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Complexation of Quaternary Ammonium Ions by Tetraester Derivatives of [3.1.3.1]Homooxacalixarene in Mobile and in Fixed Conformation

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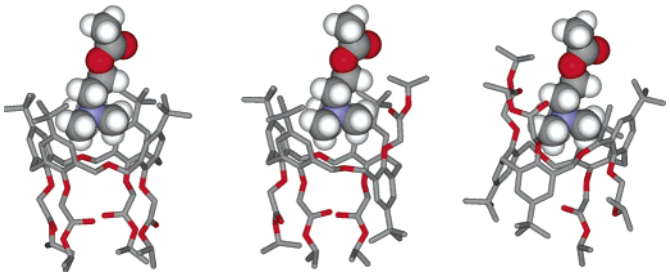

In the tetraalkylation of *p-tert*-butyl[3.1.3.1]homooxacalixarene with $BrCH_2CO_2R$ and K_2CO_3 in acetone, the initially formed cone conformer is converted into the more stable 1,4-alternate conformer when R = Me or Et, but not when R = *i*-Pr or *t*-Bu. In the case of R = *i*-Pr, derivatives in fixed 1,4-alternate conformation and in partial cone conformation were also isolated. Compounds in fixed cone conformation are good ligands for tetramethylammonium, acetylcholine, and *N*-methylpyridinium salts in $CDCl_3$, but the partial cone isomer proved to be somewhat better and even the 1,4-alternate conformer turned out to be active. The possible involvement of the ester functions as additional binding sites is discussed; moreover, an insight into the energetics of the complexation and conformational isomerization processes is given.

Introduction

The name [3.1.3.1]homooxacalixarene indicates the oxygenated homologues of calixarenes[1] in which two distal methylene groups bridging the aromatic units in the typical calix[4]arene series are replaced by CH_2OCH_2 groups.[2−4]

No and associates investigated *p*-phenyl[3.1.3.1]homooxacalixarene **1** and particularly reported on its doubly crown ether bridged and on its tetraamide derivatives.[5] Our own interest in this system is manifold. Concerning the parent compounds, we found that **1** and *p-tert*-butyl[3.1.3.1]homooxacalixarene **2**[6] are powerful ligands for uranyl ion in basic media, thus providing a stable dianionic complex core suitable for assembling supramolecular structures.[7] We also recently reported on the peculiar dynamic picture observed in the acetylation of **2** in the presence of CsF;[8] moreover, we reported on ether

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(1) (a) Gutsche, C. D. *Calixarenes*; The Royal Society of Chemistry: Cambridge, England, 1989. (b) Gutsche, C. D. *Calixarenes Revisited*; The Royal Society of Chemistry: Cambridge, England, 1997. (c) *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer: Dordrecht, The Netherlands, 1991. (d) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, The Netherlands, 2001.

(2) Masci, B. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, The Netherlands, 2001.

(3) Masci, B; Levi Mortera, S.; Persiani, D.; Thuéry, P. *J. Org. Chem.* **2006**, *71*, 504.

(4) We suggest abandoning the commonly used but ambiguous name tetrahomodioxacalix[4]arene for the present ring system, since it could also indicate the isomeric system featuring two vicinal CH_2OCH_2 groups.[2,3]

(5) (a) No, K. *Bull. Korean Chem. Soc.* **1999**, *20*, 33. (b) No, K.; Chung, H. J.; Yu, H. J.; Yang, S. H.; Noh, K. H.; Thuéry, P.; Vicens, J.; Kim, J. S. *J. Inclusion Phenom. Macrocyclic Chem.* **2003**, *46*, 97. (c) No, K.; Lee, J. H. *Bull. Korean Chem. Soc.* **2003**, *24*, 151. (d) No, K.; Bok, J. H.; Suh, I. H.; Kang, S. O.; Ko, J.; Nam, K. C.; Kim, J. S. *J. Org. Chem.* **2004**, *69*, 6938. (e) No, K. H.; Kim, J. S.; Shon, O. J.; Yang, S. H.; Suh, I. H.; Kim, J. G.; Bartsch, R. A.; Kim, J. Y. *J. Org. Chem.* **2001**, *66*, 5976. (f) No, K.; Lee, J. H.; Yang, S. H.; Yu, S. H.; Cho, M. H.; Kim, M. J.; Kim, J. S. *J. Org. Chem.* **2002**, *67*, 3165. (g) No, K.; Lee, J. H.; Yang, S. H.; Noh, K. H.; Kim, S. K.; Seo, J.; Lee, S. S.; Kim, J. S. *J. Inclusion Phenom. Macrocyclic Chem.* **2003**, *47*, 167. (h) No, K.; Lee, J. H.; Yang, S. H.; Noh, K. H.; Lee, S. W.; Kim, J. S. *Tetrahedron* **2003**, *59*, 2403. (i) Choi, J. K.; Lee, A.; Kim, S.; Ham, S.; No, K.; Kim, J. S. *Org. Lett.* **2006**, *8*, 2006.

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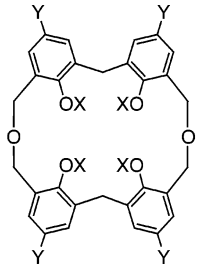
derivatives of **2**, which proved to be rather good ligands for quaternary ammonium ions in lipophilic solvents.[3,9,10] In the series including **3** and the products of partial methylation of **2**, in particular, the binding parameters could be related to the relative abundance and to the shape of the cone conformation, which regularly changed along the series.[3]

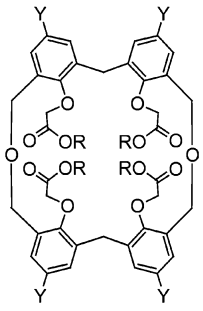


1: Y = Ph, X = H

2: Y = *t*-Bu, X = H

3: Y = *t*-Bu, X = Me

Here, we report on another family of simple derivatives, namely compounds **4**−**8**, obtained through complete etherification of **1** and **2** with alkyl bromoacetates.



4: Y = Ph, R = Et

5: Y = *t*-Bu, R = Me

6: Y = *t*-Bu, R = Et

7: Y = *t*-Bu, R = *i*-Pr

7c: cone conformation

7p: partial cone conformation

7a: 1,4-alternate conformation

8: Y = *t*-Bu, R = *t*-Bu

8c: cone conformation

No and associates already reported on **4**,[11] while **6** and **8** were already investigated with the aim at developing alkali metal ion selective electrodes based on calixarenes.[12−15] Since the most important structural features of the already reported compounds appear to have been overlooked, we undertook a systematic investigation on this family of compounds, with a special aim at obtaining strong ligands for quaternary ammonium ions thanks to the control of the conformational isomerism. The main conformations of [3.1.3.1]homooxacalixarenes are given in Figure 1.[16]

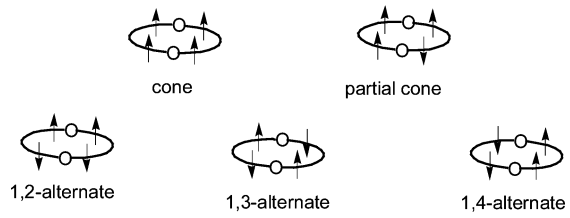


FIGURE 1. Schematic representation of the ideal conformations of [3.1.3.1]homooxacalixarenes.

The 1,4-alternate conformation was previously established in the solid state for both **4**[11] and **6**.[12] In the case of **4**, on the basis of the NMR spectra, the same conformation was reported to occur also in $CDCl_3$,[11] while for **6** and **8** the NMR spectra were not even reported, the compounds having been mainly investigated for analytical purposes.[17]

Results and Discussion

Synthesis and Structure in Solution. We started our investigation by analyzing the ^{1}H NMR spectrum of **6** in $CDCl_3$. This was in agreement with the 1,4-alternate conformation observed in the solid state,[12] but minor spurious peaks were present that did not disappear upon repeated recrystallization. The same picture was observed on investigating **5** and reinvestigating **4**, so that we concluded that for the three compounds an equilibration takes place, which is slow on the NMR time scale, and that the spurious signals should be attributed to minor conformations. In the case of **5**, the [1,4-alternate]/[cone] ratio at 298 K, as determined by ^{1}H NMR spectra, was found to be about 15 in $CDCl_3$ or $CDCl_2CDCl_2$, and about 8 in $(CD_3)_2CO$. Moreover, in this case the rate of interconversion from 1,4-alternate to cone conformation could be roughly estimated ($k = 510\ s^{-1}$ at 371 K, $\Delta G^{\#}_{371} = 17$ kcal mol^{-1}) through ^{1}H NMR spectra taken at high temperature in $CDCl_2CDCl_2$.[18] Similar contributions from minor conformations appear to occur in the case of **4** and **6**, but, as expected, the interconversion is slower with the bulkier substituents at the lower rim. We managed to obtain ligands **7** and **8**, featuring bulkier groups, in fixed conformation, and we could actually isolate **7c** and **8c** in cone conformation, **7p** in partial cone conformation, and **7a** in 1,4-alternate conformation. No evidence of conformational equilibration was obtained in these cases, even after heating several

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(7) (a) Thuéry, P.; Masci, B. *J. Chem. Soc., Dalton Trans.* **2003**, 2411. (b) Masci, B.; Gabrielli, M.; Levi Mortera, S.; Nierlich, M.; Thuéry, P. *Polyhedron* **2002**, *21*, 1125. (c) Masci, B.; Levi Mortera, S.; Thuéry, P. *Acta Crystallogr., Sect. C* **2005**, *61*, m482. (d) Masci, B.; Thuéry, P. *CrystEngComm* **2006**, *8*, 764.

(8) Masci, B.; Levi Mortera, S.; Persiani, D.; Thuéry, P. *Org. Lett.* **2006**, *8*, 4405.

(9) De Iasi, G.; Masci, B. *Tetrahedron Lett.* **1993**, *34*, 6635.

(10) Masci, B.; Finelli, M.; Varrone, M. *Chem.−Eur. J.* **1998**, *4*, 2018.

(11) No, K.; Park, Y. J.; Choi, E. J. *Bull. Korean Chem. Soc.* **1999**, *20*, 905.

(12) Arnaud-Neu, F.; Cremin, S.; Cunningam, D.; Harris, S. J.; McArdle, P.; McManus, M. A.; Schwing-Weil, M. J.; Ziat, K. *J. Inclusion Phenom.* **1991**, *10*, 329.

(13) Cadogan, A.; Diamond, D.; Cremin, S.; McKervey, A. M.; Harris, S. *Anal. Proc.* **1991**, *28*, 13.

(14) Harris, S. J.; McKervey, M. A.; Svehla, G.; Diamond, D. U.S. Patent 5,132,345, 1992.

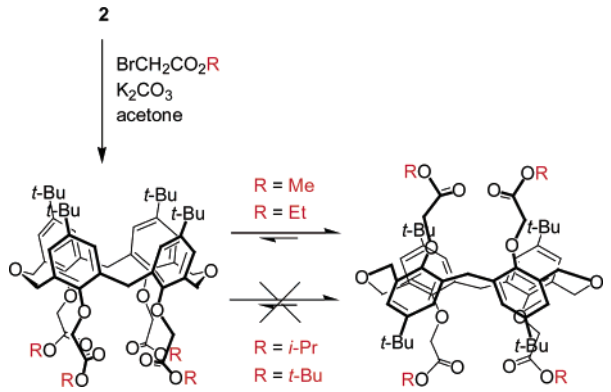
(15) In some instances, the drawings of the structures of **6** and **8** reported in refs 13 and 14 are misleading, the isomeric tetrahomodioxacalix[4]arene, namely [3.3.1.1]homooxacalixarene rather than [3.1.3.1]homooxacalixarene, being represented. This possibly explains some difficulties encountered in retrieving the above compounds from the literature but also demonstrates the usefulness of the naming system we have adopted.[2,3]

(16) 1,2-Alternate and 1,4-alternate conformations are indicated by No et al.[5,6b−e] as COC-1,2-alternate and C-1,2-alternate, respectively. The naming system we proposed in ref 2 is intended to be useful for conformation of isosubstituted homooxacalix[4]arenes in general.

(17) Compound **8** is also commercially available from Fluka under the name "potassium ionophore IV".

(18) The coalescence of the two sets of signals for CH_2O protons of the 1,4-alternate conformation from AB systems to singlet peaks was investigated, and the effect of the minor cone conformation was neglected. The determined rates ($k_{371} = 250\ s^{-1}$ and $k_{373} = 310\ s^{-1}$, obtained through the standard formula $k_{Tc} = 2.22(\Delta\nu^2 + 6J_{AB})^{0.5}$) refer to the inversion of the 1,4-alternate conformation. The overall considered sequence is: 1,4-alternate → partial cone → cone → partial cone → 1,4-alternate, and the different stability of the cone and partial cone conformations suggested that also the two values of free energy for the four involved transition states should be rather different. A statistical factor of 2 was then assumed[10] for 1,4-alternate → cone conversion and for the free energy barrier computed by the Eyring equation. The latter corresponded to 17.3 kcal mol^{-1}, but the error introduced on neglecting the effect of the cone conformation on coalescence cannot easily be estimated.

SCHEME 1



hours at 70 °C. The structure assignment was made on the basis of ^{1}H NMR and ^{13}C NMR spectra, and single-crystal X-ray diffraction in the case of **7c** and **8c**. In general, the same NMR patterns are expected for compounds in cone and in 1,4-alternate conformations. Interestingly, when **2** was reacted with isopropyl bromoacetate or *tert*-butyl bromoacetate in boiling acetone/K_2CO_3, the fixed cone compounds **7c** and **8c** were obtained as the main components in 54 and 48% yield, respectively. Combined column chromatography and recrystallization steps also allowed isolation of pure samples of **7p** and **7a**. HPLC analysis established that **7c**, **7p**, and **7a** formed in 55, 19, and 1% yield, respectively. To change the selectivity, different base/solvent systems were tested, and the most interesting result obtained was with $Me_4NOH\cdot5H_2O$ in dioxane. Although the overall yield was rather low, a clean-cut preference for the partial cone isomer was observed with this base/solvent system, and HPLC analysis indicated that **7c**, **7p**, and **7a** were formed in 8, 35, and 7% yield, respectively. The overall picture for the formation of **4**−**8** can apparently be summarized as follows: the base counterion acts as a kinetic template, which in the case of the acetone/K_2CO_3 solvent/base system (Scheme 1) promotes the formation of tetraalkylated products in the cone conformation in the whole series **4**−**8**, thanks to multiple chelation of potassium ion by the ether and ester functions at the lower rim.[19] On the basis of the observed binding of tetramethylammonium ion by **7p** (see below), the preferential formation of the partial cone conformer in the presence of Me_4NOH as a base can also be attributed to a template effect. Whenever conformational equilibration takes place, namely in the case of **4**, **5**, and **6**, the most stable 1,4-alternate conformation is found as the sole (solid state) or the prevailing (solution) conformation. It should be noted that in the case of compound **3**, the 1,4-alternate conformation is not only observed in the solid state[3] but is also the sole conformation in solution as detected by NMR spectra at low temperature.[10]

Structure in the Solid State. Compounds **7c** and **8c** crystallize as acetone solvates, and their crystal structure could be determined. The former crystallizes with two independent, but nearly identical molecules in the asymmetric unit. Both compounds are in strongly distorted cone conformations (Figures 2 and 3).

The mean plane defined by the phenolic oxygen atoms O1, O4, O8, and O11 (rms deviations 0.050 and 0.001 Å in **7c** and 0.251 Å in **8c**) can be chosen as a reference plane. It makes dihedral angles with the four aromatic rings that span the wide ranges 35.59(10)−75.90(9)° in **7c** and 44.35(11)−77.00(8)° in

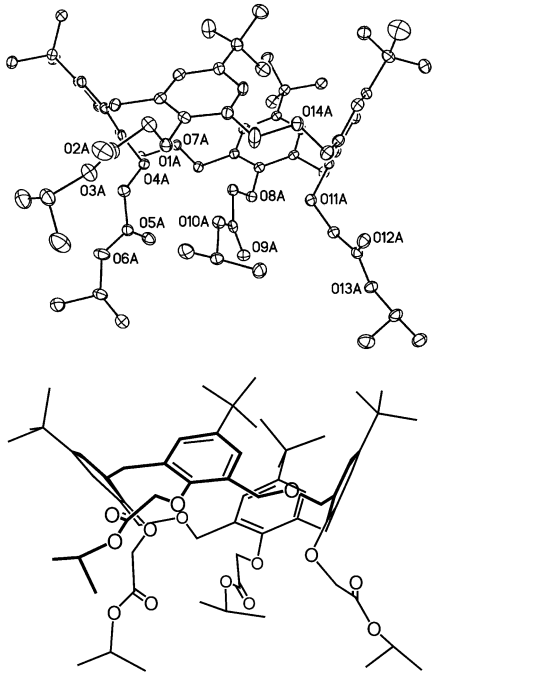


FIGURE 2. View of one of the two independent molecules in the crystal structure of **7c**·$(CH_3)_2CO$. The hydrogen atoms and solvent molecule are omitted. Displacement ellipsoids are drawn at the 30% probability level. A line drawing with the same orientation is also shown.

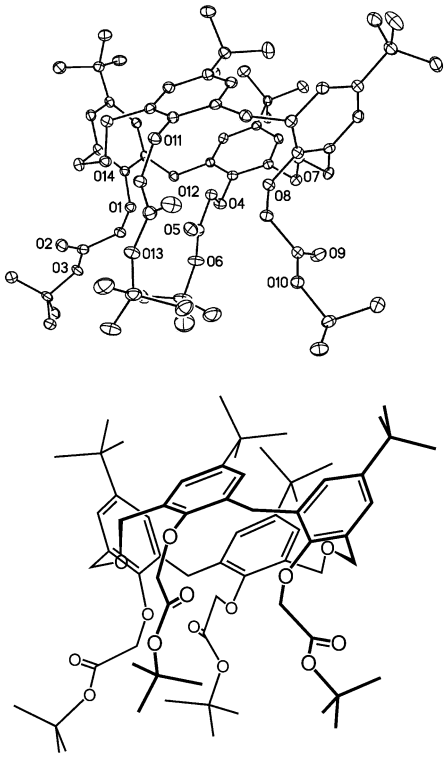


FIGURE 3. View of **8c**·$(CH_3)_2CO$ in the crystal structure. The hydrogen atoms and solvent molecule are omitted. Displacement ellipsoids are drawn at the 30% probability level. A line drawing with the same orientation is also shown.

(19) In the same conditions, the cone conformation is also observed in the case of the corresponding derivatives of calix[5]arenes with bulky substituents. See, for instance: Notti, A.; Parisi, M. F.; Pappalardo, S. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, The Netherlands, 2001.

TABLE 1. Association Constants of Ligands 3−8 in Mobile and in Fixed Conformation, and Limiting Upfield Shifts in the ^{1}H NMR Spectra of the Included Cation[a]

5	130	25	30
6	190	45	50
7a	95	20	25
7p	3200	650	1000
7c	1900	200	370
8c	2100	560	760
4	40		
3[b]	220	25	75

[a] Picrate salts, in $CDCl_3$, at 298 K. Association constants (L mol^{-1}) are given in Roman type and $\Delta\delta_\infty$ (ppm) values are given in italic type. [b] Data from ref 3.

8c. Moreover, one of the aromatic rings has its phenol ether oxygen atom pointing outward, instead of inward as in a regular cone shape. As a consequence, the associated *tert*-butyl group points inward and occupies the cavity. This tilted aromatic ring is thus nearly parallel to the opposite one, with dihedral angles of 11.9(2) and 15.7(2)° in **7c** and 10.9(3)° in **8c**. The O···O distances between opposite phenol ether oxygen atoms are slightly larger for the two nearly parallel aromatic rings [6.522-(3) and 6.335(3) Å in **7c**, 6.626(4) Å in **8c**] than for the other two rings [6.011(3) and 6.076(3) Å in **7c**, 6.269(4) Å in **8c**]. The C−O−C−C torsion angles are different for the two ether bridges in all molecules; one of the bridges is associated with two anti angles and the other is associated with two angles intermediate between anti and gauche. This distorted cone conformation is likely adopted so as to minimize the steric interactions between the four ester substituents, two of which, associated with the tilted ring and its opposite, are roughly parallel to one another, whereas the other two are directed outward.

Complexation of Quaternary Ammonium Ions. In previous work, we used complexation of quaternary ammonium ions in apolar solvents as a suitable test of the shape and size of the potential cavity of homooxacalixarenes.[3,9,10,20] Namely, in the absence of hydrophobic interactions and hydrogen bonding or ion pairing with the ligand, complexation was expected to be

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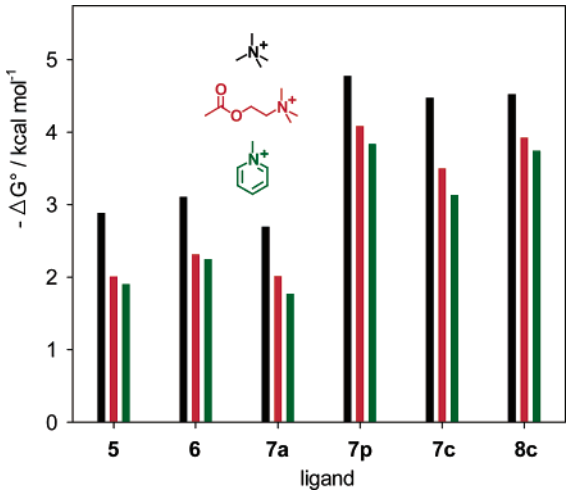


FIGURE 4. Free energy of complexation of TMAP (black), ACP (red), and NMPP (green) by ligands **5**−**8** in mobile and in fixed conformation, in $CDCl_3$ at 298 K.

mainly based on cation−π interaction[21] and to actually test the ability of the ligand to expose several aromatic faces to the included cationic guest.[22] We now report on the complexation of tetramethylammonium picrate (TMAP), *N*-methylpyridinium picrate (NMPP), and acetylcholine picrate (ACP) by ligands **4**, **5**, **6**, **7a**, **7p**, **7c**, and **8c** in $CDCl_3$ at 298 K. The technique used has been reported previously.[3,10,20] The ^{1}H NMR spectra of the salt (0.13 mmol L^{-1} for TMAP, 0.40 mmol L^{-1} for ACP, and 1.00 mmol L^{-1} for NMPP) were recorded in the absence and in the presence of varying concentrations of the ligand. Fast equilibration between free and complexed species took place, although in some cases some peak broadening was apparent. Association constants for 1:1 complexation and $\Delta\delta_\infty$ values (limiting upfield shifts for the several protons of the included cation) as obtained by the multiparameter least-squares treatment are reported in Table 1 for the tested ligand/salt pairs. TMAP was the sole investigated salt in the case of ligand **4**, which proved to be a weaker ligand than the *p-tert*-butyl analogue **6**. In Figure 4, a pictorial view is given of the measured binding energy for the *p-tert*-butyl-substituted tetraester derivatives. The association strength of the ligands **5** and **6** is comparable to that previously determined in the same conditions for other mobile derivatives that are in 1,4-alternate conformation as free ligands; the values for the tetramethyl ether **3**[3] are also reported in Table 1 for comparison purposes. On the other hand, in some instances the $\Delta\delta_\infty$ values are lower than those previously observed. In the case of **3**, the reorganization energy required to reach the cone conformation was held responsible for the

(21) (a) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303. (b) Dougherty, D. A.; Zacharias, N. *Trends Pharmacol. Sci.* **2002**, *23*, 281. (c) Cashin, A. L.; Petersson, E. J.; Lester, H. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **2005**, *127*, 350.

(22) For complexation of quaternary ammonium ions by calixarene and related ligands, see also: (a) Arduini, A.; Demuru, D.; Pochini, A. *Chem. Commun.* **2005**, 645. (b) Arduini, A.; Brindani, E.; Giorgi, G.; Pochini, A.; Secchi, A. *J. Org. Chem.* **2002**, *67*, 6188. (c) Arduini, A.; Giorgi, G.; Pochini, A.; Secchi, A.; Ugozzoli, F. *J. Org. Chem.* **2001**, *66*, 8302. (d) Arduini, A.; Pochini, A.; Secchi, A. *Eur. J. Org. Chem.* **2000**, 2325. (e) Böhmer, V.; Dalla Cort, A.; Mandolini, L. *J. Org. Chem.* **2001**, *66*, 1900. (f) Arnecke, R.; Böhmer, V.; Cacciapaglia, R.; Dalla Cort, A.; Mandolini, L. *Tetrahedron*, **1997**, *53*, 4901. (g) Tran, A. H.; Miller, D. O.; Georghiou, P. E. *J. Org. Chem.* **2005**, *70*, 1115. (h) Dalla Cort, A.; Mandolini, L. In *Calixarenes in Action*; Mandolini, L., Ungaro, R., Eds.; Imperial College Press: London, 2000.

observed modest binding; the conformational rearrangement upon inclusion of the guest cation was indicated in the ^{1}H NMR spectra by a downfield shift, small but straightforward, for the OCH_3 protons that face the aromatic rings in the free ligand but not in the complex.[3,10] With the present mobile ligands, an increase in the [cone]/[1,4-alternate] ratio on adding the salts was in most cases hardly detectable by signal integration, although the occurrence of an extensive interaction was indicated, for instance, by the marked increase in the solubility of TMAP. The above evidence suggested that even ligands in the 1,4-alternate conformation can bind quaternary ammonium ions, and the analysis of the derivatives in fixed conformation was also aimed at confirming such a hypothesis.

Figure 4 shows that in all cases the strength of the interaction decreases in the order TMAP > ACP ≥ NMPP. The guest selectivity is not very high; the K_{TMAP}/K_{NMPP} and K_{TMAP}/K_{ACP} values vary in the range 3.7−9.5 and 2.8−5.1, respectively, with the highest values being observed for ligand **7c**. As expected, the fixed cone conformations of **7** and **8** are rather strong ligands; the interaction with TMAP corresponds to almost 5 kcal mol^{-1}. They behave similarly, although the difference in the binding ability is significant for the larger cations, and the $K_{\mathbf{8c}}/K_{\mathbf{7c}}$ ratios range from 1.1 to 2.8. All the protons of the included cations, apart from those in the tail of acetylcholine, suitably face the aromatic π clouds, as indicated by the high $\Delta\delta_\infty$ values ranging between 1.2 and 2.2 ppm with these ligands.

As outlined in the previous section, the cone shape in the solid state is quite distorted; one *t*-Bu group in particular partly occludes the cavity. Thus, the ligand does not appear to be perfectly preorganized for complexation, and binding is consequently handicapped because it involves an increase in conformational energy. One of the most interesting results in Table 1 and Figure 4 is that the fixed partial cone isomer **7p** is a stronger ligand than the cone isomer **7c**. This can be partly explained by the imperfect preorganization of **7c**, but the possible involvement of the ester function as an additional binding site in **7p** must also be reckoned with. Dipole−cation interactions of this type are well-known in the case of metal ions,[23] while the pieces of evidence are scanty in the case of analogous interactions with quaternary ammonium ions.[24] Unfortunately, all the obtained crystals of **7p** did not suitably diffract, thus preventing single-crystal X-ray analysis on the free ligand. It appears that binding benefits from replacement of one of the aromatic rings of **7c** by an ester function, but subtle conformational and steric effects are superposed to the intrinsic strength of the cation−π and cation−dipole interactions. The binding ability of **7a** in fixed 1,4-alternate conformation is not strong but very significant. With respect to **7c**, in this case two ester functions replace two aromatic rings in the cavity of the ligand. Actually, in all cases the ligands can be considered to be ditopic ones; the two cavities are equivalent in the case of **7a** and very different in the case of **7c** and **8c**. The observed binding by the alternate conformations benefits from a statistical factor of 2. In all cases, the two cavities can be considered to compete for the guest cation, but the high $\Delta\delta_\infty$ values for the cone and partial cone ligands indicate that the cavity featuring a larger number of aromatic faces involves a stronger binding. A more complicated competition takes place in the case of the conformationally mobile ligands **4**, **5**, and **6**. Up to five

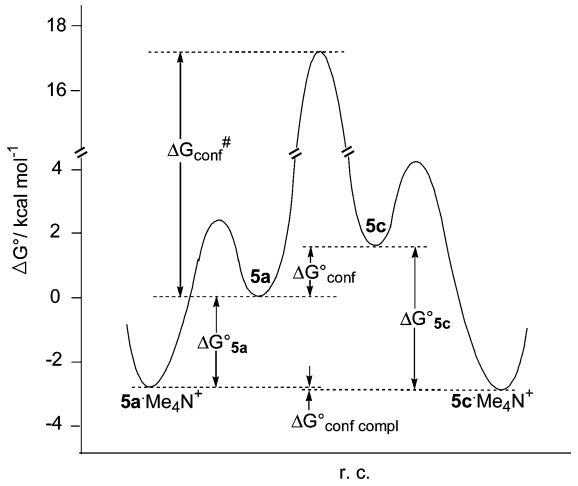


FIGURE 5. Changes in the standard molar free energy of ligand **5** on conformational equilibration and complexation at 298 K. The free energy of the two transition states for complexation has been arbitrarily drawn, while the available value of $\Delta G_{conf}^{\#}$ at 371 K is reported as a rough indication.

conformations of the ligand, featuring seven types of cavities, can be expected to compete for the guest cation. Actually, in the experiments carried out on **4**, **5**, and **6**, no evidence was obtained for a significant involvement of conformations other than 1,4-alternate and cone.

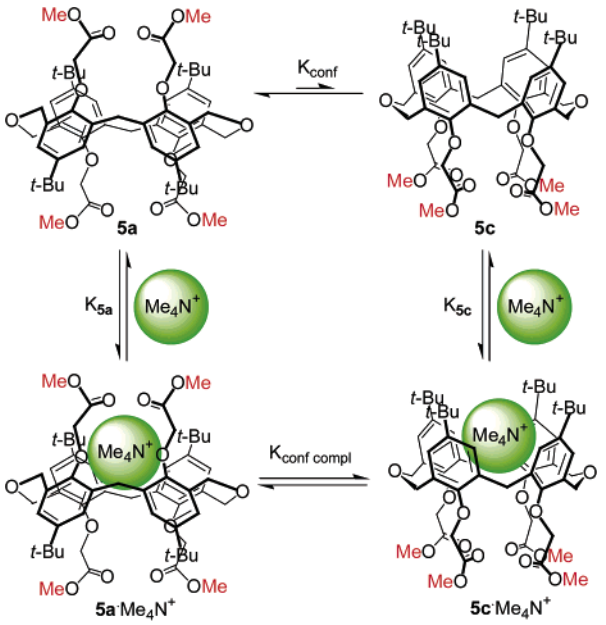
Reasonable assumptions allow us to gain a deeper insight into the energetics of the present systems. On the conformationally mobile free ligand **5** we could investigate the cone−1,4-alternate equilibrium, while on the conformationally fixed **7** we could determine the binding of the three isolated conformers. If we assume that the strength of the interaction with TMAP is roughly the same for ligands in the same conformation, irrespective of the bulkiness of the alkyl substituents (see data for **7c** and **8c** in Table 1), it follows that $K_{\mathbf{5a}} \approx K_{\mathbf{7a}}$ and $K_{\mathbf{5c}} \approx K_{\mathbf{7c}}$. All the values are thus available for the minima in the free energy profile in Figure 5, as based on the association constants defined in Scheme 2. On the other hand, we can assume that the difference in free energy between the fixed conformers **7c** and **7a** is close to that actually determined between the equilibrating **5c** and **5a**, so that the profile in Figure 5 can be assumed to hold for compound **7** as well, apart from a higher barrier preventing conformational inversion. Figure 5 shows that practically the same free energy can be estimated for the two complexed forms of **5** (and **7**); namely, the value of $K_{conf,compl}$ is about 1 and about one-half of the complexed ligand is expected to be in the cone conformation. In spite of this, an increase in the population of the cone conformer on complexation could barely be observed in only a few instances, because of the moderate values of the association constants and of the low solubility of the salt.[25] By the same token, an appreciable increase in the population of the partial cone conformation

(23) See, for instance: Tosteson, D. C. *Perspect. Membr. Biophys.* **1972**, 129.

(24) Roelens, S.; Torriti, R. *J. Am. Chem. Soc.* **1998**, *120*, 12443.

(25) Thus, for instance, in the spectra of **5** in $CDCl_3$ in the absence and in the presence of excess solid TMAP, the experimentally observed [1,4-alternate]/[cone] conformation ratio changed from 15.5 ± 0.5 to 13.9 ± 0.4 (mean values from several integrations of the *t*-Bu signals in ^{1}H NMR spectra of duplicated experiments). The latter value can be compared with the value of 12.4 that can be estimated by the following equation obtained according to Scheme 2 (with $K_{\mathbf{5a}} = K_{\mathbf{7a}}$ and $K_{\mathbf{5c}} = K_{\mathbf{7c}}$, and $[Me_4N^+]$ given by the solubility of the salt at room temperature: 0.14 mmol L^{-1}): $[alternate]_{total}/[cone]_{total} = \{(1 + K_{\mathbf{5a}}[Me_4N^+])/(1 + K_{\mathbf{5c}}[Me_4N^+])\}/K_{conf}$.

SCHEME 2



cannot be expected, in spite of its being an even better ligand than the cone isomer.[26]

Experimental Section

General Procedure for the Preparation of 4−8. A mixture of the tetraphenol, anhydrous K_2CO_3, and the alkyl bromoacetate in dry acetone was refluxed and stirred under a nitrogen atmosphere for 6 days. The solvent was then evaporated, water was added, and the mixture was neutralized (HCl) and extracted with CH_2Cl_2. After being washed with water and dried, an aliquot of the CH_2Cl_2 solution was taken in several cases for the quantitative analysis. The remaining part was evaporated, and the residue was in most cases recrystallized to isolate the main component. Representative procedures to obtain compounds **7** are given below, while an alternative preparation of **7p** and **7a** and the preparation of the other derivatives are given in the Supporting Information.

7,13,21,27-Tetra-*tert*-butyl-29,30,31,32-tetrakis(isopropoxycarbonyl)methoxy-2,3,16,17-tetrahomo-3,17-dioxacalix[4]arene (7). A mixture of **2** (1.00 g, 1.41 mmol), anhydrous K_2CO_3 (1.03 g, 7.47 mmol), and isopropyl bromoacetate (1.28 g, 7.05 mmol) in dry acetone (36 mL) was stirred and refluxed during 6 days under a nitrogen atmosphere. After the usual workup, recrystallization of the crude from chloroform/isopropanol yielded **7c** (800 mg). Column chromatography (SiO_2, eluent: $CHCl_3$) of the material recovered from the mother liquors, followed by recrystallization, afforded small amounts of pure **7a** (7 mg), **7p** (60 mg), and further **7c** (47 mg). A different alternate conformation was also detected but could not be isolated in pure form.

Cone Conformation (7c): 847 mg, 54% yield; mp 170−171 °C (from chloroform/isopropanol); MS (ES^+) *m*/*z* 1131.6 [*M* + Na], 1147.6 [*M* + K]; ^{1}H NMR: δ 1.05 (s, 36H), 1.29 (d, *J* = 6.2 Hz, 12H), 1.31 (d, *J* = 6.2 Hz, 12H), 3.38 (d, *J* = 14.0 Hz, 2H), 4.15 (d, *J* = 16.1 Hz, 4H), 4.53 (d, *J* = 11.4 Hz, 4H), 4.64 (d, *J* = 14.0 Hz, 2H), 4.66 (d, *J* = 16.1 Hz, 4H), 4.91 (d, *J* = 11.5 Hz, 4H), 5.08 (sep, *J* = 6.2 Hz, 4H), 6.98 (app s, 8H). ^{13}C NMR: δ 21.9, 30.5, 31.3, 34.0, 68.4, 69.3, 71.4, 125.6, 127.5, 131.1, 133.1, 146.3, 153.0, 169.6.

Partial Cone Conformation (7p): 60 mg, 4% yield; mp 156−157 °C (from isopropanol); MS (ES^+) *m*/*z* 1131.8 [*M* + Na]; ^{1}H NMR: δ 1.13 (s, 9H), 1.15−1.23 (overlapped 18 H), 1.20 (s, 9H), 1.21 (s, 9H), 1.30 (d, *J* = 6.2 Hz, 3H), 1.33 (d, *J* = 6.2 Hz, 3H), 1.36 (s, 9H), 3.32 (d, *J* = 12.9 Hz, 1H), 3.63 (d, *J* = 15.6 Hz, 1H), 3.79 (d, *J* = 15.6 Hz, 1H), 3.87−3.94 (overlapped, 2H), 4.09−4.48 (overlapped, 9H), 4.55 (d, *J* = 15.8 Hz, 1H), 4.73−4.83 (overlapped, 3H), 4.91−5.12 (overlapped, 5H), 5.16 (d, *J* = 12.9 Hz, 1H), 6.95 (d, *J* = 2.6 Hz, 1H), 7.03 (d, *J* = 2.6 Hz, 1H), 7.09 (d, *J* = 2.6 Hz, 1H), 7.12 (d, *J* = 2.6 Hz, 1H), 7.14 (d, *J* = 2.6 Hz, 1H), 7.27 (d, *J* = 2.6 Hz, 1H), 7.33 (d, *J* = 2.6 Hz, 1H), 7.50 (d, *J* = 2.6 Hz, 1H). ^{13}C NMR: δ 21.7, 21.8, 21.8, 21.8, 21.8, 21.9, 31.3, 31.4, 31.4, 31.5, 32.1, 34.0, 34.0, 34.1, 34.3, 37.8, 67.2, 67.3, 67.7, 67.7, 67.8, 68.1, 68.6, 69.4, 70.5, 70.7, 71.7, 71.7, 126.0, 126.7, 127.2, 127.4, 127.6, 128.0, 128.1, 128.8, 129.4, 129.8, 130.1, 130.7, 132.8, 133.0, 133.7, 134.6, 145.5, 145.8, 146.0, 147.2, 153.1, 153.9, 154.7, 154.8, 168.5, 169.0, 169.8, 170.3.

1,4-Alternate Conformation (7a): 7 mg, 0.5% yield; mp 225−226 °C (from isopropanol); MS (ES^+) *m*/*z* 1131.8 [*M* + Na]; ^{1}H NMR: δ 1.14 (d, *J* = 6.1 Hz, 12H), 1.15 (d, *J* = 6.1 Hz, 12H), 1.21 (s, 36H), 3.35 (d, *J* = 13.2 Hz, 2H), 3.73 (d, *J* = 16.1 Hz, 4H), 4.31 (d, *J* = 16.1 Hz, 4H), 4.40 (d, *J* = 10.6 Hz, 4H), 4.65 (d, *J* = 10.6 Hz, 4H), 4.94 (sep, *J* = 6.1 Hz, 4H), 5.15 (d, *J* = 13.2 Hz, 2H), 7.06 (d, *J* = 2.4 Hz, 4H), 7.15 (d, *J* = 2.4 Hz, 4H). ^{13}C NMR: δ 21.7, 21.8, 31.4, 32.2, 34.0, 67.1, 68.1, 71.3, 127.1, 128.1, 128.3, 134.7, 146.2, 154.4, 169.5.

7,13,21,27-Tetra-*tert*-butyl-29,30,31,32-tetrakis(methoxycarbonyl)methoxy-2,3,16,17-tetrahomo-3,17-dioxacalix[4]arene (5). Isolated in 66% yield; mp 215−216 °C (from chloroform/methanol); MS (ES^+) *m*/*z* 1019.5 [*M* + Na], 521.3 [*M* + 2Na]; ^{1}H NMR of the main conformation (1,4-alternate, ca. 94%): δ 1.24 (s, 36H), 3.35 (d, *J* = 13.5 Hz, 2H), 3.41 (s, 12H), 3.84 (d, *J* = 16.0 Hz, 4H), 4.19 (d, *J* = 16.0 Hz, 4H), 4.36 (d, *J* = 10.8 Hz, 4H), 4.68 (d, *J* = 10.8 Hz, 4H), 4.84 (d, *J* = 13.5 Hz, 2H), 7.17 (d, *J* = 2.3 Hz, 4H), 7.21 (d, *J* = 2.3 Hz, 4H). ^{13}C NMR of the main (1,4-alternate) conformation: δ 30.6, 31.2, 34.1, 51.1, 67.0, 70.7, 127.0, 128.1, 129.1, 133.8, 146.4, 153.6, 169.9; ^{13}C NMR of the less abundant (cone) conformation: δ 30.0, 31.2, 34.0, 51.7, 69.4, 71.1, 125.7, 127.5, 131.4, 133.0, 146.5, 152.9, 170.4.

7,13,21,27-Tetra-*tert*-butyl-29,30,31,32-tetrakis(ethoxycarbonyl)methoxy-2,3,16,17-tetrahomo-3,17-dioxacalix[4]arene (6). ^{1}H NMR spectrum of the main conformation (1,4-alternate, ca. 95%): δ 1.15 (t, *J* = 7.1 Hz, 12H), 1.21 (s, 36H), 3.35 (d, *J* = 13.5 Hz, 2H), 3.77 (d, *J* = 16.1 Hz, 4H), 4.04 (q, *J* = 7.1 Hz, 8H), 4.31 (d, *J* = 16.1 Hz, 4H), 4.41 (d, *J* = 10.6 Hz, 4H), 4.64 (d, *J* = 10.6 Hz, 4H), 5.11 (d, *J* = 13.5 Hz, 2H), 7.08 (d, *J* = 2.4 Hz, 4H), 7.16 (d, *J* = 2.4 Hz, 4H). ^{13}C NMR spectrum of the main conformation: δ 14.0, 31.2, 31.8, 34.0, 60.3, 67.1, 71.0, 127.1, 128.1, 128.2, 134.5, 146.2, 154.2, 169.8.

7,13,21,27-Tetra-*tert*-butyl-29,30,31,32-tetrakis(*tert*-butoxycarbonyl)methoxy-2,3,16,17-tetrahomo-3,17-dioxacalix[4]arene, Cone Conformation (8c). Isolated in 48% yield; mp 203−204 °C (from acetone); MS (ES^+) *m*/*z* 1187.8 [*M* + Na]; ^{1}H NMR: δ 1.07 (s, 36H), 1.49 (s, 36H), 3.37 (d, *J* = 13.8 Hz, 2H), 4.21 (d, *J* = 15.8 Hz, 4H), 4.53 (d, *J* = 11.7 Hz, 4H), 4.60 (d, *J* = 15.8 Hz, 4H), 4.73 (d, *J* = 13.8 Hz, 2H), 4.86 (d, *J* = 11.7 Hz, 4H), 6.99 (app s, 8H). ^{13}C NMR: δ 28.2, 30.8, 30.9, 31.3, 34.0, 69.2, 71.5, 81.2, 125.5, 127.4, 130.7, 133.1, 145.9, 153.0, 169.2.

In the analogous reaction reported in the literature,[13,14] the structure of the isolated material (61% yield from *tert*-butanol, mp 186.8−187.8 °C) was not determined by either NMR or X-ray diffraction analysis.

Complexation Experiments. Reference is made to previous articles[10,20] for the titration technique and data treatment in complexation experiments. Reproducibility of the data was within

(26) Namely, by analogy with the plot and the symbols in Figure 5, we expect for complexation of TMAP by the partial cone conformer that, $-\Delta G°_{5p} \leq -\Delta G°_{5c}$, but $\Delta G°_{conf}$ is higher for **5a** → **5p** than that for **5a** → **5c** (the partial cone conformation cannot be even detected in the free ligand **5**). As a consequence, at the salt and ligand concentrations of the experiments, the amount of partial cone conformation should still be very low, although in principle increased upon complexation.

15% for both K and $\Delta\delta_\infty$ parameters, while the multiple fit procedure afforded the parameters with a standard deviation lower than 2%.

Supporting Information Available: General methods for experimental procedures. Synthesis of compounds **5**, **6**, **7p**, and **8c**. ^{1}H and ^{13}C NMR spectra of compounds **5**, **6**, **7a**, **7p**, **7c**, and **8c**. Temperature, solvent, and complexation effects on the ^{1}H NMR spectra of compound **5**. Typical complexation experiment. Crystal data for compounds **7c**·$(CH_3)_2CO$ and **8c**·$(CH_3)_2CO$. Tables of crystal and refinement data, atomic positions and displacement parameters, anisotropic displacement parameters, bond lengths, and bond angles in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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