Fundamentals and Applications of Supramolecular Chemistry

Deepak Chopra
Department of Chemistry
IISER Bhopal

Week 07
Lecture 31

W7L31_Understand Nucleation and Growth processes in Crystallization

So, hello everybody, today we are going to start a new topic of discussion in which we will look at the fundamentals of the nucleation of crystallization. We have already looked at polymorphism in the last lectures, the fact that polymorphism is a very important area of interest.

We have also looked at the existence of enantiotropic and monotropic polymorphs, and in the case of enantiotropic polymorphs, we know that there is a solid-to-solid phase transition before melting, whereas in the case of monotropic polymorphs, each polymorph has its independent existence at temperatures below the melting point of one form.

Now, we are going to look at the fundamentals of nucleation, where we have a compound of interest that we would like to crystallize. And it is to be realized that the process of crystallization essentially involves a large number of molecules that are actually floating around in solution. And we see that there are concentration fluctuations in the system; there are also thermal fluctuations in the system.

So the molecules are randomly moving around in different directions, and they are also colliding with each other. And this is now a process by which we would like to facilitate crystallization using different techniques.

One such technique is lowering the temperature of the solution, which will allow the kinetic motion to be reduced so that the molecules can come close to each other, allowing intermolecular interactions to exist between them. And they can now start creating a small cluster of molecules, and then this cluster of molecules should tend to get ordered, and finally, they will form the crystal.

So, there are different steps here. First, there is the formation of a cluster that has the required number of molecules to create the essential nuclei, and these nuclei will further grow, which will then give rise to the crystal. And to achieve this crystal formation, there is a condition that is required, which is known as supersaturation. If we have undersaturated solutions, then crystallization does not proceed. If we have a very high degree of saturation, then there is precipitation of the compound.

So, we need to actually control or modulate the levels of saturation. Preferably, have low levels of supersaturation so that we can facilitate the process of crystallization. Now this can be understood very clearly by looking at this particular diagram where we have concentration as a function of temperature. We have this as one zone and we have another zone; this is the metastable zone width, this is the equilibrium solubility curve, this is the unsaturated solution which is stable, the supersaturated solution which is metastable, and this is the labile solution which is unstable. But in the case of the unsaturated solution, the solubility is less than the equilibrium thermodynamic solubility.

So, the goal then is to increase the degree of supersaturation such that the concentration of the solute exceeds the equilibrium solubility of the system, allowing it to enter the supersaturated region.

So now we are going to lower the temperature of the system. By lowering the temperature of the system, we know that crystallization will not take place in an unsaturated solution. It is only when we reach the supersaturated region or the metastable region that the process of crystallization can proceed.

So, the first step is to create an unsaturated solution, and then the second step is to increase the degree of saturation, such that the concentration of the solute is greater than the equilibrium solubility, that is, supersaturated.

And for this, there are different methods. For example, we can lower the temperature of the system, evaporate the solvent, because that increases the effective concentration of the solute, or we can add an anti-solvent, which is a miscible solvent but in which the solute has significantly less solubility.

So, the anti-solvent addition can take care of the process of increasing the degree of saturation, and the moment you enter the supersaturated region from the unsaturated region, it is not that crystallization will immediately proceed. There is a hysteresis or a time lag associated with the process of nucleation of the crystal. And the nucleation of the crystal is supposed to give me small-sized clusters, which are also referred to as nucleation aggregates.

And it is these nucleation aggregates that are actually going to grow further and give you the crystal. And once nucleation happens, and only when nucleation has reached a stage where the critical size of the nucleus has been reached, after which the growth mechanism takes place, below the critical size, growth will not occur, and there is also a tendency for the molecules in the nucleation cluster to re-dissolve back into the bulk solution.

So, you have the possibilities of the formation of the nucleus and also the dissolution of the molecules or the particles back into the solution, and these processes are controlled by local fluctuations in the concentration and also fluctuations in the thermal energy of the system.

So, the internal dynamics are extremely important in controlling the processes of nucleation, and achieving the critical size of the nucleus is extremely important; before that, no new growth will take place. So, this process of crystallization upon reaching the supersaturated region does not immediately take place, and there is a hysteresis, or time lag, associated with nucleation.

Hence, the supersaturated solution can exist in a metastable state in which it does not spontaneously crystallize. So now how do we achieve crystallization, then? Because we have now reached the metastable zone, the supersaturated zone, and the range over which this metastable zone exists is given by this particular arrow.

Now, further, if you lower the temperature, you can see that the system moves into the labile zone. So once the system moves into the labile zone, it becomes an unstable zone, and it is at this stage that the process of nucleation and crystallization begins. So now increasing the saturation further, the system moves into the labile zone which is also the unstable zone.

And it is here that the process of primary nucleation and subsequent crystallization begins. So, once you reach the labile zone, or I would say extremely high levels of supersaturation, that is when the process of primary nucleation and crystallization begins.

So, the key to getting good quality crystals in a crystallization experiment is to actually approach the labile zone first, as slowly as possible. So, you have limited nucleation that takes place. So, it is always recommended that we do not want a large number of small-sized nuclei to grow.

Rather, what we would want is a very controlled process, where only a few nuclei grow, and then these nuclei become bigger and bigger, and the crystallization proceeds in a facile manner. So, sometimes what we do is add seeds to the solution when it is in a supersaturated state, and that can possibly initiate the process of nucleation and growth.

But that is referred to as a heteronucleation process where you have added the seed, in comparison to that of a homogeneous solution where crystallization is taking place from the bulk solution. So, we have homogeneous as well as heterogeneous nucleation. We are not considering the addition of external seeds or any hetero-nucleation processes, but we would like to grow good quality crystals via the process of homogeneous nucleation.

The key is to approach the labile zone as slowly as possible. This results in the formation of a small number of nuclei, which can now possibly further grow into larger-sized crystals. So, as this process further progresses, once you have initiated the formation of a small number of nuclei, we can say that the crystallization proceeds, and the concentration of the solute decreases.

What happens? The system moves away from the labile zone, and subsequent growth takes place on relatively few nuclei that are produced. So, this we have now realized is the essence or the basis of understanding the process of nucleation, controlling nucleation, and the subsequent growth processes.

And once you have the required number of these small nuclei, then large crystals can be produced, and once large crystals are obtained, this process will continue until the process of crystallization is complete. Say you have added a solvent; the complete evaporation of the solvent takes place, and now you can take these crystals to do further experiments.

So, what we would like to do is control the number of small-sized nuclei that are formed and not have uncontrolled nucleation where we have a large number of small-sized crystals. So, the important thing is to have a relatively low degree of supersaturation; this is what is essential. A relatively low degree of supersaturation is necessary because this results in high-quality crystals, and these crystals will also have reduced defects.

So, we do not find very high levels of supersaturation because precipitation can take place, and the necessary crystallinity that is required will not be present in the crystals. You know you cannot have undersaturated solutions because then the process of nucleation does not start.

What you actually need is a metastable zone that corresponds to tuning the levels of supersaturation such that the moment you cross the supersaturation region and reach the labile region, the crystallization process begins. It is controlled; the process of formation of nuclei is slow, and subsequent growth can also take place. So, what is very important is the formation of a nucleus of the right size.

Now, in this regard, it has to be kept in mind that when the process of nucleation takes place, there is a new interface being created because you have a solution until now, but now you are creating a solid.

So, there is a solid-liquid interface. And the nucleation will only be a facile process when the free energy necessary to form the surface overcomes the energy spent in creating the surface. So, overall we would like to form the crystal. So, there is a free energy change associated with the creation of a large amount of matter; that is the volume.

So, if the free energy of creation of this bulk crystalline material exceeds the energy that is necessary to create the solid-liquid interface, then this process of nucleation will happen in a facile way. So, we need to write down this statement. This is a very important statement because there are two important factors here.

You need to create a new solid-solution interface, and the free energy available to form this interface depends on the supersaturation of the solution, as we have already seen. And the nuclei will exist if the free energy required to create the interface, or the penalty that must be paid in terms of the free energy to create the interface, is recovered from the free energy gain in forming the bulk crystalline material.

The free energy, which is available to form this interface, that is the solid-solution interface, depends on the super saturation, and the nuclei will exist if the free energy required to create the interface is recovered from the free energy gain in forming the bulk crystalline material.

So, in this regard, there are different models that have been proposed: one is the classical nucleation theory, and the other is the non-classical nucleation theory. So, in the case of classical nucleation theory, we have these ions, atoms, or molecules that are floating in solution. And what happens is that they come close to each other to form a nucleus. This is an ordered array, so this is the nucleus of the right size, and now this nucleus can grow in three different directions and can give you the crystal.

This is referred to as classical nucleation theory. Whereas in the non-classical nucleation theory, it actually follows a two-step pathway. Wherein, we have obtained the first random collection of particles, which actually contain the atoms or molecules that are floating around in the solution.

Initially, they form a dense nanocluster, and from this nanocluster, what emerges is a nucleus. So, we see here that we have this nucleus, which is formed out of this nanocluster, which is actually a dense nanocluster, and once the nuclei have been formed, that is, the process of nucleation has taken place, then the growth can happen, leading to the formation of the crystal of the desired morphology, shape, and size.

So, there are two steps. First, there is a process where these clusters actually come really close to each other and form a dense aggregate, and from this dense aggregate, the nuclei are generated, which can now further grow to give you the final crystal. So, there are two steps. This is the first step. We use the formation of dense nanoclusters, and the second is the formation of nuclei from the dense nanoclusters, followed by the growth mechanism to give you the crystal.

And there are now many experimental techniques that have been developed to validate the non-classical nucleation theory, which is more of a non-equilibrium process in comparison to the classical nucleation theory, which is more of an equilibrium process.

And it has also been observed, using different microscopic techniques, that the formation of polymorphs actually happens from this aggregation of molecules to form the dense nanocluster, and then this dense nanocluster can now form different kinds of nucleation aggregates, which can actually crystallize as different polymorphs, say P1 and P2.

And this is actually the reason for the occurrence of concomitant polymorphism, because now in the same crystallization container, we have two different sets of nuclei that can grow in different ways, giving you a set of almost near equi-energetic polymorphs P1 and P2. And sometimes it is also observed that these dense nanoclusters, which are formed, can also disaggregate in solution.

They do not aggregate; there are concentration fluctuations, where this dense nanocluster can again go back into the solution because of the thermal fluctuations and the concentration fluctuations. Then they can reassemble together, maybe in a different way, and that can crystallize to give you the other polymorph.

So, sometimes what happens is that there are concentration fluctuations and temperature fluctuations. Now, these dense aggregates or the initial set of nuclei that are formed can again redissolve back into the solution, and they can re-aggregate to form another crystal that can convert into a different phase.

So, there are a lot of interesting things that happen, and it is not necessarily the initially formed cluster or the aggregate that will give rise to a particular structure. These dynamical processes are continuously happening in the solution as well. And this particular thing has been observed in the case of one particular example.

The two-step nucleation model has been investigated in the crystallization of the olanzapine drug, and what has been shown is that you start with the crystals. You start with these kinds of crystalline surfaces, and you will see that there is the formation of nano droplets that are concentrated at the steps.

So, you have these nano droplets that are concentrated at the steps which correspond to the surface of the crystalline form of olanzapine. Now, it is these nano droplets that are initially formed which now get converted into the corresponding crystalline form.

So, it is not that the entire solution simultaneously crystallizes and forms the three-dimensional crystal, but it is actually in the process where you have the formation of these dense aggregates or dense nanoclusters, which are reflected in these nano

droplets that are happening at the steps.

Because it is a step region where further growth has to take place, these nanoclusters come and get deposited, and further growth can now occur. And these droplets will now lead to the final crystal structure of olanzapine, which is the OZPN DD, and that is the dihydrate form of olanzapine.

So, we are able to get this particular structure and this we are able to do because we are starting with OZPN-Form I lattice. So, we have the OZPN-Form I lattice now, and it converts into the dihydrate OZPN DD. However, if you actually stir the solution, then these droplets will go into the solution and crystallize as the kinetic dihydrate of OZPN, which we call OZPN DB.

So, we started with Form-I. We can either get the dihydrate, one particular polymorph because of the crystallization using the two-step nucleation model, or we can stir the solution, where the droplets now go into the bulk and then crystallize as a kinetic dihydrate of OZPN DB.

So, this has been possible to study using AFM, which is atomic force microscopy. Then people have also used electron microscopy to obtain evidence for the formation of an amorphous phase.

That is, we call this the pre-nucleation aggregate, something that is not even nucleated, but there is some evidence of the formation of some kind of clustering of particles, which do not have the necessary ordering but are essentially amorphous in nature. And this has been observed to be an indication of an amorphous phase during the process of crystallization of organic compounds.

So, microscopic techniques have been very useful to understand and validate the two-step nucleation model. I mentioned to you the different factors. So, we have a free energy requirement for the creation of the interface, which is a solid-solution interface, and we also have the free energy gain that accompanies the formation of a large volume of crystalline material. A competition between these two factors is what drives the process of nucleation and subsequent growth. And we will look into some of these processes in more detail in the next class.