FOCUS ARTICLE

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Pizzas, polymorphs and pills

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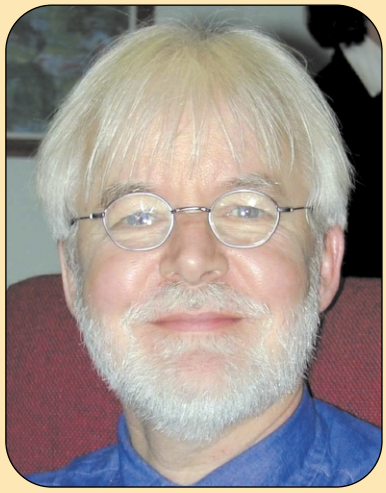
Roger Davey gives his personal view on why crystallization and crystal chemistry have become red-hot topics and on the big scientific and technical issues facing the area.

Introduction

In 1968 I had just eaten my first pizza in a restaurant at the top of Park Street in Bristol and was entering the final year of a degree course in chemistry. In the autumn term I was assigned Dr. W. J. Dunning (Bill) as my final year project supervisor. I had no idea that this chance event would have such a major impact on my life: this was to be my first encounter with crystals and crystallisation as a subject of scientific research, a subject which in various guises has dominated my working life ever since. Bill was well known for his research on the crystallisation of sucrose and the use of optical microscopy to image growth hills and macro-steps on growing crystal surfaces.[1]; indeed this was one of the few organic molecules for which any extensive crystallisation data existed at that time. I realise now that the work of German physical scientists starting with Liebig and Wohler[2] in 1832, embracing the classic overview of Ostwald,[3] in 1897, and ending with Groth's monumental 5-volume summary of crystallography,[4] in 1912, all seemed strangely forgotten in those days when x-ray crystallographers and structure solution dominated the solid state world. Today we have a database[5] containing more than a quarter of a million known crystal structures and small molecule structure solution has become routine: we have AFM techniques which can image crystal-solution interfaces with atomic resolution:[6] we have neutron and x-ray sources of such intensity that we can follow solid state processes occurring on the second timescale.[7] This experimental power and scope would have been unimaginable to Bill and yet it is now providing an environment within which history can repeat itself—over the last decade or so the scientific and business climates have conspired to produce a situation in which interest in the crystallisation of organic molecules from solution has never been higher and in which our ability to measure has never been more developed. In this highlight I want to give a personal view on why crystallisation and crystal chemistry have become red-hot topics and on the big scientific and technical issues facing the area.

It's a problem knowing where to start since there are many threads that have developed simultaneously, however if I had to single out one event which I see as pivotal it would be the Zantac Patent case.[8] This concerned the solid-state form of Glaxo's major drug, ranitidine hydrochloride, for the treatment of peptic ulcers. The case is now well-documented[8] but briefly this is a polymorphic material capable of adopting two crystal structures. A process resulting in the crystallisation of Form I was patented in 1978. 2 years later a more stable crystalline Form 2 appeared which was also patented and which subsequently became the active ingredient for Zantac formulations. In 1995 the Form 1 patent expired and by developing a process for making and marketing this form, generic companies hoped to break into what had become an annual $3.5billion business for GSK. The issue of crystallisation became central to the case—was it possible to crystallise Form 1 without at least some small amounts of Form 2—if one polymorph could nucleate then why shouldn't the other appear concomitantly?—a scientific issue that harked back to Ostwald's Rule of Stages[3,9] a century before. Eventually the generic companies got their way but the case served as a potent reminder, not only to the major drug companies but also to their shareholders and regulators, of the potential financial gains, or losses, of knowing, or not knowing, all the solid-state chemistry of their products. This realisation has been followed by demands for more stringent process control, for more thorough experimental investigation of individual systems, and resulted in increased patent activity. McCrone's famous statement[10] that 'the number of polymorphs of a material is proportional to the time spent investigating' has been taken to heart. However, under pressure to get products to market and maximise patent protection, pharmaceutical



Roger Davey graduated from Bristol University in 1969 with a BSc Hons in chemistry. He studied for his PhD at University College London and held postdoctoral positions at Imperial College London and the ETH Zurich until 1977 when he joined the chemical company ICI (later Zeneca). In 1993 he joined the Department of Chemical Engineering at UMIST where he has established a successful research group and helped to create a new centre for the study of molecular materials. Throughout his career he has studied problems associated with crystal nucleation and growth and is particularly well known for his work on molecular crystals, polymorphism and applications of crystal chemistry to industrial problems. In 2001 he was awarded a prestigious EPSRC fellowship allowing him to devote his time to research and in particular to studies of crystal nucleation.

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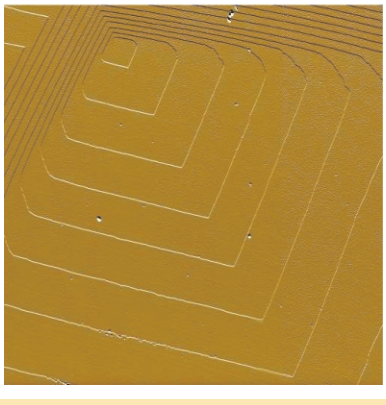
Bill Dunning

Bill was known for his work on nucleation from solution which had been stimulated by the wartime need to produce organic nitrates for high explosive use. At the Faraday Discussion on Crystal Growth in 1949 (number 5), the scene of Frank's famous proposal of the role of screw dislocations in crystal growth processes, Dunning and his co-workers Bransom and Millard gave a paper which was to have an equally great technical impact. The paper was simply entitled 'Kinetics of Crystallisation' but contained a derivation of the now famous population balance equation which they used to measure both nucleation and growth rates in a continuous precipitator and which became a major design tool for chemical engineers from the 1960s onward. He then changed tack and published a number of studies of layer growth on crystal surfaces – his work on sucrose. Compare the resolution of the 0.5 μm high spiral steps on sucrose (top) taken in 1962 by optical microscopy (D. G. Mead ' Growth of Sucrose Crystals, PhD dissertation University of Bristol, 1962, see also ref.[1]) with the AFM image (bottom) of 1.4 nm high steps on a single potassium hydrogen phthalate crystal recorded in 1999 by R. Price, G. R. Ester and P. J. Halfpenny[6] of the Department of Pure and Applied Chemistry, at the University of Strathclyde, Glasgow, UK.



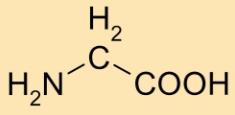
companies no longer have the time to implement a serendipitous discovery strategy, so both they and the funding agencies have thrown money at this problem—money to support the computer-aided prediction of crystal structure from molecular structure, money to support the adaptation of high-throughput screens for the creation of materials science libraries[11] and money to enable on-line process monitoring to ensure robust and reproducible crystallisation processes.[12]

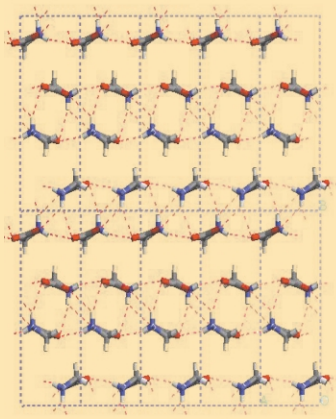
Key scientific issues

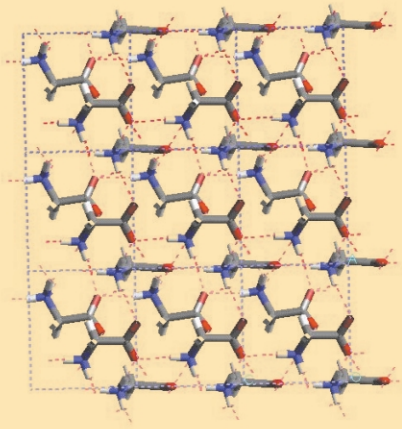
So what are the key scientific issues being addressed?—I think these can be summarised in a set of demanding questions concerning solid forms—'if I have a new molecular entity how many

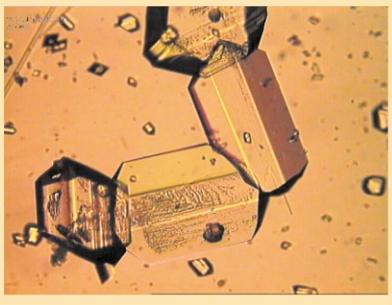
Polymorphism

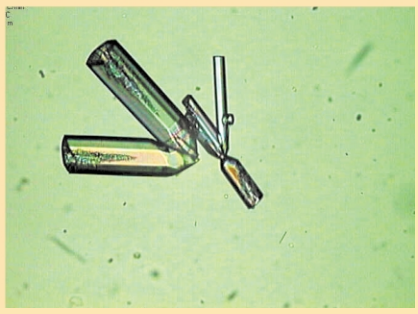
Polymorphic materials are those in which a single molecule can crystallise in two or more crystal structures. For example the simple amino acid glycine has three polymorphs. The structures of two of them α and γ are shown here. Notice how in the α form (left side) the zwitterions pack as centrosymmetric dimers while in the γ form they pack as head to tail polar chains. One consequence of these differences is apparent in the crystal morphologies which are centric prisms for α (left side) and acentric pencils for γ. A second consequence is that at room temperature the γ form is thermodynamically the more stable. This means that, in principle, a population of α crystals will ultimately transform to γ crystals. At higher temperatures this situation is reversed and the α form is thermodynamically the more stable. A system of this type in which relative stability is temperature dependant is termed enantiotropic, while one (such as l-glutamic acid) in which one polymorph is always the most stable, independent of temperature, is termed monotropic. For a complete description of structural, thermodynamic and kinetic issues surrounding polymorphs, the reader is referred to the recent and excellent text by Bernstein[8].











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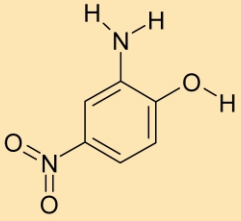
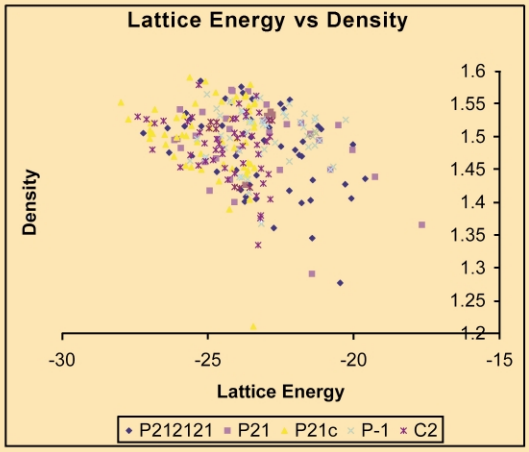
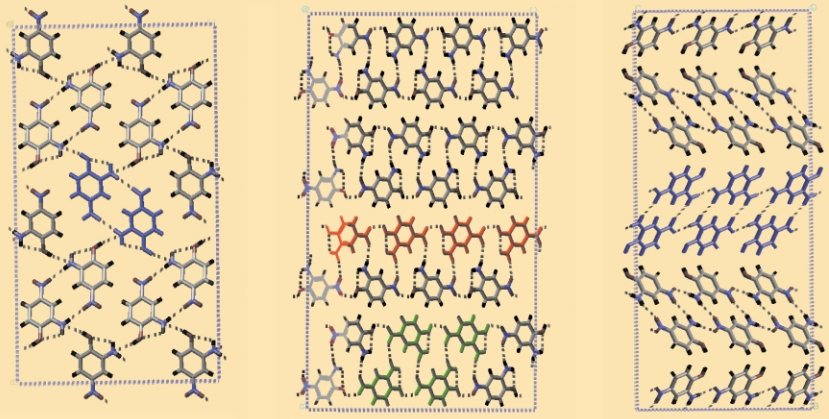
Polymorph prediction

Aminonitrophenol (ANP) was chosen because it is a small molecule with limited conformational flexibility, with no previously characterized crystal structures and 3 functional groups capable of many possible modes of assembly *via* H bonding. Accelrys Polymorph Predictor was used in the 5 most common space groups. 250 possible structures generated from the simulation were analysed. The scatter plot (density, g/cm^3 *vs.* lattice energy, kcals/mol) shows a good distribution of structures over packing space (see ref. 16 and ref. 17for details).





Some of the predicted structures:



unique solid forms will it have? How do I isolate them? Which one do I choose for my product?'

Solid forms

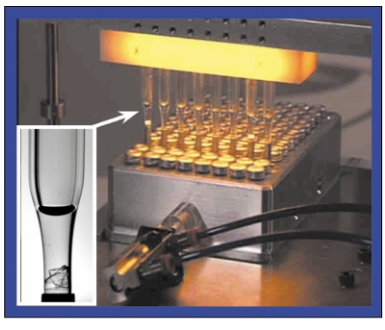
The answer to the first of these is being actively addressed computationally. The early 1990s saw the first attempts to generate hypothetical crystal structures via the construction of multimolecular aggregates packed using common symmetry operators.[13] Perhaps it was the commercially available software 'Polymorph Predictor',[14] which takes a molecular structure and outputs potential crystal structures, that really made the concept user friendly and widely available to both theoreticians and experimentalists alike. Famous 'blind trials' co-ordinated by the CCDC,[15] in which 'predictors' have been invited to have a shot at a previously unpublished structure, continue to form an essential part of this activity. Overall, it has turned out that, given the criteria of density and lattice energy traditionally used to rank the stability of crystal structures, these predictions yield many more potential structures than are observed experimentally. For example, given a small, rigid molecule such as aminonitrophenol (ANP) we found 250 possible structures[16] and for the slightly more flexible diflunisal, 300.[17] Typically the number of experimentally observed polymorphic forms of a given molecule rarely exceeds 5. This raises the issue of what other criteria might be included in the predictions to further filter them and improve the chance of finding the structures that are really possible. This realisation has recently focussed theoreticians on the kinetic processes surrounding the nucleation event since it is here that we know so little about the natural selection processes – we have elaborate kinetic formalisms which describe nucleation using thermodynamic parameters such as interfacial tension and solubility,[9] but these tell us nothing about the molecularity of this event. How does a crystallising system choose between all the possible crystal structures to end up with just one or, at most, a handful of observed ones? Up until now little attempt has been made to address this aspect of the problem. Inclusion of morphology and growth rate predictions along side structural calculations has offered some insight[18] by rejecting those potential structures which grow most slowly or which have extreme shapes. Some progress has been made using molecular dynamics to explore the processes of molecular self assembly during nucleation[19] but more work is clearly required here.

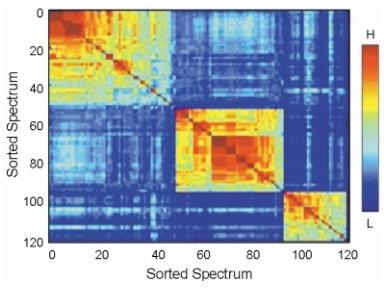
Product isolation

In the context of the second issue, that of product isolation – how do these data help us to crystallise the structures that we want in a reproducible and controlled way? Many companies are taking an experimental approach to this issue and performing high throughput screens[11] which may be considered the experimental version of structure prediction. Here with the use of automated procedures literally thousands of experiments can be performed in an attempt to explore the 'phase space' in which crystallisation occurs and discover not only all the available forms but also define the conditions for their isolation. With such capability in place it would be easy to get carried away but even this technology is no substitute for thinking and understanding. How should experiments be designed to favour specific intermolecular packing arrangements—on what rational basis should solvents be selected? Here again our understanding is lacking but one pragmatic approach[16,17] combines the results of structure prediction with experiments by analysing a total set of predicted structures in order to distil out the most commonly occurring intermolecular binding motifs. Experiments can then be focused, not on crystallising specific predicted structures but on encouraging, through solvent selection, the appearance of certain motifs. In this way, for example, from a limited experimental screen we found 3 new crystal forms for ANP and 4 for diflunisal, numbers typical for such molecules. A second approach assumes that a solution contains clusters corresponding to all the possible polymorphs and utilises monolayers or added auxiliary molecules to stabilise or inhibit the development of clusters corresponding to desired

High throughput screening (HTS)

HTS uses a combination of robotic handling together with small volume crystallisation reactors and *in situ* monitoring to enable many thousands of parallel crystallisations to be performed. The associated data are then stored, identified and binned by computer. For example, Transform Pharmaceuticals, Inc. recently reported a HT solvent screen of >10,000 crystallisations on paracetamol using combinatorial mixtures of 24 diverse solvents.[11] Each crystalliser is a 100 μl tube (see picture below), the contents of which can be imaged optically at the scientist's discretion. Raman spectra are collected as solids are generated over the course of the experiment and are compared and binned using proprietary informatics tools. The matrix plot below shows the binned paracetamol Raman data, where each red region represents samples of a given polymorph. These results are then mapped to the experimental conditions under which each of the various forms appear and are used to select samples for follow-on studies.





structures.[20] This whole isolation issue, of course, remains the holy grail of the whole business – what are molecules doing prior to the nucleation event, in the activated states that precede the appearance of a crystal? These processes occur on the timescale of 10^{-6}s and are difficult to investigate experimentally so how are we to proceed? It is obvious that molecular dynamic computations have a rather important role to play here but experimentation is essential even if related to much longer time scales. NMR measurements of chemical shift, NOE, and spin relaxations when combined with computational methods can enable intermolecular environments in the supersaturated state to be probed. Examples of this approach are to be found in the recent work of Hunter *et al*[21] who have probed various aspects of molecular assembly and Saito *et al*[22] who have observed the growth of molecular aggregates of *p*-acetanisidide in supersaturated chloroform solutions and found them to be held together by the same interactions as the crystal structure. The application of vibrational spectroscopy has been used historically as a means of exploring H-bonding interactions in both solid and liquid states and the routine availability of both *in situ* FTIR and Raman spectroscopy now offers a potentially powerful probe for the nature of intermolecular association in the supersaturated state.[23] Finally, X-ray and neutron diffraction and scattering techniques, the traditional source of detailed molecular scale structural information continue to develop in significant ways. For example, synchrotron sources make *in situ* studies of nucleating systems possible and, together with the newly developed skills in structure solution from powder XRD,[24] offer the potential to provide structural data on short-lived metastable crystalline states. Examples of this include recent work on crystallisation from melt phases which have shown the existence of previously unknown metastable forms,[25] the existence of a liquid crystalline precursor in the formation of triglyceride crystals[26] and the impact of shear on polymorph appearance in cocoa butter.[27] In all these cases diffraction studies have yielded time resolved data on the structural evolution of the crystallisation process. Ultimately, in an ideal world such solid state data would have to be considered along side equivalent information on the mother liquid phase. Fortunately this is rapidly becoming a real possibility with a combination of neutron scattering and empirical Monte Carlo simulation of fluid structure which is proving to be the 'crystallography of the liquid phase' yielding time averaged radial distribution data and correlations between atoms in the liquid state. Thus, for example, the concentration dependence of the liquid phase structure of water/butanol mixtures has been recently established[28] and the changes in coordination of methane by water molecules upon the crystallisation of methane hydrate is known precisely.[29] To run such combinations of experiments and computation is clearly not an easy task and will involve scientists in skilfully managed interdisciplinary research programmes but I believe that the stage is set for us to make a real step change to our notion of what nucleation really involves. The payback in terms of robust and secure process technology together with new product development will follow.

Selection for product development

Finally we come to selecting a form for product development and here there are many drivers. At the process operation level the choice of form may be down to minimising filtration and washing times.[9] At the product formulation level a larger number of factors may be relevant depending on the mode of action of the product. In a polymorphic system issues of storage stability are central – no point using a form which transforms to something else on storage. Thus the impact of temperature and humidity become crucial. Materials that form crystalline hydrates, for example, are generally considered a worry lest they dehydrate. Formulations that deliver biologically active ingredients for ultimate dissolution prior to crossing membranes in the human digestive tract or on plant leaves demand controlled dissolution and maximal solubility. In the pharma industry these are achieved via particle size reduction (milling), by deriving salts of active molecules to increase their aqueous solubility and sometimes by isolating amorphous solid forms. These latter are both subjects of real importance—which salt should be chosen, what sort of molecules form amorphous rather than crystalline phases? In other more obvious multiphase consumer products such as ice cream, fat spreads and deodorant sticks it is the spatial control of nucleation during product formation that is central to the creation of crystal networks that give optimum mouth feel and rheological properties. Overall, there are rich and invigorating scientific and technological challenges ahead and crucially these link very directly to the creation of new processes and products.

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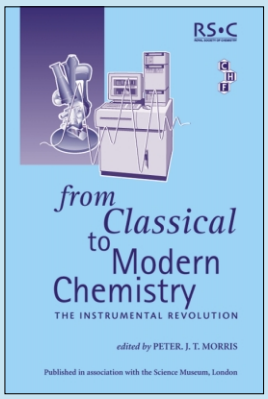
From Classical to Modern Chemistry

The Instrumental Revolution

EDITED BY P J T MORRIS

Most chemists today have either taken part in, or been affected by, the chemical revolution that has taken place over the course of the last century. Developments in instrumentation have changed not just what chemists do, but also how they think about chemistry. New and exciting areas of previously inaccessible research have been opened up as a direct result of this revolution. This is the first book to examine this instrumental revolution and goes on to assess the impact on chemical practice in areas ranging from organic chemistry and biochemistry to environmental analysis and process control, thus demonstrating how fundamental and extensive are the changes that have occurred. With contributions from internationally recognised specialists, this lavishly illustrated book provides a focal point for any historian of chemistry or chemist with an interest in this fascinating topic.



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