**Fundamentals and Applications of Supramolecular Chemistry**
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**Week 12**
**Lecture 60**

W12L60_Applications of Systems Chemistry

So, hello everybody, in the last lecture we started on systems chemistry, and we looked at the concept of how systems chemistry originated and the fact that combinatorial chemistry, dynamic combinatorial chemistry of the covalent kind, and non-covalent kinds play a very important role in generating the array of constituent molecules or the library of constituent molecules that will be expressed by molecular recognition with a particular receptor, depending upon the right electronic and steric fit.

Once we identify the key constituent, the desired efficiency or biological function can be optimized, and it is not necessary for this constituent library to be available at the time of performing the supramolecular reaction with the lock. But it can be formed anytime by the dissociation or the reversible disconnection of the constituents into components.

Then the components can again combine in different ways to give you a desired constituent that will be the best fit for the law.

So, that gives rise to the notion of the virtual dynamic community or library of molecules which are not, strictly speaking, virtual, but become available as per the requirement of the receptor or the lock; therefore, the desired activity can be achieved. So, we can now compare the combinatorial library and the virtual combinatorial library.

In this case, we have the molecular constituents; these are supramolecular constituents as well as molecular constituents. This is a collection of molecules; this is a collection of components, as I mentioned before.

The association for the formation of the combinatorial library is the covalent bond formation, whereas the virtual combinatorial library can involve covalent associations of the reversible kind or non-covalent associations. This is non-reversible because once the final target or the final set of reactions has happened and the final product has been formed, essentially it is non-reversible, but the virtual combinatorial library is of the reversible kind.

So, in this case this is called neutral, uninformed, but here it is the instruction which comes. So, the instructions come to self-assemble internally or externally.

The instructions can come for the species to undergo binding. And therefore, this is more of an adaptive dynamic process. Whereas in the case of traditional covalent chemistry, once the molecules are formed, you can achieve a large degree of diversity in terms of the molecular skeleton and in terms of architectural diversity, but by and large, once they are formed, the final target is achieved.

We work with these final targets only. Whereas in the reversible association, you can actually disengage either the covalent bond formation or the non-covalent bond processes in a reversible fashion, so that the components can again combine in different ways to give you the key constituents that function as part of the virtual combinatorial library.

So, this is an adaptive dynamic process, whereas this is the corresponding systematic stepwise process using logical methods to achieve synthesis. And when you are doing combinatorial chemistry to make the combinatorial library of molecules, we actually do not worry about the target.

Our idea is to make new exotic molecules that may have different applications. So, here this is in the absence of the target. Whereas here this is recognition directed; either it is self-assembled or in the presence of the target.

So, overall, we call this chemistry the dynamic generation of molecular and supramolecular diversity by target recognition-directed self-assembly. This is what was coined by Jean-Marie Lehn.

So, what is also important is that we now have the constituents, and the generation of the constituents is very important. Thus, the formation of the constituents depends on the conversion process where you combine the components to give a particular constituent.

It depends on the composition, and it ultimately depends on the expression, which is the amplification process. So, combinations can give rise to different combinations and compositions; the conversion process is important, and finally, once you have the library, what is the expression that leads to the amplification process?

And all the different structural and interactional features I mentioned, all the different structural and interactional features that are necessary for the formation of this dynamic library of molecules, which we call the virtual combinatory library, will be present in the final molecules and the final set of combinations. So, now we can look at some suitable examples.

So, to summarize, before we go into the example, we can say that the constituents of VCL result from a combination of its components by coherent assembly through a reversible chemical reaction which we call the molecular real molecular VCL or by

self-assembly through reversible non-covalent binding interactions which we call the supramolecular VCL.

And this is also referred to as the phenomenon of supramolecular polymorphism. Now, this is interesting because polymorphism was with respect to the arrangement of molecules, and the supramolecular association can be different for the supramolecular VCLs.

So, let us take the first example here, where we have created a virtual dynamic combinatorial library of oligomeric helicates generated from a tritopic ligand, tris pyridine, and metal ions of octahedral coordination. We can now draw it as follows.

So, I have n such constituents, plus n such Mm+ metal ions. So, we are here; we have the 5 metal ions, here we have the 6 metal ions, and here we have the 4 metal ions. And it has been observed that these corresponding oligomers are all constituents of the dynamic library and are potentially accessible by reversible interconversion.

So, when you now put in a chloride ion, it has been observed that, depending on the cavity size, if you have a chloride ion, it templates the formation of this particular oligomer, whereas, if you have a corresponding BF4- or sulfate anion, then it will template this particular 6-metal structure.

So, depending upon the anions, different kinds of helicates will be formed. So, say, you have a concentration of this particular structure now; it will reversibly dissociate to the corresponding metal ion and the corresponding tritopic ligand.

And then this tritopic ligand will again self-assemble to give thermodynamically stable entities, which will be the basis of coordination and stabilization of the chloride ion. So, this dynamic library can be created, and even the relevant molecule can be generated from this set of constituents by reversible dissociation and then association to give you the right molecule, which will be there for the target metal ion that will be sensed in the process.

And so, in this case, this chloride or BF4- is referred to as chaperones, which actually direct the self-assembly process.

This is also similar to the molecular chaperones, which are important in the folding of protein molecules into the secondary, tertiary, and quaternary structures. So, the folding process is again directed by chaperones in protein self-assembly, as well.

Now, we can take another example to demonstrate the importance of the virtual combinatorial library (VCL) concept that was devised to develop the process of recognition induced by the self-assembly of the inhibitors of the enzyme carbonic anhydrase.

So, the development of a suitable inhibitor for this particular enzyme was actually taken up by the concept of this VCL. In this regard, different components were selected.

The components contain the aldehyde and amino functionalities. And this aldehyde and amine functionality can now form the imine bond; therefore, the product contains the imine bond, and the particular imine whose structure resembles that of the inhibitor of the enzyme carbonic anhydrase was actually characterized via this process.

And if the match is not good, then again, this imine bond can undergo reversible dissociation into the corresponding aldehyde and amino. And now these aldehydes and amino acids can again combine in different ways to form another set of molecules that are part of the library, and then we will be able to direct the population toward that particular molecule, which is very specific to the inhibition of the enzyme, carbonic anhydrase.

So, we are actually here sampling a set of molecules and making new imine molecules, checking them for target binding with the inhibitory activity of the enzyme, carbonic anhydrase.

If it does not inhibit, then we actually look for another library. That library can be accessed depending on its availability. Once we give it the instruction to be produced, the reversible dissociation happens; again, the components react with each other to give a new set of libraries, and we can screen them for a design of the right inhibitor.

So, by this process of screening, what will happen is that the purpose is to shift the equilibrium population towards the imine product that has the structure which is closest to the known strong inhibitor for that enzyme. I would like to take a different color here just to emphasize the different reactants.

So, we have a set of amines A, B, C, and D; these are the components. And from the aldehyde side, we have this aldehyde, this aldehyde, and this particular aldehyde. So, these are all the components, and we can have a reaction between the amines and the aldehyde to give the imine bond formation.

So, a possibility exists of 12 products, 4 times 3. For example, we can get the reaction with this, and this can give us this particular product, or we can get the reaction of this with this, which can give us this particular product.

And we can also have another reaction to say this with the corresponding this. So, this can give us, plus, and this was formed to be almost equivalent to the actual compound, which is a strong inhibitor.

So, you can see that this compound is structurally quite similar to the compound that actually inhibits the activity of carbonic anhydrase. And also, to tell you that this is an enzyme that is used for the conversion of carbon dioxide to bicarbonate plus a proton, and this is a zinc-containing enzyme. So, in this way, you are able to actually create the components; you are able to create the dynamic library, and then the dynamic library can be screened.

In this way, you will be able to get to the required target molecule, which models that of the actual compound. Therefore, we can now produce a sufficient concentration of this particular targeted compound. The equilibrium can be shifted in such a way as to form more of this compound, first by reversible dissociation and then combination to form the desired compound, which competes with the well-known compound that is a strong inhibitor of carbonic anhydrase.

And then this process of dynamic combinatorial library is very important because it is a very powerful concept. Because when you have a set of molecules that can combine in different ways instead of wanting them to react in all possible ways and give you a large number of products, it is better if the molecules themselves decide with whom they want to assemble.

So, the process of self-assembly should be more like a self-organizing process. So, self-organization becomes a key player here rather than pushing the equilibrium or pushing the reaction conditions towards forming all possible products, such that none of the products can be obtained in abundant yield or will actually have a particular useful application.

So, the idea is that when you have this combination of molecules, they self-organize, or we know that we have heard of the self-sorting mechanism. They sort out among themselves how they will self-assemble with each other, and the resulting product must have an interesting application. Then the utility of this combinatorial approach to a library of molecules becomes extremely useful.

And we can demonstrate this very useful application of such a self-assembly process, which is mediated by non-covalent hydrogen bonds, in the design of a gel via the concept of dynamic combinatorial library (DCL) or chemistry.

So, let us take the first molecule as an example. We call this A, then we have the molecule B, then we have the molecule, I am calling this D, and the molecule C here. So, we have the amine functionality here, and we have the aldehyde functionality here. So, we can now have different combinations of aldehyde and amine to give you different products.

Four different products can be formed. These are the components of the DCL. What the system does now is a process of self-sorting or self-organization. The self-sorting or self-organization command is what is most important. And it leads to the formation of a supramolecular gel through the combination of A and B.

And so, the selection is done in such a way that the selection of the molecules or the selection of these components to combine, to give you the gel, is done in such a way that it forms the most stable supramolecular assembly and the one that also survives in this race of combination.

So, in this way, the formation of the most stable and organized self-assembly process is a reflection of prebiotic Darwinism, which is driven by self-organization. So, the process is prebiotic Darwinism, which is driven by self-organization and tells you that the particular entity that will survive is the fittest constituent.

So, the concept of the fittest constituent becomes relevant, and in this regard, this particular gel that is formed is the most stable entity. Now, let us look at the structure of this gel; I would like to draw it.

So, this gel has the N-H here, H here, H here, and it is now undergoing hydrogen bonding. Now here also there is hydrogen bonding; then here you will have, here. So, this double bond will be here. So, now we have got this hydrogen bonding N-H; this is N.

So, this will now come from N. So, this is the gel, the tetrameric gel, which is created, but what is more important is that here you have the ribose, and then here you have the ribose, here you have the ribose, here you have the ribose.

And then further, this particular amino has reacted with this particular aldehyde to form N-H and C=N double bonds. So, first the covalent association happens between A and B, and then there is a supramolecular association that creates this very stable gel structure.

So, this is the key constituent, the fittest constituent, because it involves both irreversible association and supramolecular reorganization, self-assembly to create a very stable gel-like structure. Initially, we mixed this in a 1:1:1:1 ratio, 15 millimolar each, in sodium acetate buffer.

So, under these conditions, we saw that this particular gel formed favorably. We can also have the other combinations. So, this was C. We can have A plus C to give you F.

We can have D plus C to give you G. We can have D plus B to give you H. So, we can have these four products, and what is formed is E at 39 percent, F at 8 percent, G at 42 percent, and H at 11 percent.

So, the combination of D plus E is also quite abundant at 42 percent, but none of F, G, or H form gel; it is only E that forms the gel-like structure. Therefore, in this regard, I would say that E and G are actually framing the formation of the most stable entities. Therefore, they are agonists, but F and H are antagonists in this overall library of molecules.

So, this association leading to the formation of E and G is favorable compared to that of F and H. So, this nicely depicts the overall concept of gel formation in an application of TCL.

So, with this, I hope I have been able to impress upon you, with these examples that we have discussed, the relevance of dynamic combinatorial libraries, virtual combinatorial libraries, and how these concepts can now be further utilized to understand interesting biological processes, and we can combine this chemistry to understand the origin of the formation of molecules that eventually became a part of the development of the molecules that constitute life.

So, thank you very much; with this, I think we have come to the completion of all the lectures of this course.

Thank you.