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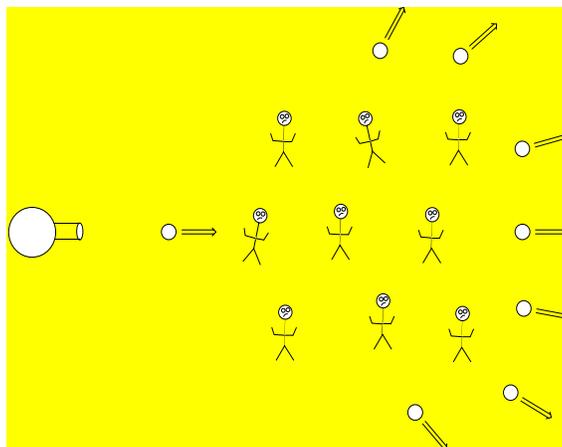
X-RAY STRUCTURE ANALYSIS LAB MANUAL:

A BEGINNER'S INTRODUCTION¹

CHAPTER XIV: GROWING SINGLE CRYSTALS

OPTIMIZED FOR USE WITH SHELXTL AND DOS

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¹ This lab manual is based on the authors experience teaching crystallography to undergraduates and MS students at Youngstown State University, his experience with the software, the SHELXTL manual (Version 5.1) from Bruker AXS (Siemens), George Sheldrick's SHELX manuals, as well as the other references listed in the appendix.

Table of Contents

SECTION 01: GROWING SINGLE CRYSTALS SUITABLE FOR DIFFRACTION ANALYSIS	3
<i>Part a: General principles of growing single crystals</i>	3
Item i: Rates of Crystal Growth.....	3
Item ii: General Conditions for Crystal Growth.....	3
Item iii: Solvent Properties and Saturated Solutions	3
Item iv: Master Several Favorite Methods	4
<i>Part b: Proven Methods for growing crystals</i>	4
Item i: Crystallization by Slow Evaporation	4
Item ii: Crystallization by Cooling	4
Item iii: Crystallization Using Mixed Solvents and Solvent Diffusion in the Gas Phase	5
Item iv: Crystallization by Solvent Layering	5
Item v: Crystallization by Diffusion Through Capillaries and Gels	6
Item vi: Crystallization From Melts	6
Item vii: Crystallization by Sublimation	6
Item viii: Crystallization Using Combinations	6
Item ix: Syntheses In Situ.....	6
Item x: The Magic of NMR Tubes.....	7
Item xi: Other Chance Methods	7
<i>Part c: What to do when proven methods fail</i>	7
Item i: Purify Your Material.....	7
Item ii: Seed Crystals.....	7
Item iii: The Role of Extraneous Materials	7
Item iv: Try, Try Again	8

Section 01: Growing Single crystals Suitable for diffraction Analysis

Part a: General principles of growing single crystals

Most synthetic chemists consider the growing of quality single crystals to be more of an art form than a science. To support this belief, they will point to many things: most often the high degree of chance that seems to be involved in getting such crystals and the fact that some people just seem to have “green thumbs.” There is much truth to these contentions but experience has shown that a fuller understanding of crystal growth and solvent properties and careful analysis of past successes and failures can lead to more consistently positive results. Indeed, protein crystallographers have achieved excellent levels success in this area and we synthetic chemists could learn a lot from their thinking process.

Item i: Rates of Crystal Growth

The laws of thermodynamics tell us that the slower a crystal grows the lower the levels of entropy induced defects to its perfection. Dramatic evidence for this can be seen in the nearly perfect crystals often observed for mineral which crystallize over periods measured in years and millennia. In a lab setting, experience has shown that crystals suitable for diffraction analysis typically grow best over periods of days. Occasionally a quality crystal will be found that formed accidentally while one was taking a solution quickly to dryness, but such cases are the happy exception. Typically when one sets up a crystallization, the best crystals will have formed between one day and a week later. In my experience, the probability of a crystallization proceeding successfully drops off dramatically after the first few weeks, although again I have seen happy exceptions to this.

Item ii: General Conditions for Crystal Growth

Most types of crystallization proceed best in areas of the lab where the temperature remains relatively constant, vibration levels are minimal, and the samples are in the dark. This is often a little used cupboard, closet, or back room. Remember, convection is generally your enemy so try to keep the temperatures relatively constant. In addition, convection is naturally lower in more viscous solvents, ones with less dependence of their density on temperature, and in narrow containers. Since crystallization always takes time and chemists are an impatient lot, there is a tendency to check the samples too often. While hard to avoid, the handling which results is generally detrimental to optimum crystal growth. I therefore recommend that one doesn't check their samples more than once a day.

Item iii: Solvent Properties and Saturated Solutions

Crystals must be grown from saturated solutions. For optimum crystal growth, the compound should be moderately soluble under the crystallization conditions. If it is too soluble then at saturation one will tend to get crystals growing together in clumps. If it is not soluble enough, then there is not enough solute around to supply the growing crystal surface and one tends to get small crystals. To get the correct solubilities one should carefully match the solute and solvent. One can start this process by consulting the literature for parameters like solvent polarity and dielectric constant as well as one's own experience. However, the best procedure is to systematically try different solvents and solvent combinations until you find a half dozen or so where your sample is moderately soluble. In my experience with neutral (and a few ionic) organometallic, inorganic, and organic compounds, the solvents of choice varied dramatically

with the class of compounds. However, I typically had the most success at growing single crystals with combinations of three solvents, namely: CH_2Cl_2 , toluene, hexanes with a few others being successful less often, namely: CDCl_3 , CH_3CN , acetone, ethanol, methanol, THF, and ether. With experience and careful experimentation, you will find a good combination for your system!

Item iv: Master Several Favorite Methods

To get really proficient at growing crystals takes sufficient practice with a method that one masters it. When this happens, one gets very attuned to subtle clues and the rate of ones success increases dramatically. Because of this phenomenon, skilled crystal gardeners will tend to have two or three techniques with which they will get almost all of their success.

Part b: Proven Methods for growing crystals

In the following sections, are listed some of the most commonly used and/or most promising methods for growing single crystals that I have used or considered using in my research.

Safety Tip: Most crystallizations involve one or more components that are moderately or extremely flammable. Although crystallizations typically involve only small solvent quantities, one must still use the best safety procedures and equipment. In particular, flammable materials must be handled with care.

Item i: Crystallization by Slow Evaporation

Perhaps the most widely used method for growing single crystals is this one in which one takes a solution of your target molecule that is not quite saturated and slowly allows the solvent to evaporate. Once saturation is reached, crystals start to form and the continued evaporation provides a continual source of solute molecules to add to the growing faces.

- Typical experimental methods include:
 - One places the solution in a vial or tube in which the lid is pierced by a small pinhole to allow the solvent vapors to slowly diffuse out.
 - One places the solution in a vial or tube in which the lid is made of a material which is somewhat permeable to the solvent vapors.
 - For air sensitive compounds, one can carry out these procedures in an inert atmosphere (i.e., a glove box, glove bag, or a larger container such as a large jar or dessicator).

Item ii: Crystallization by Cooling

In almost all cases solubility decreases with temperature. One can take advantage of this by dissolving your solute in a solvent system to give a near saturated solution at one temperature and then letting the system cool to a lower temperature. If one is blessed with access to a water bath or crystal growing cabinet that has temperature ramp capabilities, cooling times of a day to a week or more are typically chosen. Surprisingly, the cooling times of only a few hours or over night which are all that one can normally get using “natural” thermal gradients are also often successful.

- Typical experimental methods include:
 - Dissolving the sample at some elevated temperature and then insulating the container (e.g., with cotton wool, metal foil, and/or a large thermal buffer) and letting the sample cool slowly to ambient temperatures.
 - Dissolving the sample at or near room temperature and then placing the (perhaps) insulated container into an approved lab fridge or freezer.

Phase Item iii: Crystallization Using Mixed Solvents and Solvent Diffusion in the Gas

In this method, one slowly adjusts the composition of a mixed solvent system having two solvents. The solute should be moderately soluble in the “good” solvent but mostly insoluble in the “poor” solvent.

- Typical experimental methods include:
 - In one variant, you first dissolve the solute in the better solvent and then add the poorer solvent slowly.
 - Sometimes this can be done by dropwise addition of the poorer solvent.
 - Sometimes this can be done by using an extremely low velocity solvent pumps (i.e., typically a syringe pump) to add the second solvent.
 - In another variant, you remove the better solvent.
 - This can be done by having the better solvent evaporate out of the system because it is more volatile.
 - This process is aided if one adds a selective adsorbent to a container holding the sample vial.
 - In the third variant, the better solvent is removed while the poorer is added. One sets up the apparatus so that the second solvent is transferred into the mixed system (and the first solvent commonly diffuses out as well) by diffusion through the gas phase.
 - In the first apparatus, one takes a sample vial containing the solute and good solvent and places it into a second larger container having the poorer solvent in its bottom or a second sample vial.
 - In the second apparatus, two tubes are connected by a bridge through which the solvents can diffuse (i.e., this apparatus is shaped somewhat like a capital “H”).

Item iv: Crystallization by Solvent Layering

An important variant to the previous technique relies on the fact that solvents of substantially different densities mix remarkably slowly when they are not stirred. One can take advantage of this by dissolving the solute in the better solvent and then adding a (bottom or preferably top) layer of the poorer solvent. If this system is not stirred, shaken, or vibrated too much I have seen it take several days for the two layers to mix. The resulting slow diffusion of solvents across the boundary layer often results in excellent crystals growing there.

- Typical experimental methods include:
 - I commonly dissolve compounds in dense chlorinated solvents such as CH_2Cl_2 and then carefully add a top layer of less polar and less dense solvents (e.g. hexanes, ether, toluene).

- If your compound is water soluble, you can vary the density and solvent properties of the two water layers by having very different salt concentrations in each. Protein crystallographers use this technique widely.

Item v: Crystallization by Diffusion Through Capillaries and Gels

Because of their inherent viscosities and in the absence of convection, solvents typically diffuse very slowly through narrow bore capillaries.

- Typical experimental methods include:
 - This general procedure can be done with equipment shaped either as a capital “H” with the capillary being the cross bar or as a vertical tube with a constriction in the middle. The second apparatus is generally easier to make and fill.
 - I have typically dissolved my solute in a more dense solvent and placed this in the bottom half of the tube so that the solution just comes up to the middle of the constriction. I then add a second poorer solvent to the top.
 - A major variant of this technique is to bridge the two solutions with a wider bore tube filled with a gel. This produces very slow diffusion and can be used to grow great crystals but tends to work very slowly.

Item vi: Crystallization From Melts

If your compound is sufficiently thermally stable, one can often grow a crystal from a homogeneous or even heterogeneous melt. Having careful control of the cooling rate is especially critical here. This method is widely used to grow crystals of high temperature solids such as metals and metal oxides and has recently become more popular for conventional ionic compounds through the use of low temperature molten salts.

Item vii: Crystallization by Sublimation

Compounds that are sufficiently volatile at accessible vacuums can be crystallized, often from crude mixtures, to give single crystals by sublimation. In my experience, I have only seen this work for relatively volatile solids like naphthalene, Ferrocene, $M(CO)_6$, and $(\eta^5-C_5H_5)M(CO)_2(NO)$ (where $M = Cr, Mo, \text{ and } W$) but I understand it works well for many other relatively non-polar compounds.

Item viii: Crystallization Using Combinations

When these individual methods don't work, try combos. I particularly like using combinations of mixed solvent methods with cooling but many of these methods can be made to work well together.

Item ix: Syntheses In Situ

Reactions at the interface between two solutions (e.g., different layers or at a capillary junction) can be used to generate a new product that is less soluble than either starting material and hence precipitates out as single crystals. If the reaction is slow enough, this can even happen in a single phase system. I have seen such methods work with both bond forming reactions and

with redox reactions. In the latter case, one can often prepare single crystals of compounds that decompose almost instantly in solution at ambient temperature.

Item x: The Magic of NMR Tubes

If you've had occasion to search the data bases for crystal structures you may have noticed that an amazingly large number of structures are reported with deuterated solvents. This is not because people set out to crystallize from them but rather that crystals often grow "spontaneously" in NMR tubes. [Note: This is aided by the fact that many people don't clean out their NMR tubes until no clean ones are left in the lab and this beaker or "discarded" tubes it set somewhere out of the way where the boss won't see them and/or they won't cause guilt. This gives the solutions large blocks of time with no one disturbing them to grow crystals.] Most commonly, this happens because the NMR solvents one uses (e.g., CDCl_3) slowly diffuse out through the plastic caps.

Item xi: Other Chance Methods

If all else fails, don't sneer at chance. Single crystals are often found in "purification" crystallizations, dishes waiting to be washed, and other unexpected places.

Part c: What to do when proven methods fail

When your attempts at crystallization fail, there are a number of things that you should try.

Item i: Purify Your Material

Many times materials that are "analytically pure," are not pure enough for single crystal growth to be successful. Try an additional round of purification as this often improves your chances of success.

Item ii: Seed Crystals

Because growing crystals pattern themselves on their initial substrate, seed crystals of the same or similar materials will often induce the growth of single crystals of the desired size. Such seeds are often formed inadvertently from droplets of crystallizing solution splashed on the container walls. However, they can also be added on purpose. One often uses a few of the best formed crystals from previous attempts where the crystals were too small by themselves. In some cases, one can use an isomorphous seed.

Item iii: The Role of Extraneous Materials

Crystal growth typically requires a nucleating agent. Sometimes this is a seed crystal but often it is extraneous materials like dust, container walls, etc. Having just the right amount of nucleating agent is required to get great crystals.

Dust, dandruff, and grease

Unless "clean room" procedures are followed, every crystallization attempt will be effected by the presence to dust, dandruff, and other random particulates. A little normal lab

dust will sometimes seed a crystal. I have also seen crystals that apparently were seeded by traces of grease on the flask walls!

Scratches and defects in the container walls

Tiny scratches and defects on the container walls are often the nucleating site for crystal growth. Sometimes if you can't get single crystals in a new container it pays to scratch it up a little. Alternately, if you are getting too many tiny crystals to grow you should use a less scratched container.

Surface treatments of the container walls

One trick that I have seen reported for improving crystal growth is to treat the surface of the container to change its chemical nature. This is most often done by reacting the surface with reagents such as Me_3SiCl .

Item iv: Try, Try Again

The most important ingredients in the growing of quality single crystals are perseverance and patience. It is not uncommon to spend months or even years growing important crystals and succeeding after dozens or hundreds of failures.

Sequential crystal growing strategies

Most chemists employ sequential strategies where they try one or a few things at a time and then use the results to modify the procedures the next time. This typically takes only a fraction of your efforts each week to do but can be slow in terms of the number of months that pass before one is successful.

Systematic approaches to growing crystals and the exploration of crystallization: the multiplex advantage

Protein crystallographers have developed systematic methods to enhance crystal growing success. These typically involve careful explorations of the compound's "crystallization space." By this I mean the effects of temperature, time, solvent, etc., on crystal growing success. A key feature in this method is to use parallel approaches to crystal growth. For a small molecule chemist, this might translate into identifying five promising candidate solvents, and then simultaneously setting up 125 crystallizations (i.e., a 5 by 5 array to test various solvent mixtures made up five times with five different pin hole sizes in the lid). This does require more sample than sequential methods but can be done on very small scales (i.e., you only need one good crystal and this can grow from a fraction of a milliliter of solution) and will tend to give you successful results months sooner.

Make Derivatives

If your chosen compound just won't crystallize, one should often make a derivative of it. For example, I have made an ethyl rather than a methyl compound, an anisole rather than a benzene derivative, and a PF_6 rather than a BF_4 salt.

Solvates and Crystallization Agents

Many substances crystallize best as solvates. One can therefore add solvent molecules that are prone to forming such solvates (e.g., chlorinated organics such as CH_2Cl_2 , aromatics such as benzene and toluene, and water) to induce crystallization.

Inclusion Compounds and Supramolecular Complexes

Thiourea tends to form hollow channels of defined size when it crystallizes and if one adds a suitably sized substrate, it will often crystallize into these channels. Similarly, many bulky porphyrin compounds, cyclodextrins, calixarenes, and related molecules don't crystallize well in the absence of potential guest molecules. One can therefore sometimes induce the formation of host/guest supramolecular complexes by the purposeful addition of such hosts. Similarly, molecules such as crown ethers and cryptands can be added to modify the crystallization of ionic compounds.

Index of Topics and Vocabulary

acetone as a crystallization solvent 4 aromatics 9 art form than a science 3 benzene as a solvate 9 calixarenes as crystallization agents 9 CDCl ₃ as a crystallization solvent 4, 7 CH ₂ Cl ₂ as a crystallization solvent 4, 6 CH ₂ Cl ₂ as a solvate 9 CH ₃ CN as a crystallization solvent 4 chlorinated organics as solvates 9 convection is generally your enemy in single crystal growth 3 convection suppression in capillaries and gels 6 crown ethers and cryptands used to modify ionic crystallizations 9 crystal gardeners 4 crystal growth – typical times 3 Crystallization by Cooling 5 Crystallization by Diffusion Through Capillaries and Gels 6 Crystallization by Slow Evaporation 4 Crystallization by Solvent Layering 6 Crystallization by Sublimation 6 Crystallization From Melts 6 crystallization space and systematic approaches to growing single crystals 9 Crystallization Using Combinations 7 Crystallization Using Mixed Solvents and Solvent Diffusion in the Gas Phase 5 cyclodextrins as crystallization agents 9 density of solvents and rates of their mixing 6 derivatives used to help get better crystals . 9 dessicator used to grow crystals in an inert atmosphere 4 diffusion of solvents through plastic cap 7 diffusion through the gas phase 5 Dust, dandruff, and grease 8	entropy induced defects as a function of crystallization time 3 ethanol as a crystallization solvent 4 ether as a crystallization solvent 4, 6 evaporation of solvents and crystal growth 4 extraneous materials and the initiation of crystal growth 8 General Conditions for Crystal Growth 3 General principles of growing single crystals 3 glove bag used to grow crystals in an inert atmosphere 4 glove box used to grow crystals in an inert atmosphere 4 good solvents from which to grow single crystals 5 grease and its effects on crystal growth 8 green thumbs and growing crystals 3 growing of quality single crystals 3 growing single crystals 4 Growing Single crystals Suitable for diffraction Analysis 3 guest molecules required for crystallization 9 hexanes as a crystallization solvent 6 host/guest supramolecular complexes and crystallization 9 induce crystallization using solvates 9 inert atmosphere techniques for growing crystals 4 Make Derivatives 9 Master Several Favorite Methods 4 methanol as a crystallization solvent 4 mineral crystals grow over multiyear periods 3 NMR Tubes 7 nucleating agent and the initiation of crystal growth 8 Other Chance Methods 7
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poor solvents used to cause single crystals to grow	5	solvents - choosing solvents for growing single crystals.....	5
porphyrin compounds as crystallization agents	9	Supramolecular Complexes	9
protein crystallographers.....	3, 6, 9	surface treatment of container walls for growing single crystals	8
Proven methods for growing crystals	4	Surface treatments of the container walls ...	8
purification of materials as an aid to their crystallizations	7	Syntheses In Situ.....	7
Purify Your Material.....	7	synthetic chemists and the growing of single crystals	3
Rates of Crystal Growth.....	3	Systematic approaches to growing crystals and the exploration of crystallization: the multiplex advantage	8
<u>SAFETY TIP</u>	4	systematic methods to enhance crystal growing success	9
samples should be kept in the dark for single crystal growth.....	3	temperature must remain relatively constant for single crystal growth	3
saturated solutions required for crystallization	5	temperature ramping and slow crystal growing	5
Scratches and defects in the container walls	8	The Role of Extraneous Materials	8
Seed Crystals.....	8	thermal gradients.....	5
seed crystals used to induce single crystal growth	8	THF as a crystallization solvent.....	4
selective adsorbent to aid removal of better solvent.....	5	thiourea form host channels to induce crystal formation.....	9
Sequential crystal growing strategies.....	8	toluene as a crystallization solvent	4, 6
sequential strategies for growing crystals ...	8	toluene as a solvate	9
solubilities – ideal values for crystallization	3	Try, Try Again	8
solubility decreases with temperature.....	5	vibration levels need to be minimal for single crystal growth.....	3
Solvates and Crystallization Agents	9	viscosity of gels.....	6
solvates often induce crystallization	9	water as a solvate	9
solvent density and layering.....	6	What to do when proven methods fail	7
Solvent Properties and Saturated Solutions	3		
solvent pumps for slow solvent addition	5		