Binding of Acetylcholine and Quaternary Ammonium Cations to Macrocyclic and Acyclic "Phane" Esters. Evaluation of the Cation−π Primary Interaction through Adaptive Aromatic Hosts

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Abstract: A family of adaptive macrocyclic and acyclic "phane" esters has been designed to systematically investigate the interaction between aromatic rings and quaternary ammonium cations in the absence of superimposed contributions, such as hydrophobic, ion-pairing, macrocyclic, and preorganization contributions, to quantitatively evaluate the primary force at the origin of the cation−π interaction. The unprecedented association with open-chain and cyclic nonpreorganized aromatic hosts in solution is reported, including the remarkable case of binding to phenylacetate ester, that allowed the direct evaluation of the interaction with a single phenyl ring. The magnitude of the cation−π attraction has been measured in $CDCl_3$ at $T = 296$ K for picrate salts of acetylcholine (ACh) and tetramethylammonium (TMA), the latter showing the strongest interaction with cyclophane **1b** (8.3 kJ mol^{-1}). Results unambiguously confirmed that the basic driving force is a purely electrostatic attraction between the permanent charge of the cation and the aromatic ring. Experimental standard binding free energies suggest that interactions of phenyl rings are additive, each contributing 2 kJ mol^{-1} to the overall binding energy, up to a saturation limit in the range of 8 kJ mol^{-1}, consistent with tetracoordinative capabilities of quaternary ammonium cations. Cooperative effects are displayed by the ester group, itself incapable of binding. The possible origin of the ester cooperativity is discussed.

Introduction

In the past decade, the cation−π interaction has been recognized as an important intermolecular noncovalent binding force.[1] Increasing attention on the subject has been drawn by the significance of this interaction in biological context, where it plays a major role in recognition processes.[1] In particular, the interaction that is established between quaternary ammonium cations and the π electrons of aromatic rings has been shown to be involved in relevant phenomena, such as the recognition of the neurotransmitter acetylcholine by its receptors and by the active site of its esterase.[2] In the stream of an intensive investigation on the subject, a considerable number of synthetic receptors for recognition of acetylcholine and related quaternary ammonium cations have been reported,[1] the majority of which are water-soluble hosts, to mimic recognition under biological conditions. In water, attractive forces other than the cation−π, such as the electrostatic interaction of the cationic guest with anionic groups, invariably present on the host for solubility reasons, as well as hydrophobic contributions, intervene to substantially boost the primary attractive force. Indeed, association constants often exceeding 10^5 M^{-1}, comparable to those of the biological recognition sites,[2b] have been measured in several cases.[3] Loss of these contributions is expected to drastically damp the attractive force. Studies on binding of quaternary ammonium cations to neutral hosts in organic solvents of low polarity,[4] where solvophobic contributions can only play a minor role, report affinity constants $K_a < 10^3$ M^{-1}, with very few exceptions.[4g,i] Still, a substantial contribution adding to the cation−π primary interaction must come from the preorganization of the host, according to Cram's principle[5] that preorganization of a binding site is an essential factor in controlling association strength. Since structural reorganization, which can cost part or all of the binding free energy, must occur upon complexation when the host's binding site is not organized,[6] a further drop of binding ability is expected when the preorganization contribution is lost. Thus, the question arises whether an appreciable interaction between cationic guests

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(1) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303.

(2) (a) Dougherty, D. A. *Science* **1996**, *271*, 163. (b) Dougherty, D. A.; Stauffer, D. A. *Science* **1990**, *250*, 1588.

(3) (a) Petti, M. A.; Shepodd, T. J.; Barrans, R. E., Jr.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825. (b) Shepodd, T. J.; Petti, M. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1986**, *108*, 6085. (c) Schneider, H.-J.; Güttes, D.; Schneider, U. *J. Am. Chem. Soc.* **1988**, *110*, 6449. (d) Lehn, J.-M.; Méric, R.; Vigneron, J. P.; Cesario, M.; Guilhem, J.; Pascard, C.; Asfari, Z.; Vicens, J. *Supramol. Chem.* **1995**, *5*, 97. (e) Méric, R.; Lehn, J.-M.; Vigneron, J. P. *Bull. Soc. Chim. Fr.* **1994**, *131*, 579. (f) Méric, R.; Vigneron, J. P.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1993**, *129*. (g) Dhaenens, M.; Lacombe, L.; Lehn, J.-M.; Vigneron, J. P. *J. Chem. Soc., Chem. Commun.* **1984**, 1097. (h) Shinkai, S. *Tetrahedron* **1993**, *49*, 8933.

(4) (a) Stauffer, D. A.; Dougherty, D. A. *Tetrahedron Lett.* **1988**, *29*, 6039. (b) Arnecke, R.; Böhmer, V.; Cacciapaglia, R.; Dalla Cort, A.; Mandolini, L. *Tetrahedron* **1997**, *53*, 4901. (c) Casnati, A.; Jacopozzi, P.; Pochini, A.; Ugozzoli, F.; Cacciapaglia, R.; Mandolini, L.; Ungaro, R. *Tetrahedron* **1995**, *51*, 591. (d) Cattani, A.; Dalla Cort, A.; Mandolini, L. *J. Org. Chem.* **1995**, *60*, 8313. (e) Arduini, A.; McGregor, W. M.; Paganuzzi, D.; Pochini, A.; Secchi, A.; Ugozzoli, F.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1996**, 839. (f) Masci, B. *Tetrahedron* **1995**, *51*, 5459. (g) De Iasi, G.; Masci, B. *Tetrahedron Lett.* **1993**, *34*, 6635. (h) Méric, R.; Lehn, J.-M.; Vigneron, J. P. *Bull. Soc. Chim. Fr.* **1994**, *131*, 579. (i) Garel, L.; Lozach, B.; Dutasta, J. P.; Collet, A. *J. Am. Chem. Soc.* **1993**, *115*, 11652. (j) Magras, O. J.; Ortiz, A. R.; Molins, A. M.; Lebouille, P. H. P.; Sanchez-Quesada, J.; Prados, P.; Pons, M.; Gago, F.; de Mendoza, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1712. (k) Araki, K.; Shimizu, H.; Shinkai, S. *Chem. Lett.* **1993**, *205*.

(5) Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039.

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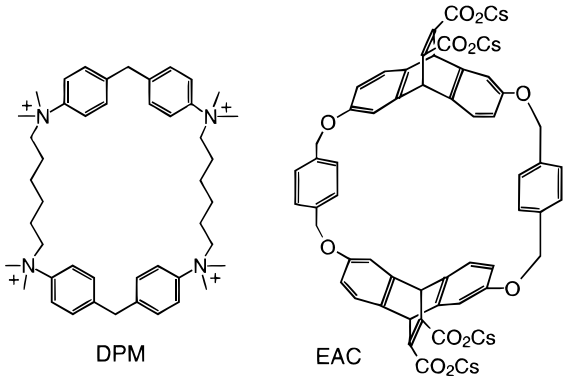
and aromatics would still be measurable when the host is devoid also of a preorganized arrangement of its binding sites, i.e., how much is the cation−π interaction worth in the absence of any superimposed contributions. Computational studies[7] reported for this interaction sizable binding energies both in a vacuum and in solution, but the need for experimental quantities has been explicitly pointed out.[8] On the other hand, X-ray structures of complexes showing evidence of close contacts between quaternary ammonium cations and aromatic rings in the solid state have been published,[9] while gas-phase studies[10] reported a value of $\Delta H^\circ = 9.4$ kcal mol^{-1} and $\Delta G^\circ = 3.5$ kcal mol^{-1} at $T = 296$ K for the dissociation energy of the tetramethylammonium−benzene complex. In the condensed phase, the magnitude of the cation−π interaction could only be estimated from differential studies in water. From association measurements of preorganized polycationic diphenylmethane-based receptors (DPM) with aromatic vs aliphatic guests,[11] the contribution to the binding energy due to the cation−π interaction was estimated by Schneider and co-workers on the order of 1−1.3 kcal mol^{-1} per aromatic ring in systems showing multiple interactions for each ring. Analogously, Dougherty and co-workers found that an ethenoanthracene-based cyclophane (EAC) preferentially binds the charged $-NMe_3^+$ group of *p*-tolyltrimethylammonium rather than the neutral $-CMe_3$ group[3a] and binds *N*-methylquinolinium more tightly than the isosteric 4-methylquinoline by 2.5 kcal mol^{-1}.[12] However, figures estimated in water are dominated by the markedly different solvating properties of the lipophilic host's cavity and of water toward charged and neutral guests, so that the assessment of the basic cation−π attractive force is not straightforward.



It is thus apparent that, to appropriately answer the question, directly measured quantitative data on the *specific* cation−π contribution to the overall interaction are needed. We thought that an evaluation of the primary binding force could be obtained in a lipophilic medium, where solvophobic effects are negligible, by means of neutral nonpreorganized hosts possessing a flexible frame capable of adapting to cationic guests. With hosts fulfilling these requirements, taking into account that in solution competition of the solvent and of the anion counteract the attractive forces operating in the gas phase, any detectable association to quaternary ammonium cations with respect to isostructural uncharged guests could essentially be ascribed to the cation−π interaction. To address this issue, we designed and prepared a family of conformationally flexible macrocyclic and acyclic oligomeric esters of the "phane" type, and we investigated by ^{1}H NMR in deuteriochloroform the binding properties of these adaptive hosts in comparison to simple aliphatic and aromatic esters vs a set of quaternary ammonium cations of different size and shape. We report here the results of a systematic investigation that provided a reliable quantitative evaluation of the magnitude in solution of the primary attracting force between aromatic rings and quaternary ammonium cations.

Results and Discussion

Design and Synthesis. The structure of EAC, representative of a class of cyclophane receptors of well-documented binding ability toward quaternary ammonium cations,[1] was taken as a model to design a related family of cyclophane esters lacking a preorganized cavity by replacing the rigid ethenoanthracene unit with simple aromatic rings free to rotate about single bonds, while keeping the *p*-xylylene moiety as the aromatic spacer. Dreiding molecular models showed that a methylene junction to aromatic rings on both sides of the ester group was required to grant conformational freedom to the cyclophane. A molecular mechanics conformational search confirmed that the resulting structure was very flexible indeed, possessing a potential energy surface characterized by a large number of very similar energy minima. Thus, cyclodimeric 1,4-xylylene-1,4-phenylene diacetate (**1b**) was selected as the parent cyclophane, and its structure was systematically varied to fit different cationic guests and to analyze the influence of structural and geometrical features on complexation properties. A four-methylene homologation was planned using the 1,4-phenylenedipropionate fragment in place of diacetate, while replacement of the 1,4-xylylene moiety with *n*-butylene and oxydiethylene residues was introduced in order to evaluate the contribution of the aromatic spacer to the overall binding strength in a flexible backbone. Monomeric and trimeric oligomers of the parent cyclophane were expected to provide information on the large-step variations of the host's size. Corresponding open-chain analogues of this set of cyclophanes, containing a variable number of aromatic rings and ester groups, were desirable to detect the occurrence of conformational and macrocyclic effects, i.e., to reveal any contribution to binding due to cyclic structure. Simple esters containing the xylyl and tolyl moiety would provide information on the basic contribution of the constituting aromatic units; and eventually, aliphatic mono-, di-, and tetraesters would be used for blank experiments to detect trivial chemical shift variations or specific contributions to binding from the ester group.

The designed macrocyclic hosts were readily available using the well-established cyclooligomerization reaction of diacyl chlorides with dibutylstannylene derivatives of diols,[13] as

(6) Diederich, F. *Cyclophanes*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry; The Royal Society of Chemistry: Cambridge, 1991; p 60.

(7) (a) Mavri, J.; Koller, J.; Hadzi, D. *THEOCHEM* **1993**, *283*, 305. (b) Kim, K. S.; Lee, J. Y.; Lee, S. J.; Ha, T.-K.; Kim, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 7399. (c) Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 4177. (d) Basch, H.; Stevens, W. J. *THEOCHEM* **1995**, *338*, 303. (e) Duffy, E. M.; Kowalczyk, P. J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1993**, *115*, 9271. (f) Pullman, A.; Berthier, G.; Savinelli, R. *J. Comput. Chem.* **1997**, *18*, 2012.

(8) Chipot, C.; Maigret, B.; Pearlman, A. D.; Kollman, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 2998.

(9) (a) Harel, M.; Quinn, D. M.; Nair, H. K.; Silman, I.; Sussman, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 2340. (b) Murayama, K.; Aoki, K. *Chem. Commun.* **1997**, 119. (c) Aoki, K.; Murayama, K.; Nishiyama, H. *J. Chem. Soc., Chem. Commun.* **1995**, 2221.

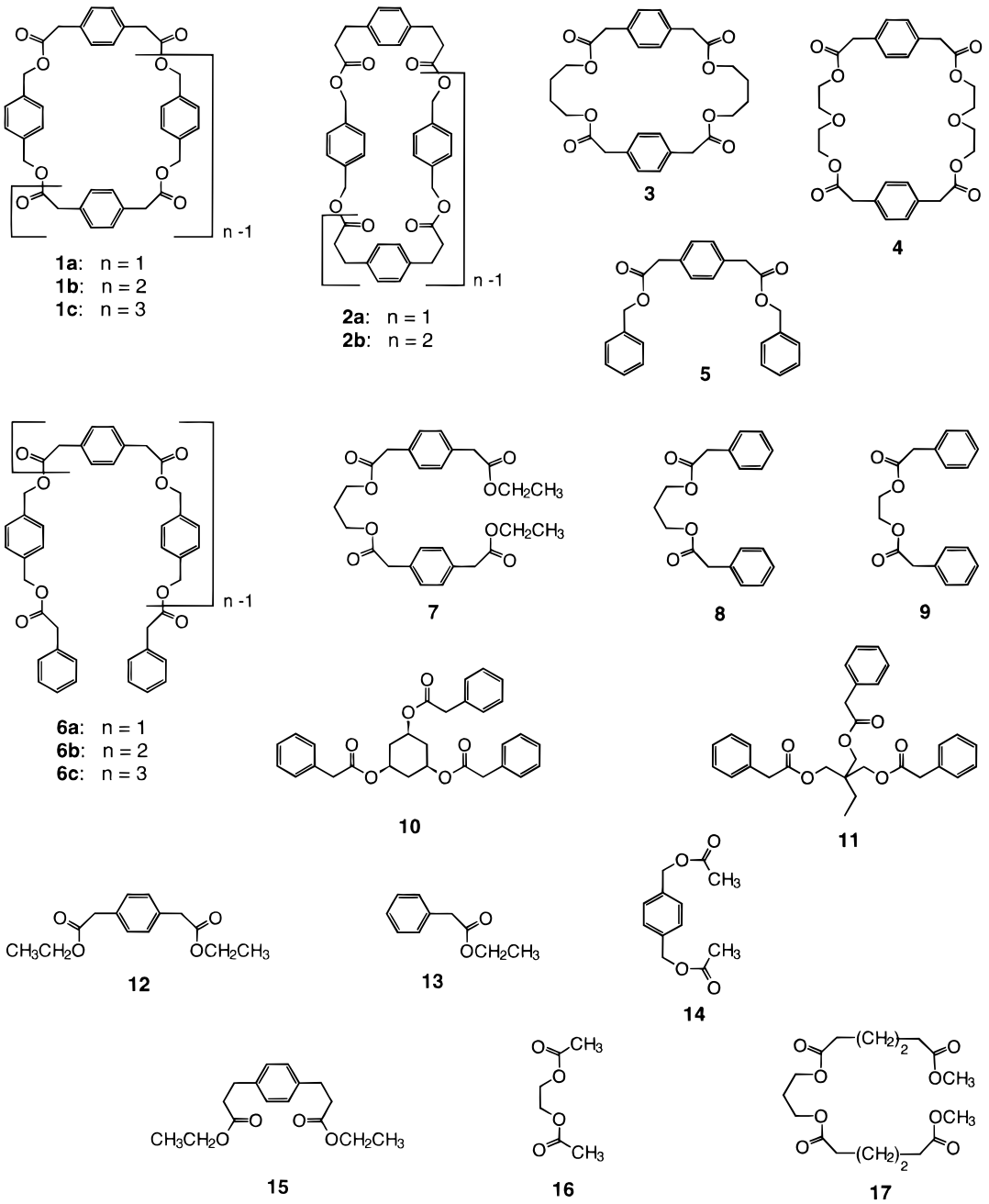
(10) Meot-Ner, M.; Deakyne, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 469.

(11) Schneider, H.-J.; Blatter, T.; Simova, S.; Theis, I. *J. Chem. Soc., Chem. Commun.* **1989**, 580.

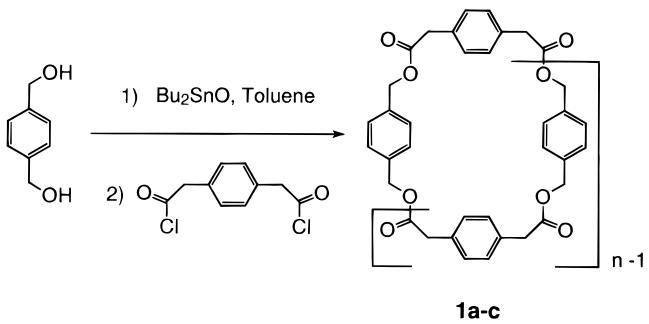
(12) Shepodd, T. J.; Petti, M. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 1983.

(13) (a) Shanzer, A.; Libman, J.; Frolow, F. *Acc. Chem. Res.* **1983**, *16*, 60. (b) Roelens, S. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1617. (c) Mandolini, L.; Montaudo, G.; Scamporrino, E.; Roelens, S.; Vitalini, D. *Macromolecules* **1989**, *22*, 3275.

Chart 1



Scheme 1



exemplified in Scheme 1 for the preparation of cyclooligomers of the parent cyclophane. The compounds prepared, which, compared to their rigid preorganized progenitors, can be collectively viewed as a class of "adaptive" phane hosts,[14] are reported in Chart 1. Monomeric to trimeric cyclophanes could be separated from the oligomerization mixture in acceptable yields by flash column chromatography. Open-chain analogues of **1a**−**c** were obtained by the same reaction, using 0.5 equiv of the diacyl chloride, followed by the addition of phenylacetyl chloride. Other open-chain esters were prepared according to standard literature methods.

Preliminary Binding Studies. In a preliminary screening, complexing properties of cyclophanes **1**−**4** were tested by ^{1}H NMR in $CDCl_3$ at $T = 296$ K vs a standard set of quaternary ammonium picrates (P), iodides (I), and tosylates (T), including tetramethylammonium (TMA), *N*-methylpyridinium (NMP), *N*-methylquinolinium (NMC), *N*-methylquinuclidinium (NMQ), and acetylcholine (ACh), to detect any observable binding

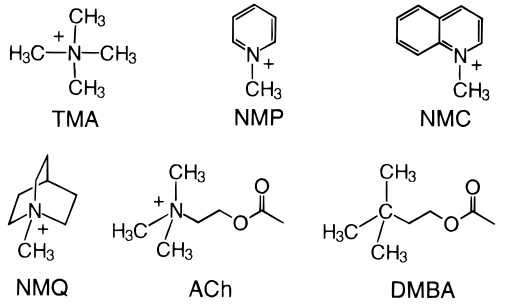
(14) The discrimination between "rigid" and "adaptive" hosts is significant, in consideration of the complete lack of affinity for cationic guests observed with the open-chain analogue of EAC, the so-called "half-molecule", used by Dougherty and co-workers as a blank test for the encapsulation in the macrocyclic cavity. See ref 3a.

Table 1. Association Constants K_a (M^{-1}) and Guest Limiting Shift Values $\Delta\delta_\infty$ (ppm) for the 1:1 Complexes of Quaternary Ammonium Tosylates (T), Iodides (I), and Picrates (P) with Cyclic and Open-Chain Phane Esters[a]

	K_a ($\Delta\delta_\infty$)					
host	TMAT	NMPI	NMPP	NMCI	NMQP	AChI
1a	n.d.	n.d.	n.d.	n.d.		n.d.
1b	3 (−1.38)	9 (−0.96)	11 (−0.88)	5 (−0.44)	7 (−0.59)	11 (−1.17)
2a	n.d.	1 (−0.60)	7 (−0.22)	2 (−0.33)		3 (−0.32)
2b	n.d.	3 (−0.20)	2 (−0.29)	4 (−0.11)	2 (−0.13)	3 (−0.24)
3	2 (−0.44)	8 (−0.42)		3 (−0.39)		10 (−0.55)
4	6 (−0.46)	5 (−0.45)		2 (−0.33)	2 (−0.56)	5 (−0.52)
7	4 (−0.52)	16 (−0.42)	10 (−0.41)	6 (−0.42)	9 (−0.22)	17 (−0.62)
9	3 (−0.39)	4 (−0.27)	4 (−0.42)	4 (−0.17)		5 (−0.34)

[a] Measured by ^{1}H NMR (200/300 MHz) at $T = 296$ K in $CDCl_3$ on 0.1−1 mM solutions of salt (Chart 2) using host concentrations up to 0.09 M and following the *N*-Me signal of the guest (n.d.: non detectable). Errors on K_a values estimated as ±20%.

Chart 2



affinity (Chart 2). All the NMR spectra showed time-averaged signals for the free and the complexed species. According to standard methods,[15] stock solutions of the guest (G) were titrated with increasing amounts of host (H), following the shift of the *N*-methyl signal (and of other signals when present) of the guest. Experimental points correctly fitted the equation of the standard binding isotherm for a 1:1 association (eq 1), giving the corresponding association constants (K_a), the chemical shift of the free guest (δ_0), and the limiting upfield shift values of the fully saturated guest relative to the free guest ($\Delta\delta_\infty$) through nonlinear least-squares regression procedures.

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

From standard errors of the regression curves, maximum errors on K_a values were estimated as ±20%. Results are reported in Table 1, together with data relative to the open-chain phane esters **7** and **9** for comparison. Inspection of data shows that, with few exceptions, the majority of K_a values lie in the range below 10 M^{-1}, indicating a substantial drop of binding ability with respect to the ethenoanthracene progenitors. Lack of detectable interaction of **1a** with any of the tested cations was demonstrated by the null shift of signals of all guests. Thus, **1a** represents the most appropriate reference host for the study, being structurally and functionally homogeneous with the set, but completely incapable of binding. Moreover, the consistently null δ variation guarantees the absence of trivial NMR shifts in lack of host−guest interactions. Unexpectedly, the highest K_a values, 16 M^{-1} (NMPI) and 17 M^{-1} (AChI), are exhibited by the open-chain phane **7**; in addition, the related host **9**, which differs from **7** merely by two carbethoxy end groups and one methylene in the spacer, does not show similar binding properties, although it possesses the same number and type of aromatic rings.

(15) Wilcox, C. S. In *Frontiers in Supramolecular Organic Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; VCH: Weinheim, 1991; p 123.

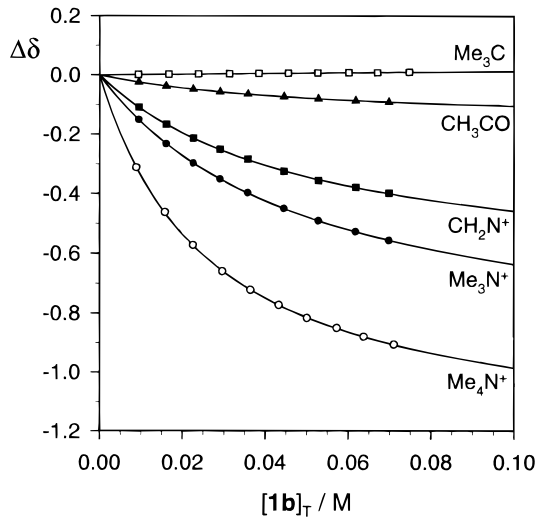


Figure 1. ^{1}H NMR titrations of 0.1 mM TMAP (○: Me_4N^+), 0.5 mM AChP (●: Me_3N^+; ■: CH_2N^+; ▲: CH_3CO) and 1 mM DMBA (□: Me_3C) with host **1b** at $T = 296$ K in $CDCl_3$. Best fit values for K_a ($\Delta\delta_\infty$): TMAP, 38 M^{-1} (−1.25); AChP, 20 M^{-1} (−1.27); DMBA, n.d. ($\Delta\delta = +0.009$ at [host] = 0.075 M). Symbols are experimental data points; lines are best fit curves calculated from eq 1 by nonlinear regression.

It can be noted that the $\Delta\delta_\infty$ of complexes of TMAT (−1.38) and AChI (−1.17) with **1b** are anomalously large for the observed K_a, suggesting that the cation is included in the host cleft, where it experiences a strong shielding by the aromatic ring current, but it suffers some kind of inhibition. We thought that such a binding inhibition may depend on the electrostatic attraction exerted on the cation by the anion. Picrate salts of TMA and ACh were tested with **1b**, on the expectation that an anion bearing a more dispersed charge would be less competitive than iodide or tosylate. In Figure 1 the corresponding titration curves are shown, from which K_a values of 38 and 20 M^{-1} and $\Delta\delta_\infty$ values of −1.25 and −1.27 were obtained for TMAP and AChP, respectively. The increase in K_a, which for TMA was 1 order of magnitude with respect to tosylate, together with unaltered $\Delta\delta_\infty$ values, confirmed that the binding inhibition was caused by the anion and could be substantially avoided with picrate. The negligible shift observed for the picrate protons excluded direct involvement of the anion in complexation through $\pi-\pi$ interaction with the host. UV spectra showed a negligible bathochromic shift of the picrate absorption maximum in the complex of TMAP with **1b** with respect to free TMAP, indicating that the ion pair is essentially unperturbed by complexation (1 nm red shift of the picrate band for a solution containing 70% of the complex). These results suggest that only solvent molecules are replaced by aromatic rings to achieve

Table 2. Association Constants K_a (M^{-1}), Free Energies of Binding $-\Delta G°$ (kJ mol^{-1}), and Guest Limiting Shift Values $\Delta\delta_\infty$ (ppm) for the 1:1 Complexes of Tetramethylammonium Picrate (TMAP) and Acetylcholine Picrate (AChP) with Cyclic and Open-Chain Phane Esters[a]

	TMAP			AChP		
host	K_a (SE)[b]	$\Delta\delta_\infty$	$-\Delta G°$	K_a (SE)[b]	$\Delta\delta_\infty$	$-\Delta G°$
1a	n.d.[c]	−0.005 (0.1 M)[d]		n.d.[c]	+0.003 (0.07 M)[d]	
1b	29.7 (0.4)[e]	−1.479[f]	8.35(3)	13.1 (0.1)[g]	−1.258[h]	6.33(2)
1c[i]	19.6 (0.6)	−0.771	7.32(8)	19.3 (0.8)	−0.592	7.3(1)
2a	4.35 (0.08)	−0.353	3.62(4)	3.45 (0.04)	−0.331	3.05(3)
2b	5.3 (0.6)	−0.246	4.1(3)	4.1 (0.3)	−0.165	3.5(2)
3	11.9 (0.5)	−0.314	6.1(1)	10.0 (0.1)	−0.344	5.67(2)
4	7.71 (0.06)	−0.493	5.03(2)	7.0 (0.2)	−0.429	4.79(7)
5	9.0 (0.3)	−0.527	5.41(8)	8.97 (0.06)	−0.442	5.40(2)
6a	6.7 (0.4)	−0.464	4.7(1)	6.3 (0.2)	−0.326	4.53(8)
6b	17.0 (0.8)	−0.450	7.0(1)	17.6 (0.6)[l]	−0.346	7.06(8)
6c	22.2 (0.2)[m]	−0.523	7.63(2)	25.2 (0.4)	−0.395	7.94(4)
7	14.4 (0.5)	−0.495	6.56(9)	13.8 (0.1)	−0.436	6.46(2)
8	4.87 (0.08)	−0.473	3.90(4)	4.47 (0.03)	−0.414	3.69(1)
9	5.3 (0.2)	−0.404	4.1(1)	4.8 (0.3)	−0.351	3.9(2)
10	10.7 (0.2)	−0.473	5.83(5)	10.3 (0.3)	−0.410	5.74(7)
11	4.8 (0.1)	−0.402	3.86(5)	4.59 (0.04)	−0.344	3.75(2)
12	7.94 (0.07)	−0.503	5.10(2)	6.18 (0.07)	−0.468	4.48(3)
13	2.16 (0.04)	−0.535	1.90(3)	1.96 (0.03)	−0.479	1.66(3)
14	n.d.[c]	−0.050 (0.27 M)[d]		n.d.[c]	−0.037 (0.27 M)[d]	
15	n.d.[c]	−0.056 (0.20 M)[d]		n.d.[c]	−0.039 (0.19 M)[d]	
16	n.d.[c]	−0.019 (0.14 M)[d]		n.d.[c]	−0.038 (0.37 M)[d]	
17	n.d.[c]	−0.021 (0.12 M)[d]		n.d.[c]	−0.016 (0.13 M)[d]	

[a] Measured by ^{1}H NMR (200/300 MHz) at $T = 296$ K in $CDCl_3$ on 0.1 mM solutions of TMAP and 0.4−1 mM solutions of AChP, using host concentrations up to 60 mg/mL. All values result from at least duplicate experiments. [b] Standard error of the nonlinear least-squares fit. [c] Nondetectable; for $K_a \leq 1$ titration curves become indistinguishable from each other in the investigated concentration range. [d] $\Delta\delta$ values observed at the indicated concentration. [e] Mean value over three runs: $K_a = 29.0 \pm 0.4$ (±1%); $\sigma = 0.8$. [f] Mean value over three runs: $\Delta\delta_\infty = -1.477 \pm 0.008$ (±0.5%); $\sigma = 0.015$. [g] Mean value over eight runs: $K_a = 13.0 \pm 0.1$ (±1%); $\sigma = 0.4$. [h] Mean value over eight runs: $\Delta\delta_\infty = -1.266 \pm 0.014$ (±1%); $\sigma = 0.04$. [i] Solubility limit: 27 mM. [l] Mean value over two runs: $K_a = 17.6 \pm 0.05$ (±0.3%). [m] Mean value over three runs: $K_a = 22.6 \pm 0.7$ (±3%).

close contact with the cation; the anion exerts a passive role, which can therefore be relegated to a constant electrostatic contribution throughout the series. While for tosylate this contribution seems to be overwhelming, in the case of picrate it is small enough to allow the observation of cation−π interactions of modest entity.

Some conclusions can be drawn from Figure 1: (a) the large upfield shift induced on TMA and ACh signals substantiates beyond doubt the inclusion of the cation into an aromatic cleft; (b) the shift of the ACh signals decreases in the order $Me_3N^+ > CH_2N^+ > CH_3CO$, but the corresponding curves consistently give the same association constant: a single binding process is observed, by which the cationic head of acetylcholine is included in the aromatic cavity, while the acetylated tail is hanging out of the cleft. To evaluate the results obtained with ACh, the isostructural 3,3-dimethylbutyl acetate (DMBA, Chart 2) was selected as the most appropriate reference guest. The titration curve of DMBA with **1b**, showing a null shift of the Me_3C signal ($\Delta\delta = +0.009$ at [**1b**] = 0.075 M), is reported in Figure 1. Comparison of the titration curves of TMA and ACh with that of DMBA provides unambiguous evidence that the interaction is electrostatic in nature and specifically involves the aromatic rings of the host and the positive charge of the guest.[16] Lack of an observable association of DMBA shows that all kinds of contributions not related to net permanent charge, such as solvophobic and van der Waals interactions and higher order dispersive forces, that give sizable contributions in the aqueous medium[11,12] and that would contribute to the same extent to binding to DMBA and to ACh in the absence of charge, are in fact undetectable in $CDCl_3$; therefore, any affinity for cationic species detected in $CDCl_3$ provides a *direct* measure of the cation−π interaction.

Evaluation of the Cation−π interaction. The preliminary screening has revealed that, in the absence of enhancing contributions, adaptive phane hosts still exhibit sizable binding to quaternary ammonium cations. In particular, TMA and ACh have shown appreciable affinity for some hosts, while the picrate anion proved to behave as a noncompetitive counterion. Since binding constants were small, a detailed analysis of the association of AChP and TMAP with **1b** was undertaken to assess the reliability of measurements of small association constants by NMR shift titrations.[17] It was found that systematic errors caused by the interference of water at low host concentration were the major source of inaccuracy, giving overestimated constants, but they could be avoided by selecting the appropriate concentration range for titrations. Results showed that, with simple experimental expedients and careful treatment of data, binding constants could be measured with ±1% accuracy, which allowed for a reliable evaluation of the magnitude of the cation−π attraction. The preliminary data of Table 1, although overestimated, still provide a correct qualitative description of the interaction.

Association constants of TMAP and AChP with the family of macrocyclic and acyclic phane esters of Chart 1 were determined in $CDCl_3$ at $T = 296$ K and are reported in Table 2. A test using benzene as a host, for comparison with the gas-phase data,[10] did not reveal any appreciable binding to TMAP: at $[C_6H_6] = 0.29$ M, a 0.05 ppm upfield shift was observed, but the association constant was below the detectable limit. Experimental evidence indicated that the binding free energy of the benzene−TMA complex measured in the gas phase was completely overwhelmed in the condensed phase. It is important

(16) A physical model for the cation−π interaction has been discussed in detail and the prominent role for electrostatics has been clearly established (see ref 1, pp 1306−1308). On account of computational work, it has been proposed that an induced-dipole component of variable extent, related to the polarizability of aromatics, may also contribute in addition to the permanent electrostatic attraction.

(17) Roelens, S.; Torriti, R. Submitted for publication.

to emphasize that data of Table 2 are solvent- and anion-dependent. $CDCl_3$ is a polar noncoordinating solvent and can indeed interact with cations through its permanent dipole moment ($\mu = 1.1$ D). Use of apolar solvents, like CCl_4, as a noncompetitive medium, is prevented by the marked insolubility of quaternary ammonium salts. Analogously, the electrostatic interaction between the cation and the anion is unavoidably included in the free energy values, although with a constant contribution throughout the series. Preliminary experiments have shown that the $CDCl_3$/picrate pair was the least competing and, hence, the most favorable system to detect interactions of small entity. The standard binding free energies reported in Table 2 represent the magnitude of cation$-\pi$ interactions relative to this reference system.

Cyclophane Hosts. In contrast to the complete binding inability of **1a** toward both TMAP and AChP, cyclophane **1b** showed toward TMAP the largest K_a and $\Delta\delta_\infty$ values of the whole set. The corresponding standard free energy of binding, $-\Delta G^\circ_{296} = 8.35$ kJ mol^{-1} (2.0 kcal mol^{-1}), demonstrates that an adaptive cyclophane of appropriate size can efficiently include a cationic guest and that the cation$-\pi$ interaction is still quite substantial even in lack of the contribution from the preorganization of the structure. AChP was bound to **1b** 2 kJ mol^{-1} less strongly. Since the cationic head of ACh has the same size and charge as TMA, the weaker association and the smaller $\Delta\delta_\infty$ value indicate that the ACh tail hampers the inclusion into the host cavity. The difference in binding strength between ACh and TMA vanishes with host **1c**, which binds equally well to both cations, showing that larger rings become insensitive to the different shape of the two guests. Although ring size and number of aromatics are significantly different, the binding free energies shown by **1b** and **1c** are of the same order. The sensitivity of **1b** to geometric requirements is suggestive of a good size-match with TMA; however, the small energy advantage measured for **1b** over **1c**, compared to the 3-fold larger $\Delta\delta_\infty$ value indicating a closer contact of the cation with the aromatic π surfaces, shows that precise size-fit is not a major issue in determining the strength of cation$-\pi$ interactions with adaptive hosts; that is, NMR shifts are more sensitive than binding strengths to geometric requirements. In apparent contrast, 1,4-phenylenedipropionate hosts **2** showed a weaker binding to both guests; while this could be anticipated for **2a** on the basis of size arguments, it was unexpected for **2b**, whose size is larger than that of **1b**.

An explanation for these results comes from the analysis of the X-ray structures of the free hosts **1a,b** and **2a,b**[18] and from molecular mechanics calculations on the corresponding complexes with TMA and ACh, for lack of crystal structures for direct comparison. The binding inability of **1a** is accounted for by the size of its cavity, which is far too narrow for any of the guests to fit in. The presence of two additional methylene spacers in **2a** gives rise to a basket-shaped cleft. The cyclophane size is such that nesting of guests on the host cleft should be allowed, and appreciable binding was indeed measured with both TMAP and AChP. Dimeric cyclophanes **1b** and **2b** adopt, as anticipated, a conformation devoid of cavities; in lack of constraints, a collapsed arrangement of the macrocycle tends to minimize empty space. Clearly, the conformation assumed by the free hosts in the solid cannot be the one responsible for binding. The observation of appreciable inclusion indicates that complexation can pay the energy cost of the conformational reorganization needed to open a cavity and orient aromatic rings for binding. This interpretation was supported by molecular mechanics calculations on the docking of TMA onto **1b**, using the X-ray structure as the starting conformation, in which the AM1-computed charge distribution was taken into account. The computational approach, although oversimplified, showed that **1b** can indeed reorganize to adequately include TMA, placing the four rings' planes at 4.45−4.49 Å from the nitrogen atom (Figure 2). The ball-and-stick picture of the side view (Figure 2A) displays the folding in the shape of a bowl of the cyclophane around the guest, a perception not delivered by the top view (Figure 2B), which shows instead the four aromatic rings equatorially positioned and oriented to face the cation perpendicularly. The goodness of match is better appreciated in the space-filling representation (Figure 2C), which exhibits a nearly

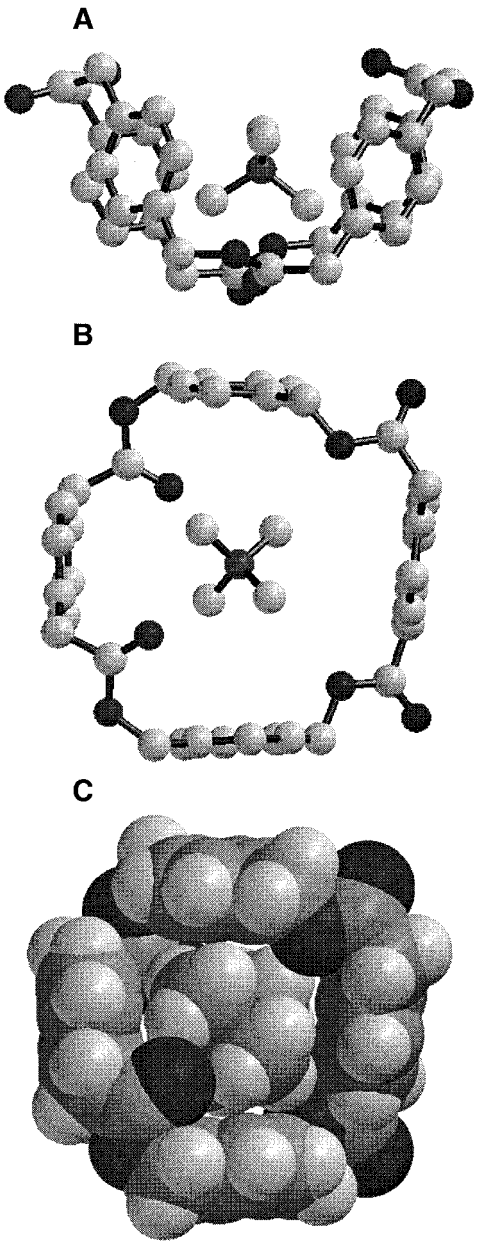


Figure 2. (A) Ball-and-stick representation of the **1b**·TMA complex (side view) calculated by docking of the guest into the host (see text). Hydrogen atoms are omitted for clarity, and nitrogen and oxygen atoms are represented in darker shades of gray. (B) As A, top view of the complex. (C) Space-filling representation of the **1b**·TMA complex (top view) calculated by docking of the guest into the host (see text). Oxygen atoms are represented in darker and hydrogen atoms in lighter shades of gray.

(18) Donati, D.; Roelens, S.; Torriti, R.; Valle, G. *Aust. J. Chem.* **1998**, *51*, 361.

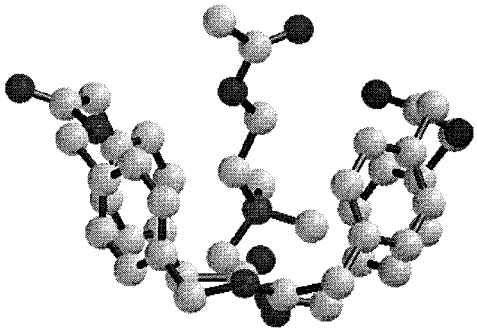


Figure 3. Ball-and-stick representation of the **1b**·ACh complex (side view) calculated by docking of the guest into the host (see text). Hydrogen atoms are omitted for clarity, and nitrogen and oxygen atoms are represented in darker shades of gray.

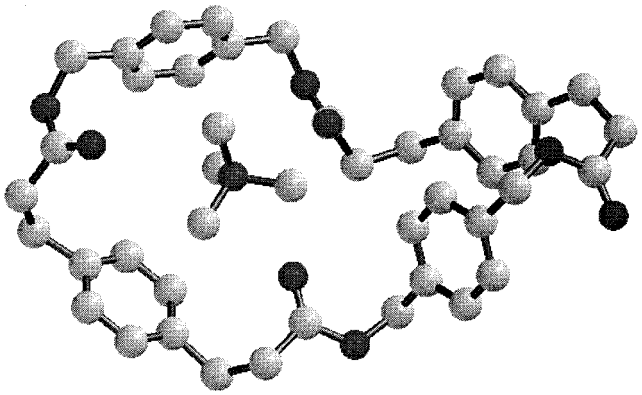


Figure 4. Ball-and-stick representations of the **2b**·TMA complex (top view), calculated by docking of the guest into the host (see text). Hydrogen atoms are omitted for clarity, and nitrogen and oxygen atoms are represented in darker shades of gray.

perfect fit of the guest into the host's cavity. Analogous results were obtained for ACh, which induced a similar reorganization of the host around its cationic head (Figure 3), except for a slightly larger distance of two of the four rings from the nitrogen atom (+0.1 and +0.2 Å). The strictly related conformations of **1b** in the two complexes and the lack of steric hindrance offered by the ACh tail in its out-of-bowl orientation support the hypothesis that the decrease in binding stength respect to TMA might be entropic in origin, in agreement with previous reports.[19] Instead, an incomplete reorganization of cyclophane **2b** explains the weaker interaction observed for this host compared to **1b**. Figure 4 (cf. Figure 2B) clearly shows that only half of the molecule is involved in the guest's inclusion, while the other half maintains a conformation similar to that of the free host in the solid, with two aromatic rings facing each other. Interestingly, the conformation of the binding half-molecule is reminiscent of that of **2a**; this analogy may explain their similar binding properties and the weaker binding exhibited with the two guests with respect to **1b**, giving the overall picture of an interaction proportional to the number of correctly oriented aromatic rings.[20]

(19) Weaker binding of ACh with respect to TMA has also been observed with cryptophane hosts and has been ascribed to the reduced rotational freedom of ACh into the cavity caused by its tail, thus an inhibition of binding of entropic nature. See ref 4i.

(20) Theoretical works (see ref 7) on the cation−π interaction between benzene and TMA have in fact shown that a minimum in the energy profile is observed for a cation approach in a direction along the 6-fold axis of benzene and the 3-fold axis of TMA, at a distance of 4.2 Å in the gas phase and 4.75 Å in water solution. Deviations from the preferred orientation are thus expected to result in lower energy of interaction, although secondary minima have been found for different orientations.

Cyclophanes **3** and **4** show binding properties in line with this picture. Replacement of the xylylene moieties in the structure of **1b** with aliphatic chains resulted in a decreased binding ability of both hosts. Differences due to chain length are within 1 kJ mol^{-1}, while the preference for TMA over ACh tends to become negligibly small with ring size. The presence of oxygen atoms in the chain does not appear to have any influence on the binding properties of **4**. It can be noted, however, that the binding energy decrease for **3** and **4** with respect to **1b** is not as large as expected, considering that only two aromatic rings are present in the structure. This is particularly evident in the binding of ACh, where **1b** is preferred over **3** by only 0.6 kJ mol^{-1}, a figure that cannot be due to a better size match on account of the smaller shifts experienced by the cation in the complex of **3** compared to **1b**. As a general conclusion, for the cyclophane hosts the interaction appears to be related to the number of aromatics, although the relationship does not seem to be straightforward.

Open-Chain Phane Hosts. The most relevant conclusion that can be drawn about open-chain hosts **5**−**13** is that they all show measurable binding to TMA and ACh. To our knowledge, binding of quaternary ammonium cations to acyclic receptors in solution is unprecedented; results demonstrate that the cation−π interaction is capable of gathering aromatic rings around a cationic guest even when these belong to an open-chain structure and, most remarkably, of binding to a single aromatic ring. Large open-chain hosts (**6b**,**c**) show binding properties similar to the large cyclophane **1c**, and energy differences between TMA and ACh complexes become negligibly small. A tendency to reach a saturation value of binding strength can be noted for both the cyclic and the open-chain phanes; this experimental observation supports the view that the number of cation−π interactions that can be established is limited by the "coordinative" capability of the guest, in agreement with computational works reporting *four* primary energy minima for the benzene−TMA complex.[7e,f] The data of Table 2 set the saturation limit in the range of 8 kJ mol^{-1}, which would represent the maximum energy gain attainable by the cation−π interaction for a quaternary ammonium picrate in $CDCl_3$ in the absence of additional contributions.

The binding free energies exhibited by the tetraester **7** are notably large for a host possessing two aromatic rings. This would point to some kind of participation of the ester group in the binding process. On the other hand, diester **16** and, more, tetraester **17** certify that in the absence of aromatic rings no measurable binding is detected dependent on ester groups. Data suggested that a cooperative role may be exerted by the ester function, itself incapable of binding. This hypothesis was confirmed by diesters **8** and **9**, which showed a drop of binding strength larger than 2.5 kJ mol^{-1} with respect to **7** by simple removal of the two ester end groups. Comparison of data for **8** and **9** with those for **7** and **3** shows that cooperativity of the ester groups is more effective for terminal than for intrachain functions. The distinct advantage exhibited by **10** over **11** can be ascribed to the constraint imposed by the cis configuration of substituents on the cyclohexane moiety, which allows the three binding sites to concertedly organize around the guest; lack of this constraint in **11** results in 2 kJ mol^{-1} weaker binding, as if not all rings could participate.

The binding properties exhibited by phenylenediacetate **12** and phenylacetate **13** are noteworthy in that they represent the first direct experimental measure in solution of the interaction between a *single* phenyl ring and quaternary ammonium cations. Cooperativity by one ester group allows the observation of

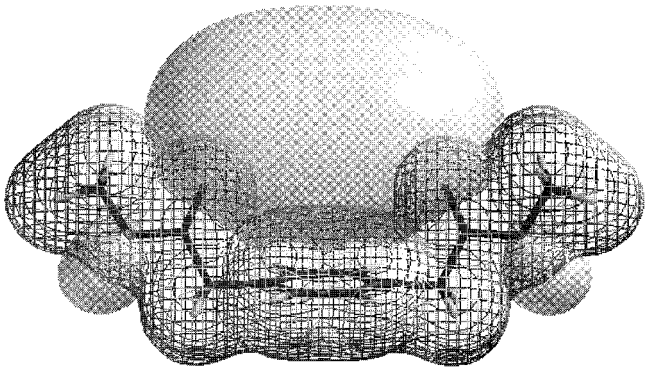


Figure 5. AM1-computed model of dimethyl 1,4-phenylenediacetate in the "cooperative conformation". Optimized geometry is depicted in polytube, electron isodensity surface in mesh and the −10 kcal mol^{-1} electrostatic potential isosurface in transparent body representation.

binding, whose strength is raised by over 3 kJ mol^{-1} by the presence of a second ester group. An entry to the origin of this cooperativity may come from comparison of **12** with the structurally related hosts **14** and **15**, which did not show detectable affinity for TMA and ACh. Molecular models indicated that the conformation allowing the ester group to participate in complexation, i.e., that with the transoid ester group plane orthogonal to the aromatic ring and the carbonyl pointing to the π face, would place the carbonyl dipoles of **12** (and **13**) in the correct orientation to cooperatively interact with the cation, while it would generate repulsive interactions between the *n*-electrons of the carbonyl oxygens and the π-orbitals of the aromatic ring for both **14** and **15**. AM1 calculations corroborated this view showing that the "cooperative conformation" resides in an energy minimum for **12** and **13**, while it does not for **14** and **15**, in which carbonyls diverge away from the aromatic face to reach an equilibrium geometry. Inability of the ester group to reach a cooperative orientation, as in **14** and **15**, makes the association with a single aromatic fall below the detectable limit. The cooperative orientation may be hampered or only partially achieved for intrachain ester groups, particularly when belonging to a cyclic structure.

The cause of enhanced binding cannot be assessed unambiguously on the basis of the available data. The role of the ester function might be to assist desolvation of the incoming guest in the binding process, by replacing $CDCl_3$ molecules with carbonyl in the solvation sphere. As a support for the desolvation assistance hypothesis, AChP was experimentally found to be 20 times more soluble in ethyl acetate than in $CDCl_3$. Alternatively, stronger binding may result from the enhanced electrostatic attraction caused by the local increase of negative charge density induced by carbonyl dipoles. The AM1-computed model of the phenylenediacetate ester (dimethyl ester for simplicity) in the cooperative conformation shows in fact that the electrostatic potential over the aromatic ring, displayed in Figure 5 as a transparent body isosurface at −10 kcal mol^{-1}, is strongly polarized toward the side of the ester groups, in contrast to the symmetrical charge distribution in benzene.[21] It should be noted, however, that carbonyls do not assume a cooperative orientation in the **1b**·TMA complex, indicating that ester cooperativity is not a prerequisite for binding with hosts possessing more than one aromatic ring.

Additivity of Aromatic Ring Contributions.[22] On the basis of regularities observed in binding free energies of the open-chain phanes, it is tempting to assign to aromatic rings an additive contribution to the overall cation−π interaction. Assuming the free energy values measured for **13** as the contribution per phenyl ring, a reexamination of data of Table 2 shows that binding energies of a fair number of hosts are accounted for with excellent approximation by simply adding this contribution for the number of phenyl rings in the structure. Thus, energies of hosts **5** and **10** are consistent with the contribution from three phenyl rings while those of **8** and **9** are consistent with the contribution from two phenyl rings. Values observed for **11** are in excellent agreement with participation of two phenyl rings only, as anticipated on the basis of structural arguments. Averaging the contributions per phenyl ring of the above six hosts, mean values of 1.95 and 1.87 kJ mol^{-1} are obtained for TMA and ACh, respectively, with a standard error of 0.04 on both values. The agreement is far too good to be accidental and strongly supports the additivity of contributions. The calculated mean values can be used to analyze the consistency of the whole set. Data for the cyclic trimer **1c** (six aromatics), as well as for acyclic **6b** (five aromatics) and **6c** (seven aromatics), all fit fairly well with the contribution from four phenyl rings, corresponding, as dicussed, to the number of energy minima predicted by theoretical work.[7e,f] It is evident that any number of aromatic rings in addition to the four allowed by the coordinative capabilities of the cation will not contribute to increase the total binding free energy, which is thus set in the range of 8 kJ mol^{-1}, as empirically inferred.[23] The binding free energies exhibited by **6a**, corresponding to a contribution somewhat smaller than expected for a host possessing three aromatics, are to be related to the adverse arrangement of the ester functions discussed for **14**, which can reasonably hamper the achievement of a correct binding conformation. On the contrary, the association exceeding the limiting value between **1b** and TMA may benefit of an extra bonus provided by the perfect match between host and guest, though of modest entity. The limited adaptivity of cyclophane **2a** accounts for energy values slightly smaller than the contribution from two phenyl rings, while the reasons for the binding worth cleanly two phenyl rings for **2b** have been discussed in detail. Eventually, hosts **3**, **4**, and **7** appear to benefit as **12** of cooperativity effects from the ester groups, enhancing the contribution from the two phenyl rings.

Conclusions. The present work shows that the cation−π interaction that is established between aromatic rings and quaternary ammonium cations is a sizable attractive force in solution even in the absence of a preorganized structure of the host and of any additional contributions. The cation−π interaction, whose electrostatic nature has been unequivocally confirmed, has been shown to be strong enough to gather aromatics belonging to flexible macrocyclic rings, and even to simple acyclic chains, into a binding arrangement. Additivity of free energy increments per aromatic ring and binding cooperativity of the ester function emerge evident from the present results but certainly need a larger support of experimental data for unambiguous assessment. With the understanding that the actual value of binding strength is relative to a specific anion and solvent, the most relevant result of the present study is the quantitative determination of the pure cation−π

(21) The calculated model possesses a fairly strong dipole moment μ = 2.94 D.

(22) The additivity of free energy increments in salt-bridge and van der Waals pairwise interactions has been proposed by Schneider on the basis of LFER analysis of a large number of literature data. See: Schneider, H.-J. *Chem. Soc. Rev.* **1994**, 227.

(23) It is a very encouraging analogy that in the gas-phase potassium ion binds up to a maximum of four benzene molecules: Sunner, J.; Nishizawa, K.; Kebarle, P. *J. Phys. Chem.* **1981**, *85*, 1814.

interaction that is, as often occurs in nature, a primary weak driving force at the origin of strong interactions.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were acquired at 200 and 50 MHz on a Varian GEMINI 2000 and at 300 and 75 MHz on a Varian VXR 300, equipped with a variable-temperature apparatus. Chemical shifts (δ) in $CDCl_3$ are given in ppm from the $CHCl_3$ signal at δ 7.26 for ^{1}H and from the $CDCl_3$ signal at δ 77.00 for ^{13}C. Electron impact (EI) mass spectra were obtained at 70 eV on a Carlo Erba Instruments QMD 1000 spectrometer. Electrospray ionization mass (ESI-MS) spectra were recorded in the positive-ion mode on a Fisons Instruments VG-Platform benchtop mass spectrometer equipped with an electrospray LC/MS interface and a single quadrupole operating at 3.8 kV. UV spectra were recorded on a Varian Cary 5 spectrophotometer. Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Osmometric measurements were performed on a Wescan 233 molecular weight apparatus. Microanalyses were obtained by combustion on a 245C Perkin-Elmer elemental analyzer. Analytical thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 F-254 precoated silica gel plates. Flash column chromatography was carried out with silica gel 60 (0.032−0.063 mm) from ICN. Molecular mechanics calculations and modeling were performed using INSIGHT II (Biosym, v. 2.3), PC SPARTAN *Plus* (Wavefunction, v. 1.5), and Macromodel[24] software packages. The ^{1}H NMR titration procedure has been described in detail elsewhere.[17] NMR data for the determination of association constants were analyzed using SIGMA Plot (Jandel, v. 1.1) software package.

Materials. Chloroform (Carlo Erba RPE) was washed several times with water, dried over $CaCl_2$, and stored in the dark over 3A and 13X activated molecular sieves. Solvents used for chromatography, ethyl acetate, petroleum ether 40−70 °C and dichloromethane, were distilled prior to use. Deuteriochloroform (Merck, 99.8%) stored in the dark over 3A and 13X activated molecular sieves was used for the NMR measurements. Experimental preparative procedures and characterization of quaternary ammonium salts and open-chain nonoligomeric esters are described in detail in the Supporting Information. Commercial ethyl phenylacetate (**13**) and 1,2-ethylene diacetate (**16**) were purified by flash column chromatography on silica gel 60 with CH_2Cl_2/EtOAc 93:7 as eluant. All other solvents and materials were used as received.

1,4-Xylylene-1,4-phenylenediacetates (1a−c). Procedure A. A suspension of 1,4-benzenedimethanol (3.31 g, 23.96 mmol, 1 equiv) and dibutyltin oxide (5.99 g, 24.06 mmol, 1 equiv) in toluene (80 mL) was refluxed overnight under nitrogen in a Dean−Stark apparatus with azeotropic removal of water. Toluene was evaporated under reduced pressure from the cooled suspension, and dried chloroform (120 mL) was added to the white residue. To the resulting suspension was added dropwise a 0.2 M solution of 1,4-phenylenediacetyl chloride (5.56 g, 24.06 mmol, 1 equiv) in dried chloroform (120 mL) in 30 min under nitrogen at room temperature with magnetic stirring. The mixture was then refluxed for 1 h and cooled to rt and the solvent evaporated under vacuum. After the residue was washed with several portions of petroleum ether to remove the dibutyltin dichloride formed in the reaction, 8.18 g of crude polyester mixture was obtained, containing **1a** (23%), **1b** (8%), and **1c** (6%) (by ^{1}H NMR). The crude was separated by flash column chromatography on silica gel 60 with CH_2Cl_2/EtOAc 97:3 as eluant. Where necessary, a second flash chromatography afforded analytically pure compounds. To maximize yields of lower oligomers, reactant concentrations were halved in the cyclooligomerization step (0.1 M) in those cases where oligomers higher than the dimer were not desired.

1a: white solid (1.454 g, 21%); mp 237−238 °C; ^{1}H NMR (0.1 M in $CDCl_3$) δ 3.36 (s, 4 H, CH_2CO), 5.03 (s, 4 H, CH_2O), 6.86 (s, 4 H, *Ar*CH_2CO), 6.96 (s, 4 H, *Ar*CH_2O); ^{13}C NMR (0.1 M in $CDCl_3$) δ 42.88 (*C*H_2CO), 66.47 (CH_2O), 129.01 [C_2 (*Ar*CH_2CO)], 129.78 [C_2 (*Ar*CH_2O)], 132.52 [C_1 (*Ar*CH_2CO)], 136.47 [C_1 (*Ar*CH_2O)], 171.16 (CO); EI-MS *m*/*z* (rel int) no M^+, 122 (13), 121 (12), 104 (100), 103 (15), 91 (10), 86 (53), 84 (91), 78 (16), 77 (11), 65 (10), 51 (12); ESI-MS *m*/*z* 335 (M^+ + K), 319 (M^+ + Na), 314 (M^+ + NH_4). Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.69; H, 5.49.

1b: white solid (344 mg, 5%); mp 204−205 °C; ^{1}H NMR (0.1 F in $CDCl_3$) δ 3.65 (s, 8 H, CH_2CO), 5.11 (s, 8 H, CH_2O), 7.19 (s, 8 H, *Ar*CH_2O), 7.20 (s, 8 H, *Ar*CH_2CO); ^{13}C NMR (0.1 F in $CDCl_3$) δ 41.20 (*C*H_2CO), 66.15 (CH_2O), 128.09 [C_2 (*Ar*CH_2O)], 129.45 [C_2 (*Ar*CH_2CO)], 132.77 [C_1 (*Ar*CH_2CO)], 135.82 [C_1 (*Ar*CH_2O)], 171.11 (CO); EI-MS *m*/*z* (rel int) no M^+, 105 (17), 104 (100); ESI-MS *m*/*z* 616 (M^+ + Na), 611 (M^+ + NH_4). Anal. Calcd for $C_{36}H_{32}O_8$: C, 72.96; H, 5.44. Found: C, 72.76; H, 5.48.

1c: white solid (172 mg, 2%); mp 209−211 °C; ^{1}H NMR (0.08 F in $CDCl_3$) δ 3.65 (s, 12 H, CH_2CO), 5.10 (s, 12 H, CH_2O), 7.23 (s, 24 H, Ar); ^{13}C NMR (0.08 F in $CDCl_3$) δ 41.04 (*C*H_2CO), 66.17 (CH_2O), 128.18 [C_2 (*Ar*CH_2CO)], 129.52 [C_2 (*Ar*CH_2O)], 132.78 [C_1 (*Ar*CH_2CO)], 135.86 [C_1 (ArCH_2O)], 171.24 (CO); EI-MS *m*/*z* (rel int) no M^+, 204 (10), 163 (14), 162 (32), 118 (100), 91 (91), 90 (40), 89 (10), 65 (24); ESI-MS *m*/*z* 928 (M^+ + K), 912 (M^+ + Na), 907 (M^+ + NH_4). Anal. Calcd for $C_{54}H_{48}O_{12}$: C, 72.96; H, 5.44. Found: C, 72.70; H, 5.70.

1,4-Xylylene-1,4-phenylenedipropionates (2a,b). 1,4-Benzenedimethanol (1.34 g, 9.70 mmol, 1 equiv), dibutyltin oxide (2.41 g, 9.68 mmol, 1 equiv), and 1,4-phenylenedipropionyl chloride (2.26 g, 9.78 mmol, 1 equiv) were reacted according to procedure A to give 3.38 g of crude polyester mixture containing **2a** (33%) and **2b** (11%) (by ^{1}H NMR).

2a: white solid (826 mg, 26%); mp 166−167 °C; ^{1}H NMR (0.1 M in $CDCl_3$) δ 2.59−2.65 (m, 4 H, CH_2CO), 2.84−2.90 (m, 4 H, C*H*$_2$-CH_2CO), 5.05 (s, 4 H, CH_2O), 6.76 (s, 4 H, *Ar*CH_2CH_2), 7.19 (s, 4 H, *Ar*CH_2O); ^{13}C NMR (0.1 M in $CDCl_3$) δ 29.90 (*C*H_2CH_2CO), 33.81 (*C*H_2CO), 65.77 (CH_2O), 127.66 [C_2 (*Ar*CH_2CH_2)], 129.73 [C_2 (*Ar*CH_2O)], 136.31 [C_1 (*Ar*CH_2O)], 136.80 [C_1 (*Ar*CH_2CH_2)], 172.43 (CO); EI-MS *m*/*z* (rel int) no M^+, 278 (27), 219 (14), 177 (26), 175 (22), 133 (15), 117 (43), 116 (13), 115 (20), 106 (13), 105 (100), 104 (78), 103 (31), 91 (52), 90 (18), 89 (16), 78 (20), 77 (31), 55 (14); ESI-MS *m*/*z* 347 (M^+ + Na), 342 (M^+ + NH_4). Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 73.75; H, 6.30.

2b: white solid (177 mg, 6%); mp 130−131 °C; ^{1}H NMR (0.1 F in $CDCl_3$) δ 2.62−2.70 [m (app t), 8 H, CH_2CO], 2.89−2.97 [m (app t), 8 H, C*H*$_2CH_2CO$], 5.06 (s, 8 H, CH_2O), 7.01 (s, 8 H, *Ar*CH_2CH_2), 7.14 (s, 8 H, *Ar*CH_2O); ^{13}C NMR (0.1 F in $CDCl_3$) δ 30.57 (*C*H_2CH_2-CO), 35.88 (*C*H_2CO), 65.76 (CH_2O), 128.28 [C_2 (*Ar*CH_2O)], 128.41 [C_2 (*Ar*CH_2CH_2)], 135.87 [C_1 (*Ar*CH_2CH_2)], 138.16 [C_1 (*Ar*CH_2O)], 172.66 (CO); EI-MS *m*/*z* (rel int) no M^+, 278 (12), 205 (11), 175 (17), 158 (15), 131 (33), 117 (41), 105 (70), 104 (100), 91 (21); ESI-MS *m*/*z* 688 (M^+ + K), 672 (M^+ + Na), 667 (M+ + NH_4). Anal. Calcd for $C_{40}H_{40}O_8$: C, 74.06; H, 6.21. Found: C, 73.96; H, 6.42.

***n*-Butylene-1,4-phenylenediacetate (3).** 1,4-Butanediol (0.92 g, 10.21 mmol, 1 equiv), dibutyltin oxide (2.48 g, 9.98 mmol, 1 equiv), and 1,4-phenylenediacetyl chloride (2.33 g, 10.08 mmol, 1 equiv) were reacted according to procedure A to give 3.26 g of crude polyester mixture, which was chromatographed with petroleum ether/EtOAc 1:1 to give dimeric *n*-butylene-1,4-phenylenediacetate (**3**) as a white solid (639 mg, 26%): mp 118−119 °C; ^{1}H NMR (0.1 F in $CDCl_3$) δ 1.55−1.61 (m, 8 H, C*H*$_2CH_2O$), 3.55 (s, 8 H, CH_2CO), 4.00−4.07 (m, 8 H, CH_2O), 7.21 (s, 8 H, Ar); ^{13}C NMR (0.1 F in $CDCl_3$) δ 25.27 (*C*H_2-CH_2O), 41.24 (*C*H_2CO), 64.35 (CH_2O), 129.42 [C_2 (Ar)], 133.02 [C_1 (Ar)], 171.31 (CO); EI-MS *m*/*z* (rel int) 496 (M^+, 20), 176 (20), 158 (97), 149 (18), 131 (50), 105 (19), 104 (100), 103 (20), 83 (14), 78 (11), 77 (10), 55 (25); ESI-MS *m*/*z* 536 (M^+ + K), 520 (M^+ + Na), 515 (M^+ + NH_4). Anal. Calcd for $C_{28}H_{32}O_8$: C, 67.73; H, 6.50. Found: C, 67.95; H, 6.63.

Oxydiethylene-1,4-phenylenediacetate (4). Diethylene glycol (1.08 g, 10.18 mmol, 1 equiv), dibutyltin oxide (2.49 g, 10.0 mmol, 1 equiv) and 1,4-phenylenediacetyl chloride (2.35 g, 10.17 mmol, 1 equiv) were reacted according to procedure A to give 3.81 g of crude polyester mixture, which was chromatographed with petroleum ether/EtOAc 1:2 to give dimeric oxydiethylene-1,4-phenylenediacetate (**4**) as colorless crystals that crystallize from the eluant (631 mg, 24%): mp 132−133 °C; ^{1}H NMR (0.1 F in $CDCl_3$) δ 3.49−3.54 (m, 8 H, CH_2O), 3.57 (s, 8 H, CH_2CO), 4.09−4.14 (m, 8 H, CH_2OOC), 7.23 (s, 8 H, Ar); ^{13}C NMR (0.1 F in $CDCl_3$) δ 40.99 (*C*H_2CO), 64.24 (CH_2O), 68.89 (*C*H_2-

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OOC), 129.47 [C_2 (Ar)], 132.90 [C_1 (Ar)], 171.24 (CO); EI-MS *m*/*z* (rel int) 528 (M^+, 19), 175 (12), 158 (62), 131 (19), 130 (24), 105 (13), 104 (100), 83 (12); ESI-MS *m*/*z* 568 ($M^+ + K$), 552 ($M^+ + Na$). Anal. Calcd for $C_{28}H_{32}O_{10}$: C, 63.63; H, 6.10. Found: C, 63.26; H, 6.21.

1,4-Xylylene-(1,4-phenylenediacetate)diphenylacetates (6a−c). 1,4-Benzenedimethanol (1.30 g, 9.41 mmol, 1 equiv), dibutyltin oxide (2.36 g, 9.48 mmol, 1 equiv), 1,4-phenylenediacetyl chloride (1.11 g, 4.80 mmol, 0.5 equiv), and phenylacetyl chloride (1.49 g, 9.64 mmol, 1 equiv) were reacted according to procedure A, adding the acyl chlorides sequentially to give 4.70 g of crude polyester mixture that was separated by flash column chromatography on silica gel 60 with CH_2Cl_2/EtOAc 97:3 as eluant. Analitically pure **6b** was obtained by crystallization from petroleum ether/EtOAc 1:1. Analitically pure **6c** was obtained by crystallization from ethyl acetate.

6a: white solid (450 mg, 26%); mp 81−82 °C; ^{1}H NMR (0.1 M in $CDCl_3$) δ 3.68 (s, 4 H, CH_2CO), 5.13 (s, 4 H, CH_2O), 7.25−7.34 (m, 14 H, Ar); ^{13}C NMR (0.1 M in $CDCl_3$) δ 41.37 (*C*H_2CO), 66.23 (CH_2O), 127.19 [C_4 (Ar)], 128.28, 128.62, 129.32 [C_2, C_3 (Ar)], 133.84, 135.91 [C_1 (Ar)], 171.36 (CO); EI-MS *m*/*z* (rel int.) no M^+, 239 (25), 238 (25), 155 (23), 130 (44), 120 (78), 104 (41), 91 (100), 65 (17); ESI-MS *m*/*z* 413 ($M^+ + K$), 397 ($M^+ + Na$), 392 ($M^+ + NH_4$). Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 77.09; H, 5.98.

6b: white solid (545 mg, 17%); mp 114−115 °C; ^{1}H NMR (0.1 M in $CDCl_3$) δ 3.67 (s, 4 H, CH_2CO), 3.69 (s, 4 H, $C_6H_5CH_2CO$), 5.14 (s, 8 H, CH_2O), 7.26−7.33 (m, 22 H, Ar); ^{13}C NMR (0.1 M in $CDCl_3$) δ 40.96 (*C*H_2CO), 41.36 ($C_6H_5CH_2CO$), 66.23, 66.29 (CH_2O), 127.20 [C_4 (Ar)], 128.30, 128.35, 128.63, 129.32, 129.58 [C_2, C_3 (Ar)], 132.78, 133.86, 135.87, 135.97 [C_1, (Ar)], 171.28, 171.36 (CO); EI-MS *m*/*z* (rel int) no M^+, 283 (12), 239 (18), 92 (12), 91 (100), 78 (10), 77 (17), 65 (29); ESI-MS *m*/*z* 694 ($M^+ + Na$), 689 ($M^+ + NH_4$). Anal. Calcd for $C_{42}H_{38}O_8$: C, 75.21; H, 5.71. Found: C, 74.99; H, 5.71.

6c: white solid (202 mg, 9%); mp 142−144 °C; ^{1}H NMR (0.07 M in $CDCl_3$) δ 3.67 (s, 8 H, CH_2CO), 3.68 (s, 4 H, $C_6H_5CH_2CO$), 5.13 (s, 12 H, CH_2O), 7.26−7.32 (m, 30 H, Ar); ^{13}C NMR (0.07 M in $CDCl_3$) δ 40.95 (*C*H_2CO), 41.36 ($C_6H_5CH_2CO$), 66.22, 66.29 (CH_2O), 127.20 [C_4 (Ar)], 128.30, 128.36, 128.63, 129.32, 129.58 [C_2, C_3 (Ar)], 132.77, 133.86, 135.87, 135.91, 135.96 [C_1 (Ar)], 171.27, 171.36 (CO); EI-MS *m*/*z* (rel int) no M^+, 382 (10), 381 (11), 354 (11), 353 (46), 352 (10), 351 (39), 325 (22), 307 (15), 306 (100), 283 (17), 265 (15), 264 (16), 263 (14), 262 (13), 261 (22), 260 (15), 259 (12), 254 (19), 253 (87), 252 (14), 251 (10); ESI-MS *m*/*z* 1006 ($M^+ + K$), 990 ($M^+ + Na$), 985 ($M^+ + NH_4$). Anal. Calcd for $C_{60}H_{54}O_{12}$: C, 74.52; H, 5.63. Found: C, 74.29; H, 5.66.

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Supporting Information Available: Experimental preparative procedures and characterization for compounds NMPI, NMCI, NMQI, NMPP, NMQP, AChP, TMAP, TMAT, 1,4-phenylenediacetyl chloride, 1,4-phenylenedipropionyl chloride, **5**, **7**−**12**, **14**, **15**, **17**, and DMBA (9 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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