Additivity and Quantification of Dispersive Interactions—from Cyclopropyl to Nitro Groups: Measurements on Porphyrin Derivatives**

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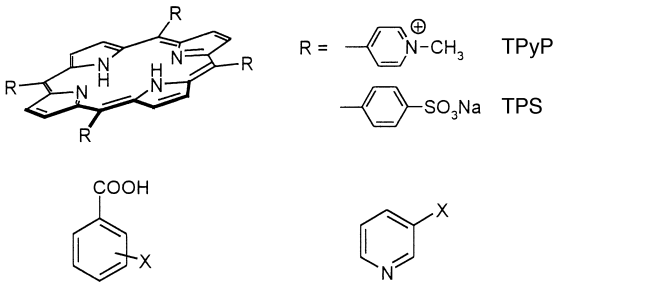
The investigation of supramolecular complexes opens up pathways to the identification of noncovalent interactions, such interactions are also of importance for biology and materials science. One example is the discovery of high-order effects in the form of cation–π interactions in organic host–guest complexes.[1] Dispersive Van der Waals interactions have hitherto defied a corresponding empirically based characterization. At the same time their theoretical calculation encounters considerable problems largely because of the need to consider polarization.[2] We report here the systematic analysis of host–guest complexes, with porphyrin derivatives in water as host molecules, which for the first time allows an unambiguous identification of dispersive interactions and provides generally applicable energy increments.

Porphyrins are made water soluble by the insertion of pyridinium or sulfonic acid moieties (TPyP or TPS, Scheme 1) into the *meso* positions, and are then highly suitable for the analysis of noncovalent interactions.[3] They show an intense



Scheme 1. Structures of porphyrins TPyP and TPS and the general formulae of the benzoic acids B and pyridines py used as guests.

absorption band at about 400 nm (Soret band) which can be readily used as a probe for the UV spectroscopic determination of equilibrium constants. Above all, however, because of their large surface, porphyrins are relatively tolerant of the necessary geometric adaptation between host and guest molecule, as long as the guest is sufficiently small. Moreover, noncovalent interactions with porphyrins and related compounds are of considerable importance in biological systems.[4]

The identification of noncovalent interactions in supramolecular structures is of limited value if the interactions cannot be energetically quantified in an adequate number of systems.[5] We have determined the complexation constant K for a number of guests (Tables 1 and 2 and Table I of the Supporting Information) with the porphyrins TPyP and TPS as host molecules by the previously described methodology.[6] In the selection of substrates attention was given to a different combination of components, for example, benzene rings,

Table 1. Substituents X of the benzoic acid derivatives **B1**–**B29** the complexation of which was investigated with the porphyrin derivatives TPyP and TPS.

	X		X		X
B1	H	**B11**	4-I	**B21**	3-NO_2
B2	4-CH_3	**B12**	4-OCH_3	**B22**	4-NO_2
B3	3,5-dimethyl	**B13**	4-$COOCH_3$	**B23**	3,5-dinitro
B4	4-$CH(CH_3)_2$	**B14**	4-$COCH_3$	**B24**	3,4-dinitro
B5	3-CH_2Cl	**B15**	3,5-dimethoxy	**B25**	3,4-difluoro
B6	4-CH_2Cl	**B16**	4-NH_2	**B26**	3,5-difluoro
B7	4-$CH{=}CH_2$	**B17**	4-SCH_3	**B27**	3,4-dichloro
B8	4-F	**B18**	4-CN	**B28**	3,5-dichloro
B9	4-Cl	**B19**	4-$CONH_2$	**B29**	3,5-dibromo
B10	4-Br	**B20**	2-NO_2		

Table 2. Further compounds, the complexation of which was investigated with the porphyrin derivatives TPyP and TPS.

	X		
Pyridine		Peptides and others	
py1	H	**Pp3**	Gly-Gly-Gly-OH
py2	3-Br	**Pp4**	Gly-Gly-Gly-Gly-OH
py3	3-CN	**Pp5**	Gly-Gly-Gly-Gly-Gly-OH
py4	3-OCH_3	**M1**	$HC{\equiv}C(CH_2)_2COOH$
py5	3-I	**M2**	$HOCH_2C{\equiv}CC{\equiv}CCH_2OH$
		M3	$CH_2{=}CHCOOH$
		M4	$CH_3CH{=}CHCOOH$
X-CH_2-CH_2-COOH		**M5**	cyclopropyl-COOH
Pr1	H	**M6**	$(cyclopropyl)_2CHOH$
Pr2	Br	**M7**	$C_6H_5CH{=}CHCOOH$
Pr3	I	**M8**	CH_3NO_2
Pr4	NO_2	**M9**	$NaNO_3$
		M10	NaI

carboxyl, and nitro groups. Our investigations confirm an astonishing additivity in the complexation energy contributions of the individual groups. This trend is illustrated in Scheme 2 for the nitro compounds investigated: a constant value of $\Delta\Delta G = 5\ kJ\,mol^{-1}$ can be assigned to the ion-pair bonding between the carboxyl group and the positively charged porphyrin, as was found in numerous complexes with the ion strengths used here.[7] A $\Delta\Delta G$ value of about $8\ kJ\,mol^{-1}$ is assigned to the bonding contribution of the benzene unit (see Table 3) from previous[6] and more recent measurements (e.g. comparison of benzoic acid **B1** and propionic acid **Pr1**, Table I of the Supporting Information). The $\Delta\Delta G$ value for the ion-pair bond and for benzene confirm the new data: a constant contribution for the nitro group of $\Delta\Delta G = 5\ kJ\,mol^{-1}$ is derived from the K values measured for three nitrobenzoic acids; this even applies, within the error limits, to aliphatic guest molecules such as nitromethane **M8** or 3-nitropropionic acid **Pr4**. As with free energy relationships, for instance of the Hammett correlation type, deviations from additive behavior normally arise if substituents are

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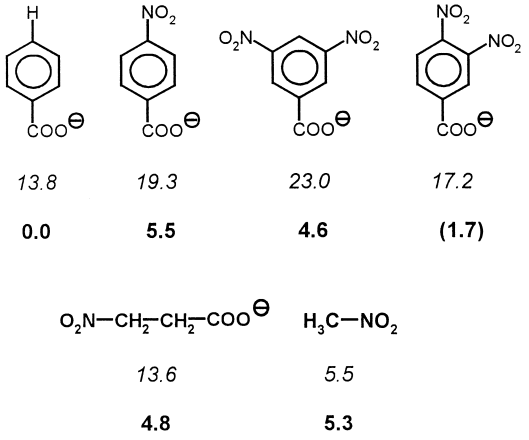

Scheme 2. Experimental bond energies ΔG [kJ mol^{-1}] (italics) with TPyP as host compound (in water at 25 °C) and bond energy increments $\Delta\Delta G$ for the nitro group (bold); $\Delta\Delta G$ is the difference between the ΔG values of the compounds with R = NO_2 and R = H.

Table 3. Bond energy increments $\Delta\Delta G$ [kJ mol^{-1}] for different substituents X.[a]

X	$\Delta\Delta G$	n[b]	X	$\Delta\Delta G$	n[b]
CH_3	< 0.5	4	I	2.95	3
$CH(CH_3)_2$	0.6	1	NH_2	0.9	1
$CH{=}CH_2$	2.4	6	OCH_3	1.75	3
C≡C-	2.6	1	$COOCH_3$	3.1	1
cyclopropyl	1.65	2	$COCH_3$	3.15	1
phenyl	8.3	6	SCH_3	2.8	1
pyridyl	6.4	5	CN	2.6	2
F	0.3	3	NO_2	4.95	5
Cl	1.65	5	$CONH_2$	2.85	5
Br	2.4	4			

[a] $\Delta\Delta G$ calculated from association constants with tetrapyridiniumporphyrin TPyP (in water, 298 K, pH 7.00 ± 0.01, phosphate buffer, ion strength I = 0.05 M, unless otherwise stated); scatter of the $\Delta\Delta G$ values for different compounds: ± 0.25 kJ mol^{-1} (± 0.35 kJ mol^{-1} for R = I, $COCH_3$). [b] n: number of the compounds used in each case for the $\Delta\Delta G$ calculation.

located in a vicinal position (example: 2-nitrobenzoic acid **B20** and 3,4-dinitrobenzoic acid **B24**). In all other cases the $\Delta\Delta G$ contributions of the substituents to the Gibbs complexation energy ΔG were additive. The additivity and applicability of the increments are illustrated in Figure 1 by a comparison of calculated and measured ΔG values.

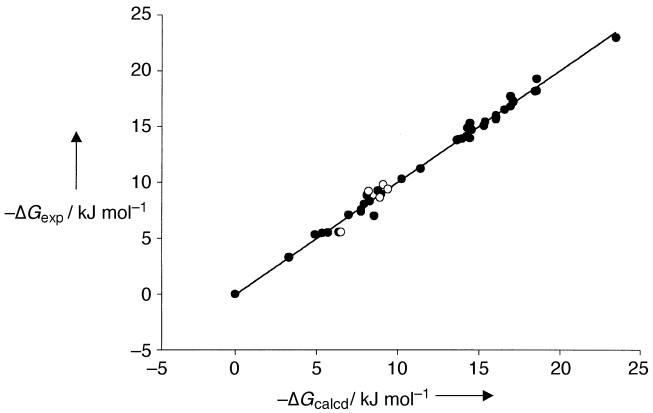

Figure 1. Calculated ΔG against measured Gibbs complexation energies. Calculation with increments from Table 3, correlation line with slope m = 1.007, correlation coefficient r = 0.996; ●: complexes with TPyP, ○: complexes with TPS.

On the basis of measured data, bond energy increments $\Delta\Delta G$ can be assigned to numerous groups (Table 3). The increase in interaction with increasing polarizability, such as within the halogens, demonstrates that these are dispersive interactions. The π electrons also produce an additive bonding contribution.[6] It is interesting that we were able to observe—considerable—noncovalent interactions of the cyclopropane rings, which is in agreement with bonding model for the three-membered ring. Moreover, the contributions of the amide and, especially, of the nitro function are also notably large. That this result is not a consequence of donor–acceptor or electrostatic interactions is confirmed in that the same ΔG values are obtained with anionic host compounds as with cationic host compounds (TPS, TPyP); the influence of salt bridges must be taken into account in the calculation (Table II of the Supporting Information). Equally the analogous and always affinity-enhancing effect of, for example, nitro, amino, and methoxy groups in benzoic acids is only compatible with a dispersive mechanism. Conjugative interactions in substituted aromatic guest compounds clearly play no significant role since an almost constant $\Delta\Delta G$ value was obtained for the nitro substituents in mono- and disubstituted aromatic and aliphatic compounds.

A considerable problem in the analysis of noncovalent interactions in water is the differentiation of solvophobic and lipophilic effects. The negligibly small contributions of the methyl groups already show that the observed associations arise only to a small measure from the hydrophobic interactions. This proposal is confirmed by the comparison of the association energies of cyclohexanoic acid and benzoic acid **B1**: although the hydrophobic surfaces of both six-membered rings are of approximately the same size cyclohexanoic acid exhibits only the value ΔG = 5 kJ mol^{-1} typical for ion-pair bonding, whereas as a result of the six-π-electron system the value for benzoic acid is ΔG = 14 kJ mol^{-1}.[6] Moreover, the measured association constants (Table I of the Supporting Information) do not correlate at all with the lipophilic nature of the substrates used or with the corresponding substituent Hansch effects.[8]

The energy increments listed in Table 3 need not only be used for interactions with porphyrins. As long as an adequate contact exists between the surfaces of the substituents and those of the host molecule a general applicability can be presumed. As with the substituent constants in the Hammett relationship, the $\Delta\Delta G$ values listed are relative quantities which, for example, in complexes with smaller host compounds or with an increase in the ionic strength of the aqueous solution decrease by a constant factor (scaling similar to the reaction constant ρ in free energy relationships). Earlier we described how the complexation energy increases considerably at very low buffer concentrations,[9] more than can be explained with the salt effects expected from Coulombic interactions.

The addition of organic solvents in aqueous medium leads, in many host–guest complexes, to a smaller association

energy by reduction not only of the hydrophobic interaction, but also of other interactions. Diederich et al.[10] have already pointed out that, because of its extremely low polarizability, water is an excellent medium for the maximization of many interactions.

The association constant of the complex from TPyP and 3,5-dinitrobenzoic acid **B23** was determined relative to the ethanol content of an ethanol–water mixture. Figure 2 shows a linear correlation of the logarithm of the association

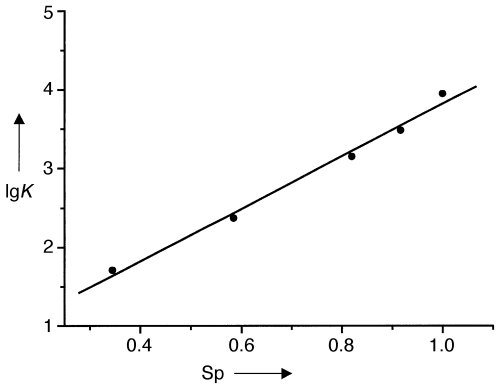

Figure 2. Solvent effect: logarithm of the association constant, lg K, for 3,5-dinitrobenzoic acid and TPyP against the solvophobic parameters Sp of ethanol–water mixtures; ●: experimental data; correlation line slope $m =$ 3.33, correlation coefficient $r = 0.995$.

constant lg K with the solvophobicity parameter (Sp)[11] ($r =$ 0.995). A linear correlation with almost an identical correlation was also found between lg K and solvent polarity E_T (R = 0.999), or simply the alcohol volume fraction[12] (Figures 1 and 2 of the Supporting Information). The slope in the correlation line lg K against Sp is at $m = 3.33$ significantly lower than in host–guest complexes with cyclodextrins as host compounds ($m = 7.0$).[13] The latter are typically stabilized by hydrophobic effects.

In conclusion we have, for the first time, successfully achieved both the mechanistic differentiation of dispersive interactions and the quantification of individual energy contributions to these interactions in a targeted investigation of organic host–guest complexes. This type of intermolecular force plays a large role in the folding of proteins, their interactions with many ligands, and in stacking interactions between nucleobases. The latter are now recognized as the dominating factor in the formation of the double helix.[14] The contributions now available for of individual substituents, for example the amino group, are of particular interest because in folded nucleic acids, exocyclic groups lie over nucleobases more frequently than the π systems themselves.[15] The rational development of new host–guest systems as well as new materials and crystal engineering strategies can benefit in that energy contributions to dispersive interactions can now be attributed to individual groups. The data obtained show that the preparatively easy introduction of, for example, two nitro groups can lead to the same intermolecular forces as that of a single phenyl group. Noteworthy is that the interactions analyzed here are strongest not in organic solvents, but, in water, in the gas state, and above all in the solid state.

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