

Design and synthesis of a C_4 -symmetrical hard-soft ditopic metal receptor by calixarene-porphyrin coupling

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A tetraphenylporphyrin capped with a calix[4]aryl amide through L-alanine pillars (compound **1**) has been synthesized. Owing to C_4 symmetry in both the tetraphenylporphyrin and the calix[4]arene this molecule still retains C_4 symmetry. As the calix[4]aryl amide moiety can bind alkali metal cations, and the porphyrin moiety can bind transition metal cations, compound **1** acts as a host molecule with a hard-soft ditopic metal-binding site. It was found that the Zn^{II} complex of **1** (complex **1**· Zn^{II}) can bind KI very strongly with $\log K_{ass} = 5.23$ ($CHCl_3$:MeCN = 4:1 v/v; 25 °C) whereas $KClO_4$ is scarcely captured by **1**· Zn^{II} . Absorption and fluorescence spectroscopic studies showed that I^- ion is bound to this cavity, interacting with both calix[4]arene-bound K^+ through electrostatic attraction and porphyrin-bound Zn^{II} through coordination as an axial ligand. The results establish that complex **1**· Zn^{II} acts as a unique ditopic receptor for I^- ion.

Introduction

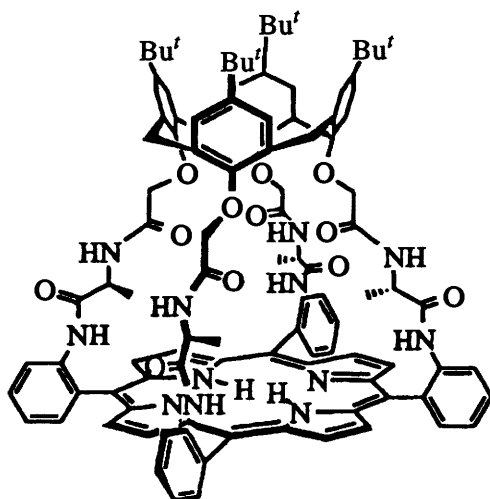
It has been shown that supramolecular porphyrins with higher-order structures act not only as unique molecular recognition sites but also as enzyme-mimicking catalytic sites.¹ Of particular interest is a family of capped porphyrins which can mediate the binding of small molecules, the oxygenation of olefins, 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. Porphyrins *a priori* have C_4 symmetry, so that the expeditious answer to this requirement is to use a C_4 -symmetric cap. Bruce and co-workers³ synthesized porphyrins capped with a 1,2,4,5-tetra-substituted benzene but the molecular symmetry was reduced to C_2 symmetry. Cyclodextrin-capped porphyrins were also synthesized⁴ but these compounds lose almost all molecular symmetry. We noticed that calix[4]arene-25,26,27,28-tetraols, cyclic tetramers made from phenol and formaldehyde, exactly satisfy this requirement because they apparently possess C_4 -symmetry. This idea prompted us to design a calix[4]arene-capped

porphyrin. We chose compound **1** as a synthetic target because this compound has several novel structural characteristics: that is, (i) it has neat C_4 symmetry, (ii) a porphyrin ring is linked to a calix[4]arene ring by four chiral pillars, and (iii) an alkali-metal binding site composed of four OCH_2CO groups and a transition-metal-binding site composed of a porphyrin are closely combined together within a molecule. We here report the synthesis of the first calix[4]arene-capped porphyrin, its spectroscopic properties, and preliminary studies on molecular recognition.⁵

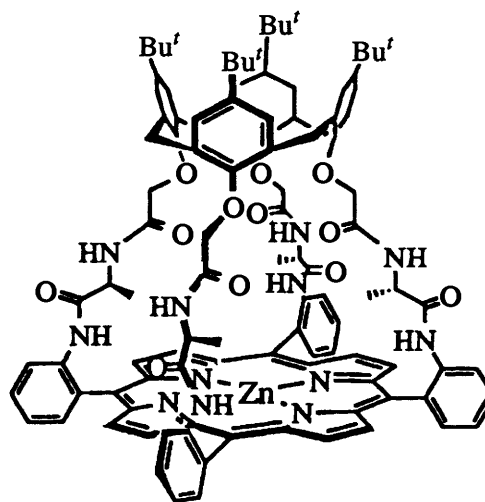
Results and discussion

Syntheses

Calix[4]arenes have a skirt-like architecture. As the edge-to-edge distance of the open upper rim is comparable to the distance between two distal phenyl units in tetraphenylporphyrins, we first planned to introduce functional groups for coupling (*e.g.*, CO_2H) into the upper rim. The literature teaches us, however, that the synthesis of the desired compounds is rather difficult⁶. In contrast, the CO_2H groups can be readily introduced into the lower rim by the reaction of calix[4]arene-



1



1· Zn^{II}

Table 1 Association constants ($\log K_{\text{ass}}$) for compound **1** and complex **1**·Zn^{II} for alkali metal salts ($M^+ X^-$) at 25 °C^a

| M ⁺ | 1 | | 1 ·Zn ^{II} | |
|-----------------|--|---------------------------------|--|---------------------------------|
| | X ⁻ = ClO ₄ ⁻ | X ⁻ = I ⁻ | X ⁻ = ClO ₄ ⁻ | X ⁻ = I ⁻ |
| Li ⁺ | 3.54 ^c | <i>b</i> | 4.84 | <i>b</i> |
| Na ⁺ | 3.10 | 3.20 | 3.69 | 3.91 |
| K ⁺ | <2 | <2 | <2 | 5.23 |
| Cs ⁺ | | | <2 | 4.72 |

^a The K_{ass} -values for MClO₄ were determined by ¹H NMR spectroscopy; CDCl₃-CD₃CN = 4:1 v/v; [**1** or **1**·Zn^{II}] = 1.00 × 10⁻⁵ mol dm⁻³, [MClO₄] = 6.00 × 10⁻⁴ mol dm⁻³. The K_{ass} -values for MI were determined by absorption spectroscopy; CDCl₃-CD₃CN = 4:1 v/v; [**1** or **1**·Zn^{II}] = 1.00 × 10⁻⁵ mol dm⁻³. ^b The solubility of LiI in this medium was too low to allow us to estimate the K_{ass} -value. ^c Since the ¹H NMR signals for compound **1** and the complexes did not split, the K_{ass} -value was determined by non-linear least-squares analysis of a plot of δ_{H} vs. [LiClO₄] (0.2–4.0 mmol dm⁻³).

The elemental analysis also supports inclusion of water molecules in the complex (see Experimental section). These water molecules could not be removed by vacuum drying. The water molecules are probably bound into the cavity, interacting with Zn^{II} and NH (or C=O) in the pillars. Since the λ_{max} of tetraphenylporphyrin·Zn^{II} complexes usually shifts to longer wavelength when these complexes accept axial ligands, this proposal is compatible with the above spectral data.

Association with alkali metal cations

It is known that calix[4]aryl ester and amide derivatives show high Na⁺ selectivity.¹³ In these systems the association constants (K_{ass}) can be readily estimated by ¹H NMR spectroscopy because the proton signals for metal complexes appear separately from those for free calix[4]arenes even at room temperature.^{13,14} Also, in compound **1** and complex **1**·Zn^{II}, the ¹H NMR signals for the alkali metal complexes appeared separately (except those for complex **1** + Li⁺) and the K_{ass} -values were readily computed from the ratio of the integral intensities. The results are summarized in Table 1. On the other hand, the ¹H NMR signals for complex **1** + Li⁺ were not separated by the addition of LiClO₄. We lowered the measurement temperature to -60 °C. Although the signals were somewhat broadened, the peaks for the Li⁺ complex did not appear separately even at this temperature. Hence, the K_{ass} -value was determined at 25 °C by non-linear least-squares treatment of a plot of δ_{H} vs. [LiClO₄] (0–0.4 mmol dm⁻³). The results imply that the rate of complexation–decomplexation for complex **1** + Li⁺ is faster than the NMR time-scale. The difference between complexes **1** + Li⁺ and **1** + Na⁺ can be accounted for by the greater ionic size of Na⁺, which makes the exchange rate slower. The difference between the systems **1** + Li⁺ and **1**·Zn^{II} + Li⁺ can be explained by rigidification of the porphyrin ring by Zn^{II} metallation which should also make the exchange rate slower.

Examination of Table 1 reveals that the K_{ass} -values for Na⁺ (10^{3.10}–10^{3.69}) are smaller than those for the Li⁺ complexes and even smaller than those for conventional calix[4]aryl esters.¹⁴ This suggests that the ionophoric cavities in species **1** and **1**·Zn^{II} are a little smaller compared with conventional calix[4]aryl esters. As determined by ¹H NMR spectral data (*vide supra*), the phenyl groups in species **1** and **1**·Zn^{II} are more or less flattened. This conformation makes the size of the ionophoric cavity constructed on the lower rim smaller. This is the origin of the Li⁺ selectivity. It is known that the ionophoric cavity with a size between Li⁺ and Na⁺ shows remarkably high selectivity for Na⁺ against K⁺.¹⁵ Table 1 shows that this is also the case in species **1** and **1**·Zn^{II}: the $\log K_{\text{ass}}$ -values for NaClO₄ are 3.10–3.69 whereas those for KClO₄ are too small to be determined by a ¹H NMR spectroscopic method.

We noticed that the association with metal iodides MI has very strange properties. As shown in Table 1, the K_{ass} -values for compound **1** are not so different between NaClO₄ and NaI. In

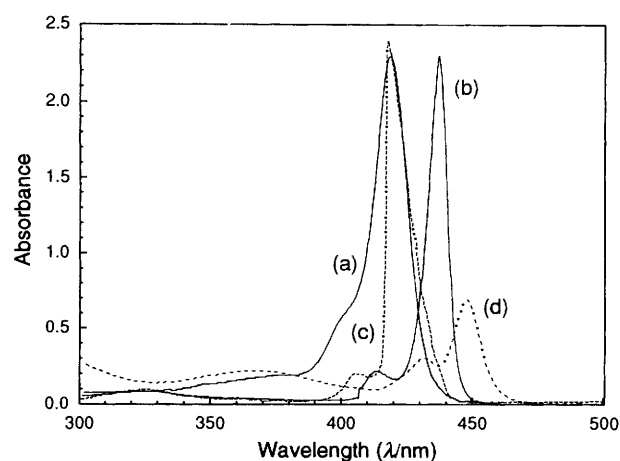


Fig. 1 Absorption spectra of (a) **1**, (b) **1**·Zn^{II}, (c) **1**·Zn^{II} + NaClO₄ and (d) **1**·Zn^{II} + NaI; 25 °C; [**1** or **1**·Zn^{II}] = 1.00 × 10⁻⁵ mol dm⁻³, [NaClO₄ or NaI] = 5.00 × 10⁻⁴ mol dm⁻³. The solvent was CHCl₃ for **1** and **1**·Zn^{II} and CHCl₃-MeCN = 4:1 v/v for **1**·Zn^{II} + NaClO₄ or NaI.

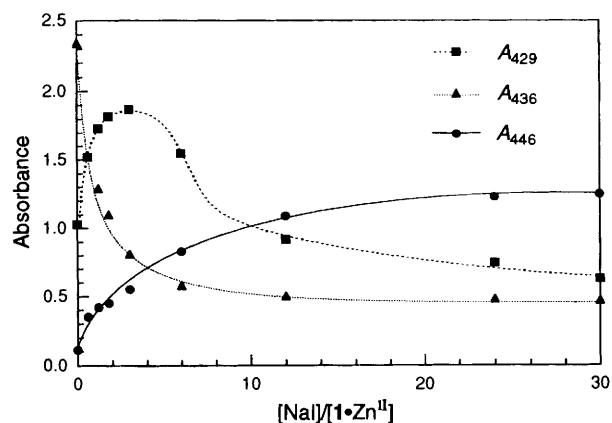


Fig. 2 Plots of A_{429} , A_{436} and A_{446} against [NaI]/[**1**·Zn^{II}]; 25 °C; CHCl₃-MeCN = 4:1 v/v; [**1**·Zn^{II}] = 1.00 × 10⁻⁵ mol dm⁻³

complex **1**·Zn^{II}, on the other hand, the K_{ass} -value for NaI is significantly greater than that for NaClO₄, and KI and CsI are bound more strongly than is NaI. The results are incompatible with the 'hole-size' concept and rather suggest that I⁻ ion plays some positive role in the binding of these large metal cations. To obtain insight into the binding mode of MI to complex **1**·Zn^{II} we thoroughly examined the absorption spectra. When NaClO₄ (50 mol equiv. to **1**·Zn^{II}) was added, the Soret band (436 nm in the absence of NaClO₄) shifted to 429 nm (Fig. 1). On the other hand, when NaI was added, the absorption band at 429 nm first increased at [NaI]/[**1**·Zn^{II}] < 4 and then decreased at [NaI]/[**1**·Zn^{II}] > 4. In addition, a new absorption maximum

increasingly appeared at 446 nm (Fig. 2). The change in the binding mode is also reflected by fluorescence spectroscopy (Fig. 3). When NaClO_4 was added, the emission maximum (619 nm in the absence of NaClO_4) shifted to 609 nm but the fluorescence intensity was only a little changed (Fig. 4). On the other hand, when NaI was added, the emission maximum shifted to 609 nm, and fluorescence intensity was increased at $[\text{NaI}]/[\text{1-Zn}^{\text{II}}] < 4$ and then the significant fluorescence quenching took place at $[\text{NaI}]/[\text{1-Zn}^{\text{II}}] > 4$ (Fig. 4). When a tetraphenylporphyrin- Zn^{II} complex was used instead of complex 1-Zn^{II} , neither the absorption spectrum nor the fluorescence intensity was changed under comparable measurement conditions. The foregoing spectral observations are reasonably explained by Scheme 2. In the NaClO_4 addition system Na^+ is bound to the calix[4]arene cavity and ClO_4^- exists as a counteranion (perhaps outside the 1-Zn^{II} cavity

because the space is too narrow to accept ClO_4^-). This species gives λ_{max} 429 nm in absorption spectroscopy and λ_{max} 609 nm in fluorescence spectroscopy. In the NaI addition system, on the other hand, a similar species is formed at $[\text{NaI}]/[\text{1-Zn}^{\text{II}}] < 4$ but at higher NaI concentration region I^- is included in the cavity and directly coordinates to Zn^{II} . The latter species features λ_{max} 429 nm in absorption spectroscopy and efficient fluorescence quenching in fluorescence spectroscopy. Since similar spectroscopic changes were not observed for a tetraphenylporphyrin- Zn^{II} complex, it is undoubtedly that the I^- -binding stems from a novel cooperative binding mode characteristic of a hard-soft ditopic binding site.

Examination with CPK molecular models suggests that I^- ion is not so large as to interact with both calix[4]arene-bound Na^+ and porphyrin-bound Zn^{II} . When KI is bound to complex 1-Zn^{II} , the CPK models suggest that I^- ion can interact with

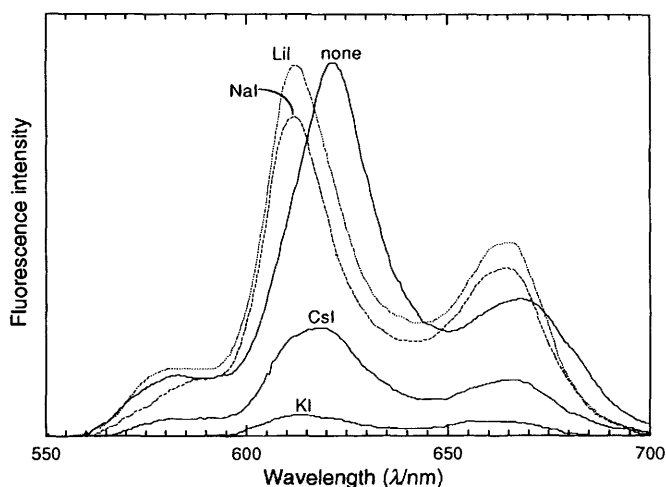


Fig. 3 Fluorescence spectra of 1-Zn^{II} : 25 °C; $\text{CHCl}_3\text{-MeCN} = 4:1$ v/v; $[\text{1-Zn}^{\text{II}}] = 1.00 \times 10^{-5} \text{ mol dm}^{-3}$, $[\text{MX}] = 2.00 \times 10^{-4} \text{ mol dm}^{-3}$

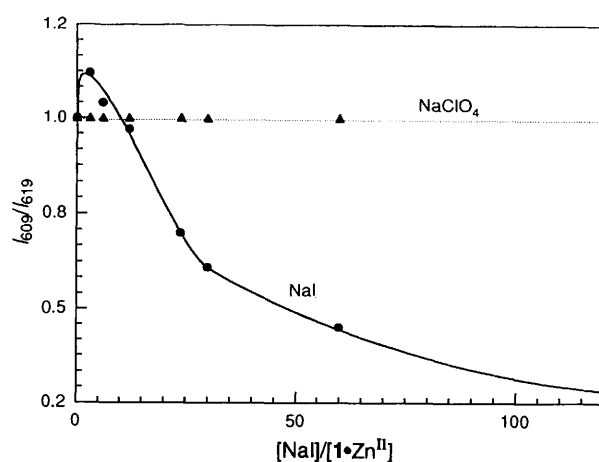
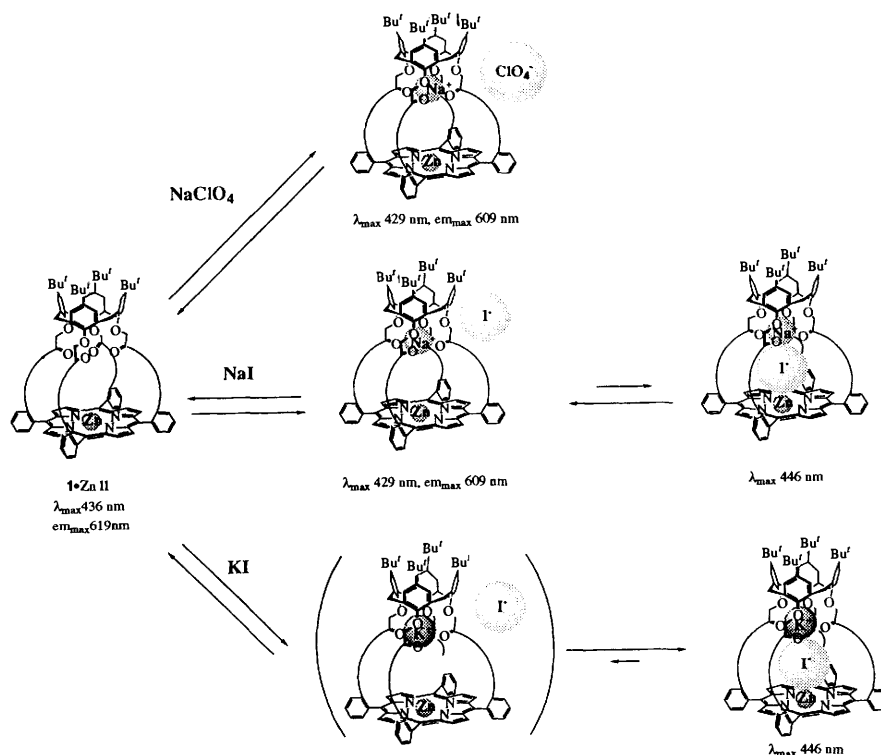


Fig. 4 Plots of I_{609}/I_{619} against $[\text{NaI}]/[\text{1-Zn}^{\text{II}}]$: 25 °C; $\text{CHCl}_3\text{-MeCN} = 4:1$ v/v; $[\text{1-Zn}^{\text{II}}] = 1.00 \times 10^{-5} \text{ mol dm}^{-3}$; excitation wavelength 437 nm



Scheme 2

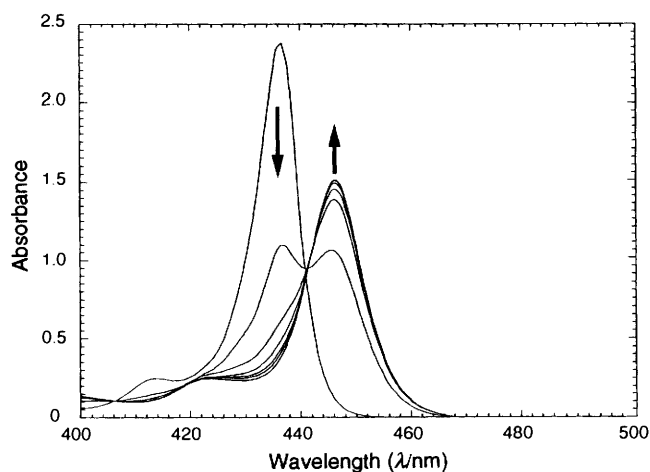


Fig. 5 Absorption spectra of $1\cdot\text{Zn}^{\text{II}}$ (1.00×10^{-5} mol dm^{-3}) in the absence and the presence of KI at 25°C in $\text{CHCl}_3\text{-MeCN} = 4:1$ v/v; $[\text{KI}]/[1\cdot\text{Zn}^{\text{II}}] = 0, 3, 6, 9, 12, 18$ and 30

both K^+ and Zn^{II} . Although the size difference between Na^+ and K^+ is slight, they behave differently in their I^- -binding owing to the rigid structure. The spectral change induced by KI addition is shown in Fig. 5. In this system the transitional λ_{max} (429 nm) observed for NaI addition did not appear but a new λ_{max} (446 nm) increased monotonically with an isosbestic point at 441 nm. In fluorescence spectroscopy, the fluorescence decreased efficiently and monotonically with increasing KI. The results show that KI and $1\cdot\text{Zn}^{\text{II}}$ form a ternary complex in one step in which I^- -ion interacts with K^+ through electrostatic attraction and Zn^{II} as an axial ligand. Similar absorption and fluorescence spectral changes were also observed for CsI but the K_{ass} -value estimated from the absorption spectral change was smaller than that for KI (Table 1). Cs^+ is probably too large to be incorporated into the ionophoric cavity in calix[4]arenes¹⁴ and the distance between calix[4]arene-bound Cs^+ and porphyrin-bound Zn^{II} is too short for I^- binding.

Conclusions

In this study we report the synthesis of a calix[4]arene-capped tetraphenylporphyrin which possesses novel structural characteristics such as a hard-soft ditopic binding-site, C_4 symmetry, chirality, etc. It was shown that when the calix[4]arene moiety binds K^+ and the porphyrin moiety binds Zn^{II} , I^- ion is captured into the cavity very strongly. Such a unique I^- -binding site can be realized by using the ditopic nature of compound **1**. The results suggest that a combination of calix[4]arene chemistry with porphyrin chemistry provides a number of novel molecular-recognition systems. We are now trying to find additional recognition abilities latently involved in compound **1**, which originate from C_4 -symmetry and chirality and which are not yet utilized in the present system.

Experimental

Materials

All chemicals were of commercial reagent quality and used without further purification with the following exceptions: THF was distilled over sodium; dimethylformamide (DMF) was distilled over sodium hydride; triethylamine was distilled over sodium hydroxide; chloroform, methanol and dichloromethane were purified by distillation. Analytical TLC was performed on commercial Merck plates coated with silica gel

KF_{254} . Silica gel used for chromatography was Wakogel C-300. Gel filtration was performed with Sephadex LH-20 using methanol as eluent. Compounds **2** and **3** were synthesized according to the methods in the literature^{7,8}.

Miscellaneous

Spectroscopic data were obtained by means of 250 MHz FT-NMR (AC-250P) for ^1H NMR spectroscopy using tetramethylsilane as reference. IR spectra were recorded on an FT/IR-5000 spectrometer. Absorption spectroscopy and fluorescence spectroscopy were measured by a Shimadzu UV-Visible spectrophotometer (UV-160A) and a Hitachi Fluorescence spectrophotometer (650-10s), respectively. Mass spectra were obtained with a Hitachi M-2500 spectrometer.

5,10,15,20-Tetrakis[2-(*N*-*tert*-butoxycarbonyl-L-alanyl-amino)-phenyl]porphyrin **4**

To a dichloromethane solution (200 cm^3) of *tert*-butoxycarbonyl-L-alanine (5.40 g, 28.6 mmol) was added dicyclohexylcarbodiimide (2.95 g, 14.3 mmol) and the solution was stirred at 0°C under N_2 for 1 h. The precipitate was removed by filtration and the filtrate was evaporated to dryness at 0°C . The residual *tert*-butoxycarbonyl-L-alanine anhydride was dissolved in dichloromethane (60 cm^3) and to this solution was added 5,10,15,20-tetrakis(2-aminophenyl)porphyrin **3** (0.80 g, 1.19 mmol). The mixture was stirred at 0°C for 1 day and the solution was then concentrated under reduced pressure. The residue was purified by silica gel chromatography followed by gel filtration to give a reddish brown solid (1.24 g, 77%); mp $> 250^\circ\text{C}$; $\nu_{\text{max}}(\text{Nujol})/\text{cm}^{-1}$ 1680 (C=O) and 1160 (C-O-C); $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}; 25^\circ\text{C}]$ -2.76 (2 H, s, NH of pyrrole), 0.08 (12 H, s, Me), 0.94 (36 H, s, Bu'), 6.14 (4 H, s, CH of alanyl), 8.11 (4 H, s, NH of alanyl), 7.55, 7.78, 7.85 and 8.31 (16 H, ArH), 8.72 (8 H, s, CH of pyrrole) and 9.01 (4 H, s, NH of aryl NH).

Deprotection of 5,10,15,20-tetrakis[2-(*N*-*tert*-butoxycarbonyl-L-alanyl-amino)phenyl]porphyrin **4**

5,10,15,20-Tetrakis[2-(*N*-*tert*-butoxycarbonyl-L-alanyl-amino)-phenyl]porphyrin **4** (650 mg, 0.48 mmol) was dissolved in trifluoroacetic acid (TFA) (9 cm^3) in the dark. The solution was stirred in an ice-bath for 3 h. The reaction was monitored by ^1H NMR spectroscopy, following the disappearance of the signal arising from *tert*-butyl protons. Excess of TFA was removed under reduced pressure. The residue was used for the next reaction without further purification.

Preparation of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis(chlorocarbonylmethoxy)calix[4]arene

This compound was prepared from 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis(hydroxycarbonylmethoxy)calix[4]arene **2** (420 mg, 0.48 mmol) according to the literature method.⁷ The product was confirmed by IR spectroscopy ($\nu_{\text{C-O}}$ 1810 cm^{-1}) and was then used for the next reaction without further purification.

Coupling reaction between the tetraacid chloride derivative of calix[4]arene and the $\alpha,\alpha,\alpha,\alpha$ -tetraamino derivative of tetraphenylporphyrin

In the dark, two THF solutions (80 cm^3 each) of the two title compounds were added simultaneously and dropwise to a THF solution (400 cm^3) of triethylamine (1.5 cm^3) in an ice-bath. The addition took 3 h. The reaction mixture was stirred at room temp. for 24 h. Precipitate was removed by filtration and the filtrate was evaporated to dryness. The residue was purified by gel filtration followed by silica gel chromatography (4 \times) to afford compound **1**, a purple solid (0.07 g, 8%); mp $> 300^\circ\text{C}$; $\lambda_{\text{max}}(\text{CHCl}_3)/\text{nm}$ 414 ($\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ 2.1×10^5), ^1H

(1.7×10^4), 542 (3.0×10^3), 585 (5.3×10^3) and 640 (1.2×10^3); δ_{H} (CDCl₃; 25 °C) –2.70 (2 H, s, NH of pyrrole), –1.17 (12 H, s, Me), 1.01 (36 H, s, Bu^t), 3.03 and 3.65 (4 H each, d each, ArCH₂Ar), 3.41 and 4.04 (4 H each, d each, OCH₂), 3.65 and 4.04 (4 H each, s each, NH of alanyl and aryl NH), 5.99 (4 H, s, CH of alanyl), 6.91 (8 H, ArH), 7.70 and 7.84 (4 H each, t each, ArH), 8.17 and 8.47 (4 H each, d each, ArH) and 8.78 (8 H, s, CH of pyrrole) (Found: C, 65.3; H, 6.3; N, 8.0. C₁₀₈H₁₁₀N₁₂O₁₂·CHCl₃·7H₂O requires C, 65.02; H, 6.26; N, 8.35%; positive SIMS [M + Na]⁺, *m/z* 1791.

Insertion of Zn^{II} into compound 1⁹

In the dark, zinc chloride (30 mg, 0.22 mmol) was added to a DMF solution of compound 1 (9 mg, 5.1 μmol) and the mixture was stirred at room temp. for 24 h. The reaction was monitored by UV-visible spectroscopy, following the shift of the Soret band from 414 nm to 436 nm. The solution was concentrated under reduced pressure and the residue was purified by alumina chromatography to give complex 1·Zn^{II} (0.009 g, 97%); mp > 300 °C; λ_{max} (CHCl₃)/nm 436 ($\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ 2.3×10^5), 570 (1.8×10^4) and 609 (4.6×10^3); δ_{H} (CDCl₃; 25 °C) –0.24 (12 H, s, Me), 1.10 (36 H, s, Bu^t), 3.03 (4 H, s, NH of aryl), 3.11 and 3.95 (4 H each, d each, ArCH₂Ar), 3.65 and 3.88 (4 H each, d each, OCH₂), 5.40 (4 H, s, CH of alanyl), 5.96 (4 H, s, NH of alanyl), 7.05 (8 H, ArH), 7.68 and 7.77 (4 H each, t each, ArH), 8.59 and 8.72 (4 H each, d each, ArH) and 8.73 and 8.77 (8 H, d each, CH of pyrrole) (Found: C, 60.6; H, 5.7; N, 7.5. C₁₀₈H₁₀₈N₁₂O₁₂Zn·2CHCl₃·6H₂O requires C, 60.65; H, 5.62; N, 7.72%; positive SIMS [M + Na + H₂O]⁺, *m/z* 1871.

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