Molecular Recognition in Aqueous Media. New Binding Studies Provide Further Insights into the Cation-π Interaction and Related Phenomena

Patrick C. Kearney, Laura S. Mizoue, Robert A. Kumpf, Jonathan E. Forman, Alison McCurdy, and Dennis A. Dougherty*

Contribution No. 8807 from the Arnold and Mabel Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

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Abstract: We describe a large number of binding studies in aqueous media designed to provide new insights into noncovalent binding interactions, especially the cation-π interaction. The studies include 7 different hosts, over 70 guests, and over 150 new binding constants. In addition to the now standard NMR methods, circular dichroism has proven to be an especially useful tool for determining aqueous binding constants. We have found that, in addition to the alkyliminium and tetraalkylammonium guests we have studied previously, sulfonium and guanidinium guests also show substantial cation-π effects. Bromination of the host greatly enhances its binding ability in a general fashion, primarily as a result of hydrophobic interactions. Addition of methoxy groups did not enhance binding, apparently as a result of a collapse of the host into a conformation that is not suitable for binding. Replacement of two benzene rings of the host by furans or thiophenes also did not enhance binding. *Ab initio* calculations provide a rationalization for this effect and suggest a clearer model for the cation-π interaction.

Introduction

Significant advances in our understanding of noncovalent binding forces in water have been made using cyclophane-based, synthetic binding sites.[1–12] Work from several labs has docu-

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(1) Diederich, F. *Cyclophanes*; The Royal Society of Chemistry: Cambridge, UK, 1991.

(2) Odashima, K.; Itai, A.; Iitaka, Y.; Koga, K. *J. Am. Chem. Soc.* **1980**, *102*, 2504–2505. Soga, T.; Odashima, K.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 4351–4354. Odashima, K.; Spoga, T.; Koga, K. *Tetrahedron Lett.* **1981**, *22*, 5311–5314.

(3) Tabushi, E.; Sasaki, H.; Kuroda, Y. *J. Am. Chem. Soc.* **1976**, *98*, 5727–5728. Tabushi, E.; Kimura, Y.; Yamamura, K. *J. Am. Chem. Soc.* **1981**, *103*, 6486–6492. Tabushi, I.; Yamamura, K.; Nonoguchi, H.; Hirotsu, K.; Higuchi, T. *J. Am. Chem. Soc.* **1984**, *106*, 2621–2625.

(4) (a) Ferguson, S. B.; Seward, E. M.; Diederich, F.; Sanford, E. M.; Chou, A.; Inocencio-Szweda, P.; Knobler, C. B. *J. Org. Chem.* **1988**, *53*, 5593–5595. (b) Smithrud, D. B.; Sanford, E. M.; Chao, I.; Ferguson, S. B.; Carcanague, D. R.; Evanseck, J. D.; Houk, K. N.; Diederich, F. *Pure Appl. Chem.* **1990**, *62*, 2227–2236. (c) Smithrud, D. B.; Wyman, T. B.; Diederich, F. *J. Am. Chem. Soc.* **1991**, *113*, 5420–5426.

(5) Berscheid, R.; Lüer, I.; Seel, C.; Vögtle, F. In *Supramolecular Chemistry*; Balzzani, V., De Cola, L., Eds.; Kluwer Academic Publishers: The Netherlands, 1992; pp 71–86. Seel, C.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 442–444. Ebmeyer, F.; Vögtle, F. In *Bioorganic Chemistry Frontiers* Springer-Verlag: Berlin, 1990; Vol. 1, pp 145–158.

(6) Goodnow, T. T.; Reddington, M. V.; Stoddart, J. F.; Kaifer, A. E. *J. Am. Chem. Soc.* **1991**, *113*, 4335–4337. Bernardo, A. R.; Stoddart, J. F.; Kaifer, A. E. *J. Am. Chem. Soc.* **1992**, *114*, 10624–10631.

(7) Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 89–112. Dhaenens, M.; Lacombe, L.; Lehn, J.-M.; Vigneron, J.-P. *J. Chem. Soc., Chem. Commun.* **1984**, 1097–1099. Dhaenens, M.; Lehn, J.-M.; Fernandez, M.-J. *New J. Chem.* **1991**, *15*, 873–877.

(8) Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 3910–3915.

(9) Schneider, H.-J.; Schiestel, T.; Zimmermann, P. *J. Am. Chem. Soc.* **1992**, *114*, 7698–7703. Schneider, H.-J.; Güttes, D.; Scheider, U. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 647–649. Schneider, H.-J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1417–1436.

(10) Webb, T. H.; Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1991**, *113*, 8554–8555.

(11) Araki, K.; Shimizu, H.; Shinkai, S. *Chem. Lett.* **1993**, 205–208. Ikeda, A.; Shinkai, S. *Tetrahedron Lett.* **1992**, *33*, 7385–7388. Murakami, Y.; Kikuchi, J.; Ohno, T.; Hirayama, T. *Chem. Lett.* **1989**, 881–884. Shinmyozu, T.; Sakai, T.; Uno, E.; Inazu, T. *J. Org. Chem.* **1985**, *50*, 1959–1963. Hisaeda, Y.; Ihara, T.; Ohno, T.; Murakami, Y. *Tetrahedron Lett.* **1990**, *31*, 1027–1030. Murakami, Y.; Kikuchi, J.; Ohno, T.; Hirayama, T.; Hisaeda, Y.; Nishimura, H.; Snyder, J. P.; Steliou, K. *J. Am. Chem. Soc.* **1991**, *113*, 8229–8242.

mented and elucidated the hydrophobic effect, electrostatic forces, donor–acceptor interactions, solvent effects, and other important factors in molecular recognition. Along with these issues, we have been especially concerned with the cation-π interaction—the stabilizing force between a positive charge and the face of an aromatic ring.[14–16] We have shown that this interaction can produce novel binding selectivities in synthetic hosts, leading to high affinities even for guests that are quite water soluble.[20] Cation-π binding of transition states can lead to novel forms of catalysis.[21] We have also proposed[22] that the cation-π interaction

(12) In aqueous media, hydrogen bonding generally has not been effectively utilized in synthetic receptors (except see: Rotello, V. M.; Viani, E. Z.; Deslongchamps, G.; Murray, B. A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1993**, *115*, 797–798). It has been well utilized in organic media.[13]

(13) Nowick, J. S.; Ballester, P.; Ebmeyer, F.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 8902–8906. Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245–255. Rebek, J., Jr. *Science* **1987**, *235*, 1478–1484. Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369–370. Muehldorf, A. V.; Van Engen, D.; Warner, J. C.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 6561–6562. Yoon, S. S.; Still, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 823–824. Wang, X.; Erickson, S. D.; Iimori, T.; Still, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 4128–4137. Hong, J.-I.; Namgoong, S. K.; Bernardi, A.; Still, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 5111–5112.

(14) Sunner, J.; Nishizawa, K.; Kebarle, P. *J. Phys. Chem.* **1981**, *85*, 1814–1820. Taft, R. W.; Anvia, F.; Gal, J.-F.; Walsh, S.; Capon, M.; Holmes, M. C.; Hosn, K.; Oloumi, G.; Vasanwala, R.; Yazdani, S. *Pure Appl. Chem.* **1990**, *62*, 17–23.

(15) (a) Deakyne, C. A.; Meot-Ner (Mautner), M. *J. Am. Chem. Soc.* **1985**, *107*, 474–479. (b) Meot-Ner (Mautner), M.; Deakyne, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 469–474.

(16) Hydrogen bonding to aromatics[17,18] and the "amino-aromatic" interaction[19] are related manifestations of this phenomenon.

(17) (a) Perutz, M. F.; Fermi, G.; Abraham, D. J.; Poyart, C.; Bursaux, E. *J. Am. Chem. Soc.* **1986**, *108*, 1064–1078. (b) Levit, M.; Perutz, M. F. *J. Mol. Biol.* **1988**, *201*, 751–754.

(18) Suzuki, S.; Green, P. G.; Bumgarner, R. E.; Dasgupta, S.; Goddard, W. A., III; Blake, G. A. *Science* **1992**, *257*, 942–945.

(19) Burley, S. K.; Petsko, G. A. *FEBS Lett.* **1986**, *203*, 139–143. Burley, S. K.; Petsko, G. A. *Weakly Polar Interactions in Proteins*; Academic Press, Inc.: 1988; Vol. 39, pp 125–189.

(20) (a) Shepodd, T. J.; Petti, M. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1986**, *108*, 6085–6087. (b) Shepodd, T. J.; Petti, M. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 1983–1985. (c) Petti, M. A.; Shepodd, T. J.; Barrans, R. E., Jr.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825–6840. (d) Stauffer, D. A.; Dougherty, D. A. *Tetrahedron Lett.* **1988**, *29*, 6039–6042. (e) Stauffer, D. A.; Barrans, R. E., Jr.; Dougherty, D. A. *J. Org. Chem.* **1990**, *55*, 2762–2767.
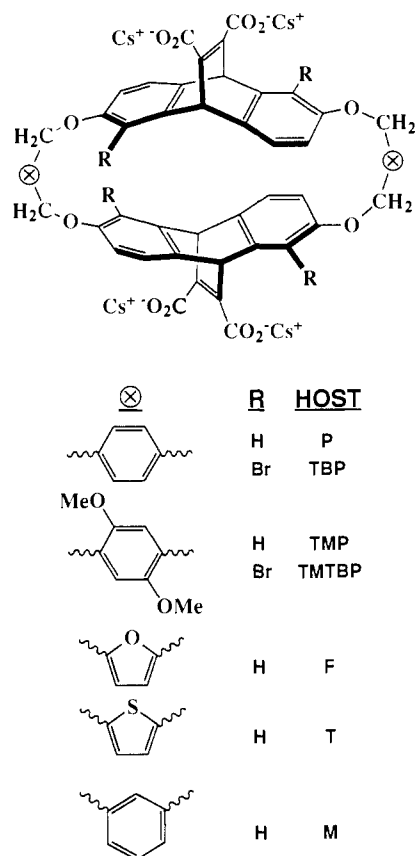
Figure 1. Definition of host structures. The structure shown is (*R,R,R,R*)-enantiomer when R = H, but it is the (*S,S,S,S*)-enantiomer when R = Br.

is important in a variety of biological receptors, especially those that bind the prototypical neurotransmitter acetylcholine (ACh). This proposal has received considerable recent support with regard to ACh binding[23] and also for binding of other neurotransmitters and agonists, both amine-based and peptide-based.[24]

In the present work, we report a number of new binding studies that provide further insights into the nature of the cation-π interaction. Computational studies on model systems have also been performed. Our prototypical, and most studied, host is P (Figure 1), so designated because *p*-xylyl groups serve to link the ethenoanthracene units which provide a concave, rigid, hydrophobic surface for binding. We have determined a large number of new binding constants to P, including several new classes of guests that substantially expand the range of cations participating. In addition, we have prepared several new hosts (Figure 1), introducing modifications to both the "linker" region (⊗) and the ethenoanthracene unit. We have also probed the impact of solvent modifications on binding. Taken in combination, the many studies described here provide a clearer picture of the cation-π interaction, along with useful general insights into aqueous molecular recognition.

Full details are given in the Experimental Section, but several technical issues should be mentioned here. NMR binding studies followed a now standard protocol. In all cases, host and guest concentrations were varied such that a broad range of percent-

bound values were covered. The EMUL/MULTIFIT package[25] was used throughout, as a recent, detailed analysis[25] revealed that this approach provides superior data fits under most circumstances. In addition, most data sets have gone through a rigorous statistical analysis that provides a meaningful estimate of the error bars for the ΔG° values reported. All host–guest combinations that have been reported previously[20] have been redetermined for the present work. Thus, all binding sets result from the same experimental protocol and have been through the same analysis. Unless explicitly noted otherwise, all NMR ΔG° values are accurate to ±0.2 kcal/mol (≥95% confidence limits). All hosts are enantiomerically pure.[26]

In several cases we have also used circular dichroism (CD) to determine binding constants. Full details of the methodology will be reported elsewhere.[28] In the present work we will describe selected CD results that are especially relevant to the discussion. In several cases, the same host-guest pair is evaluated by both NMR and CD, allowing an important double check of the methodologies. Also, the CD method operates in a lower concentration range, which is especially useful when binding constants are large or when the host is not very water soluble. As with the NMR methods, we estimate that CD determinations of ΔG° values are reliable to ±0.2 kcal/mol.

New Guests for Host P

Background. Our earlier studies[20] of P revealed a special avidity for two types of guests. The first class of potent guests (Charts I and II) is typified by *N*-methylquinolinium (**1**) and includes a wide variety of alkylated quinolines, isoquinolines, pyridines, and related structures. Such guests can produce very large binding constants to P. We shall refer to this class as iminium compounds, with the understanding that the positive charge results from alkylation, not protonation of a pyridine-type nitrogen.

The second class consists of tetraalkylammonium compounds such as ACh (**11**) and adamantyltrimethylammonium (**7**). The overall size and shape of **7** are especially well suited to the cavity of P, and it is the ideal tetraalkylammonium guest. Smaller tetraalkylammoniums such as ACh show smaller binding constants.

CPK models and computer modeling require two distinct binding conformations for P. One, the toroid form, is suited to binding the larger examples of the tetraalkylammonium class. The other binding conformation, the rhomboid form, binds the flat, iminium guests. A recent X-ray structure[29] of the tetramethyl ester of P reveals a rhomboid structure in near perfect agreement with earlier predictions. As described in detail elsewhere,[28] circular dichroism (CD) studies also provide strong support for this two-state model, as changes in the CD spectrum of P are noticeably different when binding large tetraalkylammonium vs iminium compounds.

Most of the guests we will describe are cations, and, of course, they are accompanied by counterions. However, our standard aqueous medium is a 10 mM borate buffer, and so whatever counterion is originally provided by the guest is overwhelmed by borate. Nevertheless, in order to address possible counterion effects, we have explicitly compared *N*-methylisoquinolinium (**2**)

(21) (a) McCurdy, A.; Jimenez, L.; Stauffer, D. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 10314–10321. (b) Stauffer, D. A.; Barrans, R. E., Jr.; Dougherty, D. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 915–918.

(22) Dougherty, D. A.; Stauffer, D. A. *Science* **1990**, *250*, 1558–1560.

(23) Sussman, J. L.; Harel, M.; Frolow, F.; Oefner, C.; Goldman, A.; Toker, L.; Silman, I. *Science* **1991**, *253*, 872–879. Changeux, J.-P.; Devillers-Thiéry, A.; Galzi, J.-L.; Bertrand, D. *TiPS* **1992**, *13*, 299–301.
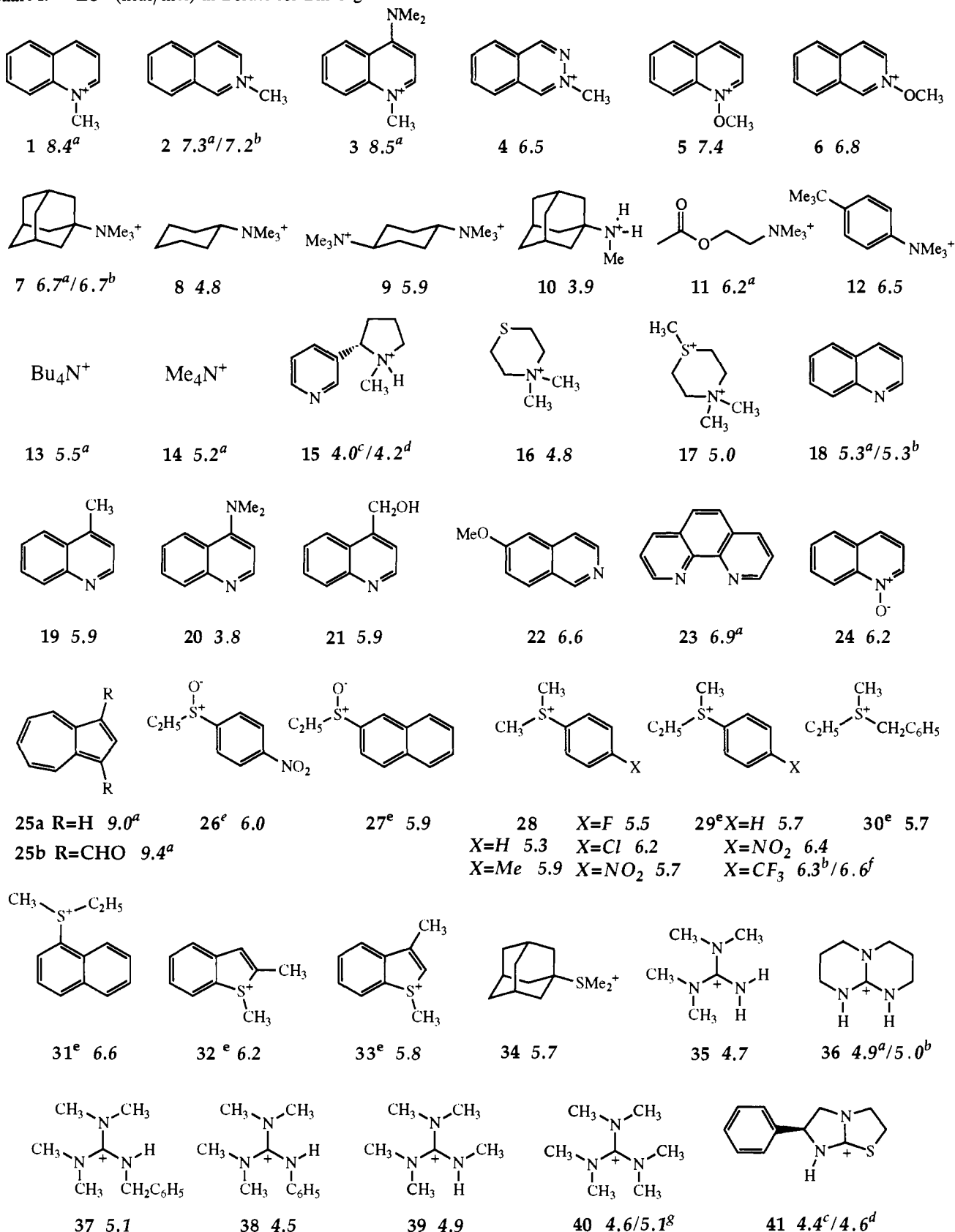
(24) Chaturvedi, V.; Donnelly-Roberts, D. L.; Lentz, T. L. *Biochemistry* **1992**, *31*, 1370–1375. le Du, M. H.; Marchot, P.; Bougis, P. E.; Fontecilla-Camps, J. C. *J. Biol. Chem.* **1992**, *267*, 22122–22130. Lentz, T. L. *Biochemistry* **1991**, *30*, 10949–10957. Trumpp-Kallmeyer, S.; Hoflack, J.; Bruinvels, A.; Hibert, M. *J. Med. Chem.* **1992**, *35*, 3448–3462.

(25) MULTIFIT differs from most fitting procedures in that chemical shift changes from *all* protons are considered together in a single least squares fit. This maximizes the ratio of observations to fit parameters, thereby producing an optimal fit. EMUL includes statistical weighting factors for each data point based on the expected error in the measurement. Full details are given in the following: Barrans, R. E., Jr. Ph.D. Thesis, California Institute of Technology, 1992. Barrans, R. E., Jr.; Dougherty, D. A manuscript in preparation.

(26) We have confirmed[28] the previous[20] assignment of the absolute configuration for host P using the excitonic chirality method of Nakanishi.[27]

(27) Harada, N.; Nakanishi, K. in *Circular Dichroic Spectroscopy: Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA; 1983.

(28) Forman, J. E.; Barrans, R. E., Jr.; Dougherty, D. A. Manuscript in preparation.

(29) Forman, J. E.; Marsh, R. E.; Schaefer, W. P.; Dougherty, D. A. *Acta Crystallogr. B.*, in press.
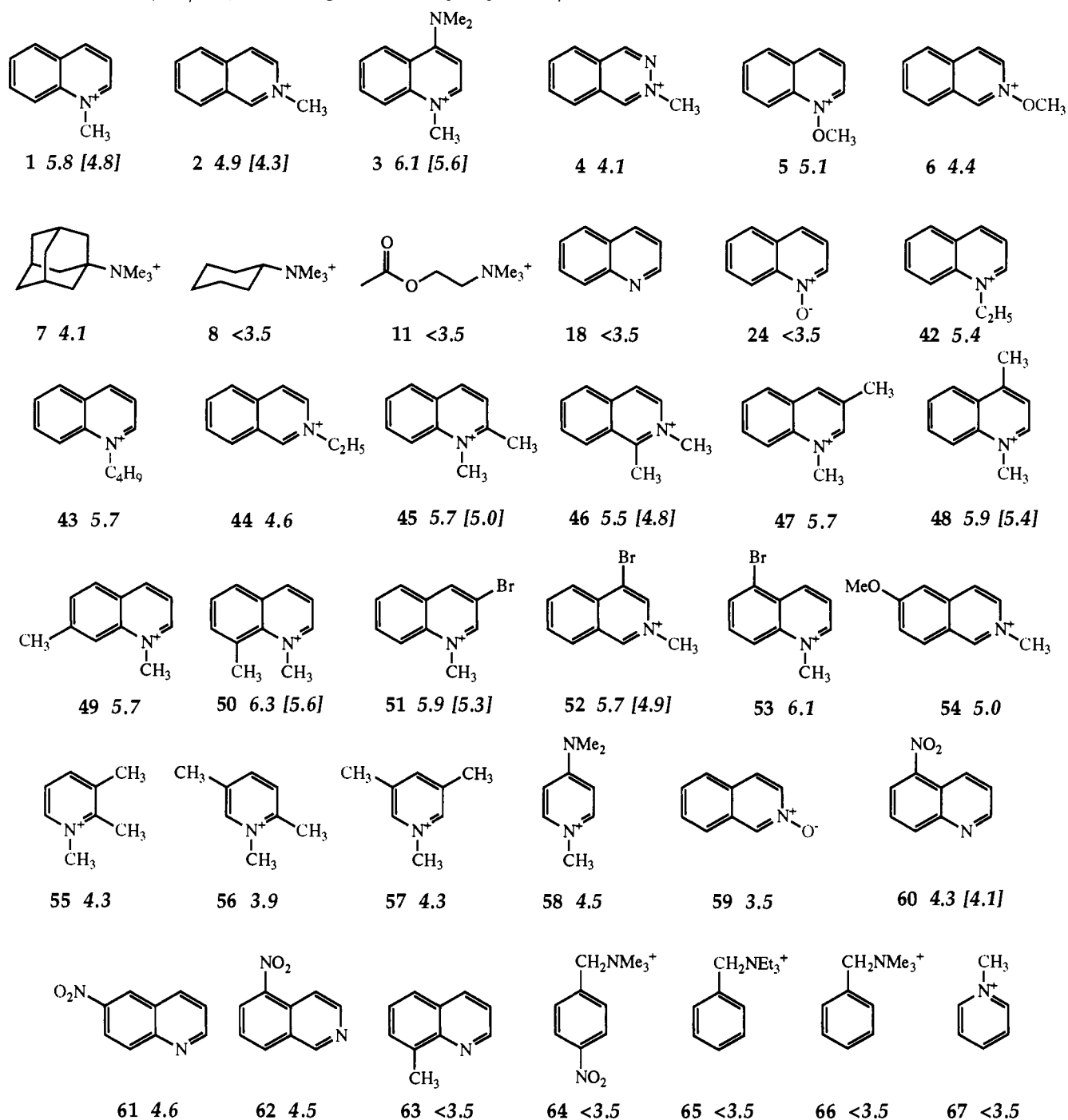
Chart I. $-\Delta G°$ (kcal/mol) in Borate for Binding to P[a]

1 8.4[a]   2 7.3[a]/7.2[b]   3 8.5[a]   4 6.5   5 7.4   6 6.8

7 6.7[a]/6.7[b]   8 4.8   9 5.9   10 3.9   11 6.2[a]   12 6.5

Bu$_4$N$^+$ Me$_4$N$^+$

13 5.5[a]   14 5.2[a]   15 4.0[c]/4.2[d]   16 4.8   17 5.0   18 5.3[a]/5.3[b]

19 5.9   20 3.8   21 5.9   22 6.6   23 6.9[a]   24 6.2

25a R=H 9.0[a]   26[e] 6.0   27[e] 5.9   28   X=F 5.5   29[e] X=H 5.7   30[e] 5.7
25b R=CHO 9.4[a]   X=H 5.3   X=Cl 6.2   X=NO$_2$ 6.4
                                            X=Me 5.9   X=NO$_2$ 5.7   X=CF$_3$ 6.3[b]/6.6[f]

31[e] 6.6   32[e] 6.2   33[e] 5.8   34 5.7   35 4.7   36 4.9[a]/5.0[b]

37 5.1   38 4.5   39 4.9   40 4.6/5.1[g]   41 4.4[c]/4.6[d]

[a] a. CD determination; b. ^{1}H NMR determination; c. R,R,R,R-host; d. S,S,S,S-host; e. Racemic guest, value less precise; f. ^{19}F NMR determination; g. Two values are for two enantiomers of guest.

iodide vs the chloride. In both borate buffer and buffer with 10% added acetonitrile (see below), the two give $-\Delta G°$ values that differ by only 0.1 kcal/mol, well within the error bars. We have also seen ionic strength effects that go in the expected direction. That is, increasing ionic strength makes the ionic guests more

water soluble and so diminishes binding constants. For example, changing from 10 mM borate buffer to a 25 mM phosphate buffer, causes the binding constant of **2** to drop by 1 kcal/mol.[21a]

Iminium Ions. It is clear that **1** is well matched to the steric and electronic characteristics of the binding site of P. In fact,

Chart II. $-\Delta G°$ (kcal/mol) for Binding to P in 10% [15%] MeCN/Borate

1 *5.8 [4.8]* 2 *4.9 [4.3]* 3 *6.1 [5.6]* 4 *4.1* 5 *5.1* 6 *4.4*

7 *4.1* 8 *<3.5* 11 *<3.5* 18 *<3.5* 24 *<3.5* 42 *5.4*

43 *5.7* 44 *4.6* 45 *5.7 [5.0]* 46 *5.5 [4.8]* 47 *5.7* 48 *5.9 [5.4]*

49 *5.7* 50 *6.3 [5.6]* 51 *5.9 [5.3]* 52 *5.7 [4.9]* 53 *6.1* 54 *5.0*

55 *4.3* 56 *3.9* 57 *4.3* 58 *4.5* 59 *3.5* 60 *4.3 [4.1]*

61 *4.6* 62 *4.5* 63 *<3.5* 64 *<3.5* 65 *<3.5* 66 *<3.5* 67 *<3.5*

we have recently established that our earlier determination[20] underestimated the affinity of P for **1**. With very large binding constants, one can obtain a proper variation of percent-bound only at concentrations that are typically too low for quantitative NMR studies. Using CD, which allows studies at lower concentrations, we have measured a $-\Delta G°_{298}$ of 8.4 kcal/mol ($K_a = 1.4 \times 10^6$ M^{-1}, $K_d = 700$ nM). Figure 2 shows **1** docked into P, with the host adopting the conformation seen in the X-ray structure.[29] The fit is excellent, and it is consistent with NMR shifts and computer modeling studies. With other iminium ions, good agreement between CD and NMR values of $-\Delta G°$ are seen. In the systems we study, NMR methods become unreliable if $-\Delta G° \geq 8$ kcal/mol. The CD method seems best suited to 4.0 $\leq -\Delta G° \leq 10.5$ kcal/mol.[30]

Perhaps the best quantitative estimate of the cation-π effect comes from the matched pair **1/19**. These two structures are

almost identical in size, shape, and hydrophobic surface area, yet the cation is more tightly bound by 2.5 kcal/mol. This is almost certainly a lower limit, since there should be a greater penalty for the desolvation that occurs on binding the cation **1** vs the neutral **19**. Indeed, relative aqueous solvation energies calculated using Monte Carlo simulations and statistical perturbation theory,[31] indicate that **1** is *much* better solvated than **19** (Figure 3).

In all solvents **2** is a poorer guest than **1**. The preference for substituents in the "α" vs the "β" position is evident in several other comparisons, such as **5/6**, **42/44**, and **50/49** (see, however, **60/61**). We ascribe this to an adverse steric interaction that arises with substituents in the β position. For the sterically

(30) For guests with strong UV absorbances, the CD method becomes unreliable if $-\Delta G° \leq 5.5$ kcal/mol.

(31) (a) Zwanzig, R. W. *J. Chem. Phys.* **1954**, *22*, 1420–1426. (b) Beveridge, D. L.; DiCapua, F. M. *Ann. Rev. Biophys. Biophys. Chem.* **1989**, *18*, 431–492. (c) Jorgensen, W. L.; Blake, J. F.; Buckner, J. K. *Chem. Phys.* **1989**, *129*, 193–200. (d) Jorgensen, W. L. *Acc. Chem. Res.* **1989**, *22*, 184–189.
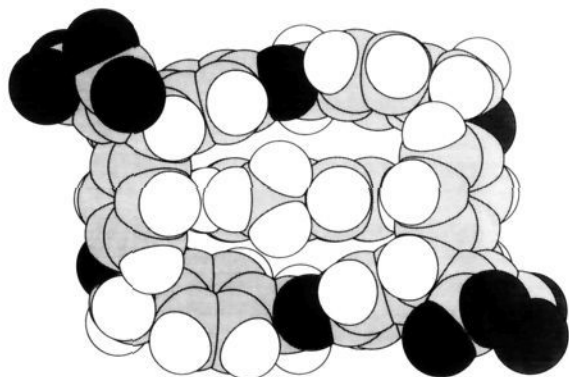
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Figure 2. Host P in the conformation found in the crystal structure of the tetraester[29] with guest **1** docked into a viable binding position.
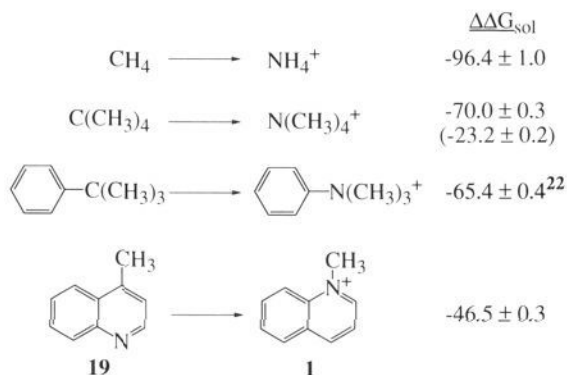
$\Delta\Delta G_{sol}$

$$CH_4 \longrightarrow NH_4^+ \qquad -96.4 \pm 1.0$$

$$C(CH_3)_4 \longrightarrow N(CH_3)_4^+ \qquad \begin{array}{c} -70.0 \pm 0.3 \\ (-23.2 \pm 0.2) \end{array}$$

 $\longrightarrow$ -65.4 ± 0.4^{22}

 $\longrightarrow$ -46.5 ± 0.3

      19   **1**

Figure 3. Calculated relative aqueous (chloroform) solvation energies (kcal/mol) for cations and analogous neutrals.

(a)

(b)

(c)

Figure 4. (a) NMR resonances of hexamethylguanidinium (**40**) when binding to host P. [Guest]$_0$ = 0.16 mM; [Host]$_0$ = 0.24 mM in borate buffer. The peak at 2.19 ppm (3,3-dimethylglutarate, internal standard) is truncated for clarity. (b) Equilibrium relationships between the *enantiomers of* **40** (G_A *and* G_B) *and their complexes with* P (HG_A *and* HG_B). (c) Space-filling models of the two enantiomers of **40**.

equivalent guests **45** and **46**, very similar binding constants are seen. Not surprisingly, hydrophobic substituents on the guest such as Br or CH$_3$ generally enhance binding. Smaller guests such as pyridine and lutidine derivatives are less well bound, further highlighting the almost perfect fit of quinolinium-type guests.

Tetraalkylammonium Guests. Structure **7** remains as the optimal quaternary ammonium guest for P, and the CD binding constant agrees well with the NMR value. Solvent effects are noticeable, such that tetraalkylammoniums that bind well in borate often do not appreciably bind when 10% acetonitrile is added. As has been seen earlier,[20] protonated amines are less well bound than fully alkylated amines (**7** vs **10**). Protonated amines are much more water soluble than tetraalkylammoniums, due at least in part to hydrogen bonding, and this should reduce the binding affinity. This is borne out by the data in Figure 3, which show that, relative to a reference hydrocarbon, a protonated amine is much better solvated than a tetraalkylammonium. An alternative way of expressing this is to note that the aqueous solvation energy of NH$_4^+$ is approximately 30 kcal/mol larger than that of NMe$_4^+$.[32] In host P, the cation-π interaction cannot overcome the desolvation penalty for protonated amines, but there are many examples in biological systems where protonated amines show significant cation-π interactions.[24]

Neutral Guests. Simple neutral guests such as quinoline (**18**) are invariably less well bound than analogous iminium ions. Hydrophobic effects are evident in the enhanced binding of **19** and **23**. Nitro-substituted guests, generally, are very well bound. We have seen this effect previously,[20] and we believe it results from favorable donor–acceptor interactions between the electron-rich host and the electron-poor guest. A cation-π interaction with the formal positive charge on the N of the NO$_2$ is also possible.

N-Oxides are better bound than the analogous imines, which is consistent with the notion of a partial positive charge at nitrogen
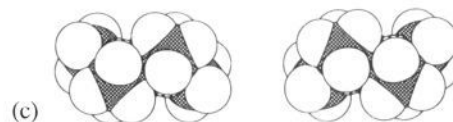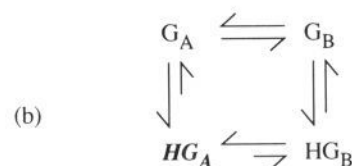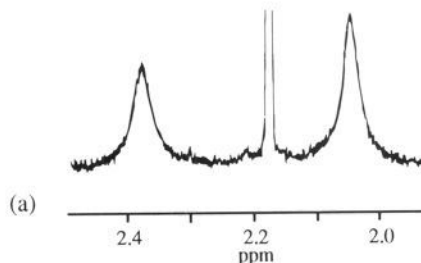
allowing a cation-π interaction. However, *N*-methyliminiums are better still, presumably due to a combination of effects including greater charge at N in the iminiums, and, in the *N*-oxides, unfavorable electrostatic interactions with the O$^-$, and favorable solvation of the O$^-$.

The most strongly bound neutral guests are the azulenes **25**, with binding constants in borate that are very large (for **25b**, K_d $\approx$ 100 nM). Binding constants in this range can only be probed by the CD method. It is tempting to ascribe the strong binding of these guests to a cation-π interaction, in which the "cation" is the seven-membered ring of the azulene. One must also note a strong hydrophobic effect, however, as these guests are relatively insoluble in water.

Sulfonium Guests. The cation-π effect is quite evident in binding sulfonium ions, which are invariably better bound than analogous sulfides.[21a] The analogue to **7**, adamantyldimethyl-sulfonium (**34**), is strongly bound. NMR shift patterns are essentially identical to those seen for **7**,[20a] indicating a similar binding geometry. The sulfonium compounds provide further examples of the various trends indicated above. Binding is improved by adding a methyl group (EtMeArS$^+$ > Me$_2$ArS$^+$); a naphthyl structure is better bound than the phenyl analogue (hydrophobic effect); and electron-withdrawing groups such as NO$_2$ and CF$_3$ enhance binding.

Guanidinium Guests. Another new class of cationic guests that we have studied are the guanidinium ions **35–41**. These flat, delocalized cations would seem to be especially well-suited to the rhomboid form of host P. In general, we find that some alkylation is necessary to achieve significant binding. Thus, arginine is not measurably bound in our aqueous buffer. However, tetramethylguanidinium (**35**) and related structures are well bound, considering that they are small, highly water-soluble guests. We assume that, as with the alkylated vs protonated amines, it is the high water solubility of structures such as arginine that limit their binding.

An especially interesting structure is hexamethylguanidinium (**40**). As shown in Figure 4, the ¹H NMR singlet that this structure displays is split into two singlets of *unequal* intensity on binding. The scheme of Figure 4 explains this observation, which is made

(32) Rao, B. G.; Singh, U. C. *J. Am. Chem. Soc.* **1989**, *111*, 3125–3133.

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possible by a fortuitous balance of rate constants. X-ray crystallography has shown that hexamethylguanidinium adopts a propeller-like, D_3-symmetric, twisted form, which is, of course, chiral (Figure 4).[33] Molecular models and computer modeling also indicate that hexamethylguanidinium is not planar.[34] Based on a number of studies of rotation barriers in **38** and related structures, one expects a barrier to rotation, and thus racemization, in the 14–16 kcal/mol range.[35] One would thus expect that at room temperature an equilibrium between the two enantiomers is readily established. However, racemization rates are slow on the NMR time scale, allowing one to see separate resonances for the two enantiomers in an appropriate chiral environment. Host P, acting as a chiral shift reagent, provides the chiral environment and produces two NMR signals. However, P is more than a chiral shift reagent, in that it binds one enantiomer of the guest significantly more tightly than the other. As shown in Figure 4, this shifts the equilibrium away from a 50:50 mixture of enantiomers and thus produces singlets of unequal intensity. Analysis of the data indicates that host P prefers one enantiomer over the other by ca. 500 cal/mol, but we are at present unable to determine which is the preferred enantiomer.

Calculations indicate that the extent of twisting in hexamethylguanidinium is near 30°. As shown in Figure 4, the steric differences between the two enantiomers are quite subtle. We consider it remarkable that P is able to differentiate between these structures. Host P, which has C_2 symmetry in the rhomboid form is also twisted in a sense, and perhaps it is this feature that allows it to sense the subtle twist in hexamethylguanidinium.

New Hosts

We have synthesized a number of new host structures that can be viewed as derivatives of P. Our focus has been to modify the electronic structure of P, with a primary goal of enhancing the cation-π interaction. In several instances, changes in binding patterns were not in the direction we anticipated. New insights into the specific nature of our host systems and the general nature of the cation-π interaction have been acquired.

Solvent Effects. Some new hosts were more prone to aggregate in borate than host P, and so many binding studies were performed in mixed solvent systems, containing 10% or 15% by volume acetonitrile in borate. We have been able to assess the impact of such solvent changes through extensive studies on host P.

For host P we have made eight comparisons (including the chloride and iodide salts of **2**) of $\Delta G°$ values determined for cationic guests in both borate and 10% acetonitrile. There is good consistency in comparing the two solvents. In borate, $-\Delta G°$ is larger by an average of 2.49 kcal/mol with a standard deviation of 0.19 kcal/mol. Thus, we can compare borate and 10% acetonitrile numbers by simply adding 2.5 kcal/mol to $-\Delta G°$ for the acetonitrile system.

A total of nine comparisons between affinities determined in 10% and 15% acetonitrile are available for host P with cationic guests. On average the 10% number is larger by 0.68 kcal/mol, with a standard deviation of 0.16 kcal/mol. Again, the effect is consistent enough to allow meaningful comparisons for binding values determined in different solvents.

The general effect of added acetonitrile is as expected. There is a significant hydrophobic component to all the binding seen here, and so adding an organic solvent would be expected to lower the binding constant. Diederich has established an excellent linear correlation between hydrophobic binding and solvent E_T-(30) values.[4b] Over the limited range of $E_T(30)$ values probed

(33) Boese, R.; Bläser, D.; Petz, W. *Z. Naturforsch.* **1988**, *43b*, 945–948.

(34) We have calculated the AM1 structure of **40** and found that it agrees very well with the X-ray structure.[33] Gobbi, A.; Frenking, G. *J. Am. Chem. Soc.* **1993**, *115*, 2362–2372.

(35) Kessler, H.; Leibfritz, D. *Tetrahedron Lett.* **1969**, *6*, 427–430. Kessler, H.; Leibfritz, D. *Chem. Ber.* **1971**, *104*, 2158–2169. Sapse, A. M.; Snyder, G.; Santoro, A. V. *J. Phys. Chem.* **1981**, *85*, 662–665. Rabiller, C.; Ricolleau, G.; Martin, M. L.; Martin, G. J. *Nouv. J. Chim.* **1980**, *4*, 35–42. Santoro, A. V.; Mickevicius, G. *J. Org. Chem.* **1979**, *44*, 117–120.

Table I. Effect of Methoxy Groups on Binding[a]

guest	TMP		P		TMTBP
	borate	10% MeCN	borate	10% MeCN	10% MeCN
1	6.5	5.3	8.4	5.8	6.5
2	5.7	4.5	7.2	4.9	5.7
7	6.0	4.0	6.7	4.1	<3.5
18	4.2	<3.5	5.3	<3.5	5.0
43	6.6			5.7	
45		5.0		5.7	6.6
46		5.3		5.5	6.3

[a] $-\Delta G°$ (kcal/mol).

here,[36] our system appears to be more sensitive to solvent polarity than Diederich's.

Tetramethoxy Host (TMP). Introduction of methoxy groups onto the linker *p*-xylylene units to make TMP (Figure 1) was intended to "improve" P in several ways. The cavity is deeper and, presumably, more electron-rich, which could enhance the cation-π interaction. In addition, it had been shown[4a] that methoxy groups increase the critical aggregation concentration (CAC) of cyclophane hosts, which would be advantageous. The host was synthesized in a manner analogous to P,[20] coupling enantiomerically pure ethenoanthracene diphenol **68** to dibromide **69**. The host did indeed prove to be resistant to aggregation in borate.

68

69
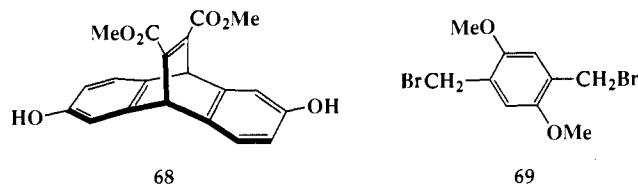
As shown in Table I, however, host TMP proved to be a universally poorer host than P. For several comparisons in borate, the difference between P and TMP is in the 1.0–1.5 kcal/mol range—a quite sizable effect. The difference is substantially reduced in 10% acetonitrile. The solvent effect can be stated another way. For three available comparisons, the differences in $-\Delta G°$ between borate and 10% acetonitrile average less than 1.5 kcal/mol for TMP. This is roughly half the increment consistently seen with P (see above), suggesting a special solvent effect with TMP.

To rationalize the poor performance of TMP, we invoke a collapsed conformation for the *unbound* host, in which the linker groups are rotated so as to position two methoxy groups in the binding cavity. Essentially, the molecule binds itself. Binding a guest then requires the unfavorable removal of the methoxy groups from the cavity, and $-\Delta G°$ is diminished accordingly. Support for this analysis comes from NMR data. The O-CH$_3$ and aryl-H resonances of the linker unit of TMP are significantly shifted upfield in water vs chloroform (host tetramethyl ester). No other resonances in TMP or P show a similar effect. This is consistent with the model, in that the methoxy groups should shift upfield like typical guest protons if they are placed inside the cavity. Also, the host collapse should be less pronounced in the more organic solvents, and so the effect is only seen in a fully aqueous environment. Further support for this model is obtained by comparing TMP to its brominated analogue, discussed below.

Tetrabromo Host (TBP). We have also modified the ethenoanthracene units of host P. As shown in Figure 5, 1,5-dibromo-2,6-dihydroxyanthracene (**70**) can be elaborated to the enantiomerically pure ethenoanthracene **74**. This compound was then used to synthesize the tetrabromo host TBP. The four bromine atoms of this host provide a deeper, less flexible cavity. We also expected that these highly polarizable halogen atoms would

(36) Solvent polarity parameters for mixed water/acetonitrile systems have been determined. Krygowski, T. M.; Wrona, P. K.; Zielkowska, U.; Reichardt, C. *Tetrahedron* **1985**, *41*, 4519–4527.
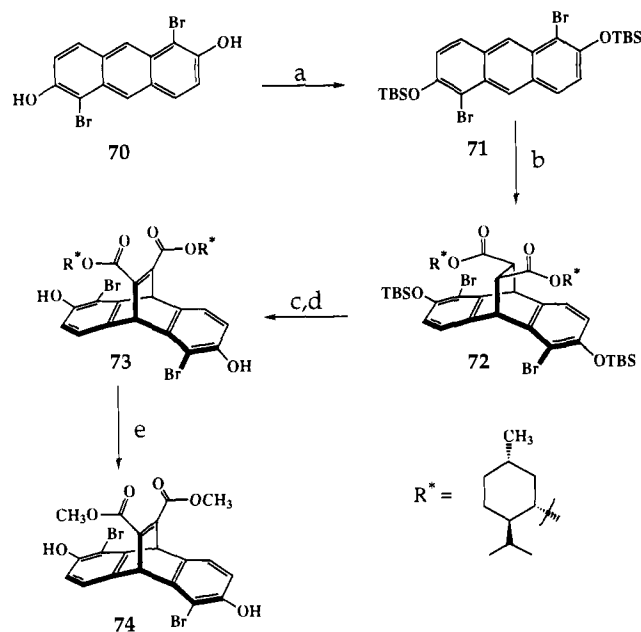
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Figure 5. Synthetic approach to dibromoethenoanthracene **74**. (a) TBS chloride, triethylamine, DMF; (b) (+)-dimenthylfumarate, Et$_2$AlCl, toluene; (c) PhSeSePh, KOt-Bu, toluene; (d) HCl (saturated aqueous), iPrOH; (e) MeSO$_3$H, MeOH.

Table II. Effect of Bromination on Binding[a]

	TBP		P	
guest	10% MeCN	15% MeCN	10% MeCN	15% MeCN
1		5.7	5.8	4.8
2	5.7	5.0	4.9	4.3
3		6.9	6.1	5.6
4	4.7		4.1	
5	5.8		5.1	
6	5.1		4.4	
7	3.8		4.1	
8	<3.5		<3.5	
11	<3.5		<3.5	
18	3.8		<3.5	
19	5.0			
24	4.4		<3.5	
33	6.0			
42	5.8		5.4	
44	5.2		4.6	
45		5.9	5.7	5.0
46	6.5	5.9	5.5	4.8
48		6.5	5.9	5.4
50		6.7	6.3	5.6
51		6.0	5.9	5.3
52	6.0	5.9	5.7	4.9
54	4.8		5.0	
59	4.0		3.5	
60	6.1	5.8	4.3	4.1
61	5.4		4.6	
62	5.9		4.5	
63	4.6		<3.5	

[a] $-\Delta G°$ (kcal/mol).

supplement the aromatic recognition elements of the basic host structure, leading to altered guest specificities.

Host TBP showed a greater tendency toward aggregation in our aqueous buffer system. As such, the binding affinities of guest molecules for TBP in borate buffer could be obtained only via CD measurements, using 1–2 μM concentrations of host. The free energies of binding ($-\Delta G°$) of four molecules were determined via this method [guest ($-\Delta G°$, kcal/mol)]: **1** (9.3), **2** (8.8), **7** (7.8), and **18** (8.1). These are very strong interactions, with K_d for the TBP/**1** pair being 130 nM. All binding affinities have increased relative to host P, but the selectivity of the cavity for charged compounds (**1**, **2**, and **7**) versus the neutral quinoline (**18**) has been reduced significantly.

The properties of the TBP receptor were further elucidated via NMR titration studies in mixed acetonitrile/borate solutions. Most compounds were studied in 10% acetonitrile solutions. In this medium however, studies of TBP with N-methylquinolinium compounds produced poorly fitting data. Satisfactory results were obtained when these compounds were studied in 15% acetonitrile solutions. A number of isoquinolinium compounds were also studied in this medium, partially to serve as references to allow comparison with the 10% acetonitrile data. The results of these studies are reported in Table II.

Upon moving from borate to 10% acetonitrile solutions, the stabilities of all host–guest complexes decrease. It is noteworthy however, that the more hydrophobic guests (**7** and **18**) experience a greater decrease in binding energy (4.0 and 4.3 kcal/mol, respectively) upon complexation with TBP than the more hydrophilic isoquinolinium guest **2** (3.1 kcal/mol). These same guest molecules, when complexed with host P, undergo a more modest and more uniform decrease in binding affinity of about 2.5 kcal/mol on moving from borate to 10% acetonitrile, as described previously.

Remarkably, the enhanced affinity of the brominated receptor for neutral compounds is still clearly demonstrated in 10% acetonitrile. Some structures that are not measurably bound by P in this solvent system are substantially bound by TBP. The effect seems quite pronounced with the nitroaromatic structures, where $\Delta\Delta G$ values (P vs TBP) as high as 1.8 kcal/mol are seen.

These observations taken together implicate nonspecific, hydrophobic interactions with the bromine atoms as largely responsible for the increased binding affinities of host TBP, relative

to host P. Additional support for this argument is provided by the results of our studies using 15% acetonitrile (Table II). Across the series of quinolinium and isoquinolinium compounds, the increase in binding affinity upon brominating the host is fairly uniform, suggestive of nonspecific interactions. Also noteworthy within this series are the data obtained for the isostructural guest molecules **45** and **46**. These guests have the same binding constants, despite very different charge distributions. Similar results are obtained for the structurally similar but electronically different guest pairs (**5** and **42**) and (**6** and **44**).

Given the large binding constants we have seen for TBP, we considered the possibility that it might produce strong binding in a purely organic solvent. As such, we performed a quick survey of several guests in CDCl$_3$, binding to the tetramethyl ester of TBP. The results were [guest ($-\Delta G°$, kcal/mol)] **1** (4.1), **2** (4.3), **18** ($\sim$0), **45** (3.8), **46** (3.7), **47** (3.6), and **52** (4.4). As we have discussed elsewhere,[20d] such substantial binding constants obtained in the absence of hydrophobic effects and any possible electrostatic contribution from the host carboxylates provide some of the most compelling evidence for the operation of cation-π interactions.

Tetramethoxytetrabromo Host (TMTBP). We have combined the modifications of TMP and TBP to produce TMTBP. This host is more water soluble than TBP but not so much so that borate was a viable solvent for NMR binding studies. Compared to the methoxy host TMP, addition of bromines greatly enhances binding (Table I). In addition to the previously described bromine effect, we believe a conformational effect is also operative here. Modeling suggests that the bromines inhibit the conformational collapse seen in TMP and so enhance the binding. NMR data are consistent with this analysis.

Overall, TMTBP is comparable to TBP, and so significantly superior to P. Thus, addition of bromines to TMP fully compensates for the adverse effects of the methoxys and produces a host comparable to TBP. Conversely, adding methoxy groups to TBP generally produces only small changes in binding. The one exception is the neutral guest **18**, for which TMTBP is a significantly better host than TBP.

Furan (F) and Thiophene (T) Hosts. In another effort to enhance the cation-π interaction, we have replaced the 1,4-phenylene groups of the linker region of P by 2,5-furan and 2,5-

Table III. Effect of Heterocyclic Linkers[c]

guest	F	T	P	M
1	5.2[a]	5.1	5.8	5.2
2	5.1	4.9	4.9	4.8
7	3.7	4.0	4.1	<3.5
8	3.7	<3.5	<3.5	<3.5
55	4.5	4.3	4.3	4.4[a]
56	4.6	4.3	3.9	4.5
57	4.6	4.2	4.3	4.3
58	4.6	4.6	4.5	4.6
64	4.1	<3.5	<3.5	<3.5
65	3.5	<3.5	<3.5	<3.5
66	3.9[b]	<3.5	<3.5	<3.5
67	3.7	<3.5	<3.5	<3.5

^{a} ±0.3 kcal/mol. ^{b} ±0.4 kcal/mol. ^{c} $-\Delta G°$ (kcal/mol; in 10% MeCN).

thiophene, to produce hosts F and T, respectively (Figure 1). Classically, furan and thiophene are considered to be electron-rich π systems,[37] and we hoped they would produce an enhanced cation-π interaction. Syntheses of enantiomerically pure F and T were conceptually straightforward, using the bis(chloromethyl) heterocycles **75** and **76** in the macrocyclization. Although F is quite soluble in our borate buffer system, binding studies in this medium gave very poor fits with our statistical analysis package. In our experience, this often indicates some kind of aggregation phenomenon. Host T appeared to be more prone to aggregate than F or P. As such, all studies on F and T were performed in the 10% acetonitrile mixed solvent system, which completely suppresses such behavior.
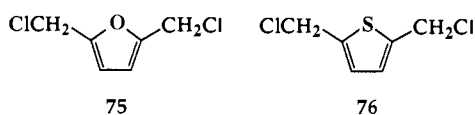

75   76

Table III presents a number of binding constants for F and T, and we will provide an overview of the data here. Certainly, there are no dramatic enhancements of binding upon introduction of the heterocyclic rings. There are some hints of F being a better host than P for some of the guests, but most fall within the ±0.2 kcal/mol error bars. We considered the possibility that the *m*-phenylene host M was the better hydrocarbon reference for F and T, in terms of both size and flexibility of the linker. NMR shift patterns of guests bound to F do in fact resemble those of guests bound to M rather than those of guests bound to P. For host T, guest shift patterns suggest a similarity to M for iminium guests, but a similarity to P for tetraalkylammonium guests. In the mixed solvent, however, the differences in binding affinities between P and M are small, and so no clear trends emerge. Certainly these results are contrary to our initial expectations. As described below, computational studies do provide some insights into the origin of the binding trends we see.

Computational Studies. We have performed a number of high quality computational studies of cation-π interactions in hopes of gaining some insights into the binding results we have seen. First, to evaluate the differences between P, F, and T, we have studied the gas-phase binding of NH_4^+ to benzene, furan, and thiophene. The calculations involve geometry optimization at the HF-6-31G** level, followed by single point energy evaluation at the MP2 level to account for correlation effects.[38] This level of theory provides results for benzene$\cdots NH_4^+$ complexes that are in good agreement with both experiment and previous calculations.[15]

(37) (a) Paudler, W. W.; Jovanovic, M. V. *Org. Magn. Reson.* **1982**, *19*, 192–195. (b) Speranza, M. In *Advances in Heterocyclic Chemistry*; Academic Press, Inc.: 1986, Vol. 40, pp 25–104.
(38) The binding energies calculated are strictly ΔE values but may be reasonably compared to ΔH values. Assuming $\Delta S°$ contributions to binding are relatively constant for closely related host/guest pairs, trends in $-\Delta G°$ values can be directly related to the calculations.

Table IV. Calculated[a] Relative Binding Energies[b] for the 1:1 π-Complexes of Benzene, Thiophene, Furan, and Pyridine with Ammonium or Sodium Cations

complex	ΔE	ΔE_{MP2}	$\Delta E_{lit.}$[c,d]
Ia	−15.1	−17.9	−16.3
IIa	−12.7	−15.2	
IIIa	−12.2	−15.3	
Ib	−15.1	−17.9	
IIb	−13.4	−16.6	
IIIb	−11.8	−14.7	
Ic	−13.9	−16.9	−15.2
IIc	−12.2	−15.7	
IIIc	−11.0	−14.0	
Id	−13.9	−16.9	
IId	−12.1	−15.6	
IIId	−10.9	−13.9	
Ie	−13.9	−16.2	−14.7
IIe	−12.5	−14.6	
IIIe	−11.8	−14.4	
If	−13.9	−16.2	
IIf	−11.4	−13.9	
IIIf	−10.6	−13.0	
$C_6H_6\cdots Na^+$	−27.1		
$C_4H_4S\cdots Na^+$	−22.8		
$C_4H_4O\cdots Na^+$	−20.6		
$C_5H_5N\cdots Na^+$	−20.0		

^{a} 6-31G**//6-31G**. ^{b} In kcal/mol. ^{c} 3-21G//STO-3G. ^{d} Reference 15a.

These are all gas-phase calculations. We have shown elsewhere[39] that inclusion of aqueous solvation can have large effects when considering the interactions of different cations with the same aromatic species. This is because cation desolvation energies are large and vary considerably with cation structure. However, in comparisons among P, F, and T, the cation is kept constant and, to a good approximation, the extent of ion desolvation on binding should be similar across the series of hosts. There will be some differences in the energetics of desolvation of the hosts across the series, but we expect this effect to be small. As such, the gas-phase calculations should provide useful information for comparing the various hosts.

As seen in Table IV, NH_4^+ shows a substantial binding preference for *benzene* over thiophene and furan in all calculated binding orientations (Figure 6). Thiophene is generally superior to furan. Typically, the structures with two hydrogens pointing down toward the aromatic are preferred over those with three or one, although such geometrical preferences are not generally strong. This observation is in agreement with previous calculations reported for benzene$\cdots NH_4^+$ complexes.[15]

These results would seem to provide some rationalization for the lack of improvement on converting P (or M) to F or T. As discussed in detail elsewhere,[39] we believe the dominant component of the cation-π interaction is electrostatic. That is, benzene behaves very much like a weak anion in these systems. As such, we have investigated the electrostatic potentials of the aromatic rings. Figure 7 shows pictorially what we have found. The electronegative O and, to a lesser extent, S alter the electrostatic potential by introducing electropositive character to the regions adjacent to the heteroatoms. These pictures do suggest that benzene should bind more strongly to a simple cation.

This analysis reveals the flaw in our initial reasoning in choosing furan and thiophene. Generally, these compounds are considered electron-rich in their *reactivity*, for example, in a Friedel-Crafts reaction.[37b] This reflects, of course, transition-state stabilization, in which the heteroatom lone pairs can stabilize a developing positive charge. However, the cation-π interaction is a much more nearly ground-state effect. The π system is only slightly distorted on binding, and so, to a good approximation, the ground-state wave function of the π system is more relevant. Given this, it can be understood why benzene is better than furan or thiophene.

We have also seen similar trends when Na^+ is used in place of NH_4^+, which makes the calculations much simpler. Again,

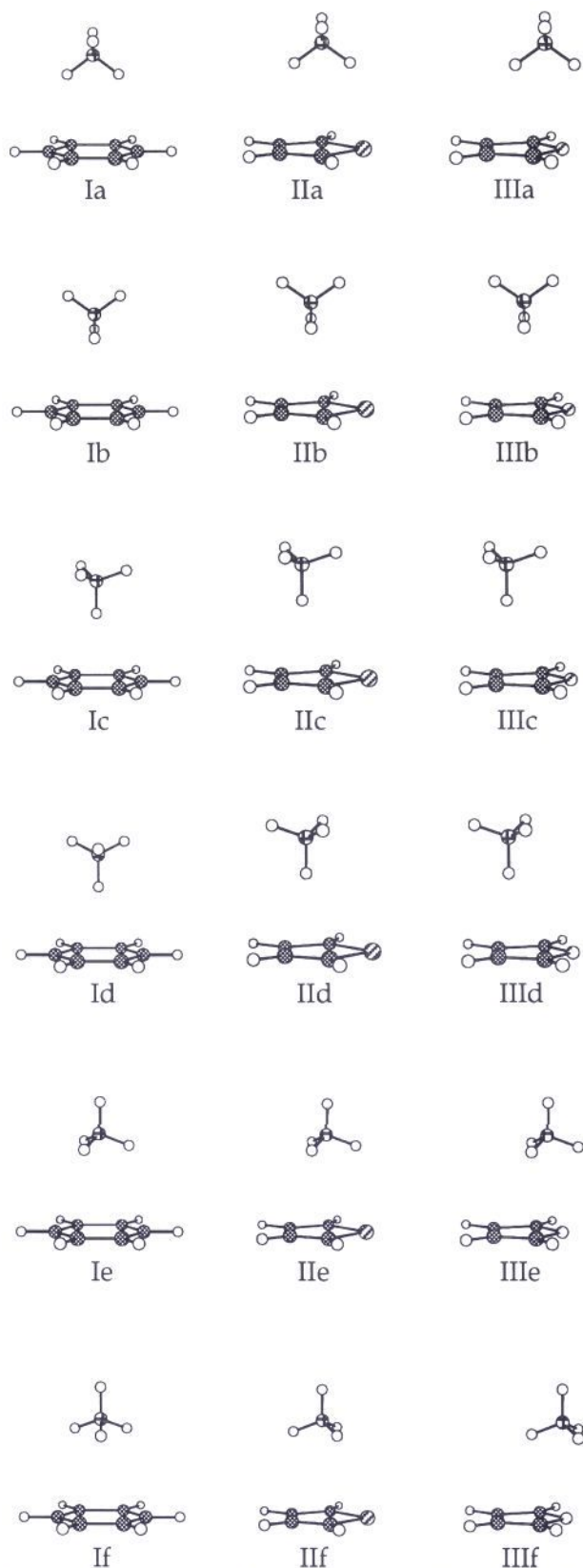(39) Kumpf, R. A.; Dougherty, D. A. *Science* **1993**, *261*, 1708.

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Figure 6. Optimized 1:1 complexes of ammonium with benzene (**Ia–If**), thiophene (**IIa–IIf**), and furan (**IIIa–IIIf**).
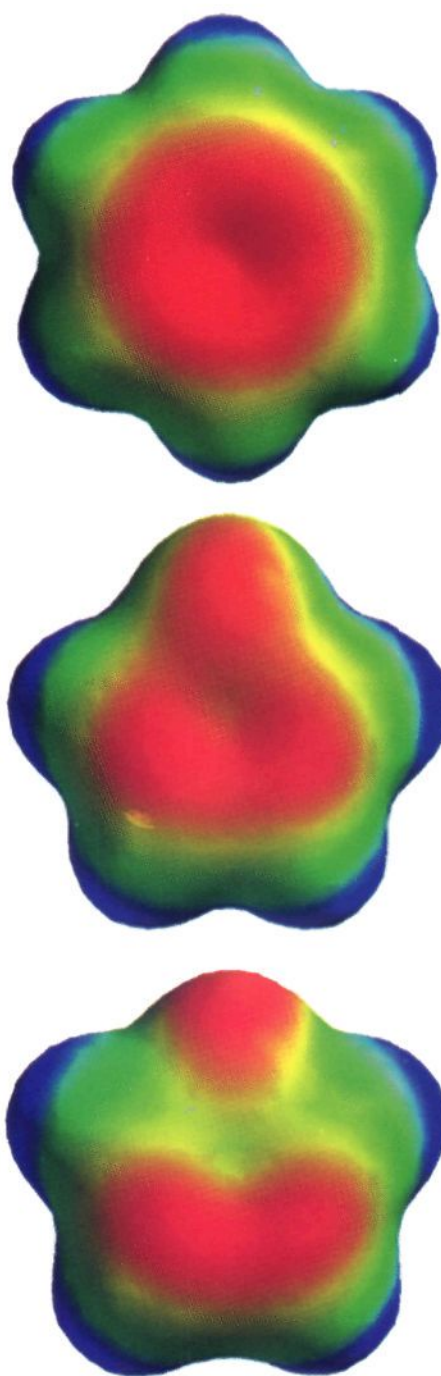

Figure 7. Calculated 6-31G**//6-31G** electrostatic potential surfaces for benzene (top), thiophene (middle), and furan (bottom). Electrostatic potential surface values range from −20.0 (red) to +20.0 (blue) kcal/mol.

the sequence is benzene > thiophene > furan for the cation-π interaction (Table IV). As expected, based on this model, pyridine is also a weaker cation binder than benzene. With Na^+, we have also probed the competition between cation-π binding and interaction with the heteroatom lone pairs. As shown in Figure 8, the $Na^+ \cdots$furan interaction is almost completely insensitive to

orientation, with all structures the same within ±10% of $-\Delta E$. For $Na^+ \cdots$thiophene, the cation-π interaction is clearly preferred over interaction with the sulfur lone pairs, while for $Na^+ \cdots$pyridine, complexation to N is preferred over the π system.

Conclusions

The studies described here provide a number of new insights into molecular recognition in aqueous media in general and the cation-π interaction in particular. New classes of cationic guests demonstrate the broad scope of the cation-π interaction. Sulfonium compounds are all well bound, and the essentially identical
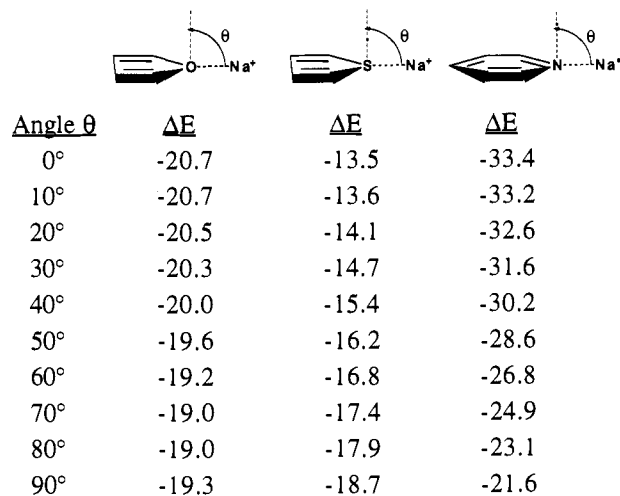
Angle θ	ΔE	ΔE	ΔE
0°	-20.7	-13.5	-33.4
10°	-20.7	-13.6	-33.2
20°	-20.5	-14.1	-32.6
30°	-20.3	-14.7	-31.6
40°	-20.0	-15.4	-30.2
50°	-19.6	-16.2	-28.6
60°	-19.2	-16.8	-26.8
70°	-19.0	-17.4	-24.9
80°	-19.0	-17.9	-23.1
90°	-19.3	-18.7	-21.6

Figure 8. The angle dependence of the 6-31G** binding energy of Na^+ with thiophene, furan, and pyridine. Energy is reported in kcal/mol.

and highly characteristic shift patterns seen for guests **7** and **34** show that trialkylsulfoniums behave very much like tetraalkylammoniums. Another new class of guests is the alkylated guanidiniums, and these flat, delocalized cations bind well. A novel case of enantiospecific binding is seen with hexamethylguanidinium (**40**), for which our chiral hosts are able to recognize a very subtle conformational effect. The neutral azulenes **25** produce very large binding constants, which may, in part, be the result of a novel cation-π interaction with the electron-deficient, seven-membered ring of the guest.

Modification of the host structures can also lead to useful information. Adding bromines (TBP) generically improves the host by providing a globally more hydrophobic environment. A surprising result is the ineffectiveness of furan and thiophene as cation binders, as revealed by studies on hosts F and T and by computational modeling. This result illustrates the danger in extrapolating conventional notions of electron-richness, which are based on reactivity patterns, to other situations. For binding interactions it is the ground-state wave function of the aromatic that is most important.

The importance of considering solvation effects on binding has also been demonstrated. Not surprisingly, adding an organic solvent to an aqueous medium diminishes binding, presumably by lessening the hydrophobic effect. The magnitude of the effect is perhaps surprising, in that only 10% added acetonitrile produces pronounced decreases in binding affinity. Monte Carlo simulations have also provided useful information on solvation. As expected, simple protonated amines such as NH_4^+ are much better solvated than analogous tetraalkylammoniums, and this rationalizes the weaker binding of protonated vs alkylated amines. Still, alkylated cations such as **1** are strongly water solvated. Clearly, binding does not completely desolvate a cation such as **1**.

Finally, these studies illustrate anew that even for systems that are designed to be extremely simple, with minimal degrees of freedom and relatively well defined interactions, noncovalent binding interactions are extremely complicated phenomena. The host TMP illustrates this, in that a seemingly benign change led to a quite deleterious effect. Clearly, a delicate interplay of hydrophobic, electrostatic, conformational, and solvation effects determines the affinity of any individual guest for a particular host. As such, it is important to study broad classes of molecules and systematic structural changes in order to document general binding influences such as the cation-π effect.

Experimental Section

General Methods. NMR spectra were recorded on JEOL JNM GX-400, Bruker AM-500, or General Electric QE-300 spectrometers. Routine

spectra were referenced to the residual proton signals of the solvents and are reported in ppm downfield of 0.0 as δ values. All coupling constants, *J*, are in Hz. Spectra from aqueous binding studies were referenced to an internal standard of 3,3-dimethylglutarate (DMG, δ 1.09). Optical rotations were recorded on a Jasco DIP-181 digital polarimeter at 298 K. All circular dichroism (CD) experiments were carried out using a JASCO J-600 spectropolarimeter with either 1.0 or 0.5 cm pathlength quartz cells. Preparative centrifugal chromatography was performed on a Harrison Research Chromatotron Model 7924T using silica plates. Melting points were determined on a Thomas Hoover melting point apparatus and are corrected.

All host solutions for NMR binding studies were prepared in borate-d buffer as described previously.[20] The host solutions were quantified by NMR integrations against a primary standard solution of DMG in borate-d.[20] For mixed-solvent binding studies, acetonitrile (10 or 15% v/v) was added as needed to aliquots of these host solutions. Guest solutions for NMR binding studies were prepared by dissolution of the compounds in the appropriate volumes of 0, 10, or 15% v/v acetonitrile in borate-d buffer. Guest solution concentrations were determined gravimetrically, by weight of solute, or through NMR integrations against DMG. All binding studies were performed by subsequent addition of aliquots of guest solutions to an NMR tube containing a solution of host compound that was initially, approximately 300 μM. Binding data were fit to an appropriate association constant, using the MULTIFIT or EMUL programs.[25]

All chloroform binding studies were performed using the tetramethyl esters of host molecules. All host and guest solutions involved were quantified by NMR integrations against a primary standard of *p*-dimethoxybenzene. All data were fit using the EMUL binding program.

Solutions for CD binding studies were prepared in borate buffer (pH = 9) prepared from water passed through a Milli-Q purification system. Host concentrations used varied between 1 and 3 μM. In a typical study, CD spectra of 5–6 solutions of equivalent host but varying guest concentrations were used. The spectra and the Δε values of the host were fit to an association constant, using the CDFIT program.[28] Guest iodide and bromide salts were exchanged for chloride using Dowex 1X8-400 ion exchange resin.

Guests **1, 10, 11, 13, 14, 15, 18, 19, 23, 24, 41, 59, 60, 61, 62,** and **63** were available from commercial sources. Compounds **3, 5, 6, 20, 22, 25, 27, 34, 36, 37, 38, 39, 40, 70, 75,** and **76** were prepared as described in the literature.[40] Guests **2, 4, 7, 8, 9, 12, 16, 17, 42, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 64, 65, 66,** and **67** were prepared through alkylation of the appropriate amines, quinolines, isoquinolines, and pyridines with the appropriate iodoalkanes. Compound **21** was prepared by reduction of 4-quinolinecarboxaldehyde with sodium borohydride.

Sulfoxides and Sulfonium Salts. These compounds were made directly from the corresponding sulfides. Except where noted, the sulfides were prepared from aryl thiol, alkyl halide, and DBU in benzene or petroleum ether as described in the literature.[41] The reaction mixture was filtered, and the filtrate was purified by column chromatography after the solvent was removed *in vacuo*.

Ethyl 2-Naphthyl Sulfide.[42] ^{1}H NMR (CDCl$_3$) δ 7.76 (m, 3H), 7.39 (m, 4H), 3.05 (q, *J* = 10.5, 2H), 1.38 (t, *J* = 10.5, 3H).

Ethyl *p*-Nitrophenyl Sulfide, Methyl *p*-Nitrophenyl Sulfide, Methyl *p*-Chlorophenyl Sulfide, Methyl *p*-Fluorophenyl Sulfide, and Methyl *p*-Tolyl sulfide have been reported previously.[43,44] Spectra are reported in ref 21a.

(4-Trifluoromethylphenyl) Ethyl Sulfide. The aryl thiol[45] was formed by the slow addition of a solution of 4-bromobenzotrifluoride in diethyl

(40) Nontrivial syntheses: **3** and **20**: see ref 21a. **5** and **6**: Katritzky, A. R.; Lunt, E. *Tetrahedron* **1969**, *25*, 4291–4305. **22**: Birch, A. J.; Jackson, A. H.; Shannon, P. V. R. *Tetrahedron Lett.* **1972**, *47*, 4789–4792. **25**: Hafnex, K.; Bernhard, C. *Ann.* **1959**, *625*, 108–123. **27**: Taddei, F. *J. Chem. Soc.* **1970**, 653–655. **34**: Kevill, D. N.; Anderson, S. W. *J. Am. Chem. Soc.* **1986**, *108*, 1579–1585. **36**: Schmidtchen, F. P. *Chem. Ber.* **1980**, *113*, 2175–2182. **37** and **38**: Bredereck, H.; Bredereck, K. *Chem. Ber.* **1961**, *94*, 2278–2295. **39**: Angyal, S. J.; Warburton, W. K. *J. Chem. Soc.* **1951**, 2492–2494. **40**: Lecher, H.; Graf, F. *Chem. Ber.* **1923**, *56*, 1326–1330. **70**: Fries, K.; Walter, R.; Schilling, K. *Ann.* **1955**, *516*, 248–285. **75**: Tarrago, G.; Marzin, C.; Najimi, O.; Pellegrin, V. *J. Org. Chem.* **1990**, *55*, 420–425. Novitskii, K. Y.; Volkov, V. P.; Yur'ev, Y. K. *Zh. Obshch. Khim.* **1961**, *31*, 538–541. **76**: Griffing, J. M.; Salisbury, L. F. *J. Am. Chem. Soc.* **1948**, *70*, 3416–3419. The compound **76** was purified by quickly passing the crude product over a pad of silica gel and eluting with 10% ether in petroleum ether.

(41) Ono, N.; Miyake, H.; Saito, T. Kaiji, A. *Synthesis* **1980**, 952.

(42) Node, M.; Nishide, K.; Ohta, K.; Fuji, K.; Fujita, E.; Hori, H. Inayama, S. *Chem. Pharm. Bull.* **1983**, *31*(2), 545–551.

(43) Evans, T. L.; Kinnard, R. D. *J. Org. Chem.* **1983**, *48*, 2496–2499.

(44) Jeminet, G.; Kergomard, A. *Bull. Soc. Chim. Fr.* **1967**, *9*, 3233–3243.

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ether to a flask containing magnesium and diethyl ether under a nitrogen atmosphere. After the addition was complete, the reaction flask was heated for 30 min. Sulfur was added to the Grignard reagent and left stirring for 1 h. The solution was acidified with 3 N HCl and extracted with ether. Extraction of this organic layer with 10% aqueous NaOH was followed by the acidification of the aqueous layer. This layer was then extracted with ether and the product thiol was distilled. The thiol was used as described above to generate the alkyl aryl sulfide: ^{1}H NMR (CDCl$_3$) δ 7.38 (d, J = 8.2, 2H), 7.22 (d, J = 8.2, 2H), 2.87 (q, J = 7.3, 2H), 1.23 (t, J = 7.3, 3H).

Ethyl Benzyl Sulfide.[46] ^{1}H NMR (CDCl$_3$) δ 7.15 (m, 5H), 3.60 (s, 2H), 2.32 (q, J = 9.0, 2H), 1.11 (t, J = 9.0, 3H).

2-Methylbenzo[*b*]thiophene.[47] The sulfide was obtained by adding *n*-butyllithium to a flask equipped with a reflux condenser of benzo[*b*]-thiophene and tetrahydrofuran under an atmosphere of nitrogen. This solution was heated to reflux for 45 min, after which it was cooled and methyl *p*-toluenesulfonate was added with further cooling. The reaction was quenched with methanol and placed in a separatory funnel with diethyl ether and water. The product was distilled at aspirator pressure: ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.3, 1H), 7.62 (d, J = 8.3, 1H), 7.25 (m, 2H), 6.95 (s, 1H), 2.57 (s, 3H).

3-Methylbenzo[*b*]thiophene.[48] (Phenylthio)acetone was formed by adding chloroacetone dropwise over 30 min to a solution of thiophenol in 30% aqueous NaOH under an atmosphere of nitrogen, maintained at 0 °C. The reaction was left to stir overnight and then was partitioned between diethyl ether and water. The organic solvent was removed *in vacuo*, and the product and phosphorus pentoxide were placed in a flask and heated to 170 °C for 30 min. The benzothiophene was extracted from the mixture and purified by column chromatography: ^{1}H NMR (CD$_3$CN) δ 7.88 (d, J = 8, 1H), 7.76 (d, J = 9, 1H), 7.38 (m, 2H), 7.19 (s, 1H), 2.42 (d, J = 1, 3H).

Sulfoxides. These compounds were synthesized by stirring the alkyl aryl sulfide with *m*-chloroperoxybenzoic acid in methylene chloride at 0 °C overnight. The product was isolated by chromatography over silica gel.

Ethyl 2-Naphthyl Sulfoxide (27).[49] ^{1}H NMR (CDCl$_3$) δ 8.16 (s, 1H), 7.92 (m, 4H), 7.57 (m, 2H), 2.96 (m, 1H), 2.84 (m, 1H), 1.18 (t, J = 7.4, 3H).

Sulfonium Tetrafluoroborate Salts. Except where noted, the sulfonium salts were all prepared from stirred, refluxing mixtures of sulfide and trimethyloxonium tetrafluoroborate in methylene chloride (which was distilled from CaH$_2$).[50] The reaction continued overnight, after which the solvent was removed *in vacuo*, and the residue was partitioned between acetonitrile and petroleum ether and washed two more times with petroleum ether. The solvent was removed *in vacuo*, and the solid was triturated twice from acetonitrile with diethyl ether. All compounds **28** and compound **29**, X = NO$_2$, have been reported previously.[51-53] Spectra are found in ref 21a.

Ethylmethylphenylsulfonium Tetrafluoroborate (29, X = H).[53] ^{1}H NMR (CD$_3$CN) δ 7.81 (m, 5H), 3.57 (m, 1H), 3.48 (m, 1H), 3.14 (s, 3H), 1.26 (t, J = 6.5, 3H).

Ethylmethyl(4-(trifluoromethyl)phenyl)sulfonium Tetrafluoroborate (29, X = CF$_3$). ^{1}H NMR (CD$_3$CN) δ 8.04 (AB, J = 9.5, $\Delta\nu$ = 22 Hz, 4H), 3.62 (m, 1H), 3.55 (m, 1H), 3.17 (s, 3H), 1.28 (t, J = 9.5, 3H); FAB-MS m/e 221 (M$^+$); HRMS 221.0613, calcd for C$_{10}$H$_{12}$F$_3$S 221.0612.

Benzylethylmethylsulfonium Tetrafluoroborate (30).[53] ^{1}H NMR (CD$_3$-CN) δ 7.50 (m, 5H), 4.52 (AB, J = 13.7, $\Delta\nu$ = 31 Hz, 2H), 3.24 (m, 1H), 3.15 (m, 1H), 2.71 (s, 3H), 1.42 (t, J = 9.5, 3H); FAB-MS m/e 203 (M$^+$); HRMS 203.0897, calcd for C$_{13}$H$_{15}$S 203.0894.

Ethylmethyl(2-naphthyl)sulfonium Tetrafluoroborate (31). ^{1}H NMR (CD$_3$CN) δ 8.53 (d, J = 5.3, 1H), 8.24 (d, J = 9.0, 1H), 8.10 (dd, J = 5.2, 9.1, 1H), 7.79 (m, 4H), 3.59 (m, 2H), 3.20 (s, 3H), 1.27 (t, J = 9.3, 3H); FAB-MS m/e 203 (M$^+$); HRMS 203.0897, calcd for C$_{13}$H$_{15}$S 203.0894.

S-methyl(2-methyl)benzo[*b*]thiophene Tetrafluoroborate (32).[54] ^{1}H NMR (acetone-d_6) δ 8.40 (d, J = 8.0, 1H), 7.94 (d, J = 8.0, 1H), 7.85 (m, 1H), 7.73 (m, 2H), 2.95 (s, 3H), 1.65 (s, 3H).

S-methyl(3-methyl)benzo[*b*]thiophene Tetrafluoroborate (33).[54] ^{1}H NMR (CD$_3$CN) δ 8.17 (d, J = 8, 1H), 7.89 (m, 2H), 7.77 (m, 1H), 6.99 (s, 1H), 3.15 (s, 3H), 2.47 (d, J = 1, 3H).

1,4-Bis(bromomethyl)-2,5-dimethoxybenzene (69). 1,4-Dimethoxy-benzene (2.76 g, 20 mmol, 1 equiv) was placed in a flask and dissolved in glacial acetic acid (13 mL). Bromomethyl methyl ether (3.6 mL, 44 mmol, 2.2 equiv) was added, and the solution was allowed to sit under nitrogen at room temperature for 12 h. An off-white precipitate was filtered off and washed with CCl$_4$. The material was then recrystallized from chloroform to yield **69** (2.54 g, 7.8 mmol, 39%): ^{1}H NMR (CDCl$_3$) δ 6.85 (s, 2H), 4.51 (s, 4H), 3.85 (s, 6H); mp 203–204 °C, lit. value[55] 206 °C.

1,5-Dibromo-2,6-bis(*tert*-butyldimethylsiloxy)anthracene (71). 2,6-Dihydroxyanthracene (4.20 g, 20.0 mmol, 1 equiv) was added to a 500-mL flask fitted with an addition funnel, an argon adapter, and a septum. The addition funnel was also sealed with a septum. The flask was then purged with argon, and the anthracene was dissolved in 80 mL of dioxane. Bromine (6.08 g, 38.0 mmol, 1.9 equiv) was dissolved in 80 mL of dioxane, and the resulting solution was transferred to the addition funnel. The bromine solution was then added to the anthracene solution over 10 min, and the resulting solution was stirred for 2 h. The reaction mixture was then filtered, and the precipitate was washed with dioxane. The mother liquor and all washings were then concentrated, using a rotary evaporator. The residue was dissolved in 80 mL of DMF. *tert*-Butyldimethylsilyl chloride (9.045 g, 60.0 mmol, 3 equiv) and triethylamine (8.40 mL, 60.3 mmol, 3 equiv) were added, and golden crystals formed immediately. These were filtered off, washed with methanol, and recrystallized from isooctane to yield the title compound (4.710 g, 7.9 mmol, 40% yield): ^{1}H NMR (CDCl$_3$) δ 8.65 (s, 2H), 7.89 (d, J = 9, 2H), 7.14 (d, J = 9, 2H), 1.08 (s, 18H), 0.30 (s, 12H).

(9S,10S,11R,12R)-1,5-Dibromo-2,6-bis(*tert*-butyldimethylsiloxy)-9,-10-dihydro-11,12-dicarboxyethenoanthracene Bis[(+)-menthyl ester] (72). An oven-dried round bottomed flask was fitted with a stopper, a septum, and an argon inlet. Di-(+)-menthyl fumarate (2.75 g, 7.0 mmol, 1 equiv, 7.0 mL of a 1 M solution in toluene) was added to the flask and cooled to 0 °C. Diethylaluminum chloride (5.063 g, 42.0 mmol, 6 equiv, 23.3 mL of a 1.8 M solution in toluene) was slowly added to the fumarate solution, which turned orange. The ice bath was removed, and the solution was allowed to come to room temperature. Protected anthracene compound **71** (4.17 g, 7.0 mmol, 1 equiv) dissolved in 40 mL of toluene was then added to the flask. After 8 h the solution had a pale yellow color, and thin-layer chromatography of the solution (silica gel plates, 3% ether in hexane) indicated complete consumption of the dimenthyl fumarate (R_f 0.35), but incomplete consumption of anthracene. Another equivalent of dimenthyl fumarate was then added. Another 0.5 equiv was added after 16 h. After 24 h the reaction mixture was poured over a chilled biphasic solution of 50 mL of toluene and 150 mL of saturated sodium potassium tartrate solution. (*Caution! Gas evolution!*) The biphasic solution was then filtered over a Celite pad. The organic layer and a further toluene extract of the aqueous phase were combined, dried with magnesium sulfate, and concentrated.

A single Diels–Alder adduct **3** (R_f 0.25) was visible by thin-layer chromatography (silica gel plates, 3% ether in hexane). Flash column chromatography (silica gel, 2–5% ether in hexane) was used to isolate the product **72** (5.73 g, 5.79 mmol, 83% yield based on the anthracene starting material): ^{1}H NMR (CDCl$_3$) δ 7.12 (d, J = 9, 2H), 6.58 (d, J = 9, 2H), 5.08 (s, 2H), 4.56 (td, 2H), 3.17 (s, 2H), 1.80–0.50 (m, 36H), 0.98 (s, 18H), 0.20 (s, 6H), 0.15 (s, 6H). **(9R,10R,11S,12S)-1,5-Dibromo-2,6-bis(*tert*-butyldimethylsiloxy)-9,10-dihydro-11,12-dicarboxyethenoan-thracene bis[(−)-menthyl ester]** can be prepared in an analogous fashion using di-(−)-menthyl fumarate.

(9R,10R)-1,5-Dibromo-2,6-dihydroxy-11,12-dicarboxyethenoan-thracene Bis[(+)-menthyl ester] (73). Compound **72** (9S,10S,11R,12R) (2.196 g, 2.20 mmol, 1.0 equiv) and diphenyl diselenide (1.107 g, 3.55 mmol, 1.6 equiv) were placed in a flask and dissolved in 50 mL of dry toluene. Potassium *tert*-butoxide (698 mg, 6.22 mmol, 2.8 equiv, 6.2 mL of a 1.0 M solution in THF) was added, and the reaction was allowed to stir for 45 min at room temperature. Isopropyl alcohol (260 mL) and HCl (37% aqueous, 16 mL) were then added, and the reaction was heated to 50 °C. After 2 days the reaction was cooled to room temperature and poured onto a biphasic solution of ethyl acetate (500 mL), NaHCO$_3$ (600 mL, saturated aqueous), and 1 M potassium phosphate buffer (pH = 7,

(45) Yachandra, V. K.; Hare, J.; Moura, I.; Spiro, T. G. *J. Am. Chem. Soc.* **1983**, *105*, 6455–6461.

(46) Takido, T.; Itabashi, K. *Synthesis* **1987**, 817–819.

(47) Shirley, D. A.; Cameron, M. D. *J. Am. Chem. Soc.* **1952**, *74*, 664–665.

(48) Werner, E. G. G. *Recl. Trav. Chim.* **1949**, *68*, 509–519.

(49) Kim, Y. H.; Lee, H. K. *Chem. Lett.* **1987**, 1499–1502.

(50) Corey, E. J.; Jautelat, M.; Oppolzer, W. *Tetrahedron Lett.* **1967**, 2325.

(51) Coward, J. K.; Sweet, W. D. *J. Org. Chem.* **1971**, *36*, 2337–2346.

(52) Angelelli, J. M.; Brownlee, R. T. C.; Katrizky, A. R.; Topsom, R. D.; Yakhonotov, L. *J. Am. Chem. Soc.* **1969**, *91*, 4500–4504.

(53) Darwish, D.; Scott, C. E. *Can. J. Chem.* **1973**, *51*, 3647–3648.

(54) Acheson, R. M.; Harrison, D. R. *J. Chem. Soc.* **1970**, 1764–1784.

(55) Syper, L.; Mlochowski, J.; Kloc, K. *Tetrahedron* **1983**, *39*, 781–792.

200 mL). After gas evolution had ceased, the organic layer was separated, dried with MgSO₄, and concentrated. The residue was then chromatographed over flash silica (35–50% ethyl acetate in isooctane) to yield the desired product (1.366 g, 1.80 mmol, 81% yield): ¹H NMR (CD₃CN) δ 7.21 (d, *J* = 8, 2H), 6.64 (d, *J* = 8, 2H), 5.83 (s, 2H), 4.79 (td, 2H), 2.15–1.70 (m, 38H). **(9S,10S)-1,5-Dibromo-2,6-dihydroxy-11,12-dicarboxyethenoanthracene bis[(–)-menthyl ester]** can be prepared from the (9R,10R,11S,12S) enantiomer of compound 72.

(9R,10R)-1,5-Dibromo-2,6-dihydroxy-11,12-dicarbomethoxyethenoanthracene (74). The (9S,10S,11R,12R) enantiomer of ethenoanthracene 73 (858 mg, 1.13 mmol) was dissolved in methanol (30 mL). Methanesulfonic acid (1.8 mL) was added, and the solution was brought to reflux. After 5 days the reaction appeared complete by thin-layer chromatography (silica gel plates, petroleum ether/ether, 1:1). The reaction mixture was then cooled to room temperature and mixed with ethyl acetate (80 mL) and 1 M potassium phosphate buffer (pH = 7, 80 mL). The organic layer and another extraction of the aqueous layer were combined, dried with MgSO₄, and concentrated. The residue was then chromatographed over flash silica (50–0% petroleum ether in ether) to yield the purified product 74 (466 mg, 0.91 mmol, 80%): ¹H NMR (CD₃CN) δ 7.30 (bs, 2H), 7.25 (d, *J* = 8, 2H), 6.62 (d, *J* = 8, 2H), 5.91 (s, 2H), 3.77 (s, 6H); [α]_D –103° (*c* 0.13, CH₃CN); EI-MS, *m/e* 508 (M⁺), 510 (M⁺ + 2), 449 (M – CO₂Me), 451 (M + 2-CO₂Me); HRMS 507.91400, calcd for C₂₀H₁₄⁷⁹Br₂O₆ 507.91571. **(9S,10S)-1,5-Dibromo-2,6-dihydroxy-11,12-dicarbomethoxyethenoanthracene** can be made from the (9S,10S,11R,12R) enantiomer of ethenoanthracene 73.

Stereochemical Assignments of Compounds 72–74. The stereochemistry at the 9,10 positions of the ethenoanthracene subunits is set during the asymmetric Diels–Alder reaction in which the dienophile, dimethyl fumarate, reacts with complete facial selectivity.[56] As such the stereochemical assignment for 72 allows for the determination of the absolute configuration of 74. The ¹H NMR spectrum of 72 shows a greater similarity to the *syn* product formed in the analogous condensation of dimethyl fumarate and 2,6-bis(*tert*-butyldimethylsiloxy)anthracene. As determined previously[20] the (S,S) and (R,R) enantiomers of 68 were synthesized from the *syn* products of the Diels–Alder reaction, when (+)- and (–)-dimethyl fumarates were used, respectively. As such the (R,R) and (S,S) enantiomers of 74 should result from the *syn* adducts produced, using (+)- and (–)-dimethyl fumarates, respectively.

Additionally a consistent relationship between the sign of [α_D] and absolute configuration has been shown to exist for a variety of C₂-symmetric bridged anthracenes.[57] The specific rotation of compound 74, when produced from (+)-dimethyl fumarate, is consistent in sign and magnitude to that of compound 68 with an (S,S) configuration, suggesting an (R,R) configuration for 74. This is consistent with our assignment of 72 as a *syn* product.

Finally, stereochemical assignment of 74 was made using the excitonic chirality method of Nakanishi.[27] A CD spectrum of the bis(dimethylaminobenzoate) derivative of bisphenol 74, prepared from (–)-dimethyl fumarate, was taken. The compound, at ca. 315 nm, displayed a strong positive Cotton effect, followed by a negative Cotton effect that was somewhat weaker due to overlap with signals of the ethenoanthracene. This is in agreement with the positive chirality expected for 74 with an (S,S) configuration. Again the information is consistent with the assignment of 72 as a *syn* product.

Macrocyclizations. As described previously,[20] the tetramethyl ester of host P was prepared by condensing 68 and *p*-bis(bromomethyl)benzene in a suspension of cesium carbonate in anhydrous DMF. The tetramethyl esters of the new host compounds (TMP, TBP, TMTBP, F, and T) were prepared similarly, using the ethenoanthracenes 68 and 74, and the appropriate bis(halomethyl) compounds, *p*-bis(bromomethyl)benzene, 69, 75, and 76. In all macrocyclizations, enantiomerically pure ethenoanthracenes were coupled, although both R,R and S,S forms were used. Workup of the macrocyclic products differed slightly from that previously reported for host P, however. After the macrocyclizations were complete, the reactions were filtered and the DMF evaporated. The residues were then chromatographed over flash silica, using either 5% ether or, equivalently, 5% ethyl acetate in methylene chloride, in order to separate the macrocyclic compounds from baseline impurities. The macrocycles were then isolated from higher order macrocycle using preparative centrifugal thin-layer chromatography (silica plates, 0–5% ether in CH₂Cl₂ gradient or, equivalently, 5% ethyl acetate in CH₂Cl₂).

TMP, Tetramethyl Ester. Yield 10%; ¹H NMR (CDCl₃) δ 7.05 (d, *J* = 8, 4H), 6.94 (d, *J* = 2, 4H), 6.69 (s, 4H), 6.42 (dd, *J* = 8, 2, 4H), 5.21 (s, 4H), 4.99 (AB, *J* = 13, Δν = 93 Hz, 8H), 3.75 (s, 12H), 3.48 (s, 12H); FAB-MS *m/e* 1028 (M⁺), HRMS 1028.3312, calcd for C₆₀H₅₂O₁₆ 1028.3255.

TBP, Tetramethyl Ester. Yield 10%; ¹H NMR (CDCl₃) δ 7.23 (s, 8H), 7.08 (d, *J* = 8, 4H), 6.41 (d, *J* = 8, 4H), 5.07 (AB, *J* = 13, Δν = 116 Hz, 8H), 3.78 (s, 12H); FAB-MS *m/e* MH⁺ cluster 1220–1230 (1225 100 integral % within cluster); HRMS 1220.9320, calcd for C₅₆H₄₁O₁₂⁷⁹Br₄ 1220.9331.

TMTBP, Tetramethyl Ester. Yield 31%; ¹H NMR (CDCl₃) δ 7.07 (d, *J* = 8, 4H), 7.05 (s, 4H), 6.56 (d, *J* = 8, 4H), 5.80 (s, 4H), 5.06 (AB, *J* = 13, Δν = 88 Hz, 8H), 3.79 (s, 12H), 3.67 (s, 12H); FAB-MS, *m/e* 1344 (M⁺); HRMS 1343.9673, calcd for C₆₀H₄₈⁷⁹Br₂⁸¹Br₂O₁₆ 1343.9635.

F, Tetramethyl Ester. Yield 5%; ¹H NMR (CDCl₃) δ 7.08 (d, *J* = 9, 4H), 6.93 (d, *J* = 2, 4H), 6.47 (dd, *J* = 2, 8, 4H), 6.27 (s, 4H), 5.24 (s, 4H), 4.88 (AB, *J* = 14 Δν = 18 Hz, 8H), 3.76 (s, 12H); ¹³C NMR (CDCl₃) δ 165.98, 156.21, 151.09, 147.06, 145.69, 136.28, 124.05, 112.28, 110.79, 110.47, 62.68, 52.36, 51.74; FAB-MS *m/e* 889 (M⁺), 857 (M – MeO), 537 (M – ethenoanthracene); HRMS of M – Na⁺ 911.2308, calcd for C₅₂H₄₀O₁₄Na 911.2316.

T, Tetramethyl Ester. Yield 8–18%; ¹H NMR (CDCl₃) δ 7.14 (d, *J* = 8, 4H), 6.92 (d, *J* = 2, 4H), 6.86 (s, 4H), 6.47 (dd, *J* = 2, 8, 4H), 5.25 (s, 4H), 5.11 (AB, *J* = 12, Δν = 18 Hz, 8H), 3.75 (s, 12H); ¹³C NMR (CDCl₃) δ 165.92, 155.61, 146.91, 145.77, 140.35, 136.22, 125.54, 124.05, 112.67, 109.71, 65.07, 52.36, 51.60; FAB-MS *m/e* 921 (M⁺), 920 (M – 1), 919 (M – 2), 889 (M – MeO), 569 (M – ethenoanthracene); HRMS of M – Na⁺, 943.1862, calcd for C₅₂H₄₀O₁₂S₂Na 943.1859.

Ester Hydrolysis. All tetraacid macrocycles were prepared from the corresponding tetramethyl esters, using the hydrolytic procedure described previously[20] for host P.

TMP, Tetraacid. ¹H NMR (borate, referenced to internal DMG δ 1.09) δ 7.21 (d, *J* = 9, 4H), 6.93 (d, *J* = 2, 4H), 6.56 (s, 4H), 6.54 (dd, *J* = 9, 2, 4H), 5.17 (s, 4H), 4.96 (AB, *J* = 10, Δν = 45 Hz, 8H), 3.17 (s, 12H).

TBP, Tetraacid. ¹H NMR (10% CD₃CN/90% borate, referenced to internal DMG δ 1.09) δ 7.45 (s, 8H), 7.28 (d, *J* = 8, 4H), 6.76 (d, *J* = 8, 4H), 5.74 (s, 4H), 5.16 (AB, *J* = 13, Δν = 102 Hz, 8H).

TMTBP, Tetraacid. ¹H NMR (10% CD₃CN/90% borate, referenced to internal DMG δ 1.09) δ 7.28 (d, *J* = 8, 4H), 7.24 (s, 4H), 6.76 (d, *J* = 8, 4H), 5.75 (s, 4H), 5.14 (AB, *J* = 13, Δν = 95 Hz, 8H), 3.76 (s, 12H).

F, Tetraacid. ¹H NMR (borate, referenced to internal DMG δ 1.09) δ 7.17 (d, *J* = 7, 4H), 6.85 (d, *J* = 2, 4H), 6.48 (dd, *J* = 2, 8, 4H), 6.19 (bs, 4H), 5.21 (s, 4H).

T, Tetraacid. ¹H NMR (10% CD₃CN/90% borate, referenced to internal DMG δ 1.09) δ 7.30 (d, *J* = 8, 4H), 7.07 (d, *J* = 2, 4H), 7.05 (s, 4H), 6.62 (dd, *J* = 2, 8, 4H), 5.26 (s, 4H), 5.23 (AB, *J* = 13, Δν = 22 Hz, 4H).

Computational Methods. Gas-Phase Calculations. *Ab initio* molecular orbital calculations were performed on benzene, thiophene, furan, pyridine, and their 1:1 complexes with ammonium or sodium cations using either the Gaussian 90[58] or Gaussian 92[59] program packages. Geometry optimizations were carried out at the 6-31G** level of sophistication (i.e., 6-31G**//6-31G**). Corrections for electron correlation were applied to all ammonium complexes in the form of a Møller–Plesset expansion truncated at the second order (i.e., MP2/6-31G**//6-31**). Estimates of the basis set superposition error (BSSE) were obtained by performing full counterpoise[60] calculations for the complexes **Ib**, **IIb**, and **IIIb**. The absolute BSSE was found to be small (0.4–0.5 kcal/mol) for each complex, and ΔBSSE within this series was negligible (approximately 0.1 kcal/mol). Consequently, the application of this correction to the rest of the complexes was considered unnecessary. Electrostatic potential energy surfaces were generated for benzene, thiophene, and furan by mapping the 6-31G**//6-31G** electrostatic potentials onto surfaces of total molecular electron density using the program Spartan.[61]

(56) (a) Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: NY; 1984, Vol. 3, Part B, Chapter 7. (b) Furuta, K.; Iwanaga, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 4507–4510.

(57) Hagishita, S.; Koriama, K. *Tetrahedron* **1972**, *28*, 1435–1467.

(58) *Gaussian 90*; Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M. A.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 1990.

(59) *Gaussian 92*; Revision A, Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 1992.

(60) Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553–566.

(61) *Spartan*, Version 2.1, Wavefunction Inc.: Irvine, CA, 1992.

Thiophene, furan, and pyridine were fully optimized in C_{2v} symmetry, while benzene and ammonium were optimized under D_{6h} and T_d symmetry constraints, respectively. Initial structures for the 1:1 π-complexes (**Ia–f, IIa–f, and IIIa–f**) were generated by placing the nitrogen atom of the ammonium cation above the ring centroid and perpendicular to the plane of the ring. The cation was oriented so that either one, two, or three hydrogens were pointing into the face of the aromatic ring. The remaining hydrogens were then either aligned with the heavy atoms of the ring or were positioned between them. Complexes **Ia–b** were optimized for C_{2v} symmetry, complexes **Ic–f** for C_{3v} symmetry, and all others (**IIa–f, IIIa–f**) were minimized under C_s symmetry constraints. The sodium cation was used to probe the potential energy surfaces of benzene, thiophene, furan, and pyridine. The 1:1 complexes with the aromatic π-systems were generated as described for the nitrogen atom of the ammonium cation above. The benzene complex was then fully minimized under C_{6v} symmetry constraints, while the thiophene, furan and pyridine complexes were optimized for C_s symmetry. In order to examine the heteroatomic regions of thiophene, furan, and pyridine, the structures of thiophene, furan, and pyridine were fixed at their minimized monomer geometries and the cation···heteroatom distance was optimized under C_s symmetry constraints for the series of angles described in Figure 8.

Solvation Studies

Relative solvation energies were calculated using statistical perturbation theory (SPT)[31] and the program BOSS.[62] All simulations were performed with double-wide sampling at constant temperature (298 K) and pressure (1 atm). Periodic boundary conditions were employed along with an 8.5 or 10 Å cutoff for the aqueous and chloroform simulations, respectively. Each simulation involved 9×10^5 steps of equilibration followed by averaging over 2×10^6 configurations. Since each perturbation involved the creation of a charge, the Born correction was applied to each calculation. Specific details for the individual simulations are described below.

Methane/Ammonium. A united atom methane molecule was placed in the center of a $17 \times 17 \times 26$ Å box containing 245 TIP4P water[63] molecules and was transformed stepwise ($\lambda = 0.15$, first two steps; $\lambda = 0.20$, last step) into an all atom ammonium molecule. Standard OPLS[64] parameters were used.

Neopentane/Tetramethylammonium. Neopentane was placed in the center of either a $17 \times 17 \times 26$ Å box containing 249 TIP4P water molecules or a $33 \times 33 \times 33$ Å box containing 262 chloroform molecules and mutated stepwise ($\lambda = 0.15$, first two steps; $\lambda = 0.20$, last step) into tetramethylammonium. Standard, united-atom, OPLS parameters were employed.

***tert*-Butylbenzene/Benzyltrimethylammonium.** *tert*-Butylbenzene was centered in a $20 \times 20 \times 20$ Å box containing 257 TIP4P water molecules and was mutated stepwise ($\lambda = 0.1$ for five steps) into benzyltrimethylammonium. Standard OPLS parameters were used with partial-atomic, AM1,[65] Mulliken charges. An all-atom potential was employed for the benzene ring, while a united-atom potential was used for the methyl groups.

Lepidine/*N*-Methylquinolinium. Lepidine was placed in the center of a $20 \times 20 \times 20$ Å box containing 260 TIP4P water molecules and was transformed stepwise ($\lambda = 0.05$ for 10 steps) into *N*-methylquinolinium. Standard OPLS all-atom parameters were used along with 6-31G**/ /AM1, Mulliken, partial-atomic charges.

(62) Jorgenson, W. L. *BOSS*, Version 2.7, Yale University, New Haven, CT, 1989.

(63) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Phys.* **1983**, *79*, 926–935.

(64) Jorgensen, W. L.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1988**, *110*, 1657–1666.

(65) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.