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^1H NMR and Calorimetric Studies of the Inclusion of Trimethylammonium Cations into Water Soluble Calixresorcinarenes

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The complexation of tetramethylammonium (TEMA), benzyltrimethylammonium (BTMA), *p*-nitrobenzyltrimethylammonium (BTMAN) and *N,N,N*-trimethylanilinium (TMA) by the tetrasulphonate derivative of the resorcinol cyclic tetramer (**1**), was studied in aqueous solution by ^1H NMR and calorimetry. Host **1** specifically recognizes the $-\text{N}^+(\text{CH}_3)_3$ group of TEMA, BTMA and BTMAN, whereas it binds TMA unselectively; TMA is included both *via* the charged group and the aromatic moiety. The binding constants of all four guests with **1**, as determined by both ^1H NMR and calorimetric titrations, show that all inclusion processes are almost equally stabilised.

ΔH° and ΔS° values, determined by direct calorimetry, reveal specific interactions that are not expressed in the ΔG° terms and indicate that we are dealing with "non-classical hydrophobic effects". The effects of the structural, conformational and electronic properties of the guests on the forces driving the inclusion processes are discussed.

Keywords: Resorcinarenes, Molecular Recognition, calorimetry, CH- π interactions

INTRODUCTION

Resorcinarenes [1] have become a widely used class of artificial receptors with several analytical applications. Resorcinarenes–octacarboxylic acids were recently used as pseudostationary phases in electrokinetic chromatography allowing an efficient separation of thirteen homologous or isomeric amines [2]. An octagalactose derivative of calix[4]resorcinarene, irreversibly adsorbed on the surface of a quartz plate, recognises selectively a target guest and leads to a novel solution-to-surface molecular transport or delivery system [3].

The interest in this class of compounds stems out of their capability to complex several polar (neutral and charged) organic molecules in aqueous solution [4]. Owing to their highly electron-rich cavity, these receptors are able to

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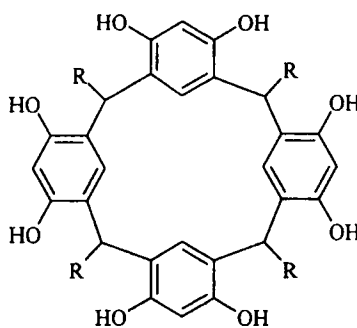
complex their targets not only *via* hydrophobic interactions, but also *via* cation- π interactions [5]. However, despite this, no paper deals with the evaluation of the enthalpy and the entropy of association, that are of some relevance in understanding the forces driving the inclusion process in water, thus allowing a fine tuning in the design and synthesis of increasingly more selective receptors. Recently we have reported on the inclusion of methylammonium cations into water-soluble calixarenes [6] and have underlined the role of both preorganisation and anchoring sites in the selective recognition of the charged group or the aromatic moiety of ditopic guests by the calixarenic hosts. In this paper we report a combined ^1H NMR, calorimetric and molecular mechanics investigation of the inclusion of four methylammonium cations, namely tetramethylammonium (TEMA), benzyltrimethylammonium (BTMA), *p*-nitrobenzyltrimethylammonium (BTMAN) and *N,N,N*-trimethylanilinium (TMA), by the water soluble resorcinarene **1**. The four guests,

although having the same charged group, are characterised by different structural, conformational and electronic properties and thus lend themselves to a systematic investigation of the effects of such properties on the forces driving the inclusion processes.

EXPERIMENTAL PART

Materials

Compound **1** was synthesised as previously described [4a]. The purity of this batch was tested by ^1H NMR spectroscopy, elemental, thermogravimetric and turbidimetric analysis. Tetramethylammonium chloride and trimethylanilinium chloride were obtained from Merck and purified by crystallization from methanol and acetonitrile, respectively. Benzyltrimethylammonium chloride and *p*-nitrobenzyltrimethylammonium chloride (Aldrich) were purified by crystallization from an ethanol:



1

$\text{R} = (\text{CH}_2)_2\text{SO}_3\text{Na}$

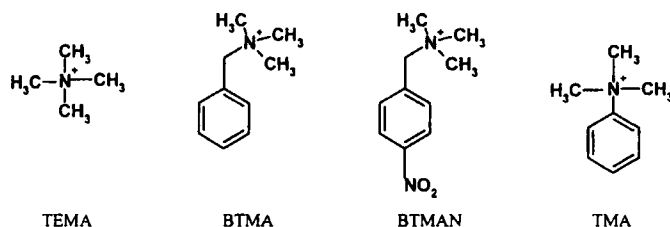


CHART I

acetone mixture (2:5 v/v). Stock solutions of the four guests were obtained by dissolving weighted amounts of their chloride salts in water. The analytical concentrations of guest solutions were determined as described in Ref. [6b].

NMR Spectra

¹H NMR spectra were obtained in D₂O at 25°C with a VARIAN INOVA 500 MHz and BRUKER DPX 400 MHz spectrometers. The association constant values for the complexes of 1 with TMA, BTMA and BTMAN were determined by following either the upfield shifts of the guest protons as a function of the host concentration, or the proton shifts of the host as a function of the guest concentration. In all cases, the measurements were carried out by choosing host and guest concentrations so that the complex concentration was never below 20% or above 80% of the component, the concentration of which was maintained at a fixed value, as recommended in the literature [7].

Calorimetry

Two different types of calorimeters were used to collect the heat data *i.e.*, a LKB 2277 Thermal Activity Monitor microcalorimeter equipped with a stainless steel cell and a Tronac 450 calorimeter equipped with a 4 ml dewar cell. All measurements were performed using the guest solutions and aqueous solutions of the host as titrant and titrate, respectively. The experimental conditions are reported in Table I.

The contribution of non chemical terms (heat of friction, heat of dilution, *etc.*) was determined in blank experiments. Determining the heat involved in the blank experiment turns out to be crucial, since this amount of heat (endothermic) is almost entirely cancelled out by the heat of reaction (exothermic) that is roughly of the same order of magnitude. For other details see Refs. [6b and 8].

Thermogravimetric Measurements

Details for thermogravimetric experiments can be found in Ref. [8a].

TABLE I Experimental conditions used for calorimetric measurements on TEMA, BTMA, BTMAN and TMA with host 1 at 25°C

C ^o _H (mol dm ⁻³)	C ^o _{TEMA} (mol dm ⁻³)	C ^o _{BTMA} (mol dm ⁻³)	C ^o _{BTMAN} (mol dm ⁻³)	C ^o _{TMA} (mol dm ⁻³)	No. of points
0.0043	0.4964				22
0.0042	0.4918				22
0.0047	0.4918				22
0.0047	0.4985				30
0.0035	0.5005				30
0.0040	0.5005				28
0.0040		0.2021			14
0.0040		0.2021			18
0.0030		0.1003			18
0.0030		0.1003			18
0.0030		0.1003			29
0.0040			0.1975		18
0.0037			0.1975		18
0.0034			0.1860		15
0.0033			0.1860		14
0.0029			0.0923		18
0.0029			0.0923		19
0.0029			0.0937		20
0.0029			0.0937		19
0.0039				0.5052	30
0.0037				0.5052	30
0.0039				0.5052	30

Calculations

In order to obtain K values from ^1H NMR titrations, the data were treated by using a non-linear least squares curve fitting procedure [9]. K and ΔH° values were obtained by using a modified version of the computer program EQDH [10].

Molecular Mechanics Calculations

The calculations were performed by inserting the molecule in a "water box" and using MM+ force field [11]. The minimization was performed by using the conjugate gradient method (Fletcher–Reeves) and was carried out until the RMS gradient reached a value of $0.1 \text{ kcal } \text{Å}^{-1} \text{ mol}^{-1}$. Other details are given in Ref. [6b].

RESULTS AND DISCUSSION

Thermogravimetric analysis of compound 1 shows a weight loss between 100° and 200°C . The ^1H NMR spectrum of the compound shows that no methanol was included into the cavity of the calixresorcinarene. The water loss ($13 \pm 1\%$; average of six runs) indicates that our product crystallizes with approximately 8 molecules of water. Elemental analysis data (Anal. Calc. for $\text{C}_{36}\text{H}_{36}\text{O}_{20}\text{S}_4\text{Na}_4 \cdot 8\text{H}_2\text{O}$: C 37.50, H 4.54, S 11.12; found C 38.31, H 4.51, S 11.15) are in excellent agreement with the thermogravimetric ones. As

the temperature increases, the anhydrous compound undergoes a sharp decomposition at 340°C . Above this temperature a plateau is observed and no other loss is detected up to 900°C ; this rules out the presence of inorganic salts. A white residue remains in the cup at the end of the scan. The quantitative analysis (*via* a turbidimetric method) [12] of this residue shows this to be essentially sodium sulphate that amounts to $27 \pm 1\%$ (average of six runs) of the anhydrous compound. The agreement between found and calculated (28%) is good and indicates that the batch employed in this work is of high purity.

Sulphonated resorcinol cyclic tetramers form inclusion complexes with a variety of organic guests [4a] and methylammonium salts [4b] in aqueous solution. These macrocyclic compounds assume a symmetrical (C_{4v}) bowl-shaped conformation [4a], which, among the four possible ones for calixresorcinarenes [13], is the most suitable for inclusion processes.

^1H NMR studies of inclusion of tetramethylammonium (TEMA) by compound 1 have been previously reported [4b]. The large saturation shift for the methyl protons of this guest indicates that the methyl groups of TEMA are incorporated into the polyhydroxy aromatic cavity of the host. The association constant is reported in Table II.

Figures 1a, 1b and 1c show the observed upfield shifts ($\Delta\delta_{\text{obs}} = \delta_{\text{obs}} - \delta_{\text{free guest}}$) for the guest protons induced by the complexation of

TABLE II Log K values and chemical shift limiting values (δ_{complex}) for the complex formation of 1 with TEMA,^a BTMA,^b BTMAN^b and TMA,^b determined by ^1H NMR spectroscopy at 25°C

Reaction	Log K	δ_{complex} (ppm)	^c	$\delta_{\text{free guest}}$ (ppm)
1 + TEMA \rightleftharpoons 1-TEMA	2.2	-0.39	$\overset{+}{\text{N}}(\text{CH}_3)_4$	3.21
1 + BTMA \rightleftharpoons 1-BTMA	2.8(1)	1.77	$\overset{+}{\text{N}}(\text{CH}_3)_3$	3.13
1 + BTMAN \rightleftharpoons 1-BTMAN	2.6(1)	1.32	$\overset{+}{\text{N}}(\text{CH}_3)_3$	3.19
1 + TMA \rightleftharpoons 1-TMA	2.3(2)	1.68	$\overset{+}{\text{N}}(\text{CH}_3)_3$	3.67

σ in parentheses.

^a Reference [12].

^b This work.

^c Protons used for the fitting procedure.

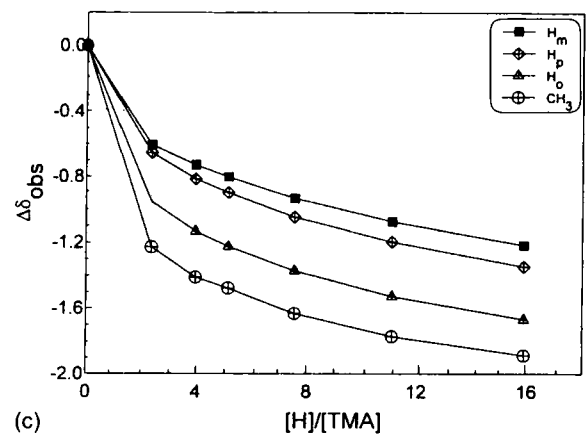
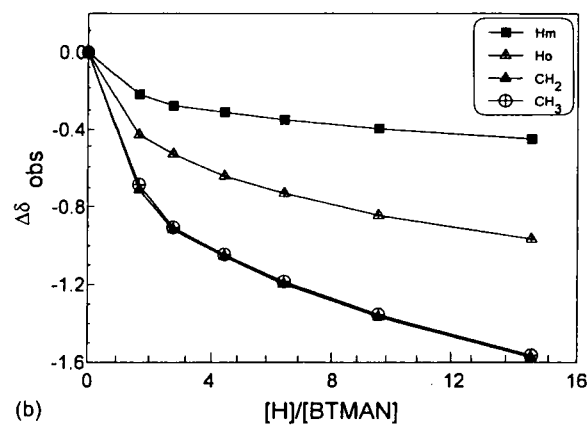
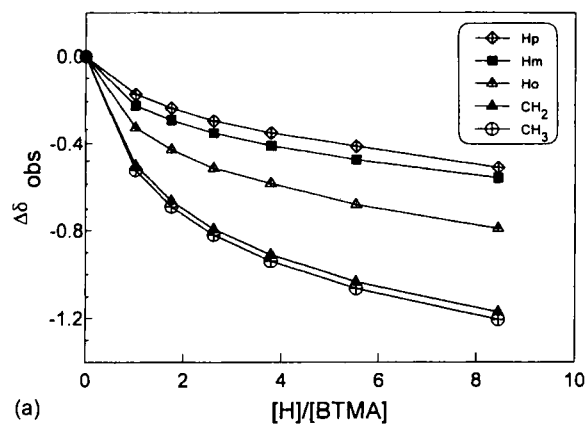


FIGURE 1 (a) Plots of $\Delta\delta_{\text{obs}}$ (ppm) versus $[1]/[\text{BTMA}]$ in D_2O , 25°C , $[\text{BTMA}] = 1.00 \times 10^{-3} \text{ mol dm}^{-3}$; (b) Plots of $\Delta\delta_{\text{obs}}$ (ppm) versus $[1]/[\text{BTMAN}]$ in D_2O , 25°C , $[\text{BTMA}] = 9.2 \times 10^{-4} \text{ mol dm}^{-3}$; (c) Plots of $\Delta\delta_{\text{obs}}$ (ppm) versus $[1]/[\text{TMA}]$ in D_2O , 25°C , $[\text{TMA}] = 2.43 \times 10^{-3} \text{ mol dm}^{-3}$.

host **1** with BTMA, BTMAN and TMA, respectively. These data were used to evaluate the binding constants (Tab. II) for the inclusion processes as well as the complexation induced shifts (CIS) through a non-linear least square analysis [9].

For **1**-BTMA the guest protons experience an upfield shift that follows the order $\text{CH}_3 > \text{CH}_2 > \text{H}_o > \text{H}_m > \text{H}_p$ (Fig. 1a). The diamagnetic shifts exerted by the aromatic host cavity on the guest protons decrease as the inclusion of the protons into the cavity decreases, thus indicating that the charged $\text{N}^+(\text{CH}_3)_3$ group of the guest is selectively included into the cavity of the host. The same trend is observed for **1**-BTMAN (Fig. 1b).

For **1**-TMA a different trend is observed. In this case, in fact, the largest upfield shift is detected for the methyl protons, followed, in the order, by the *ortho*, *para* and *meta* aromatic protons (Fig. 1c). The largest upfield shift for the methyl protons indicates that the inclusion mode having the methyl group included into the aromatic cavity of the host prevails over the mode in which the aromatic residue is incorporated by the cavity (Fig. 2). It is noteworthy that

para protons are more shielded than the *meta* ones, thus indicating that the complex exists in two different stereochemical modes of inclusion, as stated above. If the inclusion modes were specific, as found for **1**-BTMA and **1**-BTMAN as well as for other analogous systems [6b], the shifts would have followed the order $\text{CH}_3 > \text{CH}_2 > \text{H}_o > \text{H}_m > \text{H}_p$ if the charged group was included or the opposite one if the aromatic moiety was inserted into the cavity. Unselective inclusion of methylammonium cations have been previously reported in literature for derivatized calix[4]arene [6b, 14].

However in order to see whether these inclusion processes are to be regarded as "classical" or "non classical" hydrophobic effects [15], we also measured the enthalpy and entropy of binding for all our guests to our resorcinarene host through direct calorimetry. These values are reported in Table III. The log *K* values determined by titration calorimetry coincide, within the experimental error, with those obtained *via* ^1H NMR titration experiments. At first look, if one examines the ΔG° values only, all inclusion processes seem to be the same. However, the ΔH° and ΔS° values reveal

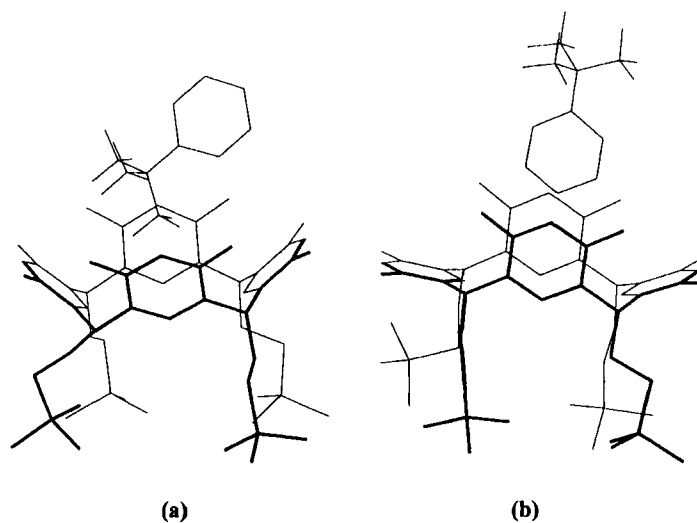


FIGURE 2 Stereochemical modes of inclusion of TMA by host **1**; (a) the guest is included by means the $\text{N}^+(\text{CH}_3)_3$ group; (b) the guest is included by means the aromatic residue.

TABLE III Log *K* values and thermodynamic parameters of complex formation of 1 with TEMA, BTMA, BTMAN and TMA (*T* = 25°C)

Reaction	Log <i>K</i>	ΔG° (kcal mol ⁻¹)	ΔH° (kcal mol ⁻¹)	ΔS° (cal mol ⁻¹ deg ⁻¹)
1 + TEMA \rightleftharpoons 1-TEMA	2.5(1)	-3.4	-1.3(2)	7(1)
1 + BTMA \rightleftharpoons 1-BTMA	2.7(2)	-3.7	-2.9(4)	2(2)
1 + BTMAN \rightleftharpoons 1-BTMAN	2.5(2)	-3.4	-5.6(8)	-8(3)
1 + TMA \rightleftharpoons 1-TMA	2.3(1)	-3.1	-4.2(2)	-4(1)

σ in parentheses.

specific interactions that are not expressed in the ΔG° terms. In fact, these inclusion complexes, although having the same ΔG° values, are characterised by somewhat different enthalpic and entropic contributions. The sign and the magnitude of the enthalpies and entropies of binding indicate that we are dealing with "non-classical hydrophobic effects" [15e]. All complexes have a favorable ΔH° and a small or even unfavorable ΔS° . This indicates that the attractive interactions, rather than the entropically favorable desolvation, is the major driving force for the inclusion of these small guests. It is the ion-dipole attraction between the positively charged guests and the electron rich π -system of the resorcinarene host that is chiefly responsible for the inclusion process. Perhaps the most interesting indication, in this respect, is the trend observed for the binding enthalpies that follows the order $\Delta H^\circ_{\text{TEMA}} < \Delta H^\circ_{\text{BTMA}} < \Delta H^\circ_{\text{BTMAN}}$. The discussion is deliberately restricted to these guests, since they are all selectively included *via* the trimethylammonium substituent; the inclusion of TMA, that occurs *via* both the trimethylammonium and the aromatic substituent, will be discussed separately.

Substitution of a benzene ring (BTMA) or a *p*-nitrobenzene moiety (BTMAN) for a TEMA hydrogen atom enhances the acceptor characteristics of the included portion which, in turn, should lead to a substantial enhancement of attractive guest-host interactions [5, 16]. This was confirmed experimentally; in fact the binding enthalpies are found to increase in the order 1-TEMA < 1-BTMA < 1-BTMAN. Obviously, the stronger the guest-host interaction, the tighter

the binding, which implies a large reduction of the degrees of freedom of the interacting particles. This results in an entropic loss that increases with the tightness of binding to the extent that masks any gain in entropy from desolvation.

These findings provide further support to an elegant study, covering a large number of guests, published by Dougherty *et al.*, that was solely based on free energy comparisons [15b].

As already mentioned, 1-TMA represents a case apart. In fact, as shown by ¹H NMR spectroscopy, 1-TMA shows two different stereochemical modes of inclusion, in which the charged ammonium group or the aromatic moiety of TMA are alternatively incorporated into the host cavity (Fig. 2); the overall enthalpic and entropic contributions reflect the dynamic equilibrium between the two modes of inclusion. Thus, in 1-TMA the relatively large enthalpic contribution also reflects the favorable π - π interaction between TMA aromatic residue and the electron-rich aromatic unit of the resorcinarene. Such a stacking interaction is known to be enthalpically driven and more favored than a typical CH- π interaction [17].

These thermodynamic data are also consistent with the presence an "extra-cavity effect" [18]. In fact, in BTMA the methylene spacer, bridging the aromatic and the trimethylammonium group moieties, causes the all BTMA molecule to be non-linear. This bending brings BTMA aromatic residue close to the resorcinarene aromatic rings thus giving rise to what has been termed "extra-cavity effect". This effect causes a small but still significant shift of the aromatic

protons of the guest. No such shift had been detected for the inclusion of BTMA by *p*-sulphonatocalix[4]arenes when the charged group is selectively included [6b]; with these more rigid and somewhat smaller cavities, the aromatic protons of BTMA remain virtually unshifted upon complexation. One has then to conclude that in host **1** the extra cavity effect is possible thanks to the larger cavity as well as to a more mobile molecule. Interestingly, the C1–C3 and C2–C4 distances (Tab. IV) of **1** are 5.81 and 10.48, respectively, whereas they are 4.99 and 9.95 for the *p*-sulphonatocalix[4]arenes.

We have also optimised the structures of all the inclusion complexes reported in the present

study (Fig. 3) and calculated some relevant guest-host distances (Tab. IV). It is clear that the encapsulation of the trimethylammonium residue (Figs. 3b, 3c, 3d, 3e) renders the cavity more symmetrical than it is in the free guest. It is also fairly evident that when inclusion takes place through the aromatic moiety (Fig. 3f) the cavity is more elongated. Such a disposition allows two aromatic rings of the host to have a face-to-face orientation, thus maximising the π – π interaction between the guest and the host. This guest-host face-to-face arrangement in **1-TMA** on one hand results in a relatively large binding enthalpy. On the other hand it causes a stiffening of the system, which accounts for the negative entropy change. The situation

TABLE IV Relevant distances (in Å) for **1** and his complexes with TMA, TEMA, BTMA and BTMAN obtained by MM + optimization

	1	1-TEMA	1-BTMA	1-BTMAN	1-TMA^a	1-TMA^b
C ₁ –C ₃	5.81	7.62	8.69	8.24	7.68	6.01
C ₂ –C ₄	10.48	9.57	8.81	9.05	9.45	10.54
C ₁ –N		4.23	4.99	4.56	4.30	
C ₂ –N		5.53	6.06	5.21	5.72	
C ₃ –N		4.27	4.61	4.53	4.34	
C ₄ –N		5.39	4.64	4.86	5.10	

^a These values refer to the binding mode (e) (Fig. 3).

^b These values refer to the binding mode (f) (Fig. 3).

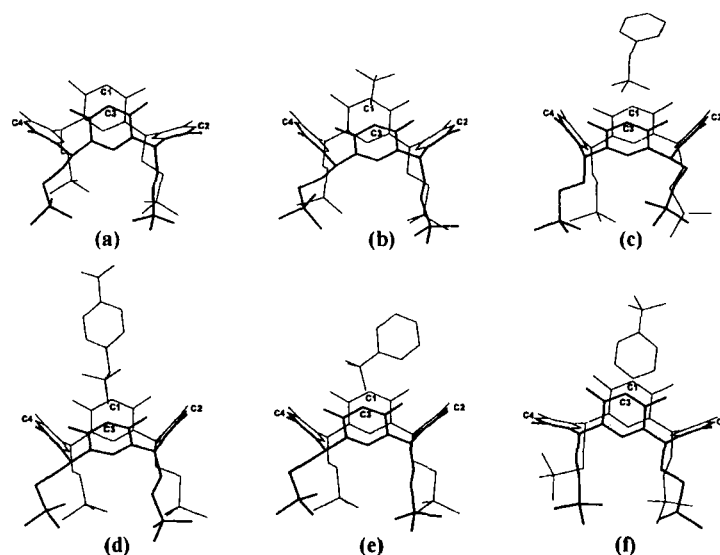


FIGURE 3 Optimized structures (Molecular Mechanics) in water generates for (a) host **1**; (b) **1-TEMA**; (c) **1-BTMA**; (d) **1-BTMAN**; (e) **1-TMA**; (f) **1-TMA**.

described above is only a "snapshot" of a more complex dynamic situation. In fact, as demonstrated for similar systems by both NMR [19] and Molecular Dynamics [20] the host undergoes a rapid C_{2v} - C_{2v} interconversion giving rise, on the average, to a C_{4v} symmetrical cavity.

CONCLUSIONS

TEMA, BTMA, BTMAN and TMA are all included into the cavity of **1** in aqueous solution. The ΔG° values for the inclusion process indicate that the reaction is roughly favoured to the same extent for the four systems presented here. However, the ΔH° and ΔS° values, determined by direct calorimetry, reveal specific interactions that are not expressed in the ΔG° terms and clearly indicate that inclusion is not strictly alike for all four guests as one might deduce from the correspondence of the free energy terms. Virtually identical ΔG° values can mask enthalpic differences that can be as large as $4.3 \text{ kcal mol}^{-1}$ as in the case of TEMA and BTMAN. Moreover, the dissection of the free energy term shows that these processes are enthalpically driven. This provides further evidence [15, 21] to the fact that the association of small particles in water is due to attractive forces between the two interacting particles rather than to their desolvation and, consequently, these processes are the result of "non-classical" hydrophobic effects [15].

Acknowledgements

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