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Synthesis and properties of a novel alkylselenium substituted phthalocyanine

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ABSTRACT

The preparation and characterization of a tetrasubstituted alkylselenium zinc(II) phthalocyanine are reported herein for the first time. The precursor 4-(butylselanyl)phthalonitrile (**4**) was obtained in 65% yield. Tetrasubstituted alkylselenium zinc(II) phthalocyanine **5** was synthesized from **4** and zinc acetate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene in butanol.

Introduction

Phthalocyanines have been found to have applications as phototoxic drugs for photodynamic therapy (PDT).[1–4] Since zinc(II) phthalocyanines carrying different peripheral substituents have been reported as efficient photosensitizers for these purposes, different synthetic routes have been postulated.

Bioisosterism is a process for molecular modification used as a strategy in medicinal chemistry for the design of new drugs.[5] However, only few phthalocyanines have been synthesized using this strategy.[6,7]

We have recently reported the synthesis and photophysical and photobiological studies of four isosteric water-soluble cationic zinc(II) phthalocyanines by using human nasopharynx KB carcinoma cells. Our results showed the efficiency of one of them 2,9(10),16(17),23(24)-terakis[(2-trimethylammonium)ethylsulfanyl] phthalocyaninatozinc(II) tetraiodide (Pc13), for suitable PDT studies.[6]

The replacement of the heteroatom attached to the phthalocyanine macrocycle generates changes in the photophysical properties of the dye, which could be important for the PDT requirements. In previous studies, we stated that sulfur-linked cationic aliphatic phthalocyanines show a higher bathochromic shift in the order of 10 nm for the Q band than the isosteric oxygen-linked cationic aliphatic phthalocyanines.[6,7]

On the other hand, it has been established that several bioactive selenium-based compounds show a large spectra of biological activities.[5,8–10] However, alkylselenium substituted dyes have received less attention than oxygen or sulfur analogous molecules. To our knowledge, only porphyrins replaced with alkylselenium groups have been synthesized, but no alkylselenium phthalocyanines have been reported.[5,11–15] Based on these results, further studies have been initiated to investigate the synthesis and spectroscopic properties of a novel selenium derivatized zinc(II) phthalocyanine complex to evaluate its properties as a potential photosensitizer for clinical purposes.

Phthalocyanine **5** was designed and synthesized as depicted in Scheme 1. The sequence begins with the reaction of the commercially available 4-aminophthalonitrile (**1**) with sodium nitrite solution followed by the addition of potassium selenocyanate to give compound **2**.[16] Noteworthy, compound **2** tends to dimerize, affording an orange solid **3** mp 184–186 °C. The formation of compound **3** can be understood taking into account that nitrile groups in positions 1 and 2 of the aromatic ring have a withdrawing effect that favors the C–Se cleavage. The selenium moiety with negative charge density, thus becomes a good nucleophile allowing the attack of a new molecule for dimerization.[17] Phthalonitriles **2** and **3** reacted with excess of sodium hydride in DMF and butyl bromide to produce **4** in 65% yield.[18,19] Attempts to obtain **4** by the reaction of 4-selenocyanatophthalonitrile (**2**) with excess of butyl bromide in methanol in the presence of 2 equiv of sodium borohydride as described elsewhere[20] gave compound **4** in 12% yield.

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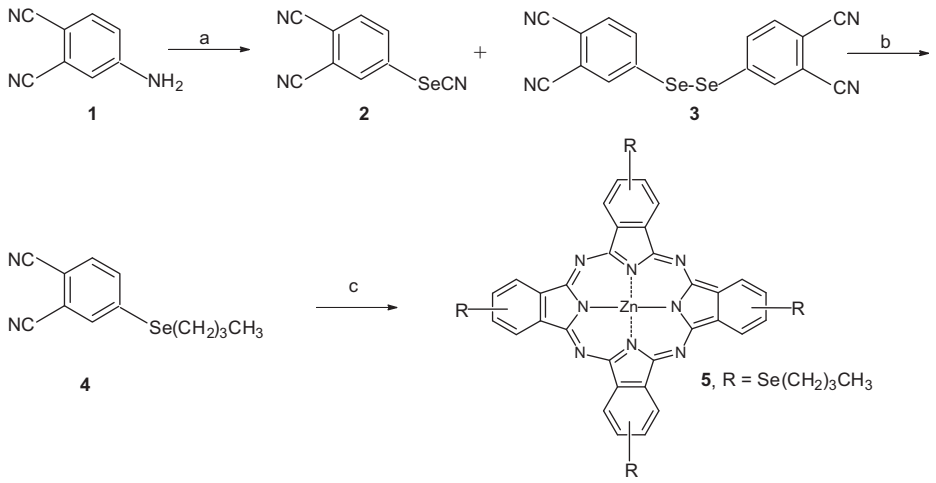

Scheme 1. Reagents and conditions: (a) HCl 2 M $NaNO_2$ 2 M; 0 °C; acetate buffer; KSeCN; 0 °C, 3 h, 75%; (b) butyl bromide, NaH, DMF, 75 °C, 3 h, 65%; (c) $Zn(AcO)_2$, DBU, BuOH, reflux, 3 h, 22%.

Phthalocyanine **5** was readily prepared by cyclotetramerization of phthalonitrile **4** by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in butanol and zinc acetate at 150 °C. This dye was purified by chromatography, followed by recrystallization to attain 22% of the desired 2(3),9(10),16(17),23(24)-tetrakis(butylselanyl) phthalocyaninatozinc(II) (**5**).[21] With regard to the solubility of phthalocyanine **5**, it is soluble in almost all organic solvents.

Intermediates **2**–**4** and phthalocyanine **5** were characterized by IR and ^{1}H NMR spectroscopy, while ESI-TOF mass spectroscopy has become the choice method for the analysis of selenium-compounds.

The UV–visible absorption spectra of phthalocyanine **5** showed a Soret band of 360 nm and a Q band at 686 nm $\varepsilon = 216{,}000\ M^{-1}\ cm^{-1}$ ($c = 4.5 \times 10^{-6}$ M). A bathochromic shift of 8–10 nm was observed for the Q-bands of phthalocyanines when oxygen and selenium were alternatively present.[6,22–24] When excited at 610 nm, **5** showed fluorescence emission spectra at 696 nm, typical of zinc phthalocyanines, at a concentration of 10^{-6} M in tetrahydrofuran (Fig. 1). Phthalocyanine **5** is an excellent singlet oxygen generator with a high value of quantum yield of singlet oxygen production (Φ_Δ) of 0.64 ± 0.03[6,7,25] as well as a fluorescence quantum yield (Φ_F) production of 0.18 ± 0.03,[6,26] basic conditions for further biological testing.[27] These values are similar to those reported for a sulfur linked zinc(II) phthalocyanine. However, the Q band absorption coefficient of alkylselenium phthalocyanine was 1.44 times higher than the Q band absorption coefficient of the sulfur dye,[6] which is relevant for dosing in PDT studies.

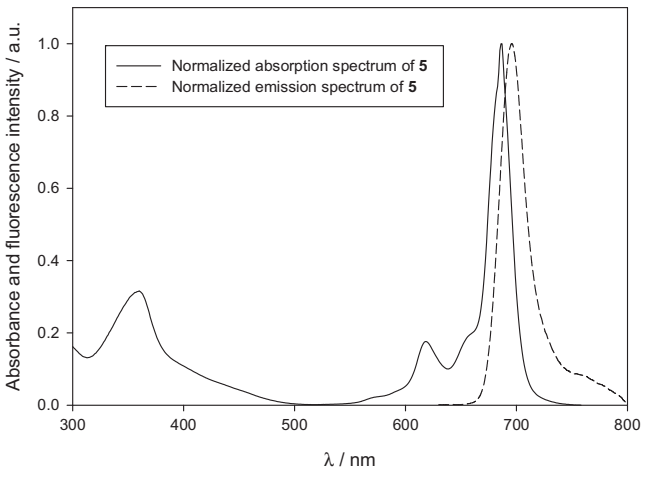

Figure 1. Absorption and fluorescence spectra of **5** in THF.

In summary, here we report the first synthesis of an alkylselenium tetrasubstituted zinc(II) phthalocyanine, likely to be a promising second-generation photosensitizer for biological purposes, on account of its excellent spectral features.

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17. *4-Selenocyanatophthalonitrile* (**2**). A mixture of 4-aminophthalonitrile (0.200 g, 1.4 mmol) and an aqueous HCl solution (2.7 mL, 5.4 mmol) was stirred at 0 °C. A cold water solution of sodium nitrite (1 mL, 2 mmol) was added dropwise. Then, sodium acetate (0.440 g, 5.4 mmol) and acetate buffer (40 mL) were added at pH 4.5. KSeCN (0.288 g, 2 mmol) was added under vigorous agitation, and the solution was kept at 0 °C for 3 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined extracts were washed with water (2 × 30 mL) and dried over Na_2SO_4. After evaporation in vacuo, the 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. Two bands were eluted and evaporated in vacuo. The residue with highest R_f was recrystallized from EtOH, **2**. Yield: 0.030 g (10%); mp 88–90 °C. IR (KBr, cm^{-1}): 3097, 3066, 3027, 2235, 2160, 1583, 1550, 1473, 1384, 1284, 1270, 1213, 1187, 1108, 1072, 842, 524. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, 1H, J = 8.25), 8.02 (m, 2H). MS (ESI): m/z (%) = $[M+H]^+$ calcd for $C_9H_4N_3Se$: 233.95650; found: $[M+H]^+$ 233.95655. Anal. Calcd for $C_9H_3N_3Se$: C, 46.57; H, 1.30; N, 18.10. Found: C, 46.73; H, 1.35; N, 18.03. *4,4′-Diselanediyldiphthalonitrile* (**3**). The residue with lowest R_f was recrystallized from EtOH. Yield: 0.215 g (75%); mp 184–186 °C. IR (KBr, cm^{-1}): 3466, 3435, 2233, 1638, 1266, 1108, 741, 706, 524. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (m, 3H), 8.01 (m, 3H). MS (ESI): m/z (%) = $[M+Na]^+$ calcd for $C_{16}H_6N_4Se_2Na$: 436.88179; found: $[M+Na]^+$ 436.88119.

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19. *4-(Butylselanyl)phthalonitrile* (**4**). A mixture of compound **3** (0.108 g, 0.262 mmol), NaH (0.053 g, 2.5 mmol) and butyl bromide (0.2 mL, 1.2 mmol) in DMF (7 mL) was stirred under an Ar atmosphere at 75 °C for 3 h. The reaction mixture was poured into water (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL) and the combined extracts were washed with water (2 × 30 mL) and dried over Na_2SO_4. After evaporation in vacuo, the 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 water-EtOH. Yield: 0.089 g (65%); mp 51–52 °C. IR (KBr, cm^{-1}): 2958, 2925, 2871, 2856, 2229, 1577, 1261, 1186, 1064, 522. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, 3H, J = 7.32), 1.49 (m, 2H), 1.78 (m, 2H), 3.07 (t, 2H, J = 7.39), 7.61 (d, 1H, J = 8.22), 7.70 (d, 1H, J = 8.31), 7.75 (s, 1H). MS (ESI): m/z (%) = $[M+H]^+$ calcd for $C_{12}H_{13}N_2Se$: 265.02387; found: $[M+H]^+$ 265.02368. Anal. Calcd for $C_{12}H_{12}N_2Se$: C, 54.76; H, 4.60; N, 10.64. Found: C, 54.43; H, 4.30; N, 10.23.
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21. *2,9(10),16(17),23(24)-Tetrakis(butylselanyl)phthalocyaninatozinc(II)* (**5**). A mixture of 4-(butylselanyl)phthalonitrile (**4**) (0.071 g, 0.268 mmol), anhydrous zinc acetate (0.150 g, 0.66 mmol), and 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) (0.2 mL, 1.34 mmol) in anhydrous butanol was stirred and heated at 150 °C under Ar for 3 h. The mixture was cooled down and evaporated in vacuo. The green solid residue was dissolved in a small volume of CH_2Cl_2–MeOH (95:5) and filtered through a silica-gel column packed and pre-washed with the same solvent. After evaporation in vacuo, the dye was recrystallized from CH_2Cl_2–hexane. Yield 0.016 g (22%). IR (KBr, cm^{-1}): 2919, 2850, 1623, 1599, 1463, 1384, 1262, 1094, 1035, 805, 742. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (t, 12H), 1.50 (m, 8H), 1.82 (m, 8H), 3.12 (t, 8H) 7.05 (br s, 4H, Ar), 7.47 (br s, 4H, Ar), 7.77 (br s, 4H, Ar). MS (ESI): m/z (%) = $[M+H]^+$ calcd for $C_{48}H_{49}N_8Se_4Zn$: 1119.00445; found: $[M+H]^+$ 1118.99899.
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