**Fundamentals and Applications of Supramolecular Chemistry**
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**Week 03**
**Lecture 15**

W3L15_Host-Guest Complexation, Thermodynamic and Kinetic Selectivity

Hello everybody. So, now let us continue our discussion from where we left in the last lecture. In the last lecture, we were talking about the hydrophobic effect. And we also talked about the importance of solvents and their role in forming solute-solvent interactions.

And also during the process of crystallization, these solvents play a very important role. And there are hydrogen bonds as well as dispersive interactions depending upon the nature of the solvent and the solute.

Now, the process of solvation, the dynamics associated with solvation is extremely important in host guest chemistry. Why, because the thermodynamic and kinetic considerations are extremely important.

And primarily we are looking at a host plus a guest in the presence of a solvent to form the host-guest complex which is solvated. And it is important to understand the role of enthalpic and entropic contributions that govern guest recognition.

So, to start with let us look at the different processes which are involved during the process of complexion of a host and a guest in the presence of a solvent. So, to start with we can now consider a three-dimensional host.

So, this is a three-dimensional host and this host to start with has been dissolved in a particular solvent. So, the host is solvated. The guest is also solvated and we will now look at the processes which takes place on thermodynamic grounds when a host complexes with a guest to form a host-guest complex.

So, to start with this is highly solvated by polar molecules, of the solvent or these are the solvent molecules you can consider. In general, you can consider this is a solvent in which I have dissolved my host and all kinds of interactions are present here.

We have already discussed you can have hydrogen bonds plus van der Waals interactions which are present. Now, if a host has to complex with a guest, the first process is the desolvation process. During the process of desolvation, now I would represent this 3D

host in a slightly simplified way just for the sake of discussion.

So, I am considering this to be my 3D host now and the desolvation has happened and the solvent molecules are now released away. So, when you have the desolvation of the host, this is enthalpically unfavorable, but entropically it is favorable.

This is because when you remove the solvent molecules then you eliminate the hydrogen bonds which stabilize the host. So, enthalpically unfavorable, but entropically you increase the number of particles in the bulk. So, this is an entropically favorable process.

As we have already realized that the host must now get pre-organized because it is a conformationally flexible host. Therefore, now there has to be a change in the conformation and the host now rearranges into a different conformation or the more active conformation before it will encapsulate the guest.

So, now you see here that there is a conformational rearrangement. This is both enthalpically and entropically unfavorable. Why because energy has to be spent by the system in trying to change the conformation to get it into the more active conformation.

And it is also entropically unfavorable because now you are going to restrict the motion of the conformationally flexible molecule. So, there is a conformation restriction. So, the entropy loss takes place and there is an enthalpy contribution because energy is necessary to change the conformation.

And it is at this stage that we discussed that if you have a pre-organized host, then the process is highly facile because this enthalpy and entropy cost will not be involved. Already during the process of synthesis this cost would have been paid during the process of preparation of the particular pre-organized host and therefore that will not play an important role now.

So, however now that we have got a pre-organized host, so this is the first stage where you have the host being solvated, the second stage which is the desolvation. The third is the conformational change. So these are the processes which happen from the host side. Now coming to the guest side, you have the guest which is actually solvated. So, this is the solvated guest.

For example, we have the different coordination complexes, and now we have the de-solvation of guest, because if the guest has to coordinate with the host, then it has to remove the solvent molecules.

So, we now get the isolated guest and the solvent molecules are in the bulk. In the next stage ,we now have the complexation process where the host and the guest complex with

each other. So now the host and the guest are going to complex with each other and this is going to be the sixth stage. So the fifth step is here, the desolvation of the guest.

Now desolvation of the guest again is like the desolvation of the host, it is enthalpically unfavored and entropically favorable. Now we have the complexation between the host and the guest. The host-guest complex has been now formed. So this process is enthalpically favorable because there are enhanced host-guest interactions. There are host-guest interactions.

And then we have got the next stage where we have the solvation of host-guest complex. Now this is the solvation of the complex and this is enthalpically favorable, but entropically unfavorable because the solvent molecules which are present in the bulk will now come and coordinate with the host-guest complex.

And overall, now at the end of the process, we see that after we have considered the desolvation and we have considered the solvation processes, effectively we see now that at the end of all these processes, this amount of solvent is still released into the bulk. And therefore, this results in favorable increase in entropy.

So overall we see that the process of complexation of the host and the guest releases solvent molecules into the bulk and therefore that increases the translational entropy of the system and therefore we say that host-guest complexation is favored by an increase in entropy of the system.

Enthalpically also it is favored because now the host-guest complex is stabilized by favorable interactions between the solvent and the host-guest complex. So, overall, the host-guest complexation dynamics are such that you have a stabilized species where desolvation processes are involved.

This conformational change which is very important and then you have the host guest complexation, followed by solvation of the host-guest complex to form the final state of the complex. So, all these processes operate and that is the reason why solvation is a very important effect. And we can take one particular example just to illustrate this particular effect.

For example, we will see now, let us say you have got a non-polar molecule or you have got a organic molecule which has got polar plus non-polar parts. Let us consider for example, you know cyclodextrin which has got some polar heads and it is solvated.

So, there are water molecules which solvate the cyclodextrin and now you add a guest. So, what will happen is that the guest molecules will now interact with the cyclodextrin, and it will form favorable host-guest interactions, and the water molecules will be

released into the bulk. Now to start with the water molecules which are interacting with the cyclodextrin cavity are not in a very stable configuration.

Why? Because they are interacting partly with the polar functional groups, but they are also interacting with the non-polar functional groups and we know that these are hydrophobic surfaces and water is a hydrophilic solvent.

So, there is a repulsion between the hydrophobic and the hydrophilic parts, and therefore the water which is interacting with the cyclodextrin cavity are considered to be high energy water molecules. They are considered to be high energy water molecules and now what happens to them that when the guest now goes and complexes with the cyclodextrin these high energy water molecules are now released into the bulk.

And there they are in a much more stable environment because they form extensive hydrogen bonding with themselves. So, hydrogen bonding between the water molecules in the bulk stabilizes these water molecules.

And the guest also gets stabilized because of the favorable hydrophobic interactions. This is because the guest can have hydrophobic parts which is interacting with the hydrophobic parts of the cyclodextrin cavity and therefore, the guest also gets stabilized in the host cavity. And we see that enthalpically, this is the favorable process because you have enhanced host-guest interactions.

And you also have hydrogen bonding between the water molecules and entropically also this is a favored process because the water molecules which were having a very ordered arrangement around the cyclodextrin cavity now get released into the bulk. Now when they get released into the bulk that increases the entropy change for the process.

Similar to what we have observed in the previous case that the water molecules which are released overall increase the entropy of the system. Here also the water molecules which were initially solvating the cyclodextrin cavity and which were in an relatively high energy arrangement now get stabilized when they form hydrogen bonds with themselves in the bulk. So, overall, this increase, this is also entropically favorable.

So, with this example, we now are able to appreciate that host-guest processes are always favorable and they are driven by an increase in the entropy of the system and these are also enthalpically favored. And now we will look at some examples related to appreciating the chelate effect and macrocyclic effect.

For example, let us consider a chemical reaction, of $Cu^{2+}$ ion in aqueous medium with different ligands whose structure I will give below, and these experiments have been done at 25 degree centigrade in water.

The ligands are as follows. NH2NH2, this is ethylene diamine, this is a open chain conformation. This is a podand, as we have discussed and now we take the corresponding cyclic ligand as represented below. So, we have a 3 ligands, ligand 1, ligand 2, ligand 3.

This particular ligand has got denticity 2, there are 2 binding sites, 2 nitrogen atoms. This one has got 4 binding sites, this also has got 4 binding sites. The thermodynamic data has been provided that is the enthalpy change, in the standard state, is minus 105 kilo joule per mole for the first complex, minus 90.4 for the second complex and minus 76.6 for the third complex.

The entropy contribution, the T delta S 0 term, in kilo joule per mole inverse has also been given, 7.1, 24.3, 64.0 and what we have to compute is the log K values, that is the binding constant, which is obtained by the complexation of the copper ion with this particular ligands. So we can see here that when copper and now binds, so in this case we will have in the first case we know that Cu2+ ions form octahedral complexes.

So, in this case, the copper ion interacts. We have the copper ion here. So, the copper ion essentially chelates with this particular ligands and we can now calculate the log K values. So, we know that delta G 0 is equal to delta H 0 minus T delta S 0. So, for the first one minus 105 minus 7.1 that is 112.1 kilo joule per mole and we know that delta G 0 is equal to minus RTlnK which is equal to minus 112.1 and we know that R is the universal gas constant 8.31, T is 298 Kelvin.

So, we can now get the value of log K by dividing the natural logarithm, the value obtained from the natural logarithm by 2.303, this will come out to be 112.1 into 10 to power 3 by 298 into 8.31 into 2.303. This will be around 19.7. So, 19.7 is the log K value for the first complex, it is 20.1, if you calculate for the other complex and it is 24.8, for the third complex.

So it is very clear that the third complex is the most stable complex because you can see in addition to the chelate effect, so you have one chelate ring here, you have another chelate ring here, you have another chelate ring here, another chelate ring here, you also have a pre-organized host, so you have the four chelate rings plus you have a pre-organized host.

The host is having a very, very rigid and constrained geometry and it also has the necessary converging sites, the nitrogen lone pair, as we have discussed have oriented towards a copper ion, to form this particular arrangement with the copper complexes with the 4 nitrogen atoms.

Contrary to that, in case of the second ligand, we do have the chelate effect which is operational, which is coming from the 3 different rings, and in the first case we only have

the chelate effect which is operational. So, the macrocyclic effect actually enhances the binding constant of the complex and you can also see that the T delta S 0 term is most favorable for the pre-organized host.

As we realized that if the host is already pre-organized, then the unfavorable entropy loss does not take place, because conformational change is not necessary. However, in terms of the open chain conformation, for example, in this case, the conformation has been drawn in a way, so that it shows you the one which will be undergoing complexation.

But you can also have the open chain conformation, where the amino groups are far away from each other, and hence the necessary conformation has to be formed and that is entropically unfavorable and that is also reflected in the low value of T delta S 0 compared to the value for the ligand 3.

And for the ligand 1 obviously, the T delta S 0 term is the least, and the enthalpy, consideration wise you can see delta H 0 decreases, because you are increasing the hydrophobic content in your molecule, you are increasing the number of carbon atoms.

Therefore, the stabilization coming from hydrogen bonding is also reduced number 1, number 2 you are also decreasing the number of NH bonds when you are going from second to third ok. So, when you go from second to third you have replaced two of the NH bonds by the ethylene spacer.

So, overall this hydrophobic-hydrophilic balance is what decides delta H 0 and a combination of both the enthalpy change and entropy term is what decides the overall stability or the binding constant of these complexes.

And now to summarize this particular week's lecture, we have seen a lot of aspects related to host-guest design. And to complete this series of lectures for the third week, the final topic which we would like to discuss in brief is about thermodynamic and kinetic selectivity.

Now, this is relevant because there are many processes in nature which do not happen at thermodynamic equilibrium. The processes are instantaneous, are fast, and many times there is a preference for one guest over the other. So, if you have, say for example, a mixture of metal ions, then you have a host which would specifically like to only bind with one metal ion and not the others.

Similarly, you can have guest molecules, but you will have a host which is only sensitive to one guest molecule and not the others. For example, these kinds of processes, are very much relevant in nature, in case of enzymes, transport proteins, etcetera.

And also, we know for example, in case of hemoglobin, in blood, it is supposed to take up only oxygen from a mixture of nitrogen, water, carbon dioxide, etc. So, it has very specific binding for oxygen out of a mixture of gases.

So, in this case, we need selectivity. And then in this regard both thermodynamic and kinetic selectivity are important. So, because hemoglobin needs to have very specific preference for oxygen therefore, it should be able to bind to oxygen very very strongly.

And then once it binds, it should be able to transport oxygen to the site of interest, and then it should be able to release the oxygen wherever it is necessary. So, binding uptake process as well as release processes, both are very important in selectivity processes. Now, we define thermodynamic selectivity as the preference of one guest over the other.

This is how we define thermodynamic selectivity and we know that in general, when you have host plus guest to give you the host-guest complex, the K in the case, is the ratio of the concentration of the complex to that of the host and the guest, and the thermodynamic selectivity is essentially the ratio of this equilibrium constant of guest 1 in comparison to that of guest 2.

So, larger is the value of this ratio, more is going to be the thermodynamic selectivity of one guest over the other. That is simply reflected in the magnitude of the equilibrium constant being higher for guest 1 in comparison to that of guest 2.

And you can play with the thermodynamic selectivity via the concept of lock and key principle which we have discussed, preorganization of the host and increasing the host-guest interactions. Whereas kinetic selectivity are the processes which involve transport of guest at the fastest rate.

So, when you have kinetic selectivity, it is the rate of the biochemical transformation or the rate of sensing and signaling that is most important. So, say you want to achieve a given biochemical transformation in the presence of a guest.

So, you have a large enzyme or a large protein molecule that senses the guest, and then once it has sensed it, the transformation takes place and then the guest, is released or you would like to transport, say specifically one particular guest. So, it has to sense it and then absorb it and then it has to also transport it at the site of action.

This involves rate processes. Kinetic selectivity does not need pre-organization. So, pre-organization or rigidification of the host is not necessary for kinetic selectivity because the enzyme undergoes rapid changes in conformation.

It goes to a series of intermediate states where there are changes in conformation to accommodate the guest and once it binds, it immediately transports, and releases the guest at the site of action and all these processes do not need pre-organization of the host.

Rather what it needs is reaching the transition state, wherein the guest has got a pretty strained geometry and perform the process to complete the reaction, so that the desired selectivity or kinetic selectivity is achieved. So, this differentiates kinetic selectivity from thermodynamic selectivity.

If you have a process where the binding is irreversible, very strong, the binding constant is high, kinetic selectivity will not be achieved. Only thermodynamic selectivity will be achieved, but kinetic selectivity is something that is related to the rate of the process. There binding is important, but the binding should not be very strong.

It is the transport process and the subsequent release at the site of action, which is of extreme relevance. So, kinetic and thermodynamic selectivity also plays a very important role in trying to understand for example, supramolecular catalysis, understanding biological processes and so on and so forth.

And we will be discussing some of these things later on in the course as well. So, with this we complete this particular lecture.

Thank you.