

## Construction of a Homooxalix[3]arene-based Dimeric Capsule Cross-linked by a Pd(II)-pyridine Interaction

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Homooxalix[3]arenes bearing 4-pyridyl groups at the 7,15,23-positions formed a dimeric complex with Pd(II). Only when the homooxalix[3]arene was preorganized to a cone conformation, a dimeric molecular capsule with  $D_{3h}$  symmetry was yielded. Mass spectral studies established that  $CD_2Cl_2$  is included in this cavity.

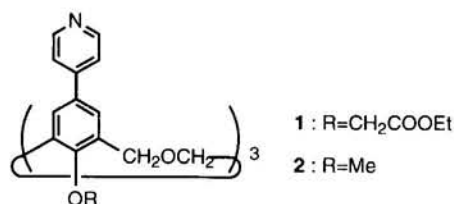
Calix[n]arenes feature a half-bowl-shaped architecture. This structural characteristic has tempted us to design a mid-air molecular capsule from two calix[n]arenes by binding two upper rim edges through "adhesive" functional groups. An early example was already reported in 1991 in which the disulfide groups were utilized for the cross-link.<sup>1</sup> However, the inclusion properties were estimated only qualitatively because of its synthetic difficulty.<sup>1</sup> It was later shown that such a biscalix[n]arene-based molecular capsule can be created according to a self-assembly manner utilizing the hydrogen-bonding interaction, but direct evidence for guest inclusion was not obtained in solution probably because of the exchange rates faster than the NMR time-scale.<sup>2,3</sup> In 1995, Rebek et al. demonstrated that calix[4]arene bearing four urea groups on the upper rim can dimerize owing to the formation of complementary hydrogen-bonds and included guests are detectable by NMR spectroscopy.<sup>4</sup> Reinhoudt et al. found, after a long-termed synthetic effort, that a covalently-linked calix[4]arene-resorcin[4]arene conjugate provides a closed inner cavity which can include small guest molecules.<sup>5</sup>

Here, it occurred to us that the utilization of a coordination bond has been an escaped idea, for Fujita et al.<sup>6</sup> and Stang et al.<sup>7</sup> have shown a number of examples that the coordination bond is very useful for the construction of self-assembled supramolecular structures. We thus designed compounds **1** and **2**: the molecular modeling with MOPAC ver.6 suggests that when two cone-homooxalix[3]arenes form an edge-to-edge dimer, pendant pyridines are exactly arranged at a right angle. This angle is particularly favorable to the cross-link by Pd(II).<sup>6,7</sup> <sup>1</sup>H NMR and mass spectroscopic studies have shown that in **1** two homooxalix[3]arenes dimerize in the presence of three equivalents of Pd(II) ( $Ph_2PCH_2CH_2PPh_2$ )-(OTf)<sub>2</sub> (**3**) and the dimeric capsule can include small molecules.<sup>8</sup>

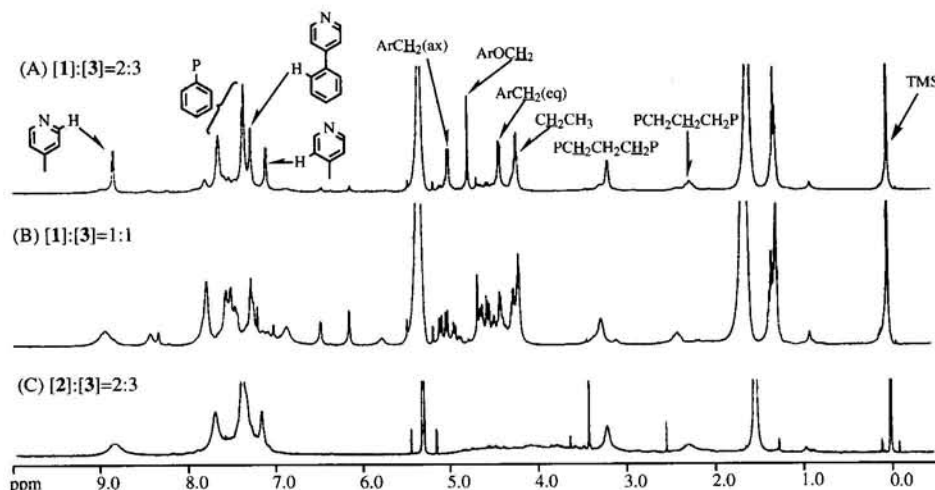
Compound **1** was synthesized from 7,15,23-tribromo-25,26,27-tris[(ethoxycarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxalix[3]arene<sup>9</sup> and diethyl-4-pyridylborane in dimethylethylene glycol in the presence of  $Pd(PPh_3)_4$  and CsF (yield 30%, mp 171.3-172.5 °C). 7,15,23-Tribromo-25,26,27-trimethoxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxalix[3]arene was prepared from 7,15,23-tribromo-2,3,10,11,18,19-hexahomo-3,11,19-trioxalix[3]arene-25,26,27-triol<sup>9</sup> by the reaction with MeI in

acetone in the presence of  $Cs_2CO_3$  (yield 93%, mp 84.9-85.2 °C) and then converted to compound **2** by the similar method (yield 35%, mp 96.7-98.4 °C). Both products were identified by IR and <sup>1</sup>H NMR spectral evidence and elemental analyses. The largest difference between **1** and **2** is that **1** is immobilized to a cone whereas **2** is conformationally still mobile.<sup>10</sup>

When **1** and **3** were mixed in  $CD_2Cl_2$ , the simple <sup>1</sup>H NMR splitting pattern was obtained only for the [1]:[3] = 2:3 ratio (Figure 1A). When the ratio was higher or lower than this value, the <sup>1</sup>H NMR spectra gave additional peaks and became very complicated (e.g., Figure 1B). Careful examination of Figure 1A reveals that all peaks can be assigned to a single phenyl unit, indicating that the 2:3 complex has a  $D_{3h}$ -symmetrical structure (for the assignment see Figure 2). It is known that in cone-calix[n]arenes the chemical shift difference ( $\Delta\delta$ ) in the geminal coupling of the  $ArCH_2Ar$  methylene protons is useful as a measure for the phenyl unit inclination: the larger the  $\Delta\delta$ , the more the phenyl units stand up.<sup>11</sup> Our recent study suggests, however, that this correlation is rather inversed in cone-homooxalix[3]arenes.<sup>9</sup> The  $\Delta\delta$  (0.30 ppm) in the  $ArCH_2O$  methylene protons (4.62 and 4.92 ppm) in **1** is enlarged to 0.58 ppm in those of the 2:3 complexes (4.41 and 4.99 ppm). This change implies that the phenyl units are more flattened for the pyridyl nitrogens to fully interact with Pd(II). The similar  $D_{3h}$ -symmetrical <sup>1</sup>H NMR spectra were also obtained in  $CDCl_3$ ,  $CDCl_2CDCl_2$ , and  $CD_2Cl_2:CD_3OD = 7.5:1.0$  (v/v). On the other hand, the spectra became complicated in  $DMF-d_7$  and  $DMSO-d_6$  even though the mole ratio of 1:3 is maintained to 2:3.

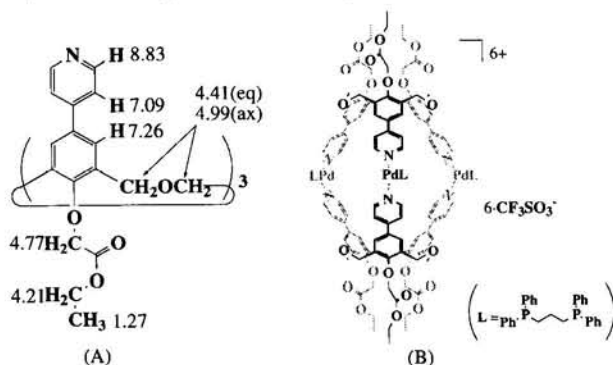


In contrast, when conformationally-mobile **2** was mixed with **3** in  $CD_2Cl_2$ , the <sup>1</sup>H NMR spectrum at [2]:[3] = 2:3 (Figure 1C) was simpler than those at other ratios. However, the peaks were significantly broadened. Since partial-cone-**2** is energetically more stable than cone-**2** (partial-cone/cone = 5.1/1.0 at -80 °C in  $CD_2Cl_2$  where the peak splitting is observable), the formation of the cone-shaped dimer from **2** and **3** accompanies an additional energy loss or even though such a dimer is formed, it still retains some molecular motion which causes the line broadening in <sup>1</sup>H NMR spectroscopy. Hence, clear evidence for the formation of the dimeric capsule was not obtained from the **2** + **3** system. The difference suggests that



**Figure 1.**  $^1\text{H}$ -NMR spectra (600 MHz) of (A)  $[1]:[3] = 2:3$ , (B)  $[1]:[3] = 1:1$ , and (C)  $[2]:[3] = 2:3$  in  $\text{CD}_2\text{Cl}_2$  at  $25^\circ\text{C}$ .  $[1]$  and  $[2]$  were maintained constant ( $1.33 \times 10^{-3} \text{ mol} \cdot \text{dm}^{-3}$ ).

preorganization of homooxalix[3]arene in a cone conformation is a prerequisite for the construction of the  $D_{3h}$ -symmetrical capsule according to a self-assembly manner.



**Figure 2.** Assignment of the protons in the  $[1]:[3] = 2:3$  complex (A) and the proposed dimeric structure (B).

The vapor pressure osmometry of **1** and **3** (in a 2:3 ratio) in  $\text{CH}_2\text{Cl}_2$  gave the MW of  $4227 \pm 390$ . This value is commensurate with the dimer (theoretical MW, 4246.92). The formation of the dimeric capsule was also supported by mass spectrometry (ESI, the measurable molecular weight < 3000). When a  $\text{CD}_2\text{Cl}_2$  solution containing **1** and **3** in a 2:3 ratio was subjected, one strong peak and a relatively weak peak appeared at 1975 [ $m/z = (M-2\text{TfO}^-)/2$ ] and 1266 [ $m/z = (M-3\text{TfO}^-)/3$ ], which were both assignable to the dimer ( $M = 4242$ ).<sup>12</sup> For the sample solution containing **1** and **3** in a 1:1 ratio, on the other hand, a strong peak and a very weak peak assignable to the 1:1 complex ( $M = 1713$ ) and the 1:2 complex ( $M = 2529$ ) appeared at 1564 [ $m/z = (M-\text{TfO}^-)$ ] and 2383 [ $m/z = (M-\text{TfO}^-)$ ], respectively. For the sample solution containing **1** and **3** in a 1:3 ratio, all peaks assignable to the 1:1, 1:2 and 2:3 complexes were observable. These mass spectral data shows that the dimer formation is highly dependent upon the ratio of **1** and **3**.

Very interestingly, the peak 1975 obtained from the  $\text{CD}_2\text{Cl}_2$  solution containing **1** and **3** in a 2:3 ratio accompanied a relatively weak peak at 2060 and the intensity was always correlated with that of 1975. This peak can be accounted for by

$m/z = [(M-2\text{TfO}^-) + 2\text{CD}_2\text{Cl}_2]/2$ .<sup>12</sup> The finding indicates that the dimer capsule includes two  $\text{CD}_2\text{Cl}_2$  molecules or the dimer structure is constructable by filling two  $\text{CD}_2\text{Cl}_2$  molecules inside the cavity.

In conclusion, the present study has demonstrated that the  $\text{Pd(II)}$ -pyridine interaction is useful to create a novel capsule-like molecule by dimerization of homooxalix[3]arene derivatives. Through this study, it was shown that the capsule formation based on the self-assembly manner requires the favorable preorganization of building-blocks, the strict pyridine- $\text{Pd(II)}$ -pyridine angle, the strict concentration ratio, and the proper solvent choice. Further study is currently continued in this laboratory.

## References and Notes

1. T. Arimura, S. Matsumoto, O. Teshima, T. Nagasaki, and S. Shinkai, *Tetrahedron Lett.*, **32**, 5111 (1991).
2. J.-D. van Loon, R. G. Janseen, W. Verboom, and D. N. Reinhoudt, *Tetrahedron Lett.*, **33**, 5125 (1992).
3. K. Koh, K. Araki, and S. Shinkai, *Tetrahedron Lett.*, **35**, 8255 (1994).
4. K. D. Shimizu and J. Rebek, Jr., *Proc. Natl. Acad. Sci. USA*, **92**, 12403 (1995); B. C. Hamann, K. D. Shimizu, and J. Rebek, Jr., *Angew. Chem., Int. Ed. Engl.*, **35**, 1326 (1996); R. K. Castellano, B. H. Kim, and J. Rebek, Jr., *J. Am. Chem. Soc.*, **119**, 12671 (1997).
5. P. Timmerman, W. Verboom, F. C. J. M. van Veggel, J. P. M. van Duynhoven, and D. N. Reinhoudt, *Angew. Chem., Int. Ed. Engl.*, **33**, 2345 (1994); P. Timmerman, K. G. A. Nierop, E. A. Brinks, W. Verboom, F. C. J. M. van Veggel, W. P. van Hoorn, and D. N. Reinhoudt, *Chem. Eur. J.*, **1**, 132 (1995).
6. M. Fujita, J. Yazaki, and K. Ogura, *J. Am. Chem. Soc.*, **112**, 5645 (1990); M. Fujita, S. Nagao, and K. Ogura, *Ibid.*, **117**, 1649 (1995).
7. P. J. Stang and D. H. Cao, *J. Am. Chem. Soc.*, **116**, 4981 (1994); P. J. Stang, D. H. Cao, S. Saito, and A. M. Arif, *Ibid.*, **117**, 6273 (1995).
8. More recently, an Italian group reported that a resorcin[4]arene bearing cyano groups can dimerize in the presence of  $\text{Pd(II)}$ , but this coordination bond is not so stable as the  $\text{Pd(II)}$ -pyridine bond: P. Jacopozi and E. Dalcanele, *Angew. Chem. Int. Ed. Engl.*, **36**, 613 (1997).
9. A. Ikeda, Y. Suzuki, M. Yoshimura, and S. Shinkai, *Tetrahedron*, **54**, 2497 (1998).
10. K. Araki, K. Inada, H. Otsuka, and S. Shinkai, *Tetrahedron*, **49**, 9465 (1993); K. Araki, K. Inada, and S. Shinkai, *Angew. Chem., Int. Ed. Engl.*, **35**, 72 (1996).
11. C. D. Gutsche, in "Calixarene," Royal Society of Chemistry, Cambridge (1989).
12. Although these species are multicharged ions and should give the peaks with 0.33 or 0.5 increment for the isotope species, they are not clearly detected because of the line-broadening in the mass spectra.