Porphyrin Receptors for Amines, Amino Acids, and Oligopeptides in Water

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Abstract: A series of water-soluble porphyrin receptors having a hydrophobic binding pocket, a Lewis acidic site (Zn), and an electrostatic recognition site (COO^- groups) were prepared. All the porphyrin receptors have a [*meso*-tetrakis(*p*-carboxyphenyl)porphyrinato]zinc (Zn·TCPP) as a common structural unit, and eight ω-carboxyalkyloxy groups (alkyloxy = methoxy (**1**), butoxy (**2**), decyloxy (**3**)) at the ortho positions of the phenyl groups. These receptors bind amines, α-amino acid esters, and oligopeptides in water with significant selectivity. For binding of hydrophilic guests, **1**, **2**, and **3** bind histamine in pH 8 buffer at 25 °C with binding constants of 157000, 31000, and 18200 M^{-1}, respectively, where the coordination (Imd−Zn) and the salt bridge (NH_3^+−$^-$OOC) stabilized the complex. The large dependence of the binding constants on the ionic strength indicated that the electrostatic interaction between the ammonium group of histamine and the carboxylate groups of receptor contributes significantly to tight binding in water. Receptors **1**−**3** also bind a cationic guest, Arg-OMe, with a binding constant of 440−11000 M^{-1}. The effective charge of the receptors for electrostatic recognition of Arg-OMe in pH 9 Borax (I = 0.1 M) at 25 °C was evaluated by the Debye−Hückel limiting law as 4.2, 4.3, and 3.0 for **1**, **2**, and **3**, respectively. These observations indicate that a salt bridge, which is exposed to water and involves hydrogen bonding, as seen in the **1**−histamine and **1**−Arg-OMe complexes, can be used as a significant recognition force. Binding of Arg-OMe by **2** and **3** was entropically driven, and binding of Arg-OMe by **1** was enthalpically driven. Therefore, the driving force of binding is desolvation from the ionic groups in the former case and the electrostatic attraction in the latter case. For binding of hydrophobic guests, **3** binds Trp-OMe or pyridine in water with binding constants of 7000−8000 M^{-1}, while **1** and Zn·TCPP bind these guests less tightly with binding constants of 20−500 M^{-1}, indicating the importance of the long alkyl chains to provide a hydrophobic binding pocket above the porphyrin plane.

Introduction

Recognition of biomolecules in water is a challenging subject in host−guest chemistry. Continuing efforts have been made to understand the mechanism of recognition and to develop an artificial receptor comparable to proteins.[1] Design of a molecule that recognizes a target molecule in nonpolar solvents is rather straightforward because contribution from solvation energy is less important than the polar interactions between receptor and guest, so that, as a first approximation, only interactions between host and guest should be considered to design the system. However, strategies successful in receptor design in nonpolar organic solvents are not always applicable to receptor design in water, since polar interactions are considerably hindered by hydration.[2] Thus, a target of water-soluble synthetic receptors is most frequently a nonpolar molecule, where hydrophobic interactions are the major driving force of binding. For instance, cyclodextrin binds hydrophobic guests such as substituted benzenes with the association constant ranging from 10^2 to 10^4 M^{-1}.[3] Because most biomolecules have polar functional groups, a general strategy to recognize such polar functional groups in water needs to be established. Recognition of polar molecules in water has two intrinsic difficulties: (1) polar functional groups are better hydrated and diminish hydrophobic interactions and (2) hydrogen bonding or electrostatic interactions between polar functional groups are weakened by hydration when compared to the interactions in nonpolar solvents; the interaction energy is sometimes comparable to changes in solvation energy and is no longer a major driving force of binding. This is seen in the weak binding of hydrophilic guests by cyclodextrins. Although modification of cyclodextrin with polar substituents improves the binding affinity compared to the parent cyclodextrin, the overall binding affinity is still moderate.[4]

A new water-soluble host having both a hydrophobic binding pocket and polar recognition groups should help in clarifying the binding mechanism of polar molecules in water. A rigid and hydrophobic porphyrin framework can be used as a receptor in water if it is solubilized by peripheral substitution by polar groups. We prepared water-soluble zinc porphyrins **1**−**3**, which have a Lewis acidic site (Zn), a salt bridge site (COO^- groups),

(1) For recent studies on molecular recognition in water, see: (a) Schneider, H.-J.; Kramer, R.; Simova, S.; Schneider, U. *J. Am. Chem. Soc.* **1988**, *110*, 6442. (b) Kral, V.; Furuta, H.; Shreder, K.; Lynch, V.; Sessler, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 1595. (c) Chen, H.; Ogo, S.; Fish, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 4993. (d) Dandliker, P. J.; Diederich, F.; Zingg, A.; Gisselbrecht, J. P.; Gross, M.; Louati, A.; Sanford, E. *Helv. Chim. Acta* **1997**, *80*, 1773. (e) Nelen, M. I.; Eliseev, A. V. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1359. (f) Metzger, A.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **1998**, *37*, 649. (g) Hossain, M. A.; Schneider, H.-J. *J. Am. Chem. Soc.* **1998**, *120*, 11208. (h) Park, H. S.; Lin, Q.; Hamilton, A. D. *J. Am. Chem. Soc.* **1999**, *121*, 8. (i) Ngola, S. M.; Kearney, P. C.; Mecozzi, S.; Russell, K.; Dougherty, D. A. *J. Am. Chem. Soc.* **1999**, *121*, 1192. (j) Inouye, M.; Fujimoto, K.; Furusyo, M.; Nakazumi, H. *J. Am. Chem. Soc.* **1999**, *121*, 1452. (k) Sirish, M.; Schneider, H.-J. *Chem. Commun.* **1999**, 907.

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(3) Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875.

(4) (a) Tabushi, I.; Shimizu, N.; Sugimoto, T.; Shiozuka, M.; Yamamura, K. *J. Am. Chem. Soc.* **1977**, *99*, 7100. (b) Tabushi, I.; Kuroda, Y.; Mizutani, T. *Tetrahedron* **1984**, *40*, 545. (c) Tabushi, I.; Kuroda, Y.; Mizutani, T. *J. Am. Chem. Soc.* **1986**, *108*, 4514.

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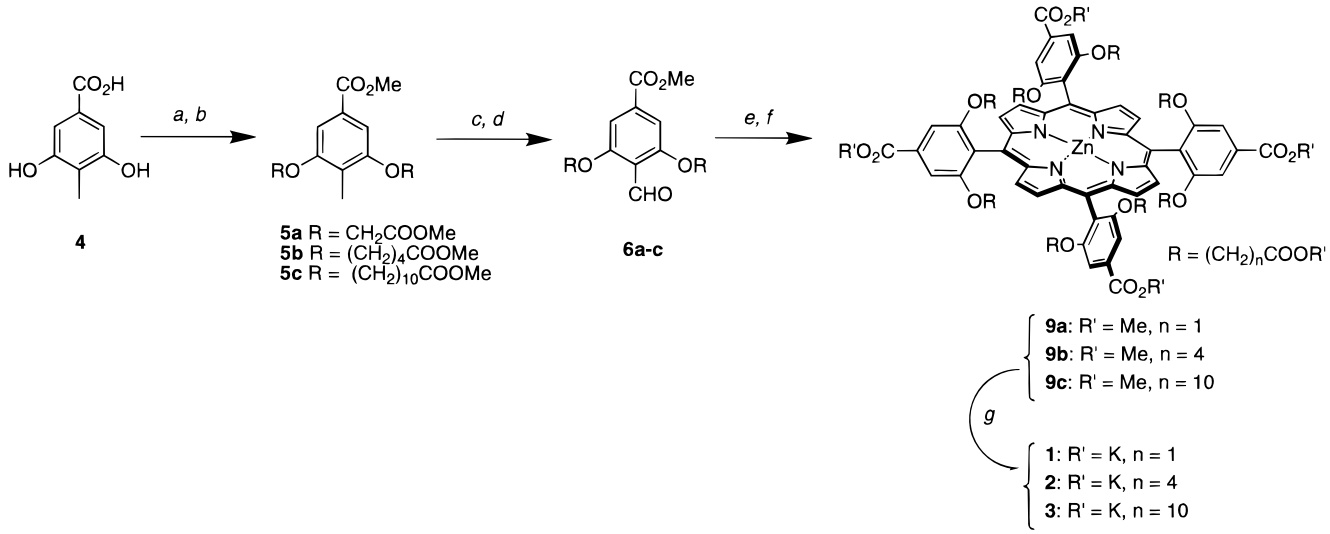
Scheme 1[a]



[a] Reagents and conditions: (a) H_2SO_4/MeOH; (b) R−Br, K_2CO_3/DMF; (c) Br_2/CCl_4, *hν*; (d) DMSO/$NaHCO_3$; (e) BF_3·OEt_2, pyrrole/CH_2Cl_2, then DDQ; (f) $Zn(OAc)_2/CHCl_3$; (g) 0.5 M KOH, MeOH, THF.

and a hydrophobic binding pocket (the porphyrin framework, aryl groups, and alkyl chains). We report here that these receptors bind both hydrophilic and hydrophobic guests such as amines, amino acids, and oligopeptides with significant selectivity in water, with particular affinity for histamine and a histidine-containing oligopeptide.[5]

Results

Synthesis and Characterization of Porphyrin Receptors. Porphyrin receptors **1**−**3** were prepared according to Scheme 1. Precursor **4** was prepared from 3,5-dihydroxybenzoic acid according to the reported method.[6] Aldehyde **6** was obtained in 45−61% yield from **4**. Condensation with pyrrole by Lindsey's method[7] afforded free base porphyrins **8a**−**c** in 15−22% yield. Zinc insertion followed by alkaline hydrolysis gave **1**−**3** in 63−75% yield. Compounds **4**−**8** were characterized by ^{1}H NMR, high-resolution mass spectroscopy, and elemental analysis. The structure and purity of **1**−**3** were confirmed by ^{1}H NMR spectroscopy. The zinc porphyrins **1**−**3** are soluble in water, and they are also soluble in a MeOH−water mixture. In Borax buffer at pH 9 (ionic strength, $I = 0.1$ M), the absorbance in the Q-band followed the Lambert−Beer law up to at least 90 μM, indicating that the porphyrin is monomeric. At pH <7.5, a gradual decrease in the absorbance in the Soret band was observed, suggesting that aggregation occurred. At pH >11, the absorbance in the Soret band increased, suggesting the deprotonation of Zn−OH_2 occurred. Thus, the binding experiments were performed at pH 8 or 9. Dynamic light scattering experiments of a solution of 0.1 mM of **3** in pH 9 Borax buffer showed that no micellar-like aggregate was formed.

Binding of Amines, α-Amino Acid Esters, and Oligopeptides. Addition of guest caused a red-shift in the Soret band, a typical spectral change due to the amino group coordination to zinc. The binding constants were determined by monitoring the absorbance changes of the Soret band as a function of guest concentrations, and fitting the saturation plot to the 1:1 binding isotherm or the 1:1 and 1:2 binding isotherm for some cationic guests: $K_1 = [P{\cdot}G]/([P][G])$, and $K_2 = [P{\cdot}G_2]/([P{\cdot}G][G])$. The binding constants K_1 and K_2 (where applicable) were determined for **1**−**3** and Zn·TCPP ([5,10,15,20-tetra(*p*-carboxyphenyl)-porphyrinato]zinc), and are listed in Table 1. Standard deviations for the curve fitting were less than 5%. For the binding by Zn·TCPP, isosbestic points were not observed. The binding isotherm for Zn·TCPP was analyzed based on the 1:1 complexation, because attempts to analyze the data based on the 1:1 and 1:2 complexation failed. Nevertheless, the standard deviations for the curve fitting were less than 5%. For other receptor−guest combinations except for the combinations involving 1:2 complexes, isosbestic points were always observed. In the following discussions, we focus only on the magnitude of K_1. The binding constants were also determined in CH_2Cl_2 using **9b**, **9c**, and Zn·TPP ([5,10,15,20-tetraphenylporphyrinato]zinc), and are listed in Table 2. Details of the binding behavior of **9a**−**c** will be reported elsewhere.

^{1}H NMR Studies of Conformations of Receptors. ^{1}H NMR spectra of the solution of **3** showed that the chemical shifts of the alkyl chain protons of **3** changed upon addition of guest or inorganic salts. Addition of NaCl to the solution of **3** in a Borax buffer caused the upfield shifts in all the alkyl methylene protons as shown in Figure 1. The assignments of signals are based on the ^{1}H−^{1}H COSY and homonuclear spin-decoupling experiments. Addition of pyridine to a solution of **3** caused upfield shifts in the H1′−H3′ resonances and downfield shifts in the H4′−H9′ resonances (Figure 2). In Figure 3, the ^{1}H NMR spectra of **2** and **3** are compared with their free bases. The resonances of all the alkyl protons are shifted downfield upon zinc insertion except for the H-4′ protons of **2**. The resonance of H-4′ protons of **2** is shifted upfield relative to that of the free base.

Enthalpy and Entropy Changes in Complexation. The enthalpy changes and the entropy changes of complexation were determined by a van't Hoff plot using the binding constants K_1 determined by UV−vis titration experiments in the temperature range of 2−25 °C. Figure 4 shows the plots of $\Delta H°$ against $\Delta S°$, indicating that there is enthalpy−entropy compensation for the binding. The values of $\Delta H°$ and $\Delta S°$ of complexation showed a substantial variation, depending on the combination of the host−guest complexes. For instance, although the binding

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Table 1. Binding Constants, K_1, K_2/M^{-1}, between Porphyrin Receptors and Amines, α-Amino Esters, or Oligopeptides in Aqueous Buffer (Borax at pH 9 and $I = 0.1$ M) at 25 °C[a]

		K_1 (K_2)[b]			
entry	guest	**1**	**2**	**3**	Zn•TCPP
1	Gly-OMe	15	43	460	16
2	Ala-OMe[c]	*e*	15	240	14
3	Ala-OMe	5	13	240	14
4	Ala-OMe[d]	*e*	13	340	14
5	Val-OMe	*f*	2	16	43
6	Leu-OMe	*f*	1	15	59
7	PhGly-OMe	*f*	2	12	27
8	Phe-OMe	30	107	1130	89
9	Trp-OMe[c]	*e*	550	7000	300
10	Trp-OMe	67	670	7160	370
11	Trp-OMe[d]	*e*	680	7600	520
12	Tyr-OMe	38	310	2750	240
13	Ser-OMe	5	8	46	9
14	His-OMe	71	410	1210	200
15	Lys-OMe	400 (100)	140	690	57
16	Arg-OMe[h]	11100 (2690)	4500 (830)	5700 (350)	67
17	Arg-OMe[c]	7430 (1670)	2540 (580)	4310 (470)	150
18	Arg-OMe[g]	2780 (700)	1050 (280)	2250 (410)	*e*
19	Arg-OMe	1400 (270)	440 (150)	1260 (90)	105
20	pyridine	14	1920	8200	21
21	butylamine	*e*	19	15	*e*
22	benzylamine	*e*	45	430	*e*
23	nicotinamide	7	340	1500	26
24	imidazole	20 (1)	2970	2610	69
25	imidazole[h]	47 (8)	2950	2660	*e*
26	imidazole[i]	190 (21)	2960	2600	68
27	histamine	2690 (100)	9500	5170	90
28	histamine[h]	13 900 (1930)	30 100	17 400	150
29	histamine[i]	157 000 (6100)	31 000	18 200	150
30	Trp-Arg-OH	83 (12)	73 (0.3)	360 (28)	*e*
31	Gly-His-Lys-OH	1	170	480	150
32	Gly-His-Lys-OH[h]	790 (2)	660	850	*e*
33	Gly-His-Lys-OH[i]	22 300 (1070)	3180	2850	270
34	Ala-NH_2	*e*	*f*	7	6
35	Lys-OH	*e*	*f*	7	8
36	Ala-OMe[j]	*e*	13	6	2
37	Leu-OMe[j]	*e*	6	*f*	11
38	Phe-OMe[j]	*e*	13	36	13
39	Trp-OMe[j]	*e*	6	94	16

[a] Averages of 2−3 independent determinations. The estimated errors in K_1 and K_2 were less than 5%. [b] K_1 and K_2 are the binding constants for 1:1 and 1:2 complexes, respectively. [c] $I = 0.02$ M (KCl). [d] $I = 0.5$ M (KCl). [e] Not determined. [f] Not bound. [g] $I = 0.05$ M (KCl). [h] $I = 0.01$ M (KCl). [i] Borax at pH 8 and $I = 0.01$ M. [j] MeOH−Borax (pH 9.0, $I = 0.1$ M) = 10:1 (v/v).

Table 2. Binding Constants, K_1/M^{-1}, between Porphyrin Receptors **9** and α-Amino Acid Esters or Amines in CH_2Cl_2 at 25 °C

guest	**9b**	**9c**	Zn•TPP[a]	guest	**9b**	**9c**	Zn•TPP[a]
Ala-OMe	75	920	4660	Phe-OMe	36	360	4910
Leu-OMe	0.5	18	6860	Trp-OMe	110	1090	8730
PhGly-OMe	*b*	13	5250	pyridine	401	4480	7720

[a] [5,10,15,20-Tetra(phenyl)porphyrinato]zinc. [b] Not bound.

constants of Arg-OMe by **1** and **3** were similar in magnitude (1400 and 1260 M^{-1}, respectively), the different signs and values of $\Delta H°$ and $\Delta S°$ (Figure 4, a vs. g) indicate that the origin of the driving force of binding is different.

Discussion

Binding of Hydrophilic Guests. Receptors **1**−**3** showed tight binding to cationic amino esters (Lys-OMe and Arg-OMe) and histamine in water (Borax, pH 9, $I = 0.1$ M). The large binding constant for histamine by **1** is noteworthy. This high affinity can be ascribed to the coordination interaction between zinc and the imidazolyl group as well as the electrostatic interaction between the carboxylate groups of **1** and the ammonium group

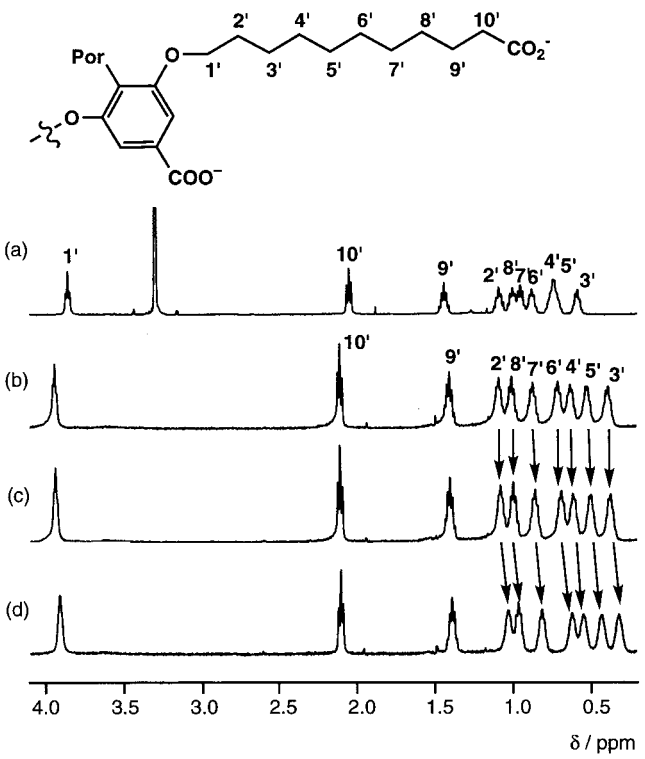

Figure 1. ^{1}H NMR spectra of a solution of **3** (1 mM) in (a) MeOH-d_4, (b) a Borax buffer at pD = 8.6 and $I = 0.1$ M, (c) a Borax buffer at pD = 8.6 and $I = 0.2$ M, and (d) a Borax buffer at pD = 8.6 and $I = 0.5$ M. The ionic strength was adjusted by adding NaCl.

of histamine. The following two observations revealed the importance of the electrostatic interactions in the binding: (1) the binding constant of histamine was much larger than that of imidazole, and (2) the binding constant of histamine at pH 9 was increased when the ionic strength was reduced from 0.1 to 0.01 M (Table 1, entries 27−28) and it was also increased when the pH was changed from 9 to 8 (Table 1, entries 28−29). Since the pK_a values of histamine are 6.1 (imidazole) and 9.9 (amino),[8] histamine with the protonated NH_2 group, which is the major species at pH 8, has much higher affinity for **1** than neutral histamine. These results indicate that the contribution of the electrostatic interaction between the COO^- groups of **1** and the NH_3^+ group of histamine was quite large even in water.[9] A molecular modeling study showed that the ammonium group of histamine can interact with two carboxylate groups of receptor **1** via hydrogen bonding (Figure 5). Receptors **1**−**3** also bind tripeptide, Gly-His-Lys-OH, with a binding constant of 2850−22 300 M^{-1} in 0.01 M Borax at pH 8. A large dependence on pH and ionic strength (Table 1, entries 31−33) suggests that the complexation is also dominated by salt bridge formation between the N-terminal NH_3^+ group of the guest and the COO^- groups of **1**−**3**.

The binding affinity for cationic amino esters, Lys-OMe and Arg-OMe, is moderate compared to that of histamine. The binding constants of Arg-OMe were decreased with an increase in the ionic strength. In contrast, the binding constants of Ala-

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(9) Hosseini et al. reported that the binding of ATP by a protonated macrocyclic polyamine was driven by hydrogen bonding between the ammonium group and the phosphate group, with the binding constant of 10^{11} M^{-1}. See: Hosseini, M. W.; Lehn, J.-M.; Mertes, M. P. *Helv. Chim. Acta* **1983**, *66*, 2454. See also: Gokel, G. W.; Abel, E. *Comprehensive Supramolecular Chemistry*; Gokel, G. W., Ed.; Pergamon Press Ltd.: Oxford, 1996; Vol. 1, p 511. Mock, W. L.; Shih, N.-Y. *J. Org. Chem.* **1986**, *51*, 4440.

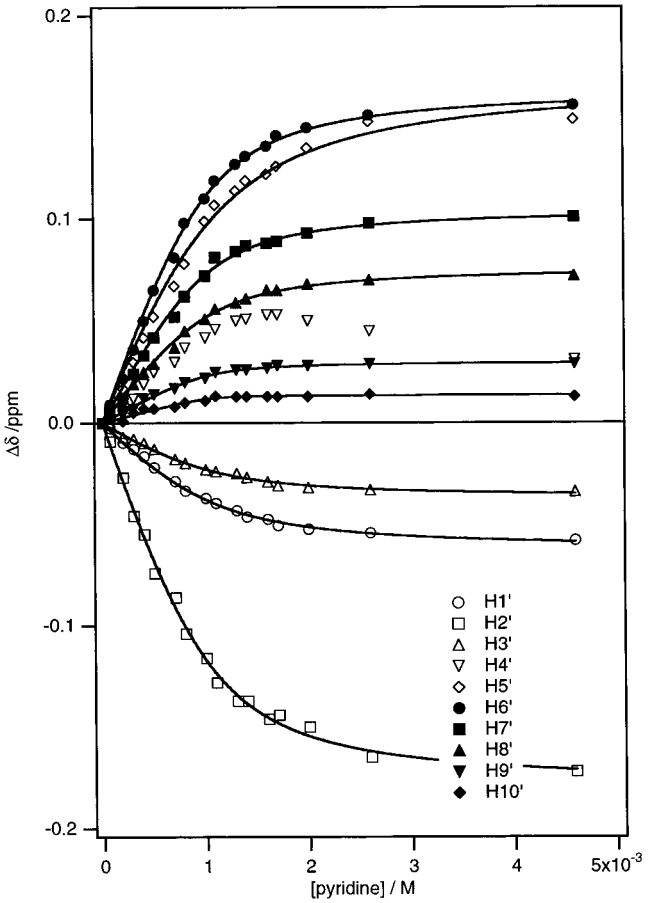

Figure 2. Plots of the complexation-induced chemical shifts ($\Delta\delta$/ppm) of **3** (1.0 mM) against the concentration of pyridine in Borax buffer at pD = 8.6 and I = 0.1 M at 298 K. Curves were calculated by a least-squares method based on 1:1 complex formation. The binding constant determined from these chemical shift displacements for all the signals except for H-4′ and H-10′ was 5900 ± 700 M^{-1}.

OMe and Trp-OMe were constant in the range of ionic strength from 0.02 to 0.5 M (Table 1, entries 2−4 and 9−11). The Debye−Hückel limiting law gives the following relationship,[1a,10] $\log K = \log K' - 1.018|z_a z_b|\sqrt{I}$ (in water, 25 °C), where K' is the binding constant at $I = 0$, and z_a and z_b are the effective charges of receptor and guest, respectively. The plots of log K against $\sqrt{I}$ afforded a straight line, and the effective charge (z_a) of **1**, **2**, and **3** for binding of Arg-OMe was determined to be 4.2, 4.3, and 3.0, respectively, if we assume that z_b is 1. These results support the view that the carboxylate groups of **1**−**3** serve as the electrostatic recognition site. The effective charge in the range of 3 to 4 suggests that only a portion of the COO^- groups contribute electrostatic interactions.

Binding of Hydrophobic Guests. The hydrophobic interaction is also important as a driving force of recognition. The binding by hydrophobic interactions becomes very strong if the contact surface area between host and guest is high. Breslow et al. reported that the cyclodextrin dimer binds a hydrophobic guest with a binding constant of 10^{10} M^{-1}.[11] If one compares the binding constants for a given hydrophobic guest such as Leu-OMe, Phe-OMe, and pyridine among **1**, **2**, and **3**, then **3** showed the largest binding constants (Table 1, entries 6, 8, and 20). This is characteristic of the receptor−guest complex formation driven by hydrophobic interactions. Although methyl esters of α-amino acids showed moderate affinity for **1**−**3**,

(10) Hossain, M. A.; Schneider, H.-J. *Chem. Eur. J.* **1999**, *5*, 1284.
(11) Breslow, R.; Chung, S. *J. Am. Chem. Soc.* **1990**, *112*, 9659.

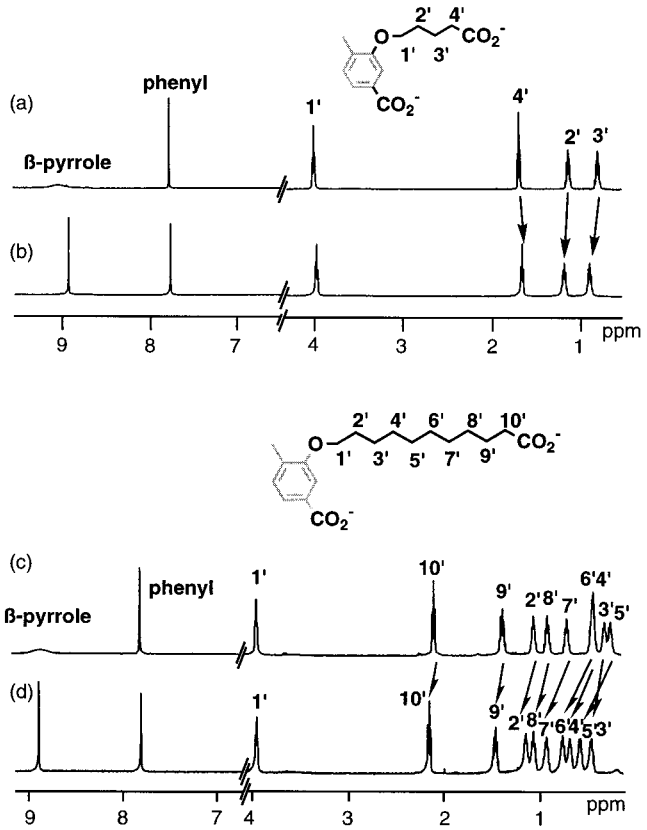

Figure 3. ^{1}H NMR spectra of a solution of **2** or **3** and the corresponding free bases in D_2O (1 mM, Borax, pD 8.6): (a) free base of **2**, (b) **2**, (c) free base of **3**, and (d) **3**.

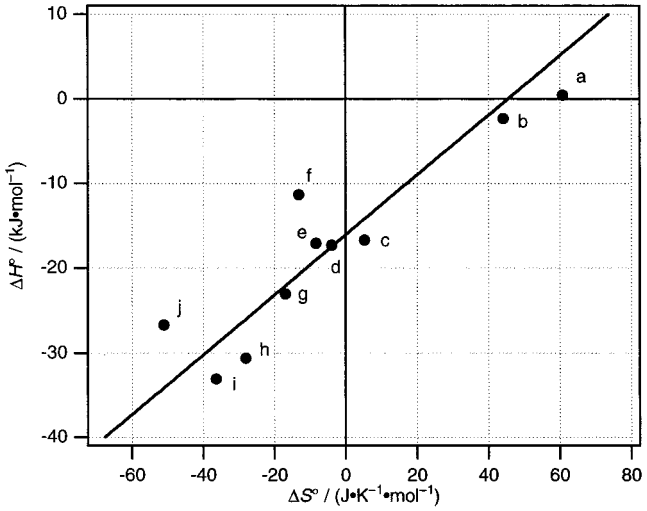

Figure 4. Plot of the enthalpy changes of complexation against the entropy changes in Borax buffer at pH 9.0 and I = 0.1 M: (a) **3**−Arg-OMe, (b) **2**−Arg-OMe, (c) **2**−py, (d) **2**−Trp-OMe, (e) Zn·TCPP-Trp-OMe, (f) Zn·TCPP-py, (g) **1**−Arg-OMe, (h) **3**−py, (i) **3**−Trp-OMe, (j) Zn·TCPP-Arg-OMe.

α-amino acids and α-amino amides showed very weak affinity (Table 1, entries 34 and 35). This is partly because the basicity of the amino group of α-amino acids and α-amino amides is higher than that of α-amino esters. For instance, the values of pK_a of Ala-OH, Ala-OMe, and Ala-NH_2 are 9.7, 7.7, and 8.2, respectively.[12] Therefore, at pH 9, most of the NH_2 group of Ala-OMe is not protonated and is able to interact with zinc, while a major part of the NH_2 group of Ala-OH is protonated and is unable to interact with zinc. The small binding constants

(12) Hay, R. W.; Morris, P. J. *J. Chem. Soc. B* **1970**, 1577.

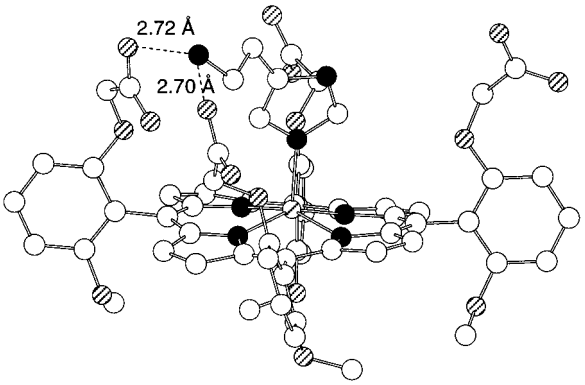

Figure 5. A possible binding geometry of a complex between protonated histamine and **1**. The distances between N of NH_3^+ and O of COO^- are 2.72 and 2.70 Å. For the modeling study, the substituents at 4′- and 6′-positions of **1** were replaced by hydrogens and methoxy groups, respectively.

of simple amines such as butylamine or benzylamine (Table 1, entries 21 and 22) are also attributable to the higher pK_a values of the amino groups, which are mostly protonated in pH 9 buffer. For α-amino acids, electrostatic repulsion between the COO^- group of α-amino acid and the COO^- groups of **1**−**3** also disfavors the binding. Verchére-Bèaur et al. reported that there is no interaction between Zn·TCPP and C-terminal free α-amino acids in water on the basis of ^{1}H NMR studies.[13]

^{1}H NMR studies (Figure 2) showed that the alkyl protons of **3** underwent a complexation-induced upfield or downfield shift upon binding pyridine, indicating that the guest binding induces conformational changes in the receptor.[14] Upfield shifts of H1′−H3′ resonances and downfield shifts of H4′−H9′ resonances suggest the following conformational changes. The C1′−C3′ carbons move toward the porphyrin framework to accommodate a hydrophobic environment for the pyridine binding, this conformational change then gives rise to the strong repulsion between the COO^- groups, and C4′−C9′ carbons will be forced to move away from the porphyrin framework. The binding constant determined from the NMR titration was 5900 ± 700 M^{-1} for the **3**−pyridine complex. Anomalous shifts were observed for the H-4′ resonance and it is difficult to explain this behavior. Zn·TCPP having no carboxyalkyl groups showed only weak affinity for most of the guests studied. These observations suggest that the ω-carboxyalkyl chains of **1**−**3** form a hydrophobic binding pocket with the porphyrin framework, and this binding pocket favors the binding of hydrophobic guest.

Surprisingly, **1**−**3** showed very weak affinity for hydrophobic bulky amino acid esters such as Val-OMe, Leu-OMe, and PhGly-OMe, although Zn·TCPP showed moderate affinity for these guests. This seems contradictory to the role of carboxyalkyl groups described above that the carboxyalkyl chains help bind hydrophobic guest. However, this behavior can be understood if one sees the same trend that **9b** and **9c** have weak affinity toward Leu-OMe and PhGly-OMe in CH_2Cl_2 (Table 2).[15] Therefore, the weak affinity of **2** and **3** for Val-OMe, Leu-OMe, and PhGly-OMe can be attributable to some steric repulsion in the small binding pocket of **2** and **3**, not to solvation-desolvation processes.

Another interesting feature is that, in CH_2Cl_2, **9b** and **9c** showed lower affinity for a given guest than Zn·TPP, while **2** and **3** showed higher affinity than **1** and Zn·TCPP for aliphatic and aromatic amino esters, suggesting that the alkyl groups of **2** and **3** stabilize the complex by strengthening hydrophobic effects and/or the zinc of **2** and **3** is reactive due to the hydrophobic environment provided by the alkyl groups. In methanol−pH 9 Borax (10:1 (v/v)), the binding constants of Ala-OMe, Leu-OMe, Phe-OMe, and Trp-OMe by **2**, **3**, and Zn·TCPP are decreased to 2−94 M^{-1} (Table 1, entries 36−39). These observations also support the important role of water in selective binding. Thus, the hydrophobic binding pocket produced in water should be an important strategy for the design of receptors in water.

Conformations of Receptors. Figure 1 shows that the chemical shifts of the alkyl groups of **3** change as the ionic strength changes or guest is added. The addition of salt will reduce the electrostatic repulsion between the COO^- groups so that the ω-carboxyalkyl groups tend to aggregate above the porphyrin plane. This will explain the upfield shifts of the alkyl protons at higher ionic strengths.

Comparison of the ^{1}H NMR chemical shifts of the alkyl protons between free base and the zinc complexes **2** and **3** (Figure 3) showed that only the resonance of the α-protons (H-4′) of the zinc complex of **2** shifted upfield relative to the free base, while the resonances of other protons are shifted downfield. This implies that there is a strong tendency for the COO^- group of **2** to intramolecularly coordinate to the zinc.

Thermodynamic Parameters of Complex Formation. The values of enthalpy changes and entropy changes of complexation were smaller in magnitude than those reported for the binding of amines or α-amino esters by zinc porphyrins in organic solvents. Typically, $\Delta H°$ ranges from −30 to −100 kJ/mol and $\Delta S°$ from −30 to −220 J/(K mol) in organic solvents.[16] The smaller values of $\Delta H°$ and $\Delta S°$ in water reported here are attributable to the enthalpy−entropy compensation effects, which are partially owing to solvation−desolvation processes.[17] The compensation temperature (T_c) determined from the slope of the plot (Figure 4) was 81 °C. Thus, at 81 °C, the free energy changes of the binding are the same among the complexes if the compensation relationship is strictly followed, leading to diminished selectivity of recognition.

Figure 4 shows that the binding of hydrophobic guest was driven enthalpically. The binding of Arg-OMe by **1** was also enthalpically driven. In contrast, the binding of cationic guest by hydrophobic receptors, **2** and **3**, is entropically driven (Figure 4, parts a and b). The origin of the entropic driving force for the binding of Arg-OMe by **2** and **3** seems to be the desolvation of the ionic groups of both receptor and guest upon salt bridge formation in a relatively hydrophobic environment. We reported that the binding of 1,2,4,5-benzenetetracarboxylate by [5,10,15,20-tetrakis(1-pentyl-3-pyridinio)porphyrinato]zinc(II) in water was entropically driven.[18] Kano et al. also reported entropically driven complexation between cationic cyclodextrin and *N*-acetylamino acids in water.[19] Thus entropically driven

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(14) Similar complexation-induced shifts were also observed for the complex between **3** and Ala-OMe, so that the shifts observed for the pyridine complex are not ascribed to the ring current effects of pyridine.

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binding seems to be a general mechanism of binding of ionic molecules having hydrophobic moieties in water.[20]

Conclusions

The present study demonstrated that anionic zinc porphyrins bind histamine and a histidine-containing oligopeptide tightly. Strong dependence of the binding affinity for these guests on ionic strength and pH revealed that electrostatic interactions between charged functional groups are an important driving force for recognition of hydrophilic guest molecules in water. Binding of ionic guest by salt-bridge formation in a hydrophobic environment was driven by entropically favorable desolvation as seen in the positive $\Delta S°$ for the **3**−Arg-OMe complex. Lower affinity of receptors in MeOH−water than in water indicated that water plays a significant role in binding energetics. Comparisons of binding affinity between hydrophilic receptor **1** and hydrophobic receptor **3** revealed that the hydrophobic binding pocket of **3** constructed in water enhances the affinity toward hydrophobic guests.

Experimental Section

General Methods. ^{1}H NMR spectra were obtained using a JEOL A-500 spectrometer and chemical shifts are reported relative to Me_4Si or residual protons of deuterated solvents. UV−vis spectra were recorded on a Hewlett-Packard 8452 diode array spectrophotometer with a thermostated cell compartment. Dynamic light scattering was performed with a 10 mW He−Ne laser. High-resolution mass spectra were obtained with a JEOL JMS-HX110A mass spectrometer using 3-nitrobenzyl alcohol as a matrix.

Materials. 3,5-Dihydroxy-4-methylbenzoic acid was prepared according to the literature procedure.[6] Methyl 11-bromoundecanoate and methyl 5-bromovalerate were prepared by esterification of the corresponding acid in a manner similar to that described for **4**.

UV−Vis Titrations. Binding constants were determined by UV−vis titrations. The details of the determination of the binding constant are as follows. Borax buffer solution was prepared by dissolving 1.53 g of H_3BO_3 in 50 mL of distilled water. The pH of the solution was adjusted to 9 by adding KOH. KCl was added to make the ionic strength 0.1 M. To ca. 2×10^{-6} M of **1**, **2**, **3**, or ZnTCPP in Borax buffer at pH 9.0 and $I = 0.1$ M was added a stock solution of guest in the same buffer at 25 °C. The decreases in absorbance at 424 nm and the increase at 434 nm in the Soret band were monitored at different concentrations of guest, with volume changes due to guest addition being taken into account during analysis. The titration was completed within 15 min after the amino ester solution was prepared to avoid any hydrolysis of the ester. Isosbestic points were observed except for the binding by Zn·TCPP and the binding involving 1:2 complexes. Assuming 1:1 and 1:2 complexation (where applicable), the binding constants were evaluated by a nonlinear least-squares parameter estimation based on the Damping Gauss−Newton method.[21]

Methyl 3,5-Dihydroxy-4-methylbenzoate (4). A solution of 3,5-dihydroxy-4-methylbenzoic acid (19.5 g, 116 mmol) in absolute methanol (400 mL) and concentrated sulfuric acid (3.5 mL) was refluxed for 12 h. After the solution was concentrated to about 100 mL, saturated aqueous $NaHCO_3$ (200 mL) was added. The aqueous layer was extracted with AcOEt (60 mL × 4) and the combined organic layers were washed with saturated aqueous NaCl (50 mL × 2) and dried over Na_2SO_4. Evaporation of the solvent and recrystallization from AcOEt/$CHCl_3$ afforded a white solid of **4** (17.1 g, 81%): ^{1}H NMR (acetone-d_6) δ 2.11 (s, 3H, Me), 3.79 (s, 3H, CO_2Me), 7.06 (s, 2H, phenyl-H), 8.48 (s, 2H, OH); HRMS (FAB) calcd for $C_9H_{10}O_4$ (M^+) 182.0579, found 182.0581. Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.19; H, 5.56.

Methyl 3,5-Bis(methoxycarbonylmethoxy)-4-methylbenzoate (5a). This compound was prepared from **4** (5.0 g) in a manner similar to that for **5c**: yield 84% (7.54 g); ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3H, CH_3), 3.79 (s, 6H, CO_2Me), 3.87 (s, 3H, CO_2Me), 4.69 (s, 4H, CH_2), 7.24 (s, 2H, phenyl-H). Anal. Calcd for $C_{15}H_{18}O_8$: C, 55.21; H, 5.56. Found: C, 54.99; H, 5.52.

Methyl 3,5-Bis(4-methoxycarbonylbutoxy)-4-methylbenzoate (5b). This compound was prepared from **4** (3.82 g) in a manner similar to that for **5c**: yield 91% (7.85 g); ^{1}H NMR ($CDCl_3$) δ 1.83 (m, 8H, CH_2), 2.11 (s, 3H, CH_3), 2.39 (t, $J = 7.0$ Hz, 4H, CH_2), 3.66 (s, 6H, CO_2Me), 3.88 (s, 3H, CO_2Me), 4.00 (t, $J = 5.5$ Hz, 4H, CH_2), 7.15 (s, 2H, phenyl-H). Anal. Calcd for $C_{21}H_{30}O_8$: C, 61.45; H, 7.37. Found: C, 61.26; H, 7.33.

Methyl 3,5-Bis(10-methoxycarbonyldecyloxy)-4-methylbenzoate (5c). A mixture of **4** (3.58 g, 21.2 mmol), methyl 11-bromoundecanoate (14.2 g, 50.8 mmol), and K_2CO_3 (15.4 g) in DMF (55 mL) was stirred at 40 °C for 24 h under N_2. After AcOEt (300 mL) was added, the organic layer was washed with saturated aqueous NaCl (50 mL × 3) and dried over $MgSO_4$. Evaporation of the solvent and washing with hexane (200 mL) afforded a white solid of **5c** (11.3 g, 95%): ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 20H, CH_2), 1.45 (quintet, $J = 7.5$ Hz, 4H, CH_2), 1.60 (quintet, $J = 7.0$ Hz, 4H, CH_2), 1.78 (quintet, $J = 7.1$ Hz, 4H, CH_2), 2.12 (s, 3H, CH_3), 2.28 (t, $J = 7.5$ Hz, 4H, CH_2), 3.65 (s, 6H, CO_2Me), 3.88 (s, 3H, CO_2Me), 3.98 (t, $J = 6.5$ Hz, 4H, CH_2), 7.16 (s, 2H, phenyl-H); HRMS (FAB) calcd for $C_{33}H_{54}O_8$ (M^+) 578.3818, found 578.3809. Anal. Calcd for $C_{33}H_{54}O_8$: C, 68.48; H, 9.40. Found: C, 68.36; H, 9.60.

Methyl 4-(Bromomethyl)-3,5-bis(methoxycarbonylmethoxy)benzoate (6a). A solution of **5a** (2.0 g, 6.13 mmol) in CCl_4 (30 mL) and benzene (15 mL) was irradiated with a 500-W lamp while Br_2 (0.99 g, 6.2 mmol) in CCl_4 (10 mL) was added dropwise over 30 min. The same workup described for **6c** gave **6a**: yield 88% (2.19 g); ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 6H, CO_2Me), 3.88 (s, 3H, CO_2Me), 4.75 (s, 2H, CH_2Br), 4.78 (s, 4H, CH_2), 7.12 (s, 2H, phenyl-H). Anal. Calcd for $C_{15}H_{17}BrO_8$: C, 44.46; H, 4.23. Found: C, 44.65; H, 4.13.

Methyl 4-(Bromomethyl)-3,5-bis(4-methoxycarbonylbutoxy)benzoate (6b). This compound was prepared from **5b** (2.0 g) in a manner similar to that for **6c**: yield 79% (1.88 g); ^{1}H NMR ($CDCl_3$) δ 1.87 (m, 8H, CH_2), 2.41 (t, $J = 7.0$ Hz, 4H, CH_2), 3.66 (s, 6H, CO_2Me), 3.89 (s, 3H, CO_2Me), 4.08 (t, $J = 5.5$ Hz, 4H, CH_2), 4.62 (s, 2H, CH_2-Br), 7.15 (s, 2H, phenyl-H); HRMS (FAB) calcd for $C_{21}H_{29}BrO_8$ (M^+) 488.1045, found 488.1061 Anal. Calcd for $C_{21}H_{29}BrO_8$: C, 51.54; H, 5.97. Found: C, 51.02; H, 6.01.

Methyl 4-(Bromomethyl)-3,5-bis(10-methoxycarbonyldecyloxy)-benzoate (6c). A solution of **5c** (3.96 g, 6.84 mmol) in CCl_4 (40 mL) was irradiated with a 500-W lamp while Br_2 (1.1 g, 6.9 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 (100 mL) was added. The organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL × 2) and saturated aqueous NaCl (50 mL × 2) and dried over $MgSO_4$. Evaporation of the solvent and recrystallization from ether afforded a white solid of **6c** (4.28 g, 95%): ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 20H, CH_2), 1.49 (quintet, $J = 7.5$ Hz, 4H, CH_2), 1.60 (quintet, $J = 7.5$ Hz, 4H, CH_2), 1.82 (quintet, $J = 7.5$ Hz, 4H, CH_2), 2.28 (t, $J = 7.5$ Hz, 4H, CH_2), 3.64 (s, 6H, CO_2Me), 3.89 (s, 3H, CO_2Me), 4.05 (t, $J = 6.5$ Hz, 4H, CH_2), 4.63 (s, 2H, CH_2Br), 7.15 (s, 2H, phenyl-H); HRMS (FAB) calcd for $C_{33}H_{54}BrO_8$ (MH^+) 657.3002, found 657.2998. Anal. Calcd for $C_{33}H_{53}BrO_8$: C, 60.27; H, 8.12. Found: C, 60.09; H, 7.88.

Methyl 4-Formyl-3,5-bis(methoxycarbonylmethoxy)benzoate (7a). A solution of powdered **6a** (2.0 g, 4.93 mmol) in DMSO (25 mL) and solid $NaHCO_3$ (3.0 g) was heated at 70 °C under N_2 with vigorous stirring for 30 min. The reaction mixture was then immediately cooled in an ice bath, poured into saturated aqueous NaCl (100 mL), and extracted with AcOEt (100 mL × 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent and purification by flash column chromatography (SiO_2, AcOEt/hexane = 1/1) afforded a white solid of **7a** (1.43 g, 85%): ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 6H, CO_2Me), 3.90 (s, 3H, CO_2Me), 4.77 (s, 4H, CH_2), 7.14 (s, 2H, phenyl-

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(21) The least-squares fitting was performed by the computer program SPANA, kindly provided by Prof. Y. Kuroda, Department of Polymer Science, Kyoto Institute of Technology, Matsugasaki, Kyoto 606-8585, Japan. e-mail: ykuroda@ipc.kit.ac.jp.

H), 10.57 (s, 1H, CHO). Anal. Calcd for $C_{15}H_{16}O_9$: C, 52.95; H, 4.74. Found: C, 52.66; H, 4.82.

Methyl 4-Formyl-3,5-bis(4-methoxycarbonylbutoxy)benzoate (7b). A solution of powdered **6b** (1.35 g, 2.76 mmol) in DMSO (30 mL) and $NaHCO_3$ (3.9 g) was heated at 90 °C under N_2 with vigorous stirring for 10 min. The same workup described for **7c** gave **7b** in 75% yield (0.88 g): ^{1}H NMR ($CDCl_3$) δ 1.85 (m, 8H, CH_2), 2.39 (t, J = 7.0 Hz, 4H, CH_2), 3.66 (s, 6H, CO_2Me), 3.92 (s, 3H, CO_2Me), 4.09 (t, J = 5.8 Hz, 4H, CH_2), 7.18 (s, 2H, phenyl-H), 10.50 (s, 1H, CHO); HRMS (FAB) calcd for $C_{21}H_{29}O_9$ (MH^+) 425.1829, found 425.1812. Anal. Calcd for $C_{21}H_{28}O_9$: C, 59.43; H, 6.65. Found: C, 59.17; H, 6.54.

Methyl 4-Formyl-3,5-bis(10-methoxycarbonyldecyloxy)benzoate (7c). A solution of powdered **6c** (3.0 g, 4.6 mmol) in DMSO (60 mL) and $NaHCO_3$ (6.0 g) was heated at 120 °C under N_2 with vigorous stirring for 10 min. The reaction mixture was then immediately cooled in an ice bath, poured into saturated aqueous NaCl (100 mL), and extracted with AcOEt (100 mL × 2). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent and recrystallization from benzene/hexane afforded a white solid of **7c** (2.26 g, 84%): ^{1}H NMR ($CDCl_3$) δ 1.27 (m, 20H, CH_2), 1.45 (quintet, J = 7.4 Hz, 4H, CH_2), 1.60 (quintet, J = 7.5 Hz, 4H, CH_2), 1.81 (quintet, J = 7.0 Hz, 4H, CH_2), 2.28 (t, J = 7.5 Hz, 4H, CH_2), 3.65 (s, 6H, CO_2Me), 3.92 (s, 3H, CO_2Me), 4.06 (t, J = 6.8 Hz, 4H, CH_2), 7.18 (s, 2H, phenyl-H), 10.51 (s, 1H, CHO); HRMS (FAB) (MH^+) calcd for $C_{33}H_{53}O_9$ 593.3689, found 593.3702. Anal. Calcd for $C_{33}H_{52}O_9$: C, 66.87; H, 8.84. Found: C, 66.21; H, 8.89.

5,10,15,20-Tetrakis(4-methoxycarbonyl-3,5-bis(methoxycarbonylmethoxy)phenyl)porphyrin (8a). This compound was prepared from **7a** (680 mg, 2 mmol) in a manner similar to that described for **8c**: yield 15% (120 mg); ^{1}H NMR ($CDCl_3$, 500 MHz) δ −2.62 (s, 2H, NH), 3.42 (s, 24H, CO_2Me), 4.05 (s, 12H, CO_2Me), 4.34 (s, 16H, CH_2), 7.57 (s, 8H, phenyl-H), 8.78 (s, 8H, β-pyrrole); UV−vis (CH_2Cl_2) λ_{max} (log ϵ) 419 (5.66), 512 (4.43), 544 (3.83), 587 (4.00). Anal. Calcd for $C_{76}H_{70}N_4O_{32}$: C, 58.84; H, 4.55; N, 3.61. Found: C, 58.15; H, 4.52; N, 3.29.

5,10,15,20-Tetrakis(4-methoxycarbonyl-3,5-bis(4-methoxycarbonylbutoxy)phenyl)porphyrin (8b). This compound was prepared from **7b** (2.122 g, 5 mmol) in a manner similar to that described for **8c**: yield 22% (527 mg); ^{1}H NMR ($CDCl_3$) δ −2.62 (s, 2H, NH), 0.83 (quintet, J = 7.5 Hz, 16H, CH_2), 0.98 (quintet, J = 7.5 Hz, 16H, CH_2), 1.51 (t, J = 7.0 Hz, 16H, CH_2), 3.06 (s, 24H, CO_2Me), 3.88 (t, J = 6.5 Hz, 16H, CH_2), 4.07 (s, 12H, CO_2Me), 7.63 (s, 8H, phenyl-H), 8.58 (s, 8H, β−pyrrole); UV−vis (CH_2Cl_2) λ_{max} (log ϵ) 422 (5.62), 515 (4.38), 548 (3.95), 590 (4.00); HRMS (FAB) calcd for $C_{100}H_{118}N_4O_{32}$ (M^+) 1886.7728, found 1886.7751. Anal. Calcd for $C_{100}H_{118}N_4O_{32}$: C, 63.62; H, 6.30; N, 2.97. Found: C, 63.37; H, 6.32; N, 2.92.

5,10,15,20-Tetrakis(4-methoxycarbonyl-3,5-bis(10-methoxycarbonyldecyloxy)phenyl)porphyrin (8c). Aldehyde **7c** (1.78 g, 3 mmol) and pyrrole (208 μL, 3 mmol) were dissolved in CH_2Cl_2 (300 mL) under N_2 and then BF_3·OEt_2 (125 μL, 0.99 mmol) was added. After the reaction mixture was stirred at room temperature for 100 min, 2,3-dichloro-5,6-dicyanobenzoquinone (510 mg, 2.2 mmol) was added and the mixture was refluxed for 2 h. The solution was then neutralized by addition of triethylamine (138 μL, 1 mmol) and evaporated. The mixture was separated by column chromatography (SiO_2, $CHCl_3$/AcOEt = 100/1−10/1) and crude product was washed with methanol thoroughly to afford a purple solid of **8c** (296 mg, yield 16%): ^{1}H NMR ($CDCl_3$) δ −2.64 (s, 2H, NH), 0.61 (quintet, J = 7.5 Hz, 16H, CH_2), 0.76 (m, 32H, CH_2), 0.88 (quintet, J = 7.5 Hz, 16H, CH_2), 0.94 (quintet, J = 7.5 Hz, 16H, CH_2), 0.97 (quintet, J = 7.5 Hz, 16H, CH_2), 1.06 (quintet, J = 7.5 Hz, 16H, CH_2), 1.45 (quintet, J = 7.5 Hz, 16H, CH_2), 2.17 (t, J = 7.5 Hz, 16H, CH_2), 3.60 (s, 24H, CO_2Me), 3.82 (t, J = 6.5 Hz, 16H, CH_2), 4.07 (s, 12H, CO_2Me), 7.62 (s, 8H, phenyl-H), 8.57 (s, 8H, β-pyrrole); UV−vis (CH_2Cl_2) λ_{max} (log ϵ) 422 (5.61), 515 (4.36), 549 (3.93), 584 (4.01); HRMS (FAB) calcd for $C_{148}H_{214}N_4O_{32}$ (M^+) 2559.5239, found 2559.6562. Anal. Calcd for $C_{148}H_{214}N_4O_{32}$: C, 69.40; H, 8.42; N, 2.19. Found: C, 69.28; H, 8.32; N, 2.15.

[5,10,15,20-Tetrakis(4-methoxycarbonyl-3,5-bis(methoxycarbonylmethoxy)phenyl)porphyrinato]zinc(II) (9a). This compound was prepared from **8a** (100 mg, 65 μmol) in a manner similar to that described for **9c**: yield 84% (87 mg); ^{1}H NMR ($CDCl_3$) δ 3.38 (s, 24H, CO_2Me), 4.05 (s, 12H, CO_2Me), 4.33 (s, 16H, CH_2), 7.57 (s, 8H, phenyl-H), 8.84 (s, 8H, β-pyrrole); UV−vis (CH_2Cl_2) λ_{max} (log ϵ) 423 (5.71), 555 (4.29), 592 (3.51); HRMS (FAB) calcd for $C_{76}H_{68}N_4O_{32}Zn$ (M^+) 1612.3106, found 1612.3073.

[5,10,15,20-Tetrakis(4-methoxycarbonyl-3,5-bis(4-methoxycarbonylbutoxy)phenyl)porphyrinato]zinc(II) (9b). This compound was prepared from **8b** (91 mg, 48 μmol) in a manner similar to that described for **9c**: yield 83% (78 mg); ^{1}H NMR ($CDCl_3$) δ 0.64 (quintet, J = 7.5 Hz, 16H, CH_2), 0.92 (quintet, J = 7.5 Hz, 16H, CH_2), 1.01 (t, J = 7.0 Hz, 16H, CH_2), 2.61 (s, 24H, CO_2Me), 3.88 (t, J = 6.5 Hz, 16H, CH_2), 4.08 (s, 12H, CO_2Me), 7.64 (s, 8H, phenyl-H), 8.66 (s, 8H, β-pyrrole); UV−vis (CH_2Cl_2) λ_{max} (log ϵ) 425 (5.64), 552 (4.32), 592 (3.23); HRMS (FAB) calcd for $C_{100}H_{116}N_4O_{32}Zn$ (M^+) 1948.6862, found 1948.6614.

[5,10,15,20-Tetrakis(4-methoxycarbonyl-3,5-bis(10-methoxycarbonyldecyloxy)phenyl)porphyrinato]zinc(II) (9c). A solution of **8c** (97 mg, 38 μmol) and $Zn(OAc)_2$-saturated methanol (15 mL) in $CHCl_3$ (110 mL) was refluxed for 3 h. After cooling, the solution was washed with saturated aqueous $NaHCO_3$ (100 mL × 2) and saturated aqueous NaCl (100 mL × 2) and dried over Na_2SO_4. Evaporation of the solvent and purification by flash column chromatography (SiO_2, $CHCl_3$/AcOEt = 1/1) and recrystallization from CH_2Cl_2/hexane afforded a pink solid of **9c** (80 mg, 80%): ^{1}H NMR ($CDCl_3$) δ 0.55 (quintet, J = 7.5 Hz, 16H, CH_2), 0.71 (m, 32H, CH_2), 0.82 (quintet, J = 7.5 Hz, 16H, CH_2), 0.93 (m, 32H, CH_2), 1.03 (quintet, J = 7.5 Hz, 16H, CH_2), 1.43 (quintet, J = 7.5 Hz, 16H, CH_2), 2.17 (t, J = 7.5 Hz, 16H, CH_2), 3.60 (s, 24H, CO_2Me), 3.82 (t, J = 6.5 Hz, 16H, CH_2), 4.07 (s, 12H, CO_2Me), 7.63 (s, 8H, phenyl-H), 8.66 (s, 8H, β-pyrrole); UV−vis (CH_2Cl_2) λ_{max} (log ϵ) 424 (5.63), 551 (4.26), 592 (3.45); HRMS (FAB) calcd for $C_{148}H_{212}N_4O_{32}Zn$ (M^+) 2621.4374, found 2621.4663.

[5,10,15,20-Tetrakis(4-carboxy-3,5-bis(carboxymethoxy)phenyl)porphyrinato]zinc(II) Potassium Salt (1). This compound was prepared from **9a** (87 mg, 54 μmol) in a manner similar to that described for **3**: yield 89% (92 mg); ^{1}H NMR (deuterated Borax buffer, pD 8.6, I = 0.1 M) δ 4.27 (s, 16H, CH_2), 7.53 (s, 8H, phenyl-H), 9.07 (s, 8H, β-pyrrole); UV−vis (Borax buffer, pH 9.0, I = 0.1 M) λ_{max} (log ϵ) 423 (5.41), 555 (3.98), 592 (3.18).

[5,10,15,20-Tetrakis(4-carboxy-3,5-bis(4-carboxybutoxy)phenyl)porphyrinato]zinc(II) Potassium Salt (2). This compound was prepared from **9b** (51 mg, 26 μmol) in a manner similar to that described for **3**: yield 84% (49 mg); ^{1}H NMR (deuterated Borax buffer, pD 8.6, I = 0.1 M) δ 0.89 (quintet, J = 7.5 Hz, 16H, CH_2), 1.19 (quintet, J = 7.5 Hz, 16H, CH_2), 1.66 (t, J = 7.5 Hz, 16H, CH_2), 3.99 (t, J = 7.0 Hz, 16H, CH_2), 7.76 (s, 8H, phenyl-H), 8.91 (s, 8H, β-pyrrole); UV−vis (Borax buffer, pH 9.0, I = 0.1 M) λ_{max} (log ϵ) 426 (5.42), 557 (4.03), 596 (3.38).

[5,10,15,20-Tetrakis(4-carboxy-3,5-bis(10-carboxydecyloxy)phenyl)porphyrinato]zinc(II) Potassium Salt (3). Zinc porphyrin **9c** (48 mg, 19 μmol) was dissolved in a solution prepared by mixing THF (36 mL), methanol (15 mL), and 0.5 M KOH (16 mL). After being stirred at room temperature for 24 h, the solution was concentrated and passed through Sephadex G-15 followed by lyophilization to afford **3** (43 mg, yield 79%): ^{1}H NMR (deuterated Borax buffer, pD 8.6, I = 0.1 M) δ 0.38 (quintet, J = 7.5 Hz, 16H, CH_2), 0.51 (quintet, J = 7.5 Hz, 16H, CH_2), 0.62 (quintet, J = 7.5 Hz, 16H, CH_2), 0.71 (quintet, J = 7.5 Hz, 16H, CH_2), 0.86 (quintet, J = 7.5 Hz, 16H, CH_2), 1.00 (quintet, J = 7.5 Hz, 16H, CH_2), 1.08 (quintet, J = 7.5 Hz, 16H, CH_2), 1.40 (quintet, J = 7.5 Hz, 16H, CH_2), 2.10 (t, J = 7.5 Hz, 16H, CH_2), 3.93 (t, J = 7.0 Hz, 16H, CH_2), 7.76 (s, 8H, phenyl-H), 8.84 (s, 8H, β-pyrrole); UV−vis (Borax buffer, pH 9.0, I = 0.1 M) λ_{max} (log ϵ) 426 (5.37), 555 (3.98), 593 (2.75).

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