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Selective Binding of D_{2h}-Symmetrical, Acetylene-Linked Pyridine/Pyridone Macrocycles to Maltoside

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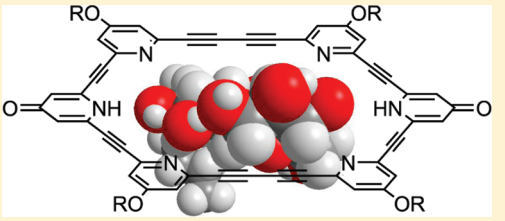
Supporting Information

ABSTRACT: A macrocyclic host molecule having pyridine−pyridone−pyridine modules for saccharide recognition was prepared by Cu(II)-mediated oxidative homocoupling of a tandem diethynyl precursor. In CH_2Cl_2, the host molecule associated with dodecyl β-maltoside much more strongly (K_a = 1.4 × 10^6 M^{-1}) than with octyl monohexosides (K_a = ca. 2 × 10^3 to 1 × 10^4 M^{-1}), accompanied with induced CDs. An all-pyridine macrocyclic host was also studied, and its binding strength with saccharides was weaker than that for the pyridine−pyridone−pyridine host.



INTRODUCTION

Macrocyclic structures with multiple hydrogen-bonding sites are efficient for constructing artificial host molecules as represented by crown ethers and calixarenes.[1] Preorganization and rigidity of macrocyclic host molecules, which reduce the entropic disadvantages upon host−guest association, produce potent host molecules. Also for saccharide recognition,[2−4] several types of sophisticated macrocyclic host molecules have been developed.[4] During the course of our study on artificial host molecules for saccharide recognition,[5,6] the acetylene-linked trimeric pyridine module in **1** and the pyridine−4(1*H*)-pyridone−pyridine module in **2** were found to be an effective module for monosaccharide recognition (Figure 1).[6] When the hydrogen bond donor and acceptor were illustrated as D and A, respectively, the former module is A−A−A-type and the latter is A−D−A-type. Selectivity for hexose, ribose, and 2-deoxyribose was realized by proper choice of these modules' built-in macrocyclic frameworks.[6a−c]

Because of electrostatic interactions, the A−D−A-type module prefers cisoid conformation.[6d] The cisoid preference seemed to be favorite to prepare D_{2h}-symmetrical monoacetylenic $(A−D−A)_2$ macrocycles[7] such as **3** (Figure 2), in which two A−D−A modules are expected to work cooperatively. However, so far we have failed to apply Sonogashira reaction to any-type precursors for the macrocyclization probably due to strong electrowithdrawing property of the pyridone ring. In this paper, we report an alternative route to a diacetylenic $(A−D−A)_2$ macrocycle **4** by utilizing oxidative homocoupling mediated by a copper(II) salt[8] for the tandem acetylene precursor **5** (Scheme 1). Our group has found that short acyclic $A−(D−A)_n−D−A$ (n = 1−4) oligomers could associate with saccharides,[6d] and more strong and selective recognition was expected to **4**. Copper(II)-mediated oxidative homocoupling was effective also for the preparation of an $(A−A−A)_2$-type macrocycle (**13**, see below) as reported previously.[9]

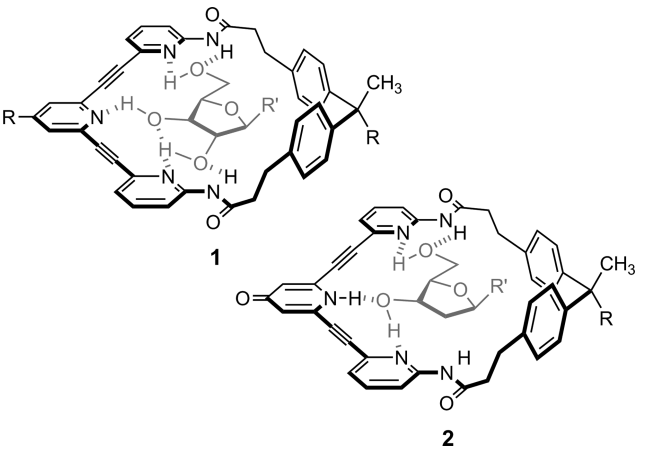


Figure 1. Macrocyclic host molecules **1** (A−A−A-type) and **2** (A−D−A-type).

RESULTS AND DISCUSSION

Preparation of Macrocyclic Host 4. The macrocyclic $(A−D−A)_2$ host **4** was prepared as shown in Scheme 2. Commercially available 2,6-dibromopyridine **6** was derivatized to 2,6-diethynyl-4-(methoxymethyl)pyridine **7**[6d] and an amphiphilic 2,6-diiodopyridine derivative **8**[5c] by reported procedures. Because 4-pyridinol is a tautomer of 4(1*H*)-pyridone, the MOM-protected 4-pyridinol **7** corresponds to a MOM-protected 4(1*H*)-pyridone block. Diyne **7** was subjected to Sonogashira reaction with an excess amount of **8** to yield a trimeric diiodide **9**, which was then coupled with (*tert*-butyldimethylsilyl)acetylene to **10**. Finally, two-step deprotection by treatment with tetrabutylammonium fluoride (TBAF) and trifluoroacetic acid (TFA) subsequently yielded the tandem precursor **5**. The oxidative dimerization of **5**

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to **4** was carried out according to Eglinton procedure using copper(II) acetate in a pyridine solution. Opposite to the case of preparation of the corresponding all-pyridine-type macrocycles,[9] macrocyclic products of bigger sizes were not detected. It is probably because cisoid conformation is stabilized in the pyridine-pyridone-pyridine alternate trimer **5** due to local dipole moments of rings, in contrast to a pyridine-pyridine-pyridine substrate that prefers a transoid conformation.[6d]

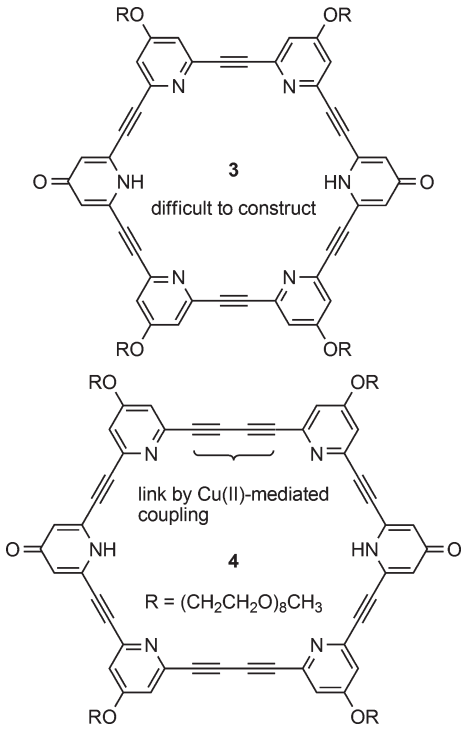
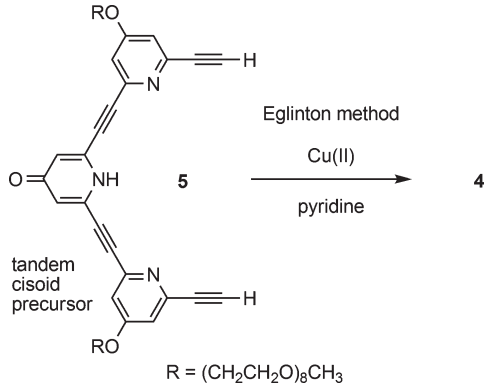


Figure 2. Design of D_{2h}-symmetrical $(A-D-A)_2$ macrocycles.

Scheme 1. Eglinton Coupling to Prepare Macrocycle 4

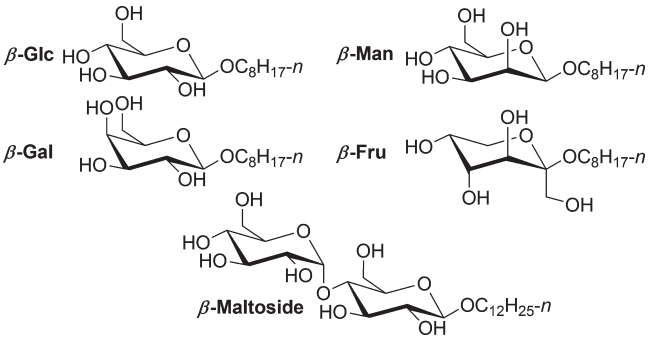


Saccharide Recognition by 4. The affinity of the macrocyclic host **4** with glycosides was studied by CD and UV−vis experiments. Four kinds of monosaccharides, octyl β-D-glucopyranoside (***β*-Glc**), octyl β-D-galactopyranoside (***β*-Gal**), octyl β-D-mannopyranoside (***β*-Man**), and octyl β-D-fructopyranoside (***β*-Fru**), and one disaccharide, dodecyl β-D-maltopyranoside (***β*-Maltoside**) were used as guest compounds (Chart 1). Disaccharide is represented by ***β*-Maltoside** because of its availability and solubility in organic solvents. When **4** was treated with the chiral glycosides in CH_2Cl_2, CD bands were induced around 350 nm as shown in Figure 3. These Cotton effects are attributed to the formation of chiral complexes of **4** with the chiral guests because **4** is achiral by itself and the guest glycosides do not absorb arround the wavelength. The achiral framework of **4** should distort in chiral way by the complexation.

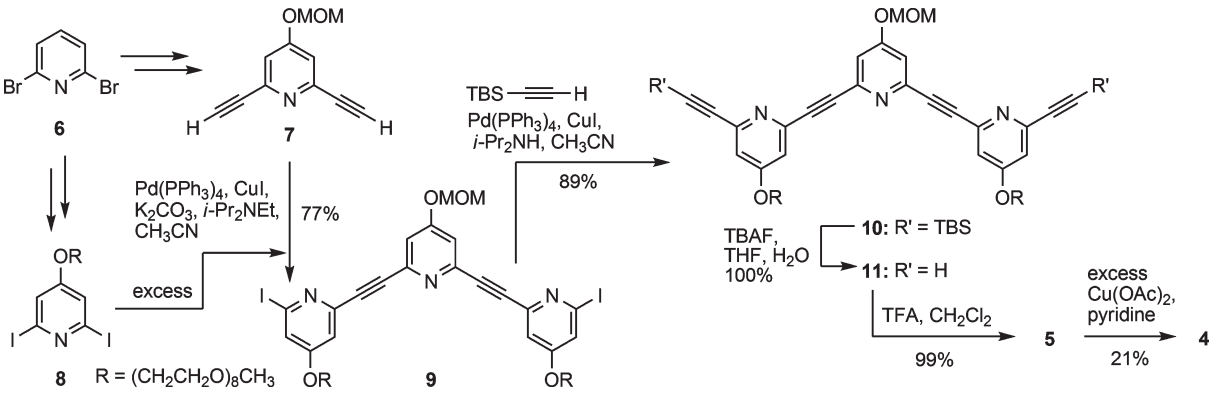
The self-aggregation tendency of **4** was studied on UV−vis spectroscopy for the CH_2Cl_2 solutions of varied concentration (3.0×10^{-4} to 5.0×10^{-7} M). The absorbance obeyed linearity (Figure S1, Supporting Information); therefore, the self-aggregation of **4** could be ignored at that concentration range.

CD and UV−vis titration experiments were carried out for **4** with ***β*-Glc**, ***β*-Gal**, ***β*-Man**, and ***β*-Maltoside** to quantitatively evaluate the host−guest associations (Figure 4 and Figure S2, Supporting Information). Figure 4 shows the changes of the CD and UV−vis spectra of **4** observed on these titration

Chart 1. Structures of Glycoside Guests



Scheme 2. Preparation of Macrocyclic $(A-D-A)_2$ Host 4



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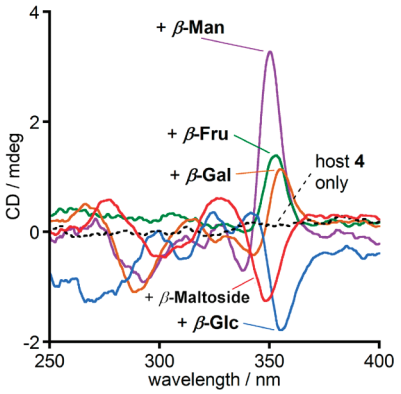

Figure 3. Induced CDs by the complexation of **4** with glycosides. Conditions: **4** (4.0×10^{-5} M), glycoside (2.0×10^{-4} M), CH_2Cl_2, 25 °C, path length = 1 mm.

experiments. Unfortunately, in some cases, the spectral changes were small because of the rigidity of the host, and the noise was not negligible. In other cases, the self-association of the glycoside guests might disturb the host–guest binding.[10] The titration curves were attempted to be fitted with 1:1 isotherms, and the binding strengths were evaluated as shown in Table 1. Among the glycoside guests examined, it was found that the UV–vis titration curve for ***β*-Maltoside** well fitted to a 1:1 isotherm (Figure 4I), and this disaccharide was much more strongly recognized by **4** than the monosaccharide guests.[11] The differences of ΔG values between (**4** and ***β*-Maltoside**) and (**4** and monosaccharides) are around 12–20 kJ mol^{-1}, which correspond to the energy of one or two hydrogen bonds between alcohol and pyridine-N or pyridone-NH.[12] This size selectivity was supposed to be due to size fitness of the pore inside **4** with the disaccharide guest. Monte Carlo simulation with a model compound **12** showed that maltoside can interact both of pyridone N–H by fitting into the pore, while monosaccharide is too small to do so (Figure 5, and Figure S3 in the Supporting Information). The host **4** has amphiphilic side chains so that it can dissolve in various solvents and even in water. In a polar solvent like acetonitrile, **4** showed a binding constant of $K_a = 1.8 \pm 0.6 \times 10^3$ with ***β*-Maltoside** (Table 1). However, unfortunately, no association has been detected with saccharides in a water solution by CD analyses.

To study the effect of the pyridone rings in **4**, all-pyridine $(A–A–A)_2$-type macrocyclic compound **13**[9] (Figure 6) was subjected to titration experiments (Figure 7, and Figure S4 in the Supporting Information). Table 1 shows the binding constants with glycosides, which are weaker by one or more orders of magnitude than those for **4**. Supported by the results of DFT calculations, these findings were rationalized as shown in Figure 8: (i) a pyridine–pyridone A–D module can catch one hydroxy group in a push–pull fashion as N···HO···HN, while a pyridine–pyridine A–A module cannot; (ii) a pyridine–pyridone module can also catch a diol in a push–pull fashion as N···HO···HO···HN. On the other hand, when a pyridine–pyridine module catches a diol, one OH hydrogen of the diol has to make two hydrogen bonds with N and O as N···HO···H···N. The predicted distances of hydrogen bonds between the pyridine–pyridone module and diol are shorter and stronger than those for the pyridine–pyridine module.

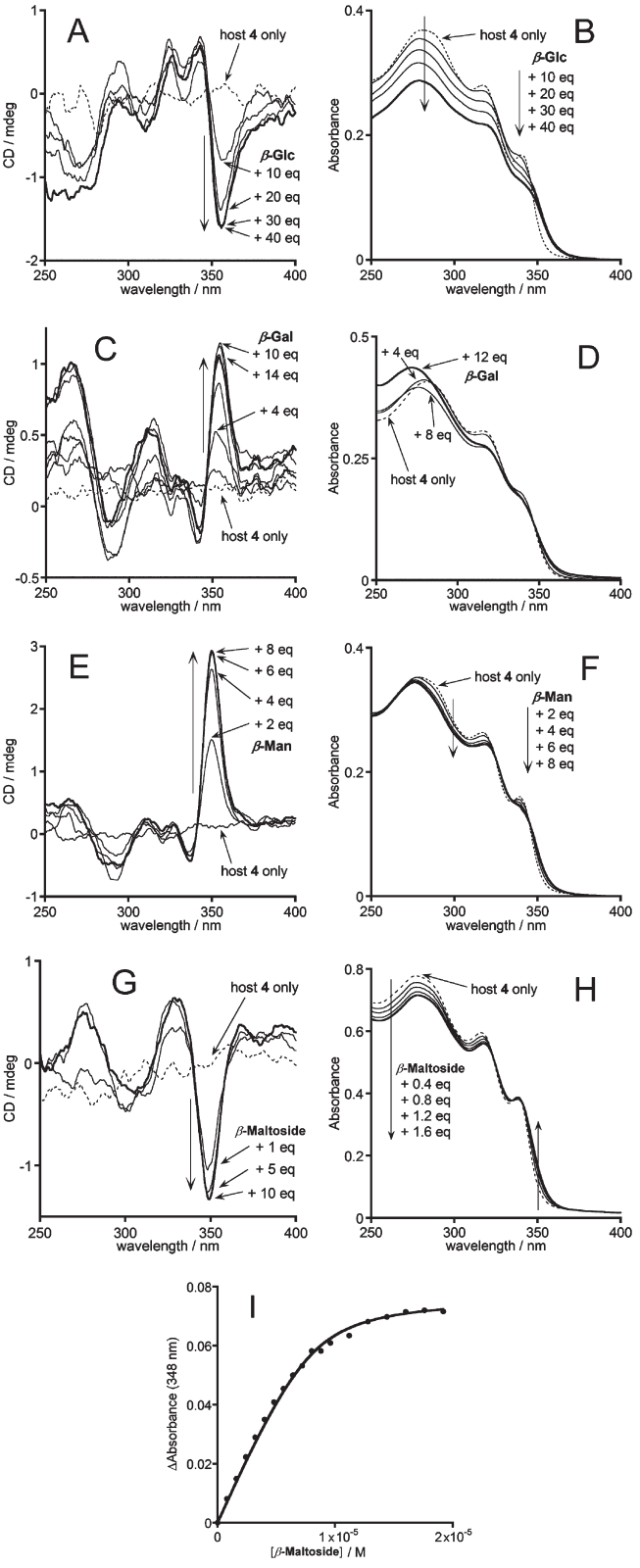

Figure 4. Changes of CD and UV–vis spectra of **4** induced by alkyl glycoside guests. Conditions: **4** (4.0×10^{-5} M (vs monosaccharides, path length = 1 mm) or 8.0×10^{-6} M (vs ***β*-Maltoside**, path length = 10 mm)), glycoside, CH_2Cl_2, 25 °C. (A) CD and (B) UV–vis spectra of **4** with ***β*-Glc**; (C) CD and (D) UV–vis spectra of **4** with ***β*-Gal**; (E) CD and (F) UV–vis spectra of **4** with ***β*-Man**; (G) CD and (H) UV–vis spectra of **4** with ***β*-Maltoside**; (I) A plot of absorbance at 348 nm vs [***β*-Maltoside**] fitted to a 1:1 isotherm.

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Table 1. Binding Strength of 4 and 13 with Guest Glycosides[a]

guest glycoside	binding with **4** K_a (M^{-1})	ΔG (kJ mol^{-1})	method	binding with **13** K_a (M^{-1})	ΔG (kJ mol^{-1})	method
monosaccharides						
***β*-Glc**	ca. 2×10^3 [c]	−18	CD	$1.8 \pm 0.2 \times 10^2$	-12.6 ± 0.4	UV−vis
***β*-Gal**	ca. 7×10^3 [c]	−22	CD	$5.8 \pm 1.9 \times 10^1$	-9.9 ± 0.9	UV−vis
***β*-Man**	ca. 1×10^4 [d]	−23	CD	ca. 3×10^2 [d]	−14	CD
disaccharide						
***β*-Maltoside**	$1.4 \pm 0.3 \times 10^6$ [b]	-35.1 ± 0.1	UV−vis	ca. 3×10^4 [b,d]	−26	CD
	$1.8 \pm 0.6 \times 10^3$ [b,e]	-18.4 ± 0.1	UV−vis			

[a] Conditions: **4** (4.0×10^{-5} M) or **13** (4.0×10^{-5} M), glycoside, CH_2Cl_2, 25 °C. [b] Concentration of **4** or **13** was 8.0×10^{-6} M. [c] Values roughly estimated from tentative curve-fitting to a 1:1 isotherm. The spectral changes were small and the influence of the noise was not negligible. [d] Values roughly estimated from tentative curve-fitting to a 1:1 isotherm. Host−guest binding was disturbed by self-association of the glycoside guests. [e] CH_3CN was used as a solvent.

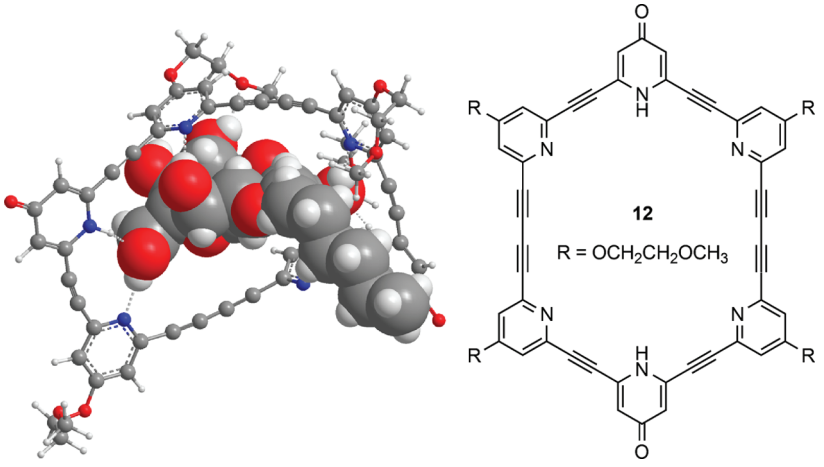

Figure 5. Structures of host−guest complexes obtained by Monte Carlo simulation. Macrocyclic model compound **12** was associated with hexyl *β*-D-maltoside. Two pyridone−pyridine moieties bind with two OH groups by a push−pull fashion as N···HO···HN. Conditions: OPLS2005 in $CHCl_3$. For the views from the different directions, see Figure S3A in the Supporting Information.

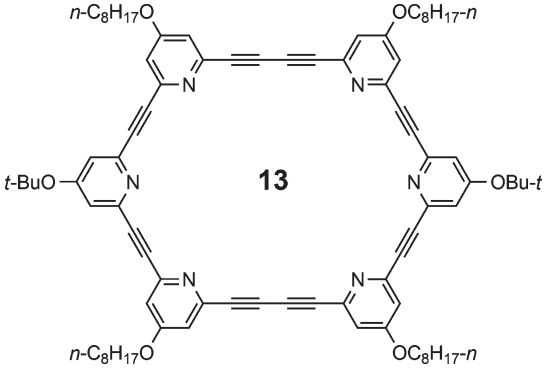

Figure 6. All-pyridine-type macrocyclic compound **13**.

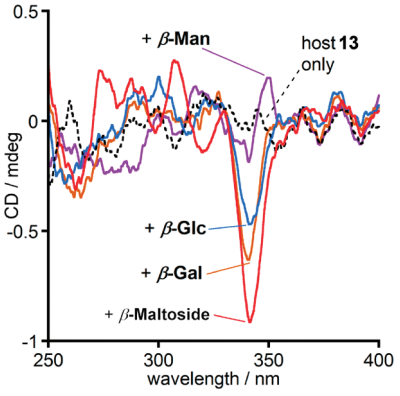

Figure 7. Induced CDs by the complexation of **13** with glycosides. Conditions: **13** (4.0×10^{-5} M), glycoside (2.0×10^{-4} M), CH_2Cl_2, 25 °C, path length = 1 mm.

CONCLUSION

A macrocyclic $(A-D-A)_2$-type rigid host molecule **4** could be prepared by Eglinton procedure, in which two 4(1*H*)pyridone and four pyridine rings are linked with acetylene bonds with D_{2h}-symmetry. The pyridone N−H and pyridine N atoms behave as hydrogen bond donor and acceptor respectively, so that alkyl glycosides can be recognized within the pore of **4**. The macrocycle **4** showed much higher affinity for disaccharide ***β*-Maltoside** than for monosaccharides. The efficiency of the

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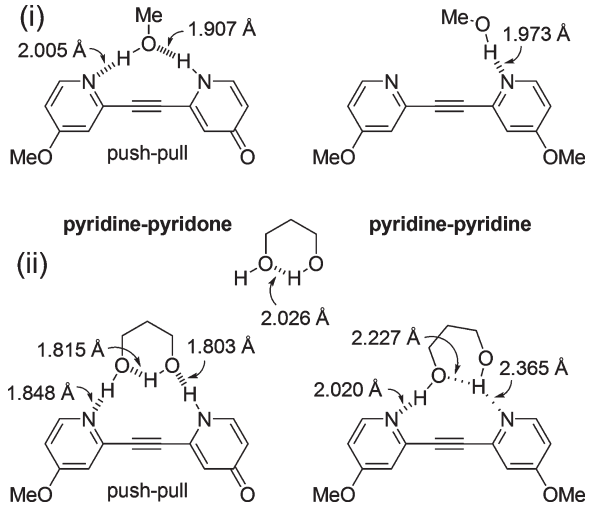

Figure 8. DFT-predicted coordinations and stabilization energies for binding of (i) methanol and (ii) propylene glycol with (left) pyridine−pyridone and (right) pyridine−pyridine modules. Conditions: DFT, B3LYP, 6-31+G(d). For details, see Figure S5 and Table S1, Supporting Information.

pyridone rings was shown by the comparison of **4** with all-pyridine compound **13**.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR spectra were recorded on a 300 or 500 MHz NMR spectrometer using tetramethylsilane (TMS) as an internal reference. ^{13}C NMR spectra were recorded on a 75 or 100 MHz NMR spectrometer. Melting points were not corrected. THF and pyridine were freshly distilled before use from sodium benzophenone ketyl and CaH_2, respectively. 2,6-Diethynyl-4-(methoxymethoxy)pyridine[6d] (**7**) and amphiphilic diiodopyridine[5c] **8** were prepared as reported in the literature. The preparation of all-pyridinic macrocyclic host **13** was described in our previous report.[9] All reactions were carried out under an argon atmosphere.

Diiodo Trimer 9. A mixture of CH_3CN (30 mL), *i*-Pr_2NEt (20 mL), $Pd(PPh_3)_4$ (69 mg, 0.06 mmol), and K_2CO_3 (0.50 g. 3.6 mmol) was bubbled with argon, and then excess amounts of diiodide **8** (5.1 g, 7.2 mmol), CuI (11 mg, 0.06 mmol), and diyne **7** (0.225 g, 1.2 mmol) with CH_3CN (10 mL) were subsequently added to the mixture. After being stirred for 1 day at room temperature, the resulting mixture was filtered through a Florisil bed to remove insoluble salts. The filtrate was concentrated with a rotary evaporator, and the resulting residue was subjected to silica gel (neutral) column chromatography (eluent; AcOEt/hexane = 4:1 → AcOEt → AcOEt/acetone = 1:1 → acetone) to afford recovered **8** (2.8 g, 55% recovery) and **9** (1.25 g, 77% based on **7**) as a light brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.37 (s, 6 H), 3.49 (s, 3 H), 3.53−3.56 (m, 4 H), 3.64−3.72 (m, 52 H), 3.85−3.88 (m, 4 H), 4.15−4.18 (m, 4 H), 5.24 (s, 2 H), 7.13 (d, J = 2.3 Hz, 2 H), 7.28 (s, 2 H), 7.30 (d, J = 2.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.6, 59.0, 68.1, 68.2, 69.1, 70.4, 70.5, 70.6, 70.9, 71.9, 86.6, 87.9, 94.0, 114.5, 115.8, 117.5, 121.4, 143.4, 143.6, 163.4, 164.5; IR (neat) 2872, 1577, 1531 cm^{-1}; ESI-HRMS m/z calcd for $C_{55}H_{81}I_2N_3NaO_{20}$ (M + Na^+) 1380.3400, found 1380.3451.

Bis(*tert*-butyldimethylsilylethynyl) Trimer 10. Diiodide **9** (1.25 g, 0.92 mmol), CuI (8.8 mg, 0.0462 mmol), and (*tert*-butyldimethylsilyl)acetylene (0.389 g, 2.77 mmol) were added successively to a mixture of $Pd(PPh_3)_4$ (53.3 mg, 0.0462 mmol) and K_2CO_3 (0.3828 g, 2.77 mmol) and in *i*-Pr_2NH (60 mL)/acetonitrile (120 mL) mixed solvent. The mixture was stirred for 24 h at room temperature and filtered through a Florisil bed to remove insoluble salts. The filtrate was evaporated, and the residue was purified by silica gel (neutral) column chromatography (eluent: CH_2Cl_2/MeOH = 20:1) to afford **10** (1.14 g, 89%) as a brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.20 (s, 12 H), 1.00 (s, 18 H), 3.37 (s, 6 H), 3.48 (s, 3 H), 3.52−3.55 (m, 4 H), 3.62−3.70 (m, 52 H), 3.85−3.88 (m, 4 H), 4.17−4.20 (m, 4 H), 5.23 (s, 2 H), 7.00 (d, J = 2.3 Hz, 2 H), 7.11 (d, J = 2.3 Hz, 2 H), 7.28 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.0, 16.4, 25.9, 56.3, 58.7, 67.6, 68.9, 70.2, 70.29, 70.34, 70.4, 70.7, 71.6, 86.8, 87.3, 93.3, 93.8, 103.6, 113.6, 114.4, 115.6, 143.5, 143.7, 144.3, 163.3, 164.7; IR (neat) 2881, 1580, 1550 cm^{-1}; ESI-HRMS m/z calcd for $C_{71}H_{111}N_3NaO_{20}Si_2$ (M + Na^+) 1404.7197, found 1404.7155.

Diethynyl Trimer 11. A mixture of **10** (0.20 g, 0.15 mmol), tetrabutylammonium fluoride (1.0 M in THF, 0.45 mL, 0.45 mmol), THF (20 mL), and two drops of H_2O was stirred for 30 min at room temperature. The resulting mixture was concentrated with a rotary evaporator, and the resulting residue was subjected to silica gel (neutral) column chromatography (eluent; acetone) to afford **11** (0.17 g, 100%) as a brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.18 (s, 2 H), 3.38 (s, 6 H), 3.49 (s, 3 H), 3.53−3.56 (m, 4 H), 3.64−3.73 (m, 52 H), 3.85−3.90 (m, 4 H), 4.19−4.22 (m, 4 H), 5.25 (s, 2 H), 7.05 (s, 2 H), 7.16 (s, 2 H), 7.29 (s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.5, 58.9, 67.9, 69.0, 70.35, 70.42, 70.8, 71.8, 82.0, 87.0, 87.3, 94.0, 113.9, 114.4, 115.6, 143.5, 143.7, 163.3, 164.8; IR (neat) 2874, 2109, 1581, 1551 cm^{-1}; ESI-HRMS m/z calcd for $C_{59}H_{83}N_3NaO_{20}$ (M + Na^+) 1176.5468, found 1176.5515.

Tandem Precursor 5. To a CH_2Cl_2 (8 mL) solution of **11** (0.17 g, 0.15 mmol) was added trifluoroacetic acid (TFA) (0.5 mL). The reaction mixture was stirred for 25 min at room temperature and then quenched with Na_2CO_3 (2 g). The mixture was diluted with saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layer was concentrated with a rotary evaporator, and the resulting residue was subjected to silica gel (neutral) column chromatography (eluent; CH_2Cl_2/MeOH = 10:1) to afford **5** (0.16 g, 99%) as a brown oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.20 (s, 2 H), 3.37 (s, 6 H), 3.53−3.56 (m, 4 H), 3.63−3.72 (m, 52 H), 3.84−3.88 (m, 4 H), 4.17−4.22 (m, 4 H), 7.02 (d, J = 2.1 Hz, 2 H), 7.10 (d, J = 2.1 Hz, 2 H), 7.12 (br s, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 59.0, 68.0, 69.1, 70.4, 70.5, 70.9, 71.8, 77.8, 81.8, 114.0, 114.7, 143.3, 143.4, 165.0; IR (neat) 3503, 3228, 2875, 2109, 1581, 1553 cm^{-1}; ESI-HRMS m/z calcd for $C_{57}H_{79}N_3NaO_{19}$ (M + Na^+) 1132.5205, found 1132.5196.

(A−D−A)$_2$-type Macrocyclic Host 4. To a mixture of $Cu(OAc)_2$ (1.0 g, 5.5 mmol) and dry pyridine (distilled from CaH_2 and bubbled with Ar before use, 400 mL) was added a dry pyridine (40 mL) solution of **5** (0.24 g, 0.22 mmol), and the mixture was stirred for 4 h at 45 °C. The resulting mixture was diluted with CH_2Cl_2 (500 mL) and washed repeatedly with 4 N HCl (300 mL × 3). The organic layer was washed with saturated aqueous $NaHCO_3$ (500 mL × 2) and concentrated with a rotary evaporator, and the resulting residue was subjected to silica gel (neutral) column chromatography (eluent; CH_2Cl_2/MeOH = 10:1) to afford **4** (0.051 g, 21%) as a brown viscous oil: ^{1}H NMR ($CDCl_3$/CD_3OD = 3:1, 300 MHz) δ 3.38 (s, 12 H), 3.54−3.72 (m, 112 H), 3.91 (br s, 8 H), 4.27 (br s, 8 H), 6.73 (s, 4 H), 7.18 (s, 4 H), 7.22 (s, 4 H); ^{13}C NMR ($CDCl_3$/CD_3OD, 100 MHz) δ 59.0, 68.7, 69.3, 70.5, 70.65, 70.74, 71.1, 72.0, 73.3, 80.3, 81.2, 92.1, 115.7, 116.4, 122.4, 132.5, 143.0, 166.0; IR (neat) 3384, 2873, 1582, 1550 cm^{-1}; ESI-HRMS m/z calcd for $C_{114}H_{153}DN_6NaO_{38}$ (M + Na^+) 2239.0233, found 2239.0241.

ASSOCIATED CONTENT

Supporting Information. Figures S1−S5, Table S1, details of theoretical analyses, and copies of NMR spectra for compounds **4**, **5**, and **9**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For selective polycyclic receptors for disaccharide recognition by Davis' group, see refs 2c,3d,g. See also refs 3n,4c−4f,4n for disaccharide-selective host molecules.

(12) The strength of hydrogen bonding of methanol with 4-methoxypyridine and 4(1*H*)-pyridone in CH_2Cl_2 was predicted as 16.1 and 11.8 kJ mol^{-1}, respectively, by DFT (B3LYP/6-31+G(d)) calculations. See Figure S2, Supporting Information.