Supporting Information

for

A new water soluble cavitand with deeper guest binding properties

Faiz-Ur Rahman\textsuperscript{a}, Hai-Na Feng\textsuperscript{a,b}, Yang Yu\textsuperscript{a}\textsuperscript{*}

\textsuperscript{a}Center for Supramolecular Chemistry & Catalysis and Department of Chemistry, College of Science, Shanghai University, 99 Shang-Da Road, Shanghai 200444, P. R. China;
\textsuperscript{b}School of Chemical and Environmental Engineering, Shanghai Institute of Technology, 100 Hai-Quan Road, Shanghai 201418, China.

Contents

Experimental ..................................................................................................................................................2
General experimental ...................................................................................................................................2
Synthesis of cavitand octa-amino hydrochloric acid salt (Cav-8NH\textsubscript{3}Cl) ...................................2
Synthesis of cavitand 2 ............................................................................................................................3
Synthesis of water soluble imidazolium functionalized cavitand (1) ......................................................3
\textsuperscript{1}H NMR, \textsuperscript{13}C NMR spectra of the cavitands ................................................................4
Mass (HR) spectra of cavitands ................................................................................................................7
\textsuperscript{1}H NMR spectra of 1 (water soluble cavitand) in different solvents .......................................10
NMR spectra of 1 in water in the presence of different binding guests ..................................................12
NMR spectra of 1 in water in the presence of small organic acid .........................................................15
NMR spectra of 3 in water in the presence of different binding guests ..................................................19
Effect of decrease in pH on vase-kite form of 1 .....................................................................................25
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. ¹H and ¹³C 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-8NH₃Cl)
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 were 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 N₂ 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 K₂CO₃ was dissolved in 30 % water/ethanol (40 mL for 0.2 mmol of Cav-8NH₃Cl) 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 NMR) 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 $\text{C}_72\text{H}_{52}\text{Cl}_4\text{N}_8\text{O}_8$: 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 $\text{C}_{88}\text{H}_{76}\text{Cl}_4\text{N}_{16}\text{O}_8$: 1624.4786, found: 1589.5091 [M-Cl]$^+$, 777.2692 [M-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 I in DMSO-$d_6$ at rt
Fig. S6 Mass spectrum of 2
Fig. S7 Mass spectrum of 1 cationic specie formed by the loss of one Cl.
**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$_2$O at rt
Fig. S11 $^1$H spectrum of I in methanol-$d_4$ at rt

Fig. S12 $^1$H spectrum of I 25 mM in D$_2$O 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$_2$O in the presence of excess cyclohexane guest at rt
Fig. S12 $^1$H spectrum of 1 in D$_2$O in the presence of excess cycloheptane guest at rt

Fig. S13 $^1$H spectrum of 1 in D$_2$O in the presence of excess cyclooctane guest at rt
Fig. S14 $^1$H spectrum of 1 in D$_2$O 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 D₂O and binding guests from bottom to top; 1 + 3-methylbutanoic acid, 1 + cyclopentylcarboxylic acid, 1 + cyclohexylcarboxylic acid, 1 + cycloheptylcarboxylic acid, 1 + adamantancarboxylic acid, excess of pure guest was added to the 1 mM solution of 1 in D₂O, 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$_2$O in the presence of excess 3-methylbutanoic acid guest at rt

**Fig. S17** $^1$H spectrum of 1 in D$_2$O in the presence of excess cyclopentylcarboxylic acid guest at rt
Fig. S18 $^1$H spectrum of 1 in D$_2$O in the presence of excess cyclohexylcarboxylic acid guest at rt

Fig. S19 $^1$H spectrum of 1 in D$_2$O in the presence of excess cycloheptylcarboxylic acid guest at rt
Fig. S20 $^1$H spectrum of 1 in D$_2$O in the presence of excess adamantane-carboxylic 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$_2$O 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$_2$O, sonicated for 1 h and analyzed by $^1$H NMR at rt.
Fig. S22 $^1$H spectrum of 3 in D$_2$O in the presence of cyclohexane guest at rt

Fig. S23 $^1$H spectrum of 3 in D$_2$O in the presence of cycloheptane guest at rt
Fig. S24 $^1$H spectrum of 3 in D$_2$O in the presence of cyclooctane guest at rt

Fig. S25 $^1$H spectrum of 3 in D$_2$O in the presence of cyclodecane guest at rt
Fig. S26 3 in D$_2$O and binding guests from bottom to top: 3 + 3-methylbutanoic acid, 3 + cyclopentylcarboxylic acid, 3 + cyclohexylcarboxylic acid, 3 + cycloheptylcarboxylic acid, 3 + adamantane carboxylic acid, excess of pure guest was added to the 1 mM solution of 3 in D$_2$O, sonicated for 1 h and analyzed by $^1$H NMR at rt.

Fig. S27 $^1$H spectrum of 3 in D$_2$O in the presence of 3-methylbutanoic acid guest at rt
Fig. S28 $^1$H spectrum of 3 in D$_2$O in the presence of cyclopentane carboxylic acid guest at rt

Fig. S29 $^1$H spectrum of 3 in D$_2$O in the presence of cyclohexane carboxylic acid guest at rt
Fig. S30 $^1$H spectrum of 3 in D$_2$O in the presence of cycloheptane carboxylic acid guest at rt

Fig. S31 $^1$H spectrum of 3 in D$_2$O in the presence of adamantancarboxylic 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 its vase form in the presence of guest (cyclohexane) and kite form in the absence of guest in D$_2$O by $^1$H 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$_2$O 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$_2$O 2) 1 in D$_2$O (1.2 mM) added with conc. HCl 10 µL (230 mM) and analyzed after 1 h 3) 1 in D$_2$O (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$_2$O (1.2 mM) + cyclohexane sonicated 1 h.