Chapter 8

Substitution and Elimination Reactions of Alkyl Halides

Paula Yurkanis Bruice
University of California, Santa Barbara

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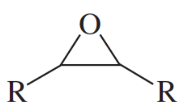
The Families of Group III

Substitution Reactions of Alkyl Halides

Group III

R—X (X = F, Cl, Br, I)
R—OH
R—OR



alkyl halides:
the first of the families in Group III

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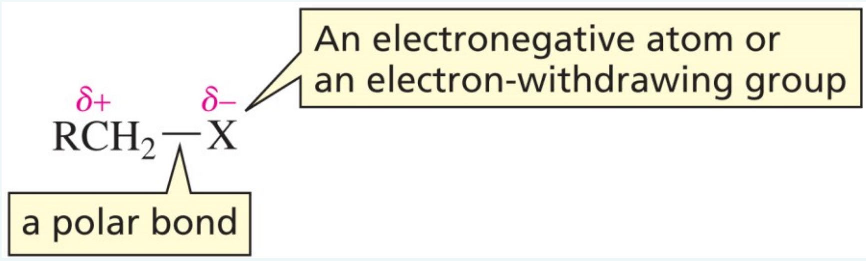
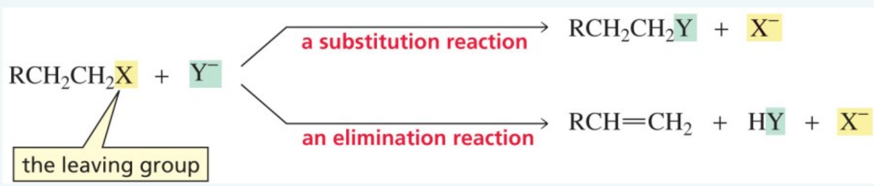
The Compounds in Group III are Electrophiles



All the compounds in Group III have an electron withdrawing atom or group that is attached to an *sp*^{3} carbon.

Because Group III Compounds are Electrophiles, they react with Nucleophiles



Substitution reaction—the electronegative group is replaced by another group.

Elimination reaction—the electronegative group is eliminated along with a hydrogen.

Alkyl Halides

alkyl halides

R—F	R—Cl	R—Br	R—I
an alkyl fluoride	an alkyl chloride	an alkyl bromide	an alkyl iodide

This chapter discusses the substitution reactions of alkyl halides.

Alkyl halides have good leaving groups.

The S_N2 Reaction

$$CH_3Br + HO^- \longrightarrow CH_3OH + Br^-$$

bromomethane   methanol

The substitution reaction is more precisely called a nucleophilic substitution reaction because the atom replacing the halogen is a nucleophile.

What is the Mechanism of the Reaction?

The kinetics of a reaction—the factors that affect the rate of the reaction—can help determine the mechanism.

$$\text{rate} \propto [\text{alkyl halide}][\text{nucleophile}]$$

$$\text{rate} = \underbrace{k}_{\text{the rate constant}} [\text{alkyl halide}][\text{nucleophile}]$$

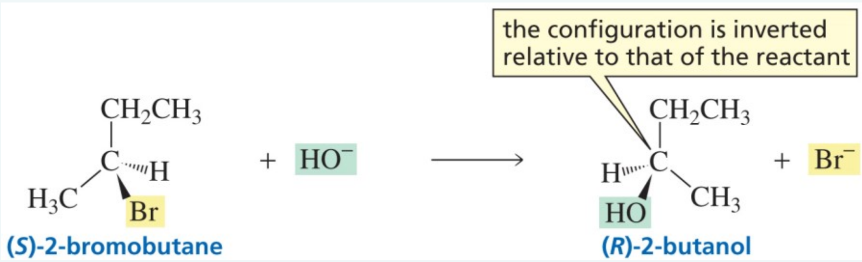
an S_N2 reaction

Relative Rates of an S_N2 Reaction

Relative Rates of an S_N2 Reaction

$CH_3{-}Br > CH_3CH_2{-}Br > CH_3CH_2CH_2{-}Br > CH_3CH(CH_3){-}Br > CH_3C(CH_3)_2{-}Br$

Inverted Configuration



If the halogen is bonded to an asymmetric center, the product will have the inverted configuration.

Summary of the Experimental Evidence for the Mechanism of an S_N2 Reaction

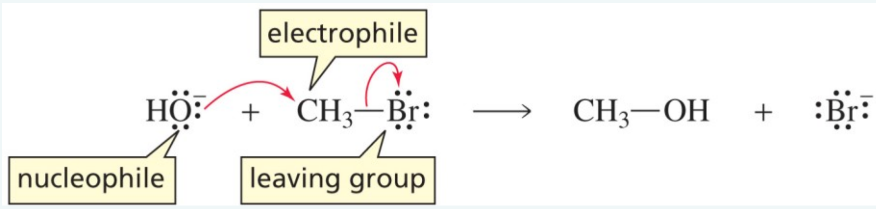
1. The rate of the reaction is dependent on the concentration of both the alkyl halide and the nucleophile.

1. The relative rate of the reaction is:

primary alkyl halide > secondary alkyl halide > tertiary alkyl halide.

3. The configuration of the product is inverted compared to the configuration of the reacting chiral alkyl halide.

Mechanism for the S_N2 Reaction of an Alkyl Halide



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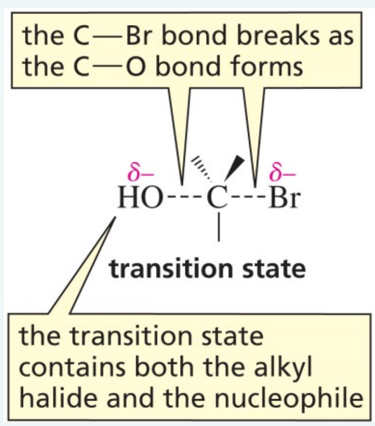
Why Bimolecular?



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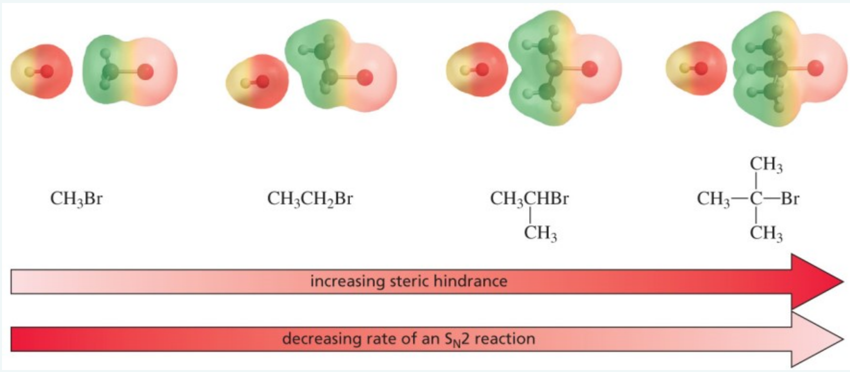
Why do Methyl Halides react the fastest and Tertiary the Slowest?



steric hindrance

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Why do Methyl Halides react the fastest and Tertiary the slowest?

relative reactivities of alkyl halides in an S_N2 reaction

most reactive > methyl halide > 1° alkyl halide > 2° alkyl halide > 3° alkyl halide < too unreactive to undergo an S_N2 reaction

The relative lack of steric hindrance causes methyl halides and primary alkyl halides to be the most reactive alkyl halides in S_N2 reactions.

Tertiary alkyl halides cannot undergo S_N2 reactions.

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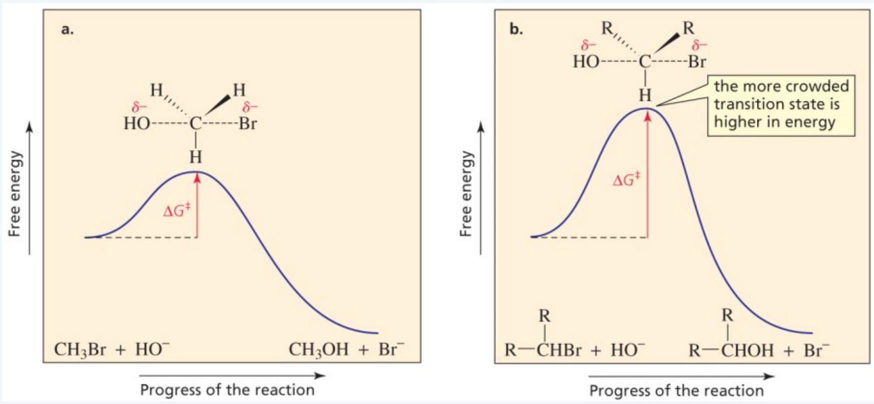
Why Steric Hindrance decreases the rate



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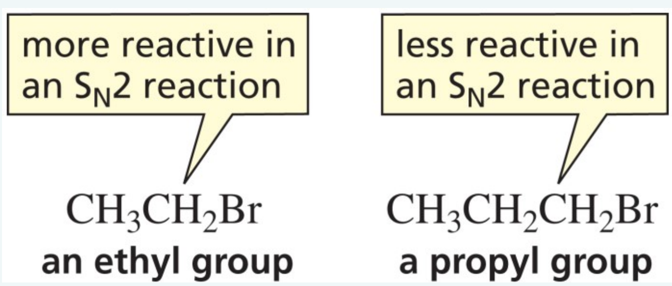
Both are Primary Alkyl Halides but they react at different rates



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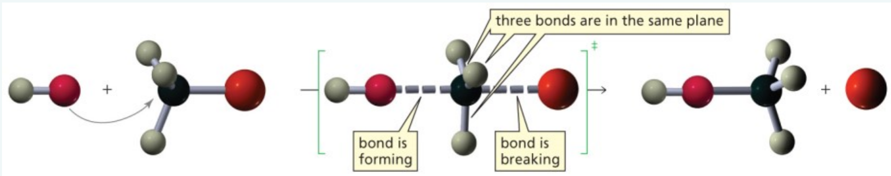
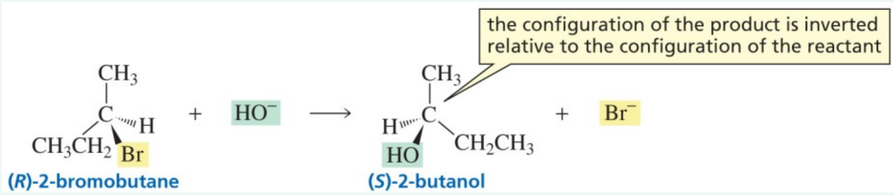
Why the configuration of the Product is inverted





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The rate of an S_N2 Reaction is affected by the Leaving Group

	relative rates of reaction	pK_a values of HX
$HO^- + RCH_2I \longrightarrow RCH_2OH + I^-$	30,000	−10
$HO^- + RCH_2Br \longrightarrow RCH_2OH + Br^-$	10,000	−9
$HO^- + RCH_2Cl \longrightarrow RCH_2OH + Cl^-$	200	−7
$HO^- + RCH_2F \longrightarrow RCH_2OH + F^-$	1	3.2

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The Weakest Base is the best Leaving Group

relative basicities of the halide ions

$I^- < Br^- < Cl^- < F^-$

weakest base, most stable base

strongest base, least stable base

relative reactivities of alkyl halides in an S_N2 reaction

most reactive

$RI > RBr > RCl > RF$

too unreactive to undergo an S_N2 reaction

Base Strength and Nucleophile Strength

relative base strengths and relative nucleophilicities

strongest base

$^-NH_2 > HO^- > F^-$

best nucleophile

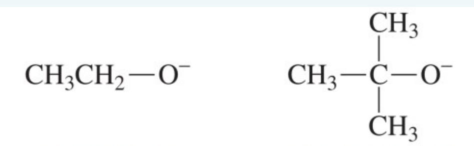
If atoms are in the same row, the strongest base is the best nucleophile.

Base Strength and Nucleophile Strength

stronger base, better nucleophile		weaker base, poorer nucleophile
HO^-	>	H_2O
CH_3O^-	>	CH_3OH
$^-NH_2$	>	NH_3
$CH_3CH_2NH^-$	>	$CH_3CH_2NH_2$

A negatively charged atom is a stronger base and a better nucleophile than the same atom that is neutral.

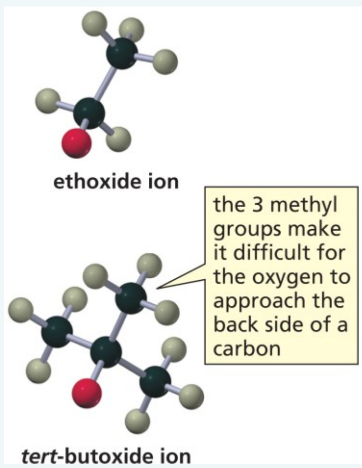
Steric Hindrance Decreases Nucleophilicity



ethoxide ion — better nucleophile

tert-butoxide ion — stronger base

Even though the *tert*-butoxide ion is a stronger base, it is a poorer nucleophile because nucleophilic attack is more sterically hindered than proton removal.



S_N2 Reactions can be used to make a variety of Compounds

$$CH_3CH_2Cl + HO^- \longrightarrow CH_3CH_2OH + Cl^-$$
an alcohol

$$CH_3CH_2Br + HS^- \longrightarrow CH_3CH_2SH + Br^-$$
a thiol

$$CH_3CH_2I + RO^- \longrightarrow CH_3CH_2OR + I^-$$
an ether

$$CH_3CH_2Br + RS^- \longrightarrow CH_3CH_2SR + Br^-$$
a thioether

$$CH_3CH_2Cl + {}^-NH_2 \longrightarrow CH_3CH_2NH_2 + Cl^-$$
a primary amine

$$CH_3CH_2I + {}^-C{\equiv}N \longrightarrow CH_3CH_2C{\equiv}N + I^-$$
a nitrile

$$CH_3CH_2Br + {}^-C{\equiv}CR \longrightarrow CH_3CH_2C{\equiv}CR + Br^-$$
an alkyne

The reactions are irreversible because a strong base displaces a weak base.

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The S_N1 Reaction

2-bromo-2-methylpropane

2-methyl-2-propanol

A tertiary alkyl halide and a poor nucleophile

The reaction is surprisingly fast, so it must be taking place by a different mechanism.

Most S_N1 reactions are solvolysis reactions: the solvent is the nucleophile.

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The rate of an S_N1 Reaction depends only on the Alkyl Halide Concentration

$$\text{rate} = k[\text{alkyl halide}]$$

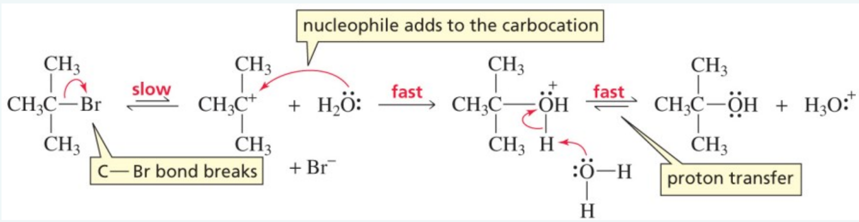
Summary of the Experimental Evidence for the Mechanism of an S_N1 Reaction

1. The rate of the reaction depends only on the concentration of the alkyl halide.

1. Tertiary alkyl halides react the fastest.

1. If the halogen is attached to an asymmetric center the product will be a pair of enantiomers.

The Mechanism



The leaving group departs before the nucleophile approaches.

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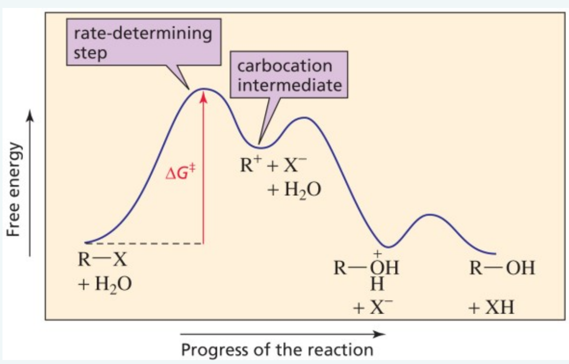
The Slow Step is Formation of the Carbocation



Tertiary alkyl halides react the fastest; they form the most stable carbocations.

Secondary and primary alkyl halides do not undergo S_N1 reactions.

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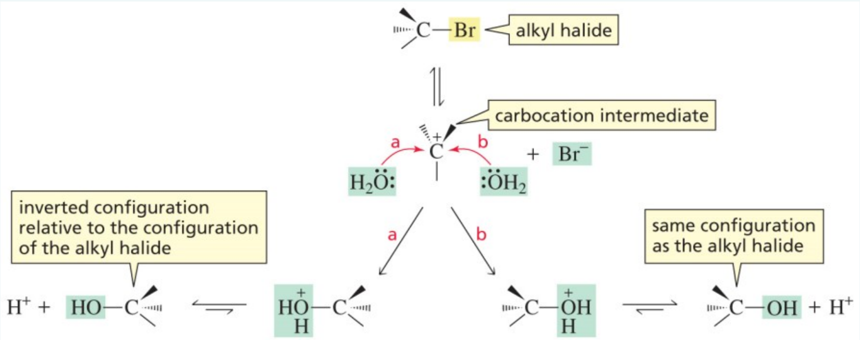
The Product is a Pair of Enantiomers



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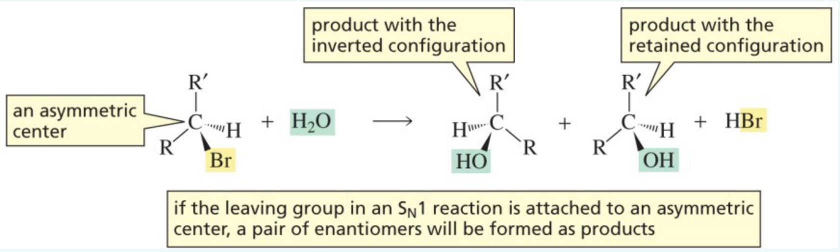
The Product is a Pair of Enantiomers



If the halogen is bonded to an asymmetric center, the product will be a pair of enantiomers.

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The Leaving Group in an S_N1 Reaction

relative reactivities of alkyl halides in an S_N1 reaction

most reactive RI > RBr > RCl > RF least reactive

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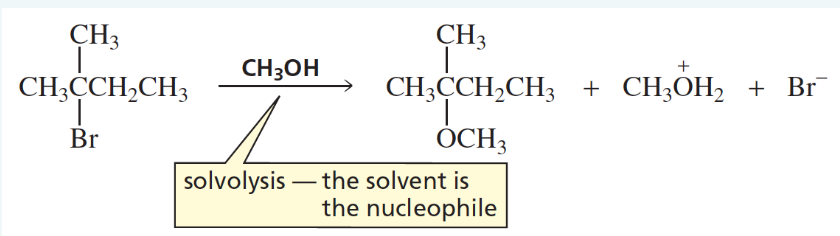
The Nucleophile in an S_N1 Reaction



Most S_N1 reactions are solvolysis reactions; the nucleophile is the solvent.

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Comparing S_N2 and S_N1 Reaction

S_N2
a one-step mechanism
a bimolecular rate-determining step
the rate is controlled by steric hindrance
product has the inverted configuration relative to that of the reactant
the leaving group: $I^- > Br^- > Cl^- > F^-$
the better the nucleophile, the faster the rate of the reaction

S_N1
a two-step mechanism with a carbocation intermediate
a unimolecular rate-determining step
the rate is controlled by stability of the carbocation
products have both the retained and inverted configurations relative to that of the reactant
the leaving group: $I^- > Br^- > Cl^- > F^-$
the strength of the nucleophile does not affect the rate of the reaction

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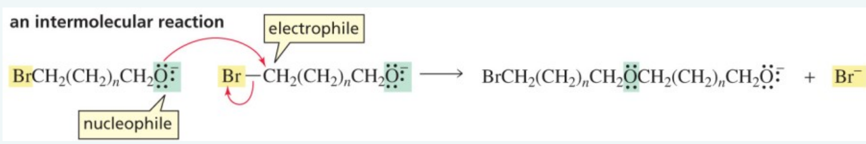
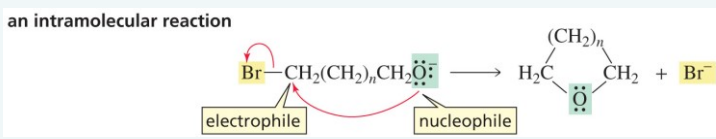
Intermolecular *versus* Intramolecular S_N2 Reactions





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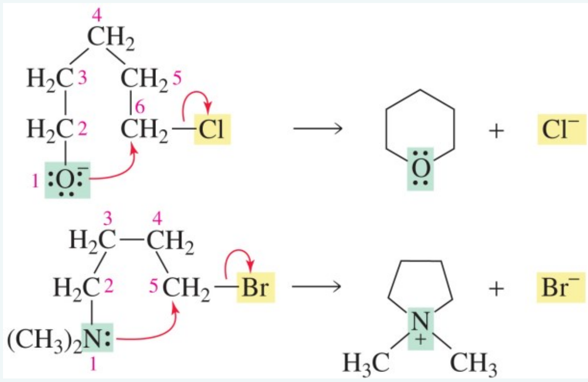
The Intramolecular Reaction is favored when a Five- or Six-Membered Ring can be formed



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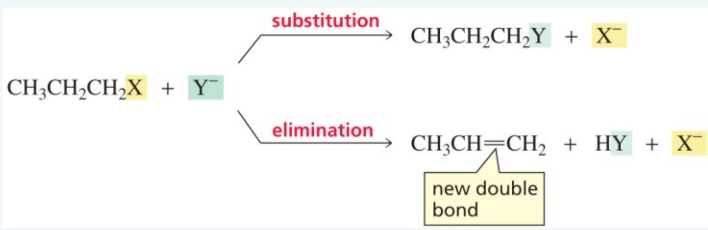
Alkyl Halides undergo Substitution and Elimination Reactions



In an elimination reaction:

a halogen is removed from one carbon and
a hydrogen is removed from an adjacent carbon.

a double bond is formed between the two carbons from which the atoms were removed.

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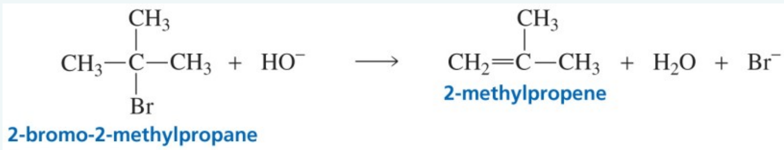
An E2 Reaction



$$\text{rate} = k[\text{alkyl halide}][\text{base}]$$

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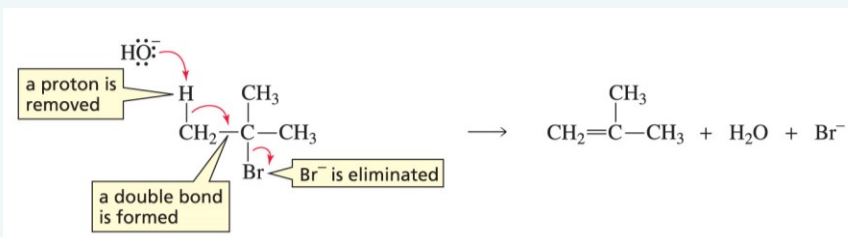
Mechanism for an E2 Reaction



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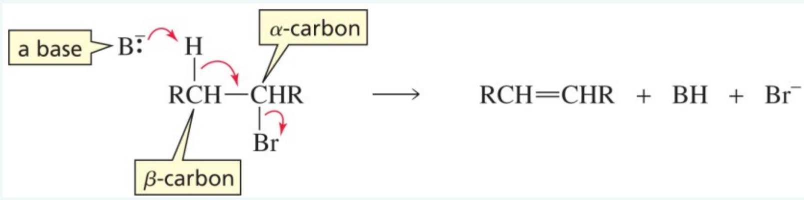
The Halogen comes off the Alpha Carbon; the Hydrogen comes off the Beta Carbon



dehydrohalogenation

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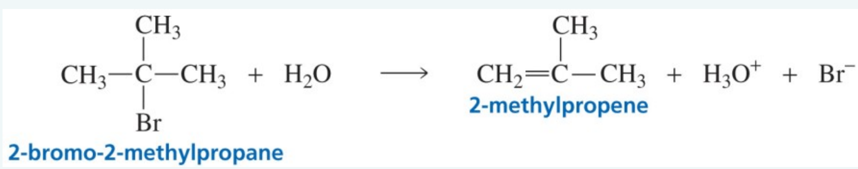
An E1 Reaction



$$\text{rate} = k[\text{alkyl halide}]$$

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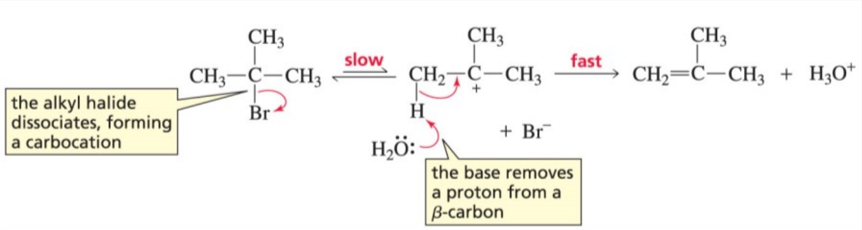
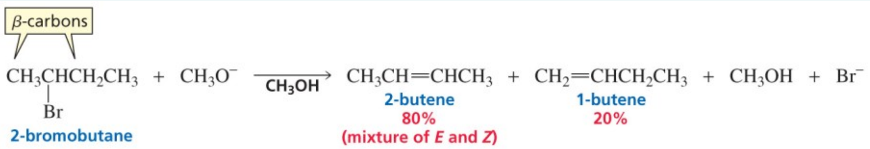
The Mechanism for an E1 Reaction



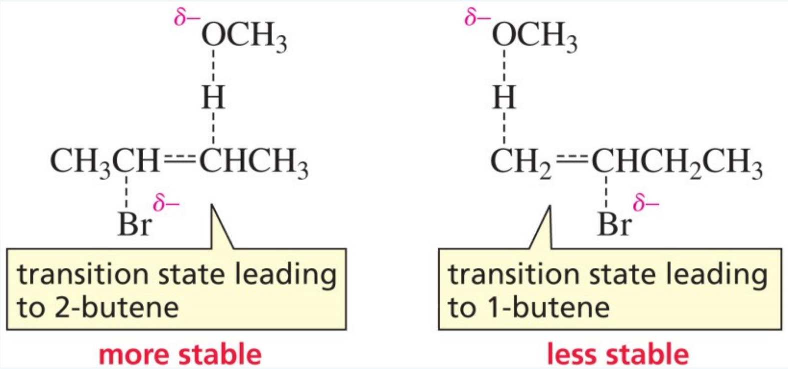
An E2 Reaction is Regioselective



The major product is the most stable alkene.

The most stable alkene is (generally) obtained by removing a hydrogen from the beta carbon that is bonded to the fewest hydrogens.

Alkene-Like Transition State



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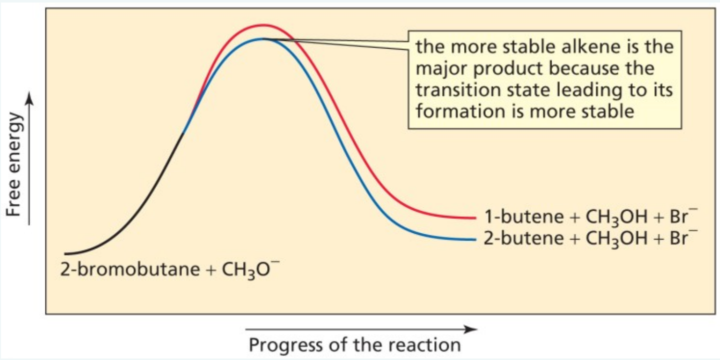
The more stable Alkene has the more stable Transition State



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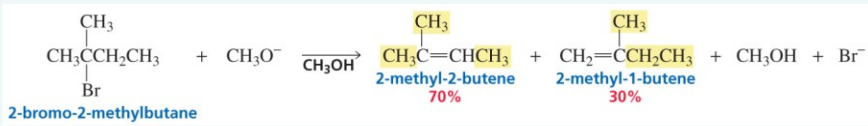
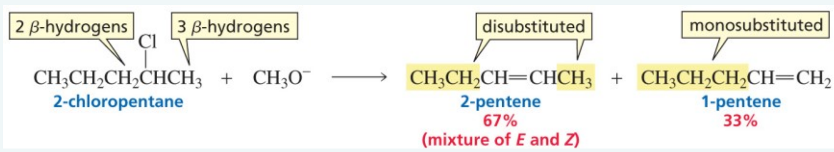
More Regioselective E2 Reactions





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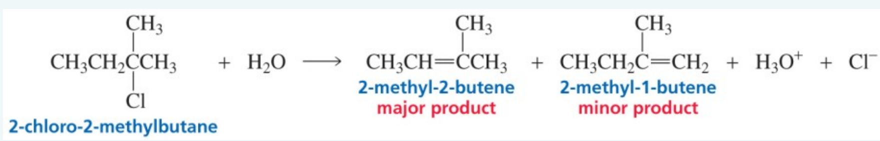
An E1 Reaction is Regioselective



The major product is the more stable alkene.

The most stable alkene is obtained by removing a hydrogen from the beta carbon that is bonded to the fewest hydrogens.

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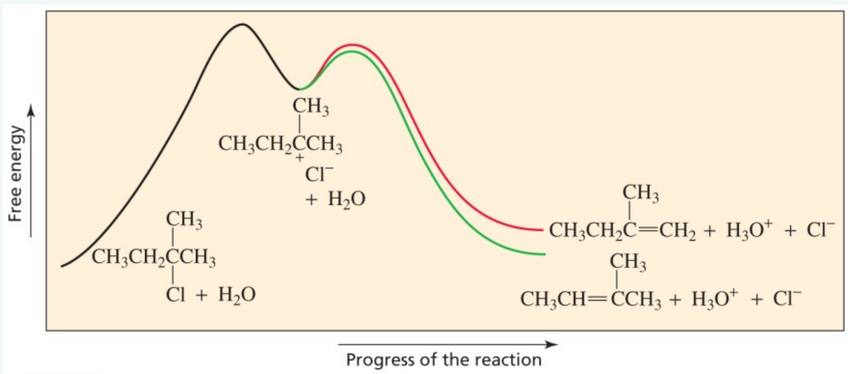
The more stable Alkene is the major product



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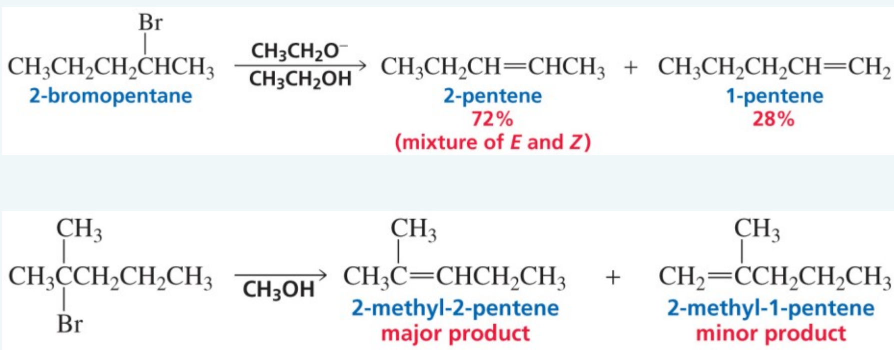
Both E2 and E1 Reactions are Regioselective



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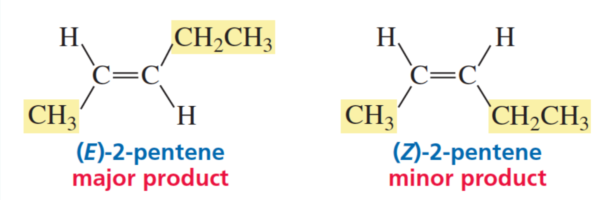
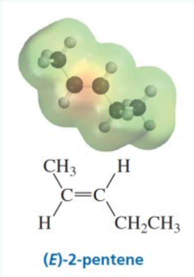
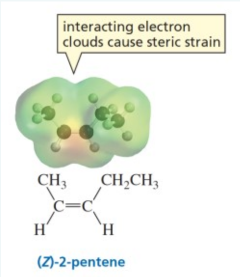
E2 and E1 Reactions are Stereoselective







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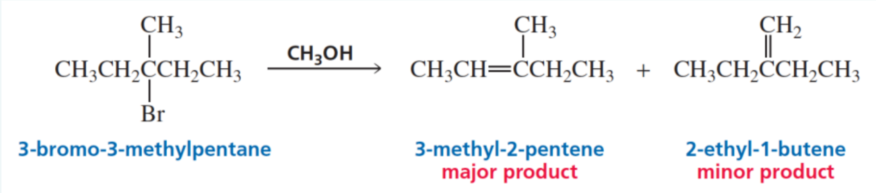
E2 and E1 Reactions are Stereoselective



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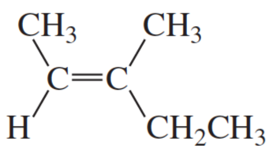
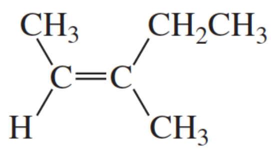
E2 and E1 Reactions are Stereoselective



(*E*)-3-methyl-2-pentene
major product



(*Z*)-3-methyl-2-pentene
minor product

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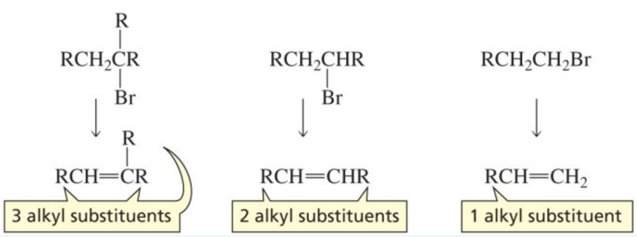
Relative Reactivities of Alkyl Halides in an E2 Reaction

relative reactivities of alkyl halides in an E2 reaction

tertiary alkyl halide > secondary alkyl halide > primary alkyl halide



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Does a Tertiary Alkyl Halide undergo S_N2/E2 or S_N1/E1 Reactions?

$$\text{rate} = \underbrace{k_1[\text{alkyl halide}]}_{\text{contribution to the rate by an } S_N1 \text{ reaction}} + \underbrace{k_2[\text{alkyl halide}][\text{nucleophile}]}_{\text{contribution to the rate by an } S_N2 \text{ reaction}} + \underbrace{k_3[\text{alkyl halide}]}_{\text{contribution to the rate by an E1 reaction}} + \underbrace{k_4[\text{alkyl halide}][\text{base}]}_{\text{contribution to the rate by an E2 reaction}}$$

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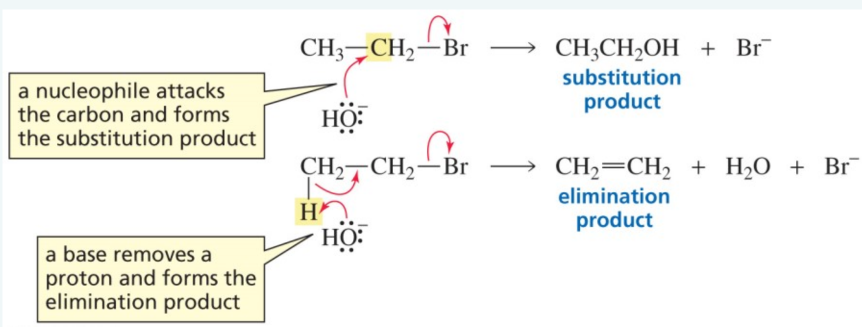
Competition between Substitution and Elimination



In an S_N2 reaction: 1° > 2° > 3° In an E2 reaction: 3° > 2° > 1°

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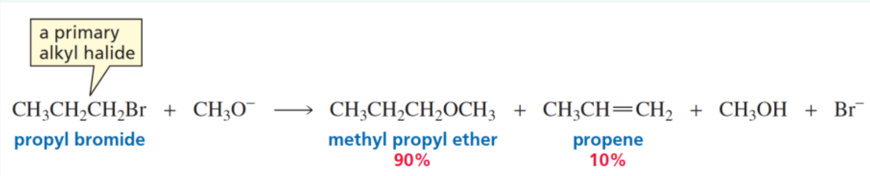
Under S_N2/E2 conditions, a Primary Alkyl Halide forms primarily a Substitution Product



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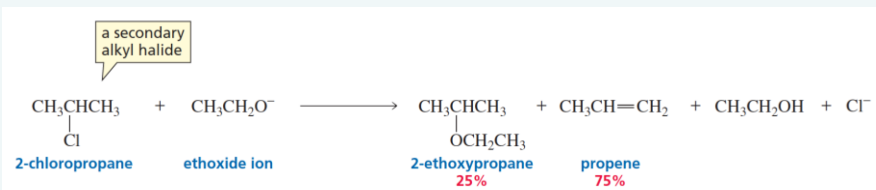
Under S_N2/E2 conditions, a Secondary Alkyl Halide forms Substitution and Elimination Products



Substitution is favored by a weak base.

Elimination is favored by a strong base.

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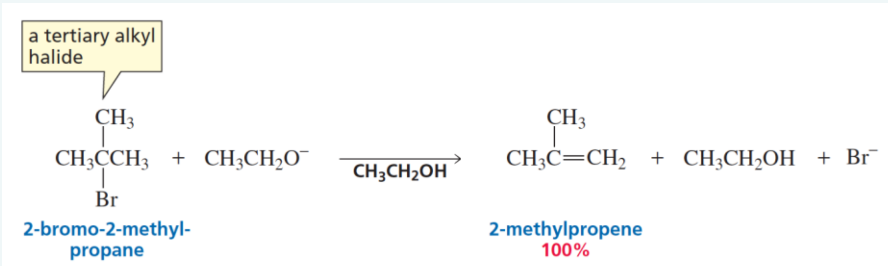
Under S_N2/E2 conditions, a Tertiary Alkyl Halide forms only an Elimination Product



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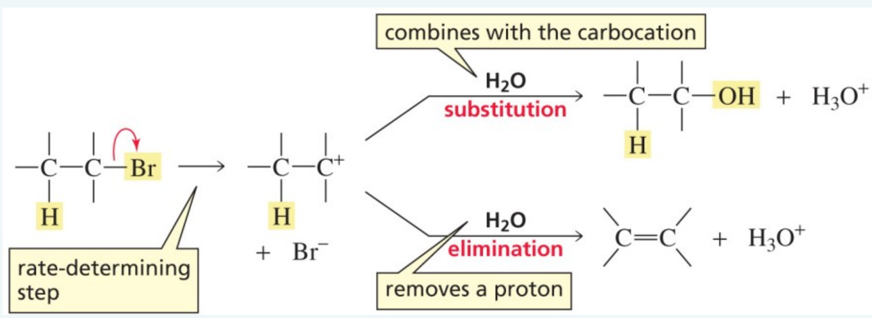
Under S_N1/E1 conditions, a Tertiary Alkyl Halide forms Substitution and Elimination Products



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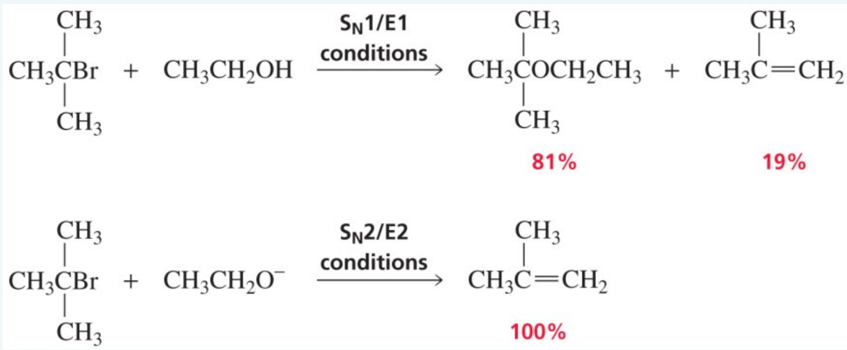
Tertiary ($S_N1/E1$): Substitution is Favored
Tertiary ($S_N2/E2$): Only Elimination

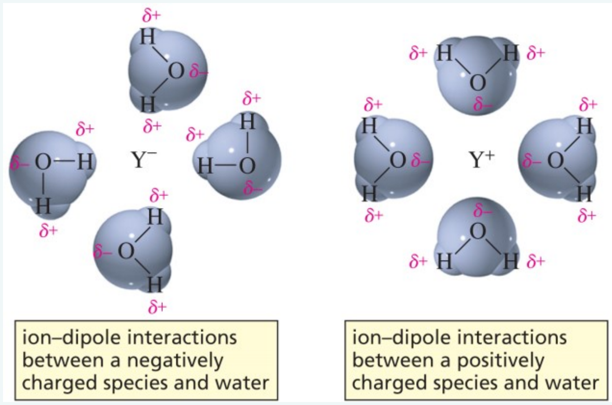


Summary of the products obtained from Substitution and Elimination Reactions

Table 8.2 Summary of the Products Expected in Substitution and Elimination Reactions

Class of alkyl halide	S_N2 versus E2	S_N1 versus E1
Primary alkyl halide	primarily substitution	cannot undergo S_N1/E1 solvoylsis reactions
Secondary alkyl halide	substitution and elimination	cannot undergo S_N1/E1 solvolysis reactions
Tertiary alkyl halide	only elimination	substitution and elimination with substitution favored

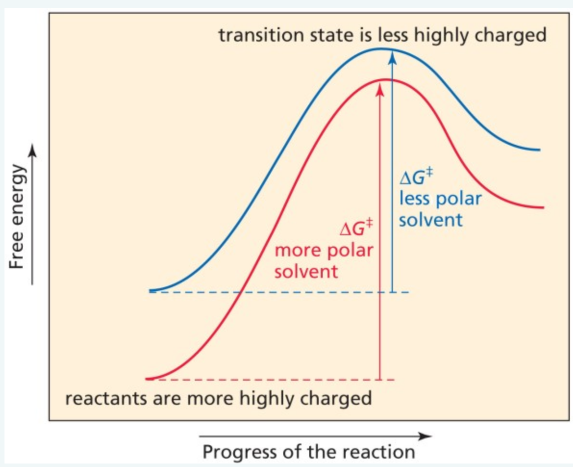
Solvation



Polar solvents stabilize charged species.

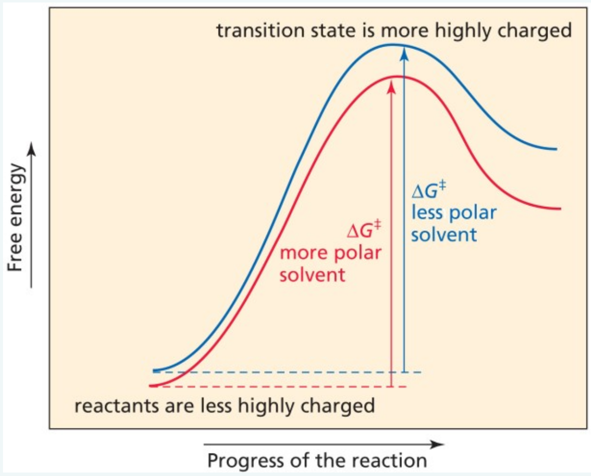
61

If a reactant is charged, increasing the polarity of the solvent decreases the Rate



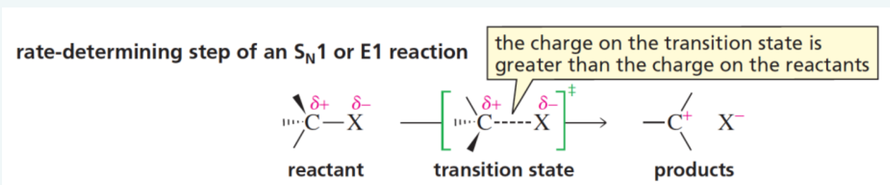
62

If the reactants are neutral, increasing the polarity of the solvent increases the Rate



63

How a solvent affects the Rate of a Reaction that does not have a Charged Reactant

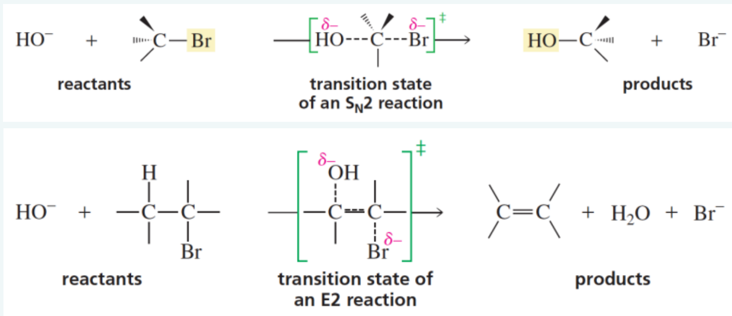


If a reactant is not charged:
the charge on the reactants will be greater than the charge on the transition state.

Increasing the polarity of the solvent will increase the rate of the reaction.

64

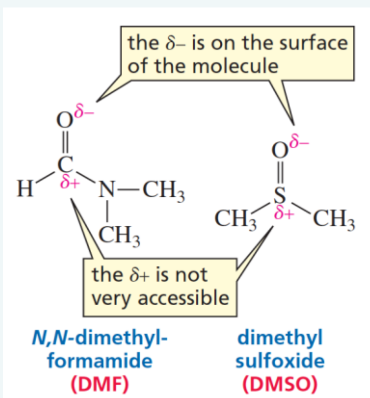
How a solvent affects the Rate of an Reaction that has a Charged Reactant

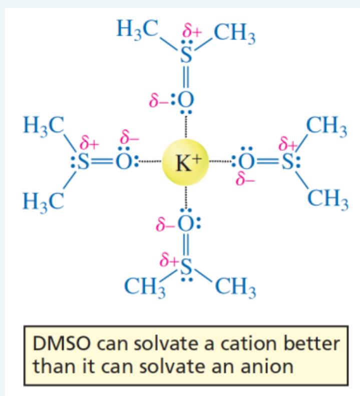


If a reactant is charged:
the charge on the reactants will be greater than the charge on the transition state.

Increasing the polarity of the solvent will decrease the rate of the reaction.

DMF and DMSO





These solvents can solvate cations (+) better than they can solvate anions (–).

William Ether Synthesis: an S_N2 Reaction

Williamson ether synthesis

$$\underset{\text{alkyl halide}}{R{-}Br} + \underset{\text{alkoxide ion}}{R{-}O^-} \longrightarrow \underset{\text{ether}}{R{-}O{-}R} + Br^-$$

67

Forming an Alkoxide Ion

$$ROH + NaH \longrightarrow RO^- + Na^+ + H_2$$

68

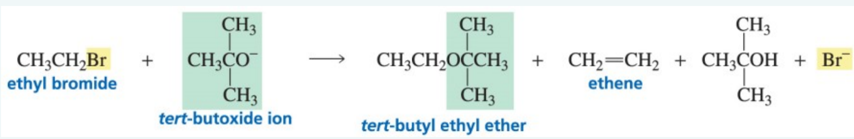
Synthesizing Butyl Propyl Ether

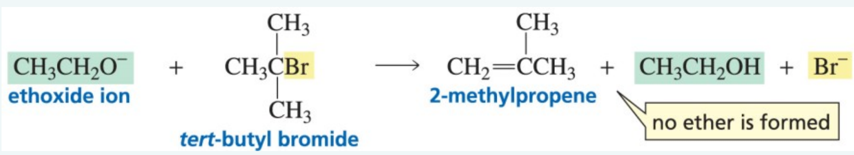
$$\underset{\text{propyl bromide}}{CH_3CH_2CH_2Br} + \underset{\text{butoxide ion}}{CH_3CH_2CH_2CH_2O^-} \longrightarrow \underset{\text{butyl propyl ether}}{CH_3CH_2CH_2OCH_2CH_2CH_2CH_3} + Br^-$$

$$\underset{\text{butyl bromide}}{CH_3CH_2CH_2CH_2Br} + \underset{\text{propoxide ion}}{CH_3CH_2CH_2O^-} \longrightarrow \underset{\text{butyl propyl ether}}{CH_3CH_2CH_2CH_2OCH_2CH_2CH_3} + Br^-$$

69

Synthesizing *tert*-Butyl Ethyl Ether





The less hindered group should be provided by the alkyl halide.

70