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Potential Energy

The Power of the Cavity

Pinglu Zhang^{1,2*}

Dr. Pinglu Zhang was born in the Zhejiang Province in China. She received her PhD degree in 2015 from Université Pierre et Marie Curie (Sorbonne University) in Paris, under the supervision of Prof. Matthieu Sollogoub. Her PhD work concerned Cyclodextrin-(N-Heterocyclic Carbene) Metal Complexes for Cavity-Dependent Catalysis. She then joined Prof. Michinori Suginome's group as a postdoctoral fellow at Kyoto University in Japan. Now, her research focuses on asymmetric catalysis with helical polymers.

Main text

When I started my PhD, I asked myself, why cyclodextrin (CD)? It had been known since the late 19th century, yet the enthusiasm of researchers for cyclodextrin chemistry never decreased. Later, I figured out: the well-defined chiral cavity of CD is a gift from nature. Not only because of the hydrophobicity of its cavity for "host-guest" chemistry¹ but also because this cavity provides a confined space, which could impose steric restrictions.² Thus, when a metal center was attached in close proximity to the cyclodextrin scaffold, the cavity could act as the secondary coordination sphere and serve as an artificial pocket in mimicking metalloenzymes.³ However, many studies have used CD as a platform or a bulky ligand in metal catalyzed reactions rather than investigation of the effect of CD cavity shape.

Clearly, the position of the metal in relation to the "pocket" plays an important role in its chemical properties. The general mode of CD-Metal association is illustrated in Figure 1A. In many cases, the flexibility of the link might cause poor selectivity in catalytic processes. Thus, capped CDs have the clear advantage of reducing the structural flexibility and forcing the metal to be close to the cavity or even encapsulated inside it; furthermore, the shape of the CD cavity might be distorted by the capped ligand. All these considerations have inspired me in the adventure of exploring the effect of cavity.

We serendipitously found an N-heterocyclic carbene (NHC)-capped CD encapsulating a metallic center in the cavity (Figure 1B).⁴ The position of the metal implies multiple interactions, including both anagostic interactions and weak hydrogen bonds, with the inner wall of the cavity (H-5 and H-3 of sugar units). Meanwhile, nature offers us several choices of cavities through different CD types (α , β , γ -CDs). In this issue of *Chem*, we use the encapsulated metal as a probe to detect the differentiation of the chemical environment in various cavity types by varying an original set of weak interactions and use nuclear magnetic resonance (NMR) to build 3D models.⁵ This way, we uncover a wide variation of cavity shapes in all our complexes. One of the challenges was to exploit the power of each cavity in a specific fashion. Given that several group 11 metals (Au, Ag, Cu) are discussed in our research, many possibilities could be explored. Firstly, we applied the corresponding Au complexes in cycloisomerizations of enynes (Figure 1C). The α -CD cavity shape accepted a carbocationic intermediate, leading to the production of a cyclopentene derivative. However, β -CD cavity imposes a different conformation with lower energy, orienting the reaction toward a cyclohexene derivative. Meanwhile, in asymmetric cycloisomerization of an N-tethered enyne, the enantioselectivity could be deduced from the cavity shape.

Obviously, the differentiation of both regioselectivity and enantioselectivity originates from the power of cavity. We can then use cavity shapes to rationalize the outcome of the catalytic reactions that proved to be cavity-dependent. When the substrate approaches the encapsulated catalytic center, it is affected by the shape and geometrical restrictions of the distorted cavity, leading to different intermediates or transition state conformations. I believe that the cavity is much more powerful than previously shown; what we observed could be just the tip of the iceberg and there is a lot of unexplored potential. For example, how about other metals other than Au as the catalytic center? Is it possible to apply this concept to other catalytic reactions to obtain variations of regioselectivity or enantioselectivity?

While I was carrying out this work, determination of interactions with the help of NMR was an energy-consuming process. When I joined Prof. Sollogoub's group, I had some concerns about the complicated NMR charts, which looked like a complicated puzzle (especially for unsymmetrically functionalized CDs). My supervisor encouraged me to be patient: "Rome was not built in one day". When I got lost in those NMR spectra, I went to enjoy a glass of beer, slept, and then started again in the morning. Gradually, I acquired the skills to complete the puzzle, each piece of which provided some structural information. In the later stages of my PhD, I was absolutely addicted to this puzzle game, and I thoroughly enjoyed resolving my complex NMR spectra.

The experience gained in the Sollogoub Lab made me relentless; I was trained not to miss tiny clues in experiments, even if it made me struggle many times. However, I retained my curiosity for the unclear and my passion for digging deep. Meanwhile, I was told not to worry about failures. Chemical work is not only

what you see in a published journal, it also includes larger amounts of unsuccessful experiments. Prof. Sollogoub once said luck is important in research, but I believe that luck can be forced: Thousand times, unsuccessful attempts taught us what to avoid, and luck would come on the way of the next try.

What is the next step in my career? Research work requires scientific skill, creative thinking, passion, curiosity and also "three Ps": patience, persistence, and perseverance. In my opinion, being a strong competitor is one of the factors that enable me to exhibit these traits. Academic research is a competitive ground, especially with all these young researchers and their wonderful innovation spirit. Great competitors inspire me, and I would love to play in this field and keep fighting. Before starting my independent career, I would like to learn more tools and broaden my view of the chemistry world, and then continue my adventure and turn my bold imaginations into reality.

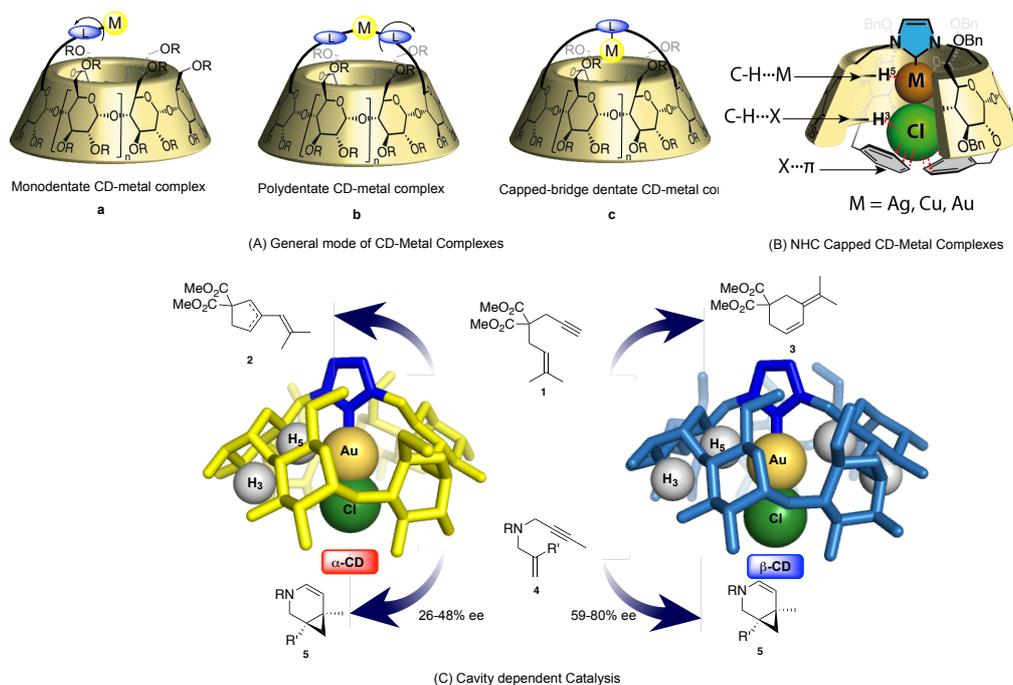


Figure 1. The Strategy of Using CD-Metal Complexes in Cavity-Dependent Catalysis

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