Preparation of Polymorphs

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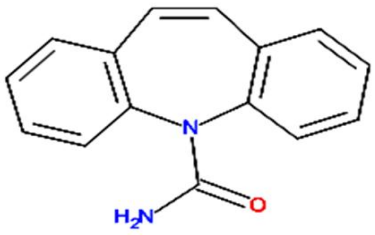
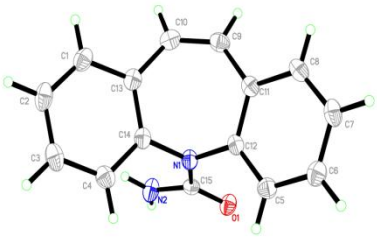
Abstract: Carbamazepine is a pain reliever and a treatment for epileptic seizures. Carbamazepine has multiple co-crystal formers as well as multiple polymorphs. In an attempt to crystallize new co-crystal forms and polymorphs, several solutions were prepared. A crystal obtained from one of the solutions was used to determine the crystal structure. The structures were determined using a Bruker SMART X2S X-ray diffractometer at 170 K.

Introduction:

Polymorphism is the ability of a compound to display multiple arrangements of its molecules in a crystal lattice. Diamond and graphite, for example, are polymorphs of the element carbon. They both consist entirely of carbon but have different crystal structures and different physical properties. This summer I have been trying to form a polymorph of Carbamazepine. Carbamazepine is an analgesic, or painkiller, and an anticonvulsant which can be used to treat epileptic seizures. With more experience, I hope to eventually form co- crystals using Carbamazepine. The simplest definition of a co-crystal is a crystalline structure made up of two or more components in a definite stoichiometric ratio. Two other drugs used in the lab are Sulfapyridine and Chloropropamide. These two drugs are more difficult to obtain both polymorphs and co- crystals. Sulfapyridine is an antibacterial drug and Chloropropamide is a drug used to treat type II diabetes. While the lab is working toward finding a co-crystal form of the three of these drugs at least thirteen co-crystals have been found with carbamazepine while no co-crystals have been found with either Chloropropamide or Sulfapyridine.



Structure of Carbamazepine

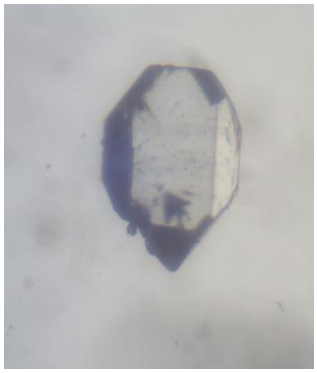


Structure of Carbamazepine form 3

Polymorphism is an important aspect of the pharmaceutical industry because it allows pharmaceutical companies to avoid patenting issues with other pharmaceutical companies. Through polymorphism, drugs are different because they contain different crystalline structures. Pharmaceutical developers would also like to know the co-crystal forms of many pharmaceutical drugs so that they can prevent situations in which a drug may have to be reformulated after production. By finding the co-crystals of these drugs we will be able to help pharmaceutical companies save money. Finding polymorphs and co-crystals are both similar processes; however, my job is to focus on finding polymorphs of carbamazepine.

Experimental:

Approximately 50 mg of solid Carbamazepine was dissolved in approximately 15 ml of solvent. My alcohols of choice are methanol and ethanol. The solution was heated at 75- 80 C and the mixture was allowed to cool to room temperature. The vial is then placed on a hot plate; the goal of heating up the mixture is to dissolve the solute into the solvent and to receive the product of a uniformly colorless solution. The 20 mL scintillation vials were covered with parafilm. At this point, the solution is cooled, labeled and set aside in order to wait for crystals to grow. The crystals formed two to three days after mixing. Depending on the crystal, different time frames are necessary for the crystals to grow. For better quality crystals, a longer evaporation time is needed.



This is a photo of an example of a good crystal. The crystal is of good crystal quality because it has a clear face.

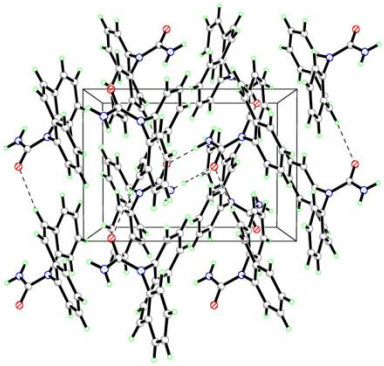
Once the crystals are formed they are then dried on filter paper and taken to the room that contains the x-ray diffractometer machine. The crystals are then placed on a slide and viewed under a microscope. While under the microscope we look for crystals with clear faces. Once you find a crystal with the clear faces that you are looking for, the crystal must be measured to make sure that it is at most forty millimeters in at least three directions. If it must be done, the crystals

can be cut with a blade but it must be done with much care to make sure that the crystal does not crack. Once the crystal is of size we grab a UV light, UV light glue, and a mounting pin to use to mount the crystals. The mounting pin is then placed near the crystal so that the transfer is an easy process. A drop of UV light glue is then added to a mounting pin and the crystal is transferred from the slide to the mounting pin. It is important to place the crystal near the furthest tip of the mounting pin. Once the crystal is toward the tip of the mounting pin the UV light should be positioned onto the crystal and the glue for about 30 seconds. This will secure the crystal onto the pin. At this point, the top can be replaced onto the mounting pin. The pin can now be placed into the X- ray diffractometer machine. The crystals for each form of Carbamazepine were mounted and data was collected at 170K on a Bruker SMART X2S automated diffractometer. A blank CD needs to be placed into the X ray diffractometer machine and the directions are followed as given on the machine. It is important to wait for a picture to pop up with a lot of dots, when you see dots that signifies peaks in the crystal. The crystal should be in the machine for about 4 hours if the machine runs properly. After about four hours, information is transferred onto a CD. The CD can be ejected and inserted onto a computer, by putting it into a computer we are able to figure out the structure and determine whether or not the crystal is a polymorph. Crystal structures were determined by direct methods and refined using the Bruker Apex II software package. The size of the colorless crystal used for data collection was measured as 0.87mm x 0.95mm x 0.97mm.

	Carbamazepine
Solvent	Methanol/ Ethanol
Space Group	$P\,1\,2_1/n\,1$
a (Å) b (Å) c (Å) β˚	7.5379(16) 11.146(2) 13.936(3) 92.891(6)
V ($Å^3$)	1169.4(4)
Z	4
R (I>4σ(I))	3.94%
S	0.797

Table 1:

This table contains information that determines whether or not the experiment of finding a polymorph has been successful. The main values are the angles of a,b,c and β˚



This is an example of a packing Diagram projected down the a axis. The structure was obtained from the Apex II software.

With the procedure mentioned much success has been reached in terms of good crystals with the solvents of methanol and 1 butanol . The results received for ethanol and1butanol however have been found before. The point of my research is to find something that has not been

found before. The results were a= 7.574 b=11.165 and c=13.963 for 1 butanol and carbamazepine. The results for methanol and carbamazepine were a= 7.5379 b= 11.146 c= 13.936. The results for using the solvent of 1 butanol and for using methanol are similar which determines that the structures are very similar. When two sets of results are the same this is not good news because it means that the substance that the crystal has formed has been formed before. One of the major points of my research is to find a crystal that has formed a polymorph that has not been found before. Finding a polymorph that has not been formed before is what my research is focusing on because while there are many polymorphs that have been found, there are also many polymorphs have not been discovered.

There are many methods that can be used in order to make crystals with carbamazepine. The method that I used the most was the method of slow evaporation. Slow evaporation usually yields form three crystals. I am currently doing more experimentation with different methods of forming crystals. Other ways to form crystals would be to use refrigeration, extreme heat, extreme cold, slow cooling, and using heated solvents to name a few methods. As my research carries on I hope to find polymorphs and co- crystals using these different methods.

A crystal was formed out of HCl, 1butanol and carbamazepine. The result was rod shaped crystals in a yellow solution. After following protocol and placing the crystal into the x ray diffractometer, the results of the machine were something that has never been seen before. Currently, we are searching to figure out if this compound is a polymorph and if it is, then there is a possibility of publishing the information..

I am going to continue to try to find polymorphs and co-crystals of carbamazepine and various solvents. I am hoping to find co-crystals and move toward finding publishable

information. My research consists of much trial and error but with patience and the will to never give up, finding polymorphs and co-crystals are possible.

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