Introduction

The power of single-crystal x-ray diffraction techniques is of no value if you do not have a single crystal. Crystal growth has often been viewed more as an art than a science, but a systematic approach can produce results when art fails. The evolution in techniques for the growth of Protein crystals over the last decade should provide inspiration for more systematic approaches to the growth of small–molecule crystals.

Solvents and Solvates

While some materials can be crystallized from the vapor phase, the vast majority are crystallized from solution. To grow crystals from a solution one must first obtain a saturated solution of the material and then make it supersaturated. During the supersaturation phase crystals will begin to grow. Thus, the choice of solvent is one of the most important parameters in the crystallization process. For materials that do not crystallize easily, the most productive approach is to simply screen a large number of solvents. If a limited amount of material is available this may require that the screening process be carried out on a micro scale. The choice of solvent is important, not only because the solvent influences the mechanism of crystal growth, but because solvent molecules are often incorporated in the growing crystal. Often the incorporation of just the right solvent molecule, or mixture of solvent molecules, will produce crystals of high quality. While one can make some rational choices, for example on the basis of hydrogen bonding potential of the target molecule, one can often not anticipate what solvent/target interactions will be desirable. Thus systematic screening of a large number of solvents or solvent mixtures may be the best approach.

Points to note:

- Use pure solvents. Avoid solvents like hexanes and petroleum ether.
- Make sure your compound is pure before you attempt to crystallize. Impure materials don’t crystallize well.
- For highly soluble materials crystal growth tend to be very fast because of high degree of supersaturation, yielding tiny imperfect crystals. In such cases make dilute to moderately concentrated solutions or choose solvents where material is not highly soluble. Slowing down the growth step can produce better crystals.
- Highly volatile solvents like diethyl ether or methanol if incorporated in the crystal may diffuse out quickly ruining the crystals. On the other hand, if they are not incorporated in the crystal, often good crystals are grown from them. Avoid them if you have an alternate choice.
- For materials which are ionic, try a polar solvent. Choice of counter ion is also important. Some counter ions should be avoided if possible as they are very likely to be disordered. Some bad ones are tetra-n-butyl ammonium, tetraethyl ammonium, tetrafluoroborate, perchlorate and hexafluorophosphate. Some good alternate choices would be triflate, sulphate and (Ph)_3P)_2N^+.
- Do not try to separate or dry the crystals. Bring your crystals to the crystallography laboratory in the mother liquor.
Saturation Techniques

Various techniques have been developed to induce the nucleation and growth of crystals. One simple method is slow cooling of a saturated solution. If crystals are obtained this way, bring them to the crystallographic laboratory in the cold container.

Another is slow evaporation of the solvent. This is often effective and a method of choice. In some cases this results in the formation of a ring of polycrystalline material above the surface of solution rather than the growth of well formed crystal. Controlling the rate of evaporation can help get better crystals. This can be done either by reducing the rate of evaporation of solvent or by cooling the solution.

Third method of choice is addition of a poor solvent to a saturated solution of a target species in a good solvent. This is usually accomplished by either diffusion of the poor solvent into the sample solution (e.g. by layering two liquids), or by vapor diffusion.

Another systematic approach to crystal growth involves incorporation of the target molecule into a lattice clathrate. Here the target molecule acts as the solvate while the clathrate host controls the crystal growth. Once the techniques are optimized for growth of the clathrate crystals they can be applied to the incorporation of a wide range of guests. This method allows growing crystals containing guests that are liquids at room temperature.

Points to note:

- Use clean and old glassware. Sometime scratching a side of the glass vessel help as it creates nucleation sites on surface.
- Avoid round bottom flasks and other large containers for crystallization purposes as they would have less nucleation sites plus they don’t fit under microscope. Use small tubes instead.
- Save and store the NMR tubes of your sample for a while and check them periodically. Very often good crystals grow in these tubes.