Fundamentals and Applications of Supramolecular Chemistry
Deepak Chopra
Department of Chemistry
IISER Bhopal
Week 11
Lecture 52

W1152_Applications of Supramolecular Coordination Cages to Organic Transformations

So, now let us continue our discussion from where we left off in the last lecture. So, we were looking at this 854-fold acceleration, which is observed during the Aza-Cope electrocyclization reaction when you start with this particular substrate, and it gives rise to this particular product.

It has been observed that when R1 is equal to hydrogen, R2 is equal to isopropyl, and R3 is equal to hydrogen, we will have this hydrogen here and isopropyl here, creating a chiral center. So, this is the induction of an asymmetric carbon atom into the organic scaffold, and in this particular reaction, with these substituents, a 854-fold acceleration in the rate was observed, along with a high turnover frequency.

So, we can now take up some discrete examples further with respect to these applications. So, let us look at Fujita's octahedral and square pyramidal cage.

So, I represent the octahedral cage as A and the square pyramidal cage as B. Let us go back for a moment. This is the [Pd6L4]12+, which is a cationic cage, where you can see the four different ligands; this is the L ligand. So, one on this face, one on this face, one on this, and one on this, and 6 palladium centers.

The corresponding square pyramidal cage has corresponding L4 ligands again at the 1, 2, 3, and 4 faces. We have the palladium centers at this particular vertex 1, 2, 3, 4, and then there is one palladium center for this particular face, and then another palladium center for this particular face.

So, overall, there are six palladium centers. That is, again, it gives the [Pd6L4]12+ macrocyclic cage. Square pyramidal cage, you see that this is open from the top face, whereas Fujita's octahedral cage has this kind of arrangement.

So, Fujita's octahedral and square pyramidal cages were used for the catalysis of the Diels-Alder reaction, which is a very popular reaction in organic chemistry, and in this case, the reaction is done in these molecular containers.

So, let us look at this particular reaction, where we have the substrates, and in the presence of first, deuterium oxide, at 80 degrees centigrade, in the presence of the supramolecular cage A, which functions as a supramolecular catalyst, we have the formation of the following product.

The second step is performed at room temperature, which gives rise to the formation of product C. However, if you actually do the reaction in D2O at room temperature in the presence of 10 mole percent of B, instead of A, it gives rise to the other regioisomer. So, this is a case of a regioselective reaction, where, when you take Fujita's octahedral cage, it gives rise to unusual regioisomers.

And also, it is interesting to see that there exist π-stacking interactions between the host and the substrate. So, there are pi stacking interactions between this substrate and the corresponding pi surfaces of the Fujita octahedral cage.

So, that kind of non-covalent interactions brings the molecules into close proximity to react with each other, leading to the formation of the unusual regioisomer. And what has also been observed is the retention of the product inside the octahedron. So, once the reaction is over, there is retention of product inside the octahedral cage.

To circumvent this problem, the reaction was now done in the presence of 10 mole percent of P, which actually led to the quantitative conversion to this product D. So, the reaction of 9-hydroxyanthracene with N-phenylhexyl maleimide actually led to the formation of the desired products.

So, in the case of B, you see, when you have the square pyramidal cage, it actually is open from the top, and it has a bigger cavity. So, the substrates can easily move into this particular cage and then easily come out, and what happens is that the product formation actually removes the planarity of the anthracene core. It removes the planarity of the anthracene moiety and facilitates the release of this product into the bulk.

So, now you see that the anthracene has lost its aromaticity; the product is easily released, which increases the efficiency of the process and also the catalytic turnover. So, overall, we see now that because of the loss of this planarity and aromaticity, the association of the anthracene with the pi-surface of the ligand of Fujita's cage is reduced and, therefore, the release of the product can take place easily.

As you can see in the case of D also, the planarity of anthracene has been removed, which facilitates the easy removal of the product into the bulk. So, this is the first application. The second application is the Knoevenagel condensation, catalyzed by a supramolecular coordination cage.

Again, here we are doing this reaction with Meldrum's acid. We are doing this condensation reaction in the presence of 1 mole percent of A: Fujita's cage, water, room temperature, and 6 hours.

It leads to a 96 percent yield of the desired product. The desired product is a condensation reaction, where the following product was obtained. And when this catalyst, the supramolecular catalyst, and the reaction barrel cavity were not utilized, the yield was less than 10 percent in the absence of the catalyst.

And in order to complete the procedure, the reaction was also done with the supramolecular coordination cage B; it was observed that the reaction goes slowly. Therefore, we observed that even with the same set of reactants and identical reaction conditions, the nature of the supramolecular cage and the geometry of the supramolecular cage play a very important role in the desired outcome of the reaction.

So, the geometrical restraints in the cavity control the reaction outcome. It is also important to keep in mind that in the previous reaction, the square pyramidal cage facilitated the reaction because there was a problem of product inhibition once formed with the cage that was overcome by using the square pyramidal B. But now in Knoevenagel condensation, the supramolecular coordination cage B does not perform satisfactorily.

The next example we would like to consider here is the rate enhancement in the 1,3-dipolar cycloaddition reactions, and this was done using the following. So, this is the reactant.

We have this as our starting material, and we can now have two possibilities. So, this will give rise to the corresponding 5-membered ring, which is this triazole product. Actually, this reaction was done in cucurbituril-6.

So, this molecular barrel was utilized to perform the cycloaddition reaction, and cucurbiturils have a strong affinity for these protonated ammonium species. Because of the cation-π interactions, there is a strong affinity, and overall, with the presence of this host, the rate enhancement is 5.5 times 10 to the power of 4, a fold increase in the rate.

So, we have this particular product; the possibility of the other product is also there. So, this is the other possibility: now this reaction does not take place; it is this particular reaction that takes place, and it leads to the formation of a regioselective product, and thus cucurbiturils function as a molecular catalyst that promotes these particular reactions.

The next reaction we would like to investigate is the acid-catalyzed Nazarov cyclization, where what was observed is a million-fold rate enhancement in a [Ga4L6]12- capsule. So, we have already looked at the structure of the [Ga4L6]12- capsule, and we are now looking at the acid-catalyzed Nazarov cyclization.

In this, you have the gallium centers here, and the reaction takes place within the cavity. Now, this is my OH group. So, these are my 1,3-pentadienols.

These give rise to the cyclopentadienes. Now, in the presence of an acid, I am not going to draw the cavity again; it is understood that this process takes place within the cavity. You have the formation of this particular species, and now it will undergo rearrangement.

So, methyl is here, and the methyl is here, methyl is here, methyl is here. So, this carbocation is being stabilized now by the electron-donating +I effect, as well as hyperconjugation, and now the proton will be lost.

So, it will give rise to the corresponding methyl cyclopentadiene. Now, interestingly, as you can see, this is an anionic supramolecular cage, and it gives rise to a cationic species. So the cationic species is electrostatically stabilized in this anionic cage, and the transition state is such that it is formed very easily now because you can see that the product is very closely related to the structure of the transition state, which involves this particular delocalization of the positive charge, and you can see that it goes by this particular process where the positive charge is stabilized over the different centers.

So, this transition state is now easily achieved; therefore, this particular supramolecular cage is able to lower the activation energy necessary to take the reaction across this transition state and to the product. But what happens is that now the catalyst, which is a supramolecular cage, binds with this particular product; product binding occurs, and because of this product inhibition, the catalyst suffers from product inhibition.

Now what we do is that this is now a diene, and we add a dienophile. The dienophile, once it is added, then undergoes the Diels-Alder reaction and gives you the final product. So, the product, because it now binds with the supramolecular cage, has to be removed now.

It can be removed easily by adding a dienophile, with which it reacts and therefore forms the Diels-Alder adduct. The Diels-Alder adduct that is formed is this one, and we have the stereochemistry here that is not defined, but we have the four methyls.

So, this particular product is formed. So finally, we see that this diene is expelled from the tetrahedral cavity by reaction with the dienophile to give the final reaction product. We can see that this natural cyclization is easily templated via this gallium capsule, which

promotes this reaction. Now we can go to another example of the effect of a cage. So, just like a cage, as we saw in a previous case, can be used to enhance the rate of the reaction, a supramolecular cage can function as a reaction inhibitor.

And this was demonstrated by Professor Nitsch's group, who actually designed a water-soluble [Fe4L6]4- cage that functions as a supramolecular protecting group. Just like you have protecting groups of the covalent kind, this [Fe4L6]4- cage functions as a supramolecular protecting group.

Why? Because it prevents the reaction, that is, the Diels-Alder reaction between furan and maleimide, ok. Let us look at this cage. This is my supramolecular cage, and here we have got SO3-, which makes it soluble.

So, this will bind here, this will coordinate here, this will coordinate here, and this will coordinate here. So, we will have 6 such ligands on the 6 edges: 1, 2, 3, 4, 5, and 6. So, this particular supramolecular cage now functions as a supramolecular protecting group because if you take furan and add maleimide, then no reaction actually takes place.

Because the furan is now present inside this particular cage, there is a strong association between this furan and this cage; therefore, maleimide is not able to perform the reaction with it. But now when you add benzene, it displaces the furan.

So now we have benzene which goes into this, and furan is displaced, and this can now react with your dienophile to give you the classical Diels-Alder product, right? So, there are a lot of interesting things that can be done with these kinds of cages by changing the nature of the ligands.

So, compared to the gallium cage, a different kind of ligand is present, and essentially, furan is tightly held here inside this; however, when you add benzene, it gets displaced, and the reaction proceeds satisfactorily. Now, we can look at the next application, where we can talk about the induction of chirality into the molecule, and this was again done by Fujita. So, we now have the enantioselective transformation by Fujita again. This work was done using Fujita's octahedral cage again.

But the cage has now been modified. Let us look at this cage. In Fujita's cage, what we had was this palladium center, which was achiral. But now we have created chirality at the palladium center. So, in the octahedral cage, what we now have at the palladium center is as follows: we have taken a chiral ligand.

Ok, and therefore you have the chirality here on the backbone. And so, the chirality is coming from the palladium side, which is the chiral center, and this is used to actually bring about the Diels-Alder reaction. We have the starting material, and we are now

treating it with this particular reagent. In the presence of water at 25 degrees centigrade and light, we call this octahedral cage E. In the presence of E, we are able to obtain the following product.

Thus, the reaction takes place at this particular double bond. So, you can see very clearly that the reaction is taking place at this particular center, and these are the two covalent bonds that form the four-membered ring.

So, this is actually the first metal-ligand coordination cage applied for an enantioselective reaction. So, this is Fujita's first metal-ligand coordination case, which is applied for an enantioselective reaction. So, now in the presence of this kind of molecular cage, the [2+2] photoaddition reaction was successfully demonstrated.

So, you can see now that with this kind of chiral cage, where the chirality comes from the backbone of the cage, although the previously reported cages, namely A and B, are not chiral.

So, this is the chiral cage, and it created the chiral compounds; the chirality was introduced via successful [2+2] photocycloaddition reactions.

So, with this, we come to the end of this lecture. In the next lecture, we will take up some more exciting examples of organic transformations that are mediated by the supramolecular reaction vessels.

Thank you.