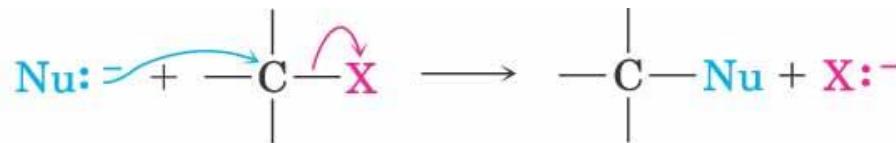


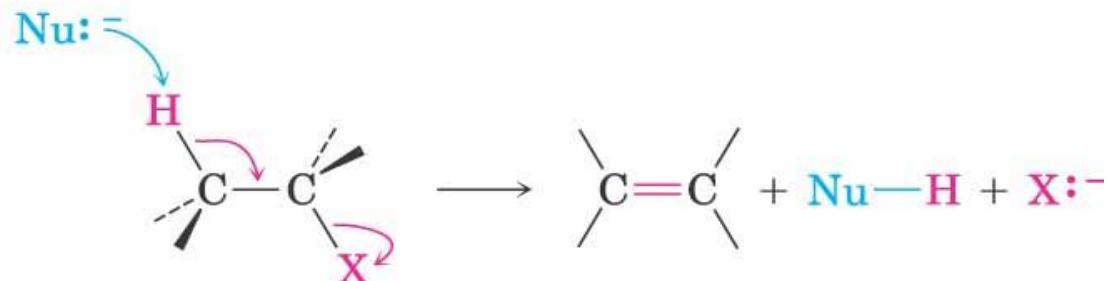
Chapter 9

Substitution and Elimination Reactions

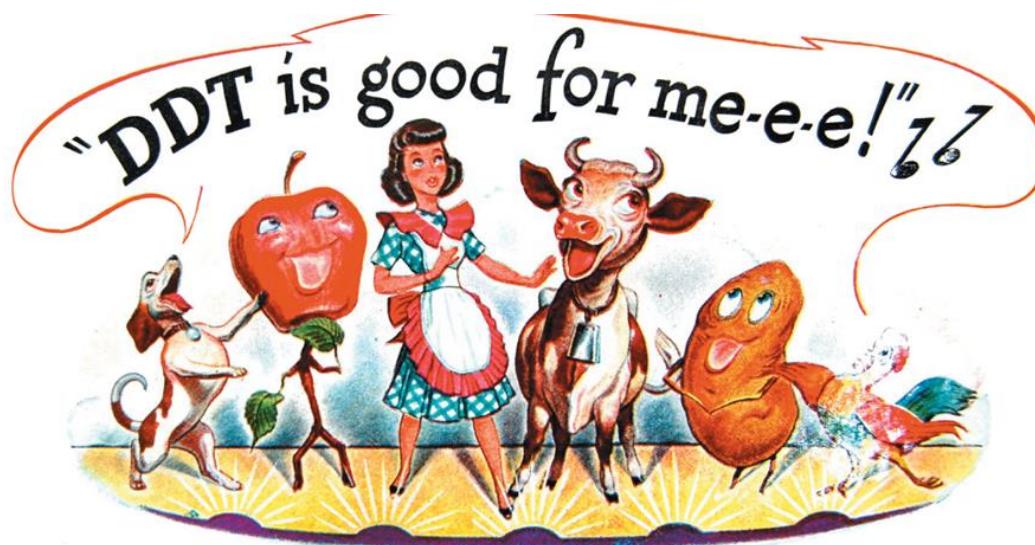
Substitution



Elimination



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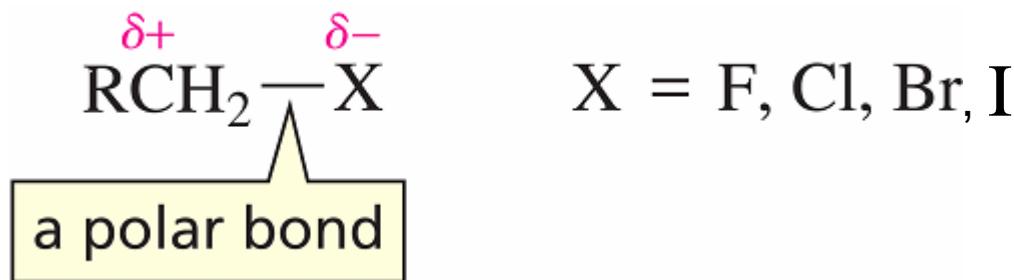


Chapter Objectives

- Be able to draw the 4 mechanisms of substitution and elimination reactions, explain their kinetics & the steps of the reactions.
- Know the factors that can affect these 4 mechanisms.
- Be able to explain the order of reactivity of the various alkyl halides for both substitution and elimination reactions.
- Be able to explain how the solvent can affect both substitution and elimination reactions.
- Be able to explain how the nucleophile can affect both substitution and elimination reactions.
- Be able to explain how the leaving group can affect both substitution and elimination reactions.
- Be able to show the differences between both substitution and elimination reactions using chiral substrates.
- Be able to work out which of a pair of reactions would take place more quickly
- Be able to work out whether a reaction will take place by the S_N1 or S_N2 or E2 or E1 routes, using the reaction conditions & solvents given.

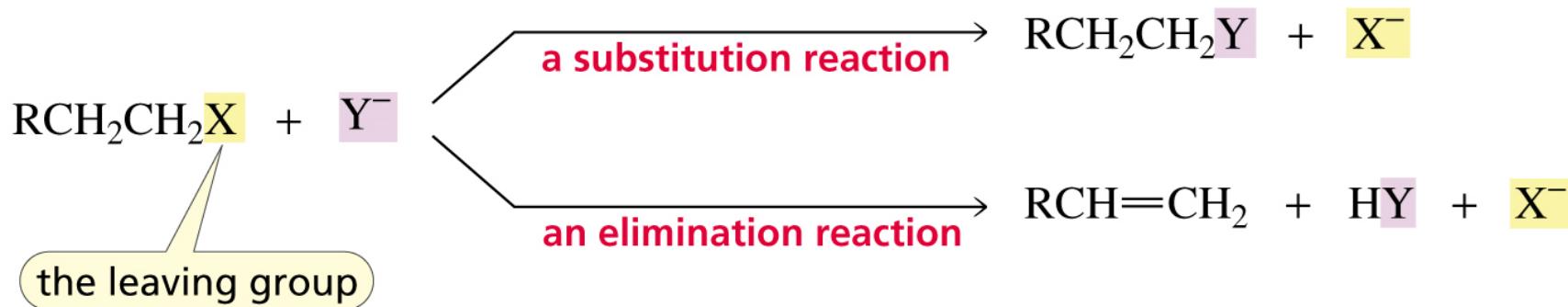
Alkyl Halides React with Nucleophiles and Bases

- Alkyl halides are polarized at the carbon-halide bond, making the carbon _____.



- Nucleophiles will replace the halide in C-X bonds of many alkyl halides (reaction as Lewis base): group that is substituted is called the “_____”
- Nucleophiles that are Brønsted bases produce elimination

Alkyl Halides Are Electrophiles, so React with Nucleophiles



substitution reaction—the electronegative group is **replaced** by another group.

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

COMMON SUBSTRATES

(Leaving group varies)

alkyl halides

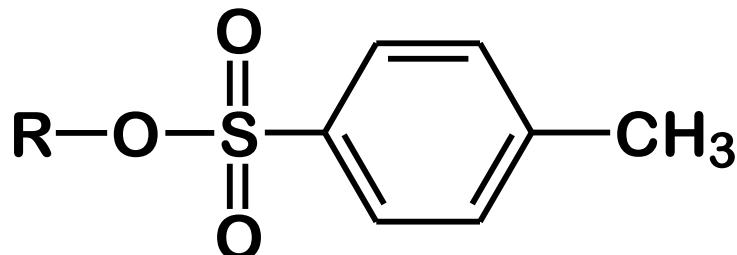


alcohols



alcohols
require acid
and then
 H_2O leaves

tosylates



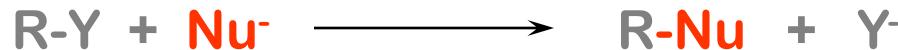
ABBREVIATION

$R-O-Ts$

alkyl *p*-toluenesulfonate

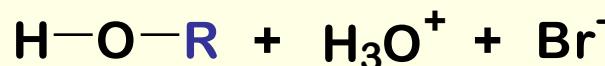
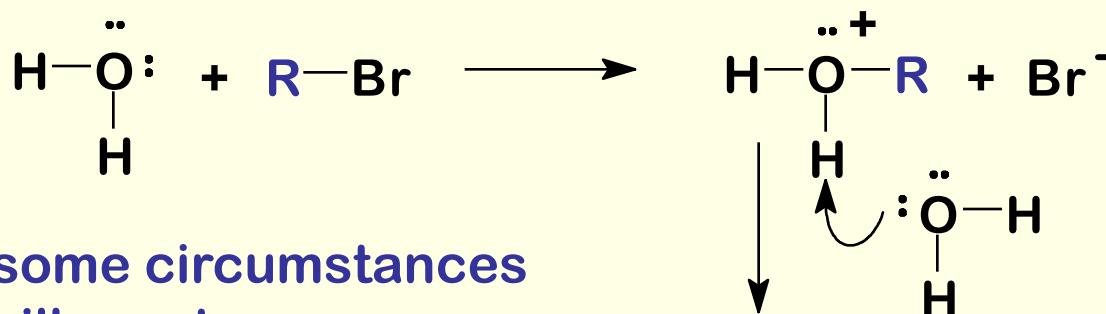
NUCLEOPHILES

A WIDE SELECTION OF NUCLEOPHILES MAKES POSSIBLE THE SYNTHESIS OF MANY TYPES OF ORGANIC COMPOUNDS:



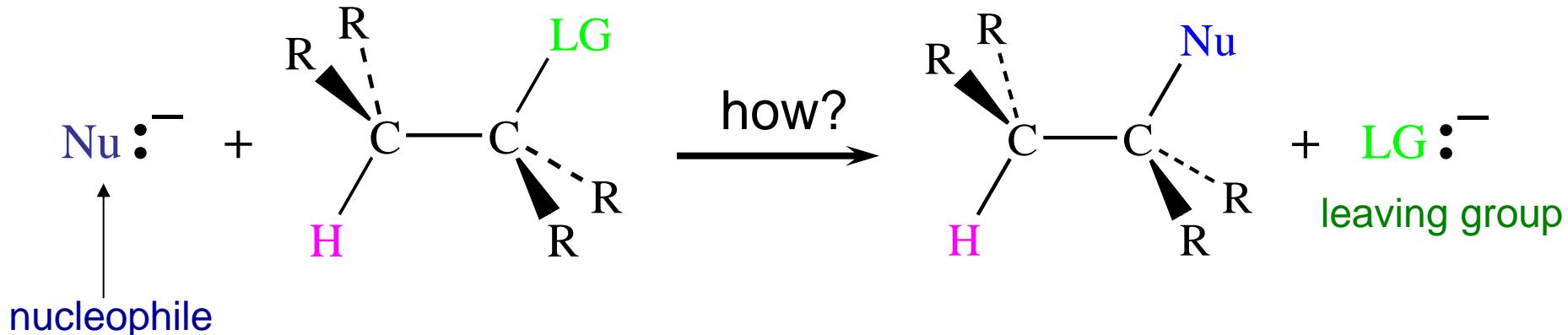
Nucleophile	Product	Class
Cl^- , Br^- , I^-	$R-X$	alkyl halides
OH^-	$R-OH$	alcohols
RO^-	$R-O-R'$	ethers
$:C\equiv N:$	$R-C\equiv N:$	nitriles
$R'-C(=O)O^-$	$R'-C(=O)OR$	esters
$R'-C\equiv C^-$	$R'-C\equiv C-R$	alkynes
$-SH$	$R-SH$	thiols

THE NUCLEOPHILE DOES NOT HAVE TO BE CHARGED



Nucleophile	Product	Class
$\text{H}-\text{O}-\text{H}$	$\text{R}-\boxed{\text{O}-\text{H}}$	alcohols
$\text{R}'-\text{O}-\text{H}$	$\boxed{\text{R}'-\text{O}-\text{R}}$	ethers
NH_3	$\text{R}-\boxed{\text{NH}_2}$	1° amines
$\text{R}'-\text{NH}_2$	$\boxed{\text{R}'-\text{NH}-\text{R}}$	2° amines

Nucleophilic substitution reactions



Two limiting mechanisms of nucleophilic substitution:

$\text{S}_{\text{N}}2$:

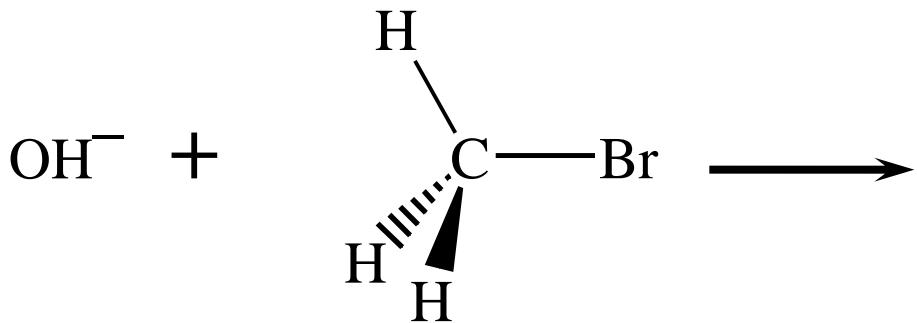
$\text{S}_{\text{N}}1$:

Bimolecular – _____ molecules are involved in the rate-determining step.

Unimolecular – _____ molecule involved in the rate-determining step.

S_N2: Substitution nucleophilic bimolecular

Example:

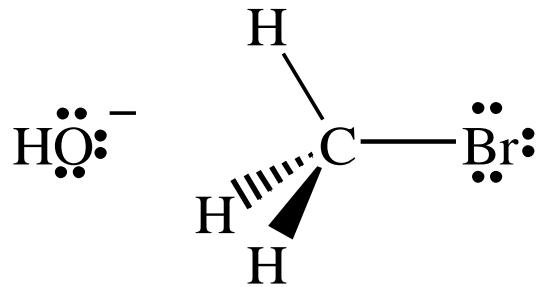


1) MECHANISM

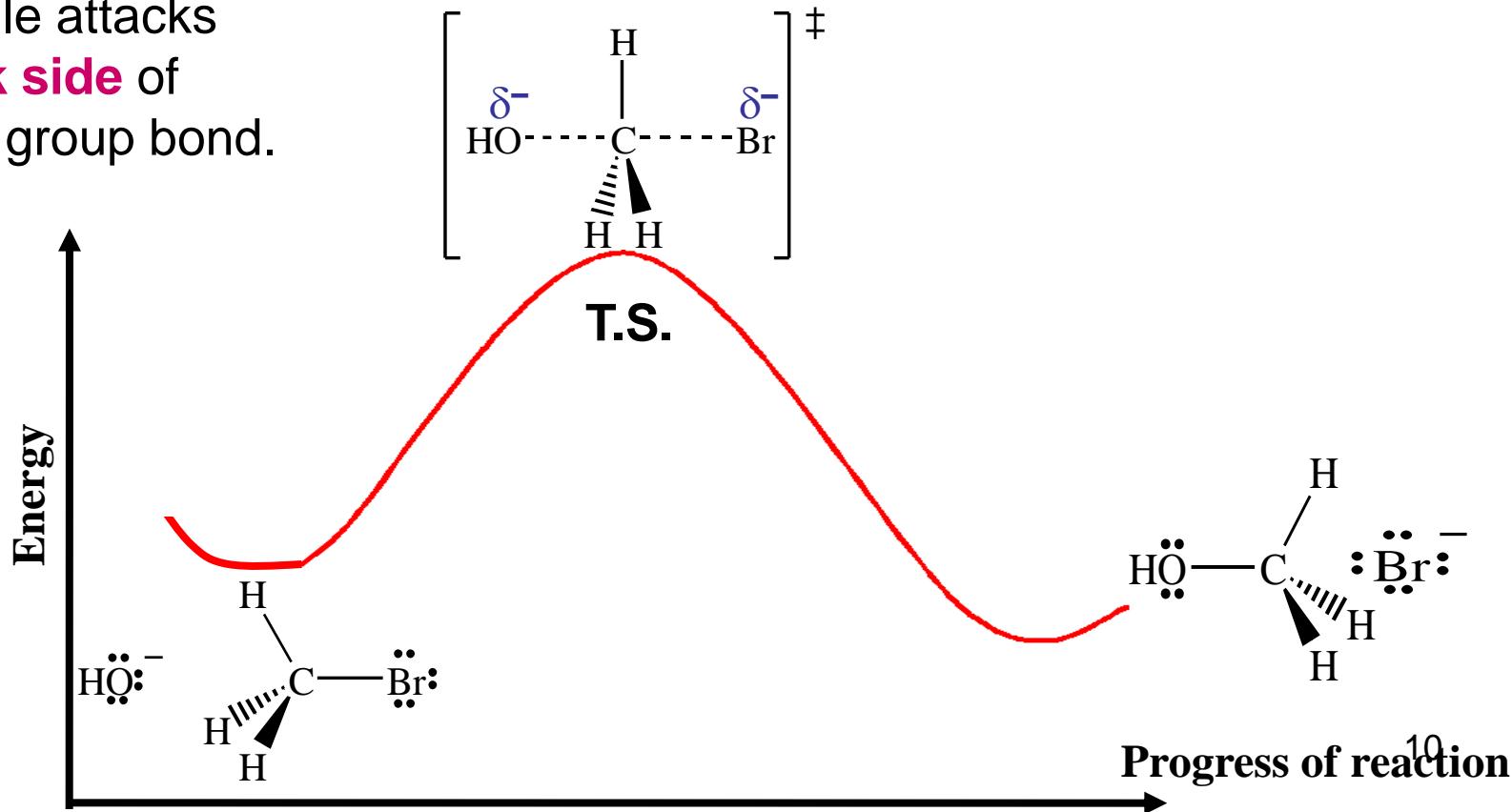
2) EVIDENCE

3) FACTORS

MECHANISM

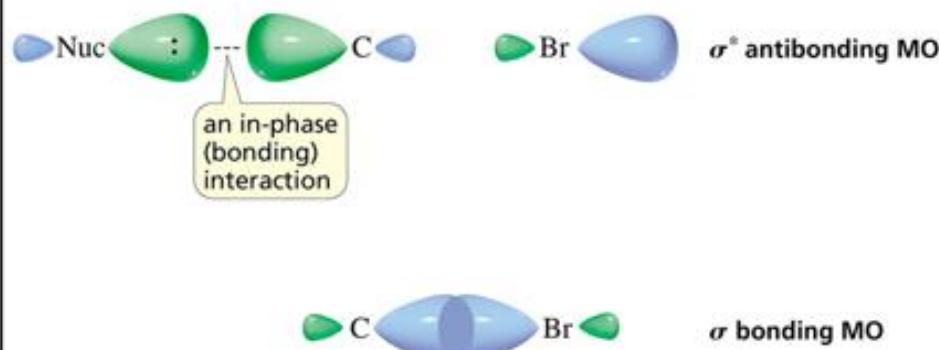


Nucleophile attacks
from **back side** of
C-leaving group bond.

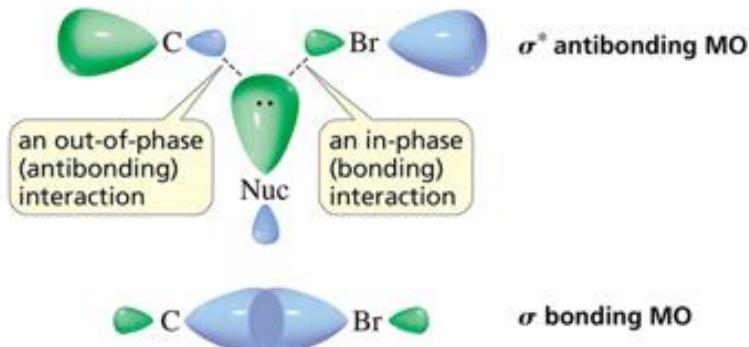


Why Back-Side Attack?

a. Back-side attack



b. Front-side attack



Why Bimolecular?

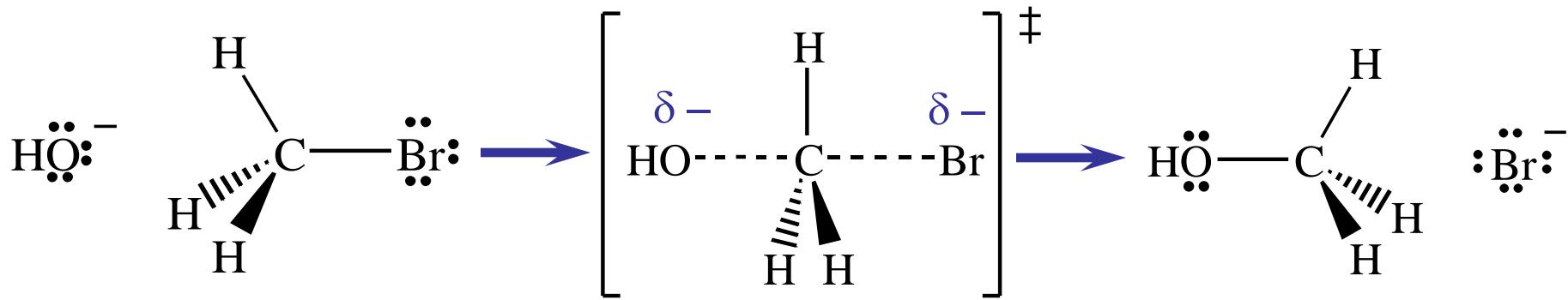
the C—Br bond breaks as the C—O bond forms



transition state
the transition state contains both the alkyl halide and the nucleophile

EVIDENCE

(a) Reaction kinetics: relationship between **rate** and **concentration**



The rate of the reaction depends of the concentrations of both the nucleophile and substrate: “_____” reaction.

If the $[\text{CH}_3\text{Br}]$ is _____, the rate of reaction _____.

If the $[\text{OH}^-]$ is _____, the rate of the reaction _____.

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

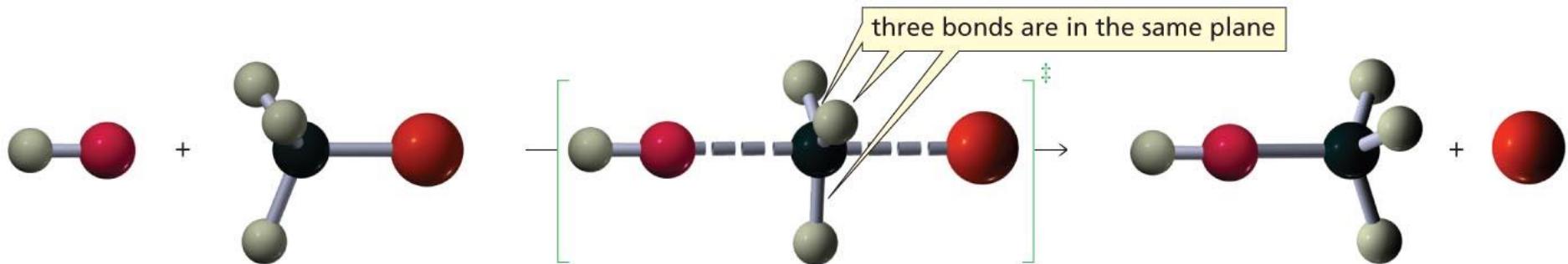
k = the rate constant

This is evidence that the reaction is **BIMOLECULAR** (both reactants taking part in rate-determining step.)

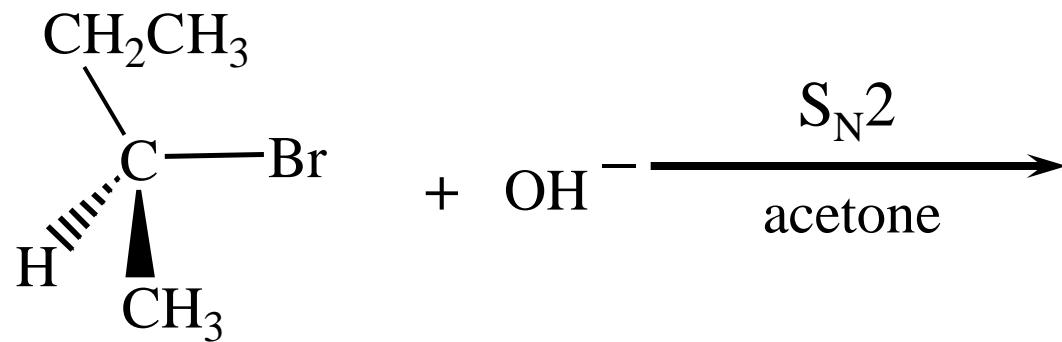
EVIDENCE

(b) Stereochemistry

S_N2 reactions at a chirality centre occur with ; “Walden Inversion”.



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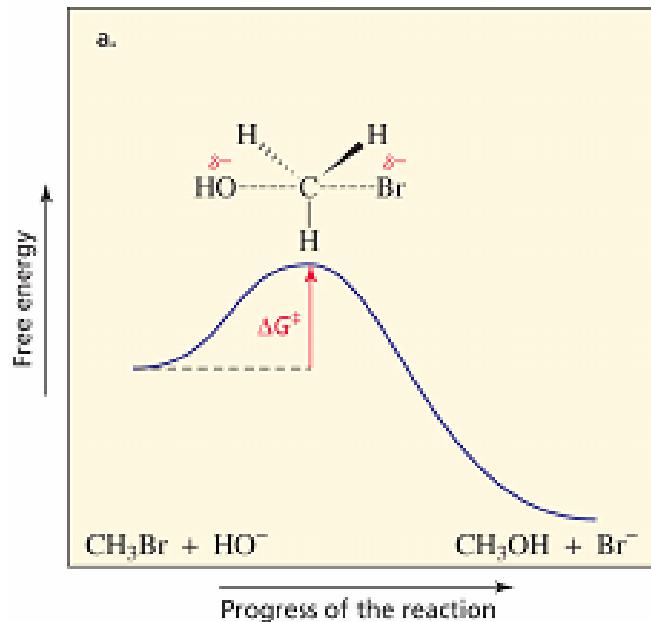


FACTORS

(a) Structure of the substrate (electrophile)

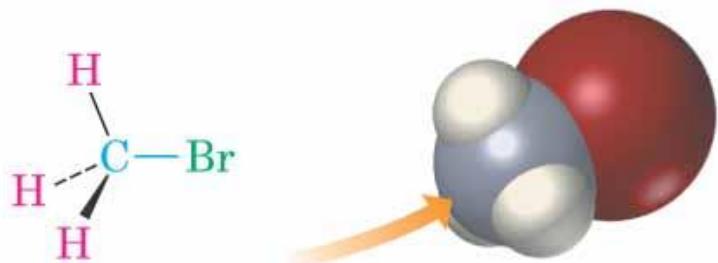
Steric hindrance: repulsive interaction in a molecule due to groups occupying a certain volume of space: decreases reactivity

relative reactivities of alkyl halides in an S_N2 reaction

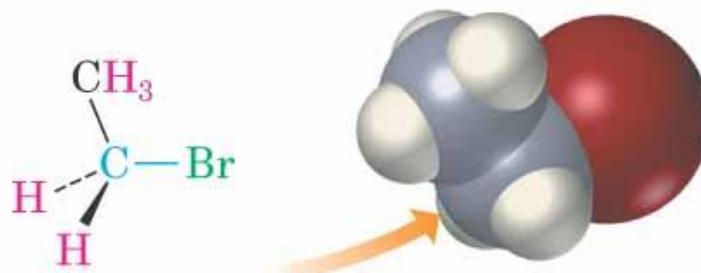


Steric effects slow down S_N2 reactions:

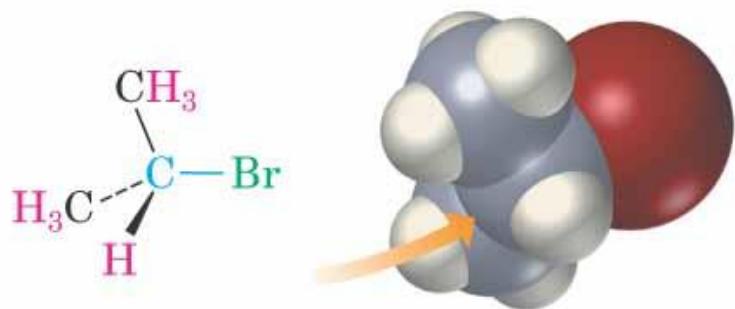
(a)



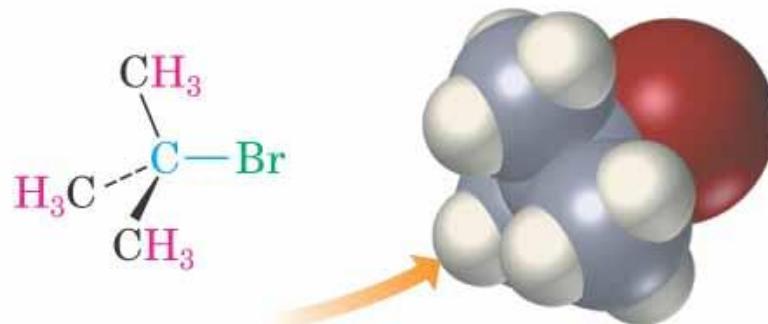
(b)



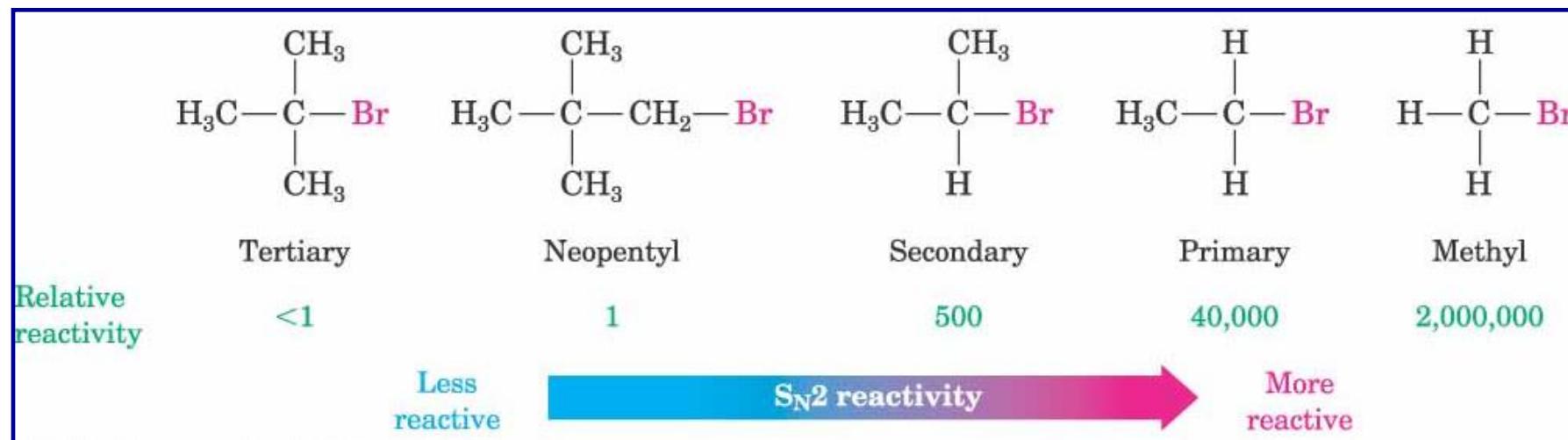
(c)



(d)

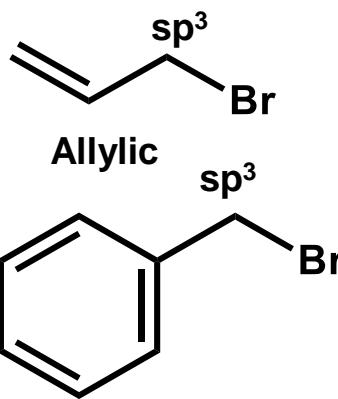


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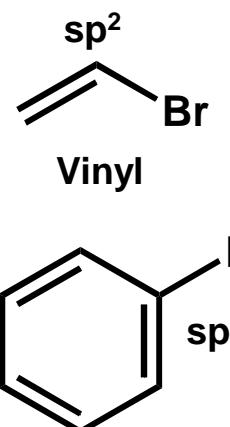


Benzyllic, allylic, vinyl and aryl alkyl halides?

Substituent	Compound	Relative Rate
Methyl	$\text{CH}_3\text{-X}$	1.0
1°	$\text{CH}_3\text{CH}_2\text{-X}$	0.33
2°	$(\text{CH}_3)_2\text{CH-X}$	0.00083
Allylic	$\text{CH}_2=\text{CHCH}_2\text{-X}$	1.3
Benzilic	$\text{C}_6\text{H}_5\text{CH}_2\text{-X}$	4.0
Vinyl	$\text{CH}_2=\text{CH-X}$	0.0
Aryl	$\text{C}_6\text{H}_5\text{-X}$	0.0

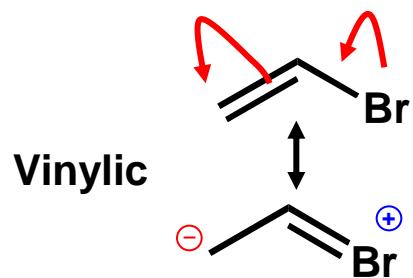


Benzyllic

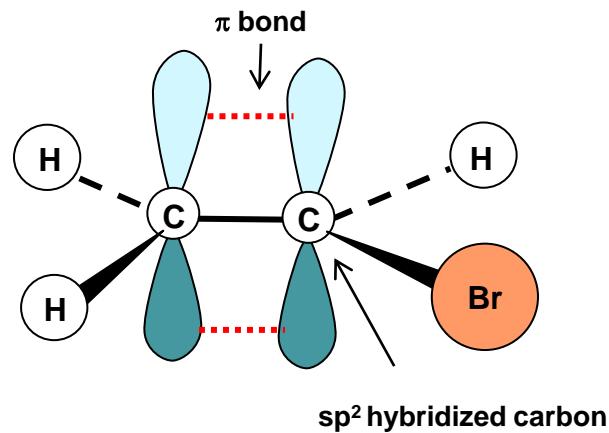
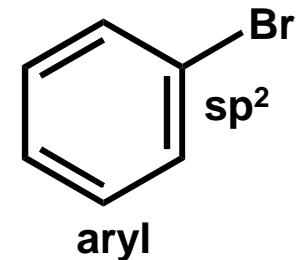


Aryl

Vinyl and aryl compounds are very nonreactive in S_N1 and S_N2



sp^2 short strong bond
Under most conditions a nucleophile will not displace the leaving group in a S_N2 reaction



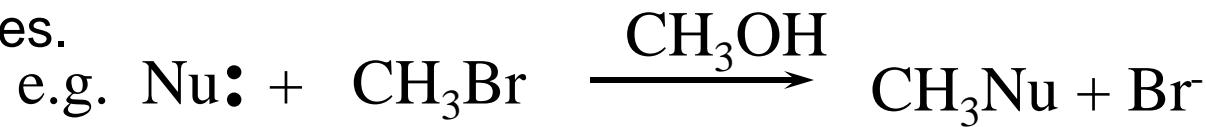
FACTORS

(b) Nature of Nucleophile

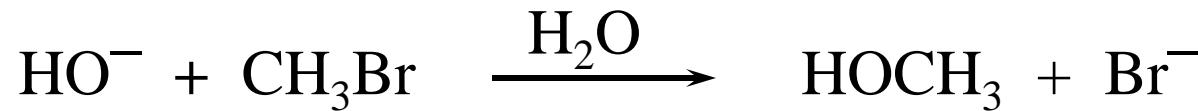
Nucleophilicity: measure of how **fast** a nucleophile displaces a leaving group in a particular reaction.

Note: Nucleophilicity relates to how **fast** the reaction proceeds. This is a **kinetic** measurement.

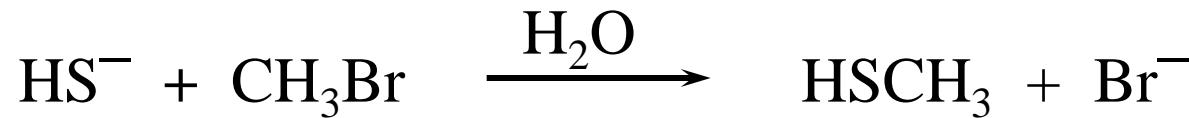
A standard set of experimental conditions has to be used to compare nucleophiles.



- example:



vs.



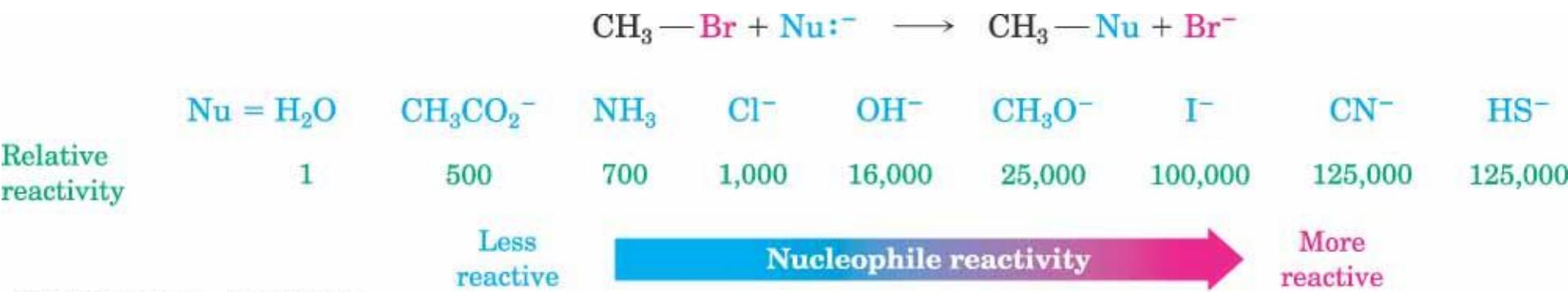
NUCLEOPHILES IN S_N2 REACTIONS

Nucleophiles are Lewis bases (electron donors). They may be neutral or anions (HO⁻, HS⁻, X⁻, RO⁻, RS⁻, RCO₂⁻, CN⁻, RC=C⁻, H₂N⁻, etc)

$$S_N2 \text{ rate} = K_2 [RX][Nu]$$



The nature of a nucleophile is important to an S_N2 reaction.



Nucleophilicity trends:

-Nucleophilicity correlates with basicity when comparing in same row of periodic table or comparing the same atom. Nucleophilicity decreases from left to right across the periodic table



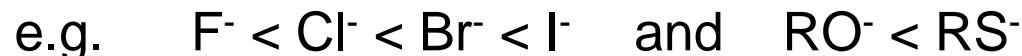
Increasing basicity;
increasing nucleophilicity

-Stronger bases are generally better nucleophiles (if nucleophiles have same reacting atom). Anions are better nucleophiles than their neutral conjugate acids



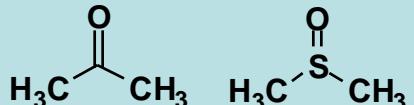
-Nucleophilicity usually increases going up a column of the periodic table. (in aprotic polar solvents, direct relationship b/w nucleophilicity and basicity maintained)

Nucleophilicity reversed in protic solvents



The Influence of Solvent on Nucleophilicity

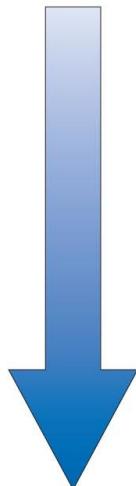
Non-hydrogen Bonding (Aprotic) Solvents



Acetone DMSO



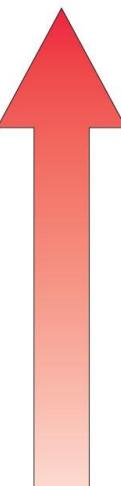
increasing size



In an aprotic medium, fluoride is the best nucleophile by virtue of its basicity and lack of solvation.

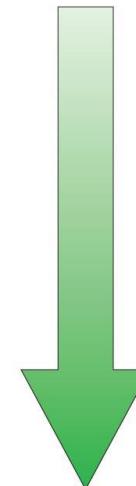
F^-
 Cl^-
 Br^-
 I^-

increasing basicity

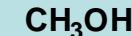


increasing nucleophilicity in an aprotic solvent

increasing nucleophilicity in a protic solvent



Hydrogen Bonding Solvents

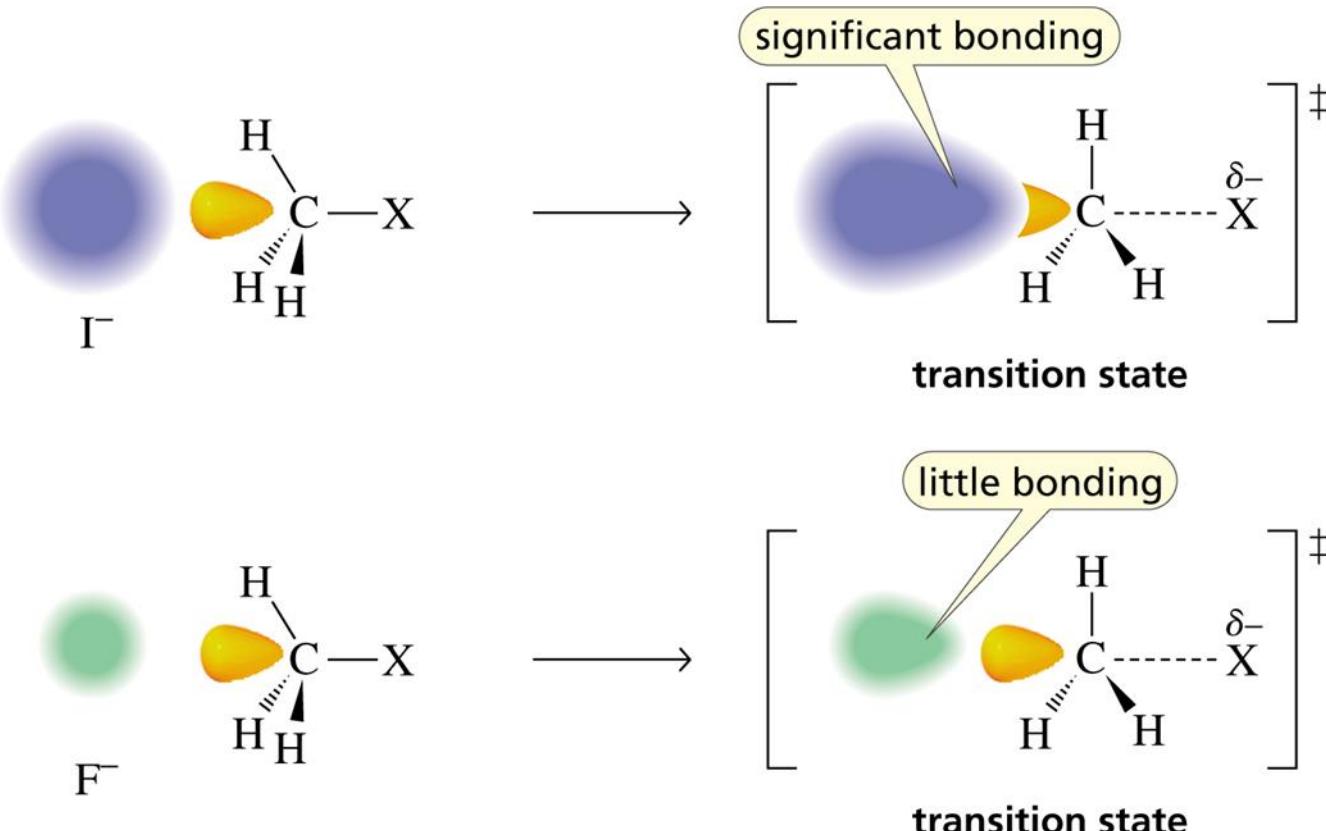


or mixtures thereof

In a protic medium, iodide is the best nucleophile by virtue of its polarizability and lack of solvation.

Polarizability

The larger the atom, the more polarizable it is (can move more freely toward a positive charge).



Iodine's electrons are far away from the nucleus, are loosely held and are polarizable. Its electrons can move freely towards a positive charge and can engage in partial bonding as it attacks the electrophilic carbon atom.

Polarizability *versus* Nucleophilicity

Does the greater polarizability of the larger atoms make up for their decreased basicity that makes them poorer nucleophiles?

No, if they are in an **aprotic polar solvent**. Iodide ion is still the poorest nucleophile.

Yes, if they are in a **protic polar solvent**. Iodide ion is now the best nucleophile.

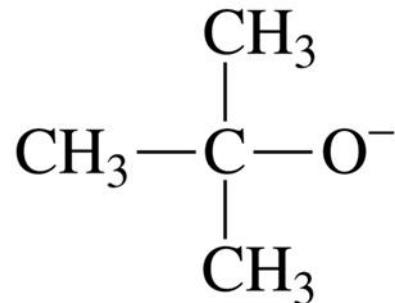
Summary:

The strongest base is the best nucleophile unless they differ in **size** and they are in a **protic polar** solvent.

Steric Hindrance NOT limited to substrate: Nucleophilicity & Steric Hindrance



ethoxide ion
better nucleophile



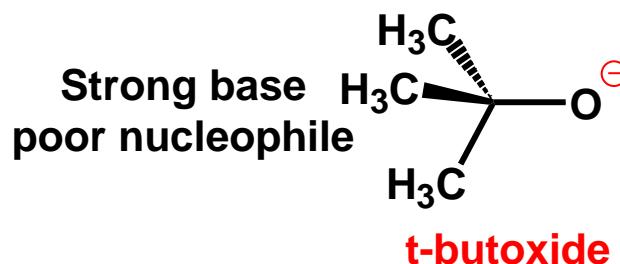
tert-butoxide ion
stronger base

tert-Butoxide ion is a stronger base than ethoxide ion, but it is a poorer nucleophile.

Its large size makes it difficult for it to approach the back side of the carbon.

Sterics of the Nucleophile: Trends in Nucleophilicity

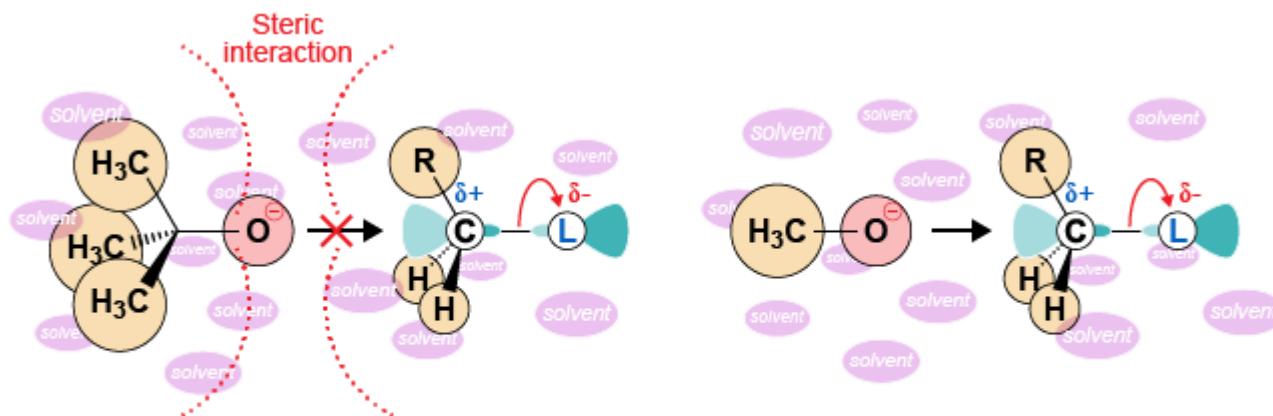
Steric Effects (hindered nucleophile) → The presence of bulky groups on the nucleophile will slow down the rate of an S_N2 reaction



t-butoxide is a stronger base than ethoxide but because it is sterically hindered, t-butoxide is a weaker nucleophile



When bulky groups interfere with a reaction because of their size we call this **steric hindrance**. Steric hindrance has little effect on basicity because basicity usually involves attack on an unhindered proton. Thus by choosing a **less hindered** or **hindered** base you can make the attacking species act like a nucleophile and perform an S_N2 reaction or react as a **Bronsted-Lowry Base and abstract a proton (E2)**. We will talk more about this later.



Steric interaction between the nucleophile and the electrophile makes it hard for the nucleophile to reach the electrophilic center.

An unhindered nucleophile will reach the electrophile at a faster rate than the sterically hindered nucleophile.

Summary of the S_N2 mechanism:

Back-side attack → inversion of configuration at chirality centres

Second-order rate law:

$$\text{Rate} = -\frac{d \text{ [substrate]}}{dt} = k [\text{Nu}^-] \text{ [substrate]}$$

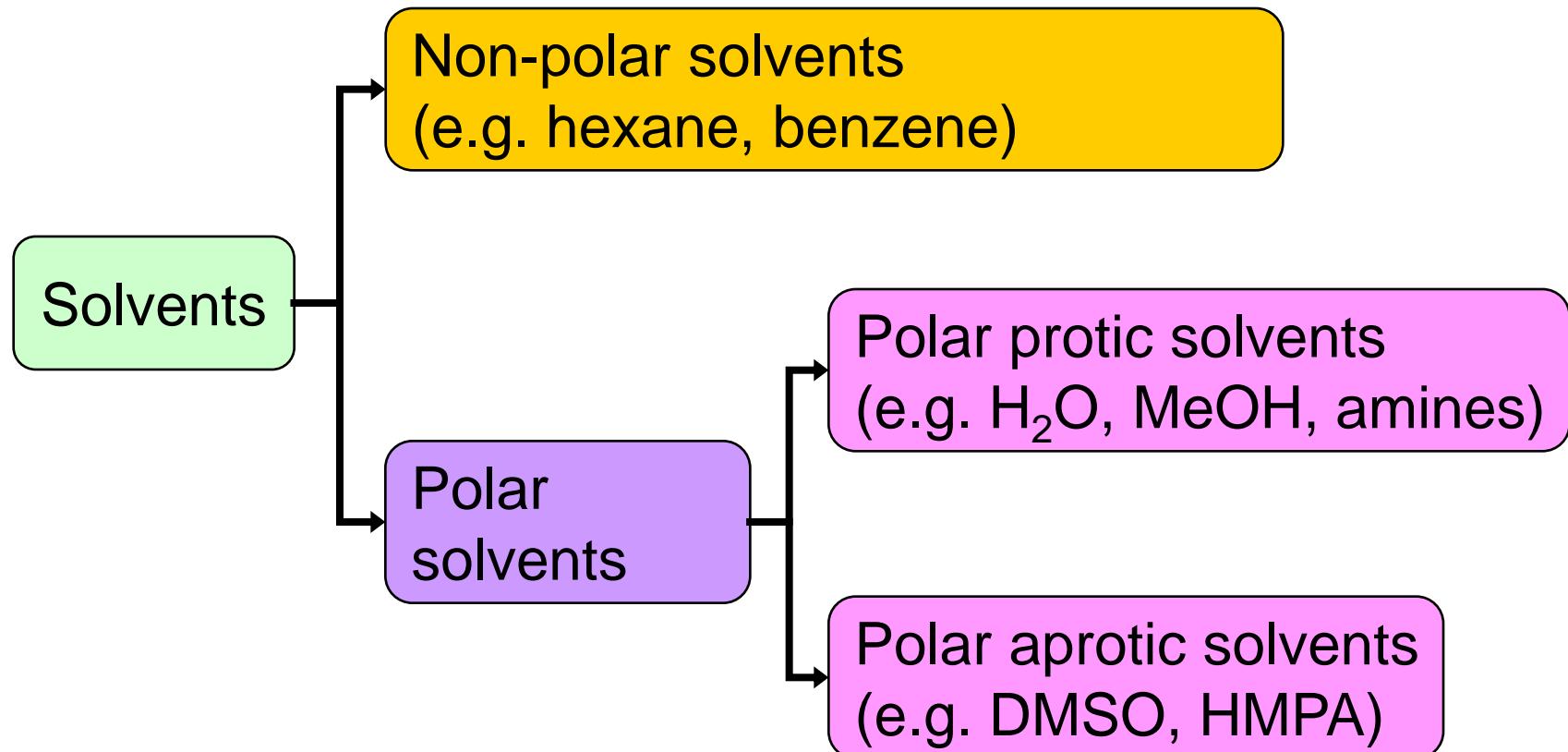
- Depends on nature of nucleophile need strong Nuc
- Depends on substrate best with sterically unhindered
- Depends on solvent best in polar aprotic solvent
- Depends on nature of leaving group what type??

FACTORS

(c) Solvent

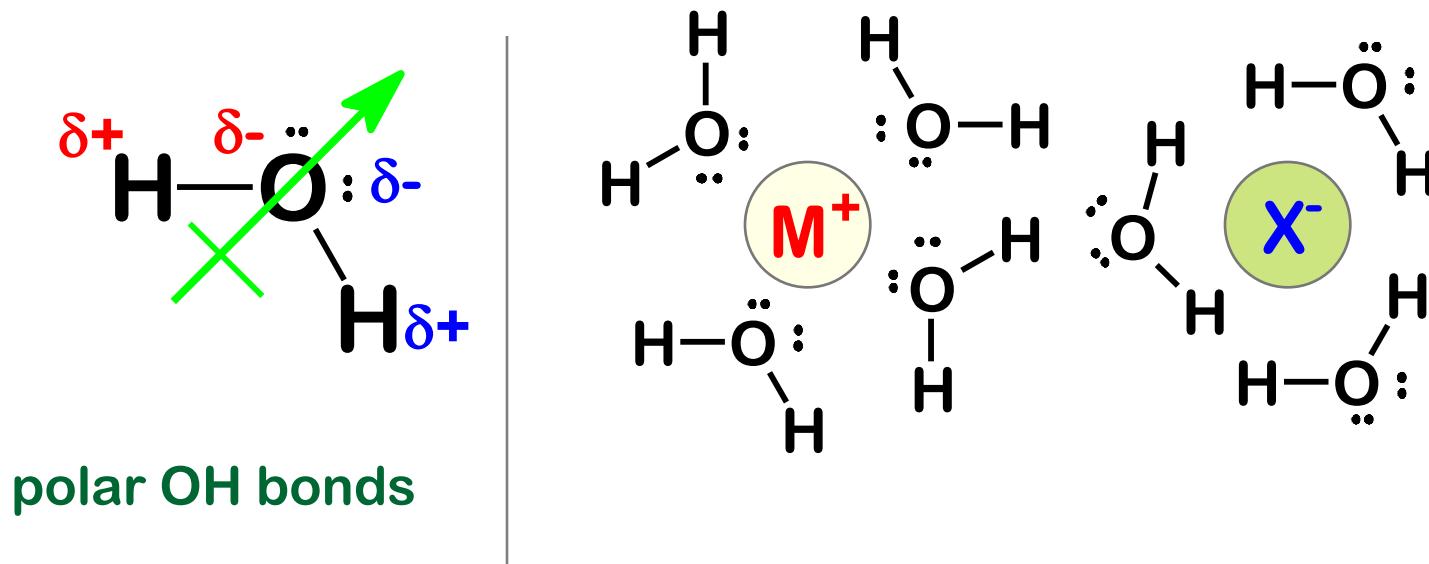
Protic solvent: a solvent that is a hydrogen bond donor. (ex: H_2O , ROH)

Aprotic solvent: a solvent that cannot serve as a hydrogen bond donor.



Protic solvents can form hydrogen bonds and can solvate both cations and anions.

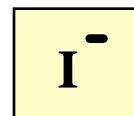
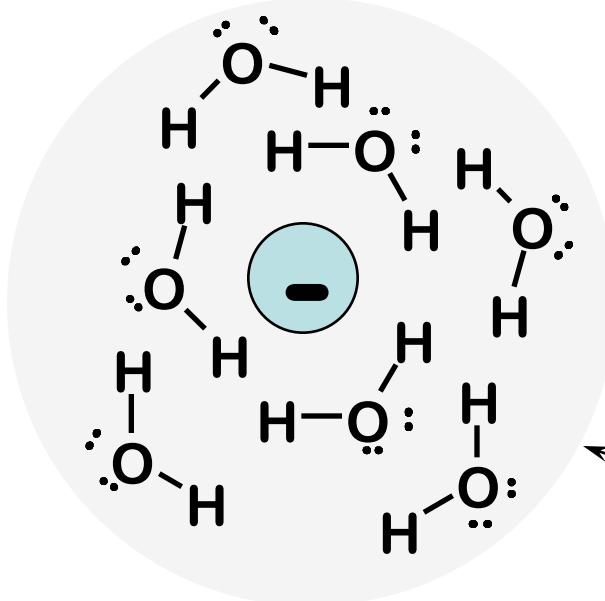
WATER AS A SOLVENT



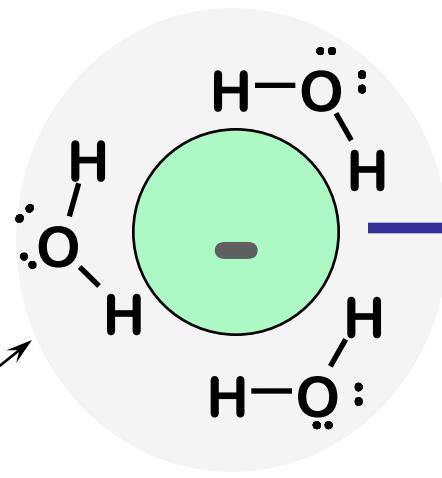
Water is a polar molecule.
Negative on the oxygen end, and positive on the hydrogen.
It can solvate both cations and anions.

SMALL IONS SOLVATE MORE HEAVILY THAN LARGE ONES

- ❖ Halide Nucleophilicity in Protic Solvents:



BETTER
NUCLEOPHILE

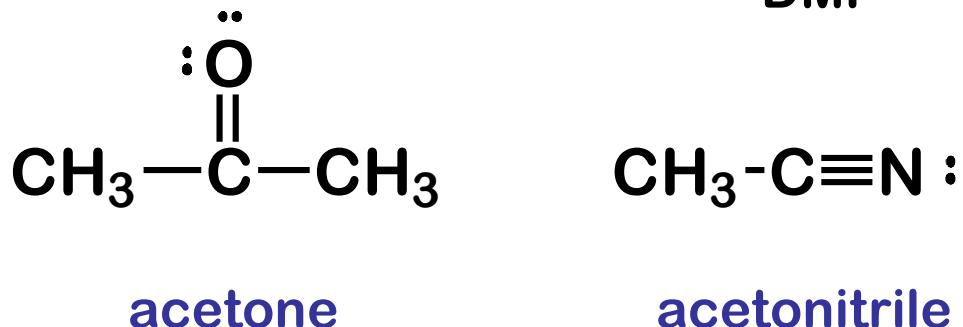
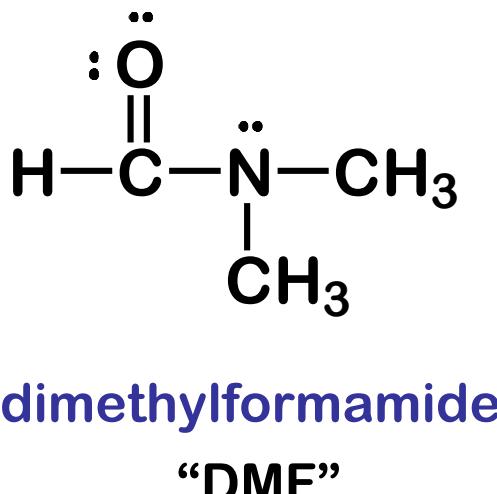
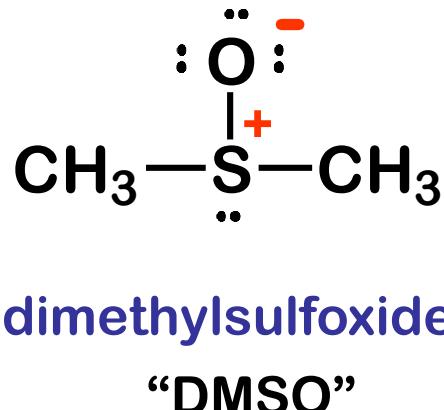


effective size is larger

solvent
shell

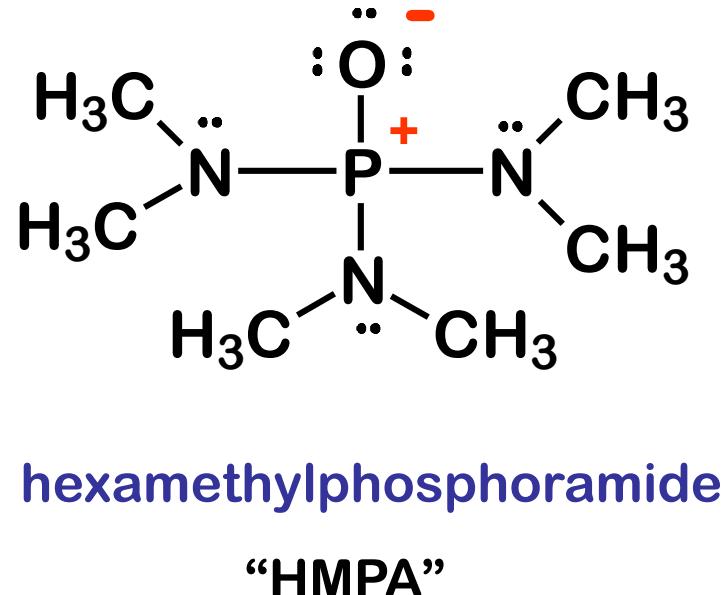
...smaller
...escapes
easily

APROTIC SOLVENTS



if scrupulously
free of water

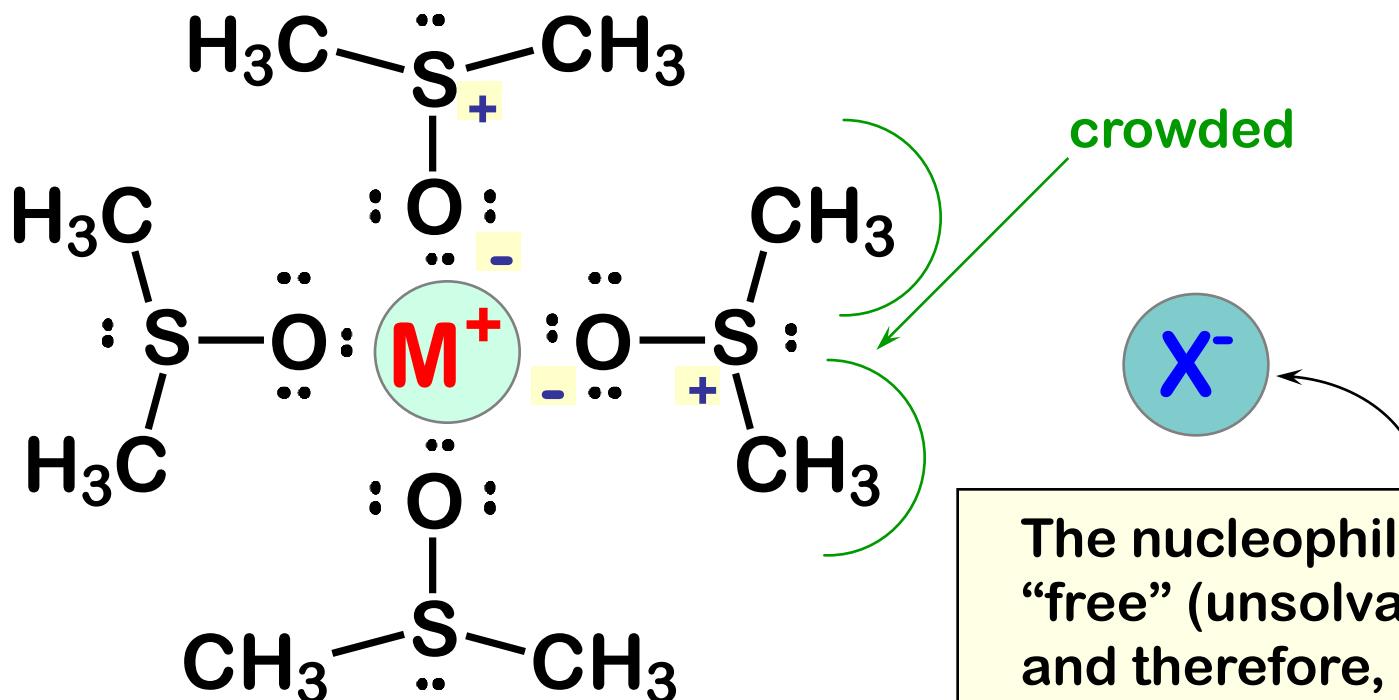
They can solvate a **cation (+)**
better than they can solvate
an **anion (-)**.



APROTIC SOLVENTS
DO NOT HAVE
OH, NH, OR SH BONDS

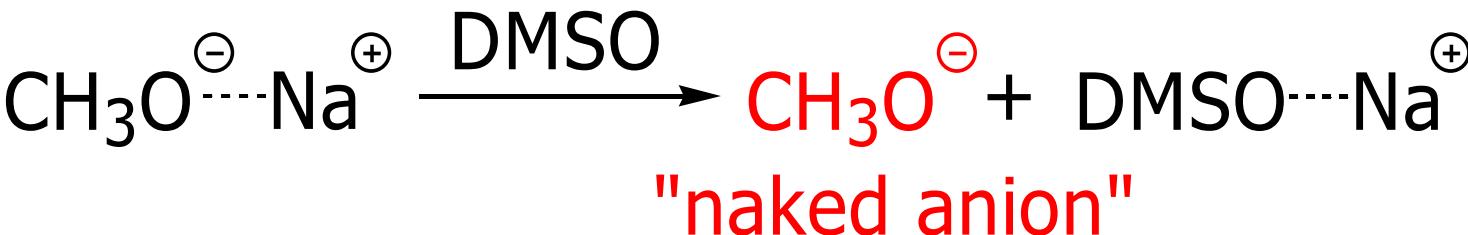
They do not form
hydrogen bonds.

APROTIC SOLVENTS SOLVATE CATIONS, BUT NOT ANIONS (NUCLEOPHILES)



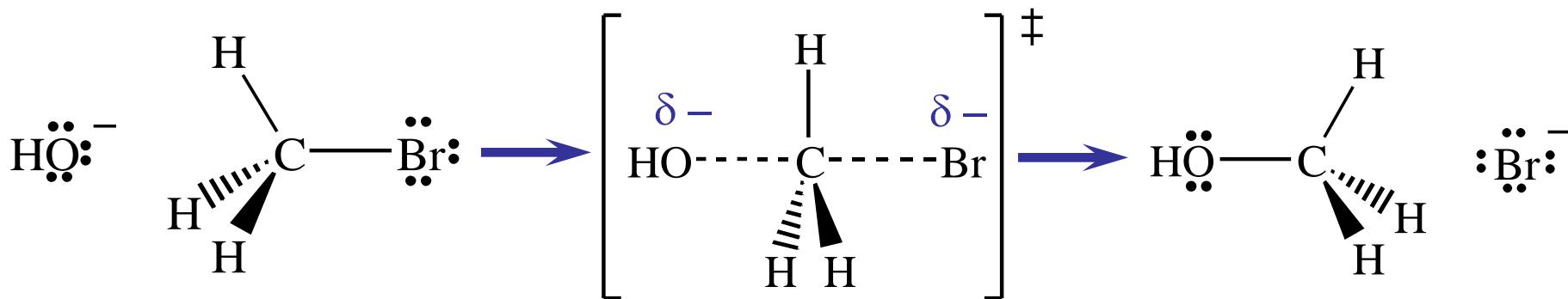
The nucleophile is “free” (unsolvated), and therefore, is small and not hindered by a solvent shell.

S_N2 reactions favored in polar aprotic solvents

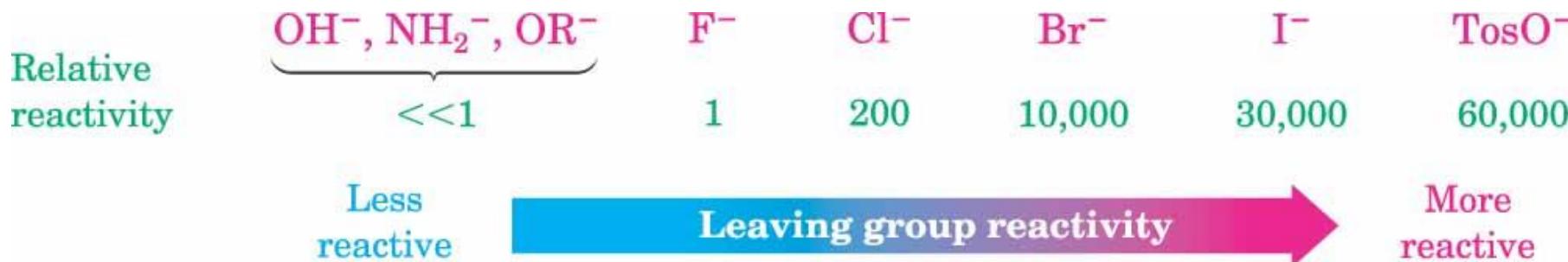


FACTORS

(d) Nature of Leaving Group



Better leaving groups can accommodate the negative charge \rightarrow stable anions.



Weakest bases – _____ : _____ leaving groups.

Leaving Groups



These compounds do not undergo $\text{S}_{\text{N}}2$ reactions.

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Good leaving groups: I^- , HSO_4^- , Br^- , Cl^- , H_2O , $\text{CH}_3\text{OSO}_3^-$, CH_3SO_3^- , CF_3SO_3^- ,
 -OTs

Poor leaving groups: F^- , CN^- , CH_3S^- , CH_3O^- , HO^- , H_2N^- , CH_3^-

For an acid HA:

- 1) As **size of A** increases, acidity of HA increases; so A^- better leaving group (down column of periodic table)
- 2) **Electronegativity** increases from left to right in periodic table; so acidity increases from left to right, A^- better leaving group from left to right
- 3) **Resonance** in A^- increases stability of anion, better leaving group (i.e. CH_3COO^- vs. CH_3O^-)

The Rate of an S_N2 Reaction is Affected by the Leaving Group

Reaction		relative rates of reaction	pK _a values of HX
H O minus reacts with R C H 2 I to yield R C H 2 O H and I minus.		30,000	-10
$\text{HO}^- + \text{RCH}_2\text{I} \longrightarrow \text{RCH}_2\text{OH} + \text{I}^-$		10,000	-9
$\text{HO}^- + \text{RCH}_2\text{Br} \longrightarrow \text{RCH}_2\text{OH} + \text{Br}^-$		200	-7
$\text{HO}^- + \text{RCH}_2\text{Cl} \longrightarrow \text{RCH}_2\text{OH} + \text{Cl}^-$		1	3.2
$\text{HO}^- + \text{RCH}_2\text{F} \longrightarrow \text{RCH}_2\text{OH} + \text{F}^-$			

Table 9.1 Common Nucleophiles/Bases

HO^-	RO^-	H_2O	ROH	RCOO^-
HS^-	RS^-	H_2S	RSH	
^NH_2	RNH^-	NH_3	RNH_2	
$\text{^C}\equiv\text{N}$	$\text{RC}\equiv\text{C}^-$			
Cl^-	Br^-	I^-		

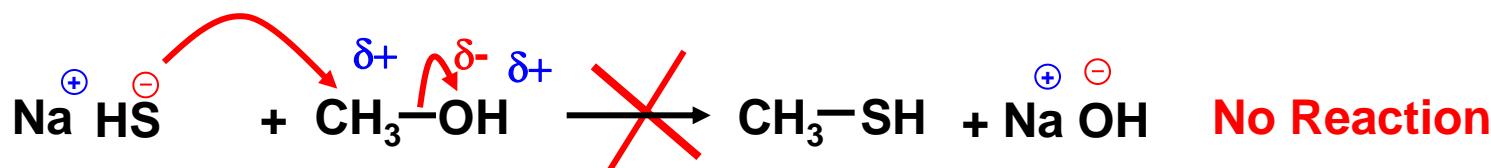
Nature of the Leaving Group

Leaving Groups: represented by “ L^- ” same as “ A^- ” for conjugate bases

The best leaving groups are those that are **STABLE ions or molecules** after they depart, i.e. **weak bases**.

Low pK_a values (**strong acids**) have good leaving groups → **stable or weak conjugate bases**

High pK_a values (**weak acids**) have poor leaving groups → **reactive or strong conjugate bases**



$$\text{H}_2\text{S } pK_a = 7$$

$$\text{HS}^- \quad pK_b = 14 - pK_a = 7$$

$$\text{H}_2\text{O } pK_a = 15.7$$

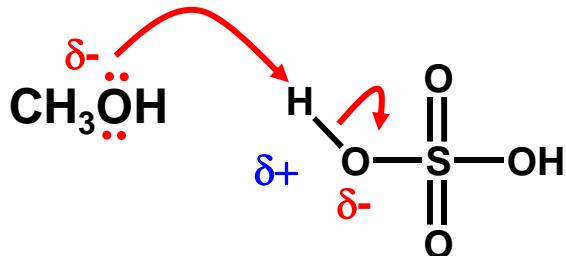
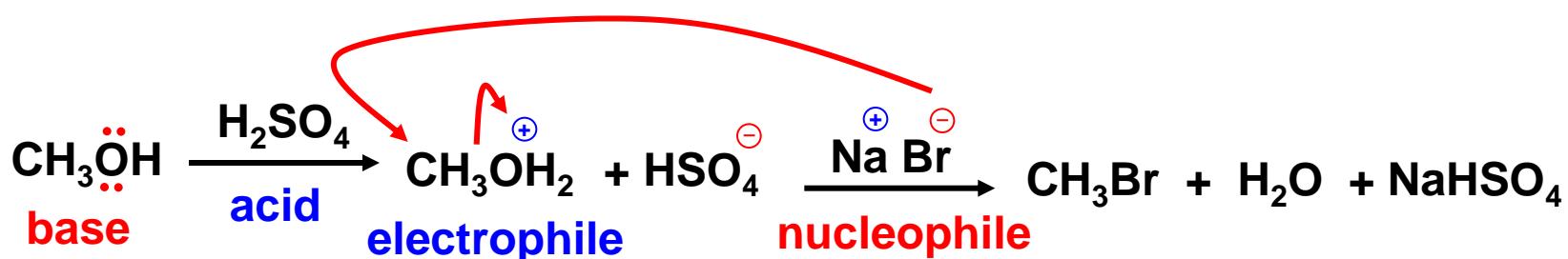
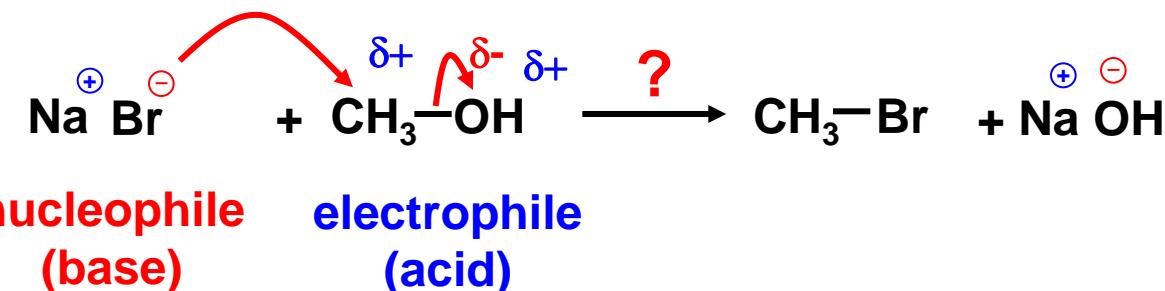
$$\text{HO}^- \quad pK_b = 14 - pK_a = -1.7$$

The Leaving Group **CANNOT** be a stronger base than the Nucleophile!!!

WHY? Leaving Group is more reactive and is a better Nucleophile than the weaker base/nucleophile. Remember the driving force of a reaction is the forming of the weaker acid/base pair i.e. the more stable-less reactive products

Nature of the Leaving Group

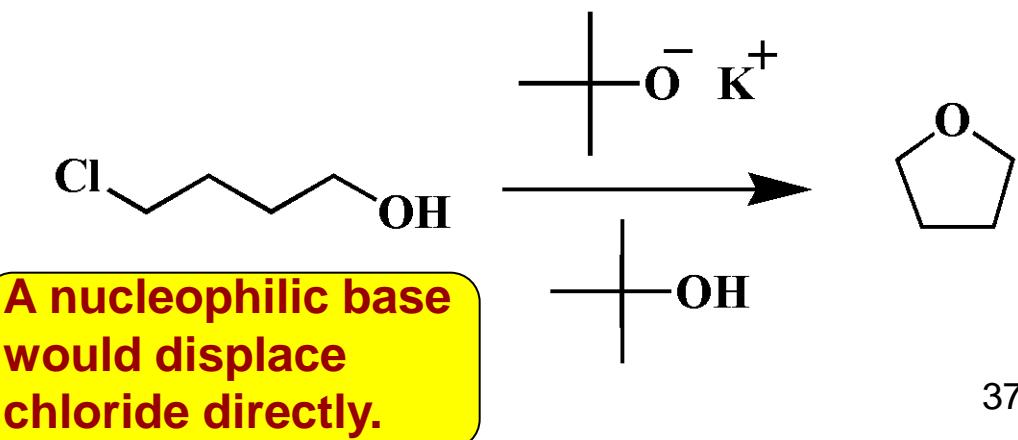
Can we convert a bad LG (strong base) into a good LG (weak base)? Depends on LG.....



Leaving Group must be a weak base

Intramolecular vs Intermolecular S_N2

Use a non-nucleophilic base to generate the oxygen anion.



Summary of the S_N2 mechanism:

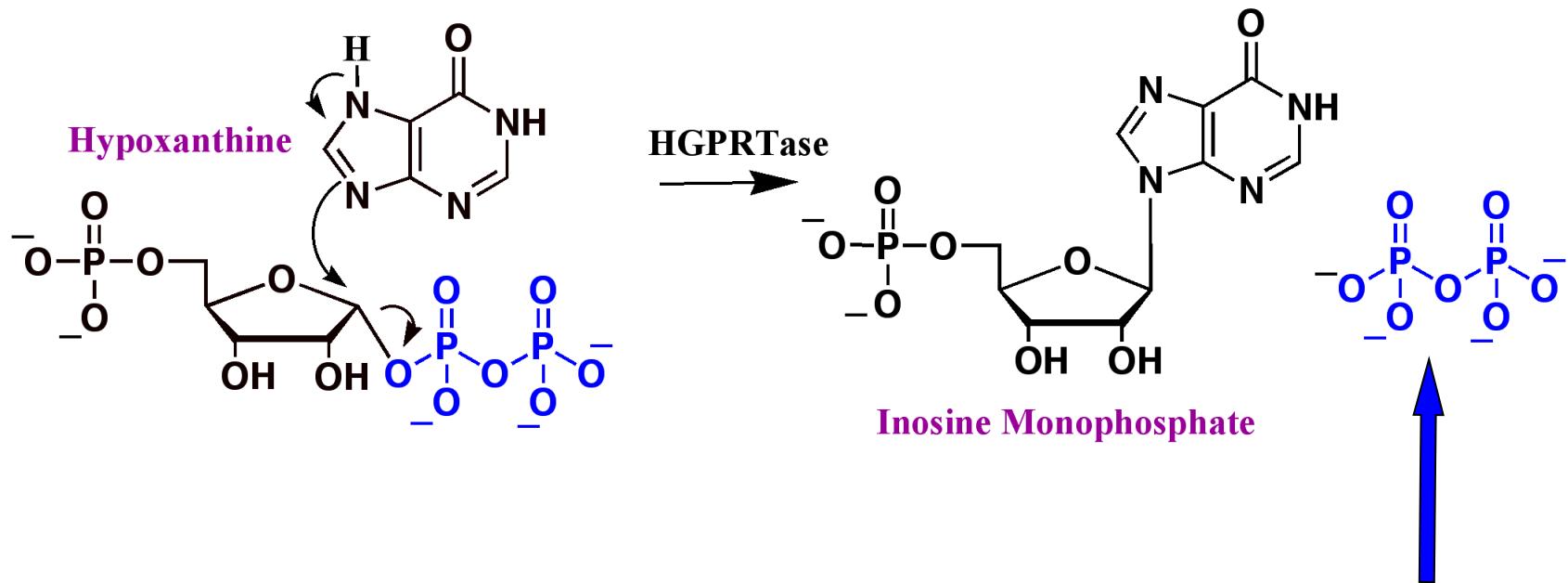
Back-side attack → inversion of configuration at chirality centres

Second-order rate law:

$$\text{Rate} = -\frac{d \text{ [substrate]}}{dt} = k [\text{Nu}^-] \text{ [substrate]}$$

- Depends on nature of nucleophile need strong Nuc
- Depends on substrate best with sterically unhindered
- Depends on solvent best in polar aprotic solvent
- Depends on nature of leaving group need weak base

Hypoxanthine Guanine Phosphoribo Transferase (HGPRTase): An S_N2-Type Enzymatic Reaction

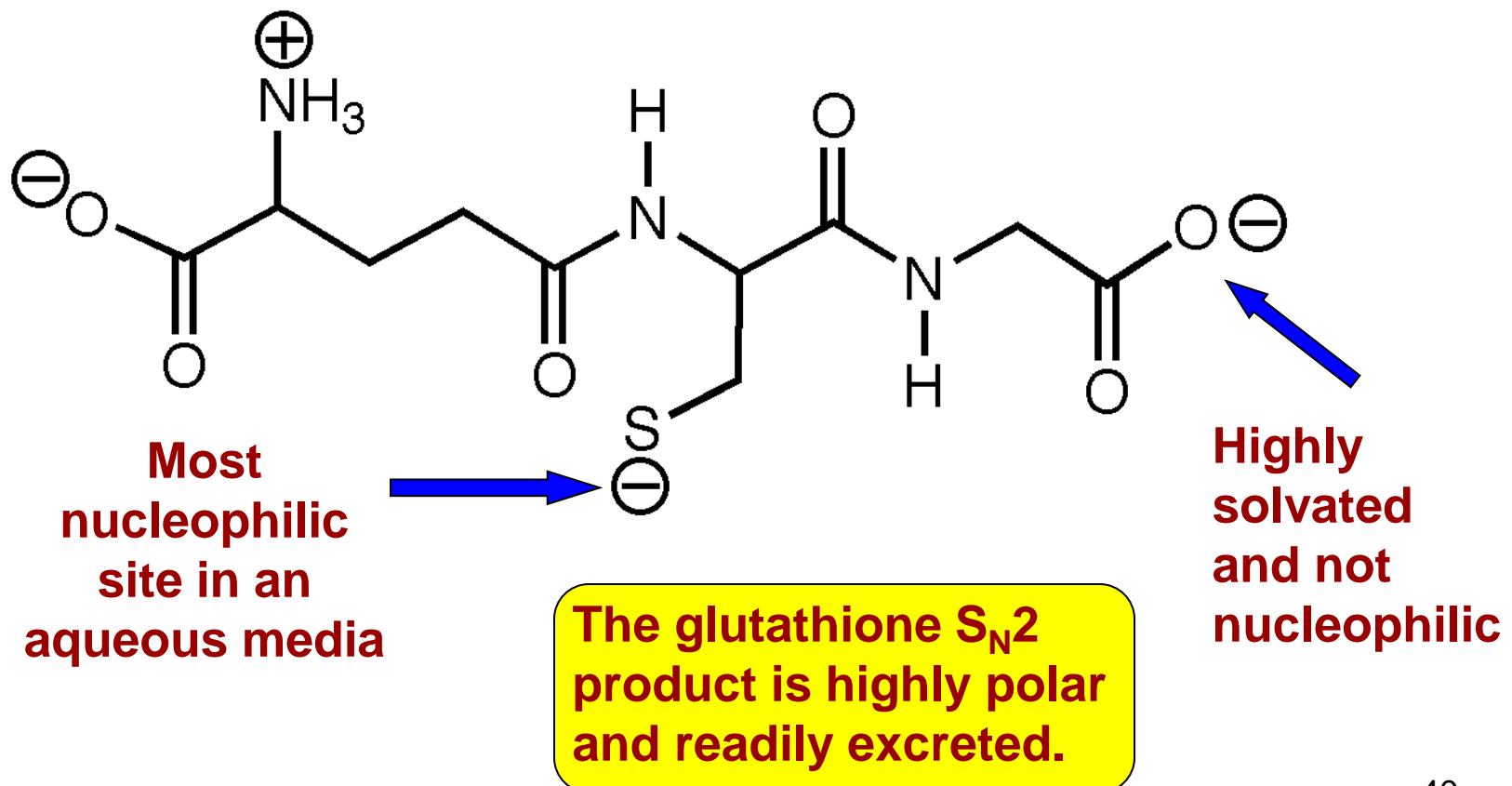


HGPRTase deficiency: severe mental retardation
(Lesch Nyhan Syndrome)

A pyrophosphate leaving group

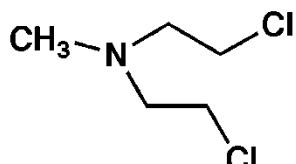
Glutathione

This is the biological nucleophile that protects us from electrophiles that react with proteins and DNA:

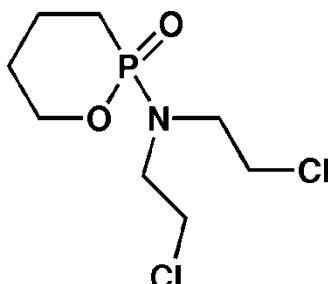


Alkylating Agents: Cancer Drugs

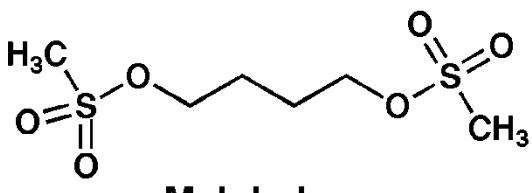
These agents add alkyl groups to DNA by an S_N2 reaction.



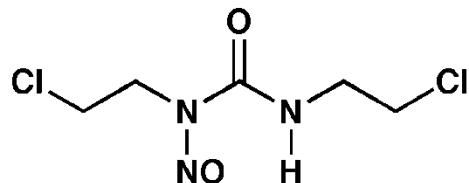
Mechlorethamine



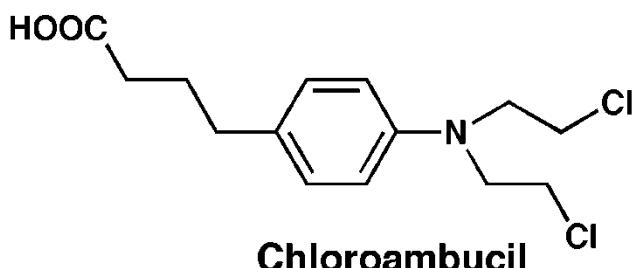
Cyclophosphamide



Melphalan

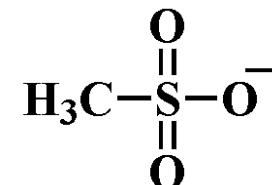


Carmustine (BCNU)



Chloroambucil

Leaving groups:

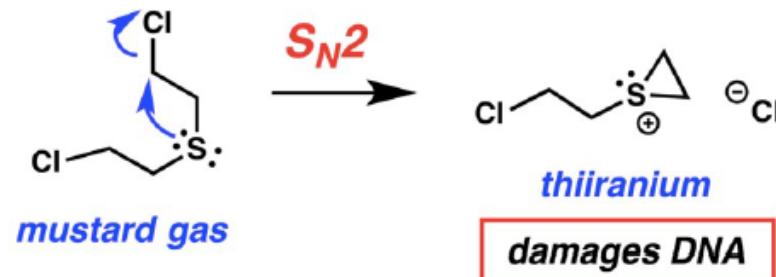


The presence of two leaving groups results in DNA crosslinking, a toxic event.

Chemical Warfare and the S_N2 Reaction

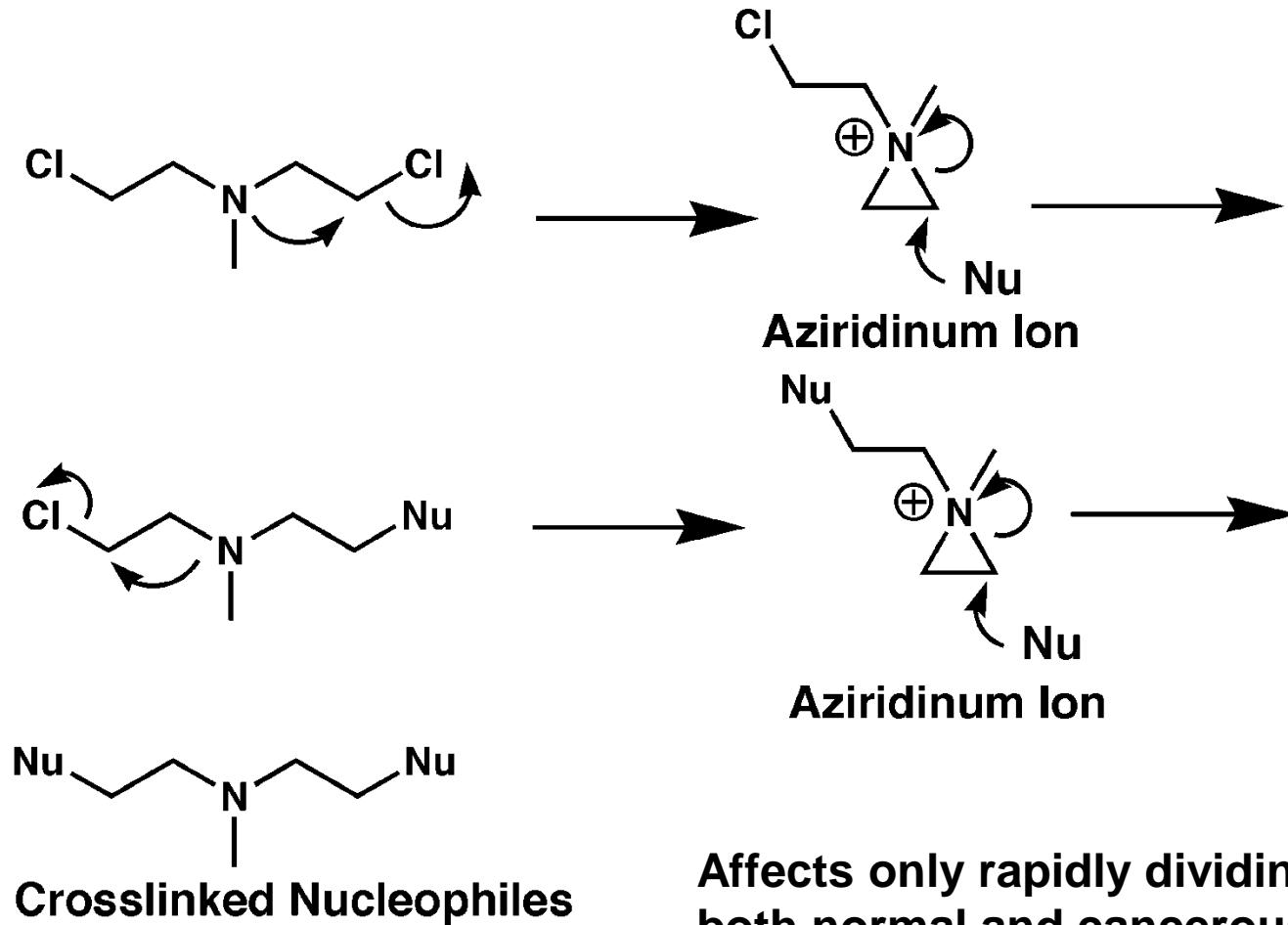


- Sulfur mustard, aka “mustard gas”
- 1st used in 1916 in WWI by Germany against British and Canadian forces near Ypres, Belgium
- Used in 8 other conflicts after WWI
- Damages DNA in cells through S_N2 reaction
- Must first cyclize through internal S_N2 into 3-member ring intermediate:



Mechlorethamine, a Nitrogen Mustard

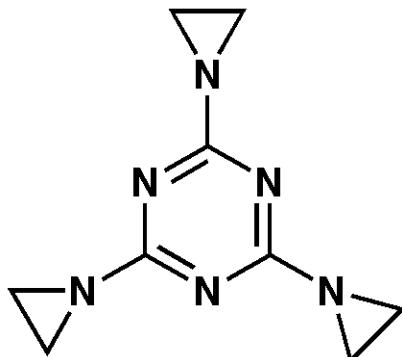
Mustard: refers to odor and color of the impure warfare agent.
Now used to treat lymphomas, breast and lung cancers.



Triethylenemelamine, an Aziridinyl Triple Alkylating Agent

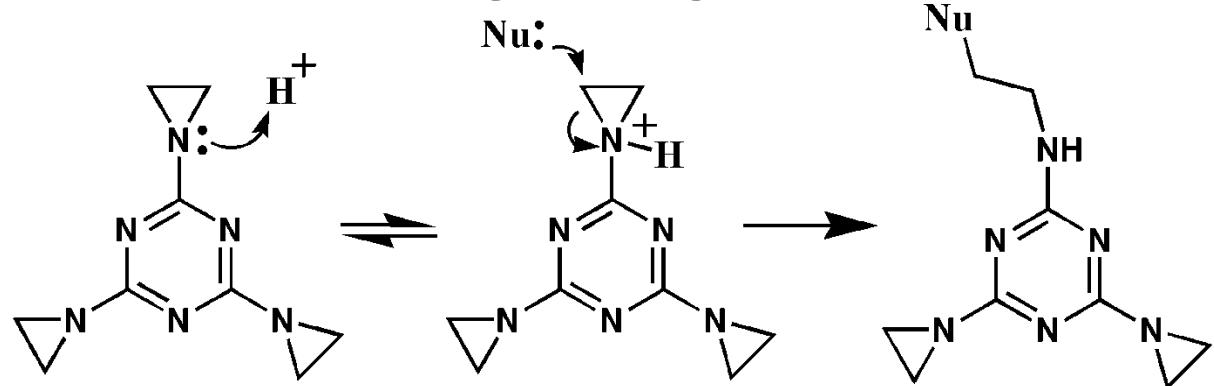
Used to treat Hodgkin's lymphoma

Requires protonation to be activated as an alkylating agent



Triethylenemelamine (TEM)

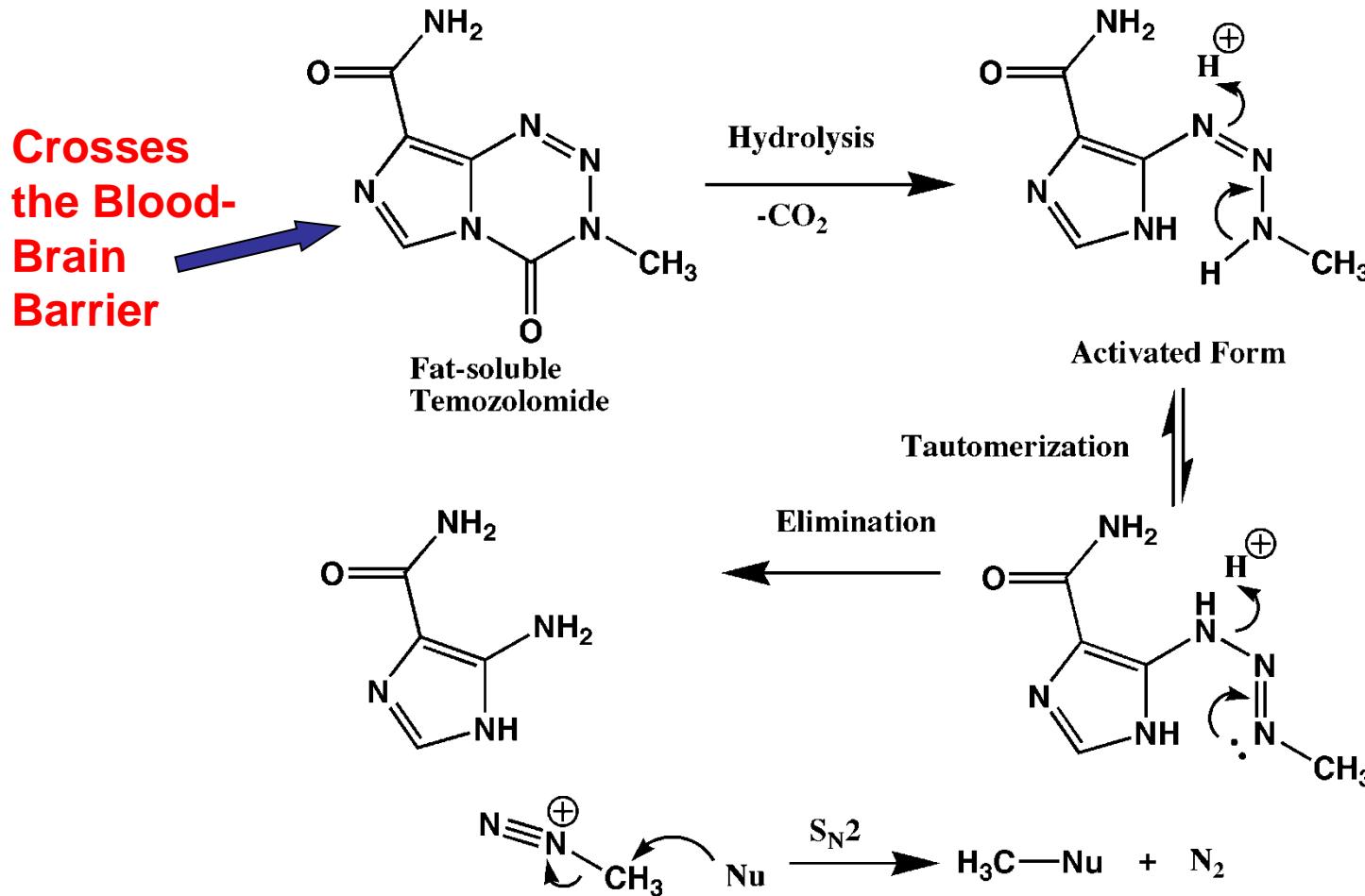
Protonation and ring opening:



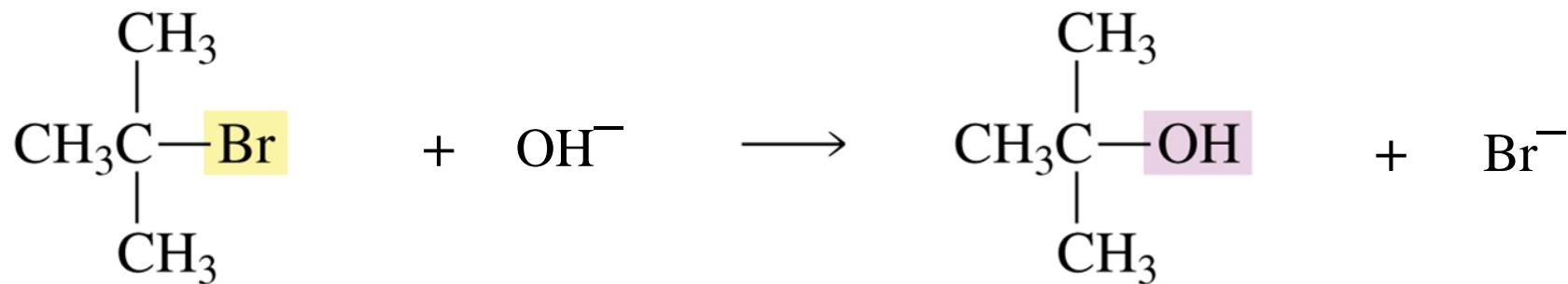
Ring opening driven by:

- Amine leaving group
- Relief of ring strain

Temozolomide: Used to Treat Brain Tumor



S_N1 : Substitution nucleophilic unimolecular



a **tertiary alkyl halide** and a **good nucleophile**

The reaction is surprisingly fast (why surprising?), so it must be taking place by a *different* mechanism.

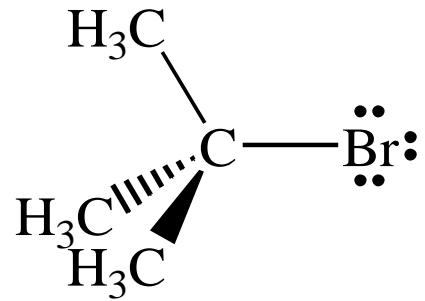
1) MECHANISM

2) EVIDENCE

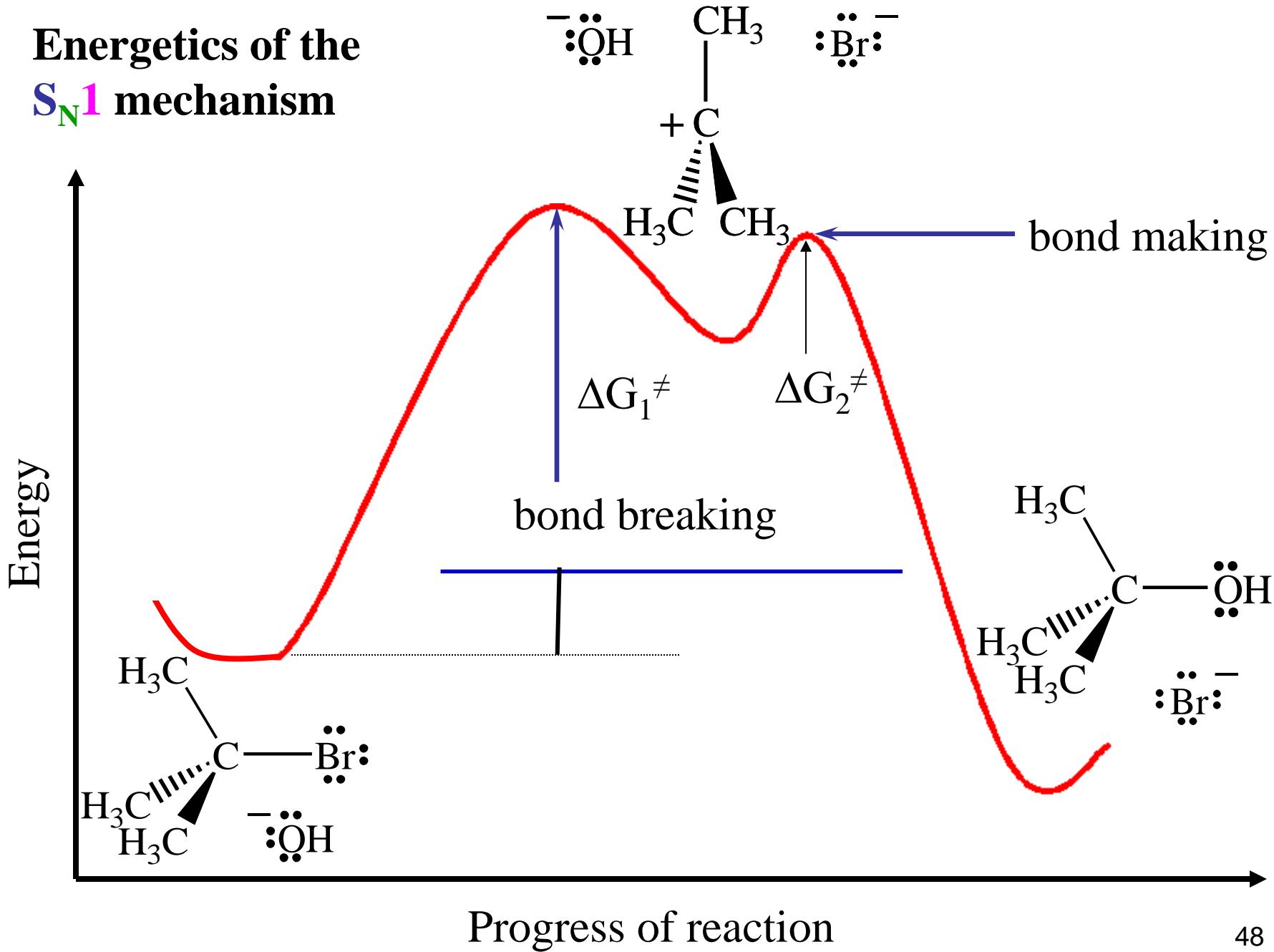
3) FACTORS

MECHANISM

Step 1: cleavage of C–Br bond to form carbocation



Energetics of the S_N1 mechanism

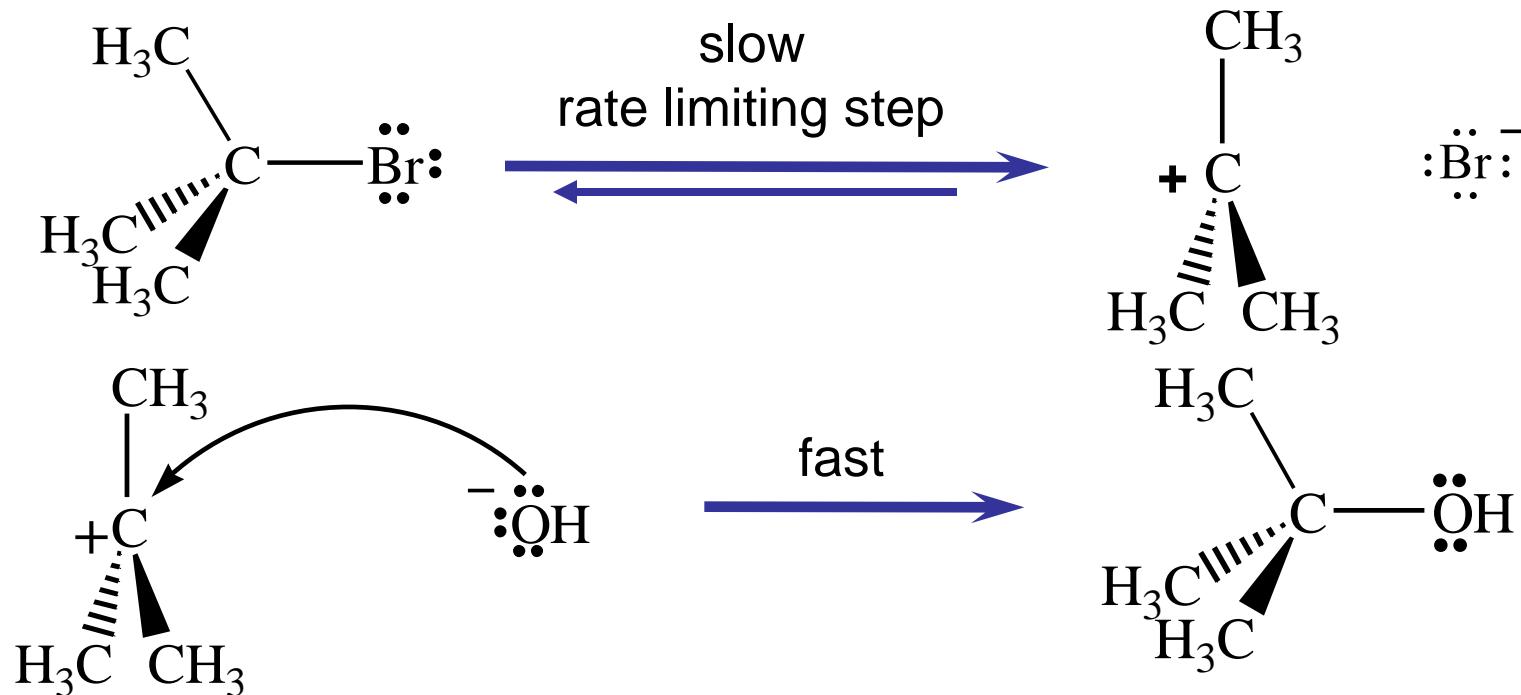


EVIDENCE

(a) Reaction kinetics

Rate of reaction depends ONLY on concentration of substrate: “_____” rxn.

$$\text{Rate} = \frac{-d[\text{substrate}]}{dt} = k [\text{substrate}]$$



Rate determining step is UNIMOLECULAR.

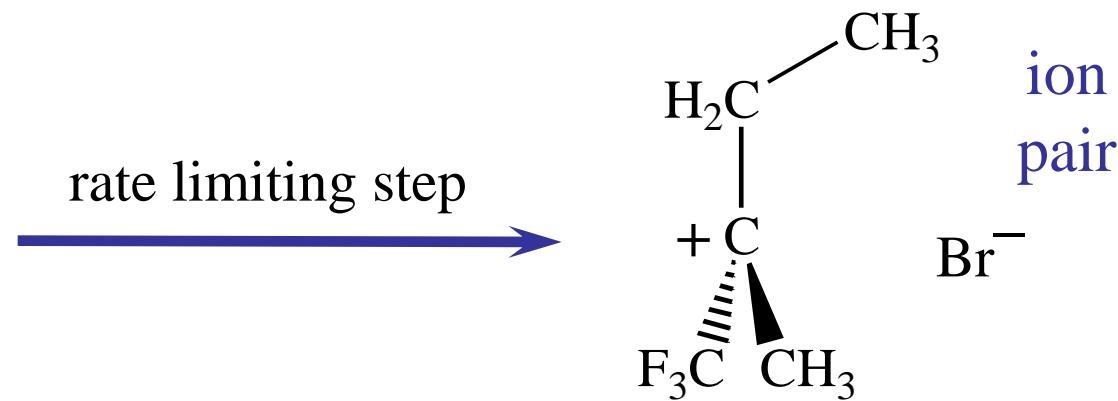
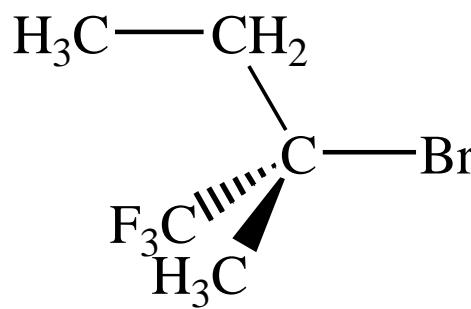
If the $[\text{CH}_3\text{Br}]$ is **doubled**, the rate of reaction _____.

If the $[\text{OH}^-]$ is **doubled**, the rate of the reaction _____.

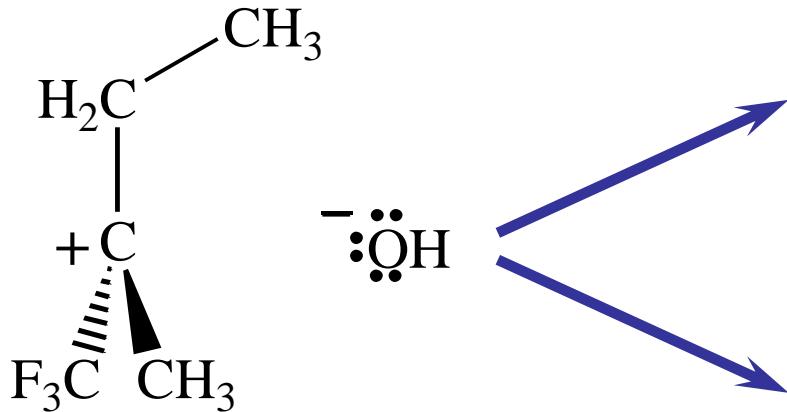
EVIDENCE

(b) Stereochemistry.

Step 1:

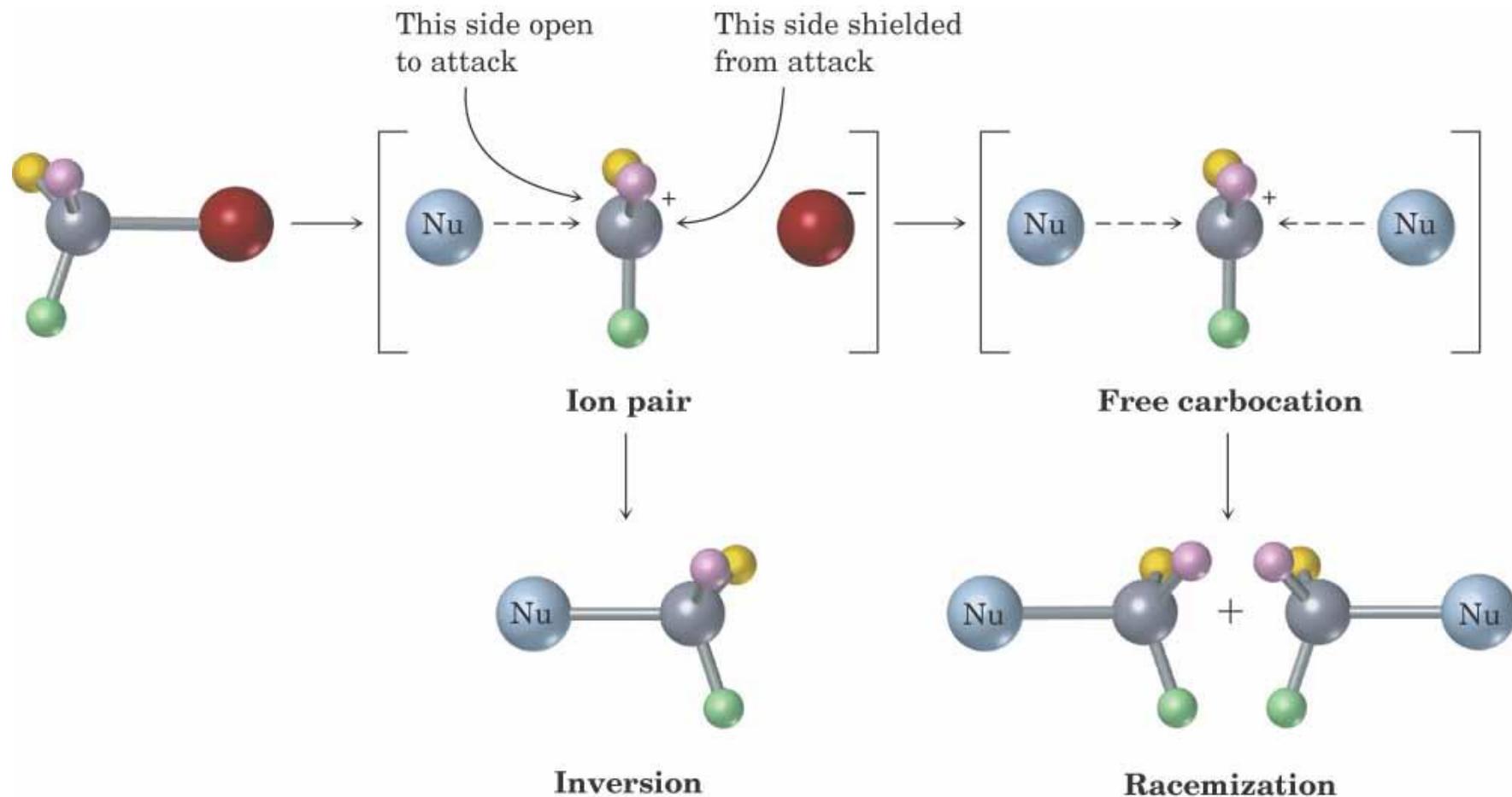


Step 2:



Both enantiomers are formed from nucleophilic attack of carbocation.

In reality, few S_N1 reactions occur with complete racemization.

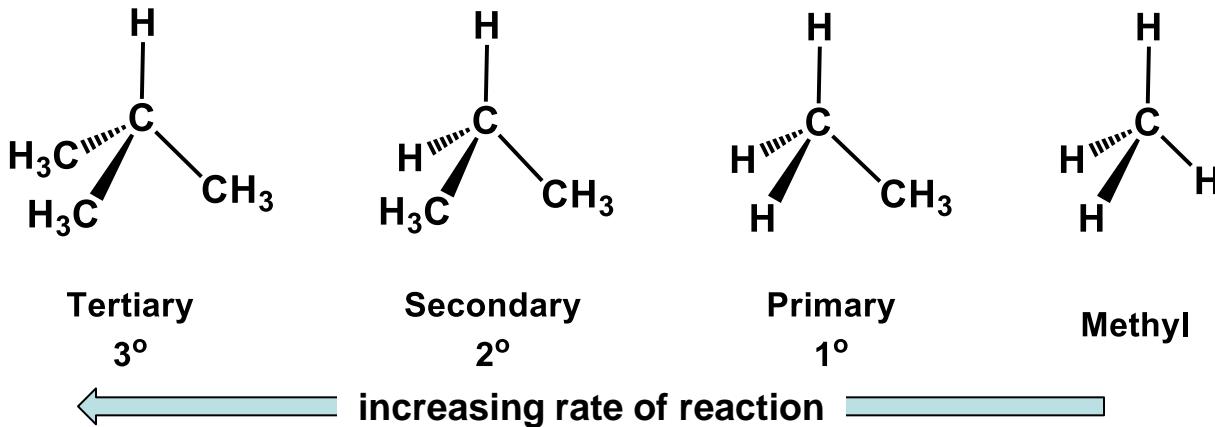


© 2004 Thomson/Brooks Cole

Generally, more inverted product is formed, because the front side is partially blocked.

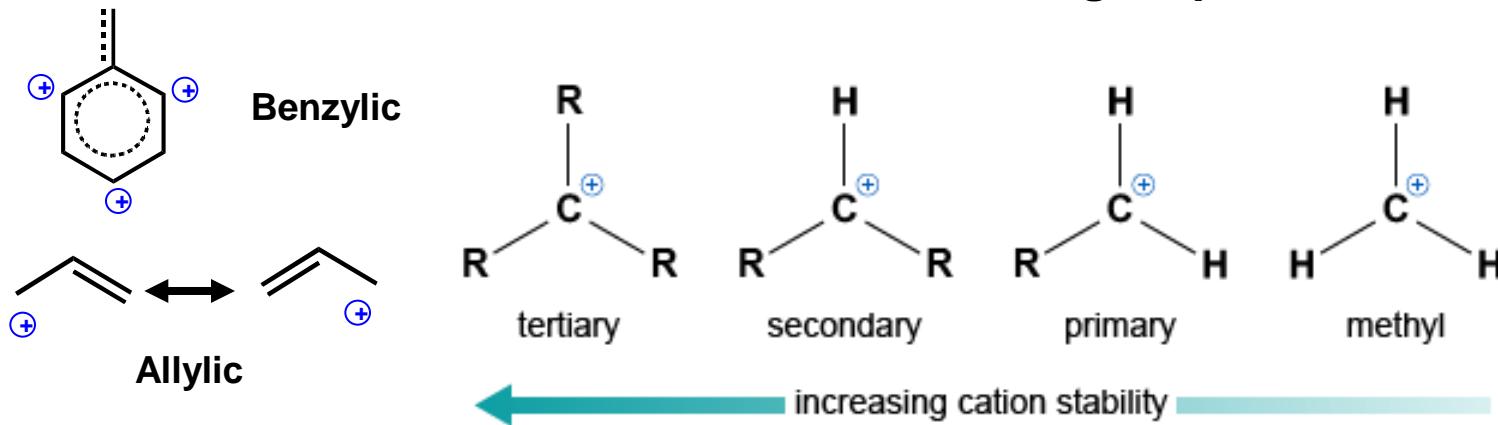
FACTORS that affect rate of S_N1 reaction

(a) Substrate (Electrophile)



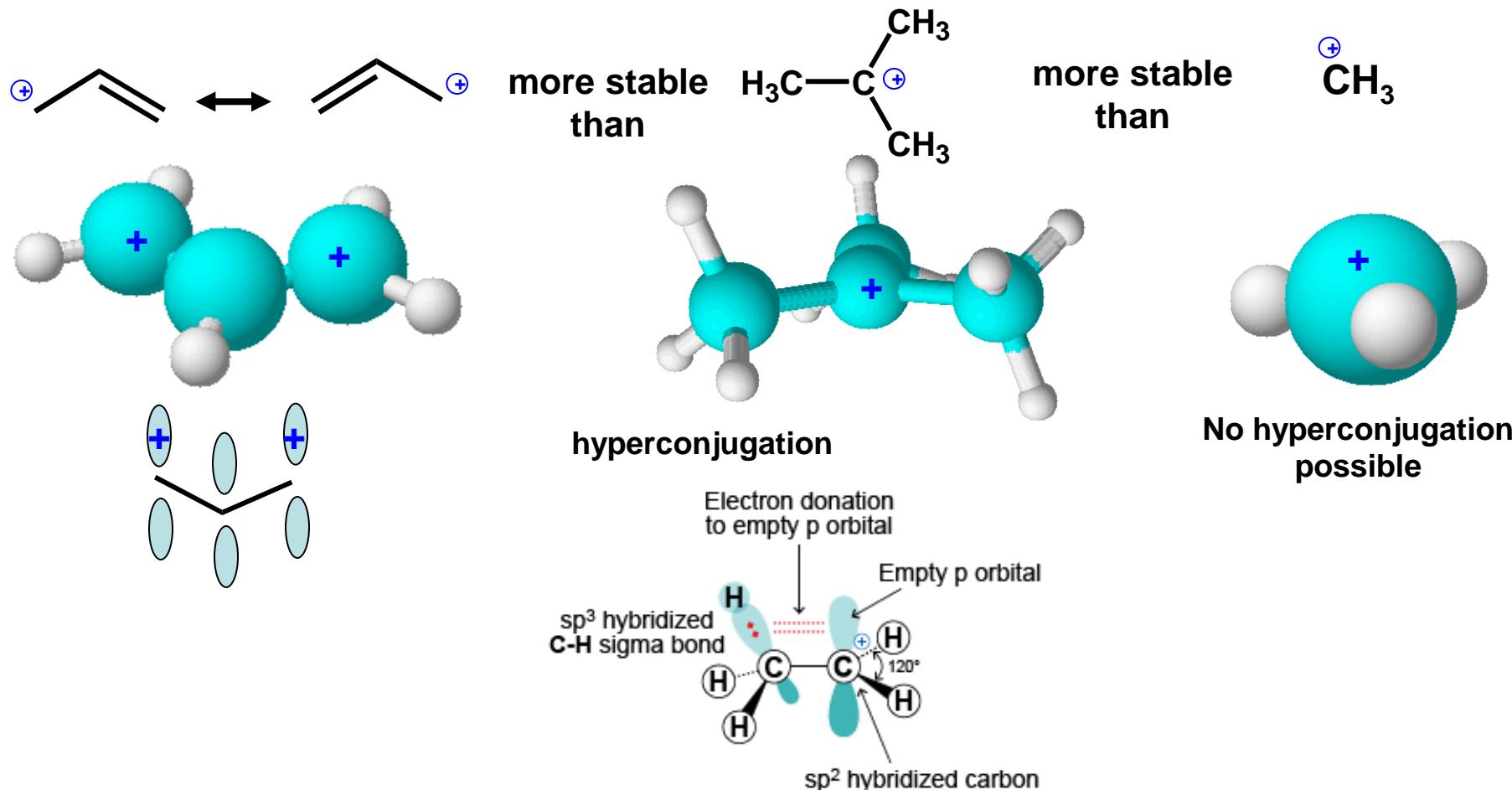
Why is the above trend observed for S_N1 reactions?

HINT: remember rate-determining step



Stability of Carbocations Review

Resonance is the most stabilizing because the charge is distributed over more than one atom. A tertiary carbocation is more stable than a secondary because hyperconjugation spreads the positive charge to the adjacent σ bonds. The methyl carbocation will not form in solution.



Effect of Structure on the Rates of S_N1 Reactions

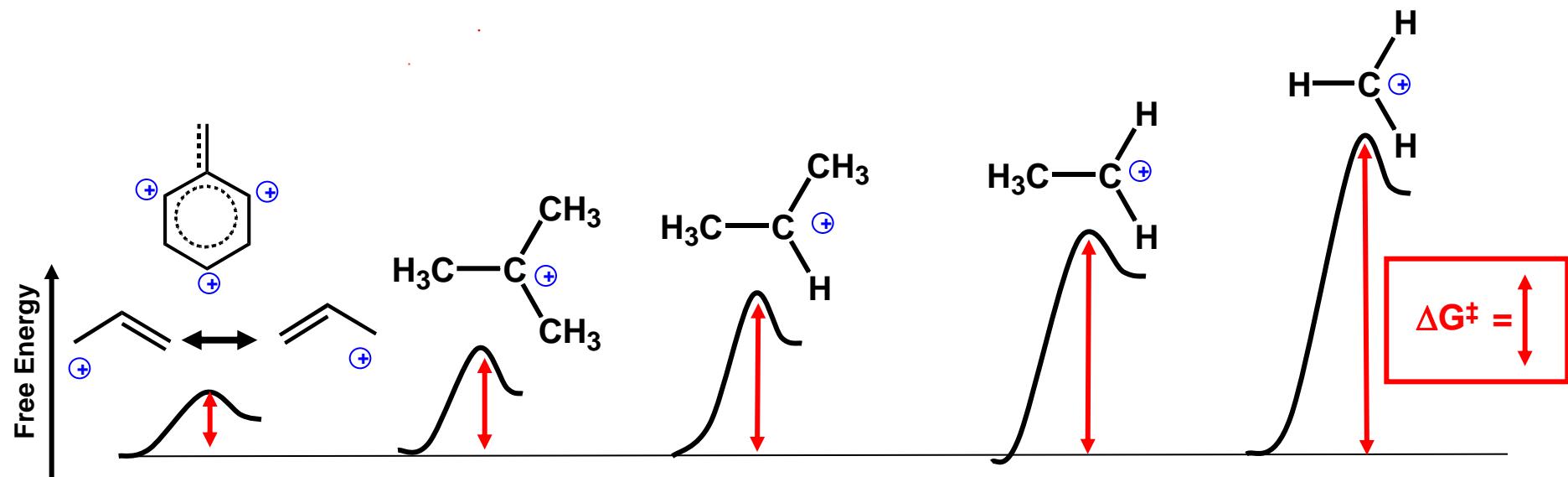
The primary factor that determines the reactivity of organic substrates in a S_N1 reaction is the relative **stability of the carbocation** that is formed (the **stability of the intermediate**).

The polar protic solvent will promote a S_N1 reaction but the carbocation must also be stabilized by the substrate through resonance or hyperconjugation.

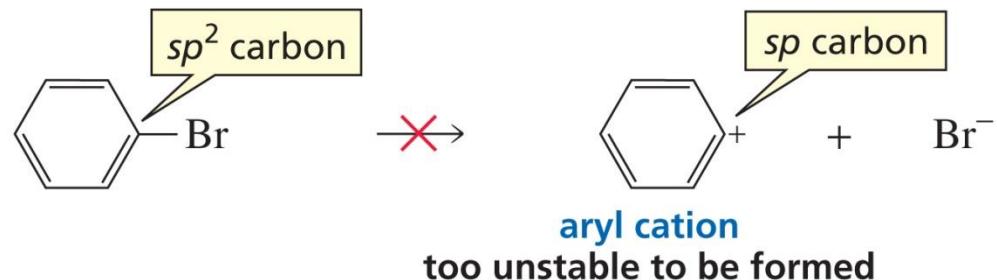
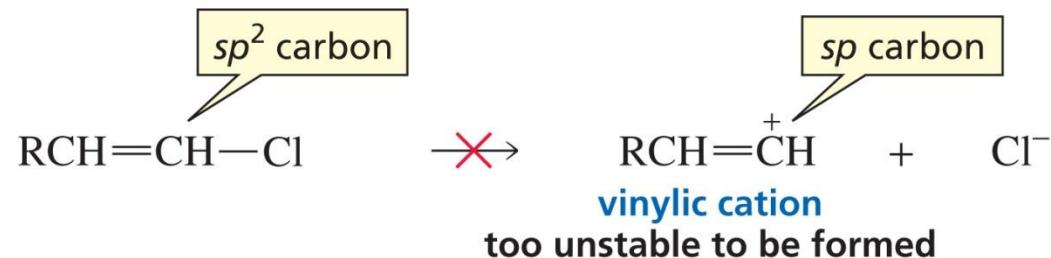
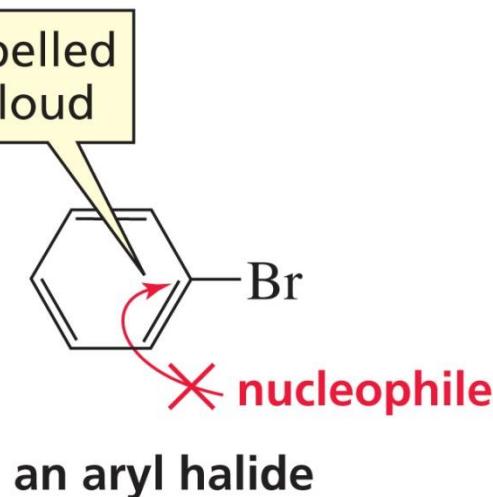
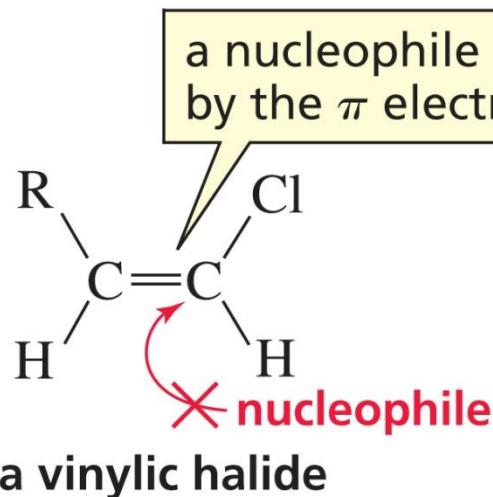
benzylic \geq allylic $>$ 3° $>$ 2° $>$ (1° and methyl will not react in S_N1 conditions)

resonance

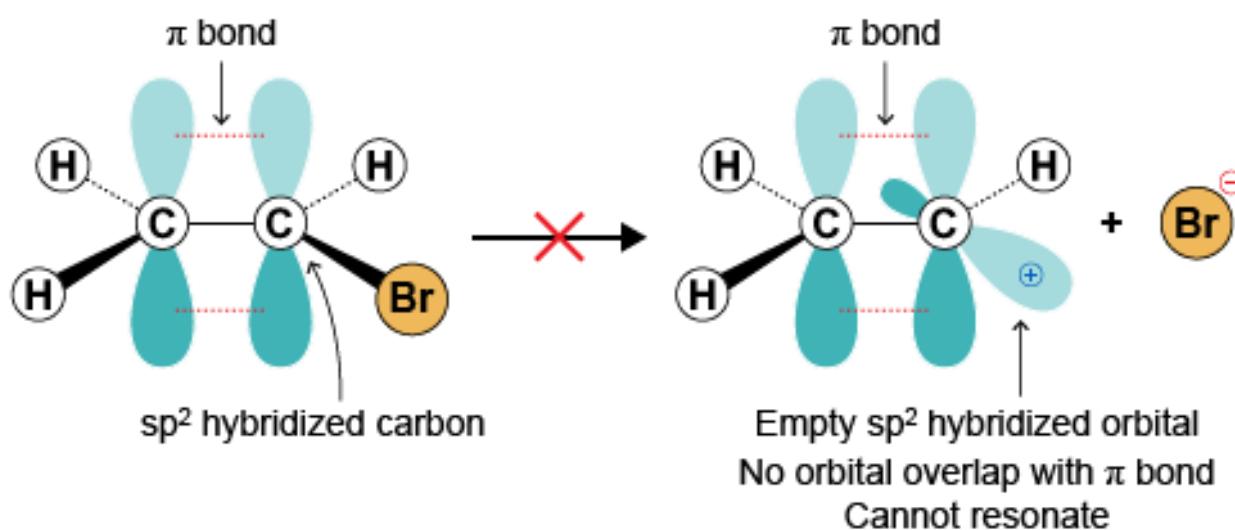
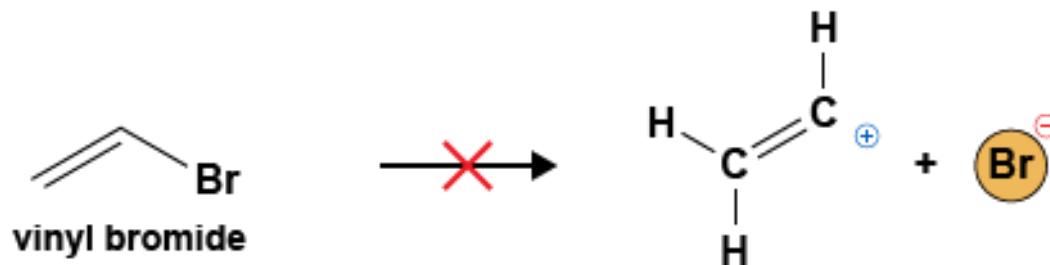
hyperconjugation



Vinylic and Aryl Halides Cannot Undergo S_N2 or S_N1 Reactions



Vinyl and aryl alkyl halides do not react under normal S_N1 conditions because the positive charge is not resonance stabilized by the π bond.



Summary of the S_N1 mechanism:

Attack at either face of carbocation → racemization at chirality centres

First-order rate law:

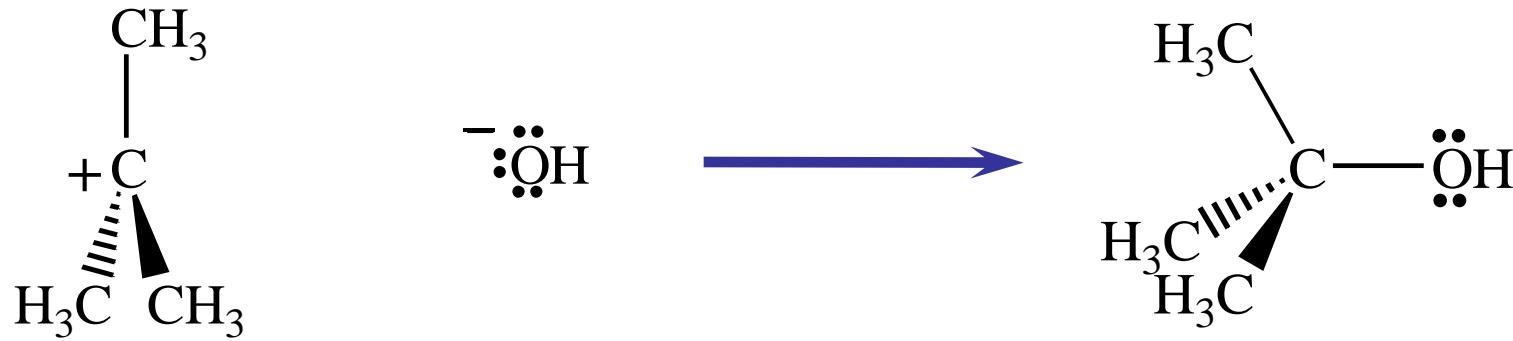
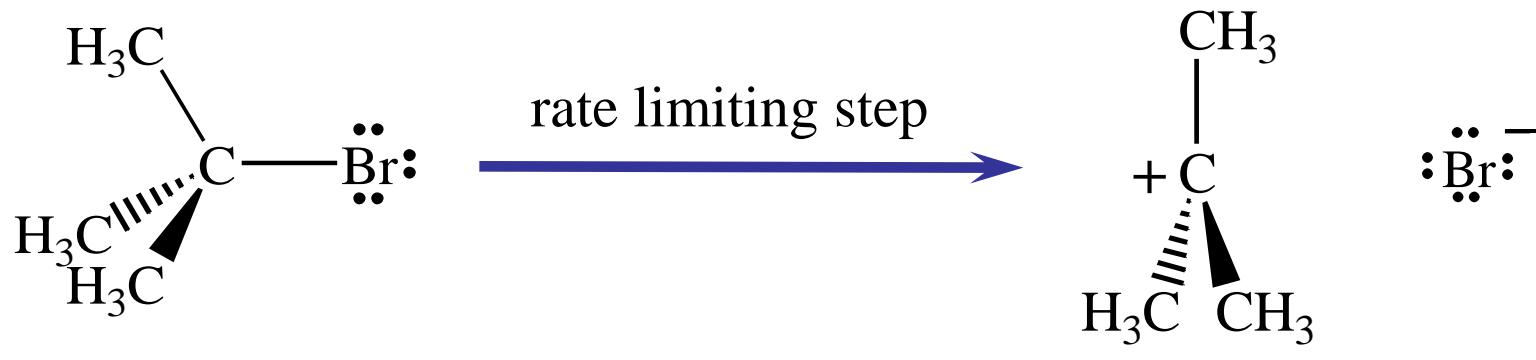
$$\text{Rate} = -\frac{d \text{ [substrate]}}{dt} = k \text{ [substrate]}$$

- effective when carbon centre sterically hindered
- Solvent effect??
- nature of nucleophile??
- nature of leaving group??

FACTORS

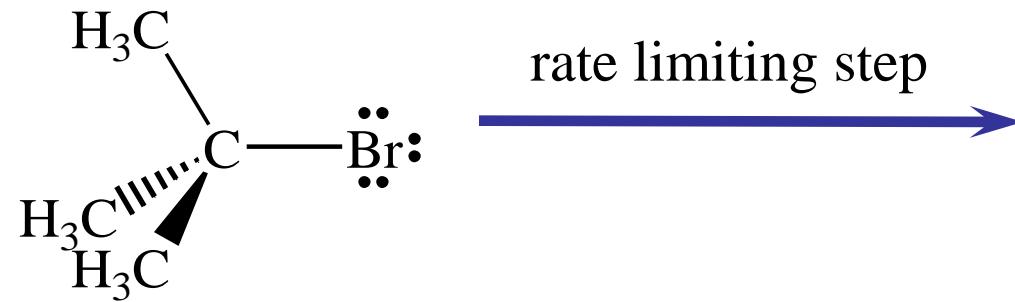
(b) Nature of Nucleophile

$\text{RS}^- \approx \text{CN}^- \approx \text{I}^- \approx \text{RO}^- \approx \text{HO}^- \approx \text{Br}^- \approx \text{Cl}^- \approx \text{NH}_3 \approx \text{CH}_3\text{CO}_2^-$
 $\approx \text{H}_2\text{O}$, etc.

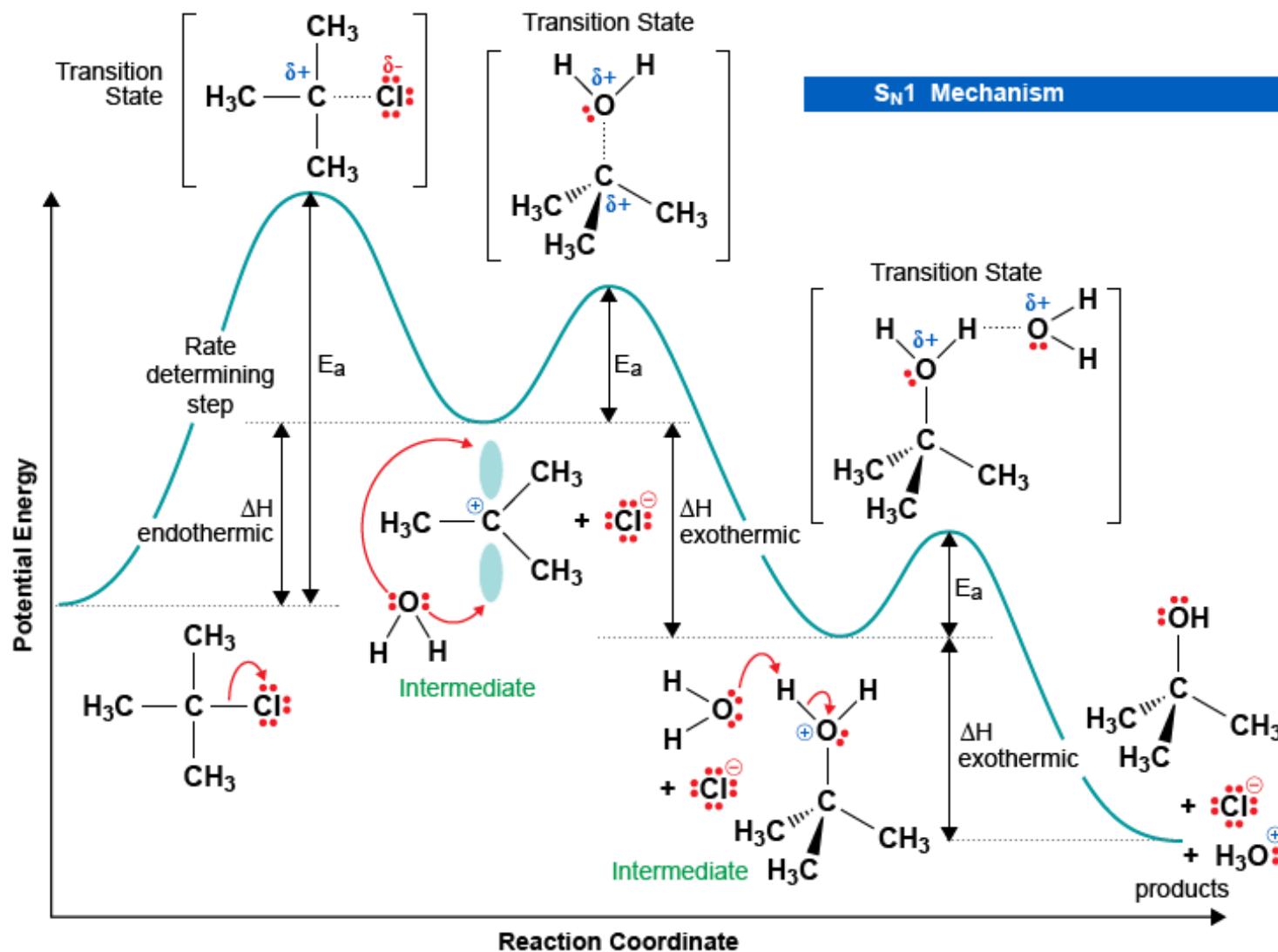


Nucleophile not involved in rate-determining step, so it **DOES NOT** affect rate.

Solvolytic reactions: many S_N1 reactions are solvolysis reactions



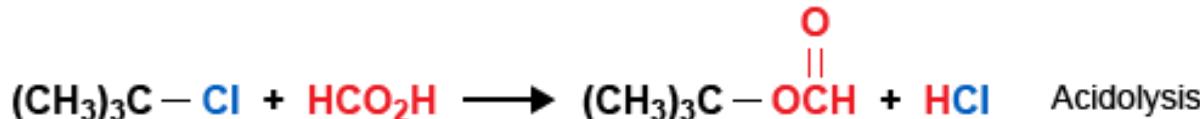
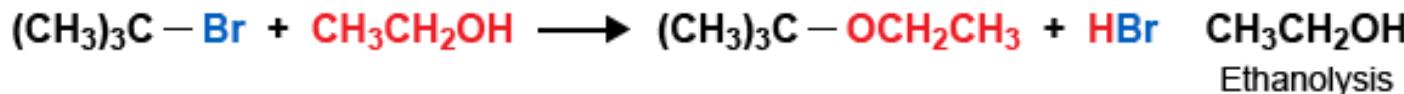
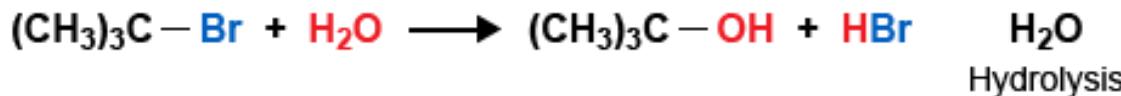
Energy diagram for solvolysis mechanism



Solvolytic Reactions

In many S_N1 reactions the **solvent is the nucleophile**. Also note that the nucleophiles in these S_N1 reactions are weak and polar protic.

Solvolytic Reactions



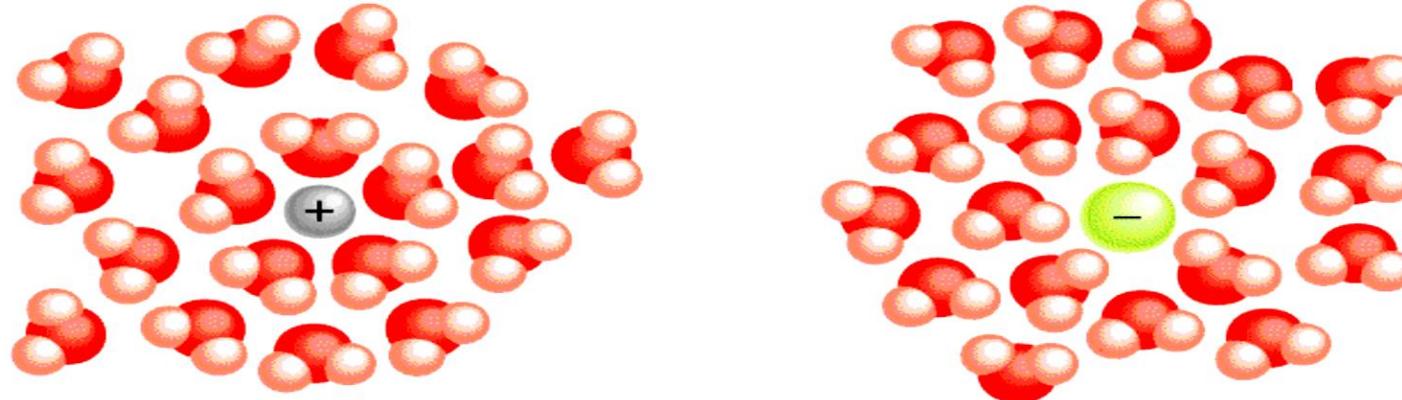
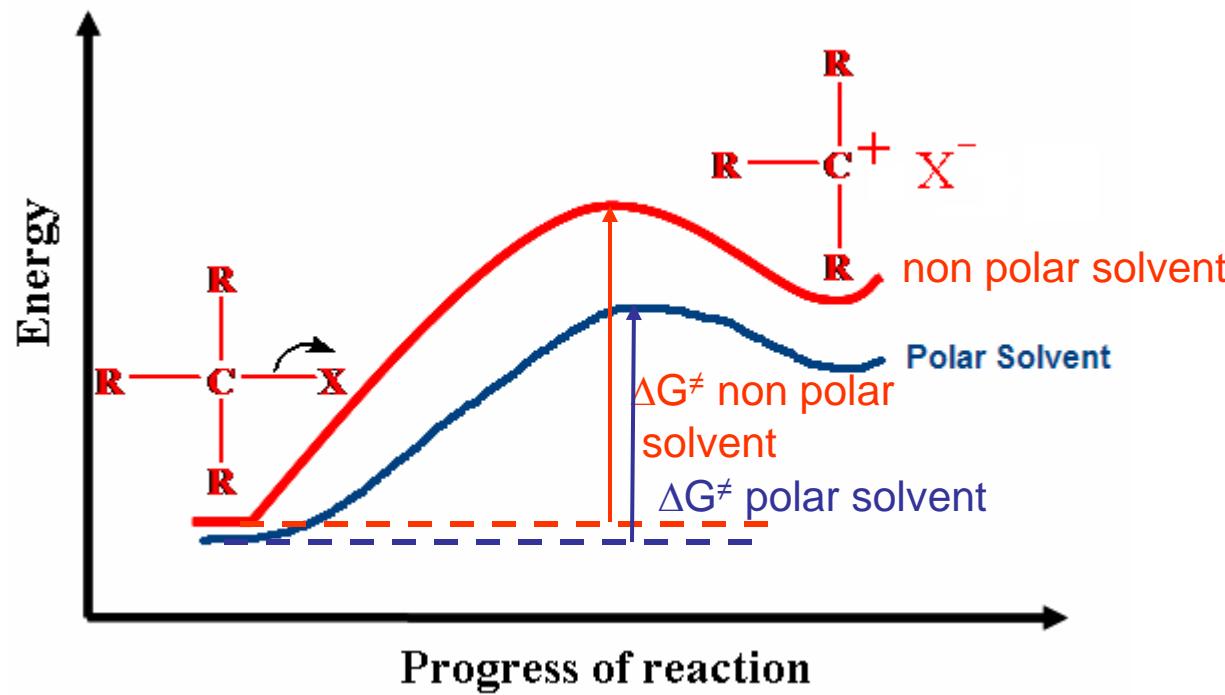
If you wanted to dissolve NaBr would you use A) hexane or B) water?

What is the first step in the multi-stepped S_N1 mechanism?

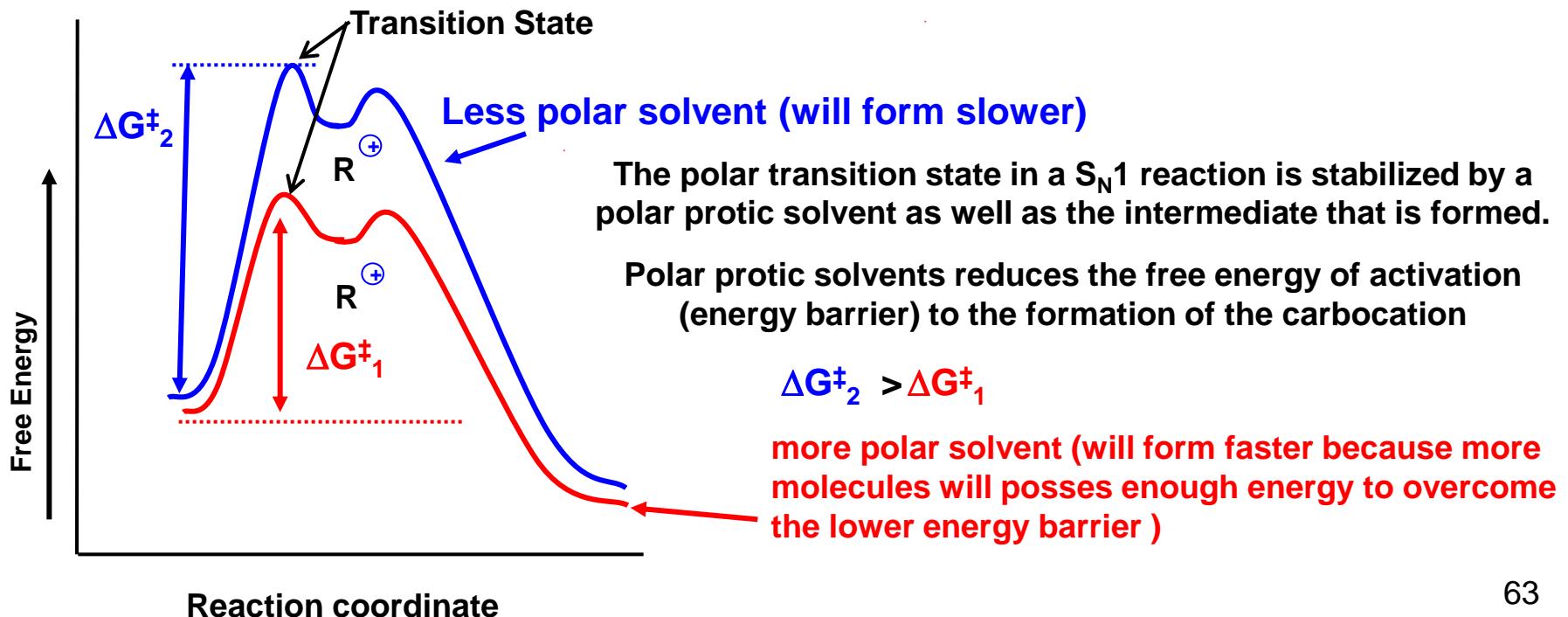
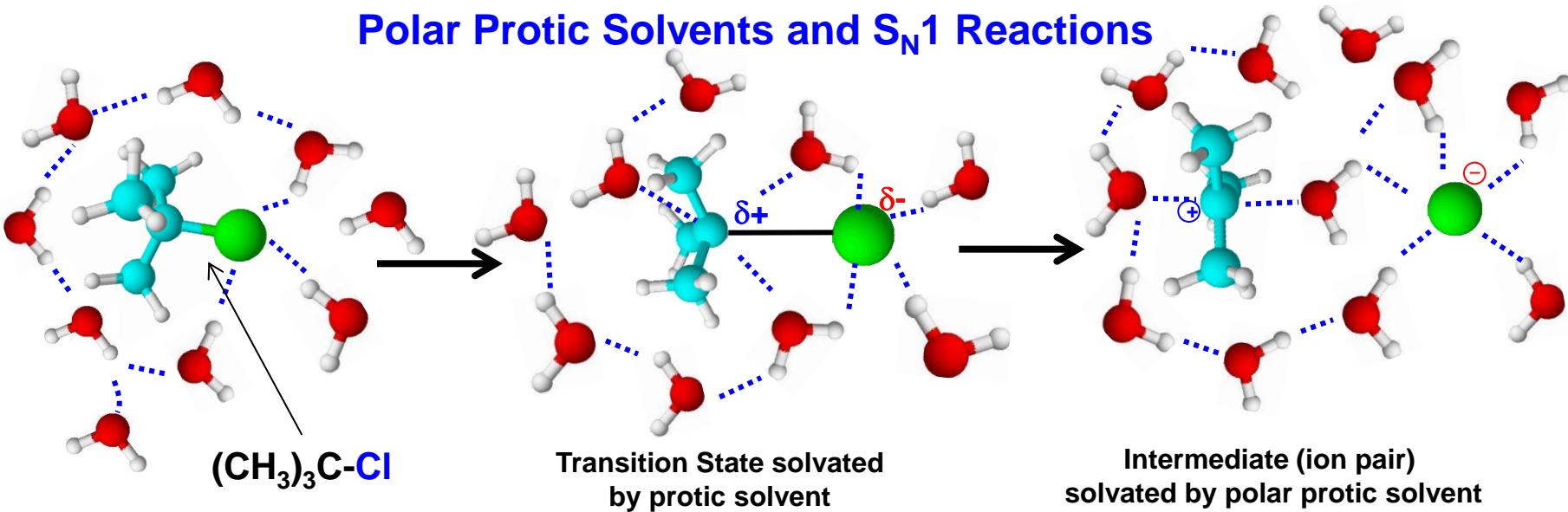
If you wanted to decrease the energy barrier to the formation of the S_N1 intermediate what solvent would you use A) aprotic or B) protic?

FACTORS (c) Solvent

S_N1 reactions are favored by **polar protic** solvents

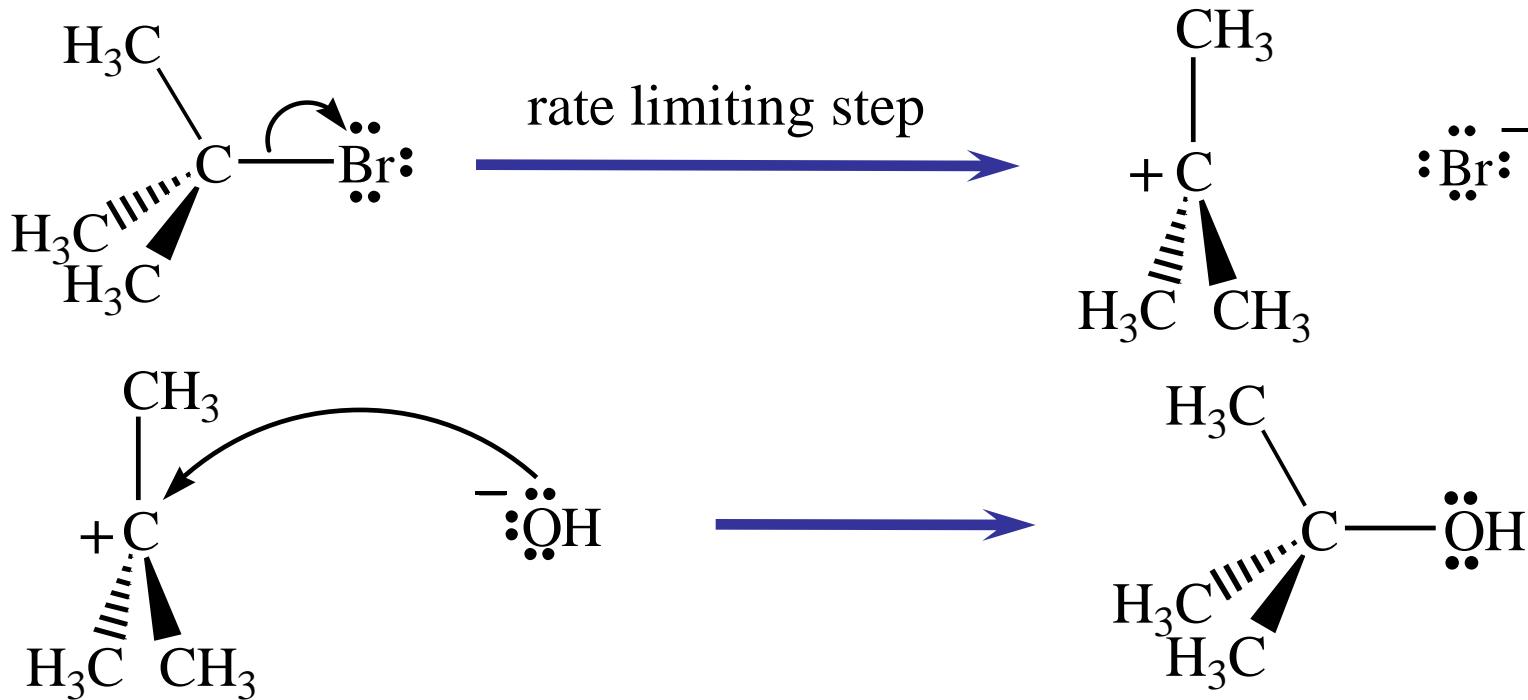


Polar Protic Solvents and S_N1 Reactions



FACTORS

(d) Nature of Leaving Group



Leaving Groups

Good Leaving Groups				Poor Leaving Groups			
	LG	Acid	pK _a		LG	Acid	pK _a
Iodide	I ⁻	HI	-10	Fluoride	F ⁻	HF	3.2
Bromide	Br ⁻	HBr	-9	Bisulfide	HS ⁻	H ₂ S	7
Chloride	Cl ⁻	HCl	-7	Cyanide	NC ⁻	HCN	9.1
Sulfonate	OSO_2R	HOSO_2R	-3	Hydroxide	HO ⁻	H ₂ O	15.7
Water	H ₂ O	H ₃ O ⁺	-1.7	Alkoxide	RO ⁻	ROH	16-18

Other good Leaving groups

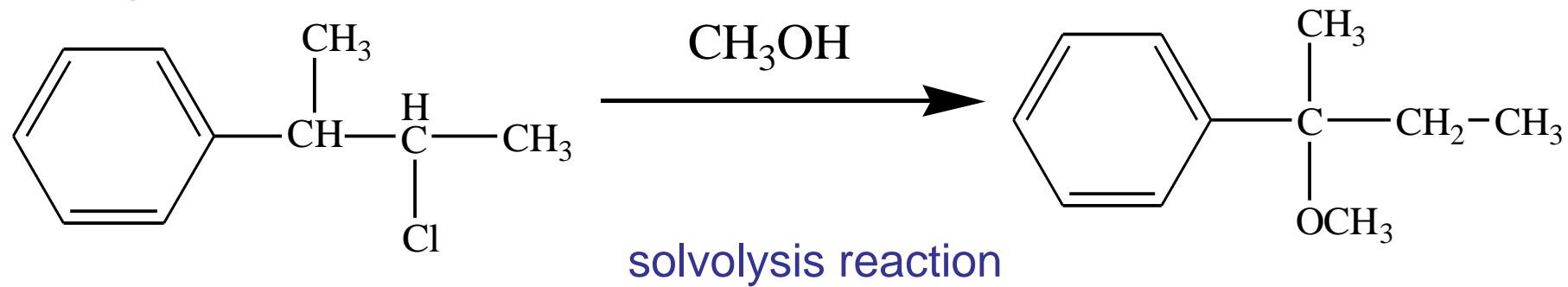
Tosylic, and methanesulfonic acids are good leaving groups because they are weak bases and poor nucleophiles.

Another very good sulfonate leaving group is Triflate. Triflic acid is an extremely strong acid making its conjugate base a very good leaving group.

Leaving Group	Structure	Acid	pK _a
Tosylate		H ₃ CC ₆ H ₄ SO ₃ H	-1.3
Mesylate		H ₃ CSO ₃ H	-2.6
Triflate		F ₃ CSO ₃ H	-14

Rearrangements can occur in S_N1 reactions

Example:



Mechanism:

Summary of the S_N1 mechanism:

Attack at either face of carbocation → racemization at chirality centres

First-order rate law:

$$\text{Rate} = -\frac{d \text{ [substrate]}}{d t} = k \text{ [substrate]}$$

- does **not** depend on nature of nucleophile
- depends on nature of leaving group
- effective when carbon centre sterically hindered
- effective in protic solvents

Competition between S_N2 and S_N1 :

Table 8.5 Comparison of S_N2 and S_N1 Reactions

S _N 2	S _N 1
A one-step mechanism	A stepwise mechanism that forms a carbocation intermediate
A bimolecular rate-determining step	A unimolecular rate-determining step
No carbocation rearrangements	Carbocation rearrangements
Product has inverted configuration relative to the reactant	Products have both retained and inverted configurations relative to the reactant
Reactivity order: methyl > 1° > 2° > 3°	Reactivity order: 3° > 2° > 1° > methyl

$$\text{rate} = k_2[\text{alkyl halide}][\text{nucleophile}] + k_1[\text{alkyl halide}]$$

contribution to the rate by an S_N2 reaction

contribution to the rate by an S_N1 reaction

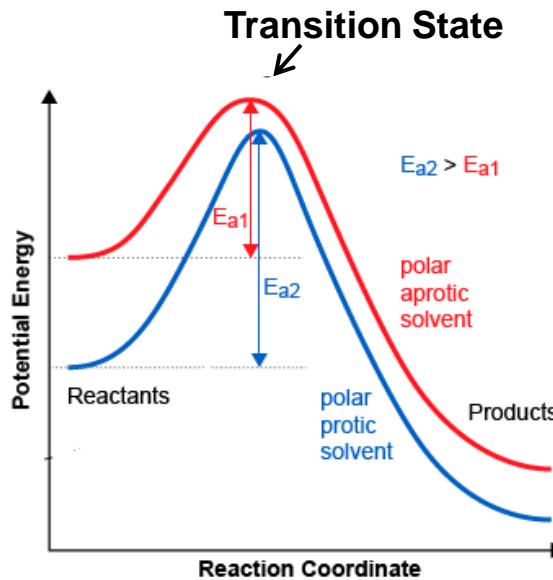
primary alkyl halides and methyl halides: **only S_N2**. They cannot form carbocations.

secondary alkyl halides: **only S_N2**. Carbocation formation is too slow to make up for the large concentration of the nucleophile in a solvolysis reaction.

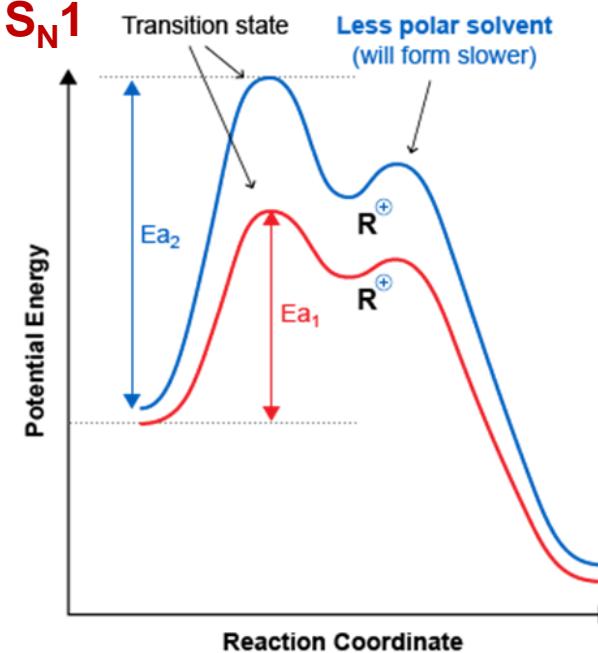
tertiary alkyl halides: **only S_N1**. They cannot undergo back-side attack. 68

Review: Totally different mechanisms

S_N2



S_N1



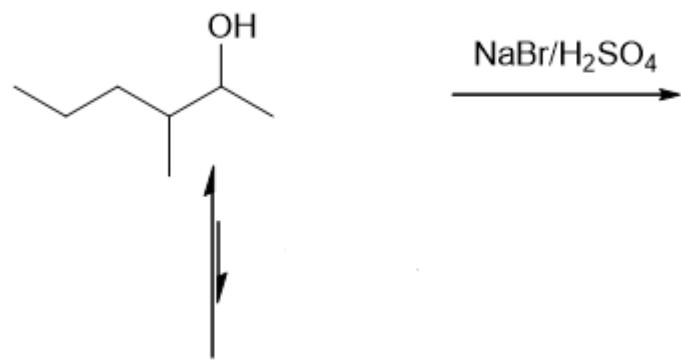
- Concerted (one step)
- Exergonic and Exothermic
- The nucleophile is either negatively charged or has a delta negative charge. It is donating electrons.
- Aprotic solvents destabilize the nucleophile, increases its potential energy, decreases the free energy of activation and increases the rate of reaction.

- Multi-stepped reaction
- The rate determining slow step is endergonic and endothermic
- The intermediate formed is ionic.
- The intermediate that is formed must be stabilized by the solvent or it will not form.
- Using a polar protic solvent decrease the free energy of activation and increases rate of formation of the intermediate

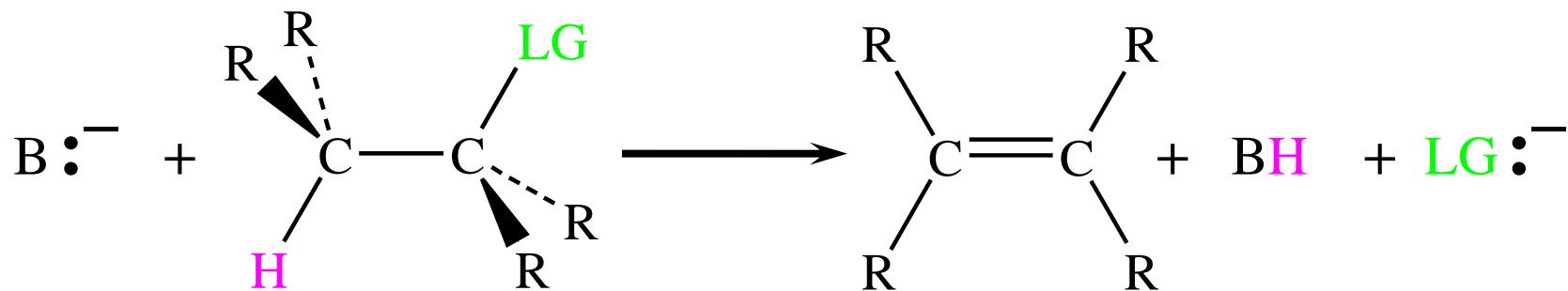
Step-by-Step procedure for Solving S_N1 or S_N2 Reactions

- **Step 1:** Add lone pairs onto the appropriate atoms and place full charges and partial charges on atoms.
- **Step 2:** Identify the nucleophile and electrophile.
- **Step 3:** Assess the nucleophile: is the attacking group or atom a good nucleophile or a poor nucleophile (polarizable, strong base, sterically hindered)?
- **Step 4:** Assess the electrophile: is the electrophile accessible to a nucleophilic attack or is it sterically hindered (allylic, benzylic, methyl, 1°, 2°, 3°, vinyl, aryl)?
- **Step 5:** Is the solvent polar protic or polar aprotic, aprotic, nonpolar protic?
- **Step 6:** This is enough information to determine if an S_N2 reaction will occur.
- **Step 7:** Use arrows to illustrate the mechanism to show bond formation and breaking. These arrows will show you what the products are!

Step-by-Step procedure for Solving S_N1 or S_N2 Reactions: Practice Problem



Elimination reactions



Two limiting mechanisms of elimination:

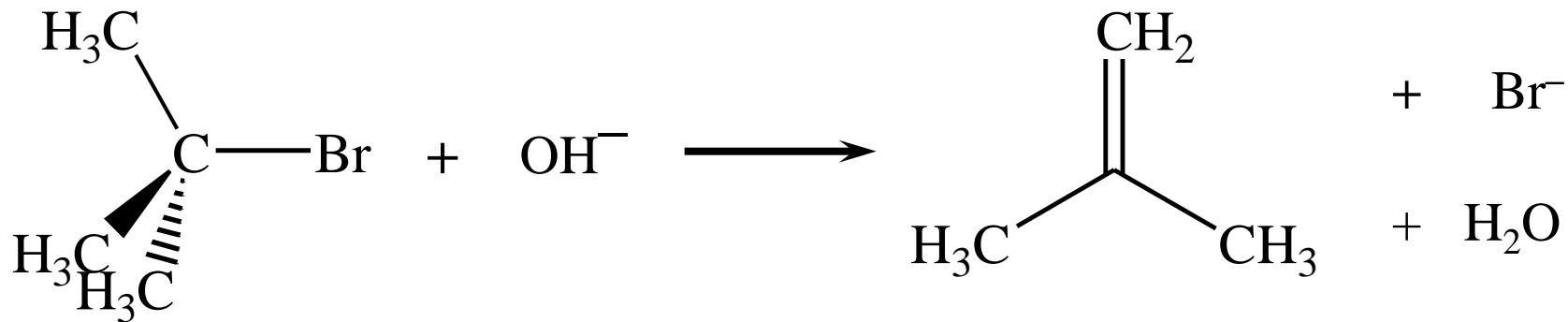
E2:

E1:

A fundamental difference between them is the timing of bond-breaking and bond-forming steps

E2: Elimination Bimolecular

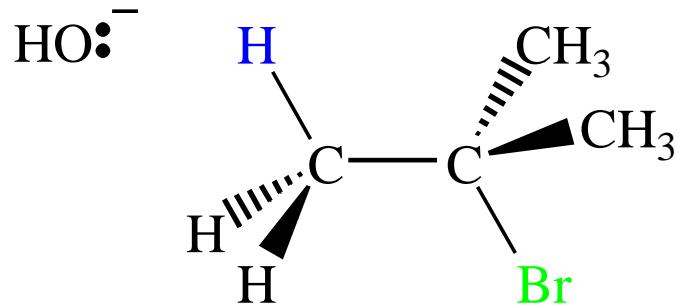
Example:



1) MECHANISM

2) EVIDENCE

1) MECHANISM



CONCERTED = only one step

All bonds are broken and formed without the formation of any intermediates.

2) KINETICS

relative reactivities of alkyl halides in an E2 reaction

most reactive → RI > RBr > RCl > RF ← least reactive

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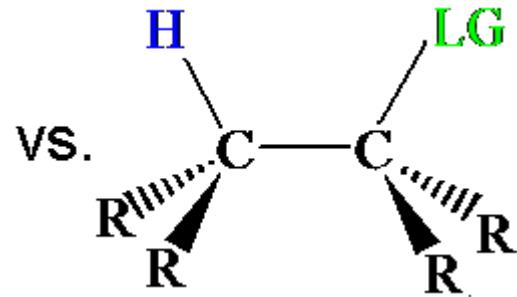
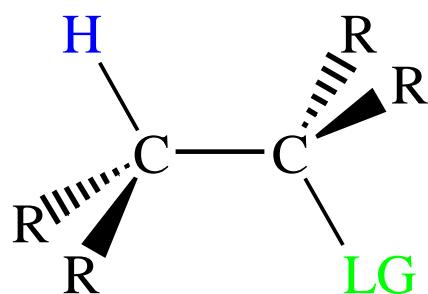
$$\text{rate} = k[\text{alkyl halide}][\text{base}]$$

Reaction favored by: Strong base, aprotic polar solvent and Heat

2) Stereochemistry

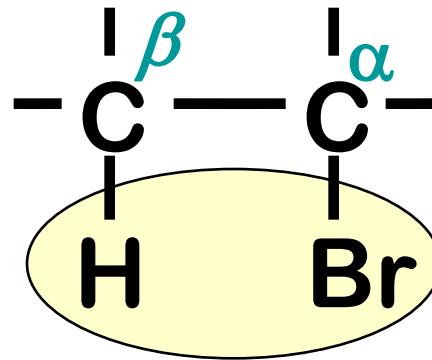
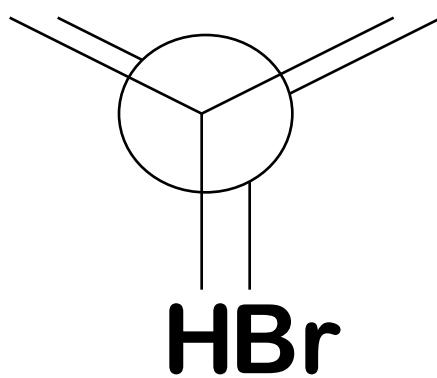
Anti-periplanar geometry required.
(H, 2 C's and LG all lie in same plane)

Newman projection:

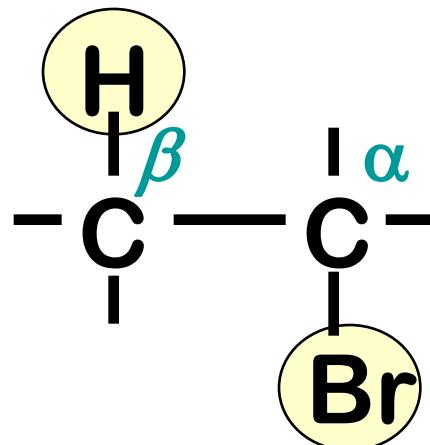
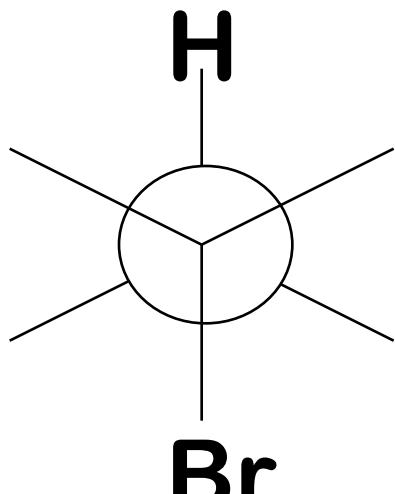


STEREOCHEMISTRY

TWO EXTREME POSSIBILITIES FOR THE ELIMINATION PROCESS

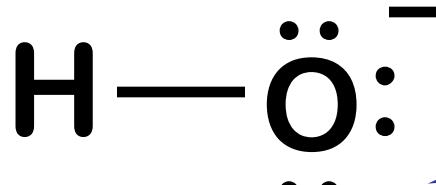


syn periplanar
elimination
not common



anti-periplanar

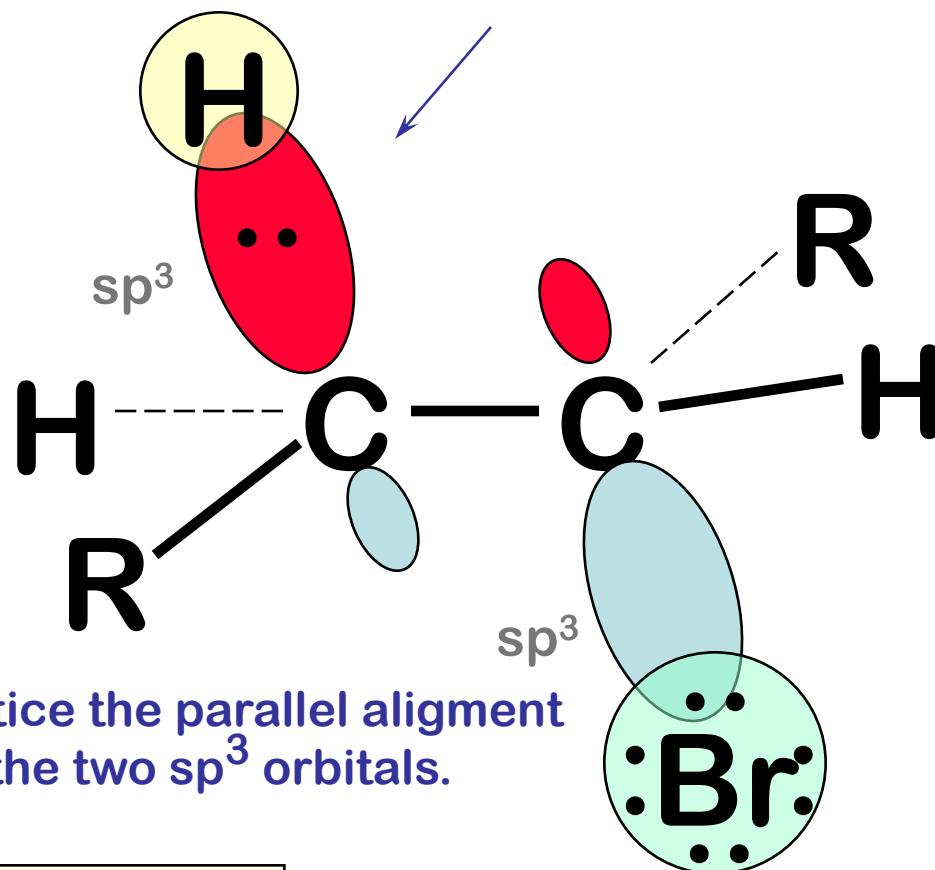
anti periplanar
elimination
observed
most often



The critical event is the removal of the β -H.

The anti-periplanar arrangement of the β -H and the halide leaving group X places the orbitals that undergo change in a perfect alignment.

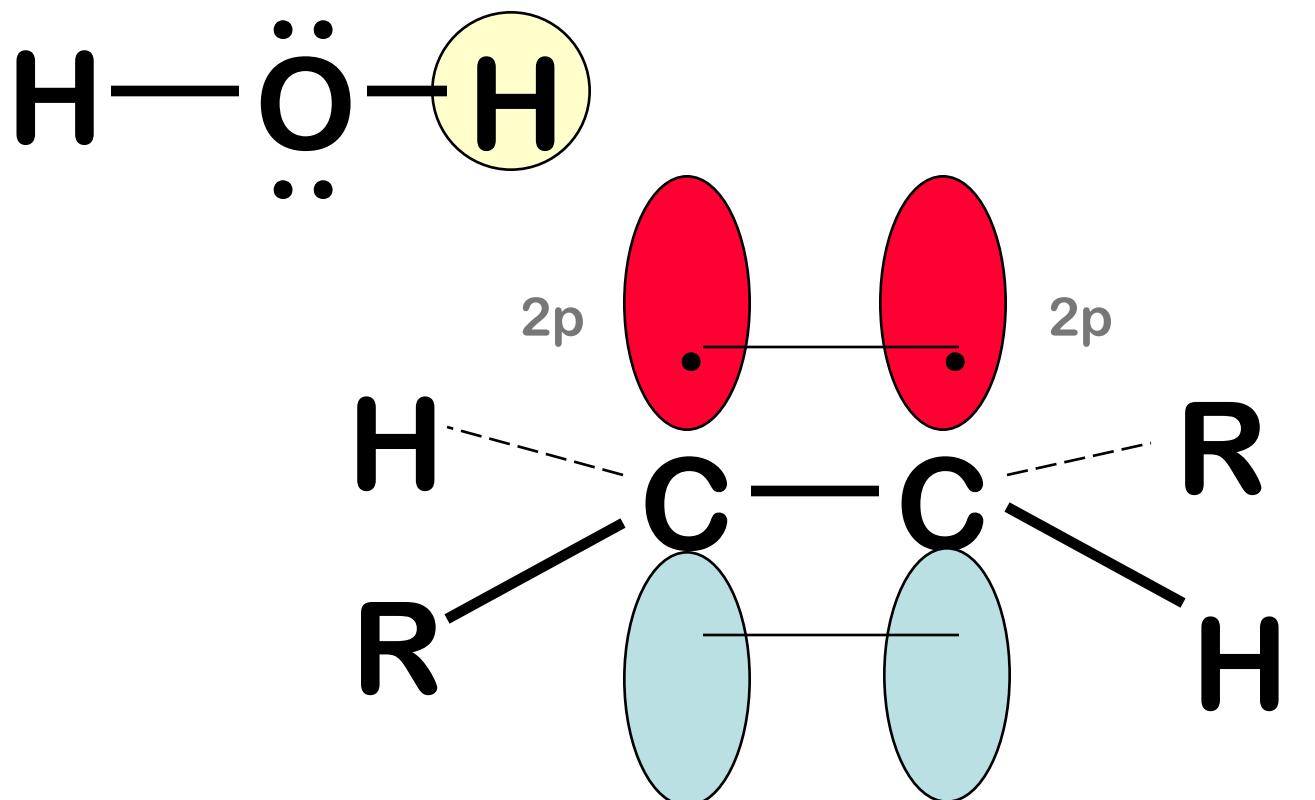
When these electrons enter the back lobe of the adjacent orbital they “push” the bonding pair out the other end (along with Br).



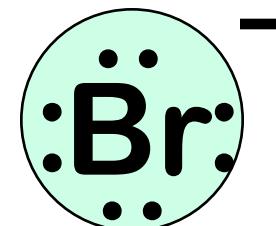
The attack of the base on the β -hydrogen starts the reaction.

The two orbitals that will form the pi bond are already parallel (anti-coplanar) so that the double can form easily. 77

Note the parallel orbitals
in the pi bond.

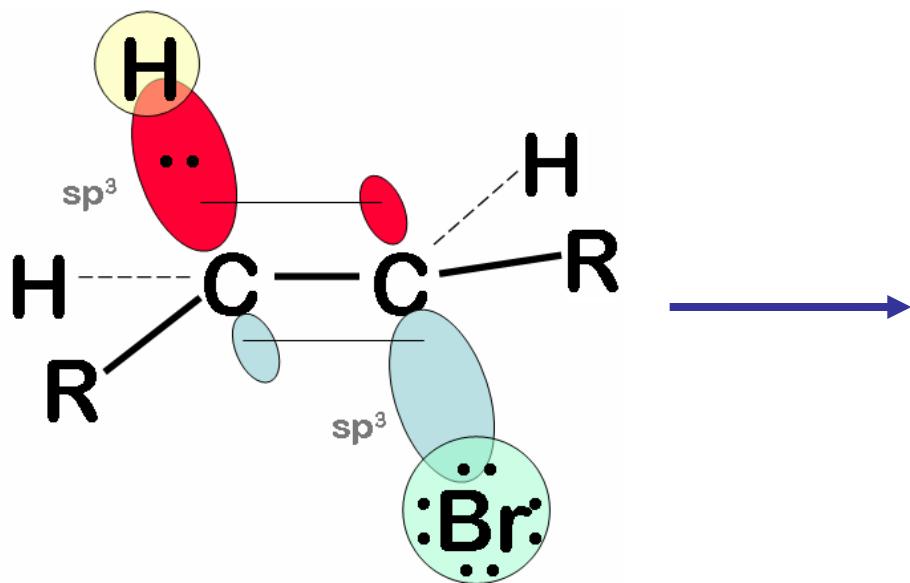
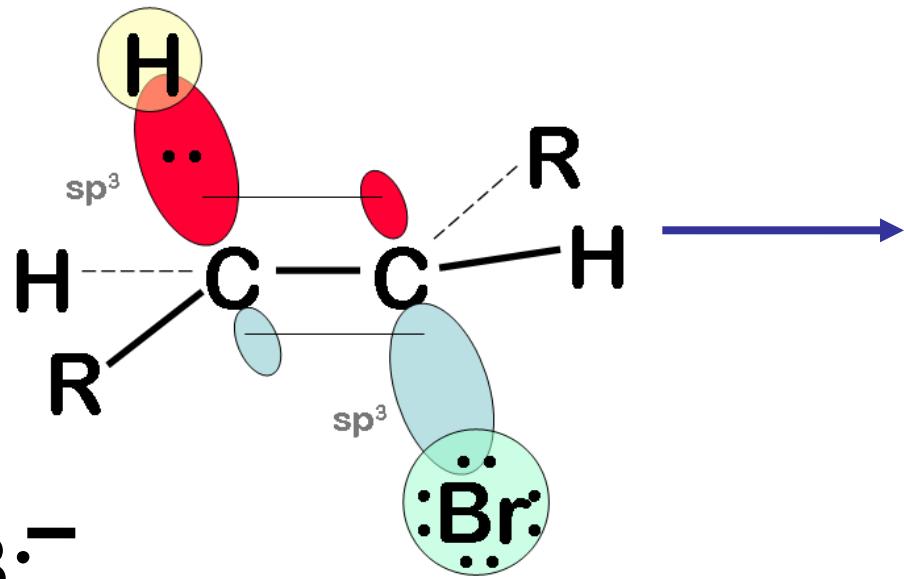


The formation of the double bond
and the loss of bromide finish it.

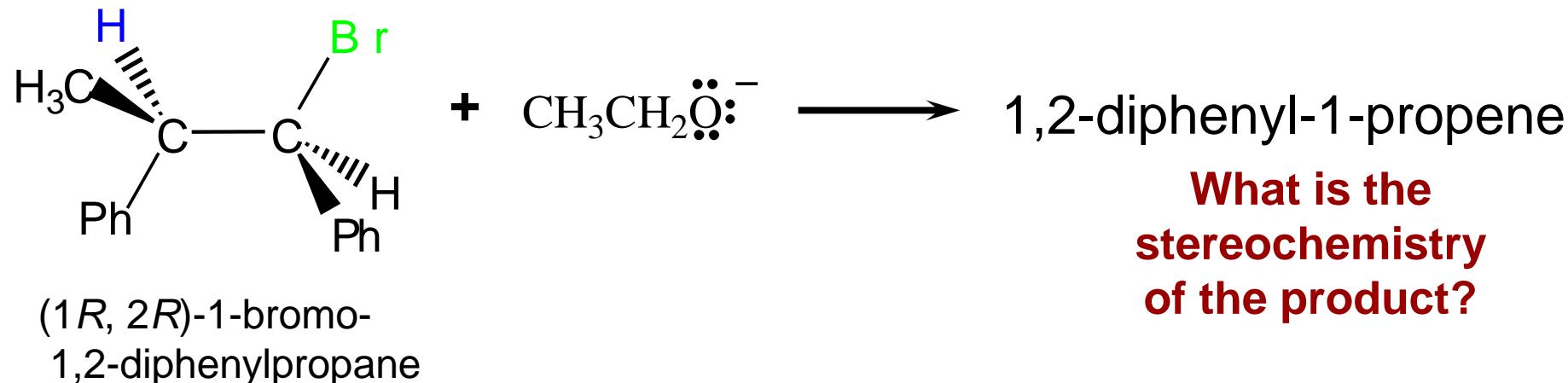


B^-

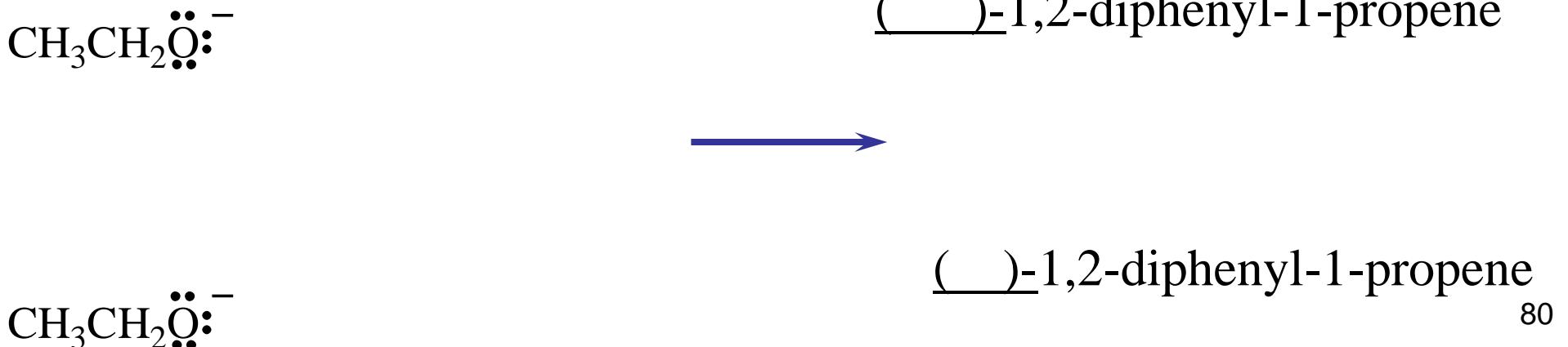
STEREOCHEMISTRY



Consider the E2 elimination reaction of (*1R, 2R*)-1-bromo-1,2-diphenylpropane:



First, redraw the molecule with the C-H and C-Br bonds periplanar:



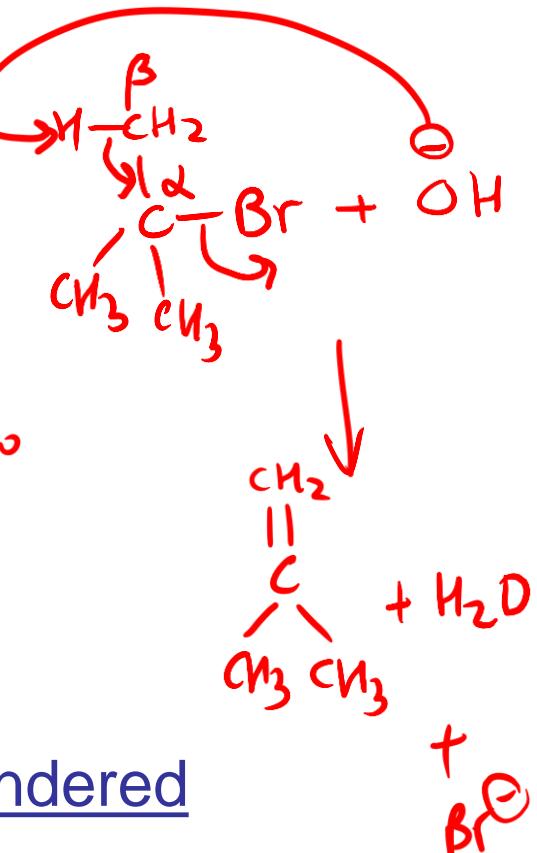
Summary of the E2 mechanism (so far):

One step reaction one T.S. No intermediate

Anti-periplanar geometry for LG and beta-H

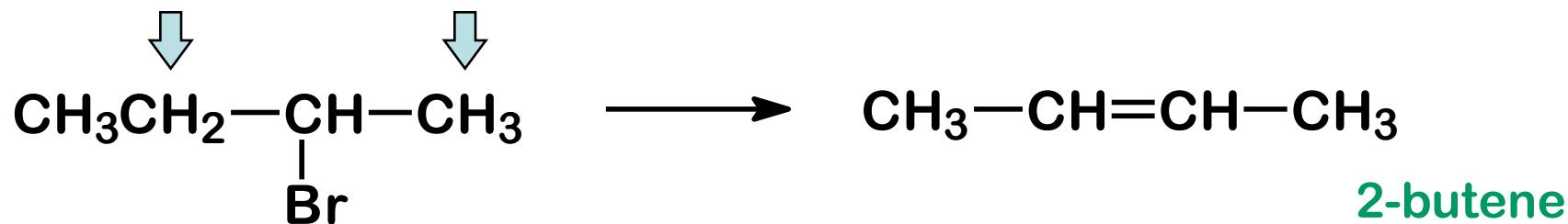
Second-order rate law:

$$\text{Rate} = -\frac{d[\text{substrate}]}{dt} = k [\text{base}] [\text{substrate}]$$

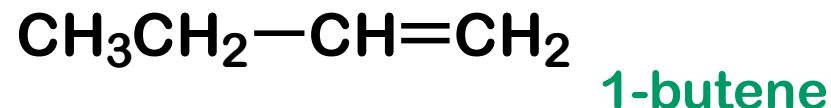


- fastest when carbon centre sterically hindered
- depends on nature of base need strong base
- depends on nature of leaving group need weak base
- effective in polar aprotic solvent
- Faster at higher temperatures
- Rxn regioselective, stereoselective and stereospecific

ELIMINATION IS REGIOSELECTIVE

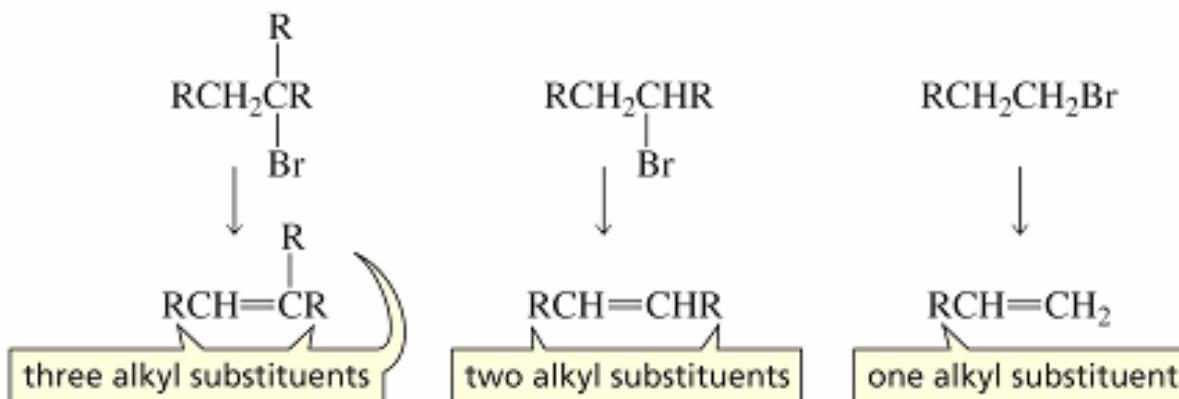


2-bromobutane



relative reactivities of alkyl halides in an E2 reaction

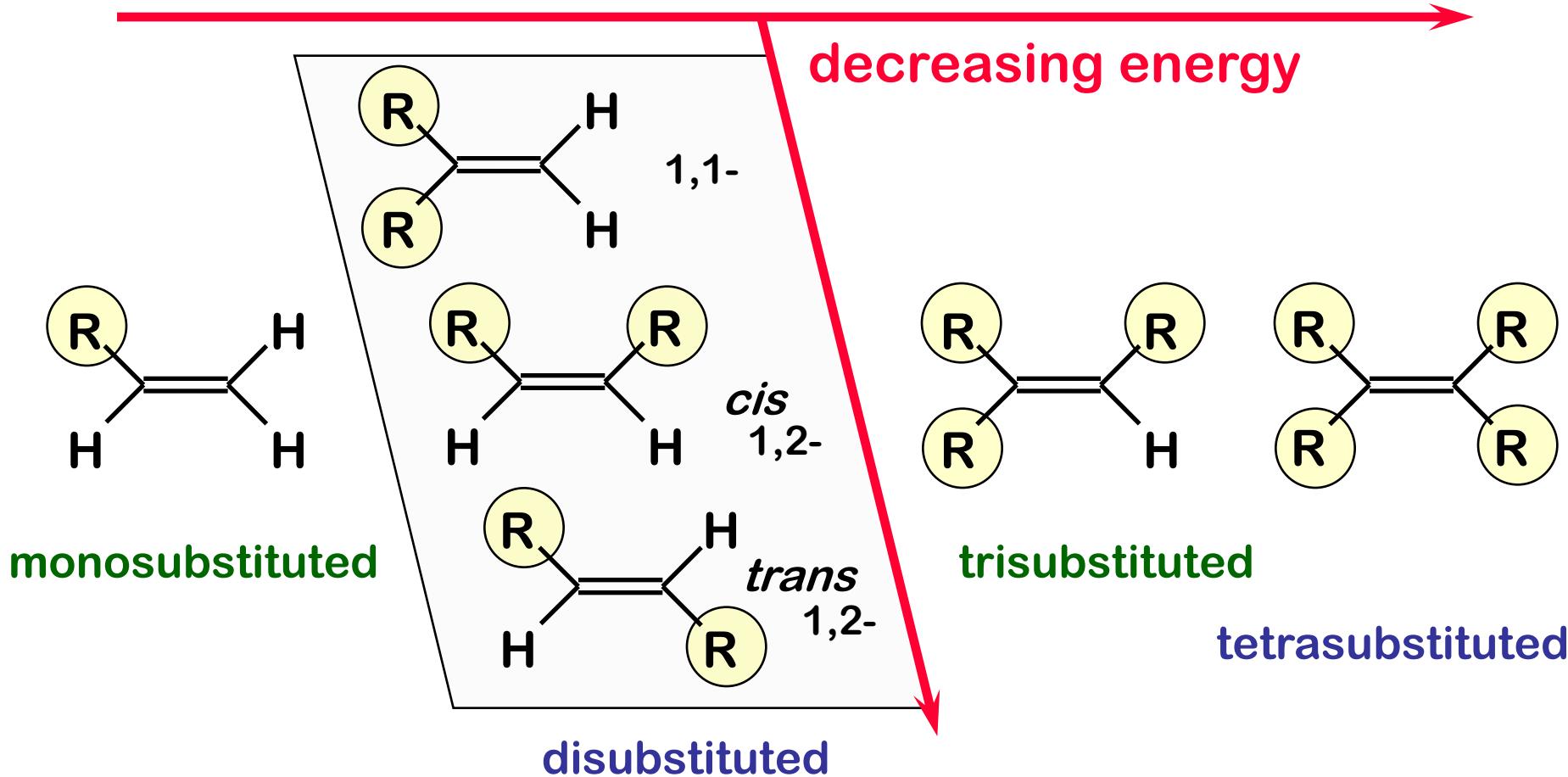
tertiary alkyl halide > secondary alkyl halide > primary alkyl halide



ALKENE ISOMERS

Different positions
of the double bond.

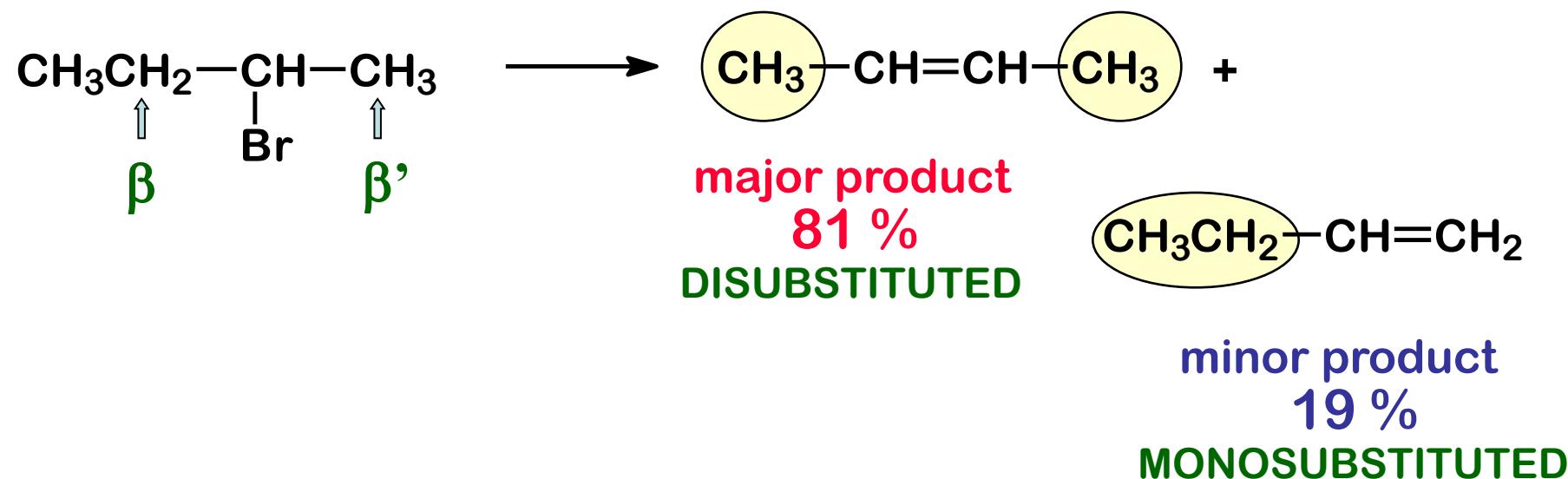
THE MORE SUBSTITUTED ISOMER IS MORE STABLE



increasing stability due to increased number of R grps 83

Zaitsev's Rule

The more substituted alkene is obtained when a proton is removed from the β -carbon that is bonded to the *fewest* hydrogens.



The carbon labelled β has the fewest hydrogens compared to carbon labelled β' so proton removed from β carbon to give more substituted alkene and the major product.

EXCEPTIONS OF THE ZAITZEV RULE

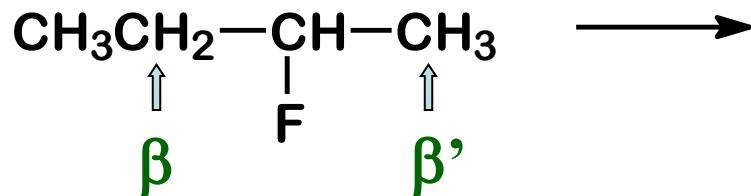
- a) Base is bulky:
- b) Starting reactant has double bond or benzene ring:

Table 10.1 Effect of the Steric Properties of the Base on the Distribution of Products in an E2 Reaction

$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{CH}-\text{CCH}_3 \\ \\ \text{CH}_3 \end{array}$ 2-bromo-2,3-dimethylbutane	Br	RO^-	\longrightarrow	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{C}=\text{CCH}_3 \\ \\ \text{CH}_3 \end{array}$ 2,3-dimethyl-2-butene	$+$	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{CHC}=\text{CH}_2 \\ \\ \text{CH}_3 \end{array}$ 2,3-dimethyl-1-butene
Base		More stable alkene		Less stable alkene		
$\text{CH}_3\text{CH}_2\text{O}^-$		79%		21%		
$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{CO}^- \\ \\ \text{CH}_3 \end{array}$		27%		73%		
$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{CO}^- \\ \\ \text{CH}_2\text{CH}_3 \end{array}$		19%		81%		
$\begin{array}{c} \text{CH}_2\text{CH}_3 \\ \\ \text{CH}_3\text{CH}_2\text{CO}^- \\ \\ \text{CH}_2\text{CH}_3 \end{array}$		8%		92%		

EXCEPTIONS OF THE ZAITZEV RULE

c) Poor leaving group: The weaker the base, the better it is as a leaving group



carbanion-like
transition state

transition state leading to
1-butene
more stable

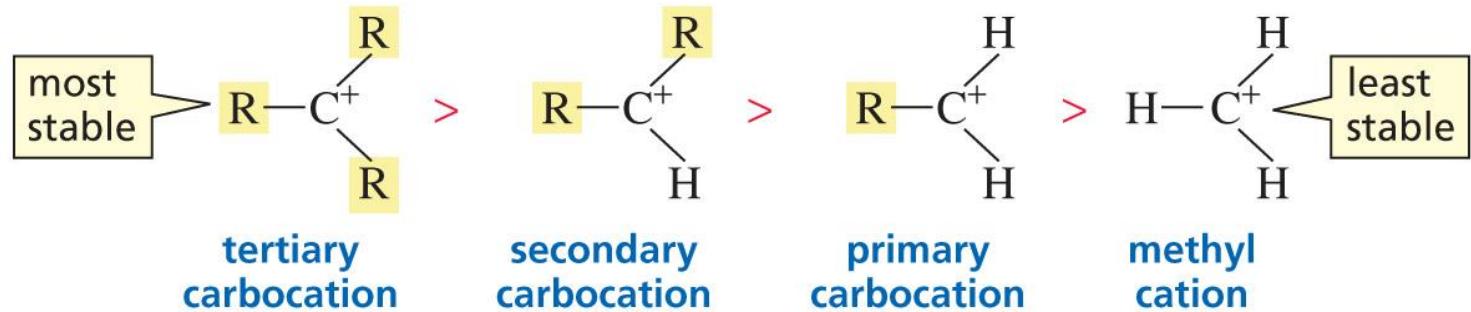


transition state leading to
2-butene
less stable

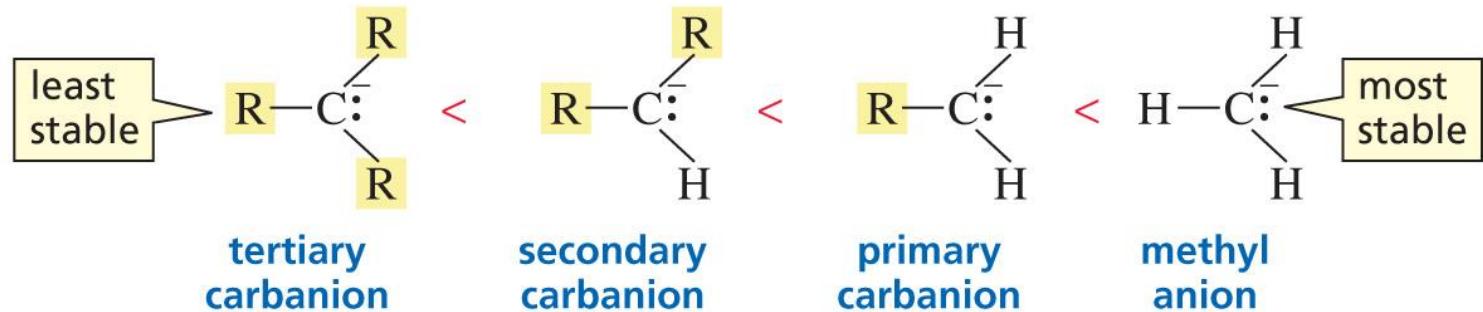
Major product of E2 elimination is more stable alkene *except:* a) reactants sterically hindered; b) reactant has double bonds or c) leaving group is poor

Relative Stabilities of Carbocations vs Carboanions

relative stabilities of carbocations



relative stabilities of carbanions



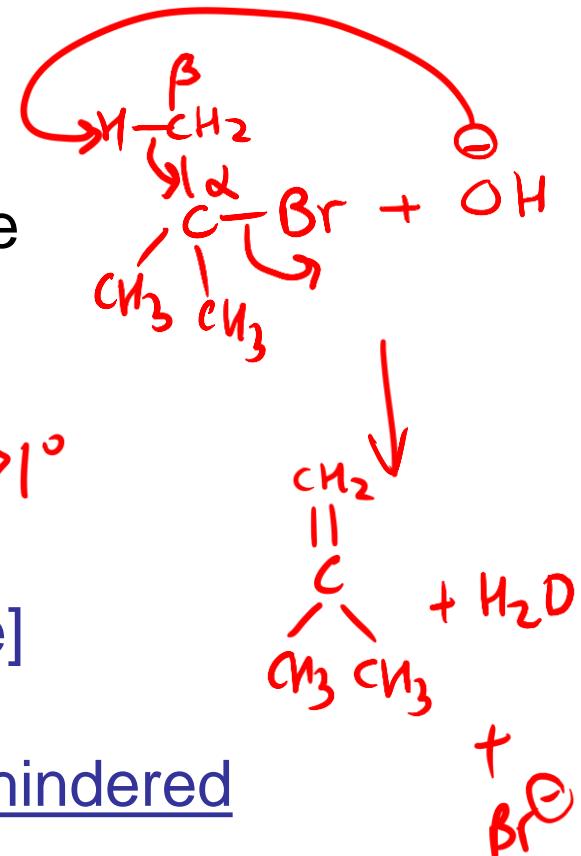
Summary of the E2 mechanism:

One step reaction one T.S. No intermediate

Anti-periplanar geometry for LG and beta-H

Second-order rate law:

$$\text{Rate} = -\frac{d[\text{substrate}]}{dt} = k [\text{base}] [\text{substrate}]$$



- fastest when carbon centre sterically hindered
- depends on nature of base need strong base
- depends on nature of leaving group need weak base
- effective in polar aprotic solvent
- Faster at higher temperatures
- Rxn regioselective, stereoselective and stereospecific

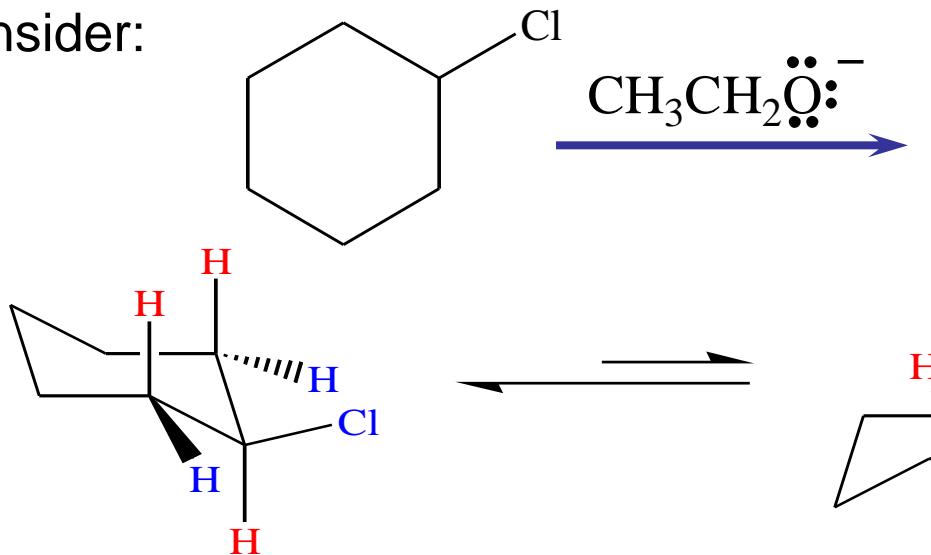
Consecutive E2 Eliminations

Example:

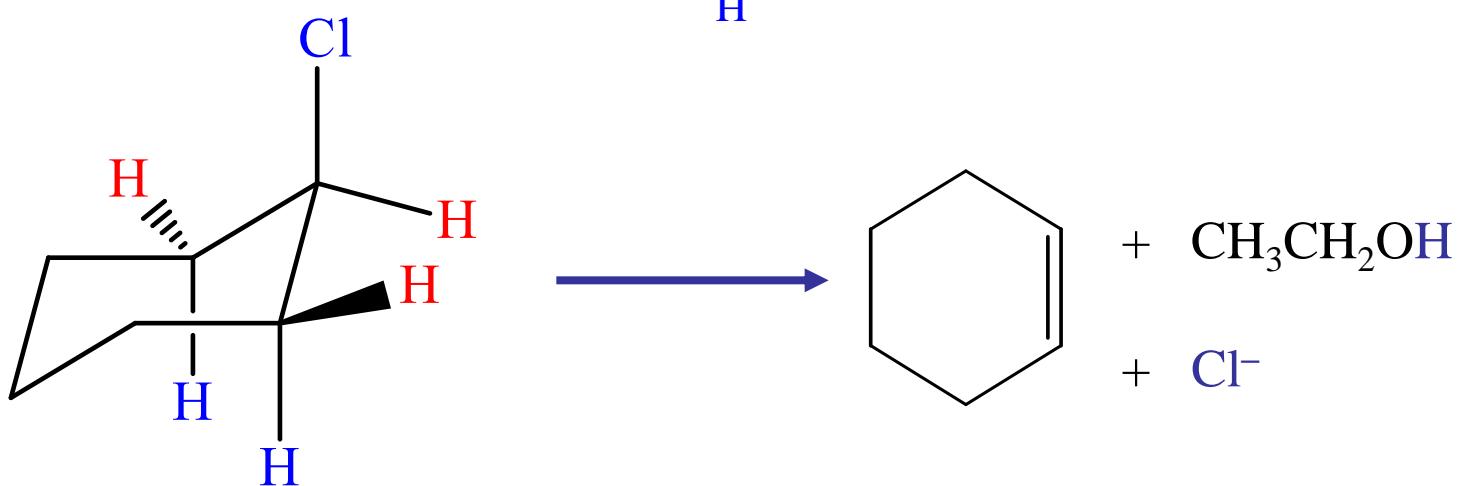
Geminal dihalides:

Vicinal dihalides:

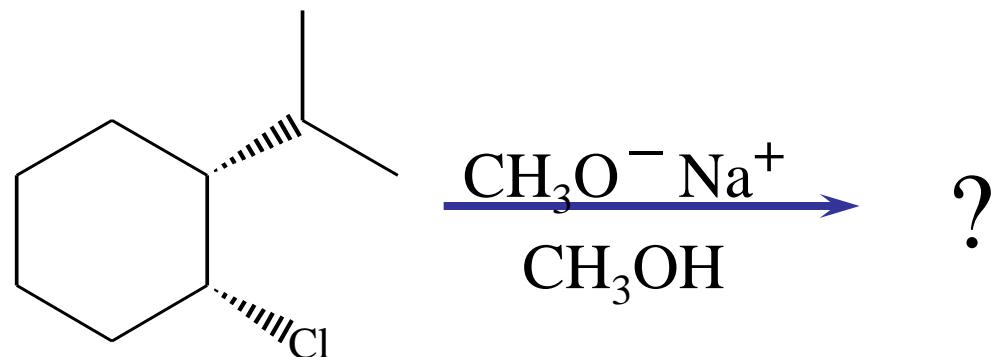
Consider:



Cl and H are not
anti to each other;
no elimination

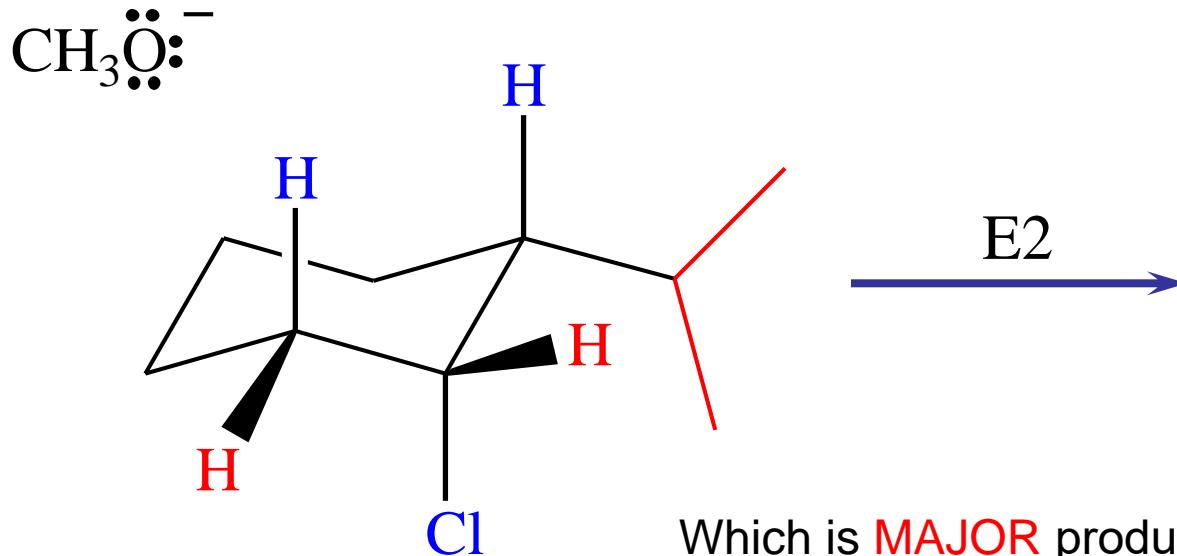
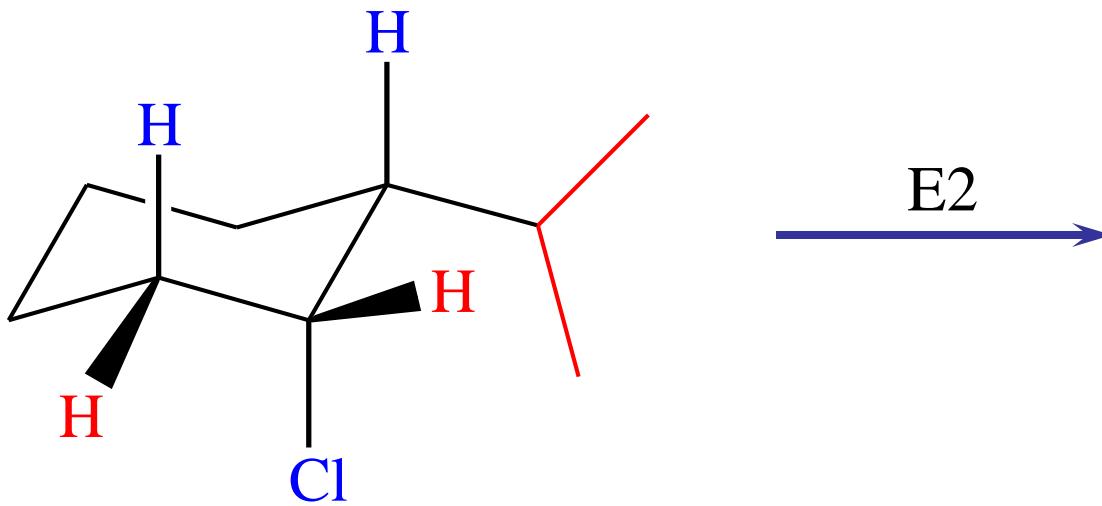


Anti-periplanar geometry: groups being eliminated must _____



(1*R*, 2*R*)-1-chloro-2-isopropylcyclohexane

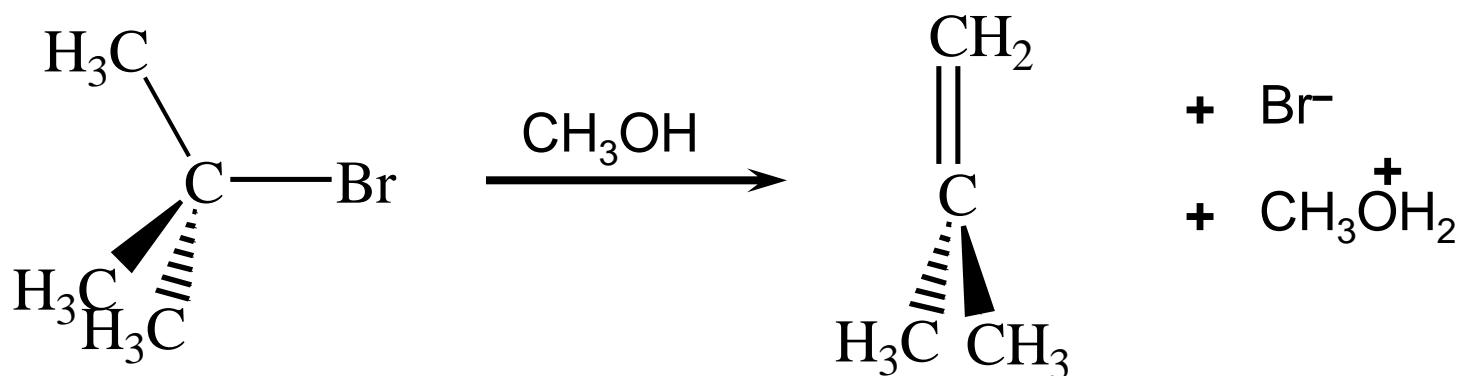




Which is **MAJOR** product? Regioselectivity.....

E1: Elimination Unimolecular

Example:

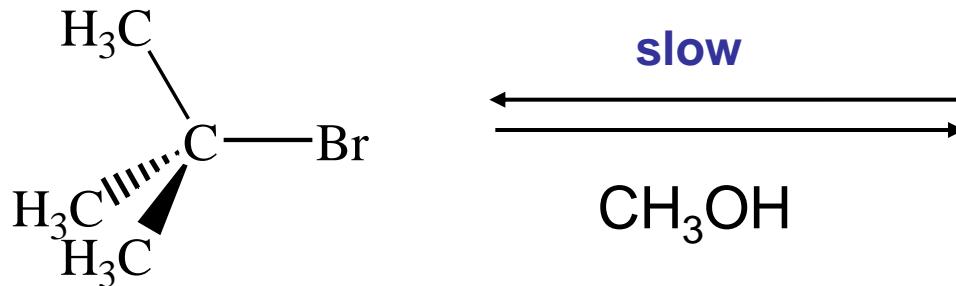


1) MECHANISM

2) EVIDENCE

1) MECHANISM

Step 1: cleavage of C–Br bond to form carbocation



Step 2: proton transfer from carbocation to base



relative reactivities of alkyl halides in an E1 reaction

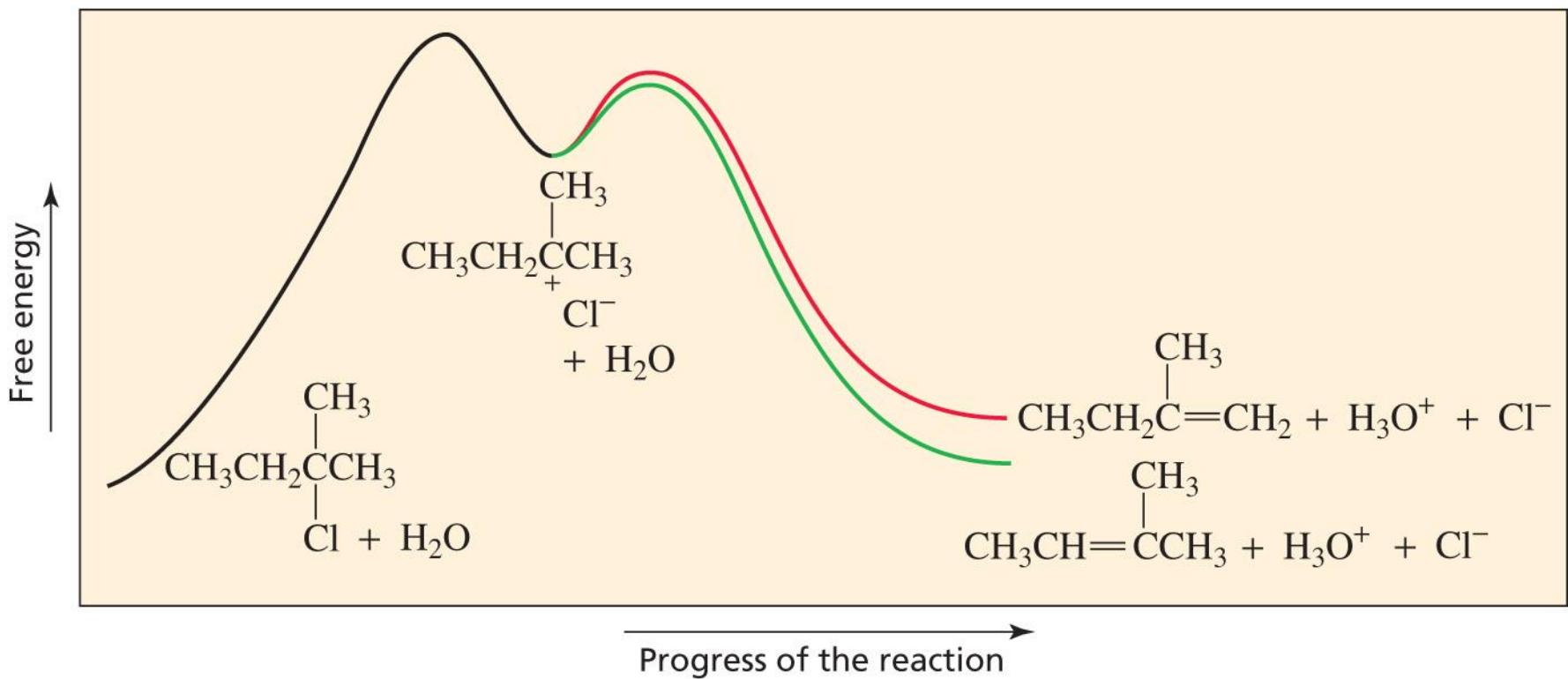
most reactive $\text{RI} > \text{RBr} > \text{RCl} > \text{RF}$ least reactive

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2) KINETICS

$$\text{Rate} = -\frac{d[\text{substrate}]}{dt} = k[\text{substrate}]$$

The More Stable Alkene is the Major Product



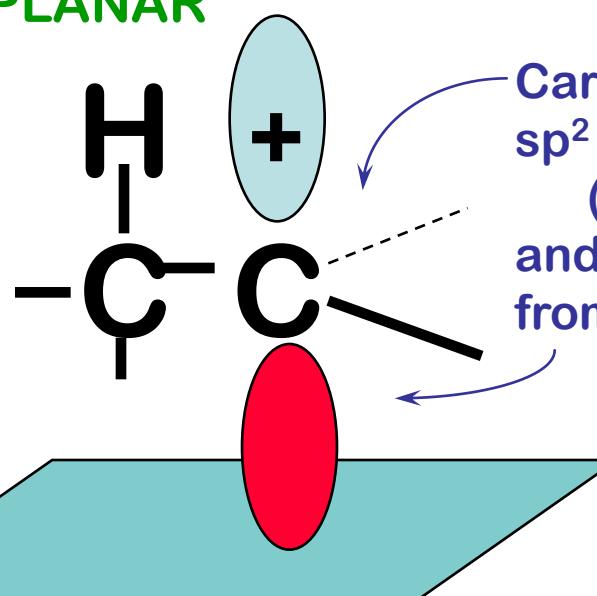
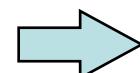
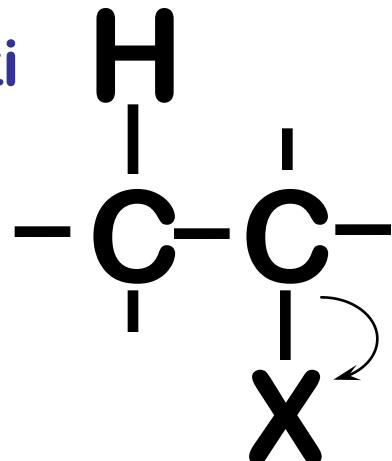
2) Stereochemistry

Periplanar geometry **not** required:

THE E1 REACTION IS NOT STEREOSELECTIVE

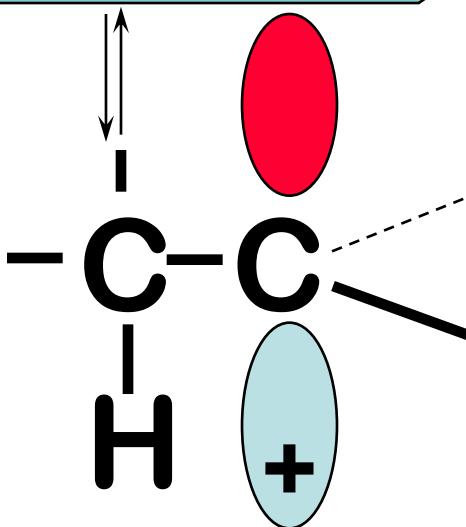
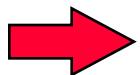
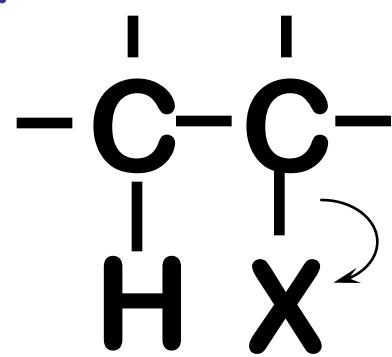
(THE OPEN CARBOCATION IS PLANAR
AND CAN ROTATE)

anti



Carbocation is
sp² hybridized
(planar)
and can react
from either side.

syn

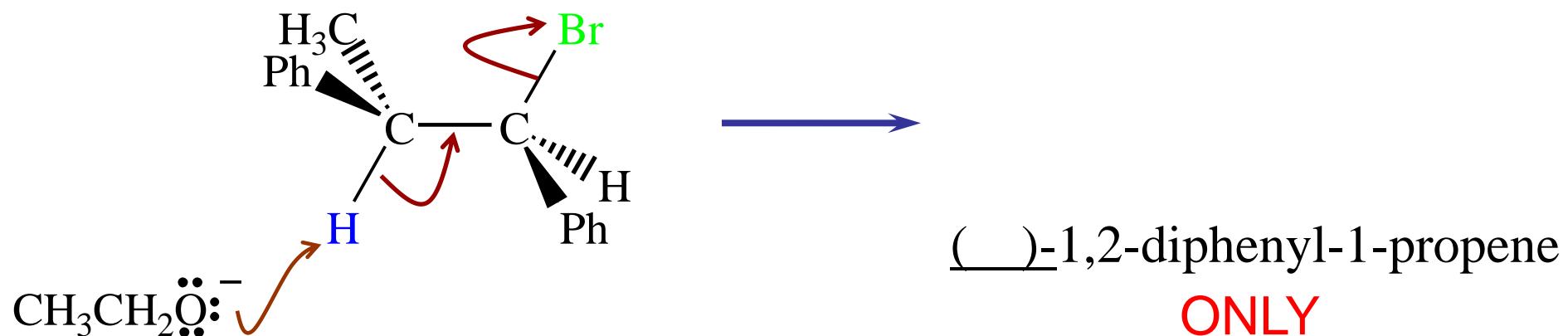


These two
carbocations
are equivalent
by **rotation** and
by symmetry.

Elimination can be either *syn* or *anti*.

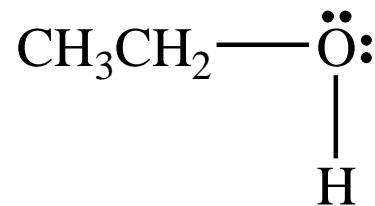
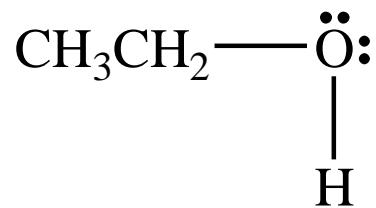
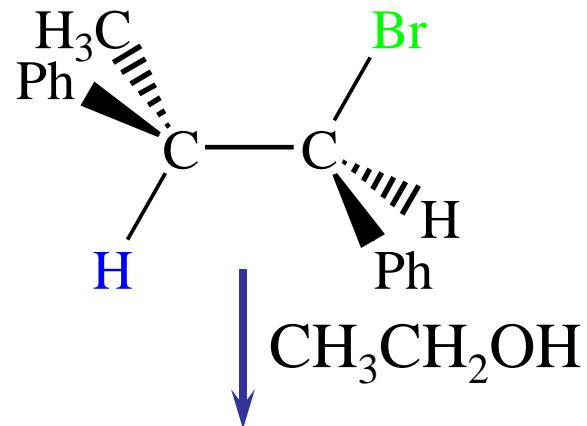
rate of C-C rotation
= 10^{10} to 10^{12} / sec

Recall from the E2 mechanism:



$(1R, 2R)$ -1-bromo-1,2-diphenylpropane

E1 mechanism:



Summary of the E1 mechanism (so far):

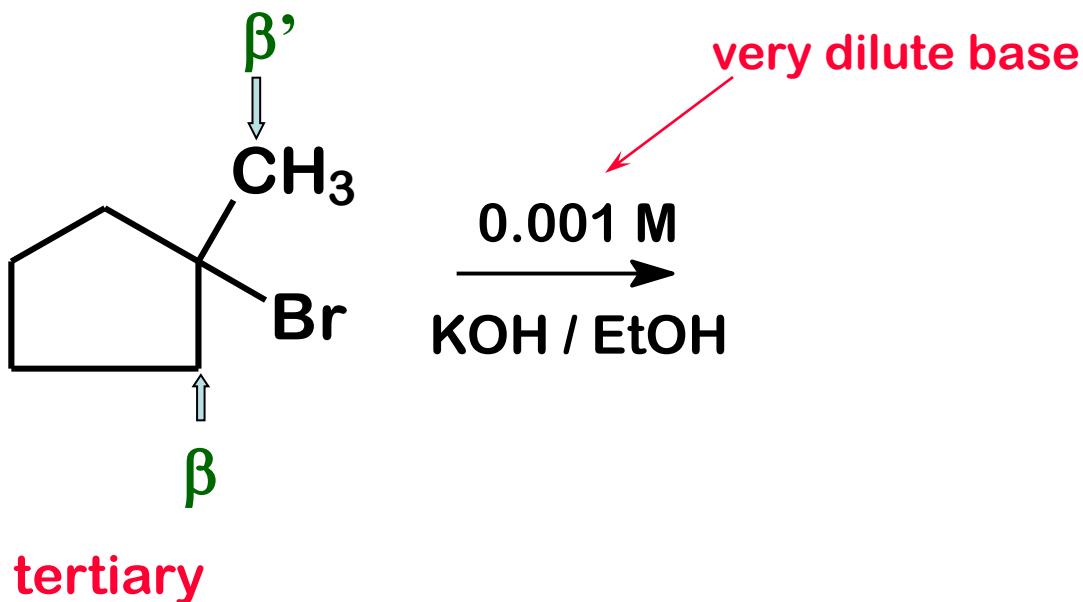
TWO step reaction TWO T.S. Carbocation intermediate

First-order rate law:

$$\text{Rate} = -\frac{d[\text{substrate}]}{dt} = k[\text{substrate}]$$

- fastest when carbon centre sterically hindered
- DOES NOT depend on nature of base **solvolytic**
- depends on nature of leaving group **need weak base**
- effective in polar protic solvent
- Faster at higher temperatures
- Rxn regioselective, stereoselective but not stereospecific ¹⁰⁰

E1 REACTION IS REGIOSELECTIVE



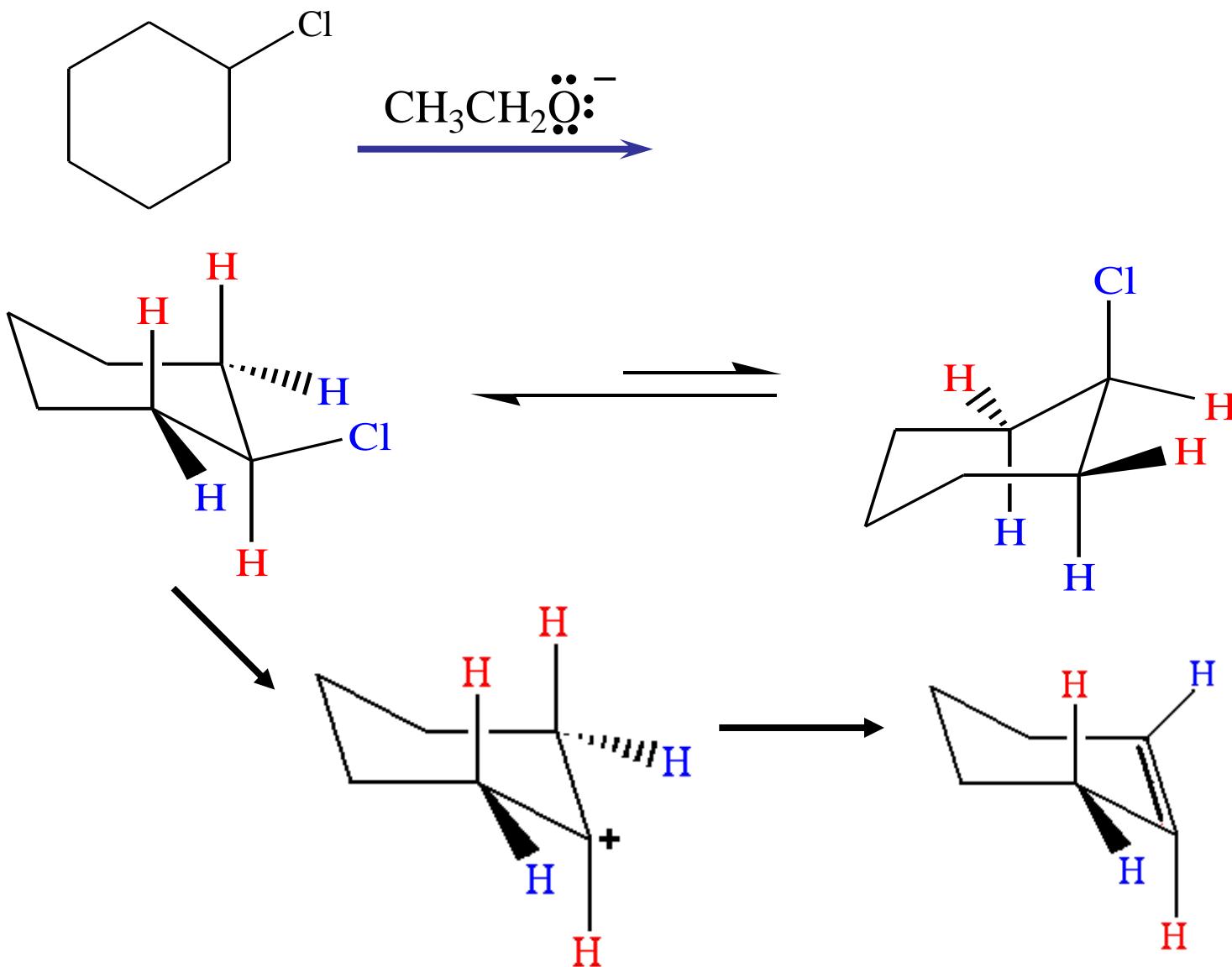
relative reactivities of alkyl halides in an E1 reaction = relative stabilities of carbocations

3° benzylic \approx 3° allylic $>$ 2° benzylic \approx 2° allylic \approx 3° $>$ 1° benzylic \approx 1° allylic \approx 2° $>$ 1° $>$ vinyl

most stable

least stable

E1 reactions of substituted cyclohexanes



COMPARISON OF β -ELIMINATION MECHANISMS

alkyl halides				alcohols
E2	E1	E1	E1 acid assisted	
strong base	weak base	neutral	acidic	
concerted	stepwise - carbocation			
Primary alkyl halides Secondary alkyl halides stereospecific anti-periplanar Aprotic polar solvent Zaitsev if stereochem allows	“solvolytic” tertiary alkyl halides			
not stereospecific				
protic polar solvent	Zaitsev	Zaitsev	Zaitsev	
carbocation rearrangements				

ALKYL HALIDE + BASE

strong base
high base conc.

weak base
low base conc.

or

solvolytic

(solvent is base)

E2 mechanism

anti-periplanar
requirement

stereospecific

regioselective

E1 mechanism

must be able to make
“good” carbocation

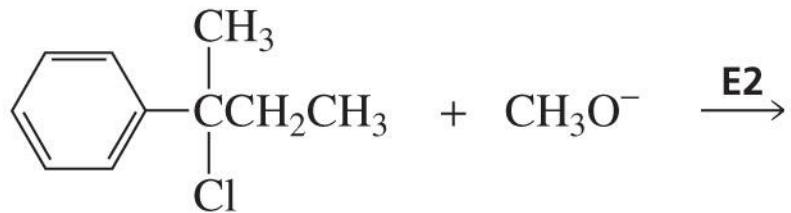
not stereospecific

regioselective

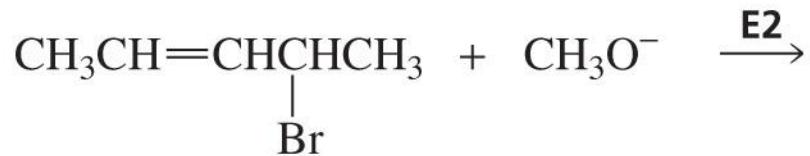
Table 9.4 Stereochemistry of Substitution and Elimination Reactions

Reaction	Products
S _N 1	Both stereoisomers (<i>R</i> and <i>S</i>) are formed (more inverted than retained).
E1	Both <i>E</i> and <i>Z</i> stereoisomers are formed (more of the stereoisomer with the bulkiest groups on opposite sides of the double bond).
S _N 2	Only the inverted product is formed.
E2	Both <i>E</i> and <i>Z</i> stereoisomers are formed (more of the stereoisomer with the bulkiest groups on opposite sides of the double bond) unless the β -carbon of the reactant is bonded to only one hydrogen, in which case only one stereoisomer is formed; its configuration depends on the configuration of the reactant.

Benzyllic and Allylic Halides Undergo E2 Reactions

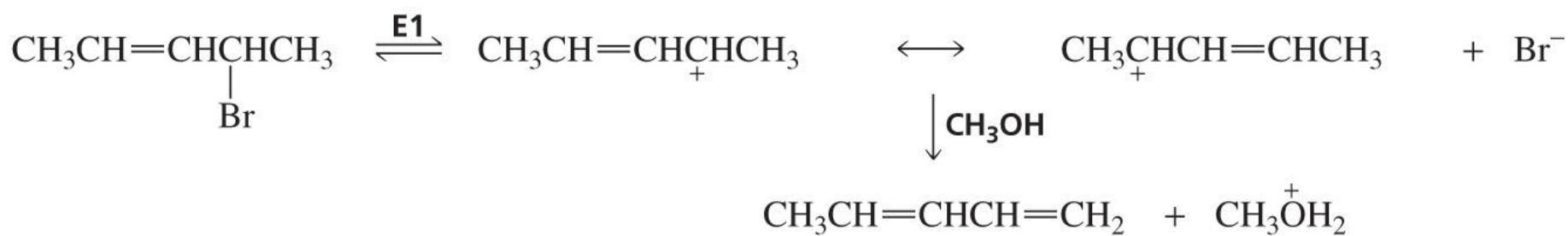
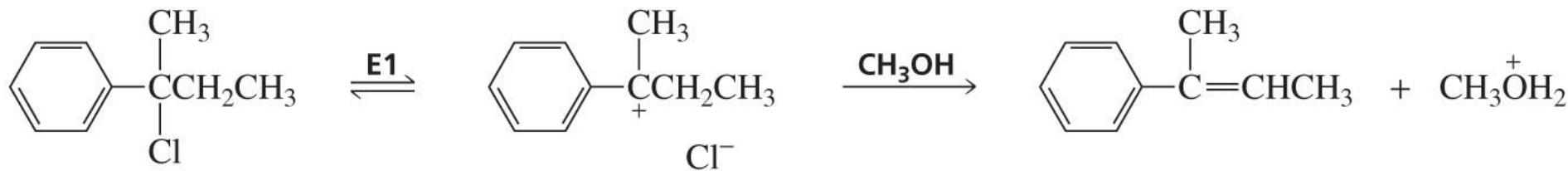


2-chloro-2-phenylbutane

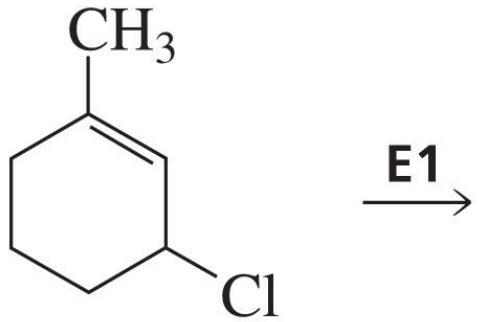


4-bromo-2-pentene

Benzyllic and Allylic Halides Undergo E1 Reactions



The E1 Reaction of Allylic Halides Can Form Two Products



Competition Between Substitution and Elimination

Alkyl halides can undergo S_N2 , S_N1 , $E2$, and $E1$

1) decide whether the reaction conditions favor $S_N2/E2$ or $S_N1/E1$

- $S_N2/E2$ reactions are favored by a high concentration of a good nucleophile/strong base

- $S_N1/E1$ reactions are favored by a poor nucleophile/weak base

2) decide how much of the product will be the substitution product and how much of the product will be the elimination product

Consider the S_N2/E2 conditions

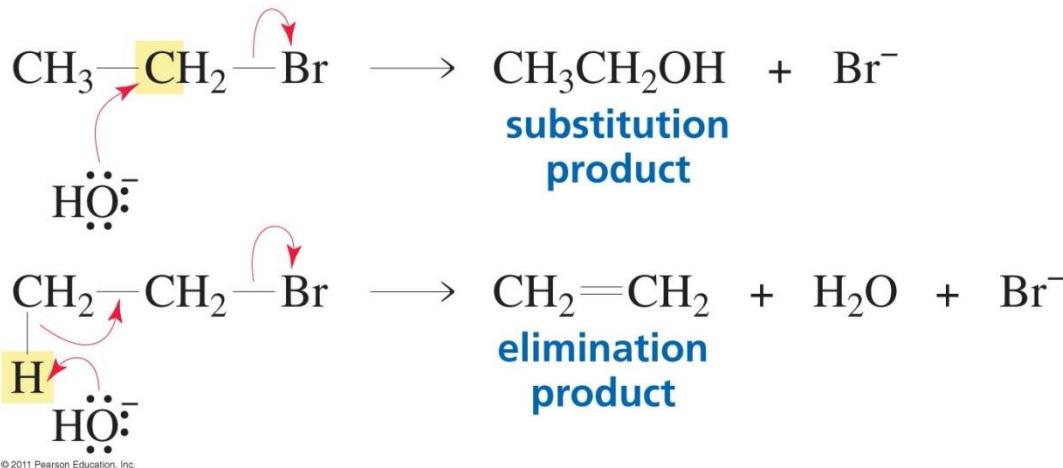
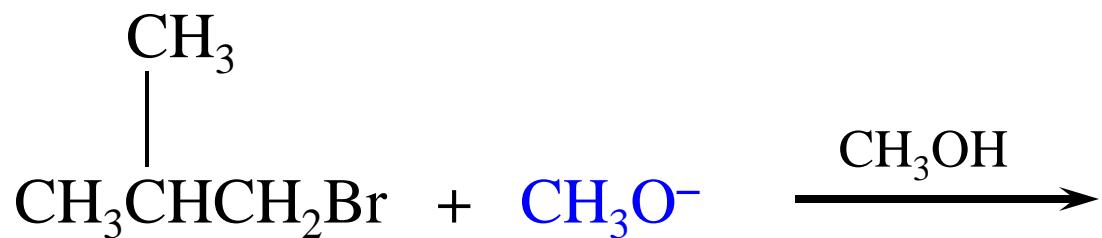


Table 9.5 Relative Reactivities of Alkyl Halides

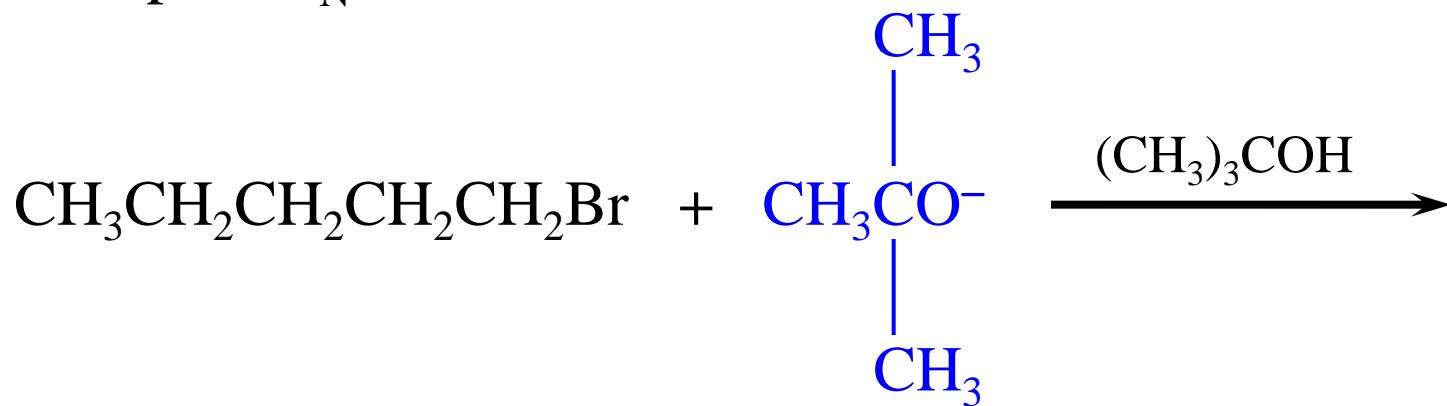
In an S_N2 reaction: $1^\circ > 2^\circ > 3^\circ$

In an E2 reaction: $3^\circ > 2^\circ > 1^\circ$

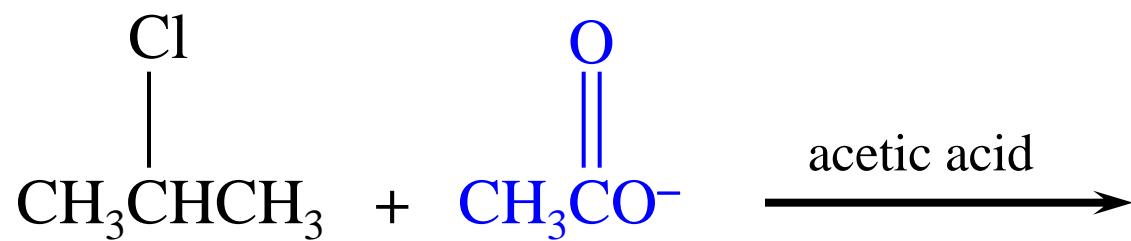
Examples: S_N2 vs E2



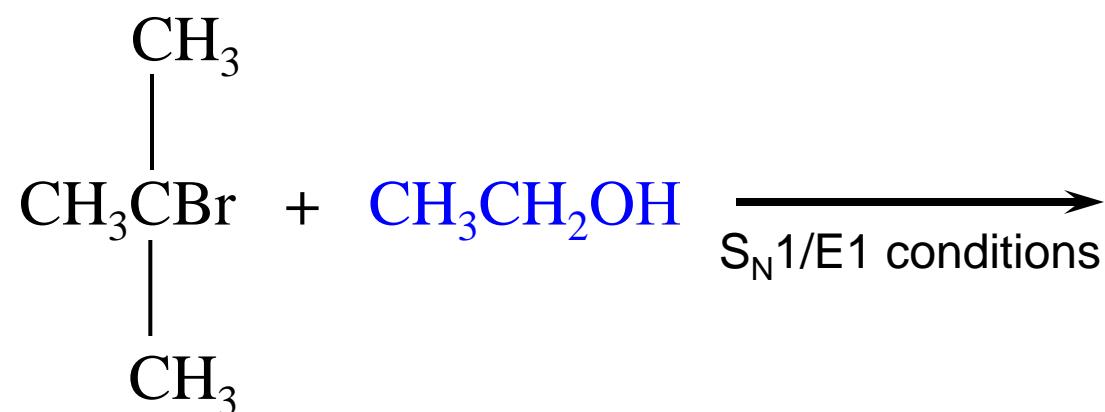
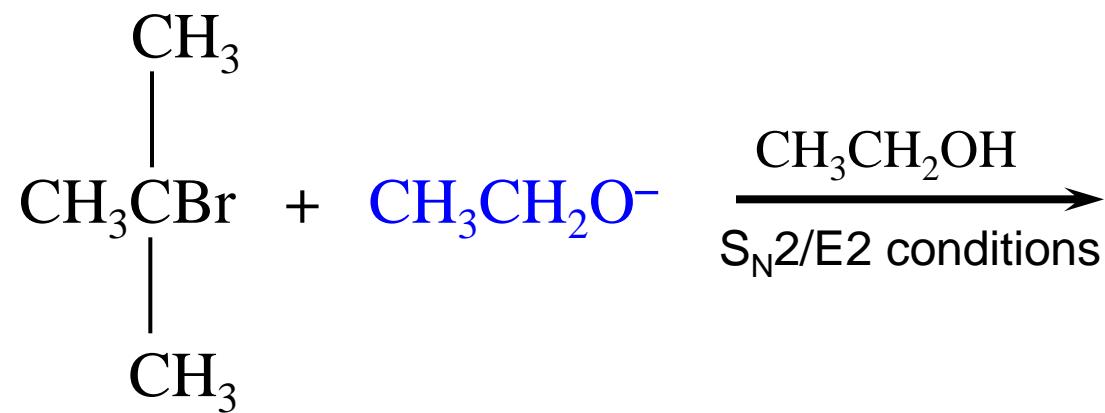
Examples: S_N2 vs E2



Examples:



Examples:



Synthesizing *tert*-Butyl Ethyl Ether

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

Synthesizing an Alkene

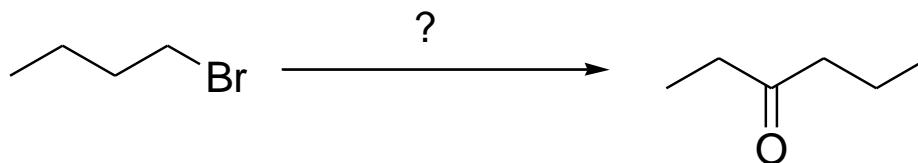
The **more hindered** group should be provided by the **alkyl halide**.

If the reactant is a tertiary alkyl halide,
use **$S_N2/E2$** conditions because it gives **only elimination**.

Converting an Alkene to an Alkyne

Retrosynthetic Analysis

Example:



Key Concepts_Substitution

- **Nucleophilic substitution reactions:** S_N1 and S_N2 . nucleophile substitutes for a halogen in alkyl halide
- **S_N2 :** bimolecular, one-step mechanism, two molecules in transition state of RDS, rate depends on concentration of alkyl halide and nucleophile, inversion of configuration for asymmetric reactants; favored by high concentration of strong nucleophile in aprotic polar solvent
- **S_N1 :** unimolecular, two step mechanism, one molecule in transition state of RDS, rate depends on concentration of alkyl halide, carbocation rearrangements can occur, racemization for asymmetric reactants, in most cases solvent is nucleophile (**solvolysis**); favored by poor nucleophile in protic polar solvent
- **Protic solvent:** hydrogen bond donors (water, alcohols, acetic acid)
- **Aprotic solvent:** NOT hydrogen bond donors (DMF, DMSO, acetonitrile, HMPA, acetone, THF, DCM, benzene, hexanes, ethyl acetate)
- Rate of reactions affected by leaving group ability: the **weaker the base, the better the leaving group**
- **Methyl halides and primary alkyl halides:** only S_N2 reaction
- **Tertiary alkyl halides:** S_N1 reaction
- **Vinylic and aryl halides:** neither S_N2 or S_N1
- **Secondary alkyl, benzylic and allylic halides:** both S_N1 and S_N2
- If reactants in the RDS are charged: **increasing solvent polarity = decrease rate of reaction**
- If reactants in the RDS are neutral: **increasing solvent polarity = increase rate of reaction**

Key Concepts_Elimination

- **Elimination reactions:** removal of HX from adjacent carbons of alkyl halide to produce alkenes; the double bond is formed between the two carbons from which the proton and halide ion were eliminated. This is called “**dehydrohalogenation**”.
- **E1** and **E2** known as “ **β -elimination reactions**”.
- **E2:** concerted, one-step, no intermediate and only one T.S.; **regioselective** -major product is most stable alkene (more substituted alkene) - and **stereoselective** - “anti” elimination favored; major alkene has bulkiest groups on opposite sides of double bond; if β -carbon has two hydrogens, both E and Z products are formed; if only one hydrogen, only one alkene formed; two groups eliminated from substituted cyclohexane must be in diaxial position
- **E1:** two step rxn, one carbocation intermediate from dissociation of alkyl halide; two T.S.; base removes proton from carbon adjacent to positively charged carbon in intermediate; carbocation can rearrange to more stable cation; **regioselective** - major product is most stable alkene (more substituted alkene) - and **stereoselective** – major alkene has bulkiest groups on opposite sides of double bond; carbocation can do both syn and anti elimination; two groups eliminated from substituted cyclohexane DO NOT have to be in diaxial position
- 1° alkyl halides: only E2 elimination (no E1)
- 2° and 3° alkyl halides: both E1 and E2
- E2 favored by same conditions as S_N2 reaction (strong base, aprotic polar solvent)
- E1 favored by same conditions as S_N1 reaction (weak base, protic polar solvent)
- **Williamson ether synthesis:** reaction of alkyl halide with alkoxide ion
- Consecutive E2 eliminations can form conjugated dienes or triple bond