

Atroposelective Self-Assembly of a Molecular Capsule from Amphiphilic Anthracene Trimers**

Akira Suzuki, Kei Kondo, Munetaka Akita, and Michito Yoshizawa*

Subtle differences between geometrical isomers of organic molecules can give rise to distinctly different structures and properties upon assembly into supramolecular aggregates. The *cis* and *trans* isomers of alkenes, and stilbene and azobenzene derivatives in particular, are much-studied motifs in supramolecular assemblies; they exhibit intriguing steric and electronic properties depending on their geometric conformation.^[1,2] Atropisomers are often found in various bioactive natural products and organometallic catalysts where the restricted rotation about the aromatic–aromatic bond creates an axially chiral element that determines the observed activity or reactivity by intermolecular interactions.^[3] The effects of atropisomerism in the self-assembly of supramolecular nanostructures,^[4] however, are relatively unexplored and are found in only a few examples of hydrogen-bonding and coordination-bonding cages^[5] where host–guest interactions were not observed. Herein we present the first atroposelective formation of a molecular capsule through hydrophobic and aromatic–aromatic interactions. The curved amphiphilic atropisomer (*cis*-**1a**; Figure 1) bearing three anthracene rings forms a dimeric capsule in an aqueous solution^[6] whereas the zigzag-shaped amphiphilic isomer (*trans*-**1a**) forms non-specific aggregates. Only the molecular capsule serves as a molecular host capable of binding small guest molecules. Close proximity to the anthracene panels favors strong host–guest charge-transfer (CT) interactions upon guest enclathration, and these tune the emissive properties of the fluorescent capsule.

We previously reported the preparation of tape-shaped anthracene trimer **1b** (R = H) composed of alternately linked anthracene rings and *meta*-phenylene spacers decorated with two hydroxy groups (Figure 1).^[7] Rotation about the anthryl–phenyl bonds is sterically restricted owing to the *ortho* substituents^[8] so that the trimer generates *cis* and *trans* atropisomers. The *cis*–*trans* equilibrium ratio of **1b** can be determined by changing solvents, but the poor water solubility of the atropisomeric pair precluded further investigations into their behavior as supramolecular subunits.^[7] Herein

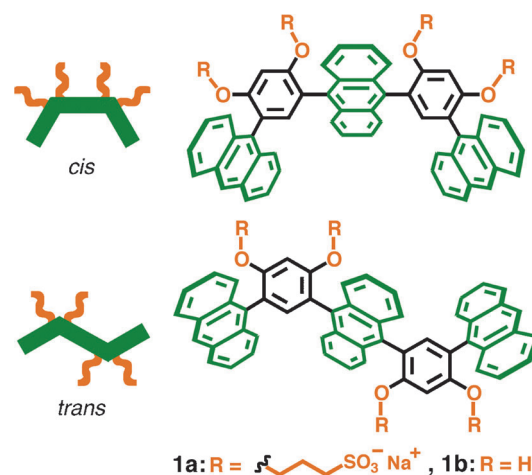


Figure 1. Amphiphilic *cis* and *trans* atropisomers **1a** and **1b**.

we replace the hydroxy substituents with sulfonates, which are readily accessible, bulky, hydrophilic groups, to obtain water-soluble, rigid atropisomers *cis*-**1a** and *trans*-**1a**. With the atropisomers in hand, we envisioned that the amphiphilic *cis*-isomer could reversibly dimerize in an aqueous solution to form a supramolecular capsule with a cavity protected by the large aromatic shells.

Atropisomers *cis*-**1a** and *trans*-**1a** were synthesized in a straightforward procedure.^[9] An aqueous NaOH solution of **1b** (10 mM) was stirred at 80°C for one day, and then a solution of 1,3-propanesultone (ca. 5 equiv per hydroxy group) in 1,4-dioxane was added to the resultant reaction mixture. The solution was further stirred at 80°C for one day to give a mixture of *cis*-**1a** and *trans*-**1a**. The *cis*-**1a** isomer is highly soluble in water (up to 150 mM), and the addition of acetone into the H₂O solution of the *cis*–*trans* isomeric mixture afforded the precipitate of *trans*-**1a**. Pure *cis*-**1a** and *trans*-**1a** were obtained as pale yellow solids in 24 and 24 % yields of isolated product (based on **1b**), respectively. Complete replacement of the hydroxy groups with alkanesulfonate groups in **1b** and the formation of **1a** was confirmed by ESI-TOF MS analysis (*m/z* = 307.56 [*M*–4Na⁺]^{4–}; Supporting Information, Figure S7). Identification of *cis*-**1a** and *trans*-**1a** was determined by the ¹H NMR spectra observed in CD₃OD:^[7] the H_b and H_a signals of *cis*-**1a** were observed at higher field than those of *trans*-**1a** (Δδ = –0.15 and –0.07 ppm, respectively), which is due to efficient shielding by the three surrounding anthracene rings (Figure 2b,e).

Selective formation of molecular capsule **2** was observed in an aqueous solution (3.0 mM) of *cis*-**1a** (Figure 2a).^[9] The ¹H NMR spectrum of *cis*-**1a** in CD₃OD showed sharp signals

[*] A. Suzuki, K. Kondo, Prof. Dr. M. Akita, Dr. M. Yoshizawa
Chemical Resources Laboratory, Tokyo Institute of Technology
4259 Nagatsuta, Midori-ku, Yokohama 226-8503 (Japan)
E-mail: yoshizawa.m.ac@m.titech.ac.jp

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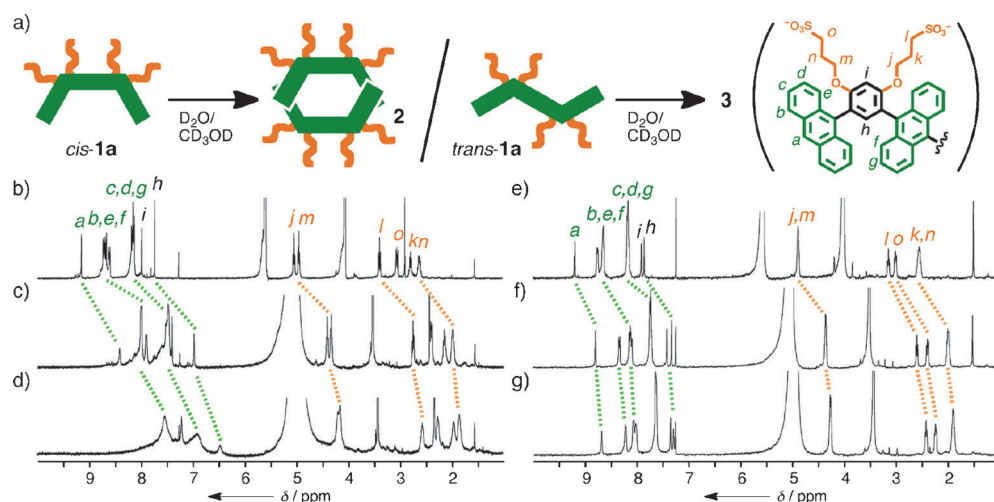


Figure 2. a) Representation of the formation of molecular capsule **2** from *cis*-**1a** and oligomeric aggregates **3** from *trans*-**1a** in aqueous solutions. b)–g) ^1H NMR spectra (400 MHz, room temperature, TMS as an external standard) of solutions of b) *cis*-**1a** and e) *trans*-**1a** in CD_3OD ; c, d) *cis*-**1a** (3.0 mM) in $\text{D}_2\text{O}/\text{CD}_3\text{OD}$, ratio c) 6:4, d) 8:2; f, g) *trans*-**1a** (<1.0 mM) in $\text{D}_2\text{O}/\text{CD}_3\text{OD}$, ratio f) 6:4, g) 8:2.

corresponding to the monomeric species (Figure 2b), but the signals gradually broadened and shifted upfield significantly in mixed aqueous solvents ($\text{D}_2\text{O}/\text{CD}_3\text{OD}$ 4:6 to 8:2 by volume). In a $\text{D}_2\text{O}/\text{CD}_3\text{OD}$ 8:2 solution (Figure 2d), the proton signals of the aromatic moieties (H_a – H_i) of *cis*-**1a** were broadened to an extent greater than those of the hydrophilic side chains (H_j – H_o), suggesting reduced conformational mobility owing to intermolecular interactions between aromatic frameworks. Presence of a single assembly was confirmed by ^1H DOSY. All of the signals in the DOSY spectrum have an identical $\log(D)$ value of -9.2 ($D = 6.2 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$) (Supporting Information, Figure S19). The formation of a dimeric capsule **2** in an aqueous solution was further confirmed by ESI-TOF MS; a (*cis*-**1a**)₂ composition fits well with peaks observed at $m/z = 506.3$ [$M - 5\text{Na}^+$]^{5–}, 638.4 [$M - 4\text{Na}^+$]^{4–}, and 858.8 [$M - 3\text{Na}^+$]^{3–} (Supporting Information, Figure S21). In sharp contrast, the ^1H NMR spectra of *trans*-**1a** in $\text{D}_2\text{O}/\text{CD}_3\text{OD}$ 6:4 and 8:2 solutions showed sharp signals with small upfield shifts (Figure 2f,g). Furthermore, *trans*-**1a** was less soluble in an aqueous solution (up to about 1 mM) and prone to generate oligomeric aggregates, which precipitated as pale yellow solids **3**.

The morphologies of **2** and **3** were then examined using atomic force microscopy (AFM). Aqueous solutions of *cis*-**1a** (3 mM) and *trans*-**1a** (<1 mM) were deposited on freshly cleaved mica surfaces and subsequently dried in the air. Representative AFM images of **2** showed small spherical particles with diameters of approximately 3 nm and narrow size distributions (± 1 nm; Figure 3a–c). This result is consistent with the dimeric capsules indicated by the NMR and MS analyses of **2**. In stark contrast to **2**, the AFM images of **3** revealed non-uniform spherical particles with heights in the range of 5–12 nm (Figure 3d–f), again supporting the formation of various aggregates (*trans*-**1a**)_n ($n = 3$ –10).

Comparison of the optimized structures of *cis*-**1a** and *trans*-**1a** clarified how initial structural differences guided the

assemblies to capsule **2** and aggregates **3** in aqueous solutions. Optimized by theoretical calculations (PM3),^[10] *cis*-**1a** features 1) a concave structure with a hydrophobic cleft defined by the flat aromatic panels, and 2) a convex hydrophilic surface covered by the alkane-sulfonate groups (Figure 4a). Thus, hydrophobic and aromatic–aromatic interactions lead *cis*-**1a** to generate the dimeric capsule **2** in an aqueous solution. The optimized structure of *trans*-**1a**, however, adopts a zigzag arrangement where the hydrophobic aromatic panels are effectively blocked by the hydrophilic sulfonate

groups (Figure 4b). Thus the *trans*-atropisomer **1a** lacks the uncovered amphiphilic surfaces and exposed aromatic surfaces needed to direct the self-assembly of a well-defined, discrete capsule, and only random aggregates were formed. An optimized molecular model of **2**, composed of two molecules of *cis*-**1a** assembled in a tennis-ball fashion,^[11] has an external diameters of approximately 3 nm, matching the heights of the observed AFM peaks, and an internal cavity with a long axis of about 1 nm (Figure 4c).

When molecular capsule **2** was treated with various quinones in aqueous solutions, ground-state host–guest CT interactions along with guest-sensitive fluorescent behavior were observed upon the formation of host–guest complexes **2**⊃(**G**)_n. Capsule **2** was combined with 2,3,5,6-tetramethylbenzoquinone (**4a**; ca. 10 equiv, suspended) in a $\text{D}_2\text{O}/\text{CD}_3\text{OD}$ 8:2 solution for 2 h at room temperature to give rise to a yellow solution (Figure 5a). Excess guest was removed by filtration and the selective formation of host–guest complex **2**⊃(**4a**)₂ was confirmed by ^1H NMR analysis (Figure 5c).^[9] The methyl signal of **4a** was found at 1.2 ppm ($\Delta\delta = -0.8$ ppm), which is due to the shielding by the nearby anthracene shells of **2** upon encapsulation. Integration of the ^1H NMR signals confirmed a 1:2 host–guest composition. In the same manner, the treatment of **2** with 2-methyl-1,4-naphthoquinone (**4b**) afforded a red solution of **2**⊃(**4b**)₂. The ^1H NMR spectrum revealed that the proton signals of the encapsulated guests **4b** in **2** were also greatly shifted upfield ($\Delta\delta = -0.5$ – 1.3 ppm). Furthermore, the aromatic signals of **2** were less broad upon the encapsulation of **4b**, indicating less conformational motion of the capsule owing to strong host–guest CT interactions. Aggregates **3** resulting from the *trans*-atropisomer **1a** showed no host behavior, as neither spectral nor color changes were observed upon treatment with quinone **4b** under similar conditions.

Spectroscopic analyses of **2**⊃(**4**)₂ established the formation of a CT complex. In the UV/Vis spectrum of **2**⊃(**4b**)₂,

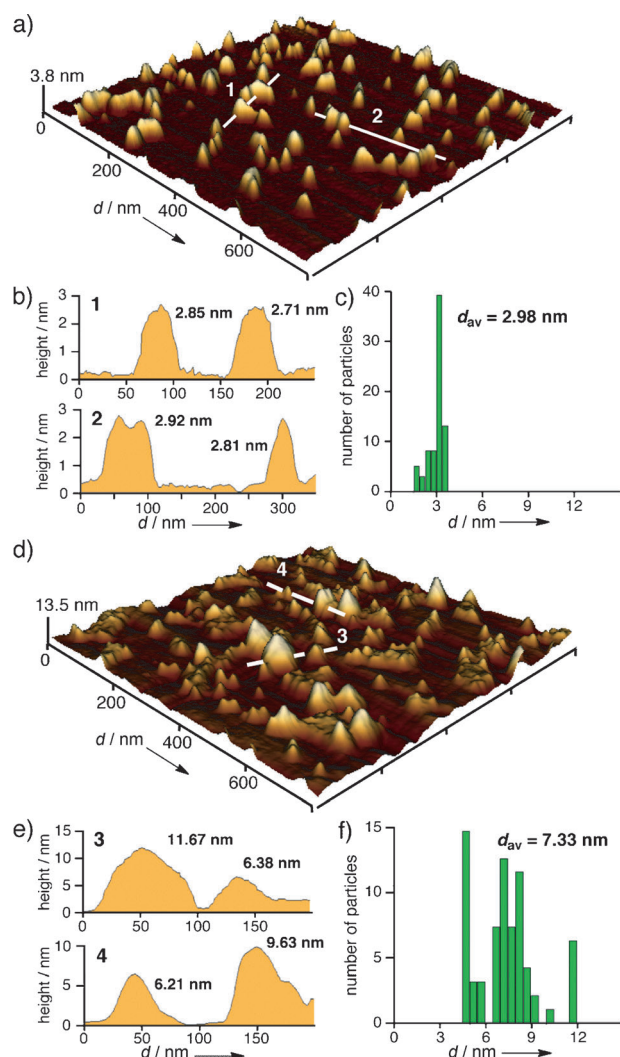


Figure 3. AFM images of aqueous solutions of a) dimeric capsule **2** (3 nm) and d) oligomeric aggregates **3** (< 1 nm) dispersed on mica. Height profiles of selected features of the AFM images of b) **2** and e) **3**. Size and number (N) distribution of the AFM images of c) **2** and f) **3**.

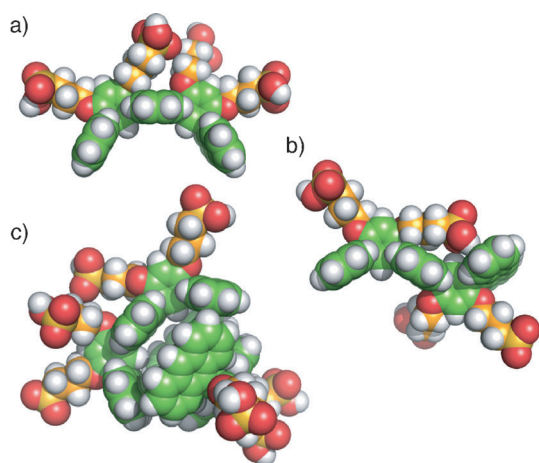


Figure 4. a) Optimized structures of a) *cis*-1a, b) *trans*-1a, and c) capsule **2** composed of two molecules of *cis*-1a by PM3 calculations without counterions and solvents.

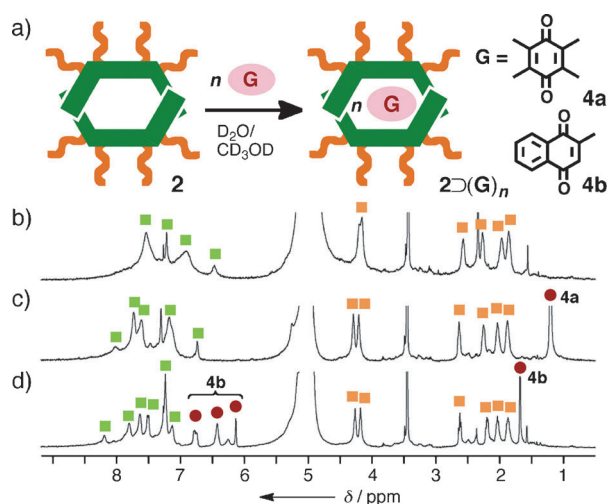


Figure 5. a) Representation of the encapsulation of quinones **4a,b** by dimeric capsule **2**. ^1H NMR spectra (400 MHz, $\text{D}_2\text{O}/\text{CD}_3\text{OD}$ 8:2, room temperature) of b) **2**, c) $2\supset(4a)_2$, and d) $2\supset(4b)_2$ complexes. Colored symbols labeling signals in the spectra correspond to the colors in the molecular structure representations.

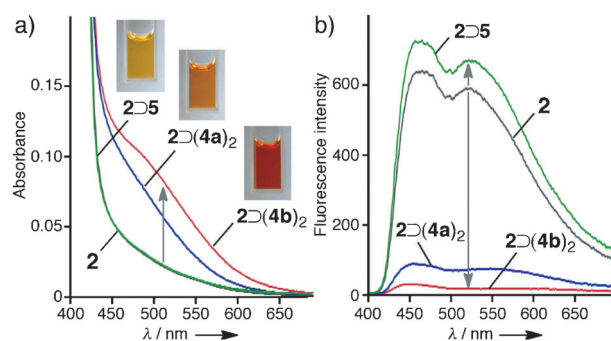


Figure 6. a) UV/Vis and b) fluorescence spectra ($\text{H}_2\text{O}/\text{CH}_3\text{OH}$ 8:2, 3.0 mM as based on *cis*-1a, room temperature, $\lambda_{\text{ex}} = 370$ nm) of **2**, $2\supset(4a)_2$, $2\supset(4b)_2$, and $2\supset 5$ complexes.

absorption bands at 320–460 nm were assigned to the π – π^* transitions of the anthracene moieties, and a new CT absorption band was observed as a shoulder around 510 nm (Figure 6a). Formation of the molecular capsule is essential for the strong host–guest interactions, as indicated by the CT band and NMR signals, because the addition of acetone to the solution of $2\supset(4b)_2$ gave a colorless solution with no CT absorption band (Supporting Information, Figures S39 and S40) that is due to the disassembly of both capsule **2** and the host–guest complex. The capsule containing two molecules of **4a** also showed a CT absorption band at around 510 nm (Figure 6a). Interestingly, capsule **2** bound one molecule of 2-methylnaphthalene (**5**), but the $2\supset 5$ complex did not show any CT bands in the UV/Vis spectrum.

The emissive properties of capsule **2** were quite sensitive to the guest identity (and the resultant CT interactions) and dramatically changed depending on the encapsulated guest molecules. Upon irradiation of the anthracene absorption band at 370 nm, capsule emission ($\lambda_{\text{max}} = 466$ nm, $\Phi_{\text{F}} = 6.3\%$) was enhanced by 1.4-fold in the presence of comparatively

electron-rich guest **5** within **2**. On the other hand, the emission decreased significantly with the electron-poor and strongly interacting guests **4a** and **4b** (0.16 and 0.05-fold, respectively; Figure 6b). Thus, the molecular capsule can behave as an unique fluorescent molecular sensor for small organic molecules.^[12]

In summary, we prepared two amphiphilic atropisomers composed of three anthracene rings linked by two phenylene spacers with peripheral hydrophilic sulfonate groups. The *cis*-atropisomer with a large concave aromatic framework gave rise to a dimeric capsule in an aqueous solution, whereas the *trans*-isomer afforded only oligomeric aggregates, as confirmed by NMR, MS, and AFM analyses. The dimeric capsule encapsulates quinone derivatives to form vibrant host–guest CT complexes. Emission intensity from the fluorescent capsule is modulated depending on the nature of the encapsulated guest molecules.^[12] Finally, we demonstrated the prominent effect of incorporating atropisomers as supramolecular subunits in the self-assembly process; only the rigid *cis*-atropisomer formed a well-defined assembly capable of encapsulating guest molecules. We believe the use of atropisomeric behavior will enrich supramolecular host–guest structures and engender new functions based on the stereochemistry.

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- [1] a) V. Balzani, A. Credi, M. Venturi, *Molecular Devices and Machines: Concepts and Perspectives for the Nanoworld*, Wiley-VCH, Weinheim, **2008**; b) J. W. Steed, J. L. Atwood, *Supramolecular chemistry*, 2nd ed., Wiley, Chichester, UK, **2009**.
- [2] a) *Smart Light-Responsive Materials: Azobenzene-Containing Polymers and Liquid Crystals* (Eds.: Y. Zhao, T. Ikeda), Wiley, Hoboken, NJ, **2009**; b) *Supramolecular Soft Matter: Applications in Materials and Organic Electronics* (Ed.: T. Nakanishi), Wiley, Hoboken, NJ, **2011**.
- [3] G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* **2005**, *117*, 5518–5563; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427.
- [4] Recent reviews: a) J. K. Klosterman, Y. Yamauchi, M. Fujita, *Chem. Soc. Rev.* **2009**, *38*, 1714–1725; b) R. Chakrabarty, P. S. Mukherjee, P. J. Stang, *Chem. Rev.* **2011**, *111*, 6810–6918; c) M. M. Safont-Sempere, G. Fernández, F. Würthner, *Chem. Rev.* **2011**, *111*, 5784–5814; d) H. Amouri, C. Desmarets, J. Moussa, *Chem. Rev.* **2012**, *112*, 2015–2041; e) M. M. J. Smulders, I. A. Riddell, C. Browne, J. R. Nitschke, *Chem. Soc. Rev.* **2013**, *42*, 1728–1754.
- [5] a) T. Kamada, N. Aratani, T. Ikeda, N. Shibata, Y. Higuchi, A. Wakamiya, S. Yamaguchi, K. S. Kim, Z. S. Yoon, D. Kim, A. Osuka, *J. Am. Chem. Soc.* **2006**, *128*, 7670–7678; b) S. Arai, D. Niwa, H. Nishide, S. Takeoka, *Org. Lett.* **2007**, *9*, 17–20; c) C. Maeda, H. Shinokubo, A. Osuka, *Org. Lett.* **2009**, *11*, 5322–5325.
- [6] Dimeric capsules: a) F. Hof, S. L. Craig, C. Nuckolls, J. Rebek, Jr., *Angew. Chem.* **2002**, *114*, 1556–1578; *Angew. Chem. Int. Ed.* **2002**, *41*, 1488–1508; b) S. Liu, B. C. Gibb, *Chem. Commun.* **2008**, 3709–3716.
- [7] J. Iwasa, K. Ono, M. Fujita, M. Akita, M. Yoshizawa, *Chem. Commun.* **2009**, 5746–5748.
- [8] a) N. Kishi, Z. Li, K. Yoza, M. Akita, M. Yoshizawa, *J. Am. Chem. Soc.* **2011**, *133*, 11438–11441; b) K. Hagiwara, Y. Sei, M. Akita, M. Yoshizawa, *Chem. Commun.* **2012**, 48, 7678–7680; c) K. Kondo, A. Suzuki, M. Akita, M. Yoshizawa, *Angew. Chem.* **2013**, *125*, 2364–2368; *Angew. Chem. Int. Ed.* **2013**, *52*, 2308–2312; d) N. Kishi, Z. Li, Y. Sei, M. Akita, K. Yoza, J. S. Siegel, M. Yoshizawa, *Chem. Eur. J.* **2013**, *19*, 6313–6320.
- [9] See the Supporting Information. In the NOESY spectra of **2**⊃(**4a**)₂ and **2**⊃(**4b**)₂, correlation signals were observed between the host and the guest. The host–guest complexes were not stable enough under ESI-TOF MS conditions, and the existence of the equilibrium between **2**⊃(**G**)₂ and **2**⊃**G** + **G** was suggested by DOSY analysis.
- [10] a) R. Castro, M. J. Berardi, E. Córdova, M. O. de Olza, A. E. Kaifer, J. D. Evanseck, *J. Am. Chem. Soc.* **1996**, *118*, 10257–10268; b) T. D. Lazzara, T. G. M. van de Ven, M. A. (Tony) Whitehead, *Macromolecules* **2008**, *41*, 6747–6751; c) F. R. P. Crisóstomo, A. Lledó, S. R. Shenoy, T. Iwasawa, J. Rebek, Jr., *J. Am. Chem. Soc.* **2009**, *131*, 7402–7410; d) N. Nishimura, K. Yoza, K. Kobayashi, *J. Am. Chem. Soc.* **2010**, *132*, 777–790.
- [11] R. Wyler, J. de Mendoza, J. Rebek, Jr., *Angew. Chem.* **1993**, *105*, 1820–1821; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1699–1701.
- [12] Although the preparation of fluorescent self-assembled molecular hosts has been reported, switchable fluorescence from the host through guest encapsulation has seldom been achieved: a) N. K. Al-Rasbi, C. Sabatini, F. Barigelletti, M. D. Ward, *Dalton Trans.* **2006**, 4769–4772; b) K. Harano, S. Hiraoka, M. Shionoya, *J. Am. Chem. Soc.* **2007**, *129*, 5300–5301; c) I. S. Tidmarsh, T. B. Faust, H. Adams, L. P. Harding, L. Russo, W. Clegg, M. D. Ward, *J. Am. Chem. Soc.* **2008**, *130*, 15167–15175; d) Z. Li, N. Kishi, K. Hasegawa, M. Akita, M. Yoshizawa, *Chem. Commun.* **2011**, 47, 8605–8607; e) Z. Li, N. Kishi, K. Yoza, M. Akita, M. Yoshizawa, *Chem. Eur. J.* **2012**, *18*, 8358–8365.