Metal-Mediated Self-Assembly of Pyridylcalixarenes: Prevention of Intramolecular Metal Chelation Is Essential in Constructing Molecular Capsules

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To construct calixarene-based molecular capsules utilizing the pyridyl−Pd(II) interaction, reactions of *cone*-pyridylcalix[4]arene **3**, *cone*-pyridylcalix[5]arene **13**, and *cone*-pyridylcalix[4]arene bis-crown **16** with square-planar Pd(II) complex **7** were investigated. Because of the coexistence of intermolecular binding and chelate-forming intramolecular binding, the reactions of *cone*-pyridylcalix[4]arene **3** or *cone*-pyridylcalix[5]arene **13** with *cis*-Pd(II) complex **7** yield complicated, structure-unknown oligomers. The short dioxyethylene bridges on the lower rim of pyridylcalix-[4]arene bis-crown **16** rigidify the *cone* conformation and thus prohibit **16** from the intramolecular binding with a metal component. Thus, two *cone*-tetrapyridylcalix[4]arene bis-crown **16** and four *cis*-Pd(II) complex molecules self-assemble into molecular capsules that exist as a *parallel/antiparallel* conformer mixture in a nearly 1:1 ratio. The results demonstrated that to prevent entropically favorable intramolecular binding is essential in constructing higher capsule-like structures with calixarene building blocks by self-assembling.

Introduction

Metal-mediated self-assembly has proved to be a very effective methodology in constructing two- or three-dimensional supramolecular architectures, such as macrocycles, molecular containers, tubular structures, interlocked and intertwined structures, and helicates, which are all useful in molecular or chiral recognition, host−guest chemistry, catalysis, and memory storage.[1] Self-assembly of large supramolecular cages using pyridyl−Pd linkages, contributed mainly by Stang and Fujita, is especially appealing.[2] On the other hand, calixarenes have almost unlimited potentials as molecular receptors and building blocks for higher molecular architectures, because of the inherent half-bowl-shaped structure.[3] This characteristic structure is particularly advantageous in the design of capsular molecules. A number of calixarene-based capsular structures in which calixarene subunits are linked by hydrogen bonds in a self-assembly way or by covalent bonds have appeared.[4−9] In contrast, there are only a few examples of studies related to metal-mediated self-assembly of calixarene analogues.[10−14] Jacopozzi and Dalcanale reported that two tetracyanocavitands self-assemble with four square-planar Pd(II) or Pt(II) complexes into a molecular capsule that can

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(1) For recent reviews, see: (a) Leininger, S.; Olenyuk, B.; Stang, P. J. *Chem. Rev.* **2000**, *100*, 853. (b) MacGillivray, L. R.; Atwood, J. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1018. (c) Caulder, D. L.; Raymond, K. N. *Acc. Chem. Res.* **1999**, *32*, 975. (d) Piguet, C.; Bernardinelli, G.; Hopfgartner, G. *Chem. Rev.* **1997**, *97*, 2005. (e) Fujita, M. *Chem Soc. Rev.* **1998**, *27*, 417. (f) Amabilino, D. B.; Asakawa, M.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Belohradsky, M.; Credi, A.; Higuchi, M.; Raymo, F. M.; Shimizu, T.; Stoddart, J. F.; Venturi, M.; Yase, K. *New J. Chem.* **1998**, *22*, 959. (g) Albrecht, M. *Chem. Soc. Rev.* **1998**, *27*, 281. (h) Jones, C. J. *Chem. Soc. Rev.* **1998**, *27*, 289. (i) Linton, B.; Hamilton, A. D. *Chem. Rev.* **1997**, *97*, 1669.

(2) (a) Olenyuk, B.; Whiteford, J. A.; Fechtenkotter, A.; Stang, P. J. *Nature* **1999**, *398*, 796. (b) Stang, P. J.; Cao, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 4981. (c) Stang, P. J.; Cao, D. H.; Saito, S.; Arif, A. M. *J. Am. Chem. Soc.* **1995**, *117*, 6273. (d) Takeda, N.; Umemoto, K.; Yamaguchi, K.; Fujita, M.; *Nature* **1999**, *398*, 794. (e) Fujita, M.; Yazaki, J.; Ogura, K. *J. Am. Chem. Soc.* **1990**, *112*, 5645. (f) Fujita, M.; Nagao, S.; Ogura, K. *J. Am. Chem. Soc.* **1995**, *117*, 1649. (g) Fox, O. D.; Dalley, N. K.; Harrison, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 7111. (h) Fox, O. D.; Leung, J. F. Y.; Hunter, J. M.; Dalley, N. K.; Harrison, R. G. *Inorg. Chem.* **2000**, *39*, 783. (i) Harrison, R. G.; Dalley, N. K.; Nazarenko, A. Y. *Chem. Commun.* **2000**, 1387.

(3) For comprehensive reviews, see: (a) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989. (b) Vicens, J., Böhmer, V., Eds. *Calixarenes*; Kluwer Academic Press: Dordrecht, 1991. (c) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (d) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713. (e) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998.

(4) (a) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931. (b) Conn, M. M.; Rebek, J., Jr. *Chem. Rev.* **1997**, *97*, 1647. (c) Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests;* Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1994.

(5) (a) Zhong, Z. L.; Ikeda, A.; Shinkai, S. *J. Am. Chem. Soc.* **1999**, *121*, 11906. (b) Koh, K.; Araki, K.; Shinkai, S. *Tetrahedron Lett.* **1994**, *35*, 8255. (c) Arimura T.; Matsumoto, S.; Teshima, O.; Nagasaki, T.; Shinkai, S. *Tetrahedron Lett.* **1991**, *32*, 5111.

(6) (a) van Loon, J.-D.; Janseen, R. G.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron Lett.* **1992**, *33*, 5125. (b) van Wageningen, A. M. A.; Timmerman, P.; van Duynhoven, J. P. M.; Verboom, W.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *Chem. Eur. J.* **1997**, *3*, 639. (d) Prins, L. J.; Huskens, J.; de Jong, F.; Timmerman, P.; Reinhoudt, D. N. *Nature* **1999**, *398*, 498.

(7) (a) Rebek, J., Jr. *Chem. Commun.* **2000**, 637. (b) Rudkevich, D. M.; Rebek, J., Jr. *Eur. J. Org. Chem.* **1999**, 1991. (c) Schalley, C. A.; Castellano, R. K.; Brody, M. S.; Rudkevich, D. M.; Siuzdak, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 4568.

(8) (a) Vysotsky, M. O.; Thondorf, I.; Böhmer, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 1264. (b) Mogck, O.; Pons, M.; Böhmer, V.; Vogt, W. *J. Am. Chem. Soc.* **1997**, *119*, 5706. (c) Mogck, O.; Böhmer, V.; Vogt, W. *Tetrahedron* **1996**, *52*, 8489. (d) Mogck, O.; Paulus, E. F.; Böhmer, V.; Thondorf, I.; Vogt, W. *J. Chem. Soc., Chem. Commun.* **1996**, 2533.

(9) MacGillivray, L. R.; Diamente, J. L. R.; Ripmeester, J. A. *Chem. Commun.* **2000**, 359.

(10) Jacopozzi, P.; Dalcanale, E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 613.

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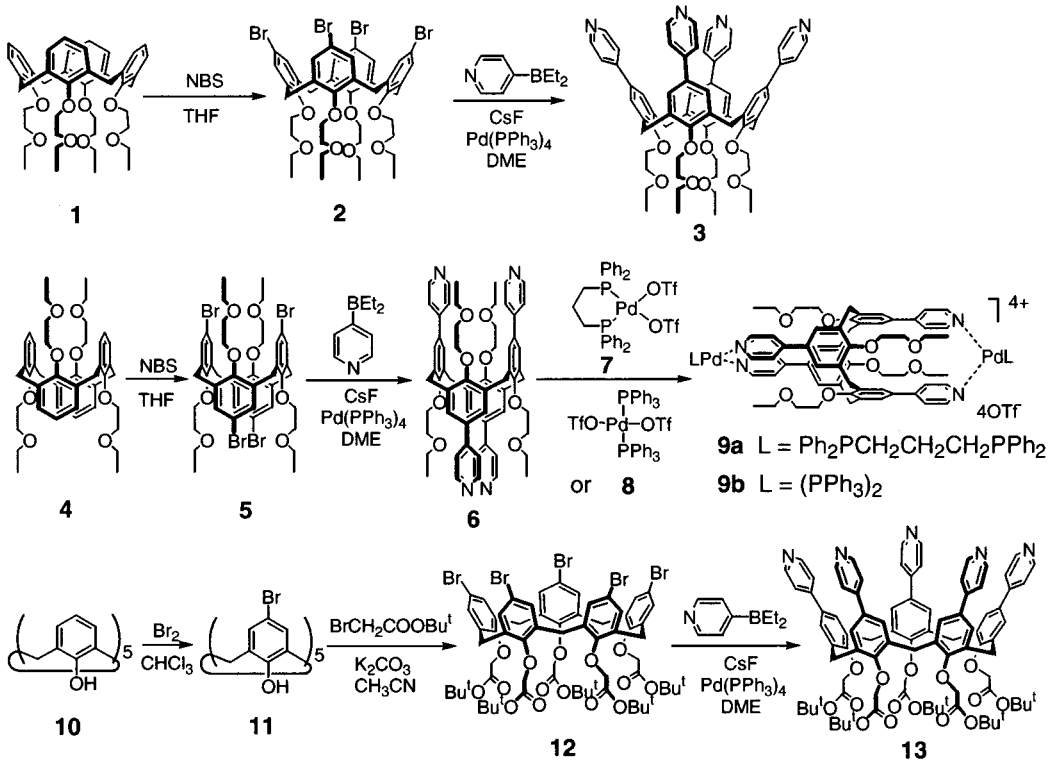
Scheme 1



encapsulate one triflate anion.[10] We found that two *cone*-tripyridylhomooxacalix[3]arene esters self-assemble with three square-planar Pd(II) complexes into a molecular capsule that can encapsulate [60]fullerene with an association constant of 39 M^{-1} in tetrachloroethane.[11] In this supramolecular capsule, the association constant can be dramatically elevated to 2100 M^{-1} upon complexation with Li^+ cation in the ester cavity on the lower rim.[11a] Very recently, Beer et al. reported Cd(II)- or Zn(II)-directed cyclic assemblies consisting of three dithiocarbamate calix[4]resorcarene cups and six metal ions; the trimeric hosts strongly bind [60]fullerene.[12] Despite these interesting homooxacalixarene- or calixresorcarene-based molecular capsules, surprisingly, any molecular capsule constructed from a "standard" calix[4]arene[3a] through metal-mediated self-assembly has never appeared. Constructing such a molecular capsule should be of apparent interest because the structural and host−guest properties of "standard" calix[4]arenes have been widely studied.

In this paper, we report self-assembled molecular capsules constructed from pyridylcalix[4]arene bis-crown **16** through pyridyl−Pd(II) interaction (for the structure see Scheme 2). An important conclusion we have reached is that prevention of intramolecular metal-chelation by molecular rigidification is essential in constructing such molecular capsules from "standard" calix[4]arenes.

Results and Discussion

With the successful example of calix[4]resorcarene-based molecular capsule[10] in mind, one may expect the *cone*-tetrapyridylcalix[4]arene **3** to self-assemble with square-planar metal complexes into a molecular capsule by a similar way. The effort to fulfill this expectation, however, has shown that the product is structure-unknown oligomers.[15] We checked the reaction of **3** and *cis*-Pd(II) complex **7** but could not get the expected $\mathbf{3}_2\cdot\mathbf{7}_4$ capsular molecule. A possible reason is the residual conformational mobility of **3**. The alkyl groups on the lower rim immobilize the benzene ring inversion in a calix[4]arene and thus suppress the interconversion between the different conformers. However, the most stable molecular conformation of the *cone*-calix[4]arene thus obtained is not a symmetrical C_{4v} cone but a pinched C_{2v} cone with two distal benzene rings almost parallel to each other and the other two almost perpendicular, shown by X-ray structures.[16] Furthermore, dynamic studies showed that two C_{2v} conformers interconvert very fast in solution at room temperature.[17,18] The energy-minimized structure of **3** is also in such a pinched *cone* conformation (Figure 1A,C).

Meanwhile, we have found that *1,3-alternate* tetrapyridylcalix[4]arene **6** intramolecularly binds not only with *cis*-Pd(II) complex **7** forming chelate **9a**, but also with *trans*-Pd(II) complex **8** forming chelate **9b**. The original idea of the study using **6** was to construct a

(11) (a) Ikeda, A.; Udzu, H.; Yoshimura, M.; Shinkai, S. *Tetrahedron* **2000**, *56*, 1825. (b) Ikeda, A.; Yoshimura, M.; Udzu, H.; Fukuhara, C.; Shinkai, S. *J. Am. Chem. Soc.* **1999**, *121*, 4296. (c) Ikeda, A.; Yoshimura, M.; Tani, F.; Naruta, Y.; Shinkai, S. *Chem. Lett.* **1998**, 587.

(12) (a) Fox, O. D.; Drew, M. G. B.; Wilkinson, E. J. S.; Beer, P. D. *Chem. Commun.* **2000**, 391. (b) Fox, O. D.; Drew, M. G. B.; Beer, P. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 135.

(13) Lim, C. W.; Hong, J.-I. *Tetrahedron Lett.* **2000**, *41*, 3113.

(14) (a) Kleina, C.; Graf, E.; Hosseini, M. W.; Cian, A. D.; Fischer, J. *Chem. Commun.* **2000**, 239. (b) Mislin, G.; Graf, E.; Hosseini, M. W.; Cian, A. D.; Kyrisakas, N.; Fischer, J. *Chem. Commun.* **1998**, 2545.

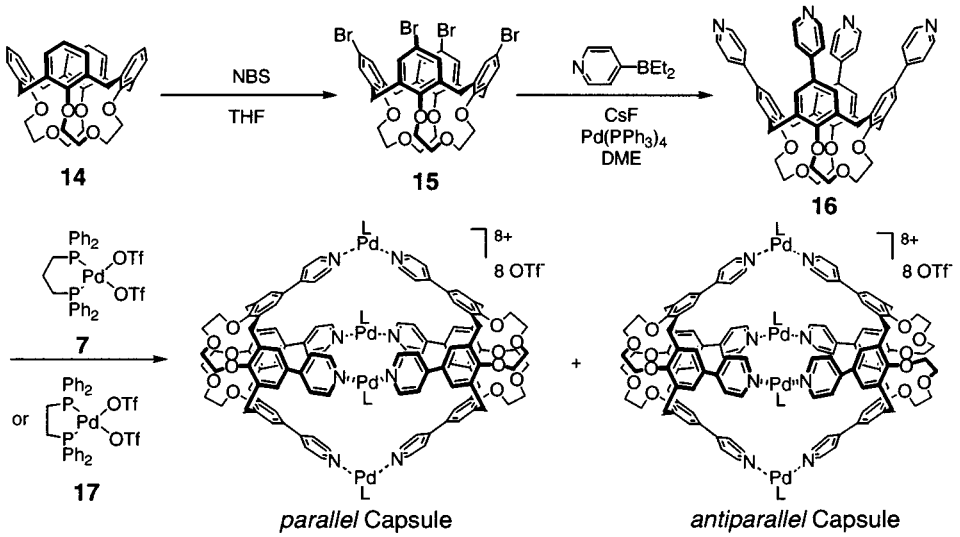
(15) The similar attempt was also made by M. Fujita's group but failed.

(16) (a) Arduini, A.; Pochini, A.; Reverberi, S.; Ungaro, R.; Andreetti, G. D.; Ugozzoli, F. *Tetrahedron* **1986**, *42*, 2089. (b) Calestani, G.; Ugozzoli, F.; Arduini, A.; Ghidini, E.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1987**, 388.

(17) Ikeda, A.; Tsuzuki, H.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2073.

(18) Arduini, A.; Fabbi, M.; Mantovani, M.; Mirone, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1995**, *60*, 1454.

Scheme 2



18a L = $Ph_2PCH_2CH_2CH_2PPh_2$
18b L = $Ph_2PCH_2CH_2PPh_2$

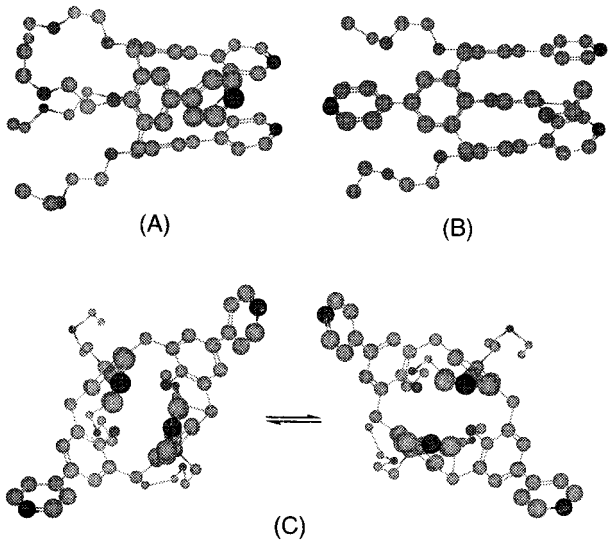


Figure 1. Energy-minimized structures of (A) **3**, (B) **6**, and (C) **3** showing the $C_{2v}-C_{2v}$ interconversion (generated with MM2 using Chem3D Pro 4.5 of CambridgeSoft).

"tubular" architecture[14] consisting of **6** and *trans*-Pd(II) complex **8**. Considering the opposite orientations of the two pairs of pyridyl groups in **6** (Figure 1B), one may expect it to self-assemble with a linear metal component (for example, bis(triphenylphosphino)palladium(II) trans complex **8**) into a polymeric tubular structure through the pyridyl−metal interaction. As expected, a 1:2 **6**/**8** mixture gave a very simple ^{1}H NMR spectrum (Figure 2B), suggesting a symmetrical structure of the product. However, the molecular weight of the product was estimated to be 2600 ± 300 by VPO measurements in chloroform, showing that the product is probably not the expected tubular structure but the intramolecularly bound chelate **9b**, whose formula weight is 2878. To form this chelate, the configuration of the trans Pd(II) complex must be changed to a cis form. Bis(diphenylphosphino)-propane cis Pd(II) complex **7** was used to confirm this notion of transformation. A 1:2 **6**/**7** mixture gave a symmetrical ^{1}H NMR spectrum (Figure 2C) which can be assigned with the chelate **9a**. The molecular weight was determined by coldspray ionization MS measurement. The coldspray ionization (CSI) MS[19] spectrum (Figure 3) shows very strong peaks at *m*/*z* 736 for [**9a** − 3OTf]$^{3+}$ and at *m*/*z* 1178 for [**9a** − 2OTf]$^{2+}$. The similarity of the ^{1}H NMR spectra (especially the signals for pyridyl protons) of the 1:2 mixtures of **6**/**8** (Figure 2B) and **8**/**7** (Figure 2C) suggests that the configuration of the Pd(II) centers in the two products must be same. Examination of CPK models showed that the cross angle of the pyridyl pairs in **9** should be smaller than 30° without distortion of the covalent bonds. Despite the predictable tension brought by the very small angle in the intramolecularly bound chelates, the entropically unfavorable intermolecularly bound tubular structures were not formed.

The finding in **6** suggests that the "parallel" pair of pyridyl moieties in **3** are ready to intramolecularly bind **7**, since the orientation of this parallel pyridyl pair in **3** is very similar with that of the pyridyl pairs in **6**, as shown by the MM2 structures (Figure 1A,B). Intramolecular binding of a pair of pyridyl moieties in **3** with a metal center causes the left pair apart far from each other, which intermolecularly bind with metal centers. This coexistence of intramolecular and intermolecular binding modes thus leads to the formation of complex oligomers. A search of literature also shows the importance of the prevention of entropically favorable intramolecular binding: in the calix[4]resorcarene-based molecular capsules, for example, the resorcarene units are methylene-bridged on the upper rim hydroxyl moieties and have very rigid *cone* conformation.[10,12]

One approach to reducing the conformational mobility of calixarenes is to make use of the interactions between the calixarene and its guests. It is known that the conformational freedom remaining in calixarene ester derivatives can be greatly reduced in a *cone* conformation enforced by complexation with appropriate metal cat-

(19) (a) Sakamato, S.; Fujita, M.; Kim, K.; Yamaguchi, K. *Tetrahedron* **2000**, *56*, 955. (b) Addition of a small amount of DMF in the sample greatly enforces the ionization strength; see: Blades, A. T.; Jayaweera, P.; Ikonomou, M. G.; Kebarle, P. *J. Chem. Pys.* **1990**, *92*, 5900.

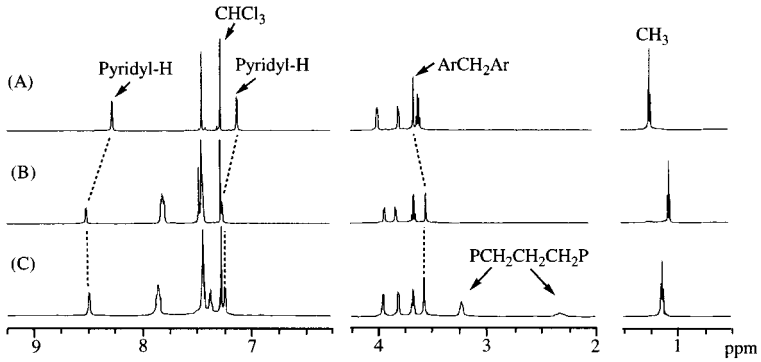


Figure 2. ^{1}H NMR spectra of (A) 2.5 mM of **6**, (B) 2.5 mM of **6** and 5 mM of **8**, and (C) 2.5 mM of **6** and 5 mM of **7** (600 MHz, $CDCl_3$, TMS, 300 K**)**.

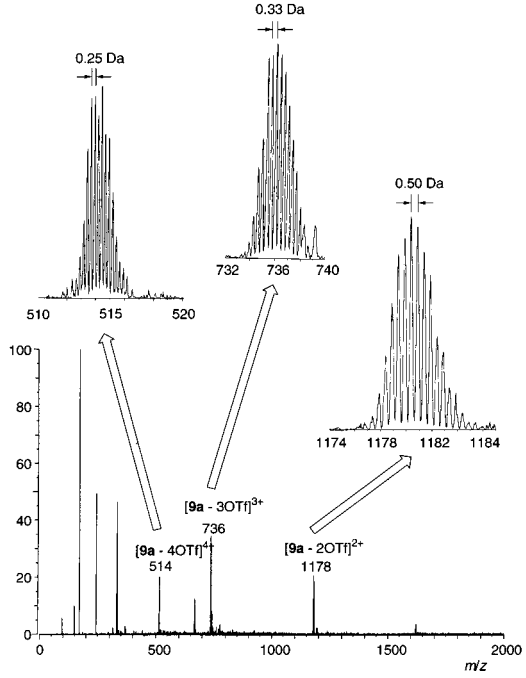


Figure 3. Coldspray ionization (CSI) MS spectrum of 1:2 mixture of **6** and **7** (needle voltage, 3.0 kV; needle current, 300−700 nA; orifice voltage, 95 V; ion source temperature, 288 K; flow rate, 17 μL/min; concentration, 12 mg/(3 mL of CH_2Cl_2 + 0.08 mL of DMF)).

ions.[20] On the other hand, covalently bridged biscalix[5]arenes[21,22] or hydrogen-bonded calix[5]arene dimer[23] can complex fullerenes much tighter than monocalix[5]arenes. In the X-ray crystallographic structures of calix[5]arene/[60]fullerene (2:1) complex, the inclination angles of the phenol rings from the mean plane composed of the five bridging methylene carbons are in the range of 133.7−135.7°: i.e., the cross angle between two adjacent phenol rings of different calixarene is about 90°.[24] We thus expected that pyridylcalix[5]arene ester **13** would form a metal-mediated dimeric molecular capsule suitable for fullerene inclusion, because the complexation with alkali metal cations or fullerenes would rigidify **13** and suppress the intramolecular binding with the metal complex. A solution of a 2:5 **13**/**7** mixture gave a very complicated and very broadened ^{1}H NMR spectrum, suggesting that no symmetrical structure was formed in it. Presumably, two of the five pyridyl groups bind intramolecularly, and the other three bind intermolecularly palladium complexes leading to oligomers. Expecting a guest rigidification effect, we added alkali metal cations (Na^+ or K^+) and fullerenes[25] (C_{60} or C_{70}) separately or simultaneously to the mixture. Unfortunately, no symmetrical NMR spectrum was obtained. Apparently, the interactions between **13** and the fullerenes or the alkali metal cations are not strong enough to prohibit the unfavorable intramolecular binding.

Since the supramolecular approach did not work, we considered that to rigidify the *cone* conformation of a calixarene by introducing covalently bonded rigid bridges would be the sole way out of the unfavorable intramolecular binding. The work of Pochini et al. showed that the calix[4]arene bis-crown-3 has a slightly distorted but very rigid cone structure.[26] We thus designed pyridylcalix[4]arene bis-crown **16** and eventually found that this rigid calix[4]arene self-assembles with *cis*-Pd(II) complexes **7** or **17** into dimeric molecular capsules **18a** or **18b** as expected.

A solution of 1:2 mixture of **16** and **7** in $CDCl_3/CD_3OD$ (5:1 v/v) mixed solvent gave a complicated but symmetrical NMR spectrum (Figure 4F), which can be assigned to the *parallel*/*antiparallel*[27] molecular capsule mixture (the structures of *parallel* and *antiparallel* **18a** are shown in Scheme 2) using a ^{1}H−^{1}H COSY spectrum. The CSI MS[19] spectrum (Figure 5) of the mixture shows the strongest peak at *m*/*z* 854 for [capsule − 5OTf]$^{5+}$, proving the existence of the capsular molecules. The ^{1}H NMR spectrum of free **16** (Figure 4A) shows two sets of AB doublets (1:1) for the $ArCH_2Ar$ methylene protons, suggesting a C_{2v} symmetry. Since **16** is considerably rigidified by bridging and sterically crowding in the lower rim,[26] this C_{2v} symmetry is not due to the C_{2v}-C_{2v} interconversion[17,18] but due to inequivalence arising from bridging four OH groups with two short diethyl ether

(20) (a) Otsuka, H.; Araki, A.; Shinkai, S. *Tetrahedron* **1995**, *51*, 8757. (b) Matsumoto, H.; Nishio, S.; Takeshita, M.; Shinkai, S. *Tetrahedron* **1995**, *51*, 4647.

(21) Haino, T.; Yanase, M.; Fukazawa, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 997.

(22) Wang, J.; Gutsche, C. D. *J. Am. Chem. Soc.* **1998**, *120*, 12226.

(23) Yanase, M.; Haino, T.; Fukazawa, Y. *Tetrahedron Lett.* **1999**, *40*, 2781.

(24) (a) Haino, T.; Yanase, M.; Fukazawa, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 259. (b) Haino, T.; Yanase, M.; Fukazawa, Y. *Tetrahedron Lett.* **1997**, *38*, 3739.

(25) The association constant between **13**·Na^+ complex and [60]-fullerene in $Cl_2CHCHCl_2$ was estimated to be 1300 ± 300 M^{-1} on the basis of the absorbance changes at 435 nm in titration of the fullerene with **13**·Na^+.

(26) (a) Arduini, A.; Fabbi, M.; Mantovani, M.; Mirone, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1995**, *60*, 1454. (b) Arduini, A.; McGregor, W. M.; Paganuzzi, D.; Pochini, A.; Secchi, A.; Ugozzoli, F.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1996**, 838.

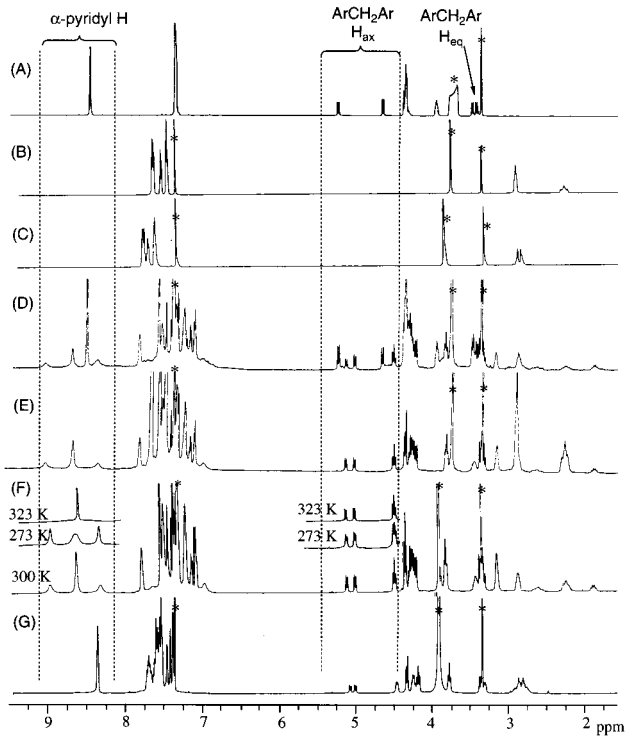


Figure 4. ^{1}H NMR spectra of (A) 2.5 mM of **16**, (B) 5.0 mM of **7**, (C) 5.0 mM of **17**, (D) 2.5 mM of **16** and 2.5 mM of **7**, (E) 2.5 mM of **16** and 10 mM of **7**, (F) 2.5 mM of **16** and 5.0 mM of **7**, with partial spectra recorded at 323 and 273 K, and (G) 2.5 mM of **16** and 5.0 mM of **17** (600 MHz, $CDCl_3/CD_3OD$ = 5:1 v/v, TMS, 300 K). The peaks marked with "*" are attributed to undeuterated solvents.

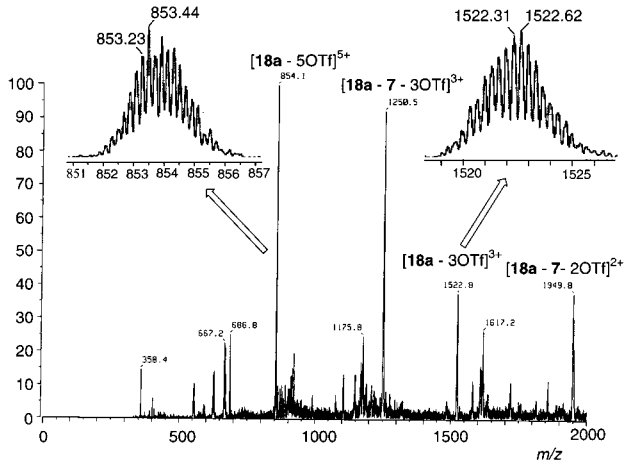


Figure 5. Coldspray ionization (CSI) MS spectrum of a 1:2 mixture of **16** and **7** (needle voltage, 2.8 kV; needle current, 300−700 nA; orifice voltage, 50 V; ion source temperature, 288 K; flow rate, 17 μL/min; concentration, 14 mg/(4 mL of CH_2Cl_2 + 0.10 mL of DMF)).

linkages. In the presence of 2 equivalents of **7**, the two sets of doublets split into four sets at nearly 1:1:1:1 integral strength (Figure 4F), which are in consistence with a nearly 1:1 mixture of the *parallel* and *antiparallel* capsules. The α-pyridine protons show three broad singlets at 8.99, 8.65, and 8.34 ppm in nearly 1:2:1 ratio, which can be explained with the rotation of the pyridyl groups. On the basis of the values of chemical shift difference of the $ArCH_2Ar$ doublets,[3] the inclination angles of benzene rings in the two capsular molecules are slightly different, and thus the N−Pd−N angles are slightly different. Sterically hindered by the bulky diphenylphosphino groups, the pyridyl groups in the less inclined capsule (with larger N−Pd−N bond angle) rotate at a rate slower than the NMR time scale. This affords the two broad singlets in a 1:1 ratio. On the other hand, the pyridyl groups in the other capsule (with smaller N−Pd−N bond angle) are less sterically hindered and rotate at a rate faster than the NMR time scale, showing one singlet. The VT NMR spectra (Figure 4F) also support this analysis. At present, however, it is not clear yet which peak set is assigned to which isomer. As shown by the NMR spectra (Figures 4D-4F), when the **16**/**7** ratio is not 2:5, the excess pyridylcalix[4]arene bis-crown or metal complex exists as the free form, scarcely infecting the molecular capsules. Only when the ratio is 2:5 do they self-assemble into the capsules quantitatively.

To further confirm the foregoing analysis, the palladium complex **7** was replaced with bis(diphenylphosphino)ethane Pd(II) complex **17**. The short ethylene linker in **17** pulls the PPh_2 groups a little far away from the pyridyl groups and thus makes it possible for the pyridyl groups to rotate faster. As expected, a 1:2 mixture of **16** and **17** gives a much simpler spectrum (Figure 4G). While the splitting pattern of the $ArCH_2Ar$ methylene protons remains almost unchanged with respect to the case of **7**, the pyridyl α protons show only one singlet, and the other peaks at the aromatic region are also greatly simplified.

Conclusions

In conclusion, this paper demonstrates why it is difficult to construct a calixarene-based molecular capsule through metal-mediated self-assembly and how to achieve this purpose. The conformational mobility remained in an unbridged *cone*-calixarene makes it possible to intramolecularly bind with a metal complex forming entropically favorable chelate bonds. The coexistence of intramolecular and intermolecular binding leads to structure-unknown oligomers in the reactions of unbridged *cone*-pyridylcalixarenes with a *cis*-Pd(II) complex. In contrast, the short diethyl ether bridges in the pyridylcalix[4]arene bis-crown **16** rigidify the *cone* conformation, prohibit the pyridyl groups to get close to each other, and thus prevent **16** from intramolecular binding with a metal component. Two *cone*-**16** molecules intermolecularly bind four *cis*-Pd(II) complex molecules self-assembling into a molecular capsule. These results show that the prevention of entropically favorable intramolecular binding is essential in constructing higher structures with calixarene building blocks through a ligand−metal coordination interaction. We believe that this result is of significance, more generally, in the construction of supramolecular architectures.

Experimental Section

Melting points were determined on a micro melting point apparatus (Yanaco MP-500D) and are uncorrected. ^{1}H NMR spectra were measured on a Bruker DRX 600 spectrometer or a Bruker AC250P spectrometer. The samples of the self-assembled structures **9** and **18** for NMR measurements were prepared by mixing the solutions of the corresponding pyridylcalixarenes and Pd(II) complexes at required ratios. Com-

pounds **1**,[28] **4**,[29] **7**,[30] **10**,[31] **14**,[26] and diethyl(4-pyridyl)borane[32] were prepared according to literature procedures. Compounds **8** and **17** were synthesized by exchanging the anion in the presence of excess AgOTf in dry dichloromethane from *trans*-$Pd(PPh_3)_2Cl_2$ and [1,2-bis(diphenylphosphino)ethane]dichloropalladium(II), respectively.

***cone*-5,11,17,23-Tetrabromo-25,26,27,28-tetrakis(ethoxyethoxy)calix[4]arene (2).** A solution of **1** (1.36 g, 1.91 mmol) and NBS (2.04 g, 11.5 mmol) in THF (20 mL) was stirred at room temperature for 20 h. The solvent was evaporated, and the residue was recrystallized from methanol, affording 1.55 g of pale yellow powder in 79% yield: mp 143−145 °C; ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ 6.81 (s, 8H, ArH), 4.45 (d, J = 13.5 Hz, 4H, $ArCH_2Ar$), 4.09 (t, J = 5.3 Hz, 8H, $ArOCH_2$), 3.76 (t, J = 5.3 Hz, 8H, $EtOCH_2$), 3.49 (q, J = 7.0 Hz, 8H, $MeCH_2$), 3.07 (d, J = 13.5 Hz, 4H, $ArCH_2Ar$), 1.18 (t, J = 7.0 Hz, 12H, CH_3); MALDI TOF MS m/z 1051.5 ($M + Na^+$). Anal. Calcd for $C_{44}H_{52}Br_4O_8$: C, 51.38; H, 5.10. Found: C, 51.63; 5.21.

***cone*-5,11,17,23-Tetra(4-pyridyl)-25,26,27,28-tetrakis(ethoxyethoxy)calix[4]arene (3).** Under nitrogen, a mixture of **2** (0.40 g, 0.39 mmol), diethyl-4-pyridylborane (0.34 g, 2.3 mmol), CsF (0.50 g, 3.3 mmol), and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) in DME (20 mL) was refluxed for 10 h. The solid was filtered off. The filtrate was evaporated to dryness, the residue was triturated with chloroform, and the solution was submitted to column chromatography (silica gel, chloroform/methanol = 50:1−10:1). 0.18 g of pale yellow solid was obtained in 45% yield: mp 232−234 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.33 (d, J = 5.7 Hz, 8H, PyH), 7.03 (d, J = 5.7 Hz, 8H, PyH), 6.98 (s, 8 H, ArH), 4.69 (d, J = 13.5 Hz, 4H, $ArCH_2Ar$), 3.32 (d, J = 13.5 Hz, 4H, $ArCH_2Ar$), 4.25 (t, J = 5.3 Hz, 8 H, $ArOCH_2$), 3.89 (t, J = 5.3 Hz, 8 H, $EtOCH_2$), 3.57 (q, J = 7.0 Hz, 8H, $MeCH_2$), 1.23 (t, J = 7.0 Hz, 12H, CH_3); MALDI TOF MS m/z 1022.5 ($M + H^+$). Anal. Calcd for $C_{64}H_{68}N_4O_8 \cdot H_2O$: C, 73.96; H, 6.79; N, 5.39. Found: C, 74.24; H, 6.72; N, 5.40.

1,3-*alternate*-5,11,17,23-Tetrabromo-25,26,27,28-tetrakis(ethoxyethoxy)calix[4]arene (5). A solution of **4** (0.82 g, 1.2 mmol) and NBS (1.10 g, 6.18 mmol) in THF (15 mL) was stirred at room temperature for 3 h. The color of the solution turned from orange to light yellow. Additional NBS (3 × 0.8 g) was added by portions at 2-h intervals until white precipitates appeared. The solvent was removed by evaporation, and the residue was recrystallized from methanol (20 mL). White fine crystals (1.06 g) were obtained in 90% yield: mp 167−169 °C; ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ 7.33 (s, 8H, ArH), 3.90−3.72 (m, 24H, OCH_2), 3.46 (s, 8H, $ArCH_2Ar$), 1.38 (t, J = 7.0 Hz, 12H, CH_3); ESI TOF MS m/z 1051.0 ($M + Na^+$). Anal. Calcd for $C_{44}H_{52}Br_4O_8$: C, 51.34; H, 5.10. Found: C, 51.31; H, 5.09.

1,3-*alternate*-5,11,17,23-Tetra(4-pyridyl)-25,26,27,28-tetrakis(ethoxyethoxy)calix[4]arene (6). A mixture of **5** (0.40 g, 0.39 mmol), diethyl(4-pyridyl)borane (0.46 g, 3.1 mmol), CsF (0.47 g, 3.1 mmol), and $Pd(PPh)_4$ (40 mg, 0.034 mmol) in DME (15 mL) was stirred for 15 h at reflux temperature for 8 h under nitrogen. Chloroform (20 mL) was added, and the precipitate was filtered off. The filtrate was evaporated to dryness. The residue was dissolved in chloroform (30 mL), washed with water (2 × 50 mL), and evaporated to dryness again. After isolation by column chromatography (silica gel, chloroform/ethanol = 20:1−5:1 v/v), 72 mg of pale yellow solid (R_f = 0.15, chloroform/ethanol 20:1 v/v, silica plate) was obtained in 18% yield: mp 78−81 °C; ^{1}H NMR (600 MHz, $CDCl_3$, TMS) δ 8.26 (d, J = 5.6 Hz, 8H, PyH), 7.44 (s, 8H, ArH), 7.11 (d, J = 5.6 Hz, 8H, PyH), 4.01 (m, 8H, $ArOCH_2$), 3.82 (m, 8H, $EtOCH_2$), 3.68 (s, 8H, $ArCH_2Ar$), 3.65 (q, J = 7.0 Hz, 8H, $MeCH_2$), 1.22 (t, J = 7.0 Hz, 12H, CH_3); ESI TOF MS m/z 1021.9 ($M + H^+$), 1043.9 ($M + Na^+$). Anal. Calcd for $C_{64}H_{68}N_4O_8 \cdot H_2O$: C, 73.96; H, 6.79; N, 5.39. Found: C, 73.92; H, 6.78; N, 5.17.

5,11,17,23,29-Pentabromo-31,32,33,34,35-pentahydroxycalix[5]arene (11). With stirring, a solution of bromine (0.198 mL, 0.614 g, 3.84 mmol) in dry chloroform (20 mL) was added dropwise to an ice-cooled solution of calix[5]arene **10** (0.40 g, 0.75 mmol) in dry chloroform (15 mL) within 1 h. After 30 min, the solvent was evaporated under reduced pressure. The yellow residue was stirred for 10 min in 30 mL of methanol. The precipitate was collected by filtration and washed with methanol untill the filtrate became colorless. Pale yellow powder (0.68 g, R_f = 0.26, chloroform/hexane = 1:1, silica plate) was obtained in 98% yield: mp > 300 °C dec; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.76 (s, 5H, OH), 7.31 (s, 10H, ArH), 3.76 (br s, 10H, $ArCH_2Ar$); MALDI TOF MS m/z 926.3 ($M + H^+$), 948.2 ($M + Na^+$). Anal. Calcd for $C_{35}H_{25}Br_5$: C, 45.44; H, 2.72. Found: C, 45.78; H, 2.91.

***cone*-5,11,17,23,29-Pentabromo-31,32,33,34,35-pentakis(*tert*-butoxycarbonylmethoxy)calix[5]arene (12).** A mixture of **11** (0.40 g, 0.43 mmol), K_2CO_3 (1.8 g, 13 mmol), and bromoacetic acid *tert*-butyl ester (1.26 mL, 1.68 g, 8.6 mmol) in dry DMF (10 mL) was stirred for 18 h at 65 °C. After cooling, the mixture was filtered, and the solid was washed with 80 mL of chloroform. The combined filtrate was washed with dilute HCl (0.01 M, 200 mL) and water (2 × 150 mL) and evaporated to dryness. The residue was stirred for 30 min in 30 mL of methanol (containing 2% of water). A pale yellow powder was obtained after filtration. The powder was dissolved in a minimum amount of dichloromethane and reprecipitated upon addition of methanol (20 mL). White powder (0.52 g) was obtained in 81% yield: mp 118−120 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.97 (s, 10H, ArH), 4.71 (d, J = 15.1 Hz, 5H, $ArCH_2$-Ar), 4.44 (s, 10H, $ArOCH_2$), 3.32 (d, J = 15.1 Hz, 5H, $ArCH_2$-Ar), 1.43 (s, 45H, $OC(CH_3)_3$); MALDI TOF MS m/z 1519.6 (M + Na^+). Anal. Calcd for $C_{65}H_{75}Br_5O_{15}$: C, 52.19; H, 5.05. Found: C, 52.08; H, 5.07.

***cone*-5,11,17,23,29-Penta(4-pyridyl)-31,32,33,34,35-pentakis(*tert*-butoxycarbonylmethoxy)calix[5]arene (13).** Under nitrogen, a mixture of **12** (0.33 g, 0.22 mmol), diethyl(4-pyridyl)borane (0.28 g, 1.9 mmol), and CsF (0.33, 2.2 mmol) in 15 mL of dry DME was stirred for 30 min at 65 °C. $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) was added, and the reaction mixture was stirred for 12 h under reflux. After cooling, the solid was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in chloroform (50 mL), washed with water (2 × 100 mL), and evaporated to dryness again. After separation by column chromatography (silica gel, $CHCl_3$/MeOH = 20:1−3:1), 65 mg of pale yellow solid (R_f = 0.2, $CHCl_3$/MeOH = 5:1) was obtained in 20% yield: mp 143−145 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (d, J = 5.6 Hz, 10H, PyH), 7.12 (s, 10H, ArH), 7.00 (d, J = 5.6 Hz, 10H, PyH), 4.89 (d, J = 15.1 Hz, 5H, $ArCH_2Ar$), 4.63 (s, 10H, $ArOCH_2$), 3.58 (d, J = 15.1 Hz, 5H, $ArCH_2Ar$), 1.46 (s, 45H, $OC(CH_3)_3$); MALDI TOF MS m/z 1487.2 ($M + H^+$), 1509.2 ($M + Na^+$). Anal. Calcd for $C_{54}H_{62}N_2O_8 \cdot (H_2O)_{1.5}$: C, 71.41; H, 6.52; N, 4.63. Found: C, 71.32; H, 6.37; N, 4.56.

5,11,17,23-Tetrabromo-25,26−27,28-bis-crown-3-calix[4]arene (15). A solution of **14** (0.33 g, 0.58 mmol) and NBS (0.60 g, 3.4 mmol) in THF (10 mL) was stirred for 1 day at room temperature. After evaporation of the solvent, the residue was washed with methanol and then recrystallized from chloroform-methanol, giving 0.40 g of pale yellow powder in 78% yield: mp > 300 °C (dec); ^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ 7.14 (s, 4H, ArH), 7.13 (s, 4H, ArH), 4.96 (d, J = 12.2 Hz, 2H, $ArCH_2Ar$), 4.37 (d, J = 12.2 Hz, 2H, $ArCH_2Ar$), 4.30−3.70 (m, 16H, OCH_2CH_2O), 3.18 (d, J = 12.2 Hz, 4H, $ArCH_2$-Ar), 3.13 (d, J = 12.2 Hz, 4H, $ArCH_2Ar$); MALDI TOF MS (dithranol) 881.2 ($M + H^+$), 903.2 ($M + Na^+$). Anal. Calcd for $C_{36}H_{32}Br_4O_6$: C, 49.12; H, 3.66. Found: C, 49.40; H, 3.85.

5,11,17,23-Tetra(4-pyridyl)-25,26-27,28-bis-crown-3-calix[4]arene (16). Under nitrogen, a mixture of **15** (0.44 g, 0.50

(27) Arduini, A.; Pochini, A.; Secchi A. *Eur. J. Org. Chem.* **2000**, 2325.
(28) Arduini, A.; Casnati, A.; Fabbi, M.; Minari. P.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *Supramol. Chem.* **1993**, *1*, 235.
(29) Ikeda, A.; Shinkai, S. *J. Am. Chem. Soc.* **1994**, *116*, 3109.
(30) Stang, P. J.; Cao, D. H.; Saito, S.; Arif, A. M. *J. Am. Chem. Soc.* **1995**, *117*, 6273.
(31) Gutsche, C. D.; Alam, I. *Tetrahedron* **1988**, *44*, 4689.
(32) (a) Ishikura, M.; Mano, T.; Oda, I.; Terashima, M. *Heterocycles* **1984**, *22*, 2471. (b) Ishikura, M.; Ohta, T.; Terashima, M. *Chem. Pharm. Bull.* **1985**, *33*, 4573.

mmol), diethyl(4-pyridyl)borane (0.48 g, 3.3 mmol), and CsF (0.70 g, 4.6 mmol) in 20 mL of DME was stirred under reflux for 1 h, and then $Pd(PPh_3)_4$ (30 mg, 0.025 mmol) was added. After the mixture was stirred for 2 days under refluxing temperature, the precipitate was filtered off, and the solvent was evaporated under reduced pressure. The residue was submitted to column chromatography (silica gel, $CHCl_3$/MeOH = 10:1−5:1 v/v), giving 0.13 g pale yellow solid (R_f = 0.2, silica, $CHCl_3$/MeOH = 10:1 v/v) in 30% yield: mp 200−202 °C; ^{1}H NMR (600 MHz, $CDCl_3$, TMS) δ 8.55 (d, J = 5.9 Hz, 8H, PyH), 7.34 (s, 4H, ArH), 7.33 (s, 4H, ArH), 7.28 (d, J = 5.9 Hz, 8H, PyH), 5.22, 4.64, 3.46, and 3.41 (d each, J = 12.2 Hz, 2H each, $ArCH_2Ar$), 4.37−4.31 (m, 12 H, CH_2O), 3.98−3.92 (m, 4 H, CH_2O); ESI-TOF MS m/z 873.6 ($M + H^+$). Anal. Calcd for $C_{56}H_{48}N_4O_6 \cdot (H_2O)_{1.5}$: C, 74.74; H, 5.71; N, 6.22. Found: C, 74.84; H, 5.57; N, 6.17.

Self-Assembled Molecular Capsules (18a,b). In an NMR tube, a solution of **16** (5.00 M, 0.300 mL) and a solution of **7** or **17** (10.0 M, 0.300 mL) in $CDCl_3/CD_3OD$ (5:1 v/v) were mixed by vigorously shaking for 5 min at room temperature. ^{1}H NMR study showed that the mixtures self-assembled quantitatively into **18a** or **18b**, respectively: ^{1}H NMR (600 MHz, $CDCl_3$/ CD_3-OD = 5:1 v/v, TMS) **18a** (1:1 *parallel*/*antiparallel* mixture) δ 9.00, 8.67, and 8.36 (br s, 4H, 8H, and 4H, respectively, PyH), 7.82−6.90 (m, 112H, PyH and ArH), 5.14, 5.03, 4.52, 4.50, and 3.41−3.30 (d, d, d, d, and m, respectively, J = 12.0 Hz, 2H, 2H, 2H, 2H, and 8H, respectively, $ArCH_2Ar$), 4.38−4.35, 4.34−4.20, and 3.86−3.81(m each, 8H, 16H, and 8H, respectively, CH_2O) 3.50−3.34 and 2.97−2.84 (m each, 4H each, *parallel* PCH_2CH_2), 3.22−3.12 (m, 8H, *antiparallel* PCH_2CH_2), 2.72−2.50 and 1.94−1.85 (m each, 2H each, *parallel* PCH_2CH_2), 2.37−2.20 (m, 4H, *antiparallel* PCH_2CH_2); **18b** (1:1 *parallel*/*antiparallel* mixture) δ 8.38 (m, 16H, PyH), 7.77−7.31 (m, 112H, PyH and ArH), 5.10, 5.03, 4.49, 4.48, 3.39, 3.34, and 3.33 (d each, J = 11.9 Hz, 2H, 2H, 2H, 2H, 4H, 2H, and 2H, respectively, $ArCH_2Ar$), 4.38−4.36 and 4.30−4.24 (m each, 8H each, CH_2O), 4.24−4.18 and 3.96−3.78 (m each, 8H each, CH_2O), 2.97−2.72 (m, 16H, PCH_2).

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