

"OF MOLECULES AND MEN"

by

PROFESSOR P T KAYE

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Mr. Pro-Vice-Chancellor, Colleagues, Ladies and Gentlemen.

Peter Atkins, in the introduction to his very readable book 'Molecules',¹ refers to chemistry as "the central science" in the sense that it provides links between the life sciences and the physical sciences, the familiar and the fundamental. The news review in a recent edition of Chemistry in Britain refers to "the political message from on high (reputedly No. 10, itself)" to the effect that "an institution with no chemistry or physics does not deserve the name of university."² That is a sentiment which at least the chemists and physicists among us will endorse, and presumably a sentiment which was shared by the founding fathers of our own institution when they appointed George Cory as Professor of Physics and Chemistry in 1904 - one of the four founding Professors of Rhodes University College.³

I am conscious, as the new Professor of Organic Chemistry, that behind me lies a tradition established by my predecessors - a tradition of service to the University and the students who have passed through it. I could refer to the contributions made by Professor Cory, Professor William Barker, and Professor John Nunn, but this evening, I would like to confine my remarks to the contributions of my immediate predecessor, Professor Emeritus Douglas Rivett. Doug Rivett, who began his association with Rhodes University as a student fifty years ago, has become something of an institution in his own right. He has achieved prominence as a natural products chemist with his studies of terpenoid compounds and has had the distinction of serving as President of the South African Chemical Institute and as editor of its journal, the South African Journal of Chemistry. Within the University, Doug has left his mark on the department and, undoubtedly, on the lives of many of the students who have passed through his hands. To hand over the reins to someone else can never be

easy, but, the remarkably gracious and supportive way in which Doug has done so is, I think, a measure of the man. When we were first considering the possibility of coming to Rhodes, it was Doug and Lettie Rivett who introduced us to the campus and the city where we now feel so much at home, and I am particularly pleased that Doug can be with us this evening.

And now, with apologies to Lewis Carroll, whose literary skills are being celebrated in the show across the road,*

"The time has come the V-P said,
to speak of many things,
of conformational analysis and heterocyclic rings,
of carbon and of hydrogen,
of molecules ... and men."

This evening I would like to say something about the development of Organic Chemistry as a modern science; something about the challenges facing organic chemists at the end of the 20th century; and something about our own research as a response to some of those challenges.

In 1802, Thomas Thomson wrote in his 'System of Chemistry' :-

"As soon as man begins to think and to reason, the different objects which surround him on all sides naturally engage his attention. He cannot fail to be struck with their number, diversity, and beauty; and naturally feels a desire to be better acquainted with their properties and uses."⁴

*This lecture coincided with the opening night of a Grahamstown production of "Through the Looking Glass".

Presumably, in response to this desire, the Greek philosophers gave thought to the nature of matter and speculated that the different forms of matter could be explained in terms of different relative proportions of the four elements of Fire, Air, Earth, and Water - an explanation espoused by many, including the Alchemists who for some 1800 years (300 BC - 1500 AD) practised their strange crafts in expectation of discovering a mythical transmuting substance called the Philosopher's Stone.⁵ This fabulous substance was believed to be capable of transmuting base metals to gold; effecting miraculous cures; and acting as the "Elixir of Life" by imparting immortality to its fortunate recipients. Alchemy appears to have been a strange mixture of mysticism and medicine, superstition and experimentation, and Jan van der Strait's painting of the 16th century alchemist at work reflects the seriousness of the undertaking as well as the development of early chemical skills and apparatus.

With the growing awareness of the value of experimental data, an embryonic Chemistry began to shed the mysticism if not the mystery of alchemy and, in 1661, Robert Boyle (regarded as the Father of modern chemistry) published his famous treatise 'The Sceptical Chymist'.⁵ His treatise rejected the notion of the four elements of Fire, Air, Earth, and Water, and promoted the view that Chemistry should involve a systematic study of nature for its own sake. And so to-day Chemistry has nothing to do with magic! But, in parenthesis, let me say that there is a kind of magic in Chemistry :-

the magic of seeing a complex molecular structure emerge as, with a pencil, you join computer-generated points in an X-ray diffraction analysis;

the magic of growing beautiful crystals;

the magic of discovery - so aptly caught in an emotive painting of the discovery of phosphorus.

There is also a sense in which chemists have struck gold - again, and again, and again - not from base metals with strange incantations, but in the isolation and synthesis of compounds which combat disease, revolutionise technology, and constitute the very fabric of modern society.

A year after Boyle wrote his treatise, Charles II was petitioned to found the Royal Society.⁶ By this time a significant transition from Alchemy to Chemistry had taken place and laboratory work was even considered a suitable occupation for gentlemen! Ironically, amongst the founder members of the Royal Society was one, Sir Kenelm Digby, who we are told "retired from a successful career in piracy to study medicinal chemistry". In deference to my colleagues in the School of Pharmaceutical Sciences, of that particular gentleman I will say no more! Charles, himself an amateur chemist, together with Robert Talbor apparently conducted experiments on quinine-containing Cinchona bark in which, as a malaria sufferer, the king must have had a particular interest. Cinchona bark had been introduced to Europe from South America a few years previously (1633) by the Spaniards. One version of the discovery of its anti-malarial properties involves a Peruvian Indian who, stricken with malarial fever, drank from a stagnant pool into which Cinchona trees had fallen. Within hours his fever subsided and news of the remedy spread to Jesuit missionaries and thence to Europe.⁷ Many other plants have long been known to be medicinally active and often extremely toxic - plants like Opium poppy (Papaver somniferum), Foxglove (Digitalis purpurea), and Deadly Nightshade (Atropa belladonna). But, while the value of these plants was obviously appreciated, any comprehension of the nature of their active principles had to await the development of modern ideas concerning the structure of matter. In fact, it was only around the middle of the 19th century that an understanding of the nature of molecules began to develop.

Peter Atkins describes molecules as specific discrete groupings of atoms into definite geometrical arrangements.¹ Of the 100 odd elements known, one is of particular interest to organic chemists; that element is carbon, and Organic Chemistry may be described as the chemistry of carbon compounds. Carbon atoms have a unique capacity for forming strong bonds between themselves and with a variety of other atoms such as hydrogen, oxygen, nitrogen, and the halogens. More organic compounds are known than compounds of all of the other elements put together and as organic chemists we are quite happy to relegate the chemistry of all the other elements in the periodic table to the Inorganic Chemists! Organic Chemistry constitutes the chemical basis of Biochemistry and Molecular Biology, Phytochemistry and Medicinal Chemistry, Petroleum Chemistry and Polymer Chemistry. Organic molecules are, in fact, ubiquitous. The colour of blood oranges, for example, is due largely to carotene and anthocyanin molecules; their sweetness to sugar molecules; their odour to terpene molecules; and their tartness to citric acid molecules.¹

With this molecular perspective we are now in a position to identify the active principles in Cinchona bark as organic molecules, and even more specifically, as alkaloids such as quinine. We need to remind ourselves, however, that while Cinchona Bark was brought to Europe as early as 1633, the alkaloid quinine was only isolated from the plant material in 1820 and its molecular structure, proposed some 100 years after that, was finally confirmed by R.B. Woodward's total synthesis as recently as 1944.⁸ One can similarly trace the chemical history of other medicinally useful plants. Thus, the analgesic properties of Opium, which have been known for some 2000 years, can be largely attributed to morphine which was isolated by Sertuner in 1806. The correct structure of morphine was formulated in 1925 by Robinson and Gulland and its total synthesis completed in 1952 by Gates and Tschudi.⁹ Similarly,

the toxic and cardiotoxic properties of Digitalis (foxglove) may now be attributed to a number of so-called cardiac glycosides such as digitoxin, hydrolytic degradation of which affords digitoxigenin; and the poisonous principles in Atropa belladonna (deadly nightshade) may be identified as tropine alkaloids such as hyoscyamine and scopolamine.¹⁰ And so one could go on. But, I hope that these selected examples will illustrate the point which I am trying to make, and that is, that through the years organic chemists have been slowly elucidating the molecular secrets of medicinally useful plant systems.

It seems, Mr. Pro-Vice-Chancellor, that concern about the quality of education is nothing new. In 1877, Hermann Kolbe, one of the most eminent organic chemists of his time, wrote :-

"Not long ago, I expressed the view that the lack of general education and of thorough training in chemistry was one of the causes of the deterioration of chemical research in Germany. Will anyone to whom my worries seem exaggerated please read, if he can, a recent memoir by a Herr van't Hoff on 'The Arrangements of Atoms in Space' a document crammed to the hilt with the outpourings of a childish fantasy. This Dr. J.H. van't Hoff, employed by the Veterinary College at Utrecht, has, so it seems, no taste for accurate chemical research. He finds it more convenient to mount his Pegasus (evidently taken from the stables of the Veterinary College) and to announce how, on his bold flight to Mount Parnassus, he saw the atoms arranged in space."¹¹

Kolbe was nearing the end of his career and was reacting to a publication by a 22-year-old Dutch scientist which had appeared two years earlier. In this publication, van't Hoff had argued for a tetrahedral arrangement of the

four groups around a central carbon atom. The same idea was proposed independently by a young French scientist, J.A. Le Bel, a few months later. Within ten years abundant evidence had accumulated to support van't Hoff's "childish fantasy" and in 1901 he became first recipient of the Nobel Prize for chemistry. The work of van't Hoff and Le Bel marked the beginning of stereochemistry - the study of chemical systems in three dimensions. Until then Chemistry had been viewed two dimensionally.

A very significant phenomenon arises when the four substituents attached to a tetrahedral carbon atom are all different; such a molecule cannot be superimposed on its mirror-image. Systems which cannot be superimposed on their mirror-images are termed chiral (from the Greek 'cheir' - a hand) and such systems are, in fact, different - although the difference is only apparent in a chiral environment. Consequently, in many molecular systems, it is necessary to define not only the CONSTITUTION (which atoms are bonded to which) but also the CONFIGURATION, i.e. the three dimensional arrangement of atoms and groups. It can be readily demonstrated that the phenomenon of chirality is not simply of esoteric interest. Biological receptor sites, at which drug interactions occur, may be expected to be inherently chiral because they are constructed from chiral molecules. Such chiral receptor sites may be expected to differentiate a chiral drug from its mirror-image and thus, the molecular configuration of a drug may be crucial in determining its effect. Examination of the constitutional formula of thalidomide, first marketed in 1956 as a sedative and mild hypnotic, reveals a tetrahedral carbon atom to which are attached four different groups. This means that thalidomide exists as two different mirror-image configurations. It now appears that only one of these configurations is teratogenic (i.e. responsible for congenital deformities). Unfortunately, thalidomide was marketed, in ignorance, as a mixture of both.¹

We have seen how the structure of organic molecules can be described in terms of CONSTITUTION and CONFIGURATION. There is, however, a third level of even greater structural sophistication, viz., CONFORMATION. Conformations are different spatial arrangements which molecules may assume without breaking covalent bonds. They arise from rotations about single bonds, bond-angle deformations, and bond-length changes. This total view of the structure of organic molecules (constitution, configuration, and conformation) is crucial to a proper understanding of their properties. This statement could be illustrated in a number of different ways, but, in this lecture I will restrict my comments to the way in which organic molecules may interact with biological receptors. This is an interest which is increasingly influencing the direction of our own research.

Drug-receptor models of varying degrees of sophistication continue to be developed. These models illustrate a kind of site-specificity. In other words, the structural characteristics of the receptor will specify or determine the complementary structural characteristics in the drug. We briefly consider three examples.

- (1) **A conceptual model** of an opiate receptor.¹² This model illustrates complementary relationships between the "receptor-surface" and a typical opioid analgesic. Thus, the receptor surface has a flat lipophilic region for binding an aromatic ring, a cavity to accommodate the bimethylene bridge of the piperidine ring, a site for binding the amine nitrogen, and so on.
- (2) **A DNA-intercalation model.**¹³ This model illustrates intercalation of an appropriately structured molecule (eg. the aminoacridine anti-bacterial, proflavine) between purine-pyrimidine base-pairs in bacterial

DNA. Quinine and related anti-malarials are believed to bind in a similar fashion. Intercalating molecules are required to have a flat section of appropriate area and to be protonated at normal cell pH.

- (3) **A Computer-graphics model.**¹⁴ This model provides a more quantitative approach and, I think, signals the way ahead. C.H. Hassal and his group, starting with captopril (an effective anti-hypertensive agent) have used computer graphics to generate a surface mesh for the locus of the sulphur atom in captopril by allowing free rotation about two of the bonds. This mesh was reduced by excluding high energy conformations and considering intersections of similar meshes for other biologically active analogues. The net result was to determine the binding co-ordinates of the enzyme receptor implicated in hypertension and, subsequently, to develop a new, potent, and long-acting anti-hypertensive agent, viz., cilazapril.¹⁵

So much for the way we have come in our understanding of the nature of molecules. Where are we going? Simple answers are seldom totally satisfactory, but one could identify four general areas in which Organic Chemistry is moving. Each area has its own challenges and each unavoidably overlaps others.

1. NATURAL PRODUCTS

Although the major focus of organic research has undoubtedly moved on, real challenges still remain. These include :- (i) the analysis of unexplored biologically active plants, especially marine plants, with a view to identifying toxic or medicinally useful compounds; and (ii) collaboration with Zoologists and Entomologists to research the sometimes complex, volatile organic mixtures which are involved in chemical communication

between animals, between insects, and even between plants and insects.

2. SYNTHESIS

In the last few decades there has been tremendous activity in the development of new methods of effecting chemical transformations. One of the major current objectives is to obtain effective chiral control in synthesis - the implications of which I will say more later.

3. MECHANISM

The continuing challenge in the study of organic reaction mechanisms is to provide appropriate descriptive models for rationalising and predicting chemical behaviour. Such models are central to the proper development of the scientific base of the discipline.

4. STRUCTURAL ANALYSIS

I need to point out that structural analyses (i.e. determinations of molecular structure) which might once have taken months or years can often now be completed in a matter of days or weeks. This is possible because of the formidable arsenal of analytical instruments now at our disposal.

Instruments such as mass spectrometers, X-ray diffractometers, and high field Fourier Transform Nuclear Magnetic Resonance spectrometers are a far cry from the bain marie - the elaborate water bath, which might once have occupied pride of place in an alchemist's laboratory! With these facilities at their disposal, organic chemists with structural analysis skills have a unique role to play in exploring the chemical-biological interface. This exploration will require significant inter-disciplinary collaboration - already a positive feature of the Rhodes research scene.

In the remaining time I would like to tell you something about our current research, high-lighting only the essential objectives and acknowledging, as I proceed, the students whose enthusiasm and dedication make our programme an encouraging reality.

We have spoken of chiral molecules like thalidomide. In nature, biosynthesis affords specific configurations of chiral molecules with remarkable stereocontrol. In the laboratory, on the other hand, generation of a chiral centre from non-chiral precursors always results in the formation of both configurations (mirror-image forms) in equal quantities. However, by utilising chiral natural products as chiral auxiliaries it becomes possible to induce a degree of stereocontrol in laboratory syntheses. In his PhD project, Robin Learmonth is looking at methods for achieving such stereocontrol in the reactions of organosilicon substrates, linked via silicon to various chiral auxiliaries. By using a combination of instrumental techniques we plan to explore the conformation of the reaction sites in an attempt to achieve meaningful stereocontrol. Molecular conformation is also a major focus in much of our other research. The chromone group is present in a number of biologically active compounds such as chromoglycic acid (used as the disodium salt in treatment of asthma)¹⁶ and Debbie Davidson, in her PhD project, is looking at the synthesis and conformational properties of chromone-2-carboxamide analogues of a biologically active tetrazolyl system. In a somewhat related MSc project, Rory Whittal is looking at methods of expanding the heterocyclic ring of flavanones to obtain what we expect to be biologically active analogues of the benzodiazepines which are widely used as minor tranquilisers. In both of these projects we hope to be able to correlate biological activity with the total molecular structure and hence draw some conclusions concerning the structural requirements of the receptor sites.

While it may often be desirable to design molecules to fit a specific receptor site, it may also be valuable to design sites for particular molecules or ions. The development of metal-specific chelating agents could have significant medical, industrial, and analytical applications. Professor Julius Rebek's group at Pittsburgh have developed a compound in which the metal-binding (chelating) groups are held in an ideal conformation for chelation.¹⁷ Here at Rhodes, Chris Hlekane is investigating the development of somewhat analogous systems as part of his MSc project. On the mechanistic front, two of our current Honours students, Moira Bode and Nontsikelelo Baartman, are currently working on projects which involve elucidation of the mechanistic details of two reactions which have been used in earlier research.^{18,19}

The remaining projects which I would like to mention have a distinctly natural products flavour (and odour!). In an MSc project, which I am very happy to be co-supervising with Dr. Steve Compton in Entomology, Tony Ware has been examining the remarkable symbiosis which has been observed between Fig trees and Fig wasps.²⁰ Female wasps enter the fig syconium through the ostiole (which subsequently closes), pollinate the flowers that line the inner cavity, and lay their eggs. The young develop to maturity within the fruit, load pollen, and escape through the re-opened ostiole - and the cycle can begin all over again. But, that is not all. There appears to be a remarkable specificity between tree and wasp, such that, with few exceptions, each Fig species has its own unique pollinating Fig wasp.²¹ We expect there to be chemical communication between plant and insect in the form of volatile organic molecules which direct the wasp to the right kind of tree. Tony has been collecting trace quantities of volatile compounds at different stages of fig development. Gas chromatographic analysis has been used to indicate the different profiles of volatiles obtained before and after pollination of a particular Fig species. The chemical aspects

of this project involve the concentration and identification of the organic molecules from various Fig species which act as cues for this remarkable symbiotic specificity.

Towards the end of 1987, I received a telephone call from Neale Bell, Senior Pharmacist at Grey Hospital, King Williamstown, asking if I could tell him anything about the toxic constituents of Tulbaghia violacea - a plant indigenous to the Eastern Cape. An infusion, prepared from the plant, is used as a tribal remedy for wind in infants. Presumably, in some cases, the remedy is effective, but in others infants are admitted to hospital with distressing symptoms and fatalities are not uncommon. Very little appears to be known about the chemical constituents of the plant and Stephanie Burton has embarked on an MSc project in which we aim to identify the major constituents. Tulbaghia violacea is related to garlic and onion species and everyone in the laboratory knows when Stephanie is working with fresh plant material!

I have set out to trace the development of my discipline into a modern science, to identify some of the challenges confronting us, and to show you that Organic Chemistry is alive and well at Rhodes University. From what I have said it will, I hope, be apparent that there has been enormous progress since the middle of the 19th century, when rudimentary ideas of molecular structure were first formulated. Organic chemists now have at their disposal well-established mechanistic theories to describe the properties of organic molecules, well-developed synthetic methodologies to effect a wide range of chemical transformations, and an array of sophisticated instrumental techniques to probe the structures of molecular systems. They are thus uniquely equipped to explore the "inner-space" of matter at a molecular level. From outer-space

the earth may seem an unremarkable planet. But, to our present knowledge it is unique, for stretched around its surface like a thin skin, no more than a few kilometres thick, is the life-sustaining, life-containing Biosphere - in one sense amazingly robust, in another exceedingly fragile.

To all of us, Mr. Pro-Vice-Chancellor, is given the opportunity to contemplate the endlessness of space, to experience the excitement of life, and to reflect with the Psalmist that we are "fearfully and wonderfully made".²³ To relatively few of us is given what I consider to be the privilege of exploring, as an organic chemist, the molecular secrets of the Biosphere - this realm of molecules and men.

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