Organic Chemistry, *Fourth Edition*

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Chapter 8

Alkyl Halides and Elimination Reactions

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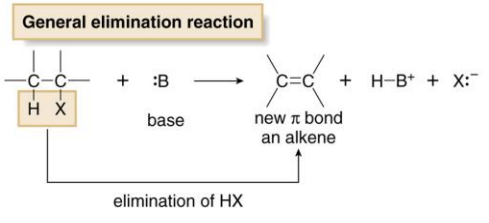
General Features of Elimination

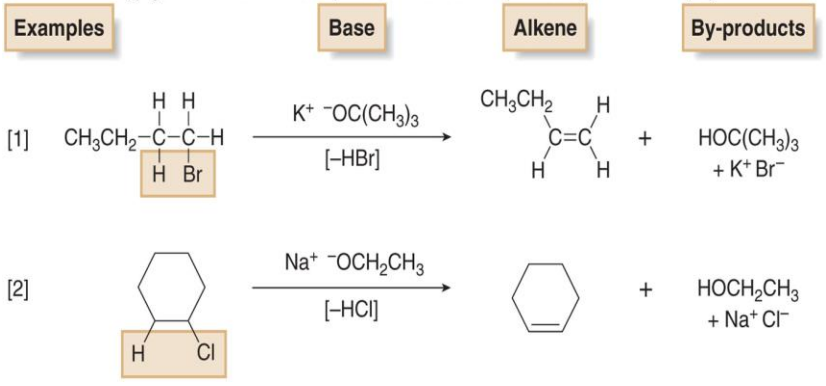
- **Elimination reactions involve the loss of elements from the starting material to form a new π bond in the product.**

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



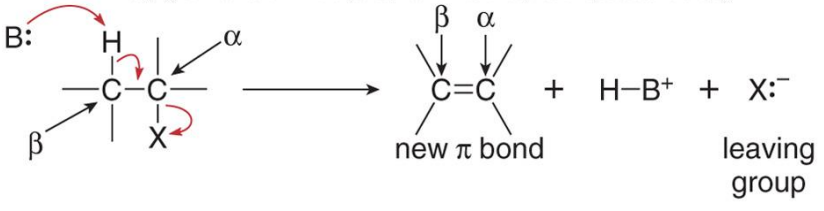
Elimination of HX

- **In both example reactions a base removes the elements of an acid, HX, from the organic starting material.**



Dehydrohalogenation

- **Removal of the elements HX is called dehydrohalogenation.**
- **<u>Dehydrohalogenation</u> is an example of β elimination.**
- **The curved arrow formalism shown below illustrates how four bonds are broken or formed in the process.**



Common Bases for Dehydrohalogenation

- **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

Structure	Name
$Na^+ {}^-OH$	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

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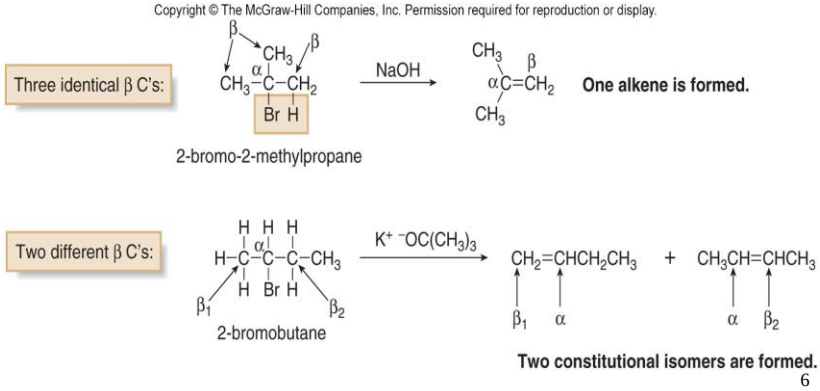
Drawing Products of Dehydrohalogenation

- **Find the α carbon.**
- **Identify all β carbons with H atoms.**
- **Remove the elements of H and X from the α and β carbons and form a π bond.**



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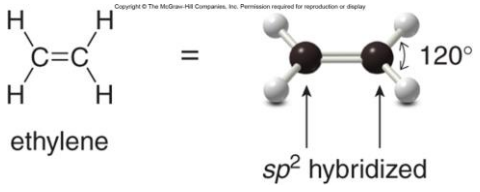
Alkenes

- **Alkenes are hydrocarbons containing a carbon-carbon double bond.**
- **Each carbon of the double bond is sp^2 hybridized.**
- **The alkene carbons are trigonal planar.**
- **The bond angles are 120°.**



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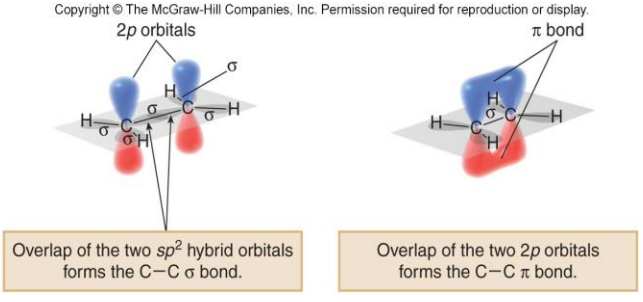
Alkene Structure

- **The double bond of an alkene consists of a σ bond and a π bond.**



- The σ bond, formed by end-on overlap of the two sp^2 hybrid orbitals, lies in the plane of the molecule.
- The π bond, formed by side-by-side overlap of two 2p orbitals, lies perpendicular to the plane of the molecule. The π bond is formed during elimination.

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Classifying Alkenes

- **Alkenes are classified according to the number of carbon atoms bonded to the carbons of the double bond.**

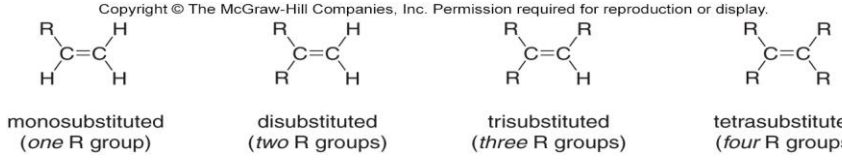
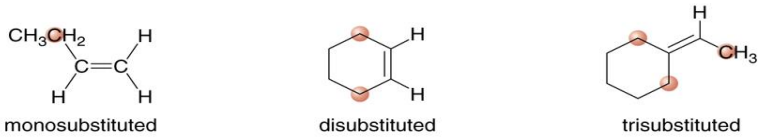


Figure 8.1

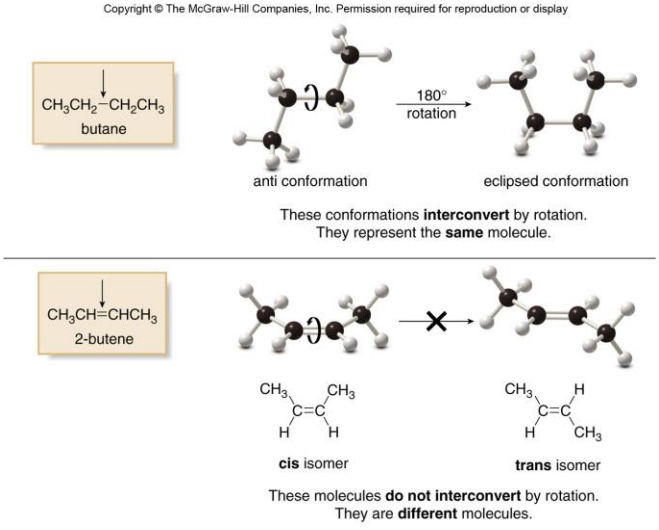


- Carbon atoms bonded to the double bond are screened in red.

Restricted Rotation About Double Bonds

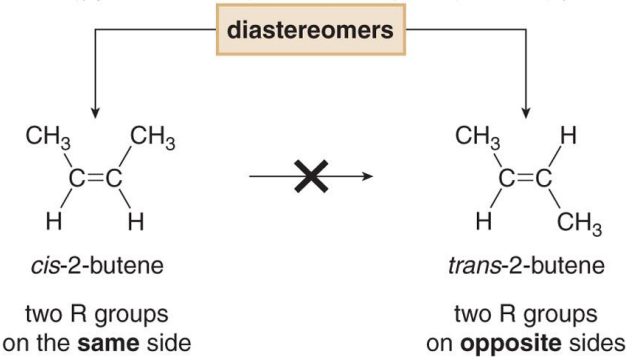
- **Recall that even though there is free rotation around single bonds, rotation about double bonds is restricted.**

Figure 8.2



Stereoisomers of Alkenes

- **Because of restricted rotation, two stereoisomers of 2-butene are possible.**
- ***cis*-2-Butene and *trans*-2-butene are diastereomers (i.e., non-mirror image stereoisomers).**



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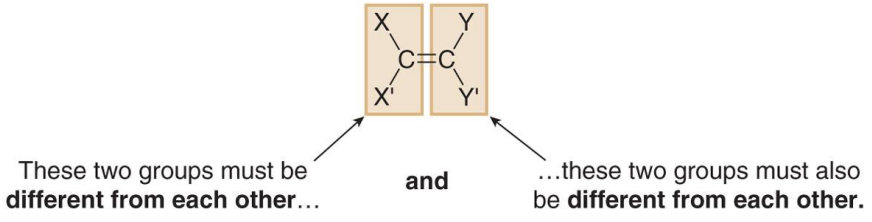
Alkene Diastereomers

- **Whenever the two groups on each end of a carbon-carbon double bond are different from each other, cis-trans isomers are possible.**

Stereoisomers on a C=C are possible when:



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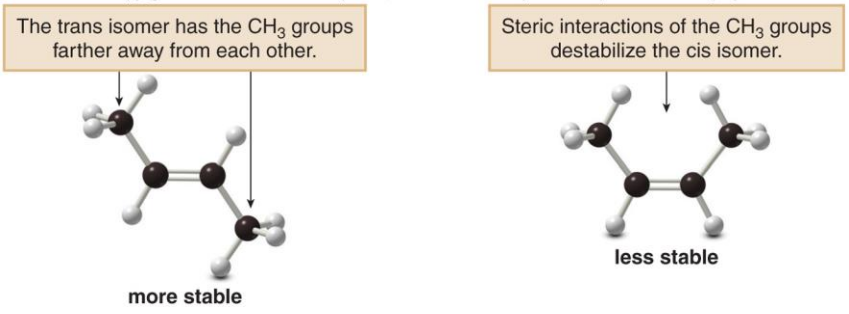
Stability of Trans Alkenes

- **In general, trans alkenes are more stable than cis alkenes because the groups bonded to the double bond carbons are further apart, reducing steric interactions.**



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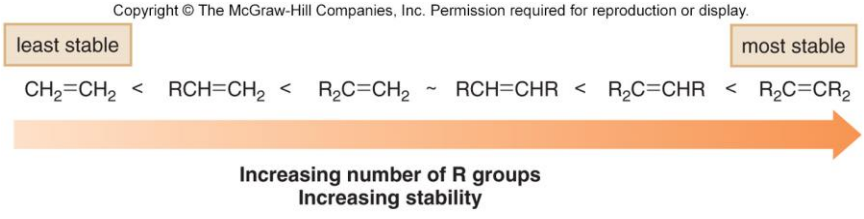
Stability in Alkenes

- **The stability of an alkene increases as the number of R groups bonded to the double bond carbons increases.**



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Stability in Alkenes

- The higher the percent *s*-character, the more readily an atom accepts electron density.
- Thus, sp^2 carbons are more able to accept electron density and sp^3 carbons are more able to donate electron density.
- Increasing the number of electron donating groups on a carbon atom able to accept electron density makes the alkene more stable.

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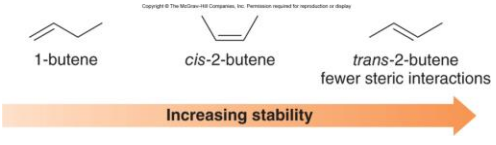
Stability in Alkenes

Example: Relative Stability of Butenes

- The 2-butenes (disubstituted) are more stable than 1-butene (monosubstituted).
- *trans*-2-Butene is more stable than *cis*-2-butene (less crowding).



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Elimination Mechanisms

- There are two mechanisms of elimination—E2 and E1, just as there are two mechanisms of substitution, S_N2 and S_N1.
- The E2 mechanism is called bimolecular elimination.
- The E1 mechanism is called 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.

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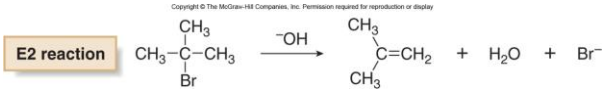
E2 Mechanism

- The most common mechanism for dehydrohalogenation is the E2 mechanism.
- It exhibits second-order kinetics, and both the alkyl halide and the base appear in the rate equation.

$$\text{rate} = k[(CH_3)_3CBr][^-OH]$$

- The reaction is concerted—all bonds are broken and formed in a single step.



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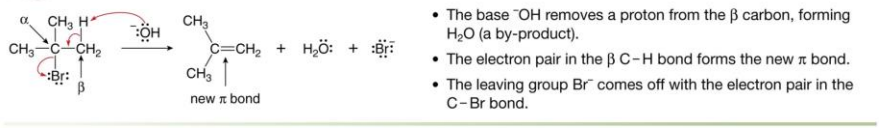
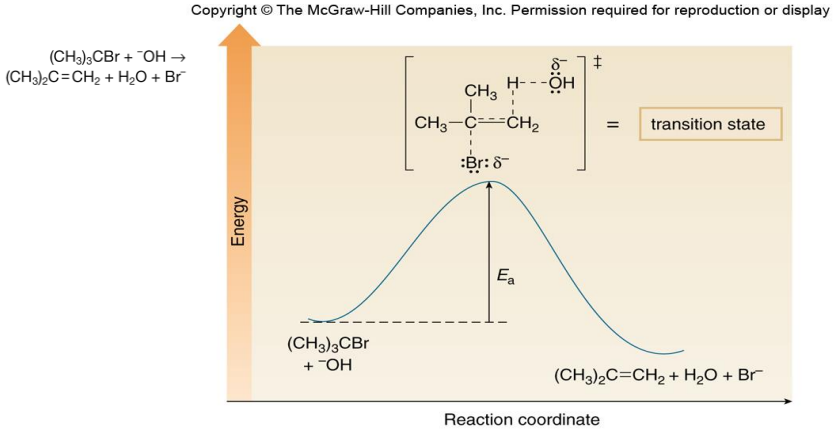
E2 Mechanism



- **There are close parallels between E2 and S_N2 mechanisms, the rate is affected by**
  - **1- the identity of the base**
  - **2- the leaving group**
  - **3- the solvent**

Energy Diagram for an E2 Reaction

Figure 8.3

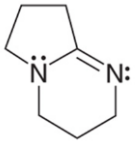


- In the transition state, the C–H and C–Br bonds are partially broken, the O–H and π bonds are partially formed, and both the base and the departing leaving group bear a partial negative charge.

1. Bases in E2 Mechanisms

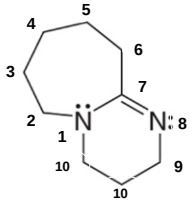
- **E2 reactions are generally run with strong, negatively charged bases like $^{-}$OH and $^{-}$OR.**
- **The base appears in the rate equation, so the rate of the E2 reaction increases as the strength of the base increases.**
- **Two strong, sterically hindered nitrogen bases called DBN and DBU are also sometimes used.**

Two useful bases for E2 reactions



DBN

1,5-Diazabicyclo(4.3.0)non-5-ene



DBU

1,8-Diazabicyclo(5.4.0)undec-7-ene

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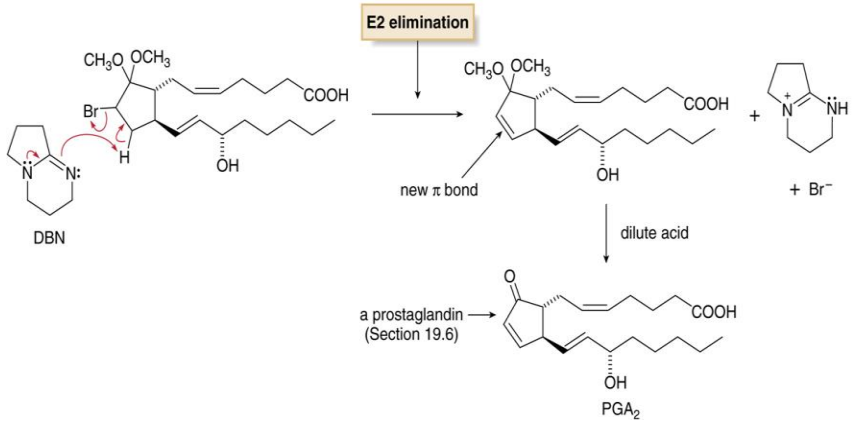
E2 Reaction with DBN

Figure 8.4



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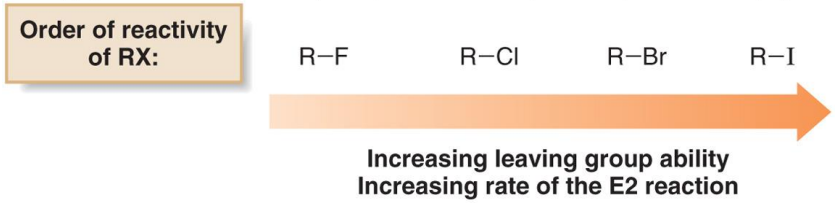
2. Leaving Group
3. Solvent

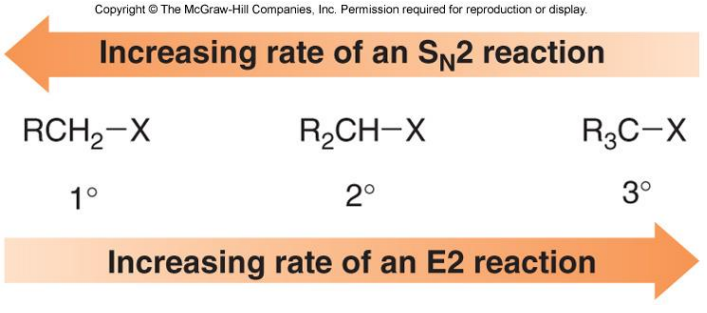
- **Because the bond to the leaving group is partially broken in the transition state, the better the leaving group the faster the E2 reaction.**



- **Polar aprotic solvents increase the rate of E2 reactions.**

4. Alkyl Halide Structure

- **The S_N2 and E2 mechanisms differ in how the alkyl halide structure affects the reaction rate.**
- **As the number of R groups increases on the carbon with the leaving group, the rate of the E2 reaction increases.**



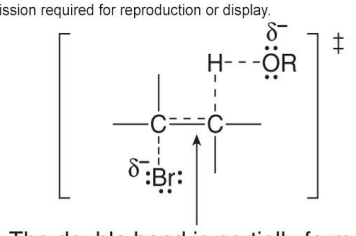
Transition States in E2 Mechanisms

- **The increase in E2 reaction rate with increasing alkyl substitution can be rationalized in terms of transition state stability.**

1. In the transition state, the double bond is partially formed.

2. This increases the stability of the double bond with alkyl substituents stabilizing 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.

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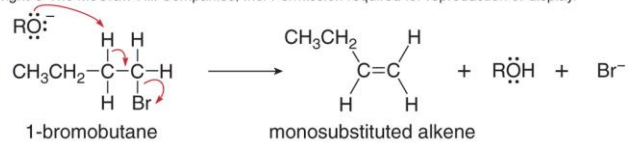
Product Stability and Rate of E2 Reactions

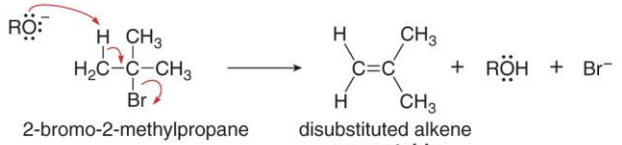
- **Increasing the number of R groups on the carbon with the leaving group forms more highly substituted, more stable alkenes in E2 reactions.**
- **In the reactions below, since the disubstituted alkene is more stable, the 3° alkyl halide reacts faster than the 1° alkyl halide.**

1° RX



1-bromobutane — monosubstituted alkene **less stable**

3° RX



2-bromo-2-methylpropane — disubstituted alkene **more stable**

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E2 Mechanism Summary

Table 8.2 Characteristics of the E2 Mechanism

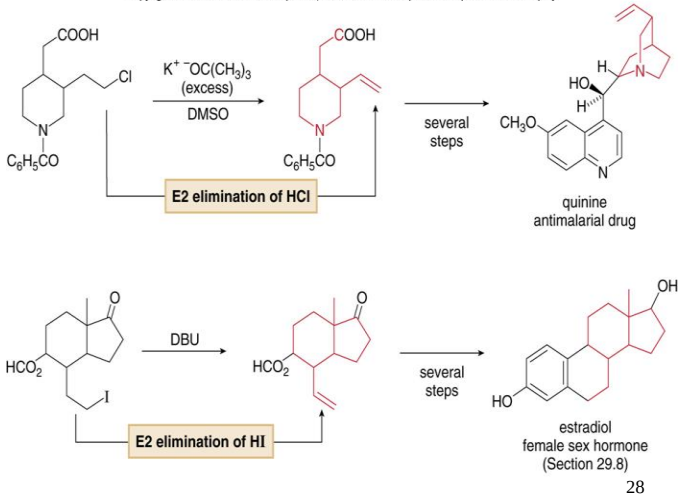
Characteristic	Result
Kinetics	• Second order
Mechanism	• One step
Identity of R	• More substituted halides react faster. • Rate: $R_3CX > R_2CHX > RCH_2X$
Base	• Favored by strong bases
Leaving group	• Better leaving group ⟶ faster reaction
Solvent	• Favored by polar aprotic solvents

E2 Reaction in Organic Synthesis

The synthesis of both quinine and estradiol involve an E2 elimination as a key step.

Figure 8.5

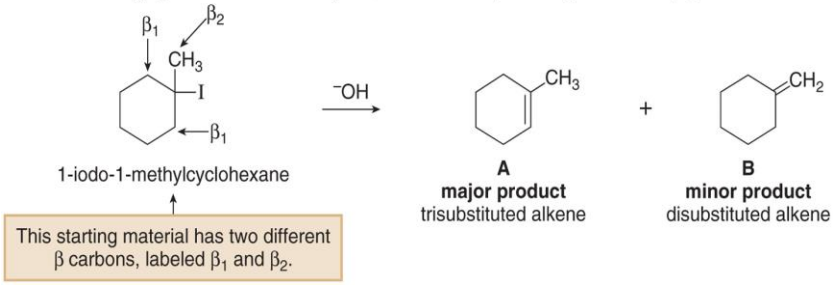
Quinine, a natural product isolated from the bark of the cinchona tree native to the Andes Mountains, is a powerful antipyretic—that is, it reduces fever—and for centuries, it was the only effective treatment for malaria.



Important in the regulation of the estrous and menstrual female reproductive cycles

The Zaitsev (Saytzeff) Rule

- When alkyl halides have two or more different β carbons, more than one alkene product can be formed.
- The Zaitsev rule predicts that the major product in β elimination has the more substituted double bond.
- This is the more stable alkene.



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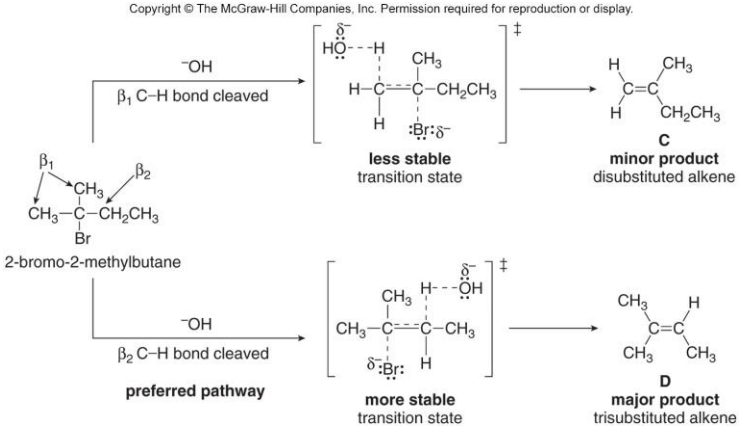
Regioselectivity of E2 Reactions

- A reaction is regioselective when it yields predominantly or exclusively one constitutional isomer when more than one is possible.
- Thus, the E2 reaction is regioselective.



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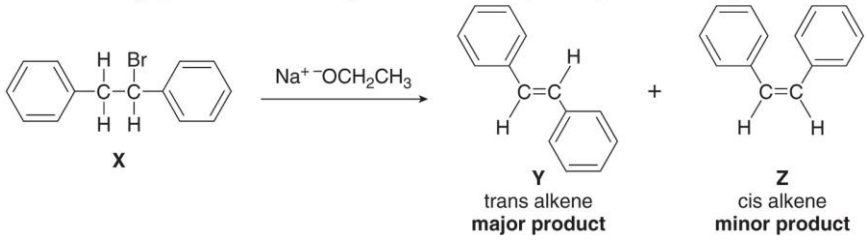
Stereoselectivity of E2 Reactions

- A reaction is stereoselective when it forms predominantly or exclusively one stereoisomer when two or more are possible.
- The E2 reaction is stereoselective because the more stable stereoisomer is formed preferentially.



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E1 Mechanism

- 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.

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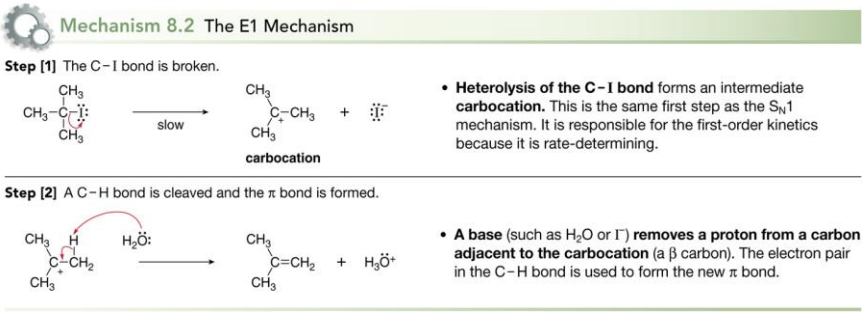
E1 Mechanism

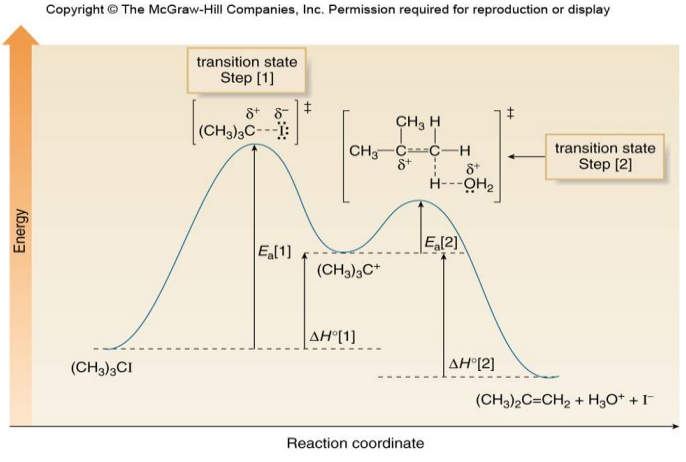


- **In an E2 reaction, the leaving group comes off as the β proton is removed, and the reaction occurs in one step.**
- **However, in an E1, the leaving group comes off before the β proton is removed, and the reaction occurs in two steps.**

Energy Diagram for an E1 Reaction

Figure 8.6

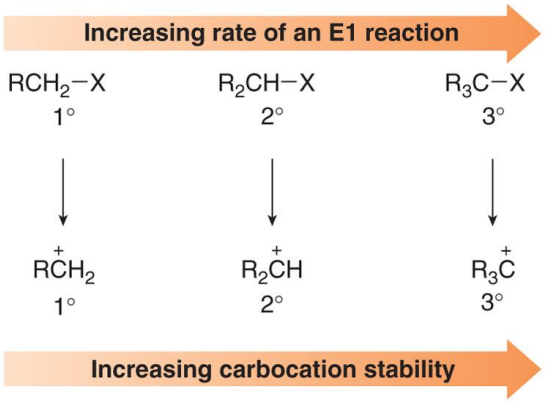
$(CH_3)_3CI + H_2O \rightarrow (CH_3)_2C{=}CH_2 + H_3O^+ + I^-$



- Since the E1 mechanism has two steps, there are two energy barriers.
- Step [1] is rate-determining.

1. Alkyl Halide Structure

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



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2. Base

- 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.
  - Weaker bases like H_2O and ROH favor E1 reactions.

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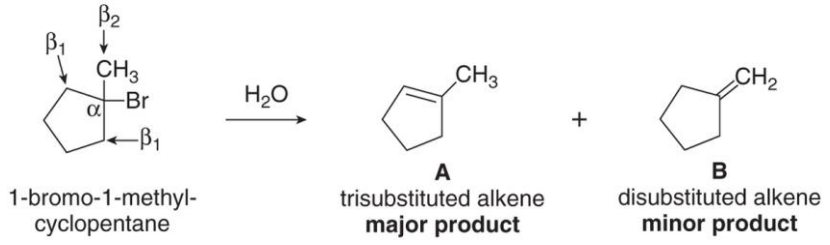
Regioselectivity of E1 Reactions

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



1-bromo-1-methyl-cyclopentane

A
trisubstituted alkene
major product

B
disubstituted alkene
minor product

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E1 Mechanism Summary

Table 8.3 Characteristics of the E1 Mechanism

Characteristic	Result
Kinetics	• First order
Mechanism	• Two steps
Identity of R	• More substituted halides react faster. • Rate: $R_3CX > R_2CHX > RCH_2X$
Base	• Favored by weaker bases such as H_2O and ROH
Leaving group	• A better leaving group makes the reaction faster because the bond to the leaving group is partially broken in the rate-determining step.
Solvent	• Polar protic solvents that solvate the ionic intermediates are needed.

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

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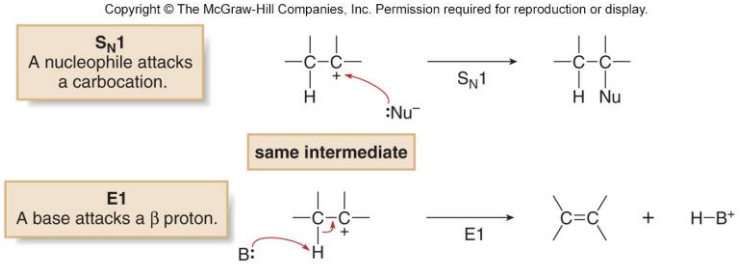
S_N1 and E1 Reactions

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



- 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.

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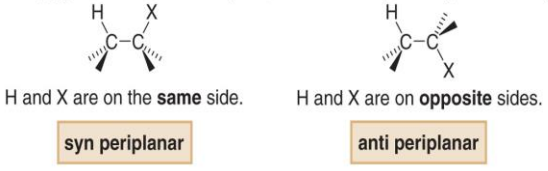
Stereochemistry of E2 Reactions

- **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.**



- 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.*

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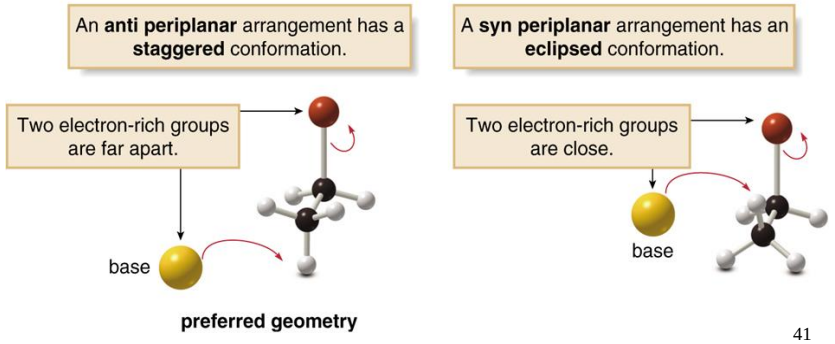
Two Possible Geometries for E2 Reactions

- **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.**

Figure 8.7



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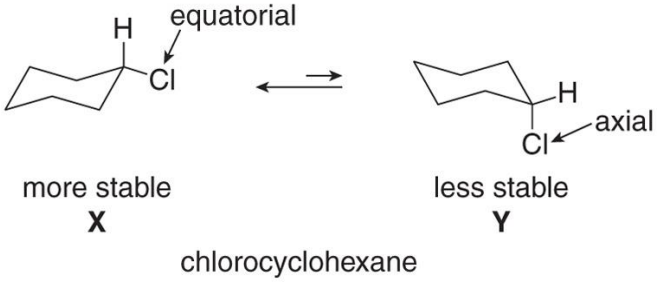
Anti Periplanar Geometry

- **The requirement of anti periplanar geometry in an E2 reaction has important consequences for compounds containing six-membered rings.**
  - **Chlorocyclohexane exists as two chair conformations.**
  - **Conformation A is preferred since the bulkier Cl group is in the equatorial position.**



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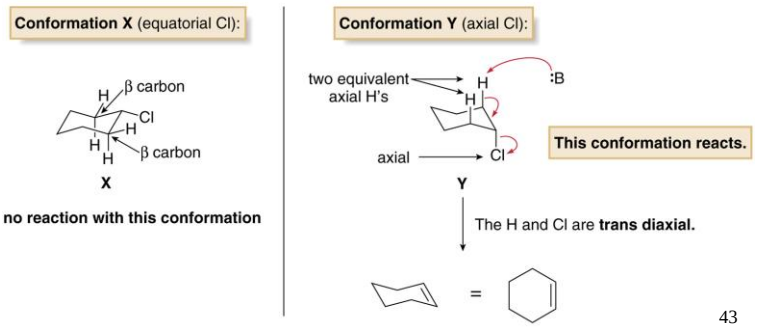
Trans Diaxial Geometry for E2 Reactions

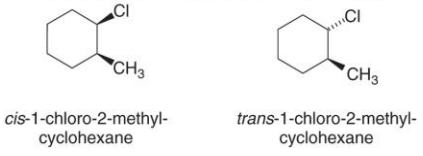
- **For E2 elimination, the C-Cl bond must be anti periplanar to the C-H bond on a β carbon, and this occurs only when the H and Cl atoms are both in the axial position.**
- **The requirement for *trans* diaxial geometry means that elimination must occur from the less stable conformer, B.**

Figure 8.8



E2 Reactions of Cis and Trans Isomers

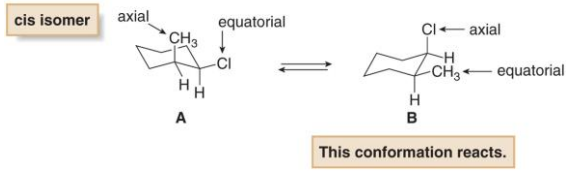
- **Consider the E2 dehydrohalogenation of *cis*- and *trans*-1-chloro-2-methylcyclohexane.**



cis-1-chloro-2-methyl-cyclohexane

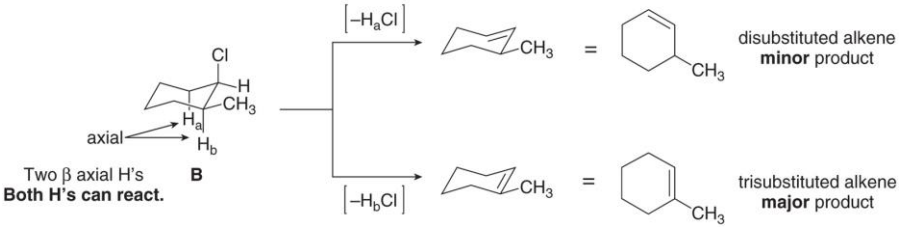
trans-1-chloro-2-methyl-cyclohexane

- **The <u>cis isomer</u>:**
- **exists as two conformations, A and B, each of which has one group axial and one group equatorial.**
- **E2 reaction must occur from conformation B, which contains an axial Cl atom.**

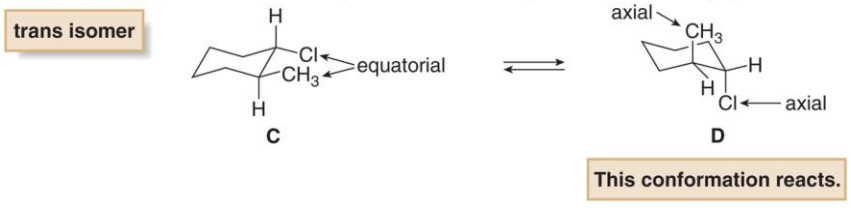


Regiochemistry of E2 Reactions on Cyclohexanes

- **Because conformation 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 Zaitsev rule.**



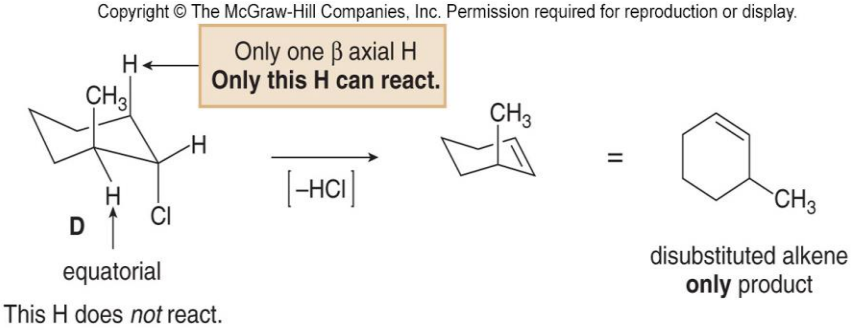
Axial Leaving Groups for E2 Reactions



- **<u>The trans isomer</u> (1-chloro-2-methylcyclohexane):**
- **exists as two conformers: <u>C</u>, having <u>two equatorial</u> substituents, and <u>D</u>, having <u>two</u> axial substituents.**
- **E2 reaction must occur from D, since it contains an axial Cl atom.**

Anti Zaitsev Products for E2 Reactions

- **Because conformer D has only one axial β H, the E2 reaction occurs only in one direction to afford a single product.**
- **The most substituted, "Zaitsev" alkene is not the major product in this case.**



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Comparison of E1 and E2 Mechanisms

- **The strength of the base is the most important factor in determining the mechanism for elimination.**

Table 8.4 A Comparison of the E1 and E2 Mechanisms

Mechanism	Comment
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.

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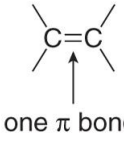
E2 Reactions and Alkyne Synthesis

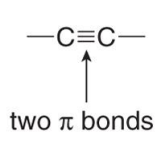
- **A single elimination reaction produces a π bond of an alkene.**
- **Two consecutive elimination reactions produce two π bonds of an alkyne.**

Alkene



One elimination reaction is needed.

Alkyne



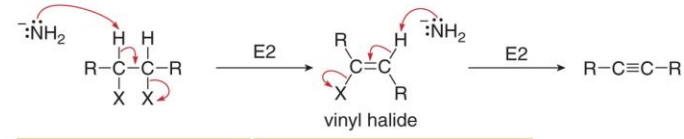
Two elimination reactions are needed.

E2 Reactions and Alkyne Synthesis

- **Two elimination reactions are needed to remove two moles of HX from a dihalide substrate.**
- **Two different starting materials can be used—a vicinal dihalide or a geminal dihalide.**

Vicinal dihalide

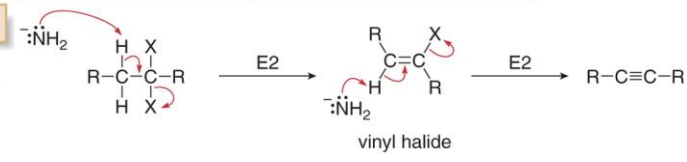
[1]



Remove one mole of HX. | Remove a second mole of HX.

Geminal dihalide

[2]



Bases for Alkyne Synthesis

- **Stronger bases are needed to synthesize alkynes by dehydrohalogenation than are needed to synthesize alkenes.**
- **The typical base used is $^{-}NH_2$ (amide), used as $NaNH_2$.**
- **$KOC(CH_3)_3$ can also be used with DMSO as solvent.**
- **Stronger bases are needed to break the stronger sp^2 hybridized C-H bonds in the second elimination reaction.**

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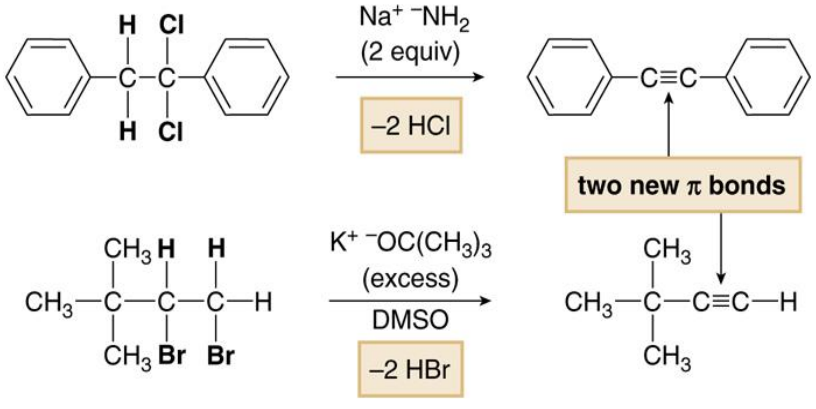
Dehydrohalogenation of Dihalides

Figure 8.9



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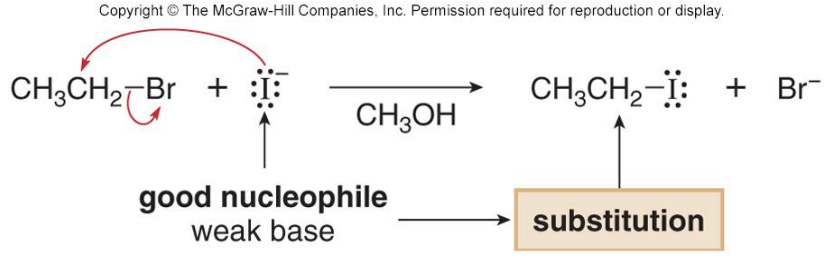
When is the Reaction S_N1, S_N2, E1, or E2?

- **Good nucleophiles that are weak bases favor substitution over elimination.**
- **These include I^-, Br^-, HS^-, ^-CN, and CH_3COO^-.**



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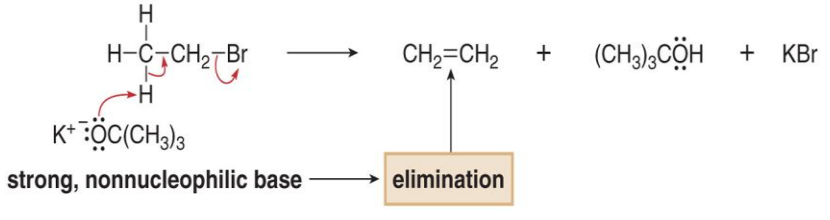
Bulky Bases Favor Elimination

- **Bulky nonnucleophilic bases favor elimination over substitution.**
  - **$KOC(CH_3)_3$, DBU, and DBN are too sterically hindered to attack tetravalent carbon.**
- **They are, however, able to remove a small proton, favoring elimination over substitution.**



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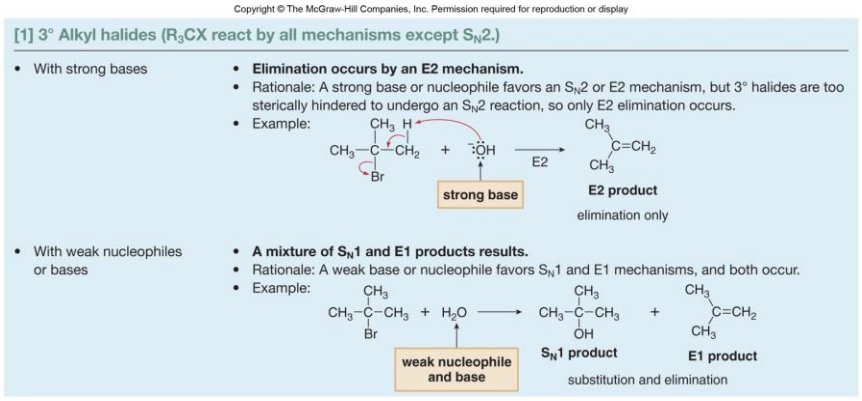
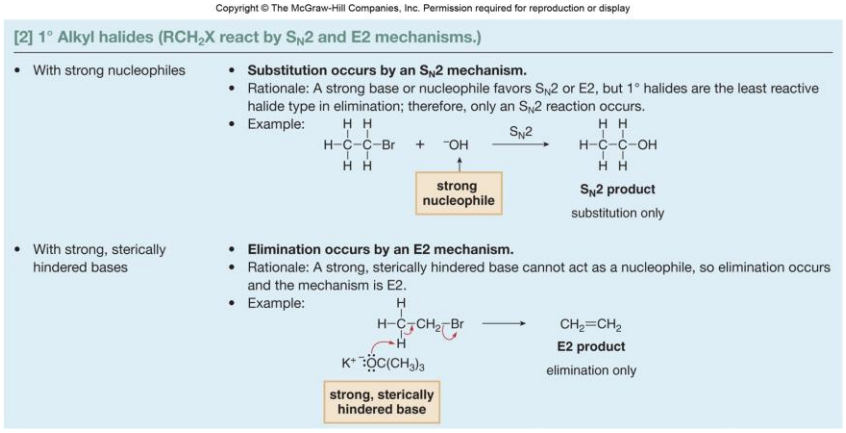
Predicting Reaction Mechanisms (S_N1, S_N2, E1, or E2)

Figure 8.10



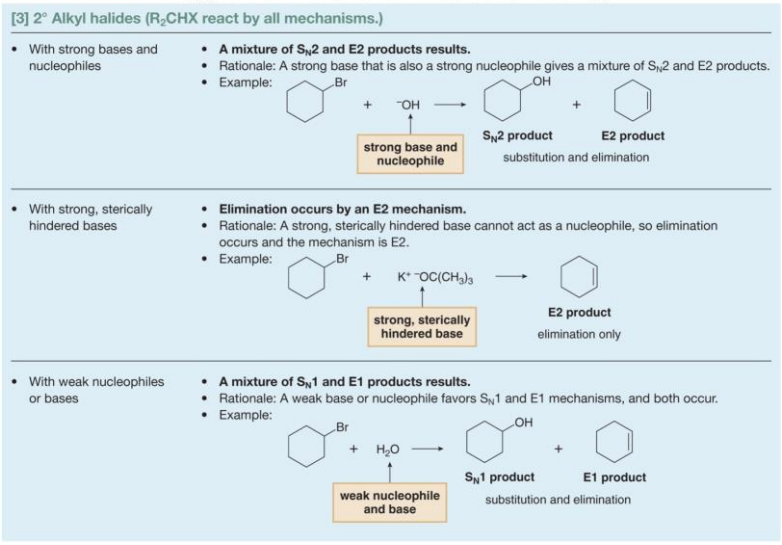
Predicting Reaction Mechanisms (S_N1, S_N2, E1, or E2)

Figure 8.10 *continued*



Predicting Reaction Mechanisms (S_N1, S_N2, E1 or E2)

Figure 8.10 *continued*



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