Growing X-ray Quality Crystals

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Topics to be Covered

- The Objective: Getting “Good” Crystals
- Why do you need good crystals anyway?
- The Right Attitude toward crystal growing
- Factors affecting crystallization
- Crystal growing techniques
- Questions and Answers/Discussion
Objective: Getting Good Crystals

- A “good” crystal is:
- 0.1-0.4 mm in at least 2 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
Why do you need good crystals anyway?

- Quality of sample characterized by maximum diffraction angle ($\theta$) -- also expressed in “resolution” (Å)
- The larger the max. diffraction angle, the greater the resolution and the greater number of data (which is necessary to adequately model the structure)
- Discerning individual atomic position requires data resolution which is greater than the bond lengths between the atoms (e.g C-C = 1.54Å)
The Effect of Limiting the Resolution of the Data
Effect of Limiting Resolution of the Data

- Electron Density Map using all available data ($\theta_{\text{max}} = 32.35^\circ$)
- Resolution = 0.66 Å
- All atomic positions are easily resolved
Limiting the Resolution of the Data

- Limited $\theta_{\text{max}} = 25.0^\circ$
- Resolution = 0.84 Å
- Peaks are beginning to flatten out
- Atomic positions are still easily resolvable
- IUCr recommended minimum resolution
Limiting the Resolution of the Data

- Limited $\theta_{\text{max}} = 19.47^\circ$
- Resolution = 1.5 Å
- Peaks start to “melt” into each other
- Individual atomic positions are still resolvable
Limiting the Resolution of the Data

- Limited $\theta_{\text{max}} = 14.48^\circ$
- 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
Limiting the Resolution of the Data

- Limited $\theta_{\text{max}} = 11.54^\circ$
- Resolution = 2.5 Å
- Metal position still discernible
- Individual atomic positions for ligand have been lost
- Lost of chemically useful information
Limiting the Resolution of the Data

- Limited $\theta_{\text{max}} = 9.59^\circ$
- Resolution = 3.0 Å
- Only metal position is discernible
- Ligand is completely “washed out”
Limiting the Resolution of the Data

- Limited $\theta_{\text{max}} = 8.21^\circ$
- Resolution $= 3.5 \text{ Å}$
- Metal electron density is “bleeding” into the traces of the ligand's electron density
Limiting the Resolution of the Data

- Limited $\theta_{\text{max}} = 7.18^\circ$
- Resolution = 4.0 Å
- Metal position is only barely above background
- No trace of ligand
Limiting the Resolution of the Data

- Limited $\theta_{\text{max}} = 6.37^\circ$
- Resolution = 4.5 Å
- Metal position cannot be differentiated from noise
Limiting the Resolution of the Data

- Limited $\theta_{\text{max}} = 5.74^\circ$
- Resolution = 5.0 Å
- Noise
The Right Attitude toward Crystal Growing for X-ray Analysis

- Growing X-ray quality crystals requires care and attention to detail
- Don't treat crystal growing in an offhand or casual way (forget what you learned in undergraduate organic chemistry labs)
- Treat it like its own miniature research project
- Don't try to skimp on the amount of material when growing crystals
General Approach to Growing X-ray Quality 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
Purify Your Compound

- Impure samples do not recrystallize as well as pure samples
- Recrystallization minimizes the presence of foreign insoluble material which increases the number of nucleating sites
- Successive crystallizations purify the compound
- Always use recrystallized material when setting up a crystal growing attempt
Solubility Profile

Solubility Profile for Compound X

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Use **CLEAN** Glassware

- Clean glassware should sheet water uniformly
- Use KOH/EtOH bath or *aqua regia* to initially clean glassware and rinse
- Follow by soap & water washing
- Follow by acetone or MeOH rinse
- Oven drying
Parallel Crystal Growing Attempts

- Combine knowledge of solubility profile with crystal growing techniques
- Set-up simultaneous crystal growing experiments
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 higher chance of lower quality crystals.
Solvent Considerations

- Moderate solubility is best (avoid supersaturation)
- Like dissolves like
- Hydrogen bonding can help or hinder crystallization. Experiment!
- Presence of benzene can help crystal growth
- Avoid highly volatile solvents
- Avoid long chain alkyl solvents can be significantly disordered in crystals. Choose solvents with “rigid geometries” (e.g. toluene)
Nucleation & Growth

- Crystals initially form via “nucleating events”
- After a crystallite has nucleated it must grow
- Nucleation sites are necessary, but ...
- Excess nucleation sites cause smaller average crystal size
- Ambient dust, filter paper fibers, hair, broken off pipette tips all provide opportunities for nucleation – take steps to remove them.
Mechanics (Crystal Growth)

- Crystals grow by the ordered deposition of the solute molecules onto the surface of a pre-existing crystal.
- Crystal growth is facilitated by the environment changing slowly over time.
- Keep crystal growth vessel away from sources of mechanical agitation (e.g. vibrations).
- Set-up away from vacuum pumps, rotovaps, hoods, doors, drawers, and so on.
- Leave samples alone for 1 week, don't “check in” with it. Your crystals are not lonely.
Time

- Quality crystals grow best over time in near equilibrium conditions
- The longer the time, the better the crystals
- Patience, patience, patience
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 b.p's and other properties.
Vapor Diffusion

- dissolve solute in solvent (purple)
- precipitating solvent (blue)
- blue should be more volatile than purple
- Don't let sides of small vessel touch vertical surface of outer vessel (prevent capillary action)
Solvent Diffusion

- 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$_2$Cl$_2$/Et$_2$O
Reactant Diffusion

- 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
Sublimation (1)

- 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.
Sublimation (2)

- Specialty sublimation glassware available
- Perform slowly
- Use small amounts of material
Convection (Principles)

- 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 solute
- Velocity of convection current is proportional to the magnitude of thermal gradient.
- Take care that gradient isn't too large – too high velocity inhibits crystal growth
Convection (Easy Way)

- 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.
Convection (Special Apparatus)

- Fill Thiele tube with solvent.
- Wrap nichrome wire around the bottom side arm and attach to Variac.
- Place solute in small container just below top side entrance.
- Apply heat.
Co-Crystallants

- 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.
Chemical Modification

- 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, $\text{BPh}_4^-$, $\text{Me}_4\text{N}^+$, $(\text{Ph}_3\text{P})_2\text{N}^+$
- Tend to disorder: $\text{Et}_4\text{N}^+$, $\text{Bu}_4\text{N}^+$, $\text{BF}_4^-$, $\text{PF}_6^-$
- Make sure counterion does not react with your compound!
Chemical Modification (Ionization of Neutral Compounds)

- If your compound is neutral and has proton acceptor or donor groups, consider ionizing the compound.
- The ionic form makes 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.
Online Resources

- Use google (around 39,000 hits for 'X-ray “crystal growing”'), the knowledge is out there!
  - [http://www.xray.ncsu.edu/GrowXtal.html](http://www.xray.ncsu.edu/GrowXtal.html)
  - [http://xrpc4.harvard.edu/xtalgrow.pdf](http://xrpc4.harvard.edu/xtalgrow.pdf)
  - [http://xray.chem.ufl.edu/growing%20tips.htm](http://xray.chem.ufl.edu/growing%20tips.htm)
  - [http://www.cryst.chem.uu.nl/growing.html](http://www.cryst.chem.uu.nl/growing.html)
  - [http://xrayweb.chem.ou.edu/notes/xtalgrow.html](http://xrayweb.chem.ou.edu/notes/xtalgrow.html)
Conclusion

- The quality and meaningfulness of your 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.
- 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.