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Cooperative Binding of Calix[4]pyrrole–Anion Complexes and Alkylammonium Cations in Halogenated Solvents

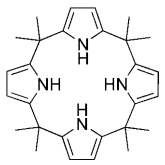
Dustin E. Gross,[a] Franz P. Schmidtchen,*[b] Wiebke Antonius,[b] Philip A. Gale,*[c] Vincent M. Lynch,[a] and Jonathan L. Sessler*[a]

Abstract: Calix[4]pyrrole–chloride interactions are affected not only by the choice of countercation in halogenated solvents, but show a specific dependence on the way in which these cations are bound within the electron rich, bowl-like calix[4]pyrrole cavity formed upon chloride anion complexation. In dichloromethane, the affinities of simple *meso*-octamethylcalix[4]pyrrole (**1**) for methyl-, ethyl-, and *n*-butylammonium chlorides are on the order of 10^5, 10^4, and $10^2\,M^{-1}$, respectively, as determined from isothermal titration calorimetry (ITC) analyses. These cation-dependent anion affinity effects, while clearly evident, are less pronounced in other halogenated solvents, such as 1,2-dichloroethane. Support for the proposed cation complexation selectivity is provided by solid state X-ray crystallographic analyses.

Keywords: anions · calix[4]pyrrole · calorimetry · cations · ion pairing

Introduction

Over the past few decades many anion receptors have been synthesized and investigated for their anion-binding capabilities.[1–6] A few of these receptors have also been studied in conjunction with cation receptors in the form of binary mixtures,[7–13] or even more effectively as ditopic ion-pair receptors,[5,14,15] and have been shown to bind ion pairs as contact ion-pairs[7,16–19] or spatially separated ion pairs.[20] An advantage of an ion-pair receptor over a simple ion receptor is that the number of competing interactions in solution (i.e., the formation of cation–anion pairs) is reduced.[21] Recently, we reported that simple *meso*-octamethylcalix[4]pyrrole (**1**) has the ability to bind ion pairs in the solid state;[22,23] these complexes consisted of a cone conformation in which the pyrrolic NHs were hydrogen bonded to the anion on one face of the macrocycle and the resulting electron-rich cavity, formed on the opposite face, contained either a cesium, imidazolium or pyridinium cation. Solvent-extraction studies, involving the use of water and nitrobenzene, provided evidence for the formation of 1:1:1 cesium/calix[4]pyrrole/halide ion-paired complexes in the organic phase (halide = chloride or bromide).[24] Preliminary NMR spectroscopic evidence for imidazolium inclusion in the calix[4]pyrrole cone conformation has also been presented.[23b]



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Furthermore during recent work we also found that the interaction of *meso*-octamethylcalix[4]pyrrole with alkylammonium and alkylphosphonium chloride salts in various organic solvents is highly dependent on the choice of solvent.[25] In more polar solvents, such as acetonitrile, nitromethane, and dimethylsulfoxide, no observable counterion effects were seen as the result of switching between different cations. However, a small effect on the countercation was seen in 1,2-dichloroethane with an even greater effect being observed in dichloromethane. Specifically, association constants on the order of $10^4\,M^{-1}$ and $10^2\,M^{-1}$ were observed, for

[a] D. E. Gross, Dr. V. M. Lynch, Prof. J. L. Sessler
Department of Chemistry and Biochemistry
The University of Texas at Austin, Austin, TX 78712 (USA)
Fax: (+1) 512-471-7550
E-mail: sessler@mail.utexas.edu

[b] Prof. F. P. Schmidtchen, W. Antonius
Department Chemie, Technische Universität München
85747 Garching (Germany)
Fax: (+49) 89-289-14698
E-mail: schmidtchen@ch.tum.de

[c] Prof. P. A. Gale
School of Chemistry, University of Southampton
Southampton SO17 1BJ (UK)
Fax: (+44) 23 8059 6805
E-mail: philip.gale@soton.ac.uk

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tetraethylammonium chloride (TEA-Cl) and tetrabutylammonium chloride (TBA-Cl), respectively, in this latter solvent. This about 100-fold difference in anion affinity was ascribed to differences in ion-pairing effects involving the chloride anion (Cl^-) and the ammonium cation (R^+) [cf. Eq. (1)] through, within the limit, either reducing the availability of the guest for calix[4]pyrrole binding [e.g., by lowering the effective chloride anion concentration on the left side of Equation (2)] or by enhancing the overall binding process through cooperative association as illustrated in Equation (3).

$$[Cl^-R^+] \rightarrow Cl^- + R^+ \quad (1)$$

$$\mathbf{1} + Cl^- \rightarrow [\mathbf{1}\cdot Cl]^- \quad (2)$$

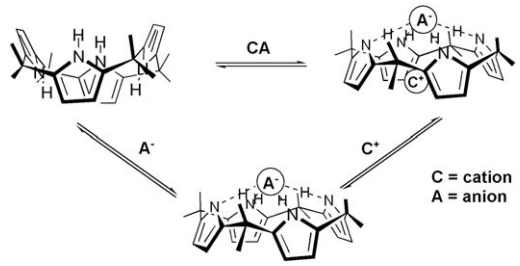
$$[\mathbf{1}\cdot Cl]^- + R^+ \rightarrow [R^+\cdot\mathbf{1}\cdot Cl^-] \quad (3)$$

In the case of ion pairing it is expected that a relatively larger cation will have a lower charge density, thus be more dissociated. This should lead to an increase in the available anion concentration and, as a result, higher affinities for the host–guest recognition process. However, inspection of the reported data (see Tables below) proved inconsistent with this assumption; therefore, we were left with an explanation involving a stepwise association process that could involve random order host/anion/cation ion-pairing or potentially sequential allosteric[20,26–28] cation–[anion-host] interactions. In an effort to differentiate between these possible scenarios and to analyze the ion-pair receptor ability of calix[4]pyrrole in more detail, we have carried out a systematic study of the energetics of chloride anion binding by calix[4]pyrrole in the presence of various countercations in halogenated solvents using ITC and have complemented these analyses with computational results (molecular dynamics in explicit solvent) and solid-state X-ray structural data.

Results and Discussion

As a starting point for investigating the effects of the countercation on the binding of chloride by calix[4]pyrrole **1**, several test alkylammonium hexafluorophosphate (PF_6^-) salts were studied. The PF_6^- anion is well-recognized for its poor H-bond acceptor ability and was not expected to bind significantly to calix[4]pyrrole. Indeed, when either TEA-PF_6 or TBA-PF_6 was titrated with **1** (or vice versa) in dichloromethane very little enthalpic response was observed by ITC. Specifically, exothermicities of $\approx$0.2 kcal mol^{-1} were observed, which are insignificant with respect to the heat of dilution of calix[4]pyrrole. The absence of any heat effects in the case of either TEA-PF_6 or TBA-PF_6 is fully consistent with the proposed lack of appreciable anion binding. Further, and perhaps more significantly in the context of exploring potential cation effects, this same lack of response rules out any significant interaction between free calix[4]pyrrole **1** (a compound known to favor the so-called 1,3-alternate conformation in the absence of a strongly bound substrate; see Scheme 1) and these two alkylammonium cations.

The next step was to test the effect of the cation on the calix[4]pyrrole-chloride complex. Towards this end, TEA-



Scheme 1. Proposed calix[4]pyrrole binding motif.

PF_6 was titrated into a mixture of TBA-Cl/**1** (20.5 mM:1.1 mM, respectively), the excess of the chloride anion being used to ensure near-complete conversion into the so-called cone complex (cf. Scheme 1). Under these conditions, a significant change in enthalpy was observed (Figure 1). This is taken as *prima facie* evidence that the smaller tetraethylammonium cation interacts with the cone-like calix[4]pyrrole–chloride anion complex.

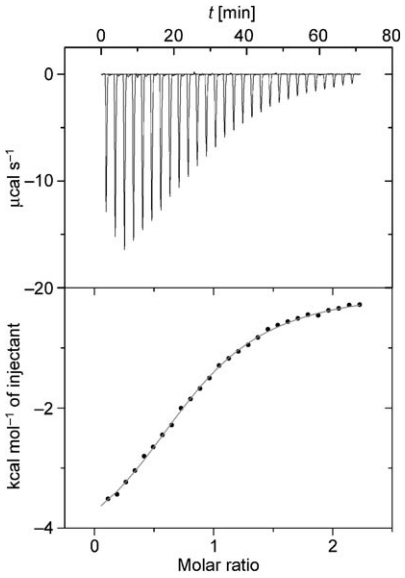


Figure 1. Titration of **1** (1.1 mM) and TBA-Cl (20.5 mM) with TEA-PF_6 (11.9 mM) at 298 K in dichloromethane.

As a control experiment, a complementary titration was carried out wherein TBA-Cl was titrated into a solution of chloride-saturated calix[4]pyrrole (prepared by using a ten-fold excess of TEA-Cl over **1**). In contrast to what was observed in the case of TEA-PF_6, this experiment resulted in very little heat evolution. Similarly, a titration of TEA-PF_6 into a solution of TBA-Cl was performed in the absence of

calix[4]pyrrole. This also gave rise to a very weak heat signal, again well within the heat of dilution (i.e., a range between 0.2 and 0.4 kcal mol^{-1}). On this basis, we propose that there is virtually no interaction between TEA-PF_6 and TBA-Cl (i.e., no shift in the putative ion-pairing equilibria). Since the TEA-PF_6 fails to show an appreciable interaction with TBA-Cl, and pristine **1** fails to bind hexafluorophosphate salts, the binding event is likely stepwise (Scheme 1), wherein the calix[4]pyrrole binds the chloride anion initially to form an electron-rich bowl-shaped cavity, which is stabilizing for a countercation of proper size.

To probe further the effect of cation size on the binding of chloride anion to calix[4]pyrrole in solvents of low polarity, the series of alkylammonium chloride salts was expanded to include cations containing a variety of alkyl substituents ranging in size from methyl groups all the way up to tetradecyl groups. Unfortunately, tetramethylammonium chloride (TMA-Cl) lacks sufficient solubility in most halogenated solvents to allow its inclusion in the present study. Nonetheless, from the range of cations studied, it becomes clear that, at least in dichloromethane, the value of the stability constants derived from the ITC studies depends on the nature of the alkyl substituents present on the tetraalkylammonium countercation (cf. Table 1). Specifically, when at least one

Table 1. Titration data for the interaction of calix[4]pyrrole **1** with alkylammonium and phosphonium chlorides in dichloromethane.[a]

Guest	$T\Delta S$ [kcal mol^{-1}]	ΔH [kcal mol^{-1}]	ΔG [kcal mol^{-1}]	K_a [M^{-1}]
A336-Cl	−4.50	−11.46	−6.96	1.2×10^5
OTMA-Cl	−3.70	−11.56	−7.86	5.9×10^5
TdTMA-Cl	−3.73	−11.56	−7.84	5.6×10^5
MTBA-Cl	−5.01	−12.05	−7.04	1.5×10^5
BnTMA-Cl	−3.40	−10.74	−7.34	2.4×10^5
BnTEA-Cl	−5.01	−10.80	−5.79	1.7×10^4
TEA-Cl[b]	−3.19	−9.32	−9.14	3.2×10^4
TPA-Cl[b,c]	–	–	–	6.6×10^2
TBA-Cl[b,c]	–	–	–	4.3×10^2
THA-Cl[c]	–	–	–	2.2×10^2
TOA-Cl[c]	–	–	–	2.4×10^2
TEP-Cl[b]	−4.68	−9.59	−4.91	3.9×10^3
TBP-Cl[b]	–	–	–	$\approx10^3$
TPhP-Cl[b]	−2.2	−6.8	−4.6	2.8×10^3
Phaz-Cl[d]	−3.02	−7.29	−4.27	1.2×10^3

[a] Data from ITC titrations run at 298 K unless otherwise indicated. Cation abbreviations are listed in the Experimental Section. [b] Values from reference [25]. [c] K_a obtained from an NMR spectroscopy titration.[29] [d] ITC titration run at 303 K.

methyl group is present on the tetraalkylammonium countercation (i.e., when OTMACl, TdTMACl, MTBACl, or BnTMACl are used as the anion source; see Experimental Section for details), chloride–calix[4]pyrrole anion affinities, K_a, of about 10^5 M^{-1} are observed in dichloromethane, whereas when the smallest alkyl group is ethyl, rather than methyl (i.e., TEACl or BnTEACl are studied), the chloride anion affinity is decreased by one order of magnitude ($K_a \approx 10^4$ M^{-1}).

This trend levels off, however, for the shortest substituent, that is, propyl (TPACl) or longer as witnessed for butyl- (TBACl), hexyl- (THACl), or octyl- (TOACl) derived salts. A particularly conspicuous pair of comparisons involves the use of TBACl versus MTBACl and TOA versus OTMA. In both cases, a thousand-fold difference in the chloride anion association constants is observed with the methyl-containing salt showing the higher affinity ($K_a = 10^2$ M^{-1} versus 10^5 M^{-1}, respectively).

A similar cation effect was seen in 1,2-dichloroethane (Table 2). However, in this solvent system, the range of affinities starts with K_a values in the upper $\approx10^5$ M^{-1} region for the methyl-containing alkylammonium chloride salts and levels off at $\approx10^4$ M^{-1} for the larger species (i.e., tetrabutyl- through tetraoctylammonium chloride).

Table 2. Titration data for the interaction of calix[4]pyrrole **1** with alkylammonium chlorides in 1,2-dichloroethane.[a]

Guest	$T\Delta S$ [kcal mol^{-1}]	ΔH [kcal mol^{-1}]	ΔG [kcal mol^{-1}]	K_a [M^{-1}]
A336-Cl	−3.87	−11.29	−7.42	2.7×10^5
OTMA-Cl	−3.87	−11.93	−8.06	8.0×10^5
MTBA-Cl	−4.89	−12.69	−7.80	5.2×10^5
BnTEA-Cl	−4.62	−11.49	−6.87	1.1×10^5
TEA-Cl[b]	−3.28	−9.87	−6.59	7.5×10^4
TBA-Cl[b]	−4.32	−10.39	−6.07	2.8×10^4
THA-Cl	−5.19	−11.15	−5.96	2.4×10^4
TOA-Cl	−5.07	−11.09	−6.02	2.6×10^4

[a] Data from ITC titrations run at 298 K. [b] Values from reference [25]. Cation abbreviations are listed in the Experimental Section.

The conclusions drawn from the above experimental work were reinforced by computational studies that involved observing MTBA-Cl and calix[4]pyrrole in molecular dynamics runs at 300 K using the GROMOS-96 modeling software including the GROMOS 45a4 force field in its latest parameterization for chloroform solvent.[30] The host and guest species were soaked in a truncated octahedral box (edge size 41.7 Å) containing 266 explicit chloroform molecules under periodic boundary conditions. Such a setup aims to represent a realistic scenario of the molecular binding events while still capturing entropic influences including those caused by individual solvent molecules. The trajectories, which were recorded over 60 picoseconds, dramatically depend on the starting configuration of the binding partners, that are indicative of non-equilibrium conditions at the end of this period. Each of the temporal pathways observed fall into two categories, both featuring the competition between the calix[4]pyrrole and the tetraalkylammonium cation for the chloride anion. In other words, if the binary calixpyrrole–chloride complex is formed first in the trajectory, the MTBA cation may associate into ternary complexes having two distinct structures: either, i) the cation adheres to the open face of the bound chloride forming a calixpyrrole complex with an intimate contact ion-pair; or ii) the cation binds with the methyl group oriented into the anion-induced bowl-shaped cavity of the calix[4]pyrrole chloride complex. This latter route is only available when all pyrrole rings are inclined towards the anionic guest (see Figure 2 and Supporting Information). Once formed, either complex struc-

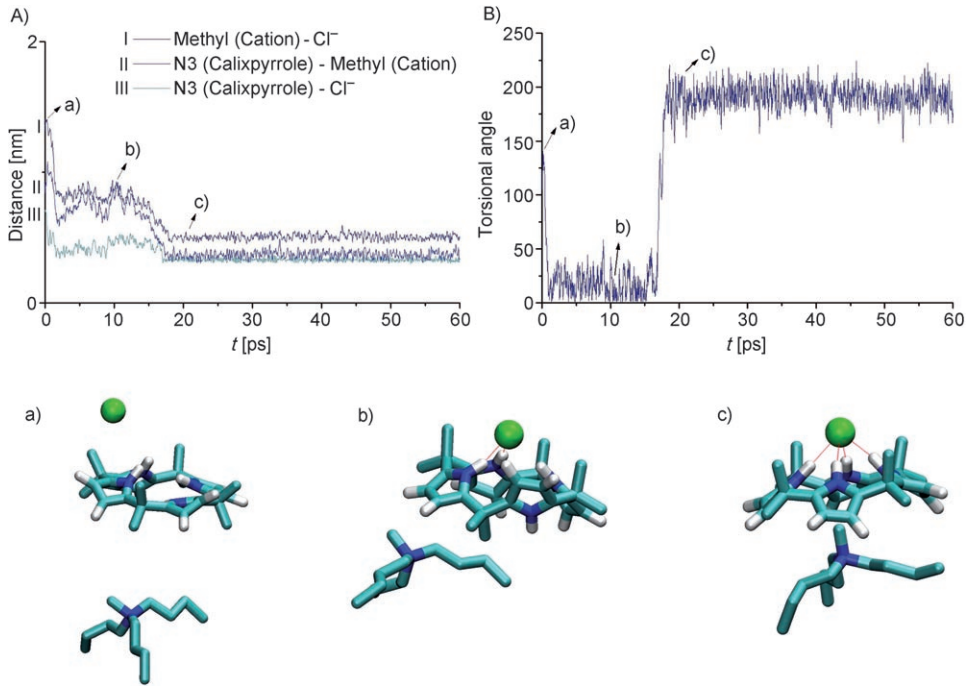


Figure 2. Molecular dynamics run on calix[4]pyrrole and MTBA chloride in explicit chloroform using periodic boundary conditions at 300 K. Panel A: Traces of selected distances versus time; N3 is one of the pyrrolic nitrogens of **1** (see Supporting Information); the arrows at a, b, and c, correspond to the structures shown below. Panel B: Trajectory of the dihedral angle between the plane of one pyrrole ring and the adjacent plane containing one axial *meso*-methyl group (see Supporting Information). The ring flip is clearly visible as a step after 17 picoseconds preceding the approach of the *N*-methyl group of the cation shortly after. A movie of the sequential binding events is presented in Supporting Information.

ture is stable for several nanoseconds at 300 K and does not dissociate or interconvert into the other. If the contact ion-pair is the first binary complex attained in the trajectory only the immediate calix[4]pyrrole–chloride–MTBA sequential complex is observed.

Taken in concert, these results contradict the expectation that larger alkylammonium salts should be less ion-paired due to the presence of a lower charge density for the cation as a whole. On the other hand, these results are consistent with a highly cooperative binding process, wherein the methyl group of a tetraalkylammonium countercation becomes bound within the cone-shaped cavity created upon the binding of chloride anion to calix[4]pyrrole.

Additional support for the above proposal comes from solid-state structural analyses. Previously, we had shown that different cations are included to different degrees within the calix[4]pyrrole cavity and that in the specific case of the TMA-Cl complex (TMA-Cl·**1**) one of the methyl groups resides within the electron-rich cavity.[25] We thus sought to determine whether analogous results would be obtained using other methylammonium cations. Towards this end, diffraction grade crystals of OTMA-Cl·**1** and MTBA-Cl·**1** were grown by the slow evaporation of dichloromethane solutions containing **1** and the requisite methyltrialkylammonium chloride salts (excess) (Figure 3). In both cases, the crystals obtained were in the form of the dichloromethane solvates. Nonetheless, for both OTMA-Cl·**1** and MTBA-Cl·**1** the methyl groups of the methyltrialkylammonium cation were found to reside within the electron rich cavity in analogy to what was seen in the case of the TMA-Cl·**1** complex reported previously.[25]

As might be expected, the distances from the lattice plane formed by the four pyrrolic nitrogen atoms to the ammonium nitrogen atom ($d_{N4–N}$) were found to be longer than the previously reported distance of 3.906 Å for TMA-Cl·**1**, that is, 3.998 and 4.187 Å for OTMA-Cl·**1** and MTBA-Cl·**1**, respectively. On the other hand, these values are still shorter than for larger alkyl ammonium cations studied previously (i.e., TEA, $d_{N4–N}$ = 4.361 Å; TPA, $d_{N4–N}$ = 6.214 Å; TBA, d_{N4-N} = 4.445 Å)[25] or analyzed in the context of the present study (i.e., BnTEA-Cl·**1**; Figure 4, $d_{N4–N}$ = 4.356 Å).

Further confirmation that a different binding behavior is

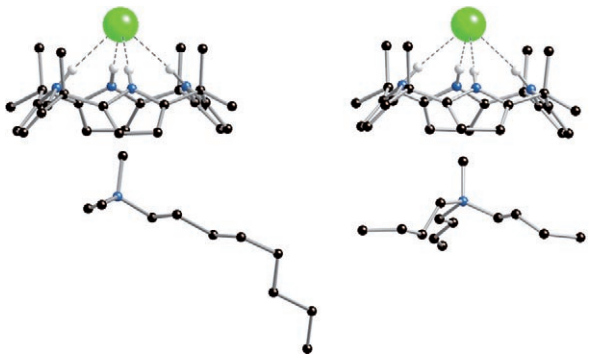


Figure 3. X-ray crystal structure of **1**·OTMA-Cl (left) and **1**·MTBA-Cl (right). Both structures have dichloromethane (solvent) and CH hydrogens removed for clarity.

observed when using different countercations was obtained by studying a series of benzoate salts, rather than chloride salts. Specifically, the binding behavior of a series of benzoate salts containing the TBA, TEA, and TMA countercations, respectively, was analyzed. In this case the TMA-OBz salt was sufficiently soluble and therefore could be included for comparison (TMA-Cl is not adequately soluble in CH_2Cl_2, as noted above).

In analogy with chloride, the results obtained from ITC titrations revealed that, once again, an observable difference

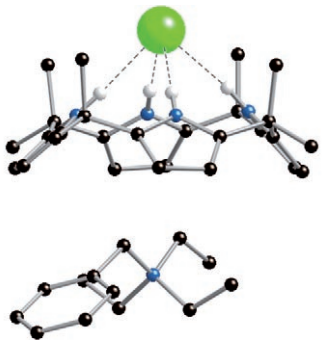


Figure 4. X-ray crystal structure of **1**·BnTEA-Cl. The CH hydrogens have been removed for clarity.

in the anion affinity is seen upon switching from TBA to TEA, and finally to TMA (Table 3). Specifically, the K_a value for the binding of benzoate anion to **1** is on the order of $10^2\,M^{-1}$ for TBA-OBz; however, the corresponding value for TEA-OBz is $10^4\,M^{-1}$, whereas that for TMA-OBz is $10^5\,M^{-1}$.

Table 3. Titration data for the interaction of calix[4]pyrrole **1** with alkylammonium benzoates in dichloromethane and 1,2-dichloroethane.

Solvent	Guest	$T\Delta S$ [kcal mol^{-1}]	ΔH [kcal mol^{-1}]	ΔG [kcal mol^{-1}]	K_a [M^{-1}]
CH_2Cl_2	TMA-OBz[a]	−4.71	−12.03	−7.32	1.9×10^5
	TEA-OBz[a]	−4.14	−10.00	−5.86	1.9×10^4
	TEA-OBz[b]	−4.57	−10.27	−5.70	1.2×10^4
	TMA-OBz[c]	−4.89	−12.05	−7.16	1.7×10^5
	TEA-OBz[c]	−5.84	−11.81	−5.97	2.3×10^4
	TBA-OBz[d]	–	–	–	2.4×10^2
DCE[e]	TBA-OBz[c]	−5.33	−11.23	−5.90	2.1×10^4
	TEA-OBz[c]	−4.95	−11.75	−6.80	9.8×10^4

[a] Data from ITC titrations run at 303 K; syringe: **1**; cell: TEA-OBz. [b] Data from an ITC titration run at 304 K; syringe: TEA-OBz; cell: **1**. [c] Data from ITC titrations run at 298 K, syringe: **1**; cell: TMA-OBz, TEA-OBz, or TBA-OBz, respectively. [d] From an NMR spectroscopy titration.[29] [e] DCE: 1,2-dichloroethane; TMA-OBz is not sufficiently soluble in this solvent to allow ITC studies to be conducted.

The energetic signatures of these interactions are characterized by high exothermicities (large negative ΔH° values) with strong opposing entropies. Furthermore, we find no dependence on the concentration or on the addition mode of TEA-OBz (i.e., titration of the salt into a solution of the calix[4]pyrrole or titration of the calix[4]pyrrole into a solution of the salt). This leads us to suggest that both components of the guest salt are taken up concurrently and with similar energies; in other words, the TEA-OBz guest is bound to calix[4]pyrrole in a highly positive cooperative fashion such that the individual anion- and cation-binding steps are indistinguishable energetically from the association of a preformed ion pair. In addition, with the congeners TEA-OBz and TMA-OBz the energetic pattern leads one to conclude that well-structured complexes are being formed. The general trend with these benzoate anion salts thus very much resembles what is seen in the chloride case, namely as the cation size decreases, the stability constant increases. Again, this finding underscores the fact that there is an effect of the countercation on the anion binding, at least under these solution-phase conditions.

Conclusion

The equilibrium studies described above characterize calix[4]pyrrole as a stoichiometric ion-pair receptor. Although the exact mechanism of this effect remains open for future discussion, based on the known chemistry of calix[4]pyrrole and the solid-state structural data alluded to above, we believe that the origin of the cation dependence on the anion-binding affinities (i.e., the observed cooperative ion-pair effect) has a structural basis. Extensive prior work has served to show that calix[4]pyrrole **1** in its uncomplexed form is extremely flexible and is a species that interconverts rapidly between all possible conformations, while on average favoring the 1,3-alternate arrangement.[31] However, it is also well-established that upon interaction with a tightly-bound anion, such as benzoate or chloride anion, calix[4]-pyrrole **1** becomes frozen into its so-called cone conformation (see Scheme 1).[31] This structural locking serves to create a cavity distal to the pyrrole NH donor atoms that can complex a tetraalkylammonium cation of suitable size and shape. The magnitude of this latter cation complexation effect is highly dependent on the structure of the tetraalkylammonium cation in question with methyltrialkylammonium salts of chloride and benzoate being bound especially well in halogenated solvents. The differences in the resulting anion binding K_a values can be appreciable, as reflected in an up to a 10^3-fold variation in the observed benzoate or chloride anion binding affinities in dichloromethane depending on the choice of countercation. As such, the results reported herein serve to underscore an emerging theme in receptor design, namely even the simplest of receptors, such as calix[4]pyrrole, can display recognition effects that are far more complex than might be inferred based on a simple analysis of their chemical structure.

Experimental Section

Reagents: All salts were purchased having ≥98% purity from commercial sources and used without further purification. Aliquat 336 (methyltridecylammonium) chloride (A336-Cl) was purchased from Acros Organics. Tetraethylammonium hexafluorophosphate (TEA-PF_6), tetrabutylammonium hexafluorophosphate (TBA-PF_6), octyltrimethylammonium chloride (OTMA-Cl), tetradecyltrimethylammonium chloride (TdTMA-Cl), methyltributylammonium chloride (MTBA-Cl), benzyltrimethylammonium chloride (BnTMA-Cl), benzyltriethylammonium chloride (BnTEA-Cl), tetraethylammonium chloride (TEA-Cl), tetrapropylammonium chloride (TPA-Cl), tetrabutylammonium chloride (TBA-Cl), tetrahexylammonium chloride (THA-Cl), tetraoctylammonium chloride (TOA-Cl), tetraethylphosphonium chloride (TEP-Cl), tetrabutylphosphonium chloride (TBP-Cl), tetraphenylphosphonium chloride (TPhP-Cl), P-5 phosphazenium chloride (Phaz-Cl), tetramethylammonium benzoate

(TBA-OBz), tetraethylammonium benzoate (TEA-OBz), tetrabutylammonium benzoate (TBA-OBz).

Microcalorimetric titrations: Both VP-ITC and MCS-ITC instruments made by MicroCal were used to determine the molar enthalpy (ΔH) of complexation. Subsequent fitting of the data to a 1:1 binding profile using Origin software provided access to the K_a and thus Gibbs free energy (ΔG) which could be used along with ΔH to determine the entropy (ΔS). Blank titrations into plain solvent were also performed and subtracted from the corresponding titration to remove any effect from the heats of dilution from the titrant. Most titrations were run at 25 °C; however, a few were run at 30 °C due to ambient conditions. In general, the differences in K_a values determined at 25 and 30 °C were within experimental error.

^{1}H NMR spectroscopic titrations: A Varian Mercury 400 MHz NMR spectrometer was used to measure the 1H NMR shifts of the NH proton of the pyrrole. Solutions of **1** were titrated with the chloride or benzoate salt at 25 °C. The titration data were plotted Δppm versus concentration of guest and fit to a 1:1 binding equation developed by Wilcox[29] using the nonlinear curve-fitting procedure in Origin software.

Computational procedures: Calix[4]pyrrole and methyltributylammonium chloride (MTBA-Cl) were constructed according to the general outlines given for the GROMOS-96 force field calculations.[30] The partial charges on the ammonium cation were adapted from the literature.[32] The individual host guest species were deliberately placed in a solvent box of chloroform and the system was energetically relaxed. The molecular dynamic runs were conducted for 60 picoseconds with few examples extending to 10 nanoseconds. Frames were taken every 30 femtoseconds. The structural analysis used the GROMOS-96 software package.[33]

X-ray crystallographic data: CCDC 686302 (**1**·OTMA-Cl), 686607 (**1**·MTBA-Cl) and 686301 (**1**·BnTEA-Cl) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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