Growing X-ray Quality Crystals

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For a more in-depth discussion:

- Paul Boyle's CCCW22 slides
- http://xray.chem.uwo.ca/Guides.html
- http://www.nottingham.ac.uk/~pczajb2/growcrys.htm
- http://www.cryst.chem.uu.nl/lutz/growing/growing.html
- http://xrayweb.chem.ou.edu/notes/xtalgrow.html
- Scientists grow diamonds from scratch in 15 minutes

Important Caveats!

- X-ray crystallography **does not** determine your compound's chemical composition
- It is a technique for determining atomic connectivity of a single crystal.
- Is your single crystal representative of the bulk composition?
- Samples submitted for X-ray crystallographic analysis need to have other characterization data (e.g. NMR, IR, MS, ESR, elemental analysis, etc.) to establish the chemical formula
- Do not make assumptions or jumps in logic that your crystal structure is actually representative of your major reaction product.

What Are Good Crystals and Why We Need Them

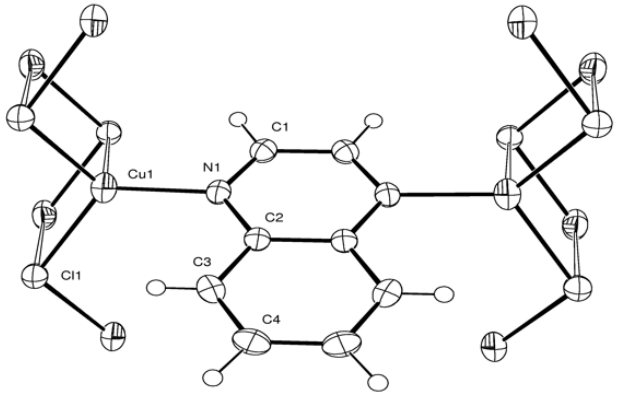
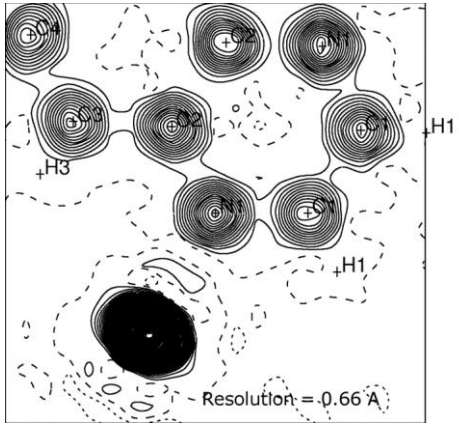
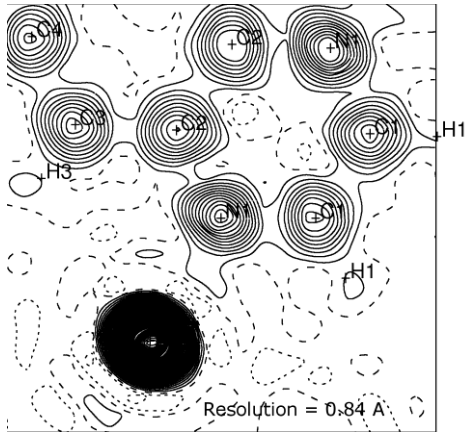
A “good” crystal:

- is 0.1 - 0.3 mm in at least two of its dimensions
- exhibits a high degree of internal order as evidenced by the presence of an X-ray diffraction pattern
- very often, but not always, shows regular faces and edges

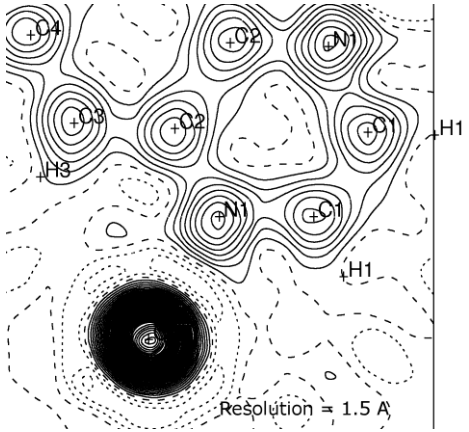
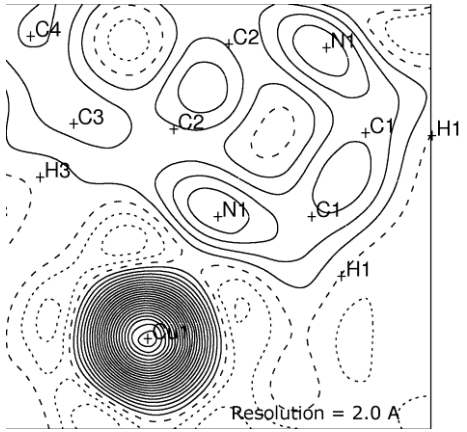
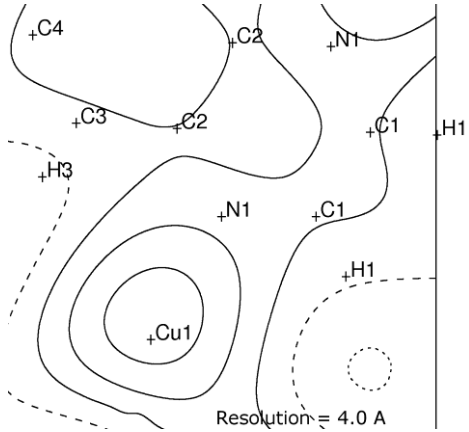
We need “good” crystals because:

- Quality of sample is characterized by maximum diffraction angle (θ); also expressed in “resolution” (Å)
- The larger the max. diffraction angle, the higher the resolution and the greater number of data (which are necessary to adequately model the structure)
- Discerning individual atomic positions requires data resolution which is higher than chemically significant distances (e.g C=O ~ 1.2 Å)

The Effect of Limiting the Resolution of the Data

The final structure	Electron density map using all available data (θmax = 32.35°) Resolution = 0.66 Å All atomic positions are easily resolved	Limited θmax = 25.0° Resolution = 0.84 Å Peaks are beginning to flatten out Atomic positions are still easily resolvable IUCr recommended minimum resolution
		

The Effect of Limiting the Resolution of the Data

Limited θmax = 19.47°	Limited θmax = 14.48°	Limited θmax = 7.18°
Resolution = 1.5 Å Peaks start to “melt” into each other Individual atomic positions are still resolvable	Resolution = 2.0 Å Metal position resolvable Only gross shape of organic ligand evident Peak positions for ligand have shifted away from true atomic positions	Resolution = 4.0 Å Metal position is only barely above background No trace of ligand
		

The Right Attitude Toward Crystal Growing for X-ray Analysis

- Growing X-ray quality crystals requires care and attention to detail
- Treat it like its own miniature research project
- If you have spent weeks or months doing your synthesis, why assume finding the correct crystallization conditions will just take a few hours?
- Do not try to skimp on the amount of material when growing crystals
- Purify your compound (using conventional crystallization and/or other purification steps)
- Consider the empirically established physical properties of your compound – sensitivities, thermal stability, etc.
- Develop a solubility profile of your compound
- Use CLEAN glassware as crystal growing vessels
- Set up crystal growing attempts in parallel utilizing different conditions

Special Considerations for Glassware

- Before setting up a crystal growing attempt think about how the crystals will be handled
- Crystals will need to extracted from the vessel without damage
- Therefore, pick a suitable crystal growing vessel

BAD: Round bottom flasks of any size

BAD: Small aperture vials (too small for spatula)

BAD: Screw top vials (shoulder causes difficulty)

GOOD: NMR tubes

GOOD: Small test tubes

GOOD: Vials without shoulders

Factors Affecting Crystallization

- Solvent – moderate solubility is best. Supersaturation leads to sudden precipitation and smaller crystal size
- Nucleation – fewer nucleation sites are better. Too many nucleation sites (i.e. dust, hairs, etc.) lower the average crystal size
- Mechanics – mechanical disturbances are bad.
- Time – faster crystallization is not as good as slow crystallization. Faster crystallization results in a higher chance of lower quality crystals

Crystal Growing Techniques

Slow Evaporation: simplest to set up.

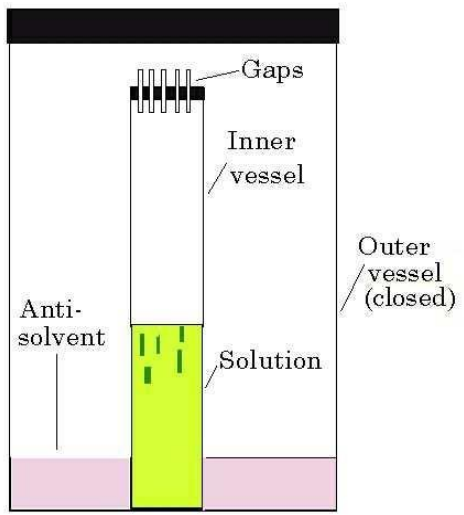
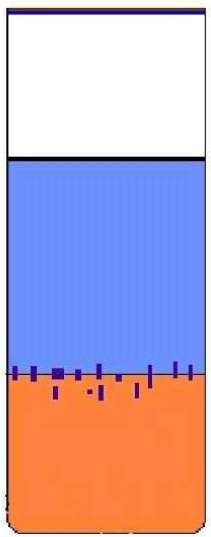
- Has drawbacks: solute can “oil out”, crystals stick to sides of vessel making them difficult to extract from vessel without breaking them.

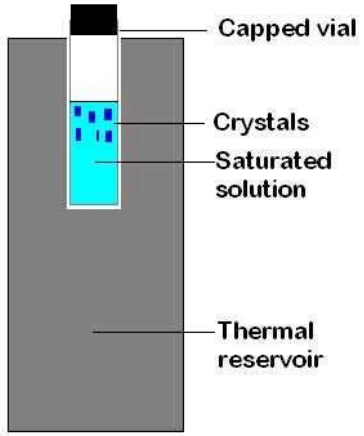
Slow Cooling: Soluble when hot, insoluble when cool.

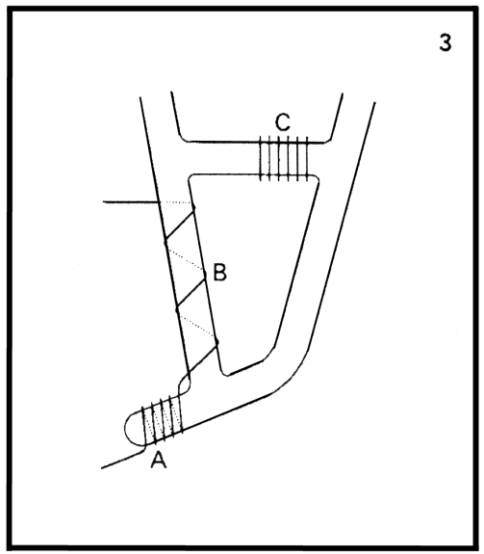
- Use Dewar to slow the cooling process.

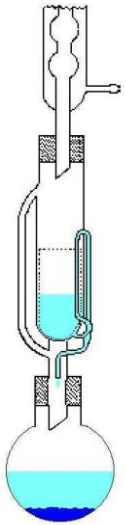
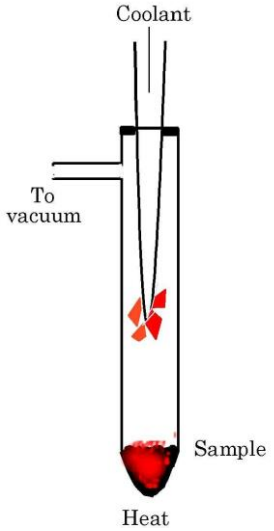
Variations: use binary or tertiary solvent mixtures.

- Use solvent with similar boiling points and other properties.
- Document the percentages of each solvent component!

Vapour Diffusion	Solvent Diffusion	Reactant Diffusion
dissolve solute in solvent (green) precipitating “anti- solvent” (pink) pink should be more volatile than green Do not let sides of small vessel touch vertical surface of outer vessel (prevent capillary action)	Good for milligram amounts Use NMR tube for best results Fill soluble more dense solvent on bottom with your solute. Fill the rest of tube with less dense precipitant solvent E.g. CH_2Cl_2/Et_2O	Set-up similar to solvent diffusion except that reactants are in different layers Good for milligram amounts Good for completely insoluble products which never go back into solution after being formed Consider using a 3rd “middle layer” solvent to mediate the reactant concentrations
		

Slow Cooling	Convection (Principles)	Convection (Easy Way)
Heat water to just below the boiling point of the solvent you plan to use Create a saturated solution of your compound in boiling solvent Transfer to solution to a test tube and cap Fill Dewar with hot water Place test tube into the Dewar and cap Dewar Let stand several days	Good for insoluble or sparingly soluble compounds Create a thermal gradient in the crystal growing vessel Solvent becomes saturated in "warm" region and deposits material in "cool" region where nucleation and crystal growth can occur. Cyclic current allows continual replenishing of the solute Velocity of convection current is proportional to the magnitude of thermal gradient. Take care that the gradient isn't too large – too high velocity inhibits crystal growth	Local cooling – simple to set up Take flat bottomed crystal growing dish and set up like slow evaporation Place vessel so that one side is against a heat sink, e.g. an outside window (in Winter at least) Placing crystal growing dish on a cool surface will not cause convection
 Crystal growth by controlled cooling		

Hope's Convection Device	Thiele Tube Convection Device
Specialty glassware can be fabricated This device designed by Håkon Hope (J. Appl. Cryst. 1971, 4, 333) Nichrome wire is used for the main [A] and subsidiary [B] heating elements. The solvent is cooled at point [C] using Cu wire or thin plastic tubing as a heat sink.	If you don't want to fabricate a special piece of glassware – improvise! Fill Thiele tube with solvent. Wrap nichrome wire around the bottom side arm and attach to Variac Place solute is small container just below top side entrance Apply heat
	

Soxhlet Extraction	Sublimation	More comments on Sublimation
Soxhlet extraction is normally used for separations. However, it can be used for crystal growing of thermally stable, sparingly soluble materials Place your solute in the sample thimble Start the solvent refluxing Crystals grow in the solvent reservoir	Good for volatile air- sensitive materials Specialty glassware is available Use minimal heat to sublime slowly Use small amounts of material	Gas to solid phase crystal growth Compound needs to be thermally stable Can be easy to set up – vacuum sealed tube of material placed in oven for several days/weeks Or more complicated – material packed in tube followed by glass wool. Place under active or static vacuum and set-up thermal gradient by heating the loaded end of the tube. Place Cu pipe around tube to create thermal gradient.
		

Chemical Modification	Ionization of Neutral Compounds	Co-Crystallants
For ionic compounds, change the counterion to change the solubility and other characteristics of your compound Ions of similar sizes tend to pack together better Use counterions with rigid geometries e.g. triflate, BPh_4^-, Me_4N^+, $(Ph_3P)_2N^+$ Tend to disorder: Et_4N^+, Bu_4N^+, $BF4^-$, PF_6^- Make sure counterion does not react with your compound!	If your compound is neutral and has proton acceptor or donor groups, consider ionizing the compound The ionic form may take advantage of hydrogen bonding to give better crystals Counterions can be changed to optimize crystal growth This will change your compound, but if you are only interested in confirming a structure, and not in detailed electronic properties, this shouldn't be a problem.	Sometimes two (or more) different compounds “co- crystallize”. Most commonly, this is a solvent molecule. Triphenylphosphine oxide has been used as a co- crystallant for both inorganic and organic compounds. Tetraaryladamantanes have been used as co- crystallant “chaperones”: Krupp, F.; Frey, W.; Richert, C. Angew. Chem. Int. Ed. 2020, 59, 15875-15879. Rami, F.; Stuerzer, T.; Richert, C.; Adam, M. Acta Cryst. 2021, A77, C883

Final Thoughts and Acknowledgments

- The quality and meaningfulness of your X-ray results is directly dependent on the quality of your sample crystal
- You can get information from a bad crystal structure, but it will be difficult to publish and makes for a weaker manuscript
- Take crystal growing as a serious part of your research project – spend the time and effort to be successful.
- There are many solvents and crystal growing techniques available – use them.

- Thank you: Sandy Blake and Doug Powell for allowing PDB to use images from their crystal growing guides.
- Thank you: Clarence Pfluger, Tony Linden, Sandy Blake, Chuck Barnes, and Andrea Sella for sharing crystal growing methods with PDB.