

Organic Chemistry

SECOND EDITION

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About the Cover: Calicheamicin (*at right*), one of the most potent cancer fighters ever discovered, is shown approaching a strand of DNA, the genetic material of living cells. This anticancer agent has only recently been found in nature. The cover is adapted from a computer-generated image provided by K. C. Nicolaou (The Scripps Research Institute and the University of California, San Diego) and Michael Peak (The Scripps Research Institute).

Calicheamicin acts by undergoing an extraordinary transformation—into a short-lived chemical species called a *radical*, which then attacks the DNA of tumor cells. As you will see in Chapter 8, radicals underlie the course of many organic reactions, including damage to normal cells that promotes aging. Chapter 14 explains in detail the action of calicheamicin and other naturally occurring antibiotics, and Chapter 25 discusses chemical defenses against damage to human cells.

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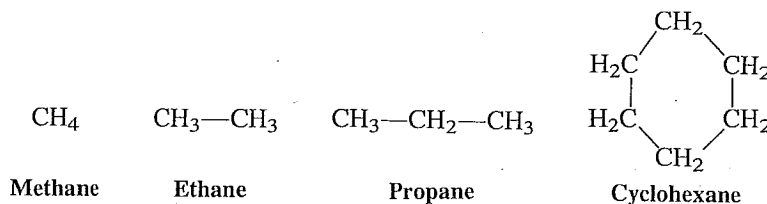
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Hydrocarbons are molecules that contain only hydrogen and carbon

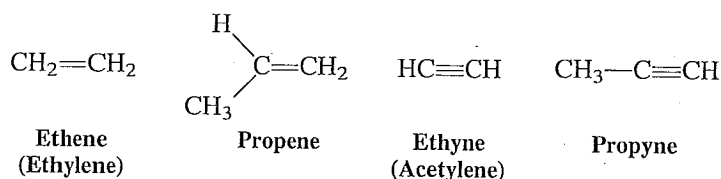
We begin our study with hydrocarbons, which have the general empirical formula C_xH_y . Those containing only single bonds, such as methane, ethane, and propane, are called **alkanes**. Molecules such as cyclohexane, whose carbons form a ring, are called **cycloalkanes**. *Alkanes lack functional groups*; as a result, they are relatively nonpolar and unreactive. The properties and chemistry of the alkanes are described in the next section and in Chapters 3 and 4.

Alkanes



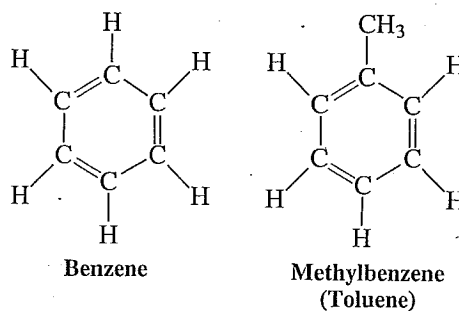
Double and triple bonds are the functional groups of **alkenes** and **alkynes**, respectively. Their properties and chemistry are the topics of Chapters 11–13.

Alkenes and Alkynes



A special hydrocarbon is **benzene**, C_6H_6 , in which three double bonds are incorporated into a six-membered ring. Benzene and its derivatives are traditionally called **aromatic**, because some substituted benzenes do have a strong fragrance. Aromatic compounds are discussed in Chapters 15, 16, 22, and 25.

Aromatic Compounds



Many functional groups contain polar bonds

Polar bonds determine the behavior of many classes of molecules. (Recall that polarity is due to a difference in the electronegativity of two atoms bound to each

other.) Chapters 6 and 7 will introduce the **haloalkanes**, which contain polar carbon-halogen bonds as their functional groups. Another example is the **hydroxy group**, $-O-H$, characteristic of **alcohols**. The symbol R (for "radical" or "residue") is commonly used to describe a hydrocarbon-derived molecular fragment. Such fragments are called **alkyl groups**. Therefore a general formula for a haloalkane is $R-X$, where X stands for any halogen. Alcohols are similarly represented as $R-O-H$. The **alkoxy group**, $-O-R$, is the characteristic functional unit of **ethers**, which have the general formula $R-O-R'$. The functional group in alcohols and those in some ethers can be converted into a large variety of other functionalities and are therefore important in synthetic transformations. This chemistry is the subject of Chapters 8 and 9.

Haloalkanes		Alcohols		Ethers	
CH_3Cl	CH_3CH_2Cl	CH_3OH	CH_3CH_2OH	CH_3OCH_3	$CH_3CH_2OCH_2CH_3$
Chloromethane (Methyl chloride)	Chloroethane (Ethyl chloride)	Methanol	Ethanol	Methoxymethane (Dimethyl ether)	Ethoxyethane (Diethyl ether)
(Topical anesthetics)		(Wood alcohol)	(Grain alcohol)	(A refrigerant)	(An inhalation anesthetic)

The **carbonyl** function, $C=O$, is found in **aldehydes** and **ketones**, and, in conjunction with an attached $-OH$, in the **carboxylic acids**. Aldehydes and ketones are discussed in Chapters 17 and 18, the carboxylic acids and their derivatives in Chapters 19 and 20.

Aldehydes		Ketones		Carboxylic Acids
$\begin{array}{c} \text{O} \\ \parallel \\ \text{HCH} \end{array}$ <p>Formaldehyde</p> <p>(A disinfectant)</p>	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{CH} \text{ or } \text{CH}_3\text{CHO} \end{array}$ <p>Acetaldehyde</p> <p>(A hypnotic)</p>	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{CCH}_3 \end{array}$ <p>Propanone (Acetone)</p>	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{CH}_2\text{CCH}_3 \end{array}$ <p>Butanone (Methyl ethyl ketone)</p> <p>(Common solvents)</p>	$\begin{array}{c} \text{O} \\ \parallel \\ \text{HCOH} \text{ or } \text{HCOOH} \end{array}$ <p>Formic acid</p> <p>(Strong irritant)</p>
<p>Other elements give rise to further characteristic functional groups. For example, alkyl nitrogen compounds are amines. The replacement of oxygen in alcohols by sulfur furnishes thiols.</p>				
				$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{COH} \text{ or } \text{CH}_3\text{COOH} \end{array}$ <p>Acetic acid (In vinegar)</p>

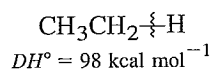
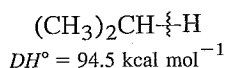
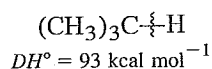
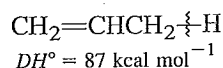
Amines	A Thiol
CH_3NH_2	CH_3SH
Methanamine (Methylamine)	Methanethiol
$CH_3N(CH_3)H$ or $(CH_3)_2NH$	(Excreted after we eat asparagus)
N-Methylmethanamine (Dimethylamine)	
(Used in tanning)	

Table 2-1 (on the next two pages) depicts a selection of common functional groups, the class of compounds to which they give rise, a general structure, and an example.

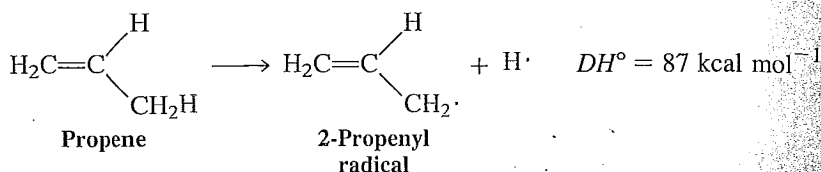
14-1 Overlap of Three Adjacent p Orbitals: Resonance in the 2-Propenyl (Allyl) System

What is the effect of a neighboring double bond on the reactivity of a carbon center? Three key observations answer this question.

Dissociation Energies of Various C-H Bonds

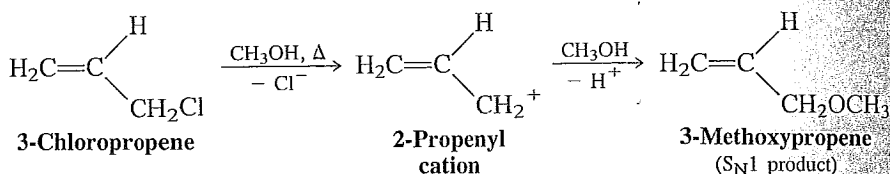


OBSERVATION 1. The primary carbon-hydrogen bond in propene is relatively weak, only 87 kcal mol^{-1} .



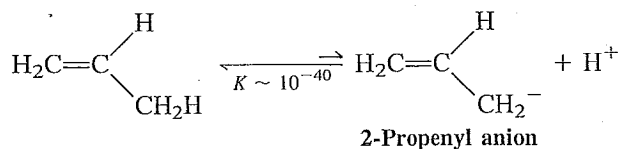
A comparison with the values found for other hydrocarbons (see margin) shows that it is even weaker than a tertiary C-H bond. *Evidently, the 2-propenyl radical enjoys some type of special stability.*

OBSERVATION 2. 3-Chloropropene dissociates relatively fast under $\text{S}_{\text{N}}1$ (solvolysis) conditions and undergoes rapid unimolecular substitution through a carbocation intermediate.



This finding clearly contradicts our expectations (recall Section 7-5). *It appears that the cation derived from 3-chloropropene is somehow more stable than other primary carbocations.* By how much? The ease of formation of the 2-propenyl cation in solvolysis reactions has been found to be roughly equal to that of a secondary carbocation.

OBSERVATION 3. The pK_{a} of propene is about 40.



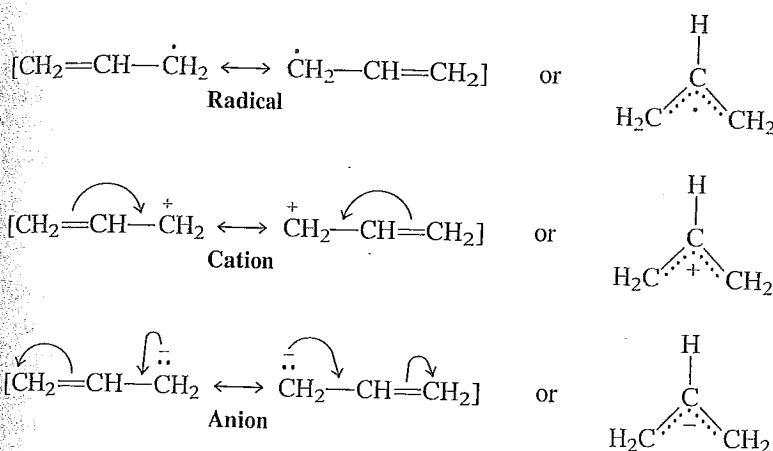
Thus, propene is considerably more acidic than propane ($\text{pK}_{\text{a}} \sim 50$), and the formation of the propenyl anion by deprotonation appears unusually favored. How can we explain these three observations?

Resonance stabilizes 2-propenyl (allyl) intermediates

Each of the preceding three processes generates a reactive carbon center—a radical, a carbocation, or a carbanion, respectively—that is adjacent to the π framework of a double bond. This arrangement seems to impart special stability.

Why? The reason is resonance and the resulting electron delocalization: Each species may be described by a pair of equivalent contributing resonance structures. These three-carbon intermediates have been given the name **allyl** (followed by the appropriate term: radical, cation, or anion). The activated carbon is labeled **allylic**.

Resonance in the 2-Propenyl (Allyl) System



Remember that resonance forms are *not* isomers but partial molecular representations. The true structure (the resonance hybrid) is derived by their superposition, better represented by the dotted-line drawings at the right of the classical picture.

The 2-propenyl (allyl) pi system is represented by three molecular orbitals

The stabilization of the 2-propenyl (allyl) system by resonance can also be described in terms of molecular orbitals. Each of the three carbons is sp^2 hybridized and bears a *p* orbital perpendicular to the molecular plane (Figure 14-1). *Make a model: The structure is symmetric, with equal C-C bond lengths.*

Ignoring the σ framework, we can combine the three *p* orbitals mathematically to give three π molecular orbitals. This process is analogous to mixing two atomic orbitals to give two molecular orbitals describing a π bond (Figures 11-1 and 11-3), except that there is now a third atomic orbital. Of the three resulting molecular orbitals, one (π_1) is bonding and has no nodes, one (π_2) is *nonbonding* (in other words, it has the same energy as a noninteracting *p* orbital) and has one node, and one (π_3) is antibonding, with two nodes, as shown in Figure 14-2.

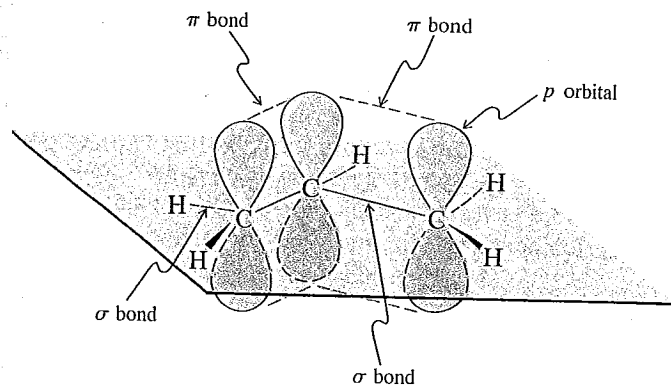


FIGURE 14-1 The three *p* orbitals in the 2-propenyl (allyl) group overlap, giving a symmetric structure with delocalized electrons. The σ framework is shown as black lines.

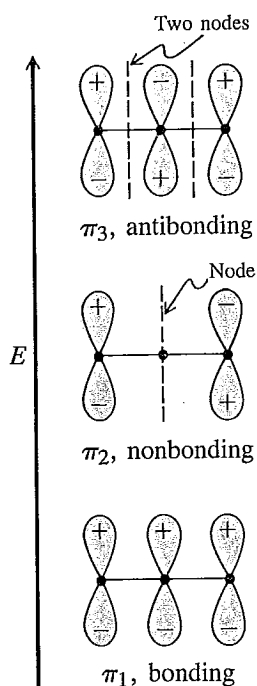


FIGURE 14-2 The three π molecular orbitals of 2-propenyl (allyl), obtained by combining the three adjacent atomic p orbitals.

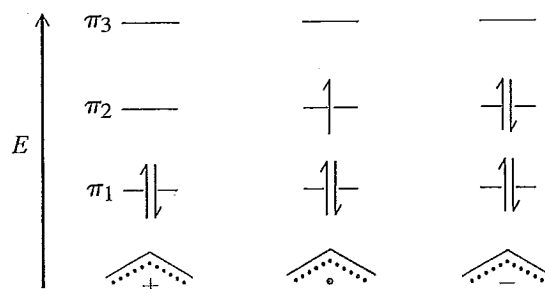
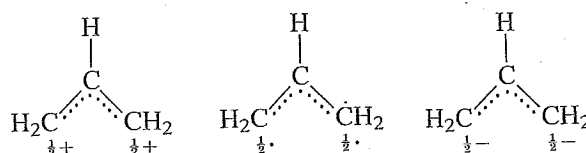


FIGURE 14-3 The Aufbau principle is used to fill up the π molecular orbitals of 2-propenyl (allyl) cation, radical, and anion. In each case the total energy of the π electrons is lower than that of three noninteracting p orbitals. Partial cation, radical, or anion character is present at the end carbons in these systems, a result of the location of the lobes in the π_2 molecular orbital.

We can use the Aufbau principle to fill in the appropriate number of π electrons (Figure 14-3). The cation, with a total of two, contains only one filled orbital, π_1 . For the radical and the anion, we place one or two electrons, respectively, into the second molecular orbital, π_2 . In all cases, the total π -electron energy of the system is lower (more favorable) than that expected from three noninteracting p orbitals—essentially because π_1 is greatly stabilized and filled in all cases, whereas the antibonding level, π_3 , stays empty throughout.

The resonance formulations for the three 2-propenyl species indicate that it is mainly the two *terminal* carbons that accommodate the charges in the ions or the odd electron in the radical. The molecular-orbital picture is consistent with this view: The three structures differ only in the number of electrons present in molecular orbital π_2 , which possesses a node passing through the central carbon; therefore, very little of the electron excess or deficiency will show up at this position.

Partial Electron Density Distribution in the 2-Propenyl (Allyl) System



In summary, allylic radicals, cations, and anions are unusually stable. In Lewis terms, this stabilization is readily explained by resonance. In a molecular-orbital description, the three interacting p orbitals form three new molecular orbitals: One is considerably lower in energy than the p level, another one stays the same, and a third moves up. Because only the first two are populated with electrons, the total π energy of the system is lowered.

14-2 Radical Allylic Halogenation

A consequence of delocalization is that resonance-stabilized allylic intermediates can readily participate in reactions of unsaturated molecules. For example, al-