Organic Chemistry

SECOND EDITION

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Cover Image by Tomo Narashima

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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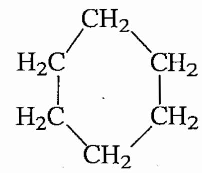
Hydrocarbons are molecules that contain only hydrogen and carbon

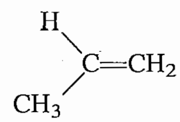
We begin our study with hydrocarbons, which have the general empirical formula C_xH_y. Those containing only single bonds, such as methane, ethane, and propane, are called **alkanes.** Molecules such as cyclohexane, whose carbons form a ring, are called **cycloalkanes.** *Alkanes lack functional groups;* 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

CH_4	$CH_3{-}CH_3$	$CH_3{-}CH_2{-}CH_3$	
Methane	**Ethane**	**Propane**	**Cyclohexane**

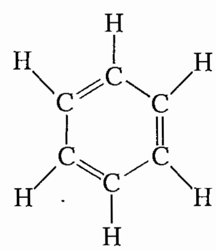
Double and triple bonds are the functional groups of **alkenes** and **alkynes,** respectively. Their properties and chemistry are the topics of Chapters 11–13.

Alkenes and Alkynes

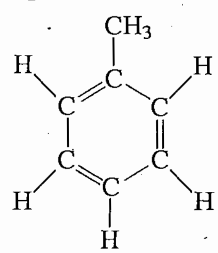
$CH_2{=}CH_2$		$HC{\equiv}CH$	$CH_3{-}C{\equiv}CH$
Ethene (Ethylene)	**Propene**	**Ethyne (Acetylene)**	**Propyne**

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



Benzene



Methylbenzene (Toluene)

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

CH_3Cl **Chloromethane (Methyl chloride)**

CH_3CH_2Cl **Chloroethane (Ethyl chloride)**

(Topical anesthetics)

Alcohols

CH_3OH **Methanol** (Wood alcohol)

CH_3CH_2OH **Ethanol** (Grain alcohol)

Ethers

CH_3OCH_3 **Methoxymethane (Dimethyl ether)** (A refrigerant)

$CH_3CH_2OCH_2CH_3$ **Ethoxyethane (Diethyl ether)** (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

HC(=O)H **Formaldehyde** (A disinfectant)

$CH_3C(=O)H$ or CH_3CHO **Acetaldehyde** (A hypnotic)

Ketones

$CH_3C(=O)CH_3$ **Propanone (Acetone)**

$CH_3CH_2C(=O)CH_3$ **Butanone (Methyl ethyl ketone)**

(Common solvents)

Carboxylic Acids

HC(=O)OH or HCOOH **Formic acid** (Strong irritant)

$CH_3C(=O)OH$ or CH_3COOH **Acetic acid** (In vinegar)

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.**

Amines

CH_3NH_2 **Methanamine (Methylamine)**

$CH_3N(H)CH_3$ or $(CH_3)_2NH$ ***N*-Methylmethanamine (Dimethylamine)**

(Used in tanning)

A Thiol

CH_3SH **Methanethiol** (Excreted after we eat asparagus)

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

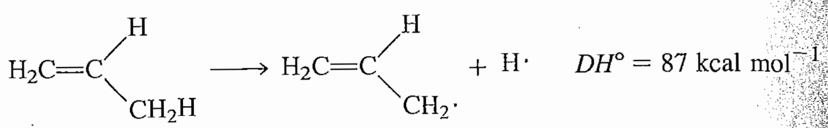
$CH_2{=}CHCH_2$–H
$DH° = 87$ kcal mol^{-1}

$(CH_3)_3C$–H
$DH° = 93$ kcal mol^{-1}

$(CH_3)_2CH$–H
$DH° = 94.5$ kcal mol^{-1}

CH_3CH_2–H
$DH° = 98$ kcal mol^{-1}

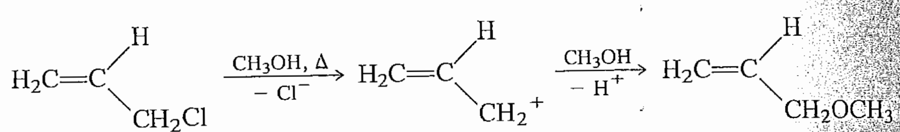
OBSERVATION 1. The primary carbon–hydrogen bond in propene is relatively weak, only 87 kcal mol^{-1}.



Propene **2-Propenyl radical**

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.*

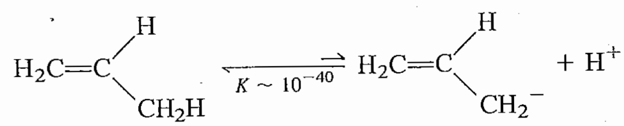
OBSERVATION 2. 3-Chloropropene dissociates relatively fast under S_N1 (solvolysis) conditions and undergoes rapid unimolecular substitution through a carbocation intermediate.



3-Chloropropene **2-Propenyl cation** **3-Methoxypropene** (S_N1 product)

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.



2-Propenyl anion

Thus, propene is considerably more acidic than propane (p$K_a \sim 50$), 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.

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