

A4 Recrystallization

Recrystallization is a common method of purifying a solid. In the simplest case, all unwanted materials are much more soluble in a particular solvent than the desired compound. The sample is dissolved in just enough hot solvent to form a saturated solution, the solution is cooled, and the crystals, which form upon cooling, are collected by suction filtration (Section A3.2). The soluble impurities remain in solution after cooling and pass through the filter upon suction filtration.

If insoluble impurities are present in the sample, they are removed by filtering the hot solution by gravity (Section A3.1) before it is allowed to cool.

These procedures are summarized in the flow chart in Figure A4.1.

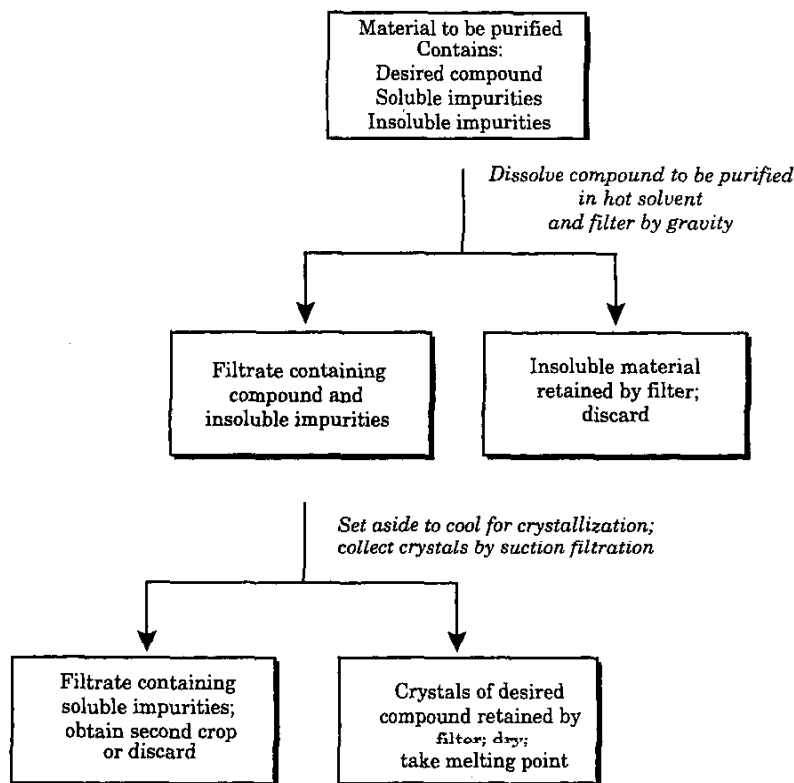


Figure A4.1: Flow chart for recrystallization of a solid.

A4.1 Dissolving the Sample

After a solvent has been chosen, either through a recommendation in the literature or by the procedure described in the lab manual, place a suitable volume of the solvent along with a boiling chip or stir bar into an Erlenmeyer flask and bring the solvent to a gentle boil. For solvents boiling below 95 °C, use the steam bath; for higher-boiling solvents, the hotplate or sand bath is appropriate. Place the solid to be recrystallized along with a boiling chip or stir bar in an Erlenmeyer flask or beaker that will be less than half filled with solution. Slowly add a small amount of the hot solvent to the solid sample to produce a slurry and begin heating the slurry while slowly adding additional hot solvent until the sample completely dissolves.

Care should be taken not to add a large excess of solvent. Based on the amount of the solid which dissolves in an initial small amount of hot solvent, the amount of additional solvent needed can be roughly estimated.

You should keep in mind that the compound may dissolve only slowly in boiling solvent, and that insoluble impurities may be present in your sample. If most of sample readily dissolves, but addition of more solvent does not appear to be dissolving the remainder, then insoluble impurities are present, and the solution should be filtered while hot as described in Section A4.3.

A4.2 Decolorizing the Solution

Colored impurities

The presence of colored impurities in a sample is obvious. Sometimes during recrystallization, colored substances remain in solution upon cooling and are removed with the solvent during suction filtration. Often colored substances are adsorbed by crystals as they are formed, giving an impure product. Because most colored impurities are preferentially adsorbed by activated charcoal, or decolorizing carbon, the addition of a small amount of activated charcoal (1-2% by weight of the sample; or 1 mg per milliliter of solution; or enough to cover the tip of a spatula), followed by gravity filtration may remove some if not most of the color. The molecules responsible for the color will be adsorbed by the carbon and can be filtered out of the solution. The carbon should be added only after the solution has cooled so that it will not boil over. After the carbon is added, the solution can be reheated to the boiling point.

A4.3 Hot Filtration

When the sample is in solution, impurities and other solids like decolorizing carbon, can be separated by gravity filtration. Vacuum filtration cannot be used in this situation because the reduced pressure in the suction flask would cause the filtrate to boil. Boiling will result in the

accumulation of crude, ugly product on the walls of the flask, which may include impurities that otherwise would remain in the solvent.

A problem in hot filtration is that the solution cools as it runs through the filter, allowing crystallization to take place. You can try to avoid premature crystallization by warming the funnel, either with steam, quickly wiping it dry with a towel, or with a flame. It also helps to pour hot solution into the filter in small amounts, so the solution does not have time to cool in the filter. A stemless funnel is always recommended; with a stemless funnel, you can avoid the problem of crystallization and clogging in the stem.

An arrangement such as that illustrated in Figure A4.3 can help when there is trouble with crystallization in the filter. Boiling the filtrate in the beaker keeps the funnel hot. Some care must be used with a flammable solvent. Once filtration is complete, transfer the filtrate to an erlenmeyer flask for crystallization.

In some cases, you must use excess solvent to minimize the problem of crystallization in the filter paper. Once the filtration is complete, remove excess solvent by distillation. This will also serve to bring back into solution any crystals that may have separated during filtration.

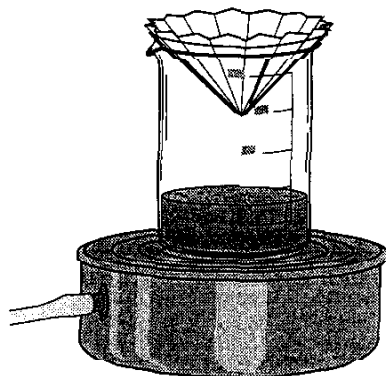


Figure A4.3: A method of preventing crystallization in the funnel during hot filtration.

Reheating the filtrate

In any cases in which crystals formed too early, reheat the filtrate to get a clear solution. Crystals that form when the hot filtrate hits the cold flask are likely to be less pure than those that separate more slowly from solution.

A4.4 Cooling

The rate of cooling determines the size of the crystals. Slow cooling tends to favor fewer and larger crystals; fast cooling tends to favor more and smaller crystals. Very large crystals are to be avoided since they often occlude the solvent and its dissolved impurities. Very small crystals are undesirable because it is difficult to wash them free of the solvent and the soluble impurities, and it takes longer to dry them. Needles between 2 and 10 mm in length are fine, as are prisms 1 to 3 mm in each dimension.

Inexperienced students often try to rush the cooling process by sticking their products in an ice bath. Don't make this mistake. Too-rapid cooling can turn a perfectly satisfactory product into powdery, amorphous crystals that are hard to collect.

The best compromise of speed, convenience, and quality of crystals usually is reached by allowing the solution to cool to room temperature on a non heat-conducting surface such as a cork ring. Sometimes it will be possible to hurry the cooling without getting overly small crystals by swirling the flask in a beaker of water at room temperature, or even by placing the flask directly in an ice bath. Usually, the rate of cooling must be quite a bit slower. Cooling can be slowed greatly by supporting the flask in a beaker of water at the temperature of the solution and allowing both to cool to room temperature. The most satisfactory procedure can only be determined by experimentation.

Preparing for Cold Filtration

Since solubility decreases with decreasing temperature, it is often a good idea to finally cool the mixture from room temperature to 0 °C (or to the freezing point of the solvent if it is above 0 °C) in a mixture of ice and water. Cooling below 0 °C is not often done, since colder baths are difficult to prepare, and because condensed water vapor can contaminate the product.

If the crystals are collected too soon, some material will be lost that would have separated from solution on further standing. The minimum acceptable time for crystallization varies from a few minutes for some substances to days for others. Again, experimentation is the only way to determine how long the product must be given to crystallize.

A4.5 Cold Filtration

When crystallization is complete, the product is collected by suction filtration. The funnel should be big enough that it will not be more than half filled with crystals. A Buchner funnel is usually big enough for any laboratory scale work. For small or microscale work, a Hirsch funnel is sometimes preferable. The suction flask should be large enough that the solution will not fill it above the tip of the funnel or the side arm of the flask.

Prepare for filtration by checking that there is a seal between the funnel and flask. Before you decant any of the crystals, wet the filter paper with a little solvent to complete the seal. Pour the crystals carefully, making sure that none escape around the edge of the filter paper.

Crystals often remain in the flask after all the solvent has been poured out. These must be scraped into the funnel and rinsed out with cold solvent. If the compound is rather soluble, even in the cold solvent from which it crystallized, it may be rinsed into the funnel with portions of the filtrate. This is a messy business, and it is far better to work hard to pour the crystals out with the liquid in the first place.

While transferring crystals into the funnel, it is best if the level of the liquid in the funnel does not fall below that of the crystals. Try not to draw air through the crystals until they have been rinsed with fresh solvent (see below). Sometimes you will need to break the vacuum in the flask in order to slow the rate of filtration sufficiently

A4.6 Washing the Crystals

As soon as the liquid has been drawn off, some fresh solvent should be poured over the crystals to wash off any liquid that contains soluble impurities. If this is not done, the soluble impurities will be deposited on the crystals when the solvent evaporates. If the product is relatively soluble in the cold solvent, one washing will have to suffice. Two washes are usually enough.

If the crystals are not matted down tight into a solid cake, release the vacuum, pour the wash liquid evenly over the crystals, and then draw it off by reestablishing a vacuum. If the crystals do form a solid cake, add the wash liquid to the crystallized matter in the funnel and pull the product apart carefully with a small spatula. Some care is required to suspend all of the product and not tear or dislodge the filter paper. Try to keep a very slight vacuum during this operation, without drawing the wash liquid through too fast. When a procedure says, "Wash thoroughly," it is probably calling for this rather tedious and delicate operation of carefully breaking up and suspending the filter cake in the wash liquid. After this has been done, the wash liquid is drawn off by suction. An alternative procedure that is sometimes appropriate is to transfer the filter cake to a beaker, add solvent, and break up and suspend the material in the beaker. Following this, collect the product again by suction filtration.

Washing with a volatile solvent

Sometimes, if a nonvolatile solvent such as acetic acid is used for recrystallization, it may be possible to wash this solvent off with a more volatile solvent so as to speed the drying of the crystals. Of course, you must be confident that the crystals are not soluble in the more volatile solvent.

A4.7 Drying the Crystals

After you have collected the crystals by suction filtration, remove as much solvent from the product as possible by continuing to draw air through the crystals while they remain in the funnel. The last traces of solvent will evaporate when the crystals are removed from the funnel and spread out to dry.

If the crystals collect as a solid cake, take extra time to draw air over them in the funnel. Failure to suck the filter cake as dry as possible before breaking it up and spreading it out to dry is a very common mistake. The filter cake should be a damp, friable solid when spread out to dry, not a mushy slurry.

A4.8 More “Tricks” of Crystallization

The preceding sections describe the normal techniques for recrystallization, but there are some common problems that can be encountered during a recrystallization. This section describes some of these difficulties and suggests some possible solutions.

Oiling Out

Sometimes, during cooling for crystallization, the product separates not as crystals but as a liquid, an “oil”. This shows up first as a cloudiness or opalescence, and then as visible droplets. An oil is undesirable because it is often an excellent solvent for impurities. When, the oil finally freezes, impurities in the oil will remain in the crystals. If most of the product separates as an oil before it solidifies, you can try recrystallizing the solidified oil, using a different solvent, or purifying the product by another method before recrystallization.

Inducing Crystallization

There are a couple ways to initiate the formation of crystals. These methods can be used to avert the formation of oil or to prompt crystallization if it doesn’t occur spontaneously.

The first thing to try is ‘scratching’ or ‘rubbing’ the flask with a glass rod or metal spatula. Be firm, yet gentle. It is easy to poke a hole in the bottom of the flask if it is not resting on a hard surface. On the other hand, you must press rather hard with the rod or spatula for rubbing to be effective.

A second tactic is the use of seed crystals. Taking just a few crystals from a previous crop and putting them in your solution will promote the growth of more crystals. Often it is enough just to stir your solution with a spatula that has touched some of the desired crystals.

In either case of scratching or adding seed crystals, the idea is to give the saturated solution a surface on which crystals can begin to form.

Failure to Crystallize

Occasionally, a solution will resist crystallization even though it is cold and supersaturated. This could be the result of impurities, or “tar,” acting as a protective colloid. If adding a seed crystal or scratching the flask with a stirring rod fail, crystallization can sometimes be initiated by cooling the mixture in a salt-ice bath (about $-10\text{ }^{\circ}\text{C}$) or a Dry Ice/acetone bath (about $-70\text{ }^{\circ}\text{C}$), depending upon the freezing point of the solvent. In some cases, the solution must be stored in a refrigerator or freezer for long periods of time—sometimes years to induce crystallization.

Wet Products

If a product separates from an aqueous solution as a fine powder, as it frequently does, it is difficult to suck the product dry during vacuum filtration. The crude, damp cake of crystals can easily be more than half water. The product can be recrystallized from a water-miscible solvent, but this often requires the use of more solvent than expected, since water in the crude product will reduce its solubility. The alternative is to recrystallize the damp material from a water-immiscible solvent. This creates an extra water phase along with the hot solution, which must be removed with a medicine dropper or pipet before hot filtration. The solution will also be saturated with water at this point.

Low-Melting Compounds

Recrystallization of low-melting compounds is not easy low melting point and high solubility in non-polar solvents usually go together. This gives you the choice of using very small volumes of non-polar solvents or using solvent pairs that include water. If water is used, the product will often separate as a liquid upon cooling. Neither alternative is very attractive.

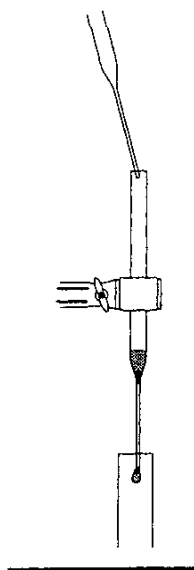


Figure A4.4: Use of a Pasteur Pipette as the filter for gravity filtration

A4.9 Microscale Recrystallization

When the amount of material is only a few hundred milligrams, or the volume of the hot solution is less than about 5 mL, the usual techniques of recrystallization cause unacceptably large losses in the two-filtration steps. An easy and inexpensive way to recrystallize on the microscale makes use of two test tubes and two Pasteur pipettes, according to the following procedure.

Choose a test tube that will be filled only about $1/8$ full by the solution, add the sample to the test tube, add the solvent, and warm the test tube in either

the steam bath or the sand bath to dissolve the sample. The amount of material will be so small that only a brief period of heating should be needed, and the relatively large size of the test tube will provide enough surface area to condense the vapors of the solvent.

After the sample has dissolved, filter the solution into a second, somewhat smaller, test tube. For a filter, use a Pasteur pipette with a tiny piece of cotton or glass wool pushed down just to the point where the body of the pipette starts to narrow to form the long tip. Stand this filter pipette on its tip in the second test tube, as shown in Figure A4.4. Using the second Pasteur pipette, transfer the hot solution from the first test tube into the top of the filter pipette, where it will run down through the cotton or glass wool into the second test tube. While the solution is draining down through the filter pipette into the second test tube, this second test tube can be warmed cautiously with either the steam bath or the sand bath so as to keep the solution in the filter pipette warm.

Cool the solution

After the solution has drained down through the filter pipette, remove the filter pipette, and set aside the second test tube, which contains the filtered solution, to cool for crystallization.

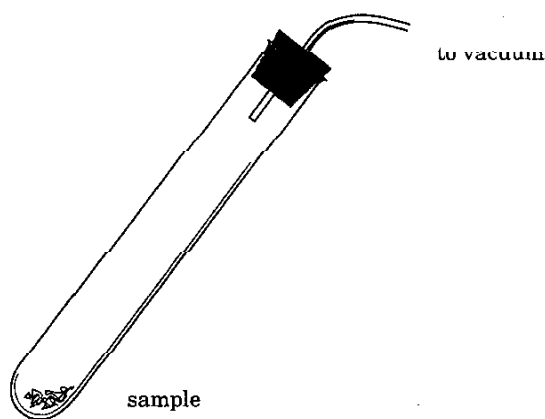


Figure A4.5: A way to dry crystals in a test tube.

Remove the solvent

After the crystals have formed, the solvent can often be removed by drawing it up into another Pasteur pipette whose tip has been pushed to the bottom of the test tube in which crystallization has taken place. If the crystals are well formed granules, wash them by adding a few drops of solvent, agitating them gently, and withdrawing the solvent with another Pasteur pipette. Alternatively, the crystals can be collected by centrifugation followed by decanting of the solvent. Then wash the

crystals by suspending the crystals in a little cold solvent, centrifuging, and decanting. Remove the wash liquid in the same way. To dry the crystals, lay the tube on its side with the bottom slightly raised or connect it to the vacuum as shown in Figure A4.5. When the crystals are dry, they can be removed from the test tube by inverting it over a piece of filter paper and tapping it with a stirring rod.

A4.10 Selection of a Suitable Solvent

A suitable solvent will dissolve the sample when the solution is hot, but not when it is cold. If you have a large amount of material, you will want to use a solvent in which the material is fairly soluble so that the volume of solvent will not be inconveniently large. On the other hand, if you have only a small sample, a solvent in which your compound is only sparingly soluble will permit you to use a volume of solvent that is not inconveniently small.

<i>Solvent</i>	<i>Boiling Point, °C</i>	<i>Density g/mL</i>	<i>Solubility in water</i>	<i>Flammability</i>
Acetic acid	118	1.05	∞	+
Acetone	57	0.79	∞	+++
Acetonitrile	80	0.79	∞	++
Benzene	80	0.88	i	+++
Carbon disulfide	45	1.26	i	++++
Carbon tetrachloride	77	1.59	i	-
Chloroform	61	1.49	i	-
Cyclohexane	81	0.78	i	+
Dichloromethane	41	1.34	i	-
Dimethylformamide	153	0.94	∞	+
Dimethylsulfoxide	153	0.94	∞	+
Dioxane	101	1.03	∞	+++
Ethanol, 95%	78	0.81	∞	++
Ether, diethyl	35	0.71	7	++++
Ethyl acetate	77	0.90	8	+++
Hexane	68	0.66	i	+++
Ligroin	60-90	0.67	i	+++
Methanol	65	0.79	∞	+
Pentane	36	0.63	i	++++
Petroleum ether	30-60	0.64	i	++++
Tetrachloroethane	146	1.60	i	-
Tetrahydrofuran	65	0.89	∞	+++
Toluene	111	0.87	i	+++
Water	100	1.00	i	-

Table A4.1: Properties of common solvents.

The best way to choose a solvent is to recrystallize small portions of your material in little test tubes, trying several solvents to see which one gives the best results. If your compound is polar,

alcohols and other water-soluble solvents are good possibilities. If your material is non-polar, hexane and other non-polar, non-water-soluble solvents can be tested. Table A4.1 lists some of the properties of the more common solvents.

Solvent Pairs

Occasionally you will wish to recrystallize a compound that is too readily soluble in some of the available solvents and not soluble enough in others. When this is necessary, a mixture of solvents can be useful. To test the suitability of a pair of solvents, prepare a hot solution of a sample of the compound in a small amount of the better solvent, and add slowly, while keeping the mixture hot, some of the poorer solvent. When a cloudiness is produced, indicating slight crystallization, add a little of the better solvent and heat the mixture until the cloudiness has been dispelled, and then allow the solution to cool. Although the solubility of a substance in a mixture of solvents usually changes gradually with the proportion of the solvents, the solubility of a substance is sometimes greatly increased or decreased by the addition of only a small amount of a better or a poorer solvent.

Some of the most often used solvent pairs are toluene/hexane, acetic acid/water, and alcohol/water, but any pair of miscible liquids can be used. Although alcohol/water mixtures are often used, they seem to promote separation of the product as a liquid.

When a recrystallization is carried out using a pair of solvents, it is often a good idea to do the hot filtration before adding the poorer solvent. The addition of the poorer solvent should then be carried out as just described. A common error is to add more of the poorer solvent than is needed to just achieve saturation of the hot solution. In extreme cases, this results in the precipitation of everything in solution, impurities as well as the desired compound.

References

Sources that contain more information about recrystallization processes include:

1. K. B. Wiberg, *Laboratory Technique in Organic Chemistry*, McGraw-Hill, New York, 1960, p. 98.
2. A. I. Vogel, *Practical Organic Chemistry*, 3rd edition, Wiley, New York, 1956, p. 122.