論 文 の 内 容 の 要 旨

論文題目　Remote Manipulation of the Binding Pocket of Self-Assembled Cages
(自己組織化錯体結合ポケットの遠隔機能制御)

氏　　名　　方　　煜

1. Introduction

The elaborate substrate specificity in the binding pocket of enzymes is often governed by the subtle variation in amino acid residues that exist, not at the interior, but at the exterior of the pocket. Even a single amino acid difference at the exterior of the pocket makes a big difference. In this way, a small difference at a given remote site is transmitted and amplified over the entire cavity through space, resulting in fine-tuning of the characters and functionality of enzymes. Synthetic coordination cages have nanometer-sized, large hydrophobic cavities where organic molecules are bound and reacted. Typically, the cage framework determines the guest-binding ability, and hence the hitherto-unbound guests require new design of other cage frameworks. In this study, we modify the remote ancillary groups on the component metal ions. As a result, the properties of the cavity are tuned remotely with using the same cage framework, without directly modifying the inside cavity.

2. Results and discussion

2.1 Synthesis and cavity comparison of cages with different pendant groups

Phenanthroline (R_2-phen)-capped cages [**1**; R = H (**1b**), Me (**1c**), 2,6-dimethylphenyl (**1d**), mesityl (**1e**)] were quantitatively self-assembled by simply mixing Pd(R_2-phen)(NO_3)$_2$ [**2**; R = H (**2b**), Me (**2c**), 2,6-dimethylphenyl (**2d**), mesityl (**2e**)] with 2,4,6-tri(4-pyridyl)-1,3,5-triazine (TPT, **3**) in H_2O/CH_3CN. Bipyridine (bpy)-capped cage (**1a**) was also prepared in a similar way. After the pyridyl coordination on Pd(II), the pyridyl a protons (PyHa) of **3** shifted downfield for **1b** and **1c** but shifted upfield for **1d** and **1e**. These different and opposite behaviors for for **1d** and **1e** indicate a significant through-space interaction between the R pendant group of **2** and the pyridyl group of **3**. X-ray single crystal diffraction of cage **1e** elucidated that the 12 bulky mesityl groups hang over the cage cavity (3.5 Å), reducing the Npy–Pd–Npy bite angle (83º) from the ideal 90º and tilting the pyridyl group of 3 (9.4º) through π–π interactions.

Superposition of cages **1a** and **1e** were done based on their crystal structures. The two cannot perfectly overlap each indicate these two cavity were different. In order to investigate the difference of the two cavities quantitatively, the cavity volumes of cages **1a** and **1e** were calculated by using the *VOIDOO* program based on their crystal structures. A virtual sphere probe with a radius of 3.36 Å were filled into the cavity of both cages and the occupied space are measured and visualized in mesh to show the cavity volume for both cages respectively. It was found that the cavity volume of **1e** with the bulky mesityl groups (380 $Å^3$) was dramatically reduced by ~20%, compared with that of **1a** (482 $Å^3$) without pendant groups. Because cages **1a** (bipyridine) and **1b** (Phenanthroline) do not have pendant groups, the both cavity volumes can be regarded as the same. In computationally optimized structures of cages **1**, due to the tiny difference of single methyl group, superposition of the cage framework between **1b** (**1d**) and **1c** (**1e**) was virtually identical and did not give any useful information.

2.2 Guest encapsulation in the shrunken cavity

To experimentally show the impact of the R pendant groups on the cage cavity, rigid tetrahedral guests **4** (362–394 $Å^3$) were employed as real probe molecules to perform the guest encapsulation into cages **1**. The inclusion yields were quite sensitive to subtle changes in both the cage and guest structures. When treated with guest **4** at 80 ºC, cage **1b** as well as cage **1a** showed no guest-binding affinity due to it too large cavity to hold such a small molecule. However, the shrunken cavity of cage **1e** firmly accommodated guest **4** in 38–75% yields. 2D NMR measurements of inclusion complex **1e•4b** indicated that **4b** is located at the cavity center with the four phenyl groups at the cavity portals. The inclusion yields of **1d•4** were almost the same as those of **1e•4**, indicating that the cavity of **1d** is shrunken to the same degree.

Notably, cage **1c** did encapsulate guest **4** in 11–18% yields. Prolonged mixing time or elevated temperature did not change the encapsulation yield. Therefore, the methyl group of **1c** is supposed to slightly push the cage framework inward to shrink the cavity to enable the holding of **4**. In short, the single methyl group difference, **1b** and **1c**, plays a critical role in the guest binding, despite the fact that the methyl group is far from the actual binding site.

Besides rigid and tetrahedral guest **4**, another flexible guest **5** was also introduced to the cage **1** by the same inclusion procedure. All cages **1a–e** showed high guest-binding affinity (66–99% yields) due to the flexible guest could extend and shrink its size to adjust any cavity.

When adamantane guest **6** was introduced, situation was reversed. Only cages **1d** and **1e** with bulky pendant groups show no guest binding at all. Four molecules of and located at the portal of the cavity. Cages **1d** and **1e** with shrunken cavity and modified portals are not suitable for guest **6**.

Thus, mere a methyl group modified the guest-binding cavity of the cage and tuned the guest binding property.

2.3 Guest motions in the shrunken cavity

The empty cage only shows two due to the free rotation of pyridine moieties. Previous investigated guest molecule are all high symmetrical and they do not .

In contrast to **4a**, the terminal –OH groups of guest **5a** enabled the quantitative guest encapsulation in all the cages. Presumably, electrostatic attractions between cationic cage **1** and deprotonated anionic **5a** stabilize inclusion complex **1•5a** in water; when the –OH groups were methylated, guest **5b** was encapsulated within cages **1c–e** but no longer encapsulated within cages **1a** and **1b**.

Although C_{2v}-symmetric guest **5a** was encapsulated within all the T_d-symmetric cages **1**, the NMR signal behaviors of the cages were totally different. With increasing the bulkiness of the R pendant groups in **1b–e**, the signal of the PyHa of **3** was gradually split and finally doubled in inclusion complex **1e•5a**. This phenomenon is attributed to the close packing and the restricted motions of **5a** in the shrunken cavity. Gradual clear split pattern suggest the restraint degree for the guest is increasing with the increasing size of the pendant groups.

All the cages **1** quantitatively formed 1:2 complexes with a-diketone **6**. In ^{1}H NMR measurements at 300 K, 12 sharp signals (with the same intensity) were monitored for triazine panel **3** because of the symmetry reduction of the cage from T_d to S_4 through tight guest-packing. With increasing temperature to 330 K, only the cage signals of **1e•(6)**$_2$ remained sharp, indicating that the guest motions were still restricted even at high temperature (Fig. 5b,d).

The only difference between cage **1d** and **1e** is the *p*-methyl group on the R pendant group of **2**. Only the most shrunken cavity frozen the guest motion in high temperature indicates that with increasing the size of pendant groups the cavity of the cage undergo a gradual reducing until 80% of ordinary cavity size. Again, the single methyl group difference, **1d** and **1e**, plays a critical role in the guest motions.

2.4 Diels-Alder reaction was accelerated by shrunk cavity

Diels-Alder reactions were dramatically accelerated by M_6L_4 cages with shrunken cavity (**1e**). The shrunken cavity brings the dienes and dienophiles into close proximity and significantly low the entropy costs of Diels-Alder reaction between them, thus Diels-Alder reactions were dramatically promoted inside the shrunken cavity. Small dienes, such as phenanthrene and fluoranthene, were activated for Diels-Alder reactions only within the shrunken cavity. Furthermore, shrunken cavity serves as a discriminating cavity environment to efficiently release the Diels-Alder product, thus furnishing the reaction in a catalytic fashion.

No catalytic reaction was observed for unmodified cavity due to product inhibition.

2.5 Bottom-up assembly from helicate to networks *via* remote metal binging site

Inspired by the findings in previous chapters that remote substituents can manipulate the functions of a synthetic host. Pyridine moiety was introduced onto the chiral linear ligand where the pyridyl groups locating far from the major metal-binding- site, referring to Schiff base units. Due to the different priorities in coordinating with metal, Schiff base units firstly bind metal ions to form helicate then the network was construct by connecting the remote pyridine moieties. Thus, the remote pyridine substituents changed the structure by bottom-up assembly.

3. Conclusion

The cavity properties of cages **1** were remotely and subtly tuned by the pendant groups of **2**. A single methyl group difference at the remote site makes a significant difference in guest species and motions within **1**. These findings correspond to the "remote control" by amino acid residues in natural enzymes, which will shed light on searching new functionality of synthetic host cages. The Diels-Alder reactions for small inert dienes were dramatically promoted within the shrunken cavity. Furthermore, catalytic Diels-Alder reaction was also achieved by shrunken cavity. Besides remote control of the functionality of the host, the remote moieties can also change the host structure *via* bottom-up assembly.

4. Publication list

1) Y. Fang, T. Murase, S. Sato, M. Fujita, *J. Am. Chem. Soc.* **2013**, *135*, 613–615.

2) Y. Fang, T. Murase, M. Fujita, *Chem. Asian J.* (full paper) in press. [DOI: 10.1002/asia.201301642]

3) X. Xi, Y. Fang, T. Dong, Y. Cui. *Angewant. Chem. Int. Ed.,* 2011, *50*, 1154-1158. (Monthly "Hot Paper", highlighted by *Nature Chemistry, Nature Chemistry*, 2011, 3, 186–187)