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Binding of Tetramethylammonium to Polyether Side-Chained Aromatic Hosts. Evaluation of the Binding Contribution from Ether Oxygen Donors

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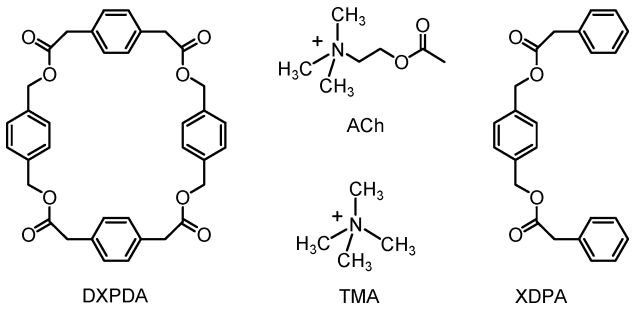
A set of macrocyclic and open-chain aromatic ligands endowed with polyether side chains has been prepared to assess the contribution of ether oxygen donors to the binding of tetramethylammonium (TMA), a cation believed incapable of interacting with oxygen donors. The open-chain hosts consisted of an aromatic binding site and side chains possessing a variable number of ether oxygen donors; the macrocyclic ligands were based on the structure of a previously investigated host, the dimeric cyclophane 1,4-xylylene-1,4-phenylene diacetate (DXPDA), implemented with polyether-type side chains in the backbone. Association to tetramethylammonium picrate (TMAP) was measured in $CDCl_3$ at $T = 296$ K by ^{1}H NMR titrations. Results confirm that the main contribution to the binding of TMA comes from the cation$-\pi$ interaction established with the aromatic binding sites, but they unequivocally show that polyether chains participate with cooperative contributions, although of markedly smaller entity. Water is also bound, but the two guests interact with aromatic rings and oxygen donors in an essentially noncompetitive way. An improved procedure for the preparation of cyclophanic tetraester derivatives has been developed that conveniently recycles the oligomeric ester byproducts formed in the one-pot cyclization reaction. An alternative entry to benzylic diketones has also been provided that makes use of a low-order cyanocuprate reagent to prepare in fair yields a class of compounds otherwise uneasily accessible.

Introduction

Due to the coordinative ability of ether oxygen atoms, polyether chains are the fundamental constituents of several classes of cyclic and open-chain receptors that are well-established ligands for metal and ammonium cations.[1] In contrast, polyether chains do not seem to contribute to the binding of quaternary ammonium cations,[2] toward which aromatics exert a well-documented attraction,[3] due to the interaction of the aromatic π system with the cationic species. This lack of affinity is surprising in consideration of the fact that, in the gas phase, both experiments and ab initio computations[4] indicate that Me_4N^+ binds with approximately equal binding enthalpies to H_2O (9.0 kcal mol^{-1}) and to benzene (9.4 kcal mol^{-1}) and toluene (9.5 kcal mol^{-1}) and that even stronger interactions are observed with polyethers (diglyme, 20.6 kcal mol^{-1}; triglyme, 24.2 kcal mol^{-1}).[4a] In the course of an investigation on the cation$-\pi$ interaction, we have shown that acetylcholine (ACh) and tetramethylammonium (TMA) exhibit binding affinity for a family of flexible, adaptive cyclophanic esters, among which dimeric 1,4-xylylene-1,4-phenylene diacetate (DXPDA) showed the best binding properties.[5]



Remarkably, sizable affinity was also detected with their open-chain counterparts such as, for example, 1,4-xylylene diphenylacetate (XDPA), caused by the cooperative contribution of the ester groups enhancing the aromatic binding sites of the host. On the basis of these results, we thought that by introducing polyether chains of variable length into the host structure, DXPDA and related open-chain aromatic esters could be the appropri-

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(1) *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, 1996; Vol. 1.

(2) Rüdiger, V.; Schneider, H.-J.; Solov'ev, V. P.; Kazachenko, V. P.; Raevsky, O. A. *Eur. J. Org. Chem.* **1999**, 1847−1856.

(3) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303−1324.

(4) (a) Deakyne, C. A.; Meot-Ner, M. *J. Am. Chem. Soc.* **1985**, *107*, 469−474. (b) Deakyne, C. A.; Meot-Ner, M. *J. Am. Chem. Soc.* **1985**, *107*, 474−479. (c) Deakyne, C. A.; Meot-Ner, M. *J. Am. Chem. Soc.* **1999**, *121*, 1546−1557.

(5) Roelens, S.; Torriti, R. *J. Am. Chem. Soc.* **1998**, *120*, 12443−12452.

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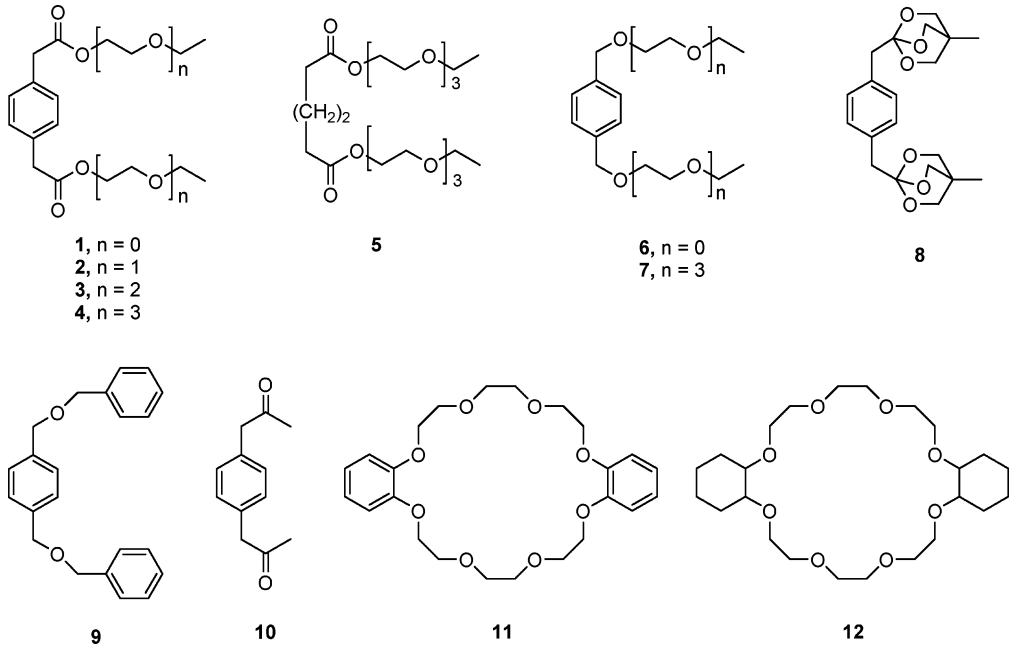
CHART 1

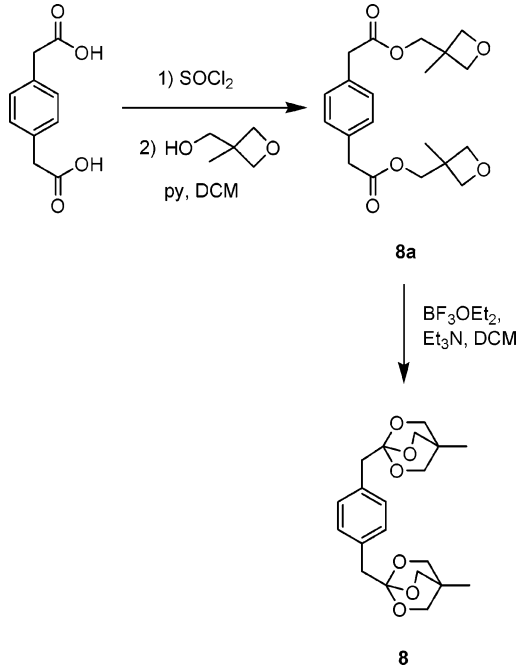


ate hosts for a quantitative evaluation of the binding capacities of polyether moieties toward quaternary ammonium cations in solution; in particular, acyclic and flexible, sidearmed cyclophane hosts, lacking preorganized binding sites, would shed light on the inherent affinity of ether oxygen donors for tetralkylammonium guests. We report here the results of a systematic study in chloroform on the binding of TMA to a set of open-chain hosts containing an aromatic binding site and a variable number of ether oxygen donors in the side chains, appropriately positioned to cooperatively interact with the guest, and of DXPDA-related cyclophanes possessing polyether-type side chains. Results unequivocally show that polyether chains participate in the binding of TMA with cooperative contributions, although the entity of the contributions is markedly smaller than that of the cation−π interaction with the aromatic binding sites.

Results and Discussion

Synthesis of Open-Chain Ligands. The open-chain hosts were based on the structure of diethyl 1,4-phenylenediacetate (**1**),[6] which displayed conveniently detectable binding properties toward ACh and TMA. The hosts prepared for the present investigation are collected in Chart 1, together with the commercially available dibenzo-24-crown-8 (**11**) and dicyclohexano-24-crown-8 (**12**), which were used as reference ligands of appropriate size for the TMA cation. Host **1** and its homologous polyoxyethylene congeners **2**, **3**, and **4** were prepared by esterification of 1,4-phenylenediacetic acid with ethanol and with mono-, di-, and triethylene glycol monoethyl ethers, respectively. The adipate **5**, the aliphatic analogue of **4**, was prepared in the same way to ascertain the host's binding ability in the absence of the aromatic binding site. To investigate the binding properties of hosts lacking cooperative contributions from ester groups, ethers **6**[7] and **7**, analogues of esters **1** and **4**, were prepared by Williamson etherification of α,α′-dibromo-*p*-xylene with ethanol and triethylene glycol monoethyl ether, respectively. The bis-ortho ester **8**, the analogue of **1** possessing geminal ether oxygen donors somewhat more organized for binding than **6** and **7**, was obtained by BF_3-catalyzed rearrangement of the bis-1,4-phenylenediacetic ester (**8a**) of the commercially available 3-methyl-3-hydroxymethyl oxetane (Scheme 1).[8] The bis-benzyl ether **9**[7] was obtained by benzylation of 1,4-benzenedimethanol with benzyl bromide and has been prepared to provide information on binding contributions arising from additional aromatic

SCHEME 1



(6) Titley, A. F. *J. Chem. Soc.* **1928**, 2576.

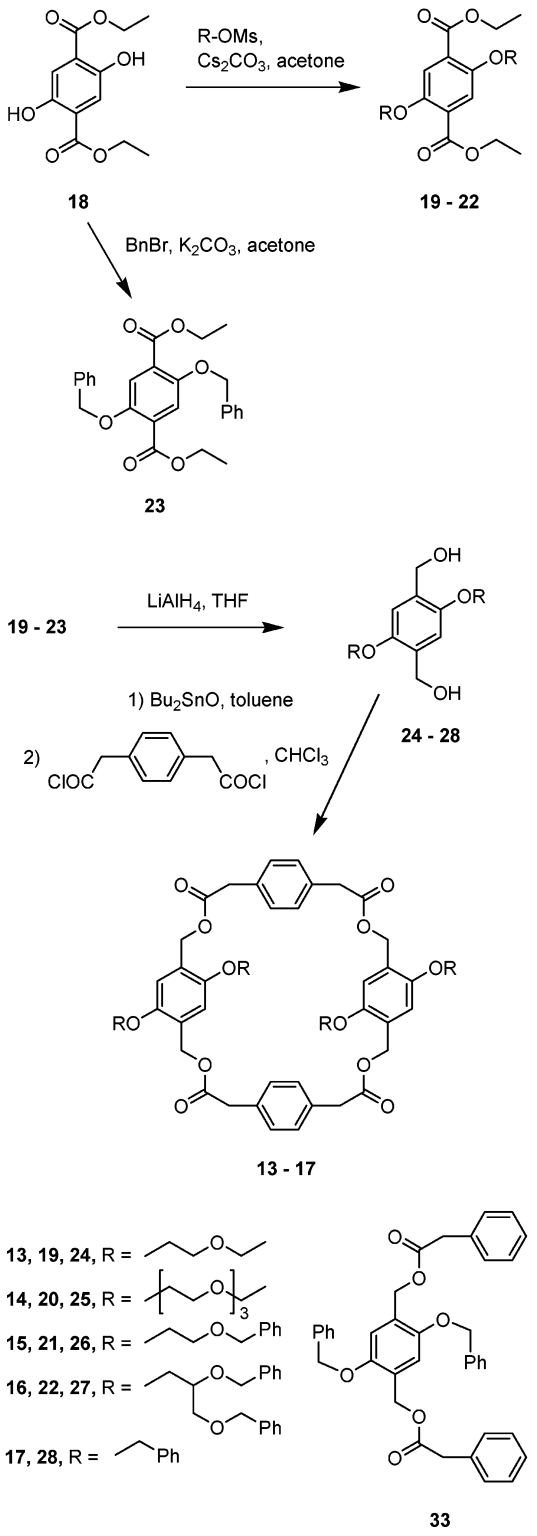
(7) Quelet, R. *Bull. Soc. Chim. Fr.* **1933**, *53*, 222−233.

(8) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571−5574.

rings with respect to **6**. The diketone **10** was prepared to ascertain whether the cooperative contribution of the ester groups in **1** would depend on the alcoholic oxygen. For the preparation of **10**, common methods for the synthesis of ketones failed because of the presence of two benzylic positions.[9] In an effort to provide an alternative entry to benzylic diketones,[13] we developed a convenient procedure relying on the treatment of 1,4-phenylenediacetyl chloride with a lower order cyanocuprate reagent, prepared by mixing MeLi and CuCN in a 1:1 ratio,[14] which afforded **10** in fair yields (≅50% unoptimized).

Synthesis of Sidearmed Cyclophane Ligands. The conveniently large upfield shifts induced on the guests signals upon binding made the macrocyclic cyclophane host DXPDA appropriate to evaluate the contribution of polyether chains in the cyclophane series. Implementation of the cyclophane structure with polyether chains may be achieved through functionalization of the backbone, provided that structural modifications should not drastically affect the stereoelectronic and conformational features of the parent host, to compare the binding properties of functionalized cyclophanes with those of DXPDA. To compromise between the above requirements and the ease of access, cyclophanes **13**−**17** were prepared starting from commercially available diethyl 2,5-dihydroxyterephthalate **18** (Scheme 2), which provided a selection of hosts bearing different oxygenated side chains. The choice of what may appear as a drastic perturbation of the parent DXPDA structure, mainly because of the conversion of two benzene rings into far more electron-rich aromatic residues, was made on account of computational work published by Dougherty and coworkers,[15] which predicted a negligible binding energy difference between benzene and phenol in cation−π complexes of alkaline cations. Terephthalate bis-ethers **19**−**23** were obtained from **18** by alkylation of phenolic hydroxyls with the mesylate of the appropriate alcohol (**19**−**22**) or with benzyl bromide (**23**), and subsequently reduced to the corresponding 1,4-benzenedimethanol derivatives **24**−**28**. The target cyclophanes **13**−**17** were obtained from the latter diols by azeotropic dehydration in the presence of di-*n*-butyltin oxide, followed by addition of 1,4-phenylenediacetyl chloride, through a well-established organotin-mediated cyclooligomerization reaction.[16] In this context, we found that a dramatic improvement in the conversion of diols into the cyclophanic tetraesters could be achieved by recycling the oligomeric

SCHEME 2



byproducts recovered from the crude reaction mixture after the isolation of the tetraester. The oligomeric mixture was reequilibrated by refluxing in toluene in the presence of catalytic amounts (10% mol) of a 1:1 mixture of di-*n*-butyltin oxide and di-*n*-butyltin chloride,[17] to

(9) Treatment of 1,4-phenylenediacetic acid with methyllithium and chlorotrimethylsilane (ref 10) or treatment of 1,4-phenylenediacetyl chloride with methylmagnesium bromide (ref 11) gave unreacted starting material exclusively after workup. On the other hand, treatment of the Grignard reagent of α,α′-dibromo-*p*-xylene with acetyl chloride gave mainly Wurtz coupling products. Yields of diketone not larger than 5% could be obtained by reacting 1,4-phenylenediacetyl chloride with $Me_2Cu(CN)Li_2$ (ref 12).

(10) Rubottom, G. M.; Kim, C.-w. *J. Org. Chem.* **1983**, *48*, 1550−1552.

(11) Sato, F.; Inoue, M.; Oguro, K.; Sato, M. *Tetrahedron Lett.* **1979**, *20*, 4303−4306.

(12) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928−3938.

(13) Diacetonylbenzene has previously been prepared by arylation of enol acetate with 1,4-dibromobenzene via tributyltin enolates catalyzed by dichlorobis(tri-*o*-tolylphosphine)palladium complex: Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 242−246.

(14) Acker, R.-D. *Tetrahedron Lett.* **1977**, *18*, 3407−3410.

(15) Mecozzi, S.; West, A. P., Jr.; Dougherty, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 2307−2308.

(16) (a) Shanzer, A.; Libman, J.; Frolow, F. *Acc. Chem. Res.* **1983**, *16*, 60−67. (b) Roelens, S. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1617−1625. (c) Mandolini, L.; Montaudo, G.; Scamporrino, E.; Roelens, S.; Vitalini, D. *Macromolecules* **1989**, *22*, 3275−3280.

SCHEME 3

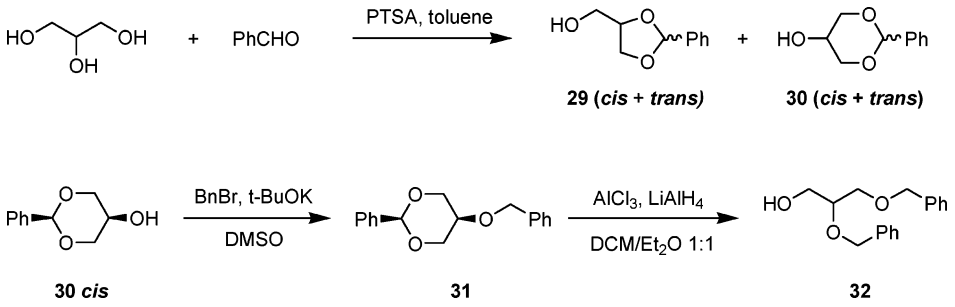


TABLE 1. Association Constants K_a (M^{-1}), Standard Free Energies of Binding $-\Delta G°$ (kJ mol^{-1}), and Guest Limiting Shift Values $\Delta\delta_\infty$ (ppm) for the 1:1 Complexes of Tetramethylammonium Picrate (TMAP) and Water (H_2O) with Open-Chain Aromatic Ligands[a]

	TMAP			H_2O		
host	K_a (SE)[b]	$\Delta\delta_\infty$	$-\Delta G°$	K_a (SE)[b]	$\Delta\delta_\infty$	$-\Delta G°$
1	7.94 (0.07)	−0.503	5.09(2)	nd[c]	0.148 (0.22 M)[d]	
2	8.08 (0.07)	−0.546	5.14(2)	2.24 (0.02)	0.667	1.98(3)
3	9.3 (0.15)	−0.514	5.49(4)	3.83 (0.07)	0.876	3.30(5)
4	12.1 (0.27)	−0.464	6.14(5)	6.43 (0.07)	1.149	4.58(3)
5	nd[c]	−0.035 (0.10 M)[d]		6.43 (0.05)	1.047	4.58(2)
6	nd[c]	−0.180 (0.30 M)[d]		nd[c]	0.210 (0.30 M)[d]	
7	5.5 (0.18)	−0.506	4.20(7)	7.96 (0.05)	1.207	5.11(1)
8	2.61 (0.05)	−0.478	2.36(5)	nd[c]		
9	3.03 (0.04)	−0.906	2.73(3)	nd[c]	0.052 (0.13 M)[d]	
10	7.3 (0.1)	−0.500	4.89(4)	nd[c]	0.227 (0.28 M)[d]	
11	14.5 (0.65)	−0.434	6.5(1)	5.18 (0.05)	1.112	4.05(2)
12	nd[c]			14.5 (0.12)	1.503	6.58(2)

[a] Measured by ^1H NMR (200/300 MHz) at $T = 296$ K in $CDCl_3$ on 0.1 mM solutions of TMAP using host concentrations up to 60 mg/mL. [b] Standard error of the nonlinear least-squares fit. [c] Nondetectable; for $K_a \leq 2$, titration curves become indistinguishable from each other in the investigated concentration range. [d] $\Delta\delta$ values observed at the indicated titrant concentration.

regenerate the entire oligomer distribution, which can be optimized in the tetraester yield by adjusting the concentration of the reacting mixture.[16c,18] Conversion yields of tetraester achieved by this reequilibration procedure can be as high as 14% (19% for the unsubstituted cyclophane DXPDA) in a single step with respect to the recovered oligomeric mixture. Furthermore, the recycling procedure could be repeated several times to progressively upgrade the conversion yield.

While the alcohol reagents used for the introduction of side chains in **19** and **20** were commercially available and that for **21** could be readily obtained by monobenzylation of ethylene glycol, the dibenzyl ether of glycerol needed for **22** required a slightly more elaborated synthesis that rested on the selective crystallization from the raw benzylidene acetal mixture of the *cis*-acetal **30-*cis***,[19] which could be obtained diastereomerically pure from diisopropyl ether on a multigram scale (Scheme 3).

Acetal **30-*cis*** was benzylated with benzyl bromide and reductively cleaved to the desired dibenzyl ether **32**.[20] Finally, the diphenylacetate **33**, the open-chain "half-molecule" of **17**, was prepared from **28** and phenylacetyl chloride to serve, together with **17**, as reference host to evaluate intrinsic differences in binding ability between the phenol-type sidearmed ligands and the unsubstituted parent cyclophane DXPDA and open-chain XDPA and to check the validity of the assumption on which their synthesis was based. The choice of the benzyl derivatives as reference hosts was dictated by the low solubility of the free hydroxy and of the methyl ether derivatives of **17**, as well as that of the corresponding derivatives of **33**, none of which was soluble enough in chloroform to allow for binding measurements.

Binding Studies. The association constants (K_a) for the 1:1 complexes of tetramethylammonium picrate (TMAP) with the above set of hosts were measured, as in previous studies,[5] in $CDCl_3$ at $T = 296$ K by ^1H NMR titrations, monitoring the time-averaged signal of the free and complexed TMA with increasing host concentration. TMAP was selected as the appropriate salt for binding measurements, because the picrate anion has been shown to be a convenient partner for TMA, to minimize the inhibiting contribution of the counterion.[21] The details of the titration procedure and of the analytical treatment of data have been described elsewhere.[22] Results for the open-chain hosts, together with those for the reference ligands **11** and **12** and for the sidearmed cyclophane hosts, along with previously determined data for DXPDA

(17) Roelens, S. *J. Chem. Soc., Chem. Commun.* **1990**, 58−60.
(18) Ercolani, G.; Mandolini, L.; Mencarelli, P.; Roelens, S. *J. Am. Chem. Soc.* **1993**, *115*, 3901−3908.
(19) Carlsen, P. H. J.; Sørbye, K.; Ulven, T.; Aasbø, K. *Acta Chem. Scand.* **1996**, *50*, 185−187.
(20) Unfortunately **29**, which is formed in roughly similar amount in the acetalization, could not be employed for the purpose. Although methods for the selective cleavage of benzylidene acetals at either the primary or the secondary oxygen are available (see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley-Interscience: New York, 1999), our efforts failed with the benzyl ether of **29**, which consistently gave the undesired bis-primary dibenzyl ether, therefore preventing the use of the whole isomeric mixture of acetals for the convergent synthesis of **32**.
(21) Bartoli, S.; Roelens, S. *J. Am. Chem. Soc.* **2002**, *124*, 8307−8315.
(22) Roelens, S.; Torriti, R. *Supramol. Chem.* **1999**, *10*, 225−232.

TABLE 2. Association Constants K_a (M^{-1}), Standard 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) with Sidearmed Macrocyclic Aromatic Ligands[a]

host	K_a (SE)[b]	$\Delta\delta_\infty$	$-\Delta G°$
DXPDA	29.7 (0.4)[c]	−1.479[c]	8.35(3)[c]
13	18.6 (0.3)	−1.290	7.19(4)
14	29.0 (1.1)	−0.780	8.29(9)
15	19.1 (0.9)	−1.267	7.3(1)
16	35.8 (0.7)	−1.255	8.81(4)
17	16.1 (0.3)	−1.003	6.84(4)
33	7.1 (0.2)	−0.510	4.82(7)
XDPA	6.7 (0.4)[c]	−0.464[c]	4.7(1)[c]

[a] Measured by ^{1}H NMR (200/300 MHz) at T = 296 K in $CDCl_3$ on 0.1 mM solutions of TMAP using host concentrations up to 60 mg/mL. [b] Standard error of the nonlinear least-squares fit. [c] Data from ref 5.

and XDPA, are reported in Tables 1 and 2, respectively. In addition, in Table 1 association data relative to water binding are also reported for open-chain hosts possessing polyoxyethylene units. Indeed, in the titration spectra of the latter, the water signal showed a downfield shift with increasing host concentration clearly describing a saturation curve, which could be correctly fitted to a 1:1 binding isotherm. Binding of water molecules is a known phenomenon for crown ethers,[23] and we could indeed determine the association constants for **11** and **12**, but these became too small to be measured for hosts lacking polyoxyethylene chains. It must be underlined that binding of water was determined concomitantly with TMA, thus under competitive conditions. The general conclusion that can be drawn from inspection of data in Table 1 is that polyether chains participate in the binding of TMA, but only to a minor extent. Variations of binding free energies are small with respect to the reference diester **1**, showing that the contributions provided by the ether oxygen donors are of minor entity compared to those from the aromatics. Nevertheless, since the reasonably large chemical shifts induced by the hosts upon binding allowed us to obtain reliable data, a quantitative evaluation of contributions from the oxygen donors could be assessed and some general conclusions could be outlined. Hosts **1**−**4**, which possess an increasing number of oxyethylene units in the side chains, exhibit increasing free energy of binding to TMAP; the same is true for binding to water, showing that polyether chains interact with both guests. However, binding behavior is different for the two guests, in that $-\Delta G°$ increments are linear for water but exponential for TMAP. This feature can be better appreciated from the plots of Figure 1, where experimental $-\Delta G°$ values were plotted vs the number of oxygen donors (n) in the side chains and fitted by linear and exponential regressions, respectively, with excellent correlation coefficients. Thus, for water, linear regression (r^2 = 0.999) gave an increment of binding free energy of 1.3 kJ mol^{-1} per added oxygen pair, while for TMAP data were fitted to eq 1 with y_0 = 4.88(4) and a = 1.419(9).

$$-\Delta G° = y_0 + (\log a)\, a^n \qquad (1)$$

The analysis shows that polyoxyethylene side chains bind TMA with small but cooperative contributions,

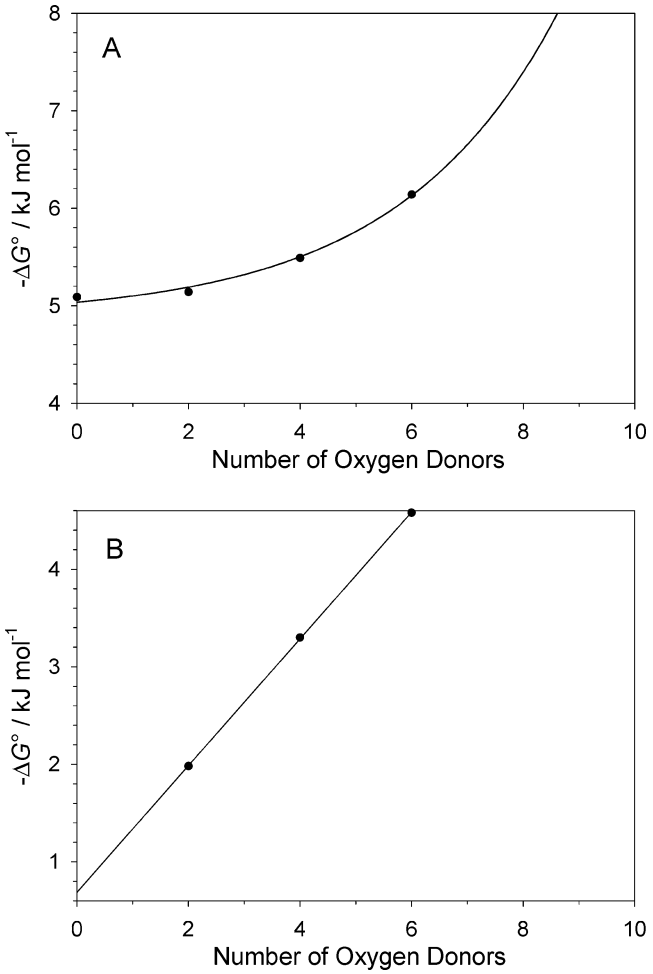


FIGURE 1. Plot of binding free energies $-\Delta G°$ in $CDCl_3$ at T = 296 K vs number of oxygen donors in the polyoxyethylene side chains for binding of TMAP (A) and H_2O (B) to open-chain hosts **1**−**4**. Symbols are experimental data from Table 1; solid lines are (A) the best fit curve obtained from eq 1 by nonlinear regression with y_0 = 4.88(4), a = 1.419(9) and (B) the best fit line from linear regression (slope = 0.650; intercept = 0.687; r^2 = 0.999). Plots are displayed on the same scale for visual comparison.

whereas they bind water with larger but independent increments. The intercept of the curve for TMA (Figure 1A), i.e., the $-\Delta G°$ value, for a null number of added polyoxyethylene units, which corresponds to the binding free energy of the parent ligand **1**, shows that the contribution of polyoxyethylene side chains to the binding of TMA, altough cooperative, is much smaller than the contribution of the aromatic, being 5-fold smaller than the latter even for six oxyethylene units. Instead, for water, the $-\Delta G°$ value (0.687 kJ mol^{-1}) of the linear regression intercept (Figure 1B) shows that **1** binds to water as strongly as each oxyethylene unit (slope = 0.650 kJ mol^{-1}), but the contribution appears to be entirely due to the two ester groups of **1** rather than to the aromatic ring, since removing the aromatic from the structure leaves the free energy of binding to water unaffected (see Table 1, **4** and **5**). On the contrary, removing the aromatic causes binding of TMA to drop below the detectable limit for **5**, confirming that the main contribution to cation binding is provided by the aromatic ring. The emerging picture is consistent with a system in which two guests

(23) Izatt, R. M.; Bradshaw, J. S.; Pawlak, K.; Bruening, R. L.; Tarbet, B. J. *Chem. Rev.* **1992**, *92*, 1261−1354.

(TMA and water) interact with two independent binding sites (aromatic and oxygen) in an essentially noncompetitive way.

Removing the carbonyl groups from **1** and **4**, to give ethers **6** and **7**, respectively, that is, converting ester groups into ether moieties, induces predictable variations: the binding free energy increases for water, whereas it decreases for TMA. For water, although figures cannot be evaluated but in the case of **4** and **7**, recalling that the contribution of two ester groups was the same as that of one single oxyethylene unit, it appears that the full contribution of two oxygen sites has been restored in **7**. Instead, for TMA, the binding free energy decrease is worth 2 kJ mol^{-1} for **7** with respect to **4** and even larger for **6** with respect to **1**. On the basis of models computed at the AM1 level of theory, we have shown[5] that ester groups, which in the binding conformation lie orthogonal to the plane of the aromatic ring, can exert a cooperative contribution to the binding of TMA by polarizing the electrostatic potential of the aromatic out of plane over one side of the ring, thus rendering the charge density fully available to interact with the cationic guest. Such a contribution is lost in the corresponding ethers, and a plausible rationale is offered by analogous calculations at the AM1 level (on the dimethyl ether for simplicity) showing that, in contrast to the ester counterpart, the ether groups depart from the cooperative orthogonal conformation to lie on the plane of the aromatic ring in the optimized geometry and that in the latter the electrostatic potential is polarized *in plane* with the aromatic ring and symmetrically distributed over the two faces (Figure 2). Accordingly, a drop of binding to TMA is observed for **8**, which is the cyclic diortho ester of **1**, due to the loss of two ester groups only partially compensated by the gain of two pairs of ether-type oxygen donors. Because of this compensation, the corresponding binding free energy becomes a measurable quantity, compared to the simple diether **6**, and exhibits a remarkable additivity of contributions: the value of $-\Delta G°$ for TMA can be obtained by adding up the contributions from one aromatic (2 kJ mol^{-1})[5] and from two oxygen pairs (0.35 kJ mol^{-1}). The association becomes measurable also for the dibenzyl ether **9**, because of the added phenyl rings that, however, do not seem to fully contribute to binding. The larger upfield shift of the complex supports participation of the phenyl rings, but their contribution is in fact definitely smaller than that expected for two aromatics. That the binding contribution of the ester group is due to the carbonyl rather than to the alcoholic oxygen is demonstrated by the diketone **10**, whose binding free energy to TMA is nearly the same as that of **1**. Comparison of data for **10**, **6**, and **1** clearly shows that the contribution from the alcoholic oxygen of the ester toward TMA is negligible.

From comparison of **1**−**10** with the two reference crown ethers **11** and **12**, it can immediately be noted that **12**, having the same size and number of oxyethylene units as **11** but lacking the two aromatic rings, does not display any binding capacity toward TMA, whereas **11** exhibits the largest value of the whole set. Thus, as expected, eight oxyethylene units cannot compensate for the loss of two aromatic rings. The contribution to $-\Delta G°$ from eight oxyethylene units can be calculated by eq 1, to give 2.3 kJ mol^{-1} (after subtracting the binding free energy

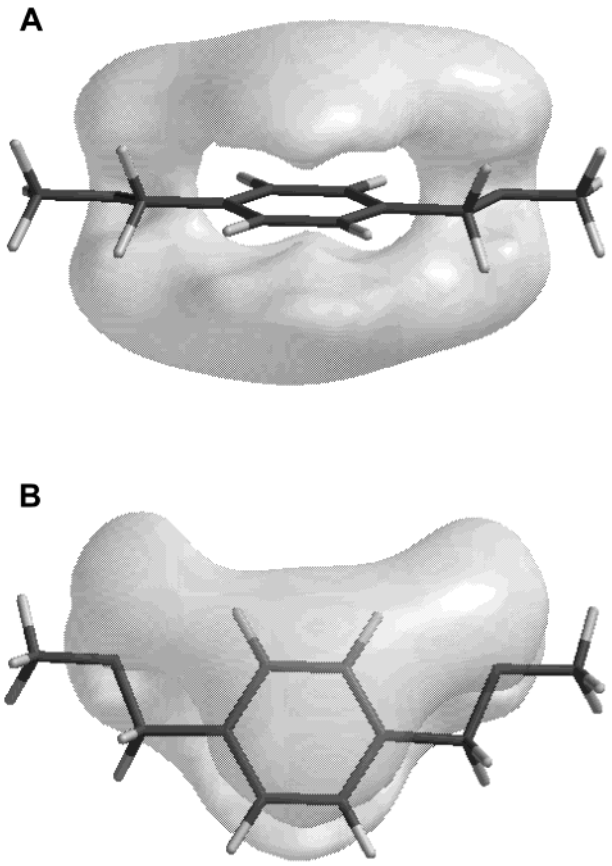


FIGURE 2. AM1-computed model of 1,4-benzenedimethanol dimethyl ether in the optimized conformation. The optimized geometry is depicted as a polytube model; the electrostatic potential isosurface at −10 kcal mol^{-1} is shown in transparent body representation: (A) side view and (B) top view with respect to the aromatic ring plane.

of **1**); by adding the value corresponding to two aromatic rings (4 kJ mol^{-1}) to this figure, $-\Delta G° = 6.3$ kJ mol^{-1} is obtained for **11**, in excellent agreement with the experimental value, supporting the conclusion that contributions are additive. On the other hand, with respect to water, **12** binds better than **11** by 2.5 kJ mol^{-1}; the $-\Delta G°$ value calculated from the linear regression for the corresponding number of oxygen donors (5.2 kJ mol^{-1}) is somewhat smaller than that of **12**, but larger than that of **11** (Table 1). For **12**, stronger binding than expected may likely be ascribed to the macrocyclic structure, more preorganized than that of the open-chain ligands, but this bonus is lost for **11**, for which binding of water may be hampered by the conformational changes imposed by the concomitant association with TMA in order to adapt the aromatic rings to bind the cation, in a sort of allosteric effect. Eventualy, the literature[24] value for the association of water to **11** gives a binding free energy $-\Delta G° = 4.25$ kJ mol^{-1}, in close agreement with the value reported in Table 1, thus providing an external check of the reliability of the present data.

Inspection of results in Table 2 confirms the general conclusion that also in the marocyclic series oxyethylene

(24) Golovkova, L. P.; Telyatnik, A. I.; Bidzilya, V. A.; Akhmetova, N. E.; Konovalova, V. I. *Teor. Exp. Chem. (Engl. Transl.)* **1985**, *21*, 238−242.

side chains do not improve cation binding by substantial amounts. In fact, with one exception, all ligands show weaker binding than the parent unsubstituted tetraester DXPDA. Introduction of four phenolic oxygen functionalities in the xylylene moieties of DXPDA is expected to raise the electronic density and, consequently, it may enhance the binding capacity of the host toward the cationic guest. Likewise, the introduction of benzyl side chains may enhance the association by incrementing the number of binding goups. In contrast, it is easily noted that neither one is the case, since the tetrabenzyloxy-substituted **17** shows a binding free energy value 1.5 kJ mol^{-1} smaller than that of DXPDA. On the other hand, comparison between the corresponding open-chain "half-molecules", the unsubstituted XPDA and the dibenzyloxy-substituted **33**, does not highlight any appreciable difference in binding to TMA, indicating that neither the electron-donating phenolic oxygens nor the benzylic side chains induce any increase in binding capacity. This evidence confirms the prediction made, in choosing the dihydroxyterephthalate reagent for the synthesis of the sidearmed macrocyclic hosts, that binding properties would not be affected by electronic factors. As expected, the free energy values for XPDA and **33** are smaller than those of their macrocyclic counterparts; this reflects the larger number of binding groups and some degree of preorganization that the macrocyclic structures, although flexible, possess compared to their open-chain analogues; however, the drop in binding strength observed for **17** with respect to DXPDA, a drop lacking for the open-chain ligands, points to a binding hindrance affecting the substituted macrocycles, which may be steric and/or conformational in origin. Taking into account such a binding inhibition, then side chains possessing an increasing number of oxyethylene units do increase the binding strength of the macrocyclic hosts as in the open-chain series. Thus, addition of one oxyethylene unit to the side chains of **17** raises the binding free energy by 0.46 kJ mol^{-1} for **15**, a value that is nearly unaffected by replacement of the terminal phenyl groups with methyl groups as in **13**, suggesting that phenyl end groups cannot easily achieve a cooperative binding conformation. Instead, three oxyethylene units in **14** raise the binding free energy by 1.45 kJ mol^{-1} with respect to **17** and by 1.1 kJ mol^{-1} with respect to its lower homologue **13**, bringing a contribution significantly larger than that of one single unit. However, while in **13** the four independent oxyethylene units can probably arrange into a binding conformation around the cation, thus exerting their full contribution, this cannot obviously be achieved by the total 12 oxyethylene units of which **14** is endowed, necessarily bringing in only a partial contribution. In terms of additivity of contributions, **13** and **15** show binding free energy increments very similar to that of the open-chain counterpart endowed with the same number of ether units (**3**), whereas **14** exhibits a binding increment slightly larger than that of the corresponding open-chain ligand possessing only *half* of its oxyethylene units (**4**). The glycerol derivative **16** is the only host for which a net increase in binding free energy is observed with respect to the parent DXPDA. This may be ascribed to the branching of the side chains, which may allow for a better adaptment to the guest, but the improvement in binding energy, 2 kJ mol^{-1} with respect to **17** and less than 0.5 kJ mol^{-1} with respect to DXPDA, is indeed very modest compared to the complexity of the structure and the number of binding groups featured. In conclusion, polyether chains are intrinsically beneficial as cooperative binding side chains, but they introduce steric/conformational constraints in the macrocyclic tetraester that override any advantages gained in binding strength.

Conclusion. From a systematic investigation of the binding contribution exerted by polyether side chains on the interaction of the tetramethylammonium cation with phanic receptors, the following conclusions have been drawn: (a) binding of the guest is primarily due to the aromatic moieties of the receptors; ether groups provide minor but cooperative contributions whenever they can achieve a binding arrangement around the cation; (b) contributions of ether groups are additive for open-chain hosts, with exponentially growing increments of binding free energy, whereas participation appears to be strongly affected by steric and/or conformational constraints for macrocyclic sidearmed hosts; (c) in contrast to aromatic rings, polyether chains preferentially bind to water than to TMA, showing binding free energy increments linearly additive; (d) for the set of phanic esters investigated, water and TMA independently interact with polyether chains and aromatic binding sites respectively in an essentially noncompetitive fashion; (e) ester groups participate in binding of TMA through the carbonyl and of water through the alcoholic oxygen. In summary, the contribution from the ether oxygen donors of polyether chains to the binding of TMA to aromatic hosts could be reliably assessed on a quantitative basis using a set of ligands featuring a systematic variation of substituents. Results confirm that the binding energies expected from gas-phase data for the interaction between TMA and oxygen donors vanish to a large extent in solution, in contrast to the cation$-\pi$ interaction established with aromatic donors, which seems to suffer to a minor extent from the transfer to the condensed phase.

Experimental Section

Synthesis of 1-[4-(2-Oxopropyl)phenyl]propan-2-one, 10. Copper(I) cyanide (582 mg, 6.50 mmol) was suspended in dry tetrahydrofuran (13 mL) and cooled to −78 °C. A 1.6 M solution of methyllithium in diethyl ether (3.55 mL, 6.58 mmol) was added dropwise and the mixture allowed to warm to 0 °C and cooled again to −78 °C. A solution of (4-chlorocarbonylmethylphenyl)acetyl chloride (657 mg, 2.84 mmol) in dry tetrahydrofuran (7 mL) was added dropwise and the mixture stirred at 0 °C for further 30 min. Methanol (10 mL) was added and the mixture poured into water (20 mL). The aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layer was washed with water (20 mL) and dried (Na_2SO_4) and the solvent removed under reduced pressure. Purification by column chromatography (petroleum ether/ethyl acetate 3:2), gave 253 mg of **10** as a white solid (47% yield). Mp: 52−53°C (lit.[13] mp: 46−47 °C). Elemental analysis: calcd, C 75.75, H 7.42; found C 76.02, H 7.51. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.15 (s, 6H), 3.68 (s, 4H), 7.17 (s, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.3, 50.5, 129.8, 133.06, 206.3. MS-EI: *m*/*z* (%) 191 (11), 190 (12) [M^+], 148 (71), 106 (12), 105 (100), 104 (49), 103 (70), 91 (42), 89 (11), 84 (17), 78 (44), 77 (78), 63 (24), 52 (14), 51 (29), 50 (21).

Synthesis of [2,5-Bis(2-ethoxyethoxy)-4-hydroxymethylphenyl]methanol, 24. General Method B. Compound **18** (3.46 g, 13.6 mmol), Cs_2CO_3 (30 g, 92 mmol), and methanesulfonic acid 2-ethoxyethyl ester (4.58 g, 27.2 mmol) were

suspended in acetone (120 mL) and refluxed to disappearance of the starting material and formation of one single product (TLC). The mixture was then filtered through Celite and the solvent evaporated. The residue was dissolved in dichloromethane (200 mL), washed with water (3 × 100 mL), and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give crude **19** (5.42 g, 100%). A solution of **19** (5.42 g, 13.6 mmol) in tetrahydrofuran (10 mL) was carefully added to a solution of $LiAlH_4$ (8 mL, 1 M solution in tetrahydrofuran) while the temperature was kept below 40 °C. After 1 h with vigorous stirring, the solution was cooled to 0 °C and ethyl acetate was added carefully to quench the excess of $LiAlH_4$. The mixture was poured into a 10% aqueous solution of HCl (300 mL) and the aqueous layer was extracted with dichlorometane (3 × 100 mL). The combined organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure to give the crude product **24** as a yellow oil (3.05 g, 9.70 mmol, 71% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22 (t, J = 7 Hz, 6H), 3.49 (q, J = 7 Hz, 4H), 3.70−3.80 (m, 4H), 4.12−4.22 (m, 4H), 4.62 (s, 4H), 6.84 (s, 2H). Product **24** was identified by ^{1}H NMR and used as such for the following macrocyclization reaction.

Synthesis of 13. General Method C. Compound **24** (1.50 g, 4.78 mmol) and dibutyltin oxide (1.19 g, 4.78 mmol) were dissolved in toluene (50 mL) in a flask equipped with a Dean−Stark apparatus, and the mixture was refluxed for 24 h. A solution of (4-chlorocarbonylmethylphenyl)acetyl chloride (1.10 g, 4.78 mmol) in $CHCl_3$ (50 mL) was added batchwise and the mixture refluxed for a further 45 min. The solvent was removed under reduced pressure and the residue washed with petroleum ether (3 × 50 mL) and purified by column chromatography (dichloromethane/ethyl acetate 3:1), giving 153 mg of **13** as a white solid (7% yield). Mp: 141−142 °C. Elemental analysis: calcd, C 66.09, H 6.83; found, C 65.91, H 6.78. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.17 (t, J = 7 Hz, 12H), 3.47 (q, J = 7 Hz, 8H), 3.55−3.60 (m, 8H), 3.65 (s, 8H), 3.81−3.86 (m, 8H), 5.08 (s, 8H), 6.54 (s, 4H), 7.22 (s, 8H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.3, 41.5, 61.9, 66.9, 68.8, 69.0, 113.1, 125.1, 129.5, 133.1, 150.4, 170.8. MS-EI: m/z (%) no M^+, 111 (34), 97 (12), 88 (11), 86 (61), 85 (22), 84 (100), 83 (38), 82 (32), 81 (79), 71 (16), 70 (11), 69 (16), 57 (27), 55 (20), 54 (11).

Synthesis of 15. General Method D. Compound **15** was first obtained from **26** according to method C on a 4.76 mmol scale (155 mg, 7.4% yield) after column chromatography (dichlorometane/5% ethyl acetate); 2.2 g (3.69 mmol based on the molecular weight of the monomer, 77% yield) of oligomeric residue was obtained from column chromatography (dichloromethane/methanol 10:1). The oligomeric residue from method C (2.2 g, 3.69 mmol), dibutyltin oxide (90 mg, 0.362 mmol), and dibutyltin chloride (110 mg, 0.362 mmol) were refluxed for 2 days in toluene (600 mL). Dipyridile (59 mg, 0.362 mmol) was added, the solution filtered to remove the precipitate (DBTC/dipyridile complex), and the solvent removed under reduced pressure. The residue was purified by column chromatography (gradient: dichloromethane/6% to 8% ethyl acetate), to give 300 mg (13.9% yield) of **15** as a white solid and 1.65 g (69% yield) of oligomeric residue that could be recycled again as described above. Mp: 127−128 °C. Elemental analysis: calcd, C 72.47, H 6.08; found, C 72.73, H 6.27. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.57 (s, 8H), 3.59−3.64 (m, 8H), 3.84−3.89 (m, 8H), 4.48 (s, 8H), 5.09 (s, 8H), 6.56 (s, 4H), 7.16 (s, 8H), 7.26−7.34 (m, 20H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 41.4, 61.9, 68.6, 68.6, 73.3, 113.1, 125.1, 127.7, 128.5, 129.5, 133.0, 138.0, 150.4, 170.9. MS-EI: m/z (%) no M^+, 111 (18), 110 (10), 98 (12), 97 (36), 96 (21), 95 (14), 91 (11), 85 (39), 84 (29), 83 (57), 82 (37), 81 (21), 71 (49), 70 (45), 69 (61), 68 (39), 67 (20), 66 (12), 56 (100), 55 (82), 54 (70).

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Supporting Information Available: General methods and materials; experimental details for the synthesis of compounds **1**−**9**, **14**, **16**, **17**, **25**−**28**, and **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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