

## Chapter 7: Haloalkanes

### 7.1. Alkyl Halides

- C(sp<sup>3</sup>)-X
- Polar covalent bonds

C-X	$\Delta E_N$
C-F	1.5
C-Cl	0.5
C-Br	0.3
C-I	0.0

- Methyl halides, primary, secondary and tertiary alkyl halides

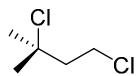
- Me-X bond strengths and bond lengths

Me-X	C-X bond strength [kJmol <sup>-1</sup> ]	C-X bond length
Me-F		
Me-Cl		
Me-Br		
Me-I		

7.1

### 7.2 Nomenclature of Haloalkanes

1. Find the longest chain
2. Number the carbons beginning at the end nearest the first substituent –R and –X have the same naming priority
3. Assign R/S, E/Z, cis/trans where applicable
4. Write the name



#### Common names

CH <sub>2</sub> Cl <sub>2</sub> Dichloromethane (Methylene chloride)	CHCl <sub>3</sub> Trichloromethane (Chloroform)	CCl <sub>4</sub> Tetrachloromethane (Carbon tetrachloride)	CH <sub>2</sub> =CHCl Chloroethene (Vinyl chloride)
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### 7.3. Nucleophilic Substitution Reactions and $\beta$ -Elimination Reactions

**General nucleophilic substitution reaction:**

General nucleophilic substitution reaction:

**Nucleophile:** The nucleophile is always a Lewis base (electron pair donor).

**Leaving Group:** The leaving group is replaced by the incoming nucleophile. When it leaves the substrate, it always takes the electron pair of the broken bond with it.

**Substrate (here R-X):** The electrophile (for example, an alkyl halide) which carries the leaving group and is attacked by the nucleophile.

There are two possible mechanisms for nucleophilic substitution reactions:

**The  $S_N2$  Reaction**

**The  $S_N1$  Reaction**

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**General  $\beta$ -elimination reactions:**

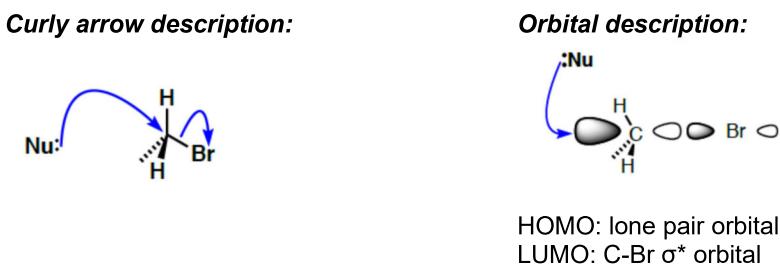
Since all nucleophiles are bases,  $\beta$ -elimination reactions are competing with nucleophilic substitution reactions.

Again, there are two possible mechanisms for  $\beta$ -elimination reactions, the *E1 reaction* and the *E2 reaction* which will be described in more detail later (Chapter 7.10 and 7.11, respectively).

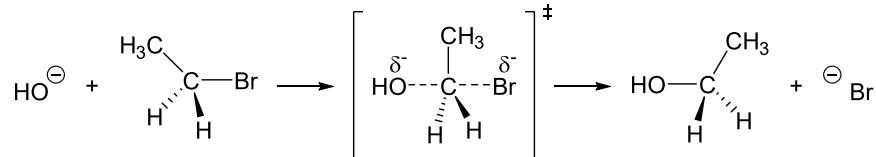
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### 7.4. The S<sub>N</sub>2 Reaction

The reaction starts with a nucleophilic attack on a saturated alkyl halide



**Mechanism:** The S<sub>N</sub>2 reaction is *concerted* (occurs in one step).



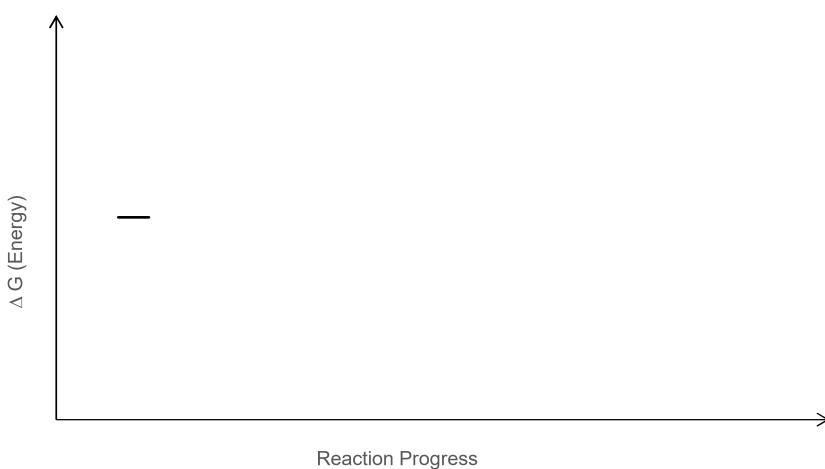
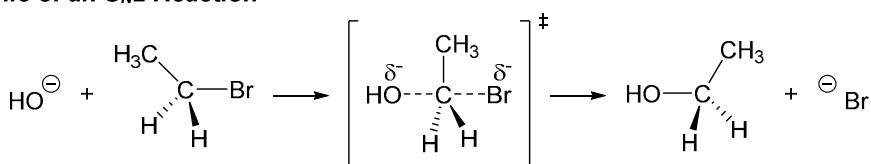
S<sub>N</sub>2 Reaction: Nucleophilic substitution *bimolecular/second order*

The rate determining step is *product formation* and *rate of reaction* depends on both the concentration of the substrate and the concentration of the nucleophile as can be seen from the rate equation:

**Rate equation:**

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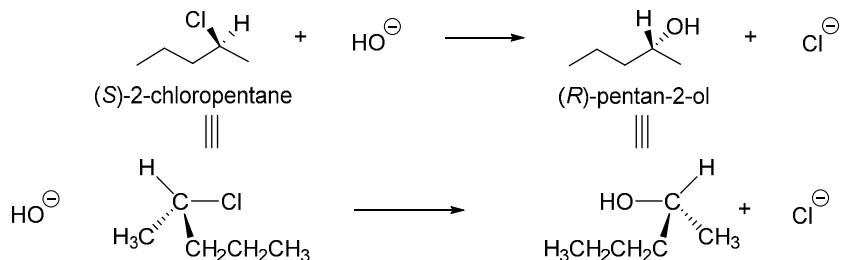
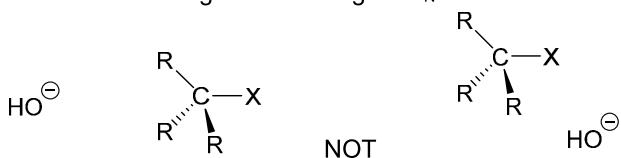
### **Energy Profile of an S<sub>N</sub>2 Reaction**



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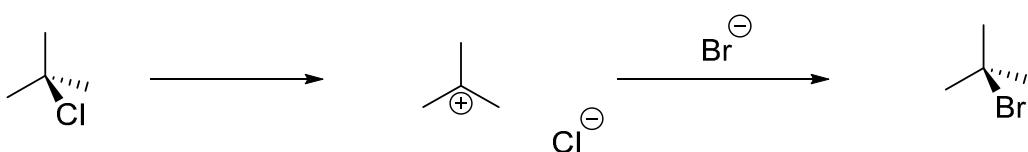
**Stereochemistry of S<sub>N</sub>2 Reaction:**

Backside attack leads to inversion of configuration during an S<sub>N</sub>2 reaction.

**7.5. The S<sub>N</sub>1 Reaction**

The S<sub>N</sub>1 reaction occurs in two steps: First the leaving group is lost thereby creating a carbocation intermediate which reacts rapidly in a second step with the nucleophile.

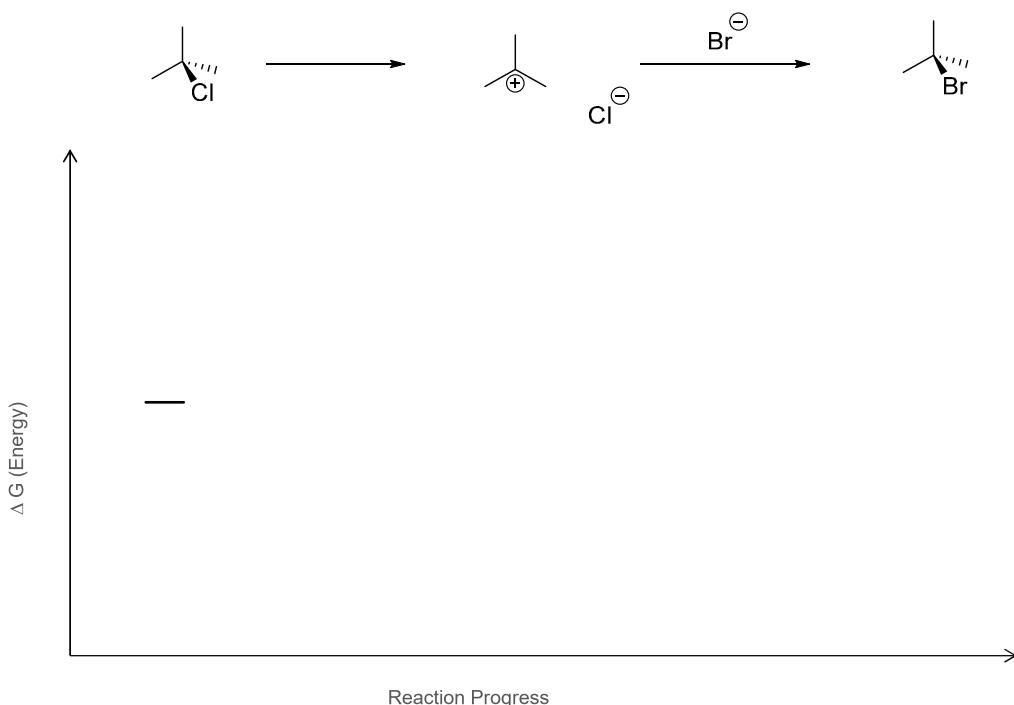
**Mechanism:** reaction occurs in 2 steps



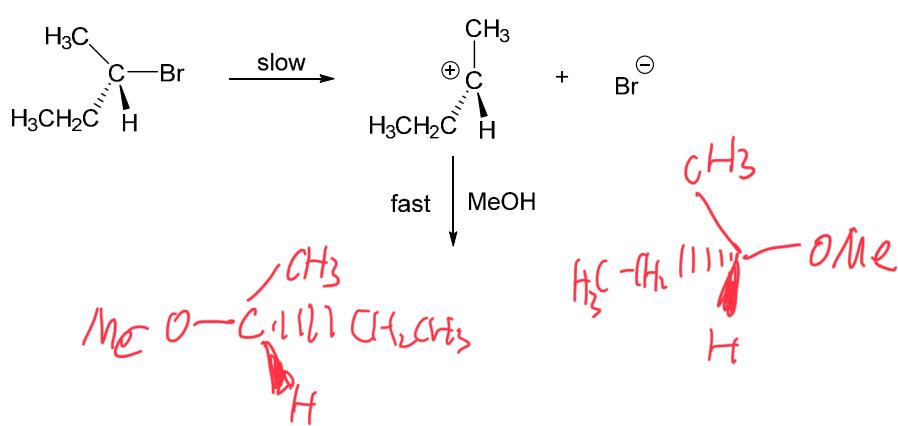
S<sub>N</sub>1 Reaction: Nucleophilic substitution *unimolecular/first order*

The rate determining step is *the formation of the carbocation (reactive intermediate)* and the *rate of reaction depends **only** on the concentration of the substrate*:

**Rate Equation:**

**Energy Profile of an S<sub>N</sub>1 Reaction****Stereochemistry:**

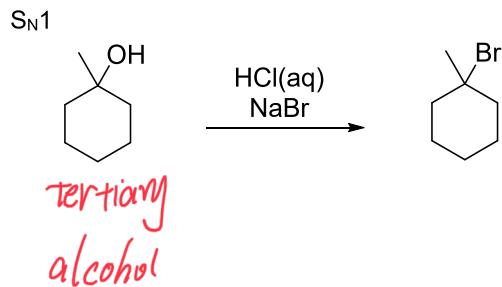
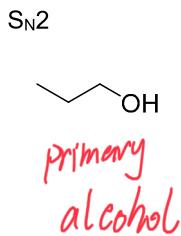
Due to the formation of the carbocation intermediate, the product of an  $S_N1$  reaction on a chiral alkyl halide is generally obtained as a racemic mixture.



## 7.6 Factors Affecting the Rates of S<sub>N</sub>1 and S<sub>N</sub>2 Reactions

### S<sub>N</sub>1 or S<sub>N</sub>2 Mechanism?

In each case, an OH group is converted to a Br, but the mechanism by which the reaction takes place is not the same.



The main factors that influence this fundamental difference in mechanism are:

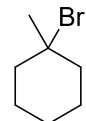
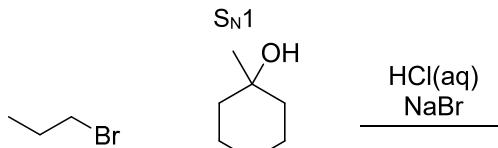
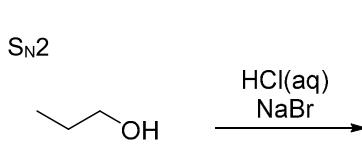
1. Substrate structure
2. Nucleophile
3. Leaving Group
4. Solvent

7.11

### a) Substrate Structure

Differences in substrate structure which determine the outcome of reaction and might favor one mechanism over the other:

- a) **Steric hindrance:** ease of nucleophile approach and transition state formation  
(Reaction on previous page)



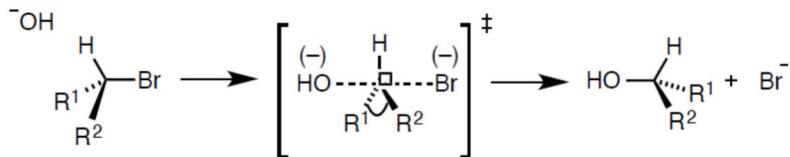
- b) **Factors that influence carbocation stability (in S<sub>N</sub>1 reactions):** hyperconjugation, π-bond and lone pair donation

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**Steric Hindrance ( $S_N2$ )**

$S_N2$  reactions become less likely the more substituents the attacked carbon has: increased steric hindrance makes the approach of the nucleophile more difficult.

Transition state: 5-coordinate, trigonal bipyramidal structure



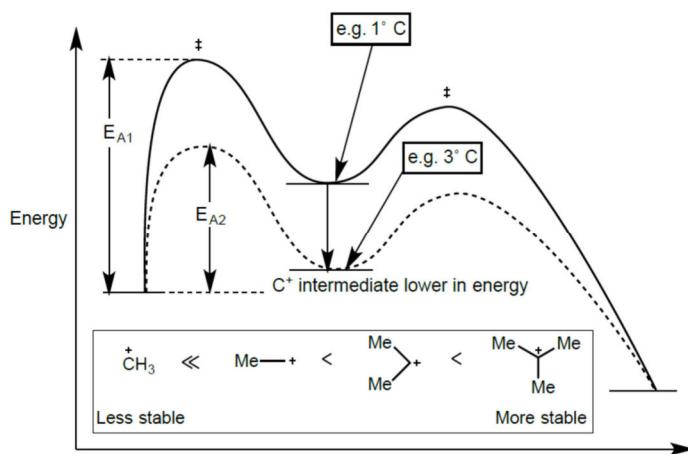
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**Carbocation Stability ( $S_N1$ )**

Carbocation: planar ( $sp^2$  hybridized), **not** tetrahedral ( $sp^3$  hybridized)!



The more substituted carbocations are, the more stable they are and the more likely it is that they will form.



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**Summary of S<sub>N</sub>1 versus S<sub>N</sub>2 based on Substrate Structure**

<b>Substrate:</b>	Me—X			
<b>Substrate Type:</b>	Me	1°	2°	3°
<b>S<sub>N</sub>1 Mechanism:</b>	Bad	Bad	Poor	Excellent
<b>S<sub>N</sub>2 Mechanism:</b>	Excellent	Good	Poor	Bad

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**b) Nature of Nucleophile**

S<sub>N</sub>1 reaction: the nucleophile is **not** important because the rate determining step (RDS) is the loss of the leaving group:

S<sub>N</sub>2 reaction: the nucleophile is **very** important because the RDS is bimolecular and involves the nucleophilic attack on the saturated carbon. *The better the nucleophile or/and the higher its concentration, the faster the reaction.*

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**Role of Nucleophile in S<sub>N</sub>2 Reactions**

For a range of nucleophiles involved in S<sub>N</sub>2 reactions where the atom forming the new bond *is the same*, **nucleophilicity correlates well with basicity**.

In this case, anions of weak acids are the best nucleophiles.

Oxyanion Nucleophile:	OH <sup>-</sup>	PhO <sup>-</sup>	AcO <sup>-</sup>	TsO <sup>-</sup>
Conjugate Acid:	H <sub>2</sub> O	PhOH	AcOH	TsOH
Approximate pK <sub>a</sub> :	16	10	5	0

If the atoms of a range of nucleophiles involved in S<sub>N</sub>2 reactions are *not the same*, **nucleophilicity often does not correlate with basicity**.

- The nucleophilicity will increase down a group in the periodic table:

Example: MeBr + X<sup>-</sup>

Nucleophile X	Conjugate acid HX	Approximate pK <sub>a</sub> of HX	Relative Rate
PhS <sup>-</sup>	PhSH	6.4	5.0 x 10 <sup>7</sup>
PhO <sup>-</sup>	PhOH	10.0	2.0 x 10 <sup>3</sup>

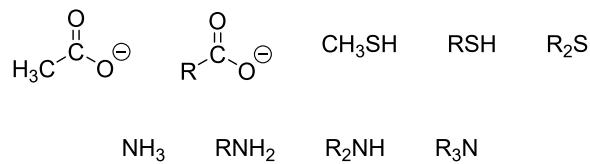
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Examples of nucleophiles:

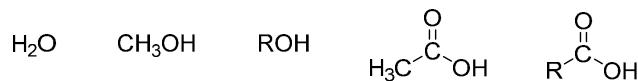
Good nucleophiles:



Moderate nucleophiles:



Poor nucleophiles:



S<sub>N</sub>2 – Good nucleophiles displace leaving group faster

S<sub>N</sub>1 – good, moderate, and poor nucleophiles all will work

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**c) Nature of Leaving Group**

The leaving group is important for both S<sub>N</sub>1 and S<sub>N</sub>2 reactions; departure of the leaving group is involved in the RDS of both mechanisms.

**a) Halides (F, Cl, Br, I) as leaving group**

- Overall, due to the decrease in C-X bond strength and greater anion stability, I<sup>-</sup> is the best leaving group and F<sup>-</sup> is a poor leaving with Br<sup>-</sup> and Cl<sup>-</sup> in between.
- Note: I<sup>-</sup> is both the best nucleophile but also the best leaving group!

**b) OH derivatives**

This reaction rarely happens:

Normally the nucleophile is basic enough and instead will simply deprotonate the alcohol instead:

OH<sup>-</sup> is normally **not** a leaving group in S<sub>N</sub>1 or S<sub>N</sub>2 reactions but it can easily be converted to an excellent leaving group.

Two possible way to convert OH to a good leaving group:

- Protonation*
- Sulfonate ester formation*

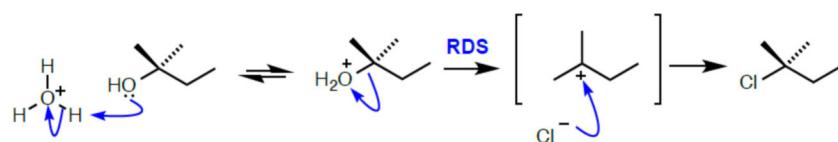
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**Protonation**

Protonation activates OH for both S<sub>N</sub>1 and S<sub>N</sub>2 reactions



Important: Protonation occurs fast and *before the RDS* (which for the S<sub>N</sub>1 reaction is the loss of water):

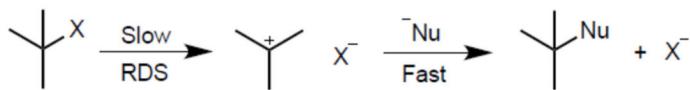


- Bad leaving group OH<sup>-</sup> with pK<sub>aH</sub> = 15.7 (H<sub>2</sub>O) is converted to a good leaving group pK<sub>aH</sub> = -1.7 (H<sub>3</sub>O<sup>+</sup>)
- The reaction would **not** work without acid; Cl<sup>-</sup> is a fairly bad nucleophile.

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**d) Solvent**

**S<sub>N</sub>1 reaction:** best in *polar, protic solvents* (e.g. water, methanol, acidic acid)

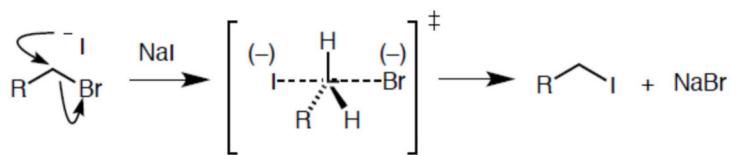


Polar protic solvents stabilize both the carbocation **and** the leaving group:

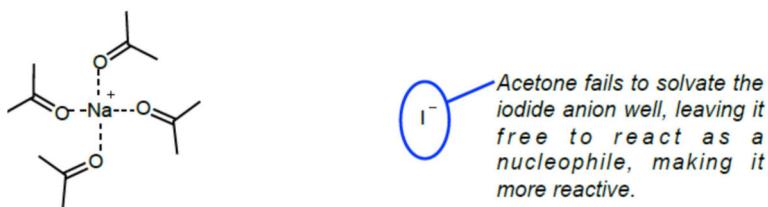


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**S<sub>N</sub>2 reaction:** best in *polar, aprotic solvents* (e.g. acetone, DMSO, DMF)



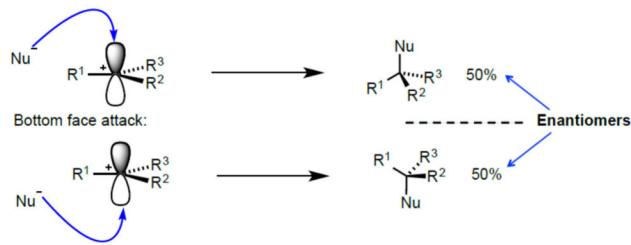
- No ions are formed in the  $S_N2$  reaction
- While cations are well solvated in polar, aprotic solvents, anions cannot interact with most polar, aprotic solvents
- Aprotic solvents increase the reactivity of the nucleophile



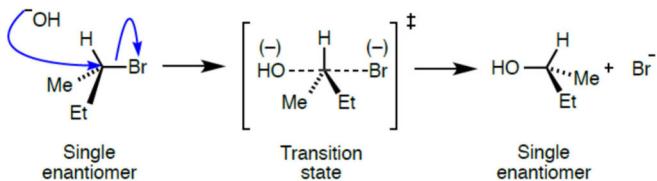
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## 7.7. Stereochemical consequences of the S<sub>N</sub>1 and S<sub>N</sub>2 reaction processes

S<sub>N</sub>1 Reaction: Normally results in a racemic mixture



S<sub>N</sub>2 Reaction: Inversion of configuration, single enantiomer

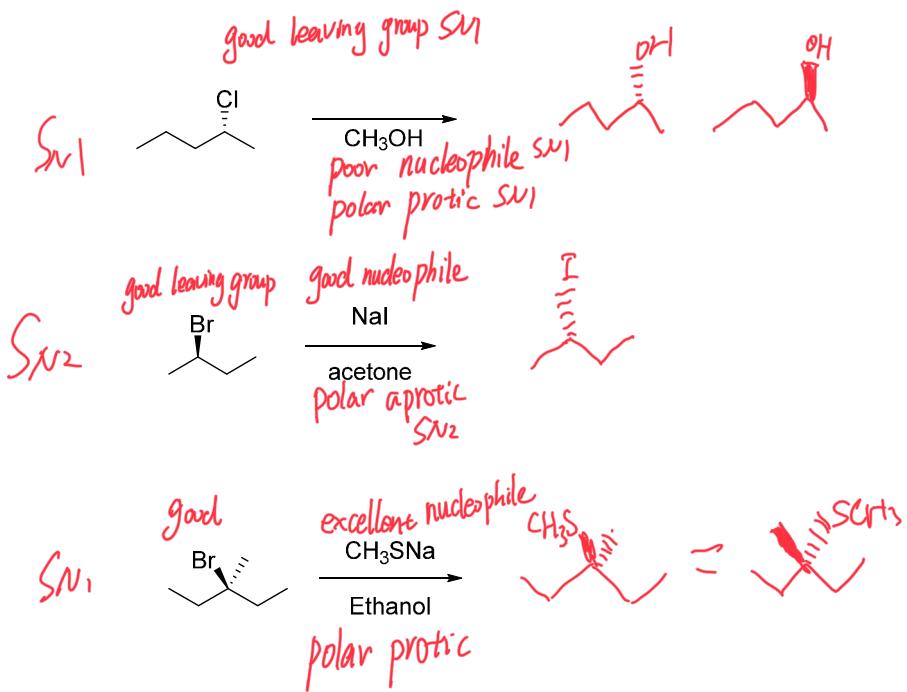


The S<sub>N</sub>2 reaction is an example of a *stereospecific reaction* (i.e. a reaction where the mechanism determines the stereochemical outcome). The reaction **must** give a single enantiomer if the reaction proceeds purely by a S<sub>N</sub>2 pathway.

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### Exercise:

Are these reactions S<sub>N</sub>1 or S<sub>N</sub>2 and what are the products?

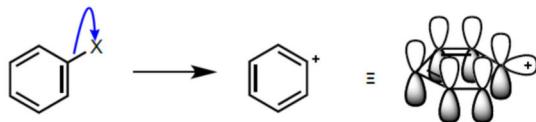


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## 7.8 Vinyl and Phenyl Halides

**The importance of hybridization state:** no S<sub>N</sub>1 or S<sub>N</sub>2 at sp<sup>2</sup> centers

No S<sub>N</sub>1 because no charge stabilization of carbocation possible:



No S<sub>N</sub>2 for many reasons, e.g. with aromatic rings:

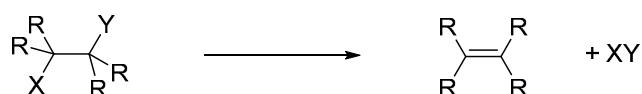
1. Approach of nucleophile repelled by electron density in double bonds.	2. Approach of nucleophile into $\sigma^*$ blocked by rest of aromatic ring.	3. Inversion of centre attacked is impossible.

7.25

## 7.9. Elimination Reactions as Competing Reactions to S<sub>N</sub>1 and S<sub>N</sub>2

Elimination reactions are the most important way for synthesizing alkenes.

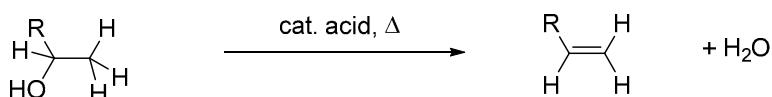
General Scheme:



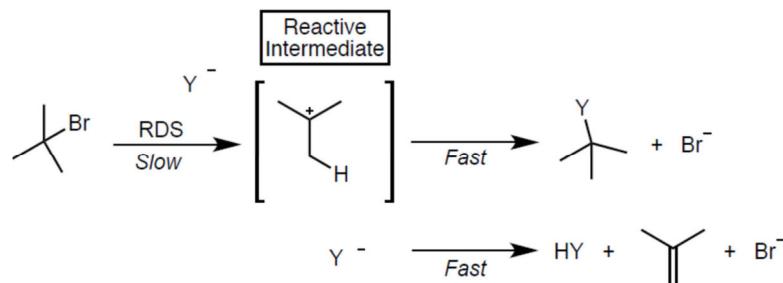
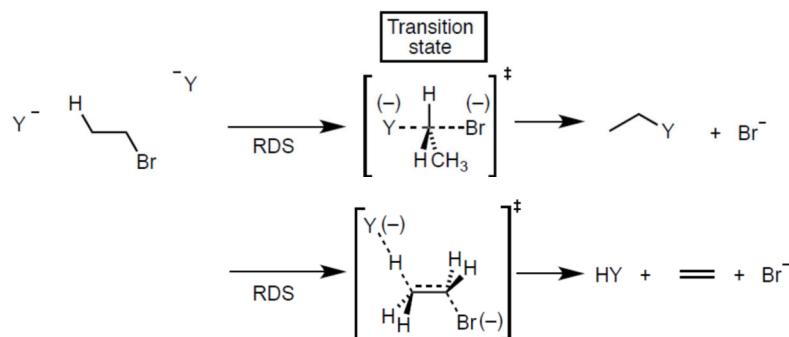
Dehydrohalogenation of alkyl halides:



Dehydration of alcohols:



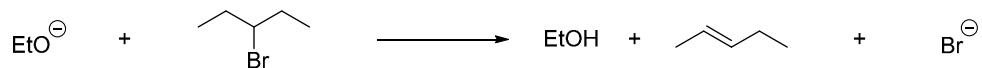
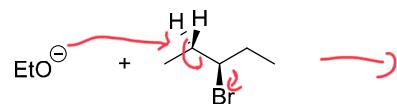
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**E1 Mechanism (versus S<sub>N</sub>1 Reaction):****E2 Mechanism (versus S<sub>N</sub>2 Reaction):**

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**7.10. The E2 Reaction**

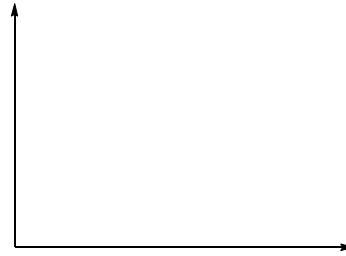
The E2 reaction occurs in one step with the base removing the proton from the  $\beta$ -carbon as the double bond forms and the leaving group leaves from the  $\alpha$ -carbon.

**Mechanism:****Rate Law and Rate Equation:**

- bimolecular reaction
- 2<sup>nd</sup> order kinetics

Since the E2 reaction occurs in a concerted fashion, the *rate of reaction* depends on both the concentration of the substrate (alkyl halide) and the base:

$$\text{Rate} =$$

**Energy Profile of an E2 Reaction**

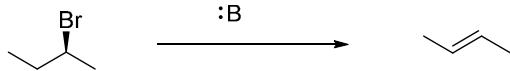
**Regioselectivity in E2 Reactions:**

The regioselectivity of the E2 reaction depends on the size of the base.

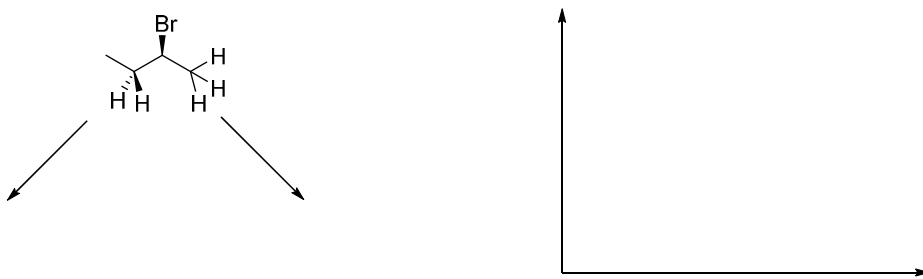
**a) small base**

- Examples of small, strong bases:

- Formation of the more substituted alkene



- More stable product but also lower transition state:



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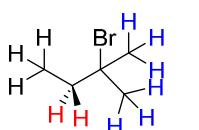
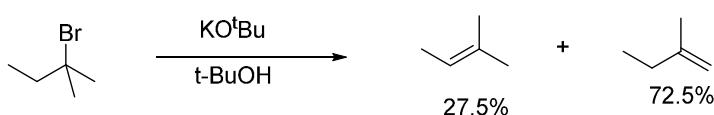
**Regioselectivity in E2 Reactions:**

The regioselectivity of the E2 reaction depends on the size of the base.

**b) bulky base**

- Examples of strong bulky bases:

- Less substituted alkene is formed faster

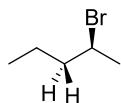


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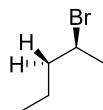
**Stereochemistry of E2 Reactions:**

The E2 reaction is a stereospecific reaction and the stereochemical outcome depends on the structure of the starting material.

a) Anti-Elimination preferred

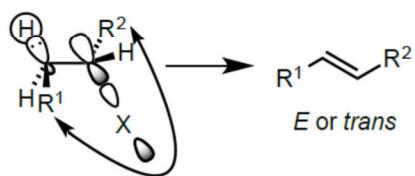


*Syn-Elimination unfavorable*

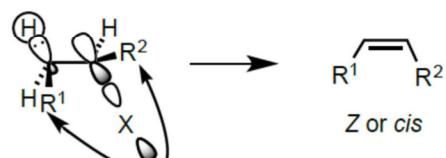


b) Starting material determines outcome:

$R^1$  and  $R^2$  fixed on opposite sides in correct elimination arrangement and in the product:



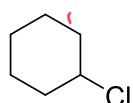
$R^1$  and  $R^2$  fixed on the same side in correct elimination arrangement and in the product:



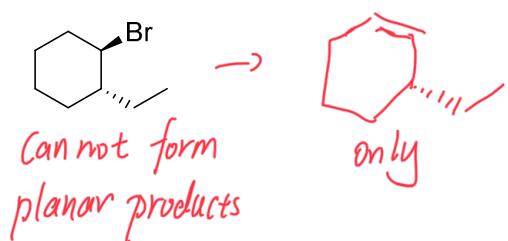
7.31

**E2 Reactions on substituted cyclohexanes**

The leaving group must adopt an axial position for anti-elimination to occur.



Exercise: Which is the major (and minor) elimination product of the following two diastereomers if a small base is used?



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### 7.11. The E1 Reaction

The E1 reaction occurs in two steps: First the leaving group is lost thereby creating a carbocation intermediate. The loss of the proton in the second step is fast.



**Mechanism:**



E1 reactions almost always accompany S<sub>N</sub>1 reactions.

**Rate Law and Rate Equation:**

- unimolecular reaction
- first order kinetics

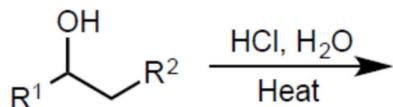
**Rate =**  
**Energy Profile of an E1 Reaction**

The rate determining step is *the formation of the carbocation (reactive intermediate)* and the *rate of reaction depends only* on the concentration of the substrate:

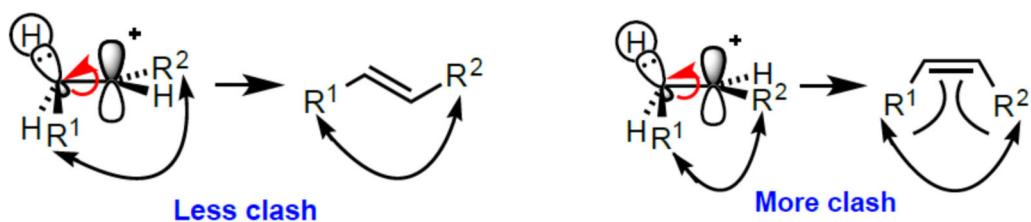
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**Stereochemistry of E1:**



With secondary substrates E1 Elimination normally gives the *trans*-isomer as major product and the *cis*-isomer as minor product.



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**7.12 Comparison of E1 and E2 Reactions****a) Substrate Structure**

Electrophile:						
Substrate Type	1°	2°	3°	α-alkoxy	Allylic	Benzyllic
E1 Mechanism:	No	OK	Good	Good	Good	Good
E2 Mechanism:	Good	OK	Also possible	Also possible	Also possible	Also possible

Tertiary substrates: Elimination mechanism for tertiary substrates can be either E1 (with weak bases) or E2 (with strong bases). The outcome is the same with tertiary structures!

Substrates that cannot undergo elimination:

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**b) Leaving Group**

The leaving group ability for E1 and E2 is the same as in nucleophilic substitutions.

Leaving Group:	Halide (Usually Br <sup>-</sup> /I <sup>-</sup> )	OH <sup>-</sup>	OH <sub>2</sub> <sup>+</sup>	TsO <sup>-</sup>	NR <sub>3</sub> <sup>+</sup>
E1 Mechanism:	Good	Never	Good (OH under acidic conditions)	Good	Good
E2 Mechanism:	Good	Never	Never (E2 always carried out under basic conditions)	Good (convert OH to OTs for successful E2)	Good

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**7.13 Substitution or Elimination?****a) Substrate Structure**

Typical S<sub>N</sub>1 reaction substrates can also work well in E1 (and often E2) elimination; those which work well in S<sub>N</sub>2 reactions are good for E2 (and sometimes E1) elimination.

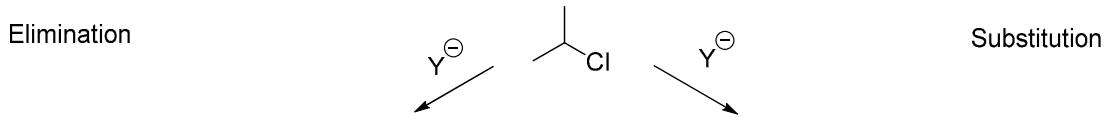
*Substrates that cannot undergo elimination:*

- molecules that do not have a β-hydrogen
- compounds that cannot become planar
- compounds that have a β-hydrogen but are unable to adopt an anti-periplanar conformation

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**b) Basicity of the Nucleophile**

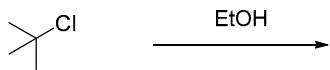
Strong bases give mainly elimination, weak bases result in substitution:



In terms of relating basicity to *overall* reaction pathway taken,  $\text{pK}_{\text{aH}}$  values are once again important.

### ***Change of reaction outcome depending on base strength:***

Treating *tert*-butyl chloride with EtOH or EtO<sup>-</sup>: The outcome of the reaction (substitution versus elimination) can be predicted using base strength alone.



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### c) Size of the Nucleophile

Basic and bulky nucleophiles prefer elimination over substitution.

- If  $Y^-$  is small: Substitution dominates for **1° substrates**:
  - If  $Y^-$  is large (e.g. KOtBu as base): Elimination generally preferred, even for 1° substrates:

**d) Temperature**

Higher temperatures favor elimination over substitution.

Elimination



Substitution

The fundamental reason for this lies in **entropy**: because two molecules become three in elimination and two molecules form two in substitution,  $\Delta S$  is greater for elimination than for substitution.

Remember:

The reaction is favorable if the free energy  $\Delta G$  is negative.



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**7.14 Summary: Elimination versus Substitution**

Nucleophile/Base Type →		Poor e.g. H <sub>2</sub> O, ROH	Weakly basic e.g. I <sup>-</sup> , RS <sup>-</sup>	Strongly basic unhindered e.g. EtO <sup>-</sup>	Strongly basic hindered e.g. 'BuO <sup>-</sup>
Substrate Structure ↓					
Methyl	Me—X	No reaction	S <sub>N</sub> 2	S <sub>N</sub> 2	S <sub>N</sub> 2
Primary (unhindered)		No reaction	S <sub>N</sub> 2	S <sub>N</sub> 2	E2
Primary (hindered)		No reaction	S <sub>N</sub> 2	E2	E2
Secondary		S <sub>N</sub> 1, E1 (slow)	S <sub>N</sub> 2	E2	E2
Tertiary		S <sub>N</sub> 1 or E1	S <sub>N</sub> 1 or E1	E2	E2

**7.15 Practice Examples: What are the products of these reactions?**