

Lecture Notes
Chem 51B
S. King

Chapter 8 Alkyl Halides and Elimination Reactions

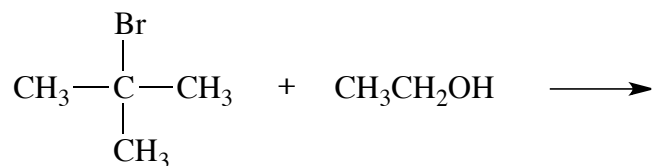
The characteristic reactions of alkyl halides are nucleophilic substitution and elimination.

I. Nucleophilic Substitution: Review

In a substitution reaction, an alkyl halide reacts with a nucleophile to give a product in which the nucleophile replaces the halogen, which is expelled as a leaving group. There are two competing mechanisms for nucleophilic substitution: S_N1 and S_N2 . A good understanding of the factors that affect substitution reactions will help in determining which mechanism will predominate (see S_N2 handout).

Important factors:

- structure of the alkyl halide
- strength of the nucleophile
- solvent (PA or PP)
- leaving group ability



Q. For the two reactions above, why does ethyl bromide react by an S_N2 reaction and *tert*-butyl bromide react by an S_N1 reaction?

A. The relative rates of the possible reactions dictate the outcome of the reaction.

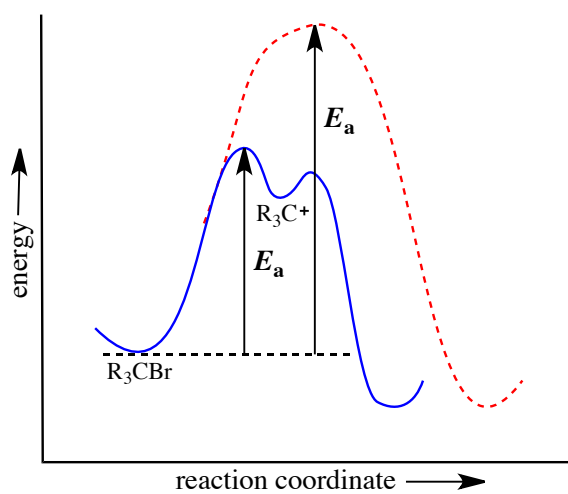
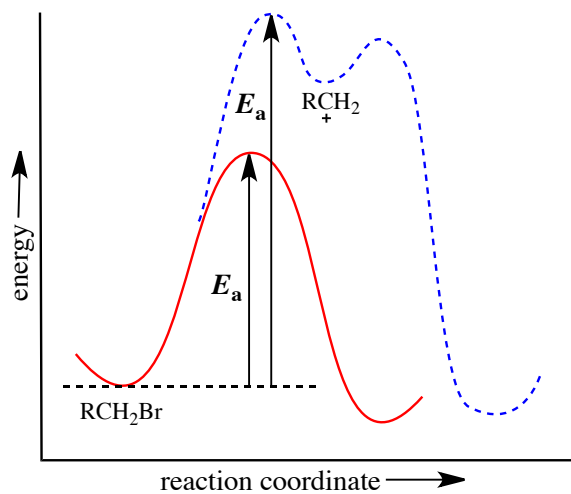
i.e. The rate of an S_N2 reaction for ethyl bromide is exceedingly faster than the rate of an S_N1 reaction for ethyl bromide.

Remember the order of reactivity:

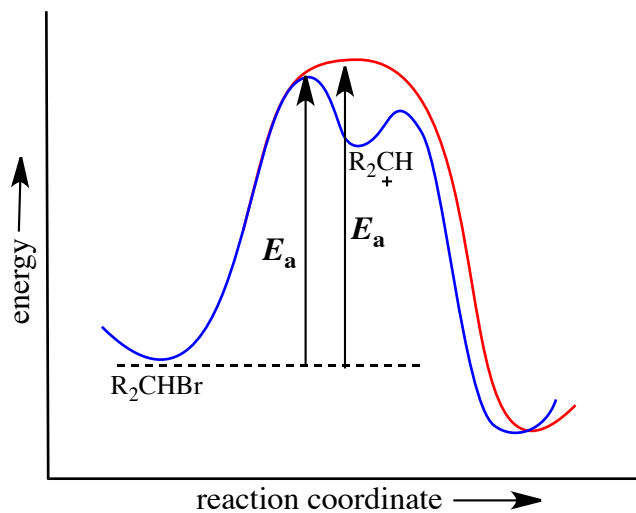
S_N2 reaction: methyl $>$ $1^\circ >$ $2^\circ >$ 3°

S_N1 reaction: $3^\circ >$ $2^\circ >$ $1^\circ >$ methyl

Compare energy diagrams for S_N1 & S_N2 reaction of a 1° & 3° alkyl halide:



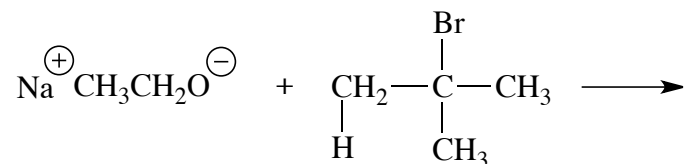
For 2° alkyl halides the rates of S_N1 vs. S_N2 are much more competitive!



- 2° alkyl halides react with good nucleophiles by S_N2 reactions.
- If a 2° alkyl halide is in a good ionizing solvent (PP) and no good nucleophile is present, S_N1 reactions will predominate.

II. Elimination Reactions

We saw that when a primary alkyl halide reacts with ethoxide ion, an S_N2 reaction takes place. When a tertiary alkyl halide reacts with the same nucleophile, a very different reaction occurs:



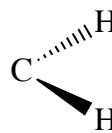
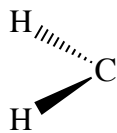
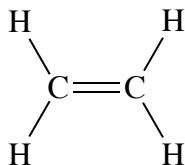
- An elimination that involves loss of two groups from adjacent carbons is called a *β-elimination*.
- Nucleophiles that are also strong bases promote the β-elimination reaction.

Elimination is in competition with nucleophilic substitution for *all* alkyl halides with β-hydrogens!

NOTICE: This reaction provides a way to synthesize *alkenes*.

II. Alkenes: Structure and Stability

Alkenes are hydrocarbons with carbon-carbon double bonds.



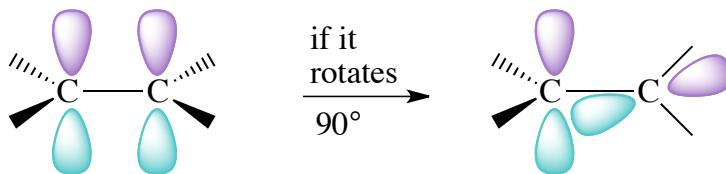
- Bond energy for a C-C double bond: 146 kcal/mole:
 83 kcal/mole for the σ -bond
 63 kcal/mole for the π -bond.
 (the π -bond has a lower bonding energy and is more reactive than the σ -bond).
- The C—C double bond **does not** undergo rotation at room temperature!

Barrier to rotation:

Compare with barrier to rotation for σ bond:

Energy available to molecules @ room temperature:

Why?



Result:

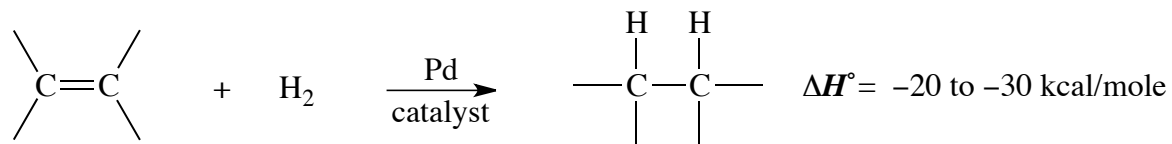


- cis-trans isomers are **stereoisomers**: the connectivity is the same - they differ only in the arrangement of their atoms in space.
- cis-trans isomers have different b.p.'s, m.p.'s and vastly different dipole moments.

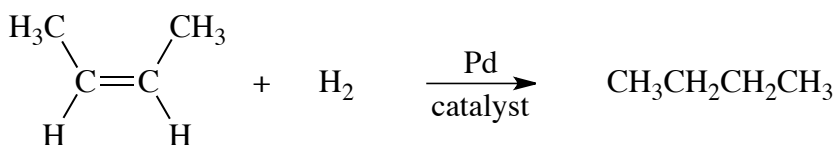
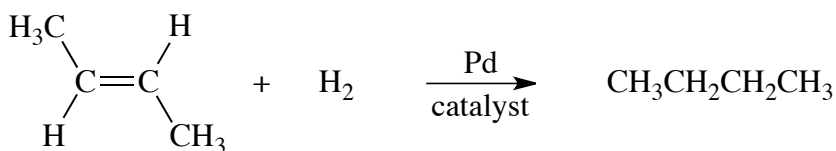
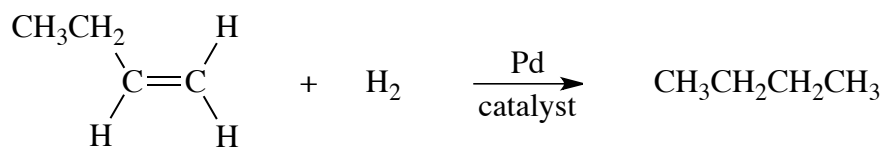
The C-C double bond is easily converted to other functional groups. Because of this, alkenes are important as intermediates in the synthesis of drugs, pesticides and other valuable chemicals. This, however, accounts for only a small fraction of the billions of pounds of alkenes used annually to make polymers.

A. Relative Stabilities of Alkenes:

Experimental heats of hydrogenation of isomeric alkenes are often used to compare their relative stabilities:



Compare:

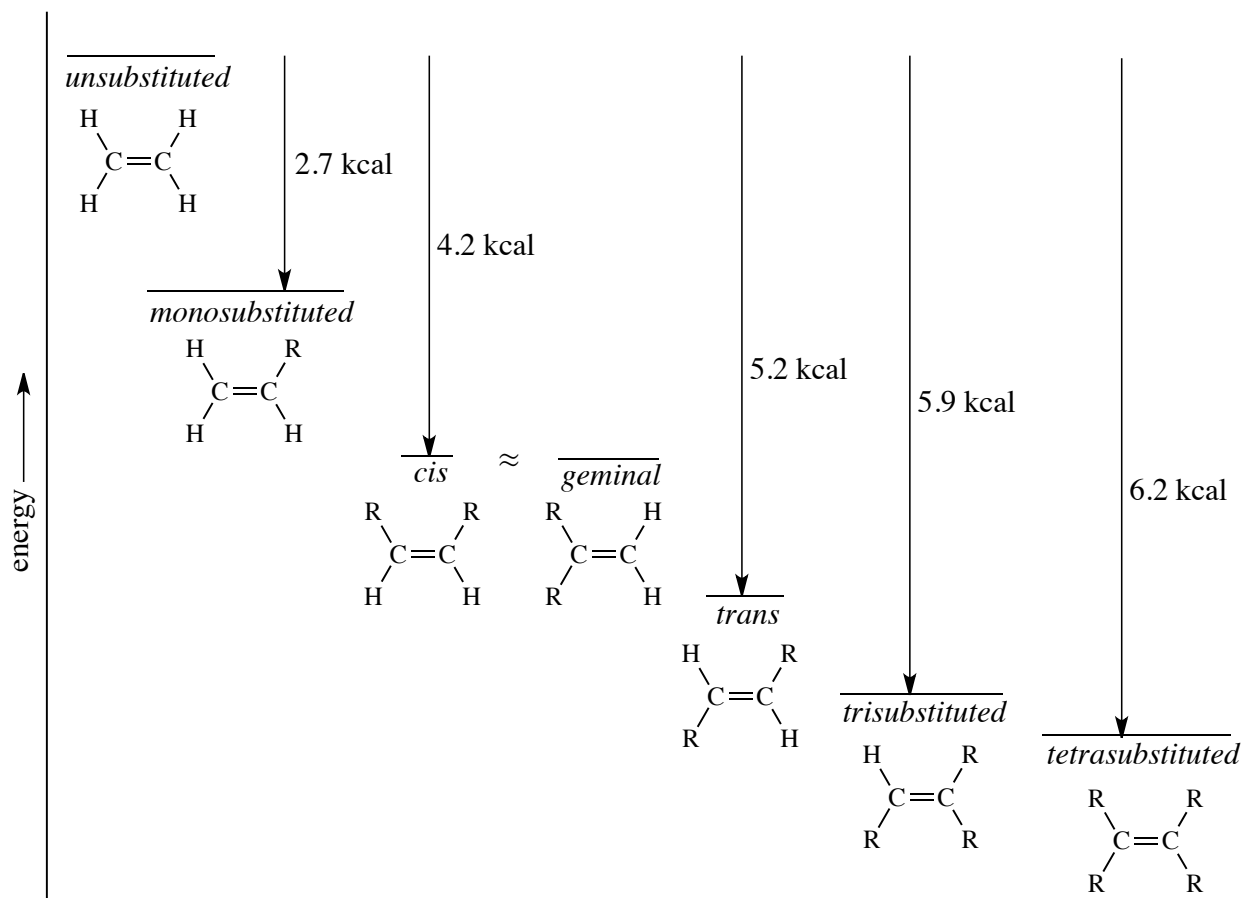


This can be shown graphically:

Note:

- The stability of an alkene increases with the number of alkyl groups that are substituted on the carbon atoms of the double bond.
- Alkenes in which groups are *trans* to each other are more stable than the corresponding *cis* alkenes.

The same process can be done for a series of alkenes:



III. The Mechanisms of Elimination

There are two types of Elimination mechanisms:

E1 which competes with $\text{S}_{\text{N}}1$

E2 which competes with $\text{S}_{\text{N}}2$

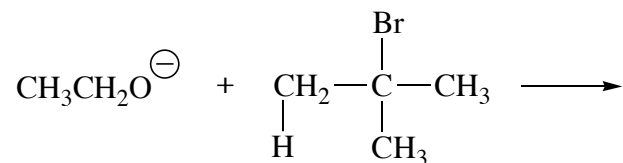
IV. E2 mechanism (Bimolecular Elimination)

This type of elimination is a dominant reaction of 3° alkyl halides in the presence of a strong base, and it competes with the $\text{S}_{\text{N}}2$ reaction for 2° & 1° alkyl halides.

A. Rate Law and Mechanism of the E2 Mechanism

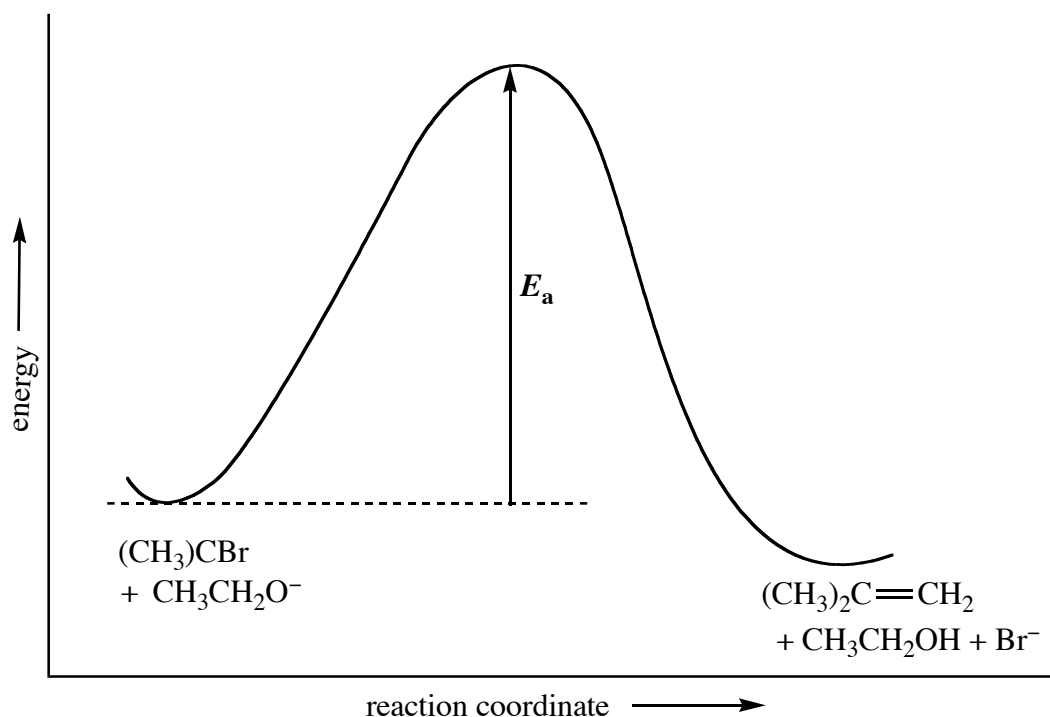
$$R \propto [\text{alkyl halide}] [\text{base}]$$

Mechanism:



This type of mechanism, involving concerted removal of a β -proton by a base and loss of a halide ion, is called an **E2** mechanism.

Energy diagram:



B. The Effect of the Base

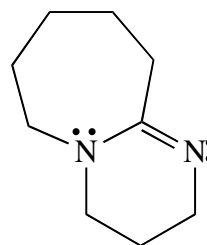
The base appears in the rate equation so the rate of the E2 reaction increases as the strength of the base increases.

E2 reactions are generally run with strong negatively charged bases like OH^- and OR^- . Two strong, *sterically hindered* bases, called **DBN** and **DBU**, are also sometimes used.



DBN

(1,5-diazabicyclo[4.3.0]non-5-ene)



DBU

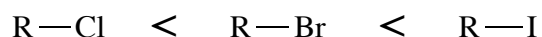
(1,8-diazabicyclo[5.4.0]undec-7-ene)

C. Solvent Effects

Polar aprotic solvents increase the rate of E2 reactions.

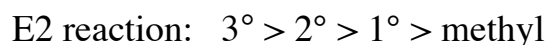
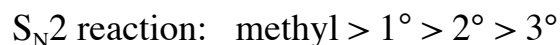
D. Leaving Group Effects

The bond to the leaving group is partially broken in the transition state, so the better the leaving group, the faster the reaction.



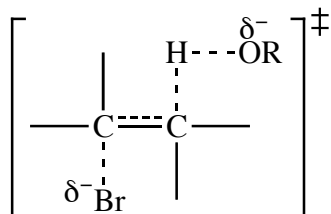
E. The Structure of the Substrate

The $\text{S}_{\text{N}}2$ and E2 reactions differ in how R groups affect the reaction rate. Bulky alkyl halides have an increased rate of reaction.

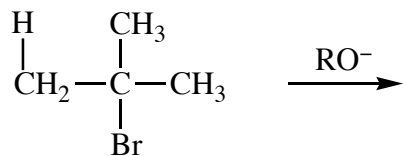
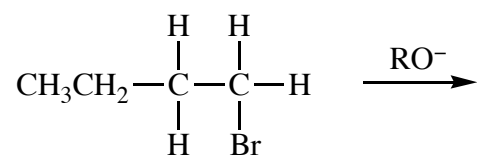


Q. Why does increasing alkyl substitution increase the rate of reaction?

A. In the transition state, the double bond is partially formed, so increasing the stability of the double bond with alkyl substituents stabilizes the transition state.

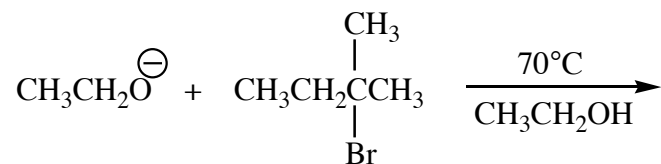


Compare:



F. Regioselectivity of the E2 Reaction: The Zaitsev Rule

When two or more elimination products are possible in an E2 reaction, the *most stable* alkene will predominate.

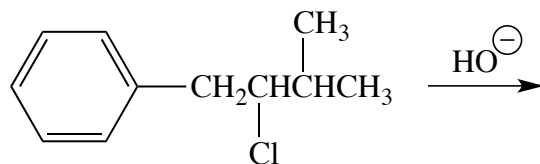


How?

Some Important Points:

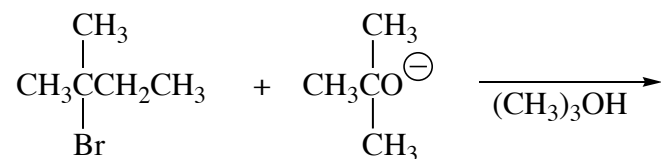
❖ **The most stable alkene is usually the most substituted alkene, but not always.**

Example:

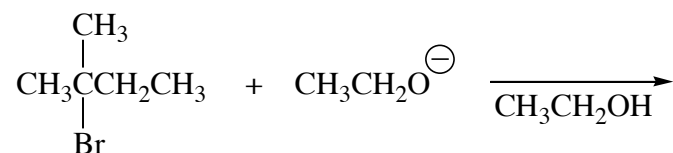


❖ **In some elimination reactions, the less stable alkene is the major product.**

This can happen when a hindered base is used with a hindered alkyl halide.

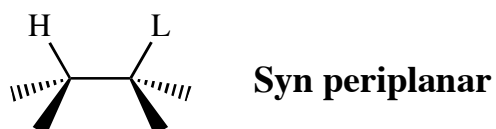


Compare with:

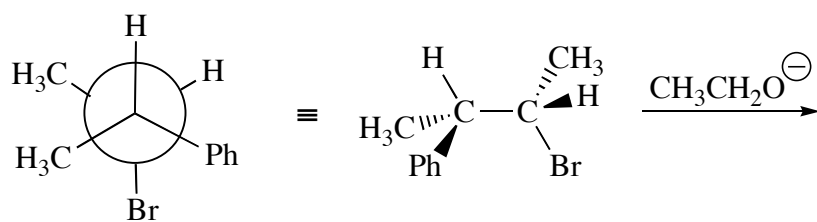


G. The Stereochemistry of the E2 Reaction:

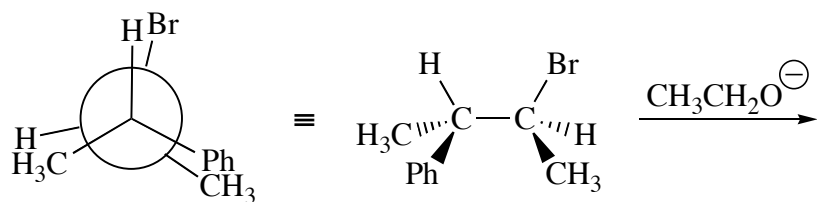
For an E2 Elimination to occur, the β -H and the leaving group must be in the same plane.



Example:



Syn elimination of the same alkyl halide does not occur! *Why?*

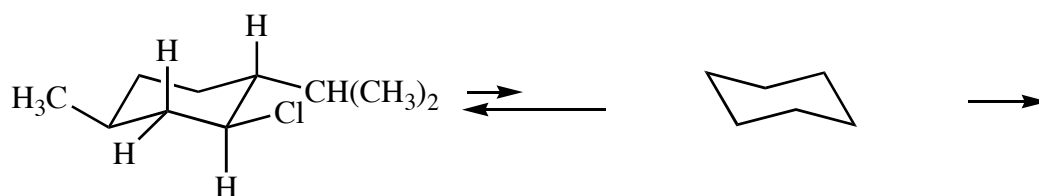


S_N2 elimination is *disfavored* because:

- Transition state has an eclipsed conformation (*anti* has staggered, which is lower in energy).
- The base and leaving group are on the same side of molecule (*sterically disfavored*).

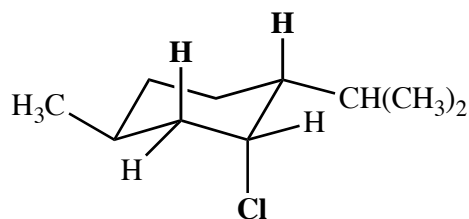
In a cyclohexane ring, the β -H and the leaving group can assume an anti periplanar conformation only when they are both axial (trans-diaxial).

Look at Menthyl Chloride:

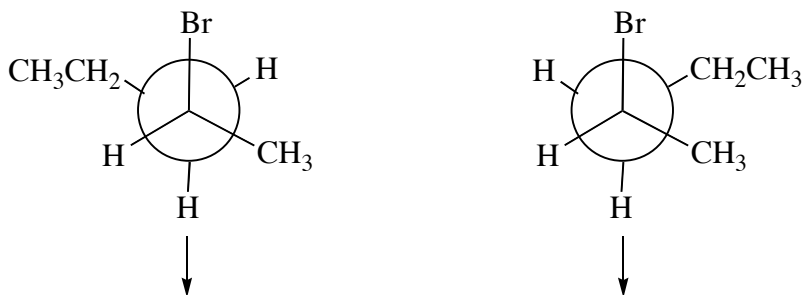
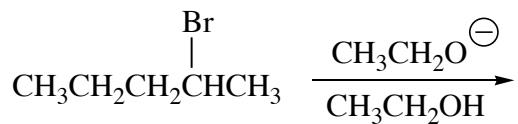


- Even though conformation **B** is less stable, Elimination occurs through this conformation because the β -H and the L.G are trans-diaxial

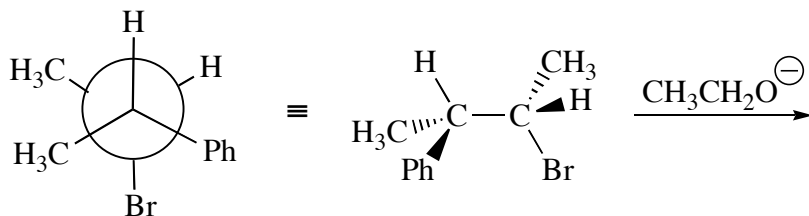
With *neomenthyl chloride*, there are two β -H's that can be eliminated:



When a mixture of stereoisomers is possible from the E2 reaction (the reactant has two hydrogens bonded to the same β -carbon), both the *cis* and *trans* isomers will form, because there are two conformers in which the groups to be eliminated are anti. *The alkene with the bulkiest groups on opposite sides of the double bond will be formed in greater yield because it is the more stable alkene:*

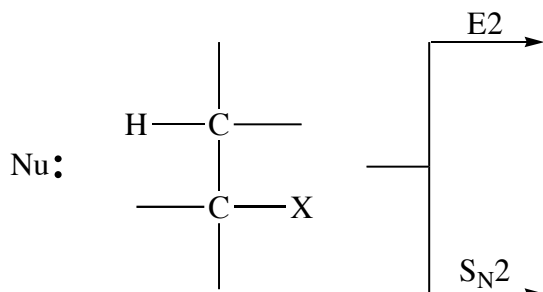


If the reactant has only one hydrogen bonded to the β -carbon, there is only one conformer in which the groups to be eliminated are anti. *The particular isomer that is formed depends on the configuration of the reactant:*



E. Competition between S_N2 vs. E2

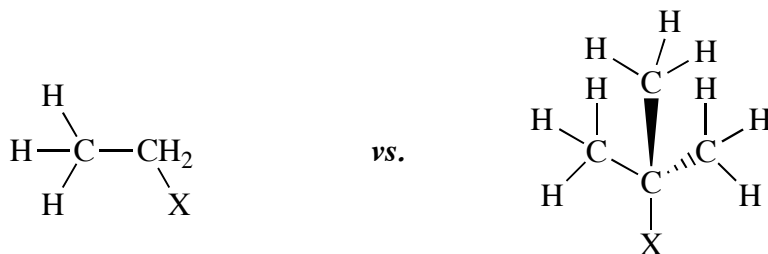
Because S_N2 and E2 reactions are in competition with each other, is there any way to favor one over the other?



What determines which will be the major pathway?

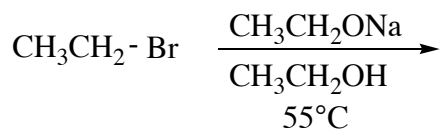
There are three factors:

1. The structure of the alkyl halide
2. The structure of the base
3. Temperature

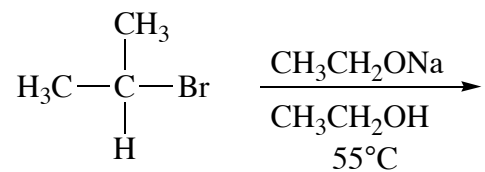


Look at reaction of ethoxide ion with 1°, 2°, & 3° alkyl halides:

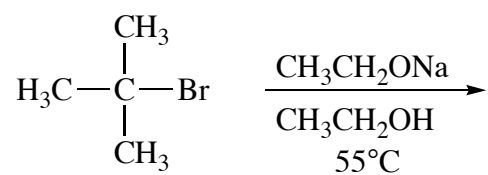
1° Halides



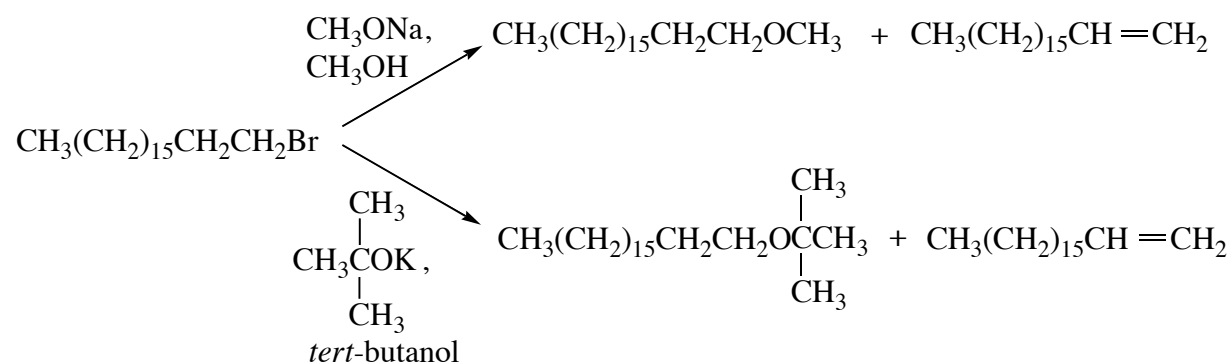
2° Halides:



3° Halides:



A bulky nucleophile (base) will also favor E2, even with 1° alkyl halides:



Why?

To favor E2 over S_N2:

- Use 2° or bulky halides + strongly basic and/or bulky nucleophiles.
- Increasing temperature also favors elimination over substitution.

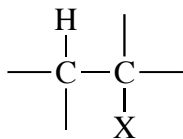
To favor S_N2 over E2:

V. E1 mechanism (Unimolecular Elimination)

A. Rate Law and Mechanism of the E1 Reaction

$$R \propto [\text{alkyl halide}]$$

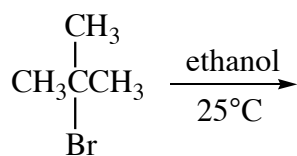
Step 1: Ionization (RDS) - the leaving group leaves



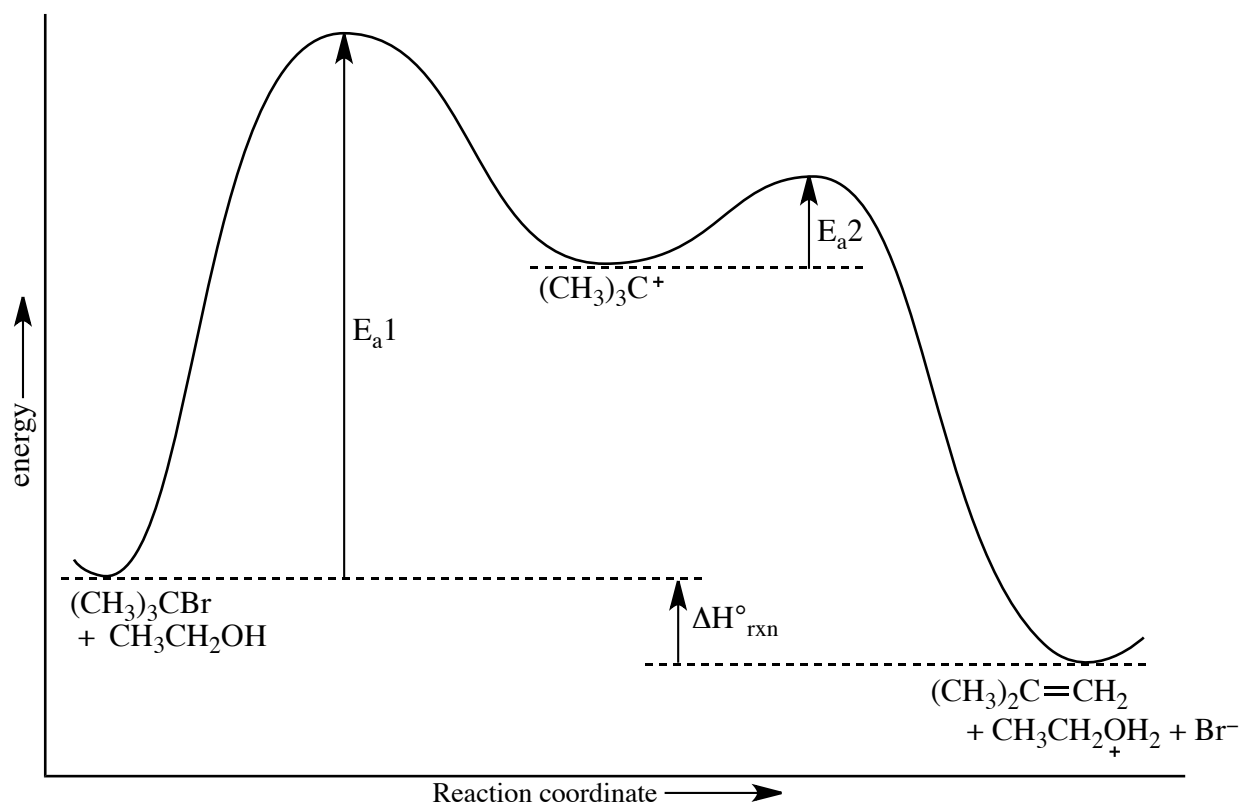
Step 2: A base abstracts a β-hydrogen (fast)

NOTICE: This is the *same* carbocation intermediate seen in the S_N1 reaction!

- The E1 and S_N1 reactions are in competition with each other and generally you will get mixtures of products.



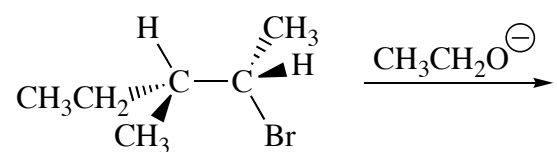
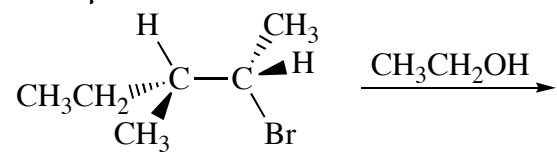
Look at the energy diagram for the E1 reaction:



Important points:

- When the alkyl halide contains more than one type of β -H, the alkene with the greatest number of alkyl substituents at the double bond will be favored.
- Just as with the $\text{S}_{\text{N}}1$ reaction, the rate of an E1 reaction corresponds to the stability of the corresponding carbocation.
- The carbocation formed in the first step of the E1 reaction is planar, so the β -H can be removed from either side.
- The major product will still be the one with the bulkiest groups on opposite sides of the double bond because it is the more stable alkene.

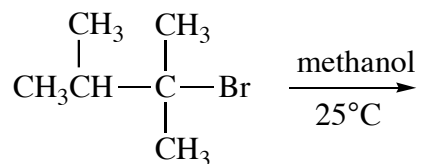
Compare:



B. Competition Between $\text{S}_{\text{N}}1$ vs. $\text{E}1$:

Both $\text{S}_{\text{N}}1$ and $\text{E}1$ reactions share a common intermediate. Both are favored by the use of poor nucleophiles (*weak bases*) and polar protic solvents.

- $\text{S}_{\text{N}}1$ is usually favored over $\text{E}1$, especially at low temperatures.
- The ratio of alkene ($\text{E}1$) to substitution ($\text{S}_{\text{N}}1$) is greater when the alkene formed contains more than two alkyl substituents at the double bond or is exceptionally stable.



- Heating will increase the percentage of E1, **but if Elimination is desired:**
- S_N1 and E1 reactions are not very useful for preparative purposes because mixtures of products are invariably formed (unless the alkyl halide has no β-hydrogens, and will not rearrange).

Summary S_N1 vs. E1 vs. S_N2 vs. E2: See summary sheets

Remember: Most strong Brønsted bases such as ethoxide are good nucleophiles; but some excellent nucleophiles, such as iodide ion are relatively weak Brønsted bases).

VI. Kinetic Isotope Effect

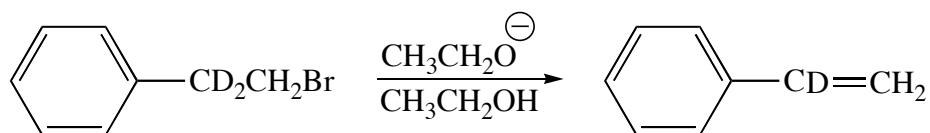
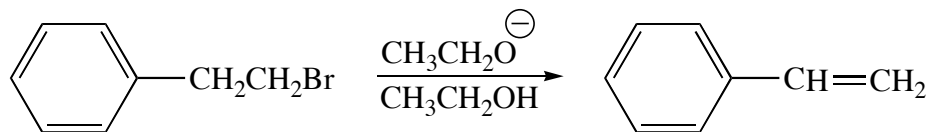
One piece of evidence that is used in determining the mechanism of a reaction is the **deuterium kinetic isotope effect**.

This effect compares the rate of a reaction for a compound containing hydrogen, with the rate of reaction for a compound in which one or more hydrogens have been replaced with deuterium, an isotope of hydrogen.

$$\text{deuterium kinetic isotope effect} = \frac{k_{\text{H}}}{k_{\text{D}}} = \frac{\text{rate constant for H-containing reactant}}{\text{rate constant for D-containing reactant}}$$

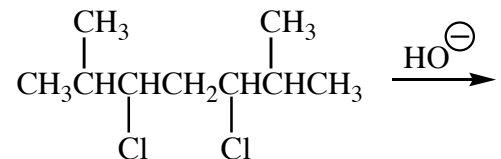
The chemical properties of deuterium and hydrogen are similar, but the C-D bond is about 1.2 kcal/mole stronger than a C-H bond. In a reaction where a **C-H bond is broken in the rate-determining step**, the reaction will be slower if the H is replaced with deuterium.

Example:

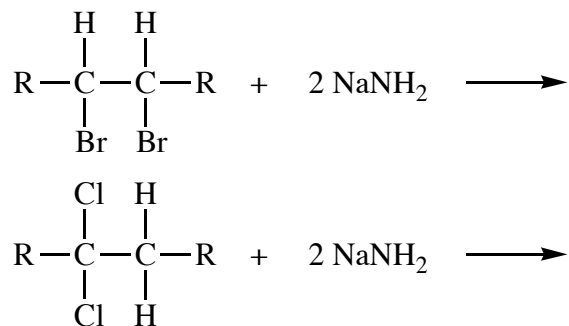


VII. Double Elimination

Alkyl dihalides can undergo two consecutive elimination reactions to give products that contain two double bonds:



If the two halogens are on the same carbon (*geminal dihalides*) or on adjacent carbon (*vicinal dihalides*), the product is an alkyne. A stronger base such as NH_2^- is needed for the second elimination to occur



Mechanism: