



The synthesis of new silicon phthalocyanines and analysis of their photochemical and biological properties



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ABSTRACT

In this study, new silicon phthalocyanine compounds were synthesized. The new neutral compound **3** is reacted with excess dimethyl sulfate to obtain quaternized derivative; **3Q**. For the synthesis of the zwitterionic complex, **3** and excess 1,3-propanedisultone were reacted in dry dimethylformamide for 24 h under nitrogen atmosphere. The structures of all compounds were characterized by using spectrophotometric techniques. Experiments which include the singlet oxygen generation and photoinactivation of the yeast *Saccharomyces cerevisiae* both in the absence and presence of light indicated that these compounds can be potentially used in photodynamic therapy or photoinactivation of some microorganisms.

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1. Introduction

Phthalocyanines (Pcs) have been one of the most extensively studied classes of organic functional materials because of their aromatic 18- π electron system which is closely related to that of the naturally occurring porphyrin ring [1–3]. Phthalocyanine blue-green pigments have outstanding stability to light, heat, acid and alkaline substances and they are insoluble in organic solvents and water. Unsubstituted metal-free and metallophthalocyanines are practically insoluble in common organic solvents and aqueous media, thereby their applications are minimized. Quaternized ammonium groups are especially useful to achieve solubility within a wide range of buffers [4–7]. In addition to their conventional use in industry, Pcs are also used in photoinactivation of bacteria and photodynamic therapy (PDT) [8]. Pcs are particularly promising photosensitizers for PDT because of their intense absorption at about 680 nm and their ability to generate singlet oxygen via Type II mechanism [9]. In mammalian cells, photodynamic treatment with phthalocyanines resulted in damage to plasma membranes [10,11], energy metabolism [12] and DNA [13]. However, the mechanism(s)

for inactivation of eukaryotic cells is not known. Studies on yeast cells which are simple eukaryotes can provide useful information about the mechanism of photoinactivation. Moreover, this information can be used to develop new methods for the treatment of yeast infections by photodynamic treatment.

Pcs have a high tendency to aggregate in solutions, which can significantly decrease their photosensitizing ability through self-quenching [14]. Aggregation is an unfavorable property of Pcs that causes difficulties in purification and characterization. In order to overcome this problem, central metals with more than four coordination numbers like silicon are preferred, because they enable the introduction of additional aggregation inhibiting substituents, thus, they highly increase the amount of monomer in solution [15]. A silicon phthalocyanine, Pc 4, has attracted considerable interest as a PDT agent since it was reported to be used in PDT in 1993 [16]. Si(IV)-Pcs containing one or two bulky axial ligands usually show reduced aggregation, enhanced water solubility, and high photodynamic efficacy. Recently, two glycosylated Si(IV)-Pcs were shown to have high phototoxicity toward human carcinoma HT29 and HepG2 cells [17]. Porphyrins have a unique therapeutic role in medicine; they have been used to image, detect and treat different forms of diseased tissue including macular degeneration and a number of different cancer types. Thus, over the past few years, we have been focusing on the

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modification of tetrapyrrole derivatives. Several porphyrazines and Pcs have been synthesized and presented for the use of many different purposes [18–20]. We report herein the synthesis of neutral bis[8-methyl-8-azabicyclo[3.2.1]octan-3-oxy][phthalocyaninato]silicon (**3**), its quaternized derivative bis[8,8-dimethyl-8-azabicyclo[3.2.1]octan-3-oxy][phthalocyaninato]silicon sulfate (**3Q**) and bis[8-methyl-8-azabicyclo[3.2.1]octan-3-(N-propanesulfonato)oxy][phthalocyaninato]silicon (**3Z**) and the characterization of all the structures was done by using ¹H-NMR, MALDI-TOF, UV–vis and fluorescence spectrometric methods.

A number of experiments on photodynamic treatment of yeast with chloroaluminum phthalocyanine have been performed with a yeast species, *Kluyveromyces marxianus* [21]. In the present study, however; the model yeast *Saccharomyces cerevisiae* was used. It is a well-characterized microorganism the genome of which was fully sequenced in 1996. Thus, it is one of the most intensively studied eukaryotic model systems [22]. In this study, the growth inhibition of *S. cerevisiae* by the photoactivation of **3Q** and the possible use of these compounds as singlet oxygen generators in PDT was studied.

2. Experimental

2.1. Materials and yeast strain used

All reagents and solvents were of reagent grade quality and were obtained from commercial suppliers; and dichloro[phthalocyaninato]silicon, 1,3-diphenylisobenzofuran (DPBF), unsubstituted zinc phthalocyaninato (ZnPc) and 9,10-antracenediyl-bis(methylene)dimalonic acid (ADMA) were purchased from Aldrich. The *S. cerevisiae* reference strain CEN.PK 113-7D [23] was kindly provided by Dr. Laurent Benbadis (INSA Toulouse, France). Yeast nitrogen base without amino acids, and dextrose were purchased from Difco and Merck, respectively. Toluene was distilled from sodium prior to use. Chromatographic purifications were performed on basic aluminum oxide columns.

2.2. Equipment

¹H-NMR spectra were recorded on a Varian Mercury 500 MHz spectrometer in dimethyl sulfoxide (DMSO-*d*₆). Chemical shifts were reported (δ) relative to Me₄Si as internal standard.

Positive ion and linear mode MALDI-MS of complexes were obtained in dihydroxybenzoic acid as MALDI matrix using nitrogen laser accumulating 50 laser shots using Bruker Microflex LT MALDI-TOF mass spectrometer.

IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrophotometer and electronic spectra on Scinco Neosys 2000 double beam UV/vis spectrophotometer with 1 cm path length quartz cuvettes in the spectral range of 300–800 nm.

Elemental analyses were performed with Thermo Finnigan Flash EA 1112 at 950–1000 °C.

Photo-irradiations were done using a 300 W halogen lamp. A 600 nm glass cut off filter (Schott) and a water filter were used to filter off ultraviolet and infrared radiation, respectively. Interference filters (Intor, 650 and 670 nm with a band width of 40 nm) was additionally placed in the light path before the sample. Light intensities were measured with a THORLABS power meter.

2.3. Synthesis of bis[8-methyl-8-azabicyclo[3.2.1]octan-3-oxy][phthalocyaninato]silicon (**3**)

A mixture of silicon(IV) phthalocyanine dichloride (70.60 mg, 0.115 mmol) (**1**), tropine (49.38 mg, 0.345 mmol) (**2**) and sodium

hydride (24.8 mg, 1.035 mmol) in toluene (35 ml) was refluxed for 24 h at 120 °C. The mixture was then centrifuged (5000 × g) for 10 min, and the filtrate was collected. After evaporating the solvent *in vacuo*, the residue was subjected to column chromatography using THF/EtAc (1/1) as eluent. Yield: 28.83 mg (% 30.42). IR ν_{max} (cm⁻¹): 3059; 2927; 2585; 1611; 1519; 1471; 1427; 1333; 1289; 1258; 1229; 1164; 1120; 1072; 1052; 924; 909; 872; 840; 801; 758; 730. UV–vis (DMF), max/nm (log ε): 349 (4.56), 609 (4.23), 672 (4.95). ¹H-NMR (δ) (DMSO-*d*₆) ppm: 9.67–9.65 (m, 8H, H_α); 8.48–8.46 (m, 8H, H_β); 2.16 (s, 6H, N–CH₃); 2.03–2.01 (m, 4H, H_b); 1.89–1.94 (m, 8H, H_c); 1.10–1.07 (m, 8H, H_a); –0.07–(–0.05) (m, 2H, O–CH). Mass (MALDI-TOF) (Fig. 1): Calculated *m/z* for [R₁+2R₂]⁺: 821.01; found: 821.94. Calculated *m/z* for [R₁+R₂]⁺: 681.51; found: 681.75. Calculated *m/z* for [R₂+R₁+O+R₁]⁺: 1237.10; found: 1237.81. Elemental analysis: Calculated C:70.22; H: 5.40; N: 17.06. Found: C: 69.55; H: 5.85; N: 18.01.

2.4. Synthesis of quaternized bis[8,8-dimethyl-8-azabicyclo[3.2.1]octan-3-oxy][phthalocyaninato]silicon sulfate (**3Q**)

The quaternization was performed according to the method reported previously reported [6]. Compound **3** (0.017 g, 0.020 mmol) was heated to 120 °C in freshly distilled dimethylformamide (DMF) (5 mL) and excess dimethyl sulfate (0.1 mL) was added dropwise. The mixture was stirred at 120 °C for 12 h, and was then cooled to room temperature. The product was precipitated with hot acetone and the precipitate was collected by centrifugation (5000 × g) for 15 min. The blue solid product was washed successively with hot ethanol, ethyl acetate, tetrahydrofuran, chloroform, hexane and diethyl ether. The resulting hygroscopic product was dried over phosphorous pentoxide. Yield: 9.05 mg % 47.65. IR ν_{max}/(cm⁻¹): 2980; 1525; 1336; 1194; 1123; 1077; 1045; 898; 736; 672. UV–vis (H₂O), max/nm (log ε): 349 (4.73), 624 (4.38), 691 (5.13). ¹H-NMR (δ) (DMSO-*d*₆) ppm: 9.80–9.71 (m, 8H, H_α); 8.52–8.45 (m, 8H, H_β); 2.51 (s, 12H, N–CH₃); 2.41–2.37 (m, 4H, H_b); 2.24–2.21 (m, 8H, H_c); 1.81–1.78 (m, 8H, H_a); –1.71–(–1.82) (m, 2H, O–CH). Mass (MALDI-TOF) (Fig. 1): Calculated *m/z* for [R₃+DHB]⁺: 1101.27; found: 1102.23. Elemental analysis: Calculated C:63.40; H: 5.32; N: 14.79. Found: C: 62.90; H: 6.05; N: 13.82.

2.5. Synthesis of bis[8-methyl-8-azabicyclo[3.2.1]octan-3-(N-propanesulfonato)oxy][phthalocyaninato]silicon (**3Z**)

The procedure was applied according to the method previously reported [24]. Compound **3** (0.02 g, 0.024 mmol) and 1,3-propanedisulfone (0.277 g, 11.38 mmol) were reacted in dry DMF for 24 h at 50 °C. After addition of CH₂Cl₂ to the mixture, the precipitate was collected by centrifugation at (5000 × g) for 15 min. To remove the excess 1,3-propanedisulfone, the precipitate was washed with acetone and CH₂Cl₂ (5 × 5 mL) and then dissolved in water. The impurities were eliminated by filtration. After addition of acetone to the filtrate, the product was obtained after centrifuged at (5000 × g) for 10 min. The crude product was dried over phosphorous pentoxide. Yield: 9.7 mg % 37.65. IR ν_{max}/(cm⁻¹): 1647; 1513; 1467; 1425; 1329; 1286; 1163; 1121; 1027; 904; 832; 753; 723. UV–vis (DMF), max/nm (log ε): 354 (3.92), 603 (3.70), 667 (4.24). ¹H NMR (δ) (DMSO-*d*₆) ppm: 9.62 (m, 8H, H_α); 8.22 (m, 8H, H_β); 3.38–3.42 (t, 4H N–CH₂–CH₂–CH₂–SO₃); 3.15 (s, 6H N–CH₃); 2.94–2.97 (t, 4H CH₂–SO₃); 2.65–2.67 (m, 4H N–CH₂–CH₂–CH₂–SO₃); 2.47–2.49 (m, 4H H_b); 2.40–2.43 (m, 8H H_c); 1.66–1.71 (m, 8H, H_a); 1.05–1.09 (t, 2H O–CH). Mass (MALDI-TOF) (Fig. 1): Calculated *m/z* for [R₁+2R₄+2Na]⁺: 1111.30;

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