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Water-soluble calix[6]arenes. Characterization of 5,11,17,23,29,35-hexasulphonate-37,38,39,40,41,42-hexahydroxycalix[6]arene and thermodynamic study of proton complex formation ☆

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Abstract

The title compound, synthesized by modifying the procedure described in literature, was characterized by NMR, IR, TG, LSIMS, ICP-AES and potentiometry, and found to be an octasodium salt. Its protonation constants were determined in aqueous solution at 25°C and $I = 0.1$ mol dm^{-3} ($NaNO_3$) and compared with literature data determined under similar conditions. Enthalpy and entropy values, determined calorimetrically under the same experimental conditions employed for the potentiometric measurements, together with NMR results, provide a detailed picture of the processes taking place in aqueous solution.

Keywords: Aqueous solution; Calixarenes; Calorimetry; Stability constants

1. Introduction

Considerable interest is currently being taken in a class of phenol–formaldehyde cyclic oligomers, usually known as calixarenes [1–3]. These macrocyclic receptors possess hydrophobic cavities capable of including molecular guests in solution [4] as

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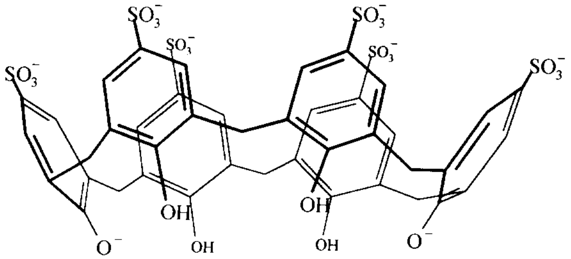
well as in the solid state [5]. Although other macromolecular systems, as for example cyclodextrins [6], also have a tridimensional cavity, calixarenes offer some advantages; in fact they (i) can be synthesized with relative ease [1] and (ii) can also adopt different conformations [7], that can be blocked in different ways [8, 9], thus offering new molecular architectures for selective recognition. Thus, calixarenes have drawn researchers' attention as to their potential use as building blocks for biomimetic systems [2]. Special effort has been devoted to the synthesis of water-soluble calixarenes [10], not only in connection with their use as models for synthetic enzymes, but also in view of their use as receptors for the selective complexation of metal ions [11] and for the inclusion of guest molecules in aqueous media [12]. Water-soluble calixarenes have also been employed to perform supramolecular catalysis in aqueous media [13].

A knowledge of the acid–base properties of these molecules is fundamental to the design of more sophisticated calixarene-based molecular devices. In connection with our previous studies on the proton complex formation of water-soluble *p*-sulphonated calix[4]arenes [14, 15], it seemed to us of interest to evaluate the influence of a greater conformational flexibility on the acidity of these ligands. Indeed, previous ^{1}H NMR studies [16] have pointed out that the coalescence temperatures concerning the conformational interconversion are lower for calix[6]arenes than for the analogous calix[4]arenes. To achieve useful information about the energetics governing the protonation process in aqueous solution, we carried out a potentiometric and calorimetric study of the protonation of 5,11,17,23,29,35-hexasulphonate-37,38,39,40,41,42-hexahydroxycalix[6]arene octasodium salt, **1**, (calix[6]arene-*p*-hexasulphonate) in the pH range 2.5–9.0 at $I = 0.1$ mol dm^{-3} ($NaNO_3$) and $T = 25$°C.



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2. Experimental

2.1. Materials

Calix[6]arene-*p*-hexasulphonate octasodium salt, **1**, was synthesized both according to the method described by Scharff et al. [17] and by modifying the procedure described by Shinkai et al. [18]. For a typical synthesis of the compound in its salt form, 1 g of 37,38,39,40,41,42-hexahydroxycalix[6]arene (1.57 mmol) was suspended in about 10 ml of sulphuric acid (96%) and the reaction mixture was kept at 80°C for

3 h under magnetic stirring. The reaction progress was monitored by checking the solubility in water of a small aliquot. The reaction was considered to be complete when no water-insoluble material was detected. After cooling, the mixture was filtered by a porous sect. The precipitate was dissolved in about 50–100 ml of water and filtered to eliminate any water-insoluble material. $Ba(OH)_2$ (saturated solution) was added to the solution until a pH of 5–6 was obtained; after digestion, $BaSO_4$ was eliminated by filtration. The solution was evaporated to dryness. The remaining powder was dissolved in 50 ml of water and filtered again to eliminate any water-insoluble material. Na_2CO_3 (0.4 N) was added until the solution reached pH = 9. After digestion, $BaCO_3$ was filtered off. The solution was treated with active charcoal and the filtrate concentrated in vacuo. The remaining white powder was dissolved in water, and filtered in order to eliminate any water-insoluble material. The filtrate was treated with active charcoal once again. The pH of the solution was adjusted to 3 by adding HNO_3 (0.2 N). The solution was maintained at 100°C for 4 h; N_2 was bubbled through. The volume of solution was reduced to about 10 ml. The pH was adjusted to 6.5–7 with NaOH (0.1 N) and the resulting solution was evaporated until the volume was reduced to 1–2 ml. Addition of ethanol caused the formation of a white precipitate that was filtered, washed twice with ethanol and dried under vacuum at 70–80°C for 6 h (yield: 50%). TLC (SiO_2): single spot on thin-layer chromatography (1-propanol:water:ethyl acetate:ammonia (30%) = 5:3:2:1 *v/v*); m.p. > 270°C; Anal. Cal. for $C_{42}H_{28}O_{24}S_6Na_8 \cdot 12H_2O$: C 33.43, H 3.47, S 12.75, Na 12.19; found: C 33.50, H 3.40, S 12.70, Na 12.20. The sodium content was also confirmed by ICP-AES (Perkin-Elmer ICP/6500 XR) working at both 589.0 and 589.6 nm. Accordingly the product will be described as an octasodium salt hereafter. The compound was also characterized by IR, LSIMS, TG and NMR.

Tris(hydroxymethyl)aminomethane (THAM) and potassium hydrogen phthalate (Merck — primary standards) were used to titrate HNO_3 and NaOH stock solutions, respectively. The ionic strength of all the solutions used for both the potentiometric and calorimetric investigations was adjusted to 0.1 mol dm^{-3} by adding the appropriate amount of $NaNO_3$. Doubly distilled water was used throughout.

2.2. E.M.F. measurements

The potentiometric measurements were carried out by means of two fully automated sets of apparatus. These are home-assembled by making use of Metrohm parts (meter, E 654; combined glass electrode, EA 125; dispenser, E 665) and are controlled by an appropriate software written in our laboratory. Resorting simultaneously to both apparatuses minimizes the risk of collecting data affected by systematic errors.

Value of E°, junction potential (E_j), K_w and Nerntian slope of the electrode system were determined by titrating HNO_3 with CO_2-free NaOH ($pH = -\log[H^+]$). The determination of these parameters in ad hoc experiments, rather than in the same experiment performed for the determination of stability constants, avoids refinement of several parameters in the same run, which could lead to error compensation. All measurements were performed at 25.0 ± 0.1°C and under

Table 1
Experimental conditions used for potentiometric measurements on calix[6]arene-*p*-hexasulphonate at 25 °C and $I = 0.1$ mol dm^{-3} ($NaNO_3$)

C_L°/(mmol dm^{-3})	Titrant NaOH/(mol dm^{-3})	pH range	No. of points
2.6	0.1003	2.5–9.0	30
1.6	0.0671	2.5–9.0	49
1.8	0.0671	2.5–9.0	34
3.4	0.0671	2.5–9.0	38
3.5	0.0671	2.5–9.0	40
3.5	0.0671	2.5–9.0	66
3.8	0.0671	2.5–9.0	36
4.9	0.1009	2.5–9.0	39
4.8	0.1009	2.5–9.0	60
3.4	0.1009	2.5–9.0	42
5.1	0.1009	3.0–9.0	41
5.3	0.1016	2.5–9.0	40
4.4	0.0995	2.5–9.0	55
4.9	0.0995	2.5–9.0	61
5.5	0.0995	2.5–9.0	63
4.0	0.1009	2.5–9.0	33
4.1	0.1009	2.5–9.0	48

nitrogen. Experimental details for the potentiometric measurements are given in Table 1.

2.3. Calorimetric and TG measurements

Most of the calorimetric measurements were performed using a Tronac 450 isoperibolic calorimeter; to avoid systematic errors we also performed two experiments with a LKB TAM equipped with a 2.5 mL stainless steel cell. All the measurements were performed at 25 °C ± 0.001 and ± 0.0002 for the Tronac and LKB calorimeter, respectively. The calorimeters were calibrated both chemically (from time to time) and electrically (twice for each single run) to check for accuracy and reproducibility. The chemical calibration was performed by titrating a solution of tris(hydroxymethyl)-aminomethane with HNO_3. The ΔH° obtained (-47.45 kJ mol^{-1}) for THAM is in good agreement with the value reported in literature [19]. The contribution of non-chemical energy terms (heat of friction, heat of dilution) was determined in separate experiments. The data, collected for the determination of the ΔH° of protonation of calix[6]arene-*p*-hexasulphonate, were corrected for all non-chemical energy terms and refined simultaneously to obtain the final ΔH° values. Details of the calorimetric measurements are given in Table 2.

Thermogravimetric data were obtained by means of a Mettler TA 3000 (sensitivity $= 2.5 \times 10^{-6}$ g). The measurements were carried out by heating samples of about 10 mg mass at 10 K min^{-1} in air from room temperature up to a final temperature of 900 °C.

Table 2
Experimental conditions used for calorimetric measurements on calix[6]arene-*p*-hexasulphonate at 25°C and $I = 0.1$ mol dm^{-3} ($NaNO_3$)

C_L°/(mmol dm^{-3})	Titrant/(mol dm^{-3})	pH range	No. of points
8.5	HNO_3 0.5036	2.5–5.2	22
8.5	HNO_3 0.5036	2.5–5.2	27
4.0	HNO_3 0.5036	2.5–5.2	31
4.5	HNO_3 0.5036	2.5–5.2	25
5.4	NaOH 0.2486	2.5–5.2	20
3.5	HNO_3 0.1919	2.5–5.2	8
3.7	HNO_3 0.1919	2.5–5.2	9

2.4. *Calculations*

Calculations concerning the calibration of the electrode system (E°, E_j, K_w) as well as the refinement of protonation constants were performed by the program SUPERQUAD [20] that refines the error squares sum based on measured electrode potentials.

The enthalpies of protonation were calculated by means of the least squares computer program DOEC [21] which minimizes the function $U = \Sigma_i(Q_{i,calc} - Q_{i,exp})^2$, where Q_i is the heat of reaction of the *i*-th point.

2.5. *IR spectra*

IR spectra were obtained in KBr by means of a Perkin-Elmer 684 infrared spectrophotometer.

2.6. *LSIM spectra*

The mass spectra were acquired by means of a double-focusing Kratos MS 50S equipped with the standard LSIMS source and a DS90 data system. The caesium ion gun was operated at 20 keV. The instrument was scanned from *m/z* 3000 to 100 with a scan rate of 10 s decade^{-1}. The accelerating voltage was 8 kV. LSIM spectra were obtained both in positive and negative mode using thioglycerol/glycerol as matrix. Caesium iodide was used to calibrate the instrument.

2.7. *NMR spectra*

NMR spectra were obtained in D_2O at 25°C with a Bruker AC-200 spectrometer. Chemical shifts (δ, ppm) were externally referenced to sodium 2,2-dimethyl-2-silapentane-5-sulphonate (DSS) in order to avoid any possible interaction with the calix[6]arene-*p*-hexasulphonate.

Other experimental details can be found elsewhere [14, 15, 22].

3. Results and discussion

The IR spectrum of calix[6]arene-*p*-hexasulphonate shows the OH stretching (ν_{OH} 3450 cm^{-1}) and the asymmetric and symmetric S = O stretching (ν_{SO}, 1175 and 1045 cm^{-1}, respectively) frequencies. These data are consistent with the salt form for the sulphonate groups of compound **1**, although they are slightly different from those obtained by Shinkai [18] for the hexasodium salt of the same product.

The mass spectra of compound **1** (Fig. 1) were consistent with the theoretical molecular weight of 1293 g mol^{-1} for the octasodium salt.

The ^1H NMR spectrum of compound **1** exhibits a sharp singlet (δ 7.51, 12 H) for benzene protons. Also the Ar-CH_2-Ar methylene protons show a sharp singlet only (δ 3.95, 12 H), which is indicative of conformational flexibility of the compound at room temperature. A slight upfield shift of both signals is observed with respect to the values previously reported for calix[6]arene-*p*-hexasulphonic acid [17] and for calix[6]arene-*p*-hexasulphonate [18].

The thermogravimetric analysis of calix[6]arene-*p*-hexasulphonate (Fig. 2) that, following the treatment described in the Experimental Section, is obtained as an octasodium salt, indicates that the compound starts losing water below 100°C; the water loss is complete below 200°C. The anhydrous compound undergoes decomposition above 270°C. This process takes place until above 500°C. Above this temperature a plateau is observed and no other loss is detected up to 900°C. A white residue remains in the cup at the end of the scan. The decomposition path of calix [6]arene-*p*-hexasulphonate resembles quite closely that observed by Scharff and Mahjoubi [23] for the analogous acidic derivative, although there are understandable differences as to both water content and residue left at the end of the run. The water loss (15 ± 0.5%; average of four runs) indicates that our product crystallizes with approximately 12 water molecules, whereas the analogous acidic product reportedly contains 16 water molecules [23]. Interestingly, the water content determined potentiometrically by making use of SUPERQUAD [20] is consistent with that determined thermogravimetrically. The analysis of the residue obtained by us, that amounts to 41 ± 2% (average of four runs) of the anhydrous product, shows this to be sodium sulphate (determined quantitatively by a turbidimetric method [24]). The agreement between found and calculated (44%) amount is good.

Log *K* values for the protonation of calix[6]arene-*p*-hexasulphonate are reported in Table 3. In the pH range investigated by us (i.e. 2.5–9.0) we only detected two titratable protons, the second of which totally dissociates above pH 6.5. Above this pH value, in fact, titration curves show a sharp potential jump and remain unbuffered for about 4 pH units. In the present study, only titration data of the buffered region below neutrality (pH 2.5–6.0) were considered. Accordingly, only the log *K* values concerning the last two protonation steps of phenolate groups are shown in Table 3. The log *K* values determined in the present study seem to be in good agreement with those reported by Scharff and Mahjoubi [23], although a significant comparison is not possible since the authors of ref. [23] omit to report the standard deviations associated with their values and do not give indications either on the number of experiments performed or on the number of data points collected. However, there is no question on

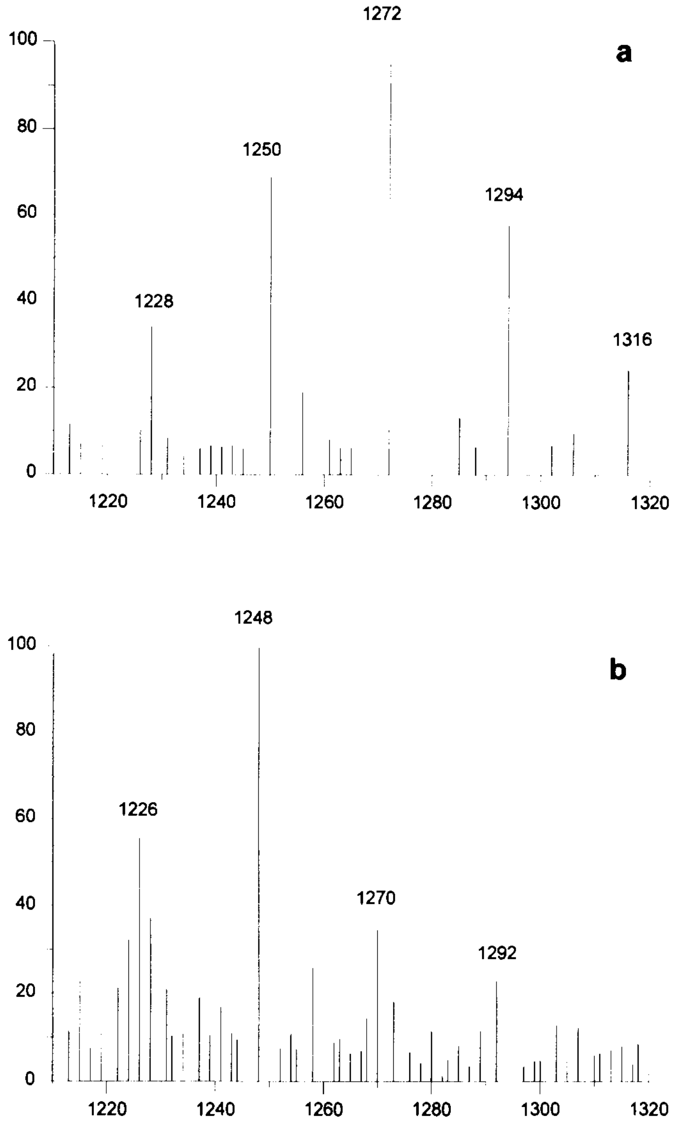

Fig. 1. LSIM spectra of calix[6]arene-*p*-hexasulphonate octasodium salt; (a) positive; (b) negative.

the number (namely 2) of hydroxyl groups that dissociate in the pH range 2.5–7.0. This, i.e. the number of protons that can be titrated below pH 7, had been a matter of great debate [23, 25, 26] for calix[4]arene-*p*-tetrasulphonate and was finally solved by our group [14] and also reconfirmed by Shinkai et al. [27].

In Table 3 we have reported the enthalpic and entropic changes associated with the last two protonation steps. Enthalpy values were obtained by direct calorimetry and are here reported for the first time; a typical calorimetric run is shown in Fig. 3. For

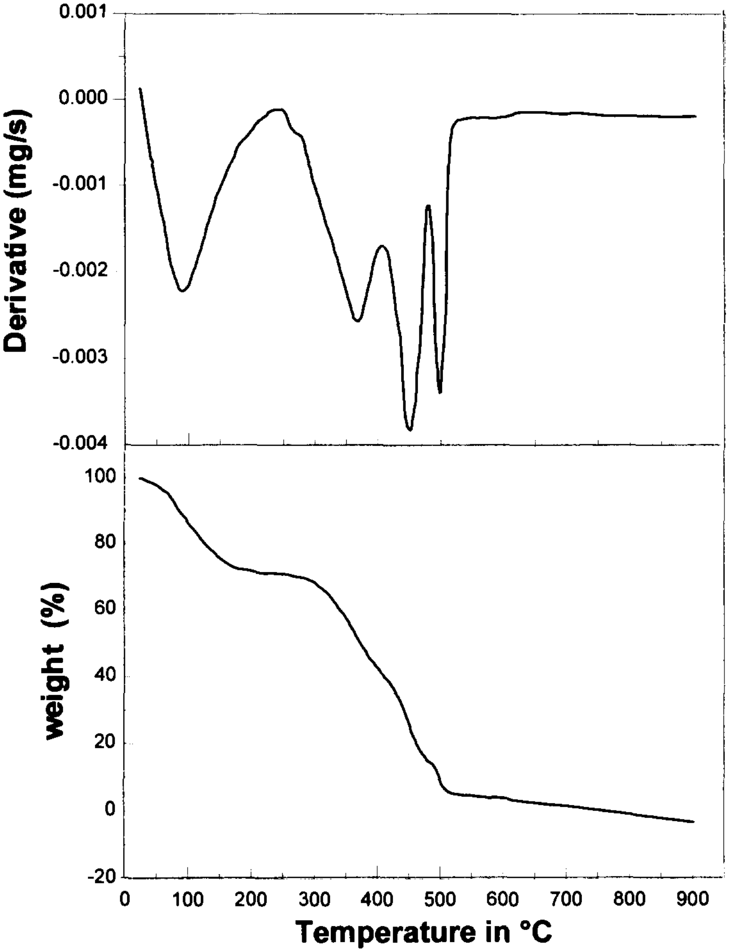

Fig. 2. TG and DTG curves for calix[6]arene-*p*-hexasulphonate octasodium salt; heating rate: 10 K min^{-1}.

Table 3
Thermodynamic parameters for the protonation of calix[6]arene-*p*-hexasulphonate[a] (L), calix[4]arene-*p*-tetrasulphonate[b] (L′) and *p*-hydroxybenzenesulphonic acid[c] (L″) at 25°C and $I = 0.1$ mol dm^{-3} ($NaNO_3$)[d]

Reaction	log *K*	Δ*G*°/(kJ mol^{-1})	Δ*H*°/(kJ mol^{-1})	Δ*S*°/(J K^{-1} mol^{-1})
$H_4L^{2-} + H^+ \rightleftharpoons H_5L^-$	4.99(9)	−28.45	0.6(2)	97.6(9)
$H_5L^- + H^+ \rightleftharpoons H_6L$	3.37(9)	−19.23	5.8(3)	84.1(9)
$H_2L'^{2-} + H^+ \rightleftharpoons H_3L'^-$	11.5(9)	−65.7	−25.9	134
$H_3L'^- + H^+ \rightleftharpoons H_4L'$	3.34	−19.04	2.59	72.5
$L''^- + H^+ \rightleftharpoons HL''$	8.62(1)	−49.16	−14.6(4)	116(2)

[a] This work. [b] Ref. [14]. [c] Ref. [29]. [d] Standard deviations in parentheses; charges of sulphonate groups are omitted for simplicity.

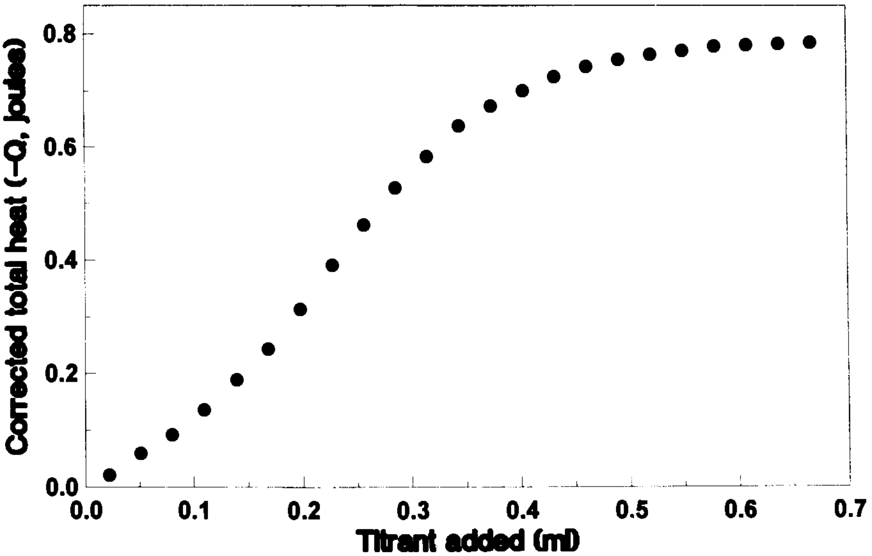

Fig. 3. Calorimetric run for the titration of 25 ml of calix[6]arene-*p*-hexasulphonate (0.004452 mol dm^{-3}) with HNO_3 (0.5036 mol dm^{-3}); pH range 5.2–2.2.

comparison, in the same table we have also reported the thermodynamic parameters for the corresponding protonation steps of calix[4]arene-*p*-tetrasulphonate; the thermodynamic parameters for the monomer (*p*-hydroxybenzenesulphonate) have also been reported [29]. It is immediately evident that the acidity of the second-last phenolic group of calix[6]arene-*p*-hexasulphonate is significantly higher than that of the corresponding group of calix[4]arene-*p*-tetrasulphonate and that this difference mainly results from the enthalpic contributions (0.6 *vs* −25.9 kJ mol^{-1}). The possibility of hydrogen bonding, proved for the calix[4]arene by means of a thermodynamic study [14] and also supported by computational studies [26], the unfavourable electrostatic repulsion [26] and the fixation of calix[4]arene-*p*-tetrasulphonate in its *cone* conformation [14] were indicated to be the factors responsible for the low acidity (log $K = 11.5$) shown by calix[4]arene-*p*-tetrasulphonate. The difference between the enthalpy values of the calix[4] and calix[6] derivatives indicates that in calix[6]arene-*p*-hexasulphonate hydrogen bonding is not as strong as in calix[4]arene-*p*-tetrasulphonate. This is to be attributed to (i) the larger ring, that causes a decrease of the electrostatic repulsion between the two negative charges (that are also delocalized over a larger system) and (ii) the greater conformational mobility of calix[6]arene-*p*-hexasulphonate, as also confirmed by the NMR results. On the other hand, log *K* values (see Table 3) show that both hydroxyl groups of calix[6]arene-*p*-hexasulphonate are as acidic as the central phenolic group of acyclic triphenols (p$K_{a1} = 4.71$) [28] whereas they are more acidic than the hydroxyl group of *p*-hydroxybenzenesulphonic acid [29]. Evidently, the phenolate anions (both the mono- and the di-anion) of calix[6]arene-*p*-hexasulphonate are stabilized by hydrogen bonding with the neighbouring undissociated phenolic hydroxyl groups.

The thermodynamic parameters obtained for the last protonation step of calix[6]arene-*p*-hexasulphonate reinforce this interpretation. In fact, they are quite similar to those of calix[4]arene-*p*-tetrasulphonate. This indicates that the entrance of the last proton destroys a favourable hydrogen bonding network. Moreover, the entropic contribution shows that the fully protonated ligand has a degree of freedom somewhat greater than that of calix[4]arene-*p*-tetrasulphonate, which is consistent with the larger mobility of the calix[6]arene derivative.

4. Conclusions

A careful choice of the experimental conditions used for the synthesis of the compound makes it possible to obtain a product of the degree of purity desirable for potentiometric and calorimetric investigations. This is possible thanks to the integrated use of different experimental techniques (NMR, IR, LSIMS, TG, ICP-AES and potentiometry) that enable cross-checking of the level of purity attained at each stage of purification by "probing" different parameters, such as the presence of undesired side-products, water content, sodium content, respondence of "theoretical" and measured potentials.

Moreover, the simultaneous use of different techniques, each one looking at the same problem from a different perspective, provides the necessary information (mobility of the compound, ΔG°, ΔH° and ΔS°) for a detailed description of the processes taking place in aqueous solution.

Acknowledgements

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