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### Thermodynamics of Complexation of Tetraalkylammonium and Rare-earth Cations with Two Sulfonatocalix[n]arenes ( $n=4$ and 6) in Aqueous Solution

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# Thermodynamics of Complexation of Tetraalkylammonium and Rare-earth Cations with Two Sulfonatocalix[n]arenes ( $n = 4$ and 6) in Aqueous Solution

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We report results of a microcalorimetry study of the association of inorganic and organic cations with two *p*-sulfonatocalix[n]arenes (host 1:  $n = 4$ ; host 2:  $n = 6$ ) in aqueous solution at 298.15 K. First, we have determined the thermodynamic parameters for the complexation between the host 2 and a series of quaternary ammonium cations. We have evaluated the influence of the pH on the structure and energetics of these organic complexes. We have also reported the association constant and enthalpy of reaction for the complexation of some rare-earth cations ( $\text{Sm}^{3+}$ ,  $\text{Dy}^{3+}$ ,  $\text{Y}^{3+}$  and  $\text{Sc}^{3+}$  cations) with the two hosts. In all cases we have observed the formation of 1:1 complexes.

Whereas the association is driven by a favourable entropy change for the inorganic cations ( $\Delta H > 0$  and  $T\Delta S \gg 0$ ), it is controlled by a favourable enthalpy change for the organic cations ( $\Delta H \ll 0$  and  $T\Delta S < 0$  or  $> 0$ ). In acidic solution, the complexes formed between host 2 and tetraalkylammonium cations are weaker than those formed with the cyclic tetramer. In neutral solution this effect is not observed. All the results are in line with a conformational change of host 2 with the pH.

**Keywords:** Complexation; Aqueous calixarene complexes; Lanthanide cations; Tetraalkylammonium cations; Enthalpy; Association constant; Microcalorimetry

## INTRODUCTION

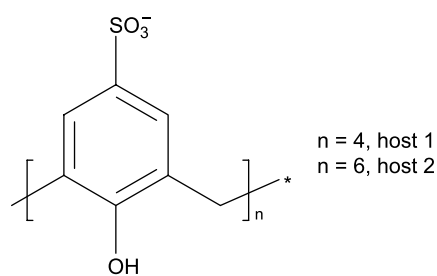
Water-soluble *p*-sulfonatocalix[n]arenes have generated considerable interest during the last two decades owing not only to their potential use for bioorganic and biomimetic chemistry [1,2], but also to their implication in the separation science of rare-earth cations [3–5]. These macrocyclic compounds are also a class of fundamental interest as simple models for the identification of the factors that govern the formation of supramolecular complexes

in aqueous media. Depending on the nature of the guest, the binding process involves several interactions (electrostatic, cation- $\pi$ ,  $\pi$ - $\pi$ , hydrophobic, hydrogen bonding, van der Waals, etc.).

In order to clarify the factors leading to the binding process in water it is essential to understand the nature of the interactions between the calixarene and several simple guest molecules taken as models. The microcalorimetric method leads to a full thermodynamic characterization of the binding process: in the case of weak complexations, this method measures both enthalpy changes and complex stability constants. We thus applied it to the study of the complexation of the *p*-sulfonatocalix[4]arene, host 1 (Scheme 1), with basic amino acids [6] and with dipeptides and tripeptides [7]. We also investigated the complexation of this receptor with various inorganic and organic cations [8,9], and neutral molecules [9] in water.

Among inorganic cations, we were particularly interested in cations representative of the lanthanide series ( $\text{La}^{3+}$ ,  $\text{Nd}^{3+}$ ,  $\text{Sm}^{3+}$ ,  $\text{Eu}^{3+}$ ,  $\text{Gd}^{3+}$ ,  $\text{Dy}^{3+}$  and  $\text{Yb}^{3+}$ ) [8]. The complexation of host 1 with these cations ( $\text{Ln}^{3+}$ ) was carried out in acidic aqueous solution (pH 2) in order to prevent hydrolysis. Such complexes are indeed interesting both from theoretical and practical viewpoints. For instance, complexes involving a rare earth cation, a crown ether and a calixarene sulfonate were recently explored for the separation of lanthanides [10,11]. Besides, the interaction of host 1 with a lanthanide cation is an attractive example of an association process involving strong electrostatic interactions.

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SCHEME 1

n = 4, host 1  
n = 6, host 2

We were also concerned by the association between host 1 and quaternary ammonium ions ( $R_4N^+$ ) [8]. This kind of association is of particular interest from a biological viewpoint in line with the recognition between the neurotransmitter acetylcholine and acetylcholine esterase [2,12]. This recognition could be stabilized by cation- $\pi$  interactions between the positively charged quaternary ammonium group of acetylcholine and the aromatic residues of the enzyme binding site [13]. To obtain a better understanding of the association process, we investigated the binding between host 1 and a series of quaternary ammonium cations ( $Me_4N^+$ ,  $Et_4N^+$ ,  $Pr_4N^+$ ,  $Bu_4N^+$ ) [8].

The thermodynamic results obtained by microcalorimetry with these organic and inorganic cations were consistent with the formation of 1:1 complexes. The results showed that the organic and inorganic cations bind in different modes. With  $Ln^{3+}$ , the complexation is entropy-driven ( $\Delta_r H^\circ > 0$  and  $T\Delta_r S^\circ \gg 0$ ) due to the partial desolvation of both metallic cation and sulfonate groups of the ligand. In opposition, for  $R_4N^+$ , the process is essentially enthalpy-driven ( $\Delta_r H^\circ \ll 0$  and  $T\Delta_r S^\circ < 0$  or  $T\Delta_r S^\circ > 0$ ) the association being governed by the inclusion of the alkyl group within the cavity and the resulted van der Waals interactions. In fact, the entropy gain due to the desolvation of the species is almost compensated by the strong entropy loss upon inclusion and, as a result, the process is enthalpy-driven.

In line with microcalorimetry experiments, molecular dynamic simulations [14–16] (MD) were carried out to yield additional information at a microscopic level. The microscopic-macroscopic relationship was investigated throughout correlations between experimental enthalpy changes and structures of complexes calculated from MD calculations. The molecular simulations were fully consistent with the analyses of the experimental data. The calculations showed that the  $R_4N^+$  are totally or partly included into the calixarene cavity, whereas the  $Ln^{3+}$  remain outside the cavity, in the vicinity of the sulfonate groups [14]. For the  $R_4N^+$  complexes, these calculations pointed out a correlation between the experimental  $\Delta_r H'^\theta$  values and

the number of atoms inserted into the cavity of the calixarene [16]. It was shown that the specific thermodynamic behaviour of  $Et_4N^+$ , which exhibited a remarkably negative enthalpy and entropy of binding, resulted from the inclusion of the largest number of atoms into the cavity accompanied by an important loss of degrees of freedom. MD simulations also checked the influence of pH on the structure and energetics of the  $Me_4N^+$  and  $Et_4N^+$  complexes [15]: except for a different network of intramolecular hydrogen bonds at the lower rim, no major structural change was detected upon varying the pH from acidic to neutral.

In order to enhance the binding strength, larger receptors were considered. For instance, Lehn *et al.* [12] underlined that the *p*-sulfonatocalix[6]arene, host 2 (Scheme 1), has a symmetry particularly well adapted to that of the quaternary ammonium group of acetylcholine. In spite of the interest for this receptor, its conformation in solution is still an open question. In solution, Gutsche and Bauer [17] obtained for the cyclic hexamers two conformations from  $^1H$  NMR data: a “winged” conformation in which the molecule transannularly pinches with two groups in “out” positions and the other four in up and/or down positions or a “hinged” conformation in which three groups are up and the other three are down. In the solid state, Atwood and co-workers [18] crystallized the sodium salt of host 2 from neutral aqueous solution and determined that the macrocycle adopts a structure that may be described as a double partial cone with three adjacent sulfonate groups up and three down (also called “hinged” or 1,2,3-alternate conformation by other groups). Wolfgang *et al.* [19] also obtained a 1,2,3-alternate conformation for the crystal structures of calix[6]arenes crystallized from hydrogen-bonding solvents. More recently, Alvarez *et al.* [20] studied in solution the effect of a number of factors on the conformational flexibility of the anionic host *p*-sulfonatocalix[6]arene by  $^1H$  NMR spectroscopic data. They demonstrated that host 2 is a flexible host that really adopts the 1,2,3- alternate conformation at room temperature but this conformational state is strongly affected by a number of factors such as the nature of the solvent, pH, temperature, as well as by the presence of appropriate guests in the solution.

In addition to the host 1, the binding of the host 2 with the basic amino-acids lysine and arginine [6], and with dipeptides and tripeptides containing lysine or arginine [7] was also investigated in our laboratory. In all cases, the thermodynamic results showed that the binding process was enthalpy-driven. Results highlighted the formation of only 1:1 complexes with the basic amino-acids whereas both 1:1 and 1:2 complexes were observed with dipeptides and tripeptides. Lehn *et al.* [12] studied by  $^1H$  NMR the binding of both the sulfonatocalix[4]

and [6]arenes by the neurotransmitter acetylcholine and related quaternary ammonium ions. They determined the association constants of  $\text{Me}_4\text{N}^+$ ,  $\text{Et}_4\text{N}^+$ ,  $\text{Pr}_4\text{N}^+$  and  $\text{Bu}_4\text{N}^+$  cations with the two guests at neutral pH. They obtained 1:1 complexes with the two *p*-sulfonatocalix[*n*]arenes. They concluded that the stronger electrostatic interaction for the hexamer is compensated in part by the less favourable conformation of host 2 as compared to the cone shape of host 1.

Because the enthalpy and entropy of complexation constitute data that clearly identified the different types of interactions involved in the formation of complexes, we chose to use the microcalorimetric technique to obtain a full thermodynamic characterization ( $K$ ,  $\Delta_r G^0$ ,  $\Delta_r H^0$  and  $\Delta_r S^0$ ) of the binding of the tetraalkylammonium cations with host 2 at pH 2. Comparison with the thermodynamic results previously obtained with host 1 in acidic solution is carried out. We check the influence of pH on the energetics of the  $\text{Me}_4\text{N}^+$  and  $\text{Et}_4\text{N}^+$  complexes. To compare directly, as it was done for host 1, the thermodynamic behaviour of both the organic and inorganic cations, we also study the complexation of host 2 with two lanthanide cations ( $\text{Sm}^{3+}$  and  $\text{Dy}^{3+}$ ) in acidic solution.

In addition to the effects on the thermodynamic properties due to the size and conformational state of host 1 and host 2, we also want to examine the trends in the thermodynamic properties of association with the rare-earth cation radius. To do so, we complete our previous work by measuring the properties for the binding of two other trivalent cations ( $\text{Y}^{3+}$  and  $\text{Sc}^{3+}$ ) by host 1.

## EXPERIMENTAL

### Solutions

The 25,26,27,28-tetrahydroxy-5,11,17,23-tetrasulfonic calix[4]arene hydrate and the 37,38,39,40,41,42-hexahydroxyl-5,11,17,23,29,35-hexasulfonic calix[6]arene hydrate were purchased from Acros Organics. The calix[4]arene was decolorized by adsorption on active carbon and dried under vacuum at 353 K. The calix[6]arene was used without further purification. From Karl-Fischer titration (Mettler Toledo DL 31), the hydration state of the calixarenes was found to be 16.0% for the calix[4]arene and 23.4% for the calix[6]arene.  $\text{YCl}_3 \cdot 6\text{H}_2\text{O}$ ,  $\text{ScCl}_3 \cdot 6\text{H}_2\text{O}$ ,  $\text{SmCl}_3 \cdot 6\text{H}_2\text{O}$ ,  $\text{DyCl}_3 \cdot 6\text{H}_2\text{O}$  were bought from Strem Chemicals (purity: 99.9%) and were used as received.  $(\text{CH}_3)_4\text{NBr}$  (Merck, 99%),  $(\text{C}_2\text{H}_5)_4\text{NBr}$  (Fluka, 99%)  $(\text{C}_3\text{H}_7)_4\text{NCl}$  (Alfa Products, 99%) and  $(\text{C}_4\text{H}_9)_4\text{NBr}$  (Fluka, 99%) were dried at 373 K, stored in a desiccator and used without further purification.

$\text{KH}_2\text{PO}_4$  (Alfa Products, 99%),  $\text{Na}_2\text{HPO}_4$  (Merck, BioChemika) were used as received.

Stock solutions of the rare-earth salts, *ca.* 0.1 mol  $\text{kg}^{-1}$ , were analyzed for cation concentration by titration with Titriplex III (Merck) following classical methods.

The pH of the organic and inorganic cations and calixarene solutions was set at about 2 with 0.01 mol  $\text{kg}^{-1}$  HCl solution and at 7.4 using a phosphate buffer. The pH was verified on a pH-meter calibrated with two different buffer solutions.

The  $\text{pK}_a$  values [21–24] reported in the literature for the *p*-sulfonatocalix[*n*]arenes indicate that, at pH 2 all the sulfonate groups located on the upper rim are deprotonated and that at pH 7 some of the hydroxy groups are dissociated in addition to the sulfonate groups, yielding the following anions: (*p*-sulfonatocalix[4]arene)<sup>5-</sup> and (*p*-sulfonatocalix[6]arene)<sup>8-</sup>.

All the solutions were prepared by weight from triply distilled water.

### Microcalorimetry

All the measurements were performed using a multichannel microcalorimeter (LKB—Thermometric 2277 Thermal Activity Monitor) equipped with a titration-perfusion vessel. Wadsö and co-workers [25–27] have thoroughly described this twin thermopile heat-conduction calorimeter and analyzed its performance.

The experiments were carried out using a 1 mL glass vessel fitted with a gold stirrer. The vessel was charged with 0.9 mL of calixarene solution (1.0 mmol  $\text{kg}^{-1}$ ) and 10  $\mu\text{L}$  of lanthanide or alkylammonium cation solution was injected in each step using a Lund syringe pump (Thermometric) equipped with a 250  $\mu\text{L}$  Hamilton syringe fitted with a gold cannula. Twenty injections were made for each titration experiment.

The solution molalities were, prior to titration, 10 mmol  $\text{kg}^{-1}$  for the lanthanide or alkylammonium cation solutions except for the study of  $\text{Me}_4\text{N}^+$  and  $\text{Et}_4\text{N}^+$  cations at pH 7 for which the concentration was 5.0 mmol  $\text{kg}^{-1}$ .

Static and dynamic calibrations were used; the power values observed upon titration ranged from 30 to 100  $\mu\text{w}$ . Separate dilution experiments were performed under the same conditions. Each experiment was repeated at least twice for reproducibility. Values for the apparent association constant  $K'$  and apparent standard enthalpy of reaction  $\Delta_r H'^\theta$  in a given medium were calculated by use of the Digitan 4.1 minimization code (Thermometric). The two series of data obtained for each system were used simultaneously in the regression analysis.

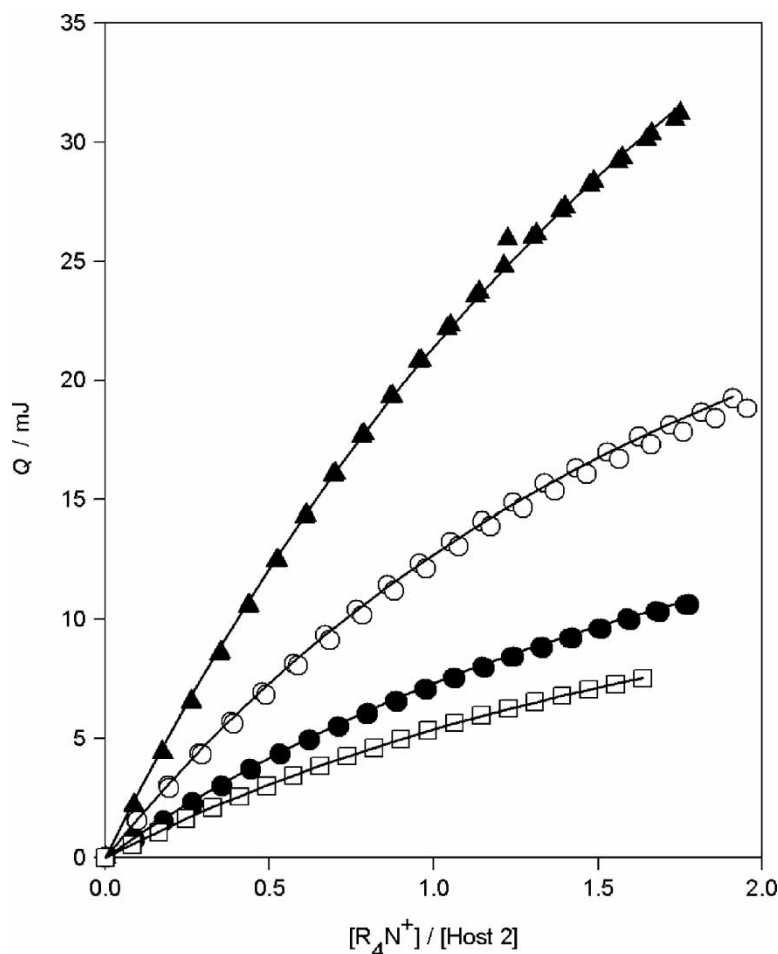


FIGURE 1 Heat effects determined by microcalorimetry for the complexation of  $\text{Me}_4\text{N}^+$  (●),  $\text{Et}_4\text{N}^+$  (▲),  $\text{Pr}_4\text{N}^+$  (○) and  $\text{Bu}_4\text{N}^+$  (□) by the *p*-sulfonatocalix[6]arene (host 2) in water at pH 2 and 298.15 K. The curves result from the non-linear least squares fit of the data using a 1:1 binding model.

## RESULTS AND DISCUSSION

The heat effects observed upon complexation of the organic cations by host 2 at pH 2 are plotted *vs* the concentration in Fig. 1. The curves result from a non-linear least-squares fit of the data using a 1:1 binding model. The quality of the fit regression shows that the 1:1 stoichiometry adequately describes the binding process. This is consistent with Lehn *et al.* [12] NMR

study. The  $K'$  and  $\Delta_r H'^{\circ}$  values resulted from these fits are reported with the estimated standard deviations in Table I. The corresponding  $\Delta_r G'^{\circ}$  and  $T\Delta_r S'^{\circ}$  values are also given. For comparison, the thermodynamic quantities obtained [8] for the complexation of the same organic cations with host 1 at pH 2 are also included in Table I.

The reported values show that for each host-guest combination, the association process is enthalpically

TABLE I Thermodynamic parameters characterizing the complexation of tetraalkylammonium cations by the *p*-sulfonatocalix[*n*]arene ( $n = 4$  and 6) in acidic aqueous solution (pH = 2) at 298.15 K<sup>†,‡</sup>.

Cations	Ligand	log $K'$	$\Delta_r G'^{\circ}$	$\Delta_r H'^{\circ}$	$T\Delta_r S'^{\circ}$
$(\text{CH}_3)_4\text{N}^+$	Host 1 <sup>¶</sup>	4.40	$-25.1 \pm 0.2$	$-26.0 \pm 0.2$	$-0.9 \pm 0.4$
	Host 2	2.57	$-14.6 \pm 0.3$	$-33 \pm 2$	$-18 \pm 2$
$(\text{C}_2\text{H}_5)_4\text{N}^+$	Host 1 <sup>¶</sup>	4.67	$-26.7 \pm 0.4$	$-41.2 \pm 0.8$	$-14.5 \pm 1.2$
	Host 2	2.53	$-14.5 \pm 0.2$	$-79 \pm 4$	$-64 \pm 4$
$(\text{C}_3\text{H}_7)_4\text{N}^+$	Host 1 <sup>¶</sup>	4.47	$-25.5 \pm 0.3$	$-23.8 \pm 0.3$	$1.7 \pm 0.6$
	Host 2	2.66	$-15.2 \pm 0.2$	$-38 \pm 2$	$-23 \pm 2$
$(\text{C}_4\text{H}_9)_4\text{N}^+$	Host 1 <sup>¶</sup>	4.21	$-24.0 \pm 0.3$	$-21.6 \pm 0.5$	$2.4 \pm 0.8$
	Host 2	2.51	$-14.3 \pm 0.4$	$-20 \pm 2$	$-6 \pm 2$

<sup>†</sup> Molar scale. <sup>‡</sup>  $\Delta_r G'^{\circ}$ ,  $\Delta_r H'^{\circ}$  and  $T\Delta_r S'^{\circ}$  in  $\text{kJ mol}^{-1}$ . <sup>¶</sup> Ref. [8].

TABLE II Thermodynamic parameters characterizing the complexation of two tetraalkylammonium cations by the *p*-sulfonato-calix[*n*]arene (*n* = 4 and 6) in neutral aqueous solution (pH = 7) at 298.15 K<sup>†,‡</sup>.

Cations	Ligand	log K'	$\Delta_r G^\circ$	$\Delta_r H^\circ$	T $\Delta_r S^\circ$
(CH <sub>3</sub> ) <sub>4</sub> N <sup>+</sup>	Host 1	5.0 <sup>¶</sup> ± 0.2 4.9 <sup>§</sup> ± 0.2	-28 <sup>¶</sup> ± 1	-24.6 <sup>¶</sup> ± 0.5	3 <sup>¶</sup> ± 1
	Host 2	4.5 ± 0.2 4.9 <sup>§</sup> ± 0.2	-26 ± 1	-27.8 ± 0.5	-2 ± 1
(C <sub>2</sub> H <sub>5</sub> ) <sub>4</sub> N <sup>+</sup>	Host 1	5.5 <sup>¶</sup> ± 0.2 5.6 <sup>§</sup> ± 0.2	-31 <sup>¶</sup> ± 1	-34.5 <sup>¶</sup> ± 0.7	-3 <sup>¶</sup> ± 2
	Host 2	4.7 ± 0.2 5.0 <sup>§</sup> ± 0.2	-27 ± 1	-33.9 ± 0.5	-7 ± 1

<sup>†</sup> Molar scale. <sup>‡</sup>  $\Delta_r G^\circ$ ,  $\Delta_r H^\circ$  and T $\Delta_r S^\circ$  in kJ mol<sup>-1</sup>. <sup>¶</sup> Ref. [15]. <sup>§</sup> Ref. [12].

favoured ( $\Delta_r H^\circ < 0$ ) and entropically unfavoured ( $\Delta_r S^\circ < 0$ ). We can observe that changing the size of the calixarene does not modify the type of interaction involved in the formation of these organic complexes since the binding remains enthalpy-driven. In fact, the inclusion of the guest into the host cavity induces a strong negative enthalpic contribution due to the van der Waals interactions and a strong positive entropic contribution due to the desolvation of the species. The formation of such a complex is also accompanied by a strong entropy loss due to the fact that the host and guest lose most of their degrees of freedom upon inclusion. As a result, the process is driven by the enthalpy. The values reported in Table I indicate that the complexes formed with host 2 appear to be relatively weak in comparison with the complexes formed with the cyclic tetramer. In fact, the affinity of organic cations for host 2 is weaker than for host 1 because the compensation between the highly unfavourable entropy of complexation and the highly favourable enthalpy of complexation is better for the larger receptor. The enthalpy changes indicate that the guests interact more strongly with host 2 than with host 1 and the entropy changes are much more unfavourable with host 2 than with host 1 probably because the more flexible hexamer loses more degrees of freedom upon binding.

It can be noticed that the negative enthalpy and entropy changes for the association of host 2 with Et<sub>4</sub>N<sup>+</sup> are remarkably more negative than with the other cations. This phenomenon previously noticed with host 1 [8] is increased with host 2. Our MD simulations of complexes of host 1 with R<sub>4</sub>N<sup>+</sup> [15] showed a correlation between the experimental enthalpy of complexation and the number of alkyl groups inside the cavity of the calixarene, the inclusion of the largest number of atoms being observed for Et<sub>4</sub>N<sup>+</sup>. The filling of the host cavity is thus maximum with Et<sub>4</sub>N<sup>+</sup>, which results in an important loss of degrees of freedom and brings the host and guest at very close distance; as a result the entropy and enthalpy changes are remarkably negative for this species. The thermodynamic properties reported here for the complexation of Et<sub>4</sub>N<sup>+</sup> by host 2 can probably be explained in

a similar way, with the largest number of atoms inside the cavity. In spite of this peculiar behaviour, the affinity of host 2 for Et<sub>4</sub>N<sup>+</sup> is not more important than for the other tetraalkylammonium cations due to a large enthalpy-entropy compensation.

We have also studied the binding between host 2 and two tetraalkylammonium cations (Me<sub>4</sub>N<sup>+</sup>, Et<sub>4</sub>N<sup>+</sup>) at neutral pH (pH = 7) to check the influence of the pH on the energetics of these organic complexes. The K' and  $\Delta_r H^\circ$  values obtained are reported in Table II. For comparison, we have also included in this table both the thermodynamic parameters previously [15] obtained with host 1 and the K values determined by Lehn *et al.* [12] by <sup>1</sup>H NMR at the same pH value. Firstly, it can be noted that the stability constants obtained by microcalorimetry are in good agreement with those deduced from NMR spectroscopy. Secondly, we observe only little change between the thermodynamic results of host 2 and host 1. This indicates that, in neutral aqueous solution, the selectivity of complexation is not much modified by varying the cavity size in contrast with it is observed in acidic solution.

Our results show that the tendency observed with host 1 in acidic solution is not modified when the pH is increased. In fact, host 1 remains in the cone conformation and the phenolate group does not play a major role in the association process. The binding modes of host 1 are thus the same at pH 2 and 7. The log K' and  $\Delta_r H^\circ$  values found for the binding of Me<sub>4</sub>N<sup>+</sup> at the two pH values are identical within the experimental errors. This is in agreement with the MD simulations [15] which pointed out only a more attractive calixarene-cation interaction energy at pH 7 but no significant change as regards the structure of the complex (insertion, solvation) and the mobility of the guest. For the Et<sub>4</sub>N<sup>+</sup> complex, we observe slightly greater variations. These are consistent with the simulations that revealed at pH 7 a calixarene-cation energy more negative than with the other cations and some modification in the mobility of the Et<sub>4</sub>N<sup>+</sup> cation but no significant difference affecting the structure of the host and guest.

In contrast with host 1, changing the pH induces significant effects for host 2. At pH 2, all the phenolic

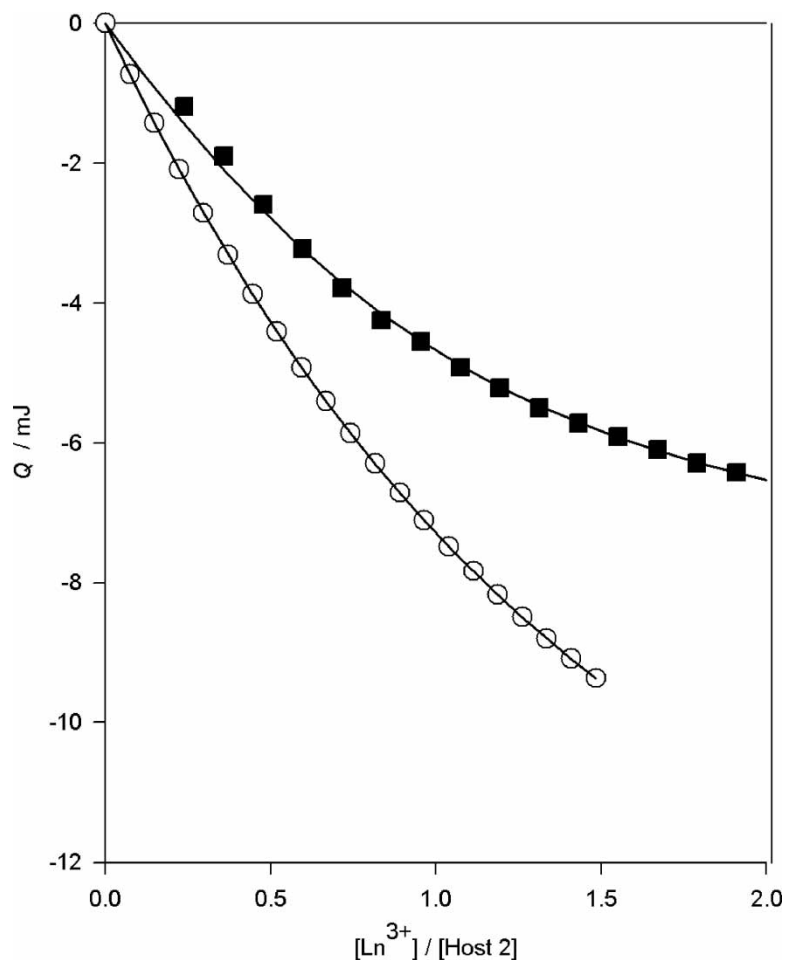


FIGURE 2 Heat effects determined by microcalorimetry for the complexation of  $\text{Sm}^{3+}$  (○) and  $\text{Dy}^{3+}$  (■) cations by the *p*-sulfonatocalix[6]arene (host 2) in water at pH 2 and 298.15 K. The curves result from the non-linear least squares fit of the data using a 1:1 binding model.

hydroxy groups of host 2 are protonated whereas at pH 7 two of them are deprotonated. However, the conformational preference of host 2 in solution is not clear. The 1,2,3-alternate conformation seems to be the stable structure for host 2 in solution under conditions that favour strong intramolecular hydrogen bonding. At neutral pH the unprotonated and protonated phenolic hydroxy groups can establish intramolecular hydrogen bonds that seem to stabilize the structure. The thermodynamic behaviour we previously [7] observed upon binding of host 2 with peptides in neutral pH solution was indeed consistent with this conformational preference. It is, however, reasonable to assume that the conformational state will be affected by a pH change. The tendency observed here upon binding of host 2 with  $\text{Me}_4\text{N}^+$  and  $\text{Et}_4\text{N}^+$  suggest a calixarene reorganization, when going from pH 7 to pH 2. All of the phenolic hydroxy groups of the calixarene being protonated at pH 2, the 1, 2, 3 -alternate conformation is surely less stabilized in acidic solution. Of course this does not constitute a definite evidence since we have no direct informations at

microscopic levels. However, it may be noticed that the assumption of a reorganization of the calixarene conformation in acidic solution is also consistent with the results obtained at pH 2 upon binding of host 2 with the lanthanide cations, as will be shown below.

The heat effects observed upon complexation of  $\text{Sm}^{3+}$  and  $\text{Dy}^{3+}$  by host 2 at pH 2 are plotted in Fig. 2.

TABLE III Thermodynamics parameters for the complexation of rare-earth metal cations by the *p*-sulfonatocalix[*n*]arene (*n* = 4 and 6) in acidic aqueous solution (pH = 2) at 298,15 K<sup>†,‡</sup>.

Cations <sup>¶</sup>	Log K'	$\Delta_r G'^{\circ}$	$\Delta_r H'^{\circ}$	$T \Delta_r S'^{\circ}$
Host 1				
$\text{Y}^{3+\S}$	3.54	$-20.2 \pm 0.4$	$11.5 \pm 0.4$	$31.7 \pm 0.8$
$\text{Sc}^{3+\S}$	3.91	$-22.3 \pm 0.4$	$13.4 \pm 0.4$	$35.7 \pm 0.8$
$\text{Sm}^{3+\parallel}$	3.82	$-21.8 \pm 0.2$	$10.4 \pm 0.2$	$32.2 \pm 0.4$
$\text{Dy}^{3+\parallel}$	3.88	$-22.1 \pm 0.3$	$10.1 \pm 0.2$	$32.3 \pm 0.5$
Host 2				
$\text{Sm}^{3+\S}$	3.69	$-21.0 \pm 0.4$	$10.1 \pm 0.4$	$31.1 \pm 0.8$
$\text{Dy}^{3+\S}$	3.54	$-20.2 \pm 0.3$	$9.2 \pm 0.3$	$29.4 \pm 0.6$

<sup>†</sup> Molar scale. <sup>‡</sup>  $\Delta_r G'^{\circ}$ ,  $\Delta_r H'^{\circ}$  and  $T \Delta_r S'^{\circ}$  in kJ mol<sup>-1</sup>. <sup>¶</sup> Counter-ion: Cl<sup>-</sup>. <sup>§</sup> Present work. <sup>||</sup> Ref. [8].

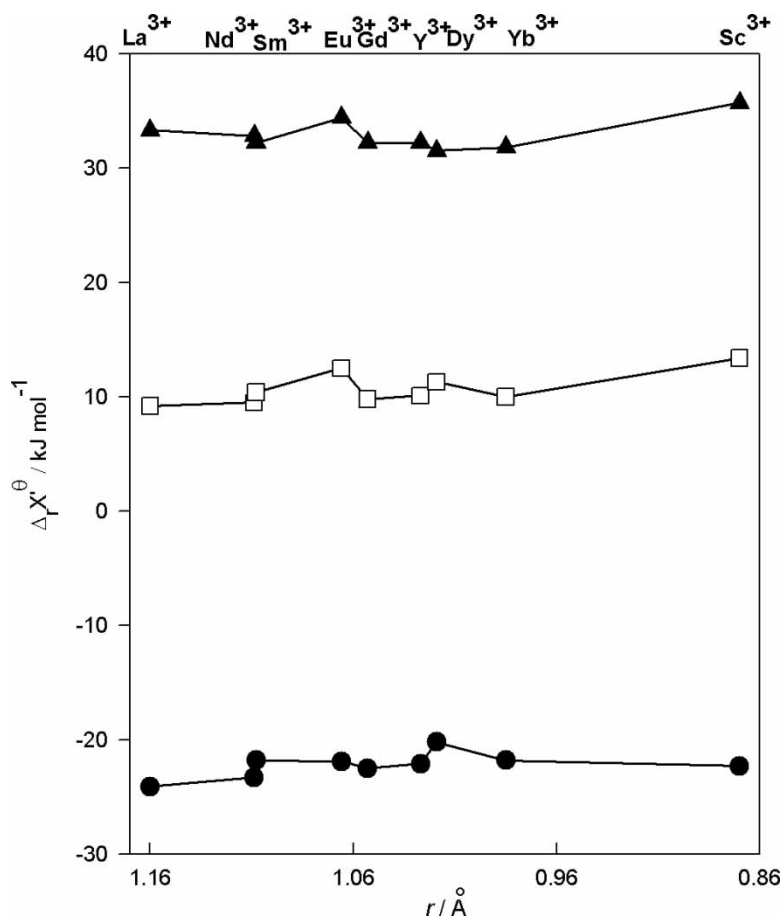


FIGURE 3 Variation of the thermodynamic properties of binding of trivalent rare-earth cations by the *p*-sulfonatocalix[4]arene (host 1) in water at pH 2 as a function of the cation radius [28]:  $\Delta_r G^\circ$  ( $\blacktriangle$ ),  $\Delta_r H^\circ$  ( $\square$ ) and  $T\Delta_r S^\circ$  ( $\bullet$ ).

The curves correspond to the non-linear least squares fit of the data using a 1:1 binding model. The  $K'$  and  $\Delta_r H^\circ$  values deduced from these fits are reported in Table III with the estimated standard deviations. The corresponding  $\Delta_r G^\circ$  and  $T\Delta_r S^\circ$  values are also given. For comparison, the thermodynamic parameters previously [8] obtained for the complexation of host 1 with the same cations are also included in Table III.

Although the quality of the fit suggests that the 1:1 stoichiometry adequately describes the binding process, we have also tried to fit the data with a 1:2 binding model: the uncertainties on the thermodynamic results were so important that we definitely excluded the possibility of formation of complexes of higher degree and concluded that host 2 only forms 1:1 complexes with  $\text{Ln}^{3+}$ . This suggests, in agreement with the results obtained with the organic cations, that host 2 does not adopt the double partial cone conformation in acidic solution.

Our results show that the binding process, which is characterized by positive entropy and enthalpy changes, is strongly entropy-driven. Such a thermodynamic behaviour is typical of purely ionic binding in water and essentially reflects the partial desolvation of the ions upon association.

The similarity between the thermodynamic parameters for the complexation of  $\text{Ln}^{3+}$  by host 1 and host 2 must be underlined. We have previously [8,14] demonstrated with host 1 that the lanthanide cation is located outside the cavity of the calixarene in the vicinity of the sulfonate groups forming an outer-sphere complex (solvent-separated complex) in which the inorganic cation preserves a certain mobility. The similarity between the two sets of thermodynamic parameters suggests that the association with host 2 also induces little conformational changes and yields an outer-sphere complex.

To further examine the selectivity of host 1 for the trivalent metal cations, we have completed our previous work [8] by studying the complexation of  $\text{Y}^{3+}$  and  $\text{Sc}^{3+}$  cations at pH 2. The thermodynamic parameters deduced from the fit of the microcalorimetric data using a 1:1 binding model are reported in Table III. The  $\Delta_r G^\circ$ ,  $\Delta_r H^\circ$  and  $T\Delta_r S^\circ$  values for the binding of the series of trivalent rare-earth metal cations by host 1 in aqueous solution at pH 2 are plotted in Fig. 3 as a function of the ionic radius [28]. The thermodynamic properties of formation of lanthanide complexes often show a discontinuity in the middle of the lanthanide series [29–32]. The main



factor explaining this discontinuity is the inner-sphere hydration number change. It is indeed now fairly well established that the lighter lanthanide cations are nine-coordinated in water whereas the heavier lanthanide cations are eight-coordinated. As expected for outer-sphere complexes and from the non-specific features of the electrostatic forces, the thermodynamic properties of binding by host 1 shown in Fig. 3 do not differ significantly across the rare earth series. Lui *et al.* [33], who studied by microcalorimetry the complexation of different water-soluble calixarenes with  $\text{Ln}^{3+}$  in acidic solution obtained positive enthalpy and entropy changes of the same order of magnitude as those we obtained with host 1.

## CONCLUSIONS

The binding of host 1 and host 2 with the  $\text{R}_4\text{N}^+$  cations in aqueous solution is found to be enthalpy-driven whatever the pH. In all cases, 1:1 complexes are formed. The inclusion of the organic cation into the cavity of the macrocyclic host is governed by van der Waals interactions. The binding by host 2 in acidic solution is characterized by highly unfavourable entropy changes and extremely favourable enthalpy changes that indicate the formation of a very compact structure. Host 2 shows an affinity for the  $\text{R}_4\text{N}^+$  ions that is weaker than shown by host 1. A very specific thermodynamic behaviour is observed upon binding of  $\text{Et}_4\text{N}^+$  by host 2, suggesting a special case of tight inclusion. Changing the pH induces significant effects in the complexation by host 2, suggesting that the conformational state of this calixarene is pH-sensitive. Host 2 probably adopts the 1,2,3-alternate conformation in neutral aqueous solution but this conformation seems to be lost in acidic aqueous solution. This is confirmed by our study of the binding of  $\text{Ln}^{3+}$  by host 2 in acidic solution: the fact that only 1:1 complexes are formed and that the thermodynamic properties of binding are almost identical to those previously obtained with host 1 indeed exclude the 1,2,3-alternate conformation for host 2. However, giving a definite answer to the possible rearrangement of the calixarene requires a better understanding of the complex structure at microscopic level.

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