Pillar[5]arene and Crown Ether Fused Bicyclic Host, Synthesis, Guest Discrimination and Simultaneous Binding of Two Guests with Different Shape, Size and Electronic Constitution

Wei-Bo Hu, Hong-Mei Yang, Wen-Jing Hu, Ming-Liang Ma,* Xiao-Li Zhao, Xian-Qiang Mi, Yahu A. Liu, Jiu-Sheng Li,* Biao Jiang* and Ke Wen*

Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, Shanghai 200062, China

Shanghai Advanced Research Institute, Chinese Academy of Science, Shanghai 201210, China

Shanghai Key Laboratory of Green Chemistry and Chemical Processes, and Department of Chemistry, East China Normal University, Shanghai 200062, China

Medicinal Chemistry, ChemBridge Research Laboratories Inc., San Diego, CA 92127, USA

School of Physical Science and Technology, ShanghaiTech University, Shanghai 201210, China

Correspondence Address
Prof. Dr. Ke Wen
Shanghai Advanced Research Institute, Chinese Academy of Science
No. 100 Haike Road, Zhangjiang Hi-Tech Park, Pudong, Shanghai, 201210 P. R. China
E-mail: wenk@sari.ac.cn

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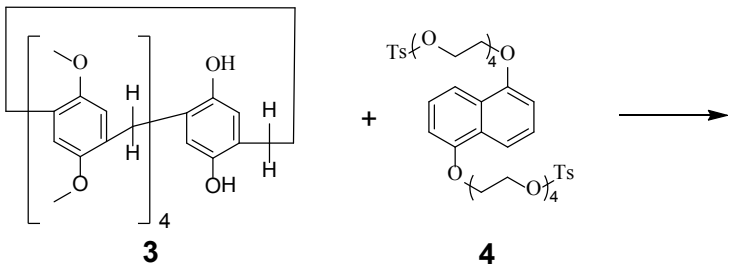
Experimental Procedures

General:

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded at 400 (400 MHz) spectrometers with TMS as the reference. Mass spectra (ESI analysis) were recorded on a micrOTOF-Q spectrometer (LC/MS). Single crystal X-ray diffraction data were collected on a SMART APEX 2 X-ray diffractometer equipped with a normal focus Mo-target X-ray tube (λ = 0.71073 Å). Data reduction included absorption corrections by the multi-scan method. The structures were solved by direct methods and refined by full-matrix least-squares using SHELXS-97. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were added at their geometrically ideal positions and refined isotropically.

Synthesis of 1:

Compounds **3**, **4** and paraquat ($MV^{2+}.2PF_6$) were prepared by literature methods. [1]



A mixture of compound **3** (300 mg, 0.42mmol), Cs_2CO_3 (411 mg, 1.26 mmol) and compound **4** (335 mg, 0.42 mmol) in 50mL DMF was heated to 85 ^{O}C under nitrogen overnight. After

cooling down to room temperature, the reaction mixture was poured into 1M HCl (100mL) and extracted with ethyl acetate (3 x 50 mL). The organic phase was combined, washed with brine and dried over anhydrous sodium sulfate. After removing the solvent, the residue was purified by silica gel column chromatography using ethyl acetate and petroleum ether (EA/PE= 1/1) as eluent affording **1** as white solid (101 mg, 0.084 mmol. Yield: 20%). ^{1}H NMR ($CDCl_3$, 400 MHz ppm): δ 7.84 (d, *J* = 8.0 Hz, 2H, naphthalene), 7.30 (t, *J* = 8.0 Hz, 2H, naphthalene), 6.81 (s, 4H, phenyl), 6.79 (s, 4H, phenyl), 6.73 (d, *J* = 8.0 Hz, 2H, naphthalene), 6.69 (s, 2H, phenyl), 4.05 (m, 4H, methylene), 3.76-3.82 (m, 14H, methylene), 3.57–3.69 (m, 34H, methylene and methyl), 3.56-3.51 (m, 8H, methylene), 3.34–3.38 (m, 6H, methylene). ^{13}C NMR ($CDCl_3$, 100 MHz ppm): δ 154.3, 150.8, 150.8, 150.6, 149.8, 128.6, 128.5, 128.3, 128.1, 126.8, 125.1, 115.0, 114.6, 114.3, 114.2, 113.7, 105.8, 70.8, 70.7, 70.5 , 70.6, 70.0, 69.3, 67.8, 56.0, 55.8, 55.6, 29.8, 29.8, 29.6, 29.5, 29.4 ppm. HR-MS: *m/z* calcd [M + Na^{+}] for $C_{69}H_{82}O_{18}Na^{+}$: 1221.53949; Found 1221.53934.

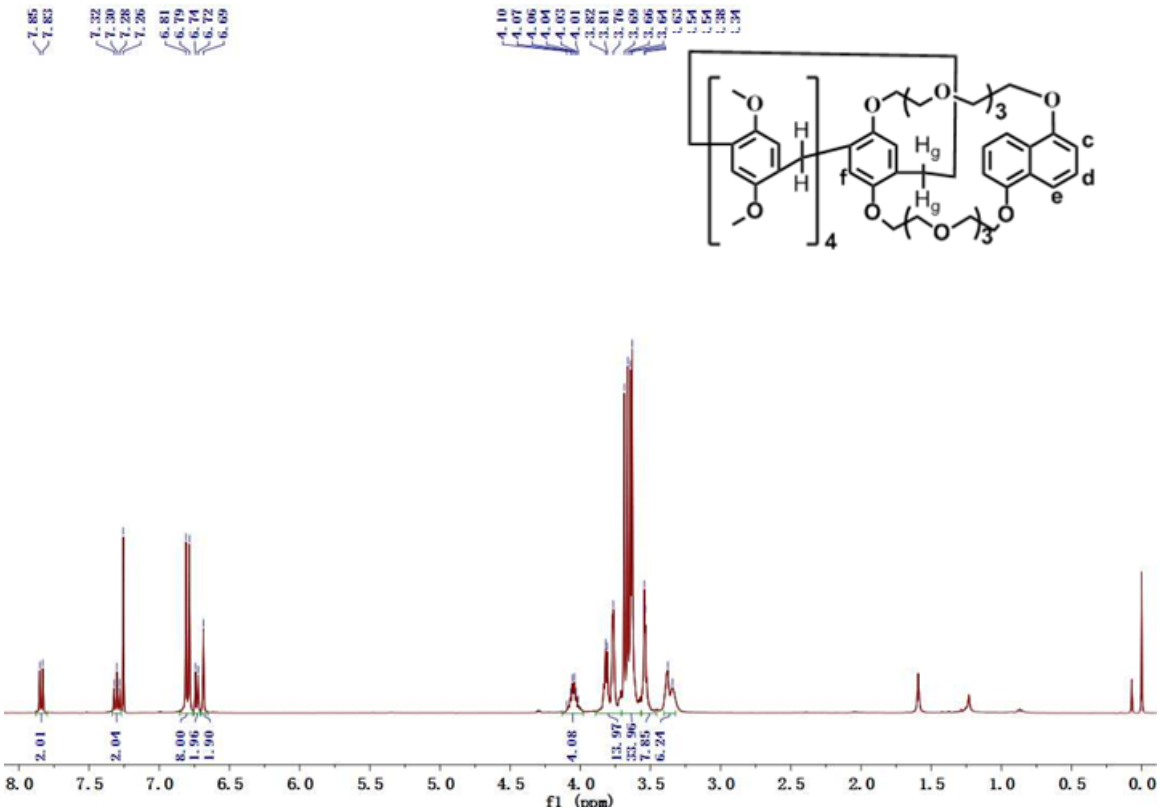


Fig. S1 ^{1}H NMR spectrum (400 MHz) of compound **1** in $CDCl_3$.

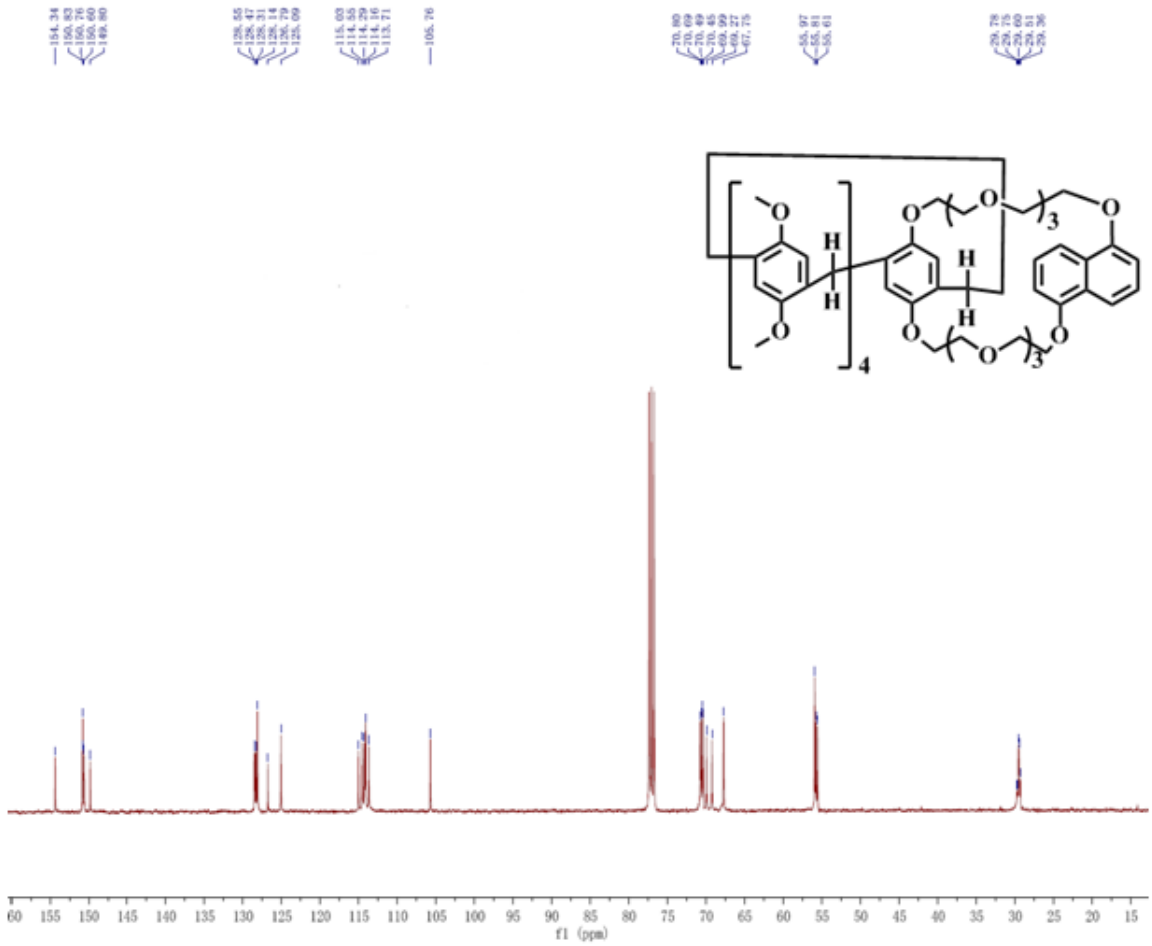


Fig. S2 ^{13}C NMR spectrum (100 MHz) of compound **1** in $CDCl_3$.

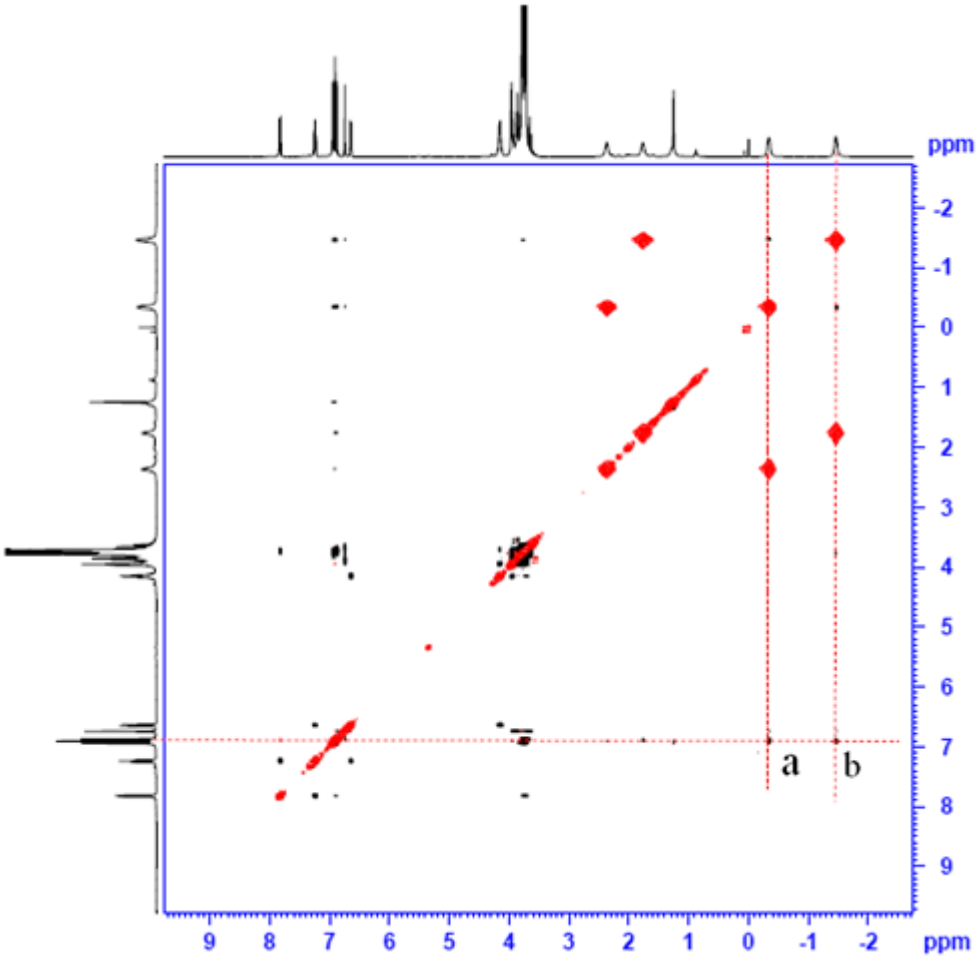


Fig. S3 2D NOESY spectrum of the mixture of **1** and **G1** in $CDCl_3$ (400 MHz, 298 K, The concentrations of **1** and **G1** are 3.0 and 5.3 mM, respectively)

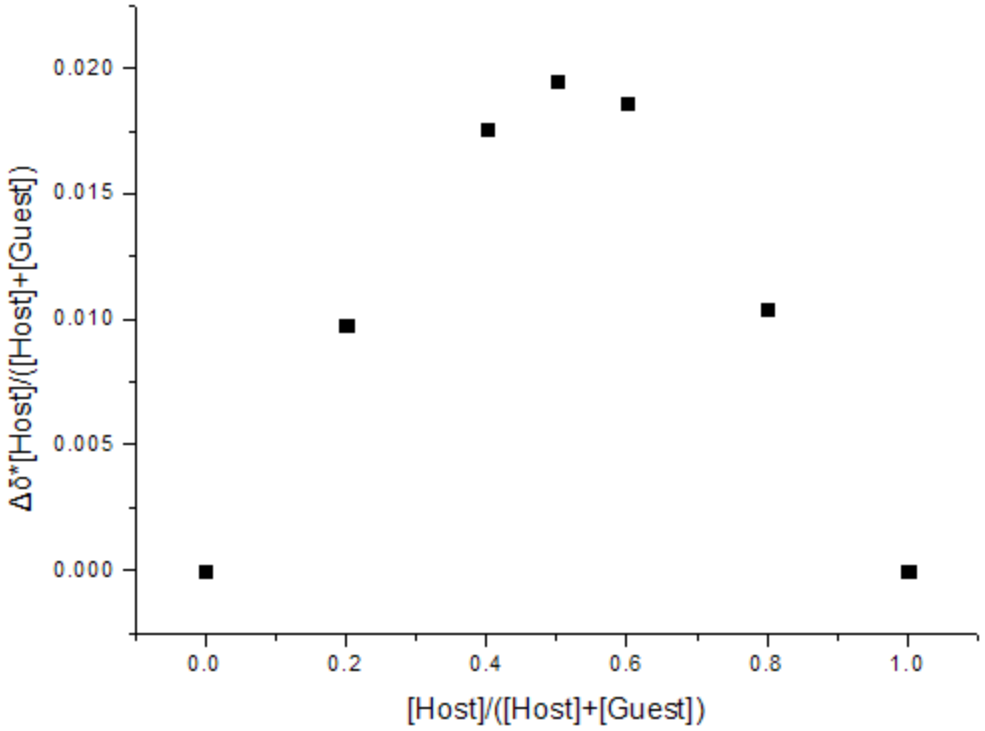


Fig. S4 Job plot showing the 1:1 stoichiometry of the complex between **1** and **G1** in acetone-d_6 by plotting the Δδ in chemical shift of **1**'s H_f (for proton designations, see Figure S1) observed by ^{1}H NMR spectroscopy against the mole fraction of complex. ([host] + [guest] = 1.0 mM).

Stoichiometry and association constant determination for the complexation between 1 and G1

In $CDCl_3$, no free guest **G1** was observed in the presence of one equivalent of **1**（**[G1]→0**，$\boldsymbol{K_a}$**→+∞**）, suggesting very strong binding affinity. So it is hard to calculate of binding constants for **G1** in $CDCl_3$. In acetone-d_6, chemical exchange is slow on the NMR time scale and peaks are observed for both complexed (**G1⊂1**) and uncomplexed species in the NMR spectra. The association constant K_a for the complex was determined by integration from a 1:3 mixture using the ^{1}H NMR single point method.

$$K_a = \frac{[\mathbf{G1 \subset 1}]}{[\mathbf{G1}][\mathbf{1}]}$$

The K_a for this complex in acetone-d_6 was calculated to be (6.1 ± 0.2) x 10^3 M^{-1}.

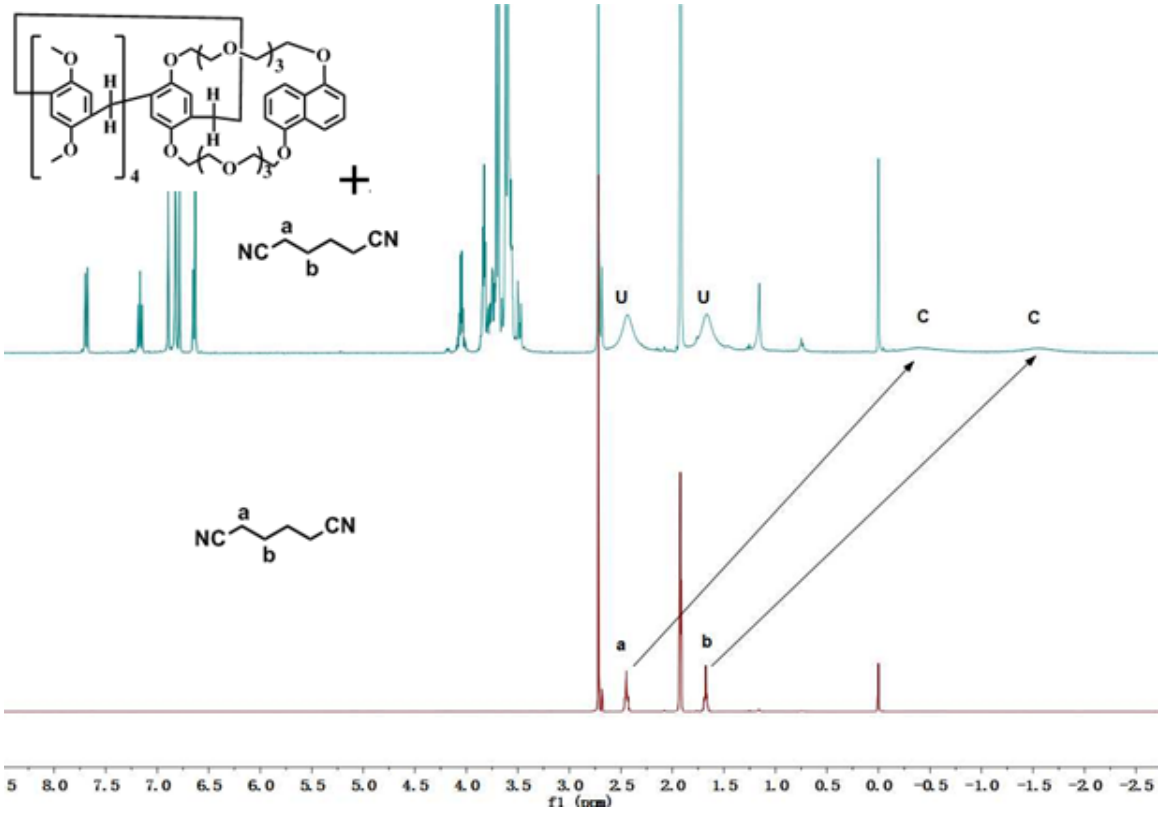


Fig. S5 ^{1}H NMR spectra (400 MHz, acetone-d_6, 298 K) of **G1** (bottom) and 1:3 mixture of **1** and **G1** (top). U = uncomplexed **G1**, C = complexed **G1**.

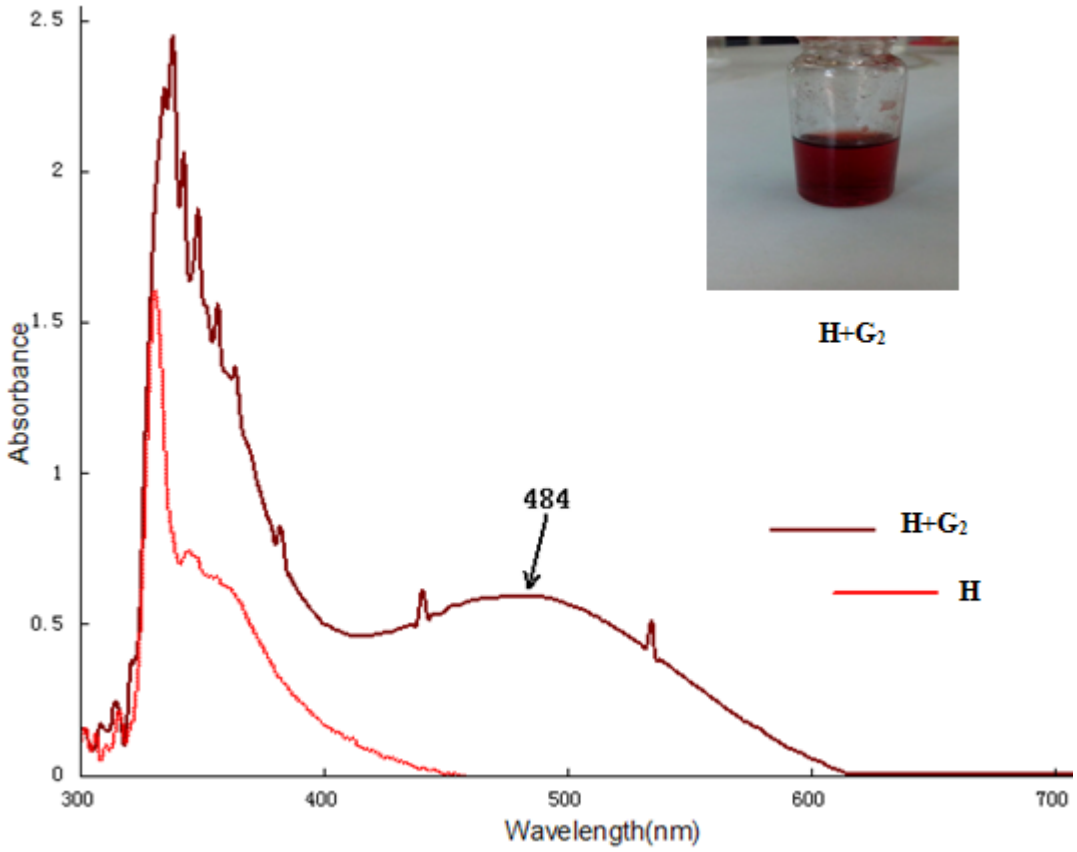
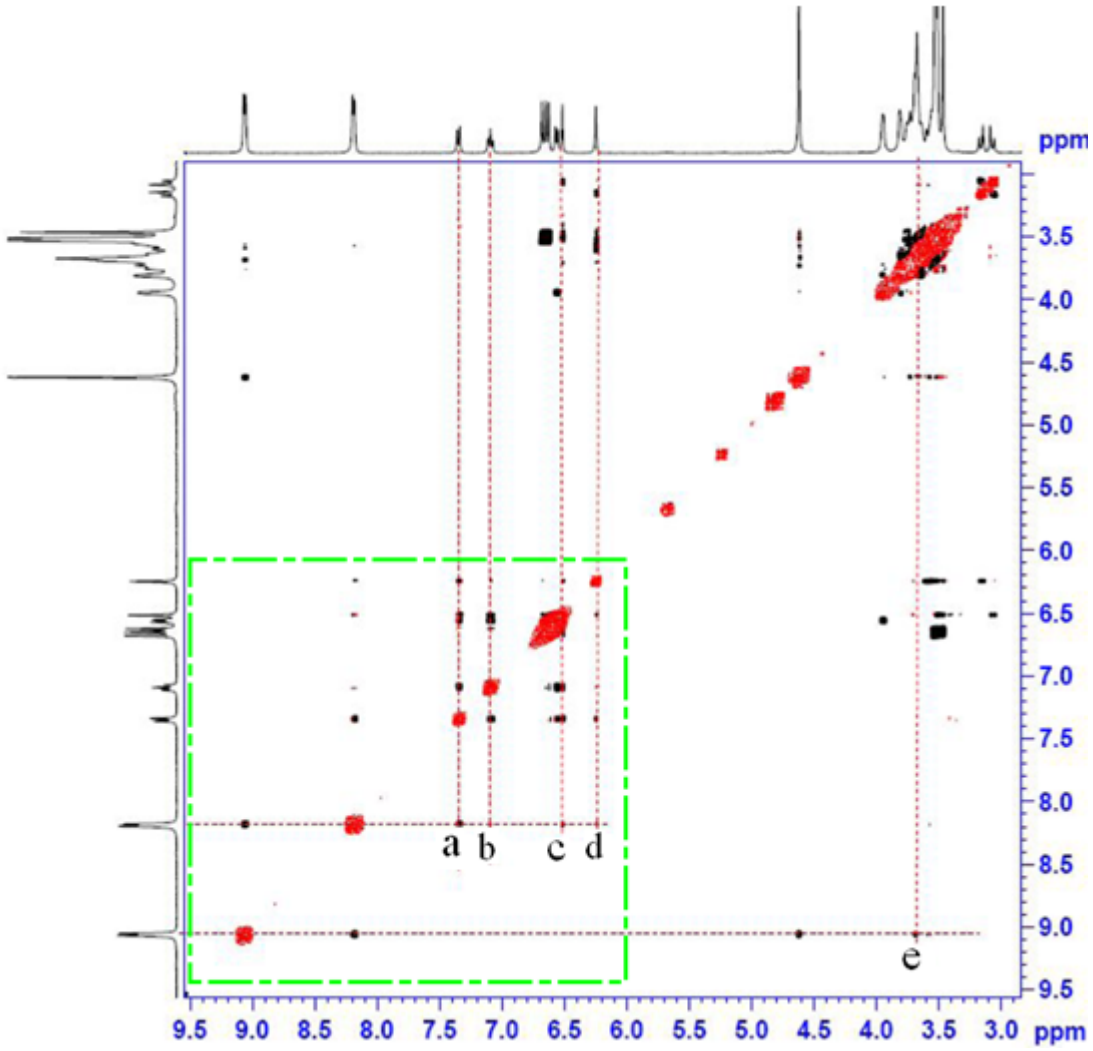
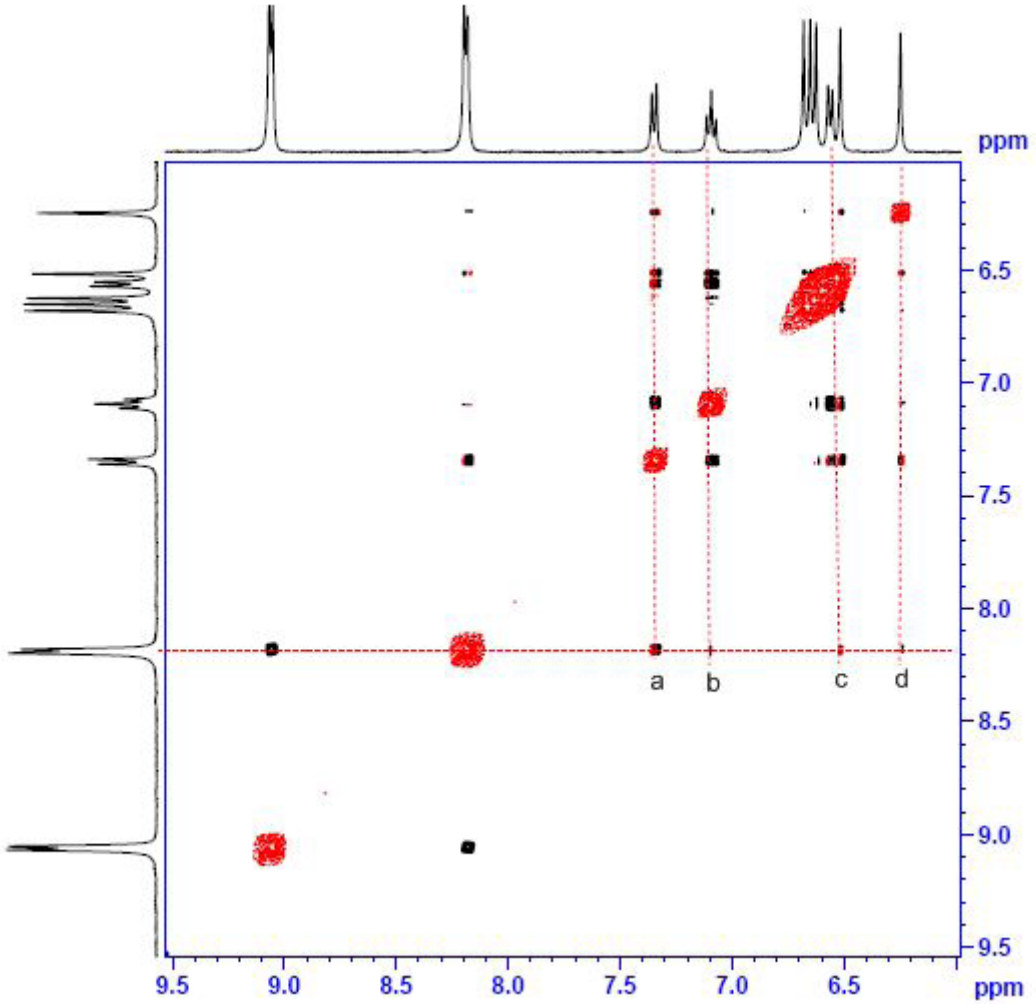


Fig. S6 UV/Vis spectra of **1** and **1** +**G2**.



(a)

Fig. S7 (a) 2D NOESY spectrum of equal molar mixture of **1** and **G2** in acetone-d_6;.



(b)

Fig. S7 (b) partial 2D NOESY spectrum shown in the green box of (a) (400 MHz, 298 K, The concentrations of host and guest are 1.0 and 1.0 mM, respectively).

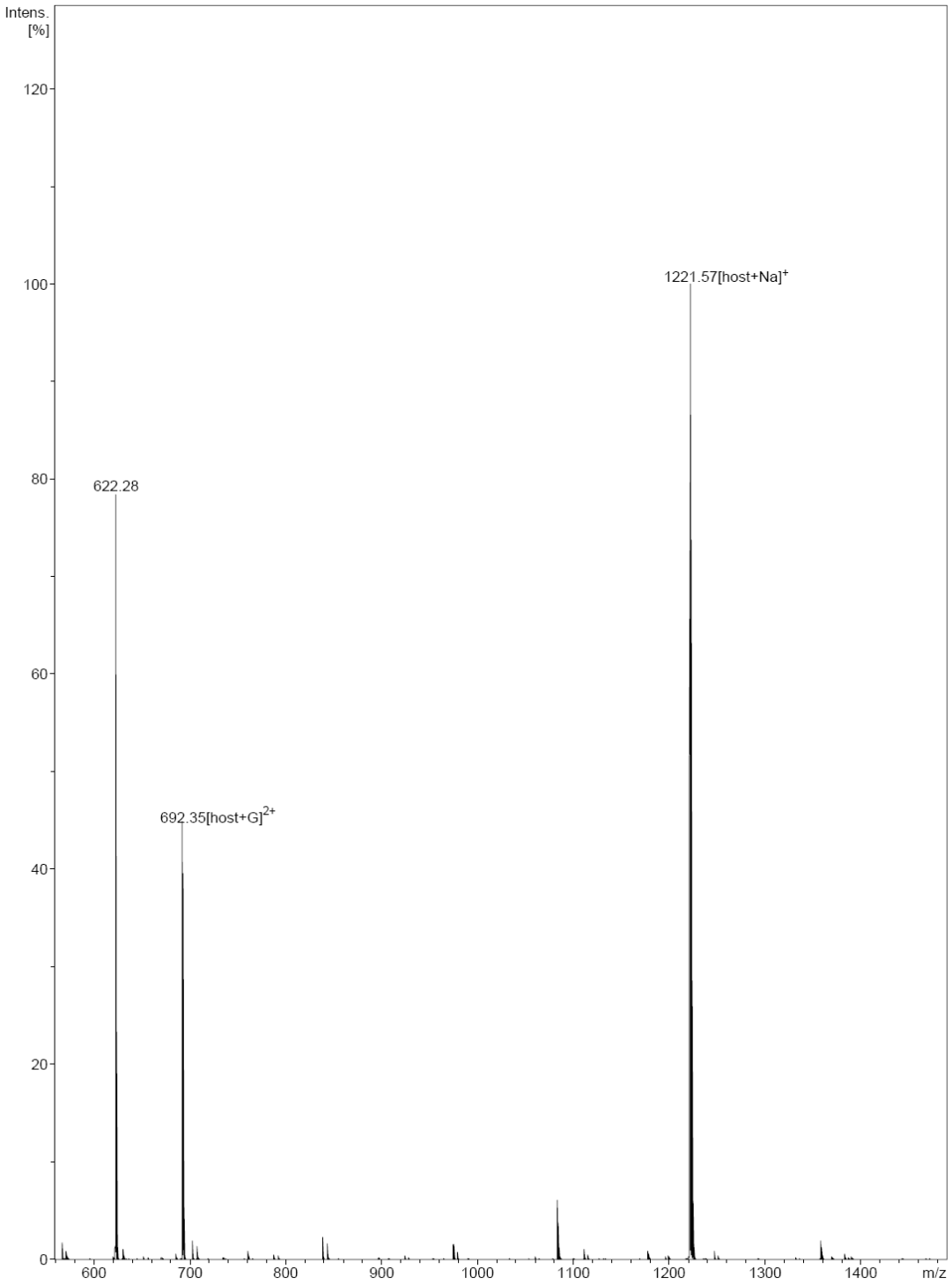


Fig. S8 Mass spectrum of host-guest complex **G2⊂1**.

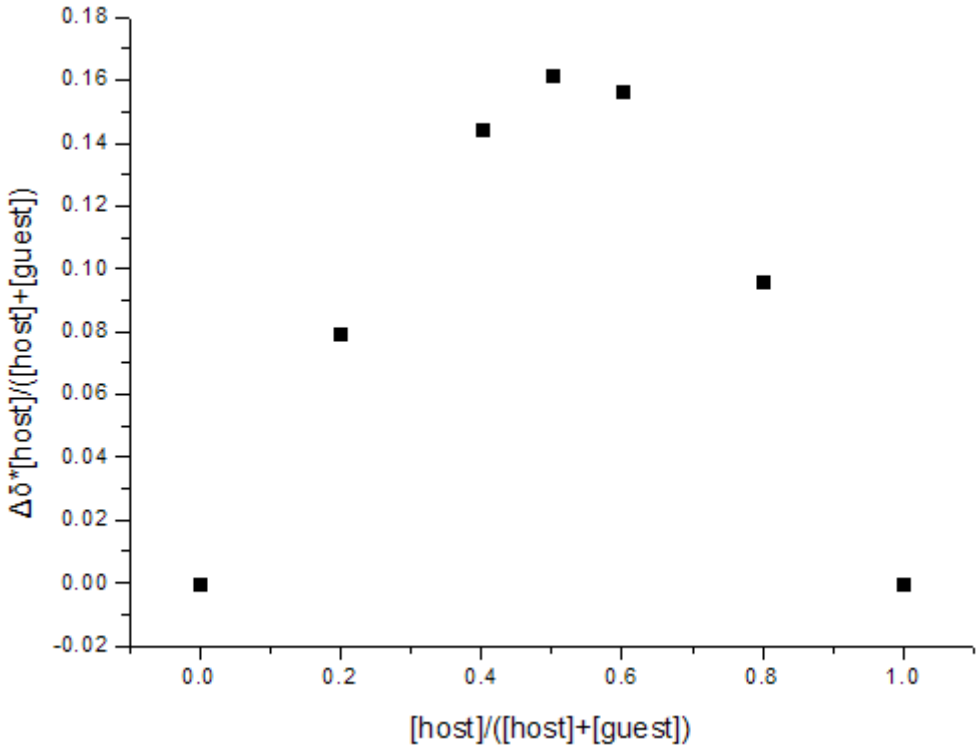


Fig. S9a Job plot showing the 1:1 stoichiometry of the complex between **1** and **G2** in acetone-d_6 by plotting the Δδ in chemical shift of **1'**s naphthalene proton H_e (for proton designations, see Figure S1) observed by ^{1}H NMR spectroscopy against the mole fraction of complex. ([host] + [guest] = 1.0 mM).

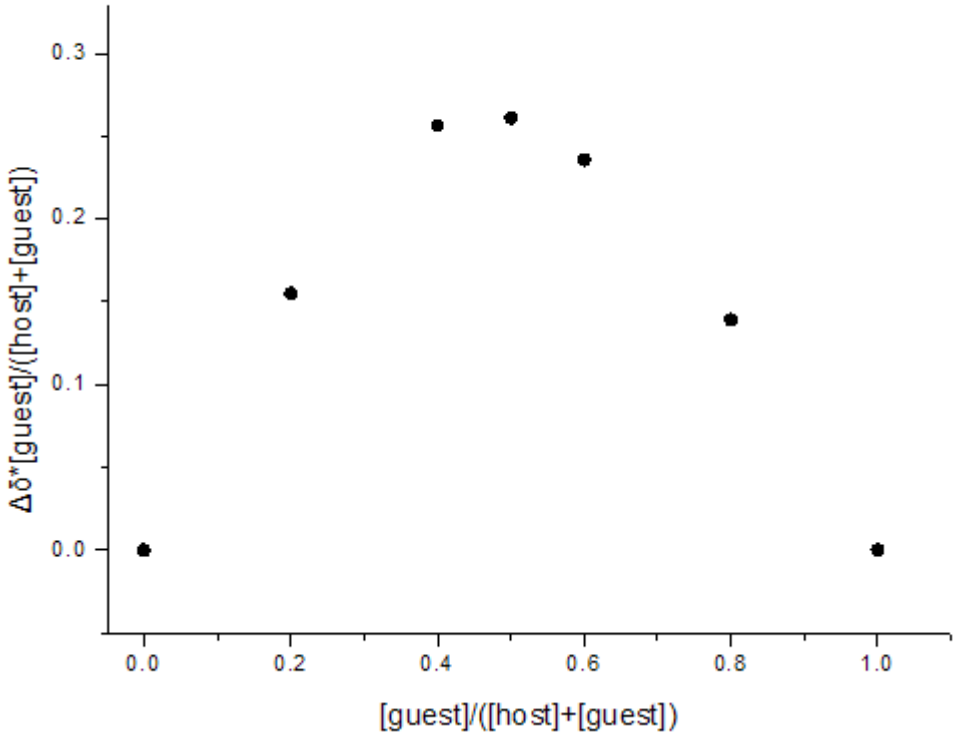


Fig. S9b Job plot showing the 1:1 stoichiometry of the complex between **1** and **G2** in acetone-d_6 by plotting the Δδ in chemical shift of **G2'**s proton Hβ (for proton designations, see Figure 2) observed by ^{1}H NMR spectroscopy against the mole fraction of complex. ([host] + [guest] = 1.0 mM).

Host-guest complexation of 1 and G2 in acetone-d_6

Stoichiometry and association constant determination for the complexation between 1 and G2

To determine the stoichiometry and association constant between **1** and **G2**, ^{1}H NMR titration was carried out with solutions which had a constant concentration of **1** (1.00 mM) and varying concentrations of **G2**. By a non-linear curve-fitting method, the association constant between the guest **G2** and host **1** was calculated. The non-linear curve-fitting was based on the equation:[2]

$$\Delta\delta = (\Delta\delta_\infty/[\mathbf{1}]_0)\,(0.5[\mathbf{G2}]_0 + 0.5([\mathbf{1}]_0+1/K\mathrm{a})-(0.5\,([\mathbf{G2}]_0{}^2+(2[\mathbf{G2}]_0(1/K\mathrm{a}-[\mathbf{1}]_0)) + (1/K\mathrm{a} + [\mathbf{1}]_0)^2)^{0.5}))$$

Where $\Delta\delta$ is the chemical shift change of H_e on **1** at $[\mathbf{G2}]_0$, $\Delta\delta_\infty$ is the chemical shift change of H_e when **1** is completely complexed, $[\mathbf{1}]_0$ is the fixed initial concentration of **1**, and $[\mathbf{G2}]_0$ is the varying concentrations of guest (Figure S8, S9, S10).

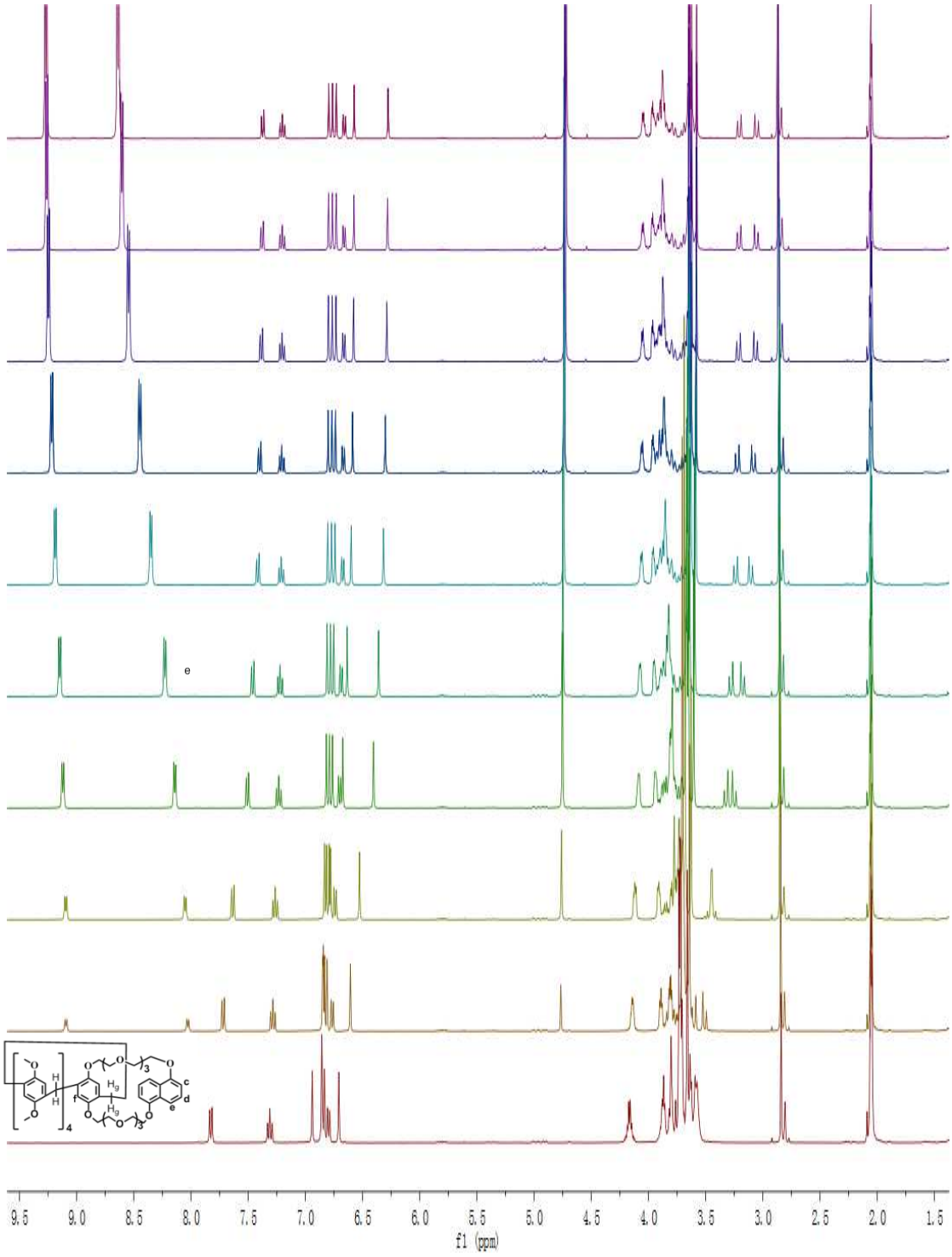


Fig. S10a ^{1}H NMR spectra (400 MHz, acetone-d_6, 298 K) of **1** at a concentration of 1.0 mM upon addition of **G2**. From bottom to top, the concentrations of **G2** were 0, 0.2, 0.4, 0.8, 1.0, 1.6, 2.0, 3.0, 4.0, 5.0 mM, respectively.

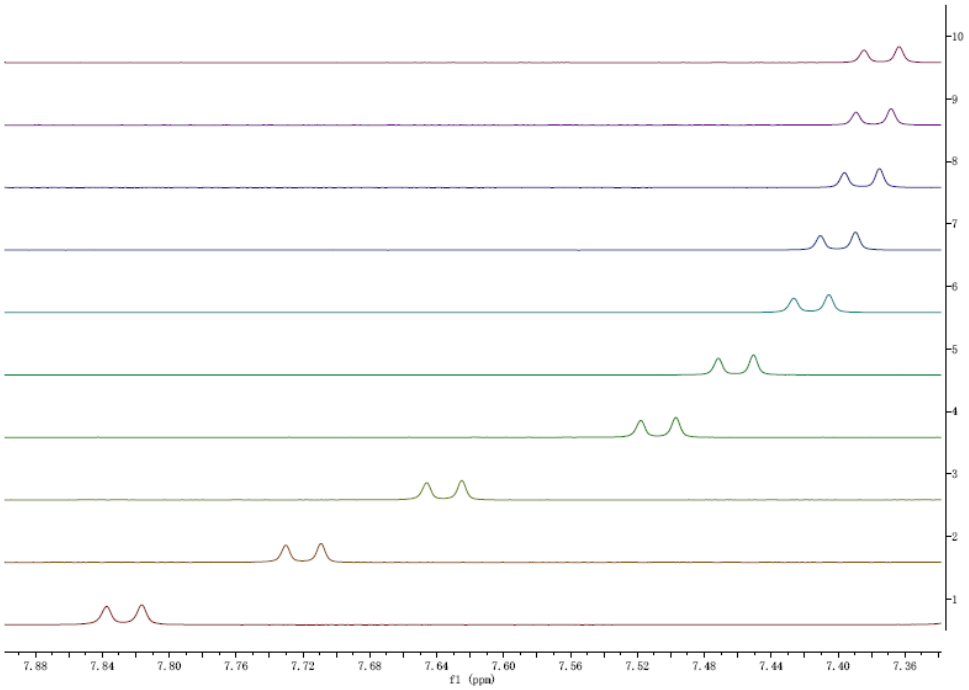


Fig. S10b ^{1}H NMR spectra of H_e peak shift of **1** upon addition of **G2** shown in Figure S8a.

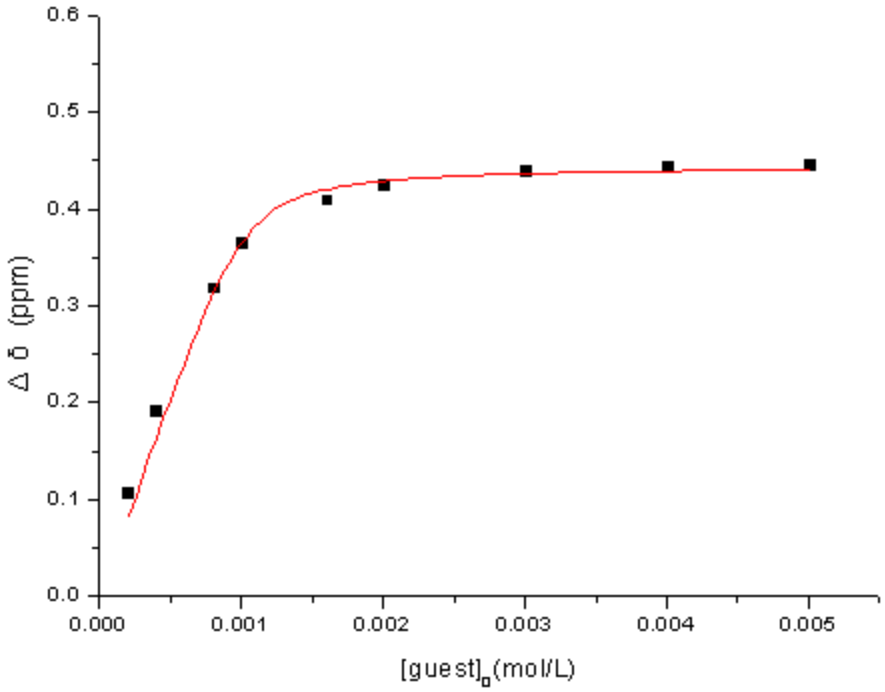


Fig. S11 The non-linear curve-fitting (NMR titrations) for the complexation of **1** (1.0 mM) with **G2** in acetone-d_6 at 298 K. The concentration of **G2** was 0, 0.2, 0.4, 0.8, 1.0, 1.6, 2.0, 3.0, 4.0, 5.0 mM. The *K*a value for **G2⊂1** complex in acetone-d_6 at 298 K is determined to be $2.6\pm0.6 \times 10^4$

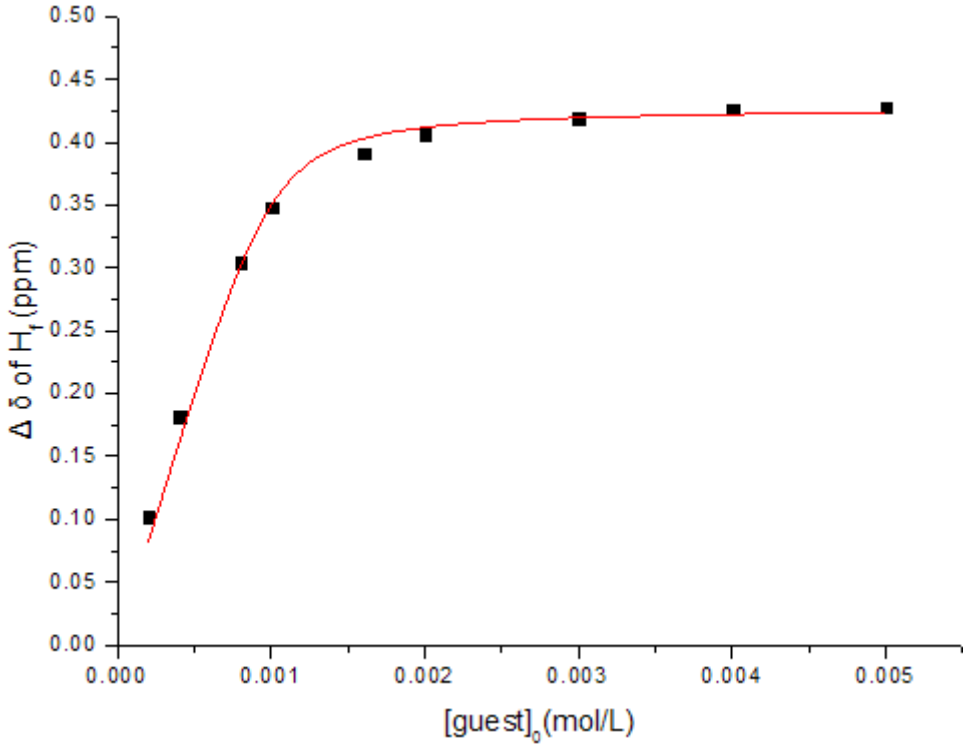


Fig. S12 The non-linear curve-fitting (NMR titrations, $\Delta\,\delta$ of H_f) for the complexation of **1** (1.0 mM) with **G2** in acetone-d_6 at 298 K. The concentration of **G2** was 0, 0.2, 0.4, 0.8, 1.0, 1.6, 2.0, 3.0, 4.0, 5.0 mM. The *K*a value for **G2⊂1** complex in acetone-d_6 at 298 K is determined to be $2.4\pm0.5 \times 10^4$

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2 a) K. A. Connors, *Binding Constants*, Wiley, New York, 1987; b) R. P. 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; c) Y. Inoue, K. Yamamoto, T. Wada, S. Everitt, X.-M. Gao, Z.-J. Hou, L.-H. Tong, S.-K. Jiang and H.-M. Wu, *J. Chem. Soc., Perkin Trans. 2*, 1998, 1807−1816.