

Fundamentals and Applications of Supramolecular Chemistry
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W3L12_Lock and Key Principle and Chelate Effect

So now let us continue our discussion about host-guest chemistry. Now the next concept is the concept of formation of clathrates or cavities. When you have the formation of the clathrate or the cavity, the host molecule can have an intrinsic cavity associated with it.

So, let us consider for example. This is the host molecule, and this is the cavity which is present. Now, this cavity which is present is now available for guest binding.

And the guest can now get included in the cavity of the host molecule via non-covalent interactions and this gives rise to inclusion compounds or inclusion complexes. And this cavity, which is intrinsic to the host, this exists both in solution as well as in the solid state.

So this host molecule, has intrinsically got a cavity and when you take this compound and you determine the structure of this compound in the solid state, this cavity is there and now when you take this compound in the solid state and dissolve it in a particular solvent, then the molecules are moving around in the solution, it still retains this intrinsic void or cavity such that the cavity can now include the guest molecule, giving rise to the formation of these inclusion compounds or complexes. So, these host molecules are called cavitands.

So, what is a cavitand? These are host molecules having intramolecular cavity, that is available to a guest for binding. And this particular cavity stays both in solution as well as in the solid state.

And the resulting complex, which is the inclusion of the guest in the cavity of the host is called a cavity. So, this is a cavitand and this is a cavity. On the other hand, we have another possibility where the gas molecules can now go and sit in the voids which are created by the crystal structure of the host molecules.

So now you see this is the crystal structure. You have the host and the guest arrangements and the voids are present. These are the voids which are present in the crystal structure and the guest molecules go and occupy these voids which are present in the crystal structure of the host.

So, these kinds of host molecules, which have this kind of arrangement are called as clathrand, and the resulting supramolecular complex is called a clathrate. So, what is a clathrand?

These are the host molecules that have got extra molecular cavities, whereas the cavitanid has got an intramolecular cavity, this has got an extra molecular cavity, and which is essentially present between 2 or more host molecules, and is of relevance in the solid state.

The resulting complex is called a clathrate. The clathrate is a host which has got extra molecular cavities which are present between the two or more host molecules where the guest molecules can now go and sit, and these are of relevance in the solid state and the resulting supramolecular complex is called a clathrate.

And we already discussed in the previous lecture we gave you an example of a chlorine hydrate which is an example of a clathrate which is an example of a clathrate. So, depending upon the association between the host and the guest that is whether the guest occupies the cavity within the host or whether it occupies the extra molecular cavity we can have either the cavitate or the clathrate formation takes place.

The next thing to keep in mind when we talk about host-guest complexation which is of relevance in supramolecular host-guest design is the principle of selectivity.

Because now you have got a given particular host of a particular shape, size and conformation and now you are going to add guests which are relatively smaller in size. And the gas can also have different electronic properties.

For example, the charge density distribution on the gas can be different. The size of the gas can be slightly different. And this can alter the nature of solute-solvent interactions between the gas and the water molecules or the solvent in which the gas has been dissolved.

And we also have the host which has been dissolved in a particular solvent. Again, we will come to the role of the solvent later, but as of now we know that the chemical properties of these host and guest can get modified in the presence of solvent.

And now we have got this different guest which are going to be sensed by the receptor which is the host molecule, and this decides the selectivity of the process and therefore the host displays a preference for a given guest or a family of guests, and a high degree of selectivity depends on the following factors.

It depends upon the complementarity of the host and the guest binding sites. We already discussed that hosts are characterized by converging binding sites and the guest are characterized by diverging binding sites.

So, there must be a good complementarity between the host and the guest binding site. The second very, very important factor which is highlighted in red is the pre-organization of the host conformation and the third one is the cooperativity amongst the binding groups.

That means the sites which are available on the host molecule are now available for binding with the guest molecule and what is the overall cooperativity amongst the binding groups.

And in this regard, we will have two types of cooperativity, we can have positive cooperativity, we can have negative cooperativity. And so, we have positive cooperativity when the affinity of the receptor for a given species increases.

When the affinity of the receptor for a given species say, for example, I call it species number 1, increases the affinity of the receptor for the second species. So, this is very important that what is positive cooperativity.

So, you have a receptor which is a host molecule, and it is able to sense say a given species that is say guest one and now the binding has taken place. And this process now enhances the affinity of the receptor species for another species of the guest molecule. In that case the effects are said to be cooperative.

And if the reverse takes place that means the affinity of the receptor for the second species is diminished once the binding with the first species takes place then it is said to be negative cooperativity.

And this particular positive cooperativity or negative cooperativity is of relevance in the binding of ligand molecules to proteins, the active site. So, positive cooperativity and negative cooperativity both can operate and what happens is that you have got a large protein.

And, say a guest molecule comes and binds to the protein which is the receptor molecule. Now, the moment the guest comes and binds with this particular protein, there is a conformational change.

There is a conformational change in the protein such that the changes in conformation can now accommodate, say another guest, say G2 which can go and fit into this particular site. Now this process is highly dynamic, because they are conformational changes which

operate at the molecular level, and this is a demonstration of positive cooperativity because the binding by the first guest with the protein receptor induces a conformational change and this we refer to as allosteric effect.

Because the changes take place in some other part of the protein, and we refer to this as allostery and that facilitates the binding of another guest molecule with the protein and thereby demonstrating positive cooperativity.

Now this positive cooperativity is of relevance, and it tells us that proteins are extremely dynamic species, and this is what is the recent understanding with respect to molecular recognition in proteins. But this challenges another well-known concept in host-guest chemistry which we call the lock and key principle.

The lock and key principle as we discussed was proposed by Emil Fischer where he said that when you have a protein in a given conformation, it is like a lock and if you have a key, then the key will only fit into those sites where it is possible to have good molecular recognition.

That means there are areas in the protein which are having voids or spaces into which this key can go and fit. There are only very specific sites into which the key molecule can go and fit itself into the lock which is reminiscent of the protein molecule. But the Lock and Key principle is assuming a very very static picture because it essentially considers a rigid structure for a protein.

That means it assumes that the protein is frozen at a particular conformation and there are some specific binding sites, into which the substrate molecule, the substrate molecule here is the molecule, which is being sensed, or the guest molecule can go and bind.

So, in biology we call the receptor substrate, substrate receptor interactions whereas in small molecule, chemistry community we say host guest interactions. So, the protein is my host and I have the guest molecule and only where the voids are present or the space is present the ligand molecule can go and simply attach itself.

This was the concept which was proposed by Emil Fischer which we called the lock and key principle. And we know that this is a very simplified picture because in reality as we have seen here the proteins are conformationally flexible entities, they are continuously changing the conformation and a protein at any moment has got an average conformation, but overall, the protein is a highly flexible entity. And there are multiple binding sites which are available within the protein.

Such that when you actually determine the overall structure, the crystal structure of a ligand protein complex, what you see is the final state of the ligand binding to a protein

site. But it may not be the exact picture because the ligand might have sampled different regions of the protein and wherever the fit, the allosteric fit was the best in terms of the enthalpy change.

And the entropy factor which we will now also be considering further in this course. Wherever these two factors facilitate the process such that the overall Gibbs free energy change associated with this molecular recognition is negative that particular association forms the most stable complex because of the association of the ligand with the protein.

We also need to keep in mind that positive cooperativity and negative cooperativity are also operational in solution when you talk about multiple guests binding or multiple equivalents of a given ligand binding with the host structure which is the protein.

So, the lock and key principle assumes a highly restrictive and frozen geometry, which is not true, it is a very, very simplified picture. But in reality, it is actually more conformationally flexible process, where the protein can sample different conformations and the ligand molecules will go and bind at specific sites governed by thermodynamic principles.

So, the lock and key principle is very important and here when you consider lock and key principle you have to assume the complementarity, as I said the complementarity of the host and the guest binding sites become very very important. And as I already told you there has to be a particular conformation of the protein in which the binding takes place most efficiently and cooperativity also plays a very very important role.

So, we need to keep in mind the size and shape of the guest molecule when it interacts with the site of a protein.

But we must also keep in mind the dynamic picture, that is what we are seeing is the final state of the system, but the system might have undergone conformational changes before the process of binding took place.

And for example, the allosteric effect can also operate there can be conformational changes happening to accommodate the gas molecules. And, positive feedback mechanism can operate, positive cooperativity can operate where more ligand molecules can get included at different sites of the protein which are facilitated by allosteric effect.

Now, the next important concept we would like to keep in mind along the same lines is the role of cooperativity and chelate effect particularly with respect to inorganic complexes.

And we will now look at this in more details where we essentially say that what is cooperativity that is two or more binding sites acting in a concerted fashion to produce a combined interaction that is stronger, than when the binding sites act independently of each other.

This is a very important definition of cooperativity. So, you have got two or more binding sites and these binding sites at the same time in a concerted fashion they produce a combined interaction such that it is much more stronger than when the binding sites act independently of each other.

So, instead of considering the effect of the sum of the individual interactions, it is observed that the combined interactions overall produced a more stronger effect compared to the role played by the sum of the individual interactions and that demonstrates positive cooperativity.

So, in the case of as I already told you when you have got two different guests which are going to bind, cooperativity represents the changes in the affinity of the host for another guest molecule as a result of binding of one guest molecule. So, once one guest molecule has binded to the host, now this activates the host further to bind another molecule and that is a measure or a demonstration of cooperativity.

And in order to demonstrate the phenomenon of cooperativity, we resort to the understanding of this phenomenon using an example of an inorganic complex, whereby we shall realize the importance of chelate effect.

Now, let us consider this particular system. So, we start with a nickel hexamine complex and now we take 3 equivalents of the base ethylenediamine which now forms the Ni(tris ethylenediamine) complex and 6 molecules of water. the log K value is 8.76 that means the equilibrium constant for this process is around 10 to the power of 9.

That means the complex which is on the right-hand side is 10 to the power of 9 times more stable than the complex on the left-hand side. Now in this case you will see that the ammonia molecules are coordinated with nickel, and these ammonia molecules can exchange with the ammonia molecules which are present in the bulk.

So, you can have exchange of ammonia molecules, and you can also have dissociation of ammonia, and then again association. But in case of the bidentate ligand even if one of the nitrogen atoms gets dissociated from the nickel center the overall ligand does not get dissociated because the other nitrogen is still coordinated with the nickel.

So, overall there is a much stronger binding of the bidentate ligand in comparison to that of the monodentate ligand.

This is what drives the stability of this complex. Why is it that the tris ethylenediamine nickel 2 plus complex is more stable is because the dissociation of the ethylenediamine ligand is not facile because it is anchored because of the presence of two nitrogen sites.

And this is what gives stability to this particular complex, and it is much more stable when compared to the hexamine nickel 2 plus complex. Now the overall thermodynamic contribution can be assessed based on the role of ΔG which comes from ΔH minus $T \Delta S$.

So, there is an enthalpy contribution, enthalpy change which contributes towards ΔG and there is an entropic term that is a change in entropy which contributes towards the ΔG , and we know that for this particular process to be thermodynamically feasible ΔG for the process must be less than 0.

And in this case, we see that on the left-hand side there are 6 nickel-nitrogen bonds, on the right-hand side also there are 6 nickel-nitrogen bonds. So, then what is the reason for the exceptional stability of this complex? Because in terms of ΔH there is not much significant change.

Enthalpy changes are practically equal to 0 because we have the same set of bonds on the left hand side as well as right hand side. But what essentially has increased is the number of particles on the right hand side. Number of particles on the right hand side is 1 for the complex plus 6 for this ammonia molecules that is 7, but here we have got 1 for hexamine nickel 2 plus and 3 ligand molecules that is 4.

So, there is an increase in a number of particles when you go from the reactant to the product and this is associated with an entropy increase because more particles are now released into the bulk of the medium and that means the number of translational degrees of freedom now increases and this represents a positive entropy change.

So, ΔS is greater than 0. That means, this is entropically favorable and because both ΔH and $T \Delta S$ contribute and this term is negative therefore, and ΔS is positive therefore, this makes ΔG negative and a thermodynamically favored process.

So, you can also look at it from the perspective of hexaqua complexes. If instead of ammonia you have got hexaqua complexes then you would have released 6 water molecules into the bulk in a similar manner.

So overall this process results in an increase in the entropy of the system. What has been

proposed is that the entropy change is $33.4 n$ Joule mole inverse Kelvin inverse, where n is the number of rings formed.

And it is because the formation of these rings which we call now as the chelate effect which is a manifestation of the entropy increase and hence the driving force for the stabilization of these complexes and that is why we say that the stability comes from the chelate effect. It is the effect of chelation of the ethylene diamine ligands that confers exceptional stability to this.

And more is the number of rings that are formed more is the entropy change associated with the process and the number of rings formed here are 3. So, the overall entropy change is approximately 33.4 into 3 that is approximately 100 joule mole inverse Kelvin inverse.

And we have looked at this aspect from thermodynamic data as well. So, let us look at the thermodynamic data for the amine complex and for the $[\text{Ni}(\text{en})_3]^{2+}$, this is minus 52 , this is 102 , this is minus 100 , minus 117 and this is ΔH minus 163 , minus 42 .

So, you can see that if you were to now look at the chelate effect, you can actually quantify the chelate effect, that is the change of change in ΔG , change of change in ΔH , and change of change in ΔS .

So, this is around minus 50 , this is around minus 17 , and this is plus 121 that is minus 42 minus or minus 163 . So, you see this is around plus 121 , the overall enthalpy change for this process is not very high, but what is important is the change in ΔS and this is approximately the same value you get from the calculation.

So, this is the magnitude of the chelate effect plus 121 joule mole inverse kelvin inverse and thus we see we can mention now that chelate effect is essentially an entropy effect. So, with this we can now appreciate the fact that entropy plays a very important role in the chelate effect which governs stabilization of complexes.

In the next lecture, we will look at more aspects of the chelate effect and take up more examples where we demonstrate the chelate effect followed by discussion on the further points on supramolecular host guest design.

Thank you.