

Fundamentals and Applications of Supramolecular Chemistry
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Lecture 51

W11L51_Supramolecular Catalysis via Self Assembled Molecular Cages

So, hello everybody, today we are going to start a new module in the eleventh week, and we are now going to look at some of the important applications of supramolecular chemistry. In the next few lectures, we are going to focus on supramolecular catalysis, particularly with respect to supramolecular reaction vessels, and we will look at supramolecular photochemical reactions.

So, we look at some very interesting aspects of supramolecular chemistry where we now try to understand whether certain chemical reactions between, say, different substrates that give rise to the desired products are actually affected by the conditions of the reaction. For example, the concentration of the reactants, the concentration of the catalyst, the nature of the solvent, the temperature, and other factors control the yields of the reaction product.

So, what was thought by the scientist is that now we can actually change the conditions such that we can promote these chemical reactions to happen in a more facile way, where we can have altered pathways for chemical reactions via altered transition states. And these transition states can be stabilized, and once these are stabilized with a relatively lower activation barrier, the reaction rates will strongly influence the outcome of the reaction and the yield of the products.

Whether these reactions can be done in supramolecular vessels made up of metal-ligand complexes to confine the reactants within these cages, formed from the self-assembled nanostructures involving metal-ligand complexes, and promote and accelerate the reaction so that this supramolecular cage essentially functions as a catalyst.

And there exist different non-covalent interactions between this supramolecular cage and the starting materials that can influence the reaction outcome, giving a very high rate enhancement similar to that observed in enzymes; thus, this became a very interesting area that we refer to as supramolecular catalysis, which is mediated, for example, by supramolecular reaction vessels.

So, with this background in mind, we would like to suggest that we can take either coordination cages or self-assembled organic capsules, which are held together by

non-covalent interactions and form a molecular barrel-like structure, into which we can put these reactants and perform the reaction. One such example we have seen is in the case of cyclodextrins, which have a hydrophobic cavity and a hydrophilic exterior, where chemical reactions can occur, and some of these function as enzyme mimics.

Thus, we can have these coordination cages to perform homogeneous catalytic reactions via supramolecular reaction vessels. What is more important is the control of the cavity environment, the selectivity in terms of binding of the reactants, and the binding selectivity, which is relatively easily achieved, as small changes in the geometries of the building blocks can lead to large changes in the overall structure and properties of such hollow polyhedral coordination units.

So, we have these hollow entities that are built up of polyhedral units and may consist of metal-ligand bonds, which we have already studied as a process of strict self-assembly. We also know, as we have mentioned, that the reaction medium affects the formation of the products depending on the binding of the reactants in subtle ways. Therefore, it is very important to use these kinds of coordination cages to achieve organic transformations.

The very limiting step here is that once the product is formed, it also has a tendency to bind with the supramolecular cage. Therefore, it is very important to enhance the process of removing the product from the coordination cage once it is formed, so that the equilibrium can be shifted towards the right-hand side.

So, this product inhibition is often encountered in this process of supramolecular catalysis, and we have to engineer ways that, once the product is formed inside the supramolecular cage, it must be removed easily in a facile way. So that more of the reactants can react to give rise to the product, which will overall exceed the rate of the reaction and also enhance the yields of the process.

Therefore, when we perform these kinds of reactions inside supramolecular cages, what is more important is the stabilization of the transition state to achieve a geometry that is closely related to that of the product.

This is very important because the reactants have now been almost pre-organized into a situation where they are able to perform the necessary reaction by changes in the electron density distribution and form the product in a facile way.

So, the geometry of the product is very closely related to the transition state through which the product formation takes place. And also, if you are able to have the self-assembled coordination cages with the help of chiral ligands, then these also provide us with the necessary asymmetric microenvironment for promoting stereoselective

reactions via non-covalent interactions between the supramolecular cage and the starting materials. So, if the supramolecular cages have chiral ligands, then this provides an asymmetric microenvironment for promoting stereoselective reactions via non-covalent interactions (NCIs).

So, in order to understand the kinetics and overall thermodynamics of the substrate reaction process, which gives you the product via a particular supramolecular cage, we have the following reactions.

So, we have the substrate, then we have the host, which are in equilibrium as governed by the rate constant for the forward reaction, k_1 , and that for the backward reaction where the substrate, you see, is a part of the host, and then we have $k(\text{catalyst})$, which we can also write as k_2 , which can give rise to the product, followed by the release of the product into the bulk solution and the host getting empty.

So, for the release of the product, k_3 must be greater than $k(-3)$, and the first step must be a fast and reversible step. So, the first step is such that the substrate must be able to bind to the supramolecular cage, but then if this process is not favorable, it should also be able to disengage and therefore, the step should be reversible.

And the second step, which is the catalytic step where the transformation of the substrate to the products actually takes place, is the rate-limiting step. So, it is in this step that the conversion to the products takes place, and we can actually represent this by the Gibbs free energy G as a function of the reaction coordinate, where we can then show that we have the substrate inside the host and that we have the product inside the host.

And finally, we have obtained the product, which occurs through a series of steps to give you the final reaction product, and this is a catalytic step. So, this is a transition state that is catalyzed; this is the ΔG for the catalytic step, and if you have to take the uncatalyzed pathway, then conversion from the substrate to the product happens, where this is a transition state for the uncatalyzed pathway; this is the dagger for the uncatalyzed pathway, and this now gives us the ΔG difference for the two transition states.

So, the transition state for the uncatalyzed reaction and the transition state for the catalyzed reaction are here, and this gives us ΔG for the transition state. And compared to the starting material, the intermediates that are formed are slightly stabilized.

They are also slightly stabilized, and finally, the product is much more stable compared to the starting material, and this stability difference is referred to as $\Delta G_0(\text{en})$, which tells you about the small change in Gibbs energy accompanying the formation of the substrate with the host.

So, overall, this is the profile of the reaction. So, when you have a catalyzed step that involves supramolecular catalysis, the initial step involves the binding of the substrate to the host. And now the reaction takes place; this is the activation energy.

So, right away you can see that the required activation energy is available when you have the supramolecular cavity or the supramolecular cage, which actually binds to the host. The chemical reaction takes place, and then the products are slightly more stable compared to the host with the substrate, finally leading to the formation of the product.

So, it is important to keep in mind that the transition state lowering takes place for a reaction that occurs by the supramolecular cage. For example, we can have a tetrahedral cage here. This is a tetrahedral cage; we have this as k_1 , k_{-1} , where now the substrate goes inside the cage; this is k_2 , which is the catalytic step, and then we have the product formation here, and then k_3 , k_{-3} , where the product is released into the bulk.

And it is also important to keep in mind that the product must not be strongly bound to the supramolecular cage; the product must be weakly bound in comparison to the substrate; otherwise, product inhibition takes place.

Now we can also account for the extraordinary activities because the transition state for the catalyzed step is stabilized in comparison to the transition state for the uncatalyzed step, which leads to the facile formation of the products.

Now, with this background in mind, scientists started designing different kinds of supramolecular cages, where they felt that these supramolecular cages could provide the necessary environment for organic transformations to take place.

So, to start with, they first thought about metal-free supramolecular assemblies; for example, they looked at crown ether, which is weakly hydrophobic and hence difficult to encapsulate non-polar guests.

So that was a limiting factor with crown ethers, and the next choice was cyclodextrins, which proved to be very successful in this regard. And then people started looking at cucurbiturils, which have this kind of molecular barrel-like arrangement and are made up of purely organic components.

We call this a molecular barrel, which can actually promote catalysis inside the molecular barrel, but the problem with cucurbituril is that there is a high affinity of the product for the cavity.

And the catalytic turnover, which is a measure of the efficiency of the catalysis process, is low. So, it is also important that when you perform supramolecular catalysis, you actually have high turnover numbers, the catalytic efficiency is high, and you are able to

repeat this procedure a large number of times without the catalyst undergoing degradation or decomposition.

So, catalytic turnover is low, and also the product inhibition is greater because it binds strongly with the cucurbiturils. So, what was thought is that, keeping in mind that some systems are positive and some are negative, in the case of organic moieties, people started designing metal-based SCs, which are called supramolecular cages. They help to overcome the problem of product binding inside the cavity.

So, it is now possible to remove the products very easily and also to have strong substrate binding inside the cavity. As you know, the first step, which we saw, is a reversible step; it should be able to bind fast, but it should also be able to disengage so that reversibility is maintained.

So, the substrate should not strongly bind to the supramolecular cage; otherwise, it will be difficult to perform the chemical reaction. So, the strong substrate binding inside the cavity and the problem of product binding, once it is formed, can be overcome if we can go for metal-based supramolecular cages.

And this has also been done, keeping in mind that the metal-ligand bonds are labile, and as we have already seen, these allow for the formation of thermodynamically controlled assemblies.

So, these cages result in large self-assembled structures, which are the thermodynamically controlled assemblies, and their formation is rapid and specific.

So, with this in mind, the first discovery of this kind of nano cage was again a case of serendipity, a serendipitous discovery by Saal Frank, who first synthesized the magnesium salt of condensed diethyl malonate.

So, let us take this diethyl malonate, treat it with methyl magnesium iodide and phosgene, and work it up with a base and water. The product formed is electrically neutral, and now we see that this has topicity 2; it is a ditopic ligand.

This is one binding domain, this is the other binding domain, and initially it was thought, looking at this composition, that magnesium is octahedrally coordinated with six such units.

But when the crystal structure was completed, it was revealed that magnesium exists in a tetrahedral environment. So, as this is a ditopic ligand, we can write it as follows. So, this is one particular binding side, this is the other binding side, and this is where we have the 1, 2, 3, 4, 5, 6 edges.

The magnesium is present here, at the ends of the tetrahedral building block, and then between the two magnesium centers, we will have the ditopic ligand. So, the ditopic ligand sits with the corresponding magnesium centers.

So, this is the tetrahedral coordination environment that surrounds every magnesium atom. Now, you see that there is a cavity inside, and this can be used for the encapsulation of molecules. However, the size is small, and therefore, it is difficult to perform reactions with large substrates; what was thought is that now large polyhedral cages can be made for effective encapsulation.

So, with this background came the pioneering work by Fujita, who developed different cages. The first popular work of Fujita was the octahedral cage.

This is the octahedron, and we can now have the coordination with the palladium here. To start with, we can have palladium sitting here at all the 6 centers. We have the 6 ligands that are present here. We have got this 1, 2, 3, and 4.

We have got these 4 ligands. So, this gives rise to the $[\text{PdL}_4]^{12+}$. 12NO_3^- is the counter ion. The other two sides can be coordinated with nitrogen coming from this particular ligand. This particular octahedral cage has now been designed. One particular face is represented here; there are 6 palladiums, so 6 2s are 12, and there are essentially 4 ligands present here: 1 here, 1 here, 1 here, and 1 here.

So, this face, this face, this face, and then this particular face; alternate faces have got this ligand backbone. Compared to this, there was another cage synthesized by Fujita, referred to as the square pyramidal cage. This is the square pyramidal cage, and all four faces—1, 2, 3, and 4—were occupied by the ligands, with palladium here, palladium here, palladium here, and palladium here.

So, again we have this square pyramidal cage, but you see that the shape of the cage is very different, and this is a bowl-shaped molecule. So, this bowl-shaped molecule was developed by Fujita, and then there was another supramolecular cage, the third one.

So, we have 2A and 2B, which were developed by Fujita; then we go to another supramolecular tetrahedral cage of the M_4L_6 type, which was developed by Caulder and Raymond for supramolecular catalysis; this uses Ga_4L_6 . So, this is 3, and the total is 12 minus charge. Overall, the charge on the supramolecular cage is also very important.

In the case of palladium, the overall charge is plus 12. So, the charges are very high, which means that there are going to be strong electrostatic interactions between the substrate and the supramolecular cage, and that is going to play a very important role.

And once the substrate enters the cage, the water molecules from inside the cage are going to be released into the bulk. So, this process is also favored thermodynamically because there are enthalpy considerations, electrostatics as a very strong binding force, and then the entropy factors, because water is now released into the bulk.

So, that increases the entropy of the water molecules and thereby favors the release of the water molecules into the bulk. So, both enthalpy and entropy considerations favor these processes. And L is a ligand with a -4 charge, so 6×4 is -24 and 4×3 is +12.

Therefore, $12 - 24$ gives it an overall charge of -12. And what is L here? L is 1,5-bis-2,3-dihydroxybenzoylamino naphthalene. This is my ligand and let us look at the structure of this ligand. So, we have the gallium. This is the N-H, this is my naphthalene ring, then this is N-H-CO, O minus, O minus.

So, this can coordinate with my gallium here. You can see that this is overall 12 minus. So, this is an anionic supramolecular cage and therefore, you can have electrostatically positive species as substrates that can get electrostatically bound inside this particular cavity.

So, what has been observed is that this particular cavity, which you call the $[Ga_4L_6]$ cage, has been utilized as a molecular container to catalyze the Aza-Cope electrocyclization reactions of allyl ammonium cations. So, the Aza-Cope electrocyclization reactions of these positively charged species occur.

These are the ammonium cations. So, definitely, they will get electrostatically attracted to these gallium $[Ga_4L_6]$ supramolecular cages. And what is the advantage of these supramolecular cages? As you see, they are similar to magnesium cages but have a larger cavity. So, let us look at this process now to see how this takes place.

We have this particular acyclic host, and what happens now inside this particular container? So, we are now going to put this molecule inside a container. Whatever the cavity size or the cavity space available to it, there it will undergo an orientational change where you can see that there is a bond rotation, which will bring these double bonds into close proximity with each other.

So that they can react with each other, we can have the reaction here. We can have this movement here; we can have this movement here, and we can have this movement here. So, this will give rise to R2, R3, Me, and Me; this is R1.

This reaction takes place, or this electrocyclization takes place, via this pre-organized substrate inside the molecular cavity of this $[Ga_4L_6]$, and once this is formed, this product is released. And where this product now is N+, Me, R3, R2, and R1.

So, this is my product, and now we can do the hydrolysis, facile hydrolysis, eliminate the dimethylamine, and it will give the corresponding aldehyde. So, this electrocyclization, as a Cope electrocyclization reaction, now takes place at an unprecedented rate. Therefore, there is an 854-fold acceleration when this reaction is performed in the supramolecular cage, and there is a high turnover for this particular reaction.

So, this is the power of doing supramolecular catalysis: you are able to perform certain reactions in bulk that do not take place at very high rates. You can actually achieve very high rates when you confine the reaction of this cationic substrate into an anionic supramolecular scaffold, which can pre-organize this particular reacting material into a preferred geometry, such that the double bonds come in close proximity to each other.

Because of the limited space, the rearrangement takes place, giving rise to the desired product, which is expelled from the cavity and can then be easily hydrolyzed to give you the corresponding aldehyde, which is the final product.

So, in the next lecture, we will look at more examples of supramolecular catalysis and their applications using other supramolecular cages to function as reaction vessels.

Thank you.