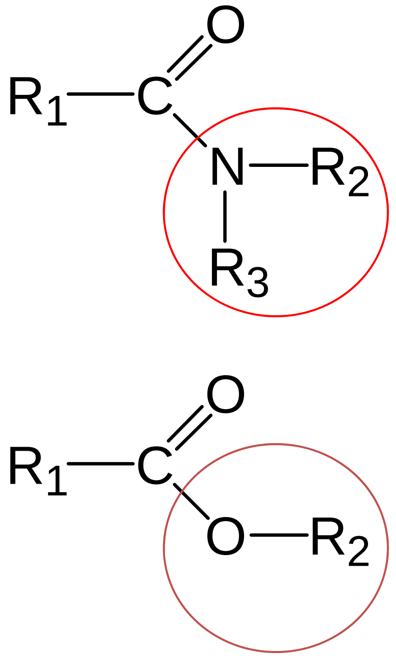


Table 13.9 Comparison of k_N and k_B Values of Some Carboxylic Acid Esters at 25°C and Influence of Leaving Group and Polar Substituents on k_N and k_B ^{a}

Compound	pK_a of ROH	Relative Value k_N	Relative Value k_B	k_B/k_N (M^{-1})
	≈ 16	1	1	7.3×10^8
	9.98	440	13	2.1×10^7
	3.96	73000	850	8.5×10^6
	≈ 15	1	1	6.6×10^8
	≈ 15	71	20	1.9×10^8
	9.98	8600	93	6.3×10^6

Hydrolysis of Acid Derivatives

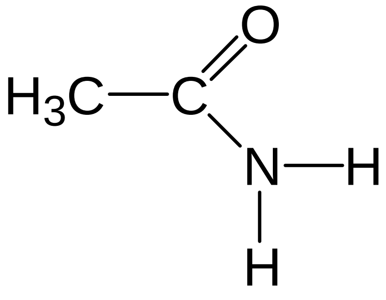
- Carboxylic acid amides
  - derivatives of *formamide* $HC(=O)NH_2$
  - *less* reactive than carboxylic acid esters
    - because $–NR_2R_3$ is poorer leaving group compared to $–OR_2$ $R_2R_3NH \rightleftarrows R_2R_3N^- + H^+$ $pK_a \sim 10$



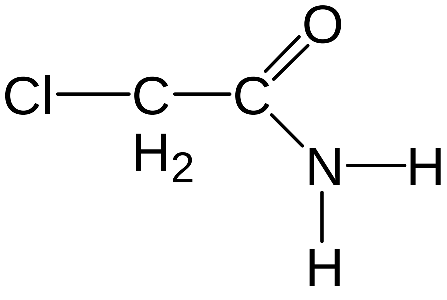
  - acid-catalyzed, base-catalyzed hydrolysis dominate

Hydrolysis of Acid Derivatives

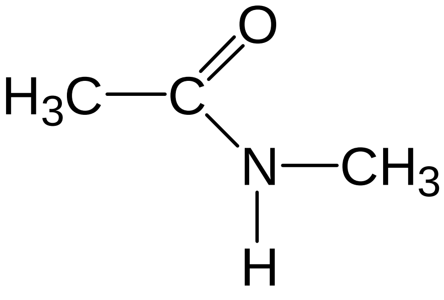
- Carboxylic acid amide nomenclature



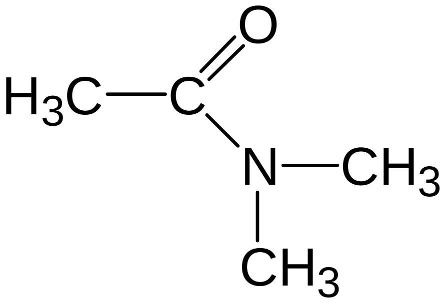
acetamide



2-chloroacetamide



N-methylacetamide

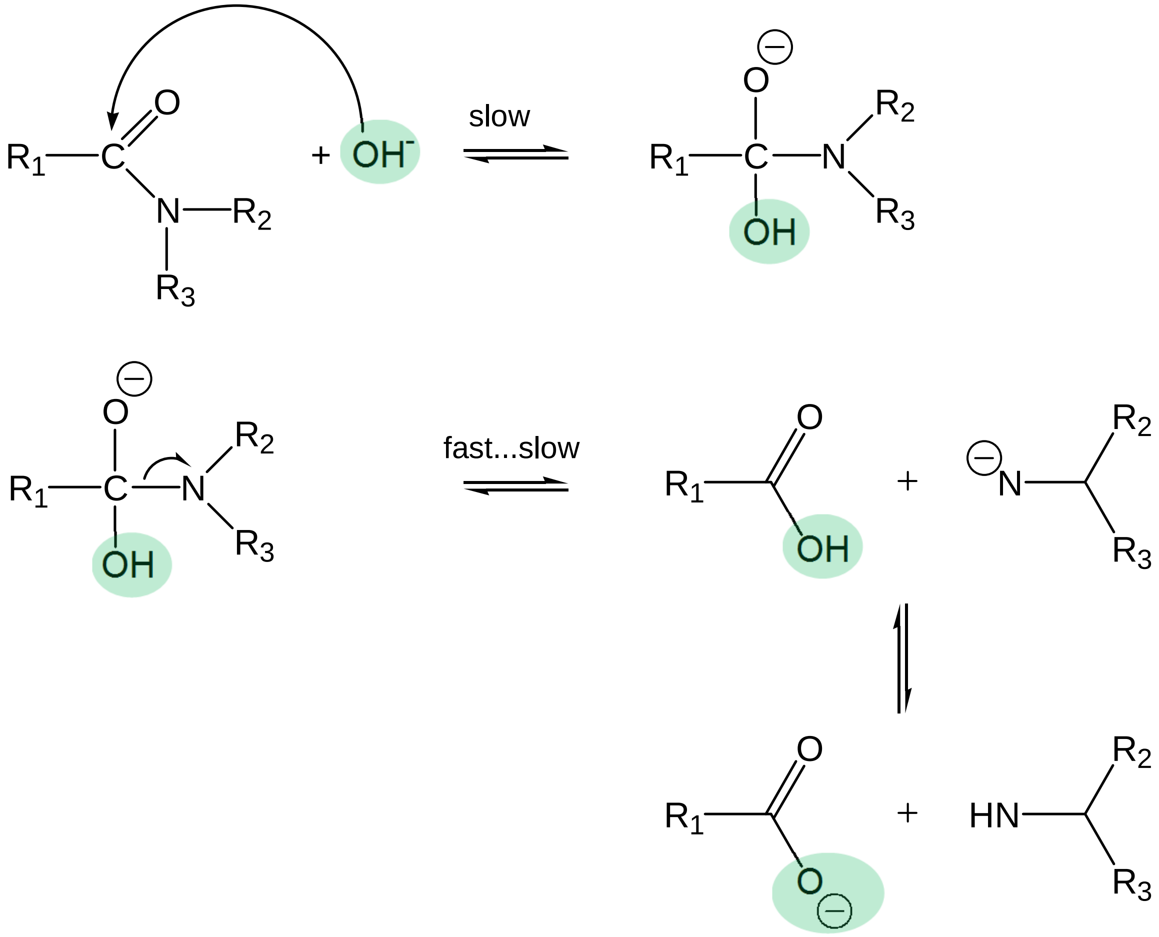


N,N-dimethylacetamide

- Numerous herbicides contain amide group

Hydrolysis of Acid Derivatives

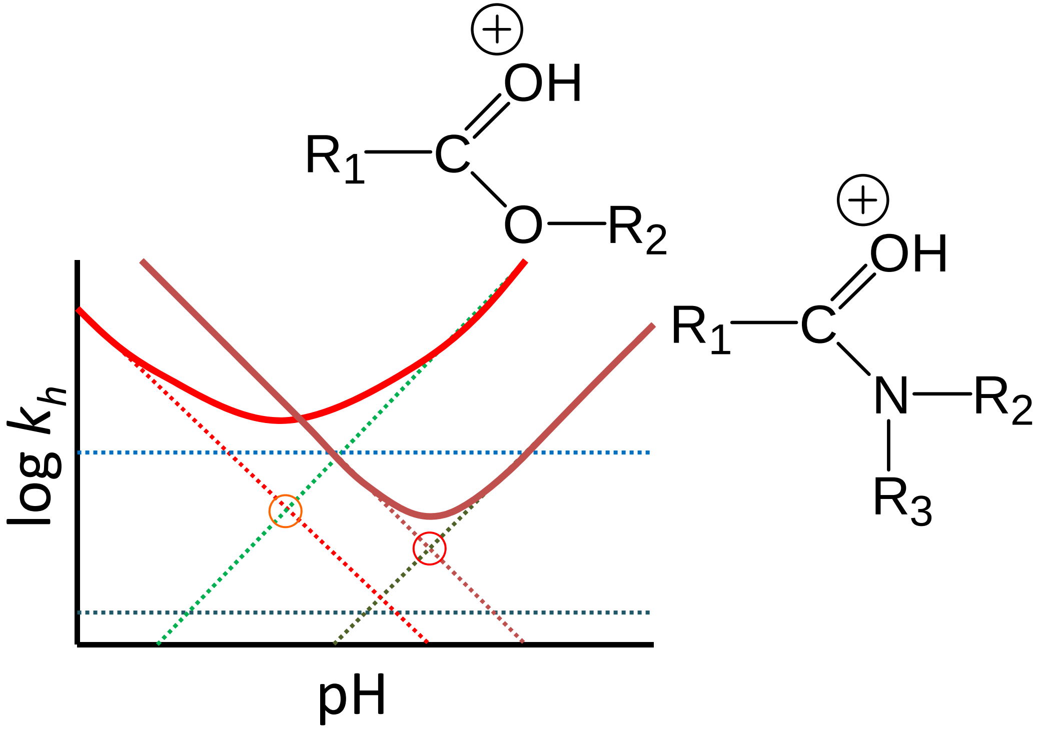
- Mechanisms
  - base-catalyzed hydrolysis
  - (neutral hydrolysis insignificant)
  - products
    - carboxylic acid
    - amine



Hydrolysis of Acid Derivatives

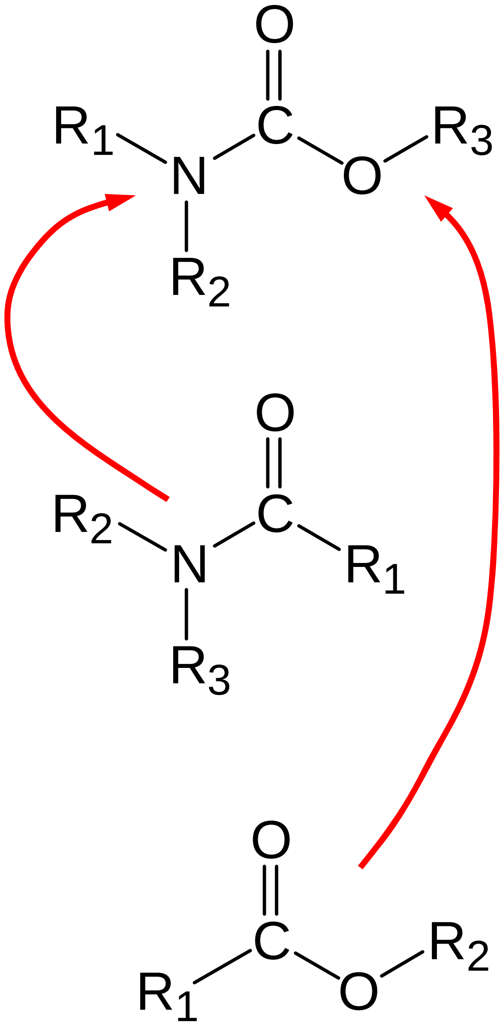
- Mechanisms
  - acid-catalyzed hydrolysis
    - amide more basic, accepts proton better
    - I_{AB} of amide > I_{AB} of ester

      (acid hydrolysis important at higher pHs for amide)



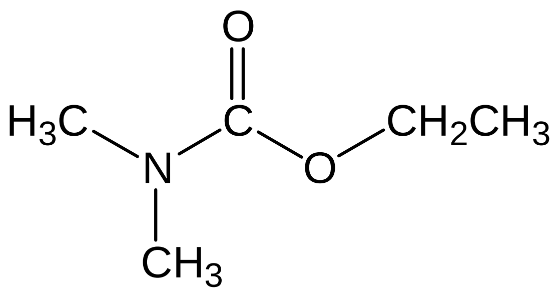
Hydrolysis of Acid Derivatives

- Carbamates
  - derivatives of *carbamic acid* $H_2NC(=O)OH$
    - ester and amide combined
    - herbicides, insecticides
  - acid-catalyzed hydrolysis unimportant
    - too acidic, won't protonate
  - products
    - alcohol, $HO\text{-}R_3$
    - amine, HNR_1R_2
    - CO_2

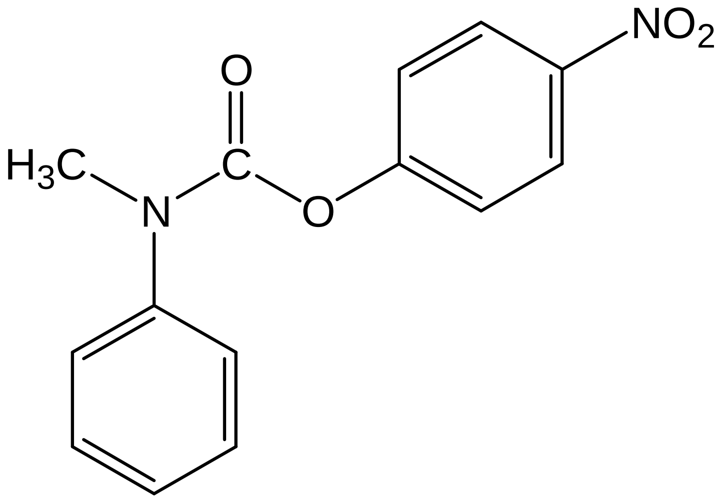


Hydrolysis of Acid Derivatives

- Carbamate nomenclature

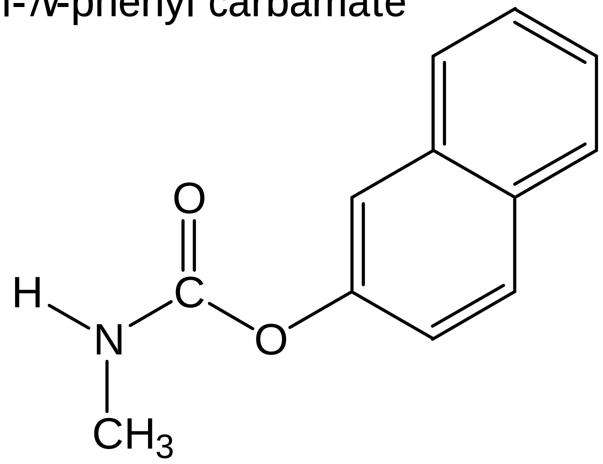


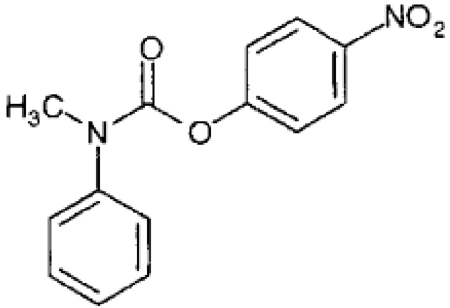
ethyl-*N*,*N*-dimethyl carbamate



4-nitrophenyl-*N*-methyl-*N*-phenyl carbamate

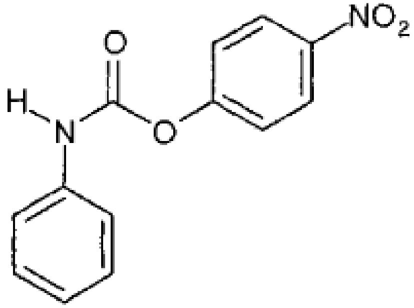
naphthyl-*N*-methyl carbamate





I

$t_{1/2}$ (pH7) = 275 yr

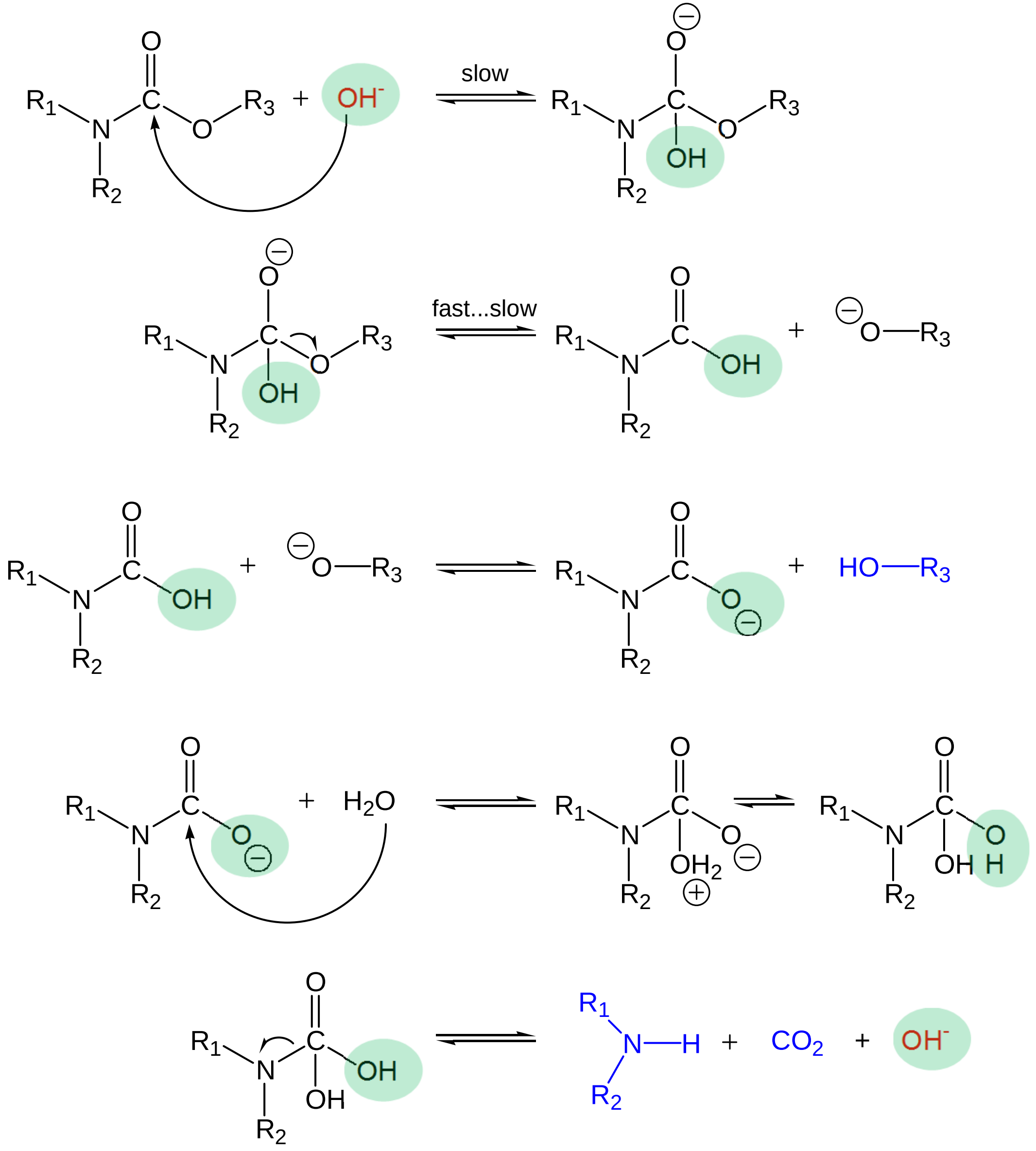


II

$t_{1/2}$ (pH7) = 25 s

Hydrolysis of Acid Derivatives

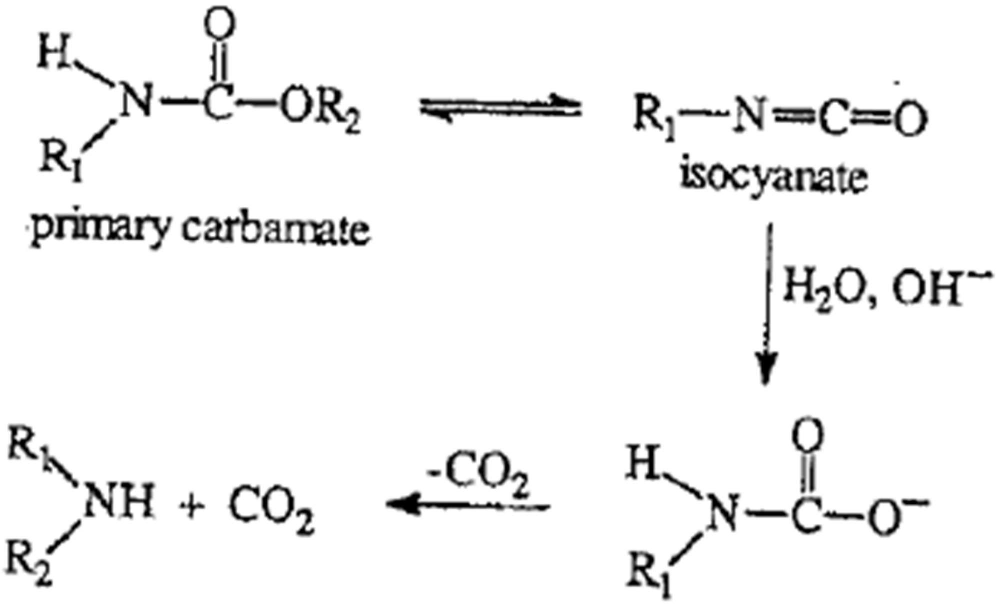
- Mechanisms
  - base-catalyzed hydrolysis
  - *leaving group controlled by* pK_a
  - usually, $-OR_3$ has lower pK_a than $-NR_1R_2$



Hydrolysis of Acid Derivatives

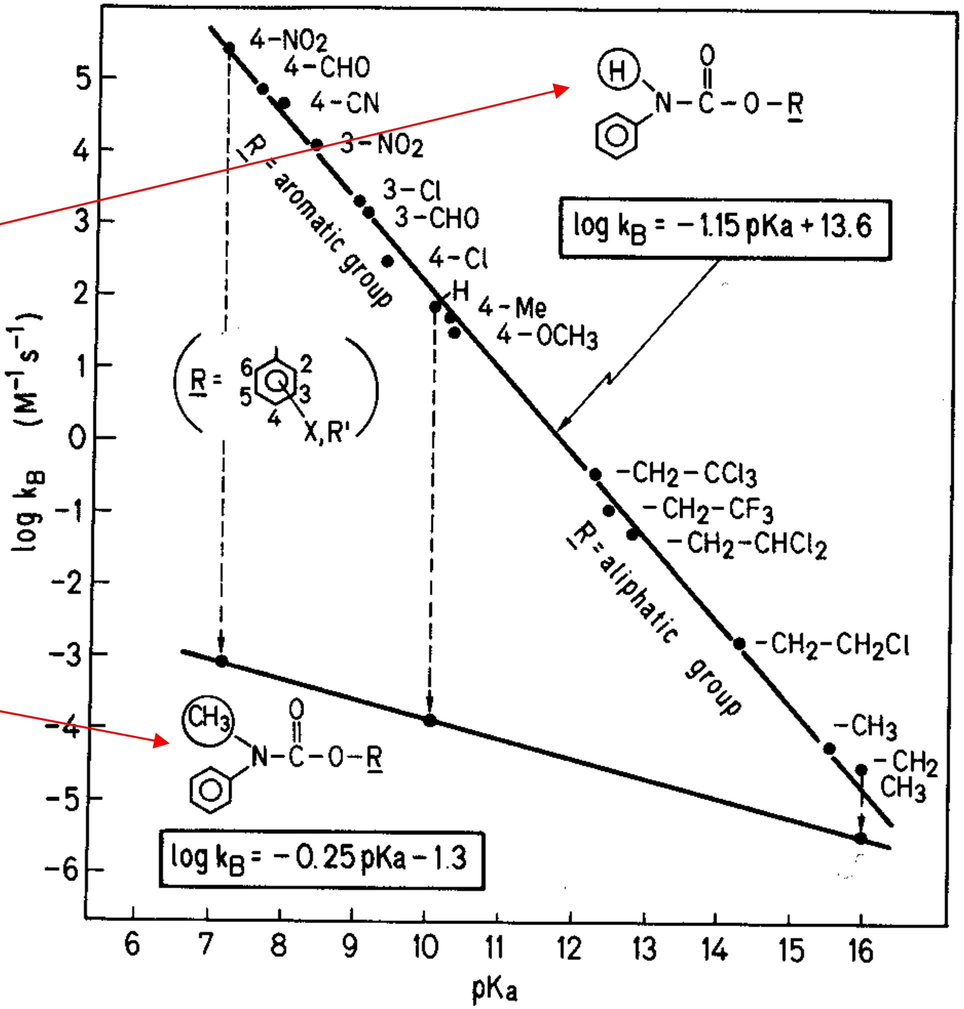
- Mechanisms

In special case of alkaline hydrolysis of N- substituted aryl carbamates another mechanism involving elimination-addition



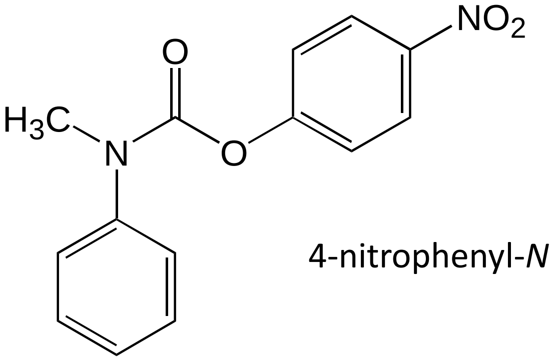
Hydrolysis of Acid Derivatives

- Carbamates
  - hydrolysis depends on amide substitution
  - *N*-substituted
    - alcohol is leaving group
    - very sensitive to alcohol pK_a
  - *N*,*N*-substituted
    - much less sensitive to alcohol pK_a



Hydrolysis of Acid Derivatives

- What is the half-life of this carbamate at pH 8?



4-nitrophenyl-*N*-methyl-*N*-phenyl carbamate

  - leaving group is 4-nitrophenol, pK_a = 7.15
  - *N,N*-methylphenyl carbamate:

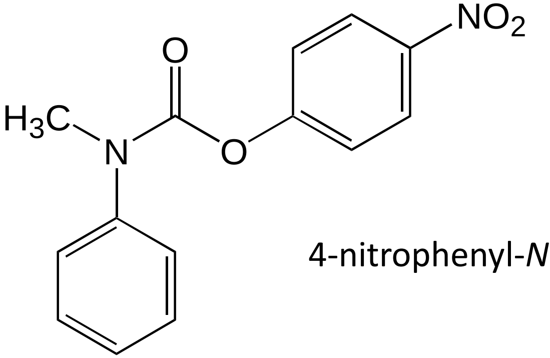
$$\log k_B = -0.25\,pK_a - 1.3$$

$$\log k_B = -0.25(7.15) - 1.3 = -3.09$$

$$k_B = 10^{-3.09}\ \mathrm{M^{-1}\,s^{-1}}$$

Hydrolysis of Acid Derivatives

- What is the half-life of this carbamate at pH 8?

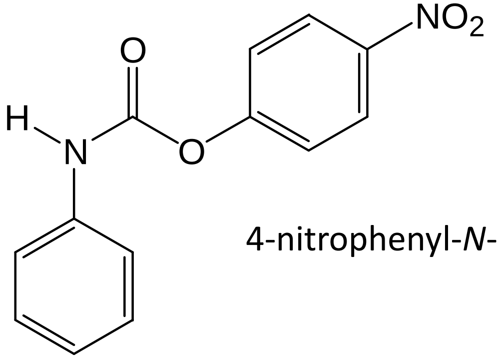


4-nitrophenyl-*N*-methyl-*N*-phenyl carbamate

  - $k_B = 10^{-3.09}\ M^{-1}\ s^{-1} = 8.2x10^{-4}\ M^{-1}\ s^{-1}$
  - $k_h = k_B[OH^-] = 8.2x10^{-10}\ s^{-1}$
  - $t_{1/2} = 27\ y$

Hydrolysis of Acid Derivatives

- What is the half-life of this carbamate at pH 8?



4-nitrophenyl-*N*-phenyl carbamate

- 4-nitrophenol, $pK_a = 7.15$
- *N*-phenyl carbamate:

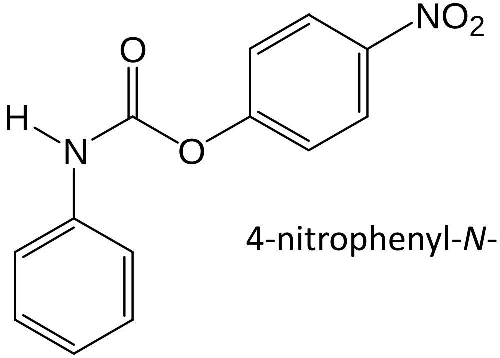
$$\log k_B = -1.15\, pK_a + 13.6$$

$$\log k_B = -1.15(7.15) + 13.6 = 5.38$$

$$k_B = 10^{5.38}\ \mathrm{M^{-1}\, s^{-1}}$$

Hydrolysis of Acid Derivatives

- What is the half-life of this carbamate at pH 8?

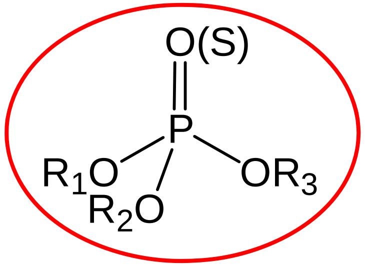


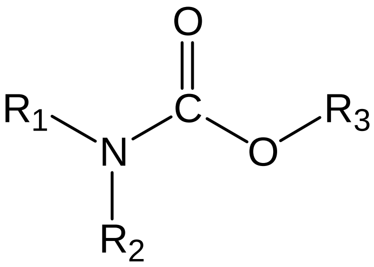
4-nitrophenyl-*N*-phenyl carbamate

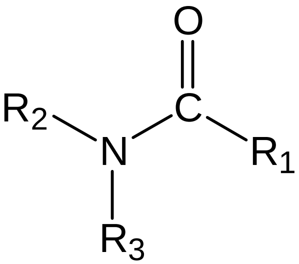
- $k_B = 10^{5.38} = 2.4\text{x}10^5\ \text{M}^{-1}\ \text{s}^{-1}$
- $k_h = \text{k}_\text{B}[\text{OH}^-] = 0.24\ \text{s}^{-1}$
- $t_{1/2} = 3\ \text{s}$

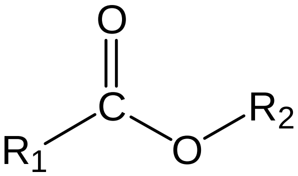
Hydrolysis of Acid Derivatives

- Phosphoric and thiophosphoric acid esters
  - pentavalent P
  - insecticides, fire retardants
  - two spots for nucleophilic substitution
    - at the phosphorus
    - at the carbon in R_1, R_2, or R_3



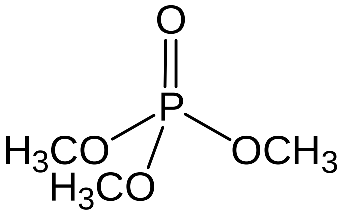




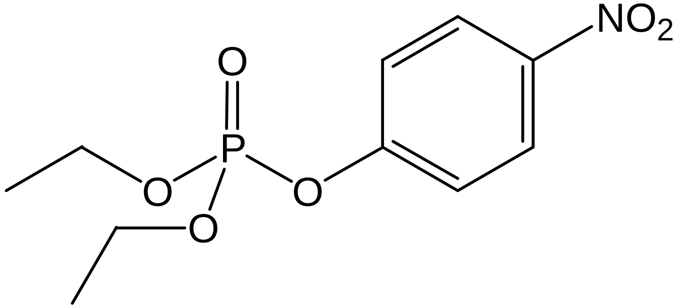


Hydrolysis of Acid Derivatives

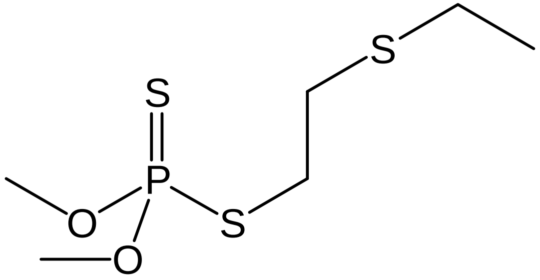
- Nomenclature



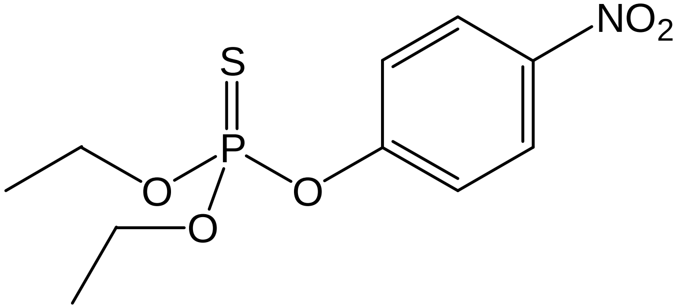
trimethylphosphate



diethyl *p*-nitrophenyl phosphate (Paraoxon)

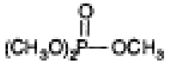
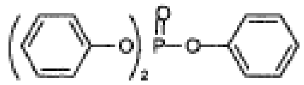
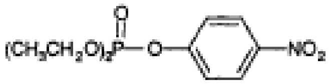
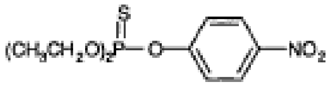
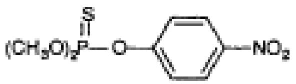
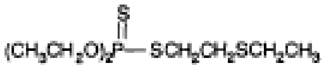
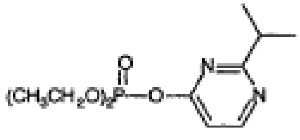
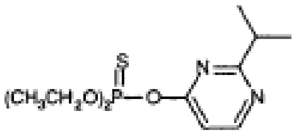


dimethyl-*S*-(2-ethylmercaptoethyl)
dithiophosphate (Thiometon)



diethyl *p*-nitrophenyl thiophosphate
(Parathion)

Table 13.12 Rate Constants k_A, k_N, and k_B, Half-Lives, $t_{1/2}$, at pH 7, and I_{NB} Values for Hydrolysis of Some Phosphoric and Thiophosphoric Acid Triesters at 25°C [a]

Compound Name	Structural Formula	k_A [b]	k_N (s^{-1})	k_B ($M^{-1}\,s^{-1}$)	$t_{1/2}$ (pH 7)	I_{NB}
Trimethylphosphate	 $(CH_3O)_2\overset{\overset{O}{\|}}{P}-OCH_3$	NI	1.8×10^{-8}	1.6×10^{-4}	1.2 yr	10.0
Triethylphosphate	 $(CH_3CH_2O)_2\overset{\overset{O}{\|}}{P}-OCH_2CH_3$	NI	$\approx 4 \times 10^{-9}$	8.2×10^{-6}	≈ 5.5 yr	10.7
Triphenylphosphate		NI	$< 3 \times 10^{-9}$	2.5×10^{-1}	320 d	< 6
Paraoxon		NI	7.3×10^{-8}	3.9×10^{-1}	72 d	7.3
Parathion		NI	8.3×10^{-8}	5.7×10^{-2}	89 d	8.2
Methylparathion		NI	1.2×10^{-7}	1.1×10^{-2}	67 d	9.0
Thiometon [c]	 $(CH_3O)_2\overset{\overset{S}{\|}}{P}-SCH_2CH_2SCH_2CH_3$	NI	1.1×10^{-7}	6.4×10^{-3}	73 d	9.4
Disulfoton [c]	 $(CH_3CH_2O)_2\overset{\overset{S}{\|}}{P}-SCH_2CH_2SCH_2CH_3$	NI	1.4×10^{-7}	2.0×10^{-3}	57 d	10.0
Diazoxon [c]		6.5×10^{-1}	2.8×10^{-7}	7.6×10^{-2}	23 d	8.6 [d]
Diazinon [c]		2.1×10^{-2}	4.3×10^{-8}	5.3×10^{-3}	178 d	8.9 [e]

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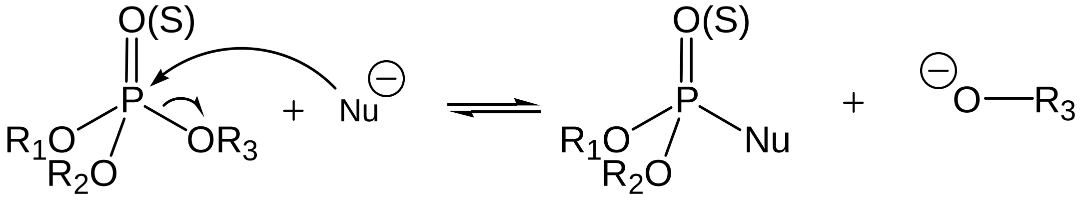
[a] Data from Faust and Gomaa (1972), Mabey and Mill (1978), and Wanner et al. (1989). [b] NI = not important. [c] At 20°C. [d] $I_{AN} = 6.4$. [e] $I_{AN} = 5.7$.

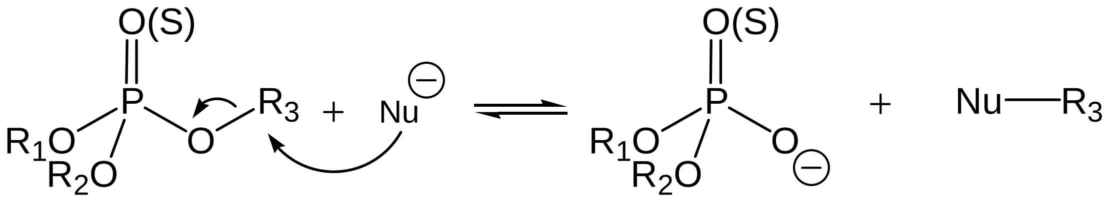
Hydrolysis of Acid Derivatives

Mechanisms

- nucleophile attacks P
  - Base-catalyzed
    - OH^- stronger nucleophile than H_2O



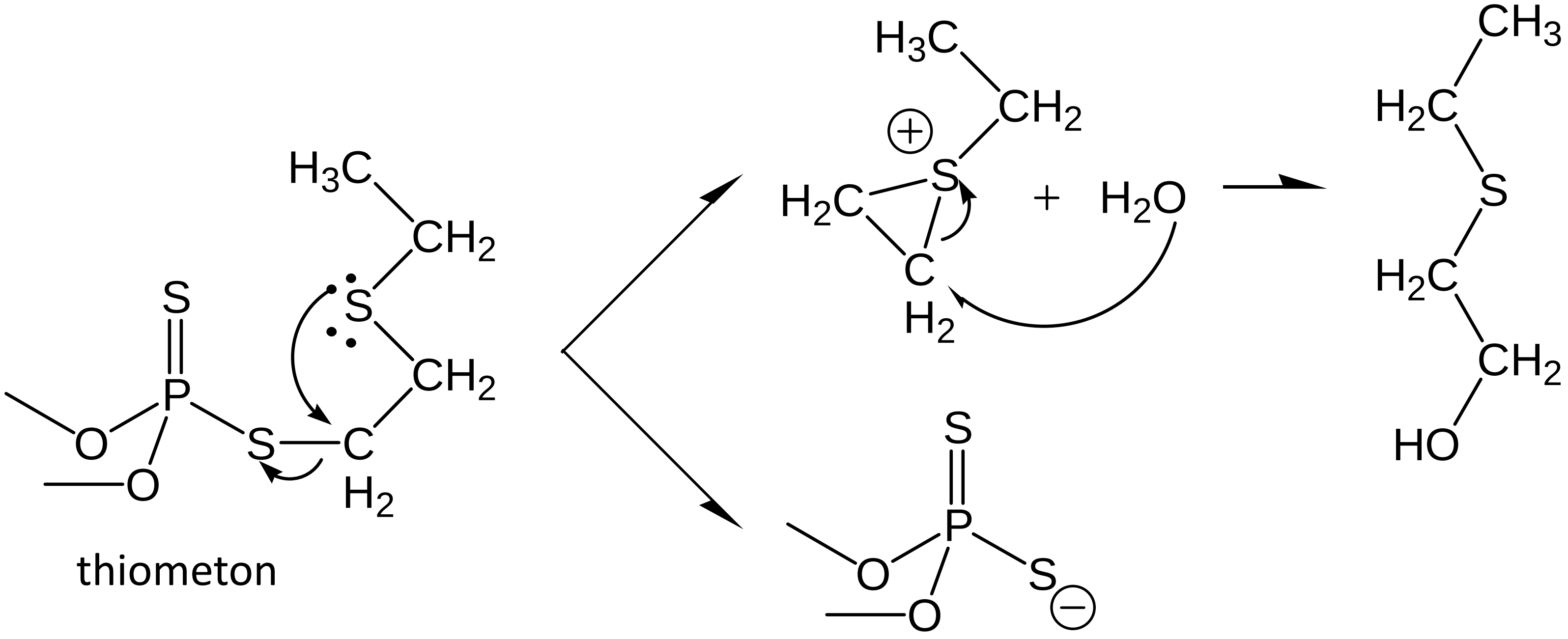
- nucleophile attacks C
  - Neutral reaction
    - usually H_2O

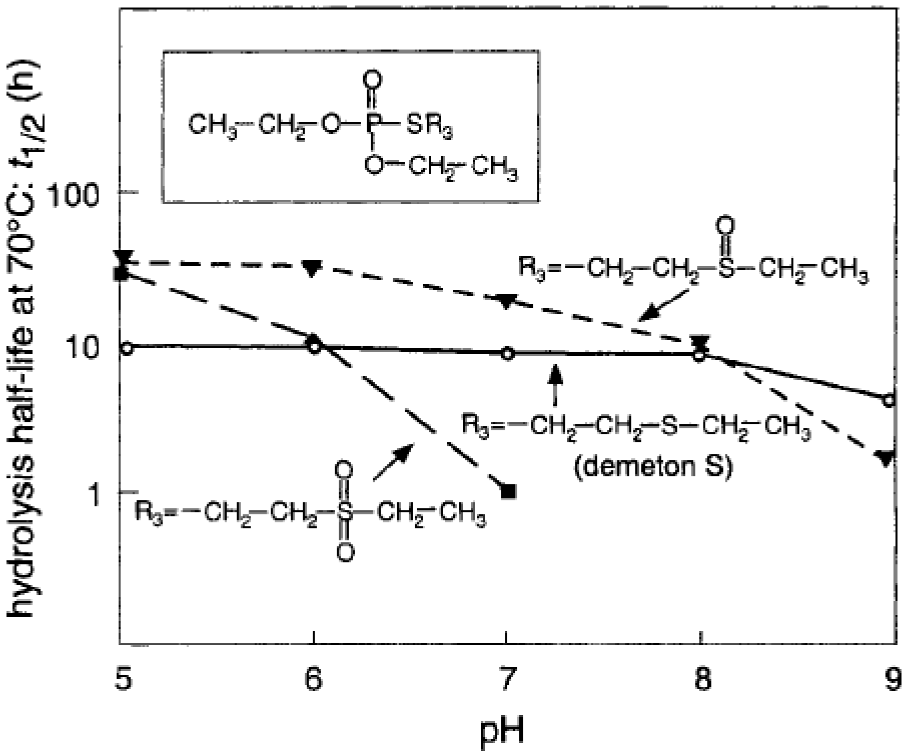


Hydrolysis of Acid Derivatives

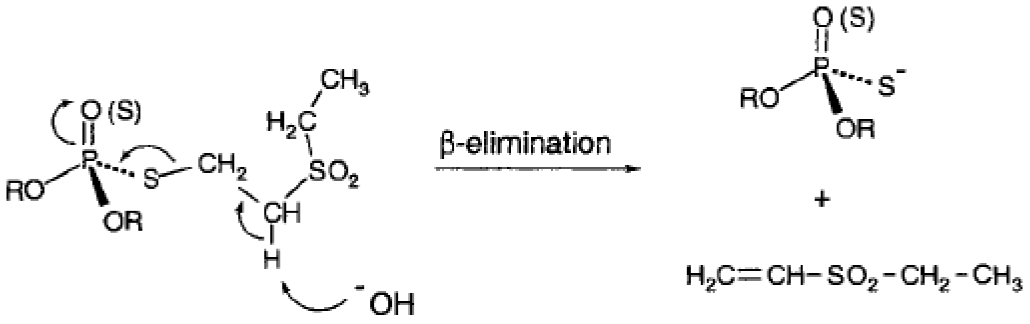
Thiophosphoric acid thioester

- internal nucleophilic substitution (S_Ni)





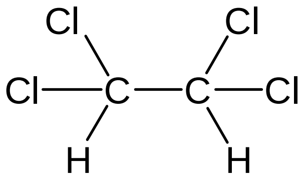
An acaricide and insecticide



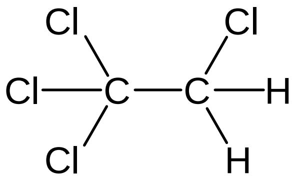
Esercizio

Hydrolysis of Chlorinated Ethanes
Which compound will hydrolyze fastest?

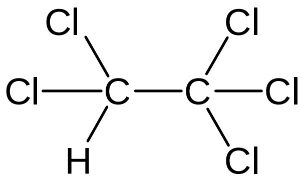
A.



B.



C.

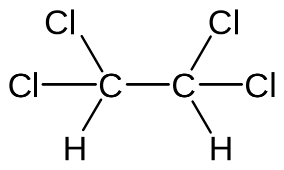


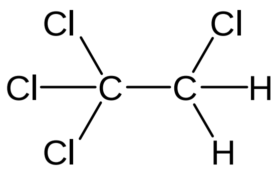
Fastest?

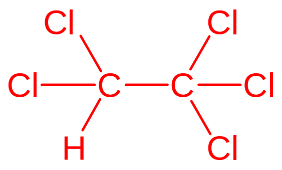
greatest k_h, shortest half-life

Hydrolysis of Chlorinated Ethanes

		1,1,2,2-tetrachloro-	1,1,1,2-tetrachloro-	pentachloro-
epilimnion	k_N (s^{-1})	$1x10^{-10}$	$4x10^{-10}$	$8x10^{-10}$
25 C	k_B (M^{-1} s^{-1})	$5x10^{-1}$	$3.5x10^{-4}$	$2.7x10^{1}$
pH 8.5	k_B [OH^-] (s^{-1})	$1.6x10^{-6}$	$1.1x10^{-9}$	$8.5x10^{-5}$
[OH^-] = $10^{-5.5}$ M	k_h (s^{-1})	$1.6x10^{-6}$	$1.5x10^{-9}$	$8.5x10^{-5}$
$K_w = 10^{-14.00}$	$t_{1/2}$ (s)	$4.3x10^{5}$	$4.6x10^{8}$	8,200
	$t_{1/2}$ (d)	5.0	5,300	0.094
	I_{NB}	4.3	8.1	3.5
hypolimnion	k_N (s^{-1})	$6.7x10^{-12}$	$2.5x10^{-11}$	$5.1x10^{-11}$
5 C	k_B (M^{-1} s^{-1})	$5.2x10^{-2}$	$1.9x10^{-5}$	$2.7x10^{0}$
pH 7.5	k_B [OH^-] (s^{-1})	$3.0x10^{-9}$	$1.1x10^{-12}$	$1.6x10^{-7}$
[OH^-] = $10^{-7.23}$ M	k_h (s^{-1})	$3.0x10^{-9}$	$2.6x10^{-11}$	$1.6x10^{-7}$
$K_w = 10^{-14.73}$	$t_{1/2}$ (s)	$2.3x10^{8}$	$2.7x10^{10}$	$4.3x10^{6}$
	$t_{1/2}$ (d)	2,700	310,000	50
	I_{NB}	5.0	8.8	4.0

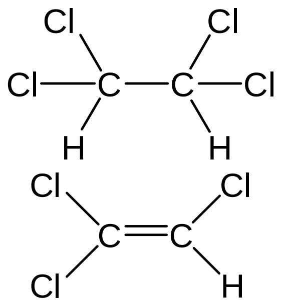




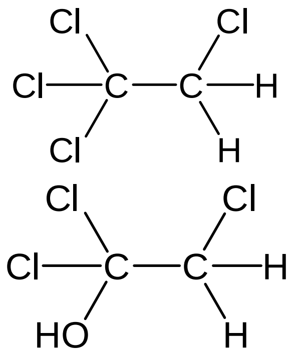


Hydrolysis of Chlorinated Ethanes

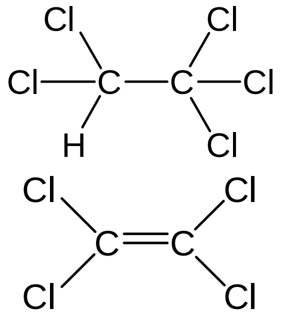
- Major products and mechanisms



  - 1,1,2,2-tca ⇒ trichloroethene
    - E_2 elimination, second-order
      - low I_{NB} (4.3): acidic, promotes elimination



  - 1,1,1,2-tca ⇒ 1,1,2-trichloroethanol(?)
    - S_N2 nucleophilic substitution, second order
      - high I_{NB} (8.1): elimination unlikely



  - pentachloroethane ⇒ tetrachloroethene
    - E_2 elimination, second-order
      - even lower I_{NB} (3.5) promotes elimination