**Fundamentals and Applications of Supramolecular Chemistry**
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**Lecture 28**

W6L28_Properties and Thermodynamics of Polymorphism

So, hello everybody, let us continue our discussion now. So, in the last lecture, we were talking about the characterization of polymorphs via single crystal XRD and powder XRD, and now we will look at some of the remaining techniques that are useful for the characterization of polymorphs.

So, the next technique is spectroscopic techniques, where we look at IR or Raman, as well as solid-state NMR. I will give you a brief overview of how these techniques are useful.

For example, let us consider a C-H...O hydrogen bond, which is participating in an interaction with a carbonyl group. Now, what happens is that when you have strong hydrogen bonding between the hydrogen and oxygen, the C=O bond tends to weaken.

The C=O bond tends to weaken because some of the electron density available on oxygen now participates in hydrogen bonding with the hydrogen atom due to its electrostatic character, and there is some polarization of the electron density from the C=O double bond towards the oxygen atom.

As a result, the carbonyl stretching frequency is now lowered, which explains the decrease in the stretching frequency of C=O. This process is referred to as a red shift, in the sense that the energy necessary to stretch the C=O bond is now reduced.

Now the C-H...O hydrogen bond is a very important signature in the IR spectrum of the compound that participates in this interaction. So, when we tend to have strong hydrogen bonding, there is a weakening of the stretching frequency of some functional groups, and that is reflected in the nature of the environment in which these interactions are present, with the corresponding changes in the IR spectra.

Raman is also complementary to IR, and Raman spectroscopy can also be performed; it has been observed that for both IR and Raman, the spectroscopic signature in the solid state for different polymorphs is going to be different.

By and large, the skeletal vibrations involving the C-C bond and C-H bonds remain the same, but it is the polar functional groups that participate in hydrogen bond formation

either as a donor or as an acceptor, which are affected by the hydrogen bonds, and the stretching frequencies of these donors and acceptors are affected.

Solid-state NMR is also another very important technique where we look at the local structure, particularly in the case of polymorphs, because the arrangement is different; the local environment is different, and this is reflected in the different spectroscopic properties; different NMR properties are affected because of the variations in the local structure.

And solid-state NMR is also very strongly indicative of the presence of disorder in the crystal structure. So, if you have, for example, a side chain that is present. So, you have an n-propyl side chain; the n-propyl side chain is continuously rotating in the crystal.

Because it is continuously rotating in the crystal, it tends to sample the independent conformations. So, you have something called side chain disorder.

So, this side chain disorder is very common in crystal structures, and because of this, the side chain tends to get populated into different orientations; this is indicative of disorder, and as a result, the spectroscopic signature of these carbon atoms in the disordered state is different compared to a propyl chain that is not rotating.

So, we can look at atomic disorder and site disorder in the crystal structure more closely by solid-state NMR, and in the case of polymorphs, the solid-state signature is going to be different. The NMR spectrum is going to be different. The next thing we would like to look at is the computational property. So, we can now evaluate the lattice energies.

And today there are many software programs that are available to compute the lattice energy of a solid. In this case, it is an organic solid, and in organic solids, the lattice energies tend to be lower compared to those of the inorganic solids.

The inorganic solids tend to have a very high magnitude of lattice energies. In comparison to organic solids, the range of lattice energies is primarily between 100 and 200 kJ/mole. This is the range of lattice energies for organic solids.

And in the case of polymorphs, the lattice energies will be different. However, the magnitude of the differences is going to be very very small. And the lattice energies can also be partitioned into the E (Coulombic) and E (dispersion) contributions; here, this is the electrostatic part, and this is the dispersion part.

So, we can have the Coulombic interactions, which also include the polarization, and this is collectively called the electrostatics term; this is the dispersion term. Together, these contribute to the overall lattice energy of an organic solid.

Then we can look at the physicochemical properties. For example, different polymorphs will have different solubilities. They will also have different IDRs; that is, the intrinsic dissolution rate will also be different for different polymorphs. IDR is actually the kinetic solubility, while the equilibrium solubility that we measure is actually an equilibrium quantity.

So, these kinds of experiments can also be done, and it has been observed that the initial rate of dissolution of a polymorph is different. Whereas, the solubility of different polymorphs is going to be different, the equilibrium solubility is not much affected; there is not much difference in the equilibrium solubility, and the differences are not significant.

However, the intrinsic dissolution rate can now be significantly different for different polymorphs. So, these are some of the very interesting ways in which we can characterize the polymorphs. Now let us look further into the thermodynamics of polymorph formation. The relative stability of a polymorph depends on its free energy G value.

We call this the G value, and the most stable polymorph is characterized by the lowest value of G. And so, under a particular set of conditions, that is, at a given temperature and pressure, the polymorph that has the lowest Gibbs free energy value is the most stable polymorph, and such a polymorph is referred to as the thermodynamic form.

Or, we can say the thermodynamic polymorph is characterized by the lowest value of G under a set of definite conditions of temperature and pressure. So, we refer to this as a thermodynamic form. This is also called the global minimum in the energy landscape.

Whereas the other polymorphs that are formed are called the kinetic polymorphs. These are also called metastable forms, and they essentially correspond to the local minima in the free energy landscape.

So, we have a free energy landscape for the different polymorphs; the one that is the local minimum is the kinetic polymorph. And the interesting thing here is that the kinetic polymorphs would always like to convert to the most thermodynamically stable polymorphs. And how fast this process takes place is something that is not defined.

It can take place within a few days to a few months. And sometimes the kinetic form has metastability associated with it. It is less stable compared to the thermodynamic polymorph.

However, it can still continue to exist for an indefinite period of time in the kinetic form, and it does not necessarily convert into the thermodynamic form unless you have

provided or given it the necessary activation energy to convert into the thermodynamic form.

Contrary to this, there are some systems and some compounds where the kinetic form tends to slowly convert over a given period of time into the thermodynamic form as well.

So, you can have a kinetic-to-thermodynamic conversion. In this regard, it is also very important to keep in mind that crystallization conditions play a very important role.

So, you can have kinetic conditions for crystallization. When I say kinetic conditions, I mean a fast rate of evaporation, and then you have kept it at room temperature.

You have utilized low boiling solvents, which tend to operate faster, and you have provided greater surface area for evaporation; that means the crystallization container has a much wider surface.

So, now, the rate of evaporation is greater. So, all these are the kinetic conditions of crystallization, and then we have the thermodynamic conditions of crystallization, where you have a slow rate of evaporation.

You use high-boiling solvents; you do the crystallization preferably at low temperatures, that is, less than 0 degrees centigrade. You can do it between, say, minus 5 to 0 degrees, or you can also do it between 0 to 4 degrees. The idea is to decrease the rate of evaporation of the solvent so that you are able to get the optimal size crystals.

So, these conditions of crystallization are very important, and it is also necessary to keep in mind that normally the formation of the solid state occurs by crystallization from either the solution, the melt of the compound, or from the vapor phase.

So, from all these states, you can have a compound that is dissolved in a particular solvent. When you evaporate the solvent from the solution, you will get the solid phase.

You can melt the compound, take it into a melt, and then allow the melt to crystallize back into the solid state, which can give the same polymorph or might not give the same polymorph, depending on the stability of the polymorphs.

You can also have an organic compound that has gone into the vapor phase, and now you can convert it back from the vapor into the solid state.

But our discussion today is primarily focused on thermodynamic considerations that involve the transition between polymorphs from solid to solid. So, we are only interested in understanding the solid, say S1 polymorph to S2 polymorph, and this is a pure phase transition that can occur between the two polymorphs S1 and S2 and S2 and S1.

So, we are more interested in the thermodynamics of understanding the interconversion between the polymorphs. As we said, you can have a kinetic form, you can have a thermodynamic form, and the kinetic form can convert to the thermodynamic form, or it can have a certain degree of metastability such that the kinetic phase can exist over a long period of time.

So, when you consider the relative stability of polymorphs, what is important is to consider the rate of transformation from one to the other.

Therefore, this rate of transformation is important, and the second thing is the time needed to attain equilibrium. The time needed to attain equilibrium defines the kinetic pathway, but the rate of transformation from one to the other defines the thermodynamic pathway.

So, the time necessary to attain equilibrium is the kinetic pathway, but the relative stability and the transformation depend upon the thermodynamic pathway. And here, something else plays a very important role. You can actually achieve the transformation of one polymorph to another using a solution-mediated process.

So there is a tendency that when you dissolve a particular polymorph in solution, it will convert into the more stable polymorph, assisted by the solution or the solvent in which you have dissolved the polymorph, and this solution-mediated process plays a very, very important role.

Now let us look at the relationship between the polymorphs in the solid state. So, to understand this, we will look at the Gibbs free energy, the quantity G, as a function of temperature, and here I have drawn the following for you. So, I am first considering a set of polymorphs: B, A, and C. This is my liquid region; this is my amorphous region.

The amorphous phase is characterized by the highest value of G, and the region where the solid line cuts the liquid phase is the melting point of C; this is the melting point of B, and this is the melting point of A.

So independently, we can see that C is the most stable form; it is characterized by the lowest value of G, and B and A are the metastable forms. The Gibbs free energy value of B is greater than that of A, greater than that of C, and that of the amorphous phase is going to be the highest. What is this point? This point is called a transition temperature: when polymorph A converts to B. So, you see here that when you start with polymorph A, this is the point at which the G values of B and A are equal to each other.

They intersect, and after this, the A phase is no longer stable. It is the B phase that is

stable, as characterized by the lower value of G. So, A converts to B at the transition temperature characterized by Tt.

So, if you have a transition between two polymorphs B and A, below the melting points of the respective polymorphs, in this case, respective polymorphs A and B, TmA and TmB are the melting points, and they actually cut the free energy isobar. This is the free energy isobar at a fixed pressure.

This is at a fixed pressure, so this is the free energy isobar. They intersect at A and B; at this point, the Gibbs free energy values are equal to each other. So, the delta G is equal to 0, and therefore there is a phase transition here.

The phase A converts into B, after which you see that there is a drop in the value of G. So, this is at the transition temperature; this happens before the melting.

So, these two polymorphs A and B are enantiotropes. We call this enantiotrophs, and the corresponding phase transition is called the enantiotropic phase transition. Please keep in mind that this is not enantiotropic, which is used for hydrogens in organic molecules to distinguish them in different environments, but this is an enantiotropic phase transition.

So, in this case, A and B are enantiotrophs. However, if you look at A and C or B and C, they all exist over the entire range of temperature before they melt at the melting points of TmB and TmC.

Therefore, B and C, or A and C, are monotrophs. So, what is a monotropic pair?

So, we have a monotropic pair, and that is such a pair in which a pair of polymorphs is classified as monotropic if one polymorph is more stable than the other at all temperatures below the melting point. And A and B are enantiotrophs because A converts into B after the phase transition temperature Tt.

After Tt, the B form is the most stable, while the A form is unstable. So, there is a thermodynamic tendency for the system to convert to the most stable form, which is characterized by the lower value of G, such that delta G is less than 0 overall for the process, okay.

So, I said delta G is less than 0 for the overall process; then the transformation will happen spontaneously, okay. So, what happens is that below Tt, A is more stable than B. Ga is less than Gb. So, A is stable, but after Tt, Gb is less than Ga.

So, B is stable, okay. A is the most stable polymorph. B is the least stable polymorph. So, there is a possibility of a spontaneous exothermic conversion of B to A. Below Tt, B can

undergo a spontaneous exothermic transition to A, and above Tt, A can undergo a spontaneous exothermic transition to B.

Now, why is this a very thermodynamically feasible process? Because below the transition temperature, if you start with the B polymorph.

And keep it, you know, for some time; it is still the unstable phase. It is the one that is a metastable phase. So, there is a possibility for it to convert to A by the release of excess Gibbs free energy, and therefore it will convert into A.

Similarly, after the phase transition temperature, it is the B form that is more stable; therefore, if you start with A, it will convert into B. So, these kinds of thermodynamic processes are well known to take place when you have polymorphs of different stabilities.

So, you can now distinguish from the Gibbs free energy diagram, which we call the GT diagrams. From the GT diagrams, you are now able to easily distinguish between whether a pair of polymorphs is enantiotropically related or monotropically related.

And for each particular polymorph, as it exists over a certain range of temperature and pressure, in the case of enantiotrophs, the stability order is reversed after the phase transition temperature.

So, before the phase transition temperature, we saw that A was stable. After the phase transition temperature, it is the B form that is more stable because there is a thermodynamic driving force associated with this process, characterized by a spontaneity in the conversion of A into B, indicated by delta G less than 0.

So, if delta G is less than 0, then that particular process is going to happen spontaneously, but if delta G is greater than 0, then that process is not going to take place. So, with this background in mind, we have now looked at different aspects of polymorphism.

And now we will look at some examples and a few case studies so that we can appreciate polymorphism better. So, now let us look at this first example where I will demonstrate polymorphism in an anti-implantation agent to you. This is an anti-implantation agent; this is a ketotetrahydroindole; there is a hydrogen here, as well as here, tetrahydro; and this is the indole derivative.

You can see this is the 5-membered indole ring; this is the nitrogen, this is the phenyl, and this is the fluorophenyl. So, this work dates back to 1980 when this particular compound was used as an anti-implantation agent, and now you can see that when crystallizations have been performed on this particular compound, we have been able to obtain two distinct morphologies: plates as well as blocks.

The plates were observed essentially in dichloromethane/hexane, and when the crystal structure was determined, it crystallized in the monoclinic crystal system.

The blocks, on the other hand, crystallized from a solution of ethanol and acetone, and these crystallized in the tetragonal crystal system. So right away you can see that there is a very clear signature of polymorphism: one is as plates, and another is as blocks.

It is also realized that crystallizing this compound under different conditions using different kinds of solvents mostly resulted in the plate form, but the block form was very rarely observed. On determining the crystal structure and examining the overall geometry of the molecule, as you can see, the C9-N1 bond and the C-C bond are very flexible, and you can see here that the torsions associated with these bonds in the two different forms are different.

In one case, this value N1-C9 is 58 degrees; in another case, it is 62 degrees, and simply the N1-C9-C10 value is 124.6, this is 118, and we can go to the C1-C15 again; it is different for the two polymorphs. So, this is essentially a signature of conformational polymorphism, where there are differences in conformation associated with the two molecules or the different molecules in the solid state.

 Now let us look at the packing. The packing is going to be very, very different. This is a plate form.In the plate form, you can see that there are C-H...O hydrogen bonds; these are the C-H...O hydrogen bonds that form chains.

And the chains you can see very clearly are along the c-axis. This is the c-axis, this is the b-axis, and the top is the a-axis. So, there is a nice connectivity of C-H...O=C hydrogen bonds; this involves the donor, and this involves the carbonyl group as an acceptor.

And another thing, you can see that these chains are parallel to each other. One chain is in this direction, and another chain is in a parallel direction. And therefore, this arrangement of molecules is non-centrosymmetric, which means there is no center of inversion in the crystal packing.

The arrangement of the molecules is non-centrosymmetric, forming these kinds of chains parallel to the c-axis. Contrary to the plate form, the block form, and the tetragonal form, you can see that the tetragonal form is a very interesting structure because, in the tetragonal form, you actually have a fourfold axis in the crystal structure, and here you can clearly see the fourfold axis, which relates these four molecules that are connected by F...F contact.

Now, this F....F contact that you see is not present in the other polymorph. In the other polymorph, the fluorines are far away from each other, but in this one, the fluorines come

together with respect to each other. They come close to each other and form this kind of cyclic tetramer.

And in addition to that, you can also see that there are C-H...π dimers here. And there is one dimer here, another dimer here, and these dimers are connected by the C-H...O hydrogen bonds.

So, you have F...F contacts, which bring 4 molecules close to each other, and then you have dimers that are connected by C-H...O. So, we can see this more clearly on the right-hand side where, in the plate form, you have got the C-H...pi chains. This is C-H, and this is the pi ring that is pointing towards the center of gravity of the 5-membered indole ring.

So, you have a C-H...π contact. This forms a linear C-H...π chain, whereas in the other case, you have a C-H...π dimer. It is interesting to see that these C-H...π interactions are quite short and these hydrogens are quite activated because of the presence of the carbonyl group.

So, these kinds of activated C-H bonds can participate in the formation of C-H...pi contacts, involving a donor with an appropriate acceptor, because the indole ring is an aromatic system. It has a lot of pi electron density.

So, this facilitates the formation of C-H...π, and the types of C-H...π in the two polymorphs are very different.

In one case, they form chains. In the other case, we have C-H...π, which forms dimers. Obviously, they involve different types of hydrogen, but the arrangement of the molecules is different.

So, with this, we come to the end of this lecture. Now, in the next lecture, we will look at a couple more examples of polymorphism and then continue our discussion further.

Thank you.