



A new hexadeca substituted non-aggregating zinc phthalocyanine



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ABSTRACT

In this work, a new hexadeca substituted zinc phthalocyanine **4** bearing hexyloxy groups in non-peripheral positions and 3-(diethylamino)phenoxy groups in peripheral positions and its corresponding water-soluble octacationic derivative **5** have been reported. The new compounds have been characterized by elemental analysis, IR, UV, NMR and mass spectra. Zinc phthalocyanine showed excellent solubility in organic solvents of wide polarity range due to its amphiphilic nature and it enabled us to carry out detailed UV–Vis studies in different solvents. Octacationic zinc phthalocyanine **5** was soluble in DMF, DMSO and water. UV–Vis spectra of **5** in DMSO, DMF and water showed sharp Q band absorption as an indication of monomeric form even in aqueous media. This property of water-soluble non-aggregating zinc phthalocyanine is promising as a photosensitizer in Photodynamic Therapy of Cancer.

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1. Introduction

Phthalocyanines (pcs), synthetic analogues of naturally occurring porphyrin family, are second generation synthetic photosensitisers for photodynamic therapy (PDT) of cancer [1,2]. In this context intense research on pcs as photosensitisers has been increasing rapidly [3–5]. In terms of their properties such as high photostability, low dark toxicity, long lived triplet state, high capability of photo-generation of singlet oxygen and intense absorption on the far red region, where tissue penetration by visible light is superior, pcs are promising candidates as photosensitisers for PDT [6]. Pcs containing diamagnetic metals or metalloids such as Zn^{2+} , Al^{3+} , Ga^{3+} have long triplet state lifetimes ($\tau > 200 \mu s$) and generate singlet oxygen with high quantum yields (ϕ) of approximately 0.3–0.5 [7]. A drawback for pcs as a photosensitiser is their tendency to form aggregates especially in aqueous media which reduces their photochemical activity [7]. One effective strategy to reduce aggregation of pcs is the introduction of long –alkyl or –alkoxy groups on non-peripheral positions which reduces the aggregation due to steric crowding above or below the plane of pc macrocycle [8]. Furthermore, substituents modify their solubility, hydrophilic-lipophilic balance and interactions with the biological systems [9].

A pc ring is generally considered as a planar aromatic macrocycle, but X-ray studies have shown that some metal ions too big or

too small for pc core can deform the planarity of the pc ring [10]. Recently, it has been also reported that substituents also can deform the planarity of pc ring and it is assumed that most of the hexadeca substituted pcs will show deformation from the planarity due to steric congestion [11–13]. These deformations leading to some exceptional chemical and spectral properties for the pcs are of intense current research interest [14,15].

Hexadeca substituted pcs are relatively less studied compared to tetra- or octa- substituted pcs [16]. Nature of the substituents are also extremely important on colour and accordingly on the absorption maxima of the pcs. Substitution of pc macrocycle with electron donating groups cause bathochromic shift on the Q band absorption of pc [17]. When identical substituents are compared, shift in absorption maxima to longer wavelengths has higher values in the case of non-peripheral positions than in peripheral positions [17]. Naturally, hexadeca-substituted pcs with substituents both on non-peripheral and peripheral positions with the electron donating groups are expected to cause even larger bathochromic shifts. This red shift is desired especially for PDT applications [17].

In the present work, the preparation of novel hexadeca substituted zinc phthalocyanine carrying hexyloxy groups on nonperipheral positions and quaternizable 3-(diethylamino)phenoxy groups on peripheral positions has been achieved in the presence of $Zn(CH_3COO)_2$ by using microwave irradiation. The water-soluble derivative **5** of pc **4** have been synthesized via the quaternization of eight tertiary amine groups with methyl iodide. A distinct feature of the pc **4** is its high sensitivity to changes in the acidity of the solvents which has been attributed to high proton affinity of meso-nitrogens [18] as encountered in some non-

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peripheral substituted pcs probably with lower planarity. We have also investigated the singlet oxygen generation capability of ZnPc and its water soluble derivative.

2. Experimental

2.1. Chemicals and instrumentation

IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR (ATR sampling accessory) spectrophotometer, electronic spectra on a Scinco S-3100 spectrophotometer by using 1 cm and 1 mm path length cuvettes at the room temperature. A Rofin Polilight PL400 Forensic Plus light source was used for the irradiation of the samples at 650 nm for qualitative singlet oxygen determination. ^1H NMR, ^{13}C spectra and gradient DQF-COSY were recorded on Agilent VNMR5 500 MHz and the spectrum was referenced internally by using the residual solvent resonances ($\delta = 7.27$ for CDCl_3 and 2.49 for $\text{DMSO}-d_6$ in ^1H NMR). Mass spectra were measured on a Micromass Quatro LC/ULTIMA LC-MS/MS spectrometer. Elemental analyses were performed by the Instrumental Analysis Laboratory of the TUBITAK Marmara Research Center. Single mode microwave reactor (CEM DISCOVER SP) was used for carrying out the synthesis of zinc phthalocyanine. All reagents and solvents were of reagent grade quality obtained from commercial suppliers. The homogeneity of the products was tested in each step by TLC. The solvents were stored over molecular sieves. Anhydrous potassium carbonate (K_2CO_3) was finely ground and dried at 100 °C. 4,5-dichloro-3,6-bis(hexyloxy)phthalonitrile (**2**) was synthesized according reported procedure [19].

2.2. Synthesis

2.2.1. Synthesis of 4,5-bis(3-(diethylamino)phenoxy)-3,6-bis(hexyloxy)phthalonitrile (**3**)

3-(diethylamino)phenol (1 g, 6 mmol) was added to a solution of 4,5-dichloro-3,6-bis(hexyloxy)phthalonitrile (0.8 g, 2 mmol) in anhydrous DMF (15 ml) under nitrogen atmosphere. After stirring for 15 min, finely ground anhydrous K_2CO_3 (2.76 g, 20 mmol) was added in small portions for 2 h with efficient stirring. The reaction mixture was stirred under nitrogen atmosphere at 120 °C for 6 h. Then the reaction mixture was cooled to room temperature and diluted with 50 ml of ethyl acetate and the solution was washed several times with 1 M aqueous NaOH and brine. The organic phase was dried with Na_2SO_4 and the solvent was evaporated under reduced pressure to give the crude product. The oily brown product was chromatographed on preparative silica gel plate (0.75 mm) with ethyl acetate/n-pentanol (1:10) mixture as eluent to give oily yellow product. Yield: 0.51 g, 39%, FTIR (ν , cm^{-1}): 3073 (Ar–H), 2966, 2930, 2871 (R–H), 2233 (CN), 1198 (Ar–O–Ar), 1172, 1021 (Ar–O–R). ^1H NMR (500 MHz, CDCl_3): δ , ppm 7.01 (2H, t), 6.35 (2H, dd), 6.03 (2H, t), 5.90 (2H, dd), 4.15 (4H, t), 3.25 (8H, q), 1.65 (4H, quin), 1.34 (4H, quin), 1.27–1.21 (8H, m), 1.10 (12H, t), 0.85 (6H, t), ^{13}C NMR (126 MHz, CDCl_3) δ ppm, 158.16, 152.97, 149.16, 146.97, 129.80, 113.08, 107.09, 105.80, 101.68, 99.70, 75.90, 44.45, 31.48, 29.93, 25.30, 22.56, 14.06, 12.58, MS: m/z 655.73 [$\text{M} + \text{H}$] $^+$, 677.78 [$\text{M} + \text{Na}$] $^+$, Anal. calc. for $\text{C}_{40}\text{H}_{54}\text{N}_4\text{O}_4$: C, 73.36; H, 8.31; N, 8.56; found C, 73.45; H, 8.35; N, 8.35%.

2.2.2. Synthesis of 2,3,9,10,16,17,23,24-oktakis-[3-dietthylamino-(phenoxy)]-1,4,8,11,15,18,22,25-oktakishexyloxyphthalocyaninatozinc(II) (**4**)

A mixture of 4,5-bis(3-(diethylamino)phenoxy)-3,6-bis(hexyloxy)phthalonitrile **3** (0.2 g, 0.3 mmol) and anhydrous zinc acetate (0.028 g, 0.15 mmol) in n-pentanol (1 ml), in the presence of a drop of 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) was irradiated by

microwave at 160 °C for 15 min. The reaction mixture was cooled to room temperature and then poured into methanol. The precipitate was filtered and washed with excess methanol. The product was purified by column chromatography twice (neutral alumina, dichloromethane/THF v/v, 30/1). After drying, ZnPc (30 mg) was obtained (yield: 14.6%). FTIR, cm^{-1} 3078 (Ar–H), 2955, 2927, 2857 (R–H), 1203 (R–O–Ar), ^1H NMR (500 MHz, CDCl_3): δ , ppm 7.01 (8H, t), 6.45 (8H, t), 6.33 (16H, dd), 4.93 (16H, t), 3.30 (32H, q), 1.82 (16H, quin), 1.34–1.10 (96H, m), 0.73 (24H, t) ^{13}C NMR (126 MHz, CDCl_3) δ , ppm 160.39, 152.10, 149.14, 147.09, 144.46, 129.39, 127.50, 106.12, 102.87, 100.76, 76.76, 44.54, 32.01, 30.33, 25.85, 22.76, 14.24, 12.80, MS: m/z 2684.89. [$\text{M} + 2\text{H}$] $^+$, Anal. calc. for $\text{C}_{160}\text{H}_{216}\text{N}_{16}\text{O}_{16}\text{Zn}$: C, 71.57; H, 8.11; N, 8.35; found C, 71.78; H, 8.42; N, 8.25%.

2.2.3. Synthesis of 2,3,9,10,16,17,23,24-oktakis-[3-diethylmethylamino-(phenoxy)]-1,4,8,11,15,18,22,25-oktakishexyloxyphthalocyaninatozinc(II) octaiodide(**5**)

Zinc phthalocyanine **4** (25 mg) and excess methyl iodide (0.25 ml) was dissolved in dichloromethane and the mixture was kept in dark for 3 weeks. The resulting precipitate was filtered off and then washed with chloroform and ethyl acetate to remove any organic impurities and subsequently dried under vacuum. Green solid was obtained with a yield of 72% (25.6 mg). ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ , ppm 7.32–7.72 (32H, m), 4.93 (16H, b), 4.02 (16H, b), 3.80 (16H, b), 3.42 (24H, b), 1.69 (16H, b), 1.29–0.9 (96H, m), 0.7 (24H, m), ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ , ppm 159.72, 152.05, 149.07, 146.45, 142.58, 131.63, 128.90, 116.82, 116.27, 110.03, 76.65, 63.86, 46.32, 31.49, 29.99, 25.46, 22.36, 14.31, 8.56. Anal. calc. for $\text{C}_{168}\text{H}_{240}\text{I}_8\text{N}_{16}\text{O}_{16}\text{Zn}$: C, 52.82; H, 6.33; N, 5.87; found C, 52.65; H, 6.22; N, 5.75%.

3. Results and discussion

3.1. Synthesis and characterization

The synthetic route followed in this work is shown in Scheme 1. Starting with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, its reduction to 4,5-dichloro-3,6-dihydroxyphthalonitrile and subsequently alkylation of the OH groups yielded 4,5-dichloro-3,6-dihexyloxyphthalonitrile (**2**) as reported earlier [19].

The synthesis of a new phthalocyanine precursor **3** has been achieved by nucleophilic aromatic substitution reaction which is frequently used for preparation of ether or thioether substituted phthalonitrile derivatives [20–22]. Displacement of two chloro groups of 4,5-dichloro-3,6-dihexyloxyphthalonitrile (**2**) with the OH function of 3-(diethylamino)phenol in the presence of K_2CO_3 as a base in dry dimethylformamide (DMF) at 120 °C results with **3** from the nucleophilic aromatic substitution reaction. The isolation and purification of the compound **3** was accomplished by preparative thin layer chromatography (TLC). Cyclotetramerization of the phthalonitrile **3** gave the phthalocyanine derivative **4**. The reaction was carried out in n-pentanol by using $\text{Zn}(\text{CH}_3\text{COO})_2$ as metal source and DBU as catalyst at 160 °C in a sealed tube under microwave irradiation for 15 min. Column chromatography on neutral alumina using dichloromethane (DCM)/tetrahydrofuran (THF) (1/1) as mobile phase was used for purification of the zinc phthalocyanine. Further quaternization of the diethylamino substituents with methyl iodide yielded water soluble derivative **5**. The structure and purity of the **3**, **4** and **5** was confirmed by IR, UV–Vis, ^1H NMR and Mass spectroscopic techniques.

The IR spectrum of **3** shows CN vibrational peak at 2233 cm^{-1} , the aliphatic C–H vibrations at 2954, 2931, 2870 cm^{-1} and aromatic C–H vibrations at 3078 cm^{-1} . In the FTIR spectra of phthalocyanine **4** the disappearance of CN vibration is an immediate indication of cyclotetramerization.

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