Large Binding Constant Differences between Aromatic and Aliphatic Substrates in Positively Charged Cavities Indicative of Higher Order Electric Effects

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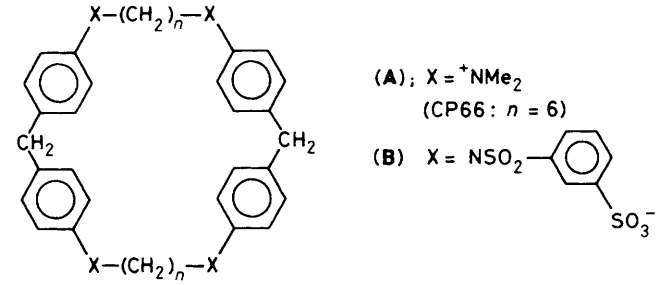
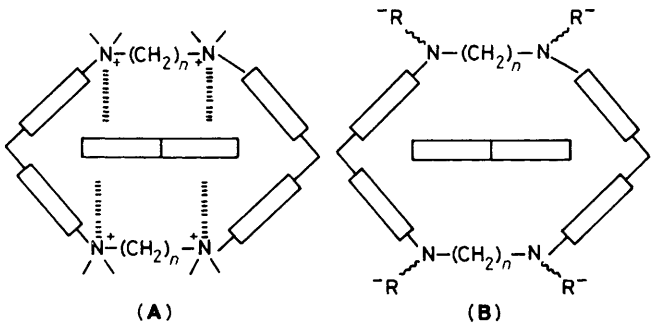
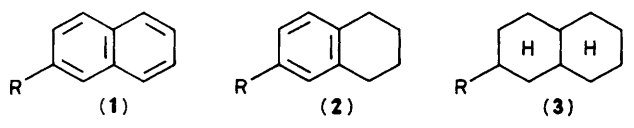
Aliphatic substrates show, in comparison to aromatic substrates of similar shape, up to 60 times lower binding constants with a cyclophane bearing $^{+}$N charges on the inside of the cavity; much smaller differences are observed with the same cyclophane bearing no charges in the vicinity of the substrate.

Electrostatic contributions to non-covalent intermolecular forces in proteins have been so far essentially described by Coulomb-type potentials.[1] *X*-ray analyses of proteins have already provided strong statistical evidence for the preferred orientations of positively charged groups towards the π-electron cloud of aromatic amino acids,[2] which is in line with related gas phase measurements and M.O. calculations for hydrogen-bonded clusters.[3] The study of synthetic host–guest complexes provides a better defined geometric environment than proteins for the analysis of non-covalent forces; after a planned variation of sizes, charges, and polarisibilities in hosts and/or guests one can obtain better defined energetic parameters for the binding. Using the cyclophanes (**A**) and (**B**) as receptor models in aqueous solution, and both aliphatic and aromatic substrates, we present numerical data for the predominance of higher order electric effects, such as ion-quadrupole or ion-induced dipole attractions in the binding of aromatic substrates in the vicinity of positively charged nitrogen.

Ion-dipole attractions have been discussed already for host–guest complexes with other cyclophanes;[4,5] they are, however, difficult to separate from simultaneously operating donor–acceptor interactions between the π-systems of host and guest, respectively. In the present study we use macrocyclic hosts in which a biphenylmethane unit[6] and alkane spacers are linked alternatively by positively charged nitrogen (**A**), or by electroneutral nitrogen (**B**),[7] to which negatively charged groups, at greater distance from the cavity, are attached. Aromatic substrates without charges have been found to bind more strongly with (**A**) than with (**B**).[7] Complexation studies with aliphatic substrates now unequivocally demonstrate that the disposition of the $^{+}$N-atom from the

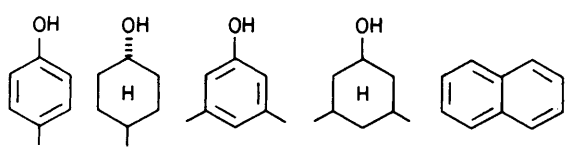




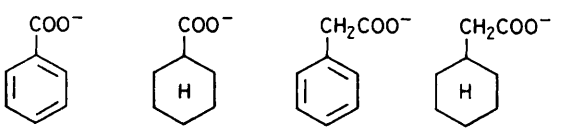


	(1)	(2)	(3)
R = H, I[b]	4.0	2.7	1.6
R = H, II[c]	4.0	3.1	
R = OH[c]	3.9	2.7	

(kcal/mol)



	(4)	(5)	(6)	(7)	(8)
With(A):	2.4[c]	0.8[c]	2.7[c]	0.5–1.1[d]	4.05[c]
[With(B):	1.8[c]	1.0–1.7[d]	1.6[c]	0.9–1.5[d]	3.1[c]]



	(9)	(10)	(11)	(12)
With(A):	3.9[e]	2.4[e]	3.8[e]	2.8[e]

Scheme 1.[a]

[a] Complexation free enthalpies $\Delta G°$ (kcal/mol) at ambient temperature with (**A**) unless noted otherwise; [b] Approximate $\Delta G°$ in H_2O derived from substrate solubility measurements with and without (**A**); [c] from n.m.r. shift titrations in CD_3OD/D_2O = 20/80 V + V; [d] Approximate $\Delta G°$ from observation of single n.m.r. shifts in 20% CD_3OD upon addition of (**A**) or (**B**), assuming 100% complexation induced shifts (CIS values) between 0.2 p.p.m. [gives upper limit for $\Delta G°$; 0.2 p.p.m. CIS were *e.g.* the largest CIS observed with (**B**) and cyclohexyltrimethyl ammonium chloride] and 0.4 p.p.m. [gives lower limit for $\Delta G°$; 0.4 p.p.m. CIS were *e.g.* obtained with (**A**) and (**10**)]. [e] $\Delta G°$ extrapolated to ionic strength of $I = 0$,[9] based on sensitivities m from salt effect measurements with (**A**) and 2-naphthoate [$m = -1.43$ from the plot of log$K$ *vs.* $\sqrt{I}/(1+\sqrt{I})$].

host (**A**) above the plane of the guest π-system is the responsible factor here. N.m.r. spectroscopic studies with aromatic ring current and electric field effect calculations[8] indicate that naphthalene derivatives indeed are encapsulated in the cavity of (**A**) in a pseudoequatorial manner suitable for such a $^+N \cdots \pi$ interaction. The analysis of solvent effects on host–guest equilibrium constants[9] indicates a large van der Waals contribution to the binding of, *e.g.*, naphthalene to (**A**).

Complexation constants for saturated substrates without highly polarizable elements have rarely been reported with water soluble cyclophane receptor models, in contrast to many measurements that have been reported with aromatic substrates.[4,6,10] Comparison of aromatic and aliphatic substrates (Scheme 1), chosen to be as similar as possible in size, shows a distinct decrease in binding free enthalpy $\Delta G°$, which with compounds (**1**)—(**5**) in cavity (**A**) amounts to 1—1.3 kcal/mol per aromatic unit. The fact that the difference in $\Delta G°$ between (**4**) and (**5**) is similar to the difference in $\Delta G°$ between (**1**)/(**2**) and (**2**)/(**3**) indicates that the observed differences are not due to too narrow cavities for the saturated substrates. This is also supported by inspection of molecular models, as well as by a decreased binding of tetralin derivatives [= (**2**)] in a slightly enlarged cyclophane with 8, instead of 6, methylene units.[11] The binding of the aliphatic substrates (**5**) and (**7**) in the more lipophilic cavity (**B**) is noticeably enhanced, in contrast to the reverse observation with naphthalene (**8**); this supports again a dominating N^+ π-electron attraction in suitable systems.

It is difficult to deduce binding energies for desolvated hosts and guests from the measured apparent complexation constants which represent a whole thermodynamic cycle. The consistent increments emerging from the measured constants, however, indicate that the attraction between a positively charged nitrogen atom and a nonbonded π-system amounts to approximately 1 kcal/mol per interaction although obviously considerable desolvation must be involved in the aqueous solution. It should be noted that most of the currently used force fields lack potentials for the discussed interactions between polarisable moieties and charges.[13]

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13 This is part 20 of our series 'Host–Guest Chemistry'; part 19: N. K. Sangwan and H.-J. Schneider, submitted.