Directionality of the Cation–π Effect: A Charge-Mediated Size Selectivity in Binding

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Forces responsible for biomolecular conformation have been clarified by the detailed study of small molecules and synthetic binding sites. Schneider has shown that positive charge in a host molecule enhances binding of aromatic, but not aliphatic, guests.[1,2] The magnitude of the attractive interaction between cations and neutral aromatic groups is impressive; Dougherty's aromatic host binds cationic guests so strongly[3] that (4-*tert*-butylphenyl)-trimethylammonium is bound such that the trimethylammonium group is within the "hydrophobic" cavity and the *tert*-butyl group is exposed to water! This has led to a reinterpretation of the structural basis for cation binding selectivity of proteins such as the acetylcholine receptor.[4]

Aromatic–aromatic interactions are also important for protein structure. A preference for face-to-edge contact of aromatics has been observed[5-7] and modeled;[8-10] a largely Coulombic explanation appears favored.[11,12] The cation–π interaction is described as a related attraction of positive charge to the anionic face of an aromatic ring, an ion–quadrupole[13,14] attraction. If this is correct, an opposite effect would be expected at the edge of an aromatic ring,[6] a point that has not been experimentally addressed. We now report our investigation of this question.

We have designed compounds **1** and **2** to allow us to study the interaction of charges with the edge of a bound aromatic ring. The simple model of Hunter and Sanders[10] would predict that positive charge would be attracted to the face and negative charge to the edge of an aromatic ring. In all of the hosts investigated to date, charged groups near the host cavity have been oriented so as to interact with the face of bound aromatic guest.[15,16]

We have prepared these macrocycles according to Scheme I.[17] The synthesis is succinct, proceeds without protecting groups, and leads to both macrocycles in high yield from the common penultimate intermediate **3**. We note also that sequential coupling of two different aryl iodides[18] would allow the construction of unsymmetrical structures.

Dissociation constants for binding of dihydroxynaphthalenes to hosts **1** and **2** are shown in Table I. As expected for hydrophobic guests, binding is stronger in D_2O than in mixed aqueous organic solvents. However, in contrast to the significantly enhanced binding of aromatics by cationic over anionic host observed by Schneider,[2] we find stronger binding by the anionic host. This is consistent with Hunter and Sanders's model. Binding by hosts of this connectivity has been described in terms of conformations **A** and **B**, Scheme II.[16] The most common binding conformation, **A**, places the host charge toward the edge but near a node in the electrostatic potential surface. It would thus be predicted to have a small effect on binding, as observed. The ring junction charge would be expected to play a larger role in conformation **B**, commonly seen with larger guests.[19]

The fact that we see a 5-fold decrease, rather than a large increase, in binding of naphthalenes by the cationic as compared to the anionic host cannot be explained simply by greater solvation of the cavity of **2**. Koga's macrocycle,[20] which should suffer even greater solvation because of its four endocyclic cationic nitrogens, binds neutral aromatics more tightly than does the corresponding anionic sulfonamide of Schneider.[1] While a differential solvation may be operative, it is clear that the attraction of cation to the aromatic is missing now that we have moved the charge. Donor–acceptor effects[11,21] would predict results opposite from our findings.

Evidence for conformation **B** has been obtained for "equatorial" binding of naphthalenes to slightly larger hosts.[16,22] We studied guests of intermediate size to see whether the ratio of anionic host affinity to cationic host affinity would increase with guest size. The seven-membered ring of tropolone showed a selectivity similar to that of the naphthalenes, but the somewhat larger acenaphthylene was bound 19 times more strongly by the anionic host. This is consistent with the idea that an ion–quadrupole interaction stabilizes binding in conformation **B** for anionic **1** and destabilizes binding in conformation **B** for cationic **2**.

Scheme I

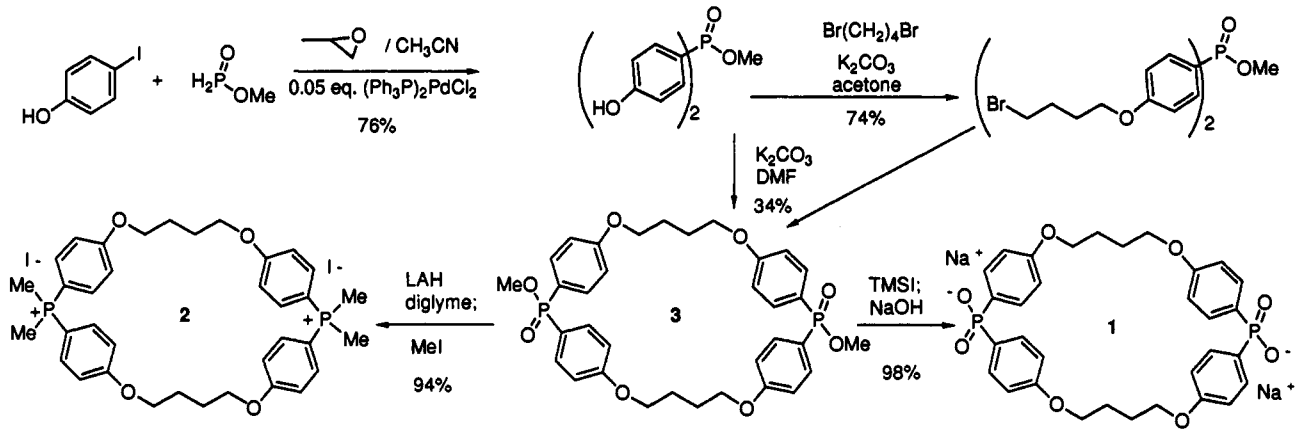

Table I. Binding of Substrates to Oppositely Charged Macrocycles **1** and **2**[a]

substrate	**1** D_2O	**1** 60:40 D_2O/CD_3OD	**2** D_2O	**2** 60:40 D_2O/CD_3OD	anion preference ratio
2,6-dihydroxynaphthalene	$(1.86 \pm 0.17) \times 10^{-3}$	$(3.95 \pm 0.24) \times 10^{-2}$		$(1.5 \pm 1.1) \times 10^{-1}$	3.8
2,7-dihydroxynaphthalene	$(4.93 \pm 0.14) \times 10^{-3}$	$(5.54 \pm 0.97) \times 10^{-2}$		$(2.9 \pm 3.4) \times 10^{-1}$	5.3
tropolone	$(6.10 \pm 1.72) \times 10^{-3}$	$(2.81 \pm 1.11) \times 10^{-2}$	$(4.26 \pm 0.57) \times 10^{-2}$	$(9.9 \pm 4.7) \times 10^{-2}$	5.3
acenaphthylene	$(7.84 \pm 0.62) \times 10^{-4}$		$(1.48 \pm 0.18) \times 10^{-2}$		19

[a] Dissociation constants (K_D in M) of substrates from hosts **1** and **2** were measured[23,24] as described in the supplementary material. Error limits are 95% confidence.

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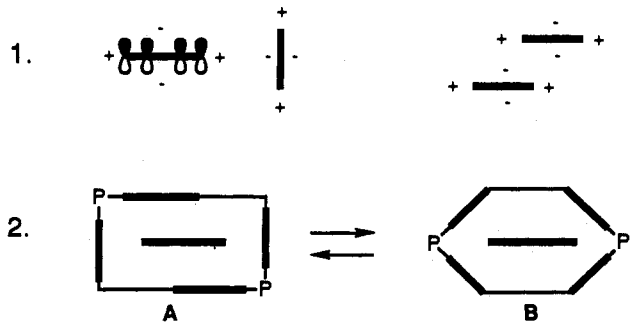
Scheme II[a]



[a] 1: Hunter and Sanders's model[10] of π–π interactions as Coulombic interactions of cationic σ framework with anionic π electrons. Heavy lines represent aromatic rings viewed edge on. 2: Schematic representation of major binding conformations of cyclophanes with aromatic guests. A has aromatic "T" and offset parallel orientations. In conformation **B**, observed with larger guests, the ring junction atoms (labeled P) are nearer the plane of the guest.

We have thus achieved a charge-mediated size selectivity in binding of neutral hydrophobic aromatic substrates. These results underscore the importance of directionality in charge–π effects and help to further delineate the forces responsible for protein structure and action. Application to enhancement of specificity in host–guest binding and catalysis is in progress.

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Supplementary Material Available: Details of dissociation constant determination, including complexation-induced NMR shifts (3 pages). Ordering information is given on any current masthead page.

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