Organic Chemistry, *Fourth Edition*

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Chapter 16
Lecture Outline

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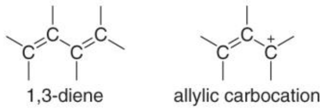
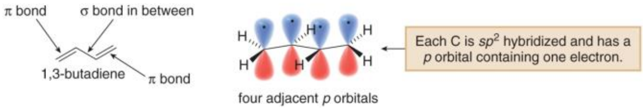
Conjugation

- **Conjugation occurs whenever *p* orbitals can overlap on three or more adjacent atoms.**
- **The *p* orbital at the allylic position is in conjugation with the double bond.**

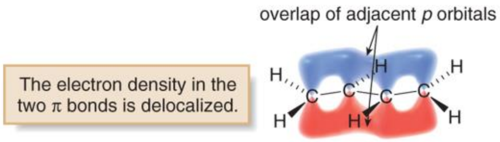


- **The four *p* orbitals on adjacent atoms make a 1,3-diene a conjugated system.**



Delocalization

- **Having three or more *p* orbitals on adjacent atoms allows *p* orbitals to overlap and electrons to delocalize.**

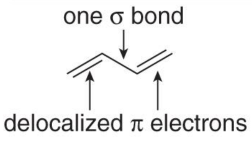


- When *p* orbitals overlap, the electron density in each of the π bonds is spread out over a larger volume, thus lowering the energy of the molecule and making it more stable.

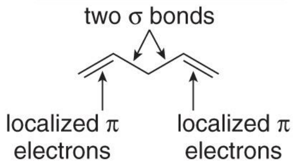
Dienes

- **1,4-Pentadiene is an isolated diene.**
- **The π bonds in 1,4-pentadiene are too far apart to be conjugated and are isolated from each other by a *sp*^{3} carbon.**

1,3-Butadiene—
A conjugated diene

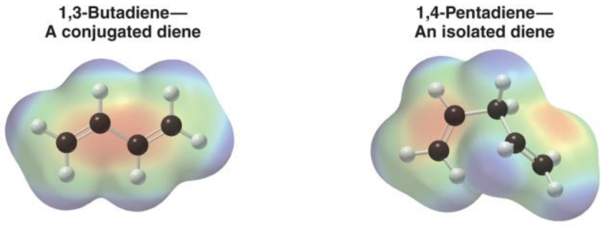


1,4-Pentadiene—
An isolated diene



Electrostatic Potential Plots for Dienes

- **You can see that in 1,3-butadiene the electron-rich area is spread out rather than localized.**



1,3-Butadiene—
A conjugated diene

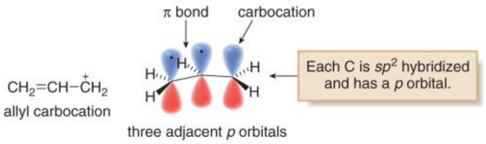
1,4-Pentadiene—
An isolated diene

The red electron-rich region is spread over four adjacent atoms.

The red electron-rich regions are localized in the π bonds on the two ends of the molecule.

Conjugation of Allylic Cations

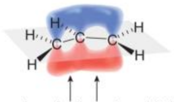
- **The allyl carbocation is another example of a conjugated system.**



Each C is *sp*^{2} hybridized and has a *p* orbital.

- Three *p* orbitals on three adjacent atoms, even if one of the *p* orbitals is empty, make the allyl carbocation conjugated.

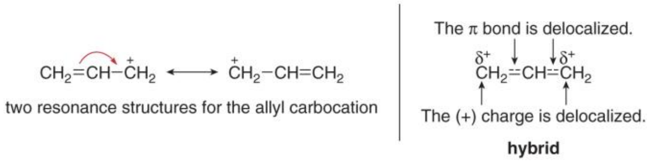
- **Conjugation stabilizes the allyl carbocation.**



overlap of adjacent *p* orbitals

Delocalized Hybrids

- **Drawing resonance structures for the allyl carbocation is a way to illustrate how conjugation delocalizes electrons.**



- **The true allyl cation is a hybrid of the two resonance forms.**
- **In the hybrid, the positive charge is delocalized over the two terminal carbons.**
- **Delocalizing the charge stabilizes the allyl carbocation, making it more stable than a normal 1° carbocation.**

Stability of Allyl Cations

- **Experimental data show that the stability of the allyl cation is comparable to a more highly substituted 2° carbocation.**

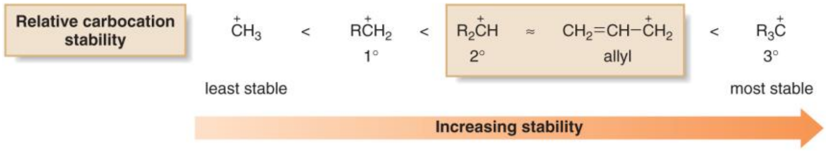
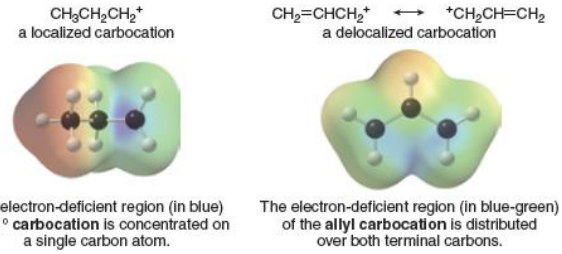


Figure 16.2
Electrostatic potential maps for a localized and a delocalized carbocation

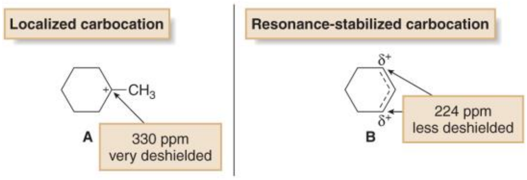


The electron-deficient region (in blue) of a 1° **carbocation** is concentrated on a single carbon atom.

The electron-deficient region (in blue-green) of the **allyl carbocation** is distributed over both terminal carbons.

Chemical Shifts of Carbocations

Figure 16.3
^{13}C chemical shifts for a localized and a resonance-stabilized carbocation

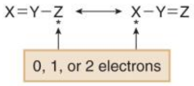


- The absorption shifts *upfield* as the amount of positive charge *decreases*.

Common Examples of Resonance

Type [1] The Three Atom “Allyl” System, X = Y − Z*

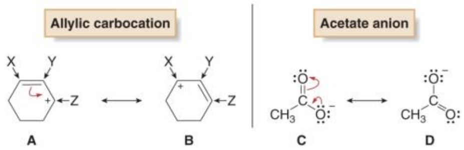
- For any group of three atoms having a double bond X=Y and an atom Z that contains a *p* orbital with zero, one, or two electrons, two resonance structures are possible:



The asterisk [*] corresponds to a charge, a radical, or a lone pair.

* = +, −, ·, or ··

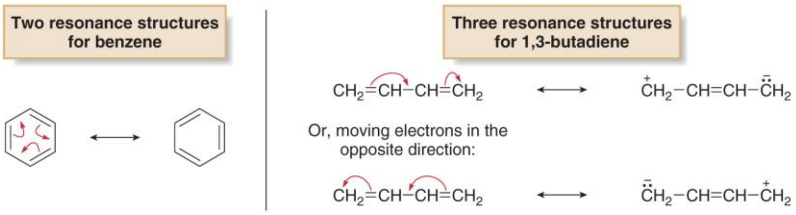
Examples are the allyl cation and the acetate anion. The two resonance structures differ in the location of the double bond, and either the charge, the radical, or the lone pair, generalized by [*].



Common Examples of Resonance

Type [2] Conjugated Double Bonds

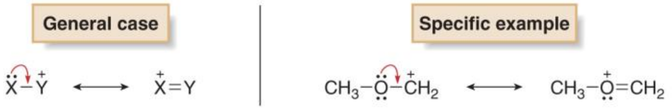
- **Cyclic, completely conjugated rings like benzene have two resonance structures, drawn by moving the electrons in a cyclic manner around the ring.**
- **Three resonance structures can be drawn for other conjugated dienes, two of which involve separation of charge.**



Common Examples of Resonance

Type [3] Cations Having a Positive Charge Adjacent to a Lone Pair

- When a lone pair and a positive charge are located on adjacent atoms, two resonance structures can be drawn.

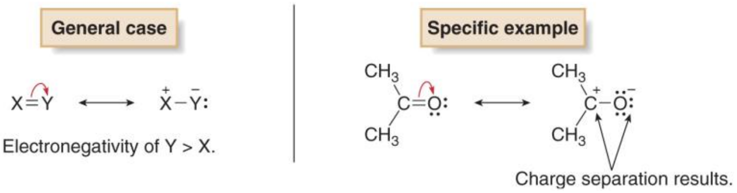


- **The overall charge is the same in both resonance structures.**
- **Based on formal charge, a neutral X in one structure must bear a (+) charge in the other.**

Common Examples of Resonance

Type [4] Double Bonds Having One Atom More Electronegative Than the Other

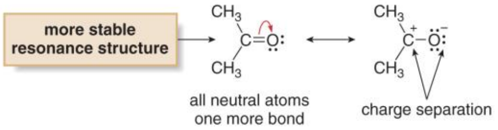
- For a double bond X=Y in which the electronegativity of Y > X, a second resonance structure can be drawn by moving the π electrons onto Y.



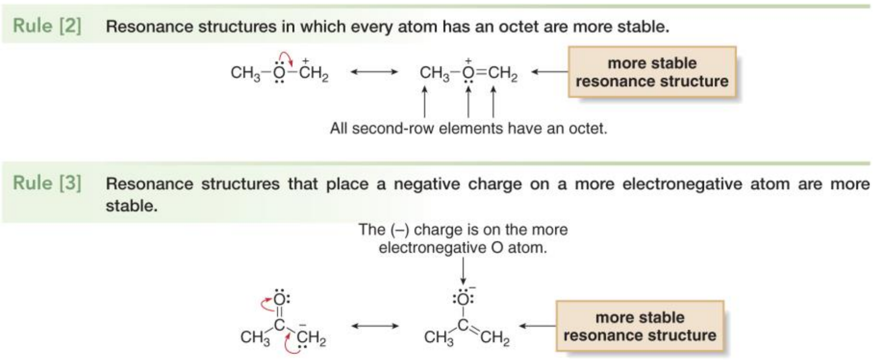
The Resonance Hybrid is a Combination of Resonance Forms

- The actual hybrid resembles the most stable resonance structure(s).
- Three rules guide the assessment of the relative stability of resonance structures.

Rule [1] Resonance structures with more bonds and fewer charges are more stable.



Resonance Hybrid Contributions

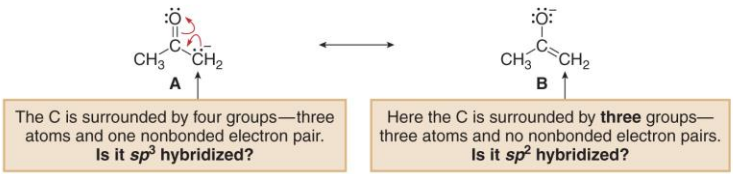


Rule [2] Resonance structures in which every atom has an octet are more stable.

Rule [3] Resonance structures that place a negative charge on a more electronegative atom are more stable.

Determining Resonance Structure

There are two Lewis structures (A and B) for the resonance-stabilized anion ($(CH_3COCH_2)^-$).



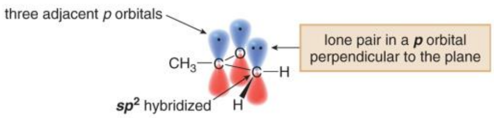
The C is surrounded by four groups—three atoms and one nonbonded electron pair. **Is it *sp*^{3} hybridized?**

Here the C is surrounded by **three** groups—three atoms and no nonbonded electron pairs. **Is it *sp*^{2} hybridized?**

- **Based on structure A, the indicated carbon is *sp*^{3} hybridized, with the lone pair of electrons in an *sp*^{3} hybrid orbital.**
- **Based on structure B, however, it is *sp*^{2} hybridized with the unhybridized *p* orbital forming the π portion of the double bond.**

p Orbitals Required for Conjugation

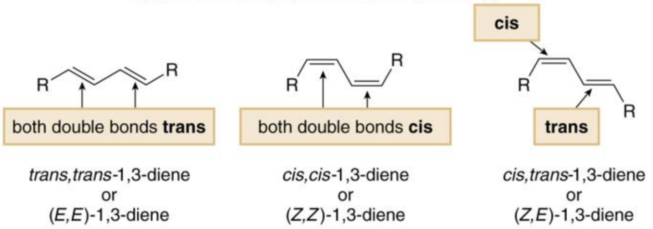
- The electron pair on the carbon atom adjacent to the C=O can only be delocalized if it has a *p* orbital that can overlap with two other *p* orbitals on adjacent atoms.
- The terminal carbon atom is sp^2 hybridized with trigonal planar geometry.
- Three adjacent *p* orbitals make the anion conjugated.
- The actual hybrid has more of the charge on the oxygen and more C=C double bond character.



- In any system X=Y−Z:, Z is sp^2 hybridized, and the nonbonded electron pair occupies a *p* orbital to make the system conjugated.

Conjugated Dienes

- Conjugated dienes are compounds having two double bonds joined by one σ bond.
- Conjugated dienes are sometimes also called 1,3-dienes.
- 1,3-Butadiene (CH_2=CH-CH=CH_2) is the simplest conjugated diene.
- Three stereoisomers are possible for 1,3-dienes with alkyl groups bonded to each end carbon of the diene.



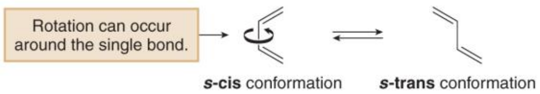
trans,trans-1,3-diene
or
(*E,E*)-1,3-diene

cis,cis-1,3-diene
or
(*Z,Z*)-1,3-diene

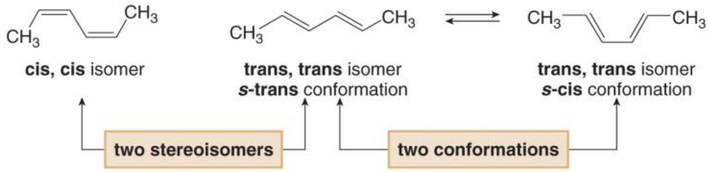
cis,trans-1,3-diene
or
(*Z,E*)-1,3-diene

Conformation of Conjugated Dienes

- **Two possible conformations result from rotation around the C–C bond that joins the two double bonds.**

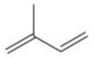


- **Stereoisomers are discrete molecules, whereas conformations interconvert.**

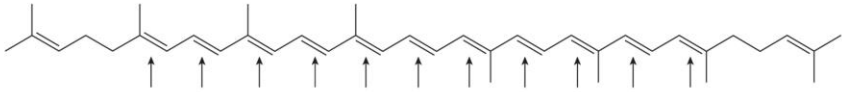


Interesting Dienes

- **Isoprene is given off by plants as the temperature rises, a process thought to increase a plant's tolerance for heat stress.**



isoprene
(2-methyl-1,3-butadiene)

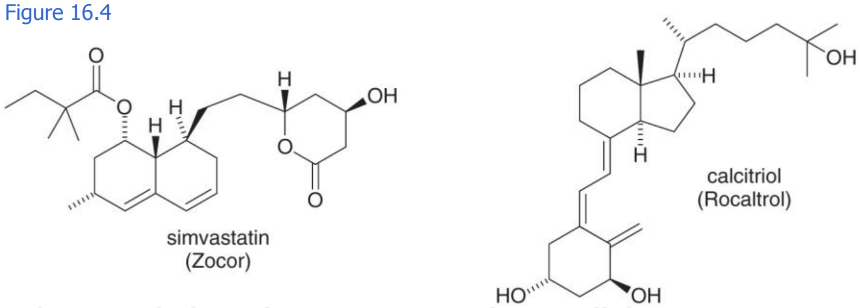


lycopene

- **Lycopene, responsible for the red color of tomatoes and other fruits, is an antioxidant.**

Biologically Active Compounds with Conjugated Double Bonds

Figure 16.4



- Simvastatin is a cholesterol lowering medicine.
- Calcitriol is used to treat hypocalcemia – low calcium levels in the blood.

Features of Conjugated Dienes

Four features distinguish conjugated dienes from isolated dienes.

[1] The C–C single bond joining the two double bonds is unusually short.

The C–C σ bond is **shorter** than the C–C σ bond in ethane.

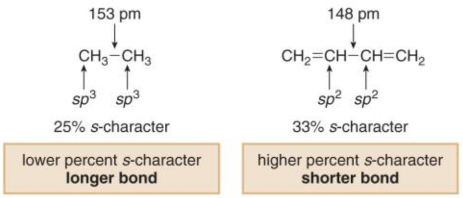
[2] Conjugated dienes are more stable than similar isolated dienes.

[3] Some reactions of conjugated dienes are different from reactions of isolated double bonds.

[4] Conjugated dienes absorb longer wavelengths of ultraviolet light.

Percent *s* Character vs. Bond Length

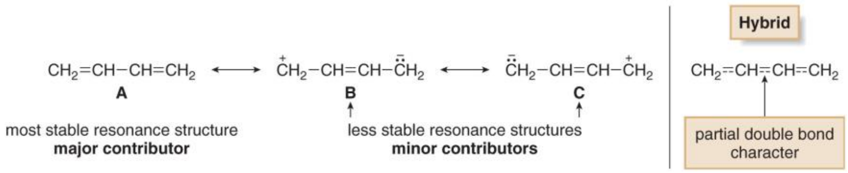
- The observed bond distances can be explained by looking at hybridization.
- Each carbon atom in 1,3-butadiene is *sp*^{2} hybridized;
  - so the central C–C single bond is formed by the overlap of two *sp*^{2} hybridized orbitals;
  - rather than the *sp*^{3} hybridized orbitals used to form the C–C bond in CH_3CH_3.



- Based on hybridization, a $C_{sp^2}-C_{sp^2}$ bond should be shorter than a $C_{sp^3}-C_{sp^3}$ bond because it is formed from orbitals having a higher percent *s*-character.

Carbon–Carbon σ Bond Length in 1,3-Butadiene

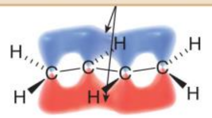
- A resonance argument can also be used to explain the shorter C–C σ bond length in 1,3-butadiene.
- Based on resonance, the central C–C bond in 1,3-butadiene is shorter because it has partial double bond character.



Orbital View of Butadiene

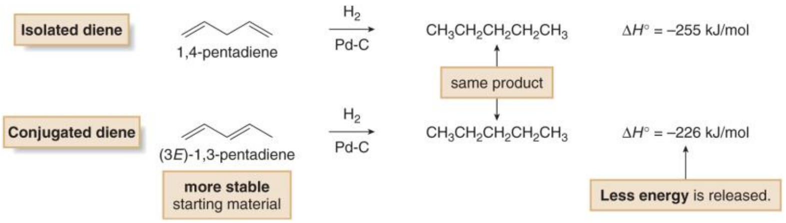
- **1,3-butadiene is a conjugated molecule with four overlapping *p* orbitals on adjacent atoms.**
- **Consequently, the π electrons are not localized between the carbon atoms of the double bonds, but rather delocalized over four atoms.**
- **This places more electron density between the central two carbon atoms of 1,3-butadiene than would normally be present.**
- **This shortens the bond.**

The overlap of adjacent *p* orbitals increases the electron density in the C−C σ bond.



Stability of Conjugated Dienes vs. Isolated Dienes

- **When hydrogenation gives the same alkane from two dienes, the more stable diene has the smaller heat of hydrogenation.**
- **The conjugated diene is more stable by 7 kcal/mol.**



Isolated diene — 1,4-pentadiene $\xrightarrow[\text{Pd-C}]{H_2}$ $CH_3CH_2CH_2CH_2CH_3$ — $\Delta H° = -255$ kJ/mol

same product

Conjugated diene — (3*E*)-1,3-pentadiene $\xrightarrow[\text{Pd-C}]{H_2}$ $CH_3CH_2CH_2CH_2CH_3$ — $\Delta H° = -226$ kJ/mol

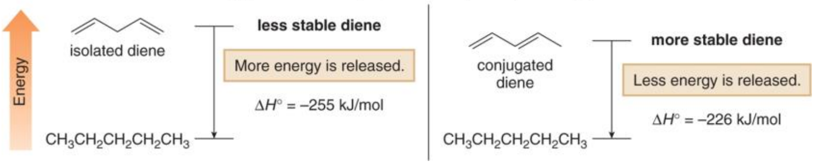
more stable starting material

Less energy is released.

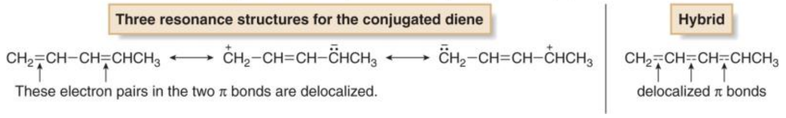
Stability of Conjugated Dienes vs. Isolated Dienes

- **An energy diagram can also show how a conjugated diene is more stable than an isolated diene.**

Figure 16.5



- **Resonance structures and hybrid for a conjugated diene.**

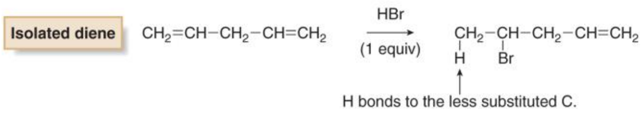


$CH_2{=}CH{-}CH{=}CHCH_3 \longleftrightarrow \overset{+}{C}H_2{-}CH{=}CH{-}\ddot{C}HCH_3 \longleftrightarrow \ddot{C}H_2{-}CH{=}CH{-}\overset{+}{C}HCH_3$

$CH_2 \overset{\cdots}{-} CH \overset{\cdots}{-} CH \overset{\cdots}{-} CHCH_3$

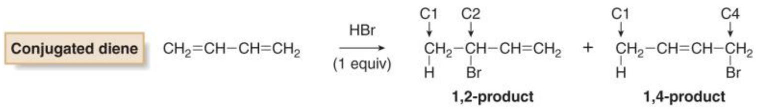
Products of Electrophilic Addition

- **Electrophilic addition of one equivalent of HBr to an isolated diene yields *one* product and Markovnikov's rule is followed.**

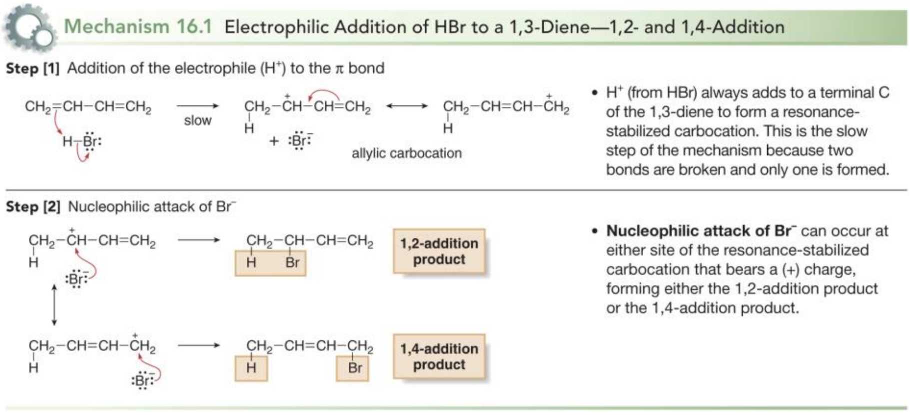


$$CH_2{=}CH{-}CH_2{-}CH{=}CH_2 \xrightarrow[\text{(1 equiv)}]{\text{HBr}} \underset{H}{CH_2}{-}\underset{Br}{CH}{-}CH_2{-}CH{=}CH_2$$

- **Electrophilic addition in conjugated dienes gives a mixture of *two* products, called the 1,2- and 1,4-addition products.**



$$CH_2{=}CH{-}CH{=}CH_2 \xrightarrow[\text{(1 equiv)}]{\text{HBr}} \underset{H}{CH_2}{-}\underset{Br}{CH}{-}CH{=}CH_2 + \underset{H}{CH_2}{-}CH{=}CH{-}\underset{Br}{CH_2}$$



Mechanism 16.1 Electrophilic Addition of HBr to a 1,3-Diene—1,2- and 1,4-Addition

Step [1] Addition of the electrophile (H^+) to the π bond

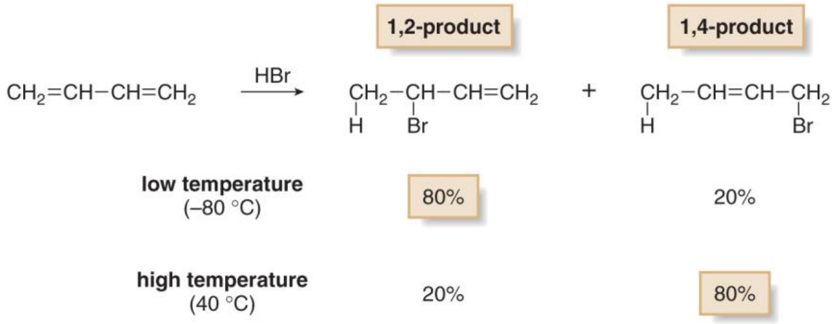
- H^+ (from HBr) always adds to a terminal C of the 1,3-diene to form a resonance-stabilized carbocation. This is the slow step of the mechanism because two bonds are broken and only one is formed.

Step [2] Nucleophilic attack of Br^-

- **Nucleophilic attack of Br^-** can occur at either site of the resonance-stabilized carbocation that bears a (+) charge, forming either the 1,2-addition product or the 1,4-addition product.

Reaction Conditions and Addition Products

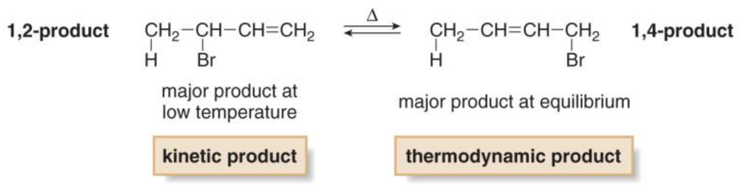
- **The amount of 1,2- and 1,4-addition products formed in electrophilic addition reactions of conjugated dienes depends greatly on the reaction conditions.**



	1,2-product	1,4-product
low temperature (–80 °C)	80%	20%
high temperature (40 °C)	20%	80%

Kinetic vs Thermodynamic Products

- **When a mixture containing predominantly the 1,2-product is heated, the 1,4-addition product becomes the major product at equilibrium.**



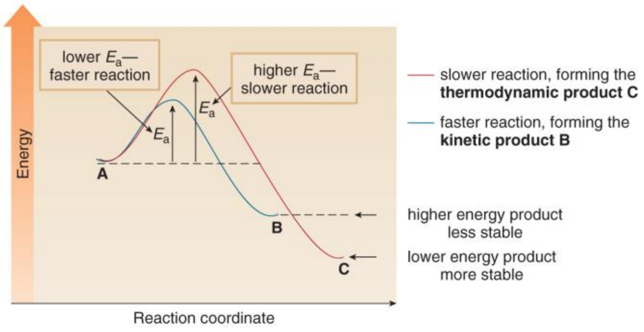
$$\underset{H}{CH_2}-\underset{Br}{CH}-CH=CH_2 \xrightleftharpoons{\Delta} \underset{H}{CH_2}-CH=CH-\underset{Br}{CH_2}$$

- The 1,2-product is formed faster because it predominates at low temperature. The product that is formed faster is called the *kinetic product.*
- The 1,4-product must be more stable because it predominates at equilibrium. The product that predominates at equilibrium is called the *thermodynamic product.*

How Kinetic and Thermodynamic Products Form

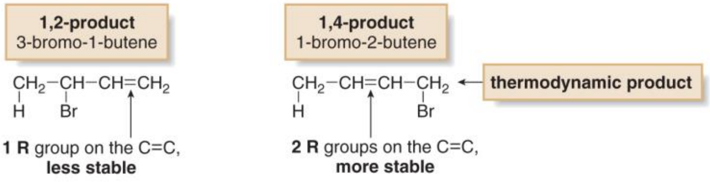
- **The rate of a reaction is determined by its energy of activation (E_a), whereas the amount of product present at equilibrium is determined by its stability.**

Figure 16.6



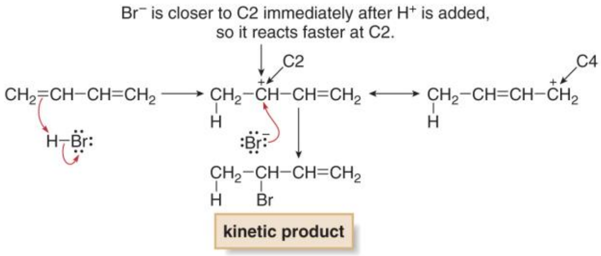
Greater Stability of 1,4-Products

- **The 1,4-product (1-bromo-2-butene) is more stable because it has two alkyl groups bonded to the carbon–carbon double bond,**
  - **whereas the 1,2-product (3-bromo-1-butene) has only one.**



- The more substituted alkene—1-bromo-2-butene in this case—is the thermodynamic product.

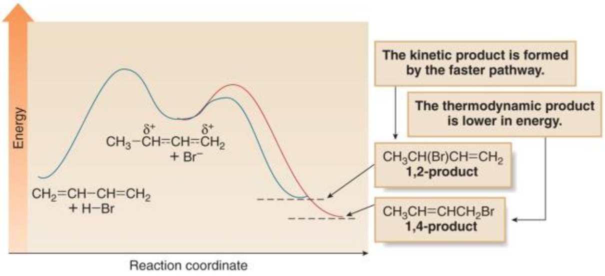
Proximity Effect for 1,2-Products



- The 1,2-product forms faster because of the proximity of Br⁻ to C2.

Energy Diagram for the Two-Step Mechanism

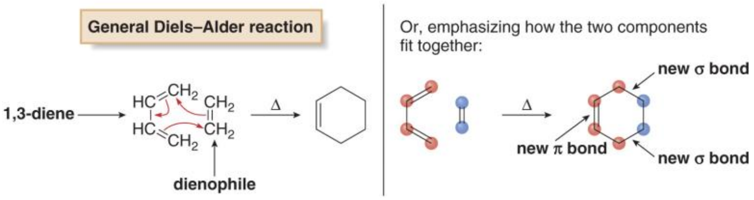
Figure 16.7



- At low temperature, the lower energy of activation pathway is followed, since most molecules do not have enough energy to overcome the higher barrier.
- At higher temperature, most molecules have enough kinetic energy to reach either transition state and equilibrium favors the more stable product.

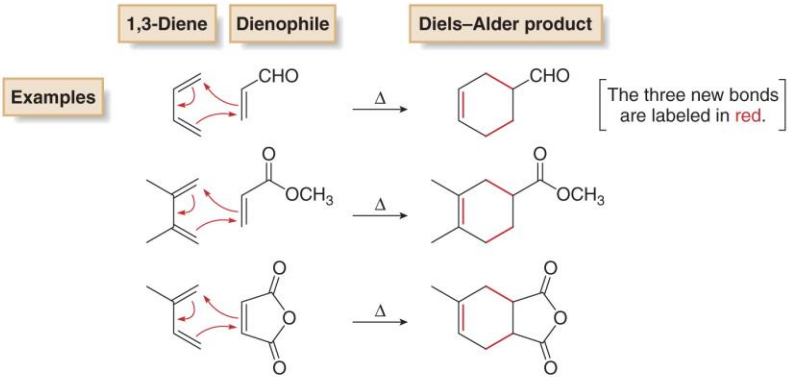
The Diels–Alder Reaction

- The **Diels–Alder reaction** is an addition reaction between a 1,3-diene and an alkene (called a **dienophile**), to form a new six-membered ring.



- Three curved arrows are needed to show the cyclic movement of electron pairs because three π bonds break and two σ bonds and one π bond form in a concerted process.
- Because each new σ bond is ~20 kcal/mol stronger than a π bond that is broken, a typical Diels–Alder reaction releases ~40 kcal/mol of energy.

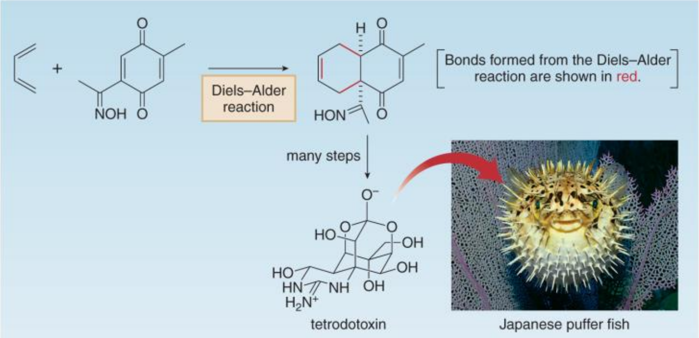
Examples of the Diels–Alder Reaction



The three new bonds are labeled in red.

Synthesis Using the Diels–Alder Reaction

Figure 16.8

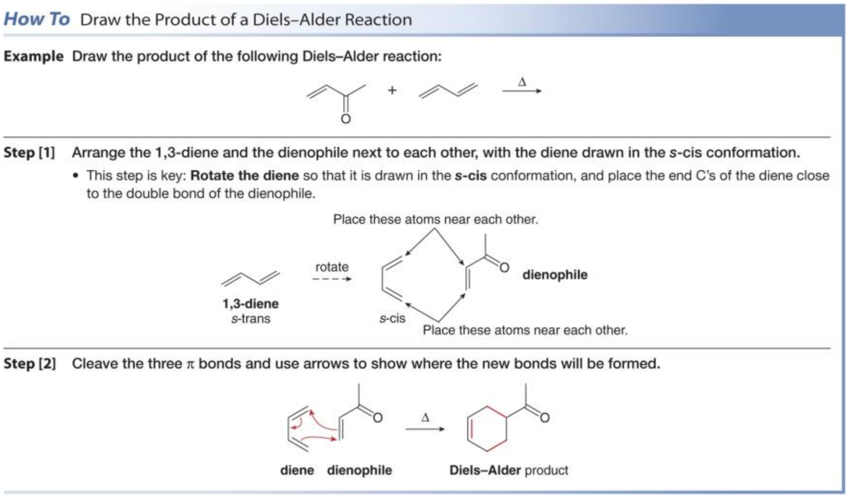


Bonds formed from the Diels–Alder reaction are shown in red.

tetrodotoxin

Japanese puffer fish

- Tetrodotoxin, a complex natural product containing several six-membered rings joined together, is a poison isolated from the ovaries and liver of the puffer fish, so named because the fish inflates itself into a ball when alarmed. Eating fish tainted with trace amounts of this potent toxin results in weakness, paralysis, and eventually death. One step in the synthesis of tetrodotoxin involves forming a six-membered ring by a Diels–Alder reaction.



How To Draw the Product of a Diels–Alder Reaction

Example Draw the product of the following Diels–Alder reaction:

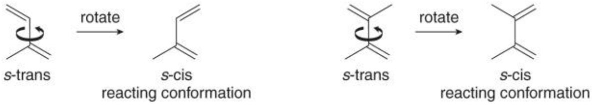
Step [1] Arrange the 1,3-diene and the dienophile next to each other, with the diene drawn in the *s*-cis conformation.

- This step is key: **Rotate the diene** so that it is drawn in the ***s*-cis** conformation, and place the end C's of the diene close to the double bond of the dienophile.

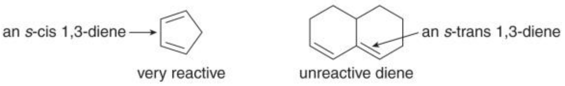
Step [2] Cleave the three π bonds and use arrows to show where the new bonds will be formed.

Rules of the Diels–Alder Reaction

1. **The diene can react only when it adopts the *s*-cis conformation.**



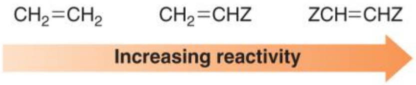
- **This rotation is prevented in cyclic alkenes.**
- **When the two double bonds are constrained to an *s*-cis conformation, the diene is unusually reactive.**
- **When the two double bonds are constrained in the *s*-trans conformation, the diene is unreactive.**



Rules of the Diels–Alder Reaction

2. **Electron-withdrawing substituents in the dienophile increase the reaction rate.**

- **In a Diels–Alder reaction, the conjugated diene acts as a nucleophile and the dienophile acts as an electrophile.**
- **Electron-withdrawing groups make the dienophile more electrophilic (and thus more reactive) by withdrawing electron density from the carbon–carbon double bond.**
- **If Z is an electron-withdrawing group, then the reactivity of the dienophile increases as follows:**



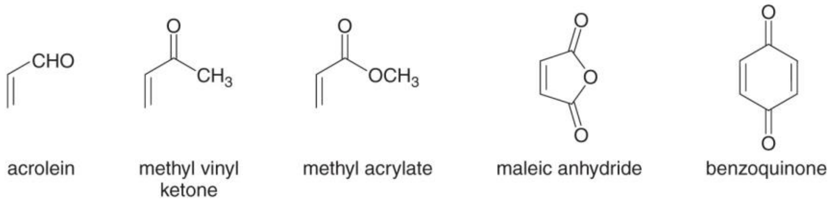
$CH_2{=}CH_2$ $CH_2{=}CHZ$ $ZCH{=}CHZ$

Increasing reactivity

Dienophiles in the Diels–Alder Reaction

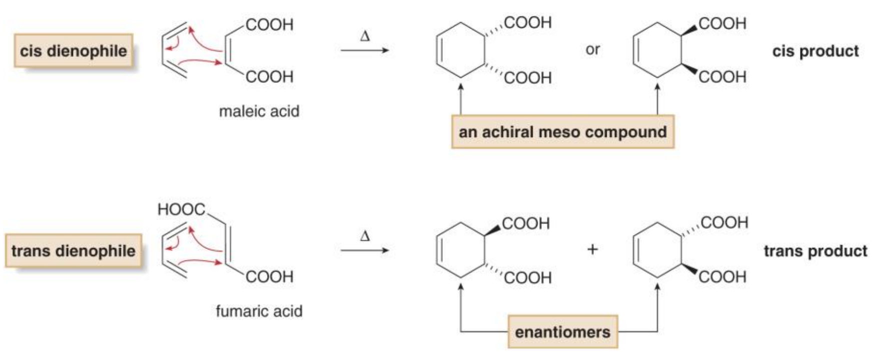
- **A carbonyl group adjacent to the double bond is an effective electron-withdrawing group because it bears a partial positive charge (δ+), which withdraws electron density from the carbon–carbon double bond of the dienophile.**
- **Some common dienophiles are shown below:**

Figure 16.9



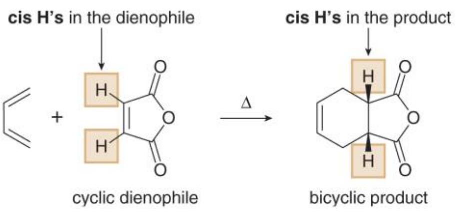
Rules of the Diels–Alder Reaction

3. The stereochemistry of the dienophile is retained.



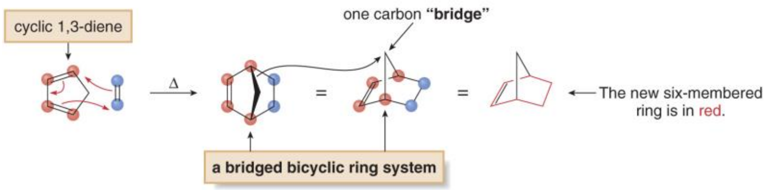
Formation of Fused Ring Systems

- **A cyclic dienophile forms a bicyclic product.**
- **A bicyclic system in which two rings share a common C–C bond is called a fused ring system.**
- **The two H atoms of the ring fusion must be cis, because they were cis in the starting dienophile.**
- **A bicyclic system of this sort is said to be cis fused.**



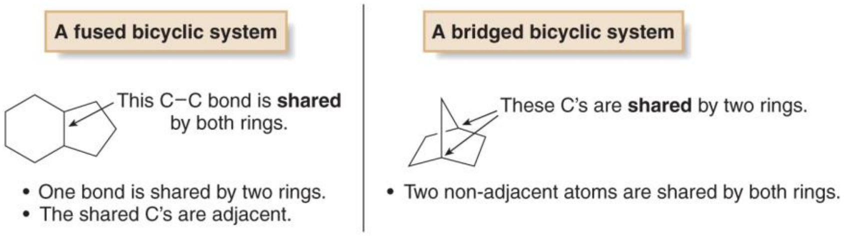
Formation of Bridged Bicyclic Ring Systems

- **When ethylene reacts with 1,3-cyclopentadiene, a new six-membered ring forms and above the ring there is a one atom “bridge.”**
- **Thus, the product is bicyclic, but the carbon atoms shared by both rings are nonadjacent.**
- **A bicyclic ring system in which the two rings share nonadjacent carbon atoms is called a bridged ring system.**



Fused and Bridged Bicyclic Ring Systems

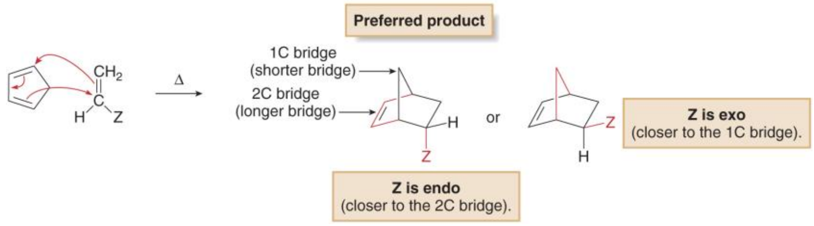
Figure 16.10



Rules of the Diels–Alder Reaction

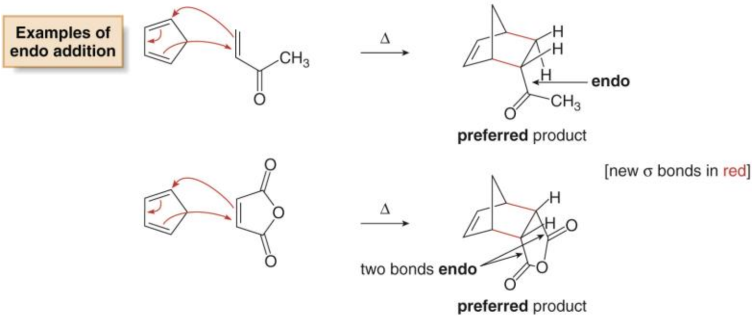
4. Preference for Endo Orientation

- When cyclopentadiene reacts with a substituted alkene as the dienophile (CH_2=CHZ), the substituent Z can be oriented in one of two ways in the product, exo or endo.
- In these cases, the endo product is preferred.



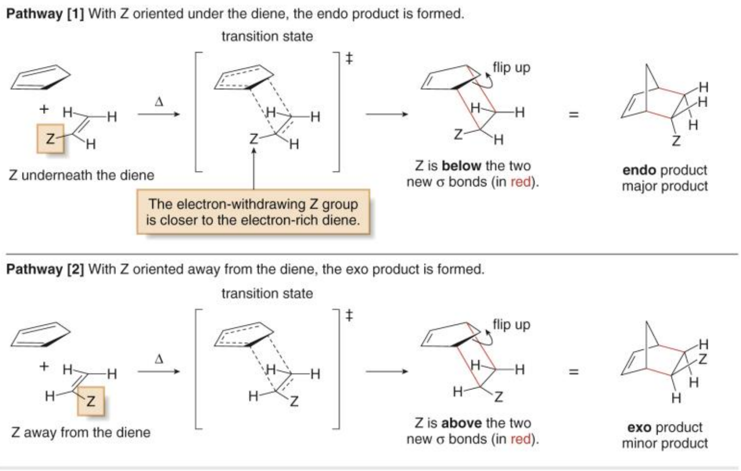
Endo Addition

- The transition state leading to the endo product allows more interaction between the electron-rich diene and the electron-withdrawing substituent Z on the dienophile.
- This is an energetically favorable arrangement.



Mechanism for Endo and Exo Addition

Figure 16.11



Pathway [1] With Z oriented under the diene, the endo product is formed.

Pathway [2] With Z oriented away from the diene, the exo product is formed.

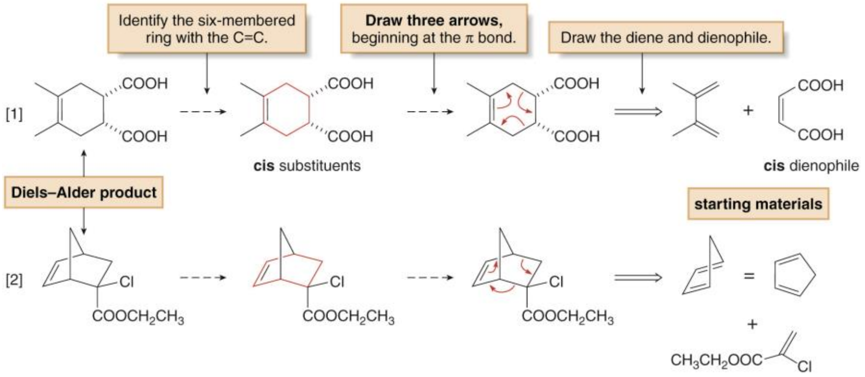
Retrosynthetic Analysis

To draw the starting materials from a given Diels–Alder adduct:

- **Locate the six-membered ring that contains the C=C.**
- **Draw three arrows around the cyclohexane ring, beginning with the π bond and two σ bonds, and forming three π bonds.**
- **Retain the stereochemistry of substituents on the C=C of the dienophile.**
  - **Cis substituents on the six-membered ring give a cis dienophile.**

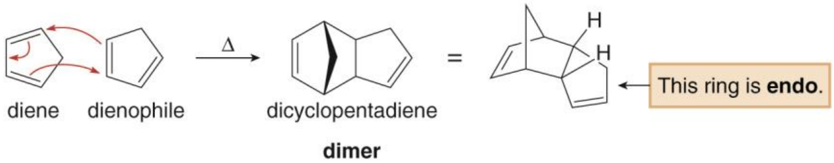
Finding the Diene and Dienophile

Figure 16.12



Diels–Alder Reaction Dimers

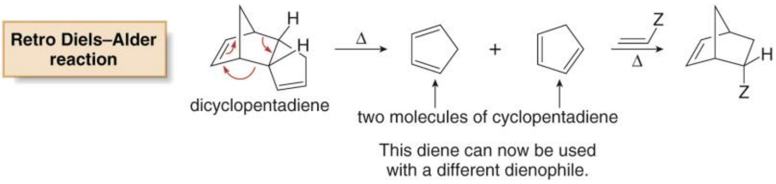
- **A reactive molecule like 1,3-cyclopentadiene readily undergoes a Diels–Alder reaction with itself: that is, 1,3-cyclopentadiene dimerizes because one molecule acts as the diene and another acts as the dienophile.**



- **The formation of dicyclopentadiene is so rapid that it takes only a few hours at room temperature for cyclopentadiene to completely dimerize.**

The Retro Diels–Alder Reaction

- When heated, dicyclopentadiene undergoes a retro Diels–Alder reaction, and two molecules of cyclopentadiene are re-formed.
- If the newly produced cyclopentadiene is immediately treated with a different dienophile, it reacts to form a new Diels–Alder adduct with this dienophile.
- This is how cyclopentadiene, used in Diels–Alder reactions, is produced.



Retro Diels–Alder reaction

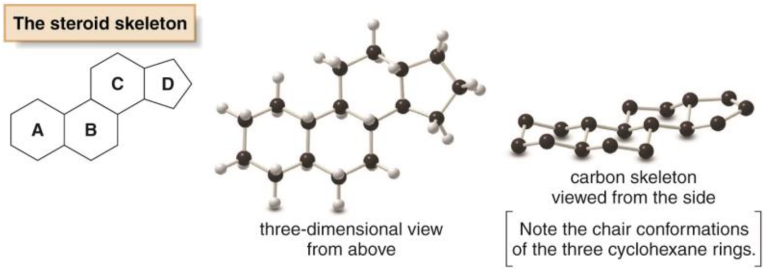
dicyclopentadiene

two molecules of cyclopentadiene

This diene can now be used with a different dienophile.

Steroid Synthesis

- Diels–Alder reactions have been widely used in the laboratory synthesis of steroids.
- Steroids are tetracyclic lipids containing three six-membered rings and one five-membered ring.
- The four rings are designated as A, B, C, and D.



The steroid skeleton

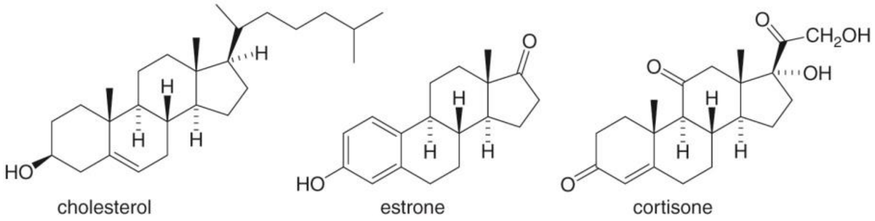
three-dimensional view from above

carbon skeleton viewed from the side

Note the chair conformations of the three cyclohexane rings.

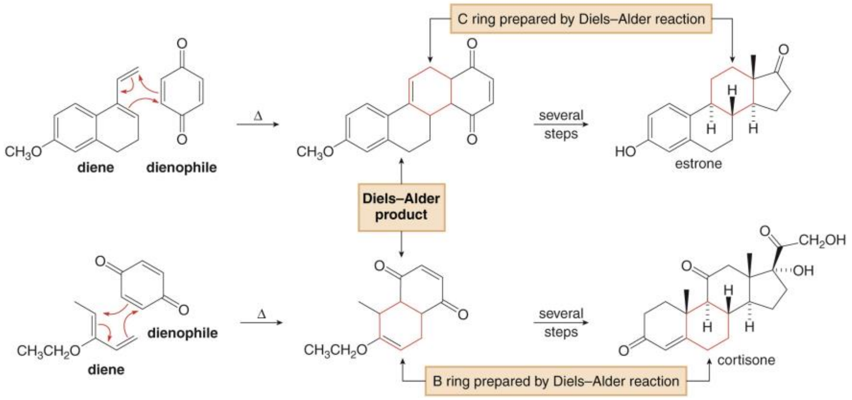
Some Common Steroids

- Steroids exhibit a wide range of biological properties, depending on the substitution pattern of the functional groups on the rings.
- Some examples of steroids are below:



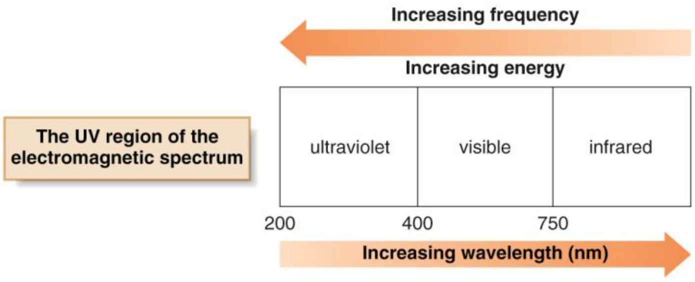
Steroid Synthesis

- The key Diels–Alder reactions used to prepare the C ring of estrone and the B ring of cortisone are as follows:



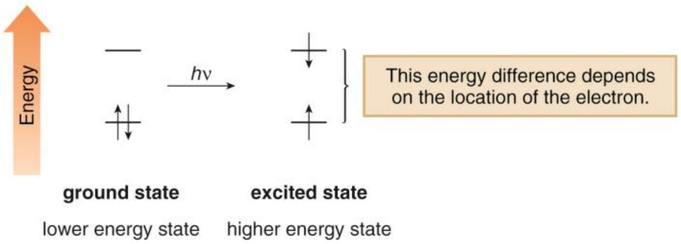
Ultraviolet Light Absorption

- The absorption of ultraviolet (UV) light by a molecule can promote an electron from a lower electronic state to a higher one.
- Ultraviolet light has a slightly shorter wavelength (and thus higher frequency) than visible light.
- The most useful region of UV light for this purpose is 200–400 nm.



Ultraviolet Light and Energy State

- When electrons in a lower energy state (the ground state) absorb light having the appropriate energy, an electron is promoted to a higher electronic state (excited state).



- The energy difference between the two states depends on the location of the electron.

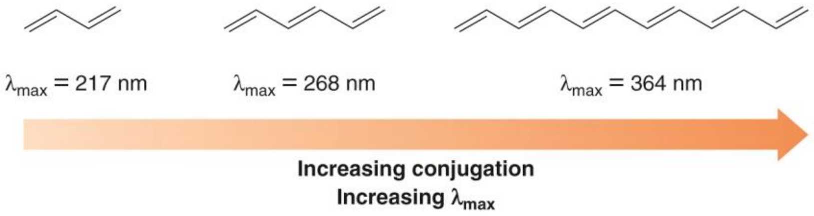
Conjugated Dienes and Ultraviolet Light

- **The promotion of electrons in σ bonds and unconjugated π bonds requires light having a wavelength of <200 nm; that is, a shorter wavelength and higher energy than light in the UV region of the electromagnetic spectrum.**
- **With conjugated dienes, the energy difference between the ground and excited states decreases, so longer wavelengths of light can be used to promote electrons.**
- **The wavelength of UV light absorbed by a compound is often referred to as its λ_{max}.**

- **Conjugated dienes and polyenes absorb light in the UV region of the electromagnetic spectrum (200–400 nm).**

Increasing Conjugation and Ultraviolet Light

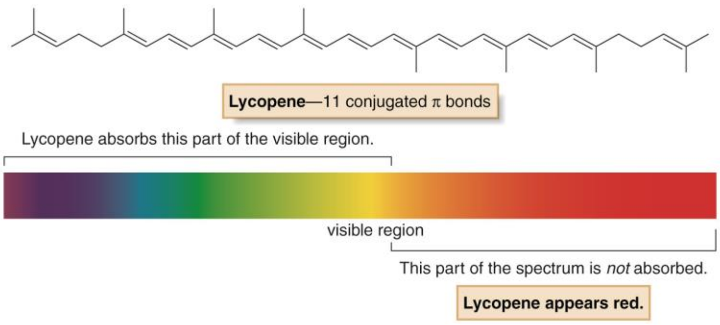
- **With molecules having eight or more conjugated π bonds, the absorption shifts from the UV to the visible region.**
- **The compound takes on the color of the light it does not absorb.**



Conjugated Dienes and Visible Light

- **Lycopene absorbs visible light at λ_{max} = 470 nm, in the blue-green region of the visible spectrum.**
- **Because it does not absorb light in the red region, lycopene appears bright red.**

Figure 16.13

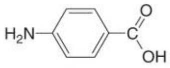


Sunscreens

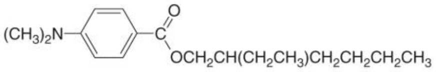
- **UV radiation from the sun is high enough in energy to cleave bonds, forming radicals that can prematurely age skin and cause cancer.**
- **However, since much of this radiation is filtered out by the ozone layer, only UV light having wavelengths >290 nm reaches the earth's surface.**
- **Much of this UV light is absorbed by melanin, the highly conjugated colored pigment in the skin that serves as the body's natural protection against the harmful effects of UV radiation.**

Sunscreens

- **Prolonged exposure to the sun can allow more UV radiation to reach your skin than melanin can absorb.**
- **Commercial sunscreens can offer some protection, because they contain conjugated compounds that absorb UV light, thus shielding the skin (for a time) from the harmful effects of UV radiation.**
- **Commercial sunscreens are given an SPF rating (sun protection factor), according to the amount of sunscreen present. The higher the number, the greater the protection.**
- **Two sunscreens that have been used for this purpose are para-aminobenzoic acid (PABA) and padimate O.**



para-aminobenzoic acid
(PABA)



padimate O