Binding properties of cavitands in aqueous solution—the influence of charge on guest selectivity†

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The charge of the upper rim has influences on the binding properties of cavitands in aqueous media.

Resorcinarene based cavitands have been extensively studied since their first introduction by Cram *et al.* in 1982.[1,2] Since their initial development, modifications have been made to the walls and upper rim, and these changes have altered their guest binding properties.

Cavitands bearing benzimidazole walls have been reported in the literature recently, and have demonstrated new properties.[3,4] Most notably, these cavitands require four molecules of water or alcohol to fold into and maintain the vase conformation,[4] even when the system operates in organic solvents. A water-soluble, tetracarboxylate derivative was reported (**1**, Fig. 1),[5,6] and has been shown to bind a variety of tetraalkylammonium salts and adamantane derivatives in a kinetically stable fashion. We have been pursuing the effect of the charge on the upper rim on its binding properties, and have subsequently synthesized and studied a tetraammonium derivative, **2** (Fig. 1).

Cavitand **2** was synthesized following the procedures developed for previous benzimidazole cavitands (Scheme 1 and supporting information†). Octanitro cavitand **3**[8] was reduced with tin chloride in the presence of hydrochloric acid to afford the octaamine compound **4**. Condensation of this octaamine with imidate **5**[9] provided the tetrabenzimidazole cavitand **6** bearing four aminocarboxybenzyl groups. These groups can be cleanly removed with HBr in acetic acid to give the tetraammonium cavitand **2** as the hydrobromide salt.[10]

Fig. 1 Minimized structures for the tetracarboxylate cavitand **1** and the tetraammonium cavitand **2** (Maestro 7.0.1, AMBER force field).[7] Pendant ethyl groups are omitted for clarity.

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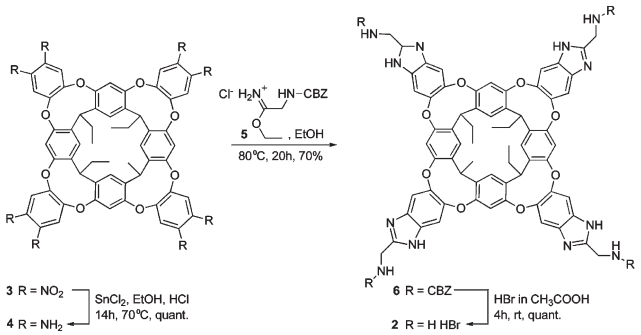


Scheme 1 Synthesis of the tetraammonium cavitand **2**.

This salt of cavitand **2** is soluble in water up to concentrations of 4 mM, and a 1 mM solution has a pH of 2.6. Under neutral conditions the cavitand is insoluble in water, and buffering to acidic pH (4.0, citric acid–NaOH–NaCl) also leads to precipitation. Unlike its tetraanionic predecessor **1**, this cavitand is also soluble in DMSO, THF, DMF and methanol, as well as mixtures of these solvents with water.

The ^{1}H NMR spectrum of **2** in water (Fig. 2) reveals that the cavitand is present in the kite conformation (C_{2v} symmetry), as indicated by the shift of the resorcinarene methine protons at 3.84 ppm[1] and the pattern of the aromatic protons. Neither the presence of suitable guests (*i.e.* adamantane, adamantanecarboxylic acid) nor high temperatures (333 K)[11] could induce the vase conformation. However, when co-solvents such as DMSO, THF or methanol are added, the ^{1}H NMR spectra of these mixtures reveal the emergence of the vase conformation (C_{4v} symmetry) of cavitand **2** (Fig. 3). The degree of protonation in these solvent mixtures is unknown. We found the best conditions to study the binding properties of this cavitand were 1 mM of host and guest in solutions of 3 : 1 D_2O : DMSO. For comparison, we also investigated the binding properties of tetracarboxylate cavitand **1** under these conditions.

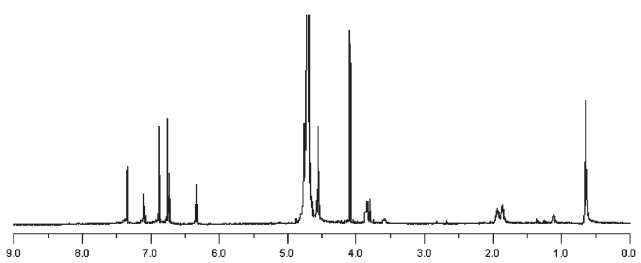


Fig. 2 ^{1}H NMR spectrum of the tetraammonium cavitand **2** in D_2O (HOD at 4.706 ppm).

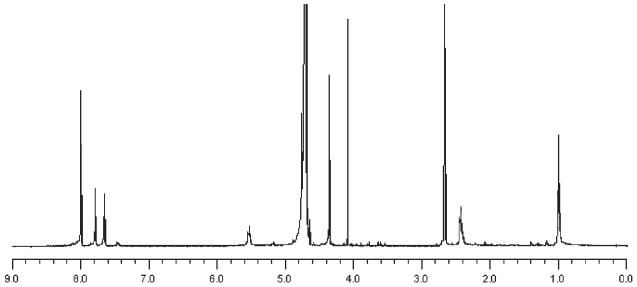
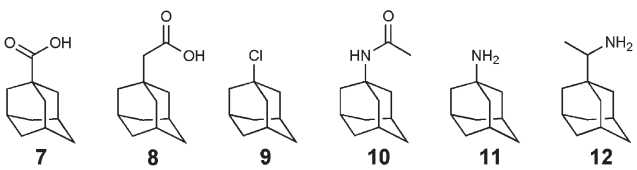


Fig. 3 ^{1}H NMR spectrum of tetraammonium cavitand **2** in 3 : 1 D_2O : DMSO-d_6.

Table 1 Association constants of adamantane derivatives and the cavitands **1** and **2** in 3 : 1 D_2O : DMSO-d_6

Guest	K_a for **1**/M^{-1a}	K_a for **2**/M^{-1b}
7	3.6×10^2	3.5×10^3
8	4.3×10^2	2.4×10^3
9	1.7×10^3	1.2×10^3
10	1.4×10^3	5.2×10^2
11	$>10^4$	n.d.[c]
12	$>10^4$	n.d.[c]

[a] pH of solution = 7.9. [b] pH of solution = 2.7. [c] Not detectable.

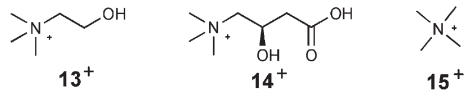


Scheme 2 Adamantane derivatives used for the binding experiments.

Table 1 shows the association constants of cavitands **1** and **2** for a series of adamantane derivatives.

Negatively charged adamantane derivatives **7** and **8** (Scheme 2) have similar association constants to the tetraammonium cavitand (3×10^3 M^{-1}), and this binding is an order of magnitude stronger than with the tetracarboxylate host. This is reasonable: unfavorable electrostatic interactions between the tetraanionic rim of host **1** are likely to result in a lower affinity of these guests for this cavitand. Neutral adamantanes **9** and **10** showed no preference for one tetraionic cavitand over the other. However, we found that while positively charged adamantane derivatives **11** and **12** form strong complexes with the tetracarboxylate cavitand ($K_a > 10^4$ M^{-1}), no kinetically stable complex formation was observed between these guests and the tetraammonium cavitand **2**.

Intrigued by this result, we studied the binding properties of cavitands **1** and **2** with tetraalkylammonium salts **13**$^+$–**15**$^+$ (Scheme 3). The driving forces available for this type of host–guest complexation now include cation–π interactions in addition to the CH–π interactions and the hydrophobic effect found upon binding the adamantane derivatives. We previously reported the association constants for tetracarboxylate cavitand **1** and guests **13**$^+$–**15**$^+$ in D_2O.[6] The binding constants observed in the current



Scheme 3 Trimethylammoniums used for the binding experiments.

Table 2 Association constants of the trimethylammoniums and the cavitands **1** and **2** in D_2O/3 : 1 D_2O : DMSO-d_6

Guest	K_a for **1**/M^{-1a}	K_a for **2**/M^{-1b}
13	2.1×10^3	n.d.[c]
14	n.d.[c]	n.d.[c]
15	8.3×10^2	n.d.[c]

[a] pH of solution = 7.9. [b] pH of solution = 2.7. [c] Not detectable.

system (3 : 1 D_2O : DMSO-d_6) follow the same trends as in pure D_2O (for example, **15** is bound less strongly than **13**), but the absolute values are slightly lower in magnitude due to the presence of DMSO as a co-solvent. As for tetracationic cavitand **2**, the additional forces on offer were apparently not enough to overcome the unfavorable electrostatic interactions between the host's upper rim and the guest, because kinetically stable complex formation was not observed by ^{1}H NMR for the compounds in Table 2. Even a guest such as L-carnitine (**14**), which bears a carboxylate moiety, cannot be coaxed into the cavity.

In summary, studies of the new positively charged cavitand **2** and the tetracarboxylate counterpart **1** in 3 : 1 water : DMSO revealed that the charge of the upper rim has a significant influence on binding specificity and magnitude. No cationic compounds are bound by the tetraammonium cavitand **2**; additionally **2** is a very specific receptor for neutral or anionic adamantane derivatives.

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Notes and references

1 J. R. Moran, S. Karbach and D. J. Cram, *J. Am. Chem. Soc.*, 1982, **104**, 5826–5828.
2 D. J. Cram, *Science*, 1983, **219**, 1177–1183.
3 H.-J. Choi, Y. S. Park, J. Song, S. J. Youn, H.-S. Kim, S.-H. Kim, K. Koh and K. Paek, *J. Org. Chem.*, 2005, **70**, 5974–5981.
4 A. R. Far, A. Shivanyuk and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2002, **124**, 2854–2855.
5 F. Hof, L. Trembleau, E. C. Ullrich and J. Rebek, Jr., *Angew. Chem., Int. Ed.*, 2003, **42**, 3150–3153.
6 S. M. Biros, E. C. Ullrich, F. Hof, L. Trembleau and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2004, **126**, 2870–2876.
7 F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440–467.
8 P. Amrhein, A. Shivanyuk, D. W. Johnson and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2002, **124**, 10349–10358.
9 T. J. Church, N. S. Cutshall, A. R. Gangloff, T. E. Jenkins, M. S. Linsell, J. Litvak, K. D. Rice, J. R. Spencer and V. R. Wang, *PCT Int. Appl. WO 9845275*, 1998.
10 D. Ben-Ishai and A. Berger, *J. Org. Chem.*, 1952, **17**, 1564–1570.
11 J. R. Moran, J. L. Ericson, E. Dalcanale, J. A. Bryant, C. B. Knobler and D. J. Cram, *J. Am. Chem. Soc.*, 1991, **113**, 5707–5714.