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Thermodynamics of Hydrophobic Interactions: Entropic Recognition of a Hydrophobic Moiety by Poly(Ethylene Oxide)–Zinc Porphyrin Conjugates

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Abstract: The recognition of 4-alkylpyridines by water-soluble poly(ethylene oxide)–zinc porphyrin conjugates was studied with a focus on the thermodynamic parameters of binding. Microcalorimetric studies indicated that binding of the alkyl group of the guest in water is driven by the entropic term ($\delta\Delta H^0 = \Delta H^0$(4-pentylpyridine)$-$ ΔH^0(4-methylpyridine)$= +1.7$ kJ mol^{-1}, $\delta T\Delta S^0 = T\Delta S^0$(4-pentylpyridine)$-$ $T\Delta S^0$(4-methylpyridine)$= +11.8$ kJ mol^{-1} at 298 K), thus showing the significance of water reorganization during host–guest interaction. The enthalpy–entropy compensation temperature of binding of 4-alkylpyridines was as low as 38 K; only below this temperature could the enthalpic term be a driving force. The binding affinity was modulated by the addition of cations and by varying the degree of polymerization of poly(ethylene oxide), which suggests that guest binding is coupled with polymer conformation.

Keywords: hydrophobic effect · polymers · porphyrinoids · receptors · thermodynamics

Introduction

The binding of various organic ligands to globular proteins is driven by a number of intermolecular forces, such as hydrogen bonding, electrostatic interactions, van der Waals interactions, and desolvation-induced entropic gain. Hydrophobic interactions[1,2] are a combination of van der Waals interactions (attractive forces between hydrophobic moieties are stronger than those between a hydrophobic moiety and water molecules) and desolvation-induced entropic gain (expelling a number of water molecules by association of two larger molecules) and are one of the important driving forces of binding in aqueous solution. In proteins that bind hydrophobic ligands such as cholesterols[3] and fatty acids,[4] an effective hydrophobic environment in water is constructed by using amino acids with a hydrophobic side chain, such as valine, leucine, methionine, and phenylalanine, and the appropriate secondary and tertiary structures. To construct a hydrophobic binding site in water, we need to prepare a large receptor to encompass the solvent-accessible guest surface effectively.[5] Besides the important roles of hydrophobic interactions in binding, water affects the reactivities of a number of chemical reactions and often alters a reaction pathway completely. Therefore, sequestration of a molecule from water in aqueous media is one of the major challenges in water-based solution chemistry.[6]

We previously prepared a zinc porphyrin with eight ω-carboxyalkyl chains as solubilizing auxiliary groups and reported the thermodynamic binding parameters of various guests.[7] The electrostatic repulsion between the carboxy groups considerably hinders the binding of hydrophobic guests. To avoid electrostatic repulsion between charged groups and to prepare a receptor with a better hydrophobic binding site, we employed neutral hydrophilic groups, that is, poly(ethylene oxide) (PEO) groups,[8] in place of the carboxylates: we reported the synthesis and binding properties of a zinc porphyrin that has four long alkyl chains with PEO terminals.[9] We found that the PEO–zinc porphyrin conjugate binds 4-alkylpyridines more tightly than the anionic zinc porphyrin receptor. Herein, we prepared new water-soluble zinc porphyrin receptors that have eight alkyl chains with PEO terminals, and the binding of 4-alkylpyridines and *N*-alkylimidazoles was investigated, with the aim of evaluating the enthalpic and entropic contributions to hydrophobic interactions in host–guest systems.

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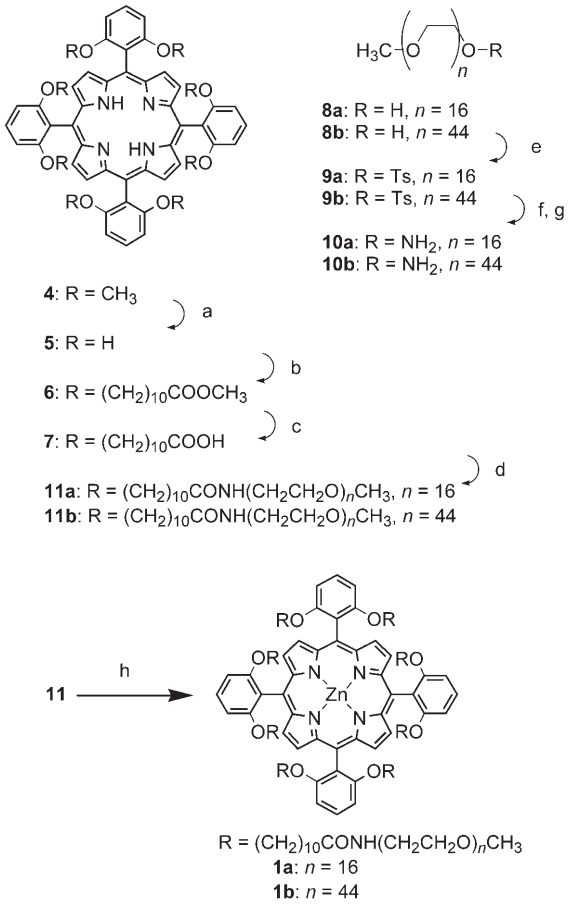
Results and Discussion

Receptor Preparation

PEO–zinc porphyrin conjugate **1a** was prepared as shown in Scheme 1. PEO **10a** with an amine group at the terminus was prepared from poly(ethylene oxide) monomethyl ether of average molecular weight 750 (**8a**). Coupling of **10a** with porphyrin octacarboxylic acid **7** gave **11a**. Compound **11a** was purified by silica-gel column chromatography and then gel-permeation chromatography on a Sephadex LH-20 column. The ^{1}H NMR spectrum of **11a** in $CDCl_3$ showed characteristic resonances at −2.59 (inner NH protons) and 8.62 ppm (singlet, β-pyrrole protons). The amide protons appeared at 6.39 ppm, which was assigned by the COSY cross-peak with the PEO methylene resonance at 3.4 ppm. Compound **11a** is soluble in water and most organic solvents. The UV/Vis spectra of **11a** in water and $CHCl_3$ showed the Soret band at 421 and 423 nm, respectively. The peak width of the Soret band in water is similar to that in $CHCl_3$, which implies that no aggregation of the porphyrin moiety of **11a** occurs in water. Zinc complex **1a** was prepared by reaction of **11a** with zinc acetate. PEO–zinc porphyrin conjugate **1b** was similarly prepared by using PEO with an average molecular weight of 2000 (**8b**). pH titration of an aqueous solution of **11b** (0.1 M $NaClO_4$) with $HClO_4$ gave a pK_a value of 2.9 for the protonation of the inner imine nitrogen atom. The structures of **1a** and **1b** are shown in Scheme 2.

Binding Equilibria in Water

UV/Vis titration of a solution of **1a** in 0.1 M aqueous potassium phosphate buffer at pH 7.0 with 4-ethylpyridine at 25 °C caused a decrease in the absorbance at 423 nm and an increase in the absorbance at 436 nm with isosbestic points (Figure 1). The binding constants for the pyridine and imidazole derivatives of **1a** and **1b** were determined by nonlinear



Scheme 1. Synthesis of PEO-appended zinc porphyrins **1a** and **1b**. Reagents: a) pyridinium hydrochloride; b) $Br(CH_2)_{10}COOMe$; c) KOH; d) **10a** or **10b**, HOBt, EDC·HCl; e) TsCl, NaOH; f) NaN_3; g) Ph_3P; h) $Zn(OAc)_2$. EDC = *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, HOBt = *N*-hydroxybenzotriazole.

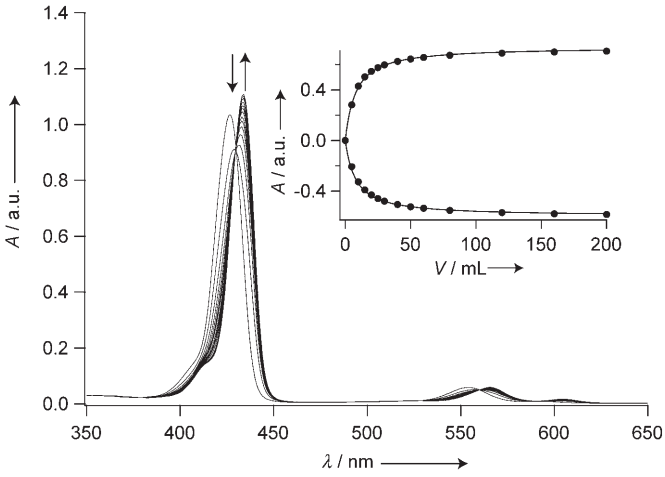


Figure 1. UV/Vis titration of **1a** with 4-ethylpyridine in potassium phosphate buffer at pH 7 and 298 K. 4-Ethylpyridine (7.65 mM, 0→200 μL) was added to of **1a** (3.13 μM, 3 mL), with the decrease in absorbance of **1a** due to dilution corrected. Inset: Plot of the absorbance at 423 (decrease) and 436 nm (increase) against the volume of 4-ethylpyridine added.

Abstract in Japanese:

ポリエチレンオキシドを結合させた亜鉛ポルフィリンによる 4–アルキルピリジンの分子認識を熱力学の立場から検討した。水中における結合平衡の熱量測定の結果、4–メチルピリジンと比べて 4–ペンチルピリジンのエンタルピー変化は 1.7 kJ mol^{-1} 不利、エントロピー変化 ($T\Delta S^o$) は 11.8 kJ mol^{-1} 有利であり、アルキル基の認識はエントロピーが有利となるために起こること、すなわち、脱水和などの水の構造変化が駆動力となっていることがわかった。アルキル基の認識のエンタルピー－エントロピー補償温度は 38 K と非常に低く、この温度より低温でのみエンタルピー項が駆動力となりうることを示した。溶媒中に共存するカチオンの種類やポリエチレンオキシドの重合度によっても結合定数は変化し、高分子のコンフォーメーションとゲストの結合が相関していることが示唆された。

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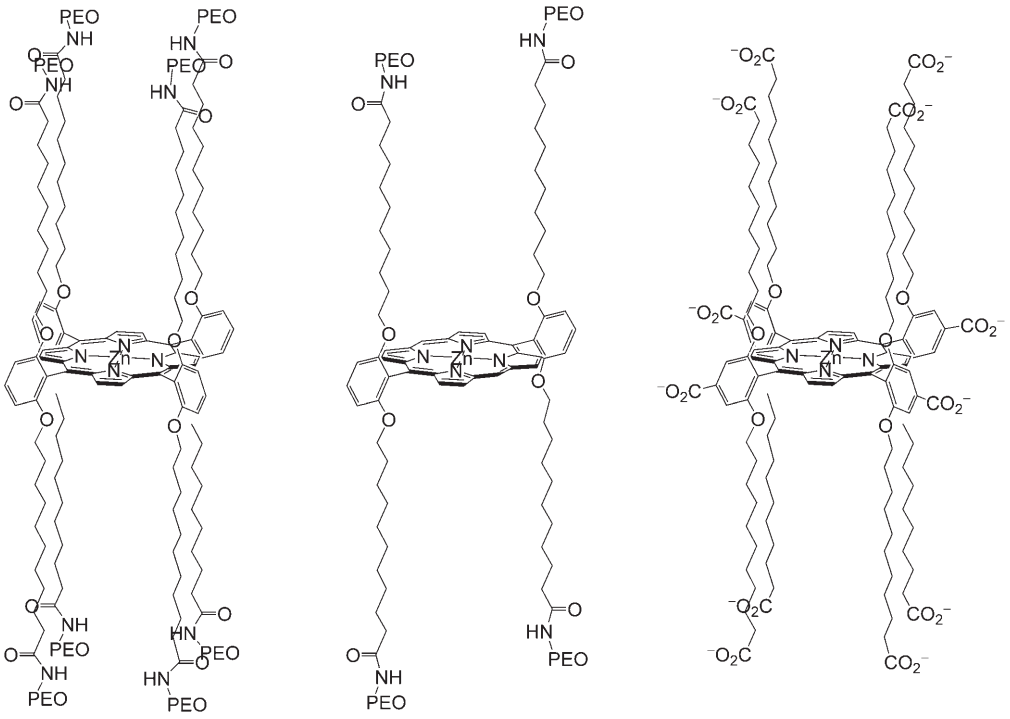

Scheme 2. Structures of the receptors.

curve fitting to the absorbance changes at two different wavelengths and are listed in Table 1.

Table 1. Binding constants and free-energy changes for the complexation of pyridine and imidazole derivatives to **1a** and **1b** in potassium phosphate buffer (0.1 M) at pH 7 and 25 °C.

Host	Guest	K[a] [M^{-1}]	$-\Delta G^{0}$[b] [kJ mol^{-1}]
1a	4-methylpyridine	19000	24.4
1a	4-ethylpyridine	54200	27.0
1a	4-propylpyridine	148000	29.5
1a	4-pentylpyridine	1250000	34.8
1b	pyridine	12000	23.3
1b	4-methylpyridine	38400	26.2
1b	4-ethylpyridine	103000	28.6
1b	4-propylpyridine	302000	31.3
1b	4-pentylpyridine	1210000	34.7
1b	4-*tert*-butylpyridine	300000	31.2
1b	4-benzylpyridine	610000	33.0
1b	*N*-methylimidazole	234	13.5
1b	*N*-ethylimidazole	303	14.1

[a] Estimated errors = ±5%. [b] $\Delta G^{0} = -RT\ln K$, $T = 298$ K.

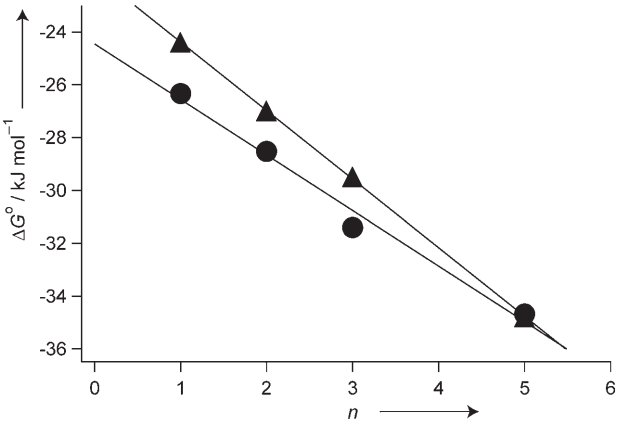

Figure 2. Plot of the free energy of binding of the 4-alkylpyridines to **1a** (▲) and **1b** (●) in potassium phosphate buffer at pH 7 and 298 K against the number of carbon atoms (n) in the guest alkyl group of the 4-alkylpyridines.

The characteristic feature of the binding constants is that the free energy of binding, $-\Delta G^{0}$, increased linearly as the alkyl group in the 4-position of pyridine became longer.[10] Figure 2 shows the plot of the free energy of binding against n, in which n is the number of carbon atoms in the alkyl group of the 4-alkylpyridines. From the slope of the plotted line, we estimated the free energy of binding per CH_2 unit. The value of $-d\Delta G^{0}/dn$ was 2.6 and 2.2 kJ mol^{-1} for **1a** and **1b**, respectively. Figure 2 shows that **1b** binds the pyridyl nitrogen atom more tightly than **1a** (more negative vertical intercept), whereas **1a** binds the alkyl group of the guest more tightly than **1b** (larger slope). The molecular weight of the PEO fragments clearly affects the hydrophobic recognition energy of the receptor: the receptor with shorter PEO chains showed a better recognition of the alkyl group of the 4-alkylpyridines. The shorter PEO chains have less steric

hindrance, or less exclusion volume, than the longer PEO chains, and **1a** can accommodate the alkyl chain of the guest more comfortably.

For the binding of the pyridyl nitrogen atom, the peak maxima of the Soret band of **1a** and **1b** in the UV/Vis spectra in CH_2Cl_2 were at 425 nm, whereas the peak maxima of **1a** and **1b** in water were at 428 and 425 nm, respectively. It is well-known[11] that coordination of an oxygen ligand to zinc porphyrin occurs with a red shift of the Soret band. Therefore, receptor **1a** with shorter PEO chains has water as an axial ligand of zinc. This explains the weaker binding of **1a** than **1b** toward pyridines.

How the balance between the hydrophilic and hydrophobic moieties of a receptor molecule impacts the binding properties is not well-characterized, and the present results suggest that a large hydrophilic moiety will have a negative effect on hydrophobic interaction between the receptor and guest. The values of $-d\Delta G^0/dn$ for **1a** and **1b** are both smaller than that for receptor **2** ($-d\Delta G^0/dn = 3.4\ kJ\,mol^{-1}$). Comparison of the hydrophobic binding between **1a**/**1b** and **2** will be discussed later on the basis of enthalpy and entropy changes of binding.

Interestingly the binding constants determined in sodium phosphate buffer were different from those determined in potassium phosphate buffer (Table 2). The binding constants

Table 2. Binding constants of pyridines to **1b** in sodium and potassium phosphate buffer (pH 7, 0.1 M) at 25 °C.

Pyridine	Sodium phosphate	Potassium phosphate
4-Methylpyridine	49500	38400
4-Ethylpyridine	197000	103000
4-Propylpyridine	650000	320000
4-*tert*-Butylpyridine	597000	300000
4-Benzylpyridine	773000	610000

for the former were approximately twice those for the latter, except for 4-methylpyridine and 4-benzylpyridine. Yanagida et al. reported that PEO binds alkali-metal ions, and the selectivity is similar to that of [18]crown-6.[12] Therefore, potassium ions are bound to the PEO chains more tightly, thus inducing conformational changes to alter binding affinity indirectly. Binding experiments except for those shown in Table 2 were carried out in potassium phosphate buffer to allow comparison of the data with those previously reported for receptor **2**.

Relative to pyridine derivatives, imidazoles showed much looser binding to receptor **1b**. This may be attributed to the hydrophilic nature of imidazoles. Recognition of the alkyl group of the imidazole guest was also ineffective as seen in the small K(EtImd)/K(MeImd) ratio (Imd = imidazole) and the $\delta\Delta G^0$ value of $-0.6\ kJ\,mol^{-1}$. Similar behavior was observed in the binding of 4-(2-hydroxyethyl)pyridine to receptor **2**, which was hindered by the hydroxy group.[9]

Binding Equilibria in Dichloromethane

The binding constants of pyridine derivatives of **1a** and **1b** in CH_2Cl_2 are listed in Table 3 along with those for receptor **2**. First, the binding affinity remained almost the same as

Table 3. Comparison of binding constants K (M^{-1}) in CH_2Cl_2 at 25 °C.

Pyridine	**1a**	**1b**	**2**[b]
Pyridine	–[a]	1210	4190
4-Methylpyridine	670	1400	9080
4-Ethylpyridine	790	1430	11500
4-Propylpyridine	830	1600	10400

[a] Not determined. [b] See reference [9].

the alkyl chains in guest became longer. Hydrophobic interactions would not work for binding in an organic solvent; the recognition of the alkyl chain was ineffective in dichloromethane. Interestingly, the binding constants observed for receptors **1a**/**1b** were consistently smaller than those observed for **2**. The binding affinity increased in the order **1a** < **1b** < **2**. The lower affinity of receptors **1a**/**1b** can be attributed to steric repulsion due to their alkyl chains or exclusion volume effects of their poly(ethylene oxide) groups.

It may be argued that coordination of the PEO ether oxygen atoms to zinc is an important factor in binding thermodynamics, as several crystal structures of coordination complexes of ethers and zinc porphyrins have been reported.[13] The average number of PEO oxygen atoms are 128, 352, and 176 for **1a**, **1b**, and **2**, respectively. If only the coordination of the PEO oxygen atom dictates the binding thermodynamics, we would expect the binding affinity to increase in the order **1b** < **2** < **1a**. Therefore, PEO oxygen coordination may occur, but it is not the major factor determining the binding affinity.

Enthalpy and Entropy Changes of Binding in Water

Enthalpy and entropy changes of binding were determined by microcalorimetric titration of a solution of **1a** in potassium phosphate buffer at pH 7.0 with 4-alkylpyridines (Table 4). The titration curves fitted best to a 1:1 binding model. The binding constants determined from the microcalorimetric titration curves were 18700, 145000, and

Table 4. Enthalpy and entropy changes in binding in potassium phosphate buffer at pH 7.0.

Host	Guest	ΔH^0 [$kJ\,mol^{-1}$]	$T\Delta S^{0}$[a] [$kJ\,mol^{-1}$]	Method
1a	4-methylpyridine	-24.5 ± 1.2	-0.2 ± 1.4	MC[b]
1a	4-propylpyridine	-23.3 ± 0.5	6.2 ± 0.5	MC[b]
1a	4-pentylpyridine	-22.8 ± 0.2	11.6 ± 0.1	MC[b]
1b	4-methylpyridine	-22.3 ± 0.7	3.8 ± 0.6	van't Hoff
1b	4-propylpyridine	-25.6 ± 0.8	5.4 ± 0.8	van't Hoff
1b	4-pentylpyridine	-19.1 ± 1.1	15.5 ± 1.1	van't Hoff
1b	4-benzylpyridine	-18.5 ± 0.8	14.6 ± 0.8	van't Hoff
1b	*N*-methylimidazole	-6.6 ± 0.1	6.9 ± 0.1	van't Hoff
1b	*N*-ethylimidazole	-3.1 ± 0.4	11.1 ± 0.3	van't Hoff

[a] $T = 25$ °C. [b] Microcalorimetric titration.

$1\,050\,000\,\text{M}^{-1}$ for 4-methylpyridine, 4-propylpyridine, and 4-pentylpyridine, respectively, which are in fairly good agreement with those determined by UV/Vis titration (Table 1). Although the free-energy difference $\delta\Delta G^0 = \Delta G^0$(4-pentylpyridine)$-\Delta G^0$(4-methylpyridine) is $-10\,\text{kJ mol}^{-1}$, the enthalpy difference $\delta\Delta H^0 = \Delta H^0$(4-pentylpyridine)$-\Delta H^0$(4-methylpyridine) is positive and only $1.7\,\text{kJ mol}^{-1}$; $\delta T\Delta S^0 = T\Delta S^0$(4-pentylpyridine)$-T\Delta S^0$(4-methylpyridine)$=$ $11.8\,\text{kJ mol}^{-1}$ at 298 K. Therefore, the tighter binding of 4-pentylpyridine relative to 4-methylpyridine can be attributed to the entropic term. Liu et al.[14] reported that chiral recognition of camphor by modified cyclodextrins is driven by entropic change. The values of $T\Delta S^0$ are plotted against ΔH^0 in Figure 3. The linear correlation shows that the $CH_2\cdots CH_2$

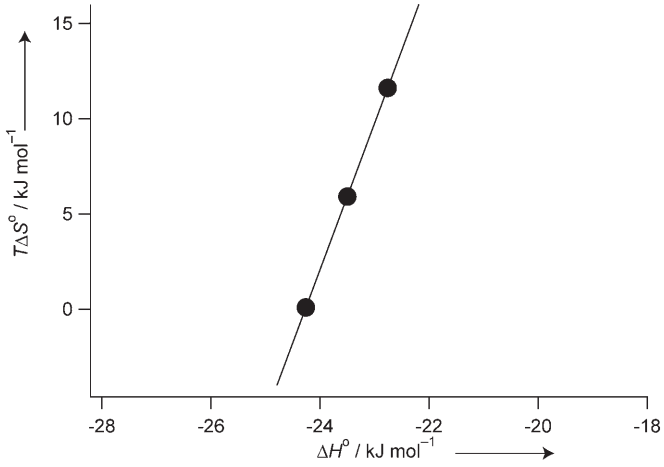

Figure 3. Plot of $T\Delta S^0$ against ΔH^0 for the binding of 4-methylpyridine, 4-propylpyridine, and 4-pentylpyridine to **1a** in potassium phosphate buffer at pH 7 and 298 K. ΔH^0 and ΔS^0 were determined by microcalorimetry.

hydrophobic interaction is characterized by $\delta\Delta H^0 = 0.4$ and $T\delta\Delta S^0 = 3.0$ kJ per CH_2 unit at 298 K. The linear correlation also shows that there is an enthalpy–entropy compensation for the recognition of the alkyl groups by **1a**. The compensation plot yields a slope of 7.7 and an intercept of $186\,\text{kJ mol}^{-1}$. The slope corresponds to the compensation temperature of 38 K: an extremely low compensation temperature was obtained. Only below this temperature could the enthalpic term be a driving force. Therefore, the entropic term is dominant at ambient temperature. The low compensation temperature implies that hydrophobic interactions consist of a number of weak elementary interactions.

The enthalpy and entropy changes of binding to cyclodextrins were analyzed by the compensation plot ($T\Delta S^0$ versus ΔH^0),[15,16,17] in which the slope and the vertical intercept are important parameters. According to Inoue et al.,[16] the slope (α) reflects the amount of conformational reorganization the host undergoes upon binding. The vertical intercept (β) is associated with the degree of desolvation upon binding. Both values of the slope and the intercept are quite large compared with those previously reported for the binding of DNA intercalators to gable-type porphyrins ($\alpha = 0.74$, $\beta = 32.2\,\text{kJ mol}^{-1}$)[18] as well for cyclodextrin–guest complexes ($\alpha = 0.9$, $\beta = 13.0\,\text{kJ mol}^{-1}$).[16a,19] Therefore, the present binding is associated with a considerable amount of conformational change and desolvation.

Enthalpy and entropy changes of hydrophobic interactions have been evaluated by using the phase transfer of alkanes and alcohols between water and organic solvents,[20] as well as the binding of alcohols and carboxylic acids to cyclodextrins.[1b,19] Abraham[20] reported that the increments per methylene group for the transfer of alkanes from hexane to water at 298 K were $\delta\Delta G^0 = 3.85$, $\delta\Delta H^0 = 2.76$, and $T\delta\Delta S^0 = -1.09\,\text{kJ mol}^{-1}$. These values indicate that hydration of alkanes is unfavorable both enthalpically and entropically, with a larger enthalpic contribution. On the basis of these data, we can deduce that hydrophobic interaction is driven by both the enthalpic term and the entropic term, the former being more important. Enthalpy and entropy changes of binding of alkanols and carboxylic acids to cyclodextrins were investigated,[17,19] and the increase in the alkyl-chain length of the guest was found to result in a negative enthalpy change and a negative entropy change. Increments per methylene group for the binding of alkanols to α-cyclodextrin in water at 298 K were $\delta\Delta G^0 = -3.0$, $\delta\Delta H^0 = -3.8$, and $T\delta\Delta S^0 = -0.8\,\text{kJ mol}^{-1}$. Thus, hydrophobic recognition of an alkyl group by cyclodextrin is enthalpically driven. Both of these studies demonstrate that the enthalpic term plays an important role in hydrophobic interactions. In contrast to these results, for the binding to **1a**, we showed that the increment per methylene group of the entropic term is positive and contributes favorably to binding, whereas that of the enthalpic term is positive and contributes unfavorably to binding. In the host–guest systems in water investigated so far, low-molecular-weight host molecules with a small number of degrees of conformational freedom were employed relative to the biological counterpart, protein. In such host–guest systems, van der Waals interactions may dominate the binding energetics and lead to the enthalpically driven binding. In our system as well as in binding by protein, the degree of conformational freedom is much larger and the induced fit to the hydrophobic surface of the guest occurs more extensively. More extensive desolvation of both host and guest is expected to occur, and this would explain the large positive entropic gain.

The enthalpy and entropy changes of binding to **1b** were determined by van't Hoff analysis of the binding constants determined in the temperature range 15–45 °C. A representative example of the van't Hoff plot is shown in Figure 4. The binding constants at each temperature were determined three to six times to check reproducibility, and the standard deviations were also estimated. The values of the enthalpy and entropy changes are listed in Table 4. The binding of alkyl pyridines to receptor **1b** was characterized by a negative enthalpy change and a positive entropy change. The tighter binding of 4-pentylpyridine relative to 4-methylpyridine was ascribed to the favorable entropic term, and this trend is similar to the case of binding to **1a**. The values of

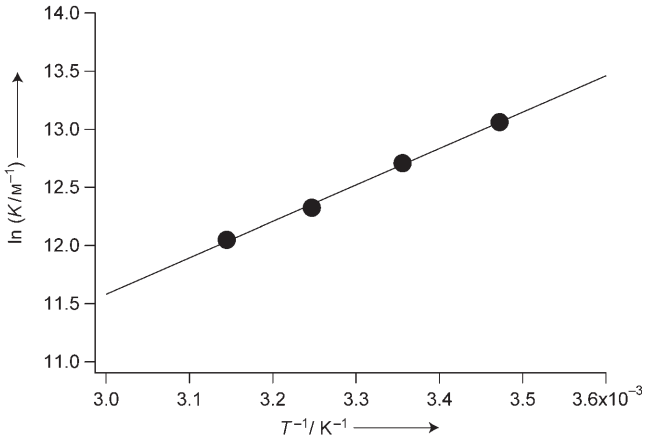

Figure 4. van't Hoff plot of the binding of 4-propylpyridine to **1b** in potassium phosphate buffer at pH 7.

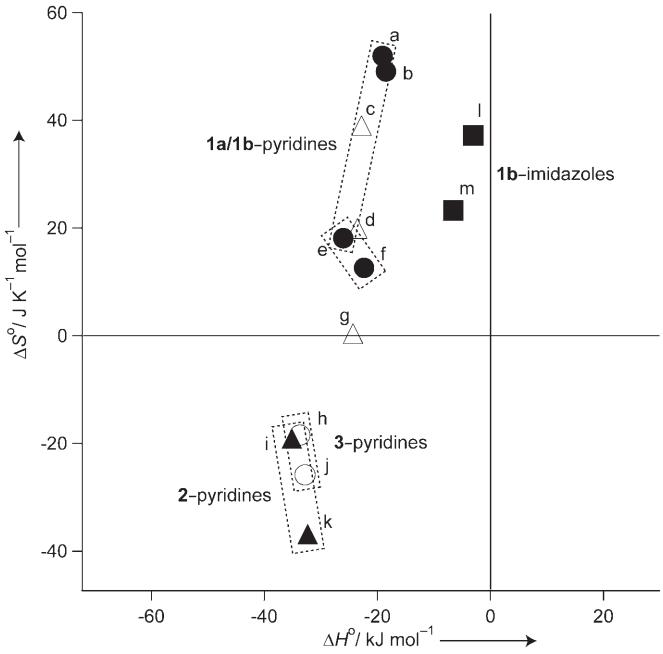

Figure 5. Plot of entropy changes versus enthalpy changes. △ = **1a** and alkylpyridines, ● = **1b** and alkylpyridines, benzylpyridine, ■ = **1b** and imidazoles, ▲ = **2** and alkylpyridines, ○ = **3** and alkylpyridines; a = **1b**–pentylpyridine, b = **1b**–benzylpyridine, c = **1a**–pentylpyridine, d = **1a**–propylpyridine, e = **1b**–propylpyridine, f = **1b**–methylpyridine, g = **1a**–methylpyridine, h = **3**–propylpyridine, i = **2**–propylpyridine, j = **3**–methylpyridine, k = **2**–pyridine, l = **1b**–ethylimidazole, m = **1b**–methylimidazole.

ΔH^0 and ΔS^0 for the binding of 4-benzylpyridine are similar to those of 4-pentylpyridine. The aromatic moiety is thus recognized through a similar mechanism as the aliphatic moiety. Loose binding of imidazoles can be attributed to the less negative enthalpy changes. The hydrophilic nature of imidazoles may resist complete dehydration even when bound in a hydrophobic cavity, and water molecules may disrupt the van der Waals contact of the nonpolar surfaces of the host and guest to lead to less favorable enthalpy changes.

Comparison of Thermodynamic Parameters of Binding between 1a/1b and 2

Figure 5 shows the plot of ΔS^0 against ΔH^0 of binding of alkylpyridines and alkylimidazoles to **1a**, **1b**, **2**, and **3**. The values of ΔH^0 and ΔS^0 for the same guest, 4-propylpyridine, decreased on going from **2** to **3** to **1** (points d, e, h, and i in Figure 5). Therefore, there is an enthalpy–entropy compensation in varying the host structure.[21] As shown in Figure 5, the enthalpy/entropy changes for binding of 4-alkylpyridines were different between **1a**/**1b** and **2**. Binding by **1a**/**1b** is characterized by positive entropic changes, binding by **2** by negative entropic changes. The number of alkyl groups thus has a dramatic impact on the binding mechanism and hydrophobic interactions. The less effective recognition of hydrophobic groups by **1a**/**1b** relative to **2** as reflected in a less negative $-d\Delta G^0/dn$ value may be attributed to the following three mechanisms:

1) The binding site of **1** is not hydrated and is stabilized by the effective intramolecular alkyl–alkyl interactions. Thus, van der Waals stabilization with guest alkyl chains is counterbalanced by the loss in intramolecular van der Waals interactions of the alkyl groups of **1**, which results in only a small enthalpic gain.

2) The larger values of ΔS^0 of **1** than those of **2** and **3** indicate that desolvation of the guest and the host occurs more extensively in **1a**/**1b**. More extensive desolvation than **2** and **3** may be attributed to the larger number of alkyl chains in **1a**/**1b** and the neutral PEO group of **1a**/**1b**, respectively.

3) The large exclusion volume of the PEO group may have negative effects on the construction of a hydrophobic recognition cavity. The smaller binding constants of **1a**/**1b** relative those of **2** in dichloromethane can be explained by greater steric repulsion between receptors **1a**/**1b** and the guest.

Figure 5 shows that, for **1b**, **2**, and **3**, both the enthaplic and the entropic terms favor binding of 4-propylpyridine over that of 4-methylpyridine or pyridine ($\delta\Delta H^0 < 0$, $\delta\Delta S^0 > 0$; point i vs. k, h vs. j, and e vs. f in Figure 5), whereas only the entropic term favors binding of 4-pentylpyridine over that of 4-propylpyridine ($\delta\Delta H^0 > 0$, $\delta\Delta S^0 > 0$; point a vs. e in Figure 5) for **1b**. Therefore, the recognition mechanism of a short alkyl chain seems to be different from that of a long alkyl chain. One possible explanation is that the alkyl group of the guest is bound in a different microscopic environment according to the alkyl-chain length (Figure 6). Although details of the hydration of **1b** are not clear, we speculate that water molecules cannot penetrate deep into the binding pocket, and the 4-propyl group is placed in a nonaquated region, whereas the terminus of the 4-pentyl group is placed in an aquated region to expel water molecules upon binding.

Figure 6 shows the structure of the complex between receptor **1b** and 4-pentylpyridine obtained by molecular-dynamics simulation with the MM3 force field in vacuo. The simulation predicts that the alkyl group of 4-alkylpyridine is

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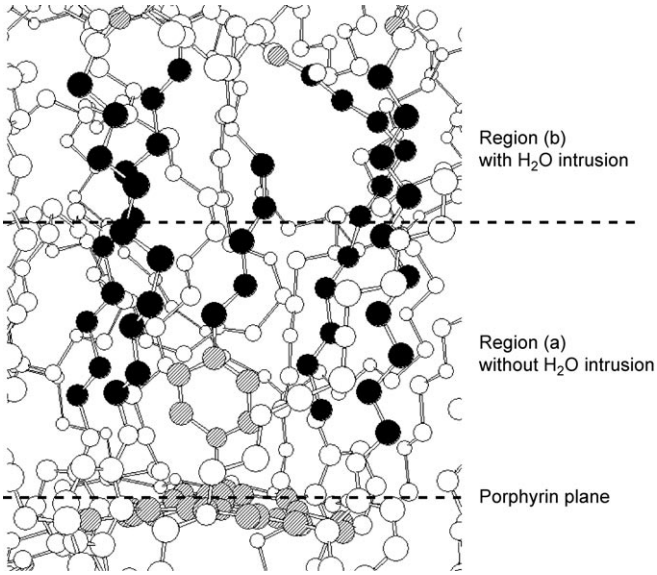

Figure 6. Molecular-dynamics simulation of the **1b**–4-pentylpyridine complex in vacuo. Atoms of the porphyrin framework and the pyridine core are shown as shaded circles, and alkyl chains of receptor and guest are as filled circles.

in van der Waals contact with the alkyl chains in **1b**. This structure supports the idea that extensive desolvation of the guest occurs upon binding as deduced from the observed large entropic changes.

Conclusions

The recognition of alkyl groups by induced-fit-type porphyrin receptors was evaluated by comparison of the thermodynamic parameters of binding of 4-alkylpyridines of varying alkyl-chain length. The free energy of binding of 4-alkylpyridines increased linearly with an increase in the number of alkyl carbon atoms of the guest for all zinc porphyrins with eight PEO–alkyl substituents (molecular weight of each PEO unit = 750; **1a**), eight PEO–alkyl substituents (molecular weight of each PEO = 2000; **1b**), and four PEO–alkyl substituents (molecular weight of each PEO = 2000; **2**); the increment in free energy is 2.6, 2.2, and 3.4 kJ mol^{-1} per CH_2 unit, respectively. The receptor with shorter PEO chains showed better recognition of the alkyl groups of the guest. Therefore, the hydrophobic/hydrophilic balance seems to be important for receptor design. The microcalorimetric study of binding by **1a** showed that the enthalpy and entropy changes also vary linearly with increasing alkyl-chain length. The entropic term becomes more favorable for binding with increasing alkyl-chain length, thus demonstrating that hydrophobic recognition is driven by the entropic term (the $CH_2\cdots CH_2$ hydrophobic interaction is characterized by $\delta\Delta H^0 = 0.4$ and $T\delta\Delta S^0 = 3.0$ kJ per CH_2 unit at 298 K). The compensation temperature was as low as 38 K, which implies that the enthalpic term could be a driving force only below this temperature. The binding constants in sodium phosphate buffer were as twice as large as those in potassium phosphate buffer, which demonstrates that cation-induced conformational changes in PEO indirectly modulate binding affinity.

Experimental Section

Equipment

Microcalorimetric titration was performed with a MicroCal VP-ITC isothermal titration calorimeter. UV/Vis spectra were recorded on a Shimadzu Multispec-1500 spectrophotometer.

Molecular-Dynamics Simulations

Molecular-dynamics simulation of the complex between **1b** and 4-pentylpyridine was performed in vacuo by using BioMedCAChe Version 5.02 with an MM3 force field and a time step of 0.001 ps at 300 K for 1000 ps, starting from a conformer of **1b** with all-*trans* extended PEO chains.

Syntheses

4: 2,6-Dimethoxybenzaldehyde (20.00 g, 120.5 mmol) was dissolved in propionic acid (1.00 L). The solution was heated to 120 °C with continuous stirring. Pyrrole (8.40 mL, 121.5 mmol) was slowly added to the heated solution, and heating was continued at 120 °C for 7 h. After the solution was cooled to room temperature, it was left to stand overnight. The purple crystalline product was isolated following the literature procedure[22] to afford 5,10,15,20-tetrakis(2,6-dimethoxyphenyl)porphyrin (**4**; 2.07 g, 8.04 %). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = -2.50$ (s, 2H; NH), 3.50 (s, 24H; OMe), 6.99 (d, $J = 8.4$ Hz, 8H; phenyl H), 7.69 (t, $J = 8.4$ Hz, 4H; phenyl H), 8.67 ppm (s, 8H; β-pyrrole); MS (FAB): $m/z = 855$ $[M+H]^+$.

5: Porphyrin **4** (0.33 g, 0.45 mmol) and pyridinium chloride (22.91 g, 0.20 mol) were placed in a 300-mL three-necked round-bottomed flask under Ar. The mixture was heated under reflux at 220 °C for 6 h. After the reaction mixture was cooled to room temperature, water (500 mL) and ethyl acetate (200 mL) were added. The organic layer was separated, washed with HCl (0.1 M, 2×150 mL) then saturated aqueous $NaHCO_3$ (2×200 mL), and dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography (SiO_2, EtOAc/THF = 4:1, 2×) afforded 5,10,15,20-tetrakis(2,6-dihydroxyphenyl)porphyrin (**5**) as a red-purple solid (0.18 g, 53.4 %). ^{1}H NMR (500 MHz, CD_3OD): $\delta = 6.82$ (d, $J = 8.3$ Hz, 8H; phenyl H), 7.47 (t, $J = 8.3$ Hz, 4H; phenyl H), 8.84 ppm (s, 8H; β-pyrrole); MS(FAB): $m/z = 743$ $[M+H]^+$.

6: Porphyrin **5** (0.21 g, 0.28 mmol) and K_2CO_3 (0.84 g, 6.13 mmol) were dissolved in dry *N*,*N*-dimethylformamide (DMF; 6.35 mL) under Ar, then methyl 11-bromoundecanoate (1.48 mL, 6.13 mmol) was added. The reaction mixture was heated at 50 °C for 3 days. After the solution was cooled to room temperature, water (200 mL) and ethyl acetate (250 mL) were added. The organic layer was separated, washed with water (3× 200 mL) then saturated aqueous $NaHCO_3$ (3×200 mL), and dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography (SiO_2, $CHCl_3$) afforded 5,10,15,20-tetrakis(2,6-bis(10-methoxycarbonyldecyloxy)phenyl)porphyrin (**6**) as a red-purple solid (0.58 g, 86.9 %). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = -2.59$ (s, 2H; NH), 0.63–1.59 (m, 128H; CH_2), 2.18–2.321 (m, 16H; CH_2), 3.59–3.73 (m, 40H; CO_2Me and CH_2), 6.95 (d, $J = 8.4$ Hz, 8H; phenyl H), 7.63 (t, $J = 8.4$ Hz, 4H; phenyl H), 8.63 ppm (s, 8H; β-pyrrole); MS (FAB): $m/z = 2329$ $[M]^+$.

7: Porphyrin **6** (0.10 g, 43.79 μmol) was dissolved in a solution prepared by mixing THF (20 mL), methanol (4 mL), and KOH (0.5 M, 6 mL) under Ar. After being stirred at room temperature for 48 h, the solution was evaporated. HCl (0.5 M, 8 mL) was added, followed by ethyl acetate (15 mL). The organic layer was washed with water (2×25 mL) then saturated aqueous NaCl (2×15 mL) and dried over Na_2SO_4. Evaporation of the solvent and purification by gel-permeation chromatography on Sephadex LH-20 (CH_3OH, 2×) afforded a purple oil of 5,10,15,20-tetrakis-(2,6-bis(10-carboxydecyloxy)phenyl)porphyrin (**7**; 58 mg, 60.1 %).

^{1}H NMR (500 MHz, CD_3OD): δ = 0.43–1.58 (m, 128H; CH_2), 2.08–2.12 (m, 16H; CH_2CO_2), 3.80–3.86 (m, 16H; CH_2), 7.06 (d, J = 8.6 Hz, 8H; phenyl H), 7.70 (t, J = 8.6 Hz, 4H; phenyl H), 8.67 ppm (s, 8H; β-pyrrole); MS (FAB): m/z = 2217 $[M]^+$.

9a: This compound was synthesized according to the reported procedure.[22] Sodium hydroxide (10.00 g, 0.25 mol) in water (50 mL) and poly(ethylene glycol)-750 monomethyl ether (**8a**; 7.50 g, 10.00 mmol) in THF (50 mL) were placed in a flask, and the mixture was cooled in an ice bath with stirring. *p*-Toluenesulfonyl chloride (1.72 g, 9.00 mmol) in THF (50 mL) was added dropwise to the mixture over 1 h with continuous stirring and cooling of the mixture below 5 °C. The solution was stirred at 0–5 °C for a further 3 h and then poured into iced water (200 mL). The mixture was extracted with $CHCl_3$ (2 × 200 mL). The combined organic extracts were washed with water (300 mL 2 ×) then saturated aqueous NaCl (300 mL) and dried over Na_2SO_4. Upon evaporation of the solvent, ω-*O*-tosylpoly(ethylene glycol)750 monomethyl ether (**9a**) of satisfactory purity was obtained[23] (8.32 g, 91.9 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.44 (s, 3H; CH_3), 3.37 (s, 3H; CH_3O), 3.57–3.71 (m, 66H; CH_2), 4.15 (t, J = 5.0 Hz, 2H; CH_2), 7.34 (d, J = 8.0 Hz, 2H; phenyl H), 7.80 ppm (d, J = 8.0 Hz, 2H; phenyl H).

10a: ω-Deoxy-ω-aminopoly(ethylene glycol)750 monomethyl ether (**10a**) was prepared according to the reported procedure[24] by using sodium azide (0.91 g, 14.00 mmol) and **9a** (8.32 g, 9.00 mmol). Yield: 6.39 g, 92.8 %. ^{1}H NMR (500 MHz, D_2O): δ = 2.84 (t, J = 5.0 Hz, 2H; CH_2), 3.41 (s, 3H; CH_3O), 3.57–3.73 ppm (m, 66H; CH_2).

11a: Amine **10a** (0.20 g, 0.27 mmol), HOBt (41 mg, 0.27 mmol), and finally EDC (51.8 mg, 0.27 mmol) were added to a solution of **7** (62 mg, 28 μmol) in CH_2Cl_2 (20 mL) at room temperature under Ar. After 46 h, the mixture was evaporated and purified by column chromatography (SiO_2, $CHCl_3$/MeOH = 10:1). Further purification by gel-permeation chromatography on Sephadex LH-20 (CH_3OH, 2 ×) afforded PEO750-appended prophyrin **11a** as a red-purple oil (204.8 mg, 89.0 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = −2.59 (s, 2H; inner H), 0.60–1.58 (m, 128H; CH_2), 2.01–2.06 (m, 16H; CH_2CONH), 3.31–3.36 (m, 40H; CONHCH_2 and OCH_3), 3.45–3.75 (m, 512H; $OCH_2OCH_2CH_2O$), 6.39 (s, 8H; CONH), 6.94 (d, J = 8.4 Hz, 8H; phenyl H), 7.62 (t, J = 8.4 Hz, 4H; phenyl H), 8.62 ppm (s, 8H; β-pyrrole); MS (MALDI-TOF, 3-indoleacrylic acid): m/z calcd for $C_{396}H_{726}N_{12}O_{144}$: 7960 $[M]^+$; found: broad peak at 6500–8600.

1a: A solution of **11a** (204 mg, 24.90 μmol) in CH_3OH (10 mL) and CH_2Cl_2 (10 mL) was mixed with saturated $Zn(OAc)_2$ (21.20 mg) in CH_3OH (2 mL), and the mixture was heated under reflux for 3 h in the dark. The solution was evaporated, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with deionized water, and the organic layer was evaporated. The product was further purified by gel-permeation chromatography on Sephadex LH-20 (CH_3OH, 2 ×) to afford PEO750-appended zinc porphyrin **1a** as a pink solid (173.3 mg, 87.4 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.60–1.58 (m, 128H; CH_2), 2.00–2.05 (m, 16H; CH_2CONH), 3.31–3.36 (m, 40H; CONHCH_2 and OCH_3), 3.45–3.75 (m, 512H; OCH_2 and OCH_2OCH_2O), 6.27 (s, 8H; CONH), 6.95 (d, J = 8.4 Hz, 8H; phenyl H), 7.62 (t, J = 8.4 Hz, 4H; phenyl H), 8.70 ppm (s, 8H; β-pyrrole).

9b: This compound was synthesized according to the reported procedure.[23] Sodium hydroxide (8.00 g, 0.2 mol) in water (40 mL) and poly(ethylene glycol)2000 monomethyl ether (**8b**; 5.01 g, 2.5 mmol) in THF (40 mL) were placed in a flask, and the mixture was cooled in an ice bath with stirring. *p*-Toluenesulfonyl chloride (0.65 g, 3.41 mmol) in THF (40 mL) was added dropwise to the mixture over 2 h with continuous stirring and cooling of the mixture below 5 °C. The solution was stirred at 0–5 °C for a further 3 h and then poured into iced water (200 mL). The mixture was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. Upon evaporation of the solvent, ω-*O*-tosylpoly(ethylene glycol)2000 monomethyl ether (**9b**) was obtained (4.66 g, 86.5 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.46 (s, 3H; CH_2), 3.39 (s, 3H; CH_3O), 3.56–3.71 (m, 200H; CH_2), 4.17 (t, J = 5.0 Hz, 2H; CH_2), 7.34 (d, J = 8.0 Hz, 2H; phenyl H), 7.80 ppm (d, J = 8.0 Hz, 2H; phenyl H).

10b: ω-Deoxy-ω-aminopoly(ethylene glycol)2000 monomethyl ether (**10b**) was prepared according to the reported procedure[24] by using sodium azide (75 mg, 1.15 mmol) and **9b** (1.66 g, 0.77 mmol). Yield: 1.44 g, 99.0 %. ^{1}H NMR (500 MHz, [D_6]dimethyl sulfoxide ([D_6]DMSO)): δ = 2.60 (t, J = 5.0 Hz, 2H; CH_2), 3.20–3.51 ppm (m, 203H; CH_3O and CH_2).

11b: Amine **10b** (1.01 g, 503 μmol), HOBt (115 mg, 754 μmol), and finally EDC (144 mg, 754 μmol) were added to a solution of **7** (58 mg, 26.2 μmol) in CH_2Cl_2 (25 mL) at room temperature under Ar. After 4 days, the mixture was evaporated and then purified by column chromatography (SiO_2, $CHCl_3$/MeOH = 10:1, 2 ×). Further purification by gel-permeation chromatography on Sephadex LH-20 (CH_3OH, 2 ×) afforded PEO-appended porphyrin **11b** as a red-purple oil. Yield: 101 mg, 21.6 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ = −2.61 (s, 2H; inner H), 0.62–1.58 (m, 128H; CH_2), 2.01–2.06 (m, 16H; CH_2CONH), 3.35–4.24 (m, 1448H, OCH_2, $CONHCH_2$, OCH_2CH_2, and OCH_3), 6.25 (br s, 3H; CONH), 6.92 (d, J = 8.0 Hz, 8H; phenyl H), 7.60 (t, J = 8.0 Hz, 4H; phenyl H), 8.60 ppm (s, 8H; β-pyrrole).

1b: A solution of **11b** (30 mg, 1.66 μmol) and $Zn(OAc)_2$-saturated methanol (2 mL) in CH_3OH (10 mL) and CH_2Cl_2 (10 mL) was heated under reflux for 3 h in the dark. The solution was evaporated, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with deionized water, and the organic layer was evaporated. The product was further purified by gel-permeation chromatography on Sephadex LH-20 (CH_3OH, 2 ×) to afford PEO-appended zinc porphyrin **1b** as a pink solid. Yield: 30 mg, 100 %. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.62–1.58 (m, 128H; CH_2), 1.99–2.06 (m, 16H; CH_2CONH), 3.35–4.24 (m, 1448H, OCH_2, $CONHCH_2$, OCH_2CH_2, and OCH_3), 6.29 (br s, 8H; CONH), 6.93 (d, J = 8.0 Hz, 8H; phenyl H), 7.60 (t, J = 8.0 Hz, 4H; phenyl H), 8.68 ppm (s, 8H; β-pyrrole).

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