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Cation-π Interactions between Neutral Calix[5]arene Hosts and Cationic Organic Guests

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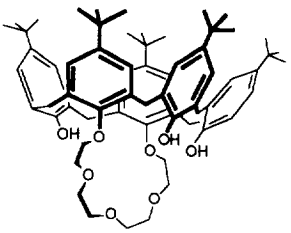
Abstract: The binding properties of the 1,3-bridged calix[5]crowns **1-3** towards a number of quaternary ammonium, phosphonium, and iminium ions have been investigated by ^{1}H NMR in $CDCl_3$ solution, where the sole driving force for association is provided by cation-π interactions. We have found that the cavity of a calix[5]arene fixed in a cone-like conformation provides a fairly efficient, but rather unselective, receptor site for quaternary salts. The conformationally mobile *p-tert*-butylcalix[5]arene (**4**) is in general a much less efficient binder than the more preorganized calixcrowns, but displays a remarkable selectivity towards *N*-methylquinuclidinium ion that is believed to arise from a good complementarity between the globe-shaped guest and the highly adaptable host. The adverse effect on complexation of the *p-tert*-butyl groups at the upper rim has been assessed by comparing the binding properties of **1** *vs.* its de-*tert*-butylated analogue **3**. Furthermore, some information on the importance of counterion and solvent effects have been obtained.

Among the various weak noncovalent forces that provide the basis for molecular recognition phenomena in biology, and that have been successfully exploited in the design and construction of synthetic hosts for molecular recognition in chemistry,[1] the cation-π interaction is receiving increasing attention in recent years.[1-11] Dougherty and his coworkers[2a] have shown that quaternary ammonium and iminium cations are efficiently encapsulated by neutral ethenoanthracene-based cyclophanes in apolar organic media through interaction of the positive charge of the cation with the π-systems of the aromatic rings of the host. Implications of the cation-π interaction for biological recognition of a variety of cationic substrates such as acetylcholine and S-adenosylmethionine, have been emphasized.[10,11]

In addition to Dougherty' s cyclophanes, other neutral cyclophane systems have been reported to bind quaternary salts in apolar solvents.[3a,4b,5,7-9] Among these, a number of calix[n]arenes[5,8] with n=4, 6, and 8, and of homooxacalixarenes[7] have been given considerable attention. Since no report has appeared on the binding properties of the less common calix[5]arenes[12] towards organic cations, and since a simple inspection of CPK molecular models revealed that the shape and size of the cavity of a calix[5]arene in its cone conformation appear to be suitable to accommodate a large variety of quaternary salts, we undertook an exploratory investigation of the binding properties of the 1,3-bridged calix[5]crown **1** towards acetylcholine (**5**) and other quaternary salts (**6-14**) in chloroform and other aprotic organic solvents. Host **1**, in which the ring inversion motion is obviously prevented by the polyether bridge, has been shown to assume a cone-like conformation.[13]



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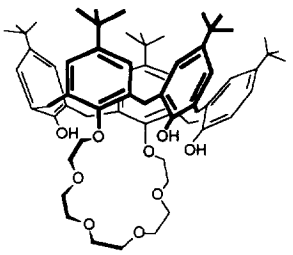

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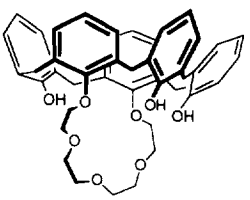

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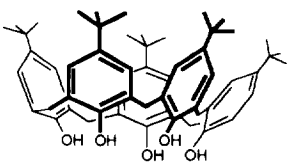

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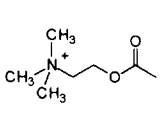
In order to obtain a wider view of the association phenomena and an insight into at least some of the structure effects involved, the binding properties of the higher homologue **2**, of the de-*tert*-butylated analogue **3**, and of the conformationally mobile[14] parent compound **4** were also investigated and compared to those of **1**.

RESULTS

Binding studies were carried out by means of standard ^{1}H NMR titrations of quaternary salt solutions whose concentrations were usually in the order of 1mM. Addition to the above solutions of increasing amounts of the host titrant up to a final concentration in the order of 15-25 mM caused regularly increasing upfield shifts ($\Delta\delta$) of the resonances of the guest. In addition to the NCH_3 (PCH_3) protons, that could be followed in most cases, the resonances of other protons were monitored whenever possible. An ideal case was met in the titration of acetylcholine iodide with **3**, where four simultaneous titration plots corresponding to the four different sets of protons of the guest were obtained (Fig. 1). A similar situation was offered by the titration of *N*-methylquinuclidinium (**9**) with **3**.



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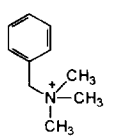

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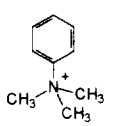

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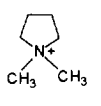

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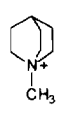

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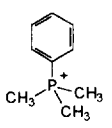

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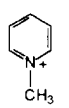

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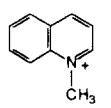

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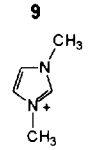

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Table 1. Stability Constants (M^{-1}), Free Energies of Binding (kcal mol^{-1}), and Limiting Upfield Shifts of the Guest (ppm) for the Complexes of Hosts **1-4** with Quaternary Salts at 30 °C.[a]

no.	Guest	Solvent	K	-ΔG°	$-\Delta\delta_{\infty}$[b]
				Host **1**	
1	**5**[c]	$CDCl_3$	47	2.3	2.33 (NCH_3), 0.25 (CH_3CO)
2	**5**[d]	$CDCl_3$	22	1.9	1.52 (NCH_3), 0.17 (CH_3CO)
3	**5**[c]	$(CDCl_2)_2$	310	3.5	0.32 (CH_3CO)
4	**5**	$(CD_3)_2CO$	<5	<0.9	0.27 (NCH_3)[e]
5	**5**	$(CD_3)_2SO$	–	–	
6	**6**[f]	$CDCl_3$	21	1.8	0.36 (NCH_3), 0.35 (CH_2)
7	**7**	$CDCl_3$	71	2.6	2.60 (NCH_3)
8	**8**[g]	$CDCl_3$	50	2.4	2.89 (NCH_3), 2.69 (α-CH_2)
9	**9**	$CDCl_3$	21	1.8	1.97 (NCH_3)
10	**10**[h]	$CDCl_3$	87	2.7	1.52 (PCH_3)
11	**11**	$CDCl_3$	9	1.3	2.62 (PCH_3)
12	**12**	$CDCl_3$	54	2.4	2.07 (α-CH)
13	**13**	$CDCl_3$	24	1.9	1.38 (NCH_3), 2.69 (α-CH), 0.92 (γ-CH)
14	**13**	$(CDCl_2)_2$	930	4.1	1.90 (NCH_3)
15	**14**	$CDCl_3$	23	1.9	1.22 (NCH_3)
				Host **2**	
16	**5**	$CDCl_3$	52	2.4	1.67 (NCH_3), 0.20 (CH_3CO)
17	**7**	$CDCl_3$	39	2.2	3.33 (NCH_3)
18	**9**	$CDCl_3$	25	1.9	1.75 (NCH_3), 2.29 (γ-CH)
19	**13**	$CDCl_3$	19	1.8	1.94 (NCH_3), 3.10 (α-CH), 1.01 (γ-CH)
				Host **3**	
20	**5**	$CDCl_3$	210	3.2	2.53 (NCH_3), 2.07 (α-CH_2), 1.68 (β-CH_2), 0.21 (CH_3CO)
21	**7**	$CDCl_3$	210	3.2	2.65 (NCH_3)
22	**9**	$CDCl_3$	81	2.6	2.33 (NCH_3), 2.38 (α-CH_2), 1.97 (β-CH_2), 1.80 (γ-CH)
23	**10**[h]	$CDCl_3$	130	2.9	2.26 (PCH_3)
24	**13**	$CDCl_3$	200	3.2	1.92 (NCH_3)
				Host **4**	
25	**5**	$CDCl_3$	<5	<0.9	0.26 (NCH_3), 0.24 (α-CH_2), 0.03 (CH_3CO)[i]
26	**7**	$CDCl_3$	<5	<0.9	0.17 (NCH_3)[l]
27	**8**	$CDCl_3$	<5	<0.9	0.55 (NCH_3)[m]
28	**9**	$CDCl_3$	68	2.5	1.83 (NCH_3), 2.07 (α-CH_2)
29	**12**	$CDCl_3$	12	1.5	1.61 (NCH_3)
30	**13**	$CDCl_3$	<5	<0.9	0.16 (NCH_3), 0.05 (β-CH), 0.13 (γ-CH)[l]

Footnotes to Table 1.

[a] Guest concentration 1 mM and iodide counterion unless otherwise stated.
[b] Calculated limiting upfield shifts unless otherwise stated.
[c] Guest concentration 0.5 mM.
[d] Guest concentration 0.7 mM, counterion chloride.
[e] Observed upfield shift at host concentration 19 mM.
[f] Counterion chloride.
[g] Guest concentration 7.3 mM.
[h] Counterion bromide.
[i] Observed upfield shifts at host concentration 27 mM.
[l] Observed upfield shifts at host concentration 18 mM.
[m] Observed upfield shift at host concentration 20 mM.

Complexation equilibria were in all cases fast on the ^{1}H NMR time scale, as shown by the fact that we never observed separate signals for free and bound guest.

Titration data points were fitted to a good precision to eq 1, that is a standard binding isotherm

$$\Delta\delta = \frac{\Delta\delta_\infty K[H]}{1 + K[H]} \tag{1}$$

for the case of 1:1 association. The upfield shift of the guest fully saturated by the host H ($\Delta\delta_\infty$) and the binding constant K were obtained as best fit parameters in a nonlinear least-square fitting procedure. Maximum errors for the determined K values can be reasonably estimated as before[9] as ±20% (±0.1 kcal mol^{-1} in $\Delta G°$). The results are summarized in Table 1. The close adherence of experimental data to eq 1 is nicely illustrated by the titration curves plotted in Fig. 1 and 2. In a number of cases (entries 4, 25-27, 30) no appreciable curvature was apparent in plots of $\Delta\delta$ *vs.* [H], thus indicating that the binding constants K were too low to render the denominator of eq 1 appreciably different from unity. An example of such a behaviour is illustrated in Fig. 2 by the $(CD_3)_2CO$ case. An extreme situation was offered by the titration of **5** with **1** in $(CD_3)_2SO$ (entry 5 and Fig. 2), for which chemical shift changes were negligibly small.

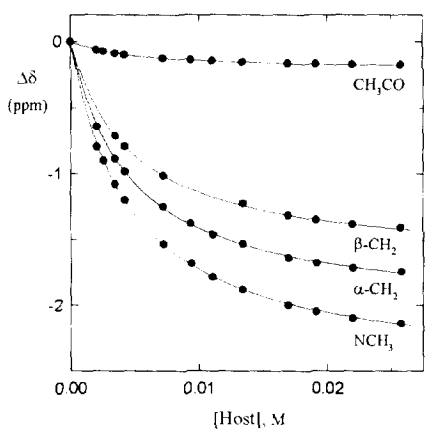

Figure 1. ^{1}H NMR titration of acetylcholine (**5**) iodide with host **3** in $CDCl_3$. Points are experimental and curves are calculated from eq 1 and the parameters listed in Table 1, entry 20.

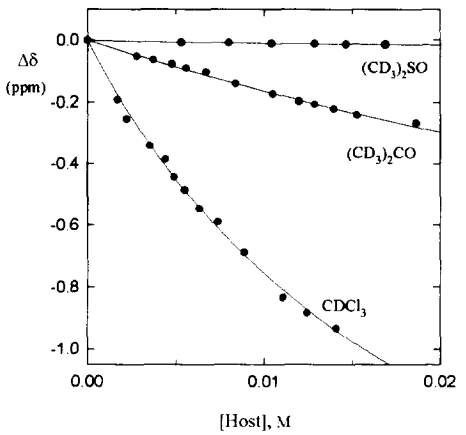

Figure 2. ^{1}H NMR titrations (NCH_3 protons) of acetylcholine (**5**) iodide with host **1** in various solvents.

DISCUSSION

All of the investigated quaternary salts form complexes of definite stability with the 1,3-bridged calixcrown hosts **1-3** in chloroform solution. The chalice defined by the five aromatic rings of a calix[5]arene fixed in a cone-like conformation offers a binding site that is well suited to the structural features of a large variety of organic cations, comprising quaternary ammonium and phosphonium compounds, as well as flat aromatic iminium ions.

The usually strong induced upfield shifts $\Delta\delta_{oc}$ of the CH protons directly bound to the atom bearing the positive charge indicates beyond doubt that complexation involves a close contact between the polar head groups and the aromatic faces of the host. When compared with $\Delta\delta_{oc}$ values for other protons in the same guest molecule, possible geometries for some of the host-guest complexes are inferred. The shift patterns observed for acetylcholine (**5**) complexes (entries 1, 2, 16, 20), that are remarkably similar to those observed in analogous complexes with homooxacalixarenes by Masci[7b] and with cryptophanes by Collet et al.,[3b] strongly suggest that the trimethylammonium head group is closely bound to the host cavity, whereas the acetoxy tail group points toward the exterior. A certain disorder caused by a more or less free rotation of the guest in the complex and responsible for some averaging between head and tail, is suggested by the fact that the induced shifts of the protons of the tail, though being small, are decidedly upfield. Shift patterns observed in complexes of *N*-methylquinuclidinium (**9**) (entries 9, 18, 22, 28), that are again remarkably similar to those observed by Masci for complexes with homooxacalixarenes,[7b] suggest a significantly more disordered situation, with almost equally populated "NCH_3-in" and "NCH_3-out" arrangements (Fig. 3).

Whenever tested, the binding properties of **2** are remarkably similar to those of **1**, thus indicating that increasing the length of the polyether bridge by one oxyethylene unit has little influence on the binding properties. On the other hand, replacement of the *tert*-butyl groups of **1** by hydrogen atoms significantly improves the binding ability of the host. Comparison of entries 20-24 with entries 1, 7, 9, 10, and 13 shows that a number of guests belonging to diverse structural types are consistently bound more strongly by the de-*tert*-butylated host **3** than by the *tert*-butylated host **1**. The adverse effect of *tert*-butyl groups on the binding

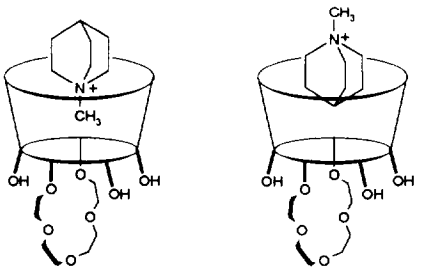

Figure 3. Schematic representations of isomeric **3**·**9** complexes as "NCH_3-in" (left) and "NCH_3-out" (right) arrangements.

ability of a calixarene host was noticed by Shinkai et al.[5a] in a qualitative comparison of the binding abilities of calix[6]arene and *p-tert*-butylcalix[6]arene toward octyltrimethylammonium bromide in chloroform, and interpreted as due to steric interference of the bulky *tert*-butyl groups with guest inclusion. In the present work, the negative influence of the frequently occurring *p-tert*-butyl groups at the upper rim of calixarenes hosts on the stability of inclusion complexes with quaternary salts is fully confirmed and assessed for a number of guest compounds.

In line with expectations based on the simple concept that a less preorganized host should be a weaker binder than a more preorganized one,[15] the conformationally mobile host **4**, unlike hosts **1** and **2**, does not yield complexes of definite stability with a number of quaternary salts (entries 25-27 and 30). It binds only weakly to *N*-methylpyridinium (**12**) (entry 29), but yields a fairly strong complex with *N*-methylquinuclidinium (**9**) (entry 28), which is in fact stronger than those formed by **1** (entry 9) and **2** (entry 18). It appears therefore that the conformationally mobile host **4** experiences selectivity features that its more preorganized bridged derivatives **1** and **2** do not. This remarkable behaviour is somewhat surprising, but not unprecedented. In a recent work[9] it was found that a conformationally mobile diphenylmethane-based cyclophane, whose cation complexing ability was tested with a number of quaternary ammonium and iminium salts including, among others, guests **8**, **9**, **12**, and **13**, yielded the most stable complex with **9** ($K=47\ M^{-1}$, $CDCl_3$, 30 °C). It was suggested that **9**, because of its globular shape, is best suited to fill the cavity of the cyclophane host in its extended thoroid conformation. A similar interpretation may apply to the present case. Inspection of molecular models indeed shows that **4** can easily adopt a snug-fitting cone conformation ready for close contacts between the five aromatic rings and the hosted cation **9**. Such an ideal conformation seems to be less accessible to host **2** due to the deformation caused by the polyether bridge. This interpretation implies that the presumably higher entropy cost of conformational freezing suffered by host **4** is more than offset by the enthalpy gain resulting from a larger number of simultaneous cation-π interactions.

Because extensive ionic association is likely to take place in solvents of low permittivity, host-guest associations involving cationic guests in chloroform and similar solvents are expected to be influenced by the nature of the counterion. Binding constants of tetramethylammonium salts to tetrahomodioxacalix[4]arene[7a] and calix[4]arene[8b] derivatives have been actually found to be strongly anion dependent. In line with the above findings, binding of **1** to acetylcholine (**5**) turned out to be anion dependent, the complex formed by the iodide being more than twice as strong as that formed by the chloride (entries 1 and 2). It is worth noting that the

induced shifts are markedly affected by the counterion, which indicates that the guest is still bound to its counterion after complexation by the host.

Some information on the role of solvent polarity on complexation is provided by entries 1, 4, and 5 (see also Fig. 2). Host **1** binds acetylcholine iodide much more weakly in acetone than in chloroform. In dimethylsulfoxide complex formation is insignificant. The empirical solvent polarity parameter $E_T(30)$ (kcal mol^{-1})[16] is 39.1 for chloroform, 42.2 for acetone, and 45.1 for dimethylsulfoxide. At least on a qualitative basis, complex stability appears therefore to bear an inverse relationship to solvent polarity. This is understandable because a substantial desolvation of host and guest partners must take place upon complexation. In the more polar solvents, the cation-π interaction cannot overcome a more severe desolvation penalty, with the result that little or no complex is formed.

A last comment is devoted to binding data in 1,1,2,2-tetrachloroethane (entries 3 and 14), where significant complex stability enhancements are observed relative to chloroform. The $E_T(30)$ value of tetrachloroethane, 39.4 kcal mol^{-1}, is so similar to that of chloroform that any explanation based on solvent polarity is out of question. The important point is that the tetrachloroethane molecule is so large that it does not fit into the calixarene cavity and leaves therefore a poorly solvated binding site. As a consequence, a lower desolvation penalty is suffered by the host upon complexation in the bulkier tetrachloroethane.[17] We further note that on going from chloroform to tetrachloroethane the **1**·**13** complex experiences a much larger stability increase than the **1**·**5** complex, with the remarkable result that **5** binds to **1** more strongly than **13** in chloroform, but the order is reversed in tetrachloroethane.

EXPERIMENTAL

All commercially available compounds were used without further purification. The salts not commercially available were obtained by reacting the corresponding amine (or phosphine) with methyl iodide. Hosts **1**,[13] **2**,[13] and **3**[18] were available from previous investigations. Host **4** was prepared according to a literature procedure.[19]

^{1}H NMR titrations were carried out in $CDCl_3$ at 30 °C with a 300 MHz spectrometer, according to a published procedure.[7b]

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