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### Homooxalixarenes. 3.<sup>1</sup> Complexation of Quaternary Ammonium Ions by Parent Homooxalixarenes in CDCl<sub>3</sub> Solution.

Bernardo Masci

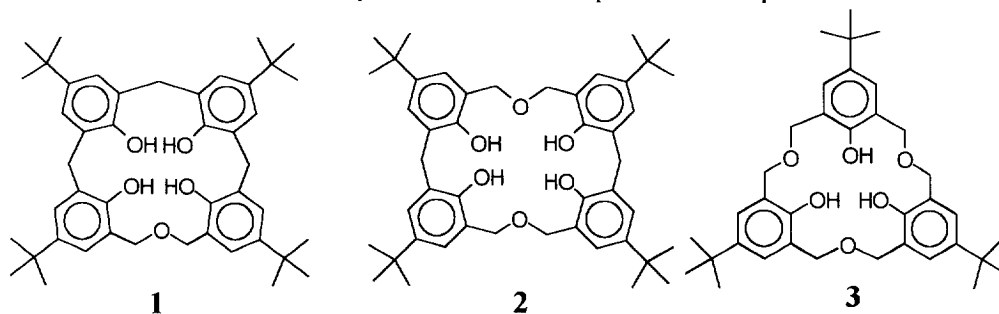
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**Abstract:** Acetylcholine iodide and other quaternary ammonium salts are complexed by the simple calixarene analogues *p-tert*-butyldihomomonooxalix[4]arene, *p-tert*-butyltetrahomodioxalix[4]arene, and *p-tert*-butylhexahomotrioxalix[3]arene in CDCl<sub>3</sub> solution. An analysis of the complexation of cations of varying structure showed that the calix[3]arene analogue is the stronger binding agent ( $-\Delta G^\circ$  up to 2.7 kcal/mol) whilst the limit shielding effects in the <sup>1</sup>H NMR spectra of the cation are larger with the two calix[4]arene analogues.

Complexation of quaternary ammonium ions by cyclophanes is a quite interesting chapter of host-guest interactions,<sup>2</sup> particularly in the light of the proposal of Dougherty, according to whom, cation- $\pi$  interaction is of paramount importance in the binding of acetylcholine to acetylcholinesterase.<sup>3</sup> An extensive analysis of the interaction with quaternary ammonium ions has been carried out in water solution on several series of synthetic polyanionic receptors, in particular by Dougherty,<sup>4</sup> Collet,<sup>5</sup> Lehn,<sup>6</sup> and Schneider,<sup>7</sup> but data on complexation by neutral hosts in lipophilic media are much less abundant<sup>8</sup> and in most cases experimental details are not reported. Being currently interested in calixarene<sup>9</sup> analogues as potential hosts for organic species, we reported that suitably bridged tetrahomodioxalix[4]arenes bind quaternary ammonium ions<sup>1b</sup> and now we report that even the simple parent homooxalixarenes 1-3<sup>10</sup> complex the above ions in CDCl<sub>3</sub> solution.

#### RESULTS AND DISCUSSION

The <sup>1</sup>H NMR spectra at 300 MHz of 1 mM solutions of several quaternary ammonium iodides have been recorded at 30.0 °C in the absence and in the presence of ligands 1, 2, and 3 at varying concentrations. The upfield shift of the peaks of the cation in conditions of fast exchange was monitored and the observed trend was generally in perfect agreement with a simple 1:1 association scheme, the observed effects being in most cases sufficiently strong and clean for an association constant and an extrapolated  $\Delta\delta_\infty$  value to be obtained with confidence by a non linear least squares treatment. All the peaks of the complexed cation could be safely



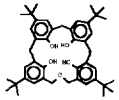
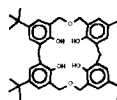
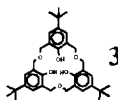
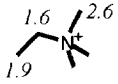
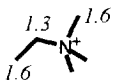
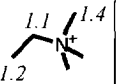
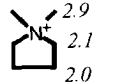
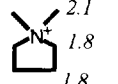
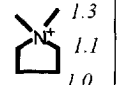
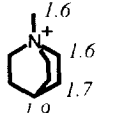
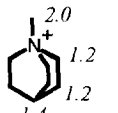
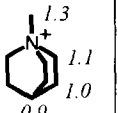
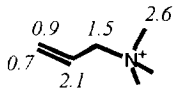
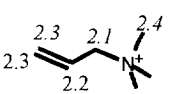
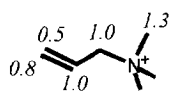
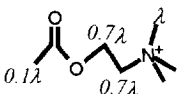
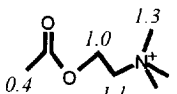
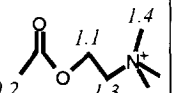
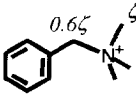
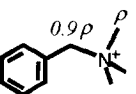
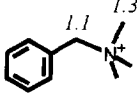
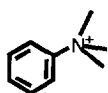
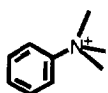
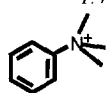
analysed apart those of the strongly coupled aromatic protons. A multiple function curve fitting treatment was eventually applied in most cases and the overall results are reported in Table 1, namely the association constants, the corresponding  $-\Delta G^\circ$  values, and the extrapolated  $\Delta\delta_\infty$  values in the various positions of the seven cations as complexed by ligands **1**, **2**, and **3**. In five cases the observed shift did not correspond to an association sufficiently strong to be confidently assessed (the formally obtained  $K$  value was lower than  $3 \text{ M}^{-1}$ ) and in these cases some directly observed effects are reported, namely the maximum observed upfield shift and the relative effect in the various positions of the cation. In general in all the investigated host-guest pairs with sufficiently strong association ( $K \geq 8 \text{ M}^{-1}$ ), standard deviations were within a few percent of the obtained parameters. In some experiments with ligand **3** the interaction could be followed up to 75% and the fit was still better (see Experimental for such a case). The used  $\text{CDCl}_3$  was stored on molecular sieves and the concentration of adventitious water in the titration conditions was checked to be about  $4 \times 10^{-3} \text{ M}$ . In some check experiments commercial  $\text{CDCl}_3$  was used as received (water content about  $2 \times 10^{-2} \text{ M}$ ) and no significant difference in the obtained parameters was apparent. The spectra of the ligands did not appreciably change when their concentration was increased nor in the presence of the salts, while the signal of adventitious water broadened on increasing the concentration of ligand **2**. The reproducibility of the results was checked in some cases and found to be within 10% for the  $\Delta\delta_\infty$  and  $K$  parameters.

Quaternary ammonium iodides, as well as primary alkylammonium and alkali metal salts which have been thoroughly investigated as guest species in the past two decades, are expected to be extensively associated in chloroform and similar solvents,<sup>11</sup> so that also the presently obtained binding constants with ligands **1** - **3** should be regarded as dependent on the nature of the anion and on the salt concentration.

On inspection of Table 1 we note that, for all the tested salts,  $K$  values are larger for ligand **3** than for ligand **1** or **2**, whilst the  $\Delta\delta_\infty$  values are in almost all cases larger with ligand **1** and **2** than with ligand **3**. Interestingly the tested cations belong to quite different families as for the number of methyl groups, the symmetry, and the type of unsaturated substituents; a selectivity is observed on changing the structure of the cation, but this appears to be a smooth one, in particular with ligand **3**. The interaction of ligands **2** and even more of ligand **1** is a very weak one with the larger (actually less compact) cations.

The differences in the observed binding ability of the three ligands can be attributed to several factors. The rather large upfield shifts reported in Table 1 indicate that the cation faces the aromatic rings in the adducts: actually the interaction between the positive charges and the  $\pi$  cloud of the aromatic systems can be considered the main driving force for the complexation.<sup>3,4,12,13</sup> In several cone-like arrangements the three host molecules appear, on inspection of CPK models, to be well suited for inclusion of the guest cations; apparently, cavities of varying size can be obtained without relevant strain increase by small changes in the torsional angles, moreover several possibilities exist for intramolecular hydrogen bonding, that could affect the relative stability of these cone-like arrangements. We couldn't so far estimate quantitatively the energy of the various conformations, but we note that the rather low selectivity observed on changing the size and the shape of the guest, can be due to the adaptability of the host structure. Shallow arrangements, stabilised by intramolecular hydrogen bonding could also account for the low sensitivity to changes in the guest structure, particularly in the case of **3**. In general, with conformationally mobile host-guest systems, the free energy gap to reach the suitable conformations for complexation and the stabilising contribution due to geometrical and charge fit between the suitably arranged partners must be summed up. The dissection is not easy on the basis of the presently available results, however the three ligands can be considered to be actually in some sort of cone-like arrangements on the basis of the conformational analysis carried out by Gutsche and Bauer<sup>14</sup> and/or the known X-ray crystal structure for the free ligands or solvates.<sup>15</sup> In a study on the conformational properties of compounds **1** - **3** mainly based on temperature dependent  $^1\text{H}$  NMR measurements, Gutsche and Bauer<sup>14a</sup> concluded that **1** adopts a cone conformation, while **2** probably adopts a flattened-cone conformation. Moreover the  $\Delta G^\ddagger$  values for conformational inversion (cone to cone interconversion) were estimated to be 12.9, 11.9, and  $<9$  kcal/mol for **1**, **2**, and **3**, respectively, in  $\text{CDCl}_3$ . The fact that **3** is the most conformationally mobile ligand does not prevent it from being possibly the most preorganized one for

**Table 1.** Complexation of quaternary ammonium iodides by homooxalixarenes: association constants, free energy changes, and extrapolated upfield shifts in the  $^1\text{H}$  NMR spectrum of the salt, in  $\text{CDCl}_3$  at  $30.0^\circ\text{C}$ .

 <b>1</b> $\text{K}, \text{M}^{-1}$ $(-\Delta G^\circ, \text{kcal/mol})$		 <b>2</b> $\text{K}, \text{M}^{-1}$ $(-\Delta G^\circ, \text{kcal/mol})$		 <b>3</b> $\text{K}, \text{M}^{-1}$ $(-\Delta G^\circ, \text{kcal/mol})$	
	$\Delta\delta_\infty, \text{ppm}$		$\Delta\delta_\infty, \text{ppm}$		$\Delta\delta_\infty, \text{ppm}$
<b>13</b> (1.54)		<b>11</b> (1.44)		<b>64</b> (2.49)	
<b>12</b> (1.49)		<b>14</b> (1.58)		<b>90</b> (2.70)	
<b>12</b> (1.49)		<b>16</b> (1.66)		<b>62</b> (2.47)	
<b>11<sup>a</sup></b> (1.44)		<b>9<sup>a</sup></b> (1.3)		<b>60<sup>a</sup></b> (2.45)	
— <sup>b,c</sup>		<b>8</b> (1.2)		<b>62</b> (2.47)	
— <sup>b,d,e</sup>		— <sup>b,d,f</sup>		<b>41<sup>d</sup></b> (2.23)	
— <sup>b,d,g</sup>		— <sup>b,d,h</sup>		<b>38<sup>d</sup></b> (2.18)	

a) The  $\Delta\delta_\infty$  values for the olefinic protons are probably less precise than the others in this table.

b) The weak association could not be confidently assessed.

c) Relative  $\Delta\delta$  are given. Maximum observed  $\Delta\delta=0.40$  ppm at 0.033 M ligand concentration.

d) The aromatic system could not be safely analyzed in the  $^1\text{H}$  NMR spectra.

e) Relative  $\Delta\delta$  are given. Maximum observed  $\Delta\delta=0.15$  ppm at 0.034 M ligand concentration.

f) Relative  $\Delta\delta$  are given. Maximum observed  $\Delta\delta=0.37$  ppm at 0.034 M ligand concentration.

g) Maximum observed  $\Delta\delta=0.25$  ppm at 0.032 M ligand concentration.

h) Maximum observed  $\Delta\delta=0.32$  ppm at 0.029 M ligand concentration.

complexation, namely two shallow, rapidly interconverting cone conformations of **3** are likely to be less self-closed than the cone-like or flattened-cone-like arrangements of **1** and **2**, which undergo a conformational inversion somewhat less rapidly. In the crystal, **3** actually looks like a shallow nest and this was considered to be the reason why guest solvent molecules were not captured.<sup>15a</sup> Very interestingly quaternary ammonium ions are now found to interact in a fairly strong manner with **3**. A tentative interpretation of the data in Table 1 is that, apart from obvious structural differences in the cavity size and shape and in the number and location of the oxygen atoms, all the tested cations are bound more strongly though less selectively by **3** than by **1** and **2** because the former ligand is better preorganized by intramolecular hydrogen bonding in an *open* conformation; however in the shallow cavity the cation is somewhat loosely bound (as for its mobility and distance from the aromatic rings), as revealed by the smaller  $\Delta\delta_{\infty}$  undergone by its protons. A trivial factor, namely the presence of one less aromatic  $\pi$  system in the cavity of **3** with respect to the cavity of **1** and **2** cannot be overlooked. It can turn out to play a role in the smaller limit shielding effect actually observed with **3**, but could also produce by itself a lower association with **3** than with **1** or **2**. Moreover in the shallower cavity a given proton of the guest cation is not likely to face two aromatic  $\pi$  clouds at the same time. It is worth noting that although a definite trend is apparent in the strength of the complexation with all the tested cations, namely  $\mathbf{1} \cong \mathbf{2} < \mathbf{3}$ , the difference in free energy is a quite small one, while, for instance, the looseness of the association (namely the degree of freedom of the bound substrate) has been held responsible by itself for some large effects in the related case of the inclusion of quaternary ammonium ions in a cryptophane.<sup>5b</sup> Obviously further investigation is needed for a safe analysis, in particular a more systematic variation of the cation structure can be useful if small differences in free energy have to be interpreted.

Useful information on the geometry of the adduct can be obtained by inspection of the data in Table 1. Methyl protons undergo in most cases the largest  $\Delta\delta_{\infty}$  shift, but the difference with respect to the other types of protons is rather small when the first three cations in Table 1 are considered, namely the most compact ones. It is also to be noted that mediated effects for the several protons in the various sets (from 1 to 9) are actually observed. The apparent lack of specificity can in principle take origin from various features of the adduct, namely: i) the aromatic walls can effectively surround the whole surface of the cation, ii) different arrangements of the ion in the cavity, with comparable stability, can exist, iii) the ion can almost freely rotate in loose complexes. Some larger differences appear in the case of acetylcholine and allyltrimethylammonium ions. While in the former case the obvious interpretation of the low shielding effect for the protons of the acetyl group is that with all the ligands this group is, on the average, removed from the zone of stronger interaction with the aromatic rings, in the latter case peculiar differences emerge for the relative shifts in the various positions when ligands **1**, **2**, or **3** are considered. Also on the geometry of the adduct a systematic variation of the cation structure should allow a safer interpretation, and interesting effects are currently being observed in the complexation of a series of aromatic cations by ligands **1** - **3**.

It is worth noting that a quite few reports appeared so far on complexation of quaternary ammonium ions in the cavity of neutral typical calixarenes. Shinkai has reported on complexation with some simple *O*-alkylated calix[4]arenes, calix[6]arenes, and calix[8]arene in  $\text{CDCl}_3$  or  $\text{CDCl}_3\text{-CH}_3\text{CN}$  mixtures<sup>16,17</sup> and with a calix[6]arene capped at the upper rim,<sup>18</sup> which appears to be a fairly good complexing agent at low temperature.

## CONCLUSIONS

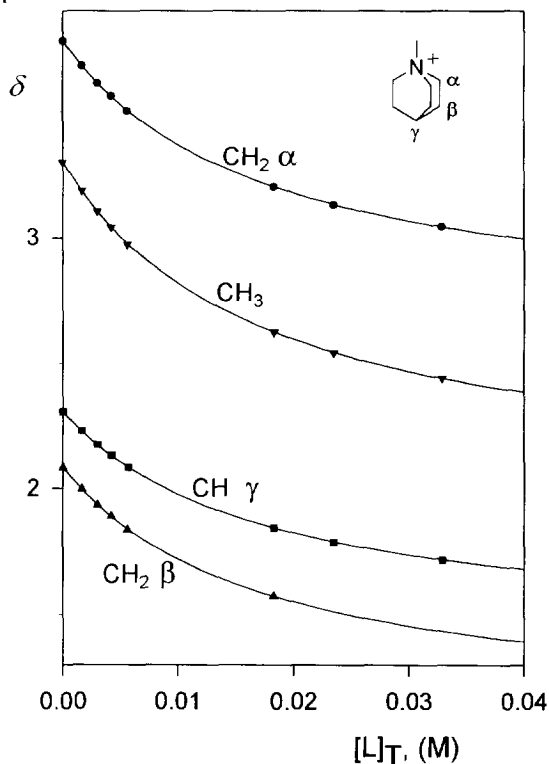
According to our general strategy, interesting host compounds for organic species can be obtained by spacing the aromatic nuclei of relatively small calixarenes with groups longer than methylenes.<sup>1</sup> Even the simple calixarene analogues we deal with in the present paper exhibit binding properties towards organic ions which have quite a few precedents in the chemistry of uncharged typical calixarene compounds. Namely, the binding ability, though rather low, can be cleanly investigated. Even in the cases in which a quantitative assessment is not possible, the experimentally observed effects are quite marked, and the inclusion of the

cation in the calixarene-like cavity seems out of question. Within the general plan of investigating the binding properties of homooxalixarene compounds of varying complexity, the simple parent structures play an important role and we will use them for a systematic investigation of several involved effects. In particular, **3** can be useful for this purpose, as it seems possible to measure its complex forming ability with a large number of salts.

### EXPERIMENTAL

The compounds **1**, **2**, and **3** were prepared as reported by Gutsche and Dhawan;<sup>10</sup> compound **1** was actually obtained as a by-product in the preparation of **2**<sup>10</sup> rather than by the directed synthesis. The preparation of the salts not commercially available was trivial, namely they were obtained by reacting the commercially available tertiary amine with methyl iodide, ethyl iodide, or allyl iodide in ether.

<sup>1</sup>H NMR spectra were taken on a Bruker AC 300 spectrometer and TMS was used as an internal standard. CDCl<sub>3</sub> was from Merck (99.8% deuteration) and was stored on activated 4Å molecular sieves. Typically two solutions in CDCl<sub>3</sub> were prepared for the NMR experiments: solution A with 1.00×10<sup>-3</sup> M salt and solution B with 1.00×10<sup>-3</sup> M salt and up to 3.5×10<sup>-2</sup> M ligand. Aliquots of solution A were added to solution B and/or aliquots of solution B were added to solution A. The additions were carried out with microsyringes and the volumes were assumed to be additive. Spectra were taken at four to nine ligand concentrations for each salt-ligand pair. The equation  $K = [\text{salt-ligand}]/([\text{uncomplexed salt}][\text{uncomplexed ligand}])$  was assumed to hold, and the statistical treatment of the values of observed  $\delta$  vs. [total ligand] was carried out through Jandel Scientific SigmaPlot for Windows program. An example of the observed effects and of the fit to the simple association scheme is reported in Figure 1. The percent standard error in the K and  $\Delta\delta_{\infty}$  parameters was in the present case lower than 0.6.



**Figure 1.** Complexation of *N*-methylquinuclidinium iodide by **3** in CDCl<sub>3</sub> at 30.0 C. Plots of  $\delta$  values for the various types of protons in the cation vs. total ligand concentration; the points are experimental and the curves are calculated from the parameters optimised through the multiple function curve fitting procedure. Two data points are missing for CH<sub>2</sub> β protons due to peak superposition (with the peak for adventitious water).

## ACKNOWLEDGEMENTS

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17. Apparently in the communications in ref. 16  $\log K$  stands for  $\ln K$ , namely the reported  $\log K$  values contrast with the reported free energy changes,<sup>16a</sup> or with the statements on the weakness of the complexation in solution.<sup>16b</sup>
18. Takeshita, M.; Nishio, S.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 4032-4034.