

Crystallization in the laboratory

Crystallization belongs to the oldest techniques used in chemical laboratories. Nevertheless crystallization is referred to as more of an art than a science. In many cases crystallization is more difficult and less successful than other techniques like distillation or chromatography. Additionally there is often a lack in education about crystallization techniques. Many textbooks don't treat this topic.

As stated in many introductory chemistry textbooks, crystallization should start, if the concentration of a solution is higher than the corresponding solubility product. In fact, crystallization is kinetically hindered. This leads to the metastable condition of supersaturation: The concentration is higher than the solubility product, but crystallization has not yet started. This condition of supersaturation is the optimal condition for crystal growing. In fact it is the only condition for crystal growing: If the concentration is higher, uncontrolled spontaneous crystallization sets in; if the concentration is lower, already formed crystals will dissolve.

An often-used process in the laboratory is therefore the cooling of the reaction mixture until the state of supersaturation is achieved. But as stated before, crystallization is kinetically hindered and will not start, even if you wait for month. What you need are crystal seeds. The generation of these crystal seeds (nucleation) is the most difficult part of the whole crystallization process.

You can try out one of the following techniques for nucleation:

1. Nucleation is in most cases an endothermic process. Evaporation of the solvent at increased temperatures is therefore a better choice for getting crystal seeds than just cooling down. If the first crystals are visible, the growing of the crystals is thereafter controlled by lowering the temperature (crystal growing is exothermic in most cases). N.B. Crystallization at higher temperatures can lead to other crystal forms compared to lower temperatures. Sodium sulfate crystallizes as decahydrate when crystallized below 305.53 K and without hydrate water when crystallized above 305.53 K. Calcium carbonate prefers the aragonite and vaterite modifications at higher temperatures and the calcite modification at lower temperatures.
2. The solution is cooled down until (uncontrolled) spontaneous crystallization sets in. The solution is then warmed up until nearly all of the crystals are dissolved again. The remaining crystals are allowed to grow by controlled cooling. N.B.: Unfortunately, many chemists are proud of having crystals at all. They don't have the courage to re-dissolve the crystals. They just bring the results of the uncontrolled spontaneous crystallization to the crystallographer. The quality of these crystals is very poor and in many cases also the results of the structure determination.
3. Ultrasound often helps to get crystal seeds. Ultrasound is used in cleaning baths, but can also be generated by scratching at the glass of the crystallization vessel.
4. Heterogeneous nucleation. Nucleation can be affected considerably by the presence of mere traces of impurities in the system. Impurities may act as inhibitors or accelerators.

Golden rules

1. "Don't crystallize in the dark." Many chemists put their crystallization vessels to a dark place, leave it there for hours, days or month, and wait somewhere else. That's the wrong way. You have to watch the process!!! If the first crystal seeds are visible, you must control the growing process (temperature, cooling rate). If no crystal seeds are visible you have to change something.
2. "Don't crystallize too concentrated." Crystallization from too concentrated solutions often leads to glass, syrup or other unpleasant results. Good examples are sugars, which are very soluble in water. They therefore form high concentrations and nearly never crystallize from water. Better choose a solvent (or

were obtained by slow evaporation of the solvent" is to no help to the reader.

5. "Don't use glass vessels." With evaporation the solvent creeps up the walls of a glass vessel, because the hydroxyl-groups of the silicate glass make it hydrophilic. Nucleation occurs therefore outside the solution. Much better are vessels made of polypropylene or teflon. The solvent doesn't creep up these vessels. You can also make glass vessels hydrophobic by silanation.
6. "Use acceptors." Many substances are difficult to crystallize because the system doesn't contain acceptors for hydrogen bonds. The Cambridge Structural Database contains more than 350 substances crystallized as picrates. In other cases triphenylphosphine oxide can be used alternatively (**M.C. Etter, P.W. Baures, *J. Am. Chem. Soc.* (1988) 110, 639-640**).