

Crystal Growing

The “Touch”

I was taught that crystal growing is a knack (a special ready capacity that is hard to analyze and teach), not an art (a skill acquired by experience, study or observation). In some ways this is true, an art can be taught and learned, while a knack is something that you just can do. To me juggling is a knack, try as you might to teach me to juggle and you will fail. The same is true about crystal growing. We all know some people who can grow crystals quite by accident and some that could not grow a crystal if their science depended on it. With that said, there are techniques that could help even those of us who grow the worst crystals (or none at all). One story is told of a research group that could grow beautiful crystals of a compound in their old laboratories but when they moved to a new lab, they could not. It seems that the old lab was filled with “seed” crystals in the form of dust particles and these microscopic crystals would perpetuate the crystallization flasks and “seed” new crystal growth. Such variables can make or break a crystal grower; so much care must be taken to insure the number of random variables is kept to a minimum. With some practice you may find that you have the “touch” for growing good crystals. If not maybe this sheet may help.

Introduction

Crystals form when the concentration of a solution is higher than the solubility of the product. This of course is a thermodynamic process; however the production of crystals is governed by kinetic mechanisms. This kinetic/ thermodynamic battle leads to a condition called supersaturation, a condition where the concentration of the solution is higher than the solubility product but where crystals have not been produced. This is a good thing. It is from the supersaturated solution that thermodynamics will rule and crystals will grow. The trick is to reach this condition and to keep it stable while the crystals slowly form. Unfortunately the supersaturated solution is often stable for long periods of time (years!) and the crystals must be “jump” started by a process called nucleation. By controlling the nucleation step you can grow really big or exceedingly small crystals.

Prepare the crystal growing bench and crystallization ware.

- Choose an area to grow crystals that is draft, dust and vibration free and away from sources of variable light, heat, cold and high traffic.
- Clean the area well. Try to eliminate sources of dust. Remove or cover any metal surfaces that have rusted. Replace tattered pipe insulation, peeling paint and old wall coverings. Move chemicals especially powdered samples to a new location, wash the area and remove any trace of powdered crystals that can “seed” crystallization experiments.
- Do not weigh powdered samples near your “clean” area.

- Keep your dust out of the experiment. You are the largest source of dust. Wearing gloves, face and hair covering will reduce the primary sources of dust near your bench.
- Run a clean filtered compressed air line or purchase compressed air cans and routinely sweep the area and the glassware before use..
- Use 10ml NMR or Raman tubes for crystallization tubes. These tubes are polished on the inside which reduces the nucleation sites.
- Clean the glassware well. Use very dilute soap solutions and rinse very thoroughly. Test the glassware to make sure it is clean. Avoid drying glassware in an oven. Clean the glassware and blow dry with clean filtered compressed air or nitrogen. Store the glassware in re-sealable plastic containers until needed. (note : Glassware is not necessarily the best crystallization vessels for aqueous compounds. The glass is hydrophilic and aqueous solution will “creep” up the sides of the vessels, leading to crystals formed outside the solution)
- Use a high power lamp to detect small particles in solvents and solutions before use to detect the presence of particulate.
- Set up a shelf for crystal growing. Make it eye level, so that you can see your crystal growing vials without disturbing them. Place two HEAVY weights on opposite ends of the shelf to reduce vibrations.
- Set up a refrigerator for only growing crystals. Add heavy weights inside to reduce vibrations. Limit access to it. Only one or two people should be allowed to open it and then only a few times a day. Place unglazed tiles inside and place crystallization ware directly on them (buffers sudden changes in temperature). Place beakers (glass) of ice in the freezer and set crystallization ware in them (buffers sudden changes in temperature).

Prepare solvents and solutes for use

- Use clean doubly distilled, cold filtered solvents or buy ultra-pure solvents.
- Store solvents for crystallization in new clean glass bottles. Dividing the bulk solvent between several bottles will lessen the accidental contamination of the entire solvent supply.
- The compound that is to be crystallized should be ultra-pure. (A crystal that is grown from heterogeneous solutions may contain contaminants, is hard to reproduce and cannot be easily explained to the referees!)
- If counter ions are necessary choose ones of approximately the same size as the compound.
- Choose counter ions carefully. Counter ions can react (sometimes violently) with your compound (e.g. avoid ClO_4^-).
- Choose solvents carefully. Many solvents will react with your compound (e.g. CH_2Cl_2 should not be used with Cu^+ because of Cl^- abstraction by copper).

Tools

- Probes. Metal picks and needles
- Paint brush. Very small paint brush (0.001) use to pick up small crystals
- Microscope slides. Ring slides

- Super glue and epoxy
- Mineral oil. Degas and store over metallic potassium
- Apazone grease (T) and vacuum grease.
- Paratone (STP without the additives)
- Unglazed tiles
- Hand-held illuminated magnifiers
- Zip lock bags (place air sensitive samples in purge and seal)

Set up the crystallization experiment

- Choose the right solvents and prepare a saturated solution. Your compound should be moderately soluble in the chosen solvent.
- Choose the right crystallization vials. NMR tubes work well (see above). New test tubes and sample vials can be used. A tapered tube, such as a centrifuge tube works well for evaporation methods. Avoid old scratched glassware.

Nucleation is (in most cases) an endothermic process, while crystal growth is an exothermic process. You must *add* heat to jump start nucleation and *remove* heat for crystal growth.

Bulk Crystallization

- **Slow cooling 1.** Supersaturated solutions can often be achieved by heating the solute on a hot plate, which will facilitate the nucleation process. Once the supersaturated solution is prepared do not remove it from the hot plate. Instead, turn the hot plate off and allow the solution and the plate to cool down together. This will lead to “spontaneous” crystals. By reheating the solution you can then re-dissolve most (but not all of the crystals). A second cooling will then produce better and bigger crystals.
- **Slow cooling 2.** Prepare the supersaturated solution. Heat a dewar by pouring a small amount of hot liquid into it (old thermos bottles work well too). Place the hot saturated solution, in a capped vial, into the dewar and place an insulated material (e.g. foam peanuts) on top of it. Finally cap the dewar with a cork. Let cool (can take hours). Place the dewar in the refrigerator if need. To aid in nucleation the apparatus can be placed in a ultrasound cleaning bath.
- **Slow evaporation 1.** Prepare a supersaturated solution. Place the solution in a V-vial or a centrifuge tube that has a screw lid. Place in an upright position and crack the lid. Solution will slowly evaporate in a few days.
- **Slow evaporation 2.** Prepare a supersaturated solution. Place the solution in a side-armed flask (or a vacuum flask) and attached your compressed air line to it. Place glass wool or a fritted tube in the opening and flush the apparatus with clean air (or nitrogen). Control the flow rate to the desired rate of evaporation (a few hours to a few months). Evaporation will cause the flask to cool, so compensate if necessary.
- **Slow evaporation 3.** Prepare a supersaturated solution, preferably in a tapered container, such as a centrifuge tube and place in a dry chamber (desiccator) that contains a solvent absorption material (enough material to absorb all of the solvent). Allow to stand.

- **Slow evaporation 4** (reverse diffusion). Prepare a supersaturated solution and place in a centrifuge tube. Find a test tube that is large than the centrifuge tube. Choose a solvent that is less volatile than the saturated solution (see below for vapor diffusion) and place an equal amount in the large test tube. Introduce the centrifuge tube into the larger tube (see diagram 1) and seal the large tube. Solvent will slowly diffuse from the centrifuge tube to the large tube in effect reducing the volume of the solute.
- **Mixed solvent method.** Prepare a supersaturated solution. Choose a solvent which will precipitate the compound from the supersaturated solution. Save a few ml of the solute and then slowly add the precipitating solvent until the precipitate is seen. Introduce a small amount of the saved solute (or the original solvent) until the solution clears (or heat the solution gently until the precipitate dissolves) Place the resulting solution in a pre-heated dewar and put the dewar and contents in the refrigerator.
- **Vapor diffusion 1.** Prepare a supersaturated solution and place in a 10ml NMR tube. Find a test tube that is large than the NMR tube (you may have to cut the NMR tube before hand). Choose a solvent, that precipitates the compound and that is more volatile than the saturated solution (see below for vapor diffusion) and place five times the amount of the solute in the large test tube. Introduce the NMR tube into the larger tube (see diagram 1) and seal the large tube. Solvent will slowly diffuse from the large tube to the NMR tube. (a peanut butter jar and a sample vial can also be used, use your imagination)
- **Vapor diffusion 2.** Hanging drop. This method works well for aqueous solutions. Prepare a supersaturated solution. Pipette a small drop of the solution to a siliconized microscope slide cover (~22mm). The drop should “stand” up due to high surface tension of the material. Add a small amount (~1/10 of the drop volume) of the precipitant and carefully stir it into the drop (avoid air bubbles). Prepare a dish and place a sealant on its lip. The slide cover should cover the dish completely and make an airtight seal with the dish. Invert the slide cover and place the hanging “drop” over the precipitant. Allow to stand
- **Solvent diffusion 1.** Prepare a supersaturated solution. Select a precipitation solvent (the amount should be about 5 times the amount of the saturated solution). Pour the least dense of the two solutions into a test tube. Insert a 1.5ml disposable pipette to the bottom of the test tube and secure it. Insert a small plug of glass wool into the pipette. Add the second solution, drop by drop, into the pipette and allow the solution to drain to the bottom of the test tube, slowing pushing the less dense solution up the tube. When you are finished there will be two layered solutions in the test tube. Crystals will form at the interface of the two solutions.
- **Solvent diffusion 2** Set up the diffusion apparatus as stated above. Instead of the solution and solvent use two of the reactants. Layer one reactant on an other and allow to stand.
- **Solvent diffusion 3.** (micro amounts) Prepare the sample by dissolving in an appropriate solvent. Select a second solvent that will precipitate the sample. Take the least dense liquid and add to a melting point tube with a syringe. Spin the melting point tube in a centrifuge to remove the air bubbles. Add the next solvent by inserting the syringe needle to the bottom of the melting point tube and slowly

injecting the liquid. Seal the tube and let it sit. Depending on the amount of material a NMR tube can also be used.

- **Gel diffusion.** Prepare a glass U-tube and fill with a gel (). On one side of the U-tube add one reactant and the other on the opposite end. Allow the reactants to diffuse through the gel until they form an interface. Reactants can be replaced by supersaturated solution and a precipitating solvent. Acta Cryst. (1965) 19, 483.

Solid to Solid

- **Sublimation 1.** Volatile compounds can be sublimed. Place the compound in a sealed ampule, under vacuum and place in an oven or tube furnace. Heat ampule to sublimation point. Allow solid to sublime and then turn oven off. Allow to stand.
- **Sublimation 2.** Volatile compounds can be placed in a long tube which has a vacuum adapter attached to one end. Tap the compound to the bottom of the tube and place a glass wool plug somewhere near the middle of the tube. Place the tube inside a metal tube. Turn the tube vertically and place the bottom of the tube into an oil bath. Pull a vacuum on the tube and heat the oil bath.

Convection techniques.

- **Convection 1.** Prepare a saturated solution by heating. Place into a large sealed sample vial. Turn sample horizontally and place the bottom of the vial against a warm surface and the top of the vial in a cooler environment. Keep the temperature gradient small.
- **Convection 2.** Prepare a 4ml solution in which the compound is slightly soluble. Add enough compound to the solution so that some sample remains undissolved. Transfer the solution and undissolved compound to a 5ml NMR tube and place the tube into a centrifuge tube. Be sure to pack the tube in tight with packing material (aluminum foil will work). Spin the tube and contents forcing the undissolved material to the bottom of the NMR tube. Set up a hot plate/stirrer with a small crystallization dish with oil placed on the hot plate. Add a paper clip to the oil as a stir rod. Place the NMR tube into the oil in such a way as to place it near the edge of the oil dish. Tilt the tube at about a 45° angle. About 1/4 of the tube should be over the hot plate. The rest should be away from the plate. Secure in place with a ring stand. Slowly bring the oil temperature up, all the while stirring the oil. Do not over heat. The temperature gradient between the cool end of the tube and the hot end should not be large. Do not heat the solution to boiling! Crystals will form in the cool end of the tube.
- If crystals fail to form from supersaturated cooled solutions try acoustic shock to induce crystallization. (i.e. shout at your crystal vial! It may or may not help the crystallization process, but it will relieve your stress).
- Try to forget about your samples (freeze and forget). Go on holiday. Give your crystals more time to grow undisturbed.

Co-crystallization

Co-crystallizing a “hydrogen bonding acceptor” may help. Try adding picrate or triphenylphosphine oxide to your solutions and repeat your crystallization technique. see *J. Amer. Chem. Soc.* **1988**, *110*, 639- 640

Seed Crystals.

Saturated solutions can be “seeded” with small crystals. Form crystals as described above. If the crystals are too small they can be used as “seed” crystals. Be sure to keep them wet (with some exceptions sugar, salt etc.). Remove some crystals and redissolve the remaining crop. Create the supersaturated solution and cool. Reintroduce the “seed” crystals and let stand. A one pot method can be employed with “U” tubes (see above). In this case carefully decant some crystals to one side of the “U” and freeze with dry ice bath. The remaining crop can then be redissolved by heating the other side of the “U” tube. When cooled the frozen crystals can be allowed to warm up and then transferred to the saturated solution. This procedure can be repeated several times, each time “seeding” with larger and larger crystals.

Fun Crystals Sugar Crystals

Slowly add 32 grams (two cups) of refined sugar in 1 gram portions to 160 ml (3/4 cup) of hot stirred water. Pour into a tall jar and allow to cool. Prepare a wooden stir stick by dipping one end in water and then into small sugar crystals. Make a hole in a plastic tube lid and insert the non-dipped end of the wooden stick into the hole. Slowly place the stick and lid into the solution. Adjust the stick so that it does not touch the bottom of the jar. Set in a quiet place. In a day or so you will have “rock” candy. A second crop of crystals can be grown from the same solution. Remove the wooden stick and re-dissolve any crystals that have grown in the jar. Prepare a new stick. Add a few holes to the lid to allow for the evaporation and reintroduce the stick into the cool solution. Allow to sit for days, months or years. Very large crystals can be grown with this procedure.

Mounting Techniques

- Air sensitive crystals can be pipetted from the solution to a “ring” microscope slide. The solution with a few crystals can then be immediately covered with oil (Paratone). If necessary add some of the solution to the oil to resist dissolving the crystal. With epoxy resin (or grease) attached to the mounting fiber pick up a crystal and draw it back through the oil, leaving most of the solution behind. Move the crystal over the microscope slide to remove unwanted oil. When ready quickly move your crystal to a cold stream.
- Thin “hair” loops can be used instead of glass fibers (Hampton). Use rigid (0.2 micron) 0.5-0.7mm loops to mount the crystals near the top of the loop (not

necessarily in the loop). Loops are best used at very low temperatures where the oil freezes solid.

- Mounting crystals in capillaries. Choose a capillary that is slightly larger than the crystal that is to be mounted. If needed, slip a small piece of filter paper soaked in the solution to the bottom of the capillary. Pick up the crystal with some vacuum grease and a small glass fiber (a small pipette can also be used to pipette solution and crystal into the capillary). Slip the crystal down the capillary. Do not push all the way down. To seal the capillary you can use a small birthday candle. Wrap the capillary in a wet towellete in such a way as to cover the crystal. Hold the capillary and place the flame near the edge of the towelette. A gentle pull will separate the capillary and seal it.

Air-sensitive crystals

Normally even the most air sensitive crystals (we call them sudden death crystals) will survive in heavy Paratone oil, for a few hours. If your crystals are very sensitive, then other techniques can be explored.

Cold plates.

Unglazed tiles work well as cold plates for crystal mounting. Place a tile in a freezer for a few hours. Move the tile to a microscope that is adjacent to the diffractometer (within a foot is preferred) and pipette crystals/solution on to it. The tile will absorb the solvent, hopefully leaving the crystals dry and cold. Work quickly before frost gathers on the crystals, mount and move a crystal to the cold stream. Alternatively dry crystals can be placed on the plate in the freezer and moved to the microscope.

Crushed dry ice is placed in a crystallization dish and a glass plate is placed on top, to form a level surface. The dish is placed beneath a microscope. Crystals/solution is pipetted on to the glass surface. Working quickly, before frost gathers on the crystal and the solvent freezes, mount and move a crystal to the cold stream. Alternatively dry crystals can be placed on the plate in the freezer and moved to the microscope.

Dry Box methods.

To mount air sensitive crystals, without the introduction of oil or grease coatings, you will need to use an environmentally controlled area, such as a dry box. Crystals can be mounted in a dry box, without the use of a microscope, if the crystals are large and well formed or you are willing to waste capillaries and/or time.

To mount crystals in capillaries in a dry box: find a glass plate (1/2 inch thick) and attach to long thin pieces of clay near the top and bottom. Press into the clay several capillaries making sure they are secured tightly to the plate. Construct several fibers by pulling a long thin glass rod. Break the fibers in such a way as to leave the larger un-pulled fragment of the glass rod still attached to the fiber. You will need at least four of these fibers (in case of breakage). Fill a syringe with high vacuum grease. Be careful not to

include air pockets in the grease. This is best done in a dry box with degassed grease. Move all instruments and a few large ziplock bags (large enough to hold the glass plate) to the dry box. Attach a large page sized magnifying sheet (found in office supply stores) to the dry box window in such a way as to magnify your work area. Place the plate on a lab jack and bring the plate up to viewing position. Tap a few crystals on to the plate and select one. Move the crystal to a capillary and carefully position a crystal deep into the tube (takes some practice). Repeat for all other crystals. Several crystals can be placed into each tube, if you separate them by a few millimeters!. If the crystals will not wedge, try placing a small amount of grease behind them (later you can tap the crystals into the grease). When complete take the syringe filled with grease and insert grease into each capillary opening, making sure that the opening is completely filled. Add extra grease to completely cover the capillary openings. Slip the plate with the capillaries into a zip lock bag and remove from the dry box. Seal as described earlier.

Mounting crystals without capillaries in a dry box.

Find a small 30ml crystallization dish. In the bottom of the dish place some clay. To the lip of the dish add a line of grease and attach a glass plate in such a way as to form an air tight seal. Move the dish to a dry box. In the box select a crystal and mount on a low temperature pin. With hemostats (remove the locking mechanism on the hemostat) move the pin to the bottom of the dish and secure it to the clay. Fasten the cover plate (possibly with more grease) to the lip of the dish, making an air tight seal. Move the dish to the cold stream. Carefully slide the cover slip off of the dish allowing the cold nitrogen from the stream to completely fill the dish. With the hemostats remove the pin and slide the crystal/pin up into the nozzle. With your free hand remove the dish and attach the goniometer head to the diffractometer. Slide the pin into the goniometer head. Practice this move with sugar crystals before attempting it with your sample.

Crystal mounting in a vacuum tube.

An *insitu* purge chamber can be constructed from a simple vacuum tube. Attach a capillary tube(s) with clay to the inside of a 50ml side arm vacuum tube in such a way as to position the capillary below the vacuum tube's side arm. Move the tube to a dry box and transfer the dry crystals. Seal the tube and move to the crystal mounting table. Attach the N₂ or Ar line to the side arm, remove seal and begin purge. Move to the microscope. With a long thin glass fiber dipped in vacuum grease, select a crystal from the bottom of the tube and move it to the capillary. Carefully push the crystal down the capillary tube until it wedges or is positioned well below the capillary opening. With a syringe filled with vacuum grease, seal the top of the capillary. Carefully remove capillary and seal in a normal fashion. Practice this procedure with sugar crystals before attempting to move the more valuable samples.

This process can be modified for mounting slightly air-sensitive crystals without the use of a capillary in a cold stream. In this case attach a mounting pin, with clay, to a glass rod. Insert pin, dipped in grease, into the tube and select crystal. While still purging

move apparatus to the diffractometer. Quickly remove pin from tube, detach from rod and move the pin to the cold stream. Practice this move first, with sugar crystals, so that it takes less than 3 seconds.

Mounting temperature sensitive crystals

If your crystals melt at room temperature you may need to try this method.

From a crucible holder construct a cradle. In the center of the cradle wedge a piece of filter paper. Bend the cradle wires in such a manner as to suspend the filter paper a few centimeters below a six inch dewar lip. Fill the dewar one-half full with liquid nitrogen and attach the cradle. The cradle should be above but not in the liquid nitrogen. Move dewar to a freezer. With precooled forceps move the temperature sensitive crystals to the filter paper in the suspended cradle. Move the dewar to a microscope (the microscope base may need to be modified before hand). Dip a pin in Apeazon T grease. Clamp the pin with a hemostat. With the clamped bin move quickly to the dewar and attach a preselected crystals. You have only a few seconds to do this before the grease freezes. The idea is to attach the crystal and allow the grease to freeze to it. LEAVE the pin/hemostat/crystal in the Dewar, resting on the cradle, and move the dewar to the diffractometer. Quickly move the crystal/bin/hemostat to the cold stream (three seconds or less). Push the pin up into the cold stream nozzle and then down to the pre-attached goniometer head. Practice this procedure with ice crystals before attempting it on your sample.

A modification of this procedure is to use a Coddington illuminator (or other light magnifying device, instead of a microscope. Large crystals are necessary for this operation. The larger the crystal the more time allowed between Dewar and cold stream. This method also works well with loops.

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