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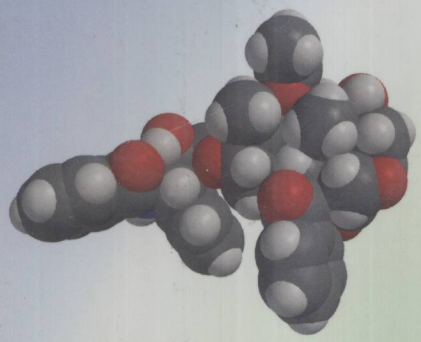

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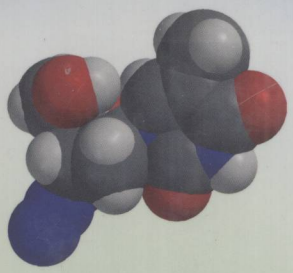

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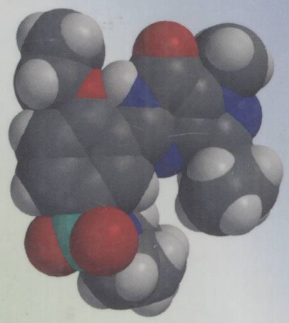

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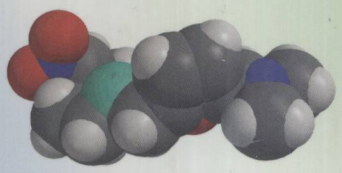
MOLECULES AND MEDICINE



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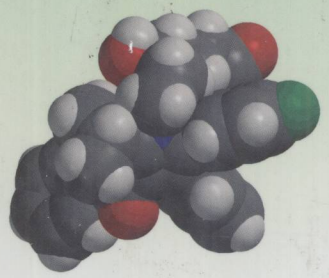

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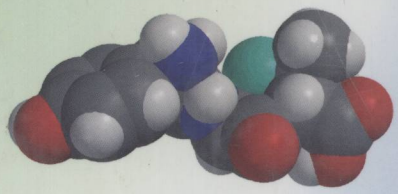

Amoxicillin (Amoxil)

E.J. Corey • Barbara Czakó • László Kürti

MOLECULES AND MEDICINE

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MOLECULES AND MEDICINE

THE WILEY BICENTENNIAL–KNOWLEDGE FOR GENERATIONS

Each generation has its unique needs and aspirations. When Charles Wiley first opened his small printing shop in lower Manhattan in 1807, it was a generation of boundless potential searching for an identity. And we were there, helping to define a new American literary tradition. Over half a century later, in the midst of the Second Industrial Revolution, it was a generation focused on building the future. Once again, we were there, supplying the critical scientific, technical, and engineering knowledge that helped frame the world. Throughout the 20th Century, and into the new millennium, nations began to reach out beyond their own borders and a new international community was born. Wiley was there, expanding its operations around the world to enable a global exchange of ideas, opinions, and know-how.

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William J. Pesce
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PREFACE

This book is intended for a broad readership, starting with curious and thoughtful college undergraduates and, reaching beyond, to professionals and researchers in the life sciences and medicine. It is hoped that it will also be useful to the educated lay person with an interest in health and medicine.

An effort has been made to integrate chemistry, biology, drug discovery and medicine in a way that is clear and self-explanatory. Heavy use has been made of chemical structures, since they provide a fundamental key to the language of life and the human activities that flow from it. Our age has seen the rapid evolution of molecular medicine as a critical part of the broader fields of health care and the biochemical basis of human disease. The understanding of human illness at the molecular level has brought, and will bring, great benefit to mankind.

There is a price to be paid in any attempt to understand molecular medicine, because that comprehension requires an ability to decipher chemical structures, which many have regarded as too onerous. One purpose of this book is to demonstrate that an adequate understanding of chemical structures is easily within the reach of most educated people, and well worth the effort. Pages 4-31 of this book aim to provide the insights and background required to appreciate the architecture of therapeutic molecules and their target proteins, as they parade though the subsequent pages of this book.

"*Molecules and Medicine*" delves into the discovery, application and mode of action of well over one hundred of the most significant molecules now in use in modern medicine. It is limited to *centamolecules*, i.e. molecules with molecular weights in the hundreds (several hundred times more than a hydrogen atom). The important and rapidly developing area of macromolecular therapy, which involves *much larger molecules* (macro-molecules), such as biologically active proteins and monoclonal antibodies, is a different story, and another book.

We have tried to minimize the amount of prior knowledge required of the reader by providing much background information, both chemical and biomedical. An effort has also been made to be concise as well as clear. A large amount of material has been compressed into a small space for each therapeutic agent. Generally, each medicine is allotted just one page. One advantage of this modular arrangement is that it facilitates the reading of the book in small installments and also its use as a reference work. The therapeutic agents in this book are arranged in sections according to the type of medical condition they treat.

There are also numerous sections in the book that provide biomedical background. For instance, there are two-page to eight-page summaries of topics such as inflammation, metabolic syndrome, immunology, drug resistance, cancer and neurotransmission. These are placed at strategic locations throughout the book.

The structural representations of proteins in this book are in the public domain and may be downloaded from http://www.pdb.org.

In the process of writing this book we have come to appreciate ever more keenly the enormous amount of human talent and effort that has enabled the extraordinary advances in molecular medicine since its advent several decades ago. To the countless chemists, physicians, biologists, educators and other professionals who have participated in this venture we extend our gratitude and thanks. This book is a tribute to them all.

The writing of this work has also been motivated by the realization that the advance of molecular medicine can be even more remarkable during the coming decades of this century, if a steady flow of dedicated and able young people into all the key areas of research in the life sciences can be maintained. If this book plays just a minor part in enhancing progress in molecular medicine and human well-being, our small effort will have been amply rewarded.

A NOTE ON THE USE OF THIS BOOK

Structures of Molecules and Proteins

Those who are not familiar with the notation used to describe the structures of organic compounds will profit from a close reading of pages 4-22 of this book. Others can read through this part quickly and proceed to the next section (pages 26-31) that reviews the notation used in the book for the structures of proteins.

The coordinates for each of the protein structures shown in the book are in the public domain and can be accessed electronically.

Accessing X-Ray Crystal Structure Data Files Online – The Protein Data Bank

All the crystal structure files can be downloaded from http://www.pdb.org by entering the four-character PDB ID that is indicated in red at the bottom of the page where the protein is displayed or in the reference section. For example, on page 63 in the entry for sitagliptin (Januvia™), the X-ray crystal structure of sitagliptin bound to the target protein DPP-4 is displayed. The access code (PDB ID) for this crystal structure appears below the picture as **1X70** along with the corresponding reference.

Graphic Rendering of X-Ray Crystal Structure Data Using PyMol

The renderings of the X-ray crystal structure data were developed by the authors using the software PyMol v0.99 (DeLanoScientific LLC, http://www.delanoscientific.com). For a description of the Protein Data Bank, *see*:

H.M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T.N. Bhat, H. Weissig, I.N. Shindyalov, P.E. Bourne: The Protein Data Bank. *Nucleic Acids Research*, *28,* 235-242 (**2000**).

Organization and References

The discussion of each of the therapeutic agents in the book is limited to one page, and, consequently, much in the way of detail has been omitted. For this reason, a number of up-to-date references on other aspects of each agent are given both at the bottom of the appropriate page and at the end of each section. The page numbers on which detailed references are listed for each therapeutic agent are highlighted in green at the bottom of the pages. Additional information on the pharmacology and properties of each medicinal agent can be found in:

Goodman & Gilman's The Pharmacological Basis of Therapeutics. Laurence L. Brunton, John S. Lazo and Keith L. Parker (Editors); (McGrawHill, 11th Edition, **2006**).

Other recent texts that provide much useful background information are:

(1) L. Stryer et al. *Biochemistry*, (W.H. Freeman, 6th Edition, **2007**)

(2) B. Alberts et al. *Molecular Biology of the Cell* (Garland Science, 4th Edition, **2002**)

(3) Weinberg, R.A. The Biology of Cancer (Garland Science, **2007**)

(4) *The Merck Manual of Diagnosis and Therapy.* M.H. Beers and R.S. Porter (Editors). (Merck & Co., 18th Edition, **2006**)

The references that appear in this book can serve as a portal to a great deal of information on the chemistry, biology and medicine relevant to the therapeutic agent and disease area. Additional material can be located by appropriate database- and internet searching (e.g., using SciFinder Scholar™, MEDLINE™ or Google™).

A **glossary** and an **index** appear at the end of the book.

Online Reader Feedback for the Authors

There is a website for this book maintained by the authors, the address for which is:

http://moleculesandmedicine.info/

Readers can use this website to provide comments or feedback on "*Molecules and Medicine*". The website will also contain certain useful updates. The authors invite the views of non-scientists who have read pages 4-31.

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PART I.

INTRODUCTION

We live in a troubled, but wonderful time. It is our good fortune to witness and benefit from scientific advances that would have been literally unimaginable to our grandparents. However, there are dark clouds on the horizon. The rate of growth of scientific knowledge has been so great as to outstrip the ability of our society to assimilate it, the capacity of the educational system to teach it properly, and the wisdom of government adequately to sustain and apply it. There is widespread indifference to science among the young. Even medical science, which touches the lives of us all, is generally left to the practitioners. Whatever the reason for this disparity between the importance of science and the lack of general public understanding, it is important to address it.

In this book we try to take a few steps in this direction. Specifically, the pages to follow tell the tales of many molecules that can qualify as miracles of modernity. These relatively small, highly-structured clusters of atoms, the principal therapeutic agents of modern medicine, can perform in a way that would have been considered miraculous to our ancestors. Such "miracle molecules" can save countless human lives, prolong human life, alleviate pain and suffering, control cells, tissues and organs millions of times their size, and bring enormous material gains through commercial sales of billions of dollars per year. Such molecules also can serve as tools to probe the molecular nature of life processes and disease states and pave the way for the discovery of other effective medicines.

The molecules at the core of this book have been carefully selected from several thousand therapeutic agents that have been used in medicine at one time or another. The development of each of them, arduous and costly though it might have been, represents an enormously valuable investment with very large and ongoing benefits. In the course of discovering all these wonderfully useful molecules, we have learned more about the discovery process itself and have developed an ever expanding set of new discovery tools. The invention of these new platforms for innovation is being powered by dramatic advances in technology, computing and the underlying chemical and biomedical sciences.

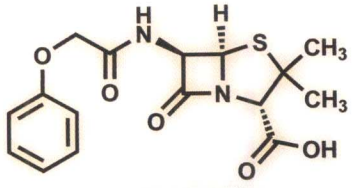
The very next section of this book provides a step-by-step introduction to the understanding of the architecture of organic molecules and the general principles that govern structures of molecules. In addition, we explore the fundamental forces that hold molecules together and that allow them to recognize and bind to one another. The affinity of molecules for one another is central to the biological activity of therapeutic agents and to life itself. The section on how to read the chemical diagrams of small molecules is followed by another tutorial on understanding much larger structures, the proteins of life.

It seems quite possible that, in the next century or so, effective treatments for most illnesses will emerge. Disease, premature death, suffering and pain may no longer be a part of the human condition. Humans will as a matter of course live out a full and healthy lifespan, and then depart with grace and dignity. The famous poem of Lady Gio in "The Tale of the Heike" describes the life process and its end in an eloquent and happy way:

Grasses of the plain,
Springing up and withering,
They all fare alike.
Indeed the lot of all things
Is but to wait for autumn.

An impossible dream? Perhaps, but the immense effort required will be well worthwhile, because the gain will be incalculable. The achievements of modern science and technology provide both encouragement and inspiration.

For instance, we are now able to trace our universe back some 14 billion years to an unbelievably hot object, with a temperature of about 10^{32} Kelvin (10 followed by 32 zeros), and more than a million times smaller than the period at the end of this sentence. From this inferno of exceedingly small and simple objects, the first elements, hydrogen and helium, formed about a million years later, to be followed by all the other objects of the universe – the chemical elements, stars and galaxies, and an unknown collection of other forms of matter and energy, and finally the earth and life upon it. Surely, a time will come when our knowledge of life, intelligence, disease and health will dwarf that of the present.



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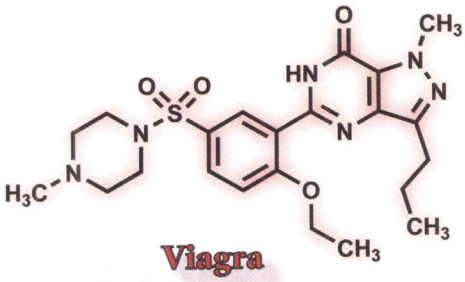

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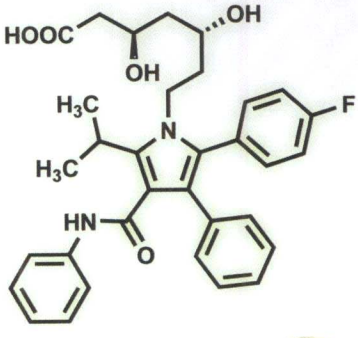
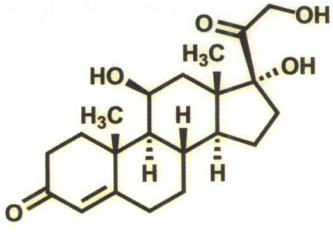
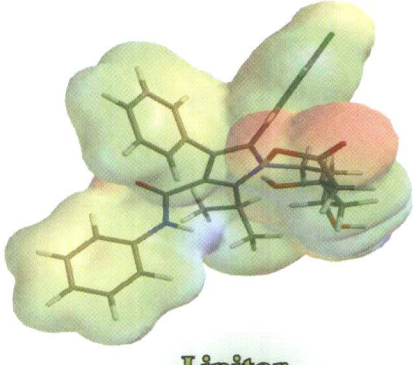
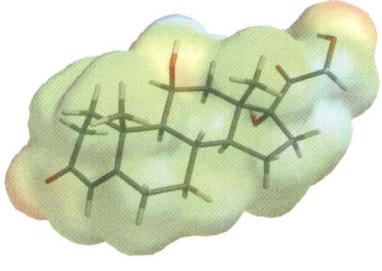






Lipitor



Cortisol

UNDERSTANDING STRUCTURAL DIAGRAMS OF ORGANIC MOLECULES

Introduction. Some Sample Molecules

The Simplest Molecule, H_2

Hydrogen, the simplest element, has atomic number *one* because it contains just *one* proton in the nucleus and *one* electron that surrounds it. A hydrogen atom is so reactive that it will *totally* combine with another hydrogen atom to form the simplest molecule, H_2. This process, the simplest of all chemical reactions, takes place extremely rapidly and with the release of much energy because the energy content of H_2 is much less than two isolated hydrogen atoms. The chemical equation for the reaction is:

Equation 1. Two hydrogen atoms combine to form one hydrogen molecule (H-H) with the evolution of energy.

In equation 1, the dots represent electrons. The chemical bond that holds H_2 together is designated by a double dot, or simply, by a line between the hydrogens. Because the electrons are shared equally, the molecule is nonpolar. This type of two-electron bond is called a covalent single bond. Although an electron has a mass, it is very small ($9x10^{-28}$ g, at rest), and behaves like a wave. In addition, because of the Heisenberg uncertainty principle, its position and momentum cannot both be known precisely. Its location is best described in a probabilistic way as a cloud-like representation (Figure 1).

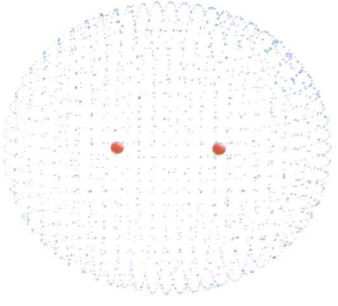


Figure 1. Approximate representation of the spatial distribution of electrons in an H_2 molecule about the nuclei (red spheres). The outer layer of dots encloses about 90% of the total electron cloud.

Helium, a Chemically Inert Element

Helium (He), atomic number *two*, has *two* protons in the nucleus and *two* surrounding electrons. The atom is stable chemically because it neither combines with itself nor reacts with other elements. The reason for this inertness is that two is the maximum number of electrons that can be accommodated in the available orbital. This orbital allows the electrons to distribute themselves like a cloud with spherical symmetry about the nucleus. This orbital is called the 1*s* orbital. The other orbitals of He are so high in energy that they are not accessible for chemical bonding with any atom or chemical fragment. Helium is the simplest of the inert elements. These elements share the feature of having the full complement of electrons in the available orbitals.

Nature of the Chemical Bond in H_2

In H_2, each H contributes a 1*s* *atomic orbital* (AO), leading to the formation of two *molecular orbitals* (MO's), one of lower energy than the AO and the other of higher energy. The two electrons of H_2 can occupy the lower energy MO, and so H_2 is stabilized relative to two H atoms, as the diagram in Figure 2 illustrates.

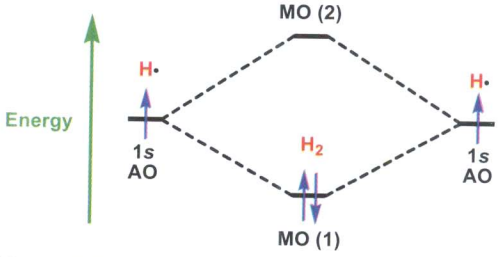


Figure 2. Energy diagram for the combination of two H atom 1*s* AO's to form two MO's of diatomic H_2. The electrons occupy the lower, bonding MO(1) and are shown as blue arrows. MO(2) is an orbital that is not occupied by electrons because of its high energy. MOs can hold only two electrons. These electrons must have opposite spins.

One simple way of thinking about the electron in the H atom is to consider it like a cloud of gas around the nucleus that is kept in place by the electrostatic attraction between the negative electron and the positively charged proton. Once H_2 is formed, the two