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Thermodynamics of the Complexation of the *p*-Sulfonatocalix[4]arene with Simple Model Guests in Water: a Microcalorimetric Study

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The formation of supramolecular complexes in water involves interactions of various types which are not always easy to identify, especially when complicated species are involved. A complete thermodynamic characterization of the binding process, which includes the enthalpies and entropies of complexation, is obviously one of the key elements in identifying the stabilizing factors and in understanding how the host and guest assemble. In order to thermodynamically characterize typical interactions of various types, we have thus undertaken a microcalorimetric study of the complexation of *p*-sulfonatocalixarenes with simple guests bearing different functional groups. Association constants, free energies, enthalpies and entropies for the complexation of the *p*-sulfonatocalix[4]arene with normal alcohols, alkylammonium, carboxylate and guanidinium ions in water, at pH 7.5 and 298.15 K, are reported. The properties for the binding of lysine and arginine, which bear similar functional groups, are also given. The comparison of the thermodynamic behaviour of these different guests allows the driving factors to be identified. This may constitute a starting point for the understanding of the recognition of more complicated guests.

INTRODUCTION

The *p*-sulfonatocalixarenes are able to complex a variety of organic compounds as well as inorganic cations in water [1–5]. Depending on the guest, different types of interactions may be involved (ionic, hydrophobic, van der Waals, $\pi-\pi$, cation$-\pi$, hydrogen bonding, etc.). Each of these interactions implies a partial desolvation of the host and guest and also some modification of the translational, rotational and internal degrees of freedom of the species upon binding. The thermodynamic characterization of the binding process is obviously one of the key elements in identifying the stabilizing factors and in understanding how the host and guest assemble. However, the stability constants alone, that is the Gibbs free energies, cannot clearly identify the driving forces: we have shown, for instance, that a complex purely of the ionic type and a complex controlled by van der Waals interactions can be characterized by similar association constants whereas their enthalpies and entropies of complexation are totally different [4], in agreement with the dissimilar structures obtained by molecular dynamics [6]. A complete thermodynamic characterization of the binding process which includes the enthalpies and entropies of complexation is thus essential.

Microcalorimetry is a powerful tool for measuring the thermodynamic parameters that characterize interacting molecules because it not only gives enthalpy changes but may also yield association constants, even in the case of weak interactions [7–10]. We have used this technique to study, in particular, the complexation in water of three sulfonatocalix[*n*]arenes ($n = 4$, 6 and 8) with the basic amino acids lysine and arginine [3] and, more recently, with lysine or arginine-containing dipeptides and tripeptides [5]. We have also used it to compare the binding of inorganic and organic cations by the tetrameric *p*-sulfonatocalix[4]arene [4]. The thermodynamic properties have shown that these species bind in very different modes, which are

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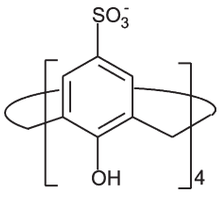

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not simple to identify in the case of guests bearing miscellaneous groups. In order to thermodynamically characterize typical interactions of various kinds in water, we have thus undertaken a microcalorimetric study of the complexation of *p*-sulfonatocalixarenes with simple guests bearing different functional groups. This may constitute a starting point for the understanding of the recognition of more complicated guests.

In the present paper, we thus report the association constants, free energy, enthalpy and entropy changes for the complexation of linear chain alcohols and ions of the alkylammonium, carboxylate and guanidinium types by the *p*-sulfonatocalix[4]arene, **1**, in water at pH 7.5 and 298.15 K. The choice of these particular guests has been motivated by the fact that they bear groups similar to those contained in lysine and arginine.

EXPERIMENTAL

Materials

25,26,27,28-Tetrahydroxy-5,11,17,23-tetrasulfonatocalix[4]arene was purchased from ACROS. It was decolorized by adsorption on active carbon and dried under vacuum at 80°C. Methanol dried (Merck, pro analysi >99.5%), ethanol absolute (Merck, pro analysi >99.8%), 1-propanol (Fluka, puriss >99.5%), 1-butanol (Fluka, puriss >99.5%), 1-pentanol (Fluka, puriss >99%), 1,4-butanediol (Fluka, purum >99%), 1,5-pentanediol (Fluka, purum >97%), ammonium chloride (Fluka, biochemika microselect >99.5%), methylamine hydrochloride (Fluka, purum >98%), ethylamine hydrochloride (Fluka, puriss >99%), 1,4-diaminobutane dihydrochloride (Fluka, purum >99%), 1,5-diaminopentane dihydrochloride (Fluka, puriss >99%), butyric acid (Fluka, purum >99%), valeric acid (Fluka, purum >98%), caproic acid (Fluka, purum >98%), 4-aminobutyric acid (Fluka, purum >98%), 5-aminovaleric acid (Fluka, purum >97%), 6-aminocaproic acid (Fluka, puriss >99%), L-2,4-diaminobutyric acid dihydrochloride (Fluka, biochemika >97%), guanidine hydrochloride (Fluka, biochemika >99%), methylguanidine hydrochloride (Aldrich, 98%), ethylguanidine sulfate (Aldrich, 98%), L-lysine monohydrochloride (Fluka, biochemika >99.5%) and L-arginine monohydrochloride (Fluka, biochemika >99.5%) were used as received. The salt solutions were prepared by neutralizing the acids with 1.00 mol L^{-1} NaOH.

All the solutions were prepared by weight from triply distilled water. The exact concentration of the calixarene solutions was determined by potentiometric titration and the pH was set at 7.5 with 1.00 mol L^{-1} NaOH. The pK_a values [11] reported in the literature for the *p*-sulfonatocalix[4]arene indicate that all the sulfonic acid groups and one of the hydroxy groups are dissociated at pH 7.5, yielding the following anion: (*p*-sulfonatocalix[4]arene)$^{5-}$. We have chosen to control the pH by using NaOH instead of a phosphate buffer in order to avoid any interference of the buffer with the substrates, in particular with those bearing a guanidinium group. It is indeed important to avoid proton transfer as far as possible because it may significantly perturb the heat effect if the standard molar enthalpy of proton exchange happens to be large. Considering the pK_a values, none of the studied species is involved in proton exchange under the present conditions, as shown by the constancy of the pH value (±0.1) upon titration. This is also confirmed by the fact that measurements in phosphate buffer yield similar results [12].

Microcalorimetry

All the measurements were performed at 298.15 K using a multichannel microcalorimeter (LKB-Thermometric 2277 Thermal Activity Monitor) equipped with a titration-perfusion vessel. Wadsö and co-workers have thoroughly described this twin thermopile heat-conduction calorimeter, specified its working conditions and analysed its performance [13–15]. In the present case, the 1 mL stainless steel titration vessel was charged with 0.8 mL of calixarene solution and 8 μL of guest solution was injected in each step using a Lund syringe pump (Thermometric) equipped with a 250 μL Hamilton syringe fitted with a stainless steel cannula. 20 injections were made for each titration experiment. The solution molalities were, prior to titration, set at 0.008 mol kg^{-1} for the calixarene (0.016 mol kg^{-1} for the complexations with the alcohols) and varied from 0.08 to 0.16 mol kg^{-1} for the guests. Static and dynamic calibrations were used. The power values observed upon titration ranged from 30 to 100 μW. Separate dilution experiments were performed under the same conditions: since the heat of dilution of the calixarene was found to be negligible, the heat effects observed upon titration were simply corrected for the heats of dilution of the guests. Each experiment was repeated three times to verify reproducibility. Values for the apparent association constant K' and apparent standard molar enthalpy of

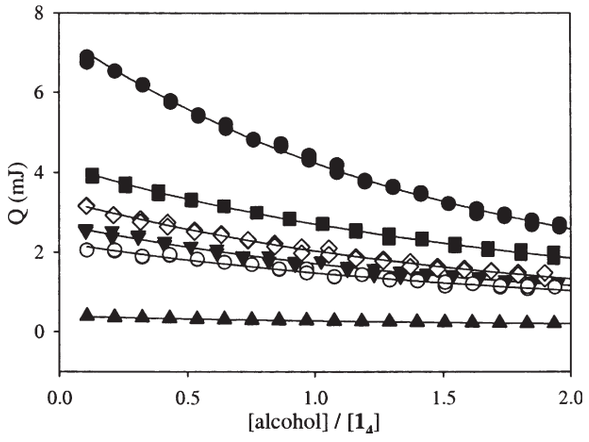

FIGURE 1 Heat effects, corrected for the dilution, observed upon titration of ethanol (■), 1-propanol (●), 1-butanol (▼), 1-pentanol (◇), 1,4-butanediol (▲) and 1,5-pentanediol (○) by *p*-sulfonatocalix[4]arene $\mathbf{1}_4$ in water at pH 7.5 and 298.15 K. The curves correspond to the non-linear least-squares fit of the data using a 1:1 binding model.

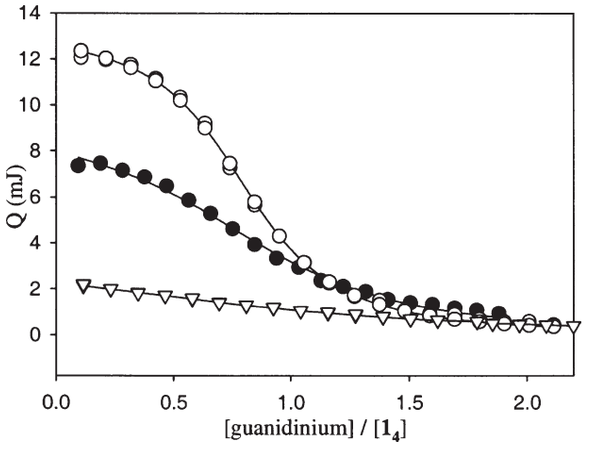

FIGURE 3 Heat effects, corrected for the dilution, observed upon titration of guanidinium (▽), methylguanidinium (●) and ethylguanidinium (○) ions by *p*-sulfonatocalix[4]arene $\mathbf{1}_4$ in water at pH 7.5 and 298.15 K. The curves correspond to the non-linear least-squares fit of the data using a 1:1 binding model.

reaction $\Delta_r H'^\circ$ in the given medium were calculated by use of the Digitam 4.1 minimization program (Thermometric), the three series of data obtained for each system (60 points) being treated simultaneously in the regression analysis. The titration curves are shown in Figs. 1–4.

RESULTS AND DISCUSSION

The results of the microcalorimetric titrations of **1** with ethanol, 1-propanol, 1-butanol, 1-pentanol, 1,4-butanediol and 1,5-pentanediol in water at pH 7.5 have been fitted with a 1:1 binding model, yielding the thermodynamic properties listed in Table I. With methanol, we did not detect any heat effect, which suggests that there is no significant complexation of this guest. The association constants reported in the literature from ^{1}H NMR data ($\log K' = 1.5$ for ethanol and 1-propanol) [16,17] and from headspace gas chromatography ($\log K' = 1.8$ for 1-butanol and 1-pentanol) [18] are slightly larger than those determined by microcalorimetry.

The values reported in Table I show that in all cases, except for 1,4-butanediol, $\Delta_r H'^\circ \ll 0$ and $T\Delta_r S'^\circ < 0$. This thermodynamic behaviour is typical [19] of what is observed upon inclusion of an apolar solute into the lipophilic cavity of a ligand through van der Waals interactions, which gives rise to negative enthalpic and entropic contributions that

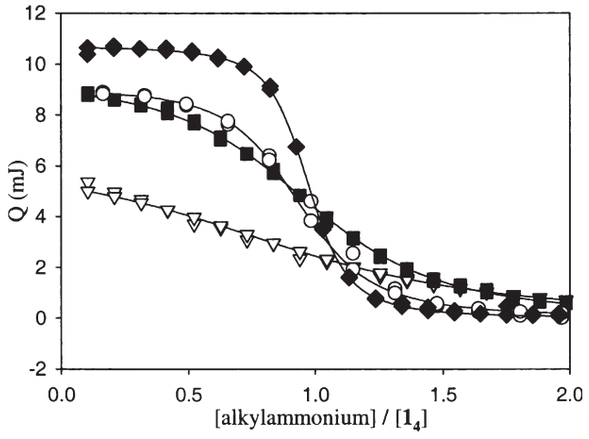

FIGURE 2 Heat effects, corrected for the dilution, observed upon titration of methylammonium (▽), ethylammonium (■), 1,4-butanediammonium (○) and 1,5-pentanediammonium (◆) ions by *p*-sulfonatocalix[4]arene $\mathbf{1}_4$ in water at pH 7.5 and 298.15 K. The curves correspond to the non-linear least-squares fit of the data using a 1:1 binding model.

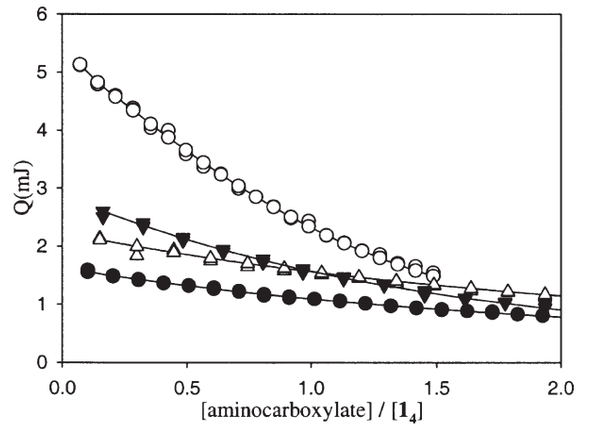

FIGURE 4 Heat effects, corrected for the dilution, observed upon titration of 4-aminobutyrate (●), 5-aminovalerate (○), 6-aminocaproate (▽) and 2,4-diaminobutyrate (▼) ions by *p*-sulfonatocalix[4]arene $\mathbf{1}_4$ in water at pH 7.5 and 298.15 K. The curves correspond to the non-linear least-squares fit of the data using a 1:1 binding model.

TABLE I Thermodynamic properties for the binding of alcohols by the *p*-sulfonatocalix[4]arene in water at pH 7.5 and 298.15 K[*,†,‡]

Guest	$\log K'$	$\Delta_r G'^\circ$	$\Delta_r H'^\circ$	$T\Delta_r S'^\circ$
CH_3-OH		No significant heat effect		
C_2H_5-OH	1.04 ± 0.08	−6.0 ± 0.4	−13.4 ± 0.7	−7.4 ± 1.1
C_3H_7-OH	1.34 ± 0.04	−7.6 ± 0.2	−16.6 ± 0.8	−9.0 ± 1.0
C_4H_9-OH	1.58 ± 0.05	−9.0 ± 0.3	−18.0 ± 0.6	−9.0 ± 0.9
$C_5H_{11}-OH$	1.63 ± 0.05	−9.3 ± 0.2	−20.1 ± 0.6	−10.8 ± 0.9
$HO-C_4H_8-OH$	1.28 ± 0.12	−7.2 ± 0.7	−4.4 ± 1.0	2.8 ± 1.7
$HO-C_5H_{10}-OH$	1.43 ± 0.03	−8.2 ± 0.2	−19.3 ± 0.9	−11.1 ± 1.1

[*] K' and $\Delta_r H'^\circ$ deduced from the non-linear least-squares fit of the data using a 1:1 binding model. [†] Molar scale. [‡] $\Delta_r G'^\circ$, $\Delta_r H'^\circ$ and $T\Delta_r S'^\circ$ in kJ mol^{-1}.

largely outweigh the positive contributions due to the desolvation of the species. This thermodynamic behaviour is indeed due to the fact that the host and guest involved in the formation of an inclusion complex lose most of their degrees of freedom. This is accompanied by a strong entropy loss which masks the entropy gain due to the desolvation of the species upon binding and, as a result, the process is driven by the enthalpy associated with the van der Waals interactions. Diederich and co-workers [19], who thoroughly examined this type of binding, underlined the fact that this thermodynamic behaviour is in sharp contrast with what is observed for processes driven by the classical hydrophobic interaction ($\Delta_r H'^\circ \approx 0$ and $T\Delta_r S'^\circ > 0$) [20,21].

The results in Table I thus imply that the alkyl chain of the alcohol is tightly inserted into the lipophilic cavity of the host, as required by the fall off with r^{-6} of van der Waals forces. The fact that methanol is not complexed suggests that the OH group does not penetrate into the cavity, probably because the enthalpic cost of its dehydration is so important that it cannot be compensated by the enthalpic contribution associated with the inclusion of only one CH_3 group. Furthermore, the fact that the $\Delta_r H'^\circ$ and $T\Delta_r S'^\circ$ values are almost the same for 1-pentanol and 1,5-pentanediol is consistent with the inclusion of only the alkyl chain. CPK (Corey–Pauling–Koltun) models show indeed that the pentyl chain of 1,5-pentanediol suits remarkably well the *p*-sulfonatocalix[4]arene cavity and that the two OH groups are above the upper rim. The situation is different when the alkyl chain is shorter. The results in Table I show that there are important positive contributions to both $\Delta_r H'^\circ$ and $T\Delta_r S'^\circ$ when going from 1-butanol to 1,4-butanediol: $\{\Delta_r H'^\circ[HO-C_4H_8-OH] - \Delta_r H'^\circ [C_4H_9-OH]\} = 13.6\,\text{kJ mol}^{-1}$ and $\{T\Delta_r S'^\circ[HO-C_4H_8-OH] - T\Delta_r S'^\circ[C_4H_9-OH]\} = 11.8\,\text{kJ mol}^{-1}$. This suggests that upon inclusion the butyl chain, which is less bulky than the pentyl chain, penetrates more deeply and, in so doing, drags one of the OH groups of the diol towards the interior of the cavity. Then, as a result of the partial desolvation of the hydroxy group, the enthalpy and entropy of binding increase.

The results of the microcalorimetric titrations of **1** with methylammonium, ethylammonium, 1,4-butanediammonium and 1,5-pentanediammonium ions in water at pH 7.5 have been fitted with a 1:1 binding model, yielding the thermodynamic properties listed in Table II. We did not detect any heat effect with the ammonium ion, as noticed previously at pH 2 [4]. Table II has been completed with the values obtained for the complexation of propylammonium to heptylammonium ions by Stödeman and Dhar [22] at pH 7.1 and with the values we obtained

TABLE II Thermodynamic properties for the binding of alkylammonium ions by the *p*-sulfonatocalix[4]arene in water at 298.15 K[*,†,‡]

Guest	$\log K'$	$\Delta_r G'^\circ$	$\Delta_r H'^\circ$	$T\Delta_r S'^\circ$
NH_4^+ [¶]		No significant heat effect		
$CH_3-NH_3^+$ [¶]	2.74 ± 0.03	−15.6 ± 0.2	−9.9 ± 0.2	5.7 ± 0.4
$C_2H_5-NH_3^+$ [¶]	3.25 ± 0.06	−18.5 ± 0.4	−14.8 ± 0.4	3.7 ± 0.8
$C_3H_7-NH_3^+$ [§]	4.12 ± 0.01	−23.50 ± 0.06	−16.89 ± 0.06	6.61 ± 0.08
$C_4H_9-NH_3^+$ [§]	4.01 ± 0.01	−22.88 ± 0.06	−17.94 ± 0.07	4.94 ± 0.09
$C_5H_{11}-NH_3^+$ [§]	3.81 ± 0.01	−21.72 ± 0.04	−20.24 ± 0.06	1.48 ± 0.07
$C_6H_{13}-NH_3^+$ [§]	3.60 ± 0.01	−20.57 ± 0.02	−20.42 ± 0.05	0.15 ± 0.07
$C_7H_{15}-NH_3^+$ [§]	3.39 ± 0.01	−19.35 ± 0.03	−20.86 ± 0.06	−1.51 ± 0.07
$^+H_3N-C_4H_8-NH_3^+$ [¶]	4.02 ± 0.09	−23.0 ± 0.5	−13.5 ± 0.3	9.5 ± 0.8
$^+H_3N-C_5H_{10}-NH_3^+$ [¶]	4.26 ± 0.08	−24.3 ± 0.5	−15.4 ± 0.2	8.9 ± 0.7
$(CH_3)_4-N^+$ [‖]	4.40 ± 0.03	−25.1 ± 0.2	−26.0 ± 0.2	−0.9 ± 0.4
$(C_2H_5)_4-N^+$ [‖]	4.67 ± 0.07	−26.7 ± 0.4	−41.2 ± 0.8	−14.5 ± 1.2
$(C_3H_7)_4-N^+$ [‖]	4.47 ± 0.05	−25.5 ± 0.3	−23.8 ± 0.3	1.7 ± 0.6
$(C_4H_9)_4-N^+$ [‖]	4.21 ± 0.05	−24.0 ± 0.3	−21.6 ± 0.5	2.4 ± 0.8

[*] K' and $\Delta_r H'^\circ$ deduced from the non-linear least-squares fit of the data using a 1:1 binding model. [†] Molar scale. [‡] $\Delta_r G'^\circ$, $\Delta_r H'^\circ$ and $T\Delta_r S'^\circ$ in kJ mol^{-1}.
[¶] Present work at pH 7.5. [§] Ref. 22 (at pH 7.1). [‖] Ref. 4 (at pH 2).

TABLE III Comparison of the enthalpies and entropies of binding of the alkylammonium ions with those of the alcohols*

X	$\Delta_r H'°[X–NH_3^+]$ $- \Delta_r H'°[X–OH]\}$	$T\Delta_r S'°[X–NH_3^+]$ $- T\Delta_r S'°[X–OH]\}$
C_2H_5	−1.4	11.1
C_3H_7	−0.3	15.6
C_4H_9	0.06	13.9
C_5H_{11}	−0.14	12.3

* $\Delta_r H'°$ and $T\Delta_r S'°$ in kJ mol^{-1}.

previously for the complexation of tetramethylammonium to tetrabutylammonium ions at pH 2 [4]. In all cases, the binding process appears to be exothermic and strongly enthalpy-driven. Our values for the alkylammonium ions are in excellent agreement with those reported by Stödeman and Dhar [22] whereas the values we have found for the alkyldiammonium ions differ significantly from theirs [23]. The procedure followed by Stödeman and Dhar for the titration of **1** by the alkyldiammonium ions [23] may explain this discrepancy, the volume of the injections being possibly too large for a good equilibration of the solution; a more standard procedure seems to have been used with the alkylammonium ions [22]. The results of Table II show that the enthalpy of binding becomes more favourable as the length of the alkyl chain increases, reaching a plateau for the pentylammonium ion. A similar trend was observed for the alcohols (Table I) although the plateau could not be so clearly identified because the series was limited to pentanol. This plateau is consistent with the fact that the pentyl group gives the optimal fit of the cavity, as shown by CPK models.

The fact that no heat effect is detected with NH_4^+ suggests that this ion is not significantly complexed by **1**. Of course, this does not constitute definite evidence since purely entropic bindings, although scarce, do exist. It may be noticed that K^+, whose thermodynamic properties of hydration are similar to those of NH_4^+ [24], does behave like NH_4^+. In contrast, divalent and trivalent cations such as Ca^{2+} and La^{3+} do form relatively strong complexes with host **1** in water [4]: these purely ionic bindings are characterized by $\Delta_r H'° > 0$ and $T\Delta_r S'° \gg 0$, due essentially to the desolvation of the charged species. Possibly, the entropic contribution associated with the dehydration of the monovalent cations is not sufficiently positive to compensate the unfavourable enthalpic contribution: the entropy of hydration of K^+ or NH_4^+ is indeed 3 times smaller than that of Ca^{2+} and 5 times smaller than that of La^{3+} whereas the enthalpy of hydration of K^+ or NH_4^+ is 5 times smaller than that of Ca^{2+} and 10 times smaller than that of La^{3+} [24]. It is interesting to note that the thermodynamic properties for the binding of Ca^{2+} by **1** in water at pH 2 ($\Delta_r G'° = -19$ kJ mol^{-1}; $\Delta_r H'° = 3.0$ kJ mol^{-1}; $T\Delta_r S'° = 22$ kJ mol^{-1}) [4] are comparable to those for the ion-pairing reaction between Ca^{2+} and SO_4^{2-} in water ($\Delta_r G'° = -13$ kJ mol^{-1}; $\Delta_r H'° = 7$ kJ mol^{-1}; $T\Delta_r S'° = 20$ kJ mol^{-1}) [25] and that those for the binding of La^{3+} by **1** in water at pH 2 ($\Delta_r G'° = -24$ kJ mol^{-1}; $\Delta_r H'° = 9$ kJ mol^{-1}; $T\Delta_r S'° = 33$ kJ mol^{-1}) [4] are comparable to those for the ion-pairing reaction between La^{3+} and $Fe(CN)_6^{3-}$ in water ($\Delta_r G'° = -21$ kJ mol^{-1}; $\Delta_r H'° = 8$ kJ mol^{-1}; $T\Delta_r S'° = 29$ kJ mol^{-1}) [25]. This suggests that two or three SO_3^- groups of host **1** interact with the metal ion (two with Ca^{2+} and three with La^{3+}). According to Schneider and Yatsimirsky [21], the number of single interactions in multiply bound host–guest complexes can be estimated by correlating the association constant at zero ionic strength with the product of the total charges of guest and host. Applying their linear equation ($\log K = 0.04 + 0.57\ Z_A Z_B$) to the La^{3+}–**1** and Ca^{2+}–**1** complexes, we get a mean value of 2.5 for the charge of host **1**, which is consistent with the involvement of two or three sulfonate groups. This is in agreement with the molecular dynamics simulations of the La^{3+}–**1** complex in water [6].

It is interesting to compare the binding of the alkylammonium ions with that of the alcohols. In order to do so, we have reported in Table III the values corresponding to the differences $\{\Delta_r H'°[C_nH_{2n+1}–NH_3^+] - \Delta_r H'°[C_nH_{2n+1}–OH]\}$ and $\{T\Delta_r S'°[C_nH_{2n+1}–NH_3^+] - T\Delta_r S'°[C_nH_{2n+1}–OH]\}$. Obviously, the replacement of an OH group by a NH_3^+ group does not significantly change the enthalpy but increases the entropy of binding by about 13 kJ mol^{-1}. This clearly shows that the binding of **1** with the alkylammonium ions, as well as with the alcohols, is controlled by the favourable enthalpic term resulting from the inclusion of the hydrocarbon chain into the ligand cavity. It is, however, the desolvation of the NH_3^+ and SO_3^- groups upon their ionic interaction which governs the entropy of binding and which explains why the affinity of **1** for the alkylammonium ions is much higher than that for the alcohols. The results for the 1,4-butanediammonium and 1,5-pentanediammonium ions (Table II) show that the addition of a second NH_3^+ group at the opposite end of the alkyl chain only slightly increases the affinity: $\{\Delta_r H'°[^+H_3N–C_5H_{10}–NH_3^+] - \Delta_r H'°[C_5H_{11}–NH_3^+]\} = 4.8$ kJ mol^{-1} and $\{T\Delta_r S'°[^+H_3N–C_5H_{10}–NH_3^+] - T\Delta_r S'°[C_5H_{11}–NH_3^+]\} = 7.4$ kJ mol^{-1}. This indicates that the second ionic binding is not as efficient as the first one, the second NH_3^+ group being not in a suitable position.

Table II shows, except for $(C_2H_5)_4–N^+$ which exhibits a remarkably negative enthalpy and entropy of binding, that the thermodynamic behaviour of the tetraalkylammonium ions is similar to that of the alkylammonium ions, the governing factor being the inclusion of one or several chains of

TABLE IV Thermodynamic properties for the binding of carboxylate ions by the *p*-sulfonatocalix[4]arene in water at pH 7.5 and 298.15 K[*,†,‡]

Guest	log *K′*	$\Delta_r G'^\circ$	$\Delta_r H'^\circ$	$T\Delta_r S'^\circ$
$C_3H_7-COO^-$		No significant heat effect		
$C_4H_9-COO^-$		No significant heat effect		
$C_5H_{11}-COO^-$		No significant heat effect		
$^+H_3N-C_3H_6-COO^-$	1.36 ± 0.15	−7.8 ± 0.8	−17.3 ± 0.5	−9.5 ± 1.3
$^+H_3N-C_4H_8-COO^-$	2.26 ± 0.06	−12.9 ± 0.3	−24.2 ± 1.2	−11.3 ± 1.5
$^+H_3N-C_5H_{10}-COO^-$	1.18 ± 0.05	−6.7 ± 0.3	−20.0 ± 0.7	−13.3 ± 1.0
$^+H_3N-CH(COO^-)-C_2H_4-NH_3^+$	1.95 ± 0.05	−11.1 ± 0.3	−10.3 ± 0.6	0.8 ± 0.9
$^+H_3N-CH(COO^-)-C_4H_8-NH_3^+$	2.87 ± 0.03	−16.4 ± 0.2	−13.3 ± 0.3	3.1 ± 0.5

[*] *K′* and $\Delta_r H'^\circ$ deduced from the non-linear least-squares fit of the data using a 1:1 binding model. [†] Molar scale. [‡] $\Delta_r G'^\circ$, $\Delta_r H'^\circ$ and $T\Delta_r S'^\circ$ in kJ mol^{-1}.

the R_4N^+ ion into the cavity of **1**, as shown by our recent molecular dynamics simulations in water [6]. These simulations have also shown that the complexation of $(C_2H_5)_4-N^+$ corresponds to the inclusion of the largest number of methylene groups, which explains the peculiar thermodynamic behaviour of this species.

In Table IV are reported the results deduced from the microcalorimetric titrations of **1** with butyrate, valerate, caproate, 4-aminobutyrate, 5-aminovalerate, 6-aminocaproate, L-2,4-diaminobutyrate ions and L-lysine in water at pH 7.5. No heat effect was detected with butyrate, valerate and caproate ions, suggesting that these species are not complexed by **1**: obviously, the favourable van der Waals interactions associated with the inclusion of the non-polar chain into the cavity are not large enough to compensate for the unfavourable $COO^- - SO_3^-$ repulsion. The results of Table IV show that complexation becomes possible when a NH_3^+ group is added at the opposite end of the alkyl chain. It may be noticed, however, that the complexes formed between host **1** and these functionalized carboxylate ions are rather weak, the affinities being closer to those observed with the alcohols than to those oberved with the alkylammonium ions, due to a much less favourable entropy. The addition of another NH_3^+ group, on the α carbon, gives positive contributions to both $\Delta_r H'^\circ$ and $T\Delta_r S'^\circ$: going from $^+H_3N-C_3H_6-COO^-$ to $^+H_3N-CH(COO^-)-C_2H_4-NH_3^+$ yields enthalpy and entropy increases of 7.0 kJ mol^{-1} and 10.3 kJ mol^{-1}, respectively, and going from $^+H_3N-C_5H_{10}-COO^-$ to $^+H_3N-CH(COO^-)-C_4H_8-NH_3^+$ yields enthalpy and entropy increases of 6.7 kJ mol^{-1} and 16.4 kJ mol^{-1}, respectively. This can be compared with the enthalpy and entropy increases observed upon addition of a second NH_3^+ group on the pentylammonium ion (4.8 kJ mol^{-1} and 7.4 kJ mol^{-1}, respectively).

The thermodynamic properties for the binding of guanidinium, methylguanidinium, ethylguanidinium and L-arginine ions by **1** in water at pH 7.5 have been reported in Table V. Whereas monovalent ions such as K^+ or NH_4^+ are not complexed by host **1**, for the reasons given above, the binding of $^+H_3N-C(=NH)-NH_2$ is characterized by $T\Delta_r S'^\circ > 0$ and $\Delta_r H'^\circ < 0$, the process being entropy-controlled. The fact that the guanidinium ion can be involved in π−π interactions with the phenyl units of the host cavity, which gives a negative enthalpic contribution, probably explains the difference with ammonium ion. Addition of an alkyl group, as in $^+H_3N-C(=NH)-NH-CH_3$ and $^+H_3N-C(=NH)-NH-C_2H_5$, gives negative contributions to both $T\Delta_r S'^\circ$ and $\Delta_r H'^\circ$, as a result of the van der Waals interactions upon inclusion of the alkyl chain into the host cavity. The comparison of the thermodynamic behaviour of the ethylguanidinium ion with that of the ethylammonium ion is interesting: $\{\Delta_r G'^\circ[^+H_3N-C(=NH)-NH-C_2H_5] - \Delta_r G'^\circ[C_2H_5-NH_3^+]\} = -0.1$ kJ mol^{-1}, $\{\Delta_r H'^\circ[^+H_3N-C(=NH)-NH-C_2H_5] - \Delta_r H'^\circ[C_2H_5-NH_3^+]\} = -1.6$ kJ mol^{-1} and $\{T\Delta_r S'^\circ[^+H_3N-C(=NH)-NH-C_2H_5] - T\Delta_r S'^\circ[C_2H_5-NH_3^+]\} = -1.5$ kJ mol^{-1}. This is consistent with a less important desolvation of the guanidinium group and with π−π interactions. L-Arginine, $^+H_3N-C(=NH)-NH-C_3H_6-CH(COO^-)-NH_3^+$, seems to behave like a simple alkylguanidinium ion with a longer chain, the negative contributions to $T\Delta_r S'^\circ$ and $\Delta_r H'^\circ$ being of

TABLE V Thermodynamic properties for the binding of guanidinium ions by the *p*-sulfonatocalix[4]arene in water at pH 7.5 and 298.15 K[*,†,‡]

Guest	log *K′*	$\Delta_r G'^\circ$	$\Delta_r H'^\circ$	$T\Delta_r S'^\circ$
$^+H_3N-C(=NH)-NH_2$	2.40 ± 0.14	−13.7 ± 0.8	−5.4 ± 0.7	8.3 ± 1.6
$^+H_3N-C(=NH)-NH-CH_3$	3.04 ± 0.10	−17.4 ± 0.6	−14.5 ± 0.7	2.9 ± 1.3
$^+H_3N-C(=NH)-NH-C_2H_5$	3.26 ± 0.13	−18.6 ± 0.8	−16.4 ± 1.0	2.2 ± 1.8
$^+H_3N-C(=NH)-NH-C_3H_6-CH(COO^-)-NH_3^+$	3.25 ± 0.02	−18.6 ± 0.1	−21.1 ± 0.3	−2.5 ± 0.4

[*] *K′* and $\Delta_r H'^\circ$ deduced from the non-linear least-squares fit of the data using a 1:1 binding model. [†] Molar scale. [‡] $\Delta_r G'^\circ$, $\Delta_r H'^\circ$ and $T\Delta_r S'^\circ$ in kJ mol^{-1}.

the order of what could be expected for propyl or butylguanidinium ion.

In order to have a better understanding of the role of the different functional groups, let us compare, in Fig. 5, the thermodynamic behaviour of guests bearing different groups on a pentyl chain, this choice being motivated by the fact that the pentyl group ideally fits the cavity of **1**. The histograms of Fig. 5 represent $\Delta_r G'^\circ$, $\Delta_r H'^\circ$ and $-T\Delta_r S'^\circ$ values: this implies that what appears below zero is favourable to binding whereas what appears above zero is unfavourable. Obviously, $C_5H_{11}-OH$, $HO-C_5H_{10}-OH$ and $^+H_3N-C_5H_{10}-COO^-$ show the same thermodynamic behaviour ($\Delta_r H'^\circ \approx -20\,kJ\,mol^{-1}$ and $T\Delta_r S'^\circ \approx -11\,kJ\,mol^{-1}$), which means that in all three cases binding with **1** essentially involves inclusion of the alkyl chain. This suggests that the end charges of the zwitterionic species $^+H_3N-C_5H_{10}-COO^-$ form an intramolecular ion pair ("salt bridge") in pure water and that this pair is unperturbed upon complexation with **1** (Fig. 6). When the NH_3^+ group is not "neutralized" by COO^-, as in $C_5H_{11}-NH_3^+$ and $^+H_3N-C_5H_{10}-NH_3^+$, then the entropy of binding is positive because of the desolvation upon ionic binding with the SO_3^- groups. The thermodynamic behaviour observed upon binding of L-lysine, $^+H_3N-CH(COO^-)-C_4H_8-NH_3^+$, resembles that observed with $C_5H_{11}-NH_3^+$ and $^+H_3N-C_5H_{10}-NH_3^+$. This suggests that the charges of the α-NH_3^+ and COO^- groups of lysine more or less cancel each other and that the ε-NH_3^+ group is involved in ionic binding with the SO_3^- groups of the host, yielding a positive entropy of binding. The fact that the enthalpy of binding is less negative for lysine than for $C_5H_{11}-NH_3^+$ and $^+H_3N-C_5H_{10}-NH_3^+$ may be explained by the inclusion of a shorter chain (C_4H_8). The binding of arginine, $^+H_3N-C(=NH)-NH-C_3H_6-CH(COO^-)-NH_3^+$, can be explained in a similar way, with additional negative enthalpic and entropic contributions due to π–π interactions.

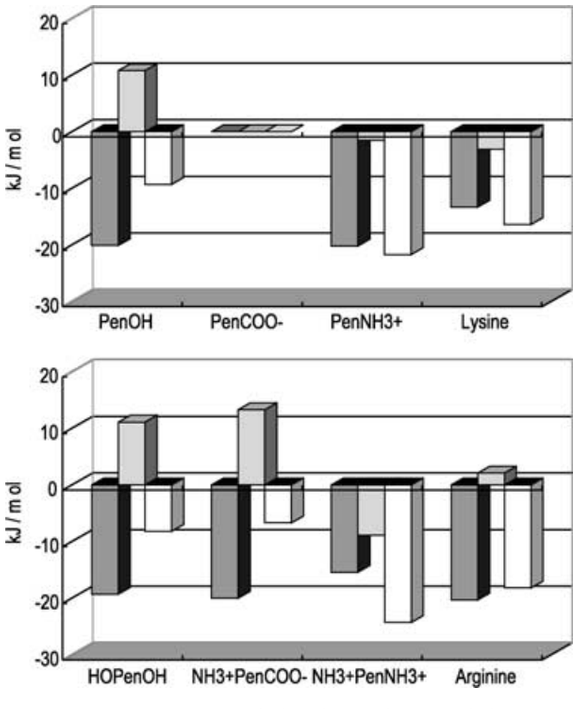

FIGURE 5 Comparison of the thermodynamic behaviour of guests bearing different groups on a pentyl chain. Themodynamic properties for the binding with the *p*-sulfonatocalix[4]arene in water at pH 7.5 and 298.15 K: $\Delta_r G'^\circ$ (❒) ; $\Delta_r H'^\circ$(■) ; $-T\Delta_r S'^\circ$(▒).

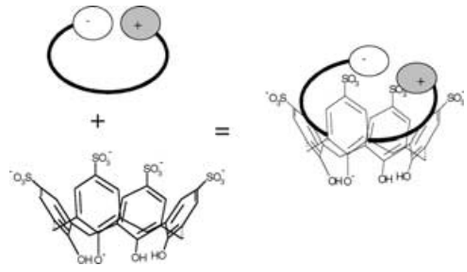

FIGURE 6 Schematic representation of the complexation of the zwitterionic species $^+H_3N-C_5H_{10}-COO^-$ by the *p*-sulfonatocalix[4]arene in water at pH 7.5 and 298.15 K.

CONCLUSIONS

Whereas the association constants are inclusive properties that cannot clearly identify the driving forces, the enthalpies and entropies of binding constitute a distinctive set of data that allows the identification of the different types of interactions involved in the formation of supramolecular complexes. The results reported in the present work allow the factors governing the binding of simple guests with the *p*-sulfonatocalix[4]arene in water at pH 7.5 and 298.15 K to be identified.

For all the guests studied here, whatever the hydrophilic groups, charged or neutral, on the alkyl chain, the binding process is enthalpy-driven. It is the inclusion of the alkyl chain into the lipophilic cavity of the macrocyclic host, through van der Waals interactions, that makes complexation possible. The thermodynamic properties for their inclusion ($\Delta_r H'^\circ \ll 0$ and $T\Delta_r S'^\circ < 0$) are in sharp contrast to what is observed for processes driven by the classical hydrophobic interaction ($\Delta_r H'^\circ \approx 0$ and $T\Delta_r S'^\circ > 0$). The host and guest involved in the formation of an inclusion complex lose most of their degrees of freedom: this is accompanied by a strong entropy loss which masks the entropy gain due to the desolvation of the species upon binding and, as a result, the process is enthalpy-driven. In the cases

studied here, the pentyl chain gives the most favourable fit of the cavity. The addition of a functional group on the pentyl chain essentially modifies the entropy of binding. As a result, the affinity is more important for the species that bear groups that are more strongly desolvated upon binding: for instance, the affinity for Pen–NH_3^+ is more important than that for Pen–OH because the NH_3^+ group is involved in ionic interactions with the SO_3^- groups of the host and is thus desolvated whereas the OH group remains in the solvent.

Whereas purely ionic binding such as that observed between Ca^{2+} or La^{3+} and host **1** is characterized by $\Delta_r H'^\circ > 0$ and $T\Delta_r S'^\circ \gg 0$, due to the desolvation of the charged species, monovalent ions such as NH_4^+ and K^+ are not complexed because the entropic contribution associated with their dehydration is not sufficiently positive to compensate for the unfavourable enthalpic contribution. Whereas the ammonium ion is not complexed, the guanidinium ion is, the binding process being entropy-controlled ($\Delta_r H'^\circ < 0$ and $T\Delta_r S'^\circ \gg 0$). The difference between these two monovalent ions is explained by the involvement of the guanidinium ion in $\pi-\pi$ interactions with the phenyl units of the calixarene, which yields a favourable enthalpic contribution that exceeds the unfavourable enthalpy of dehydration. The fact that the process is entropy-driven shows, however, that the governing factor is the dehydration of the species.

The presence of three charged groups on the alkyl chain, as in lysine or arginine, makes the problem more complicated. However, comparison of the thermodynamic behaviour of the amino acids with that of simpler guests allows the driving forces to be identified. Our results clearly show that the binding of lysine or arginine by the *p*-sulfonatocalix[4]arene in water at pH 7.5 is governed by the inclusion of the alkyl chain of the amino acid into the host cavity. Besides, the fact that additional negative enthalpic and entropic contributions are observed upon binding of arginine shows that the guanidinium group of the amino acid is involved in $\pi-\pi$ interactions with the phenyl units of the calixarene.

A better understanding of these binding processes requires the determination of the structure of the complexes in solution. In order to do so, we are presently performing molecular dynamics simulations of some of these systems in aqueous solutions.

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