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Endo-cavity Complexes between Calix[6]arene Dianions and Aliphatic Ammonium Cations: Structure of a Hexylammonium Complex by X-ray Crystallography

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The interactions of calix[6]arene and *p-tert*-butylcalix[6]-arene with aliphatic amines in acetonitrile solution were studied by spectrophotometric titrations in the UV region and ^{1}H NMR spectrometry. Calix[6]arenes can undergo two deprotonations by aliphatic amines and the extent of the second proton transfer is mainly governed by the size of the α-substituent of the amine. ^{1}H NMR spectra show that the macrocycle adopts a 1,2,3-alternate conformation and that the α-hydrogens of the ammonium ions are shielded by the π-clouds of the aromatic rings. The X-ray crystal structure of the dihexylammonium complex of the *p-tert*-butylcalix[6]arene dianion, reported here, confirms the 1,2,3-alternate conformation and shows one of the two ammonium moieties encapsulated in the inner cavity of the macrocycle.

Keywords: Ammonium cations; Molecular recognition; Inclusion compounds; Calixarenes

INTRODUCTION

Calixarenes and their derivatives have been proposed as artificial receptors for ammonium cations by their inclusion in the calixarene [1–3]; for example, as heparine mimics [4] and as amino acid binders in the aqueous phase [5]. There is no unique mode of complexation of calixarenes and ammonium cations; some are reported as having an *endo*-ammonium-calix and others an *exo*-calix structure [6–8].

Structures elucidated by X-ray diffraction methods have revealed, along with hydrogen-bonded structures, short contacts between ammonium and calix realized by C—H—π and N^+—CH—π interactions as, for example, in salts of *p-tert*-butylcalix[4]arene with 1,4-butanediamine [9], and calix[4]arene and piperidine [10]. The structure of the triethylammonium salt of the calix[6]arene dianion, however, is in a distorted 1,2,3-alternate conformation [11], in which one phenolate unit interacts with one ammonium ion via a single hydrogen bond, without any additional important interactions. Unfunctionalized calixarenes are stronger acids than the corresponding monomeric phenols, unmistakable evidence for the presence of strong intramolecular hydrogen bonds promoting the stabilization of the phenolate ion [12].

In the presence of amines, calixarenes can be deprotonated to give salts whose structure is dependent on both electrostatic force and steric hindrance. Salts of *p-tert*-butylcalix[6]arene and *p-tert*-butylcalix[8]arene with tertiary amines exist in equilibrium between ion pairs and separated ions in benzonitrile and nitrobenzene [13–15], and in these cases, only one proton transfer from calixarene to amine was observed [16].

The present work aims to shed new light on the complexation of calix[6]arenes with amines by revealing the influence of the structure of the amine on the stoichiometry of the acid–base reaction and the values of the association constants. The interactions between calix[6]arene or *p-tert*-butylcalix[6]-arene and amines in acetonitrile were studied by UV–visible spectrophotometric titrations and by ^{1}H NMR spectroscopy. The structure of

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the bis-hexylammonium *p-tert*-butylcalix[6]arene dianion was determined by single-crystal X-ray techniques. The results disclose new aspects in the calix[6]arene–amine interaction, showing a second proton transfer step and the formation of an adduct in which the ammonium ion is sited in the pseudo-calixarene cavity defined by the aromatic rings of the calixarene dianion.

RESULTS AND DISCUSSION

Spectrophotometric titrations of calix[6]arene and *p-tert*-butylcalix[6]arene using aliphatic amines were carried out in acetonitrile and show the appearance of a band centered at 300 nm (calix[6]arene) or 310 nm (*p-tert*-butylcalix[6]arene) corresponding to the absorption of the phenolate ions. With all amines used in this work, the proton transfer reaction is quantitative for the first deprotonation of the calixarene. Upon addition of an excess of amine, a second and less favorable proton transfer reaction occurs with some amines. As a consequence, a break in the plot of absorbance versus total concentration of amine is observed (Fig. 1). The *tert*-butyl groups of *p-tert*-butylcalix[6]arene decrease the acidity of the phenolic hydroxyls, inhibiting the second proton transfer reaction, while the first transfer is still quantitative for all amines used. Unlike the results observed for the reactions of calix[4]arene and amines [17], there is no straightforward relationship between the magnitude of the second proton transfer and the basicity of the amine [18] (Table I).

As the first proton transfer is extremely favorable and is shown to be quantitative upon addition of one equivalent of amine, the second deprotonation can be considered separately and treated theoretically in terms of the association process described in Scheme 1. Treatment of the data using nonlinear regression analysis for the proposed model is in good agreement with the experimental results and allows calculation of the values of the association constants corresponding to the second proton transfer, *K* (see Table I).

The main factor that governs the magnitude of *K* is the sterical hindrance regarding the ability of the ammonium cation to be accommodated in the cavity of the calixarenes. The dependence of the values of *K* on the volume of the alkyl chain of the amine is clearly observed by comparing the titrations made with amines of similar basicities but different steric crowding, such as hexylamine and *tert*-butylamine, or piperidine and dipropylamine. In both cases a decrease in proton transfer for the most crowded amines is observed, consistent with the formation of a complex between the calixarene dianion and an ammonium ion, for which the steric requirements affect the magnitude of the value of *K*. The same data show that the increase from two to three hydrogens atoms available for hydrogen bonds, in the ammonium ion, is not an important factor in the control of the magnitude of the complexation equilibrium. Thus, the major role played by steric factors in the second proton transfer reaction suggests a process that uses the inner space of the calixarene cavity.

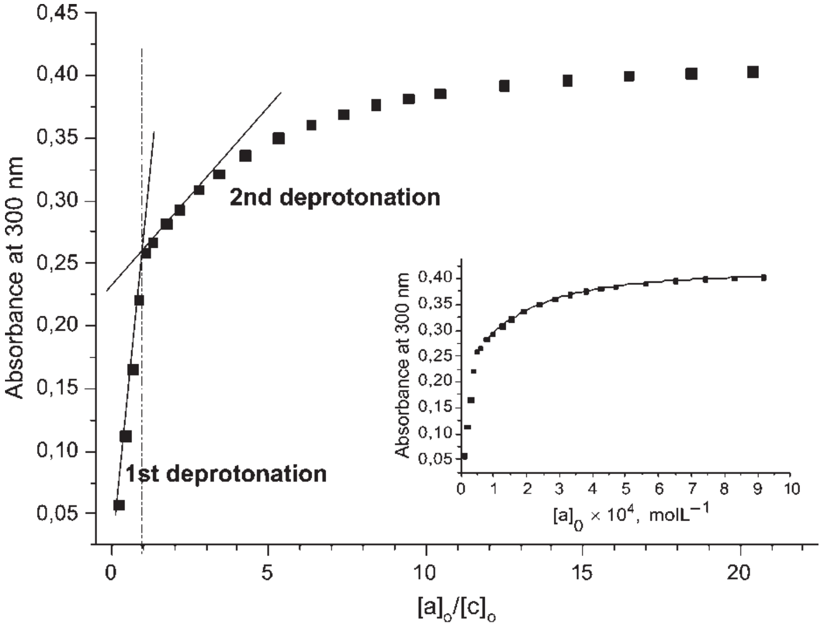

FIGURE 1 Plot of absorbance at 300 nm versus the ratio of total concentrations of amine and calixarene from the titration of calix[6]arene (4.49×10^{-5} mol L^{-1}) with hexylamine. The intersection of the straight lines shows a break in the titration curve at $[a]_o/[c]_o = 1$. Insert: plot of absorbance at 300 nm versus total concentration of amine added for the same titration. The continuous line at the upper part of the plot is the fit of the model proposed to the experimental data.

TABLE I Values of equilibrium constants (K/M^{-1}) for the reactions between calix[6]arene monoanion and aliphatic amines in acetonitrile, at 298 K; and values of pK_a of the respective ammonium ions in the same solvent

Amine	K*	pK_a‡
Hexylamine	5.0×10^3	(18.26)§
Ethylenediamine	3.5×10^3	18.46¶
tert-Butylamine	†	18.14
Piperidine	2.5×10^3	18.92
Dipropylamine	3.5×10^2	(18.75)**

* Uncertainty of 10% in K values. † The extent of the second proton transfer is too small to be evaluated. ‡ Ref. 12. § Value of pK_a for *n*-butylamine. ¶ Refers to $H_2N(CH_2)_2NH_3^+ \rightarrow H_2N(CH_2)_2NH_2 + H^+$. ** Value of p$K_a$ for diethylamine.

$$\mathrm{calix(OH)_6 + RNH_2 \longrightarrow calix(OH)_5O^- + RNH_3^+}$$

$$\mathrm{calix(OH)_5O \;\; + RNH_2 \xrightleftharpoons{\mathbf{K}} calix(OH)_4(O\;)_2^{-}\cdots RNH_3^{+}}$$

SCHEME 1 Reaction between calix[6]arene and amine.

It is important to note that the second amino group in ethylenediamine is not protonated and the NH_2 group does not contribute with additional interactions with the calixarene host. In fact, the lower value of *K* compared to that of hexylamine may be attributed to the destruction of dipolar interactions with the solvent upon complexation with calixarene.

The proton NMR spectra contribute to elucidation of the structure of the complexes. The low solubility of the salts of calix[6]arenes and piperidine did not allow NMR spectra to be obtained and the lowest values of the amine:calixarene molar ratios reported in Table II are the minimal ratios to achieve complete solubility of the amine–calixarene salts. Some values of proton chemical shifts are shown in Table II and these were compared with values for trifluoroacetic acid (TFA) salts to obtain δ values of fully protonated amines.

The association constants determined by spectrophotometric methods indicate that, for calix[6]arene-hexylamine acetonitrile solution at 10^{-2} M, all the amine added is protonated. Therefore, the δ values of the amine signals for the NMR spectra recorded for the 1.44:1 solution, which is the lowest concentration of amine needed to solubilize the calixarene, should be considered as the contribution of free ammonium plus complexed ammonium, while at the 4.41:1 molar ratio the values of δ also correspond to the neutral amine. As far as *p-tert*-butylcalix[6]arene is concerned, the association becomes detectable at the concentration used in the acquisition of NMR spectra (10^{-2} M).

The values of the chemical shifts are in agreement with the proposed *endo*-cavity complexation. This can be seen by the shielding α- and β-hydrogens of the ammonium cation formed by the amine in the presence of calix[6]arenes with respect to those of the ammonium formed in the presence of TFA in acetonitrile. The values of δ of the α-CH_2 of hexylammoniun with calix[6]arene and *tert*-butylcalix[6]arene, respectively, are 1.01 and 0.96 ppm lower than the value with TFA, thus providing clear evidence for the entrance of part of the aliphatic chain into the cavity of the calix.

The conformation of the calix[6]arene dianion in the complex with hexylamine was determined, by the presence of two doublets and one singlet for the methylenic hydrogens, as being 1,2,3-alternate, giving raise to two semi-calixes. This conformation is characteristic of the dianion, because each phenolate can be stabilized by hydrogen bonds from the neighboring phenolic units and the repulsion between the anions and between the lone pairs of oxygen atoms is minimized. In this orientation, the ammonium cation can participate in a cyclic array of hydrogen bonds with the hydroxyls of calixarene phenolate, approximating the carbon chain to the shielding region of the aromatic rings. In the case of tertiary amines, as in triethylamine [11], the restriction to only one hydrogen bond and the steric hindrance of the alkyl chain can displace the ammonium to a position more directly connected to the oxy-anion, as already observed in the solid state.

TABLE II ^{1}H NMR chemical shifts (δ) of amines in neutral form and in the presence of acids, calix[6]arene, *p-tert*-butylcalix[6]arene and trifluoroacetic acid (TFA), at different molar proportions

		No acid	Calix[6]arene		*p-tert*-Butylcalix[6] arene		TFA
Hexylamine							
Molar ratio			1.44:1*	4.41:1*	1.77:1*	4.60:1*	1:1*
δ	α-CH_2	2.57	1.90†	2.31	1.95†	2.31	2.91
	$(CH_2)_4$	1.29	1.3–1.0	1.4–1.1	‡	‡	1.30–1.63
	CH_3	0.89	0.84	0.89	0.83	0.88	0.89
t-Butylamine							
Molar ratio		1.75:1*	3.46:1*				1:1
Δ	CH_3	1.07	0.89	0.97	§	§	1.35

* Amine–calixarene molar ratio. † Signal overlaps with that of acetonitrile. ‡ Signal overlaps with that of *tert*-butyl hydrogens of *p-tert*-butylcalix[6]arene. § *tert*-Butylamine *p-tert*-butylcalix[6]arene salt is insoluble.

X-ray Data

The structure of the salt of hexylammonium and the *p-tert*-butylcalix[6]arene dianion determined by X-ray diffraction methods shows two hexylammonium cations for each calix[6]arene unit. One hexylammonium cation (labeled starting from N8) is immersed in the cavity formed by three aromatic rings, and binds the oxygens of the other phenolic units by hydrogen bonds. This arrangement defines another semi-calixarene moiety (Fig. 2).†

The aliphatic chain of this hexylammonium cannot adopt a fully extended conformation because of the sterical hindrance of the calixarene *t*-butyl groups. Therefore, the molecule displays the torsional angles N8–C81–C82–C83 and C81–C82–C83–C84 of 60.89(4)° and 56.28(4)°, respectively, indicating a *gauche* relation, unusual in unbranched molecules, for which the preferred angle is 180° with *anti* conformation, showing that the aliphatic chain must fit the space restricted by the cavity of calixarene to allow the hydrogen bond interactions between ammonium cation and phenolic oxygens. The rest of the chain is in an extended conformation, occupying the space defined by the aromatic rings of the calixarene.

The other hexylammonium interacts with one phenolate (O61) and two ethanol molecules through hydrogen bonds. Its carbon chain bends with two sets in *gauche* conformation [dihedral angles of C74–C75–C76–N7 and C73–C74–C75–C76 of 65.6(7)° and 62(1)°, respectively], and occupies a position parallel to the phenolate ring. The *tert*-butylcalix[6]arene moiety is in the 1,2,3-alternate conformation, forming two semi-calixarenes. This conformation is favored by the presence of the dianion, which is stabilized by strong (O^-)–HO interactions, with short distances (Table III), where each phenoxide take two phenol units and forms a substructure with three hydrogen-bonded units. The phenoxide oxygen (O31) does not interact directly with the *endo* ammonium cation, which would be favored by dipolar attractive forces. The NH_3^+ (N8) is hydrogen bonded to two hydroxyl oxygens that belong to one of the semi-calixes [N8–O41 = 2.732(3) Å; N8–O21 = 2.805(3) Å] and to a phenolic oxygen from the other semi-calix [N8–O11 = 3.000(3) Å].

TABLE III Selected hydrogen bond lengths (Å) and angles (°) in the crystal structure of dihexylammonium-*p-tert*-butylcalix[6]arene diphenolate*

Donor	Acceptor	D—A	D—H···A
O1—H1	O51	2.727(4)	177
O2—H2	O31	2.733(3)	168
N7—H7A	O2	2.794(4)	161
N7—H7B	O1	2.840(4)	163
N7—H7C	O61	2.671(4)	155
N8—H8A	O11	3.000(3)	151
N8—H8B	O41	2.733(3)	145
N8—H8C	O21	2.805(3)	152
O11—H11	O61	2.530(3)	159
O21—H21	O31	2.520(3)	169
O41—H41	O31	2.534(3)	166
O51—H51	O61	2.486(3)	165

* O1 and O2 belong to ethanol; N7 belongs to *exo* ammonium and N8 to the *endo* ammonium; O31 and O61 are phenoxide oxygens; O11, O51, O21 and O41 belong to phenolic hydroxyls.

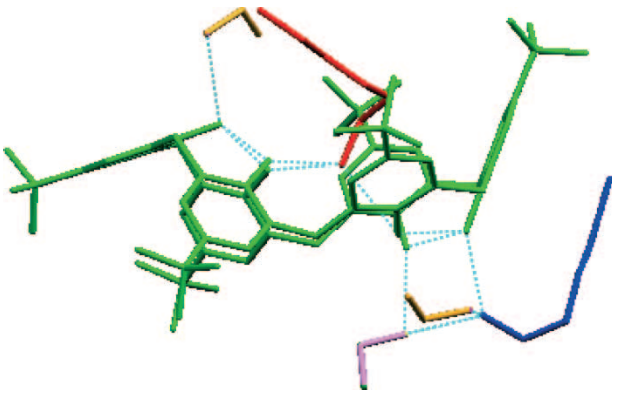

FIGURE 2 *Endo* hexylammonium (red), *exo* hexylammonium (blue), the *tert*-butylcalix[6]arene (green) cavity and ethanol molecules with O1 (violet) and O2 (orange). The contents are the same as those of Fig. 3, including those obtained by symmetry.

EXPERIMENTAL

p-tert-Butylcalix[6]arene and calix[6]arene were synthesized as described in the literature [19]. Acetonitrile was spectroscopic grade (Carlo Erba) and the amines (Sigma and Aldrich) were dried over molecular sieves and used without further purification. UV–visible measurements were carried in an HP8452 "diode array" and NMR spectra were obtained using a Bruker-200 MHz spectrometer.

X-ray Crystallographic Study

Single crystals of the complex of bis-hexylammonium *p-tert*-butylcalix[6]arene diphenolate were obtained by slow evaporation from ethanol. Data were collected on an Enraf-Nonius Kappa-CCD diffractometer with graphite-monochromated Mo Kα ($\lambda = 0.71073$ Å), up to 50° in 2θ, and final unit cell parameters were based on all reflections. The temperature was controlled using an Oxford Cryosystem low-temperature device operating at 120 K. Data collection was carried out using the COLLECT program [20]. Integration and scaling of the reflections were performed with the HKL Denzo-Scalepack system of programs [21] and numerical absorption corrections were performed [22]. The structure was solved using direct methods with

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†This representation was made using the program Mercury 1.1.2 from the Cambridge Crystallographic Data Centre: Cambridge, UK.

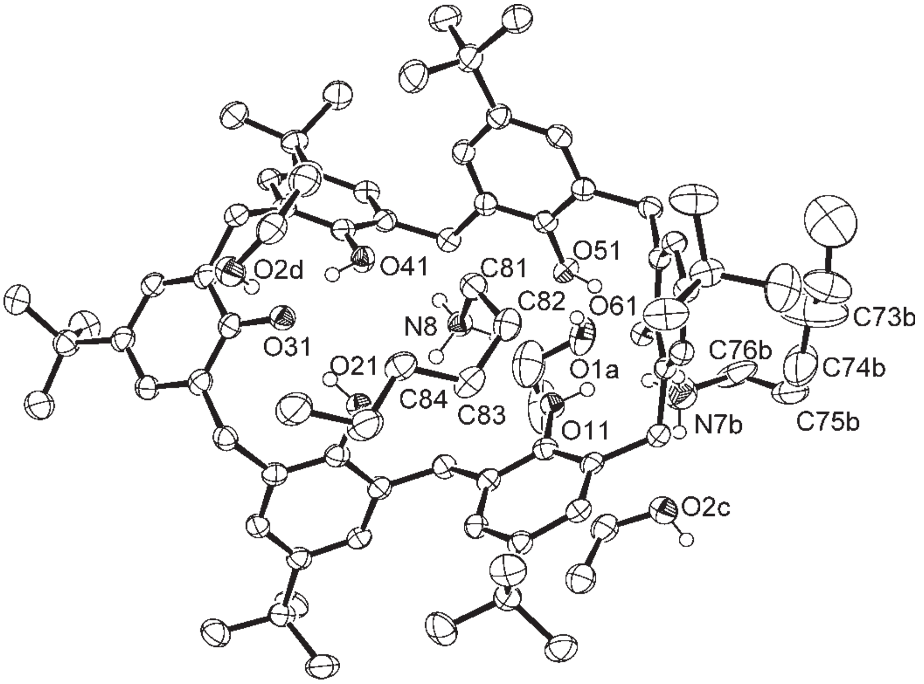

FIGURE 3 ORTEP projection of *p-tert*-butylcalix[6]arene dianion, hexylammonium cations at *endo*-calix (N8) and *exo*-calix (N7) positions, and ethanol molecules, with the numbering of atoms cited in the text. Hydrogen atoms not involved in hydrogen bonds were omitted for clarity (molecules labeled with letters were generated by symmetry: $a = 2 - x, -1/2 + y, 1/2 - z$; $b = 1 - x, -1/2 + y, 1/2 - z$; $c = 1 - x, -1/2 + y, 1/2 - z$; $d = 1 + x, y, z$).

SHELXS-97 [23]. The model was refined by full-matrix least-squares on F^2 by with SHELXL-97 [24]. All hydrogen atoms were located at theoretical positions and refined with the riding model. Hydrogen atoms were set isotropic with a thermal parameter 20% greater than the equivalent isotropic displacement parameter of the carbon to which each one was bonded; this percentage was set to 50% for the hydrogen atoms of methyl groups.

Crystal data: C66 H82 O6, 2(C6 H16 N), 2(C2 H6 O), $M = 1267.85\,\mathrm{g\,mol^{-1}}$, $0.10 \times 0.18 \times 0.20\,\mathrm{mm}$, monoclinic, $P2_1/c$, $Z = 4$, $\mu_{\mathrm{Mo}} = 0.068\,\mathrm{mm^{-1}}$, $a = 13.0070(10)$, $b = 22.8650(10)$, $c = 26.3870(10)\,\mathrm{\AA}$, $\beta = 99.990(10)°$, $V = 7728.6(8)\,\mathrm{\AA}^3$, 25 186 reflections measured, 13 562 unique, $R(\mathrm{int}) = 0.023$, final $R = 0.0822$.

Crystallographic data for the structure reported in this article have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 230298. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk; http://www.ccdc.cam.ac.uk).

Figure 3 is an ORTEP [25] projection of dihexylammonium *p-tert*-butylcalix[6]arene diphenolate.

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