

Chemical Crystallography
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Lecture – 57
Polymorphs – 2

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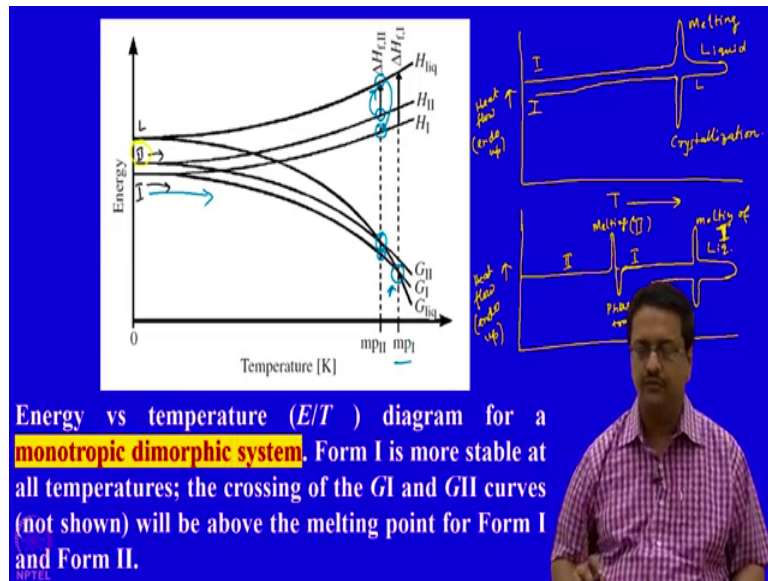
PhD students, Department of Chemical Sciences

IISER Mohali.



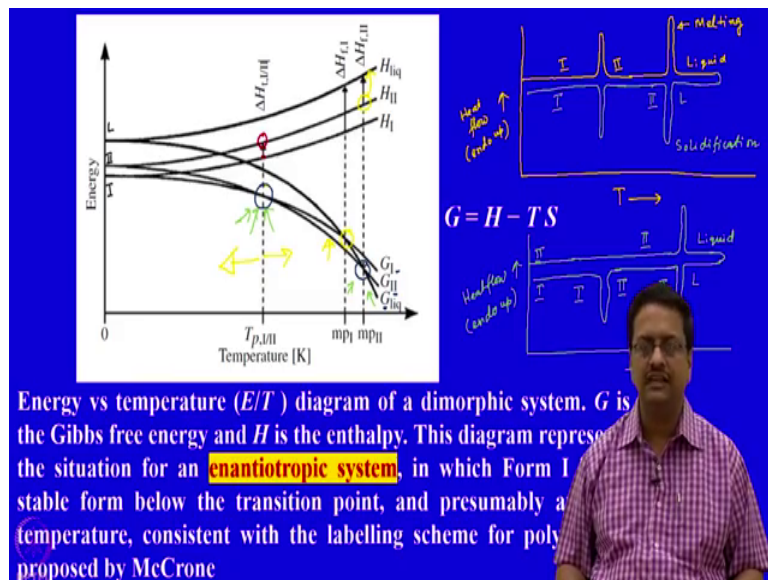
Welcome back to the course of Chemical Crystallography. As you remember we have been discussing about the polymorphism and characterization of Polymorphs. So, we will continue our discussion today.

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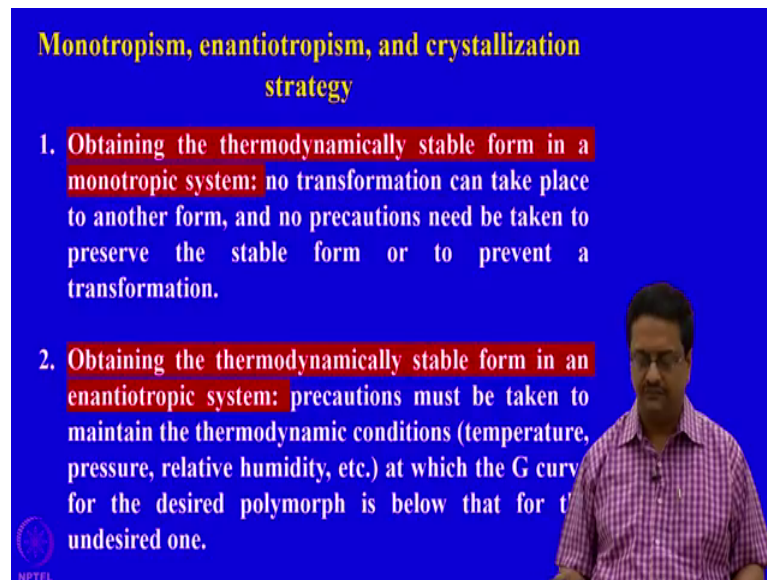


So, here is the slide where we ended in the last lecture and discussed about monotropic dimorphic systems and also enantiotropic dimorphic systems we will continue from here.

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Monotropism, enantiotropism, and crystallization strategy

1. **Obtaining the thermodynamically stable form in a monotropic system:** no transformation can take place to another form, and no precautions need be taken to preserve the stable form or to prevent a transformation.
2. **Obtaining the thermodynamically stable form in an enantiotropic system:** precautions must be taken to maintain the thermodynamic conditions (temperature, pressure, relative humidity, etc.) at which the G curve for the desired polymorph is below that for the undesired one.

So, when we have can identify monotropism and enantiotropism we should be able to obtain different thermo phases using different methods. So, how to obtain the thermodynamically stable form in a monotropic system? So, what is a monotropic system? This one is a monotropic system where the G curves of form 1 and form 2 do not intersect before melting.

So, in this case, no transformation can takes place to another form and no precautions need to be taken to preserve the stable form or prevent a transformation simply because, the G curves of form 1 and form 2 do not intersect. How to obtain the thermodynamically stable form in an enantiotropic system? See remember in the enantiotropic system, the G curve form 1 and form 2 intersect at an intermediate temperature.

So, for that precautions must be taken to maintain the thermodynamically stable conditions the little temperature pressure relative humidity etcetera; so that the G curve of the desired polymorph is below that particular undesired polymorph.

So, if we want form 1 then, we must be below this particular temperature. If we want form 2, we must be above this particular temperature to get that particular form in abundance. Obtaining the thermodynamically metastable form in a monotropic system so, as you know in a monotropic system the thermodynamically unstable or metastable is fair form 2.

So, a kinetically controlled transformation may take place to the undesired thermodynamically stable form. So, to prevent such a transformation it may be necessary to employ drastic conditions to reduce kinetic effects that is very low temperature or very dry conditions storage in the darkness etcetera. So, what we mean is suppose if we have formed a form 2 in case of a monotropic system and we want to keep it trapped.

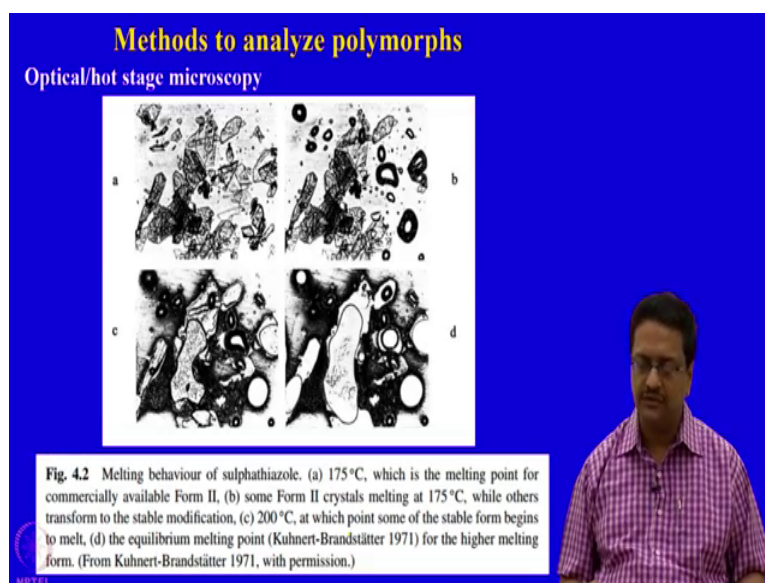
The example is diamond which is a metastable phase, it has a tendency to get converted to graphite which is the amorphous form, but that transformation is kinetically very slow and hence diamond takes enormous amount of time to get converted to graphite.

So, similarly there may be some polymers which are thermodynamically unstable, but kinetically conversion to a more thermodynamic phase may be very slow at extremely low temperatures like liquid nitrogen temperature and so on. How to obtain the thermodynamically metastable form in an enantiomeric enantiotropic system? The information for obtaining and maintaining this form is essentially found in the energy temperature diagram which is this one.

So, if you want to trap the metastable form at a given temperature, you have to know this particular diagram very well. Suppose if we want that the form 1 to remain as form 1 beyond the terms of transition temperature from a form 1 to form 2 what one has to do is to heat form 1 at a very very high rate so that at the transition temperature there is not enough time for the phase to get converted from 1 to 2 but rather it maintains the form one and goes heated and then we can determine the temper melting point of form one by doing a very fast heating.

Similarly, if we have form phase 2 in the higher temperature which is here and if we are cooling it at a very high speed at very high cooling rate, then form 2 will not get converted to form 1 at the transition temperature, but will still remain as form 2 and will be stable at room temperature for a while.

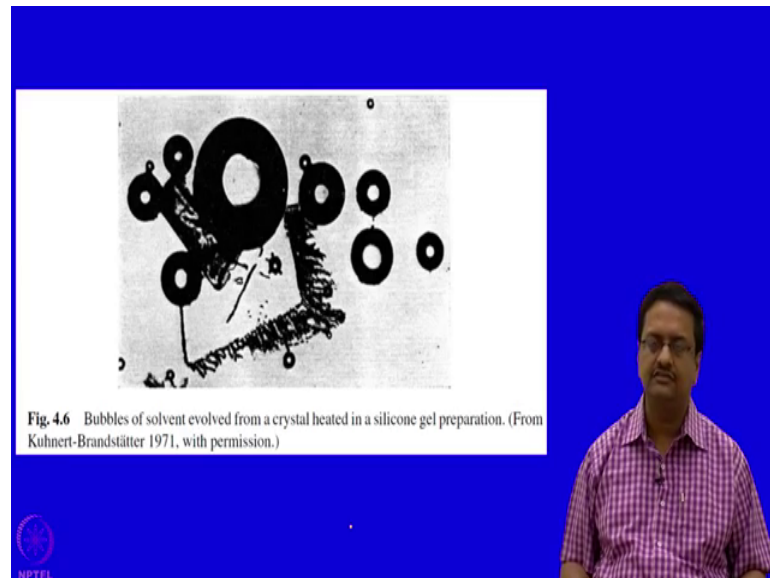
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There are different methods to analyze these polymorphs. One of them is optical or hot stage microscopy. What we can see here that, these compound sulphathiazole in the figure a at 175 degree which is the melting point of the commercially available form 2, one particular phase is has started melting. Some form 2 crystals melting at 175 degree C, while the others transform to a stable modification.

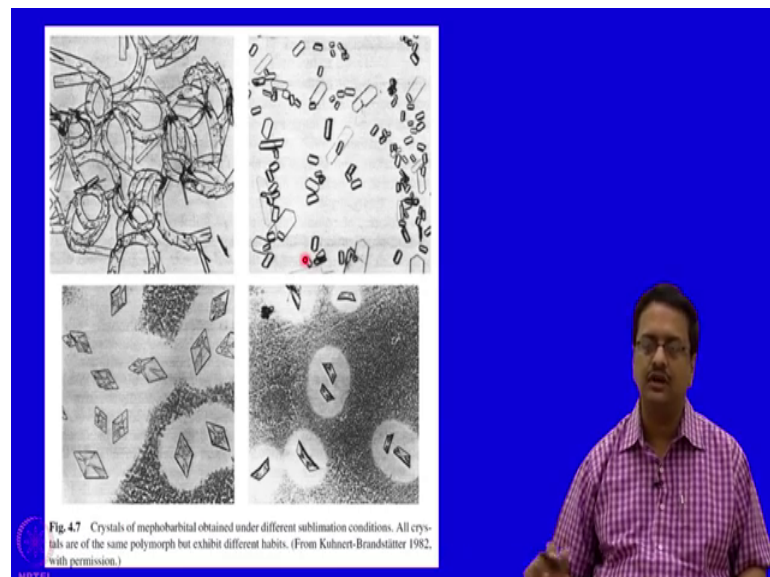
And then a 200 degree C entigrade at which point some of the stable forms begin to melt and at d the equilibrium melting point of higher melting form. So, slowly under microscope we can observe different phenomena happening at different temperatures which can also simultaneously be followed using differential scanning calorimetry. These figures have been adopted from the book by Joel Ornstein where these figures have been taken from different literatures as indicated at the bottom.

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Here, we can see that some solvent bubbles evolved out from a crystal heated under hot stage microscopy as well. So, if we have any solvent in crystalline phases and on heating those solvent evaporates, we can identify that solvent loss under hot stage microscopy as well.

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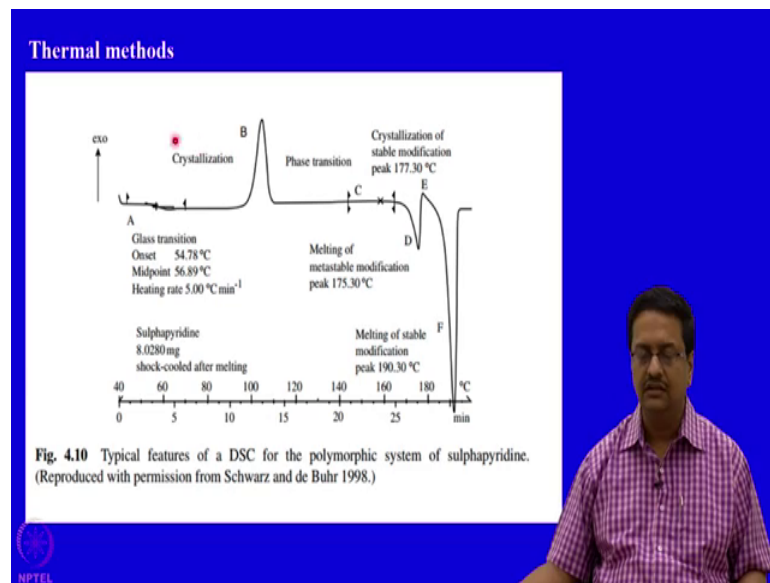


In this case here a crystal of a compound mephobarbital. This is obtained under different sublimation conditions what we see here these crystals have different habits or different morphologies. Here these crystals are like rib tips or ribbons, here these crystals are like

prisms. These ones are rhombus shaped and these are trapezium shape. So, these shapes are all different, but it was found that all these different habit habits are crystal shapes represented one particular polymorph.

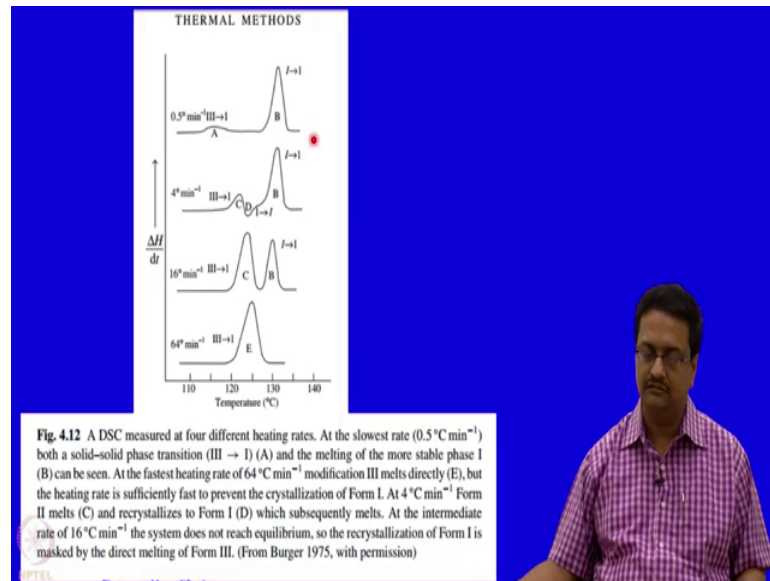
So, this indicates that the optical observation of different shapes or sizes may not indicate that these are polymorphs.

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So, this is a thermal plot that I was trying to draw in the previous slides where you can see there is a glass transition. Remember this plot is exothermic up, a crystallization happening as exothermic. So, that is a phase transition and there are melting of metastable phase and the melting of stable polymorph and so on. These behaviors can be absorbed if we do any the differential scanning calorimetry experiment with the polymorphs.

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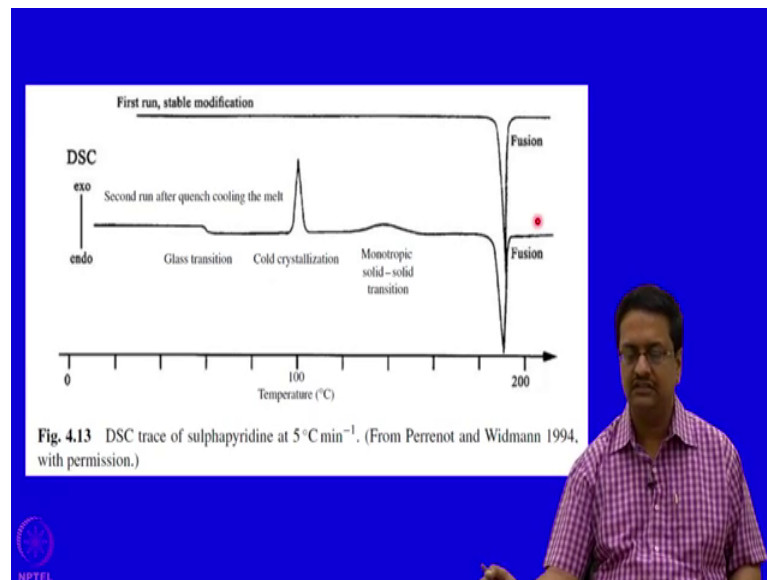


So, this is one example where a slower rate of heating allows a phase transition from 3 to 1 and then 1 melts to liquid. A faster rate of heating allows phase transition of 3 to 1 and then 1 melts to liquid and again 1; 1 goes to it should be 2 and then 2 melts at higher temperature.

At 16 degree 16 degree per minute heating rate 3 melts to converts to 1 and then 1 melts to liquid like this and that much much faster rate that a 64 degree per minute heating rate form 3 directly gets converted to a liquid phase at about 125 degree Centigrade temperature.

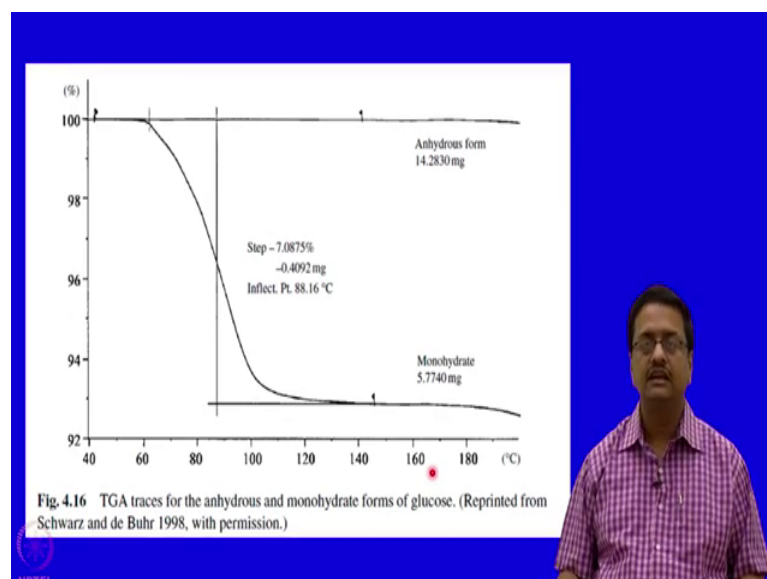
So, these plots indicate the heating rate in at the in a DSC experiment is very important to observe different physical transformations.

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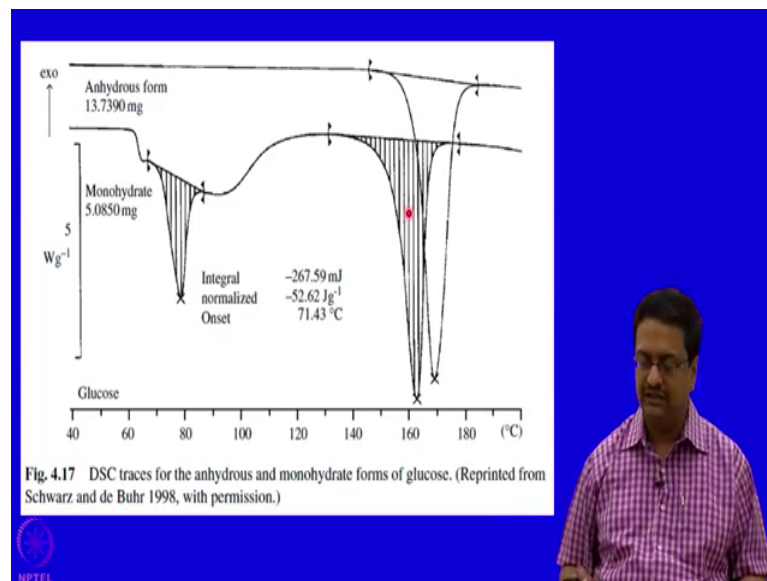
So, this is a DSC trace of sulphapyridine at 5 degree Centigrade per minute where what we can see is during the first run, the stable modification goes and melts, but when the stable modification has been cooled to room temperature and is run again it undergoes a glass transition, then it has a crystallization and then a monotropic solid to solid phase transition and a fusion. So, these type of plots indicate monotropic relationship between the 2 particular polymorphs.

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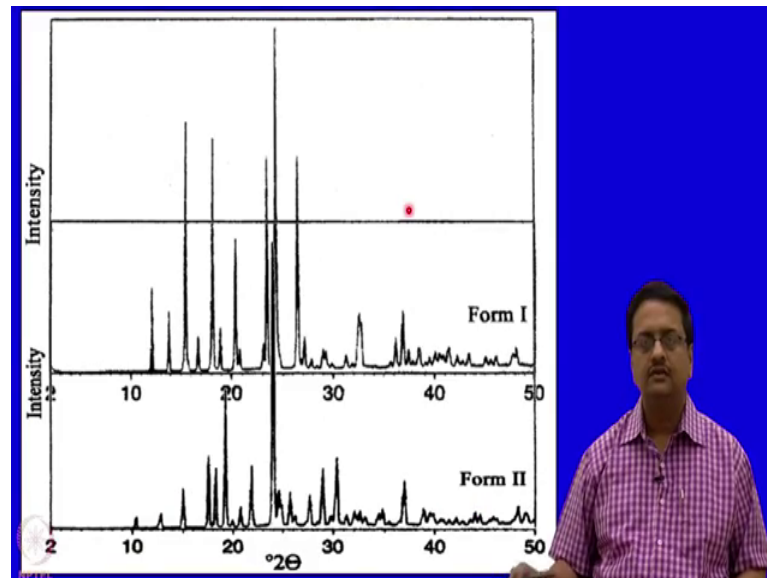
So, here there are the, it is the thermogravimetric trace for 2 different forms of glucose. The top one is anhydrous form which on heating does not lose its mass and it continues as a straight line where, the monohydrate of glucose on heating slowly loses 1 molecule of water and the mass of the substance is reduced to a lower value to about 93 percent, that is 7 percent weight loss corresponds to loss of 1 water molecule. So, the solvents or solvent emerge when you do thermogravimetric, it will have different types of solvent losses indicated like this.

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So, this TGA and DSC together one can identify that the solvent loss is associated with a heat transfer and a melting as well.

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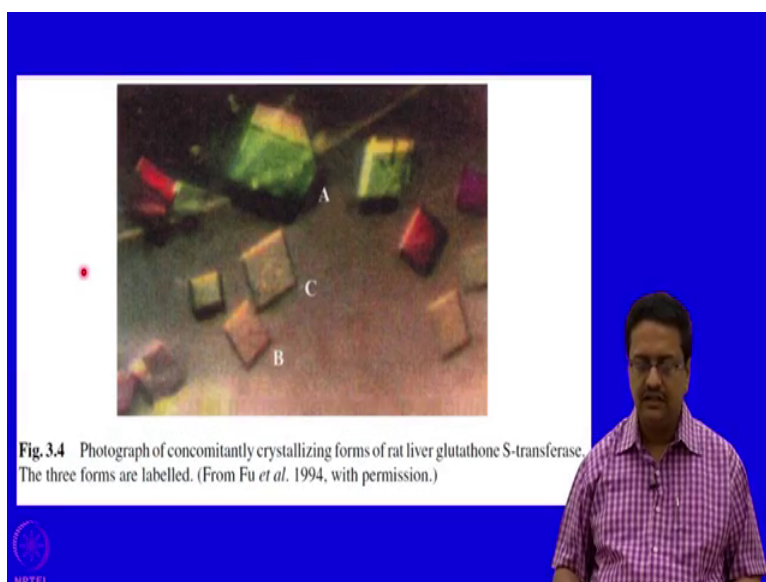
Now, the most important method of identifying different crystalline phases is to do powder x ray diffraction. So, here we have the powder diffraction data of a particular compound form 1 and form 2. And you can see that the peak positions and the intensity ratios are different for 2 different crystal structures of 1 particular compound. So, when the powder diffraction pattern of 1 particular compound crystallizes in different methods are different, we indicate that these are polymorphic modifications.

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So, here there are 3 concomitant polymorphs of crystalline oxonol. So, you can see there are three different colors colorless orange and yellow. So, this indicates that different crystalline forms of a particular compound may have different colors as well and you can see these are different shapes as well.

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So, here this is a photograph of concomitantly crystallizing forms of a rat liver glutathione glutathione s transferase. So, the three forms are labelled as A, B and C and you can see these forms have different morphologies.

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Thermochemistry and conformational polymorphism of a hexamorphic crystal system: ROY
J. Am. Chem. Soc. 2000, 122, 585-591

Table 1. Crystal Data and Data Collection Parameters^a

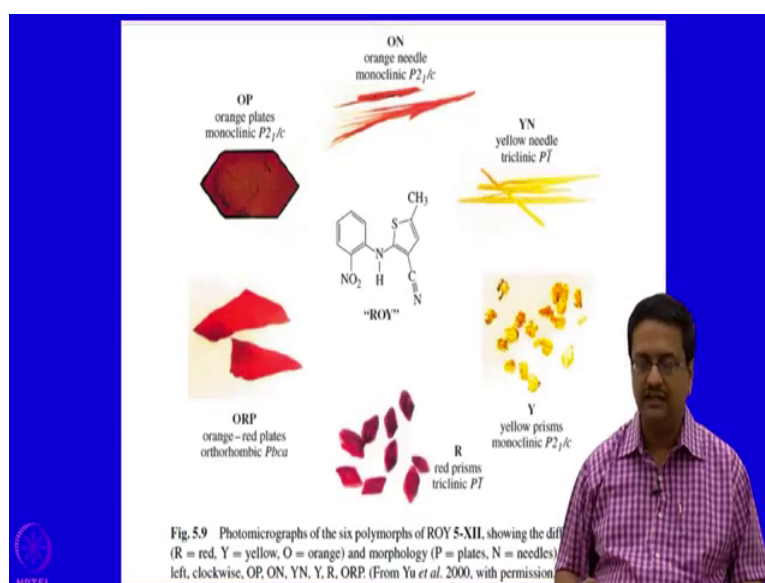
form	Y	ON	OP	R	YN	ORP
crystal system	monoclinic	monoclinic	monoclinic	triclinic	triclinic	orthorhombic
space group [No.]	$P2_1/n$ [14]	$P2_1/c$ [14]	$P2_1/n$ [14]	$P1$ [2]	$P1$ [2]	$Pbca$ [61]
description	yellow prism	orange needle	orange plate	red prism	yellow needle	orange-red plate
crystal size, mm	0.49 × 0.47 × 0.25	0.30 × 0.15 × 0.08	0.27 × 0.22 × 0.13	0.25 × 0.13 × 0.10	0.04 × 0.075 × 0.5	0.1 × 0.2 × 0.3
<i>a</i> , Å	8.5001(8)	3.9453(7)	7.9760(9)	7.4918(5)	4.5918(8)	13.177(3)
<i>b</i> , Å	16.413(2)	18.685(1)	13.319(2)	7.7902(5)	11.249(2)	8.0209(18)
<i>c</i> , Å	8.5371(5)	16.3948(4)	11.676(1)	11.9110(8)	12.315(2)	22.801(5)
α , °	90	90	90	75.494(6)	71.194(3)	90
β , °	91.767(7)	93.830(5)	104.683(8)	77.806(6)	89.852(4)	90
γ , °	90	90	90	63.617(6)	88.174(3)	90
volume, Å ³	1190.5(4)	1205.9(3)	1199.9(4)	598.88(7)	601.85(19)	2488.8(10)
<i>Z</i>	4	4	4	2	2	8
<i>D</i> _{calc} , g cm ⁻³	1.447	1.428	1.435	1.438	1.431	1.431
<i>T</i> , K	293	293	293	293	296	296
radiation ^b	Mo K α	Cu K α	Cu K α	Cu K α	Mo K α	Mo K α
μ , mm ⁻¹	0.256	2.33	2.34	2.35	0.266	0.266
<i>F</i> (000)	536.0	536.0	536.0	268.0	268.0	268.0
reflins collected	2095	2629	2612	2298	4239	4239
unique reflins	1956	2283	2437	2184	2690	2690
<i>R</i>	0.033	0.042	0.049	0.037	0.050	0.050
<i>R</i> _w ^c	0.044	0.055	0.122	0.050	0.100	0.100
GOF	1.415	1.392	1.000	1.428	0.839	0.839

^a Empirical formula: C₂₁H₂₇N₃O₅S. MW: 259.29. ^b Mo K α (0.71073 Å), Cu K α (1.54184 Å).

This is the well known a classic example of a particular compound roy which has 6 different polymorphs with different colors. And what you can see here is that the space groups are either P 2 1 by N or P 2 1 by C, which are interconvertible, some of them have p 1 bar space group and some has P B C A space group.

So, the crystal system spans from triclinic to monoclinic to orthorhombic, space group from P 1 bar to P 2 1 by say it to PBCA and you can see that the volumes range about 1100 1200 for triclinic it is 600 and orthorhombic it is 2400.

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The most important aspect is that this particular compound all these crystals forms have different colors and different morphologies. So, this different color and morphology are sort of indicators that these are different crystal forms.

And one has to characterize them by powder x ray diffraction, single crystal x ray diffraction and of course, the one has to conduct with carry out the DSC's to understand the thermal behavior whether they are monotropic or enantiotropic phases and so on.

So, with this I would like to conclude saying that the method of x ray diffraction is a very useful technique as you might have learned that one can establish the crystal structure of a substance. You can identify different phases using powder x ray diffraction. One can determine structures from powder x ray and single crystal x ray diffraction elucidate the complete three dimensional structure.

We can use a combination of powder x ray diffraction, single crystal diffraction and other physical measurements to identify polymorphs and characterized them appropriately.