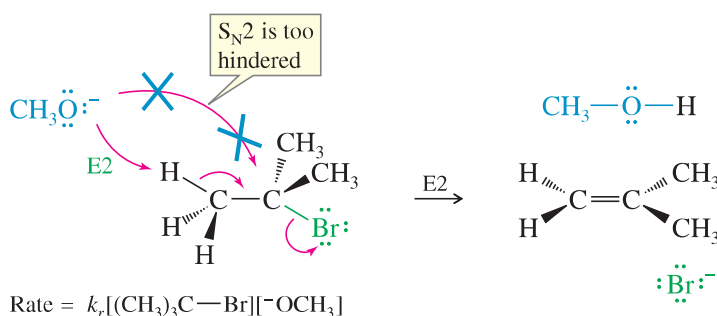


PROBLEM 7-22

When (1-bromoethyl)cyclohexane is heated in methanol for an extended period of time, five products result: two ethers and three alkenes. Predict the products of this reaction, and propose mechanisms for their formation. Predict which of the three alkenes is the major elimination product.

7-12 Bimolecular Elimination: The E2 Reaction

Eliminations can also take place under second-order conditions with a strong base present. As an example, consider the reaction of *tert*-butyl bromide with methoxide ion in methanol. Methoxide ion is a strong base as well as a strong nucleophile. It attacks the alkyl halide faster than the halide can ionize to give a first-order reaction. No substitution product (methyl *tert*-butyl ether) is observed, however. The S_N2 mechanism is blocked because the tertiary alkyl halide is too hindered. The observed product is 2-methylpropene, resulting from elimination of HBr and formation of a double bond.



The rate of this elimination is proportional to the concentrations of both the alkyl halide and the base, giving a second-order rate equation. This is a *bimolecular* process, with both the base and the alkyl halide participating in the transition state, so this mechanism is abbreviated **E2** for *Elimination, bimolecular*.

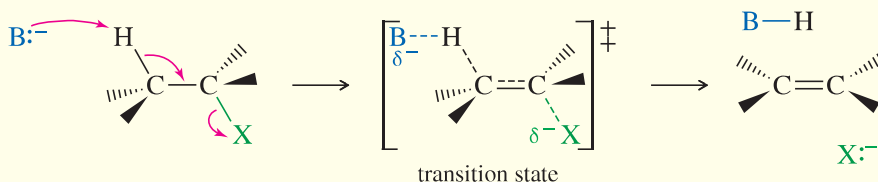
$$\text{E2 rate} = k_r[\text{RX}][\text{B}^-]$$

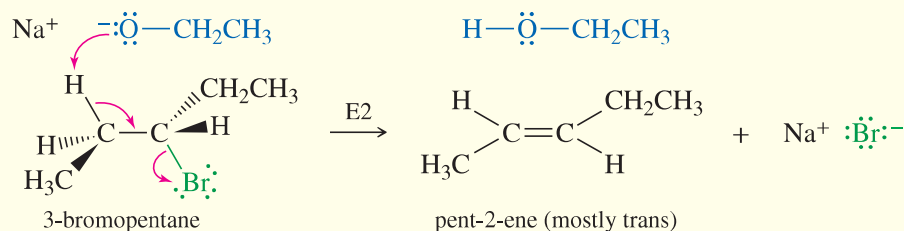
In the E2 reaction just shown, methoxide reacts as a *base* (removing a proton) rather than as a *nucleophile* (forming a bond to carbon). Most strong nucleophiles are also strong bases, and elimination commonly results when a strong base/nucleophile is used with a poor S_N2 substrate such as a 3° or hindered 2° alkyl halide. Instead of attacking the back side of the hindered electrophilic carbon, methoxide abstracts a proton from one of the methyl groups. This reaction takes place in one step, with bromide leaving as the base abstracts a proton.

In the general mechanism of the E2 reaction, a strong base abstracts a proton on a carbon atom adjacent to the one with the leaving group. As the base abstracts a proton, a double bond forms and the leaving group leaves. Like the S_N2 reaction, the E2 is a *concerted* reaction in which bonds break and new bonds form at the same time, in a single step.

**KEY MECHANISM 7-3 The E2 Reaction**

The concerted E2 reaction takes place in a single step. A strong base abstracts a proton on a carbon next to the leaving group, and the leaving group leaves. The product is an alkene.



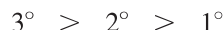
EXAMPLE: E2 elimination of 3-bromopentane with sodium ethoxide.

The order of reactivity for alkyl halides in E2 reactions is $3^\circ > 2^\circ > 1^\circ$.

PROBLEM 7-23

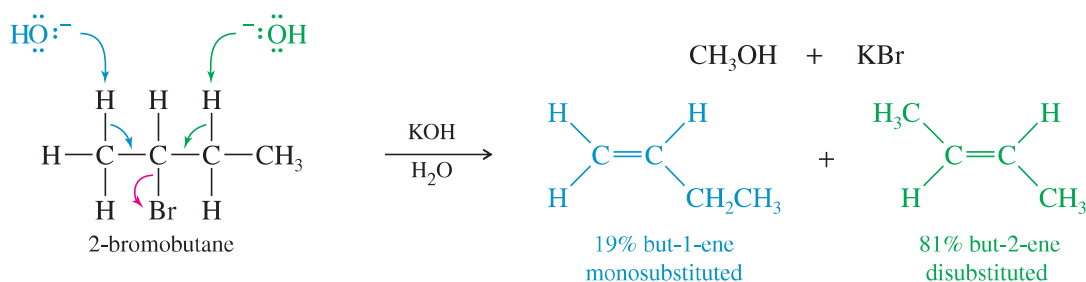
Under second-order conditions (strong base/nucleophile), $\text{S}_{\text{N}}2$ and E2 reactions may occur simultaneously and compete with each other. Show what products might be expected from the reaction of 2-bromo-3-methylbutane (a moderately hindered 2° alkyl halide) with sodium ethoxide.

Reactivity of the Substrate in the E2 The order of reactivity of alkyl halides toward E2 dehydrohalogenation is found to be

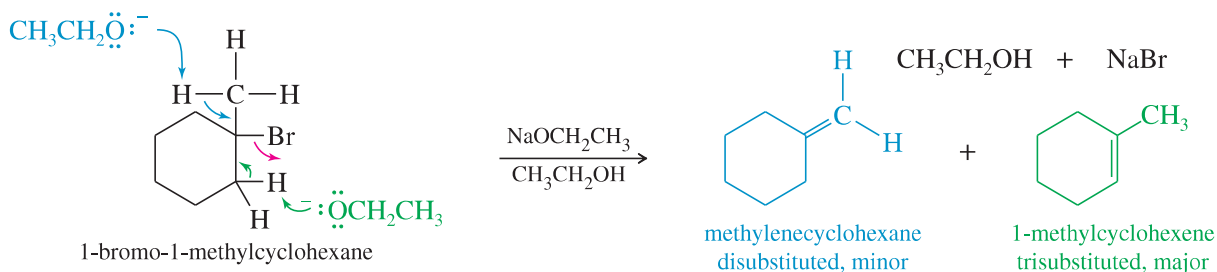


This reactivity order reflects the greater stability of highly substituted double bonds. Elimination of a secondary halide gives a more substituted alkene than elimination of a primary halide. Elimination of a tertiary halide gives an even more substituted alkene than a secondary halide. The stabilities of the alkene products are reflected in the transition states, giving lower activation energies and higher rates for elimination of alkyl halides that lead to highly substituted alkenes.

Mixtures of Products in the E2 The E2 reaction requires abstraction of a proton on a carbon atom next to the carbon bearing the halogen. If there are two or more possibilities, mixtures of products may result. In most cases, Zaitsev's rule predicts which of the possible products will be the major product: the most substituted alkene. For example, the E2 reaction of 2-bromobutane with potassium hydroxide gives a mixture of two products, but-1-ene (a monosubstituted alkene) and but-2-ene (a disubstituted alkene). As predicted by Zaitsev's rule, the disubstituted isomer but-2-ene is the major product.



Similarly, the reaction of 1-bromo-1-methylcyclohexane with sodium ethoxide gives a mixture of a disubstituted alkene and a trisubstituted alkene. The trisubstituted alkene is the major product.

**PROBLEM-SOLVING HINT**

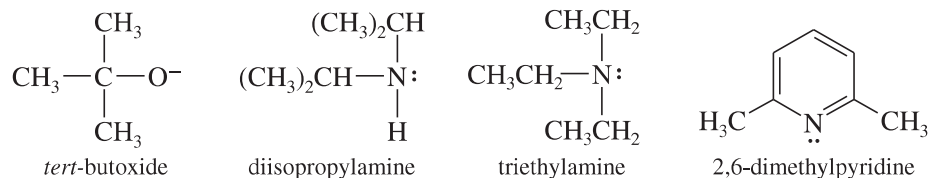
Zaitsev's rule usually applies in E2 reactions unless the base and/or the leaving group are unusually bulky.

PROBLEM 7-24

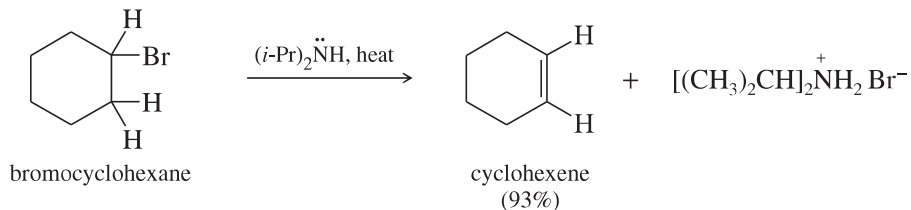
- Predict the elimination products of the following reactions. When two alkenes are possible, predict which one will be the major product. Explain your answers, showing the degree of substitution of each double bond in the products.
- Which of these reactions are likely to produce both elimination and substitution products?
 - 2-bromopentane + NaOCH₃
 - 3-bromo-3-methylpentane + NaOMe (Me = methyl, CH₃)
 - 2-bromo-3-ethylpentane + NaOH

7-13 Bulky Bases in E2 Eliminations; Hofmann Orientation

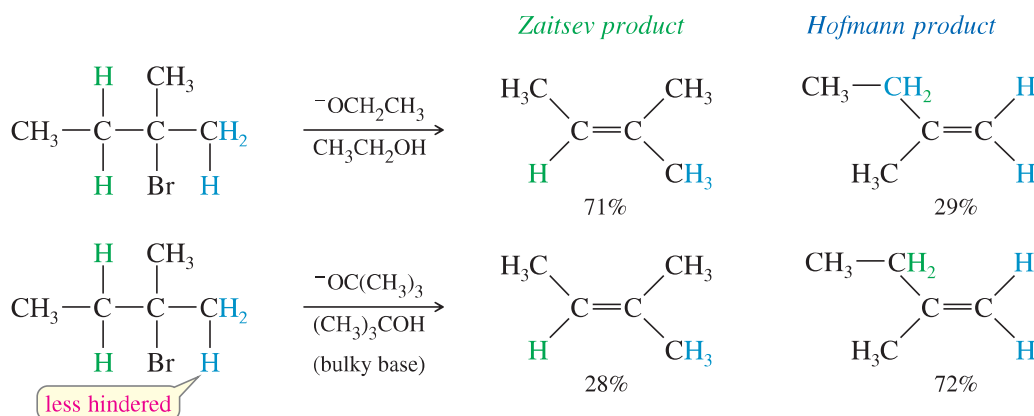
Use of a Bulky Base If the substrate in an E2 elimination is prone to substitution, we can minimize the amount of substitution by using a bulky base. Large alkyl groups on a bulky base hinder its approach to attack a carbon atom (substitution), yet it can easily abstract a proton (elimination). Some of the bulky strong bases commonly used for elimination are *tert*-butoxide ion, diisopropylamine, triethylamine, and 2,6-dimethylpyridine.



The dehydrohalogenation of bromocyclohexane illustrates the use of a bulky base for elimination. Bromocyclohexane, a secondary alkyl halide, can undergo both substitution and elimination. Elimination (E2) is favored over substitution (S_N2) by using a bulky base such as diisopropylamine. Diisopropylamine is too bulky to be a good nucleophile, but it acts as a strong base to abstract a proton.



Formation of the Hofmann Product Bulky bases can also accomplish dehydrohalogenations that do not follow the Zaitsev rule. Steric hindrance often prevents a bulky base from abstracting the proton that leads to the most highly substituted alkene. In these cases, it abstracts a less hindered proton, often the one that leads to formation of the least highly substituted product, called the **Hofmann product**. The following reaction gives mostly the **Zaitsev product** with the relatively unhindered ethoxide ion, but mostly the Hofmann product with the bulky *tert*-butoxide ion.

**PROBLEM 7-25**

For each reaction, decide whether substitution or elimination (or both) is possible, and predict the products you expect. Label the major products.

- 1-bromo-1-methylcyclohexane + NaOH in acetone
- 1-bromo-1-methylcyclohexane + triethylamine (Et_3N)
- chlorocyclohexane + NaOCH_3 in CH_3OH
- chlorocyclohexane + $\text{NaOC}(\text{CH}_3)_3$ in $(\text{CH}_3)_3\text{COH}$

7-14 Stereochemistry of the E2 Reaction

Like the $\text{S}_{\text{N}}2$ reaction, the E2 follows a **concerted mechanism**: Bond breaking and bond formation take place at the same time, and the partial formation of new bonds lowers the energy of the transition state. Concerted mechanisms require specific geometric arrangements so that the orbitals of the bonds being broken can overlap with those being formed and the electrons can flow smoothly from one bond to another. The geometric arrangement required by the $\text{S}_{\text{N}}2$ reaction is a back-side attack; with the E2 reaction, a coplanar arrangement of the orbitals is needed.

E2 elimination requires partial formation of a new pi bond, with its parallel p orbitals, in the transition state. The electrons that once formed a $\text{C}-\text{H}$ bond must begin to overlap with the orbital that the leaving group is vacating. Formation of this new pi bond implies that these two sp^3 orbitals must be parallel so that pi overlap is possible as the hydrogen and halogen leave and the orbitals rehybridize to the p orbitals of the new pi bond.

7-14A Anti-Coplanar and Syn-Coplanar E2 Eliminations

Figure 7-10 shows two conformations that provide the necessary coplanar alignment of the leaving group, the departing hydrogen, and the two carbon atoms. When the hydrogen and the halogen are **anti** to each other ($\theta = 180^\circ$), their orbitals are aligned. This is called the **anti-coplanar** conformation. When the hydrogen and the halogen eclipse each other ($\theta = 0^\circ$), their orbitals are once again aligned. This is called the **syn-coplanar** conformation. Make a model corresponding to Figure 7-10, and use it to follow along with this discussion.

Of these possible conformations, the anti-coplanar arrangement is most commonly seen in E2 reactions. The transition state for the anti-coplanar arrangement is a staggered conformation, with the base far away from the leaving group. In most cases, this transition state is lower in energy than that for the syn-coplanar elimination.

The transition state for syn-coplanar elimination is an eclipsed conformation. In addition to the higher energy resulting from eclipsing interactions, the transition state suffers from interference between the attacking base and the leaving group. To abstract the proton, the base must approach quite close to the leaving group. In most cases, the leaving group is bulky and negatively charged, and the repulsion between the base and the leaving group raises the energy of the syn-coplanar transition state.

Application: Biochemistry

Enzyme-catalyzed eliminations generally proceed by E2 mechanisms and produce only one stereoisomer. Two catalytic groups are involved: One abstracts the hydrogen, and the other assists in the departure of the leaving group. The groups are positioned appropriately to allow an anti-coplanar elimination.

For example, one of the steps in cellular respiration involves elimination of water from citric acid to give only the Z isomer of the product, commonly called *cis*-aconitic acid.

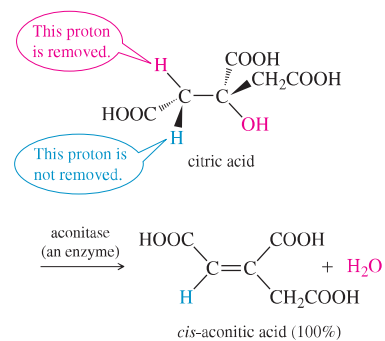
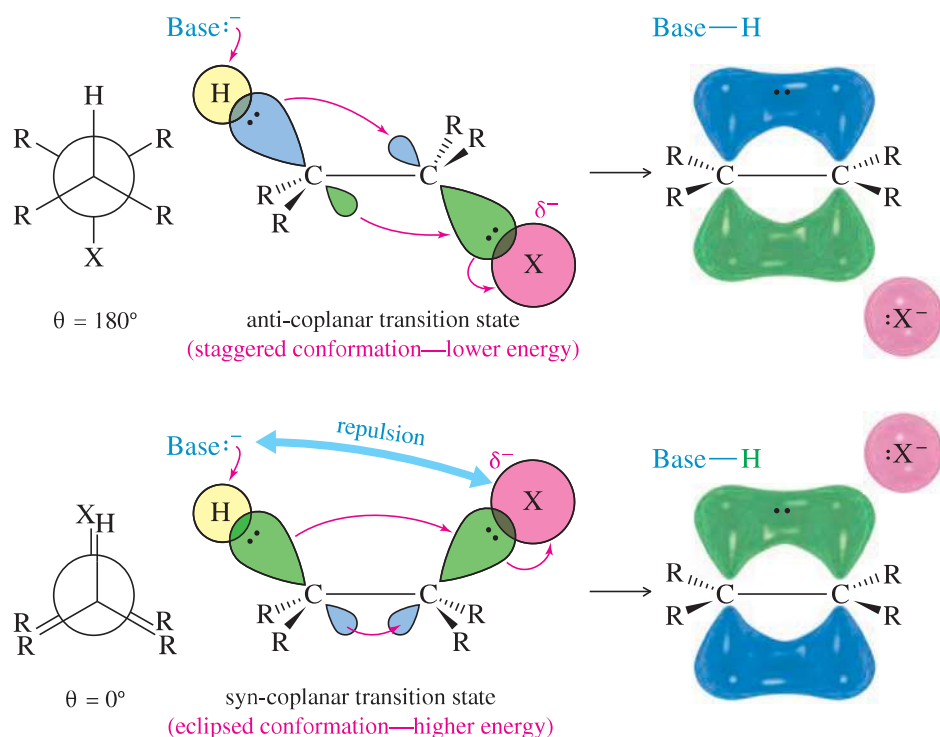
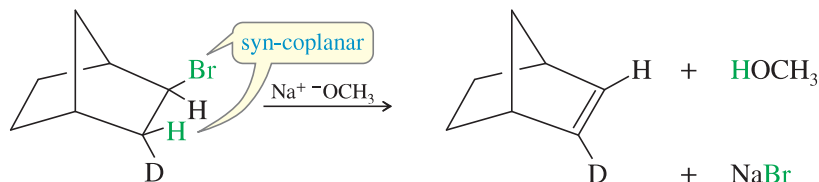


FIGURE 7-10

Concerted transition states of the E2 reaction. The orbitals of the hydrogen atom and the halide must be aligned so that they can begin to form a pi bond in the transition state.

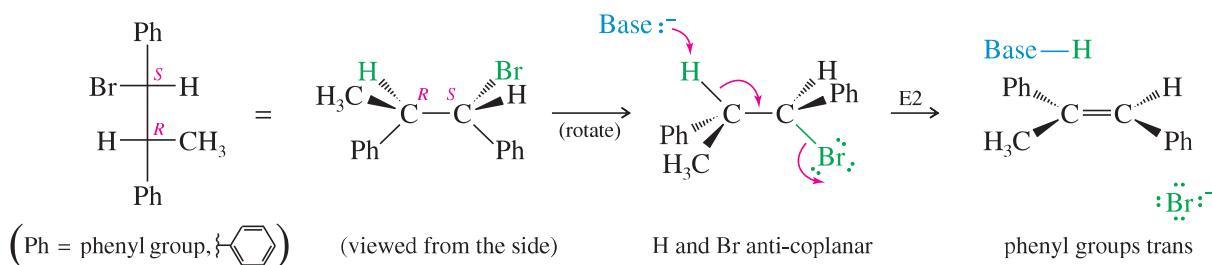


Some molecules are rigidly held in eclipsed (or nearly eclipsed) conformations, with a hydrogen atom and a leaving group in a syn-coplanar arrangement. Such compounds are likely to undergo E2 elimination by a concerted syn-coplanar mechanism. Deuterium labeling (using D, the hydrogen isotope with mass number 2) is used in the following reaction to show which atom is abstracted by the base. Only the hydrogen atom is abstracted, because it is held in a syn-coplanar position with the bromine atom. Remember that syn-coplanar eliminations are unusual, however, and anti-coplanar eliminations are more common.



7-14B Stereospecific E2 Reactions

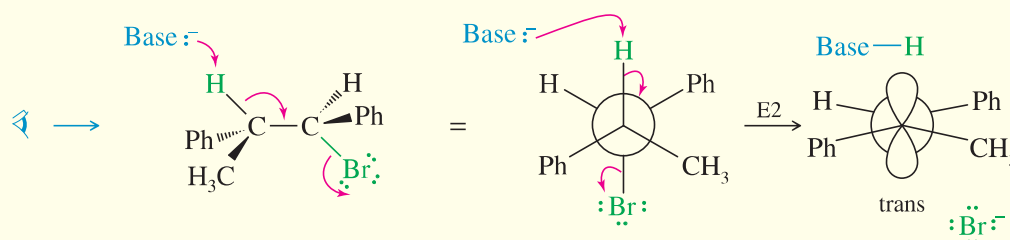
Like the $\text{S}_{\text{N}}2$ reaction (Section 6-12), the E2 is **stereospecific**: Different stereoisomers of the reactant give different stereoisomers of the product. The E2 is stereospecific because it normally goes through an anti-coplanar transition state. The products are alkenes, and different diastereomers of starting materials commonly give different diastereomers of alkenes. The following example shows why the E2 elimination of one diastereomer of 1-bromo-1,2-diphenylpropane gives only the trans isomer of the alkene product.



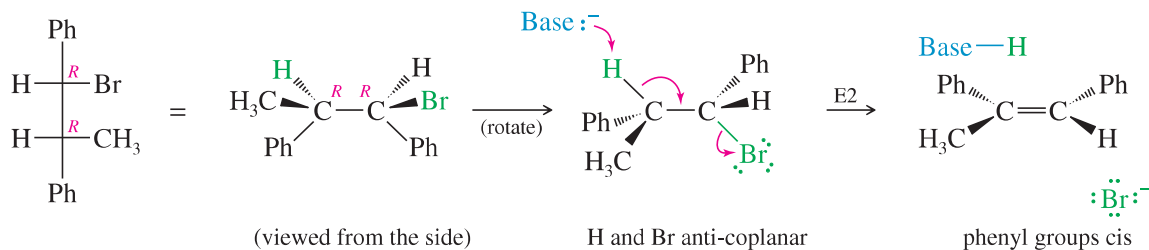
If we make a model and look at this reaction from the left end of the molecule, the anti-coplanar arrangement of the H and Br is apparent.

MECHANISM 7-4 Stereochemistry of the E2 Reaction

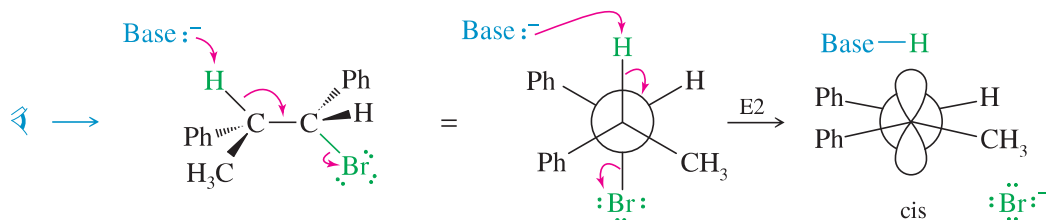
Most E2 reactions go through an anti-coplanar transition state. This geometry is most apparent if we view the reaction sighting down the carbon-carbon bond between the hydrogen and leaving group. Viewed from the left:



The following reaction shows how the anti-coplanar elimination of the other diastereomer (*R,R*) gives only the *cis* isomer of the product. In effect, the two different diastereomers of the reactant give two different diastereomers of the product: a stereospecific result.



Viewed from the left end of the molecule:



PROBLEM 7-26

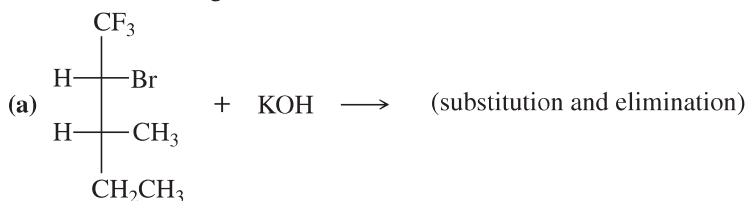
Show that the (*S,S*) enantiomer of this (*R,R*) diastereomer of 1-bromo-1,2-diphenylpropane also undergoes E2 elimination to give the *cis* diastereomer of the product. (We do not expect these achiral reagents to distinguish between enantiomers.)

PROBLEM-SOLVING HINT

Don't try to memorize your way through these reactions. Look at each one, and consider what it might do. Use your models for the ones that involve stereochemistry.

PROBLEM 7-27

Make models of the following compounds, and predict the products formed when they react with the strong bases shown.

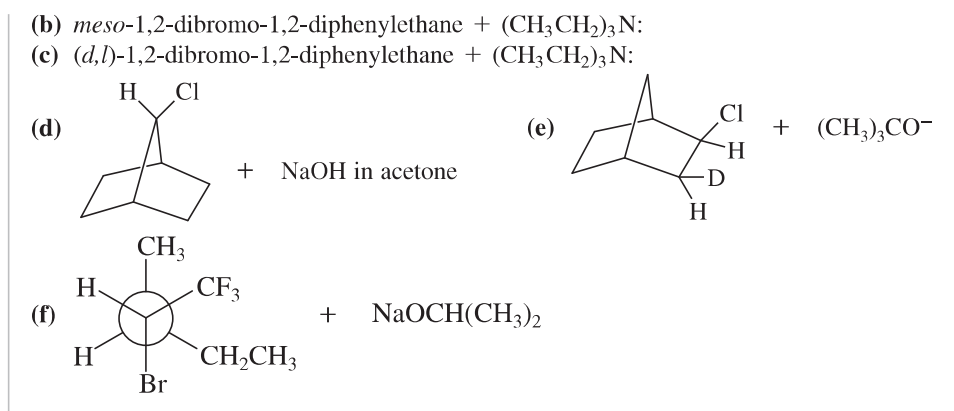


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PROBLEM-SOLVING HINT

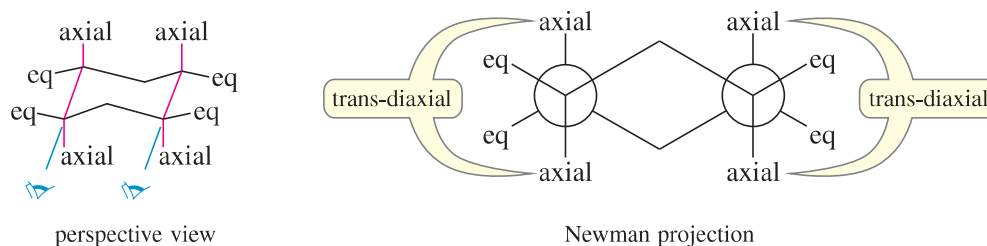
Anti-coplanar E2 eliminations are common.

Syn-coplanar E2 eliminations are rare, usually occurring when free rotation is not possible.



7-15 E2 Reactions in Cyclohexane Systems

Nearly all cyclohexanes are most stable in chair conformations. In the chair, all the carbon–carbon bonds are staggered, and any two adjacent carbon atoms have axial bonds in an anti-coplanar conformation, ideally oriented for the E2 reaction. (As drawn in the following figure, the axial bonds are vertical.) On any two adjacent carbon atoms, one has its axial bond pointing up and the other has its axial bond pointing down. These two bonds are trans to each other, and we refer to their geometry as **trans-diaxial**.



An E2 elimination can take place on this chair conformation only if the proton and the leaving group can get into a trans-diaxial arrangement. Figure 7-11 shows the E2 dehydrohalogenation of bromocyclohexane. The molecule must flip into the chair conformation with the bromine atom axial before elimination can occur.

(You should make models of the structures in the following examples and problems so that you can follow along more easily.)

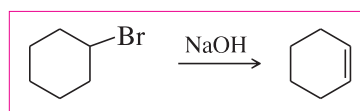
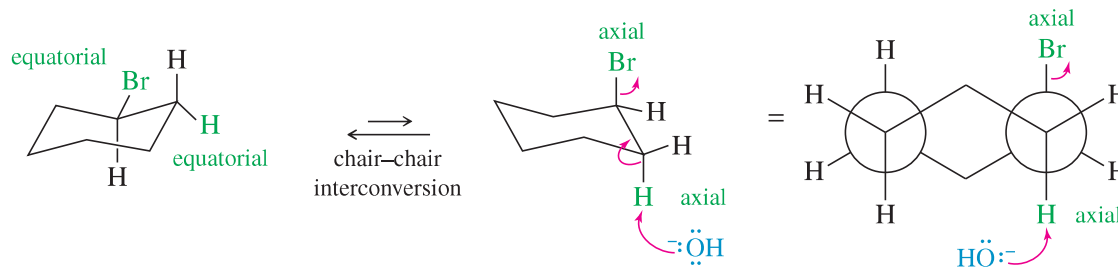


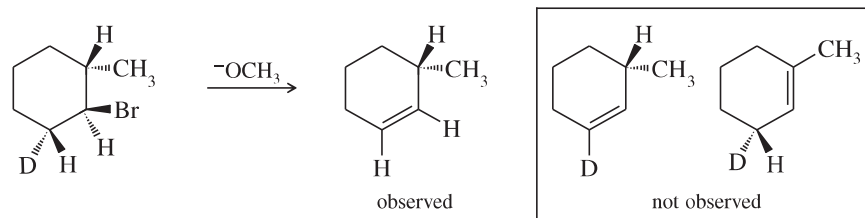
FIGURE 7-11

E2 eliminations on cyclohexane rings. E2 elimination of bromocyclohexane requires that both the proton and the leaving group be trans and both be axial.

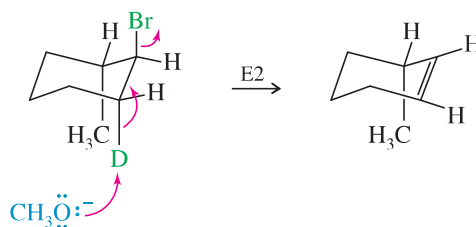


SOLVED PROBLEM 7-5

Explain why the following deuterated 1-bromo-2-methylcyclohexane undergoes dehydrohalogenation by the E2 mechanism to give only the indicated product. Two other alkenes are not observed.

**SOLUTION**

In an E2 elimination, the hydrogen atom and the leaving group must have a trans-diaxial relationship. In this compound, only one hydrogen atom—the deuterium—is trans to the bromine atom. When the bromine atom is axial, the adjacent deuterium is also axial, providing a trans-diaxial arrangement.

**PROBLEM 7-28**

Predict the elimination products of the following reactions, and label the major products.

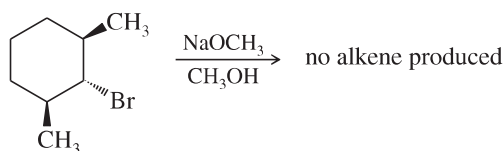
- (a) *cis*-1-bromo-2-methylcyclohexane + NaOCH₃ in CH₃OH
 (b) *trans*-1-bromo-2-methylcyclohexane + NaOCH₃ in CH₃OH

PROBLEM-SOLVING HINT

In a chair conformation of a cyclohexane ring, a trans-diaxial arrangement places the two groups anti and coplanar.

PROBLEM 7-29

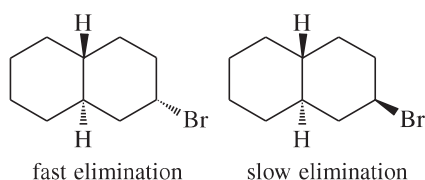
When the following stereoisomer of 2-bromo-1,3-dimethylcyclohexane is treated with sodium methoxide, no E2 reaction is observed. Explain why this compound cannot undergo the E2 reaction in the chair conformation.

**PROBLEM-SOLVING HINT**

Look for a hydrogen trans to the leaving group; then see if the hydrogen and the leaving group can become diaxial.

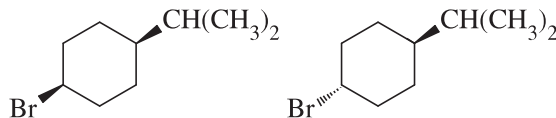
PROBLEM 7-30

- (a) Two stereoisomers of a bromodecalin are shown. Although the difference between these stereoisomers may seem trivial, one isomer undergoes elimination with KOH much faster than the other. Predict the products of these eliminations, and explain the large difference in the ease of elimination.



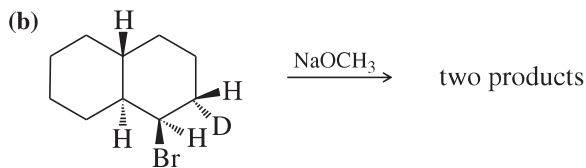
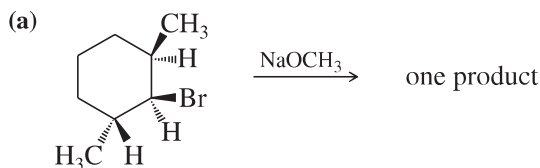
(continued)

(b) Predict which of the following compounds will undergo elimination with KOH faster, and explain why. Predict the major product that will be formed.



PROBLEM 7-31

Give the expected product(s) of E2 elimination for each reaction. (*Hint: Use models!*)



7-16 Comparison of E1 and E2 Elimination Mechanisms

Let's summarize the major points to remember about the E1 and E2 reactions, focusing on the factors that help us predict which of these mechanisms will operate under a given set of experimental conditions.

Effect of the Base The nature of the base is the single most important factor in determining whether an elimination will go by the E1 or E2 mechanism. If a strong base is present, the rate of the bimolecular reaction will be greater than the rate of ionization, and the E2 reaction will predominate (perhaps accompanied by the S_N2).

If no strong base is present, then a good solvent makes a unimolecular ionization likely. Subsequent loss of a proton to a weak base (such as the solvent) leads to elimination. Under these conditions, the E1 reaction usually predominates, usually accompanied by the S_N1 .

- | | |
|-----|--|
| E1: | Base strength is unimportant (usually weak). |
| E2: | Requires strong bases. |

Effect of the Solvent The slow step of the E1 reaction is the formation of two ions. Like the S_N1 , the E1 reaction critically depends on polar ionizing solvents such as water and the alcohols.

In the E2 reaction, the transition state spreads out the negative charge of the base over the entire molecule. There is no more need for solvation in the E2 transition state than in the reactants. The E2 is therefore less sensitive to the solvent; in fact, some reagents are stronger bases in less polar solvents.

- | | |
|-----|---------------------------------------|
| E1: | Requires a good ionizing solvent. |
| E2: | Solvent polarity is not so important. |

Effect of the Substrate For both the E1 and the E2 reactions, the order of reactivity is

- | | |
|---------|---|
| E1, E2: | $3^\circ > 2^\circ > 1^\circ$ (1° usually will not go E1) |
|---------|---|

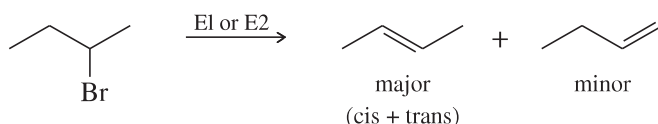
In the E1 reaction, the rate-limiting step is formation of a carbocation, and the reactivity order reflects the stability of carbocations. In the E2 reaction, the more substituted halides generally form more substituted, more stable alkenes.

Kinetics The rate of the E1 reaction is proportional to the concentration of the alkyl halide [RX] but not to the concentration of the weak base. It follows a first-order rate equation.

The rate of the E2 reaction is proportional to the concentrations of both the alkyl halide [RX] and the strong base [B:⁻]. It follows a second-order rate equation.

$$\begin{aligned} \text{E1 rate} &= k_r[\text{RX}] \\ \text{E2 rate} &= k_r[\text{RX}][\text{B}:^-] \end{aligned}$$

Orientation of Elimination In most E1 and E2 eliminations with two or more possible products, the product with the most substituted double bond (the most stable product) predominates. This principle is called **Zaitsev's rule**, and the most highly substituted product is called the **Zaitsev product**.



E1, E2: Usually Zaitsev orientation.

Stereochemistry The E1 reaction begins with an ionization to give a flat carbocation. No particular geometry is required for ionization.

The E2 reaction takes place through a concerted mechanism that requires a coplanar arrangement of the bonds to the atoms being eliminated. The transition state is usually anti-coplanar, although it may be syn-coplanar in rigid systems.

E1: No particular geometry required for the slow step.
E2: Coplanar arrangement (usually anti) required for the transition state.

Rearrangements The E1 reaction involves a carbocation intermediate. This intermediate can rearrange, usually by the shift of a hydride or an alkyl group, to give a more stable carbocation.

The E2 reaction takes place in one step with no intermediates. No rearrangement is possible in the E2 reaction.

E1: Rearrangements are common.
E2: No rearrangements.

SUMMARY Elimination Reactions

	E1	E2
Promoting factors		
base	weak bases work	strong base required
solvent	good ionizing solvent	wide variety of solvents
substrate	3° > 2°	3° > 2° > 1°
leaving group	good one required	good one required
Characteristics		
kinetics	first order, $k_r[\text{RX}]$	second order, $k_r[\text{RX}][\text{B}:^-]$
orientation	most substituted alkene	most substituted alkene
stereochemistry	no special geometry	coplanar transition state required
rearrangements	common	impossible