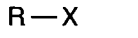
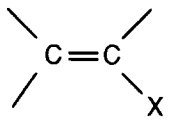
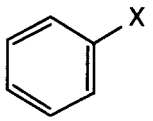
CHAPTER 6: Alky Halides: Nucleophilic Substitution and Elimination
(No sections omitted)

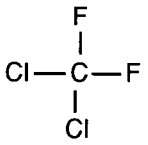
Types of Organohalogen Compounds:

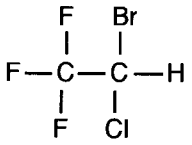






Common Uses: section 3





DDT

Nomenclature: No new rules, halogen has no priority. For name as substituent, drop "ide" add "o". Example: chloride becomes chloro

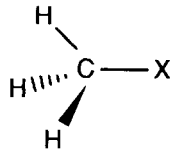
new terms: vicinal dihalide - two halogens on adjacent carbons

geminal dihalide- two halogens on the same carbon

Structure:

1°/ 2°/ 3° determined by the type of carbon the halogen is bonded to

Example - In a 1° halide, the halide is bonded to a 1° carbon atom.



Physical Properties:

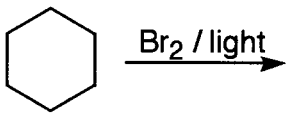
types of intermolecular attractions:

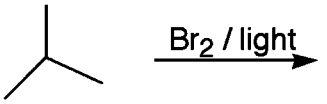
1.

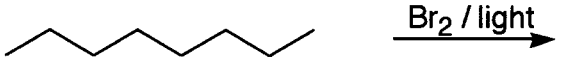
2.

Preparation:

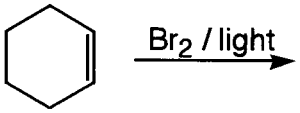
1. Free radical halogenation: (Caution - mixtures of products) Best results when a single major product is produced. Remember:bromine is more selective than chlorine.



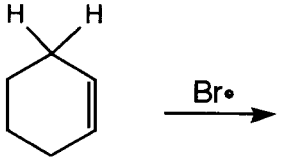




2. Allylic brominaton:

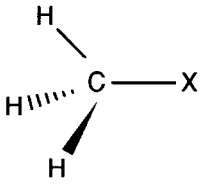


Reason for selectivity: Consider first step of propagation

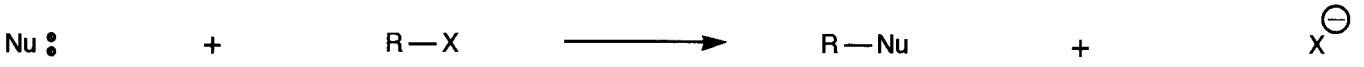


Better reagent:

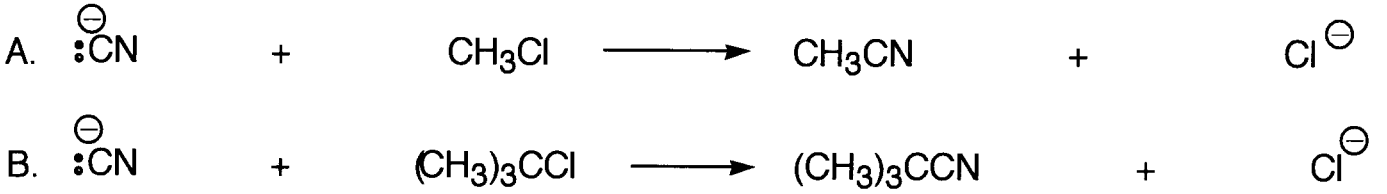
Nucleophilic Substitution Reactions



General Reaction:



Two specific reactons:



Both reactions are nucleophilic substitution reactions, but **A** and **B** proceed through different mechanisms. Before proposing a mechanism for each, we consider two kinds of experimental evidence:

1. The kinetics of the reaction. - Examine rate changes in relation to changes in the concentrations of the reactants.

2. The stereochemistry of the products.

Reaction A

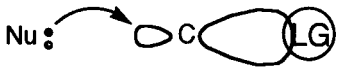
1. Kinetics: Observations - if conc. of Nu is doubled -

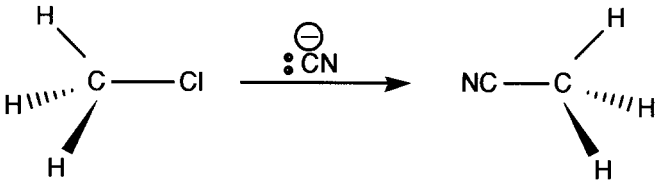
if conc. of substrate is doubled -

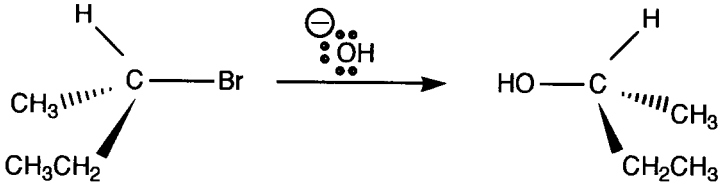
rate =

The Mechanism:

2. Stereochemistry: Nucleophile (Nu) begins to form bond to electrophilic carbon while leaving group (LG) is still bonded. Nu donates electron pair to the small back lobe of the sp^3 hybrid that forms bond to LG. This is called "backside attack" and results in inversion of carbon's configuration (Walden Inversion). Carbon configuration is turned "inside out."



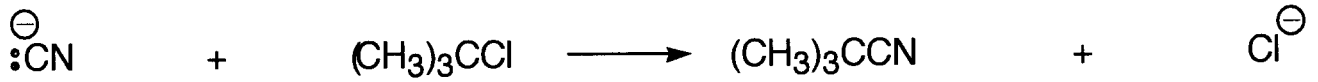




S_N2 is a **stereospecific** reaction - a particular stereoisomer reacts to give one specific stereoisomer of the product, even though another is possible.

S_N2 summary: 1. rate = k[Nu] [substrate]
2. bimolecular TS
3. proceeds with 100% inversion

Reaction B



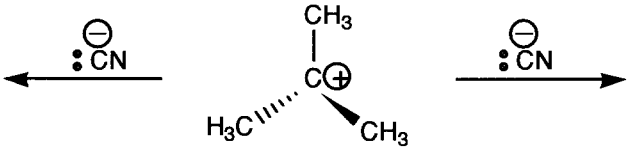
1. Kinetics: Observations - if conc. of substrate is doubled -

if conc. of Nu is doubled -

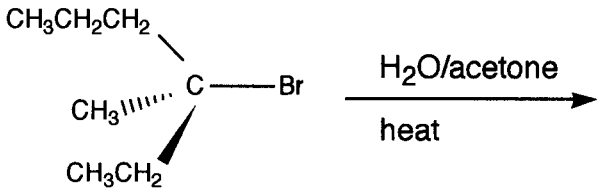
rate =

The Mechanism:

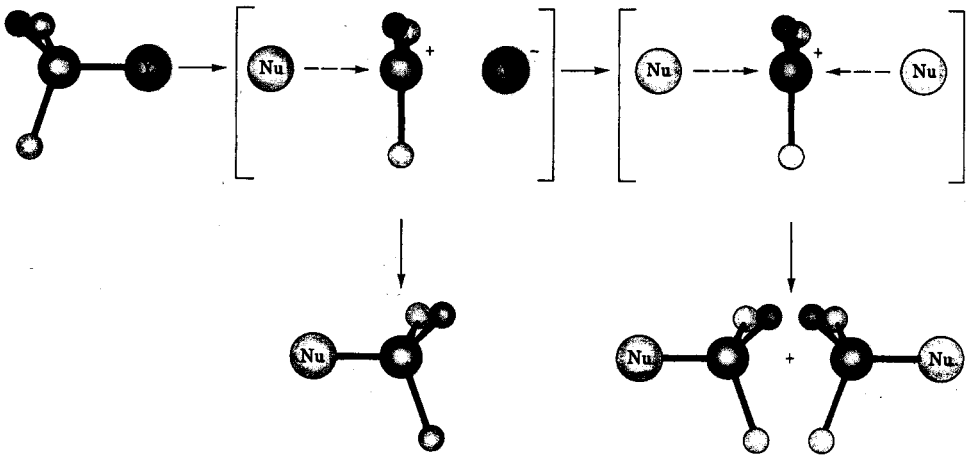
2. Stereochemistry: Nu attacks after LG has left. Nu attacks a planar carbocation and can attack from either side. Attack from the opposite side of the LG's original position results in inversion of the carbon's configuration. Attack from the same side as the LG's original position results in retention of the carbon's configuration. This result is known as **racemization** of stereochemistry. The S_N1 process is not stereospecific.



Racemization Example:



S_N1 summary: 1. rate = k[substrate]
2. unimolecular TS for RDS
3. proceeds with racemization (may not get a 50/50 mixture due to ion pair formation)



We've looked at two reactions, two mechanisms for nucleophilic substitution of alkyl halides: S_N1 and S_N2. We are left with a BIG QUESTION: What determines which mechanism is taking place in the reaction of a given alkyl halide?

Simple Answer: Rate - faster pathway wins

Factors that Affect Rate:

1. Substrate Structure

2. Nature of the Leaving Group

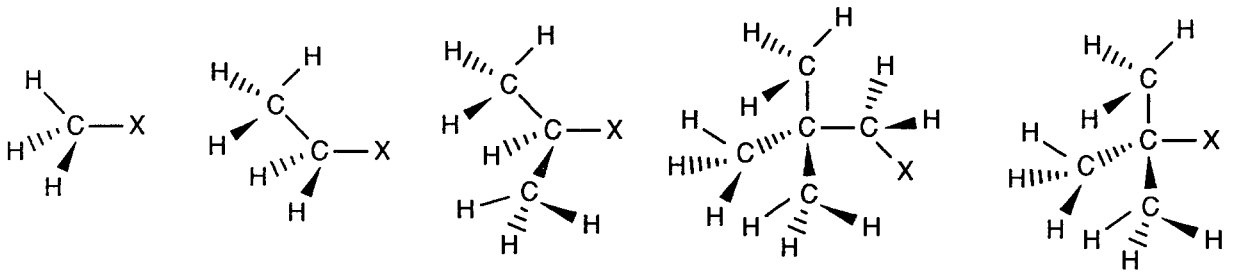
3. Concentration and Reactivity (Strength) of the Nucleophile (S_N2 only)

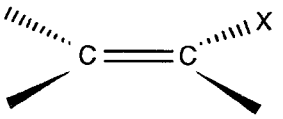
4. Solvent

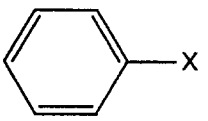
Substrate Structure vs Reaction Rate

S_N2 Process:

Relative Reaction Rates for Alkyl Halides:





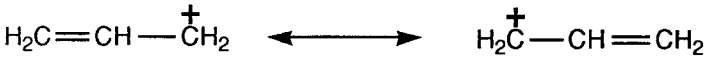


Substrate Structure vs Reaction Rate

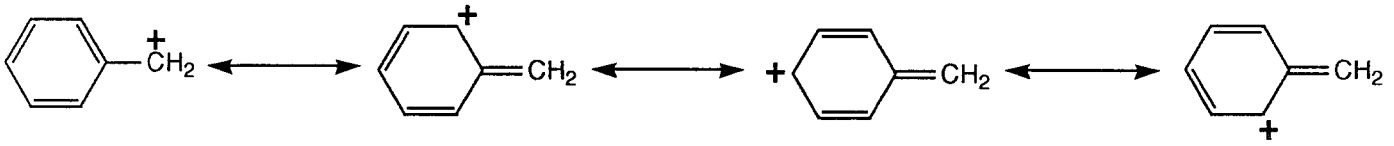
S_N1 Process:

Relative Reaction Rates for Alkyl Halides:

Allyl C+ :

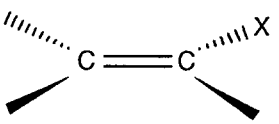


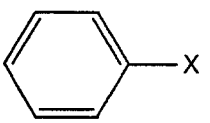
Benzyl C+ :



Order of C+ stability:

3° allylic/benzylic > 3° = 2° allylic/benzylic > 2° = 1° allylic/benzylic > 1° > methyl





S_N1 / S_N2 Competition:

CH_3X	1°	2°	3°

Nature of the Leaving Group - Same influence on rate in S_N1 and S_N2
- only the timing of the departure is different

- LG must be electron withdrawing - must polarize the C - X bond - must put $\delta+$ charge on C

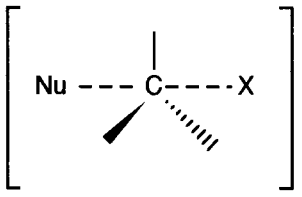
- LG must form a stable species (a stable anion, a neutral molecule - a weak base)

- The weaker the base formed -

Order of Reactivity of Alky Halides (by S_N1 or S_N2):

RI	RBr	RCl	RF

How is reaction rate affected by the LG?

S_N2 

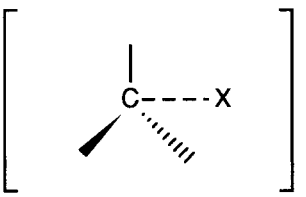
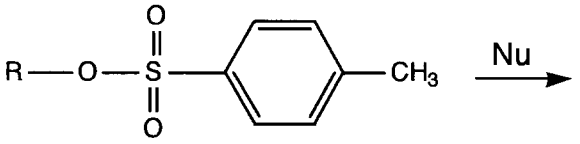
S_N1 

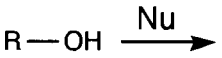
Table 6 - 4 gives other good LG

Example:

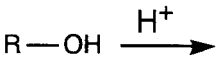


Strong bases make bad leaving groups in S_N1 and S_N2 processes.

Example:



But, under acidic conditions:



Concentration and Strength of Nucleophile

a) concentration

S_N1 -

S_N2 -

b) strength (nucleophilicity - affinity for the $\delta+$ carbon)

S_N1 -

S_N2 -

strong Nu -

weak Nu -

Trends in Nucleophilicity (Affinity for a positive or δ+ carbon atom)

1. A negatively charged nucleophile is stronger than its conjugate acid.

2. Nucleophilicity decreases from left to right in the periodic table. Electronegative elements "hold on" to lone pairs more tightly; therefore lone pairs are less available to form new bonds.

3. Nucleophilicity increases down a group in the periodic table as size and polarizability increase. Larger atoms hold outer electrons more loosely so electrons move more freely toward a positive charge. This contributes to earlier and stronger bonding in the transition state.

4. Bulky groups on the nucleophile decrease nucleophilicity.

Strength of the Nucleophile and the S_N1/S_N2 Choice for 2° Substrate

Strong Nu necessary

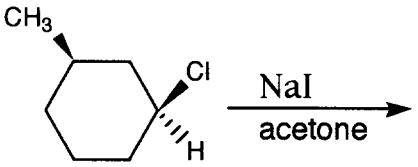
Weak Nu OK

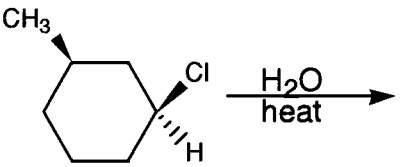
Strong Nu favors S_N2

Weak Nu favors S_N1

CAUTION: Does not mean a 1° substrate with a weak Nu will proceed by S_N1 or a 3° substrate with a strong Nu will proceed by S_N2!!

Example:





Solvent (influence on rate)

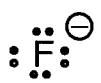
$S_N2 \Longrightarrow$

Table 6-3 lists nucleophiles in order of strength in a particular type of solvent:

The trends in nucleophilicity were also determined in this type of solvent.

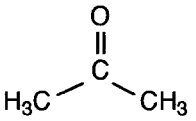
Example: $I^- > Br^- > Cl^- > F^-$

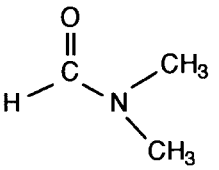
Consider how the protic (hydroxylic) solvent interacts with Nu:

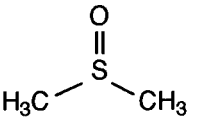


Now consider nucleophilicity in a polar, aprotic (nonhydroxylic) solvent.

Examples:







polar:

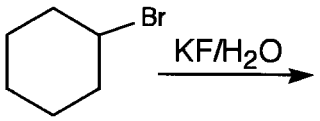
aprotic:

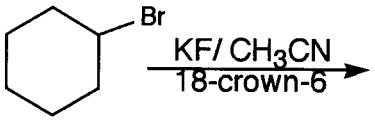
Using a polar, aprotic solvent greatly increases the rate of the S_N2 process. Switching from a hydroxylic solvent to an aprotic solvent can increase the rate as much as one million times!

protic solvent:

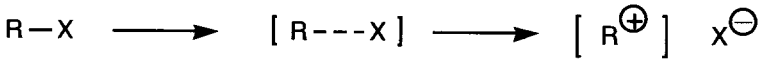
aprotic solvent:

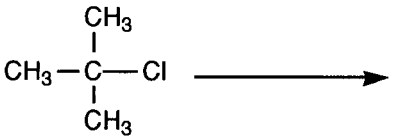
Example:





Solvent effect on S_N1 ⟹





The more polar the solvent ⟹

Higher the dielectric constant, the more polar the solvent.

	dielectric const.	relative rate of t-BuCl ionization
H_2O		
MeOH		
EtOH		
Acetone		
Ether		
Hexane		

Protic solvents ⟹

Solvent Summary:

S_N2: Solvent affects strength of Nu. Aprotic solvents destabilize Nu (Nu is not solvated well), so increase the strength of Nu. Aprotic solvent is not required.

S_N1: Solvent facilitates ionization by stabilizing the TS, the carbocation and the LG. Protic solvent is required for significant ionizaton.

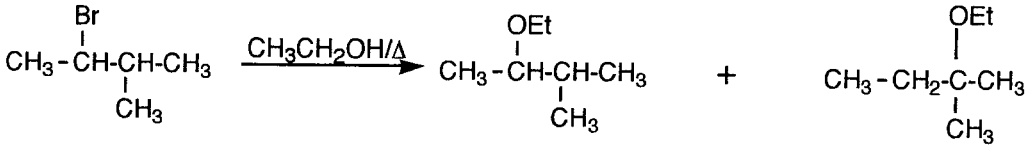
Summary of S_N1/S_N2 choices:

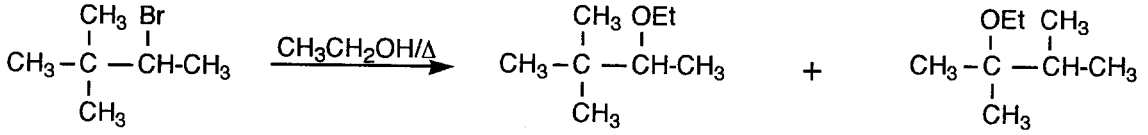
CH_3X, 1°

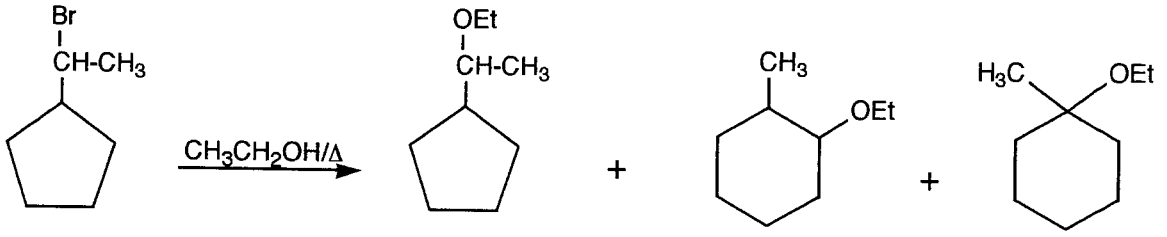
3°

2°, allyl, benzyl

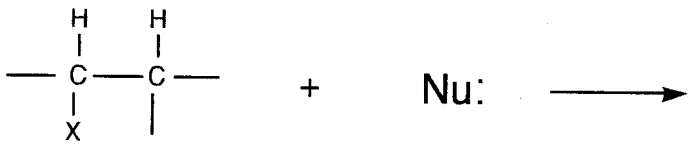
Carbocation Rearrangement : Any that can rearrange, WILL!!

I. 

II. 

III. 

Elimination Reactions:



Two pathways: (timing of bond breaking and forming different as in S_N1/S_N2)

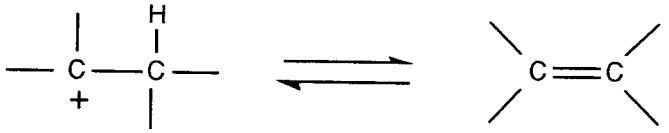
E1 : elimination, unimolecular - TS of RDS involves a single molecule, the substrate

rate = k[RX]

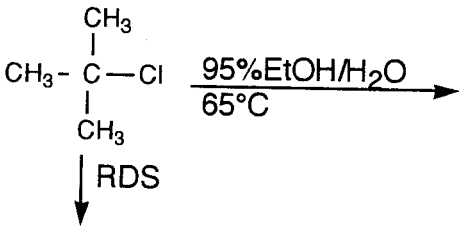
Mechanism:

step 1:

step 2:



Consider the reaction and mechanism:

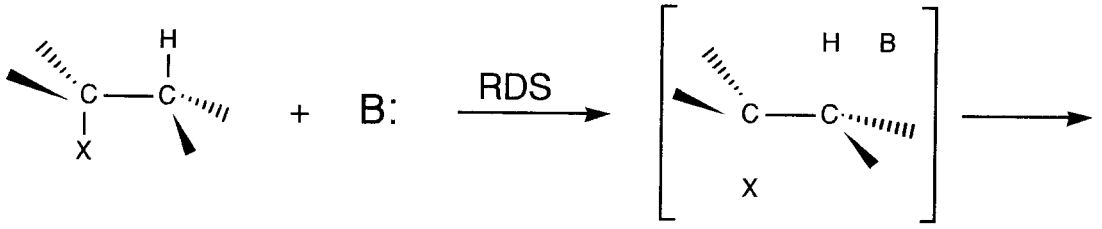


Order of reactivity by E1: 3° 2° 1°

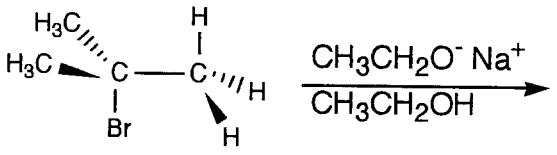
E2 : elimination, bimolecular - TS of RDS involves two molecules, the substrate and Nu

rate = k[RX] [Nu]

Mechanism:

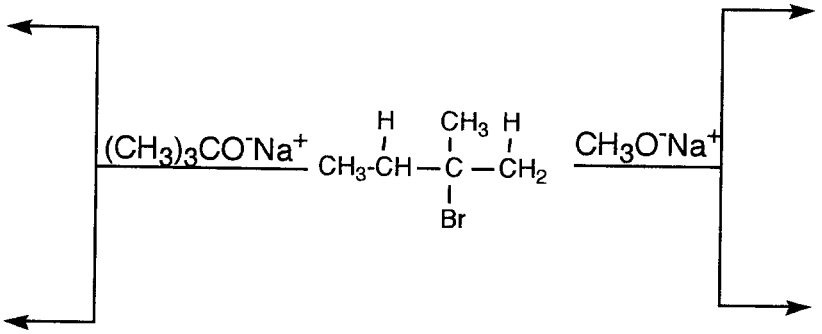


Consider the reaction and mechanism:



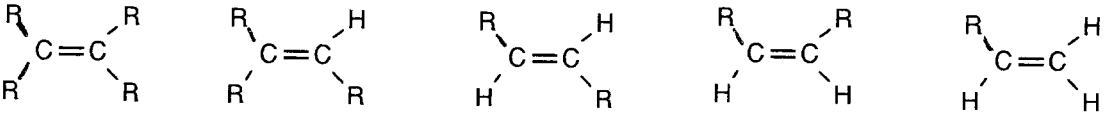
Order of reactivity by E2: 3° 2° 1°

Orientation of Elimination and Alkene Stability:



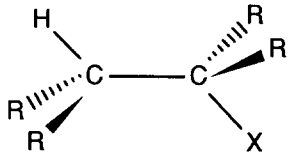
Saytzeff's Rule: In an elimination, the more highly substituted alkene (more stable) alkene predominates

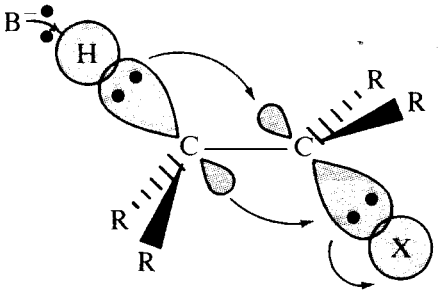
order of alkene stability

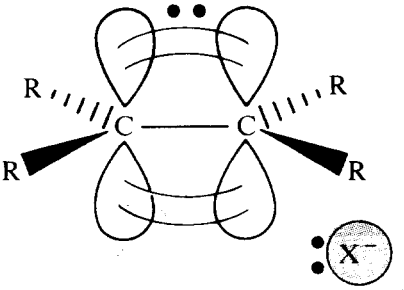


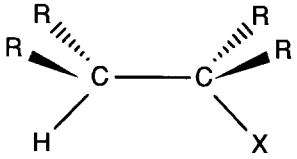
Stereochemistry of E2: A stereospecific reaction

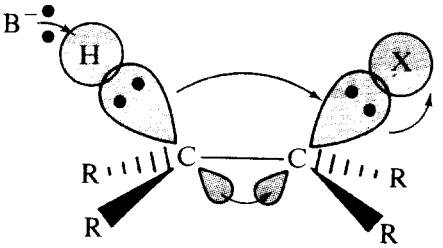
1. All four substrate atoms involved in the reaction must be coplanar. Two conformations meet this requirement.

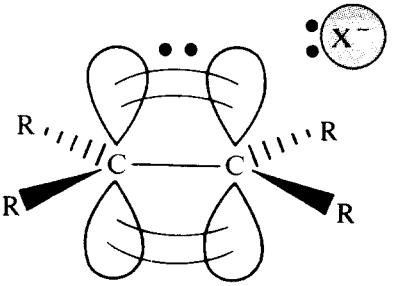




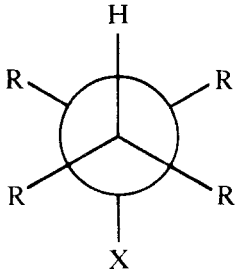


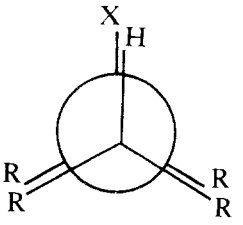




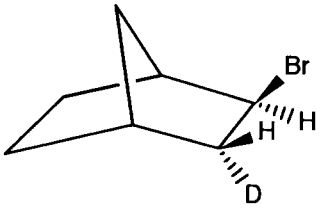


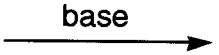
2. Preferred conformation:

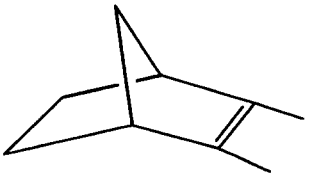




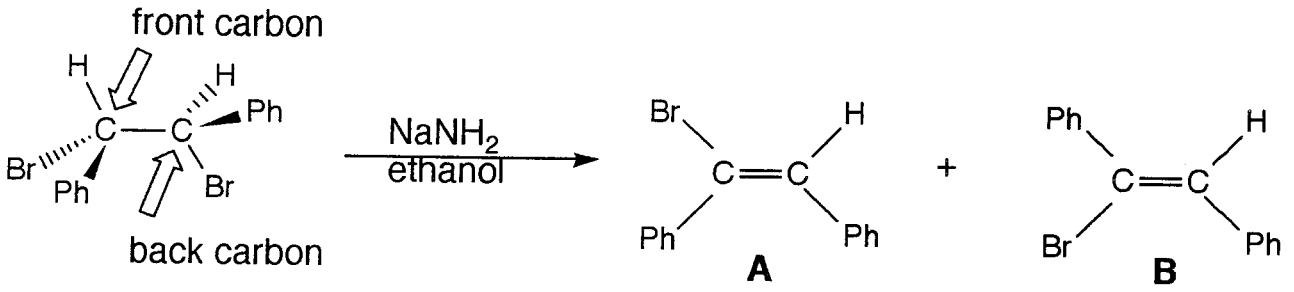
Exception to preferred conformation:



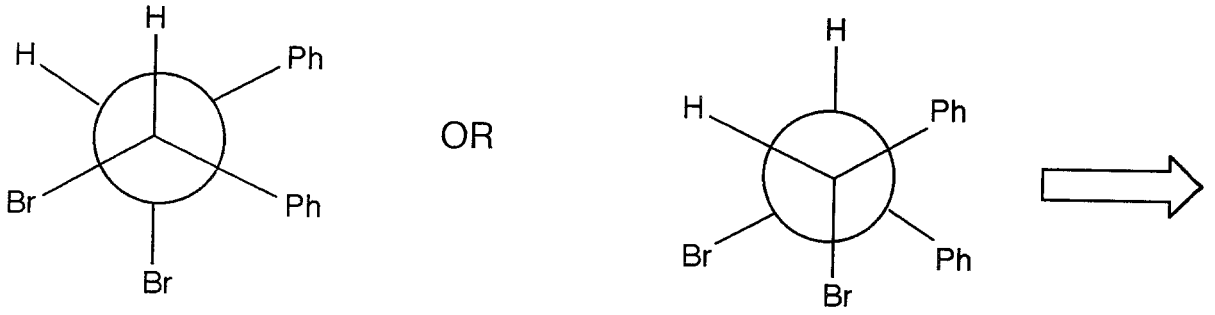




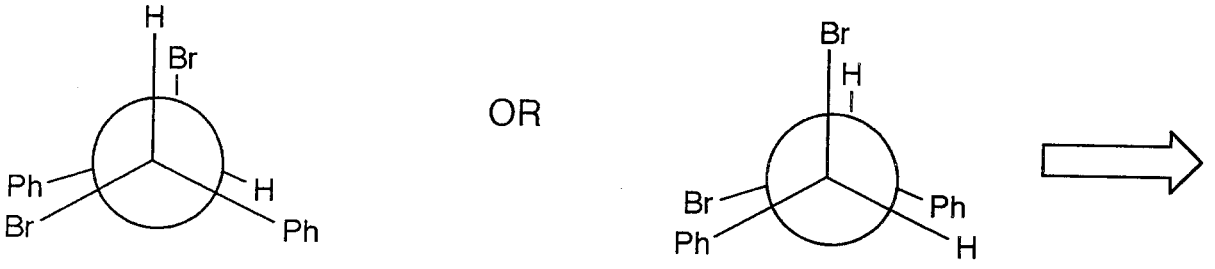
Experimental Evidence for Anti-periplanar (Co-planar) Geometry in E2 Process:



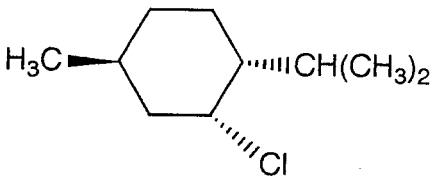
Anti-periplanar result:



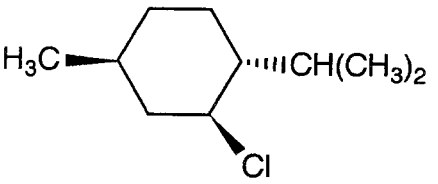
Syn-periplanar result:



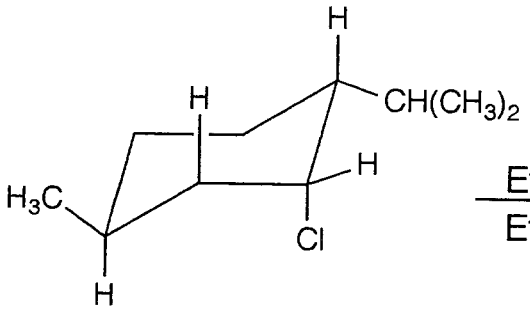
Experimental Evidence for 1,2 - Diaxial Requirement in E2 Process on Cyclohexyl Substrates



A. neomenthyl chloride

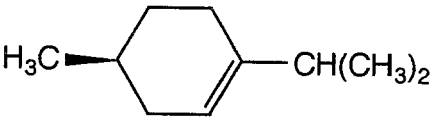


B. menthyl chloride

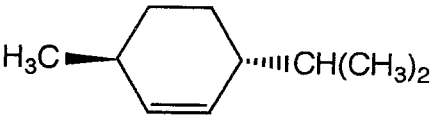


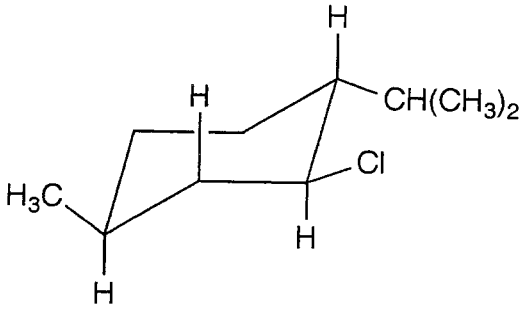
A. neomenthyl chloride

$EtO^- Na^+$
EtOH

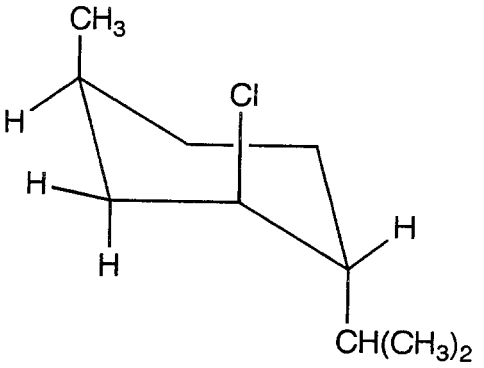


+

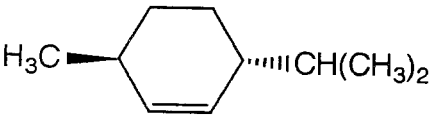




B. menthyl chloride



$EtO^- Na^+$
EtOH



Substitution vs Elimination (Wade summaries: sections 6-16 and 6-22)

Nu = strong base
(^-OH, RO^-, $^-NH_2$, $RC{\equiv}C:^-$)
bulky bases particularly
favor E2 ($tBuO^-$)

Nu = weak base

S_N2 / S_N1 / E1 / E2*

- CH_3, 1°, 2°, allylic/benzylic
- Strong Nu, but weak base such as iodide, HS^-, RS^-, or ^-CN
- faster rate in aprotic solvents

- 3°, 2°, allylic/benzylic
- Weak Nu
- ionizing solvent is necessary
- S_N1 usually major process high T increases E1

*Exception: 1° halide with a strong, <u>unhindered</u> base - S_N2 gives major product

Examples:

1. $CH_3CH_2Br + CH_3CH_2O^-Na^+ \xrightarrow[55°C]{EtOH} CH_3CH_2OCH_2CH_3 + CH_2{=}CH_2$
   90% (S_N2) 10% (E2)

2. $CH_3(CH_2)_{15}CH_2CH_2Br + (CH_3)_3CO^-K^+ \xrightarrow{tBuOH} CH_3(CH_2)_{15}CH_2CH_2OC(CH_3)_3 + CH_3(CH_2)_{15}CH{=}CH_2$
   15% (S_N2) 85% (E2)

3. $CH_3\underset{Br}{C}HCH_3 + CH_3CH_2O^-Na^+ \xrightarrow{EtOH} CH_3CH{=}CH_2 + CH_3\underset{OCH_2CH_3}{C}HCH_3$
   79% (E2) 21% (S_N2)

4. $CH_3\underset{Br}{C}HCH_3 + NaI \xrightarrow{acetone} CH_3\underset{I}{C}HCH_3$ ~100% (S_N2)

5. $CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}Br$

   $\xrightarrow[CH_3CH_2OH]{CH_3CH_2O^-Na^+}$ $CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}OCH_2CH_3$ + $CH_2{=}\overset{CH_3}{\underset{CH_3}{C}}$
   3% (S_N1) 97% (E2)

   $\xrightarrow[50°C]{CH_3CH_2OH}$ $CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}OCH_2CH_3$ + $CH_2{=}\overset{CH_3}{\underset{CH_3}{C}}$
   80% (S_N1) 20% (E1)