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Novel thiol-derivatized zinc(II) phthalocyanines

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ABSTRACT

Preparation and characterization of tetrasubstituted zinc(II) phthalocyanines in which sulfur is not linked to the macrocycle are reported herein for the first time. Thioacetic acid S-[3-(3,4-dicyano-phenoxy)-propyl]ester (**4**) was synthesized in 55% yield from 4-nitrophthalonitrile and thioacetic acid S-(3-hydroxy-propyl)ester (**3**). Tetrasusbtituted thiol-derivatized zinc(II) phthalocyanine **5** was obtained from **4** and zinc acetate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene in butanol. Treatment of **5** with sodium methoxide afforded phthalocyanine **6**.

Phthalocyanines play a major role in modern photochemistry. Complexation of phthalocyanines with metal ions has an influence on their photophysical properties. These compounds are used as catalysts as well as photoreceptors in electrographic printing.[1] In medicine, the dyes have been found to qualify as effective phototoxic drugs for photodynamic therapy.[2] All these applications require compounds of various solubility and high purity degrees in order to prevent by-products from impairing their photoconducting and optical characteristics. Thiol-derivatized metallophthalocyanine complexes show excellent spectroscopic and photochemical properties, such as wavelength absorption over 700 nm.[3] A systematic comparison of oxygen and sulfur as covalent linkers on octasubstituted zinc(II) phthalocyaninates shows a bathochromic shift of 30 nm in the absorption and emission maxima, and of 60 nm in the triplet-triplet absorption spectra when alkylsulfanyl moieties instead of alkyloxyl moieties were present.[4] Recently, the effectiveness in photodynamic therapy of 2,3,10,16,17,23,24-octakis[(N,N-dimethylamino)ethylsulfanyl] phthalocyaninatozinc(II) was demonstrated by using MCF-7c3 human breast cancer cells and LM2 adenocarcinoma implanted subcutaneously in Balb/c mice.[5]

Generally, thiol-derivatized metallophthalocyanine complexes have been less explored than other metallophthalocyanine derivatives, most of the compounds being those phthalocyaninates in which sulfur is linked to the macrocycle.[3,4] The presence of thiol groups at the end of alkyl peripheral substituents of the macrocycle could improve, on the one hand, dye amphiphilicity and, on the other hand, their linkage to carriers as well as nanoparticle preparation.[6] To our knowledge, only the synthesis and characterization of 1,4,8,11,15,18-hexahexyl-22-methyl-25-(11-mercaptoundecyl)phthalocyaninatozinc(II) complex have been reported so far,[6c] tetrasubstituted phthalocyanines with thiol groups at the end of the alkyl peripheral substituents of the macrocycle have not been described in the literature. The great interest in the development of the above-mentioned compounds has led us to investigate the synthesis and spectroscopic characterization of the novel thiol-derivatized zinc (II) phthalocyanine complexes.[4,7]

The synthesis of phthalocyanines **5** and **6** is shown in Scheme 1. The sequence begins with the reaction of methyl 3-mercaptopropionate (**1**) with acetic anhydride to give 3-acetylsulfanyl-propionic acid methyl ester (**2**). The reaction of compound **2** with diborane in tetrahydrofuran at room temperature afforded thioacetic acid S-(3-hydroxy-propyl) ester (**3**). Phthalonitrile **4** was obtained in good yields, by reaction of 4-nitrophthalonitrile with the corresponding nucleophile **3**.[8,9] Phthalocyanine **5** was readily prepared by cyclotetramerization of phthalonitrile **4** employing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in butanol and zinc acetate at 130 °C.[10a,11] This dye was purified by chromatography, followed by recrystallization to attain 41% of the desired 2(3), 9(10), 16(17),23(24)-tetrakis[(3-acetyl-sulfanyl)propoxy]phthalocyaninatozinc(II) (**5**). Treatment of **5** in an alkaline solution at room temperature, followed by addition of Dowex 50 W-X2 to neutralize the solution, in order to prevent zinc loss, gave the desired phthalocyanine **6** in 30% yield.[10b]

On the other hand, when the benzoyl group was applied to protect the thiol group, thiobenzoic acid S-(3-hydroxy-propyl) ester (**7**) was obtained. Reaction of **7** with 4-nitrophthalonitrile gave **8**

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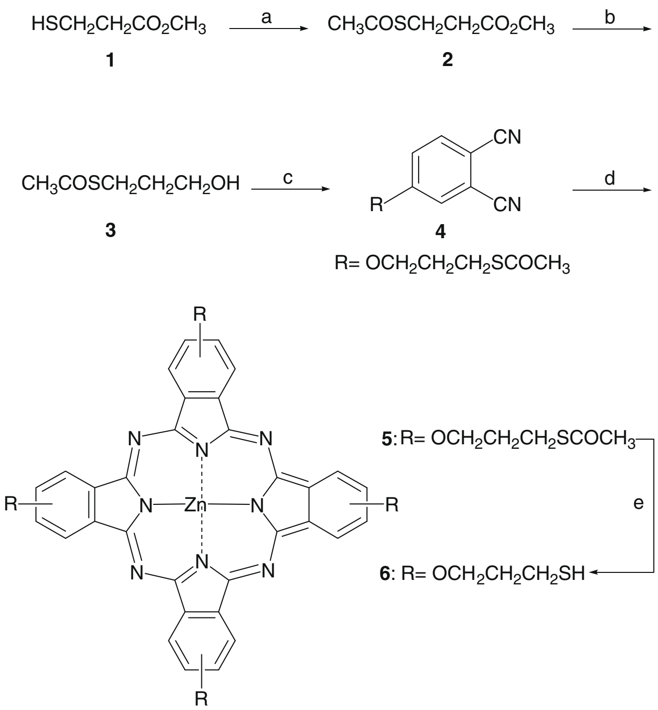
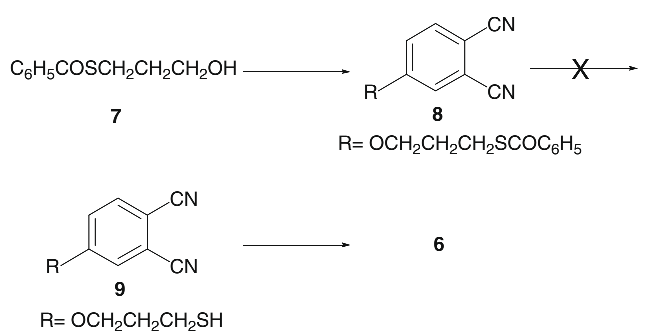
in 64% yield. However, deprotection of **8** at room temperature as well as by heating in an alkaline solution failed.[12] The desired dinitrile **9** precursor of phthalocyanine **6** was not obtained (Scheme 2). In contrast, synthesis of phthalocyanine **6** could be easily carried out through the sequence depicted in Scheme 1.

With regard to the solubility of the new phthalocyanines, both dyes have markedly different solubility properties while **5** is soluble in almost all organic solvents, **6** is fully soluble in methanol and tetrahydrofuran and is partially soluble in water.

Intermediates were characterized by mass spectrometry employing an APPI/APCI dual ionization technique. Over the last few years, HPLC–MS using the electrospray (ESI) ionization mode has become the choice method for the analysis of thiol-compounds. Alternatively, atmospheric pressure chemical ionization (APCI) and more recently, atmospheric pressure photospray ionization (APPI) interfaces were also introduced. This technique shows several advantages over ESI such as the possibility of detecting more apolar compounds and lowering the ion suppression phenomena. Besides, it was demonstrated[13] that APPI is more sensitive than ESI or APCI for non-polar compounds and has shown higher



Scheme 1. Reagents and conditions: (a) Ac_2O, reflux, 3 h, 94%; (b) B_2H_6, THF, rt, 48 h, 63%; (c) 4-nitrophthalonitrile, K_2CO_3, DMF, 60 °C, 24 h, 55%; (d) $Zn(AcO)_2$, DBU, BuOH, reflux, 1 h, 41%; (e) NaOMe 0.1 M, rt, 12 h, Dowex 50 W-X2, 30%.



Scheme 2.

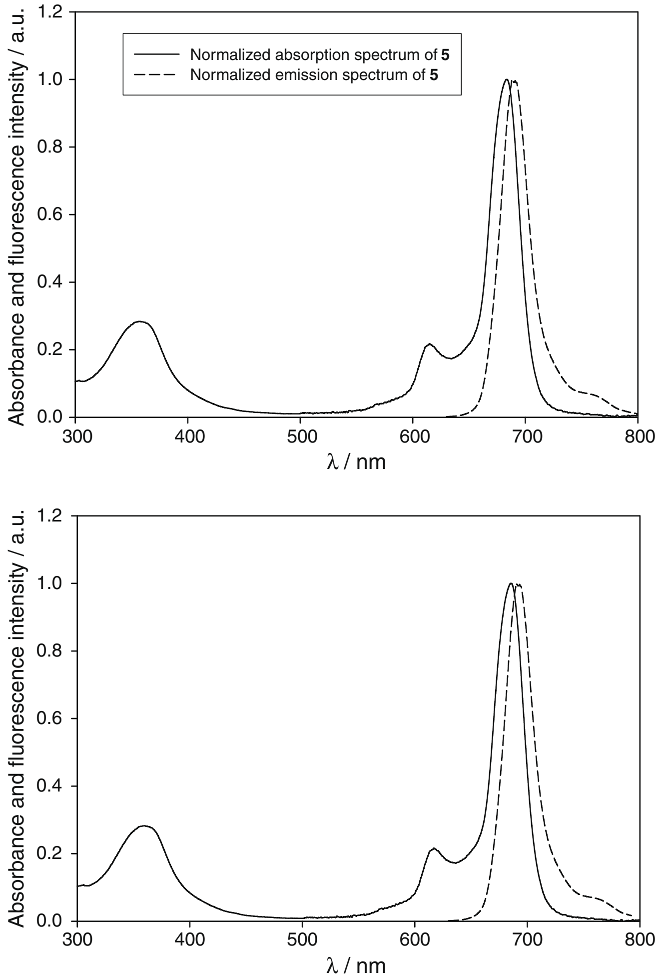


Figure 1. Absorption and fluorescence spectra of **5** and **6** in THF.

signal-to-noise ratios essentially due to lower chemical background noise. Also, it was impossible to achieve the molecular ion under the GC/MS/EI ionization conditions for synthetic intermediates; therefore, in order to solve that issue, an APPI/APCI dual ionization technique was used. Phthalocyanines **5**–**6** were characterized by electrospray ionization-quadrupole time-of-flight (ESI-QTOF) mass spectrometry. The isotopic cluster ions and the fragmentation patterns were consistent with the structures proposed.

The UV–vis absorption spectra of phthalocyanines **5**–**6** showed a Soret band of 358 nm and 360 nm and a Q band at 684 nm and 686 nm, respectively. Such bathochromic shift into the therapeutic window could be useful for biomedical applications such as tissue imaging and photodynamic therapy.[2] Typical fluorescence emission spectra of zinc phthalocyanines were also observed (Fig. 1). Phthalocyanines **5**–**6** are excellent singlet oxygen generators with a high value of quantum yield of singlet oxygen production (Φ_Δ) of 0.59–0.61[14] as well as a fluorescence quantum yield (Φ_F) production of 0.34,[15] basic conditions for further biological testing.

In summary, we have prepared and characterized two tetrasubstituted zinc(II) phthalocyanines. One of them, that having the free thiol group, is likely to be a promising second-generation photosensitizer for biological purposes, on account of its significant solubility.

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8. Thioacetic acid S-[3-(3,4-dicyano-phenoxy)-propyl] ester (**4**). A mixture of **3** (0.40 g, 2.98 mmol), 4-nitrophthalonitrile (0.10 g, 0.58 mmol), and K_2CO_3 (0.61 g, 4.4 mmol) in anhyd DMF (5 mL) was heated at 60 °C and stirred under Ar for 24 h. After cooling down, the mixture was poured into H_2O and then extracted with CH_2Cl_2 (4 × 30 mL). The combined extracts were washed with H_2O (3 × 30 mL) and dried over Na_2SO_4, and then evaporated in vacuo. The solid residue was dissolved in a small volume of CH_2Cl_2, and filtered through a silica-gel column packed and pre-washed with the same solvent. After evaporation of the solvent, the residue was recrystallized from EtOH. Yield: 0.083 g (55%); mp 106–108 °C; IR (KBr): 3081, 2923, 2573, 2228, 1737, 1598, 1582, 1562, 1492, 1468, 1390, 1360, 1342, 1283, 1258, 1192, 1167, 1019, 962, 871, 833, 718, 622, 594 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56 (s, 3 H, CH_3), 2.26 (m, 2 H, $CH_2CH_2CH_2$), 3.24 (t, 2 H, CH_2O), 4.20 (t, 2 H, SCH_2), 7.23 (d, 1 H, Ar), 7.55 (s, 1 H, Ar), 7.71 (d, 1 H, Ar); MS (APPI/APCI): *m*/*z* (%) = $[M+H]^+$ calcd for $C_{13}H_{12}N_2O_2S$: 261.0985; found: $[M+H]^+$ 261.0997. Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76. Found: C, 60.15; H, 4.67; N, 10.80.
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10. (a) 2(3), 9(10), 16(17), 23(24)-tetrakis[(3-acetylsulfanyl)-propoxy]phthalocyaninatozinc(II) (**5**). A mixture of **4** (0.05 g, 0.19 mmol), anhyd $Zn(OAc)_2$ (0.05 g, 0.22 mmol), and DBU (0.1 mL, 0.67 mmol) in anhyd BuOH (5 mL) was stirred and heated at reflux temperature under Ar for 1 h. After evaporation in vacuo, the residue was treated with CH_2Cl_2 (5 mL) and centrifuged to eliminate the $Zn(OAc)_2$ excess. The organic solution was evaporated in vacuo leaving a blue- green solid which was then dissolved in CH_2Cl_2 and filtered through a column of silica-gel packed and pre-washed with the same solvent. The title compound was eluted with CH_2Cl_2–MeOH (9:1). After evaporation of the solvent, the dye was recrystallized from CH_2Cl_2–hexane. Yield: 0.022 g (41%); IR (KBr): 3099, 2933, 1727, 1697, 1446, 1359, 1324,1265, 1206, 1106, 984, 844, 739, 527 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.60 (br s, 12 H, CH_3), 2.15 (m, 8 H, $CH_2CH_2CH_2$), 3.23 (m, 8 H, CH_2O), 4.19 (m, 8 H, SCH_2), 7.22 (br s, 4 H, Ar), 7.61 (br s, 4 H, Ar), 7.74 (br s, 4 H, Ar); ESI-TOF MS: *m*/*z* $[M^+]$ calcd for $C_{52}H_{48}N_8O_8S_4Zn$: 1106.1763; found: $[M^+]$ 1106.1861; UV–vis (THF): λ_{max} (ε, M^{-1} cm^{-1}) = 684 nm (142035); Fluorescence emission (THF): λ_{max} = 688 nm; Singlet oxygen quantum yields (Φ_Δ): 0.59; Fluorescence quantum yields (Φ_F): 0.35. (b) 2(3), 9(10), 16(17), 23(24)-tetrakis[(3-mercapto)propoxy]phthalocyaninatozinc(II) (**6**). Phthalocyanine **5** (0.005 g, 0.0045 mmol) was suspended in anhyd MeOH (1 mL). 0.1 M NaOMe soln (1 mL) was added and the solution was stirred for 12 h. Dowex 50 W-X2 was added to neutralize the solution and then the ion exchanger was filtered off. After evaporation of the solvent in vacuo, the residue was dissolved in a small volume of MeOH and filtered through a column of silica-gel packed and pre-washed with the same solvent. A blue-green residue was obtained after the evaporation of the solvent in vacuo; this was recrystallized from CH_2Cl_2–hexane. Yield: 0.0013 g (30%); IR (KBr): 3409, 2929, 2317, 1617, 1436, 1294, 1258, 1046, 667 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.52 (br s, 4 H, SH), 2.05 (m, 8 H, $CH_2CH_2CH_2$), 2.58 (m, 8 H, SCH_2), 4.01 (m, 8H, CH_2O), 6.83 (br s, 4 H, Ar), 6.94 (br s, 4 H, Ar), 7.19 (br s, 4 H, Ar); ESI-TOF MS: *m*/*z* $[M^+]$ calcd for $C_{44}H_{40}N_8O_4S_4Zn$: 938.1347; found: $[M^+]$ 938.1425; UV–vis (THF): λ_{max} (ε, M^{-1} cm^{-1}) = 686 nm (137419); Fluorescence emission (THF): λ_{max} = 690 nm; Singlet oxygen quantum yields (Φ_Δ): 0.61; Fluorescence quantum yields (Φ_F): 0.34.
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