Supporting Information

for

A new water soluble cavitand with deeper guest binding properties

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Contents

Experimental

General experimental

All analytical grade solvents and reagents purchased from commercial sources were used without further purification. Glyoxal was purchased from J&K Chemical Company Ltd., Shanghai China. ^{1}H and ^{13}C NMR analyses were performed using Bruker AVANCE III HD 600 MHz spectrophotometer. Positive ions high-resolution mass analyses were performed on Bruker micrOTOF II machine.

Synthesis of cavitand octa-amino hydrochloric acid salt (Cav-8NH_3Cl)

A modified procedure was used as reported previously [1], 1, equivalent, 1.5 g of octa-nitro cavitand was taken in 80 mL of ethanol and cooled to 0 °C in an ice bath. 35 mL of conc. HCl was added slowly to it while keeping the mixture temperature at 0 °C. 120 Equivalents 28 g of tin(II) chloride dihydrate was added slowly added to the mixture in several portions. The flask containing the mixture was taken out from the ice bath, degassed and added with N_2 three times and immersed to an oil bath preheated at 110 °C. The mixture was stirred vigorously and maintained at these conditions for 2 h. It was cooled to rt and octa-amino cavitand hydrochloric acid salt precipitate was filtered from the cold reaction mixture, washed successively with cold (0 - 5 °C) 3N aq. HCl, acetonitrile, ether and the solid recovered was dried under high vacuum. It was recovered in quantitative yield and used in the next step without further purification. The analytical was similar to that reported previously.

Synthesis of cavitand 2

8 Equivalents of K_2CO_3 was dissolved in 30 % water/ethanol (40 mL for 0.2 mmol of **Cav-8NH_3Cl**) in a round bottom flask. 1 Equi. of octa-amino cavitand HCl salt was added to it with vigorous stirring and the mixture was further stirred for 10 min at rt. 8 Equivalents of glyoxal (40% solution in water) was added to it in one portion with constant stirring. The reaction mixture was

stirred at rt, during this time the white solid suspension turned pale resulting in a yellowish white solid precipitation. The mixture was stirred for 18 h to get maximum of the solid product. The yellowish white solid was filtered and washed thoroughly with water and absolute ethanol. It was pure enough (checked by ^{1}H NNR) to be used in further analysis or the next step of the reaction. It was recovered in >90% yield. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.73 (s, 8H), 7.74 (s, 8H), 7.22 (s, 4H), 6.79 (s, 4H), 4.21 (t, *J* = 7.3 Hz, 4H), 3.53 (t, *J* = 6.0 Hz, 8H), 2.36 – 2.04 (m, 8H), 1.80 – 1.66 (m, 8H) ppm. ^{13}C NMR (150 MHz, chloroform-*d*) δ 154.2, 149.9, 144.4, 140.2, 131.6, 123.9, 118.3, 113.6, 44.6, 35.6, 30.1, 28.7 ppm. HR-MS (ESI): Calcd. for chemical formula $C_{72}H_{52}Cl_4N_8O_8$: 1296.2662, found: 1297.2734.

Synthesis of water soluble imidazolium functionalized cavitand (1)

80 mg of **Cav-2** was taken in 10 mL 1-methylimidazole and heated at 90 °C for 18 h. The mixture was cooled to rt and added with 30 mL of acetone, 50 mL n-hexane and cooled to 0 °C. A white solid precipitated was filtered and washed with acetone. The recovered solid was further suspended in 20 mL of acetone and heated at reflux (65 °C) for 6 h. The obtained suspension was cooled to rt, filtered, washed further with cold acetone and dried under high vacuum. 84 mg (84%) of white to light yellow solid product was recovered. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.52 (s, 4H), 8.7 (s, 8H), 8.59 (s, 8H), 8.22 (s, 4H), 8.15 (s, 4H), 8.10 (s, 4H), 7.81 (s, 4H), 5.55 (t, *J* = 8.1 Hz, 4H), 4.37 (t, *J* = 6.4 Hz, 8H), 3.92 (s, 12H), 2.86 – 2.74 (m, 8H), 1.84 – 1.78 (m, 8H) ppm. ^{13}C NMR (150 MHz, DMSO-d_6) δ 154.8, 154.2, 145.7, 141.2, 137.4, 135.9, 126.7, 124.0, 123.6, 123.1, 116.8, 49.7, 36.3, 34.2, 31.2, 28.4 ppm. HR-MS (ESI): Calcd. for chemical formula $C_{88}H_{76}Cl_4N_{16}O_8$: 1624.4786, found: 1589.5091 $[M\text{-}Cl]^+$, 777.2692 $[M\text{-}2Cl]^{2+}$.

^{1}H NMR, ^{13}C NMR spectra of the cavitands

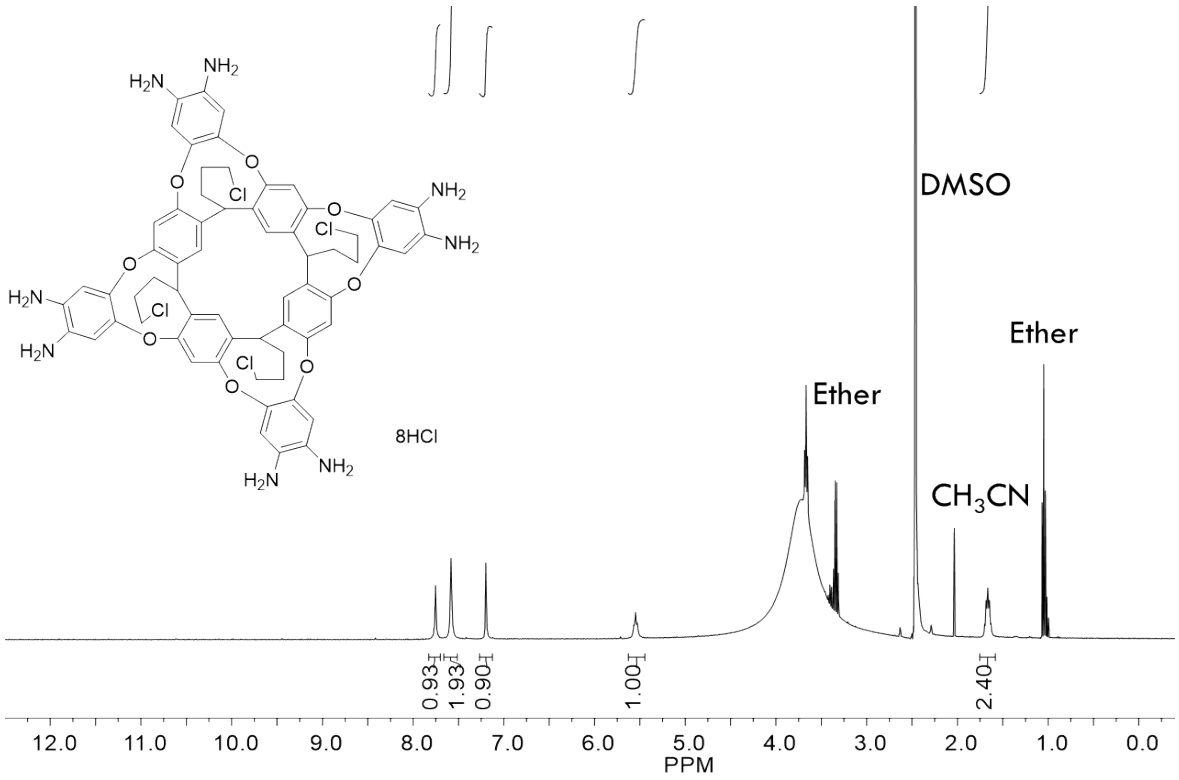

Fig. S1 ^{1}H NMR spectrum of **Cav-8NH$_3$Cl** in DMSO-d_6 at rt

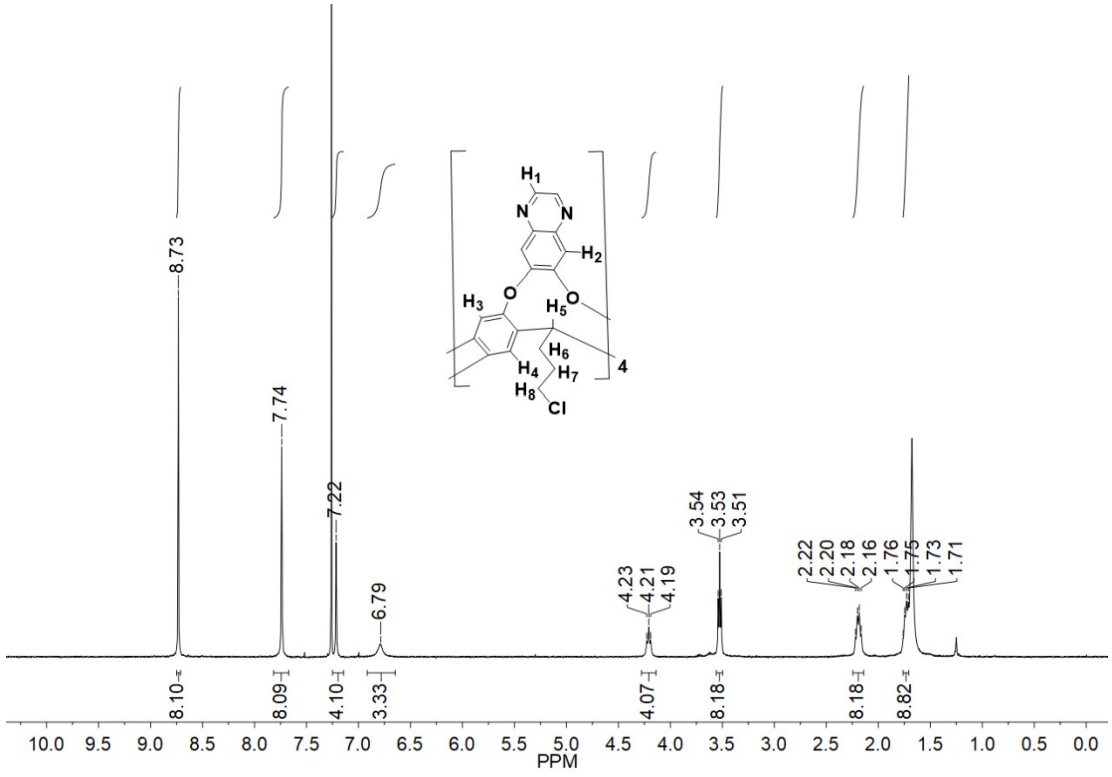

Fig. S2 ^{1}H NMR spectrum of **2** in $CDCl_3$ at rt

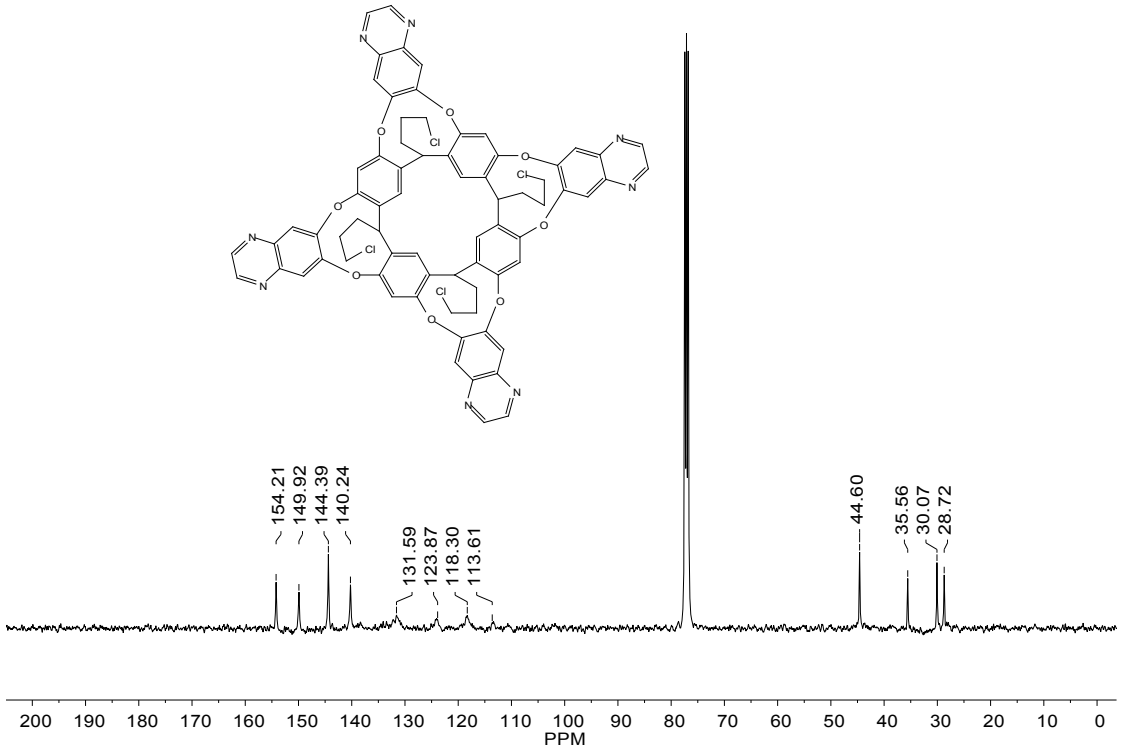

Fig. S3 ^{13}C NMR spectrum of **2** in $CDCl_3$ at rt

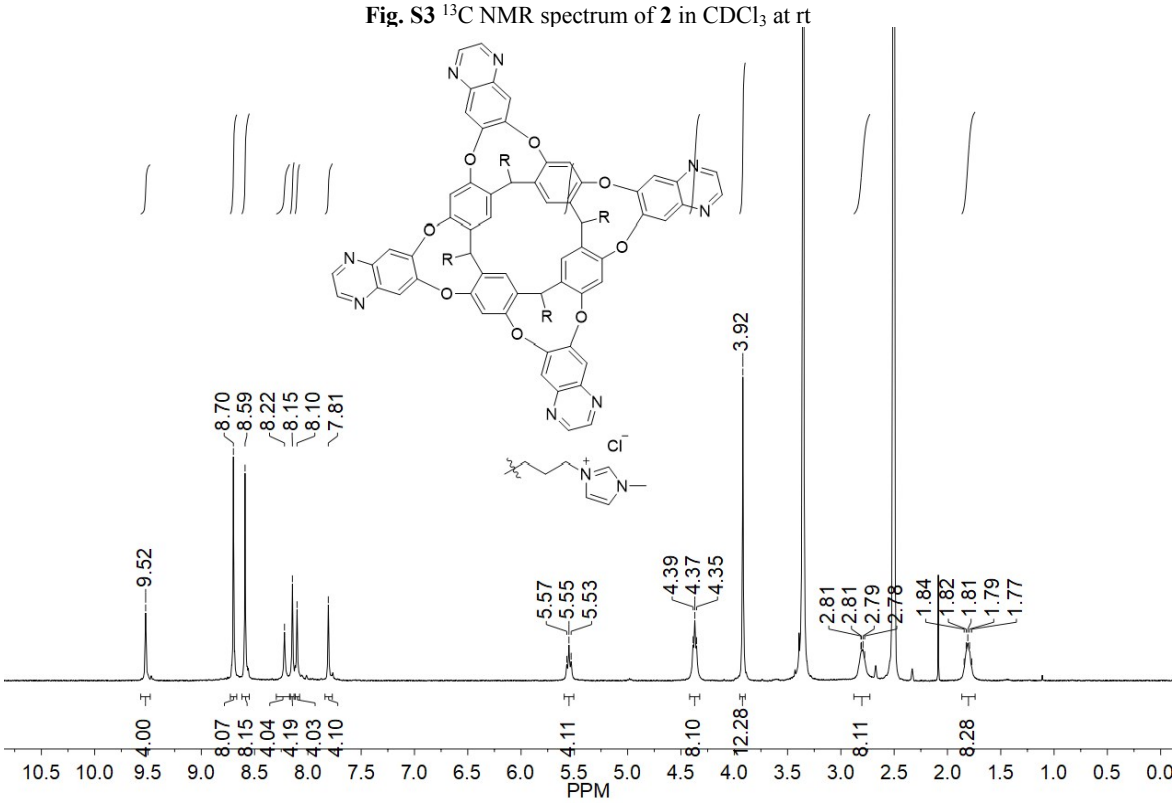

Fig. S4 ^{1}H spectrum of **1** in DMSO-d_6 at rt

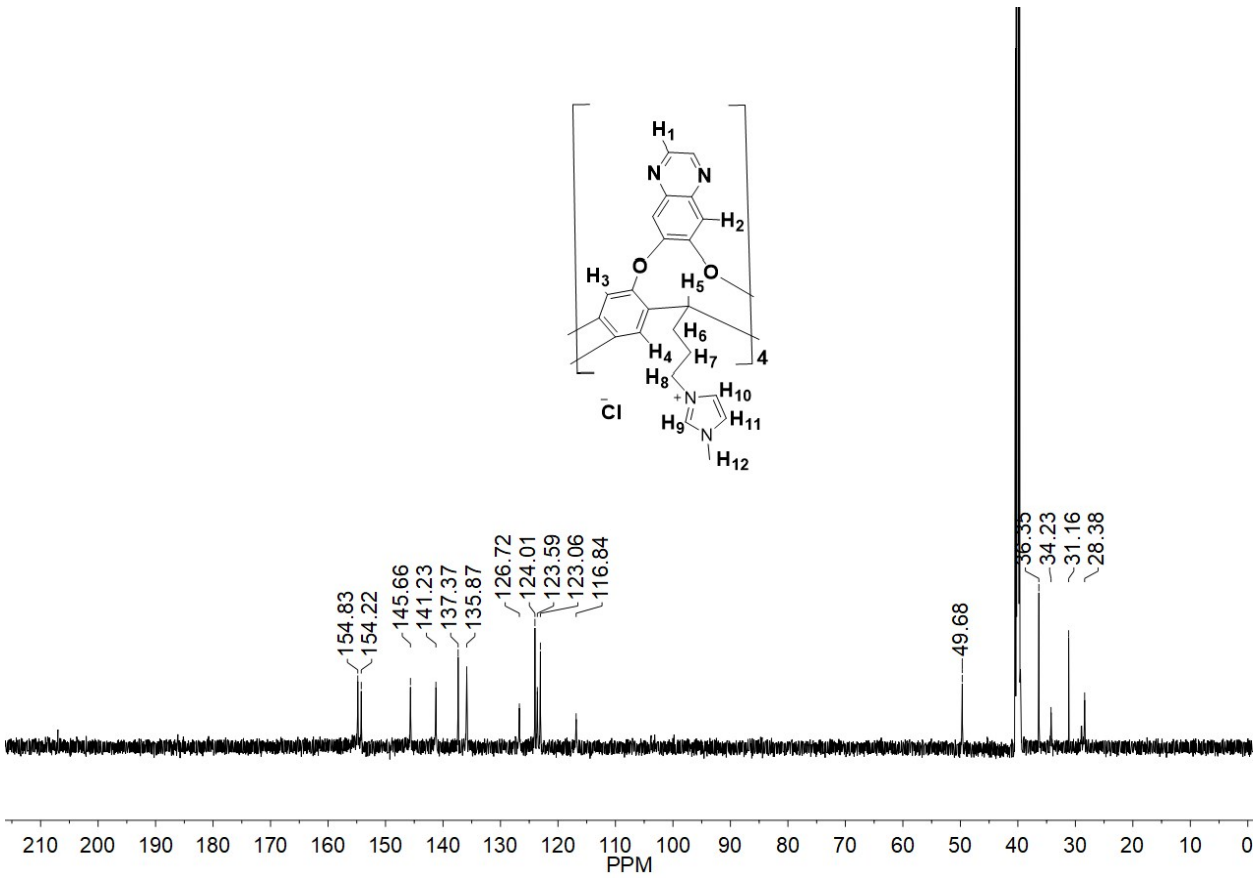

Fig. S5 ^{13}C NMR spectrum of **1** in DMSO-d_6 at rt

Mass (HR) spectra of cavitands

Display Report

Analysis Info

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Comment			

Acquisition Parameter

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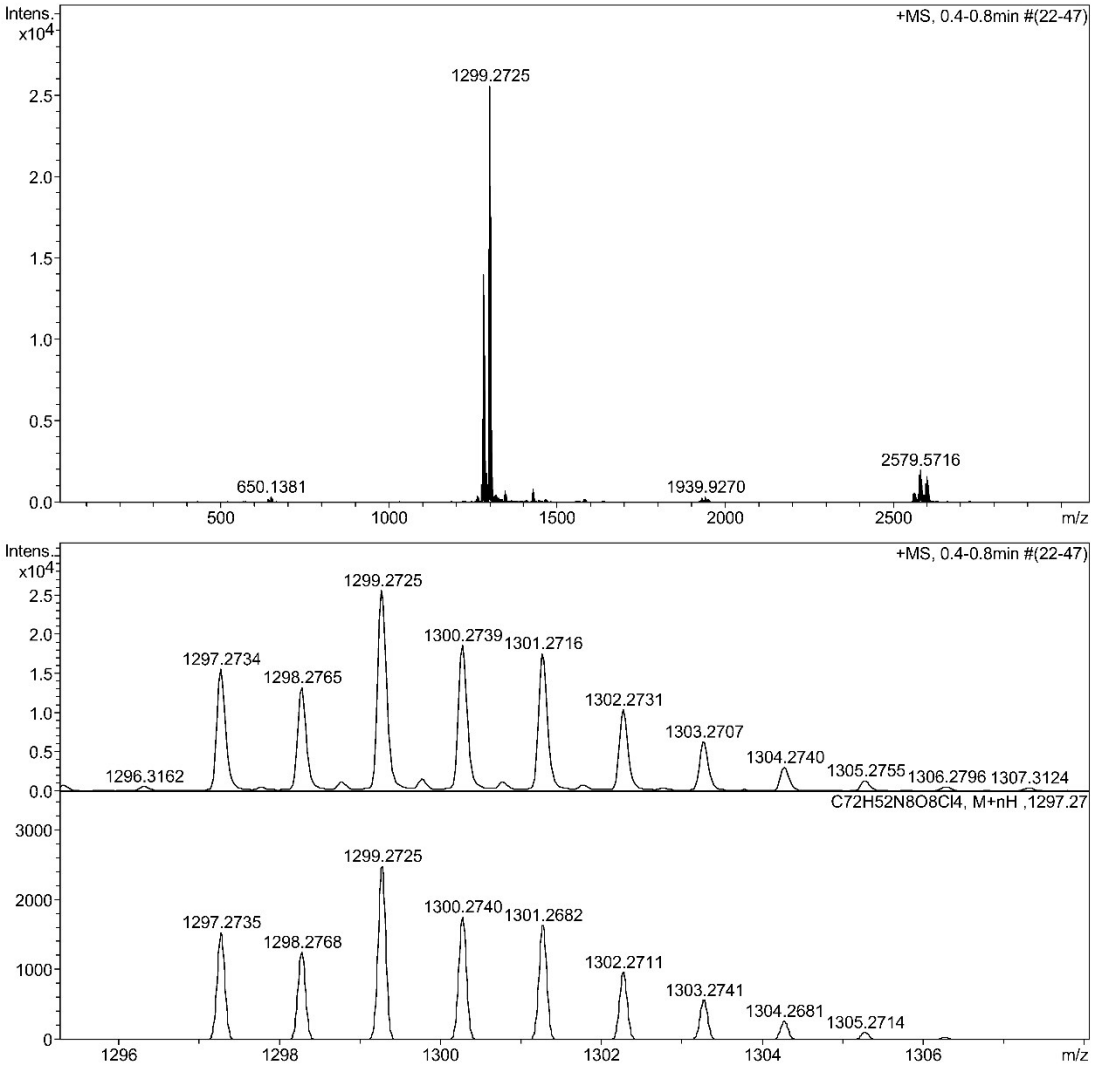

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Fig. S6 Mass spectrum of **2**

Display Report

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Acquisition Parameter

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Scan End	3000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste

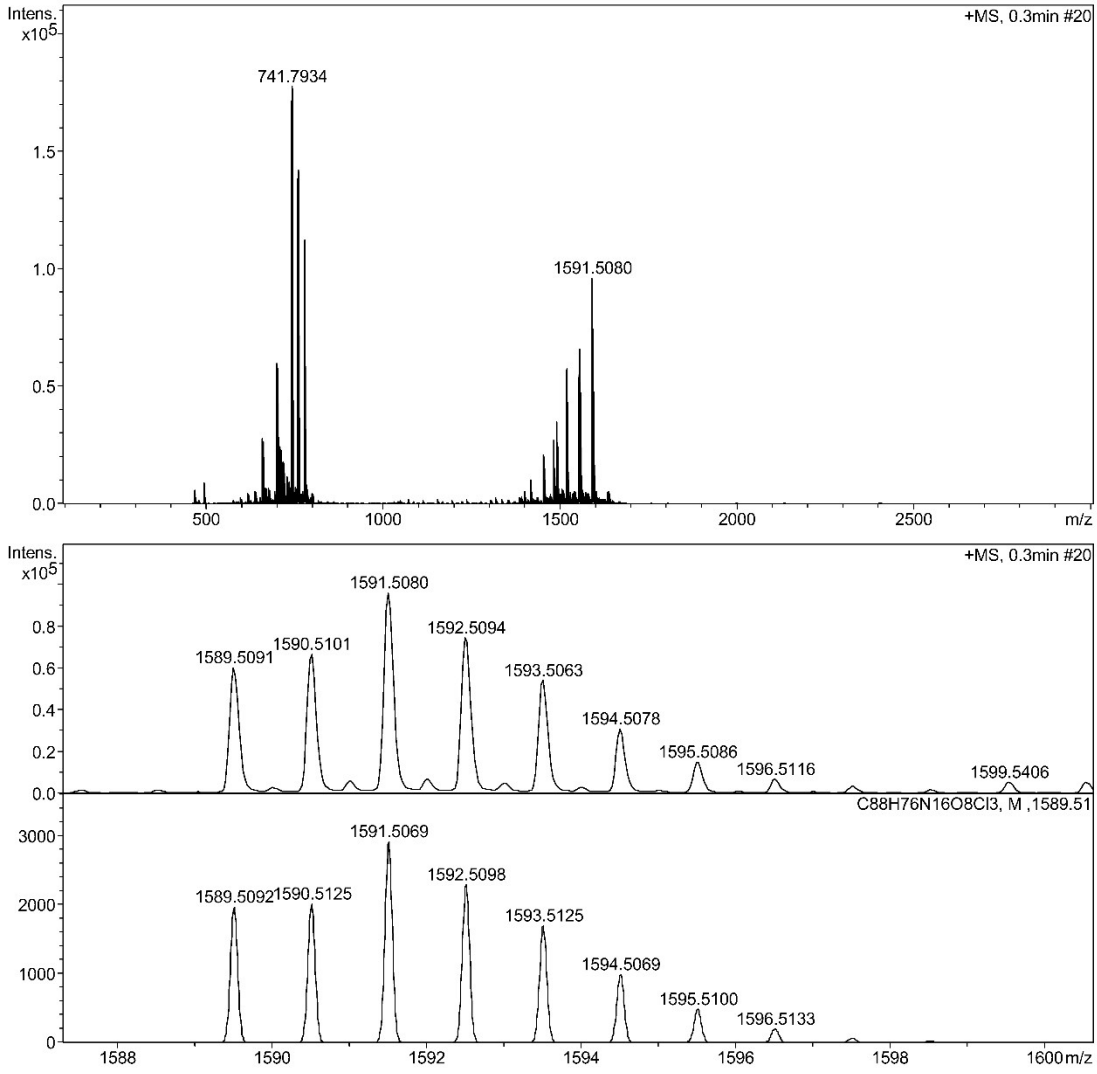

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Fig. S7 Mass spectrum of **1** cationic specie formed by the loss of one Cl.

Display Report

Analysis Info

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Sample Name	3	Instrument / Ser#	micrOTOF II 10257
Comment			

Acquisition Parameter

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Scan End	3000 m/z	Set End Plate Offset	-500 V	Set Divert Valve	Waste

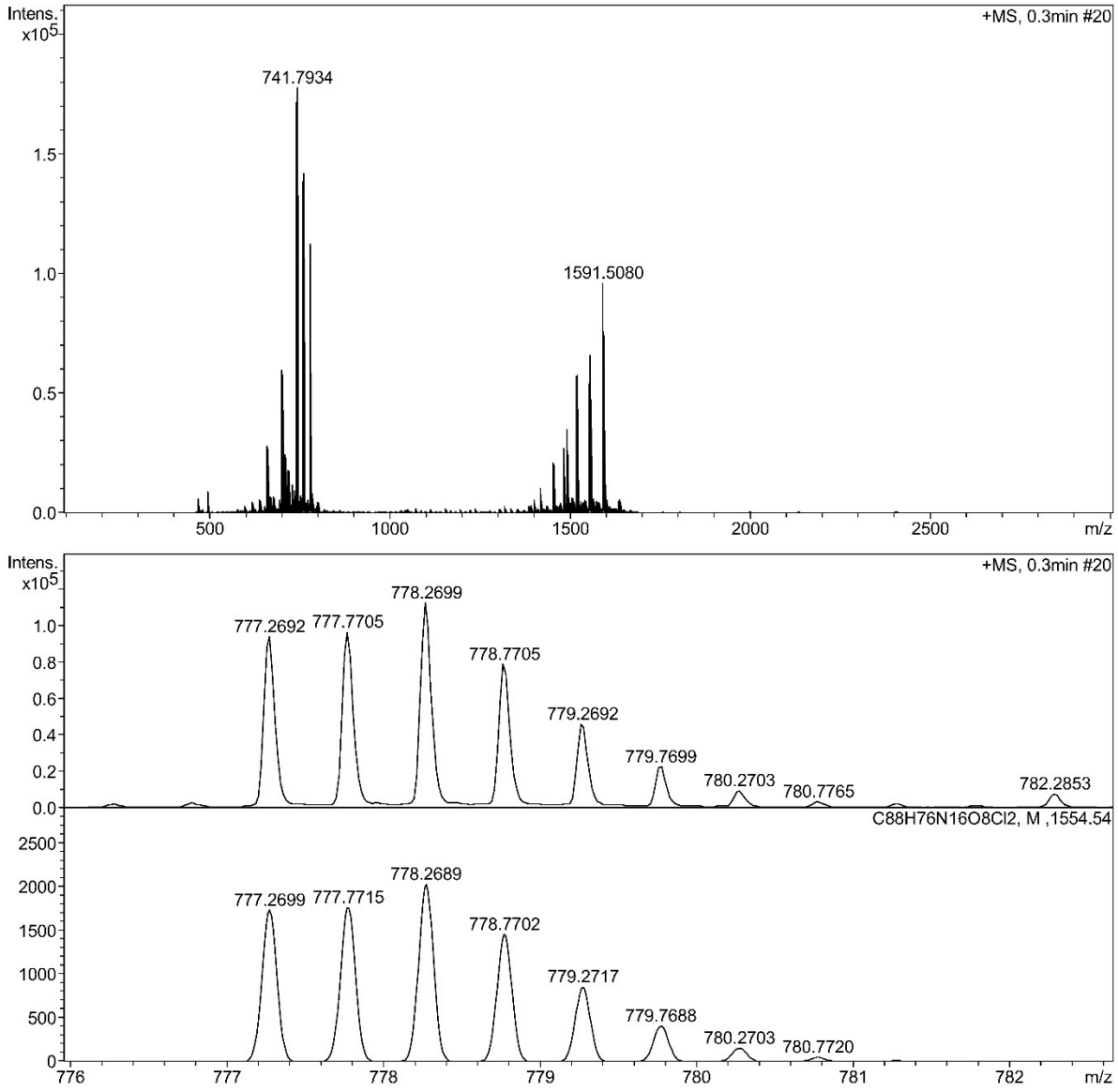


Fig. S8 Mass spectrum of **1**, dicationic specie formed by the loss of two Cl.

^{1}H NMR spectra of 1 (water soluble cavitand) in different solvents

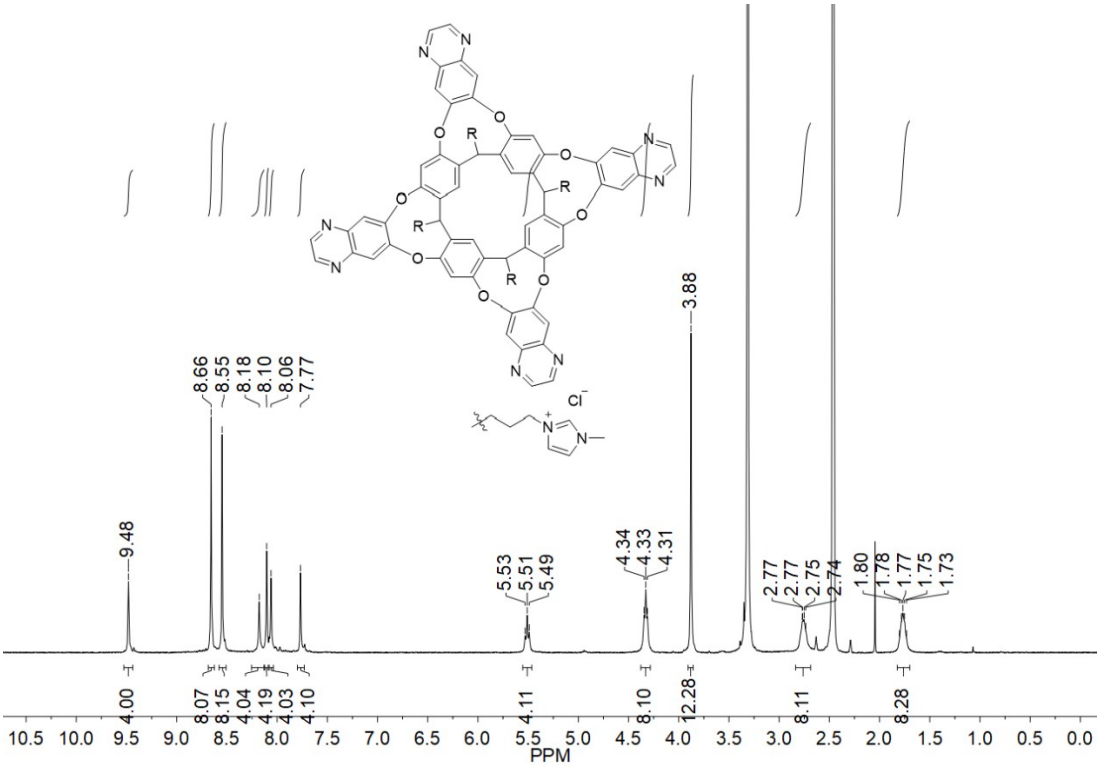


Fig. S9 ^{1}H spectrum of **1** in DMSO-d_6 at rt

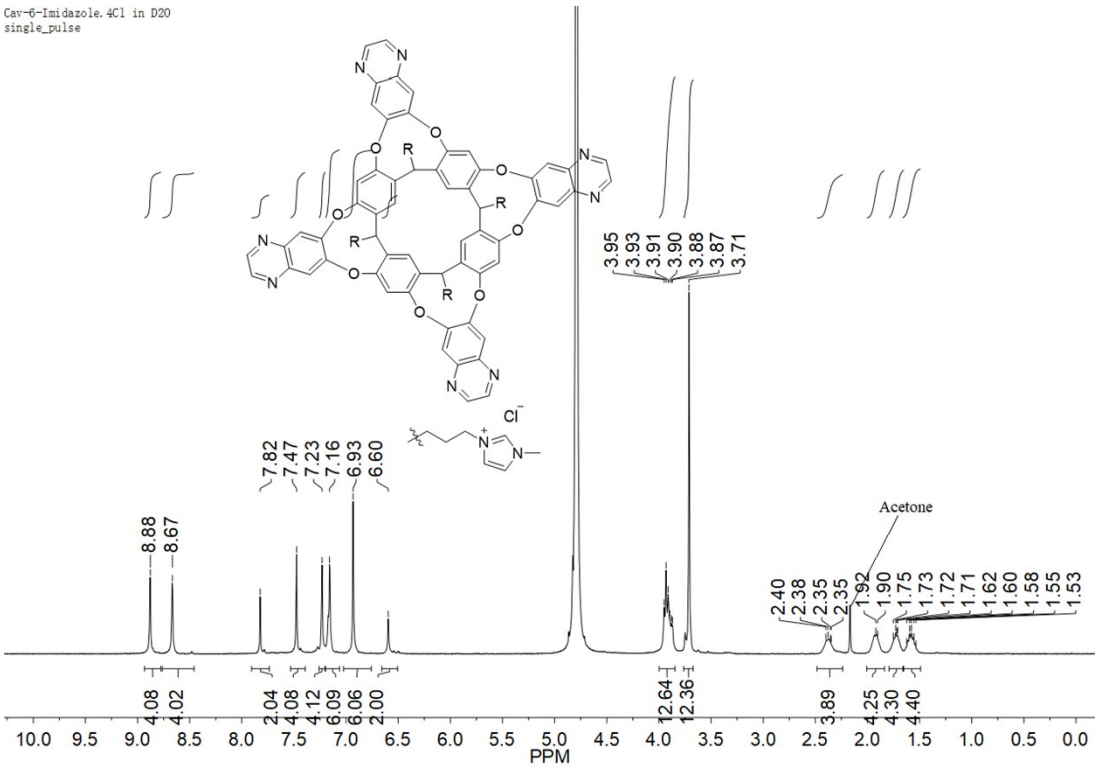


Fig. S10 ^{1}H spectrum of **1** in D_2O at rt

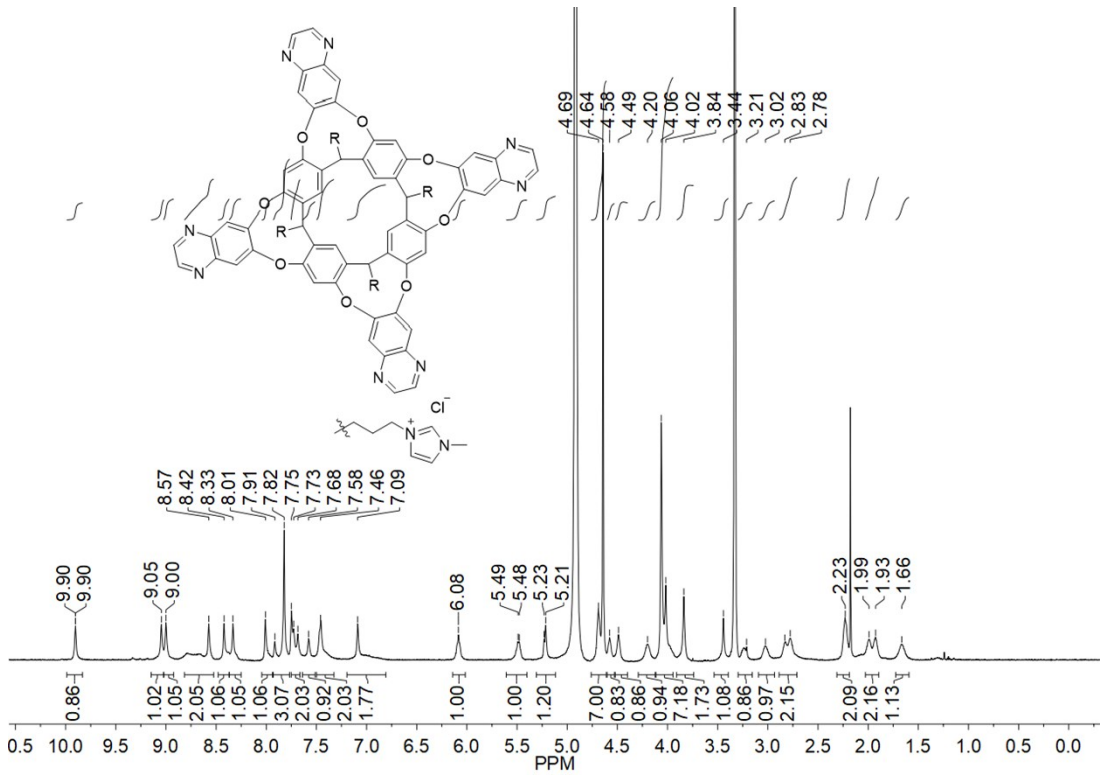


Fig. S11 ^{1}H spectrum of **1** in methanol-d_4 at rt

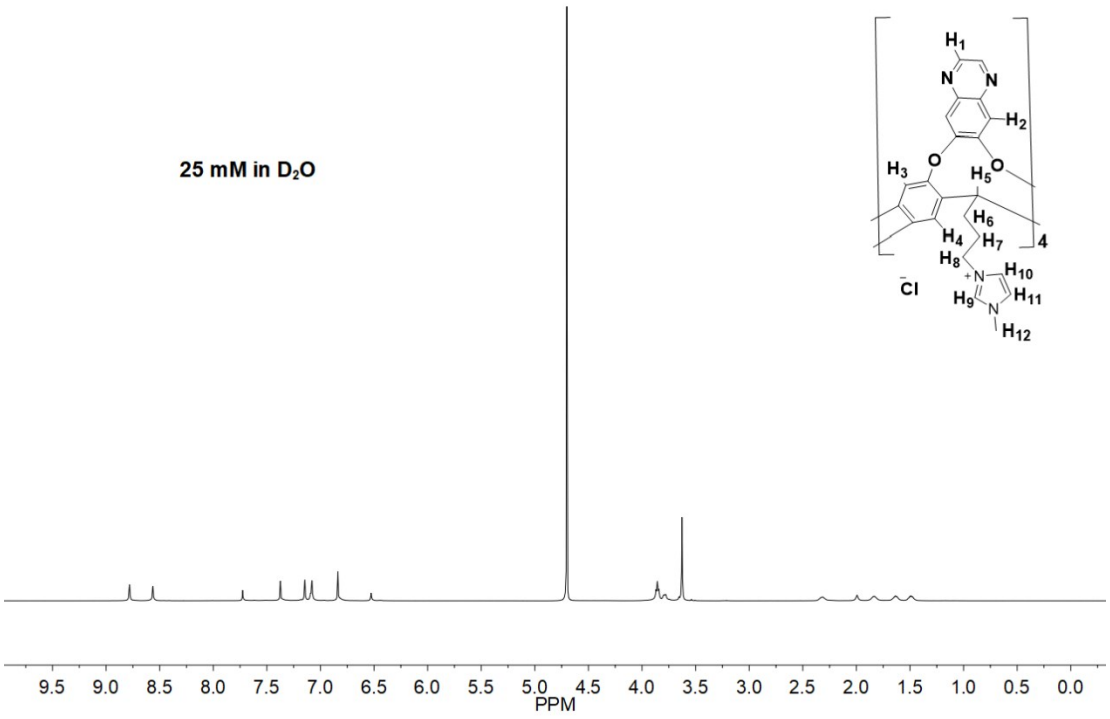


Fig. S12 ^{1}H spectrum of **1** 25 mM in D_2O at rt

NMR spectra of 1 in water in the presence of different binding guests

1 mM, 0.5 mL of **1** was taken in NMR tube and excess pure guest was added to the tube, it was shaken well to mix the guest in water. The sample was sonicated for 1 h and the ^{1}H NMR spectroscopic analysis was performed.

A single peak for all protons of each cyclic alkane guest was observed which showed that the guest is not fixed and rotating constantly in the cavity.

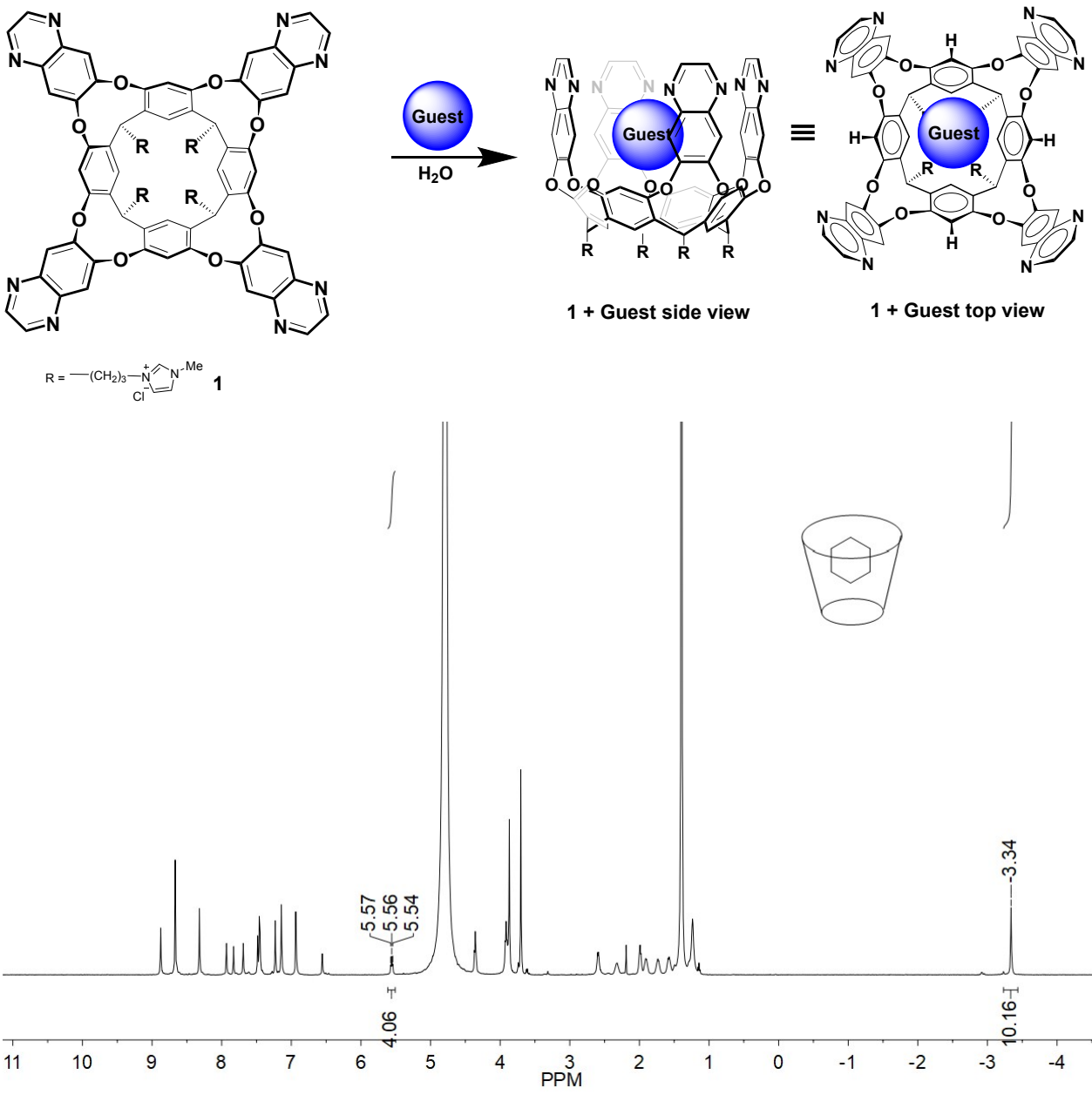


Fig. S11 ^{1}H spectrum of **1** in D_2O in the presence of excess cyclohexane guest at rt

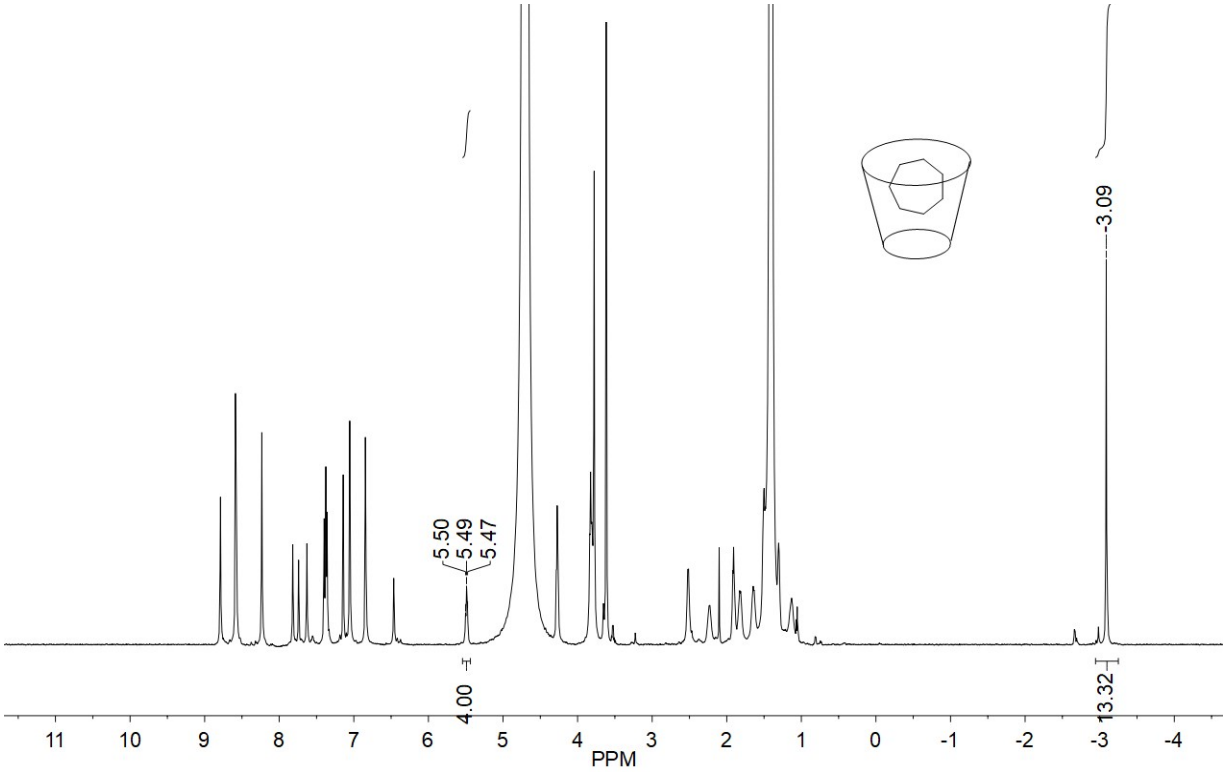


Fig. S12 ^{1}H spectrum of **1** in D_2O in the presence of excess cycloheptane guest at rt

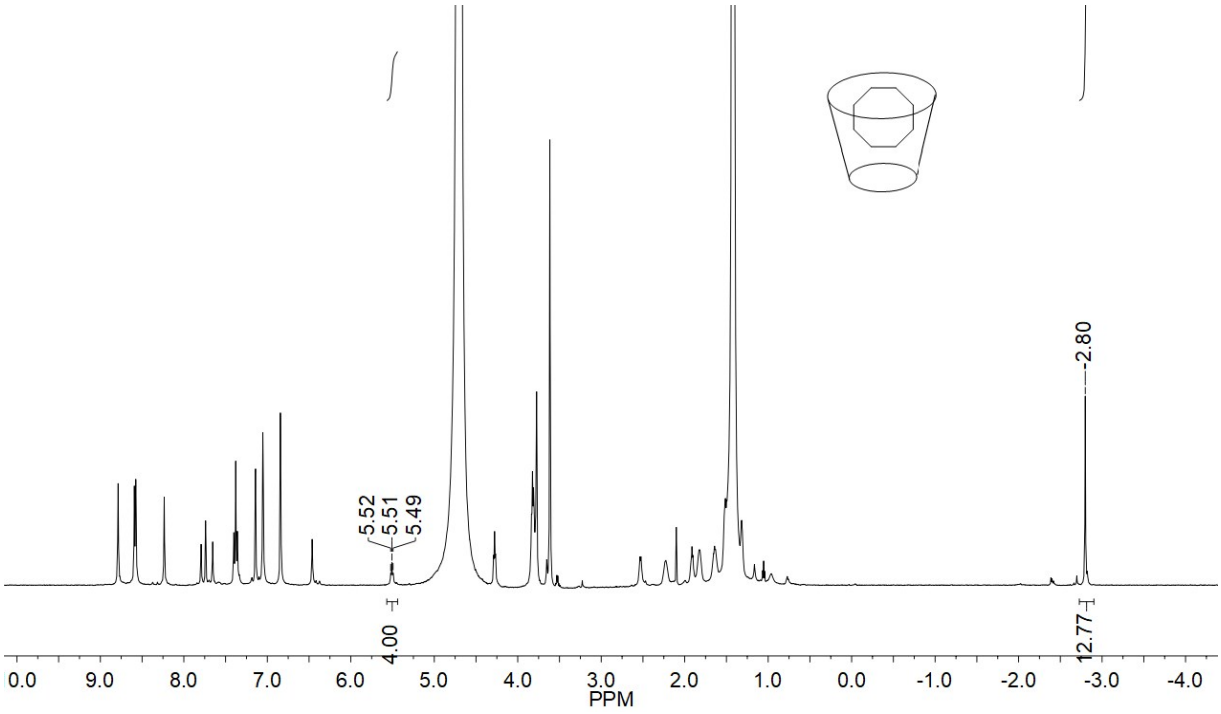


Fig. S13 ^{1}H spectrum of **1** in D_2O in the presence of excess cyclooctane guest at rt

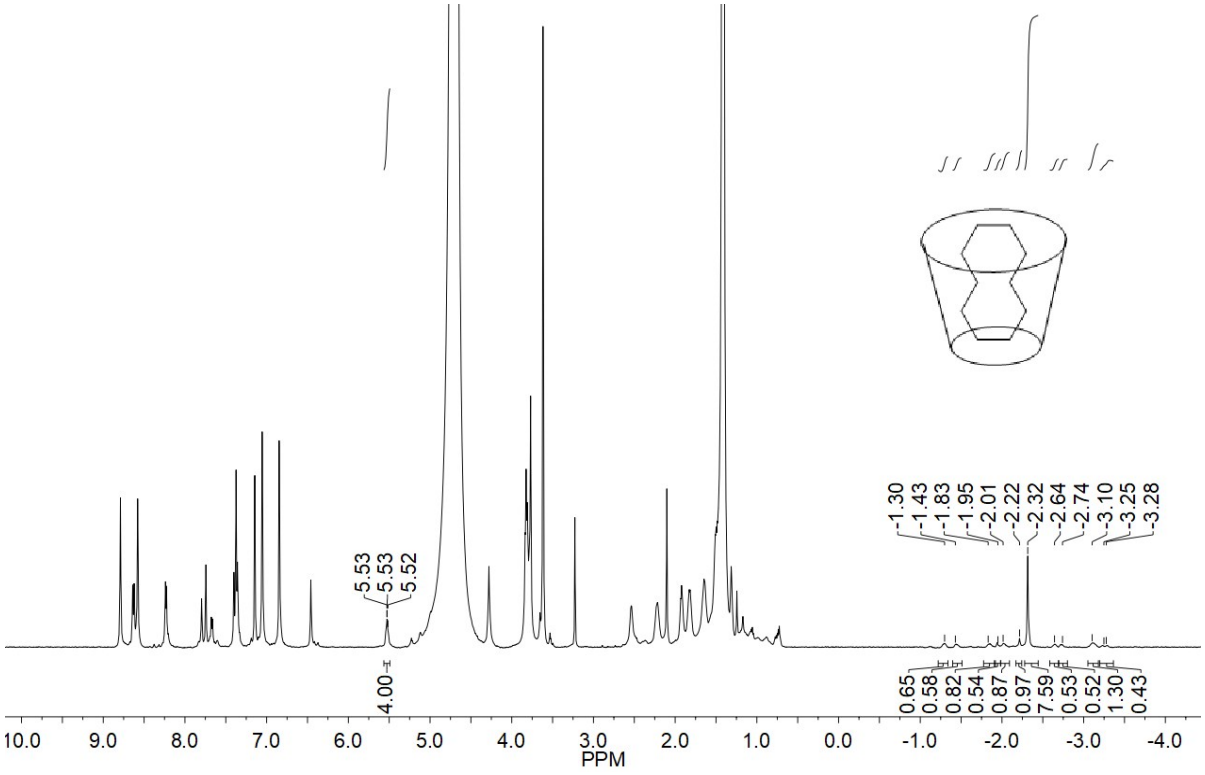


Fig. S14 ^{1}H spectrum of **1** in D_2O in the presence of excess cyclodecane guest at rt

NMR spectra of 1 in water in the presence of small organic acid

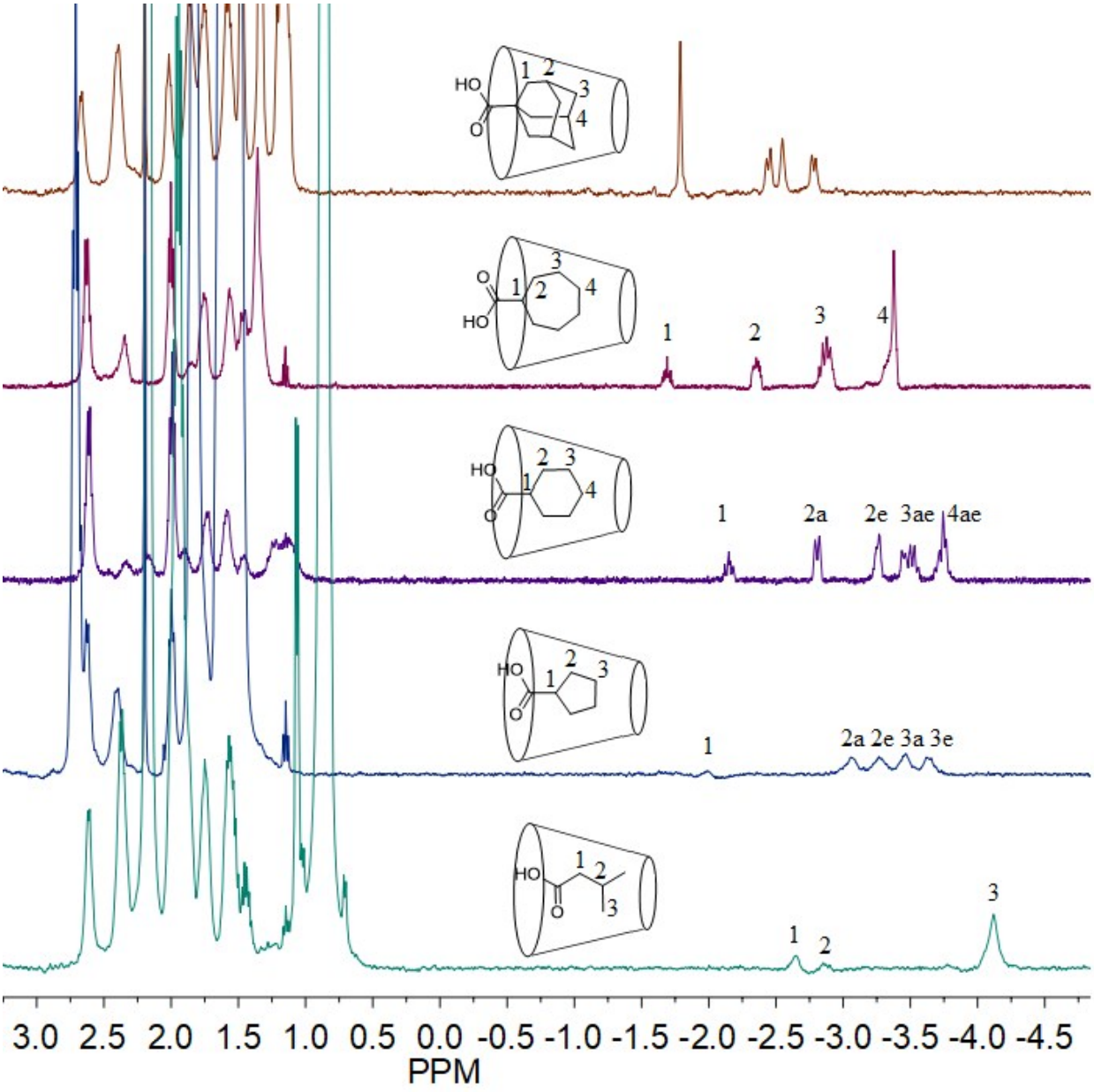


Fig. S15 **1** in D_2O and binding guests from bottom to top; **1** + 3-methylbutanoic acid, **1** + cyclopentylcarboxylic acid, **1** + cyclohexylcarboxylic acid, **1** + cycloheptylcarboxylic acid, **1** + adamantanecarboxylic acid, excess of pure guest was added to the 1 mM solution of **1** in D_2O, sonicated for 1 h and analyzed by ^1H NMR at rt. Numbering represent the peaks assigned to each proton group while "a" represent axial while "e" represent equatorial protons.

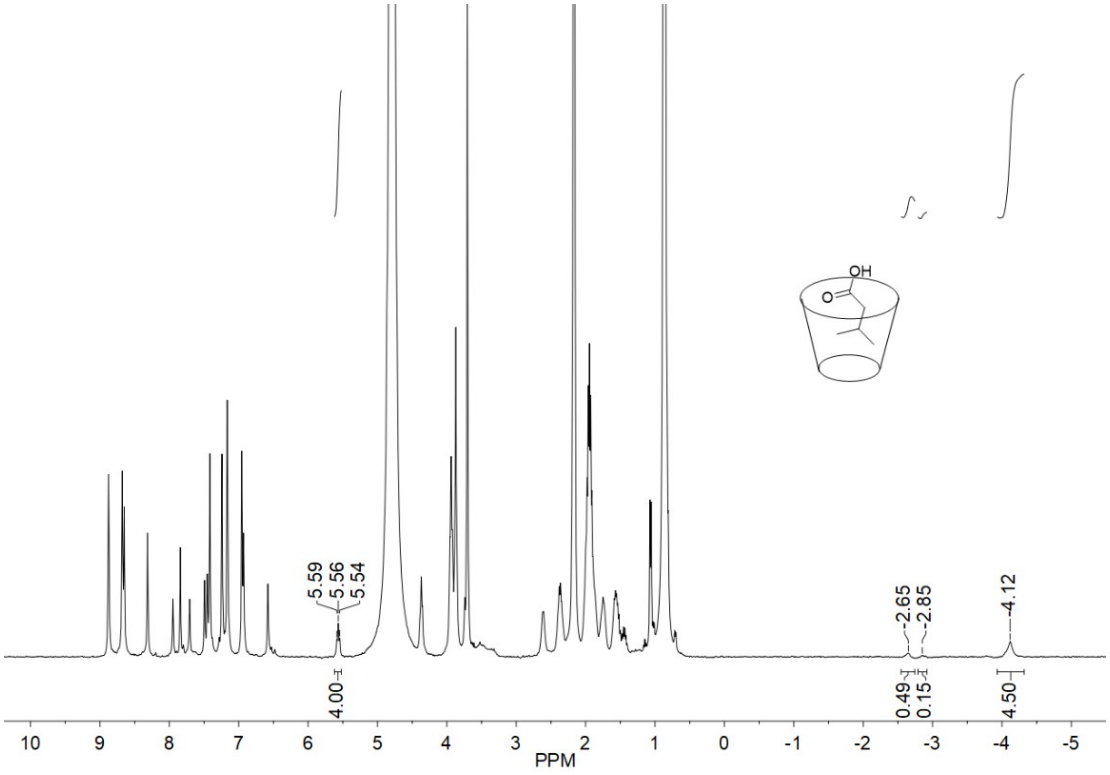


Fig. S16 ^{1}H spectrum of **1** in D_2O in the presence of excess 3-methylbutanoic acid guest at rt

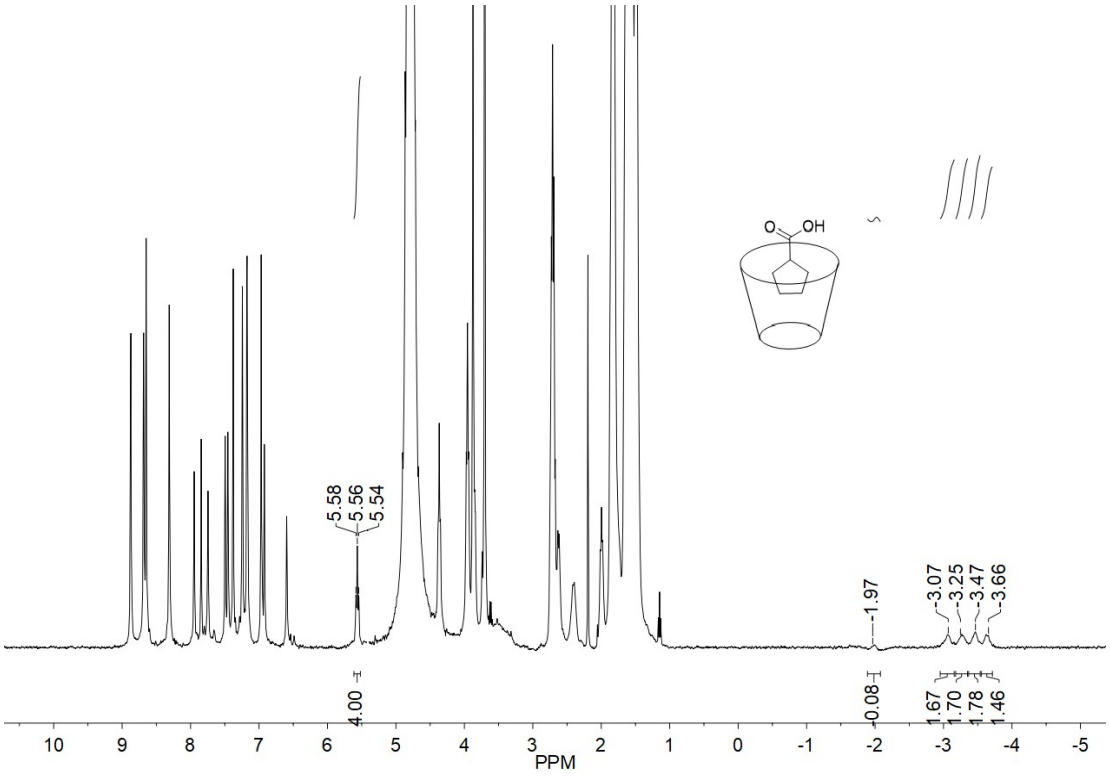


Fig. S17 ^{1}H spectrum of **1** in D_2O in the presence of excess cyclopentylcarboxylic acid guest at rt

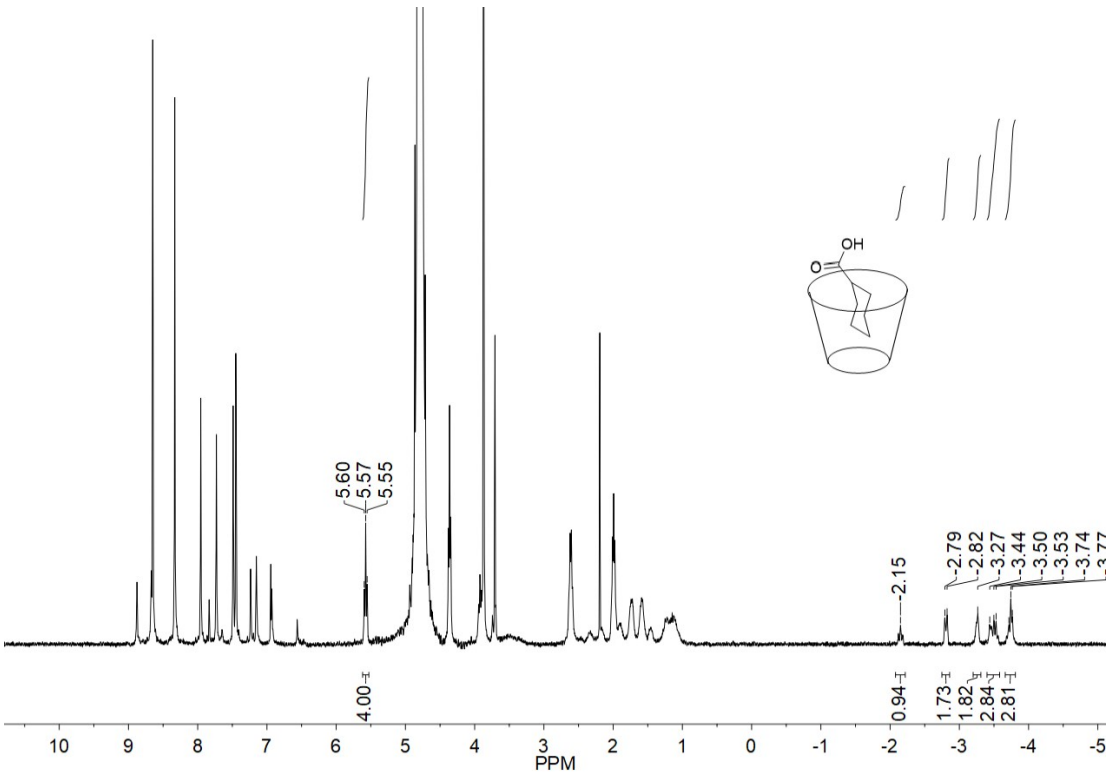


Fig. S18 ^{1}H spectrum of **1** in D_2O in the presence of excess cyclohexylcarboxylic acid guest at rt

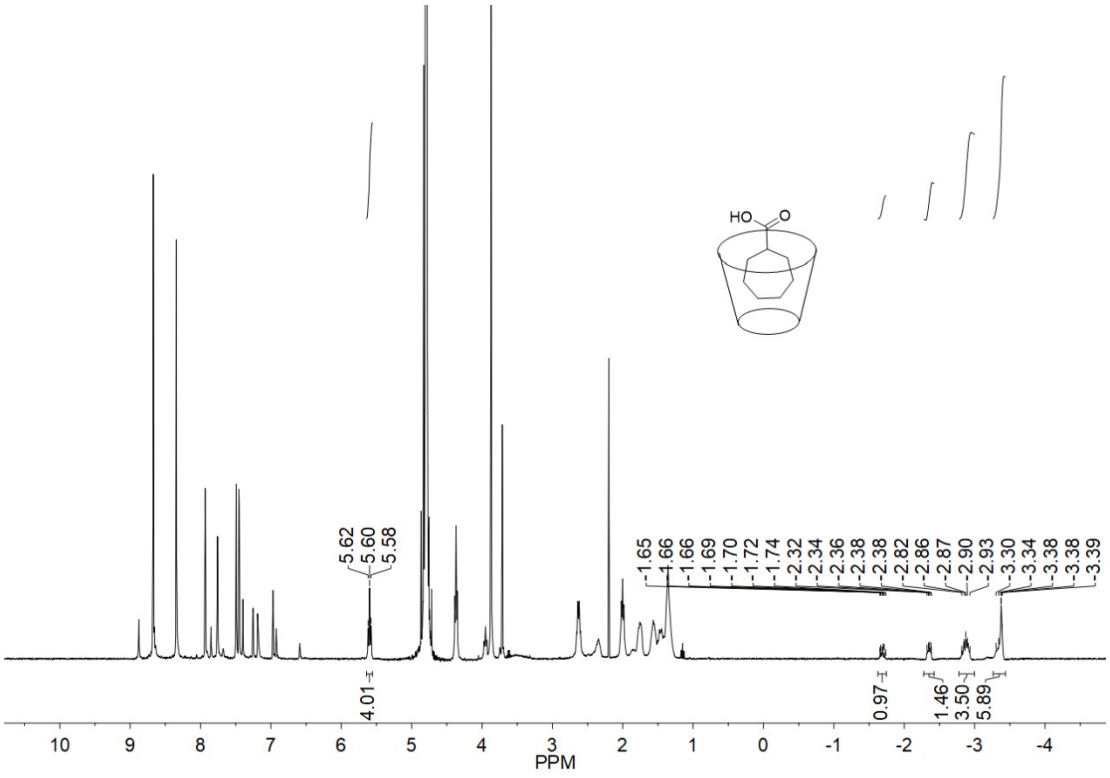


Fig. S19 ^{1}H spectrum of **1** in D_2O in the presence of excess cycloheptylcarboxylic acid guest at rt

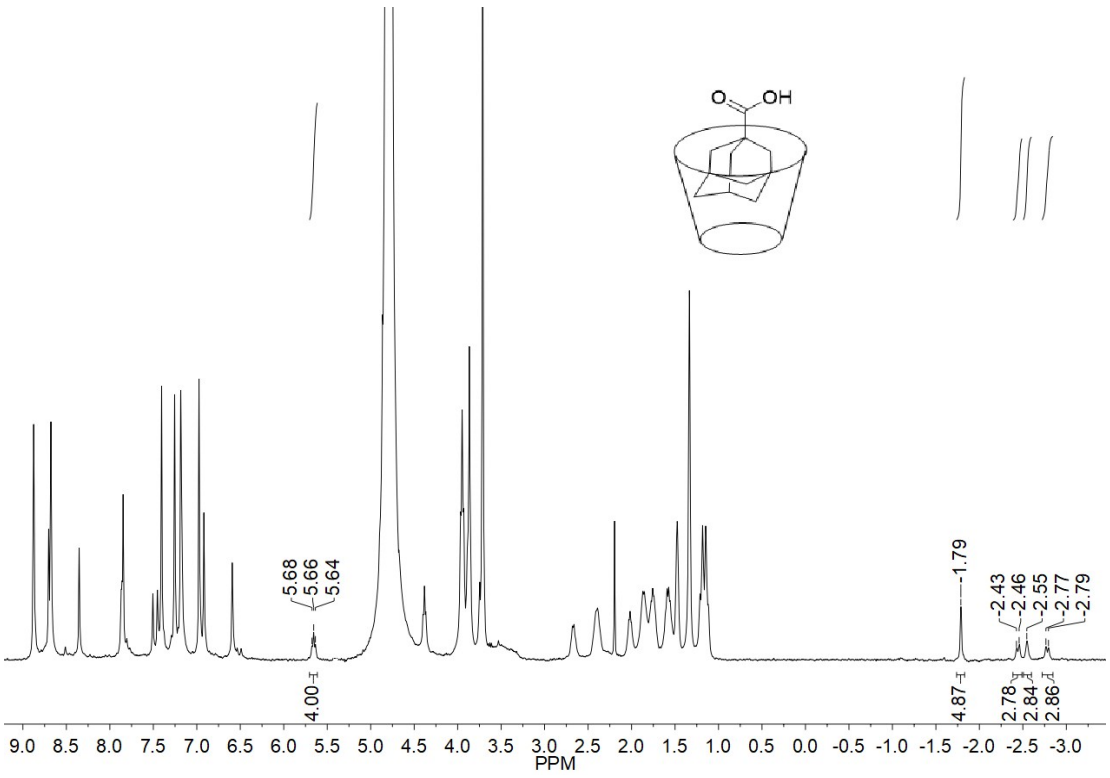
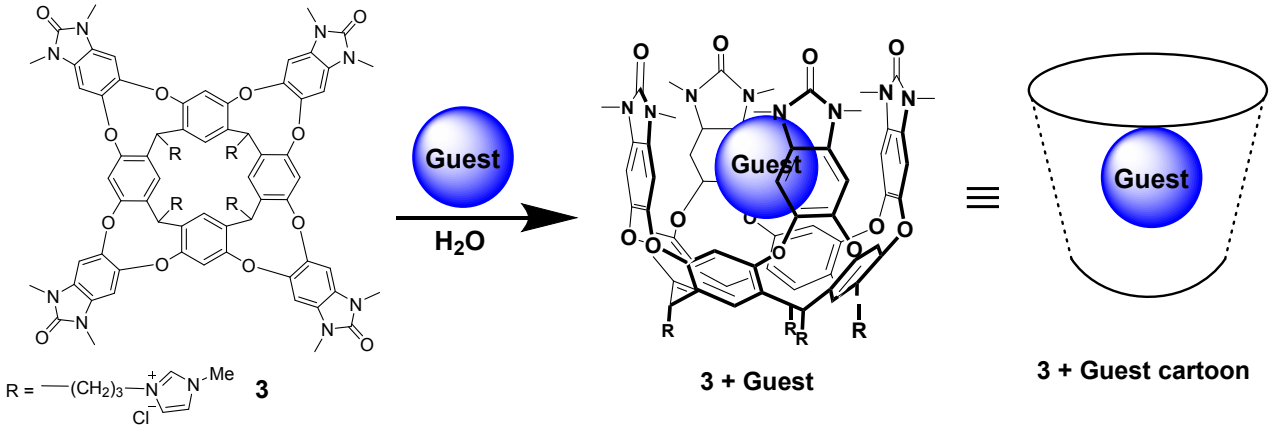


Fig. S20 ^{1}H spectrum of **1** in D_2O in the presence of excess adamantanecarboxylic acid guest at rt

NMR spectra of 3 in water in the presence of different binding guests

1 mM, 0.5 mL of **3** was taken in NMR tube and excess pure guest was added to the tube, it was shaken well to mix the guest in water. The sample was sonicated for 1 h and the ^{1}H NMR spectroscopic analysis was performed.



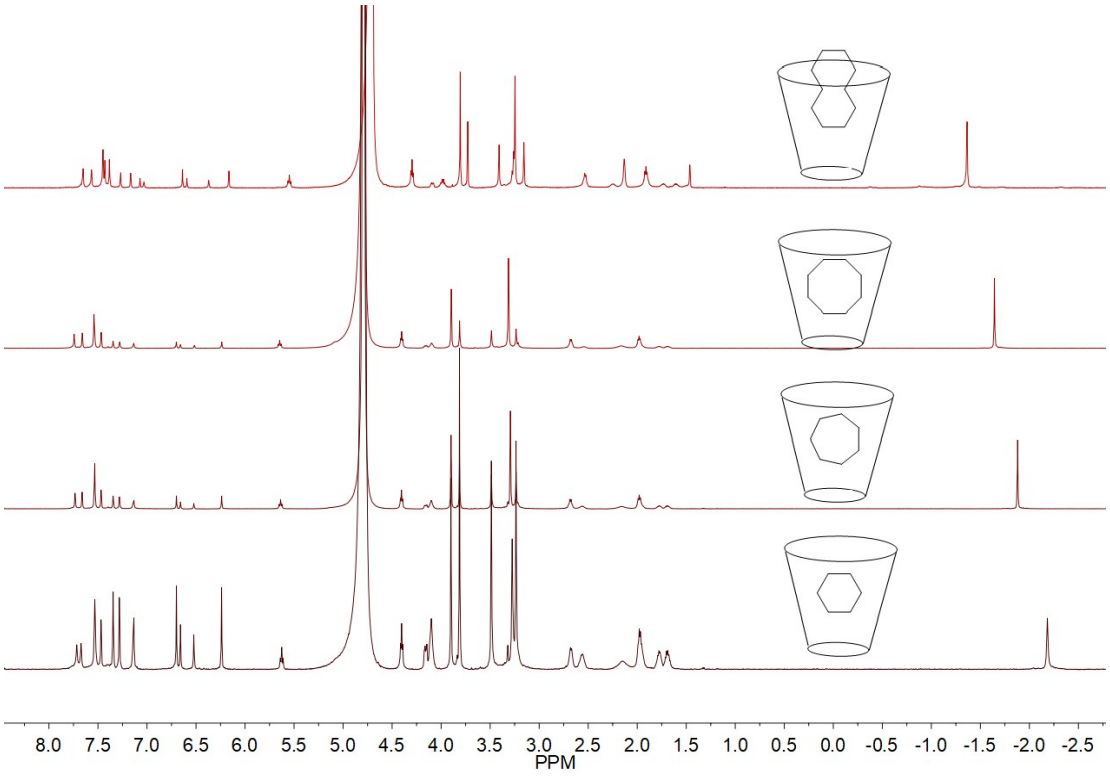


Fig. S21 3 in D_2O and binding guests from bottom to top; **3** + cyclohexane, **3** + cycloheptane, **3** + cyclooctane, **3** + cyclodecane, excess of pure guest was added to 0.5 mL, 1 mM solution of **3** in D_2O, sonicated for 1 h and analyzed by ^{1}H NMR at rt.

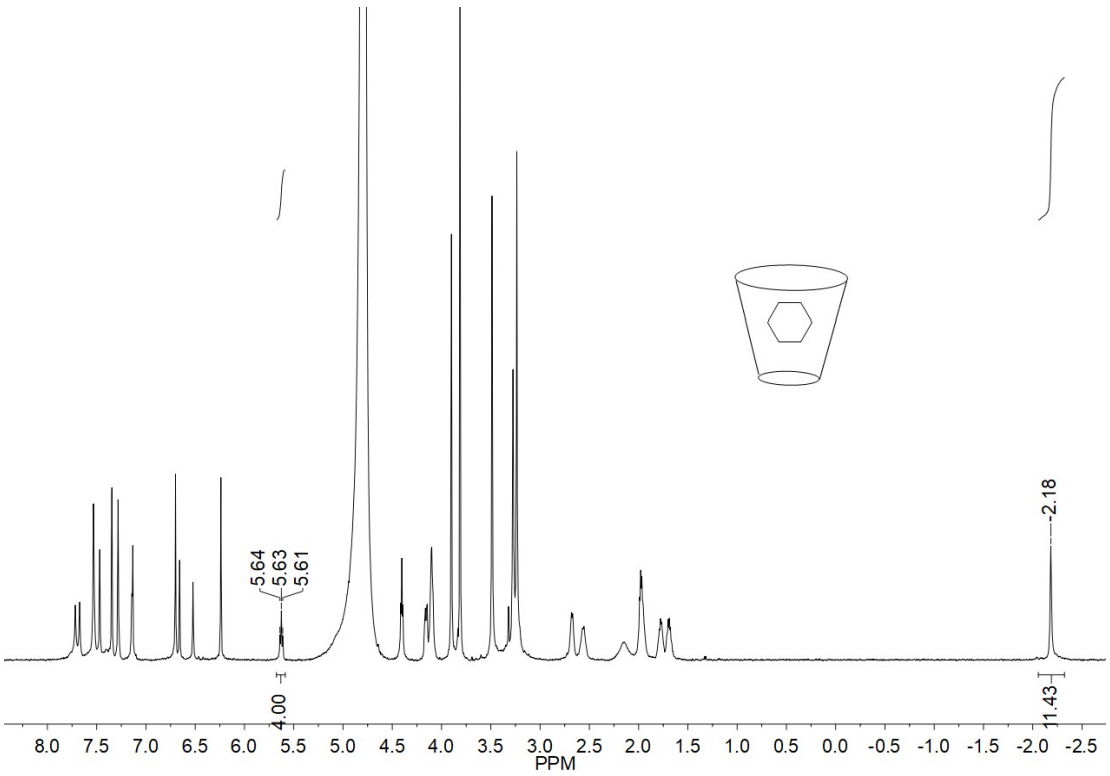


Fig. S22 ^{1}H spectrum of **3** in D_2O in the presence of cyclohexane guest at rt

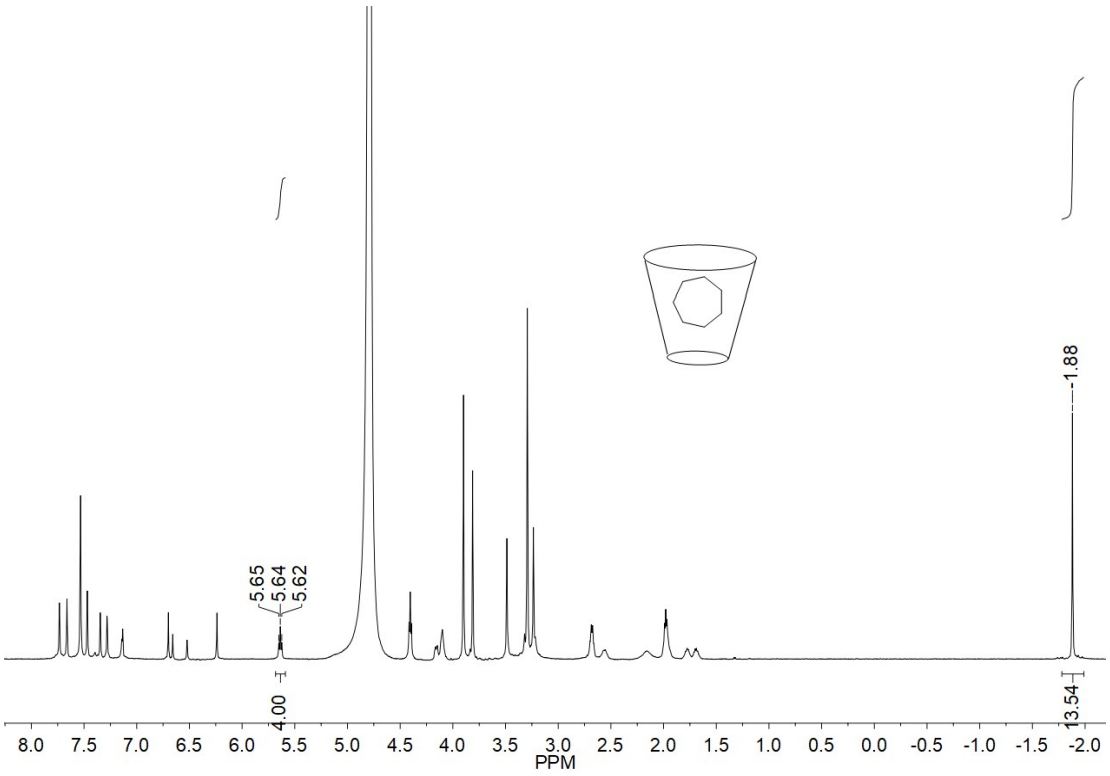


Fig. S23 ^{1}H spectrum of **3** in D_2O in the presence of cycloheptane guest at rt

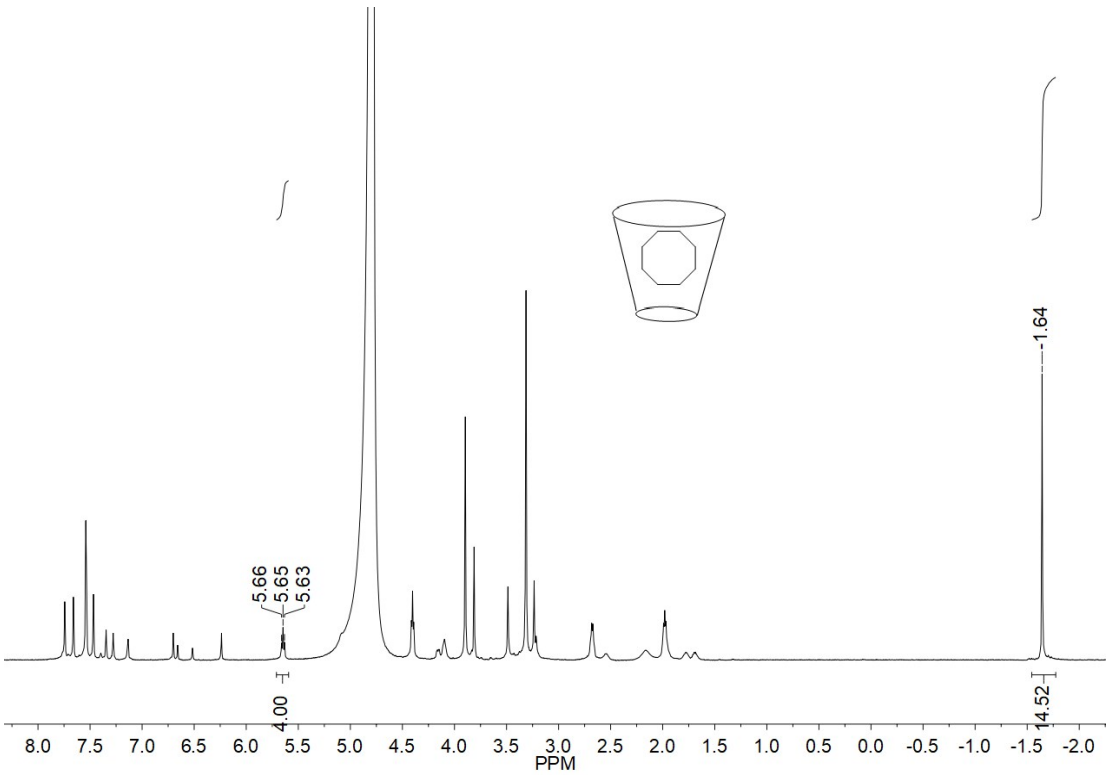


Fig. S24 ^{1}H spectrum of **3** in D_2O in the presence of cyclooctane guest at rt

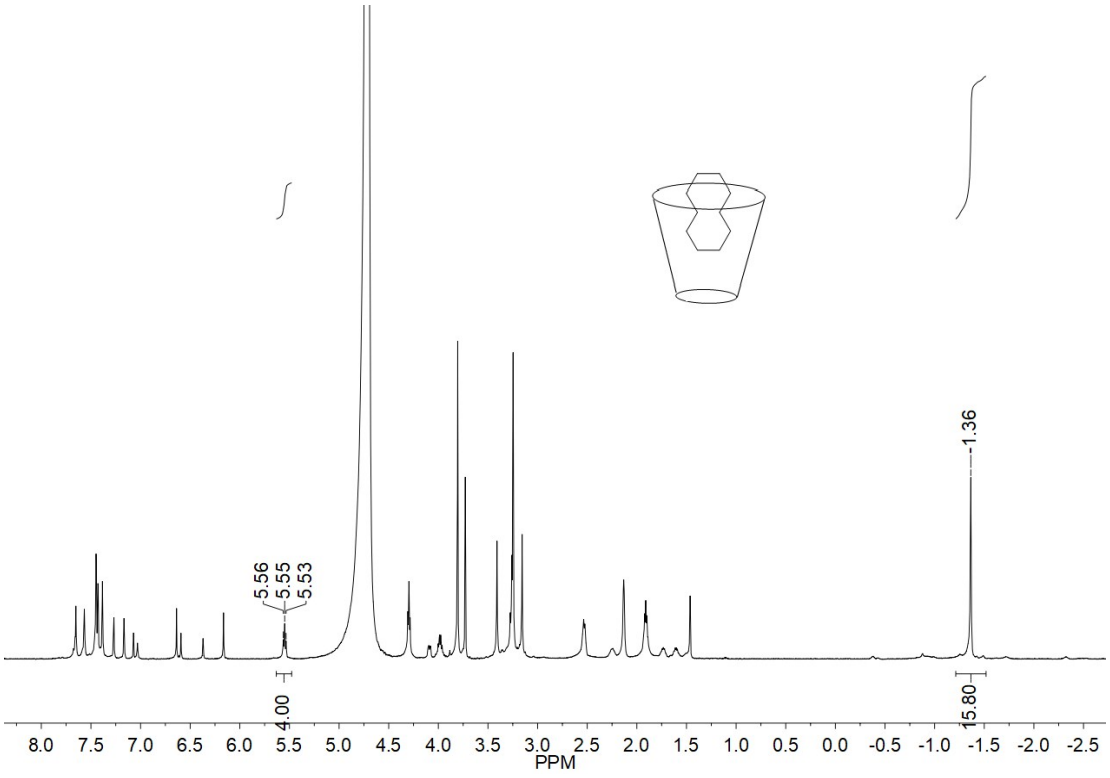


Fig. S25 ^{1}H spectrum of **3** in D_2O in the presence of cyclodecane guest at rt

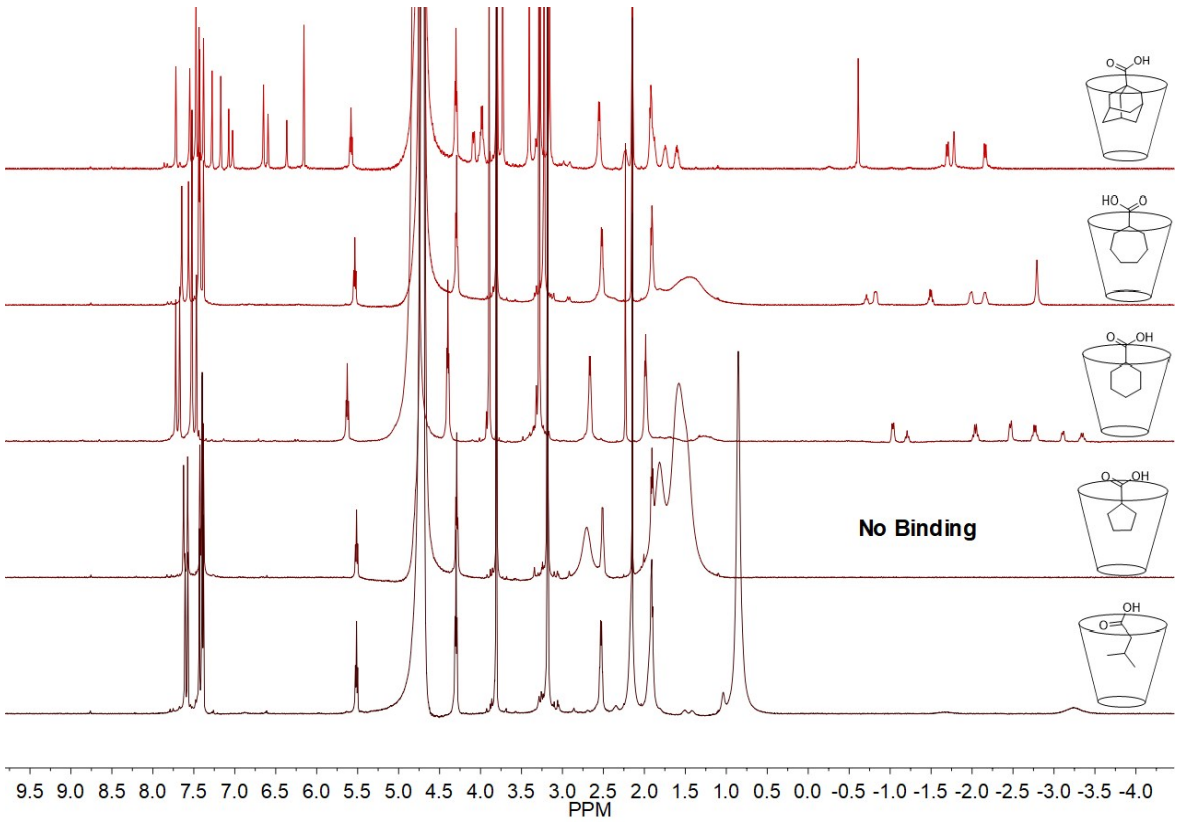


Fig. S26 **3** in D_2O and binding guests from bottom to top; **3** + 3-methylbutanoic acid, **3** + cyclopentylcarboxylic acid, **3** + cyclohexylcarboxylic acid, **3** + cycloheptylcarboxylic acid, **3** + adamantanecarboxylic acid, excess of pure guest was added to the 1 mM solution of **3** in D_2O, sonicated for 1 h and analyzed by ^1H NMR at rt.

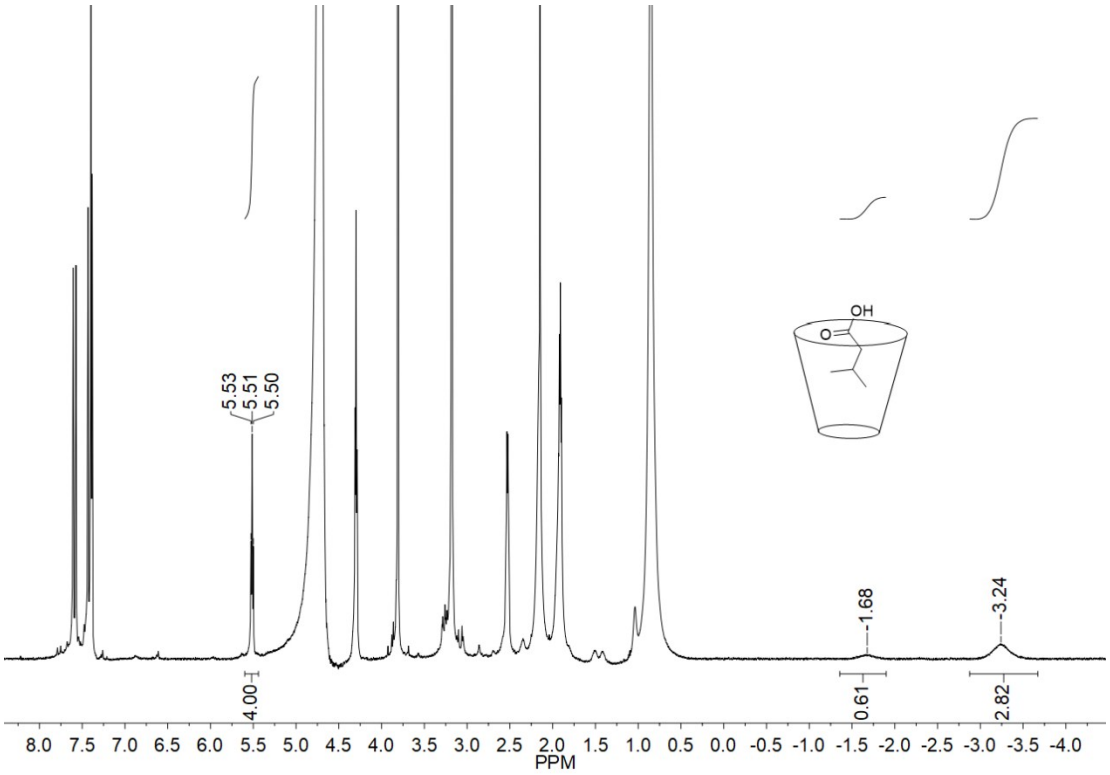


Fig. S27 ^1H spectrum of **3** in D_2O in the presence of 3-methylbutanoic acid guest at rt

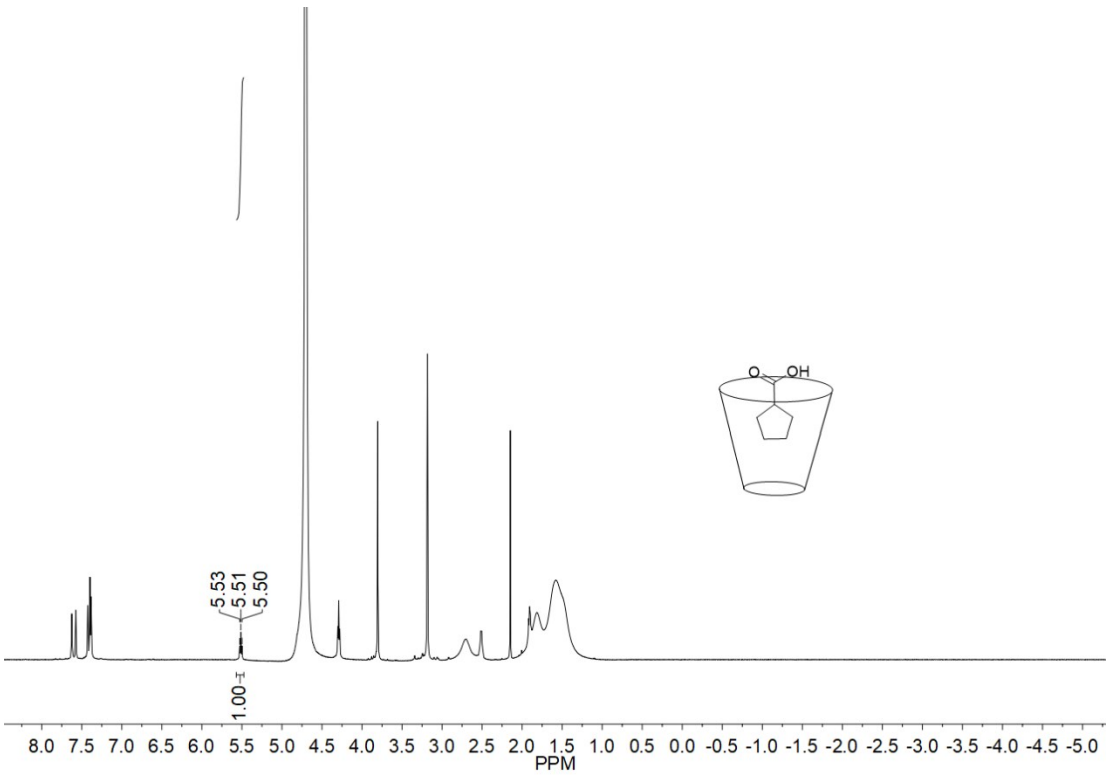


Fig. S28 ^{1}H spectrum of **3** in D_2O in the presence of cyclopentane carboxylic acid guest at rt

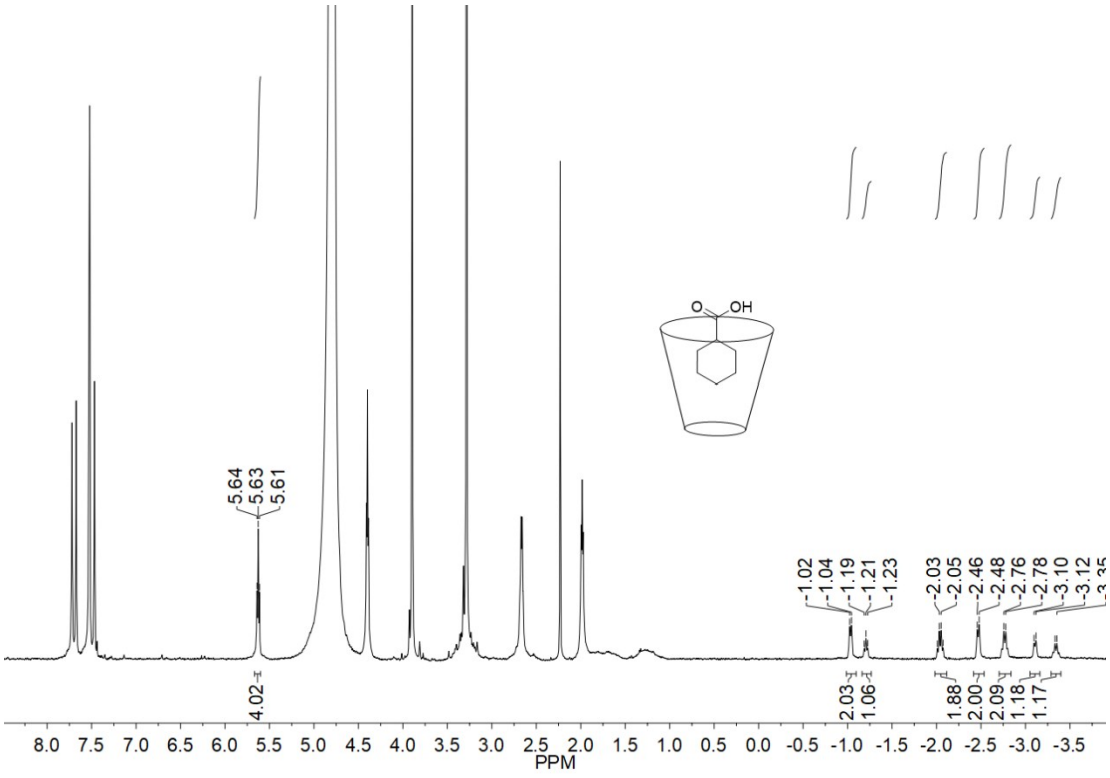


Fig. S29 ^{1}H spectrum of **3** in D_2O in the presence of cyclohexane carboxylic acid guest at rt

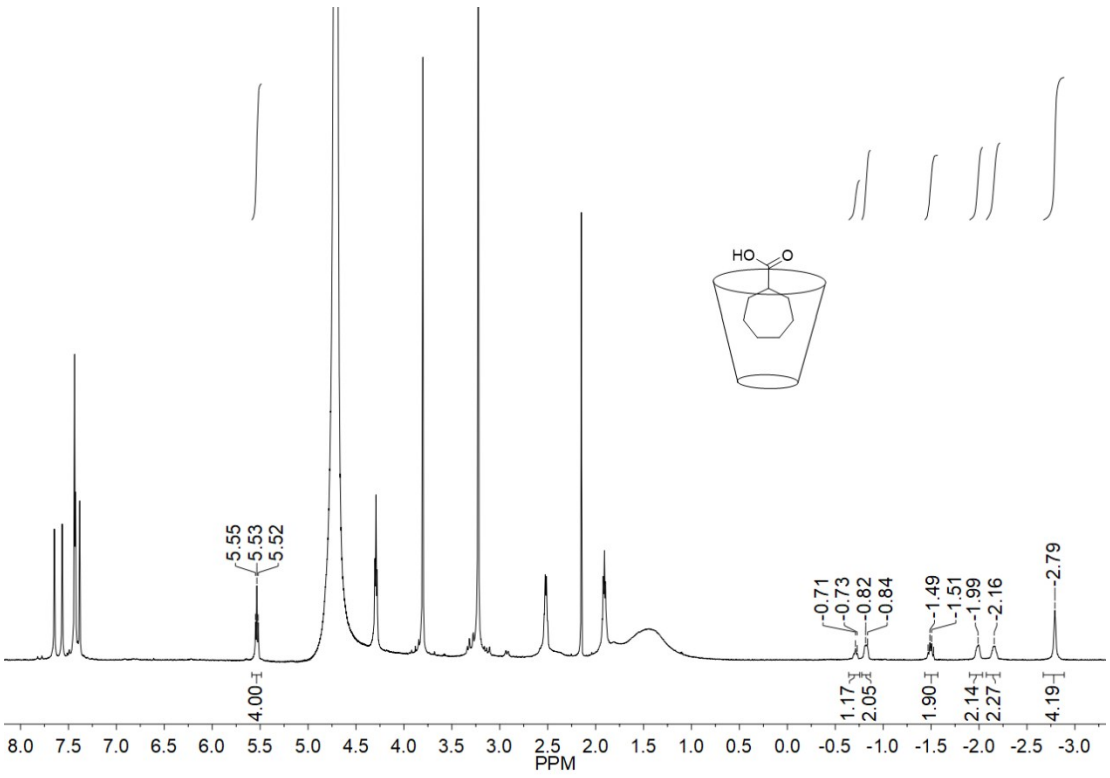


Fig. S30 ^{1}H spectrum of **3** in D_2O in the presence of cycloheptane carboxylic acid guest at rt

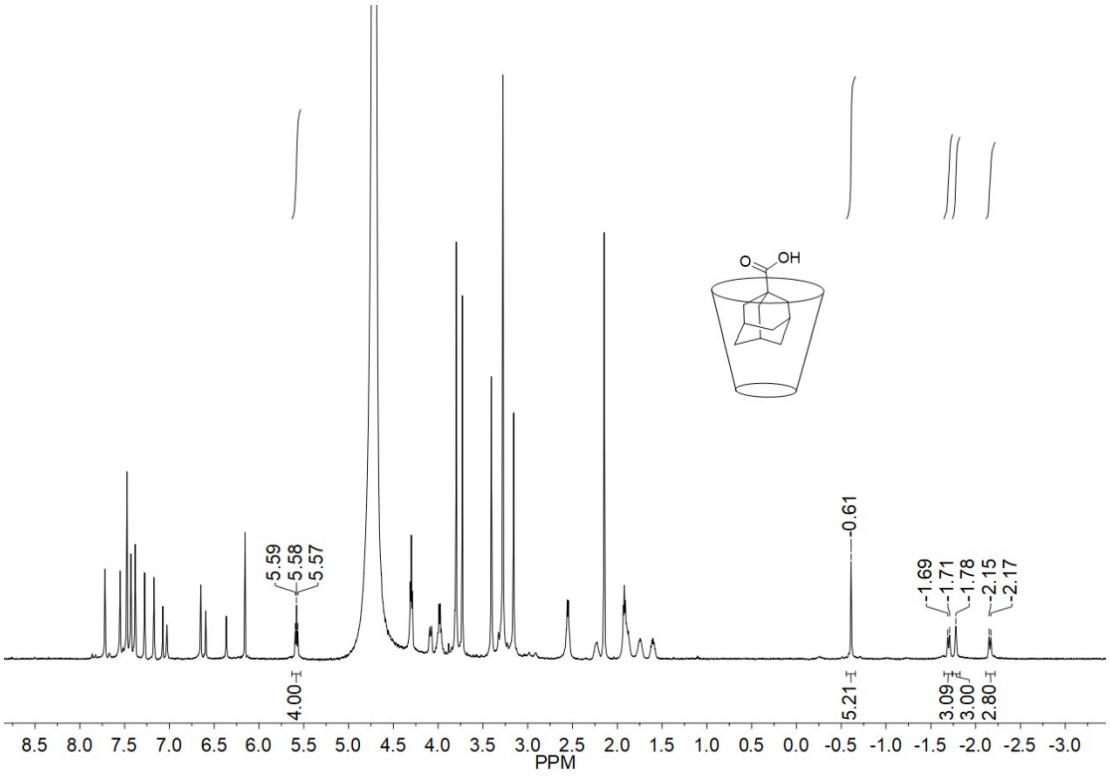


Fig. S31 ^{1}H spectrum of **3** in D_2O in the presence of adamantanecarboxylic acid guest at rt

Effect of decrease in pH on vase-kite form of 1

The effect of decrease in pH was checked for water soluble cavitand **1** in it's vase form in the presence of guest (cyclohexane) and kite form in the absence of guest in D_2O by ^1H NMR spectroscopy (Fig. S32). **1** showed no changes in its conformations showing no effect of decrease in pH on its vase conformation. Similarly, in D_2O in the absence of guest the kite conformation of **1** also remain the same as no changes were observed in the protons chemical shifts of the particular conformation. We observed slight changes in the quinoxaline protons chemical shifts showing the protonation of the nitrogen atoms but this protonation did not affect the particular conformation of the **1**. From these experimental results, we concluded that the water-soluble cavitand both conformations could not be affected by the changes in pH showing resistance to pH mediated conformational changes that is unlikely to the previously reported cavitand by Crams and co-workers.

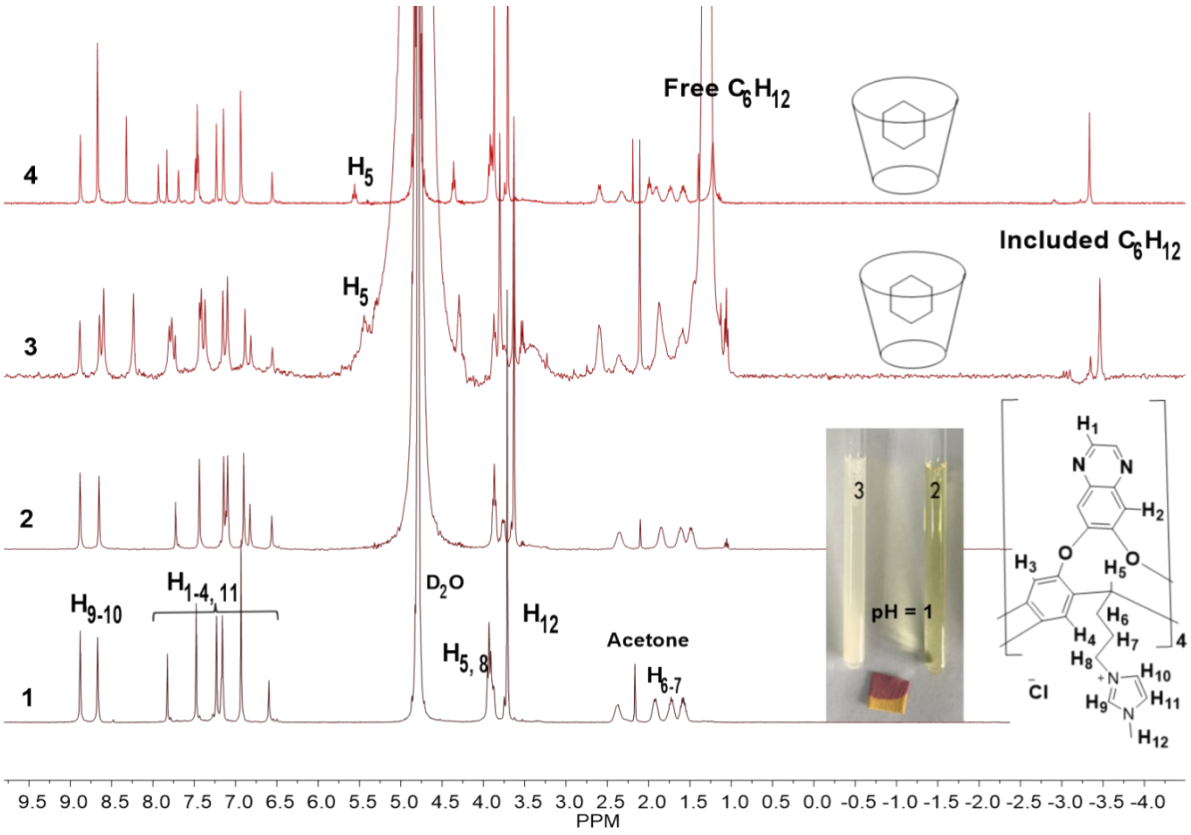


Fig. S32 Effect of pH on vase-kite forms of water soluble **1**: NMR spectrum from bottom to top 1) **1** in D_2O 2) **1** in D_2O (1.2 mM) added with conc. HCl 10 µL (230 mM) and analyzed after 1 h 3) **1** in D_2O (1.2 mM) + cyclohexane sonicated for 1 h and added with conc. HCl 10 µL (230 mM) and analyzed after 1 h 4) **1** in D_2O (1.2 mM) + cyclohexane sonicated 1 h.

[1] S. Mosca, Y. Yu, J. Rebek, Jr., Preparative scale and convenient synthesis of a water-soluble, deep cavitand, *Nat Protoc*, **2016**, *11*, 1371-87.