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Static and Dynamic Behavior of 2:1 Inclusion Complexes of Cyclodextrins and Charged Porphyrins in Aqueous Organic Media

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Abstract: Two heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TMe-β-CD) molecules strongly include the peripheral substituents at the 5- and 15-positions of the charged meso-tetrasubstituted porphyrins, $PorSub_4$ [$TPPS_4$ (Sub = *p*-C_6H_4-SO_3^-), TPPOC3PS (*p*-C_6H_4-O-$(CH_2)_3$-*p*-C_6H_4-SO_3^-), TCPP (Sub = *p*-C_6H_4-CO_2^-), and TPPOC3Py (*p*-C_6H_4-O-$(CH_2)_3$-Py^+Br^-), where Py^+ = *N*-alkylpyridinium] in aqueous ethylene glycol. The binding constants (K_1 and K_2) and the rate constants (k_1 and k_2) for formation of the 1:1 and 2:1 complexes of TMe-β-CD and $PorSub_4$ were determined. Both the binding constants and the rate constants for anionic $TPPS_4$, TCPP, and TPPOC3PS were much larger than those for cationic TPPOC3Py. The smaller k_1 and k_2 values for TPPOC3Py indicate a higher barrier for penetration of a cationic guest into the TMe-β-CD cavity. The methyl groups at the rims and the cavity wall of the host are positively polarized due to the inductive effect of the ethereal oxygens. The positively polarized rims and interior of the host cavity should prevent the penetration of the cationic substituent of TPPOC3Py into the TMe-β-CD cavity. The 2:1 TMe-β-CD−$PorSub_4$ complexes are extraordinary stable in aqueous solutions, even in the case of cationic TPPOC3Py. Formation of both 1:1 and 2:1 complexes is promoted by negative and large enthalpy changes, suggesting a strong van der Waals interaction as the main binding force.

Introduction

It is expected that cyclodextrin (CD) provides a microscopically apolar environment around the center of a porphyrin ring and prevents self-aggregation of the porphyrin if the CD molecules deeply include the substituents at the meso positions of the porphyrin. If CDs actually show such a function, they might act as the simplest apoprotein models. Several studies have been carried out with interactions of water-soluble porphyrins and CDs. Naturally occurring porphyrins such as deuteroporphyrin IX, hematoporphyrin IX, and coproporphyrin III, without aryl groups at the meso positions of the porphyrins, form very weak complexes with γ-CD, having binding constants (K) of about 16−35 M^{-1} in water.[1] The weak complexation of these porphyrins is ascribed to the absence of appropriate CD-binding sites in the porphyrins. In comparison, several synthetic porphyrins having ionic aryl substituents at the meso positions have been shown to form relatively stable complexes of CDs and the porphyrins. Inclusion of the ionic aryl substituents of a porphyrin by CD was first reported by Manka and Lawrence,[2] who found the formation of a trans-type 2:1 complex of heptakis(2,6-di-*O*-methyl)-β-CD (2,6-DMe-β-CD) and protonated TPPOC3A (Table 1). The K values for the 1:1 (K_1) and 2:1 complexation processes (K_2)

$$\mathrm{Por} + \mathrm{CD} \overset{K_1}{\rightleftharpoons} \mathrm{Por{-}CD} \quad (1)$$

$$\mathrm{Por{-}CD} + \mathrm{CD} \overset{K_2}{\rightleftharpoons} \mathrm{CD{-}Por{-}CD} \quad (2)$$

have been determined by means of absorption spectroscopy in 0.05 M succinic acid buffer at pH 5 and 60 °C to be $(7.7 \pm 0.7) \times 10^4$ and $(5.9 \pm 1.1) \times 10^4$ M^{-1}, respectively.[3] The result indicates a strong ability of the *O*-methylated β-CD to yield the 2:1. Mosseri et al. studied complexation of anionic metalloporphyrins such as Fe(III)$TPPS_4$ and Zn(II)$TPPS_4$ with β-CD.[4,5] Although they reported the 4:1 complexes of β-CD and metalloporphyrins, the stoichiometry of the complexes needs be reconsidered.[6] The complexation of an anionic porphyrin free base with native β-CD was examined by Ribó et al.[7] On the

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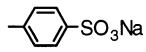
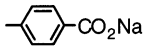
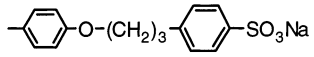
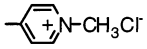
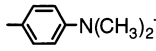
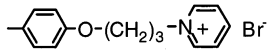
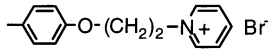
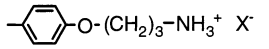
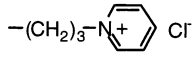
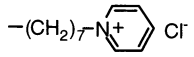
Table 1. Abbreviations of 5,10,15,20-Tetrasubstituted Porphyrins

abbreviation	substituent
$TPPS_4$	
TCPP	
TPPOC3PS	
TMPyP	
TAPP	
TPPOC3Py	
TPPOC2Py	
TPPOC3A	
PC3Py	
PC7Py	

basis of ^{1}H NMR data, they assumed the formation of a trans-type 2:1 complex of β-CD and $TPPS_4$ having a structure similar to that of TPPOC3A. Other research groups, however, reported the K values for complexation of $TPPS_4$ with β-CD (440−5600 M^{-1}) by assuming a 1:1 complex.[8−10] In previous papers,[11,12] we reported different behavior of CDs toward cationic and anionic guests: anionic compounds can penetrate into the hydrophobic CD cavities, while cationic ones cannot. As partial confirmation of this model, we presented the apparent pK_a values of the various diprotonated porphyrins in the presence of CDs. The pK_a value of anionic $TPPS_4$ in water (5.4) drastically decreases upon complexation with heptakis(2,3,6-tri-*O*-methyl)-β-CD (TMe-β-CD) (ΔpK_a = 5.0), while the effect of β-CD is much weaker (ΔpK_a = 1.2). ^{1}H NMR spectroscopy reveals the formation of the trans-type 2:1 complex of TMe-β-CD and $TPPS_4$ in which the secondary OCH_3 group sides of the CD molecules face each other. On the other hand, cationic TMPyP (Table 1) does not interact with either β-CD or TMe-β-CD at all (ΔpK_a = 0). Another cationic porphyrin, TAPP, shows little tendency to bind to any CDs. On the basis of these results, the following model is proposed:

(1) The cavities of both β-CD and TMe-β-CD are favorable for loading anionic porphyrin guests but unfavorable for cationic ones.

(2) β-CD forms a relatively weak complex with $TPPS_4$.

(3) TMe-β-CD has a strong tendency to include the peripheral aryl groups of $TPPS_4$, and two TMe-β-CD molecules cover the center of the porphyrin to provide a microscopically apolar environment.

Previous studies in this area are mostly qualitative and speculative. Quantitative investigations on both static and dynamic behavior of the complexation make it possible to understand totally the interactions between ionic porphyrins and CDs. The present study reveals the novel properties of TMe-β-CD as the host for ionic porphyrins and the mechanism for extremely strong complexation in such a host−guest system.

Experimental Section

Preparation of Porphyrins. TPPOC2Py and TPPOC3Py (Table 1) were prepared according to the procedures described in the literature.[13] $TPPS_4$, purchased in the protonated form (Tokyo Kasei), was dissolved in water and passed through a DOWEX HCR-W2 ion-exchange column (Na form) to obtain the $TPPS_4$ tetrasodium salt. Elemental analysis indicated the formation of $Na_4TPPS_4 \cdot 7H_2O$. TCPP (Table 1) in the protonated form (Tokyo Kasei) was dissolved in water and neutralized with equimolar NaOH. Water was evaporated, and the residue was dried under vacuum. TPPOC3PS was synthesized as follows. A mixture of 4-(3-bromopropyl)benzenesulfonyl chloride (10 mmol), phenol (8 mmol), and K_2CO_3 (14.5 mmol) in 100 mL of acetone was stirred for 16 h at room temperature under Ar. The reaction mixture was filtered to remove K_2CO_3, and acetone was evaporated from the filtrate. The residue was dissolved in chloroform and washed with water saturated with NaCl. The residue obtained after evaporation of the chloroform was purified by silica gel column chromatography with chloroform−hexane (3:2) to yield pure phenyl 4-(3-bromopropyl)benzenesulfonate (99% yield). The product was identified by ^{1}H NMR and FAB-MS. Phenyl 4-(3-bromopropyl)benzenesulfonate (11.3 mmol) was reacted with 5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrin (0.59 mmol) in 100 mL of DMF containing K_2CO_3 (39 mmol) with stirring for 3 days under Ar. After evaporation of DMF, the residue was dissolved in dichloromethane and washed with water saturated with NaCl. The dark purple solid obtained by evaporation of dichloromethane was purified by silica gel column chromatography with chloroform−methanol (100:1) to obtain pure 5,10,15,20-tetrakis{4-[3-(4-phenoxysulfonylphenyl)propoxy]-phenyl}porphyrin (32% yield). The product was identified by ^{1}H NMR and FAB-MS. 5,10,15,20-Tetrakis{4-[3-(4-phenoxysulfonylphenyl)-propoxy]phenyl}porphyrin (22.5 μmol), methanol (5 mL), and 1,4-dioxane (50 mL) were placed in a flask, and 30 mL of 10 M aqueous NaOH was added. After being stirred at 60 °C for 48 h, the reaction mixture was neutralized by addition of 1 M aqueous HCl and dissolved in 400 mL of water. After the mixture was washed with chloroform, water was evaporated under reduced pressure, and the residue was dissolved in methanol. The inorganic salt was removed by filtration. The solid that precipitated upon addition of acetone was collected by filtration. Such a desalting procedure was repeated three times, and the dark brown solid finally obtained was washed with water−acetone (4:1), to give TPPOC3PS. Anal. Calcd for $C_{80}H_{66}N_4O_{16}S_4Na_4$: C, 57.62; H, 4.71; N, 3.36. Found: C, 57.98; H, 4.43; N, 3.41.

Other Materials. TMe-β-CD (Nacalai) was purchased and used as received. β-CD (Nacalai) was washed with THF using a Soxhlet extractor to remove the antioxidant and dried.

Spectroscopy. Absorption spectra were recorded on a Shimadzu UV-2100 spectrophotometer. ^{1}H NMR spectra were taken using a JEOL JNM-A400 spectrometer (400 MHz). Sodium 3-trimethylsilyl[2,2,3,3-$^2H_4$]propionate (TSP, Aldrich) was used as an external standard. FAB MS spectra were recorded on a JEOL JMS-700 spectrometer.

Methods. Determination of K_1 and K_2 values was performed by measuring the absorption spectral changes of a porphyrin ([Por]$_0$ = 2 × 10^{-6} or 2 × 10^{-5} M) as a function of CD concentration.[14] Na_2CO_3 was used to adjust pH. Titration curves obtained by plotting the changes

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in optical densities (ΔA) at four wavelengths (Q-bands) vs $[CD]_0$ were analyzed by a nonlinear least-squares method (damping Gauss−Newton method) using a computer program developed by one of the authors (Y.K.). The reproducibility of the data was checked by repeating all experiments at least three times.

The complexation and dissociation rate constants (k_1, k_2, k_{-1}, and k_{-2}) were determined by following ΔA after the solutions of CD and porphyrin were rapidly mixed using a UNISOKU stopped-flow apparatus with a multichannel photodiode array.

$$\mathrm{Por} + \mathrm{CD} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{Por{-}CD} \tag{3}$$

$$\mathrm{Por{-}CD} + \mathrm{CD} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{CD{-}Por{-}CD} \tag{4}$$

The data were analyzed by a nonlinear least-squares method (damping Gauss−Newton method) using the computer program REDAP developed by Kuroda et al.[15] Five time courses, obtained by altering [TMe-β-CD]$_0$, were fitted by a set of k_1, k_{-1}, k_2, and k_{-2} values to heighten the reliability of this method. The reliability of this method was checked by another analytical method, kindly offered by Prof. R. Pasternack (Swarthmore College), where unknown parameters are reduced to three (k_1, k_{-1}, and k_2) by assuming [Por] $\ll$ [TMe-β-CD]. The agreement of both methods was satisfactory (Supporting Information).

^{13}C spin−lattice relaxation times (T_1) were measured for TMe-β-CD (0.1 M) and a mixture of TMe-β-CD (0.1 M) and $TPPS_4$ (0.05 M) in D_2O under Ar using a JEOL JNM-A400 spectrometer. The inversion−recovery pulse sequence (180°−t−90°), with a relaxation delay at least 5 times longer than the longest T_1, was employed. The data were analyzed by curve fitting using a program loaded in the NMR apparatus. Reproducibility was checked by repeating the experiments at least three times. The T_1 values for $TPPS_4$ alone were measured in DMSO-d_6 because $TPPS_4$ (0.05 M) in D_2O aggregates spontaneously.

Results

^{1}H NMR Spectroscopy. The ^{1}H NMR spectral changes of $TPPS_4$ (1×10^{-3} M) were measured in D_2O as a function of [TMe-β-CD]$_0$, and the results are shown in Figure 1. $TPPS_4$ has been known to aggregate spontaneously in aqueous solution at high concentration and/or in the presence of inorganic salt.[16] As shown in Figure 1, the signal due to the ortho protons (H^o) of $TPPS_4$ (1×10^{-3} M) is broadened in D_2O without TMe-β-CD, while that due to the meta protons (H^m) appears as a sharp doublet. The broadening of H^o is ascribed to self-aggregation of $TPPS_4$. New ^{1}H NMR signals appear upon addition of TMe-β-CD, and the growth of the signals levels off at [TMe-β-CD]$_0$ $= 2 \times 10^{-3}$ M. The NMR spectrum is composed of two sets of the signals due to $TPPS_4$ complexed with TMe-β-CD. The assignment of each signal was achieved by measuring H−H COSY and ROESY spectra of the $TPPS_4$−TMe-β-CD complex (Supporting Information). The ^{1}H NMR spectrum also reveals the formation of the trans-type 2:1 complex of TMe-β-CD and $TPPS_4$. Other types of complexes cannot explain such a simple ^{1}H NMR spectrum.

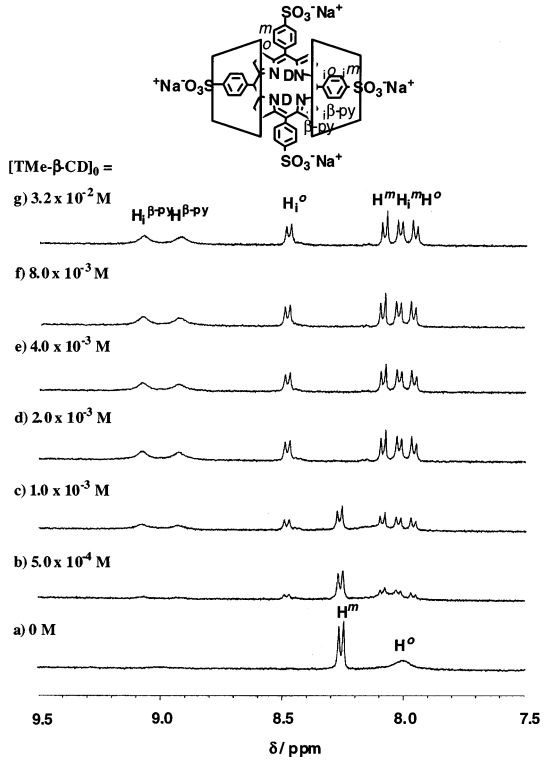

Figure 1. ^{1}H NMR spectra of $TPPS_4$ (1.0×10^{-3} M) in D_2O at 25 °C in the absence and in the presence of various amounts of TMe-β-CD.

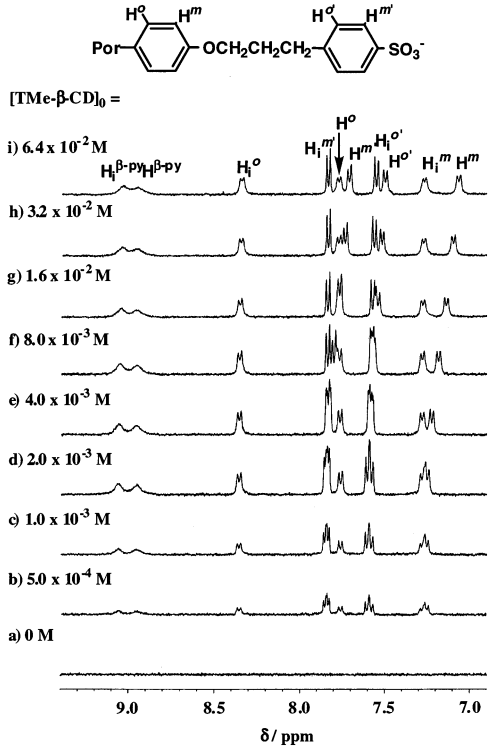

Figure 2. ^{1}H NMR spectra of TPPOC3PS (1.0×10^{-3} M) in D_2O at 25 °C in the absence and in the presence of various amounts of TMe-β-CD. "i" represents the protons inside the CD cavity.

In the case of TPPOC3PS (Figure 2), two sets of signals due to two phenyl rings in the free and included forms were observed with TPPOC3PS until two equivalent amounts of TMe-β-CD were added, though splits of the signals of H^m and H_i^m, $H^{o\prime}$ and $H_i^{o\prime}$, and $H^{m\prime}$ and $H_i^{m\prime}$ (where "i" indicates the proton belonging to the group included in the CD cavity) were very

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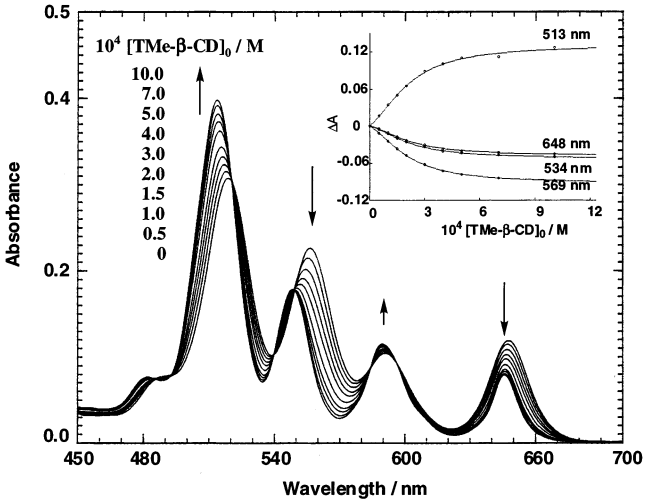

Figure 3. Absorption spectra of TPPOC3Py (2.0×10^{-5} M) in EG−H_2O (3:1) containing various amounts of TMe-β-CD at 25 °C. Inset: Changes in absorbances (ΔA) of TPPOC3Py (2.0×10^{-5} M) upon addition of TMe-β-CD in EG−H_2O (3:1) at 25 °C. The solid lines are the best fit to an equation for the 1:1 and 1:2 equilibria: $K_1 = 2300 \pm 900$ M^{-1}, $K_2 = 9400 \pm 200$ M^{-1}.

small. Since no signals were observed for free TPPOC3PS because of self-aggregation, the ^{1}H NMR spectrum of the porphyrin in the presence of 2×10^{-3} M TMe-β-CD is ascribed to the 2:1 complex. At [TMe-β-CD]$_0$ > 2×10^{-3} M, the signals due to the terminal phenyl rings ($H^{o'}$ and $H^{m'}$) as well as the meta protons of the inner ones (H^m) of TPPOC3PS start to split, again yielding two sets of clearly separated signals ($H^m-H_i^m$, $H^{o'}-H^{m'}$, and $H_i^{o'}-H_i^{m'}$). Such marked splitting seems to be due to formation of 3:1 and/or 4:1 complexes of TMe-β-CD and TPPOC3PS. The ROESY spectrum of the 2:1 complex of TMe-β-CD and TPPOC3PS (Supporting Information) shows the strong cross-peaks between H_i^o of the guest and the protons at the 3- (H-3) and 5-positions of the host (H-5) and H_i^m of the guest and H-5 of the host. The TMe-β-CD molecules of the 2:1 complex penetrate deeply to cover the center of the porphyrin ring.

Meanwhile, the formation of only the trans-type 2:1 complex of TMe-β-CD and TPPOC3Py was verified by means of NMR spectroscopy (Supporting Information). Self-aggregation of this porphyrin has been studied previously.[17] Upon addition of TMe-β-CD, the higher self-aggregates were dissociated to the TPPOC3Py monomer by forming the trans-type 2:1 complex.

Binding Constants. The K values for complexation of all charged porphyrins with TMe-β-CD in water were too large to be determined. In all cases, the absorption spectral changes of the porphyrins were saturated at 2 equiv concentration of TMe-β-CD, indicating the formation of the extremely stable 2:1 complexes of TMe-β-CD and the porphyrins in water. We then employed aqueous organic solvents to reduce the K values. Under the present conditions for measuring absorption spectra, Beer−Lambert's law was maintained with all porphyrins used in aqueous organic solvents without CD, even in pure water. Therefore, self-aggregation of the porphyrins need not be considered. The absorption spectral changes of TPPOC3Py in 75% (v/v) ethylene glycol (EG)−25% H_2O (EG−H_2O (3:1)) upon addition of TMe-β-CD are shown in Figure 3 as a typical example. Regular changes with seven isosbestic points were observed. Other porphyrin−TMe-β-CD systems show similar spectral changes. The titration curves obtained are shown in the inset of Figure 3, where the four titration curves plotted at different wavelengths were fitted with a set of K_1 and K_2 values. The titration curves for all systems studied here were not fitted with an equation for 1:1 complexation but were well fitted with the equation for 2:1 complex formation. The binding constants obtained are summarized in Table 2. To the best of our knowledge, only one example has been reported of the K_1 and K_2 values for complexation of porphyrin with CD. Dick et al. reported the K_1 and K_2 values for complexation of TPPOC3A and 2,6-DMe-β-CD to be $(7.7 \pm 0.7) \times 10^4$ and $(5.9 \pm 1.1) \times 10^4$ M^{-1}, respectively, in water at pH 5.0 and 60 °C.[3] The results obtained here in EG−H_2O (3:1) make possible a comparison of the binding behavior of cationic TPPOC3Py with that of anionic porphyrins. Both the K_1 and K_2 values for the anionic porphyrins ($TPPS_4$, TCPP, and TPPOC3PS) are much larger than those for cationic TPPOC3Py. The binding constants for the TPPOC3PS−TMe-β-CD complex were too large to be determined, even in EG−H_2O (3:1). Previously, we found that cationic TMPyP and TAPP scarcely interact with TMe-β-CD.[11,12] Judging from these results, we can conclude that the stability of cationic porphyrin−TMe-β-CD complexes is lower than that of anionic porphyrin complexes. Comparing the results for $TPPS_4$ with those for TPPOC3PS, it can be concluded that the complex of TPPC3PS having the amphiphilic peripheries is much more stable than that of $TPPS_4$ having more hydrophilic peripheries. TPPOC3PS forms the trans-type 2:1 complex, even in neat EG (dielectric constant $\epsilon = 37.7$) and methanol ($\epsilon = 32.63$), but not in DMSO ($\epsilon = 46.6$).

Table 2. Binding Constants for Complexation of Charged Porphyrins with TMe-β-CD in Various Solvents at 25 °C

porphyrin	solvent[a]	K_1/M^{-1}	K_2/M^{-1}
$TPPS_4$	EG−H_2O (3:1)	$(2.0 \pm 1.3) \times 10^4$	$(5.8 \pm 1.5) \times 10^4$
$TPPS_4$	EG	0	0
TPPOC3PS	EG	$(8.7 \pm 2.2) \times 10^3$	$(9.1 \pm 1.3) \times 10^4$
TPPOC3PS	CH_3OH	$(2.9 \pm 0.9) \times 10^2$	$(2.9 \pm 0.2) \times 10^2$
TPPOC3PS	DMSO	0	0
TCPP	EG−H_2O (3:1)	$(1.7 \pm 1.4) \times 10^4$	$(2.0 \pm 1.1) \times 10^5$
TPPOC3Py	EG−H_2O (1:1)	$(4.6 \pm 2.4) \times 10^4$	$(4.4 \pm 1.6) \times 10^5$
TPPOC3Py	EG−H_2O (3:1)	$(2.3 \pm 0.9) \times 10^3$	$(9.4 \pm 0.2) \times 10^3$
TPPOC3Py	EG	0	0

[a] The K values for complexation of $TPPS_4$ in H_2O and EG−H_2O (1:1), TPPOC3PS in H_2O, EG−H_2O (1:1), and EG−H_2O (3:1), TCPP in H_2O and EG−H_2O (1:1), and TPPOC3Py in glycerol−H_2O (1:1) were not determined because the K_1K_2 values were too large.

The complexation of $TPPS_4$ with native β-CD in water was also examined. Previous studies reported the binding constants for the 1:1 complex of β-CD and $TPPS_4$.[8−10] The absorption spectral changes of $TPPS_4$ in water upon addition of β-CD were measured (Supporting Information). Under the present conditions ([$TPPS_4$] = 2×10^{-6} M), $TPPS_4$ does not aggregate spontaneously. At higher β-CD concentrations, deviation from an isosbestic point was observed, clearly indicating simultaneous formation of the 1:1 complex and a complex having a stoichiometry other than 1:1. The titration curves for this system were fit well with the equations for 2:1 complexation. The K_1 and K_2 values in water (but not in aqueous EG) at 25 °C are $(1.7 \pm 0.3) \times 10^4$ and $(2.3 \pm 0.4) \times 10^3$ M^{-1}, respectively. The K_1 value is considerably larger than the reported values, which have been evaluated assuming formation of only the 1:1 complex.[8−10]

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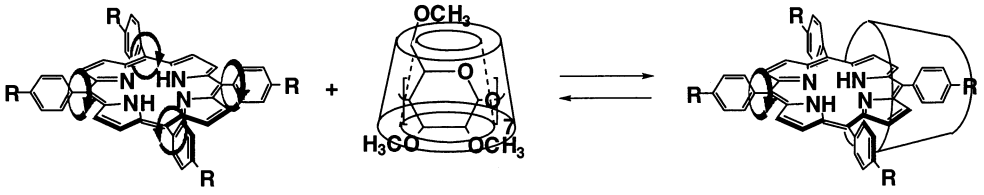

TPPOC3Py: R = -O(CH$_2$)$_3$-Py$^+$Cl$^-$ **TMe-β-CD**

Figure 4. Change in rotational freedom of the peripheral substituents of TPPOC3Py upon complexation with TMe-β-CD.

Table 3. Rate Constants for Formation and Dissociation of 1:1 and 2:1 Complexes of TMe-β-CD and Charged Porphyrins in Aqueous EG at 25 °C

porphyrin	solvent	k_1/M^{-1} s^{-1}	k_{-1}/s^{-1}	k_2/M^{-1} s^{-1}	k_{-2}/s^{-1}
$TPPS_4$	EG−H_2O (3:1)	$(3.0 \pm 0.9) \times 10^4$	4.6 ± 0.1	$(5.3 \pm 0.4) \times 10^4$	0.43 ± 0.01
TPPOC3PS	EG−H_2O (3:1)	$(1.8 \pm 0.1) \times 10^5$	0.24 ± 0.01	$(3.9 \pm 0.1) \times 10^4$	$(4.8 \pm 0.3) \times 10^{-3}$
TPPOC3Py	EG−H_2O (1:1)	$(1.3 \pm 0.1) \times 10^4$	0.41 ± 0.01	$(3.6 \pm 0.1) \times 10^3$	$(2.6 \pm 0.1) \times 10^{-2}$
TPPOC3Py	EG−H_2O (3:1)	$(8.7 \pm 0.2) \times 10^3$	3.9 ± 0.1	$(1.9 \pm 0.1) \times 10^3$	0.16 ± 0.01
TPPOC2Py	EG−H_2O (1:1)	$(1.1 \pm 0.1) \times 10^4$	0.35 ± 0.01	$(3.7 \pm 0.1) \times 10^3$	$(3.2 \pm 0.5) \times 10^{-2}$

Table 4. Thermodynamic Parameters for Complexation of $TPPS_4$ and TPPOC3Py with CDs

		1:1 complex		2:1 complex	
system	solvent	$\Delta H°$/kJ mol^{-1}	$\Delta S°$/J mol^{-1} K^{-1}	$\Delta H°$/kJ mol^{-1}	$\Delta S°$/J mol^{-1} K^{-1}
$TPPS_4$/TMe-β-CD	EG−H_2O (3:1)	-61 ± 9	-121 ± 29	-46 ± 4	-62 ± 12
$TPPS_4$/β-CD	H_2O	10 ± 4	119 ± 13	-5 ± 1	48 ± 3
TPPOC3PS/TMe-β-CD	EG	-40 ± 4	-50 ± 12	-37 ± 2	-31 ± 5
TPPOC3Py/TMe-β-CD	EG−H_2O (1:1)	-72 ± 9	-152 ± 32	-35 ± 6	-9 ± 20
TPPOC3Py/TMe-β-CD	EG−H_2O (3:1)	-44 ± 2	-86 ± 6	-25 ± 2	-9 ± 7
TPPOC3Py/TMe-β-CD	DMSO−H_2O (1:1)	-77 ± 4	-171 ± 12	-42 ± 4	-39 ± 13

No complex was formed in EG−H_2O (1:1). The ability of β-CD to form a complex with $TPPS_4$ is much weaker than that of TMe-β-CD.

Kinetics. To further probe the basis for a cavity of CD being favorable for loading an anionic guest but unfavorable for a cationic one, rate constants for the forward and backward processes (eqs 3 and 4) were determined. The time courses of the optical density changes (ΔA) of a porphyrin after mixing with various amounts of TMe-β-CD were fitted by a set of k_1, k_{-1}, k_2, and k_{-2} values (Supporting Information). The results are listed in Table 3. The k_1 values for the anionic porphyrins ($TPPS_4$ and TPPOC3PS) are much larger than those for the cationic ones (TPPOC3Py and TPPOC2Py) under similar solvent conditions. This result verifies our previous conclusion that the CD cavity is more favorable for loading an anionic guest than a cationic one.[11,12] Comparison of the data obtained for TPPOC3Py with those for TPPOC3PS is the best way to determine the difference in complexation between cationic and anionic porphyrins. The k_1 value for TPPOC3PS in EG−H_2O (3:1) is ca. 20 times larger than that for TPPOC3Py, while the k_{-1} value for TPPOC3PS is ca. 16 times smaller than that for TPPOC3Py. Therefore, the stability constant for the 1:1 complex of TPPOC3PS is over 300 times larger than that for TPPOC3Py in EG−H_2O (3:1). The K_1 and K_2 values evaluated from the rate constants are in agreement with those obtained from the spectral titrations, within the range of the experimental error.

Thermodynamics. Thermodynamic parameters provide further insight into the charge discrimination for complexation by CDs. The thermodynamic parameters for the present systems were determined from the van't Hoff plots (Supporting Information). The results are listed in Table 4. In the complexation of $TPPS_4$ with TMe-β-CD in EG−H_2O (3:1), the negative and large enthalpy changes ($\Delta H°$) promote the 1:1 and 2:1 complexation, while the negative entropy changes ($\Delta S°$) suppress the complexation. A large entropy loss was observed, especially for 1:1 complex formation. Essentially the same patterns were obtained for the case of TPPOC3Py. The thermodynamic parameters for the complexation of TPPOC3Py with TMe-β-CD in EG−H_2O (1:1) are studied here for comparison. The first step, formation of the 1:1 complex, is associated with negative and large $\Delta H°$ and $\Delta S°$, while $\Delta S°$ dramatically increases in the second complexation, formation of the 2:1 complex. Rotational motion of three peripheral substituents seems to be seriously restricted when a TMe-β-CD molecule includes a p-C_6H_4-O-(CH$_2$)$_3$-Py$^+$ group (Figure 4), yielding a negative and large $\Delta S°$. Meanwhile, the second complexation, formation of the 2:1 complex, does not lead to a major reduction in the motional freedom of the 1:1 CD−porphyrin complex. This might be the reason for the negative but small $\Delta S°$ in the second step. Essentially the same discussion can be applied for the other systems, except for $TPPS_4$−β-CD. Thermodynamic patterns for complexation of $TPPS_4$ with native β-CD in water are completely different from those with TMe-β-CD. The first complexation of $TPPS_4$ with β-CD is promoted by the positive and large $\Delta S°$. Here $\Delta H°$ is positive. The second step of complexation is also dominated by the entropy term. There are several examples of CD complex formation which are accompanied by positive $\Delta S°$ values.[18,19] Dehydration from host and/or guest upon complexation has been assumed as a main reason for the positive $\Delta S°$.[18,20] Since both primary and secondary OH groups of β-CD are solvated by water, extensive dehydration from both rims of the β-CD cavity should occur when a peripheral substituent of the guest penetrates into the CD cavity. Dehydra-

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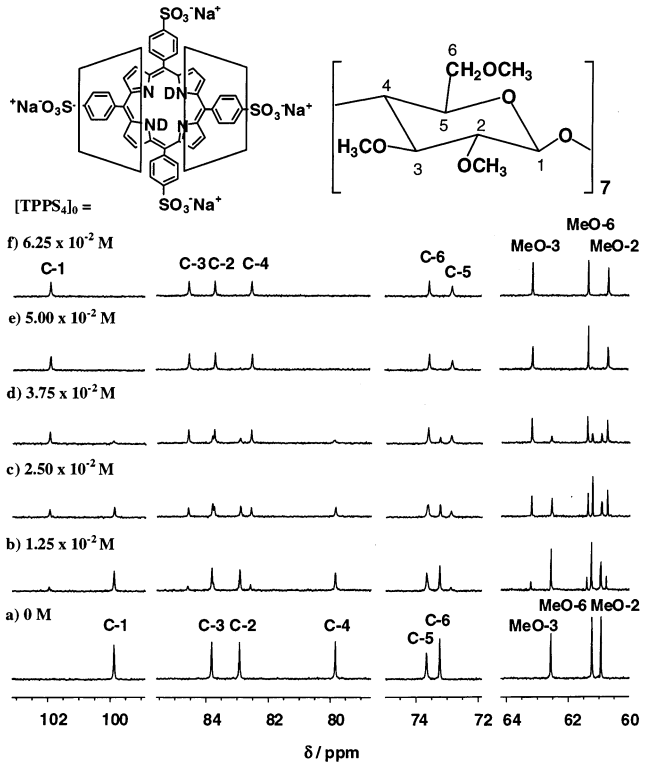

Figure 5. ^{13}C NMR spectra of TMe-β-CD (0.1 M) in D_2O at 25 °C in the absence and in the presence of various amounts of $TPPS_4$. "C-*n*" denotes the ^{13}C nucleus of TMe-β-CD at the *n*-position.

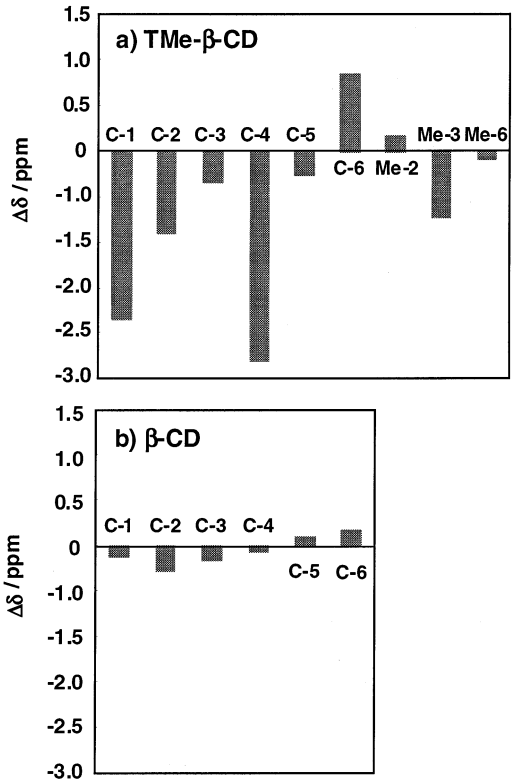

Figure 6. Complexation-induced chemical shift changes ($\Delta\delta = \delta_{free} - \delta_{obs}$) of the ^{13}C nuclei of (a) TMe-β-CD and (b) β-CD complexed with $TPPS_4$ in D_2O: (a) $[TPPS_4]_0/[\text{TMe-}\beta\text{-CD}]_0 = 0.05$ M/0.1 M; (b) $[TPPS_4]_0/[\beta\text{-CD}]_0 = 0.08$ M/0.01 M.

tion also occurs from the charged guest. Therefore, it is quite reasonable to assume that a positive $\Delta S°$ is ascribed to the increase in freedom of the system due to desolvation from both β-CD and $TPPS_4$ upon complexation. Of course, dehydration from both host and guest also occurs in complexation of TMe-β-CD. Strong van der Waals interactions between guest and TMe-β-CD seem to hide the contribution of dehydration to the thermodynamic parameters.

^{13}C NMR Spectroscopy and ^{13}C Spin−Lattice Relaxation Times. To study the dynamic behavior of complexation of the 2:1 complex of TMe-β-CD and $TPPS_4$, ^{13}C NMR spectra and ^{13}C spin−lattice relaxation times (T_1) were measured. The ^{13}C NMR spectral changes of TMe-β-CD (0.1 M) were taken in D_2O as a function of $[TPPS_4]_0$, and the results are shown in Figure 5. Each signal was assigned by ^{1}H−^{13}C COSY and COLOC (correlation spectroscopy via long-range coupling spectrum). At $[TPPS_4]_0 < 0.05$ M ($[\text{TMe-}\beta\text{-CD}]_0/[TPPS_4]_0 < 2.0$), ^{13}C signals due to bound and free TMe-β-CD were detected independently. At $[TPPS_4]_0 = 0.05$ M ($[\text{TMe-}\beta\text{-CD}]_0/[TPPS_4]_0 = 2.0$), all signals were ascribed to the 2:1 complex of TMe-β-CD and $TPPS_4$. The signals due to the ^{13}C nuclei at the 1- and 4-positions (C-1 and C-4, respectively) markedly shift to lower magnetic fields upon complexation with $TPPS_4$. In aqueous solution, per-*O*-methylated CDs such as TMe-α- and TMe-β-CDs are more flexible than native CDs such as α- and β-CDs because of the absence of intramolecular hydrogen bonds.[21] Therefore, per-*O*-methylated CDs change their conformations upon inclusion of guests (induced-fit-type complexation).[21] It has been known that the signals due to C-1 and C-4 of TMe-β-CD shift most markedly upon inclusion of a guest.[22] In complexation with $TPPS_4$, TMe-β-CD changes its conformation to optimize the intermolecular interactions. Complexation-induced chemical shift changes (CIS, $\Delta\delta$) of native β-CD are shown in Figure 6, together with those of TMe-β-CD. All ^{13}C signals of β-CD are scarcely affected by $TPPS_4$, suggesting that the structure of β-CD is hardly altered upon complexation with $TPPS_4$. The structure of β-CD is stabilized by the intramolecular hydrogen bonding between the secondary OH groups at the 2-positions and at the 3-positions of adjacent glucopyranose units.[23]

The T_1 values of the ^{13}C nuclei of TMe-β-CD were determined by an inversion−recovery method. The inversion−recovery pattern (Supporting Information) was analyzed to obtain a T_1 value for each ^{13}C nucleus. The results are listed in

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Table 5. ^{13}C Spin−Lattice Relaxation Times (NT_1) of TMe-β-CD (0.1 M) in D_2O in the Absence and in the Presence of $TPPS_4$ and $ZnTPPS_4$ (0.05 M) at 25 °C

	NT_1/s								
system	C-1	C-2	C-3	C-4	C-5	C-6	C-2Me	C-3Me	C-6Me
TMe-β-CD	0.20	0.21	0.21	0.20	0.20	0.24	2.49	2.13	2.58
TMe-β-CD/$TPPS_4$	0.19	0.19	0.20	0.18	0.20	0.22	2.73	1.92	2.55
TMe-β-CD/$ZnTPPS_4$	0.20	0.20	0.21	0.19	0.20	0.23	2.70	2.06	2.61

Table 6. ^{13}C Spin−Lattice Relaxation Times (NT_1) of $TPPS_4$ and $ZnTPPS_4$ (0.05 M) in DMSO-d_6 and Those of $TPPS_4$ and $ZnTPPS_4$ (0.05 M) in D_2O in the Presence of TMe-β-CD (0.1 M) at 25 °C

	NT_1/s					
system	C^o	C_i^o	C^m	C_i^m	$C^{\beta py}$	$C_i^{\beta py}$
$TPPS_4$/DMSO-d_6	0.19		0.20			
$TPPS_4$/TMe-β-CD	0.15	0.17	0.15	0.17		
$ZnTPPS_4$/DMSO-d_6	0.21		0.21		0.15	
$ZnTPPS_4$/TMe-β-CD	0.15	0.19	0.16	0.18	0.15	0.16

Table 5 as NT_1 values, where N is the number of directly attached hydrogens. In the absence of $TPPS_4$, the NT_1 values of the ^{13}C nuclei (C-1−C-5) which are the components of the glucopyranose ring are almost constant (0.20−0.21 s). The NT_1 value of C-6 is larger than those of other nuclei because C-6 is the methylene carbon attached to the glucopyranose ring and has more freedom of motion as compared with the ring carbons. Upon complexation with $TPPS_4$, the NT_1 values of all carbon nuclei except for the methyl carbon at the 2-position (C-2Me) become smaller than those of TMe-β-CD alone. Although the changes in the NT_1 values are small, it may be concluded that the fluctuating motion of TMe-β-CD is reduced upon complexation with $TPPS_4$.

The T_1 values of $TPPS_4$ were also determined, and the results are summarized in Table 6. To observe the pyrrole β-carbon, the zinc(II) complex of $TPPS_4$ ($ZnTPPS_4$) was also used as the guest.[24] The signal of the pyrrole β-carbons of free base $TPPS_4$ is broadened because of tautomerism of the deuteriums attached to the pyrrole nitrogens. Since both $TPPS_4$ and $ZnTPPS_4$ aggregate spontaneously in D_2O at high concentration, the measurements of the relaxation times of these porphyrins were carried out in DMSO-d_6, which is more viscous than D_2O. The NT_1 values of the phenyl carbons of $TPPS_4$ and $ZnTPPS_4$ significantly decrease upon complexation with TMe-β-CD, suggesting that the rotational motion of the peripheral substituents is strictly restricted by inclusion. The NT_1 values of the carbons of the phenyl rings (C^o and C^m) which are located at the outside of the CD cavity are smaller than those of the phenyl rings (C_i^o and C_i^m) included in the CD cavity. There may be some probability of rotation for the phenyl rings included in the CD cavities, though the rotation of the phenyl rings sandwiched between two CD molecules is strictly inhibited. The NT_1 values of C^o and C^m of $TPPS_4$ and $ZnTPPS_4$ are 0.15−0.16 s, which are the same as the NT_1 values of the β-carbons of pyrroles ($C^{\beta py}$ and $C_i^{\beta py}$). The relaxation times of β-pyrrole reflect the motion of the whole complex. Therefore, it can be concluded that the rotational motion of the phenyl rings sandwiched by the CD molecules is completely restricted.

(24) $ZnTPPS_4$ also formed a very stable 2:1 complex with TMe-β-CD, and the K_1 and K_2 values in EG−H_2O (3:1) were $(8.2 \pm 4.3) \times 10^3$ and $(9.2 \pm 1.7) \times 10^3$ M^{-1}, respectively.

Discussion

The motivating interest in this work is the mechanism for interactions of charged guests with neutral CD hosts. There are several examples of inclusion of anionic guests to hydrophobic CD cavities.[25] In contrast, inclusion of cationic guests into CD cavities is scarcely known. A few studies[26−29] on inclusion of cationic guests into CD cavities suggest that a cationic guest can slip through a hydrophobic CD cavity to form pseudorotaxane, if the final inclusion complex is thermodynamically stable. Concerning the interactions of porphyrins having cationic peripheries with CD, Manka and Lawrence[2] reported first the 2:1 rotaxane-type complex of TPPOC3A and 2,6-DMe-β-CD in aqueous solution. In all of these cases, the cationic parts of the guests are located at the outside of the CD cavities. We found previously that TMPyP and TAPP, whose cationic peripheries are attached directly to the porphyrin ring, form very unstable complexes with any CD, though a corresponding anionic guest, $TPPS_4$, forms a very stable 2:1 complex with TMe-β-CD.[11,12] The TMe-β-CD-$TPPS_4$ complex is so stable that the formation of this 2:1 complex can be detected by means of MALDI-TOF MS (Supporting Information). These results suggest that the inside of a CD cavity is favorable for loading anionic guests but not for cationic ones. To generalize this feature of CD, we studied the interactions of cationic porphyrins having an ability to form pseudorotaxanes with CD in more detail. To the best of our knowledge, only one example has been reported with kinetics on complexation of ionic guests with CD, which shows that multicationic groups at the ends of a guest decelerate penetration of the guest into the β-CD cavity because of a repulsive interaction between the host and the guest.[29] Kinetic study will certainly provide definite evidence for ion selectivity of CD.

Since the K values for complexation of the porphyrins used in this study with TMe-β-CD in water were too large to be determined, the measurements were carried out in aqueous EG solutions. In the same solvent, the K_1 and K_2 values as well as the k_1 and k_2 values for the anionic porphyrins are much larger than those for the cationic ones. Both the k_1 and k_2 values for

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cationic TPPOC3Py in EG−H_2O (3:1) are over 1 order of magnitude smaller than those for anionic $TPPS_4$ and TPPOC3PS. These results clearly reveal that an anionic guest penetrates into the CD cavity more easily than does a cationic guest. What is the reason for such a difference in inclusion phenomena between anionic and cationic guests?

Solvation to a guest molecule may affect the rate of complexation. If cationic TPPOC3Py is solvated by the H_2O and/or EG molecules more strongly than anionic $TPPS_4$ or TPPOC3PS, the complexation of this cationic guest should proceed more slowly. However, it is unlikely. The energy required for desolvation from $TPPS_4$ or TPPOC3PS should be larger than that from TPPOC3Py, because the SO_3^- group in the anionic porphyrin is hydrated strongly through the hydrogen-bonding interaction.[30] We have to consider another mechanism. An answer may be derived by considering the microscopic polarity of the CD cavity. The electronegative oxygen atoms are regularly arranged at the upper and lower rims of the CD cavity. Since the numbers of the oxygen atoms on the primary OCH_3 group side (upper side) and on the secondary OCH_3 group side (lower side) of TMe-β-CD are 7 and 14, respectively, the inside of the CD cavity as well as the methyl groups at the rims seems to be polarized positively via an inductive effect. Mulliken's population obtained from the MOPAC calculation supports this assumption (Supporting Information). The negatively polarized charges on the ethereal oxygens at the rims of the CD cavity may be dispersed through hydrogen bonding with the water and/or EG molecules. Therefore, an anionic guest can penetrate into the positively polarized CD cavity. Meanwhile, the positively polarized rims and interior of the TMe-β-CD cavity may act as a barrier for penetration of a cationic guest. None of the porphyrins examined in the present study form complexes with TMe-β-CD in DMSO, though a relatively stable 2:1 complex with TPPOC3PS is formed in neat EG or methanol. Since no hydrogen bonds are formed between DMSO and TMe-β-CD, the anionic guest may be repelled by the negatively polarized rims of the CD cavity. It has been shown that 5,15-diphenylpoprhyrin, a neutral porphyrin, forms a trans-type 2:1 complex with 2,6-DMe-β-CD in DMSO.[31] It can be considered, therefore, that protic polar solvents such as H_2O, EG, and methanol play an important role in reducing the electrostatic repulsion between negatively charged guests and CD.

In all of the complexation processes of TMe-β-CD, both $\Delta H°$ and $\Delta S°$ show negative values. The thermodynamic data indicate the absence of participation of classic hydrophobic interactions in complexation. The negative and large $\Delta H°$ values can be interpreted in terms of the strong van der Waals interactions between host and guest. The larger $\Delta S°$ value for the second complexation step compared with that for the first step suggests that the reduction in the freedom of rotational motion in the first step is more serious than that in the second step. The restriction of rotational motion of the peripheral substituents of $TPPS_4$ upon complexation with TMe-β-CD is confirmed from the ^{13}C spin−lattice relaxation times. It is interesting that the rotational motion of the sulfonatophenyl groups sandwiched by two CD cavities is restricted more seriously than the rotational motion of those included by TMe-β-CD (Table 6).

The phenyl rings attached directly to the porphyrin ring are very important for stabilizing the complexes. All porphyrins which form stable TMe-β-CD complexes have such phenyl rings. Meanwhile, no complexes are formed in the cases of PC3Py and PC7Py (Table 1), whose meso positions are substituted by the alkyl groups with the pyridinium moiety at the terminals. The alkyl groups are too small to provide effective van der Waals contacts.[32] The effect of guest structure on complexation as well as the thermodynamic parameters clearly suggests strong van der Waals interactions between the host and the guest as the essential force for forming stable inclusion complexes. Diederich et al. proposed a mechanism for strong van der Waals interactions in aqueous solution.[33] The effects of EG on reduction in K value may be explained by Diederich's mechanism.

The thermodynamic parameters for complexation of $TPPS_4$ with native β-CD in water are completely different from those for complexation with TMe-β-CD. Namely, both of the complexation processes are driven by the positive $\Delta S°$ values. There are several examples of entropically dominated complexation of anionic guests with neutral or cationic CDs.[18−20] Such phenomena are explained by dehydration from both host and guest upon complexation, yielding an entropic gain.[18,20] Benz and co-workers measured the negative and large $\Delta H°$ and relatively small but positive $T\Delta S°$ for complexation of ionene-6,10 with α-CD. They claimed the participation of hydrophobic interactions in complexation.[28] If classic hydrophobic interactions contribute to the present complexation, then positive $\Delta S°$ should also be observed in the complexation of TMe-β-CD, which is more hydrophobic than β-CD. The dehydration from β-CD seems to play an important role in the present system. Such a drastic difference in thermodynamics between β-CD and TMe-β-CD causes the difference in inclusion phenomena of charged porphyrins and CDs.

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Supporting Information Available: ROESY spectra of the TMe-β-CD−$TPPS_4$ complex, ^1H NMR spectral changes of TMe-β-CD upon complexation with $TPPS_4$, van't Hoff plots for determination of $\Delta H°$ and $\Delta S°$ for the TPPOC3Py−TMe-β-CD system, the inversion−recovery pattern for determination of T_1 of the ^{13}C nuclei of the $ZnTPPS_4$−TMe-β-CD complex, MALDI-TOF MS of the $TPPS_4$−TMe-β-CD complex, ^1H NMR spectral changes of $TPPS_4$ upon complexation with β-CD, a table indicating reliability of the analytical method for determination of the rate constants, and the analytical data of TPPOC3PS and its precursors (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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