Nucleophilic reactions II: Kinetics

### S<sub>N</sub>2: Relative nucleophilicity

- Study of nucleophilic substitution of methyl halides for various nucleophiles:
  - Methyl halides (CH<sub>3</sub>X) have similar relative reactivity toward different nucleophiles
  - Swain & Scott (1953):

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

 $k_{Nu}$  = 2<sup>nd</sup>-order rate const. for a nucleophile of interest  $k_{H_2O}$  = 2<sup>nd</sup> order rate const. for H<sub>2</sub>O

 $n_{Nu,CH_3Br}$  = a measure of the nucleophilicity of the nucleophile of interest

*s* = sensitivity of the organic molecule to nucleophilic attack



n<sub>Nu,CH3</sub>Br---?

- Set CH<sub>3</sub>Br as a reference compound to measure the nucleophilicity
- Set H<sub>2</sub>O as a reference nucleophile
- By observing a nucleophilic substitution reaction between CH<sub>3</sub>Br and Nu, n<sub>Nu,CH<sub>3</sub>Br</sub> can be determined:

$$n_{Nu,CH_{3}Br} = log \left[ \frac{(k_{Nu})_{CH_{3}Br}}{(k_{H_{2}O})_{CH_{3}Br}} \right] * so, \ n_{H_{2}O,CH_{3}Br} = 0$$

• 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	$n_{_{Nu,CH_3Br}}a$
CIO <sub>4</sub>	<0
$H_2O$	0
NO <sub>3</sub>	1.0
F	2.0
SO <sub>4</sub> <sup>2-</sup>	2.5
CH <sub>3</sub> COO <sup>-</sup>	2.7
Cl-	3.0
$HCO_3$ , $HPO_4^2$	3.8
Br	3.9
OH-	4.2
I <sup>-</sup>	5.0
CN <sup>-</sup> , HS <sup>-</sup>	5.1
$S_2O_3^{2-}$	6.1 <sup>b</sup>
PhS <sup>-</sup>	6.8 <sup>b</sup>
S <sub>4</sub> <sup>2-</sup>	7.2 <sup>b</sup>

<sup>*a*</sup> Data from Hine (1962). <sup>*b*</sup> Data from Haag and Mill (1988a).

## S<sub>N</sub>2: 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<sub>2</sub>O is abundant ([H<sub>2</sub>O] $\uparrow$ ), so a nucleophile should compete with hydrolysis
- Define [Nu]<sub>50%</sub> as the nucleophile concentration that satisfies:

 $[Nu]_{50\%}k_{Nu} = [H_2O]k_{H_2O}$ 1<sup>st</sup> order rate of Nu reaction 1<sup>st</sup> order rate of hydrolysis

assuming s=1,  $k_{Nu} = k_{H_20} \times 10^{n_{Nu,CH_3Br}}$ 

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

55.3 = molar concentration of water (M) @ 25 °C

## S<sub>N</sub>2: Determining significance

- Use [Nu]<sub>50%</sub> to determine whether a nucleophile is significant
- Freshwater vs. saline water
  - Freshwater [Cl<sup>-</sup>] ~ 10<sup>-4</sup> M → Cl<sup>-</sup> not a significant nucleophile
  - Seawater [Cl<sup>-</sup>] ~ 0.5 M → Cl<sup>-</sup> a significant nucleophile
- pH sensitivity of hydrolysis reaction
  - Low & neutral pH → OH<sup>-</sup> not a significant nucleophile
  - High pH (e.g., pH>11) → OH<sup>-</sup> a significant nucleophile

**Table 13.5** CalculatedConcentration of NucleophileRequired to Compete with Waterin an  $S_N 2$  Reaction with AlkylHalides Assuming an s Value of 1

Nucleophile	$[Nu]_{50\%}^{a}(M)$
NO3	~6
F <sup>-</sup>	$\sim 6 \times 10^{-1}$
SO4 <sup>2-</sup>	$\sim 2 \times 10^{-1}$
Cl-	$\sim 6 \times 10^{-2}$
HCO <sub>3</sub>	$\sim 9 \times 10^{-3}$
HPO <sub>4</sub>	$\sim 9 \times 10^{-3}$
Br <sup>-</sup>	$\sim 7 \times 10^{-3}$
OH-	$\sim 4 \times 10^{-3}$
I_	$\sim 6 \times 10^{-4}$
HS <sup>-</sup>	~4 × 10 <sup>-4</sup>
CN <sup>-</sup>	~4 × 10 <sup>-4</sup>
$S_2O_3^{2-}$	$\sim 4 \times 10^{-5}$
S4 <sup>2-</sup>	$\sim 4 \times 10^{-6}$

<sup>*a*</sup> Eq. 13-5 using the  $n_{\text{Nu,CH}_3\text{Br}}$  values given in Table 13.3.

## S<sub>N</sub>1 & S<sub>N</sub>2: Leaving groups

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• Reaction rates for methyl halides:  $CH_3Br \sim CH_3I > CH_3CI > CH_3F$ 



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# S<sub>N</sub>1 & S<sub>N</sub>2: Effect of EDGs & resonance

**Table 13.6** Hydrolysis Half-Lives and Postulated Reaction Mechanisms at 25°C of Some Monohalogenated Hydrocarbons at Neutral pH<sup>*a*</sup>

	Type of Carbon	$t_{1/2}$ (Hydrolysis)			Dominant Mechanism(s)	
Compound	to Which L is Attached	L = F	Cl	Br	I	tution Reactions
R-CH2-L	primary	≈30 yr <sup>b</sup>	340 d <sup>b</sup>	20–40 d °	50–110 d <sup>d</sup>	S <sub>N</sub> 2
н₃с сн-∟ н₃с	secondary		38 đ	2 d	3 d	S <sub>N</sub> 2 S <sub>N</sub> 1
СН <sub>3</sub> H <sub>3</sub> CL CH <sub>3</sub>	tertiary	50 d	23 s			S <sub>N</sub> 1
CH2=CH-CH2-L	allyl		69 d	0.5 d	2 d	$S_N 2 \dots S_N 1$
CH2-L	benzyl		15 h	0.4 h		$S_N 2 S_N 1$

<sup>*a*</sup> Data taken from Robertson (1969) and Mabey and Mill (1978). <sup>*b*</sup> R = H. <sup>*c*</sup> R = H, C<sub>1</sub> to C<sub>5</sub>-*n*-alkyl. <sup>*d*</sup> R = H, CH<sub>3</sub>.

Nucleophilic reactions I: Overview

### **Nucleophiles & nucleophilic substitution**

#### • 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

 $Nu: +R - L \implies R - Nu + L:$ 

- S<sub>N</sub>2 & S<sub>N</sub>1 mechanisms

## Nucleophiles & hydrolysis

- Important nucleophiles in the environment
  - High abundance of water (and OH<sup>-</sup> for high pH)
  - Water is usually the most significant among the environmental nucleophiles

#### Hydrolysis

 A reaction in which a water molecule (or OHion) substitutes for another atom or group of atoms present in an organic molecule Table 13.1 Examples of Important Environmenal Nucleophiles

	C104
	$H_2O$
for	NO <sub>3</sub>
city carl	F
hiliá ted	SO <sup>2-</sup> , CH <sub>3</sub> COO <sup>-</sup>
leop atura	CI <sup>-</sup>
nuc a s:	HCO <sub>3</sub> ,HPO <sub>3</sub> <sup>2-</sup>
sing on at	NO <sub>2</sub>
actic	PhO <sup>-a</sup> , Br <sup>-</sup> , OH <sup>-</sup>
inc.	I <sup>-</sup> , CN <sup>-</sup>
	$HS^{-}, R_2 NH^{b}$
	$S_2O_3^{2^-}, SO_3^{2^-}, PhS^-$
<sup>a</sup> Ph = C <sub>4</sub>	H <sub>s</sub> (phenyl)

<sup>a</sup> Ph = C<sub>6</sub>H<sub>5</sub> (phenyl) <sup>b</sup> R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>

Nucleophiles and/or bases						
Reactants		Products	Reaction Number			
Nucleophi	ilic Substitutions at	Saturated Carbon Atoms				
CH <sub>3</sub> Br + H <sub>2</sub> O	<b>_</b>	CH₃OH + H <sup>+</sup> + Br <sup>−</sup>	(1)			
Methyl bromide		Methanol				
CH <sub>3</sub> Cl + HS <sup>-</sup>		CH₃SH + CI <sup>−</sup>	(2)			
Methyl chloride		Methane thiol (Methyl mercaptan)				
О II CH <sub>3</sub> O—Р(ОСН <sub>3</sub> ) <sub>2</sub> + Н <sub>2</sub> О		О II CH <sub>3</sub> OH + <sup>-</sup> O—Р(ОСН <sub>3</sub> ) <sub>2</sub> + H <sup>+</sup>	(3)			
Trimethylphosphate		Methanol Dimethylphosphate				
	$\beta$ -Eliminat	ion				
$Cl_2HC-CHCl_2 + HO^-$		$CI_2C=CHCI + CI^+ H_2O$	(4)			
1,1,2,2-Tetrachloroethane		Trichloroethene				

## **Table 13.2** Examples of Environmentally Relevant Chemical Reactions Involving Nucleophiles and/or Bases



• S<sub>N</sub>2 mechanism



#### • S<sub>N</sub>2 mechanism

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

• S<sub>N</sub>1 mechanism



extent of reaction (reaction coordinate)

#### • S<sub>N</sub>1 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 carboncation complex
- $\Delta^{\dagger}G^{0}$  depends on the stability of the cation
- Follows a first-order kinetic rate law:

$$\frac{d[R_1 R_2 R_3 C - L]}{dt} = -k[R_1 R_2 R_3 C - L]$$

 $k = 1^{st}$  order rate constant (s<sup>-1</sup>)