Foundations of Molecular Pharmacology

Volume 1

Medicinal and Pharmaceutical Chemistry

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Preface

This text has emerged from some thirty years of teaching undergraduate courses and conducting research in medicinal and pharmaceutical chemistry. It is conceived essentially as a foundation course in the basic principles of organic chemistry applied to the study of medicinal agents and the formulations in which they are used. It is intended primarily to cater for the needs of undergraduate students of pharmacy and medicinal chemistry up to Honours level. References to original papers, however, should extend its use to postgraduate students and others engaged in the search for new drugs.

My intention was to contain the text within the covers of a single volume, concentrating essentially on the fundamental groundwork chemistry which must of necessity be taught in any undergraduate course. Experience, however, has shown the value of more general discussion of certain selected topics of wide general applicability in the study of drug action, and it was always my objective to conclude the book in this way. In the event, I have been defeated, partly by the ramifications of the subject, but mainly by my enthusiasm and attempts to achieve a realistic degree of coverage. Publishing costs, too, have risen enormously in the ten years of writing. Attempts to overcome the twin difficulties of coverage and cost, therefore, left no alternative other than to divide the book between two volumes.

It is just possible that some readers may find virtue in the necessity which has forced this publication of the Foundations of Molecular Pharmacology in two separate volumes. I hope, nonetheless, that serious students will not be deterred by this somewhat artificial division from pursuing the broader approach to the subject contained in Volume 2. In order, therefore, to reinforce the continuity of the subject, I have provided a system of cross-referencing between chapters, both within and between the two volumes. Such cross-references are denoted by two numbers, the first indicating volume, and the second chapter; thus, for example, (**1**, 13) indicates Volume 1, Chapter 13, and (**2**, 5) Volume 2, Chapter 5.

The basic philosophy underlying the text is that those concerned with the design and use of drugs and medicines are interested fundamentally in properties rather than in methods of manufacture. Accordingly, the chemistry in this book almost entirely ignores the synthesis of medicinal agents. Instead, attention is focused, in Volume 1, on the physical and chemical properties of medicinal agents, pharmaceutical additives and cellular components, that determine the way in which they interact with each other. To achieve this end, substantial accounts of relevant intermediary tissue metabolism, drug transport and metabolism, and other factors affecting both stability and availability of drugs from

dosage forms have been brought together in the general body of the text. This approach emphasises the close similarity between chemical and biochemical transformations, and should help to give students and others engaged in the design of new drugs a better understanding of the fundamental mechanisms which control interactions between drugs and body chemistry.

The more general, but essentially similar approach to the Chemical Basis of Drug Action adopted in Volume 2, which reinforces the basic principles for the specialist, should also appeal in its own right to clinical pharmacologists and others whose interests lie rather more in the action and use of drugs than in their design.

Since this book is designed to assist in the education of students, many of whom will be engaged in later life in the handling and use of drugs in practice, I have deliberately chosen to draw my examples from drugs in current use in western medicine. My text, however, is essentially British, and British Approved Names, denoted by italics, are used throughout, notwithstanding the difficulties that this may make for North American readers. Fortunately, British and American drug nomenclature is convergent, but where important and confusing differences still exist, I have endeavoured to overcome them by also giving the United States Adopted Name.

It is an unfortunate fact of life that the vast majority of modern drugs have chemical structures which are infinitely more complex than those of the simple examples commonly used in most textbooks of organic chemistry. Indeed, their very complexity frequently presents an educational hurdle, so that students of medicinal and pharmaceutical chemistry often fail to grasp the essential simplicity of drug action mechanisms and transformations. I am, therefore, most grateful to the publishers for their help and co-operation in the use of printing devices involving bold type and colour to focus attention on the simple stepwise transformations of otherwise complex compounds.

I am very much indebted to my colleagues, past and present, and friends, who between them provided the stimulus to write this book, and all those who, once I was embarked upon it, so patiently answered my questions, and helped to resolve the many problems I inevitably encountered. I am especially grateful to Dr G. A. Smail and Dr R. E. Bowman, both of whom read the entire original draft and commented so helpfully upon it. I am sure others will still find errors, oversights and misconceptions, but there would have been many more without the help of these two colleagues. For similar reasons, I am also grateful for all the many valuable comments and criticisms I received from the Athlone Press's own anonymous referees. My most grateful thanks are also due to Tom Moody for help with the preparation of diagrams, to Dr N. C. Dhar for assistance in locating and checking references, and especially to my ever willing Secretary; Mrs Sylvia Cohen, for her invaluable help in typing the manuscript, for countless hours devoted to the dull routine of checking text and references at every stage right through to the final proofs, and for her help in compiling the index.

The time I have taken to write this book has been taken away from many things I might otherwise have done, and most of all, taken from my wife, Anne, and our family. Their tolerance and support made it possible. I have tried to make this book one that they, too, can be proud of, and worthy of the hours of pleasure in their company which I have sacrificed.

1978 John B. Stenlake

Contents

Contents of Volume 2

1 Introduction

Pharmaceutical Chemistry is the study of the chemistry of drugs. It is concerned primarily with the chemical and physico-chemical properties of drugs insofar as these are relevant to an understanding of their action on living tissue. Drug action, also, can only be explained in its ultimate analysis in terms of chemical and physico-chemical reactions of the drug with the chemical constituents of living matter. Of necessity, therefore, the subject also embraces the study of the so-called receptor molecules of living tissue with which drugs react, and in this sense Pharmaceutical Chemistry can be considered to bear the same relationship to Biochemistry as Pharmacology does to Physiology. It is based, however, on the study of chemical properties and chemical reactions rather than physiological reactions, and employs the art, technique and method of the chemist, with all the refinements of modern physico-chemical methods of analysis to study both drug and drug–tissue–receptor interactions.

The very complexity of living matter even in the simplest organism presents a phenomenal problem to the would-be-investigator of the chemical reactions of drugs with the molecules of living tissues. Often all too little is known of the precise structure of receptor molecules to permit analysis of the exact mechanism of their reaction with drugs. This is especially true of the natural biopolymers such as peptides, proteins, nucleic acids and carbohydrates. For this reason, more than any other, Pharmaceutical Chemistry was for many years concerned almost entirely with the study of the properties of the drug molecules themselves. This aspect of the subject, limited though it is, is no less essential than it ever was, but the refinements which are now possible with modern separation and analytical methods are slowly allowing extension of the subject to include interpretation of the all-important drug–receptor interactions in the basically chemical, rather than merely descriptive terms, which is so essential to the full development of the subject.

Pharmaceutical Chemistry must, therefore, eventually aim to explain both the symptomatic and curative properties of drugs in man and domestic animals, and in the same way also to provide an understanding of the toxic reactions of drugs which have selective host-parasite action, and which are used to control and eradicate infection by pathogenic bacteria, viruses, and multi-cellular parasites. The complex structural and tissue organisation of higher animals requires consideration of the chemical and physico-chemical properties of drugs responsible for the various processes at tissue level, which together lead

Table 1. The Periodic Table of Elements

	METALS												NON-METALS					
Group	IA	IIA	IIIB	IVB	VB	VIB	VIIB	VIII			IB	IIB	IIIA	IVA	VA	VIA	VIIA	0
Period																		
1	H																	He
2	Li	Be											B	C	N	O	F	Ne
3	Na	Mg	Transition metals										Al	Si	P	S	Cl	Ar
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
5	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
6	Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
7	Fr	Ra	Ac															
Lanthanides					Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
Actinides					Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lw

to the observed response. Consideration must, therefore, be given to each of the following gross factors which can influence response to the drug:

(a) absorption and transport,
(b) selectivity of location,
(c) selectivity of action,
(d) bio-transformation,
(e) excretion.

Appreciation of the rôle of these factors in drug–receptor interactions at molecular level rests in the first instance on an understanding of the forces leading to bonding between atoms and molecules, and of other relevant forms of non-bonded interaction between molecular species. Secondly, it requires an understanding of the influence which small modifications in chemical structure of drugs can have on their physical properties and chemical reactivity. The modifying influence of the additives and processes used in pharmaceutical formulation must also be considered as factors affecting the mechanism of drug–receptor interactions.

Pharmaceutical chemistry is concerned largely with organic compounds. A number of inorganic compounds, including water, various elements, their ions and certain complex ions are also of considerable importance, and require consideration for a full understanding of the action of drugs. The **Periodic Table** of elements is set out (Table 1) for reference.

ATOMIC STRUCTURE

The Atom

Atoms consist essentially of a positively-charged **nucleus** made up of a number of **protons** and **neutrons** surrounded by associated negatively-charged **electrons**. Since protons are positively charged and neutrons have no charge, the overall charge of the nucleus is determined by the number of protons it contains. Each element has a different number of protons in its nucleus and this number is known as the **Atomic Number** of the element. The mass of the atom is concentrated almost entirely in the nucleus since the mass of an electron is only about 1/1840th of that of a proton or neutron. The nett charge on any atom is zero, hence the number of nuclear protons must equal the number of extra-nuclear electrons.

Many elements have several different **isotopes**. Hydrogen, for example, has an Atomic Number of 1. There is one proton in the nucleus, hence one extra-nuclear electron. The hydrogen nucleus can, however, contain either none, one or two *neutrons* and so there are three forms of the element. All have one proton and one electron and thus identical chemical properties. The isotope with one neutron and mass number, two, is the isotope, deuterium. That with two neutrons and mass number, three, is tritium.

Extra-nuclear Electrons

The extra-nuclear electrons can be considered either as particles rotating in orbits about the nucleus, or as stationary waves having a maximum amplitude at a surface or **orbital** about the nucleus. According to the classical theory of Bohr and Sommerfeld, based on the observation of the emission spectrum of hydrogen, the extra-nuclear electron of hydrogen can be considered as a particle orbiting about the nucleus in a defined 'shell' with a fixed radius determined by the electrostatic force between the electron and the nucleus. The wave-like properties of electrons were proposed by De Broglie, who drew an analogy between the behaviour of light and other forms of radiation involving electrons. The problem of measuring the precise location and momentum of an electron gave rise to the **Heisenberg uncertainty principle**. This stated that both the precise position and the momentum of an electron cannot ever be known at the same time. Application of this concept in wave mechanics has therefore led to a modification of the classical concept of electron orbits, in which the *probability* of finding an electron at various distances from the nucleus is defined by a three-dimensional **orbital**. Thus, the orbital delineates a three-dimensional surface in relation to the nucleus of the atom, in which there is the highest probability of finding a particular electron.

The energy level of each orbital is defined by principal, n, orbital, l, and magnetic, m, quantum numbers, with restrictions on the possible values of l and m as in the Bohr–Sommerfeld concept. Each orbital, however, may accommodate only two electrons, which by the **Pauli exclusion principle** must have opposed spins, since according to this principle no two electrons in the same atom can have the same values for the four quantum numbers, n, l, m and s. It is this principle which establishes that each electron in an atom is unique in its total energy content, and which therefore determines the total number of electrons which can be accommodated at each of the principal energy levels (or shells in the classical concept). Thus, when $n = 1$, the only possible value of l is zero. Therefore, there is only one orbital at this energy level, which at most can accommodate two electrons with opposed spins. This is the so-called 1s orbital, which is present in hydrogen and helium, containing one and two electrons respectively (p. 5). The terminology, 1s, which is used to describe this orbital, defines the principal quantum number, one; the letter s, however, is derived from a reference to the associated line spectrum and not to the spin quantum number and refers to the fact that $l = 0$.

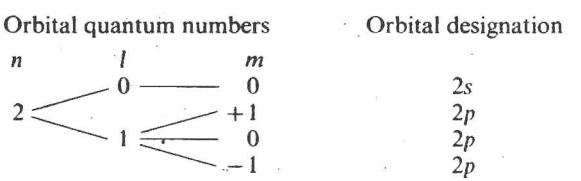

Fig. 1. Permissible values of azimuthal and magnetic quantum numbers when $n = 2$

Similarly, when $n = 2$, possible values of l are 0 and 1, and possible values of m are $+1$, 0, and -1. Figure 1 shows the combinations of these permissible values for n, l and m and defines four orbitals, each of which is capable of accommodating a maximum of two electrons with opposed spins ($s = +\frac{1}{2}$ or $-\frac{1}{2}$). These four orbitals are the 2*s* and three 2*p* orbitals which are progressively filled in the elements lithium, beryllium, boron, carbon, nitrogen, oxygen, fluorine and neon in the first short period of the Periodic Table (Table 1).

Table 2 shows the possible combinations of values attributable to the principal orbital and magnetic quantum numbers, which define the various atomic orbitals and determine the maximum possible number of electrons which can be accommodated at each of the principal energy levels from one to five. The order in which individual orbitals are filled is shown in Table 3. This depends, however, on their relative energy levels (Fig. 2) so that they are not filled exactly in sequence.

The shapes of atomic orbitals are important, and are determined by the energy state of their electrons. The two 1*s* electrons occupy a single three-dimensional orbital (1*s* orbital) which is spherically symmetrical about the nucleus, but separated from it by a region or spherical nodal surface in which the probability of finding an electron approaches zero. Figure 3 is a planar (two-dimensional) representation showing the relationship of the 1*s* orbital to the nucleus in the atoms of hydrogen and helium as might be seen in sectional view. The only differences between the orbitals of the two atoms are that of size, and that in hydrogen, the orbital contains a single unpaired electron, whilst in helium, there are two electrons with opposite spins in the one orbital.

Table 2. Disposition of Electrons in Shells and Energy States

Quantum number			Orbital designation	Number of electrons
n	*l*	*m*		
1	0	0	1*s*	2
2	0	0	2*s*	2
	1	0, ±1	2*p*	6
3	0	0	3*s*	2
	1	0, ±1	3*p*	6
	2	0, ±1, ±2	3*d*	10
4	0	0	4*s*	2
	1	0, ±1	4*p*	6
	2	0, ±1, ±2	4*d*	10
	3	0, ±1, ±2, ±3	4*f*	14
5	0	0	5*s*	2
	1	0, ±1	5*p*	6
	2	0, ±1, ±2	5*d*	10
	3	0, ±1, ±2, ±3	5*f*	14
	4	0, ±1, ±2, ±3, ±4	5*g*	18

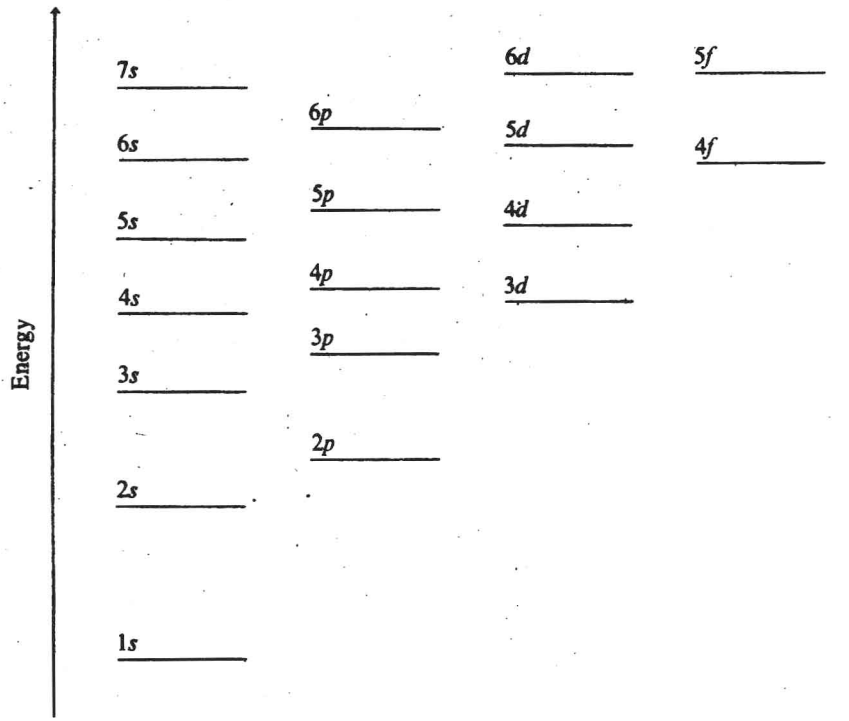

Fig. 2 Relative energy levels of atomic orbitals

It must be remembered, however, that Fig. 3 is merely a sectional two-dimensional representation of a three-dimensional structure. The spatial relationship between the nucleus and the orbital could perhaps be imagined as similar to that of the pip at the centre of an orange relative to the skin of the orange.

Similarly, the 2*s* valency electrons of lithium and beryllium, elements three and four in the Periodic Table, occupy a 2*s* orbital, which is spherically symmetrical about both the nucleus and the 1*s* orbital, and separated from the latter by a spherical nodal plane in which the probability of finding an electron also approaches zero (Fig. 4). Like the 1*s* orbital, the 2*s* orbital may contain a single (unpaired) electron as in lithium, or two electrons with opposite (paired) spins as in beryllium. Both 1*s* and 2*s* orbitals being spherically symmetrical, however, are not directionally orientated, and the completion of such orbitals by the receipt of electrons in chemical combination gives rise to bonds which have no element of directional orientation.

The three 2*p* orbitals are directionally orientated, so that the probability of finding an electron is greater in certain directions than in others. They are dumb-bell shaped, and directed at right angles to each other along notional axes.

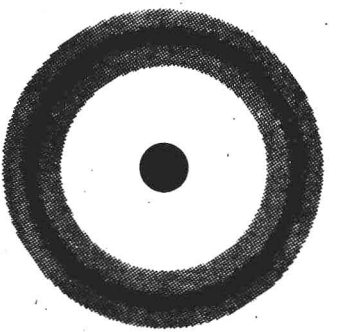

Fig. 3 Planar representation of the relationship between the 1s orbital and the nucleus in the hydrogen and helium atoms

These axes are designated x, y and z axes, and the orbitals corresponding to them are described as $2p_x$, $2p_y$ and $2p_z$ orbitals respectively. Each orbital exhibits a **nodal plane**, passing through the nucleus of the atom at right angles to the axis, in which the probability of finding an electron is zero, thereby creating the 'dumb-bell' shape (Fig. 5).

The entry of electrons into the three equivalent $2p$ orbitals is governed by **Hund's rules**, which are based on the fact that mutual repulsion energy will be less if the electrons have unpaired spins. For this reason, when electrons are added successively as in the elements boron, carbon, nitrogen, oxygen, fluorine

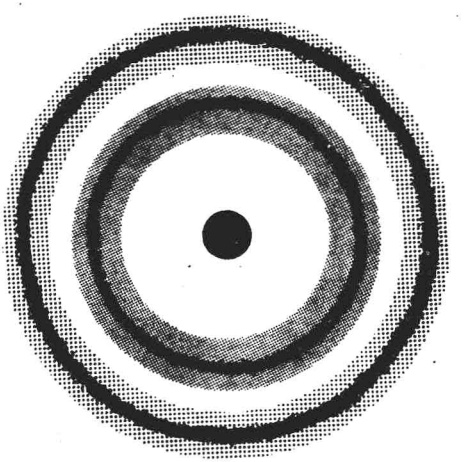

Fig. 4 Planar representation of 1*s* and 2*s* orbitals in lithium and beryllium

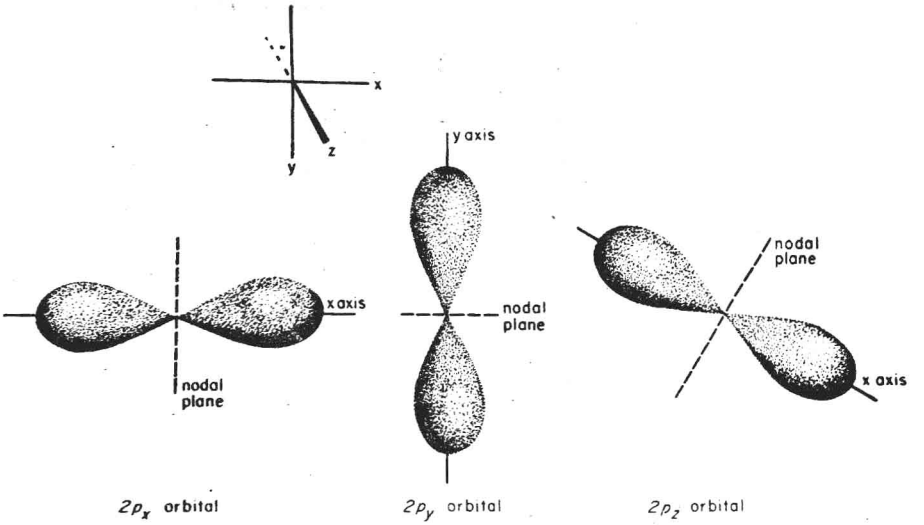

Fig. 5 Dumb-bell shaped $2p$ orbitals

and neon, as many orbitals as possible are singly occupied before any pairing occurs. It follows also that in the ground state, two electrons each occupying a pair of equivalent orbitals, tend to have parallel spins.

Valency

The electronic theory of valency is based on the assumption that normally only the electrons in the highest energy state (i.e. the outermost orbital) participate in the formation of chemical bonds. In some cases, only electrons in the highest sub-levels are involved; in others, lower sub-levels in either the highest principal energy state or next highest principal energy state are also implicated. The theory, due to Kossel (1916) and Lewis (1916), relates the chemical stability of the rare gases to the possession of a complete set of electrons in the highest energy state. In all but helium, which has only two extra-nuclear electrons in the 1*s* level, this means an **octet** consisting of two *s* and six *p* electrons (Table 3).

Atoms combine by the gain or loss or sharing of valency electrons in an attempt to achieve the stable octet configuration of the inert gases by the formation of chemical bonds. Three principal types of chemical bond are recognised in the formation of chemical compounds:

(a) electrovalent,
(b) covalent,
(c) co-ordinate-covalent.

All three, together with a number of low energy bonding forces, such as hydrogen bonding, van der Waals bonding, and charge-transfer complexing, are also important in the interaction of drugs with biological receptor molecules (**2**, 2).