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Water-soluble pentasulfonatocalix[5]arene: selective recognition of ditopic trimethylammonium cations by a triple non-covalent interaction

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Abstract—The inclusion of tetramethylammonium and ditopic trimethylammonium cations by the water-soluble pentasulfonatocalix[5]arene **1** has been studied at neutral pH by ^{1}H NMR and compared with the homologous tetrasulfonatocalix[4]arene **2**. Unlike host **2**, host **1** selectively binds the ditopic trimethylammonium ions by three different non-covalent interactions. Remarkably the flexible host **1** exhibits both more efficiency and selectivity in the complexation of ditopic methylammonium ions with respect to similar more preorganised calix[4]arene receptors.

Water-soluble calixarenes[1] are becoming increasingly important in Supramolecular Chemistry[2] because they allow the study of the basic forces involved in the host–guest recognition processes in a solvent where most biological processes occur. In the last few years we have extensively investigated the recognition properties of some water-soluble calix[4]arenes and resorcinarenes towards quaternary ammonium ions,[3,4] native amino-acids,[5] radicals[6] and small neutral organic molecules.[7] We have shown that these organic guests are bound to the calixarene receptors by the cooperative effect of the hydrophobic interaction inside the host cavity (CH–π or π–π) and the electrostatic attraction that occurs at the upper rim of the receptor. We have now extended these studies to the inclusion behaviour of the water-soluble and conformationally flexible pentasulfonatocalix[5]arene **1** in order to evaluate the role of both the wider calixarene cavity and the nature of the non-covalent interactions on the molecular recognition of organic substrates. Here we report on the inclusion of methylammonium cations.

Pentasulfonatocalix[5]arene hexasodic salt **1** was synthesised as reported in literature.[8] The inclusion properties of **1** towards tetramethylammonium (TEMA), trimethylanilium (TMA), benzyltrimethylammonium (BTMA) and *p*-nitrobenzyltrimethylammonium (BTMAN) were investigated by ^{1}H NMR in D_2O at pD = 7.3. In all cases the signals of guest protons are observed as averaged single resonances because of the fast exchange on the NMR time scale between free and complexed guest. The guest protons included into the host cavity experience an upfield shift, as compared with the uncomplexed guest, owing to the ring current effect of the aromatic nuclei of the host. The binding constants were obtained by ^{1}H NMR titration experiments by keeping the guest concentration fixed ($1 \times 10^{-3}\,\mathrm{mol\,dm^{-3}}$) and allowing the host concentration to vary. The proton upfield shifts were treated by using a non-linear least-square fitting procedure.[9] Log$K$ values for the complex formation of TEMA, TMA, BTMA and BTMAN with host **1** are reported in Table 1. To the best of our knowledge these are the first ^{1}H NMR experimental data in solution ever reported for the inclusion properties of a water-soluble calix[5]arene receptor. In the same table are also reported log$K$ values previously obtained for the same guests with the homologous flexible cone host **2** and the similar blocked cone hosts **3** and **4**.

Keywords: Calixarenes; Molecular recognition; Methylammonium cations; Water-soluble receptors.

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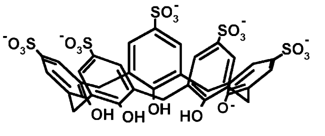
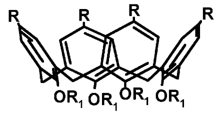
Table 1. Log*K* values[a] for the complex formation of TEMA, TMA, BTMA and BTMAN with hosts **1**–**4**; pD = 7.3 at 25 °C

Complex	Log*K*	Included moiety	Complex	Log*K*	Included moiety
1–TEMA	3.6 (1)	$N^+(CH_3)_4$	**3**–TEMA	3.6[c]	$N^+(CH_3)_4$
1–TMA	4.2 (1)	$–N^+(CH_3)_3$	**3**–TMA	3.4[d]	–Ar
1–BTMA	4.0 (1)	$–CH_2N^+(CH_3)_3$	**3**–BTMA	3.3[d]	Aspecific
1–BTMAN	5.1 (1)	$–CH_2N^+(CH_3)_3$	**3**–BTMAN	3.4[d]	$–N^+(CH_3)_3$
2–TEMA	4.9[b]	$N^+(CH_3)_4$	**4**–TEMA	2.4 [c]	$N^+(CH_3)_4$
2–TMA	4.6[b]	Aspecific	**4**–TMA	2.2[d]	$–N^+(CH_3)_3$
2–BTMA	4.1 (1)	Aspecific	**4**–BTMA	1.7[d]	$–N^+(CH_3)_3$
2–BTMAN	4.2 (1)	$–N^+(CH_3)_3$	**4**–BTMAN	1.7[d]	$–N^+(CH_3)_3$

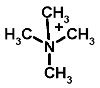
[a] σ in parentheses.
[b] Refs. 10 and 11.
[c] Ref. 3c.
[d] Ref. 3b.



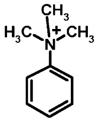
1



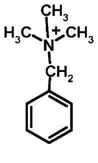
2 $R = SO_3^-$ $R_1 = H$
3 $R = SO_3^-$ $R_1 = CH_2COO^-$
4 $R = H$ $R_1 = CH_2COO^-$



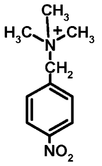
TEMA



TMA



BTMA



BTMAN

The inspection of the data reported in Table 1 reveals that the inclusion properties of the host **1** are remarkably different from calix[4]arene hosts **2**, **3** and **4**, as regards both the efficiency and the selectivity of binding. Log*K* value found for **1**–TEMA complex is about one logarithmic unit lower than the value found for the homologous host **2** with the same guest. The inclusion of TEMA for both systems is essentially due to the synergy of (i) the electrostatic interaction between the charged moiety of the guest and the sulfonato groups at the host upper rim[3] and (ii) the CH–π interaction between the activated methyl groups of the guest and the aromatic nuclei of the host.[12] Owing to the wider cavity of **1**, the host–guest electrostatic interaction is less efficient, thus decreasing the stability of **1**–TEMA complex with respect to the **2**–TEMA one. Both TMA and BTMA are included into the calix[4]arene **2** more efficiently than the receptor **1**, but the stability of calix[4]arene **2** complexes decrease in the order **2**–TEMA > **2**–TMA > **2**–BTMA, whereas calix[5]arene **1** is able to include more efficiently both TMA and BTMA rather than TEMA, thus confirming the different inclusion properties of **1**.

Host **1** does not behave like the homologous **2** also in the mode of recognition of TMA and BTMA. The complexed induced shifts (CIS) of guest protons are in the sequence $\Delta\delta_{CH_3} > \Delta\delta_{H_{ortho}} > \Delta\delta_{H_{meta}} > \Delta\delta_{H_{para}}$ for TMA (Fig. 1a) and $\Delta\delta_{CH_2} > \Delta\delta_{CH_3} > \Delta\delta_{H_{ortho}} > \Delta\delta_{H_{meta}} = \Delta\delta_{H_{para}}$ for BTMA (Fig. 1b). This indicates that TMA and BTMA are selectively included in the mode depicted in the Figure 1c and d, respectively. It is noteworthy that all guest protons are upfield shifted indicating that they are all incorporated into the host cavity. On the contrary, host **2** alternatively binds the aliphatic or the aromatic moiety of TMA[11] and BTMA (Fig. 2a), as revealed by the different sequence of the complexed induced shifts (CIS) ($\Delta\delta_{CH_3} > \Delta\delta_{CH_2} > \Delta\delta_{H_{ortho}} = \Delta\delta_{H_{para}} > \Delta\delta_{H_{meta}}$) (Fig. 2b). These data suggest that the wider cavity of calix[5]arene **1** is able to include, in the selective mode shown above, both the charged group and the aromatic moiety of ditopic TMA and BTMA guests in order to achieve a synergy of three weak interactions, namely the π–π interaction[13] between the aromatic ring of the guest and the phenolic units of **1**, the electrostatic and the CH–π interaction which, as above reported, are responsible of the inclusion of TEMA into the host **1** and **2**. Differently TMA and BTMA are inserted in the tighter cavity of **2** alternatively with either the charged or the aromatic group. Only two interactions (either the π–π and the electrostatic or the CH–π and the electrostatic, depending on the inclusion mode) are hence involved in the formation of both **2**–TMA and **2**–BTMA complexes.

Preliminary molecular modelling results[14] support this hypothesis, showing that the aromatic ring of TMA or BTMA is able to interact by a 'face to face' stacking interaction with the aromatic rings of calix[5]arene cavity while the methylammonium group is the most deeply included into the host cavity. As an example of molecular modelling of these systems the optimised structure of **1**–BTMA complex is reported in Figure 3.

The complexation data of BTMAN highlight the role played by the π–π interaction on the inclusion processes of ditopic methylammonium ions by the calix[5]arene **1**. The presence of the electron withdrawing nitro group in the *para*-position of the aromatic ring of BTMAN, enhances the efficiency of the π–π interaction of aromatic BTMAN ring with the phenolic units of the host cavity. Thus log*K* value found for **1**–BTMAN (Table 1) is about one logarithmic unit higher than both

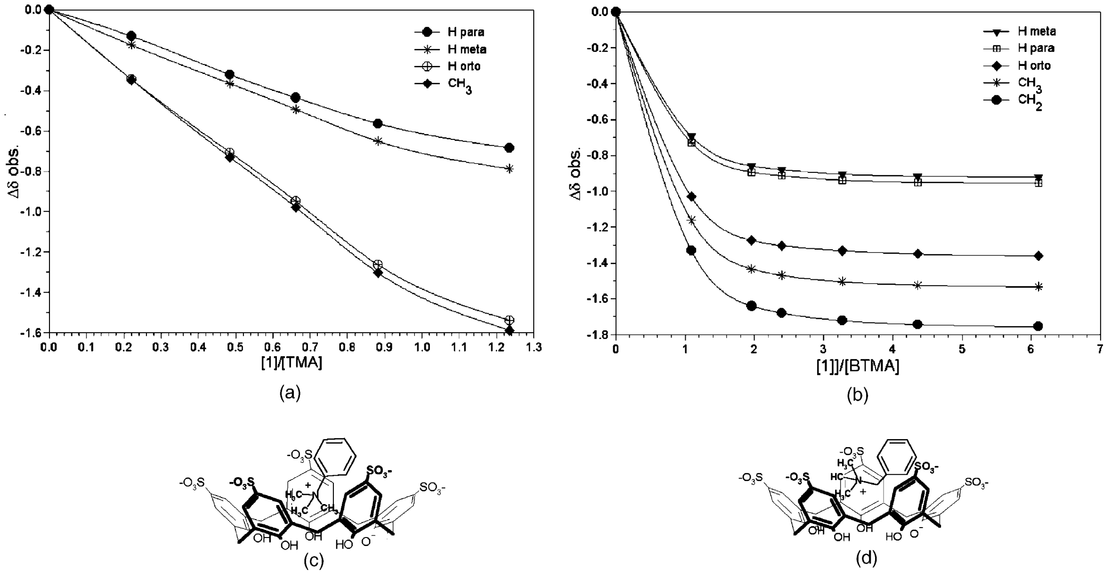


Figure 1. Plots of $\Delta\delta_{obs}$ (ppm) versus (a) [**1**]/[TMA] and (b) [**1**]/[BTMA] in D_2O, 25 °C, [TMA] = [BTMA] = 1×10^{-3} mol dm^{-3}, pD = 7.3 (0.1 mol dm^{-3} phosphate buffer). Mode of inclusion of (c) TMA and (d) BTMA into host **1**.

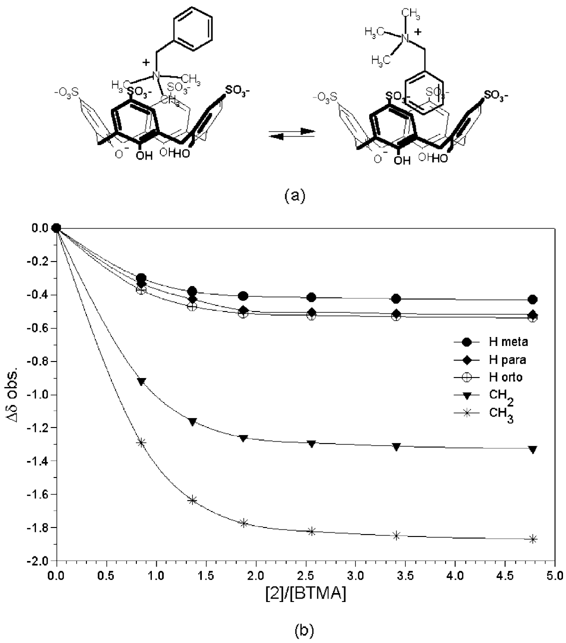


Figure 2. (a) Modes of inclusion of BTMA into host **2**. (b) Plots of $\Delta\delta_{obs}$ (ppm) versus [**2**]/[BTMA] in D_2O, 25 °C, [BTMA] = 1×10^{-3} mol dm^{-3}, pD = 7.3 (0.1 mol dm^{-3} phosphate buffer).

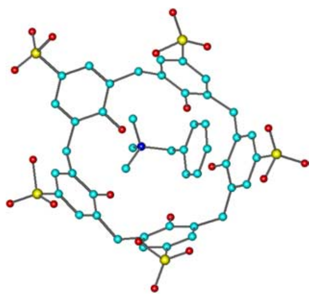


Figure 3. Optimised structure in water (Molecular Mechanics, Hyperchem®, serial number 510-10001631) generated for **1**–BTMA complex (top view). Hydrogen atoms are omitted for clarity.

1–BTMA and **1**–TMA systems. Interestingly in the case of the inclusion of BTMAN by the homologous host **2**, where the π–π interaction is not involved in the complexation process, the stability of **2**–BTMAN is comparable with the **2**–BTMA one. As expected the CIS diagrams reveal that both the aliphatic and the aromatic moieties of BTMAN are incorporated into the cavity of host **1** (Fig. 4a) (both aromatic and aliphatic protons are significantly upfield shifted), whereas only the aliphatic moiety is incorporated into the cavity of host **2** (Fig. 4b) (only methylammonium and methylene protons undergo significant diamagnetic shifts). These findings clearly indicate that both the aromatic and aliphatic moieties of BTMAN can be hosted simultaneously only by the wider cavity of calix[5]arene **1**. A whole of three non-covalent interactions is thus achievable exclusively by the host **1** complexes.

The stability constants of conformationally mobile receptors **1** and **2** compared with those of the preorganised hosts **3** and **4**, blocked in the *cone* conformation, reveal that **1** and **2** are able to bind more efficiently all the investigated trimethylammonium cations. This is probably due to the ability of flexible hosts **1** and **2** to adapt their cavities to the size of the guests by an induced fit process. Induced fit recognition is often more efficient (although less selective) than complexation by more preorganised receptors. To the best of our knowledge the complexation behaviour of the calix[5]arene **1** then represents a rare case of molecular recognition by induced fit that provides at the same time both more efficiency and selectivity.

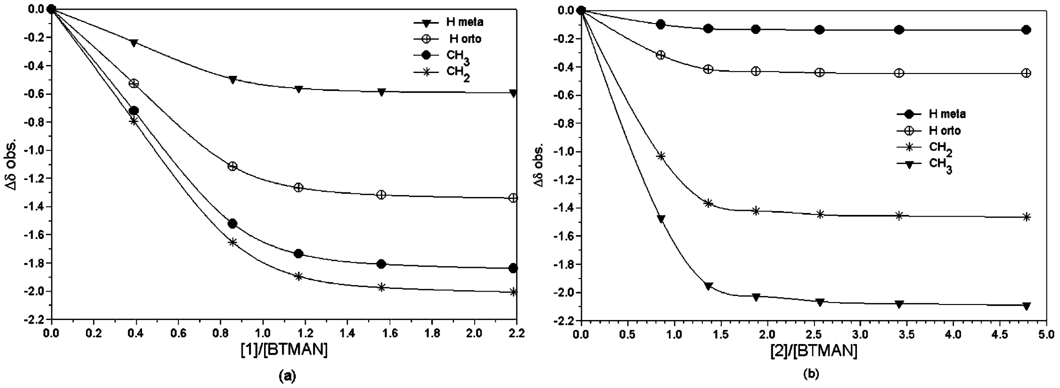


Figure 4. Plots of $\Delta\delta_{obs}$ (ppm) versus (a) [**1**]/[BTMAN] and (b) [**2**]/[BTMAN] in D_2O, 25 °C, [BTMAN] = 1×10^{-3} mol dm^{-3}, pD = 7.3 (0.1 mol dm^{-3} phosphate buffer).

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