Crystal growing

Peter G Jones

In recent years structure determination by x-ray crystallography has become a commonly used technique in chemistry, largely due to the development of automatic diffractometers, powerful computers and elegant programs. More and more chemists are thus encountering the technique and need to familiarise themselves with some of its fundamentals. Since most institutions have specialist crystallographers to deal with the technical problems of data collection, structure solution and refinement, the essential rôle of the chemist is often restricted to the provision of suitable crystals.

Although many compounds emerge from preparative procedures in 'crystalline' form, these crystals are rarely suitable for structure determination. The following special procedures are often used to prepare good single crystals.

1. *Slow cooling of saturated solutions.* The flask and solvent to be used should be dust-free. The flask of warm solution is allowed to cool in a Dewar of warm water over a period of several days. This classical method often gives results when method 2 is inapplicable (*eg* when the compound is soluble in most liquids).

2. *Liquid diffusion.* This is normally the most successful method of obtaining single crystals (*see Fig. 1*). A small amount of solution is placed in the tube and a suitable precipitant is layered carefully down the side of the tube on to the solution. This second liquid should be less dense than, and miscible with, the solvent. The tube is then corked and left to stand undisturbed for 24 hours. As the precipitant diffuses into the solution, crystals form at the interface. A suitable volume ratio solvent/precipitant is 1 : 4 or 1 : 5; the solution should be sufficiently concentrated to form an immediate turbidity at the interface. If no crystals have formed in 24 hours, try again with a stronger solution. Commonly used solvent/precipitant pairs are water/acetone; chloroform or methylene chloride/petroleum ether or cyclohexane; and I have had considerable success with formic acid/diisopropyl ether. This method is also suitable when only small quantities of material are available (about 0.1 ml solution is quite adequate).

3. *Vapour diffusion.* The principle is

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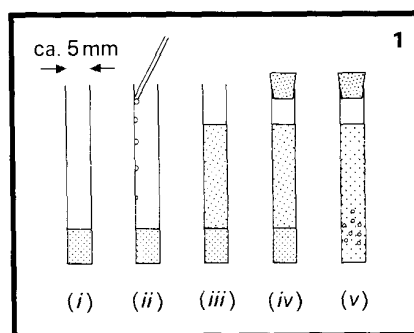
Fig. 1. The liquid diffusion method. (*i*) Solution of compound to be crystallised. (*ii*)–(*iii*) Slowly layer on the precipitant. (*iv*) Stopper and leave overnight: Do not disturb. (*v*) Crystals form at the interface.

the same as the previous method, but the precipitant is allowed to diffuse into the solution from the vapour phase (*see Fig. 2*). Advantages of this method are that several tubes may be set up in the same container (a sealed desiccator is often used) and that very small quantities may be used (on a spot plate). Crystal formation is somewhat slower (several days).

4. *Convection methods.* A simple apparatus invented by Hope[1] is based on continuous convection (*Fig. 3*).

5. *Diffusion of reacting solutions.* Compounds arising as precipitates by reaction of two solutions may often be obtained in crystalline form by layering one reacting solution on the other. If both reactants are in the same solvent, the layering may be facilitated by adding small amounts of other liquids to adjust the densities. A 'buffer layer' of pure solvent or a fine porosity frit may be used to prevent excess immediate precipitation. This method is slower than 2 because reaction must be complete before the mixture is disturbed.

6. *Use of seed crystals.* If other methods provide crystals which, although of reasonable quality, are too small, then these may profitably be used as seed

crystals for method 1. The seed crystals should be drawn off in a pipette together with some mother liquor—if allowed to dry, seed crystals lose their effectiveness—and run into the warm saturated solution. This method has been used to prepare very large crystals (several mm³) for neutron diffraction; as a general rule, the fewer the seeds, the bigger the resulting crystals.

Crystal quality

The quality of crystals cannot be instantly recognised *in situ*; examination with a microscope is necessary. Remove *some* of the crystals from their mother liquor and place them on a slide. Do *not* remove all of them, even if the compound is known to be air stable, because crystals often decompose by loss of solvent of crystallisation once out of contact with the mother liquor.

A good single crystal will normally have well-formed, clear faces; a crazed or fibrous appearance is an indication of poor quality. If crystals have grown in clumps, single crystals may often be separated with a needle, or cut off with a scalpel or razor blade. To prevent crystals from flying off and becoming lost, they can be anchored to the slide with a *trace* of silicone grease.

If a microscope with a polarising attachment is available, the identification of good crystals is made much easier. When a good single crystal is viewed between crossed polars (*ie* black background) it will probably show up brightly;

Fig. 2. The vapour diffusion method. (*i*) Solution of compound to be crystallised. (*ii*) Introduce precipitant and stopper firmly. (*iii*) Crystals form after some days.
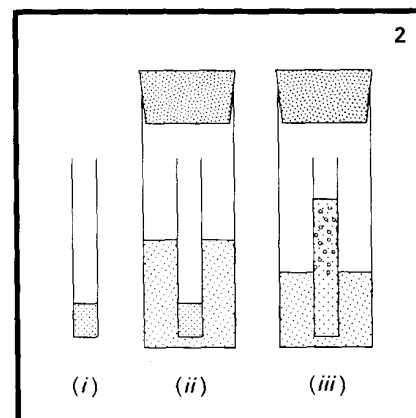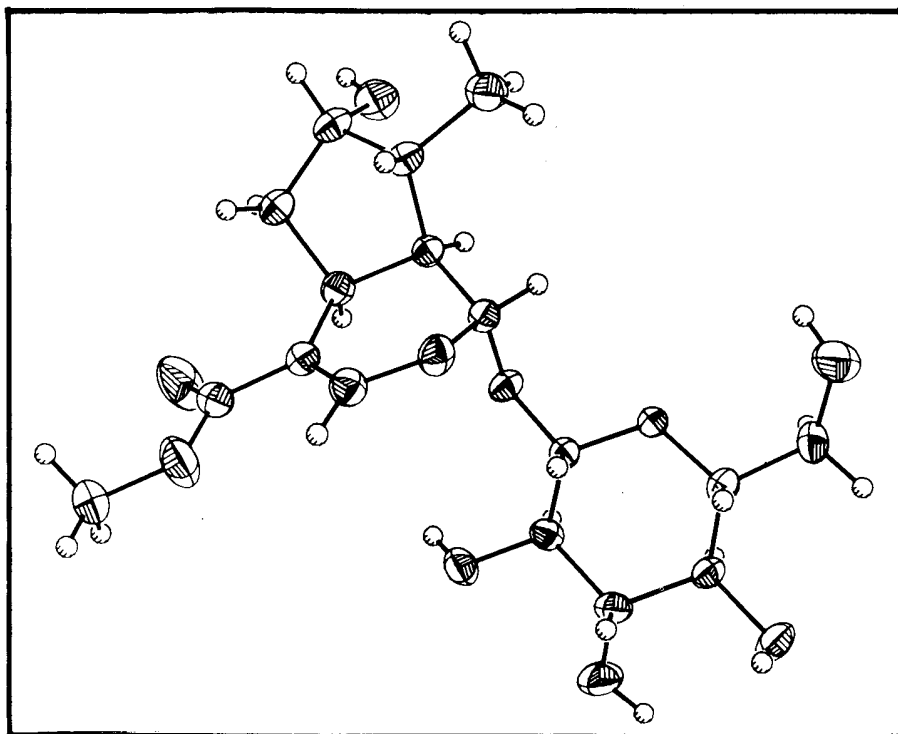
A typical organic crystal structure determination yields this picture of the natural product loganin. Carbon and oxygen atoms are represented as thermal ellipsoids of 50 per cent probability (*ie* there is a 50 per cent chance of finding an atom within its ellipsoid during its thermal vibrations). Hydrogen atoms are plotted as spheres of constant radius.

on rotation of the slide, all parts of the crystal should extinguish the light sharply and simultaneously. (Cubic and some other high symmetry crystals are rare exceptions to this behaviour.) If one part of the crystal is bright and another part is dark it is probably not a single crystal. The crystal must of course be transparent for this procedure.

Crystal size and shape are important. Equidimensional crystals are best, though plates or needles may often be used. The optimum size and shape are determined by the type of atoms present. If only light atoms are present, *eg* typical organic structures containing carbon, nitrogen, oxygen and perhaps a few phosphorus, sulphur or chlorine atoms, the crystal may be of medium to large size, in crystallographic terms, about 0.3 to 0.7 mm in the longest direction. (Few diffractometers can provide a uniform x-ray beam larger than 0.8 mm diameter, and it is essential that the whole crystal always remains in the beam.) If heavier atoms are present, the crystal will absorb x-rays to an appreciable extent; large crystals cannot then be used because few x-rays will get through! By way of compensation, however, such materials usually diffract x-rays more strongly, so smaller crystals are quite usable. A suitable size would be 0.1 to 0.3 mm maximum, depending on the 'heaviness' of the atoms present—a crystal as small as 0.03 mm may be adequate if it is very strongly diffracting. The effects of absorption are enhanced

by extremes of shape such as plates or needles, and these shapes are therefore best avoided (reflected beams will be attenuated much more when passing along the long axis of a needle than when perpendicular to it). Modern programs are, however, capable of applying effective absorption corrections in most cases.

Finally, when you have obtained reasonable-looking crystals, take them (at least some still in the mother liquor) to your crystallographer. He can then decide whether to mount them with mother liquor in a capillary; this is not usually done unless necessary, as the capillary scatters x-rays, leading to a high background level and less precise measurements. Since the waiting list to use the diffractometer may be several months your compound, even if 'air stable', may decompose over this period. I have suffered several disappointments due to sublimed or hydrolysed crystals! If your crystals are at all likely to misbehave, warn the crystallographer.

Why do you want the structure?

Before requesting an x-ray structure it is as well to ask yourself exactly what you want to know. There are three main reasons for wanting a structure.

1. To identify an unknown compound. Although crystallography is becoming a routine analytical technique, it is still time- and resource-consuming. It is therefore best to exhaust other, more conventional, approaches (ir, nmr, elemental analysis) first. Even if the exact

nature of the compound is unknown, any information (*eg* what elements are present, whether the compound is optically active) will help the crystallographer.

2. To obtain accurate interatomic distances and angles. For normal organic structures with no elements heavier than chlorine, bond lengths and angles will probably have an accuracy of 0.005 Å, 0.5° or slightly better. However, since x-rays are diffracted by electrons, any atoms appreciably lighter than the rest will be less accurately located—if at all! Thus, hydrogen atom positions will be relatively inaccurate in organic structures (C—H bond lengths to accuracy 0.02 Å or less). In the presence of heavy elements (*eg* the heavier transition elements) first row elements will be similarly affected and locating hydrogen atoms is usually impossible.

3. To determine the absolute configuration of a chiral compound. This is a less common, but still important requirement. The determination of absolute configuration depends on the measurement of small intensity differences between related pairs of reflections; these differences are greater (and the determination thus facilitated) (*i*) when heavy elements are present and (*ii*) when longer wavelength radiation is used. With copper radiation (1.54 Å) the absolute configuration may, with luck, be determined when only first row elements are present. Modern practice is however to use molybdenum radiation (0.71 Å), which is absorbed less; in this case bromine or heavier elements will probably be needed.

Choice of compound

To some extent the chemist may have several possibilities open to him in choosing a compound for x-ray analysis, *eg* different side chain substituents,

Fig. 3. **Apparatus for crystal growth by convection. The substance of which crystals are required is placed at the bottom left. A and B are heating coils and C is a cooling coil. Crystals form near C and are carried to the bend (bottom right) by convection currents.**[1]
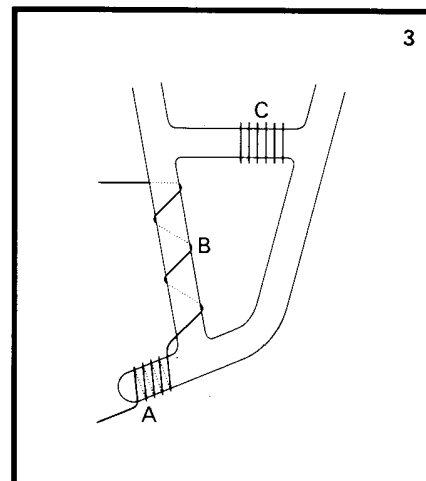
counter-ions or solvates. A sensible choice may make both his and the crystallographer's work much easier. The following guidelines should therefore be observed if at all possible.

1. Try to reduce the possibilities of disorder. X-ray analysis assumes that the contents of each unit cell are identical. If groups are free to rotate, or can occupy different positions in different cells, this assumption is only true in an average sense and structure refinement can become difficult. This phenomenon is known as disorder. Relatively small, highly symmetrical ions (eg BF_4^-, ClO_4^-, PF_6^-, SO_3F^-) are unlikely to partake in strong secondary interactions such as hydrogen bonds and are thus often disordered; bulky ions (eg Ph_4As^+, $(Ph_3P)_2N^+$, BPh_4^-, picrate) are less likely to rotate freely and their use as counterions is strongly recommended. Similarly, torsionally symmetric groups such as CH_3, CF_3, PO_3 (especially when bonded to sp^2 atoms and therefore experiencing no torsional energy barrier) and long $-(CH_2)_n-CH_3$ side chains (as in sterols and many other natural products) are often disordered. The most recommended substituent is phenyl; this is rarely disordered and has the additional advantage that phenyl derivatives often crystallise more easily.

2. Avoid low melting point solids or liquids. Low temperature x-ray work, although possible, is often beset with
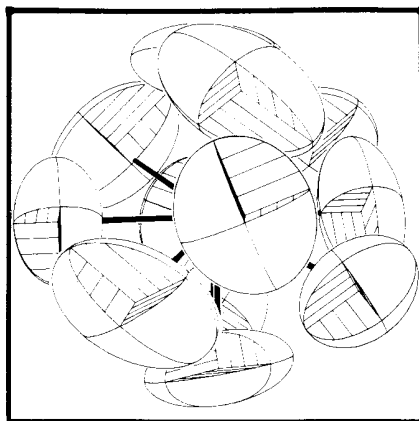
The problems engendered by the use of highly symmetrical, small ions. This is an SbF_6^- ion, which shows a virtually spherical distribution of its F atoms. It has been refined as if it were occupying two different sites, but the large size of the F ellipsoids shows clearly that the disorder must be more severe. (I am grateful to Dr Gabriela Weber for this example).

practical difficulties and always requires frequent attention. Low melting point solids, if not cooled, often exhibit some form of disorder due to their high thermal motion.

3. The choice of solvent is often dictated by what will give the best crystals. Solvent of crystallisation may, however, often be disordered, especially for solvents such as benzene, $CHCl_3$, and CH_2Cl_2 which form no strong secondary interactions to other molecules. It is usually best to get crystals first and worry about this later.

4. Fifteen years ago the solution of an organic crystal structure normally depended on the incorporation of a heavy atom (often iodine or bromine) into the structure. Vastly improved structure solving methods now render this unnecessary, and it can in fact often be a disadvantage; the precision of light atom location is reduced, and organic bromides and iodides often decompose when irradiated.

5. Make sure the compound is the right one! Simple checks may be possible, eg if the compound is meant to contain phosphorus and fluorine, check its nmr spectra. Your friendly local crystallographer will not be amused if time is wasted on the wrong structure, and this happens more frequently than one might imagine.

6. Check that the structure has not been done before! The Cambridge Crystallographic Data Centre reviews yearly all structures containing at least one C—H bond (*Molecular structures and dimensions*); inorganic structures are presented in the BIDICS series of publications from McMaster University, Canada. Both should be in most university chemical libraries.

Reference

1. Hope, *J. Appl. Cryst.*, 1971, **4**, 333.