Fundamentals and Applications of Supramolecular Chemistry

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Week 05
Lecture 26

W6L26_Polymorphism in Molecular Crystals

So, hello, everybody. Now, let us start this week with a discussion on different topics, particularly focusing on a very important topic of industrial relevance, which is related to the field of crystal engineering, known as polymorphism.

So, we are going to look at different aspects of polymorphism. What is polymorphism? Why does polymorphism occur? How do we control polymorphisms? What are the regulatory aspects of polymorphism?

Because polymorphism is a very important phenomenon in the drug industry, the agrochemical industry, and different fields of material science and engineering as well. And we are then going to take up some specific case studies of polymorphism, and then we are going to look at the next aspect, which is co-crystallization: why co-crystallization is important, what the purpose of doing co-crystallization experiments in the industry is, and some other relevant applications. So, to start with, let us go to the definition.

So, today we are going to discuss polymorphism and co-crystallization in the next few lectures. So, polymorphism is a phenomenon in which a given chemical substance can exist in multiple forms. Therefore, you can have any compound in nature.

You can have an organic compound, an organometallic compound, an inorganic complex, a peptide, an amino acid, a protein, or a particular chemical substance that exists in at least two distinct or different internal arrangements in the crystal, which is referred to as polymorphism.

So, this is a very, very important phenomenon. This is an observation that happens in nature in which a given crystalline substance exists in at least two distinct or different internal arrangements in the crystal.

So, you have a chemical substance, and when this particular chemical substance crystallizes in a given crystal structure, it is characterized by at least two distinct or different internal arrangements of that substance inside the crystal.

And the word polymorphism comes from the Greek word, which is called poly, meaning many, and morph, which refers to the form. So, we also refer to polymorphism as the existence of different forms of chemical substances.

So, it also refers to the existence of different crystalline forms of a substance, and there are different nomenclatures. We can say form alpha, beta, gamma, or we can say form 1, 2, 3, and so on and so forth.

So, these are the different crystalline forms of a given substance, and this is referred to as polymorphism; morph essentially refers to the form, and it is also characterized by the shape or habit of the crystal. So, the first indication that you possibly have polymorphism is that you take any particular substance and crystallize it under different conditions, and then you will see the existence of different morphologies.

So, the existence of different types of crystals with different morphologies, that is, of different shapes and habits, is a possible indication of polymorphism.

So, this is the first signature that you possibly have for polymorphism, and then the idea is to take these different morphologies. Now, for example, we can have a compound that crystallizes as needles; it can also crystallize as prisms, and it can also crystallize as blocks.

Okay, and then it can also crystallize as thick plates, and depending on the thickness, the plates can also be thin, and sometimes we can have an irregular shape as well. So, these refer to the different morphologies, that is, different crystal shapes and habits, and these are indicative of polymorphism.

The next way to check for polymorphism is to look at the technique of single crystal X-ray diffraction, where you determine the unit cell, and the determination of the unit cell tells you whether you have polymorphism or not.

So, if you get different lattice parameters, this is a very strong indication of polymorphism. It is also possible that you can have different morphologies, but when you do the unit cell check, you do not get any change in lattice parameters, i.e., no change in lattice parameters takes place.

So, because there is no change in lattice parameters, it is not indicative of polymorphism. It refers to the fact that the internal structure is possibly, and I am using the word possibly here, similar; the chances are very, very high that the internal arrangement of these crystals is similar.

But there are also very rare cases where you can have the same unit cell, but the molecules may have arranged in different ways inside the crystal structure. But for that,

you will have to collect the full diffraction data, determine the structure, and then conclude whether polymorphism is present or not.

And the reverse is also possible: you can have different unit cells even when the morphology is similar. Now, how do we overcome this problem? So, the idea is that once you have done crystallization and you have the crystallization container in which you have different kinds of crystals that look similar in terms of shape, size, and morphology, the idea is to randomly pick good quality, at least 7 to 8 crystals and check the unit cells.

Chances are that one or two of these will correspond to a different unit cell, and then it is an indication that the compound that has crystallized has two polymorphs. Now, this is a random sampling, and this is a statistical process where you at least screen a minimum number of crystals so that you get a possible indication of polymorphism by the existence of different unit cells.

So, it all depends on the kind of efforts you are willing to put into investigating your batch of crystals. In most cases, the chemists are more interested in knowing the molecular structure only. They are not really interested in the solid-state diversity or the aspects of polymorphism of that particular compound.

But interestingly, it is the solid-state diversity that renders polymorphism very interesting, and the properties that you get from this phenomenon are also expected to be different; therefore, this is a very, very interesting area of investigation and further research.

So, now both things are possible: you can have the same unit cell for different morphologies, and you can have different unit cells for the same morphology, and that will allow you to establish whether you have polymorphism or not. Now, what are some very important features of polymorphs?

So, to start with, we said that they have different crystal structures, which means that the arrangement of atoms, ions, or molecules is different, and the implications of this are that the physical properties and, in some cases, the chemical properties of the polymorphs are different.

So, to start with, we can say, for example, the density of the solid, the melting point, solubility, etc., lattice energy; these are some of the properties that are going to be different for different polymorphs.

So, these are some of the most important characteristics of polymorphs: it is a solid-state phenomenon; definitely, the occurrence of polymorphism and the relevance of polymorphism are only in the solid state. Because once the compound has dissolved in a particular solvent, either in an aqueous medium or in other polar or non-polar solvents,

the molecules largely exist in the solvated state, where they exist as monomers and can exhibit their characteristic chemical reactivity.

But some of the most important properties are, as I mentioned to you, density, melting point, solubility, and lattice energy. These are going to be very, very different. This also has implications in terms of applications.

So, this has implications for the applications of polymorphism in the drug industry, the dyes and pigments industry, agrochemicals, and electronic materials. For example, we have optoelectronic materials, which also affect the thermal and electrical conductivity of materials, and then you can also have energetic materials, which find applications in the design and synthesis of rocket propellants, fuels, and so on.

So, there are a large number of industries that are affected by this phenomenon of polymorphism, and therefore this has very important significance in the pharmaceutical industry.

And as I mentioned, all kinds of substances, whether they are of organic or inorganic origin, do exhibit polymorphism, and the literature is now populated with a large number of studies involving a large number of molecules now exhibiting this phenomenon of polymorphism. Now, when was polymorphism discovered? So, it was first discovered by Eilhardt Mitscherlich.

So, you know we have all heard of the Mitscherlich Law of Isomorphism. So, it was Eilhardt Mitscherlich, in 1820, who identified the different crystal structures of calcium carbonate, corresponding to the calcite and aragonite phases.

And he also looked at phosphates; he looked at arsenates as well. So, he proposed different crystal structures and different polymorphic phases for these kinds of inorganic substances.

Then it was in 1832 that F. Wohler and J. Liebig discovered polymorphism in benzamide, and then in 1938 J. M. Robertson and A. Ubbelohde discovered dimers in resorcinol, that is, 1,3-dihydroxybenzene. So, these are some of the very early discoveries in the field of polymorphism.

Some of the most relevant ones started with Mitscherlich's benzamide. Benzamide is a very simple substance, but polymorphism was discovered way back in 1832, and in the recent past few decades, people have again looked at benzamides; then in 1938, Robertson and Ubbelohde discovered polymorphism in the case of resorcinol.

And today there are some other common substances. For example, acetylcoumarin, which exists as polymorphs, is a thiophene derivative that exhibits color polymorphism and is

known to be a carbonitrile derivative; it has a cyano group, a methyl group, and one of the N-H groups is replaced by a nitrophenyl group. So, the thiophene derivative exhibits color polymorphism.

And there are nice, different colors you get from these crystals, along with different morphologies, and this is one of the compounds that has been characterized for the largest number of polymorphs in the database.

So, the database we have is called the Cambridge Structural Database, where we have a large number of crystal structures reported to date, and there, for this particular thiophene derivative, the largest number of polymorphs has been reported.

So, now the next thing we would like to learn about is polymorphism. So, this is the initial background on polymorphism. Now, let us go and explore something more at the molecular level regarding the phenomena of polymorphism.

So, the phenomena of polymorphism are broadly classified into three categories: types of polymorphism. Number one, we have conformational polymorphism; number two, we have packing polymorphism; number three, we have pseudo polymorphism.

In polymorphism, there are also two additional phenomena that have been observed, which we refer to as concomitant polymorphism and disappearing polymorphism. So, these are two very, very interesting phenomena that also exist. Now, we will address each of these one by one.

First, let us look at the other observations with respect to polymorphism. So, what happens is that during the process of crystallization of a compound, we will explore the aspects of crystallization in more detail in the lectures later on this week.

But as of now, when you are trying to crystallize a compound under a particular set of crystallization conditions. For example, in the combination of solvents used with different techniques and at different temperatures. For example, you can do it at room temperature, or you can do a low-temperature crystallization.

This space, which you are giving to the compound to sample and explore before it crystallizes, is referred to as the domain of crystallization. And it can so happen that this domain for crystallization, which we also call the occurrence domain, can overlap for two different sets of polymorphs.

So, polymorphs have another important property: the lattice energy is different, and the differences in lattice energy are very small, between 1 to 3 to 4 kilocalories per mole. So,

you can still have, in principle, a theoretically infinite number of arrangements possible for a given compound.

So, you can crystallize a compound where you can actually sample; infinite possibilities exist—an infinite number of arrangements—but what you realize experimentally is only a few of these arrangements, which correspond to the Gibbs free energy minima; these correspond primarily to the thermodynamic minima.

You can also obtain the kinetic minima where the kinetic crystallization conditions are satisfied, allowing you to acquire kinetic polymorphs.

So, basically, what is happening is that it is an overlap of this crystallization domain in which two different polymorphs with two different arrangements, but having almost similar lattice synergies, can crystallize out simultaneously, and that phenomenon is referred to as concomitant polymorphism.

So, in the case of concomitant polymorphism, the polymorphs are obtained under identical conditions of crystallization in the same crystallization container. So, the same crystallization container will have both of these particular polymorphs, and as I mentioned to you, there is an overlap between the occurrence domains.

That is the space given for the compound to crystallize under a given set of conditions, referred to as the crystallization domain, and when these domains overlap, the chances of the existence of concomitant polymorphism occur.

So, for example, you can take a beaker and say that you have put in a particular solvent, or a mixture of solvents, and you have taken the compound of interest to crystallize; you can say that you can have needles along the faces.

So, you can have a needle sticking to the side walls of the beaker, and the base, the bottom, which is the circular area, can have plates. Because you see that the solvent is slowly evaporating and the compound of interest is crystallizing out.

So, you have different points of contact of the crystallizing molecule with the surfaces; that is, you can have the base surface, and you can also have the side surfaces. It is very common that you might get needles on the side walls, and you will get these plates. Sometimes you can get both plates and needles on the circular face.

So, the first morphological indication of polymorphism is that you have these two distinct morphologies: you have the plates, you have the needles, and therefore, this is indicative of polymorphism.

Now the idea is to remove these crystals from the crystallizing medium or to allow the solvent to evaporate and then take out these crystals, mount them, check the unit cell, and verify whether they possibly exist as polymers or not.

So, this is the ratio in which you get the ratio of obtaining 2 polymorphs, and that depends upon the crystallization conditions, the amount of the solute to start with, the amount of the compound you have taken to crystallize, the size of the container, or the volume of the container you have considered, and then the shape of the container.

For example, you can do it in these 5 ml beakers, but you can also do it in glass vials or a small conical flask. You can do it in NMR tubes. And there are different apparatuses, different glassware that is available to crystallize these compounds, and these provide you with the necessary platform, the surface of the container, and how much you have exposed it to the environment, what the rate of evaporation of the solvent is, and so on and so forth to determine the possible existence of concomitant polymorphs.

And during the process of crystallization, we actually close the top with parafilm, and we make holes in it; we make perforations in these. So that the solvent evaporates very slowly and good-sized crystals of nice quality can be obtained for doing the diffraction experiments.

So, this field of crystallization is itself an independent research area, but when you do these crystallization experiments, the possibility of getting concomitant polymorphs does exist, and this observation involves seeing different kinds of morphology. Also, sometimes you will see that you have different morphologies and different colors.

So, you will see one is orange, one is light yellow, one is deep red, and one is light orange. You can also get different kinds of colors along with the different morphologies. Sometimes you can get similar morphologies but with different colors.

So, that is also indicative of color polymorphism and the possibility of having concomitant polymorphs in the same crystallization container. Then comes the phenomenon, a very important phenomenon of disappearing polymorphs wherein, say you have crystallized a particular compound, you got one particular polymorph.

Now, the next time you try to crystallize that particular compound, the initially obtained polymorph does not crystallize. You always get a new polymorph, and no matter what you do, if you change the conditions of crystallization, you screen it very extensively using different methods.

You take polar solvents, polar non-polar solvent combinations, or non-polar solvents; you change the temperature and the crystallization containers. Sometimes you even change the laboratory where you are trying to crystallize that particular compound so that you do

not have any possible contamination in the air that can possibly interfere with the formation of the initially obtained form.

So this is a very, very important exercise in the pharmaceutical industry that people would always like to reproduce the initially obtained form.

So, the initially obtained form, which is no longer crystallizing, is possibly the kinetic form, which would have been formed at a faster rate, but is now very difficult to control; therefore, what you are now obtaining when you crystallize it regularly is the thermodynamic form.

So, you are not able to reproduce the kinetic form; whenever you try to crystallize, you are only getting the thermodynamic form. So, the ability to isolate and characterize the kinetic form becomes extremely difficult, and this has severe implications in the pharmaceutical industry.

These are some of the things we will also explore later because the kinetic form is the one that has the higher Gibbs free energy.

Therefore, it is more readily available in terms of bioavailability; it can have a higher dissolution, and therefore, the overall pharmacological property of that particular polymorph can be compromised.

If you do not have the kinetic form but have the thermodynamic form, it is because the latter is much more stable and might have reduced solubility compared to the kinetic form. So, it is very important to be able to get the desired kinetic form, but if you do not get it, then that particular form becomes the disappearing polymorph.

Some of this group of scientists believes that there is nothing called disappearing polymorph. It is just that the exact conditions of crystallization and its exact means mean you have everything to worry about. Even the room in which you are trying to crystallize that particular form is important.

Most of the time when we do crystallization, we will have dust particles, and we will have a slightly dirty room in which we are doing the crystallizations. And now, if you go to a new lab where the dust is less and you do not have suspended particulate matter, then maybe crystallization might become difficult, and what you might get is a completely different polymorph compared to what you would have gotten in an otherwise unclean or relatively old lab.

So, because you are not able to exactly reproduce the conditions of crystallization, getting the disappearing form again becomes very, very difficult. And there have been some case studies where they are trying to obtain it. It has been very important, as I told you; this

has implications for the pharmaceutical industry.

Now, let us go to the types of polymorphism. So, we looked at first at conformational polymorphism. Now, in the case of conformational polymorphism, we have a given molecule that has been crystallized, and it is observed after the determination of the crystal structure. So, we will discuss the different techniques of crystallization of polymorphs after some time. But once you have determined the structure of the two polymorphs, we will now see the conformation of the molecule. Differences in the molecular conformation in the solid-state lead to conformational polymorphism.

I will write it as CP. So, differences in molecular conformation in the solid state can give rise to this particular conformational polymorphism. So, you have a molecule that has been dissolved in a solution, and there are different degrees of freedom associated with the different rotatable bonds in the molecule.

When you are crystallizing this particular molecule, it is just one of those conformations that has been crystallized, but the other conformations also exist. So, if you now change the conditions of crystallization, the chances are that you will be able to crystallize the same molecule with a different conformation, and the relationship between these two structures is that they exhibit conformational polymorphism.

Essentially, the challenge involved here is that there is a competition between the very subtle non-bonded interactions that try to lock a given conformation and the intermolecular interactions between the molecules that try to change the conformation of the molecule.

So, these events take place parallelly, and it is the competition between this event, that is, the ability to lock the molecule in a given conformation and freeze it out or to make it flexible and allow for different intermolecular interactions to exist between the different molecules, thereby adapting a different conformation.

And it is these two factors, the subtle balance between these two factors, which leads to the discovery of conformational polymorphism. So, essentially, we have got a rotatable bond which is present that essentially gives rise to this phenomenon.

Now, for example, as I was telling you about the thiophene derivative, let us look at the structure of the thiophene derivative. You have this cyano-substituted carbon nitrile and methyl, and then here you have the NH.

So, here you have the nitro compound. So, this is the thiophene derivative, and it exhibits flexibility in torsion around this particular bond. Keep in mind that this particular N-H is involved in an intramolecular hydrogen bond.

So, this particular conformation is locked, but there is flexibility about the CN bond that leads to conformational polymorphism, and this also exists in different colors, like red, orange, yellow, light red, deep orange, deep yellow, and that is why this is also referred to as ROY; its code name is actually ROY because it exhibits color polymorphism. Another very interesting compound exhibits conformation polymorphism.

I am drawing the structure here. It is this particular compound that has rotatable bonds, and therefore, has the ability to exhibit conformation polymorphism. In the second case, we have packing polymorphism, where you will essentially have a molecule that has the same conformation in different crystalline arrangements, but the arrangement of the molecules, due to the presence of different intermolecular interactions that comes from the concept of synthons, as we discussed in crystal engineering, is different.

So, it is the arrangement of the primary synthon blocks or the primary synthon units in different ways in the crystal structure that gives rise to the phenomenon of packing polymorphism.

And in the third case, we have pseudo polymorphism, where the crystal structure includes solvents. For example, water, chloroform, acetone, methanol, ethanol, isopropanol, and so on.

So, you have a compound that is crystallized without the solvent, which is an anhydrous form, and you also have the compound that is crystallized with the solvent, which is held by strong hydrogen bonding.

So, this is also referred to as the solvatomorph of the parent drug. It is not strictly polymorphism because you have another chemical entity, the solvent, which is included in the crystal structure, and therefore, this is referred to as pseudopolymorphism.

However, pseudopolymorphism, particularly the hydrates, is extremely important in the pharmaceutical industry because they exhibit enhanced properties, for example, enhanced solubility because of the presence of water in them.

So, that is why these pseudopolymorphs, particularly the hydrates, are very relevant because of their enhanced properties and important relevance in the pharmaceutical industry.

So, with this, we have looked at the types of polymorphs, and in the next lecture, we will continue further into the field of polymorphism.