Synthesis and Photophysical Properties of Some PEG Substitued Titanyl Phthalocyanine Derivatives

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Summary: Polyethylene glycol substituted titanyl phthalocyanine was prepared in two steps starting from phthalonitrile and characterized by FT-IR, UV-vis spectrophotometry, and fluorescence spectrophotometry. The titanyl phthocyanine derivatives (TiOPcs) showed high solubility in common organic solvents, such as, CH_3Cl and DMF. These compounds decreased in absorbance intensity with increase of molecular weight of polyethylene glycol at maxima wavelength of visible range. The fluorescence spectra showed a fluorescence emission near 690 nm with a quantum yield of 0.05–0.32 ($\lambda_{ex} = 625$ nm).

Keywords: fluorescence; photodynamic therapy; titanyl pthalocyanine; UV-vis spectroscopy; water-soluble polymers

Introduction

Photodynamic therapy (PDT)[1–4] is a phototherapeutic method for destroying tumors by the formation of cytotoxic radicals from photoreactions with irradiation. PDT requires a photosensitizer that can be accumulated selectively in tumors and subsequent localized tumor irradiation. Also, photosensitizers with relatively long absorption wavelength are suitable for effective photodynamic action. Phthalocyanine (Pc), a close relative of the porphyrin macrocycle, is the parent compound, one of the most frequently studied classes.[5–7] Pcs exhibit advantageous photophysical properties for PDT including photostability, a long lifetime of the photoexcited triplet state and a high molar absorption in the red region of the visible spectrum. However, many of the applications of Pc derivatives have been limited by the lack of solubility of peripherally unsubstituted macrocycles. Over the past decades, a large variety of peripherally substituted Pc derivatives have been synthesized in order to improve the solubility.[8,9] Presently, Pc derivatives substituted with hydrophilic groups are good candidates for use as PDT of cancer.[10] In this study, to explore a new photosensitizer with a good solubility, we synthesized the novel titanyl phthalocyanine derivatives (TiOPcs) with various ethylene glycol molecules on the peripheral position. Ethylene glycol is well known for its bicompitibility and non- toxicity.

The molecular structures of synthesized TiOPcs have been characterized by FT-IR and ^{1}H NMR. The photophysical properties of the TiOPcs have been monitored by UV-vis spectrophotometry and fluorescence spectrophotometry.

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Experimental

Materials and Measurements

1,2-Dicyanobenzene (DCNB), 4,5-dichlorophthalonitrile, polyethylene glycol (PEG)

(Mw 4000, 6000) and titanium (IV) butoxide ($Ti(OBu)_4$) were purchased from Sigma-Aldrich. Urea and 1-octanol were purchased from Shinyo Pure Chemicals. Dimethylformamide (DMF) and diethylene glycol monomethyl ether (DGME) were purchased from Junsei chemical. All reagents were of analytical grade and were used as state at being received the suppliers without further purification. FT-IR spectra (KBr pellets) were recorded on a Jasco FT/IR-460 Plus spectrometer. ^{1}H NMR spectra (300 MHz) were recorded in $CDCl_3$ using a Varian Unity Plus 300 NMR spectrometer. UV-vis and fluorescence spectra were obtained on an Optizen 2120UV spectrometer and on a Hitachi fluorescence spectrophotometar F-4500, respectively.

Synthesis

Compounds 3a–3c (Figure 1) were prepared in two-step synthesis described in Refs.[11–14] In the first step, alkoxychlorophthalonitriles 2 were formed from 4,5-dichlorophthalonitrile 1 and the corresponding DGME or PEG. The second step was the base catalyzed cyclotetramerization of the phthalonitirles.

Synthesis of Titanyl Phthalocyanine (TiOPc)[12]

A mixture of DCNB (0.51 g, 4 mmol), $Ti(OBu)_4$ (0.37 g, 1.1 mmol), urea (0.12 g, 2 mmol) and 1-octanol (5 ml) was heated at 150 °C under N_2 for 6 h. After addition of methanol to the reaction mixture followed by refluxing for 30 min, fine blue crystals were collected by filtration, washed with toluene, methanol and water, and then dried at 100 °C under vacuum for 3 h. Yield: 53%. FT-IR (KBr, cm^{-1}): 1608 (C=N), 1412 (aromatic C–H, C=C), 1334 (C–N), 1069, 965, 730 (Ti–N).

Synthesis of Alkoxychlorophthalonitrile (2a–2c)

DGME or PEG (4 mmol) and dry sodium carbonate (1.70 g, 16 mmol) in DMF were heated for 30 min under stirring and N_2 gas. A solution of 4,5-dichlorophthalonitrile (0.39 g, 2 mmol) in DMF was then added and the mixture was heated at 70 °C for 24–48 h. After cooling, the reaction mixture was filtered and the solvent was removed under reduced pressure. Compound 2a was purified by chromatography on silica column with dichloromethane/ethyl acetate

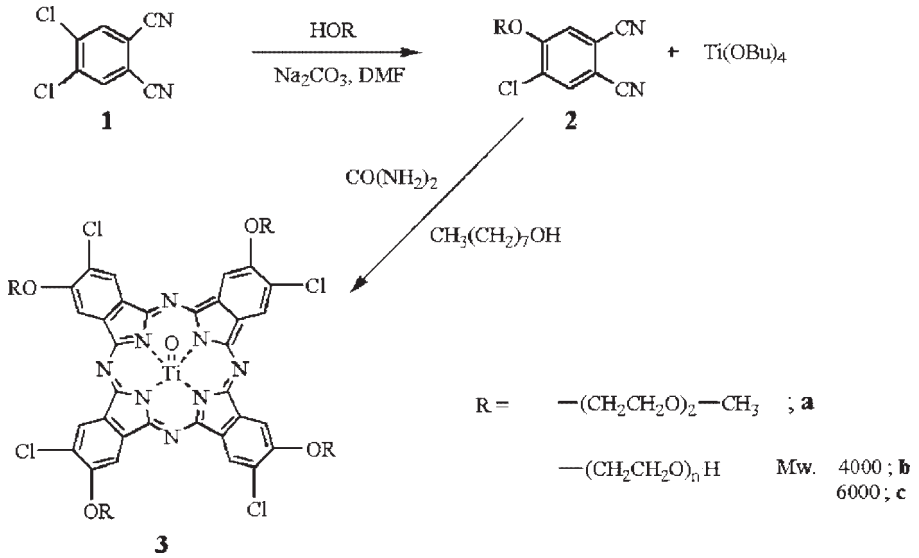

Figure 1.
Preparation of titanyl phthalocyanine (TiOPc) derivatives.

(1:1, v/v) as eluent. Both 2b and 2c were further purified by high performance liquid chromatography (HPLC) with acetonitrile/water (1:5, v/v). FT-IR (KBr, cm^{-1}): 2233 (C≡N), 1586 (C=C), 1264, 1028 (C–O str.), 1112 (CH_2–O–CH_2), 1013 (aromatic–Cl).

Synthesis of Alkoxychlorotitanyl Phthalocyanine (3a–3c)

A mixture of alkoxychlorophthalonitrile (4 mmol), $Ti(OBu)_4$ (0.37 g, 1.1 mmol), urea (0.12 g, 2 mmol), and 1-octanol was heated 150 °C under N_2 for 24 h. After addition of methanol to the reaction mixture followed by refluxing for 30 min, deep green blue crystals were collected by filtration, washed with solvents (3a: toluene, methanol and water; 3b: toluene and methanol; 3c: toluene and ether), and then dried in a vacuum oven at 50–100 °C. FT-IR (KBr, cm^{-1}): 3a: 1669 (C=N), 1421 (aromatic C–H, C=C), 1367 (C–N), 1220, 1078 (C–O str.), 1013 (aromatic-Cl), 935, 743 (Ti–N); 3b: 1626 (C=N), 1446 (aromatic C–H, C=C), 1360 (C–N), 1261, 1110, (C–O str.), 1013 (aromatic–Cl), 963, 743 (Ti–N); 3c: 1636 (C=N), 1466 (aromatic C–H, C=C), 1342 (C–N), 1280, 1102 (C–O str.), 1013, (aromatic–Cl), 963, 796 (Ti–N); ^{1}H-NMR (300MHz, $CDCl_3$, ppm): δ 9.04, 7.84, 6.49–6.20 (m, aromatic C–H), 3.80–3.63 (m, –CH_2CH_2O–), 2.18–2.17 (–OH).

Results and Discussion

TiOPcs were synthesized by a two-step procedure. In the first step, 2a, 2b, and 2c were prepared by substitution reaction of 4, 5-dichlorophthalonitrile with the corresponding alkoxy group in the presence of Na_2CO_3. Nitrile derivatives were isolated by chromatography. The cyclotetramerization of nitrile with $Ti(OBu)_4$ in the presence of urea was performed in 1-octanol.

The characteristic nitrile (C≡N) stretch at 2233 cm^{-1} of 2 disappears upon formation of the phthalocyanine. The split ether stretching frequencies are prominent for both the phthalonitriles and the phthalocyanines in the range of 1100–1264 cm^{-1}. Upon metallation the N–H stretching frequency at 3300 cm^{-1} disappears.

The major advantage of Pcs over porphyrins is that their Q bands are at longer wavelengths and have much higher intensity than the Q bands of porphyrins. Most Pcs are practically insoluble in water, so their application requires lipid based delivery system. On the other hand, the water-soluble derivatives have a tendency for aggregation, reducing their photodynamic activity. The extended π-system exhibits a high aggregation tendency forming dimeric and oligomeric species in solution. The nature of peripheral substituents and surroundings influence the degree of aggregation; with bulky groups decreasing, long alkyl chains, lower temperature, and higher concentration increasing this phenomenon. Also, TiOPc shows both problems of poor solubility and strong aggregation in solutions using polar protic solvents (e.g. water or ethanol).

First, we explored the solubility of phthalocyanine analogues 3a, 3b and 3c (Table 1). Compared with TiOPc, the TiOPcs containing alkoxy groups noticeably solubility in various solvents.

The absorption spectra of TiOPc in trifluoroacetic acid/dichloromethane and 3b in dichloromethane are given in Figure 2. The spectra show the typical

Table 1.
Solubility of TiOPc derivatives

Compound	Ether	Dichloromethane	Chloroform	DMF	Ethanol	Water	Acetone
3a	□	□	○	○	□	×	□
3b	×	○	○	○	□	×	×
3c	×	○	○	○	○	○	×

Solubility in 100 mg / mL
○: soluble; ×: insoluble; □: slightly

Soret and Q-bands, characteristic of Pcs. In this study, at the Q-band (long wavelength), absorption intensity around 680~700 nm of TiOPcs decreases steadily as increasing alkoxy group and showed broad peaks. The spectra of 3a, 3b and 3c showed a strong absorption band around 630~650 nm. Generally, as the longer the PEG chains are induced, the efficiency to disstack the aggregates in water is higher.

Upon addition of long PEG chains, the characteristic blue-shifted Q band at 639 nm, due to the dimeric species, diminishes, while the Q band at 685 nm ascribed to the monomeric species increases.[15] Unfortunately, as shown in Figure 2, these observations do not appear to this current case. The longer the PEG chains that were added, the absorption spectra of near 630 nm increased owing to the dimeric species formation. In addition, this dimeric species formation phenomenon became larger in water. We can interpret this observation in the following way: the chemically linked PEG on the TiOPc likely decreases their mobility more than blending with PEG in solvent. For this reason, it is reasonable to suppose that the chemically linked PEG will not be good enough to wrap the TiOPc molecules to prevent its stacking. Consequently, the aggregation tendency may be affected by the nature of peripheral substituents more than the properties of solvent.

The steady-state fluorescence emission spectra of 3a, 3b and 3c were performed in dichloromethane. By comparison with TiOPc as a reference, the values of fluorescence quantum yields (Φ_F) were obtained in dichloromethane. Values of fluorescence quantum yields are shown in Table 2. The fluorescence quantum yields of Pcs were calculated by comparison of the area below the corrected emission spectrum with that of TiOPc as a fluorescence standard exciting at $\lambda_{ex} = 625$ nm.

$$\Phi_{unk} = \Phi_{std}(I_{unk}/A_{unk})(A_{std}/I_{std}) \times (\eta_{unk}/\eta_{std})^2 \quad (1)$$

The quantum yields for fluorescence were determined using Equation (1), [16] where Φ_{unk} is the fluorescence quantum yield of the sample, Φ_{std} is fluorescence

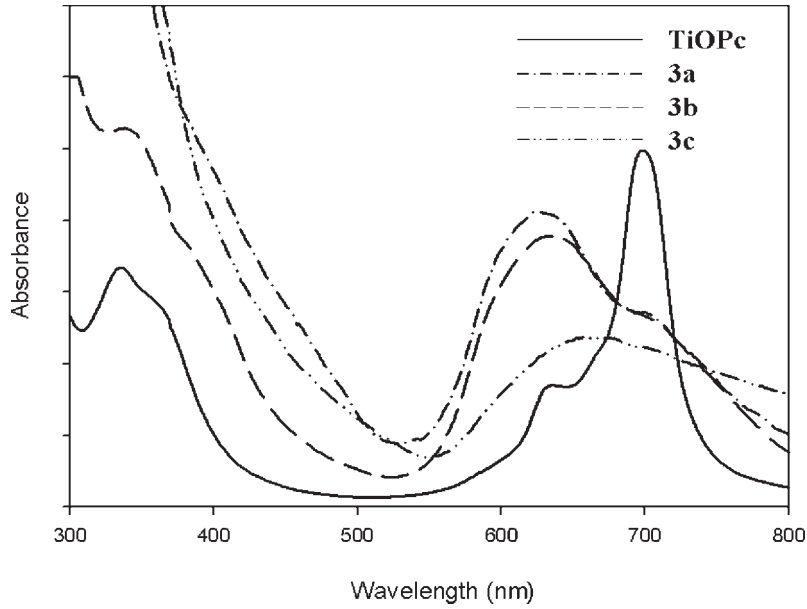

Figure 2.
Absorbance spectra of TiOPc in trifluoroacetic acid/dichloromethane, 3a, 3b, and 3c in dichloromethane (4×10^{-5} M).

Table 2.
Absorption, fluorescence emission and fluorescence quantum yields data for 3a, 3b and 3c

Compound	Absorption Maxima (nm)	Emission Maxima (nm) $\lambda_{ex} = 625$ nm	Fluorescence Quantum Yields
3a	626, 699	690	0.32
3b	633, 699	691	0.05
3c	656	693	0.05

quantum yield of the standard (TiOPc), I_{unk} and I_{std} are the integrated emission intensities of the sample and the standard, respectively, A_{unk} and A_{std} are the absorbances of the sample and the standard at the excitation wavelength, respectively, and η_{unk} and η_{std} are refractive indexes of the corresponding solutions. Upon excitation at 625 nm, TiOPcs showed a fluorescence emission near 690 nm with a quantum yield of $0.05 \sim 0.32$. The intensity of fluorescence emission and quantum yield of 3a were larger than those of 3b and 3c. Dennis has showed that the fluorescence intensity increases when PEG agents are added. [15] In other words, the fluorescence intensity is a relevant indicator of stacking to form aggregates. In this work, the fluorescence emission is similar to the results obtained by UV-vis spectrophotometry.

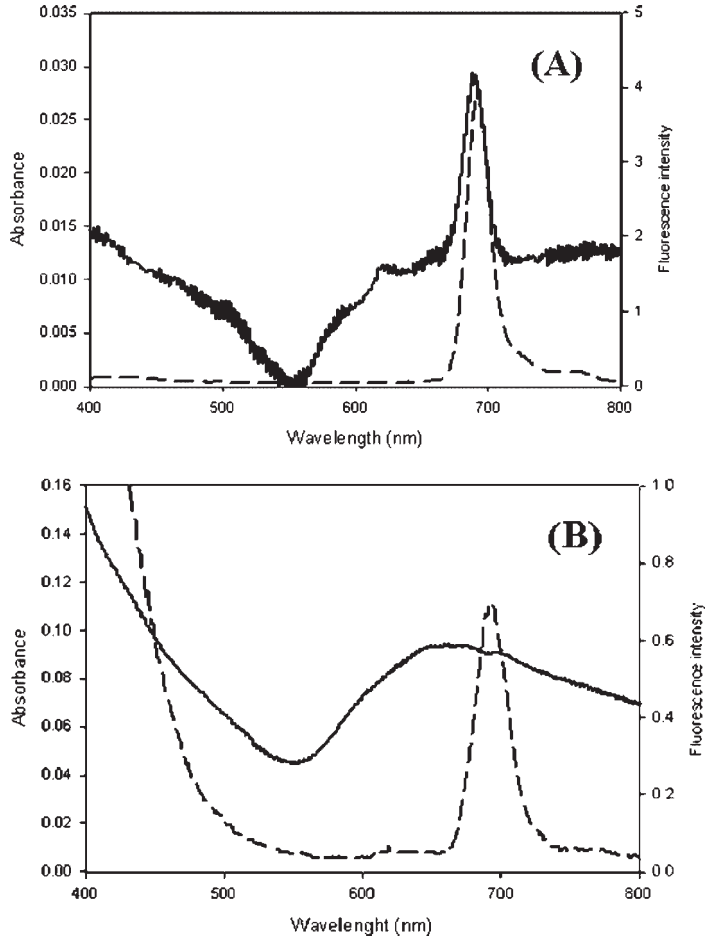

Figure 3.
Absorption (solid line) and fluorescence (dashed line) spectra of (A) 3a and (B) 3c in dichloromethane: The excitation wavelength for the fluorescence spectra is 625 nm.

These behaviors can be demonstrated as an effect by the increase of the aggregation.

Conclusion

The present work introduced the preparation, characterization and physical properties of novel TiOPcs, which have been peripherally substituted with ethylene glycol groups. TiOPcs are promising second generation photosensitizers for PDT because of their many desirable features. However, on account of their aggregation tendency and the lack of solubility in water, their applications are very limited. For this reason, in this work was investigated for the hydrophilic and non-aggregated TiOPcs based on ethylene glycol derivatization. Although synthesized TiOPcs have a tendency toward aggregation, they have good solubility. To have wide potential application in PDT, synthesis of the TiOPc derivatives using various ethylene glycol goups remain as a matter to be discussed further.

Acknowledgement: The authors of this paper would like to thank Brain Korea 21 project (Ministry of Education & Human Resources Development), and Applied Rheology Center (Ministry of Science and Technology) for financial support of this research.

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