Molecular Recognition of Amines and Amino Esters by Zinc Porphyrin Receptors: Binding Mechanisms and Solvent Effects

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Zinc porphyrin receptors bearing 12 ester groups in the meso phenyl groups (**1**−**3**) were prepared, and binding of amines and α-amino esters was studied with emphasis on the binding mechanisms. The X-ray crystallographic analysis of 5,10,15,20-tetrakis(2,6-bis(carbomethoxymethoxy)-4-carbomethoxyphenyl)porphyrin (free base of **1**) showed that the receptor has a binding pocket above the porphyrin plane. UV−visible titration experiments revealed that the zinc porphyrin receptors bound amines and α-amino esters with binding constants (K_a) ranging from 0.5 to 52 700 M^{-1} in CH_2Cl_2 at 25 °C. The ester functional groups of **1** assisted the binding of aromatic α-amino esters (K_a = 8 000−23 000 M^{-1} in CH_2Cl_2 at 25 °C) and inhibited the binding of bulky aliphatic α-amino esters (K_a = 460 M^{-1} for Leu-OMe in CH_2Cl_2 at 25 °C), indicating that CH−π type interactions and steric repulsions control the selectivity. The binding of amines and α-amino esters was tight both in a nonpolar solvent (CH_2Cl_2) and in a polar solvent (water) but loose in a solvent of intermediate polarity (H_2O−MeOH (1:1)), demonstrating that two competitive driving forces are operating: (1) attractive electrostatic forces between host and guest such as coordination of the amino group to the zinc atom, and (2) entropic forces stemming from desolvation as well as enthalpic forces due to the host−guest dispersion forces. The former forces drive the binding in CH_2Cl_2 while the latter forces drive the binding in water. The enthalpy changes in the binding in CH_2Cl_2 and those in water range from −50 to −30 kJ mol^{-1} and from −35 to 0 kJ mol^{-1}, respectively. The entropy changes in CH_2Cl_2 and those in water range from −120 to −60 J K^{-1} mol^{-1} and from −50 to +60 J K^{-1} mol^{-1}, respectively. Thus the binding in CH_2Cl_2 is characterized by large negative enthalpy changes, while that in water by less negative entropy changes. These thermodynamic parameters also indicate that host−guest polar interactions (enthalpic forces) drive the binding in CH_2Cl_2 while both host−guest dispersion interactions (an enthalpic force) and desolvation (an entropic force) drive the binding in water. Enthalpy−entropy compensation observed for the binding in water indicates that the binding of amines and amino esters in water by zinc porphyrins is associated with conformational changes as well as a high degree of dehydration. In CH_2Cl_2, no clear compensation was observed, consistent with the mechanism that neither desolvation processes nor conformational changes contribute significantly to the binding energetics.

Introduction

Elucidation of fundamental forces driving host−guest complexation[1] is important in a variety of areas such as drug design, protein engineering, and gene technology. For instance, rational design of drugs is reviewed,[2] and it is emphasized that the binding mode of the drug to the receptor is quite different from expectation based on, for example, molecular modeling. The difficulties in the rational design are ascribed to (1) lack of understanding of relative importance of solvation energy in the binding energetics (hydrophobic interactions) and (2) lack of understanding of conformational flexibility of receptor proteins (induced-fit binding). For the role of solvation, it is well-known that both binding affinity and selectivity of synthetic receptors are significantly influenced by changing solvent polarity.[3,4] Therefore to design a receptor, we need to know the media or microenvironment where the binding site exists. In some instances, we even need to design the microenvironment around the binding site.[5,6] The molecular recognition in the protein inner cavity or on the surface of the bilayer membranes involves interfacial properties between organic solvent and water, and the microscopic environment is not so simple such as in pure organic solvents or in water. Therefore more elaborate understanding of the driving forces of binding in various microenvironments should be helpful to design a receptor for a compound of biological interest under relevant circumstances.

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Two types of forces are involved in the binding processes: direct interactions between a host molecule and a guest molecule and interactions between host/guest molecules and solvent molecules. Both of these interactions can be the driving force of the binding. Host−guest complexation can be classified into three categories depending on polarity of the host/guest molecules and polarity of the media: (1) When host and guest have polar functional groups, the electrostatic interaction between the polar functional groups can be the driving force of binding. A typical example of this class of binding is the binding of metal cations by crown ethers through host−guest attractive electrostatic forces. (2) When host and guest are nonpolar, both dispersion forces between host and guest and the desolvation of polar and cohesive solvent molecules can drive the binding. For instance, cyclodextrins bind apolar organic guests mainly through desolvation-driven hydrophobic forces in water.[7] (3) When host and guest molecules possess both polar functional groups and apolar moieties, then both forces, host−guest interactions and desolvation, can be the driving forces of binding.

It is known that the binding of a polar guest is favored in a less polar solvent,[8] whereas the binding of a nonpolar guest is most favorable in a polar and cohesive solvent such as water.[3] For representative examples of solvent effects on the binding constant (K_a) of polar guests, the values of log K_a of sodium and potassium by 15-crown-5 are 0.7 and 0.7, respectively, in water while 3.24 and 3.43, respectively, in MeOH. Similarly, the values of log K_a of sodium and potassium by 18-crown-6 are 0.8 and 2.0 in water and 4.35 and 6.08 in MeOH, respectively.[9] Therefore changing the solvent from water to MeOH gives rise to the $10^{2.5}$-fold to $10^{4.1}$-fold increase in binding constants of metal cations by the crown ethers.[10] Adrian and Wilcox reported that the binding affinity of amine by a hydrogen-bond-based receptor is reduced by the addition of water to chloroform.[11] As examples of solvent effects on the binding of an apolar guest, Siegel and Breslow reported that the binding constant of anisole by β-cyclodextrin in DMSO is 2 orders of magnitude smaller than that in water.[12] Diederich and co-workers determined the binding affinity of a cyclophane receptor for pyrene in various solvents, and it decreases monotonically in the following order: water > ethanol > acetone > carbon disulfide, a result suggesting that binding of apolar guests driven by desolvation and host−guest dispersion forces occurs in a wide range of solvents.[3,13]

We focus on the binding in which both polar and nonpolar functional groups participate in the binding interactions, because a number of molecules of biological interest have both polar and apolar groups as important interaction groups. In the previous paper,[14] we reported that water-soluble porphyrin receptors show selective molecular recognition of amines and amino acids in water, particularly for a charged guest. As a complementary study, in this paper, we performed a study of the complexation of porphyrin receptors with several amines and α-amino esters in CH_2Cl_2, and the results are interpreted by comparison with the molecular recognition behaviors of the water-soluble receptors having a structurally similar binding pocket. The objectives of the present study are twofold: first, to clarify details of host−guest interactions, and second, to gain deeper insight into the roles of solvent molecules in the energetics of molecular recognition.

Results and Discussion

Synthesis of Zinc Porphyrin Receptors and Determination of Binding Constants. Zinc porphyrins bearing ester groups **1**−**4** and a simple zinc tetraphenylporphyrin **5** were employed as receptors in organic solvent, and zinc porphyrins bearing carboxylate groups **1a**−**3a** and **6** were employed as receptors in water. The aromatic macrocycle of porphyrin provides a rigid framework for a preorganized binding pocket, as well as versatile spectroscopic methods for detection of binding events.[15] One disadvantage is that porphyrins have a pronounced tendency to undergo face-to-face dimerization, especially in polar solvents. Therefore we designed receptors having substituents on both faces of porphyrin to avoid the porphyrin's aggregation. Preparation of porphyrins bearing bulky substituents above and below the porphyrin plane is a synthetic challenge, and Lindsey and co-workers performed elaborate investigations into the porphyrin synthesis from benzaldehyde bearing bulky substituents at the ortho positions. They reported that reaction of benzaldehydes bearing 2,6-dibenzyloxy groups with pyrrole proceeds in $CHCl_3$ in relatively high yields.[16,17] Receptors **1**−**4** were thus prepared[14] following Lindsey's method.

These receptors are soluble in a variety of solvents including chloroform, ethyl acetate, and THF. The ester receptors **1**−**4** can be readily made soluble in water by hydrolysis, by keeping the geometry of the binding site almost intact. Therefore we can compare the binding affinity toward guest in various solvents. The structures of these receptors were characterized by ^{1}H NMR and high-resolution mass spectroscopy. For the free base of **1**, a crystal suitable for X-ray crystallographic study was obtained and the structure was also confirmed by X-ray diffraction study. Crystal data and experimental details for the free base of **1** are sumarized in Table 1. The molecular structure of the free base of **1** is shown in Figure 1. The porphyrin framework was planar. The average distance of the 24 atoms of carbon and nitrogen of the porphyrin framework from the least-squares plane obtained from the 24 atoms was 0.009 Å, with the largest distance (0.05 Å) observed for one of the

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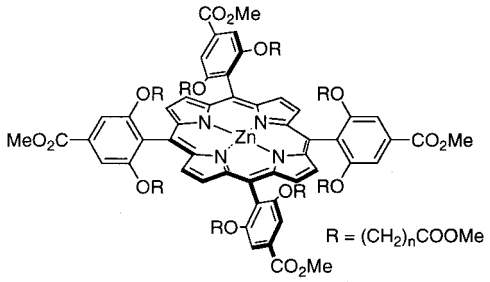

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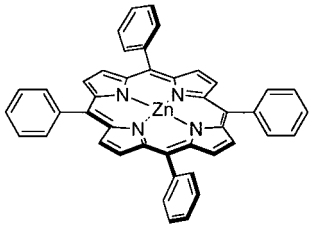
3: n = 10
4: R = Me



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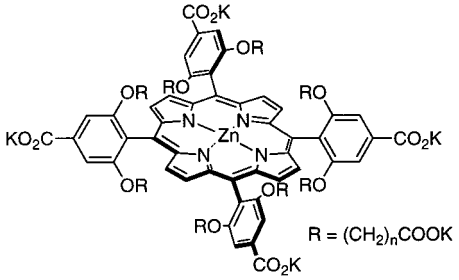
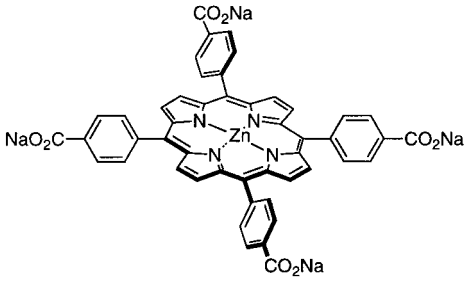


1a: n = 1
2a: n = 4
3a: n = 10



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nitrogens. The phenyl groups are not perpendicular to the porphyrin plane, and the dihedral angle between the porphyrin plane and the phenyl plane was 73.3°−73.4°. In the crystal, one of the methyl groups of the methoxycarbonylmethoxy substituents was located on the porphyrin plane of the neighboring molecule (Figure 2). The distances between the carbon of the methyl group and the two nitrogens of the next porphyrin were 3.42 and 3.49 Å. Thus, the methyl group was bound in the binding pocket of the next porphyrin, forming an inclusion polymer in the crystal.

The binding constants of amines and amino esters in CH_2Cl_2 were determined by UV−visible spectroscopic titration. Addition of guest caused a red shift in the Soret band of the porphyrin receptors, a typical spectral change

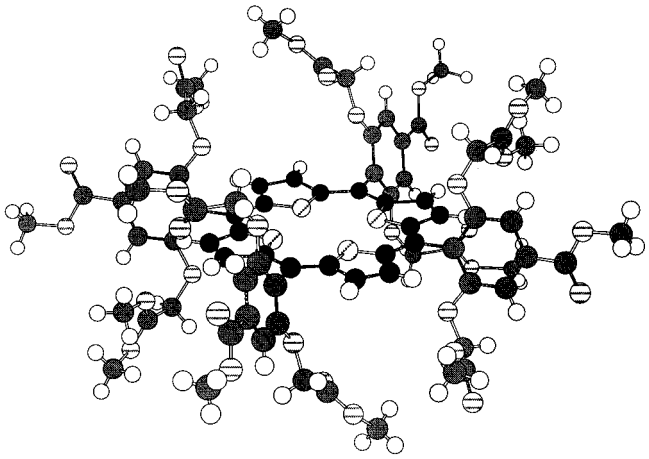

Figure 1. Structure of the free base of **1** determined by X-ray crystallographic study. One of the methoxy groups and the carobonyl oxygens in the ortho position was disordered and appeared at 60% and 40% occupancy. The inner NH hydrogens cannot be located from the difference Fourier map.

Table 1. Crystal Data and Experimental Details for the Free Base of 1·2CH₃OH

formula	$C_{78}H_{76}O_{34}N_4$
formula weight	1613.46
color	violet
crystal system	monoclinic
space group	$P2_1/c$
a, Å	13.501(3)
b, Å	21.378(5)
c, Å	13.766(3)
β, deg	98.40(1)
V, Å^3	3930(1)
Z	2
scan mode	ω scan
2θ max	54.2°
d_{calc}, g cm^{-3}	1.36
λ, Å (Mo Kα)	0.71069
μ (Mo Kα), cm^{-1}	1.08
T, K	298
no. of reflections observed	8132
no. of reflections used ($I_0 > 3.00\sigma(I_0)$)	4315
no. of variables	532
R	0.063
R_w	0.073
goodness of fit indicator	2.67

due to the amino group coordination to the zinc atom.[18] The spectral shift in the Soret band of a solution of **2**−**4** in CH_2Cl_2 from 423 to 434 nm and that of **1** from 420 to 431 nm was similar to that of a solution of **1a**−**3a** in water (from 424 to 434 nm in **2a**−**3a** and from 421 to 431 nm in **1a**), confirming that the coordination of the amino group of guest to the zinc atom occurs both in CH_2Cl_2 and in water. The binding constants were determined by monitoring the absorbance changes of the Soret band as a function of guest concentrations at 25 °C and fitting the saturation plot to the 1:1 binding isotherm: K_a = [porphyrin·guest]/([porphyrin][guest]). Standard deviations for the curve fitting are less than 5%. For all combinations of the receptors and the guests, isosbestic points were always observed in the UV−visible spectral titration, suggesting that the receptor and the guest form a 1:1 complex exclusively.[19] The binding

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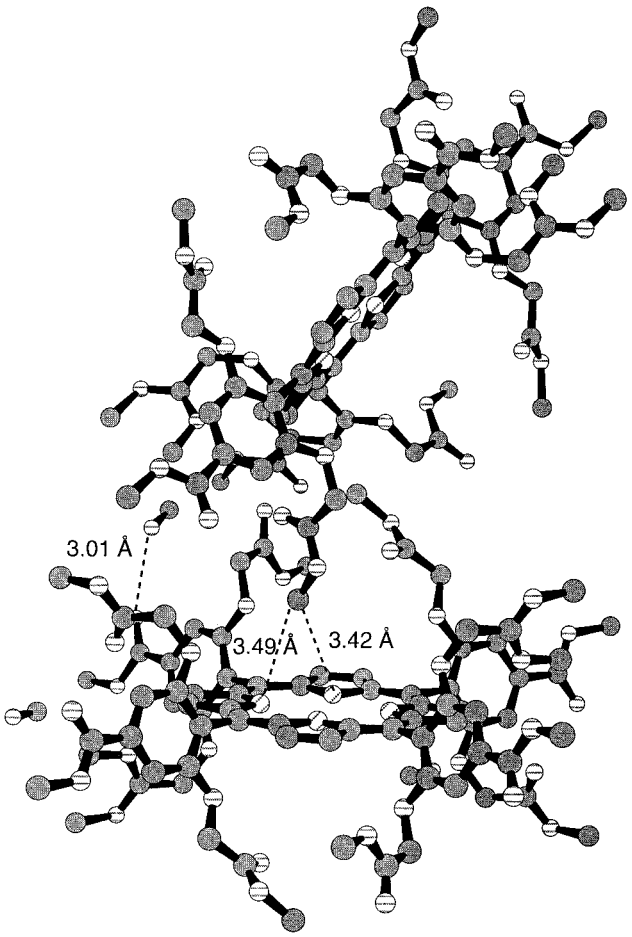

Figure 2. Packing of the free base of **1**. The methoxy group in the ortho position is in van der Waals contact (the C−N distances, 3.42 and 3.49 Å) with the next porphyrin's nitrogens and carbons to form an inclusion polymer in the crystal. A methanol molecule is weakly hydrogen bonded to the carbonyl group of the ester group in the para position, where the O−O distance was 3.01 Å.

constants K_a for **1**−**5** are listed in Table 2. Receptors **1**−**5** bound amines and amino esters with binding constants ranging from 300 to 53 000 M^{-1} in CH_2Cl_2 at 25 °C except for some host−guest combinations involving **2** and Leu-OMe and PhGly-OMe, which formed very loose complexes. Binding constants and thermodynamic parameters for the binding of amines and amino esters by **1a**−**3a** in water and aqueous MeOH were reported in the previous paper.[14]

Solvent Effects on Binding Affinity. In Figure 3 are compared the binding free energies ($-\Delta G°$) in CH_2Cl_2, aqueous MeOH, and water. The binding affinity decreases from CH_2Cl_2 to MeOH−water and then starts to increase to water. Competitive binding of water or MeOH to the zinc atom could, at least in part, explain the smaller binding constants in aqueous MeOH compared to those in CH_2Cl_2.[20] The binding affinity of nitrogen, oxygen, phosphorus, and sulfur donors toward ZnTPP was compared, and binding constants of an oxygen donor are 1 order of magnitude smaller than those of a nitrogen donor.[21] Therefore water or MeOH can competitively bind to the zinc atom when used as a solvent, particularly in

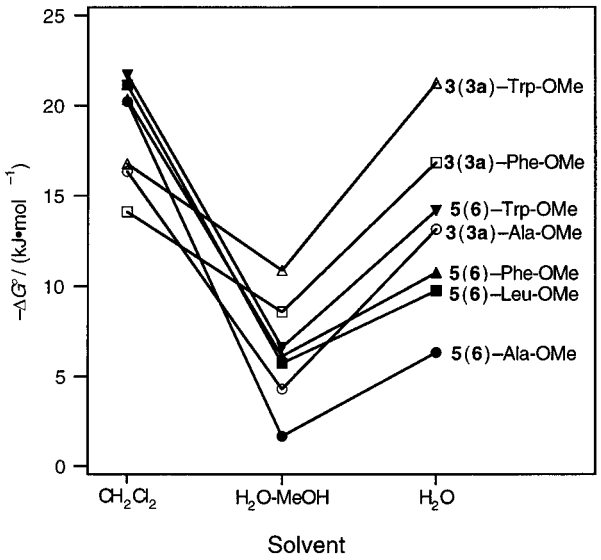

Figure 3. Free energy changes, $-\Delta G°$, of binding by zinc porphyrin receptors in three solvents, CH_2Cl_2, MeOH−borax pH 9.0 (1:1), and borax pH 9.0 at 25 °C. In CH_2Cl_2, ester receptor **3** and ZnTPP **5** are used, and in MeOH−borax and in borax, carboxylate receptors **3a** and **6** were used.

Table 2. Binding Constants (K_a) of Amines and Amino Esters by Zinc Porphyrin Receptors in CH_2Cl_2 and in Borax Buffer at 25 °C

In CH_2Cl_2

	K_a/M^{-1}					
	1	**2**	**3**	**4**	**5**	pK_a[a]
pyridine	2 920	401	4 480	3 650	7 720	5.34
n-BuNH_2	21 200	255	5 960	12 700	40 000	11.48
t-BuNH_2	9 110	249	4 740	6 530	14 000	11.44
$PhCH_2NH_2$	21 100	179	3 330	6 690	12 000	9.0
$PhCH_2CH_2NH_2$	52 700	477	6 900	17 500	46 000	9.96
$PhCH_2CH_2CH_2NH_2$	21 300	224	4 940	11 800	45 000	10.8
Ala-OMe	4 210	75	918	2 170	4 660	7.74
Leu-OMe	461	0.5	18	580	6 860	7.62
PhGly-OMe[b]	1 600	*c*	13	926	5 250	6.63
Phe-OMe	8 560	36	364	2 160	4 910	7.0
Trp-OMe	22 700	110	1 090	3 940	8 730	7.3

In Borax Buffer pH 9.0

	K_a/M^{-1}		
	1a	**2a**	**3a**
Ala-OMe[d]	5	13	240
Phe-OMe[d]	30	107	1 130
Trp-OMe[d]	67	670	7 160

[a] The dissociation constants of RNH_3^+ in water, pK_a values, are taken from ref 29. [b] Phenylglycine methyl ester. [c] No interaction was observed in the UV−visible spectrum. [d] Binding data for **1a**−**3a** in water, taken from ref 14.

1a, in which the zinc atom is relatively exposed to the solvent. Sanders and co-workers, we and others also reported that binding of various guests by zinc porphyrins in chloroform is weakened by adding a polar cosolvent such as water, alcohol, and ether.[6,22,23] Poorer binding ability in aqueous MeOH than in CH_2Cl_2 can be ascribed to the deactivation of the acidity of the zinc atom in a

(20) Preliminary UV−vis titration experiments showed that the binding constants of EtOH, acetone, THF, and AcOEt by **5** in CH_2Cl_2 were 8.9, 0.9, 47, and 1.1 M^{-1}, respectively.

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(23) For some host−guest pairs with incomplete complementarity, addition of polar cosolvent makes the binding tight. See ref 22.

polar environment. But the increased affinity by changing the media from aqueous MeOH to water should be ascribed to another mechanism involving solvophobic interactions.

As shown in Table 2, the binding constants of Ala-OMe, Phe-OMe, and Trp-OMe by **1** in CH_2Cl_2 are larger than the corresponding binding constants of **2** and **3**, while the binding constants of Ala-OMe, Phe-OMe, and Trp-OMe by **1a** in water are smaller than those of **2a** and **3a**.[14] Thus, these hydrophobic guests are bound to host with longer methylene chains more tightly in water. Therefore, long methylene chains in host **3a** provide a hydrophobic environment to assist the binding of nonpolar guest in water, while they showed weakly inhibitory effects on binding in CH_2Cl_2.

The solvent effects shown in Figure 3 suggest that there are two competing driving forces; polar interaction between host and guest directly drives binding in apolar media such as CH_2Cl_2, and the desolvation from the host−guest interacting surfaces drives binding in a polar solvent such as water.

Because polar interactions such as Lewis acid/Lewis base interactions and hydrogen bonding between host and guest will be diminished in a polar solvent[11,24] and contribution from desolvation of host−guest contact surface will be dominant in a polar solvent, we can expect that importance of these two interactions will switch at some solvent with intermediate polarity. Hunter and coworkers[25] reported that, as the solvent polarity decreases from water to chloroform, the strength of the intramolecular interaction between aromatic rings goes through a minimum at DMSO and then starts to increase again. Other studies also reported a similar behavior regarding the solvent effects on molecular recognition, although the range of solvent polarity studied was more limited owing to the solubility problems.[26]

Nature of Host−Guest Interactions in CH_2Cl_2. The solvent effects observed in our porphyrin−guest systems indicate that the binding in CH_2Cl_2 is primarily driven by polar interactions between host and guest. The first candidate for the polar host−guest interactions is the coordination interaction between the zinc atom and the amino group, which is known to be electrostatic in origin.[21,27] If this is the case, the basicity of the amino group mainly determines the magnitude of the binding constants.[28] To evaluate the validity of this mechanism, the plot of $-\Delta G°$ of binding by **5** against pK_a of the amino group of guest is shown in Figure 4a.[29] The correlation coefficient between the two quantities is 0.82, showing that the basicity is certainly one of important factors for the binding mechanism of **5**. A similar plot is shown for **1** in Figure 4b, where the correlation was poor. The correlation coefficients are 0.43, 0.58, 0.72, and 0.75 for **1**, **2**, **3**, and **4**, respectively (plots not shown for **2**−**4**). The poor correlations for **1** and **2** indicate that there are

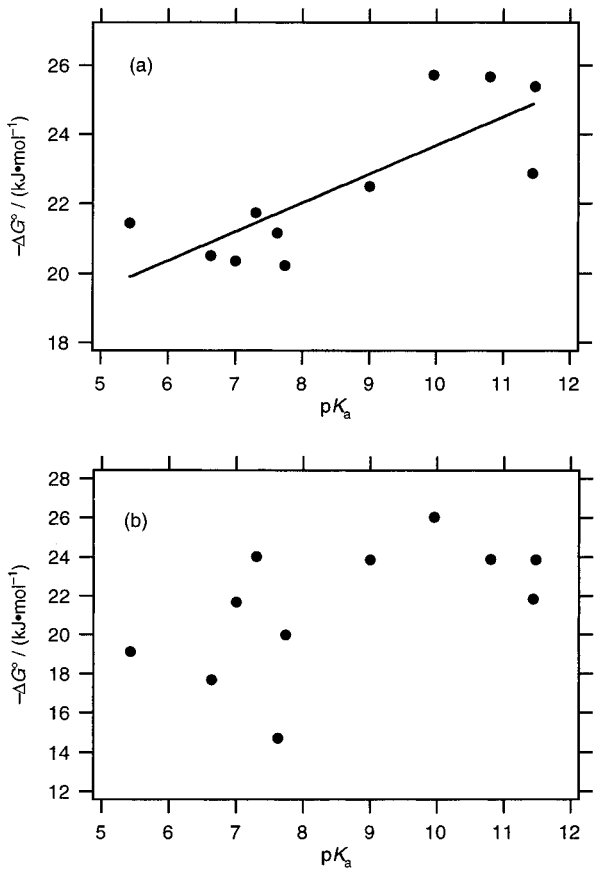

Figure 4. Plot of $-\Delta G°$ of binding by zinc porphyrin receptors in CH_2Cl_2 at 25 °C against pK_a values of the amino group of guest. (a) **5**−guest complexation (correlation coefficient, r = 0.82) and (b) **1**−guest complexation (r = 0.43).

contributions from factors other than basicity of the amino group to the binding energetics of **1** and **2**.[30]

Role of Ester Groups of Porphyrin Receptors in Binding Selectivity. As a general trend, binding constants decrease in the order **5** > **1** > **4** > **3** ≫ **2**. To examine the origin of the weak binding ability of **2**, the ^{1}H NMR spectra of the zinc complexes **1**−**3** are compared with those of the free base ligands in Figure 5. For **1** and **3**, the resonance of the terminal methyl groups in the 2,6-positions of the phenyl groups appeared at the same magnetic field as that of the free base ligand, while the resonance of the terminal methyl groups of **2** is shifted upfield. Therefore, one of the ester groups intramolecu-

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(30) In contrast, in water, the correlation coefficients between $-\Delta G°$ and pK_a were −0.04 (guest = Ala-OMe, Phe-OMe, and Trp-OMe) and −0.49 (guest = pyridine, butylamine, benzylamine, Ala-OMe, Leu-OMe, PhGly-OMe, Phe-OMe, and Trp-OMe) for **1a** and **3a**, respectively. For instance, amines are bound less tightly to **1a**−**3a** than amino esters. These negative correlation coefficients can be rationalized by the existence of pre-equilibrium in which more basic amines are more easily protonated and to be deactivated as a Lewis base for zinc.

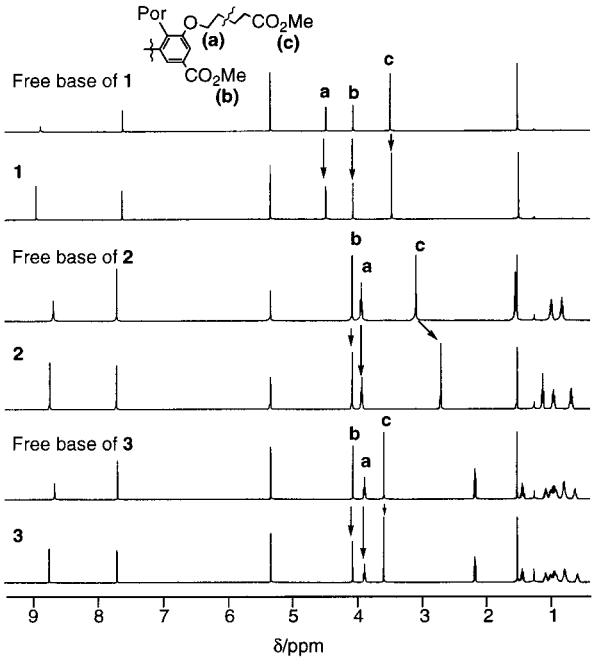

Figure 5. ^{1}H NMR spectra of zinc complexes of **1**−**3** and free bases of **1**−**3** in CD_2Cl_2 at 23 °C.

larly coordinates to the zinc in **2** and is subject to the ring current effects of the porphyrin π electrons. This was also supported by molecular modeling studies, showing that the geometry for the C═O···Zn interaction is plausible. Therefore the weak binding ability of **2** should be ascribed to the quenching of the zinc acidity by the intramolecular ester coordination.

For guest binding selectivity, weak binding of Leu-OMe and PhGly-OMe by **1**−**3** is noteworthy. Water-soluble receptors **1a**−**3a** also showed reduced binding affinity toward Val-OMe, Leu-OMe, and PhGly-OMe in water.[14] Therefore this weak binding should be attributable to the host−guest interaction and not to the desolvation processes. The ability to discriminate Leu-OMe or PhGly-OMe from Ala-OMe is high in **2** and **3** and low in **1**. Therefore the longer flexible methylene chains of the receptors help discriminate these amino esters. To date, a number of zinc porphyrins were reported to bind amino esters,[31−47] but much reduced affinity toward Leu-OMe and PhGly-OMe is unprecedented. Several zinc tetra-

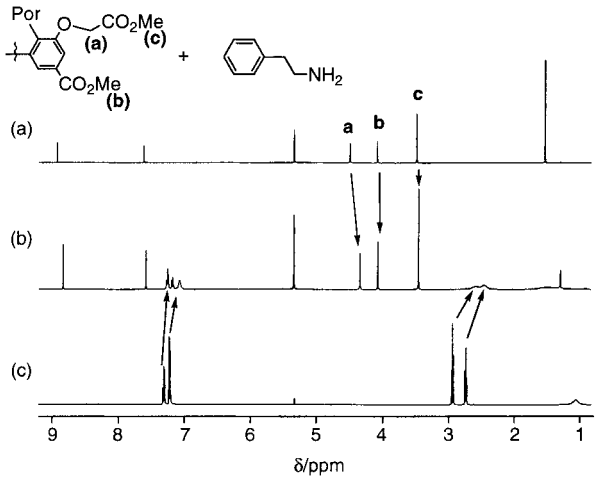

Figure 6. ^{1}H NMR spectra of **1**, the **1**−phenylethylamine complex, and phenylethylamine in CD_2Cl_2 at 25 °C. The concentration of **1** was 1.0 mM. The spectrum of **1** only (a), **1** + phenylethylamine (6.07 mM) (b), and phenylethylamine only (c).

arylporphyrins having bulky substituents at the 2 and 6 positions of the aryl groups do not show weak affinity toward Leu-OMe or PhGly-OMe.[43,44,46] The origin of the weak affinity of Leu-OMe and PhGly-OMe is not clear, but it is probably due to a mechanism in which the bulky side chain group of these guests forced the guest molecule to adopt an unfavorable conformation such as the undesirable orientation of the ester groups.[48] This effect is quite sensitive to small changes in the guest structure. For instance, PhGly-OMe is bound weakly, whereas Phe-OMe is bound as strongly as Ala-OMe.

For another example of steric effects[49,50] or cavity effects[51,52] on binding selectivity, the ratio of binding constant of butylamine to that of *tert*-butylamine decreases in the order **5** > **1** > **4** > **3** > **2**. The space of the binding sites of receptors decreases in the order **5** > **4** > **1** > **2** > **3**. Thus, **5** having the largest binding site showed the best discrimination between butylamine and *tert*-butylamine. Thus there seems no steric repulsion between the -$(CH_2)_n$COOMe groups and the *tert*-butyl group. This observation implies that the steric repulsion between the zinc porphyrins and Leu-OMe occurs at a place distant from the Zn−N coordination site.

CH−π Interactions. The ratios of K_a of aromatic amino esters such as Phe-OMe and Trp-OMe to that of Ala-OMe were large for **1**. The large affinity of **1** toward aromatic amino esters suggests that there are some attractive interactions between the CH_2COOMe group of

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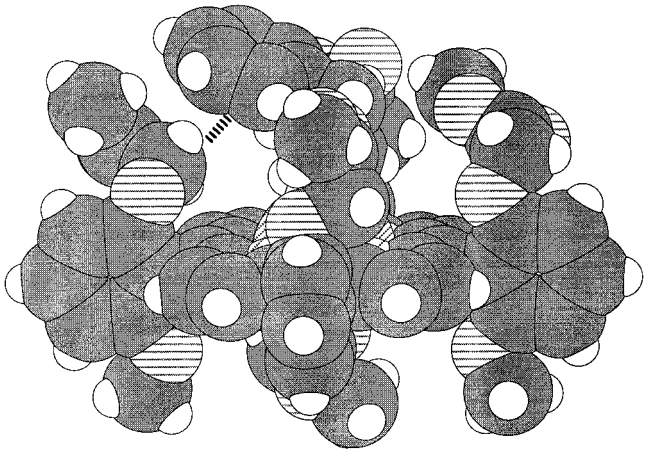

Figure 7. A plausible structure of the **1**−phenylethylamine complex consistent with ^{1}H NMR studies. The methylene group of **1** is close to the phenyl group of the guest. The geometry was optimized by Spartan 3.1, using a PM3 Hamiltonian. A model compound for **1** was used, where the methoxycarbonyl groups of the other face of the porphyrin were replaced with hydrogens.

1 and the aromatic side chain. The ^{1}H NMR spectrum of **1** is compared with that of the complex between **1** and phenylethylamine (Figure 6). The methylene protons (OCH_2COOCH_3) of the complexed **1** was 0.16 ppm upfield from those of the uncomplexed **1**, showing that the methylene protons point into the shielding region of the phenyl group of phenylethylamine in the complex. It should be noted that there are eight methylene groups and the observed shifts are the average of these eight methylene resonances. Therefore, the complexation-induced shift of 0.16 ppm amounts to a 1.3 ppm upfield shift for one methylene group, which is a significant shift. The CH−π interaction[53−56] between the phenyl group and the acidic methylene protons may contribute to the stabilization of the complex.[57] By molecular modeling studies, we obtained a structure shown in Figure 7, where the methylene protons are on the phenyl group of the guest. For aromatic amines, very tight binding of $PhCH_2CH_2NH_2$ by **1** is noteworthy, which may also be ascribed to the attractive interaction between the phenyl group and the ester group.

High affinity for aromatic guests and poor affinity for bulky amino esters such as Leu-OMe of **1**−**3** demonstrated that even flexible ester groups near the binding site can alter the binding selectivity significantly.

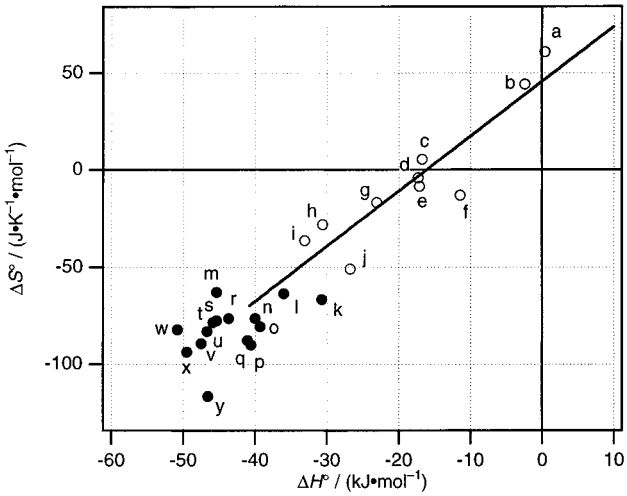

Figure 8. Plots of $\Delta S°$ against $\Delta H°$ of binding of amines and α-amino esters by **1a**−**3a** and **6** in borax buffer at pH 9.0, I = 0.1 M (○) and of binding by porphyrin receptors **2**−**3** and **5** in CH_2Cl_2 (●). In the borax buffer, (a) **3a**−Arg-OMe, (b) **2a**−Arg-OMe, (c) **2a**−pyridine, (d) **2a**−Trp-OMe, (e) **6**−Trp-OMe, (f) **6**− pyridine, (g) **1a**−Arg-OMe, (h) **3a**−pyridine, (i) **3a**−Trp-OMe, (j) **6**−Arg-OMe. In CH_2Cl_2, (k) **2**−Ala-OMe; (l) **3**−Ala-OMe; (m) **5**−$PhCH_2CH_2NH_2$; (n) **3**−Trp-OMe; (o) **2**−$PhCH_2CH_2NH_2$; (p) **2**−pyridine; (q) **2**−^{n}BuNH$_2$; (r) **5**−Ala-OMe; (s) **5**−pyridine; (t) **5**−Trp-OMe; (u) **3**−$PhCH_2CH_2NH_2$; (v) **3**−pyridine; (w) **5**−^{n}BuNH$_2$; (x) **3**−^{n}BuNH$_2$; (y) **2**−Trp-OMe. For a−j, see ref 14. A line was drawn by least-squares line fitting to the data in water (a−j).

Table 3. Enthalpy Changes ($\Delta H°$, kJ mol^{-1}) and Entropy Changes ($\Delta S°$, J K^{-1} mol^{-1}) in Binding of Amines and Amino Esters by Zinc Porphyrin Receptors in CH_2Cl_2

	2		**3**		**5**	
	$\Delta H°$	$\Delta S°$	$\Delta H°$	$\Delta S°$	$\Delta H°$	$\Delta S°$
pyridine	−41.1	−87.7	−47.5	−89.4	−45.4	−77.6
n-$BuNH_2$	−40.6	−90.1	−49.5	−93.8	−50.8	−82.2
$PhCH_2CH_2NH_2$	−39.3	−80.5	−46.7	−83.0	−45.4	−63.1
Ala-OMe	−30.7	−66.7	−36.0	−63.7	−43.7	−76.3
Trp-OMe	−46.6	−116.5	−40.0	−76.5	−45.9	−78.5

Enthalpy and Entropy Changes of Binding. Enthalpy and entropy changes of the binding were determined by van't Hoff analysis ($\ln K_a = -(1/RT)\Delta H° + (1/R)\Delta S°$; R is the gas constant) of binding constants in the temperature range of 5−25 °C. The values of the enthalpy and entropy changes are listed in Table 3. In Figure 8 are shown the plots of $\Delta S°$ against $\Delta H°$ of binding in CH_2Cl_2 and of binding in water.[14]

As seen in Figure 8, the values of $\Delta H°$ and $\Delta S°$ are readily grouped into two regions depending on the media used. Binding in CH_2Cl_2 is always associated with large

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negative enthalpy changes and large negative entropy changes. The negative enthalpy changes can be ascribed to the coordination interaction between the zinc and amine, and the negative entropy changes can be ascribed to the restriction of translational, rotational, and internal rotational motions upon binding. In organic solvent such as CH_2Cl_2, solvation energy is not very large and the enthalpy changes directly reflect the attractive interactions between host and guest. The values of $\Delta H°$ of -30 to -50 kJ mol^{-1} are comparable to the reported $\Delta H°$ for zinc porphyrin−guest complexation in organic solvents.[45,46,50,58−60] In contrast, enthalpy changes and entropy changes are close to zero in water, reflecting the compensation effects of desolvation. One origin of the difference in $\Delta H°$ and $\Delta S°$ between water and CH_2Cl_2 shown in Figure 8 is desolvation from polar functional groups such as the zinc and the amino group. In water, dehydration of polar substituents largely masks the negative enthalpy changes of host−guest interactions. The values of $\Delta S°$ of -50 to $+60$ J K^{-1} mol^{-1} observed for **1a**−**3a** and **6** in water are in the range of $\Delta S°$ observed for the complexation by cyclodextrins[61,62] and other water-soluble receptors.[26,63]

Thermodynamics of Salt Bridge and Hydrogen Bonding Interactions. Positive entropy changes were observed for the binding of Arg-OMe in water, which is ascribed to dehydration from the ionic groups upon salt bridge formation.[64,65] Ionic groups are most strongly hydrated, so that salt bridge formation leads to a large entropy gain owing to the gain in translational motional freedom of the released water molecules. For the binding of Arg-OMe by **1a**, the salt bridge should be exposed to water. Thus, the number of dehydrated water molecules may be smaller and the entropic gain due to dehydration was smaller than that for **2a**(**3a**)-Arg-OMe complexation as shown in a and b vs g in Figure 8.

For the binding of amine by a hydrogen-bond-based host, Adrian and Wilcox reported that the addition of water to chloroform has no especially large effect on the free energy changes in the binding, but it has a significant effect on the enthalpy and entropy changes; both values were closer to zero when water is added.[11] Release of water molecules, which have interacted with hydrogen bonding functional groups, upon binding thus significantly contributes to $\Delta H°$ and $\Delta S°$.

Comparison of Binding by Zinc Porphyrins with Binding by Cyclophanes and Crown Ethers. Thermodynamics of binding in an aqueous solution is complicated by desolvation processes and is not well understood.[2,3,66] Solvent effect on the enthalpy changes and the entropy changes of binding is a key to understanding molecular recognition in water. The larger enthalpic gain in the apolar solvent as seen in Figure 8 is in sharp contrast to the solvent effects on the binding of pyrene by the cyclophane, where enthalpic gain is larger in polar solvents than in apolar solvents.[13] For the binding of pyrene by the cyclophane, neither host nor guest has any polar functional group. As a result, only nonpolar interactions such as dispersion forces are operating between host and guest. The larger enthalpic gain in polar solvents implies that the net stabilization due to host−guest dispersion forces will be larger with decreasing the polarizability of solvent (that is, with increasing solvent polarity). Similarly, for binding of benzene derivatives by cyclodextrins in water, an enthalpic gain is observed and is ascribed to London's dispersion force.[67]

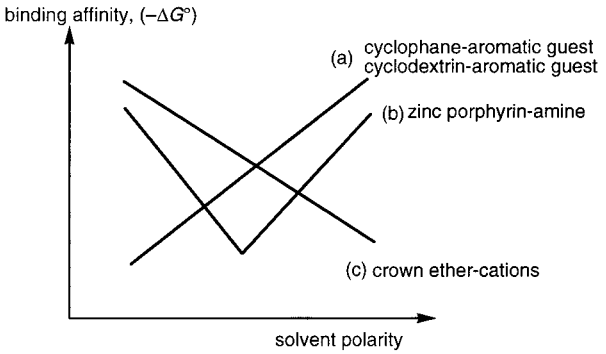

Figure 9. Schematic representation of the relationship between binding affinity and solvent polarity for host−guest complexation driven by nonpolar and solvophobic forces (a), electrostatic forces (c), and both of these forces (b).

In Figure 9 are schematically illustrated the effects of solvent polarity on the binding free energy. For binding of apolar guests to an apolar binding site of receptors such as cyclodextrins and cyclophanes (Figure 9, a), binding is favored in polar solvents. For binding of ionic guests to a polar binding site of receptors such as crown ethers (Figure 9, c), the binding is favorable in apolar solvents. For the binding of a guest by a receptor, both of which have polar and apolar functional groups at the contact surface, such as the combination of zinc porphyrins and amino acid derivatives (Figure 9, b), the binding affinity is high in both polar and apolar media and low in a solvent with intermediate polarity.

As an empirical rule, the magnitude of free energy changes originated from desolvation is known to be proportional to the contact surface area. Contribution of desolvation in water to the binding free energy was estimated to be 0.025 kcal/mol/Å^2 from the free energy changes of transfer of amino acids from water to ethanol by Chothia.[68] Both polar amino acids and nonpolar amino acids show similar dependence of desolvation energy on the accessible surface area. Importance of the solvent cohesive interactions was also demonstrated by the relationship between the binding energy and surface tension of the solvents by Connors and Sun.[69] All of these

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studies revealed that desolvation-driven binding should be important if host−guest contact surface area is large and the solvent is polar. In contrast, for the binding of cations by crown ethers, the contact surface area is obviously smaller, and the desolvation energy may not be very significant as to overcome the host−guest interaction energies. Thus, it is reasonable that the binding mechanism of crown ethers is dominated by host−guest electrostatic interactions even in polar solvents, whereas that by cyclodextrins and porphyrin receptors is governed by both solvation interactions and host−guest polar and nonpolar interactions.

If host and guest have polar functional groups, the complementary arrangement of polar functional groups of host and guest is important to avoid electrostatic repulsion at the contact surface. We found that there is no spectral change in the solutions of the free bases of **1a**−**3a** upon addition of pyridine or histamine in water (borax buffer, pH 9.0), although the zinc complexes (**1a**−**3a**) showed tight binding. Therefore complementary electrostatic potential near the zinc atom of host and the amino group of guest is necessary for tight binding to occur.

If the polar groups of host and guest do not participate in the host−guest interactions, it is important that these polar groups retain the favorable solvation in the complex, as demonstrated by Diederich and co-workers.[13a,70]

We can summarize the binding mechanism as follows. If guest is apolar and the media is water, London's dispersion forces between host and guest is one of the driving forces owing to the low polarizability of water. This process leads to the enthalpic gain. Desolvation from the contact surfaces also contributes to stabilization of the complex.[71] This leads to the entropic gain. The net result is that a negative enthalpy change and a negative entropy change are observed. The negative entropy change does not necessarily imply that desolvation-driven entropic gain plays a minor role, because the intrinsic entropy loss upon bimolecular association is large. The negative enthalpy changes and the negative entropy changes observed for the binding by cyclodextrins and zinc porphyrin receptors in water suggest a significant contribution of London's dispersion forces to the overall enthalpy changes, except for the binding of ionic guests. If host and guest have ionic functional groups and interact via a salt bridge, there is a considerable contribution from desolvation from the ionic groups to the entropic gain.

The classical picture of hydrophobic interactions stresses the importance of entropic gain from the desolvated water. However, the host−guest studies and protein denaturation studies[72] revealed that the enthalpic gain due to van der Waals interactions are significant in describing the hydrophobic effects.[24,73−78]

Induced-Fit and Desolvation-Driven Binding As Evidenced by Enthalpy−Entropy Compensation. As shown in Figure 8, plots of $\Delta S°$ against $\Delta H°$ of binding in water (○) showed an enthalpy−entropy compensation, i.e., the negative enthalpy change causes the negative entropy change. However, plots of $\Delta S°$ against $\Delta H°$ of binding in CH_2Cl_2 (●) showed no clear compensation effects. We suggest that the enthalpy−entropy compensation is originated from two different sources: (1) restriction of motion of host and guest molecules due to mutual attractive forces and (2) enthalpic loss due to desolvation and entropic gain due to motional freedoms of desolvated molecules. In water, both of these processes contribute to the observed enthalpy−entropy compensation, so that we observed clear compensation. In CH_2Cl_2, the former process will contribute to the compensation effect but contribution from the latter process might be minor and the observed compensation was not clear.

In the compensation process originated from host−guest motional restriction, the flexibility of host and guest molecules is important. Searle and Williams reported that entropic cost of a restriction of a single bond rotation owing to some attractive forces between host and guest is around 11 J K^{-1} mol^{-1}.[79] We also estimated the internal rotational entropy to be 20 J K^{-1} mol^{-1} from the binding experiment using zinc porphyrin receptors.[46] Restriction of the internal single bond rotation by host−guest attractive forces ($\Delta H° < 0$) will cause this entropy loss ($\Delta S° < 0$), leading to the enthalpy−entropy compensation. If both of host and guest are rigid, we should observe a minimal compensation. The compensation effect will be maximum if flexible host and flexible guest form an induced-fit type complex.[80]

As to the second source of compensation, the enthalpy−entropy compensation originated from desolvation should be distinct if the number of desolvated solvent molecules increases as the host−guest attractive interactions are larger, which in turn is proportional to the contact surface area of host and guest. It should be noted that this compensation will be best observed in a strongly solvating polar solvent such as water. Both the conformational restriction owing to the host−guest multipoint interactions as well as the desolvation from the contact surface contribute to the slope of the correlation line in the plot of $\Delta S°$ against $\Delta H°$.

Inoue et al. proposed that the two quantities, the slope and the intercept of the plot of $T\Delta S°$ against $\Delta H°$, can be used to estimate the conformational changes and the degree of desolvation during host−guest complexation, respectively.[62] From the data shown in Figure 8, the slope α is 0.81 and the intercept $T\Delta S°$ is 3.1 kcal/mol in the complexation between zinc porphyrin receptors and amines or amino esters in water (correlation coefficient $r = 0.914$). The compensation relationship observed for α-, β-, and γ-cyclodextrins gives the slope α of 0.9 and the intercept $T\Delta S°$ of 3.1 kcal/mol,[62] being very close to the values observed in our water-soluble zinc porphyrin receptor system. These values suggest that both induced-fit type conformational changes and desolvation contribute considerably to the overall

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energetics of binding by zinc porphyrins in water. As supporting evidence for the induced-fit binding, in the ^{1}H NMR spectra there are characteristic shifts in the alkyl protons of **3a** upon complexation, showing that the alkyl groups at the 2,6-positions modify their conformation to accommodate a guest.[14]

The host−guest polar interactions, the contact surface area, flexibility of host and guest molecules, and polarity of solvent are important parameters determining the enthalpy and entropy changes in binding. If the contact surface area is small, then the host−guest polar interactions should be the main driving force. If the contact surface area is large and the solvent is polar and cohesive, all of desolvation, host−guest polar interactions, and host−guest nonpolar (dispersion) interactions play a significant role in the thermodynamics of binding. Recognition of molecules of biological interest such as protein or DNA is associated with a large contact area, and regulation of the desolvation should be important for the rational design of the system.

Conclusions

The present study clarified the relative importance of intermolecular interactions in molecular recognition of amines and α-amino esters by zinc porphyrin receptors. The driving force of binding was discussed in terms of two classes of interactions, the host−guest interactions and solvation interactions. The binding affinity was high both in CH_2Cl_2 and in water and low in water−MeOH. Thus we suggest that two driving forces competitively contribute to the overall binding free energy. The host−guest electrostatic interactions are important for the binding selectivity in organic solvents, while desolvation-driven binding is dominant in water. For the binding in CH_2Cl_2, the ester groups of the zinc porphyrin receptors contributed to the tight binding of aromatic guests, and the long alkyl chains of the zinc porphyrins contributed to the loose binding of Leu-OMe and other bulky amino acid esters. Relatively flexible carbomethoxyalkyl groups can dictate the binding selectivity of the receptors. The difference in solvent polarity manifests itself by compensation effects of $\Delta H°$ and $\Delta S°$. Clear compensation was observed in water, reflecting the importance of induced-fit conformational changes and desolvation processes for binding in water.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 500 MHz, and chemical shifts are reported relative to Me_4Si or residual protons of deuterated solvents. High-resolution mass spectra were obtained using 3-nitrobenzyl alcohol as a matrix. The binding constants were determined as previously described.[14] X-ray diffraction data were collected at 295 K with a Rigaku CCD diffractometer (Mercury). Crystals for the X-ray study were obtained by recrystallization of the free base of **1** from methanol.

Materials. Porphyrins **1**−**3** and **1a**−**3a** were prepared according to the published procedures.[14]

Methyl 3,5-Dimethoxy-4-methylbenzoate (7). A mixture of 3,5-dihydroxy-4-methylbenzoic acid[81] (1.3 g, 7.7 mmol), K_2CO_3 (2.5 g), and dimethyl sulfate (2.5 mL) in acetone (15 mL) was refluxed for 4 h. After AcOEt (50 mL) was added, the organic layer was washed with saturated aqueous NaCl and dried over $MgSO_4$. Evaporation of the solvent and recrystallization from EtOH afforded a white solid of **7** (1.4 g, 87%): ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H), 3.85 (s, 6H), 3.90 (s, 3H), 7.21 (s, 2H); HRMS (FAB) calcd for $C_{11}H_{14}O_4$ (M^+) 210.0892, found 210.0884. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.68; H, 6.66.

Methyl 4-Bromomethyl-3,5-dimethoxybenzoate (8). A solution of **7** (1.0 g, 4.8 mmol) in CCl_4 (28 mL) was irradiated with a 500-W lamp while Br_2 (525 mg, 3.28 mmol) in CCl_4 (10 mL) was added dropwise over 30 min. The progress of the reaction was monitored by TLC (SiO_2, AcOEt/hexane = 1/4). After the reaction was completed, AcOEt (50 mL) was added. The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried over $MgSO_4$. Evaporation of the solvent and recrystallization from ether afforded a white solid of **8** (0.97 g, 70%): ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 3.92 (s, 6H), 4.63 (s, 2H), 7.20 (s, 2H); HRMS (FAB) calcd for $C_{11}H_{13}BrO_4$ (MH^+) 287.9997, found 287.9989.

Methyl 4-Formyl-3,5-dimethoxybenzoate (9). A solution of powdered **8** (730 mg, 2.52 mmol) in DMSO (16 mL) and $NaHCO_3$ (1.85 g) was heated at 70 °C under N_2 with vigorous stirring for 25 min. The progress of the reaction was monitored by TLC (SiO_2, AcOEt/hexane = 1/1). The reaction mixture was then immediately cooled in an ice bath, poured into saturated NaCl (40 mL), and extracted with AcOEt. The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent and recrystallization from benzene/hexane afforded a white solid of **9** (425 mg, 75%): ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 9H), 7.23 (s, 2H), 10.50 (s, 1H); HRMS (FAB) calcd for $C_{11}H_{12}O_5$ (MH^+) 224.0684, found 224.0677. Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 58.64; H, 5.36.

5,10,15,20-Tetrakis(4-methoxycarbonyl-2,6-dimethoxyphenyl)porphyrin (10). Aldehyde **9** (224 mg, 1 mmol) and pyrrole (69 μL, 1 mmol) were dissolved in CH_2Cl_2 (100 mL) under N_2 and then BF_3·OEt_2 (42 μL, 0.33 mmol) was added. After the reaction mixture was stirred at room temperature for 80 min, 2,3-dichloro-5,6-dicyanobenzoquinone (170 mg, 0.75 mmol) was added, and the mixture was refluxed for 2 h. The solution was then neutralized by addition of triethylamine (46 μL) and evaporated. The mixture was separated by column chromatography (SiO_2, $CHCl_3$/AcOEt = 100/1 to 10/1), and the crude product was washed with methanol thoroughly to afford a purple solid of **10** (87 mg, yield 32%): ^{1}H NMR ($CDCl_3$) δ −2.57 (s, 2H), 3.55 (s, 24 H), 4.08 (s, 12H), 7.66 (s, 8H), 8.60 (s, 8H); UV−vis (CH_2Cl_2) λ_{max} (log ϵ) 419 (5.56), 513 (4.27), 545 (3.68), 592 (3.72); HRMS (FAB) calcd for $C_{60}H_{54}N_4O_{16}$ (M^+) 1086.3534, found 1086.3536. Anal. Calcd for $C_{60}H_{54}N_4O_{16}$: C, 66.29; H, 5.01; N, 5.15. Found: C, 66.02; H, 5.29; N, 4.90.

[5,10,15,20-Tetrakis(4-methoxycarbonyl-2,6-dimethoxyphenyl)porphyrinato]zinc(II) (4). A solution of **10** (52 mg, 48 μmol) and $Zn(OAc)_2$-saturated methanol (9 mL) in $CHCl_3$ (50 mL) was refluxed for 1.5 h. After cooling, the solution was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried over Na_2SO_4. Evaporation of the solvent and washing with methanol thoroughly afforded a pink solid of **4** (52 mg, 95%): ^{1}H NMR ($CDCl_3$) δ 3.55 (s, 24H), 4.08 (s, 12H), 7.67 (s, 8H), 8.68 (s, 8H); UV−vis (CH_2Cl_2) λ_{max} (log ϵ) 421 (5.61), 548 (4.29), 586 (3.36); HRMS (FAB) calcd for $C_{60}H_{52}N_4O_{16}Zn$ (M^+) 1148.2668, found 1148.2714.

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Supporting Information Available: Tables of structure factors and positional parameters for the free base of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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