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A Calix[4]arene-porphyrinatozinc Conjugate which Features the Cooperative Action of a Cation-π Interaction and Metal Coordination

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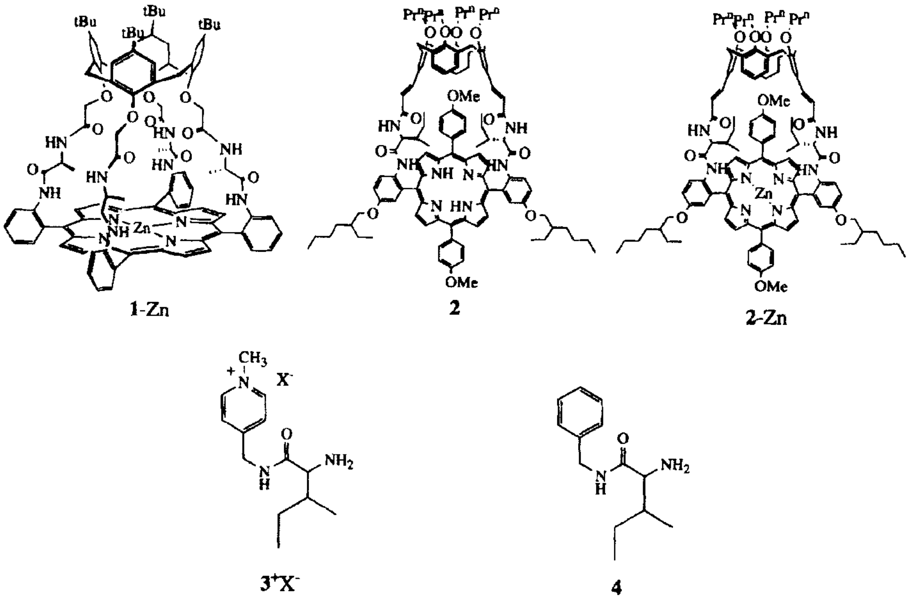
A calix[4]arene(cone)-capped tetraphenylporphyrinatozinc (2-Zn) in which two distal-phenyl *p*-positions in calix[4]arene are linked to two distal *meso*-phenyl groups in tetraphenylporphyrinatozinc was synthesized *via* 12 steps. This calix[4]arene-porphyrinatozinc conjugate showed a high affinity toward a guest molecule, C-(1-methylpyridinium-4-methylamino)-L-isoleucine owing to a cooperative action of the cation-π interaction between the calix[4]arene cavity and the 1-methylpyridinium moiety and the coordination of the amino group to Zn(II).

Keywords: Calixarene, porphyrin, cation-π interaction, cooperative action, cage molecule

It has been shown that supramolecular porphyrins with higher-order structures act not only as unique molecular recognition sites but also as enzyme-mimicking catalytic sites [1]. Of particular interest is a family of capped porphyrins which can mediate binding of small molecules, oxygenation of olefins, shape-selective molecular recognition, *etc.* [2]. When one wishes to add the function of chiral discrimination to capped porphyrins, they should of course be chiral and, desirably, retain high molecular symmetry to achieve high enantiomeric selectivity: this situation is well demonstrated by the importance of C_2 symmetry in asymmetric syntheses. As an attempt to design functionalized porphyrins with high symmetry, we previously synthesized a calix[4]arene-capped porphyrin (compound **1**: see Scheme 1 for the structure) [3, 4]. This compound retains high C_4 symmetry. Its Zn(II) complex (**1**-Zn) showed a very interesting binding property that the metal-binding site in the calix[4]arene lower rim and the coordination site in the porphyrinatozinc moiety act cooperatively to specifically trap KI to the inner cavity of **1**-Zn [3]. However, the cavity was too small to accept organic guest molecules and too rigid to metallate the porphyrin with transition metals other than Zn(II) [3].

To obtain an enlarged cavity between a calix[4]arene and a porphyrin the molecular-design strategy was reconsidered. The first improved point is that the upper rim (open side of calix[4]arene) is used for the connection in order to create a large inner sphere. In **1** using the lower rim (closed side of calix[4]arene) the

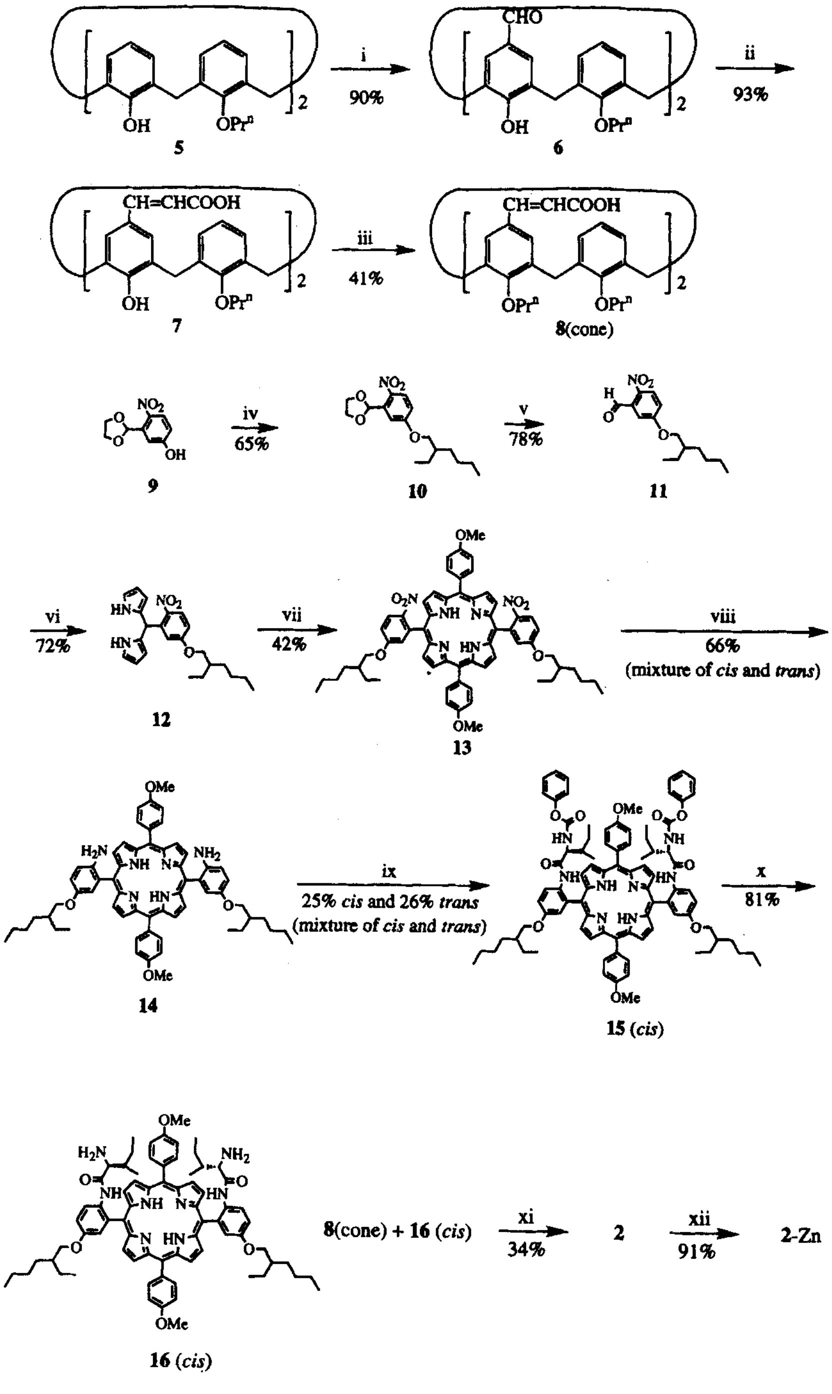


SCHEME 1 Structures of calix[4]arene-porphyrin conjugates and substrates.

cavity is pinched at the lower rim. The second improved point is to insert spacers (—CH = CH—CO—) into the *p*-positions of the upper rim. Since the synthesis of a four-pillared calix[4]arene-porphyrin conjugate seemed relatively difficult, we decided to begin with a two-pillared one (compound **2**). Examination of CPK molecular models reveals that the inner sphere is large enough to accept α-amino acid derivatives. We have found that **2** can be synthesized *via* 12 steps and **2**-Zn includes substrate **3**$^+$ utilizing both the cation-π interaction between the calix[4]arene cavity and the pyridinium group and the coordination of the amino group to Zn(II) [5].

Compounds **2** and **2**-Zn were synthesized according to Scheme 2. Compound **2** (mp 135.2 °C) was identified by ^{1}H NMR, Mass (positive SIMS, $[M+1]^+$ 1884) [6] and Uv-visible absorbance [7] spectra and elemental analysis [8]. Compound **2**-Zn (mp 161.5 °C) was identified by ^{1}H NMR and Uv-visible absorbance [9] spectra and elemental analysis [10]. Two 2-ethylhexyl groups were introduced in order to enhance the solubility of **2** into organic solvents. L-Isoleucine was chosen for both the solubility and the moderate steric crowding around the cavity.

To obtain an insight into the binding site of **2**-Zn for substrates **3**$^+$X$^-$ and **4** we characterized the 1:1 mixtures with NOE in ^{1}H NMR spectroscopy (400 MHz, $CDCl_3$: CD_3OD = 12:1 v/v, 25 °C). When the benzyl ($PhCH_2$) protons in **4** (4.43 ppm) were irradiated, only the NOE peak for the *o*-protons appeared at 7.25 ppm. When the pyridiniummethylene (Py^+CH_2) protons in **3**$^+$Cl$^-$ (4.42 and 4.83 ppm) were irradiated, the appearance of several NOE peaks was observed but they were mostly broadened. The result suggests that the molecular motion of **3**$^+$Cl$^-$ is significantly suppressed in the presence of **2**-Zn. We thus repeated the NOE measurement at −40 °C. As shown in Figure 1, the NOE peaks for the *m*-protons (6.31 ppm) and the CH = CH protons (5.36 and 6.09 ppm) in **2**-Zn as well as those for the 2- and 3-pyridinium protons (8.79 and 8.09 ppm) in **3**$^+$Cl$^-$ appeared with respect to the 4.83 ppm Py^+CH_2 proton. These results consistently support the view that **4** is bound to Zn(II) in **2**-Zn from the exogeneous direction whereas



SCHEME 2 (i) Cl_2CHOMe, $SnCl_4$ in $CHCl_3$; (ii) $CH_2(COOH)_2$, piperidine in pyridine; (iii) Pr^nI, NaH in DMF; then, 15% Me_4NOH in THF (for the hydrolysis of the propyl esters); (iv) 2-ethyl-1-bromohexane, KI, K_2CO_3 in acetone; (v) 60% $HClO_4$ (15 ml) in THF (50 ml); (vi) pyrrole, CF_3COOH; (vii) *p*-anisaldehyde, BF_3OEt_2 in CH_2Cl_2-EtOH (150:1 v/v); then, 2,3-dichloro-5,6-dicyanobenzoquinone; (viii) $SnCl_2{\cdot}2H_2O$ in 1,4-dioxane-conc. HCl (1:1 v/v); (ix) *N*-carbobenzyloxy-L-isoleucine, 1-isopropyl-3-(3-dimethylaminopropyl)-carbodiimide, 1-hydroxybenzotriazole in THF; then, column chromatography (silica gel, $CHCl_3$); (x) BF_3OEt_2, Me_2S in CH_2Cl_2; (xi) for **8**(cone), $(COCl)_2$ in CCl_4; then, **16** (*cis*), NEt_3 in THF; (xii) $Zn(CH_3COO)_2{\cdot}2H_2O$ in DMF.

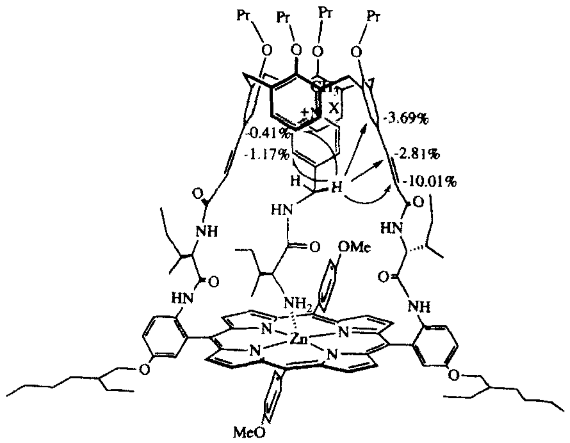


FIGURE 1 NOE peak intensities for a 1:1 mixture of 2-Zn and $3^{+}Cl^{-}$ (5 m mol dm^{-3} each) with respect to the 4.83 ppm $Py^{+}CH_2$ proton: 400 MHz, $CDCl_3$: CD_3OD = 12 : 1 v/v, −40°C).

$3^{+}Cl^{-}$ is bound inside the cavity by a cooperative action of the cation-π interaction between the calix[4]arene moiety and the pyridinium ring and the coordination of the amino group to Zn(II). Examination of CPK molecular models reveals that when the amino group of 3^{+} coordinates to Zn(II) in the porphyrin center, the *N*-methylpyridinium moiety can be exactly included in the calix[4]arene cavity and that the $Py^{+}CH_2$ methylene protons exist in the close vicinity of the CH = CH group.

Association constants (K) were estimated by an absorption spectroscopic method. Figure 2 shows a spectral change in the Soret band induced by added *n*-butylamine. It is seen from Figure 2 that the Soret band (λ_{max} 432 nm) increases with increasing *n*-butylamine concentration with an isosbestic point at 428 nm. The K was determined from the analysis of a plot of A_{432} *vs.* n-butylamine concentration according to a Benesi-Hildebrand equation: $K = 3.7 \times 10^3$ dm^3 mol^{-1}. The spectral change induced by added $3^{+}Ph_4B^{-}$ (Ph_4B^{-} was used to solubilize 3^{+} into the CH_2Cl_2 solution) or **4** was similar to that shown in Figure 2. The K values were estimated to be 7.9×10^3 dm^3 mol^{-1} for $3^{+}Ph_4B^{-}$ and 1.3×10^3 dm^3 mol^{-1} for **4**. We believe that the cooperative action of the cation-π interaction and the Zn(II) coordination between **2-Zn** and 3^{+} is responsible for the greater K of 3^{+} relative to **4**.

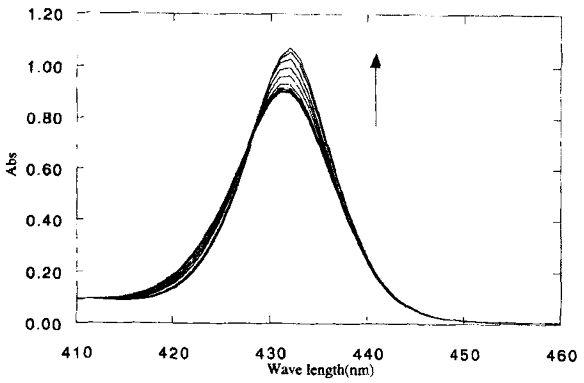


FIGURE 2 Spectral change in the Soret band of **2-Zn** (2.5×10^{-6} mol dm^{-3}) induced by added *n*-butylamine: 25 °C, [*n*-$BuNH_2$] = 0 ~ 2.5×10^{-3} mol dm^{-3}, CH_2Cl_2.

Further applications of the present system to the electron-transfer from the porphyrin to quenchers bound to the calix[4]arene cavity, the D- *vs.* L-isomer discrimination of α-amino acid substrates, the cooperative action for the binding of CsI [3], the catalytic hydrolysis of acetylcholine, *etc.* are currently continued in these laboratories. The emerging data suggest that **2-Zn** bearing a π-basic cavity and a Lewis-acidic metal as well as two chiral pillars behaves as a unique host molecule for molecular recognition.

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[6] By preparative TLC separation (silica gel, chloroform-ethyl acetate = 40:1 v/v) two compounds were isolated. The first compound with $R_f = 0.11$ was **2**. The second compound obtained in 3% yield with $R_f = 0.16$ gave *z/e* 3767 in positive SIMS. This molecular weight corresponds to a 2 + 2 adduct ($[2M + 1]^+$).

[7] UV-vis (CH_2Cl_2) λ_{max} (ε) 424.0 (201120), 517.0 (10780), 555.5 (7080), 592.5 (4310) and 648.5 (1980).

[8] Found: C, 72.62; H. 7.35; N, 5.41%. Calcd for $C_{120}H_{138}N_8O_{12}\cdot 5.5H_2O$: C, 72.66; H, 7.57; N, 5.65%.

[9] UV-vis (CH_2Cl_2) λ_{max} (ε) 431.5 (321760), 561.0 (14400) and 603.0 (5990).

[10] Found: C, 71.41; H. 7.47; N, 4.93%. Calcd for $C_{120}H_{136}N_8O_{12}Zn\cdot 4.0$; H_2O: C, 71.36; H, 7.19; N, 5.55%.