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From diatomics to drugs and dividends

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Abstract

The path from diatomic molecule spectroscopy to molecular modelling and drug discovery is described, along with aspects of the commercialisation of research. It is a history tightly coupled with the advances in computers over the past 50 years, but with a future full of opportunity.

Keywords: Computational chemistry; Drug discovery; Grid computing; Commercialisation

1. Introduction

My career, like that of so many people, is a testament to the 'cock-up' theory of history. Although it is possible with hindsight to discern some sort of plan and to ascribe wise decisions about significant changes in direction, in fact chance has been the major factor.

The birthdate of 1 October 1939 meant missing compulsory military service by a single day and coming to Oxford as a student 2 years earlier than anticipated. Starting research in 1961 determined that I was part of the first generation of scientists to use computers as opposed to the pioneers who had developed them. The subsequent 50 years have been strongly coupled to hardware advances.

In the early 1960s the UK computer industry was second to none, and at Oxford having a Ferranti Mercury put us in a strong position. In particular the crystallographers guided by Dorothy Hodgkin did wonderful and Nobel Prize winning studies. Chemists were a little way behind, but in the Physical Chemistry Laboratory Ken Lawley did some very early Monte Carlo work and I, working on diatomic molecule spectroscopy as a student of Richard Barrow, stumbled into trying to use the machine, described by one of my senior colleagues as 'far too complex for a chemist ever to use'.

2. Diatomics

My first research was a study of the spectrum of diatomic chlorine where one of the points of interest was the variation of the dissociation energies of the halogens. The heavier members of the series hold together at greater interatomic distances than one might expect. This led me to try to calculate the potential curves using the Rydberg–Klein–Rees method [1]. This involves computing a couple of integrals of the form:

$$f(U) = \frac{1}{2\pi(2\mu)^{1/2}} \int_0^{I'} \frac{\mathrm{d}I}{\{U - E(I,K)\}^{1/2}}, \qquad g(U) = \frac{1}{2\pi(2\mu)^{1/2}} \int_0^{I'} \frac{(\partial E/\partial K)\,\mathrm{d}I}{\{U - E(I,K)\}^{1/2}}$$

where $f = (1/2)(r_{max} - r_{min})$, $g = (1/2)((1/r_{max}) - (1/r_{min}))$, $I = h(v + (1/2))$, $K = (h^2/8\pi^2\mu)J(J+1)$.

My 'breakthrough' was to realise that with a computer, any integral can be evaluated numerically and all the complex and in some cases incorrect analytical solutions could be avoided [2]. Computers looked like a good idea.

Intending initially to go to Harvard to work with Bill Klemperer, I took a deviation and spent a year's post-doctoral spell with Carl Moser in Paris to learn how to do *ab initio* calculations on diatomics using the software originally by Bob Nesbet of IBM and improved by Dick Stevens. What I could bring to the party was a knowledge of good spectroscopic questions which *ab initio* calculations might help solve.

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Table 1
Spin–orbit coupling constants

	Calculated (cm^{-1})	Observed (cm^{-1})
BeH	2.3	2.14
CH	30.4	28.0
OH	141.4	139.7
SH	362.0	382.4

Together with Georges Verhaegen we settled the nature of the ground state of BeO which in principle could be either a triplet or a singlet. To do this we did the first open-shell calculations of excited electronic states as opposed to using virtual orbitals [3].

An even more intriguing problem was the nature of the first excited states of molecules like BeF and MgF. Here there is no doubt that they are $^2\Pi$ states, but calculation suggests that they should be so-called 'regular' with the 1/2 component closer to the ground state than the 3/2 sub-level, but the experimental spin–orbit coupling constant has the wrong sign for that to be true.

To resolve this dilemma, together with Timothy Walker, one of my first graduate students, we calculated, for the first time, diatomic spin–orbit coupling constants [4,5]. The results as Table 1 shows were impressive.

This still however did not explain the anomaly in the alkaline earth halide molecules. To resolve that we were pushed into calculating the so-called Λ-doubling constants which are off-diagonal spin–orbit coupling matrix elements [6].

$$P = 4\sum \frac{\langle {}^2\Pi|\mathrm{H}_{80}|^2\Sigma\rangle\langle {}^2\Pi|B(\mathrm{L}^+ + \mathrm{L}^-)|^2\Sigma\rangle}{E_\pi - E_\Sigma}$$

and

$$q = 2\sum \frac{\langle {}^2\Pi|B(\mathrm{L}^+ + \mathrm{L}^-)|^2\Sigma\rangle^2}{E_\pi - E_\Sigma}$$

Yet again these calculations, performed using perturbation theory, were amazingly accurate and encouraged us to try to calculate the Λ-splitting in CH. This, in the 1960s, was a very important problem as molecules were starting to be discovered in interstellar space. First was OH seen from its Λ-doubling spectrum, but CH could not be found even though it had to be the precursor of the many organic species being discovered. We made a prediction which proved to be better than the terrestrial experiment (Table 2): a real triumph for theory [7].

By the late 1960s I was then something of an expert on *ab initio* calculations, and even published a book on the topic [7], but only experienced with diatomic molecules.

Table 2
Off-diagonal spin–orbit coupling

	Splitting in CH (MHz)
Terrestrial experiment	3374 ± 20
Astronomical experiment	3335.47 ± 0.01
Calculation	3311

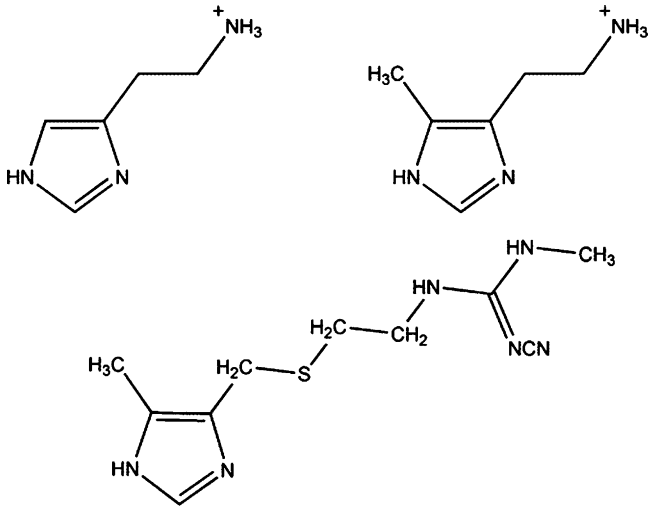

Fig. 1. The histamine monocation: the 4-methyl compound and cimetidine.

3. Drugs

The jump to drugs and applying computers to problems in molecular pharmacology was again unplanned. Out of the blue in 1968 I received a letter from Anthony Roe of Smith Kline and French asking me my opinion about a paper which computed the conformational energy of histamine (Fig. 1).

Not surprisingly, since histamine is a 1:2 disubstituted ethane the calculations indicated that there are two stable conformers, the trans and gauche (or more properly antiperiplanar and synclinal conformers). It went on to hypothesize that the then known distinct pharmacological actions could be mediated by one conformer for the H1 activity and the other for H2, acid secretion in the gut. Finding inhibitors of H2 activity was the research topic of Jim (now Sir James) Black and his team, with Robin Ganellin leading the medicinal chemistry. That problem drew me into a collaboration which both fascinated me and changed the direction of my own research. Trying to understand why 4-methyl histamine is an H2 agonist but does not affect the H1 receptor led to work on essential conformations for activity [8].

The idea of using theoretical chemistry to help discover biologically active molecules was sufficiently outrageous for it to be necessary to write a book on the topic, and hence the publication in 1977 of *Quantum Pharmacology* [9]. This was written in part because the outline won a prize from the publishers, Butterworth, that helped finance a sabbatical at Stanford and Berkeley.

The real spurt in research activity in the area came in the early 1980s when colour graphics was introduced. I believe that we were the first to publish the description of the work as 'computer-aided molecular design' in 1983 when we published what were probably the first colour graphic molecular displays (Fig. 2) [10], obtained from a black and white screen by shooting part of the figure through a red filter and the other part through a blue one, after rewinding the film.

Colour enabled non-specialists to see what was going on in enzymes and provided a real boost to the subject. I well