

CH 209 – Basic Organic Chemistry

Reaction mechanisms: Elimination reactions (E2, E1, E1cB)



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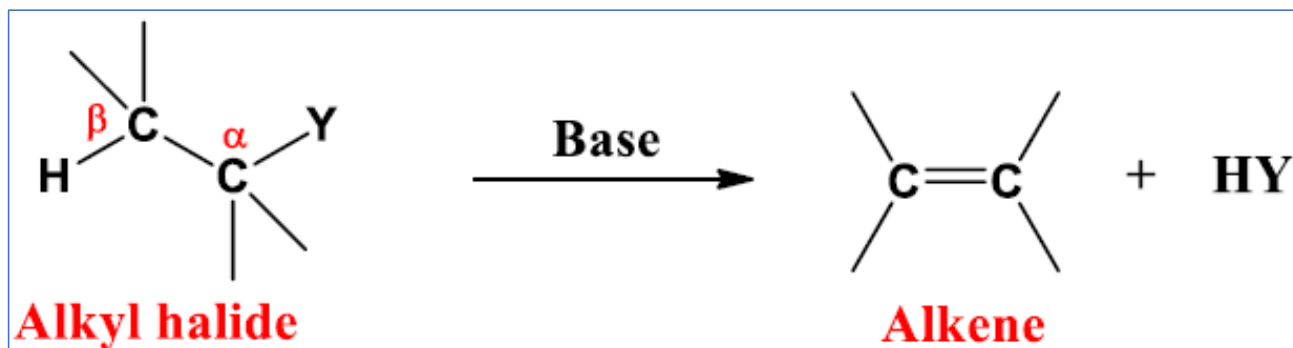
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Elimination reactions

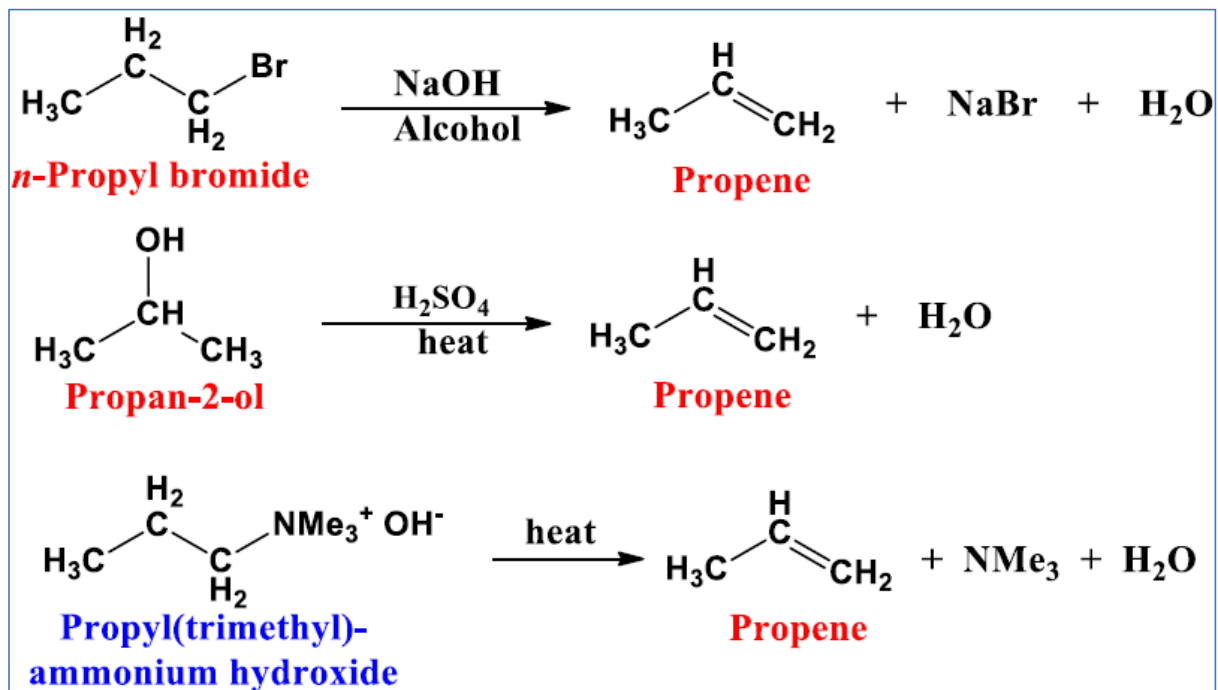
- In elimination reactions, two atoms or groups are removed from a molecule
- Formation of multiple bond occurs
- In the majority of elimination reactions, the atoms or groups are lost from adjacent carbon atoms, one of them very often being a proton and the other a good leaving group.



Key point – H from one carbon atom and a leaving group (typically a halide) from the adjacent carbon atom.

Elimination reactions

- Carbon that is connected to leaving group is designated as α – carbon
- The adjacent carbon from which the hydrogen atom is removed is called the β carbon
- 1,2 or α, β elimination or simple the β elimination



Mechanisms of elimination reactions

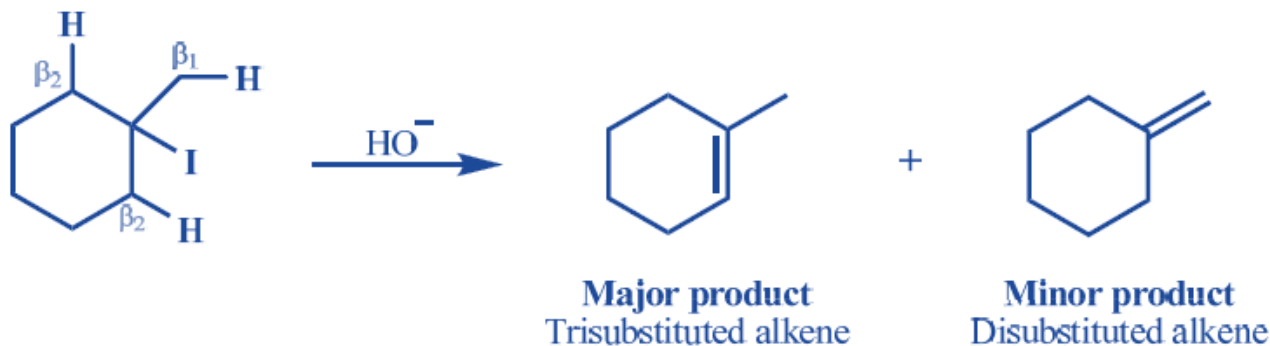
The elimination reaction consists of three fundamental events, and they are:

- *Proton removal*
- *C-C pi bond is formed*
- *There is a breakage in the bond of the leaving group*

- All can happen simultaneously in a concerted manner (Or)
- First, loss of leaving group and then proton removal while pi-bond formation (Or)
- First proton removal, then the loss of leaving group while pi-bond formation

Zaitsev's rule (or Saytzeff's rule, Saytzev's rule)

- When alkyl halides have two or more different β carbons, more than one alkene product can be formed.
- In such cases, the major product is the more stable product—the one with the more substituted double bond. This phenomenon is called the Zaitsev rule



- The Zaitsev product or the more substituted alkene product is more stable than the less substituted product.
- Thermodynamically controlled

Types of elimination reactions

- Just as there are two mechanisms of substitution (S_N2 and S_N1), there are two mechanisms of elimination (E2 and E1).

- E2 mechanism — bimolecular elimination

$$\text{Rate} = k_2[\text{R-X}][\text{B:}]$$

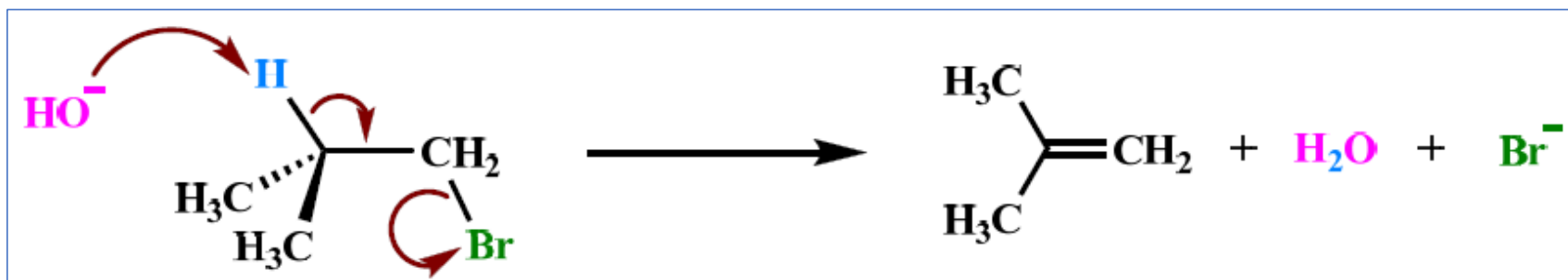
- E1 mechanism — unimolecular elimination

$$\text{Rate} = k_1[\text{R-X}]$$

- The E2 and E1 mechanisms differ in the timing of bond cleavage and bond formation, analogous to the S_N2 and S_N1 mechanisms.
- E2 and S_N2 reactions have some features in common, as do E1 and S_N1 reactions.

The E2 mechanism

- E2 stands for bimolecular elimination
- One step mechanism in which carbon hydrogen and carbon halogen bonds break to form a double bond C=C π bond
- Two leaving groups (often a hydrogen and a halogen) need to be *anti-periplanar*



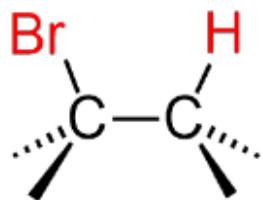
$$\text{rate} = k[(\text{CH}_3)_3\text{CCH}_2\text{Br}] [\text{OH}^-]$$

How does energy profile diagram look like?

E2 eliminations – stereochemical implications

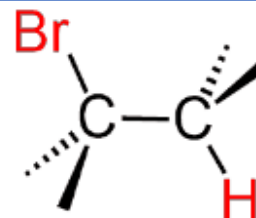
- The special alignment of the β -hydrogen and the leaving group in the transition state is required
- If the β -hydrogen and the leaving group are on the same side of the molecule, it is called a *syn* periplanar
- If the β -hydrogen and the leaving group are on opposite sides of the molecule, it is called an *anti*-periplanar
- E2 elimination occurs in the anti-periplanar geometry since this is the low-energy staggered conformation of the alkyl halide.

E2 eliminations – stereochemical implications



syn periplanar

β -H and Br on the same side.



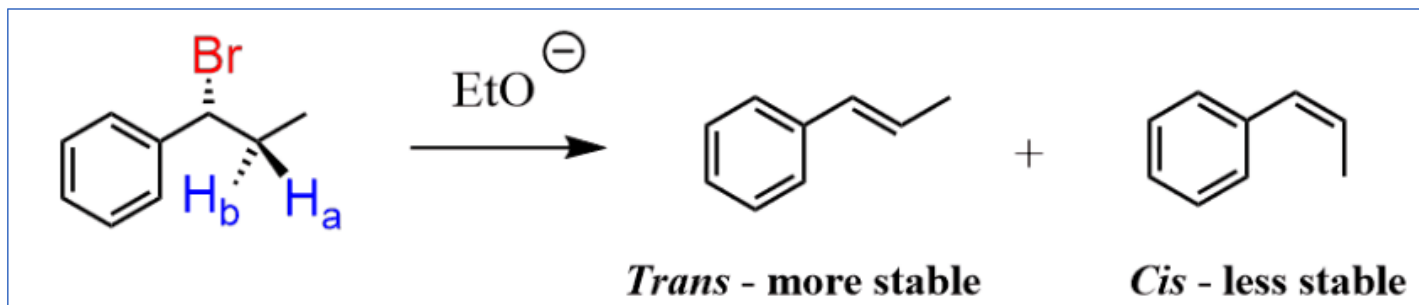
anti periplanar

β -H and Br on opposite sides.

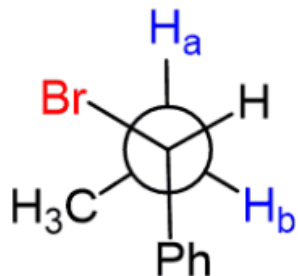
How does *anti*-periplanar geometry explain the stereochemistry of the E2 reaction?

E2 eliminations – stereochemical implications

How does anti-periplanar geometry explain the stereochemistry of the E2 reaction?

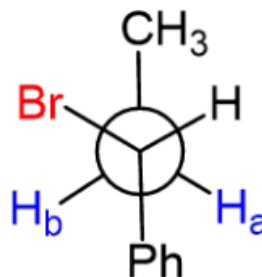


Conformation 1



$\beta\text{-H}_b$ *anti*-periplanar
to the leaving group

Conformation 2

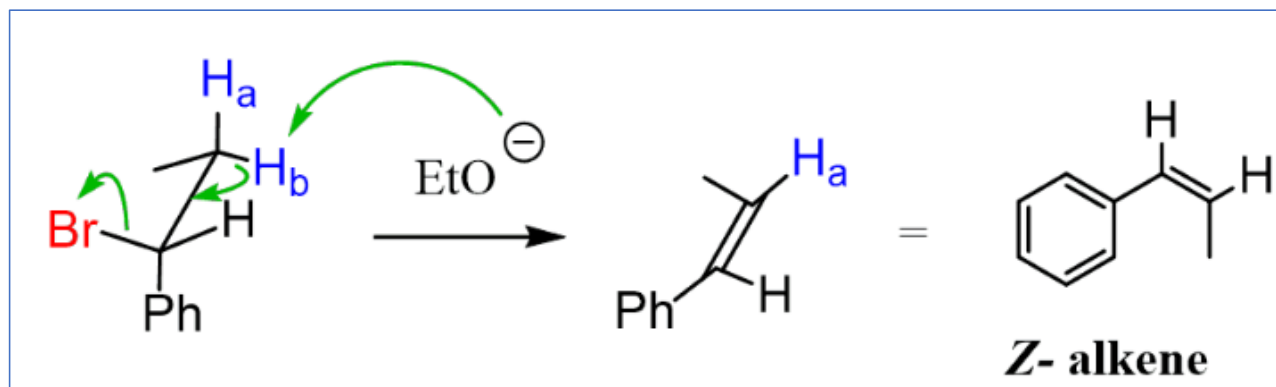
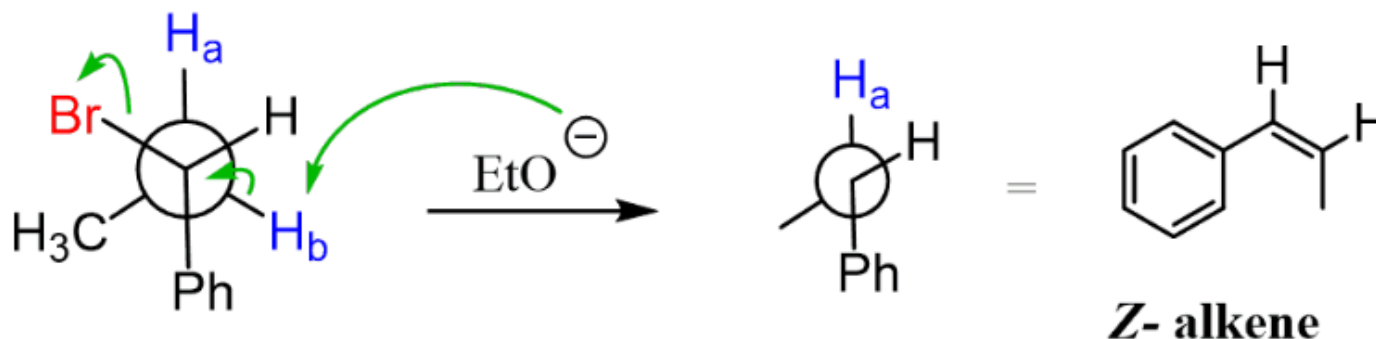


$\beta\text{-H}_a$ *anti*-periplanar
to the leaving group

There are two conformations that allow having a β -hydrogen anti-periplanar to the leaving group:

E2 eliminations – stereochemical implications

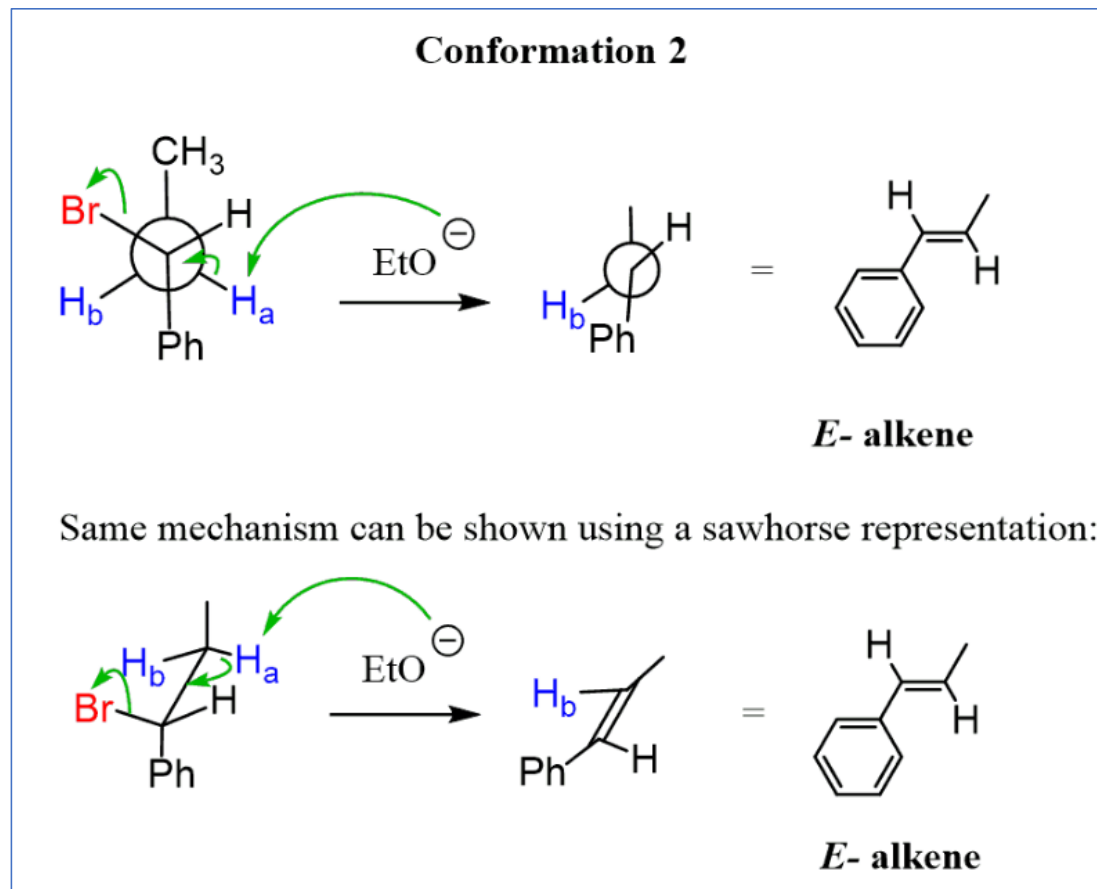
Conformation 1



- The first conformation leads to the formation of the cis alkene.
- Not stable (the extra gauche interaction between the methyl and phenyl groups as seen in the [Newman projection](#).)

E2 eliminations – stereochemical implications

- The second conformation puts the phenyl and methyl groups at anti geometry and there is only one gauche interaction between the methyl and Br groups.



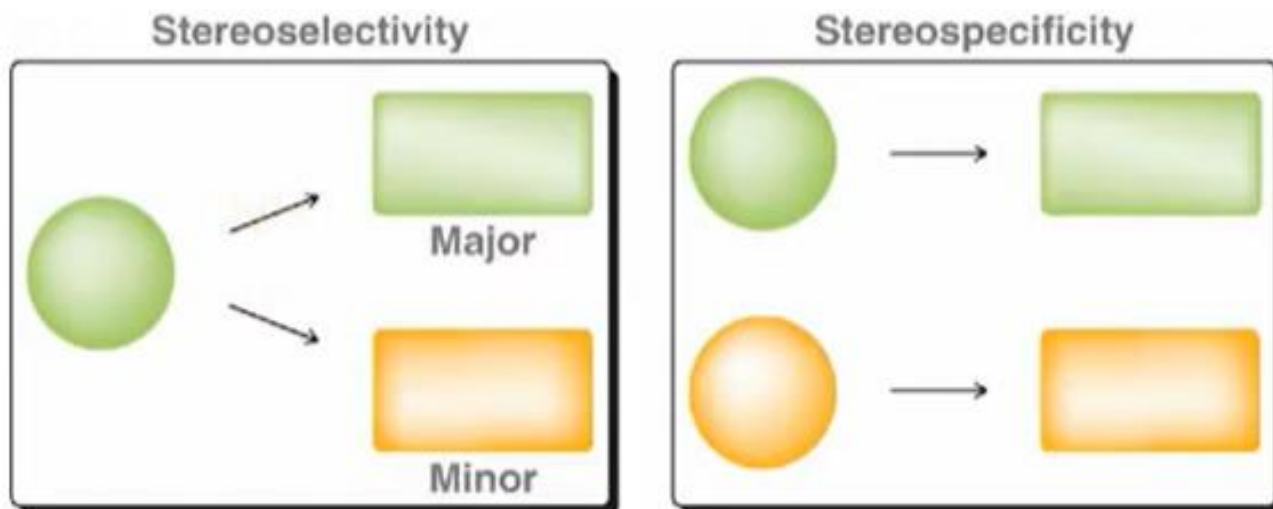
- E2 reaction is stereoselective when there are two β -hydrogens and selects the more stable, thermodynamic product

E2 eliminations – stereochemical implications

- E2 eliminations are stereospecific as well

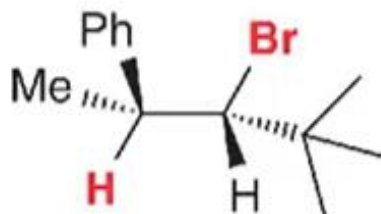
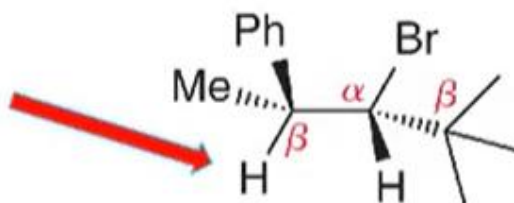
Stereospecificity: stereochemistry of the reactants controls the outcome of the reaction. The substrate is stereoisomeric and results in one stereoisomer as the product

Stereoselectivity: The substrate can produce two isomers as products, where one is the major product



E2 eliminations – stereochemical implications

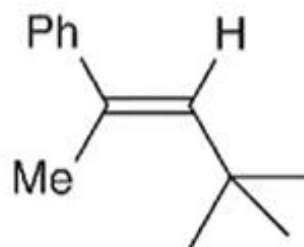
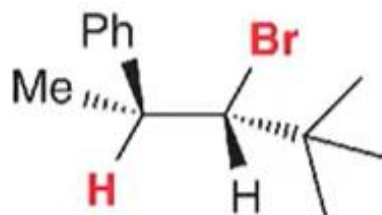
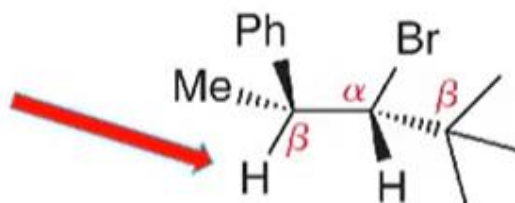
There is only one
 β -hydrogen to be removed
For E2 elimination to occur



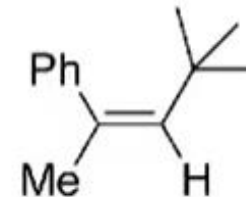
Write the possible product

E2 eliminations – stereochemical implications

There is only one
 β -hydrogen to be removed
For E2 elimination to occur

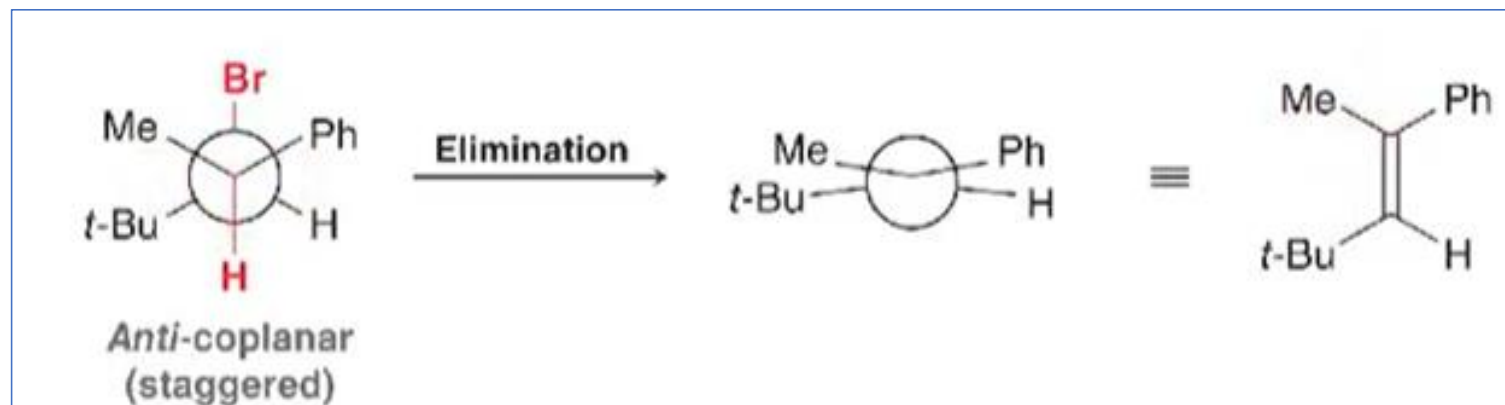
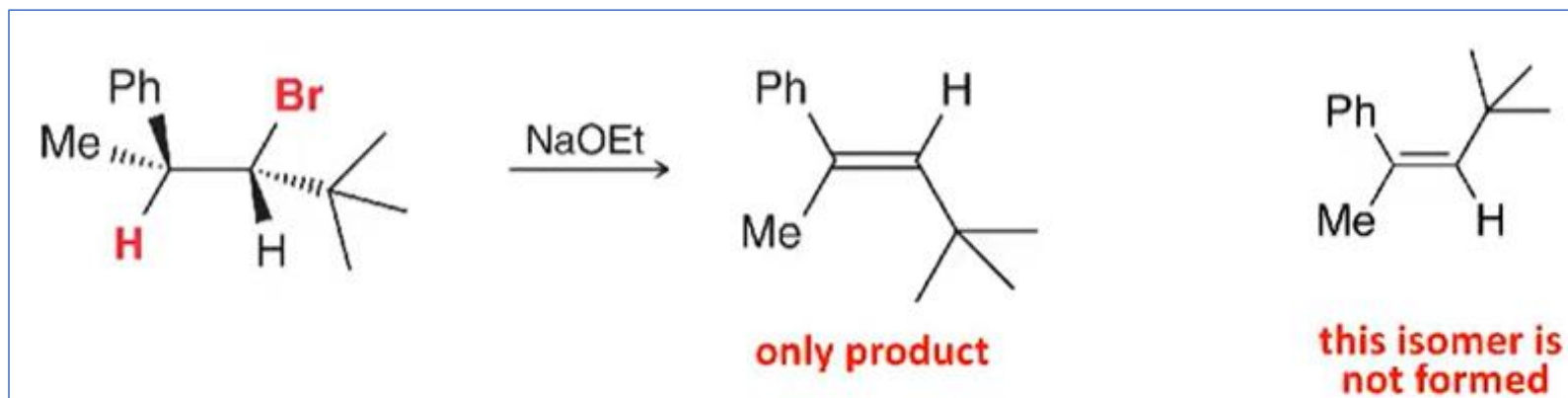


only product



this isomer is
not formed

E2 eliminations – stereochemical implications



E2 eliminations – stereochemical implications

Write the only possible products



E2 Eliminations – 6 membered rings

- The stereochemical requirement of an anti-periplanar geometry in an E2 reaction has important consequences for compounds containing six-membered rings.

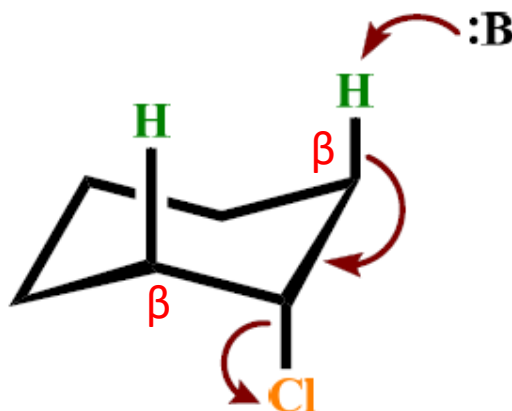
Cyclohexane



- For E2 elimination, the C—Cl bond must be anti-periplanar to the C—H bond on a β carbon, and this occurs only when the *H and Cl atoms are both in the axial position*.

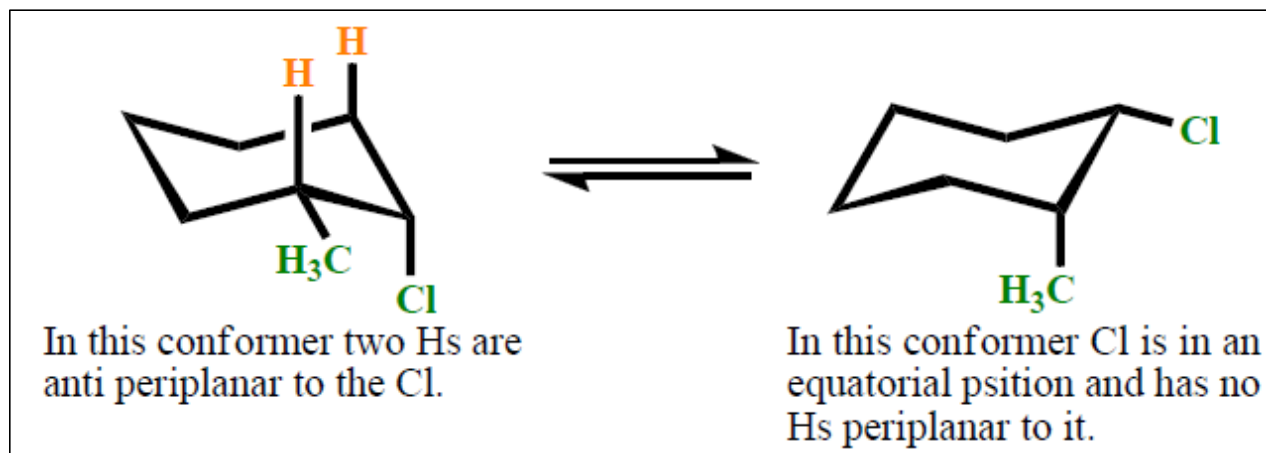
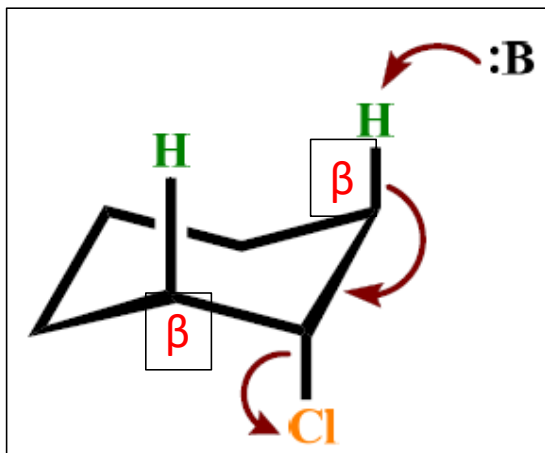
E2 Eliminations – 6 membered rings

- For E2 elimination, the C—Cl bond must be anti-periplanar to the C—H bond on a β carbon, and this occurs only when the H and Cl atoms are both in the axial position.
- The requirement for trans-diaxial geometry means that elimination must occur from the less stable conformer

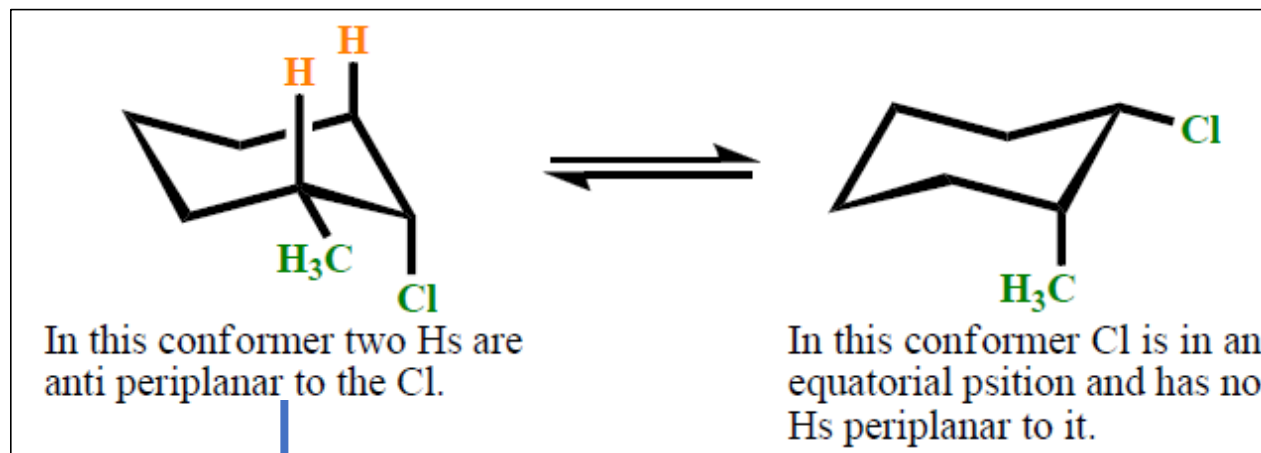


E2 Eliminations – 6 membered rings

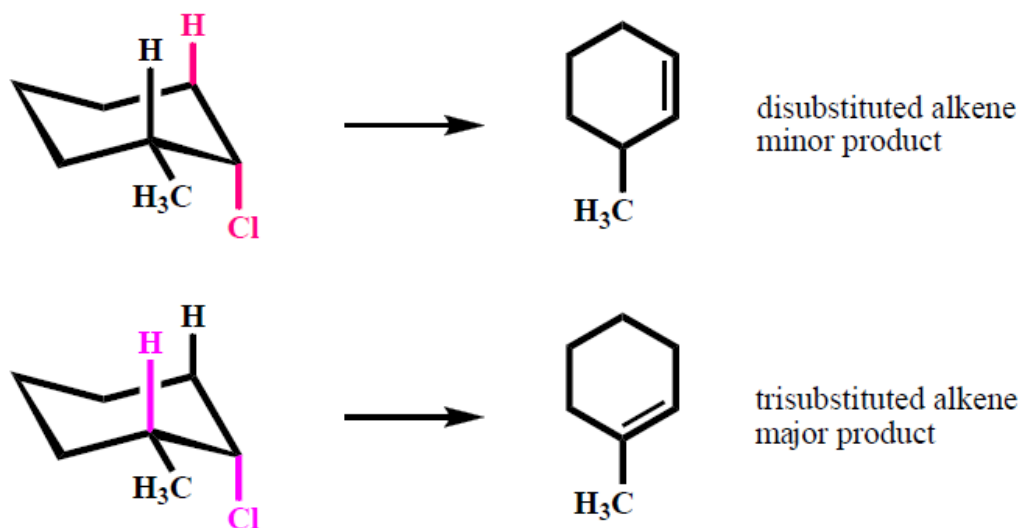
- For E2 elimination, the C—Cl bond must be anti-periplanar to the C—H bond on a β carbon, and this occurs only when the H and Cl atoms are both in the axial position.
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E2 Eliminations – 6 membered rings



What are the possible products?



E2 Eliminations – 6 membered rings

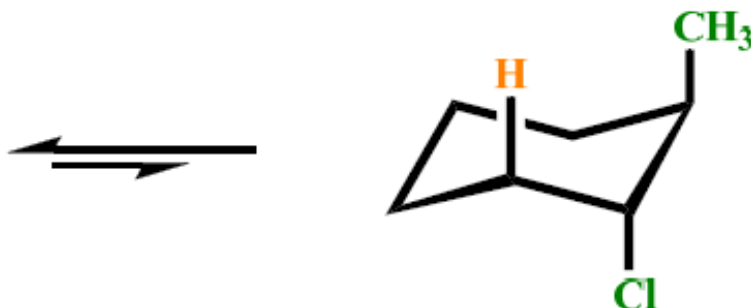


Any β -H ?

Leaving group and

H are periplanar??

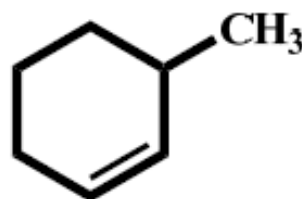
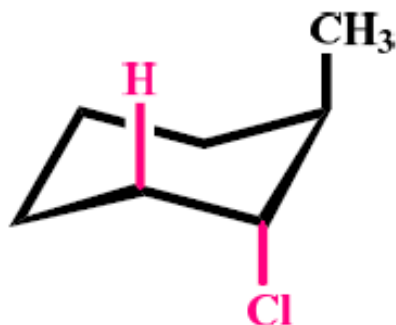
Is this Cis or trans?



In this conformer one H and one CH_3 are anti periplanar to the Cl.



Possible products?



In this case Zaitsev rule is not followed due to the requirement of anti-periplanar

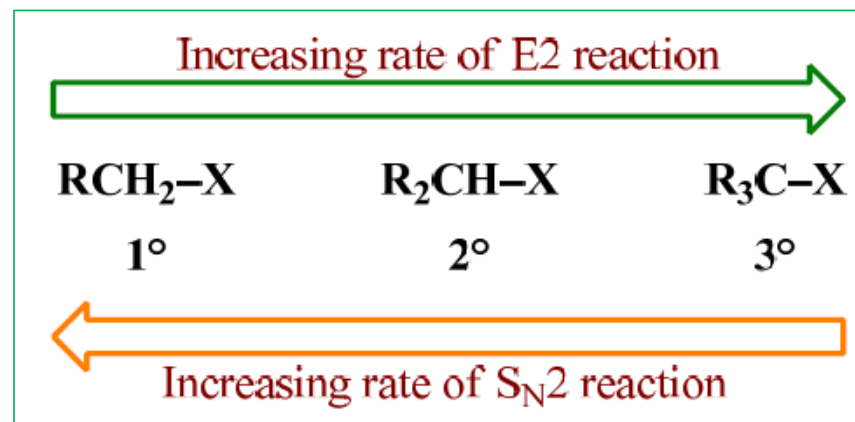
Factors affecting the rate of E2 reaction

- Substrate
 - Base
 - Leaving group
 - Solvent
-
- There are close parallels between E2 and S_N2 mechanisms in how the identity of the base, the leaving group and the solvent affect the rate.

Factors affecting the rate of an E2 reaction

Substrate

- As the number of R groups on the carbon with the leaving group increases, the rate of the E2 reaction increases.
- The increase in E2 reaction rate with increasing alkyl substitution can be rationalized in terms of transition state stability
- In the transition state, the double bond is partially formed. Thus, the transition state for a more substituted alkene is lower in energy, reducing the activation energy for the reaction and making the reaction faster.



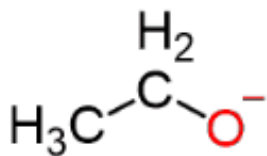
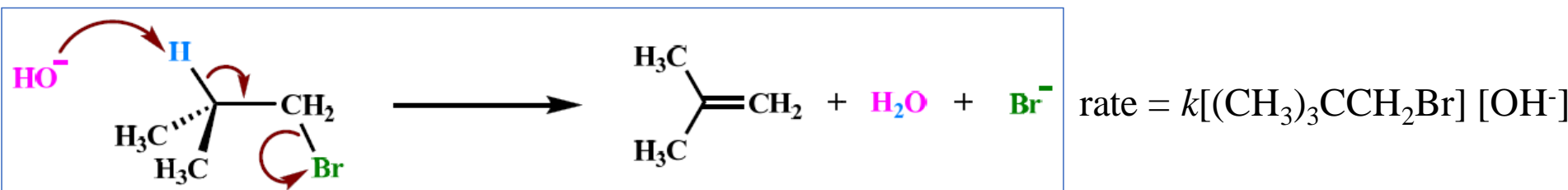
E2 reactions are **regioselective** and favor the formation of Zaitsev products.



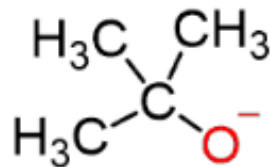
Factors affecting the rate of an E2 reaction

Base

- E2 reactions are generally run with strong, negatively charged bases like OH^- and OR^-



Ethoxide



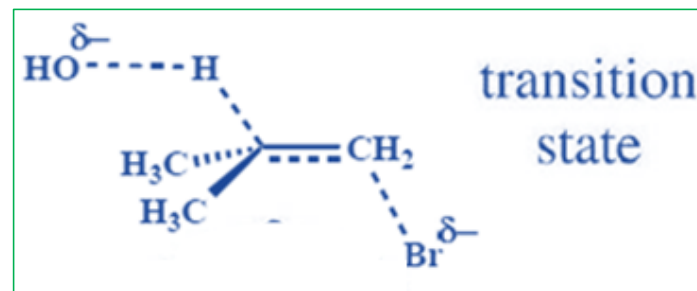
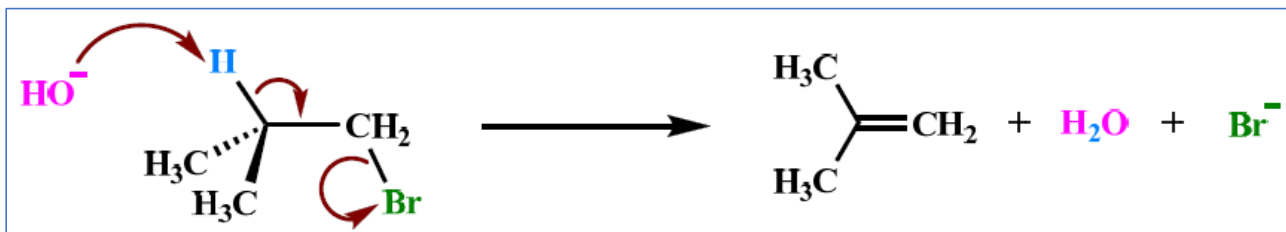
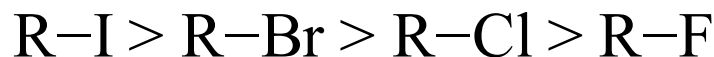
t-Butoxide

Which is more basic?

Factors affecting the rate of an E2 reaction

Leaving group

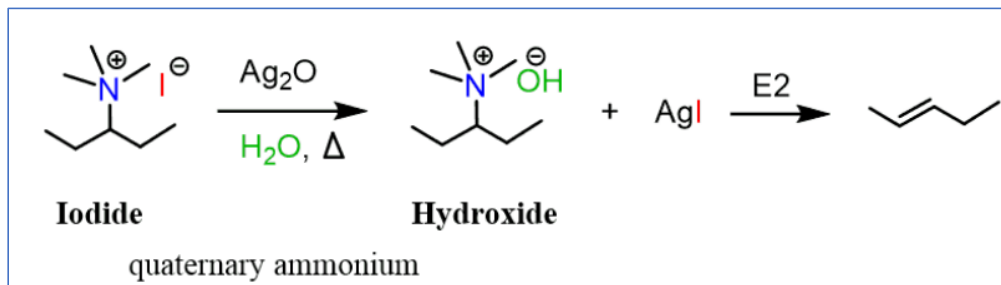
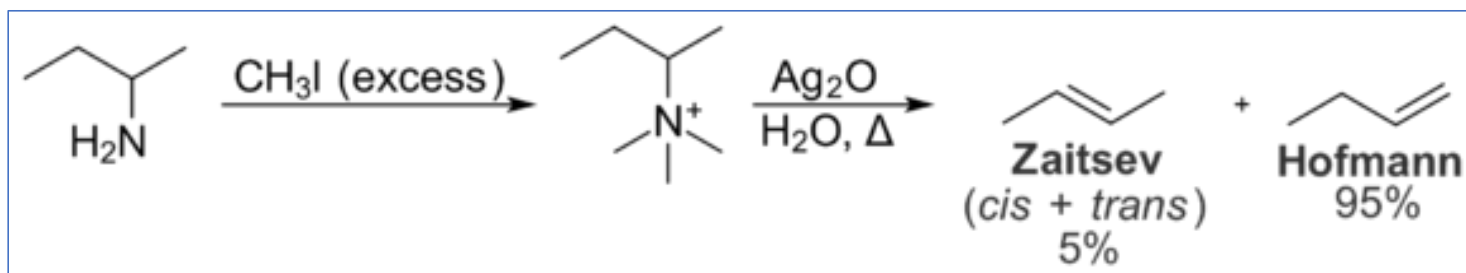
- There is a partial breaking of the bond to the leaving group in the transition state.
- So, the better the leaving group the faster the E2 reaction.



The Hofmann elimination

Amines as leaving groups

- Hofmann elimination is an elimination reaction of an amine to form alkenes.
- The least stable alkene (the one with the fewest substituents on the carbons of the double bond), called the **Hofmann product**, is formed.



Why not just use a hydroxide instead of Ag_2O and where is the hydroxide actually coming from when Ag_2O is added?

The Hofmann elimination

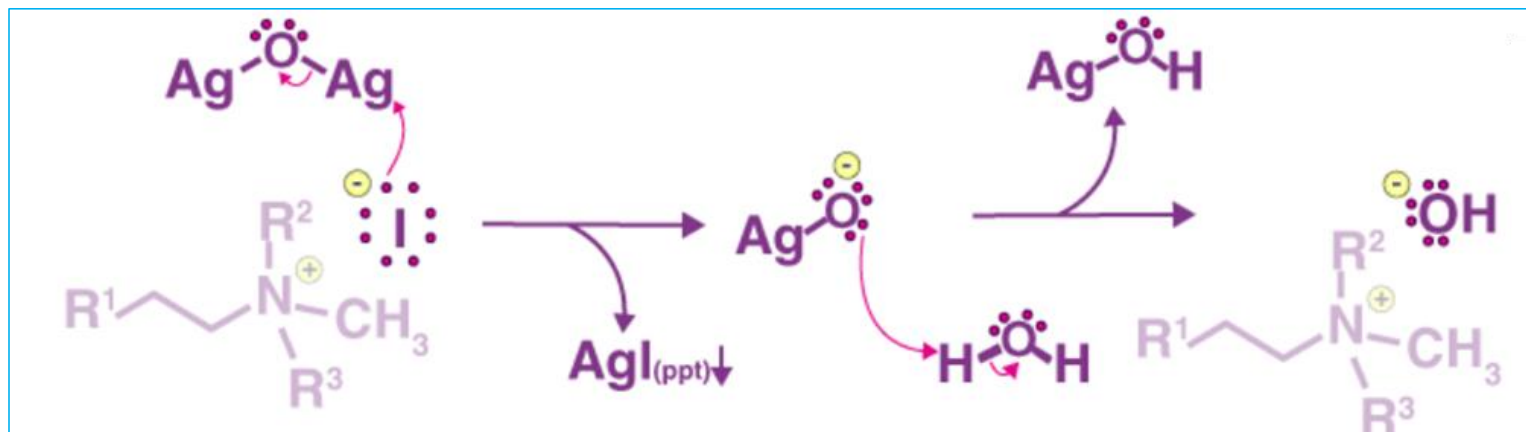
Iodide is a large ion



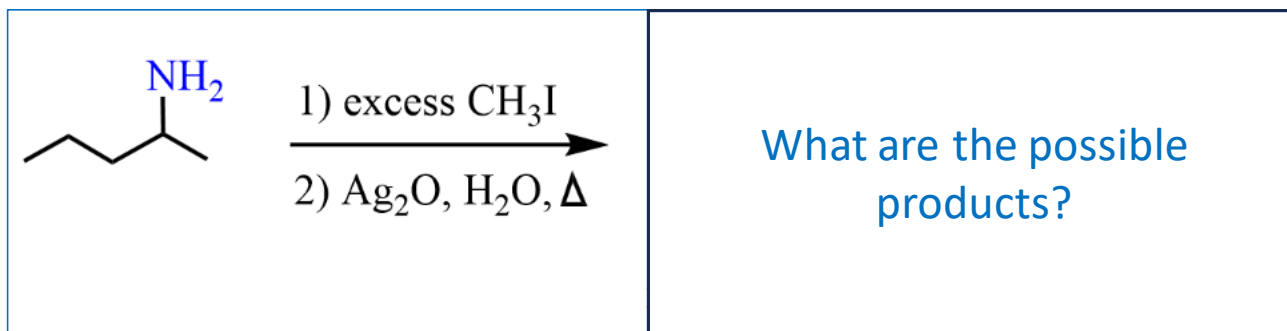
Negative charge blocks the base

- Iodide is a counter ion and not the leaving group here
- Leaving group is 4° ammonium group

- **Silver oxide captures the iodide forming a nice precipitate** and replacing the counterion of the quaternary ammonium salt with a hydroxide.

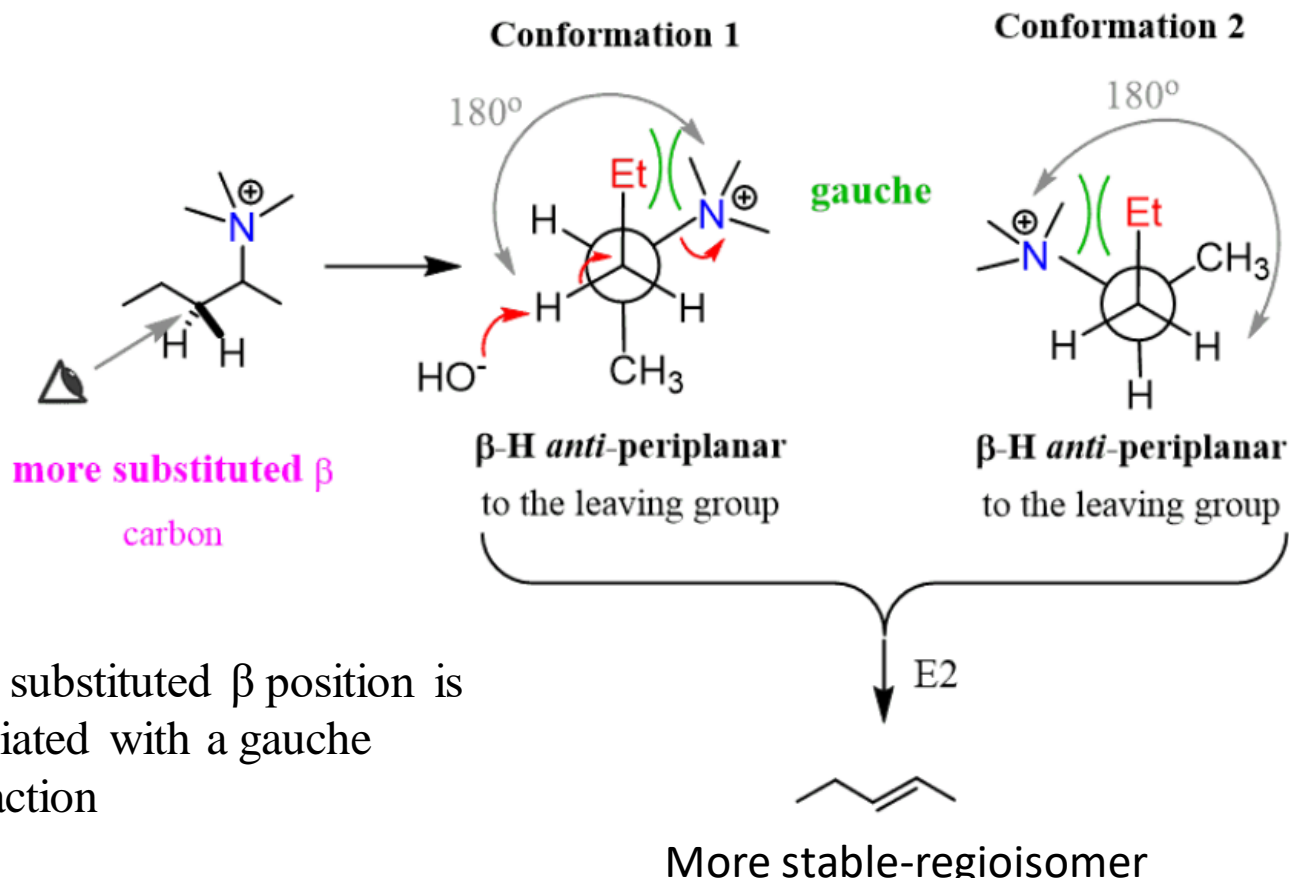
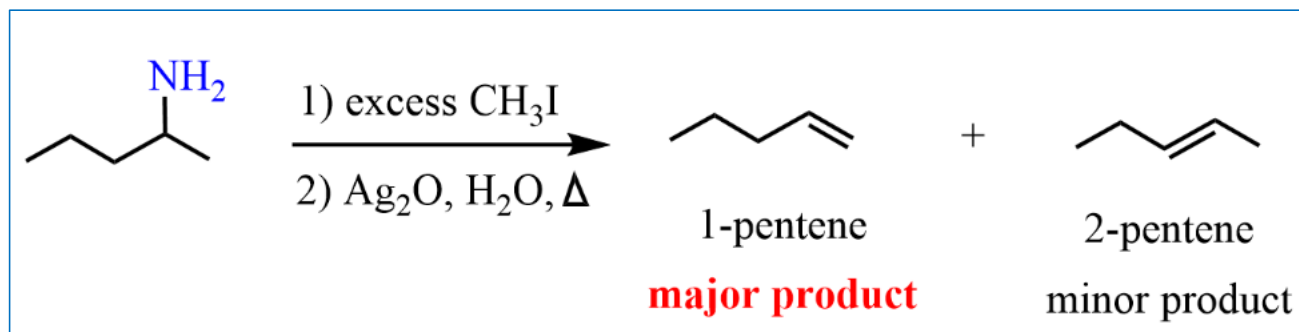


The Hofmann elimination - Regioselectivity



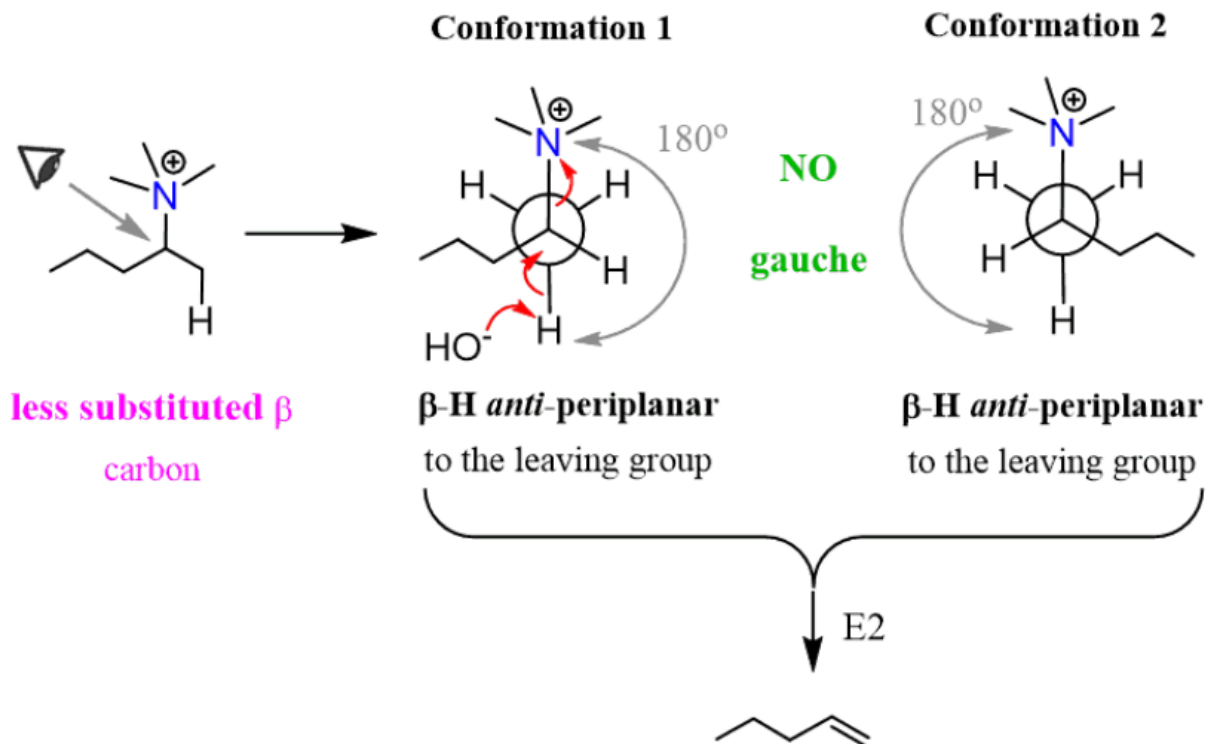
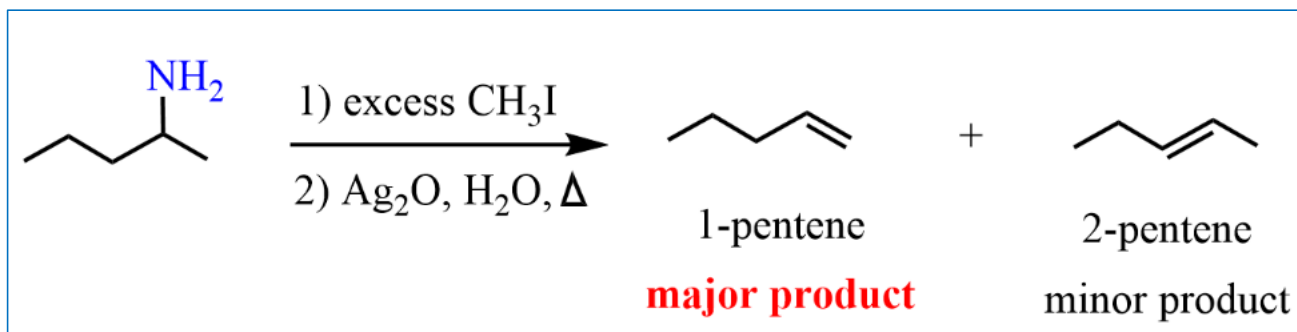
How can you explain formation of less stable regioselective isomer as major?

The Hofmann elimination - Regioselectivity



- more substituted β position is associated with a gauche interaction

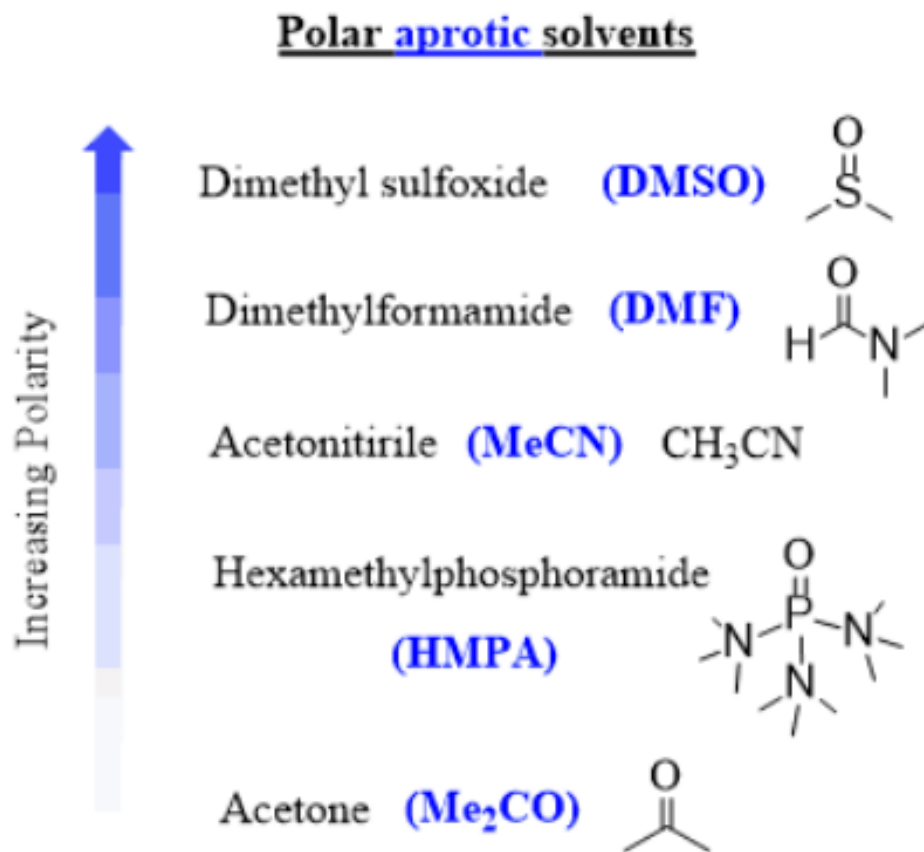
The Hofmann elimination - Regioselectivity



Factors affecting the rate of an E2 reaction

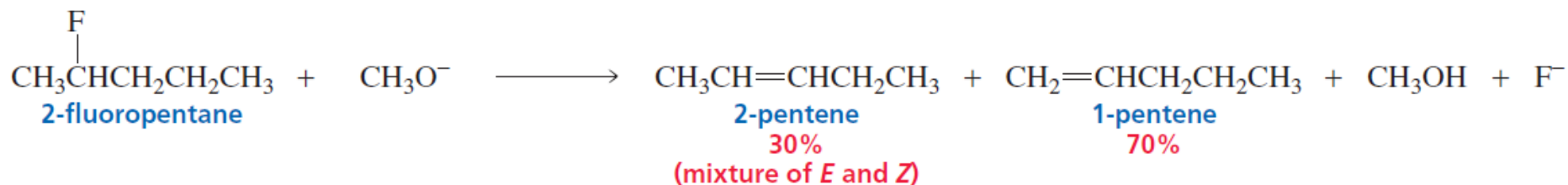
Solvent

Like S_N2 , polar aprotic solvents favour E2 reactions

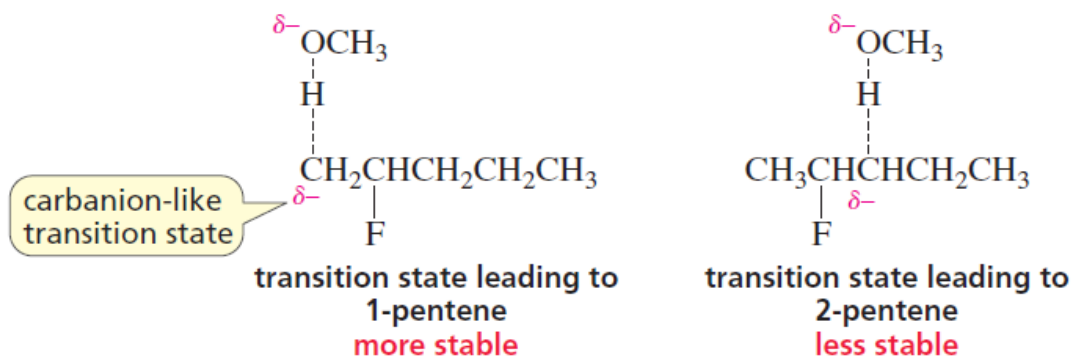


E2 eliminations – The case of Alkyl fluorides

- Alkyl Fluorides Preferentially Form the Less Stable Alkene



$ \begin{array}{c} \text{X} \\ \\ \text{CH}_3\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \end{array} + \text{CH}_3\text{O}^- \longrightarrow \begin{array}{c} \text{CH}_3\text{CH}=\text{CHCH}_2\text{CH}_2\text{CH}_3 \\ \text{(mixture of } E \text{ and } Z) \end{array} $				
Leaving group	Conjugate acid	pK _a	More stable product	Less stable product
X = I	HI	−10	81%	19%
X = Br	HBr	−9	72%	28%
X = Cl	HCl	−7	67%	33%
X = F	HF	3.2	30%	70%



E2 eliminations – the case of bulky base

Table 9.4 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 \\ \quad \\ \text{CH}_3 \quad \text{Br} \end{array} + \text{RO}^- \longrightarrow \begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{C}=\text{CCH}_3 \\ \\ \text{CH}_3 \end{array} + \begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{CHC}=\text{CH}_2 \\ \\ \text{CH}_3 \end{array} $		
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%

E2 eliminations summary

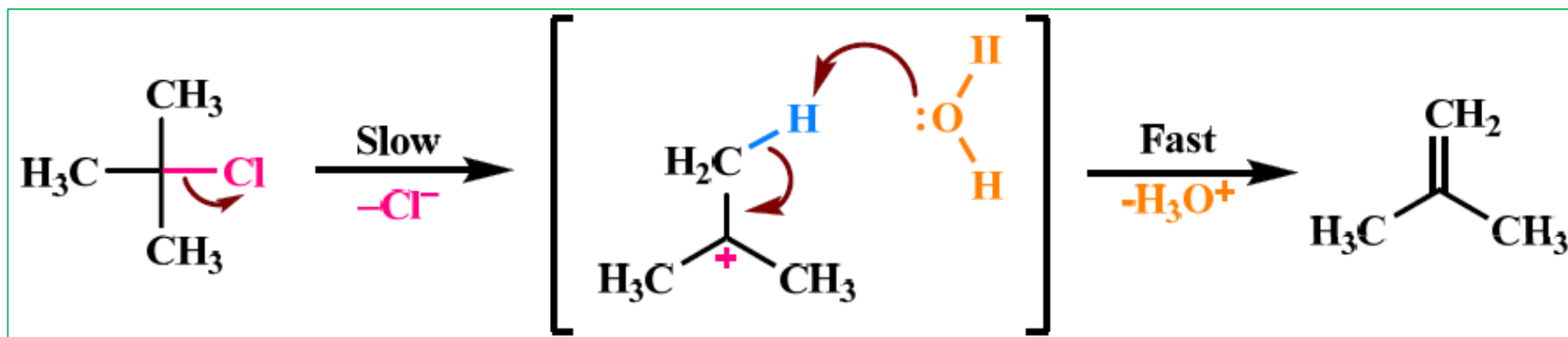
Kinetics	–	Second order
Mechanism	–	Single step
Identity of R group	–	More substituted halides react faster Rate: $R_3CX > R_2CHX > RCH_2X$
Strength of the base	–	Stronger bases favor the reaction
Leaving group	–	Better leaving group leads to faster reaction rates
Type of solvent	–	Favored by polar aprotic solvents

Stereochemical implications

- Anti-periplanar requirement
- Regioselective follows Zaitsev rule
- Stereoselective – selects the more stable one
- Stereospecific – stereoisomerism of substrate is conserved

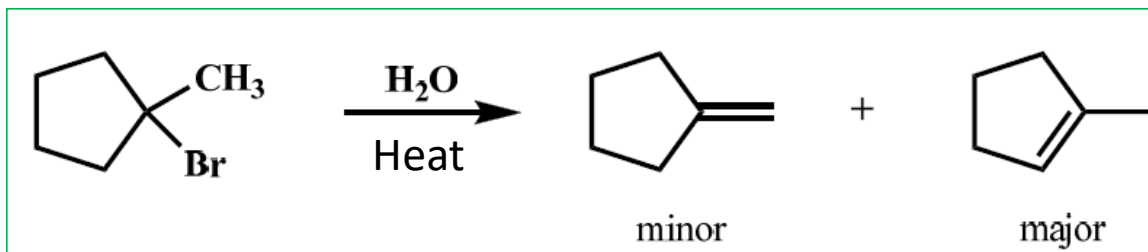
The E1 elimination

- The E1 reaction proceeds via a two-step mechanism: the bond to the leaving group breaks first before the π bond is formed. The slow step is unimolecular, involving only the alkyl halide.

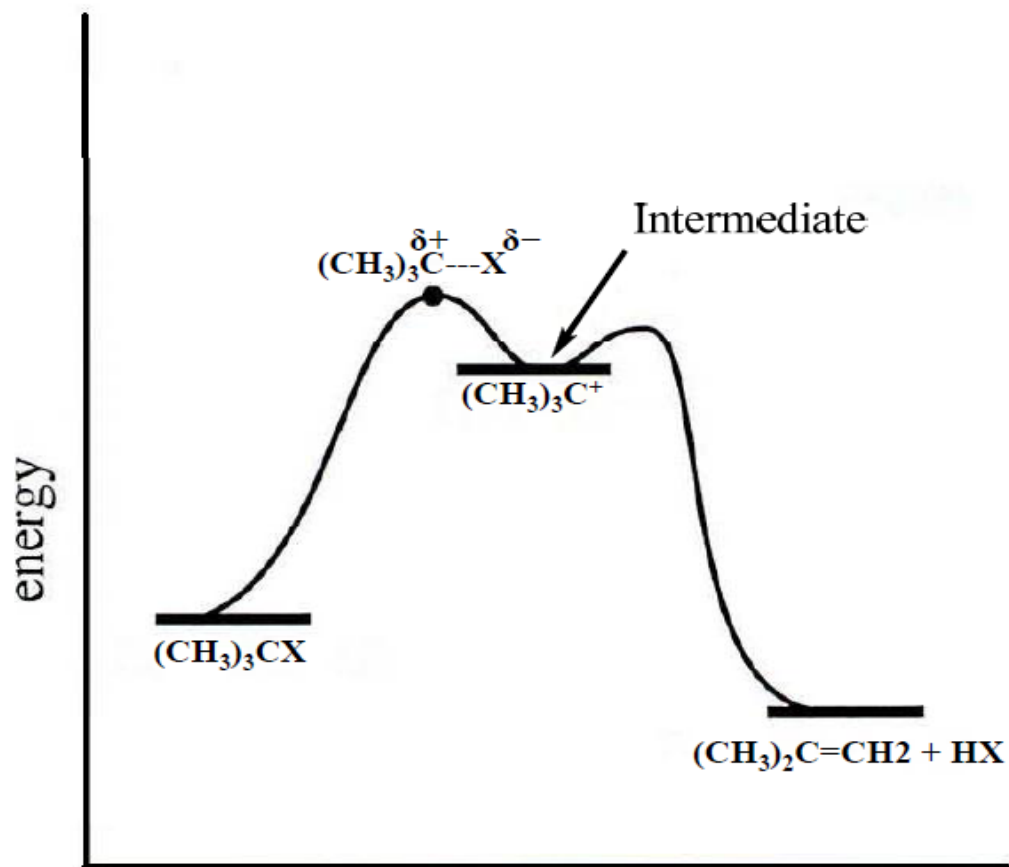
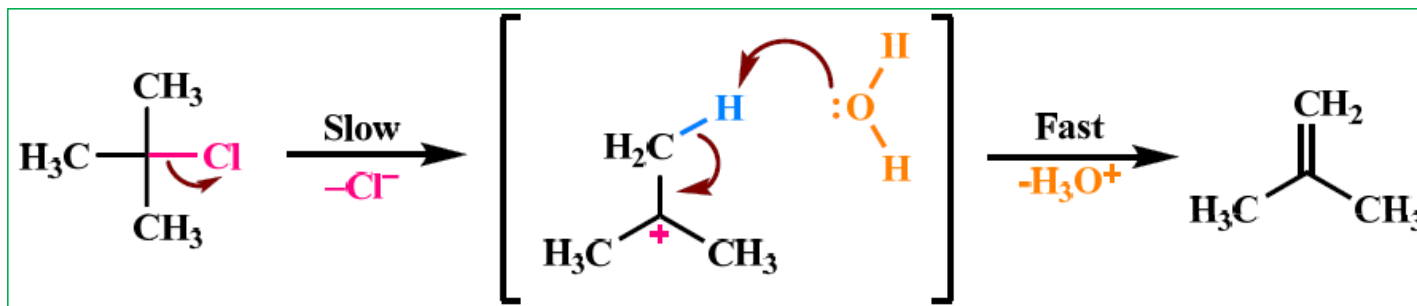


It exhibits first-order kinetics, **rate** = $k[(\text{CH}_3)_3\text{CCl}]$

- E1 reactions also are regioselective and follow Zaitsev rule

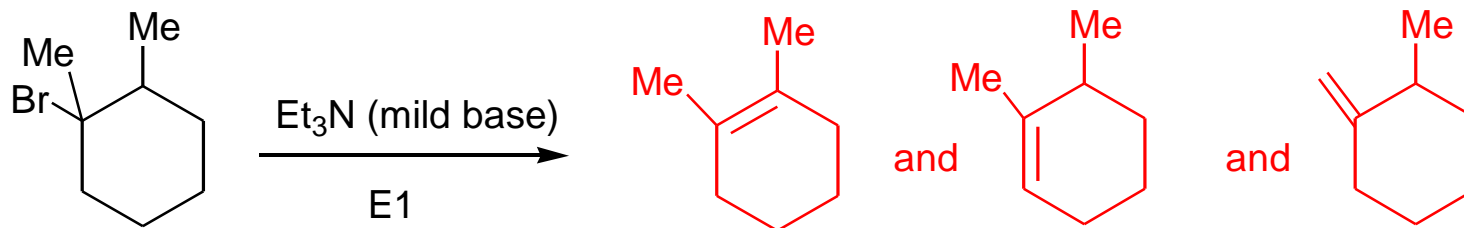


Energy profile of an E1 reaction

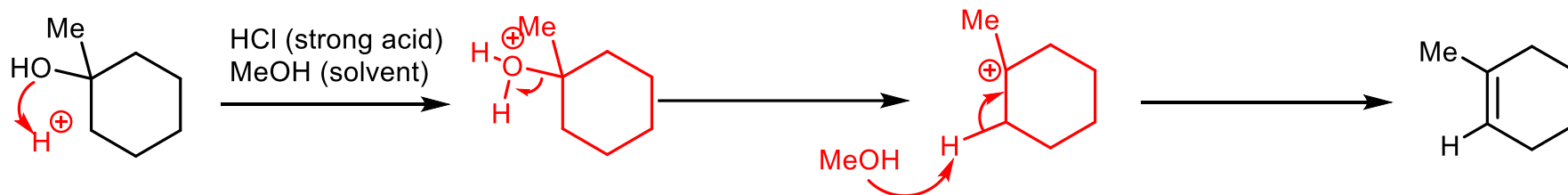


The E1 elimination

Identify the major product?



-OH as a leaving group



Why is acid needed when the alcohol is the leaving group – why can't we rely on a base?

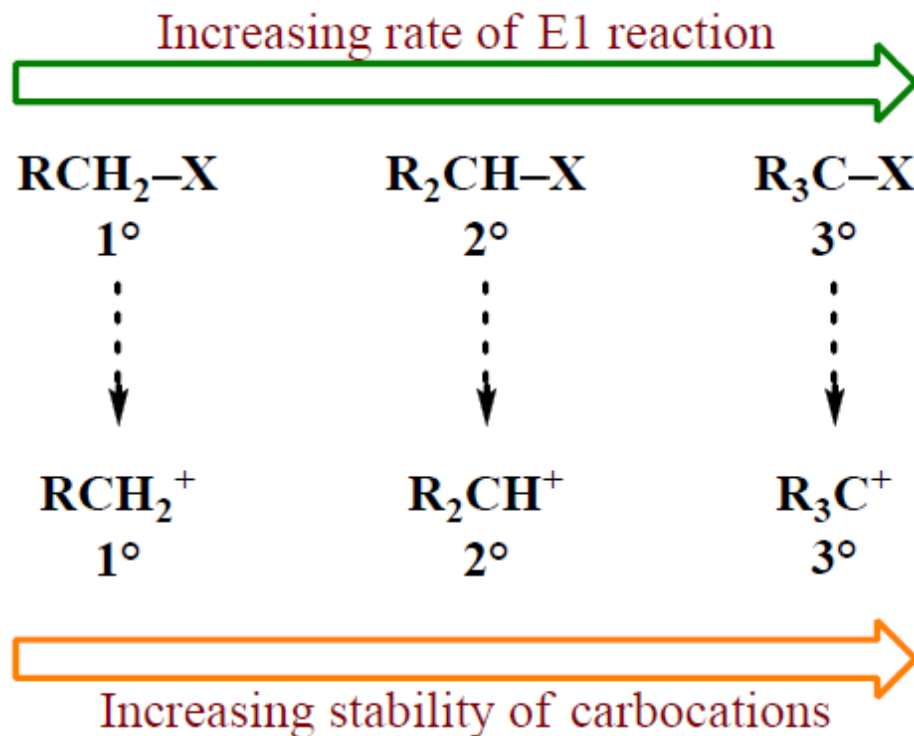
Factors affecting the rate of E1 reaction

- Substrate
 - Base
 - Leaving group
 - Solvent
-
- There are close parallels between E1 and S_N1 mechanisms in how the identity of the base, the leaving group and the solvent affect the rate.

Factors affecting the rate of an E1 reaction

Substrate

- As the number of R groups on the carbon with the leaving group increases, the rate of the E1 reaction increases.



Factors affecting the rate of E1 reaction

- Substrate
- Base: Favoured by weak bases such as water, alcohol, etc.
- Leaving group: Better leaving group
- Solvent: Polar protic solvents
- There are close parallels between E1 and S_N1 mechanisms in how the identity of the base, the leaving group and the solvent affect the rate.

E1 eliminations summary

Kinetics	–	First order
Mechanism	–	Two steps
Identity of R group	–	More substituted halides react faster Rate: $R_3CX > R_2CHX > RCH_2X$
Strength of the base	–	Favored by weaker bases such as H_2O and ROH
Leaving group	–	Better leaving group leads to faster reaction rates. Just as in S_N1 reactions, the rate determining step involves the $C-X$ bond cleavage
Type of solvent	–	Favored by polar protic solvents, which can stabilize the ionic intermediates

Eliminations and substitutions

Table 9.7 Summary of the Products Expected in Substitution and Elimination Reactions

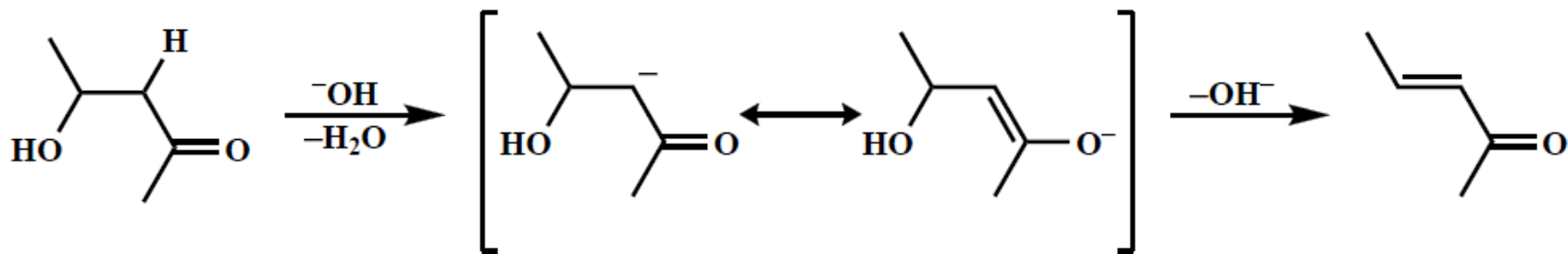
Class of alkyl halide	S_N2 and E2	S_N1 and E1
primary	primarily substitution, unless there is steric hindrance in the alkyl halide or nucleophile, in which case elimination is favored	cannot undergo S_N1 /E1 solvolysis reactions
secondary	both substitution and elimination; the stronger and bulkier the base and the higher the temperature, the greater the percentage of elimination	cannot undergo S_N1 /E1 solvolysis reactions
tertiary	only elimination	both substitution and elimination with substitution favored

E1cB elimination

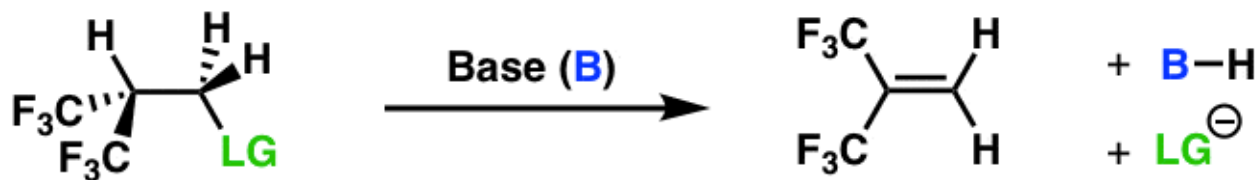
- An elimination reaction that happens when a compound bearing a poor leaving group and an acidic hydrogen is treated with a base.



- E1cB stands for **E**limination **U**nimolecular **c**onjugate **B**ase. The reaction is unimolecular from the conjugate base of the starting compound.
- The electron withdrawing group (EWG) can be a carbonyl group, a nitro group, etc.

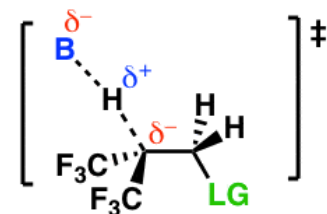
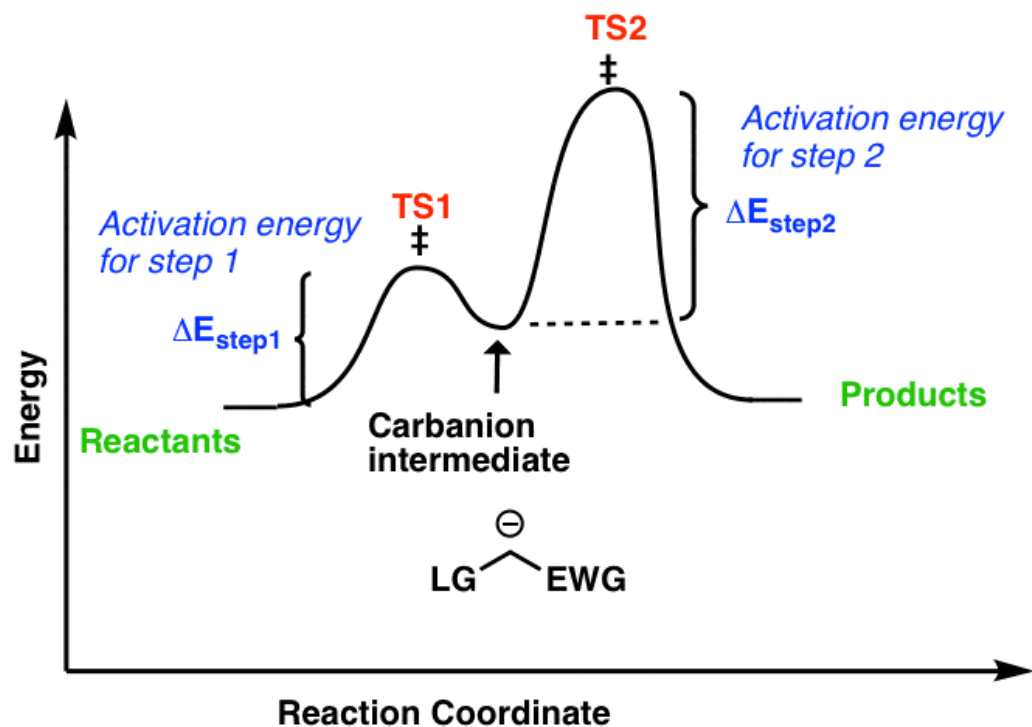


E1cB elimination

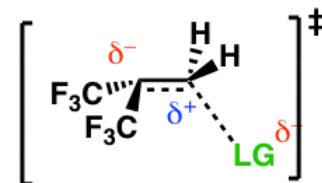


Reaction Coordinate Diagram For An E1cB Reaction

for a case where deprotonation is fast, and elimination is slow



Deprotonation to give carbanion (fast step)



Formation of pi bond with loss of leaving group (rate determining step)

E1cB elimination

- **How might we determine that some reactions follow an E1cB mechanism versus an E2 mechanism? How do you know the difference?**
- Kinetic isotope effect
- C-D (deuterium) bonds are slightly shorter (and stronger) than comparable C-H bonds.
- If C-H bond breaking occurs in the rate determining step, then the rate for the reaction of the C-H compound (k_H) should be slightly faster than the rate of the deuterium labelled analog with a C-D bond (k_D).

E1cB elimination

Comparing the E1, E2, and E1cB Mechanisms

E1

Two steps

- 1) C-LG breaks
- 2) C-H breaks
C-C (pi) forms



Carbocation intermediate

Carbocation stabilized by electron **donating** groups

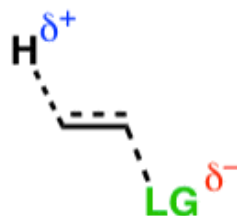
Assisted by **good** leaving groups

No strict requirement on stereochemistry of C-H and C-LG

E2

One step

- C-H breaks, C-C (pi) forms
C-LG breaks, all at same time



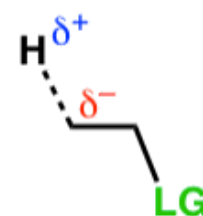
No intermediate (concerted)

C-H and C-LG are **anti**

E1cB

Two steps

- 1) C-H breaks
- 2) C-LG breaks
C-C (pi) forms



Carbanion intermediate

Carbanion stabilized by electron **withdrawing** groups

Assisted by **poor** leaving groups

No strict requirement on stereochemistry of C-H and C-LG