

**SYNTHESIS AND SPECTROSCOPIC INVESTIGATIONS OF TRIFLUOROETHOXY SEMI-COATED
ZINC(II) PHTHALOCYANINE**

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Abstract: Trifluoroethoxy semi-coated zinc(II) phthalocyanine **1** has been synthesized and characterized. The aggregation state of **1** was investigated by UV-vis and steady-state fluorescence spectra. The fluoroethoxy Pc **1** was found to stay non-aggregation independent of concentrations in dioxane. With our expectation, the strong emission was observed in line with the absorption spectra of **1**.

Keywords: phthalocyanine, aggregation, fluorine, fluorescence, photodynamic therapy

Introduction

The suppression and control of aggregation properties of phthalocyanines (Pcs) both in solvent and solid film only by their inherent specificity without any external source is a challenge in material science, especially for solar cells, sensors, and photodynamic therapy (PDT) [1-3]. The outstanding optical and photosensitizing properties of Pcs with both a wider absorbing range of the spectrum and high luminescence quantum yields are often perturbed in a randomly aggregated state [4]. Free from molecular aggregation is particularly desirable for solar cells and photodynamic therapy because self-association quenches fluorescence and interferes with the formation of singlet oxygen [3, 5]. In addition, controlling the aggregation of phthalocyanine (Pc) macrocycles should be an indispensable factor for nonlinear optical applications [6]. Among there are several examples of aggregation-free Pcs, we are interested in the trifluoroethoxy-coated Pcs [7-25, 29-30]. Further to the highly specific reasons to make use of trifluoroethoxy (TFEO)

group for suppression of aggregation of Pcs, the introduction of trifluoromethylated functional groups into biologically attractive molecules is one of the most reliable strategies to improve the original biological activity in pharmaceutical science [31, 32]. We recently synthesized the trifluoroethoxy substituted zinc(II) Pcs conjugated with deoxyribonucleosides and found their prominent nature of avoiding aggregation with appropriate properties as photodynamic therapy agents [25]. As an extension of our work on phthalocyanine chemistry [7, 8, 25-28], we required a highly fluorescent TFEO semi-coated Pc as a novel PDT agent. Although two examples of trifluoroethoxy semi-coated Pcs with Fe(II) or Ti(IV) have been reported, both of them do not show any fluorescence properties due to the paramagnetism of central metal ions [29, 30]. Here we report the synthesis and properties of TFEO semi-coated zinc(II) Pc 1. With our expectation, the Pc 1 indicates non-aggregation and highly fluorescent property which are suitable for PDT (Figure 1).

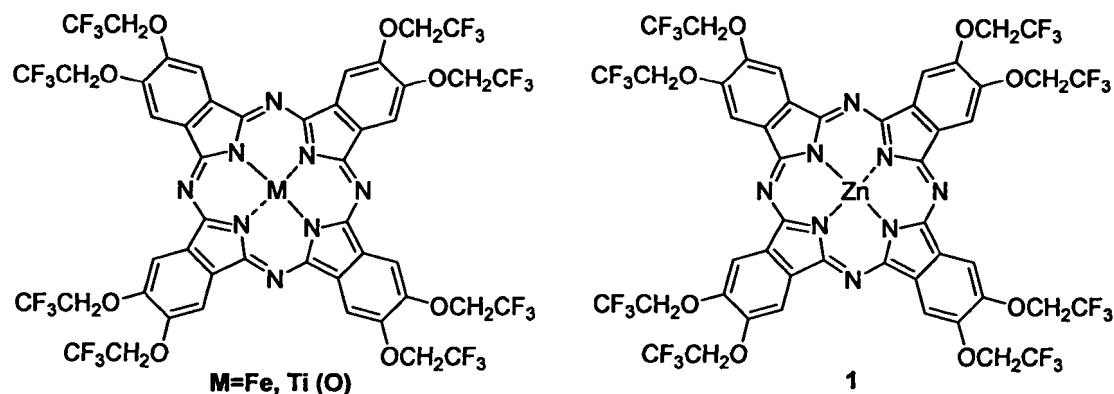
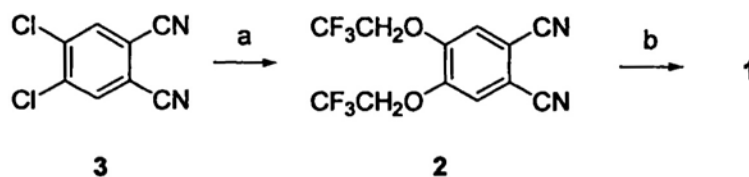


Figure 1:

TFEO semi-coated Pcs

Results and Discussion

The TFEO *semi-coated* phthalocyanine, zinc 2, 3, 9, 10, 16, 17, 23, 24-octakis(2,2,2-trifluoroethoxy)phthalocyaninate 1 was synthesized via following procedure (Scheme 1). First, 4,5-bis(2,2,2-trifluoroethoxy)phthalonitrile 2 was prepared from the dichloro precursor 3 by nucleophilic substitution using trifluoroethanol in 80% yield [33]. Then cyclization of 2 by refluxing in 2-dimethylaminoethanol with zinc chloride as a metal template gave desired Pc 1 in 67%. The purity and identities of the Pc were confirmed by reverse-phase HPLC, ^1H and ^{19}F NMR, and the isotopic distributions of Zn in MALDI-TOF MS spectra (Figure 2 and 3).



Scheme 1: Synthesis of **1**: (a) $\text{CF}_3\text{CH}_2\text{OH}$, K_2CO_3 , DMF, $0\text{ }^\circ\text{C}$ to rt, 80%. (b) ZnCl_2 , 2-dimethylaminoethanol, reflux, 67%.

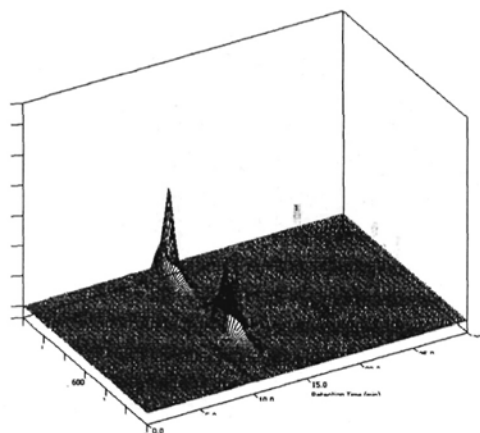


Figure 2: HPLC chart of **1**: $t_R=13.0$ min ($\text{H}_2\text{O}:\text{MeCN}:\text{THF}=8:42:50$, 0.3 mL/min).

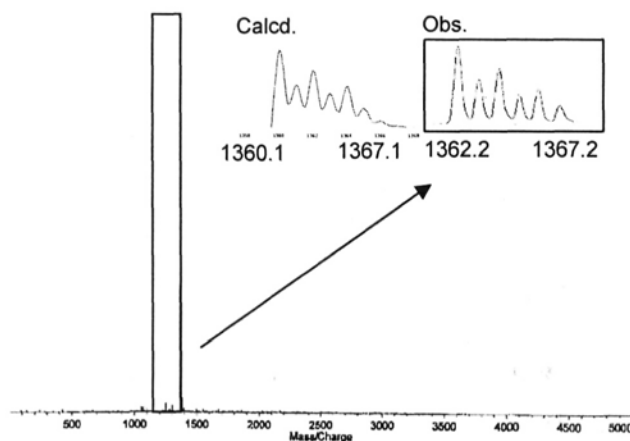


Figure 3: MALDI-TOF MS Spectrum of **1** (dithranol): $m/z = 1362.2\text{--}1367.2$ ($[\text{M}+\text{H}^+]$, isotopic pattern).

The solubility of TFEO semi-coated Pc **1** is limited only in coordinating solvents such as dioxane, acetone, pyridine or THF. The UV-vis spectrum of **1** in dioxane shows a Q-band at 666 nm and a Soret band at 353 nm in usual absorption region of Pcs, which indicates **1** existing as an aggregation-free monomer in solution (Figure 4) [4]. After addition of **1**

vol% of pyridine, the Q-band and Soret band were shifted to 669 and 359 nm, respectively, by coordination of pyridine to the central Zn of Pc [34]. The bands of β -substituted **1** were blue-shifted compared to those of α -substituted ones, which is an identical feature between α -substituted Pcs and β -substituted ones [21]. The outer TFEO substituents have less effect to the electronic state of Pc macrocycle, although inner coating influenced the absorption spectra as significant red-shifting [21].

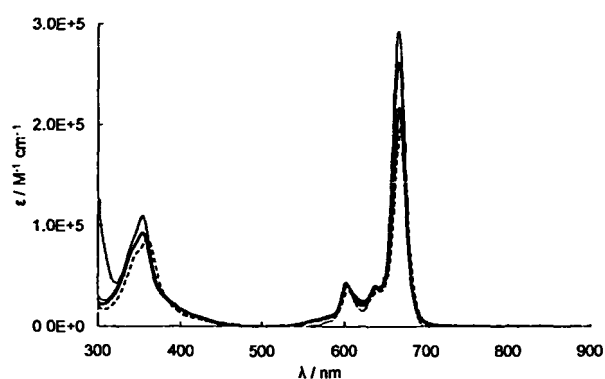
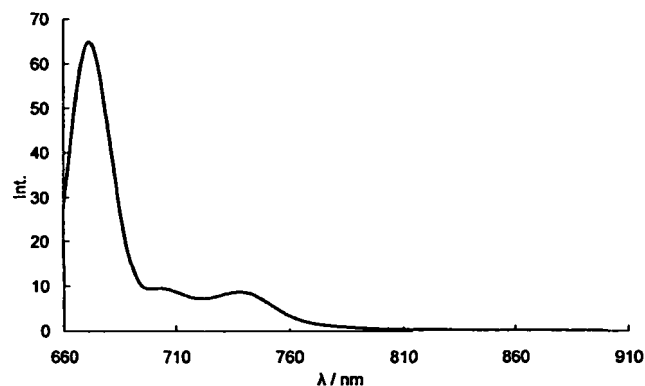


Figure 4: UV-vis spectra of **1** in dioxane (bold to thin lines: 1.0×10^{-4} M to 1.0×10^{-6} M, and dashed line: 1.0×10^{-4} M with 1 vol% of pyridine).

We finally investigated the steady-state fluorescence spectrum in dioxane (Figure 5). While the semi-coated Fe(II) or Ti(IV) Pc does not show any fluorescence, the emission of **1** was strong due to β -substitutions having less effect on the optical properties of **1** and also the non-aggregation state ($\lambda_{em} = 671$ nm; $\Phi_f = 0.41$). These phenomena also supported the



results in electronic spectra mentioned above.

Figure 5: Steady-state fluorescence spectrum of **1** in dioxane.

Conclusions

In conclusion, the TFEO semi-coated zinc(II) Pc was synthesized. The Pc **1** possesses non-aggregation state and strong fluorescence in dioxane. These properties should be suitable for PDT agent. Antitumor activity of **1** as a photosensitizing agent for use in PDT is now under investigation.

Experimental

General

All solvents were dried and distilled according to standard procedures. All of the reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica-gel plate (60F-254). Column chromatography was carried out on a column packed with silica gel 60N spherical neutral size 63-210 μm . ^1H (200 or 400 MHz), ^{13}C and ^{19}F NMR spectra were taken on a Varian Gemini-200 or 400 spectrometer. Chemical shifts are expressed in ppm downfield from tetramethylsilane. Infrared (IR), UV-vis and steady-state fluorescence spectra were recorded on a JASCO FT/IR-200 Spectrometer, V-530 spectrometer and FP-6200 Fluorospectrometer, respectively. Quantum yields were calculated following the procedure mentioned before [35]. Mass spectrum of MALDI-TOF were taken on a SHIMADZU Axima CFR plus. Reverse phase HPLC analyses were performed on a JASCO PU-2080 Plus using 4.6 x 250 mm Develosil

ODS-HG-5 column and MD-2015 multiwavelength detector.

Synthesis

4,5-Bis(2,2,2-trifluoroethoxy)phthalonitrile (2)

A mixture of 4,5-dichlorophthalonitrile 3 [33] (1.97 g, 10.0 mmol), potassium carbonate (5.53 g, 40.0 mmol) and DMF (20 mL) was added with 2,2,2-trifluoroethanol (2.86 ml, 40.0 mmol) at 0 °C and stirred at 40 °C for 40 h. After cooling it to room temperature, water was added to the solution. The precipitates were collected by filtration and purified by silica-gel column chromatography (AcOEt: hexane = 2: 8). 2.58 g, 80%.

$C_{12}H_6F_6N_2O_2$; M.W.: 324.18; 1H -NMR ($CDCl_3$, 400 MHz): δ 4.51 (q, $J = 7.8$ Hz, 4H), 7.35 (s, 2H) ^{13}C -NMR ($CDCl_3$, 100.6 MHz): δ 67.25 (q, $J = 36.8$ Hz, 1C), 111.46, 114.54, 120.06, 122.43 (d, $J = 278$ Hz, 1C); ^{19}F -NMR ($CDCl_3$, 376 MHz): δ -74.26 (t, $J = 7.8$ Hz, 6F); IR (KBr): 3143, 3073, 2956, 2890, 2813, 2665, 2237, 1766, 1602, 1579, 1528, 1454, 1409, 1360, 1309, 1271, 1230, 1217, 1138, 1103, 1070, 1037, 974, 891, 727, 664 cm^{-1}

Zinc 2,3,9,10,16,17,23,24-octakis(2,2,2-trifluoroethoxy)phthalocyaninate (1)

The phthalonitrile 2 (100.0 mg, 0.308 mmol) and zinc chloride (21.0 mg, 0.15 mmol) in 2-dimethylaminoethanol were refluxed for 24 h. After cooling it to room temperature, the mixture was diluted with water. The precipitates were collected by filtration and purified by silica-gel column chromatography (acetone: hexane = 3: 7). 70.1 mg, 67 %.

$C_{48}H_{24}F_{24}N_8O_8Zn$; M.W.: 1362.10; 1H -NMR (acetone- d_6 , 200 MHz): δ 5.27 (br q, $J = 8.4$ Hz, 16H), 8.51 (br s, 8H); ^{19}F -NMR (acetone- d_6 , 188 MHz): δ -72.6 (br t, $J = 8.4$ Hz, 24F); IR (KBr): 1496, 1457, 1405, 1263, 1170, 1103, 1076, 964, 882, 743, 660 cm^{-1} ; MALDI-TOF MS (dithranol): $m/z = 1362.2$ -1367.2 ($[M+H]^+$, isotopic pattern); HPLC: ($H_2O:MeCN:THF = 8:42:50$, 0.3 mL/min), $t_R = 13.0$ min; UV-vis (1.0×10^{-4} M in dioxane): λ_{max} (log ϵ) = 666 (5.33), 603 (4.60), 353 (4.96) nm; Fluorescence (dioxane): $\lambda_{em} = 671$ ($\Phi_f = 0.41$).

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