Growing Crystals That Will Make Your Crystallographer Happy

Paul D. Boyle
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Practically every chemist knows the necessity of recrystallization as a method of purification. What is less well known, however, is methods by which "X-ray quality" crystals may be obtained. The purpose of this monograph is to briefly and informally outline some of the methods which can be used to obtain single crystals suitable for X-ray diffraction studies. This monograph is meant neither to be rigorous nor exhaustive, but rather, a sort of practical "how to" cookbook.

The Goal

The goal in growing crystals for a single crystal X-ray diffraction experiment is to grow single crystals (obviously) of suitable size. The optimum size for a crystal is one which has dimensions of 0.2–0.4 mm in at least two of the three dimensions. Most potential structure determinations are thwarted by a lack of suitable crystals.

General Considerations

The factors during crystal growth which affect the size of the crystals are, solubility of compound in the solvent chosen for recrystallization, the number of nucleation sites, mechanical agitation to the system, and time.

Solvent. Choose a solvent in which your compound is moderately soluble. If the solute is too soluble, this will result in small crystal size. Avoid solvents in which your compound forms supersaturated solutions. Supersatuated solutions tend to give crystals which are too small in size.

Nucleation. The fewer sites at which crystals begin to grow will result in fewer crystals each of larger size. This is desirable. Conversely, many nucleation sites results in a smaller average crystal size, and is not desirable. In many recrystallizations ambient dust in the laboratory provide sites of nucleation. It is important to minimize dust or other extraneous particulate matter in the crystal growing vessel.

Mechanics. Mechanical disturbance of the crystal growing vessel results in smaller crystals. Let the crystals grow with a minimum of disturbance. This means: Don't try to grow crystals next to your vacuum pump, and don't pick up the vessel everyday to check on how your crystals are growing. Set up the crystal growing attempt, in a quiet, out of the way place and forget about it (if possible!) for a week.

Time. This is related to mechanics. Crystals fully recognize that patience is a virtue and will reward those who practice it.

Techniques

Crystal growing is an art, and there are as many variations to the basic crystal growing recipes as there are crystallographers. The recipes given below are ones which I have either tried or I have read about and sound reasonable. The techniques chosen will largely depend on the chemical properties of the compound of interest: Is the compound air sensitive, moisture sensitive? Is it hygroscopic? etc. etc.

Slow Evaporation. This is the simplest way to grow crystals and works best for compounds which are not sensitive to ambient conditions in the laboratory. Prepare a solution of the compound in a suitable solvent. The solution should be saturated or nearly saturated. Transfer the solution to a **CLEAN** crystal growing dish and cover. The covering for the container should not be air tight. Aluminium foil with some holes poked in it works well, or a flat piece of glass with microscope slides used as a spacer also will do the trick. Place the container in a quiet out of the way place and let it evaporate. This method works best where there is enough material to saturate at least a few milliliters of solvent.

Slow Cooling. This is good for solute-solvent systems which are less than moderately soluble and the solvent's boiling point is less than 100 C. Prepare a saturated solution of the compound where is the solvent is heated to just it's boiling point or a just below it. Transfer the solution to a **CLEAN** large test tube and stopper. Transfer the test tube to a Dewar flask in which hot water (heated to a temperature of a couple of degrees below the solvent boiling point). The water level should exceed the solvent level in the test tube, but should not exceed the height of the test tube. Stopper the Dewar flask with a cork stopper and let the vessel sit for a week. A more elaborate version of this involves a thermostated oven rather than a Dewar flask.

Variations on Slow Evaporation and Slow Cooling. If the above two techniques do yield suitable crystals from single solvent systems, one may expand these techniques to binary or tertiary solvent systems. The basic rationale for this is by varying the solvent composition one may inhibit growth of certain crystal faces and promote the growth of other faces, yielding crystals of suitable morphology and size. If you choose this route for growing crystals, it absolutely necessary to record the solvent composition you use! If crystal growing is an art, growing crystals from binary or tertiary solvent mixtures is that much more imprecise. Remember reproducibility is paramount in science.

Vapour Diffusion. (excerpted and paraphrased from Stout and Jensen p. 65). This method is good for milligram amounts of material. A solution of the substance is prepared using solvent S1 and placed in test tube T. A second solvent, S_2, is placed in a closed beaker, B. S_2 is chosen such that when mixed with S_1 the solute will become less soluble. The test tube containing S_1 is then placed in the beaker and the beaker is sealed. Slow diffusion of S_2 into T and S_1 out of T will cause crystals to form. If S_2 is more volatile than S1 the solvent level will increase and prevent microcrystalline crusts from forming on the sides of T.

Solvent Diffusion (Layering Technique). This method also is good for milligram amounts of materials which are sensitive to ambient laboratory conditions (air, moisture). Dissolve the solute in S_1 and place in a test tube. **SLOWLY** dribble $S_2$2 into the tube so that S_1 and S_2 form discreet layers. This will only be successful if 1) The density of $S_2 < S_1$ and 2) Care is exercised in creating the solvent layer. I have found that a syringe is the best way to add the second solvent. The narrower the tube , the easier it is to build up the layer. Five millimeter NMR tubes are excellent vessels to use for this crystal growing technique. CH_2Cl_2/Et_2O is a good solvent combination to try this method (if your compound is insoluble in ether).

Reactant diffusion. This similar to the other diffusion methods except that solutions of the reactants are allowed to diffuse into one another. If the product of the reaction is insoluble, crystals of the product will form where the reactants mix. There is mention in the literature of this technique being used with diffusion in silica gels (see *Acta Cryst.* **1965**, *19*, 483).

Sublimation. The most important factor here is rate of sublimation. To get good sized crystals, the sublimation should be done slowly.

Convection. One may attempt to grow crystals by convection by creating a thermal gradient in the crystal growing vessel. The idea behind this method is that the solution becomes more saturated in the warm part of the vessel and is transferred to the cooler region where nucleation and crystal growth occur. To create the convection one may use either local heating or local cooling. The velocity of the convection current is proportional to the thermal gradient across the vessel. Care must be taken to not make the gradient too large, or the convection will be too rapid and inhibit crystal growth.

To use local cooling, simply take a flat bottomed crystal growing dish (similar to what one would use for slow evaporation) and place one side of it against the heat sink. Normally, simply placing the vessel against a cold outside window will suffice. Notice that the heat sink needs to be against the side of the vessel. Laying the vessel on a cool surface will not induce convection.

A Thiele tube with a resistive heater attached to it makes a good apparatus to grow crystals by local heating convection. The solvent flow should be in the bottom sidearm and out the top side arm. If you need or want to use this method, see me for the details.

Co-crystallants. If you are not getting suitable crystals from other crystallization methods, you can try to co-crystallize your compound with a "crystallization aid". In the literature (see *J. Amer. Chem. Soc.* **1988**, *110*, 639–640) triphenylphosphine oxide (TPPO) has been used as a cocrystallant for organic molecules which are proton donors. Obviously, this method of crystallization is not for all compounds, but for those it is, the results may be rewarding. Essentially this method of crystal growing is the same as slow evaporation except that an equimolar amount of TPPO is added to the solution. I suppose that the other crystallization methods outlined above would also work with this method.

Counterions. If your compound is ionic, and is not giving suitable crystals with a given counterion, perform a metathesis reaction to change the counterion. Very often the crystal quality will improve when a different counterion used. Ions of similar size tend to pack together better and subsequently give better crystals. In addition, you might also get more desirable physical properties for your crystal. For example, the sodium salt of your compound might be hygroscopic, but the tetramethyl ammonium salt might not be or at least, less so. When selecting possible counterions, avoid ions which contain large non-rigid groups (like n-tetrabutyl ammonium). Use ions which have very limited conformational flexibility. A word of warning: *Make sure that whatever ion use for your metathesis does not react with your ion of interest!*

I hope this compilation of crystal growing techniques proves to be useful. It's generally not possible to predict which method will work best for a given compound; choose the method which sounds appealing to you and try it. You will save yourself a lot of time if you do purification recrystallizations before attempting to grow single crystals of the material. If you are sure your compound is pure and a crystal growing technique is not giving suitable crystals change the solvent or the method. If one system does not yield suitable crystal after a couple of tries it is not going to yield good crystals after the tenth or hundredth time. Be intuitive, imaginative, but above all else stick to the basics - no dust, disturbance and a lot of patience.

References

Stout and Jensen, *X-ray Structure Determination A Practical Guide*
Skoog and West, *Fundamentals of Analytical Chemistry,* 3rd. Ed.