



# 30

## Orbitals and Organic Chemistry: Pericyclic Reactions

### Organic KNOWLEDGE TOOLS

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Most organic reactions take place by polar mechanisms, in which a nucleophile donates two electrons to an electrophile in forming a new bond. Other reactions take place by radical mechanisms, in which each of two reactants donates one electron in forming a new bond. Both kinds of reactions occur frequently in the laboratory and in living organisms. Less common, however, is the third major class of organic reaction mechanisms—*pericyclic reactions*.

A **pericyclic reaction** is one that occurs by a concerted process through a cyclic transition state. The word *concerted* means that all bonding changes occur at the same time and in a single step; no intermediates are involved. Rather than try to expand this definition now, we'll begin by briefly reviewing some of the ideas of molecular orbital theory introduced in Chapters 1 and 14 and then looking individually at the three main classes of pericyclic reactions: *electrocyclic reactions*, *cycloadditions*, and *sigmatropic rearrangements*.

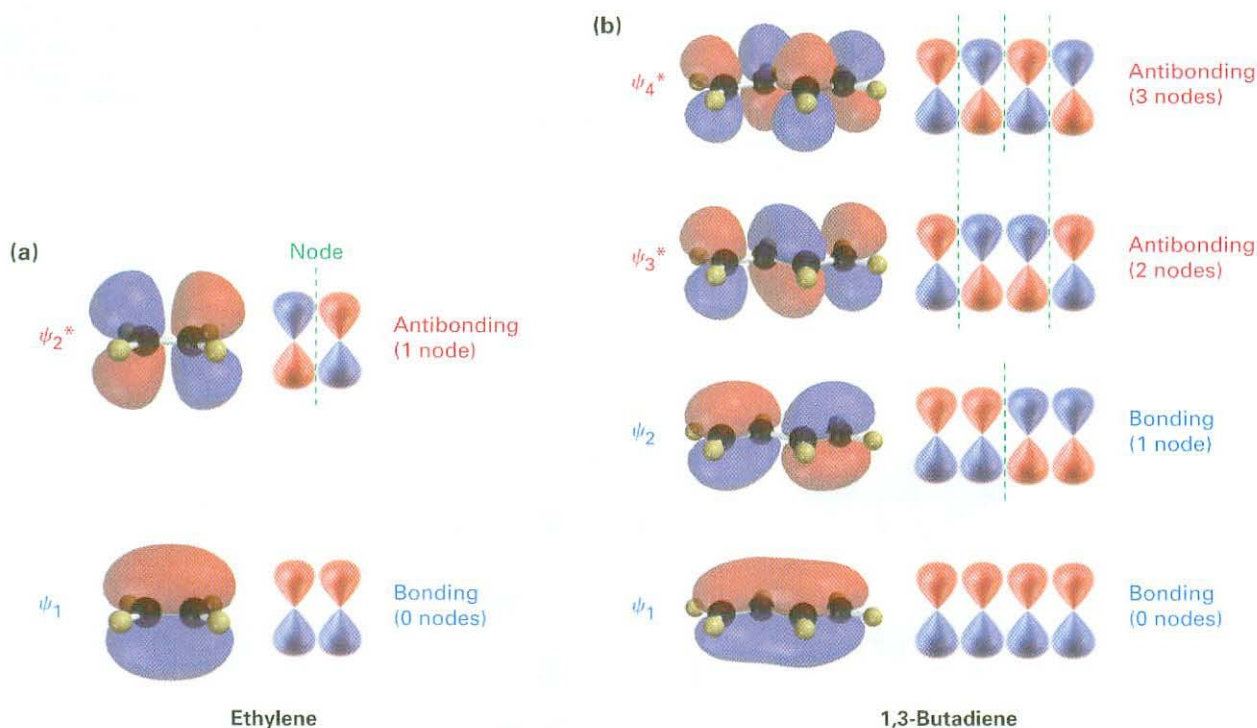
### WHY THIS CHAPTER?

The broad outlines of both polar and radical reactions have been known for nearly a century, but our understanding of pericyclic reactions emerged more recently. Prior to the mid-1960s, in fact, they were even referred to on occasion as “no-mechanism reactions.” They occur largely in laboratory rather than biological processes, but a knowledge of them is necessary, both for completeness in studying organic chemistry and in understanding those biological pathways where they do occur.

### 30.1 Molecular Orbitals and Pericyclic Reactions of Conjugated Pi Systems

A conjugated polyene, as we saw in Section 14.1, is one with alternating double and single bonds. According to molecular orbital (MO) theory, the *p* orbitals on the *sp*<sup>2</sup>-hybridized carbons of a conjugated polyene interact to form a set of

$\pi$  molecular orbitals whose energies depend on the number of nodes they have between nuclei. Those molecular orbitals with fewer nodes are lower in energy than the isolated  $p$  atomic orbitals and are *bonding MOs*; those molecular orbitals with more nodes are higher in energy than the isolated  $p$  orbitals and are *anti-bonding MOs*. Pi molecular orbitals of ethylene and 1,3-butadiene are shown in Figure 30.1.



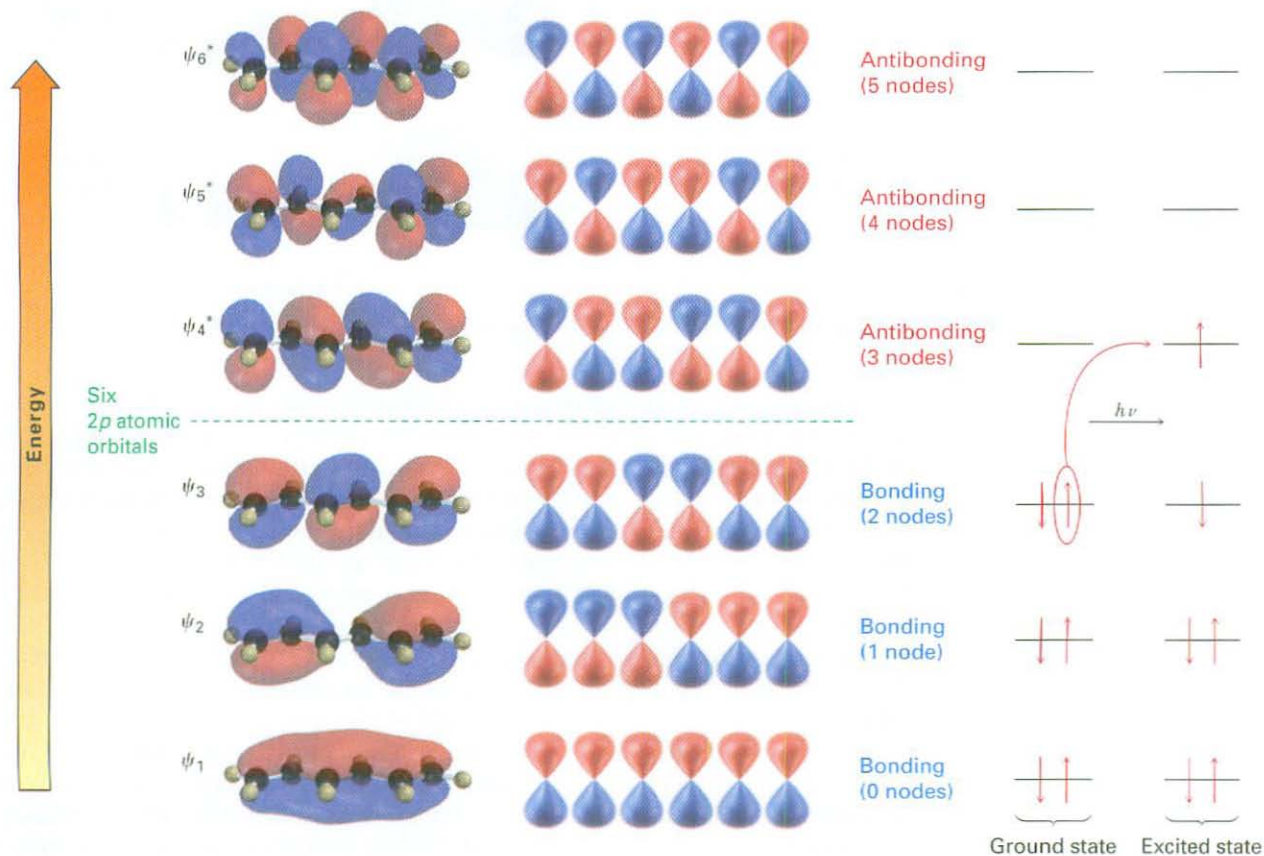
**Figure 30.1** Pi molecular orbitals of (a) ethylene and (b) 1,3-butadiene.

A similar sort of molecular orbital description can be derived for any conjugated  $\pi$  electron system. 1,3,5-Hexatriene, for example, has three double bonds and six  $\pi$  MOs, as shown in Figure 30.2. In the ground state, only the three bonding orbitals,  $\psi_1$ ,  $\psi_2$ , and  $\psi_3$ , are filled. On irradiation with ultraviolet light, however, an electron is promoted from the highest-energy filled orbital ( $\psi_3$ ) to the lowest-energy unfilled orbital ( $\psi_4^*$ ) to give an excited state (Section 14.7), in which  $\psi_3$  and  $\psi_4^*$  are each half-filled. (An asterisk denotes an antibonding orbital.)

What do molecular orbitals and their nodes have to do with pericyclic reactions? The answer is, *everything*. According to a series of rules formulated in the mid-1960s by R. B. Woodward and Roald Hoffmann, a pericyclic reaction can take place only if the symmetries of the reactant MOs are the same as the symmetries of the product MOs. In other words, *the lobes of reactant MOs must be of the correct algebraic sign for bonding to occur in the transition state leading to product*.

If the symmetries of reactant and product orbitals match up, or correlate, the reaction is said to be **symmetry-allowed**. If the symmetries of reactant and product orbitals don't correlate, the reaction is **symmetry-disallowed**.

Robert Burns Woodward	Roald Hoffmann	Kenichi Fukui
<p><b>Robert Burns Woodward</b> (1917–1979) was born in Boston, Massachusetts. He entered the Massachusetts Institute of Technology at age 16, was expelled, reentered, obtained a B.S. degree at age 19, and received a Ph.D. at age 20. He then moved to Harvard University, where he joined the faculty in 1940 at age 23 and remained as professor until his death. His vast scientific contributions included determining the structure of penicillin, pioneering the use of spectroscopic tools for structure elucidation, and turning the field of synthetic organic chemistry into an art form. He received the 1965 Nobel Prize for his work in organic synthesis.</p>	<p><b>Roald Hoffmann</b> (1937–) was born in Zloczow, Poland, just prior to World War II. As a boy, he survived the Holocaust by hiding in the attic of a village schoolhouse. In 1949, he immigrated to the United States, where he received an undergraduate degree at Columbia University and a Ph.D. at Harvard University in 1962. During a further 3-year stay at Harvard as Junior Fellow, he began the collaboration with R. B. Woodward that led to the development of the Woodward–Hoffmann rules for pericyclic reactions. In 1965, he moved to Cornell University, where he remains as professor. He received the 1981 Nobel Prize in chemistry.</p>	<p><b>Kenichi Fukui</b> (1918–1998) was born in Nara Prefecture, Japan, and received a Ph.D. in 1948 from Kyoto Imperial University. He remained at Kyoto University as professor of chemistry until 1982 and then became president of that institution from 1982 to 1988. He received the 1981 Nobel Prize in chemistry, the first Japanese scientist to be thus honored.</p>



**Figure 30.2** The six  $\pi$  molecular orbitals of 1,3,5-hexatriene. In the ground state, the three bonding MOs are filled. In the excited state,  $\psi_3$  and  $\psi_4^*$  each have one electron.

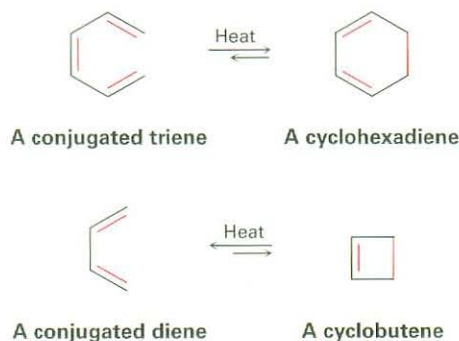
Symmetry-allowed reactions often occur under relatively mild conditions, but symmetry-disallowed reactions can't occur by concerted paths. Either they take place by nonconcerted, high-energy pathways, or they don't take place at all.

The Woodward–Hoffmann rules for pericyclic reactions require an analysis of all reactant and product molecular orbitals, but Kenichi Fukui at Kyoto Imperial University in Japan introduced a simplified version. According to Fukui, we need to consider only two molecular orbitals, called the **frontier orbitals**. These frontier orbitals are the **highest occupied molecular orbital (HOMO)** and the **lowest unoccupied molecular orbital (LUMO)**. In ground-state 1,3,5-hexatriene, for example,  $\psi_3$  is the HOMO and  $\psi_4^*$  is the LUMO (Figure 30.2). In excited-state 1,3,5-hexatriene, however,  $\psi_4^*$  is the HOMO and  $\psi_5^*$  is the LUMO.

**Problem 30.1** | Look at Figure 30.1, and tell which molecular orbital is the HOMO and which is the LUMO for both ground and excited states of ethylene and 1,3-butadiene.

## 30.2 Electrocyclic Reactions

The best way to understand how orbital symmetry affects pericyclic reactions is to look at some examples. Let's look first at a group of polyene rearrangements called *electrocyclic reactions*. An **electrocyclic reaction** is a pericyclic process that involves the cyclization of a conjugated polyene. One  $\pi$  bond is broken, the other  $\pi$  bonds change position, a new  $\sigma$  bond is formed, and a cyclic compound results. For example, a conjugated triene can be converted into a cyclohexadiene, and a conjugated diene can be converted into a cyclobutene.

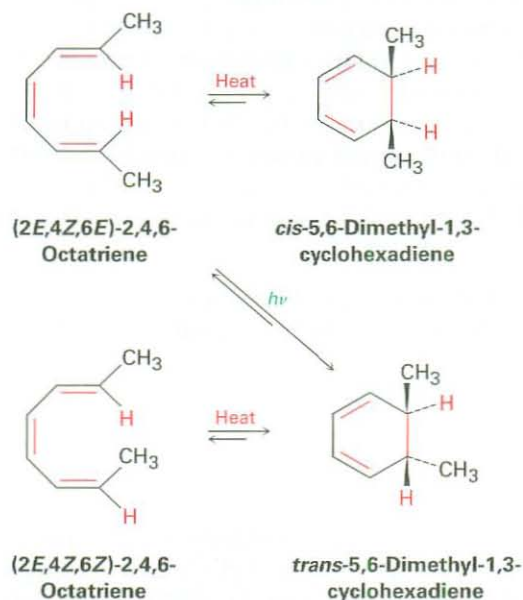


Both reactions are reversible, and the position of the equilibrium depends on the specific case. In general, the triene  $\rightleftharpoons$  cyclohexadiene equilibrium favors the cyclic product, whereas the diene  $\rightleftharpoons$  cyclobutene equilibrium favors the unstrained open-chain product.

The most striking feature of electrocyclic reactions is their stereochemistry. For example, (2*E*,4*Z*,6*E*)-2,4,6-octatriene yields only *cis*-5,6-dimethyl-1,3-cyclohexadiene when heated, and (2*E*,4*Z*,6*Z*)-2,4,6-octatriene yields only *trans*-5,6-dimethyl-1,3-cyclohexadiene. Remarkably, however, the stereochemical results change completely when the reactions are carried out under what are called **photochemical**, rather than thermal, conditions. Irradiation, or *photolysis*,

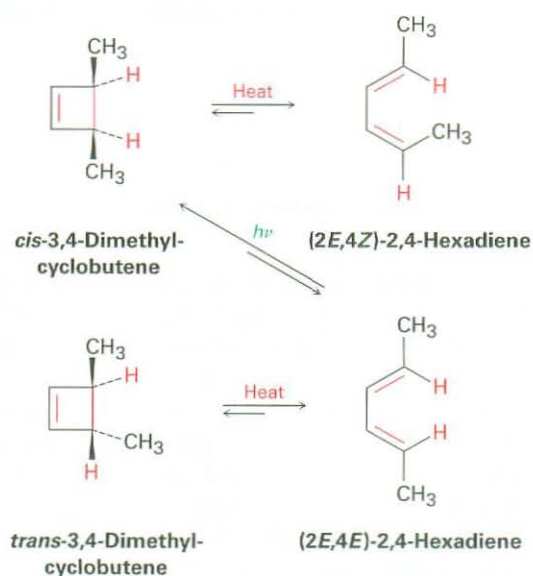
of  $(2E,4Z,6E)$ -2,4,6-octatriene with ultraviolet light yields *trans*-5,6-dimethyl-1,3-cyclohexadiene (Figure 30.3).

**Figure 30.3** Electrocyclic interconversions of 2,4,6-octatriene isomers and 5,6-dimethyl-1,3-cyclohexadiene isomers.



A similar result is obtained for the thermal electrocyclic ring-opening of 3,4-dimethylcyclobutene. The *trans* isomer yields only  $(2E,4E)$ -2,4-hexadiene when heated, and the *cis* isomer yields only  $(2E,4Z)$ -2,4-hexadiene. On UV irradiation, however, the results are opposite. Cyclization of the  $2E,4E$  isomer under photochemical conditions yields *cis* product (Figure 30.4).

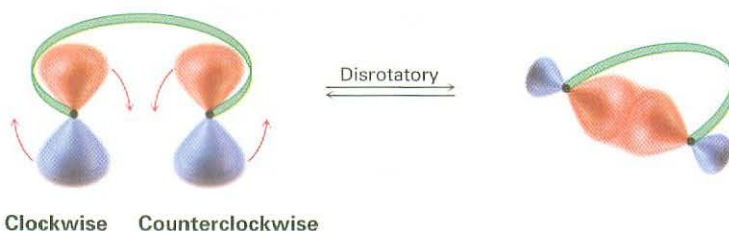
**Figure 30.4** Electrocyclic interconversions of 2,4-hexadiene isomers and 3,4-dimethylcyclobutene isomers.



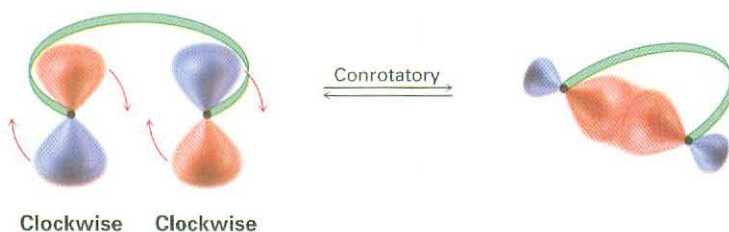
To account for these results, we need to look at the two outermost lobes of the polyene MOs—the lobes that interact when bonding occurs. There are two possibilities: the lobes of like sign can be either on the same side or on opposite sides of the molecule.



For a bond to form, the outermost  $\pi$  lobes must rotate so that favorable bonding interaction is achieved—a positive lobe with a positive lobe or a negative lobe with a negative lobe. If two lobes of like sign are on the *same* side of the molecule, the two orbitals must rotate in *opposite* directions—one clockwise and one counterclockwise. This kind of motion is referred to as **disrotatory**.



Conversely, if lobes of like sign are on *opposite* sides of the molecule, both orbitals must rotate in the *same* direction, either both clockwise or both counterclockwise. This kind of motion is called **conrotatory**.



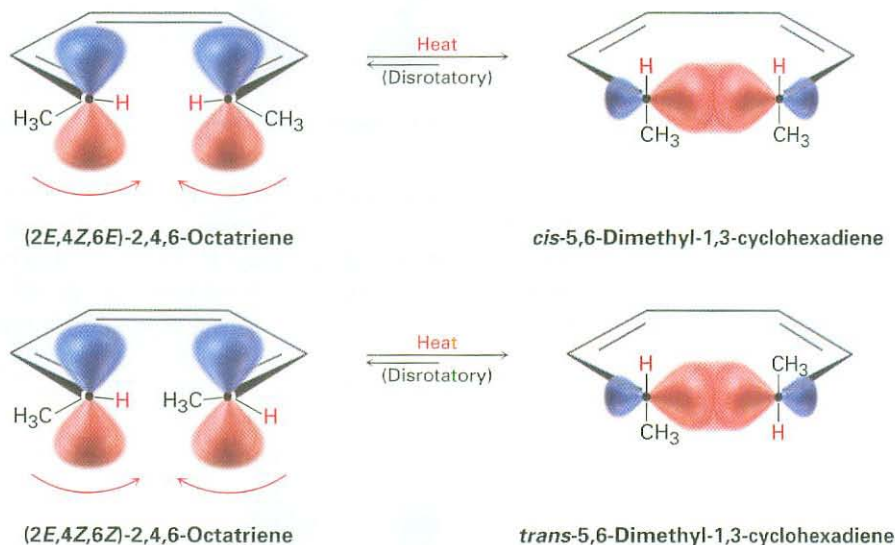
## 30.3 Stereochemistry of Thermal Electrocyclic Reactions

How can we predict whether conrotatory or disrotatory motion will occur in a given case? According to frontier orbital theory, *the stereochemistry of an electrocyclic reaction is determined by the symmetry of the polyene HOMO*. The electrons in the HOMO are the highest-energy, most loosely held electrons, and are therefore most easily moved during reaction. For thermal reactions, the ground-state

electronic configuration is used to identify the HOMO; for photochemical reactions, the excited-state electronic configuration is used.

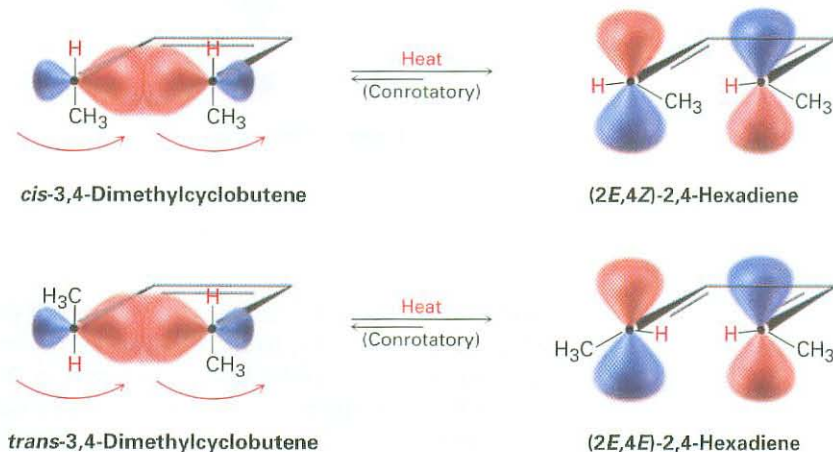
Let's look again at the thermal ring closure of conjugated trienes. According to Figure 30.2, the HOMO of a conjugated triene in its ground state has lobes of like sign on the same side of the molecule, a symmetry that predicts disrotatory ring closure. This disrotatory cyclization is exactly what is observed in the thermal cyclization of 2,4,6-octatriene. The *2E,4Z,6E* isomer yields *cis* product; the *2E,4Z,6Z* isomer yields *trans* product (Figure 30.5).

**Active Figure 30.5** Thermal cyclizations of 2,4,6-octatrienes occur by disrotatory ring closures. Sign in at [www.thomsonedu.com](http://www.thomsonedu.com) to see a simulation based on this figure and to take a short quiz.

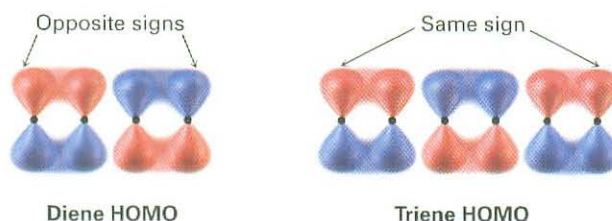


In the same way, the ground-state HOMO of a conjugated diene (Figure 30.1) has a symmetry that predicts conrotatory ring closure. In practice, however, the conjugated diene reaction can be observed only in the reverse direction (cyclobutene  $\rightarrow$  diene) because of the position of the equilibrium. We therefore find that the 3,4-dimethylcyclobutene ring *opens* in a conrotatory fashion. *cis*-3,4-Dimethylcyclobutene yields (*2E,4Z*)-2,4-hexadiene, and *trans*-3,4-dimethylcyclobutene yields (*2E,4E*)-2,4-hexadiene by conrotatory opening (Figure 30.6).

**Figure 30.6** Thermal ring-openings of *cis*- and *trans*-dimethylcyclobutene occur by conrotatory paths.



Note that a conjugated diene and a conjugated triene react with opposite stereochemistry. The diene opens and closes by a conrotatory path, whereas the triene opens and closes by a disrotatory path. The difference is due to the different symmetries of the diene and triene HOMOs.



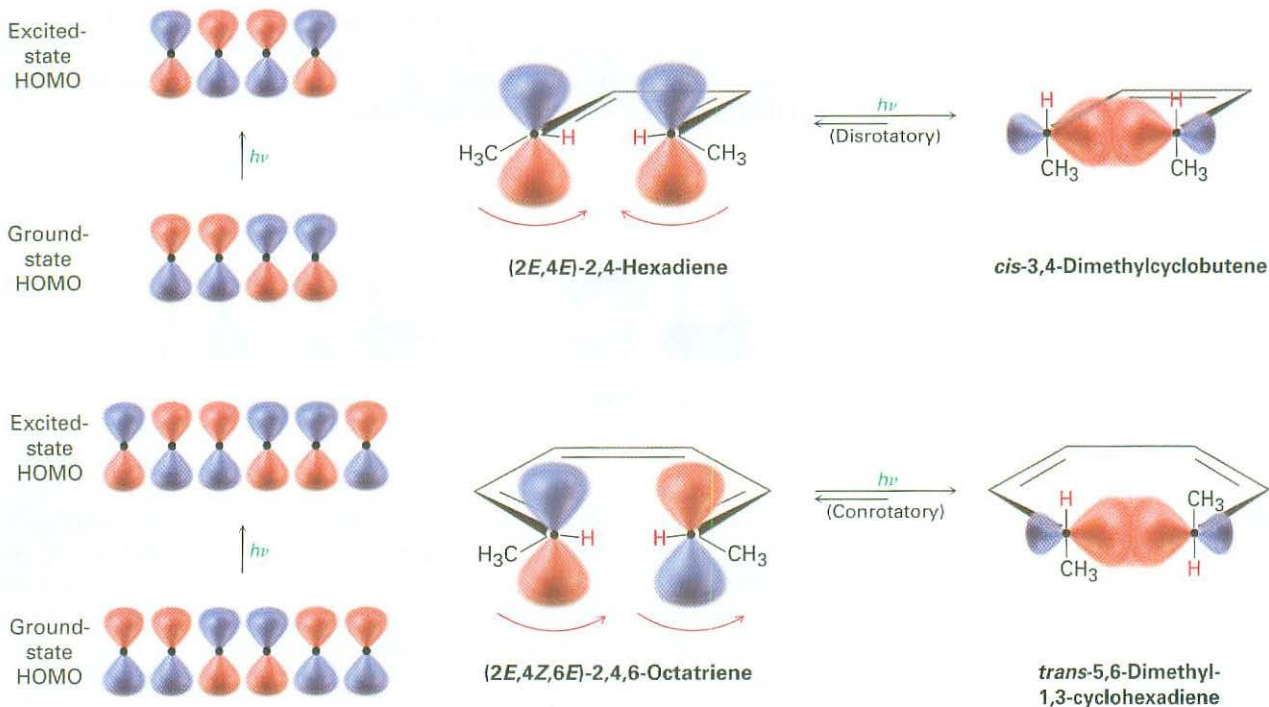
It turns out that there is an alternating relationship between the number of electron pairs (double bonds) undergoing bond reorganization and the stereochemistry of ring opening or closure. Polyenes with an even number of electron pairs undergo thermal electrocyclic reactions in a conrotatory sense, whereas polyenes with an odd number of electron pairs undergo the same reactions in a disrotatory sense.

- Problem 30.2** Draw the products you would expect from conrotatory and disrotatory cyclizations of (2*Z*,4*Z*,6*Z*)-2,4,6-octatriene. Which of the two paths would you expect the thermal reaction to follow?
- Problem 30.3** *trans*-3,4-Dimethylcyclobutene can open by two conrotatory paths to give either (2*E*,4*E*)-2,4-hexadiene or (2*Z*,4*Z*)-2,4-hexadiene. Explain why both products are symmetry-allowed, and then account for the fact that only the 2*E*,4*E* isomer is obtained in practice.

## 30.4 Photochemical Electrocyclic Reactions

We noted previously that photochemical electrocyclic reactions take a different stereochemical course than their thermal counterparts, and we can now explain this difference. Ultraviolet irradiation of a polyene causes an excitation of one electron from the ground-state HOMO to the ground-state LUMO, thus changing their symmetries. But because electronic excitation changes the symmetries of HOMO and LUMO, it also changes the reaction stereochemistry. (2*E*,4*E*)-2,4-Hexadiene, for instance, undergoes photochemical cyclization by a disrotatory path, whereas the thermal reaction is conrotatory. Similarly, (2*E*,4*Z*,6*E*)-2,4,6-octatriene undergoes photochemical cyclization by a conrotatory path, whereas the thermal reaction is disrotatory (Figure 30.7).





**Figure 30.7** Photochemical cyclizations of conjugated dienes and trienes. The two processes occur with different stereochemistry because of their different orbital symmetries.

Thermal and photochemical electrocyclic reactions *always* take place with opposite stereochemistry because the symmetries of the frontier orbitals are always different. Table 30.1 gives some simple rules that make it possible to predict the stereochemistry of electrocyclic reactions.

**Table 30.1** Stereochemical Rules for Electrocyclic Reactions

Electron pairs (double bonds)	Thermal reaction	Photochemical reaction
Even number	Conrotatory	Disrotatory
Odd number	Disrotatory	Conrotatory

**Problem 30.4** What product would you expect to obtain from the photochemical cyclization of  $(2E,4Z,6E)$ -2,4,6-octatriene? Of  $(2E,4Z,6Z)$ -2,4,6-octatriene?

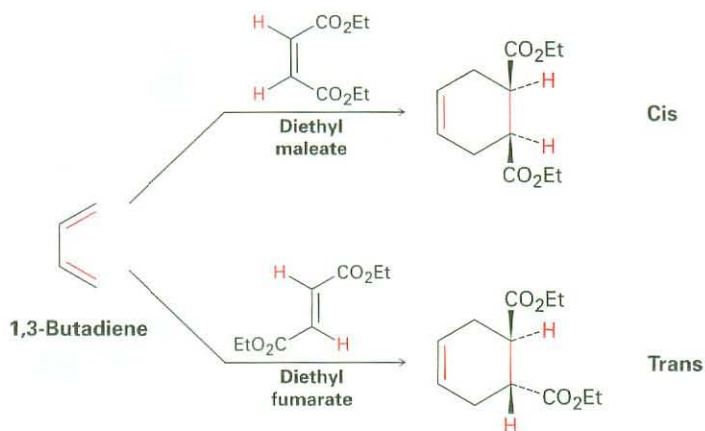
## 30.5 Cycloaddition Reactions

A **cycloaddition reaction** is one in which two unsaturated molecules add to one another, yielding a cyclic product. As with electrocyclic reactions, cycloadditions are controlled by the orbital symmetry of the reactants. Symmetry-allowed

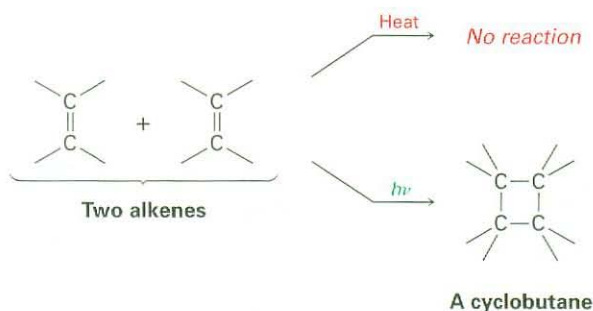
ThomsonNOW Click *Organic Interactive* to learn to predict whether electrocyclic reactions are "allowed" or "forbidden."

processes often take place readily, but symmetry-disallowed processes take place with difficulty, if at all, and then only by nonconcerted pathways. Let's look at two examples to see how they differ.

The Diels–Alder cycloaddition reaction (Section 14.4) is a pericyclic process that takes place between a diene (four  $\pi$  electrons) and a dienophile (two  $\pi$  electrons) to yield a cyclohexene product. Many thousands of examples of Diels–Alder reactions are known. They often take place easily at room temperature or slightly above, and they are stereospecific with respect to substituents. For example, room-temperature reaction between 1,3-butadiene and diethyl maleate (*cis*) yields exclusively the *cis*-disubstituted cyclohexene product. A similar reaction between 1,3-butadiene and diethyl fumarate (*trans*) yields exclusively the *trans*-disubstituted product.

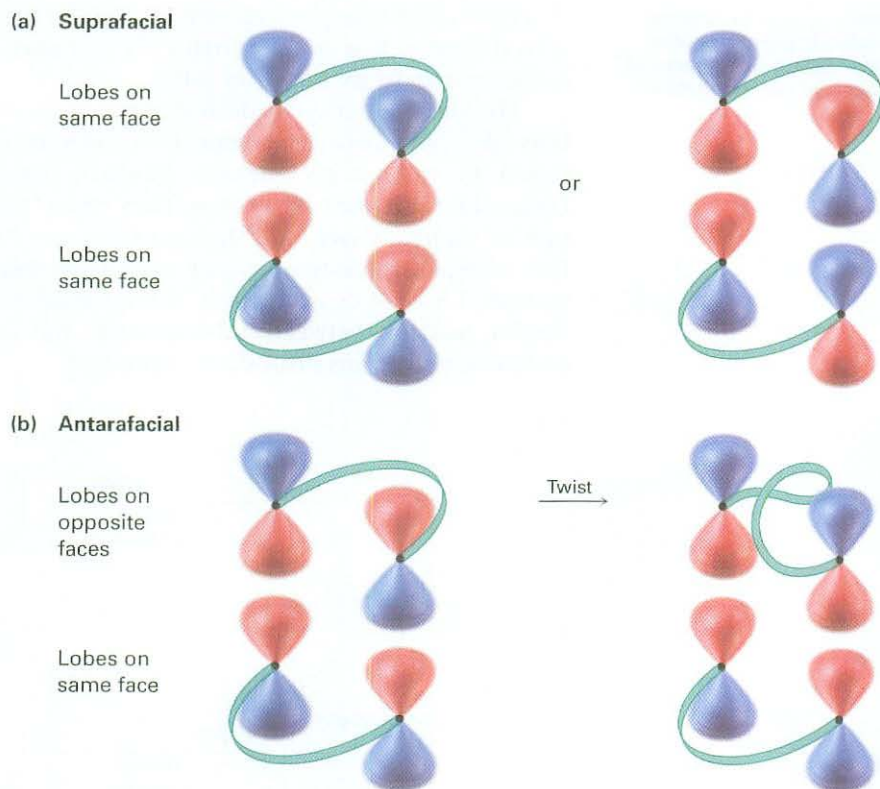


In contrast with the  $[4 + 2]$ - $\pi$ -electron Diels–Alder reaction, the  $[2 + 2]$  thermal cycloaddition between two alkenes does not occur. Only the photochemical  $[2 + 2]$  cycloaddition takes place to yield cyclobutane products.



For a successful cycloaddition to take place, the terminal  $\pi$  lobes of the two reactants must have the correct symmetry for bonding to occur. This can happen in either of two ways, called *suprafacial* and *antarafacial*. **Suprafacial** cycloadditions take place when a bonding interaction occurs between lobes on the same face of one reactant and lobes on the same face of the other reactant. **Antarafacial** cycloadditions take place when a bonding interaction occurs between lobes on the same face of one reactant and lobes on *opposite* faces of the other reactant (Figure 30.8).

**Figure 30.8** (a) Suprafacial cycloaddition occurs when there is bonding between lobes on the same face of one reactant and lobes on the same face of the other reactant. (b) Antarafacial cycloaddition occurs when there is bonding between lobes on the same face of one reactant and lobes on opposite faces of the other, which requires a twist in one  $\pi$  system.



Note that both suprafacial and antarafacial cycloadditions are symmetry-allowed. Geometric constraints often make antarafacial reactions difficult, however, because there must be a twisting of the  $\pi$  orbital system in one of the reactants. Thus, suprafacial cycloadditions are the most common for small  $\pi$  systems.

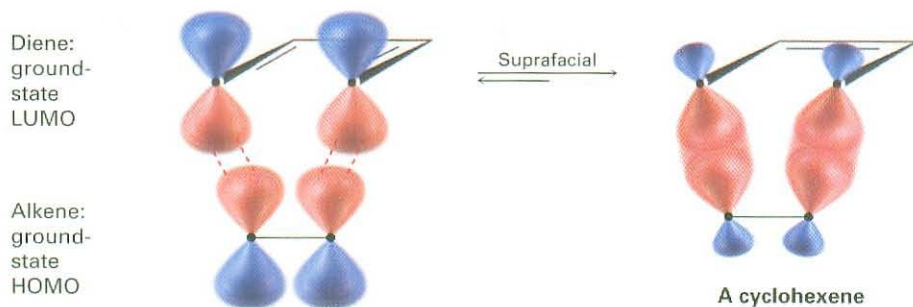
## 30.6 Stereochemistry of Cycloadditions

**ThomsonNOW** Click *Organic Interactive* for an interactive exercise in predicting products from cycloaddition reactions.

How can we predict whether a given cycloaddition reaction will occur with suprafacial or with antarafacial geometry? According to frontier orbital theory, a cycloaddition reaction takes place when a bonding interaction occurs between the HOMO of one reactant and the LUMO of the other. An intuitive explanation of this rule is to imagine that one reactant donates electrons to the other. As with electrocyclic reactions, it's the electrons in the HOMO of the first reactant that are least tightly held and most likely to be donated. But when the second reactant accepts those electrons, they must go into a *vacant*, unoccupied orbital—the LUMO.

For a  $[4 + 2]$ - $\pi$ -electron cycloaddition (Diels–Alder reaction), let's arbitrarily select the diene LUMO and the alkene HOMO. The symmetries of the two ground-state orbitals are such that bonding of the terminal lobes can occur with suprafacial geometry (Figure 30.9), so the Diels–Alder reaction takes place readily under thermal conditions. Note that, as with electrocyclic reactions, we need be concerned only with the *terminal* lobes. For purposes of prediction, interactions among the interior lobes need not be considered.

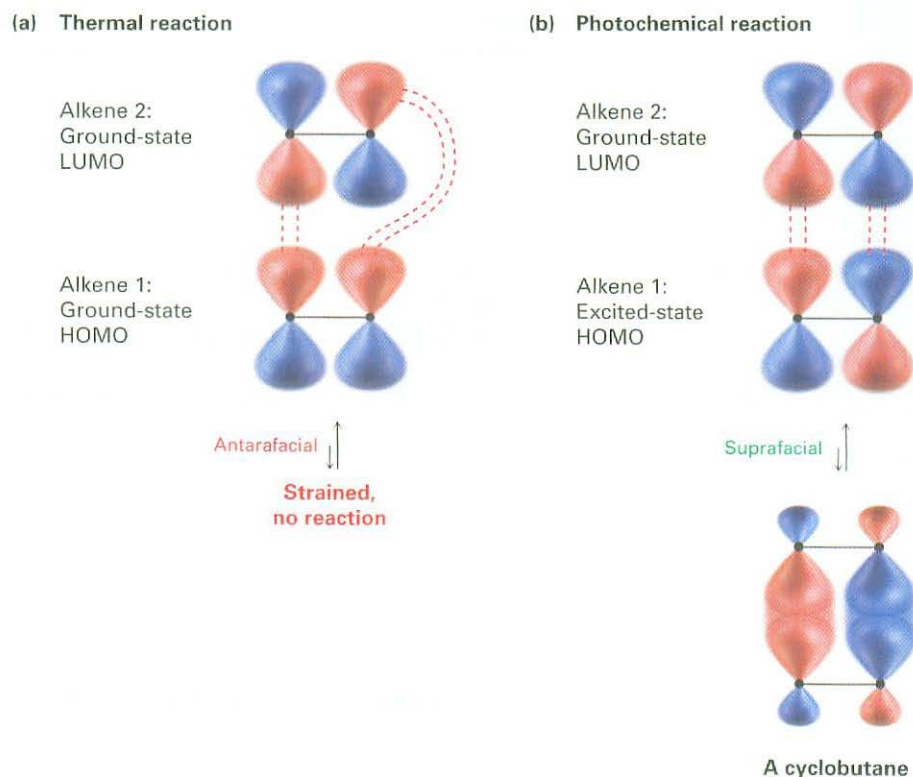
**Figure 30.9** Interaction of diene LUMO and alkene HOMO in a suprafacial  $[4 + 2]$  cycloaddition reaction (Diels–Alder reaction).



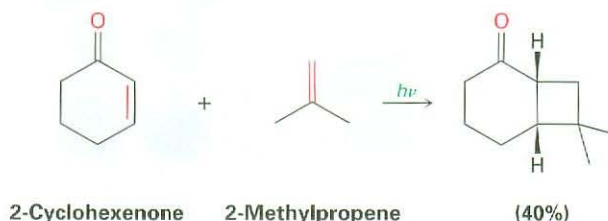
In contrast with the thermal  $[4 + 2]$  Diels–Alder reaction, the  $[2 + 2]$  cycloaddition of two alkenes to yield a cyclobutane can only be observed photochemically. The explanation follows from orbital-symmetry arguments. Looking at the ground-state HOMO of one alkene and the LUMO of the second alkene, it's apparent that a thermal  $[2 + 2]$  cycloaddition must take place by an antarafacial pathway (Figure 30.10a). Geometric constraints make the antarafacial transition state difficult, however, and so concerted thermal  $[2 + 2]$  cycloadditions are not observed.

In contrast with the thermal process, photochemical  $[2 + 2]$  cycloadditions *are* observed. Irradiation of an alkene with UV light excites an electron from  $\psi_1$ , the ground-state HOMO, to  $\psi_2^*$ , which becomes the excited-state HOMO. Interaction between the excited-state HOMO of one alkene and the LUMO of the second alkene allows a photochemical  $[2 + 2]$  cycloaddition reaction to occur by a suprafacial pathway (Figure 30.10b).

**Figure 30.10** (a) Interaction of a ground-state HOMO and a ground-state LUMO in a potential  $[2 + 2]$  cycloaddition does not occur thermally because the antarafacial geometry is too strained. (b) Interaction of an excited-state HOMO and a ground-state LUMO in a photochemical  $[2 + 2]$  cycloaddition reaction is less strained, however, and occurs with suprafacial geometry.



The photochemical [2 + 2] cycloaddition reaction occurs smoothly and represents one of the best methods known for synthesizing cyclobutane rings. For example:



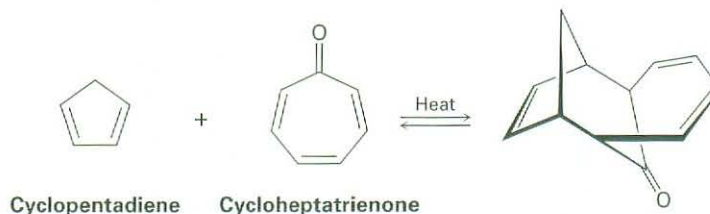
Thermal and photochemical cycloaddition reactions always take place with opposite stereochemistry. As with electrocyclic reactions, we can categorize cycloadditions according to the total number of electron pairs (double bonds) involved in the rearrangement. Thus, a thermal Diels–Alder [4 + 2] reaction between a diene and a dienophile involves an odd number (three) of electron pairs and takes place by a suprafacial pathway. A thermal [2 + 2] reaction between two alkenes involves an even number (two) of electron pairs and must take place by an antarafacial pathway. For photochemical cyclizations, these selectivities are reversed. The general rules are given in Table 30.2.

**Table 30.2** Stereochemical Rules for Cycloaddition Reactions

Electron pairs (double bonds)	Thermal reaction	Photochemical reaction
Even number	Antarafacial	Suprafacial
Odd number	Suprafacial	Antarafacial

**Problem 30.5** What stereochemistry would you expect for the product of the Diels–Alder reaction between (2*E*,4*E*)-2,4-hexadiene and ethylene? What stereochemistry would you expect if (2*E*,4*Z*)-2,4-hexadiene were used instead?

**Problem 30.6** 1,3-Cyclopentadiene reacts with cycloheptatrienone to give the product shown. Tell what kind of reaction is involved, and explain the observed result. Is the reaction suprafacial or antarafacial?

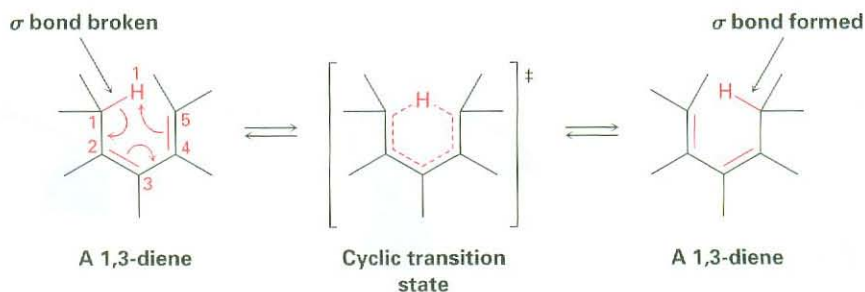


## 30.7 Sigmatropic Rearrangements

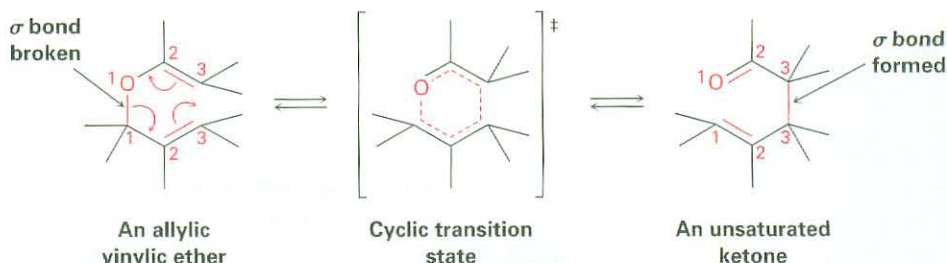
ThomsonNOW Click *Organic Interactive* to predict products from a variety of sigmatropic rearrangement reactions.

A **sigmatropic rearrangement**, the third general kind of pericyclic reaction, is a process in which a  $\sigma$ -bonded substituent atom or group migrates across a  $\pi$  electron system from one position to another. A  $\sigma$  bond is broken in the reactant, the  $\pi$  bonds move, and a new  $\sigma$  bond is formed in the product. The  $\sigma$ -bonded group can be either at the end or in the middle of the  $\pi$  system, as the following [1,5] and [3,3] rearrangements illustrate:

A [1,5] sigmatropic rearrangement



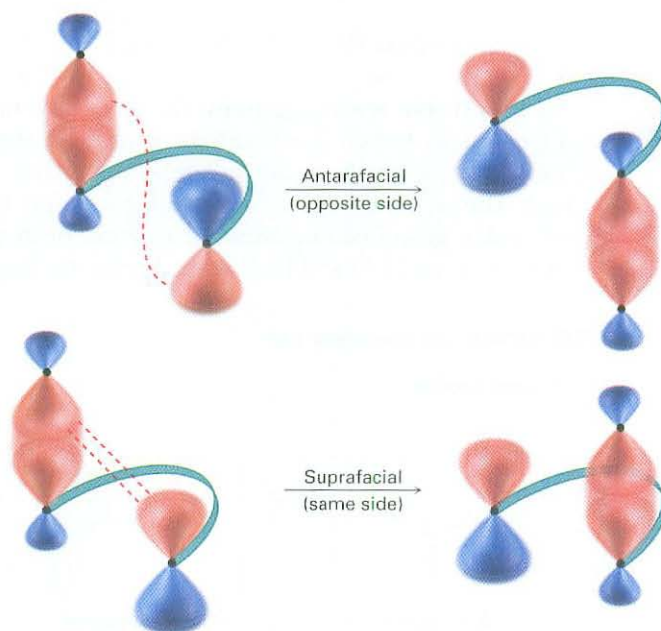
A [3,3] sigmatropic rearrangement



The notations [1,5] and [3,3] describe the kind of rearrangement that is occurring. The numbers refer to the two groups connected by the  $\sigma$  bond and designate the positions in those groups to which migration occurs. For example, in the [1,5] sigmatropic rearrangement of a diene, the two groups connected by the  $\sigma$  bond are a hydrogen atom and a pentadienyl group. Migration occurs to position 1 of the H group (the only possibility) and to position 5 of the pentadienyl group. In the [3,3] Claisen rearrangement (Section 18.4), the two groups connected by the  $\sigma$  bond are an allylic group and a vinylic ether group. Migration occurs to position 3 of the allylic group and also to position 3 of the vinylic ether.

Sigmatropic rearrangements, like electrocyclic reactions and cyclo-additions, are controlled by orbital symmetries. There are two possible modes of reaction: migration of a group across the same face of the  $\pi$  system is called a *suprafacial* rearrangement, and migration of a group from one face of the  $\pi$  system to the other face is called an *antarafacial* rearrangement (Figure 30.11).

**Figure 30.11** Suprafacial and antarafacial sigmatropic rearrangements.

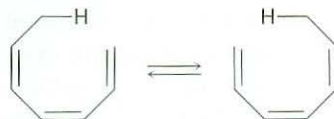


Both suprafacial and antarafacial sigmatropic rearrangements are symmetry-allowed, but suprafacial rearrangements are often easier for geometric reasons. The rules for sigmatropic rearrangements are identical to those for cycloaddition reactions (Table 30.3).

**Table 30.3** Stereochemical Rules for Sigmatropic Rearrangements

Electron pairs (double bonds)	Thermal reaction	Photochemical reaction
Even number	Antarafacial	Suprafacial
Odd number	Suprafacial	Antarafacial

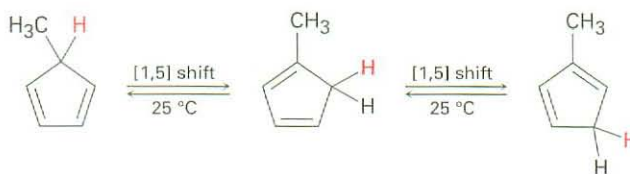
**Problem 30.7** Classify the following sigmatropic reaction by order  $[x,y]$ , and tell whether it will proceed with suprafacial or antarafacial stereochemistry:



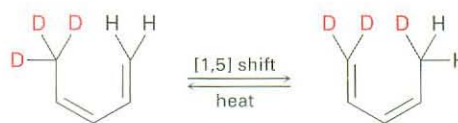
## 30.8 Some Examples of Sigmatropic Rearrangements

Because a  $[1,5]$  sigmatropic rearrangement involves three electron pairs (two  $\pi$  bonds and one  $\sigma$  bond), the orbital-symmetry rules in Table 30.3 predict a suprafacial reaction. In fact, the  $[1,5]$  suprafacial shift of a hydrogen atom across

two double bonds of a  $\pi$  system is one of the most commonly observed of all sigmatropic rearrangements. For example, 5-methyl-1,3-cyclopentadiene rapidly rearranges at room temperature to yield a mixture of 1-methyl-, 2-methyl-, and 5-methyl-substituted products.

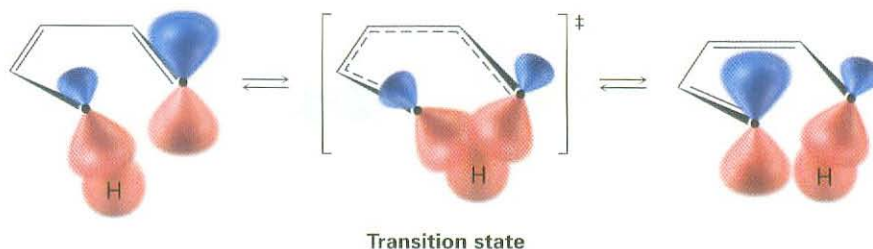


As another example, heating 5,5,5-trideuterio-(1,3Z)-1,3-pentadiene causes scrambling of deuterium between positions 1 and 5.



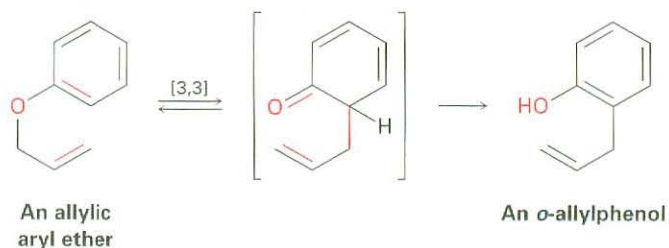
Both these [1,5] hydrogen shifts occur by a symmetry-allowed suprafacial rearrangement, as illustrated in Figure 30.12. In contrast with these thermal [1,5] sigmatropic hydrogen shifts, however, thermal [1,3] hydrogen shifts are unknown. Were they to occur, they would have to proceed by a strained antarafacial reaction pathway.

**Figure 30.12** An orbital view of a suprafacial [1,5] hydrogen shift.



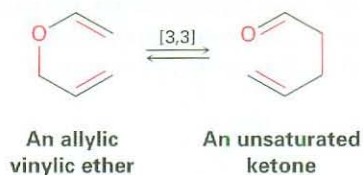
Two other important sigmatropic reactions are the Claisen rearrangement of an allyl aryl ether discussed in Section 18.4 and the Cope rearrangement of a 1,5-hexadiene. These two, along with the Diels–Alder reaction, are the most useful pericyclic reactions for organic synthesis; many thousands of examples of all three are known. Note that the Claisen rearrangement occurs with both allylic *aryl* ethers and allylic *vinyl* ethers.

#### Claisen rearrangement

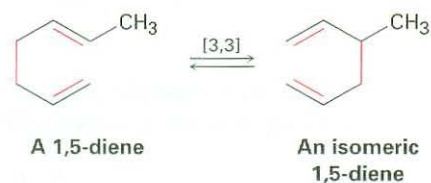




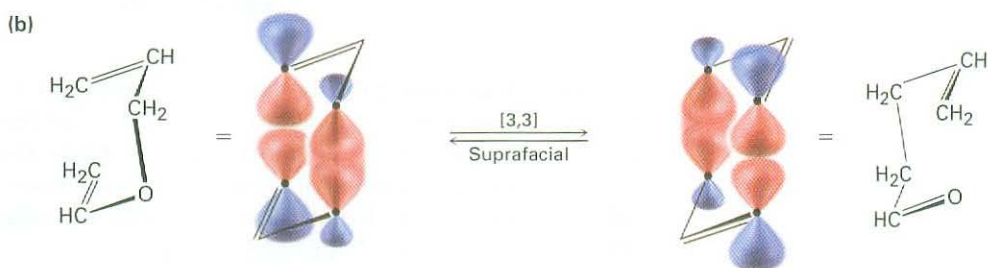
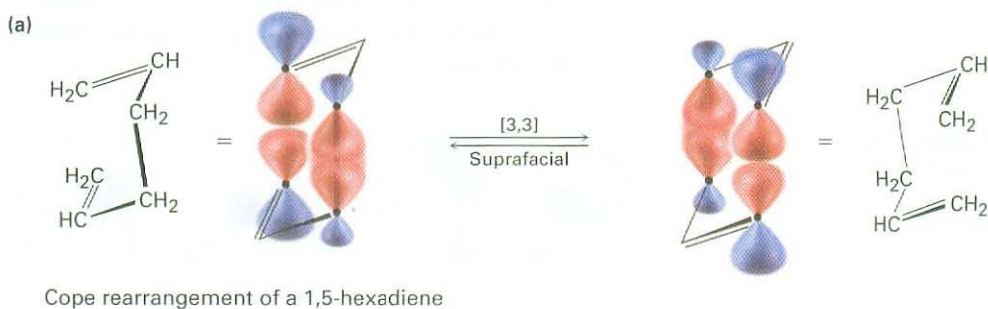
## Claisen rearrangement



## Cope rearrangement



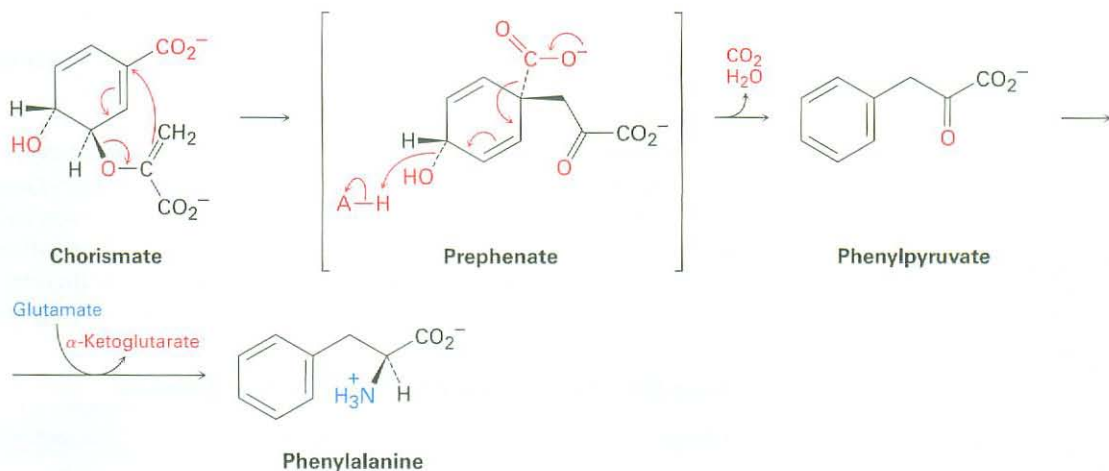
Both Cope and Claisen rearrangements involve reorganization of an odd number of electron pairs (two  $\pi$  bonds and one  $\sigma$  bond), and both react by suprafacial pathways (Figure 30.13).



**Figure 30.13** Suprafacial [3,3] (a) Cope and (b) Claisen rearrangements.

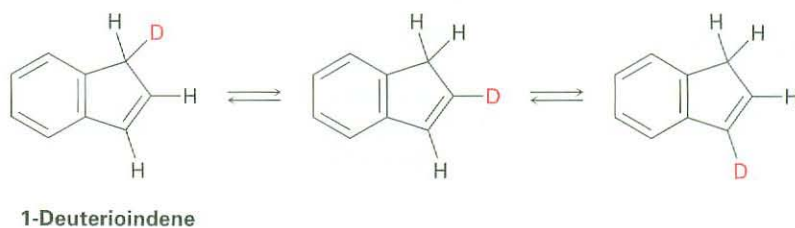
Biological examples of pericyclic reactions are relatively rare, although one much-studied example occurs during biosynthesis in bacteria of the essential amino acid phenylalanine. Phenylalanine arises from the precursor chorismate,

through a Claisen rearrangement to prephenate, followed by decarboxylation to phenylpyruvate and reductive amination (Figure 30.14). You might note that the reductive amination of phenylpyruvate is the exact reverse of the transamination process discussed in Section 29.9, by which amino acids are deaminated. In addition, reductive amination of ketones is a standard method for preparing amines in the laboratory, as we saw in Section 24.6.

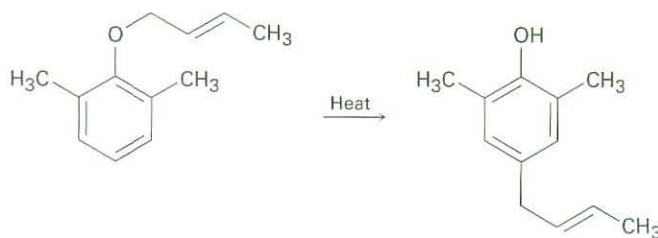


**Figure 30.14** Pathway for the bacterial biosynthesis of phenylalanine from chorismate, involving a Claisen rearrangement.

**Problem 30.8** Propose a mechanism to account for the fact that heating 1-deuterioindene scrambles the isotope label to all three positions on the five-membered ring.



**Problem 30.9** When a 2,6-disubstituted allyl phenyl ether is heated in an attempted Claisen rearrangement, migration occurs to give the *p*-allyl product as the result of two sequential pericyclic reactions. Explain.



## 30.9 A Summary of Rules for Pericyclic Reactions

How can you keep straight all the rules about pericyclic reactions? The summary information in Tables 30.1 to 30.3 can be distilled into one mnemonic phrase that provides an easy way to predict the stereochemical outcome of any pericyclic reaction:

The Electrons Circle Around (TECA)

Thermal reactions with an *Even* number of electron pairs are Conrotatory or Antarafacial.

A change either from thermal to photochemical or from an even to an odd number of electron pairs changes the outcome from conrotatory/antarafacial to disrotatory/suprafacial. A change from both thermal and even to photochemical and odd causes no change because two negatives make a positive.

These selection rules are summarized in Table 30.4, thereby giving you the ability to predict the stereochemistry of literally thousands of pericyclic reactions.

**Table 30.4** Stereochemical Rules for Pericyclic Reactions

Electronic state	Electron pairs	Stereochemistry
Ground state (thermal)	Even number	Antara-con
	Odd number	Supra-dis
Excited state (photochemical)	Even number	Supra-dis
	Odd number	Antara-con

**Problem 30.10** Predict the stereochemistry of the following pericyclic reactions:

- The thermal cyclization of a conjugated tetraene
- The photochemical cyclization of a conjugated tetraene
- A photochemical [4 + 4] cycloaddition
- A thermal [2 + 6] cycloaddition
- A photochemical [3,5] sigmatropic rearrangement

## Focus On . . .

## Vitamin D, the Sunshine Vitamin

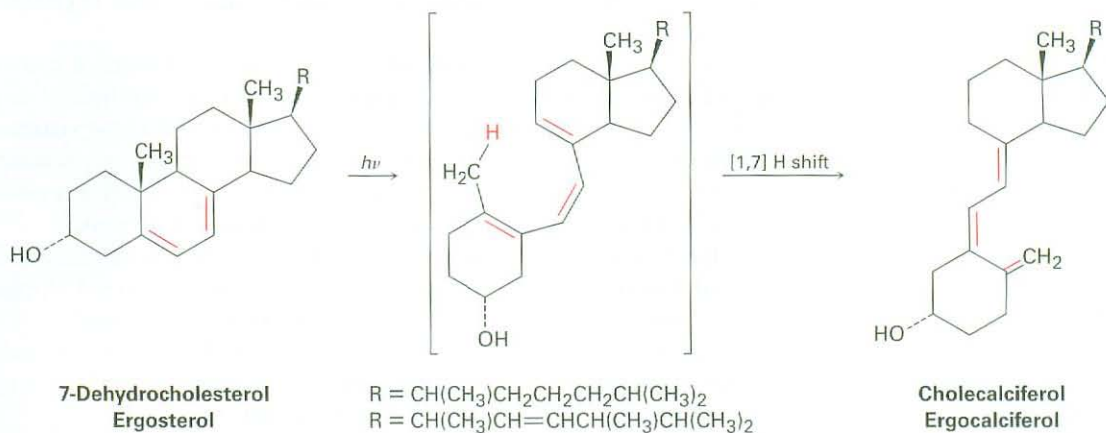


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Synthesizing vitamin D takes dedication and hard work.

Vitamin D, discovered in 1918, is a general name for two related compounds, *cholecalciferol* (vitamin D<sub>3</sub>) and *ergocalciferol* (vitamin D<sub>2</sub>). Both are steroids (Section 27.6) and differ only in the nature of the hydrocarbon side chain attached to the five-membered ring. Cholecalciferol comes from dairy products and fish; ergocalciferol comes from some vegetables. Their function in the body is to control the calcification of bones by increasing intestinal absorption of calcium. When sufficient vitamin D is present, approximately 30% of ingested calcium is absorbed, but in the absence of vitamin D, calcium absorption falls to about 10%. A deficiency of vitamin D thus leads to poor bone growth and to the childhood disease known as *rickets*.

Actually, neither vitamin D<sub>2</sub> nor D<sub>3</sub> is present in foods. Rather, foods contain the precursor molecules 7-dehydrocholesterol and ergosterol. In the presence of sunlight, however, both precursors are converted under the skin to the active vitamins, hence the nickname for vitamin D, the "sunshine vitamin."



Pericyclic reactions are unusual in living organisms, and the photochemical synthesis of vitamin D is one of only a few well-studied examples. The reaction takes place in two steps, an electrocyclic ring-opening of a cyclohexadiene to yield a hexatriene, followed by a sigmatropic [1,7] H shift to yield an isomeric hexatriene. Further metabolic processing in the liver and the kidney introduces several  $-\text{OH}$  groups to give the active form of the vitamin.

## SUMMARY AND KEY WORDS

antarafacial, 1187  
 conrotatory, 1183  
 Cope rearrangement, 1193  
 cycloaddition reaction, 1186  
 disrotatory, 1183  
 electrocyclic reaction, 1181  
 frontier orbital, 1181  
 highest occupied molecular orbital (HOMO), 1181  
 lowest unoccupied molecular orbital (LUMO), 1181  
 pericyclic reaction, 1178  
 photochemical reaction, 1181  
 sigmatropic rearrangement, 1191  
 suprafacial, 1187  
 symmetry-allowed, 1179  
 symmetry-disallowed, 1179

A **pericyclic reaction** is one that takes place in a single step through a cyclic transition state without intermediates. There are three major classes of pericyclic processes: electrocyclic reactions, cycloaddition reactions, and sigmatropic rearrangements. The stereochemistry of these reactions is controlled by the symmetry of the orbitals involved in bond reorganization.

**Electrocyclic reactions** involve the cyclization of conjugated polyenes. For example, 1,3,5-hexatriene cyclizes to 1,3-cyclohexadiene on heating. Electrocyclic reactions can occur by either **conrotatory** or **disrotatory** paths, depending on the symmetry of the terminal lobes of the  $\pi$  system. Conrotatory cyclization requires that both lobes rotate in the same direction, whereas disrotatory cyclization requires that the lobes rotate in opposite directions. The reaction course in a specific case can be found by looking at the symmetry of the **highest occupied molecular orbital (HOMO)**.

**Cycloaddition reactions** are those in which two unsaturated molecules add together to yield a cyclic product. For example, Diels–Alder reaction between a diene (four  $\pi$  electrons) and a dienophile (two  $\pi$  electrons) yields a cyclohexene. Cycloadditions can take place either by **suprafacial** or **antarafacial** pathways. Suprafacial cycloaddition involves interaction between lobes on the same face of one component and on the same face of the second component. Antarafacial cycloaddition involves interaction between lobes on the same face of one component and on opposite faces of the other component. The reaction course in a specific case can be found by looking at the symmetry of the HOMO of one component and the **lowest unoccupied molecular orbital (LUMO)** of the other component.

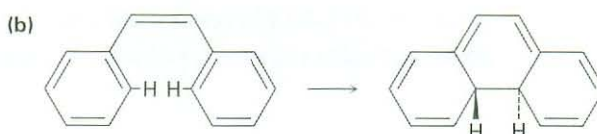
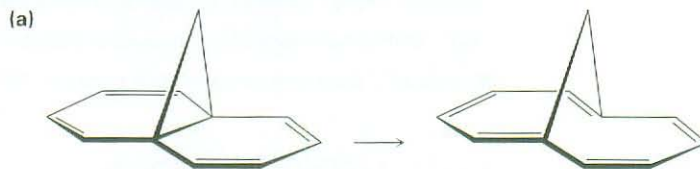
**Sigmatropic rearrangements** involve the migration of a  $\sigma$ -bonded group across a  $\pi$  electron system. For example, Claisen rearrangement of an allylic vinylic ether yields an unsaturated carbonyl compound, and **Cope rearrangement** of a 1,5-hexadiene yields an isomeric 1,5-hexadiene. Sigmatropic rearrangements can occur with either suprafacial or antarafacial stereochemistry; the selection rules for a given case are the same as those for cycloaddition reactions.

The stereochemistry of any pericyclic reaction can be predicted by counting the total number of electron pairs (bonds) involved in bond reorganization and then applying the mnemonic “The Electrons Circle Around.” That is, **thermal** (ground-state) reactions involving an even number of electron pairs occur with either conrotatory or antarafacial stereochemistry. Exactly the opposite rules apply to **photochemical** (excited-state) reactions.



## ADDITIONAL PROBLEMS

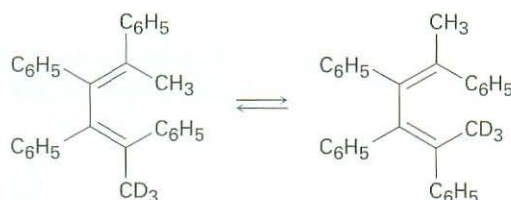
- 30.13** ■ Have the following reactions taken place in a conrotatory or disrotatory manner? Under what conditions, thermal or photochemical, would you carry out each reaction?



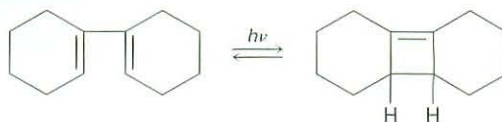
- 30.14** ■ What stereochemistry—antarafacial or suprafacial—would you expect to observe in the following reactions?

- (a) A photochemical [1,5] sigmatropic rearrangement  
 (b) A thermal [4 + 6] cycloaddition  
 (c) A thermal [1,7] sigmatropic rearrangement  
 (d) A photochemical [2 + 6] cycloaddition

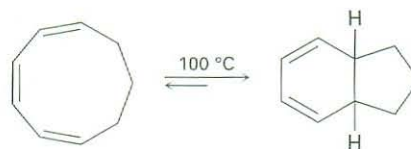
- 30.15** The following thermal isomerization occurs under relatively mild conditions. Identify the pericyclic reactions involved, and show how the rearrangement occurs.



- 30.16** ■ Would you expect the following reaction to proceed in a conrotatory or disrotatory manner? Show the stereochemistry of the cyclobutene product, and explain your answer.

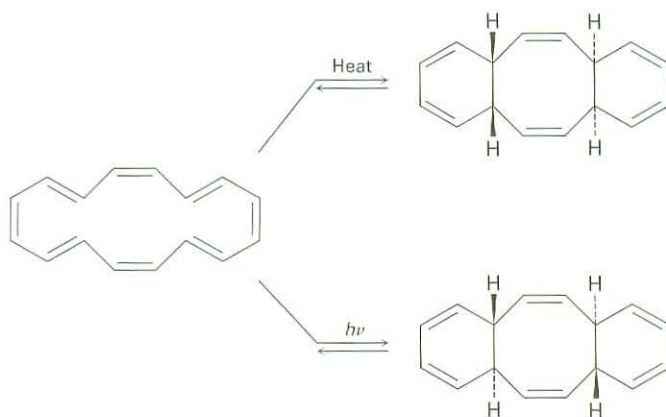


- 30.17** Heating (1*Z*,3*Z*,5*Z*)-1,3,5-cyclononatriene to 100 °C causes cyclization and formation of a bicyclic product. Is the reaction conrotatory or disrotatory? What is the stereochemical relationship of the two hydrogens at the ring junction, cis or trans?

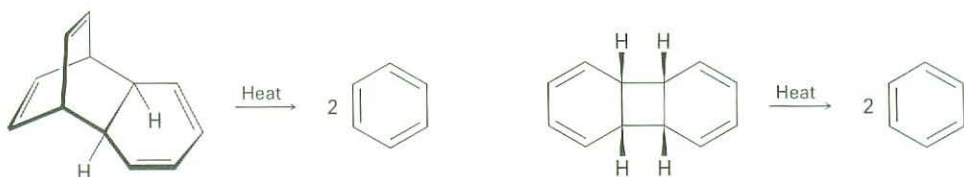


(1*Z*,3*Z*,5*Z*)-1,3,5-Cyclononatriene

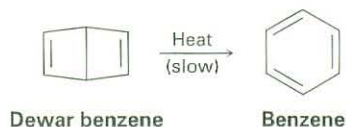
- 30.18** (2*E*,4*Z*,6*Z*,8*E*)-2,4,6,8-Decatetraene has been cyclized to give 7,8-dimethyl-1,3,5-cyclooctatriene. Predict the manner of ring closure—conrotatory or disrotatory—for both thermal and photochemical reactions, and predict the stereochemistry of the product in each case.
- 30.19** Answer Problem 30.18 for the thermal and photochemical cyclizations of (2*E*,4*Z*,6*Z*,8*Z*)-2,4,6,8-decatetraene.
- 30.20** The cyclohexadecaoctaene shown isomerizes to two different isomers, depending on reaction conditions. Explain the observed results, and indicate whether each reaction is conrotatory or disrotatory.



- 30.21** ■ Which of the following reactions is more likely to occur? Explain.



- 30.22** Bicyclohexadiene, also known as *Dewar benzene*, is extremely stable despite the fact that its rearrangement to benzene is energetically favored. Explain why the rearrangement is so slow.



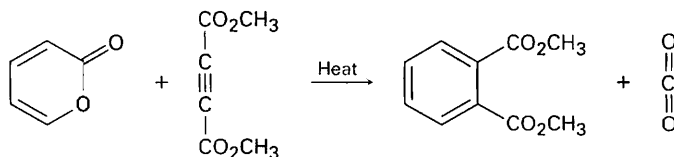
- 30.23** ■ The following thermal rearrangement involves two pericyclic reactions in sequence. Identify them, and propose a mechanism to account for the observed result.



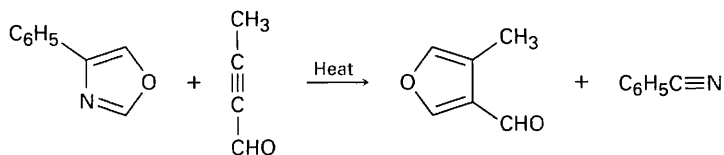




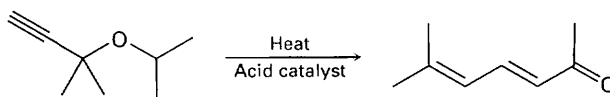
**30.29** The following reaction takes place in two steps, one of which is a cycloaddition and the other of which is a *reverse* cycloaddition. Identify the two pericyclic reactions, and show how they occur.



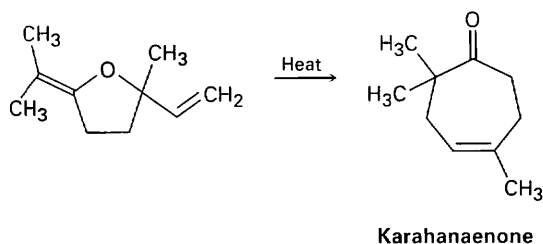
**30.30** Two sequential pericyclic reactions are involved in the following furan synthesis. Identify them, and propose a mechanism for the transformation.



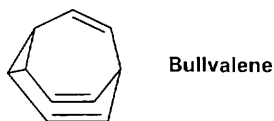
**30.31** The following synthesis of dienones occurs readily. Propose a mechanism to account for the results, and identify the kind of pericyclic reaction involved.



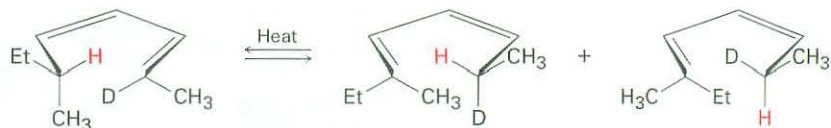
**30.32** Karahanaenone, a terpenoid isolated from oil of hops, has been synthesized by the thermal reaction shown. Identify the kind of pericyclic reaction, and explain how karahanaenone is formed.



**30.33** The <sup>1</sup>H NMR spectrum of bullvalene at 100 °C consists only of a single peak at 4.22 δ. Explain.



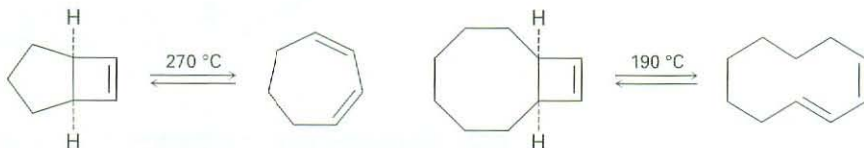
- 30.34** The following rearrangement was devised and carried out to prove the stereochemistry of [1,5] sigmatropic hydrogen shifts. Explain how the observed result confirms the predictions of orbital symmetry.



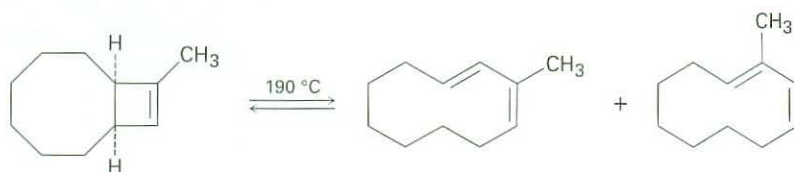
- 30.35** The following reaction is an example of a [2,3] sigmatropic rearrangement. Would you expect the reaction to be suprafacial or antarafacial? Explain.



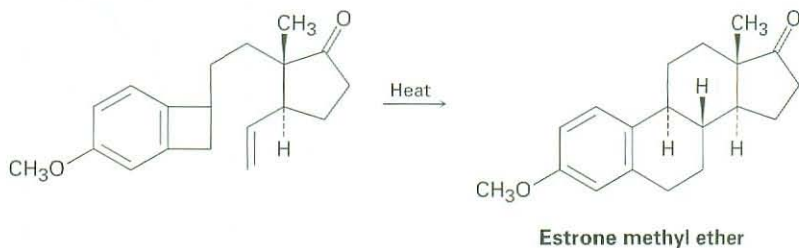
- 30.36** When the compound having a cyclobutene fused to a five-membered ring is heated, (1*Z*,3*Z*)-1,3-cycloheptadiene is formed. When the related compound having a cyclobutene fused to an eight-membered ring is heated, however, (1*E*,3*Z*)-1,3-cyclodecadiene is formed. Explain these results, and suggest a reason why opening of the eight-membered ring occurs at a lower temperature.



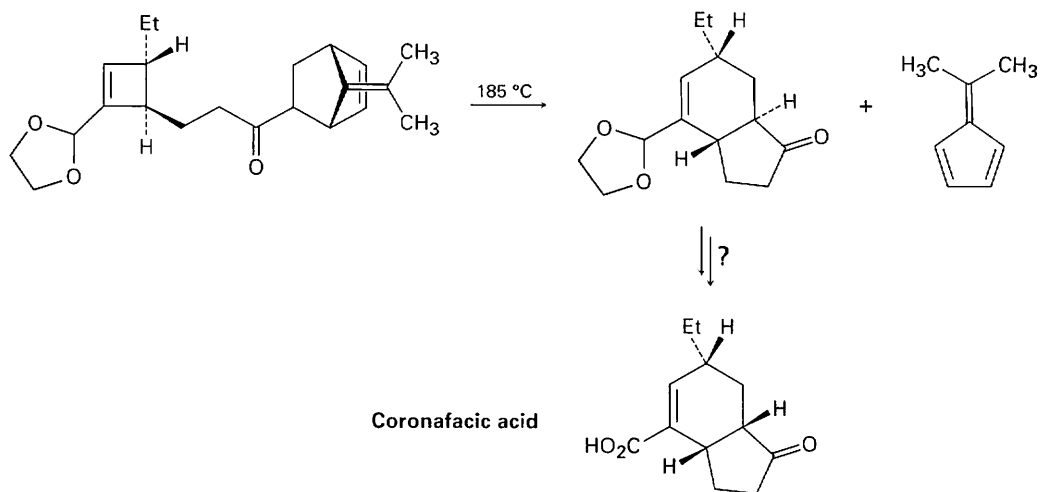
- 30.37** In light of your answer to Problem 30.36, explain why a mixture of products occurs in the following reaction:



- 30.38** ■ The sex hormone estrone has been synthesized by a route that involves the following step. Identify the pericyclic reactions involved, and propose a mechanism.



**30.39** Coronafacic acid, a bacterial toxin, was synthesized using a key step that involves three sequential pericyclic reactions. Identify them, and propose a mechanism for the overall transformation. How would you complete the synthesis?



**30.40** The following rearrangement of *N*-allyl-*N,N*-dimethylanilinium ion has been observed. Propose a mechanism.

