

Supplementary Information

Metal-dependent selective formation of calix[4]arene assemblies based on dynamic covalent chemistry

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Experimental

Materials and methods.

Reagents and solvents were purchased from commercial sources and used without further purification. ^1H NMR spectra were recorded on a Bruker Avance Neo 400 (400 MHz) or a Bruker Avance Neo 600 (600 MHz). ^{13}C NMR spectra were recorded on a Bruker Avance Neo 600 (150 MHz). Chemical shifts were referenced with respect to tetramethylsilane (^1H , 0 ppm) as an internal standard or the solvent residual peak (^{13}C , 77.16 ppm for CDCl_3). ESI-TOF mass spectra were recorded on a Bruker Daltonics micrOTOF II. Recycling preparative gel permeation chromatography (GPC) was performed with a Japan Analytical Industry LaboACE LC-5060 equipped with JAIGEL 2HR columns. Preparative thin layer chromatography was performed on a precoated plate (2 mm, silica gel Merck Kieselgel 60F245).

The synthetic precursors, 4-bromo-2-(methoxymethoxy)benzaldehyde,¹ 5,11,17,23-tetrabromo-25,26,27,28-tetrakis(*N,N'*-diethylaminocarbonylmethoxy)calix[4]arene (**3a**),² and 5,11,17,23-tetrabromo-25,26,27,28-tetrapropoxycalix[4]arene (**3b**)³ were prepared according to the literatures.

Synthesis of boronate ester 2.

Under nitrogen atmosphere, a solution of 4-bromo-2-(methoxymethoxy)benzaldehyde (2.50 g, 10 mmol), potassium acetate (3.80 g, 39 mmol), and bis(pinacolato)diboron (2.29 g, 9.0 mmol) in dry DMF (15 mL) was prepared in a Schlenk tube. After degassing with nitrogen, $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (0.816 g, 1.0 mmol) was added to the mixture. The resultant mixture was stirred at 90 °C for 12 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with chloroform (100 mL \times 3). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The crude material was purified by silica gel column chromatography (chloroform) to obtain boronate ester **2** (1.36 g, 4.66 mmol, 52%) as a yellow oil. ^1H NMR (600 MHz, CDCl_3) δ 10.54 (d, J = 1.2 Hz, 1H), 7.82 (d, J = 7.5 Hz, 1H), 7.58 (s, 1H), 7.51 (d, J = 7.5 Hz, 1H), 5.35 (s, 2H), 3.54 (s, 3H), 1.35 (s, 12H); ^{13}C NMR (150 MHz, CDCl_3) δ 190.15, 158.86, 137.68 (br), 128.06, 127.45, 127.37, 120.71, 94.64, 84.45, 56.75, 24.97; Anal. Calcd for $\text{C}_{15}\text{H}_{21}\text{BO}_5 \cdot 0.6\text{H}_2\text{O}$: C, 59.47; H, 7.39. Found: C, 59.43; H, 7.12.

Synthesis of 4a.

Under nitrogen atmosphere, boronate ester **2** (181 mg, 0.62 mmol), 5,11,17,23-tetrabromo-25,26,27,28-tetrakis(*N,N'*-diethylaminocarbonylmethoxy)calix[4]arene (**3a**) (60.0 mg, 0.050 mmol), cesium carbonate (135 mg, 0.41 mmol), and dry DMF (1 mL) were mixed in a two-necked flask. After degassing with nitrogen, $\text{Pd}(\text{PPh}_3)_4$ (11.9 mg, 0.010 mmol) was added to the mixture. The mixture was stirred at 90 °C for 16 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with chloroform (100 mL \times 3). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The crude material was purified by GPC and preparative thin layer

chromatography to obtain **4a** (10.9 mg, 7.1 μ mol, 14%) as a yellow solid, mp 188–190 °C; ^1H NMR (600 MHz, CDCl_3) δ 10.32 (s, 4H), 7.57 (d, $J = 8.4$ Hz, 4H), 6.97 (s, 8H), 6.87–6.86 (m, 8H), 5.46 (d, $J = 13.2$ Hz, 4H), 5.064 (s, 8H), 5.059 (s, 8H), 3.41 (d, $J = 13.2$ Hz, 4H), 3.40 (s, 12H), 3.38 (q, $J = 7.2$ Hz, 8H), 3.36 (q, $J = 7.2$ Hz, 8H), 1.19 (t, $J = 7.2$ Hz, 12H), 1.12 (t, $J = 7.2$ Hz, 12H); ^{13}C NMR (150 MHz, CDCl_3) δ 189.24, 168.50, 159.65, 157.59, 148.53, 135.43, 134.02, 128.37, 127.58, 123.71, 120.05, 112.69, 94.49, 71.93, 56.64, 40.98, 40.16, 32.34, 14.50, 13.27; HRMS (ESI-TOF) m/z exact mass [**4a** + Na] $^+$ 1555.6856, $\text{C}_{88}\text{H}_{100}\text{N}_4\text{O}_{20}\text{Na}$ requires 1555.6823.

Synthesis of **1a**.

Concentrated hydrochloric acid (1 mL) was added to a solution of **4a** (10.9 mg, 7.1 μ mol) in THF (2 mL) and the mixture was stirred at room temperature for 12 h. The reaction mixture was poured into water and extracted with chloroform (50 mL \times 3). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The residue was purified by reprecipitation from chloroform/hexane to yield **1a** (4.2 mg, 3.1 μ mol, 43 %) as a white solid, mp 189–194 °C; ^1H NMR (600 MHz, CDCl_3) δ 10.93 (s, 4H), 9.71 (s, 4H), 7.29 (d, $J = 7.8$ Hz, 4H), 6.99 (s, 8H), 6.80 (d, $J = 7.8$ Hz, 4H), 6.75 (s, 8H), 5.47 (d, $J = 13.8$ Hz, 4H), 5.05 (s, 8H), 3.40 (d, $J = 13.8$ Hz, 4H), 3.37 (q, $J = 7.1$ Hz, 8H), 3.35 (q, $J = 7.1$ Hz, 8H), 1.19 (t, $J = 7.1$ Hz, 12H), 1.11 (t, $J = 7.1$ Hz, 12H); ^{13}C NMR (150 MHz, CDCl_3) δ 195.86, 168.46, 161.70, 157.91, 149.63, 135.46, 133.87, 133.55, 127.77, 119.10, 118.51, 114.88, 71.93, 40.97, 40.15, 32.43, 15.48, 13.26; HRMS (ESI-TOF) m/z exact mass [**1a** + Na] $^+$ 1379.5792, $\text{C}_{80}\text{H}_{84}\text{N}_4\text{O}_{16}\text{Na}$ requires 1379.5775.

Synthesis of **4b**.

Under nitrogen atmosphere, boronate ester **2** (597 mg, 2.04 mmol), 5,11,17,23-tetrabromo-25,26,27,28-tetrapropoxycalix[4]arene (**3b**) (118 mg, 0.13 mmol), cesium carbonate (339 mg, 1.04 mmol), and dry DMF (3 mL) were mixed in a two-necked flask. After degassing with nitrogen, $\text{Pd}(\text{PPh}_3)_4$ (36.1 mg, 31.2 μ mol) was added to the mixture. The mixture was stirred at 90 °C for 16 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with chloroform (100 mL \times 3). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The crude material was purified by GPC to obtain **4b** (149 mg, 0.12 mmol, 92%) as a pale yellow solid, mp 218–220 °C; ^1H NMR (600 MHz, CDCl_3) δ 10.32 (s, 4H), 7.56 (d, $J = 7.8$ Hz, 4H), 6.97 (s, 8H), 6.88 (s, 4H), 6.86 (d, $J = 7.8$ Hz, 4H), 5.08 (s, 8H), 4.59 (d, $J = 13.5$ Hz, 4H), 3.97 (t, $J = 7.5$ Hz, 8H), 3.41 (s, 12H), 3.34 (d, $J = 13.5$ Hz, 4H), 2.01 (sext, $J = 7.5$ Hz, 8H), 1.07 (t, $J = 7.5$ Hz, 12H); ^{13}C NMR (150 MHz, CDCl_3) δ 189.11, 159.61, 157.42, 148.45, 135.53, 133.76, 128.36, 127.25, 123.76, 120.02, 112.59, 94.47, 77.37, 56.61, 31.34, 23.44, 10.47; HRMS (ESI-TOF) m/z exact mass [**4b** + H] $^+$ 1249.5539, $\text{C}_{76}\text{H}_{80}\text{O}_{16}\text{H}$ requires 1249.5519.

Synthesis of **1b**.

Concentrated hydrochloric acid (2 mL) was added to a solution of **4b** (78.2 mg, 63 μmol) in THF (5 mL) and the mixture was stirred at room temperature for 15 h. The reaction mixture was poured into water and extracted with chloroform (100 mL \times 3). The combined organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The crude material was purified by GPC to obtain **1b** (51.8 mg, 48 μmol , 77%) as a pale yellow solid, mp 260–264 $^{\circ}\text{C}$; ^1H NMR (600 MHz, CDCl_3) δ 10.93 (s, 4H), 9.71 (s, 4H), 7.29 (d, $J = 8.4$ Hz, 4H), 6.97 (s, 8H), 6.80 (d, $J = 8.4$ Hz, 4H), 6.74 (s, 4H), 4.58 (d, $J = 13.5$ Hz, 4H), 3.96 (t, $J = 7.5$ Hz, 8H), 3.31 (d, $J = 13.5$ Hz, 4H), 2.00 (sext, $J = 7.5$ Hz, 8H), 1.05 (t, $J = 7.5$ Hz, 12H); ^{13}C NMR (150 MHz, CDCl_3) δ 195.85, 161.71, 157.75, 149.58, 135.61, 133.86, 133.32, 127.45, 119.11, 118.45, 114.86, 77.37, 31.47, 23.44, 10.47; HRMS (ESI-TOF) m/z exact mass [**1b** + H] $^+$ 1073.4490, $\text{C}_{68}\text{H}_{64}\text{O}_{12}\text{H}$ requires 1073.4471.

Preparation of **5a**.

A solution of 1,3-propanediamine in $\text{CDCl}_3/\text{CD}_3\text{CN}$ (1:1) (25 mM, 40 μL , 1.0 μmol , 2 equiv) was added to a solution of **1a** in $\text{CDCl}_3/\text{CD}_3\text{CN}$ (1:1) (1 mM, 500 μL , 0.5 μmol) and the mixture was left for 24 h at room temperature. The ^1H NMR spectrum showed the formation of **5a** as the major product, **5a**: ^1H NMR (600 MHz, $\text{CDCl}_3/\text{CD}_3\text{CN}$, 1:1) δ 13.6 (br, 6H), 12.9 (br, 6H), 8.50 (s, 6H), 7.94 (s, 6H), 7.53 (s, 12H), 7.41 (d, $J = 8.4$ Hz, 6H), 7.28–7.27 (m, 12H), 6.51 (d, $J = 7.8$ Hz, 6H), 6.45 (s, 12H), 6.05 (dd, $J = 7.8, 1.5$ Hz, 6H), 5.97 (d, $J = 1.5$ Hz, 6H), 5.31 (s, 6H), 5.26 (d, $J = 13.4$ Hz, 8H), 4.67 (s, 6H), 3.77 (t, $J = 6.4$ Hz, 12H), 3.45–3.32 (m, 62H), 1.19 (t, $J = 7.6$ Hz, 18H), 1.18 (t, $J = 6.9$ Hz, 18H), 1.13 (t, $J = 7.3$ Hz, 18H), 1.08 (t, $J = 7.1$ Hz, 18H); ESI-MS m/z 2151.6 [**5a** + 2H] $^{2+}$, 2162.6 [**5a** + H + Na] $^{2+}$, 2173.6 [**5a** + 2Na] $^{2+}$.

Preparation of [**7a**•2Na] $^{2+}$.

A solution of 1,3-propanediamine in $\text{CDCl}_3/\text{CD}_3\text{CN}$ (1:1) (25 mM, 40 μL , 1.0 μmol , 2 equiv) and a solution of sodium triflate in $\text{CDCl}_3/\text{CD}_3\text{CN}$ (1:1) (25 mM, 20 μL , 0.5 μmol , 1 equiv) were added to a solution of **1a** in $\text{CDCl}_3/\text{CD}_3\text{CN}$ (1:1) (1 mM, 500 μL , 0.5 μmol), and the mixture was left for 24 h at room temperature. The ^1H NMR spectrum showed the exclusive formation of [**7a**•2Na] $^{2+}$: ^1H NMR (600 MHz, $\text{CDCl}_3/\text{CD}_3\text{CN}$, 1:1) δ 13.49 (br, 8H), 8.42 (s, 8H), 7.60 (s, 16H), 7.31 (d, $J = 7.8$ Hz, 8H), 7.00 (dd, $J = 7.8, 1.8$ Hz, 8H), 6.97 (d, $J = 1.8$ Hz, 8H), 4.63 (s, 16H), 4.62 (d, $J = 12.6$ Hz, 8H), 3.67 (t, $J = 6.9$ Hz, 16H), 3.58 (d, $J = 12.6$ Hz, 8H), 3.45 (q, $J = 7.2$ Hz, 16H), 3.19 (q, $J = 7.2$ Hz, 16H), 2.07 (quint, $J = 6.9$ Hz, 8H), 1.21 (t, $J = 7.2$ Hz, 24H), 1.19 (t, $J = 7.2$ Hz, 24H); ^{13}C NMR (150 MHz, $\text{CDCl}_3/\text{CD}_3\text{CN}$, 1:1) δ 167.16, 164.48, 160.65, 153.29, 142.99, 137.32, 135.75, 131.09, 127.11, 117.24, 116.83, 114.18, 73.76, 56.51, 39.79, 39.47, 31.28, 29.13, 13.10, 12.13; ESI-MS m/z 1456.2 [**7a** + 2Na] $^{2+}$.

Preparation of **5b**.

A solution of 1,3-propanediamine in CDCl₃/CD₃CN (1:1) (25 mM, 40 μL, 1.0 μmol, 2 equiv) was added to a solution of **1b** in CDCl₃/CD₃CN (1:1) (1 mM, 500 μL, 0.5 μmol), and the mixture was left for 24 h at room temperature. The ¹H NMR spectrum of the mixture showed the formation of **5b** as the major product. A small portion of the sample was further purified by GPC. **5b**: ¹H NMR (400 MHz, CDCl₃/CD₃CN, 1:1) δ 12.8 (br, 12H), 8.47 (s, 6H), 8.00 (s, 6H), 7.56 (s, 12H), 7.40 (d, *J* = 7.6 Hz, 6H), 7.27–7.25 (m, 12H), 6.54 (d, *J* = 7.9 Hz, 6H), 6.41 (s, 12H), 6.04 (dd, *J* = 7.9, 1.4 Hz, 6H), 5.96 (s, 6H), 4.54 (d, *J* = 13.4 Hz, 12H), 4.17 (t, *J* = 8.0 Hz, 12H), 3.74–3.69 (m, 36H), 3.32 (d, *J* = 13.4 Hz, 12H), 1.84 (sext, *J* = 6.8 Hz, 12H), 1.69 (sext, *J* = 6.8 Hz, 12H), 0.95 (t, *J* = 7.5 Hz, 18H), 0.88 (t, *J* = 6.7 Hz, 18H); ESI-MS *m/z* 1724.8 [**5b** + 2H]²⁺.

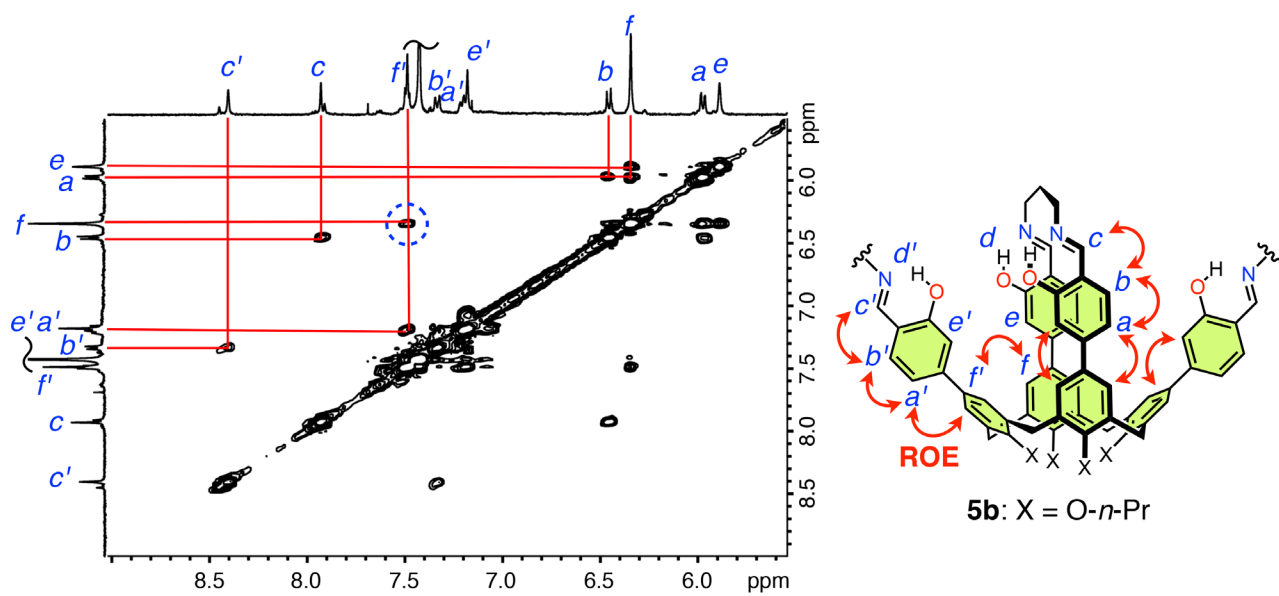


Fig. S1. ^1H ROESY spectrum of **5b** prepared by the reaction of **1b** with 2 equiv of 1,3-propanediamine (600 MHz, $\text{CDCl}_3/\text{CD}_3\text{CN}$, 1:1).

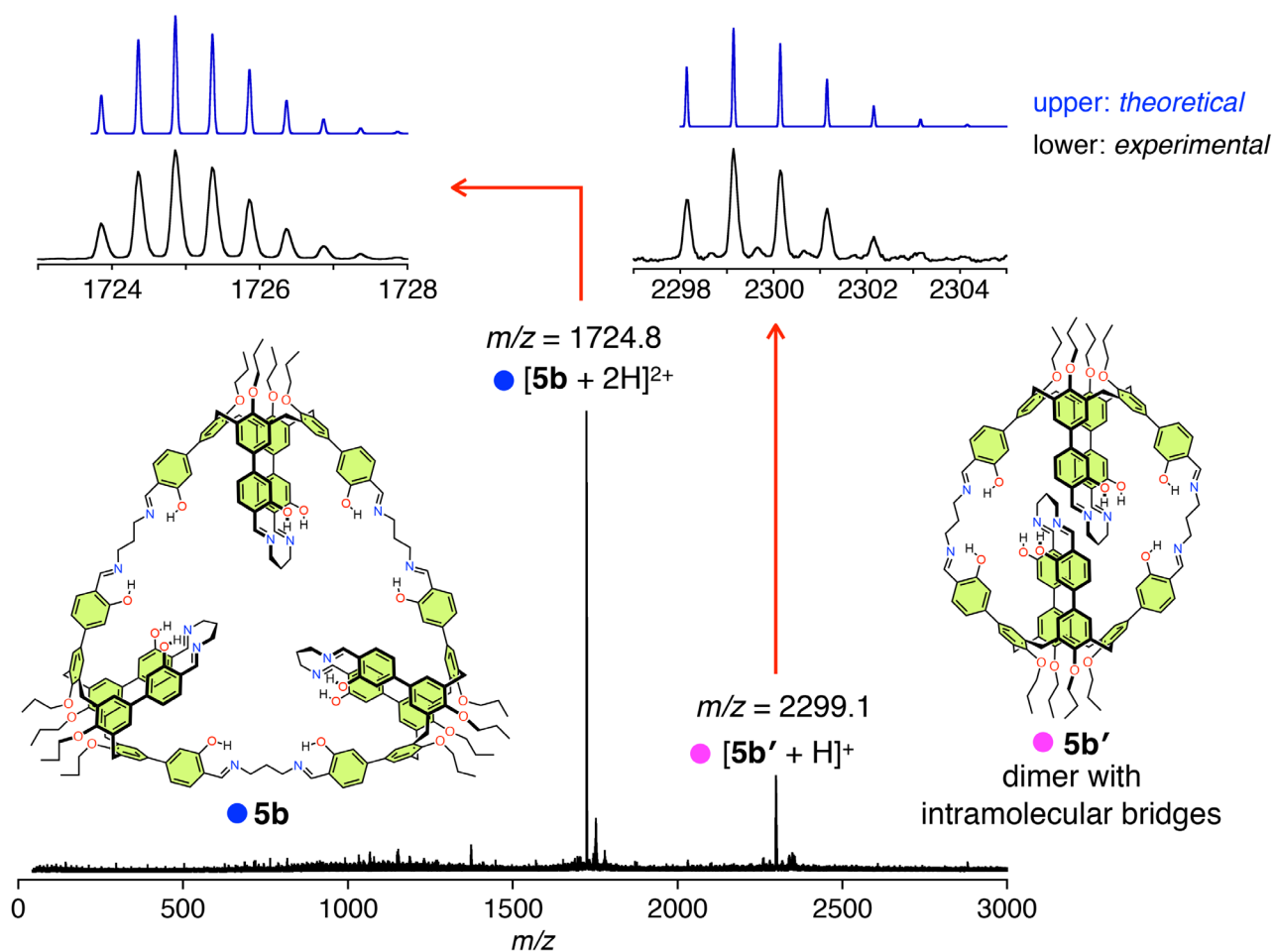


Fig. S2. ESI-TOF mass spectrum of a reaction mixture of **1b** with 2 equiv of 1,3-propanediamine, showing the peak for macrocyclic trimer **5b** as the main product. The peak at $m/z = 2299.1$ corresponds to the [2+4] condensation product of **1b** and 1,3-propanediamine, which can be assigned to the macrocyclic dimer **5b'** with intramolecular bridges.

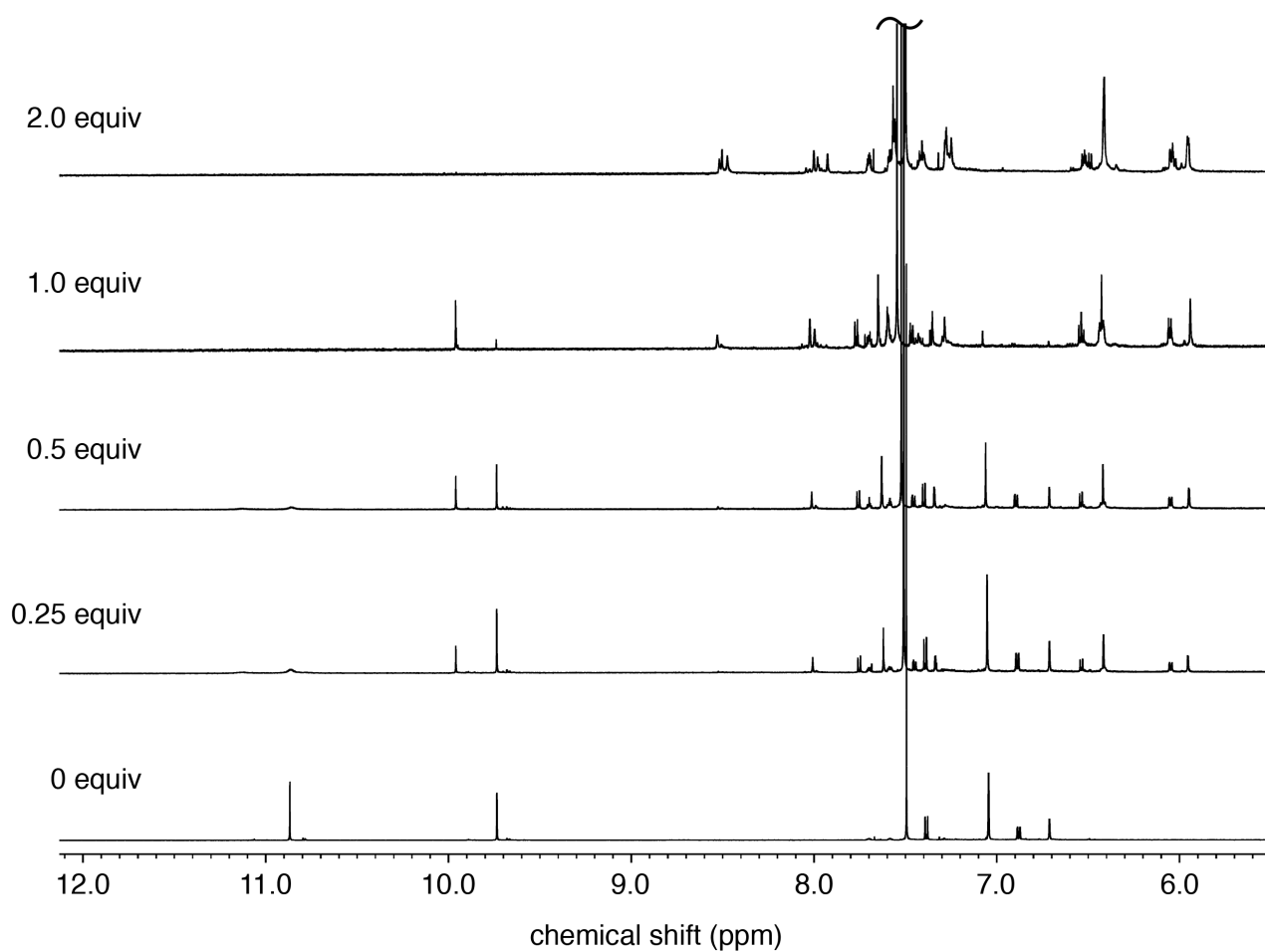


Fig. S3. ¹H NMR spectral changes of **1b** upon the addition of 1,3-propanediamine (600 MHz, CDCl₃/CD₃CN, 1:1, [**1b**] = 1 mM).

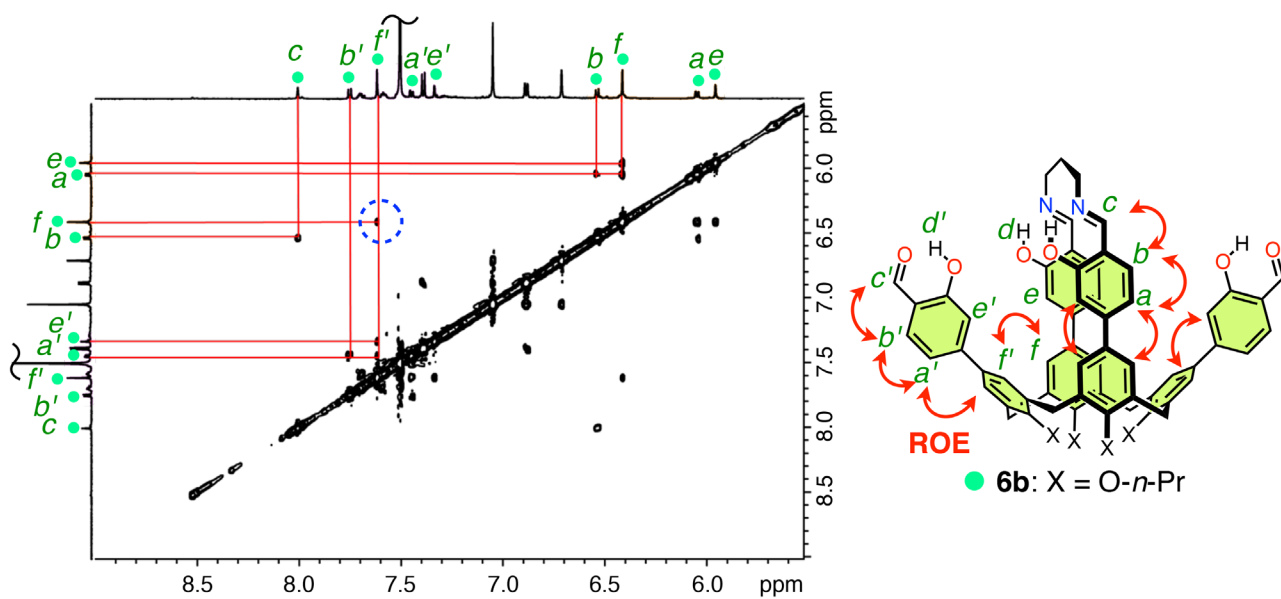


Fig. S4. ¹H ROESY spectrum of **6b** prepared by the reaction of **1b** with 0.5 equiv of 1,3-propanediamine (600 MHz, CDCl₃/CD₃CN, 1:1).

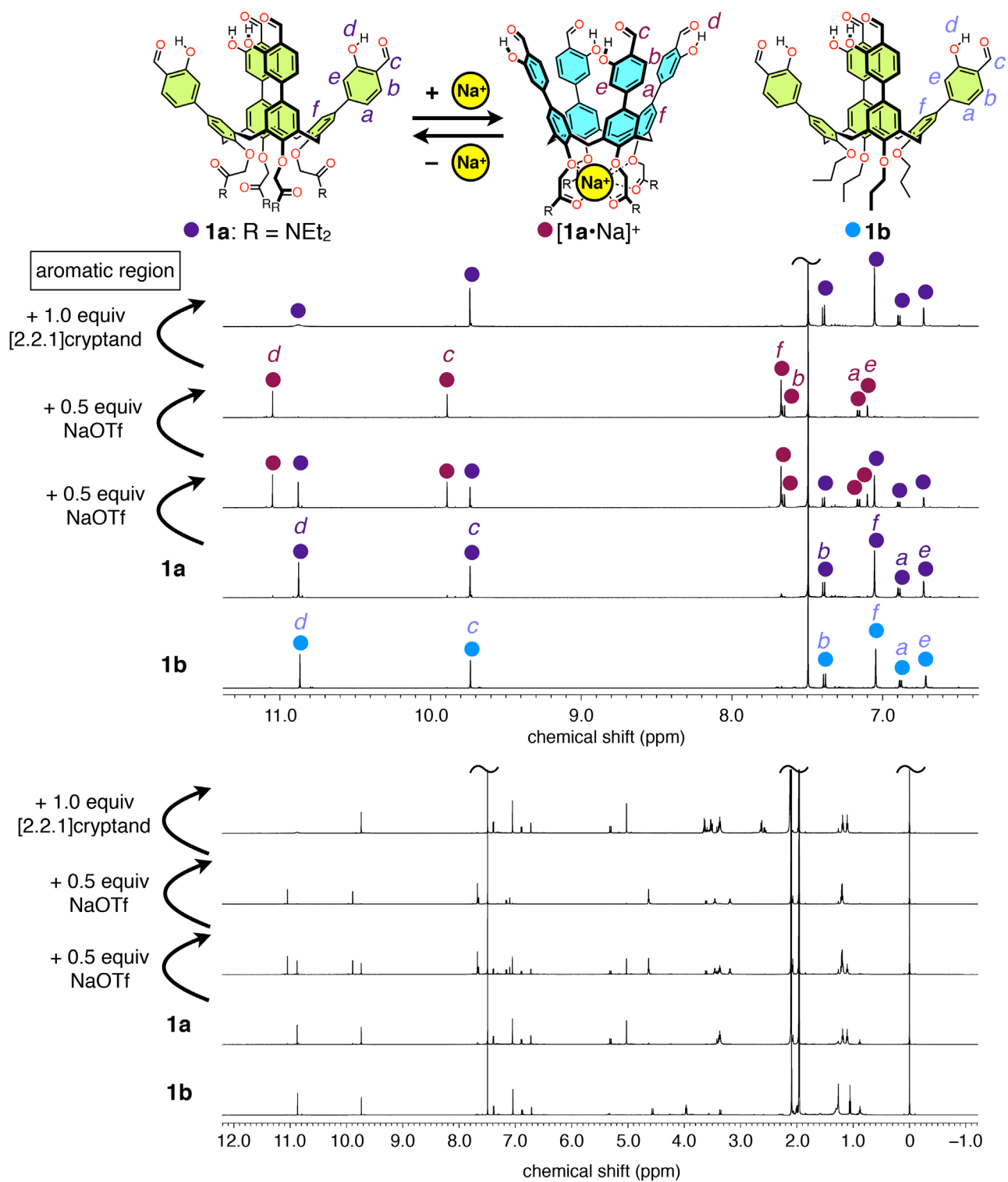


Fig. S5. Comparison of ^1H NMR spectra of **1a** and **1b**, and ^1H NMR spectral changes of **1a** upon the addition of NaOTf and [2.2.1]cryptand (600 MHz, CDCl₃/CD₃CN, 1:1, [**1a**] = [**1b**] = 1 mM).

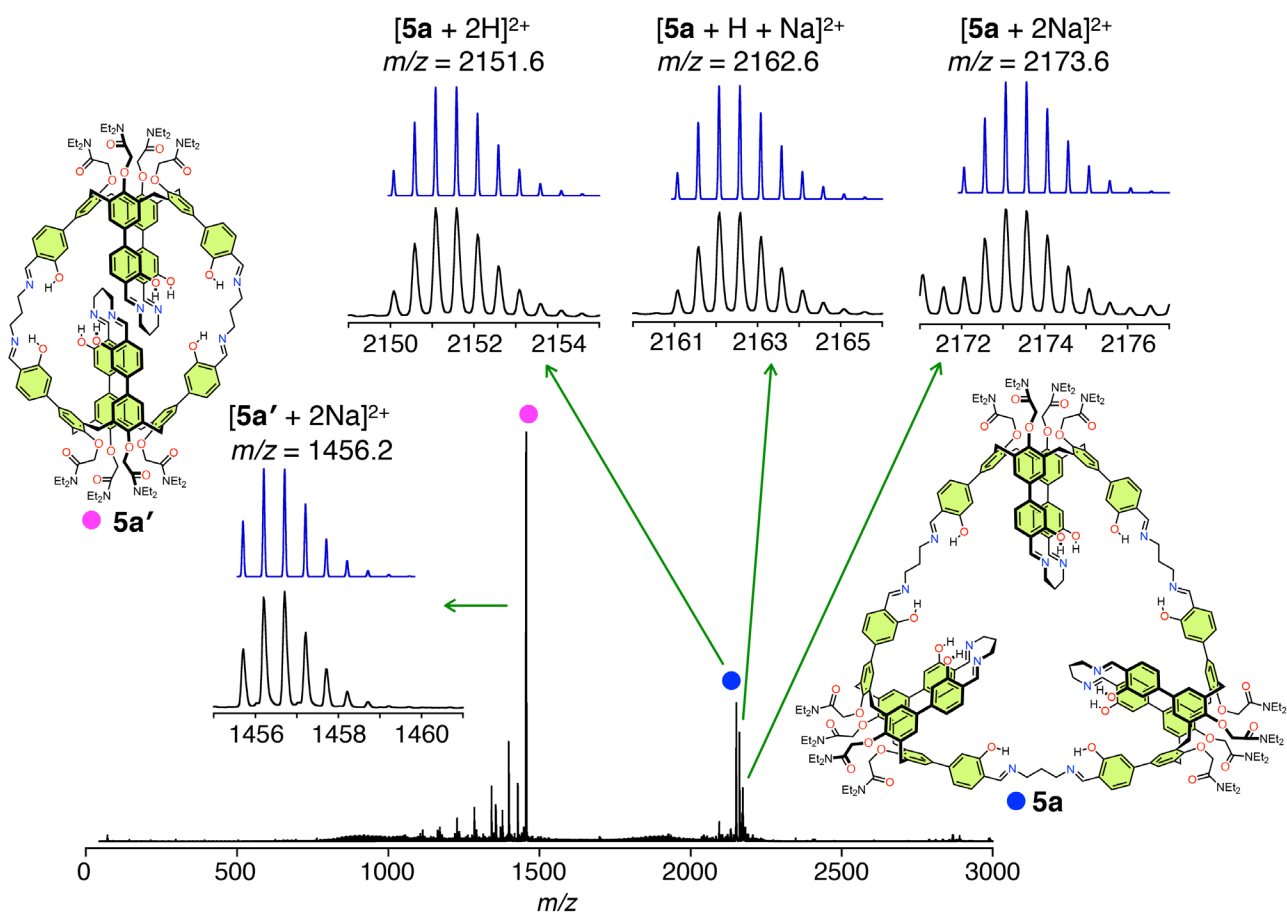


Fig. S6. ESI-TOF mass spectrum of a reaction mixture of **1a** with 2 equiv of 1,3-propanediamine.

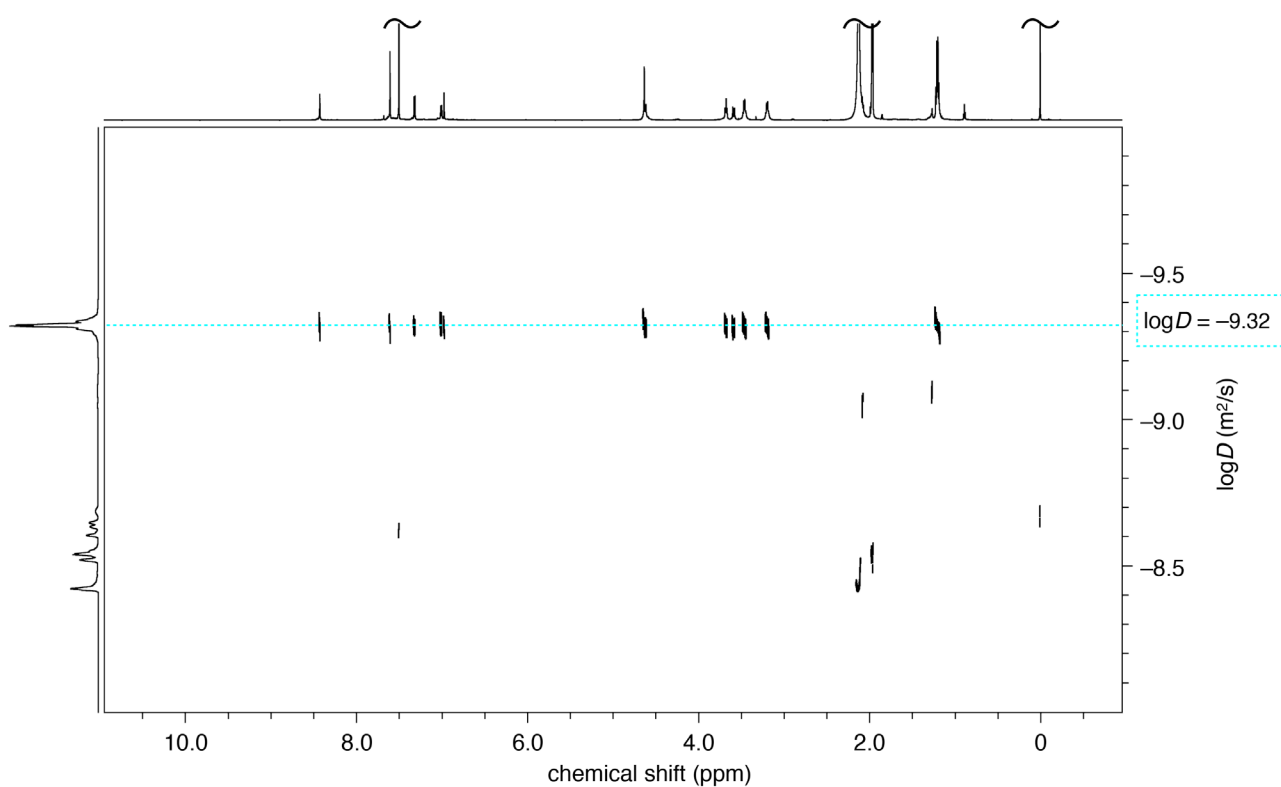


Fig. S7. ¹H DOSY spectrum of [7a•2Na]²⁺ prepared by the reaction of **1a** with 2 equiv of 1,3-propanediamine in the presence of 1 equiv of NaOTf (600 MHz, CDCl₃/CD₃CN, 1:1).

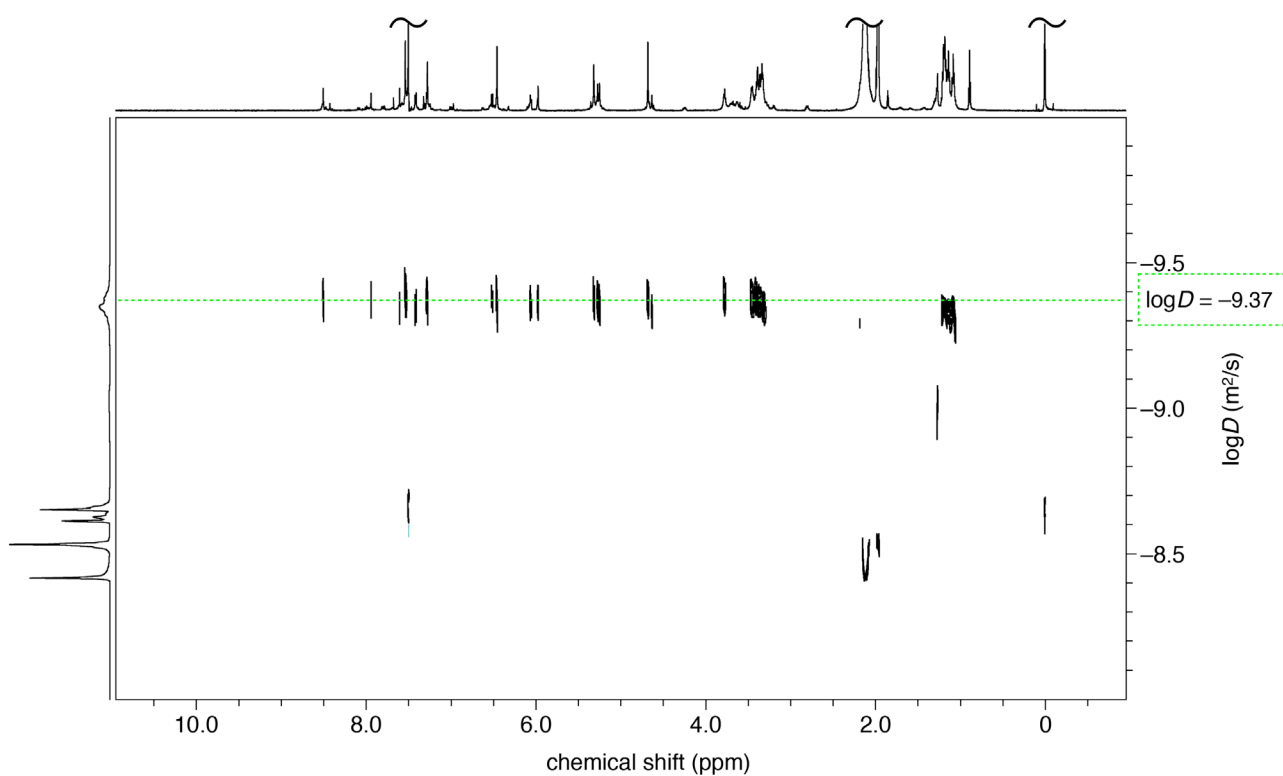


Fig. S8. ^1H DOSY spectrum of **5a** prepared by the reaction of **1a** with 2 equiv of 1,3-propanediamine (600 MHz, $\text{CDCl}_3/\text{CD}_3\text{CN}$, 1:1).

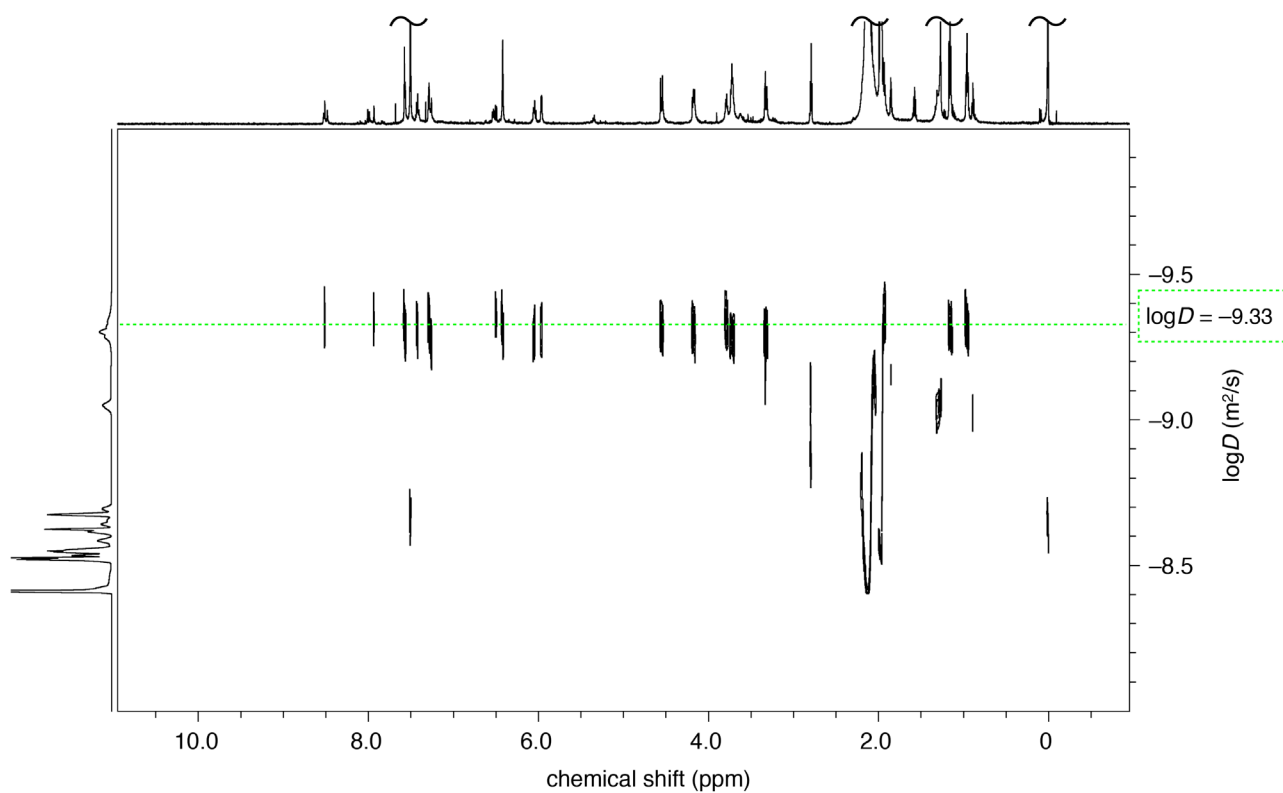


Fig. S9. ^1H DOSY spectrum of **5b** prepared by the reaction of **1b** with 2 equiv of 1,3-propanediamine (600 MHz, $\text{CDCl}_3/\text{CD}_3\text{CN}$, 1:1).

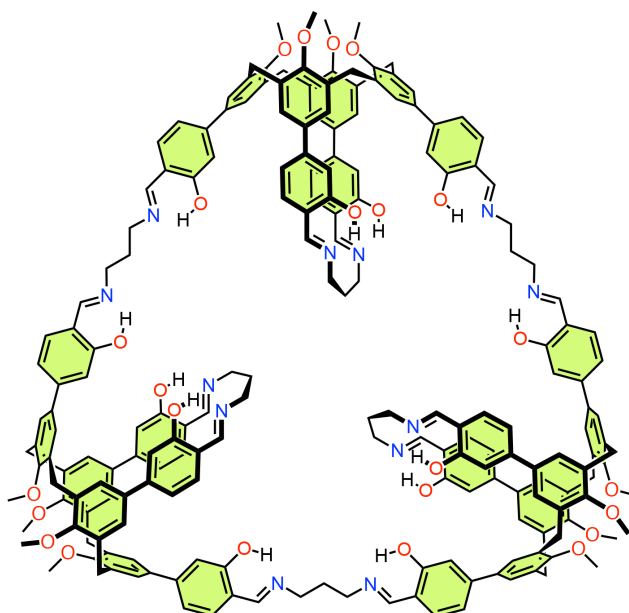
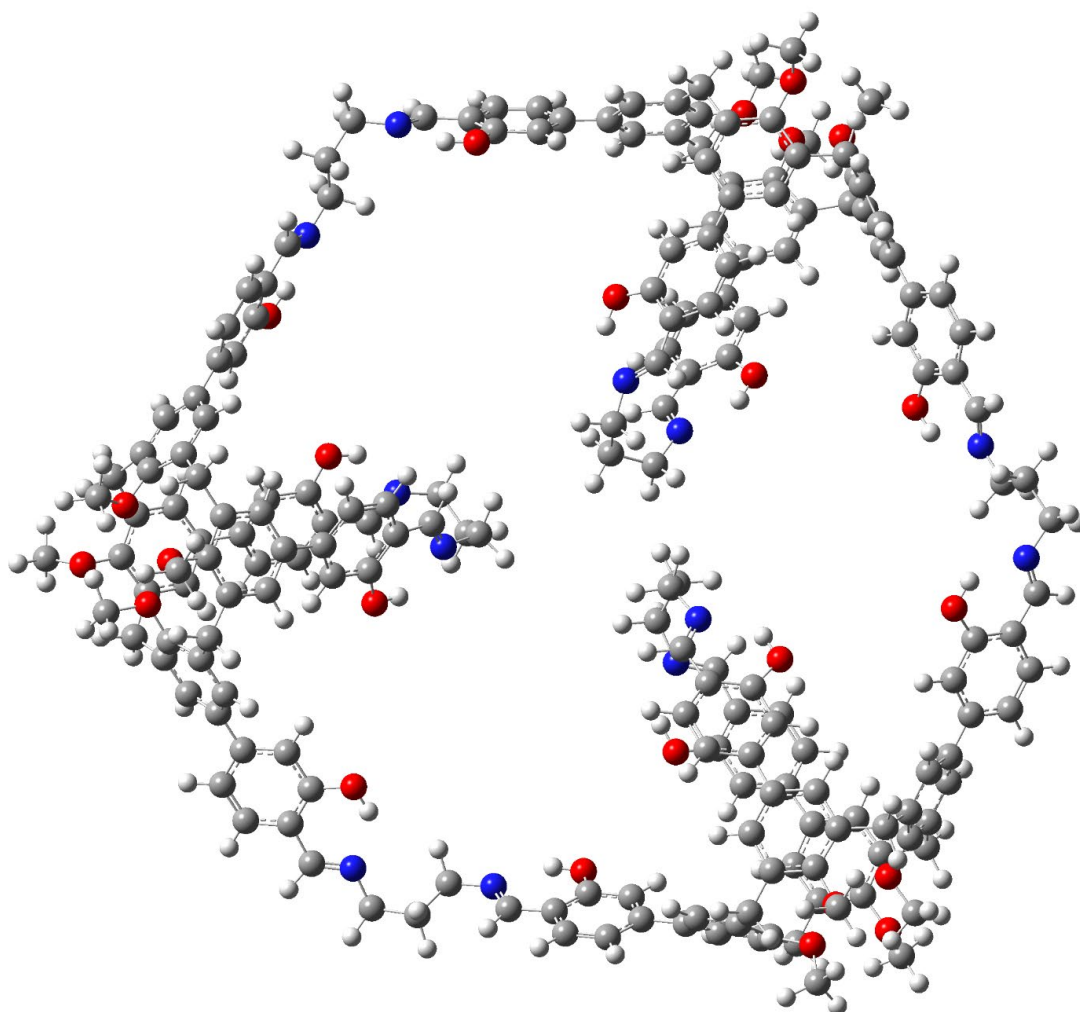


Fig. S10. Optimized structure of the macrocyclic trimer **5c** (AM1; Gaussian 09),⁴ which is the methyl analogue of **5a** (amide) and **5b** (propyl).

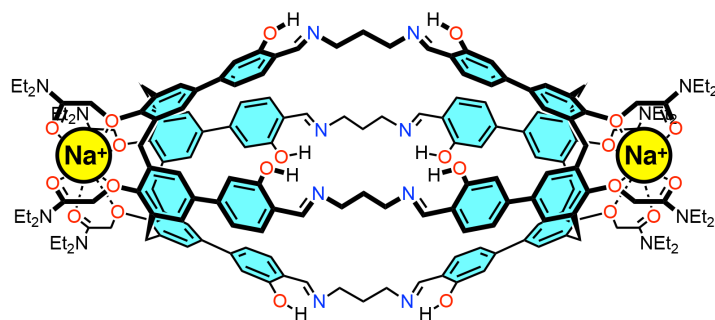
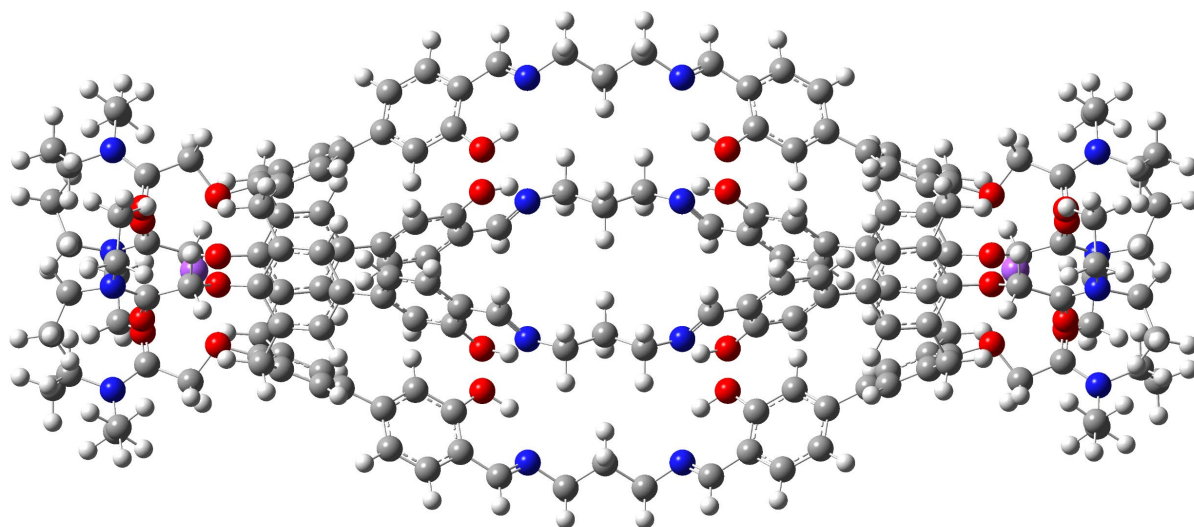


Fig. S11. Optimized structure of capsular-shaped dimeric cage $[7\mathbf{a}\cdot 2\text{Na}]^{2+}$ (PM6; Gaussian 09).⁴

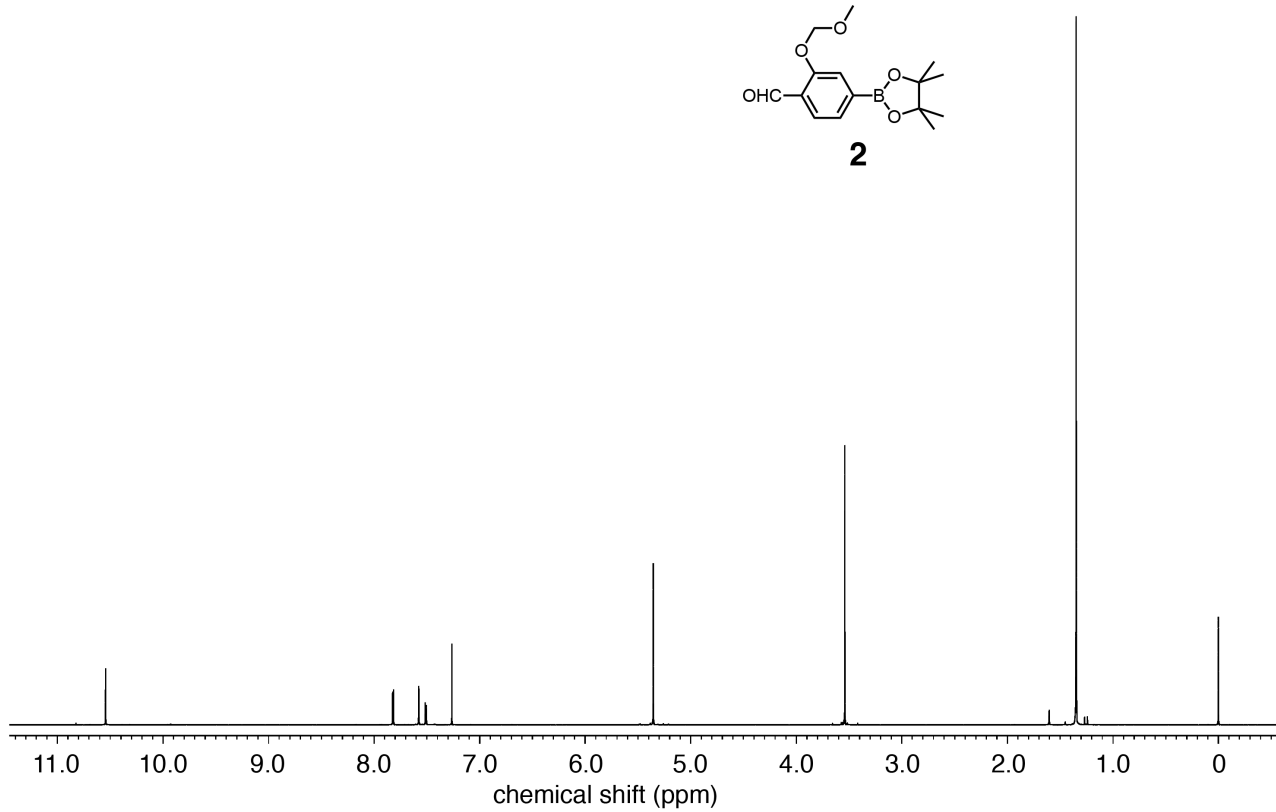
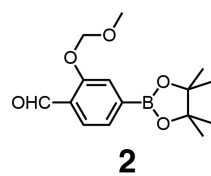


Fig. S12. ¹H NMR spectrum of **2** (600 MHz, CDCl₃).

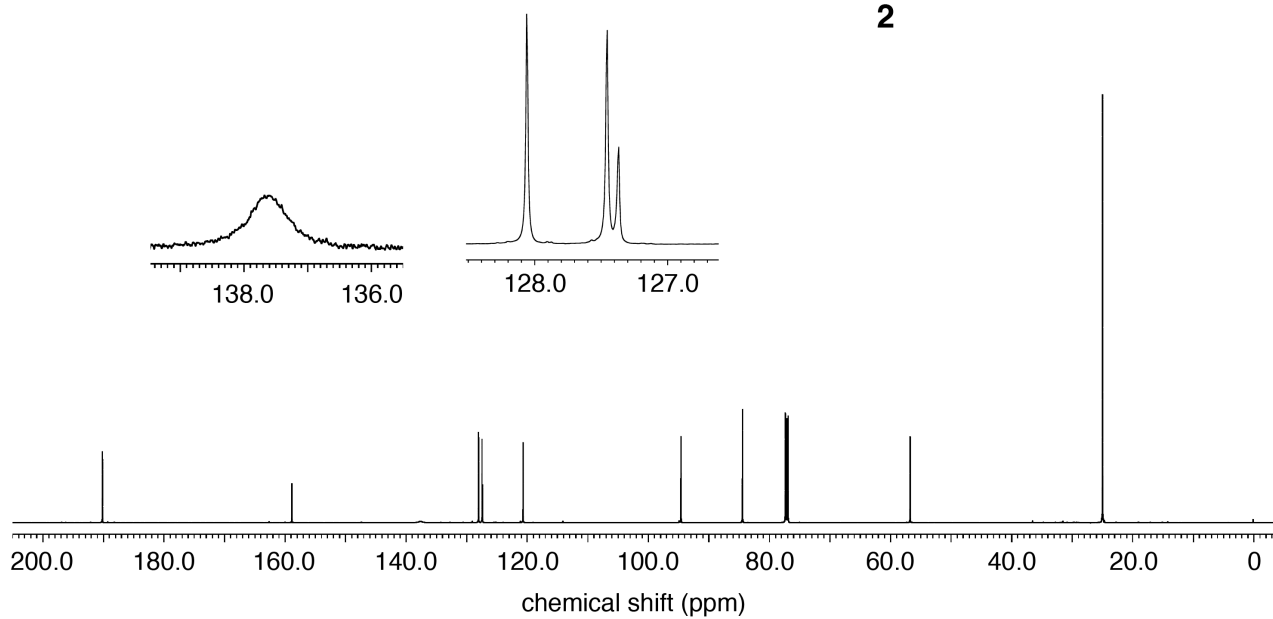
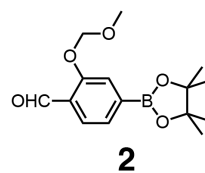


Fig. S13. ^{13}C NMR spectrum of **2** (150 MHz, CDCl_3).

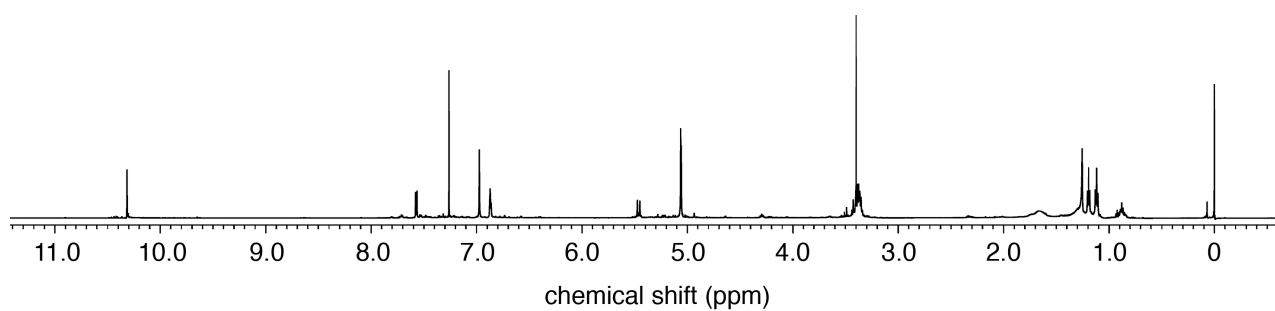
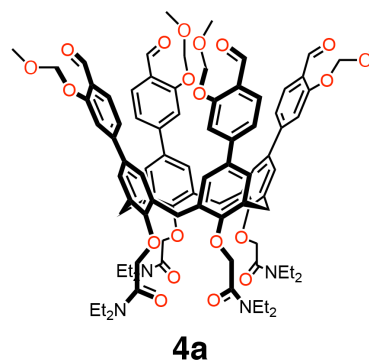


Fig. S14. ¹H NMR spectrum of **4a** (600 MHz, CDCl₃).

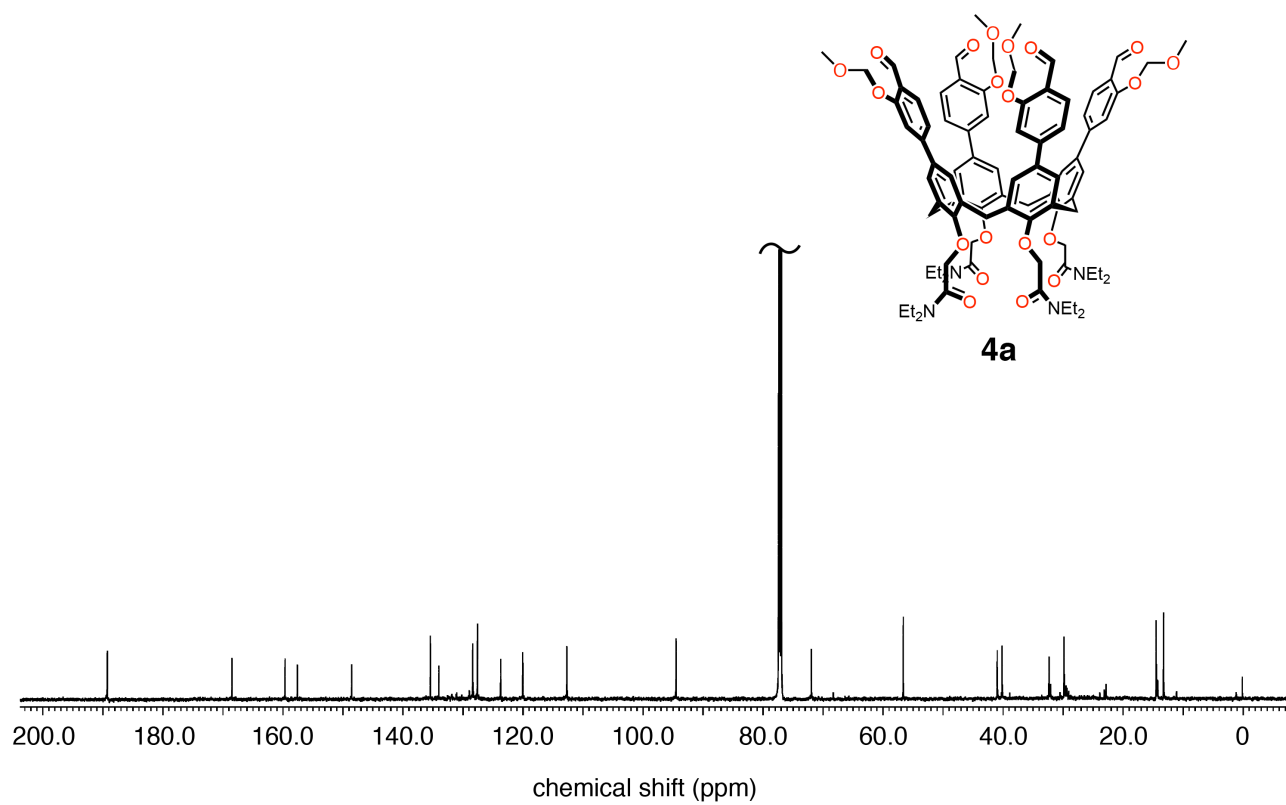


Fig. S15. ^{13}C NMR spectrum of **4a** (150 MHz, CDCl_3).

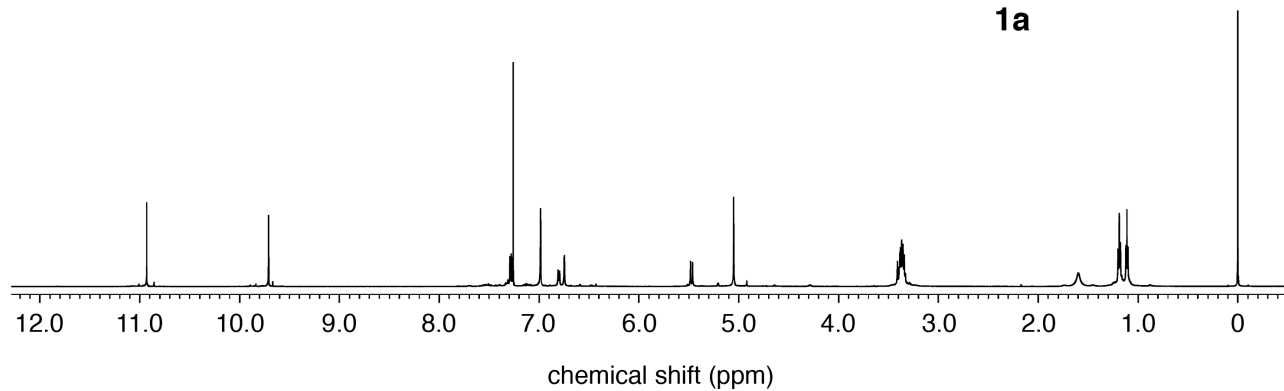
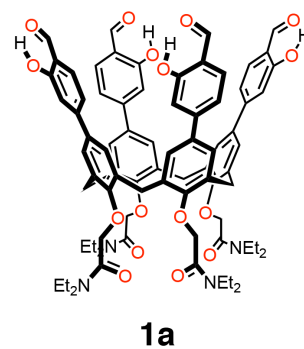


Fig. S16. ^1H NMR spectrum of **1a** (600 MHz, CDCl_3).

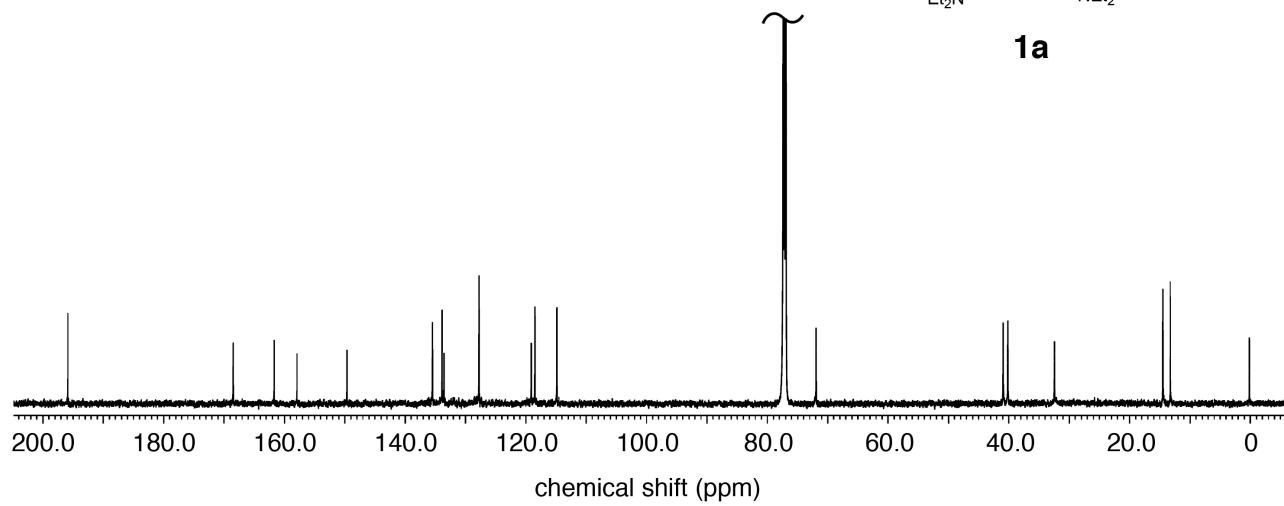
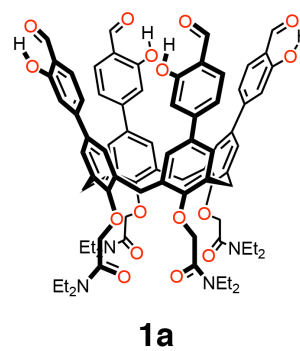


Fig. S17. ¹³C NMR spectrum of **1a** (150 MHz, CDCl₃).

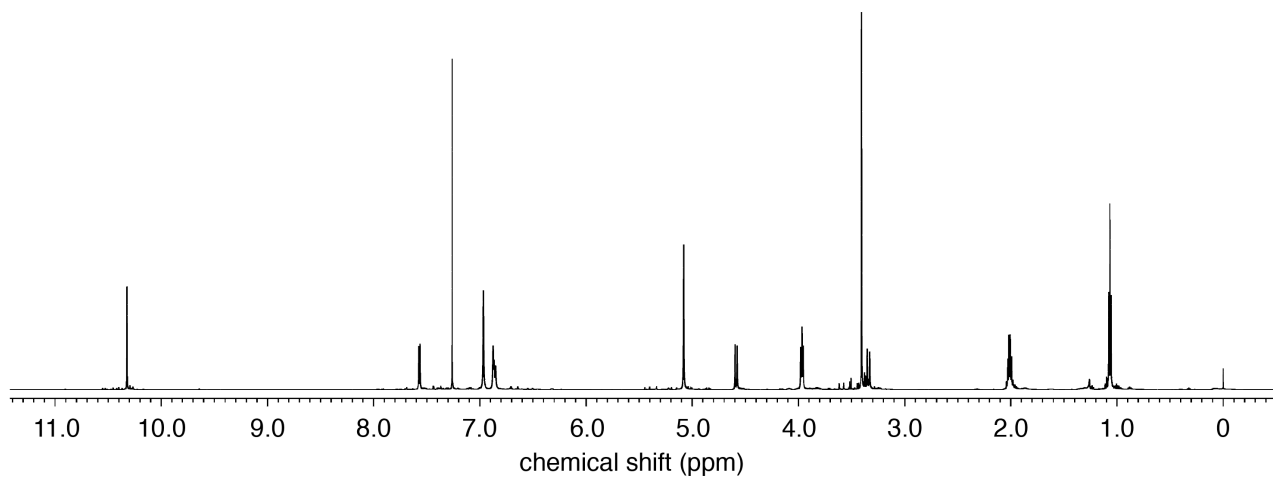
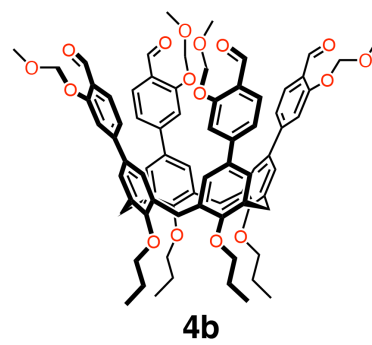


Fig. S18. ^1H NMR spectrum of **4b** (600 MHz, CDCl_3).

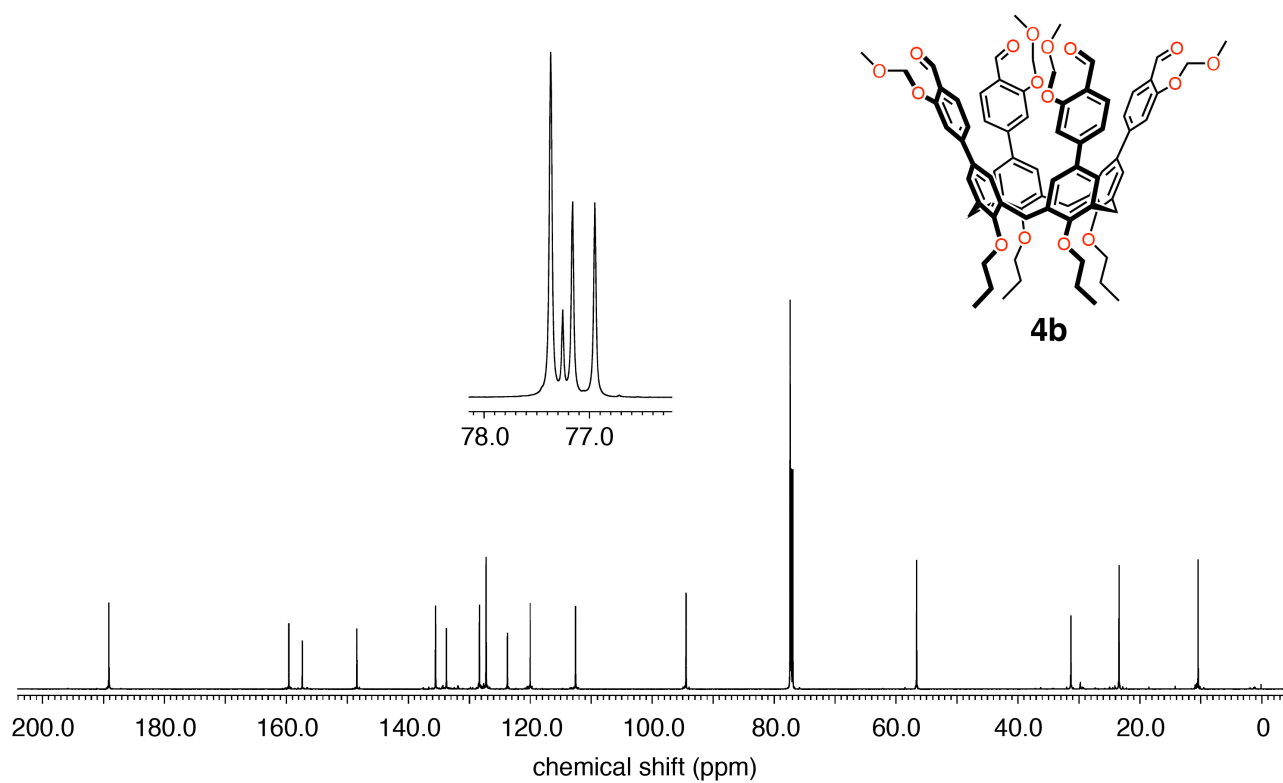


Fig. S19. ^{13}C NMR spectrum of **4b** (150 MHz, CDCl_3).

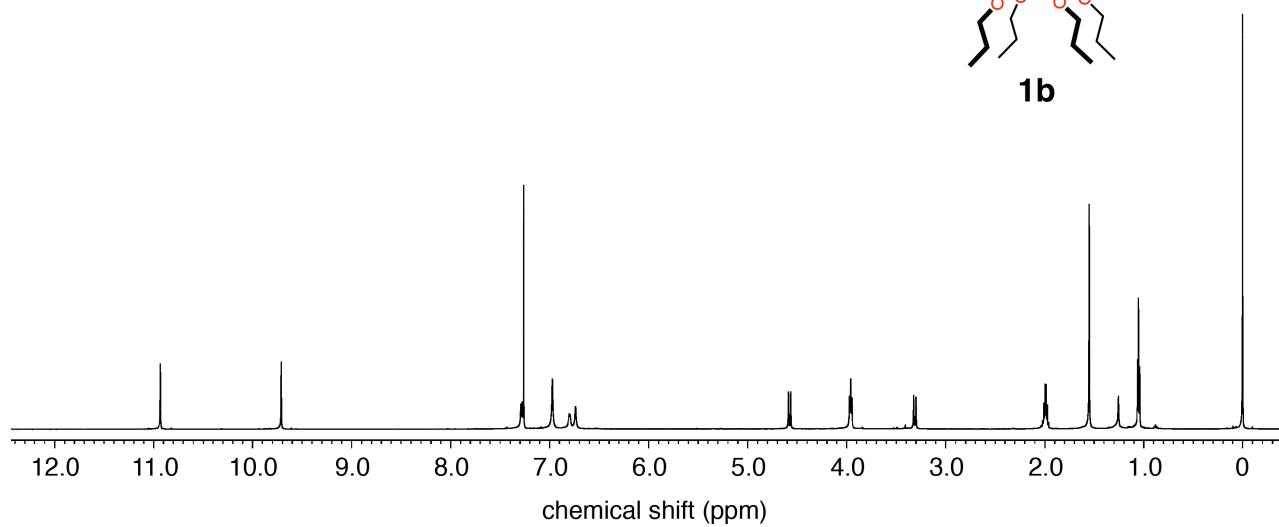
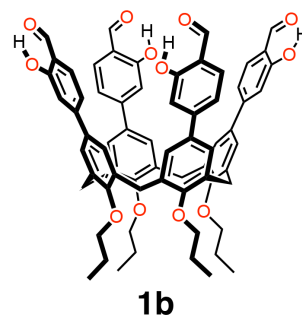


Fig. S20. ^1H NMR spectrum of **1b** (600 MHz, CDCl_3).

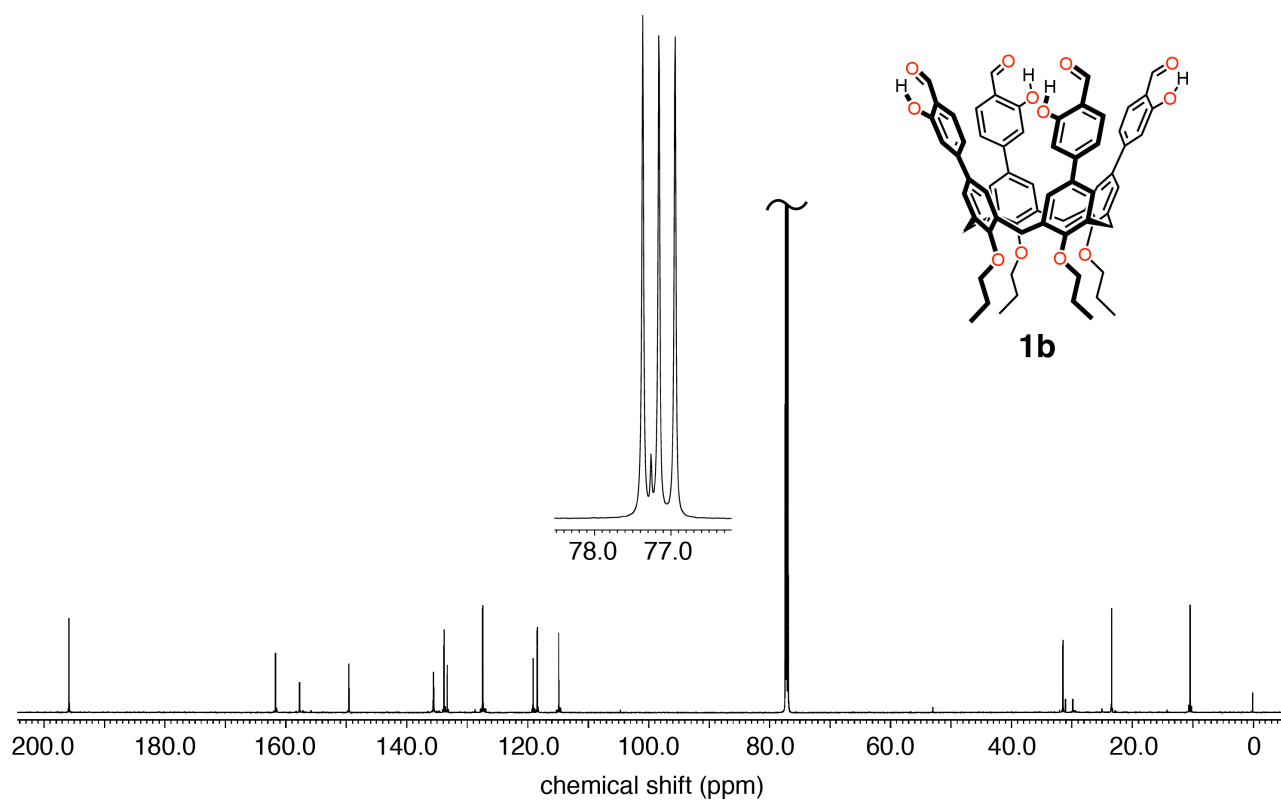


Fig. S21. ^{13}C NMR spectrum of **1b** (150 MHz, CDCl_3).

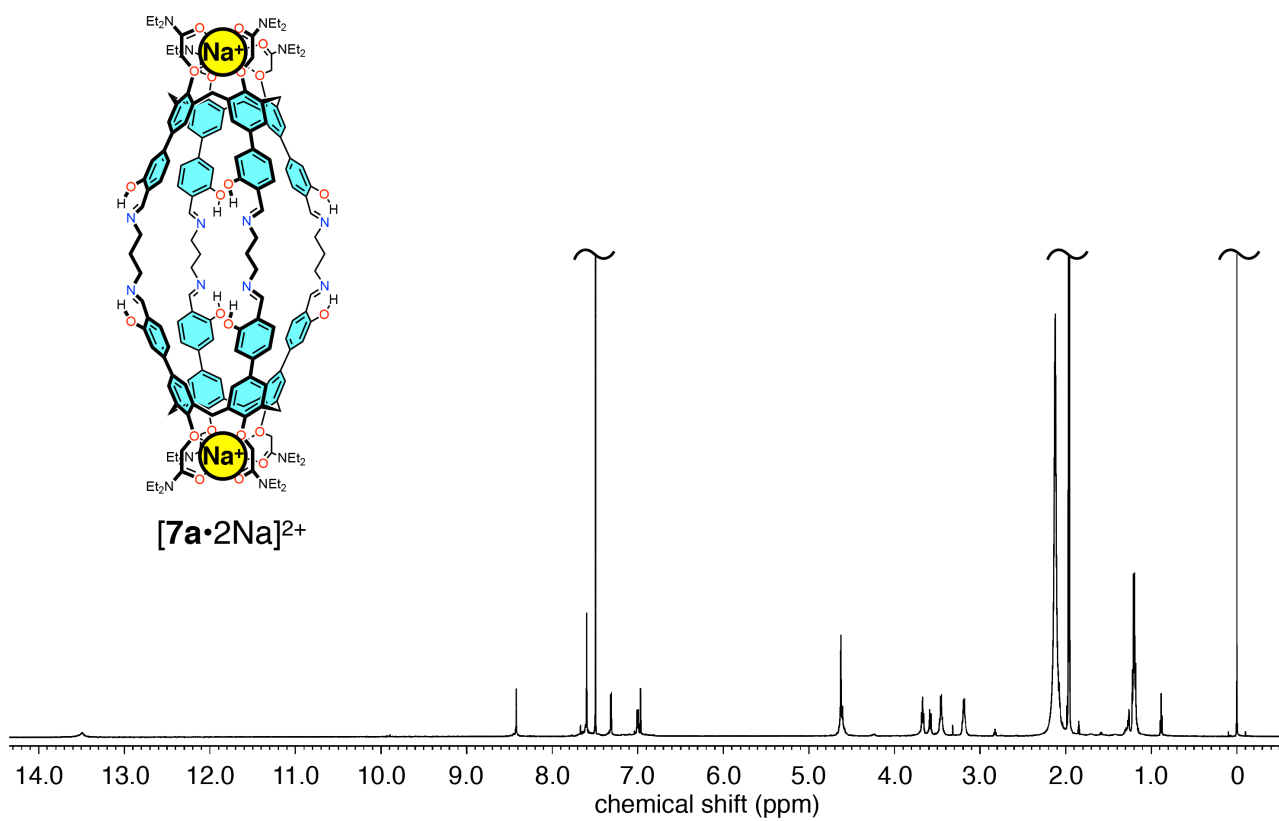


Fig. S22. 1H NMR spectrum of $[7a \cdot 2Na]^{2+}$ prepared by the reaction of **1a** with 2 equiv of 1,3-propanediamine in the presence of 1 equiv of NaOTf (600 MHz, $CDCl_3/CD_3CN$, 1:1).

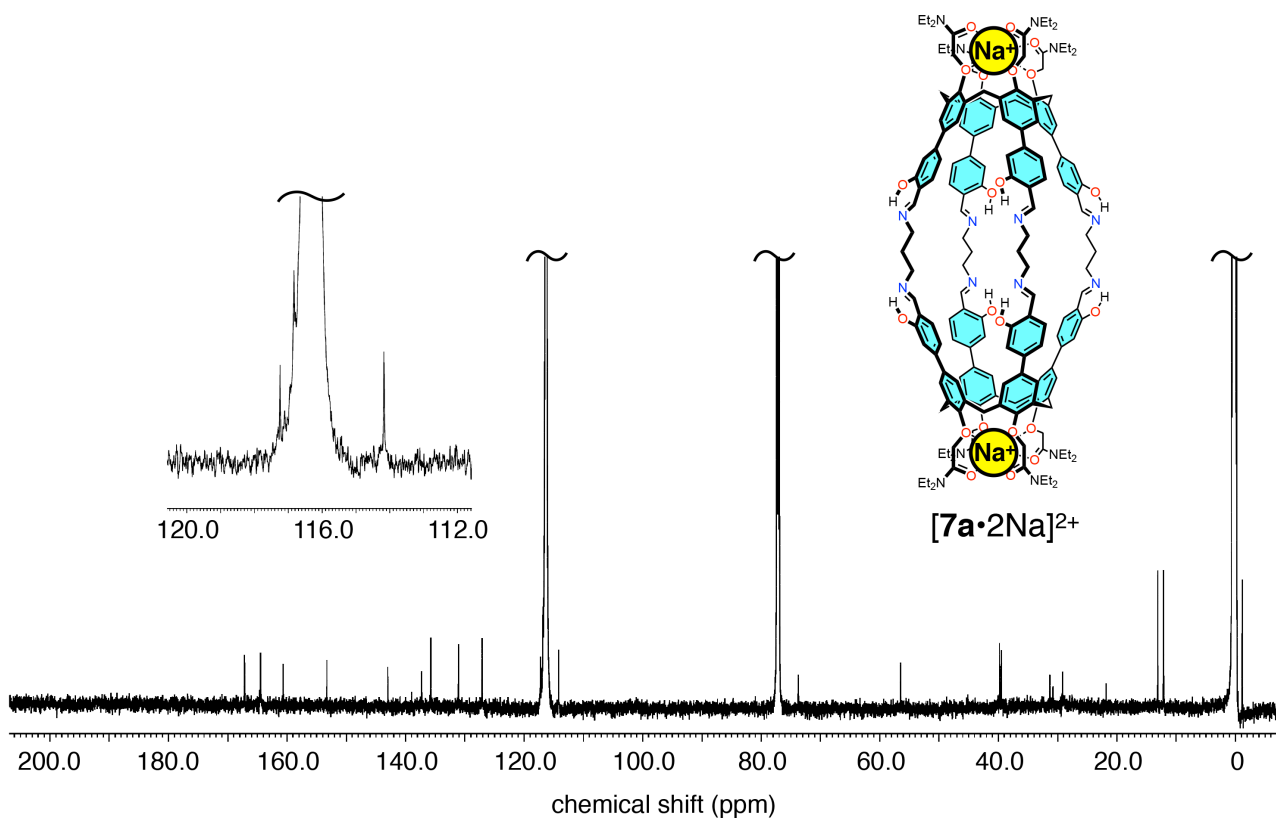


Fig. S23. ^{13}C NMR spectrum of $[\mathbf{7a}\cdot 2\text{Na}]^{2+}$ prepared by the reaction of **1a** with 2 equiv of 1,3-propanediamine in the presence of 1 equiv of NaOTf (150 MHz, $\text{CDCl}_3/\text{CD}_3\text{CN}$, 1:1).

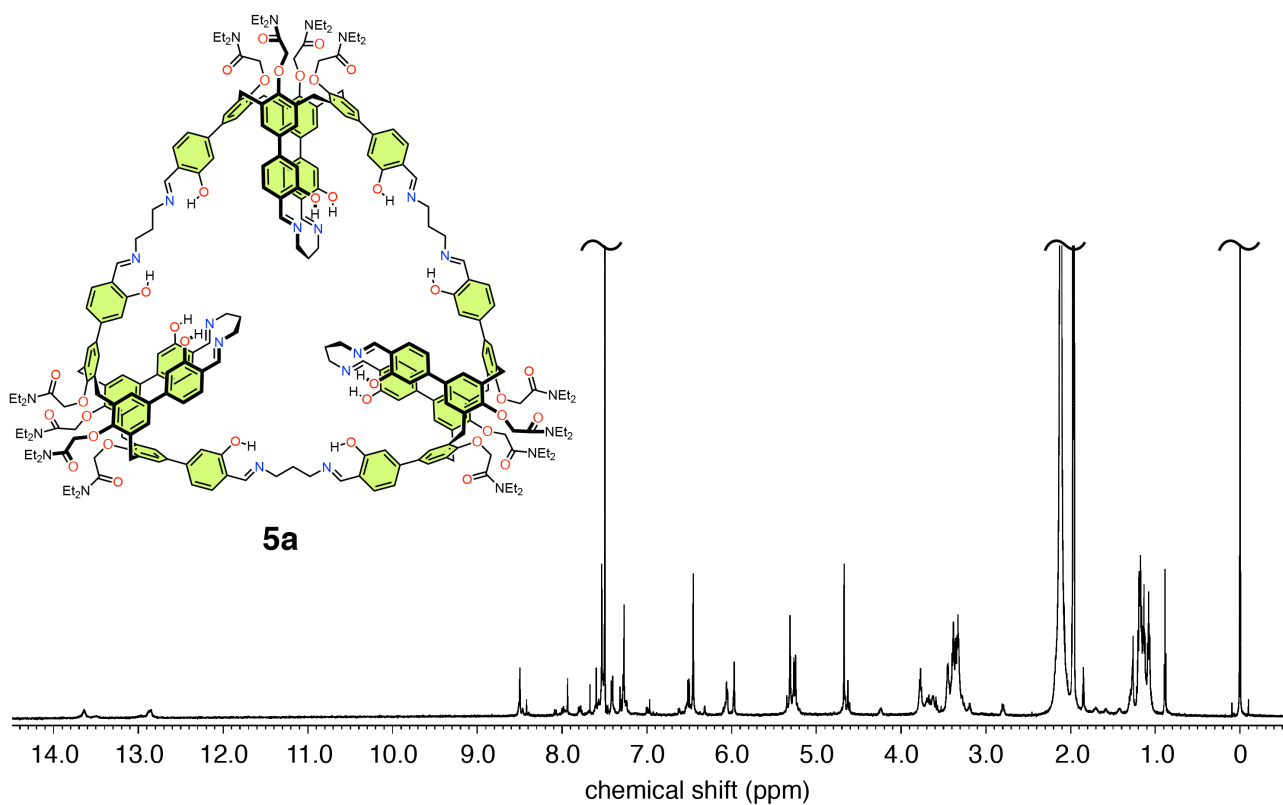


Fig. S24. ^1H NMR spectrum of **5a** prepared by the reaction of **1a** with 2 equiv of 1,3-propanediamine (600 MHz, $\text{CDCl}_3/\text{CD}_3\text{CN}$, 1:1).

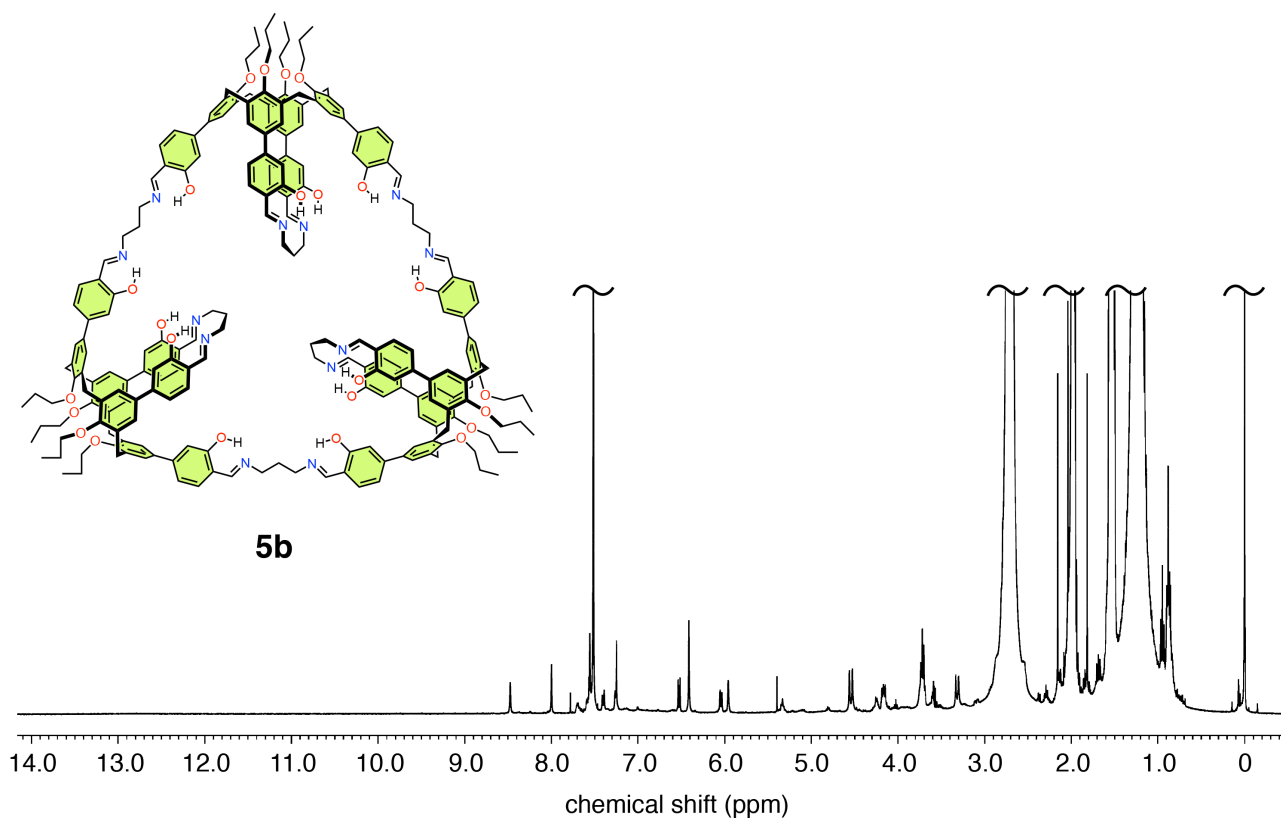


Fig. S25. ^1H NMR spectrum of **5b** prepared by the reaction of **1b** with 2 equiv of 1,3-propanediamine (400 MHz, $\text{CDCl}_3/\text{CD}_3\text{CN}$, 1:1).

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