Fundamentals and Applications of Supramolecular Chemistry

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Week 04
Lecture 20

W4L20_Host Guest Complexation in Cyclodextrins

So, hello everybody, let us now continue our discussion from where we left off in the last lecture. In the last lecture, we discussed the host-guest inclusion property of calixarenes, where we saw that in calixarenes, we have polar regions, a central non-polar region, and preferential interactions depending on the nature of the guest with both the polar and non-polar regions.

We looked at the role of cations; for example, we looked at small cations that interact with the oxophilic region and larger cations that preferably interact with the pi surfaces. Then we looked at a different conformation of calixarenes, and so on and so forth.

Now, today we are going to discuss another very interesting class of compounds, which is very, very important and very, very popular in the applications industry, called cyclodextrins. So, cyclodextrins are very, very important molecules, and they have different applications.

One of the most important applications of cyclodextrin to start with is that it is used as a packaging molecule. Packaging in the sense that it is used for packaging different kinds of dyes, pigments, drug molecules, and so on.

One particular example I would like to emphasize here is that, in the drug industry, the packaging of the drug molecule with cyclodextrin is very, very important. So, most of the time what you have is a drug molecule that is not very soluble.

So, in order to make the drug highly soluble, it is now packed into this cyclodextrin capsule or the cyclodextrin powder, and then this cyclodextrin powder is able to contain it; it is essentially a molecular container that has an intrinsic cavity.

This cavity is present either in the solid state or in solution, similar to what we observed in the case of calixarene. And it has a void that can now contain the drug molecule, which is then released at the site of action once the cyclodextrin dissolves in the gastrointestinal tract.

So, it can modulate the cyclodextrin, which can now be used to modulate the solubility profile of the drug, and it is also an excellent biological transport molecule; that is, it can transport the drug to the site of action in a very, very efficient way.

Now, why is this particular property achieved so nicely in the case of cyclodextrins? So, let us look at what cyclodextrins are; essentially, these are cyclic oligosaccharides comprising either 6, 7, or 8 D-glucopyranoside linkages.

So, there are 6 such D-glucopyranoside linkages, which are the essential building blocks, and they are essentially linked by the 1,4-glycosidic bond. So, this is to start with the chemical composition of cyclodextrin, and it has a very rigid pre-organized host. They have well-separated polar and non-polar regions; that is, we can say these are hydrophilic and these are lipophilic or hydrophobic.

So, we have two distinct regions, similar to those of calixarenes, but they are very, very rigid and pre-organized. Some of the most important properties of cyclodextrins are, as I told you, that they are very important in the food industry and the drug industry.

And what is very important when it comes to application is looking at the economic viability of the compound. That is how easy it is to make the compound, how easily it is available, and what the cost is of making this particular packaging molecule. It has been observed that, in the case of cyclodextrin, large quantities and tons of cyclodextrin have been produced at a very nominal cost.

So, what makes it attractive is that it is economically viable, the cost of production is lower, and this is very important when it comes to the drug industry because we have to keep in mind that it is essential to look at the fundamental aspects of supramolecular chemistry, but when it comes to translating or achieving a desired application to reach the market.

Then the cost of production becomes a very important factor, and here the cost of the packaging unit—in this case, the packing molecule—which is going to modulate the different physical and chemical properties of my drug of interest—should be economically viable.

And the second most important thing is that, because you are going to package this particular molecule and bind it with the drug using non-covalent interactions, it should be entirely non-toxic, because any chemical component that goes into the body can have a certain toxicity.

But in this case, this is extremely non-toxic over the entire dosage range of the drug molecule. The third thing is that it is a fully saturated molecule. There are no pi bonds present; that is, there is no unsaturation. So, it is purely a sigma framework-driven molecule.

So, it is fully saturated, and let us now look at the structure of this particular compound: how does this particular molecule look? So, we can draw the corresponding cyclodextrin to start with.

You have got 1, 2, 3, 4. So, we have the OH here, we have the OH here, we have the primary group here, OH here, OH here, the primary one here, then we have the primary one here, the primary hydroxyl group here, the secondary hydroxyl group here, and similarly we have the primary group here as well as the primary group here.

And we can add the corresponding OH as well as OH. So, you can see very clearly that these are 6 units of D-glucopyranoside linkages, and this constitutes alpha-cyclodextrin.

What is important to realize is the stereochemical disposition of the secondary hydroxyl groups. These are the secondary hydroxyl groups, and these are the primary hydroxyl groups. And you can also see that they are connected by the glycosidic linkage that is 1, 2, 3, 4, ok. So, this is the connection: this is the 1 position, 2, 3, and 4 positions, and again this is 1, 2, 3, and 4. So, they are connected by the 1,4-glycosidic linkage.

And these are essentially the carbohydrate moieties that connect to each other to form this 6-membered structure, creating the 6 units of T-glucopyranoside. Now, when the number of units is 7, this is referred to as beta cyclodextrin, and when the number of units increases to 8, it is referred to as gamma cyclodextrin.

So, we have three independent cyclodextrins: alpha, beta, and gamma, and it is important to realize how they essentially look. So, we can represent cyclodextrins in a way similar to that of calixarenes. We can represent them as follows: these are more bucket-like molecules, which have, you know, this hydrophobic cavity, and we have the primary hydroxyl groups.

And secondary hydroxyl groups are on the upper M. This is the upper M. The upper rim and the lower rim have these hydroxyl groups, and this is the hydrophobic cavity. So, this is a very, very interesting molecule because it has a very, very rigid conformation. It is highly pre-organized, and you can see that it has a spherical curvature.

So that curvature is quite sharp, and any molecule that has both hydrophobic and hydrophilic content can now go, be trapped, and safely sit in the void or cavity created by this particular cyclodextrin molecule. The drug molecule of interest can be trapped here depending on the shape and size of the drug.

This drug will be included here, and now this cyclodextrin, which contains the drug molecule, can be transported and first dissolved. It dissolves, and the drug is released at

the site of action. Now this is the shape representation of a cyclodextrin, and what has been observed is the following: we can now specify some of the most important geometrical dimensions of this particular cyclodextrin, which we call the anatomy.

So, what has been observed is that this particular separation is 13.7 angstroms, and then the inner one is 5.7 angstroms, which is for your alpha cyclodextrin containing the 6 units. For the corresponding beta cyclodextrin, because the size is larger, the dimensions increase to 15.3 and 7.8 angstroms, and for gamma cyclodextrin, it is further increased to 16.9 angstroms and 9.5 angstroms; that is, the outer rim and the inner rim dimensions are given.

So, naturally, as the size of the rim increases, the size of the cavity also increases, and we will be able to put in relatively larger guest molecules into these cyclodextrins. And some of the most important properties of the cyclodextrins I would like to mention have actually been obtained.

For example, the number of glucose units. In the case of alpha, beta, and gamma, this is 6, this is 7, and this is 8. What is the ring size? The ring sizes are 30, 35, and 40. So, as the ring size increases, what are the internal cavity diameters, which are 5 angstroms, 6.2 angstroms, and 8 angstroms? And what is the standard enthalpy change in solution in kilojoules per mole, which is 32.1, 34.7, and 32.3?

It increases slightly for beta but drops for gamma, and the entropy change for the solution in joules per mole per Kelvin is 157.7, 48.9, 61.4. These are chiral compounds; cyclodextrins are actually chiral compounds and therefore, the optical rotation values at 25 degrees centigrade are 150.5 degrees, 162, and 427.

And what is the cavity volume, in 1 gram of CD, in cubic centimeters, 0.1, 0.14, and 0.20, and the pKa value at 25 degrees centigrade is 12.33, 12.20, and 12.08? So, these are some of the most important physical properties of alpha, beta, and gamma cyclodextrins.

And now we would like to look at, keeping in mind these important properties, the host-guest complexation behavior of this class of molecules. So now, let us look; we know that when we have host-guest complexation, the most important factor is the steric fit between the guest and the cavity of the host, followed by the release of high-energy water molecules.

A combination of hydrophobic interactions between the host and the guest and hydrogen bonds between the water molecules, which are expelled from the interior of the host molecule into the bulk, is favorable on both enthalpic and entropic grounds. So, keeping this in mind, what has been investigated is the binding of different guests of alpha CD in water.

Let us take different molecules here. For example, we have taken this nitrophenol, then we have taken the phenoxide ion, the nitrophenolate ion; this is the nitrophenolate. Then we take the hydroxyl compound, which now contains 2,6-substituted methyl groups.

So, this is the methyl group here and the methyl group here, which are at the 2 and 6 positions. We take the corresponding phenolate ion as well, then change the position of the methyl groups to 3 and 5, and also take the corresponding phenolate ion for these compounds.

So, now we have taken 6 different guesses: 1, 2, 3, 4, 5, and 6, and what is reported are the log K values. The log K values are 2.32, 3.36, 1.78, 3.07, and practically there is no binding observed when we have the 3,5-dimethyl nitrophenol, or we have the corresponding phenolate of the same compound.

We see that practically there is no binding between this particular guest molecule and the host, which is alpha cyclodextrin. So, it is important to understand how the trends in this log K are observed. So, to start with, the first observation is that the binding of the phenolate ion is, in general, greater than that of the hydroxyl compound. So, when you have phenol, the binding is lower compared to that of the phenolate ion.

This indicates enhanced hydrogen bonding between the hydroxyl groups of the cyclodextrin and the phenolate ion. So, it is not that there is no hydrogen bonding; obviously, there also is hydrogen bonding with the phenolic groups, but O minus has a greater charge density, so the strength of the hydrogen bond is greater, and therefore the binding is also much greater.

So, what is the structural model that has been proposed to account for this thermodynamic data? It is as follows: let us consider this to be the cavity, and this is the molecule that comes and sits here.

As you can see in the structure I showed you, we have the secondary hydroxyl groups on the upper rim and the primary hydroxyl groups on the lower rim. So, we have got these secondary hydroxyl groups here, but we also have the water molecules, which can not only extensively hydrogen bond with the secondary hydroxyl groups that are exposed on the rim, but they can also hydrogen bond with the O minus ion.

So, there is strong solvation, and there is very strong solvation of the host-guest complex, and definitely because the upper rim is wider, it has much more space available to accommodate the methyl groups now.

So, this particular guest can now be easily accommodated here, but when the methyl group is present in this position, there is a steric clash between the hydrophobic cyclodextrin cavity and the methyl groups. So, this particular molecule here cannot be included in the cavity because, as you go into the cyclodextrin, the size of the cavity decreases, and in this particular molecule, the span of the molecule is greater because the methyl groups are exposed.

So, because of this, it does not have the right steric fit to be included in the cyclodextrin cavity, and therefore there is no association of these guest molecules with the cyclodextrin host when we have methyl groups at the 3 and 5 positions. So, this is a very interesting case where you can actually put methyl substituents at very specific positions and modify the hydrophobic nature of the guest so that it can still undergo host-guest complexation with the cyclodextrin cavity.

And instead of taking this kind of phenolate groups, people have now also taken CH3(CH2)nX. You can also take this kind of groups, where X is equal to fluoro, chloro, bromo, and you can have hydrogen bonding between this X and the exposed water molecules, as well as the OH groups of the secondary hydroxyl groups of the cyclodextrin moiety.

Now it is important to keep in mind that we need to have a strong solute-solvent interaction, where the solute is now the host and the guest together. So, you have the stabilization of the host-guest complex in solution. But many times, in many cases, the host-guest complexation itself is not very favorable, and in that case, what happens is that we are able to get crystal structures of cyclodextrin, which are different arrangements.

And sometimes what happens is that the size of the drug molecule or the size of the guest molecule is large, but your cyclodextrin does not have a large enough cavity. Now what happens is that the cyclodextrin gets included in the crystal structure; it forms a layer of molecules, and this layer has larger size voids.

Therefore, we can pack in a greater amount of molecules, or we can include slightly larger sizes of the guest into this particular host as well. So, the crystal structure of cyclodextrin has different packing arrangements, and we can now consider, for example, the head-to-tail arrangement, where we can have—sorry to start with—I would first represent the head-to-head arrangement. So, you can see here that this is the head, this is the tail, this is the head, this is the tail.

So, you have got a head-to-head arrangement of these cyclodextrin moieties inside the unit cell, and then they can repeat themselves. So, this is one particular head-to-head arrangement; we can have the head-to-tail arrangement. So this is the second one; we can have the head-to-tail arrangement. For example, we can have it this way.

This is the head, this is the tail. Now we again have the head, and we have the tail. Then we again have the head, and we have the tail. And we have the centrosymmetrically related component as well.

So, you can now see this is the head, this is the tail, this is the head, and this is the tail. So, this is an arrangement in one direction, this is in the anti-parallel direction such that they are related by a center of symmetry in the crystal packing, and this again you can say tail, head, tail, head, tail, head; this kind of arrangement is there.

We can also have a layer-type arrangement. Let us look at the third one. We can have a layer-type arrangement. So, we form these kinds of layers; this is a layer-type arrangement where we have these overall layers being formed, and we can also have the herringbone arrangement. So, we have this one layer in one arrangement; this is in the perpendicular orientation. This perpendicular orientation is called the herringbone arrangement.

And now you can see here that when you have this particular arrangement head to tail, you have this void cavity that extends. Here, you also have the void cavity that extends. But here, the void cavity does not propagate.

So, the suitable arrangements in which the void cavity can extend can now allow you to include slightly larger-sized guests as well into these particular voids. What has been observed is that, just to give you a few examples, alpha-cyclodextrin includes benzene, methanol, 1-propanol, and 3-iodopropanoic acid.

Whereas in the case of beta cyclodextrin, it has been possible to include benzene and benzyl alcohol, and gamma cyclodextrin includes water molecules by and large. So, if you want larger-sized guests to be included, then we can take this extended hydrophobic cavity.

This is the extended hydrophobic cavity that can now include guest molecules. With this particular background in mind, we can now look at some of the most important applications of these compounds. One application I have mentioned is in the drug industry, where it is very relevant; for example, in analytical chemistry.

As I told you, it is a chiral compound; therefore, these cyclodextrins can be used for making chiral columns, which can be used for the separation of organic molecules; that is one application.

They are used in the food and cosmetics industry. They are used in pharmaceuticals, and they also find applications in enzymology and other biological processes. So, how does it do this exercise? How does it achieve this desired property?

So, as I already talked about with respect to the pharmaceutical co-crystals, you can improve the bioavailability of the drug. Because now you can encapsulate the drug inside this cyclodextrin, it can then be transported to the site of action.

And the next thing is that it enhances the stability of the drug with respect to photochemical degradation, moisture, pH, etc. Now, it is very important to keep in mind that the drug industry produces these drugs in large quantities, and they are also transported from one place to another.

Now, these are very sensitive. It can happen that the drug is very sensitive to light, very sensitive to moisture, can take up water, and is also sensitive to acidic and basic conditions. So, in order to improve the shelf life of the drug, you would like to enhance its stability.

The shelf life is the time for which the drug is stored before it is given to the customer for consumption. The stability of the drug can be enhanced by encapsulating it in a carrier molecule like cyclodextrin. So, the cyclodextrin definitely enhances the stability and shelf life of the drug. And the resulting cyclodextrin-drug complex is a powder that is easy to handle. The next thing is that it is added as a flavoring agent with various compounds.

So, say you are adding a flavoring agent; for example, in the food industry, you are adding this flavoring agent. So, then you can mix the flavoring agent with different compounds, plus this cyclodextrin, and make them more resistant to oxidation, thermal decomposition, and loss by sublimation.

So, if the compound of interest, the flavoring agent, or the particular organic molecule that is being used has a property that it can sublime easily. Then this encapsulation with cyclodextrin can make it more resistant to minimizing the processes of sublimation, thermal decomposition, as well as any oxidation process. And so, as you can see now, overall, these are some of the most important applications, and most importantly, it is also used to make the sunblock lotions that are in the cosmetics being utilized.

For example, in sunblock lotion, cyclodextrin has also been added again to increase stability and to prevent photolytic processes from taking place, where the decomposition of the compound can occur in the presence of light.

So, I hope that with this lecture we have been able to know and understand the importance of cyclodextrin, and this essentially completes the host-guest complexation behavior. Now, starting next week, we will go on to the next module, which will talk about crystal engineering and other aspects of supramolecular chemistry.

Thank you.