Journal of Molecular Structure 1102 (2015) 190–196

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Synthesis and photophysicochemical studies of poly(ethylene glycol) conjugated symmetrical and asymmetrical zinc phthalocyanines

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ARTICLE INFO

Article history:
Received 26 June 2015
Received in revised form
28 August 2015
Accepted 29 August 2015
Available online 3 September 2015

Keywords:
Symmetrical zinc phthalocyanine
Asymmetrical zinc phthalocyanine
Click
Star polymer
Photodynamic therapy

ABSTRACT

Synthesis and characterization of poly(ethylene glycol) conjugated symmetrical and asymmetrical zinc phthalocyanines (ZnPcs) is described. Copper (I) catalyzed azide-alkyne cycloaddition (CuAAC) click reaction between azide functional methoxypoly(ethylene glycol) (mPEG-N_3) and tetra terminal alkynyl substituted ZnPc yields star polymer with ZnPc core. Furthermore, CuAAC click reaction between asymmetrically terminal alkynyl substituted zinc phthalocyanine (aZnPc) and mPEG-N_3 yields aZnPc end functionalized PEG. Spectral, photophysical (fluorescence quantum yield), photochemical (singlet oxygen (Φ_Δ), and photodegradation quantum yield (Φ_d) properties of the symmetrically, and asymmetrically PEGylated ZnPcs are investigated to be used as sensitizers in photodynamic therapy (PDT). The quantum yield values of fluorescence (Φ_F) and singlet oxygen generation (Φ_Δ) for water soluble symmetrically PEGylated ZnPc in aqueous solution are calculated as 0.01 and 0.14 respectively, suggesting its potential as photosensitizer in PDT treatment.

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1. Introduction

Phthalocyanines (Pcs) and their derivatives are colored 18 π-electron aromatic planar macrocycles that are used in a number of applications because of their high chemical stability, architectural flexibility, diverse coordination properties, and good spectroscopic characteristics [1]. The interest in Pcs has been recently expanded to other hi-tech applied fields such as catalyst, photovoltaics, optical data storage, energy transfer, electrophotography, etc. [2–8]. More recently, photodynamic therapy (PDT) has gained considerable interest as a new application area of Pcs [9]. Pcs are excellent photosensitizing agents due to their strong absorbance at long wavelengths and high chemical and photo-stability. However, the insolubility, and high tendency for aggregation of unsubstituted Pcs' especially in aqueous solution limit their potential application in PDT [10–12]. In PDT application, the medicine is given into the patient's blood stream, and since the blood itself is a hydrophilic system, water solubility becomes important for a potential PS in PDT [13,14]. The most widely used method for improving the solubility of Pcs' is based on attaching multiple hydrophilic or amphiphilic substituents to the periphery or the core of Pcs such as carboxylates [15,16], sulfonates [16,17], phosphonates [18], pyridinium ions [19], hydroxyl groups [20], peptides [21], oligonucleotides [22], and quaternized amines [23]. Functionalization of Pcs with poly(ethylene glycol) (PEG) is becoming increasingly important due to the chemical inertness, biocompatibility, improved serum life, and tumor cell accumulation of PEG and related PEGylated Pcs [24–28]. McKeown et al. first reported the synthesis of water-soluble Pc-centered poly (ethyleneoxy) species by the cyclotetramerization of phthalonitrile-capped oligo (ethyleneoxy) precursors of modest DP (3, 8, 12 and 16) [29,30]. Another group has prepared PEGylated zinc(II)-phthalocyanines containing one, two, or eight tri(ethylene glycol) chains. They have found that PEGylated Pcs are highly soluble in polar solvents such as acetone, *N*,*N*-dimethylformamide (DMF), and dimethylsulfoxide (DMSO). However, the yields were in the range of 1–8% and no information was presented about the solubility PEGylated Pcs in aqueous solution [25]. Ng et al. reported the synthesis, spectroscopic properties, and in vitro photodynamic activities of a series of silicon(IV)

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http://dx.doi.org/10.1016/j.molstruc.2015.08.067
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phthalocyanines covalently linked with two short PEG chains at the axial positions [31]. They also documented the complexation with bovine serum albumin (BSA) and the effects of halogen substitution on the PDT efficiency [32]. Same group have reported the synthesis, photophysical properties, and in vitro photodynamic activities of glucoconjugated silicon(IV) phthalocyanines containing tetraethylene glycol chains [33]. Another group has reported the synthesis of uncharged, water-soluble Pcs with low molecular weight ($\leq$750) PEG branches covalently bound on their peripheral positions [34]. However, the efficient synthesis of PEGylated Pcs remained a challenge since the traditional synthesis methods are not only enormously time consuming, but also require tedious purification steps. Recently, Haddleton et al. have reported the synthesis of octa-substituted Pc and copper Pc (CuPc) with different chain lengths of monomethyl ether polyethylene glycol (mPEG) through combining a phenolic Mitsunobu reaction with CuAAC click reaction [35]. They found that the PEGylated CuPc complexes are highly soluble and non-aggregated in common organic solvents (dichloromethane, tetrahydrofuran, DMF, etc.) and also exhibit good water solubility.

Most recently, we have reported the syntheses of Pc-containing well-defined polystyrene (PS) and poly(*tert*-butyl acrylate) (P*t*BA) in which phthalocyanine compound is either end-group or core. Targeted Pc-functionalized polymers were synthesized by CuAAC click reaction between asymmetrically- or symmetrically tetra terminal alkynyl substituted Pcs and azide end-functionalized PS and P*t*BA [36,37]. In continuation of our recent studies on Pc-containing polymers [36–38], we present here for the first time the synthesis, characterization, and photophysicochemical behaviors of symmetrically, and asymmetrically PEGylated ZnPcs. There is very limited study on water soluble Pc derivatives, and especially on photochemical procedures such as singlet oxygen generation, etc. of these valuable compounds. Thus, this study can shed light on hitherto barely sufficient literature about the potentials of phthalocyanine polymer conjugates as photosensitizers in PDT.

2. Experimental

2.1. Characterization

The gel permeation chromatography measurements of polymers were obtained from an Agilent instrument (Model 1100) consisting of a pump, a refractive index (RI), and ultraviolet (UV) detectors, a column oven, and three Macherey Nagel columns (103S, 104S, 105S). 0.01 M LiBr/DMF was used as an eluent at a flow rate of 0.7 mL/min at 50 °C. Toluene was used as an internal standard. The molecular weight of the polymers was calculated based on linear poly(methyl methacrylate) standards (Polymer Laboratories). Absorption spectra in the UV–Visible region were obtained with a Shimadzu 2001 UV spectrophotometer. Fluorescence spectra were measured using a Varian Eclipse spectrofluorometer using 1 cm path length cuvettes at room temperature. Photo-irradiations for singlet oxygen determination were measured using a General Electric quartz line lamp (300 W). A 600 nm glass cut off filter (Schott) and a water filter were used to filter off ultraviolet and infrared radiations respectively. An interference filter (Intor, 700 nm with a bandwidth of 40 nm) was additionally placed in the light path before the sample. Light intensities were measured with a POWER MAX5100 (Mol electron detector incorporated) power meter.

2.2. Chemicals

N,N,N′,N″,N″-Pentamethyldiethylenetriamine (PMDETA; 99%; Aldrich) was distilled over NaOH before use. Methoxypoly(ethylene glycol) azide (mPEG-N_3) (1) (Sigma Aldrich, PEG average $M_n = 2000$), (with the used GPC configuration $M_{n,GPC} = 3900$; $M_w/M_n = 1.05$). All starting materials were purchased from major suppliers and used without any further purification. 2,9(10),16(17),23(24)-tetrakis(pent-4-ynoxy)phthalocyaninato-zinc(II) (2) and 9,16,23-tri-tert-butyl-2-(pent-4-ynoxy) phthalocyaninatozinc(II) (3) were synthesized according to the previously published procedure [34,35]. Zinc(II) phthalocyanine (ZnPc), 1,3-diphenylisobenzofuran (DPBF), DMSO were purchased from Aldrich and zinc tetrasulfophthalocyanine ($ZnPcS_4$) was synthesized according to literature method [39]. 9,10-Antracenediyl-bis(methylene)dimalonic acid (ADMA) was purchased from Fluka.

2.3. Syntheses

2.3.1. Symmetrically PEGylated ZnPc (4)

1 (0.177 g, 0.0885 mmol), DMF (3 mL) were added to a 25 mL of Schlenk tube and stirred until a homogenous mixture is obtained and then added PMDETA (27.7 μL, 0.1326 mmol), CuBr (0.0190 g, 0.1326 mmol), 2 (0.02 g, 0.0221 mmol). Reaction mixture was degassed by three freeze pump thaw (FPT) cycles, left under nitrogen and stirred at 45 °C for 48 h. After the specified time, the star polymer was isolated by diluting polymer mixture with tetrahydrofuran (THF) and passing through an alumina column to remove the metal salt. The excess of THF was evaporated under reduced pressure. The resulting polymer was dissolved in THF, precipitated in 10-fold excess of diethyl ether. The dissolution-precipitation procedure was repeated two times. The recovered star polymer was dried in a vacuum oven at 40 °C for 24 h. Yield = 75%; $M_{n,GPC} = 25700$; $M_{n,theo} = 16500$; $M_w/M_n = 1.06$, relative to PS standards.

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.2–7.9 (br, Ar*H* of Pc), 7.7 (br, C*H* of triazole ring), 7.6–7.4 (br, Ar*H* of Pc), 5.0 (m, OCH_2 of Pc), 4.6–4.4 (br, OCH_2 of PEG), 2.2–0.8 (m, aliphatic protons of PEG, and Pc). FT-IR γ (cm^{-1}): 2973.0 (Ar–H); 2887.27 (CH, aliphatic); 1466.67 (C═C, phenyl), 1104.45 (C–O). UV–vis (DMSO): λ_{max} nm (log ε) 344 (4.49), 632 (4.19), 681 (4.52).

2.3.2. Asymmetrically PEGylated ZnPc (5)

1 (0.0662 g, 0.033 mmol), DMF (3 mL) were added to a 25 mL of Schlenk tube and stirred until a homogenous mixture is obtained and then added PMDETA (20.6 μL, 0.099 mmol), CuBr (0.0142 g, 0.099 mmol), 3 (aZnPc) (0.0274 g, 0.033 mmol). Reaction mixture was degassed by three FPT cycles, left under nitrogen and stirred at 45 °C for 48 h. The purification procedure was similar to that described previously. Yield = 75%; $M_{n,GPC} = 4620$; $M_{n,theo} = 4730$; $M_w/M_n = 1.06$, relative to PS standards.

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.2–7.9 (br, Ar*H* of Pc), 7.7 (br, C*H* of triazole ring), 7.6–7.4 (br, Ar*H* of Pc), 5.0 (m, OCH_2 of Pc), 4.6–4.4 (br, OCH_2 of PEG), 2.2–0.8 (m, aliphatic protons of PEG, and Pc). FT-IR γ (cm^{-1}): 2940.16 (Ar–H); 2865.37 (CH, aliphatic); 1460.26 (C═C, phenyl), 1158.61 (C–O). UV–vis (DMSO): λ_{max} nm (log ε) 343 (4.21), 614 (3.86), 681 (4.43).

3. Results and discussion

CuAAC click reaction serves as a new approach to widen the Pc structural diversity through the incorporation of several functional group(s) and polymeric precursors.

3.1. Characterization of PEGylated Pcs

CuAAC click reaction between mPEG-N_3 (1) and tetra terminal alkynyl substituted zinc phthalocyanine (2) yielded star polymer with zinc phthalocyanine core (4), as illustrated in Scheme 1. Since

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