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Water soluble calix[4]arenes. A thermodynamic investigation of proton complex formation*

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Thermodynamic parameters of protonation of calix[4]arene-*p*-tetra sulphonate were potentiometrically and calorimetrically determined in aqueous solution at 25 °C and $I = 0.1$ mol dm^{-3} ($NaNO_3$). These values were compared with literature findings. ΔH° and ΔS° values reveal that the penta-anion protonation is energetically costly. In this connection the role played by hydrogen bonding and the cone conformation stabilization are critically discussed. Proton formation constants of the calix[4]arene-*p*-tetrasulphonate-tetra-carboxylate derivative in the cone conformation were also potentiometrically determined under the same experimental conditions.

Calixarenes are a new class of macrocyclic phenolic compounds which are experiencing wide interest in supramolecular chemistry.[1–4] *p-tert*-Butylcalix[4]-, -calix[6]- and -calix[8]arenes, which can be easily synthesized on a large scale, have been used as cation carriers in liquid membranes and have been proved to selectively transport Cs^+ over other alkai metal cations.[5] The same compounds have been functionalized both at the upper rim (aromatic nuclei) and at the lower rim (phenolic OH groups) to construct more complex receptors molecules.[2,3]

Of special interest are the water soluble calixarenes. After the first report by Ungaro and coworkers,[6] new compounds have been synthesized and studied for metal ion complexation, inclusion of neutral molecules and catalysis in aqueous media.[7,8]

Despite this, only Shinkai and coworkers have determined the proton formation constants of calix[4]arenes in aqueous solution.[9] According to these findings the calix[4]arene-*p*-tetrasulphonate should have pKa values of <1, 3, 4 and >11, respectively, for the removal of the four phenolic protons. This seemed rather surprising to us, since the X-ray structure of calix[4]arene-*p*-tetrasulphonate, from crystals obtained at pH 9, shows this to be the calix[4]arenesulphonate ion associated with five sodium ions.[10] Thus, according to this investigation only one phenolic proton seems to dissociate up to pH 9.

Since the knowledge of the number of dissociable protons of the simplest members of the calix[4]arene series is a crucial step for the design of more sophisticated calixarene-based enzyme mimics, it seemed of interest to undertake a study of the protonation of two members of the calix[4]arene-*p*-tetrasulphonate series, namely (1) and (2) (Chart 1). The latter compound, which is blocked in the "cone" conformation,[11] was included to evaluate the influence of a "less constrained" but fixed geometry on the acidity of the ligand. The study was carried out potentiometrically at $I = 0.1$ mol dm^{-3} ($NaNO_3$). We have also carried out a detailed calorimetric study in order to have a better picture of the energetics governing the protonation process in aqueous solution. To the best of our knowledge this is the first calorimetric study ever reported for such systems.

Compound (1) was synthesized following both the classical way[12] and a method recently described for calix[6]arene-*p*-tetrasulphonate.[13] It was done so to double check that we were obtaining the same data regardless of the route followed for the synthesis.

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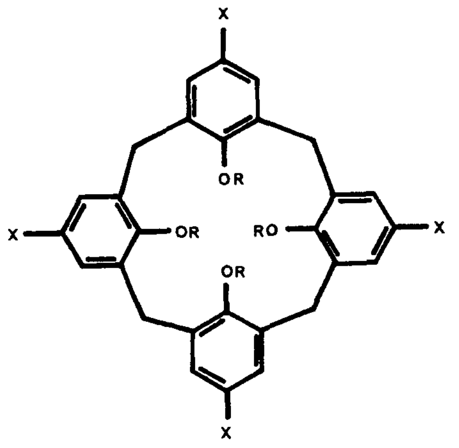

1 R = H, X = SO_3H
2 R = CH_2COOH, X = SO_3H

Chart 1

EXPERIMENTAL SECTION

Materials

Calix[4]arene-*p*-tetrasulphonate (1) was synthesized according to the method proposed by Shinkai *et al.*[12]. The reaction gave a product that contained Na_2CO_3 impurity. Sodium carbonate was eliminated by acidifying the product (at pH of ca. 3) and then boiling the solution. After neutralization the calixarene was precipitated by adding methanol. ^1H NMR (D_2O at 20 °C) and IR (KBr) data were identical with those previously reported.[12] Atomic absorption spectroscopy (Na) and elemental analysis showed the product to be the pentasodium salt. Anal. $[(C_{28}H_{19}O_{16}S_4Na_5)8H_2O]$C,H.

Calix[4]arene-*p*-tetrasulphonic acid was prepared following the method described by Scharff *et al.* to synthesize the homologous calix[6]arene-*p*-tetrasulphonic acid.[13] Mp > 280 °C. ^1H NMR spectrum (D_2O at 20 °C) is identical with that of the homologous pentasodium salt. Anal. $[(C_7H_6O_4S)_4 10H_2O]$C,H.

The synthesis of 5,11,17,23-tetrasulphonate-25,26,27,28-tetrakis(carboxymethoxy)calix[4]arene(calix[4]-carbox) followed the method described by Ungaro *et al.*[11] The ^1H NMR spectrum indicates that the product obtained following this method is in the cone conformation.

Thermogravimetric analysis (Mettler TA 3000; sensitivity = 2.5×10^{-6} g) was run for all three compounds. For calix[4]arene-*p*-tetrasulphonate (pentasodium salt) the water loss is virtually complete below 200 °C. This loss amounts on the average to 15%. The compound undergoes decomposition above 300 °C.

For calix[4]arene-*p*-tetrasulphonic acid the water loss is also complete below 200 °C but decomposition takes place at a lower temperature (200 °C). The average water loss is equal to 20%.

The average water loss for calix[4]carb is ca. 12% and it is complete below 200 °C. Decomposition starts immediately above 300 °C.

Stock solutions of HNO_3 and NaOH were standardized by titrations with primary standard tris(hydroxymethyl)aminomethane (THAM) (Merck) and potassium hydrogen phthalate (Merck), respectively. Sodium nitrate (Merck) was used without further purification. All solutions were prepared with doubly distilled water. Grade A glassware was employed throughout.

E.M.F. measurements

The potentiometric measurements were carried out by means of four fully automated sets of apparatus. All of them made use of Metrohm equipment (meter, E 654; combined glass electrode, EA 125; dispenser, E 665) and were controlled by two IBM (or IBM compatible) PCs. Each computer was able to control two potentiometric set ups simultaneously by using an appropriate program written in our laboratory. Values of E^0, E_j and nernstian slope of the electrode system were determined by titrating 2.5 mL of HNO_3 ($I = 0.1$ mol dm^{-3}) with CO_2-free NaOH. The titration cells were thermostated at 25.0 ± 0.1 °C, and all solutions were maintained under an atmosphere of nitrogen, which was bubbled through a solution of the same ionic strength and temperature as those of the solutions under study. Magnetic stirring was employed. The ionic strength was maintained at 0.1 mol dm^{-3} ($NaNO_3$). To avoid systematic errors and check for reproducibility, experiments were run simultaneously in two of the four different sets of potentiometric apparatus. Checks on the pH stability of each solution to be titrated showed no detectable drift in e.m.f. over a period of at least 90 minutes. Experimental details for the potentiometric measurements are given in Table 1. As shown in this table, solutions were titrated in one of the two following ways:

(a) the calix[4]arene was dissolved in water and titrated with standard HNO_3;

(b) the appropriate amount of HNO_3 was added to a solution of the ligand which was then titrated with standard NaOH. Obviously, when the ligand was synthesized according to the procedure described in reference 13 (i.e. in its acidic form) ca. four equivalents of NaOH were added to neutralize the four sulphonic acid groups and thus bring the pH to the desired starting point.

Table 1 Experimental conditions of potentiometric measurements at 25 °C and $I = 0.1$ mol dm^{-3} ($NaNO_3$)

	C_L^0/mmol dm^{-3}	*Titrant (mol dm^{-3})*		*pH range*	*No. of points*
LIGAND (1)	6.9	NaOH	0.0965	2.5–4	52
	6.8	NaOH	0.0965	2.5–4	37
	8.4	HNO_3	0.1003	2.5–4	36
	5.6	NaOH	0.0965	2.5–4	70
	7.8	HNO_3	0.0402	2.5–11	88
	7.8	HNO_3	0.0402	2.5–11	88
	7.0	HNO_3	0.0402	2.5–11	84
	6.4	HNO_3	0.0402	2.5–4	87
	7.1	HNO_3	0.0402	2.5–4	86
	7.1	NaOH	0.1006	2.5–11	58
	7.1	NaOH	0.1006	2.5–11	87
	8.7	HNO_3	0.0402	2.5–4	53
	8.2	HNO_3	0.0402	2.5–4	48
	8.4	HNO_3	0.0402	2.5–4	50
	7.8	NaOH	0.1006	2.5–11	50
	7.3	NaOH	0.0996	2.5–11	53
	7.0	NaOH	0.1016	2.5–4	22
	7.7	NaOH	0.1016	2.5–10.3	34
	7.0	NaOH	0.0994	2.5–11	35
	4.9	NaOH	0.0994	2.5–11	37
	4.1	NaOH	0.0994	2.5–11	41
LIGAND (2)	6.6	NaOH	0.1009	2.5–5	76
	6.7	NaOH	0.1009	2.5–5	66
	6.7	NaOH	0.1009	2.5–5	71
	7.9	NaOH	0.1009	2.5–5	153

Calorimetric measurements

The calorimetric measurements were performed at 25.000 ± 0.001 °C using a Tronac 450 isoperibolic calorimeter equipped with a 25 mL titration Dewar. Essentially, two sets of experiments were performed.

(a) Solutions of the ligand at pH of ca. 11 or 4 were titrated with standard HNO_3.

(b) Solutions at a pH of ca. 2.5 were titrated with standard CO_2-free NaOH. The titration data thus obtained (a total of 169 points from six independent titrations), corrected for all non-chemical energy terms determined in separate experiments, were refined simultaneously to obtain the final ΔH° values. Details of the calorimetric measurements are given in Table 2.

Table 2 Experimental conditions of calorimetric measurements for calix[4]arene-*p*-tetrasulphonate at 25 °C and $I = 0.1$ mol dm^{-3} ($NaNO_3$)

C_L^0/mmol dm^{-3}	*Titrant (mol dm^{-3})*		*pH range*	*No. of points*
9.4	HNO_3	0.4021	2.5–4	17
7.3	HNO_3	0.4021	2.5–4	14
6.1	HNO_3	0.5020	2.5–11	16
4.6	HNO_3	0.5020	2.5–11	32
4.6	NaOH	0.2482	2.5–11	50
4.7	NaOH	0.2482	2.5–11	40

Calculations

Calculations concerning the calibration of the electrode system (E^0, slope and E_j), were performed by the least-squares computer program ACBA[14] that refines the parameters of an acid-base titration by using a non-linear least-squares method minimizing the function $U = \Sigma(V_{\text{expl},i} - V_{\text{calc},i})^2$, where V_i is the volume of the titrant added at the i-th point. The potentiometric data concerning ligand purities and protonation constants were handled both by ACBA[14] and SUPERQUAD.[15] This latter program refines the error square sum based on measured electrode potentials. By minimizing two different functions, i.e. the error square sum in added volumes (ACBA) and the error square sum in measured electrode potentials (SUPERQUAD) the probability of fitting systematic errors is drastically reduced.

The enthalpies of formation were computed by means of the least squares computer program DOEC,[16] which minimizes the function $U = \Sigma(Q_{i,\text{calc}} - Q_{i,\text{exptl}})^2$, where Q_i is the heat of reaction of the i-th point.

RESULTS AND DISCUSSION

Typical potentiometric curves for the titration of calix[4]arene-*p*-tetrasulphonate with NaOH and

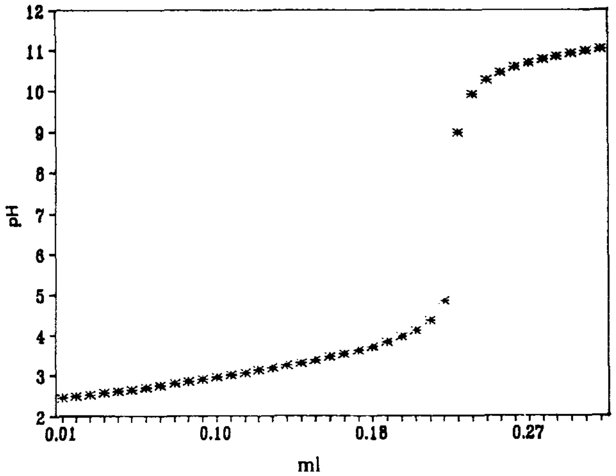

Figure 1 Titration of calix[4]arene-p-tetrasulphonate with NaOH 0.1 M.

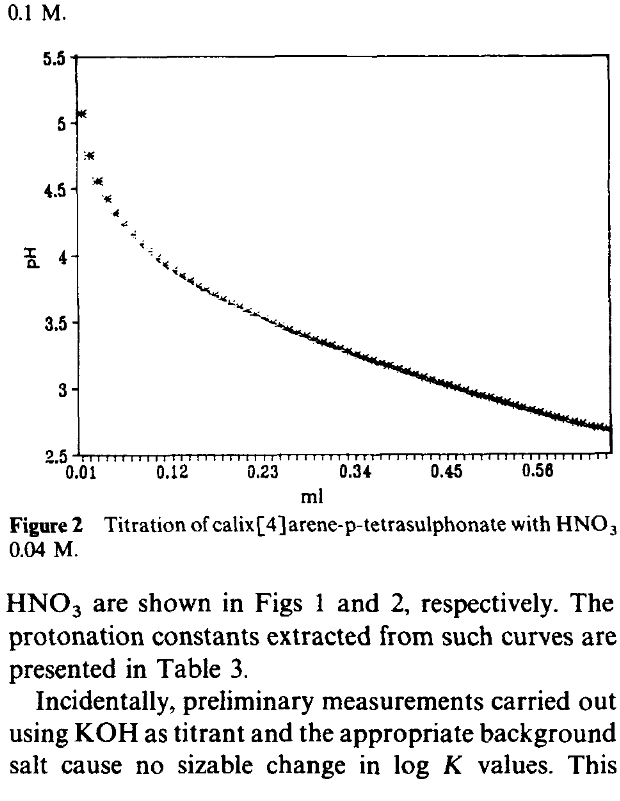

Figure 2 Titration of calix[4]arene-p-tetrasulphonate with HNO_3 0.04 M.

HNO_3 are shown in Figs 1 and 2, respectively. The protonation constants extracted from such curves are presented in Table 3.

Incidentally, preliminary measurements carried out using KOH as titrant and the appropriate background salt cause no sizable change in log *K* values. This would exclude any major sodium- or potassium-calix[4]arene-*p*-tetrasulphonate complex in aqueous solution, unless both these cations form complexes of the same stability. However, this needs further investigation.

A discussion of these data is difficult because of the scarcity of literature values, obtained under the same experimental conditions. In fact some pKa's for a closely related compound, i.e. *p*-nitrocalix[4]arene, are reported in the literature, but they have been obtained either in water/tetrahydrofuran[9] or in ethanol/water[17] mixtures. Consequently, our data can only be compared to those published by Shinkai *et al.* for the calix[4]arene-*p*-tetrasulphonate.[9] As shown in Table 3, there is a significant discrepancy between the literature data and that of this study. In fact in the pH range investigated by us (i.e. 2.5–11) we only detected two titrable protons, having protonation constants equal to 11.5 and 3.34, respectively; various attempts to detect the proton, which according to the literature data[9] should correspond to pKa = 4, failed, regardless of the procedure followed to perform the potentiometric experiment or the strategy used for the data treatment (see Table 1 and *Experimental section*). The good data fit obtained when refining simultaneously the data collected by scanning the pH upwards and downwards together with the fact that the fit, as well as the protonation constants, remained unchanged, makes us confident as to the number of protons which can be titrated in the pH range 2.5–11. In addition, our data are consistent with the thermogravimetric experiments; in fact the purity determined potentiometrically by making use of both ACBA and SUPERQUAD computer programs is practically coincident with the water loss determined thermogravimetrically. Clearly, the relatively large imprecision (0.1) of the first protonation constant is to be ascribed primarily to the pH range investigated, which at the upper limit (i.e. pH = 11) is still 0.5 log units below the log *K* value. On the other hand, exploring even higher

Table 3 Proton formation constants of calix[4]arene-*p*-tetrasulphonate (H_2L^{2-}) at 25 °C and $I = 0.1$ mol dm^{-3} ($NaNO_3$)

Reaction	*log K*	$\Delta G°$ *kcal mol*$^{-1}$	$\Delta H°$ *kcal mol*$^{-1}$	$\Delta S°$ *cal mol*$^{-1}$ *deg*$^{-1}$
$H_2L^{2-} + H^+ = H_3L^-$	11.5(1)[a]	−15.7	−6.2(4)	32(1)
$H_3L^- + H^+ = H_4L$	3.34(4)	−4.55	0.62(3)	17.2(3)
$L^{4-} + H^+ = HL^{3-}$	>11[b]			
$HL^{3-} + H^+ = H_2L^{2-}$	4			
$H_2L^{2-} + H^+ = H_3L^-$	3			
$H_3L^- + H^+ = H_4L$	<1			

[a] This work; σ in parentheses.

[b] Reference [9].

4-Hydroxybenzensulphonic acid: log $K = 8.66$, $\Delta H° = -4$ kcal mol^{-1}, $\Delta S° = 28$ cal mol^{-1} deg^{-1}.[18]

alkalinity regions becomes risky because (i) of the response of the glass electrode above pH 11 (although, in order to minimize this problem, we made use of a "high alkalinity" glass electrode) and (ii) the species with a pKa of 11.5 might overlap with the region of existence of the species in which one more phenolic group deprotonates.

The enthalpy and entropy changes associated with the formation of the proton complexes deserve some comments. In particular, the formation of the species having pKa = 11.5 is both enthalpically and entropically favored, while the formation of the species with a pKa = 3.34 is only entropically favored (Table 3). Hereafter these two species (i.e. H_2L^{2-} and H_3L^-) will be referred to as "basic" and "acidic" species, respectively. Literature data[19] indicate that the proton complex formation of phenols is both enthalpically and entropically favored in agreement with the values found for the first protonation step of calix[4]arene-*p*-tetrasulphonate. Moreover, the protonation of the "basic" species is enthalpically more favored than the protonation of *p*-hydroxybenzensulphonate[18] (-6.2 vs -4 kcal mol^{-1}). The $\Delta S°$ value is also slightly more positive in the case of the calix[4]arene-*p*-tetrasulphonate, most probably owing mainly to the statistical contribution. To explain the larger enthalpy values, it has to be considered that the incoming proton experiences the field of two charged oxygen atoms, which obviously results in a field stronger than that due to the anion of *p*-hydroxybenzensulphonate. In addition, the thermodynamic parameters suggest that, in this protonation step, the fixation of the calixarene "cone" conformation, as indicated by ^1H NMR data obtained at pH 9 in aqueous solution[9] as well as by X-ray crystal structure analysis[10], is not perturbed.

The unfavorable protonation enthalpy of the "acidic" species indicates that an energetically "costly" process is taking place at this stage. Having in mind that at pH below 2 the calixarene becomes conformationally more mobile due to decrease of hydrogen bond strength,[9] the endothermic enthalpy change can be ascribed to the less favorable proton-oxygen interaction in the "acidic" species compared to that pertinent to the "basic" species. Thus the stabilization of the calix[4]arene-*p*-tetrasulphonate pentaanion in the "cone" structure, due to the strong adjacent hydrogen bonds, causes a remarkable increase (5.3 log units) of the acidity of the first hydroxyl group compared to *p*-hydroxybenzensulphonic acid (see Table 3). This acidity difference is also found for *p*-*tert*butylcalix[4]arene and acyclic *p*-*tert*butylphenol in TMF, as recently reported by Shinkai *et al.*[21]

Questions arise as concerns the existence of the so called "superacidic proton" (pKa < 1).[9] The existence of such a dissociable proton is in contrast with the following observations:

(i) X-ray structural analysis of calix[4]arene-*p*-tetrasulphonate, obtained from an aqueous solution at pH 9[10] reveals that the calixarene is associated with five sodium ions;

(ii) the analysis of the product obtained by us from a neutral aqueous solution shows the calixarene to be a pentasodium salt.

The stability constants for the protonation of calix[4]carbox are reported in Table 4. These values are roughly those one would expect for a tetracarboxylic ligand.[16] The log *K* for the last protonation step is very close to the log *K* for the protonation of phenoxyacetate.[17] This would indicate that the four carboxylic groups do not influence one another significantly. However, calorimetric studies are underway to see whether log *K*'s, which result from the combination of both enthalpy and entropy values, "conceal" any subtle difference.

Table 4 Proton formation constants of 5,11,17,23-tetrasulphonate-25,26,27,28-tetrakis(carboxymethoxy)calix[4]arene (*L*)[a] at 25 °C and $I = 0.1$ mol dm^{-3} ($NaNO_3$)

Reaction	*log K*
$L + H = HL$	1.57(3)[b]
$HL + H = H_2L$	3.97(2)
$H_2L + H = H_3L$	3.27(3)
$H_3L + H = H_4L$	3.03(3)

[a] Charges are omitted for clarity.

[b] σ in parentheses.

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