

















Organic Chemistry – The Functional Group Approach

 alkane (no F.G.) non-polar (grease, fats) tetrahedral	 alcohol polar (water soluble) tetrahedral	 halide non-polar (water insoluble) tetrahedral	 alkene non-polar (water insoluble) trigonal
 alkyne non-polar (water insoluble) linear	 aromatic non-polar (water insoluble) flat	 aldehyde/ketone polar (water soluble) trigonal	 imine polar (water soluble) trigonal

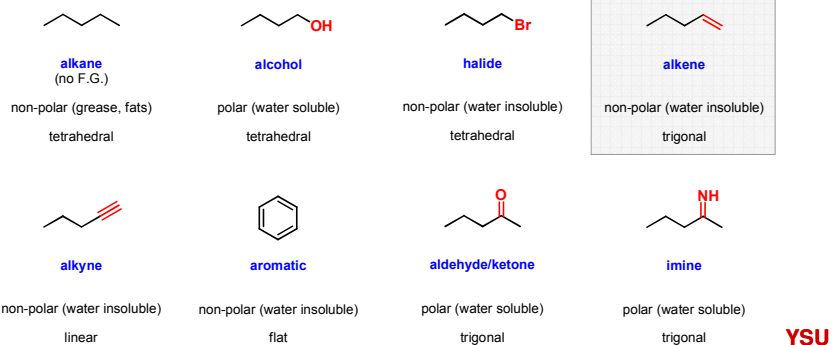
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Organic Chemistry – The Functional Group Approach

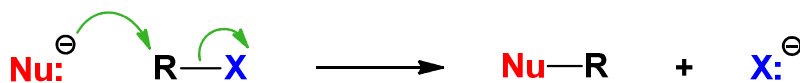
 alkane (no F.G.) non-polar (grease, fats) tetrahedral	 alcohol polar (water soluble) tetrahedral	 halide non-polar (water insoluble) tetrahedral	 alkene non-polar (water insoluble) trigonal
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Organic Chemistry – The Functional Group Approach



Carey Chapter 8 - Nucleophilic Substitution at sp^3 C

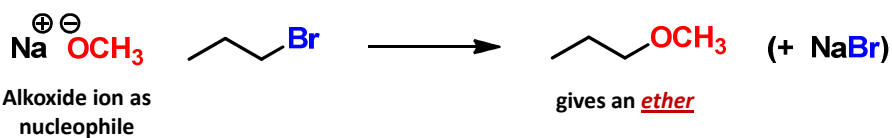


- **nucleophile** is a Lewis base (electron-pair donor)
- often negatively charged and used as Na^+ or K^+ salt
- substrate is usually an **alkyl halide**

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8.1 Functional Group Transformation by S_N2

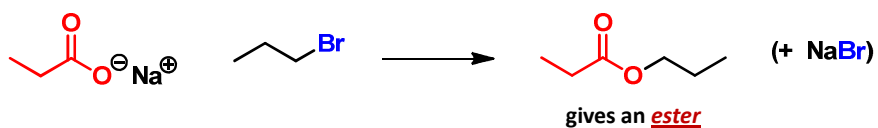
Table 8.1 Examples of Nucleophilic Substitution



- Referred to as the *Williamson ether synthesis*
- Limited to primary alkyl halides
- Run in solvents such as diethyl ether and THF

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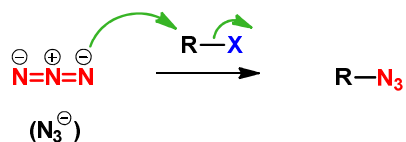
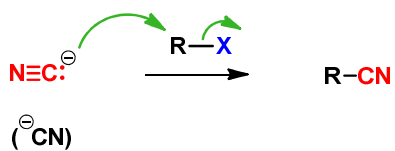
Carboxylate Ion as the Nucleophile



- Not very useful – *carboxylates are poor nucleophiles*
- Limited to primary alkyl halides
- Run in solvents such as diethyl ether and THF
- Better ways of forming esters later in 3720

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Cyanide and Azide Ions as Nucleophiles



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Halides as Nucleophiles – Finkelstein Reaction

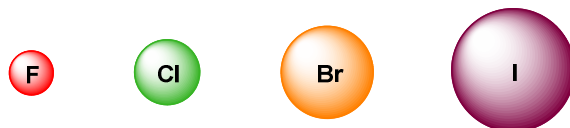


- NaI is soluble in acetone, NaCl and NaBr are not
- NaCl and NaBr precipitate from reaction mixture
- Drives equilibrium to iodide (Le Châtelier's principle)

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8.2 Relative Reactivity of Halide Leaving Groups

- Halides are very good leaving groups
- I^- better than Br^- which is better than Cl^-

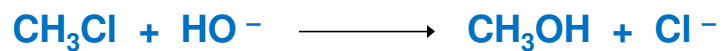


F^- is not used as a leaving group

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8.3 The S_N2 Mechanism of Nucleophilic Substitution

Example:

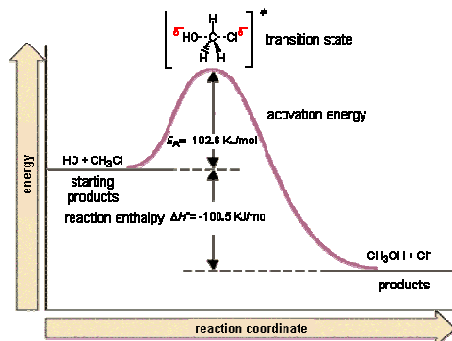


$$\text{rate} = k[CH_3Cl][HO^-]$$

inference: rate-determining step is bimolecular

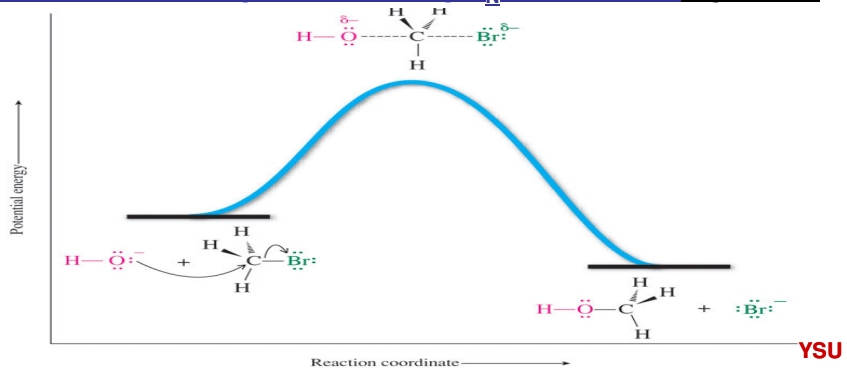
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8.3 The S_N2 Mechanism of Nucleophilic Substitution



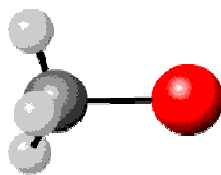
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Inversion of Configuration During S_N2 Reaction – Figure 8.1



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Inversion of Configuration During S_N2 Reaction



<http://www.bluffton.edu/~bergerd/classes/cem221/sn-e/SN2.gif>

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8.4 Steric Effects in Substitution (S_N2) Reactions - Figure 8.2

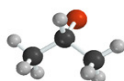
Least crowded—
most reactive



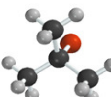
CH₃Br



CH₃CH₂Br

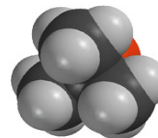
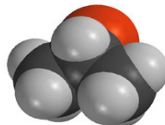
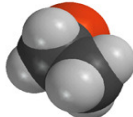


(CH₃)₂CHBr



(CH₃)₃CBr

Most crowded—
least reactive



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Relative Rates of Reaction of Different Primary Alkyl Bromides

TABLE 8.3 Effect of Chain Branching on Reactivity of Primary Alkyl Bromides Toward Substitution Under S_N2 Conditions*

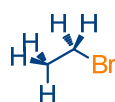
Alkyl bromide	Structure	Relative rate [†]
Ethyl bromide	CH ₃ CH ₂ Br	1.0
Propyl bromide	CH ₃ CH ₂ CH ₂ Br	0.8
Isobutyl bromide	(CH ₃) ₂ CHCH ₂ Br	0.036
Neopentyl bromide	(CH ₃) ₃ CCH ₂ Br	0.00002

*Substitution of bromide by lithium iodide in acetone.

[†]Ratio of second-order rate constant *k* for indicated alkyl bromide to *k* for ethyl bromide at 25°C.

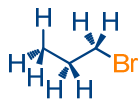
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Relative Rates of Reaction of Different Primary Alkyl Bromides



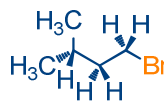
ethyl bromide

1.0



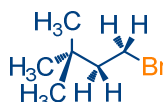
propyl bromide

0.8



isobutyl bromide

0.036



neopentyl bromide

0.00002

Local steric environment has a dramatic effect on reaction rates

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8.5 – Nucleophiles and Nucleophilicity

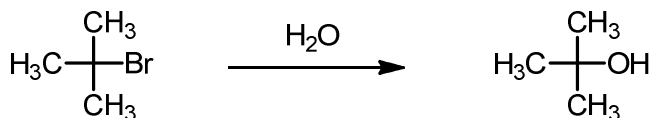
TABLE 8.4 Nucleophilicity of Some Common Nucleophiles

Reactivity class	Nucleophile	Relative reactivity*
Very good nucleophiles	I^- , HS^- , RS^-	$>10^5$
Good nucleophiles	Br^- , HO^- , RO^- , CN^- , N_3^-	10^4
Fair nucleophiles	NH_3 , Cl^- , F^- , RCO_2^-	10^3
Weak nucleophiles	H_2O , ROH	1
Very weak nucleophiles	RCO_2H	10^{-2}

*Relative reactivity is $k(\text{nucleophile})/k(\text{methanol})$ for typical S_N2 reactions and is approximate. Data pertain to methanol as the solvent.

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8.6 The S_N1 Reaction Revisited

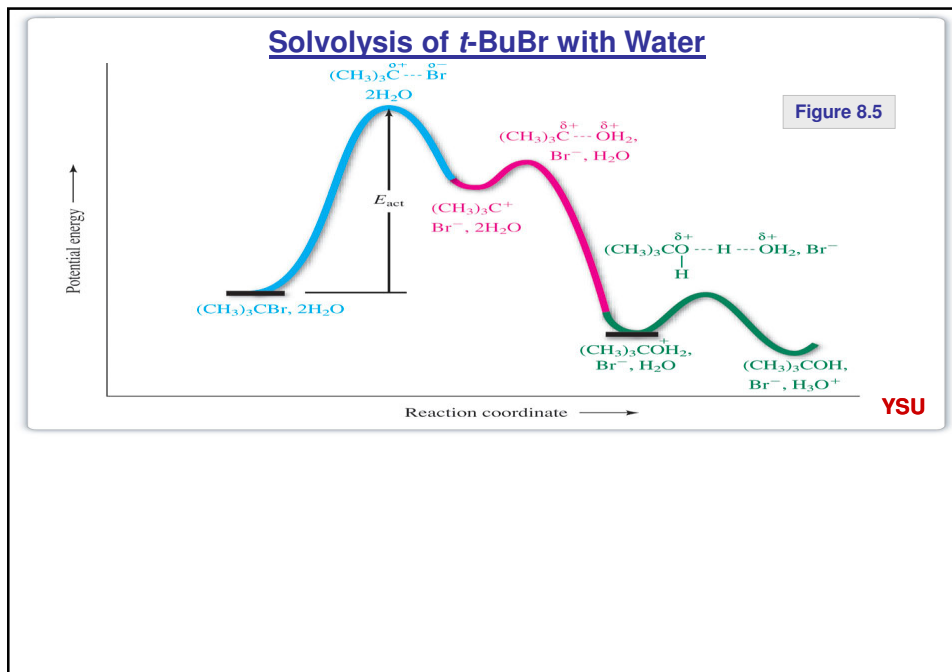


Tertiary system - favours S_N1 - carbocation possible

Carbocation will be the electrophile

Water will be the nucleophile

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8.7 Relative rates of reaction by the S_N1 pathway

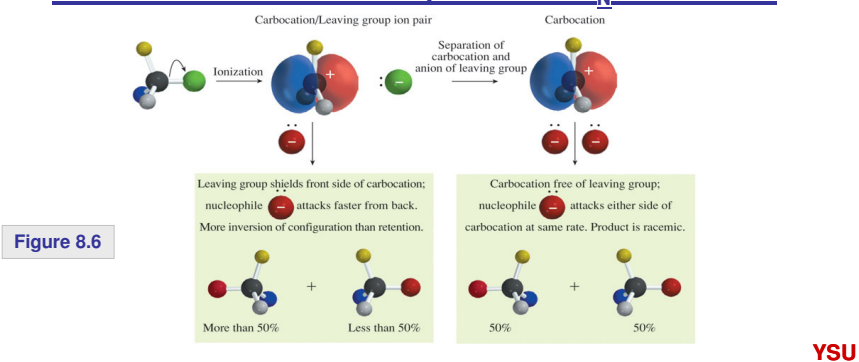
TABLE 8.5 Reactivity of Some Alkyl Bromides Toward Substitution by the S_N1 Mechanism*

Alkyl bromide	Structure	Class	Relative rate
Methyl bromide	CH ₃ Br	Unsubstituted	0.6
Ethyl bromide	CH ₃ CH ₂ Br	Primary	1.0
Isopropyl bromide	(CH ₃) ₂ CHBr	Secondary	26
<i>tert</i> -Butyl bromide	(CH ₃) ₃ CBr	Tertiary	~100,000,000

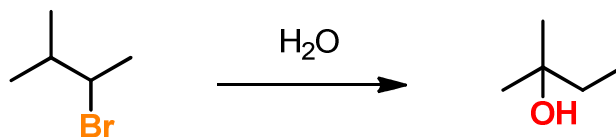
*Solvolysis in aqueous formic acid.

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8.8 Stereochemical Consequences in S_N1 Reactions



8.9 Carbocation Rearrangements Also Possible in S_N1



- Look for change in the product skeleton relative to substrate.
- Rearrangement (alkyl or hydride shift) to generate a **more stable** carbocation.

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8.10 Choice of Solvent for S_N1 is Important

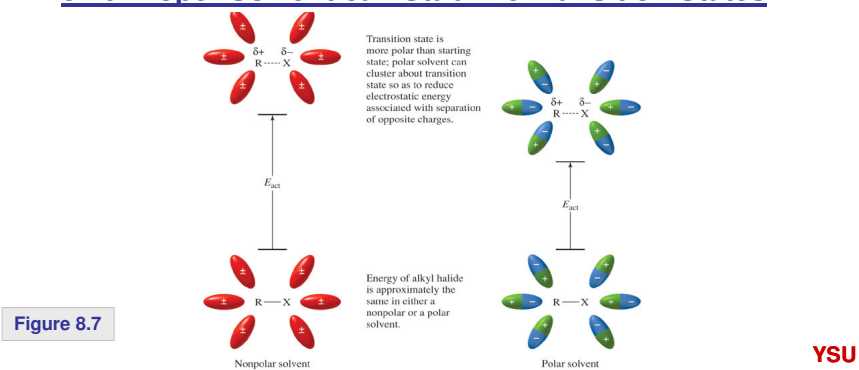
TABLE 8.6 Relative Rate of S_N1 Solvolysis of *tert*-Butyl Chloride as a Function of Solvent Polarity*

Solvent	Dielectric constant ϵ	Relative rate
Acetic acid	6	1
Methanol	33	4
Formic acid	58	5,000
Water	78	150,000

*Ratio of first-order rate constant for solvolysis in indicated solvent to that for solvolysis in acetic acid at 25°C.

Polar solvents (high dielectric constant) will help stabilize ionic intermediates **YSU**

8.10 Proper Solvent can Stabilize Transition States



8.10 Choice of Solvent Important in S_N2

TABLE 8.7 Relative Rate of S_N2 Displacement of 1-Bromobutane by Azide in Various Solvents*

Solvent	Structural formula	Dielectric constant ϵ	Type of solvent	Relative rate
Methanol	CH_3OH	32.6	Polar protic	1
Water	H_2O	78.5	Polar protic	7
Dimethyl sulfoxide	$(\text{CH}_3)_2\text{S}=\text{O}$	48.9	Polar aprotic	1300
<i>N,N</i> -Dimethylformamide	$(\text{CH}_3)_2\text{NCH}=\text{O}$	36.7	Polar aprotic	2800
Acetonitrile	$\text{CH}_3\text{C}\equiv\text{N}$	37.5	Polar aprotic	5000

*Ratio of second-order rate constant for substitution in indicated solvent to that for substitution in methanol at 25°C.

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Solvation of a Chloride by Ion-dipole

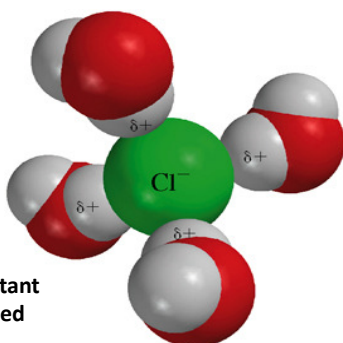
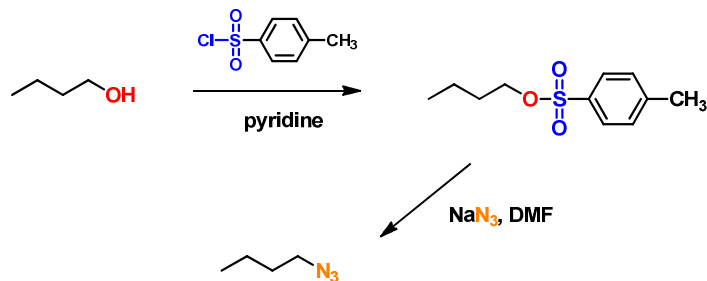


Figure 8.3

Choice of solvent is important for S_N2 - **polar aprotic** used most often

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8.12 Sulfonate Ester Leaving Groups



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8.12 Sulfonate Ester Leaving Groups

TABLE 8.8 Approximate Relative Leaving-Group Abilities*

Leaving group	Relative rate	Conjugate acid of leaving group	pK _a of conjugate acid
F ⁻	10 ⁻⁵	HF	3.1
Cl ⁻	10 ⁰	HCl	-3.9
Br ⁻	10 ¹	HBr	-5.8
I ⁻	10 ²	HI	-10.4
H ₂ O	10 ¹	H ₃ O ⁺	-1.7
CH ₃ SO ₂ O ⁻	10 ⁴	CH ₃ SO ₂ OH	-2.6
TsO ⁻	10 ⁵	TsOH	-2.8
CF ₃ SO ₂ O ⁻	10 ⁸	CF ₃ SO ₂ OH	-6.0

*Values are approximate and vary according to substrate.

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