Electrostatic Attraction of Counterion Dominates the Cation−π Interaction of Acetylcholine and Tetramethylammonium with Aromatics in Chloroform

Sandra Bartoli and Stefano Roelens*

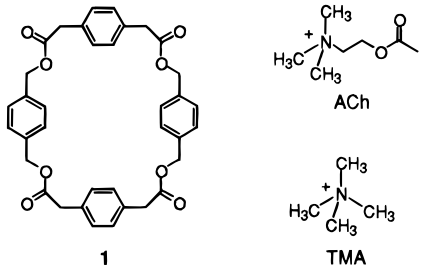
CNR, Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, Dipartimento di Chimica Organica Università di Firenze, I-50121 Firenze, Italy

Received July 12, 1999

The cation−π interaction which is established between quaternary ammonium cations and aromatics has raised an increasing interest because of its biological implications.[1] Evidence has been reported that it might, in fact, be involved in biochemical processes such as, for example, the recognition of the neurotransmitter acetylcholine.[2] To quantitatively assess the nature and the entity of the primary attractive force underlying the cation−π interaction, in a recent work[3] we have systematically investigated the interaction of quaternary ammonium cations with neutral, adaptive aromatic hosts in a lipophilic noncoordinating solvent ($CDCl_3$), focusing on acetylcholine (ACh) and tetramethylammonium (TMA) (Chart 1), and unambiguously confirmed its electrostatic nature. Having to deal with very weak interactions, the choice of a noncompetitive counterion was crucial: to our surprise, among the considerable number of papers on the cation−π interaction[1] no mention could be found concerning the role of the anion in binding,[4] as if it were not involved in the complexation process. In water, Coulombic attraction between cation and anion 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,[5] and has been shown to be effective even when the anions are remotely located from the cation binding site.[6] For this very reason, lack of participation of the counterion can by no means be expected in organic solvents, where ion-pairing interactions are generally stronger than those in water.[7] We report here experimental evidence that the adverse contribution of the counterion constitutes such a substantial part of the overall interaction that it may completely suppress cation binding; therefore, neglect of this contribution may prevent a correct evaluation of the receptor's binding ability and of the cation−π interaction energetics.

Following our previous investigation,[3] binding of ACh and TMA to cyclophane **1** (Chart 1) was studied at $T = 296$ K by ^{1}H NMR titrations[8] in $CDCl_3$ vs a systematic variation of the counterion over a significant range of commonly employed anions.[9] The results reported in Table 1 show not only a dramatic variation of binding energy for the same complex along the series but also that, with an unfavorable choice of the counterion, the interaction can fall below the detectable limit. Since picrate, the anion allowing the strongest association, showed no evidence of active participation in binding,[3] it can be concluded that the counterion participates in the binding process with a passive and adverse electrostatic contribution, which inhibits to a variable extent the cation−π interaction.[10] Conversely, it appears that cation complexation behaves as a probe of the ion-pairing interaction, in such a way that the observed free energy of binding may give, on a relative scale, an evaluation of the electrostatic attraction between the cation and the anion. In other words, the host/ion-pair complex appears to behave as if the electrostatic energy involved, beyond solvation, would partition between the interaction of the cation with the host and that of the cation with the anion: the weaker the cation−anion attraction, the stronger the cation−π interaction.

Chart 1



1

A rationale for the influence exerted by the counterion on the cation−π interaction is not straightforward. A theoretical treatment of the interaction of an ion-pair of complex structure with a third-party interacting species of complex nature itself is, to our knowledge, not yet available.[11] Thus, while results obtained for halides may be related to the size of the anion, this can hardly be extended to the whole set. Interestingly, the "goodness" of anions as cation partners in binding was found to be somehow related to the solubility of their TMA and ACh salts: strongest binding was observed for the least soluble salts and vice versa (see Table 1), suggesting that factors determining the solubility of salts in $CDCl_3$ may also govern the ion-pairing interaction, as well as the cation-to-host binding. With the exclusion of tosylate, which shows anomalous solubility, a fairly good linear free energy relationship ($r = 0.91$) was, indeed, found between $-\Delta G°$ and log S, regardless of 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 and a null binding free energy for a ca. 4 M solubility (Figure 1).[12] For large cations with diffuse charge distribution (TMA and ACh),[6a] in a dipolar solvent of low permittivity and significant dipole moment ($CDCl_3$, $\epsilon_r = 4.81$; μ

*Correspondence to Dr. Stefano Roelens, CNR−Centro Composti Eterociclici, Dipartimento di Chimica Organica, Università di Firenze, Via Gino Capponi, 9 I-50121 Firenze, Italy. Phone: +39-055-275-7658. Fax: +39-055-247-6964. E-mail: roelens@chimorg.unifi.it.

(1) Ma, J. C.; Dougherty, D. A. *Chem Rev.* **1997**, *97*, 1303.
(2) Dougherty, D. A.; Stauffer, D. A. *Science* **1990**, *250*, 1558.
(3) Roelens, S.; Torriti, R. *J. Am. Chem. Soc.* **1998**, *120*, 12443.
(4) The only exception concerns the effect of the anion on complexation of quaternary ammonium cations exerted through hydrogen bonding to the host: Jeong, K.-S.; Hahn, K.-M.; Cho, Y. L. *Tetrahedron Lett.* **1998**, *39*, 3779.
(5) (a) Lehn, J.-M.; Méric, R.; Vigneron, J. P.; Cesario, M.; Guilhem, J.; Pascard, C.; Asfari, Z.; Vicens, J. *Supramol. Chem.* **1995**, *5*, 97. (b) Méric, R.; Vigneron, J. P.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1993**, *129*. (c) Dhaenens, M.; Lacombe, L.; Lehn, J.-M.; Vigneron, J. P. *J. Chem. Soc., Chem. Commun.* **1984**, 1097. (d) Harrowfield, J. M.; Ogden, M. I.; Richmond, W. R.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Perkin Trans. 2* **1993**, 2183. (e) Schneider, H.-J.; Güttes, D.; Schneider, U. *J. Am. Chem. Soc.* **1988**, *110*, 6449.
(6) (a) Ngola, S. M.; Kearney, P. C.; Mecozzi, S.; Russel, K.; Dougherty, D. A. *J. Am. Chem. Soc.* **1999**, *121*, 1192. (b) Nelen, M. I.; Eliseev, A. V. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1359.
(7) Price, E. In *The Chemistry of nonaqueous solvents*; Lagowski, J. J., Ed.; Academic Press: New York, 1966; Vol. 1, p 67.
(8) The experimental technique and the precision achieved have been described in detail: Roelens, S.; Torriti, R. *Supramol. Chem.* **1999**, *10*, 225.
(9) Popular inorganic anions, like tetrafluoroborate and hexafluorophosphate, could not be used because their TMA and ACh salts were completely insoluble in $CDCl_3$.
(10) In the presence of active participation of the anion, inhibition of cation complexation caused by the anion binding to the host was observed in the association of alkylammonium salts to a macrocyclic phosphine oxide disulfoxide: Savage, P. B.; Holmgren, S. K.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 4069. We thank a reviewer for calling our attention to this work.
(11) 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.
(12) See Supporting Information.

10.1021/ja992415u CCC: $18.00
Published on Web 12/03/1999

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}	<3[e]		<2.7
	TFA	2.9×10^{-4}	11.7 (0.2)	1.170	6.05(3)
	TsO	3.5×10^{-3}	<3[e]		<2.7
	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	5.4×10^{-4}	19.3 (0.2)	0.996	7.29(2)
	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] Standard error of the nonlinear regression. [e] For $K_a < 3$, titration curves become indistinguishable from each other in the investigated concentration range.

= 1.1 D), the solubility decrease observed for salts of anions of increasingly dispersed negative charge matches the notion that a diffuse charge interacts poorly with solvent dipoles.[13] For the very same reason, poor interaction between cations' and anions' poles has to be expected and, in turn, this matches with effective cation binding. Thus, charge dispersion might be determinant for both solubility and binding, in such a way that a fully operating cation−π interaction might imply complete insolubility of the salt. In agreement, tetraphenyl borate, which can be anticipated a very "good" anion in terms of charge delocalization, gave highly insoluble salts with both cations that did not allow an evaluation of binding constants.

To support the above interpretation, we thought that the "goodness" of a poor anion may be increased by converting it into a more charge-dispersed species. TMA chloride (TMAC) is a reasonably soluble but rather poorly bound salt; on the other hand, chloride ions are known to form stannate complexes with organotin chlorides,[14] in which the negative charge is distributed over the complex's atoms. Variable amounts of dimethyltin dichloride (DMTC) were added to TMAC stock solutions, and the corresponding association constants to **1** were measured by ^{1}H NMR titrations. Results reported in Table 2 (Figures 2 and 3)[12] clearly show that binding constants increase with DMTC concentration, up to a saturation limit for the fully formed stannate complex. Its binding energy, the largest value observed in this work, is markedly larger than that exhibited by TMAC, whereas its solubility is significantly smaller. Addition of dibutyltin dichloride (DBTC) instead of DMTC (Figures 2 and 4)[12] gave an analogous trend, but the binding constant at saturation was half the value for DMTC and its binding free energy 1.6 kJ mol^{-1} lower; correspondingly, the TMA salt of dibutyltin stannate was 40-fold more soluble than that of dimethyltin stannate. Eventually, addition of diphenyltin dichloride to TMAC, which should enhance binding by extending charge dispersion on the two phenyl rings, did not allow binding measurements because of the complete insolubility of the salt. A strictly analogous picture was observed for ACh chloride (AChC) in the presence of DMTC

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[d]	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] Standard error of the nonlinear regression. [d] Saturated solution.

(Table 2). The results obtained for the stannate anions clearly supported the charge dispersion hypothesis and ruled out a simple dependence of the anion "goodness" on size. Consistently, the NfO/TfO and the AcO/TFA pairs confirm that charge dispersion and not size increase improve cation's binding; on the contrary, the increase of solubility generally associated with size matches with a drop in binding energy and might reflect stronger interactions with the solvent and the cation.

Still, the way through which ion-pairing effects are transmitted to the cation−π interaction remains to be understood. Tetraalkylammonium cations are very polarizable species, and thus very sensitive to mutual polarization effects;[15] on account of this property, we propose that the transmission of electrostatic effects between the ion-pair and the host−guest complex occurs through a charge polarization mechanism, by which a nonsymmetrical charge distribution is induced on the cation by the anion. It follows that the higher the anion's charge density, the stronger the cation's charge polarization: cation's charge becomes therefore increasingly less available for interaction with the host, and the result is a weaker binding. The binding energy variation for a series of counterions would thus be ascribed to the polarization component of the cation−π interaction.[16] Work is in progress to support this proposal.

In conclusion, experimental evidence indicated that ion-pairing and cation−π interactions are strongly correlated and that correlation effects cannot be neglected in the interaction energetics. An adequate description of the cation−π interaction must take into account that the host−guest complex is a three-part system in which the actual cation−π interaction is substantially modulated by the attraction exerted on the cation by the anion. The finding that the affinity of quaternary ammonium cations for aromatics is strongly affected by interacting negative charges may have an impact on the knowledge of the recognition mechanisms of ACh by its biological binding sites.

Supporting Information Available: Correlation plot of binding free energy vs solubility for complexes of **1** with ACh and TMA (Figure 1); plot of association constants for complexes of **1** with tetramethylammonium chloride (TMAC) in the presence of R_2SnCl_2 ligands (L) for different L/TMA ratios (Figure 2); and titration plots of TMAC with **1** in the presence of dimethyltin chloride (DMTC, Figure 3) and of dibutyltin chloride (DBTC, Figure 4) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA992415U

(13) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, 1988; p 27.

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

(15) Grunwald, E.; Highsmith, S.; I, T.-P., In *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; Wiley-Interscience: New York, 1974; Vol. 2, p 447.

(16) In contrast, the variation in cation−π binding energy for a series of aromatics binding to the sodium cation is due to the electrostatic component of the binding. See: Mecozzi, S.; West, A. P.; Dougherty, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 2307.