Fundamentals and Applications of Supramolecular Chemistry
Deepak Chopra
Department of Chemistry
IISER Bhopal
Week 05
Lecture 23

W5L23_Supramolecular Host Strategy: Trimesic Acid and Dianin's Compound

So, hello everybody. So now let us continue our discussion further with respect to channel-like structures or clathrates. We will now be considering pure organic molecules as a host that will form a supramolecular structure and create voids into which the gas molecules can sit.

So, to start with, let us consider organic molecules forming clathrates, and then they can include different guest molecules, for example, water. So, we can take the example of trimesic acid, which has been observed to form different kinds of complexes with water. And what is also very important is the kind of supramolecular host-like structure that trimesic acid forms to include different kinds of guest molecules.

So, we have different building blocks when it comes to trimesic acid. Let us look at the building blocks. We have got these carboxylic acid groups. Now it can form hydrogen bonds, the O-H...O hydrogen bonds, and this can further interact. 1, 2, 3, 4, 5, and now we can have the last one, which will be O, OH, and so effectively these will be hydrogen bonded as well.

So now this forms a 1, 2, 3, 4, 5, 6, a hexamer, cyclic hexamer motif-like structure, and now you can see that there is a large void in the center. So, this can actually contain guest molecules.

For example, we can have water molecules that are present, and the water molecules can also associate through hydrogen bonding, forming these channel-like structures with trimesic acid. You have a channel, and into this channel, you will have the voids where you can have the guest molecules.

So, this creates a hexagonal channel-like structure, and the dimensions of this cavity are so large that they are also able to include organic molecules.

There have been reports where different kinds of organic molecules that are actually liquid at room temperature have been crystallized along with this trimesic acid. In other words, trimesic acid has been found to be a very good crystallizing agent.

For example, if you have a molecule or a drug molecule, such as a drug molecule that is liquid at room temperature. And you would like to determine the structure of the compound, but it is a liquid at room temperature.

So, what we can actually do is template and crystallize this drug molecule along with this trimesic acid. Because the trimesic acid forms a structure that has large voids, the drug molecule can go into the voids and sit. And from X-ray crystallography, you can now determine the three-dimensional structure of the drug.

So, this is an extremely useful approach that utilizes the concept of channel structures, a supramolecular host to include different kinds of molecules of different shapes and sizes, crystallizes them together with the trimesic host, and determines the structure of different kinds of molecules that are liquids at room temperature.

You can also take metal complexes, organometallic complexes, and try to crystallize them in the host framework of this trimesic acid. And you can also do chiral drugs because chirality is very important, and we would like to know which particular enantiomer of the drug has crystallized.

So, the pure drug, which is the enantiomeric form, can also be crystallized, and the structure can be determined. So, trimesic acid has very unique applications in functioning as a supramolecular host to include solvent molecules as well as drug molecules.

So, we can now go to another case where it is not necessary for you to have an intrinsic void associated with the crystal structure. There are many cases now that have been observed in which, even if there is a little bit of space available and you have a particular guest that can actually occupy the little bit of void space present, it is still able to form a host-guest complex.

For example, this motivation involves trying to include a guest molecule into a crystal structure that does not have any voids to start with. So, the question is, can we include guest molecules in crystal structures where the available voids are very, very few?

And what kind of guest can we select that can be included in these voids? So, the motivation came from this work where people have crystallized benzene and hexafluorobenzene. On the basis of the fact that both, being low-temperature solids, have a melting point of 5.5 for benzene and 5.2 for hexafluorobenzene.

So, they are both liquids at room temperature. But when you actually make a co-crystal or a 1:1 donor-acceptor complex, the resulting compound, the resulting co-crystal, melts at a much higher point. It is solid below 24 degrees centigrade, and you can see very clearly from the molecular electrostatic surface potential that there is a nice complementarity that exists.

The C_6F_6 has a positive electrostatic potential, and benzene in the central region has a negative electrostatic potential, and it is the complementarity between the negative and positive electrostatic potentials that favors the stacking of these host-guest interactions, or you can say the donor-acceptor complexes.

So, with this in mind, it has been demonstrated that if you take this particular substrate and ethynyl-substituted benzamide, and it also has an amide functionality in the center, there is a strong donor and a strong acceptor, and you take different substituents and different isomers.

So, you can have R equal to fluorine in the ortho, meta, and para isomer; you can have a trifluoromethyl group in the ortho, meta, and para positions. You can have the chloro and the bromo, and the three different isomers.

So, you can have a set of 12 molecules and then try to understand the inclusion behavior of this hexafluorobenzene, because benzene is relatively electron-rich, hexafluorobenzene is electron-deficient, and they can interact with each other.

After a careful investigation of the crystal structure, these are the views of the donor-acceptor complex. You will see that the hexafluorobenzene sits above the phenyl ring through the stacking interactions. The same thing happens when you have the fluorobenzene moiety interacting with hexafluorobenzene.

Now, when you change it to the other isomer, the meta isomer, the para CF_3 isomer, it obviously becomes a different molecule. So, in the case of TF, when you have the trifluoromethyl, the hexafluorobenzene interacts with the same benzene ring having a CF_3 substituent; the same is true for the chloro.

But now, when you go to the meta chloro, surprisingly it switches over to the ethynyl-substituted benzene ring, and there we see the interaction between the donor and the acceptor, and when it is bromo again, it is on the ethynyl side.

So, you get this interesting set of inclusion complexes with hexafluorobenzene as the guest included in the crystal structure of the host molecule, which is the ethynyl-substituted benzamide, and what favors this stacking is the pi...pi interactions.

And it is also very clear from the electrostatic potential why these donor-acceptor complexes are very tightly bound. For example, we can see that this is the electrostatic potential surface of the benzamide molecule.

You can see the negative regions in red and the positive regions, which are the hydrogen atoms, in blue. This is the MESP of hexafluorobenzene; you can see that the fluorines are highly electronegative. So, the electrostatic potential is negative; for the central part, it is positive.

So, it is now the complementarity between this positive part and the negative part of the benzene nucleus or the ethynyl substituted part that actually allows for these donor-acceptor interactions to take place.

And this is well exemplified in all the cases that very well demonstrate the nice electrostatic complementarity between the negative region of the ethynyl-substituted benzene ring and the positive region of the hexafluorobenzene.

And this is what actually drives electrostatic interactions, which is what drives these kinds of pi-pi stacking, as nicely demonstrated in all these complexes. Along the same lines, we were also interested to see whether there can be some structural changes; as we already looked at in the previous lecture, we have a parent molecule which need not have the solvent that is called the apo host, and it can also include the solvent that is called the solvated form. We can actually modify the structure of the solvated form to access different phases.

Now, here in this particular compound, a specific molecule of para-fluoroethynyl-substituted benzamide was observed. You can see the crystal structure now. In the crystal structure, you will see that there are not many voids; however, what is the available volume you see is the available volume in the parent structure.

So, if you now look at the available void or the space, you can see that hexafluorobenzene is a planar molecule. It is like a flat molecule, and it is able to easily intercalate and get included in this void that is present down the plane of the board or down the plane of this computer.

So, now you can see very nicely that it goes and sits in the voids. It is stabilized by the pi...pi stacking. But overall, the stabilization is not very strong, and desolvation can easily take place.

When desolvation happens you will see that the solvent goes out and there is some change in the volume, but overall, the packing remains compact, and you see this is the void space which is available for the hexafluorobenzene to go and sit.

At the same time, you can see that there is no solvent hexafluorobenzene sitting between these π rings, and there is some change in the distance between these π rings as well. So, this opens up a bit, and you can see here that the primary crystal packing is the N-H...O

hydrogen bonds, which are actually held by these weak C-H...F hydrogen bonds. So, both strong hydrogen bonds and weak hydrogen bonds create this three-dimensional structure, and the voids that are available, as shown in pink, can now include the hexafluorobenzene.

This is to show the shape requirement and the volume requirement, as it fits very nicely into the voids that are created. But then the structure does not have intrinsically high porosity or a high void volume. They are not only able to intercalate, but they can also be easily removed, and this desolvation process now results in a single crystal to single crystal phase transition, where you can see that the final structure does not have the solvents. The solvents have essentially been removed, and there is a partial, you know, collapse of the structure in the sense that now the molecules come close to each other, thereby indicating that desolvation can happen in a very facile way in the structures without the loss of crystallinity, and thus we are able to determine the structure after the loss of the solvent. Normally, the solvent is expelled or the guest is expelled; the crystallinity is lost, and the structure collapses, but in this case, we are very nicely able to capture the single crystal to single crystal phase transition.

Now, with this in mind, let us go to another example to complete the discussion. We will now look at the Dianin compound, which is also called a hexahost strategy. Now, let us look at the structure of a Dianin compound first. The motivation came from the fact that phenols can form crystal structures containing O-H...O hydrogen bonds.

And we can now make, this is oxygen, this is methyl, this is methyl, and we have got the substituted phenol. So, at the para position, we have replaced it with this particular hydrophobic moiety, which has the oxygen atom here, and this is a chiral center.

So, this is a chiral compound called the Dianin compound, and this compound is very versatile and very unique because it has been found to include a large type of guest molecules in the crystal structure.

So, what is unique about the Dianin compound? The Dianin compound forms a hexameric host structure, and how does it do that? So, we have R = -OH. Here we see that this is the hexa host; you can see the O-H...O hydrogen bonding.

The R groups are anti to each other, okay. So, this R is top, the next one is bottom, then it is top, then it is bottom, it is top, and then this is bottom.

So, we have this top-up and down arrangement of the R groups such that it minimizes the sterics because this is the R group here, and the formation of the hexa host is driven by this OH group.

And you have this one particular hexa host, and then there is another hexa host arrangement at the bottom, and in between, you will also have some R groups present here. So, you have 3 R groups at the top, 3 at the bottom, and now you see that there is a void created here, and this void can now include different guests.

So, there is one hexa host at the top, another hexa host at the bottom, and there is a lot of void space now available into which the guest molecules can go and sit. So, this is a very unique type of structure, and this clearly shows the cage-like structure that is present in the hexa host Dianin compound.

And the next question was whether we can maintain this host structure by modifying the substituents or by modifying the atoms that are present either on the ring or on the phenyl side. So, whether modification will allow us to maintain this inclusion behavior. So, now we see that we can say Dianin's compound.

I am writing it as DC. It is a versatile host because of the formation of this hexa host complex and two such hexa hosts forming a net structure that has voids that can include different kinds of guest molecules. So, it is a versatile host, and it can include a wide range of organic and inorganic guests.

For example, argon, glycerol, sugars, and more importantly, SF_6. And what is SF_6? It is an insulating gas used in the electrical industry. So, these are some of the interesting features of this versatile host, and what has been observed is that the ratio of host to guest is 6:1.

So, 6 molecules of the host and 1 molecule of the guest are present, and this is consistent with the hexameric structure. So, the next thing is, what about the other compounds? With ethanol, methanol, and acetone, it forms 6:2, or we can say 3:1. That means two molecules of acetone, butanol, or ethanol are present. In the case of methanol, it is 6:3 because methanol is smaller in size compared to ethanol or acetone, so we have 3:1.

In the case of piperidine, it is 1:1. What has been observed is that the solvent molecules, like ethanol or butanol, actually undergo a liquid-like motion, even at very low temperatures, inside the void structure.

So, the next question is, can we maintain the robust host structure by modifying Dianin's compound? If we modify Dianin's compound, can we actually alter the host structure, which is very robust? Why is it robust?

Because of strong OH...O hydrogen bonding. The formation of this hexahost, the clathrate property, or the inclusion property of this Dianin's compound is very robust. So, what we can do here now is draw the structure. This is my Dianin's compound.

I am labeling it as 2, and I am labeling this as 4, number-wise. So, 1, 2, 3, and 4, and we can now make different modifications under different strategies.

So, strategy 1 is the perturbation of the substitution pattern at C2 and C4; this is strategy 1. Strategy 2 involves changing the OH group to other functionalities, such as SH or NH2. Strategy 3, the replacement of etheric oxygen with sulfur or selenium, and Strategy 4, the addition of substituents to the aromatic ring.

So, whether we add some R1 or R2 group here, whether this particular hexa host remains constant. And what has been proposed is that it essentially has a structure of this type where the dimensions are 20 picometers, 630 picometers, 420 picometers, and this is around 11 Angstroms.

So, overall, this is what the arrangement is and what happens to these dimensions or changes in the structure when you incorporate these strategies.

So, according to the first strategy, the results are as follows: if you change the substitution, instead of, say, methyl, you put ethyl or propyl or butyl. Now, according to the results of strategy 1, the removal of one of the methyl groups results in a host with a much wider cavity.

So, it becomes 7.1 angstroms versus 4.2 angstroms. So, this particular region here where we have the methyl groups becomes much wider because the sterics are reduced. And then the replacement of the C4 methyl group.

So according to strategy 2, if you now replace this particular methyl group here, it forms a different structure that does not exhibit clathrate behavior. So first we made a modification here; now we actually replaced this methyl group, and it does not form a similar structure. Sorry, this was still strategy one, I would have to say.

Now, in strategy 2, if you replace OH with NH2, then again, the clathrate property is lost. So, this OH is very important for forming the hexahost. If you replace it with NH2, there is again a loss in clathrate property.

And in strategy 3, if you replace oxygen with sulfur, it still exhibits the clathrate property. It still has the clathrate property, a 6:1 stoichiometry, and a slightly wider cavity because now we have S-H...S hydrogen bonds.

So, the cavity is slightly widened because of the presence of this relatively longer S-H...S hydrogen bond, and now the sulfur analog is very efficient in trapping dimethyl mercury.

Because this is a very toxic compound, this particular host, which is the sulfur analog of it, can be utilized to efficiently trap dimethyl mercury, and the resulting complex can be stored under high vacuum for several days.

Only under high vacuum is this being stabilized. If you replace the substituents according to the last strategy, for example, if you set R1 to methyl, then it still forms a clathrate-type structure. However, the sizes of the cavities will change when you replace R1 with methyl.

When you fuse another phenyl ring here, the structure completely changes, and it does not exhibit any clathrate behavior. So, you can now see the entire spectrum of changes, that you have first done substitution at C2 and C4.

Perturbation of the substitution pattern, if you do it further, if you replace one of them, remove one of the methyl groups, it leads to the same structure but with a wider cavity.

But if you replace or remove C4, then it does not have the clathrate structure. Removal of OH results in the loss of clathrate behavior. Replacing oxygen with sulfur results in the clathrate structure, but it has a slightly elongated or wider cavity because of the S-H...S hydrogen bonds. And that is a very good host for trapping dimethylmercury, which is kept under vacuum for many days.

Then, modification at the phenyl side with methyl still maintains Dianin's structure. However, the cavities are modified, and replacement with phenyl again alters the structure completely, and there is no clathrate property.

So, with this, we have now seen the versatility of Dianin's compound and the spectrum of structures and host-guest interactions it can have depending on the structure of the parent compound.

So, the parent compound structure is important. Whether it creates the necessary cavity and is an organic molecule that can now include different kinds of guests, starting from different solvents to various inorganic compounds, like SF_6 or dimethylmercury, as well. So, with this, we come to a close of the discussion on host-guest complexation involving clathrates. In the next lecture, we will now go to a new topic called crystal engineering.

Thank you.