

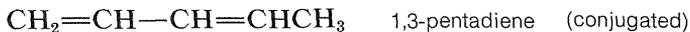
POLYFUNCTIONAL COMPOUNDS. ALKADIENES. APPROACHES TO ORGANIC SYNTHESIS

Organic compounds of natural origin rarely have simple structures. Most have more than one functional group in each molecule. Usually the chemical behavior of a functional group is influenced significantly by the presence of another functional group, especially when the groups are in close proximity. Indeed, the complexities that are associated with polyfunctionality are of central importance in biochemical reactions and in the design of organic syntheses. For this reason, you will need to gain experience in judging how and when functional groups in the same molecule interact with one another. We will start by considering the chemistry of alkadienes, which are hydrocarbons with *two* carbon-carbon double bonds.

13-1 GENERAL COMMENTS ON ALKADIENES

The molecular properties of alkadienes depend on the relationship between the double bonds, that is, whether they are **cumulated**, **conjugated**, or **isolated**:

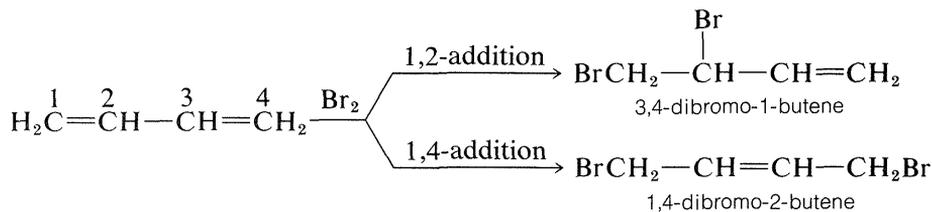




The properties of a compound with isolated double bonds, such as 1,4-pentadiene, generally are similar to those of simple alkenes because the double bonds are essentially isolated from one another by the intervening CH_2 group. However, with a conjugated alkadiene, such as 1,3-pentadiene, or a cumulated alkadiene, such as 2,3-pentadiene, the properties are sufficiently different from those of simple alkenes (and from each other) to warrant separate discussion. Some aspects of the effects of conjugation already have been mentioned, such as the influence on spectroscopic properties (see Section 9-9B). The emphasis here will be on the effects of conjugation on chemical properties. The reactions of greatest interest are addition reactions, and this chapter will include various types of addition reactions: electrophilic, radical, cycloaddition, and polymerization.

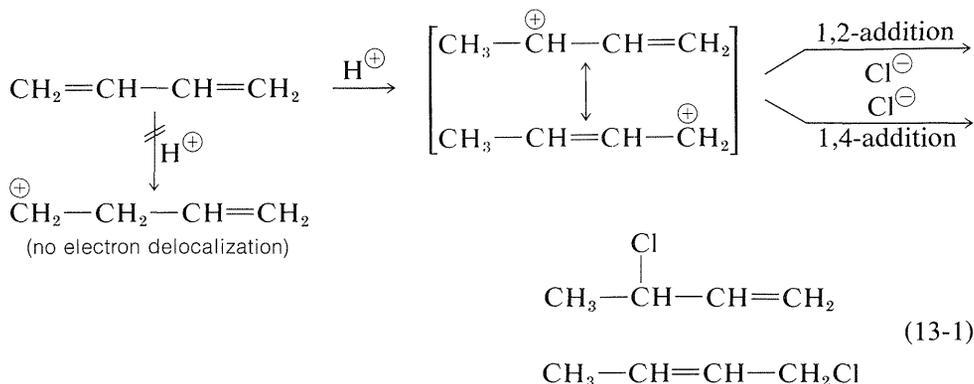
13-2 1,3- OR CONJUGATED DIENES. ELECTROPHILIC AND RADICAL ADDITION

The reactions of 1,3-butadiene are reasonably typical of conjugated dienes. The compound undergoes the usual reactions of alkenes, such as catalytic hydrogenation or radical and polar additions, but it does so *more readily* than most alkenes or dienes that have isolated double bonds. Furthermore, the products frequently are those of 1,2 *and* 1,4 **addition**:

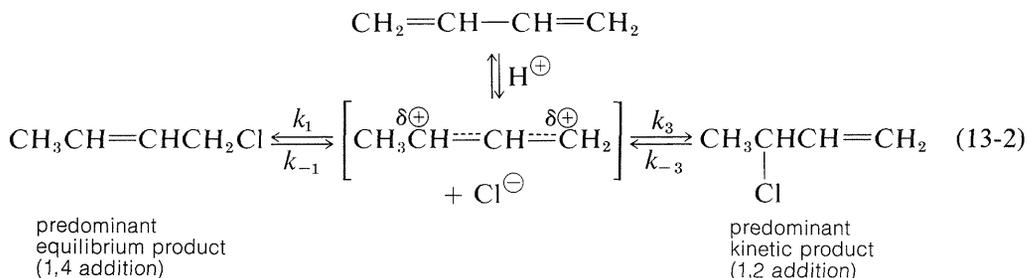


Formation of both 1,2- and 1,4-addition products occurs not only with halogens, but also with other electrophiles such as the hydrogen halides. The mechanistic course of the reaction of 1,3-butadiene with hydrogen chloride is shown in Equation 13-1. The first step, as with alkenes (Section 10-3A), is formation of a carbocation. However, with 1,3-butadiene, if the proton is added to C1 (but not C2), the resulting cation has a substantial delocalization energy, with the charge distributed over two carbons (review Sections 6-5 and

6-5C if this is not clear to you). Attack of Cl^\ominus as a nucleophile at one or the other of the positive carbons yields the 1,2- or the 1,4- addition product:



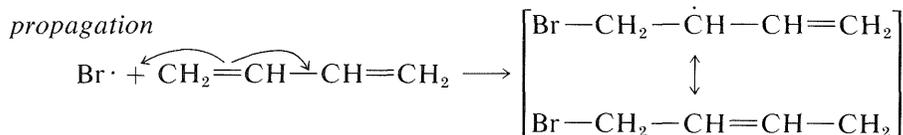
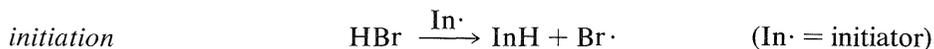
An important feature of reactions in which 1,2 and 1,4 additions occur in competition with one another is that the ratio of the products can depend on the temperature, the solvent, and also on the *total time of reaction*. The reason for the dependence on the reaction time is that the formation of the carbocation is *reversible*, and the ratio of products at equilibrium need not be the same as the ratio of the *rates* of attack of Cl^\ominus at C1 and C3 of the carbocation. This is another example of a difference in product ratios resulting from kinetic control *versus* equilibrium control (e.g., see Section 10-4A).



The fact is that at low temperatures the 1,2 product predominates because it is formed more rapidly, and the back reactions, corresponding to k_{-1} or k_{-3} , are slow (Equation 13-2). However, at equilibrium¹ the 1,4 product is favored because it is more stable, not because it is formed more rapidly.

¹The equilibrium ratio is obtained as follows. At equilibrium $k_1/k_{-1} = [\text{CH}_3\text{CH}=\text{CHCH}_2\text{Cl}]/[\text{R}^\oplus][\text{Cl}^\ominus]$ and $k_{-3}/k_3 = [\text{R}^\oplus][\text{Cl}^\ominus]/[\text{CH}_3\text{CHClCH}=\text{CH}_2]$, in which R^\oplus is the concentration of delocalized carbocation. Multiplication of these equations gives $k_1k_{-3}/k_{-1}k_3 = [\text{CH}_3\text{CH}=\text{CHCH}_2\text{Cl}]/[\text{CH}_3\text{CHClCH}=\text{CH}_2] = K_{\text{eq}}$.

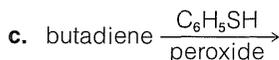
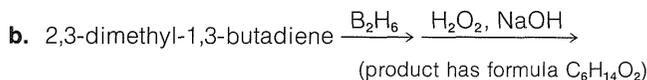
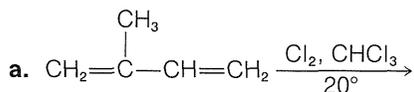
Conjugated dienes also undergo addition reactions by radical-chain mechanisms. Here, the addition product almost always is the 1,4 adduct. Thus radical addition of hydrogen bromide to 1,3-butadiene gives 1-bromo-2-butene, presumably by the following mechanism:



Exercise 13-1 1,4-Pentadiene is different from propene in some of its chemical properties; for example, removal of the hydrogens at the 3-position by attack of radicals is much easier than the removal of those on the methyl group of propene. Explain why this should be so. (The rules of Section 6-5B will be helpful in this connection.)

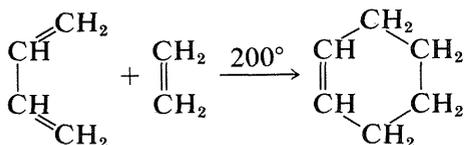
Exercise 13-2 Draw an energy diagram, analogous to Figure 10-10 representing the reaction of Equation 13-1 for the addition of HCl to 1,3-butadiene, that reflects the fact that the 1,4 adduct is more stable, but is formed less rapidly than the 1,2 adduct. (Notice that of the two ways a proton from HCl can add to 1,3-butadiene, only *one* gives a carbocation that is delocalized.)

Exercise 13-3 Write the structures of the intermediates and the addition products expected in each of the following reactions (you may wish to review Chapters 10 and 11):



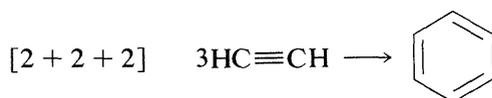
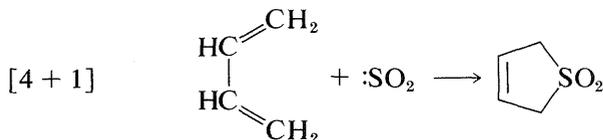
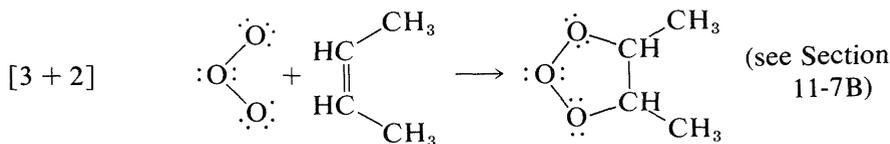
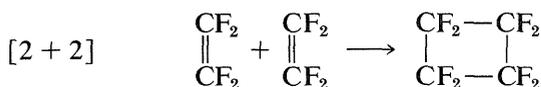
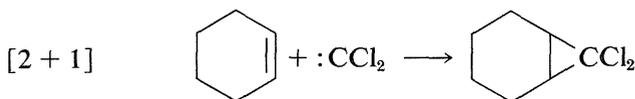
13-3 CYCLOADDITION REACTIONS

There are a variety of reactions whereby rings are formed through addition to double or triple bonds. An especially simple example is the addition of ethene to 1,3-butadiene to give cyclohexene:



This is the prototype **Diels–Alder** reaction, which has proved so valuable in synthesis that it won its discoverers, O. Diels and K. Alder, the Nobel Prize in chemistry in 1950.

The Diels–Alder reaction is both a 1,4 addition of ethene to 1,3-butadiene and a 1,2 addition of butadiene to ethene. It can be called a [4 + 2] cycloaddition and as such results in the formation of a six-membered ring. Many other cycloadditions are known, such as [2 + 1], [2 + 2], [3 + 2], [4 + 1], [2 + 2 + 2], and so on, which give different sizes of rings. Some specific examples follow:

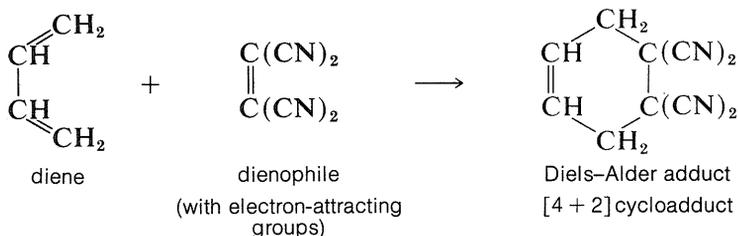


The synthetic importance of these reactions is very great and, because many of them often involve dienes, we will discuss their general characteristics in this chapter. The most valuable cycloaddition reaction almost certainly is the [4 + 2], or Diels–Alder, reaction and will be discussed in detail.

13-3A [4 + 2] Cycloadditions

There is one very important point you should remember about the Diels–Alder reaction: The reaction usually occurs well only when the [2] component is substituted with electron-attracting groups and the [4] component is substituted with electron-donating groups, or the reverse. The most common arrangement is to have the alkene (usually referred to as the **dienophile**)

substituted with electron-attracting groups such as $-\text{CO}_2\text{H}$, $-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}$, or $-\text{C}\equiv\text{N}$. For example,



A list of the more reactive dienophiles carrying electron-attracting groups is given in Table 13-1. Ethene and other simple alkenes generally are poor dienophiles and react with 1,3-butadiene only under rather extreme conditions and in low yield.

However, when the diene is substituted with several electron-attracting groups such as chlorine or bromine, electron-donating groups on the *dienophile* facilitate the reaction. Many substances, such as 2-methylpropene, that act as dienophiles with hexachlorocyclopentadiene simply will not undergo [4 + 2] addition with cyclopentadiene itself:

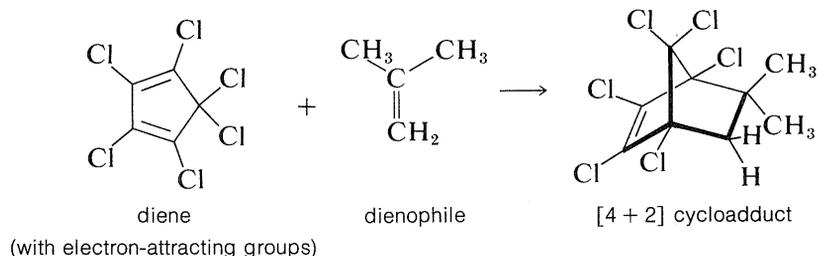
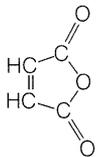
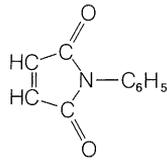
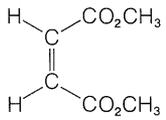
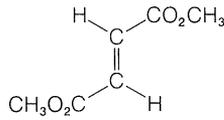


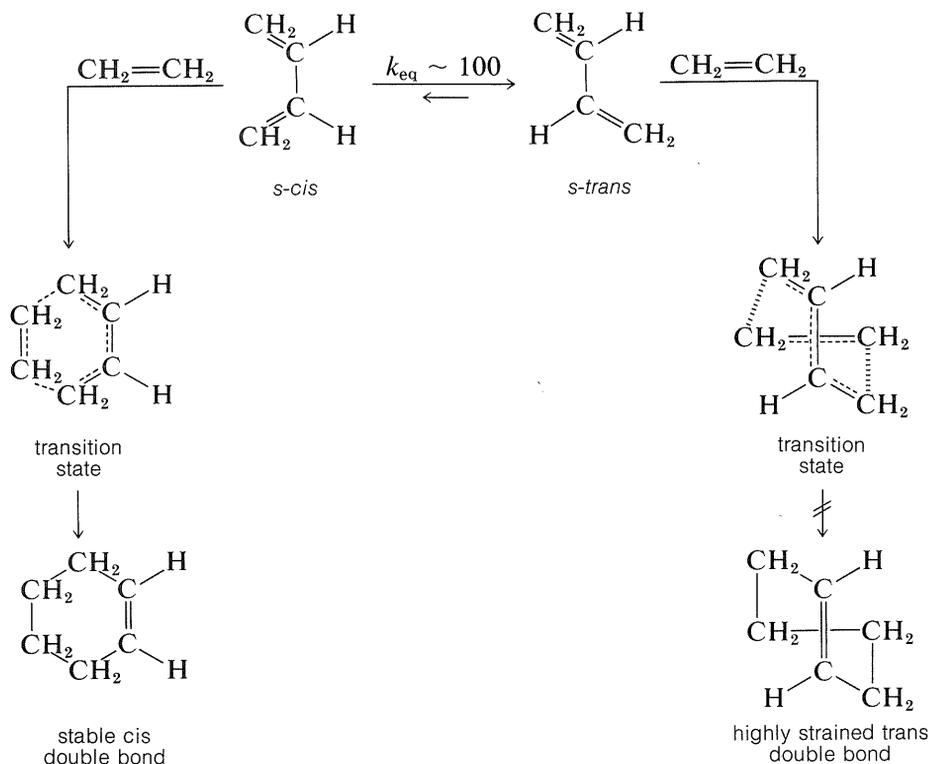
Table 13-1

Reactive Dienophiles with 1,3-Butadiene and Similar Dienes

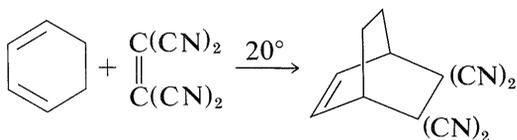
Name	Formula	Name	Formula
tetracyanoethene	$(\text{NC})_2\text{C}=\text{C}(\text{CN})_2$	propenenitrile (acrylonitrile)	$\text{CH}_2=\text{CH}-\text{CN}$
2-butenal (crotonaldehyde)	$\text{CH}_3\text{CH}=\text{CH}-\text{CHO}$	propenal (acrolein)	$\text{CH}_2=\text{CH}-\text{CHO}$
3-phenylpropenoic acid (cinnamic acid, cis and trans)	$\text{C}_6\text{H}_5\text{CH}=\text{CH}-\text{CO}_2\text{H}$	ethyl propenoate (ethyl acrylate)	$\text{CH}_2=\text{CH}-\text{CO}_2\text{C}_2\text{H}_5$
<i>cis</i> -butenedioic anhydride (maleic anhydride)		<i>N</i> -phenyl- <i>cis</i> -butenimide (<i>N</i> -phenylmaleimide)	
dimethyl <i>cis</i> -butenedioate (dimethyl maleate)		dimethyl <i>trans</i> -butenedioate (dimethyl fumarate)	
1-nitropropene	$\text{CH}_3\text{CH}=\text{CH}-\text{NO}_2$	2-nitro-1-phenylethene	$\text{C}_6\text{H}_5\text{CH}=\text{CH}-\text{NO}_2$

The Diels–Alder reaction is *highly stereospecific*. The diene reacts in an unfavorable conformation in which its double bonds lie in a plane on the same side (*cis*) of the single bond connecting them. This *s-cis* (or **cisoid**) conformation is required to give a stable product with a *cis* double bond. Addition of ethene to the alternate and more stable (**transoid**) conformation would give an impossibly strained *trans*-cyclohexene ring. Possible transition states for reaction in each conformation follow, and it will be seen that enormous mo-

lecular distortion would have to take place to allow addition of ethene to the transoid conformation:

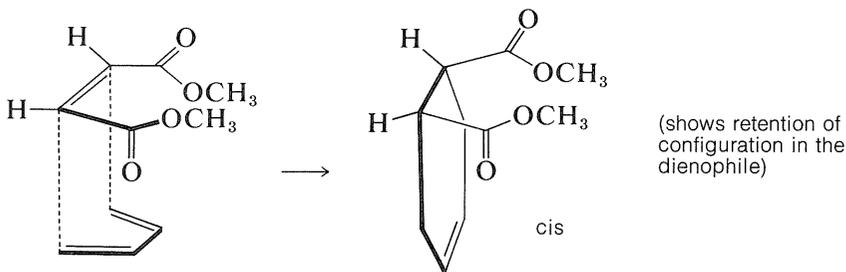


Cyclic dienes usually react more readily than open-chain dienes, probably because they have their double bonds fixed in the proper conformation for [4 + 2] cycloaddition, consequently the price in energy of achieving the *s-cis* configuration already has been paid:

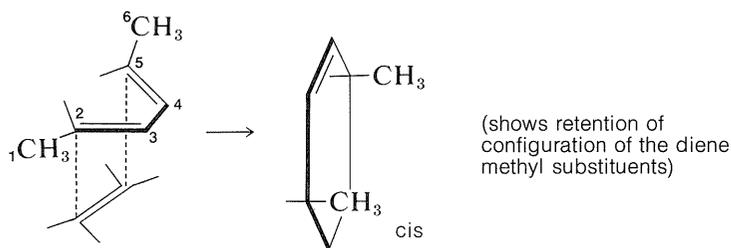


Further evidence of stereospecificity in [4 + 2] additions is that the configurations of the diene and the dienophile are *retained* in the adduct. This means that the reactants (or addends) come together to give *suprafacial* addition. Two examples follow, which are drawn to emphasize how suprafacial

addition occurs. In the first example, dimethyl *cis*-butenedioate adds to 1,3-butadiene to give a *cis*-substituted cyclohexene:



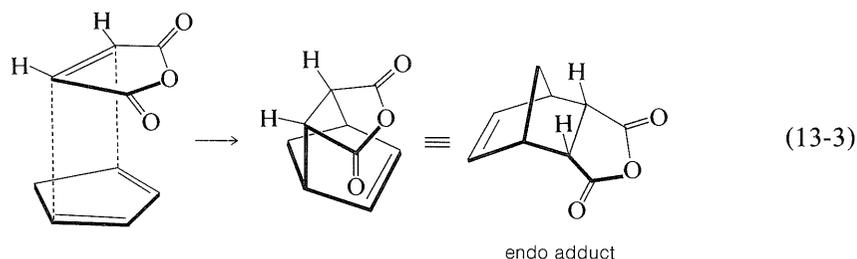
In the second example, suprafacial approach of a dienophile to the 2,5 carbons of *trans,trans*-2,4-hexadiene is seen to lead to a product with two methyl groups on the same side of the cyclohexene ring:

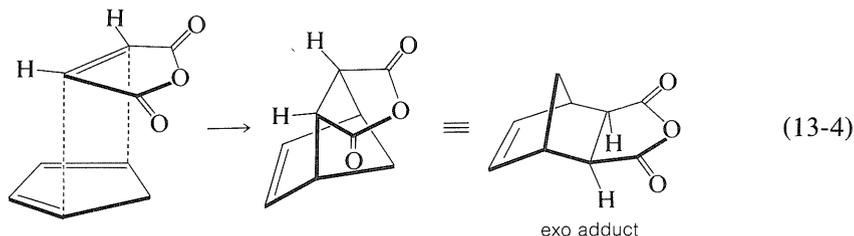


(The use of models will help you visualize these reactions and their stereochemistry.)

Exercise 13-4 What products would you expect from the Diels–Alder addition of tetracyanoethene to *cis,trans*-2,4-hexadiene and *cis,cis*-2,4-hexadiene? Explain.

There is a further feature of the Diels–Alder reaction that concerns the stereochemical orientation of the addends. In the addition of *cis*-butenedioic anhydride (maleic anhydride) to cyclopentadiene there are two possible ways that the diene and the dienophile could come together to produce different products. These are shown in Equations 13-3 and 13-4:



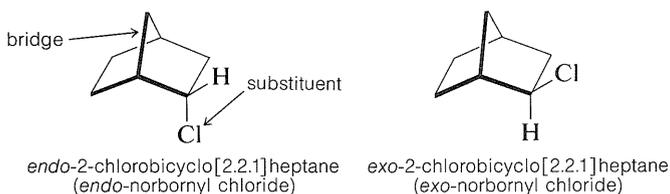


In practice, the adduct with the *endo*² configuration usually is the major product. As a general rule, Diels-Alder additions tend to proceed to favor that orientation that corresponds to having the diene double bonds and the unsaturated substituents of the dienophile closest to one another. This means that addition by Equation 13-3 is more favorable than by Equation 13-4, but the degree of *endo-exo* stereospecificity is not as high as the degree of stereospecificity of suprafacial addition to the diene and dienophile.

There are exceptions to favored *endo* stereochemistry of Diels-Alder additions. Some of these exceptions arise because the *addition reaction is reversible*, dissociation being particularly important at high temperature. The *exo* configuration is generally more stable than the *endo* and, given time to reach equilibrium (cf. Section 10-4A), the *exo* isomer may be the major adduct. Thus *endo* stereospecificity can be expected only when the additions are subject to *kinetic control*.

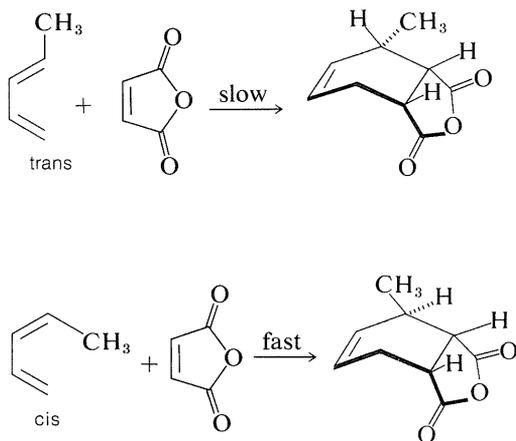
The reactivities of dienes in the Diels-Alder reaction depend on the number and kind of substituents they possess. The larger the substituents are, or the more of them, at the ends of the conjugated system, the slower the reaction is likely to be. There also is a marked difference in reactivity with diene configuration. Thus *trans*-1,3-pentadiene is substantially less reactive toward a given dienophile (such as maleic anhydride) than is *cis*-1,3-pentadiene. In fact,

²In general, the designation *endo* or *exo* refers to configuration in bridged or polycyclic ring systems such as those shown in Equations 13-3 and 13-4. With reference to the bridge atoms, a substituent is *exo* if it is on the same side as the bridge, or *endo* if it is on the opposite side. Further examples are



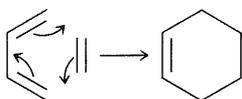
In drawing *endo* and *exo* isomers, it is best to represent the actual spatial relationships of the atoms as closely as possible. The cyclohexane ring is shown here in the boat form (Section 12-3A) because it is held in this configuration by the methylene group that bridges the 1,4 positions. If you do not see this, we strongly advise that you construct models.

a mixture of the *cis* and *trans* isomers can be separated by taking advantage of the difference in their reactivities on cycloaddition:



13-3B Mechanism of the Diels–Alder Reaction

There is little evidence to support simple radical or polar mechanisms (such as we have discussed previously) for the Diels–Alder reaction. As the result of many studies the reaction seems best formulated as a process in which the bonds between the diene and the dienophile are formed essentially simultaneously:



In other words, the reaction is *concerted*, there being no evidence for any discrete intermediate. Referring to Figure 13-1, we may say that the reaction follows curve A and not curve B on the plots of energy versus reaction coordinate. Although it is difficult to prove experimentally that the reaction is concerted, we shall see in Chapter 21 that there are theoretical reasons to expect it to be so, despite the high degree of ordering (unfavorable entropy, Section 4-4B) that the transition state must have in order that all of the participating bonds can be made and broken at once.

We already have discussed a few addition reactions that appear to occur in a concerted manner. These include the addition of diimide, ozone, and boron hydrides to alkenes (Sections 11-5, 11-7A, and 11-6B). Concerted reactions that have cyclic transition states often are called **pericyclic reactions**. Other examples will be considered in later chapters.

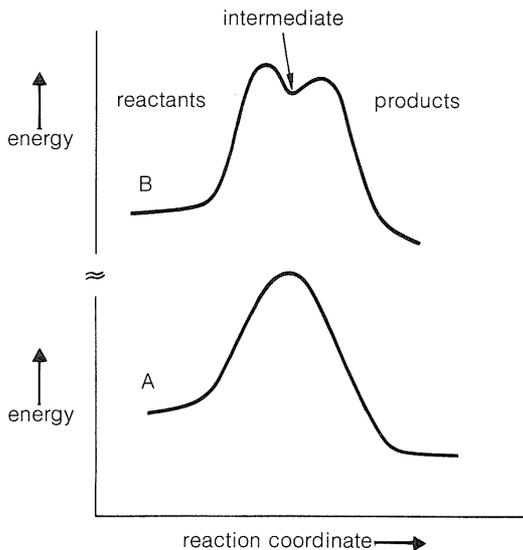
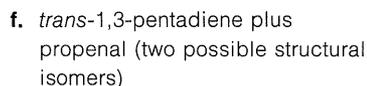
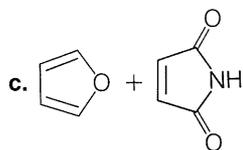
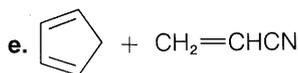
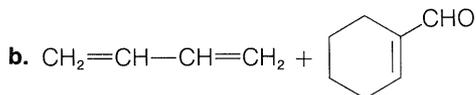
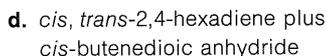
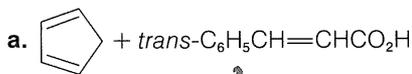


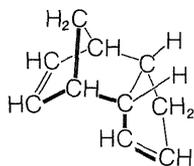
Figure 13-1 Schematic representation of energy versus reaction coordinate for (A) a concerted reaction and (B) a stepwise reaction involving formation of an unstable intermediate. Curve B has been drawn to have the highest energy point (the transition state) come *before* the intermediate is formed. For many processes the highest energy point comes *after* the intermediate is formed. If the highest energy point comes after the intermediate is formed, then the intermediate will be more or less in equilibrium with the reactants.

Exercise 13-5 Draw the two possible orientations of diene to dienophile for the addition of *cis*-butenedioic anhydride to *trans,trans*-2,4-hexadiene. Which adduct would you expect to form preferentially? Explain.

Exercise 13-6 Predict the [4 + 2] addition products of the following reactions; show your reasoning:

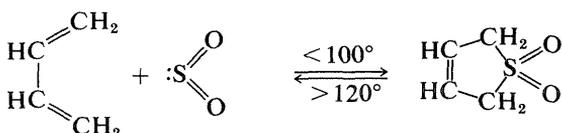


Exercise 13-7 The following hydrocarbon degrades on heating by a reverse Diels-Alder reaction. What product(s) does it give?

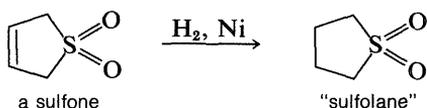


13-3C A [4 + 1] Cycloaddition

We indicated previously that sulfur dioxide (SO_2) and 1,3-butadiene form a [4 + 1] cycloaddition product:

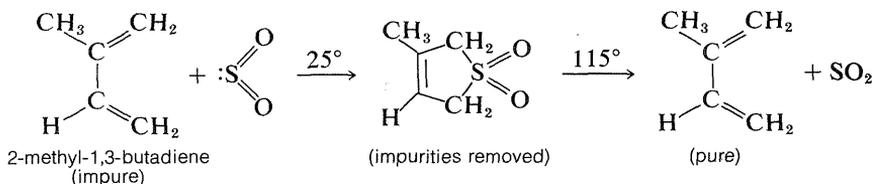


This reaction is more readily reversible than most Diels-Alder reactions, and the product largely dissociates to the starting materials on heating to 120° . The cycloadduct is an unsaturated cyclic **sulfone**, which can be hydrogenated to give the saturated cyclic sulfone known as “sulfolane”:

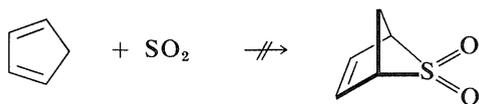


This compound is used extensively in the petrochemical industry as a selective solvent.

The reversibility of the diene- SO_2 cycloaddition makes it useful in the purification of reactive dienes. 2-Methyl-1,3-butadiene (isoprene) is purified commercially in this manner prior to being polymerized to rubber (Section 13-4):

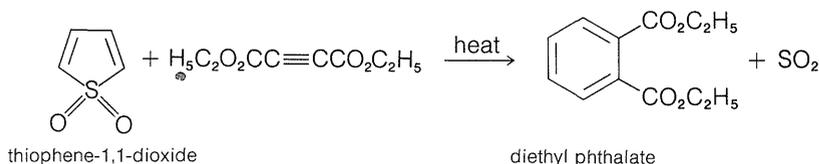


Neither 1,3-cyclopentadiene nor 1,3-cyclohexadiene react with sulfur dioxide, probably because the adducts would be too highly strained:



Exercise 13-8* Formation of the addition product of SO_2 and 1,3-butadiene has $\Delta H^\circ = -16.5$ kcal mole $^{-1}$ for the vapor phase. Assuming the equilibrium constant K is unity at 100°C , calculate ΔS° for the reaction. Compare this value with the ΔS° that you can calculate for addition of ethene to 1,3-butadiene, which has $\Delta G^\circ = -27$ kcal and $\Delta H^\circ = -47$ kcal. Estimate the temperature in $^\circ\text{C}$ that would be required for the equilibrium between ethene and 1,3-butadiene to have $K = 1$. (You may be interested to know that an early route for preparation of 1,3-butadiene involved passing cyclohexene through a tube containing a red-hot wire spiral, $\sim 900^\circ\text{C}$.)

Exercise 13-9* Diethyl phthalate is formed by heating thiophene-1,1-dioxide and diethyl butynedioate:

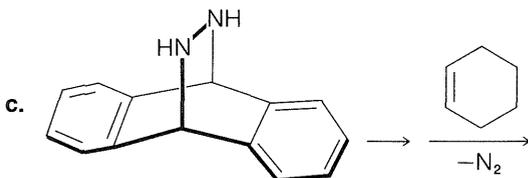


Show the steps involved in this reaction, with the knowledge that the dioxide by *itself* does not decompose at the reaction temperature.

Exercise 13-10* Draw structures for the possible [4 + 2] addition or decomposition products in the following reactions:

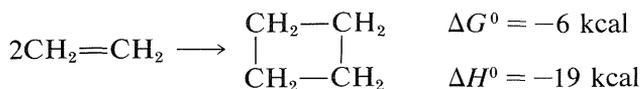
a. dimerization of 2-methylpropenal (methacrolein), $\text{CH}_2=\text{C}(\text{CH}_3)\text{CHO}$, (two possible structural isomers)

b. 1-ethenylcyclohexene + $\text{SO}_2 \xrightarrow{100^\circ}$



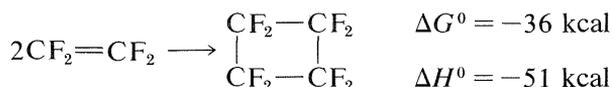
13-3D Some [2 + 2] Cycloadditions

Many naturally occurring organic compounds contain six-membered carbon rings, but there are relatively few with four-membered carbon rings. After encountering the considerable ease with which six-membered rings are formed by [4 + 2] cycloadditions, we might expect that the simpler [2 + 2] cycloadditions to give four-membered rings also should go well, provided that strain is not too severe in the products. In fact, the dimerization of ethene is thermodynamically favorable:

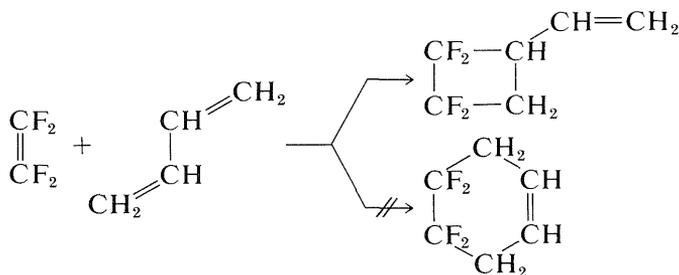


Nonetheless, this and many other [2 + 2] cycloaddition reactions do not occur on simple heating.

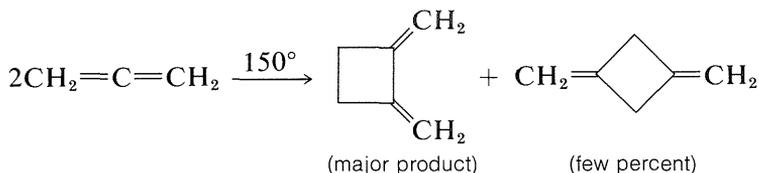
However, there are a few exceptions. One is the dimerization of tetrafluoroethene, which perhaps is not surprising, considering the favorable thermodynamic parameters:

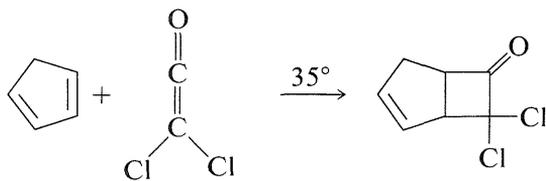
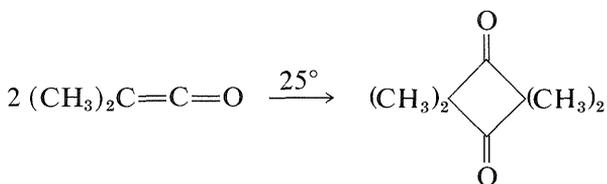
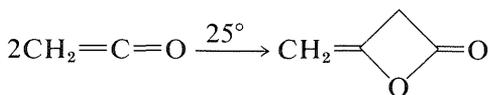


What is surprising is that addition of $\text{CF}_2=\text{CF}_2$ to 1,3-butadiene gives a cyclobutane and *not* a cyclohexene, although the [2 + 2] product probably is about 25 kcal mole⁻¹ less stable than the [4 + 2] product:

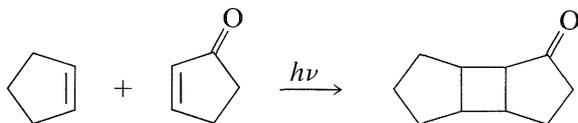


Such [2 + 2] *thermal* additions generally are limited to polyhaloethenes and a few substances with cumulated double bonds, such as 1,2-propadiene ($\text{CH}_2=\text{C}=\text{CH}_2$) and ketenes ($\text{R}_2\text{C}=\text{C}=\text{O}$). Some examples follow:





Many [2 + 2] cycloadditions that do not occur by simply heating the possible reactants can be achieved by *irradiation* with ultraviolet light. The following example, [2 + 2] addition of 2-cyclopentenone to cyclopentene, occurs photochemically but not thermally:



In all such photochemical cycloadditions the energy required to achieve a *cycloaddition* transition state, which can amount to 100 kcal mole⁻¹ or more, is acquired by absorption of light.

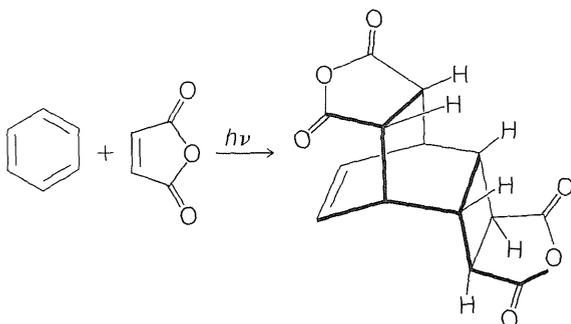
Thermodynamically unfavorable cycloaddition products can be formed photochemically. A striking example is the photochemical conversion of norbornadiene to quadricyclene. The reverse of this reaction can occur with almost explosive violence in the presence of appropriate metal catalysts or on simple heating:



Why do some [2 + 2] cycloadditions occur thermally and others photochemically? What is special about fluoroalkenes and cumulated dienes? The answers are complex, but it appears that most *thermal* [2 + 2] cycloadditions,

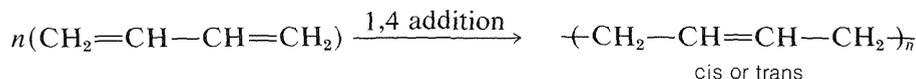
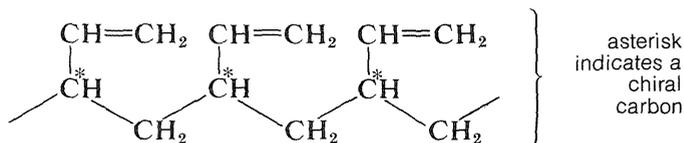
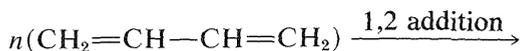
unlike the Diels–Alder [4 + 2] cycloadditions, go by *stepwise* routes (see Section 21-11). Why the two types of thermal cycloaddition have different mechanisms will be discussed in Sections 21-10A and B.

Exercise 13-11* Suggest a mechanism to show how the following compound may be formed by irradiation of a solution of *cis*-butenedioic anhydride (maleic anhydride) in benzene:



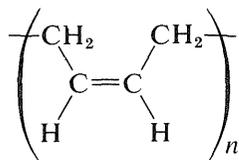
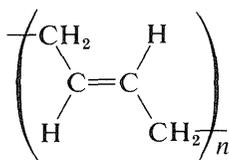
13-4 POLYMERIZATION REACTIONS OF CONJUGATED DIENES

The general character of alkene polymerization by radical and ionic mechanisms was discussed briefly in Section 10-8. The same principles apply to the polymerization of alkadienes, with the added feature that there are additional ways of linking the monomer units. The polymer chain may grow by either 1,2 or 1,4 addition to the monomer. With 1,3-butadiene, for example,



In 1,2 addition, a chiral carbon (marked with *) is created as each molecule of the monomer adds to the growing chain radical. The physical properties of the polymer greatly depend on whether these carbons have the same or different configurations, as we will show in greater detail in Chapter 29. However, in polymer nomenclature, an **isotactic** polymer is one with essentially all chiral carbons having the same configuration, whereas an **atactic** polymer has a *random* ordering of the chiral carbons with different configurations.

For polymerization of 1,3-butadiene by 1,4 addition, there are no chiral carbons, but there is the possibility of *cis-trans* isomerism:

*cis*-1,4-polybutadiene*trans*-1,4-polybutadiene

Exercise 13-12 Formulate chain initiation, propagation, and termination steps for the polymerization of 1,3-butadiene by a mixture of 1,2 and 1,4 addition using a peroxide catalyst. Consider carefully possible structures for the growing-chain radical. Show the expected structure of the polymer and calculate ΔH° for the polymerization reaction.

A polymer made of identical repeating units is called a **homopolymer**. If the units are nonidentical, as when different monomers are polymerized, the product is called a **copolymer**.

Many of the polymers formed from conjugated dienes are elastic and are used to manufacture synthetic rubbers. The raw polymers usually are tacky and of little direct use, except as adhesives and cements. They are transformed into materials with greater elasticity and strength by **vulcanization**, in which the polymer is heated with sulfur and various other substances called **accelerators**, with the result that the polymer chains become cross-linked to one another by carbon-sulfur and carbon-carbon bonds. Some of the cross-linking appears to occur by addition to the double bonds, but the amount of sulfur added generally is insufficient to saturate the polymer. With large proportions of sulfur, hard rubber is formed such as is used in storage-battery cases.

Because of the many double bonds present, diene rubbers are sensitive to air oxidation unless **antioxidants** are added to inhibit oxidation.

Table 13-2
Synthetic Rubbers

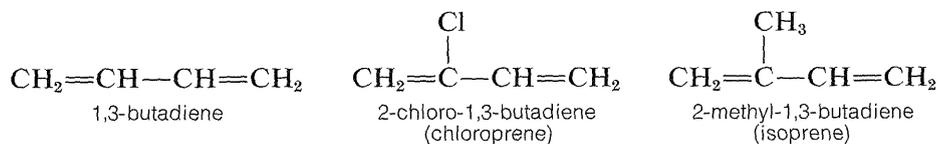
Monomer	Formula	Catalyst	Polymer	Type of addition
1,3-butadiene	$\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$	Li	polybutadiene	~100% cis 1,4
1,3-butadiene	$\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$	Na	polybutadiene	24–30% cis and trans 1,4
1,3-butadiene and ethenylbenzene (styrene)	$\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$ $\text{C}_6\text{H}_5\text{CH}=\text{CH}_2$	<i>a</i>	GRS ^b	
1,3-butadiene and propenenitrile (acrylonitrile)	$\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$ $\text{CH}_2=\text{CH}-\text{CN}$	<i>a</i>	Buna N ^c	
2-chloro-1,3-butadiene (chloroprene)	$\text{CH}_2=\text{CH}-\underset{\text{Cl}}{\text{C}}=\text{CH}_2$	<i>a</i>	neoprene	mostly trans 1,4
2-methyl-1,3-butadiene (isoprene)	$\text{CH}_2=\text{CH}-\underset{\text{CH}_3}{\text{C}}=\text{CH}_2$	Li or Ziegler	essentially identical with natural rubber	~100% cis 1,4
2-methylpropene and 2-methyl-1,3-butadiene (isoprene)	$(\text{CH}_3)_2\text{C}=\text{CH}_2$ $\text{CH}_2=\text{CH}-\underset{\text{CH}_3}{\text{C}}=\text{CH}_2$	AlCl_3	butyl rubber	

^aNo simple formula can be given, but peroxide-type catalysts, particularly peroxosulfate salts, are used most commonly.

^bGRS means *Government Rubber-Styrene* type and is an obsolete notation introduced during World War II.

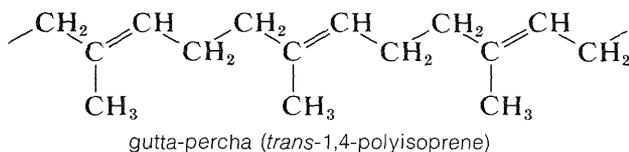
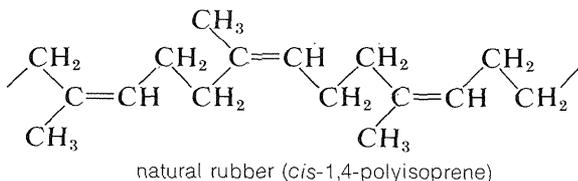
^cOriginally developed in Germany during World War II.

The more important dienes for the manufacture of synthetic rubbers are 1,3-butadiene, 2-chloro-1,3-butadiene (chloroprene), and 2-methyl-1,3-butadiene (isoprene):



Several rubbers that have desirable properties of elasticity, flexibility, abrasive resistance, and resistance to chemicals are listed in Table 13-2. The homogeneity of these polymers depends greatly on the way in which they are prepared, particularly on the polymerization catalyst employed. A synthetic

rubber that is virtually identical to natural Hevea rubber is made from 2-methyl-1,3-butadiene (isoprene) using finely divided lithium metal or transition-metal catalysts; the product is formed almost exclusively by *cis* 1,4 addition³:



Gutta-percha, the *trans* 1,4-isomer of natural rubber, is hard and brittle at room temperature. The reason for the difference in properties between the *cis* and *trans* isomers readily can be seen by inspecting molecular models. The chains with *trans* double bonds are able to lie along side of each other, forming a semicrystalline array, as shown in Figure 13-2. This ordered arrangement cannot be deformed easily, hence the material is hard and brittle. However, when the double bonds are *cis*, steric hindrance prevents the chains from assuming a similar ordered structure and the bulk of the material exists in a

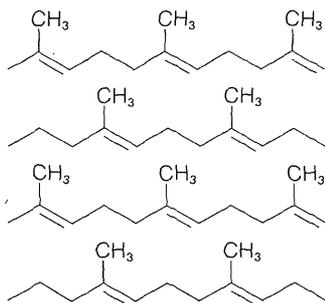


Figure 13-2 Schematic representation of the configuration of chains in gutta-percha (*trans*-1,4-polyisoprene)

³Synthetic rubber has provided severe competition for natural rubber and, for many years, it seemed as though rubber plantations eventually would become extinct. However, rising petroleum prices and higher 2-methyl-1,3-butadiene costs coupled with methods developed for greatly increasing the output of rubber latex per tree, and the fact that natural rubber has superior properties in radial automobile tires, have reversed the trend and rubber plantations currently are being expanded.

noncrystalline (amorphous) state with randomly oriented chains. When the *cis* polymer is stretched, the chains straighten out and tend to become oriented; but because this is an unstable state, the material snaps back to the amorphous state when released. The overall process accounts for the elastic properties of rubber and other similar materials.

Polymerization of 2-methylpropene in the presence of small amounts of 2-methyl-1,3-butadiene (isoprene) gives a copolymer with enough double bonds to permit cross-linking of the polymer chains through vulcanization. The product is a hard-wearing, chemically resistant rubber called "butyl rubber." It is highly impermeable to air and is used widely for inner tubes for tires.

13-5 CUMULATED ALKADIENES

13-5A Structure and Stereoisomerism

The 1,2-dienes, which have cumulated double bonds, commonly are called allenes. The simplest example is 1,2-propadiene,



A ball-and-stick model of 1,2-propadiene suggests that the two double bonds, and hence the terminal methylene groups, should lie in different planes at right angles to each other (Figure 13-3). The same stereochemistry is predicted by an atomic-orbital representation (Figure 13-4). In this formulation each of two electrons of the central atom form collinear *sp* σ bonds to the terminal *sp*²-hybridized carbons. The two remaining electrons of the central carbon occupy *p* orbitals and form π bonds through overlap of these *p* orbitals and the *p* orbitals of the terminal carbons.

Allenes of the type $\text{RR}'\text{C}=\text{C}=\text{CRR}'$ are *chiral* molecules and can exist in two stereoisomeric forms, one being the mirror image of the other and neither being superimposable on the other (i.e., *enantiomers*, Figure 13-5).

Verification of the chirality of such allenes (originally proposed by van't Hoff in 1875) was slow in coming and was preceded by many unsuccess-

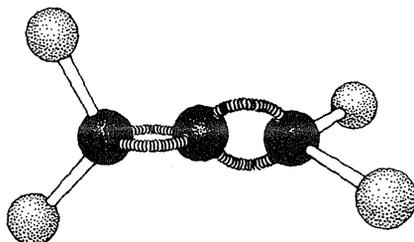


Figure 13-3 Ball-and-stick model of 1,2-propadiene

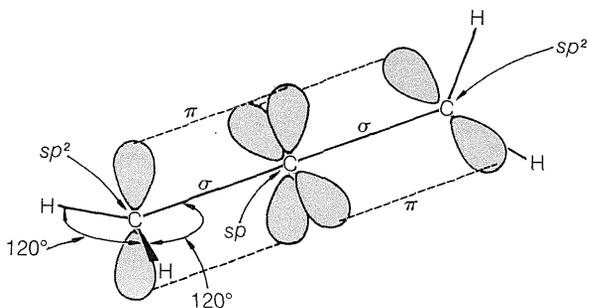


Figure 13-4 Atomic-orbital model of 1,2-propadiene

ful attempts to resolve suitably substituted allenes into their enantiomers. The first successful resolutions were achieved in 1935 for the enantiomers of two compounds **1** and **2**. This was a classic achievement because it dispelled the suspicion prevalent at the time that rotation about the bonds of the cumulated diene system was free enough to preclude the isolation of configurationally stable enantiomers.

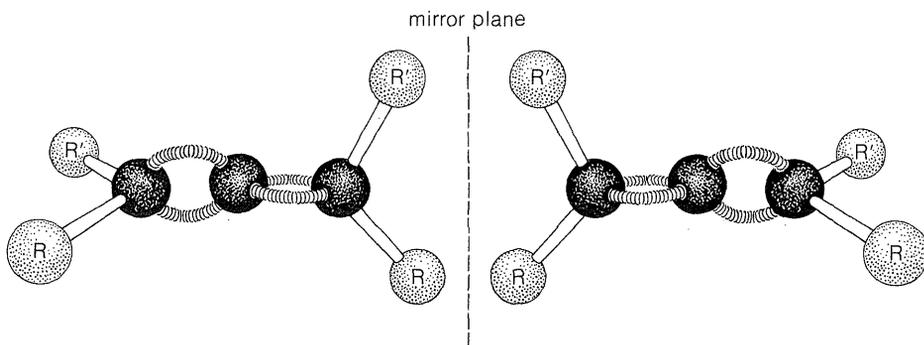
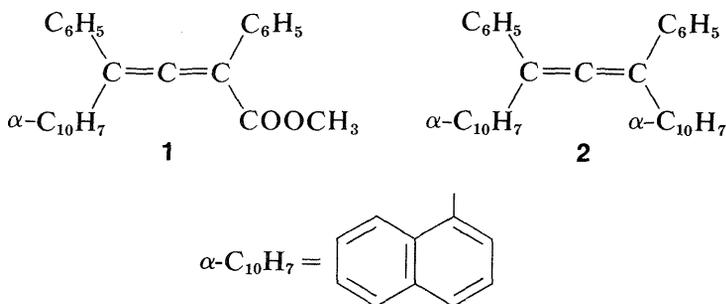
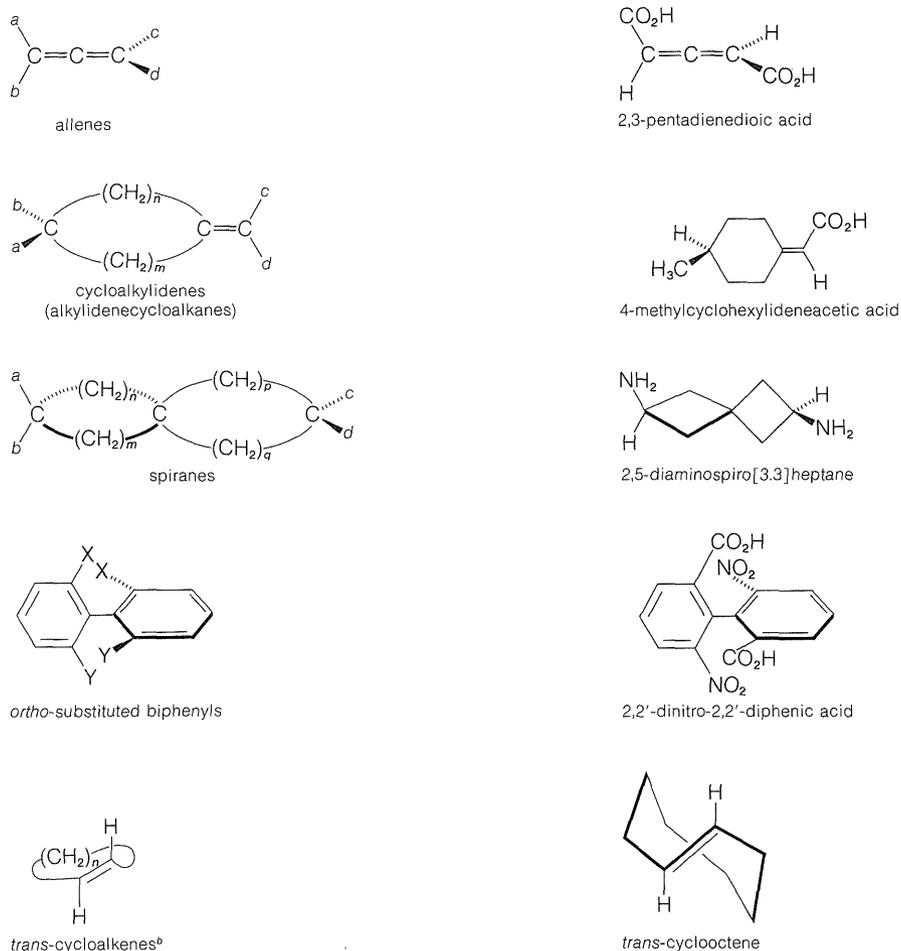


Figure 13-5 Enantiomers of a substituted allene of the type $RR'C=C=CRR'$

Table 13-3

Examples of Chiral Substances Resulting from Restricted Rotation About Double or Single Bonds^a



^aFor chirality in the substances shown $a \neq b$, $c \neq d$, and $X \neq Y$; only one enantiomer is shown.

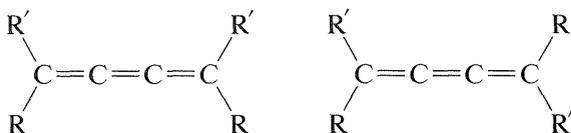
^bSee Section 12-7

The chirality observed in this kind of substituted allene is a consequence of dissymmetry resulting from restricted rotation about the double bonds, not because of a tetrahedral atom carrying four different groups. Restricted rotation occurs in many other kinds of compounds and a few examples are shown in Table 13-3, which includes *trans*-cycloalkenes (Section 12-7), cycloalkylidenes, spiranes, and *ortho*-substituted biphenyl compounds. To have enantiomers, the structure must not have a plane or center of symmetry (Section 5-5).

The chirality of biphenyls results from restricted rotation about a *single* bond imposed by the bulky nature of ortho substituents. Models will help you visualize the degree of difficulty of having the substituents pass by one another. If $X = H$ and $Y = F$ (Table 13-3), the enantiomers are not stable at room temperature; if $X = H$ and $Y = Br$, they are marginally stable; if $X = H$ and $Y = I$, the rate of loss of optical activity is about 700 times slower than with $Y = Br$. This is in keeping with the fact that the atomic size of the halogens increases in the order $F < Br < I$.

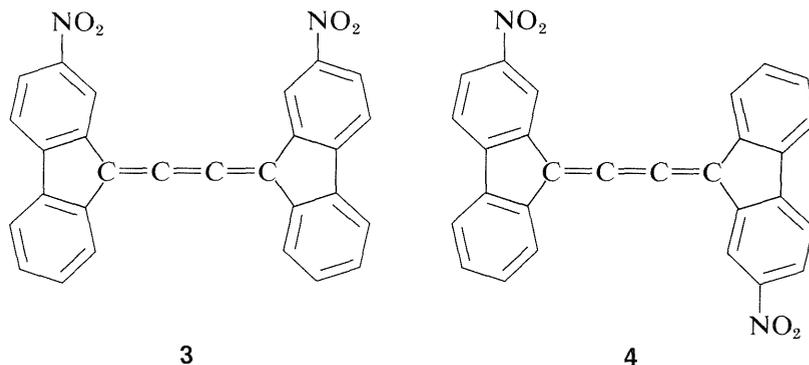
Cis-Trans Isomerism

In a cumulated triene, or any cumulated polyene with an *odd* number of double bonds, the atoms connected to the terminal carbons lie in the same plane, just as they do in an ordinary alkene. Van't Hoff pointed out that suitably substituted cumulated polyenes of this type should then have cis and trans forms:



cis and trans forms of a cumulated triene

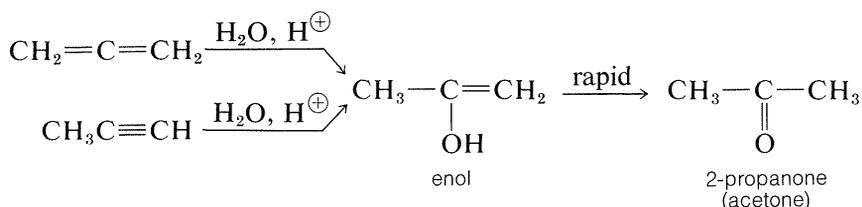
Like the resolution of allenes, the separate existence of cis and trans isomers of cumulated trienes was not verified until many years after van't Hoff's original predictions, but a separation finally was achieved, in 1954, by R. Kuhn and K. Scholler for compounds **3** and **4**:



There are relatively few cis-trans forms of 1,2,3-alkatrienes known. They appear to interconvert readily on mild heating, which suggests that one of the double bonds has a lower rotational barrier than is normal for an alkene double bond.

13-5B Chemistry of Allenes

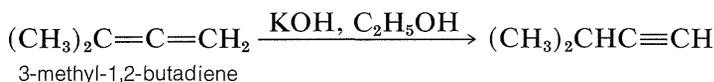
The properties of allenes are similar to those of alkenes, although the pure compounds often are difficult to prepare and are not indefinitely stable. Allenes undergo many of the usual double-bond reactions, being readily hydrogenated, adding bromine, and being oxidized with potassium permanganate solution. The hydration of allenes resembles the hydration of alkynes in giving initially an unstable enol that rapidly rearranges to a ketone:



Allenenes are not as stable as dienes with conjugated or isolated double bonds. The heats of hydrogenation (Table 11-2) indicate that the order of stability is conjugated dienes > isolated dienes > cumulated dienes. The relative instability of allenes probably reflects extra strain as the result of one carbon atom forming two double bonds. 1,2-Propadiene is slightly more strained than propyne, its heat of hydrogenation being about 2 kcal mole⁻¹ greater than that of propyne. It is not surprising then that 1,2-propadiene isomerizes to propyne. This isomerization occurs under the influence of strongly basic substances such as sodium amide in liquid ammonia or potassium hydroxide in ethyl alcohol:



$$\Delta G^0(g) = -2 \text{ kcal}$$

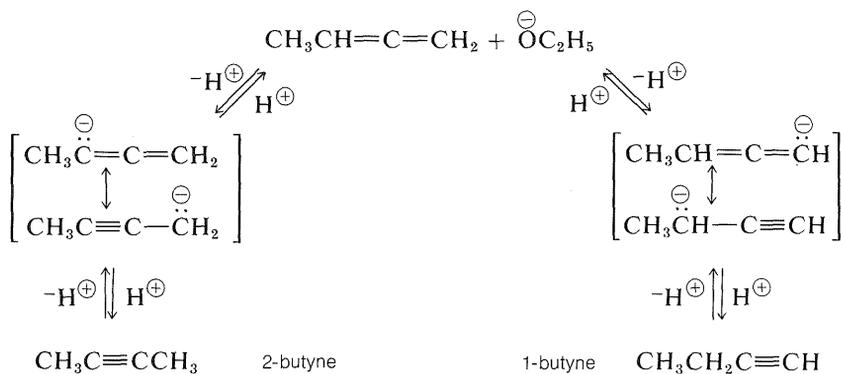


$$\Delta G^0(g) = -2.5 \text{ kcal}$$

Indeed, one of the difficulties associated with syntheses of allenes and alkynes (which often are carried out in the presence of strong bases) is the concurrent formation of isomerization products.

The basic catalyst in the isomerization of 1,2-butadienes to butynes acts by removing an alkenic proton from the hydrocarbon. Two different anions can be formed, each of which is stabilized by electron delocalization involving the adjacent multiple bond. Either anion can react with the solvent by proton transfer to form the starting material or an alkyne. At equilibrium the most

stable product, which is 2-butyne, predominates [1-butyne(g) \rightleftharpoons 2-butyne(g), $\Delta G^0 = -4.0 \text{ kcal mole}^{-1}$]:



Exercise 13-13* The rearrangement of 1,2-butadiene to 2-butyne shown above uses ethoxide ion as a basic *catalyst*. When one mole of 1,2-butadiene is treated with one mole of sodium amide in liquid ammonia, and water is added, the product is 1-butyne. Show the steps involved and explain why the product is different when an equivalent amount of a very strong base is used. (You may wish to review Section 11-8.)

13-6 APPROACHES TO PLANNING PRACTICAL ORGANIC SYNTHESSES

Chemistry is unique among the physical and life sciences in one very important respect. It can be manipulated extensively to man's design. That is, molecular structures can be designed and then constructed by choosing appropriate chemical reactions. This is **chemical synthesis**, which has been developed to such a degree that the economies and indeed the living standards of the industrialized nations have come to depend on it. Not everyone agrees that the present state of civilization in the industrialized nations is a way station to the millenium. But whether one agrees or not, there is no question that chemical synthesis has played an enormous role in making possible the accessories of modern life.

Chemical synthesis is not a science that can be taught or learned by any well-defined set of rules. Some classify synthesis as more art than science because, as with all really creative endeavors, to be very successful requires great imagination conditioned by a wealth of background knowledge and experience. The problems of synthesis basically are problems in design and

planning. Given the objective of synthesizing a specific organic compound, there always is a variety of ways that the objective can be achieved, either from the same or from different starting materials. What we hope to do here is to show how one can go about developing efficient syntheses from available starting materials. However, *practice* in planning syntheses is imperative to obtaining a good grasp of the principles and problems involved. This will be up to you; no one else can do it for you. Practice also will help greatly to convert short-term memories of organic reactions to longer-term memories through repeated review and demonstrated relevance.

13-6A Methodology

In almost all syntheses the **target compound** is defined precisely, both as to structure and stereochemistry. Regardless of whether the synthesis is destined to be carried out on an industrial scale or on a laboratory scale, careful planning is required. The usual methodology for the planning stage involves two, not wholly independent, steps. First, one considers the various possible ways the desired *carbon skeleton* can be constructed, either from smaller molecules or by changes in some existing skeleton. Second, means are considered for generation of desired *functional groups* on the desired carbon skeleton. In many cases, the desired functional groups can be generated as a consequence of the reactions whereby the desired skeleton itself is generated. Alternative syntheses almost always are possible and one should proceed on the notion that the first sequence one thinks of is unlikely to be the best.

The choice of the best route usually is made by considering:

1. The availability of the starting materials
2. The cost of the starting materials and the equipment needed
3. The simplicity of the various steps and the scale of synthesis
4. The number of separate steps involved
5. The yield in each step
6. The ease of separation and purification of the desired product from by-products and stereoisomers

These considerations are dealt with in the following sections and in subsequent chapters.

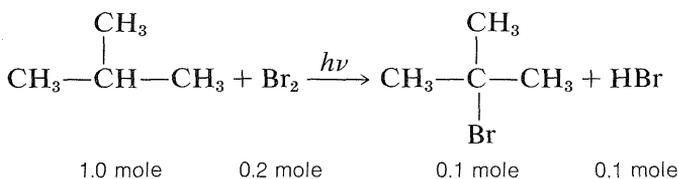
13-6B Starting Materials

Availability of the starting materials obviously is a limiting factor in any synthetic operation. As far as laboratory-type synthesis is concerned, “availability” means that the starting materials either may be bought “off the shelf” or may be prepared easily by standard methods from other inexpensive and available compounds. For large-scale industrial syntheses, the limiting factor usually is the cost of the starting materials, including the energy required.

But in some cases the limiting factor may be problems in disposal of the by-products. Costs will vary according to geographical location and will fluctuate widely, as with crude oil costs, so as to cause obsolescence and constant change in the chemical industry. However, it is worth remembering that the cheapest organic starting materials available are methane, ethene, ethyne, propene, butenes, benzene, and methylbenzene (toluene). Any chemical that can be prepared easily in high yield from one of these hydrocarbons is likely to be relatively inexpensive, readily available, and useful as a starting material in more involved syntheses.

13-6C The Yield Problem

Among the factors considered in choosing among several possible synthetic routes is: Which gives the best yield? The definition of **yield** and its distinction from another useful term, **conversion**, should be clearly understood. To help you understand, consider a specific example, the bromination of 2-methylpropane to give *tert*-butyl bromide as the desired product. This type of reaction is carried on best with an excess of hydrocarbon to avoid polysubstitution (Section 4-5), and if we use such an excess of hydrocarbon, bromine will be the **limiting reagent**. This means simply that the amount of the desired product that could be formed is determined, or limited, by the amount of bromine used:



Suppose we start with one mole of hydrocarbon and 0.2 mole of bromine and, after a specified reaction time, 0.1 mole of bromine has reacted. If only the desired product were formed, and there were no other losses of hydrocarbon or bromine,

$$\% \text{ conversion} = \frac{\text{moles of limiting reagent reacted}}{\text{moles of limiting reagent initially present}} = \frac{0.1}{0.2} \times 100 = 50\%$$

If there are no losses in isolating the product or in recovering unused starting material, then

$$\% \text{ yield} = \frac{\text{moles of product}}{\text{moles of limiting reagent reacted}} = \frac{0.1}{0.1} \times 100 = 100\%$$

Now suppose all of the 0.2 mole of bromine reacts, 0.08 mole of the desired product can be isolated, and 0.7 mole of hydrocarbon is recovered. Under these circumstances, the percent conversion is 100%, because all of the bromine has reacted. The yield can be figured in different ways depending on

which starting material one wishes to **base the yield**. Based on bromine (which would be logical because bromine is the more expensive reagent) the yield of *tert*-butyl bromide is $(0.08/0.2) \times 100 = 40\%$. However, one also could base the yield of *tert*-butyl bromide on the unrecovered hydrocarbon, and this would be $[0.08/(1.0 - 0.7)] \times 100 = 27\%$.

Exercise 13-14 Suppose one treated 100 g of propene with 125 g of chlorine in the presence of water and isolated 25 g of excess propene, 130 g of 1,2-dichloropropane, 40 g of 1-chloro-2-propanol, and no chlorine from the reaction mixture. Calculate a percent yield and a percent conversion for the products based (a) on propene and (b) on chlorine.

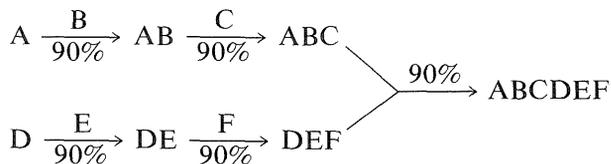
In a multistep synthesis, the overall percent yield is the product of the fractional yields in each step times 100 and decreases rapidly with the number of steps. For this reason, a low-yield step along the way can mean practical failure for the overall sequence. Usually, the best sequence will be the one with the fewest steps. Exceptions arise when the desired product is obtained as a component of a mixture that is difficult to separate. For example, one could prepare 2-chloro-2-methylbutane in one step by direct chlorination of 2-methylbutane (Section 4-5A). But because the desired product is very difficult to separate from the other, isomeric monochlorinated products, it is desirable to use a longer sequence that may give a lower yield but avoids the separation problem. Similar separation problems would be encountered in a synthesis that gives a mixture of stereoisomers when only one isomer is desired. Again, the optimal synthesis may involve a longer sequence that would be stereospecific for the desired isomer.

One way of maximizing the yield is to minimize the number of sequential steps and, whenever possible, to use *parallel* rather than *sequential* reactions. For example, suppose that we wish to synthesize a compound ABCDEF by linking together A,B,C,D,E, and F. The sequential approach would involve at least five steps as follows:



If each of these steps proceeds in 90% yield, the overall yield would be $(0.90)^5 \times 100 = 59\%$.

One possible parallel approach would involve synthesis of the fragments ABC and DEF followed by the combination of these to ABCDEF:



There are still at least five reaction steps, but only three sequential steps; and if each of these proceeds in 90% yield, the overall yield would be $(0.90)^3 \times 100 = 73\%$. The parallel approach is especially important in the synthesis of polymeric substances such as peptides, proteins, and nucleic acids in which many subunits have to be linked.

Finally, product yields are very dependent on manipulative losses incurred in each step by isolating and purifying the synthetic intermediates. The need to minimize losses of this kind is critically important in very lengthy syntheses.

Exercise 13-15 Syntheses have been carried out with one hundred or more sequential reactions. If the yield in each step is 99%, what would be the overall yield after one hundred steps? Repeat the calculation for a yield of 99.9% in each step. What do you conclude from these calculations about the importance of yield in multistep syntheses? (It is interesting to contemplate how even simple organisms can synthesize molecules by what appear to be sequences of 10,000 or more separate steps with very few, if any, errors, and what means the organisms have to check the accuracy of the sequence after each incorporation of a new subunit.)

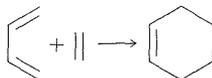
13-7 BUILDING THE CARBON SKELETON

According to the suggested approach to planning a synthesis, the primary consideration is how to construct the target carbon skeleton starting with smaller molecules (or, alternatively, to reconstruct an existing skeleton). Construction of a skeleton from smaller molecules almost always will involve formation of carbon-carbon bonds. Up to this point we have discussed only a few reactions in which carbon-carbon bonds are formed and these are summarized in Table 13-4. Other important reactions that can be used to enlarge a carbon framework will be discussed in later chapters.

The most logical approach to planning the synthesis of a particular carbon framework requires that one work *backward* by mentally fragmenting the molecule into smaller pieces that can be “rejoined” by known C-C bond-forming reactions. The first set of pieces in turn is broken into smaller pieces, and the mental fragmentation procedure is repeated until the pieces correspond to the carbon skeletons of readily available compounds. There almost always will be several different backward routes, and each is examined for its potential to put the desired functional groups at their proper locations. In almost all cases it is important to use reactions that will lead to pure compounds without having to separate substances with similar physical properties.

Table 13-4

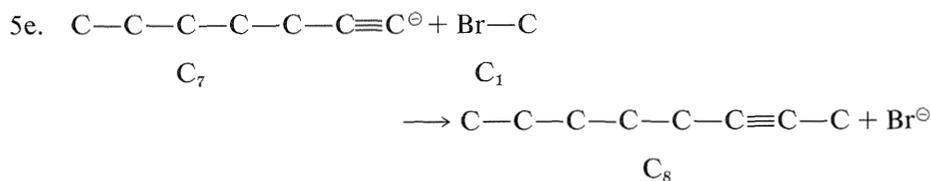
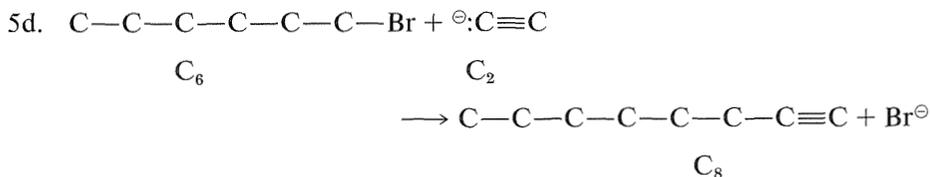
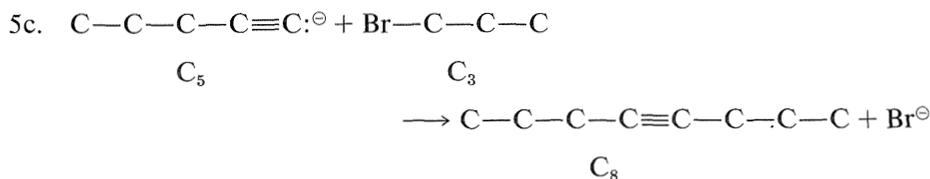
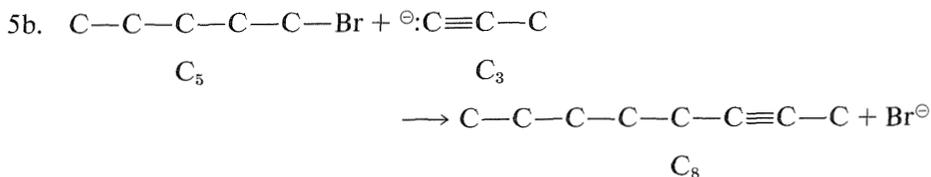
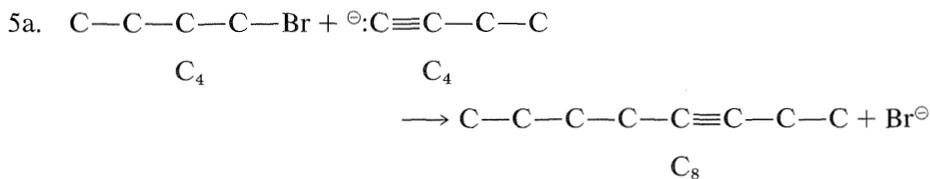
Some Carbon-Carbon Bond-Forming Reactions with Section References

Reaction	Section reference
1. Addition of carbon electrophiles to alkenes: $R^{\oplus} + \begin{array}{c} \diagup \\ \text{C}=\text{C} \\ \diagdown \end{array} \longrightarrow R-\begin{array}{c} \\ \text{C} \\ \end{array}-\begin{array}{c} \\ \text{C}^{\oplus} \\ \end{array} \xrightarrow{RH} R-\begin{array}{c} \\ \text{C} \\ \end{array}-\begin{array}{c} \\ \text{C} \\ \end{array}-H + R^{\oplus}$	10-9
2. Addition of carbon nucleophiles to suitably activated alkenes: $R:\ominus + \begin{array}{c} \diagup \\ \text{C}=\text{C} \\ \diagdown \end{array} \longrightarrow R-\begin{array}{c} \\ \text{C} \\ \end{array}-\begin{array}{c} \\ \text{C}^{\ominus} \\ \end{array} \xrightarrow{RH} R-\begin{array}{c} \\ \text{C} \\ \end{array}-\begin{array}{c} \\ \text{C} \\ \end{array}-H + R:\ominus$	10-6
3. Addition of carbon radicals to alkenes: $R\cdot + \begin{array}{c} \diagup \\ \text{C}=\text{C} \\ \diagdown \end{array} \longrightarrow R-\begin{array}{c} \\ \text{C} \\ \end{array}-\begin{array}{c} \\ \dot{\text{C}} \\ \end{array} \xrightarrow{RX} R-\begin{array}{c} \\ \text{C} \\ \end{array}-\begin{array}{c} \\ \text{C} \\ \end{array}-X + R\cdot$	10-7
4. Addition polymerization reactions: $n(\text{C}=\text{C}) \longrightarrow \left(\begin{array}{c} \\ \text{C} \\ \end{array} - \begin{array}{c} \\ \text{C} \\ \end{array} \right)_n$	10-8
5. Displacement reactions with alkynide anions: $RC\equiv C:\ominus + R'X \longrightarrow RC\equiv CR' + X^{\ominus}$	11-8C
6. Displacement reactions with cyanide ion: $\ominus\text{C}\equiv\text{N} + \text{RX} \longrightarrow \text{RC}\equiv\text{N} + \text{X}^{\ominus}$	8-7F
7. Coupling reactions of 1-alkynes: $2\text{RC}\equiv\text{CH} \xrightarrow{\text{Cu(I)}} \text{RC}\equiv\text{C}-\text{C}\equiv\text{CR}$	11-8D
8. [4 + 2] Cycloaddition: 	13-3A
9. [2 + 2] Cycloaddition: 	13-3D

Example

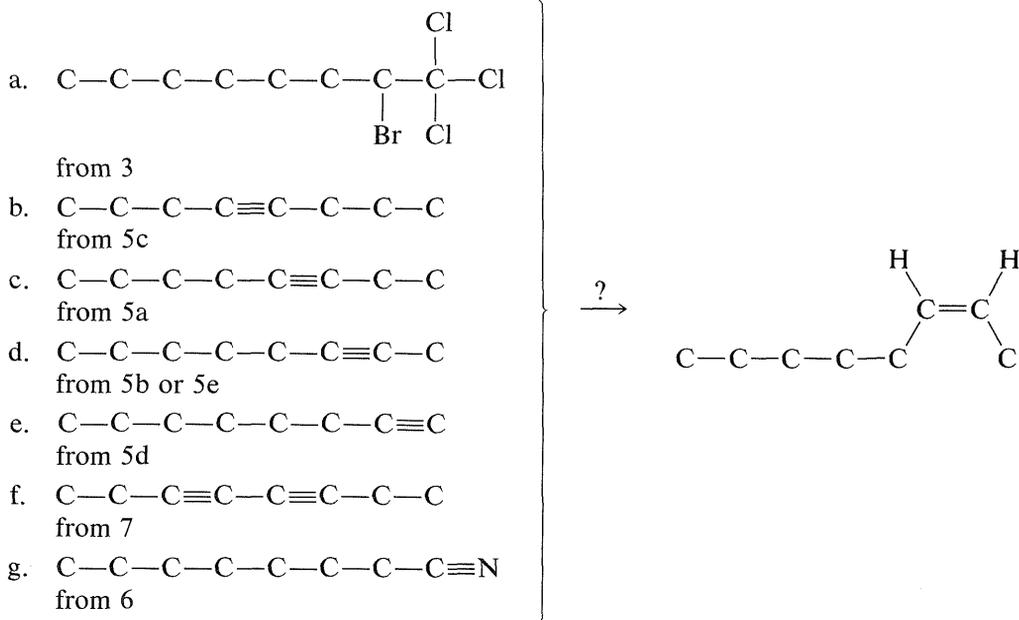
A typical synthesis problem would be to devise a preparation of *cis*-2-octene, given the restrictions that the starting materials have fewer than eight carbons, and that we use the C–C bond-forming reactions we have discussed up to now. The reasoning involved in devising an appropriate synthesis with the given restrictions will be outlined for this example in detail.

Reaction 5 could be useful for all of the possible ways of dividing C_8 . Some of the possible combinations are:



This does not exhaust the possibilities because, as 5b and 5e show, Reaction 5 can be used to make the same C_8 compound from different sets of starting materials.

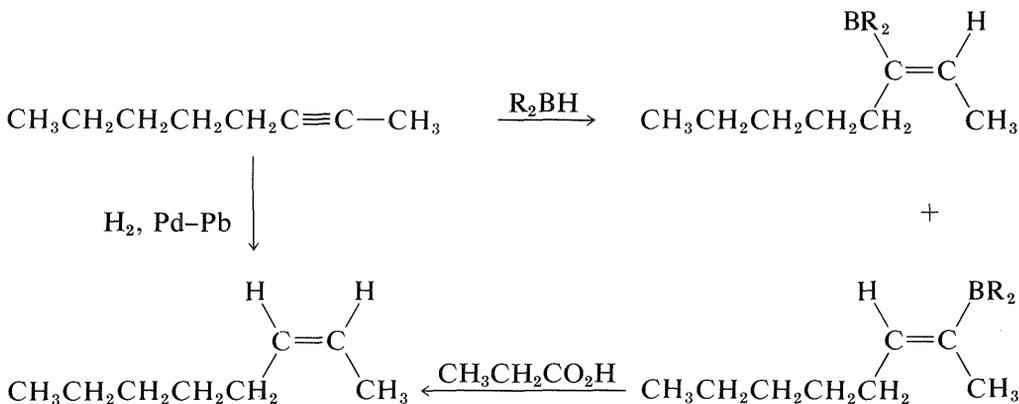
We now have to consider how to convert the C₈ materials that we might make into *cis*-2-octene. The possibilities are:



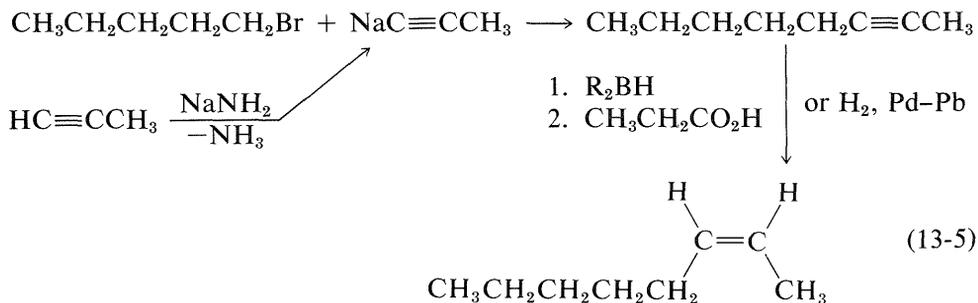
Of these, d is the obvious choice for first consideration because it has its functionality, a single triple bond, between the same two carbons we wish to have joined by a *cis* double bond in the product. Now, we have to ask if there are

reactions that will convert $-\text{C}\equiv\text{C}-$ to *cis*- $\begin{array}{c} \text{H} \quad \text{H} \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \end{array}$. Two possibilities

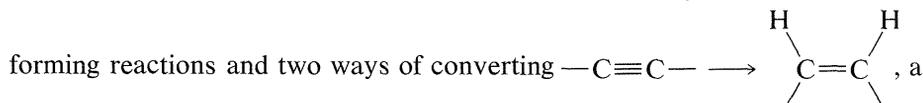
were mentioned previously—hydrogenation of a triple bond with the Lindlar catalyst (Section 11-2B) and hydroboration followed by treatment with propanoic acid (Section 11-6D):



Either of these two reactions provides a simple and straightforward way of converting 2-octyne to *cis*-2-octene, so a satisfactory answer to the original problem is



You can see that even with having available only seven C-C bond-



considerable amount of logical screening is required to eliminate unsuitable possibilities. The skilled practitioner makes this kind of diagnosis quickly in his head; at the outset you will find it useful to write the steps in your screening in the same way as we have done for this example.

13-8 INTRODUCING FUNCTIONALITY

As we have seen in the previous section, it may be easy to construct the carbon skeleton of the target compound of a synthesis, but with a reactive functional group at the wrong carbon. Therefore it is important also to have practice at shifting reactive entry points around to achieve the final desired product. We shall illustrate this form of molecular chess with reactions from previous chapters. A typical problem may be to devise syntheses for achieving the following conversions:

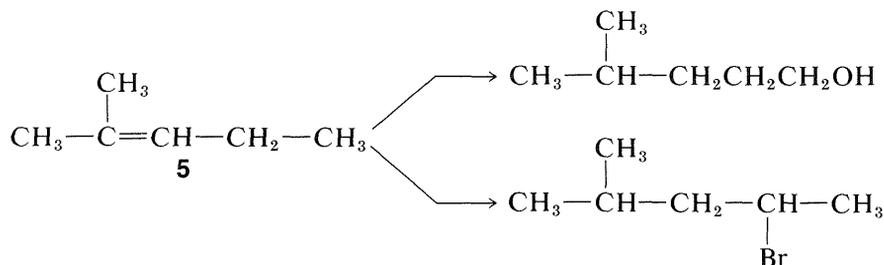


Table 13-5
Summary of Useful Synthetic Transformations

Transformation	Section	Transformation	Section
$R-H \xrightarrow[-HX]{X_2} R-X$	4-5	$-C\equiv C- \xrightarrow{H_2O} \begin{array}{c} O \\ \\ -C-C- \\ \\ H \end{array}$	10-5A
$R-H \xrightarrow[-H_2O]{HNO_3} R-NO_2$	4-6	$n \times \begin{array}{c} \diagup \\ C=C \\ \diagdown \end{array} \rightarrow \left(\begin{array}{c} \\ -C-C- \\ \end{array} \right)_n$	10-8
$R-X \xrightarrow[-X^\ominus]{Y^\ominus} R-Y$	8-3 to 8-7 ^a	$\begin{array}{c} \diagup \\ C=C \\ \diagdown \end{array} \xrightarrow{RH} \begin{array}{c} \\ -C-C- \\ \quad \\ H \quad R \end{array}$	10-9
$R-X \xrightarrow[-HX]{HY} R-Y$	8-3 to 8-7 ^a	$\begin{array}{c} \diagup \\ C=C \\ \diagdown \end{array} \xrightarrow{H_2} \begin{array}{c} \\ -C-C- \\ \quad \\ H \quad H \end{array}$	11-2 to 11-4 ^{b,e}
$ROH \xrightarrow[-H_2O]{HX} RX$	8-7D, 8-7E	$-C\equiv C- \xrightarrow{H_2} \begin{array}{c} \diagup \\ C=C \\ \diagdown \\ \quad \\ H \quad H \end{array}$	11-2B ^e
$\begin{array}{c} H \\ \\ -C-C-X \\ \quad \end{array} \xrightarrow{-HX} \begin{array}{c} \diagup \\ C=C \\ \diagdown \end{array}$	8-8 to 8-9 ^{a,b}	$\begin{array}{c} \diagup \\ C=C \\ \diagdown \end{array} \xrightarrow{HN=NH} \begin{array}{c} \\ -C-C- \\ \quad \\ H \quad H \end{array} \xrightarrow{-N_2}$	11-5 ^e
$\begin{array}{c} \diagup \\ C=C \\ \diagdown \end{array} \xrightarrow{X_2} \begin{array}{c} \\ -C-C- \\ \quad \\ X \quad X \end{array}$	10-2 to 10-3C, 10-7A ^b	$\begin{array}{c} \diagup \\ C=C \\ \diagdown \end{array} \xrightarrow{R_2BH} \begin{array}{c} \\ -C-C- \\ \quad \\ H \quad BR_2 \end{array}$	11-6A to 11-6C
$\begin{array}{c} \diagup \\ C=C \\ \diagdown \end{array} \xrightarrow{HX} \begin{array}{c} \\ -C-C- \\ \quad \\ H \quad X \end{array}$	10-3D, 10-3G, 10-4, 10-6, 10-7	$\begin{array}{c} \\ -C-C- \\ \quad \\ H \quad BR_2 \end{array} \rightarrow \begin{array}{c} \\ -C-C- \\ \quad \\ R_2B \quad H \end{array}$	11-6C
$\begin{array}{c} \diagup \\ C=C \\ \diagdown \end{array} \xrightarrow{XY} \begin{array}{c} \\ -C-C- \\ \quad \\ X \quad Y \end{array}$	10-4A ^{b,c} , 10-7 ^d	$RBR'_2 \xrightarrow{H^\oplus, H_2O} RH$	11-6D
$\begin{array}{c} \diagup \\ C=C \\ \diagdown \end{array} \xrightarrow{H_2O} \begin{array}{c} \\ -C-C- \\ \quad \\ H \quad OH \end{array}$	10-3E to 10-3G, 10-4	$RBR'_2 \xrightarrow{H_2O_2} ROH$	11-6D
$-C\equiv C- \xrightarrow{X_2} \begin{array}{c} \diagup \\ C=C \\ \diagdown \\ \quad X \\ X \end{array}$	10-5	$RBR'_2 \xrightarrow{H_2N-OSO_3H} RNH_2$	11-6D
$-C\equiv C- \xrightarrow{HX} \begin{array}{c} \diagup \\ C=C \\ \diagdown \\ \quad H \\ X \end{array}$	10-5	$-C\equiv C- \xrightarrow{R_2BH} \begin{array}{c} \diagup \\ C=C \\ \diagdown \\ \quad \\ H \quad BR_2 \end{array}$	11-6A

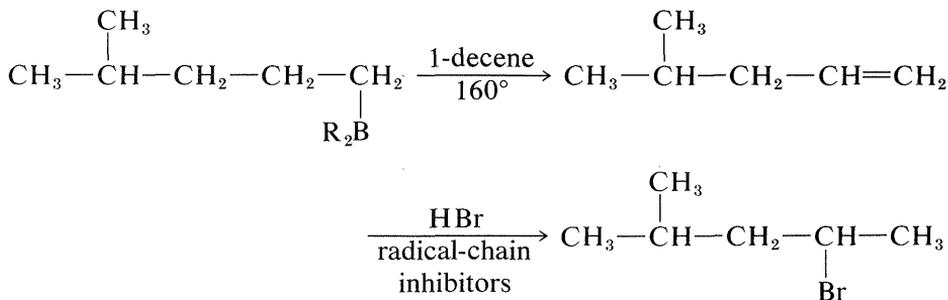
Table 13-5 (continued)

Summary of Useful Synthetic Transformations

Transformation	Section	Transformation	Section
	11-6D		11-7D
	11-6D		11-8
	11-7A		11-8
<p style="text-align: center;">(suprafacial)</p>	11-7C		11-8C
<p style="text-align: center;">(antarafacial)</p>	11-7D		11-8D

^aSummary in Study Guide. ^bA number of similar reactions not widely used for synthesis can be achieved by cleavage of a cyclopropane ring; summary in Table 12-4. ^cSummary in Table 10-2. ^dSummary in Table 10-3. ^eSummary in Table 11-3.

be avoided because it would give 1-bromo-4-methylpentane (Section 10-7):



A very brief summary of the transformations that we have studied so far, which do not change the carbon skeleton, is given in Table 13-5 along with appropriate section references. In using this table, it is necessary to check the specific sections to be sure the reaction is applicable to the conversion that you wish to achieve and to determine the proper conditions for the reaction.

13-9 CONSTRUCTION OF RING SYSTEMS BY CYCLOADDITION REACTIONS

Another example of a synthesis problem makes use of the cycloaddition reactions discussed in this chapter. Consider the synthesis of bicyclo[2.2.1]heptane, **9**, from compounds with fewer carbons.



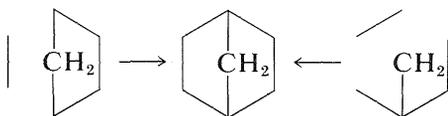
bicyclo[2.2.1]heptane, **9**

Whenever a ring has to be constructed, you should consider the possibility of cycloaddition reactions, especially $[4+2]$ cycloaddition by the Diels–Alder reaction. A first glance at **9**, written in the usual sawhorse-perspective formula, might lead to overlooking the possibility of constructing the skeleton by $[4+2]$ addition, because the compound seems only to be made up of five-membered rings. If the structure is rewritten as **10**, the six-membered ring stands out much more clearly:

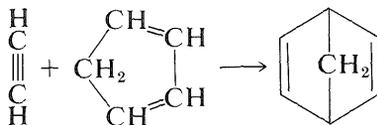
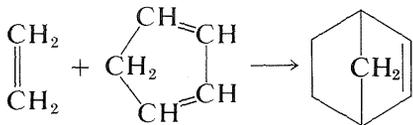


bicyclo[2.2.1]heptane, **10**

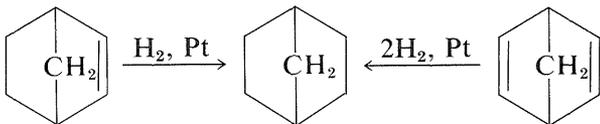
If we now try to divide the six-membered ring into $[2]$ and $[4]$ fragments, we find that there are only two *different* ways this can be done:



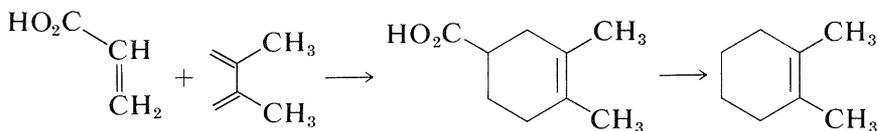
The left division corresponds to a simple $[4+2]$ cycloaddition, whereas the right division corresponds to a complex reaction involving formation of three ring bonds at once. Actual Diels–Alder reactions require diene and dienophile starting materials, and two possibilities, using 1,3-cyclopentadiene as the diene and ethene or ethyne as dienophile, follow:



Either of the products can be converted to bicyclo[2.2.1]heptane by hydrogenation (Table 13-5):



Neither ethene nor ethyne is a very good dienophile but [4 + 2] cycloadditions of either with 1,3-cyclopentadiene go well at temperatures of 160–180° because 1,3-cyclopentadiene is a very reactive diene. Achieving the overall result of addition of ethene or ethyne to a less reactive diene could necessitate a synthetic sequence wherein one of the reactive dienophiles listed in Table 13-1 is used to introduce the desired two carbons, and the activating groups are subsequently removed. An example follows:



Reactions that can be used to remove a $-\text{CO}_2\text{H}$ group will be discussed in Chapter 18.

A number of synthesis problems follow, and in working these it will be helpful to write your reasoning in the way we have done for our examples in this section.

Exercise 13-16 Devise a synthesis of 2-chloro-2,4,4-trimethylpentane from organic compounds with four carbons or less and any necessary inorganic reagents. Your synthesis should involve the C–C bond-forming reactions listed in Table 13-4 and other reactions shown in Table 13-5. The product should be 2-chloro-2,4,4-trimethylpentane and not a mixture of its isomers.

Exercise 13-17 Show how each of the following compounds could be synthesized from the indicated starting material and other appropriate organic or inorganic reagents. Specify the reaction conditions, mention important side reactions, and justify the practicality of any isomer separations.

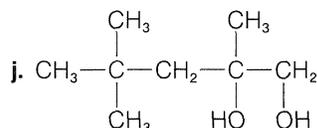
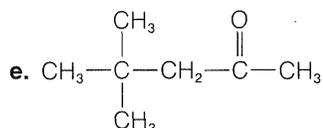
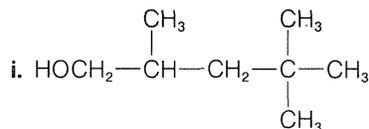
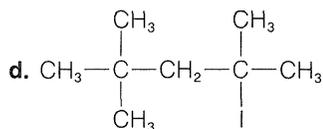
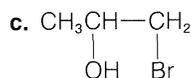
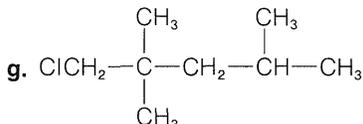
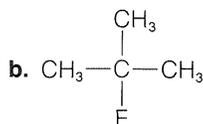
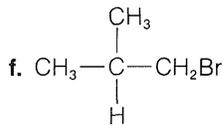
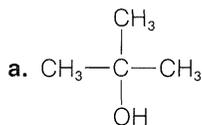
a. 1,3-butadiene from ethyne

b. 2-hexyne from propyne

c. CC1OC1 from 2-butyne

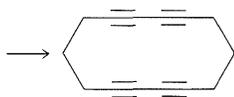
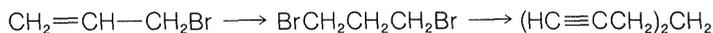
d. cyanocyclohexane from 1,3-butadiene

Exercise 13-18 Indicate how you would synthesize each of the following compounds from ethene, propene, 2-methylpropene, or 2-methylpropane, and appropriate inorganic reagents. Specify reagents and the reaction conditions, and justify the practicality of any isomer separations. If separations are not readily possible, estimate the proportion of the desired compound in the final product.



Exercise 13-19 Assume that it is necessary to synthesize *meso*-1,4-diphenyl-2,3-butanediol. How could you do this if the only organic reagents at your disposal are methylbenzene and ethyne? In devising a suitable scheme, use any inorganic reagents you consider necessary and specify the reaction conditions (catalysts, solvent, use of acids or bases, and temperature) as closely as possible.

Exercise 13-20 The following key intermediates can be used in a synthesis of cyclo-tetradeca-1,3,8,10-tetrayne. Write the reagents and conditions for achieving transformations between the key intermediates. Be as specific as possible. Notice that more than one step may be involved in any given transformation.

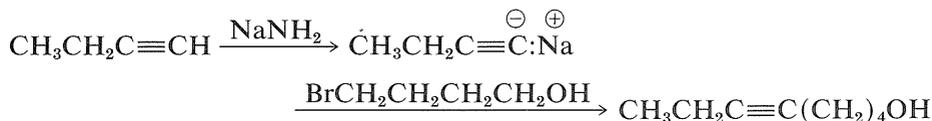


cyclo-tetradeca-1,3,8,10-tetrayne

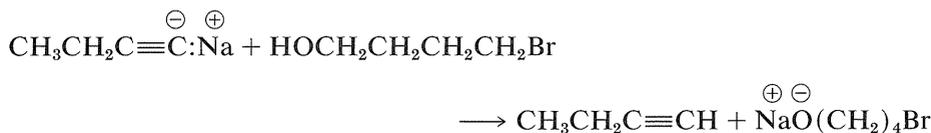
13-10 PROTECTING GROUPS IN ORGANIC SYNTHESIS

One of the major problems in organic synthesis is the suppression of unwanted side reactions. Frequently the desired reaction is accompanied by reaction at other parts of the molecule, especially when more than one functional group is present. Functional groups usually are the most reactive sites in the molecule, and it may be difficult or even impossible to insulate one functional group from a reaction occurring at another. Therefore any proposed synthesis must be evaluated at each step for possible side reactions that may degrade or otherwise modify the structure in an undesired way. To do this will require an understanding of how variations in structure affect chemical reactivity. Such understanding is acquired through experience and knowledge of reaction mechanisms and reaction stereochemistry.

To illustrate the purpose and practice of functional group protection, let us suppose that the synthesis of *cis*-2-octene, which we outlined in Section 13-7, has to be adapted for the synthesis of 5-octyn-1-ol. We could write the following:



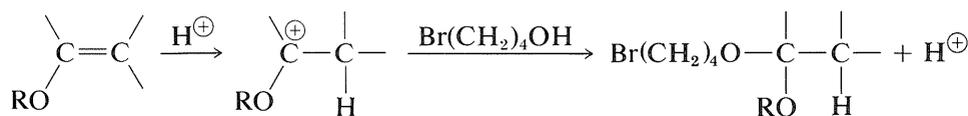
However, the synthesis as written would fail because the alkyne is a weaker acid than the alcohol (Section 11-8), and the alkynide anion would react much more rapidly with the acidic proton of the alcohol than it would displace bromide ion from carbon:



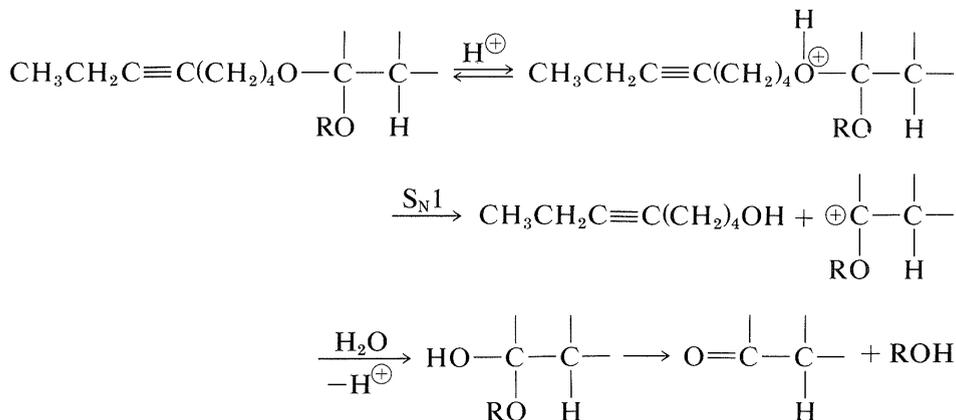
The hydroxyl group of 4-bromo-1-butanol therefore must be protected *before* it is allowed to react with the alkynide salt. There are a number of ways to protect hydroxyl groups, but one method, which is simple and effective, relies

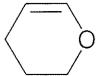
on the fact that unsaturated ethers of the type $\begin{array}{c} \diagup \quad \diagdown \\ \text{C}=\text{C} \\ \diagdown \quad \diagup \\ \text{RO} \end{array}$ are very reactive

in electrophilic addition reactions (Section 10-4). An alcohol readily adds to the double bond of such an ether in the presence of an acid catalyst:



The protected compound is a much weaker acid than the alkyne, and the displacement reaction can be carried out with the alkynide salt without difficulty. To obtain the final product, the protecting group must be removed, and this can be done in dilute aqueous acid solution by an S_N1 type of substitution (Sections 8-7D and 8-7E):



Exercise 13-21 Devise a synthesis of 3-hexyn-1,6-diol from two-carbon compounds using the unsaturated cyclic ether, , as a protecting reagent for hydroxyl groups.

Additional Reading

L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, John Wiley and Sons, Inc., New York, 1967. This is an exhaustive compendium of the properties, sources, and uses of the reagents used in synthetic work. It is strictly a reference work and is invaluable as such to the practicing organic chemist.

R. E. Ireland, *Organic Synthesis*, Prentice-Hall, Inc., Englewood Cliffs, N.J., 1969. The methodology of synthesis of complex compounds is discussed in detail.

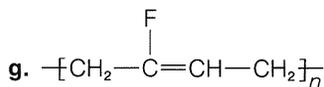
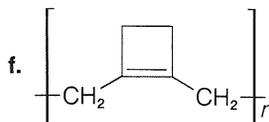
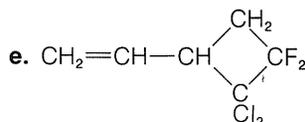
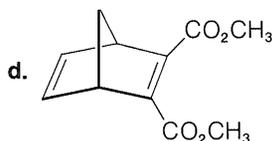
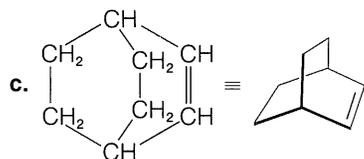
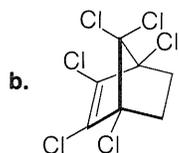
Supplementary Exercises

13-22 Using the proposed mechanism for the Diels–Alder reaction, explain why you would *not* expect a reactive dienophile to form [4 + 2] cycloaddition products

with the following compounds:

- 1,3-butadiyne
- 3,4-dimethylenecyclobutene (Refer to Section 6-6.)
- 3-methylenecyclohexene

13-23 Write the *last* step in a synthesis of each of the following substances (give approximate reaction conditions):



13-24* 1,2-Propadiene adds hydrogen chloride to yield 2-chloropropene. However, the possibility exists that initial attack of a proton might lead to the 2-propenyl cation (Section 6-6), which then would react with chloride ion to form 3-chloropropene. Using the rules for application of the resonance method (Section 6-5B) and the atomic-orbital model for 1,2-propadiene (Figure 13-4), rationalize why a 2-propenyl cation might not be formed easily by addition of a proton to 1,2-propadiene and why 2-chloropropene is the observed product.

13-25 How many stereoisomers would you expect for each of the following compounds? Indicate your reasoning and draw appropriate structural formulas for each one.

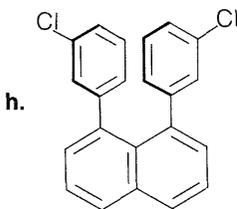
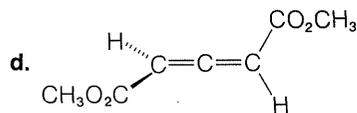
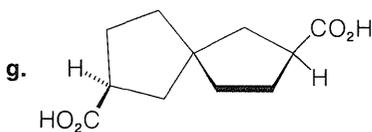
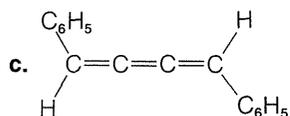
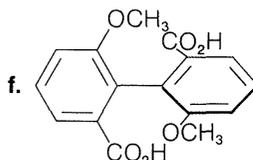
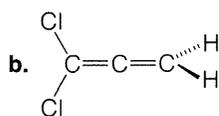
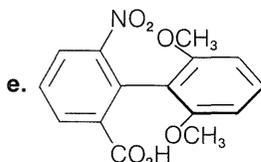
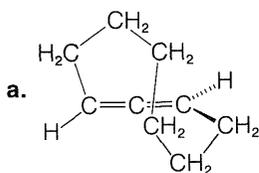
- | | |
|--------------------------------|-----------------------------------|
| a. 1,3-pentadiene | e. 1,3-dichloro-1,2-propadiene |
| b. cyclodecene | f. 1,4-dichloro-1,2,3-butatriene |
| c. 1,2,3-trimethylcyclopropane | g. ethylidene-3-methylcyclohexane |
| d. 2,4,6-octatriene | |

13-26 Write structural formulas for the products you would expect from each of the following reactions:

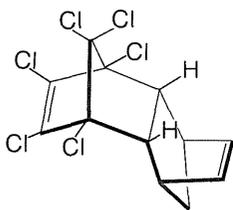
- 1,2-propadiene and hypochlorous acid (1 mole)
- 1,3-pentadiene with hydrogen chloride (1 mole)
- ozonization of 1,3-butadiene followed by reduction with zinc

- d. 1,3-butadiene with hypochlorous acid (2 moles)
 e. 1,3-butadiene with propenoic acid followed by bromine
 f. 2,3-pentadiene and iodine monochloride

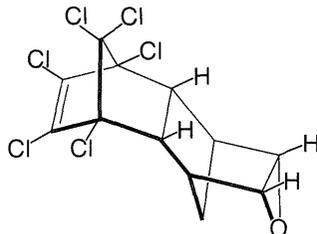
13-27 Which of the following structures are chiral and which are achiral? (Models will be very helpful.)



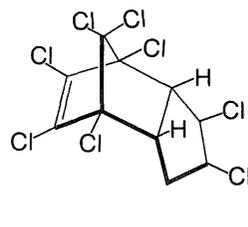
13-28* Several widely used pesticides are highly chlorinated polycyclic compounds derived from hexachloropentadiene. They include Aldrin, Dieldrin, and Chlordane. Use of these substances is to be curtailed greatly because of undesirable environmental effects.



Aldrin



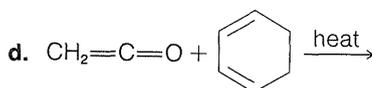
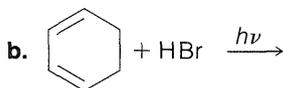
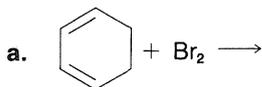
Dieldrin



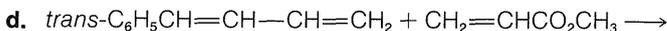
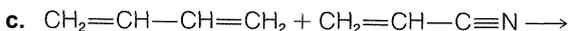
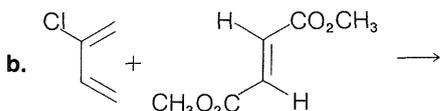
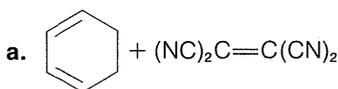
Chlordane

Suggest a plausible synthesis for each of these compounds from readily available C_2 – C_5 compounds, including hexachlorocyclopentadiene. Proceed as in Section 13-7 to see how the carbon framework can be broken down to more familiar smaller fragments and then reconstructed by known reactions.

13-29 Suggest reasonable structures for the products of the following reactions:



13-30 Draw structures for the products of each of the following reactions, each of which takes place at room temperature or higher. Indicate the stereochemistry expected.

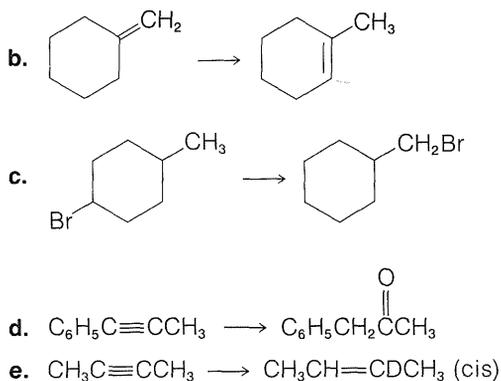


13-31* In Section 10-5 we showed that ethyne is much less reactive toward chlorine than is ethene. The same is true for hydrogen chloride. However, when hydrogen chloride adds to 3-butenyne, it adds to the triple bond instead of the double bond, thereby forming 2-chloro-1,3-butadiene instead of 3-chloro-1-butyne. With reference to the discussion in Section 13-2, explain why the order of reactivity of the double and triple bonds of 3-butenyne toward electrophilic reagents may be different from that of ethene and ethyne?

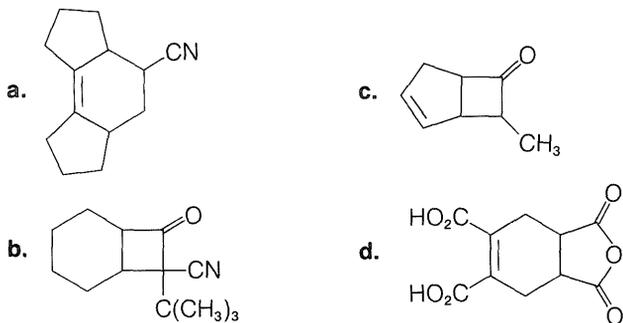
13-32 Draw structures for the different ways in which a monomer unit could be added to a growing chain in a radical-chain polymerization of 2-chloro-1,3-butadiene.

13-33 Show how you would carry out the following transformations. Notice that each is an example of changing the position or nature of the functional group without affecting the carbon skeleton.

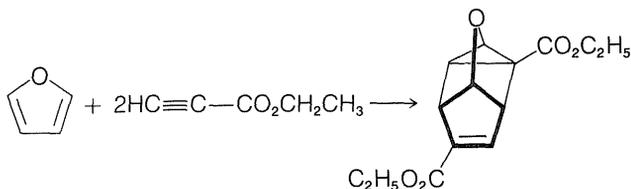




13-34 Cycloaddition reactions are valuable for the synthesis of carbocyclic compounds. Each of the following compounds can be formed by either a [4+2] or [2+2] cycloaddition as a last step in the synthesis. Draw the structures of the reagents you think would undergo cycloaddition to give the compounds shown.



13-35 The following reaction occurs in good yield. Show the steps involved in forming the product.



13-36* Indicate the steps involved in the following synthesis of bicyclo[4.2.0]-2,4,6-octatriene (benzocyclobutene):

