HETEROCYCLES, Vol. 93, No. 2, 2016, pp. 580 - 592. © 2016 The Japan Institute of Heterocyclic Chemistry
Received, 31st August, 2015, Accepted, 12th November, Published online, 14th December, 2015
DOI: 10.3987/COM-15-S(T)44

A D_{3h}-SYMMETRIC MACROCYCLE ALTERNATINGLY COMPOSED OF PYRIDINE AND BENZYL ALCOHOL UNITS LINKED WITH ACETYLENE BONDS

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Abstract — A macrocyclic compound alternatingly composed of three pyridine and three benzyl alcohol units linked with acetylene bonds was developed as a new type of D_{3h}-symmetric hexagonal shape-persistent macrocycles with a host function. The macrocycle was prepared via several steps of Sonogashira reaction and proved to interact with halide anions, especially chloride on the basis of ^{1}H NMR studies.

Dedicated to Professor Lutz F. Tietze on his 75th Birthday

INTRODUCTION

In this decade, shape-persistent macrocycles (SPM) and their characteristics have attracted chemists in the fields not only of heterocyclic chemistry but also of supramolecular chemistry.[1] One type of SPM frames consisted of six aromatic rings linked with six acetylene bonds in a hexagonal shape, which has been built by Sonogashira reaction[2] and alkyne metathesis.[3] It has been reported that such SPM compounds performed self association by π,π-stacking to form fibril structures[4] and host-guest association in their hole.[5,6]

During the course of our study, it seemed attractive to place hydrogen-bonding functional groups inside a macrocycle with expectation that preorganization works effectively in the rigid architecture. Figure 1 shows macrocyclic host molecules we have developed for saccharide recognition.[6]

Here we wish to report the macrocycle **1** (Figure 1, lower right), in which three pyridine and three benzyl alcohol units were alternatingly linked with acetylene bonds at their 2,6-positions. The target could be prepared by Sonogashira reaction between two kinds of trimeric precursors at the key cyclizing step.[6] The

three hydroxymethyl groups in **1** were expected to collaborate as a tripodal hydrogen-bonding module.[7] Indeed, halide anion recognition could be observed on the basis of ^{1}H NMR spectroscopy.[8]

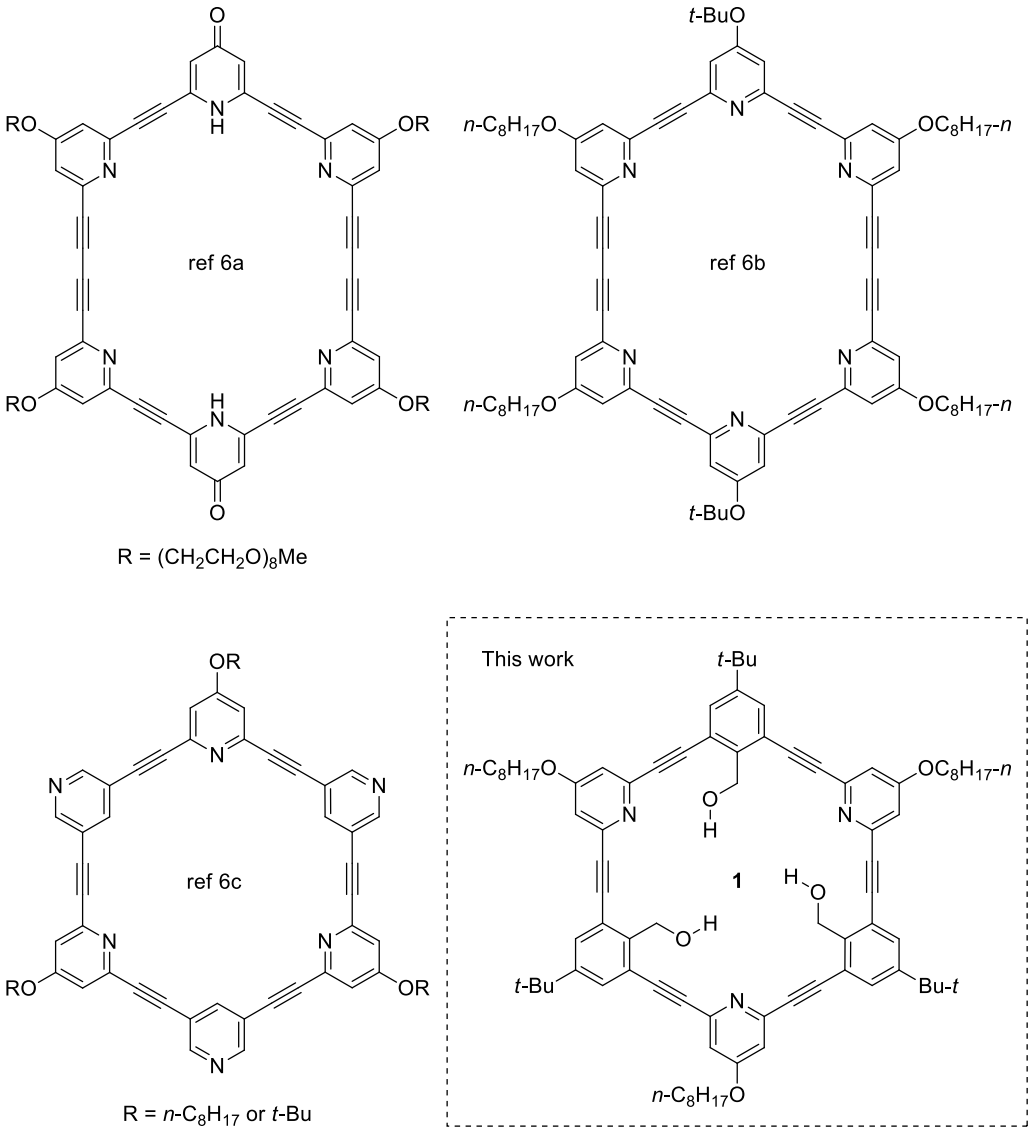
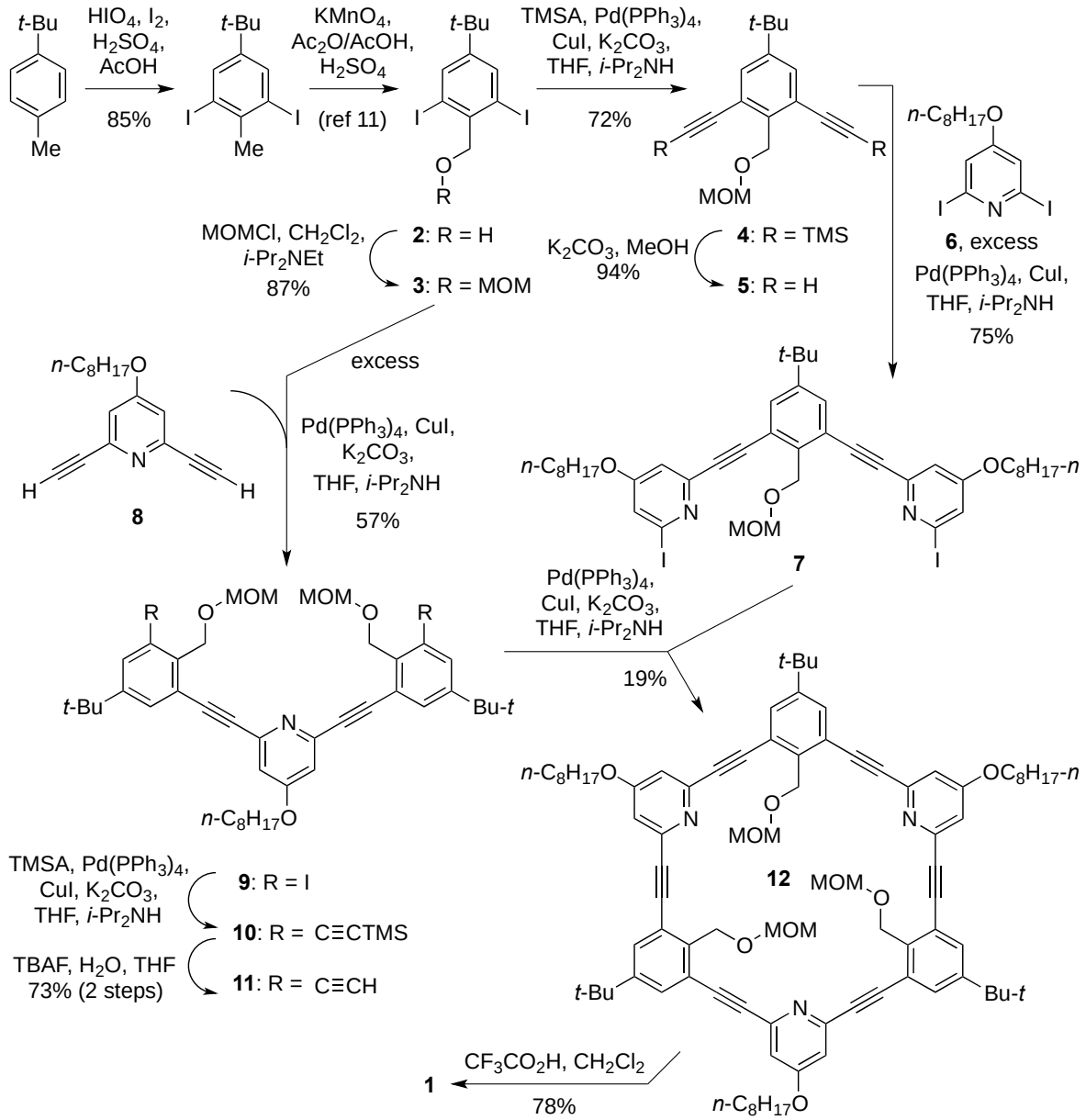


Figure 1. Our precedent macrocyclic host molecules[6] and target **1** developed herein.

RESULTS AND DISCUSSION

The synthetic route to **1** was shown in Scheme 1. In this preparation MOM-protection on OH groups is indispensable because Sonogashira reaction of MOM-free substrates caused side reactions to give a complex mixture.[9] From 1-*tert*-butyl-4-methylbenzene, 4-*tert*-butyl-2,6-diiodobenzyl alcohol (**2**) was prepared by the reported procedure via oxidative diiodination[10] followed by benzylic oxidation.[11] The alcohol **2** was converted to MOM ether **3** and Sonogashira reaction of **3** with two equivalent of trimethylsilylacetylene (TMSA) gave **4**, which was then treated with K_2CO_3 in MeOH to afford diyne **5**. Sonogashira reaction using the diyne **5** and an excess amount of 2,6-diiodo-4-(octyloxy)pyridine (**6**)[12]

furnished I-(pyridine)-(benzyl alcohol)-(pyridine)-I trimeric block **7**. On the other hand, I-(benzyl alcohol)-(pyridine)-(benzyl alcohol)-I trimeric block **9** was obtained by Sonogashira reaction of 2,6-diethynyl-4-(octyloxy)pyridine (**8**)[12] with an excess amount of diiodide **3**. The diiodide **9** was converted to HC≡C-(benzyl alcohol)-(pyridine)-(benzyl alcohol)-C≡CH **11** via TMS-protected intermediate **10** by Sonogashira reaction with two equivalent of TMSA followed by treatment with TBAF.



Scheme 1. Preparation of **1**. TMSA = trimethylsilylacetylene, TBAF = tetrabutylammonium fluoride.

Macrocyclization was carried out by tandem Sonogashira reaction between **7** and **11** to give hexameric SPM framework **12**, and finally its MOM groups were removed by treatment with trifluoroacetic acid to afford the target **1**. The ^{1}H NMR spectra of **7**, **11**, **12**, and **1** were shown in Figure 2.

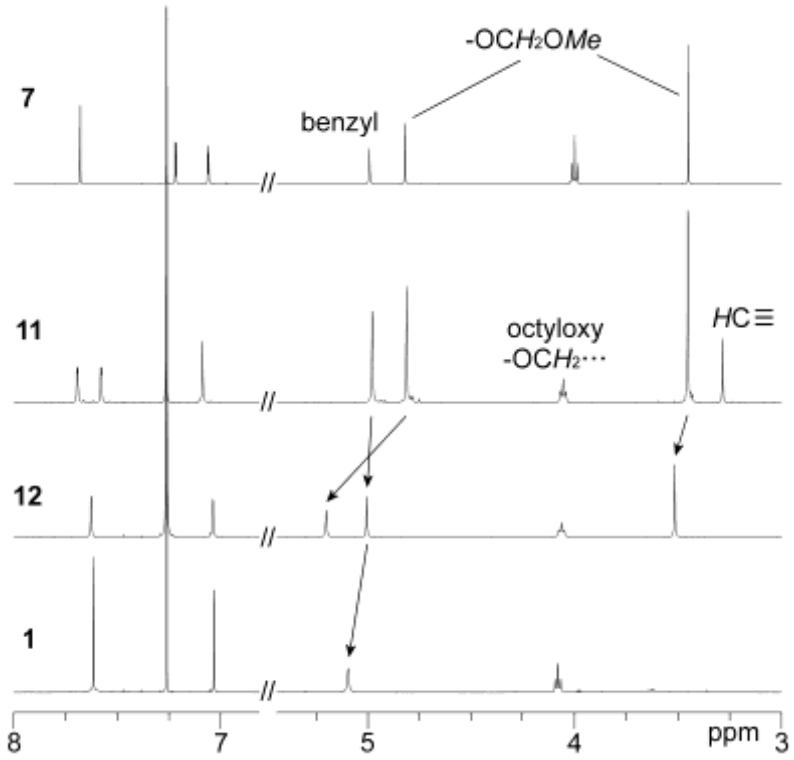


Figure 2. ^{1}H NMR spectra of cyclization precursors **7** and **11**, cyclized products **12** and **1**. Conditions: $CDCl_3$, 23 °C, 500 MHz

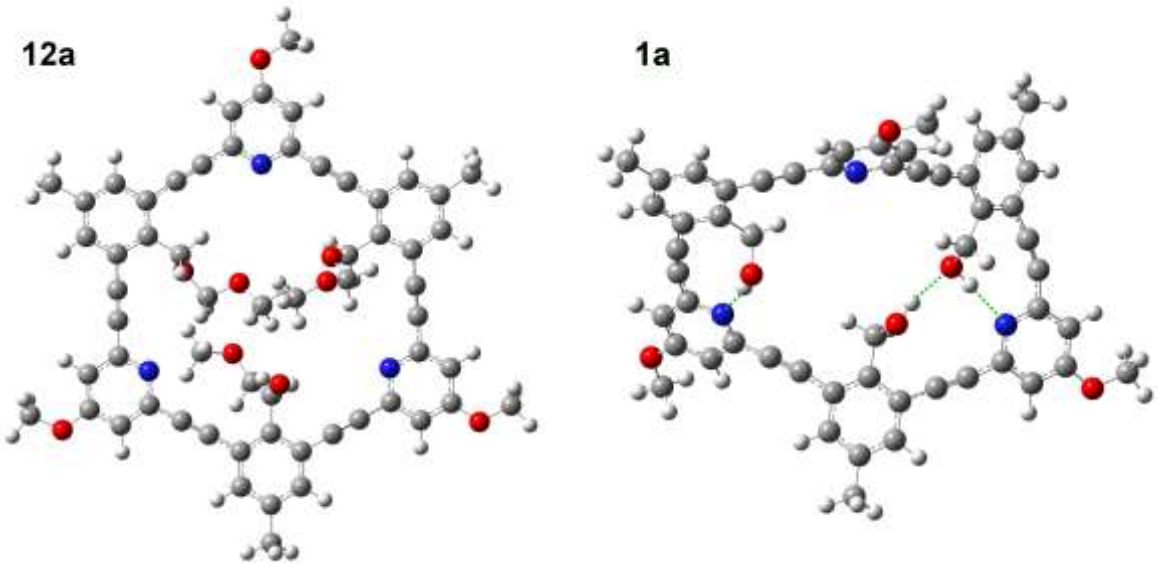


Figure 3. Optimized structures of model compounds (left) **12a** and (right) **1a** obtained by DFT calculation. Conditions: B3LYP/6-31G(d,p). In these model compounds, octyl and *tert*-butyl groups of **12** and **1** were simplified to methyl groups. Intramolecular hydrogen bonds in **1a** are represented as green dotted lines.

After cyclization, the ^{1}H NMR signal of MOM-methylene protons of **12** moved downfield due to proximity with negative atoms in pyridine and other MOM groups. It is supported by the molecular model by DFT calculation by using model compounds **12a** (Figure 3, left). On the other hand, the signals of benzylic protons did not shift so much after the cyclization.[13] Only two aromatic singlets were observed in both cases of **12** and **1**, reflecting their high symmetry.

The DFT optimization of the model **1a** showed unexpected distortion by intramolecular hydrogen bonding (Figure 3, right). This distortion may hinder π-stacking assembly by loss of planarity and may retard guest recognition by competition in hydrogen-bonding interaction. Actually, self-association and guest recognition ability of **1** were not so significant as our previous SPM hosts in Figure 1 as follows. On the basis of the concentration dependence of **1** on its UV-vis spectra, no meaningful deviation from Beer's law could be observed for the solutions of **1** in CH_2Cl_2 at the concentration range from 1.0×10^{-3} to 1.0×10^{-5} M. Simplicity of the NMR spectrum of **1** may reflect the equilibrium among distorted conformers faster than NMR time scale.

When **1** was treated with octyl β-D-glucopyranoside in CH_2Cl_2, UV-vis and CD spectra showed no meaningful additive effect. The ^{1}H NMR spectrum of that glucoside in $CDCl_3$ showed subtle downfield shift for O*H* ($\Delta\delta = 0.06 \sim 0.15$ ppm) and upfield shift for 1-C*H* proton ($\Delta\delta = 0.009$ ppm) by the addition to **1**. Other kinds of hydrogen-bonding molecules such as octyl β-D-galactopyranoside, methyl β-D-ribofranoside, acetic acid, isobutyric acid, tetraethylenepentamine, and triazine were attempted to associate with **1**, however, ^{1}H NMR studies in $CDCl_3$ showed no positive results.

After the trial and error, it was found that **1** could interact with halide anions. When ^{1}H NMR spectra of **1** (5.0×10^{-4} M) in $CDCl_3$ in the presence and the absence of benzyltriethylammonium chloride (5.0×10^{-3} M) were compared, upfield shift was observed for signals of benzylic protons of **1** (Figure 4, ●). Other kinds of ammonium halides were also subjected, and the results were summarized in Table 1. Ionic hydrogen bonding could work between halide anion and hydroxy groups of **1** in the narrow room inside the host. The host-guest affinity was quantitatively evaluated by titration experiments. The association constants K_a between **1** and benzyltriethylammonium chloride and bromide were determined to be 1.9×10^2 M^{-1} and 1.2×10^2 M^{-1}, respectively, by ^{1}H NMR titration experiments observing benzylic protons at 23 °C.

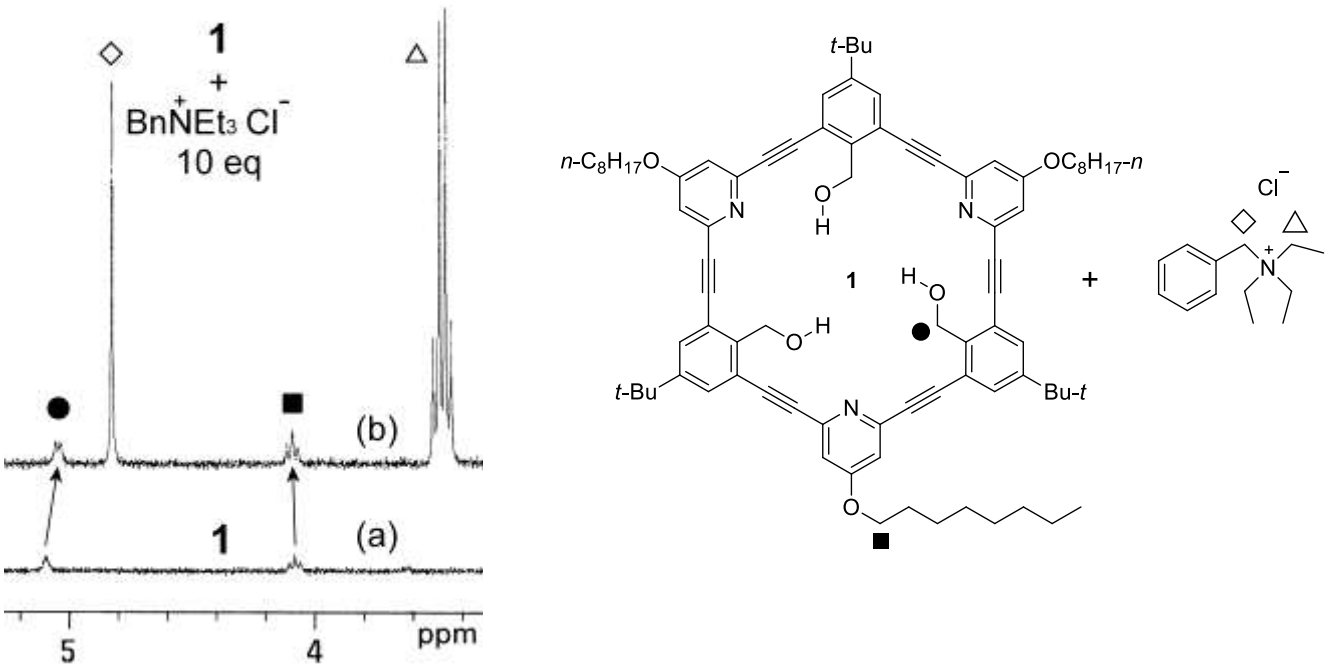
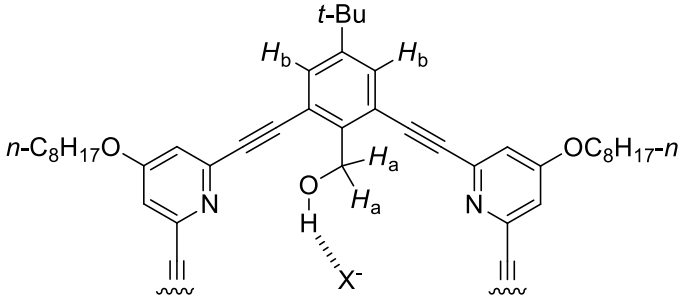


Figure 4. ^{1}H NMR signals for methylene groups of (a) **1**, (b) a mixture of **1** and benzyltriethylammonium chloride. The symbols indicate the assignment. Conditions: **1** (5.0×10^{-4} M), benzyltriethylammonium chloride (5.0×10^{-3} M), $CDCl_3$, 23 °C, 300 MHz.

Table 1. Chemical shift changes induced by host-guest association of **1** and ammonium halides



			δ and $\Delta\delta$ observed (ppm) $\Delta\delta = \delta(\mathbf{1}\cdot X^{-1}) - \delta(\mathbf{1})$				
protons at benzyl alcohol units of **1**		without guest	$BnEt_3N^+\cdot X^-$		$Bu_4N^+\cdot X^-$		
			Cl	Br	F	Cl	Br
benzyl (H_a)	δ	5.095	5.046	5.051	5.086	5.080	5.086
	$\Delta\delta$		−0.049	−0.044	−0.009	−0.015	−0.009
aromatic (H_b)	δ	7.029	7.045	7.047	7.036	7.041	7.036
	$\Delta\delta$		+0.016	+0.018	+0.007	+0.012	+0.007

Conditions: **1** (5.0×10^{-4} M), ammonium halide (5.0×10^{-3} M), $CDCl_3$, 23 °C, 300 MHz.

Judging from Table 1 and the association constants, the affinity of halide anions with **1** seems to be in the order of $Cl^- > Br^- \sim F^-$, although hydrogen bonding of OH with F^- is generally stronger than that with Cl^- and Br^-.[14] This curiosity could be rationalized by DFT calculation using model compound **1a** (Figure 5). When the structures of complexes **1a**·Cl^- and **1a**·Br^- were optimized, the macrocyclic framework was planar (Figure 5, left), and the strength of anionic hydrogen bonding would be reflected to the affinity. On the other hand, F^- was so small to form three hydrogen bonds that the framework of **1a**·F^- has to distort like a boat conformation (Figure 5, right). Actually the additive effect of Bu_4N^+·F^- on the ^1H NMR spectrum was weak to suggest that the contribution of associate was little. Benzyltriethylammonium halide salts gave bigger anisotropy than tetrabutylammonium halide salts, therefore ammonium cation would still affects on **1a**·X^- by some kinds of electrostatic interaction.

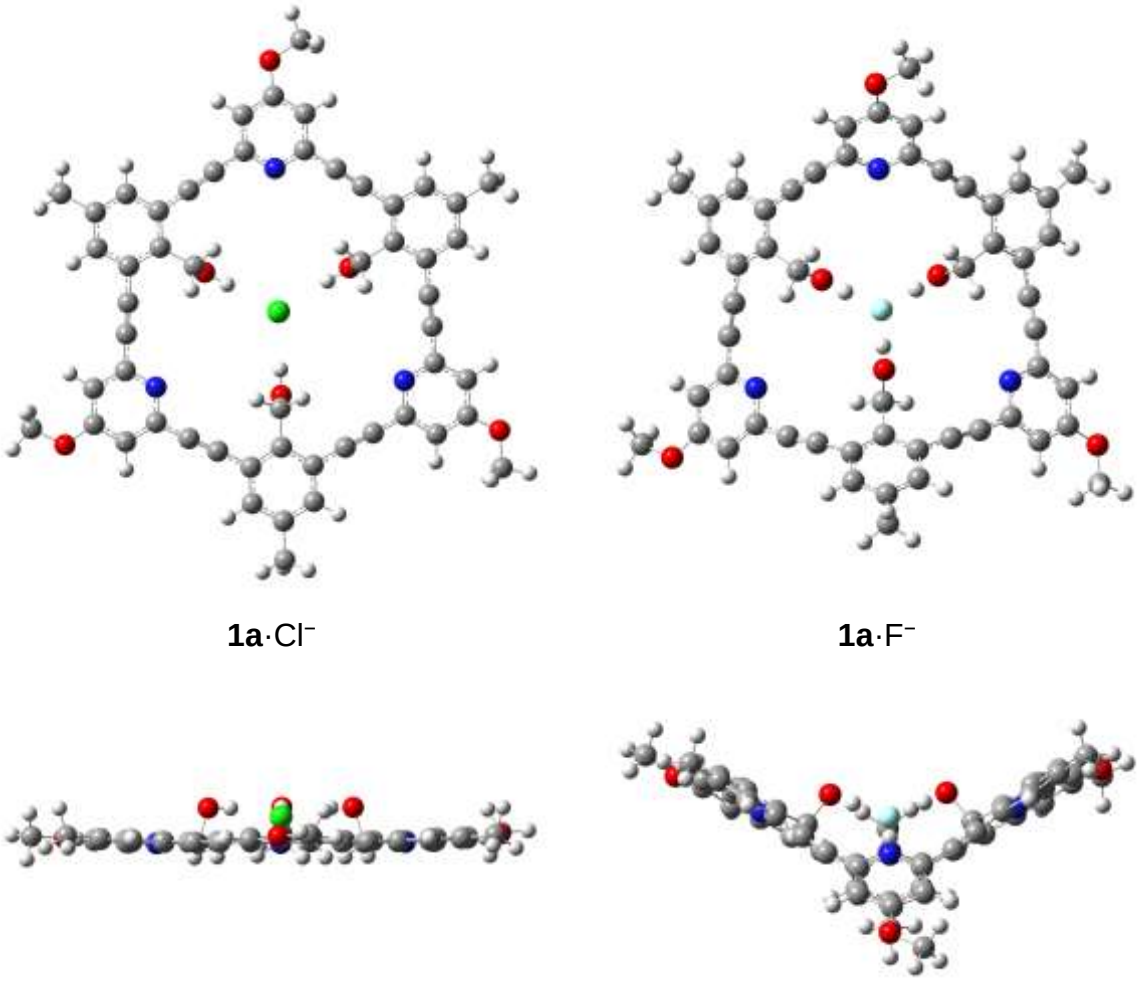


Figure 5. Structures of complexes of model compound **1a** with (left) Cl^- and (right) F^- from top and side views predicted by DFT calculation. Conditions: B3LYP/6-31G. The distances between H and Cl were 2.271~2.281 Å and those between H and F were 1.566~1.578 Å. Taking the smaller perturbation on ^1H NMR into account, contribution of fluoride complex shown here would be little.

In summary, we developed a D_{3h}-symmetric macrocyclic host molecule bearing three pyridine and three benzyl alcohol units which were linked with acetylene bonds. The scaffold was built by several steps of Sonogashira reaction in that MOM-protection worked well to avoid side reaction. Host-guest association was studied on the basis of ^{1}H NMR, and halide anions, especially chloride were found to interact with the host. Hydrogen-bonding organic compounds such as glycosides could not be recognized efficiently, probably because the room inside the host **1** was too small to accommodate guest organic molecules and the recognition was in competition with intramolecular hydrogen bonding.

EXPERIMENTAL

General. ^{1}H and ^{13}C NMR spectra were recorded on JEOL ECA500II and Varian Gemini300 spectrometers with tetramethylsilane as an internal reference. ESI-TOF-HRMS analyses of analyte solutions in MeOH were carried out with a JEOL JMS-T100LC mass spectrometer. IR spectra were measured with a JASCO FT/IR-460plus spectrometer. Melting points were measured with a Yanaco MP-500D apparatus and are uncorrected. All reactions were carried out under an argon atmosphere. THF was freshly distilled from a solution of sodium benzophenone ketyl radical before use.

Starting Materials. 2,6-Diiodo-4-(octyloxy)pyridine[12] (**6**) and 2,6-diethynyl-4-(octyloxy)pyridine[12] (**8**) were prepared according to the reported procedures.

5-*tert*-Butyl-1,3-diiodo-2-methylbenzene. This compound was prepared by Suzuki's iodination procedure.[10] To a mixture of 4-*tert*-butylmethylbenzene (17.2 g, 116 mmol), $HIO_4 \cdot 2H_2O$ (17.4 g, 76 mmol), and I_2 (38.4 g, 151 mmol) was added H_2O (27 mL), AcOH (130 mL), and H_2SO_4 (4 mL) subsequently. The mixture was stirred at 70 °C for 68 h and after cooling, diluted with H_2O (250 mL), and extracted with Et_2O (100 mL). The Et_2O layer was washed with 10% NaOH (100 mL) and 10% $NaHSO_3$ (100 mL) subsequently, dried over Na_2SO_4, and concentrated by a rotary evaporator. The residue was subjected to silica gel column chromatography to give 5-*tert*-butyl-1,3-diiodo-2-methylbenzene as a dilute brown oil (40 g, 85%), of which ^{1}H NMR spectrum agreed with the literature data.[15] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (s, 2 H), 2.71 (s, 3 H), 1.26 (s, 9 H).

5-*tert*-Butyl-1,3-diiodo-2-(methoxymethoxymethyl)benzene (3). A solution of 5-*tert*-butyl-1,3-diiodo-2-(hydroxymethyl)benzene[11] (**2**) (12.5 g, 30 mmol) in CH_2Cl_2 (90 mL, dried with $MgSO_4$ before use) was cooled with an ice bath, and *i*-Pr_2NEt (20.5 mL) was added to this solution at 0 °C. Chloromethyl methyl ether (12.1 g, 150 mmol) were subsequently added to this solution slowly at 0 °C, and the mixture was stirred for 20 min at that temperature, and then treated with saturated $NaHCO_3$ aqueous solution (250 mL). The organic layer was dried over Na_2SO_4 and concentrated by rotary evaporator, and the residue was purified by silica gel column chromatography (eluent: hexane/AcOEt = 20:1) to afford **3** (12.0 g, 87%) as a dilute yellow oil. IR (KBr) ν 2962, 2878, 1579, 1513, 1383, 1149,

1102, 1052, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.85 (s, 2 H), 4.91 (s, 2 H), 4.80 (s, 2 H), 3.52 (s, 3 H), 1.27 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.2, 138.3, 137.7, 100.4, 96.8, 78.7, 56.0, 34.3, 31.0; HRMS (ESI-TOF) *m*/*z* calcd for $C_{13}H_{18}NaI_2O_2$ ($[M + Na]^+$): 482.9294; found: 482.9111.

5-*tert*-Butyl-2-(methoxymethoxymethyl)-1,3-bis(trimethylsilylethynyl)benzene (4). A solution of diiodide **3** (68 mg, 0.15 mmol) in *i*-Pr_2NH (10 mL) was bubbled with argon, and to this solution were added $Pd(PPh_3)_4$ (9.6 mg, 0.0083 mmol), CuI (0.79 mg, 0.0042 mmol), and K_2CO_3 (170 mg, 1.3 mmol). The mixture was stirred for 1 h at room temperature, and trimethylsilylacetylene (TMSA) (120 mg, 1.25 mmol) was added to the mixture. After stirring for 18 h at room temperature, and the reaction mixture was diluted with Et_2O (10 mL), and filtered. The filtrate was concentrated by a rotary evepolator, and subjected to silica gel column chromatography (eluent: CH_2Cl_2/hexane = 1:3) to give **4** (43 mg, 72%) as a colorless oil. IR (KBr) ν 2960, 2900, 2879, 2151, 1590, 1400, 1250, 1151, 1106, 1061, 1043 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.48 (s, 2 H), 4.84 (s, 2 H), 4.78 (s, 2 H), 3.46 (s, 3 H), 1.28 (s, 9 H), 0.26 (s, 18 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.1, 138.2, 130.3, 124.1, 103.2, 97.6, 97.0, 66.5, 55.1, 34.5, 31.0, −0.1; HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{36}NaO_2Si_2$ ($[M + Na]^+$): 423.2152; found: 423.2173.

5-*tert*-Butyl-1,3-diethynyl-2-(methoxymethoxymethyl)benzene (5). A mixture of **4** (30 mg) and K_2CO_3 (100 mg) in MeOH (10 mL) was stirred for 30 min at room temperature. The resulting mixture was filtered and the filtrate was concentrated by a rotary evaporator and subjected to silica gel column chromatography (eluent: CH_2Cl_2/hexane = 2:1 to 3:2) to give **5** (18 mg, 94%) as a colorless oil. IR (KBr) ν 3289, 2957, 2883, 2105, 1590, 1398, 1150, 1105, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.55 (s, 2 H), 4.89 (s, 2 H), 4.77 (s, 2 H), 3.45 (s, 3 H), 3.26 (s, 2 H), 1.30 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.3, 138.6, 130.9, 123.3, 96.6, 81.7, 80.5, 65.8, 55.4, 34.5, 30.9; HRMS (ESI-TOF) *m*/*z* calcd for $C_{17}H_{20}NaO_2$ ($[M + Na]^+$): 279.1361; found: 279.1336.

5-*tert*-Butyl-1,3-bis(6-iodo-4-octyloxy-2-pyridylethynyl)-2-(methoxymethoxymethyl)benzene ("I-(pyridine)-(benzyl alcohol)-(pyridine)-I", 7). A mixture of THF (30 mL) and *i*-Pr_2NH (30 mL) was bubbled with argon for 30 min, and 20 mL of this mixture was put aside. Subsequently 2,6-diiodo-4-(octyloxy)pyridine[12] (**6**, 3.7 g, 8.2 mmol), $Pd(PPh_3)_4$ (69 mg, 0.059 mmol), CuI (5.7 mg, 0.030 mmol), and K_2CO_3 (0.82 g, 5.9 mmol) were added to the mixed solvent, and diyne **5** (0.38 g, 1.48 mmol) was added into it slowly with the reserved THF/*i*-$PrNH_2$ solvent. The mixture was stirred under reflux for 5 h, and diluted with CH_2Cl_2 (120 mL), and filtered through a celite bed to remove insoluble materials. The filtrate was concentrated with a rotary evaporator and subjected to silica gel column chromatography (eluent: CH_2Cl_2) to give **7** (1.0 g, 75%) as a pale yellow solid. Mp 85−86 °C; IR (KBr) ν 2951, 2927, 2855, 2218, 1578, 1531 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.68 (s, 2 H), 7.22 (d, J = 2.3 Hz, 2 H), 7.06 (d, J = 2.3 Hz, 2 H), 4.99 (s, 2 H), 4.82 (s, 2 H), 4.00 (t, J = 6.3 Hz, 4 H), 3.45 (s, 3 H),

1.82−1.76 (m, 4 H), 1.46−1.43 (m, 4 H), 1.34−1.25 (m, 25 H), 0.89 (t, J = 7.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.0, 151.6, 144.3, 138.5, 131.3, 123.2, 120.6, 117.8, 114.3, 96.5, 90.8, 88.1, 68.7, 65.8, 55.4, 34.7, 31.8, 31.0, 29.21, 29.17, 28.7, 25.8, 22.6, 14.1; HRMS (ESI-TOF) m/z calcd for $C_{43}H_{56}NaI_2N_2O_4$ ($[M + Na]^+$): 941.2227; found: 941.2252.

2,6-Bis{[5-*tert*-butyl-3-iodo-2-(methoxymethoxymethyl)phenyl]ethynyl}-4-(octyloxy)pyridine ("I-(benzyl alcohol)-(pyridine)-(benzyl alcohol)-I", 9). To mixed solvent of THF (10 mL) and *i*-Pr_2NH (5 mL) (bubbled with argon for 1 h before use) diiodide **3** (180 mg, 0.39 mmol), $Pd(PPh_3)_4$ (3.7 mg, 3.2 μmol), CuI (0.30 mg, 1.6 μmol), and K_2CO_3 (55 mg, 0.40 mmol) were added and the mixture was stirred for 1 h at room temperature. To this mixture 2,6-diethynyl-4-(octyloxy)pyridine[12] (**8**, 20 mg, 0.080 mmol) was added, and the mixture was stirred for 15 h at room temperature. The resulting mixture was diluted with Et_2O (20 mL) and filtered. The filtrate was concentrated by a rotary evepolator, and subjected to silica gel column chromatography (eluent: CH_2Cl_2/hexane = 1:1 to CH_2Cl_2) to give **9** (42 mg, 57%) as a dilute yellow oil. IR (KBr) ν 2956, 2929, 2876, 2218, 1580, 1551 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89 (d, J = 1.7 Hz, 2 H), 7.67 (d, J = 1.7 Hz, 2 H), 7.09 (s, 2 H), 4.95 (s, 4 H), 4.82 (s, 4 H), 4.05 (t, J = 6.3 Hz, 2 H), 3.48 (s, 6 H), 1.84−1.81 (m, 2 H), 1.49−1.46 (m, 2 H), 1.36−1.26 (m, 26 H), 0.90 (t, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.4, 153.2, 144.6, 138.6, 138.2, 130.6, 123.7, 113.6, 101.7, 96.5, 91.7, 87.3, 71.5, 68.5, 55.7, 34.6, 31.8, 31.0, 29.3, 29.2, 28.8, 25.9, 22.7, 14.1; HRMS (ESI-TOF) m/z calcd for $C_{43}H_{55}NaI_2NO_5$ ($[M + Na]^+$): 942.2067; found: 942.2088.

2,6-Bis{[5-*tert*-butyl-2-(methoxymethoxymethyl)-3-(trimethylsilylethynyl)phenyl]ethynyl}-4-(octyloxy)pyridine ("TMS-C≡C-(benzyl alcohol)-(pyridine)-(benzyl alcohol)-C≡C-TMS", 10). A mixture of THF (100 mL) and *i*-Pr_2NH (100 mL) was bubbled with argon, and to this mixed solvent were added **9** (3.0 g, 3.3 mmol), $Pd(PPh_3)_4$ (0.15 g, 0.13 mmol), CuI (0.012 g, 0.065 mmol), and K_2CO_3 (1.8 g, 13 mmol). Trimethylsilylacetylene (TMSA) (1.9 g, 19 mmol) was added slowly to the mixture, which was stirred for 11 h at 80 °C. The reaction mixture was diluted with Et_2O (500 mL) and filtered through a celite bed. The filtrate was concentrated by a rotary evepolator, and the residue was crude product of **10**, which was brought to the next step without further purification.

2,6-Bis{[5-*tert*-butyl-3-ethynyl-2-(methoxymethoxymethyl)phenyl]ethynyl}-4-(octyloxy)pyridine ("HC≡C-(benzyl alcohol)-(pyridine)-(benzyl alcohol)-C≡CH", 11). A mixture of **10** (2.8 g, 3.2 mmol, crude product), tetrabutylammonium fluoride (TBAF) (1.0 M in THF solution, 2.7 mL, 2.7 mmol), THF (15 mL), and two drops of water was stirred for 5 min at room temperature. The resulting mixture was concentrated by a rotary evaporator and the residue was subjected to silica gel column chromatography (eluent: CH_2Cl_2) to give **11** (1.7 g, 73% from **9**) as a dilute yellow oil. IR (KBr) ν 3289, 2955, 2928, 2875, 2218, 1581, 1552 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 (d, J = 1.7 Hz, 2 H), 7.58 (d, J = 1.7 Hz, 2 H),

7.09 (s, 2 H), 4.98 (s, 4 H), 4.81 (s, 4 H), 4.06 (t, J = 6.3 Hz, 2 H), 3.45 (s, 6 H), 3.29 (s, 2 H), 1.84−1.81 (m, 2 H), 1.50−1.45 (m, 2 H), 1.40−1.29 (m, 26 H), 0.90 (t, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.5, 144.6, 141.0, 138.5, 131.2, 131.1, 123.4, 113.5, 96.5, 91.5, 87.2, 81.8, 80.7, 68.5, 65.7, 55.4, 34.6, 31.8, 31.0, 29.3, 29.2, 28.8, 25.9, 22.7, 14.1; HRMS (ESI-TOF) m/z calcd for $C_{47}H_{57}NaNO_5$ ($[M + Na]^+$): 738.4134; found: 738.4091.

MOM-protected pyridine-benzyl alcohol macrocyclic compound 12. A mixture of THF (311 mL) and i-Pr_2NH (311 mL) was bubbled with argon for 1 h, and 80 mL of this mixture was put aside. Diiodide **7** (0.29 g, 0.31 mmol), $Pd(PPh_3)_4$ (14 mg, 0.012 mmol), CuI (1.2 mg, 0.0062 mmol), and K_2CO_3 (0.17 g, 12 mmol) were added to the mixture, and diyne **11** (0.22 g, 0.31 mmol) was added into it slowly with the reserved THF/i-$PrNH_2$ (80 mL) solvent. The mixture was stirred under reflux for 47 h, and diluted with CH_2Cl_2 (500 mL), and filtered through a celite bed. The filtrate was concentrated by a rotary evepolator, and subjected to silica gel column chromatography (eluent: CH_2Cl_2 to hexane/AcOEt = 10:1) to give **12** (83 mg, 19%) as a colorless solid. Mp 131−132 °C; IR (KBr) ν 2954, 2926, 2855, 2217, 1581, 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (s, 6 H), 7.04 (s, 6 H), 5.20 (s, 6 H), 5.01 (s, 6 H), 4.06 (t, J = 6.3 Hz, 6 H), 3.52 (s, 9 H), 1.84−1.81 (m, 6 H), 1.50−1.45 (m, 6 H), 1.40−1.29 (m, 51 H), 0.90 (t, J = 7.0 Hz, 9 H); HRMS (ESI-TOF) m/z calcd for $C_{90}H_{111}NaN_3O_9$ ($[M + Na]^+$): 1400.8218; found: 1400.8263.

Pyridine-benzyl alcohol macrocyclic compound 1. A solution of MOM ether **12** (24 mg, 0.017 mmol) in CH_2Cl_2 (1 mL) was treated with trifluoroacetic acid (1 mL) by stirring for 6.5 h at room temperature. The resulting mixture was neutralized with an excess amount of saturated aqueous $NaHCO_3$, and the CH_2Cl_2 layer was dried over Na_2SO_4 and concentrated by a rotary evaporator. The resulting residue was subjected to silica gel column chromatography (eluent: CH_2Cl_2 to hexane/AcOEt/CH_2Cl_2 = 6:1:2) to give **1** (17 mg, 78%) as a colorless solid. Mp 125−127 °C; IR (KBr) ν 3239, 2954, 2926, 2855, 2221, 1585, 1552 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (s, 6 H), 7.03 (s, 6 H), 5.09 (s, 6 H), 4.08 (t, J = 6.6 Hz, 6 H), 1.85−1.82 (m, 6 H), 1.49−1.44 (m, 6 H), 1.38−1.28 (m, 51 H), 0.89 (t, J = 6.9 Hz, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.2, 158.6, 144.0, 143.4, 130.8, 122.9, 112.6, 90.7, 87.9, 68.7, 34.6, 31.8, 31.1, 29.23, 29.20, 28.8, 25.4, 22.7, 14.1; HRMS (ESI-TOF) m/z calcd for $C_{84}H_{99}KN_3O_6$ ($[M + K]^+$): 1284.7171; found: 1284.6827.

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