

Associations with Porphyrins in Water: Quantification by Constant Free Energy Increments

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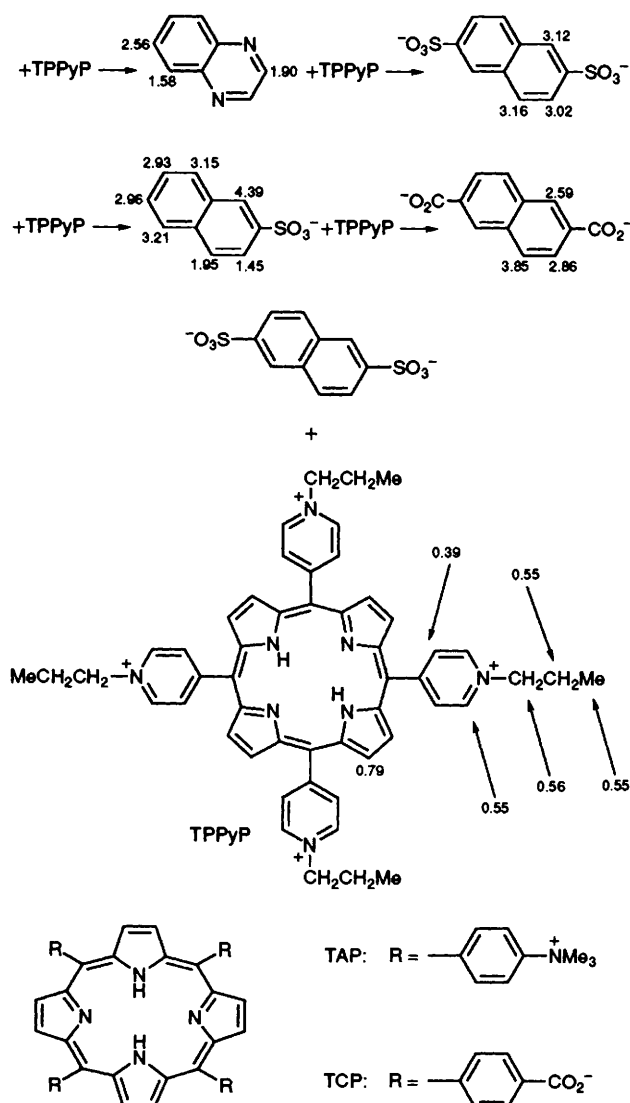
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Association constants of porphyrins bearing cationic or anionic substituents in the *meso*-position with many aromatic ligands are reported and can be described by constant factors; comparison with saturated ligands show that van der Waals and not solvophobic interactions prevail for such π -systems.

Non-covalent interactions with porphyrins are of much current interest in view of their biological significance,¹ in particular their role in targeting DNA,^{2,3} and their use in catalytic³ or photochemical⁴ systems. Associations of many aromatic substrates with porphyrins bearing ionic substituents have been investigated in water.⁵⁻⁷ However, in spite of detailed investigations,^{5,8} no general scheme was found until now which would allow prediction of association energies for such complexes. Hunter and Sanders⁹ provided simplified calculational models aiming mostly at *structural* predictions of associations between porphyrins, which again do not deliver the interaction energies responsible for the function of many systems in solution. The same problem arises with theoretical approaches based on MO¹⁰ or force field calculations.¹¹ In the present paper we want to demonstrate how the systematic

analysis of a large number of equilibria between porphyrins and ionic as well as electroneutral ligands can lead to an incremental description of the total free energy of association ΔG_t . This LFER-type of approach^{11a,b} has been successfully used until now for the description of over 60 ion pairs¹² including DNA groove binders,¹³ of over 120 crown ether and cryptand complexes with alkali and ammonium ions,¹⁴ and with peptide-like hydrogen bond associations.¹⁵

Porphyrin associations have the advantage of being evaluated easily by observation of Soret band changes. As long as we stayed at concentrations of ligands not higher than four times above the dissociation constant K we observe almost always excellent isobestic points indicative of only one type of complex. The porphyrins used were *meso*-tetra(4-*N*-propylpyridinium)porphyrin TPPyP,¹⁶ *meso*-tetra(4-*N*-trimethylanilinium)porphyrin TAP¹⁷ as water-soluble cationic accep-







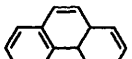


Scheme 1 Selected CIS values ([ppm], positive sign: upfield shifts)

Table 1 Total free energies of complexation (ΔG_t) and van der Waals contributions (ΔG_{vdw}) derived from ΔG_t^a

L	Ligand	TPPyP		TAP	
		ΔG_t	ΔG_{vdw}	ΔG_t	ΔG_{vdw}
1		12.9	7.9	—	—
2		13.3	8.3	—	—
3		19.3	9.3	13.4	8.4
4		20.1	15.1	20.9	15.9
5		20.9	15.9	19.5	14.5
6		24.1	14.1	23.8	13.8
7		28.9	18.9	23.0	18.0
8		13.1	8.1	—	—
9		8.0	—	—	—

^a From measurements of K at 298 ± 1 K in water, unless noted otherwise; free complexations enthalpies ΔG in (kJ mol⁻¹) units.

Table 2 Total free energies of complexation ΔG_t with electroneutral and anionic ligands^a

L	Ligand	TPPyP ΔG_t	TAP ΔG_t	TCP	
				ΔG_t	ΔG_{vdw}
10		6.2	6.2	—	—
11		6.4	7.3	—	—
12		16.7 ^b	16.2 ^b	—	—
13		16.1	16.3	—	—
14		19.0 ^b	18.0 ^b	—	—
15		—	—	19.1	14.1
16		—	—	—	15.8

^a See footnote (a) to Table 1. ^b Extrapolated from data in H₂O–MeOH; the log *K* values showed linear dependence on the MeOH content (vol%) from 10 to 50% methanol.

tors, and *meso*-tetra(4-carboxyphenyl)porphyrin TCP¹⁸ as an anionic counterpart. In agreement with Pasternack *et al.*¹⁹ and Fiel *et al.*²⁰ we find no indication of TPPyP dimer formation, for which Kano *et al.*⁵ and Brookfield *et al.*²¹ describe association constants of 10⁷ dm³ mol⁻¹. Equilibrium constants *K* for a 1:1 complex between porphyrin and ligand were obtained with excellent correlation using standard non-linear least-square fit procedures.²² Between 20 to 80% complexation there was no systematical deviation from the 1:1 model fit, and the standard deviation of *K* was below 7%. Only in some cases and with higher ligand concentrations (not reported in this communication) deviations were found, which then were fitted with an appropriate computer program.

In view of sufficient water solubility most of the data were collected with cationic porphyrins and anionic aromatic ligands (Table 1). For the dissection of Coulomb-type and van der Waals contributions ΔG_{vdw} we proceed similar as earlier¹² with the analysis of aromatic ion pairs and subtract from the total (experimental) free energy of association ΔG_t the expected Coulomb factor, which is approximated as $\Delta G_c = n \times 5 \text{ kJ mol}^{-1}$, where *n* = number of possible salt bridges, see eqn. (1).

$$\Delta G_{vdw} = \Delta G_t - n \times 5 \text{ kJ mol}^{-1} \quad (1)$$

The single value of 5 kJ mol⁻¹ is the one obtained from many ion pairs, ranging from zinc sulfate¹² to DNA complexes.¹³ The essential condition^{10b} that each anion matches *one* counterion at a given time was secured by inspection of molecular models. With the obvious deviation of the terephthalate **3** and TAP, where simultaneous contact is excluded by the long distances between the +N groups, all ΔG_{vdw} values obtained this way were gratifyingly consistent, with 8.5 ± 1 kJ mol⁻¹ for benzene systems, and 15 ± 1 kJ for the naphthalene derivatives. Only the dicarboxylate **7** showed a

somewhat larger value, which might relate to the higher electron density in this ligand.

Similar values for the van der Waals contributions were obtained from measurements with the anionic porphyrin TCP, and, more significant, with electroneutral ligands again showing almost twice as large contributions for the naphthalene-like frameworks compared to the six-membered rings (Table 2). Surprisingly, the introduction of nitrogen atoms—which was necessary in view of water solubility—did not alter the ΔG_{vdw} values significantly.

The results seem to be in line with hydrophobic effects both of entropic or of 'non-classical'²³ enthalpic nature, the latter originating in cohesive interactions which are disturbed to a lesser degree upon association of two lipophilic parts to one. This effect was believed by Kano *et al.*⁵ to dominate on the basis of enthalpy measurements. Both hydrophobic effects should increase with the surface areas excluded from water,²⁴ which, however, is not quite in line with our observations. Most important, measurements with saturated frameworks such as **8** or **9**, which do have quite similar surface areas to the aromatic systems show the complete absence of any van der Waals contributions (Table 1). This leaves high order, in particular dispersive mechanisms as the dominant factor in the π - π or 'stacking' interactions. Attractive dipole-dipole contributions by small charge separations *e.g.* in C–H bonds also can play a role, but are obviously unimportant for saturated frameworks although these also do contain somewhat polar C–H groups. More likely are contributions from dipoles induced by the permanent charges in the porphyrin derivatives, although the +N or COO⁻ groups lie outside the π moieties which in view of the NMR spectroscopic results (see below) are more at the centre of the macrocycle. We note that these van der Waals effects also are exceptionally strong in water as a result of its extremely low polarizability. The high polarizability of the π electrons leads to van der Waals effects obviously not as a function of lipophilic area: if we divide the ΔG_{vdw} values by the number of aromatic carbon atoms participating we arrive at a surprisingly constant value, namely with **1–3**, **8**, **10**, **11**: (6 atoms) average 1.26 ± 0.23 kJ; with **4–6**, **12**, **13**, **15**, **16**: (10 atoms) 1.54 ± 0.10 kJ and with **14** (14 atoms): 1.33 kJ.

Preliminary NMR studies indicate that the dominating conformations contain the porphyrin and the aromatic substrate essentially in a plane-to-plane stacking orientation centred at the macrocycle. The shift changes upon 100% complexation ('CIS-values') were obtained from single measurements in solutions in which the complexation degree could be calculated from the independently determined equilibrium constants; the CIS data (Scheme 1) show typical upfield shifts both from the porphyrin on the ligand as well as on the porphyrin by the ring current of the aromatic substrates.

We conclude, that association energies in water with these systems can be easily factorized into ΔG values of 5 kJ per mol and salt bridge, and about 1.4 kJ per mol and π -electron. Although the comparison to saturated ligands allows mechanistic conclusions, at least eliminating solvophobic forces as major contribution, it should be stressed that the constant increments described here are independent of any mechanistic arguments and may find wide applications to other supra-molecular complexes. Preliminary studies²⁵ indicate that similar additive increments are operating also in metalloporphyrins as long as the coordination sphere is saturated by the porphyrin, such as with copper derivatives, in contrast *e.g.* to zinc porphyrins.

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