Concerning the Effects of Aromatic Ring Fluorination on the Cation−π Interaction and Other Molecular Recognition Phenomena in Aqueous Media

Sarah M. Ngola and Dennis A. Dougherty*

Arnold and Mabel Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

Received February 27, 1998

The "polar" nature of simple aromatics is increasingly being recognized as an important contributor to molecular recognition events, playing a key role in the cation−π interaction[1,2] and in polar−π interactions in general.[3−5] At the heart of such interactions is the large, permanent quadrupole moment of benzene.[6,7] Hexafluorobenzene also has a large permanent quadrupole moment, but one that is opposite in sign to that of benzene (Figure 1). For this reason, a stacking interaction between benzene and hexafluorobenzene is expected to be favorable, and a number of experimental and theoretical studies support this, especially in the solid state.[8−13]

A key remaining question is whether phenyl−perfluorophenyl interactions are strong enough to have a significant impact on molecular recognition events in solution. In recent years, several investigations of the effects of fluorination on molecular recognition have appeared, primarily emphasizing $\pi-\pi$ stacking interactions.[10,14−18] In the present work, we use the cation−π interaction—a strong intermolecular force that has a large electrostatic component[19,20]—to evaluate the extent to which fluorination alters the molecular recognition properties of aromatic systems. In particular, we evaluate the fluorinated derivative (**2**) of the well-characterized cyclophane host **1**. Since such systems bind both neutral aromatic and cationic guests, such studies can contrast the effects of fluorination on $\pi-\pi$ vs cation−π interactions. To the extent that such interactions are large and predictable, fluorinated systems could be quite useful in efforts at rational drug design. In addition, fluorination of aromatic residues in biological systems can be a powerful tool for pinpointing sites involved in cation−π interactions.[21−23]

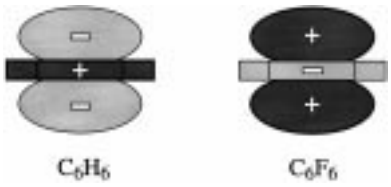
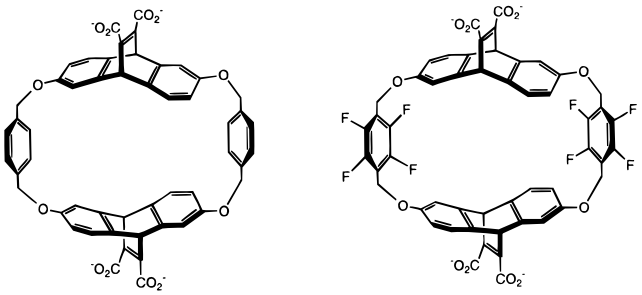


Figure 1. Schematics of the quadrupole moments of benzene and hexafluorobenzene.



1 **2**

Cyclophane host **1** is a general receptor for organic ammonium and imminium ions and is the prototype structure used to characterize cation−π interactions in aqueous molecular recognition.[24,25] When host **1** binds a guest such as *N*-methylquinolinium (**3**), the two xylyl "linker" rings contact the face of the cationic guest directly in what is considered to be a stabilizing, cation−π interaction. Replacement of the xylyl linking groups of host **1** with tetrafluoroxylyl groups as in host **2** should thus provide a telling test of the role of electrostatics in the cation−π interaction. Note that a full reversal of the quadrupole moment of benzene occurs only with hexafluorobenzene, and a significant portion of the cation−π interaction is contributed by aromatics of the ethenoanthracenes, which are unchanged on going from **1** to **2**. Still, we anticipate a measurable drop in cation binding if electrostatic interactions are important. Host **2** was synthesized by a straightforward modification of the procedures used to make host **1** and a number of variants with modified linkers, and binding constants in aqueous buffer were determined by ^{1}H NMR using established protocols.[24]

Host **2** is a generally poorer host than **1**, but the effect is certainly larger for cationic guests (Figure 2). Especially telling is the comparison **3**/**4**, a nearly isosteric pair that has previously been used as a strong indicator of the cation−π interaction.[24] The preferential binding of the cationic guest is substantially reduced in **2**. The less dramatic change in

(1) Dougherty, D. A. *Science* **1996**, *271*, 163−168.
(2) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303−1324.
(3) Cozzi, F.; Cinquini, M.; Annunziata, R.; Dwyer, T.; Siegel, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 5729−5733.
(4) Cozzi, F.; Siegel, J. S. *Pure Appl. Chem.* **1995**, *67*, 683−689.
(5) Burley, S. K.; Petsko, G. A. *Adv. Protein Chem.* **1988**, *39*, 125−189.
(6) Luhmer, M.; Bartik, K.; Dejaegere, A.; Bovy, P.; Reisse, J. *Bull. Soc. Chim. Fr.* **1994**, *131*, 603−606.
(7) Williams, J. H. *Acc. Chem. Res.* **1993**, *26*, 593−598.
(8) Coates, G. W.; Dunn, A. R.; Henling, L. M.; Dougherty, D. A.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 248−251.
(9) Coates, G. W.; Dunn, A. R.; Henling, L. M.; Ziller, J. W.; Lobkovsky, E. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 3641−3649.
(10) Cozzi, F.; Ponzini, F.; Annunziata, R.; Cinquini, M.; Siegel, J. S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1019−1020.
(11) West, A. P., Jr.; Mecozzi, S.; Dougherty, D. A. *J. Phys. Org. Chem.* **1997**, *10*, 347−350.
(12) Hernandez-Trujillo, J.; Costas, M.; Vela, A. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 2441−2443.
(13) Williams, J. H.; Cockcroft, J. K.; Fitch, A. N. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1655−1657.
(14) Fei, X.; Hui, Y.-Z.; Rudiger, V.; Schneider, H.-J. *J. Phys. Org. Chem.* **1997**, *10*, 305−310.
(15) Gilliard, R. E.; Stoddart, J. F.; White, A. J. P.; Williams, B. J.; Williams, D. J. *J. Org. Chem.* **1996**, *61*, 4504−4505.
(16) Hunter, C. A.; Lu, X.-J.; Kapteijn, G. M.; van Koten, G. *J. Chem. Soc., Faraday Trans.* **1995**, *91*, 2009−2015.
(17) Laatikainen, R.; Ratilainen, J.; Sebastian, R.; Santa, H. *J. Am. Chem. Soc.* **1995**, *117*, 11006−11010.
(18) Ballardini, R.; Balzani, V.; Credi, A.; Brown, C. L.; Gillard, R. E.; Montalti, M.; Philip, D.; Stoddart, J. F.; Venturi, M.; White, A. J. P.; Williams, B. J.; Williams, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 12503−12513.
(19) Mecozzi, S.; West Jr., A. P.; Dougherty, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 2307−2308.
(20) Mecozzi, S.; West Jr., A. P.; Dougherty, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 10566−10571.
(21) Thorson, J. S.; Chapman, E.; Murphy, E. C.; Schultz, P. G.; Judice, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 1157−1158.
(22) Nowak, M. W.; Kearney, P. C.; Sampson, J. R.; Saks, M. E.; Labarca, C. G.; Silverman, S. K.; Zhong, W.; Thorson, J.; Abelson, J. N.; Davidson, N.; Schultz, P. G.; Dougherty, D. A.; Lester, H. A. *Science* **1995**, *268*, 439−442.
(23) Kearney, P. C.; Nowak, N. W.; Zhong, W.; Silverman, S. K.; Lester, H. A.; Dougherty, D. A. *Mol. Pharmacol.* **1996**, *50*, 1401−1412.
(24) Kearney, P. C.; Mizoue, L. S.; Kumpf, R. A.; Forman, J. E.; McCurdy, A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1993**, *115*, 9907−9919.
(25) Petti, M. A.; Shepodd, T. J.; Barrans, R. E., Jr.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825−6840.

S0022-3263(98)00361-2 CCC: $15.00
Published on Web 06/18/1998

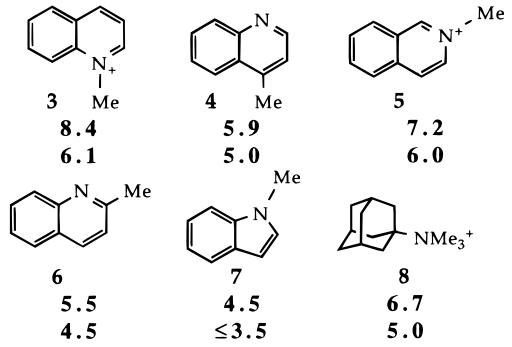


Figure 2. Binding of selected guests by cyclophanes **1** (top number) and **2** (bottom number) ($-\Delta G°_{298}$, kcal/mol) obtained by ^{1}H NMR in pD 9 buffer at 298 K using protocols described previously.)[24]

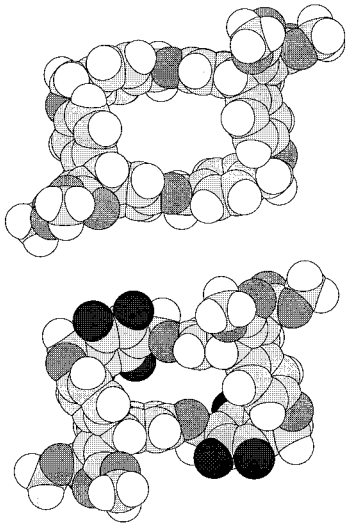


Figure 3. CPK representations of the X-ray structures of **1E** (top) and **2E** (bottom) Color scheme: H, white; C, light gray; O, dark gray; F, black.

the **5**/**6** pair is consistent with previous observations that guest **5** is relatively insensitive to changes in linker structure.[24]

The diminished binding of neutral guests by **2** was not anticipated. Highly fluorinated compounds are hydrophobic, but they are also lipophobic.[26] Perhaps this leads to a generically poorer binding site. For an alternative explanation, we note that in one idealized conformation of these hosts, the linker rings lie over phenyl rings of the ethenoanthracene units. When the linkers are tetrafluorophenyl this could be a favorable interaction, causing a collapse of the host in the unbound state, and thereby generically diminishing its binding ability. In the X-ray structure of the tetraester host **1** (**1E**, Figure 3), no such interaction is seen, and instead esters from an adjacent molecule partially fill the cavity.[27]

To test this second model, we have determined the X-ray crystal structure of the tetraester of host **2** (**2E**). As shown in Figure 3, the cavity of **2E** is indeed collapsed relative to the cavity of **1E**. The major cause of the collapse is an alteration of the $C_{aryl}-O-CH_2-C_{aryl}$ dihedral angles. However, the "collapse" in **2E** is not severe enough to produce any intramolecular stacking-type interactions between fluorinated and nonfluorinated rings, and examination of the

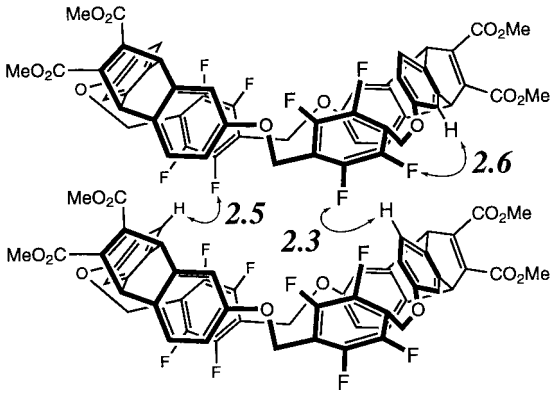


Figure 4. Close H···F contacts in the crystal structure of **2E**. Two molecules from the lattice are shown in an edge-on view. Two H···F contacts are intermolecular (2.3 and 2.5 Å) and one is intramolecular (2.6 Å).

crystal packing of **2E** reveals no *inter*molecular aryl–polyfluoroaryl stacking interactions. However, there are very close, intermolecular and intramolecular $C_{aryl}-F\cdots H-C_{aryl}$ interactions (Figure 4), and the latter may be part of the reason for the conformation change on going from **1E** to **2E**. This edge-to-edge interaction is, of course, consistent with electrostatic reasoning.[28] However, we do not expect the intramolecular F···H interaction to be strong enough to explain the generic 1 kcal/mol drop in binding affinity in **2**. Of course, the conformation of **2** in solution may be different from that of **2E** in the solid, but we can say the X-ray structure provides no strong support for the stabilization by collapse model.

As always, a number of phenomena are involved when studying molecular recognition in aqueous media, and detailed quantitative analyses can be challenging. Nevertheless, it is clear that replacing two of the six aromatic rings of **1** with tetrafluoroaromatics to produce **2** substantially affects binding, and the effect is largest with cationic guests such as **3** and **8**. This adds strong support to arguments that cation–π interactions are important in such systems and that fluorinating aromatics can substantially alter their binding properties. The results here are qualitatively and quantitatively comparable to very recent work by Schneider run in the "reverse" mode—using fluorinated guests and a cationic cyclophane host known to make use of cation–π interactions—in which fluorination also leads to a decrease in binding affinity.[14] An additional effect seen only in the present study is an apparent general drop in binding effectiveness even for neutral guests upon fluorinating the host. It will be interesting to see whether this effect is unique to the present system or whether it represents a general recognition phenomenon. While some questions remain, the results described here and elsewhere do suggest that fluorination can be used to rationally alter the electrostatics of aromatic rings, with predictable consequences for molecular recognition.

Acknowledgment. We thank the National Science Foundation for support of this work and Michael Day for determining the X-ray structure of **2E**.

Supporting Information Available: ORTEP drawing of the crystal stucture of **2** and details of synthetic procedures (3 pages).

JO980361L

(26) Dunitz, J. D.; Taylor, R. *Chem. Eur. J.* **1997**, *3*, 89–98.
(27) Forman, J. E.; Marsh, R. E.; Schaefer, W. P.; Dougherty, D. A. *Acta Crystallogr.* **1993**, *B49*, 892–896.
(28) Shimoni, L.; Glusker, J. P. *Struct. Chem.* **1994**, *5*, 383–397.