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Inversion of Chirality

Solvent- and Achiral-Guest-Triggered Chiral Inversion in a Planar Chiral *pseudo*[1]Catenane**

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Chiral inversion systems have received a great deal of interest because they offer new applications in chemical sensing, enantioselective catalysis, and in the chirality switching of liquid crystals and photoluminescence.[1] However, chiral inversion has only been demonstrated in a few artificial molecules, such as helical oligomers and polymers[2,3] and axially chiral compounds.[4] In the present study, we present a new chiral inversion system, triggered by achiral guests and solvents, in a novel artificial molecule consisting of a planar chiral macrocyclic compound, pillar[5]arene (Figure 1 a).[5–10,12,13]

Pillar[5]arenes were first reported in 2008[5] and were used as hosts to create novel supramolecular assemblies.[6] The planar chirality of pillar[5]arenes is caused by the substitution position of the alkoxy groups.[7] The units can rotate around the methylene bridges, meaning that pillar[5]arene has two equivalent most stable conformations (*pS* and *pR*), as shown in Figure 1 a. Interconversion between *pS* and *pR* occurs by rotation of these units at 25 °C in solution.[7a] Inhibiting this rotation is necessary to isolate the two enantiomers. One approach to hinder this rotation is to modify both rims with bulky substituents.[7b] The other approach is to form a rotaxane consisting of a pillar[5]arene wheel and a guest axle.[7c] Based on these approaches, we have successfully isolated planar chiral *pS*- and *pR*-pillar[5]arenes and [2]- and [3]-rotaxanes consisting of *pS*- and *pR*-pillar[5]arene wheels.[7b,c] However, the planar chirality of these molecules is static because the rotation of the units is completely inhibited. Herein, we report dynamic planar chiral inversions based on a new bicyclic structure based on pillar[5]arene, a *pseudo*[1]catenane **1** (Figure 1 c), in which the guest is an alkyl chain connected to one pillar[5]arene unit.

Rotation of the pillar[5]arene unit connecting the alkyl chain causes inclusion and de-threading of the alkyl chain; thus **1** can be assigned as a *pseudo*[1]catenane. The inclusion and de-threading of the alkyl chain induces planar chiral inversion; thus **1** has four conformers: in-*pS*-**1**, in-*pR*-**1**, out-*pS*-**1**, and out-*pR*-**1** (Figure 1 c). Guests and solvents can be included in the cavity of **1**, and thus trigger the inclusion and de-threading of the alkyl chain. We show that achiral guests and solvents trigger the dynamic planar chiral inversions of **1**.

A *pseudo*[1]catenane **1** was prepared by a Sharpless click reaction between 1,12-diazidododecane and an A1/A2 dialkynylated pillar[5]arene **2**[8] (Figure 1 d). Purification of the crude product from the reaction mixture by silica gel chromatography afforded **1** in 17 % yield. The chemical structure of **1** was fully characterized by ^{1}H, ^{13}C, 2D ^{1}H–^{1}H COSY, HSQC, HMBC NMR spectroscopy, and high-resolution FAB mass spectrometry. Figure 2 shows the ^{1}H NMR spectrum of **1** and a model compound **3** in $CDCl_3$ at 25 °C. The signals from the alkyl chain of **1** (Figure 2 b, peaks a–e) were shifted upfield compared with that of **3** (Figure 2 a, peaks A–E). The two-dimensional nuclear Overhauser effect spectrum of **1** (Supporting Information, Figure S2) has correlations between the signals from phenyl and methylene protons of pillar[5]arene wheel and methylene protons of the alkyl chain. These data indicate the alkyl chain was mainly included in the pillar[5]arene cavity in $CDCl_3$. Pillar[5]arenes form complexes with linear alkanes in $CDCl_3$,[9] and in a similar way **1** mainly forms a self-inclusion structure in $CDCl_3$. The proton signal from the methylene moieties adjacent to the O atoms (Figure 2 b, peak h) was split into two groups of doublets with a 1:1 integration ratio, suggesting that rotation of the units did not occur or occurred slowly on the timescale of a 500 MHz spectrometer.[7b] Five singlet peaks from phenyl protons were observed (Figure 2 b). This indicates that the structure of **1** was highly symmetric and stereoregular. Considering the possible chiral structures, all of the substituents at both rims should have the same orientation.[7] The same symmetric pillar[5]arenes mainly obtained by immobilization of the conformation owing to lower energy than the other conformers.

Chiral-phase HPLC measurements were performed to investigate the planar chirality of **1**. Two peaks of equal area were observed (Supporting Information, Figure S3), indicating **1** was racemic, that is, a 1:1 mixture of in-*pS*-**1** and in-*pR*-**1**. These fractions were collected and UV/Vis and circular dichroism (CD) spectra were measured (Figure 3 a).

The CD spectra of these fractions were mirror images, indicating enantiopure in-*pS*-**1** and in-*pR*-**1** had been collected. Calculations allowed the first and second fractions to be assigned as in-*pS*-**1** and in-*pR*-**1**, respectively.[7c]

1,4-Dicyanobutane (Figure 1 b, G1) forms very highly stable 1:1 host–guest complexes with pillar[5]arenes. The association constants K_a of the complexes between G1 and pillar[5]arenes are generally greater than 10^4 L mol^{-1},[10] while the K_a of the host–guest complexes between linear alkanes and pillar[5]arenes are very weak ($K_a = 10$–100 L mol^{-1}).[9] The crystalline structure of the 1:1 G1–pillar[5]arene complex

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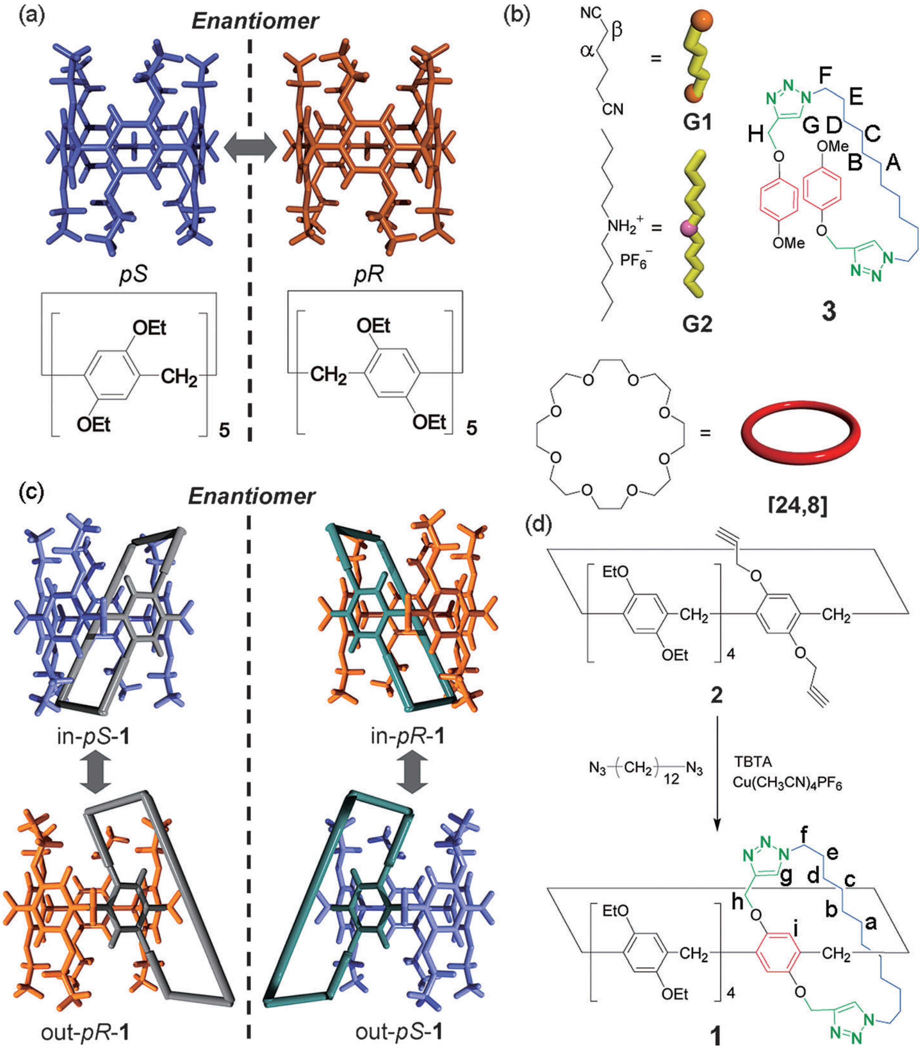

Figure 1. a) Planar chirality of pillar[5]arene. b) Competitive guests (G1 and G2) and a competitive host ([24,8]). c) Four conformers and d) synthesis of a *pseudo*[1]catenane **1**.

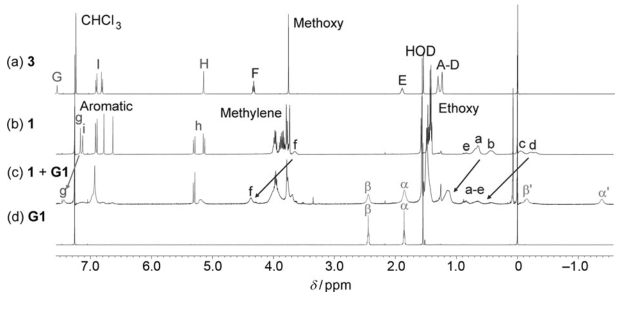

Figure 2. a) ^{1}H NMR spectra (500 MHz, 5 mM, CHCl$_3$, 25 °C) of a) **3**, b) **1**, c) an equimolar mixture of **1** and G1, and d) G1.

was completely characterized by X-ray analysis.[10] The very stable host–guest complexation derives from multiple non-covalent interactions such as CH–π, CH–N and CH–O interactions between pillar[5]arene and G1. Thus, G1 was added as a competitive guest for the alkyl chain, which is a constituent part of **1**. Upon the addition of one equivalent of G1 to **1** (Figure 2c), new additional peaks (peaks α′ and β′) were observed along with the pristine proton peaks of G1 (peaks α and β). These additional peaks were the methylene proton peaks of G1 in a complex with **1**, which were also observed in the host–guest complexes of G1 with other pillar[5]arenes.[10] At the same time, downfield shifts in the signals from the alkyl chain (peaks a–e) and the triazole group (peak g) were observed. The cavity size of pillar[5]arenes is about 5.5 Å, which just accommodates a single linear alkane.[5,6,9] The K_a of the G1–pillar[5]arene complex is several orders of magnitude higher than that of the alkyl chain–pillar[5]arene complex,[9,10] thus inclusion of G1 in the cavity of **1** causes de-threading of the alkyl chain moiety from the cavity of **1**. Figure 3b shows the CD spectra of the first fraction (in-*pS*-**1**) with the guest G1. The sense of the observed CD spectra had changed dramatically from positive to negative as the concentration of G1 increased, indicating that the addition of the achiral guest G1 induced the planar chiral inversion from in-*pS*-**1** to out-*pR*-**1** (Figure 4a). The opposite planar chiral inversion from in-*pR*-**1** to out-*pS*-**1** was also induced by the addition of achiral G1 to the second fraction (Supporting Information, Figure S4). The association constants between in-*pS*-**1** and G1, and between in-*pR*-**1** and G1 as determined by CD titrations were $(7.1\pm0.13)\times10^2$ L mol^{-1} and $(7.3\pm0.19)\times10^2$ L mol^{-1}, respectively (Supporting Information, Figure S5).[11] The association constants between pillar[5]arene derivatives and G1 are generally $>10^4$ L mol^{-1},[10] and thus the alkyl chain is strongly included in the cavity of **1** and acts as a competitive guest to G1.

Linear ammonium cations are also good guests for pillar[5]arenes ($K_a > 10^3$ M^{-1}).[12] Thus, an ammonium cation (G2, Figure 1b) was added to the second fraction (in-*pR*-**1**). Inclusion of G2 into the cavity of **1** was also observed by ^{1}H NMR measurements (Supporting Information, Figure S6). Upon addition of G2, a decrease in the negative CD intensities was observed (Figure 5a). Because the association constants between G2 and pillar[5]arenes are weaker than those between G1 and pillar[5]arenes, inversion of chirality did not complete. Nevertheless, G2 can also act as a guest and induce the de-threading of the alkyl chain of **1**. We expected that G2 could be removed from the cavity of **1** with the assistance of the crown ether [24]crown-8 ([24,8]). The addition of [24,8] to a mixture of **1** and G2, resulted in an

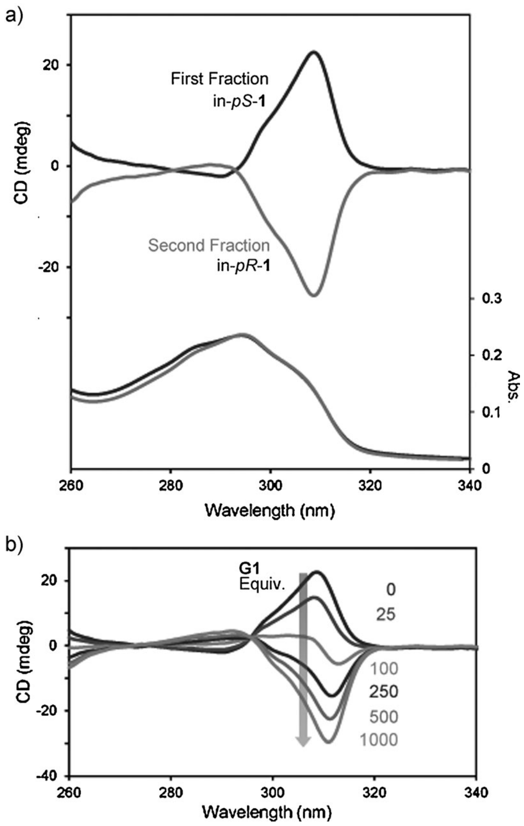

Figure 3. a) CD and absorption spectra (40 μM, $CHCl_3$, 25 °C) of the first and second fractions. b) CD spectral changes (40 μM, $CHCl_3$, 25 °C) of the first fraction (in-*pS*-**1**) upon addition of G1 (0–1000 equiv to **1**).

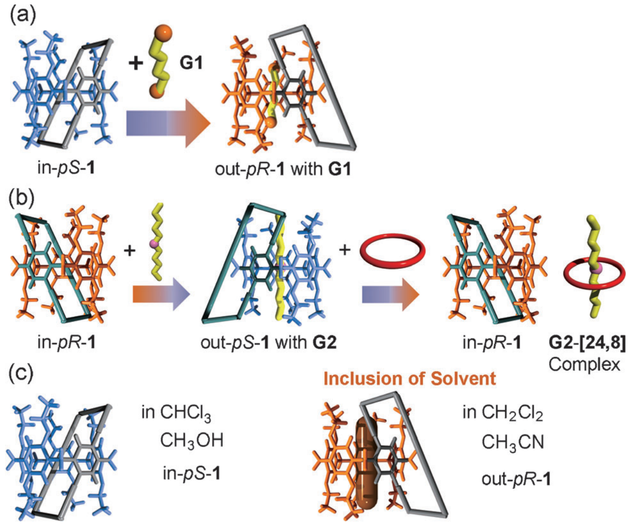

Figure 4. Representations of a) the planar chiral inversions triggered by a) achiral guest G1, b) alternating addition of achiral guest G2 and host [24,8], and c) inclusion of achiral solvents.

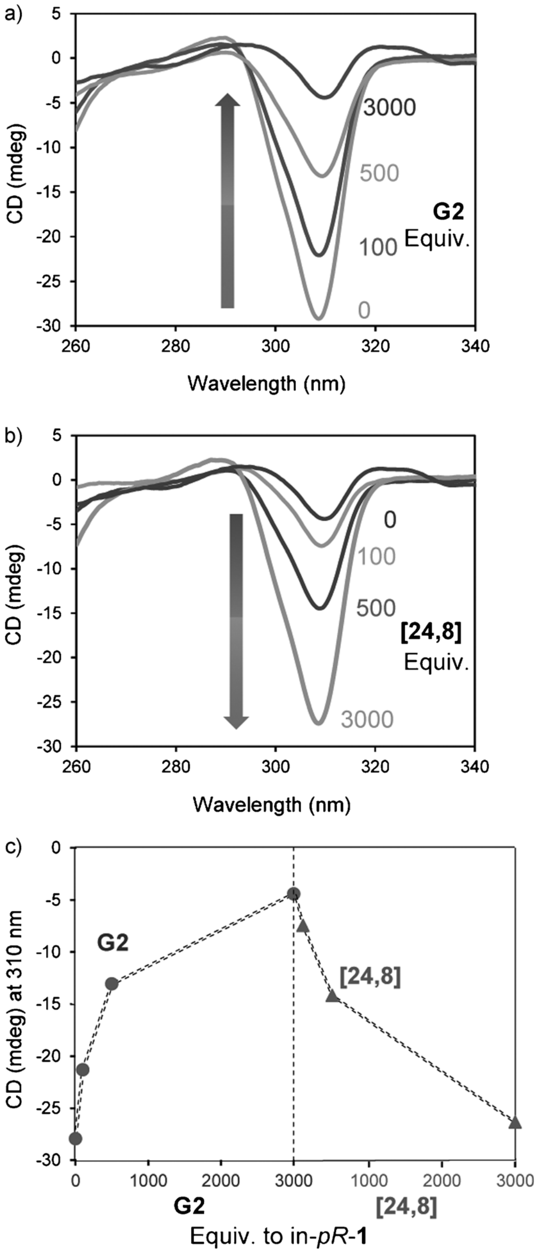

Figure 5. Achiral guest- and host-triggered reversible planar chiral inversion. CD spectral changes (40 μM, $CHCl_3$, 25 °C) of a) a second fraction (in-*pR*-**1**) upon addition of G2 (0–3000 equiv to **1**) and b) a mixture of the second fraction and G2 upon addition of [24,8] (0–3000 equiv to **1**). c) Change in CD intensity at 310 nm upon addition of G2 and [24,8] to a solution of the second fraction.

increase of negative CD intensities (Figure 5b). The CD intensities almost recovered to their initial state (Figure 5c), indicating that the G2- and [24,8]-triggered planar chiral inversions are reversible (Figure 4b). The addition of G2 and the subsequent inclusion of G2 in the cavity of in-*pR*-**1** cause the transformation from in-*pR*-**1** to out-*pS*-**1**. Further addition of a competitive host [24,8] to the mixture induced a transformation from out-*pS*-**1** to in-*pR*-**1**. Overall, we reversibly converted between in-*pS*-**1** and out-*pR*-**1** with alternating addition of the competitive achiral guest G2 and the achiral host [24,8].

Figure 6a shows the CD spectra of the first fraction in different solvents. In CH_3OH, positive CD signals were observed. In the ^1H NMR spectrum of **1** in CD_3OD, the proton signals from the alkyl chain (Figure 6b, peaks a–e) of **1** were upfield compared with model compound **3** (Figure 2a,

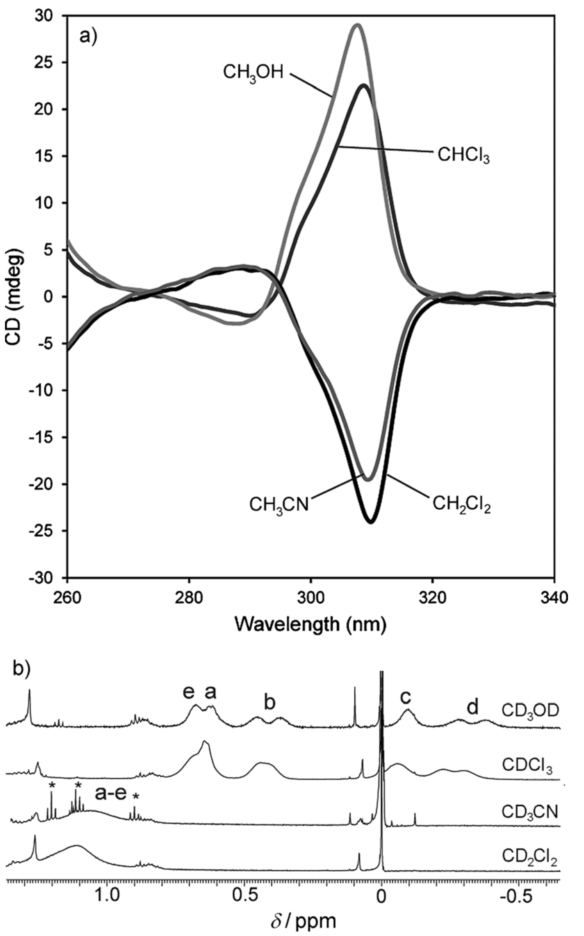

Figure 6. Achiral solvent-triggered planar chiral inversion. a) CD spectra (40 μM) of the first fraction in CH_3OH, $CHCl_3$, CH_3CN, and CH_2Cl_2. b) ^{1}H NMR spectra (500 MHz, 5 mM, 25 °C) of **1** in CD_3OD, $CDCl_3$, CD_3CN, and CD_2Cl_2. The peaks with an asterisk derive from *n*-hexane. *n*-Hexane could not be removed owing to the host–guest complexation of *n*-hexane with **1**.

peaks A–E). These observations are similar to chloroform and indicate the alkyl chain is mainly included in the cavity in these solvents (in-*pS*-**1**; Figure 4c). In contrast, the CD signals of this fraction are negative in CH_2Cl_2 and CH_3CN (Figure 6a). In these solvents, the proton signals of the alkyl chains were observed at downfield (Figure 6b). These solvents act as guests and are included in the pillar[5]arene cavity (out-*pR*-**1**, Figure 4c). The inclusion of CH_2Cl_2 and CH_3CN into the cavity of pillar[5]arenes was completely characterized by single X-ray crystalline analysis.[5,13] Thus, the small size differences between these solvents can be detected by the sense of the positive and negative CD signals using **1**. The opposite planar chiral inversions induced by these achiral solvents were also observed in the second fraction (Supporting Information, Figure S7).

To determine the rate of the pirouetting between in-**1**/out-**1** conformers, we measured variable-temperature ^{1}H NMR spectra of **1** in these deuterium solvents. In CD_3CN, we can detect two proton signals from the triazole group from the self-inclusion and de-threaded structures of **1** (Supporting Information, Figure S8), but cannot in the other deuterium solvents (Supporting Information, Figures S9–S11). The populations of the self-inclusion and de-threaded structures in CD_3CN were calculated using the integration ratio of these peaks. The thermodynamic parameters were determined using a van't Hoff plot (Supporting Information, Figure S12). ΔH and ΔS were found to be -20.3 ± 43 kJ mol^{-1} and -81.4 ± 1.6 J mol^{-1} K^{-1}, respectively. ΔG extrapolated to 25 °C was 4.00 ± 0.91 kJ mol^{-1}, which is consistent with inclusion of acetonitrile in the cavity at 25 °C.

In conclusion, we synthesized a new chiral pillar[5]arene structure for the first time, *pseudo*[1]catenane **1**, which shows complete chiral inversion upon addition of achiral guest and solvents.[14] Host–guest complexation is the driving force for the chiral inversion. The planar chiral inversion system will be useful for chiral switches or sensors because planar chiral inversions take place by capturing and releasing achiral guests and reflecting the minute size difference of solvents.

Experimental Section

1: Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (31.8 mg, 60.0 μmol) and $[Cu(CH_3CN)_4]PF_6$ (22.3 mg, 60.0 μmol) were added to a solution of **2**[8] (54.7 mg, 60.0 μmol) and 1,12-diazidododecane (15.1 mg, 60.0 μmol) in chloroform (300 mL), and the mixture was stirred at 25 °C for 12 h. The resulting solution was concentrated in vacuo. Column chromatography (silica gel, chloroform) afforded *pseudo*[1]catenane **1** (36.5 mg, 31.0 μmol, Yield: 17 %). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.17$ (s, 2H, triazole), 7.13 (s, 2H, phenyl), 6.92 (s, 2H, phenyl), 6.89 (s, 2H, phenyl), 6.78 (s, 2H, phenyl), 6.63 (s, 2H, phenyl), 5.30 (d, 2H, $J = 12.1$ Hz, methylene), 5.14 (d, 2H, $J = 12.6$ Hz, methylene), 3.56–4.04 (m, 30H, methylene), 1.38–1.50 (m, 24H, methyl), 0.55–0.80 (br, 8H, methylene), 0.32–0.54 (br, 4H, methylene), −0.14–0.05 (br, 4H, methylene), −0.40–0.14 ppm (br, 4H, methylene). ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 150.2$, 149.7, 149.6, 149.3, 143.4, 131.4, 128.6, 128.1, 127.8, 123.6, 119.7, 115.1, 114.4, 114.3, 63.9, 63.6, 63.3, 63.1, 49.7, 29.8, 29.3, 29.2, 28.9, 28.4, 27.6, 24.5, 15.4 ppm. HRFABMS: *m/z* Calcd for $C_{69}H_{91}N_6O_{10}$ $[M+H]^+$: 1163.6797, found 1163.6792.

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[1] a) H. Maeda, Y. Bando, K. Shimomura, I. Yamada, M. Naito, K. Nobusawa, H. Tsumatori, T. Kawai, *J. Am. Chem. Soc.* **2011**, *133*, 9266–9269; b) H. Hayasaka, T. Miyashita, M. Nakayama, K. Kuwada, K. Akagi, *J. Am. Chem. Soc.* **2012**, *134*, 3758–3765; c) J. Suk, V. R. Naidu, X. Liu, M. S. Lah, K. S. Jeong, *J. Am. Chem. Soc.* **2011**, *133*, 13938–13941; d) E. Yashima, K. Maeda, Y. Okamoto, *Nature* **1999**, *399*, 449–451; e) R. Eelkema, M. M. Pollard, J. Vicario, N. Katsonis, B. S. Ramon, C. W. M. Bastiaansen, D. J. Broer, B. L. Feringa, *Nature* **2006**, *440*, 163.
[2] Reviews: a) E. Yashima, K. Maeda, H. Iida, Y. Furusho, K. Nagai, *Chem. Rev.* **2009**, *109*, 6102–6211; b) E. Yashima, K. Maeda, Y. Furusho, *Acc. Chem. Res.* **2008**, *41*, 1166–1180.
[3] a) H. Miyake, K. Yoshida, H. Sugimoto, H. Tsukube, *J. Am. Chem. Soc.* **2004**, *126*, 6524–6525; b) H. Miyake, H. Kamon, I. Miyahara, H. Sugimoto, H. Tsukube, *J. Am. Chem. Soc.* **2008**, *130*, 792–793; c) M. Fujiki, *J. Am. Chem. Soc.* **2000**, *122*, 3336–3343; d) T. Yamada, Y. Nagata, M. Suginome, *Chem. Commun.*

2010, *46*, 4914 – 4916; e) Q. Gan, Y. Ferrand, N. Chandramouli, B. Kauffmann, C. Aube, D. Dubreuil, I. Huc, *J. Am. Chem. Soc.* **2012**, *134*, 15656 – 15659; f) R. M. Meudtner, S. Hecht, *Angew. Chem.* **2008**, *120*, 5004 – 5008; *Angew. Chem. Int. Ed.* **2008**, *47*, 4926 – 4930.

[4] a) B. L. Feringa, R. A. van Delden, N. Koumura, E. M. Geertsema, *Chem. Rev.* **2000**, *100*, 1789 – 1816; b) B. L. Feringa, *Acc. Chem. Res.* **2001**, *34*, 504 – 513; c) N. Ruangsupapichat, M. M. Pollard, S. R. Harutyunyan, B. L. Feringa, *Nat. Chem.* **2011**, *3*, 53 – 60.

[5] T. Ogoshi, S. Kanai, S. Fujunami, T. Yamagishi, Y. Nakamoto, *J. Am. Chem. Soc.* **2008**, *130*, 5022 – 5023.

[6] Reviews: a) T. Ogoshi, *J. Inclusion Phenom. Macrocyclic Chem.* **2012**, *72*, 247 – 262; b) T. Ogoshi, T. Yamagishi, *Bull. Chem. Soc. Jpn.* **2013**, *86*, 312 – 332; c) T. Ogoshi, T. Yamagishi, *Eur. J. Org. Chem.* **2013**, DOI: 10.1002/ejoc.201300079; d) P. J. Cragg, K. Sharma, *Chem. Soc. Rev.* **2012**, *41*, 597 – 607; e) M. Xue, Y. Yang, X. Chi, Z. Zhang, F. Huang, *Acc. Chem. Res.* **2012**, *45*, 1294 – 1308.

[7] a) T. Ogoshi, K. Kitajima, T. Aoki, T. Yamagishi, Y. Nakamoto, *J. Phys. Chem. Lett.* **2010**, *1*, 817 – 821; b) T. Ogoshi, K. Masaki, R. Shiga, K. Kitajima, T. Yamagishi, *Org. Lett.* **2011**, *13*, 1264 – 1266; c) T. Ogoshi, D. Yamafuji, T. Aoki, K. Kitajima, T. Yamagishi, Y. Hayashi, S. Kawauchi, *Chem. Eur. J.* **2012**, *18*, 7493 – 7500.

[8] T. Ogoshi, D. Yamafuji, D. Kotera, T. Aoki, S. Fujinami, T. Yamagishi, *J. Org. Chem.* **2012**, *77*, 11146 – 11152.

[9] a) T. Ogoshi, K. Demachi, K. Kitajima, T. Yamagishi, *Chem. Commun.* **2011**, *47*, 10290 – 10292; b) T. Ogoshi, T. Aoki, R. Shiga, R. Iizuka, S. Ueda, K. Demachi, D. Yamafuji, H. Kayama, T. Yamagishi, *J. Am. Chem. Soc.* **2012**, *134*, 20322 – 20325; c) Z. Zhang, Y. Luo, J. Chen, S. Dong, Y. Yu, Z. Ma, F. Huang, *Angew. Chem.* **2011**, *123*, 1433 – 1437; *Angew. Chem. Int. Ed.* **2011**, *50*, 1397 – 1401.

[10] X. Shu, S. Chen, J. Li, Z. Chen, L. Weng, X. Jia, C. Li, *Chem. Commun.* **2012**, *48*, 2967 – 2969.

[11] Compound **1** was equilibrium between two forms, though alkyl chain of **1** mainly included in the cavity in $CDCl_3$. Thus, the K_a are apparent values.

[12] a) C. Han, G. Yu, B. Zheng, F. Huang, *Org. Lett.* **2012**, *14*, 1712 – 1715; b) M. Ni, Y. F. Guan, L. Wu, C. Deng, X. Y. Hu, J. L. Jiang, C. Lin, L. Y. Wang, *Tetrahedron Lett.* **2012**, *53*, 6409 – 6413; c) T. Ogoshi, K. Demachi, K. Kitajima, T. Yamagishi, *Chem. Commun.* **2011**, *47*, 7164 – 7166.

[13] T. Boinski, A. Szumna, *Tetrahedron* **2012**, *68*, 9419 – 9422.

[14] The bicyclic structures have been referred as “molecular chameleons” and “catenane chameleons” because of color changes induced by inclusion of guests: a) R. Wolf, M. Asakawa, P. R. Ashton, M. G. López, C. Hamers, S. Menzer, I. W. Parsons, N. Spencer, J. F. Stoddart, M. S. Tolley, D. J. Williams, *Angew. Chem.* **1998**, *110*, 1018 – 1022; *Angew. Chem. Int. Ed.* **1998**, *37*, 975 – 979; b) D. A. Leigh, K. Moody, J. P. Smart, K. J. Watson, A. M. Z. Slawin, *Angew. Chem.* **1996**, *108*, 326 – 331; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 306 – 310. However, their enantiomers have not been isolated because their enantiomers undergo rapid inversion at room temperature.