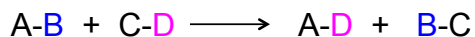


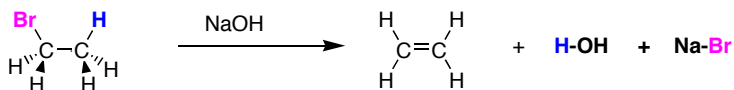
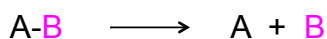
Chapter 7 Substitution Reactions

7.1 Introduction to Substitution Reactions

Substitution Reactions: two reactants exchange parts to give new products



Elimination Reaction: a single reactant is split into two (or more) products. Opposite of an addition reaction (Chapter 8)



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Nucleophilic Substitution – A nucleophile may react with an alkyl halide or equivalent (electrophile) such that the nucleophile will displace the halide (leaving group) and give the substitution product.

Characteristics of a good leaving group

- Good leaving groups tend to be electronegative, thereby withdrawing electron density from the C–LG bond making C more electrophilic (δ^+).
- Leaving group depart with a pair of electrons and often with a negative charge. Good leaving groups can stabilize a negative charge, and are the conjugate bases of strong acid.

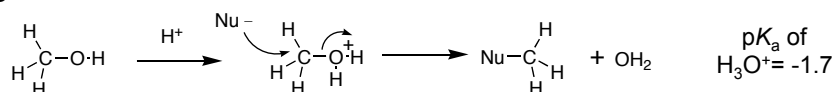
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Increasing reactivity in the nucleophilic substitution reactions



LG:	HO ⁻ , H ₂ N ⁻ , RO ⁻	F ⁻	Cl ⁻	Br ⁻	I ⁻
Relative Reactivity:	<<1	1	200	10,000	30,000
pKa:	>15	3.1	-3.0	-5.8	-10.4

Charged Leaving Groups: conversion of a poor leaving group into a good one



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7.2 Alkyl Halide

Naming Halogenated Organic Compounds - Use the systematic nomenclature of alkanes; treat the halogen as a substituent of the alkane.

F - fluoro Cl - chloro Br - bromo I - iodo

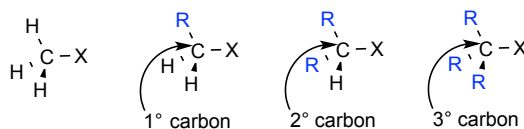
Structure of Alkyl Halides

Reactivity of alkyl halide is dictated by the substitution of the carbon bearing the halogen

primary (1°) : one alkyl substituent

secondary (2°) : two alkyl substituents

tertiary (3°) : three alkyl substituents



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7.3 Possible Mechanisms for Substitution Reactions

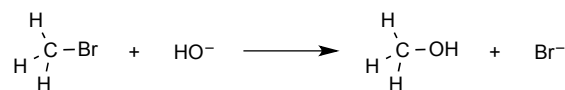
Concerted – bond making and bond breaking processes occur in the same mechanistic step with no intermediate.

Stepwise (non-concerted) – reaction goes through distinct steps with a discrete reaction intermediate(s).

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7.4 The S_N2 Mechanism

Kinetics



$$\text{rate} = k [\text{CH}_3\text{Br}] [\text{OH}^-]$$

[CH₃Br] = CH₃Br concentration

[OH⁻] = OH⁻ concentration

k = rate constant

Second-order reaction (bimolecular) – the rate is dependent on the concentration of both reactants (nucleophile and electrophile)

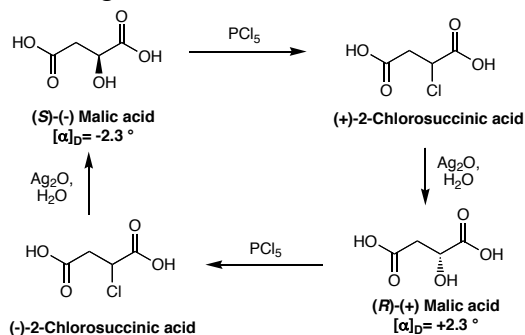
If [OH⁻] is doubled, then the reaction rate is doubled

If [CH₃-Br] is doubled, then the reaction rate is doubled

S_N2 – Substitution, Nucleophilic, bimolecular (2nd order)

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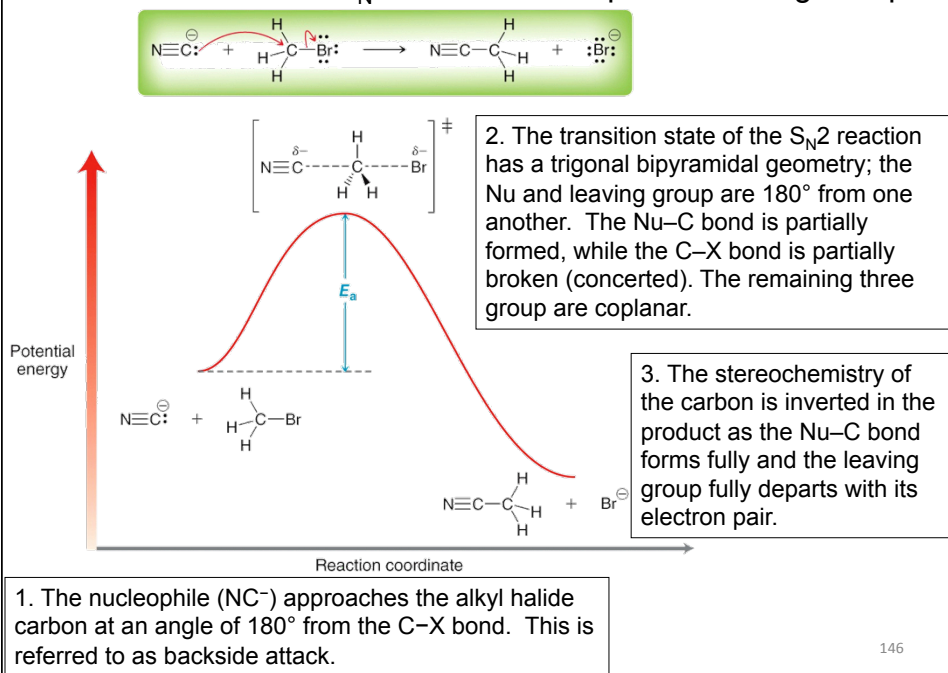
Stereospecificity of S_N2 Reactions – the displacement of a leaving group in an S_N2 reaction has a defined stereochemistry (Walden Inversion). This results from backside attack by the nucleophile and inversion of configuration.



The rate of the S_N2 reaction is dependent upon the concentration of both reactants (nucleophile and electrophile) and is stereospecific; thus, a transition state for product formation involving both reactants (concerted reaction) explains these observations.

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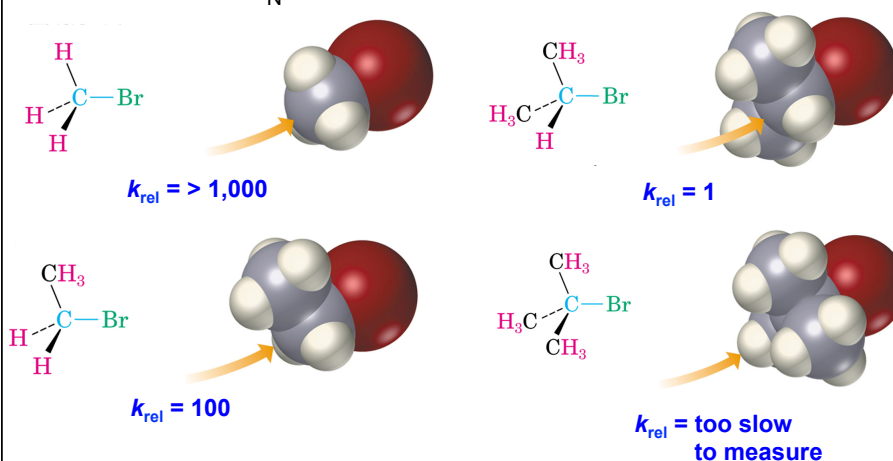
The mechanism of the S_N2 reaction takes place in a single step



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Structure of the Substrate

The degree of substitution (sterics) of the alkyl halide has a strong influence on the S_N2 reaction.

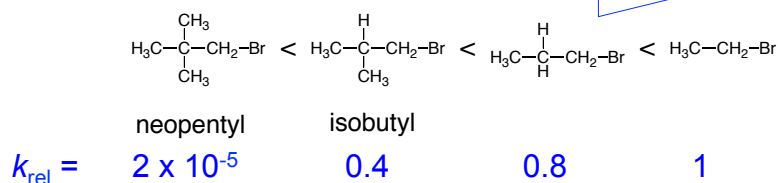


Steric crowding at the carbon that bears the leaving group slows the rate of the S_N2 substitution.

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Steric crowding at the carbon adjacent to the one that bears the leaving group can also slow the rate of the S_N2 reaction

Increasing reactivity in the S_N2 reaction



7.5 The S_N1 Mechanism

Kinetics: first order reaction (unimolecular)

$$\text{rate} = k [\text{R-X}] \quad [\text{R-X}] = \text{alkyl halide conc.}$$

The nucleophile does not appear in the rate equation – changing the nucleophile concentration does not affect the rate of the reaction.

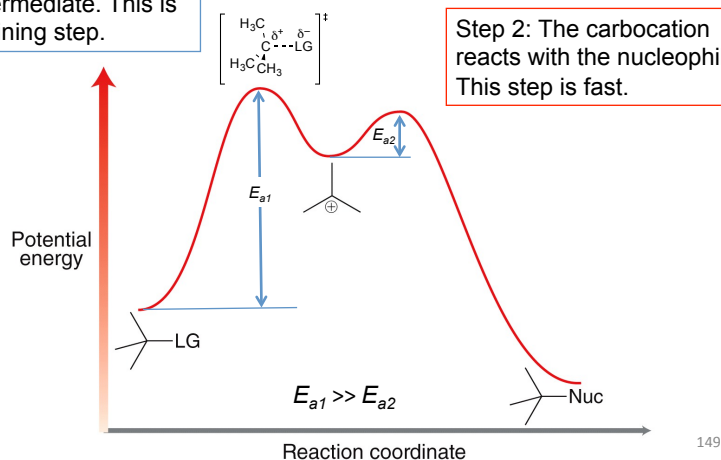
S_N1 – Substitution, Nucleophilic, unimolecular (1st order)

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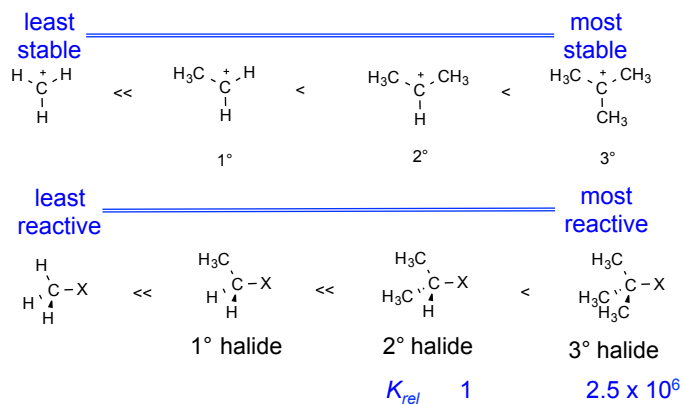
Must be a two-step reaction, with involvement of the nucleophile in the second step. The overall rate of a reaction is dependent upon the slowest step (rate-determining step)

Step 1: Spontaneous dissociation of the 3° alkyl halide generates a carbocation intermediate. This is the rate-determining step.

Step 2: The carbocation reacts with the nucleophile. This step is fast.



Structure of the Substrate – Formation of the carbocation intermediate is rate-determining. Thus, carbocation stability greatly influences the reactivity. The order of reactivity of the alkyl halide in the S_N1 reaction parallels the carbocation stability.



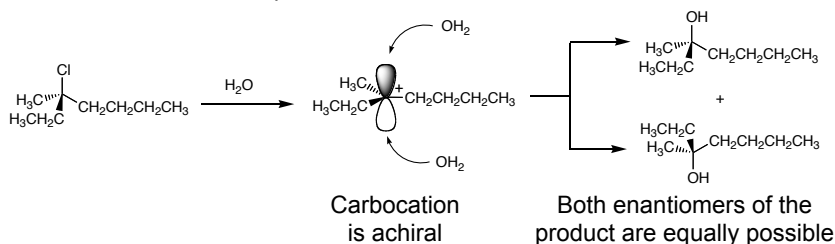
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Primary (1°) alkyl halides undergo nucleophilic substitution by an S_N2 mechanism only

Secondary (2°) alkyl halides can undergo nucleophilic substitution by either an S_N1 or S_N2 mechanism

Tertiary (3°) alkyl halides undergo nucleophilic substitution by an S_N1 mechanism only

Stereochemistry of S_N1 Reactions – A single enantiomer of a 3° alkyl halide will undergo S_N1 substitution to give a racemic product (both possible stereoisomers at the carbon that bore the halide of the reactant).



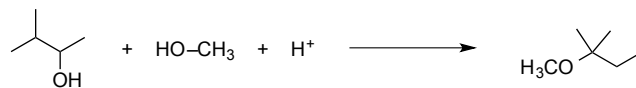
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Summary of the S_N1 and S_N2 Reactions

	S _N 1	S _N 2
Mechanism	Two Steps $R-X \rightarrow R^+ + X^- \xrightarrow{Nu:} R-Nu$	One Step $R-X + Nu: \rightarrow R-Nu + X^-$
Kinetics	1st order (unimolecular) rate = k [R-X] Ionization = rate determining step (1st step), 2nd step does not affect the rate	2nd Order (bimolecular) rate = k [R-X] [Nu:] one step reaction
Stereochemistry	Racemization	Inversion
Carbon (sp³) Electrophile	Favored by electrophiles that can best stabilize a carbocation. alkyl halide reactivity: 3° > 2° >> 1°	Steric hindrance controlled alkyl halide reactivity: CH ₃ > 1° > 2° no reaction for 3°
Competing Reactions	Elimination (E1) Carbocation rearrangements	Elimination (E2) by strongly basic nucleophiles

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7.6 Drawing the Complete Mechanism of an S_N1 Reaction

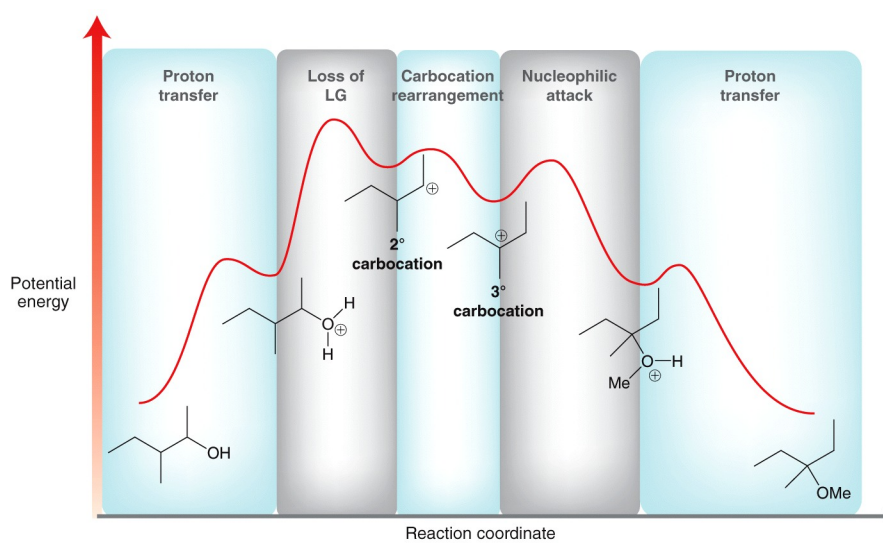


Proton transfer at the beginning of an S_N1 processes

Carbocation rearrangements during an S_N1 processes

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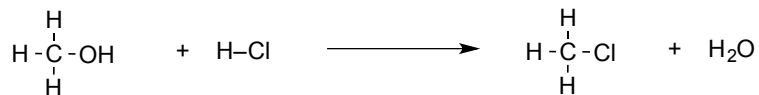
Summary of the S_N1 processes and its energy diagram



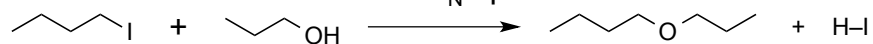
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7.7 Drawing the Complete Mechanism of an S_N2 Reaction

Proton transfer at the beginning of an S_N2 processes



Proton transfer at the end of an S_N2 processes



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Proton transfer before and after an S_N2 processes



7.8 Determining Which Mechanism Predominates

Substrate (alkyl halide): sterics (S_N2) vs carbocation stability (S_N1)

methyl and 1° alkyl halides favor S_N2

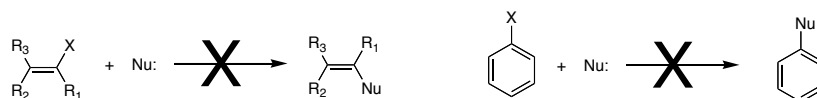
3° alkyl halides favor S_N1

2° alkyl halides can react by either S_N1 or S_N2

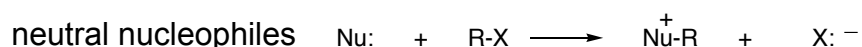
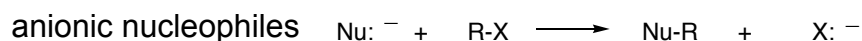
allylic and benzylic alkyl halides can react by either S_N1 or S_N2

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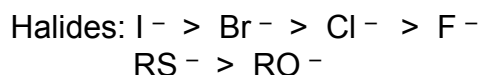
The carbon bearing the halogen (C–X) must be sp^3 hybridized - alkenyl (vinyl) and aryl halides do not undergo nucleophilic substitution reactions.



Nucleophile: *Nucleophilicity* is the term used to describe the reactivity of a nucleophile. The measure of nucleophilicity is imprecise. The S_N2 reaction favors better nucleophiles



Nucleophilicity usually increases going down a column of the periodic chart. (polarizability and solvation)



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Anionic nucleophiles are usually more reactive than neutral nucleophiles (e.g., $\text{RO}^- > \text{ROH}$). However, anionic nucleophiles are usually more basic, which can lead to an increasing of competing elimination reactions.

Solvolysis: a nucleophilic substitution in which the nucleophile is the solvent (usually for S_N1 reactions).

Leaving Group: Good leaving groups are favors for both S_N1 and S_N2 reactions.

Good leaving groups are the conjugate bases of strong acids. The ability to stabilize neagative charge is often a factor is judging leaving groups. (Fig 7.27)

Sulfonates (conjugate base of sulfonic acids) are excellent leaving groups.

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Fig 7.27, p. 323

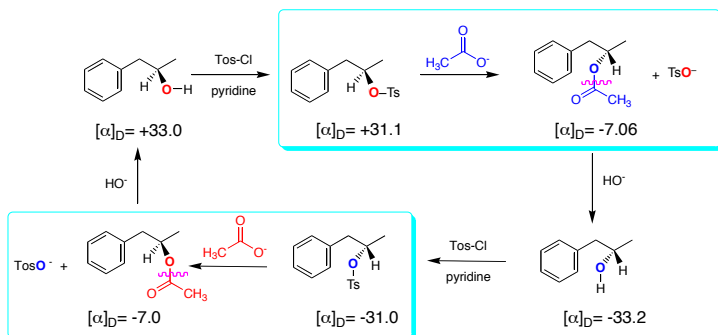
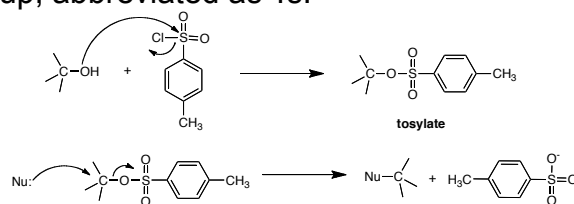
Acid	pK _a	Conjugate base
Strongest acid		Most stable base
I-H	-11	I [⊖]
Br-H	-9	Br [⊖]
Cl-H	-7	Cl [⊖]
	-3	
	-2	

		Least stable base
	15.7	HO [⊖]
	16	
	18	
	38	
Weakest acid		Bad leaving groups

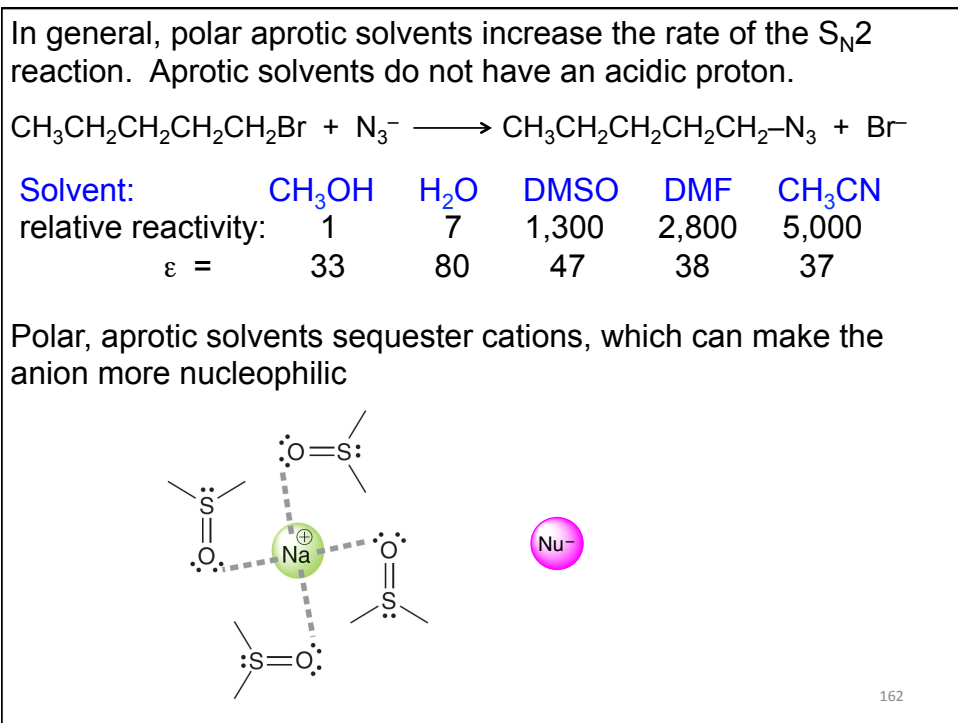
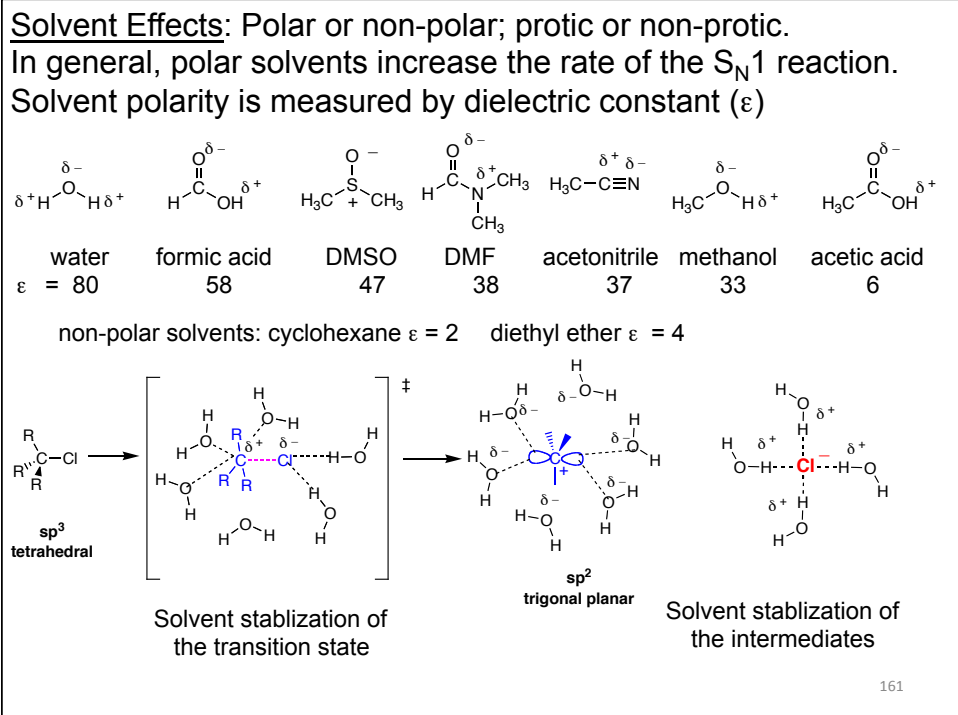
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Sulfonates (ester of a sulfonic acids) - Converts an alcohols (very bad leaving group) into an excellent one (sulfonate).

p-toluenesulfonate ester (tosylate): converts an alcohol into a leaving group; abbreviated as Ts.



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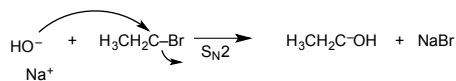
Summary of the S_N1 and S_N2 Reactions

	S _N 1	S _N 2
Carbon (sp³) Electrophile	Favored by 3° alkyl halides or sulfonates 2°, benzylic, or allylic can also react by an S _N 1 mechanism	Favored by CH ₃ and 1° alkyl halides or sulfonates > 2° 2°, benzylic, or allylic can also react by an S _N 2 mechanism
Nucleophile	Nature of the nucleophile has no affect on rate. In general, S _N 1 use neutral, weak nucleophiles	Favored by more reactive nucleophiles RS ⁻ > NC ⁻ > I ⁻ > RO ⁻ > HO ⁻ > Cl ⁻
Leaving Groups	Favored by good leaving groups	-OTs ~ -I > -Br > -Cl > -OH ₂
Solvent Effect	Favored by polar, protic solvents. <i>Solvolysis</i> : polar protic (H-bonding) solvents act as the nucleophile	Favored by polar, aprotic solvents. CH ₃ CN > DMF > DMSO Disfavored by polar protic (H-bonding) solvents
Competing Reactions	Elimination (E1) Carbocation rearrangements	Elimination (E2) by strongly basic nucleophiles

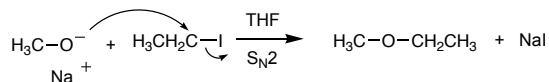
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7.9 Selecting Reagents to Accomplish Functional Group Transformation – converting one functional group into another.

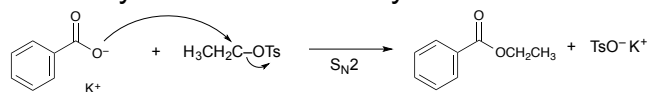
... with water or hydroxide affords an ...



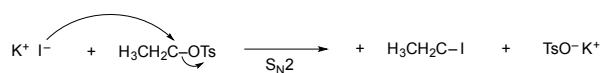
... with an alcohols or alkoxides affords an ...



... with an carboxylic acids or carboxylate anions affords an ...

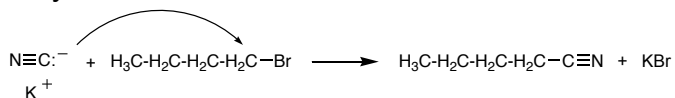


... with halide ions affords an ...

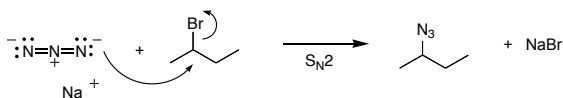


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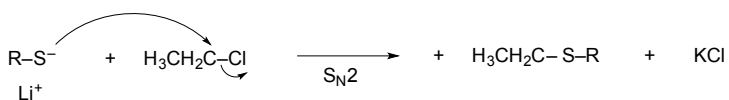
... with cyanide anion affords a



... with azide anion affords alkyl azides



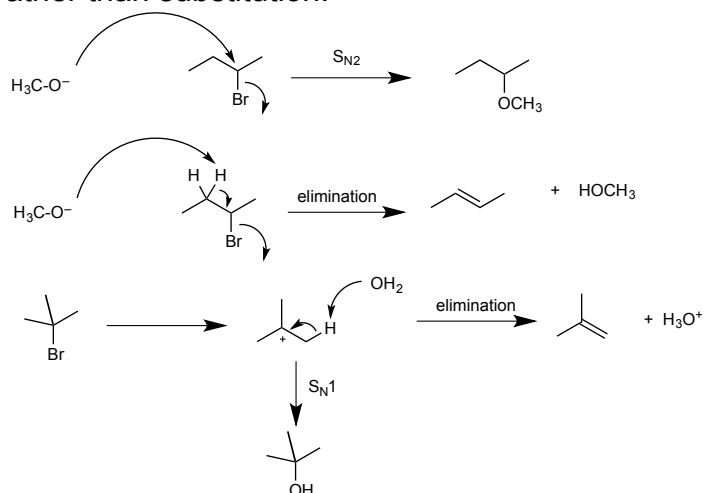
... with an thiol or thiolate ions affords a



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Chapter 8: Alkenes: Structure and Preparation via Elimination Reactions

8.1 Introduction to Elimination Reactions – Nucleophiles are Lewis bases. They can also promote elimination reactions of alkyl halides rather than substitution.



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