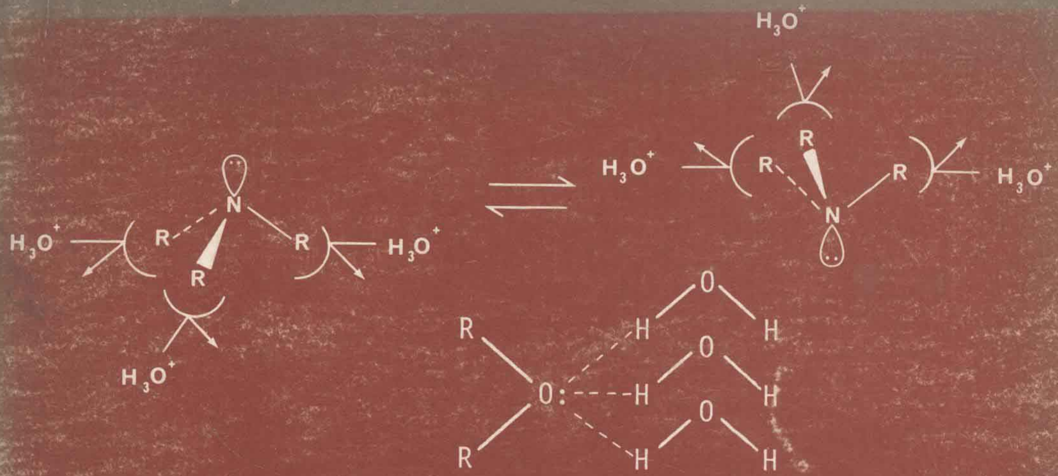
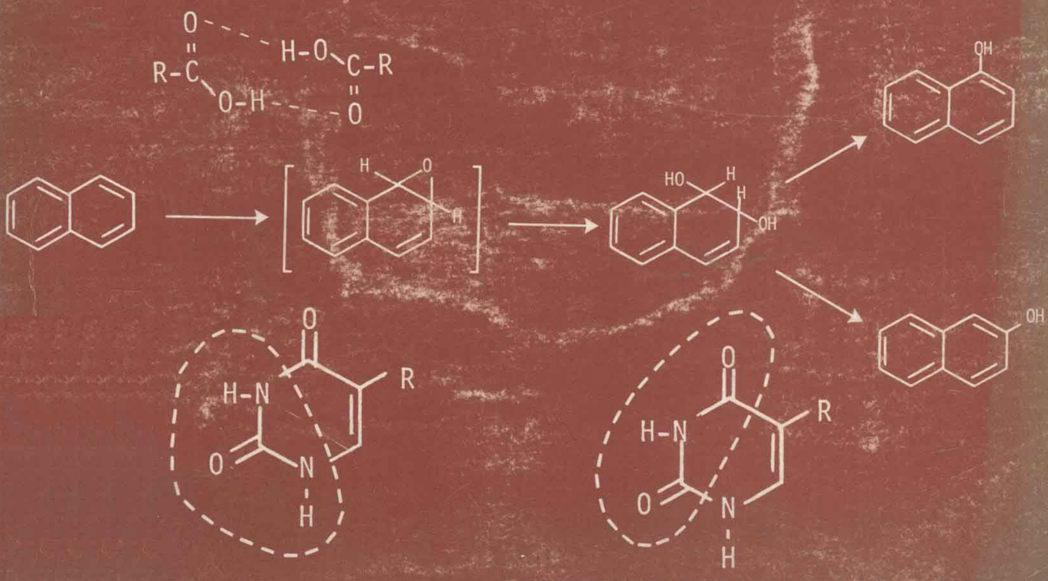


Review of Organic Functional Groups

Introduction to Medicinal Organic Chemistry

THOMAS L. LEMKE



Review of Organic Functional Groups

Introduction to Medicinal Organic Chemistry

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Introduction

This book has been prepared with the intent that it may be used as a self-paced review of organic functional groups. Were the material covered in this book to be presented in a conventional classroom setting, it would require 14 to 16 formal lecture hours. With this in mind, you should not attempt to cover all of the material in one sitting. A slow, leisurely pace will greatly increase your comprehension and decrease the number of return reviews of the material. You should stop and review any section that you do not completely understand. At the end of each section, questions are asked that you should be able to answer. If you do not understand the answer to any question, return to the appropriate section of the book and review it again.

OBJECTIVES

The following outline is a general review of the functional groups common to organic chemistry. It is the objective of this book to review the general topics of nomenclature, physical properties (with specific emphasis placed on water and lipid solubility), chemical properties (the stability or lack of stability of a functional group to normal environmental conditions, referred to as in vitro stability), and metabolism (the stability or lack of stability of a functional group in the body, referred to as in vivo stability). There will be no attempt to cover synthesis, nor will great emphasis be placed on chemical reactions except when they relate to the physical or chemical stability and mechanistic action of drugs. This review is meant to provide background material for the formal pharmacy courses in medicinal chemistry. The objectives are presented in the following manner to aid in focusing attention on the expected learning outcomes.

Upon successful completion of the book, the following goals will have been attained:

a. The student will be able to draw a chemical structure given a common or official chemical name.
b. The student will be able to predict the solubility of a chemical in:
   1. an aqueous acid solution
   2. water
   3. an aqueous base solution
c. The student will be able to predict and show, with chemical structures, the chemical instabilities of each organic functional group under conditions appropriate to a substance "sitting on the shelf," by which is meant conditions such as air, light, aqueous acid or base, and heat.
d. The student will be able to predict and show, with chemical structures, the metabolism of each organic functional group.

To help you master these skills, the information is presented in the following outline form:

A. **Nomenclature**
   1. Common
   2. Official (IUPAC)
B. **Physical-Chemical Properties**
   1. Physical properties—related to water and lipid solubility
   2. Chemical properties in vitro—stability or reactivity of functional groups "on the shelf"
C. **Metabolism—in vivo**
   Stability or reactivity of functional groups "in the body"

RECOMMENDED PREPARATION

In order to maximize learning and to provide perspective in the study of the book, it would be helpful to read certain background material. It is highly recommended that a textbook on general organic chemistry be reviewed and consulted as a reference book while using this book. Pay special attention to the sections on nomenclature and physical-chemical properties.

Contents

1

Water Solubility and Chemical Bonding

At the outset, several definitions relating to organic compounds need to be discussed.

For our purposes, we will assume that an organic molecule will dissolve either in water or in a nonaqueous lipid solvent. That is, the organic molecule will not remain undissolved at the interphase of water and a lipid solvent. If a molecule dissolves fully or partially in water, it is said to be hydrophilic or to have hydrophilic character. The word hydrophilic is derived from "hydro," referring to water, and "philic," meaning loving or attracting. A substance that is hydrophilic may also be referred to, in a negative sense, as lipophobic. "Phobic" means fearing or hating, and thus lipophobic means lipid hating, which therefore suggests that the chemical is water loving.

If an organic molecule dissolves fully or partially in a nonaqueous or lipid solvent, the molecule is said to be lipophilic or to have lipophilic character. The term lipophilic or lipid loving is synonymous with hydrophobic or water heating, and these terms may be used interchangeably.

Hydrophilic	water loving
Lipophobic	lipid hating
Lipophilic	lipid loving
Hydrophobic	water hating

In order to predict whether a chemical will dissolve in water or a lipid solvent, it must be determined whether the molecule and its functional groups can bond to water or the lipid solvent molecules. THIS IS THE KEY TO SOLUBILITY. If a molecule, through its functional groups, can bond to water, it will show some degree of water solubility. If, on the other hand, a molecule cannot bond to water, but instead bonds to the molecules of a lipid solvent, it will be water insoluble or lipid soluble. Our goal is therefore *to determine to what extent a molecule can or cannot bond to water.* To do this, we must define the types of intermolecular bonding that can occur between molecules.

What are the types of intermolecular bonds?

1. Van der Waal Attraction

The weakest type of interaction is electrostatic in nature and is known as van der Waal attraction. This type of attraction occurs between the nonpolar portion of two molecules and is brought about by a mutual distortion of electron clouds making up the covalent bonds (Fig. 1–1). This attraction is also called the induced dipole interaction. In addition to being weak, it is temperature dependent, being important at low temperatures and of little significance at high temperatures. The attraction occurs only over a short distance, thus requiring a tight packing of molecules. Steric factors therefore strongly influence van der Waal attraction. This type of chemical bonding is most prevalent in hydrocarbon and aromatic systems. Van der Waal forces are approximately 0.5 to 1.0 kilocalories per mole for each atom involved. Van der Waal bonds are found in lipophilic solvents but are of little importance in water.

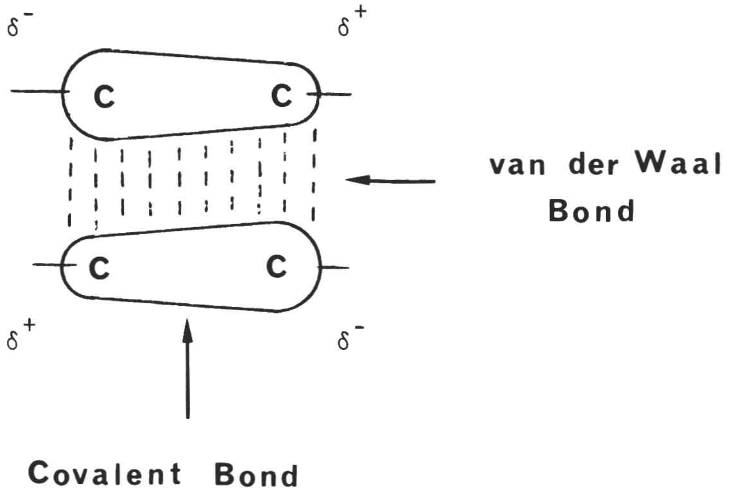


Fig. 1–1. Van der Waal attraction resulting from distortion of covalent bonds

2. Hydrogen Bond (Dipole-Dipole Bonding)

A stronger and important form of chemical bonding is the dipole-dipole bond, a specific example of which is the hydrogen bond (Fig. 1–2). A dipole results from the unequal sharing of a pair of electrons making up a covalent bond. This occurs when the two atoms making

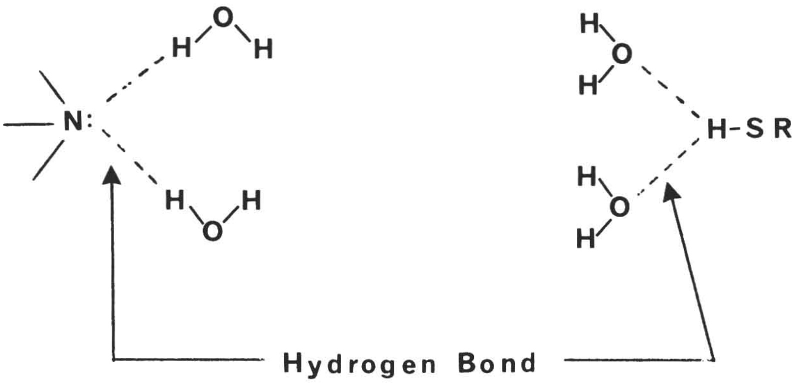
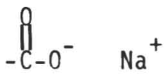


Fig. 1–2. Hydrogen bonding of an amine to water and a thiol to water

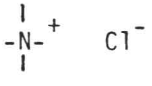
up the covalent bond differ significantly in electronegativity. A partial ionic character develops in this portion of the molecule, leading to a permanent dipole, with the compound being described as a polar compound. The dipole-dipole attraction between two polar molecules arises from the negative end of one dipole being electrostatically attracted to the positive end of the second dipole. The hydrogen bond can occur when at least one dipole contains an electropositive hydrogen (e.g., a hydrogen covalently bonded to an electronegative atom such as oxygen, sulfur, nitrogen, or selenium), which in turn is attracted to a region of high electron density. Atoms with high electron densities are those with unshared pairs of electrons such as amine nitrogens, ether or alcohol oxygens, and thioether or thiol sulfurs. While hydrogen bonding is an example of dipole-dipole bonding, not all dipole-dipole bonding is hydrogen bonding. Water, the important pharmaceutical solvent, is a good example of a hydrogen-bonding solvent. The ability of water to hydrogen bond accounts for the unexpectedly high boiling point of water as well as the characteristic dissolving properties of water. The hydrogen bond depends on temperature and distance. The energy of hydrogen bonding is 1.0 to 10.0 kcal/mole for each interaction.

3. Ionic Attraction

A third type of bonding is the ionic attraction found quite commonly in inorganic molecules and salts of organic molecules. This is formed by the attraction of a negative atom for a positive atom. The ionic bond involves a somewhat stronger attractive force of 5 kcal/mole or more and is *least* affected by temperature and distance.



$$-\overset{\displaystyle O}{\overset{\|}{C}}-O^{-} \quad Na^{+}$$



$$-\underset{|}{\overset{|}{N}}-^{+} \quad Cl^{-}$$

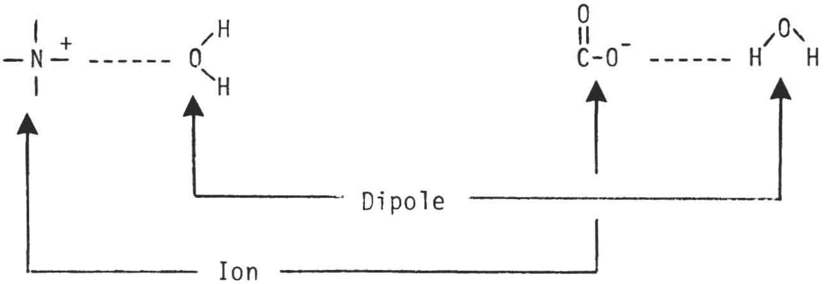


Fig. 1–3. Ion-dipole bonding of a cationic amine to water and an anionic carboxylate to water

4. Ion-Dipole Bonding

Probably one of the most important chemical bonds involved in organic salts dissolving in water is the ion-dipole bond (Fig. 1–3). This bond occurs between an ion, either cation or anion, and a formal dipole, such as is found in water. The following two types of interactions may exist.

a. A cation will show bonding to a region of high electron density in a dipole (e.g., the oxygen atom in water).
b. An anion will bond to an electron-deficient region in a dipole (e.g., the hydrogen atom in water).

The ion-dipole is a strong attraction that is relatively insensitive to temperature or distance. When an organic compound with basic properties (e.g., an amine) is added to an aqueous acidic medium (pH below 7.0), the compound may form an ionic salt that, if dissociable, will have enhanced water solubility owing to ion-dipole bonding. Likewise, when an organic compound with acidic properties (e.g., carboxylic acids, phenols, unsubstituted or monosubstituted sulfonamides, and unsubstituted imides) is added to an aqueous basic medium (pH above 7.0), the compound may form an ionic salt, which, if dissociable, will have enhanced water solubility owing to ion-dipole bonding. Both of these examples are shown in Figure 1–3.

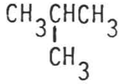
Water is an important solvent from both a pharmaceutical and a biologic standpoint. Therefore, when looking at any drug from a structural viewpoint, it is important to know whether the drug will dissolve in water. To predict water solubility, one must weigh the number and strength of hydrophilic groups in a molecule against the lipophilic groups present. If a molecule has a large amount of water-loving character, by interacting with water through hydrogen bonding or ion-dipole attraction, it would be expected to dissolve in water. If a molecule is deficient in hydrophilic groups but instead has a lipophilic portion capable of van der Waal attraction, then the molecule will most likely dissolve in nonaqueous or lipophilic media.

In reviewing the functional groups in organic chemistry, an attempt will be made to identify the lipophilic or hydrophilic character of each functional group. Knowing the character of each functional group in a drug will then allow an intelligent prediction of the overall solubility of the molecule by weighing the importance of each type of interaction. This book is organized in such a way that each functional group is discussed individually. Yet, when dealing with a drug molecule, the student will usually find a polyfunctional molecule. The ultimate goal is that the student should be able to predict the solubility of the actual drugs in water, aqueous acidic media, and aqueous basic media. Therefore, to use this book correctly and to prepare yourself for the drug molecules, it is recommended that you read through Chapter 16 after studying each functional group. This will help you put each functional group into perspective with respect to polyfunctional molecules.

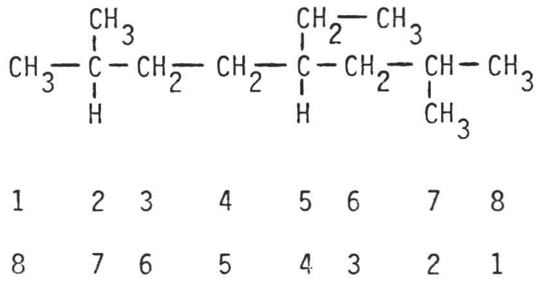
2

Alkanes (C_nH_{2n+2})

A. Nomenclature. The nomenclature of the alkanes may be either common or official nomenclature. The common nomenclature begins with the simplest system, methane, and proceeds to ethane, propane, butane, and so forth. The "ane" suffix indicates that the molecule is an alkane. This nomenclature works quite well until isomeric forms of the molecule appear (e.g., molecules with the same empirical formulas but different structural formulas). In butane, there are only two ways to put the molecule together, but as we consider larger molecules, many isomers are possible, and the nomenclature becomes unwieldy. Thus, a more systematic form of nomenclature is necessary. The IUPAC (International Union of Pure and Applied Chemistry) nomenclature is the official nomenclature.

CH_4	Methane
CH_3CH_3	Ethane
$CH_3CH_2CH_3$	Propane
$CH_3CH_2CH_2CH_3$	n-Butane
 $CH_3\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_3$	iso-Butane

IUPAC nomenclature requires that one find the longest continuous alkane chain. The name of this alkane chain becomes the base name. The chain is then numbered so as to provide the lowest possible numbers to the substituents. The number followed by the name of each substituent then precedes the base name of the straight-chain alkane. An example of naming an alkane according to IUPAC nomenclature is shown in Figure 2–1. The longest continuous chain is



$$CH_3-\underset{H}{\overset{CH_3}{C}}-CH_2-CH_2-\underset{H}{\overset{CH_2-CH_3}{C}}-CH_2-\underset{CH_3}{CH}-CH_3$$

Fig. 2–1. 2,7-Dimethyl-4-ethyloctane

eight carbons. This chain can be numbered from either end. Numbering left to right results in substituents at positions 2 (methyl), 5 (ethyl), and 7 (methyl). The name of this compound would be 2,7-dimethyl-5-ethyloctane. Numbering from right to left gives alkane substituents at the 2, 4, and 7 positions. This compound would be 2,7-dimethyl-4-ethyloctane. To determine which way to number, just add the numbers that correspond to the substituent locations. From left to right, one has 2 + 5 + 7, which equals 14. When numbering from right to left, one has 2 + 4 + 7, which equals 13. Therefore, the correct numbering system is from right to left, giving 2,7-dimethyl-4-ethyloctane.

B. Physical-Chemical Properties. We wish to consider the following questions: Are alkanes going to be water soluble, and can water solubility or the lack of it be explained? The physical-chemical properties of alkanes are readily understandable from the previous discussion of chemical bonding. These compounds are unable to undergo hydrogen bonding, ionic bonding, or ion-dipole bonding. The only intermolecular bonding possible with these compounds is the weak van der Waal attraction. For the smaller molecules with one to four carbon atoms, this bonding is not strong enough to hold the molecules together at room temperature, with the result that the lower-member alkanes are gases. For the larger molecules with 5 to 20 carbon atoms, the induced dipole-induced dipole interactions can occur, and the energy required to break the increased amount of bonding is more than is available at room temperature. The result is that the 5- to 20-carbon atom alkanes are liquids. One can see from Table 2–1 that the boiling point increases consistently as more van der Waal bonding occurs.

The effects of adding an alkane to water are depicted in Figure 2–2. Water is an ordered medium with a considerable amount of intermolecular bonding, indicated by its high boiling point (i.e., high in respect to its molecular weight). In order to dissolve in or to mix with water, foreign atoms must break into this lattice. Sodium chloride (table salt), which is quite water soluble, is an example of a

Table 2–1.
Boiling Points of Common Alkanes

	Boiling Point(°C)
Propane	-42.0
n-Butane	-0.5
n-Pentane	36.1
n-Hexane	69.0
n-Heptane	98.4
n-Octane	126.0

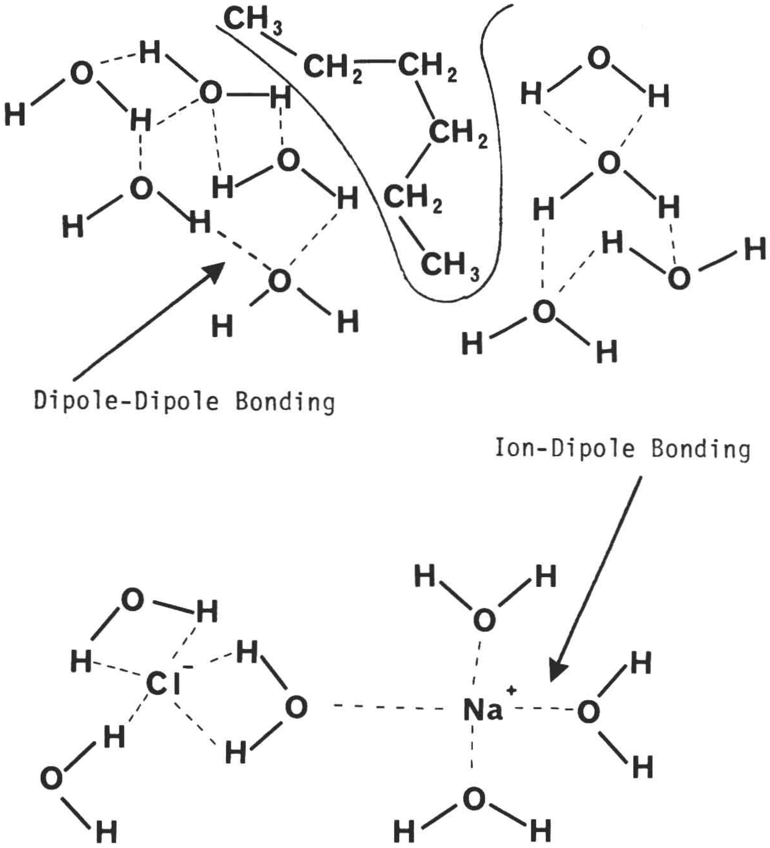


Fig. 2–2. Diagram of n-hexane's lack of solubility in water and the solubility of sodium chloride in water through ion-dipole bonding