Fundamentals and Applications of Supramolecular Chemistry

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Week 08
Lecture 38

W8L38_Examples of anion binding

So, hello everybody. Now let us continue the discussion further on anion binding. In the previous lecture, we looked at the role of pH in influencing the binding of different species with a given host. So, we looked at the soccer ball complex, where the change in the pH can actually influence the binding of either a cationic species, a neutral species, or an anionic species depending on whether the host is neutral, partially protonated, or completely protonated.

Now, we will look at the next factor that influences the selectivity of anions, and that is the shape. So, the shape selectivity is something we explore here, and in order to look at this particular shape selectivity, we will now consider the following ligand, which is drawn as follows.

And so, this is referred to as a complex. So, for this particular complex, we are now going to protonate the nitrogens. We call this the [H6-tren]6+ complex, so you can see this is a hexa-cationic host, and it has a large cavity associated with it. This cavity can now include different kinds of anions, so this cavity is cylindrical in nature.

It essentially resembles a cylinder, and we can now have different kinds of anions. For example, we can first start with the halides: fluoride, bromide, and iodide. The magnitude of the equilibrium constant is given: 4.19, 3.0, 2.6, and 2.15, and the log K value is 4.30 for the azide ion.

The position of all the atoms in the anion-bound complex has been determined by X-ray crystallography. So, X-ray crystal structures have been determined for all the anionic complexes that are bound to this particular H6-tren complex, and what has been observed is the following: when you look at the fluoride anion, it is the one that has the highest charge density.

So, in the case of fluoride, it is positioned somewhere here; this is the position of fluoride. Whereas in the case of chloride, it is positioned more at the center. In the case of bromide, it is also more or less positioned in the vicinity of chloride.

So, bromide and iodide, being larger in size, are able to be accommodated more towards the center of the cavity, whereas the fluoride is more towards one side; that means there is unsymmetrical binding or bonding in the case of fluoride. Now, in the case of fluoride, we have strong [N-H]+ F- hydrogen bonds.

These are charge-assisted hydrogen bonds, and the distance between the N and F minus, which means the donor atom and the acceptor atom, is 2.72 angstroms.

And all these distances can now be obtained by careful inspection of the crystal structure. In the case of chloride, it is around 3.2 to 3.4 angstroms. In the case of bromide, it is around 3.3 to 3.5 angstroms.

So, now what is more interesting to observe in this particular case is that fluoride is the most extensively solvated, but it is also the fluoride that has the highest value of the binding constant.

So, the magnitude of the binding constant follows the order of solvation. In fact, it is a surprising result because if solvation is greater, then more energy must be spent in desolvation to enhance the binding; but essentially, what drives the system is the larger number of enthalpically favorable N-H...F- hydrogen bonds that facilitate the association process.

The strength of the hydrogen bond decreases when the electronegativity drops to chloride, bromide, and iodide, thereby indicating a reduced binding constant. What is more interesting is that in the case of the azide now, if you now look at the azide.

The azide is positioned symmetrically, such that it interacts with these hydrogen bonds. In the case of azide, there is the formation of [N-H]+N- hydrogen bonds, and the magnitude of the binding constant is highest for azide because it indicates a nice steric fit. So, the shape of the azide ion is linear, and it fits very nicely into the cylindrical cavity created by the hexa-tren host.

So, the cationic host has a cavity, and this is more of a cylindrical cavity; this linear azide molecule is able to fit very nicely sterically into this particular cavity, thereby engaging in strong N-H...N hydrogen bonds, which is reflected in the large magnitude of the binding constant. So, the factors that drive anion binding here, we saw in the case of fluoride, are the small size and high charge.

In the case of azide, it is both the topological shape and the charge distribution. So, both, these factors play an important role; here it is the shape in the case of azide, and the charge distribution, and so overall we will see that electrostatics provides the driving force.

And this is enhanced by increased electrostatic forces, enhanced by an increase in the number of hydrogen bonds. So, these are the factors that are reflected in the enhanced binding of azide in this particular hexa-tren complex. Now, what was also done is that, in order to improve the binding with the fluoride, a slightly modified guest was taken.

In this host, we have again hexaprotonated it, and the fluoride can now come and sit in the center and form [N-H]+ F- hydrogen bonds. After looking carefully at the crystal structure, it was observed that the N...F distances are 2.76 to 2.86 angstroms, the magnitude of the log K is 11.2, and there is more symmetrical binding.

So, chemists can make fascinating molecules; they can modify the substrate in a way that actually allows for enhanced fluoride binding in a slightly modified hexa-cationic host, where the side chain has been truncated and the fluoride is now able to participate in the same set of hydrogen bonds.

And because you have now truncated the side chain, the cavity size also reduces, and the fluoride has a small size.

So that allows for a nice steric fit and for fluoride to be included in the crystal structure. So, this kind of features have been observed, which talk about the relevance of shape selectivity in governing anion binding. The next important set of complexes, which are also relevant in understanding biological anion receptors, means proteins that are sensitive to anions; in this regard, another very important receptor is the arginine residues.Now in the case of the guanidinium, we can see that the guanidinium unit is present on the arginine residue.

Let us draw that structure. For example, we can see here that this is my guanidine, and it is actually appended to the arginine residue. So, this is my arginine, and now we have the protonation of this; the protonation of this makes it NH2+ and now we can have different receptors that can form hydrogen bonds, forming N-H...O- hydrogen bonds with acetates.

So, this becomes a very interesting binding motif, where the acetates are sensed by the guanidinium cation. Now, the property of guanidinium is as follows: guanidinium, which is the protonated form, is an excellent anion binding site because it remains protonated over a wide range of pH. So, the pKa is 13.5 for the species, [CN3H6]+.

So, this is a protonated form, and you can see that the pKa of this is 13.5; therefore, its Bronsted acidity is very low. It would not like to release the proton very easily. Because it is stable over a wide range of pH, that means it will have pKa = 13.5. The other anions with which it binds also exist in this pH range.

For example, we would like to look at phosphates, or we would like to look at [HPO4]2- or [H2PO4]-. If you are looking at this kind of anion, then we will see that they all have negative charges. These negative charges will essentially interact with the cationic host, and the phosphate will also exist in the same range of pH in which the guanidinium moieties exist. So, that is why they have this very important property: they exist under the same basic conditions at which the phosphate moiety exists.

Now this is very interesting because what has been isolated is the methyl guanidinium cation. So, we have the methyl guanidinium cation, and it is stabilized by [H2PO4]-. This is my phosphate ion. So, this is strong hydrogen bonding: [N+H]...O- and N-H...O. You have these strong hydrogen bonds in the solid state.

So, they are responsible for the strong affinity of the guanidinium moiety with the phosphate moiety. There is strong energetic stabilization because of these hydrogen bonds that exist between the species. But what is observed is that now we have a strong affinity and this energetic stabilization. Hence, people started designing different kinds of receptors or hosts to sense phosphate anions, and in this regard, the first two important hosts were designed.

Let me draw the structures of those two hosts. These are slightly larger structures. So, this has a positive charge here. This is the positive charge here.This is the positive charge. So, this has threefold symmetry.

So, this is one particular host, which was designed, and this is a cationic host, which can sense the phosphate anion, and another host was designed, where we have the positive charge here. So, this is the host P. Both of these hosts were actually synthesized, designed, and as you can see, there is a lot of hydrophobic content in this, but they also have a lot of polar content. They have three-fold symmetry, but surprisingly, the value of log K was 2.4 for this, and log K was only 1.7.

So, this experiment completely failed because until now we had assumed that in order to have good binding, the size of the host should be larger and the anion should be able to sit in the voids created by the cationic host. But in this particular case, these experiments did not work. So, one possible reason is that the phosphate is too small to fit into the cavity, and number two, this is a rigid host. It is rigid because it wants to maintain the delocalization at the guanidine moieties.

So, that makes it quite rigid. So, this particular host is quite a rigid host because it has to maintain planarity to ensure delocalization. And the third thing is the extensive solvation of the host itself. So, in the previous case, we saw that although the anion, which is the guest, can be solvated, it tends to get included in the structure.

In this case, now the host tends to get highly solvated, and because it is highly solvated, it is not able to participate extensively in anion binding. So, that becomes a limitation of sorts, and in order to improve this particular process much more research went on, in this guanidinium based cationic moieties, and then some modifications were proposed, which actually led to enhanced binding in case of guanidinium moieties.

So, what was the modification that was proposed? The following substrate was then designed. Now you can see that chemists can make fascinating molecules. They can modify the templates. So, you now see that this is a modified guanidinium host, and now you see there is a reduction in positivity. So, it is only positive in this particular region, but it also has enhanced lipophilicity.

So, when you have got reduced positive charge, and you have got enhanced lipophilicity, then the extensive solvation will not take place, that will minimize the solvation, and therefore this kind of force is expected to have much stronger binding with the phosphate anion.

This work was done by a scientist called Schmithchen, in 1980, and as we can see that you have reduced the solvation, because you have reduced the hydrophilic core, and you have enhanced the lipophilicity.

So, now the binding with para-nitrobenzoate anion, and you know we have already looked at this fact that now you have got benzoate anion, so it can interact with N-H via these hydrogen bonds and when it will interact, the magnitude of the equilibrium constant now becomes 1.4 into 10 to the power 5 molar inverse in chloroform.

So, when these experiments were done in chloroform, and in the presence of para nitro benzoate the magnitude of the binding constant becomes very high.

So modified guanidinium host can now actually enhance this kind of processes. Another particular host was also designed, which modifies this binding with the anion, particularly the phosphate-based anions and why phosphate-based anions are important because they have a lot of applications in biological systems.

For example, we looked a little at enzyme mimics, and phosphates and other derivatives of phosphates, like oligo phosphates, are very important in the biological system. So, we can now take another modified host, for example, we can take this one now. Now, here we have got cooperative bonding, because you will have, this side the guanidine moiety, this side also you have the guanidine, and they can interact with the phosphate.

And what has been observed is the magnitude of the equilibrium constant now is 5 into 10 to the power 4 molar inverse in acetonitrile. So, this is the magnitude of the binding constant, when you have the corresponding RO2POO- and this also functions as a supramolecular catalyst.

Because, if you now want to do a transesterification reaction, where you replace R with some R', then the rate for that particular reaction is 300-fold enhanced, in comparison to that of the uncatalyzed reaction, this is the enhancement in the rate.

So, when you want to do the trans esterification reaction, using this particular phosphate, replace OR with OR', then that reaction proceeds 300 fold faster, in the presence of this particular supramolecular catalyst, that is the guanidinium moiety, which is strongly hydrogen bonded with the phosphate, and this strong hydrogen bond, actually lowers the activation energy necessary for the esterification process and achieves faster reaction rates.

So, keeping these things in mind we have now seen that you can actually, have modified guanidine residues, which can actually modulate the anion binding characteristics.

The last example, which I would like to discuss is, you can also use hydride sponge, combined with Lewis acid chelates to complex anions. This is another very versatile approach which has been adopted. For example, let us look at this case, where we have NMe2, there is a lot of electron density here, and now we add in a proton, and what does the proton do?

So, we have got this proton, now the proton is essentially the positive charge here, and it also interacts with this lone pair. So, we have this delocalized system, and we call this resonance assisted [N-H-N]+ hydrogen bond. So, the proton is definitely very stabilized in this particular arrangement.

On the same lines, we can now actually have Lewis acidic sites. We consider, BMe2, boron-based Lewis acidic sites, and now we add in a hydride ion, and the source of hydride ion comes from Et3BH-. So, triethyl borohydride, and it will interact strongly with the boron center here and form this hydride bridge.

Okay, and the interaction energy, is approximately 70 kJ/mol, that means, the hydride ion interacts strongly with the boron center, and this negative charge can now be delocalized over the two boron centers. Therefore, this electron deficient complex, the boron complex, functions as a hydride sponge, that can absorb hydride ion, and forms the tetrahedral complexes, whereby anions, the hydride ions can be effectively captured in this process.

So, hydride sponge also, is a very interesting mechanism, when it comes to sequestration of anions. Now, in the next lecture, we will now go on to other types of applications of anions. We will now look at biological anion receptors and some applications of ion transports, particularly cationic ion transport as well as anionic transports in structural biology.

Thank you.