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Relation	

Controllable Direction of Porphyrin Derivatives in Two Cyclodextrin Cavities

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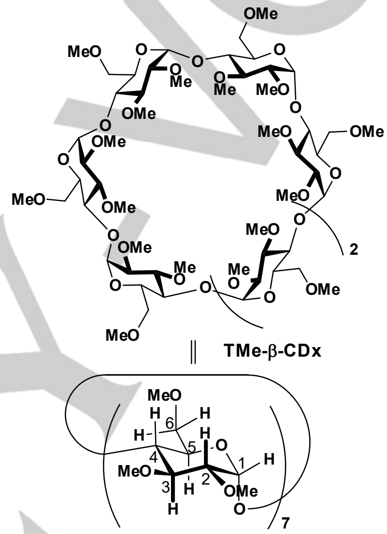
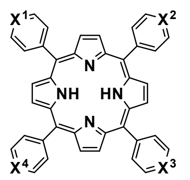
Abstract: Porphyrin•trimethyl-β-cyclodextrin (TMe-β-CDx) complexes have pseudorotaxane structures in which two *meso*-phenyl and/or pyridyl moieties penetrate the upper rim of two TMe-β-CDx molecules. Porphyrin derivatives with one to three pyridyl moieties at *meso*-positions formed complexes with TMe-β-CDx in which penetration of the upper rim of the two TMe-β-CDxs by the pyridyl moieties was minimized. In contrast, in TMe-β-CDx complexes formed with porphyrin derivatives with two 2-methoxyphenyl moieties and two pyridyl moieties, the pyridyl moieties penetrated the upper rim of the two molecules because steric hindrance prevented penetration by the 2-methoxyphenyl moieties.

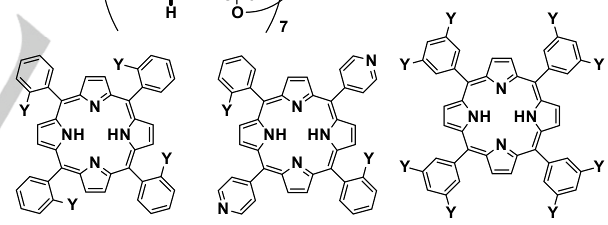
Introduction

Much research has focused on the preparation of water-soluble porphyrins for applications in various materials and medicines, including photosensitizers for DNA cleavage,[1–4] photodynamic cancer therapy,[5–8] photosynthetic systems,[9–11] and photocurrent generation.[12–16] The two most common water-soluble preparation methods are a chemical method, through introducing water-soluble substituents,[5–8,17] and a physical method, through mixing with water-soluble solubilizing agents.[18–21] The physical method using solubilizing agents has three advantages over the chemical method: (i) Various hydrophobic porphyrin derivatives can be used as guest molecules; (ii) many aqueous solutions of porphyrin derivative•solubilizing agent complexes are stable for several months; and (iii) complex functionalization can be





	X1	X2	X3	X4
1:	CH	CH	CH	CH
2:	N	CH	CH	CH
3:	N	N	CH	CH
4:	N	CH	N	CH
5:	N	N	N	CH
6:	N	N	N	N



7 (Y = -OMe) **8** (Y = -OMe) **9** (Y = -OMe)

Figure 1. Compound structures.

achieved by selecting appropriate solubilizing agents. Cyclodextrins, which comprise a chain of six to eight D-glucose monomers connected through the C1 and C4-positions, provide hydrophobic cavities for guest molecules as water-soluble solubilizing agents. In particular, porphyrin•trimethyl-β-cyclodextrin (TMe-β-CDx, comprising seven D-glucose monomers, Figure 1) complexes with pseudorotaxane structures, in which two *meso*-phenyl moieties penetrate the upper rim of two TMe-β-CDx molecules, have been formed using porphyrin derivatives with four phenyl substituents in the *meso*-positions.[20,22,23] When porphyrin derivatives with four phenyl moieties are incorporated into two TMe-β-CDx molecules, two types of phenyl moiety are present, namely, two penetrating the upper rim of the two TMe-β-CDx molecules and two sandwiched between the two TMe-β-CDx molecules. The functional groups in these phenyl moieties influence intracellular uptake. [8,24] These two types of phenyl

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moieties are predicted to have different interactions with cellular surfaces. Therefore, for medicinal applications, it is important to control the direction of functional porphyrin derivatives containing several types of phenyl groups within the two CDx cavities. In this study, we have investigated the preparation of TMe-β-CDx complexes with porphyrin derivatives containing phenyl and/or pyridyl moieties at the *meso*-positions. Furthermore, we determined the direction of these porphyrin derivatives in TMe-β-CDx complexes using ^{1}H NMR and X-ray crystallographic analysis.

Results and Discussion

Porphyrin derivative (**1**–**6**)•TMe-β-CDx complexes (Figure 1) were prepared according to a previously described procedure,[21–23] and their formation was confirmed using UV–Vis absorption and ^{1}H NMR spectroscopy (Figures 2, 3, and S1). The UV–Vis spectra of complexes **1**–**6**•TMe-β-CDx showed similar absorption maxima (λ_{max}). For example, **4**•TMe-β-CDx had an absorption maximum (λ_{max}) at 415 nm in water, corresponding to the Soret band of the porphyrin, and four bands at 510, 543, 588, and 642 nm, which were attributed to the porphyrin Q bands (Figure 2). No broadening of the absorption spectra of complexes **1**–**6**•TMe-β-CDx was observed (Figure 2). These results suggested that **2**–**6** existed in an isolated state in the two cyclodextrin cavities, in a similar manner to **1** in complex **1**•TMe-β-CDx (Figure 4). From the ^{1}H NMR spectra, the relative stoichiometry of **2**–**6** and TMe-β-CDx in complexes **2**–**6**•TMe-β-CDx was determined to be 1:2 based on the peak intensities of **2**–**6** and TMe-β-CDx (Figure S1).

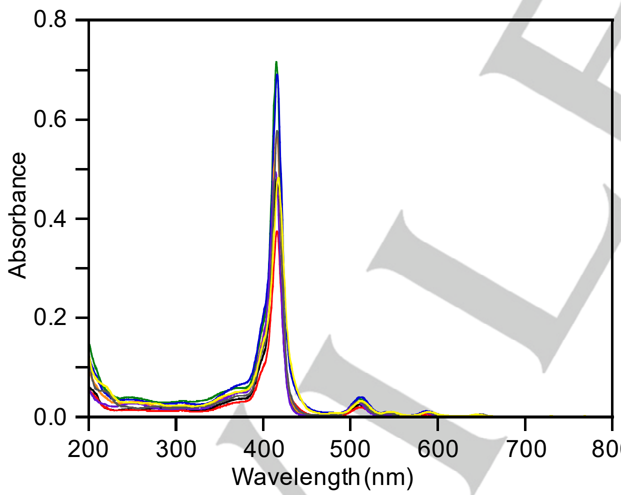

Figure 2. UV–Vis absorption spectra of (a) **1**•TMe-β-CDx (black line), **2**•TMe-β-CDx (red line), **3**•TMe-β-CDx (green line), **4**•TMe-β-CDx (blue line), **5**•TMe-β-CDx (orange line), **6**•TMe-β-CDx (purple line), **8**•TMe-β-CDx (yellow line), and **9**•TMe-β-CDx (grey line) complexes in D_2O at 25 °C ([Complex] = 0.02 mM, 1-mm cell).

Complexes **1**•TMe-β-CDx and **6**•TMe-β-CDx had only one conformation (Figure 4), with the same groups penetrating the upper rim of the two TMe-β-CDx molecules. One H-1 proton peak appeared in the ^{1}H NMR spectra of these complexes (Figures 1, 3b (red circle), and 3g (blue circle)). In contrast, complex **3**•TMe-β-CDx had only one conformation (Figure 4), but with different groups (pyridyl and phenyl) penetrating each upper rim. Therefore, two H-1 proton peaks appeared for complex **3**•TMe-β-CDx (Figure 3d, red and blue circles), suggesting that the H-1 proton peaks were separated due to both pyridyl and phenyl groups penetrating the upper rim of the two TMe-β-CDx molecules. Downfield (blue circle) and upfield (red circle) peaks were assigned to the H-1 proton peak of TMe-β-CDx penetrated by pyridyl and phenyl groups, respectively, by comparing the chemical shifts with those of complexes **1**•TMe-β-CDx and **6**•TMe-β-CDx. Complexes **2**•TMe-β-CDx, **4**•TMe-β-CDx, and **5**•TMe-β-CDx had two possible conformations. However, the ^{1}H NMR spectra of complexes **2**•TMe-β-CDx and **4**•TMe-β-CDx contained only one peak assigned to the H-1 proton of TMe-β-CDx penetrated by a phenyl group (Figures 3c and 4e, red circles). These results suggested that only phenyl groups penetrated the upper rim of the two TMe-β-CDx molecules in complexes **2**•TMe-β-CDx and **4**•TMe-β-CDx. In the ^{1}H NMR spectrum of **5**•TMe-β-CDx, two peaks were assigned to H-1 proton peaks of TMe-β-CDx penetrated by pyridyl and phenyl groups (Figure 3f, red and blue circles). This result suggested that one phenyl and one pyridyl group penetrated the upper rims of the two respective TMe-β-CDx molecules in the **5**•TMe-β-CDx complex. This indicated that complexes **2**•TMe-β-CDx, **4**•TMe-β-CDx, and

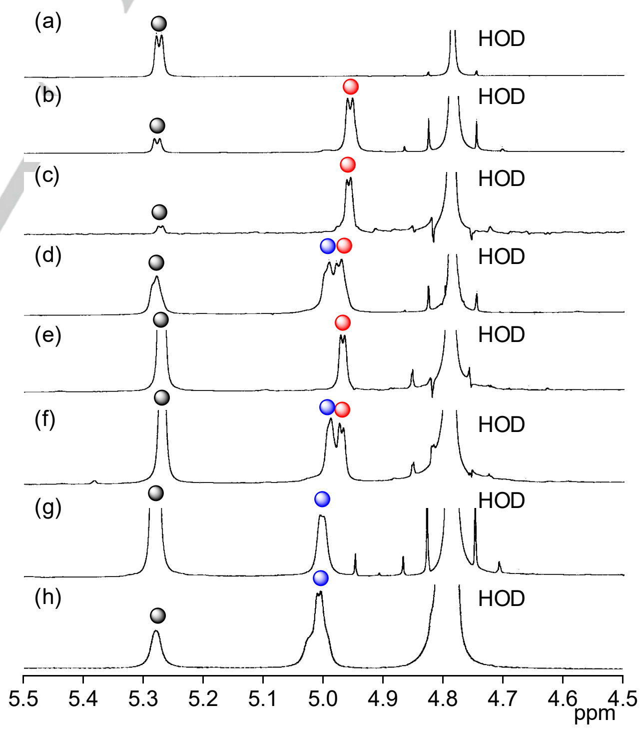

Figure 3. Partial ^{1}H NMR spectra of (a) TMe-β-CDx, (b) **1**•TMe-β-CDx, (c) **2**•TMe-β-CDx, (d) **3**•TMe-β-CDx, (e) **4**•TMe-β-CDx, (f) **5**•TMe-β-CDx, (g) **6**•TMe-β-CDx, and (h) **8**•TMe-β-CDx complexes in D_2O at 25 °C (●: free TMe-β-CDx, ●: TMe-β-CDx penetrated by benzene moieties in the complex, ●: TMe-β-CDx penetrated by pyridine moieties in the complex).

5•TMe-β-CDx each formed only one major conformer (b', d', and e' in Figure 4, respectively). Therefore, the phenyl group penetrated the upper rim of TMe-β-CDx more readily than the pyridyl group.

To further confirm that the conformation of complex **4**•TMe-β-CDx was structure d' (Figure 4), its 2D ^{1}H–^{1}H COSY and NOESY spectra were measured (Figures 5, S2, and S3). Peaks of **4** in complex **4**•TMe-β-CDx were assigned using the 2D ^{1}H–^{1}H COSY spectrum (Figures 5a and S2), and the 2D ^{1}H–^{1}H NOESY spectrum was used to determine the correlation between protons of **4** and TMe-β-CDx in complex **4**•TMe-β-CDx (Figures 5b and S3). Figure 5b shows cross peaks between phenyl protons H^3, H^4, and H^5 of **4** and H-3, H-4, OMe^3, and OMe^4 protons in the lower rim of TMe-β-CDx. In contrast, cross peaks were observed between pyridyl protons H^6 and H^7 of **4** and H-6 and OMe^6 protons in the upper rim of TMe-β-CDx, indicating that pyridyl moieties penetrated the upper rim of TMe-β-CDx. Therefore, the NOESY spectrum clearly showed that complex **4**•TMe-β-CDx complex comprised conformation d', as shown in Figure 4 in aqueous solution. This conclusion was consistent with the prediction based on the H-1 proton peak of TMe-β-CDx.

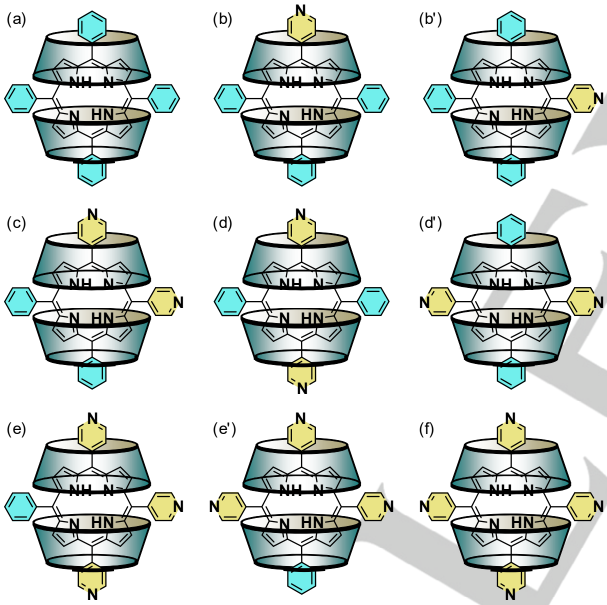

Figure 4. Schematic illustrations of all possible conformations of porphyrin derivative (**1**–**6**)•TMe-β-CDx complexes.

We next investigated why the phenyl group penetrated the upper rim of TMe-β-CDx more readily than the pyridyl group. Kano *et al*. reported that cationic porphyrin derivatives, such as 5,10,15,20-tetrakis-(1-methyl-4-pyridyl)-21*H*,23*H*-porphine tetrachloride salt or 5,10,15,20-tetrakis(4-*N*-trimethylaminobenzyl)-21*H*,23*H*-porphine tetrachloride salt, hardly interacted with TMe-β-CDx, in contrast to anionic porphyrins.[24] They concluded that, in general, the microscopically positive environment of the CDx cavity seemed to promote penetration by anionic guest molecules, but prohibited incorporation of cationic guest molecules into the CDx cavity.[24] Phenyl groups in the *meso*-position of **4** were very close to H-6 protons of TMe-β-CDx in the X-ray crystal structure of the **4**•TMe-β-CDx complex. Although **4** is a neutral compound, pyridyl protons at the *meso*-position of **4** have a δ+ charge due to resonance structures, as shown in Figure S4. Therefore, if a pyridyl moiety penetrates the upper rim of TMe-β-CDx, electrostatic repulsion may arise between pyridyl and H-6 protons, which both have δ+ charges.

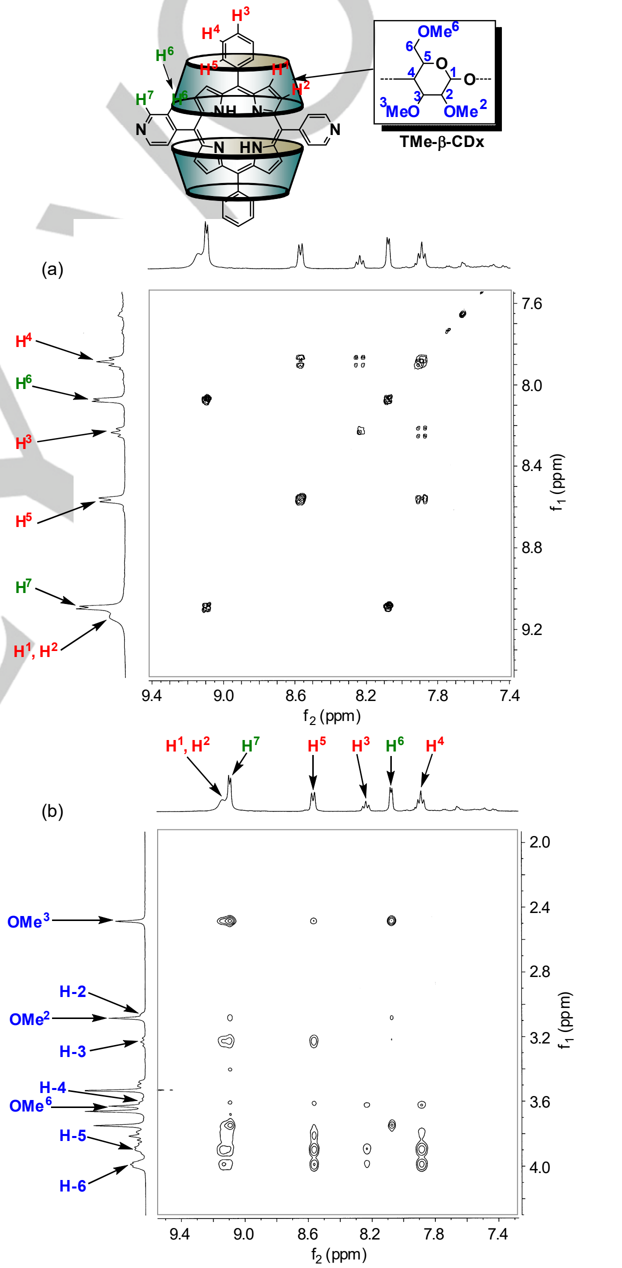

Figure 5. (a) 2D ^{1}H–^{1}H COSY and (b) 2D ^{1}H–^{1}H NOESY spectra of **4**•TMe-β-CDx in D_2O at 25 °C.

To control the direction of the porphyrin derivatives, we synthesized **7** and **8** (Figures S5 and S6) containing 2-methoxyphenyl moieties in the *meso*-position. We expected the 2-methoxyphenyl moiety to be prevented from penetrating the upper rim of TMe-β-CDx by steric hindrance. However, as confirmed by UV–Vis absorption and ^{1}H NMR spectra, TMe-β-CDx complexation with **7** containing four 2-methoxyphenyl moieties was scarce in water (Figures S7 (black line) and S8). In contrast, porphyrin **9**, containing four 3,5-dimethoxyphenyl moieties, was able to form a complex with TMe-β-CDx (Figures 2 (grey line), S7 (blue line), and S9), indicating that methoxy groups in the 3 and 5-positions did not inhibit complexation. However, porphyrin **8**, containing two 2-methoxyphenyl moieties in a *trans* configuration, formed a complex with TMe-β-CDx (Figures 2 (yellow line) and S7 (red line)). The conformation of complex **8**•TMe-β-CDx was confirmed by 1D ^{1}H NMR and 2D ^{1}H–^{1}H COSY and NOESY spectra (Figures 3h, 6, S10, S11, and S12). The ^{1}H NMR spectra of complex **8**•TMe-β-CDx were complicated (Figure S10) because two atropisomers were present, but peaks were assigned using 2D ^{1}H–^{1}H COSY and NOESY spectra (Figures 6, S11, and S12). As shown in Figure 3h, the presence of only one H-1 proton peak in complex **8**•TMe-β-CDx clearly indicated that the conformation was either d or d' in Figure 4. The broadening of the H-1 peak was probably due to the presence of two atropisomers. The chemical shift of the peak was close to that of complex **6**•TMe-β-CDx. These results suggested that two 2-methoxyphenyl moieties of **8** did not penetrate the upper rim of TMe-β-CDxs, but interposed the two TMe-β-CDxs, as shown in conformation d in Figure 4.

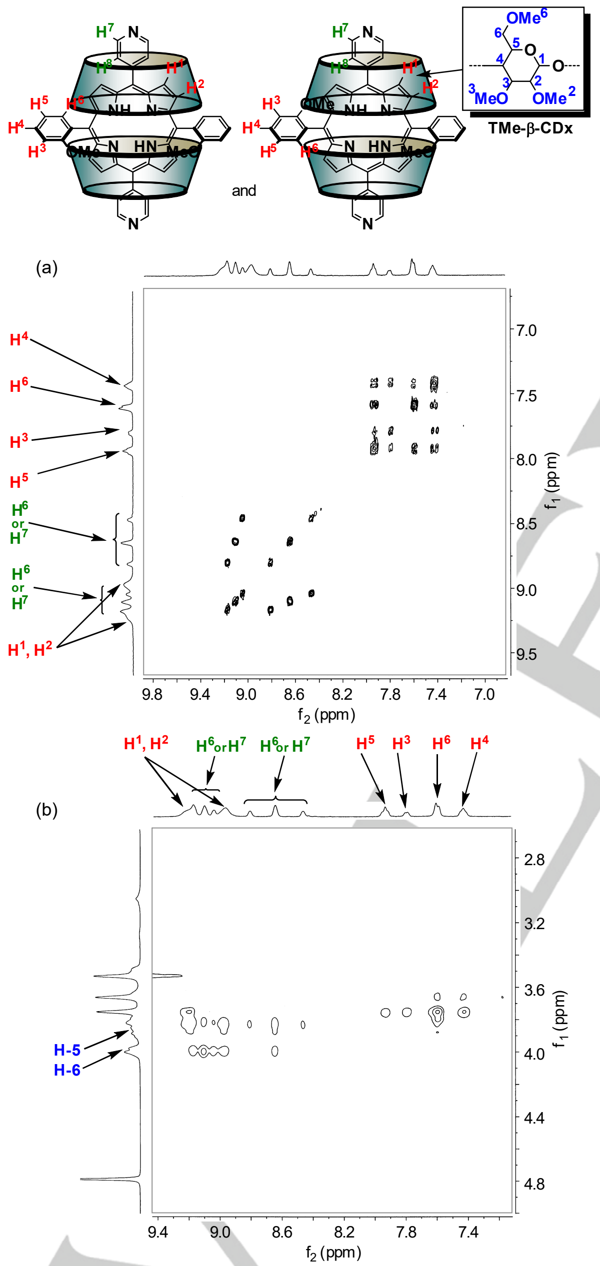

Figure 6. (a) 2D ^{1}H–^{1}H COSY and (b) 2D ^{1}H–^{1}H NOESY spectra of **8**•TMe-β-CDx in D_2O at 35 °C.

To confirm these conformations, single crystals of complexes **4**•TMe-β-CDx and **8**•TMe-β-CDx were submitted to X-ray crystallographic analysis (Table S2). These single crystals were grown by incubation in water at 50 °C according to a previously described procedure (Figures 7, S13, and S14).[22,23] The crystals of complexes **4**•TMe-β-CDx and **8**•TMe-β-CDx showed 1:2 stoichiometry. Phenyl and pyridyl moieties in complex **4**•TMe-β-CDx were determined by comparison with the bond lengths and angles of benzene and pyridine reported previously (Tables 1 and S3).[25,26] Complex **4**•TMe-β-CDx had a conformation in which the two phenyl moieties penetrated the TMe-β-CDx molecules (structure d' in Figure 4). In contrast, complex **8**•TMe-β-CDx had a conformation in which the two pyridyl moieties penetrated the TMe-β-CDx molecules (structure d in Figure 4). These results were consistent with the conformations determined by ^{1}H NMR spectra in water.

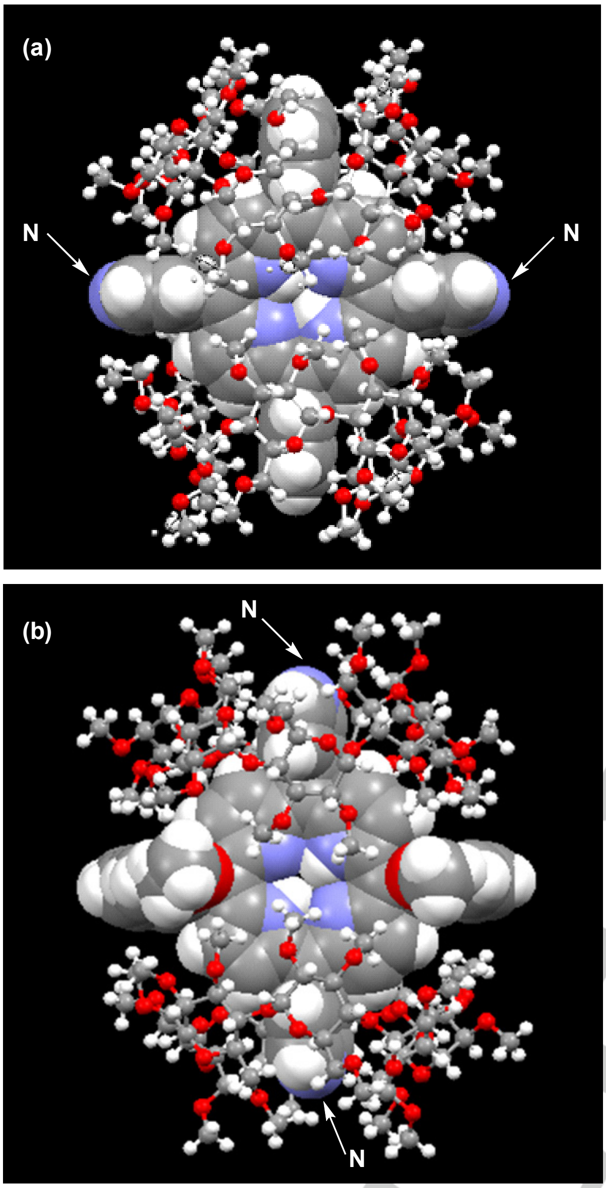

Figure 7. X-ray structures of (a) **4**•TMe-β-CDx and (b) **8**•TMe-β-CDx complexes.

Table 1. Bond lengths and bond angles in **4**•TMe-β-CDx complexes.

Bond	Bond length (Å)	Angle	Bond angle (°)
Average dC(para)–C(meta)	1.362(12) (1.361)[a]	Averaged C(meta)–C(para)–C(meta)	118.8(7) (120±0.63)[a]
Averaged C–N	1.340(11) (1.335)[b]	Averaged C–N–C	116.7(7) (117.67)[b]

[a] Values in parentheses indicate the bond lengths or angles of benzene from Refs. 25 and 26. [b] Values in parentheses indicate bond lengths or angles of pyridine from Refs. 25 and 26.

Conclusions

When four porphyrin derivatives (**2**–**5**) with phenyl and pyridyl moieties at the *meso*-positions formed complexes with two TMe-β-CDx molecules, the phenyl moieties preferentially penetrated the upper rim of TMe-β-CDx because penetration by pyridyl moieties was less stable owing to electrostatic repulsion. Therefore, complexes **2**•TMe-β-CDx and **4**•TMe-β-CDx adopted only one conformation in which the pyridyl moieties did not penetrate the upper rim of TMe-β-CDx. Furthermore, complexes **3**•TMe-β-CDx and **5**•TMe-β-CDx adopted only one conformation to minimize the number of pyridyl moieties penetrating the upper rim of TMe-β-CDx. In contrast, compound **8**, containing two 2-dimethoxyphenyl and two pyridyl moieties in a *trans* configuration, formed a complex in which the two pyridyl moieties preferentially penetrated the upper rim owing to steric hindrance preventing penetration by the two 2-methoxyphenyl moieties. These results showed that the molecular direction of porphyrin derivatives in the two cyclodextrins was controllable.

Experimental Section

Materials

Compounds **1** and **6** were purchased from Tokyo Chemical Industries Co. Ltd. (Tokyo, Japan) and Sigma-Aldrich Chemical Co., Inc. (St. Louis, MO, USA), respectively. TMe-β-CDx was purchased from Wako Pure Chemical Industries Ltd. (Tokyo, Japan). Compounds **2**–**5**,[27] **7**,[28] and **9**[29] were synthesised using methods previously described in the literature.

5,15-Bis(2-methoxyphenyl)-10,20-di(pyridin-4-yl)porphyrin (**8**)

4-[Di(1H-pyrrol-2-yl)methyl]pyridine (223.3 mg, 1.00 mmol), 2-methoxybenzaldehyde (136.1 mg, 1.00 mmol), and trifluoroacetic acid (620 μL, 8.0 mmol) were dissolved in dichloromethane (130 mL) and stirred while purging with nitrogen for at least 30 min. The reaction mixture was stirred for 1 h at room temperature followed by the addition of triethylamine (115 μL, 8.0 mmol). The reaction mixture was evaporated and dioxane (150 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 680 mg, 3.0 mmol) were added. After heating at reflux for 2 h, more DDQ (225 mg, 1.0 mmol) was added and reflux continued for 1 h. The solution was then cooled to room temperature and evaporated to dryness. The residue was purified three times by column chromatography on silica gel using chloroform/methanol (19:1, v/v) and chloroform/hexane (19:1 and 9:1, v/v), respectively, as eluents. After solvent evaporation, the resultant purple solid was washed with acetone. Yield, 3% (mixture of two atropisomers); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, in ppm): δ 9.02 (d, J = 5.6 Hz, 4H; 3,5-Py), 8.84 (d, J = 4.7 Hz, 4H; β-H (methoxy side)), 8.76 (d, J = 4.7 Hz, 4H; β-H (methoxy side)), 8.16 (d, J = 4.3 Hz, 4H; 2,6-Py), 8.00 (m, 2H; 2-methoxy-Ph), 7.80 (m, 2H; 4-methoxy-Ph), 7.39–7.34 (m, 4H; 3,5-methoxy-Ph), 3.61 and 3.60 (s, 6H; -OMe), 2.76 (br s, 2H; NH); UV/Vis ($CHCl_3$): λ_{max} = 419, 515, 548, 588, and 646 nm; HR-ESI-MS: *m/z* calcd. for $[C_{44}H_{33}N_6O_2]^+$: 677.26595; found: 677.26630 $[M]^+$.

Preparation of TMe-β-CDx complexes of **1**–**9**

Compound **1** (1.8 mg, 3.0 × 10^{-6} mol) and TMe-β-CDx (8.6 mg, 6.0 × 10^{-6} mol) were placed in an agate capsule with two agate-mixing balls, and the resulting mixture was vigorously agitated at 30 Hz for 20 min using a high-speed vibration mill (MM 200; Retsch Co., Ltd., Haan, Germany). The solid mixture was suspended in pure water (1.5 mL) to produce a dark purple emulsion. Subsequent centrifugation (18,000 ×g, 25 °C, 20 min) removed nondispersed **1** from the solution. The concentration of **1** in the **1**•TMe-β-CDx complex was determined to be 2.36 mM by measuring the absorbance of the solution at 415 nm in water (molar absorption coefficient of water-soluble complex **1**•TMe-β-CDx, ε_{415} = 3.30 × 10^4 dm^3 mol^{-1} cm^{-1}). TMe-β-CDx complexes of porphyrins **2**–**9** were also prepared using the above procedure.

Crystallization of TMe-β-CDx complexes of **4** and **8**

Aqueous solutions of **4**•TMe-β-CDx and **8**•TMe-β-CDx complexes (1.5 mL) were prepared using the above procedure. Dark red crystals formed after leaving the final solutions to stand for 1–2 days at 50–60 °C.

Crystallographic study

X-ray diffraction data for **4**•TMe-β-CDx and **8**•TMe-β-CDx complexes were collected with a Bruker APEX II ULTRA system using MoKα radiation at 223 K and 173 K, respectively. A total of 19,315 and 46,518 reflections were collected, of which 19,315 and 30,011 were unique, for **4**•TMe-β-CDx and **8**•TMe-β-CDx complexes, respectively. All calculations were performed using the Bruker SAINT crystallographic software package except for refinement, which was performed using SHELXL. Crystallographic data for these structures have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1822743 and 1822742.

UV–Vis Absorption Spectra

UV–Vis spectra were recorded using a UV-3600PC spectrophotometer (Shimadzu Corp., Kyoto, Japan). All experiments were performed at 25 °C in a 1-mm cell.

Acknowledgements

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Conflict of interest

The authors declare no conflicts of interest.

Keywords: porphyrins • cyclodextrins • host–guest systems • molecular recognition

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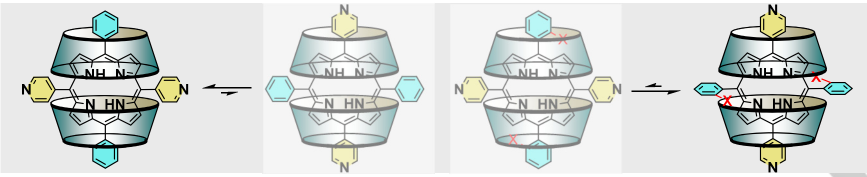

When porphyrin derivatives with one to three pyridyl moieties in the *meso*-position are incorporated into two trimethyl-β-cyclodextrins, their direction is controlled by steric hindrance of the phenyl moieties in the *meso*-position.

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Controllable Direction of Porphyrin Derivatives in Two Cyclodextrin Cavities