Counteranion Effect on Complexation of Quats by a Neutral Calix[5]arene Receptor

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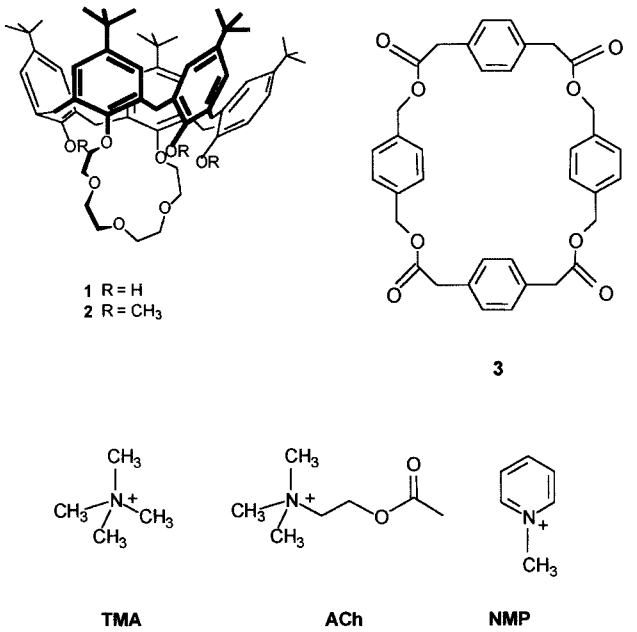
Introduction

Cation−π interactions play a fundamental role in the formation of complexes between quats and natural or artificial receptors.[1] The latter include cyclophanes,[2−6] cryptophanes,[7] calixarenes,[8] and acyclic receptors endowed with aromatic subunits.[5a,9,10]

Particular attention has been devoted in recent years to studies involving neutral receptors in organic solvents of low polarity, such as chloroform and similar solvent systems. Since an extensive cation−anion association takes place in media of low permittivity, the nature of the counteranion accompanying a cation guest is expected to influence host−guest associations. Some information that cation−π interactions are indeed influenced by counteranions can be found in the earlier literature.[11−13] More systematic investigations on the subject have been reported only recently.[5b,6,9]

We have recently shown that the cavity of a calix[5]arene, fixed in the cone conformation by the presence of a polyoxyethylene bridge between the phenolic units A and C, is suitable to host a large variety of quats with medium to high affinities.[13] We report here on a quantitative investigation of the influence of commonly used counteranions on the binding properties of calixcrown **1** toward tetramethylammonium (TMA), acetylcholine (ACh), and *N*-methylpyridinium (NMP) salts. A comparison with the permethylated derivative **2** was carried out in selected cases (Chart 1).

Chart 1



Results and Discussion

The tool of choice for the detection and measurement of host−guest interactions between aromatic hosts and quats is ^{1}H NMR spectroscopy.[14] Titration experiments were carried out as previously described[13] by adding increasing amounts of host (up to 25 mM) to very dilute, homogeneous solutions of quaternary salts.

In chloroform, the complexation equilibria were in all cases fast on the ^{1}H NMR time scale and the signals of the guest remained sharp during titration. In addition to the NCH_3 protons, the resonances of other protons were monitored whenever possible. Typical titration plots based on the CH_3CO protons of ACh are shown in Figure 1.

An interesting finding, which is unprecedented in studies of cation−π interactions, is that the methyl protons of tosylate and the aromatic protons of picrate salts experienced small but clearly detectable upfield shifts during titration. Chemical shift variations defined in all cases titration plots, consistent with plots obtained from the protons of the guest. A typical example of multiple titration experiment is shown in Figure 2.

No chemical shift changes of the resonances of the phenolic hydroxyls of **1** were ever observed, which makes any possible interaction with counteranions through hydrogen bonding very unlikely. Consistently, the permethylated derivative **2** gave, whenever tested, binding

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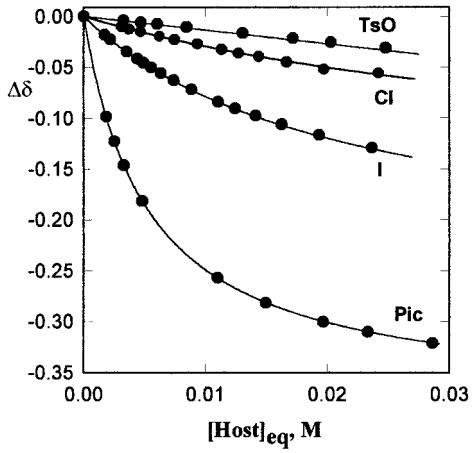

Figure 1. ^{1}H NMR titration curves of different salts of acetylcholine (CH_3COprotons) with host **1**.

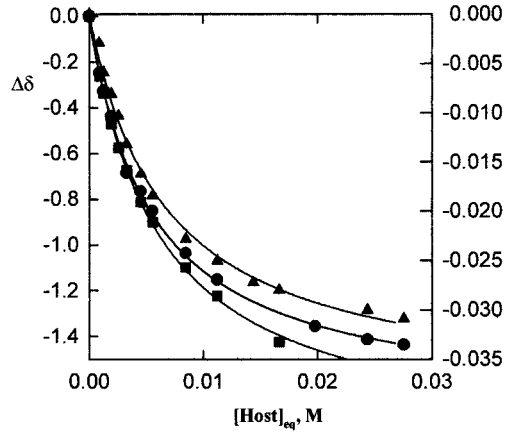

Figure 2. Titration of NMP Pic with host **1**: (■) NCH_3 and (●) α-*CH* (left-hand ordinate); (▲) H-Pic (right-hand ordinate). Points are experimental and curves are calculated from the parameters listed in Table 1.

constants and chemical shift variations that were indistinguishable, or very nearly so, from those of **1** (see footnotes e and f to Table 1).

A number of experiments were carried out in 1,1,2,2-tetrachloroethane, where addition of the host titrant caused broadening of the NCH_3 signal to such an extent that its position during titration could not be determined with any precision. Titration data in this solvent were based on the CH_3CO protons of ACh and/or protons of picrate and tosylate counteranions.

The data listed in Table 1 show that inclusion of the guest into the host cavity is strongly favored by the picrate counterion and strongly disfavored by the tosylate counterion, as revealed by earlier reports.[11,12] A comparison with published data on the stabilities of complexes of TMA and ACh salts with cyclophane **3** in chloroform[5b] shows exactly the same stability trends among counter-

Table 1. Limiting Upfield Shifts ($\Delta\delta_\infty$) and Association Constants (K) for Complexes of Host 1 with Quats at 30 °C

solvent	quat	anion[a]	$-\Delta\delta_\infty$ (ppm)	K (M^{-1})[b]
$CDCl_3$	TMA	TsO	3.20 (N-CH_3), 0.071 (CH_3 TsO)	30 ± 4
		Cl	2.80 (N-CH_3)	100 ± 12
		TFA	2.37 (N-CH_3)	390 ± 50
		Pic	2.49 (N-CH_3), 0.14 (*H*,Pic)	2200 ± 340
	ACh	TsO	0.30 (N-CH_3), 0.03 (CH_3CO), 0.01 (CH_3 TsO)[c]	<5
		Cl	1.53 (N-CH_3), 0.17 (CH_3CO)[d]	22 ± 4[d]
		I[e]	2.33 (N-CH_3), 0.25 (CH_3CO)[d]	48 ± 10[d]
		Pic[f]	0.39 (CH_3CO), 0.14 (*H*, Pic)	180 ± 10
	NMP	I	2.07 (N-CH_3)	54 ± 4
		Pic	1.72 (N-CH_3), 1.90 (α-*CH*), 0.039 (*H*, Pic)	160 ± 16
$(CDCl_2)_2$	TMA	TsO	0.070 (CH_3 TsO)	170 ± 38
		Pic	0.043 (*H*, Pic)	3300 ± 260
	ACh	I	0.32 (CH_3CO)[d]	310 ± 22[d]
		Pic	0.39 (CH_3CO), 0.038 (*H*, Pic)	500 ± 180

[a] TsO = *p*-toluensulfonate; TFA = trifluoroacetate; Pic = picrate. [b] Errors calculated as ±2σ (95% confidence limit). [c] Observed upfield shifts at a host concentration of 25 mM. [d] Data from ref 13. [e] For the complex between host **2** and AchI: $-\Delta\delta_\infty$ 0.24 (CH_3CO), K = 53 ± 4. [f] For the complex between host **2** and AChPic: $-\Delta\delta_\infty$ 0.37 (CH_3CO), 0.17(*H*, Pic), K = 186 ± 10.

anions, namely, Pic > TFA > Cl > TsO with TMA and Pic > I > Cl with ACh.[15] Binding constants with host **1** are much larger and much more sensitive to the adverse effect of ion pairing than those with host **3** (K < 30 M^{-1}), whose more open and less preorganized structure as compared with that of **1** presumably requires a less deep penetration of the guest into the host cavity and a less effective separation of the anion from the complexed cation. Binding constants in 1,1,2,2-tetrachloroethane are, as expected,[13] higher than in chloroform, but the order among anions is the same in both solvents.

Two general factors should be considered as providing a rationale for the adverse effect of ion pairing in cation−π interactions. One of these factors is purely electrostatic. Recent theoretical calculations have shown that a strong decrease—on the order of 10 kcal mol^{-1}—of the benzene−NH_4^+ interaction occurs upon complexation with formate ion, which results from a strong intermolecular polarization from formate to ammonium.[17] The other factor is steric in nature. It originates from the fact that the guest is still bound to its counteranion after complexation by the host, as previously shown by us[13] and others[5b] and fully confirmed in the present work not only by the anion-dependent $\Delta\delta_\infty$ values of the complexed cations but also by the upfield shifts experienced by the picrate and tosylate counteranions in the titration experiments. As a consequence, the space available to the counteranion in the surroundings of the cation partner is limited upon inclusion of the cation into the host cavity, as shown by structure I in Figure 3, where tentative structures of the host−cation−anion ternary complexes are sketched. Given that the bowl-shaped cavity of **1** is not wide enough to accommodate simultaneously both partners of the ion pair guest, the only possible arrangement in which there are close contacts between the anion and the faces of the aromatic rings is that represented by structure II. Recent calculations carried out by Russel

(15) Totally different trends, namely, Cl > Br > I[9] and Tos ≫ I > Pic,[6] have been reported for the stability of complexes of quats with neutral receptors in which the presence of acidic OH and/or NH groups allows strong interactions with counteranions through hydrogen bonding. Anion complexation by the receptor may result in an increase of the cation affinity of the receptor itself by as much as three to 4 orders of magnitude.[6a,b] We suspect that hydrogen bonding to the chloride counteranion is of some importance in the complexation of a series of quats by tetrapeptides[10] and of acetylcholine by calix[6]arene derivatives[16] (see also ref 8, p 96 and p 106).

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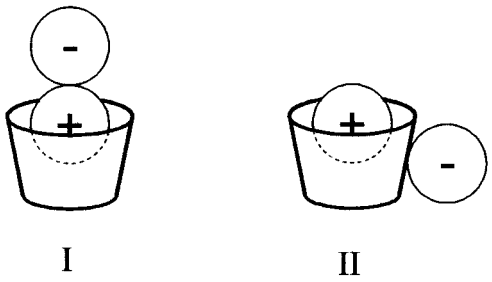

Figure 3. Schematic representation of tentative structures of the host−cation−anion ternary complex.

and Dougherty and their co-workers[2] have shown that the electrostatic attraction in a vacuum between Na^+ and Cl^- —set at a distance of 7.5 Å—is strongly enhanced by an intervening benzene ring, on account of its polarizability. We propose therefore that structure II, either alone or in a rapid equilibrium with structure I, provides a realistic description of the host−quat−anion complex.[18] This proposal also holds for those anions which are silent in the ^{1}H NMR.

Conclusions

Binding of quats to neutral receptors in chloroform is strongly influenced by counteranion nature. Combination of quantitative data from our own and others' investigations[5b,6c11,12] indicates that the stability order Pic > TFA > I > Br > Cl > TsO appears to be quite general, in that it turns out to be independent of the nature of both host and guest cation. This is consistent with the simple notion that the intensity of cation−anion interaction in the ion pair is stronger the smaller the anion and that a significant fraction of that interaction is lost upon inclusion of the cation partner in the host cavity to give a host−cation−guest ternary complex. Clearly, the above reasoning easily applies to spherically symmetrical anions, but the facts that the highest stability is found with picrate, a bulky anion with a broadly distributed charge, and the lowest stability with the highly unsymmetrical tosylate, where the negative charge is concentrated on three adjacent oxygen atoms, fit in with the general interpretation.

The situation is markedly different in the presence of such strong and specific interactions as hydrogen bonding between the neutral receptor and counteranion.[6a,b,9] In these systems large increases in cation binding affinities with a substantial reversal of stability order among anions may be observed.

Experimental Section

All commercially available compounds were used without further purification. Calixarenes **1** and **2** were prepared as previously described.[19] *N*-Methylpyridinium iodide was available from a previous investigation.[13] *p*-Toluenesulfonate and trifluoroacetate salts were prepared by reacting the corresponding acid with the appropriate quaternary ammonium hydroxide. *N*-Methylpyridinium, tetramethylammonium, and acetylcholine picrates were obtained from the corresponding iodide salts by anion exchange with silver picrate. ^{1}H NMR spectra were recorded on a Bruker AC 300 spectrometer, and TMS was used as an internal standard. All ^{1}H NMR titrations were run at 30 °C according to a published procedure.[13]

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(18) A referee called our attention to a recent paper on the "picrate effect" on extraction selectivities of benzo-crown ethers for alkali metal cations (Talanova, G. G.; Elkarim, N. S. A.; Talanov, V. S.; Hanes, R. E., Jr.; Hwang, H.-S.; Bartsch, R. A.; Rogers, R. D. *J. Am. Chem. Soc.* **1999**, *121*, 11281−11290). In this paper convincing evidence was presented that the "picrate effect" results from $\pi-\pi$ interactions between Pic^- and the aromatic unit(s) in the ionophore. It seems therefore likely that with aromatic counteranions structure II is stabilized to some extent by interactions of the same kind with the external face of an aromatic subunit in the calixarene receptor.

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