Stereochemistry and thermodynamics of the inclusion of aliphatic and aromatic anionic guests in a tetracationic calix[4]arene in acidic and neutral aqueous solutions†‡

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A cationic calix[4]arene derivative binds both aliphatic and aromatic anions in aqueous solution thanks to concerted electrostatic and hydrophobic interactions. ^{1}H NMR and potentiometric data show that the host flexibility changes as a function of pH. ^{1}H NMR and isothermal titration calorimetry (ITC) studies, also supported by ESI-MS data, show that inclusion yields supramolecular complexes of the guest$\subset$host type only. Binding becomes weaker as the pH increases due to rigidification of the host in neutral aqueous solutions, and is enthalpically favoured for all the supramolecular complexes, regardless of pH.

Introduction

One of the main goals of supramolecular chemistry is the synthesis and study of artificial receptors having both good affinity and high selectivity for guest molecules in water.[1] The reason for this lies mainly in the unique role of water in living systems. Water participates in solvation processes through ion-dipole and hydrogen bonding, and underlies the hydrophobic effect.[2] However, the unique properties of water pose a crucial problem: ideally, a good artificial receptor should have a high water solubility and yet make the most of non-covalent processes. The first requirement is hardly met by complex organic structures, and this explains why many artificial receptors have been studied in non-aqueous solvents.[3]

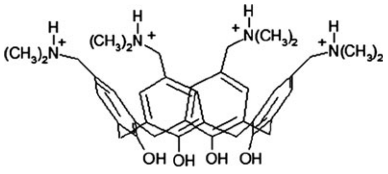
Thus, it is not surprising that whilst cation recognition in water has received much attention and is now a well-established area of supramolecular chemistry, the coordination chemistry of anions has experienced rapid development only in recent years,[4] even though anions are almost ubiquitous, especially throughout biological systems. Molecules such as DNA, ATP and phospholipids are all anionic under physiological conditions; pollutants, such as phosphate-containing pesticides that have been blamed for eutrophication, are also anionic.[5] The synthesis of artificial anion receptors, that took its first steps from the pioneering work of Park and Simmons,[6] and received new impetus following the work of Lehn *et al.*,[7] is particularly challenging for a series of reasons.[8] In fact, (i) *ceteris paribus*, the charge-to-radius ratio is lower for anions than for cations, (ii) the geometry of anions differs markedly from anion to anion, (iii) anions may be highly solvated and (iv) anions are often sensitive to pH, which leaves a narrow window for their recognition.

Even more challenging is the synthesis of receptors that can be used in water, as testified by the comparatively limited number of papers dealing with molecular recognition in this solvent.

Calixarenes fit the purpose as they are available in a wide variety of geometries and may be turned into water soluble entities with relative ease. Amide,[9] polyamine or polyammonium[10] calixarene-based receptors have been employed for anion coordination. Since their strength and selectivity of complexation depends both on electrostatic interactions (charge) and structural effects (topology and/or dimensions),[11] they may be optimized by conveniently arranging the binding groups on a calixarene-based scaffold of suitable size and shape.[12]

However, to date, the recognition of anions in water by this class of receptor has not been explored as widely as for cations.[13] In the present study, we have focused our attention on 5,11,17,23-tetrakis-[(dimethylammonium)methyl]-25,26,27,28-tetrahydroxy-calix[4]arene[14] (H_8L^{4+}) (Scheme 1), which lends itself to the complexation of anionic guests in aqueous solution.

To the best of our knowledge, this host has been shown to only include neutral aromatic guests in aqueous solution under fairly acidic conditions (pD 1.4),[15] and has been reported to exist as a zwitterion in organic solvents through indirect



Scheme 1

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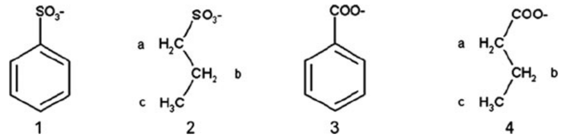

Scheme 2

evidence.[14] However, no detailed study has ever been performed in plain water. In the present paper, we report the results of combined potentiometric, ^1H NMR and isothermal titration calorimetry (ITC) studies on the host, with the intention of evaluating its acid–base properties, conformational behaviour and capability of complexing selected anionic guests in water at pH values compatible with the existence of the guests in their anionic form (Scheme 2).

Results and discussion

Host characterization

Thermogravimetric and potentiometric analyses. Thermogravimetric analysis of the bare host showed that it lost weight up to 100 °C; no further loss was detected up to 220 °C. Above this temperature, decomposition took place in two steps; the solid was fully decomposed (weight loss 100%) by the time the crucible reached 500 °C, and the thermogram remained practically flat up to the maximum temperature reached in our experiments (800 °C). All the above observations indicate that (i) the solid contains unbound water only (*ca.* 10%) and (ii) the solid does not contain inorganic compounds; this makes the compound suitable for potentiometric analysis. It is noteworthy that the ligand impurity determined by potentiometry (9%)[16] is of the same order of magnitude as that determined thermogravimetrically (10%). The potentiometric analysis also showed that the host (H_8L^{4+}) may loose up to two protons in the pH range explored,[17] the pK_{a1} and pK_{a2} values being 3.29 and 8.15, respectively, resulting from the deprotonation of the OH group of the lower rim and one of the four ammonium groups located in the upper rim (Fig. 1).

Further support for the existence of this species in aqueous solution was provided by electrophoretic experiments, which may be found in the ESI.‡

Interestingly, the hydroxyl pK_{a1} value is very close to that of the analogous *p*-tetrasulfonate anionic derivative.[18] The "unusual" acidity of the phenolic group of H_8L^{4+} shows that the strong intramolecular hydrogen bond between the phenolate and the three phenolic units of the lower rim is independent of the nature of the substituents present on the upper rim of the calix[4]arene scaffold.[18] Unfortunately, the precipitation that occurs following the deprotonation of the first ammonium group prevents a detailed analysis of the acid–base characteristics of the upper rim groups. However, the potentiometric study showed that the energetics of guest inclusion can only be investigated in buffered solutions to avoid also taking into account the protonation/deprotonation heat contribution, resulting from proton exchange with the ligand, which is beyond the scope of the present study.

^1H NMR experiments. The signals of the host recorded for a series of solutions of increasing concentration remained practically unchanged, which leads to the exclusion of micelle formation within the concentration range explored (5×10^{-4}–1.5×10^{-2} mol dm^{-3}). The ^1H NMR analysis of the host at pD 2.3 and 7.1 was consistent with the structural symmetry of the cone macrocyclic scaffold.

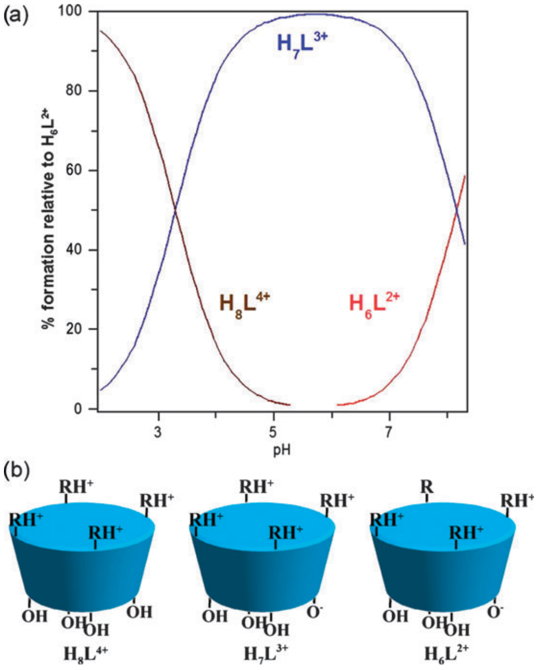

Fig. 1 (a) Distribution diagram for the protonation of the host (C_{host} = 3.5×10^{-3} mol dm^{-3}). (b) A schematic representation of the species existing in the different pH regions.

The signal of the methylene bridge (Ar–CH_2–Ar) changed with pH; the singlet detected under acidic conditions (Fig. 2a) turned into a peak that became so broad under neutral conditions (Fig. 2b) that it was hardly distinguishable from the baseline.

The singlet detected at pD 2.3, where the receptor is fully protonated (Fig. 1) and exists as H_8L^{4+}, indicates that the host rapidly interconverts between two identical cone conformations. Under neutral conditions, the marked broadening of the signal of the methylene bridge protons indicates that the cone-to-cone interconversion of the calix[4]arene scaffold is hampered to some extent by the loss of the first proton: the negative charge resulting from the deprotonation of one phenolic unit enhances the lower rim intramolecular hydrogen bond. This accounts for the unusual acidity of the phenolic unit that is now well established for the analogous sulfonate (anionic) derivative.[18,19] On the other hand, if the first deprotonation step were to involve a cationic ammonium group, this would cause a significant upfield shift of the signals of both the methyl and methylene protons bound to the nitrogen atom. Since there is no ^1H NMR evidence for these shifts, pK_{a1} may only refer to the dissociation of one of the phenolic hydroxyl groups.

Guest inclusion

^1H NMR. The interaction of the host with the anions shown in Scheme 2 was studied by ^1H NMR titrations in deuterated,

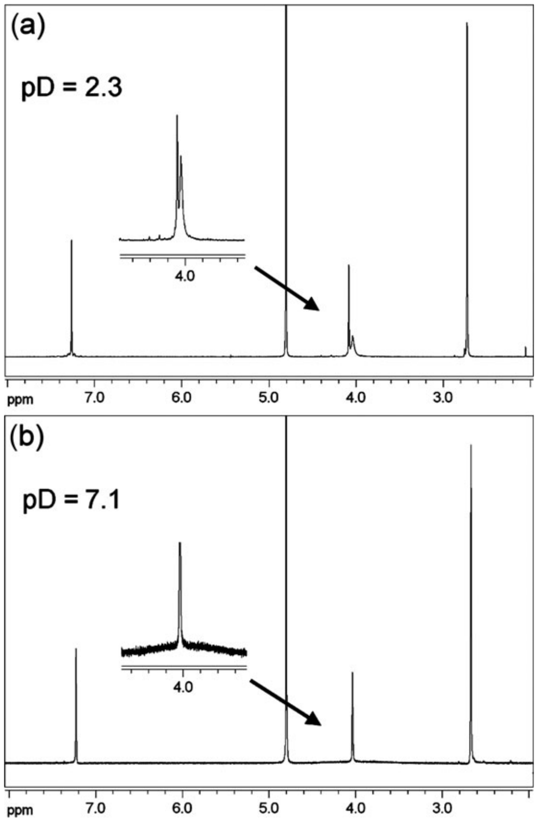

Fig. 2 ^1H NMR spectra of the host at (a) pD 2.3 and (b) 7.1 in D_2O at 25 °C.

buffered aqueous solutions[20] to determine both the stereochemistry of their inclusion and their binding constants. The sulfonates were studied both under acidic and neutral conditions, while the investigation of the carboxylates was restricted to pD 7.1, where the guests exist as anions.

Upon inclusion, the guest proton signals shift to higher fields; for example, Fig. 3 shows how the signals of the benzoate protons shifted to higher fields with increasing host concentration.

The $\Delta\delta_{max}$ ($\Delta\delta_{max}$ is equal to $\delta_{complex} - \delta_{free\ guest}$) values for the inclusion of the guests investigated are shown in Table 1.

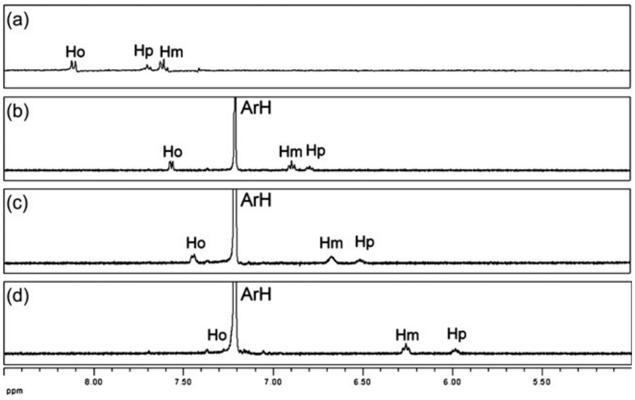

Fig. 3 ^1H NMR titration spectra for the H_7L^{3+}/benzoate system at pD 7.1; (a) uncomplexed guest, $C_{host}/C_{benzoate}$ = (b) 1.86, (c) 3.67 and (d) 8.00, respectively.

Table 1 $\Delta\delta_{max}$ for the CIS in D_2O at pD 2.3 and 7.1

		$\Delta\delta_{max}$[a]	
Guest	Proton	pD 2.3	pD 7.1
1	*ortho*	−1.41(1)	−1.30(1)
	meta	−2.51(1)	−2.36(2)
	para	−3.47(1)	−3.29(2)
2	a	−1.02(1)	−0.82(5)
	b	−1.25(1)	−0.95(6)
	c	−2.12(1)	−1.55(9)
3	*ortho*		−1.11(2)
	meta		−2.04(3)
	para		−2.61(4)
4	a		−0.48(2)
	b		−0.63(2)
	c		−0.88(3)

[a] σ are given in parentheses.

The inclusion is fast on the NMR timescale and, thus, guest signals are detected as single (time-averaged) resonances due to rapid exchange between the free and complexed species. The complexation induced shifts (CIS) provide details on the arrangement of the guests within the host cavity.

The signals attributed to the protons of **3** shift markedly to higher fields ($H_p > H_m > H_o$), indicating that the organic moiety of the aromatic guest is included in the cavity of the host.

For the alkyl derivatives, such as **4**, the $\Delta\delta_{max}$ sequence follows the order $H_c > H_b > H_a$; this shows that aliphatic guests are also included in the hydrophobic pocket of the host, with the charged group pointing outward.

The binding mode is corroborated by molecular modeling, which leads to the optimized structures shown in Fig. 4.

This figure shows that the guests are included in the apolar cavity of the calix[4]arene with their anionic portion tilting towards its (positively charged) rim; this electrostatic interaction assists the π–π (benzoate) or CH–π (butanoate) interactions. Such assistance is well documented for the inclusion of polar and cationic guests into anionic calixarenes.[21]

The trend of upfield shifts, as well as CIS, in sulfonate anions **1** and **2** is similar to that of the analogous carboxylate guests, indicating that their inclusion takes place through the same binding mode.

All the guests are included thanks to concerted hydrophobic and electrostatic effects, resulting from π–π or CH–π interactions, and from an electrostatic interaction between the anionic portion of the guest and the positively-charged groups of the host. It is worth noting that the $\Delta\delta_{max}$ values for **1** and **2** (Table 1) are greater in acidic conditions than in neutral conditions.

Both sulfonate anions are characterized by a binding strength that decreases with increasing pD. The greater flexibility of the host (H_8L^{4+}) in acidic conditions allows the hydrophobic portion of guests to be better accommodated; in other words, the hydrophobic interaction is maximized when the host fits better the geometrical requirements of the guest, thanks to its enhanced conformational flexibility.

In any case, the chemical shifts may be satisfactorily fitted to a 1 : 1 binding model, regardless of the nature of the guest included and the pD value (see the Energetics of inclusion

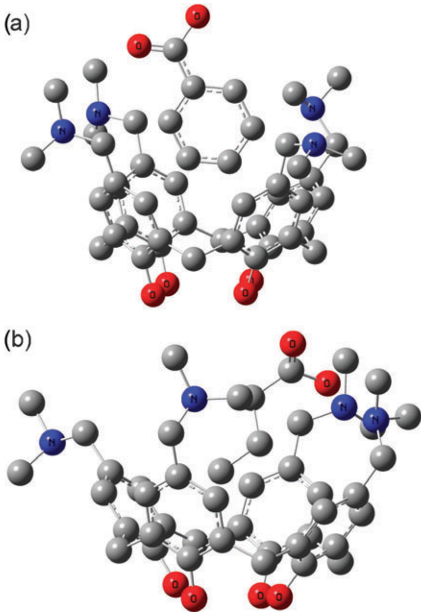

Fig. 4 Optimized structures for the inclusion of (a) **3** and (b) **4** in the host.

section). The existence of guest$\subset$host species having a 1 : 1 stoichiometry is further supported by the ESI-MS results (see ESI‡).

Energetics of inclusion. Inclusions were studied in buffered solutions to minimize the contribution resulting from the interaction (association/dissociation) of the host with the proton. In analogy with ^{1}H NMR measurements, the inclusion of benzenesulfonate (**1**) and 1-propanesulfonate (**2**) was studied calorimetrically at two different pH values (namely 2.0 and 6.8); benzoate (**3**) and butanoate (**4**) were studied at pH 6.8 only, since at pH 2.0, the concomitant and different degrees of protonation of the carboxylate residue (benzoate: pK_a = 4.20 and ΔH = 0.15 kJ mol^{-1}; butanoate: pK_a = 4.88 and ΔH = −0.18 kJ mol^{-1})[22] of these two guests would contribute to the overall heat to different extents. A typical enthalpogram is reported in Fig. 5.

ITC confirmed the picture outlined by NMR concerning both the model and the binding constant values. In fact, the calorimetric study showed that all the systems presented here may be modelled by taking into account 1 : 1 species only. In addition, the binding constants determined *via* ITC reproduced the values obtained by NMR (Table 2), provided due allowance was made for the different experimental procedures and conditions employed.[23] The relatively large error associated with the thermodynamic values of **2**$\subset$host and **4**$\subset$host (host = H_7L^{3+}) at pH 6.8 can be ascribed to the small binding constants of these two complexes.

To the best of our knowledge, the log K values shown in Table 2 are among the first ever values to be obtained for the inclusion of organic anions into calix[4]arenes in pure water, and as such, are hardly comparable with literature data. In fact, though the host has previously been employed by Baur *et al.*,[15] the data concerned the inclusion of non-polar guests and were obtained under slightly different experimental conditions (pD 1.4; *ca* 1% of methanol was added to the aqueous solution). More recently, the binding constants for the interaction of citrate and the aminodiacetate derivative of 1,8-naphthalimide with a calix[4]arene bearing imidazolium pendants in plain water (800 ± 200 and 4200 ± 150 mol^{-1} dm^3 for citrate and the 1,8-naphthalimide derivative at pH 7, respectively) have been reported.[24] These values cannot be straightforwardly compared with our values either, since the two anions are not reported to be included but are suggested instead to form a 1 : 1 species *via* "peripheral complexation near the upper rim of the host, presumably driven by weak electrostatic and hydrogen bonding interactions between the carboxylate and imidazolium groups".

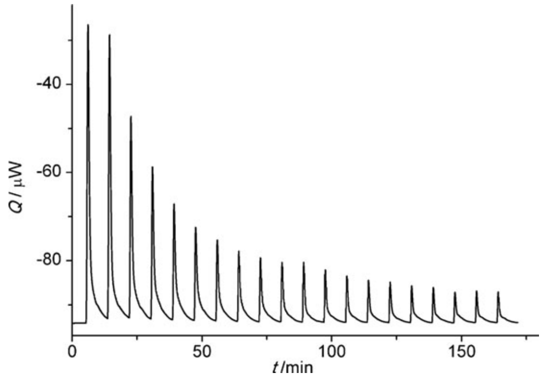

Fig. 5 The isothermal calorimetric titration of **3** into a solution of H_7L^{3+} at pH 6.8 and T = 25 °C.

In any case, the ΔH° and ΔS° values reported by us are the first ever obtained for the inclusion of organic anions into calix[4]arenes in plain water. Splitting the stability constant values into enthalpic and entropic terms reveals that the real situation is more complex than that indicated by the binding constants alone (Fig. 6).

Formation of the supramolecular assemblies is enthalpically favored, regardless of the pH, anionic function and the aliphatic or aromatic nature of the guest. Aromatic guests are better included than their analogous aliphatic anions, regardless of pH, and their larger stability constants result from a larger enthalpic contribution. Clearly, the π–π interactions taking place in the aromatic guest$\subset$host assemblies is more effective than the CH–π interactions taking place in the aliphatic guest–host complexes.[25]

It is also interesting to note that the stability of both the benzenesulfonate and the propanesulfonate adducts at pH 2.0 is larger than that measured at pH 6.8 by *ca.* 0.5 log K units. The greater flexibility of the host at pH 2.0 most likely allows better accommodation of the guest at this pH. This shows that "plasticity" rather than pre-organization may be the key to self-organization.[26] However, a closer look at the related thermodynamic quantities reveals that such a difference results from a combination of factors. Propanesulfonate inclusion is favored both enthalpically and entropically at both pH values. The inclusion of benzenesulfonate, while still being enthalpically-driven at both pH values, has an unfavorable entropic contribution at pH 6.8. In the benzenesulfonate$\subset$host assembly, the enthalpic difference, due to the differing flexibility of the host at acidic and neutral pHs, which is fairly evident in the propanesulfonate$\subset$host assembly, is probably

Table 2 Log *K* values and thermodynamic parameters for the host–guest complexes[a]

		NMR	ITC		
Guest	pH	Log *K*	Log *K*	$\Delta H°$/kJ mol^{-1}	$\Delta S°$/J K^{-1} mol^{-1}
1	2.0	3.09(1)	3.03(8)	−16.79(2)	2(2)
	6.8	2.44(1)	2.38(1)	−15.28(1)	−5.7(3)
2	2.0	2.24(2)	2.0(2)	−10.36(1)	3.5(3)
	6.8	1.66(1)	1.54(4)	−6.23(2)	8.7(6)
3	6.8	2.32(1)	2.16(1)	−12.51(1)	−0.5(2)
4	6.8	1.50(2)	1.2(3)	−1.2(2)	20(5)

[a] σ are given in parentheses.

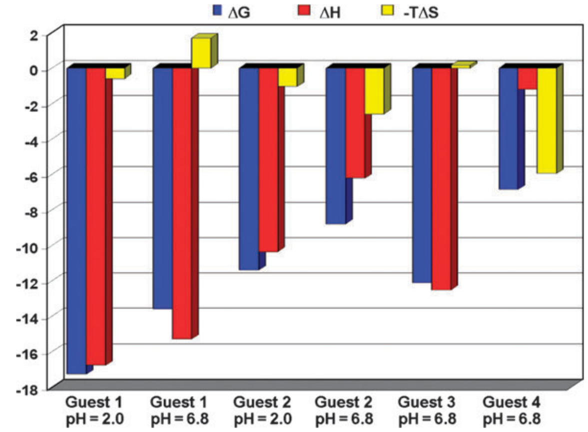

Fig. 6 Thermodynamic parameters for the inclusion of **1**, **2**, **3** and **4** at 25 °C in water.

levelled-off by the strong enthalpy contribution due to the π–π interaction.

Concluding remarks

In conclusion, we have shown that both aliphatic and aromatic guests are included in the tetracationic host depicted in Scheme 1, thanks to concerted hydrophobic (π–π or CH–π) and electrostatic interactions. The $\Delta H°$ and $\Delta S°$ values obtained in our ITC study reveal specific molecular interactions that are not expressed in the log *K* values. The inclusion process is enthalpically favored, regardless of the nature of the guest and the anionic function, and its strength changes with pH due to the varying conformational flexibility of the calix[4]arene scaffold at acidic and neutral pHs. Our data also indicate that better inclusion of the aromatic guest can be ascribed to stronger (enthalpy favored) π–π interactions, and that such interactions prevail over the opposing the pH-dependent stiffening of the receptor. Other systems are currently being investigated, the inclusion of which may be tuned as a function of pH, and that will hopefully also change more markedly with pH.

Experimental

Materials

The host was obtained according to the procedure described by Gutsche and Nam.[14] Its purity was checked, both by potentiometric and thermogravimetric measurements.

Cone-5,11,17,23-tetrakis(*N*,*N*-dimethyl)ammoniummethyl-25,26,27,28-tetrahydroxy-calix[4]arene tetrachloride (yield 79%): δ_H (500 MHz, D_2O, pD = 2.3, 25 °C): 7.26 (s, 8H, Ar–*H*), 4.08 (s, 8H, Ar–CH_2–N), 4.04 (s, 8H, Ar–CH_2–Ar) and 2.73 (s, 24H, $N(CH_3)_2$).

Tetracationic cone-5,11,17,23-tetrakis(trimethylammonium)-25,26,27,28-tetrapropoxy-calix[4]arene, employed as a reference compound for the electrophoresis experiments, was prepared as described in ref. 17.

Stock solutions of nitric acid and sodium hydroxide, employed for the potentiometric measurements, were standardized with tris(hydroxymethyl)aminomethane and potassium hydrogen phthalate (both Merck primary standards), respectively. The guests and all the chemicals used to buffer the solutions were obtained from Sigma-Aldrich and used as received, after drying. Thin layer chromatography (TLC) was carried out on silica gel plates (Merck 60, F254) and column chromatography was carried out on silica gel 60 (Merck, 0.063–0.200 mm). All reactions were carried out under a nitrogen atmosphere unless otherwise stated. High purity water (Millipore, Milli-Q Element A 10 ultrapure water) and A grade glassware were employed throughout. ESI mass spectra were recorded on a HP 1100 Series LC/MSD spectrometer.

^1H NMR spectroscopy

^1H NMR spectra were recorded in D_2O at 25 °C using a Varian Inova 500 spectrometer. Chemical shifts (δ) are expressed in ppm and referenced to residual undeuterated solvent. NMR data were processed using MestReC software (http://www.mestrec.com).

For the inclusion studies, different aliquots of a standard host solution were added to guest solutions having the same concentration (10^{-3} mol dm^{-3}, 10^{-1} mol dm^{-3} phosphate buffer, D_2O). The host : guest ratio ranged from 0.5 : 1 to 12 : 1 to ensure that the amount of complex formed ranged from 20 to 80% of the guest. The binding constant values were obtained by measuring the chemical shifts of the protons of the guests as a function of the host : guest ratio. The complexation-induced shift data (CIS) were treated using HyperNMR (see the Calculations section). Several models were taken into consideration but, except for the 1 : 1 model, were always rejected by the program.

Modeling

Molecular modeling calculations were performed in two steps. In the first, the atomic charges of each single molecule were calculated by the PM6 method (Mopac 2007™; http://openmopac.net/mopac2007.html). In the second step, the host, as well as the anions, were inserted into boxes containing 500 water molecules and minimized (Hyperchem™ 7.5 molecular modeling software, trial edition; Molecular Mechanics, amber force field; http://www.hyper.com). Finally, the anions were included into the calixarene, and the resulting complexes inserted into a box containing 500 water molecules and minimized (algorithm: Polak-Ribière, conjugate gradient; termination condition = 0.01 kcal Å^{-1} mol^{-1}).

EMF measurements

Potentiometric measurements were carried out by means of two home-assembled fully automated apparatus sets (Metrohm components: E654 meter, E665 dispenser, combined micro pH glass electrode) controlled by appropriate software and set up in our laboratory. Values of E°, E_j, K_w and the Nernstian slope of the electrodic system were determined in separate experiments by titrating nitric acid with CO_2-free sodium hydroxide. To determine the protonation constants, solutions of the ligand with concentrations ranging from 2.7 to 3.7 × 10^{-3} mol dm^{-3} were titrated with 0.1 mol dm^{-3} sodium hydroxide (pH range: 2.5–8.2). Seven independent runs were collected, each run comprising 60–70 points. The initial pH was always adjusted to 2.5. The onset of precipitation was hardly detectable by the naked eye but was clearly indicated by the constant drifting of the meter reading, which started at around pH 8.15–8.20. To avoid systematic errors and verify reproducibility, the EMF values of each experiment were read at different time intervals. All measurements were carried out at 25.0 ± 0.1 °C under an atmosphere of argon. The ionic strength was maintained at 0.1 mol dm^{-3} (sodium nitrate).

Thermal analysis and calorimetric measurements

Thermogravimetric analysis of the host was carried out using a Perkin-Elmer TGS-2 instrument. Typically, host samples (*ca.* 2 mg) were heated under a controlled atmosphere (air) from 50 to 800 °C (heating rate 10 °C min^{-1}).

The isothermal titrations were carried out by using a TA ITG2 nano-calorimeter equipped with a 250 μL injection syringe. All titrations were run in overfilled mode, and thus the heat generated does not require any correction, either for liquid evaporation or for the presence of the vapor phase. The power curve was integrated using NanoAnalyze (TA Instruments) to obtain the gross heat evolved in the reaction. The calorimeter was calibrated before and after each run by introducing known power values through built-in precision resistors. Solutions containing the appropriate guest (*ca.* 2 × 10^{-1} mol dm^{-3}) were added to a solution of the host (1–2 × 10^{-3} mol dm^{-3}). The net heat of the reaction was calculated by subtracting the heat evolved/absorbed during blank experiments, in which the titrant was added to a solution containing the same chemicals as the reaction run, except for the host. The total number of data points for each guest–host system ranged from 50 to 60.

Calculations

To obtain protonation constants, the potentiometric data were refined using Hyperquad,[16] which minimizes the error square sum of the measured electrode potentials and also allows for the simultaneous refinement of data from different titrations. Log β and ΔH values for the inclusion processes were obtained by HypΔH (http://www.hyperquad.co.uk/hypdeltah.htm), a routine of the same software, through a non-linear iterative refinement of the sum of the squared residuals, U,

$$U = \Sigma(\Delta H_{\text{corr}} - \Delta H_{\text{calc}})^2$$

where ΔH_{corr} and ΔH_{calc} are the observed evolved heats (corrected for blank effects) and the calculated heats, respectively. HyperNMR (http://www.hyperquad.co.uk/hypnmr.htm) was employed to fit the chemical shifts obtained by ^{1}H NMR spectroscopy.

Acknowledgements

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