**Fundamentals and Applications of Supramolecular Chemistry**

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**Week 03**
**Lecture 14**

W3L14_Thermodynamics of Host-Guest Complexation, Role of Solvent

So, let us continue our discussion. So, in the previous lecture we were looking at the role of conformational flexibility of the ligand and the role of pre-organization. So, let us now go a bit more into the details of pre-organization of the ligand and its effect on the binding constant in host-guest complexation behavior.

So, just to recapitulate, we can look at the podands which are the open conformation of the ligand which has the donor atoms position and you can see that this forms the host-guest complex and this is operating because of the chelate effect.

In the next case we have got a close conformation or we have got a cyclic conformation with the donor atoms position here and then when the guest approaches, we form the metal complex the host-guest complex, where the stability comes from the operation of both the chelate effect as well as the macrocyclic effect.

And as we discussed already that the macrocyclic effect is the additional stability imparted to the system because of the presence of the pre-organized conformation.

Why the pre-organized conformation is important because there is no energetic penalty paid to actually change the conformation and make it adopt the right conformation for binding. So, because that energetic penalty has already been contributed in the process of synthesis the ligand the macrocyclic effect becomes operational.

And if you now want to enhance the magnitude of the macrocyclic effect, then we can further make a more rigidified host. For example, we can have a bicyclic host, which has the same set of donor atoms, and has got a bicyclic host in the sense, one is this bicyclic system, cyclic, and this is the another cyclic system, and then in the presence of guest we can have the corresponding macrobicyclic host guest complex and the magnitude of the binding constant was found to increase.

LogK3 greater than LogK2 greater than LogK1 which reflects the fact that increasing degree of host organization results in enhanced magnitude of the binding constant. Now, it has now been realized that the delta G 0, that is the Gibbs free energy change for the

process assuming that we are doing the experiments at room temperature, that is at 25 degree centigrade.

The magnitude of the binding constant is related to the Gibbs free energy change. More negative is going to be the Gibbs free energy change the higher is going to be the binding constant. And we also know that the Gibbs free energy change comes from the enthalpy change for the process minus the entropic contribution.

In the case of the open conformation, there is an entropic penalty as already discussed we have to change the conformation of the ligand and bring it into a more rigid structure whereby it loses its degrees of freedom.

So, thus the entropic term becomes unfavorable and to offset the unfavorable entropic term the delta H 0 has to be sufficiently large so that the delta G 0 for the process is negative. And, because the delta G 0 for the open conformation is lower, we adopt a cyclic conformation where the entropy change for the process is minimum because there is no entropic penalty now.

That has been paid again during the time of synthesis because we have made a cyclic conformation, we have made a closed system. So, this unfavorable entropy loss does not take place and therefore, the T delta S 0 term is more negative compared to the open conformation and this results in delta G 0 being more negative for the closed system and I say the closed system it means the cyclic system.

And in order to evaluate these thermodynamic processes, these quantities, the thermodynamic parameters have been evaluated in two particular systems. Let us see how the pre-organization of the ligand plays a very important role in complexation with the guest.

So, let us consider this particular example. And we have a metal ion M n+. Here we also have the same metal ion complexing, to start with, this is the system A, which is essentially a podand.

So, we call these cyclic systems here as corands. So, this is a cyclic system which we called as corand and what has been reported is the following. The thermodynamic data reported for these complexes A and B is given here, log K is equal to 11 and it is 15.3 for the complex B. The delta H 0 is minus 44 and this is minus 62 and T delta S 0 is minus 20 and this is minus 26.

So, right away we can see that there is an increase in the value of log K by around 10 to the power 4 times. So, here we can see very clearly that the ligand B is pre-organized. So,

this is the operation of the macrocyclic effect because the conformation of the ring has already been pre-defined, it is already a rigid conformation.

The donor atoms as we know that host has got the converging site property, you can see that the donor atoms are converging towards the metal ion and they are already oriented for effective binding with the metal ion. Also, we know that if the ligand were open, when the ligand was in the open conformation, and we have to now bring it into the closed conformation.

For example, in the case of the podand, we will have to minimize the lone pair-lone pair repulsions and that has to be overcome by favorable metal-ligand interactions. So, the overall enthalpy contribution comes from the maximization of the metal-ligand bonds and the minimization of the unfavorable lone pair-lone pair repulsions.

Now, because this thing is more severe in case of podand, this reflects in the delta H 0 value being slightly less negative for A compared to that of B. Because in case of B already the organization of the ligand is more rigid, it is already pre-organized, the lone pairs are specially positioned. So, overall, now the unfavorable repulsions have been taken care of.

So, now it is the maximization because of the lone pair-metal binding which dictates the delta H 0 term. And from the entropy change also you can see that the T delta S 0 term is more negative for B complex again justifying the favorable entropy which is present in the case of B complex compared to A complex.

Here in case of A we have realized that the entropic penalty has to be paid during the process of change in conformation of the podand to bind with this particular ligand. So, you can see here this is one chelate ring, this is another chelate ring, this is another chelate ring, this is another chelate ring. There are two 5 membered chelate rings and there are two 6 membered chelate rings.

So, two 5 membered rings and two 6 membered rings are operational. Here you have got one 6 membered ring and here you have got two 5 membered rings. So, overall, the chelate effect is also more in case of B and the ring being cyclic in nature the ligand being cyclic in nature, it is pre-organized therefore, the macrocyclic effect also operates.

So, the extra stability originates from both the greater number of chelate rings as well as the macrocyclic effect which results in high value of the binding constant for complex B compared to that of the complex A. And this experiment has been done in case of both the metal ions.

That is copper ion as well as zinc ion to demonstrate the role of pre-organization in metal-ligand complexation. We have now realized that pre-organization plays a very, very important role in case of binding.

And now we would now like to go and try to explore the next topic in the series wherein we would like to look at the role of solvents. Role of solvents in host-guest complexation behavior. So, this is a very important entity.

The solvent is an important chemical entity in host-guest complexation behavior. Now why is a solvent very important? The solvent is important because it has to stabilize the host and the guest via solute solvent interactions.

So we have got the host molecule. It has to be solvated by the solvent molecules such that there are enthalpy changes associated with the process which is negative. Similarly we can have the guest molecules which has to be solvated by the solvent molecules such that the enthalpy change for the process is negative.

So, the fact that solute-solvent interactions are very important because the enthalpy change associated for the process is very negative and why is the enthalpy change negative is because there are different kinds of interactions via hydrogen bonding primarily between the host/guest and solvent molecules.

We can see that water can form hydrogen bonds with the host molecules. Okay water can form hydrogen bonds with the host molecules, chloroform can form hydrogen bonds, with say a carbonyl group. Say, we have got organic compound, which is called a carbonyl group, and we have got chloroform it can form a C-H...O hydrogen bond.

Similarly, you can have formamide, which can form hydrogen bonds with the host molecules. So, these are the polar functionalities, these are the acidic hydrogens, which can form hydrogen bonds with the host molecules.

So, more is the number of hydrogen bonds more extensive is going to be the solvation between these polar entities and the acceptor atoms which are the electronegative atoms on the host molecule.

We can also have interactions between non polar functionalities, like for example benzene, with an organic molecule, which is the host, which has got also a pi system. So, we can have favorable interactions, between benzene, there is a non-polar part with the non-polar part of the host.

So, you can have these pi...pi stacking interactions between the solvent molecules as well as the host molecule. Now what is the proof that these solute-solvent interactions are present?

The proof is that when you will crystallize these host molecules from the solvent then you will see that the solvent molecules are included in the crystal structure.

And as we discussed that you have got voids in the crystal structure where the solvent molecules can now go and get included and they are actually held by either the dispersive interactions or the strong hydrogen bonds.

So, in large number of cases for example, when crystallization has been done from water molecules, water has been included in the crystal structure. When the crystallization has been done from other polar molecules, like for example, methanol, ethanol, propanol, butanol, these polar solvents have also been included in the crystal structure and they form strong O-H...O or O-H...N hydrogen bonds with the host molecules.

That means there is a strong hydrogen bonding between the solvent and the host molecule and when you crystallize it out, because these are favorable on enthalpy grounds, there is enthalpy change negative associated with solute-solvent interactions. They tend to get crystallized out and stabilize the crystal structure as well.

So, these polar solvents can also interact with the oxygen and the nitrogen donor atoms on the host molecules. We can also have a dichloromethane which is very common which gets included in the crystal structure.

Dimethyl sulfoxide interesting, $CH_3SOCH_3$ here, the sulfonyl group actually accepts hydrogen bonds. So it accepts hydrogen bonds from the host molecule. So host molecules need not always have the acceptor atoms. It can also have the hydrogen bond donors which are present on the host molecule.

The hydrogen bond donors on the host molecule can interact with the more electronegative oxygen atoms on the solvent forming N-H...O hydrogen bonds and these can lead to inclusion of DMSO in the crystal structure.

Same thing we can have for N,N-dimethyl formamide. $HCONH_2$, you will see that the carbonyl group participates in hydrogen bonds with the NH or the OH groups of the host molecule. So, it is not necessary always the donor atoms participate, but it can also be the more hydrogen bond donors from the host molecule which interact with the solvent forming strong hydrogen bonds and therefore getting included in the crystal structure. And it has been observed that large number of structures do have formamide or DMSO included in the crystal structure.

Even ethyl acetate is another polar solvent which gets included in the crystal structure and sometimes hexane is also used with crystallization because ethyl acetate or DCM are

very polar solvents and they tend to evaporate fast. So, hexane is added so as to lower the rate of evaporation of the solvent.

And sometimes depending upon the nature of interactions between the host molecules and the solvent, more than one different kind of solvent can also get included in the crystal structure. So, the crystal structure need not always have a single solvent, it can also have more than one solvent which were used during the process of crystallization.

The process of crystallization is such that you need to have the solvents which dissolve the compound and then crystallization takes place and there are many other properties of the solvent which play a very important role.

For example, in addition to hydrogen bond donor and hydrogen bond acceptor. These are the two fundamental properties we looked at with respect to solvents at the chemical level. At the molecular level the solvent can have a hydrogen bond donor or it can be a hydrogen bond acceptor.

But what is also important further, is the dipole moment of the solvent which is reflecting the fact that how polar my molecule is, dipole moment of the solvent, dielectric constant of the solvent. Dielectric constant, surface tension, viscosity etcetera.

So some of these properties are very important for solvents as well and the literature has the values for all these physical properties of different solvents, dipole moment, dielectric constant, surface tension and viscosity and these also play a very important role in the deciding the properties of solute-solvent interactions.

Now keeping in mind that solute-solvent interactions are very important, and now that most of the experiments in supramolecular chemistry are going to be done in solution, the role of the solvent becomes very important.

And in this regard what has been proposed is that when you need to keep in mind, let us say you have got a organic molecule. Organic molecule has got polar regions as well as non-polar regions. Now, if you add water it is the polar functional groups which will interact with the water molecules.

This is an indication of strong hydrogen bonding. So, this is an indication of hydrophilicity that means the water molecules interact with the host molecules favorably.

However, if the water molecules do not interact with the host molecules favorably, why, because the host molecules can have non-polar functional groups, then the non-polar functional groups repel the polar functional groups.

For example, the hydrogen atoms of the polar molecule, then it is a measure of hydrophobicity. So, hydrophilicity and hydrophobicity are two very important aspects when it comes to considering solute-solvent interactions, and hydrophilicity.

So, the interactions between the solvent and the host molecules is favorable. And when you say it is favorable, it essentially means the free energy change of the solvent molecules, which if it were to be hydrophilicity, that means there is a favorable interaction between the water molecules and the host molecules, and the free energy change associated with the solvent molecules is going to be negative.

If it is negative that is the free energy change is negative then it indicates hydrophilicity, but if the free energy change which is associated with the solvent molecules is positive then it indicates hydrophobicity. And this is something which has been very well realized. For example, if you take leaf and you have these veins and if you take water droplets then it has been observed that the water droplets will come close to each other and they will form a large droplet of water on the surface of the leaf.

Why? Because there are strong unfavorable hydrophobic interactions between the water molecules and the surface of the leaf. So, these interactions are unfavorable because the leaf of the surface is hydrophobic and the driving force is that the water molecules now interact with each other form larger droplets because of the favorable hydrophilic interaction between themselves.

So, water-water interactions lead to coalescence and because the overall process is associated with the negative Gibbs free energy change it is favorable. And the fact that these coalesce together and form larger water droplets is a measure of hydrophilicity. And the fact that these water molecules now repel the leaf surface indicates that non-polar parts always try to be with each other whereas the polar function always try to be with each other.

And this is a reflection of the so called hydrophobic effect. So, the hydrophobic effect is a proof that in a system when you have polar functional groups and non-polar functional groups, the non-polar functional groups will always try to come close to each other and avoid the polar functional groups, as has been demonstrated in this case.

And the polar functional groups will always try to interact with each other and because of the favorable hydrogen bonds, because of the hydrophilicity associated with the processes, this phenomenon, is referred to as the hydrophobic effect.

And, this is what also is operational in all kinds of biological systems, that is the hydrophobic effect is something which is ubiquitous whether you have a biological system or a small molecule system, always the polar parts try to be with each other, and

the non polar parts try to be together. And, this balance between the hydrophilicity and the hydrophobicity is what decides the overall stability of the system.

So, a favorable balance between hydrophilicity and hydrophobicity is what decides the overall stability. For example, in terms of the overall Gibbs free energy change associated with the process, wherein the role of solvent is very important, both these hydrophilicity and hydrophobicity decides the overall stability of the system.

So, now in the next class, we will discuss more about the role of solvent processes in host-guest complexation and take up further examples.

Thank you.