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ATTRACTIVE INTERACTIONS BETWEEN NEGATIVE CHARGES AND POLARIZABLE ARYL PARTS OF HOST–GUEST SYSTEMS*

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NMR measurements of associations between simple organic host and guest molecules bearing alternatively negatively charged groups and electroneutral π-moieties show in aqueous solutions weak but distinct attractions reaching approximately 2 kJ mol^{-1} and X$^-$/arene unit. A similar value is observed for the complex between a calixarene with 4-sulfonato groups and toluene, for which the NMR shifts indicate an orientation with the guest methyl substituent upwards. The conformational fit of the selected complexes is checked by molecular mechanics simulations.

The orientation of charged groups above the plane of an aromatic moiety is a frequently occurring structural motif in synthetic host–guest systems as well as in biopolymers. In particular, the presence of positively charged nitrogen leads to stabilization of such arrangements which is visible in solid state protein structures showing NH_3^+ groups of basic amino acids oriented towards aromatic side chains,[1] or recently in the binding site of cholinesterase with phenyl groups around the NMe_3^+ unit of choline.[2] Several studies of synthetic host–guest complexes have indicated that such a stabilization occurs in solution,[3] and they have provided a value[3d,e] of approximately 2 kJ mol^{-1} and N^+/arene unit in water as the extremely unpolarizable solvent. If it is correct to conclude that this attraction is primarily due to a dipole induced in the arene,[3] one should expect a similar Van der Waals attraction if the positive charge is replaced by a negative one. To the best of our knowledge, this has not been investigated experimentally until now. Measurements of synthetic host–guest equilibria have the advantage of providing not only structural evidence without intervening packing forces in crystals but in particular also association energies.

Ideally, one would like to use conformationally restrained complexes in rather rigid cavities of hosts bearing negative charges close to the aromatic moiety of the guest as models. In contrast to their positively charged counterparts, however, suitable cyclophanes[4] are unknown to date. The only exception are some calixarenes,[5] which, however, lack the very close contact between charge and aromatic cloud that is characteristic of complexes with positively charged cyclophanes.

We first chose a number of host and guest systems (**H1/G2; H2/G2; H3/G3**) which have a negative charge as much as possible in perpendicular contact with the π-surface. These conformational conditions were secured by computer-aided simulations of the corresponding complexes (Figure 1) with the help of CHARMm[6] energy minimizations. The simulations aim only at controlling the possible geometric fit of the selected systems. Explicit calculations of the thermodynamic cycle involved in the complexation are virtually impossible, because of the lack of the Van der Waals potentials for induced dipoles in available force fields; just these interactions are the ones dominating in the complexes studied here. Aggregates formed in the absence of cavities play an important role in many 'stacking' type complexes;[7] they have been investigated earlier, mostly without the help of NMR data which now can shed light on their structure.

The necessarily weak[3,8] interactions require the use of high concentrations of one component, which together with solubility problems makes it difficult to carry out NMR titrations as usual with solvents containing the necessary amount of water;[9] occasionally, overlapping signals generate additional problems.

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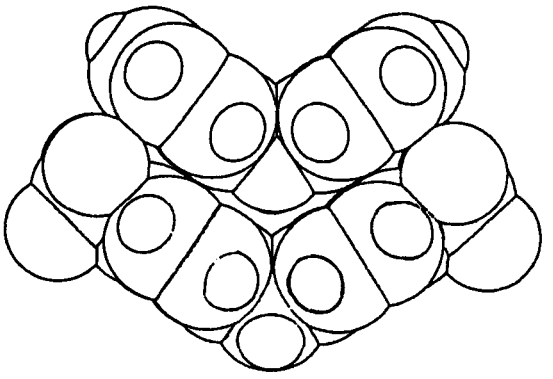

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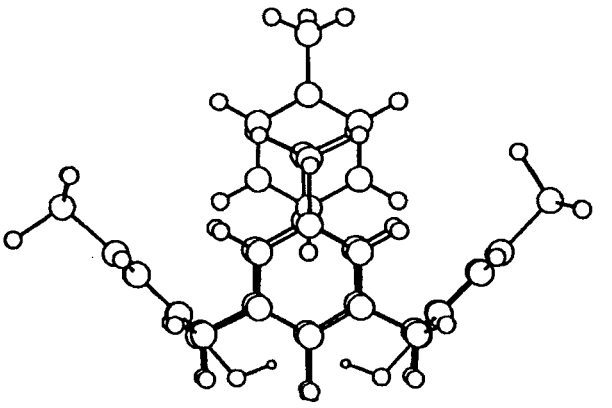

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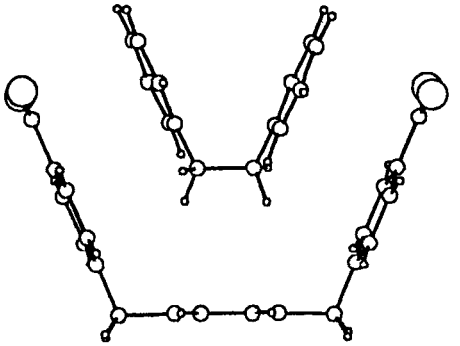

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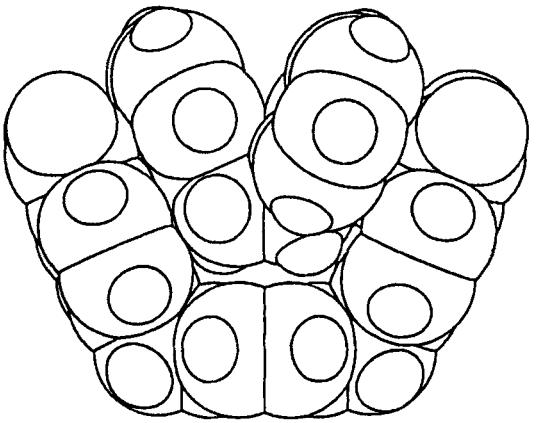

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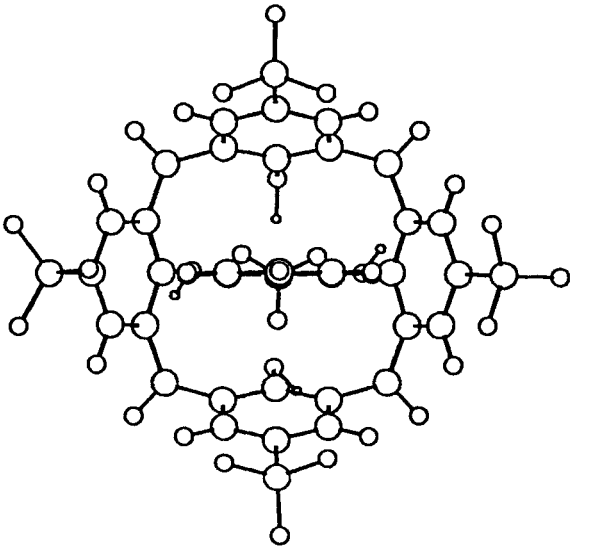

(e)

Figure 1. Plots from CHARMm/QUANTA simulations for the complexes: (a) **H1/G1**; (b, c) **H2/G2**; (d, e) **H3/G3**.

Table 1. Association constants K and complexation induced shift (CIS) values[a]

	ROH (%)		H_a	H_b	H_c	K_{av}	ΔG
H1($X=^+NMe_3$) + **G1**	5		0·21	0·39	0·40		
		K	*17·4*	*17·3*	*16·2*	*17·0*	7·0
H1($X=SO_3^-$) + **G1**	20		0·24	–[b]	0·09[c]		
		K	*8·0*	–	–	*8·4*	5·3
	60		0·095		0·11		
		K			*3·0*[d]		2·7
H1($X=SO_3^-$) + CH_2I_2	20		0·63	–	–	*1·0*	0·0
H2($X=O^-$) + **G2**($Y=CH_2$)	75		0·31[d]	–[b]	–[b]		
		K	*2·4*	–	–	*2·4*	2·2
G2($Y=CH_2$) + **H2**($X=CO_2^-$)	95		–[b]	0·29	0·31		
		K	–	*1·3*	*1·3*	*1·3*	0·4
H1($X=NMe_3^+$) + **G2**($Y=CH_2$)	95		–[f]	0·11[d]	–[b]		
H2($X=O^-$) + **G2**($Y=CHNH_2$)	75		0·11	– b	–[b]		
H3($X=SO_3^-$) + **G3**(R=H)	5		1·73	–	–		
		K	*1·7*	–	–	*1·3*	0·65
H4 + **G3**($R=CH_3$)	20		0·11	CH_3:	0·17		
		K	*10*	*5*		*7·0*	4·8

[a] From NMR titrations at 300 ± 2 K. K in mol l^{-1}; CIS (on guest G) in ppm (positive sign indicates upfield CIS); ΔG in kJ mol^{-1}, with CD_3OD as solvent ROH as indicated. Average error in K = 10%, in CIS δ = 0·002 ppm unless noted otherwise.

[b] Signal masked during entire titration.

[c] Signal masked during several titration steps; CIS obtained from single measurements at known degrees of complexation.

[d] Maximal obtained shift value, *not* CIS.

[e] K calculated by comparison of experimental shifts with CIS values of known complexes.

[f] No fitting possible due to low solubility.

[g] Protons other than H_a could not be measured due to overlapping (H_b at δ = 7·307 ppm, H_c and H_a at δ = 7·260 before complexation) and poor signal/noise ratios.

Nevertheless, the results (Table 1) generally confirm the postulated attraction between π-systems and negative charges, and give values for this interaction in the range of approximately 2 kJ mol^{-1}. A related value has also been deduced indirectly from earlier studies of aromatic ion pairs.[8]

The diphenylmethane systems **H1/G1** actually exhibit an association constant for $X = SO_3^-$ similar to that for $X = NMe_3^+$, which is also shown for comparison in Table 1. Noticeably, the complex induced shift (CIS) value observed with positive charge is particularly large for the p-proton H_c (Table 1), which is to be expected for a complex geometry with all p-carbon and the CH_2 or NH atoms of both host and guest in one plane (Figure 2a). The opposite situation, with a very small CIS at the p-position H_c, is found for the complex with $X = SO_3^-$, indicating a mutual displacement of the aryl rings (Figure 2b) with a subsequently diminished ring current anisotropy effect on H_c: such a slight displacement will replace *repulsions* between permanent negative charges of the π-cloud and of the substituent X by *attractions*, as the π-cloud can still be polarized by the X^- charge even if the charge is not exactly above the arene centre. The small CIS values for H_a in both complexes are a consequence of these protons being located further outside the shielding cone; besides, one has to bear in mind that in particular H_b and H_c are strongly influenced by electric field effects[10] stemming from the charges at X.

The dibenzylbenzene–diphenylethane combination **H2** and **G2** again can show an ideal geometric match (see Figure 2b,c). Unfortunately, all derivatives as well as the extended systems **H3/G3** were sparingly soluble in water; however, the equilibrium constants derived even in high percentage alcohol/water solvents support the order of magnitude generally observed for X^-/arene interactions (Table 1). Thus, the attenuation effect in going from 20% to 60% CD_3OD was determined for **H1** + **G1** to be about 50% in ΔG of the complexation; if one applies a corresponding factor to the ΔG observed with **H2** + **G2** or **H1** + **G2** one arrives again at 1–2 kJ mol^{-1} for each charge/arene attraction increment. Even diiodomethane is complexed by **H1** with $X = SO_3^-$ in a similar way as with $X = NH_3^+$ due to the relatively high polarizability of iodine, although the decreased match as well as the simultaneous action of the charges on two *adjacent* (C—I—) bonds in this case lowers the constant.

The calixarene system **H4** with toluene as guest was investigated as it offered a unique opportunity to measure a *cyclic* host with negative charges. The tetrasulfonato calixarene[1] **H4**, studied first by Shinkai

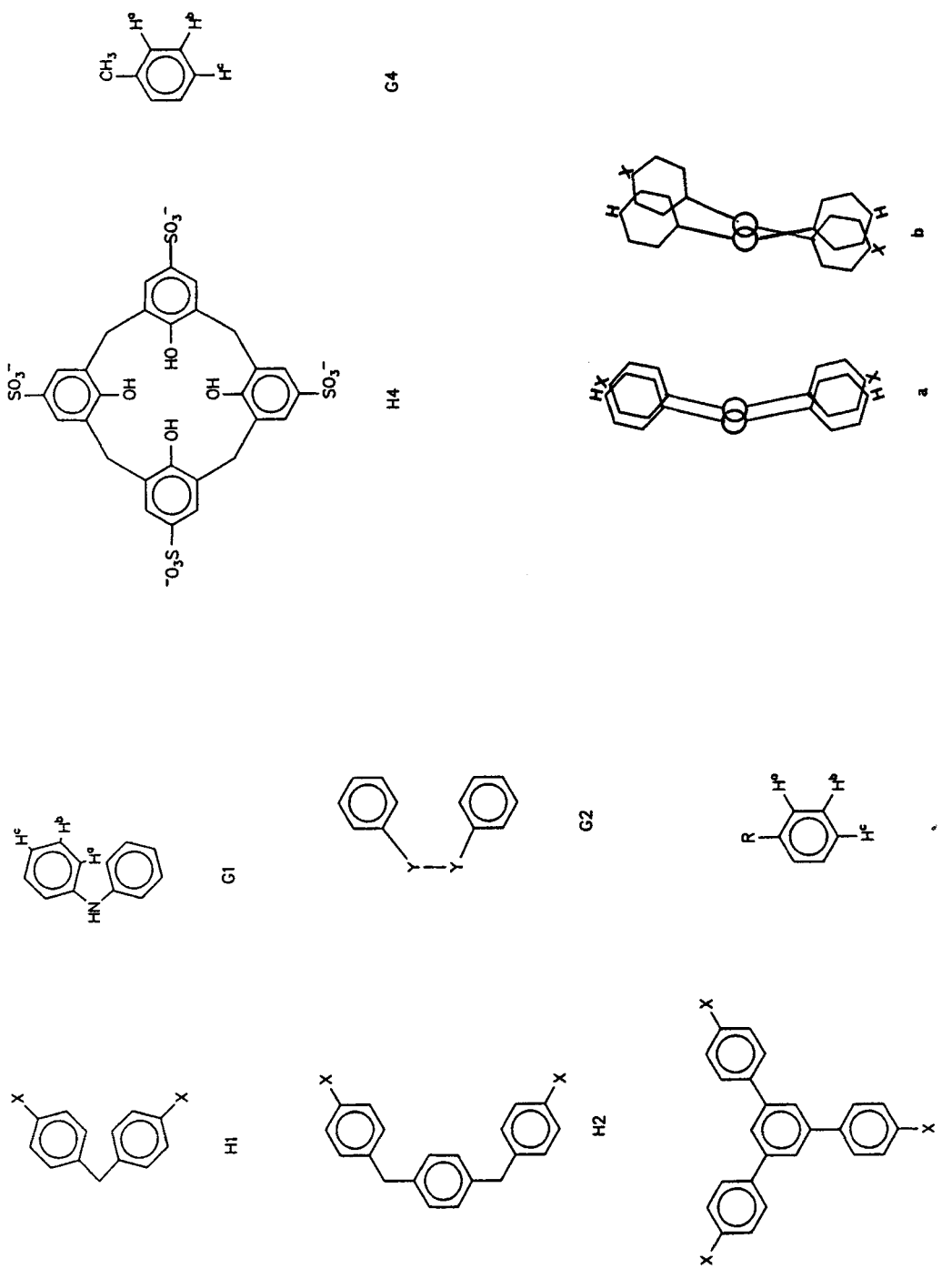

Figure 2. Disposition of complexes **H1/G1** with X = NMe_3^+ (2a) and X = SO_3^- (2b), illustrating the origin of the CIS differences at p-H_c. (double bonds are omitted)

et al.,[11a] is known to adopt a cone conformation, which is also seen in the CHARMm simulations of the complex (Figure 1c, d). The gas-phase minimizations showed a negligible strain involved if the host aryl groups seek a close contact to the toluene host; the orientation of the **G3**–methyl group inside the calixarene cavity (not shown in Figure 1c, d) instead of the methyl group up is predicted by these simplified calculations (relying only on dispersive interactions) to be less favourable by at least 20 kJ mol^{-1}. The observed CIS value on the CH_3 protons (Table 1) indeed is in better agreement with the orientation shown in Figure 1c, d. The complexation free energy observed is again in the order of the other values, although in this case the attraction by the dipoles induced by the two sulfonato groups on the guest phenyl rings in contact may be helped by an attraction between the negative host charges and the positively charged protons at the toluene guest molecule. We believe this to be the first evidence of the inclusion of the electroneutral guest toluene in a calixarene in solution.[12]

Finally, we address the question of the degree to which the observed binding could be the consequence of dispersive or solvent-driven attraction between electroneutral lipophilic surfaces of host and guest. A direct answer could be provided if corresponding totally uncharged systems were amenable to equilibrium measurements. Unfortunately, all attempts to prepare monodisperse homogeneous solutions of such electroneutral systems with the high concentrations required in aqueous solutions failed. However, we can draw conclusions from the observation that a cyclophane with negative charges (for the sake of solubility) far outside of a contact with naphthalene as guest showed a ΔG decrease from 17 to 13 kJ mol^{-1} [3d] compared with the value observed for the host with a positively charged N^+ in contact with the arene guest. Second, if lipophilic interactions were the dominating factor in the observed associations, one should expect a higher constant for the **H2** + **G2** combination, in contrast to the experimental finding of considerably larger constants for **H1** + **G1**. Third, the weak binding in the complex **H3**/**G3** even in water with only 5% methanol is in line with the guest surface being restricted essentially to the contact with the electroneutral centre of the extended host surface.

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