Medicinal Chemistry

A Biochemical Approach

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Preface

Medicinal chemistry has undergone many changes since ancient herbalist days, but none seem to be as significant and fruitful as the rapid elucidation of the molecular, biochemical mechanisms of drug action achieved in the past 25 years. Only our full understanding of these mechanisms can lead to a mature, exact, and predictive science of molecular pharmacology and rational drug design. This book is an attempt to combine the many possible approaches to the study and teaching of medicinal chemistry into a rational and coherent didactic discipline; it departs from the classical organization and proportions seen elsewhere in order to promote progressive and creative ways of viewing the chemistry and mode of action of drugs.

The organic chemical approach to drug classification was long ago abandoned as irrational. The widely used pharmacokinetic classification organizes drugs according to their therapeutic action on organs (such as the central nervous system or thyroid gland), pathological syndromes (as with anticonvulsant drugs or antilipidemic agents), or identical therapeutic effects (e.g., local anesthetics or antimalarials). While this more recent classification is practical for the pharmacist or physician, it is nevertheless as arbitrary as the structural classification. Such an organizational system is not only an obstacle to attempts to correlate the actions of different "classes" of drugs, it also hinders the emergence of much needed leads in rational drug design. The case of the antineoplastic action of many antibiotics comes to mind: while classified differently and used in distinct syndromes, both these and other antineoplastic agents act on DNA.

It is therefore timely that the new generation of medicinal chemists become aware of the fact that a basic understanding of drug action is possible only on a molecular rather than a cellular or organismic level. Using biochemical pharmacology as a framework and unifying structure, the young medicinal chemist should become a truly interdisciplinary practitioner from the start, rather than evolving slowly from a training in organic chemistry or pharmacology, as many of us have done. The molecular approach will nevertheless often overlap with the classical pharmacodynamic organization of drugs. The concept of H_1-antihistamines as a group or steroid hormones as a chemically defined family remains valid because their mode of action happens to be cohesive. On the other hand, "tranquilizers" cannot be squeezed into the old categories. They are found in this book among drugs acting on the dopaminergic as well as GABAergic receptors and are also discussed in connection with the biophysical state of neuronal membranes.

To support the main body of a book that discusses drugs on the basis of their molecular targets, considerable space has been devoted to the physicochemical principles of drug action and receptor-effector theories, as well as to an overview of the methods of receptor characterization. The latter is not meant to be a minitextbook of instrumental techniques; instead it is aimed at giving the student an understanding of the armamentarium of methods that has lead to the continuing explosion of molecular insight into drug action. A short chapter on drug distribution and metabolism and another on the principles of drug design round out the picture of the multidisciplinary requirements in the practice of modern medicinal chemistry as a homogeneous discipline. Drug synthesis and immunological aspects of drug action are not covered, and the drugs cited serve as examples rather than as a comprehensive list of relevant pharmaca. Their choice was dictated not by their availability in North America but by their inherent scientific or therapeutic interest. To aid the pharmacy student, the Appendix lists the generic and proprietary names of drugs, their pharmacological actions, and some of their physicochemical characteristics. It also serves as a drug and formula index. Drugs are also grouped by pharmacological activity.

The references at the end of each section are highly selective. Relatively few research papers are listed; instead, the emphasis is on reviews and symposia. Keeping in mind parsimony in building library collections, a relatively narrow selection of sources was used. Major standard work are not cited routinely and redundantly but are listed at the end of this preface.

In keeping with the molecular-biochemical bias of this book, a knowledge of basic organic and biochemistry is assumed, but advanced undergraduates as well as graduate students and professionals may find the treatment clear.

Many people have helped in my presumptuous attempt to produce a single-author text. Much of the manuscript was written during a sabbatical stay at the Division of Pharmacology of the University of California at San Diego and during a shorter visit at the Department of Pharmaceutical Chemistry of the University of California at San Francisco. I am most grateful to Palmer Taylor and to Manfred Wolff for their hospitality and help in making available to me the marvelous resources of the University of California.

Pavel Hrdina (University of Ottawa), Leslie Humber (Ayerst Laboratories, Montreal), and Thomas Sandor (Université de Montréal) read individual chapters and supplied valuable information, updating, and corrections. My colleague Mark Doughty read the whole first draft and added his erudition. To all of them, my heartfelt thanks. My main editor, grammarian and critic was, however, my wife, Heather, who immeasurably improved the style and structure of the book as well as the author's disposition after a long day of writing. Doris Tooby in Montreal and Sandra Dutky in La Jolla typed a good part of the initial versions cheerfully and efficiently. The original illustrations are the careful work of Catherine Bata.

I look forward to a dialogue with readers and welcome their additions and criticism.

Montreal T.N.
September 1983

SOME MAJOR WORKS ON MEDICINAL CHEMISTRY

Albert (1979). *Selective Toxicity*, 6th ed. Chapman and Hall, London.

E. J. Ariëns (Ed.). *Drug Design*, 10 vols. Academic Press, New York.

J. R. Cooper, F. E. Bloom, and R. H. Roth (1982). *The Biochemical Basis of Neuropharmacology*, 4th ed. Oxford University Press, New York.

W. O. Foye (Ed.) (1981). *Principles of Medicinal Chemistry*, 2nd edn. Lea and Febiger, Philadelphia.

A. G. Gilman, L. S. Goodman, and A. Gilman (Eds.) (1980). *The Pharmacological Basis of Therapeutics*. 6th edn. MacMillan, New York.

N. J. Howe, M. M. Milne, and A. F. Pennel (Eds.) (1978). *Retrieval of Medicinal Chemical Information*, ACS Symposium Series 84. American Chemical Society, Washington, D.C.

L. L. Iversen, S. D. Iversen, and S. H. Snyder (Eds.) (1975). *Handbook of Psychopharmacology*, 17 vols. Plenum Press, New York.

J. W. Lamble (Ed.) (1981). *Towards Understanding Receptors*. Elsevier Biomedical Press, Amsterdam.

J. W. Lamble (Ed.) (1982). *More About Receptors*. Elsevier Biomedical Press, Amsterdam.

D. Lednitzer and L. A. Mitscher (1976, 1980). *Organic Chemistry of Drug Synthesis*, 2 vols. Wiley, New York.

E. E. J. Marler (Ed.) (1982). *Pharmacological and Chemical Synonyms*. 7th edn. Excerpta Medica/Elsevier, Amsterdam.

M. Sittig (1979). *Pharmaceutical Manufacturing Encyclopedia*. Noyes Data, Park Ridge, N. J.

C. O. Wilson (Ed.) (1982). *Griswold and Doerge's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 8th edn. Lippincott, Philadelphia.

M. Windholz (Ed.) (1984). *The Merck Index*, 10th edn. Merck, Rahway, N. J.

M. E. Wolff (Ed.) (1979–81). *Burger's Medicinal Chemistry*, 4th edn., 3 parts. Wiley-Interscience, New York.

PERIODICALS

Annual Reports of Medicinal Chemistry. Academic Press, New York.

Annual Reviews of Biochemistry. Annual Reviews Inc., Palo Alto, CA.

Annual Reviews of Neuroscience. Annual Reviews Inc., Palo Alto, CA.

Annual Reviews of Pharmacology and Therapeutics. Annual Reviews Inc., Palo Alto, CA.

Arzneimittelforschung. Editio Cantor, Aulendorf, W. Germany.

Biochemical Pharmacology. Pergamon Press, New York.

Drugs of the Future. Prous S. A., Barcelona.

European Journal of Medicinal Chemistry. Societé d'Études de Chimie Thérapeutique, France.

Journal of Medicinal Chemistry. American Chemical Society, Washington.

Medicinal Research Reviews. Wiley, New York.

Molecular Pharmacology. Academic Press, New York.

Progress in Drug Research. Birkhäuser, Basel.

Progress in Medicinal Chemistry. Elsevier/North Holland, Amsterdam.

Trends in Pharmacological Sciences. Elsevier Biomedical Press, Amsterdam.

Contents

Medicinal Chemistry

1

Physicochemical Principles of Drug Action

All drug molecules interact with biological structures, such as lipoprotein receptors, biomembranes, nucleic acids, or small molecules. This interaction triggers a series of steps that ultimately results in a macroscopic, physiological change that constitutes the drug effect. Only by first unraveling the relatively simple primary interaction between the drug molecule and a macromolecular structure can drug activity at the cellular level be understood. Organs and whole organisms are immensely more complex than individual cells, and require the understanding of many more parameters.

Drug transport from the site of application to the site of action, as well as the drug-stimulus relationship, depend on physicochemical and geometrical properties inherent in the structure of the drug molecule. This correlation applies equally to the physicochemical properties of the biological macromolecules with which the drug interacts. However, our knowledge of these macromolecules lags far behind our experience with small compounds. Consequently, in order to achieve rational drug design, the ultimate goal of medicinal chemistry, we have to study the chemical and physical properties of drug molecules and their targets, and correlate the sum of these molecular properties with the biological effects of drug–receptor interactions.

This chapter discusses the applications of physicochemical principles to the molecules and modes of action of drugs. Since all biological reactions take place in an aqueous medium or at the interface of water and a lipid, the properties of water and this boundary layer have to be dealt with.

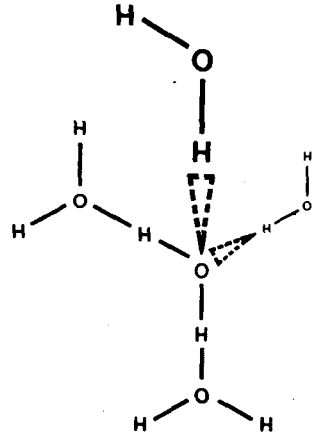
1. ROLE AND STRUCTURE OF WATER

Life is based on water, the major constituent of living organisms and their cells. Besides being a universal solvent or dispersing agent, water participates in many reactions, and its role is therefore much more than that of an inert medium: it is a very reactive and unusual chemical compound. Solubility, surface activitiy, hydrogen bonding, hydrophobic bonding, ionization, and effects on macromolecular conformation (e.g., in drug receptors) all involve water.

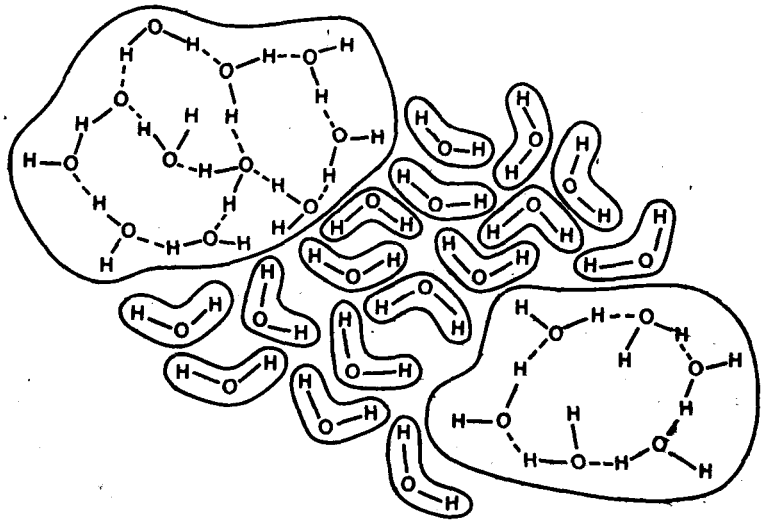
1.1. The Structure of Bulk Water

Water structure is the consequence of the unique and unusual physical properties of the H_2O molecule. It has a higher melting point, boiling point, and heat of vaporization than such hydrides of related elements as H_2S, H_2Se, and H_2Te, or such isoelectronic compounds as HF, CH_4 or NH_3. These properties are all a measure of the strong intermolecular forces acting between individual water molecules, which do not let the ice crystal collapse or the molecule leave the surface of the liquid phase easily when heated. These forces result from the high polarity of water caused by the direction of the H—O—H bond angle, which is 104.5°. The

Fig. 1.1. Schematic diagram of water structure. (A) Tetrahedral hydrogen bonding of a water molecule in ice. (B) "Flickering clusters" of liquid water in a two-dimensional diagram.



(A)



(B)

more electronegative oxygen attracts the electron of the O—H bond to a considerable extent, leaving the H with a partial positive charge (δ^+), while the O atom acquires a partial negative charge (δ^-). Since the molecule is not linear, H_2O has a *dipole moment*. The partial positive and negative charges of one water molecule will electrostatically attract their opposites in other water molecules, resulting in the formation of *hydrogen bonds*: (Fig. 1.1). Such noncovalent bonds can also be formed between water and hydroxyl, carbonyl, or NH groups, as discussed later in Sec. 7.3 of this chapter.

In *ice*, each oxygen atom is bonded to four hydrogen atoms by two covalent and two hydrogen bonds, When ice melts, about 20% of these H bonds are broken, but there is a strong attraction between water molecules even in water vapor. *Liquid water* is therefore highly organized on a localized basis: the hydrogen bonds break and reform spontaneously, creating and destroying transient structural domains, the so-called "flickering clusters." However, because the half-life of any hydrogen bond is only about 0.1 nanoseconds (10^{-10}), the existence of these clusters has statistical validity only.

1.2. The Solvent Properties of Water

Water will interact with ionic or polar substances and destroy their crystal lattices. Since the resulting hydrated ions are more stable than the crystal lattice, solvation results. Water has a very high dielectric constant (80 Debye units vs. 21 D of acetone), which counteracts the electrostatic attraction of ions, thus favoring further hydration. The dielectric constant of a medium can be defined as a ratio of forces: the force acting between two charges in a vacuum and the force between the same two charges in the medium or solvent. According to Coulomb's law

$$F = \frac{q_1 q_2}{Dr^2}$$

where F is the force, q_1 and q_2 are the charges, and r is the distance separating them. D, the dielectric constant, is a characteristic property of the medium. Since D appears in the denominator, the higher the dielectric constant, the weaker the interaction between the two charges.

Polar functional groups of nonionic organic compounds such as aldehydes, ketones, and amines (possessing free electron pairs) form hydrogen bonds readily with water, and dissolve to a greater or lesser extent, depending on the proportion of polar to apolar moieties in the molecule.

Solutes cause a change in water properties because the hydrate "envelopes" that form around solute ions are more organized and therefore more stable than the flickering clusters of free water. As a result, ions are water-structure breakers. The properties of solutions, which depend on solute concentration, are different from those of pure water; the differences can be seen in such phenomena as the freezing-point depression, boiling-point elevation, and increased osmotic pressure of solutions.

Water molecules cannot use all four possible hydrogen bonds when in contact with hydrophobic (water-hating) molecules. This restriction results in a loss of

entropy, a gain in density, and increased organization. So-called "icebergs"—water domains more stable than the flickering clusters in liquid water—are formed. Such "icebergs" can form around single apolar molecules, producing inclusion compounds called *clathrates*. Apolar molecules are thus water-structure formers.

The interaction between a solute and a solid phase—like a drug with its lipoprotein receptor—is also influenced by water. Hydrate envelopes or icebergs associated with one or the other phase will be destroyed or created in this interaction, and may often contribute to conformational changes in macromolecular drug receptors and, ultimately, to physiological events.

Selected Readings

F. Franks (Ed.) (1972). *Water. A Comprehensive Treatise.* Vol. 1. *The Physics and Physical Chemistry of Water.* Plenum, New York.

A. L. Lehninger (1982) *Principles of Biochemistry*, Chap. 4. Worth, New York.

B. Pullman (1978). Aspects of biomolecules in their surroundings: hydration and cation binding. In: *Frontiers in Physicochemical Biology* (B. Pullman, Ed.) Academic Press, New York, pp. 143–163.

2. SOLUBILITY

Because a large percentage of all living structures consists of water, all biochemical reactions are based on small molecules dissolved in an aqueous phase (like the cytosol) or on macromolecules dispersed in this phase—usually both. The nonaqueous structures of cells, such as plasma membranes or the membranes of organelles, are of a lipid nature, and can dissolve hydrophobic, nonpolar molecules. In either case, a highly significant physical property of all physiologically and pharmacologically important small molecules is their solubility, because only in solution can they interact with the cellular and subcellular structures that carry drug receptors, thus triggering pharmacological reactions. Theoretically, there are no absolutely insoluble compounds, every molecule is soluble in both the aqueous and nonaqueous lipid "compartments" of a cell. The degree of solubility, however, differs in each compartment. The proportion of these concentrations at equilibrium—or ratio of solubilities—is called the *partition coefficient*, and will be discussed in detail in the next section.

Solubility is a function of many molecular parameters. Ionization, molecular structure and size, stereochemistry, and electronic structure will all influence the bonding interaction between a solvent and solute. As we have seen in the previous section, water forms hydrogen bonds with ions or with polar nonionic compounds through —OH, —NH, —SH, and —C=O groups, or with the nonbonding electron pairs of oxygen or nitrogen atoms. The ion or molecule will thus acquire a hydrate envelope and separate from the bulk solid; that is, it dissolves. The interaction of nonpolar compounds with lipids is based on a different phenomenon, the hydrophobic interaction (see Sec. 7.2), but the end result is the same: formation of a molecular dispersion of the solute in the solvent. Adrien Albert (1979) discusses these correlations in his excellent book.

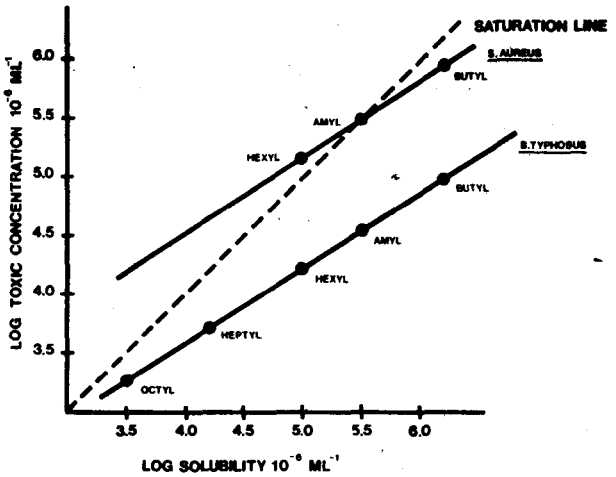


Fig. 1.2. Bactericidal concentration of primary aliphatic alcohols *versus* their water solubility. Since the two axes have the same scale, the saturation line has a slope of one. (Data from J. Ferguson (1939) *Proc. Roy. Soc.* (B) *127*:387).

There are few examples where solubility in only one phase correlates with pharmacological activity. One example is the local anesthetic activity of *p*-aminobenzoic acid esters which is directly proportional to their lipid solubility. Another thoroughly investigated correlation is that between the bactericidal activity of aliphatic alcohols with their solubility (Fig. 1.2).

In the homologous series beginning with *n*-butanol and ending with *n*-octanol, the bactericidal activity increases with increasing molecular weight (i.e., the log toxic concentration decreases) in cultures of the sensitive gram-negative *Bacillus typhosus*. Even the rather water-insoluble octanol is active in a concentration below the saturation point. The "saturation line" in Fig. 1.2 is a diagonal line with a slope of unity (log solubility vs. log solubility, since the scales of the ordinate and abscissa are identical).

If the same homologous series is tested on cultures of the less sensitive *Staphylococcus aureus* (dotted line), the activity line is displaced toward higher concentrations. While *n*-butanol and *n*-pentanol are active, higher members of the series fail to kill the bacteria because the necessary concentration cannot be reached; it is higher than the saturation concentration, thus lying above the saturation line. This interesting interpretation of the "cutoff" point in this homologous series was proposed by J. Ferguson (see Albert, 1979).

Bactericidal aliphatic amines show a cutoff point at dodecylamine, the C_{12} member of the homologous series, even though amines have no solubility problems like the alcohols. However, the next member of the homologous series, the C_{14} amine, is at the critical micelle formation point (see Sec. 4.1), and this compound, or higher members of the series, can contribute fewer and fewer monomeric molecules to the solution. Since monomers are essential to the bactericidal activity, this results