Synthesis of a water-soluble bis(*m*-phenylene)-32-crown-10-based cryptand and its pH-responsive binding to a paraquat derivative

Xiaofan Ji, Mingming Zhang, Xuzhou Yan, Jinying Li and Feihe Huang*

MOE Key Laboratory of Macromolecular Synthesis and Functionalization, Department of Chemistry, Zhejiang University, Hangzhou, Zhejiang 310027, P. R. China,

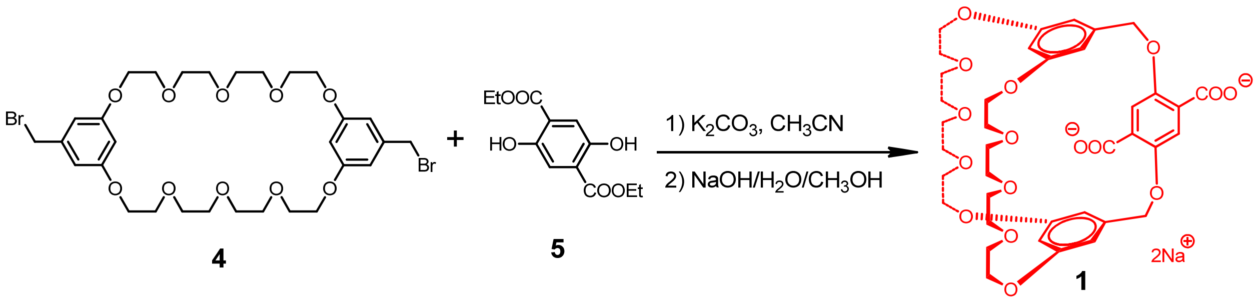
Fax and Tel: +86-571-8795-3189; Email address: fhuang@zju.edu.cn.

Electronic Supplementary Information (16 pages)

1. Materials and methods

All reagents were commercially available and used as supplied without further purification. Compounds **4**[S1] and **6**[S1] were synthesized by published literature procedures. Compound **5** was purchased from J&K. ^{1}H NMR spectra were collected on a temperature-controlled 400 MHz or 500 MHz spectrometer. ^{13}C NMR spectra were recorded on a Bruker AVANCE DMX-400 or DMX-500 spectrometer. Low-resolution electrospray ionization mass spectra (LRESI-MS) were obtained on a Bruker Esquire 3000 plus mass spectrometer (Bruker-Franzen Analytik GmbH Bremen, Germany) equipped with an ESI interface and an ion trap analyzer. High-resolution electrospray ionization mass spectra (HRESI-MS) were obtained on a Bruker 7-Tesla FT-ICR mass spectrometer equipped with an electrospray source (Billerica, MA, USA). The melting points were collected on a SHPSIC WRS-2 automatic melting point apparatus.

2. Synthesis of compound **1**



A mixture of **4** (180 mg, 0.250 mmol), **5** (64.0 mg, 0.250 mmol) and CH_3CN (50 mL) was prepared. This mixture was added *via* a syringe pump at 1 mL/h to a suspension containing K_2CO_3 (345 mg, 2.50 mmol) in CH_3CN (250 mL) at reflux under nitrogen gas protection. After complete addition, the mixture was stirred at reflux for 5 days. Potassium carbonate was filtered off and CH_3CN were removed with a rotaevaporator. The residue was dissolved in CH_2Cl_2 and washed with water. Removal of CH_2Cl_2 followed by column chromatography (petroleum ether/ethyl acetate, 1:1 *v*/*v*) afforded a white solid. The white solid (130 mg) was dissolved in CH_3OH (50 mL), then a saturated aqueous solution of NaOH (50 mL) was added. The mixture was stirred at reflux for 1 day. Removal of solvents followed by column chromatography (CH_3OH) afforded a white solid which was washed by water to remove NaOH, and vacuum dried (120 mg, 60%). Mp: 118.6–120.2 °C. The maximum concentration of **1** in water: 5.00 mM. The ^1H NMR spectrum of **1** is shown in Fig. S1. ^1H NMR (400 MHz, D_2O, 298 K) δ (ppm): 6.92 (2H, s), 6.46 (4H, $J = 2.1$ Hz, d), 6.20 (2H, $J = 2.1$ Hz, t), 5.05 (4H, s), 3.95–3.75 (8H, m), 3.70–3.60 (8H, m), 3.55–3.45 (16H, m). The ^{13}C NMR spectrum of **1** is shown in Fig. S2. ^{13}C NMR (125 MHz, DMSO, 298 K) δ (ppm): 171.15, 147.58, 141.34, 133.72, 115.40, 105.61, 101.06, 70.31, 70.12, 69.29, 68.82, 67.38. LRESIMS is shown in Fig. S3: *m*/*z* 757.3 $[M - 2Na + H]^-$ (100%). HRESIMS: *m*/*z* calcd for $[M - Na]^-$ $C_{38}H_{44}NaO_{16}^-$, 779.2533; found 779.2512; error −2.7 ppm.

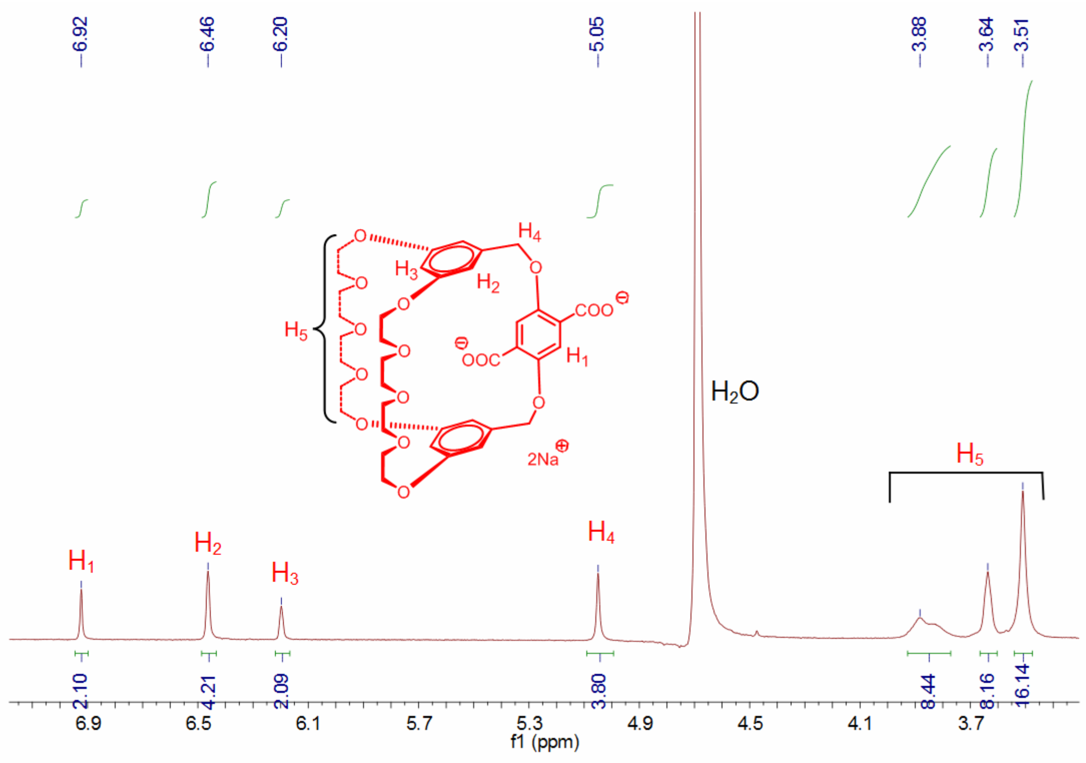


Fig. S1 ^{1}H NMR spectrum (400 MHz, D_2O, 298K) of **1**.

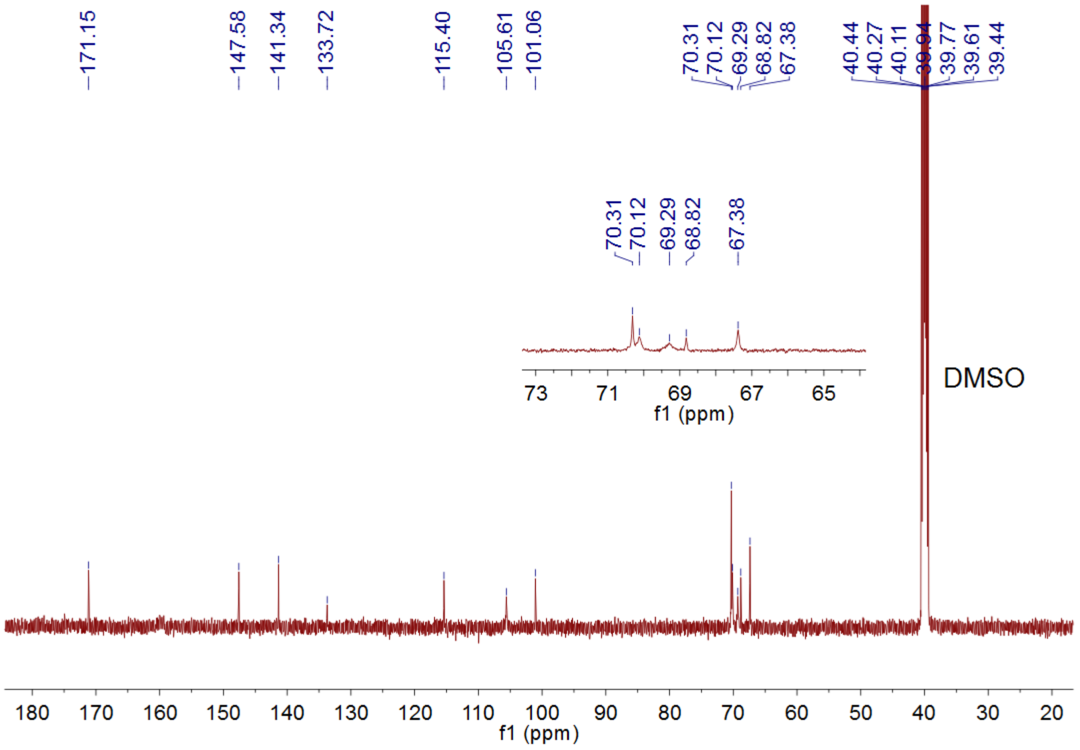


Fig. S2 ^{13}C NMR spectrum (125 MHz, DMSO, 298K) of **1**.

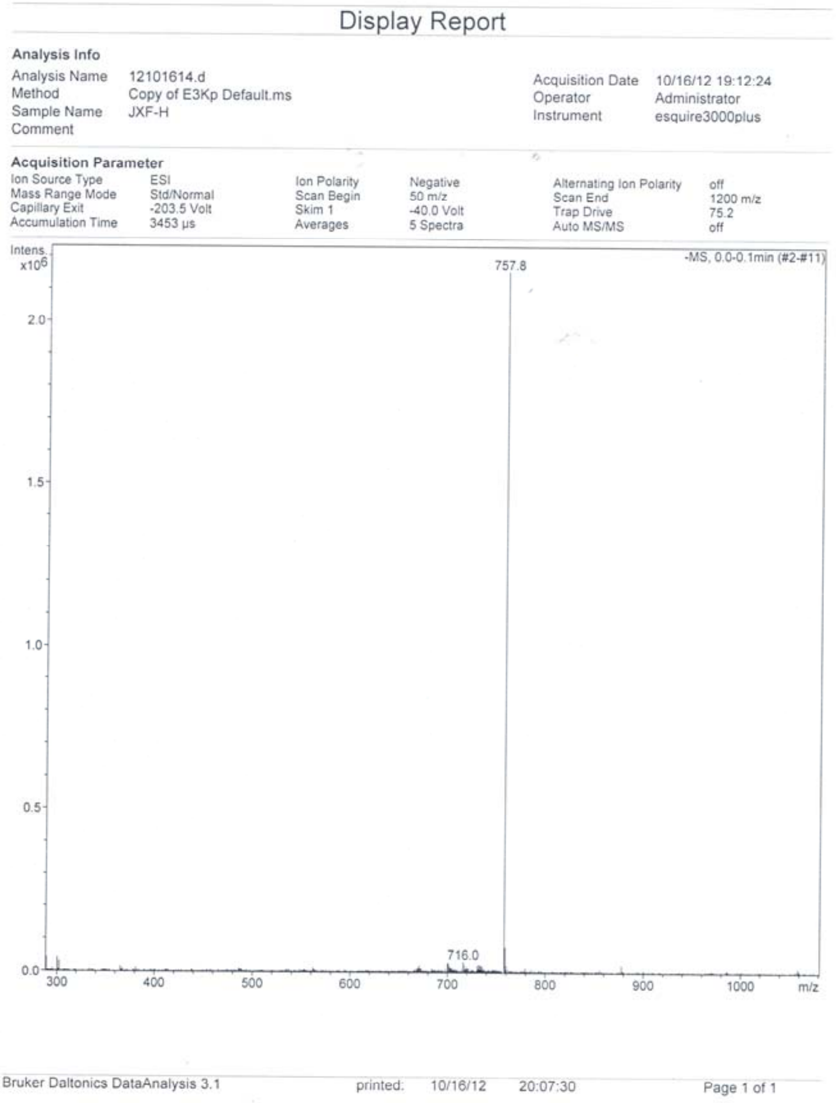


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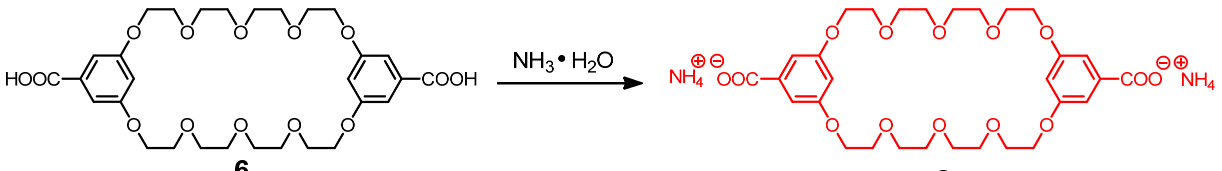
Fig. S3 LRESI mass spectrum of **1**.

*3. Synthesis of compound **2***



6

2

A mixture of **6** (0.630 g, 1.01 mmol) and $NH_3{\cdot}H_2O$ (25 mL, 14 M) was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure and the residue was dried in vacuum. The product was obtained as a white solid (0.66 g, 99%). Mp: 118.0–120.1 ºC. The ^1H NMR spectrum of **2** is shown in Fig. S4. ^1H NMR (400 MHz, D_2O, 298 K) δ (ppm): 6.88 (4H, s), 6.45 (2H, s), 3.95–3.88 (8H, m), 3.69–3.62 (8H, m), 3.57–3.49 (16H, m). The ^{13}C NMR spectrum of **2** is shown in Fig. S5. ^{13}C NMR (125 MHz, DMSO, 298 K) δ (ppm): 168.76, 159.55, 138.71, 107.82, 104.14, 70.46, 70.43, 69.34, 67.72. LRESIMS is shown in Figure S6: *m*/*z* 623.2 $[M - 2NH_4 + H]^-$ (100%). HRESIMS: *m*/*z* calcd for $[M - 2NH_4 + H]^-$ $C_{30}H_{39}NO_{14}^-$, 623.2351; found 623.2307; error −7.1 ppm.

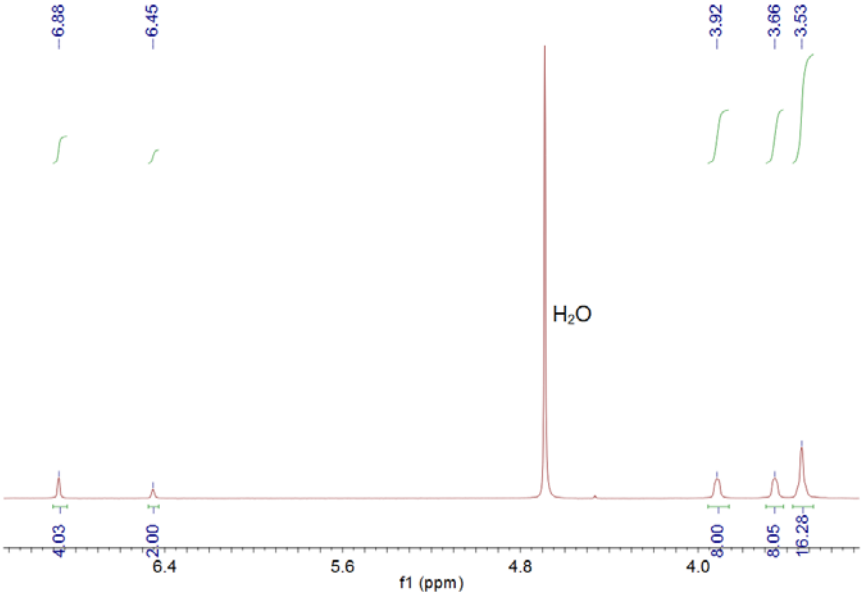


Fig. S4 ^1H NMR spectrum (400 MHz, D_2O, 298K) of **2**.

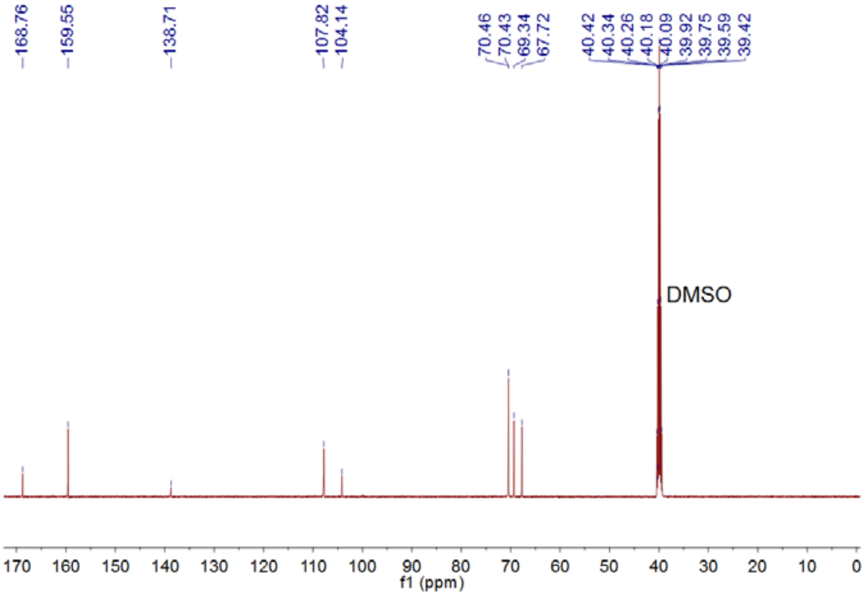


Fig. S5 ^{13}C NMR spectrum (125 MHz, DMSO, 298K) of **2**.

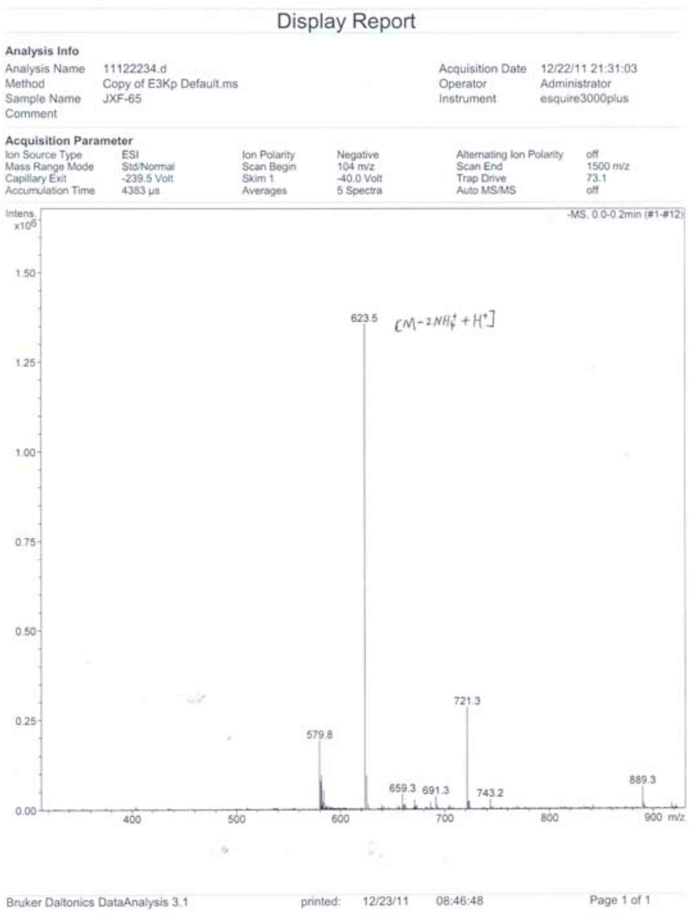


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Fig. S6 LRESI mass spectrum of **2**.

*4. Job plots of **1⊃3** and **2⊃3** based on UV-Vis data in H_2O*

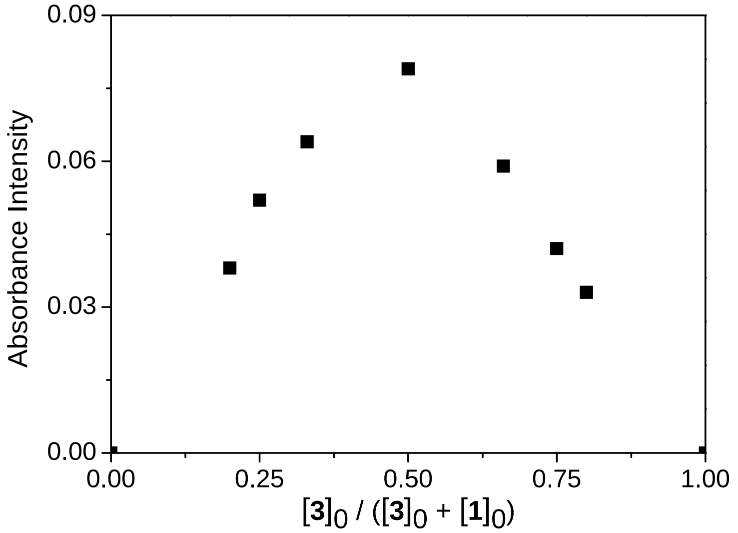


Fig. S7 Job plot showing the 1:1 stoichiometry of the complexation between **1** and **3** in H_2O. $[\mathbf{1}]_0 + [\mathbf{3}]_0 = 0.500$ mM. $[\mathbf{1}]_0$ and $[\mathbf{3}]_0$ are the initial concentrations of **1** and **3**, respectively.

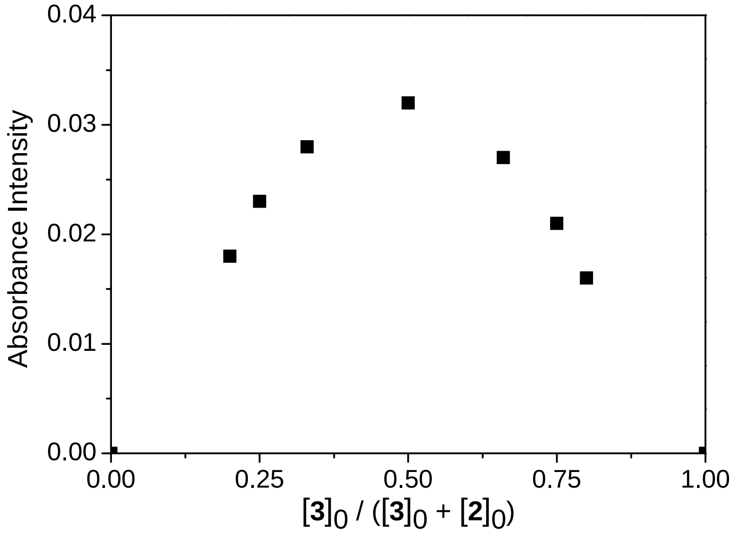


Fig. S8 Job plot showing the 1:1 stoichiometry of the complexation between **2** and **3** in H_2O. $[\mathbf{2}]_0 + [\mathbf{3}]_0 = 0.500$ mM. $[\mathbf{2}]_0$ and $[\mathbf{3}]_0$ are the initial concentrations of **2** and **3**, respectively.

5. Determination of association constants of ***1*** *$\supset$* ***3*** *and* ***2*** *$\supset$* ***3*** [S2]

The association constants of complexes **1**$\supset$**3** and **2**$\supset$**3** were determined by probing the charge-transfer band of the complexes by UV-Vis spectroscopy and employing a titration method. Progressive addition of a water solution with high guest **3** concentration (10.0 mM) and low host **1** or **2** concentration (1.00 mM) to a water solution (pH = 7.0, 298 K) with the same concentration of host **1** or **2** resulted in an increase of the intensity of the charge-transfer band of the complex. Treatment of the collected absorbance data at λ = 380 nm with a non-linear curve-fitting program afforded the corresponding association constants (K_a): 2.0 (± 0.4) × 10^4 M^{-1} for **1**$\supset$**3**, and 1.7 (± 0.1) × 10^3 M^{-1} for **2**$\supset$**3**.

The non-linear curve-fitting (Origin 7.5 program) was based on the equation:

$$A = (A_\infty/[H]_0)\,(0.5[G]_0 + 0.5([H]_0+1/K_a) - (0.5\,([G]_0^2 + (2[G]_0(1/K_a - [H]_0)) + (1/K_a + [H]_0)^2)^{0.5})) \qquad \text{(Eq. S1)}$$

Where A is the absorption intensity of the charge-transfer band (λ = 380 nm) at $[G]_0$, A_∞ is the absorption intensity of the charge-transfer band (λ = 380 nm) when the host is completely complexed, $[H]_0$ is the fixed initial concentration of the host, and $[G]_0$ is the initial concentration of the guest.

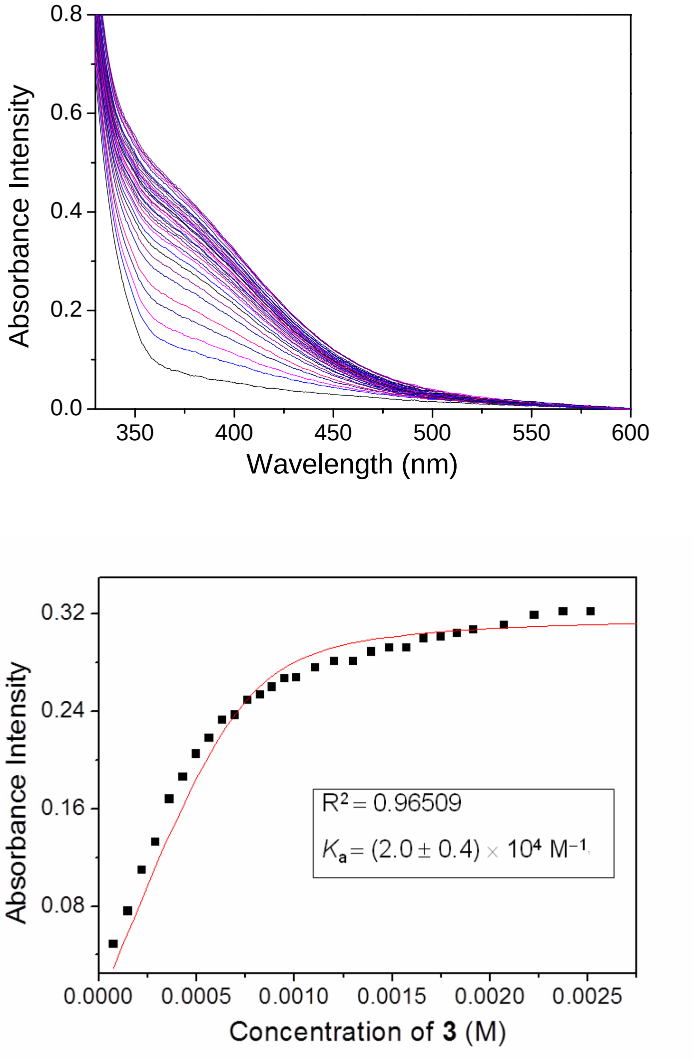


Fig. S9 Titration curve (top) and non-linear fitting curve (bottom) of host **1** and guest **3**.

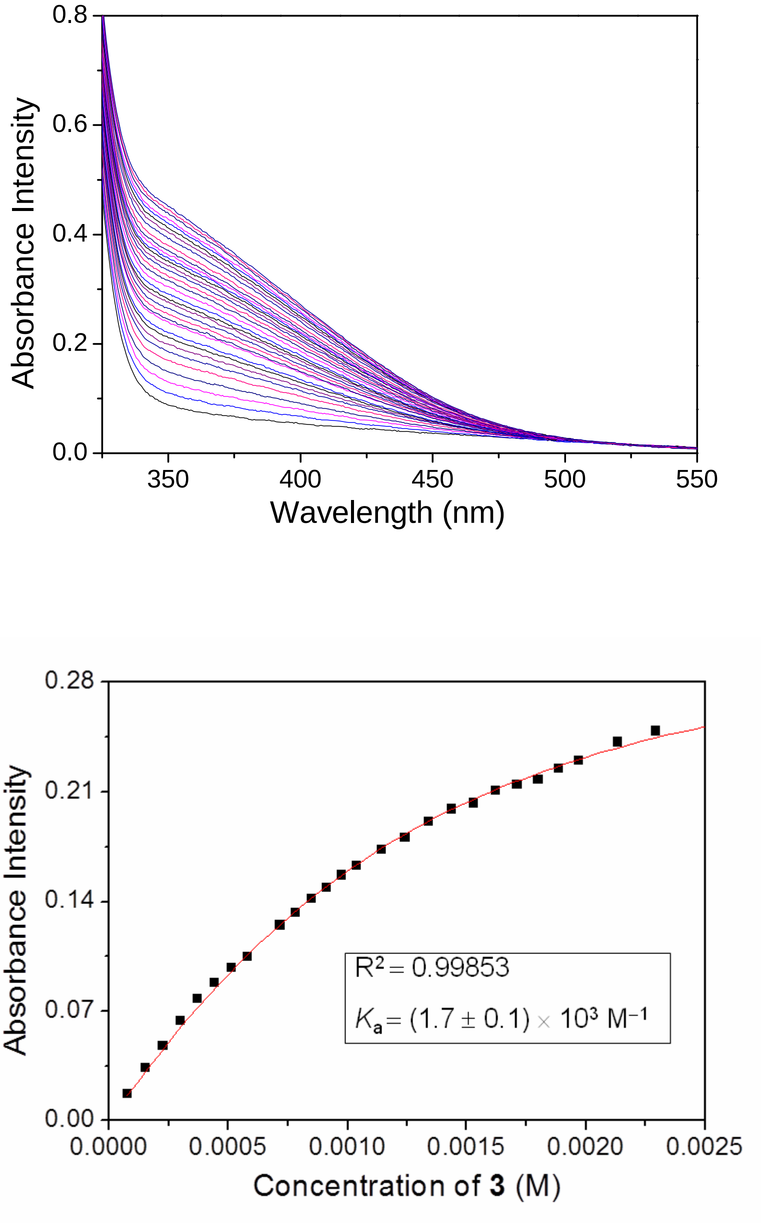


Fig. S10 Titration curve (top) and non-linear fitting curve (bottom) of host **2** and guest **3**.

*6. Electrospray ionization mass spectra of **1** and **3**, and **2** and **3** in H_2O*

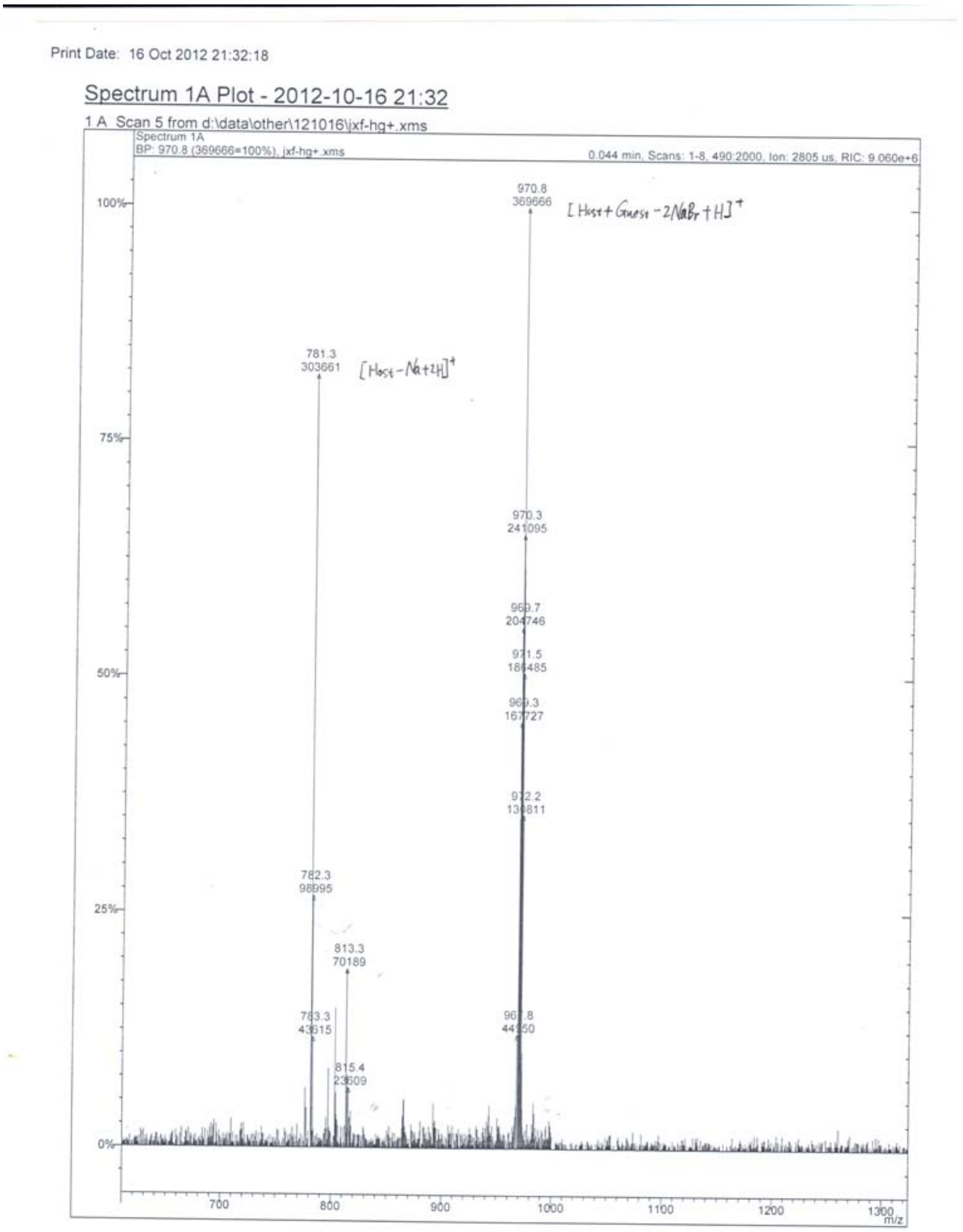


Fig. S11 Positive electrospray ionization mass spectrum of **1** and **3** in H_2O, giving strong mass fragments at *m/z* 970.8 (100%) and 781.3 (82.5%), corresponding to $[\mathbf{1}\supset\mathbf{3} - 2Na - 2Br + H]^+$ and $[\mathbf{1} - Na + 2H]^+$, respectively.

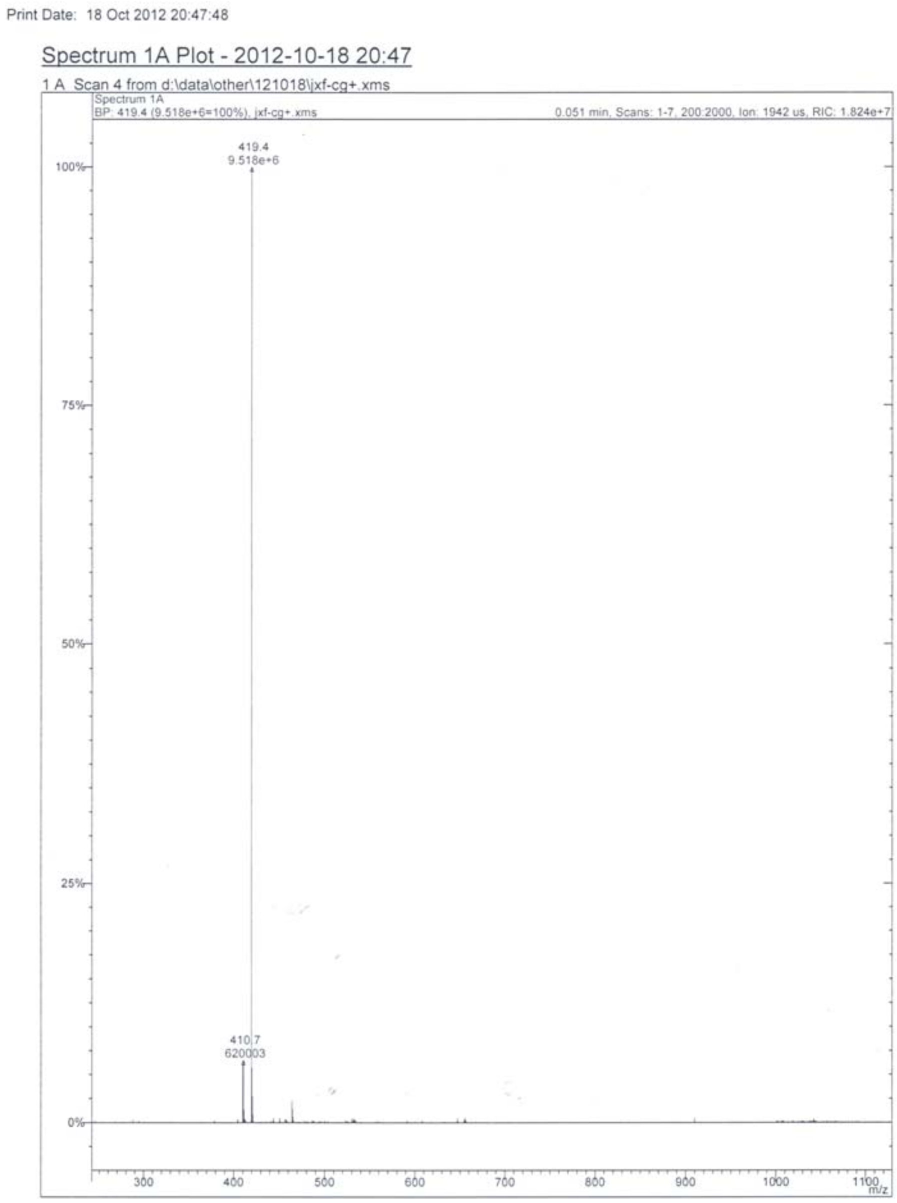


Fig. S12 Positive electrospray ionization mass spectrum of **2** and **3** in H_2O, giving strong mass fragments at *m/z* 419.4 (100%), corresponding to $[\mathbf{2}\supset\mathbf{3} - 2NH_4 - 2Br + 2H]^{2+}$.

7. Partial NOESY NMR spectra of **1** *and* **3, 2** *and* **3** *in* D_2O

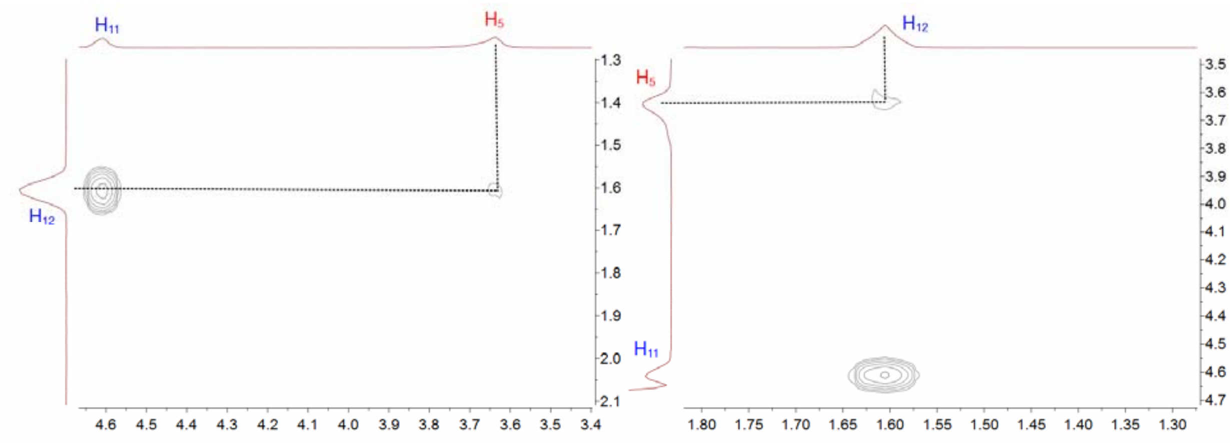


Fig. S13 Partial NOESY NMR (500 MHz, D_2O, 298 K) spectrum of a solution of 3.00 mM **1** and **3**.

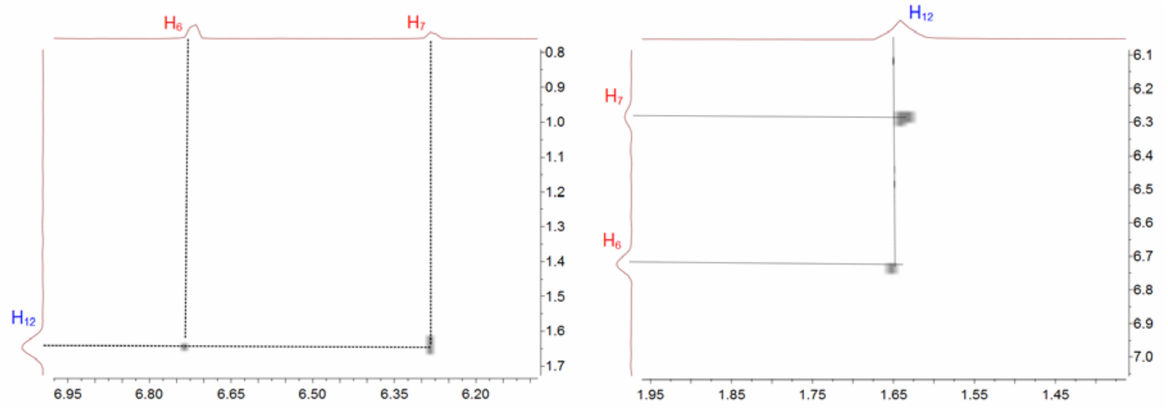


Fig. S14 Partial NOESY NMR (500 MHz, D_2O, 298 K) spectrum of a solution of 3.00 mM **2** and **3**.

*8. Partial ^{1}H NMR spectra of the pH-controlled complexation between **2** and **3***

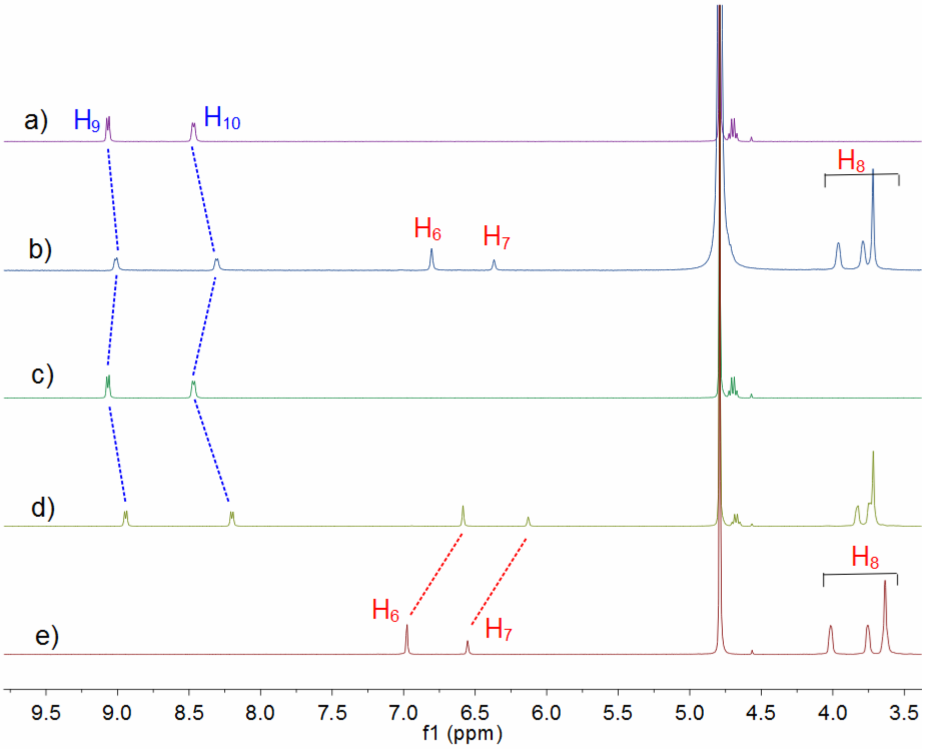
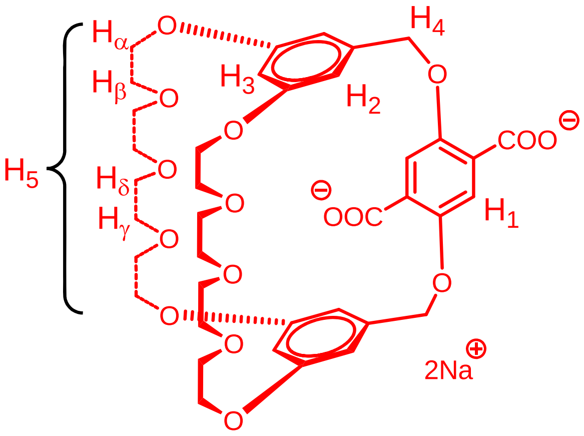


Fig. S15 Partial ^{1}H NMR spectra (400 MHz, D_2O, 298 K): a) **3**; b) a solution of 2.00 μL of aqueous HCl solution, 1.50 mg NaOH, and 0.500 mL of 3.00 mM **2** and **3**; c) a solution of 2.00 μL of aqueous HCl solution and 0.500 mL of 3.00 mM **2** and **3**; d) 3.00 mM **2** and **3**; and e) **2**.

*9. COSY and NOESY NMR spectra of **1** in D_2O*



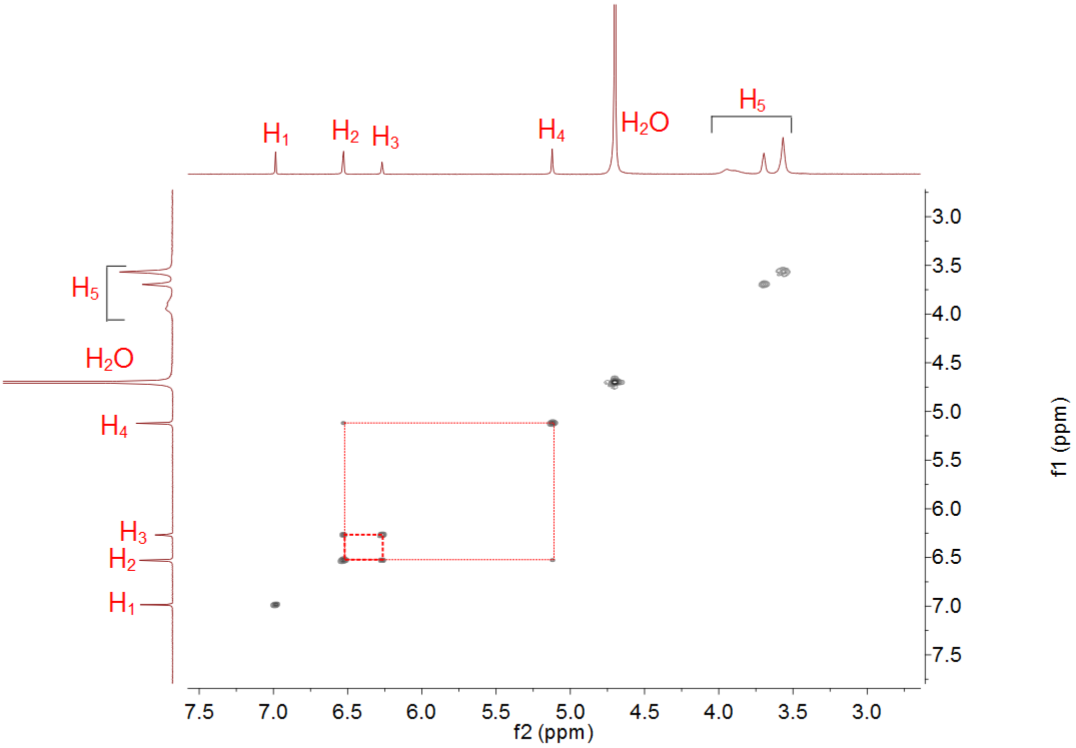


Fig. S16 COSY NMR (500 MHz, D_2O, 298 K) spectrum of 3.00 mM **1**. Correlated signals were observed between H_2 and H_3 and between H_2 and H_4 in D_2O.

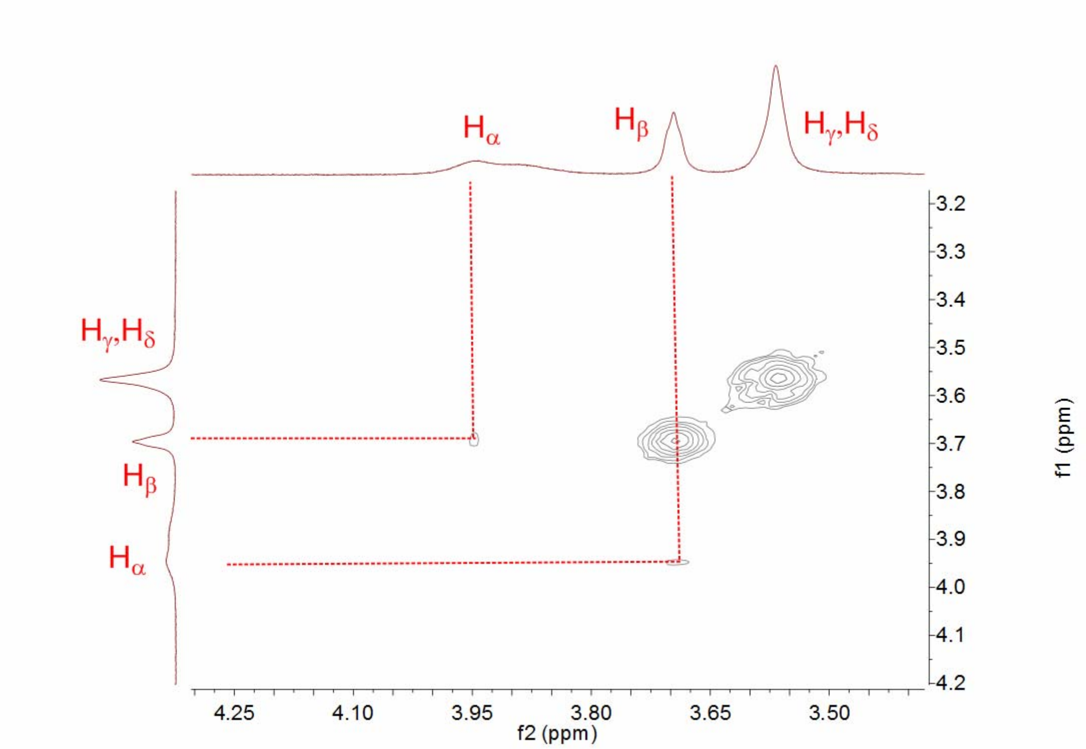


Fig. S17 Partial COSY NMR (500 MHz, D_2O, 298 K) spectrum of 3.00 mM **1**. A correlated signal was observed between H_α and H_β in D_2O.

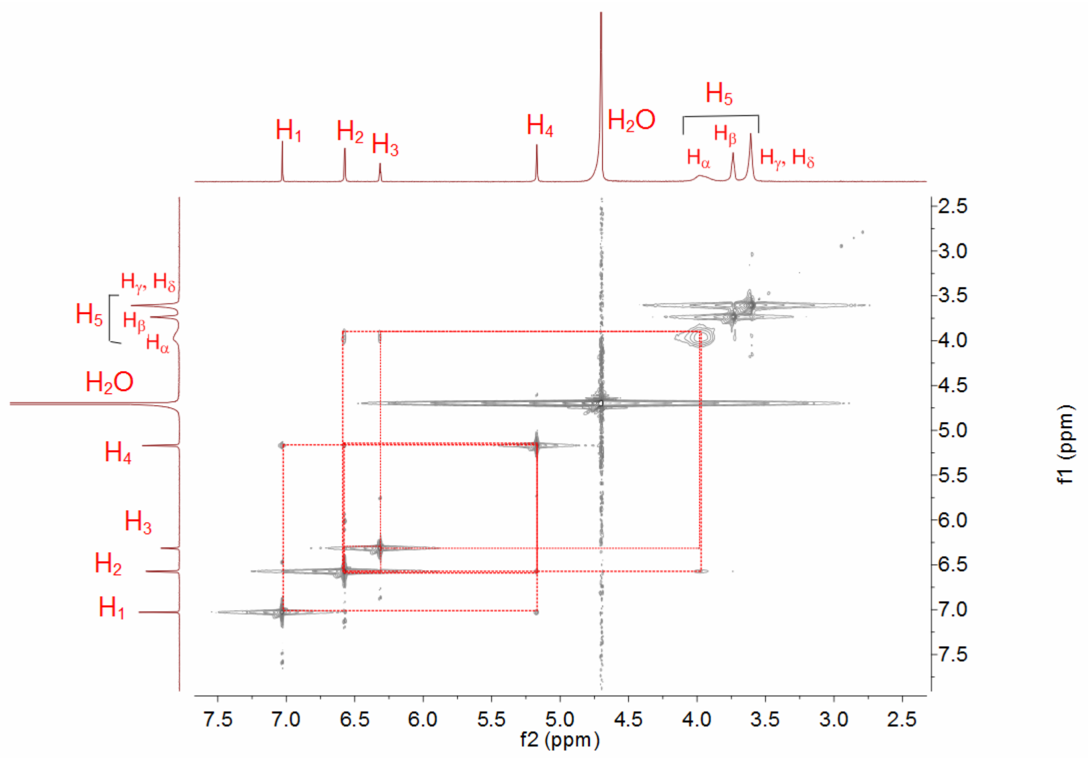


Fig. S18 NOESY NMR (500 MHz, D_2O, 298 K) spectrum of 3.00 mM **1**. Correlated signals were observed between H_2 and H_3, between H_1 and H_4, between H_2 and H_4, between H_α and H_3, and between H_α and H_2 in D_2O.

References:

S1. H. W. Gibson and D. S. Nagvekar, *Can. J. Chem.* 1997, **75**, 1375–1384.

S2. (a) K. A. Connors, *Binding Constants*; Wiley: New York, 1987; (b) Corbin, P. S. Ph.D. Dissertation, University of Illinois at Urbana-Champaign, Urbana, IL, 1999; (c) P. R. Ashton, R. Ballardini, V. Balzani, M. Belohradsky, M. T. Gandolfi, D. Philp, L. Prodi, F. M. Raymo, M. V. Reddington, N. Spencer, J. F. Stoddart, M. Venturi and D. J. Williams, *J. Am. Chem. Soc.* 1996, **118**, 4931–4951.