

**Life at high pressure**

At Southampton University in the mid-1950's organic chemistry became my main love, from the arcane formulae and elegant structures of natural products to the synthetic *tours de force* of the great chemists such as Robert Woodward. Spells of vacation work in Poole gas works laboratories, analysing the iron oxides in the purifiers for sulfur (extracted with toluene over a bunsen), moisture and cyanide at £3.50 per week still made chemistry an exciting subject for a career. However, it was when courses reached discussions of reaction mechanisms that I knew what I really wanted to study and to make inroads on the unexplored territory which was revealed when lecturers frankly admitted that many reactions were not understood. Accordingly I accepted an invitation with alacrity to work for a PhD under Norman Chapman and the mechanisms of epoxide ring-opening were the topic prescribed (since the sponsor made epoxy resins). The first task was to build a thermostat tank from bits and pieces lying around and then to evolve an analytical

---

\* Thimble Cottage, Orchard Lane, East Hendred, Wantage, UK OX12 8JW.

---



method for analysing primary, secondary and tertiary amines from mixtures. After Chapman went to Hull, Eric Parker took over supervision and we produced a review which became a best seller and thirty years on had a Golden Citation award.<sup>1</sup> A period of postdoctoral work followed, in Ottawa studying alkaloid biosynthesis, at CalTech measuring enzyme kinetics where we found definitive proof of the acylated enzyme intermediate in reactions of chymotrypsin and with Richard Cookson back at Southampton. Up to this period, laboratory instrumentation was emerging from the primitive. UV and IR spectrometers were now commercial but NMR instrumentation largely home made. Three years were then spent at the University of Victoria, a two year college recently established as a full university. It was an exciting time planning and teaching the first full syllabus, trying to compete with the other provincial universities in Vancouver and still to get some research done with very few facilities.

Although Uvic is now a very prestigious establishment, it was the lack of research facilities which decided the next move to the University of Reading where I remained for the next 32 years. There I began work on such diverse topics as halogenations, charge-transfer complexes and mass spectral fragmentation mechanisms also being able to take a sabbatical year in Auckland with Peter de la Mare and working on phenol halogenations.

In the 1970's there was active controversy concerning concertedness of cycloadditions while at the same time I became aware of the effect of pressure on reaction rates, through a paper by Hill, which I naively thought would resolve the matter. Accordingly an application for money went to the SRC and they obligingly made a grant to build a high pressure optical kinetic cell to a design by NPL. This was a monstrous steel affair which took four men to lift and was designed by physicists. Measurements were made on Diels–Alder reactions at up to 2 kbar and on dipolar and other cycloadditions but concertedness could not be established by volumes of activation alone on account of the electrostriction present in non-concerted reactions which were dipolar. Still, the technique was fascinating and I went to Frankfurt to learn how to do high pressure work properly from Helmut Kelm and his co-workers with some of whom I remain in collaboration.<sup>2</sup> My current optical cell I can hold in the palm of my hand while diamond anvil cells going to megabars are no bigger.<sup>3</sup> So began a period in which the effect of high pressure on many reactions in solutions was studied; (2 + 2) cycloadditions, anion–cation recombinations, cheletropic reactions, electrophilic displacements at tin, polymerizations, the Baylis–Hillman reaction, hydroboration, organophosphorus chemistry, the Wittig reaction and Swern oxidation to name the most interesting. We were able to come up with evidence for the origin of tunnelling in hydrogen transfer reactions, a matter which has recently been revived.<sup>4</sup> Also a reliable criterion for the E1cb mechanism of ester hydrolysis (a positive volume of activation) was established. The acceleration of rate by pressure can be applied to facilitating synthesis and I persuaded Ken Ashcroft to design a piston-cylinder apparatus for synthesis at 10 kbar. This design has proved to be a great success (cover picture) and I eventually acquired two with two others from the University of Belfast.

Then a very active period of high pressure synthesis followed: intramolecular Diels–Alder reactions, difficult syntheses of phthalocyanines, Diels–Alder reactions of pyrroles, difficult Wittig reactions and Baylis–Hillman reactions of ketones. We were able to make Fraser Stoddart a convert to high pressure methods by successfully carrying out the multiple Diels–Alder reactions making molecular LEGO which he subsequently developed into potential information systems. All this work led to the most pleasant collaborations with numerous research groups the world over and the apparatus was made available for all.

In the late 1980's an interest in biochemistry developed since, while it was known that high pressure can kill bacteria, the mechanism was not understood. There was then technology developing in Japan for food sterilization by pressure. Superior fruit drinks were on the market with long shelf life. Accordingly I joined an EU-initiated project on high pressure food treatment. We found the conditions of pressure, temperature and time to kill *E. coli* and that this occurred by making membranes permeable, denaturing enzymes and wrecking DNA. The creatures were clever enough, however, for some to repair themselves making the method while suitable for acidic foods

unlikely to be licensed for treatment of meats which could contain pathogens.

Latterly interests have returned to solvent effects and studies on coordination in supercritical fluids and in ionic liquids. High pressure remains the area in which I have spent the greater part of my working career and where my interests remain. I have made many friends through the European High Pressure Research Group and AIRAPT, two organizations and their conferences devoted to high pressure techniques and to which I would commend future researchers.

I am very grateful to the Royal Society of Chemistry for their recognition in the award of the Josef Loschmidt prize this year.

## References

- 1 N. S. Isaacs and R. E. Parker, *Chem. Rev.*, 1959, **59**, 737.
- 2 N. S. Isaacs, *Liquid Phase High Pressure Chemistry*, Wiley, Chichester, 1981.
- 3 N. S. Isaacs and W. B. Holzapfel, *High Pressure Techniques in Chemistry and Physics*, OUP, Oxford, 1997.
- 4 N. S. Isaacs, K. Javaid and E. Rannala, *Nature*, 1977, **268**, 372; N. S. Isaacs, in *Isotopes in Organic Chemistry*, ed. E. Bunel and C. C. Lee, Elsevier, Amsterdam, 1984, vol. 6, pp. 67–106.