

hours of examining maps. In the end the 2 Zn insulin crystal structure was completed, with all protein atoms identified and a comprehensive and detailed description of the water structure. A good deal of this methodological research was never published in detail, which is a pity, but a reflection of the pressures successful protein crystallographic groups often experience.

Dorothy's influence in insulin research was important. It was of great significance in China where an insulin crystallographic programme was initiated in the mid 1960s following the successful accomplishment of the hormone's chemical synthesis. The research led by Liang Dong-cai, was greatly encouraged by Dorothy, and she had great pleasure comparing the insulin structures determined in Oxford and Beijing in 1971. The subsequent growth of protein crystallography in China owes a great deal to the success of their insulin study and

Dorothy's support for it. Other examples of protein crystallographic research being started from the Oxford research are the laboratories of Ted Baker in Palmerston North (New Zealand), Guy and Eleanor Dodson (in York), Tom Blundell (in London) and Vijayan (in India) all of whom worked on insulin with Dorothy at Oxford.

After her retirement in 1977 Dorothy continued to work on insulin, giving lectures and in her research concentrating on the refinement of the 2 Zn insulin crystal with the 1.5 Å spacing data. The approach was strictly crystallographic and the protein atoms and the solvent molecules were analysed and refined as rigorously as possible. This study keeps a standard for protein structure analysis and its completion 50 years after the initial experiments illustrates the persistence Dorothy showed in her research and the immense achievement it represents.

Chemical crystallography – Past, present and future

Jack D. Dunitz

Organic Chemistry Laboratory, Swiss Federal Institute of Technology, ETH-Zentrum, CH-8092 Zurich, Switzerland

WE must not forget that the name of the Oxford laboratory was the Chemical Crystallography Laboratory. I think that may have been one of the reasons I wanted to go there. What I knew about chemistry was based mainly on Pauling's book *The Nature of the Chemical Bond*, and what I knew about crystallography came from the first volume of *The Crystalline State* written by Bragg. A Chemical Crystallography Laboratory seemed like the sort of place where I could combine my interest in these two fields, which was unbounded, with my scanty knowledge.

At that time, remember, fifty years ago, chemists were still arguing and even sometimes quarreling about the molecular structures of simple natural products. A would show that the structure of some compound deduced in B's laboratory was incorrect, and a year later B would turn the tables on A by showing that the revised structure was also wrong. In contrast, the structures determined by X-ray crystallography had a satisfying impression of definiteness about them. Molecules were revealed to correspond to objects of definite size and shape, not just intellectual constructs designed to explain chemical reactivity. There was a price to be paid, of course. In the course of determining the structure of a compound by crystallography, no new chemistry was done, nothing new was learned about the chemical reactivity of the compound in question. It seemed to me then, naive as I was, that as one learned more about the systematics

of molecules, it ought to be possible to fill this gap, to deduce chemical properties from molecular structure.

One problem was that, in those days, it took a lot of time and work to determine the structure of even a single relatively simple organic molecule. Also some luck. We knew then practically every organic structure that had ever been determined; who had done it, how it had been solved – there was not much choice, trial and error, or some variant of the heavy-atom method. Two-dimensional Fourier projections, using Beever's-Lipson strips or Robertson boards, were about the limit of computational practicability. Even if one went to the trouble of collecting three-dimensional diffraction data, it was a daunting task to do the necessary calculations. This is why most crystal structures determined in those days had a short cell dimension, short enough so that there was not too much atomic superposition in the corresponding two-dimensional projection.

Chemical crystallography? Ionic structures were reasonably well understood; Pauling's Rules were enough to rationalize them and even to predict unknown structures. In the organic chemistry area there was less to boast about, although there were one or two notable achievements. Through J. M. Robertson's work, for example, the bond lengths in aromatic hydrocarbons could be correlated with simple theoretical models – resonance structures. But for the most part, one had to

look optimistically into the future. Considering the complexity of chemical structure and reactivity, a data bank of about fifty structures does not offer much possibility for correlating the two. That was the Past.

I shall speak about the present as it passed me by during the past half century. Thanks to the development of so-called direct methods, made possible by newly developed mathematical models combined with enormous increases in computing power and advances in automated measuring devices, the determination of medium-to-large organic and organometallic crystal structures gradually became more or less routine. This does not mean that the structure of every new compound can be solved automatically but many of them can. In many cases the limiting factor is the availability of crystals. One result has been the accumulation of a vast amount of systematic information about crystal and molecular structure, which has profoundly transformed the whole science of chemistry. I summarize this briefly:

1. Molecular structure. a) Constitution: Influence on synthetic chemistry; liberation from burden of proof of structure via synthesis. b) Configuration: Use of anomalous scattering yields absolute structure. c) Conformation: Information about the balance among various non-bonded interactions was essential for the development of molecular mechanics.

2. Atomic motion in solids. The recognition that the anisotropic 'temperature factors' or displacement parameters (ADPs) determined in single crystal X-ray and neutron diffraction analyses are meaningful. For many years they were widely regarded as junk.

3. Experimental electron density distributions.

In the meantime the main focus of interest for many chemical crystallographers has shifted from the molecular to the intermolecular (supramolecular) level of organization.

4. Crystal packing. The study of weak (non-covalent) intermolecular interactions; atom-atom potentials. Polymorphism. We are still unable to predict with confidence the crystal structure of a compound, given its molecular formula. The structure of minimum potential energy is the stable one at 0 K but not necessarily at room temperature.

5. Solid state chemistry. Photochemical and thermal reactions. Let us remember that the topochemical approach to solid-state chemical reactions, which transformed the subject, was pioneered by the late Gerhard Schmidt, one of Dorothy's most influential students. The study of the influence of 'tailor-made' impurity additives on differential face development has led to insights into crystal growth processes (and to an independent confirmation of the correctness of absolute configurations determined by anomalous dispersion methods!).

6. Structure correlation. The recognition that the changes within a structural fragment in different crystal and

molecular environments is often coupled in a characteristic way that gives insight into the chemical behaviour of the fragment. A link between the 'statics' of crystals and the 'dynamics' of reacting chemical systems. Structure-energy relationships.

The influence of all this on 20th century chemistry has been profound – in fact many areas of present day chemistry are unthinkable without the help of modern crystallography. It seems ironic that this progress, almost unimaginable 50 years ago, has been accompanied by the virtual disappearance of crystallographic research in many chemistry departments. Crystal structures are now often, perhaps even mostly, determined as part of a service, and, while this is generally done with great speed and efficiency, the service crystallographer almost always has too much to do, she has no time to think about the broader implications of her results – or even to check them for possible mistakes and misinterpretations. Disorder effects can still cause problems that are sometimes recognized as such, sometimes not. The world production of single-crystal X-ray analyses now runs at something more than 10,000 structures a year. With the advent of various kinds of area detectors and still more efficient computers, this mass production of essentially unchecked crystallographic data is going to increase still further. In any case, results of most current crystallographic studies remain unpublished or receive only scant mention in chemical journals. Thus a vast amount of metrical information about molecular structure and about intermolecular interactions is being accumulated. Much of this information – of the published part at least – is being collected in computer readable form in the Cambridge Structural Database (CSD). Whatever the original intentions may have been, this has now developed into a scientific instrument for studying the systematics of molecular and supramolecular structure. Nowadays, I can hardly imagine that anybody reads, say *Acta Crystallographica C*, in order to broaden their general knowledge. It is read only by people interested in the details of some particular structure or class of structures, and I even suspect that many articles are doomed never to be read by anybody once they have appeared in print. So nowadays almost the *only* way to find details of particular structures or classes of structures is through the CSD. The same is undoubtedly true also for the Brookhaven Protein Data Bank. It seems essential that these two organizations should be kept running smoothly and efficiently until well into the coming century, otherwise the only people who will be acquainted with any particular crystal structure are the people who solved it – or the people for whom it was solved – and their near neighbours.

There is no time left to say more about the future, and perhaps that is just as well.