Fundamentals and Applications of Supramolecular Chemistry

Deepak Chopra

Department of Chemistry

IISER Bhopal

Week 05

Lecture 24

W5L24_Crystal Engineering, Chemical Reaction in Solids

So, hello everybody. Now, let us continue our discussion on the next topic. Today, we will be discussing a very fascinating and exciting area that is termed crystal engineering.

And this area has been developed by Professor Gautam Radhakrishnan Desiraju, who is currently a professor in the Department of Solid State and Structural Chemistry Unit, SSCU at IISc Bengaluru.

Prior to this, he was in the Department of Chemistry at the University of Hyderabad, where he developed this very interesting area of crystal engineering. And the idea was to extend the concepts of hydrogen bonding to understand the formation of crystals.

And the next very important contribution was whether we could utilize the understanding of hydrogen bonds between the different functional groups in the construction of the crystal structure, and this crystal structure would have different applications in terms of various physical and chemical properties.

So, this is what he termed crystal engineering, which is the understanding of intermolecular interactions. For example, hydrogen bonds, halogen bonds, and pi-pi stacking in the context of crystal packing, and then utilizing this knowledge in the prediction of crystal structures of different compounds.

So first is the understanding of intermolecular interactions, for example, hydrogen bonds and halogen bonds, in the context of crystal packing, which gives the desired crystal structure and the desired connectivity between the molecules to form solids having certain physical and chemical properties, and then utilizing this knowledge to predict unknown crystal structures of different kinds of compounds.

Now this exercise is referred to as crystal structure prediction. So, predicting a crystal structure is also very important, and the knowledge obtained from these intermolecular interactions can be utilized in the prediction of crystal structures.

Now, before we go into the details of crystal engineering, let us compare molecular chemistry and crystal engineering.

So, in molecular chemistry, it is important to synthesize new molecules by mixing, say, A and B, or reacting A plus B to give new compounds C, where this process involves bond making and bond breaking. Whereas, in the case of crystal engineering, it is the synthesis of the crystal by the process of crystallization.

So, you have a compound, say A, which is a solid at room temperature, and it is dissolved in a particular solvent. Then, in the liquid, you allow it to crystallize. Now, n molecules of A can crystallize to form the crystal.

So, you have a particular organic compound that you have prepared; the compound can be a solid or a liquid at room temperature, and you would like to crystallize it now. Obviously, a liquid compound will not give you a stable crystal; it will only be stable at low temperatures.

However, a compound can be dissolved in a particular solvent from which you can crystallize out the compound, and this is actually referred to as a supramolecular reaction.

This is a supramolecular reaction in which there is no process of bond breaking and bond making involved, but what is essentially involved is the formation of hydrogen bonds between the molecular entities to give rise to this periodic arrangement of molecules that we call a crystal.

So, when it comes to molecular chemistry, the individual atoms are very important. We talk about the atoms and the reactivity profiles of the atoms, but when it comes to crystal engineering, it is actually the entire molecule that participates in crystal formation. Here it is that these are the specific atoms that undergo processes of bond making and bond breaking.

In the case of molecular chemistry, we are making and breaking covalent bonds primarily, but in the case of crystal engineering, we are working with intermolecular non-covalent bonds. In the case of molecular chemistry, what is important to us as a whole is the reactivity profile of the molecule, and here it is the crystal.

So, the net process in a molecular reaction is to form new molecules, and here it is to form new crystals. In molecular chemistry, there exists a concept of synthon such that you can actually have a target molecule, and you can actually break down this target molecule into specific fragments using the idea of the retrosynthetic approach or the disconnection approach, where the individual fragments have been obtained by a logical dissection or trisection of the bonds that are present in the final target molecule. And that is referred to as the disconnection approach or retrosynthetic analysis.

Along the same direction, you have a crystal that is built up of hydrogen bonds because of the specific functionalities. So, you can actually go back and dissect these hydrogen bonds because you know that these hydrogen bonds form due to the presence of certain functional groups.

So, it is also possible to break down the crystal structure into smaller fragments via an understanding derived from the hydrogen bonds present due to the different functional groups. And so, the individual building blocks that are obtained are molecules. The final connection is the crystal structure, and in between, we have these supramolecular synthons that connect by hydrogen bonds, eventually giving you the crystal.

So the concept of supramolecular synthons becomes important. In the case of molecules, the concept of structural isomers is very important, but in the case of crystal engineering, the concept of polymorphism is very important, where you have a given crystal structure and a given molecule crystallizing in a particular crystal structure.

However, under different conditions, you can obtain different crystal structures of the same molecule, resulting in the formation of polymorphs; this phenomenon is referred to as polymorphism. We will discuss more about polymorphism in the later lectures.

The next thing is that when we talk about reactivity, we discuss a transition state through which the reacting molecules must go before they convert into the final product, which varies in the case of crystal engineering.

It is the process of nucleus formation, specifically crystal nucleation and growth, that is most important. So, the formation of the crystal is very important, and crystallization can take place under kinetic conditions or thermodynamic conditions.

Now, kinetic conditions are actually fast, rapid conditions of crystallization and are done at room temperature in solvents that are highly polar and have the ability to evaporate very quickly, whereas the thermodynamic conditions involved in crystallization at very low temperatures maintain thermodynamic equilibrium and involve solvents that do not evaporate very quickly.

So, these kinds of crystallization take place over a period of many days to sometimes months. But what is critical in the formation of the final crystal is the formation of nuclei and the growth of these nuclei to give you the three-dimensional crystal structure or the three-dimensional crystal.

And it is a chemical reaction that is very important in molecular chemistry, whereas in the case of crystal engineering, it is the crystallization process that is extremely important.

So, crystallization is a very important technique, and we know that in the field of crystallization, we spend a lot of time trying to crystallize molecules; therefore, this becomes a supramolecular reaction compared to the traditional covalent bond-making and breaking reactions involving molecular compounds.

So, now we know what a crystal is. The crystal is a periodic array of molecules that is held together by weak non-covalent interactions to produce matter of macroscopic dimensions. So, ultimately, we know that when we have crystals, they can exist in different morphologies like plates, blocks, needles, etc.

And inside the crystal, we have this periodic arrangement of molecules that are held together by these interactions to produce matter of macroscopic dimensions. And there is an amazing level of precision because the arrangement of molecules is at a very, very well-defined precise location, and when a crystal forms, it actually utilizes the symmetry operations of the space group to pack the molecules in the crystal.

And when the process of crystallization takes place, it is the geometrical shape of the molecule, the geometrical shape and size, and the nature of different functional groups that participate in crystal formation.

So, what we essentially consider is that the molecule acts as a node; a molecule is considered a node, and then you have a functional group as Fg1 and Fg2, and now it is the interaction between Fg2 and Fg1. We have the node molecule, Fg1, and then this process continues, with the recognition between Fg1 and Fg2 occurring through hydrogen bonds or different non-covalent interactions, giving rise to 0-dimensional, 1-dimensional, or 3-dimensional structures.

And you can represent this particular molecule as a node, and the connections can be called the nodal connections that connect the different nodes. For example, take the molecule HCN; it forms a nice linear C-H...N hydrogen bond and creates a one-dimensional array.

This is a chain, and this is a one-dimensional chain-like structure. Now, what crystal engineering says is that if you were to have an acetylene group in a molecule and a cyano group, then these will interact with each other via the C-H...N hydrogen bond.

So, this C-H...N hydrogen bond, will always be present in the crystal structure of an organic molecule containing the acetylene linkage and the cyano functional group. So, when you have this kind of specifics and this recognition is always primarily observed in crystal structures.

This operation, where we recognize different functional groups, constitutes what is called a supramolecular synthon. The supramolecular synthon has been coined by Professor Desiraju, who identifies these non-covalent building blocks that are present in different crystal structures, and depending on the type of functional groups, we can have different kinds of supramolecular synthons.

And now if we consider another molecule, for example, one that has the acetylene linkage as well as the cyano group, this kind of one-dimensional chain will be formed again, constituted of the highly acidic acetylene hydrogen with the nitrogen atoms of the cyano group forming C-H...N hydrogen bonds.

So, we see here again that the supramolecular synthon is present in the crystal structure of another molecule. This is the 4-ethynyl-4-cyano-benzene, okay?

And you can now extend this to the biphenyl as well. So, if you have a biphenyl system, and if you have the cyano and the ethynyl group, this can continue further. So, this is referred to as a supramolecular synthon, and along the same lines, we can now identify different kinds of supramolecular synthons. Let us go to the next one so we can have the classical acid synthon.

We have a carboxylic acid that is present in the molecule. Now, traditionally, whenever you have a carboxylic group, it will form the zero-dimensional dimeric synthon. This is a very common observation, and therefore crystal structures of compounds containing the carboxylic group will have the synthon. But you can also have the non-dimeric, where you form this kind of chain. You can have a chain-like structure, okay.

So, this forms a one-dimensional chain-like structure, but this is rare; however, you can also have it present in some of the crystal structures. Similarly, when you have an amide functionality, it can also interact through these very specific N-H...O=C hydrogen bonds, forming dimers and cyclic dimers.

And another key feature of this dimer is that it is centrosymmetric. That means there is an inversion point or a center of symmetry associated with this dimer that relates the individual molecules. You can also have, instead of the dimer, a chain, so you can have this one-dimensional chain consisting of N-H...O hydrogen bonds.

So, N-H...O hydrogen bonds can form dimers as well as chains, and it has been observed by looking at a large number of crystal structures that N-H...O chains are very, very common in comparison to the N-H...O dimers, and we can also now have other combinations. For example, say you have an acid and a functional group that contains a CN double bond along with an NH group.

So, it will form an O-H...N hydrogen bond and an N-H...O hydrogen bond. So, this is very, very specific because it essentially tells you that if you have a carboxylic acid along with the N-H and the C=N, then it will form this kind of dimeric motif, which is also called a supramolecular synthon.

So this is a cyclic dimer that is constituted from N-H...N hydrogen bonds. So what it tells us is that if you have the specific functionality, then they will form these kinds of N-H...N hydrogen bonds, forming these dimeric aggregates. These hydrogen bonds listed here are strong hydrogen bonds.

For example, O-H...O and N-H...O hydrogen bonds, and these are N-H...N hydrogen bonds. And what was the most important contribution of Professor Desiraju was that he now wanted to extend the concept of supramolecular synthons to weaker interactions, particularly those involving the C-H...O hydrogen bonds and C-H...N hydrogen bonds in particular.

So the concept was proposed that if you have relatively acidic donors and strong acceptors, then C-H...O hydrogen bonds are also unique and exist. In many cases, in the absence of strong hydrogen bond donors and acceptors, it is the C-H...O hydrogen bonds and the C-H...N hydrogen bonds that play a very important role in crystal packing.

So, let us look at some examples of where these kinds of hydrogen bonds are present and constitute supramolecular synthons. So, in this particular case, we can see that this is an alpha, beta unsaturated system and this particular hydrogen is acidic and therefore it can participate in a C-H...O hydrogen bond. It is connected to an sp2 carbon, and hence it forms a C-H...O hydrogen bond; this is a dimer, and it is also a centrosymmetric dimer because this is the center of inversion present here as well. And along the same lines, we can now have this kind of dimers as well, where you have the alpha, beta unsaturated group present.

And this is the vinyl group; this is the CH2=CH vinyl group present, and again this forms a C-H…O hydrogen bond. Now in this case, again it was a vinyl group, but it was the alpha hydrogen that was involved, and here it is the beta hydrogen that is involved; it is the alpha hydrogen that is involved in the formation of these C-H...O dimeric units.

And we can now extend the concept of hydrogen bonds to even larger-sized supramolecular synthons. For example, we can look at this particular case. So, you can now see the hydrogen bonding that exists here:

N-H...O, N-H...N, and N-H...O. So, we can call this a donor of hydrogen; this is an acceptor; this is a donor; this is an acceptor; this is an acceptor; this is a donor.

So, this is a very specific type of bonding. Whenever you have these kinds of functional groups present, they will form these kinds of DADADA motifs, and this kind of specific information is actually coded in the system. So, this kind of assembly process forming crystals has these very specific hydrogen bonds that are present.

And we can also now change this in the following way.

So now we have N-H...O hydrogen bonds, N-H...N hydrogen bonds, and N-H...O hydrogen bonds. So, here we can see that we have a donor, and this is an acceptor; this is an acceptor, and this is a donor.

So, we have a very different kind of arrangement here now. And now we can extend this further and we can now look at other cases. For example, we can also have, if you have a doubly bonded system, a C-H and a cyano, then it forms C-H...N dimers, and we can extend this further.

So, now we can say that this particular dimer does not have a center of inversion, but this one has a center of inversion. So, we have got two different types of dimers, and we can also now invoke halogen bonding.

So, if hydrogen is replaced by chlorine, we can have the Cl...N halogen bonds, which can form these kinds of structures. And we can extend this further to include N-H. So, say you have an N-H donor and you now have a nitro group present in the molecule; it will participate in the formation of this particular motif where this functions as a bifurcated donor, okay.

So now N-H interacts with both oxygen atoms in the nitro group, forming this kind of N-H...O hydrogen bond where the oxygen comes from the nitro group. You can also have, in place of NH, iodine as part of the organic molecule, and these can also interact with your oxygen atoms via iodine...oxygen halogen bond to constitute the supramolecular synthon.

We can have other examples as well, where you can have this kind of arrangement, where an acetone molecule is interacting with a compound containing two N-H functional groups, and here you can see that this is a bifurcated acceptor.

So, all these possibilities exist in the case of the formation of different kinds of motifs, and we can also look at the phenyl ring where we have already examined the perpendicular motif. So, you can have parallel stacking, or you can also have perpendicular stacking.

So you can have the C-H...π or you can have the π...π stacking, and these also constitute synthons. So, this has become a very interesting subject now because we are able to identify the synthons, and what is most important is that we would like to see the history of supramolecular synthons.

When did supramolecular chemistry and the field of crystal engineering actually start in 1960? When organic chemists started doing solid-state organic reactions, solid-state organic reactions and this particular work were first pioneered by Smith, who was interested in performing dimerization reactions in the solid state, involving double bonds.

We wanted to look at the reactivity profiles of compounds that contain these double bonds. So the idea is that if you have a double bond and you have another double bond, these can undergo dimerization to give you the cyclobutane ring.

Can we do a similar kind of process involving double bonds in molecules in the solid state, such that these double bonds are actually pre-organized in the solid state and are within the reacting distance, such that when you shine light of a particular frequency, they undergo this stage of self-assembly where they form the four-membered ring?

So, now in the next lecture, we will be looking at more fundamental aspects of crystal engineering and how this field started and eventually culminated in a very exciting area of research.

Thank you.