Porphocyanine: An Expanded Tetrapyrrolic Macrocycle

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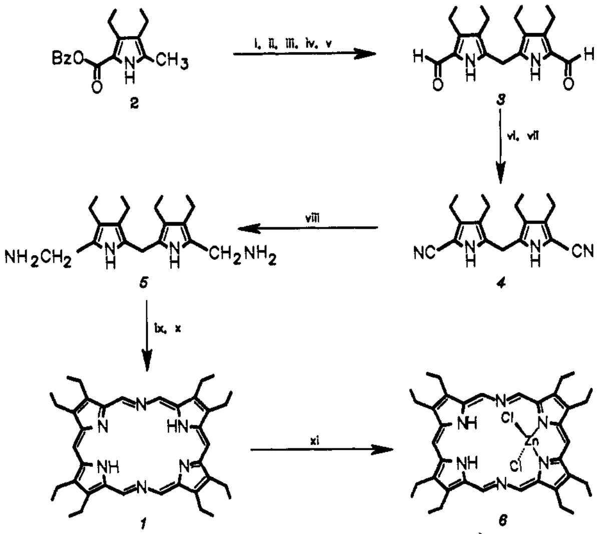
Porphyrins both fluoresce and produce singlet oxygen when irradiated with visible light, and the use of porphyrins for the diagnosis and treatment of malignant tissue and pathogens has stimulated significant interest in recent years.[1] To minimize absorption by natural chromophores in blood and other tissues and thereby achieve a greater depth of light penetration, we have opted to prepare, through modifications of the porphyrin periphery, stable chlorin and bacteriochlorin-like systems which exhibit strong absorptions above 630 nm.[2–4] However, others have focused their attention on larger polypyrrolic macrocycles,[5–11] the "expanded porphyrins" which exhibit similar long wavelength absorptions and some of which have been shown to be good singlet oxygen producers and may thus offer certain advantages over porphyrins as potential photosensitizers. We report here the synthesis, spectroscopic properties, and crystal structure (of the zinc derivative) of a novel expanded tetrapyrrolic macrocycle **1**. The chromophore of compound **1** has been named porphocyanine, since it incorporates the combined structural features of porphyrins and phthalocyanines. In addition to four pyrrolic nitrogen atoms, porphocyanine offers two additionial nitrogen atoms and a larger central binding core (compared to porphyrins) which may allow for coordination to larger metal ions such as Gd or Tc, complexes of which have been shown to have applications as radiopharmaceuticals and paramagnetic contrast agents in magnetic resonance imaging.[12]

Scheme I ^{a}



^{a} (i) $Pb(OAc)_4/CH_3COOH$; CH_3COOH/H_2O (4:1 v/v), reflux; (ii) H_2, 10% Pd/C, THF; (iii) DMF reflux; (iv) C_6H_5COCl; (v) $NaHCO_3$, H_2O; (vi) NH_2OH, NaOAc, EtOH, 60 °C; (vii) Ac_2O, 100 °C; (viii) $LiAlH_4$, THF, 0 °C, N_2; (ix) THF/CH_3OH, reflux, N_2; (x) O_2, CH_2Cl_2, room temperature; (xi) $ZnCl_2$, CH_3OH/CH_2Cl_2.

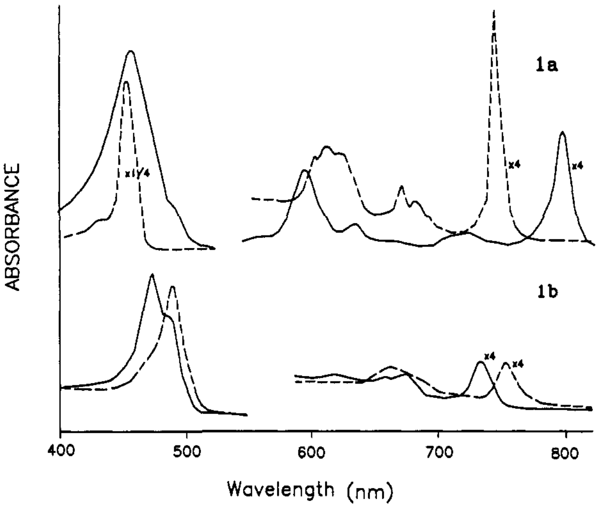


Figure 1. (a) Optical spectrum of octaethylporphocyanine **1** in CH_2Cl_2 (—) and in CH_2Cl_2/CF_3COOH (- - -). (b) Optical spectrum of **6** in CH_2Cl_2 (—) and in CH_2Cl_2/Et_3N (- - -).

The dipyrrolic precursor to porphocyanine **1** is a 5,5′-bisformyldipyrromethane (**3**), which is accessible in five steps starting from pyrrole **2**[13] in >50% overall yield (Scheme I). Treatment of **3** with hydroxylamine in ethanol under an inert atmosphere produced an isomeric mixture of the bis oximes, which were dehydrated using acetic anhydride to give the biscyanodipyrromethane **4** in 60% overall yield (from **3**). Reduction of **4** with $LiAlH_4$ in THF produced the unstable 5,5′-bis(aminomethyl)dipyrromethane (**5**), which was used directly in the subsequent condensation step after quenching the excess reagent. The bis(aminomethyl)dipyrromethane (**5**) undergoes self-condensation (with loss of ammonia) in refluxing $CH_3OH–THF$ to give, after oxidation, a 24% yield of **1**.[14]

The optical spectrum of **1** in CH_2Cl_2 (Figure 1a) exhibits an intense Soret-like absorption at λ = 457 nm with less intense bands at 592, 633, 728, and 797 nm, strongly suggesting a fully conjugated aromatic porphyrin-like structure for the macrocycle. It fluoresces at 805 nm in THF and at 750 nm in THF/CH_3COOH (λ_{exc} = 450 nm). The aromaticity is further confirmed

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[14] Spectroscopic data for **1**: ^1H NMR (1% TFA in $CDCl_3$) δ −5.75 (br, 4H), 2.30 (2t, J = 7.8 Hz, 24H), 4.78 (2q, J = 7.8 Hz, 16H), 11.97 (s, 2H), 13.75 (s, 4H); UV–vis λ (ϵ) 457 (2.4×10^5), 592 (1.7×10^4), 633 (5.8×10^3), 728 (3.2×10^3), 797 (2.7×10^4) nm in CH_2Cl_2, 453 (7.6×10^5), 600 (1.0×10^4), 609 (1.2×10^4), 623 (1.1×10^4), 669 (8.4×10^3), 682 (5.0×10^3), 744 (4.4×10^4) nm in TFA/CH_2Cl_2; HRMS (EI) for $C_{38}H_{48}N_6$ (M^+) calcd 588.3941, found 588.3933. Spectroscopic data for **4**: ^1H NMR ($CDCl_3$) δ 1.10 (t, J = 7.8 Hz, 6H), 1.25 (t, J = 7.8 Hz, 6H), 2.45 (q, J = 7.8 Hz, 4H), 2.60 (q, J = 7.8 Hz, 4H), 3.90 (s, 2H), 8.45 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 15.3, 15.7, 17.1, 18.4, 23.0, 97.2, 115.2, 122.6, 129.7, 137.7; HRMS (EI) for $C_{19}H_{24}N_4$ (M^+) calcd 308.2001, found 308.2002; IR ($CDCl_3$) ν_{CN} = 2211 (strong), ν_{NH} = 3443 (medium).

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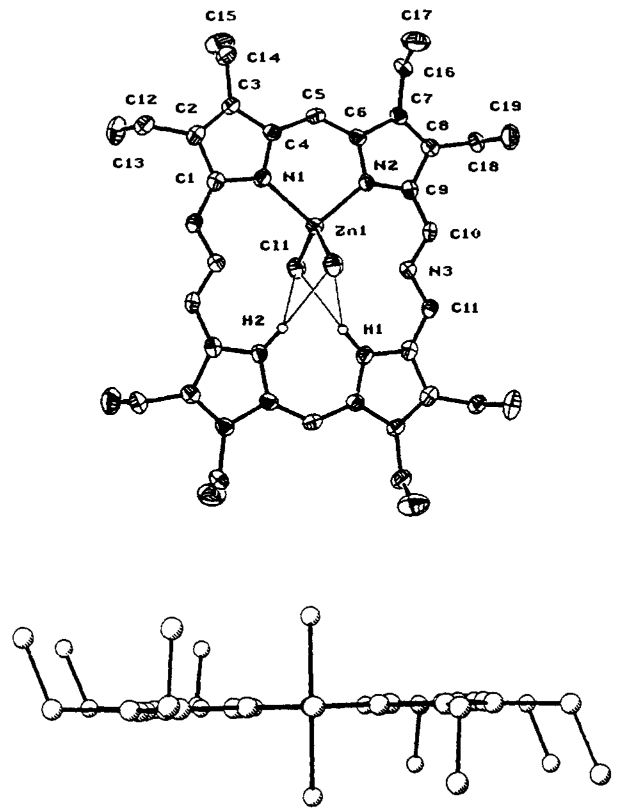

Figure 2. Top, view of **6** showing the tetrahedral coordination around zinc and hydrogen-bonding interactions of NH and chlorine ligands. Some relevant bond lengths (Å) are Zn–N1 2.050, Zn–N2 2.063, Zn–Cl1 2.247, Zn–Cl2 2.240. Bottom, side view of **6** showing the planarity of porphyocyanine framework. Mean deviation from the plane is 0.0095 Å.

by the downfield shift of the peripheral ring (methine) protons [δ = 11.95 (s, 2H), 13.75 (s, 4H)] and the upfield shift of the inner pyrrolic-NH protons ($\delta = -5.75$) in the ^{1}H NMR spectrum (1% TFA/$CDCl_3$). The chemical shifts are also indicative of a larger diamagnetic ring current when compared with octaethylporphyrin [δ = 10.66 (methine), −3.85 (NH)]. Furthermore, unlike in the vinylogous porphyrins,[8] where the methine protons point inward ($\delta = -9.54$), the unique imine linkages of porphocyanine have the methine protons pointing outward, thus providing a larger central core for metal coordination.

Insertion of zinc into porphocyanine **1** was carried out by refluxing a solution of **1** with $ZnCl_2$ in CH_2Cl_2–CH_3OH (1:1). The product **6**[15] exhibits a distinctly different visible spectrum (Figure 1b), which on treatment with base (Et_3N or DBU) leads to a red shift of the long wavelength visible band from 736 to 762 nm (reversed by neutralization with CH_3COOH). This suggested the existence of acidic pyrrolic protons, which was confirmed by the presence of a sharp singlet at $\delta = -5.50$ (2H) in the ^{1}H NMR spectrum. The neutral complex **6** and its anionic form fluoresce at 738 and 766 nm, respectively (λ_{exc} = 456 nm). The single crystal X-ray structure of **6** (Figure 2) reveals that the metal is tetrahedrally coordinated to two pyrrolic nitrogens and two chlorine atoms, leaving the other two pyrrolic nitrogens protonated with hydrogen-bonding interactions to chlorines.[16] As predicted by computer modeling,[17] the porphocyanine framework is essentially planar, with a measured core size of 5.70 Å between the two imine nitrogens and 5.92 Å between the two pyrrole nitrogens. Furthermore, the six nitrogen atoms form a pseudohexagonal geometry which should favor the coordination of actinides.[18] Experiments aimed at complexing various metal ions are currently in progress.

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Supplementary Material Available: Tables listing atomic coordinates, thermal parameters, and various intramolecular distances and angles (18 pages); observed and calculated structure factors (15 pages). Ordering information is given on any current masthead page.

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(15) Spectroscopic data for **6**: ^{1}H NMR ($CDCl_3$) δ −5.50 (s, 2H), 2.14, 2.20, 2.24, 2.27 (4t, J = 7.8 Hz, 24H), 4.48, 4.53, 4.60, 4.62 (4q, J = 7.8 Hz, 16H), 11.20, 11.38 (2s, 2H), 13.30, 13.55 (2s, 4H); UV-vis 464, 476, 656, 666, 736 nm in CH_2Cl_2, 480, 658, 762 nm in Et_3N/CH_2Cl_2; HRMS (FAB) for $C_{38}H_{48}Cl_2N_6Zn$ (M^+) calcd 722.2603; found 722.2608.

(16) Single crystals were obtained by slow diffusion of diethyl ether into chloroform solution of **6**. Two chloroform solvate molecules per Zn-porphocyanine were found. Crystal data: $C_{40}H_{50}Cl_8N_6Zn$, FW = 963.88, orthorhombic, space group *Pbca* (No. 61), with $a = 21.334(4)$, $b = 27.335(7)$, and $c = 7.892(2)$ Å, $V = 4603(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.39$ g·cm^{-3}. The structure was solved by the Patterson method and was refined by full-matrix least-squares procedures to $R = 0.057$ and $R_w = 0.053$ for 1843 reflections with $I \geq 3\sigma(I)$. The molecule is situated at a crystallographic inversion center. The Zn and N–H positions are (1:1) disordered about the center of symmetry and were assigned 50% occupancy.

(17) Biosym InsightII program, San Diego, CA.

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