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Dispersive interactions in supramolecular porphyrin complexes

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Abstract—Lipophilic interactions with several water-soluble synthetic porphyrins are reviewed, including the design of new artificial receptors for peptides and nucleotides. The binding free energies ΔG with a large number of substrates RX with substituents X show, that hydrophobic contributions found with saturated frameworks are negligible compared to dispersive forces; stacking with aromatic compounds is essentially a function of the number of participating π-electrons. The dispersive forces become apparent in the strong ΔG increase from X=F to Cl to Br to I, and in the high ΔG found also e.g. for X=NO_2. Even amides form relatively strong complexes, showing additive behavior with some oligopeptides. Additivity of rather constant $\Delta\Delta G$ values for many substituents is generally observed and will allow the construction of a parameter scale for dispersive interactions. With charged substrates the ion pair contribution at the applied medium ionic strength is invariably about 5 kJ/mol. The presence of anions at usual buffer concentrations diminish in particular the stacking/dispersive interactions.

1. Introduction

Non-covalent interactions with porphyrins are of broad interest in view of their biological role, including those in P450 enzymes,[1] of their reactions with nucleic acids,[2] of their use as oxidation catalysts and for electron transfer reactions,[3] and of their increasing implementation in artificial receptors for a large variety of analytes,[4] and more recently of new materials.[5] Characterization of the relevant intermolecular forces not only helps to understand on a molecular basis the function of important biological systems, but also to design recognition-directed synthetic assemblies. The evaluation of association constants in systematically varied supramolecular complexes can furnish binding free energy increments for the participating species, which is a help to disentangle the various non-covalent binding mechanisms.[6]

The large surface of porphyrins lends itself primarily to all kind of lipophilic and/or hydrophobic interactions. Many investigations have been devoted to stacking effects with porphyrins, which dominate also their intercalation between the bases of nucleic acids.[2] The present paper primarily reviews our investigations of porphyrin complexes in aqueous media.[7] Water is the medium of biological systems, and the solvent of the lowest polarizibility and therefore the medium of choice for van der Waals interactions. As with other supramolecular complexes, such as with cyclodextrins, the first mechanistic problem then lies in the separation of solvophobic and intermolecular forces.

2. Hydrophobic or lipophilic interactions?

2.1. Salt bridge contributions if ion pairs are present

The analyses of porphyrin complexes offers one of the few clear-cut clues for the absence of significant hydrophobic forces in comparison to lipophilic forces. In contrast to for instance cyclodextrins, which bind both aromatic and aliphatic guest molecules efficiently, we found the contributions of saturated frameworks in complexes as shown in Scheme 1 to be negligible. For the sake of solubility in water the porphyrins are equipped with either positively or negatively charged side groups in the *meso*-position. If one uses ionic guest compounds the charges also produce Coulomb contributions, which by comparison with a large number of smaller substrates such as substituted benzoic acids can be described with a rather constant binding free energy increment of $\Delta G_{Coul}=5\pm1$ kJ/mol per salt bridge.[7] The same number has been derived from more than 100 organic ion pair measurements in water;[8] it holds for intermediate ionic strength as used in the present cases, but increases up to 8 kJ/mol at zero ionic strength, following surprisingly well the Debye–Hückel correlation.[9] It should be stressed that the Coulomb interaction decreases if geometric mismatch does not allow the formation of contact ion pairs. A strong lipophilic interaction can optimize itself by an induced fit at the expense of a weaker salt bridge; this can lead to very small electrostatic contributions with e.g. nucleotide–porphyrin complexes (see later). A difference of $\Delta G_{Coul}=5\pm1$ kJ/mol is also seen if one compares benzoic acid e.g.

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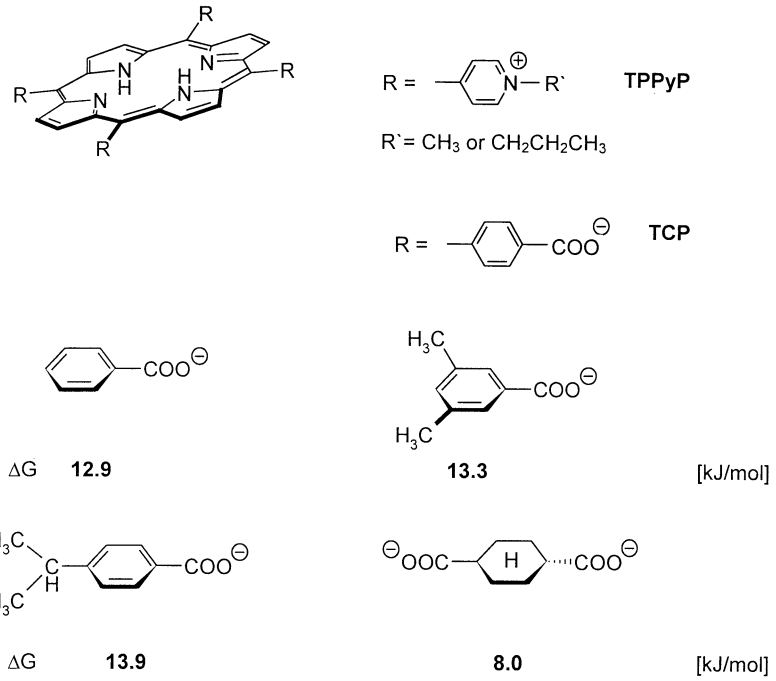


Scheme 1. The porphyrin derivatives TPPyP and TCP used as host compounds and guest molecules with free binding energies ΔG [kJ/mol, water, 25°C, 0.05 M buffer, pH 7.0], illustrating the absence of significant hydrophobic contributions.

with electroneutral pyridine etc. lending further credit to the applied free energy factorization.

The examples shown in Scheme 1 demonstrate, that aliphatic C–H fragments in the guest molecules do not enlarge the observed affinity within an scatter of ±1 kJ/mol. Most striking is the absence of any binding contribution from the cyclohexane moiety in the corresponding 1,4-dicarboxylate, although the shape is very similar to that of a phenyl derivative (Fig. 1). Conventional descriptions of hydrophobic interactions[10] vary between 100 and 400 kJ/mol/A^2; the complexation energies we observe for the phenyl derivatives etc. indicate that the lower value is more realistic.

2.2. Stacking with aromatic compounds

Aromatic compounds including, for instance fullerenes, are

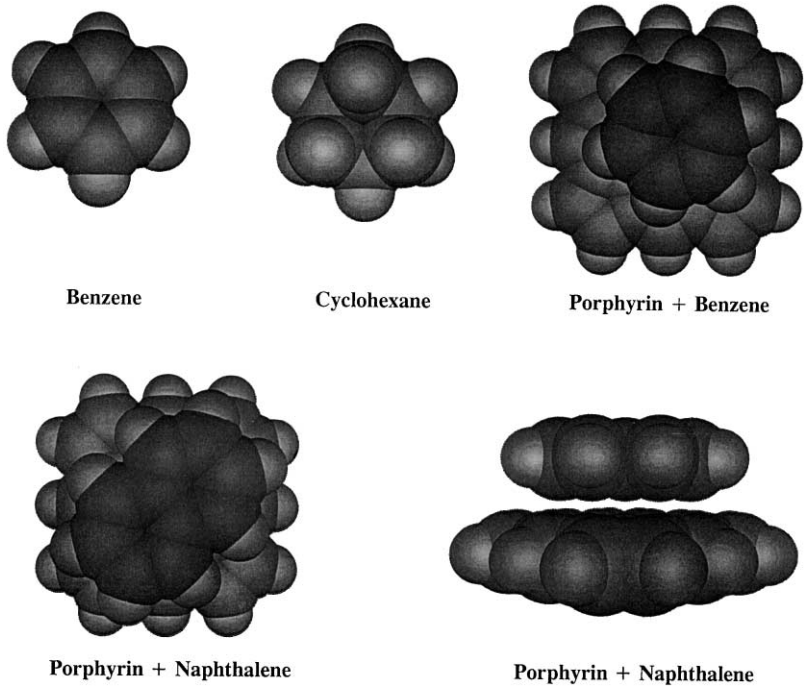
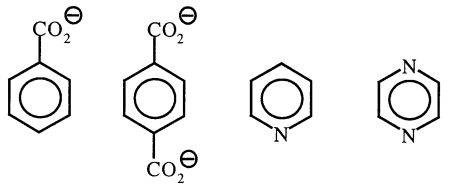
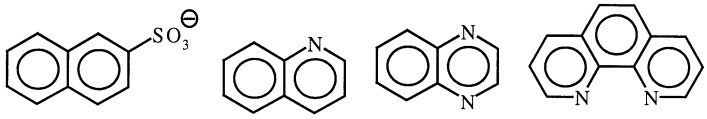


Figure 1. Illustration of selected face-to-face complexes with porphyrin, and the size of the π-moieties involved (gas phase simulations with CHARMm; substituents are omitted for the sake of clarity).



with **TPPyP**	**12.9**	**19.3**	**6.2**	**6.4**
with **TCP**	-	-	**6.2**	**7.3**



with **TPPyP**	**20.1**	**16.7**	**16.1**	**19.0**
with **TCP**	-	**16.3**	**16.2**	**18.0**

Scheme 2. Representative ΔG values [kJ/mol, water, 25°C] for aromatic compounds stacked with porphyrins.

well known to bind to porphyrins, an issue also important for self-aggregation of these compounds.[11] Measurements with either the positively charged TPPyP or the anionic TCP and guest compounds of a phenyl shape invariably give a free binding energy of $\Delta G_{disp}=7.2\pm1.5$ kJ/mol if one subtracts a $\Delta G_{Coul}=5$ kJ/mol for the ion pairs (Scheme 2). If the size of aromatic guest is increased to a naphthalene shape one observes $\Delta G_{disp}=15.8\pm1.8$ kJ/mol, again with several compounds the same value. For ligands with three condensed three rings the ΔG_{disp} increases to 18.5 kJ/mol, although for this only few examples were measured. Noticeably, water-soluble ligands such as quinoline, which do not

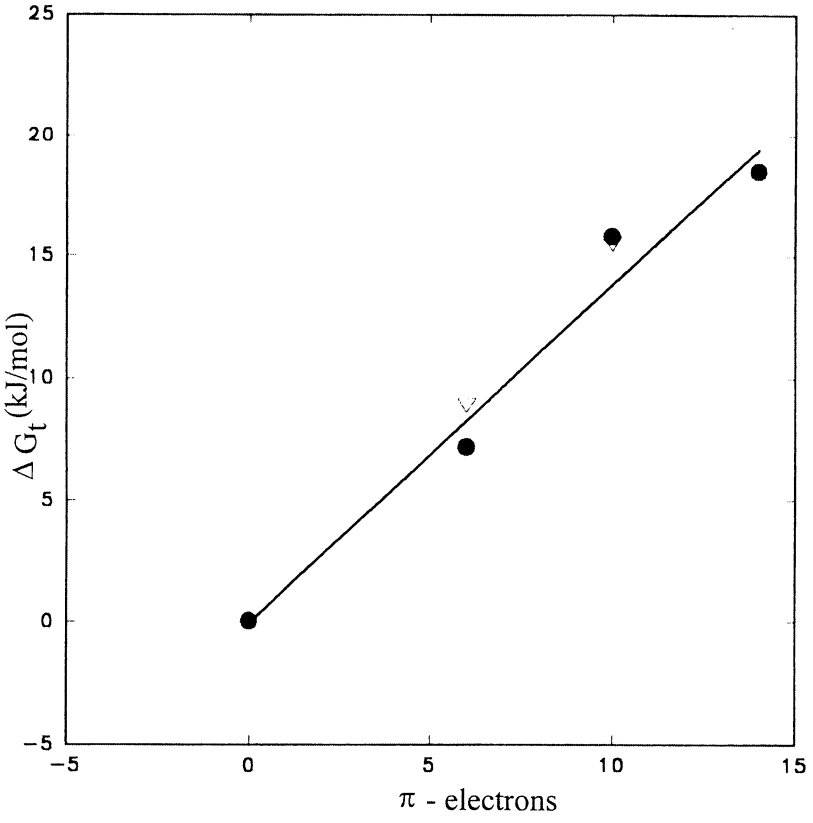
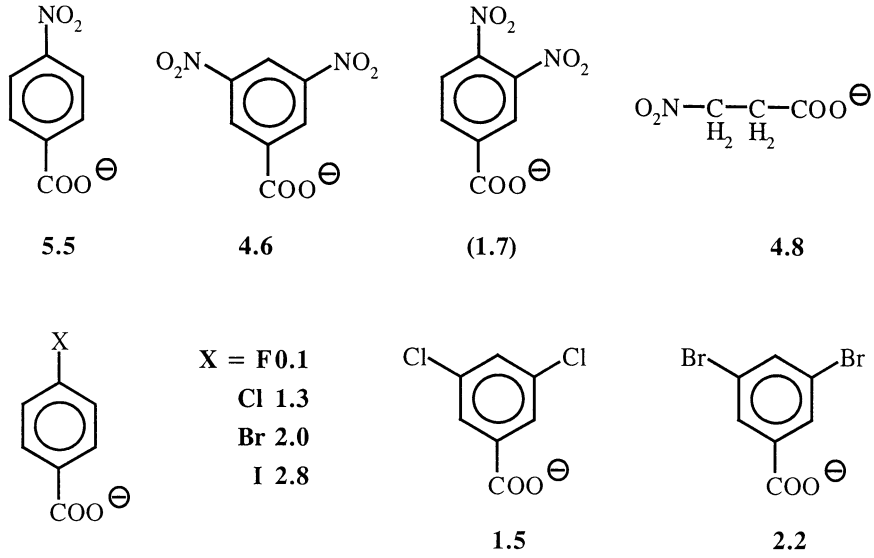


Figure 2. A plot of ΔG vs. the number n of π-electron present in the aromatic guest compounds (values with $n=6$ are the average of six systems), after correction of ΔG for ion pairing, where applicable).



Scheme 3. Selected $\Delta\Delta G$ values [kJ/mol, water, 25°C] for heterosubstituted compounds.

need ionic groups and corrections for Coulombic forces yield the same total ΔG as the ionic examples do after the correction for ion pairing.

Formation of face-to-face associations is evident from the observed ^{1}H NMR upfield shifts of porphyrin signals: edge-to-face complexation should lead also to downfield shifts of porphyrin signals by the ring current effect of the ligand. As illustrated in Fig. 1 the size of the π-system of the guest molecule is always smaller than that of the porphyrin host, which is even additionally increased by the aromatic *meso*-substituents. This makes the complexes free from random deviations due to insufficient geometric matching, and leads to the maximal stacking energies expected between aromatic molecules. The ΔG_{disp} values show less linear correlations with the surface area of the ligands than with number of π-electrons in the guest molecule (Fig. 2). In this context it is noteworthy, that intercalation strength in DNA has been found to also depend primarily on the size of the aromatic ligand, and is e.g. very similar for naphthalene and quinoline derivatives.[12]

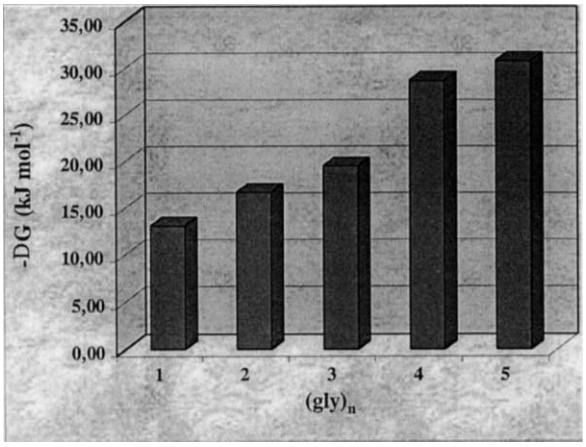
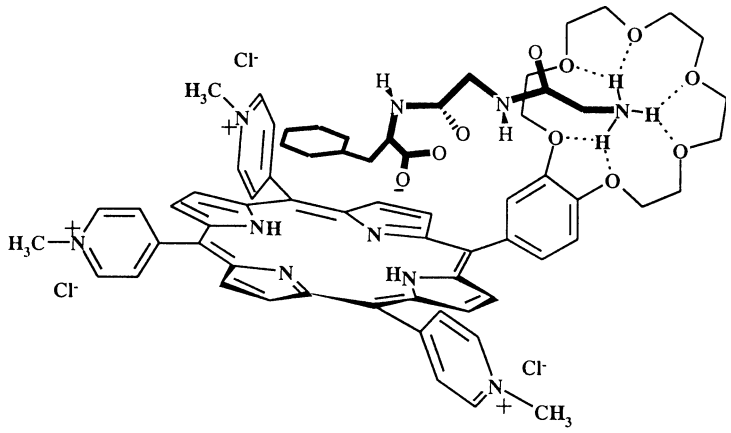


Figure 3. Binding free energy ΔG increase with the length of a peptide (receptor H1 and oligo-glycines).

One of the intriguing features of porphyrin is the possibility to implement metal cations in the center and to study their interactions with various organic ligands,[13] a topic of obvious relevance for heme or cytochrome systems. With Cu(II) complexes one finds surprisingly similar ΔG values as with the apo-porphyrin, with Zn(II), however, a decrease in ΔG. This is in line with the known square planar coordination with Cu(II), whereas Zn(II) requires an additional axial ligand—e.g. water and/or anions from the salt which interferes with the stacking of a guest compound. The Coulomb part remains unchanged as the total charge of the underlying porphyrin is not altered by metalation with M(II) cations.

2.3. Increments lipophilic/dispersive interactions with substituents

Whereas alkyl substituents lead to negligible ΔG changes (see earlier), the opposite is true for e.g nitro groups. We have now systematically varied substituents in benzoic acids, and extended this study to functional compounds with skeletons different from benzoates.[14] The results (selected examples Scheme 3) show for substituted benzoates strikingly constant values for each substituent X as long as the X groups are not in vicinal position to other substituents. Thus, the $\Delta\Delta G$ for X=NO_2 is within ±0.2 kJ/mol the same for the 3- and 4-mono-substituted compound and the 3,5-di substituted benzoate. Even the $\Delta\Delta G$ observed with simple nitromethane is within error the same! The same regular behavior is seen with other heterosubstituents, which show additive $\Delta\Delta G$ values. These analyses allow us to derive for the first time a set of substituent parameters for dispersive interactions.[14] The selected data given in Scheme 3 indicate, that the influence of substituents can be as large as that of an aromatic ring itself and does not correlate with other known substituent parameters. Obviously, the electron withdrawing or donating effects of the substituents on the aromatic moiety is negligible in comparison to the effects exerted by the X group itself. The strong ΔG increase seen e.g. from X=F to I (Scheme 3) clearly indicates that dispersive forces dominate here, which of course reflect also



Scheme 4. The porphyrin-based peptide receptor H1, with phy-gly-gly as guest.

polarizability. Introduction of heterosubstituents is synthetically well established and can greatly enhance dispersive interactions: the substituent $\Delta\Delta G$ parameters derived here can help to design new assemblies and new bioactive compounds. It should be kept in mind, that optimal recognition relies on geometric matching; due to their large surface this poses no restriction in open porphyrin complexes with ligands in which all substituents are still in contact with the π-surface of the host. In contrast, such substituents e.g. in DNA or RNA intercalators may well not be in full contact with the opposing nucleobases.

Of particular interest for biological systems is the strong effect of amide groups,[15] very likely due to contacts between the porphyrin and the amide oxygen atoms, which bear a large partial negative charge of high polarizibility. The additivity of the underlying $\Delta\Delta G$ values for each group becomes clear in the almost linear ΔG increase with the number of amide functions in oligopeptides (Fig. 3). The carbonyl oxygen in esters bears much less negative charge which explains why the complexation of porphyrins with esters in contrast to amides is very small.[15]

2.4. A porphyrin-based peptide receptor

Dispersive interactions with the porphyrin surface can be used for the design of new receptors,[4] particularly if an effort is made to implement additional recognition units by modification of the underlying porphyrin skeleton. The host H1 shown in Scheme 4 is a highly sensitive receptor for peptides, based essentially on the abovementioned interactions of the amide groups with the porphyrin moiety and the binding of the peptide N-terminus with the crown ether unit.[16] The C-terminus interacts with the permanent positive charge of the porphyrin itself. Such a combination allows selective complexation of unmodified, natural peptides in homogenous aqueous solution,[16,17] which until now was a rather elusive aim of supramolecular chemistry.[18] The complexation is accompanied by changes in the Soret band extinction which vary with the nature of the peptide.

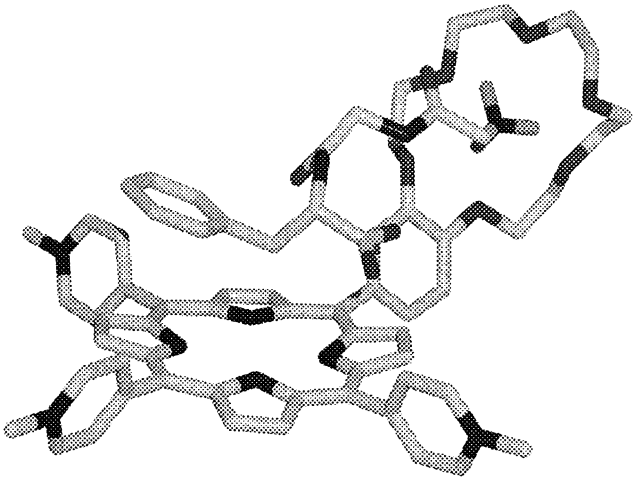


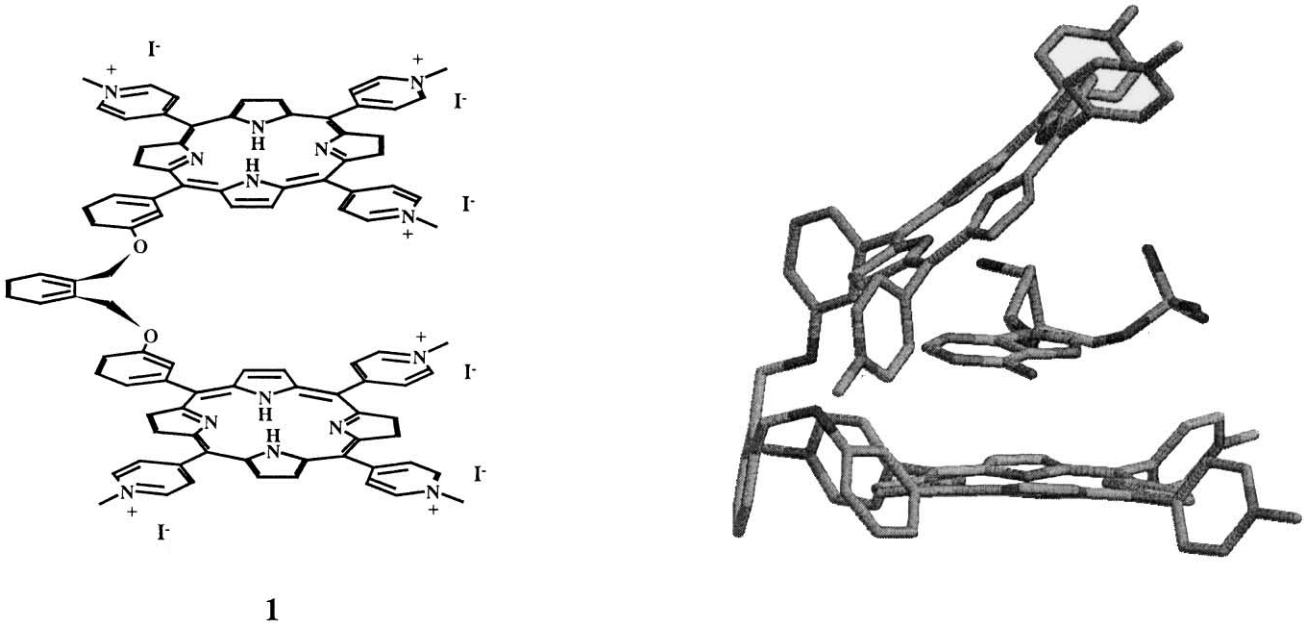
Figure 4. A computer simulated structure (CHARMm) illustrating the stacking of a phenyl ring of the tripeptide gly-gly-phe with the porphyrin moiety.

Although the crown ether unit is essential for the peptide recognition, most of the binding energy is due to the dispersive interactions with the amide groups, the contribution increasing with the length of the peptide. A crude factorization of the free energy contribution would attribute only about 5 kJ/mol to the ion pairing with the C-terminus and about the same to the crown ether unit. With a tetrapeptide for instance, the total ΔG amounts to 28 kJ/mol, which means that about 80% are due to dispersion forces. With solvents other than water, such as methanol the interaction with the crown is increased by orders of magnitude,[17] but the dominating dispersive part will decrease. As a consequence of the large porphyrin surface accommodating aryl-sidegroups of the peptide in many positions the sequence selectivity of H1 is small in comparison to an earlier receptor.[17] However, the gly-gly-phe peptide which in simulations shows a particular good stacking (Fig. 4) is characterized by a rather large extinction change at the 410 nm transition of the complex.

3. Strong complexation of nucleosides by doubled stacking interactions

3.1. Salt effects affect both electrostatic and stacking interactions

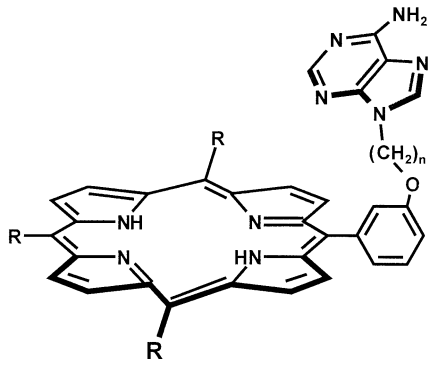
The dimeric porphyrin cleft H2 shown in Scheme 5 complexes nucleotides and nucleosides with affinities up to micromolar ranges.[19] The total binding energies come close to the sum of single association energies between



Scheme 5. Complexation of AMP with the porphyrin cleft H2.

e.g. TPPyP and corresponding nucleotides. Most remarkable, the binding of nucleosides was found to be often as strong as that of nucleotides, in spite of the possible ion pairing with the phosphate groups. This demonstrates that dispersive forces in such systems can be so strong that they 'overwhelm' other contributions, e.g. by preventing optimal contact between anion and cation. The larger hydrophilicity of ionic groups such as phosphate can then also diminish the total interactions. The absence of Coulomb attraction forces in presence of effective stacking has been shown also for complexes with other large aromatic systems, e.g. of the azapyrenium type: no affinity increase was observed there in going from AMP to ADP and ATP.[20]

Recent measurements revealed, that salts have an unexpected large influence on the binding of nucleosides and nucleotides with porphyrins.[15] The observed affinity changes go far beyond usual salt effects on ion pairs[9] which follow the Debye–Hückel equation, and can be larger for uncharged species than for ions. Thus, if one compares log K values with TPPyP in 0.1 M buffer and close to zero ionic strength the number for ATP increases from 3.4 to 4.5, whereas for adenosine one observes an even larger increase from 2.6 to 4.5. At very low ionic strength even simple salts such as NH_4Cl or Na_2HPO_4 associate with TPPyP with apparent log K values as large as 4.6.[15] In consequence, at usual buffer concentrations the porphyrin surface is 'covered' with anions, which diminishes also significantly all stacking interactions with nucleobases or other polarizable entities. For these reasons literature data on association constants of e.g. porphyrin–nucleotide complexes can be off by orders of magnitude if measured at high buffer concentrations.



Scheme 6. The hybrid porphyrin-nucleobase structure H3 with self-stacking indicated by H NMR shifts.

3.2. Attempts to combine porphyrin stacking with hydrogen bonding

It would be intriguing to combine the high affinities which can be reached for the binding of nucleotides and nucleosides by porphyrins with Watson–Crick type hydrogen bonding in order to achieve base selectivity. This has been tried with host compounds like H3, which contain nucleobases as recognition unit attached by spacers of variable length to a porphyrin.[21] Base pairing has been used several times for the design of selective host compounds, but invariably aprotic media and therefore lipophilic nucleobase derivatives had to be used. Porphyrin-based systems such as H3 would offer an approach to complexation with the natural substrates and in aqueous medium. However, it turned out that water in these open structures is still too efficient for hydrogen bonds: while there is efficient complexation of nucleotides, we find no significant discrimination between the different nucleobases. As shown in Scheme 6 the covalently attached nucleobase itself stacks with the porphyrin, with the consequence that its surface is not fully available for stacking with the analyte, leading to lower affinities than with the underlying TPPyP. The formation of the self-stacked entities in H3 is visible in upfield NMR shifts, which are diminished in non-aqueous media (see Scheme 6); it is also characterized by red shifts of the

Soret band, which are 3–6 nm for adenine derivatives, and 1–2 nm for thymine derivatives.

4. Conclusions

The large aromatic surface of porphyrins makes them convenient 'playground' for the study of intermolecular interactions. The Soret band offers the additional advantage of a built-in optical signal, which is also useful for future sensor applications. The evaluation of binding energies with systematically varied substrates gives insight in biologically important interactions and leads to quantification of group contributions in molecular recognition processes, which can be used for the design of new synthetic assemblies. Medium effects, in particular those from salts and organic co-solvents have until now often overlooked influence on porphyrin interactions. Stacking effects with aromatic substrates can be replaced and/or enhanced by substituents of high polarizibility. Modification of the porphyrin skeleton open the way to new, highly sensitive synthetic receptors which can recognize also natural compounds in aqueous environment.

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