Organic Chemistry

Alkyl Halides & Elimination Reaction

by

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Expected Outcomes

In the completion of this chapter, student will have the ability to:

- Classify alkyl halides
- Draw and name alkyl halides using IUPAC nomenclature
- Describe physical properties and example of alkyl halides
- Compare and write nucleophilic substitution (S_N2 and S_N1) and elimination (E1 and E2) of alkyl halides

Contents

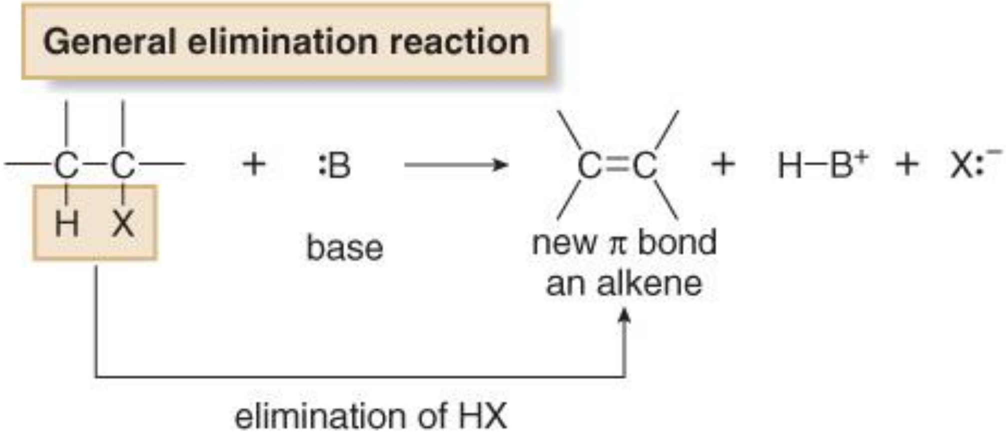
- Organic synthesis
- mechanism of elimination

Elimination reactions

General Features:

- Elimination reactions involve the loss of elements from the starting material to form a new π bond in the product.

◆ **Alkyl halides undergo elimination reactions with Brønsted–Lowry bases. The elements of HX are lost and an alkene is formed.**



General elimination reaction

- The most common bases used in elimination reactions are negatively charged oxygen compounds, such as HO^{-} and its alkyl derivatives, RO^{-}, called alkoxides.

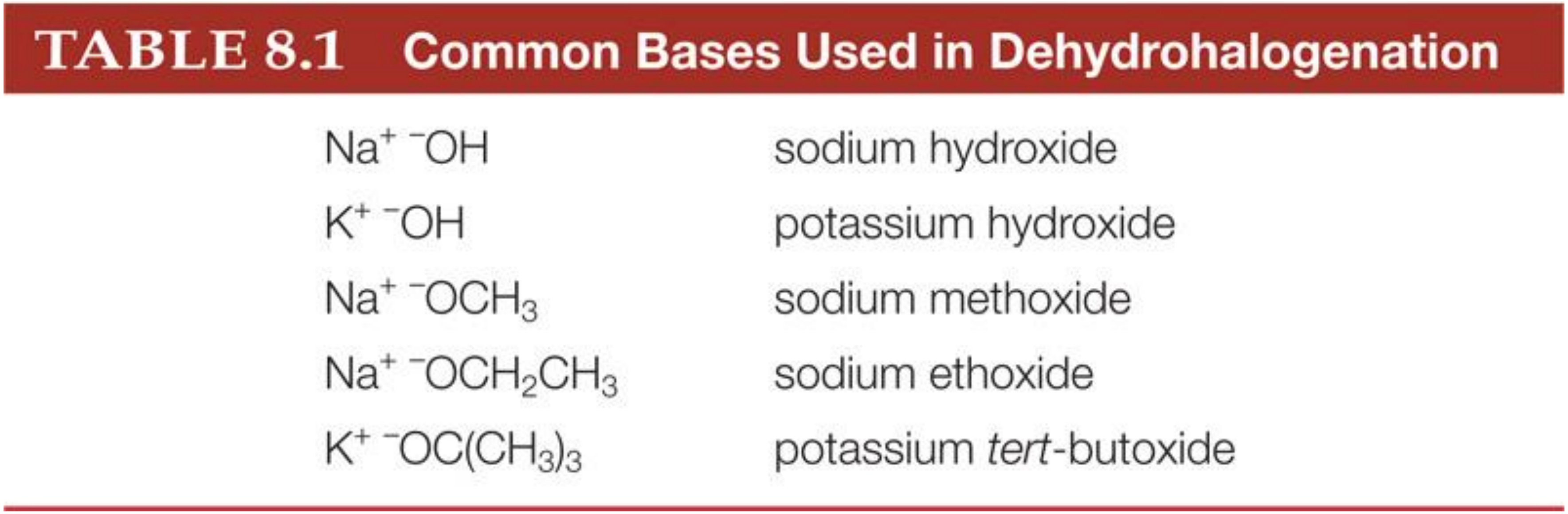
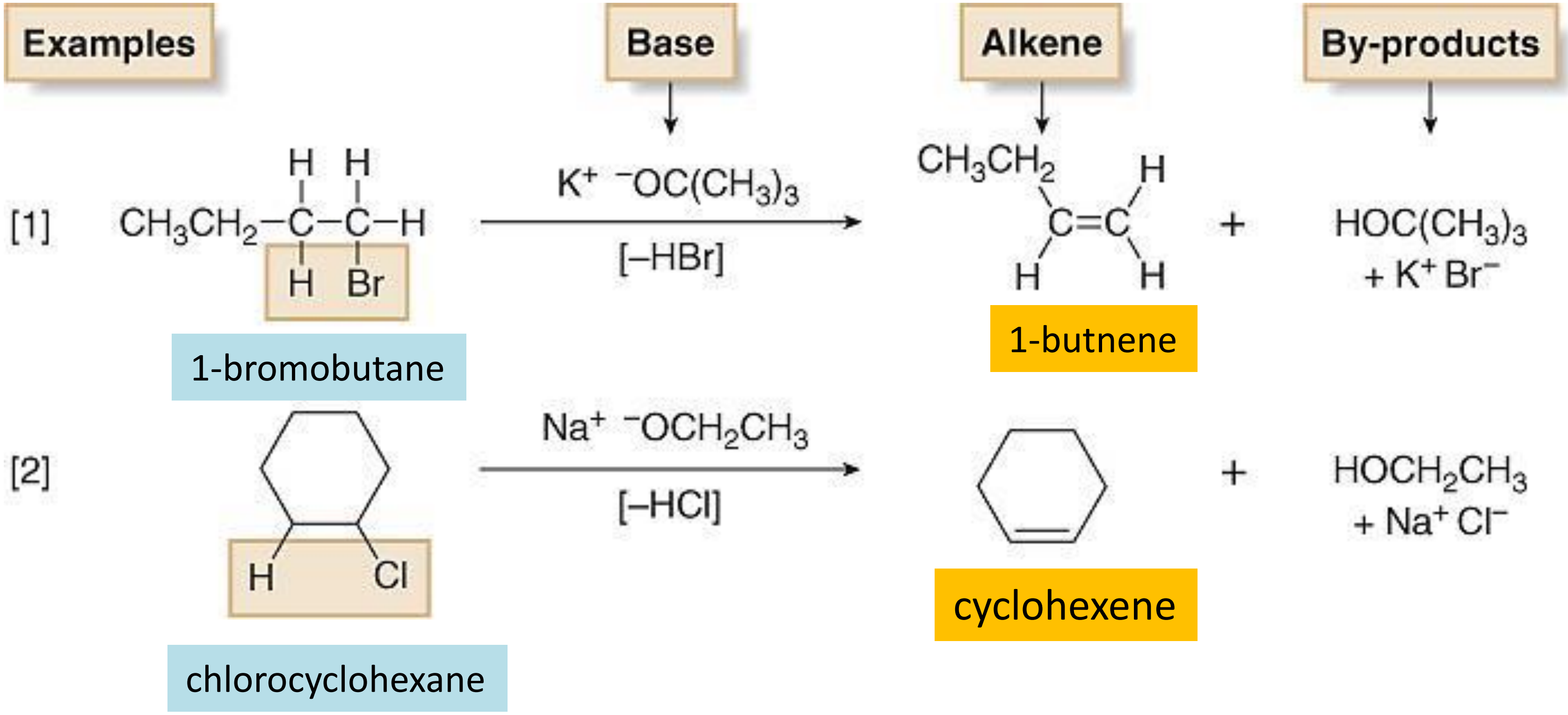


TABLE 8.1 Common Bases Used in Dehydrohalogenation

$Na^{+}\ {}^{-}OH$	sodium hydroxide
$K^{+}\ {}^{-}OH$	potassium hydroxide
$Na^{+}\ {}^{-}OCH_3$	sodium methoxide
$Na^{+}\ {}^{-}OCH_2CH_3$	sodium ethoxide
$K^{+}\ {}^{-}OC(CH_3)_3$	potassium *tert*-butoxide

Elimination Reaction with Strong Bases

- Equations [1] and [2] illustrate examples of elimination reactions. In both reactions a base removes the elements of an acid, HX, from the organic starting material.



Alkyl Halide & Elimination Reaction

- **Beta elimination** (elimination of a H on a carbon at the β-position relative to the carbon bearing the halide atom)

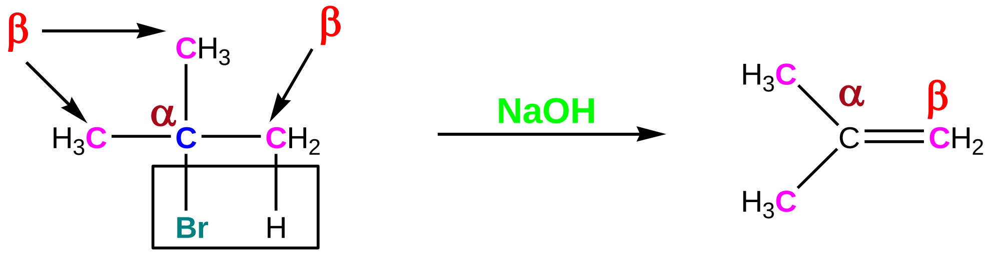
- What if there are >1 type of β- hydrogen, elimination of either leading to the formation of >1 alkene. Which alkene formation is favoured ?

- Saytzeff (Zaitsev) rule: In elimination reactions, the alkene with the greatest number of alkyl groups on the doubly-bonded carbon atoms predominates in the product mixture.

Products of Elimination Reaction:

- To draw any product of dehydrohalogenation—Find the α carbon. Identify all β carbons with H atoms. Remove the elements of H and X form the α and β carbons and form a π bond.

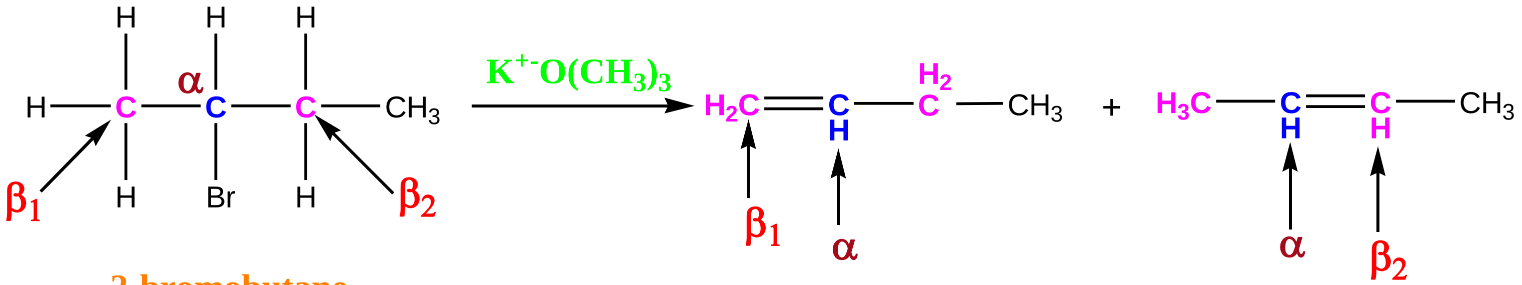
Three identical β C's:



One alkene is formed.

2-bromo-2-methylpropane

Two different β C's:



2-bromobutane

Two constitutional isomers are formed

Mechanisms of Elimination

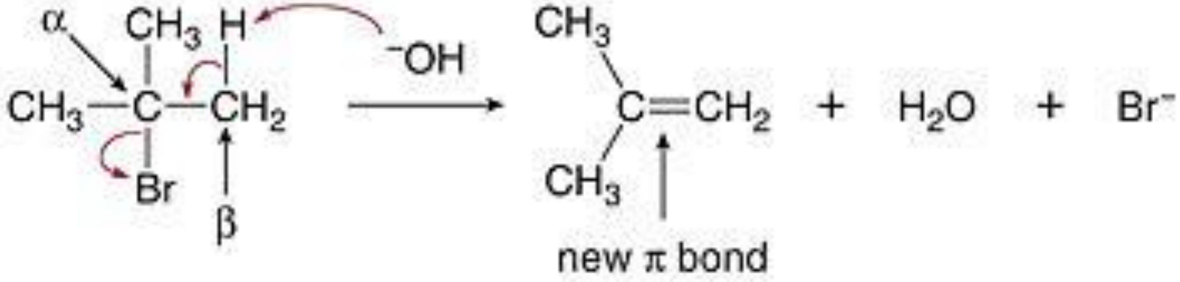
- There are two mechanisms of elimination—E2 and E1.
- E2 mechanism—bimolecular elimination
- E1 mechanism—unimolecular elimination
- The E2 and E1 mechanisms differ in the timing of bond cleavage and bond formation, analogous to the S_N2 and S_N1 mechanisms.
- E2 and S_N2 reactions have some features in common, as do E1 and S_N1 reactions.

E2 Mechanism

- The most common mechanism for dehydrohalogenation is the E2 mechanism.
- The reaction is **concerted** - all bonds are broken and formed in a single step.

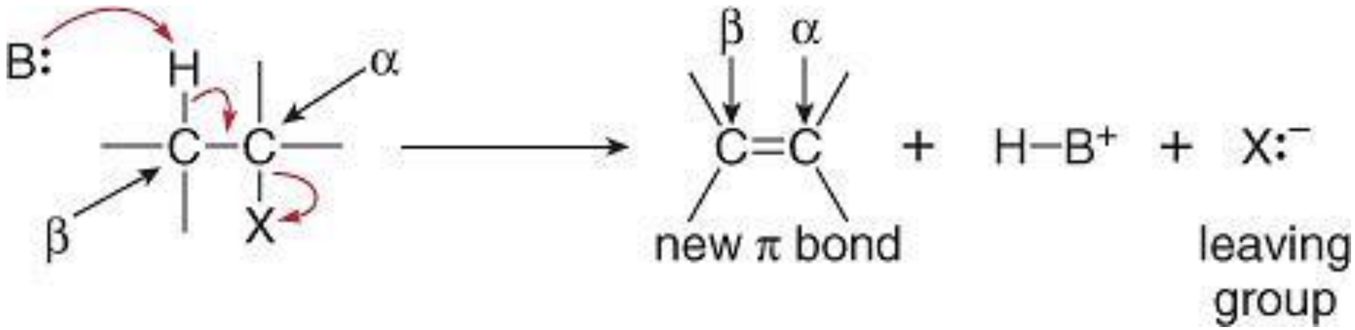
MECHANISM 8.1

The E2 Mechanism



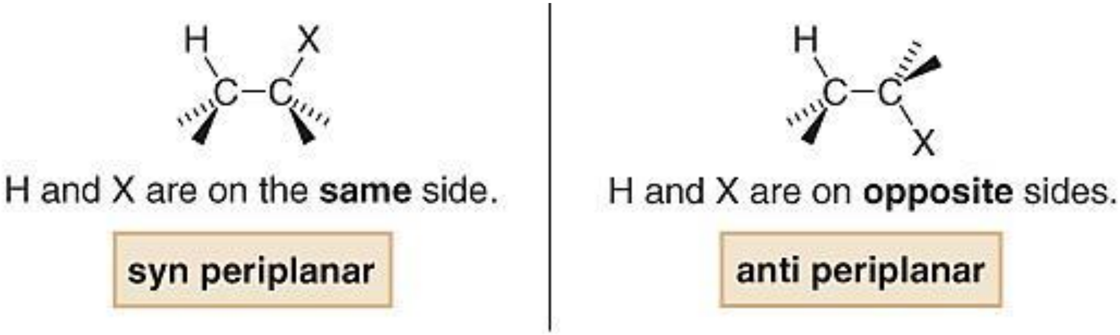
- The base ^-OH removes a proton from the β carbon, forming H_2O (a by-product).
- The electron pair in the β C – H bond forms the new π bond.
- The leaving group Br^- comes off with the electron pair in the C – Br bond.

- Dehydrohalogenation is an example of β elimination.
- The curved arrow formalism shown below illustrates how four bonds are broken or formed in the process.



Stereochemistry of the E2 Reaction

- The transition state of an E2 reaction consists of four atoms from an alkyl halide—one hydrogen atom, two carbon atoms, and the leaving group (X)—all aligned in a plane. There are two ways for the C—H and C—X bonds to be coplanar.



H and X are on the **same** side.

syn periplanar

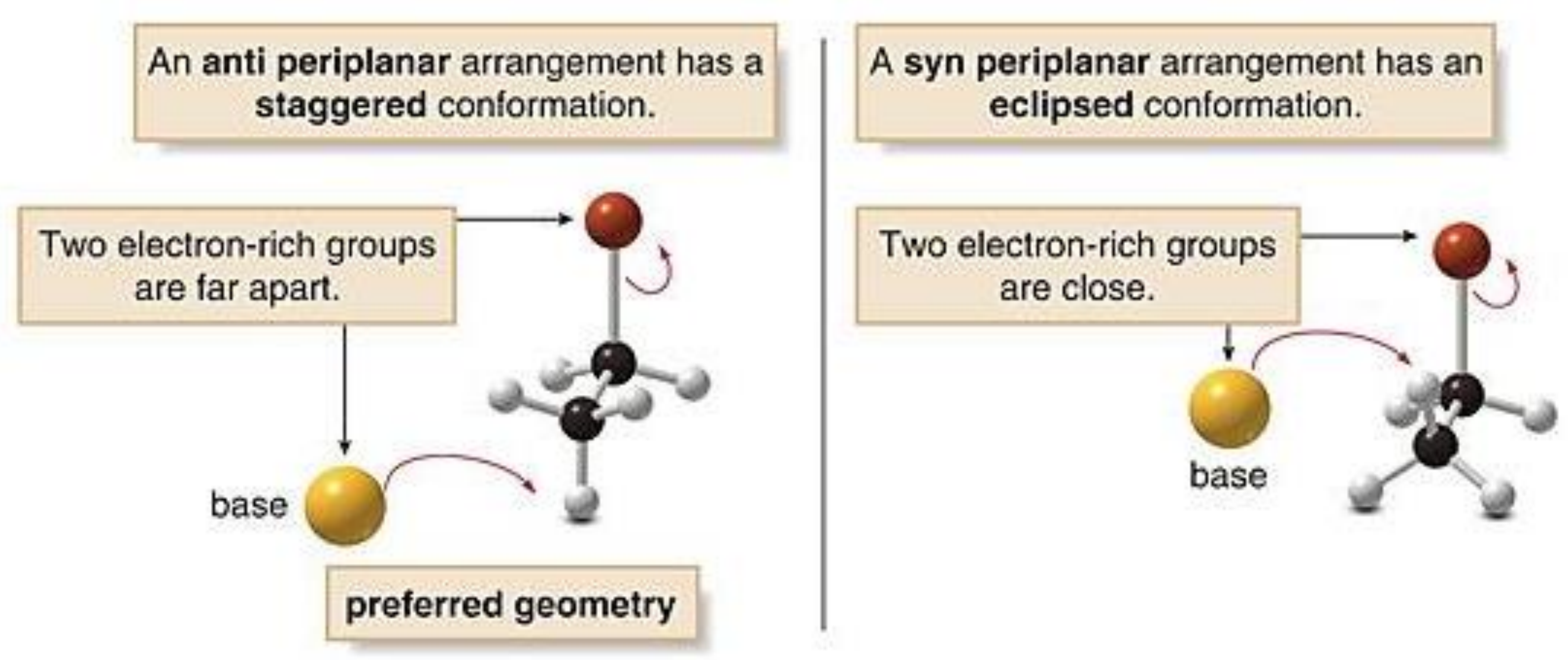
H and X are on **opposite** sides.

anti periplanar

◆ The H and X atoms can be oriented on the same side of the molecule. This geometry is called *syn periplanar.*

◆ The H and X atoms can be oriented on opposite sides of the molecule. This geometry is called *anti periplanar.*

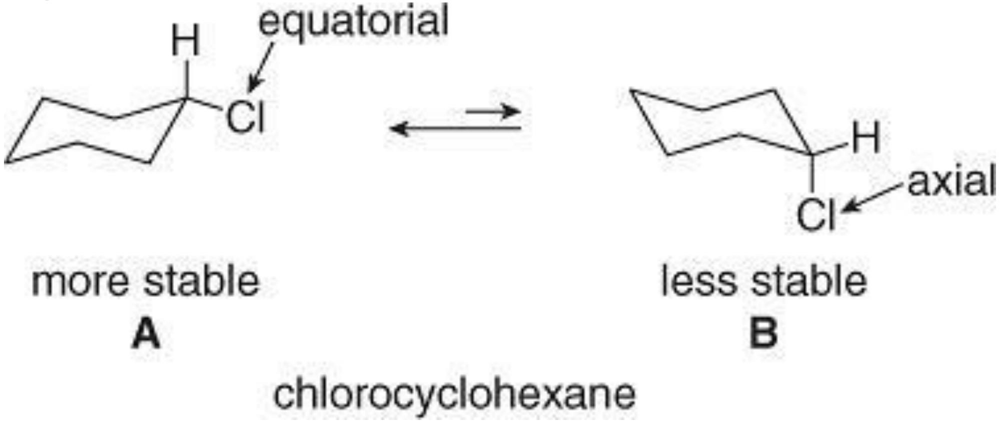
Anti Conformation Preferred for the E2 Reaction



- **E2 elimination** occurs most often in the **anti periplanar geometry**. This arrangement allows the molecule to react in the lower energy staggered conformation, and allows the incoming base and leaving group to be further away from each other.

Elimination in Cyclic Systems:

- The stereochemical requirement of an anti periplanar geometry in an E2 reaction has important consequences for compounds containing six-membered rings.
- Consider chlorocyclohexane which exists as two chair conformers. Conformer A is preferred since the bulkier Cl group is in the equatorial position.

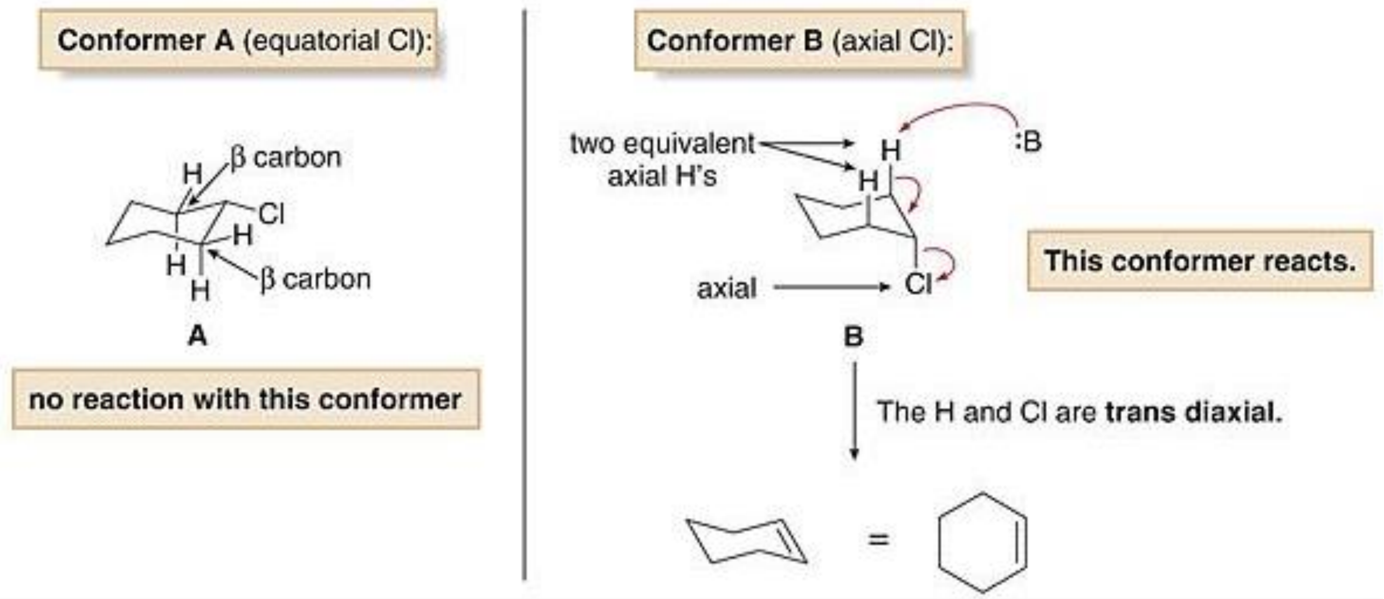


- For E2 elimination, the C-Cl bond must be anti periplanar to the C—H bond on a β carbon, and this occurs only when the H and Cl atoms are both in the axial position. The requirement for trans diaxial geometry means that elimination must occur from the less stable conformer, B.

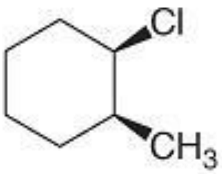
- For Elimination, the Cl group must be in the axial position of cyclohexane ring

Figure 8.8 The trans diaxial geometry for the E2 elimination in chlorocyclohexane

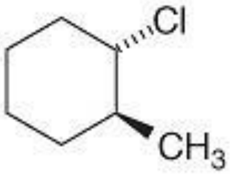
- In conformer **A** (**equatorial** Cl group), a β C−H bond and a C−Cl bond are never anti periplanar; therefore, no E2 elimination can occur.
- In conformer **B** (**axial** Cl group), a β C−H bond and a C−Cl bond are **trans diaxial; therefore**, E2 elimination occurs.



E2 dehydrohalogenation of *cis*- and *trans*-1-chloro-2-methylcyclohexane:

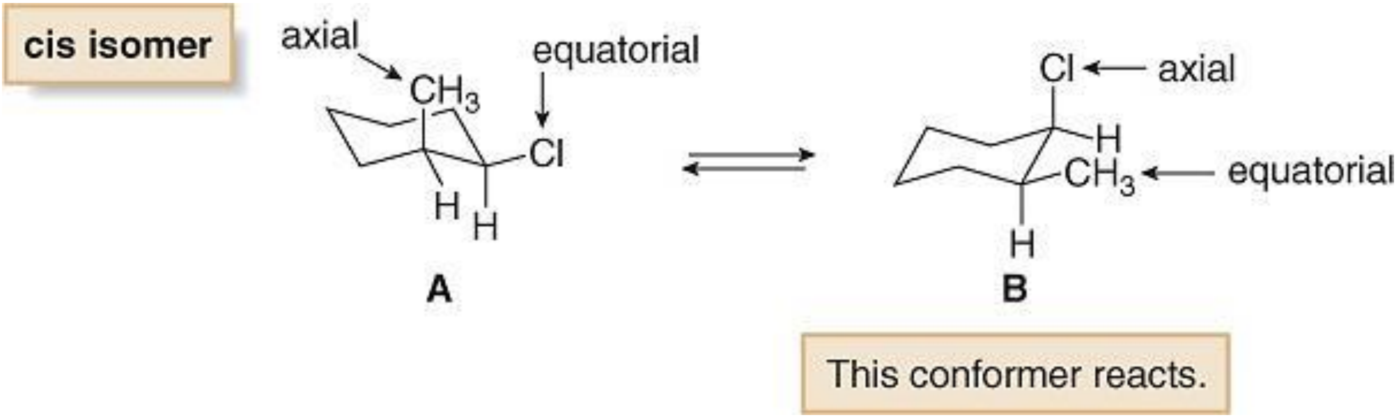


cis-1-chloro-2-methyl-cyclohexane

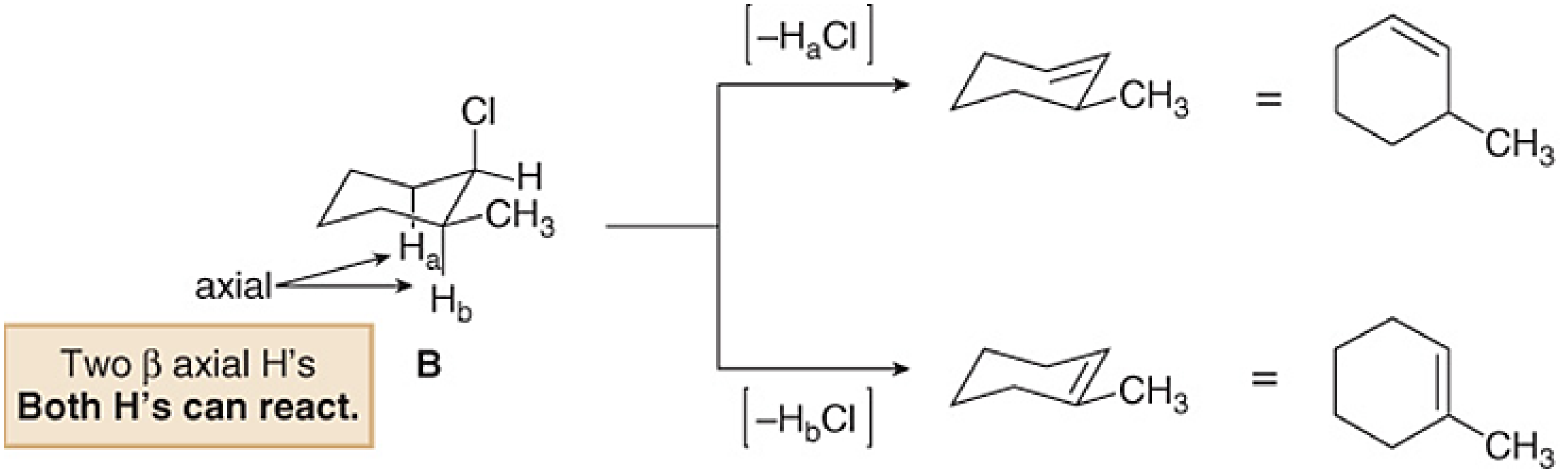


trans-1-chloro-2-methyl-cyclohexane

- **The *cis* isomer** exists as two conformers, A and B, each of which has one group axial and one group equatorial. E2 reaction must occur from conformer B, which contains an axial Cl atom.

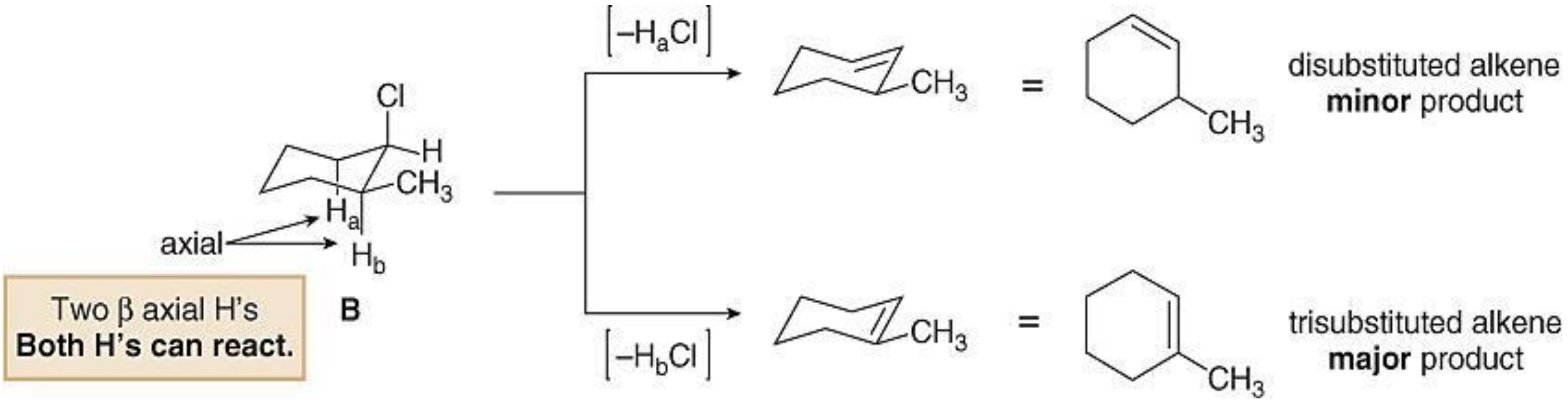


- Because conformer B has two different axial β hydrogens, labeled H_a and H_b, E2 reaction occurs in two different directions to afford **two** alkenes.
- The major product contains the more stable trisubstituted double bond, as predicted by the Saytzeff (Zaitsev) rule. (The more substituted alkene is the more stable).

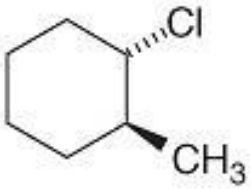


Saytzeff (Zaitsev) rule:

(The more substituted alkene is the more stable).

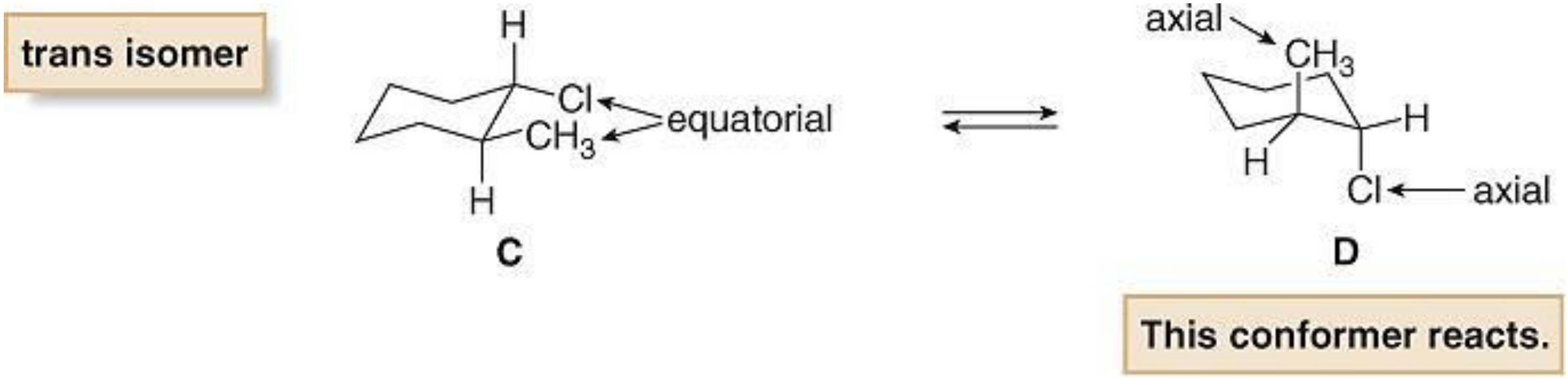


- **The trans isomer** of 1-chloro-2-methylcyclohexane exists as two conformers: C, having two equatorial substituents, and D, having two axial substituents.

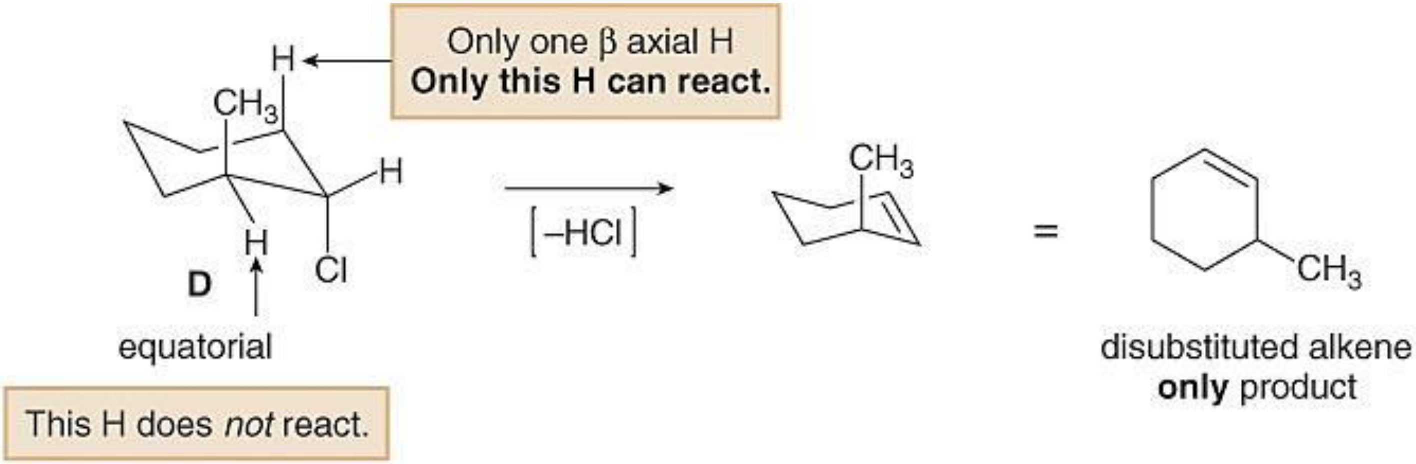


trans-1-chloro-2-methylcyclohexane

- E2 reaction must occur from D, since it contains an axial Cl atom.



- Because conformer D has only one axial β H, E2 reaction occurs only in one direction to afford a single product. This is not predicted by the Zaitzev rule.



◆ In conclusion, with substituted cyclohexanes, E2 elimination must occur with a trans diaxial arrangement of H and X, and as a result of this requirement, the more substituted alkene is not necessarily the major product.

Alkyl halides & Elimination Reaction

Regioselectivity (regioselective)

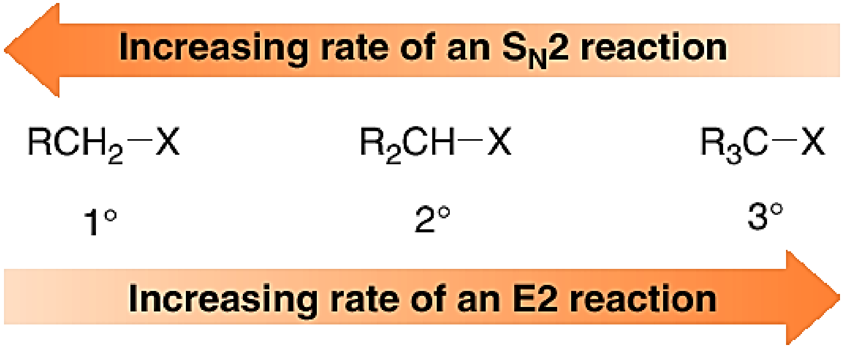
A regioselective reaction is one in which one direction of bond making or breaking occurs preferentially over all other possible directions.

Alkyl Halides and Elimination Reactions

Mechanisms of Elimination—E2

- The S_N2 and E2 mechanisms differ in how the R group affects the reaction rate.

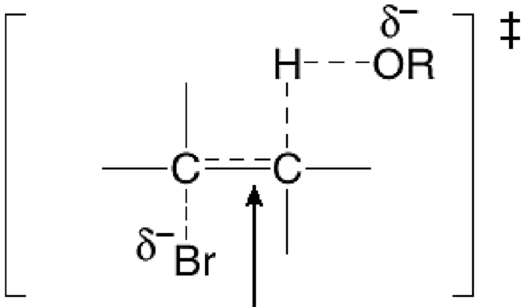
- **As the number of R groups on the carbon with the leaving group increases, the rate of the E2 reaction increases.**



Alkyl Halides and Elimination Reactions

Mechanisms of Elimination—E2

- 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, increasing the stability of the double bond with alkyl substituents stabilizes the transition state (i.e., lowers E_a, which increases the rate of the reaction).



Transition state for an E2 reaction with an alkoxide $^{-}$OR as base

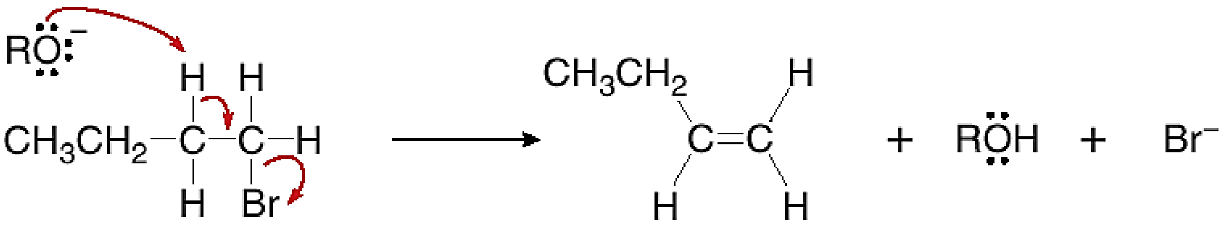
The double bond is partially formed.

Alkyl Halides and Elimination Reactions

Mechanisms of Elimination—E2

- Increasing the number of R groups on the carbon with the leaving group forms more highly substituted, more stable alkenes in E2 reactions.
- In the reactions below, since the disubstituted alkene is more stable, the 3° alkyl halide reacts faster than the 1^0 alkyl halide.

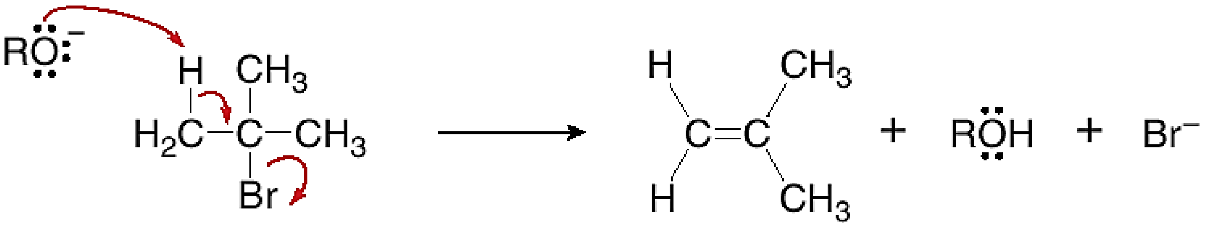
1° RX



1-bromobutane

monosubstituted alkene
less stable

3° RX



2-bromo-2-methylpropane

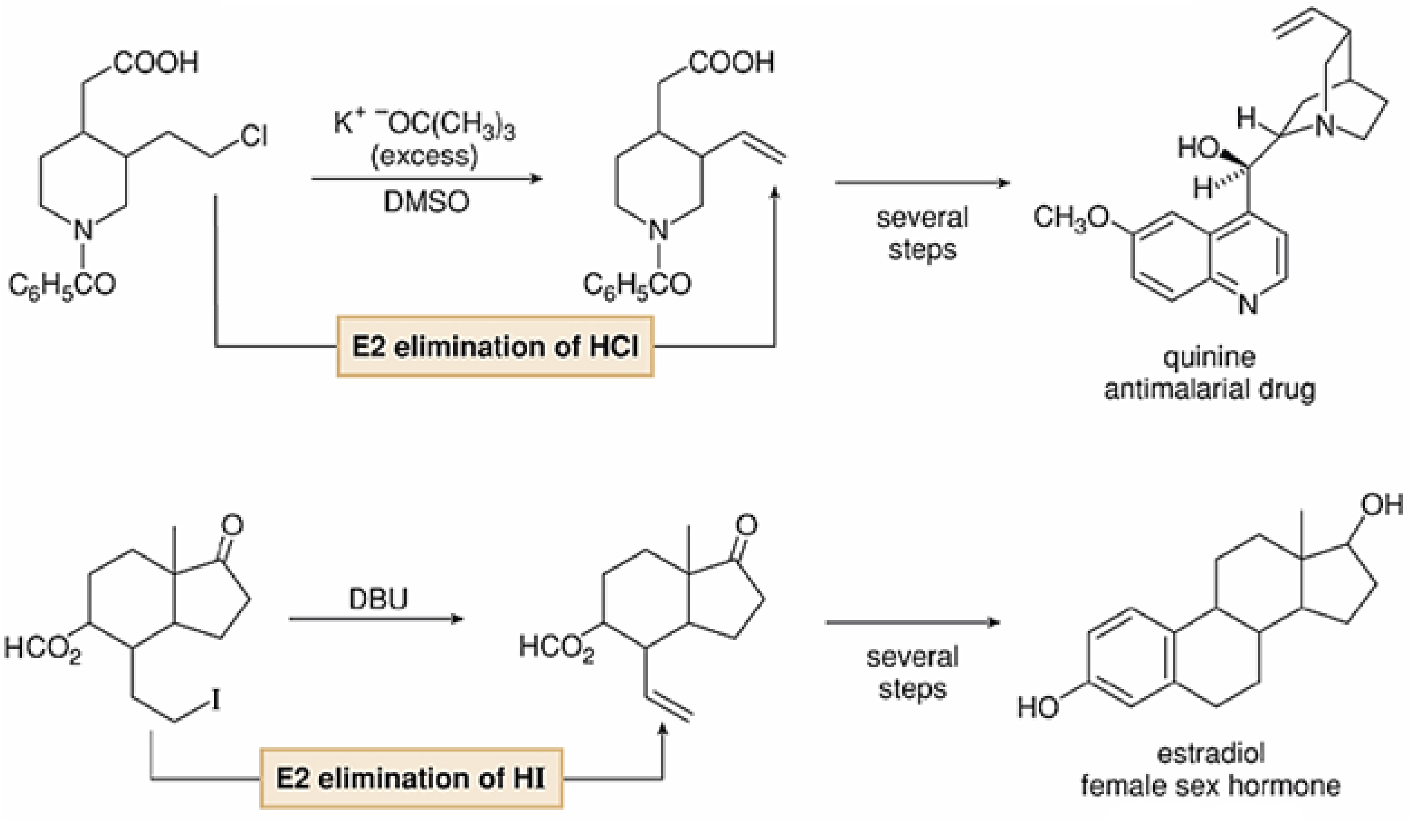
disubstituted alkene
more stable

Alkyl Halides and Elimination Reactions

Mechanisms of Elimination—E2

Two examples of the E2 reaction used in organic synthesis

Quinine, a natural product isolated from the bark of the Cinchona tree native to the Andes Mountains, is a powerful antipyretic—that is, it reduces fever—and so for centuries, it was the only effective treatment for malaria.



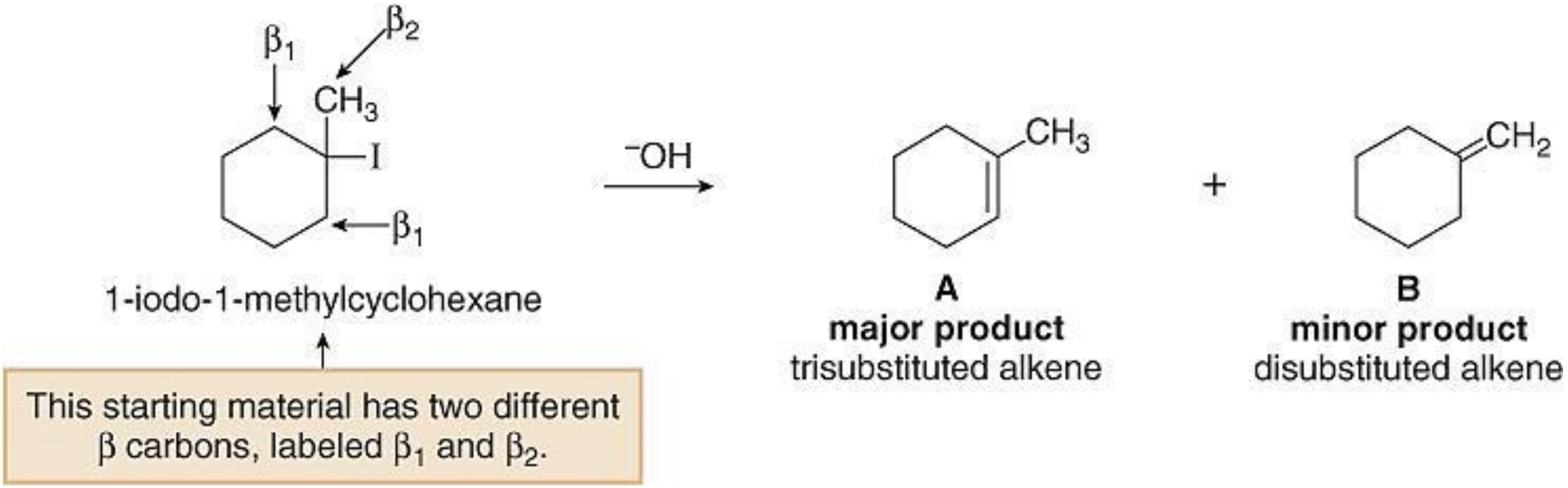
quinine
antimalarial drug

estradiol
female sex hormone

Alkyl Halides and Elimination Reactions

The Zaitsev (Saytzeff) Rule

- Recall that when alkyl halides have two or more different β carbons, more than one alkene product is formed.
- When this happens, one of the products usually predominates.
- The major product is the more stable product—the one with the more substituted double bond.
- This phenomenon is called the Zaitsev rule.



1-iodo-1-methylcyclohexane

This starting material has two different β carbons, labeled β_1 and β_2.

A
major product
trisubstituted alkene

B
minor product
disubstituted alkene

E1 Reactions

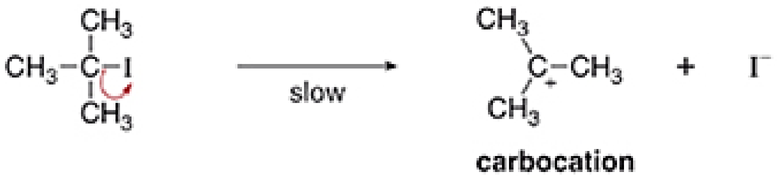
- The dehydrohalogenation of $(CH_3)_3CCl$ with H_2O to form $(CH_3)_2C{=}CH_2$ can be used to illustrate the second general mechanism of elimination, the E1 mechanism.
- An E1 reaction exhibits first-order kinetics:

$$\text{rate} = k[(CH_3)_3CCl]$$

- 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.
- The E1 and E2 mechanisms both involve the same number of bonds broken and formed. The only difference is timing. In an E1, the leaving group comes off before the β proton is removed, and the reaction occurs in two steps. In an E2 reaction, the leaving group comes off as the β proton is removed, and the reaction occurs in one step.

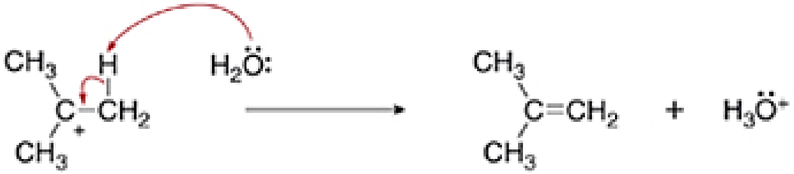
Mechanism 8.2 The E1 Mechanism

Step [1] The C–I bond is broken.



- **Heterolysis of the C–I bond** forms an intermediate **carbocation.** This is the same first step as the S_N1 mechanism. It is responsible for the first-order kinetics because it is rate-determining.

Step [2] A C–H bond is cleaved and the π bond is formed.

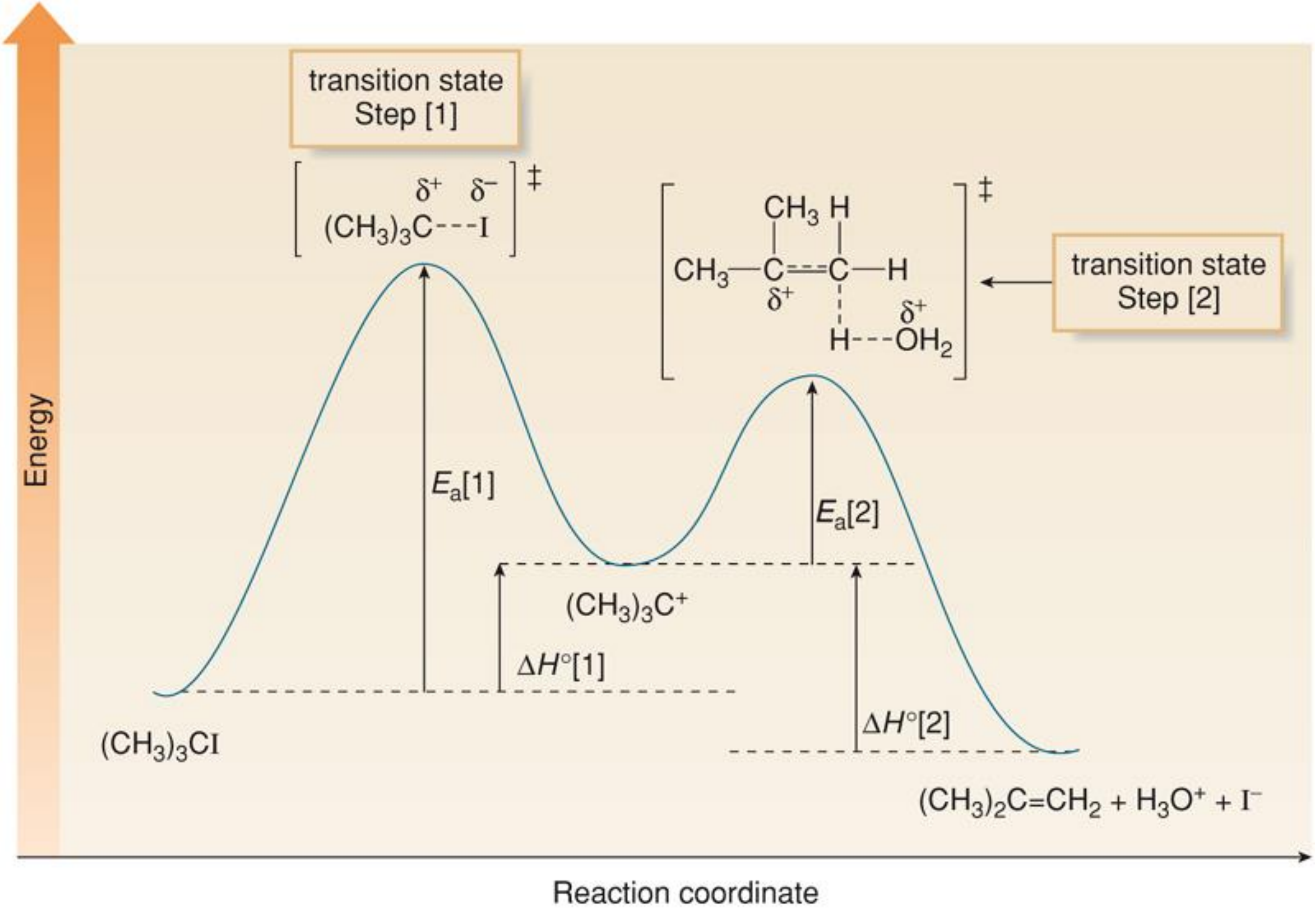


- **A base** (such as H_2O or I^-) **removes a proton from a carbon adjacent to the carbocation** (a β carbon). The electron pair in the C–H bond is used to form the new π bond.

Energy diagram for an E1 reaction:

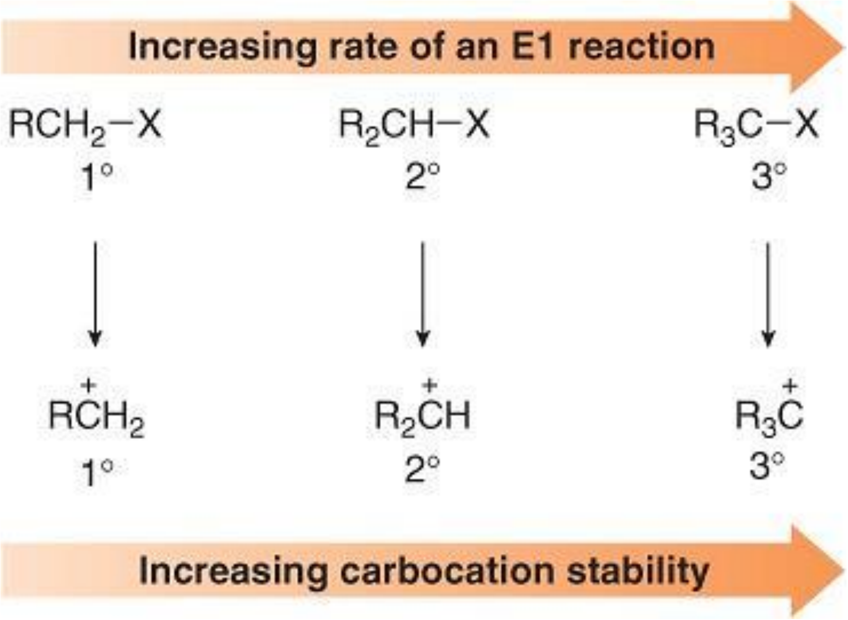
$$(CH_3)_3CI + H_2O \rightarrow$$
$$(CH_3)_2C{=}CH_2 + H_3O^+ + I^-$$

- Since the E1 mechanism has two steps, there are two energy barriers.
- Step [1] is rate-determining; $E_a[1] > E_a[2]$ making the transition state for Step [1] higher in energy.



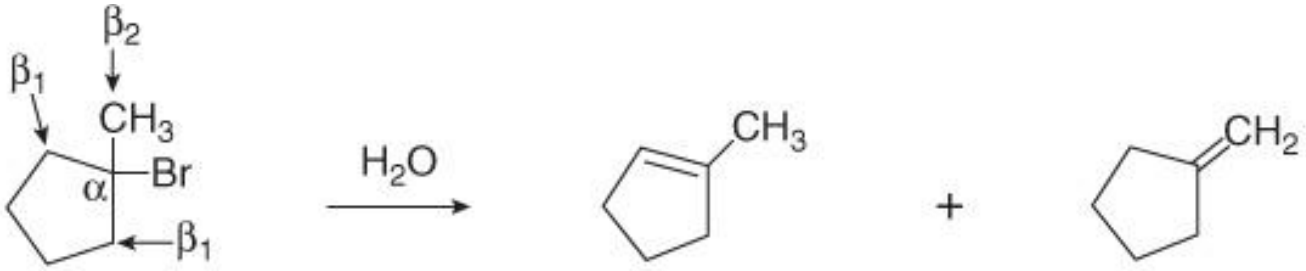
Effect of alkyl halide type on E1

- The rate of an E1 reaction increases as the number of R groups on the carbon with the leaving group increases.



- **The strength of the base usually determines whether a reaction follows the E1 or E2 mechanism. Strong bases like ^-OH and ^-OR favor E2 reactions, whereas weaker bases like H_2O and ROH favor E1 reactions.**

- **E1 reactions are regioselective, favoring formation of the more substituted, more stable alkene.**
- **Zaitsev's rule applies to E1 reactions also.**



1-bromo-1-methyl-cyclopentane

A
trisubstituted alkene
major product

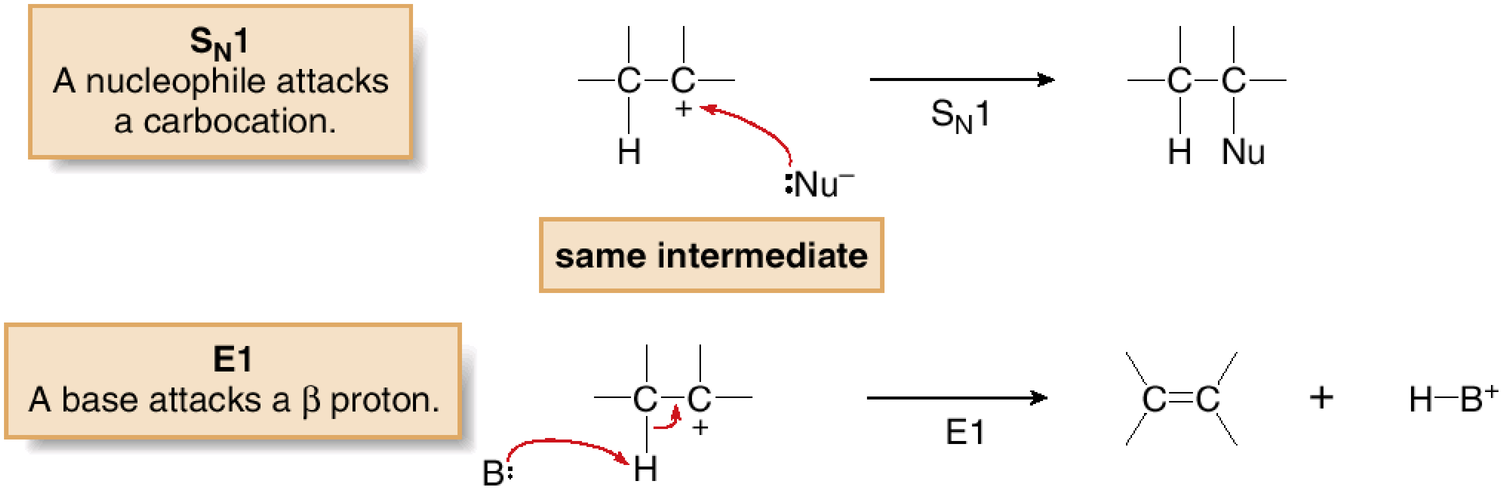
B
disubstituted alkene
minor product

two different β carbons labeled β_1 and β_2

Regioselective reaction

S_N1 and E1 Reactions

- S_N1 and E1 reactions have exactly the same first step—formation of a carbocation. They differ in what happens to the carbocation.



S_N1
A nucleophile attacks a carbocation.

same intermediate

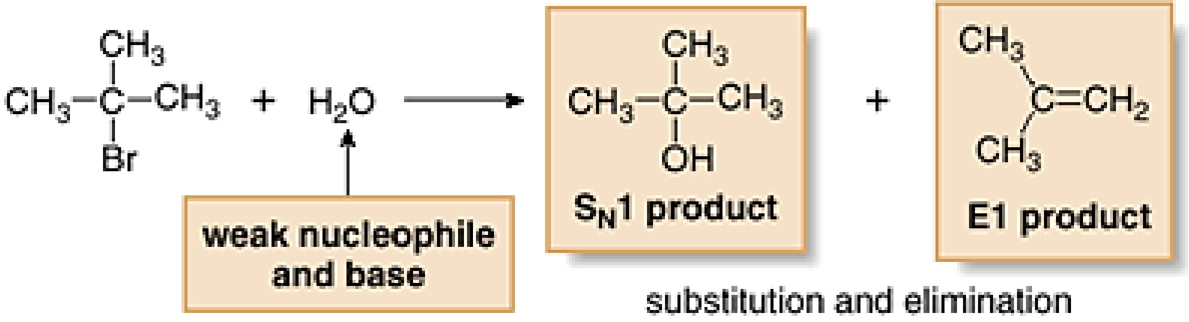
E1
A base attacks a β proton.

- In an S_N1 reaction, a nucleophile attacks the carbocation, forming a substitution product.
- In an E1 reaction, a base removes a proton, forming a new π bond.

Because E1 reactions often occur with a competing S_N1 reaction, E1 reactions of alkyl halides are much less useful than E2 reactions

- With weak nucleophiles or bases

- **A mixture of S_N1 and E1 products results.**
- Rationale: A weak base or nucleophile favors S_N1 and E1 mechanisms, and both occur.
- Example:



substitution and elimination

When is the Mechanism E1 or E2?

- The strength of the base is the most important factor in determining the mechanism for elimination. **Strong bases favor the E2 mechanism**. **Weak bases favor the E1 mechanism**.

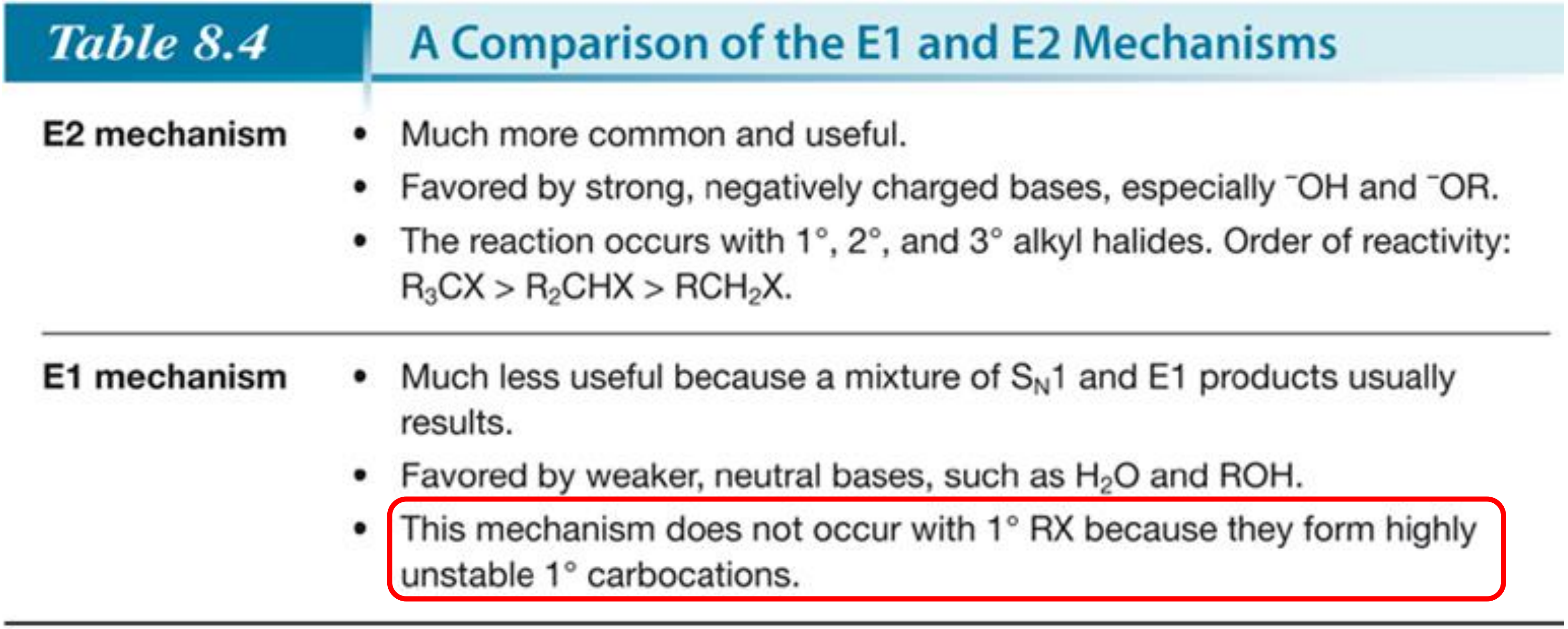


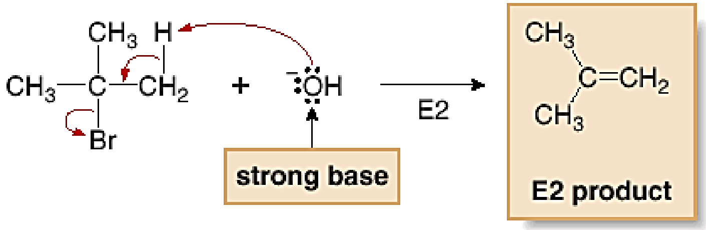
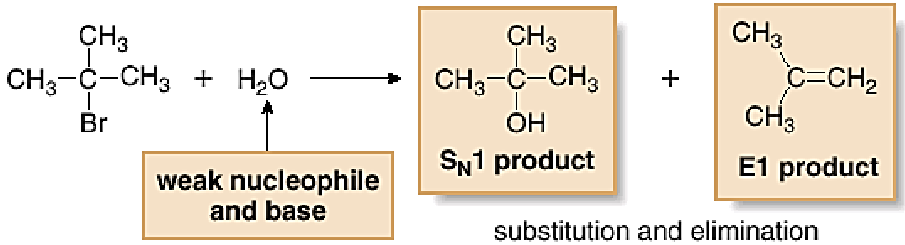
Table 8.4 A Comparison of the E1 and E2 Mechanisms

E2 mechanism	• Much more common and useful. • Favored by strong, negatively charged bases, especially ^{-}OH and ^{-}OR. • The reaction occurs with 1°, 2°, and 3° alkyl halides. Order of reactivity: $R_3CX > R_2CHX > RCH_2X$.
E1 mechanism	• Much less useful because a mixture of S_N1 and E1 products usually results. • Favored by weaker, neutral bases, such as H_2O and ROH. • This mechanism does not occur with 1° RX because they form highly unstable 1° carbocations.

Predicting the Mechanism from the Reactants—S_N1, S_N2, E1 or E2.

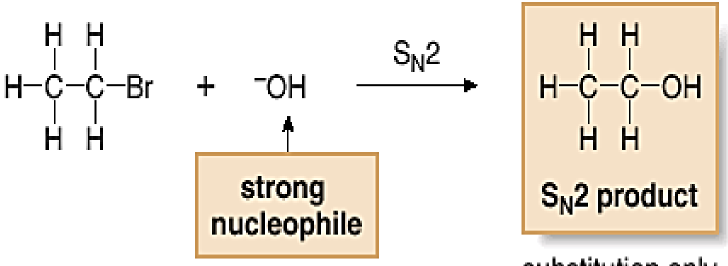
Determining whether an alkyl halide reacts by an S_N1, S_N2, E1, or E2 mechanism

[1] 3° Alkyl halides (R_3CX react by all mechanisms except S_N2.)

• With strong bases	• **Elimination occurs by an E2 mechanism.** • Rationale: A strong base or nucleophile favors an S_N2 or E2 mechanism, but 3° halides are too sterically hindered to undergo an S_N2 reaction, so only E2 elimination occurs. • Example:  elimination only
• With weak nucleophiles or bases	• **A mixture of S_N1 and E1 products results.** • Rationale: A weak base or nucleophile favors S_N1 and E1 mechanisms, and both occur. • Example:  substitution and elimination

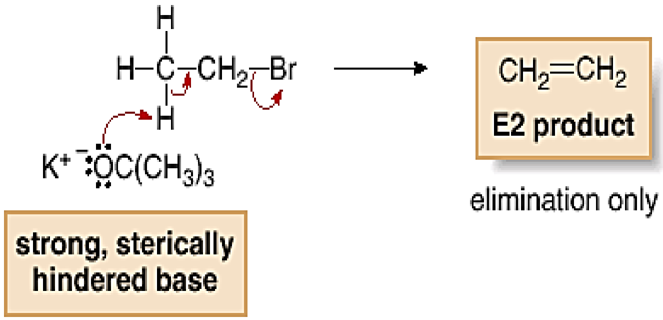
[2] 1° Alkyl halides (RCH_2X react by S_N2 and E2 mechanisms.)

- With strong nucleophiles
  - **Substitution occurs by an S_N2 mechanism.**
  - Rationale: A strong base or nucleophile favors S_N2 or E2, but 1° halides are the least reactive halide type in elimination; therefore, only an S_N2 reaction occurs.
  - Example:



substitution only

- With strong, sterically hindered bases
  - **Elimination occurs by an E2 mechanism.**
  - Rationale: A strong, sterically hindered base cannot act as a nucleophile, so elimination occurs and the mechanism is E2.
  - Example:

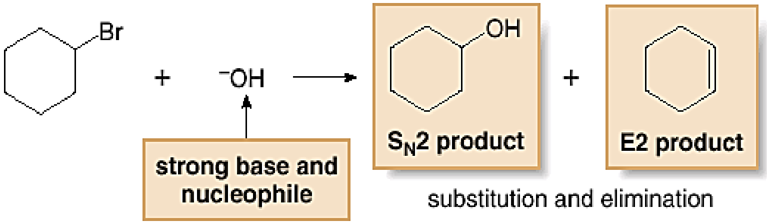


elimination only

[3] 2° Alkyl halides (R_2CHX react by all mechanisms.)

- With strong bases and nucleophiles

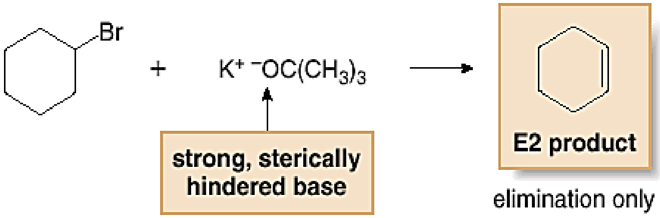
- **A mixture of S_N2 and E2 products results.**
- Rationale: A strong base that is also a strong nucleophile gives a mixture of S_N2 and E2 products.
- Example:



substitution and elimination

- With strong, sterically hindered bases

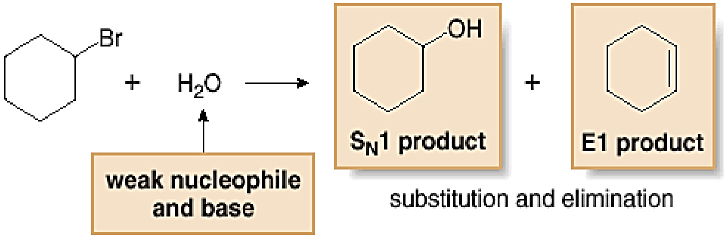
- **Elimination occurs by an E2 mechanism.**
- Rationale: A strong, sterically hindered base cannot act as a nucleophile, so elimination occurs and the mechanism is E2.
- Example:



elimination only

- With weak nucleophiles or bases

- **A mixture of S_N1 and E1 products results.**
- Rationale: A weak base or nucleophile favors S_N1 and E1 mechanisms, and both occur.
- Example:



substitution and elimination

Summary

- Alkyl halides undergo two kinds of nucleophilic substitution: SN1 and SN2, and two kinds of elimination: E1 and E2.
- SN2 and E2 are bimolecular one-step reactions
- SN1 and E1 are unimolecular two step reactions
- SN1 lead to a mixture of stereoisomers
- SN2 inverts the configuration on an asymmetric carbon
- The major product of a elimination is the most stable alkene
- SN2 are E2 are favoured by strong nucleophile/strong base
- SN2 reactions are favoured by primary alkyl halides
- E2 reactions are favoured by tertiary alkyl halides