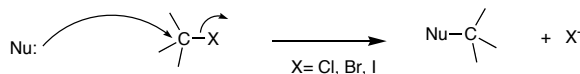


Chapter 8: Nucleophilic Substitution

8.1: Functional Group Transformation By Nucleophilic Substitution

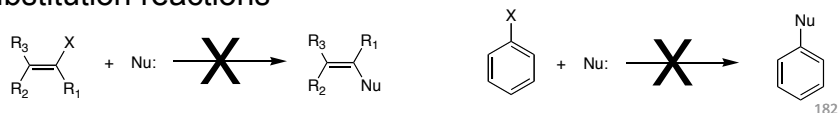


Nucleophiles are Lewis bases (electron-pair donor)

Nucleophiles are often negatively charged (more reactive) and used as their Li^+ , Na^+ , or K^+ salt

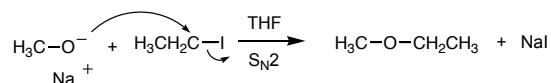
Nucleophiles react with alkyl halide (electrophile) to give substitution products.

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

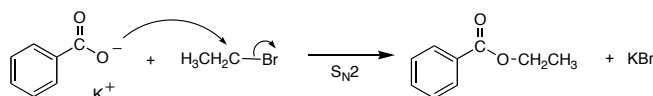


Reactions of an alkyl halide . . .

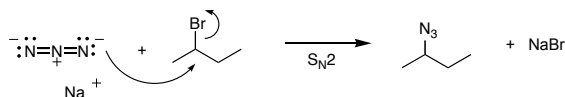
. . . with an alkoxide affords an ether



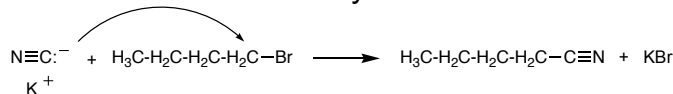
. . . with a carboxylate anion affords an ester



. . . with cyanide anion affords nitriles

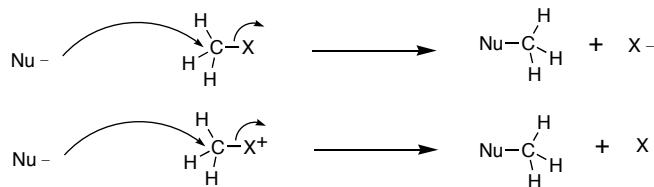


. . . with azide anion affords alkyl azides



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8.2: Relative Reactivity of Halide Leaving Groups



The leaving group is usually displaced with a negative charge

The best leaving groups are those with atoms or groups that can best stabilize a negative charge.

Good leaving groups are the conjugate bases of strong acids



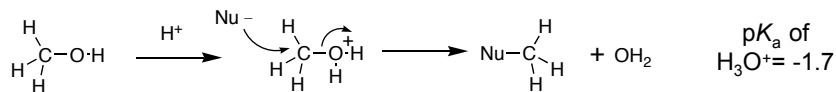
the lower the pK_a of H-X, the stronger the acid.

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Increasing reactivity in the nucleophilic substitution reactions

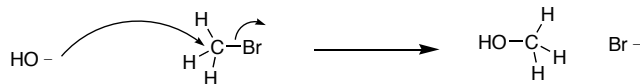
LG:	HO^- , H_2N^- , RO^-	F^-	Cl^-	Br^-	I^-
Relative Reactivity:	$\ll 1$	1	200	10,000	30,000
pK_a :	>15	3.1	-3.0	-5.8	-10.4

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



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8.3: The S_N2 Mechanism of Nucleophilic Substitution



If [OH⁻] is doubled, then the reaction rate may be doubled
 If [CH₃-Br] is doubled, then the reaction rate may be doubled

The rate is linearly dependent on the concentration of two reactants is called a second-order reaction (bimolecular)

For the disappearance of reactants:

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

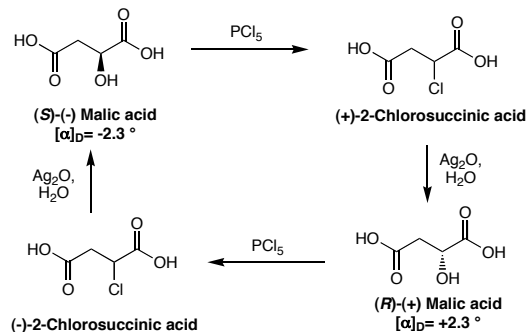
[CH₃Br] = CH₃Br concentration

[OH⁻] = OH⁻ concentration

k = constant (rate constant)

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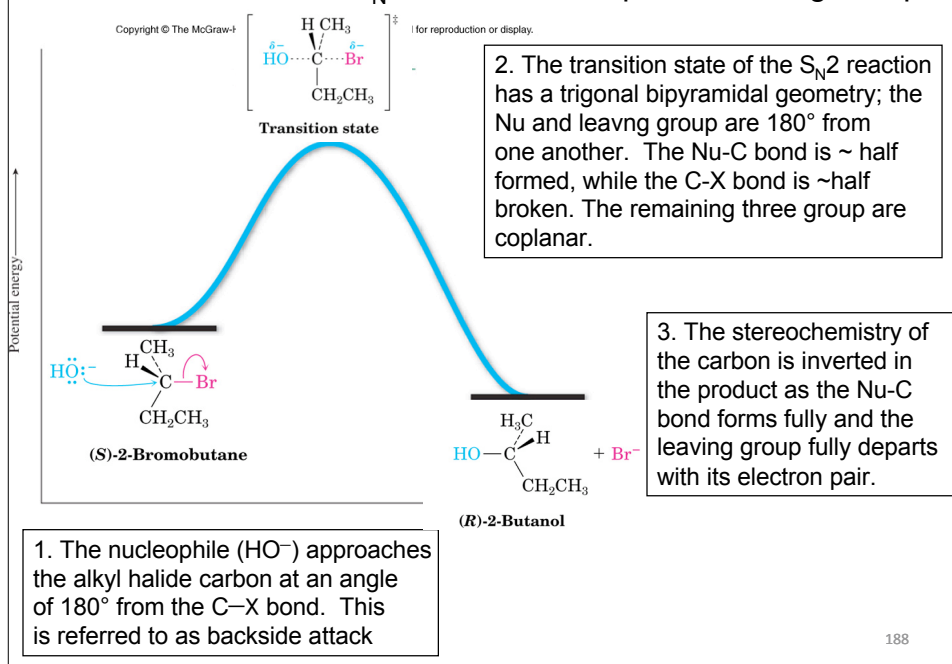
The displacement of a leaving group in an S_N2 reaction has a defined stereochemistry (Walden Inversion)



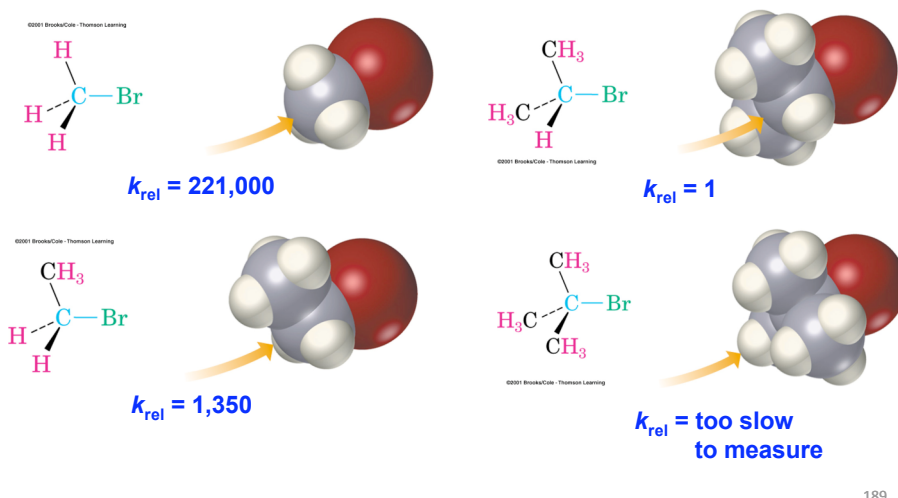
The rate of the S_N2 reaction is dependent upon the concentration of reactants; thus, the transition state for product formation must involve both reactants and explain the stereospecificity .

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

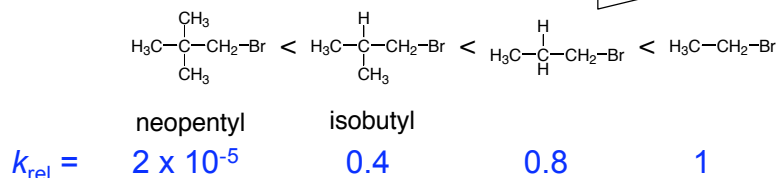


8.4: Steric Effects and S_N2 Reaction Rates - The rate of the S_N2 reaction is governed by steric effects of the alkyl halide. Steric crowding at the carbon that bears the leaving group slows the rate of the S_N2 substitution.

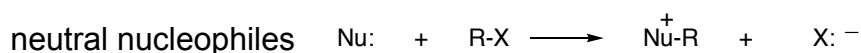
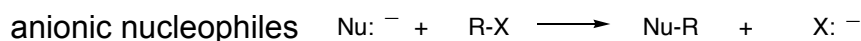


Steric crowding at the carbon adjacent to the one that bears the leaving group can also slow the rate of the S_N2 reaction

Increasing reactivity in the S_N2 reaction 



8.5: Nucleophiles and Nucleophilicity - *Nucleophilicity* is used to describe the reactivity of a nucleophile. The measure of nucleophilicity is imprecise.



Solvolysis: a nucleophilic substitution in which the nucleophile is the solvent. 190

Table 8.4: Nucleophilicity of common nucleophiles

nucleophile	relative rate
I ⁻ , HS ⁻ , RS ⁻	>10 ⁵
Br ⁻ , HO ⁻ , RO ⁻ , CN ⁻ , N ₃ ⁻	10 ⁴
NH ₃ , Cl ⁻ , F ⁻ , RCO ₂ ⁻	10 ³
H ₂ O, ROH	1
RCO ₂ H	10 ⁻²

Factors that control nucleophilicity:

1. Basicity - Nucleophilicity roughly parallels basicity when comparing nucleophiles that have the same attacking atom

Nu:	CH ₃ O ⁻	HO ⁻	CH ₃ CO ₂ ⁻	H ₂ O
relative reactivity:	25,000	16,000	500	1
pK _a of the conj. acid:	15.5	15.7	4.7	-1.7

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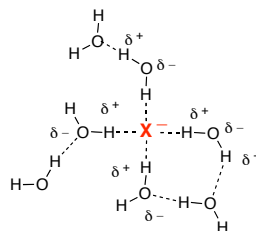
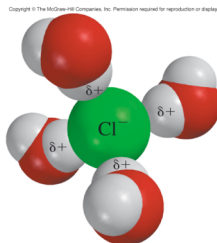
Nucleophilicity usually increases going down a column of the periodic chart. Thus, sulfur nucleophiles are more reactive than oxygen nucleophiles. Halides: $I^- > Br^- > Cl^- > F^-$.

Negatively charged nucleophiles are usually more reactive than neutral nucleophiles.

Note that elimination is a competing reaction with nucleophilic substitution; more basic nucleophile can promote elimination

Factors that control nucleophilicity:

2. Solvation: small negative ions are highly solvated in protic solvents; large negative ions are less solvated and are more reactive.



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8.6: The S_N1 Mechanism of Nucleophilic Substitution

kinetics: first order reaction (unimolecular)

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

The overall rate of a reaction is dependent upon the slowest step: rate-limiting step

The nucleophile does not appear in the rate expression- changing the nucleophile concentration does not affect the rate of the reaction.

Must be a two-step reaction.

Unimolecular kinetic for nucleophilic substitution is observed for tertiary alkyl halides

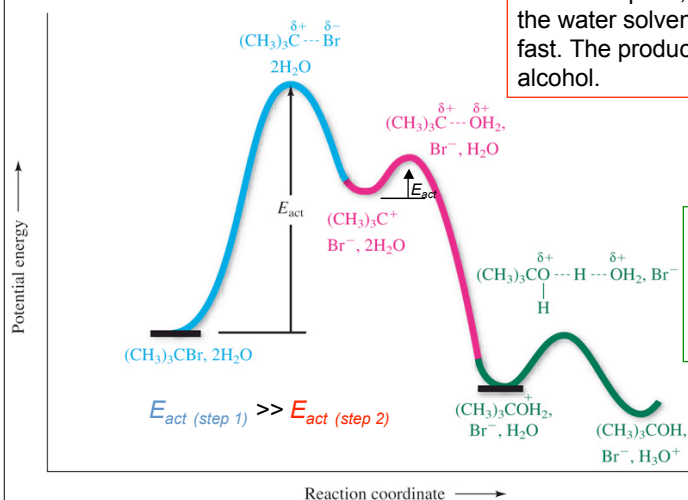
In general, the S_N1 reactions is not stereospecific - nucleophilic substitution of a chiral tertiary alkyl halide leads to a racemic product.

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The Mechanism of the S_N1 Reaction

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

2. The carbocation reacts with the nucleophile, in this case the water solvent. This step is fast. The product is a protonated alcohol.



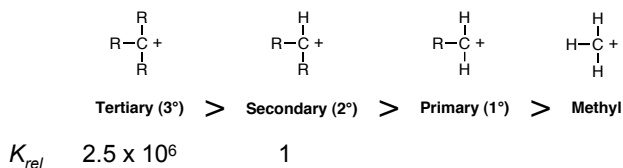
3. Loss of a proton from the protonated alcohol affords the 3° alcohol, which is the overall product of the reaction.

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8.7: Carbocation Stability and S_N1 Reaction Rates

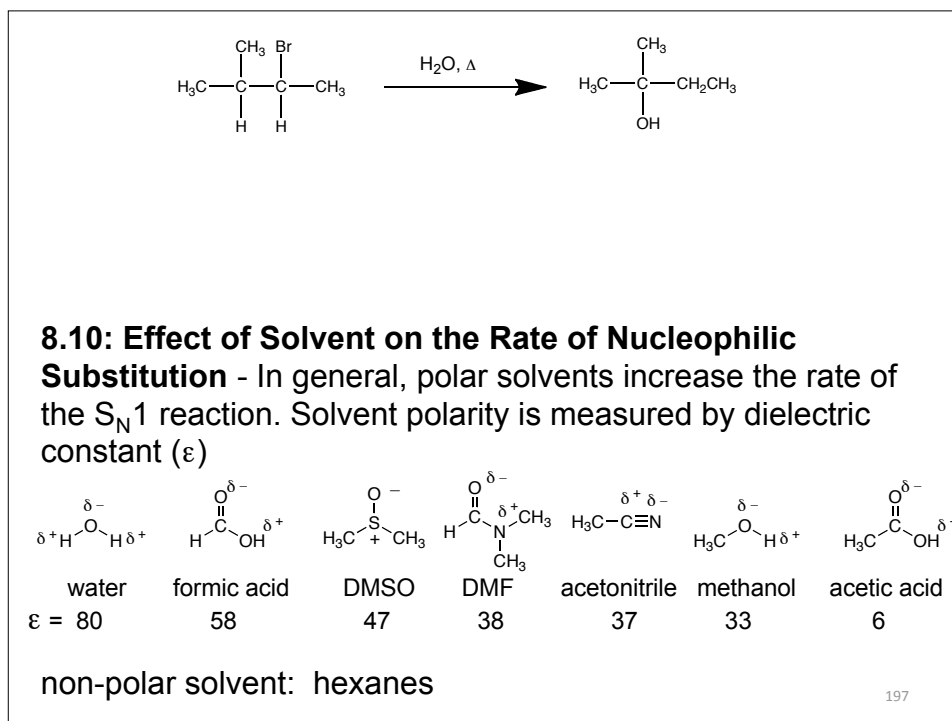
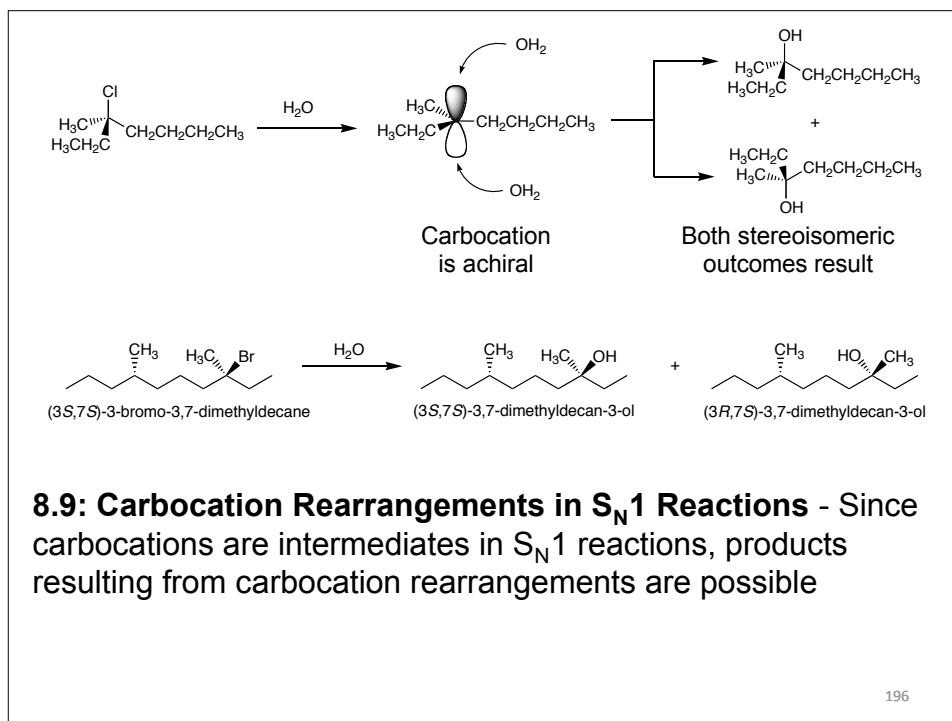
Formation of the carbocation intermediate is rate-limiting. Thus, carbocation stability greatly influences the reactivity.

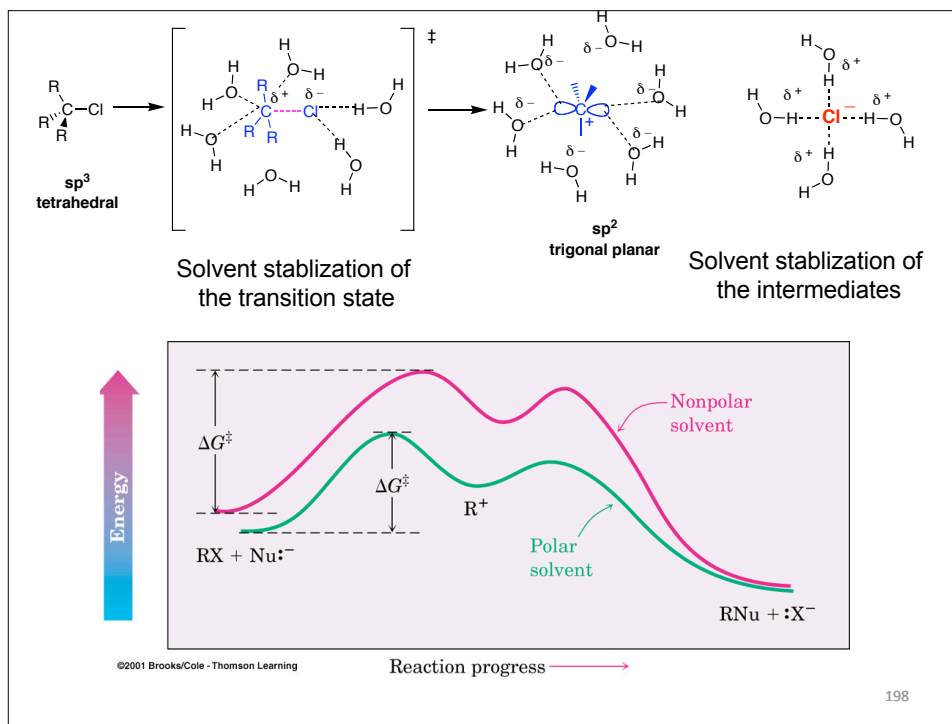
The order of reactivity of the alkyl halide in the S_N1 reaction exactly parallels the carbocation stability



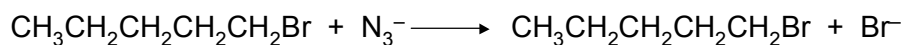
8.8: Stereochemistry of S_N1 Reactions - is actually a complicated issue. For the purpose of Chem 220a, sect. 1 the stereochemistry of the S_N1 reaction results in racemization. A single enantiomer of a 3° alkyl halide will undergo S_N1 substitution to give a racemic product (both possible stereoisomers at the carbon that bore the halide of the reactant).

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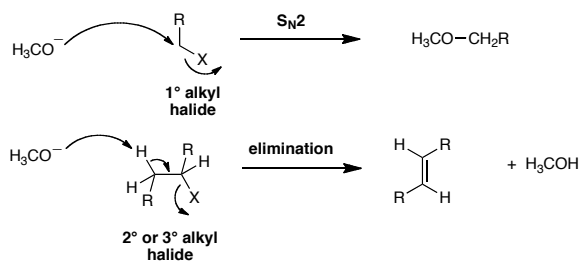
In general, polar aprotic solvents increase the rate of the $\text{S}_{\text{N}}2$ reaction. Aprotic solvents do not have an acidic proton.



Solvent: CH_3OH H_2O DMSO DMF CH_3CN
 relative reactivity: 1 7 1,300 2,800 5,000

8.11: Substitution and Elimination as Competing Reactions

Nucleophiles are Lewis bases. They can also promote elimination reactions of alkyl halides rather than substitution

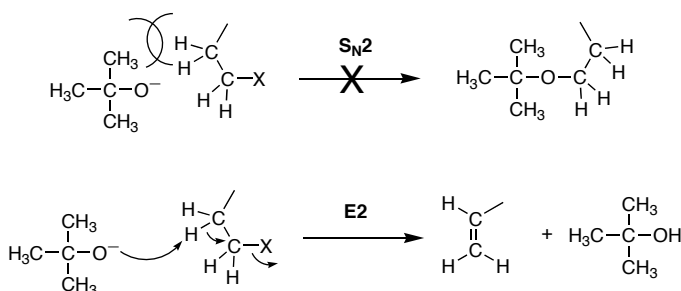
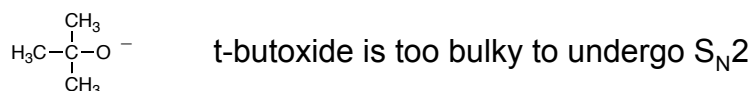


Elimination is a competitive reaction with nucleophilic substitution.

S_N2 vs E2

For primary alkyl halides S_N2 is favored with most nucleophiles

E2 is favored with "bulky" bases (t-butoxide)



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Secondary halides:

E2 is competitive with S_N2 and often gives a mixture of substitution and elimination products

S_N2 is favored with nucleophiles that are weak bases - cyanide ion, azide ion, thiolate ion, halide ion

Tertiary Halides:

E2 elimination occurs with strong bases such as HO^- , RO^- , H_2N^- (strongly basic conditions)

E1 elimination occurs with heat and weak bases such as H_2O or ROH . (neutral conditions)

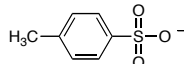
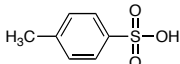
The E1 elimination product is often a minor product with the major product arising from S_N1 reaction.

S_N2 reactions does not occur with 3° halides

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8.12: Nucleophilic Substitution of Alkyl Sulfonates

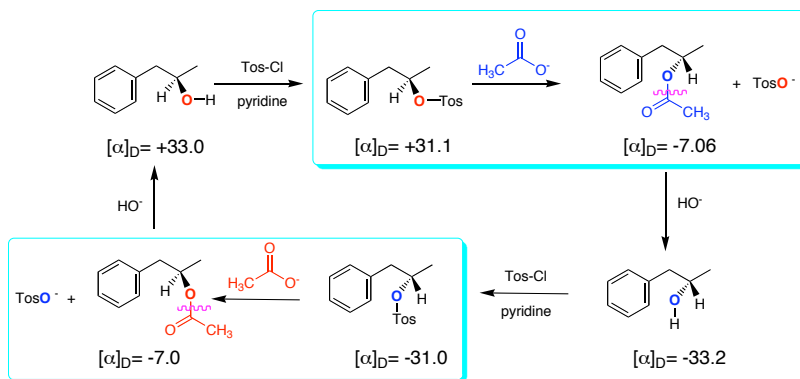
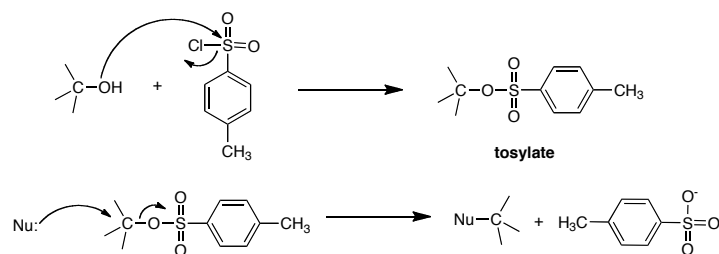
Good leaving groups are the conjugate bases of strong acids

Leaving group	conjugate acid	pK_a
F^-	HF	3.5
H_2O	H_3O^+	-1.7
Cl^-	HCl	-7
Br^-	HBr	-9
I^-	HI	-10
		-2.8

Sulfonates are excellent leaving groups.

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

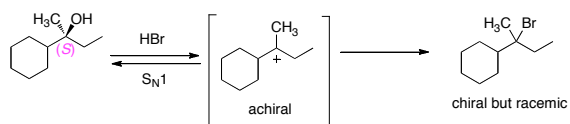
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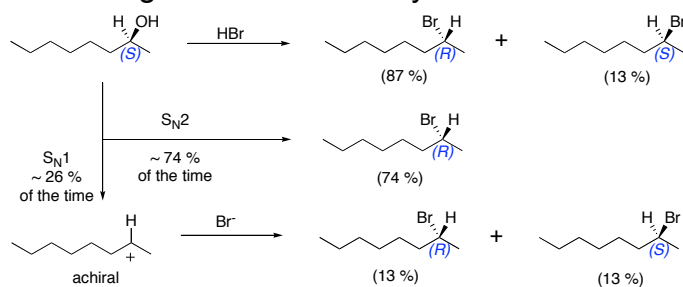
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8.13: Looking Back: Reactions of Alcohols with Hydrogen Halides

3° alcohols proceed by an S_N1 mechanism- racemization occurs through an achiral 3° carbocation



2° alcohols proceed by both an S_N1 and S_N2 mechanism- partial scrambling of stereochemistry



We will assume that 2° centers proceed by an S_N2 mechanism

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