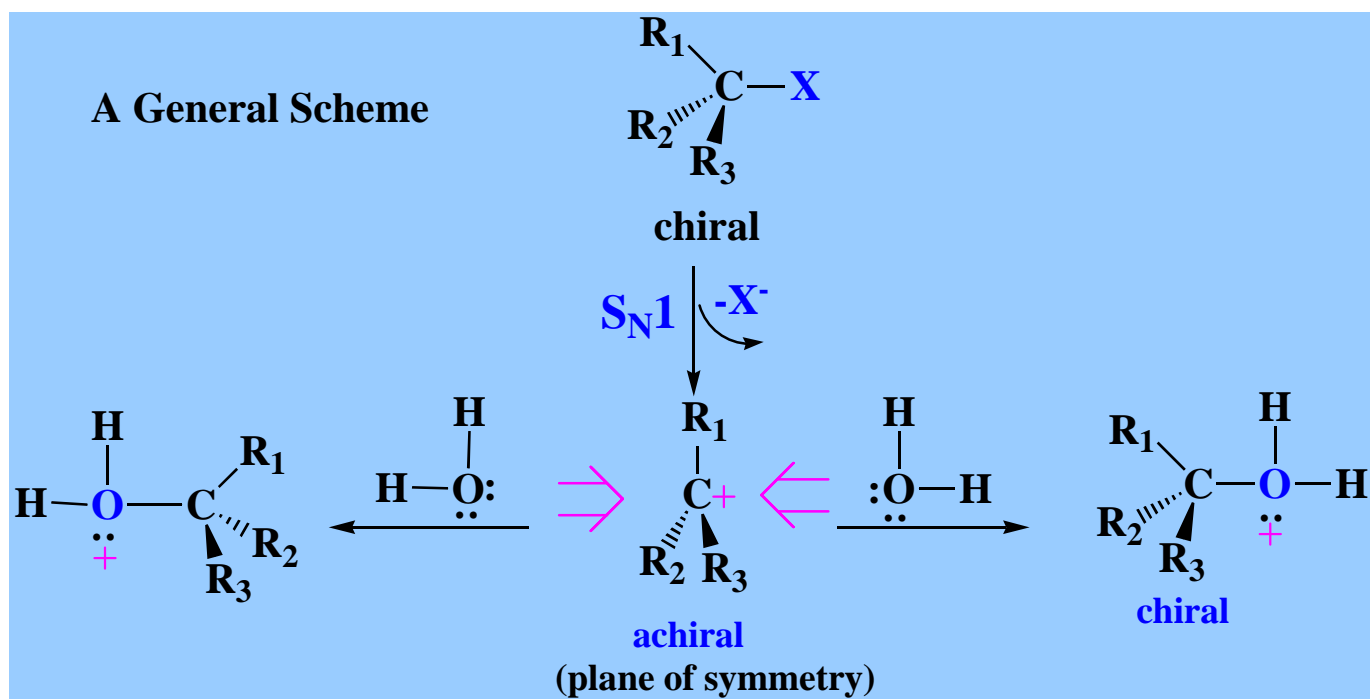


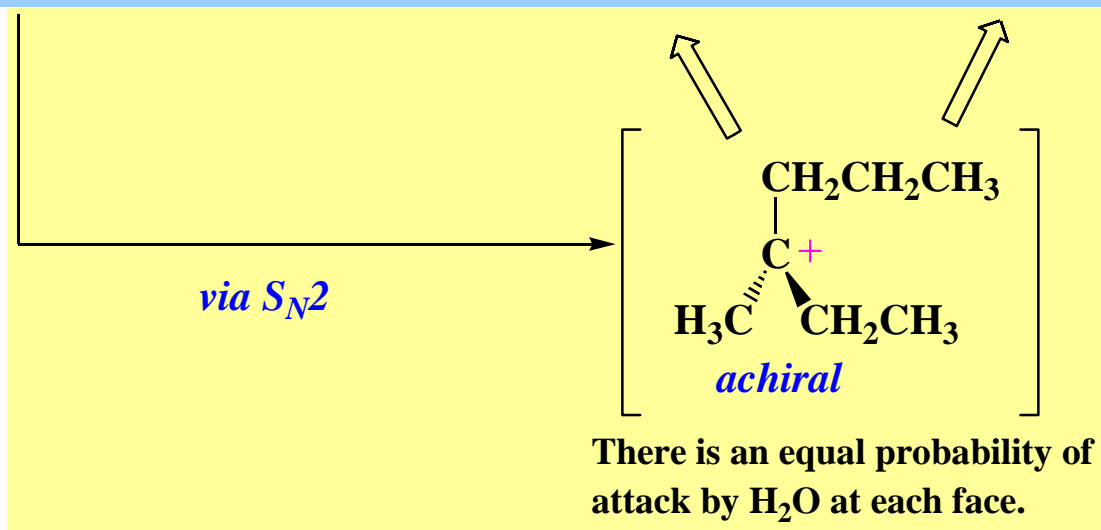
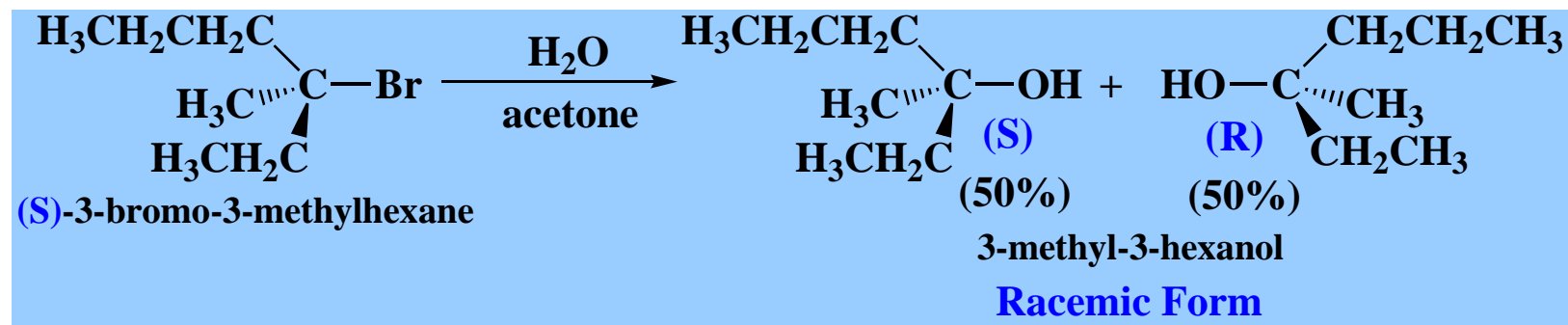
Stereochemistry of the S_N1 Reaction

Because carbocations have a trigonal planar geometry, they possess a **plane of symmetry** and are **achiral**. Therefore, a **racemic form** of a chiral product is predicted in reactions that involve carbocation intermediates.

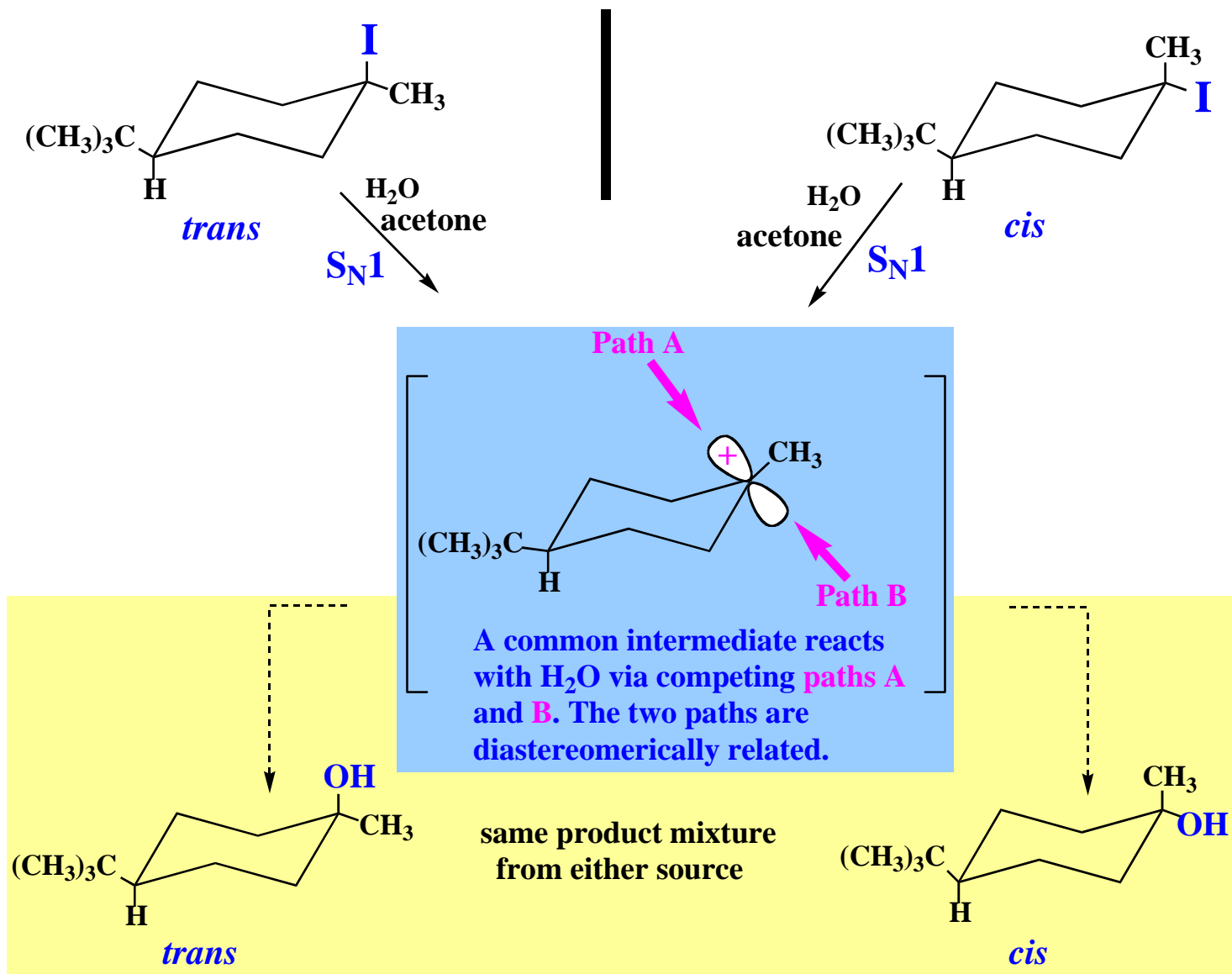


There are **equal probabilities** of reaction at the two faces of the carbocation. The two oxonium ions formed in equal amounts are **enantiomers**. A **racemic form** of the product is necessarily produced.

Example: The Hydrolysis of (S)-3-Bromo-3-methylhexane



Reaction Scheme

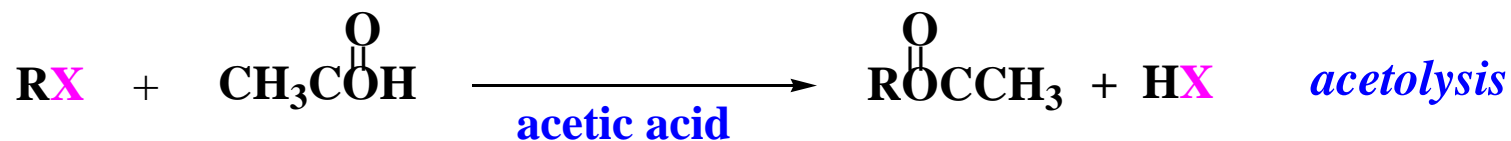
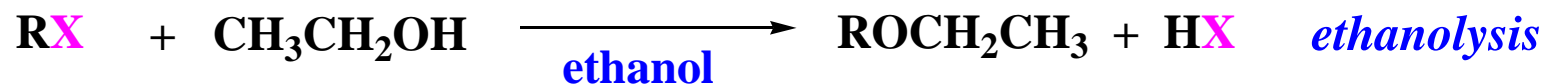
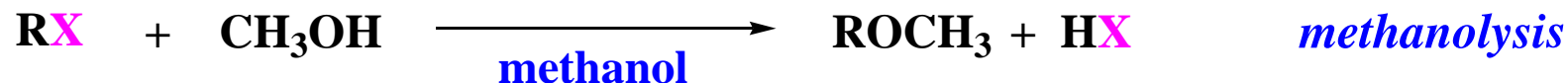


Solvolysis

A nucleophilic substitution reaction where the solvent is the nucleophile is called **solvolysis**.

When water is the solvent, the term **hydrolysis** is used.

Methanolysis means methanol is the nucleophile/solvent.



Factors Influencing the Rates of the S_N1 and S_N2 Reactions

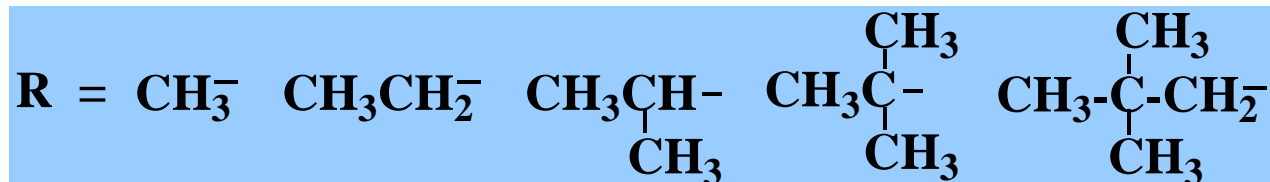
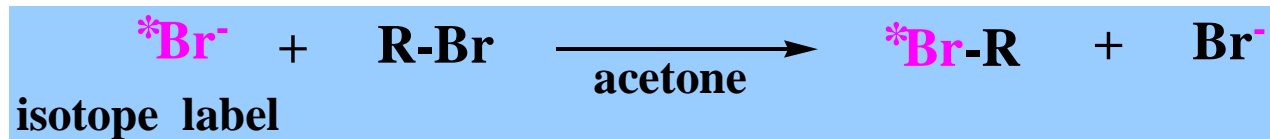
The S_N1 and S_N2 are always potentially **competitive pathways** for any nucleophilic substitution reaction. However, because of structural, electronic, and other factors, one pathway usually dominates.

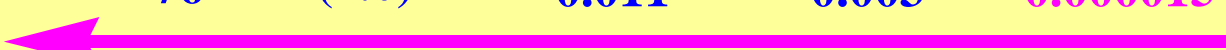
Effect of Structure on the S_N1 and S_N2 Reactions

A change in alkyl group substitution around the reacting carbon influences nucleophilic substitution by the S_N1 and S_N2 mechanisms in **opposite** ways.

An Example: Incorporation of isotopic bromine in RBr

Relative second-order rate constants in acetone
at 25°C for the S_N2 reaction:



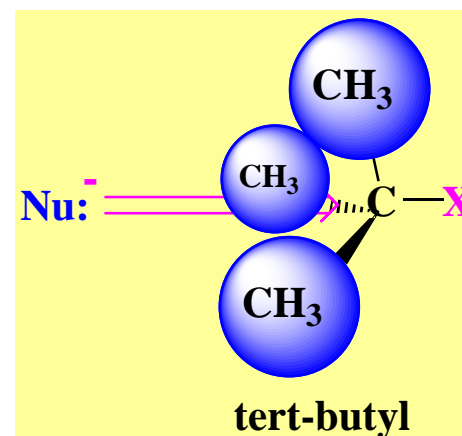
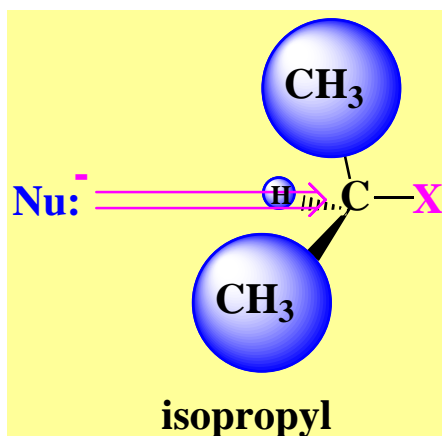
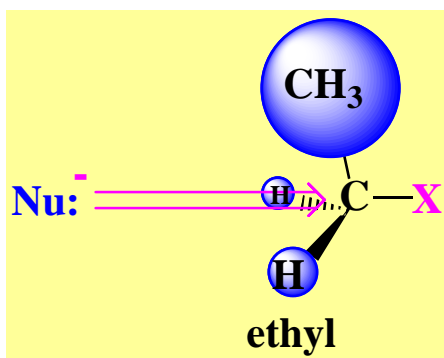
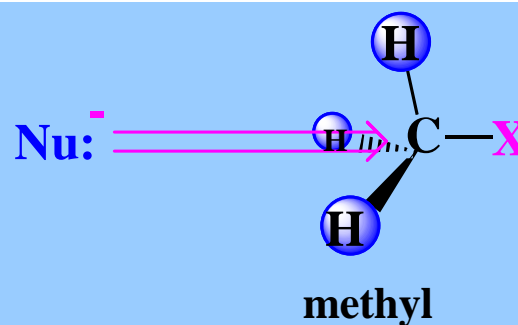
relative rate	76	(1.0)	0.011	0.003	0.000015
					
	faster				

This study shows that methyl bromide reacts 25,000 times faster than tert-butyl bromide, and 5 million times faster than neopentyl bromide, in this S_N2 reaction.

The Steric Effect

This slowdown in the rate of the S_N2 reaction with increasing alkyl substitution around the reaction center is attributed to a **steric effect**, increasing steric hindrance in approaching the reaction center by the incoming nucleophile.

The incoming **nucleophile** approaches the carbon center on an axis opposite the leaving group. Groups larger than H attached to the carbon center screen this line of approach.



increasing steric hindrance

The S_N1 Mechanism

The primary factor that determines the reactivity of RX compounds in the S_N1 reaction is the **stability of the carbocation intermediate**. Structural and electronic factors that stabilize a carbocation promote the S_N1 mechanism in nucleophilic substitution.

The reactivity order of RX compounds in nucleophilic substitution reactions by the S_N1 mechanism is:

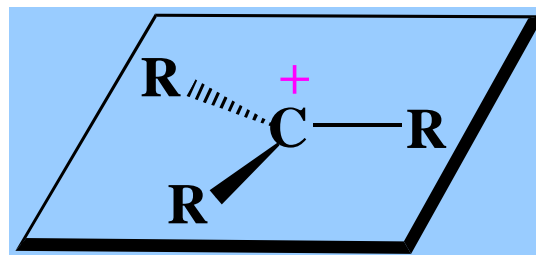
tertiary-RX > secondary-RX > primary-RX > methyl-RX

which reflects the stability of the carbocation intermediate.

The Structure of Carbocations

Carbocations are **trivalent carbon** species with a **positive charge**.

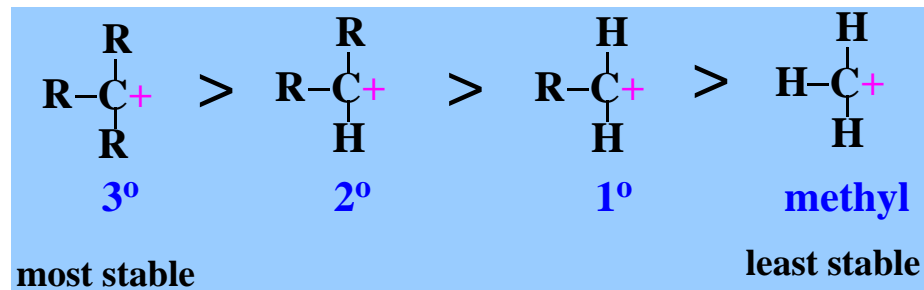
Carbocations are **locally planar** with the three valences in a plane.



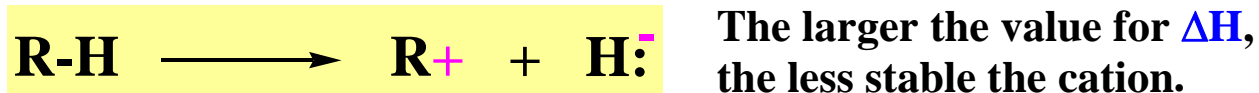
A trigonal planar geometry is predicted by VSEPR theory.


Relative Stabilities of Carbocations

Many experiments indicate the **stability order** of carbocations is:



Gas phase experiments (in the absence of solvation) provide ΔH values for simple alkanes undergoing the heterolytic process:

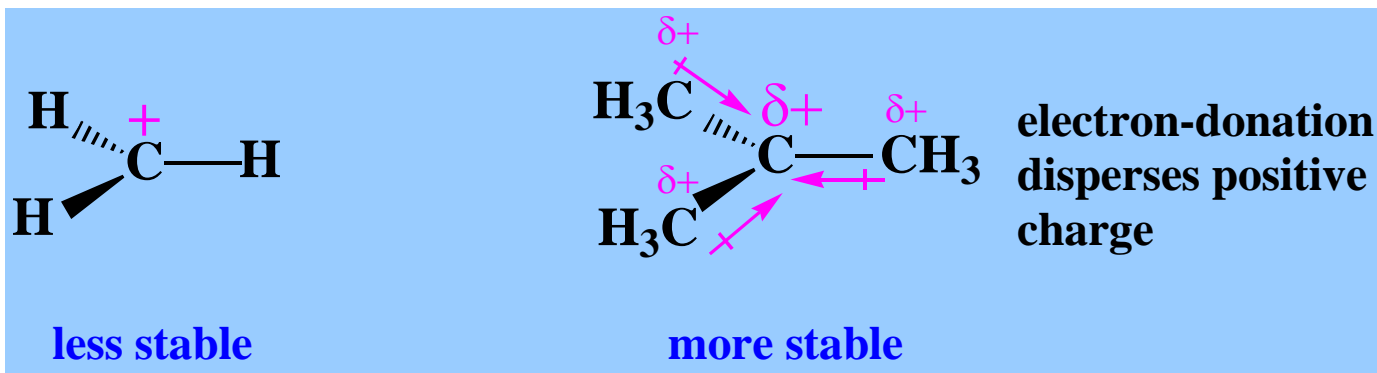


cation	CH_3^+	CH_3CH_2^+	$\text{CH}_3\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{C}}}^+$	$\text{CH}_3\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{C}}}^+$
ΔH (kJ/mol)	1305	1142	1035	961
	 increasing stability			

Source of Carbocation Stability Order

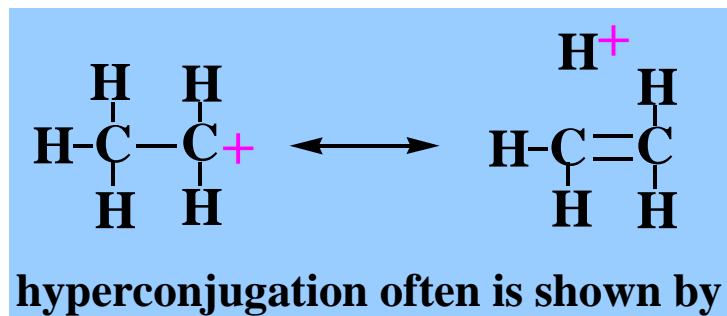
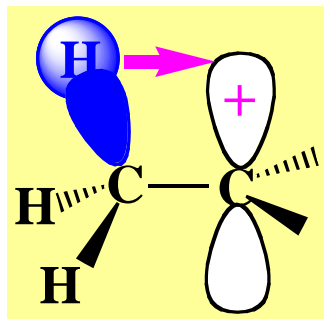
Inductive Effect

Replacement of a hydrogen with an alkyl group around the carbocation center stabilizes the positive charge by the **inductive effect**, electron donation through the sigma bonds. **The alkyl group is electron-donating relative to hydrogen.**

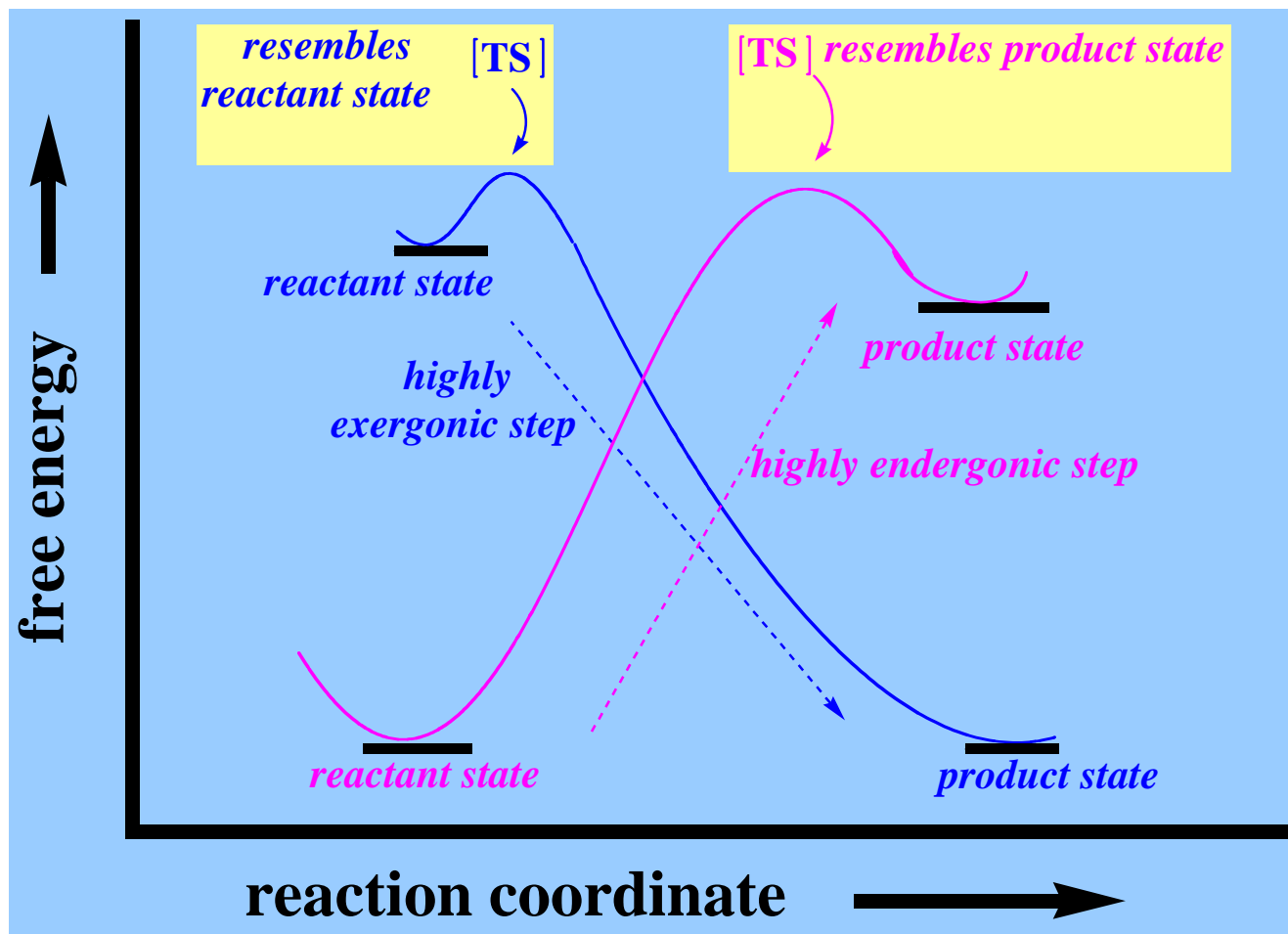


Hyperconjugation

Interaction of the **sigma electrons** in the C-H bond of the methyl group with the empty p-orbital of the carbocation disperses and stabilizes the positive charge.



The Hammond-Leffler Postulate



According to the Hammond-Leffler Postulate, since S_N1 processes are **highly endergonic**, the transition state comes late along the reaction coordinate and **resembles the carbocation state**. Factors that stabilize carbocations will stabilize the TS in an S_N1 reaction leading to a faster rate.

Nucleophile Strength

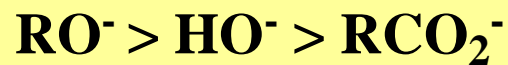
Nucleophile strength means "reactivity." A good nucleophile reacts rapidly with a substrate.

Some General Observations

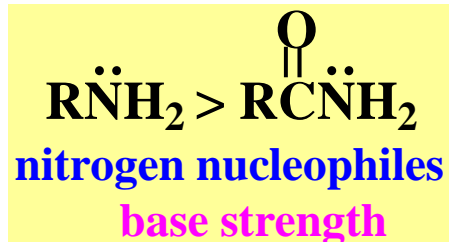
- (1) A negatively charged nucleophile always reacts faster with a substrate than its conjugate acid.

relative reactivities $\text{RO}^- > \text{ROH}$ $\text{HO}^- > \text{HOH}$ $\text{NH}_2^- > \text{NH}_3$

- (2) In a group of nucleophiles with the same nucleophilic atom, nucleophile strength parallels base strength.



oxygen nucleophiles
base strength



Nucleophile Strength and Base Strength

A strong correlation is often seen between base strength and nucleophile strength: **stronger bases are better nucleophiles**.

Exceptions exist, however. For example, hydroxide ion (HO^-) is a stronger base than cyanide ion ($:\text{N}\equiv\text{C}^-$), but cyanide is a better nucleophile towards RX compounds.

Polar Aprotic Solvents: Enhanced Reactivity of Nucleophiles in $\text{S}_{\text{N}}2$ Reactions

Aprotic solvents do not have hydrogen atoms attached to highly electronegative atoms, and do not participate in hydrogen bonding.

Many aprotic solvents are nonpolar, or have low polarity and do not dissolve ionic materials. The **polar aprotic solvents** dissolve ionic materials and selectively interact with cations through dipole-charge interactions.

Example: The Halides as Leaving Groups

leaving group ability $I^- > Br^- > Cl^- > F^-$

This order of leaving group ability of the halides in R-X compounds is consistent with the acidity order of the hydrogen halides, and the related base strength of the halide ions.

order of acid strength $H-F \ll H-Cl < H-Br < H-I$
weakest *strongest*

pK _a	3.2	-2.2	-4.7	-5.2
-----------------	-----	------	------	------

order of base strength $F^- \gg Cl^- > Br^- > I^-$

Influence of the Leaving Group on Chemical Reactivity

The typical relative reactivities of RX compounds in S_N2 reactions differ greatly because of the different leaving group abilities of the halides.

R-I	R-Br	R-Cl	R-F
30,000	10,000	200	1

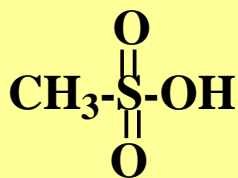


often a good choice
for organic synthesis

Other Good Leaving Groups

Another important class of good leaving groups are the sulfonate esters, $R-O_3SR'$, that produce stable **sulfonate anions** in nucleophilic substitution reactions.

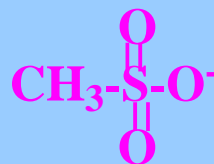
Acids



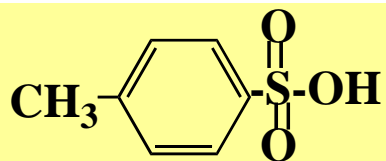
methanesulfonic acid

$$K_a = 16$$

Stable Anions

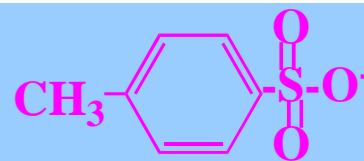


methanesulfonate anion

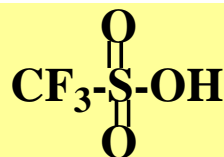


p-toluenesulfonic acid

$$K_a \sim 10$$

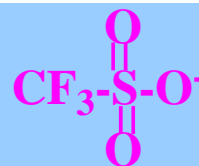


p-toluenesulfonate anion



trifluoromethanesulfonic acid

"triflic acid" a very strong acid



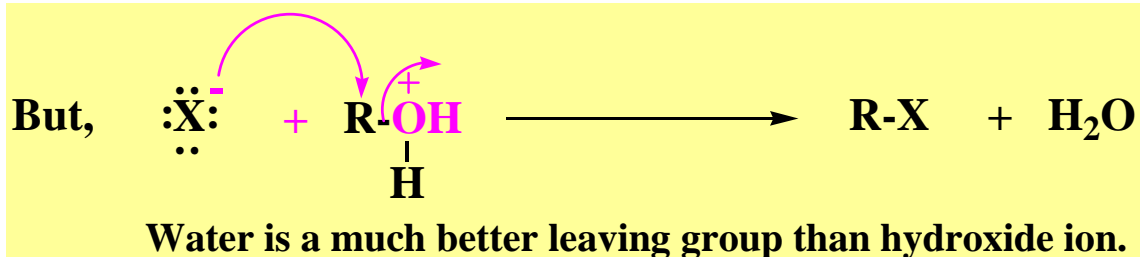
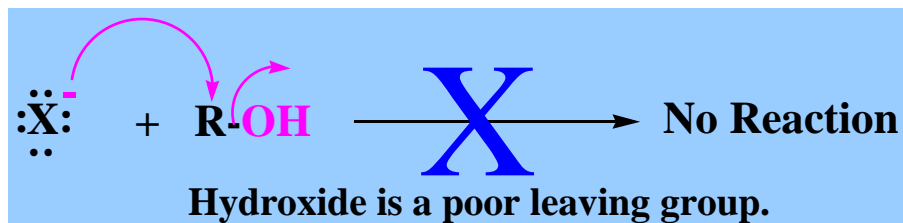
a "super"
leaving group

trifluoromethanesulfonate anion

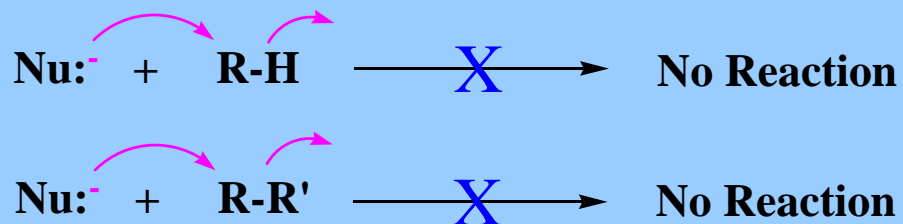
"triflate" anion

Acid-Promoted Leaving Group

Poor leaving groups sometimes can be chemically modified to turn them into better leaving groups. An example is the protonation of the hydroxyl function of an alcohol.



Note: **Very strong bases** such as simple carbanions (R:^-) and hydride (H:^-) **are never leaving groups** because of the instability of the anionic leaving groups that results in very unfavorable energetics.



Summary of S_N1 and S_N2 Reactions

These two modes of nucleophilic substitution of alkyl halides are always potential competing reactions. Often, one path dominates.

The S_N1 reaction is favored by:

substrates that form relatively **stable carbocations**, such as tertiary halides

weak nucleophiles

solvents of high ionizing ability (high ϵ)

The S_N2 reaction is favored by:

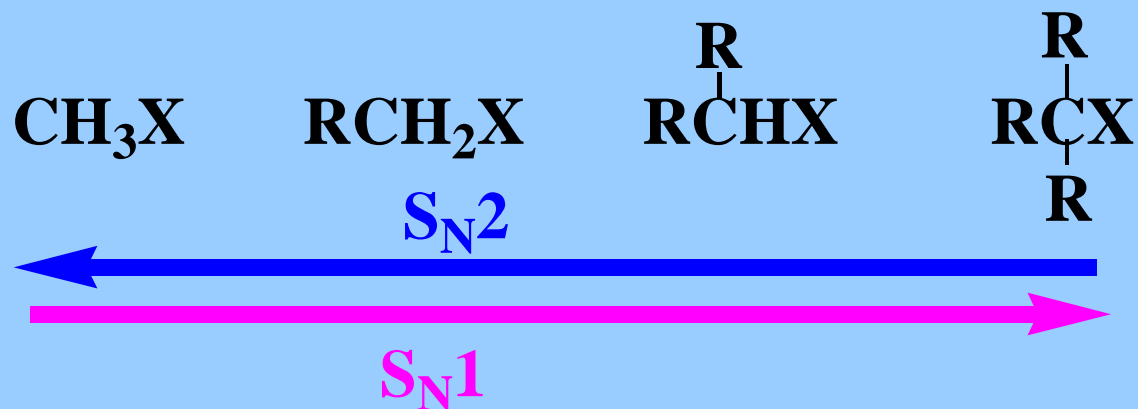
use of relatively **unhindered substrates** such as methyl and primary RX

strong nucleophiles (usually strong bases)

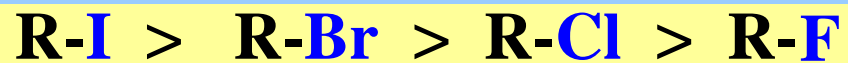
polar aprotic solvents

Summary of S_N1 and S_N2 Reactions

Overall for R-X:



The effect of the **leaving group** is the same for the S_N1 and S_N2 reactions.



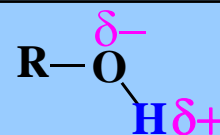
Solvent Effects on S_N2 Reactions

The choice of solvent greatly influences the rate of nucleophilic substitution reactions. Important solvent properties are **polar/nonpolar** and **protic/aprotic**. Often a solvent is classified as polar protic, polar aprotic, or nonpolar.

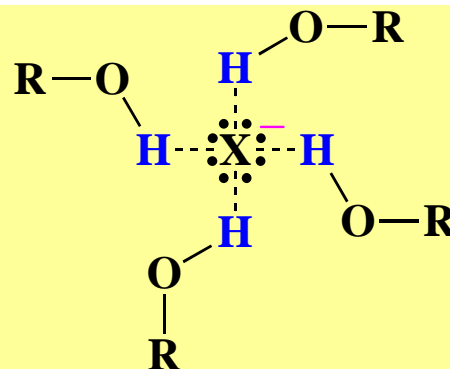
Polar Protic Solvents

Protic solvents have hydrogens attached to highly electronegative atoms, such as O and N, that form **hydrogen bonds** to nucleophiles. Protic solvents are also **polar solvents** and are often called **polar protic solvents**.

Water and alcohols are polar protic solvents.



Halide ions interact with polar protic solvents through hydrogen bonding:



Nucleophile Stability and Reactivity

The strength of the H-bonding increases with the **density** of the negative charge on X^- . **Fluoride ion**, the smallest halide, has the largest negative charge density and strongest H-bonding interaction with polar protic solvents. This interaction **stabilizes the ion and decreases its nucleophile strength** in polar protic solvents.

Reactivity Order of Halide Ions in Polar Protic Solvents



weakest solvation

strongest solvation

Gas Phase Reactivity

Reactivity order of halide ions in the gas phase: $F^- > Cl^- > Br^- > I^-$

In the absence of solvent, the reactivity order of the halide ions parallels their base strength.

Nucleophile Strength and Base Strength

A strong correlation is often seen between base strength and nucleophile strength: **stronger bases are better nucleophiles.**

Exceptions exist, however. For example, hydroxide ion (HO^-) is a stronger base than cyanide ion ($:\text{N}\equiv\text{C}^-$), but cyanide is a better nucleophile towards RX compounds.

Polar Aprotic Solvents: Enhanced Reactivity of Nucleophiles in $\text{S}_{\text{N}}2$ Reactions

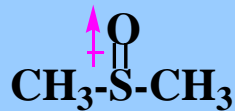
Aprotic solvents do not have hydrogen atoms attached to highly electronegative atoms, and do not participate in hydrogen bonding.

Many aprotic solvents are nonpolar, or have low polarity and do not dissolve ionic materials. The **polar aprotic solvents** dissolve ionic materials and selectively interact with cations through dipole-charge interactions.

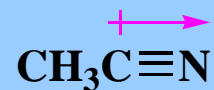
Examples of Polar Aprotic Solvents



N,N-dimethylformamide
(DMF)

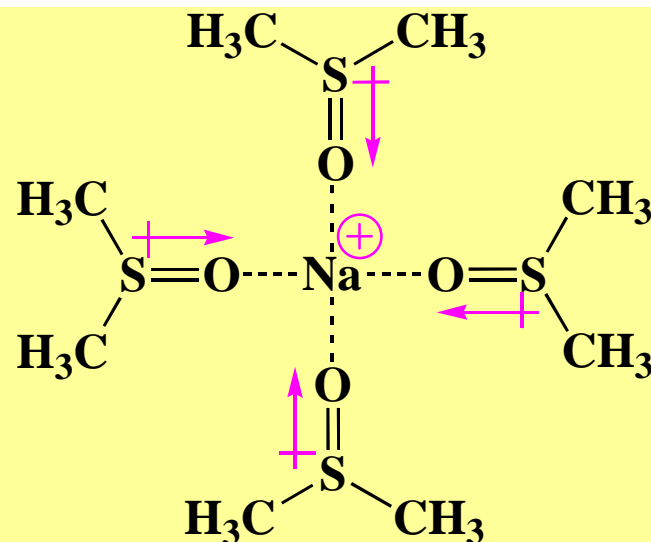


dimethyl sulfoxide
(DMSO)



acetonitrile

Polar aprotic solvents
selectively solvate cations
through dipole-charge
interactions.



While polar aprotic solvents strongly interact with cations,
they do not solvate anions (nucleophiles) very well.

"Naked Anions" in Polar Aprotic Solvents

Because anions are weakly solvated, and because there is little cation-anion association in polar aprotic solvents, the term "naked anions" is often used to describe the state of anions in these solvents.

Naked anions are very reactive as nucleophiles and bases.

The Reactivity of Naked Anions

The reactivity order of the halides in DMSO is the same as in the gas phase where there is no solvation:

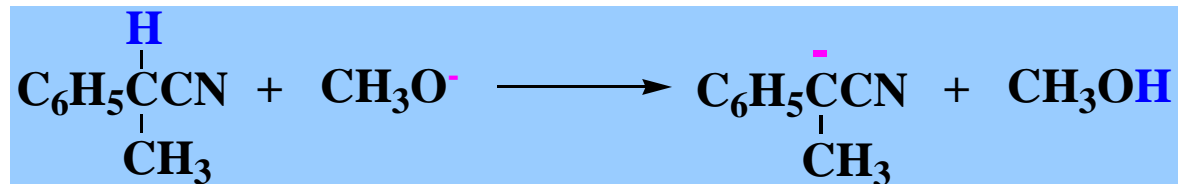


The reactivity of nucleophiles towards a single substrate increases dramatically in polar aprotic solvents:



<i>solvent</i>	<i>relative rate</i>	
CH₃OH	0.9	} protic solvents
H₂O	1.0	
HCONH₂	14.1	
CH₃CN	35,800	} polar aprotic solvents
HCON(CH₃)₂	708,000	

For the proton transfer (acid-base) reaction:

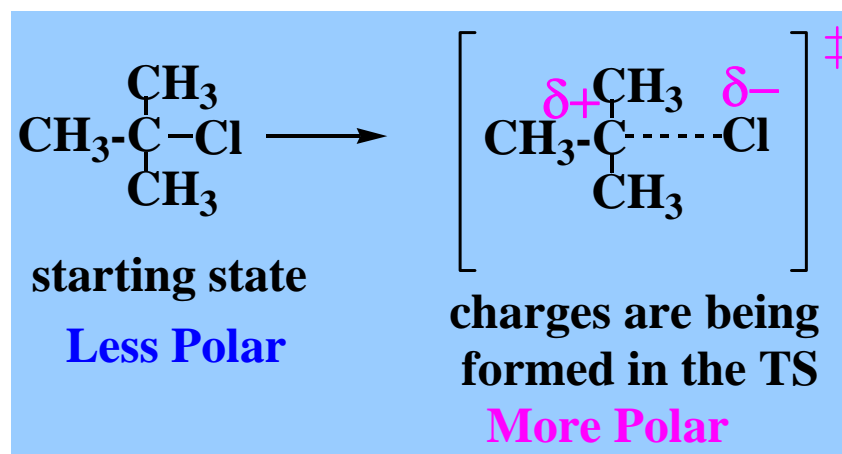


$$\frac{\text{Rate in DMSO}}{\text{Rate in CH}_3\text{OH}} = 10^9$$

Solvent Effects on the S_N1 Reaction

Solvent polarity typically influences the rate of chemical reactions where the starting and transition states **differ significantly in polar character**.

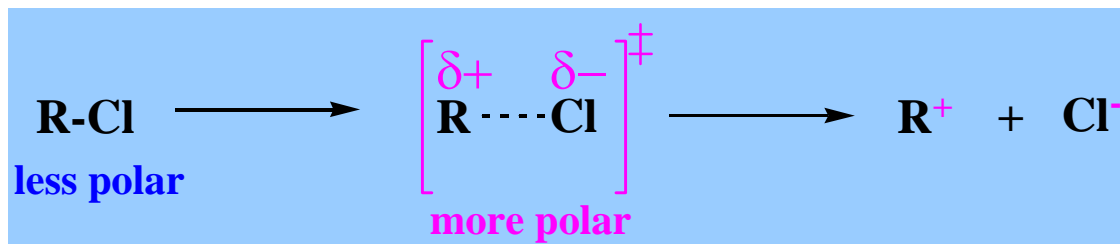
The S_N1 reaction usually has a transition state that is much **more polar** than the starting state.



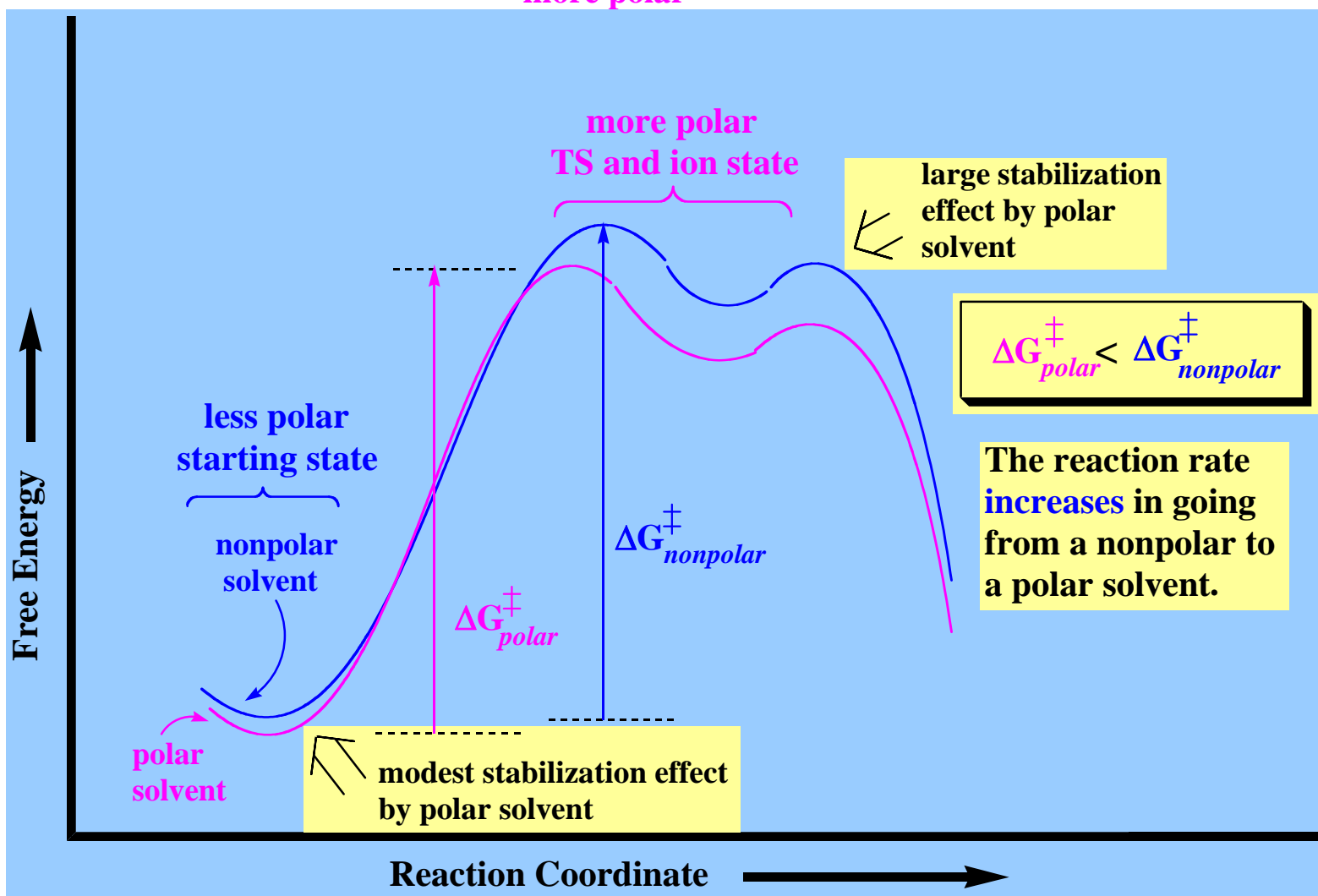
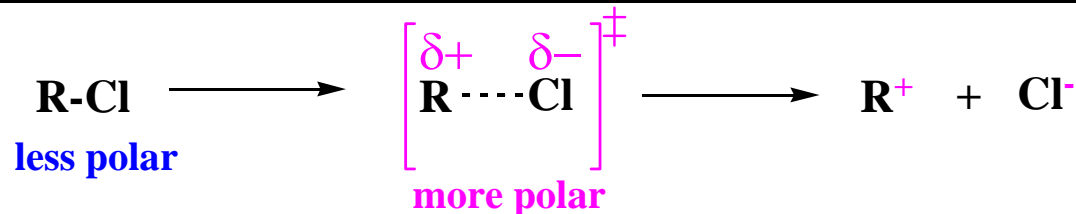
To determine how a change in solvent affects the rate of a reaction, it is necessary to determine the change in energy on both the starting and transition states. If the solvent change decreases the ΔG^\ddagger , the rate increases.

Change from a Less Polar to a More Polar Solvent

When there is a change from a **less polar to a more polar solvent**, the rate of an S_N1 reaction generally increases because the energy of the more polar transition state decreases more than the energy of the less polar starting state.



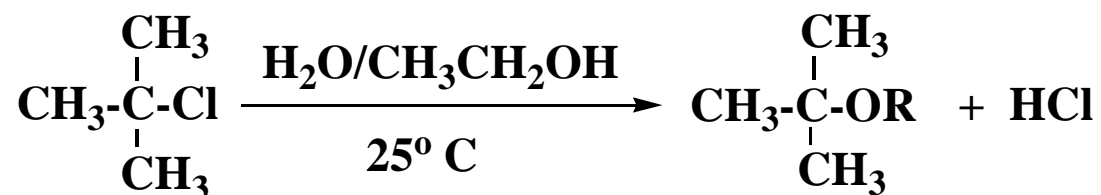
Free Energy Changes for the Rate-Determining Step of an S_N1 Reaction in Nonpolar and Polar Solvents





A Measure of Solvent Polarity: Dielectric Constant

One measure of solvent polarity is the **dielectric constant, ϵ** , that measures the ability of a solvent to screen the electrostatic attraction between opposite charges. As a solvent interacts with and stabilizes charges, the attractive forces decrease. The higher the value of ϵ , the more stable the ions, the more the attractive forces are screened, and the easier it is to **separate the charges as in the TS for the S_N1 reaction.**

Example: The Solvolysis of tert-Butyl Chloride



solvent	100% ethanol	90%	80%	70%	60%	50%	40%	...100% water
ϵ	24	<i>increasing polarity</i> 						80
relative rate	—	1.0	5.3	23.5	73.6	214	756	—
		<i>increasing rate of reaction</i> 						

Specific Solvent Effects in the S_N1 Reaction: Hydrogen Bonding

Polar protic solvents typically are very rate enhancing in S_N1 reactions because they specifically interact with the **leaving group** by **hydrogen bonding**. This interaction provides an additional mode for charge dispersal and stabilization of the transition state.

Example: The Methanolysis of tert-Butyl Chloride

Hydrogen bonding by methanol molecules helps disperse developing charge in the transition state.

