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Binding of Acetylcholine and Tetramethylammonium to a Cyclophane Receptor: Anion's Contribution to the Cation−π Interaction

Sandra Bartoli and Stefano Roelens*

Contribution from the CNR, Istituto di Chimica dei Composti Organometallici, Dipartimento di Chimica Organica, Università di Firenze, Polo Scientifico, I-50019 Sesto Fiorentino, Firenze, Italy

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Abstract: The interaction of the lipophilic cyclophane **1** with several acetylcholine (ACh) and tetramethylammonium (TMA) salts has been investigated in deuteriochloroform to ascertain the influence of the counterion on the cation−π interaction. Reliable association constants have been measured for 17 salts of commonly used anions; corresponding binding free energies $-\Delta G^\circ$ ranged from over 8 kJ mol^{-1} down to the limit of detection. The dramatic dependence of the binding energy on the anion showed that the latter takes part in the process with a passive and adverse contribution, which inhibits cation binding even to complete suppression in unfavorable cases. Thermodynamic parameters for the association of **1** with TMA picrate demonstrate that binding is enthalpic in origin, showing a substantial enthalpy gain ($\Delta H^\circ = -16.7$ kJ mol^{-1}) and an adverse entropic contribution ($\Delta S^\circ = -27.9$ J mol^{-1} K^{-1}). A correlation has been found between the "goodness" of anions as binding partners and the solubility of their salts. Conversion of the anion into a more charge-dispersed species, for example, conversion of chloride into dialkyltrichlorostannate, improves cation binding substantially, indicating that charge dispersion is a main factor determining the influence of the anion on the cation−π interaction. DFT computational studies show that the variation of the binding free energy of TMA with the counterion is closely accounted for by the electrostatic potential (EP) of the ion pair: guest binding appears to respond to the cation's charge density exposed to the receptor, which is determined by the anion's charge density through a polarization mechanism. A value of $-\Delta G^\circ = 38.6$ kJ mol^{-1} has been extrapolated for the free energy of binding of TMA to **1** in chloroform but in the absence of a counterion. The transmission of electrostatic effects from the ion pair to the cation−π interaction demonstrates that host−guest association is governed by Coulombic attraction, as long as factors (steric, entropic, solvation, etc.) other than pure electrostatics are not prevalent.

Introduction

Since the first experimental evidence reported by Kebarle and co-workers two decades ago,[1] the cation−π interaction, that is, the interaction of a cationic species with the π electrons of aromatic rings, has firmly established its relevance among noncovalent forces.[2] Interest in the field was stimulated by the postulated involvement of the cation−π interaction in biochemical events, such as potassium transport through transmembrane channels and recognition of biologically relevant quaternary ammonium cations, for example, the neurotransmitter acetylcholine, by receptors and enzymes.[2,3] Following Lehn's seminal work,[4] several research groups have devoted a considerable effort to the synthesis of receptor molecules possessing aromatic cavities for the investigation of binding properties toward quaternary ammonium cations,[2,5] a significant number of which are neutral hosts for binding studies in lipophilic solvents. Although largely unappreciated, in the overall binding interaction the counterion, an unavoidable presence in solution, plays a fundamental role. As a matter of fact, the large body of data was primarily gathered on quaternary ammonium cation−aromatic interactions regardless of the environment contribution; the anion contribution, in particular, has received little attention, even though strong ion-pairing interactions have to be expected in low-polarity media.[6] In water, counterion effects are predictably damped; Dougherty and co-workers could not detect any appreciable difference between iodide and chloride in the binding of *N*-methylisoquinolinium to a cyclophane receptor

* Correspondence to: Dr. Stefano Roelens, CNR - ICCOM, Dipartimento di Chimica Organica, Università di Firenze, Polo Scientifico, Via della Lastruccia, 13, I-50019 Sesto Fiorentino, Firenze, Italy. Telephone: +39-055-457-3546. Fax: +39-055-457-3570. E-mail: stefano.roelens@unifi.it.

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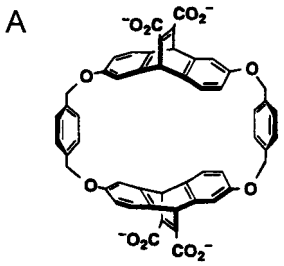
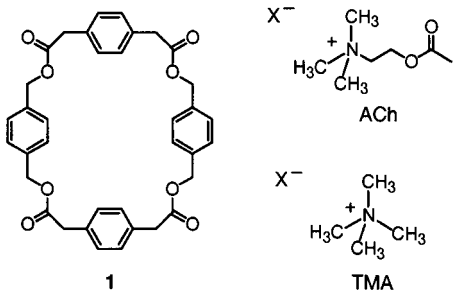
(A) in aqueous medium, although the authors pointed out that



in the borate buffer employed the anion was overwhelmed by borate.[7] On the other hand, Coulombic attraction between cation and anion in water has been demonstrated to contribute to binding for systems in which anionic groups, placed on the receptor structure for solubility reasons, give rise to ion-pairing interactions with the cationic guest;[8] electrostatic interactions with anionic groups have been shown to be effective even when these are remotely located from the cation binding site.[9] In organic solvents, the counterion may exert a more or less profound influence on cation binding depending on the polarity of the medium,[10] but in general, electrostatic and ion-pairing effects will never be negligible.[6] In addition, anions have been shown to play an active role by inhibiting or enhancing cation binding in cases where (hydrogen) bonding to the receptor takes place.[11] In lack of active participation, earlier evidence[12] and more recent studies[13] on the anion contribution in host−guest associations of quaternary ammonium cations with neutral receptors have shown unambiguous dependence of association constants on the anion used.

Among these efforts, we have systematically investigated the interaction of quaternary ammonium cations with neutral, adaptive cyclophane hosts in a lipophilic noncoordinating solvent ($CDCl_3$), to quantitatively assess the nature and the entity of the primary attractive force underlying the cation−π interaction.[14] In the course of our studies, seeking for a noncompetitive counterion that would not hamper measurements of the weak interactions investigated, we found that the anion employed could have a dramatic effect indeed on the cation−receptor association;[15] we reported experimental evidence that the adverse electrostatic contribution of the counterion constitutes such a substantial part of the overall interaction that it may completely suppress cation binding; therefore, neglecting this contribution may prevent a correct evaluation of receptor's binding ability and of the cation−π interaction energetics. We now report here a full account of our experimental and computational studies aiming to evaluate quantitatively the anion's contribution and to elucidate the nature and the origin of the anion's role in the interaction of quaternary ammonium salts with the aromatic binding sites of a cyclophane receptor (**1**), focusing on acetylcholine (ACh) and tetramethylammonium (TMA) salts.



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Results and Discussion

Binding Studies. The effect of the counterion on binding of ACh and TMA to cyclophane **1** was studied by ^{1}H NMR titrations under the same conditions of our previous investigations,[14] in $CDCl_3$ at $T = 296$ K, by varying the anion over a range as broad as possible. The number of accessible anions was limited by the solubility of their salts; for example, widely used anions such as tetrafluoroborate and hexafluorophosphate could not be used because their TMA and ACh salts were completely insoluble in $CDCl_3$. With these limitations, reliable binding data were obtained for five ACh salts and 12 TMA salts, showing association constant values ranging from 3 to 30 M^{-1} and corresponding binding free energies ranging from 2.6 to 8.4 kJ mol^{-1} (Table 1). Although the observed binding is rather weak, the large upfield shift values and the accuracy of measurements[16] ensure that the association constants are reliable. The main conclusion that can be drawn from the data reported in Table 1 is that the damping effect of the anion on binding free energies can be dramatic indeed, to such an extent that association can be completely inhibited by an unfavorable choice of the counterion. Such is the case of acetate and tosylate, whose association constants become too small to be accurately measured, despite the low standard error (SE) of the fit, due to an insufficient extent of complexation ($\leq$20%) in the accessible titration range. At the other end, the strongest binding was observed with picrate, which might be therefore suspected to be directly involved in complexation. By detection of spectral variations for the anion, picrate has been shown to actively participate, through $\pi-\pi$ interactions, in the binding of alkali metal cations to ionophores containing aromatic units.[17] After careful check, active participation of picrate was ruled out on the basis of UV and NMR spectroscopic evidence,[14b] which

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Table 1. Solubilities S (mol L^{-1}), Association Constants K_a (L mol^{-1}), Guest Limiting Upfield Shift Values $-\Delta\delta_\infty$ (ppm), and Standard Free Energies of Binding $-\Delta G°$ (kJ mol^{-1}) of 1:1 Complexes of ACh and TMA Salts with **1**[a]

guest	anion[b]	S[c]	K_a (SE)[d]	$-\Delta\delta_\infty$	$-\Delta G°$
ACh	Cl	$1.0\ 10^{-1}$	3.68 (0.05)	1.069	3.21(3)
	Br	$6.4\ 10^{-3}$	4.83 (0.06)	1.097	3.88(3)
	I	$4.8\ 10^{-4}$	11.4 (0.1)	1.168	5.99(2)
	Pic	$6.9\ 10^{-4}$	13.1 (0.1)	1.258	6.33(2)
	2,4-DNN	$7.8\ 10^{-4}$	6.9 (0.2)	0.945	4.75(7)
TMA	Cl	$1.1\ 10^{-3}$	6.6 (0.1)	1.150	4.64(4)
	AcO	$1.1\ 10^{-1}$	2.88 (0.08)[e]	1.484	2.60(7)
	TFA	$2.9\ 10^{-4}$	11.7 (0.2)	1.170	6.05(3)
	TsO	$3.5\ 10^{-3}$	2.91 (0.04)[e]	1.247	2.63(3)
	MsO	$2.9\ 10^{-4}$	6.6 (0.1)	0.982	4.64(4)
	TfO	$7.4\ 10^{-5}$	22.7 (0.2)	1.249	7.68(3)
	NfO	$5.6\ 10^{-4}$	11.6 (0.1)	1.404	6.03(2)
	PFF	$8.9\ 10^{-4}$	14.5 (0.2)	1.030	6.58(4)
	Pic	$1.3\ 10^{-4}$	29.7 (0.4)	1.479	8.35(3)
	2,4-DNF	$9.7\ 10^{-5}$	27.8 (0.5)	1.445	8.18(4)
	2,6-DNF	$6.0\ 10^{-3}$	8.26 (0.09)	1.031	5.20(2)
	2,4-DNB	$2.9\ 10^{-3}$	7.7 (0.3)	0.996	5.0(1)

[a] Measured by ^{1}H NMR (200/300 MHz) at $T = 296$ K in $CDCl_3$ on 0.1−1 mM solutions of salt, using host concentrations up to 0.1 M. [b] Pic: picrate; DNN: dinitro-1-naphthate; NfO: nonaflate (nonafluorobutanesulfonate); PFF: pentafluorophenate; DNF: dinitrophenate; DNB: dinitrobenzoate. [c] Measured by integration of the N-Me signal vs an internal standard (Me_2SO_2). [d] The standard error of the nonlinear regression is reported in parentheses. [e] For $K_a < 3$, the extent of complexation becomes too small (≤20%) in the investigated concentration range for accurate measurements, despite the low SE value.

did not show any spectral differences on the anion's signals between the free and the complexed species; consequently, active participation was also excluded for anions showing weaker association than picrate. It can thus be concluded that the counterion exerts a passive and inhibitory role on the cation−π interaction, depending on its structural features and electrostatic properties. From another point of view, binding free energy variations may monitor variations in the electrostatic attraction between the cation and the anion within the ion-pair, that is, weaker binding may reflect stronger cation−anion attraction and vice versa; altogether, ion-pairing and cation-binding interactions appear to be strongly correlated so that their mutual influence must be taken into account in the interaction energetics.

Thermodynamic Parameters. In this context, it is relevant to establish whether the observed binding is enthalpic or entropic in origin. Indeed, examples of entropically driven complexation of quaternary ammonium cations are known,[18] although these are reported in water, where hydrophobic effects are significant. Should this be the case, to ascribe the effect of anions to the electrostatic energy partitioning within the host−guest complex would be vain. To clarify this aspect, we evaluated the thermodynamic parameters relative to the binding of TMA picrate to **1** from the association constant temperature dependence, measured by variable temperature NMR experiments in the 24−57 °C range.[19] The results obtained through standard van't Hoff analysis are depicted in Figure 1, where a van't Hoff plot with best fit straight line is reported. Linear regression of data gave $\Delta H° = -16.7$ kJ mol^{-1} and $\Delta S° = -27.9$ J mol^{-1} K^{-1}, with an excellent correlation coefficient ($r = 0.997$).[20] In agreement with Dougherty's results on binding of quaternary

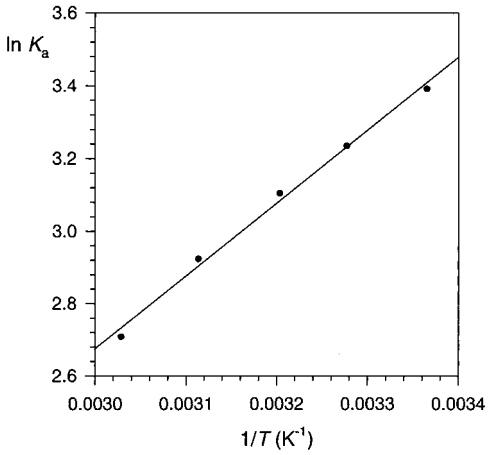

Figure 1. Van't Hoff plot for the 1:1 host−guest complex between TMA picrate and **1** in $CDCl_3$. Dots are experimental data points, solid line is best fit line from linear regression of data: $\Delta H° = -16.7$ kJ mol^{-1}, $\Delta S° = -27.9$ J mol^{-1} K^{-1} ($r = 0.997$).

ammonium cations to the corresponding methyl esters of the cyclophane receptors of type A in $CDCl_3$,[21] we thus found that the interaction is enthalpic in origin, showing a substantial enthalpy gain and an adverse entropic contribution, as expected for a bimolecular association process driven by electrostatic forces. In addition, results support the hypotheses made[14b] that in $CDCl_3$ solvent organization and solvophobic effects, for which positive entropy contributions should be expected, are negligible and that the whole ion pair, rather than the dissociated cation, is bound to the cyclophane receptor **1**, since negligible entropy contributions would be expected for a reaction in which the number of species is invariant.[21]

Solubility. It may be tempting to ascribe the inhibiting effect of the counterion to atomic electronegativity or to anion's charge density. This intuitive correlation may hold true for spherical ions such as the halides, for which experimental evidence may be related to the anion's size or to the ionic radius, but it can hardly be extended to anions of more complex nature and structure. On the other hand, three-body systems of complex structure, such as the adducts investigated in this work, are to our knowledge not yet amenable to a theoretical treatment;[22] therefore, to understand the origin of the anion's inhibiting contribution on the cation−π interaction we resorted to an empirical approach. We interestingly found that an inverse relationship exists between binding constants and solubility of TMA and ACh salts; while salts initially chosen for their appreciable solubility in $CDCl_3$, like tosylates or acetates, gave very weak association, perhaps counterintuitively, strong binding was measured for poorly soluble salts. Comparison of binding constants with the solubility values S collected in Table 1, measured in the reaction medium under the titration conditions, suggests that cation binding may depend on the same factors governing the solubility of salts in $CDCl_3$. A dependence of binding constants on solvation energy is, however, not as

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(19) See Supporting Information.
(20) The slight curvature that can be noted in the van't Hoff plot with respect to the linear regression line is likely due to nonzero heat capacity effects, which can be considered negligible in the investigated temperature range, as warranted by the excellent correlation coefficient of the regression. For a detailed study on heat capacity effects, see ref 21.
(21) Stauffer, D. A.; Barrans, R. E., Jr.; Dougherty, D. A. *J. Org. Chem.* **1990**, *55*, 2762.
(22) Known theories are concerned with interactions *within* the ion pair. See, for example: *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; Wiley−Interscience: New York, 1974; see also ref 6a.

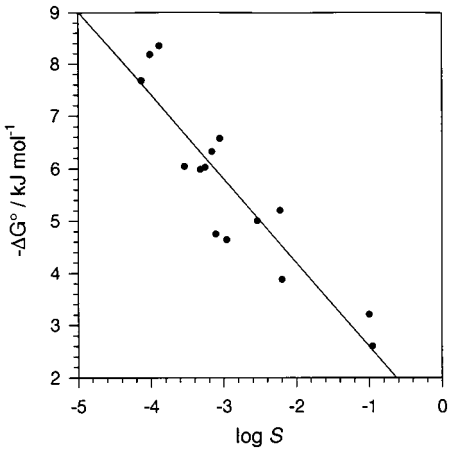

Figure 2. Plot of binding free energies $-\Delta G°$ vs solubilities log S for complexes of **1** with ACh and TMA salts (excluding TsO and MsO) in $CDCl_3$ at $T = 296$ K. Symbols are experimental data from Table 1; best fit line is calculated by linear regression (*slope* $= -1.605$; *intercept* $= 0.995$; $r = 0.91$).

straightforward as it may appear at first sight; since the cation is invariant along the series, solubility changes should be determined mainly by solvation of the anion, whereas binding should compete with the solvation shell of the cation. With the exclusion of tosylate and mesylate, which are quite out of range, a fairly good linear free energy relationship ($r = 0.91$) was found between $-\Delta G°$ and log S for 15 different salts, regardless of the cation's structure, that gives an average increment of binding energy of 1.6 kJ mol^{-1} for a 10-fold solubility decrease of the guest salt (Figure 2). Extrapolation of the correlation line to $-\Delta G° = 0$ indicates that salts whose solubility would exceed 4 M would have no tendency to bind to cyclophane **1**. Thus, the selection of conveniently soluble salts turned out to be inappropriate. The described evidence matches the notion that, as opposed to species featuring high charge density, large charge-diffused anions are expected to interact weakly with large charge-diffused cations, like and TMA and ACh,[9a] as well as with dipolar solvents,[23] like $CDCl_3$ ($\mu = 1.1$ D). By the same token, this may suggest that a poorly soluble salt will feature a cation more available for binding than that belonging to a strongly interacting, strongly solvated ion pair. Charge dispersion on the anion will thus play a key role in both solubility and binding properties.

Assisting Ligands. A clear-cut evidence that anion's charge dispersion strongly affects cation binding was obtained by converting a counterion exhibiting marked inhibition effects into a more charge-dispersed species. From the data of Table 1 it can be noted that TMA chloride (TMAC) is a quite soluble salt but, in fact, rather poorly bound to **1**. TMAC was conveniently selected because chloride ions and organotin chlorides are known to form stannate complexes,[24] in which the negative charge brought by the anion is spread over all the atoms bound to tin in the complex.

On the basis of the above considerations, the resulting TMA stannate is thus expected to exhibit *lower* solubility but a *larger* binding constant than that of the parent chloride. Stannate complexes were generated in situ but, to avoid treatment of multiple equilibria, binding experiments were performed by adding, in separate runs, known amounts of dimethyltin dichloride (DMTC) or dibutyltin dichloride (DBTC) to stock solutions of TMAC in $CDCl_3$ and measuring by ^{1}H NMR titrations the association constants to **1** for each concentration of the assisting ligand.[19] A marked increase of the binding constant with increasing ligand concentration was observed for both stannates (Table 2); the typical saturation trend with a plateau region followed by K_a (Figure 3) provided the value of the association constant corresponding to a fully formed stannate complex. In the case of DMTC, it is noteworthy that while the solubility of the TMA stannate is significantly smaller than that of the parent TMAC, showing a 3-fold decrease at the highest ligand concentration, its association with the cyclophane receptor is markedly stronger, showing a 2-fold binding enhancement with respect to TMAC; indeed the free energy of formation of the host−guest complex between **1** and [TMAC·DMTC] turned out

Table 2. Association Constants K_a (L mol^{-1}), Guest Limiting Upfield Shift Values $-\Delta\delta_\infty$ (ppm), and Standard Free Energies of Binding $-\Delta G°$ (kJ mol^{-1}) of 1:1 Complexes of TMA and ACh Chloride Guests (G) with **1** in the Presence of R_2SnCl_2 Ligands (L)[a]

salt	ligand	[L][b]	[G][b]	K_a (SE)[c]	$-\Delta\delta_\infty$	$-\Delta G°$
TMAC	none	0	1.10[d]	6.6 (0.1)	1.150	4.64(4)
	Me_2SnCl_2	0.46	0.14	22.0 (0.9)	1.306	7.6(1)
		2.3	0.13	31.1 (0.9)	1.456	8.46(7)
		22.5	0.40	32.0 (0.5)	1.513	8.53(4)
		41.5	0.42[d]	35.9 (0.6)	1.536	8.81(4)
	Bu_2SnCl_2	2.5	1.00	11.85 (0.06)	1.334	6.08(2)
		3.8	0.40	17.1 (0.2)	1.310	6.99(2)
		10.0	0.40	19.3 (0.1)	1.292	7.29(1)
		51.9	0.48	18.4 (0.3)	1.386	7.17(4)
AChC	none	0	1.15	3.68 (0.05)	1.069	3.21(3)
	Me_2SnCl_2	27.0	0.43	21.5 (0.3)	1.287	7.55(3)

[a] Measured by ^{1}H NMR (200/300 MHz) at $T = 296$ K in $CDCl_3$, using host concentration up to 0.1 M. [b] Concentration $\times 10^3$ in mol L^{-1}. [c] The standard error of the nonlinear regression is reported in parentheses. [d] Saturated solution.

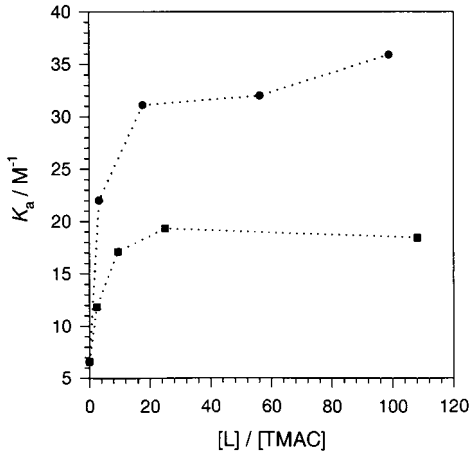

Figure 3. Association constants K_a for complexes of **1** with tetramethylammonium chloride (TMAC) in the presence of R_2SnCl_2 ligands (L) for different L/TMAC ratios. (●) R = Me (DMTC). (■) R = *n*-Bu (DBTC). Data are from Table 2.

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(24) See, for example: Altmann, R.; Jurkschat, K.; Schürmann, M.; Dakternieks, D.; Duthie, A. *Organometallics* **1998**, *17*, 5858.

to be the strongest cation−π interaction measured in this work. In the case of titrations performed employing DBTC,[19] the observed increase in K_a was not as pronounced as that for DMTC (Figure 3), giving a binding free energy enhancement 1.6 kJ mol^{-1} smaller, although significant with respect to TMAC (2.5 kJ mol^{-1}). Not unexpectedly, smaller binding enhancement corresponds to higher solubility of the TMA dibutylstannate, which is 40-fold more soluble than TMA dimethylstannate, in good agreement with the solubility increase that could be anticipated from the $-\Delta G°$/log S correlation reported in the previous section. Titration experiments with ACh chloride (AChC) in the presence of DMTC fully supported the results obtained for TMA (Table 2); an enhancement of binding free energy greater than 2-fold was achieved by converting chloride into the corresponding stannate.

In conclusion, experimental evidence obtained with assisting ligands clearly demonstrates that the inhibiting effect of the counterion on the cation−π interaction is significantly attenuated by factors promoting dispersion of the anion's charge. Results also confirm the inverse relationship between binding and solubility, while they do not support a dependence of the anion's contribution on size; the larger dibutylstannate does not induce stronger binding than the smaller dimethylstannate, which is in fact a more effective counterion. In agreement with these conclusions, comparison of data obtained for NfO versus TfO and for AcO versus TFA from Table 1 confirms that charge dispersion rather than size increase is the factor responsible for the observed binding enhancement and that, on the contrary, the increase of solubility generally associated with size corresponds to weaker binding and might reflect stronger interaction with the solvent.

Electrostatic Potential and Charge Polarization. Experimental data thus indicate that cation binding is dominated by the influence, enthalpic in origin, exerted by the counterion and that the effect is modulated by the charge dispersion capabilities of the anion. Still, the way through which the inhibiting contribution of the anion is transmitted to the cation−π interaction remains to be explained. Tetraalkylammonium cations are very polarizable species and thus very sensitive to mutual polarization effects;[25] it seems plausible that the transmission of electrostatic effects between the ion pair and the host−guest complex may occur through a charge polarization mechanism, by which a nonsymmetrical charge distribution is induced on the cation by the anion. As a consequence, the higher the anion's charge density, the stronger the cation's charge polarization; the cation's charge becomes therefore increasingly less available for interaction with the host, resulting in weaker binding. A recent computational work on the ternary complex between benzene and ammonium formate[26] gives unequivocal support to this hypothesis, showing that charge distribution of the ammonium ion is strongly affected by the presence of formate. While hydrogens proximal to the formate are almost unaffected, the distal hydrogens are distinctly less positive; this charge polarization, due to a substantial intermolecular charge transfer (CT) from the formate to the ammonium cation, markedly decreases the interaction energy of ammonium with benzene because the charge accepting ability of the former is saturated by ion-pairing with formate.

To validate our hypothesis, the occurrence of a correlation between the charge polarization of the cation and the host−guest binding energy was sought, using the electrostatic potential (EP) as the most informative property to describe cation's charge distribution. Indeed, from ab initio computational studies on the binding of the Na^+ cation to a set of substituted aromatic rings,[27] Dougherty and co-workers found an excellent linear correlation between the calculated binding energies and the electrostatic potential computed for the aromatics at the location occupied by the cation. The same approach has been successfully employed by Wilcox and co-workers[28] and by Smith and co-workers[29] for the association energies of hydrogen-bonded receptor−substrate pairs. Two substantial differences of our systems from the above examples must be outlined: (a) in all cases, the electrostatic potential approach was applied to two-body systems, whereas in our case a three-body system is involved, that is, a cyclophane receptor (**1**) interacting with an ion pair (TMAX, AChX); (b) as opposed to Dougherty's system, we are studying the interaction between an invariant aromatic binding site (**1**) and a set of "different" cations, owing their difference to the variation brought about on the same TMA (ACh) cation by the ion-pairing interaction with a varying anion. The approach translates therefore into evaluating the EP of the ion pair, which is the actual bound species in chloroform, where it appears to be dissociated for less than 0.5%, as detected from conductivity measurements.[30] The crucial point is to reliably represent the electrostatic potential of the ion pair *at* the receptor binding site. To this end, the assumption was made that the region of the ion pair exposed to the receptor for binding is the van der Waals surface of the cation remote from the anion contact. The assumption was based on modeling studies on the **1**·TMA and **1**·ACh geometries,[14b] showing that in the complex the flexible cyclophane wraps around the cation from one side, leaving the other side available for ion-pairing with the counterion and, as discussed above, on the lack of spectroscopic evidence (NMR, UV) in favor of *direct* involvement of the anion in the complex, both aspects pointing to the establishment of interaction between the cation and the two partners from opposite sides. On the basis of this assumption, we calculated the EP *at* the van der Waals surface of the ion pair and (arbitrarily) selected for comparison across the series the largest positive value on the cation's side exposed to the receptor as the value "felt" by the receptor. This way the three-body system could be amenable to a two-body system in which the global electrostatic contribution of the ion pair is represented by the resultant EP at a significant point. The TMA picrate model, showing the EP (blue = positive, red = negative) mapped onto the van der Waals surface is reported as a representative example (Figure 4), showing that the largest positive density (deepest blue) is indeed concentrated on the methyl hydrogens located most remotely from the picrate anion, thus facing the receptor cleft. Computational results, obtained for a set of ion pairs of ACh and TMA by treatment at the DFT level of theory, are collected in Table 3, where electrostatic potential EP values are

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(30) Unpublished results from this laboratory.

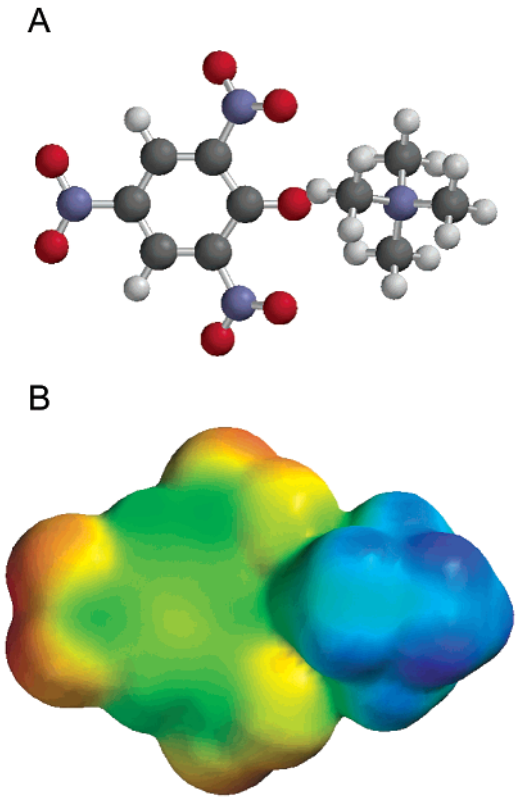

Figure 4. (A) Geometry-optimized TMA picrate in ball-and-stick representation; (B) electrostatic potential mapped onto the van der Waals surface of the geometry-optimized TMA picrate. EP is represented in levels of color from red (negative) to blue (positive).

reported for a number of common anions; other charge related properties, such as the dipole moment μ and the charge-transfer CT, as well as the net stabilization energy $-\Delta E$, were also computed for the investigated set (Table 3). Given the complexity of the investigated systems, binding energies of ion pairs to cyclophane **1** are computationally prohibitive; computational results are therefore compared to the experimental binding free energies from Table 1. It must be emphasized that computed quantities calculated in vacuo are correlated to experimental values measured in chloroform; assuming to a first approximation that solvation effects are similar along the series, because host and guest are kept invariant, the occurrence of correlations would indicate whether the observed binding data depend on any *intrinsic* properties of the ion pair.

TMA Ion Pairs. EP values were computed for the anion-free TMA cation and for a set of 18 out of 20 anions. Two anions, for which experimental binding free energies are available, are missing, namely nonaflate (NfO) and 2,4-dinitrobenzoate (2,4-DNB), because reliable geometries could not be obtained for the corresponding ion-pairs; the same applies to the stannate anions, whose binding data are available from Table 2; for this reason, μ, CT, and $-\Delta E$ are also lacking. Plotting calculated EP values versus experimental $-\Delta G°$ values for the 10 anions for which both are available,[19] and excluding tosylate that was largely out of range, an excellent linear correlation was obtained for the remaining nine anions with $r^2 = 0.989$, which raised to $r^2 = 0.998$ for eight anions out of nine, excluding mesylate as well (Figure 5). Such an excellent correlation leaves no doubt on the ability of the EP property to accurately account for the binding of the ion pair to the receptor

Table 3. Calculated Electrostatic Potential EP (kcal mol^{-1}), Dipole Moment μ (*D*), Charge Transfer CT (e$^-$), Stabilization Energy $-\Delta E$ (kcal mol^{-1}) of ACh and TMA Ion-Pairs, and Extrapolated Standard Free Energies of Binding $-\Delta G°_{Ext}$ (kJ mol^{-1}) of 1:1 Complexes of the Corresponding ACh and TMA Salts with **1**

guest	anion[a]	EP[b]	μ	CT	$-\Delta E$[c]	$-\Delta G°_{ext}$[d]
ACh[e]	none	107.763	4.993			
	Cl	36.715	10.988		99.17	
	Br	37.426	11.433		95.82	
	I	39.586	12.703		87.95	
	Pic	47.815	18.464		73.66	
TMA	none	111.198	0.004			38.62
	F	34.677	10.195			1.22
	Cl	41.590	13.478	0.787	88.90	4.60
	Br	42.805	14.021			5.19
	I	45.232	15.240			6.38
	BF4	47.708	15.692			7.59
	ClO4	52.471	19.113			9.92
	NCO	48.839	19.433			8.14
	NCS	52.697	21.648			10.03
	PF6	53.777	19.412			10.55
	AcO	37.511	10.204	0.794	99.78	2.60
	TFA	44.708	14.421	0.868	86.23	6.12
	TsO	42.991	12.153	0.883	82.31	5.28
	MsO	42.751	11.774	0.850	85.62	5.16
	TfO	47.920	15.614	0.914	76.05	7.69
	NfO	*f*	*f*	*f*	*f*	*f*
	PFF	45.253	16.276	0.725	81.91	6.39
	Pic	49.362	17.212	0.921	73.18	8.40
	2,4-DNF	49.068	19.508	0.879	74.29	8.25
	2,6-DNF	42.673	11.051	0.919	82.28	5.13
	2,4-DNB	*f*	*f*	*f*	*f*	*f*

[a] Pic: picrate; TFA: trifluoroacetate; NfO: nonaflate (nonafluorobutanesulfonate); PFF: pentafluorophenate; DNF: dinitrophenate; DNB: dinitrobenzoate. [b] Largest positive value of the ion-pair's electrostatic potential on its van der Waals surface. [c] Net stabilization energy from optimized geometries of ions. [d] Values extrapolated from the EP correlation regression. [e] *gauche* Conformation. [f] Unreliable geometry.

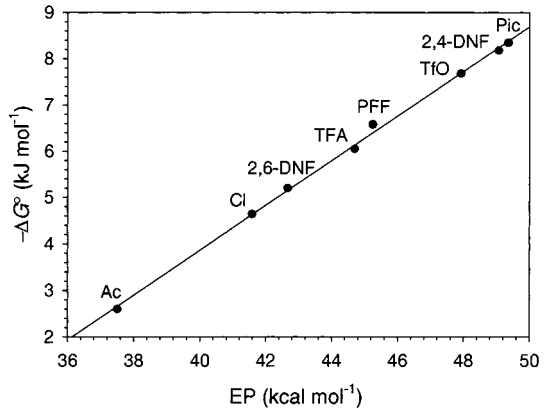

Figure 5. Plot of ion-pair electrostatic potential vs standard free energy of binding to **1** for the set of TMA salts, with the exclusion of tosylate and mesylate (see text). Symbols are experimental $-\Delta G°$ and calculated EP data points from Tables 1 and 3 respectively; solid line is best fit line calculated by linear regression: slope = 0.483; intercept = −15.441; correlation cefficient $r^2 = 0.998$.

and on the fact that binding of TMA tosylate cannot be accounted for by pure electrostatics. In consideration of the fact that charge distribution is reflected in the dipole moment μ of the ion pair, $-\Delta G°$ values were also plotted versus the calculated μ values of the scrutinized salts but, although a general trend was apparent, correlation was clearly much poorer.[19] Even worse was the correlation of $-\Delta G°$ values versus CT values, showing that although charge transfer from the anion to the cation is quite substantial for several ion pairs, it does not appropriately describes the association to the receptor.[19] To check the ability

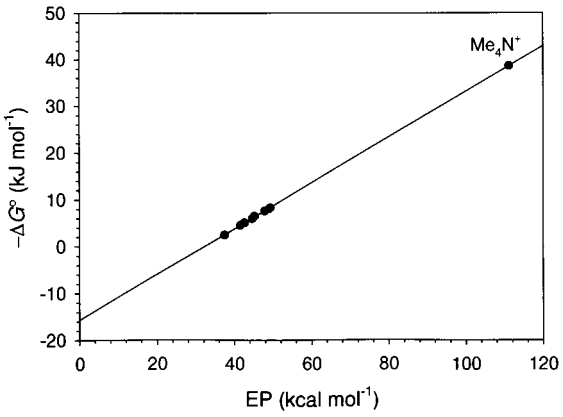

Figure 6. Plot of EP vs $-\Delta G°$ for the set of TMA salts, with the exclusion of tosylate and mesylate, extrapolated from experimental $-\Delta G°$ values with best fit line calculated by linear regression. Data are from Table 3.

of experimental binding energies of probing the cation−anion interaction in the ion pair, $-\Delta G°$ values were plotted versus the interaction energy $-\Delta E$ calculated for the examined salts.[19] Although a reasonable correlation is observed with the exclusion of tosylate, it is clearly of lower quality ($r^2 = 0.92$) than that obtained for EP. Binding free energies are indeed related to the ion-pair interaction energies, but the latter are not as closely predictive as EP values appear to be. Thus, binding interactions more closely probe the effective cation's charge resulting from charge polarization within the ion pair than the ion-pair interaction energy itself. Considering the excellent correlation between EP and $-\Delta G°$, the evidence that tosylate is not out of range in the plot of EP versus $-\Delta E$[19] tells that the anomalous behavior of this anion lies in its binding free energy, which is definitely smaller than expected from computed properties. Whether this is dependent on specific binding factors or solvation effects, it cannot be assessed from the present data, but it is certainly noteworthy the NMR evidence, reported in a recent work,[31] that at least some of the four methyl groups of TMA in the TMA-benzenesulfonate ion pair are located above the benzene ring, suggesting that some kind of cation$-\pi$ competition with the cyclophane receptor may occur in addition to ion-pairing effects. From the EP/$-\Delta G°$ correlation some interesting conclusions can be drawn: (a) the sensitivity of the binding interaction to EP is rather low; the slope of the linear regression indicates that the binding free energy increment is 1 order of magnitude smaller than that of EP ($-\Delta\Delta G° = 0.12$ ΔEP), that is, *strong* variations in the ion-pair charge polarization induce *weak* variations in the binding attraction to the receptor. (b) If a physical meaning can be attributed to the intercept of the regression, the -15.4 kJ mol^{-1} value of binding free energy for EP = 0 would indicate that in the absence of a positive charge on TMA the interaction would be *repulsive* (Figure 6); this result suggests that for an effective charge on the TMA cation lower than a threshold value, that is, for EP < 32 kcal mol^{-1}, the ion pair has no tendency to desolvate in order to bind to **1**. The EP of TMA fluoride is just above the treshold value; therefore, anions polarizing the ion-pair charge more strongly than fluoride would deplete cation binding. (c) Extrapolation of the binding free energy that would pertain to the TMA cation in the absence of its counterion gives $-\Delta G° =$ 38.6 kJ mol^{-1} (Figure 6); compared to the experimental data, this value shows that more than 80% and up to nearly 100% of the binding free energy is lost because of the presence of the anion. Furthermore, binding free energies can be estimated by interpolation for those anions whose TMA salts are beyond the solubility range accessible for experimental measurements (Table 3). Thus, PF_6 and NCS appear to be very good partners for TMA, although more than 70% of the binding energy would still be lost. These results are consistent with, and provide a strong support to, the relationship between binding energies and solubility empirically observed in chloroform for the investigated ion pairs.

ACh Ion Pairs. The anions considered in the case of ACh ion pairs, although very few, clearly show that binding properties cannot be predicted on the basis of pure electrostatic factors. The results could be anticipated on account of the factors of different origin which necessarily add to electrostatics. For nonspherical cations, such as acetylcholine, host−guest interactions are obviously dependent on geometric as well as steric requirements, in particolar in the presence of nonspherical counterions. Furthermore, entropic factors are expected to play a major role, in consideration of the restricted rotational freedom of the guest inside the host's cleft with respect to TMA.[32] Equilibrium geometries are also a problem in the computational treatment. A conformational search gave the *gauche* conformer as the most stable isomer, but the *anti* conformer is also a populated conformation.[33] The full polarization DFT treatment gave an energy difference between the two conformers of 1.42 kcal mol^{-1}, but this value is not large enough to assess which is the binding conformation selected by the complex. Calculations were tested with both conformers and fortunately the results were qualitatively in agreement; the properties were thus computed for the *gauche* conformer, chosen as the most populated conformation. Calculated EP values were plotted versus the available esperimental binding free energies; although the trend exhibited by the few data is analogous to that observed for TMA ion pairs, from the plot it is evident that correlation failed.[19] While the halogens appear to correlate well, although with a markedly larger sensitivity, the picrate anion is much outside correlation to justify a common rationale; such a deviation may depend on steric factors. Because of the ACh tail, picrate may not find an accessible location in the region opposite to the cation.

In view of the fact that inductive and dispersive contributions play a substantial role in the cation$-\pi$ interaction of ammonium ion and even more so for tetraalkylammonium ions,[26,34] it is quite surprising indeed that electrostatics so closely account for the variation of binding free energy along the series of anions. In agreement with Dougherty's conclusions on the interaction of sodium ion with substituted aromatics, we found that the influence of the anion on the cation$-\pi$ interaction, exerted through polarization of the cation's charge, can be quantitatively

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described on account of pure electrostatic terms, as long as specific solvation or structural factors do not play a significant role. Since EP is calculated on the van der Waals surface of the ion pair, it is reasonable to ascribe such an unexpected dependence on the fact that electrostatics govern the long-range attraction, while inductive (polarization, CT) and dispersive (correlation) contributions will became relevant on shorter-range distances.[35] Even more remarkable is the fact that correlation with ion pair's EP was found for *experimental binding energies in solution*, whereas previously reported correlations were found for *calculated binding energies in vacuo*.[27] In this context, it should be emphasized that experimental data provide binding free energies ($\Delta G°$), while the computed binding energies (ΔE) reported to correlate with EP are amenable to binding enthalpies (ΔH), although they are not strictly the same quantity. The finding of an excellent correlation between EP and $\Delta G°$ analogous to that described for ΔE clearly indicates that entropy variations give a constant contribution to binding along the series; exceptions may therefore be related to significant entropic contributions to binding or to specific entropy-driven solvation effects.

Conclusions

Experimental results demonstrate that anions have a strong influence on cation$-\pi$ interactions and that ion-pairing effects cannot be neglected in the interaction energetics. The anion's contribution is electrostatic in nature, and it is mainly determined by the extent of dispersion of the negative charge, which dominates both the solubility of the salt and the host−guest association. Computational studies show that experimental binding energies are closely accounted for by the electrostatic potential of the ion pair, as long as factors other than pure electrostatics are not prevalent, and that more than 80% of the binding free energy is lost because of the presence of the counterion. The main conclusion of this work is that an adequate description of the cation$-\pi$ interaction in solution must take into account that the host−guest complex is a three-partner system in which the actual cation$-\pi$ interaction is substantially modulated by the attraction exerted on the cation by the anion through a charge polarization mechanism. In addition, the present work unequivocally provides experimental support to previous literature conclusions on ternary cation$-\pi$ complexes based on computational results. The conclusions reached on the anion's role in the binding of quaternary ammonium cations add a further contribution to the understanding of the factors involved in the recognition mechanisms of ACh by its biological binding sites.

Experimental Section

General. ^{1}H NMR spectra were acquired at 200 MHz on a Varian GEMINI 2000 and at 300 MHz on a Varian VXR 300, equipped with a variable temperature apparatus. Chemical shifts (δ) in $CDCl_3$ are given in ppm from the residual $CHCl_3$ signal at δ 7.26 as a secondary internal reference. Regression analysis of NMR data was performed using the SIGMA PLOT (SPSS, v. 5.0) software package. Density functional, molecular mechanics geometry optimization, and conformational search calculations and modeling were performed using SPARTAN (Wavefunction, v. 5.1), PC SPARTAN *Pro* (Wavefunction, v. 1.0.5), INSIGHT II (Biosym, v. 2.3), and Macromodel[36] software packages. Microanalyses were obtained by combustion on a 245C Perkin-Elmer elemental analyzer.

Materials and Techniques. The preparation of cyclophane **1** has been described elsewhere.[14b] The TMA and ACh salts employed were commercial samples when available or prepared by reaction of tetramethylammonium hydroxyde with the appropriate acid or, alternatively, by ion-exchange from TMA and ACh halides and the sodium or potassium salt of the desired anion. The purity required for association constants measurements was achieved either by crystallization or by repeated washings with acetonitrile and chloroform and was checked by ^{1}H NMR and elemental analysis. Deuteriochloroform (Merck, 99.8%, over Ag foil) used for the NMR measurements was stored in the dark over 3A and 13X activated molecular sieves. Solubilities in $CDCl_3$ were measured by preparing saturated solutions of the investigated salts and adding known amounts of a stock solution of an internal standard (dimethyl sulfone, DMS) in a 5 mm NMR tube; acquisition of the ^{1}H NMR spectra with the appropriate recycle time ($5T_1$ of the DMS line, the longest relaxing signal) and subsequent integration of the *N*-Me signal versus the DMS signal provided solubility values as an average of at least three independent measurements. Association constants were obtained by ^{1}H NMR titration experiments, performed directly in the NMR tube by adding with a Hamilton microsyringe known amounts of salt's stock solution (0.1−1 mM) to a weighted amount of **1**, through a concentration range up to 0.1 M. A 1:1 association of TMA and ACh salts to **1** has been previously demonstrated;[14b] experimental data were therefore fitted to the equation of the 1:1 binding isotherm, in which [H] is the host's concentration, by nonlinear regression methods.

$$\Delta\delta = \delta_{obs} - \delta_0 = K_a[H]\frac{\Delta\delta_\infty}{(1 + K_a[H])}$$

A detailed description of the titration procedure and of the analytical treatment has been published elsewhere.[14a] Thermodynamic parameters were obtained by using the the above technique to measure association constants at several temperature values, ranging from 24 to 57 °C, carefully corrected versus a calibration curve of the VT apparatus obtained with ethylene glycol, and fitting experimental data to the van't Hoff equation through standard linear regression methods.

$$R \ln K_a = -\Delta H°(1/T) + \Delta S°$$

Titrations in the presence of assisting ligands were performed by adding variable amount of the appropriate dialkyltin dichloride to a saturated solution of TMA chloride and diluting with pure solvent to the desired concentration after filtration when necessary, due to the lower solubility of the stannate salts. The actual concentrations were measured by integration of the ^{1}H NMR signals against internal DMS as above.

Computational Methods. Ion pairs can be appropriately treated by density functional (DFT) computational methods, which explicitly take into account electron correlation at reasonable computational costs. This level of theory, especially if extended basis sets are used, has been shown to perform well with electrostatic complexes,[37] in which dispersive forces, neglected by existing functionals,[37a,b] play a negligible role. According to the supermolecular approach, ion pairs were thus treated as a single entity including all the electrons of the two partners in the field of all nuclei, and properties were calculated at the DFT level of theory with the nonlocal perturbative Becke−Perdew (pBP86) model[38] using the full polarization DN** basis set provided by the

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SPARTAN software package. Results were dependent on the geometry of the ion pair; while the equilibrium geometry of ion pairs of spherical anions was usually unambiguous, for more complex, nonspherical anions the search for the equilibrium geometry was somewhat trickier. An initial geometry was found by molecular mechanics methods, using the MMFF94 force field,[39] running a conformational search when necessary. The initial geometry was then submitted to geometry optimization by DFT, using the pBP functional with DN basis set including numerical polarization (DN*). The final energy and properties calculations on the optimized ion pair were performed at the full polarization pBP/DN** level. Since final ion-pair stabilization energies were much larger than binding free energies ($|\Delta E| \gg |\Delta G°|$), it was assumed that their equilibrium geometries were not affected by complexation. Ion pair electrostatic potentials, EP, were calculated by the point charge method as the energy of interaction of a point positive charge with the nuclei and electrons of the ion pair and mapped onto an electron density isosurface at 0.002 e/au^3 isovalue. CT and μ values were calculated using atomic charges based on fits to electrostatic potential. Stabilization energies $-\Delta E$ were obtained as the difference between the total ion-pair energy and the energy of the individual ions optimized independently. For ACh, the *gauche* conformer was used for computing $-\Delta E$ values.

Acknowledgment. We are grateful to Mrs. Brunella Innocenti, Dipartimento di Chimica Organica, Università di Firenze, for kindly providing microanalyses of compounds used in this work.

Supporting Information Available: Table of variable temperature data for **1**·TMAP, titration plots of TMAC with **1** in the presence of dimethyltin (DMTC) and dibutyltin (DBTC) chlorides, correlation plots of experimental binding free energies for complexes of **1** with properties calculated for the set of investigated salts (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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