CHEMICAL CRYSTALLOGRAPHY

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Keywords: crystal structure determination, molecular structure, molecular geometry, absolute structure and configuration, X-rays, single crystal diffraction, powder diffraction, ambient and non-ambient conditions, displacement parameters, charge density, excited states, databases, problem structures, intermolecular interactions, structure correlation, pharmaceuticals, microporous materials, optical materials, electronic materials, magnetic materials

Contents

Summary

Chemical crystallography is the application of diffraction techniques to the study of structural chemistry. A frequent purpose is the identification of natural products, or of the products of synthetic chemistry experiments; however, detailed molecular geometry, intermolecular interactions and absolute configuration can also be studied. Structures can be studied as a function of temperature, pressure or the application of electromagnetic radiation, or magnetic or electric fields: such studies comprise only a small minority of the total.

While the majority of structure analyses are routine, the need to determine structures from increasingly difficult samples continually presents new challenges: limited crystal quality can appear as weak diffraction, disordered atoms, twinning or large regions of diffuse solvent. Some of these difficulties can be at least partially overcome by employing more powerful radiation sources. Because the extent of diffraction depends on the number of electrons an atom has, identifying the positions of hydrogen atoms using X-ray diffraction can be problematic, as can distinguishing atoms with similar atomic numbers.

In addition to their inherent information content in terms of identification and geometric characterization, the results also provide the necessary input for various types of calculation and modeling such as *ab initio* molecular orbital calculations and protein docking studies.

The results of chemical crystallography are indispensable throughout chemical research, but are of particular significance in certain research-intensive industrial sectors, for example those involving pharmaceuticals, microporous materials and optical, electronic and magnetic materials. They also contribute to many aspects of life sciences, including

pharmaceutical research, drug processing and the study of life under extreme conditions.

1. Introduction

Chemical crystallography is based on the phenomenon of X-ray (or neutron) diffraction, the principles of which are described elsewhere. It determines the crystal structure and thereby the molecular or ionic structure of materials in order to illuminate aspects of their chemistry and function. Given the extensive range of the types of studies undertaken, and the speed at which the field is evolving and changing, it is not possible to provide a definition of chemical crystallography which is simultaneously simple, accurate and comprehensive. However, the key feature of a chemical crystallographic study is one where the objective is to answer a question which in some significant aspect is chemical in character.

The range of materials which is studied comfortably includes simple metal salts and large molecules containing many hundreds of atoms. Chemical crystallography deals with crystalline materials and so excludes those in amorphous and glassy states, as well as plastic crystals, liquid crystals and quasi-crystals. It also generally excludes viruses, proteins, DNA and other very large molecules which fall under the remit of macromolecular crystallography or polymer science.

Although the majority of studies involve routine procedures using standard instrumentation, chemical crystallography is not limited to a particular experimental technique: for example, the type, intensity and wavelength of radiation can vary, as can experimental conditions such as temperature and pressure. However, virtually all non-routine experiments utilize apparatus which is recognizable as a modification or close analogue of either a single crystal or a powder diffractometer. Although powder methods for structure determination are advancing rapidly and are often the only viable technique when sufficiently large single crystals are not available, the main repository of chemical crystallography results, the Cambridge Structural Database (CSD) comprising 541,748 organic and organometallic crystal structures at 1 January 2011, listed only 2003 structures as having been determined by powder diffraction methods. For this reason, the main emphasis of this chapter will be on single crystal methods. One characteristic of chemical crystallography experiments is that diffraction data are collected to atomic resolution.

An experiment will generally involve the determination, geometric description, analysis and comparison of the arrangement of atoms in crystals of chemical compounds. The stereotypical experiment involves the determination of a crystal structure of a novel reaction product in order to characterize it in terms of the elements present and their relative disposition. This provides a form of chemical analysis, establishes the connectivity, and yields values for geometric parameters including bonded distances, valence angles and torsion angles. A chemical crystallographic study may also have more specific objectives such as the identification of which tautomer of a molecule is present, determining the relative or absolute configuration of a molecule, or delineating the geometry and mode of extension for an extended structure. However, this stereotype

falls far short of an adequate description of the range of possible experiments, as will be clear from the types of study described below.

The results of chemical crystallographic investigations are applied to diverse areas, including structural chemistry, molecular modeling, materials design, medicinal chemistry, structural biology and chemical informatics.

2. Types of Study

2.1. Fixed Temperature Studies

The majority of chemical crystallographic studies by far comprise one experiment at a single fixed temperature, either at the ambient temperature of the laboratory ("room temperature") or at a specific lower temperature provided by a cryostat. In the last two decades low temperature data collection has developed from a difficult technique that was employed only when it was essential, for example to study low-temperature phases or highly unstable compounds, to one which is now standard in many laboratories. This change has been driven by a number of factors, principally the advent of nitrogen cryostats which are affordable, reliable, stable, simple to use and permit cooling of crystals down to *ca.* 80 K. At the same time the advantages of routine low temperature data collection have become more widely appreciated: these can include the stabilization of sensitive compounds and a reduction in dynamic disorder, but the most general benefit lies in the enhancement of the measured intensities of reflections at higher diffraction angles as a result of the reduction in atomic motion upon cooling. Thus, in a particular crystal these reflections may be too weak to measure at ambient temperature, but cooling the crystal, typically to a temperature between 90 and 180 K, will often render them measurable. A lower temperature, for example 100 K rather than 150 K, may lead to a further reduction in atomic motion but may also promote the damaging formation of ice on the crystal. The exact temperature selected is often therefore a matter of individual choice.

Low temperature data collection has particular advantages for chemical crystallography, where the compounds studied often contain light atoms, chains of atoms with the potential for extensive motion, and isolated structural units which are free to rotate or librate within the crystal lattice. Moreover, crystals of molecular compounds are typically grown from solution, which can lead to the inclusion of solvent molecules in the lattice: the loss of even a small fraction of these can severely degrade the quality of the crystal, and cooling is an effective method of preventing this.

2.1.1. An Outline of a Routine Single Crystal Experiment

In a standard chemical crystallography experiment, shown schematically in Figure 1, a sample is first examined for shape and optical behavior using a polarizing optical microscope. A single crystal with an average dimension of approximately 0.1—0.4 mm is selected and attached to a glass fiber supported within a metal pip mounted on a goniometer head which allows the crystal to be positioned centrally in the beam of the

diffractometer (Figure 2). If preliminary exposures indicate a diffraction pattern with reflections of adequate intensity, acceptable shape and regular spacing, the crystal is deemed suitable. Depending on the instrument, it is either necessary or desirable at this point to determine the unit cell of the crystal and its orientation on the diffractometer: knowing the unit cell allows checking against databases of known cells to ensure that the crystal is not of a material for which a structure has already been reported.

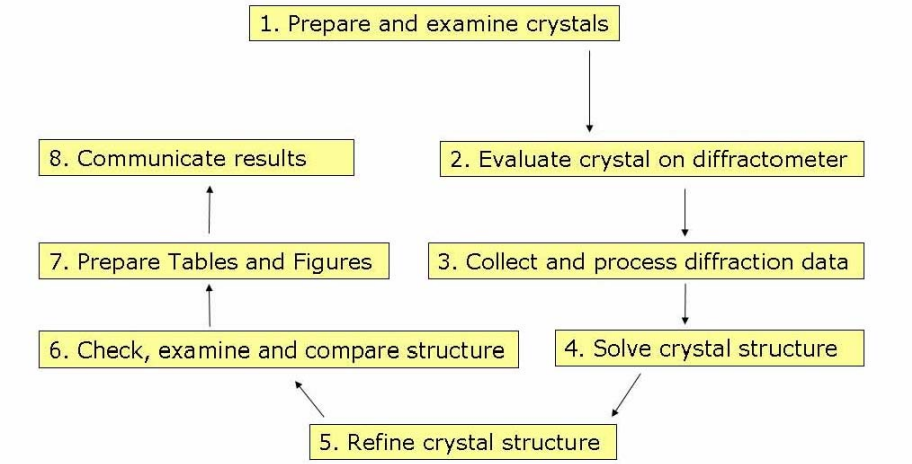

Figure 1. Outline of a typical single crystal structure determination.

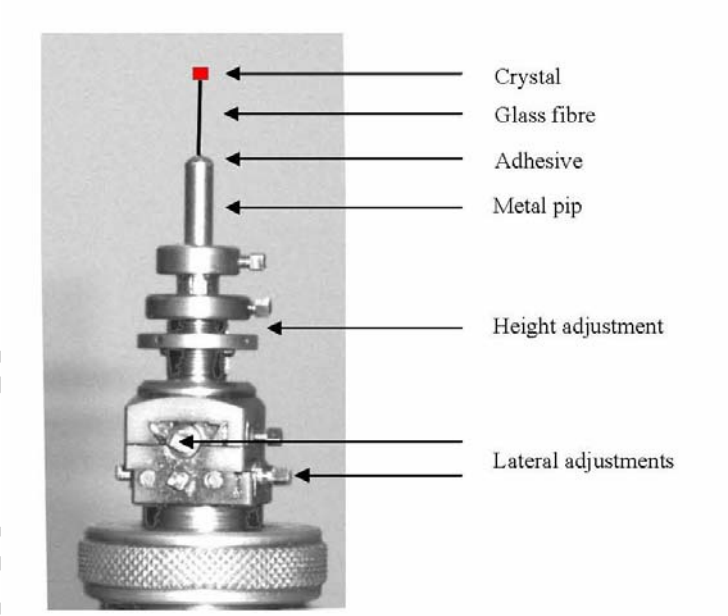

Figure 2. A red crystal mounted on a glass fiber. The fiber is glued to a metal pip which fits into the well of a goniometer head, ready for mounting on a diffractometer.

The crystal is then exposed to the radiation so that the diffraction pattern can be collected using an appropriate detector, and processed in order to produce reflection amplitudes for structure solution and refinement. Structure solution is a necessary step because the reflection data do not contain the phase information necessary to define the positions of the atoms in the asymmetric unit: currently most chemical structures are solved by direct methods, with heavy atom methods accounting for most of the remainder. Whichever solution technique is used, the aim is to produce an initial

approximate model of the structure (Figure 3 left) which can be optimized by least squares refinement and augmented by including atoms in positions identified from peaks in difference Fourier maps. Alternation of these two procedures leads to the discovery of all detectable atoms and the final optimization of their positions and other parameters. Depending on the composition of the sample and the radiation used, it may be necessary to make corrections for the effects of absorption by the crystal. At the end of the refinement, the structure is subjected to a final, formal check on its validity: specialized software carries out a large number of tests against a battery of test criteria, principally to ensure that severe problems such as incomplete refinement, incorrect space group choices and erroneous atom type assignments are flagged, but also to detect less serious issues and provide suggestions for improvement.

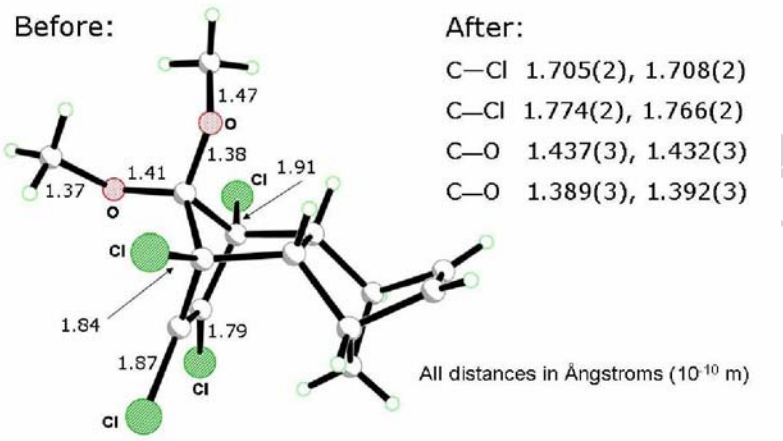

Figure 3. An illustration of the initial model obtained from a structure solution program before refinement (left): note the discrepancies between chemically equivalent distances. On the right is a tabulation of the values of chemically equivalent pairs of bond distances at the end of the refinement: note that within each pair the values are closely similar, but that the pairs are distinct from each other. The numbers in parentheses are standard uncertainties: the value of 1.705(2) Å indicates a carbon-chlorine distance of 1.705 Å with a standard uncertainty of 0.002 Å.

Knowledge of the positions of atoms allows the calculation of distances between pairs of atoms, valence angles involving three adjacent atoms, torsion angles for sets of four sequential atoms, and other geometric parameters. This is the basis for the determination of the geometry of the chemical units in the structure, and it applies equally to the geometry of chemically distinct units and to the relationships between these units within the crystal lattice: these are broadly referred to as intramolecular and intermolecular geometry, respectively. As well as yielding geometric parameters, knowing where the atoms are means that it is possible to generate highly effective illustrations of a structure such as that shown as Figure 4. These allow the detailed examination of individual structures, as well as comparisons between structures: the features of interest will depend on the objectives of the study, as discussed in the Introduction.

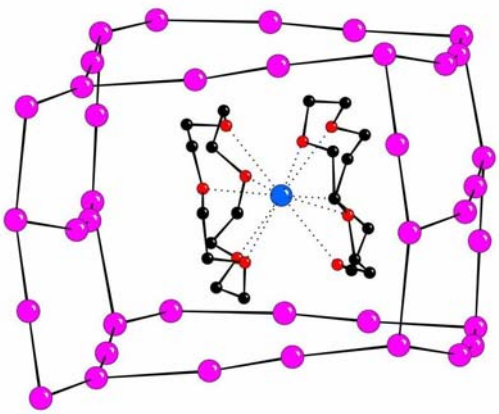

Figure 4. A view of a coordination complex between a cyclic ether (black and red circles) and a potassium cation (blue circle), encapsulated in a cage formed by iodine atoms and iodide anions (magenta circles). The cage forms part of an extended polyiodide network.

The final step includes the generation of tables of selected geometry parameters and high-quality illustrations in order to be able to communicate the results: a scientific publication may contain one or more of these for each crystal structure. At this point, it is advisable to make copies of the final versions of all relevant computer files for the purposes of backup and archiving.

2.1.2. Topic 1: Intermolecular Interactions

While the chemical identity and the internal geometry of a molecule or ion often comprise the principal (or only) points of interest, the fact that the crystal is composed of a regularly repeating array of structural units infers the – possibly significant – presence of neighbors. While weak, non-directional van der Waals interactions are present in all crystals, some contain other interactions which are stronger and more specific in direction (see for example Figure 5). These include various types and strengths of hydrogen bond, $\pi-\pi$ interactions between aromatic rings, halogen-halogen contacts and ionic, $O\cdots S$, $S\cdots S$ and $Cl\cdots Si$ interactions, all of which can operate both within and between molecules. The interest for this section lies with the latter, where knowledge of intermolecular interactions can, for example, provide insights into how the crystal has been assembled from its constituent molecules and/or ions, and how these interactions might be manipulated to produce materials which exhibit extended structures and desirable properties such as porosity.

For example, the structure illustrated in Figure 5 is of a molecule based on the thiophene ring system in which a sulfur atom is one of the five atoms of the planar ring; the ring carries one cyano substituent and one hydroxy substituent. The extended sheet structure shown can be visualized as being built up by first linking molecules into chains by means of $OH\cdots N$ hydrogen bonds in which the hydroxy hydrogen atom is the donor and the cyano nitrogen atom is the acceptor. The chains of molecules are then cross-linked into sheets through $O\cdots S$ interactions. The significance of each type of interaction can be assessed by comparing its geometry against tabulations of van der Waals radii; for hydrogen bonds, the linearity of units such as $OH\cdots N$ provides a

further indication of their significance. In this structure, such an analysis would indicate that the $OH\cdots N$ hydrogen bonds are more significant than the $O\cdots S$ interactions.

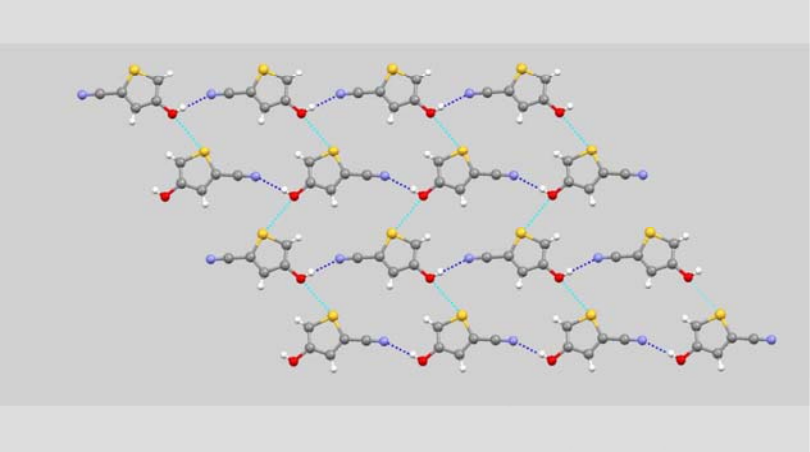

Figure 5. Part of a sheet of molecules linked by OH···N hydrogen bonds (shown as dark blue dashed lines) and by O···S interactions (shown as cyan dashed lines). Atoms are identified by colour: yellow for S, red for O, blue for N, grey for C and white for H.

The determination of the positions of hydrogen atoms by X-ray diffraction is subject to severe limitations on accuracy and precision. The reasons for this and its consequences are discussed in Section 3.2.

2.1.3. Topic 2: Relative and Absolute Configuration

A common reason for undertaking a crystal structure determination is to identify the products of an organic chemistry reaction. In addition to establishing the elemental composition, connectivity and general geometry of the molecule, it is often necessary to establish the configuration at one or more asymmetric centers. Where the structure also contains an asymmetric centre of previously established configuration, it is trivial to determine the configuration of any new centre relative to the pre-existing one. This has no other limitations, and requires no experimental procedures which are not part of a routine structure determination.

In contrast, where the determination of relative configuration is impossible or irrelevant, the determination of absolute configuration depends exclusively on data provided by the diffraction experiment, and its feasibility is governed largely by the elemental composition of the sample and the wavelength of the radiation used. The crystal must contain more than one element (usually excluding hydrogen) and the feasibility is enhanced by the presence of heavier elements and the use of longer wavelength radiation. Because the probability of success is improved where high-angle data are available, data collection at low temperature is very beneficial. Finally, collection of all available reflections improves the reliability of the determination. As is obvious from the foregoing, not all experiments are viable: for example, using short-wavelength radiation to study a molecule containing carbon, oxygen and hydrogen may give no dependable information on absolute configuration. Recent advances have exploited

advanced statistical methods to optimize the reliability of absolute configuration determinations, but in general such an experiment can be challenging even with longer wavelength radiation. A common technique used to boost the chance of success is to carefully synthesize a derivative containing a heavy element such as bromine.

2.2. Variable Temperature Studies

There are relatively few examples of systematic reports of structure determinations of a material at different temperatures. The purpose of such an experiment can be to investigate how the structure or some aspect, property or region of it varies as a function of temperature. The unit cell volume, individual unit cell parameters, intermolecular contacts, molecular conformation, the degree of aggregation, polymorphism, the extent of disorder and individual geometry parameters are some of the factors which might be investigated. Variable temperature studies are often instigated in the light of external observations or measurements such as colour changes or variations in magnetic or other properties: the aim of a study is to determine whether there are structural correlations with or explanations for the observed behavior. For example, it might be possible to establish a link between the colour change in a material and a conformational change in its crystal structure.

Variable temperature work may be demanding in terms of the experimental conditions required. Lower temperatures that those achievable with nitrogen cryostats (*ca*. 80 K) will require more complex and expensive helium cryostats capable of cooling samples to 10–20 K or lower. The lowest temperatures are essential for specific studies, for example to investigate the structural aspects of magnetic transitions which occur at very low temperatures. Cryostats can often be operated to produce some degree of heating, but producing higher temperatures will require a dedicated heating device, for example in the study of phase transitions in a mineral between 600 and 1300 K. The design of an experiment will require the specification of start and end temperatures, and the temperature increments and ramp rates to be used. It may also be necessary to allow a period for the sample to equilibrate between the end of the temperature ramp and the beginning of the data collection.

In addition to observing structural changes in materials as a function of temperature, it is also possible to analyze the behavior of their anisotropic displacement parameters in order to isolate temperature-dependent from temperature-independent contributions. If a description of the temperature-dependent large-amplitude molecular motions in crystals can be developed in terms of correlated atomic displacements it becomes possible to extract calculated vibrational frequencies which can be compared with experimental values (*e.g.*, Bürgi and Capelli, 2000). Estimates can also be obtained for the values of thermodynamic functions such as heat capacity and entropy.

Static and dynamic disorder can only be formally distinguished by executing structure determinations at two or more temperatures, as described in Section 3.3.

2.3. Variable Wavelength Studies

Although multiple-wavelength techniques are very well established for macromolecular crystallography (Helliwell, 2005), in the form of multi-wavelength anomalous dispersion (MAD; see Helliwell, 2005), their application to chemical crystallography is far rarer (Helliwell, 2000; Cianci *et al*., 2005) and is usually undertaken to solve very specific problems. One general example is where sites in a crystal are occupied by elements with similar atomic numbers, and therefore similar X-ray scattering power, so that refinement against data collected using the standard laboratory Mo or Cu X-ray sources will not generally provide sufficient scattering contrast between the elements involved. In order to achieve this, a wavelength-tunable X-ray source (*i.e.*, a synchrotron) is generally required.

An example of the kind of problem which can be approached using a multiple-wavelength technique is that which occurs for structural models for nickel-iron hydrogenase: the two metals have similar atomic numbers (28 and 26, respectively) and their locations may therefore be difficult to distinguish in a routine experiment. Collecting datasets at the *K* absorption edges of both Ni (1.488 Å) and Fe (1.743 Å) shows enhancement of the signal in the difference Fourier map at the appropriate site for each element.

A more challenging problem occurred for a zeolite-like molecular sieve with the framework composition $Na_6[Co_{0.2}Zn_{0.8}PO_4]_6.6H_2O$ where the lack of scattering contrast between Co (Z = 27) and Zn ($Z = 30$) at the Mo $K\alpha$ wavelength used for the initial data collection made it impossible to identify the distribution of the substituted Co over two crystallographically distinct Zn sites. Synchrotron X-ray datasets were taken close to the *K* absorption edges of Zn (1.283 Å) and Co (1.608 Å), and also at a 'neutral' wavelength of 1.45 Å. The resulting difference Fourier maps led to an unambiguous characterization of the sites: the Co is very largely localized on just one of the Zn sites.

2.4. Compression Studies

Reducing the temperature of a crystal from ambient temperature to 100 K will typically result in a reduction in the unit cell volume of a few percent. In contrast, the application of pressures of 50–100 kbar may result in a contraction which is ten times greater, indicating why pressure is by far the more potent thermodynamic variable, capable of inducing major structural and other changes. Although they comprise less than 0.1% of structures reported in the CSD, for example, studies at elevated pressures are becoming more common as the result of the development of apparatus (practical high-pressure cells, high-intensity radiation sources and area detector diffractometers) and techniques (for crystal mounting, pressure measurement and data acquisition) over the last half-century. The ability to vary pressure further extends the scope for studies of the solid state: the behavior of materials under pressure is relevant to areas as diverse as pharmaceutical processing, materials science and the study of life under extreme conditions.

High pressure structural studies arose largely from geology and astronomy: much of the condensed matter in the universe exists at high pressure, whether in rocky planets, gas giants or stars. An archetypal study might have investigated the response of a mineral

structure to increasing pressure, up to that found at the relevant depth within the Earth. More recently, the range of materials studied has broadened, most notably to include simple organic compounds, but also larger, biologically-relevant molecules ranging in size from amino acids to proteins, and metal coordination complexes.

The most widely used design for high pressure cells is that of the diamond-anvil cell (DAC). One version of this is a compact device (*ca*. 4.0 x 3.5 x 1.8 cm) which is capable of generating pressures of the order of 100 kbar, but can be accommodated on a standard diffractometer. The essential components of the DAC are shown in Figure 6. The sample chamber is created from a hole drilled in a metal gasket held between the diamond anvils; pressure applied to the end plates by tightening Allen screws are transferred *via* the anvils and a hydrostatic fluid to a small crystal. The diamond anvils have traditionally been supported on disks of beryllium: while this metal is essentially transparent to short-wavelength *X*-rays, it contaminates the diffraction pattern with a pervasive background which can cause various problems, and alternative supports are being developed. High pressure experiments present other challenges, not least because the geometry of the DAC can severely limit the proportion of unique reflections which can be measured in cases of lower symmetry, and because several of its components contribute to the diffraction pattern. Pressures are usually measured by including within the chamber a small shard of a calibrant (*e.g.*, ruby), and measuring the pressure-dependent shift in its fluorescence band. This procedure requires only a standard Raman or other spectrometer and is non-invasive. Because the stored energy in a DAC is extremely small, even a total failure of the cell would involve no hazard.

Figure 6. (a) A view of a diamond anvil cell (DAC) for high pressure crystallography; (b) a schematic view of a DAC. The sample compartment (arrowed) contains hydrostatic fluid, the sample and a small ruby for measuring the pressure.

A high pressure experiment might involve the measurement of a dataset at ambient pressure, largely to check that there are no problems with the experimental configuration, followed by the incremental application of pressure: after each increment, a dataset is taken. The number of datasets will be determined by the initial purpose of the experiment, the compression behavior that is revealed during the course of the experiment, and limited by the point at which the crystal or the metal gasket fails. An initial survey using large increments in pressure may reveal regions of interest

which can then be investigated more closely. The resulting structures at each pressure are examined in order to discover the details of how the material reacts to compression: application of the first few tens of kbar is likely to affect only the weak, intermolecular contacts leading to shrinkage in the unit cell volume and possible rearrangement of the structural units; higher pressures can lead to changes within molecules and ions, for example in their conformation or internal geometry; at even greater compression, chemical reactions such as polymerization are possible. Observed changes across the pressure range may include the generation of new polymorphs, the reorganization of hydrogen bonding networks, changes in molecular organization or conformation, the closer approach of structural units and modifications to electron configuration.

The phenomenon of polymorphism is of crucial importance to the pharmaceutical industry because two polymorphs of the same drug compound may have quite different physical properties, affecting anything from its processing to its effectiveness and safety as a medical treatment. Legal challenges can and have been mounted to patents on the basis of a claim that a new polymorph, not detailed in the existing patent, has been found. The search for polymorphs is therefore an area of major interest to the industry and its collaborators. Some stages of the processing, notably tabletting, involve the direct application of pressure to the drug compound, a procedure which potentially carries the risk of inducing unwanted phase changes, and compression is well-known as a source of new polymorphs. Drugs which have been studied under pressure so far include the analgesic paracetamol, the insomnia treatment zopiclone and piracetam which is used to treat age-associated mental decline and nervous system disorders.

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Biographical Sketch

Alexander Blake received his BSc (Hons) degree in chemistry from the University of Aberdeen, UK, in 1976 and gained a PhD in main group inorganic chemistry from the same institution in 1980. Subsequently he undertook postdoctoral work at the University of Exeter, UK, on synthetic metallocene chemistry for solar energy conversion and at the University of Edinburgh, UK, on the crystallography of low-melting organic and main-group inorganic compounds.

From 1985 to 1995 he worked as a Research Fellow/Crystallographer in the Department of Chemistry, University of Edinburgh where he further developed the structural chemistry of low-melting materials. In 1995 he moved to the School of Chemistry of the University of Nottingham, UK, where he established a Crystal Structure Facility. He was promoted to Senior Research Officer in 1996, Principal Research Officer in 1999 and to a Chair in Chemical Crystallography in 2007. He is the author of over 880 peer-reviewed papers and since 2006 he has directed a research program studying the behavior of transition metal coordination complexes at high pressures [Allan D.R., Blake A. J., Huang D., Prior T. J., Schröder M. (2006). High pressure co-ordination chemistry of a palladium thioether complex: pressure *versus* electrons, *Chem. Commun*., pp. 4081–4083].

Prof. Blake is a Fellow of the Royal Society of Chemistry (CChem FRSC) and was Vice-President of the British Crystallographic Association (BCA) from 2007–2010. He is the Deputy Editor of *Acta Crystallographica Section C*, a journal of the International Union of Crystallography (IUCr). He was the

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