



Enhanced triplet state parameters for zinc carboxy phenoxy phthalocyanine following conjugation to ascorbic acid: Effects of adsorption on single walled carbon nanotubes



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ABSTRACT

Zinc phthalocyanine bearing four ascorbic acid units (formed via ester bond between zinc carboxy phenoxy phthalocyanines and ascorbic acid) was synthesized and characterized using different spectroscopic methods. The complex (with or without ascorbic acid) was further adsorbed onto single walled carbon nanotubes (SWCNTs) and further characterized using Raman spectroscopy, X-ray diffractometry, transmission electron microscopy and thermogravimetric analysis. The photophysical properties of the complexes were studied. The synthesized complex showed better photophysical properties when compared to the carboxy phenoxy phthalocyanines alone, this is evident in the increase of the triplet quantum yields (Φ_T), triplet life-times (τ_T) and singlet oxygen quantum yields (Φ_Δ). The zinc phthalocyanines bearing ascorbic acid showed improved triplet life-times even in the presence of SWCNTs.

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1. Introduction

The effective interaction of the photo-excited triplet state of metallophthalocyanines (MPcs) with ground state molecular oxygen (3O_2) to generate singlet oxygen (1O_2) (the chief cytotoxic species responsible for cancerous cells destruction) has made MPcs good candidates as photosensitizers for photodynamic therapy (PDT) [1–3]. As a result, MPcs are in different phases of clinical trials [1,3,4]. One of the ways to improve the photophysical properties of MPc in selective tumor destruction is to develop targeting strategies which include conjugating MPcs to compounds that are over-expressed in cancer cells and have the ability to generate singlet oxygen [5–7].

Ascorbic acid (AA) has a long history in the treatment of cancer. Cameron et al. [8–10] showed that patients who received ascorbate survived 300 days longer than controls. Studies have shown that the intravenous administration of ascorbate in pharmacological concentration can selectively kill cancer cells [11–14]. Ascorbic acid is a well-known antioxidant and would be expected to quench singlet oxygen and other reactive oxygen species (ROS) required for PDT. The effect of ascorbic acid on the photophysical properties of phthalocyanines is reported for the first time in this work. We conjugated ascorbic acid to previously reported zinc tetra carboxy

phenoxy phthalocyanine (ZnTCPPc (**1**)) [15] complex. We show in this work that when AA is linked to Pc complex through a phenyl bridge there is considerable increase in the triplet quantum yield at the same time lengthening the triplet life-time, with a corresponding increase in singlet oxygen quantum yield in organic media.

The PDT effect of MPc or MPc-AA conjugate can be further improved by immobilizing them on delivery agents such as single walled carbon nanotubes (SWCNTs) that have anticancer properties [16]. SWCNTs are drug carriers that can absorb light in the near infrared region, thus killing cancer cells through photothermal (PTT) effect [17–21]. SWCNTs covalently functionalized with carboxylic acid (represented as SWCNT-COOH) were used in this work, instead of unfunctionalized SWCNTs. Covalent functionalization involves the introduction of functional groups to either the ends or the side wall of the SWCNTs by creating defect sites through oxidation. This process affects the extended π system of the SWCNTs backbone, thus influencing the electronic properties [22–26]. Functionalized SWCNTs have the additional advantage of increasing drug specificity and increasing their solubility in aqueous media. Unlike unfunctionalized SWCNTs which have hydrophobic surface [27], functionalized SWCNTs have the ability to move across cellular membranes with less cytotoxic effects compared to the unfunctionalized SWCNTs [18].

In this report, the photophysical properties of ZnTCPPc (**1**) when directly conjugated to ascorbic acid via ester bond are examined.

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The conjugate is represented as: ZnTCPPc-AA (**2**) (Scheme 1A). Complexes **1** and **2** were further immobilized into SWCNT-COOH, represented as ZnTCPPc-AA-SWCNT (**3**) (Scheme 1B) and ZnTCPPc-SWCNT (**4**) respectively.

2. Experimental

2.1. Materials

Zinc phthalocyanine (ZnPc), ascorbic acid, N,N'-dicyclohexylcarbodiimide (DCC), dimethylaminopyridine (DMAP) and lipophilic Sephadex LH-20 microbeads were from Sigma Aldrich. Single-walled carbon nanotubes (SWCNT-COOH, 1–5 nm in diameter and 1–5 μm in length) were obtained from Nanolab. Dimethylsulfoxide (DMSO), hexane, dimethylformamide (DMF), and tetrahydrofuran (THF) were obtained from SAARCHEM. ZnTCPPc [15] was synthesized according to literature methods.

2.2. Equipment

Absorption spectra were recorded on a Shimadzu UV-Vis 2550 spectrophotometer and fluorescence emission and excitation spectra on a Varian Eclipse spectrofluorimeter using a 360–1100 nm filter. The absorbance ranged between 0.04 and 0.05 at the excitation wavelength for all samples.

Fluorescence life-times were measured with a FluoTime 300 'EasyTau' spectrometer (PicoQuant GmbH) using a time correlated single photon counting (TCSPC) technique. The samples were excited at 670 nm with a diode laser (LDH-P-670, 20 MHz repetition rate, 44 ps pulse width, PicoQuant GmbH). The detector employed was a Peltier cooled Photomultiplier (PMA-C 192-M, PicoQuant GmbH).

Laser flash photolysis experiments were performed to determine the triplet decay kinetics. The excitation pulses were produced by a tunable laser system consisting of an Nd:YAG laser (355 nm, 135 mJ/4–6 ns) pumping an optical parametric oscillator (OPO, 30 mJ/3–5 ns) with a wavelength range of 420–2300 nm (NT-342B, Ekspla) as the detector. The details have been reported [28]. Triplet life-times were determined by the exponential fitting of the decay curves using Origin-Pro 8 software.

Time resolved phosphorescence of singlet oxygen at 1270 nm was used to determine the singlet oxygen quantum yields of all the complexes in DMSO, details have been described by Modisha et al. [29]. The singlet oxygen phosphorescence signal was compared with that of ZnPc standard.

X-ray powder diffraction (XRD) patterns were recorded on a Bruker D8 Discover equipped with a Lynx-Eye Detector, using Cu K α radiation (=1.5405 Å, nickel filter). Data were collected in the range from 10° to 100°, scanning at 1° min⁻¹ with a filter time-constant of 2.5 s per step and a slit width of 6.0 mm. Details have been provided [30].

Mass spectra data were collected with a Bruker AutoFLEX III Smart beam TOF/TOF mass spectrometer. The instrument was operated in the positive ion mode using an m/z range of 400–3000 amu. The spectra were acquired using α -cyano-4-hydroxycinnamic acid as the MALDI matrix, with a 355 nm Nd:YAG laser as the ionizing source. Infrared spectra were recorded on a Perkin-Elmer Universal ATR Sampling accessory spectrum 100 FTIR spectrometer. Elemental micro analysis was measured using Vario MICRO cube.

Raman spectra were obtained using a Bruker RAM II spectrometer (equipped with a 1064 nm Nd:YAG laser and a liquid nitrogen cooled germanium detector). Solid samples diluted with KBr were used. Thermogravimetric analysis (TGA) were recorded

on a Shimadzu DTG-TG 60H with a gas flow of 120 ml/min and operated under a nitrogen atmosphere at 10 °C/min.

Transmission electron microscopy (TEM) images were obtained using a Zeiss Libra TEM 120 model operated at 90 kV.

2.3. Synthesis

2.3.1. Synthesis of ZnTCPPc-AA (**2**) conjugate, Scheme 1A

ZnTCPPc (**1**) (0.1 g, 0.089 mmol) was stirred with 0.02 g (0.098 mmol) of DCC for 24 h in DMF to activate the carboxy groups of the Pc substituent. After this time, 0.062 g (0.098 mmol) of ascorbic acid and 5 mg (0.04 mmol) of DMAP were added and the mixture further stirred for 48 h according to modified literature method [31]. The solid product was precipitated out of solution using ethanol, and repeatedly washed with ethanol to remove unreacted DCC and DMAP which were soluble in ethanol. The product was further washed with de-ionized water to remove unreacted ascorbic acid. The solid product was further purified by silica gel column chromatography using the solvent mixture of THF and hexane (95:5 v/v) as eluent.

ZnTCPPc-AA (**2**): Yield, 86% (0.135 g), UV-Vis (DMSO), λ_{max} (nm) (log ϵ): 681 (5.6), 614 (5.1), 354 (6.0). Anal. Calc. for C₈₄H₅₆N₈O₃₂Zn: C, 57.49; H, 3.22; N, 6.39. Found: C, 57.46; H, 3.00; N, 5.10%. MALDI-TOF-MS (m/z): 1754 amu, Found: 1756 [M+2H]⁺. IR [(ATR) ν_{max} /cm⁻¹]: 3437–3093 (O–H str.), 1694 and 1600 (C=O), 1387 (O–H bend), 1091 and 1043 (C–O–C str.). ¹H NMR (600 MHz, DMSO-*d*₆): δ /ppm: 8.9–8.8 (d, 4H, Ar-H), 8.5 (m, 4H, Ar-H), 8.1–8.0 (d, 8H, Ar-H), 7.7 (m, 4H Ar-H), 7.5–7.3 (m, 8H, Ar-H), 4.72–4.70 (b, 4H, CH), 3.72–3.69 (b, 4H, CH), 3.41–3.40 (b, 8H, CH₂).

2.3.2. Synthesis of the adsorbed (immobilized) ZnTCPPc-AA-SWCNT (**3**) conjugate, Scheme 1B

ZnTCPPc-AA (**2**) was immobilized onto SWCNT-COOH according to literature methods for immobilization of other Pcs [32] with slight modification as follows: 30 mg of SWCNT-COOH were ultrasonicated for 20 min in 2 ml of DMF to give a brown colored suspension. ZnTCPPc-AA (**2**) (0.02 g, 0.01 mmol) was added to the solution to give a blue suspension and the resulting mixture was stirred for 4 days to give a dark blue solution indicating the adsorption of complex **2** onto SWCNT-COOH. Ethanol was added and the solid product was obtained by centrifugation. The solid product was repeatedly washed using ethanol.

ZnTCPPc-AA-SWCNT (**3**): UV-Vis (DMSO) λ_{max} (nm): 683. IR [(ATR) ν_{max} /cm⁻¹]: 3412–3184 (O–H str.), 1635 and 1599 (C=O), 1391 (O–H bend.), 1136 (C–O–C str.). [Raman ν_{max} /cm⁻¹]: 2549 (G*), 1590 (G), 1281 (D).

2.3.3. Synthesis of ZnTCPPc-SWCNT (**4**) adsorbed

ZnTCPPc was immobilized onto SWCNT-COOH, using similar procedure as explained for complex **3** above.

ZnTCPPc-SWCNT (**4**): UV-Vis (DMSO), λ_{max} (nm): 682. IR [(ATR) ν_{max} /cm⁻¹]: 3377–3088 (O–H str.), 1664 and 1596 (C=O), 1384 (O–H bend.), 1088 (C–O–C str.). [Raman ν_{max} /cm⁻¹]: 2550 (G*), 1589 (G), 1281 (D).

2.4. Photophysical parameters

Triplet (Φ_T) and fluorescence (Φ_F) quantum yields for complexes **1–4** were determined using the comparative methods as described before [33–36]. ZnPc in DMSO was employed as a standard for triplet quantum yield (Φ_T) = 0.65 [33] and fluorescence quantum yield (Φ_F) = 0.20 [36]. Singlet oxygen quantum yields (Φ_{Δ}) were determined using the time resolved phosphorescence decay curve at 1270 nm as described before [29,37] using ZnPc as a singlet oxygen quantum yield standard ($\Phi_{\Delta}^{\text{std}}$ = 0.67 [38]).

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