Fundamentals and Applications of Supramolecular Chemistry

Deepak Chopra
Department of Chemistry
IISER Bhopal

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Lecture 59

W12L59_Systems Chemistry

Hello everybody, today we will be discussing a new topic in supramolecular chemistry, where we will be looking at a combination topic that has become important in the field of supramolecular chemistry because there have been many developments in molecular biology where a large number of structures have been determined. For example, protein structures, peptides, and virus structures were being determined.

On the other hand, chemistry was also growing tremendously at a very fast pace because organic molecules, different kinds of organic synthesis, total synthesis, and various fields of chemistry, such as organometallic catalysis, were all developing. But what was important is that supramolecular chemistry came in between, or bridges both these fields, where we take the knowledge from chemistry to make new building blocks and then want to model the processes that happen in life.

So, the synergy between chemistry and biology became very important. Biology is more complex in the sense that there are a large number of constituents, different types of constituents having specific functionality, and where shape, size, and molecular weight all play a very important role.

Chemists are more interested in making new molecules that have a defined set of functional groups. For example, the focus has been, by and large, to design and make new organic molecules that involve total synthesis, such as that of natural products.

Today the focus is on areas like C-H activation, where new catalysts have been developed to introduce specific functionalities on the organic scaffold. But then there is supramolecular chemistry, which is actually a very interesting area.

Now that you have heard about so many lectures in this course, you realize the potential of this area. What is the purpose of learning chemistry? The purpose of learning chemistry is to understand the origin of life, why life exists on Earth, how life originated on Earth, how the small specific set of atoms started combining to form molecules, and then how these molecules formed larger molecules and eventually proteins, which are enzymes that are actually the workhorses of cells and biological functions.

And then we also have the important theory of Darwin, which talks about the evolution that occurred in biology. And therefore, the idea was that instead of trying to make specific molecules only with predefined targets, it is possible to make an array of molecules that can also reversibly dissociate, then form, and then again associate to make different kinds of molecules that have a specific function.

For example, we have an enzyme, and we would like a certain ligand to inhibit the activity of that particular enzyme.

Now, the ligand that has the best steric and electronic fit with a specific portion of the enzyme is what is going to give you the desired activity. And as we have already realized, there is a competition between kinetics and thermodynamics.

Life is actually an example of non-equilibrium thermodynamics. It is more like the dynamical processes at play because if thermodynamics were to rule, then the end product is essentially carbon dioxide and water. But we know life still exists; that means there are non-equilibrium processes at play that sustain life on Earth.

So, the question that was asked by a supramolecular chemist is whether we can design ligands in a specific way by creating a pool or a library of molecules, which will not be present initially in the process of identifying the potent ligand that will best fit with the enzyme, but which can be created instantaneously by suitable combinations of chemicals to give you the constituents that actually specifically dock or interact with a protein, leading to the amplification of the process of molecular recognition.

And this entire discussion, which I have presented to you, was actually propelled by Professor Jean-Marie Lehn, and it gave rise to the foundation of systems chemistry. So, just to give you a couple of salient features about systems chemistry, it is a union of supramolecular chemistry and prebiotic chemistry with theoretical biology and research on complex systems to address problems related to the origin of life and the search for a deeper understanding of the structural and dynamic prerequisites leading to chemical self-replication and self-reproduction.

And third, which is most relevant to systems chemistry, is chiral symmetry, where we have chiral symmetry breaking in nature. Because when life started on Earth, there was a specific chirality that was utilized to create the molecules of biological and chemical interest.

So, what is the origin of chirality? In principle, we have both chiral forms, but it is one of the chiral forms that is utilized for making molecules that support life on Earth. So, what the implications of these concepts are is that we would like to understand the origin of life, and life is based on homochirality.

The interesting thing is that when these homochiral molecules were being designed or synthesized, they were done without any chiral environment.

So, that is the interesting thing: the utilization of one kind of chiral handedness that emerged without any chiral environment. This is what is intriguing; this is what is puzzling: how did this process happen? Because we actually know that today, synthetically, if you would like to make a specific chiral enantiomer, then you have to induce the necessary chirality into the system.

For example, if you want to have enantioselectivity, it can only result from the chiral information that resides in the system. For example, you have to make the catalyst or one of the reagents or one of the reactants that has to be chiral.

So, the chirality or that information about the chirality has to be coded or prescribed within the system; it has to be stored as memory in the system, and only then can it lead to enantioselectivity in a chemical reaction.

And when you are going to do these chemical reactions in the laboratory, unless you have the chiral information, the outcome of a reaction will be a racemate. That is, when you do a chemical reaction in the absence of chiral information, it will create a racemate with a 50% to 50% distribution of enantiomers.

So, these are some of the challenging problems that systems chemistry would like to address, and we would now like to explore some aspects of systems chemistry and how it all became very relevant. So, now there is a merging ground.

As I told you, we have vast chemical knowledge of chemical structures, and we have knowledge about different forms of life. So, can we have a synergy between these two areas, where we will combine them to give rise to the interface?

Today, science is highly interdisciplinary, and people are working at the interfaces of physics, chemistry, and biology. So, this will give rise to the fascinating areas of systems chemistry and systems biology, where supramolecular chemistry is going to play a very important role in combining these two fields.

And to achieve this particular process, what has been developed is actually the principle of, or the concept of, constitutional dynamic chemistry, which we call CDC. We can also call it dynamic combinatorial chemistry, DCC. That is how it is being addressed today, but initially, when it was proposed by Professor Jean-Marie Lehn, we started with the concept of constitutional dynamic chemistry.

So, we are able to make certain bonds by reacting certain functional groups, and we make certain molecules. And if during the process of molecular recognition, we would like to now change this particular molecule that binds, then this formed molecule has to dissociate into the starting components.

Then, again, we will have to have different components, and we will have to have the suitable combinations. So that we get the desired constitution of the molecule that best fits the target of interest, the one where this fitting is the best tends to get amplified or become more well recognized within the system of interest.

So, this concept of constitutional dynamic chemistry became very important, and it can be divided into two parts: molecular, which is dynamic covalent chemistry, and supramolecular, which is dynamic non-covalent chemistry.

Thus, if we want to exercise dynamic covalent chemistry, we will have to utilize the knowledge of reversible covalent reactions, and this will involve the reversibility of non-covalent interactions. So, when certain interactions form, you can again reversibly dissociate back into the starting materials, utilizing this concept of non-covalent interactions, thereby creating dynamic non-covalent chemistry.

And this is important because selectivity is important in chemistry, as we have to identify or select molecules that satisfy a specific function of interest. The fact that non-equilibrium electrochemistry is very important was actually recognized way back in 1861, when the formose reaction was proposed by A. Butlerov.

In 1861, he proposed the mechanism of the formation of sugars from formaldehyde, which forms glycoaldehyde, and then the higher aldoses and ketoses. And this formose reaction takes place under alkaline conditions and in the presence of minerals like calcium and barium.

And when this process happens, it is actually creating a library of molecules that are interconverting into the higher aldoses and ketoses. So, during this process of the formose reaction, the library is already being created by nature, and then these libraries can combine to give the higher sugar molecules, which have higher molecular weights.

So, the process of this dynamic combinatorial chemistry essentially constitutes a network of organic reactions, forming oligomers, either linear or cyclic, of varying sizes and compositions. So, this is the basis of dynamic combinatorial chemistry. Now let us look at this overall sequence of events regarding what we are trying to achieve through the synthesis or creation of this library of molecules.

And now we have the components to start with. The components here, for example, include a square, a pentagon, this particular shape, and another particular shape. Now, there is a selection; this is the equilibrium process, and this is a library selection. So, we can have different kinds of combinations here. So, we can have a combination of this, this, and this to give this particular product.

We can have this one, this one, and this one. We can have this one combining with this one and this one. These are the constituents. These are the components. The constituents have been formed by the combination of the different components, and then we can have thermodynamic pathways, and here we can have a receptor.

Now, say the receptor has this particular shape. So, this is my receptor, and I can actually have a thermodynamic selection, or I can have a kinetic selection, depending on the shape of this particular cavity. So, as you can see, what will fit in here is this particular molecule that fits into this particular cavity. So, this is the lock, and this is the key.

So, lock and key fit. And this process can take place by thermodynamic as well as by kinetic procedures. Now, the most important thing is that there are different steps in this process. So, we saw that step 1 is a dynamic library of keys generated and reversibly associated.

These are the components, the fragments, and there is a reversible process operating that forms these constituents, and at any moment the reversible dissociation can take place, allowing the components to combine again to give the constituents; this is the first step. And the second step, which is very important, is that the receptor, which is also the lock, amplifies, or favors—this is important—the expression of the key or constituent that binds best to it; that is thermodynamics, or that forms fastest with it; that is kinetics.

So, all this knowledge of supramolecular chemistry is very useful for creating these constituents. And what is important is that it is not necessary for all these constituents of the library to be present at the same time.

Depending on what the requirements are for the key to fit into the lock, these active molecules can be generated at the time of the requirement for the steric process. So, this library, or the keys, does not have to be formed before the addition of the receptor or the lock. Because once you identify the receptor, or the lock, these constituents can then go back to the components and form new constituents, identifying what kind of steric or electronic requirements are needed to interact with the lock.

So, before the addition of the receptor lock, these libraries or keys will not be present, and this illustrates the notion of a virtual dynamic combinatorial library.

We call it VDCL; sometimes we can also call it a virtual dynamic library. So, now this very important concept of a virtual library comes into play, which is not really virtual in the true sense; it is virtual by means of the fact that it is not necessary for these keys to be there or for the constituents to be present.

And as I mentioned, once we identify what the best fit for this lock is, then the system can actually prepare, through a series of reversible dissociation and then association processes, the right molecule that will now specifically bind with the target, leading to the amplification of the signal or the response; therefore, we are able to identify the very key substrates that can bind with the receptors of interest.

So, this is the philosophy behind the concept of a virtual dynamic combinatorial library, or combinatorial chemistry, which we are talking about.

And then there are different kinds of bonds that are actually involved in this process. So, we can look at reversible covalent bond formation by different processes. For example, through different processes of chemical reactions, we have the carbonyl and RNH2, which can reversibly associate to form the amine.

We have the formation of hemiketal, so this can form reversibly. Then we have the aldol reaction, which can form the aldol disulfide bonds, which can form disulfide linkages.

The Diels-Alder reaction, which can happen between a diene and a dienophile, will give the cycloaddition product. So, we can have these kinds of reversible covalent bond formations. We can also have reversible interactions. For example, we can have M^{n+} plus Lm to give you $[MLm]^{n+}$. We can have $RCO2^{-}$ hydrogen-bonded with our amine group.

We can have donor-acceptor interactions to give you the donor-acceptor adducts, and this can be further combined with reversible processes. For example, we can have cis-trans isomerization, bond rotation, and so on and so forth. So, these are the dynamic processes that are involved in the creation of the virtual molecular and supramolecular CLs.

Virtual molecular and supramolecular combinatorial libraries can actually be created via the wealth of information derived from reversible covalent bond formation, reversible interactions, and the reversible processes that are at play. This is just a snapshot of some of the most important processes that operate.

So, in the next lecture, we will take up some specific examples that demonstrate the applications of this virtual library, as well as combinatorial chemistry in action.

Thank you.