QnAs with Kendall N. Houk

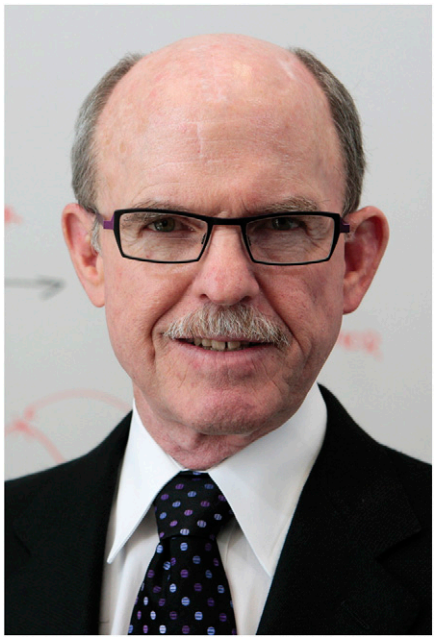
Kendall Houk, a recently elected member of the National Academy of Sciences and the Winstein Chair in Organic Chemistry at the University of California, Los Angeles, uses computational and theoretical chemistry to illuminate the underlying rules of organic and synthetic chemistry. By understanding how basic chemical reactions work, Houk can design molecules and enzymes to catalyze increasingly complex reactions. In his Inaugural Article, Houk uses molecular dynamics techniques to study the intricate underpinnings of the Diels-Alder reaction, a classic organic chemistry phenomenon first described in the 1920s. Here, he describes how theoretical and computational chemistry, bolstered by major advances in computing power, could have a major impact on science in coming years.

PNAS: You helped create something of a recipe book for chemical reactions. How has that work influenced chemistry and science?

Houk: We studied many different classes of reactions and came up with various kinds of rules for understanding why things happen the way they do. These results have influenced how people interpret chemistry. One example is the discovery of what controls the stereoselectivity involved in electrocyclic reactions, a concept we named "torquoselectivity." In this type of reaction, a bond is broken and twisted during the course of the reaction, so there is a torque on that bond that causes it to twist one way or another. We figured out how different groups cause this twisting to occur in one particular way. So, we explained some chemistry that was known at the time and predicted some new chemistry. Then we studied that experimentally and found that we could predict the product of the reaction based on our electronic theory, even when the result was the opposite of what everyone expected to find based on steric effects.

PNAS: Predicting the structures of proteins that catalyze chemical reactions could open new paths of research. What opportunities lie ahead?

Houk: The potential is really awesome, but we have just begun! The idea is to design a catalyst for any reaction that is important: an important drug or a commercial product, for example. We use computational design methods—quantum mechanics and molecular dynamics from our group, along with David Baker's Rosetta computer program—to design a protein that will be a catalyst. Our collaborators purchase the gene, tailormade to be expressed in *Escherichia coli*, and then it is made in the quantities needed for testing. So the combination of computational design and what is, at least for biologists, routine molecular biology, can lead to a catalyst for whatever reaction is needed, if we can get this all to work properly.



Kendall N. Houk.

PNAS: Has that approach been successful?

Houk: Yes, we have used these computations to figure out a sequence that will catalyze a reaction nature has not yet developed. We do a lot of designs, and Baker's group makes hundreds of proteins. In the best cases, half of those [proteins] might be modest catalysts—but in the worst cases, none of them work. These results are breakthroughs in demonstrating that enzyme design creation can work. Unfortunately, the reactions we are doing are ones that we chose not because they are particularly important but because we thought there was a good chance we could succeed. We've beaten really enormous odds, but we have really just scratched the surface of what is possible. Future developments in theory and computing power should make computational design work much better.

PNAS: Your Inaugural Article strays from the idea of enzyme design. Can you explain how your latest research fits into your repertoire?

Houk: This paper is hard-core physical chemistry, using molecular dynamics techniques to study the Diels-Alder reaction in detail to understand how it happens. We conducted a time-resolved study of how these reactions happen by creating simulations, basically movies, of molecules coming together and reacting. The idea is to understand how the reaction happens, not just that *a* goes to *b* and *b* goes to *c*, but to actually follow how the bonds are forming and how the atoms are moving as these things come together. Using the massive computing power we have now, we get a degree of resolution of the mechanism that was not really possible before. It takes a lot of computer time, but as a result we now have unprecedented insight into how this reaction occurs.

In our Inaugural Article, for example, we, along with Chuck Doubleday at Columbia University (New York City) and Kersey Black at Keck Science (Claremont, CA), tackle a big question that people have argued about for many years: if two bonds form during a reaction, do they both form at same time or does one form first and then the other later on? We find that for the simplest Diels-Alder cycloaddition, it only takes about 5 femtoseconds on average between the formation of the two bonds. That is much less time than it takes for a vibration of a bond, so we consider that as occurring simultaneously.

PNAS: Looking back, what experience really kick-started your research career?

Houk: I was lucky to start my PhD work with [Robert Burns] Woodward just at the time when the Woodward-Hoffmann rules were being invented, and I was in a great environment. It was also at a time when the focus on theory in organic chemistry was very much emphasized. So I got caught up in that. Eventually, that drove my whole career to many excellent places. I am very happy with everything that followed.

Beth Azar, *Freelance Science Writer*