

**Fundamentals and Applications of Supramolecular Chemistry**  
**Deepak Chopra**  
**Department of Chemistry**  
**IISER Bhopal**  
**Week 09**  
**Lecture 45**

W9L45\_Role of Secondary Coordination Sphere in Chemical Transformations

Hello everybody, today we are going to discuss the role of the secondary coordination sphere in supramolecular chemistry. So, we have already realized now that different kinds of metal ligand complexes have been prepared in the literature. For example, the square planar complex, the octahedral complex, or the tetrahedral complex has primary stabilization that comes from the metal-ligand bonding, which involves the overlap between the orbitals on the metal atom as well as the ligand atoms.

So, there is a strong overlap in this covalent bonding, but it is also important to keep in mind that this is the primary coordination sphere, as proposed by Werner. And Werner was a scientist who actually started this area of metal-organic complexes, and he made different kinds of colored complexes, and he was also able to account for the composition and later on the geometry of these complexes. But what is also important to keep in mind is that the formation of these complexes is stabilized by intermolecular non-covalent interactions as well.

So, between the ligand backbone, which is coordinated to the metal, you can also have hydrogen bonds or other non-covalent interactions that can stabilize the metal-ligand complex, and the presence of these interactions beyond the primary sphere has been observed to influence the reactivity profiles of these metal-ligand complexes.

It influences the reactivity profiles of these metal-ligand complexes; that is, these kinds of non-covalent interactions, which are present, and this set of intermolecular interactions, which now influences the other chemical reactions that are going to happen in the presence of this metal complex, is the influence of the secondary coordination sphere.

So, the next thing to keep in mind is that, say, now you are going to have a substrate molecule that is going to interact with this metal-ligand complex. So, we can have a substrate molecule; now we have the ligand.

We have the ligand here; there can also be non-covalent interactions (NCIs) between the substrate molecule and the ligand. And based on the nature of these interactions and the strength of these interactions, it can again influence the reactivity profile of the substrate, with, say, another reagent, say R, to give you the corresponding product plus  $ML_3$ , which can be coordinated by a solvent or another ligand that is present.

So, in this way, the presence of these non-covalent interactions, which constitute the secondary sphere, can influence the reaction outcomes depending on how the stabilization of this complex takes place.

So, what happens is that because of these non-covalent interactions, it can influence, as I told you, it can first of all stabilize small molecule substrates as well as reactive intermediates. So, the formation of a substrate plus reagent gives an intermediate, I, and this intermediate can be stabilized by non-covalent interactions.

Thus, stabilize small molecule substrates as well as reactive intermediates via NCIs. It can lead to an increased concentration of the substrate molecules; at the primary coordination sphere (PCS), it can modify the redox potential of the transition metal of interest via a peripheral change in the ligand environment.

So, these are some of the changes that can take place when you actually have these non-covalent interactions that constitute the secondary coordination sphere. Also, this has huge implications in enzyme catalysis, or you know when a substrate binds to the receptors in the case of enzymes. Substrates that bind with the enzyme are already pre-organized to provide proper activation for the reaction of interest.

And we also have redox enzymes where you can have electrons, protons, and substrates. These are all the active species that participate in the transformations, and the pre-organization of the substrate allows for the facile exchange of electrons or protons between the substrate molecules and the reaction medium to facilitate the rapid conversions, thus facilitating organic transformations.

For example, organocatalysis is again where you have the hydrogen bonding activation on the catalyst, which then interacts with the substrate molecules in specific ways to bring about chiral induction. So, these are some of the most important attributes of the secondary coordination sphere. We can also generalize this by saying that you can have a metal-ligand, and now we can have the secondary coordination sphere, which depends upon the kind of substituents that are present.

You can have a boron, electron-deficient Lewis acid species; you can have  $\text{SO}_3^-$ ; you can have  $\text{R}_3\text{N}^+$ ; you can have alkoxide; you can have  $\text{NHR}$ ; you can have crown ether; and appendages on this metal-ligand complex.

So, the kind of interactions you are going to have with these functional groups, which template the primary coordination sphere, will actually influence all these aspects of chemical reactions. Now we will look at some of the most relevant examples in this regard. So let us first look at example 1: the formation of supramolecular hydrogen-bonded bidentate ligands using secondary phosphine oxides. So, here we can have different examples.

For example, we can consider that this one is in equilibrium with the metal phosphinous acid. Thus, it can coordinate with the metal ion. So, this is the metal phosphinous acid, and this is an example of tautomerism. When you have  $R_1 = R_2$ , equal to an electron-withdrawing group, then the reaction is driven towards the right, so you have a sufficient concentration of this particular tautomer. Here, phosphorus is in the 3 oxidation state; here, phosphorus is in the 5 oxidation state.

And the strength of this metal-phosphorous bond is comparable to the metal-phosphine bond as well. So, how can we generate these metal complexes? Number 1, the use of an external base. For example, we can have a metal in a particular oxidation state, +2 times the phosphinous acid, and one equivalent of the base, minus the HB that is removed, and we now have  $M^{n+}$  coordinated with phosphorus here. So, we have the coordination with phosphorus; this is the complex now. So,  $R_1$  and  $R_2$ .

One equivalent of the base abstracts one proton from here. One of the ligands becomes  $O^-$  and the other ligand is  $OH$ . So, you have this intramolecular  $O-H...O^-$  hydrogen bond on this metal-ligand backbone. This is the secondary coordination sphere, and we have the metal that coordinates with the phosphorus lone pair. So, the phosphorus coordination involves the lone pair of phosphorus coordinating with the metal ion. This is one way. When you have used an external base, you can also use an internal base.

For example, you can use  $M^{n+} X^- + 2 R_2R_1-P-OH$ . I am not writing the stereochemistry anymore;  $HX$ , and this  $X$  can be either  $-OMe$  or  $-OAc$ , and it will give rise to this particular metal phosphinous acid complex. Now, these kinds of complexes are interesting because they can help in hydrogen activation. So, these are two ways by which you can generate the active concentration of these metal phosphinous acid molecules. We can now look at SPO-assisted hydrogen activation.

So, we now have the hydrogen molecule. It now polarizes the  $H-H$  bond. We can activate this; now we form this  $Pt-P(PPh_2)-OH$ , which is  $PPh_2-OH$ ,  $PPh_2O$ , and we have got this hydrogen here. So, we get the  $Pt-H$  bond; this is the hydride species, and this is the  $OH$  here. Now, this species can be used in the hydrogenation of aldehydes.

So, let us take one particular example, where you have this B catalyst, 10 equivalents of acetic acid, toluene as a solvent, 40 bar pressure for hydrogen, and 95 degrees centigrade. So, this is the double bond, which is being reduced, the carbonyl link being reduced to the corresponding alcohol. The conversion is 37 percent here. The reagent that was proposed or the catalyst is B. In the presence of this catalyst, we are able to reduce the aldehyde to the corresponding primary alcohol.

Modifications of these catalysts have also been used; this is reaction 1. For example, we can look at another reaction: cinnamaldehyde can be reduced to the corresponding alcohol as well. And so, it is a chemoselective reaction because it can now selectively reduce this

particular double bond without touching this particular double bond. And this is done in the presence of a slightly modified catalyst, Ir(I)COD, so we have the Ir(I)COD here, and then we have the P-tBu-Ph-OH. So, in the presence of this particular catalyst, you can see that in this catalyst there is again an O-H...O intramolecular hydrogen bond.

And at room temperature, 2.5 hours and only 5 bar pressure, in presence of THF solvent, you will be able to get the corresponding alcohol, where we can now see, that this particular double bond is untouched, the conversion rate is greater than 97 percent and the turnover frequency is greater than 1000.

So, you can see here that such high efficiency of this process is when we consider this kind of catalyst, which actually has stabilization in the primary coordination sphere. Here you can see the stabilization coming.

So, this kind of chemical transformation can be achieved. Another example is that you can reduce para-nitrobenzaldehyde to the corresponding para-nitrobenzyl alcohol as well. Here, the conversion is also greater than 99 percent. So, this is one important application. We will now go to the next application of such a catalyst, where the secondary coordination sphere, which is hydrogen-bonded, plays a very important role in the transformation.

We will now look at an example. So, we will now look at urea-phos ligands. Here, the design is as follows. We have a phosphorus atom.

Now we have a spacer. This is the ligand design. We have the urea moiety now, and this is R3. Now we bring in another molecule, the spacer-N(H)-CO-NH-R3, PR1R2.

Now we know that the N-H...O forms hydrogen bonds. There is an N-H...O hydrogen bond between the urea. This is something we have already studied in supramolecular chemistry. Now we can actually pre-organize because of the dimer formation; these two spacer molecules come close to each other, and the phosphorus can now coordinate with a metal ion due to their lone pair of electrons.

So, when they coordinate with the metal ion, this metal can actually be palladium or rhodium. In the presence of a metal, it will lead to the formation of this species. So, phosphorus will be here; phosphorus will be here; it will coordinate with the metal.

We will have the R1, R2, R1, R2. Then we will have the spacer; we will have the spacer here. This is the spacer, and this is the hydrogen bond. So, now you see, this is the hydrogen bonding in the ligand backbone, and now you can have the metal that can coordinate with this bidentate self-assembled complex.

So, we label it as C, and this has also been utilized in achieving organic transformations. For example, we can consider that in the presence of C, it has been observed that we get a chiral center here, and the enantiomeric excess is 97 percent.

And what is the exact ligand that has been used for this purpose is as follows: this is the particular ligand. This is the urea part, the urea derivative, and then we have the spacer, and then we have the phosphine backbone. So here R1 is equal to hydrogen, R2 is equal to methyl, and R3 is equal to phenyl. So, when this is the particular catalyst, we have this particular transformation: the reduction at the double bond. Again, the reduction takes place at this particular region specifically.

Now we can further modify. In chemistry, we can modify the backbone further, and we can achieve different organic transformations, particularly chiral transformations, so now we would like to make the backbone chiral, that is, the phosphorus chiral.

So, this is example 3 now. The P-chiral urea phosphorus-based ligands and their application are in the rhodium-catalyzed hydrogenation of dimethyl itaconate and N-acetyl dehydrophenylalanine.

So let us write down the reaction conditions, and before that we will also show you how the catalyst is made, that is P-chiral urea phos. So, we start with the chiral phosphorus, -Ph, O-tolyl group, -NH-CO-NH<sub>2</sub>, and we add Rh(COD)<sub>2</sub>BF<sub>4</sub>- in the presence of methyl chloride at 0 degrees centigrade. This is the rhodium, and it will now coordinate with the phosphorus, which is the chiral phosphorus. This is the spacer.

So, here we can see that there can be N-H...O hydrogen bonding in this particular region. This is the hydrogen-bonded backbone, and this is my chiral catalyst. I can label this now as the D catalyst, which has a chiral backbone which is also supported by hydrogen bonds. We can now use this particular substrate, which is diethyl itaconate. So, this is E, diethyl itaconate, and this is F.

In the presence of the catalyst D, hydrogen gas, 10 bar, 5 hours, and 0 degrees centigrade, we are able to achieve the transformation, and this becomes the chiral center. The conversion happens, and the enantiomeric excess is low at 33 percent. On the contrary, when we do it in the corresponding N-acetyl dehydrophenylalanine, this is E, now this is F, then we will get the corresponding C(=O)-NH-COOH, which is 99 percent ee.

And what has been recommended is that the hydrogen bonding between the urea and the substrate. So, the urea moiety is present in catalyst D, and the substrate is responsible for the observed enantioselectivity.

So, these are some of the important applications of the secondary coordination sphere, which also influences biological molecules; particularly, it operates in the case of enzymes, and I would like to illustrate a few examples of that as well. So, first we can look at the active site of the vanadium nitrogenase's secondary coordination sphere.

Now, we have iron, sulfur, carbon, iron, and then this is fused with iron, sulfur, iron, and Fe, S, and this is the vanadium center, and there is a sulfur here, which bridges these two iron

centers. This is the vanadium atom sitting here, coordinated to oxygen, oxygen,  $\text{CH}_2\text{CO}_2^-$ ,  $\text{CH}_2\text{CO}_2^-$ . And now, between these two iron centers, we have X.

Sorry, we have this X bridging ligand and H; this H hydrogen bonds with this carbonyl group. This is GLN, glutamine, and this is histidine. So this is the active site; this is the active site of V-nitrogenase, and here you can see that this pre-organization is important. So, you have the clusters, the cubane clusters, which are fused at the carbon center.

We have the vanadium-active site. And we have this site, which is again stabilized by hydrogen; this particular site is there, but overall species are stabilized by hydrogen bonding between the histidine and glutamine with the corresponding XH. So, you can see that this kind of secondary coordination sphere can actually influence the reaction outcomes with these clusters.

We can take another example, of the other active site, where we can see the effect of the secondary coordination sphere in the nickel-iron CODH active site. So, this is the carbon monoxide dehydrogenase, the CODH, and we have here the pendant histidine and lysine, that are positioned to interact with bound  $\text{CO}_2$ , to lead to reduction. Because you know that atmospheric carbon dioxide can now be efficiently trapped and then reduction can be performed to form the reduced products.

For example, we can form the  $\text{RCO}_2^-$  units. So, this trapping of  $\text{CO}_2$  leading to the reduction of carbon dioxide can be facilitated via this carbon monoxide dehydrogenase. At the active site, we have the histidine and lysine. So, we can look at this active site now, N-H. So, histidine is a wonder molecule; it is present in many applications.

So, you can see this is my carbon dioxide. And it is now connected to nickel; this is coordinated with iron; this is cysteine, histidine; and now this is sulfur; this is sulfur. So, there are 2 sulfur atoms and then there is iron here; this is iron, this is sulfur, this is connected here, this is also connected by iron, this is connected by iron, and this in turn is sulfur, which connects with this, and this also connects here.

And then we have this particular connection here. And here, the nickel is connected to cysteine. So, this is the active site where you can see the nickel center, the iron, and the  $\text{CO}_2$ , along with the strong hydrogen bonding that stabilizes the carbon dioxide molecule, which can then lead to the reduction of the  $\text{CO}_2$  group.

So, again you see the role of the secondary coordination sphere, which is stabilized by hydrogen bonds, and the effects of these hydrogen bonds are felt in regions that are beyond the primary coordination sphere. So, I hope that in this lecture, I have been able to highlight the relevance of these important interactions, you know, which exist in the secondary coordination sphere and which influence the reactivity profiles.

Thank you.