Fine Tuning of the Cavity Size in Calixarene-Like Cyclophanes: A Complete Series of Homooxacalix[4]arene Ligands for Quaternary Ammonium Ions**

Bernardo Masci,* Marco Finelli, and Maurizio Varrone

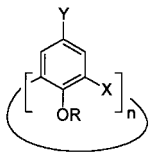
Abstract: Only a few oxygenated homologues of calixarenes have been reported to date, although a large number of structures can be envisaged. These can give rise to a practically new and interesting class of cyclophanes and deserve a systematic investigation. The synthesis is reported of the whole set of *p-tert*-butylhomooxacalix[4]arene compounds with methylated phenol functions and with various combinations and permutations of CH_2 and CH_2OCH_2 units in the connections between the aromatic units. The homooxacalix[4]-arenes obtained constitute a set of cyclophanes (5 compounds besides the typical calix[4]arene) in which the size of the potential cavity and the conformational mobility, as investigated by NMR techniques, smoothly increase as the number of the CH_2OCH_2 groups is increased. Monooxa- and dioxa-homologues are found to exist in solution in only one of the possible main conformations; cone conformations appear to be disfavored in general. In spite of the lack of preorganization, the prepared compounds appear to be suitable hosts for organic cations. When tetramethylammonium picrate and *N*-methylpyridinium iodide are considered as possible guests in $(CDCl_2)_2$ solvent, while no evidence of association is obtained in the case of the reference calix[4]arene compound and weak binding is observed with the monooxa analogue, fairly strong complexes ($-\Delta G^\circ$ values of up to 3.8 kcal mol^{-1}) are formed with dioxa- to tetraoxa-compounds. These are among the most effective neutral ligands for tetramethylammonium salts, particularly when simple monocyclic structures are considered. Several features of the complexation are discussed in the light of the controlled change in the host structure, which proves to be a powerful tool in the evaluation of the effects of steric and charge complementarity on binding.

Keywords: calixarenes · cyclophanes · host–guest chemistry · macrocyclic ligands · quaternary ammonium ions

Introduction

Cyclophanes[1] of the general structure **1**, with $X = CH_2$ and varying Y, R, and *n*, constitute the thoroughly investigated family of calixarene compounds.[2, 3]

Calixarene analogues are also known with X longer than CH_2 in one or more sites of the macrocyclic structure, for example homocalixarenes with $X = CH_2CH_2$[4] or $CH_2CH_2CH_2$,[5, 6] and hetero analogues with $X = CH_2OCH_2$,[7] CH_2SCH_2,[8] or CH_2NRCH_2.[9] In the case of the oxygenated analogues, named homooxacalixarenes, the relation to calixarenes is not only a formal one; some of these compounds are actually formed together with true calixarenes upon heating of alkaline mixtures of phenols and formaldehyde. Three compounds in this series, namely **2**–**4**, are relatively well-known materials,[7] while the isolation of a small sample of the pure compound only has been reported in the case of **5**.[10] In general, homooxacalixarenes appear in the literature from time to time, and some recent papers deal with



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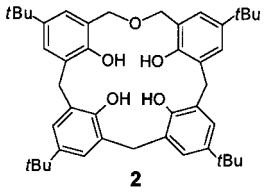

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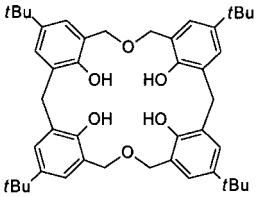

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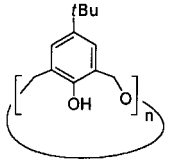

4: n = 3
5: n = 4

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[**] Homooxacalixarenes, Part 4. For Part 3, see ref. [16].

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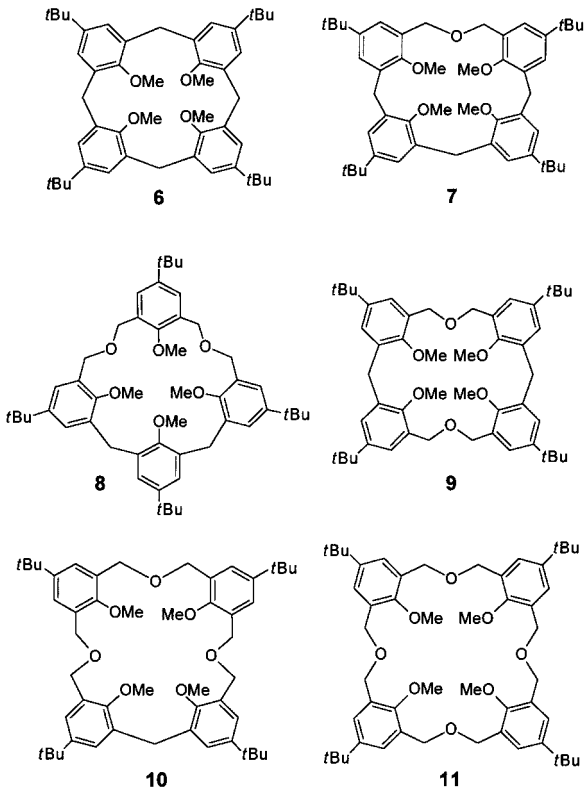
either **2**[11] or **4** and related compounds;[12, 13] however, almost no attention has been paid to homooxacalixarenes as a class of compounds, so we decided to start a systematic investigation. We have already reported on simple synthetic strategies to produce polycyclic ether derivatives related to **3**[14] and **5**,[15] as well as on the complexation of quaternary ammonium ions in organic media by a tricyclic derivative of **3**[14] and by the simple parent compounds **2**–**4**.[16]

Many features of the chemistry of homooxacalixarenes still await investigation. In particular, it should be noted that reported structural variations consist of a few compounds with alkylated phenol functions or with *para* substituents other than *tert*-butyl;[11–13, 17] however, the fundamental systems of known homooxacalixarenes are only those of compounds **2**–**5**, namely dihomooxacalix[4]arene, tetrahomodioxacalix[4]-arene, hexahomotrioxacalix[3]arene, and octahomotetraoxacalix[4]arene, repectively. Since we want to investigate homooxacalixarenes systematically, we must take into consideration the large variety of fundamental rings which are actually conceivable, and in this paper we report on the several possible homooxacalix[4]arene systems, that is, all compounds **1** with $n = 4$, Y = *t*Bu, R = CH_3, and X = CH_2 and/or CH_2OCH_2 in the same ring (compounds **6**–**11**).



In addition to a structural investigation, we were also interested in the family of compounds **6**–**11** to test their properties as hosts for positively charged organic guests. In recent years there have been several reports on the complexation of organic cations in solution,[18] even in the absence of effective noncovalent interactions, such as ion-pairing, hydrophobic forces, hydrogen bonding, or π–π interactions. In particular, Dougherty,[19] Collet,[20] and Lehn[21] have developed classes of polycyclic cyclophanes that complexed quaternary ammonium salts not only as polyanionic hosts in water, but also as neutral ligands in lipophilic solvents, thus unequivocally demonstrating the important role of cation–π interactions.[22] Our results indicated that neutral homooxacalixarene compounds could also be effective in organic solvents—actually they appeared to be a very versatile series because compounds of quite different structure could be obtained and proved to work.[14–16, 23] We felt it was necessary to assess the importance of the type of ring in this kind of complexation, and to this end, a homogeneous series of compounds had to be tested. Since it is better to perform this assessment on simple structures, in the absence of special substitutions, bridging moieties, or intramolecular hydrogen bonding, methyl ethers appeared to be the compounds of choice.

Results and Discussion

Structure and names: We can think of an infinite series of oxygenated homologues of calixarenes which contain mixed X groups in structure **1**, such as CH_2, O, CH_2CH_2O, CH_2OCH_2, OCH_2O, $CH_2CH_2OCH_2$, OCH_2CH_2O, and so on. However, if we restrict ourselves to the typical series of homooxacalixarenes with X = mixed CH_2 and CH_2OCH_2 groups within the same compound, we have four possible fundamental structures when $n = 3$, six structures when $n = 4$, eight structures when $n = 5$ and so on, for these 2*m*-homo-*m*-oxacalix[*n*]arenes in which $0 \le m \le n$. The possible ring structures in the case of $n = 4$ are those of compounds **6**–**11**, compounds with a different number of CH_2OCH_2 groups and isomeric structures being considered. The current nomenclature of calixarenes can work well (see the Experimental Section), but abridged names, such as tetrahomodioxacalix[4]arene used so far to indicate compounds with the same ring type as **9** are clearly ambiguous, since the name should also apply to the isomer **8**. We wish to stress here that the bracketed numbers used in the cyclophane nomenclature to indicate the length of the bridges allow the ring system of these *meta*-cyclophanes (MCP) to be immediately identified.[24] The situation is summarized in Table 1 for the current

Table 1. Tetramethoxy-*p*-*tert*-butylhomooxacalix[4]arenes and nomenclature of the homooxacalixarene systems.

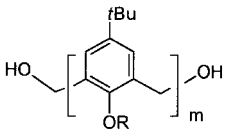
Compound	Current name for the macrocyclic system	Bridges in MCP[a]	References
6	calix[4]arene	[1.1.1.1]	known compound[b]
7	dihomooxacalix[4]arene[c]	[3.1.1.1]	known compound[d]
8	tetrahomodioxacalix[4]arene	[3.3.1.1]	new ring system[e]
9	tetrahomodioxacalix[4]arene	[3.1.3.1]	new compound
10	hexahomotrioxacalix[4]arene	[3.3.3.1]	new ring system
11	octahomotetraoxacalix[4]arene[f]	[3.3.3.3]	new compound

[a] Length of the bridges in the *meta*-cyclophane (MCP) structure. [b] See ref. [25]. [c] Also named bishomooxacalix[4]arene (ref. [26]) and in a few cases dihomomonooxacalix[4]arene to stress the presence of only one oxygen atom in the ring (ref. [16]). [d] See refs. [11b, 11c]. [e] The tetraester compound with this ring system, reported in ref. [27], actually appears to be a derivative of **3**. [f] Hampton et al. (ref. [12]) do not use this nomenclature. They distinguish the compounds with all CH_2OCH_2 bridges (oxacalixarenes) from those with mixed CH_2 and CH_2OCH_2 bridges (homooxacalixarenes).

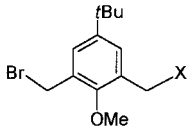
nomenclature of the various ring systems to which **6**–**11** belong and for precedents in the literature.

If we look at **6**–**11** from a different point of view, we can see that the structure gradually changes along the series from a calixarene to a crown ether-like compound.

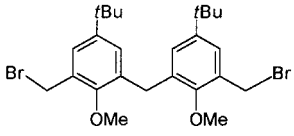
Synthesis: Calixarene derivatives are currently obtained through reactions at the upper or the lower rim of the polyphenol macrocycles.[2, 3] As the parent homooxacalixarenes are available only in a few cases (compounds **2**, **3**, **4**, and a few analogues of **4**) our alternative synthetic approach proves to be particularly useful. It consists of the alkylation of the phenol functions of hydroxymethylated phenols, followed by a Williamson reaction between hydroxymethylated and analogous bromomethylated phenylethers. The method has been reported for the preparation of macropolycyclic polyethers in the series of octahomotetraoxacalix[4]arenes,[14] namely [3.3.3.3]MCP, and of tetrahomodioxacalix[4]arenes,[15] namely [1.3.1.1]MCP, and is extended in the present work to obtain new cyclic systems. The diols and the dibromides actually combined in the final Williamson ring closure reactions are compounds **15**–**18**, **20,** and **21**.



12: R = H, m = 1
13: R = H, m = 2
14: R = H, m = 3
15: R = Me, m = 1
16: R = Me, m = 2
17: R = Me, m = 3



18: X = Br
19: X = OH



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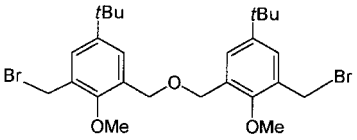

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Powdered KOH in dioxane was the base/solvent system employed.[28] The homooxacalix[4]arene compound was in general the only product isolated through column chromatography in a pure form. The yields (not optimized) are fair to good and template effects of the K^+ counterion are possibly at work.[29] Compound **7**, which is a known compound,[11b, 11c] has now been prepared through methylation of **3** with Me_2SO_4 in acetone/K_2CO_3. This procedure has also been used in an alternative preparation of **9**.

NMR spectra and conformational analysis: Conformational isomerism in homooxacalix[4]arene compounds is expected to be more complicated than in calix[4]arenes, due to reduced symmetry as well as to greater mobility. The relative orientation (parallel or antiparallel) of the aromatic units of these calix[4]arene homologues should be a fundamental conformational feature, and cone, partial cone, and alternate conformations[2, 3] should be taken into account; the number of different conformations of these types depends on the number and position of the CH_2OCH_2 groups in the macrocycle. The actual expected conformations for compounds **6**–**11** and the like are schematically represented in Figure 1. Only **11**, which has four connecting groups of the same type, has the

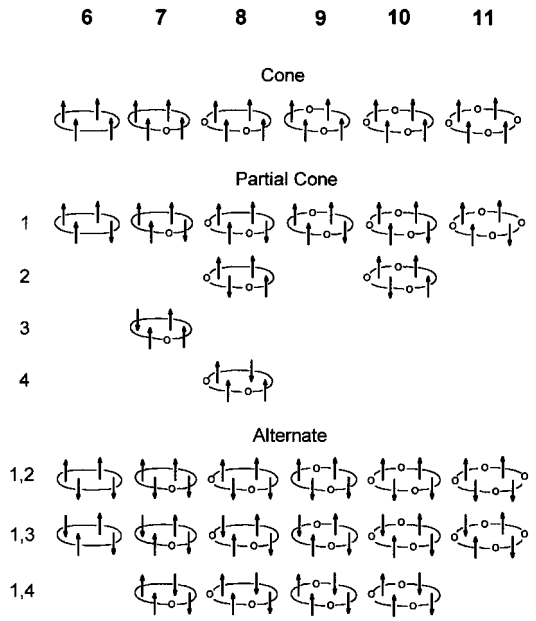

Figure 1. Schematic representation of the main conformations of compounds **6**–**11** and the like. The tip of the arrows indicates (for instance) the *para* substituent. Only one enantiomer is considered in the case of chiral forms. The aromatic unit 1 is located in the bottom right in all the schematic representations in this figure.[30]

same possibilities as calix[4]arene **6**, while in the other cases up to three partial cone and/or up to three alternate conformations can, in principle, occur.[30] In the enlarged structures, the angles between the aromatics and the main ring will be different with respect to those in **6**; moreover, several more conformations are expected to exist within the main families reported in Figure 1, owing to the presence of the CH_2OCH_2 units. Obviously, the ease of interconversion between conformers should depend not only on the nature of the alkyl groups and on the *para* substituents, but also on the number and relative position of the CH_2OCH_2 groups in the macrocycle.

The ^{1}H NMR spectra (300 MHz, in $CDCl_3$ at 298 K) of **7**–**10** are very simple and show sharp singlet signals (but for the coupled ArH protons), in contrast with that of **6**. Fast conformational equilibration obviously occurs for **7**–**11**, as no coupling of the geminal protons is observed. Protons in **6**–**11** can be grouped according to five types of chemical environment. When the several ^{1}H NMR signals related to a given type are considered, it is seen that the weighted mean value is shifted more and more downfield as the number of oxygen atoms increases along the series **7**, **8**–**9**, **10**, **11**. The signals for the *t*Bu groups are only slightly sensitive; however, quite regular trends are observed in all other cases. The

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overall shift along the series is $\Delta\delta = 0.22$ (ArH and CH_2OCH_2), 0.12 ($ArCH_2Ar$), and 0.26 ($ArOCH_3$).[31] Regular trends are also observed for several types of signals in the ^{13}C NMR spectra.

The most interesting regions of the ^1H and ^{13}C NMR spectra are shown in Figure 2 and Figure 3, respectively. Figure 2 shows in particular that most OCH_3 signals are

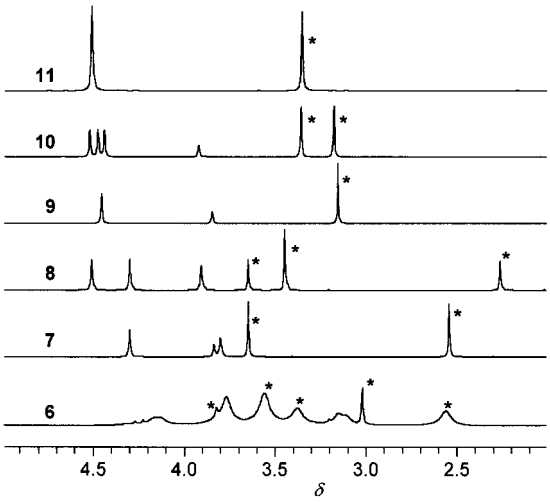


Figure 2. ^1H NMR spectra of compounds **6**–**11** in the region $\delta = 2.0-5.0$, in $CDCl_3$ at 298 K. Signals for OMe groups are starred.

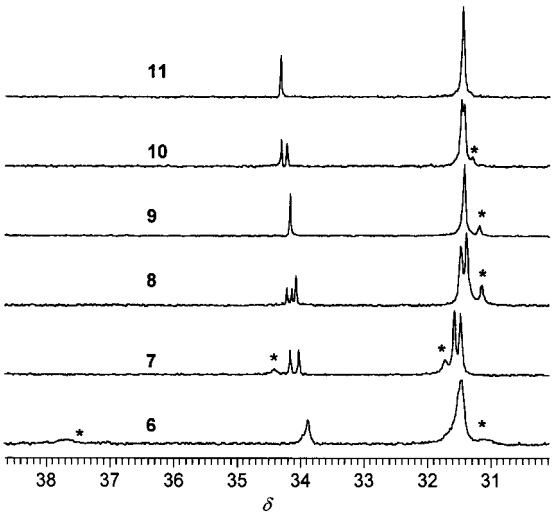
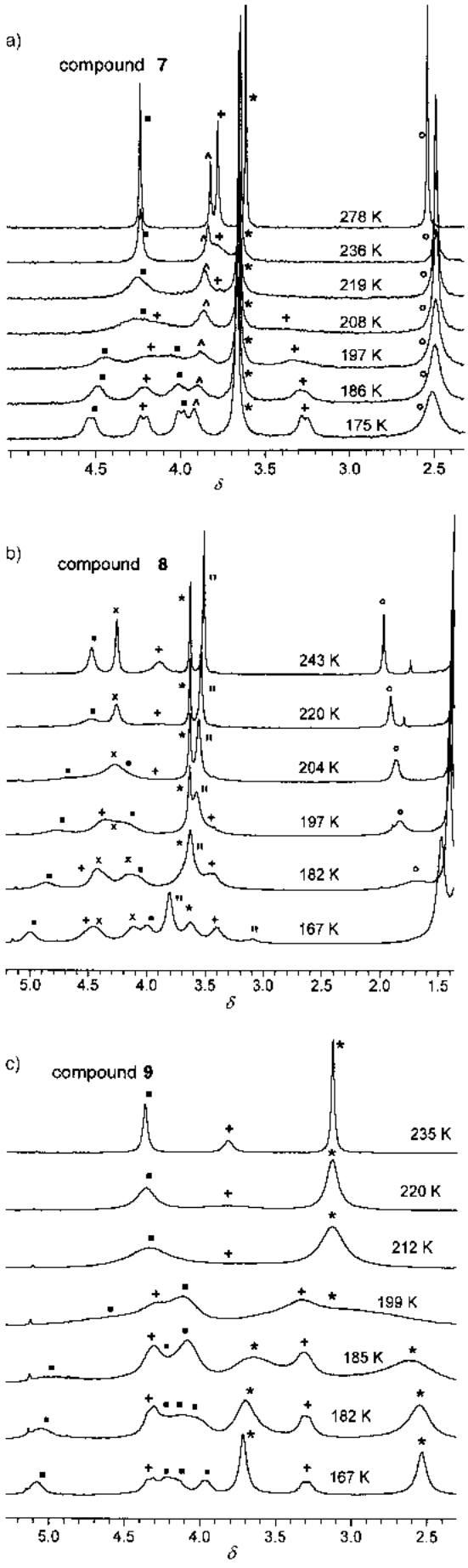


Figure 3. ^{13}C NMR spectra of compounds **6**–**11** in the region $\delta = 30.1-38.6$, in $CDCl_3$ at 298 K. ArCH_2Ar signals are starred.

shifted upfield with respect to the typical value of $\delta = 3.8$, which is observed, for instance, in the acyclic compounds **15**–**21**. The effect is very strong in the spectrum of **7** (signal at $\delta = 2.54$) and in the spectrum of **8** (signal at $\delta = 2.26$); significant upfield shifts are also observed with **9**–**11**. The obvious interpretation is that the corresponding methoxy groups face the rings of other aromatic units in highly populated conformations. On the other hand, in the ^{13}C NMR spectra, the $ArCH_2Ar$ signals (Figure 3) can be found for compounds **8**–**10** at about $\delta = 31$, whereas in the case of **7** a signal can be found at $\delta = 31.7$ and a smaller one at $\delta = 34.4$.[32] On extending, the criterion first established for calix[4]arenes[33] and successfully applied also to larger homologues to homooxacalixarenes,[34] a *syn* arrangement of the aromatic rings can be predicted for all the $ArCH_2Ar$ moieties of **8**, **9**, and **10** and for one type in **7**. Further insight into conformational behavior was gained through ^1H NMR spectra at low temperature in CD_2Cl_2; specifically, extensive signal splitting was observed. Figure 4 shows the most interesting regions in the spectra of compounds **7**–**9** at selected temperatures. Our data for **7** (Figure 4a) are somewhat at variance with those recently reported:[11b, 11c] we observed simple patterns indicating the presence of one main conformation. The singlet for CH_2OCH_2 protons and the larger singlet for $ArCH_2Ar$ protons split into AB systems at low temperature, while the other signals, including the smaller signal for $ArCH_2Ar$, do not split.[35] When the ^{13}C NMR evidence is also considered, the overall picture for **7** is consistent with the compound being in a 1,4-alternate conformation as shown in Figure 1.[36] A C_2 axis passes through the oxygen atom in the ring and the opposed methylene carbon of a distorted *anti*-arranged $ArCH_2Ar$ moiety, to which the signal at $\delta = 34.4$ in the ^{13}C NMR spectrum can be attributed.[37] Two equivalent OMe groups face aromatic rings in this arrangement, which appears to be consistent with that found in the crystal.[38] The rate of exchange between 1,4-alternate and inverted 1,4-alternate conformations at the temperatures of signal coalescence corresponds to an apparent $\Delta G^{\ddagger}_{210}$ value of 9.7 kcal mol^{-1}.[39]

In the case of **9**, the $ArCH_2Ar$ singlet at $\delta = 3.8$ in the ^1H NMR spectrum (Figure 4c) splits on cooling into an AB system, with signal coalescence at ≈ 207 K. At somewhat lower temperatures all the other signals split: the aromatic AB system into two AB systems and the *t*Bu singlet into two singlets (not shown in Figure 4), the OCH_3 singlet into two singlets, and the $ArCH_2O$ singlet into two and eventually four signals (two AB systems). The shielding effect experienced by the OCH_3 protons is not compatible with the cone conformation. On the other hand, the overall picture is consistent with the 1,4-alternate main conformation (Figure 1) exchanging with the inverted 1,4-alternate. A further motion can be investigated: the exchange between two equivalent distorted 1,4-alternate conformations which have two types of aromatic units, two types of $ArCH_2O$, and only one type of $ArCH_2Ar$ groups. Conformations with a center of symmetry are suggested by CPK models (in particular with methoxy groups on either 1,3 or 2,4 aromatic units pointing at each other) and are compatible with the spectra. Estimates for the interconversion of the 1,4-alternate conformations and for the interconversion of the distorted forms are approximately $\Delta G^{\ddagger}_{205} = 9.3$ kcal mol^{-1} and $\Delta G^{\ddagger}_{191} = 8.8$ kcal mol^{-1}, respectively.[40]

In the case of **8** a 2-partial cone conformation (Figure 1) seems to be present on the basis of ^{13}C NMR evidence, that is a *syn*–*syn* arrangement in the $ArCH_2ArCH_2Ar$ moiety, and of the strong shielding effect on one OCH_3 group in the ^1H NMR spectrum. The singlet signals of methylene protons split into AB systems at low temperature (Figure 4b), apparently according to a simple pattern, although peaks are partly superimposed, gradually shifted on changing the temperature, and somewhat broadened throughout. $\Delta G^{\ddagger}_{205}$ for the interconversion between a 2-partial cone conformation and the equivalent inverted one can be estimated to be about



9.4 kcal mol^{-1}.[41] At very low temperatures, broadening of the OCH_3 singlets is observed. The signal at $\delta = 3.6$ is found in a practically fixed position and only starts to broaden. The singlet found at $\delta \approx 2.3$ at 298 K (in $CDCl_3$) is found at $\delta \approx 2.0$ at 243 K (in CD_2Cl_2) and is shifted further upfield at lower temperatures: the broadened signal eventually disappears, also as a result of the presence of a strong *t*Bu signal at $\delta = 1.6$. The signal at $\delta = 3.5$ is somewhat shifted back downfield on cooling, and eventually it appears to split into a large singlet at $\delta = 3.8$ and a small one at $\delta = 3.1$. This can probably be related to the presence of two different conformations within the 2-partial cone family. Roughly speaking, they could differ by the dihedral angle (either close to 180° or close to 90°) between the fourth aromatic unit and the opposed aromatic unit of the $ArCH_2ArCH_2Ar$ moiety. In the latter arrangement the methoxy group points more directly inside the cavity and should be more strongly shielded. The gradual shift of the signal positions should indicate that the latter conformation becomes more and more important when the temperature is lowered. The two equivalent OCH_3 groups in **8** should lose the shielding effect of the fourth aromatic unit in such a normal arrangement. We can estimate that, at the lowest attained temperature, about 85% **8** is in this conformation (large signal at $\delta = 3.8$) and 15% in the conformation schematically indicated as a 2-partial cone at almost 180° (smaller signal at $\delta = 3.1$). Actually, the differences between cone and partial cone vanish if the fourth aromatic ring has an almost perpendicular orientation with respect to the other three aromatics.

The interconversion among the conformations represented in Figure 1 is likely to occur through the flipping of one aromatic unit at a time. In the case of **7**, the stages for such an inversion through one of the shortest paths are: 1,4-alternate, 1-partial cone, cone, enantiomeric 1-partial cone, inverted 1,4-alternate. Also, the inversion of the 1,4-alternate conformation of **9** should involve three intermediates and a symmetric free-energy profile with two values for the free energy of the transition states, while for the inversion of the 2-partial cone conformation in **8** three intermediates with four different free-energy values for the transition states should be considered. We should correct the computed $\Delta G^{\ddagger}$ values for statistical factors since not all the species which have passed through the highest free-energy barrier undergo inversion of conformation. In the hypothesis that, in a given inversion, the values of the free energy for the structurally different transition states differ enough,[42] then corrected values at the same temperature should be $\Delta G^{\ddagger}_{205} = 9.4, 9.4, 9.0$ kcal mol^{-1} for **7**, **8**, and **9**, respectively. When the uncertainty due to these statistical factors is taken into account, along with the uncertainty in the coalescence temperatures (± 0.4 °C in the most unfavorable cases) and in $\Delta\nu$ values, $\Delta G^{\ddagger}$ values cannot be held accurate to

Figure 4. ^{1}H NMR spectra at low temperatures in CD_2Cl_2 for compounds **7**–**9**. Only the central region of the spectra is shown. Symbols mark the proposed splitting patterns of the signals of $ArCH_2O$ protons (■, ×), $ArCH_2Ar$ protons (+, ^), and OCH_3 protons (*, ", ○). The small peaks at $\delta = 5.1$ and 1.8 are due to the solvent (^{13}C satellite) and to adventitious water.

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less than ± 0.5 kcal mol^{-1}. Actually, a less uncertain comparison of the mobility can be made through the direct comparison of the rate of conformational inversion, since data at the same temperature(s) are available or can be interpolated: namely, $k_{206} = 280$, 490, and 600 s^{-1}, for **7**, **8**, and **9**, respectively.

On cooling the CD_2Cl_2 solution of **10,** no signal splitting was observed, although broadening of the $ArCH_2$ and CH_3 singlets occurred and the broadened $ArCH_2Ar$ signal could hardly be detected at 167 K.[43] In the ^{1}H NMR spectra of **11** in CD_2Cl_2 some signal broadening could only be observed at the lowest attained temperatures. We can then conclude that, in this complete series of cyclophanes, the ease of flipping of the aromatic units changes regularly in the order **11** > **10** > **9** ≥ **8** ≥ **7** > **6**. Rather similar mobilities are found for **7**, **8**, and **9**, and interestingly they are also close to that of pentamethoxy-*p*-*tert*-butylcalix[5]arene, for which $\Delta G^{\neq}$ has been estimated to be 9.3 kcal mol^{-1} or slightly less in $CDCl_3$.[34b] A comparison can also be made, in the case of **7** and **9**, with the parent phenolic compounds **2** and **3** which appear to be in cone conformations ($\Delta G^{\neq}$ for cone interconversion: 12.9 and 11.9 kcal mol^{-1}, respectively).[44] The higher barriers observed in the case of the parent compounds can safely be attributed to the disturbance in the intramolecular hydrogen bonding required to attain the transition state(s),[45] while the steric hindrance due to methoxy groups passing through the annulus is expected to become less and less important as the ring size increases from **6** to **7** and to **9**.

Detailed and sophisticated conformational analyses of **6** can be found in the literature.[46] Even on inspection of the simple spectrum in Figure 2 it is evident that the compound exists as a mixture of several conformations, in contrast with **7**, **8**, and **9**, which appear to exist in CD_2Cl_2 solution in essentially only one of the main conformations indicated in Figure 1.

In the case of **10** and **11** we have no direct information on the actually existing conformation(s), but we can note that the signals for OCH_3 protons are significantly shifted upfield with respect to the standard value ($\delta = 3.8$), notwithstanding the downfield shift effect observed for all types of signals as the number of CH_2OCH_2 groups in the ring increases. This indicates that for **10** and **11**, as well as for compounds **7**, **8**, and **9,** cone conformations with deep cavities, that is with almost parallel aromatics, should be disfavored.

In the above analysis we made reference to the established conformational pattern in typical calix[4]arenes and adapted it to our homologues (Figure 1). The results obtained in the low-temperature experiments can be accommodated within this simple reference scheme, but the relation between large homologues and the typical calix[4]arene **6** is a far one, and from an energetic point of view the main conformational families may be at variance with those suggested in Figure 1. Specifically, in large rings the flipping of the aromatic units could, in principle, become a relatively easy step with respect to other rearrangements between populated conformations with the same up/down orientation of the aromatic units. The last condition almost occurs in the case of **9**, while in the case of **8** we commented that differences between cone and partial cone conformations can vanish.

Complexation studies: Dougherty first stressed the importance of cation–π interactions in such important biological systems as the acetylcholine/acetylcholinesterase complex, and he developed a class of cyclophanes based on the rigid ethenoanthracene unit that proved to be effective in the complexation of quaternary ammonium ions, both as polyanionic ligands in water and as neutral ligands in halogenated solvents.[19] Reference is made to the recent review by Ma and Dougherty[22] for the theoretical aspects of the interaction and for the relevant literature on both artificial receptors and biological structures. The X-ray crystal structure has been reported recently for a solid-state inclusion complex between a neutral cavitand and acetylcholine chloride.[47] We simply note here that quaternary ammonium salts and the corresponding *N*-alkylpyridinium salts in the aromatic series are suitable test guests for our homooxacalixarene ligands in lipophilic solvents, namely the cations are rather large species which, in the absence of contributions such as hydrophobic forces and ion pairing or classical H-bonding with the ligand,[48] should interact essentially with the aromatic clouds of the cyclophane system,[22] and actually test the ability of the host to exhibit several aromatic faces to the included species. Our former idea[14–16] that enlarging the spacers between the aromatic rings in a calix[4]arene structure should enable the cavity to host organic species was fully confirmed by the behavior of compounds **7**–**11**, which, in contrast with **6**, bound the two tested salts, tetramethylammonium picrate (TMAP) and *N*-methylpyridinium iodide (NMPI) in $(CDCl_2)_2$ solvent. The two salts were chosen as representatives of two quite different families in their shape and charge distribution, while $(CDCl_2)_2$ proved to be a suitable solvent for both ligands and salts. The technique used for the complexation investigation has been described in a previous paper.[16] The ^{1}H NMR spectra of the cation were recorded at 303.1 K in 1.00 mM solutions of the salt, in the absence and in the presence of varying concentrations of the ligand. The results of the multiparameter least-squares treatment on the basis of a 1:1 association equilibrium, that is association constants and limiting upfield shift in the various positions of the complexed cation, are reported in Table 2. The strength of the complexation on changing the ligand structure is graphically represented by the $-\Delta G^{\circ}$ profiles in Figure 5. In control experiments with more diluted salt solutions, the ligands also proved to be effective in $CDCl_3$ solvent.[49]

Table 2. Association constants and limiting upfield shifts in the ^{1}H NMR spectra of the included cation in the complexation of 1.00 mM tetramethylammonium picrate (TMAP) and *N*-methylpyridinium iodide (NMPI) by ligands **6**–**11** in $(CDCl_2)_2$ at 303.1 K.

Ligand	TMAP		NMPI	
	K, M^{-1}	$-\Delta\delta_\infty$, ppm	K, M^{-1}	$-\Delta\delta_\infty$, ppm[a]
6	–[b]		–[b]	
7	24	0.8	40	1.2, 1.0, 0.5, 0.4
8	270	1.4	120	1.0, 1.1, 0.7, 0.6
9	610	1.6	77	1.0, 1.0, 0.7, 0.6
10	450	1.8	190	1.4, 1.9, 1.4, 1.3
11	470	1.7	190	1.2, 1.6, 1.2, 1.1

[a] Limiting shifts on signals of Me, α, β, and γ protons, respectively. [b] No significant shift was observed.

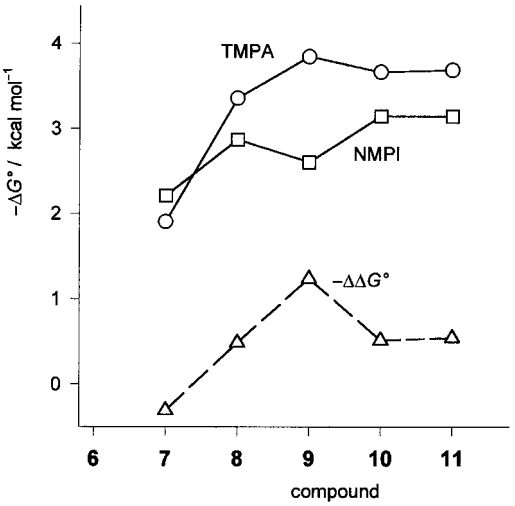

Figure 5. Free-energy profiles for the complexation of tetramethylammonium picrate (TMAP) and *N*-methylpyridinium iodide (NMPI) on changing the structure of the ligands **7**–**11**, in $(CDCl_2)_2$ at 303.1 K. No association was observed with compound **6**. The third profile refers to the salt selectivity, namely $-\Delta\Delta G^\circ = -\Delta G^\circ_{TMAP} + \Delta G^\circ_{NMPI}$.

As already noted with compounds **2**–**4**,[16] simple monocyclic compounds can work fairly well in the complexation of organic cations in lipophilic media. In the case of **2**–**4**, intramolecular hydrogen bonding could be held responsible for a substantial organization of the ligand in a conelike conformation that is suitable for the inclusion of the cation, while in the case of **7**–**11** no special preorganizing factor can be invoked. Actually, the cone conformations, expected to be effective for complexation, appear to be relatively unstable in the case of the free ligands **7**–**11**. Despite this handicap, **8**–**11** bind TMAP and NMPI fairly well, and the complexes are, in general, stronger than those reported for some parent analogues,[16] although a direct comparison cannot be made owing to the differences in the solvent and in the tested guests. Qualitatively, we should conclude that the entropic loss for the association, the expense for conformational reorganization and freezing, and the disturbance to ion association of the salt, are more than offset by the favorable interactions between the included cation and the aromatic walls of the cone-arranged ligand. To this end there appears to be a large tolerance for changes of $CH_2 \leftrightarrow CH_2OCH_2$ in the ligand structure, namely, it is not simply a case of a single given compound apparently being suitable for complexation, but all the members of the family, provided they are large enough, are effective. The ligand selectivity is rather low in the range **8**–**11,** while the complexes are somewhat weaker in the case of **7** and no evidence of complexation is found in the case of **6**. The conformational properties of the $ArCH_2OCH_2Ar$ moiety are of fundamental importance for this broad effectiveness: the aromatics in $ArCH_2OCH_2Ar$ can become very flexible hinges and be set without relevant strain at the right distance and with the proper orientation for optimum interaction with the included cation. The presence in the structure of such effective hinges in addition to the classical $ArCH_2Ar$ ones of calixarenes results in high adaptability, and the ligand, in a certain range of host–guest sizes, can be thought to behave (admittedly with some exaggeration) as a close-fitting elastic belt. Although experimental results for a direct comparison are not available, we think that such alternative spacers as those occurring in $ArCH_2CH_2CH_2Ar$ or $ArCH_2CH_2Ar$ analogues should not be so effective due to larger torsional strains or occupancy of the cavity.

The salt selectivity changes in a very interesting way, as indicated by the profile of $-\Delta\Delta G^\circ = -\Delta G^\circ_{TMAP} + \Delta G^\circ_{NMPI}$ in Figure 5. The change of sign on passing from **7** to the larger ligands, the quite regular profile[50] with a peak selectivity for **9**, and the range of selectivity spanned, should be noted. From a different point of view we could consider that the values of the K_{TMAP}/K_{NMPI} ratios are 2.4 ± 0.1 for **8**, **10**, and **11**, 0.6 for **7**, and 7.9 for **9**. The high value for **9** results from the simultaneous occurrence of a maximum for K_{TMAP} and of a minimum for K_{NMPI}.

In principle, complexation can induce changes in the chemical shift in the ^1H NMR spectra of both the guest and the host. Although in the present investigation the latter effect was small in most cases, clear-cut evidence of conformational changes on complexation could be obtained. Namely, the signals of the OCH_3 groups which underwent the strongest shielding effects in the free ligands were also shifted backwards to their typical position, as expected to occur for cone conformations, in the presence of the guest.[51]

The ^1H NMR limiting upfield shifts undergone by the included cation can, in principle, give information on the geometry of the complex, since the shielding effects are related to the position of a given nucleus with respect to the aromatic rings in the complex.[52] The interpretation is not always straightforward, because families of complexes with comparable stability but significantly different geometry can occur in solution, and several specific effects can be lost in the mean recorded shifts. Nevertheless, we can guess that the nuclei for which the strongest shielding effects are observed face aromatic rings in relatively stable and populated arrangement(s).

Only one signal can be monitored in the case of tetramethylammonium ion (TMA), while in the case of *N*-methylpyridinium ion (NMP) the effects on the protons in four positions can be investigated, which will be directly indicated as α, β, γ, and Me. The obtained $\Delta\delta_\infty$ values are reported in Table 2 and can be more easily analyzed in the graphical presentation given in Figure 6. In all cases, the effects are quite strong, ranging from $\Delta\delta_\infty = -0.4$ to -1.9. The profile for TMA is a regular one and the observed sequence for the strength of the shielding is $\mathbf{7} < \mathbf{8} \leq \mathbf{9} \leq \mathbf{10} \geq \mathbf{11}$. In the case of NMP, the profiles observed on changing the ligand are almost parallel for the α, β, and γ protons, the effect varying in the order $\alpha > \beta > \gamma$.[53] Moreover, the shielding effects are much higher with ligands **10** and **11** than with the smaller terms: $\mathbf{7} \leq \mathbf{8} = \mathbf{9} < \mathbf{10} \geq \mathbf{11}$. In the case of Me all values are within a restricted range, namely $\Delta\delta_\infty = -1.20 \pm 0.2$, and the sequence is somewhat different, namely $\mathbf{7} \geq \mathbf{8} = \mathbf{9} < \mathbf{10} \geq \mathbf{11}$. For a given ligand the effect in the various positions of complexed NMP is, in almost all cases, that expected on the basis of the proximity to the nitrogen atom: $\alpha = Me > \beta > \gamma$. In fact, the point with the maximum positive charge density tends to face centrally the aromatic π clouds[54] and the closer the guest protons are to it, the more strongly they are shielded. A few

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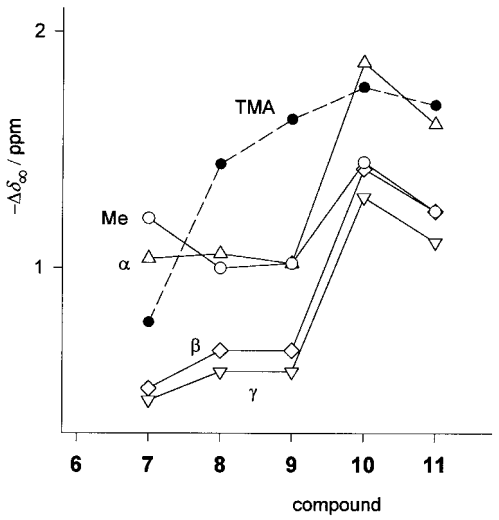

Figure 6. Limiting upfield shift on the ^{1}H NMR signals of the included guest cation as a function of the host structure. Values for included tetramethylammonium ion (TMA) and for α,β,γ, and Me signals in included *N*-methylpyridinium ion.

deviations are found, with an anomalous position of Me in the sequence. Specifically, the Me values are close to those of the β protons for **11** and **10**, close to those of α protons only in the case of **9** and **8**, and even higher than those for α protons in the case of **7.** The relative importance of the shielding effects on Me protons relative to those on the other positions can be calculated as $3\Delta\delta_{\infty Me}/(\Delta\delta_{\infty\gamma}+2\Delta\delta_{\infty\beta}+2\Delta\delta_{\infty\alpha})$, the values being 1.04, 0.75, 0.78, 0.55, 0.55 for compounds **7**–**11**, respectively. In principle, several different geometries are possible for a given host–guest pair, and a complete description is difficult. Figure 7 schematically represents some of the possible orientations of the complexes as the cavity size increases. To interpret the shielding effects on Me we can

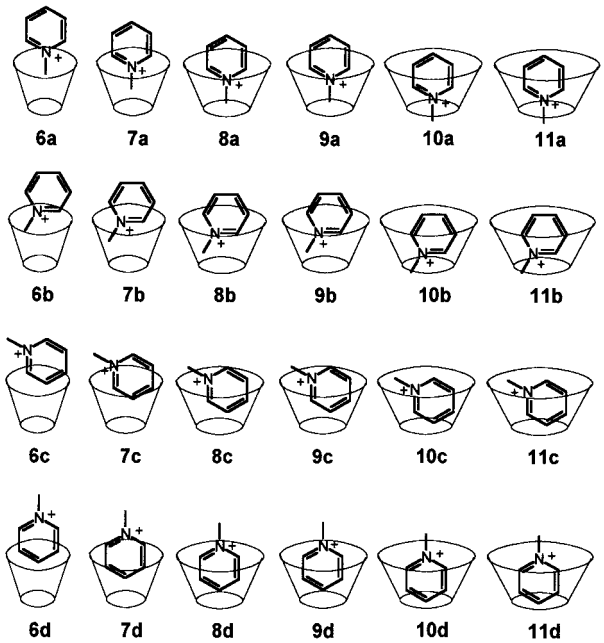

Figure 7. Schematic representation of different inclusion geometries of *N*-methylpyridinium ion in the ligands **6**–**11**.

simplify the picture by making particular reference to the arrangements **6a**–**11a** in the first row of Figure 7, which should be important in the whole series of ligands. The Me group of NMP can be included among the *tert*-butyl groups in the upper rim of **6** (structure **6a**) but the guest can hardly be included with the nitrogen atom facing the aromatic rings. No complexation is observed because of the lack of significant cation–π interaction. Compound **7** is the smallest effective ligand of the group: NMP will be partly included and Me will reasonably be the most deeply penetrating part. With **8** and **9** ligands the cation can be included more centrally with respect to the aromatic walls and the protons in α and in Me will experience a similar shielding effect. On the other hand, the cation can be included so deeply in the large ligands **10** and **11** that in stable and populated arrangements of the complex its methyl group can reasonably face the oxygen atoms in the lower rim rather than the aromatic π clouds, so that the observed shielding effect is reduced. Obviously, the relative importance of structures such as **10d** and **11d** could also contribute to this effect.

If, on the other hand, we overlook such details as those suggested by Figure 7, we can say that a gross agreement holds between the profiles in Figure 6 and those in Figure 5. Since the picture is somewhat complicated for NMPI, mean values can be considered for the $\Delta\delta_\infty$ values on the 8 protons of the cation, namely $\Delta\delta_\infty=(\Delta\delta_{\infty\gamma}+2\Delta\delta_{\infty\beta}+3\Delta\delta_{\infty Me})/8$. In Figure 8 $-\Delta\delta_\infty$ vs. $-\Delta G^\circ$ data for both salts are reported,

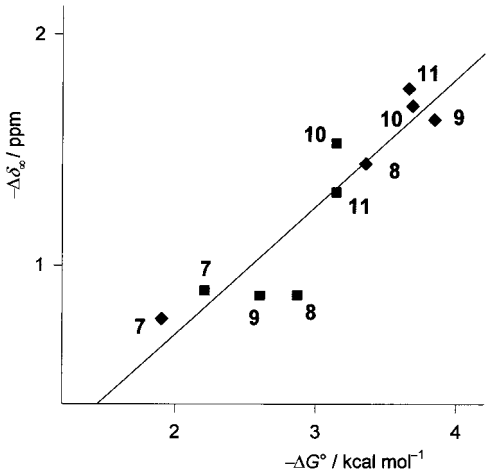

Figure 8. Limiting shielding effects in the ^{1}H NMR spectra of included cations vs. the free energy of complexation, in $(CDCl_2)_2$ at 303.1 K, between ligands **7**–**11** and tetramethylammonium picrate (◆) or *N*-methylpyridinium iodide (■, mean effect on the 8 protons of the cation).

together with the straight line obtained from the linear regression (slope 0.55 ± 0.08; intercept 0.40 ± 0.26; correlation coefficient 0.918). A rough correlation can actually be found, although the line has been drawn for reference purposes only. There is no general physical reason for such a correlation to hold, since, for instance, a perfectly built-in complex, with the aromatic faces fitting close to the positive charges and with large upfield shifts, can be unstable because of severe reorganizational strain in the ligand. On the other

hand it may happen that this conformational handicap is not very different in a series of ligands (possibly, to some extent, the energetic expense of suitable conelike conformations in our series) and two physically different, but related, phenomena show similar trends. In fact, the more deeply the cation is included in the cavity, the stronger are both the cation–π attractive interaction and the shielding of the protons facing the π systems, as seen in the NMR spectra.

Cation–π interactions can be strong enough to account entirely for the observed association picture: A significant stabilization is expected with four suitably oriented aromatics if even a small fraction of the binding energy in the gas phase survives in our complicated real system, since the benzene–TMA interaction in a vacuum is fairly strong, $-\Delta H^{\circ} = 9.4\ \mathrm{kcal\,mol^{-1}}$.[55, 22] Other possible interactions can, in principle, contribute to the binding; in particular cation–oxygen atom dipole and (in the complexation of NMPI) π–π interactions[56] should be taken into account.[57] The strongest association is observed with TMAP–**9**, namely with an aliphatic cation that cannot reasonably interact with more than two oxygen atoms. Moreover, no clear-cut difference between quats and aromatic analogues is generally apparent in the studies we are carrying out on homooxacalixarenes of varying structure;[23] the mere difference in the shape of the cation apparently accounts for the observed effects. We then think that π–π and cation–oxygen atom dipole interactions only play a secondary role in most cases. For a safer assessment of the relative importance of the factors contributing to binding, the systems should be further investigated with both computational and experimental (UV/Vis spectroscopic, electrochemical, advanced NMR, X-ray crystallographic) techniques.[58]

In general, salt association greatly complicates the complexation of ionic species in media of low polarity, and ion-paired species (or higher aggregates) are also likely to occur in the present case. The fact that clean association pictures, apparently in agreement with the 1:1 association of a free cation with a neutral ligand, are experimentally observed, should be due to the actual association, in a simple case, of the ion pair with the ligand, to give an ion-paired complexed cation. The presence of the anion should, in principle, affect both the apparent K value and the arrangement of the cation within the ligand. An extensive investigation is currently being carried out on these and other homooxacalixarene systems to assess the effect of cation, solvent, and counterion.

Conclusions

Homooxacalixarenes are introduced here as a large family of compounds, with quite a variety of structures and interesting ligating properties. Formal substitution of each CH_2 bridge in a calixarene with the longer CH_2OCH_2 spacer gives rise to these *m*-cyclophanes, and a complete series of homooxacalix[4]arenes is now synthetically available. While retaining several features of the typical calix[4]arenes, these compounds have cavities modified in shape and size in a continuous way, depending on the number and position of the longer spacers. This possibility of fine-tuning the basic cavity should be compared with the coarse regulation available in the typical calixarene series, namely calix[4]arene, calix[5]arene, calix[6]arene and so on. Further regulation of the cavity can be performed with homooxacalixarenes, as well as with calixarenes, through suitable functionalization at the lower and upper rim. However, it is important to ascertain the basic properties of this practically new family of ligands in the absence of constraints, such as those given by hydrogen bonding, crowded substituents, and bridging units. With respect to calix[4]arenes, these compounds have, in general, both a larger conformational mobility and a larger number of conformations. According to NMR investigations, the tetramethyl ethers we are dealing with appear not to be preorganized in conelike conformations suitable for the complexation of organic cations. Nevertheless, fairly strong complexation of quats in halogenated solvents occurs and has been quantitatively analyzed. This means that the flexible monocyclic structure can effectively make the four aromatic π clouds interact at the right distance and with the proper orientation with the included cation, thus overcoming several expected entropic and enthalpic handicaps. The number of neutral host systems that have been reported to work well for the complexation of quaternary ammonium ions is not very large, and the compounds reported here are among the most effective ones, particularly when monocyclic structures are considered.[22] An especially interesting comparison is that with typical calixarenes: fairly strong complexation has been reported to take place in a few cases, for example, in the series of calix[4]arenes with a cone-rigidified doubly bridged de-*tert*-butylated compound;[59] in the series of calix[5]arenes with polyoxyethylene-bridged compounds;[60, 61] in the series of calix[6]arenes with a bridged tetraamido derivative,[62] with a capped ligand which is effective at low temperatures,[63] and with a specially substituted ligand designed to bind phosphocholine.[64] But in no case, either for H-bonding organized-parent compounds or for simple derivatives, did the monocyclic calixarenes show ligating properties comparable to those of compounds **7**–**11** for this kind of ion.

Complexation of ionic species in low polar solvents is a complicated matter, and often the host–guest effects looked for, such as π–cation attraction, are obscured by solvent effects and by anion–cation attraction. Only through a systematic investigation can the various contributing factors be assessed, and controlled change in the host structure proves to be a powerful tool to this end.

It is worth noting that the interest in cation–π interaction is relatively recent and that only in a very few cases are systematic experimental data available for neutral hosts.[22] Furthermore, a satisfactory computational approach to systems of the type we are dealing with should correctly take into account not only the solvated host in its several expected conformations and the solvated cationic species, but also the solvated counterion and the expected ion-pairing effects in media of low polarity.

Compounds **6**–**11** and the like are obviously promising ligands for several types of metal and organic cations besides the reported ones.

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Experimental Section

General methods: Commercially available chemicals were used as received unless otherwise indicated. Bromination reactions were carried out in dry apparatus. The Williamson alkylation reactions were carried out under an atmosphere of N_2 throughout. Dioxane was treated with powdered KOH at 70 °C and filtered prior to use. Additions in cyclization reactions were performed at a constant rate with the aid of an infusion pump. Column chromatography was carried out on 230–400 mesh silica gel (Merck). Mass spectra were obtained with a Fisons Instruments VG-Platform Benchtop LC-MS (positive ion electrospray mass spectra, ESP^+). Melting points (uncorrected) were obtained in sealed, evacuated capillaries in the case of the cyclic products **7**, **8**, **9**, and **11**. NMR spectra were recorded on a Bruker AC 300 spectrometer with TMS as an internal standard. CD_2Cl_2 (Acros), $(CDCl_2)_2$ (Fluka), and $CDCl_3$ (Merck) were stored over activated molecular sieves (4 Å). In low-temperature ^1H NMR experiments, 4% CH_3OH in CD_3OD was used to calibrate the temperature. Reference is made to a previous paper for the titration technique and data treatment.[16] On repeating the complexation experiments, K and $\Delta\delta_\infty$ values were found to be reproducible within 15%, while in a given run the multiple-fit procedure afforded the parameters (two for TMA and five for NMP) with a small % standard deviation (< 1% in most cases).

1,3-Bis(hydroxymethyl)-5-*tert*-butyl-2-methoxybenzene (**15**): A mixture of compound **12**[65] (2.80 g, 13.3 mmol), MeI (1.6 mL, 26 mmol), and K_2CO_3 (3.6 g, 26 mmol) in acetone (20 mL) was heated at 45 °C under vigorous stirring for 9 h. Volatile materials were evaporated, water was added, and after extraction with ether, washing with water, drying (Na_2SO_4), and solvent evaporation, the oily residue was crystallized from CCl_4 at 4 °C to give **15**. Yield: 1.81 g (61%); m.p. 87–89 °C; ^1H NMR: $\delta = 1.32$ (s, 9H, *t*Bu); 2.08 (t, $J = 6.0$ Hz, 2H, OH); 3.85 (s, 3H, OCH_3); 4.73 (d, $J = 6.0$ Hz, 4H, CH_2O); 7.34, (s, 2H, ArH); ^{13}C NMR: $\delta = 31.4$, 34.5, 61.2, 62.1, 126.0, 133.1, 147.5, 153.8; MS (ESP^+): $m/e = 247$ $[M+Na]^+$; anal. calcd for $C_{13}H_{20}O_3$: C 69.62, H 8.99; found C 69.48, H 8.89.

Bis(5-*tert*-butyl-3-hydroxymethyl-2-methoxyphenyl)methane (**16**): A mixture of compound **13**[7] (15.0 g, 40.3 mmol), MeI (10 mL, 0.16 mol), and K_2CO_3 (36 g) in acetone (120 mL) was heated at 45 °C under vigorous stirring for 7 h. The mixture was then poured into water, neutralized (HCl), and extracted with ether. The crude product, obtained after drying (Na_2SO_4) and solvent evaporation, was crystallized first from $CHCl_3$/hexane and then from acetone to give **16**. Yield: 9.17 g (57%); m.p. 114.5–116 °C; ^1H NMR: $\delta = 1.23$ (s, 18H, *t*Bu); 2.51 (s, 2H, OH); 3.72 (s, 6H, OCH_3); 4.06 (s, 2H, $ArCH_2Ar$); 4.72 (s, 4H, CH_2O); 7.02, (d, $J = 2.9$ Hz, 2H, ArH), 7.25 (d, $J = 2.9$ Hz, 2H, ArH); ^{13}C NMR: $\delta = 29.4$, 31.3, 34.3, 61.3, 61.7, 124.2, 127.6, 132.9, 132.9, 146.9, 154.1; MS (ESP^+): $m/e = 424$ $[M+Na]^+$, 440 $[M+K]^+$; anal. calcd for $C_{25}H_{36}O_4$: C 74.97, H 9.06; found C 74.72, H 8.89.

5-*tert*-Butyl-1,3-bis[(3-hydroxymethyl-5-*tert*-butyl-2-methoxyphenyl)-methyl]-2-methoxybenzene (**17**): A mixture of compound **14**[7] (3.00 g, 5.60 mmol), Me_2SO_4 (2.0 mL, 21 mmol), and K_2CO_3 (5.6 g, 40 mmol) in acetone (20 mL) was refluxed under vigorous stirring for 6 h. After evaporation in vacuo, addition of water, neutralization (HCl), extraction with ether, drying (Na_2SO_4), and ether evaporation, crystallization from CCl_4 gave **17**. Yield: 2.75 g (85%); m.p. 139–141 °C; ^1H NMR: $\delta = 1.15$ (s, 9H, *t*Bu), 1.22 (s, 18H, *t*Bu), 2.17 (t, $J = 6.1$ Hz, 2H, OH), 3.60 (s, 3H, OCH_3), 3.75 (s, 6H, OCH_3), 4.09 (s, 4H, $ArCH_2Ar$), 4.75 (d, $J = 6.1$ Hz, 4H, CH_2O), 6.94, (s, 2H, ArH), 7.03, (d, $J = 2.2$ Hz, 2H, ArH), 7.21 (d, $J = 2.2$ Hz, 2H, ArH); ^{13}C NMR: $\delta = 29.6$, 31.4, 34.2, 34.3, 60.8, 61.3, 62.1, 124.1, 126.1, 127.8, 132.6, 132.8, 133.4, 146.4, 146.9, 154.3, 154.6; MS (ESP^+): $m/e = 533.9$ $[M+Na]^+$, 616 $[M+K]^+$; anal. calcd for $C_{37}H_{52}O_5$: C 77.05, H 9.09; found C 76.73, H 9.42.

1,3-Bis(bromomethyl)-5-*tert*-butyl-2-methoxybenzene (**18**): PBr_3 (0.70 mL, 7.4 mmol) was added through a syringe pipette to a stirred and ice-cooled solution of **15**, (1.67 g, 7.4 mmol) in dioxane (30 mL) over a period of 20 min. After an additional 8 h at room temperature, water was added, the mixture was neutralized with $NaHCO_3$ and, after extraction with ether, it was dried (Na_2SO_4) and solvent evaporated in vacuo. The residue was crystallized from petrol ether (40–70)/acetone to give **18** (2.30 g, 88% yield). M.p. 92–94 °C (ref. [66]: 88–89 °C).

1-Bromomethyl-5-*tert*-butyl-3-hydroxymethyl-2-methoxybenzene (**19**): This was obtained, together with the dibromide **18**, from **15** and PBr_3: PBr_3 (0.40 mL, 4.2 mmol) was added through a syringe pipette to a stirred and ice-cooled solution of **15** (2.00 g, 8.91 mmol) in dioxane (20 mL) over a period of 10 min. The mixture was left to react for 90 min at room temperature, and then worked up as reported for compound **18**. The residue obtained after evaporation under vacuum at room temperature was subjected to column chromatography (eluent: chloroform) to give **18** (yield: 790 mg, 25%), and **19** (yield: 830 mg, 32%) which was recrystallized from hexane. M.p. 73–75 °C; ^1H NMR: $\delta = 1.31$ (s, 9H, *t*Bu), 3.93 (s, 3H, OCH_3), 4.58 (s, 2H, $ArCH_2Br$), 4.73 (s, 2H, $ArCH_2O$), 7.35 (app. s, 2H, ArH); ^{13}C NMR: $\delta = 28.3$, 31.4, 34.5, 61.4, 62.1, 127.2, 128.1, 130.6, 133.6, 147.8, 154.1; MS (ESP^+): $m/e = 310$ $[M+Na]^+$; anal. calcd for $C_{13}H_{19}O_2Br$: C 54.37, H 6.67; found C 54.44, H 6.89.

Bis(3-bromomethyl-5-*tert*-butyl-2-methoxyphenyl)methane (**20**): PBr_3 (1.20 mL, 12.6 mmol) was added through a syringe pipette, over a period of 30 min, to a stirred and ice-cooled solution of **16** (5.00 g, 12.5 mmol) in dioxane (45 mL). Stirring was continued for an additional 17 h at room temperature, then cold water was added and the mixture was neutralized with $NaHCO_3$. The mixture was extracted with ether and dried (Na_2SO_4), and the solvent evaporated. The residue was crystallized from hexane, followed by column chromatography (eluent: chloroform) on the mother liquors to give **20**. Yield: 3.60 + 1.82 g (83%); m.p. 98–99 °C; ^1H NMR: $\delta = 1.22$ (s, 18H, *t*Bu), 3.82 (s, 6H, OCH_3), 4.05 (s, 2H, $ArCH_2Ar$), 4.60 (s, 4H, CH_2Br), 7.00 (d, $J = 2.9$ Hz, 2H, ArH), 7.26 (d, $J = 2.9$ Hz, 2H, ArH); ^{13}C NMR: $\delta = 29.0$, 29.8, 31.3, 34.3, 61.4, 126.4, 128.9, 130.4, 133.2, 147.2, 154.5; MS (ESP^+): $m/e = 549$ $[M+Na]^+$, 565 $[M+K]^+$; anal. calcd for $C_{25}H_{34}O_2Br_2$: C 57.05, H 6.51; found C 56.95, H 6.65.

Bis[(3-bromomethyl-5-*tert*-butyl-2-methoxyphenyl)methyl]ether (**21**): A solution of **19** (696 mg, 2.43 mmol) in dioxane (25 mL) was added over a period of 75 min to a stirred mixture of **18** (2.47 g, 0.71 mmol), powdered KOH (1.0 g, 15 mmol), and dioxane (10 mL) heated to 70 °C. The mixture was heated and stirred for an additional 100 min, then cold water was added and the mixture neutralized with HCl. After extraction with ether, washing with water, drying (Na_2SO_4), and solvent evaporation under vacuum at room temperature, column chromatography (eluent: hexane/chloroform 2:1) afforded unreacted **18** (yield: 1.34 g, 54% of the starting material) and **21** (yield: 550 mg, 41% with respect to added **19**). A fast recrystallization from MeOH gave an analytically pure sample of **21**. M.p. 94–96 °C; ^1H NMR: $\delta = 1.31$ (s, 18H, *t*Bu), 3.89 (s, 6H, OCH_3), 4.59 (s, 4H, $ArCH_2O$ or $ArCH_2Br$), 4.64 (s, 4H, $ArCH_2O$ or $ArCH_2Br$), 7.35 (d, $J = 2.4$ Hz, 2H, ArH), 7.44 (d, $J = 2.4$ Hz, 2H, ArH); ^{13}C NMR: $\delta = 28.6$, 31.3, 34.4, 62.3, 67.6, 128.0, 128.0, 130.5, 131.0, 147.4, 154.4; MS (ESP^+): $m/e = 578$ $[M+Na]^+$; anal. calcd for $C_{26}H_{38}O_5$: C 56.13, H 6.52; found C 56.25, H 6.68.

7,13,19,25-Tetra-*tert*-butyl-27,28,29,30-tetramethoxy-2,3-dihomo-3-oxacalix[4]arene (**7**): Compound **2**[11a] (387 mg, 0.57 mmol), K_2CO_3 (850 mg, 6.15 mmol), and Me_2SO_4 (750 mg, 5.95 mmol) were reacted in boiling acetone (15 mL) for 9 h with vigorous stirring. The mixture was then poured into a stirred mixture of ice and water. The water was filtered off and the solid material collected, repeatedly washed with water, and recrystallized from acetone. Acetone was apparently included in the obtained solid (310 mg, 69% yield of a 1:1 complex according to the integrals in ^1H NMR spectra). The solvent-free product was obtained through addition of ether and methanol and evaporation under vacuum. M.p. 181–183 °C (ref. [11b]: 160–161.5 °C); ^1H NMR: $\delta = 1.21$ (s, 18H, *t*Bu), 1.31 (s, 18H, *t*Bu), 2.54 (s, 6H, OCH_3), 3.65 (s, 6H, OCH_3), 3.80 (s, 4H, $ArCH_2Ar$), 3.84 (s, 2H, $ArCH_2Ar$), 4.30 (s, 4H, $ArCH_2O$), 6.95 (d, $J = 2.2$ Hz, 2H, ArH), 7.17 (unresolved, 4H, ArH), 7.28(d, $J = 2.2$ Hz, 2H, ArH); ^{13}C NMR: $\delta = 31.5$, 31.6, 31.7, 34.0, 34.1, 34.4, 60.4, 60.8, 65.5, 125.6, 126.0, 126.6, 128.1, 130.3, 132.9, 133.2, 135.0, 145.0, 145.3, 154.3, 155.5; MS (ESP^+): $m/e = 758$ $[M+Na]^+$, 774 $[M+K]^+$; anal. calcd for $C_{45}H_{58}O_5$: C 80.07, H 9.05; found C 80.21, H 9.28.

7,15,21,27-Tetra-*tert*-butyl-29,30,31,32-tetramethoxy-2,3,10,11-tetrahomo-3,11-dioxacalix[4]arene (**8**): A solution of **18** (352 mg, 1.01 mmol) and **17** (583 mg, 1.01 mmol) in dioxane (15 mL) was added over a period of 150 min to a stirred suspension of powdered KOH (700 mg, 11 mmol) in dioxane (15 mL) heated to 80 °C. The mixture was heated and stirred for an additional 8 h, then water was added and, after neutralization with HCl, extraction with ether, drying (Na_2SO_4) and solvent evaporation, column chromatography (eluent: chloroform) gave **8**. Yield: 400 mg (52%) as white crystals which could be recrystallized from MeOH. M.p. 158–160 °C; ^1H NMR: $\delta = 1.20$ (s, 18H, *t*Bu), 1.28 (s, 9H, *t*Bu), 1.28 (s, 9H, *t*Bu), 2.25 (s, 3H, OCH_3), 3.45 (s, 6H, OCH_3), 3.65 (s, 3H, OCH_3), 3.91 (s, 4H,

$ArCH_2Ar$), 4.30 (s, 4H, $ArCH_2O$), 4.51 (s, 4H, $ArCH_2O$), 7.14 (d, $J = 2.3$, 2H, ArH), 7.16 (s, 2H, ArH), 7.18 (d, $J = 2.3$, 2H, ArH), 7.29 (s, 2H, ArH); ^{13}C NMR: $\delta = 31.2$, 31.4, 31.5, 34.1, 34.2, 34.3, 60.7, 61.1, 61.8, 65.7, 67.3, 126.5, 126.8, 127.8, 128.1, 129.9, 130.5, 133.6, 133.9, 145.6, 145.6, 146.0, 154.4, 155.0, 155.6; MS (ESP$^+$): $m/e = 788$ $[M+Na]^+$, 804 $[M+K]^+$; anal. calcd for $C_{50}H_{68}O_6$: C 78.50, H 8.96; found C 78.77, H 8.95.

7,13,21,27-Tetra-*tert*-butyl-29,30,31,32-tetramethoxy-2,3,16,17-tetrahomo-3,17-dioxacalix[4]arene (**9**): A solution of **20** (590 mg, 1.12 mmol) and **16** (450 mg, 1.12 mmol) in dioxane (20 mL) was added over a period of 4.5 h to a stirred suspension of powdered KOH (600 mg, 9 mmol) in dioxane (20 mL) heated to 70 °C. The mixture was heated and stirred for an additional 5 h, then water was added and, after neutralization with HCl, extraction with $CHCl_3$, drying (Na_2SO_4), and solvent evaporation, column chromatography (eluent: chloroform) gave **9** (yield: 200 mg (23 %)) that was recrystallized from EtOAc.

In an alternative preparation of **9**, compound **3**[7] (312 mg, 0.440 mmol) was reacted with Me_2SO_4 (0.70 mL, 0.74 mmol) and K_2CO_3 (1.0 g, 7.2 mmol) in boiling acetone (15 mL) under vigorous stirring for 4 d. After solvent evaporation, chloroform was added and the insoluble materials discarded. The residue obtained after evaporation was subjected to column chromatography (eluent: chloroform) to give **9**. Yield: 185 mg, (55 %). M.p. 243 – 245 °C; ^1H NMR: $\delta = 1.24$ (s, 36H, *t*Bu), 3.16 (s, 12H, OCH_3), 3.85 (s, 4H, $ArCH_2Ar$), 4.46 (s, 8H, $ArCH_2O$), 7.11 (d, $J = 2.2$ Hz, 4H, ArH), 7.22 (d, $J = 2.2$ Hz, 4H, ArH); ^{13}C NMR: $\delta = 31.2$, 31.4, 34.2, 61.5, 66.7, 126.7, 128.0, 130.0, 134.0, 145.7, 155.0; MS (ESP$^+$): $m/e = 788$ $[M+Na]^+$; anal. calcd for $C_{50}H_{68}O_6$: C 78.50, H 8.96; found C 78.61, H 9.24.

7,15,23,29-Tetra-*tert*-butyl-31,32,33,34-tetramethoxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[4]arene (**10**): A solution of **21** (470 mg, 0.845 mmol) and **16** (338 mg, 0.845 mmol) in dioxane (9 mL) was added over a period of 120 min to a stirred suspension of powdered KOH (500 mg, 8 mmol) in dioxane (9 mL) heated to 70 °C. The mixture was heated and stirred for an additional 12 h, then water was added and, after neutralization with HCl, extraction with ether, drying (Na_2SO_4), and solvent evaporation, column chromatography (eluent: chloroform) gave **10**. Yield: 170 mg (25 %). The white powder obtained after evaporation of the solvent under vacuum proved to be highly soluble in all commonly used organic solvents and could not be crystallized. M.p. 73 – 76 °C; ^1H NMR: $\delta = 1.24$ (s, 18H, *t*Bu), 1.29 (s, 18H, *t*Bu), 3.18 (s, 6H, OCH_3), 3.36 (s, 6H, OCH_3), 3.92 (s, 2H, $ArCH_2Ar$), 4.44 (s, 4H,$ArCH_2O$), 4.48 (s, 4H,$ArCH_2O$), 4.52 (s, 4H,$ArCH_2O$), 7.19 (d, $J = 2.4$ Hz, 2H, ArH), 7.23 (d, $J = 2.4$ Hz, 2H, ArH), 7.33 (d, $J = 2.2$ Hz, 2H, ArH), 7.36 (d, $J = 2.2$ Hz, 2H, ArH); ^{13}C NMR: $\delta =$ 32.1, 32.1, 32.2, 35.0, 35.1, 62.6, 63.1, 67.7, 68.3, 127.2, 128.7, 128.9, 129.0, 131.0, 131.2,131.2 134.4, 146.7, 147.1, 155.8, 156.3; MS (ESP$^+$): $m/e = 818$ $[M+Na]^+$; anal. calcd for $C_{51}H_{70}O_7$: C 77.04, H 8.87; found C 76.81, H 8.93.

7,15,23,31-Tetra-*tert*-butyl-33,34,35,36-tetramethoxy-2,3,10,11,18,19,26,27-octahomo-3,11,19,27-tetraoxacalix[4]arene (**11**): A solution of **18** (875 mg, 2.50 mmol) and **15** (560 mg, 2.50 mmol) in dioxane (17 mL) was added over a period of 100 min to a stirred suspension of powdered KOH (1.4 g, 22 mmol) in dioxane (17 mL) heated to 75 °C. The mixture was heated and stirred for an additional 6 h, then water was added and, after neutralization with HCl, extraction with $CHCl_3$, drying (Na_2SO_4), and solvent evaporation, column chromatography (eluent: chloroform) gave **11** (yield: 440 mg, 53 %) which was recrystallized from acetone. M.p. 198 – 199.5 °C; ^1H NMR: $\delta = 1.29$ (s, 36H, *t*Bu), 3.36 (s, 12H, OCH_3), 4.51 (s, 16H, $ArCH_2O$), 7.37 (s, 8H, ArH); ^{13}C NMR: $\delta = 32.2$, 35.1, 63.2, 68.0, 128.6,131.2, 147.3, 156.1; MS (ESP$^+$): $m/e = 848$ $[M+Na]^+$; anal. calcd for $C_{52}H_{72}O_8$: C 75.69, H 8.80; found C 75.45, H 8.97.

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or CH_2OCH_2 (analogously CH_2 or CH_2SCH_2 in homothiacalixarenes, and so on) and we simply propose that the numbers should be used which indicate the length of the bridges in naming the cyclophane, that is 1 and 3. 3 should have priority with respect to 1, and no further number is needed, since the number of 3 states already indicates the number of oxygen atoms and the overall number of 3 and 1 states already indicates the *n* value in structure **1**. Since cyclophane-bracketed numbers obviously cannot be used within calixarene nomenclature nor, for instance, can compound **8** be indicated as a [3.3.1.1]homooxacalixarene, we provisionally indicate it in the laboratory as a [3.3.1.1]homooxacalixphane. A quick identification of the cyclic system will be more and more appreciated on increasing the number of aromatic residues. Manuscripts on large homologues are in preparation.

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[31] The estimate of these mean values in the case of **6** is somewhat difficult. It has been carried out for OCH_3 signals and the obtained value actually appears to be out of the regular trend.

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[37] For a discussion of two cases in which the signal is in an intermediate position between $\delta = 31$ and 38, see: J. O. Magrans, J. de Mendoza, M. Pons, P. Prados, *J. Org. Chem.* **1997**, *62*, 4518–4520.

[38] As can be inferred from ref. [11c].

[39] a) The exchange rate constant at the coalescence temperature for AB signals giving rise to a singlet was obtained through the standard equation $k_c = 2.22(\Delta\nu^2 + 6J_{AB}^2)^{(1/2)}$. $k_{205} = 260\ s^{-1}$ (signals of $ArCH_2O$ protons) and $k_{216} = 600\ s^{-1}$ (signals of $ArCH_2Ar$ protons). The corresponding $\Delta G^{\neq}$ values obtained by the application of the Eyring equation (mean value: 9.68 ± 0.09 kcal mol^{-1}) should be corrected for a statistical factor, see below; b) the mean values of the temperature ranges are reported for $\Delta G^{\neq}$; c) a $\Delta G^{\neq}$ value of 10 kcal mol^{-1} was reported in ref. [11c], although the compound was considered to exist as a mixture of conformations and the process referred to was not indicated.

[40] $\Delta G^{\neq}_{202} = 9.30$ kcal mol^{-1} from $k_{202} = 370\ s^{-1}$ (signals of $ArCH_2O$ protons) and $k_{207} = 300\ s^{-1}$ (signals of $ArCH_2Ar$ protons). $\Delta G^{\neq} = 8.84 \pm 0.07$ kcal mol^{-1} from $k_{182} = 113\ s^{-1}$ (signals of *t*Bu protons) and $k_{200} = 777\ s^{-1}$ (signals of OCH_3 protons).

[41] $\Delta G^{\neq}_{205} = 9.38 \pm 0.03$ kcal mol^{-1} from $k_{205} = 400\ s^{-1}$ (signals of $ArCH_2O$ protons) and $k_{207} = 300\ s^{-1}$ (signals of $ArCH_2Ar$ protons).

[42] So, for instance, in the case of **7**, lacking any information, we could consider as limiting cases that the two values of ΔG° of the four transition states are either the same or very different. In the former case, for 1 mole passing over the first free energy barrier, 0.25 mole reach the inverted 1,4-alternate and 0.75 mole revert to the original one, then $k = 4k_c$. If, on the other hand, the stability of the transition states is significantly different, only one intermediate has to be considered, with 0.5 mole reverting back, and $k = 2k_c$ The apparent value of $\Delta G^{\neq}_{205} = 9.7$ kcal mol^{-1} should be corrected to give $\Delta G^{\neq}_{205} = 9.1$ kcal mol^{-1} in the former case, and $\Delta G^{\neq}_{205} = 9.4$ kcal mol^{-1} in the latter case.

[43] If in this case too only one main conformation was involved and the eventually split signals were separated by $\delta \approx 1.0$, as observed in the case of **7**–**9**, the inversion of the existing conformation should occur with $\Delta G^{\neq}_{167} \approx 7$ kcal mol^{-1}.

[44] C. D. Gutsche, L. J. Bauer, *J. Am. Chem. Soc.* **1985**, *107*, 6052–6059.

[45] Also for the parent compounds, the values of $\Delta G^{\neq}$, estimated from the observed rate of exchange, should be corrected for statistical reversion if multistep pathways are followed. The uncertainty due to these factors should not dramatically affect the present comparison.

[46] a) L. D. Groenen, J.-D. van Loon, W. Verboom, S. Harkema, A. Casnati, R. Ungaro, A. Pochini, F. Ugozzoli, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1991**, *113*, 2385–2392; b) T. Harada, J. M. Rudzinski, S. Shinkai, *J. Chem. Soc. Perkin Trans. 2* **1992**, 2109–2115; c) J. Blixt, C. Detellier, *J. Am. Chem. Soc.* **1994**, *116*, 11957–11960.

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[48] For an analysis of the mechanisms of molecular recognition see: H.-J. Schneider, *Angew. Chem.* **1991**, *103*, 1419–1439; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1417–1436.

[49] Solvent effects on complexation of quaternary ammonium ions by several neutral homooxacalixarene ligands will be dealt with in a forthcoming paper.

[50] In such profiles as those in Figures 5 and 6, a homologous series is considered, except for the isomers **8** and **9**. For that pair we could consider the property of either compounds or the mean value of the property, when the purely regular structural change should be stressed. We obviously consider both compounds because the plots are merely illustrative, but there is no physical reason to prefer the sequence **7**–**8**–**9**–**10**–**11** over **7**–**9**–**8**–**10**–**11**.

[51] Since the fraction of complexed ligand was actually small in all cases, owing to the relatively low salt concentration and the relative weakness of the complexes, the highest observed effects (ligands **8**–**11** with TMAP) were in the order of 0.1 ppm. A full quantitative treatment on more suitable ligands will be reported in a forthcoming paper.

[52] a) H.-J. Schneider, *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 412–419; b) H.-J. Schneider, V. Rüdiger, U. Cuber, *J. Org. Chem.* **1995**, *60*, 996–999, and references therein.

[53] In all cases $\beta > \gamma$. The difference is small but always larger than the experimental uncertainty. Although the obtained $\Delta\delta_\infty$ cannot be considered to be reproducible to less than 0.1 ppm in duplicated experiments, the relative effects in the various positions can be determined more precisely. The $\Delta\delta_\infty$ values obtained from the multiparameter fitting procedure have been approximated to 0.01 ppm in Figure 5 and to 0.1 ppm in Table 2.

[54] The partial charges in the various positions of the cation should be considered in a less approximated analysis.

[55] a) M. Meot-Ner (Mautner), C. A. Deakyne, *J. Am. Chem. Soc.* **1985**, *107*, 469–474; b) for very recent ab initio calculations, see: A. Pullman, G. Berthier, R. Savinelli, *J. Comput. Chem.* **1997**, *18*, 2012–2022.

[56] a) C. A. Hunter, J. K. M. Sanders, *J. Am. Chem. Soc.* **1990**, *112*, 5525–5534; b) C. A. Hunter, *Chem. Soc. Rev.* **1994**, 101–109.

[57] In some systems the interaction of homooxacalixarenes with oxygen atoms can be very important. For hydrogen-bonded complexes of primary alkylammonium ions, see ref. [13a].

[58] We think, in particular, of the detailed analysis carried out on the important self-assembling systems based on paraquat–aromatic

polyethers, as developed by Stoddart and associates; for reviews see: a) D. B. Amabilino, F. M. Raymo, J. F. Stoddart, in *Comprehensive Supramolecular Chemistry*, *Vol. 9* (Eds.: M. W. Hosseini, J.-P. Sauvage), Pergamon, Oxford, **1996**, pp. 85–130; b) D. B. Amabilino, J. F. Stoddart, *Chem. Rev.* **1995**, *95*, 2725–2828; c) R. E. Gillard, F. M. Raymo, J. F. Stoddart, *Chem. Eur. J.* **1997**, *3*, 1933–1940.

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