Fundamentals and Applications of Supramolecular Chemistry

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Lecture 19

W4L19_Host Guest Complexation in Calixarenes

So, hello, everybody. Let us now continue our discussion. In the last lecture, we were discussing the kinetic template effect and the thermodynamic template effect, which are very important in forming cyclic rings of a particular size.

And this is preferred because there is always competition between intramolecular reactions and the formation of the acyclic chain. So, using the concept of the high dilution principle, we are now able to engage the starting materials in a manner that brings the reactant species into the preferred orientation in the presence of a certain cation that serves as a template. So, the reaction can take place and then form the cyclic ring.

We also looked at the thermodynamic template effect and some of the most important examples pertaining to the template effect. Now, we are going to go to the next class of molecules where we are going to look at neutral molecules that have an intramolecular cavity, which means there is an open space present when the molecule is formed, and this void or space exists whether the compound is in solution or in the solid state.

So, this intracavity persists when the molecule exists in solution or in the solid state. And we have already discussed this; this refers to the formation of cavitates and clathrates depending on whether you have an intrinsic cavity or an extrinsic cavity.

Complexation now involves organic molecules that can be either polar, non-polar, or a combination of polar and non-polar substituents. And in this regard, we are going to look at two important classes of molecules.

We will first look at calixarenes and then we will look at cyclodextrins. And both these classes of molecules are very important because they have a combination of polar and non-polar substituents present on them. And essentially, these molecules are also referred to as molecular containers with an enforced concave surface.

So they look like a molecular container, a tub-like arrangement, a bucket-like arrangement that is the shape these particular molecules adopt in the solution or in the solid state, and then you can now have guest molecules that can come and interact with the different polar portions as well as non-polar portions of this molecular container or these cyclic hosts, which have non-polar content as well as polar content.

There are some general properties associated with host-guest complexation because we now have a neutral organic molecule that is going to interact with a neutral guest in the presence of solvent molecules, which are also organic solvents, such as benzene, methanol, chloroform, and so on.

So, essentially the origin of the interactions that are going to dictate these kinds of host-guest recognition, unlike hydrogen bonds or cation-pi interactions or anion-pi interactions, is primarily going to involve dipole-dipole interactions, where the host molecule and the guest molecule have dipole moments, and the greater the magnitude of the dipole moment, the greater the stabilization energy due to the interaction of the host and the guest molecules with each other.

And the solvent molecules here also play a very important role, and we have already looked at this in the hydrophobic effect, where you have a host molecule that is solvated by the water molecules. Now, the guest comes and sits.

These high-energy water molecules are released into the bulk. So, enthalpically it is favored and also entropically it is favored because the initially ordered array of water molecules is now released into the bulk, and therefore, the overall entropy change is positive.

And therefore, from a thermodynamic consideration, hydrophobic effects primarily drive host-guest complexation behavior in molecules that are neutral and have associated with an intracavity. And in most cases, it will be seen that it is the hydrophobic portion of the host that interacts with the hydrophobic portion of the guest. So, they are primarily hydrophobic interactions or lipophilic interactions that drive host-guest behavior.

So, overall, the driving force is not very strong, unlike hydrogen bonds or cation-pi interactions, because here we have the hydrophobic portions that interact with each other. Primarily, these are of a dispersive nature, and it will be more appropriate if we can modify or introduce more polar substituents, or if we can introduce some anionic feature either on the guest molecule or on the host molecule.

In that case, that can drive the process of molecular recognition to a greater extent. And the first molecule we will be referring to in this series is calixarene, so let us look at what the calixarene molecule looks like. So, the calixarene molecule has been drawn; I will draw the calixarene molecule for you.

And we have got a tertiary butyl group here, a tertiary butyl group here, a tBu group here, and a tBu, and in the interior, we have got a hydroxyl group. So, this is the representation of a para-tertiary butyl calix-[4]-arene, and this compound is prepared by the reaction of

alcohol in the presence of formaldehyde and an acidic source, which will lead to the formation of this particular para-tertiary butyl calix-[4]-arene.

In this case, the reaction proceeds via the activation of the formaldehyde molecule, and this is followed by the reaction of the alcohol moiety containing the tBu group to form the monomer, which is then further protonated.

The water molecule goes away, the carbocation is generated, and the carbocation further undergoes reaction with the nucleophilic center. So, this further undergoes reaction now with the and in this case, we now get the dimer.

So, in this case, the reaction proceeds, and we are now finally able to have the ring closure, which will give me the calix-[4]-arene. Now, this calix-[4]-arene, which is formed now, has the tertiary butyl group present here; these are the nonpolar parts, and the polar hydroxyl groups are also present here, forming a hydrogen-bonded array. So, this is the lower rim, and this is the upper rim, which is hydrophobic.

This is hydrophilic because it has the hydroxyl groups present, and now this particular site can interact with polar solvents or it can interact with cations, okay. And this can interact with non-polar substances; this is non-polar in nature, so it can interact with the guests, which also have a non-polar nature, as well as the gas, which can further interact with the tertiary butyl groups.

And this is the cavity, which is present; in this intracavity, we can now include different kinds of guests. For example, we can include toluene. It has been observed that if you take toluene, it interacts with this hydrophobic surface through the C-H...π hydrogen bonds, and we know that the tertiary butyl groups are present.

So, these are electron-rich surfaces; the C-H is the donor, and the pi is the acceptor, and we have these C-H...pi hydrogen bonds, which lead to the inclusion complex of toluene with the calixarene.

The next thing that we must realize with respect to calixarene is that this particular molecule is conformationally quite flexible. It is conformationally quite flexible, and it exists in different conformers. Let us look at the different conformers in which this particular calixarene exists.

This particular conformation is called the cone conformation. It is called a cone conformation because, in this particular conformation, all the polar groups are on one side and the nonpolar groups are on the other side.

So, we can represent it as follows: all the polar oxygens are on one side, and the

nonpolar R groups are on the other side, and this exists in equilibrium with the partial cone conformation. This is the partial cone conformation where one of the R groups flips over to the other side, and then we have the other two conformations as well, which are referred to as the 1,2-alternate, and this is in equilibrium with the 1,3-alternate.

So, these are the four different conformations in which my calix-[4]-arene can exist: we have the partial cone conformation, we have the 1,2 alternate, and we have the 1,3 alternate conformation as well. The cone conformation is a very stable conformation because we have these OH...O hydrogen bonds that stabilize it. However, when this OH group is replaced by the OR group, the hydrogen bonds are absent.

So, it was also very important to see that now, if you add different kinds of cations of different sizes, what the effect on the complexation behavior will be. So, if you have added, for example, lithium ion or sodium ion, these are oxophilic because they love oxygen atoms. So, the lithium ions and sodium ions coordinate with the oxygen atoms here.

They can also coordinate with the oxygen atoms in the partial cone because, in the partial cone, one of the oxygen atoms is above, but the three oxygen atoms are still below, so they can still have a coordination. So, it is the partial cone and the cone conformation that are stabilized when you have these oxophilic species like lithium and sodium.

However, when you have the larger size species now, there is a change in the conformation. When you have larger-sized species, like, for example, the silver ion or the potassium cation, then we get the 1,3 alternate conformer or the partial cone conformer.

We get the 1,3 alternate conformer or the partial cone conformer when we have the larger size silver ion and the potassium ion, and what has been observed is that these are stabilized by cation-π interactions.

This is because now the silver ion is able to approach the interior cavity, it is able to approach the walls of this bucket-shaped molecule, and form cation-pi interactions with silver, as well as with potassium, which is also involved in the cation-pi interactions.

Now there is some important data to support the existence of these conformations. For example, in CDCl3 and deuterated acetonitrile, in a 10 to 1 volume-by-volume ratio in this solution at minus 50 degrees centigrade, it has been observed that the calix-[4]-arene exists in a 70 to 30 ratio.

So, we can now consider, for example, in general, R. So, R is equal to hydrogen, and Y is equal to methyl.R is equal to hydrogen, Y is equal to methyl, R is equal to tertiary butyl, Y is equal to methyl, R is equal to hydrogen, and Y is equal to n-propyl.

So, we can consider examples 1, 2, and 3, and we will look at some important data related to the existence of conformations of these calix-[4]-arenes, 1, 2, and 3. So, when you have the CDCl3 solution, what has been observed is that the calix-[4]-arene 1 exists in a 17 to 30 ratio as the partial cone and cone isomer when you have the OH group.

So, the partial cone is to cone isomers; it exists in these two particular conformations, in this ratio, and we also know that if the solvent is highly polar, then the population of the cone conformer is the highest. So, the more polar the solvent, the greater the population of the cone conformer; this is because all the oxygen atoms are on one side and the non-polar portion is on the other side.

This makes it much more polar, having a higher dipole moment. However, the partial cone conformers can exist in non-polar solutions, and we see that the polar conformation, that is, the cone conformer, is also highly pre-organized for binding because all the oxygen atoms are in the lower rim and are more oriented towards interacting with the cationic species.

Whereas, if the conformation changes to the partial cone, then it is not as pre-organized for binding as the cone conformer. So, in that case, what happens is that if you now consider compound 2. In what has been observed, in the case of compound 2 when y is equal to methyl, if you treat it with Ag plus and K plus, then it is a partial cone or the 1,3-alternate conformer.

If you treat it with sodium or lithium, then it is the cone or the partial cone, and if you treat it with a methyl ammonium compound, then it exists in the cone conformation.

In the cone conformation, what has been observed is that the NH3+ group, so now we have got cone conformation. So, the NH3 plus, which is actually the guest molecule, can now enter the cavity created by the calix-[4]-arene and get stabilized by N-H...π hydrogen bonds.

Again, this is preferred because you still have the cation-dipole interactions. Overall, this is the cationic species that interacts with the other calix-[4]-arene moiety and gets stabilized by N-H...π hydrogen bonds.

So, the guest is able to form strong N-H...pi hydrogen bonds, and as I already mentioned, if one of the molecules, that is, for example, the guest molecule, is polar or cationic in nature or has, you know, a higher dipole moment, then that will increase the magnitude of the stabilization energy and result in an enhanced binding constant for this particular species.

Now the thing is that when you have these non-polar groups like methyl, or you have hydrogen and tertiary butyl, and R equals H, these kinds of moieties are not very soluble in water.

These are essentially insoluble molecules, and if you want to actually make them soluble in water, then R is equal to SO3 minus Na plus; that is, a sulfonate group has to be now introduced on the calix-[4]-arene backbone.

So, now you see that we are going to have a calix-[4]-arene, which has $SO_3^-Na^+$ and the oxygens are sitting here. You can have this OH, or you can have it as R, but now you have got the sulfonated groups, and this makes the calix-[4]-arene soluble.

And also, because it is now soluble in water, there are extensive hydrogen bonding interactions between calix[4]arene and water. And what has been observed is that now, when you have these calix-[4]-arene moieties, there exists hydrogen bonding, that is O-H...π, between the water molecules and the π surface of the calix-[4]-arene, but these water molecules, in turn, are also hydrogen bonded further with this water molecule.

So, you have this extensive solvation of the calix-[4]-arene when you have these water molecules that are present on the rim of the sulfonate groups. So, when you have a highly polar calix-[4]-arene that is now further templated with highly polar functional groups like sulfonate, water molecules can extensively hydrogen bond with it via O-H...π interactions, and these water molecules can further form a network with the bulk water molecules, while the sulfonate groups can also form hydrogen bonds with the water molecules.

So, overall, there are extensive solute-solvent interactions between the solvent and the calix-[4]-arene, and this results in enhanced stabilization, which in turn increases the solubility of these calix-[4]-arenes as well.

Overall, these calix-[4]-arenes have many applications, and people have also looked at how we can transport metal cations across these calix-[4]-arenes because they were trying to understand whether we can have mimics of crown ethers, just like crown ethers are able to transport cations efficiently.

For example, sodium and potassium; people also wanted to see that this compound has a hydrophobic interior and a hydrophilic exterior. You have the polar functional groups that can also sequester cations and transport them efficiently.

In this regard, what has been observed is that for lithium, sodium, and potassium cations, the rate of cation transport across the phase boundary, reported in moles per meter squared per second, is multiplied by 10 to the power of 8; this particular value is being reported. That is the amount of the cation that is being transported across the phase

boundary in moles per unit area per unit time: 10 for lithium ion. So, when you have the calixarene for n=6, it is 10, and when you have it for n=8, it drops to 2, and for potassium hydroxide, the values are 13 and 10.

However, for cesium hydroxide, the values dramatically improve to 810 and 996. And then, if you were to increase the size further, as well as the charge, for example, barium, it drops to 3.2, whereas no data have been reported for n equal to 8. So, lithium is not transported efficiently whether you have calix-[6]-arene or calix-[8]-arene, which is larger in size.

Potassium is not transported efficiently, but it is only the cesium, which has a slightly larger size and can stabilize itself very efficiently through cation-pi interactions, that is transported because it is captured first; then it is transported very efficiently, and the amount transported is very high, 810 and 996, for both the calixarenes.

And if you were to increase it to barium, the charge, because you increase the charge; however, it does not enhance the cation transport. People have actually looked at the structure and shown very clearly that the caesium ion stabilizes itself by caesium ion cation-π interactions in the structure.

And, also, this is a nice steric fit; the cesium cation is slightly larger in size, and the volume it needs is also appropriate for it to fit into the cavity created by the calixarene. In fact, even better, the calix-[8]-arene facilitates the transport in a very facile way.

So, this selective transport of metal cations is what has been achieved using these calixarenes. So, these are some of the important aspects of calixarenes. In the next lecture, we will now discuss cyclodextrins.

Thank you.