Crystallization Methods & Crystal Quality Evaluation

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Single crystals – important warnings

- 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 subjected to X-ray crystallographic analysis need to have **other characterization** data (e.g. NMR, IR, MS, elemental analysis, etc.) to establish the **chemical formula**.
- **Don't make assumptions** that your crystal structure is representative of your major reaction product. Every conclusion needs to be backed with empirical evidence.

Single crystals – general considerations

Growing X-ray quality crystals requires **care** and **attention to detail**!

Regardless of the crystallization technique used, always:

- ✓ **Purify** your compound (using conventional crystallization and/or other purification steps) – Make sure your sample is **pure**, without decomposition and/or side products and free of other residues (silica gel, broken glass, filter paper, stir bar, etc). An impure sample is the largest impediment towards success.
- ✓ **Be patient**! Crystals need time to grow. Crystals formed rapidly are most likely of poor quality. Usually, several days to weeks is ideal.
- ✓ **Avoid disturbance**. Set up crystallization experiments in a quiet environment (far from pumps, compressors, fridges, glove boxes, etc.). Only pick up the sample when you can see crystals using a flashlight.

Single crystals – general considerations

- ✓ **Never remove the solvent**! Frequently, solvent molecules co-crystallize with your compound, making them integral parts of the crystal lattice. Also, **moderate solubility** is the best. Supersaturation leads to sudden precipitation and smaller crystal size.
- ✓ Use **clean glassware** to avoid contaminant nucleation sites. Fewer nucleation sites are better. Too many nucleation sites (i.e. dust, hairs, etc.) lower the average crystal size.
- ✓ Pick a **suitable** crystal growing **vessel** – Crystals will need to extracted from the vessel without damage (Bad vessels: round bottom flasks, small aperture vials, screw top vials; Good vessels: small test tubes, vials without shoulders)

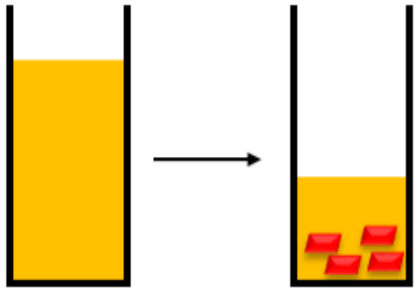
Factors affecting crystallization

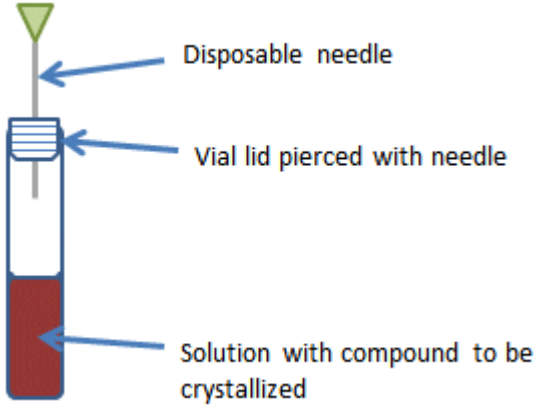
- ✓ **Solvent** – moderate solubility is the best. It avoids supersaturation that leads to sudden precipitation and smaller crystal size.
  - Use the gold rule "Like dissolves like".
  - **Avoid** highly **volatile** solvents.
  - **Prefer** solvents with **rigid** geometries (ex: long chain alkyl solvents can be highly disordered in crystals)
  - Check whether **hydrogen bonds** help or hinder crystallization.
- ✓ **Nucleation** – fewer nucleation sites are better. Too many nucleation sites (i.e. dust, hairs, etc.) lower the average crystal size

Crystallization techniques *

Using a **single solvent**:

- ✓ **Slow evaporation**





Advantages: Easy

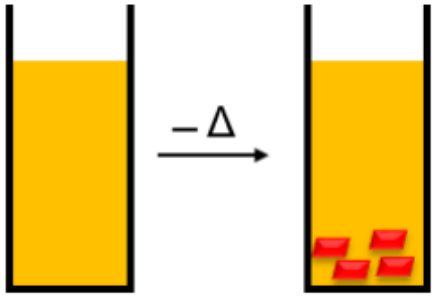
Disadvantages: Needs a lot of material. Starts with (almost) saturated solution, which can lead to too much nucleation. Crystals can have an outer oily layer and stick to the vessel (difficult to extract them without breaking). Not good for air-sensitive compounds. Often don't work.

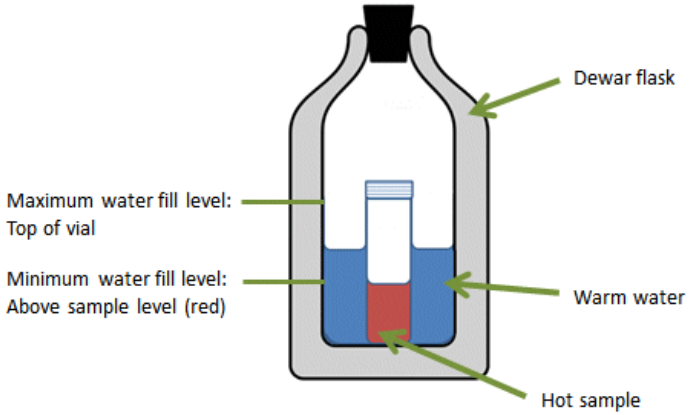
* Always evaluate different techniques. Don't use only a single method!

Crystallization techniques

Using a **single solvent**:

- ✓ **Slow cooling**: either starting from hot solutions or from room temperature.





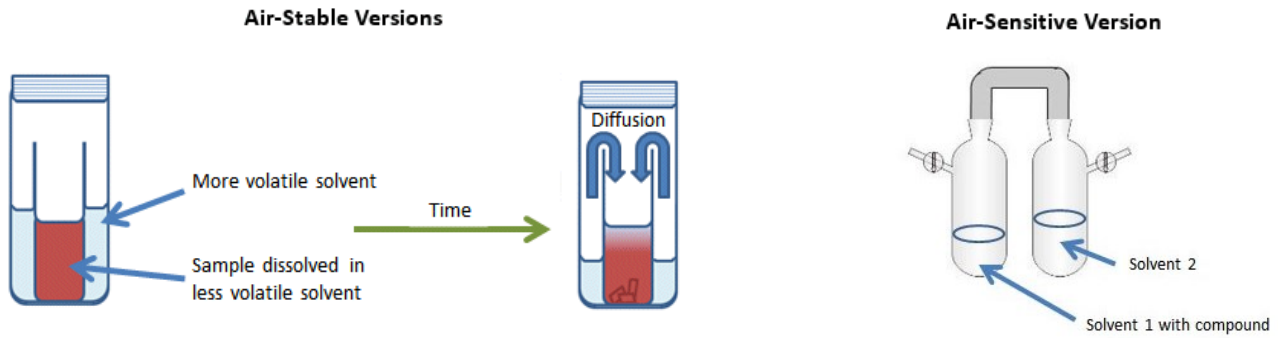
Advantages: Easy. Best results for only moderately soluble substances. Can be used for air-sensitive compounds (using Schlenck tubes or similar).

Disadvantages: Needs a lot of material. Starts with saturated solution, which leads to too much nucleation. Crystals can be disordered or twinned. Not good for air-sensitive compounds. Often don't work.

Crystallization techniques

Using a **mixture of solvents**:

- ✓ **Vapor diffusion**: needs a solvent and an anti-solvent (with a good vapor pressure – more volatile than the initial solvent). The sample should be concentrated, but not supersaturated. Regulate the diffusion speed by varying the temperature.



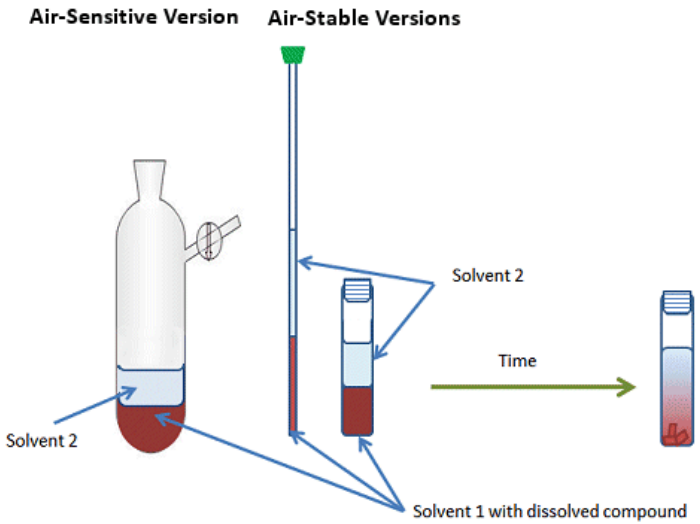
Advantages: Works well with small amounts. Parameters are easy to control. Usually gives good crystals.

Disadvantages: Finding two suitable solvents can be hard.

Crystallization techniques

Using a **mixture of solvents**:

- ✓ **Layer diffusion**: needs a solvent and an anti-solvent, which must be mixable.
  Freezing the lower layer before adding the second liquid, allows a much easier and clean separation between the two layers.



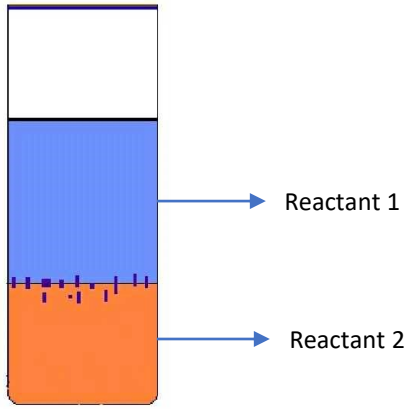
Advantages: Works well with small amounts. Parameters are easy to control.

Disadvantages: Finding two suitable solvents can be hard.

Crystallization techniques

Using a **mixture of solvents**:

✓ **Reactant diffusion**: similar to solvent/layer diffusion but reactants are in different layers.
Good for milligram amounts.
Consider using a third layer (solvent middle layer) to mediate reactant concentrations

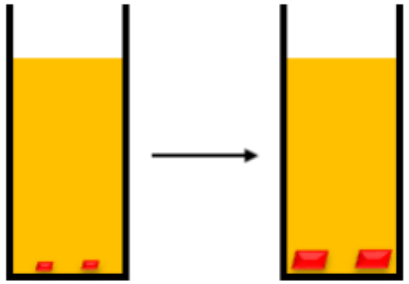


Advantages: Good for highly insoluble compounds.

Disadvantages: Finding two suitable reactants that can form crystals after reacting instead of powders.

Crystallization techniques

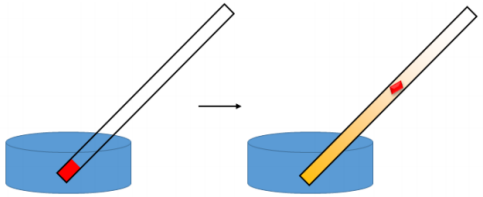
- ✓ **Seeding**: The seed crystals give already well-developed nucleation sites that allow for continued depositing of material.



Advantages: Good for growing very large crystals.

Disadvantages: Requires already well-defined crystals that are too small for diffraction.

- ✓ **Convection**: A saturated solution is formed by gentle heating. The presence of a thermal gradient results in the saturated solution slowly diffusing to a cooler portion of the apparatus through convection at which point the solution cools and nucleation occurs and crystals can grow.

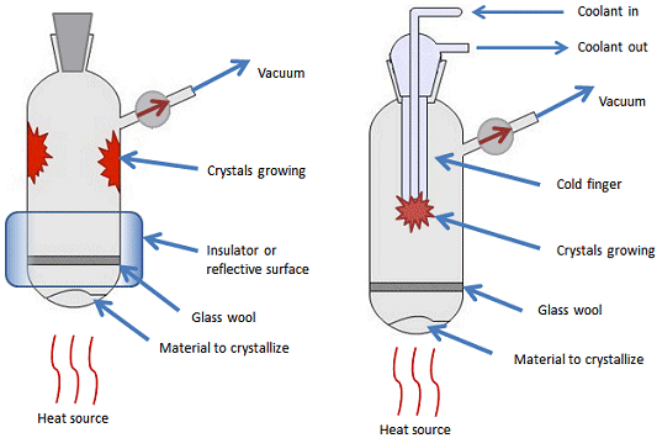


Advantages: Excellent for small quantities. Can give high quality crystals.

Disadvantages: Can require custom made apparatus. Can be difficult to obtain the right thermal gradient.

Crystallization techniques

✓ **Sublimation**: This method only works if your material readily sublimes.



Advantages: Controlling the temperature and pressure of the sublimation can allow for precise conditions for growing high quality crystals.

Disadvantages: Crystals that grow too quickly are prone to twinning.

✓ **Other methods**:

- Gel permeation
- Vapor-solid diffusion
- Scratching
- Guest/Host molecules
- Co-crystallization
- Electrocrystallization

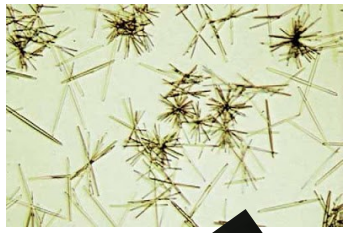
What is a good crystal?

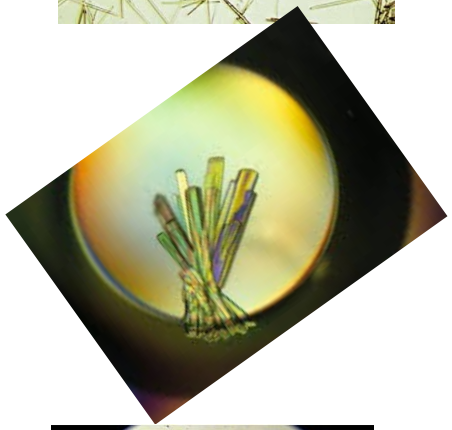
Consider the following*

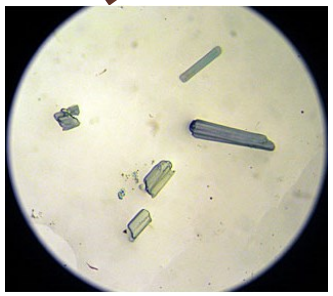
- ✓ 0.1 mm to 0.4 mm in size (in at least two of its dimensions)
- ✓ Clear and uniform in color with (very often, but not always) well defined faces and edges
- ✓ Grown from a clear not cloudy solution
- ✓ Maintains integrity after cutting to an appropriate size (no splintering)
- ✓ Refracts in polarized light (exception: cubic space groups)
- ✓ Diffracts X-rays with discrete spots, well spaced apart, that move with each new frame

* not all applies to all types of crystals and growing techniques

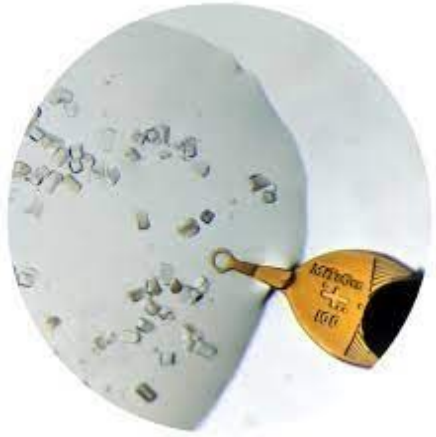
How good are your crystals for SCXRD?







Mounting crystals on a nylon loop



Online resources

- 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
- Crystal-Growing-Tips-and-Methods-xe0crh.pdf (cpb-us-w2.wpmucdn.com)
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