Quantum pharmacology

Second edition

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PREFACE to Second edition

The guarded optimism of the first edition of this book has proved to be well justified. In the intervening five years many of the hopes and speculations have become reality. Many pharmaceutical companies now employ specialists using theoretical methods; graduate students with experience in this area are much in demand.

Sceptics used to ask the small body of practitioners to name the drug discovered by theory. Still there is no simple answer to that question, but there are many instances where theoretical calculations have made a significant contribution towards the development of novel active compounds. Evidence for this includes the naming of computational chemists on patents.

The process is accelerating, above all due to developments in the computing world. The day of the minicomputer is being followed by the era of the micro. The most recent microcomputers have the sort of computing power previously associated with expensive mainframe machines. The use of mini- and microcomputers obviates the need for professional operators and has removed the cost restriction which meant that only generously funded academic institutions could explore the field. In addition, the new generation of computer graphics devices, especially those incorporating colour, permit the results of theoretical calculation to be displayed in a readily assimilable form.

The range of problems being studied has expanded so that now one of the more active areas is the field of agrochemicals: herbicides, fungicides and pesticides. Improvements in theoretical methods as well as computers have permitted the study of larger and larger molecules and systems of molecules, to the extent that perhaps the most exciting current work is in the realm of enzyme binding sites. If ever a drug is found using almost solely theoretical methods, it is likely to be by the design of completely novel enzyme blockers.

The new edition follows the pattern of the original. Part I, a summary of molecular pharmacology, has been extensively rewritten. Part II, the summary of molecular quantum mechanics, has relatively minor changes. The third section, on applications, is almost entirely new. The bibliography which constitutes Part IV has been brought up to date to December 1981.

Many colleagues and former students have been of significant help in the revision but I must thank in particular Keith Davies, Graham Durant, Keith Heritage, George Jaroskiewicz and above all Hilary Little. Joy Johnson again typed the manuscript and drawings were done by David Kozlow, save for those produced using computer graphics by Keith Davies.

Preface to first edition

It is tempting to add a question mark to the title of this book. Even the generous-spirited may feel that it is premature to start applying the methods of molecular quantum mechanics to the problems of medicinal chemistry, while sceptics will certainly feel that pharmacology is far too complex to be clarified by purely theoretical calculations.

These doubtful views are not in line with the current state of either molecular pharmacology or molecular quantum mechanics. Both subjects have advanced to the point where the problems of one are susceptible to the methods of the other. A major factor which has prevented widespread application of quantum chemistry to medicinal chemistry has been the fact that very few people are experts in both disciplines. In general, medicinal chemists are trained as organic chemists, while quantum mechanicians are more at home with computers and algebra than with dose–response curves or nerve impulses.

The aim of this book is to enable the medicinal chemist and pharmacologist to appreciate enough of the methods and uses of molecular quantum mechanics to apply the techniques, and to show the theoretician who has the techniques available, what problems may be clarified by these methods.

The field is one of great complications with many major questions unanswered, so that it is important to proceed with caution. Unfortunately, merely running a molecular orbital calculation for a given molecule is so simple once one is shown how to use a standard computer program that some over-facile work has been published. This should not, however, compromise the whole subject. With care the contribution of theoretical methods can be illuminating and should stand alongside and complement the experimental structural methods such as X-ray diffraction and nuclear magnetic resonance.

The intention is that this book should serve as an introduction for two sets of experts into the field of the other, or a newcomer into both. The work is divided into four parts so that readers familiar with the content of one particular section can avoid it and find the rest of the topic complete. After giving a brief selective account of molecular pharmacology and molecular quantum mechanics, the applications of one to the other are treated in Part III. Finally, Part IV is a complete bibliography of the subject up

to the end of 1976. In this way researchers new to the topic and stimulated to try out the techniques, which can be done with no previous background using generally available computer programs, will have available a complete account of all previous work.

In writing a book which crosses the boundaries between scientific disciplines one is dependent on help from friends and colleagues. The following people, listed alphabetically, gave me assistance either by discussion or by reading parts of the manuscript, but I must single out Dr Barrie Hesp of ICI Pharmaceuticals Division whose help and patience have been invaluable. I should like to express my appreciation to John Barltrop, David Beveridge, Alison Brading, Robin Ganellin, Keith Heritage, Stephen Moore and John Northup. I am also indebted to David Kozlow and Maria Weil who did the drawings and to Joy Johnson who typed the original manuscript.

Finally I should like to thank Butterworths whose generous fellowship enabled me to write this book in three of the world's loveliest and most stimulating locations.

Berkeley, Oxford, Stanford W.G.R.

Introduction

The men of genius who developed quantum mechanics in the 1920s and 1930s predicted an end to experimental chemistry, suggesting that it would become merely a branch of applied mathematics. Those early hopes or fears have proved groundless. Despite the fact that, in principle, the solution of the Schrödinger wave equation contains all the answers, in practice experimental chemistry still thrives.

For a period of over thirty years the theoretical chemist had to be content with perfect solutions of equations for the hydrogen atom and approximate solutions for a narrow range of very small chemical entities such as the helium atom, the hydrogen molecular ion and daringly enough, the hydrogen molecule. If one reads some theoretical chemical journals, one could be forgiven for believing that these small systems remain the obsession of theoreticians. However, since about 1960 there has been a rapid qualitative and quantitative change; a change brought about not by theoretical advances but by the advent of increasingly powerful computers.

Using what are only crude brute-force mathematical techniques, the computer has enabled the theoretical chemist to solve an approximate form of the Schrödinger equation to an arbitrary level of accuracy for larger and larger molecular systems. There are now numerous examples where these theoretical calculations can produce more precise details of molecular properties than can experiment. Such calculations may be expensive in terms of computer time and one may question the intrinsic value of some of the calculations which are performed, but it is not open to question that at the present time the methods of molecular quantum mechanics are sufficiently sophisticated to answer questions of molecular physics. For example, the water molecule, H_2O, has a bond angle between the two OH bonds which may be computed to an accuracy beyond the measuring capacity of spectroscopy. The barrier to inversion of the ammonia molecule, NH_3, can be calculated to any desired accuracy if one takes enough care with the computation. Even a tiny energy difference such as that between the energy levels responsible for the radio-astronomical detection of CH has been calculated more accurately than laboratory experiment allows.

In many ways the problems of molecular physics in which one considers an *isolated molecular species* are solved. It may be preferable or cheaper

to measure a molecular property, such as a bond length or dipole movement, than it is to calculate the value, but the calculation can be done. In this realm the calculation will be more useful when the experiment cannot be performed, perhaps because the molecular species cannot be synthesized or is unstable and short-lived under experimental conditions. The calculations treat the molecule as totally isolated in space. This is a reasonable approximation to the experimental situation pertaining in gas-phase spectroscopic studies or in interstellar space.

The molecules which are within the scope of the most accurate theoretical methods are only slightly smaller in terms of the number of atoms they contain than many of the molecules which are of key importance to molecular pharmacologists, such as neuro-transmitters or drugs. It is tempting then to use the same type of theoretical calculation to probe the questions to which the pharmacologist would like an answer.

Before yielding to this temptation, however, several very important extra qualifications and safeguards must be discussed. There are many aspects of pharmacology which must be stressed if the theoretical calculations are not to be so naive as to be ludicrous.

An obvious theoretical restriction is imposed by the fact that the interesting molecules are large by comparison with those handled confidently by theoretical chemists. This means that even if the more rigorous methods of calculating molecular wave functions are employed, then large amounts of computer time may be required. As an alternative, one of the more rapid but less reliable approximate methods may be used. It will become clear later when we discuss the problems in more detail that the substitution of approximate for more rigorous theoretical methods is even more likely to be necessary because we will be interested not in one single molecular entity, but in a series of compounds and furthermore a range of geometries, conformations and tautomeric or ionic forms of each. The necessity of doing a large number of calculations may force us to use the approximate or semi-empirical molecular orbital methods for the immediate future.

None of the semi-empirical or *ab initio* molecular orbital methods is sufficiently reliable for its predictions to be accepted without question. Thus a primary qualification on any theoretical calculation is that the results and predictions should be in accord with some measured physical property. The obvious experimental results which can be used to test the reasonableness of calculations are X-ray crystallographic data, n.m.r. solution conformation or dipole moments for charge distributions with, in some cases where the data are available, nuclear quadrupole resonance studies or neutron scattering results.

The theoretical calculations should be consistent with these experimental findings; not necessarily in perfect agreement, since it must be stressed yet again that the calculations refer in general to the isolated gas-phase molecule, while crystallography is performed on a solid form and n.m.r. most frequently on rather concentrated solutions.

Not one of these three environments is exactly appropriate to the situation where the molecule of interest is involved in a biological process in a living system. In such surroundings it may be in a lipid or aqueous phase with a protein surface and a variety of ions in the vicinity, and in an ionic form

different from the most abundant species which is found in solution at so-called 'physiological' pH.

Much effort is being expended by theoreticians on the fascinating problem of just how water as a solvent affects the gas-phase molecule. This difficult and worthwhile problem will not, if solved, provide all the answers which would make the results of gas-phase calculations transferable to the biological situation.

The nature of the appropriate biological environment of a pharmacologically interesting molecule at the active moment is unknown. Consequently, the only way to make any progress in understanding is to do what is normally done in biological experiments when there are many variables, some of which are unknown, and one wishes to isolate the effect of a particular parameter. The normal practice is to do a lot of experiments and then to use statistics to highlight important and significant relationships between activities and parameters. This is quite different from the manner in which a physicist uses statistics. He tends to measure one thing knowing that all other variables are constant and statistics are only employed as a means of estimating the accuracy with which a single property has been measured as the result of a series of repetitive experiments.

The problem of the exact nature of the appropriate environment puts the theoretical chemists in exactly the same quandary as any medicinal chemist seeking a relationship between molecular structure and biological activity. We will of necessity have to consider a series of chemically similar molecules with a range of biological activities and seek a consistent theory which will explain the biological variation. The choice of such a series will be arbitrary within certain limits and only statistical support will be satisfactory if a convincing theory emerges.

Many calculations on single molecular species have been published as separate articles. These are not without interest and have proved helpful to experimentalists, but on their own they cannot logically provide a theoretical explanation of any form of activity. A set of calculations on a single molecule, which may supply, for example, a potential energy surface for the changing conformation of a flexible molecular species, ought to be considered as a sophisticated form of molecular model building rather than an end in itself.

Any medicinal chemist who has sought to understand the relationship between structure and activity will have found molecular models such as Dreiding models or the approximate space-filling CPK (Corey, Pauling, Kolthun) models profoundly illuminating. The models give a good indication of which molecular shapes of the small biological molecule are ruled out on atom–atom repulsion grounds. Whereas space-filling models represent atoms as shapes with hard edges, calculations provide 'soft-edges' in the form of a varying potential energy as one group of a molecule approaches another, rather than an 'on-off' indication at the point where hard edges touch.

At least in the field of small molecules no one has the effrontery to publish the results of playing around with molecular models, but the same cannot be said of those who perform calculations. Conformational calculations on single species are interesting but they must be insufficient to provide a theory of activity. A precise description of the molecular shape and charge

distribution which is essential for activity can only come from the study of a series of compounds, preferably with each member of the series considered in a wide range of conformations of all possible ionic and tautomeric forms. The reliability of the theory can then be judged objectively by the number of compounds fitting the theory; confidence can be increased by adding test examples and the theory is capable of refutation or modification by means of further experiment.

For the theoretician, working in his own form of isolated environment, the desirability of working with a series of compounds and their activities presents a further problem. From where can he obtain the data? This may appear to be a ridiculous question when the pharmacological literature is full of lists of similar compounds with varying activities of one sort or another. However, as we will discuss later, the pharmacologist has many problems in producing data on biological activities because of the number of possible variables. Much published work refers to experiments on live animals (*in vivo* experiments) where such variables as the weight, age or sex of the animal may be significant, as may factors such as absorption and metabolism. Even experiments on tissues or parts of living systems (*in vitro* experiments) may be crucially dependent on the precise way in which the experiment has been performed. It is a great trap for a theoretician with a background in physical science to treat published biological data as he would published physical measurements. Data on the same problem from different sources may not be comparable. In the experience of the author the safest and most satisfactory way of dealing with this problem is to work directly with the organic chemists who are making the molecules and in collaboration with the pharmacologists who are making the biological measurements. This may mean that the ideal collaboration is with the research group of a pharmaceutical company and in the experience of the author few collaborations have ever proved so stimulating or scientifically beneficial.

With so many cautionary words it is perhaps necessary to state clearly why, if there are so many hazards, it still seems timely to apply the methods of theoretical chemistry to pharmacology, apart from the desire of scientists in a pure and relatively esoteric field to tackle problems of obvious importance and, dare one say it, relevance. There are a number of reasons ranging from the pure to the practical and even commercial.

Firstly, there may be factors of importance which cannot be discovered in any other way than by calculation. Structures measured by crystallographers or n.m.r. spectroscopists are used in considerations of structure and activity but, apart from the obvious fact of the environmental effect, there is no logical reason to suppose that a small molecule performs its functions in the biological context while in the stable shape adopted in the solid state or in bulk solution. Indeed in many areas of physical biochemistry, induced changes of conformation on binding of one molecular species to another are an essential feature. Satisfactory calculations should indicate not only which forms of a molecule are likely to be possible crystal structures or solution structures (and these are frequently not identical even for simple molecules) but also the whole range of possible shapes within any given energy above the most stable form. Detailed use of calculations may indicate a precise non-equilibrium form which is a prerequisite for activity, or the barriers to interconversion of one metastable form to another

and approximate rate constants for the transition. In this way, the theoretical calculations are a complementary and possibly essential addition to experimental structural studies. If we consider the conformational potential energy of a molecule as represented on a map with energy contours, then, if we neglect environmental perturbations, the X-ray data will provide a single point on the surface probably corresponding to the lowest point; n.m.r. will provide details of areas of the map surrounding any minimum deep enough to provide a sizeable population of conformers in an equilibrium situation, while theoretical calculations can, with care, provide full details of the whole map, the peaks and slopes as well as the valleys.

Another advantage of calculations is that they are capable of producing not only the energy of the molecule for a given configuration of the constituent atoms, but also any molecular property either of the entire molecule or more importantly at localized points within the molecule. Much effort in the realm of structure–activity work consists of correlating activity with measured bulk-molecular properties. Theoretical calculations offer the possibility of correlating not just a property of the whole molecule, such as dipole moment, but rather the charge on particular atoms or any other sub-molecular property.

Of all the many properties of a molecule which may be computed from a quantum mechanical calculation perhaps the most widely useful is the electronic distribution or the potential field which electrons and nuclei generate. The chemistry and biological activity of molecules must ultimately be explicable in terms of the behaviour of electrons. Until very recently the only drawback to the use of this fundamental information has been the difficulty of displaying the information in a comprehensible manner. The growth of sophisticated computer graphics systems has removed the dilemma and promises to provide a major stimulus to the use of quantum mechanical methods.

Once calculations have proved that they can yield a satisfactory explanation of activity, then a third potential advantage becomes apparent. The calculations may be performed without first synthesizing the molecule. Thus, if there is confidence in the calculations, they can then be run before the organic chemist does his synthetic work and the pharmacologist his testing. Ideally, this would greatly reduce the number of molecules synthesized and screened by removing the ones which are unlikely to be interesting. This state of affairs is only dawning, but if achieved would make the work of the organic chemist more stimulating as he would have to design specific properties into the smaller number of molecules he was making. It would also have the commercial attraction of reducing the number of compounds synthesized and screened in the search for more effective drugs.

Although the problems involved are far from simple, it does seem that there is every advantage in applying quantum mechanics to pharmacological problems. Quantum mechanics is particularly appropriate as it can tell us in a fairly direct way about the density of electrons in molecules. It must be remembered that atomic nuclei just provide a framework on which to hang varying electron densities. When a small molecule approaches the active site of a receptor molecule it is the varying charge density of the two species which will interact. If loose terminology may be applied, the receptor 'sees' a structured cloud of electron density, not a set of point atoms.

It is perhaps presumptuous but illuminating to try to define the question to which the pharmacologist and medicinal chemist would like an answer. They would like to know 'what is the precise three-dimensional electron density adopted by an active molecule at the instant it performs its essential role?' Molecular quantum mechanics may be the best means of providing an answer.

Part I

Molecular pharmacology

Contents

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Chapter 1

Small molecules in biology

The success of molecular biology has convinced almost everyone that biology is in principle ultimately explicable in molecular terms. It is obvious that biological structures are based on proteins, nucleic acids, polysaccharides, lipids and other polymeric organic molecules. Strangely enough, in many respects these huge molecular species involving many thousands of atoms are better understood than the small molecules with only perhaps about twenty atoms which are also of great importance in biology, even if present in tiny quantities.

The chief role of the small molecule is in control systems. Even with plants the use of small molecules in control is obvious and demonstrable. Hormones are frequently small molecules. Very small quantities may dramatically affect growth or behaviour, not only in plants but also in human beings. The reproductive cycle in women, for example, is controlled by steroid hormones released into the blood stream. Hormones provide slow response and long-lasting control since the 'message' in the form of a molecular substance is carried in the blood and takes some time to reach all areas of the living system. Its effect lasts for as long as there are hormone molecules present. For the higher organisms rapid response and control are provided by the nervous system. The body is far more than a set of functioning structures. It can detect changes affecting it and reacts by readjusting itself. Nerve cells are not indefinitely long conductors like wires, but have discrete lengths. The connection between nerve cells and between nerves and the muscles they control is of a chemical nature. These chemicals, or *neuro-transmitters*, are small molecules which again are highly potent in the sense that injection of very small amounts into a living system can have a dramatic effect.

Much of pharmacology is concerned with the study of the mode of action of these various neuro-transmitters, and molecular pharmacology attempts to define the role of the transmitter in molecular terms.

Some molecules synthesized by the organic chemist and usually similar to the naturally occurring active molecule but not found in the living system will, when injected, produce a similar effect to the natural compound possibly by acting in its place. Such molecules, along with the naturally occurring molecules, are referred to as *agonists*.

The theory of the mode of action of small molecules in biological control

which we will discuss in more detail later involves the interaction between the small molecule and a macromolecule with a specific active site. That is, the small molecule, perhaps a neuro-transmitter or synthetic agonist, interacts with a *receptor*. Some synthetic non-natural molecules may bind to the same receptor as a naturally active molecule in such a way that the receptor is blocked and the natural transmitter is rendered ineffective. Such blocking molecules are called *antagonists*. Antagonists may bind in exactly the same or similar manner as the molecule which they are preventing from acting or may have their effect as a result of some other interference with the natural process. In the next chapter we will consider this in more detail.

Drugs include both agonists and antagonists which produce a result which is clinically desirable in a given instance, such as the lowering of blood pressure or increase of heart-rate.

Molecular pharmacology is at its most advanced state when consideration is focused on the role of a particular molecule in a biological mechanism in which the nature of the small molecule is highly specific: minute changes in chemical structure give enormous changes in biological activity. Other active molecules have low specificity or seem to have an effect based on physical properties, such as colligative properties, rather than chemical structure.

For the latter case, the explanation of activity is not as precisely molecular as in the cases where binding between the small molecule and the receptor produces the ultimate observed reaction. For this reason we will discuss mostly the cases where receptor ideas seem to be most well-founded, considering first of all the nervous system.

Nerves

The nervous system consists of a network of *nerves*. Some can transmit messages about the detection of stimuli to the brain and are called *sensory nerves*; others working in the opposite direction, carrying the message which leads to some reaction, are called *motor nerves*. The message is in the form of an electrical impulse. A nerve is a collection of *nerve fibres* gathered together like the strands of an electric cable (*Figure 1.1*). Each nerve fibre

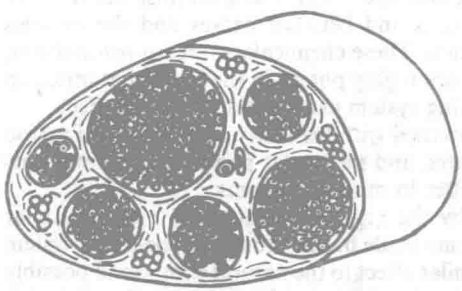

Figure 1.1. Cross section of a nerve trunk with individual nerve fibres grouped into six separate groups