Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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To cite this Article Lehn, Jean-Marie , Meric, Robert , Vigneron, Jean-Pierre , Cesario, Michele , Guilhem, Jean , Pascard, Claudine , Asfari, Zouhair and Vicens, Jacques(1995) 'Binding of acetylcholine and other quaternary ammonium cations by sulfonated calixarenes. Crystal structure of a [choline-tetrasulfonated calix[4]arene] complex', Supramolecular Chemistry, 5: 2, 97 — 103
To link to this Article: DOI: 10.1080/10610279508029480
URL: http://dx.doi.org/10.1080/10610279508029480

SUPRAMOLECULAR CHEMISTRY, Vol. 5, pp. 97-103
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Binding of acetylcholine and other quaternary ammonium cations by sulfonated calixarenes. Crystal structure of a [choline-tetrasulfonated calix[4]arene] complex

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(Received December 30, 1993)

The water-soluble tetra- and hexasulfonated calix[4] and calix[6]arenes bind very strongly the neurotransmitter acetylcholine and other quaternary ammonium cations with association constants K_s up to 4×10^5 M^{-1} for NEt_4^+. The high affinities for choline and acetylcholine (K_s= 5×10^4 to 8×10^4 M^{-1}) are comparable to those of the biological recognition sites. The crystal structure of the [choline-tetrasulfonated calix[4]arene] complex was determined. Two complexes A and B were observed in the asymmetric unit. In each one, the choline inserts its N-terminal inside the cavity of the receptor. The calix[4]arene adopts a single cone conformation but the choline substrate is in an extended conformation in complex A and adopts two other folded conformations in complex B (75%-25%). The very high association constants and the crystal structure provide important information about the nature of the binding in this biologically most relevant complex.

INTRODUCTION

The binding of quaternary ammonium molecular substrates by macrocyclic receptors has been a subject of much activity in recent years. Most of these studies involved water-soluble receptors bearing negatively charged groups[1-11] although some reports on the size selective binding of ammonium ions by neutral receptors in water[12] as well as in organic media[13-17] have been recently published. Of special interest, from the biological point of view, is the binding of the neurotransmitter acetylcholine and of related quaternary ammonium ions.[18]

The binding of molecular cations in water is a very complicated phenomenon in which electrostatic forces and hydrophobic effects play a major role but other factors have also to be considered. The stabilizing cation-π interactions between the positive charge of the ammonium cation and an electron rich aromatic ring could be of special importance, particularly in biological recognition of the neurotransmitter acetylcholine.[3,19,20] This agrees with the determination of the structure of the binding site of acetylcholine in acetylcholine esterase (AChE) showing a narrow pocket surrounded by 14 aromatic residues with no negative charge in the immediate vicinity.[21] Biological results are in line with these views.[22] Very recently, it was suggested that the degree of freedom of the bound substrate may also play a significant role; a relatively loose association would be more favorable than a tight lock and key pairing to achieve a strong binding of quaternary ammonium species in water.[8b]

Acetylcholine binding by a biological receptor involving interaction with both lipophilic and anionic residues[23], further enhancement of binding strength should result from constructing artificial lipophilic anionic cavities better suited to its geometry. Such receptor molecules would take advantage of the synergistic effect of electrostatic forces and apolar groups as defined for

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speleands and speleate complexes[1] Corey-Pauling-Koltun (CPK) models show that water-soluble calixarene derivatives delineate appropriate cavities, the symmetry of the calix[6] derivative being particularly well adapted to that of the quaternary ammonium group of acetylcholine. Indeed it has been shown that tetrasodium *p*-sulfonatocalix[n]arenes **1** (n=4) and **2** (n=6) form 1:1 complexes with trimethylanilinium chloride and 1-adamantyltrimethylammonium chloride in D_2O and the association constants (K_s) were estimated by the NMR method.[9] ^1H and ^{13}C NMR studies of the complex formed from the calix[4]arene derivative and trimethylanilinium chloride, in D_2O, showed that the substrate is bound to the cone-shaped cavity of the calixarene. It was assumed that in acidic medium the phenyl moiety lies in the cavity whereas in neutral medium both the trimethylammonium and the phenyl moiety are included nonspecifically. X-ray crystallographic studies of the complex crystallized from acidic aqueous solution confirmed this conclusion.[9d] Recently the binding of trialkylferrocenylmethyl ammonium derivatives by **2** was also described.[10]

Our early interest in the binding process of neurotransmitters, specifically of choline and acetylcholine,[1a] led us to also investigate their interaction with polysulfonated calixarenes. We report here the complexation of a series of quaternary ammonium cations by the *p*-sulfonatocalix[4] and [6]arenes **1** and 2, as well as the crystal structure of a choline-*p*-sulfonated calix[4]arene complex.

EXPERIMENTAL SECTION

At the beginning of this work the calix[4] and calix[6] *p*-sulfonic acids **1** and **2** were prepared according to Scharff et al.[24] These compounds are now commercially available from Janssen Chimica.

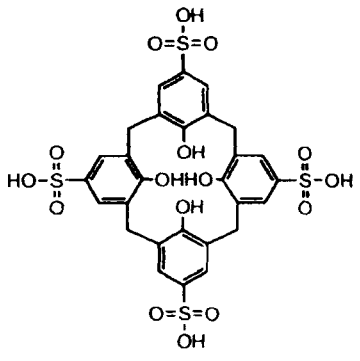
Determination of association constants

Proton NMR spectra were recorded on a Bruker AC 200 spectrometer. Stability constants, log K_s, and limiting chemical shifts, $\Delta\delta_{lim}$, were calculated from the plots of substrate chemical shifts $\Delta\delta$ as a function of macrocycle: substrate ratio, obtained by diluting an aqueous mixture of **1** or **2** (10^{-3} M) and of the substrate (10^{-4} M), adjusted to pD 7.3 with a 0.1 M phosphate buffer, at *ca* 23°C, with an aqueous solution of the substrate at the same concentration (10^{-4} M). In this manner, the concentration of the substrate was kept constant (10^{-4} M) while the concentration of **1** and **2** varied from 10^{-3} M to 3×10^{-5}M. In the case of **2**, competition experiments 1) between NBu_4^+ taken as reference substrate and $PhNMe_3^+$ or NMe_4^+ 2) between $PhNMe_3^+$ as reference and $MeCO_2$ CH_2-$CH_2NMe_3^+$ or $HOCH_2CH_2NMe_3^+$, gave ratios of stability constants consistent with the direct method. All substrates were used as halide salts.

X-ray structure determination for the [choline-tetrasulfonated calix[4]-arene] complex

A solution of 100 mg of calix[4]arene sulfonic acid **1** and 32 mg of choline chloride in 4 mL of water was brought to pH 7.3 by adding 1N NaOH. This solution was evaporated to dryness; the residue was dissolved in 0.7 mL of water and 1.57 mL of MeOH were added. The open vial containing this mixture was placed in a closed larger vial containing 4 mL of THF. The diffusion of THF in the water-MeOH mixture gave crystals suitable for X-ray studies.

A crystal of $0.5\times0.65\times1.0$ mm^3 was used in a sealed glass capillary. The intensities of 15399 reflections were measured with a Philips PW1100 4-circle diffractometer using monochromatized CuK_α radiation [speed 0.1° s^{-1}, width (1+0.4 tang θ)°, mode ω/2θ]. An empirical absorption correction was applied (μ=3.2 mm-1). The 8813 independent and significant [I>3σ(I) reflections were



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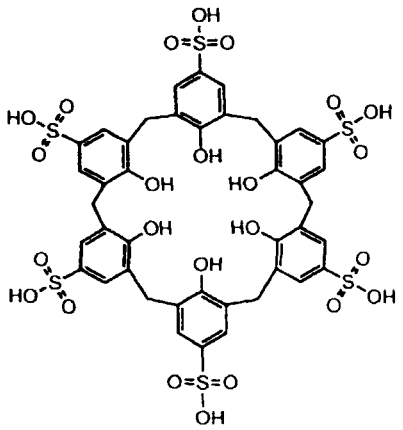

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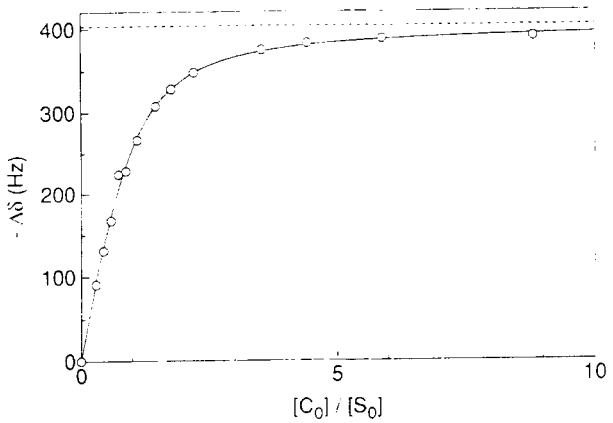

Figure 1 Plots of the observed (open circles) and calculated (curve) upfield shifts Δδ (in Hertz at 200 MHz) of the ^{1}H-NMR CH_3 signal of acetylcholine obtained by progressive addition of the substrate S to the artificial receptor **1** in aqueous solution at pH 7.3, 23°C.

used to solve[25] and refine[26] the structure. Anisotropic thermal parameters were refined (with the exception of minoritary disordered atoms) during F-based blocked least-squares refinement (1237 variable parameters, in 4 blocks). Hydrogen atoms were calculated at theoretical positions whenever possible and introduced in structure factors calculation with isotropic temperature factors. The final R index was 0.064 (R_w=0.069). The crystallographic data are collected in Table 2.

RESULTS AND DISCUSSION

Determination of the association constants

When various ammonium cations were added to **1** and **2** in aqueous solution their ^{1}H NMR spectra displayed large upfield shifts Δδ, which reached a limiting value at a high proportion of calixarenes (Figure 1). The curves Δδ=f[C]/[S], ([C] and [S] being the calixarene and substrate concentrations, respectively) indicated the formation of a 1:1 complex and the association constants K_s were determined by a non-linear least squares method[27] (Table 1).

The two compounds **1** and **2** form remarkably stable complexes with all the cationic ammonium substrates studied and the large shielding effects observed indicate that inclusion of the substrates into the aromatic cavities of the receptor probably takes place. Except entries 2,3 and 4 (Table 1), the stability constants are approximatively the same for the complexes of the two calixarenes but the limiting ^{1}H NMR upfield shifts $\Delta\delta_{lim}$ are always greater with the calix[4]arene than with the calix[6]arene derivative, even with similar stability constants. In fact in the solid state a cone conformation is observed for the calix[4]arene-sulfonate[28] whereas the calix[6]arene-sulfonate adopts a double partial cone conformation[29]. If the solid-state conformation is assumed to reflect that of the solution state[30] there is no direct correlation between the binding properties of **1** and **2**. It may be that the stronger electrostatic interaction expected for the hexa-anionic **2** with respect to the tetracharged **1** is compensated in part by the less favorable conformation of **2** as compared to the cone shape of **1**.

The shift of the terminal methyl signals decreases along with the length of the alkyl chain which is in favor of an inclusion of the quaternary ammonium cation within the cavity. The selectivity which is about the same in the two series, $Et_4N^+ > Me_4N^+ > Pr_4N^+ > Bu_4N^+$ (Table 1, entries 1, 2, 3, 4 and 6,7) may be taken to illustrate the opposite effects of the lipophilicity and of the steric interactions, the ethyl group showing the best balance between the two. As for the class of receptors termed speleands, that form inclusion complexes, speleates, with molecular substrates of various geometries[1,31], the binding properties of the sulfonated derivatives **1** and **2** result from the synergistic operation of electrostatic interactions and of hydrophobic effects. The role of the cation-π interactions[3,13] or the CH-π interaction[11] between highly polarized CH_3-N moieties of the guest and electron rich aromatic rings of the host is, here, difficult to evaluate.

The upfield shifts of the methyl signals and the K_s values of the complexes formed with choline derivatives are remarkable indeed (Table 1, entries 8–10). These are the highest values ever reported for the acetylcholine

Table 1 Stability constants log K_s and limiting ^{1}H NMR upfield shifts $\Delta\delta_{lim}$ calculated for the complexes of calixarenes **1** and **2** with cationic molecular substrates

Entry	Substrate	calix[4]		calix[6]	
		log K_s[a]	$\Delta\delta_{lim}$[b]	log K_s[a]	$\Delta\delta_{lim}$[b]
1	NMe_4^+	4.9	371.5	4.9	258.2
2	NEt_4^+	5.6	253.4	5.0	218.1
3	NPr_4^+	4.5	154.7	4.2	70.6
4	NBu_4^+	4.0	124.1	3.2	59.8
5	$PhNMe_3^+$	4.6	273.7	4.5	261.8
6	$PhCH_2NMe_3^+$	4.6	369.3	4.6	263.7
7	$PhCH_2NEt_3^+$	4.9	292.1	4.8	165.9
8	$HOCH_2CH_2NMe_3^+$	4.7	399.3	4.8	263
9	$MeCO_2CH_2CH_2NMe_3^+$	4.7	403.4	4.9	264.9
10	$MeCOSCH_2CH_2NMe_3^+$	4.7	378.5	4.7	272.4

[a] log K_s ± 0.2; K_s in 1 mol^{-1}. [b] Shifts of the terminal Me signals given in Hz at 200 MHz.

Table 2 Crystal structure data for the complex of **1** with choline

Formula	$[(C_{28}H_{24}O_{16}S_4)^{5-}, (C_5H_{14}NO)^+]_2, 8Na^+, 14H_2O$
Weight	2109.9
Crystal system	triclinic
Space group	$P\bar{1}$
Cell dimensions	
a(Å)	14.713 (6)
b(Å)	18.267(7)
c(Å)	19.353(8)
α(deg)	106.03(5)
β(deg)	112.18(6)
γ(deg)	102.13(4)
V(Å^3)	4331(3)
Z	2
d_X(gcm^{-3})	1.62
R	0.064

binding by an artificial receptor and are comparable to those of the biological recognition sites[3c,32]. They agree with preliminary biochemical studies; the rate of hydrolysis of the acetylthiocholine by the acetylcholinesterase decreases steadily in the presence of increasing concentration of calix[6]arene derivative **2** showing a competition between the enzyme and the artificial receptor.[33]

Crystal structure of the [choline-tetrasulfonated calix[4]arene]-complex

The complex formed between the choline cation and the tetrasulfonated calix[4]arene **1** was crystallized and its structure was determined by X-ray crystallography. Crystallographic data are collected in Table 2. Two complexes A and B were observed in the asymmetric unit (Figure 2). In each one, the choline inserts its N terminal inside the cavity of the receptor. The calix[4]arene adopts a single cone conformation but the choline substrate is in an extended conformation in complex A, and in two other folded conformations in complex B (75%-25%).

Calix[4]arene conformation

The tilt angles of the aromatic rings with the methylene mean plane are listed in Table 3: in each complex, one phenyl ring is less tilted (ca.119°) than the 3 others (ca. 128° ± 5°), and therefore make smaller dihedral angles with its neighboring aromatic rings. This tilt is important with respect to the relative positions of the phenolic oxygens, and the S···S distances correlate this disposition. The distances between the oxygens are of two types in each complex (see Table 4): three short distances (2.58Å average) and a long one (2.92Å average). For each complex, two hydrogen atoms were clearly located, linking two terminal oxygens through hydrogen bonds (Figure 3):

O3aH·····O2a: 2.58Å and O4aH···O1a: 2.64Å (A)

O2bH·····O1b: 2.63Å and O3bH···O4b: 2.52Å (B)

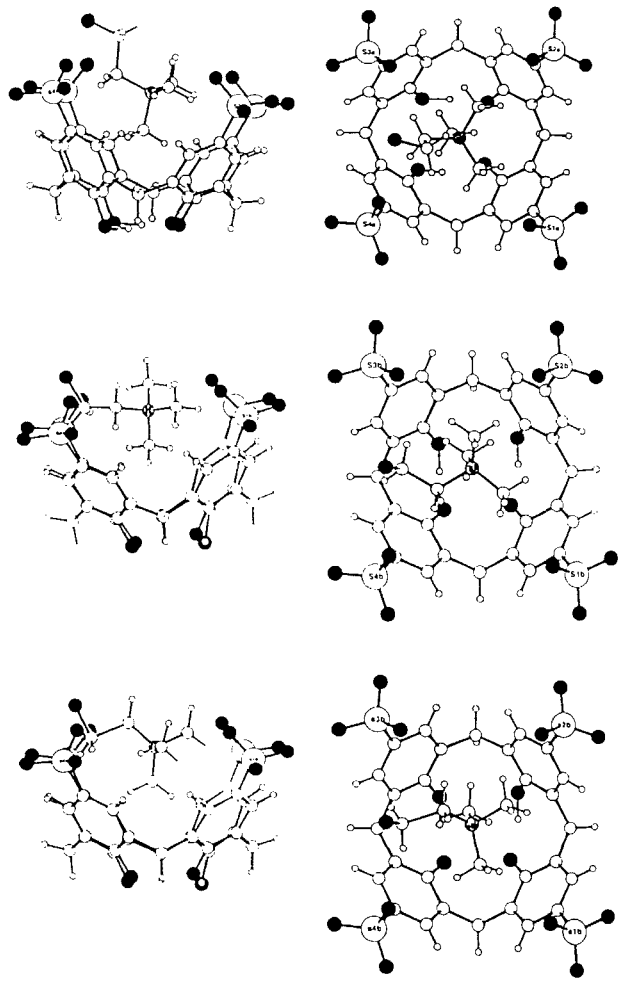

Figure 2 Ortep representations of the choline-calix[4]arene **1** complexes, side and top views: (a) complex A; (b) complex B: (top) major component of the choline (75%); (bottom) choline in its minor (25%) conformation.

No hydrogen atoms could be found between O2A and O1a, nor between O1b and O4b, but their extremely short contact: 2.53(1)Å (A) and 2.49(1)Å (B) suggests a hydrogen atom in a flip-flop position. This pattern of

Table 3 Dihedral angles of the aromatic rings in the calix[4]arene molecule **1**: *(a)* with the methylenic mean plane (=ring); *(b)* between themselves

(a)

Ring	Complex A	Complex B
Ph 1	127	133
Ph 2	127	119
Ph3	123	126
Ph 4	119	131

(b)

	Complex A				Complex B		
	Ph2	Ph3	Ph4		Ph1	Ph3	Ph4
Ph1	110	110	108	Ph1	112	101	114
Ph2		111	113	Ph2		103	111
Ph3			104	Ph3			115

three shorter and one longer O···O distance with only three hydrogen atoms is consistent with the pK_a values for **1**: the first dissociation occurs at very acidic pH values, whereas the residual three dissociations occur at relatively high pH.[24b,34,35] The phenolic O···O distances found in calix[4]arene sulfonate are much longer: between 2.60 and 2.92Å.[29b] The C-O bond lengths show no significant difference (<3s).

Insertion and conformation of the choline substrate

The choline molecule is inserted inside the cavity of the calix[4]arene, with the positively charged N terminal directing axially one of its methyl groups towards the bottom. The linear molecule emerges from the cavity with its hydroxyl pointing between two sulfonates framing a "window" (Figure 4). This contrasts with the structure of **1** with C_6H_5-NMe_3^+ where the phenyl group is located in the cavity.[9d]

Complex A

The choline chain is completely extended with *trans* torsion angles (see Table 5). The choline oxygen OHa points between sulfonates S3 and S4, with the choline oxygen at 3.16Å from O34 and 3.42Å from O13. This "window" is where the phenolic oxygens are the farthest apart (2.90Å). OHa stands at 6.64Å above the basal methylene mean plane of the basket, well above the highest sulfonate oxygen (ca. 4.9Å height). The C5 methyl group, deeply inserted in the basket, is situated at 2.5Å from the methylene mean plane. It is approximately in the center of the cavity, somewhat closer to C43 (3.45Å versus 3.7Å average). The close distances from the methyl groups to the sulfonate oxygens are noteworthy:

choline	sulfonates	
C3a	O22	2.99Å
C4a	O21	3.03Å

Table 4 Correlation between O...O and S...S distances: underlined values correspond to the probable flip-flop H-bond; bold values: correspond to the large O...O distance

Complex A

	O2	O3	O4		S2	S3	S4
O1	*2.53*		2.64	S1	*7.24*		7.38
O2		2.58		S2		7.47	
O3			**2.90**	S3			**6.96**

Complex B

	O2	O3	O4		S2	S3	S4
O1	2.63		*2.49*	S1	*7.79*	7.38	
O2		**2.94**		S2		**6.98**	
O3			2.52	S3			7.90

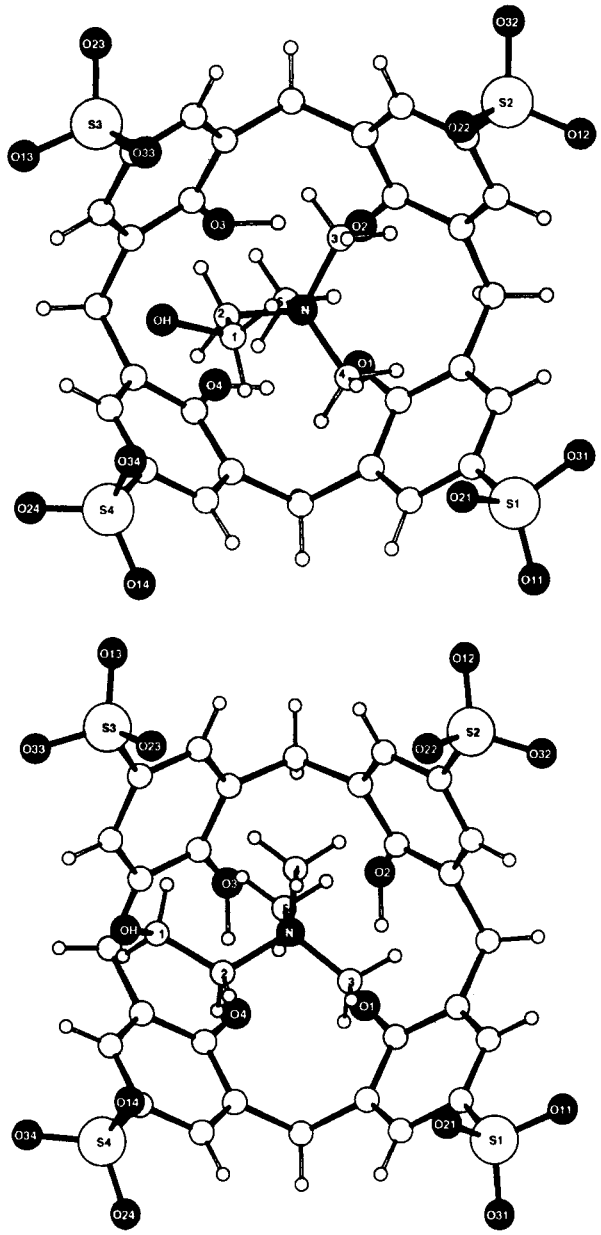

Figure 3 Numbering of the complexes. Are labelled: all the choline atoms, and, for sake of clarity, only the sulfonates and phenolic oxygens; (a) complex A (minor); (b) complex B (major).

Complex B

The substrate has two conformations, obtained by rotation around C2-N and keeping the C1-OHb and the Nb in the same position. Both conformations are folded (see Table 5), the major one having 75% of occupancy. The hydroxyl group is directed into the window between S3 and S4. The phenolic O3 and O4 being hydrogen bonded, the phenyl rings are more strongly tilted (130°) and accordingly, S3 and S4 are further apart: 7.90Å. OHb is at 3.33Å from O14 and 3.76Å from O3. Short contacts are also observed between the carbon atoms and the sulfonate oxygens:

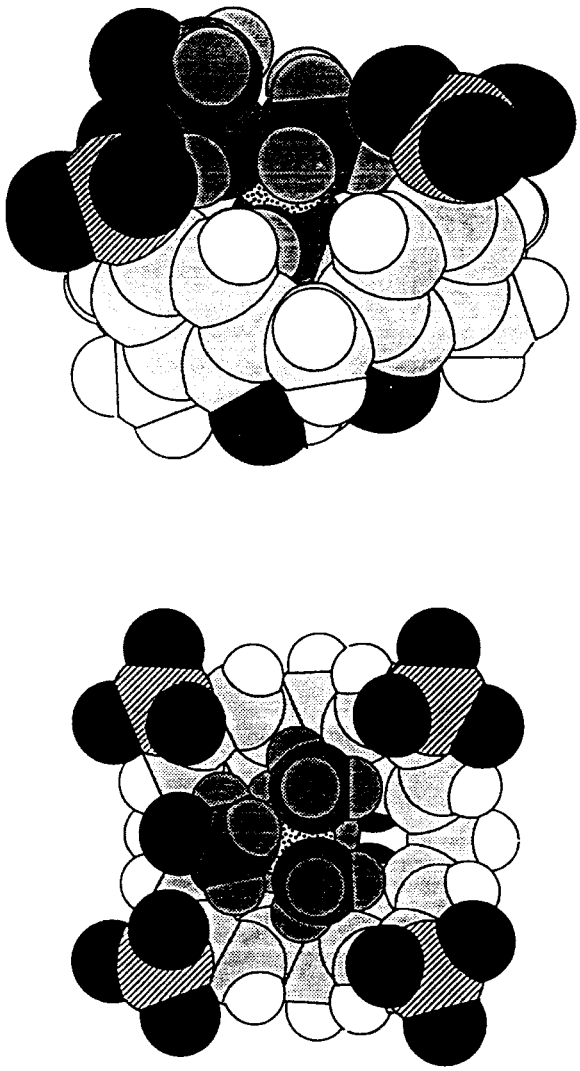

Figure 4 CPK representations of the form A of the [choline, **1**] complex: top (bottom) and side (top) views.

Choline	sulfonate	
C4	O22	3.42
C3	O21	3.36
C2	O14	3.07
C4′ (minor)	O22	3.07

In this complex, the choline sticks less out of the basket, OHb being only at 5.7Å above the basal plane. The calix B conformation is identical to that of calix A. C5 is situated at 2.7Å from the basal plane, and is nearly equidistant from the aromatic rings: C5···C43: 3.45Å (average other distances: 3.9Å).

Table 5 Torsion angles of the choline unit

Complex A	Complex B		
	conf.major.(75%)	conf.minor(25%)	
OHa-C1-C2-N	164°	-114°	153°
C1-C2-N-C5	172°	-67°	62°

C5 is the methyl group directed towards the bottom

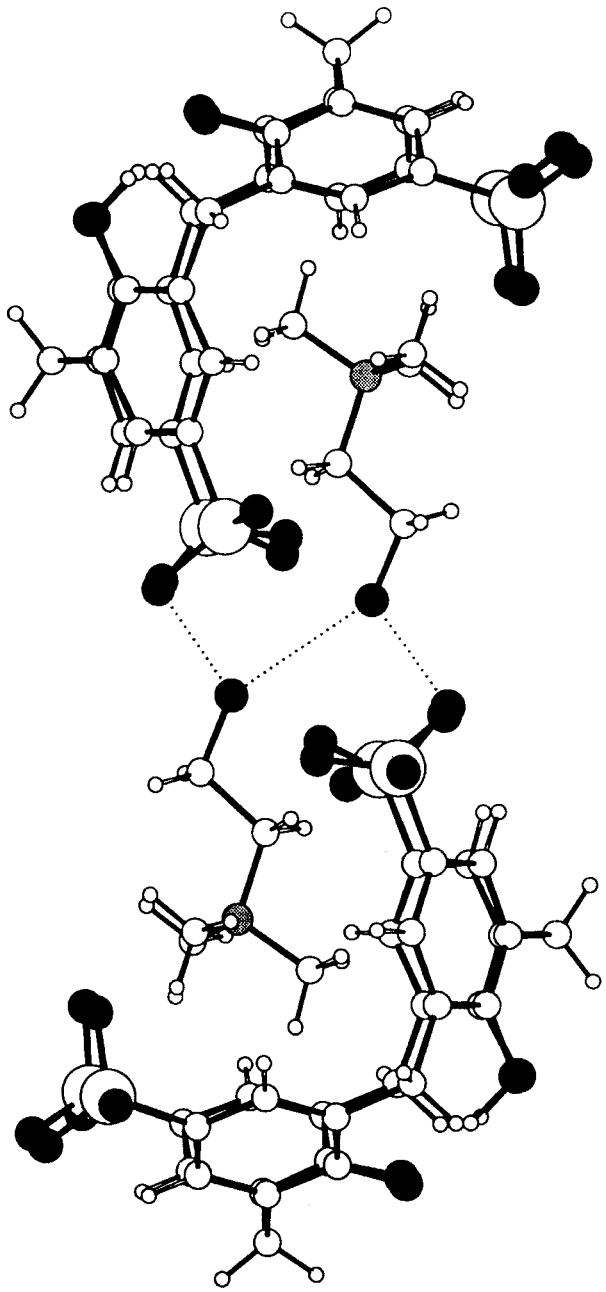

Figure 5 Representation of two complexes A, centrosymmetrically related, with short O···O distances.

The very short contacts observed between the choline atoms and those of the calixarene groups are in line with strong interactions with the substrate and with the high stability of the complex.

Intermolecular interactions

Figure 5 shows the disposition of two complexes A related by a center of symmetry: the two calixarene cones are in reverse position, with the large openings facing each other and slightly offset. Thus, the choline

molecule inserted in one calix is in short contact with both the second calix and its own substrate: OHa (x,y,z)·····OHa (1-x, 1-y, 1-z): 3.07Å; OHa (x, y, z)·····O13a (1-x, 1-y, 1-z): 2.84Å.

Most probably, the latter distance is a hydrogen bond between the choline hydroxyl and the oxygen O1 of the sulfonate S3. It is also possible that a three-center system exists between OHa and O1a (′) and OHa(′) (centrosymmetrically related), but the hydrogen atom was not located on a difference map.

The situation is slightly different with complex B and its centrosymmetrical partner. Although the relative disposition is identical, these two molecules are further apart, and the closest distance is between OHb and the oxygen O1 (′) of sulfonate S1 (′): 3.30Å.

All these complexes are completely surrounded by sodium cations and water molecules. There are 8 sodium cations, one of them (Na4) being disordered between two sites (75-25%). There are 14 water molecules, 5 of them situated in two sites with 75-25% occupancy. The sodium coordination is generally octahedral, the cations being bonded to water molecules, sulfonates oxygens and choline oxygen.

Charge equilibration

Each calixarene bears 4 minus charges (sulfonates) plus one between the phenolic oxygens, as we assumed the presence of a hydrogen oscillating between 2 of them. The total of 10 minus charges in the asymmetric unit is counterbalanced by the 8 sodium cations and the two cholines. This agrees with the results obtained from the crystal structures of the tetraethylammonium salt of the monoanion of *p-tert*-butylcalix[4]arene[16] as well as of the NMe_4^+ complex of **1** described in this issue[36].

ACKNOWLEDGEMENTS

We thank Professor M. Goeldner and Dr. L. Peng for preliminary biochemical studies.

REFERENCES

1 *(a)* Dhaenens, M.; Lacombe, L.; Lehn J.-M.; and Vigneron, J.P.; *J. Chem. Soc., Chem. Commun.*, **1984**, 1097; *(b)* Dhaenens, M.; Fernandez, M.-J.; Lehn J.-M.; and Vigneron, J.-P.; *New J. Chem.*, **1991**, *15*, 873; *(c)* Méric, R.; Vigneron J.-P.; and Lehn, J.-M.; *J. Chem. Soc., Chem. Commun.*, **1993**, 129.

2 Schneider, H.-J.; Güttes D.; and Schneider, U.; *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 647; Schneider, H.-J.; and Schneider, U.; *J. Org. Chem.*, **1987**, *52*, 1613; Schneider, H.-J.; Güttes D.; and Schneider, U.; *J. Am. Chem. Soc.*, **1988**, *110*, 6449.

3 *(a)* Petti, M.A.; Shepodd, T.J.; Barrans, Jr R.E.; and Dougherty, D.A.; *J. Am. Chem. Soc.*, **1988**, *110*, 6825; *(b)* Stauffer, D.A.; Barrans, Jr R.E.; and Dougherty, D.A.; *J. Org. Chem.*, **1990**, *55*, 2762; *(c)* Dougherty, D.A.; and Stauffer, D.A.; *Science*, **1990**, *250*, 1588, *(d)* Kearny, P.C.; Mizoue, L.S.; Kumpf, R.A.; Forman, J.E.; McCurdy, A.; Dougherty, D.A.; *J. Am. Chem. Soc.*, **1993**, *115*, 9907.

4 Vögtle, F.; Merz T.; and Wirtz, H.; *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 221; Merz, T.; Wirtz H.; and Vögtle, F.; *Angew. Chem. Int. Ed. Engl.*, **1986**,

5 Jarvi, E.T.; and Whitlock, H.W.; *J. Am. Chem. Soc.*, **1982**, *104*, 7196.

6 Miyake, M.; Kirisawa M.; and Koga, K.; *Tetrahedron Lett.*, **1991**, *32*, 7295.

7 Poh B.-L.; and Lim, C.S.; *Tetrahedron*, **1990**, *46*, 3651.

8 *(a)* Collet, A.; Dutasta J.-P.; and Lozach, B.; *Bull. Soc. Chim. Belg.*, **1990**, *99*, 617; *(b)* Garel, L.; Lozach, B.; Dutasta, J.-P.; Collet, A.; *J. Am. Chem. Soc.*, **1993**, *115*, 11652.

9 *(a)* Shinkai, S.; Araki K.; and Manabe, O.; *J. Am. Chem. Soc.*, **1988**, *110*, 7214; *(b)* Arimura, T.; Kubota, K.; Araki, K.; Shinkai S.; and Matsuda, T.; *Tetrahedron Lett.*, **1989**, *30*, 2563; *(c)* Shinkai, S.; Araki, K.; Matsuda T.; and Manabe, O.; *Bull. Chem. Soc. Jpn.*, **1989**, *62*, 3856; *(d)* Shinkai, S.; Araki, K.; Matsuda, T.; Nishiyama, N.; Ikeda, H.; Takasu I.; and Iwamoto, M.; *J. Am. Chem. Soc.*, **1990**, *112*, 9053; *(e)* Shinkai, S.; Araki, K.; Kubota, M.; Arimura T.; and Matsuda, T.; *J. Org. Chem.*, **1991**, *56*, 295.

10 Zhang, L.; Macias, A.; Lu, T.; Gordon, J.I.; Gokel G.W.; and Kaifer, A.E.; *J. Chem. Soc., Chem. Commun.*, **1993**, 1017.

11 Kobayashi, K.;. Asakawa, Y; and Aoyama, Y.; *Supramol. Chem.*, **1993**, *2*, 133.

12 Bates, P.S.; Kataky R.; and Parker, D.; *J. Chem. Soc., Chem. Commun.*, **1993**, 691.

13 Stauffer, D A.; Dougherty, D.A.; *Tetrahedron Lett.*, **1988**, *29*, 6039.

14 Collet, A.; Dutasta, J.-P.; Lozach B.; and Chauvet, J.-P.; *Abstr. Int. Symp. Macrocyclic Chem.*, **1991**, *16*, KL 21.

15 De Iasi G.; and Masci, B.; *Tetrahedron Lett.*, **1993**, *34*, 6635.

16 Harrowfield, J.M.; Ogden, M.I.; Richmond, W.R.; Skelton, B.W.; and White, A.H.; *J. Chem. Soc. Perkin Trans 2*, **1993**, 2183.

17 Lippman, T.; Wilde, H.; Pink, M.; Schafer, A.; Hesse, M.; Mann, G.; *Angew. Chem., Int. Ed. Engl.*; **1993**, *32*, 1195.

18 Triggle, D.J.; *Chemical Aspects of the Autonomic Nervous System*, Academic Press, London, 1965.

19 Schneider, H.-J.; Blatter, T.; Simova, S.; Theis, I.; *J. Chem. Soc., Chem. Commun.*, **1989**, 580.

20 For a comprehensive review see Diederich, F.; *Cyclophanes*, Royal Society of Chemistry, Cambridge (1991), Chapt. 4.

21 Sussman, J.-L.; Harel, M.; Frolow, F.; Gefner, C.; Goldman, A.; Toker, L.; Silman, I.; *Science*, **1991**, *253*, 872.

22 Changeux, J.-P.; Devillers-Thiéry, A.; Galzi, J.-L.; Bertrand, D..; *TIPS*, **1992**, *13*, 299.

23 Maelicke, A.; *TIBS*, **1991**, *16*, 355 and references cited therein.

24 *(a)* Scharff, J.-P.; Mahjoubi, M.; Perrin, R.; *C.R. Acad. Sci. Paris*, **1990**, *311*, 73; *(b)* Scharff, J.-P., Mahjoubi, M.; Perrin, R.; *New. J. Chem.*; **1991**, *15*, 883.

25 Sheldrick, G.M.; SHELXS 86, Program for the solution of crystal structures, University of Göttingen, Germany, 1986.

26 Sheldrick, G.M.; SHELX 76, Program for crystal structure determination, University of Cambridge, England, 1976.

27 Program NLSQ. We thank Professor H.W. Whitlock, Jr., University of Visconsin, for providing a copy of this program.

28 Coleman, A.W.; Bott, S.G.; Morley, S.D.; Means, C.M.; Robinson, K.D.; Zhang, H.; Atwood, J.L.; *Angew. Chem. Int. Ed. Engl.*, **1988**, *27*, 1361.

29 *(a)* Atwood, J.L.; Clark, D.L.; Juneja, R.K.; Orr, G.W.; Robinson, K.D.; Vincent, R.L.; *J. Am. Chem. Soc.*, **1992**, *114*, 7558; *(b)* Atwood, J.L.; Orr, G.W.; Hamada, F.; Vincent, R.L.; Bott, S.G.; Robinson, K.D.; *J. Incl. Phenom.*, **1992**, *14*, 37.

30 See reference (28) in 29 (a).

31 Canceill, J.; Collet, A.; Gabard, J.; Kotzyba-Hibert F.; and Lehn, J.-M.; *Helv. Chim. Acta*, **1982**, *65*, 1894; Lehn, J.-M.; *Angew. Chem.*, **1988**, *100*, 91; *Angew. Chem., Int. Ed. Engl.*, **1988**, *27*, 89.

32 Hasan, F.B.; Cohen, S.G.; and Cohen, J.B.; *J. Biol. Chem.*; **1980**, *255*, 3998.; Hasan, F.B.; Elkind, J.L.; Cohen, S.G.; and Cohen, J.B.; *ibid*, **1981**, *256*, 7781; Cohen, S.G.; Lieberman, D.L., Hasan, F.B.; and Cohen, J.B.; *ibid*, **1982**, *257*, 14087.

33 Goeldner, M.; Peng, L.; Lehn, J.-M.; Méric, R.; Vigneron, J.-P.; unpublished results.

34 Yoshida, I.; Yamamoto, N.; Sagara, F.; Ishii, D.; Ueno, K.; and Shinkai, S.; *Bull. Chem. Soc. Jpn.*, **1992**, *65*, 1012.

35 Arena, G.; Cali, R.; Lombardo, G.G.; Rizzarelli, E.; Sciotto, D.; Ungaro, R.; and Casnati, A.; *Supramol. Chem.*, **1992**, *1*, 19.

36 Atwood, J.L.; Barbour, L.J.; Junk, P.C.; Orr, G.W.; *Supramol. Chem.*, **1995**, *5*, 105.