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Crystallization and Polymorphic Transitions in Materials

The research project that I have been assigned deals with the polymorphism. Polymorphs are the ability of a substance to exist in more than one distinct crystalline form. This is an important consideration for characterizing the properties of drug candidates. Chlorpropamide is a compound that is known to treat type 2 diabetes. I have been working on trying to crystallize and co crystallize chlorpropamide in order to create new polymorphs and create a more stable structure for the usage by drug pharmaceutical companies. By using the process of slow evaporation I create crystals by dissolving inorganic solutes into organic solvents using heat. After a couple days to weeks a crystal will form. The whole idea of co crystallization comes from looking at the structures of these compounds when made into crystals. You see that there is an opening in the structures and the objective is to "fit" another substance into that opening for a more stable structure. The problem is finding the right thing to fit into that opening. This summer I attempted to crystallize and co crystallize the substance chlorpropamide first with caffeine and then with salicylic acid. The solvents that I plan to stick to are polar solvents such as methanol, ethanol, propanol, etc. I also have to make sure that the crystals are clear. I can take pictures of the crystals for future use and also cut them into the correct size, less than 1 mm, mount it, and put it into the x-ray diffraction machine. After that the information from there goes onto a disk where you can then tell whether or not you have came up with something. From the disk you print out a sheet that has some

information about the crystal that was found. Some of the information that comes from the sheet is shown below in chart form:

	Chlorpropamide
Solvent	propanol
Space Group	P 21 21 21
a (Å) b (Å) c (Å) β°	5.2268(16) 9.078(3) 26.586(8) 90(3)
V ($Å^3$)	1261.5(7)
Z	4
R (I>4σ(I))	6.23%
S	1.060

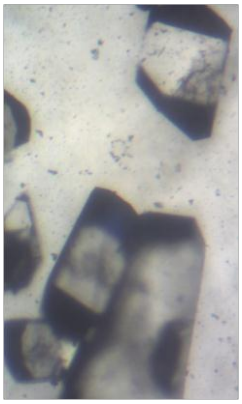
When making crystals you simply put a little of the solute into a small vial and then add enough solvent to dissolve it. When making co crystals it's a little more

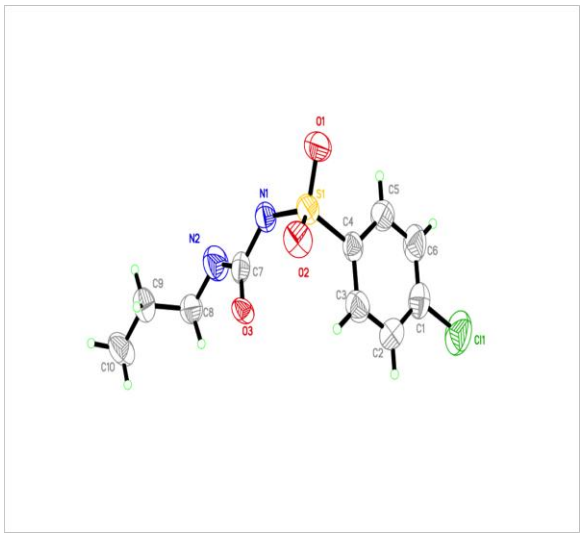
difficult. You have to determine the mole-to-mole ratio of both solutes in order to put in a 1:1 ratio. Once you figure that out you add both solutes and then add the solvent. You have to add enough solvent until it dissolves or is almost dissolved. Next for both crystallization and co crystallization, you put the vials onto the heating table and allow the mixture to heat up and completely dissolve so that it becomes a homogeneous mixture. Once you are certain that it has all been dissolved then you take it off the heating table and cut a piece of Para film to cover the top of the vial. All chlorpropamide crystals were prepared by slow evaporation from a saturated solution of chlorpropamide, either salicylic acid or caffeine and a solvent. Mixtures were allowed to stand at room temperature for a few days or weeks after mixing. Single crystals were collected from the evaporation mixtures and allowed to air dry. The crystals for each form of Chlorpropamide were analyzed using X-ray Crystallography at 170 K on a Bruker SMART X2S automated diffractometer. Data has not yet been collected. This means that the crystal structures have not yet been determined. Eventually they will be determined by direct methods and refined using the Bruker ApexII software package. Lastly, you label the vial.

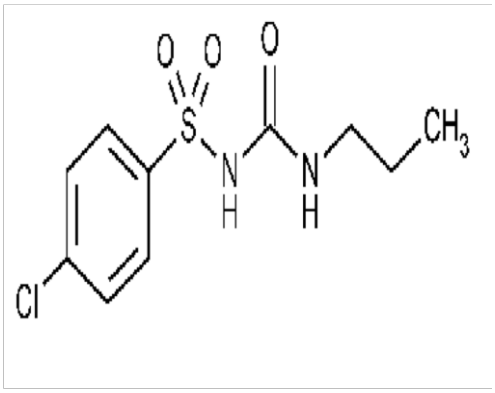
At first I was using polar solvents such as alcohols and acetates. So far I have been using the solvents ethanol, methyl ethyl ketone, ethyl acetate, cyclohexane, benzene, 1-propanol, 2-propanol, and 1-butanol. So far I have gotten crystals for chlorpropamide with methanol, ethanol, tetrahydrofuran, 1-propanol, 2-propanol, and methyl, ethyl ketone. I have also made co-crystals of chlorpropamide and salicylic acid with ethanol, ethyl acetate, methyl ethyl ketone, and 2-propanol. I was able to get some clear crystals from the chlorpropamide, salicylic acid, and benzene, which I have to put in the x-ray

diffractor to see if I get anything. Seeing as I didn't get as many usable crystals as I wanted, I did a second trial of the mixtures that I had previously did. Some of the crystals weren't usable because they didn't evaporate slow enough, so I had to change some factors to help slow down the process. The main thing was to not sit the vial on the table immediately after taking it off of the heating table because the table is really cold. So I generally sit it on a pile of napkins or I have a cup filled with napkins that I set the vials in to slow down the cooling process. So far I have 8 other vials that I am waiting to see if any usable crystals come about. With slow evaporation of co crystals it has been taking at least a month before you see anything form so I have to be patient. Next I will try using more chlorpropamide and a co factor because I found out that using a larger amount should help the crystals to develop faster.

The combination of chlorpropamide and 2-propanol were able to give me clear crystals that I was able to put into the diffractometer. No usable results were found, however I was able to see the structure of chlorpropamide when crystallized. I also was able to see different was that the crystal is packed down different axes. Chlorpropamide is made up of a ring of carbons all with hydrogen's attached and one with a chlorine attached to that ring. Also attached to that ring is a sulfur with two oxygen's double bonded to it. Also attached to the sulfur is a nitrogen with a hydrogen attached followed by a carbon with double bonded oxygen and another nitrogen with an attached hydrogen. Lastly are a string of three carbon's with hydrogen's attached. Pictures of the crystals and it structure are below:

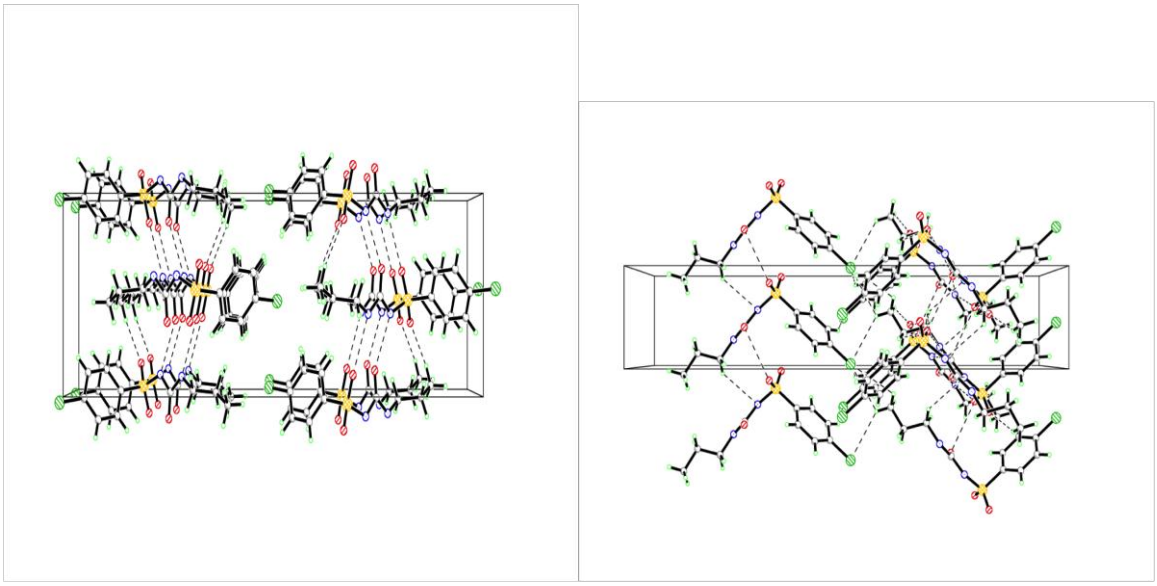


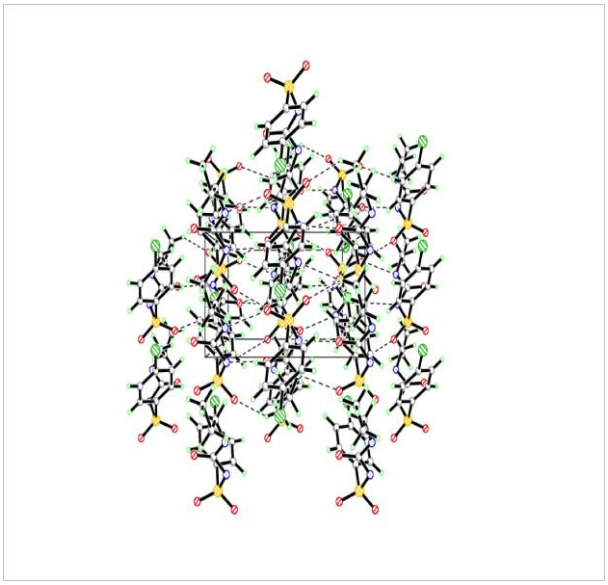




My goals for this summer were simple. I wanted to successfully co crystallize chlorpropamide, which was halfway achieved. I was able to get some crystals but no results were able to be collected. I also hoped that after this summer, I would know for sure whether or not research is something that I would like to pursue as a career. I definitely think that this is something that I could see myself doing. I also want to be able to use all the equipment in the lab with no problems or no help at all and be able to explain in depth exactly what I am working on. I am able to use the majority of the equipment now. I just need a little more practice with the APEX software. The APEX software is where you use the results you got from the diffractor to get the structure of the crystal and the packing diagrams. Packing diagrams just show how the structure of the

crystal is packed together. There are generally three packing diagrams that you get from the software. Here is an example packing diagrams:





Lastly, I wanted to have enough researched gathered so that I can travel with the PREM program and present my findings at seminars. I don't think I achieved this goal but hopefully during the fall I can gather more information and have enough to be able to go. The most important goals of mine were to be able to leave with better speaking and

presenting skills. I do think that my speaking skills have gotten a little better after the poster session.

My future plans include waiting for the next 8 vials to produce some crystals and then running them in the machine if usable crystals form. After that I have some more solvents that I would like to start using to see if I can get something out of those. I'm planning on using less polar solvents next. The next solvents that I plan to use are methanol, t-butanol, pentanol, hexane and benzene. Once I go through two trials of the next group of solvents I want to try a new procedure. Want to try a new procedure because for some reason, even when the both solutes are added and crystals are formed, both of the solutes don't end up in the crystals, which is one of the main problems we are having. This procedure is when I put the two solutes chlorpropamide and salicylic acid/caffeine into a bowl and grind them together so that they will already be somewhat mixed by the time that I put them in the vial. Then I can add the solvent and hopefully the crystals that form will have both of the solutes in there. Hopefully that will work. If not I will be looking for new procedures and new solvents to use. Overall this is a very repetitive process. You generally are doing the same steps over and over again except for when you have a little minor tweaking that you have to do in order to force better results. I haven't really gotten any results yet, and I am hoping that over the remaining course of this program that it changes. I am looking forward to getting some more crystals and testing them to see if I come up with any results. Some facts that I have learned this summer are that chlorpropamide crystallizes with less polar solvents such as ethanol, propanol, etc. Co crystallizing chlorpropamide takes about a month for the slow evaporation process to complete and for crystals to form. In order to save some time it

was suggested to use more chlorpropamide and co factor. This has not yet been tested and should be tested in future studies. Future studies will also include trying to successfully make more co crystals of chlorpropamide and getting results. Support for this research came from NSF-PREM, NIH-RISE and NIH-RCMI.