

Chemical Crystallography
Prof. Angshuman Roy Choudhury
Department of Chemical Sciences
The Indian Institute of Science Education and Research, Mohali

Lecture – 56
Polymorphs-1

(Refer Slide Time: 00:16)

Chemical Crystallography

Dr. Angshuman Roy Choudhury

Assistant Professor

Department of Chemical Sciences, IISER Mohali

Web: <http://14.139.227.202/Faculty/angshurc/profile.php>

E-mail: angshurc@iisermohali.ac.in

Tutors:

Ms. Anamika Avni and Ms. Labhini Singla

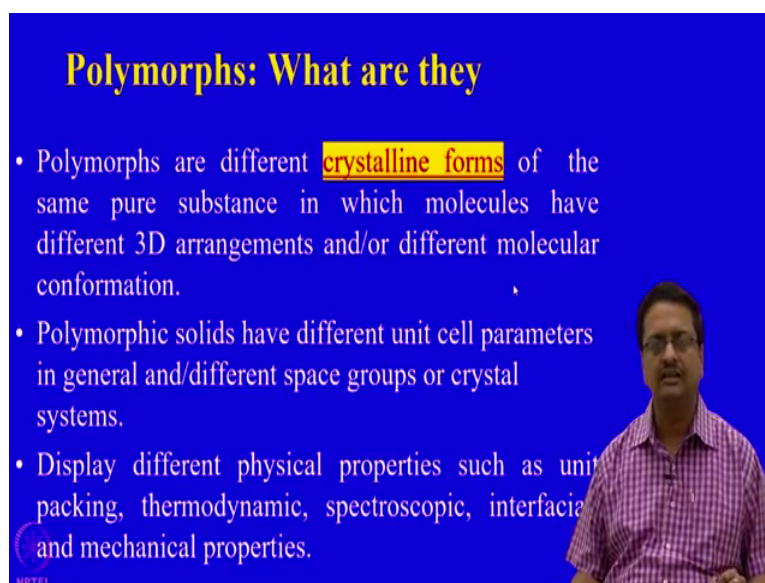
PhD students, Department of Chemical Sciences

IISER Mohali.



Welcome back to the course of ~~chemical~~ Chemical crystallography Crystallography. Today is the last lecture on this course. And today we are going to discuss about a phenomena called Polymorphism. So, the point of discussion is polymorphism in molecular crystals.

(Refer Slide Time: 00:32)

The image shows a video frame with a blue background. At the top, the title "Polymorphs: What are they" is written in yellow. Below the title, there are three bullet points in white text. The first bullet point says "Polymorphs are different crystalline forms of the same pure substance in which molecules have different 3D arrangements and/or different molecular conformation." The second bullet point says "Polymorphic solids have different unit cell parameters in general and/different space groups or crystal systems." The third bullet point says "Display different physical properties such as unit packing, thermodynamic, spectroscopic, interfacial and mechanical properties." In the bottom right corner, there is a small inset video of a man with glasses wearing a pink and white checkered shirt. The NPTEL logo is visible in the bottom left corner of the slide.

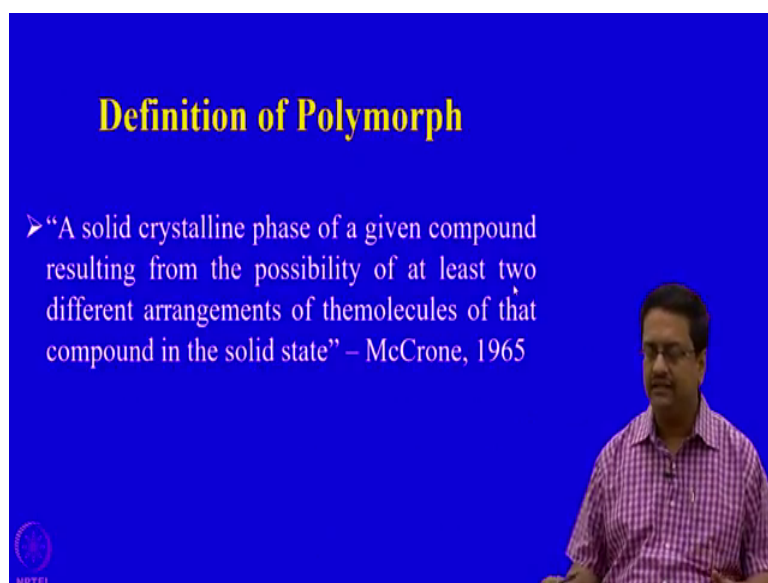
Polymorphs: What are they

- Polymorphs are different **crystalline forms** of the same pure substance in which molecules have different 3D arrangements and/or different molecular conformation.
- Polymorphic solids have different unit cell parameters in general and/different space groups or crystal systems.
- Display different physical properties such as unit packing, thermodynamic, spectroscopic, interfacial and mechanical properties.

To start we need to define, what is polymorphism, what are they, and how we should classify them. So, polymorphs are different crystalline forms of the same substance in which molecules have different three-dimensional arrangements, and or different molecular conformation. So, polymorphic solids have generally different unit cell parameters, different space groups, and many times it may have different crystal systems as well.

So, these different crystalline forms of same compound display various different physical properties such as different unit cell packing, and resulting into different physical behavior, thermodynamic properties like different melting points, spectroscopic properties like may have different color. And then there may be interfacial and some other mechanical properties which are different for two different materials.

(Refer Slide Time: 01:31)



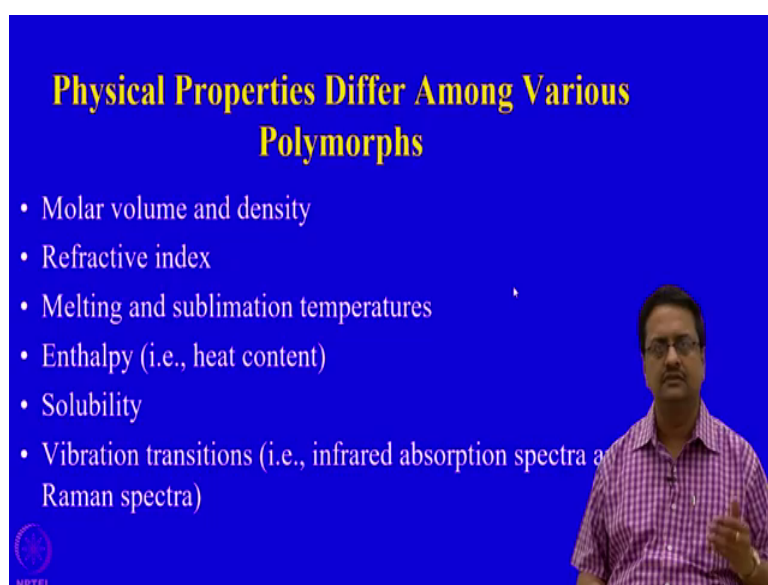
Definition of Polymorph

➤ “A solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state” – McCrone, 1965

The slide features a blue background with yellow text for the title and a white text for the definition. A small NPTEL logo is visible in the bottom left corner. A speaker in a purple checkered shirt is visible in the bottom right corner of the slide frame.

In 1965, McCrone, defined polymorphs as a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of molecules of compound in the solid state, which actually means that a particular compound, when you try to crystallize it from different methods, using different solvents or different methods like slow evaporation, rapid evaporation, solvent drop grinding method or vapour diffusion method, if you end up getting two crystalline states which have different outer X-ray diffraction pattern, then we termed call them as polymorphs.

(Refer Slide Time: 02:16)



Physical Properties Differ Among Various Polymorphs

- Molar volume and density
- Refractive index
- Melting and sublimation temperatures
- Enthalpy (i.e., heat content)
- Solubility
- Vibration transitions (i.e., infrared absorption spectra and Raman spectra)

The slide features a blue background with yellow text for the title and white text for the list. A small NPTEL logo is visible in the bottom left corner. A speaker in a purple checkered shirt is visible in the bottom right corner of the slide frame.

So, physical properties of polymorphs differ in various polymorphs. The molar volume and density may be different. The refractive and index melting point and sublimation temperatures may be different. The enthalpies of those solid crystalline forms will be different. The solubility of those different crystal structures in a given solvent may be different. And of course some vibrational transitions like infrared, absorption spectroscopy, and Raman spectra may be different for those different crystal structures.

(Refer Slide Time: 02:53)

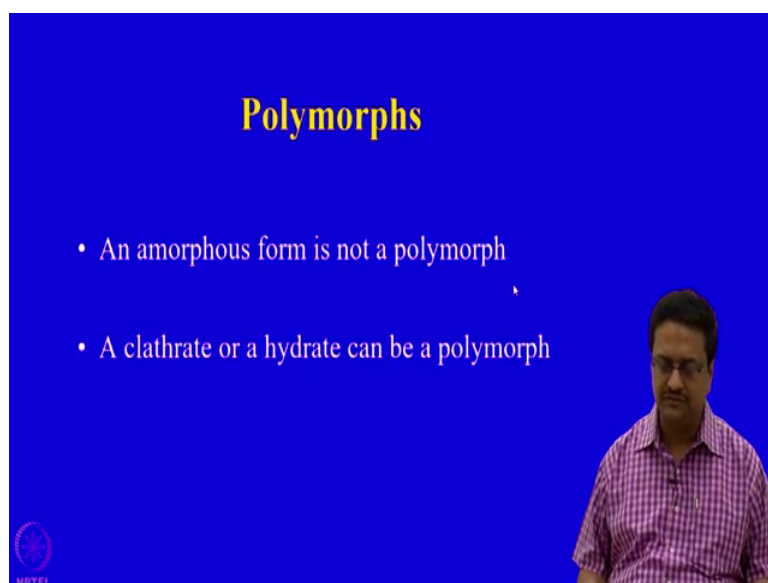
Physical Properties Differ Among Various Polymorphs (contd)

- Dissolution rate
- Stability
- Hardness
- Compactibility
- Handling, flow, and blending

NPTEL

In addition, there may be differences in dissolution rate, differences in solubilities, hardness, compactibility, handling procedural, flow, and blending methods, like one polymorph may be free flowing one polymorph may be sticky. These are different physical properties that are seen to be different in case of different polymorphs.

(Refer Slide Time: 03:18)



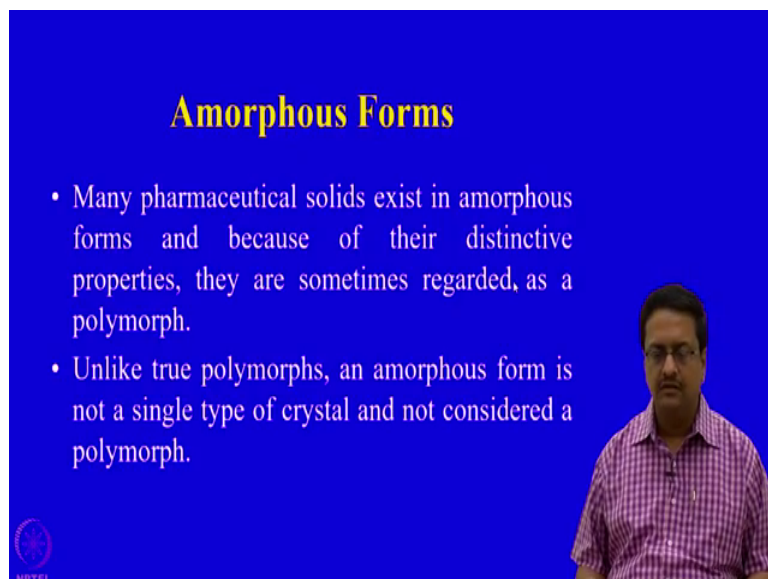
Polymorphs

- An amorphous form is not a polymorph
- A clathrate or a hydrate can be a polymorph

The slide features a blue background with the title 'Polymorphs' in yellow. Two bullet points are listed in white text. A presenter in a pink checkered shirt is visible in the bottom right corner. The NPTEL logo is in the bottom left corner.

An amorphous form is not a polymorph, because if an amorphous form does not represent a single phase, it may be a mixture of two or more different non crystalline phases. And hence it cannot be called as a polymorphs. So, a clathrate or a hydrate can be called a polymorph.

(Refer Slide Time: 03:39)



Amorphous Forms

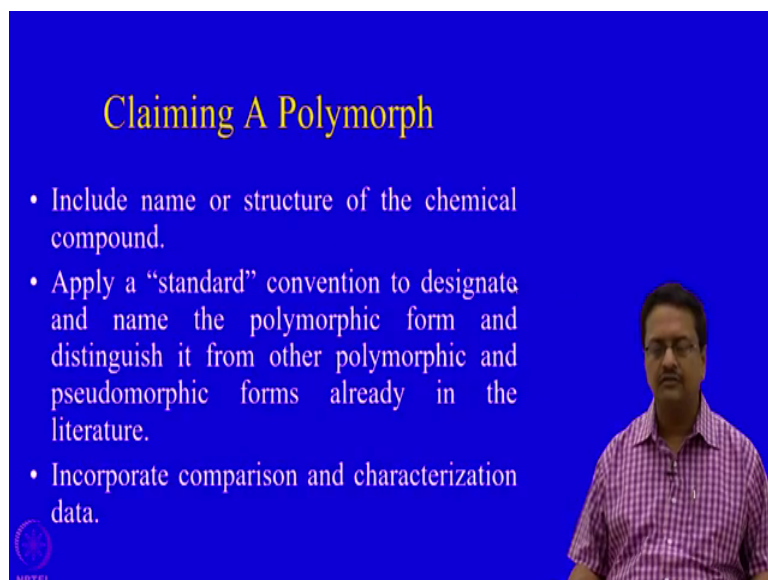
- Many pharmaceutical solids exist in amorphous forms and because of their distinctive properties, they are sometimes regarded, as a polymorph.
- Unlike true polymorphs, an amorphous form is not a single type of crystal and not considered a polymorph.

The slide features a blue background with the title 'Amorphous Forms' in yellow. Two bullet points are listed in white text. A presenter in a pink checkered shirt is visible in the bottom right corner. The NPTEL logo is in the bottom left corner.

Many pharmaceutical solids exist in amorphous forms, and because of their distinctive properties, they are sometimes regarded as a polymorph in pharmaceutical industry, but

unlike true polymorphs an amorphous form is not a single type of crystal, and not considered as a polymorphs in general.

(Refer Slide Time: 04:00)



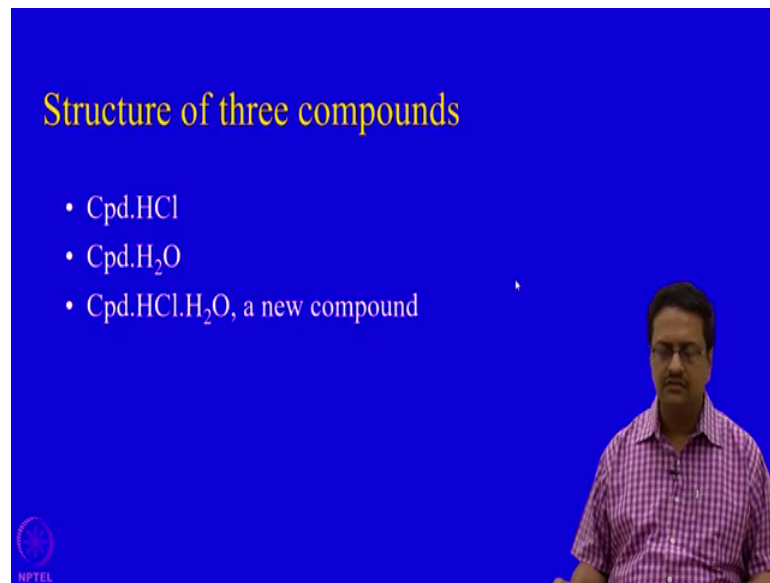
The slide has a blue background with yellow text for the title and white text for the bullet points. A small circular logo with 'NPTEL' is in the bottom left corner. A video inset of a man in a pink checkered shirt is on the right side.

Claiming A Polymorph

- Include name or structure of the chemical compound.
- Apply a “standard” convention to designate and name the polymorphic form and distinguish it from other polymorphic and pseudomorphic forms already in the literature.
- Incorporate comparison and characterization data.

So, when we try to claim that we have generated a new polymorph, we first include the name or structure of the chemical compound. Apply a standard convention to designate, and name the polymorphic forms, and distinguish it from other polymorphs, and pseudo polymorphic forms already in the literature: uUsing some physical methods. And incorporate comparison, and characterization data for the new crystalline form that has been identified.

(Refer Slide Time: 04:32)

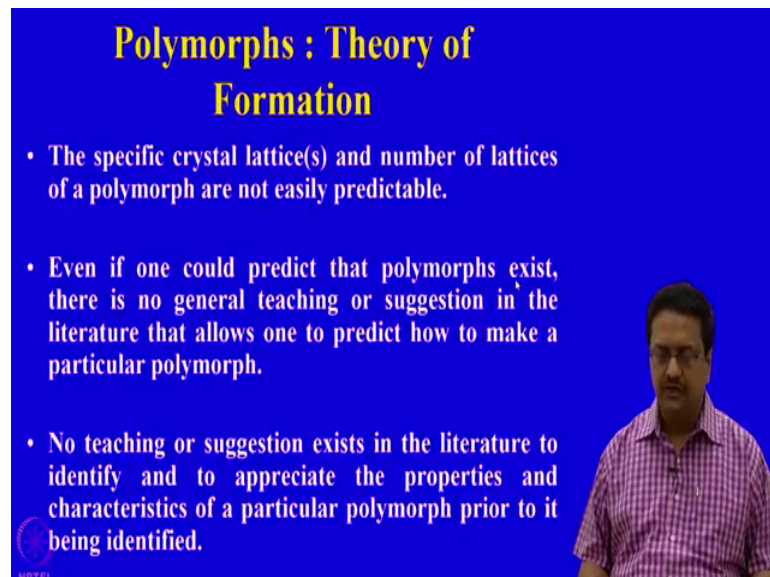


Structure of three compounds

- Cpd.HCl
- Cpd.H₂O
- Cpd.HCl.H₂O, a new compound

So, suppose we have a particular compound with hydrochloride or HCL as a coformer. A compound when can crystallize with water molecule, and a compound can crystallize with both the HCL, and water. So, then this becomes a new compound and not a polymorph.

(Refer Slide Time: 04:52)



Polymorphs : Theory of Formation

- The specific crystal lattice(s) and number of lattices of a polymorph are not easily predictable.
- Even if one could predict that polymorphs exist, there is no general teaching or suggestion in the literature that allows one to predict how to make a particular polymorph.
- No teaching or suggestion exists in the literature to identify and to appreciate the properties and characteristics of a particular polymorph prior to it being identified.

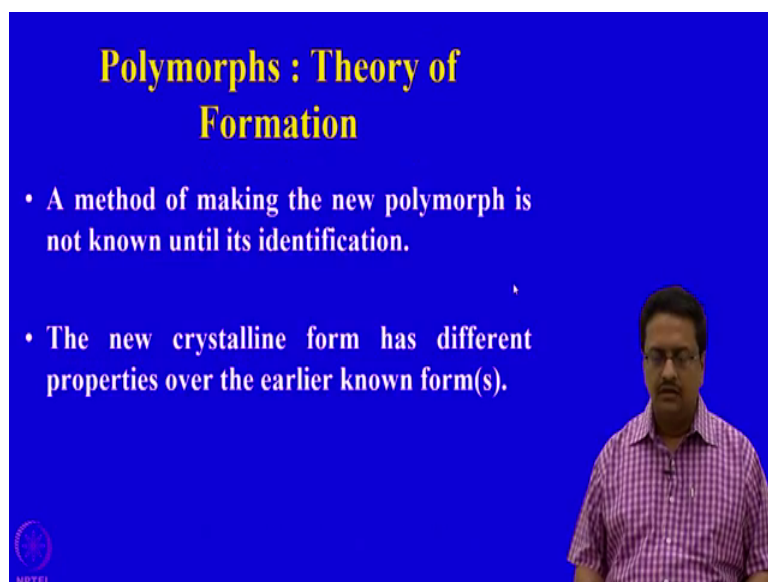
So, polymorphs generation is a very important phenomena in pharmaceutical industry and in general in crystal engineering community. So, there are few theories that we need

to understand behind the formation of polymorphs. The specific crystal lattices, and number of lattices of a polymorphic polymorph are known not known easily.

The ~~the~~ specific crystal lattices, and number of lattices of a polymorph are not easily predictable. Even if one can could predict that polymorphs exist, there is no general teaching or suggestion in the literature that shows, how one can predict to make a particular polymorph. And no teaching or suggestion exists in the literature to identify, and to appreciate the properties and characteristics of a particular polymorph prior to it being identified.

So, what we are trying to indicate is that just by looking at a molecule a chemical sketch it is not possible to predict whether it will have more than one crystalline forms. If it can have more than one crystalline forms, then how those forms can be generated, nowadays there are some crystallographic software some packages where the computational the tools are used to predict different polymorphs, but it is not always experimentally achievable.

(Refer Slide Time: 06:24)



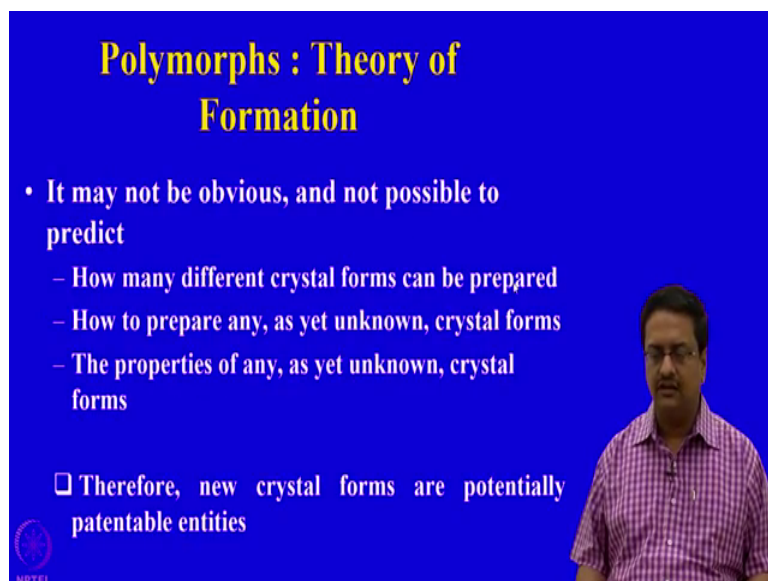
Polymorphs : Theory of Formation

- A method of making the new polymorph is not known until its identification.
- The new crystalline form has different properties over the earlier known form(s).

The slide features a blue background with yellow text for the title and white text for the bullet points. A small NPTEL logo is visible in the bottom left corner. A presenter, a man with glasses wearing a purple checkered shirt, is shown in the bottom right corner of the slide frame.

A method of making a new polymorph is not known until it has been identified. And the new crystalline form has a different properties over the earlier known forms. Until and unless somebody does an experiment, and arrives at a new particular crystalline form, we cannot a priori predict that this particular form will be found or it will not be formed.

(Refer Slide Time: 06:49)



Polymorphs : Theory of Formation

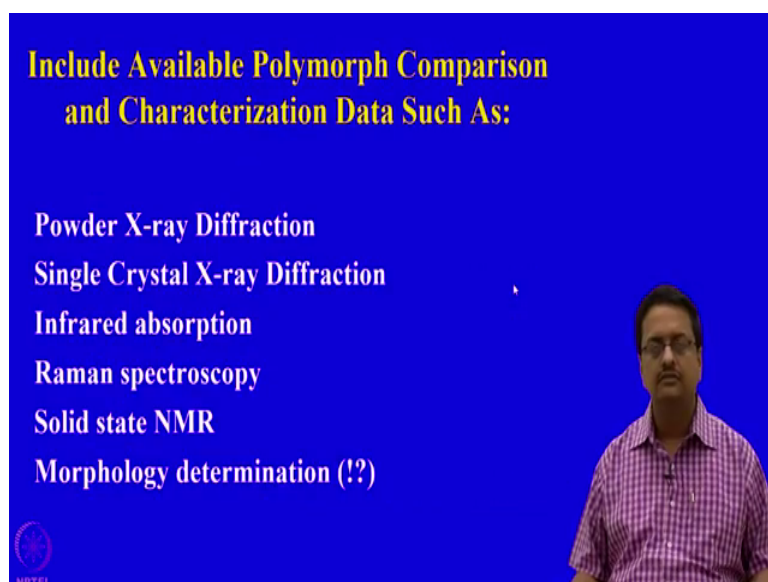
- It may not be obvious, and not possible to predict
 - How many different crystal forms can be prepared
 - How to prepare any, as yet unknown, crystal forms
 - The properties of any, as yet unknown, crystal forms
- Therefore, new crystal forms are potentially patentable entities

NPTEL

The slide features a blue background with yellow text for the title and white text for the bullet points. A small NPTEL logo is in the bottom left corner. A man in a purple checkered shirt is visible on the right side of the slide.

It may not be obvious, and not possible to predict few things like how many different crystal forms can be prepared from a particular compound. How to prepare any as yet unknown crystal forms, and the properties of any unknown crystal form. So, these predictions are not yet possible. Therefore, a new crystal forms are potentially patentable entity.

(Refer Slide Time: 07:15)



Include Available Polymorph Comparison and Characterization Data Such As:

- Powder X-ray Diffraction
- Single Crystal X-ray Diffraction
- Infrared absorption
- Raman spectroscopy
- Solid state NMR
- Morphology determination (!?)

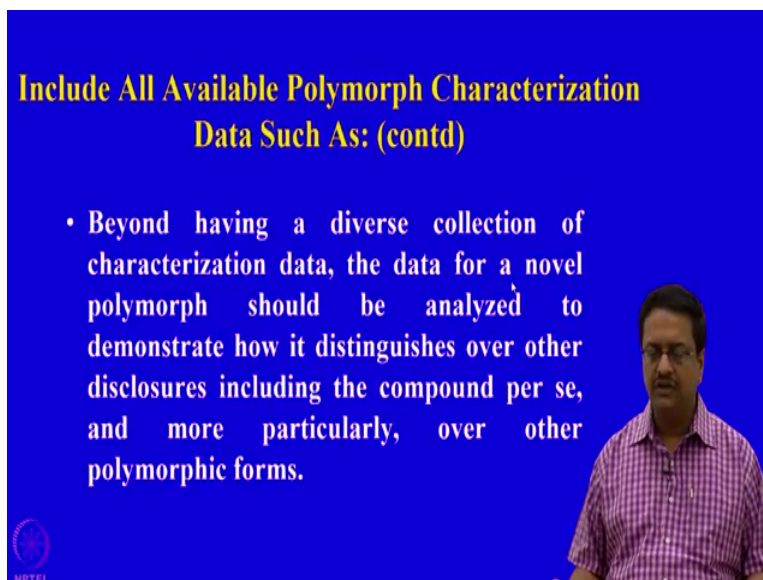
NPTEL

The slide features a blue background with yellow text for the title and white text for the list. A small NPTEL logo is in the bottom left corner. A man in a purple checkered shirt is visible on the right side of the slide.

So, when we try to characterize these crystalline forms, we use different methods. The first and foremost important method is called an x ray diffraction. Then if we can grow a

single crystal one can do single crystal x ray diffraction to infiltrate the structure, we can do I R or Raman spectroscopy, solid state NMR, and also we can identify polymorphs by morphology, but it can lead to some difficulty.

(Refer Slide Time: 07:44)

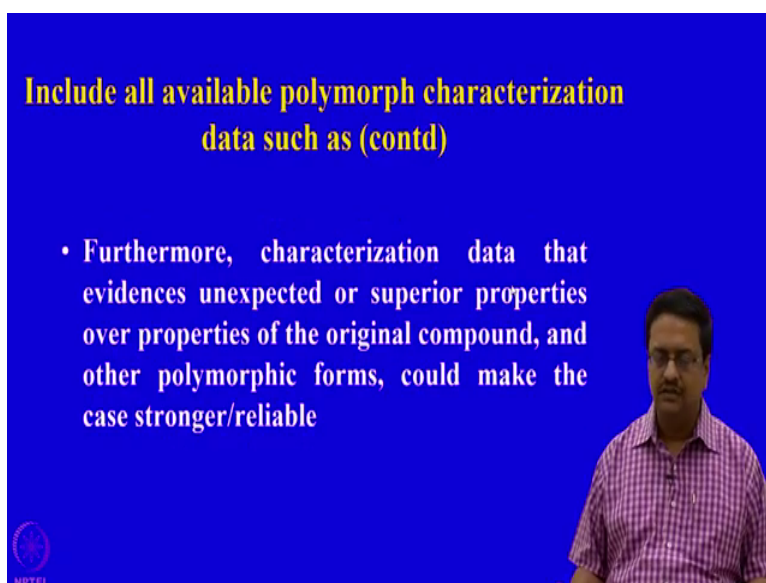


Include All Available Polymorph Characterization Data Such As: (contd)

- Beyond having a diverse collection of characterization data, the data for a novel polymorph should be analyzed to demonstrate how it distinguishes over other disclosures including the compound per se, and more particularly, over other polymorphic forms.

So, beyond having a diverse collection of characterization data the data for a novel polymorph should be analyzed to demonstrate how it distinguishes over other disclosures including the compound per se, and more particularly, over the other polymorphic form. So, we need to establish the superiority of this particular form to be able to use it in lieu of the original form.

(Refer Slide Time: 08:12)



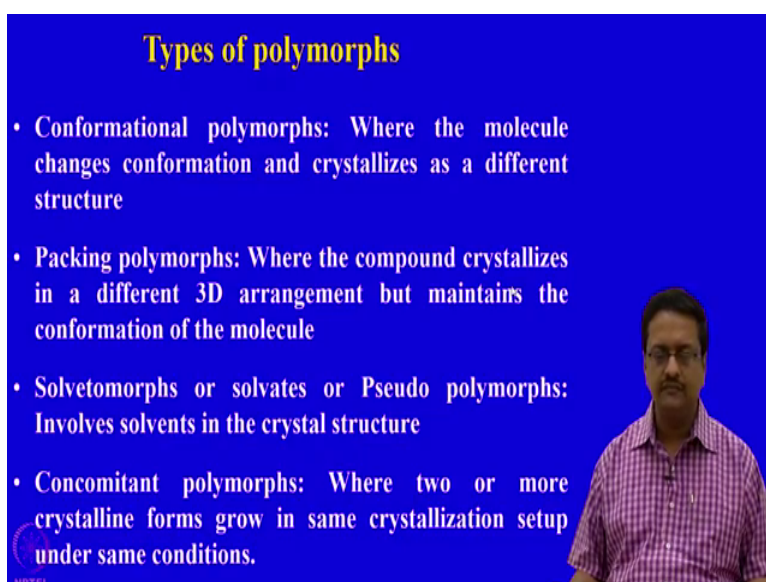
Include all available polymorph characterization data such as (contd)

- Furthermore, characterization data that evidences unexpected or superior properties over properties of the original compound, and other polymorphic forms, could make the case stronger/reliable

NPTEL

In addition, the characterization data that evidences unexpected or superior properties over properties of the original compound, and other polymorphic forms could make a stronger or reliable case.

(Refer Slide Time: 08:25)



Types of polymorphs

- Conformational polymorphs: Where the molecule changes conformation and crystallizes as a different structure
- Packing polymorphs: Where the compound crystallizes in a different 3D arrangement but maintains the conformation of the molecule
- Solvetomorphs or solvates or Pseudo polymorphs: Involves solvents in the crystal structure
- Concomitant polymorphs: Where two or more crystalline forms grow in same crystallization setup under same conditions.

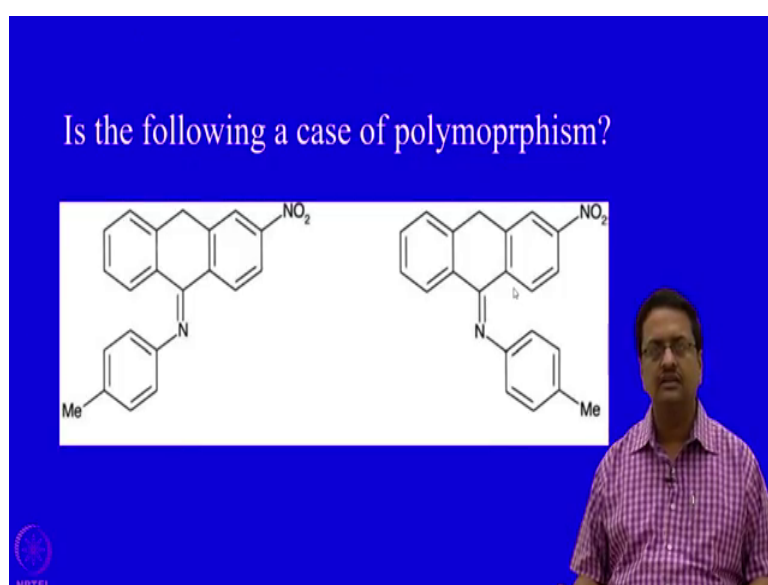
NPTEL

So, there are different types of polymorphs that has been characterized in the literature. The first type of characterization is leaded. First type of classification is conformational polymorphs, where the molecule changes conformation and crystallizes as a different molecule different structure. Packing polymorphs where the compound crystallizes in

different three-dimensional arrangement, but maintains the conformation of the molecule unchanged.

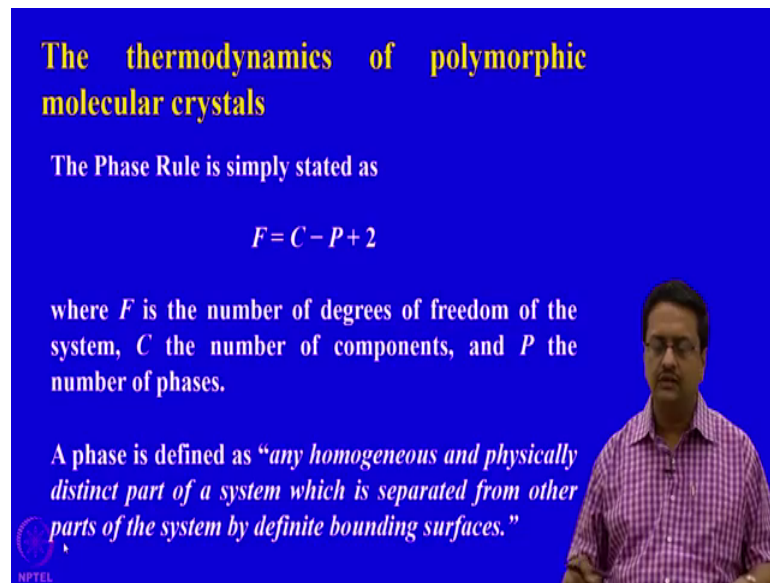
Solvatomorphs or solvates or pseudo polymorphs are crystal structures of the same compound which involves the solvent. And lastly the concomitant polymorphs where two or more crystalline forms may grow in the same crystallization setup under the same conditions. So, these are like twins these are growing from same solvent under the same temperature and pressure, and same conditions of rate of evaporation.

(Refer Slide Time: 09:23)



So, now the question is if we have these two compounds in crystals are they polymorphs, you can see that these two compounds are geometrical isomers. Here this C double bond N is having a trans arrangement with the nitro group, and the methyl group. Here the nitro group and a methyl group on the phenyl ring are in this is arrangement. So, these two are not polymorphs rather these two are different compounds. So, two polymorphs should not have any difference in their bonding features.

(Refer Slide Time: 09:59)



The thermodynamics of polymorphic molecular crystals

The Phase Rule is simply stated as

$$F = C - P + 2$$

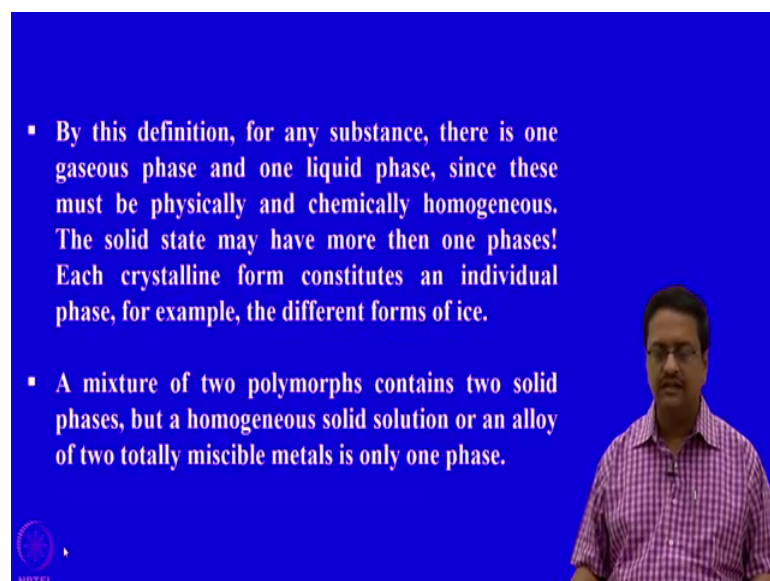
where F is the number of degrees of freedom of the system, C the number of components, and P the number of phases.

A phase is defined as “*any homogeneous and physically distinct part of a system which is separated from other parts of the system by definite bounding surfaces.*”

NPTEL

But, now we need to understand the thermodynamics of polymorphic forms of molecular crystals. We know the Gibb's phase rule as stated as F equal to C minus P plus 2 where F is the number of degrees of freedom of the system. C the number of components, and P the number of phases. And we define a phase as any homogenous and physically distinct part of a system which is separated from other parts of the system by definite bounding surfaces.

(Refer Slide Time: 10:33)

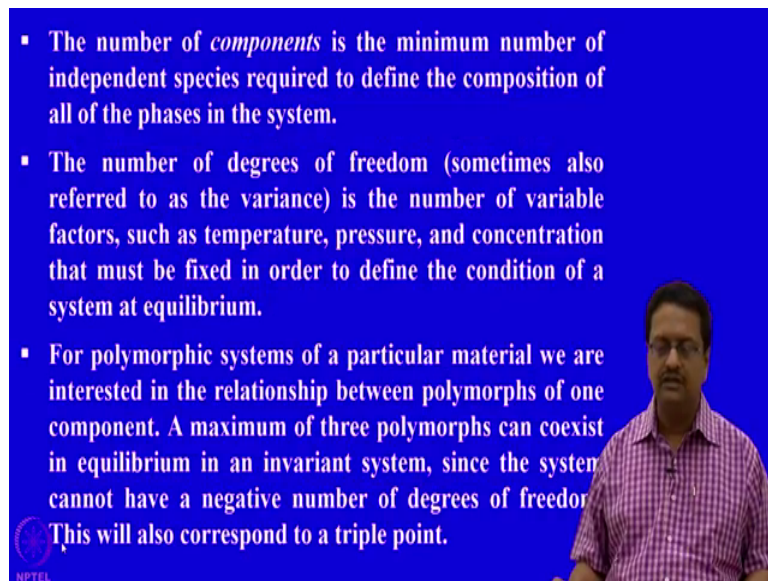


- By this definition, for any substance, there is one gaseous phase and one liquid phase, since these must be physically and chemically homogeneous. The solid state may have more than one phases! Each crystalline form constitutes an individual phase, for example, the different forms of ice.
- A mixture of two polymorphs contains two solid phases, but a homogeneous solid solution or an alloy of two totally miscible metals is only one phase.

NPTEL

So, by this definition, for any substance, there is one gaseous phase and one liquid phase, since these must be physically and chemically homogeneous. And the solid state may have more than one phases existing together. So, each crystalline form constitutes an individual phase, for example, the different forms of ice. A mixture of two polymorphs contains two solid phases, but a homogeneous solid solution or an alloy of two totally immiscible metals is only one phase.

(Refer Slide Time: 11:07)



▪ The number of *components* is the minimum number of independent species required to define the composition of all of the phases in the system.

▪ The number of degrees of freedom (sometimes also referred to as the variance) is the number of variable factors, such as temperature, pressure, and concentration that must be fixed in order to define the condition of a system at equilibrium.

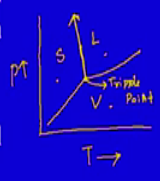
▪ For polymorphic systems of a particular material we are interested in the relationship between polymorphs of one component. A maximum of three polymorphs can coexist in equilibrium in an invariant system, since the system cannot have a negative number of degrees of freedom. This will also correspond to a triple point.

NPTTEL

The number of component is the minimum number of independent species required to define the composition of all the phases. And number of degrees of freedom is the number of variables that are temperature, pressure, concentration that must be fixed in order to define the condition of the system at equilibrium. So, for polymorphic systems of a particular material, we are intended in the relation interested in the relationship between polymorphs of one component. A maximum of three polymorphs can coexist in equilibrium in an invariant system, and since the system cannot have negative number of degrees of freedom. So, this will also correspond to a triple point.

(Refer Slide Time: 11:57)

- The number of degrees of freedom (sometimes also referred to as the variance) is the number of variable factors, such as temperature, pressure, and concentration that must be fixed in order to define the condition of a system at equilibrium.
- a one-component system in one phase, say a gas, would have two degrees of freedom
- a one component system in two phases (liquid and gas) would have one degree of freedom (A phase boundary)
- a one component system with three phases would have no degrees of freedom (A triple point)

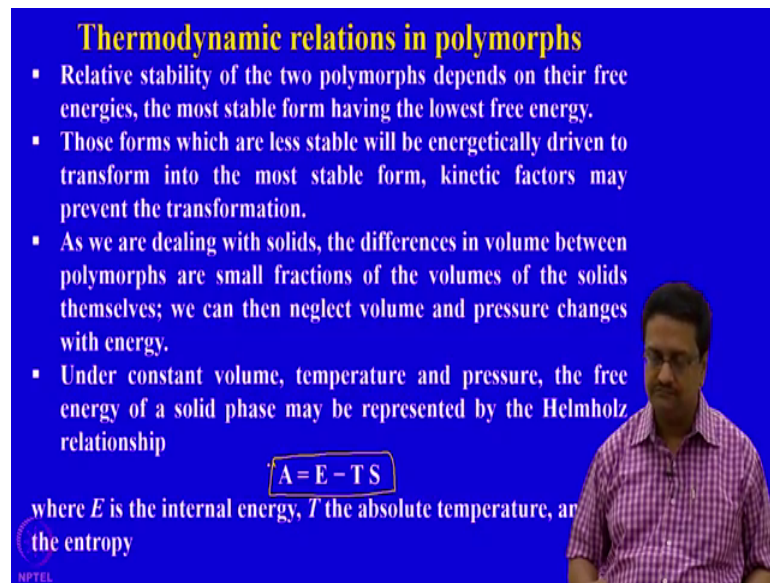


The number of degrees of freedom is the number of variable factors such as temperature, pressure and concentration and that must be fixed. So, a one-component system is one phase, say gas would have two ~~two~~ degrees of freedom as we know. A one component system in a two phase equilibrium that is liquid and gas, would have one degree of freedom that is a phase boundary. And a one component system with three phases would have no degrees of freedom that is called a triple point.

So, here I would like to just remind you about the phase diagram of water. To explain this let me draw the phase diagram of water. Here, in phase diagram of water we plot pressure in the y-axis, absolute temperature in x axis, and we know that for water we have a negative slope for solid liquid interface that is this line has a negative slope, and this is the vapor, so solid liquid and vapor. So, if we are located somewhere at in any one phase region, we have simultaneously two degrees of freedom.

When we are sitting on one particular line, say for example solid liquid phase boundary, we do not we have only one degree of freedom, so if we change one component either temperature or pressure simultaneously the other one also changes, and the equilibrium is maintained. And when the three phases coexist this point is called the triple point where at that point we cannot change anything without disturbing the equilibrium of three phases.

(Refer Slide Time: 14:07)



Thermodynamic relations in polymorphs

- Relative stability of the two polymorphs depends on their free energies, the most stable form having the lowest free energy.
- Those forms which are less stable will be energetically driven to transform into the most stable form, kinetic factors may prevent the transformation.
- As we are dealing with solids, the differences in volume between polymorphs are small fractions of the volumes of the solids themselves; we can then neglect volume and pressure changes with energy.
- Under constant volume, temperature and pressure, the free energy of a solid phase may be represented by the Helmholtz relationship

$$A = E - TS$$

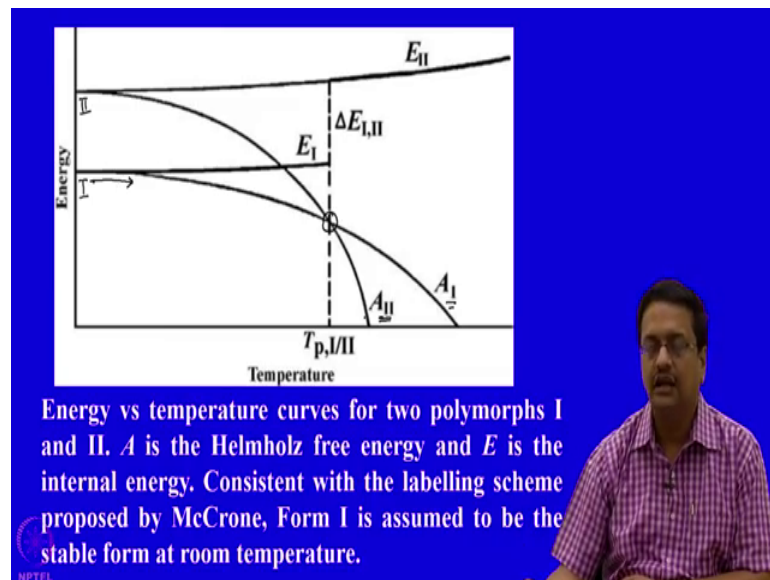
where E is the internal energy, T the absolute temperature, and S the entropy

NPTEL

So, the relative stability of the two polymorphs depend on their energies, and although is the most stable form is the one which has the lowest energy. Those forms which are less stable will be energetically driven to transform into the most stable form. So, kinetic factors may prevent such transformation.

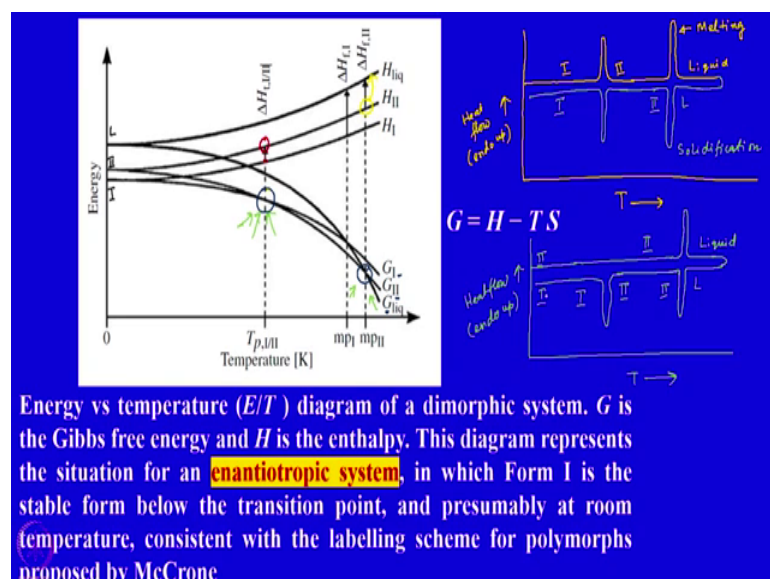
So, as we are dealing with solids the differences in the volume between polymorphs are small fractions of volumes of the solid themselves, so we can then neglect the volume and pressure changes with energy. So, under constant volume, and temperature and pressure the free energy of the solid may be represented by Helmholtz relationship as shown here A equal to E minus $T S$, so where E is the internal energy, and T is the absolute temperature, and S is the entropy of the particular solid form.

(Refer Slide Time: 15:10)



If we try to plot the energy versus temperature for two different polymorphs, what we can see is that suppose this one is the polymorph 1, and this one is for the polymorph 2, so the energy of polymorph 1 is lower than energy of polymorph of 2 at a very low temperature. And when we are increasing the temperature for polymorph 1, at one point we see that the Helmholtz free energy that is A value for the form 2 meets, the A value of form 1 at this particular junction, and beyond this point the A value for form 2 is lower than the form 1. So, if we are heating form 1 at this particular transition temperature form 1 should get converted to form 2, and it should exist at higher temperature.

(Refer Slide Time: 16:16)



So, here we are trying to show the Gibbs free energy versus temperature plot where it is $G = H - TS$, and what we have here is the energy versus temperature diagram of a dimorphic system. So, what we have here is the form 1, which is the most stable form at low temperature, this is the form 2, and that is the liquid phase of that particular compound.

So, now here what we see is that at a particular temperature while heating gives energies of the 2 phases become equal, and beyond that temperature the Gibbs energy of phase 2 is lower compared to Gibbs energy of phase 1. So, what happens in this case is, if we are heating form 1 beyond this temperature form 1 gets converted to form 2, and then when that form 2 reaches this particular point, where it meets the G of liquid form 2 melts.

So, if we try to see this phenomena using differential scanning calorimetric, what should we see, suppose we are plotting the heat flow versus temperature form 1, so on heating form 1 at some temperature gets converted from form 1 to form 2, and what we have is the form 2 having higher energy compared to form 1, so form 1 will absorb energy, and get converted to form 2. So, if we plot the endothermic transformations up, then this transformation of form 1 to form 2 is an endothermic transformation it absorbs heat. So, we should see a peak.

So, before the peak it is form 1 after the peak it is formed 2, and then when we are heating this form 2 meets, the G line for the liquid at much higher temperature, and then at that temperature it melts. As we know melting is an endothermic process, as we know the melting is an endothermic process, once again form 2 takes up more heat, and goes to the higher energy level for the liquid. So, once again we have another endothermic peak indicating the melting. So, on this side the other right hand side we have the liquid. So, this peak indicates melting.

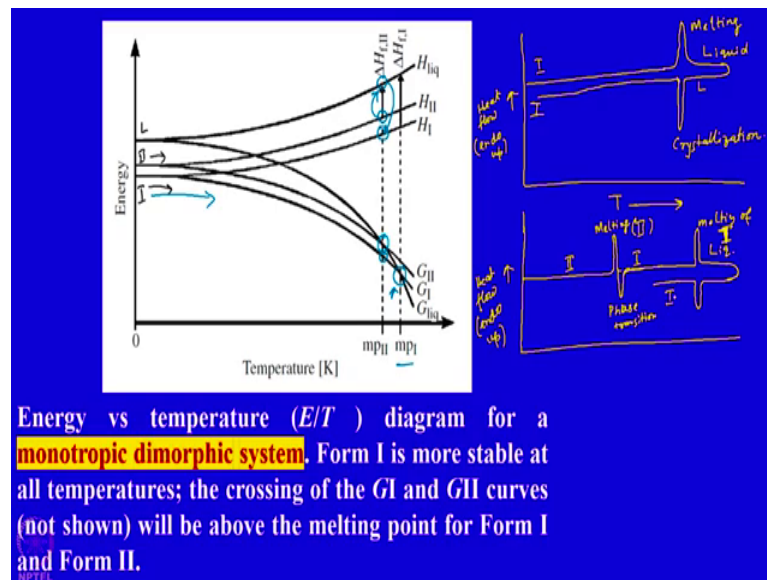
Now, if we start cooling this molten liquid what should happen, so when we start cooling this liquid at that point this liquid is being cooled from here backwards that means, again when the liquid crosses the G curve for the phase 2 the form 2 will be crystallized. And crystallization is exothermic process, so it will be a solidification peak like that from liquid to form 2. And then when we are further cooling once again at that particular temperature beyond that when we go lower form 1 is more stable compared to form 2, so again transformation from form 2 to form 1 will take place.

So, if such a thing happens that one phase can be converted to the other, and it can reversibly come back then this particular system is called the enantiotropic system. But, now you remember if we had done the react experiment by starting with form 2, if a form 2 is formed during an experimental process by some means, which is thermodynamically unstable form. So, if we do the experiment with the corresponding thermodynamically unstable form, what should happen, if we do the D S C analysis of the same thing.

So, we again write heat flow endo up, and the temperature on x axis. So, now, I am heating a phase form 2, which is thermodynamically unstable, but then this form 2 continues to remain as form 2 at this particular junction temperature where there should have been a change of form 1 to 2, but then it since it is already 2 there is no change. So, this particular form straight away goes, and melts at the melting point of form 1, so this is form 2, and this is liquid.

But, now when we try to cool this liquid, what should happen is that the liquid is solidified at the solidification temperature at that point. And then when we are further cooling it when again the phase form 2 is crossing this particular temperature, it should get converted to form 1, and we end up getting form 1. So, we started with form 2, we ended up getting form 1 after the first cycle. So, now it indicates that we have got the thermodynamically stable phase from the thermodynamically unstable phase, which was somehow formed during the experimental process. So, this type of system is called the enantiotropic systems.

(Refer Slide Time: 23:06)



The other possibility of a similar dimorphic system can be shown like this where the energies are formed 1 2, and the liquid phase are formed here. The corresponding H and G's are shown, and what we see is the plots for G for 1 and 2 do not intersect at any point before their melting points. So, what happens if we do a D S C of such a system.

So, we again plot the heat flow in y axis with endo up and temperature in the x axis. So, if we have started with form 1, which is the thermodynamically stable form on heating from a low temperature in this direction form 1 does not get converted to form 2 at any point, because the G line for form 1 is not meeting the G line of form 2 at any point. So, form 1 melts at this particular temperature, which is the melting point of form 1. So, what happens when we do simple D S C form 1 goes, and straight away melts at its melting point melting is endothermic process.

So, now if we again try to solidify this liquid is cooled from higher temperature at the melting point, again the solid form 1 should form from the liquid, and the DSC stress should be very very similar to what I have drawn here. This peak indicates crystallization. But, if we had done this react experiment with form 2, what we could have seen form 2, we remember is thermodynamically unstable phase, and it has a melting point which is lower than that of the form 1.

So, if we are heating this sample from room temperature at its melting point, it will first melt. So, in terms of energy on melting this form 2 goes from here to there by absorbing

that much energy, but then at that particular temperature form 1 has a lower energy. So, immediately the molten liquid will solidify back to form one. So, this molten liquid will immediately solidify to give you form 1. And will generate a an exothermic peak like this which will then indicate that form 2 is melted or molten, and phase transition has taken place to form 1. And then when we heat this form 1, further it goes and melts; melting of form 1, and this is melting of form 2.

So, once again if we cool this form 1, we would get the crystallization peak, and it will crystallize as form 1, and not as form 2. So, when we see some behavioral thermal behavior like this, we turn this particular system as monotropic dimorphic crystalline system. So, today in this part of this lecture on polymorphism, we have learned about the definition of polymorphs, classification of polymorphs in terms of their crystal structures. And also we have learned what are monotropic and enantiotropic crystal phases in polymorphs and we have understood how these different say types of polymorphs will behave in the differential scanning calorimetric experiments.

So, what it indicates that if we have generated particular polymorph or if we have generated a large number of polymorphs of a particular compound, then we must do a careful differential scanning calorimetric experiment to identify whether it is a monotropic system or an enantiotropic system. So, in the next lecture, we will continue this discussion.