

Ligand-Porphyrin Complexes: Quantitative Evaluation of Stacking and Ionic Contributions¹

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Association energies of 3 porphyrins bearing *meso*-4-pyridinium, 4-anilinium, or 4-benzoate substituents (**TPPyP**, **TPA**, **TCP**) are evaluated in water with 23 different ligands. UV titrations show excellent fit and constant values (usually $\pm 10\%$) for the equilibrium constants K evaluated at different wavelengths as well as isosbestic points, securing 1:1 complexes as well as negligible self-association of the porphyrins. Complexation-induced proton NMR shifts (CIS) show shielding of the ligands by up to -8.0 ppm, and of up to -3.4 ppm on the porphyrins with aromatic ligands; they agree with tight face-to-face conformations. Ionic binding contributions can be factorized with 5.2 ± 1.1 kJ per mol and per salt bridge (or ion pair). After subtraction of the salt bridge increments, constant binding free energies are observed with $\Delta G_{\text{vdw}} = 7.2 \pm 1.5$ kJ mol⁻¹ for all benzene derivatives and $\Delta G_{\text{vdw}} = 15.8 \pm 1.8$ kJ mol⁻¹ for all naphthalene-like, and $\Delta G_{\text{vdw}} = 18.5 \pm 0.5$ kJ mol⁻¹ for phenanthrene-like derivatives. Deviations are observed with bulky substituents like ⁺NMe₃ or SO₃⁻ groups which allow no close contact between the aromatic planes, as evident from CHARMM simulations. Heterocyclic electroneutral ligands show the *same* constant ΔG_{vdw} values, independent of number and position of the heteroatoms. Comparison of 33 different ΔG_{vdw} contributions with the number of double bonds occurring in the ligands yields, for the first time, a comprehensive description of stacking interactions with an increment of 1.4 ± 0.15 kJ per mol and π -electron. Measurements with saturated ligands of comparable surface show *no* ΔG_{vdw} contributions, indicating that the stacking is not driven by solvophobic but by van der Waals forces. Copper(II) in the porphyrins (**CuTPPyP**) leads within ± 0.4 kJ mol⁻¹ to the same association energies as without metal, whereas introduction of zinc leads to a decrease by usually 3.4 kJ mol⁻¹. Axial orientations of the ligands are observed with complexes of α,ω -diaminoalkanes with a gable or sandwich Zn-porphyrin dimer. The ΔG_{cplx} values, measured in chloroform, increase with the match between the Zn and the N atoms. Measurements of K in binary methanol-water mixtures with four complexes (e.g. **TPPyP** + phenanthroline) show linear correlations with solvent polarity or hydrophobicity parameters. Linear correlations are also found for the first time between the complexation-induced Soret band wavelength changes and the corresponding ΔG_{cplx} values.

Introduction

Although a large number of synthetic porphyrin host-guest systems with intricate structures have been studied,²⁻¹⁷ relatively little is known about the mechanisms involved in the formation of the corresponding

supramolecular complexes. The predictability of pertinent intermolecular interactions is of particular importance in view of the potential uses of porphyrins as anticancer,¹⁸⁻²⁰ anti-viral,²¹ or antimalaria²² drugs, as structural probes and target systems for nucleic acids,²³⁻³⁰ and in catalytic²³ or light-converting³¹ systems. In spite of detailed investigations especially by the groups of

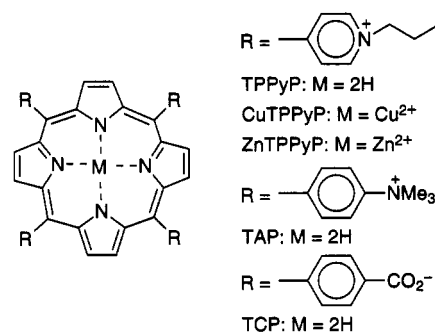
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Kano,^{2,32-38} Shelnutz,⁴ Tran-Thi,³ and others³⁹⁻⁴⁸ on associations between water-soluble porphyrins and aromatic substrates, it was not possible until now to derive rules or quantitative predictions of the underlying non-covalent interactions. The recent theoretical approaches by Hunter and Sanders⁴⁹ yield a simplifying model for the expected general structures of porphyrin associations, but no values for the actual complexation constants. The corresponding interaction *energies* represent the essential basis both for the understanding of many biological properties as well as for the practical uses of porphyrins; they remain, however, rather elusive until now in spite of many promising experimental^{2-4,32-48,50,51} and several theoretical^{49,52,53} investigations. We have set out to derive a comprehensive description of such association free energies from a systematic analysis of mostly water-soluble porphyrin-ligand complexes, including those with copper or zinc coordination.⁵⁴

Associations of aromatic ligands with porphyrins also provide an excellent insight into nature and magnitudes of π - π stacking interactions. These van der Waals forces play an important role in many biological⁵⁵ and supramolecular⁵⁶ complexes; again, actual values of these interactions are until now as unknown as their origin. Introduction of ionogenic groups into aryl rings in the meso position of porphyrins provides not only water solubility but also constant salt-bridges to substrates with complementary charges, thus allowing a factorization of the different binding contributions which we have successfully applied to a variety of other supramolecular

Scheme 1. Structures of TPPyP, CuTPPyP, ZnTPPyP, TAP, and TCP



complexes.^{53a,57} These porphyrins provide a large aromatic surface, the interactions of which then can be studied with organic substrates of systematically varied size and electron distribution. A further advantage lies in the sensitivity of the Soret bands toward association with organic ligands which in contrast e.g. to many supramolecular cyclophane complexes allows convenient evaluation of equilibrium constants by UV/vis techniques. The ring currents of the porphyrins finally lead to valuable insight into the solution structures by straightforward NMR measurements.

Experimental Details

Compounds. Structures of compounds are given in Schemes 1 and 3. Purities were checked by NMR (Bruker AM400), FAB-MS (Varian-Mat 311), and TLC if possible. As elemental analysis was often difficult as a result of hygroscopicity, ¹H-NMR quantitative analysis using exactly known amounts of an internal standard (e.g. dioxane) was used to show purities of always >95%. All porphyrins were obtained as purple or brown-red crystals or powders with melting points >300 °C; their NMR and UV/vis (Kontron Uvikon 860) data agreed with literature data unless noted otherwise.

Most of the porphyrins **P** (Scheme 1) were prepared according to literature procedures (TPPyP,⁵⁸ TAP,⁵⁹ TCP⁶⁰ (¹H NMR Table 1, UV/vis Table II, supplementary material), with the following variations:

5,10,15,20-Tetrakis(4-propylpyridinium)porphyrin bromide (TPPyP) (the chloride is described,⁵⁸ however without experimental details): *meso*-tetrakis(4-pyridyl)porphyrin (Aldrich) (200 mg, 0.32 mmol) and excess 1-bromopropane (1.2 mL, 12.8 mmol) in DMF (200 mL) were refluxed for 2 h. The precipitate was filtered and washed thoroughly with CHCl₃. Further purification was performed by recrystallization in a water/acetone mixture to give 249 mg (70%) of the water-soluble porphyrin TPPyP.

ZnTPPyP/ Metalation of TPPyP. TPPyP (0.1 g, 90 μmol) was dissolved in 100 mL of water. Zinc acetate (0.12 g, 0.5 mmol) was added to the porphyrin solution. The solution was refluxed with stirring. When the formation of ZnTPPyP was complete, as indicated by the electronic absorption spectra (about 3 h), the solution was concentrated to about 20 mL and saturated KBr solution was added to precipitate the compound. The crystalline product was filtered and dried to constant weight.

1,5-Bis[*p*-(10,15,20-triphenylporphyrin-5-yl)phenoxy]pentane⁶¹ (DP) (Scheme 3). 5,10,15-Triphenyl-20-(*p*-hydroxyphenoxy)

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Table 1. Association Free Energies (ΔG_t in H₂O, 25 °C); van der Waals (ΔG_{vdw}) Contributions per π -Electron (all in kJ/mol); Wavelength Changes of the Soret Band ($\Delta\lambda$, nm)

	ΔG_t	ΔG_{vdw}	per π	$\Delta\lambda$	ΔG_t	ΔG_{vdw}	per π	$\Delta\lambda$
	TPPyP				TAP			
L1	8.0			2.5				
L2	<5.7							
L5	6.2	6.2	1.03	4.5	6.2	6.2	1.03	2.5
L6	6.4	6.4	1.07	4.0	7.3	7.3	1.22	3.5
L7	6.4	6.4	1.07	3.5	5.9	5.9		1.0
L8	12.9	7.9	1.32	6.5	10.3	5.3		6.3
L9	13.3	8.3	1.38	9.0	11.6	6.6	1.10	4.0
L10	13.1	8.1	1.35	10.0	11.8	6.8	1.13	6.0
L11	19.3	9.3	1.55	12.0	13.4	8.4	1.40	6.8
L12	17.8			12.0	15.7			7.0
L13	24.6			10.0	22.9			8.0
L15	16.1	16.1	1.61	11.0	16.3	16.3	1.63	10.0
L16	16.7	16.7	1.67		16.2	16.2	1.62	
L17	20.1	15.1	1.51	18.0	20.9	15.9	1.59	10.8
L18	20.9	15.9	1.59	14.0	19.5	14.5	1.45	7.3
L19	24.1	14.1	1.41	18.5	23.8	13.8	1.38	11.8
L20	28.9	18.9	1.89	23.0	23.0	18.0	1.80	10.8
L22	25.5	15.5		18.0	23.0	13.0		8.0
L23	19.0	19.0	1.90		18.0	18.0	1.29	
L24	22.5			16.5	19.4			8.0
L25	20.9			17.0	18.8			5.5
L26	27.0			11.5	23.9			8.5
	TCP							
L15	15.8	15.8	1.58	11.0				
L21	19.1	14.1	1.41	7.5				

nyl)porphyrin⁶² (83 mg, 130 μ mol), 1,5-dibromopentane (7 μ l, 52 μ mol), and Cs₂CO₃ (170 mg) suspended in DMF (10 mL) were stirred at 70 °C for 4 h. After the reaction, 50 mL of H₂O was added to the mixture. The precipitate was collected by filtration and washed thoroughly by H₂O and MeOH, dried, and purified on Al₂O₃ (CHCl₃ as eluent). The first band was collected, which was recrystallized in CHCl₃/MeOH (yield 36 mg, 42%). ¹H NMR (CDCl₃, TMS): δ -2.83 (s, 4H), 2.02 (m, 2H), 2.19 (m, 4H), 4.39 (t, 4H, J = 6.26 Hz), 7.34 (d, 4H, J = 8.60 Hz), 7.75 (m, 18H), 8.15 (d, 4H, J = 8.52 Hz, within error same as before with 8.60 Hz), 8.22 (m, 12H), 8.84 (d, 12H), 8.91 (d, 4H). UV/vis (CHCl₃): 418, 514, 550, 588, 643 nm. FAB-MS m/z 1330.0 (M⁺, calcd 1329.612 for C₉₃H₆₈N₈O₂).

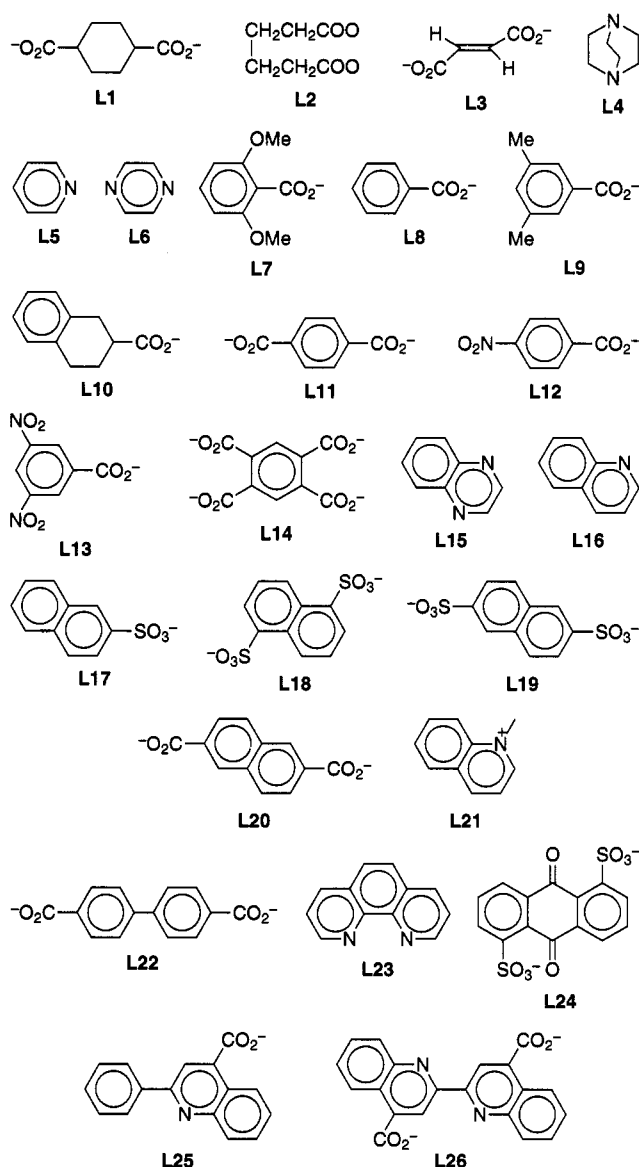
Metalation of DP⁶¹ (Zn₂DP). Porphyrin dimer free base DP (30 mg, 25 μ mol) and Zn(OAc)₂·2H₂O were refluxed in a mixture of CHCl₃ (10 mL) and MeOH (3 mL) until no absorptions were found from the metal-free porphyrin in the visible range (2 h). Then 20 mL of H₂O was added to the mixture. The precipitate was purified on silica gel with CHCl₃ as eluent. TLC (eluent: CHCl₃): R_f = 0.91. The first fraction was the Zn₂-diporphyrin (yield 19 mg, 52%). ¹H NMR (CDCl₃): δ 2.01 (m, 2H), 2.18 (m, 4H), 4.38 (t, 4H, J = 6.26 Hz), 7.33 (d, 4H, J = 8.53 Hz), 7.75 (m, 18H), 8.15 (d, 4H, J = 8.47 Hz), 8.21 (m, 12H), 8.95 (d, 12H, J = 5.65 Hz), 9.02 (d, 4H, J = 4.74 Hz). UV/vis (CHCl₃): 421 (1.7 \times 10⁶), 550 (7.28 \times 10⁴), 592 (1.58 \times 10⁴).

α,α' -Bis[*p*-((10,15,20-tri-*p*-methoxyphenyl)porphyrin-5-yl)phenoxy]xylo⁶¹ (DP') (Scheme 3). The gable porphyrin dimer DP' was prepared from 5-(4-hydroxyphenyl)-10,15,20-tris(4-methoxyphenyl)porphyrin⁶² using the same method as for DP. ¹H NMR (CDCl₃, TMS): δ -2.70 (s, 4H), 4.08 (s, 18H), 5.45 (s, 4H), 7.28 (m, 12H), 7.42 (d, 4H, J = 8.47 Hz), 7.78 (s, 4H), 8.14 (m, 8H), 8.87 (m, 8H).

Metalation of Porphyrin Dimer DP'.⁶¹ Zn₂DP' was prepared using the same procedure as Zn₂DP (yield 66%). UV/vis (DMF): 428.0, 560.0, 600.5 nm. FAB-MS m/z 1670.6 (94.72) (M⁺, calcd 1670.542 for Zn₂C₁₀₂H₇₄N₈O₈).

The substrates (ligands L1 to L26, Scheme 2) were commercially available and purified by recrystallization if necessary prior to use.

Scheme 2. Structures of Ligands



Methods. UV/Vis Titrations. In accordance with procedures published earlier,⁶³ complexation constants K were evaluated by measuring the extinctions by adding ligands **L** to the porphyrin **P** solutions so that the expected proportion of complexation was between about 20% and 80%. The porphyrin concentrations were usually around 2×10^{-6} M < **P** < 1×10^{-5} M so that the Soret band extinctions were around 1.0 (for typical titration conditions see supplementary material Section). Preliminary measurements with, e.g., **TPPyP** secured Lambert–Beer linearities within **P** concentration ranges from 10^{-7} to 10^{-3} M. That under these conditions self-aggregation of the porphyrins is negligible—in contrast to several literature claims^{2,32–37}—was furthermore established by the excellent agreement of observed extinctions E to a 1:1 association model, based on nonlinear least squares fitting.⁶³ Moreover, the equilibrium constants K obtained showed within the usual error ($\pm 10\%$) no dependence on the chosen wavelength (Figure 1; Table 3, supplementary material), in contrast to well-documented cases with simultaneous formation of other than 1:1 equilibria.⁶⁴ Finally, the observation of isosbestic

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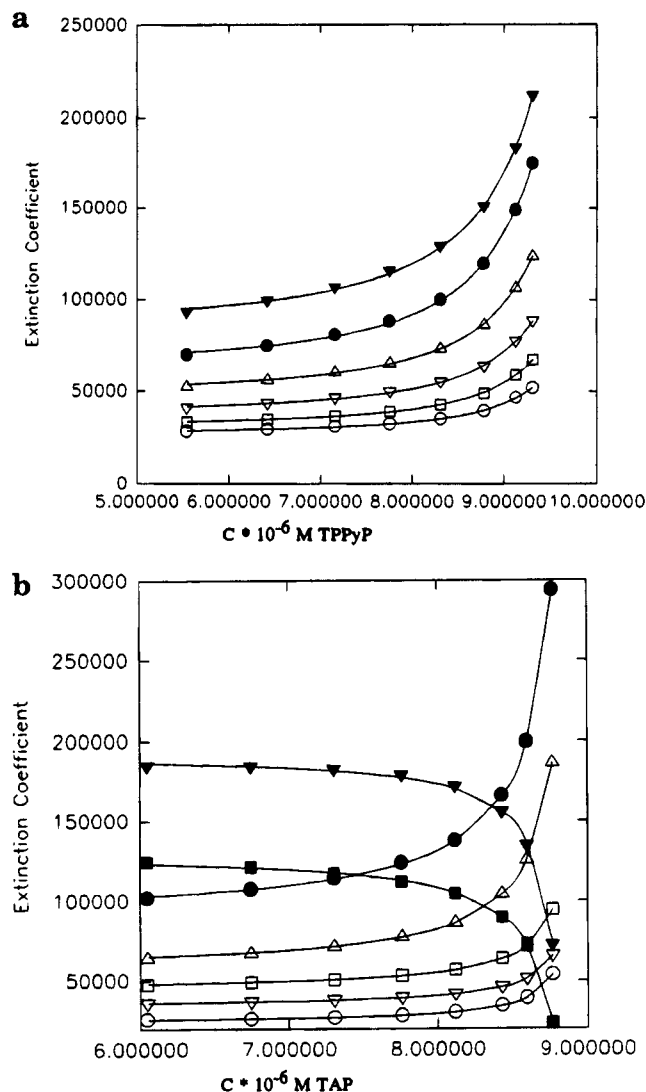


Figure 1. Fitting curves at different wavelengths. (a) **TPPyP** + **L26**; (○) λ 390 nm; (□) 395 nm; (▽) 400 nm; (△) 405 nm; (●) 410 nm; (▽) 415 nm. The corresponding association constants ($K \times 10^{-4} \text{ M}^{-1}$) are as follows: 5.25, 5.54, 5.42, 5.52, 5.62, 5.28. (b) **TAP** + **L26**: (○) λ 390 nm; (▽) 395 nm; (□) 400 nm; (△) 405 nm; (●) 410 nm; (▽) 425 nm; (■) 430 nm. The corresponding association constants ($K \times 10^{-4} \text{ M}^{-1}$) are as follows: 1.54, 1.62, 1.56, 1.60, 1.50, 1.41, 1.53.

points (Figure 2) also indicated the presence of 1:1 complexes; deviations were found only if the ligand is a nitrogen-containing heterocycle bound to **ZnTPPyP**, or if the concentration of the ligand was too high.

NMR Shifts. In view of the high association constants, the use of NMR shifts for K determinations was not practical; the shift values for 100% complexation (CIS, see Tables 2 and 3) were obtained by single measurements in D_2O , using (trimethylsilyl)propanesulfonate sodium salt (TSP) as internal reference, with known concentrations of **P** and **L**, allowing correction for the degree of complexation on the basis of the independently determined K values. Signal assignments were based on symmetry considerations, coupling constants, and comparison with similar compounds, in some cases also on HOMO-COSY experiments.

Results and Discussion

Associations with Metal-Free Porphyrins. Earlier studies with now more than 60 cases have shown that in water the formation of a salt bridge yields a value of

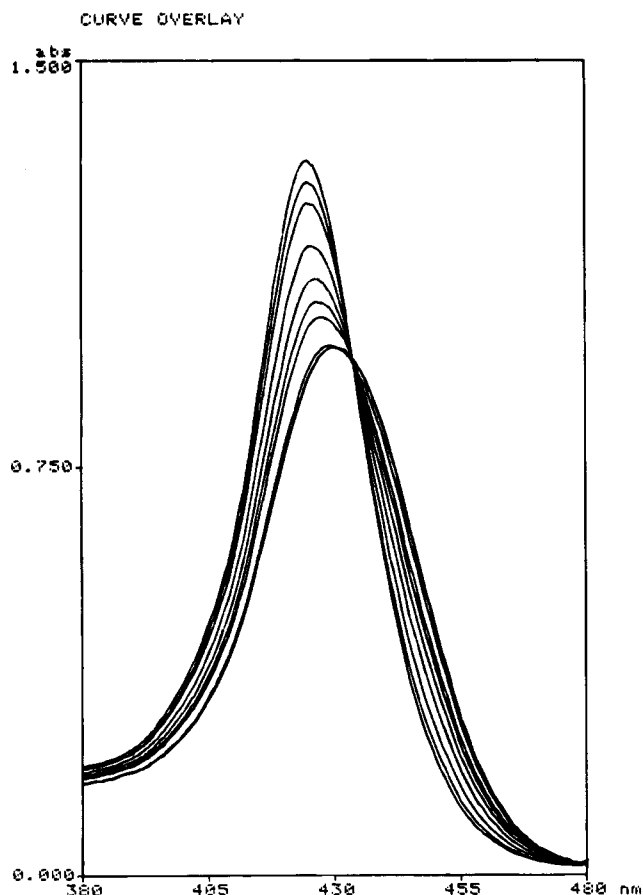


Figure 2. UV/vis spectra of **TPPyP** as a function of the concentration of 2,6-naphthalenedicarboxylate with the isosbestic point.

$5 \pm 1 \text{ kJ/mol}$, almost independent of the nature of the interacting ions.^{65,66} A similar value, although somewhat less constant (see below), is visible in the porphyrin associations if we compare e.g. the difference in association free energies $\Delta\Delta G$ between electroneutral ligands such as **L5**, **L6**, **L15**, and **L16** with those bearing 1 charge (**L8** to **L10**, **L17**, **L21**) and 2 charges (**L11**, **L18**, **L20**) (Table 1). An exception is the naphthalene-disulfonate **L18**, which may relate to the known steric hindrance of the 1- and 5-positions in this ring. For similar reasons *o*-methoxy groups (**L7**) lead to a smaller $\Delta\Delta G$ value, which is also observed in the complex of **TAP** with **L11**: here the bulky $^+\text{NMe}_3$ group prevents a close contact between the **L**- and **P**- π -surfaces. A close contact between the aromatic fragments in the case of **L22** requires some additional strain energy for flattening the biphenyl part, which leads to a lower $\Delta\Delta G$ value. Nitro substituents such as in **L12** and **L13** enhance the binding, presumably due to additional attraction with the negative charges on the N-O group as well as to the extended polarizable system. Some of the larger aromatic ligands such as **L25** and **L26** showed smaller ΔG values due to steric hindrance of association and cannot be accommodated at the porphyrin core as visible by CHARMM-simulated conformations.

(64) Schneider, H.-J.; Xiao, F. *J. Chem. Soc., Perkin Trans. II* **1992**, 387.

(65) Schneider, H.-J.; Blatter, T. *Angew. Chem.* **1992**, *104*, 1244; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1207.

(66) Schneider, H.-J.; Schiestel, T.; Zimmermann, P. *J. Am. Chem. Soc.* **1992**, *114*, 7698.

Table 2. CIS Values of Ligands (ppm) (in D₂O, 25 °C)

ligand	H ₁	H ₂	H ₃	H ₄	H ₅	H ₆	H ₇	H ₈	Me
L8	δ ₀		7.86	7.47	7.53				
	TPPyP		-0.90	-1.53	-1.77				
	TAP		-0.51	1.10	0.59				
L9	δ ₀		7.34		7.05				2.18
	TPPyP		-1.43		-3.00				-1.85
	TAP		1.18		-2.31				-1.18
L11	δ ₀		7.87						
	TPPyP		-3.19						
	TAP		-0.60						
L12	δ ₀		7.81	8.08					
	TPPyP		-5.22	-4.91					
	TAP		-3.53	-3.73					
L13	δ ₀		8.98		9.12				
	TPPyP		-3.65		-3.82				
	TAP		-4.47		-7.99				
L15	δ ₀		8.54	8.54		7.64	7.64	7.64	7.64
	TPPyP		-1.90	-1.90		-1.58	-2.56	-2.56	-1.58
	TAP		-1.33	-1.33		-1.24	-1.88	-1.88	-1.24
	TCP		-0.35	-0.35		-0.32	-0.46	-0.46	-0.32
L17	δ ₀	8.35		7.85	8.01	8.01	7.66	7.66	7.98
	TPPyP	-4.39		-1.45	-1.95	-3.21	-2.96	-2.93	-3.15
	TAP	-3.45		-0.27	-0.86	-1.85	-2.27	-2.27	-1.81
L18	δ ₀		8.87	7.76	8.23				
	TPPyP		-2.71	-1.18	-4.13				
	TAP		-5.35	-2.85	-4.26				
L19	δ ₀	8.43		7.94	8.19				
	TPPyP	-3.12		-3.02	-3.16				
	TAP	-1.52		-1.91	-1.28				
L20	δ ₀	8.23		7.97	8.06				
	TPPyP	-2.59		-2.86	-3.85				
	TAP	-2.00		-1.88	-2.82				
L21	δ ₀		9.22	8.04	9.12	8.04	8.37	8.40	8.27
	TCP		-4.57	-4.83	-5.99	-4.32	-5.05	-4.36	-4.94
L22	δ ₀		7.80	7.97					
	TPPyP		-2.03	-4.30					
	TAP		-1.88	-4.48					
L24	δ ₀		7.21	6.39	6.42				
	TPPyP		-1.59	-2.03	-2.53				
	TAP		-1.52	-2.08	-2.39				

ligand	H ₁	H ₂	H ₃	H ₄	H ₅	H ₆	H ₇	H ₈	Me
L26	δ ₀		8.34		8.23	7.77	7.93	8.23	
	TPPyP		-2.74		-3.91	-2.23	-2.81	-2.27	
	TAP		-1.03		-2.09	-1.57	-1.90	-1.24	

Computer-aided molecular modeling, based on the CHARMM force field,⁶⁷ confirmed that sufficient contact between the charged parts of porphyrin and ligand exists in the complexes (Figure 3), and that indeed bulky groups such as in **L19** hinder the approach of the aromatic surfaces. The face-to-face geometry was secured by the NMR shifts observed *both* on the ligands and on the porphyrins. In all cases the CIS values (Table 2) of up to -8 ppm on the ligands reflect the known high shielding effects of the porphyrin ring current.⁶⁸ More important, the typical anisotropy effects of the aromatic ligands on the porphyrin ring exclude significant participation of axial association even with nitrogen-containing heterocycles and e.g. **ZnTPPyP** (see below).

From the observed $\Delta\Delta G$ values it is obvious that the extension of the aromatic surface from benzene (C₆) to naphthalene (C₁₀) and anthracene- or phenanthrene-like systems (C₁₄) leads to the expected increase of complexation strength. It is striking that one can describe the association energy as the sum of rather constant increments, which amount to 5.2 kJ/mol for the salt bridge—in accordance with our earlier findings.^{53b,c,65,66} The re-

maining van der Waals contributions $\Delta\Delta G_{\text{vdw}}$ were then obtained by subtracting from the total ΔG_{cplx} 5 kJ/mol for each salt bridge and yielded 7.2 ± 1.5 kJ/mol for ligands with 6 π -electrons (ligands **L7–L14**), 15.8 ± 1.8 kJ/mol for those with 10 π -electrons (**L17–L21**), and 18.5 ± 0.5 kJ/mol for those with 14 π -electrons (**L23**). Most important, this factorization also holds for electroneutral as well as for heterocyclic ligands (**L5**, **L6**, **L15**, **L16**), which bear an additional lone pair at the nitrogen. This, however, cannot interact with the porphyrin moiety to the same degree as it is oriented away from the macrocyclic plane.

Solvophobic or van der Waals Interactions? Further insight into the mechanism of the lipophilic interactions was obtained from measurements with fully or partially saturated ligands (**L1**, **L10**). The absence of π -electrons in these frameworks leads to a complete absence of any attractive interactions with the porphyrins, although their lipophilic surface is within error the same as of the corresponding aromatic ligands. Therefore, solvophobic driving forces which should be a function of the water-exclusion surface in such associations⁶⁹ must

(67) (67) See, for example, Brünger, A. T.; Karplus, M. *Acc. Chem. Res.* **1991**, *24*, 54.

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(69) (a) Page, M. I.; Jencks, W. P. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1678. (b) Jencks, W. P. *Ibid.* **1981**, *78*, 4046. (c) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw Hill: New York, 1969.

Table 3. CIS Values of Porphyrins (ppm) (in D₂O, 25 °C)

1 Porphyrin = TPPyP						
	CH ₃	βCH ₂	αCH ₂	pyrrole CH	H ₀	H _m
δ ₀	1.78	2.92	5.52	9.68	9.54	9.91
L8	-0.55	-0.55	-0.56	-0.31	-0.49	-0.55
L9	-0.95	-0.95	-0.95	-0.99	-0.88	-0.94
L10	-1.02	-1.02	-1.02	-0.92	-1.02	-0.99
L11	-0.30	-0.77	-0.79		-0.68	-0.79
L12	-0.56	-0.57	-0.56	-0.64	-0.46	-0.52
L13	-0.51	-0.51	-0.51	-0.82	-0.49	-0.48
L15	-0.27	-0.22	-0.22	-0.20	-0.12	-0.15
L17	-0.42	-0.43	-0.44		-0.49	-0.46
L18	-0.62	-0.61	-0.65	-0.80	-0.59	-0.64
L19	-0.55	-0.55	-0.56	-0.79	-0.39	-0.55
L20	-0.30	-0.30	-0.32	-0.56	-0.26	-0.33
L22	-0.53	-0.53	-0.56	-1.01	-0.80	-0.62
L24	-0.50	-0.49	-0.50		-0.41	-0.49
L26	-0.56	-0.59	-0.7		-0.67	-0.73

2 Porphyrin = TAP				
	CH ₃	pyrrole CH	H ₀	H _m
δ ₀	4.90	9.33	8.26	8.67
L8	-2.94		0.91	-0.30
L9	-1.63	-2.90	0.15	-0.85
L10	-2.18	-0.46	0.33	-0.38
L11	-1.92	-3.38	-0.02	-0.58
L12	-1.58	-0.53	0.36	-0.08
L13	-0.92	-0.74	0.12	-0.12
L15	-1.39	-0.30	0.71	0.25
L17	-1.14	-0.35	0.38	-0.15
L18	-2.01		-0.06	-0.46
L19	-1.23		-0.01	-0.19
L20	-1.27	-0.81	-0.42	-0.45
L22	-1.10	-0.69	0.12	-0.33
L24	-1.51	-0.87	-0.17	-0.73
L26	-1.12		-0.17	-0.34

3 Porphyrin = TCP			
	pyrrole CH	H ₀	H _m
δ ₀	8.90	7.61	8.27
L15	-1.89	0.41	0.07
L21	-0.29	0.17	1.18

be excluded as a responsible driving force. It is gratifying that in accordance with this conclusion a fairly linear correlation of the ΔG_{vdw} values is found for the first time simply with the number of π -electrons in the ligands (Figure 4). That high-order effects such as dipoles induced by full or partial charges or dispersion interactions which are extremely distance-dependent represent the major driving force for porphyrin associations in water is also in line with the high sensitivity of the observed ΔG values on steric distortions by substituents.

For the first time a correlation between the association energies ΔG_{cplx} and the changes of the wavelength of the Soret band in the different complexes is observed (Figure 5), which again speaks against solvophobic binding mechanisms and supports dominating dispersive interactions which can relate to increasing HOMO–LUMO mixing between the aromatic systems. One should note, however, that there is no evidence for any charge transfer in terms of typical CT bands and that good correlations are only observed with TPPyP (Figure 5), to a lesser degree with TAP (Figure 2, supplementary material).

Notwithstanding the exclusion of hydrophobic effects as significant binding contribution, we observe a distinct decrease of the ΔG_{cplx} values with decreasing water content (Figure 6, Table 4, supplementary material). Similar observations have been made earlier⁶³ and have been attributed to solvophobic effects. With TPPyP and TAP as porphyrins and phenanthroline or quinoline as

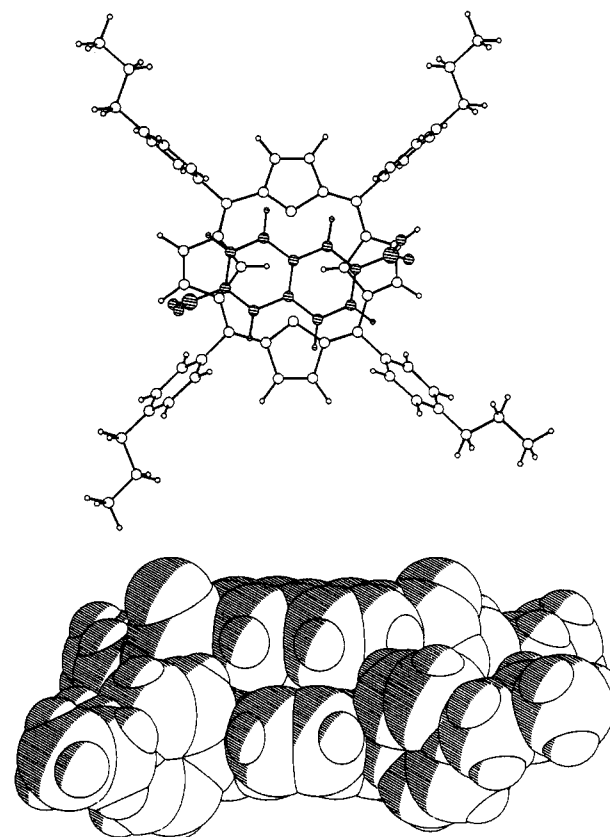


Figure 3. CHARMm/QUANTA simulations of the complex TPPyP + L20 (naphthalene-2,6-dicarboxylate).

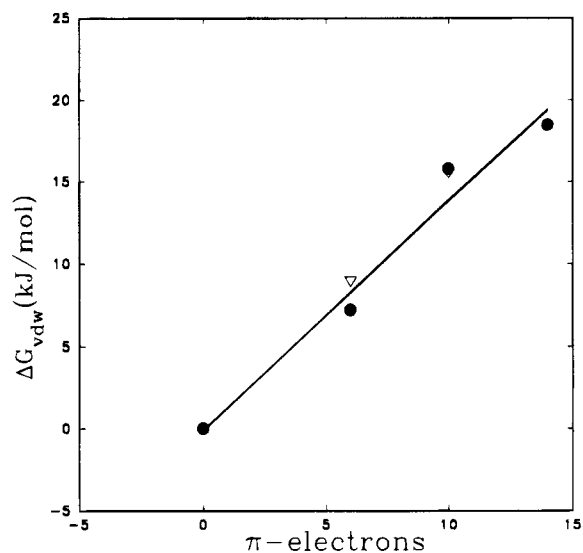


Figure 4. Correlation of stacking contributions ΔG_{vdw} vs number n of π -electrons in the ligands. (●) with metal-free porphyrins; (▽) Cu-porphyrin (the points given are average for each n).

ligand, linear free energy correlations are obtained with solvophobicity parameters S_p (Figure 6a) which have been shown earlier⁶³ to represent the best solvent parameter for the description of hydrophobic effects. The slope a as well as the abscissas $\log K^\circ$ of the corresponding correlation of a vs $\log K^\circ$ (Figure 3, supplementary material) fits well to earlier results with solvent effects on host–guest complexes, placing lipophilic contributions in the porphyrin associations with sensitivities (slopes) $4.1 < a < 5.0$ close to azoniacyclophane-arene ($a = 4.0$)

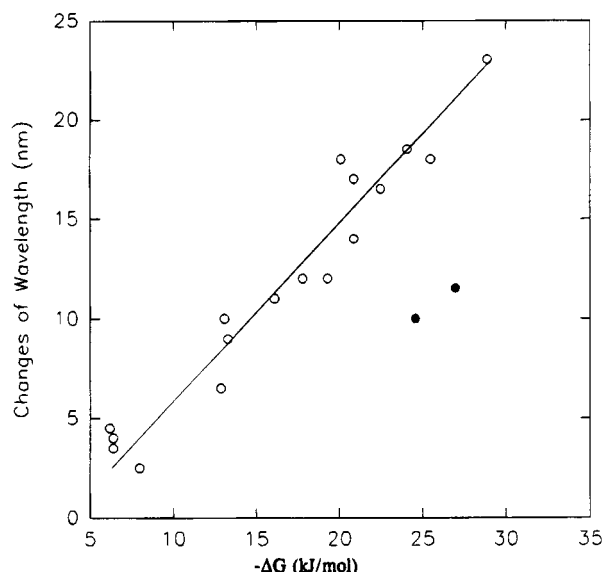


Figure 5. Changes of Soret band wavelength maxima vs ΔG_{cplx} for **TPPyP** complexes; deviations (for **L13** and **L26**): see text.

and well below cyclodextrin complexes ($\alpha = 7.0$). We note, however, that correlations with similar linearity are obtained with *polarity* parameters E_T of the methanol-water mixtures used (Figure 6b), and even with the corresponding vol/vol ratios. In view of the obvious parameter intercorrelations, the results do not necessarily point to a hydrophobic origin of the associations with porphyrins. They are equally compatible with the monotonic increase of polarizability from the extreme low value of pure water to methanol, which due to the high molarity of the solvent will compete efficiently with the aromatic ligands.

Associations with Metal Porphyrins. Zinc as well as copper ions have been introduced into the cationic porphyrin **TPPyP** in order to study the binding variations with organic ligands (Table 4). Since the net charge in the porphyrin itself does not change upon metalation, one expects the ionic binding contribution to ligand complexation to remain constant if no additional distortions are present. The ΔG_{cplx} values with the copper host **CuTPPyP** indeed are close to the measurements with the corresponding porphyrin free base **TPPyP** as well, as even the complexation-induced Soret band changes, whereas the zinc derivative **ZnTPPyP** shows ΔG_{cplx} values distinctly smaller by up to 3 kJ/mol (Table 4). On the other hand, a nitrogen compound such as DABCO **L4** shows no detectable binding with the **CuTPPyP** but sizeable values with **ZnTPPyP**. All this is in accord with the usual planar coordination of Cu^{2+} ions by 4 nitrogens and the known coordination number 5 for Zn^{2+} which requires a water molecule or a nitrogen from the ligand. Since aromatic ligand coordination from the opposite side of the porphyrin ring is still possible, the corresponding associations are not reduced by more than 1 to 4 kJ/mol (e.g. with **L3**, **L14**, **L17**–**L20**).

The NMR CIS values (Table 5) which due to the paramagnetic effect of Cu^{2+} could only be determined with the Zn complexes, support that the coordination of the aromatic substrates is still largely face-to-face, as has been demonstrated by Shelnut⁷⁰ even for Fe^{3+} –porphy-

rin–phenanthroline complexes where the nitrogen lone pair would be available for the empty Zn orbital. (Complexes with pyridine or quinoline could not be evaluated due to poor fitting even with allowance for complexes other than 1:1, and also due to too low solubility with quinoline.) The induced shifts differ not in sign but in magnitude from those in the metal-free complexes, which may be due also to geometry distortions which have large influence on the porphyrin anisotropy effects.⁶⁸ The small CIS values on fumarate **L3** indicate that this ligand is located more at the positively charged periphery of the porphyrin as to be expected; the same holds for the highly charged and hydrophilic tetracarboxylate **L14**. The shieldings induced by the aromatic ligands on the zinc **ZnTPPyP** porphyrin have values similar to those with the zinc-free systems. This indicates that at least in water as solvent the interaction of ligand heteroatoms (or carboxylate oxygen) with the central zinc ion is not strong enough to lead to axial instead of face-to-face conformations.

Binding of Diamines to Zinc-Porphyrin Dimers.

The combination of several porphyrin units by covalent bonds can lead to stronger binding of suitable polytopic ligands as well as to better defined complex geometries; such systems have been described by several groups mostly in the form of macrocyclic porphyrinophanes.^{5,71} Preliminary attempts to synthesize such water-soluble macrocycles on the basis of e.g. acid chlorides derived from **TCP** or of 5,10,15,20-tetra(*p*-pyridyl)porphyrin led mostly to polymers even under high dilution conditions. Starting from the monofunctional porphyrins **MP** and **MP'**, however, pure "gable"-type dimers **DP** and **DP'** could be prepared which allowed for the study of the dependence of complexation strength on the distance between the porphyrin centers. The latter can easily be varied by the choice of spacers **S** of variable length (Schemes 3 and 4).

The complexation of a series of polyamines with **A1** and **A7** (Table 6) suggests the expected dependence of ΔG_c , measured for solubility reasons in chloroform, on the distance d between the porphyrin centers, or Zn atoms, which was estimated from CHARMM simulations. In contrast, Danks et al. found with a porphyrinophane not such a chain length selectivity.^{5,71} All amines showed good fit to the 1:1 model as well as isosbestic points, with the exception of **A5** and **A7**, in which the presence of additional nitrogen atoms in the center of the chain can give raise to additional complexes (see Scheme 4). Primary amines show much higher complexation ΔG_{cplx} , indicating steric hindrance of the N lone pair donation to Zn by the methyl group in the tertiary amines. The highest affinity is found for **A7** which by CHARMM simulation has a α,ω -N–N distance of 7.3 Å, which compares favorably with the Zn–Zn distance of 11.5 Å, from which the Zn–N distance of 2×2.14 Å (taken from a related crystallography study⁷²) must be subtracted. The NMR shift effects of these aliphatic amines on the porphyrin are as expected small, up to –0.4 ppm; they do show splitting in up to 11 different signals (Table 9, supplementary material). The CIS values (Table 8, supplementary material) of the polyamines showed shielding by the porphyrin decreasing from up to –8.7 ppm at

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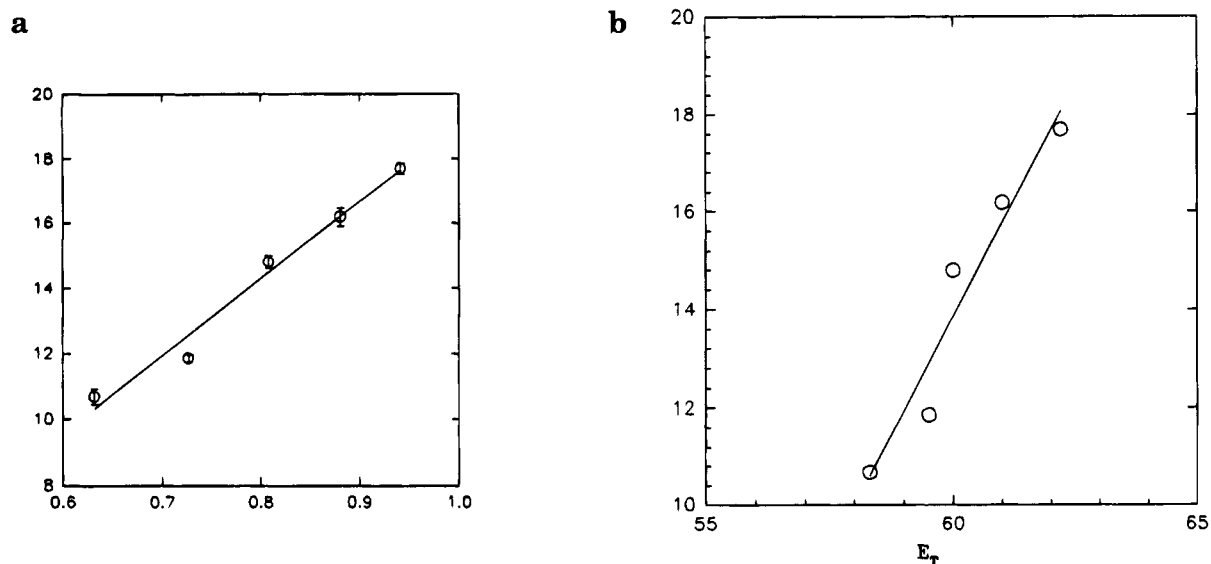


Figure 6. Solvent effects on the complex TPPyP + phenanthroline in methanol–water mixtures, 25 °C: (a) ΔG [kJ mol^{-1}] vs solvophobicity parameters S_p ; (b) vs solvent polarity parameters E_T .

Table 4. Association Energies ΔG_{cplx} (in H_2O , 25 °C) of Metal Porphyrin Complexes, van der Waals Contributions (ΔG_{vdw}) per π -Electrons (all in kJ/mol), and Wavelength Changes of the Soret Band ($\Delta\lambda$, nm)

	CuTPPyP				ZnTPPyP	
	ΔG_t	ΔG_{vdw}	per π	$\Delta\lambda$	ΔG_t	$\Delta\lambda$
L3	9.5			3.0	8.4	3.0
L4					13.2	4.0
L14	19.0	9.0	1.5	8.0	17.3	11.5
L17	20.0	15.0	1.50	13.0	17.1	10.0
L18	19.6	14.6	1.46	11.0	17.4	4.0
L19	24.2	14.2	1.42	15.0	20.8	9.0
L20	28.7	18.7	1.87	17.0	25.1	14.0

Table 5. CIS Values (ppm) of Substrates Induced by ZnTPPyP (in D_2O , 25 °C)

substrate	H ₁	H ₂	H ₃	H ₄	H ₅	H ₆	H ₇	H ₈
L3	δ_0	6.75						
L4	δ_0	-2.06						
L14	δ_0		7.50					
L17	δ_0	8.35	7.85	8.01	8.01	7.66	7.66	7.98
L19	δ_0	-6.23	-1.27	-2.12	-3.93	-4.45	-4.45	-4.16
L20	δ_0	8.43	7.94	8.19				
L19	δ_0	-1.66	-2.10	-1.40				
L20	δ_0	8.23	7.97	8.06				
L20	δ_0	-2.00	-2.60	-2.10				

Table 6. Binding Constants K , Binding Energies, Changes of Soret Band in Complexes of the Zinc-Containing "Gable" Dimer Porphyrins DA with Amines, and Distances between Nitrogens^a (K in M^{-1} , ΔG in kJ/mol ; CDCl_3 , 25 °C, $\Delta\lambda$ in nm, d in Å)

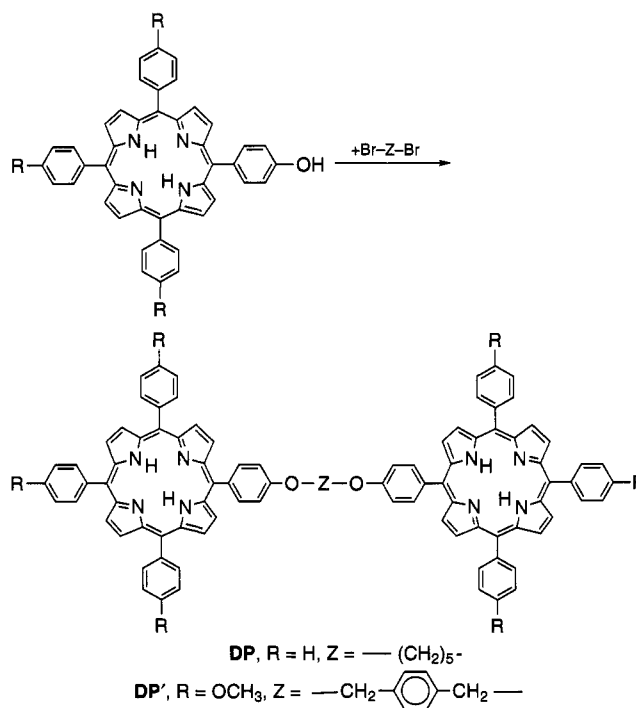
amine	ligand	$K \times 10^{-3}$	$-\Delta G$	$\Delta\lambda$	d
A1	$\text{Me}_2\text{N}(\text{CH}_2)_3\text{NMe}_2$	7.46	22.1	5	4.98
A2	$\text{H}_2\text{N}(\text{CH}_2)_4\text{NH}_2$	56.68	27.1	4	6.24
A3	$\text{H}_2\text{N}(\text{CH}_2)_6\text{NH}_2$	55.37	27.0	5	8.76
A4	$\text{Me}_2\text{N}(\text{CH}_2)_6\text{NMe}_2$	11.42	17.4	3.5	8.82
A5	$\text{Me}_2\text{N}(\text{CH}_2)_3\text{NH}(\text{CH}_2)_3\text{NMe}_2$	16.20	24.0	5	4.96, 9.90
A6	$\text{H}_2\text{N}(\text{CH}_2)_8\text{NH}_2$	38.27	26.1	7	11.30
A7	$\text{H}_2\text{N}(\text{CH}_2)_2\text{NH}(\text{CH}_2)_2\text{NH}_2$	556.4	32.8	4	3.72, 7.27

^a Distances (d) between nitrogens are from CHARMM/Quanta.

the NCH_2 protons to -3 ppm at the central CH_2 , as expected for the orientations shown in Scheme 4.

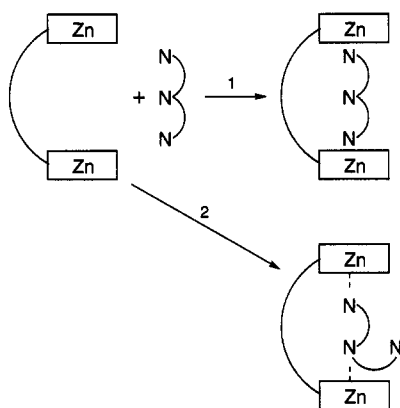
Conclusions. As with many biologically important structures the functions of porphyrin complexes rest on

Scheme 3



the simultaneous action of different noncovalent interactions. The present study shows that systematic variation of host-guest components allows us to identify and to quantify experimentally at least the ionic part of such associations in water with a constant increment of 5 ± 1 kJ per mol and salt bridge and the lipophilic part with 1.4 ± 0.2 kJ per mol and interacting π -electron of aromatic ligands. The increment derived for the first time for this stacking interaction necessarily shows a relatively large spread as the result of the strong dependence of the high order van der Waals effect on the host-guest distance which can increase by bulky substituents in the components. The observed NMR shielding effects clearly rule out significant contributions of edge-to-face conformations, which should lead to at least partial deshielding of the porphyrin protons. Macrocyclic porphyrinophanes certainly would allow e.g. the applica-

Scheme 4



tion of NOE techniques for an improved conformational analysis (for the present associations the NOE effects were too small even with spin-lock techniques). However, the use of such cyclic hosts could at the same time impose geometric constraints to the possible conformations which might well blur the interactions to be studied.

That saturated frameworks only show association in the presence of additional interactions, such as ion pairs or metal coordination with ligand heteroatoms, is of significance for the understanding of biologically or

catalytically effective complexes as well as for the mechanism of the lipophilic arene associations. That van der Waals and not solvophobic interactions play the major role here is supported by the observed dependence of the Soret band maxima on the association constant and sheds light also on other complexes involving π - π stacking.

Acknowledgment. Our work is supported by the Deutsche Forschungsgemeinschaft, Bonn, and the Fonds der Chemischen Industrie, Frankfurt. W.M. thanks the Chinese Educational Committee for a stipend.

Supplementary Material Available: Tables of ^1H NMR shifts, UV/vis data for TPPyP, TAP, and TCP, association K and extinction coefficients from different wavelengths, solvent effects ΔG_{oplx} as a function of water content, different correlations of K with solvophobicity parameters S_p , CIS values of ZnTPPyP complexes, NMR data for "gable" dimers DP, etc., CIS values of amines in DP complexes, and CIS values on Zn₂DP complexes and figures of distances between charged groups in porphyrins and ligands (from CHARMm/QUANTA), Soret band maxima changes vs ΔG_{oplx} for TAP complexes, and solvophobicity correlation (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.