

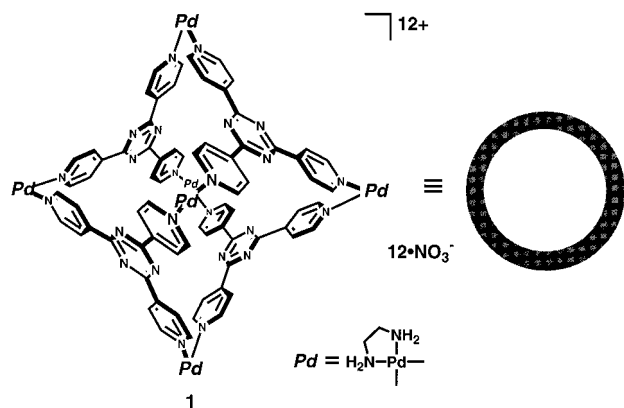
“Ship-in-a-Bottle” Formation of Stable Hydrophobic Dimers of *cis*-Azobenzene and -Stilbene Derivatives in a Self-Assembled Coordination Nanocage

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Stabilization¹ and activation² of molecules enclathrated in the cavity of cage molecules have been topics of special current interest. A recent rapid progress in such molecular enclathration chemistry³ is partly the result of the development of the facile preparation of cage compounds by noncovalent synthesis exploiting hydrogen⁴ and coordination bonds.⁵ Transition metal-mediated self-assembly^{6,7} has recently allowed the highly effective construction of hollow, nanosized coordination cage **1** which en-



clathrates large neutral guest molecules at a fixed position of the cavity in a 1:4 host–guest ratio.⁸ Here we report the remarkable ability of cage **1** for the selective enclathration of “C-shaped”

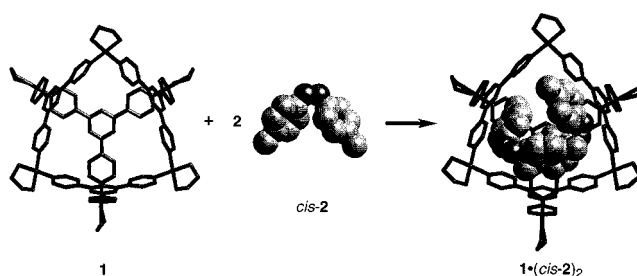
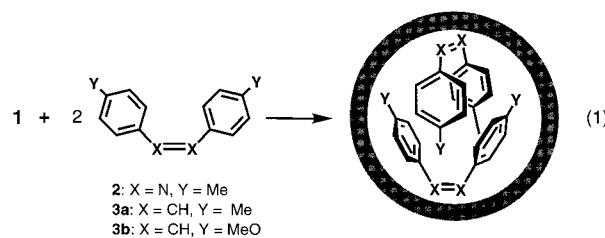


Figure 1. “Ship-in-a-bottle” formation of a hydrophobic dimer of *cis*-2 in the cavity of **1**. The structure of **1**·(*cis*-2)₂ complex is minimized.¹¹

molecules such as *cis*-azobenzene and -stilbene derivatives. These guest molecules are enclathrated in the cavity through the “ship-in-a-bottle” formation of a hydrophobically interacted dimer with a topology reminiscent of Rebek’s hydrogen-bonded “tennis ball”⁹ (eq 1). We also show that the hydrophobic dimer of azobenzene



derivative is considerably stabilized and does not undergo *cis*–*trans* isomerization.

Selective dimer formation of *cis*-4,4′-dimethylazobenzene (**2**) in nanocage **1** was observed in the following experiment. When a saturated hexane solution (1 mL) of **2** (*cis*–*trans* 1:6 mixture) was stirred with a D₂O solution of **1** (42.4 mM, 1 mL) for 0.5 h at room temperature, the NMR measurement of the aqueous phase showed the enclathration of only one isomer of **2**, which was confirmed to have *cis* stereochemistry by NMR after being extracted with CDCl₃. Host–guest ratio (**1**:*cis*-**2**) was estimated to be 1:2 by ¹H NMR integration and **1**·(*cis*-**2**)₂ complex was formed in 22% yield.¹⁰ The significant upfield shifting of the proton signals of *cis*-**2** is consistent with the enclathration in the cavity of **1** (CH₃: Δδ –2.6; ArH: Δδ –2.1 to –2.3).

Noteworthy is that *cis*-**2** is significantly stabilized by the enclathration. Thus, monitoring **1**·(*cis*-**2**)₂ complex by NMR displayed that *cis*-**2** in the cavity would not isomerize to a *trans* isomer even after a few weeks under visible light at room temperature. Molecular modeling based on a force-field calculation¹¹ suggested that the remarkable stabilization of the *cis* isomer was attributed to the formation of hydrophobic dimer of *cis*-**2** in the cavity. A minimized **1**·(*cis*-**2**)₂ complex structure involves a spherical dimer of *cis*-**2**, which nicely fits the cavity of **1** (Figure 1).

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(10) **1**·(*cis*-**2**)₂ complex: ¹H NMR (500 MHz, D₂O) δ = 9.29 (d, *J* = 5.3 Hz, 24 H, PyH_α), 8.63 (d, *J* = 5.3 Hz, 24 H, PyH_β), 4.6–4.9 (br s, 16 H, Ar), 2.97 (s, 24 H, –NCH₂CH₂N–), –0.32 (s, 12 H, CH₃); ¹³C NMR (125 MHz, D₂O) δ = 169.0 (Cq), 152.7 (CH), 148.2 (Cq, azobenzene), 144.9 (Cq), 135.3 (Cq, azobenzene), 128.1 (CH, azobenzene), 125.5 (CH), 119.1 (CH, azobenzene) 46.9 (CH₂), 18.6 (CH₃, azobenzene).

(11) Molecular dynamics calculations and energy minimizations were conducted using standard methods implemented in the Cerius² 3.0 package on a Silicon Graphics Octane machine.

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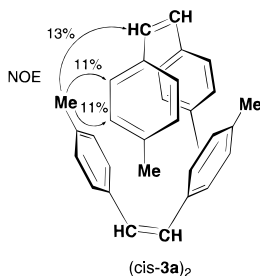
(3) Cram, D. J.; Cram, J. M. *Container molecules and their guests*; RSC, Cambridge: MA, 1994.

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(5) Self-assembled cage compounds containing metals: (a) Saalfrank, R. W.; Stark, A.; Peters, K.; Schnering, H. G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 851. (b) Baxter, P.; Lehn J.-M.; DeCian, A.; Fischer, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 69. (c) Mann, S.; Huttner, G.; Zsolnai, L.; Heinze, K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2808. (d) Baisel, T.; Powers, R. E.; Raymond, K. N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1084. (e) Jacopozi, P.; Dalcanale, E.; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 613. (f) Hartshorn, C. M.; Steel, P. J. *J. Chem. Soc., Chem. Commun.* **1997**, 541. (g) Parac, T. N.; Caulder, D. L.; Raymond, K. N. *J. Am. Chem. Soc.* **1998**, *120*, 8003.

(6) (a) Fujita, M.; Oguro, D.; Miyazawa, M.; Oka, H.; Yamaguchi, K.; Ogura, K. *Nature* **1995**, *378*, 469. (b) A related complex: Stang, J. P.; Olenyuk, B.; Muddiman, D. C.; Smith, R. D. *Organometallics* **1997**, *119*, 3094.

An NMR NOE experiment strongly supported the hydrophobic dimer formation. When 4,4'-dimethylstilbene (**3a**, *cis:trans* = 6:4 mixture), an olefinic analogue of **2**, was treated with **1** in D₂O, the selective enclathration of *cis*-**3a** dimer was again observed.¹² In the ¹H NMR of **1**•(*cis*-**3a**)₂ complex, strong NOEs (11–13%)



were observed between the methyl and the other protons of *cis*-**3a**. These NOEs must be correlated intermolecularly in the dimer because free *cis*-**3a** in CDCl₃ is silent in an NOE measurement. NOEs were also observed between the host and the guest protons in good accordance with the optimized host–guest geometry.

“Ship-in-a-bottle” assembly of the hydrophobic dimer in the cage is suggested by an NMR observation and molecular modeling. Dimerization of *cis*-**2** prior to enclathration is unlikely because the dimension of the spherical dimer (ca 11 Å in diameter) is larger than that of the window of **1** (ca 7 Å in diameter).

(12) **1**•(*cis*-**3a**)₂ complex: ¹H NMR (500 MHz, D₂O) δ = 9.19 (d, *J* = 5.5 Hz, 24 H, PyH_α), 8.50 (d, *J* = 5.5 Hz, 24 H, PyH_β), 4.60 (s, 4 H, CH=, stilbene), 2.97–4.44 (d, *J* = 7.4 Hz, 8 H, Ar, stilbene), 4.08 (d, *J* = 7.4 Hz, 8 H, Ar, stilbene), 2.85 (s, 24 H, -NCH₂CH₂N-), -0.44 (s, 12 H, CH₃); ¹³C NMR (125 MHz, D₂O) δ = 169.9 (Cq), 152.9 (CH), 145.6 (Cq), 134.3 (Cq, stilbene), 133.2 (Cq, stilbene), 129.2 (CH, stilbene), 127.7 (CH, stilbene), 127.2 (CH, stilbene), 125.9 (CH), 47.3 (NH₂CH₂), 19.7 (CH₃, stilbene).

(13) Guest-exchange properties similar to eq 2 in a 1:1 host–guest complexation has been recently reported: Szabo, T.; Hilmersson, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 6193.

(14) **1**•(*cis*-**4**)₂ complex: ¹H NMR (500 MHz, D₂O) δ = 9.11 (d, *J* = 5.5 Hz, 24 H, PyH_α), 8.49 (d, *J* = 5.5 Hz, 24 H, PyH_β), 4.82 (br s, 8 H, Ar), 4.38 (br s, 4 H, Ar), 2.86 (s, 24 H, -NCH₂CH₂N-). **1**•(*trans*-**4**)₂ complex: ¹H NMR (500 MHz, D₂O) δ = 9.10 (d, *J* = 5.4 Hz, 24 H, PyH_α), 8.47 (d, *J* = 5.4 Hz, 24 H, PyH_β), 6.40 (br s, 2 H, Ar), 6.28 (br s, 4 H, Ar), 5.55 (d, *J* = 7.4 Hz, 4 H, Ar), 2.86 (s, 24 H, -NCH₂CH₂N-); ¹³C NMR (125 MHz, D₂O) δ = 170.3 (Cq), 153.1 (CH), 150.7 (Cq, azobenzene), 146.1 (Cq), 131.6 (CH, azobenzene), 128.9 (Ar, azobenzene), 126.2 (CH), 119.2 (Ar, azobenzene), 47.7 (NH₂CH₂).

(15) Nishio, M.; Hirota, M.; Umezawa, Y. *The CH/π Interaction*; Wiley-VCH: New York, 1998.

(16) It is interesting that *trans*-**5** is not directly enclathrated by **1** but can be enclathrated via isomerization to *cis*, enclathration, followed by reisomerization to *trans*.

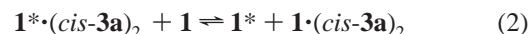
(17) **1**•(*cis*-**3b**)₂ complex: ¹H NMR (500 MHz, D₂O, 333K) δ = 9.67 (d, *J* = 5.9 Hz, 24 H, PyH_α), 8.98 (d, *J* = 5.9 Hz, 24 H, PyH_β), 5.55 (br s, 8 H, Ar, stilbene), 4.54 (br s, 8 H, Ar, stilbene), 3.75 (s, 4 H, CH=, stilbene), 3.40 (s, 24 H, -NCH₂CH₂N-), 2.64 (s, 12 H, CH₃O); ¹³C NMR (125 MHz, D₂O, 333K) δ = 169.6 (Cq), 156.6 (Cq stilbene), 153.22 (CH), 146.0 (Cq), 129.6 (Ar, stilbene), 128.4 (Cq, stilbene), 127.7 (CH=, stilbene), 126.4 (CH), 113.1 (Ar, stilbene), 55.0 (CH₃O), 47.8 (NH₂CH₂).

(18) Upon the addition of 1,3,5-trimethoxybenzene to **1**, the color of the solution turned yellow immediately and the quantitative formation 1:4 complex was observed. However, strong charge-transfer band was not observed.

(19) **1**•(*cis*-**5a**)₂ complex: ¹H NMR (500 MHz, D₂O, 333K) δ = 9.63 (d, *J* = 6.4 Hz, 24 H, PyH_α), 8.95 (d, *J* = 6.4 Hz, 24 H, PyH_β), 5.29 (d, 8 H, *J* = 7.8 Hz Ar), 4.45 (d, 8 H, *J* = 7.8 Hz Ar), 3.35 (s, 24 H, -NCH₂CH₂N-), 2.76 (s, 12 H, CH₃O), 0.84 (s, 8 H, CH₃); ¹³C NMR (125 MHz, D₂O, 333K) δ = 169.7 (Cq), 155.4 (Cq dibenzyl), 153.30 (CH), 145.8 (Cq), 129.2 (Cq, dibenzyl), 127.9 (Ar, dibenzyl), 126.3 (CH), 112.9 (Ar, dibenzyl), 55.1 (CH₃O), 47.8 (NH₂CH₂), 28.9 (CH₃, dibenzyl).

Therefore, two guest molecules should be subsequently but not simultaneously enclathrated in the cavity and turned in situ into the stable hydrophobic dimer. The in situ formed spherical dimer is too large to be declathrated rapidly. Thus, free and complexed species are not averaged on the NMR time scale even at elevated temperatures. This slow enclathration–declathration is a sharp contrast to the behavior of other substituted aromatics whose free and complexed forms are averaged.

Nevertheless, a NOESY experiment showed cross-peaks between enclathrated *cis*-**3a** and free host **1**. This result evidences the presence of the following equilibrium (eq 2) which is a slow exchange process between free and complexed host **1** within a relaxation time of 1¹³

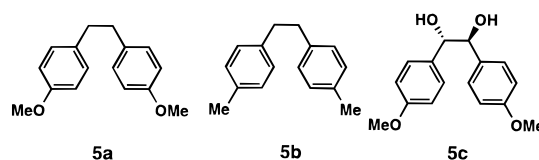


where **1*** indicates magnetically saturated **1**.

Despite the presence of the slow-exchange process, however, intermediary 1:1 complex **1**•(*cis*-**3a**) was not observed by NMR. This fact reveals that a strong positive cooperative effect works in the enclathration of *cis*-**3a** leading to the selective formation of the stable hydrophobic dimer.

Interestingly, the dimer formation of unsubstituted azobenzene (**4**) was not observed. Although this guest was also enclathrated in a exclusively *cis*-selective fashion, simple 1:1 complexation was observed under the same conditions.¹⁴ This result suggests that, in the formation of **1**•(*cis*-**2**)₂, efficient intermolecular CH-π interaction¹⁵ between methyl protons and aromatic rings is particularly important for the dimer formation. Enclathrated *cis*-**4** was easily isomerized to the *trans* isomer even at room temperature in the dark¹⁶ in sharp contrast to the behavior of the *cis*-**2** dimer.

Complexation with some related guest molecules is worthy of comment. Methoxy-substituted stilbene **3b** gave remarkably stable dimer complex **1**•(*cis*-**3b**)₂ in a quantitative yield.¹⁷ The spherical dimer structure of *cis*-**3b**, again confirmed by NOE, seems to be significantly stabilized by a host–guest charge-transfer interaction. Thus, on complexation of **3b** with **1**, the color of the solution immediately turned orange, and UV–vis absorption spectroscopy showed a strong charge-transfer band at 429 nm.¹⁸ Due to the relatively strong host–guest interaction, the motion of the *cis*-**3b** dimer in the cage is slow; guest signals are very broad around 25 °C and become sharp at elevated temperatures. Surprisingly, even flexible ethylene derivative **5a** gave dimer complex **1**•(**5a**)₂,¹⁹ which should be stabilized by the charge-transfer interaction between electron-deficient **1** and electron-rich **5a** as supported by a charge-transfer band appearing at 400 nm. In contrast, less electron-rich **5b** and less hydrophobic **5c** did not give the dimer complexes.



Supporting Information Available: NMR (1D and 2D) and UV–vis spectrum of the host–guest complexes (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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