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Tetrahedron Letters 45 (2004) 7435–7440
Tetrahedron Letters

Design and synthesis of ninhydrin-based cyclophanes as potential neutral receptors for quaternary ammonium cations

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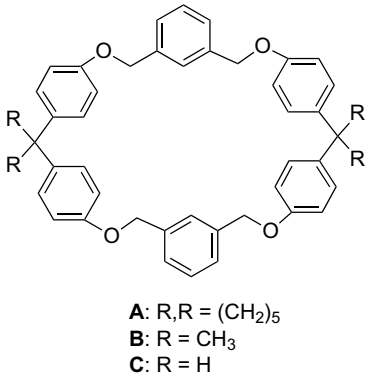
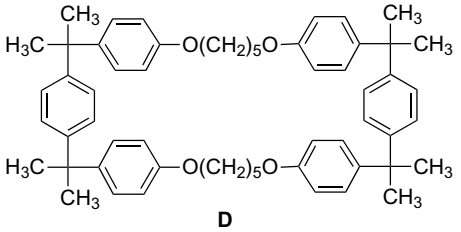
Received 27 May 2004; revised 5 July 2004; accepted 13 August 2004

Abstract—Four ninhydrin-based cyclophanes **4a**, **4b**, **6a**, and **6b** were designed and synthesized. Two rectangular type cyclophanes (**4a** and **4b**) and two square type cyclophanes (**6a** and **6b**) were prepared in 8–43% yields.

Due to the well-known coordinative ability of oxygen atoms of ether, polyether chains are the fundamental constituents of many classes of cyclic and acyclic receptors that are well established ligands for metal and ammonium cations.[1] However, the contribution of the polyether chains for the binding of quaternary ammonium cations is not an important factor.[2] A more important contribution for the binding of quaternary ammonium cations is believed to arise from the attraction between the positive charge of the guest and the electron rich faces of the aromatic rings (cation-π interaction).[3]

Although the complexation of quaternary ammonium cations by negatively charged cyclophanes in aqueous phase has been extensively studied,[4] the binding of quaternary ammonium cations by neutral cyclophane hosts in non-aqueous solution is less common.[5,6] Thus, the design and synthesis of neutral hosts for the binding of quaternary ammonium cations in organic media is a





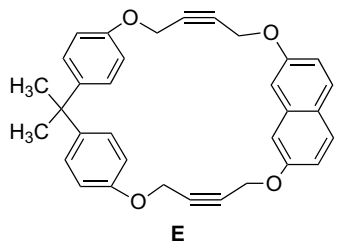


Figure 1.

Keywords: Cyclophanes; Ninhydrin; Receptors; Quaternary ammonium cations.
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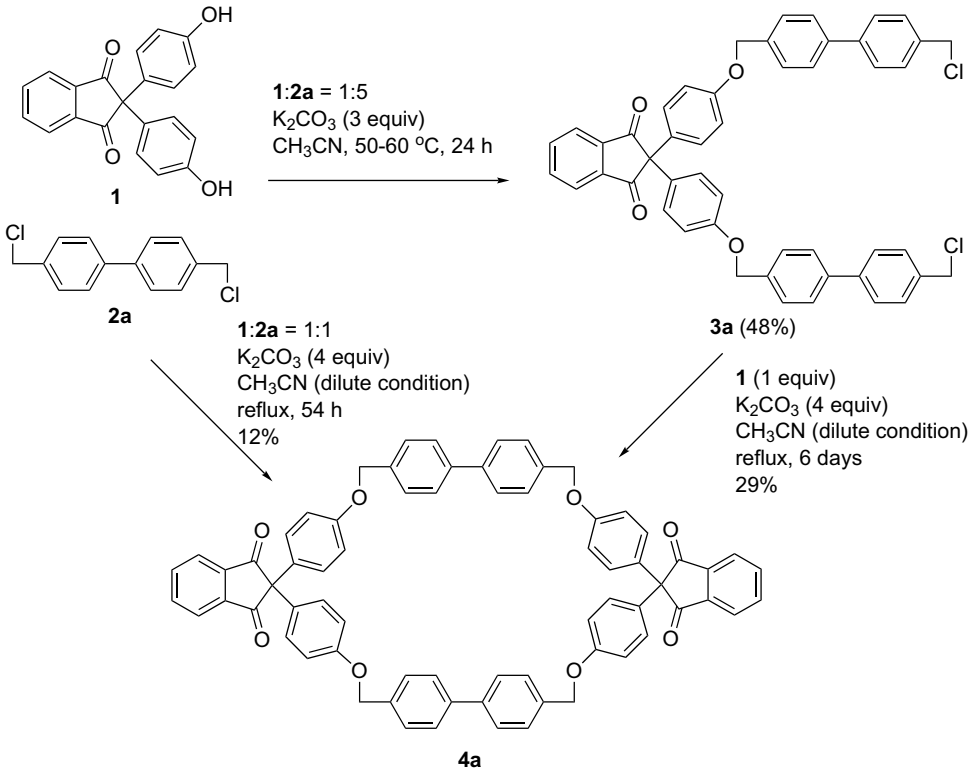
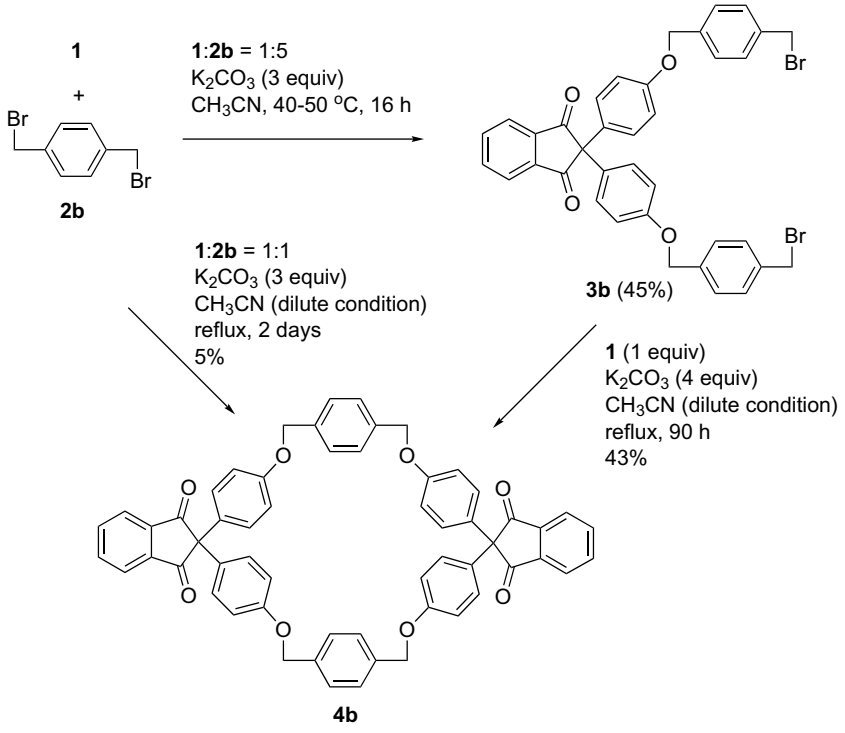
doi:10.1016/j.tetlet.2004.08.078



Scheme 1.



Scheme 2.

very important target. Most of the reported neutral cyclophanes have been synthesized from bisphenol derivatives.[6,7] Recently, Cort and Mandolini have reported the synthesis and binding properties of novel cyclophane **A**–**C** (Fig. 1).[6a] The most efficient cyclophane **A** for the quaternary ammonium cations was prepared from

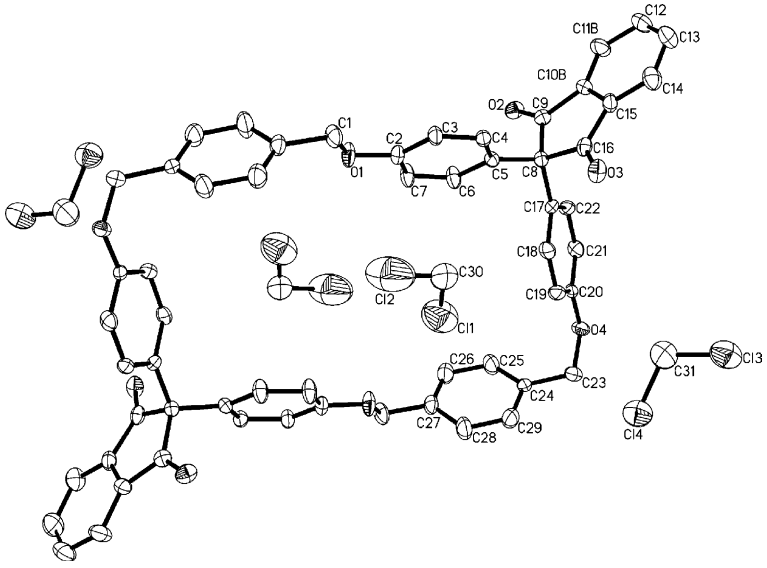
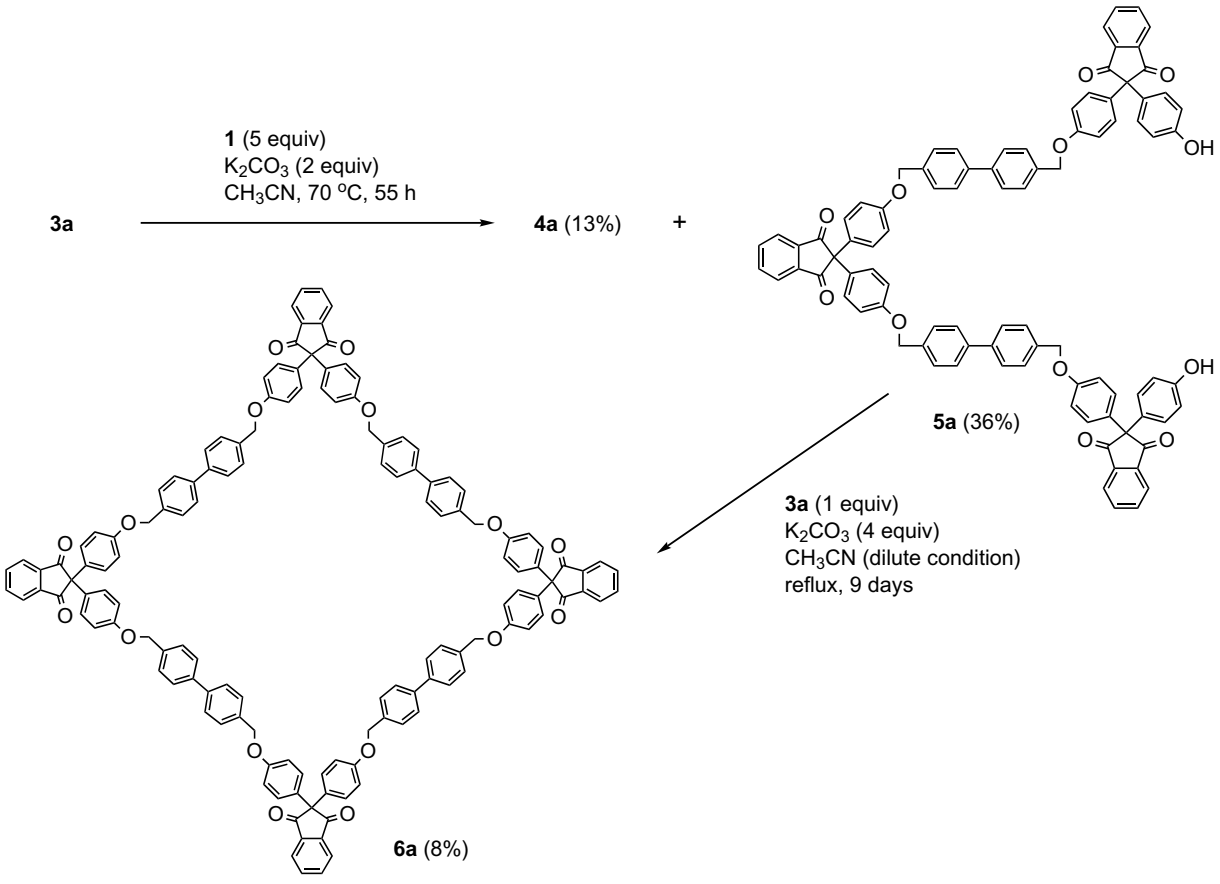


Figure 2. ORTEP drawing of cyclophane **4b**.



Scheme 3.

1,3-bis(bromomethyl)benzene and 1,1′-bis(hydroxyphenyl)-cyclohexane in 10% yield. Bisphenol-based other cyclophanes like as **D** and **E** have been synthesized.[6b,c]

We think the moderate yields of products and less-effective binding properties of the cyclophanes **A**–**E** might arise from the flexibility of the linkage. Cort and Mandolini already described in their paper that the cyclophanes showed a substantial degree of conformational looseness.[6a] Among the cyclophanes, the pentamethylene analog **A** is the least mobile than other analogs. Thus, we intended to synthesize the analogs of **A**–**C** with more rigid linker. 2,2′-Bis(4-hydroxyphenyl)-1,3-indanedione (**1**) can act as the rigid linker.[8] Moreover the

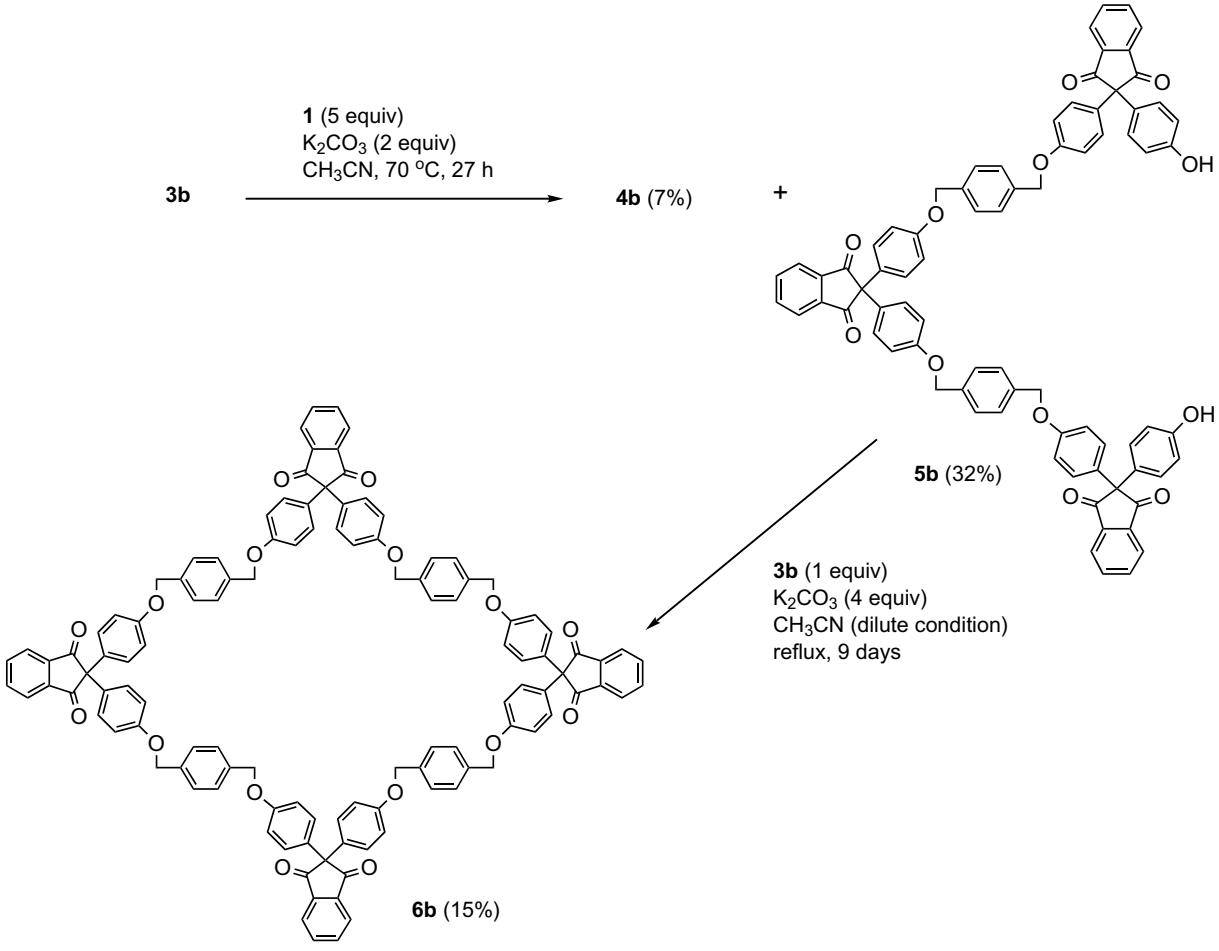
oxygen atoms at the ninhydrin moiety could serve as another strong complexation site.

The starting material **1** was synthesized form ninhydrin and phenol in the presence of H_2SO_4 in acetic acid in 76% yield.[8] We prepared two cyclophanes **4a** and **4b** starting from **1** and 4,4′-bis(chloromethyl)-1,1′-biphenyl (**2a**) and α,α′-dibromo-*p*-xylene (**2b**) as shown in Schemes 1 and 2. We used stepwise method[5a] initially for the preparation of **4a** and **4b**. As expected, the cyclophanes **4a** and **4b** were obtained in good yields presumably due to the less mobile conformation of the intermediates **3a** and **3b**, and the partner **1**. We could obtain the same compounds **4a** and **4b** directly although in lower yields from the reaction of **1** and **2a** or **2b**.[5a]

The synthesis of rectangular type cyclophanes **4a** and **4b** is straightforward (Schemes 1 and 2). The reaction of **1** and **2a** (1:5 ratio) in the presence of K_2CO_3 in CH_3CN gave the intermediate **3a** in 48% yield after 24 h at 50–60 °C. The reaction of **3a** and **1** (K_2CO_3, CH_3CN, reflux, 6 days) afforded the final product **4a** in 29% yield in dilute condition (0.3 mmol of **3a** in 100 mL of CH_3CN). The cyclophane **4a** can also be prepared directly in 12% yield from the reaction of **1** and **2a** in a dilute condition. Similarly, the reaction of **1** and **2b** (1:5 ratio) in the presence of K_2CO_3 in CH_3CN gave the intermediate **3b** in a similar yield (45%) after 16 h at 40–50 °C. The reaction of **3b** and **1** (K_2CO_3, CH_3CN, reflux, 90 h) afforded the final product **4b** in 43% yield in dilute condition (0.3 mmol of **3b** in 100 mL of CH_3CN). The cyclophane **4b** can also be prepared directly in 5% yield from the reaction of **1** and **2b** in a dilute condition (Scheme 2).[9]

The structures of **4a** and **4b** were confirmed by ^1H, ^{13}C NMR, MALDI-TOF mass, and eventually by X-ray structure analysis for **4b**.[10] The ORTEP drawing of **4b** is shown in Figure 2. As shown, two molecules of CH_2Cl_2 were positioned inside and two outside of the cyclophane. The inside CH_2Cl_2 guest was positioned in a manner that the slightly acidic hydrogen atoms of CH_2Cl_2 directing the benzene ring of phenol moiety presumably by the weak cation-π interaction.[3,6d,e] Maybe this is the reason why the growing of crystal of **4b** was successful in a mixed solvent of Et_2O and CH_2Cl_2.[6d,e]

As a next trial we started the preparation of square type cyclophanes such as **6a** and **6b**. The synthesis of these compounds is depicted in Schemes 3 and 4, respectively. The reaction of **3a** and **1** (1:5 ratio) in CH_3CN (70 °C, 55 h) gave **4a** (13%) and desired intermediate **5a** in moderate yield (36%). The reaction of **5a** and **3a** under dilute conditions afforded **6a** in 8% isolated yield. Similarly, the reaction of **3b** and **1** (1:5 ratio) in CH_3CN (70 °C,



Scheme 4.

27 h) gave **4b** (7%) and desired intermediate **5b** in 32% yield. The reaction of **5b** and **3b** under dilute conditions afforded **6b** in 15% isolated yield. The structures of **6a** and **6b** were also confirmed by ^{1}H, ^{13}C NMR, MALDI-TOF mass.[11] Unfortunately, our attempts to grow single crystals of **6a** and **6b** failed at this stage presumably due to their conformational flexibility.

We expected that the cyclophanes **4a**, **4b**, **6a**, and **6b** could recognize the quaternary ammonium cations by the cation-π interaction[6a,7a,d] as well as some non-polar compounds such as biphenyl or naphthalene with the aid of π–π interaction.[4l,6b,c] However, unfortunately, we could not find any suitable guest until now. We carried out NMR binding studies with some guest molecules including *N*-methylpyridinium iodide, benzyltrimethylammonium bromide, *p*-cresol, biphenyl, naphthalene, anthracene, azobenzene. But, the expected upfield shifts of guest molecules in NMR spectra were negligible in all the cases, which suggested insufficient inclusion into the host molecule.[12] Further studies on the binding properties of the cyclophanes and growing of the crystals are under progress.

Acknowledgements

This work was supported by a Korea Research Foundation Grant (KRF-2002-015-CP0215). We would like to express our thanks to Dr. Sangku Lee (KRIBB, Taejon) and Prof. CheHun Jung (Department of Chemistry, CNU) for their helpful taking of MALDI-TOF mass spectra.

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9. The synthesis of **4a** and **4b** follows the typical experimental procedures. The macrocyclization was conducted in dilute condition (0.3 mmol/100 mL). After the reaction, removal of CH_3CN, usual aqueous workup with CH_2Cl_2 followed by column chromatographic purification process (CH_2Cl_2/hexanes, 1:17) we obtained the desired products. Spectroscopic data of **4a** and **4b** are as follows.
Compound **4a**: 29%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.11 (s, 8H), 6.80 (d, $J = 9.0$ Hz, 8H), 7.11 (d, $J = 9.0$ Hz, 8H), 7.38 (d, $J = 8.1$ Hz, 8H), 7.52 (d, $J = 8.1$ Hz, 8H), 7.87–7.90 (m, 4H), 8.06–8.08 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 65.83, 69.66, 109.73, 114.92, 115.32, 124.04, 127.30, 127.47, 127.96, 129.78, 129.96, 130.82, 136.11, 136.19, 140.27, 141.45, 157.84, 200.05; MALDI-TOF calcd for $C_{70}H_{48}O_8$+Na 1039.3247, found 1039.3324.
Compound **4b**: 43%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.08 (s, 8H), 6.78 (d, $J = 9.0$ Hz, 8H), 7.10 (d, $J = 9.0$ Hz, 8H), 7.28 (s, 8H), 7.87–7.90 (m, 4H), 8.05–8.08 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 65.85, 69.56, 115.29, 124.03, 127.04, 129.79, 130.84, 136.08, 136.69, 141.47, 157.81, 200.03; MALDI-TOF calcd for $C_{58}H_{40}O_8$+Na 887.2621, found 887.2651.
10. Single crystals of **4b** were obtained by crystallization of pure **4b** from the mixed solvent (ether and CH_2Cl_2) according to the literature.[6e] Crystal data for **4b**: empirical formula $C_{31}H_{24}Cl_4O_4$, $Fw = 602.30$, crystal dimensions $0.30 \times 0.20 \times 0.20\,mm^3$, monoclinic, space group $P\,2(1)/n$, $a = 6.7567(4)$ (Å), $b = 11.0494(7)$ (Å), $c = 37.858(3)$ (Å), $\alpha = 90°$, $\beta = 90.660(2)°$, $\gamma = 90°$, $V = 2826.2(3)$ (Å)^3, $Z = 4$, $D_{calcd} = 1.416\,mg/m^3$, $F_{000} = 1240$, Mo Kα ($\lambda = 0.71073$ (Å)), $R_1 = 0.0899$, $wR_2 = 0.2332$ ($I > 2\sigma(I)$).

11. Spectroscopic data of square compounds is as follows. Compound **6a**: 8%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.07 (s, 16H), 6.90 (d, J = 9.0 Hz, 16H), 7.18 (d, J = 9.0 Hz, 16H), 7.44 (d, J = 8.1 Hz, 16H), 7.57 (d, J = 8.1 Hz, 16H), 7.85–7.91 (m, 8H), 8.03–8.08 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 66.24, 69.70, 114.99, 124.07, 127.33, 127.84, 129.93, 130.58, 136.00, 136.10, 140.48, 141.54, 158.21, 200.18; MALDI-TOF calcd for $C_{140}H_{96}O_{16}$+Na 2055.6596, found 2055.6754. Compound **6b**: 15%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.02 (s, 16H), 6.87 (d, J = 9.0 Hz, 16H), 7.16 (d, J = 9.0 Hz, 16H), 7.37 (s, 16H), 7.85–7.89 (m, 8H), 8.04–8.08 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 66.23, 69.63, 114.95, 124.06, 127.57, 129.92, 130.56, 136.09, 136.65, 141.53, 158.15, 200.16; MALDI-TOF calcd for $C_{116}H_{80}O_{16}$+Na 1751.5344, found 1751.5177.

12. As an example, the upfield shifts data (in parts per million) of *N*-methylpyridinuim iodide with cyclophane **4b** are as follows ($CDCl_3$, host:guest = 2.5:1): 0.018 (*N*-CH_3), 0.032 (H-4), 0.084 (H-2).