Dr. Kenneth Raymond is a Chancellor’s Professor in the Department of Chemistry at University of California, Berkeley. Professor Raymond has been interested in a variety of topics in bioinorganic chemistry and coordination chemistry. In this interview, we focus on one of his specialties, the assembly of highly symmetric supramolecular clusters. We discuss not only the role of symmetry in the formation of such molecular structures but also the application of these clusters in catalytic chemistry.

Berkeley Scientific Journal: How did you get involved in research in chemistry?

Kenneth Raymond: I liked chemistry since I was 12 years old. I was 12 years old when I got my first chemistry set. My mother thought I was too young when I wanted it two years earlier. In those days, real chemicals came in those chemistry sets! In high school, I had a really good chemistry teacher who also taught physics. He let me have free run of the lab for making standard solutions. Aside from almost killing myself a couple of times, that was a really good experience!

Also, it got me into Reed College, which turned my life around. In my first two years of high school, I had a math teacher that was sort of egg shaped and wore these purple dresses. She would be up next to the chalkboard and would get this perfect white ring around her. And she looked just like an Easter egg. She thought I was rude and I’m sure that’s true. She gave me bad grades for behavior but all of the people I was tutoring in the class were getting A’s. So, by my reckoning at the time, I thought I was winning this battle.

In my junior year, I decided I didn’t want to be a juvenile delinquent; I wanted to be an intellectual. And that turned out to be more productive.

BSJ: And was it at Reed that you began focusing on chemistry?

KR: I started doing undergraduate research at Reed after my freshman year. And Reed had this undergraduate thesis. It’s up there on the shelf but I won’t show it to you, it’s too embarrassing. An undergraduate research thesis was great preparation for the PhD. The PhD was almost easy by comparison. My best friend at Northwestern Graduate School and I were probably the two best-prepared students. He was from Harvard; I was from Reed. So I was in a hurry; I went straight from graduate school to my job here. I have never applied for a job in my life!

BSJ: Really?

KR: It was a different world. My PhD supervisor was a very well known inorganic chemist at Northwestern.

He pulled me into his office at the end of my second year and said, “Well Ken, things are going fast for you this year. What do you want to do in the future? Not industry right?”

I said, “I don’t think so.”

“No.”

“So you want to be an academic?”

“Yeah, what do I do?”

“Don’t worry I’ll take care of it.”

Next thing you know, I get a phone call from Caltech, Berkeley, and Riverside. So I went off to give talks. Harry Gray, who just turned 80, introduced me at my interview at Caltech and I was so nervous—I had just turned 25. I got up and said, “It is very nice to be here at MIT.” True story! He thought it was a joke and everybody laughed. Things got easier after that and I got the job of my dreams and I kept it. Very dull job history; I’ve been here my whole career!
BSJ: So what is supramolecular chemistry and how did you first get interested in it?
KR: For me, it's a relatively recent interest. It only goes back 20 years, probably as long as you have been on the planet. I had a long-standing research interest in biological iron chemistry, especially transport and storage. The way we store iron is in ferritin. Ferritin is a supramolecular protein. It always has exactly 24 subunits, never 23, never 25. It has high octahedral symmetry.

One day I was staring at this in new kind of way. How does this work? I looked at the crystal structure in some detail. It was already an accurate structure and you could see a four-fold interaction site, a four-fold octahedron. There are hydrogen bonds, hydrophobic interactions and so forth. All of which add up to a substantial interaction. But its direction is like a lock and a key where the lock and key are 90 degrees apart. So that forms a tetramer with four-fold symmetry.

Elsewhere on the protein, there's a three-fold interaction site. Now, the lock and the key are 60 degrees apart. That says, “Form a trimer with three-fold symmetry.” So, how do you do both of these? You make the angle between those interactions equal half the tetrahedral angle: the magic angle of the cube, 54 degrees. The only thing that can form is a 24-mer with octahedral symmetry.

So I had two thoughts at the time… One was, “This is obvious, I must be the last person on the planet to understand this.” But if you look in the literature, there was nothing in the description like I just gave you! So, the second thought was less pleasant, “This is nonsense, you’re fooling yourself.”

But, if it’s real, it’s a recipe for how to make things. So I set about to make clusters where the interactions are not hydrogen bonds, but metal-ligand interactions. Those are directional, rather strong, and are reversible! That’s really important, that’s a key to supramolecular chemistry.

It’s like a Lego set: there are a million ways to put it together in the wrong way, but only one correct solution. So, in the case of supramolecular clusters, if you make a mistake in linking things, you have got to be able to back out of it. That got me started. One of the early clusters we made has been like the Energizer Bunny: it just keeps running! And we keep discovering that it does new things. Our current record is already counting, and you could count really fast, it would be the end of the universe before you got to that number.

BSJ: Could you elaborate on how chemical synthesis can be regarded as beautiful?
KR: Well, behind you is a supramolecular structure called the quartz crystal. Now, that’s only supramolecular in the interior of the Earth at very high temperatures. In other words, you can crystallize it under equilibrium conditions. It’s way too cold to be reversible now, but it’s chiral of course.

How do you take SiO₂, just a chunk of silica, and make a chiral structure out of it? Well, it crystallizes in spirals and half the time they’re right-handed and half the time they’re left-handed. Once the crystal starts, if it grows perfectly, it’s all the chirality. And it’s beautiful, right? Why do we like gem stones? Because of their beautiful colors; but also because they have these faceted surfaces and they scatter light.

BSJ: Do you think what exactly underpins beauty in chemistry would be some degree of symmetry?
KR: I think so. I’m sure there are as many opinions on that as there are chemists, but I think so. Well actually, I think a very large subset would agree with me. That was the whole point of this book. Symmetry is terribly important in all kinds of areas. There’s a wonderful book, Symmetry and the Monster. It talks about 10⁵² symmetry elements. That’s a number that if you started counting, and you could count really fast, it would be the end of the universe before you got to that number.

BSJ: Why was the initial interest only in ferritin?
KR: I wasn’t trying to reproduce ferritin. The same analysis and argument would work for the protein viral coats. Why are they 60mers or 120mers or 180mers? There may be three different proteins, they trimmerize and then 60 of those trimmers get together to form the viral capsid. The simplest capsids are for bacteriophages. The virus that gives you a cold uses a bigger cluster to hide its nucleic acid. But in each case, it’s a question of how to package nucleic acid inside a robust protective coat.

BSJ: Talking more fundamentally, we read this chapter you wrote in the book, Beauty in Chemistry…
KR: I hope you enjoyed it. I had fun writing it! You wouldn’t know this because you don’t know the whole field, but these are some quite prominent supramolecular chemists.

BSJ: Were other symmetric biological clusters similar to ferritin known at the time?
KR: Yes, protein viral capsids with icosahedral symmetry. Icosahedral symmetry has 60 symmetry operations.

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BSJ: You’ve already briefly covered this, but how would you explain the mechanisms behind supramolecular clusters to the general audience?
KR: Well, the most interesting thing I think is that it is a way to make complex structures out of simple subunits, and nature uses it that way. I mean these viral capsids are huge, but they’re composed of much smaller individual proteins. It’s potentially
BSJ: But once the cluster is formed, it would be satisfying the lowest energy?
KR: Yes, exactly. That makes it the lowest state. Each metal wants to have three of these catechols around it so for the specific cluster, and each of the ligands wants to have both of its ends coordinated to a metal so there are no loose sticky ends. That then makes it the lowest energy state. But I interpreted your question as, “In a very general way, is the most symmetric structure always the lowest energy?” I would say no. You have to build it that way.

BSJ: Perhaps even more fundamentally, what do we know about accounting for symmetry in thermodynamics. Can it be quantified?
KR: Well, in physics it’s terribly important. All these string theories are dealing with multidimensional spaces and symmetry between particles and antiparticles and so forth. It’s very important. It’s also terribly important in chemistry, in that, for chemical bonding there are wave functions. Those wave functions of an atom have required symmetry. Any wave function, whether it’s a guitar string or a hydrogen atom, the different wave functions are orthogonal to each other. That’s why if you pluck a guitar string, you may hear a transient note for a minute, but then the note that continues is a single tone. You can make a harmonic of it, that harmonic is orthogonal to the fundamental. Same thing happens with the atomic wave function. Symmetry is very important there because it helps you analyze the quantum mechanics so all of the theory behind bonding.

BSJ: But once you have the ∆G° free energy, can you account for symmetry in that regard? That is, the reaction being driven purely due to a symmetric reason?
KR: I think not as easily in thermodynamics as in quantum mechanics. In fact, I started a course here years ago on chemical applications of group theory. Group theory is a mathematical application of symmetry.

BSJ: What does that tell us about the evolutionary selectivity for symmetrical structures?
KR: That’s a great question, and people are still arguing about that. [At the most fundamental of levels], the neutrino is chiral. When it travels through space it can have a spin this way or this way.

BSJ: In regards to having a host system, why do the clusters have to be symmetric? Does it relate to the need for repeated assembly or dissociation of subunits?
KR: Well, let’s suppose that, instead of one identical ligand, all six were different. How many different isomers will there be, how many products will there be? It will be an awful mess! In order to have one simple thing, you have to have symmetry and make all of those ligands equivalent. Nature does the same thing.

BSJ: But if you had to catalyze a different reaction that required different space in the host… Why would it be beneficial to rely only on symmetry in terms of formation of symmetric supramolecular structure compared to making some other non-symmetric cluster?
KR: Perhaps even more fundamentally, what do we know about accounting for symmetry in thermodynamics. Can it be quantified?
KR: Why, yes! But even if I’m making another cluster, I want it to be one thing, not a thousand different things. So if I make another cluster, I want all components to be the same, because otherwise I do not know what I have in solution.

BSJ: We were wondering what exactly happens at molecular level in the cluster. Is the cluster being formed around the host, or is the host being taken in?

KR: Usually, the latter. We do what we call “templating” in some cases, where the guest interaction will help to form the cluster. Usually, we make the cluster separately and then have the guest as a reactant. Most of what we’ve been doing recently is using the cluster like a little enzyme. It is chiral, but the only thing chiral about it is the structure. We can have a guest come in, catalyze their chemistry, and then it’s important that the products are not good guests. Because you want to spit the products out and go around the cycle again. We’ve shown in several cases, that it is really an enzyme-like mechanism that follows Michaelis–Menten kinetics.

BSJ: So, it is not like the cluster is completely encapsulating, but more that the substrate is sitting on an active site in an enzyme?

KR: It sort of is. Remember, the trick is to get the angle between the thee-fold axis and the two-fold axis fifty-four degrees? We initially did that by a lot of computer design and testing different structures. The three-fold axis is built in, because these are metal ions, so these are six-coordinate. The two-fold axis we built into the ligand. It has structural memory. The chirality of this vertex is random, initially, but ones we set it, all the other vertices, because of planarity, have to have the same chirality.

BSJ: So it clearly is very flexible?

KR: It is, and of course that is true with enzymes, too. People have often made mistakes. You know you look at a potassium channel protein and say, “Oh, potassium could never fit through there.” But that’s nonsense, because they are rocking and rolling all the time, the structures are very dynamic.

BSJ: Why, does the tetrahedral confirmation specifically often underlie supramolecular cluster formation?

KR: The simplest of the polyhedra is the tetrahedron. So, I thought I would start simple. Now, one thing we tried to make early on was an octahedral symmetry. And you haven’t seen that because it didn’t work! That doesn’t mean it never will work but that the approach I was trying didn’t work. We’re interested in doing that, though. I have a couple students who are working on expanded clusters and different cluster designs. For example, a tetrahedral cluster where the ligand occupies the face of the tetrahedron.

So, it has three bidentate [directing] groups and so the stoichiometry would be four metals and four ligands, instead of 4:6. And it’s easier to extend that. It’s easier to make it bigger. Of course, the longer you make the ligand, the volume goes up as the cube of the extension of the length. So, we can make bigger clusters.

BSJ: So, is the tetrahedral the largest working cluster you have created so far?

KR: Yes

BSJ: Is that, then, a limiting factor in the type of reactions you can catalyze?

KR: Well, there are lots of people who are making supramolecular systems. Our system is unique in that it is inherently chiral. And that means that you can catalyze chiral reactions. And in the last year we discovered that we can do photochemistry and electrochemistry inside the cluster. So, this thing is going off in new directions. Until all the gold is the last twenty years. And the answer is: they both look good but do not do anything! So, we have been trying to disprove that. We are trying to do things inside the cluster.

BSJ: Does it matter, in your case, if it forms an enantiomer?

KR: We can get enantiomeric excess from reactions that start with a non-chiral substrate. The only thing that is chiral, [in that case], is the flask in which we are doing the reaction!

Manraj: How exactly are you directing it towards one conformation?

KR: To be honest, I can observe it, but I can’t predict it. I wish I could. You ask about how the exchange occurs and the dilation of the aperture by twisting the naphthalene rings is a pretty low energy process. Initially, I thought that we must be breaking a bond up here but that takes a fair amount of energy. So, this process is fast on the laboratory scale, milliseconds, but slow on the NMR time scale. That’s how guest exchange occurs. If you have two molecules of the same volume, one that looks like an American football, and the other that looks like a soccer ball, the American football is faster going in and out, because the dilation of the aperture is smaller.

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mined out, I'm going to keep mining it!

BSJ: What are some of the ways in which the reaction rates [of the catalyzed reactions] can be accelerated?
KR: Well, I'll give you an answer that is not really an answer. We must be binding the transition state. Do I know what that looks like? No, I don't really.

I'll give you another example. What you learn in beginning organic chemistry is that SN1 reactions racemize and SN2 reactions, that have a chiral carbon center, invert the absolute stereochemistry. But, we have an SN2 reaction that retains the absolute stereochemistry.

How does that work? Well, we have a chiral molecule. If you do hydrolysis in water, you get 84% retention of the chirality. If you catalyze it inside the cluster, you get 74% retention. And how does that work? I can give you two limiting explanations… If the leaving group goes off, we get an SN1 reaction. But it's snuggled up next to this naphthalene, a pi complex that is not free to rotate. So, now when the new entering group comes in, it comes in from the same side and we get retention of stereochemistry.

Now, I'll give you the opposite extreme: SN2. The naphthalene acts as a nucleophile and displaces the leaving group. Now entering group that comes in, displaces again. So, in fact we've have two SN2 reactions! Which is true? Well, how do they differ? They differ in the transition state! In SN1 this would be something like a 3-3.5 angstrom (Å) distance. If it's SN2, it'll be more like 1.5 Å. Pretty big difference! But I can't see the transition state. So, the only way we're going to be able to answer this is theory.

BSJ: We talked about some of the promising developments already but where do you see the research in supramolecular chemistry going?
KR: Lots of things, I think! Almost all of my career, I've shamelessly stolen from nature. She has no patents; she has no copyrights! So, I look to nature. What does nature use supramolecular systems for? To deliver things; to protect things. So, drug delivery systems may be an application. To catalyze things. So that would be my speculation for the future.

BSJ: And in regards to green chemistry and environmental chemistry, how would the supramolecular systems concept be used to remove harmful species? Would the structure be able to capture such species?
KR: At the moment, it better be a really expensive toxic species. These are not cheap molecules. So, you cannot be talking about carbon sequestration. That's too high volume and too cheap. But back to the delivery idea, it's very hard to get drugs across the blood-brain barrier, and yet, our antibodies get across that barrier all the time. And they're really big! How does that work and can you mimic that process? Chad Mirkin at Northwestern has shown that you can coat gold particles with DNA and they go into cells. The gold molecule is huge, but it goes into cells. So, all kinds of new methods of delivery and transport might be enabled by this.

BSJ: If you were to use it as a drug delivery system, how would you control when the host is released? But can you direct the intake and outtake of the host?
KR: I don't know, that's your job! I'm just spinning ideas right now. Those are all problems that will need to be solved but I think we're already at the stage where these kinds of ideas have real applications. Does that mean they're going to be easy to do and solve all problems? No.

BSJ: Where does the equilibrium lie in these reactions?
KR: In the reactions we are catalyzing? We're going downhill in energy but we're getting it up over the transition state a lot faster than it would have while just sitting in solution. But in our photochemistry, we're making an higher energy molecule. So, we have shown that the cluster absorbs light and then it can deliver that light energy to a guest inside it, if it is an appropriate guest. That triggers a rearrangement and forms a higher energy product. It's a solar energy conversion…

BSJ: Like a photosystem…
KR: Yeah! And we're arguing that the DOE should give us more money for this. Most people when they talk about photochemical energy are talking about something that you're going to burn as a fuel. Those are really cheap. So, our chemistry would really never be useful for that because it is too expensive. But if you're making high value chemicals, then it makes sense! It's catalytic and using the sunlight.

BSJ: Why is it so expensive?
KR: They're kind of hard to make; ask my students! My hero in science was, and is, Linus Pauling. I met him a few times… two of his children went to Reed and I have been at cocktail parties at his house! He was so brilliant on so many different things. He's the one who said that enzymes bind what today we would call the transition state. And that's what we're trying to do. I want to be able to do some theory on these so that I can predict the next reaction we can catalyze rather than just try one and see if it works.

BSJ: Thank you very much for the time, professor!
KR: Nice to meet you all and good luck with your Berkeley careers and thereafter!

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