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Synthesis and Type I/Type II photosensitizing properties of a novel amphiphilic zinc phthalocyanine

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Abstract

A novel amphiphilic zinc phthalocyanine (ZnPcLTs) has been synthesized, which possesses good amphiphilicity, and low aggregation. The generation efficiency of singlet oxygen and other active oxygen species' trapping rate studies were studied by electron spin resonance (ESR) spectroscopy. The results indicated that the photosensitizer possessed a higher active oxygen species generation efficiency than that of hematoporphyrin. The results of photodamage experiments towards calf-thymus DNA indicated that ZnPcLTs is a promising photosensitizer candidate for photodynamic therapy.

Keywords: Sulfonated zinc phthalocyanine; Active oxygen; Amphiphilicity; ESR; PDT

1. Introduction

Sulfonated zinc and aluminum phthalocyanine derivatives have attracted a considerable amount of attention as second-generation photosensitizers for treatment of malignant tumors by photodynamic therapy (PDT) in the last decade [1–3]. Their PDT efficiency not only depends on the formation of the cytotoxic species ($^1O_2$, $O_2^{-\cdot}$ and $OH^{\cdot}$) but also depends on the amphiphilicity of photosensitizer [4,5]. Since a hydrophilic character benefits the transport of a drug in the body, and its lipophilicity benefits its uptake by tumor cells, the amphiphilicity of a photosensitizer is therefore considered to be an important factor in the design of a new photosensitizer [6–8]. Phthalocyanines have been studied as potential PDT photosensitizers; but, the large conjugated π-system leads to a strong stacking tendency in solution, which usually decreases their luminescence quantum yield, shortens their triplet state lifetime by enhancement of internal conversion, and so reduces their photosensitizing efficiency. The dye is more active in its monomeric state [9,10]. It is, therefore, important to develop a phthalocyanine which is both amphiphilic and nonaggregated, but the study of these compounds for use in PDT is still in its infancy [2,11,12].

Of the phthalocyanines, zinc phthalocyanine tetrasulfonate (ZnPcTs) has been more investigated as a PDT photosensitizer. Since it is not only highly aggregated in aqueous solution, as shown by spectroscopic studies, but is also a strongly hydrophilic photosensitizer, its photodynamic activity is lower than its disulfonate analogue (ZnPcDs), which has more amphiphilic structure [2,6,13]. We report herein the synthesis and photophysical properties of a novel zinc phthalocyanine (ZnPcLTs) containing sulfonated naphthoxy substituents (shown in

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Fig. 1). The introduction of naphthoxy substituents not only enhances the lipophilic character of the molecule, but also prevents its molecular aggregation in solution for steric reason, potentially resulting in superior photophysical characteristic enhanced PDT properties.

2. Experimental

2.1. Materials

2,2,6,6-Tetraethyl-4-piperidone (TEMP), 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO), 1,4-diazabicyclo[2,2,2]octane (DABCO), superoxide dismutase (SOD), sodium benzoate and 9,10-diphenylanthracene (9,10-DPA) were all purchased from Aldrich Chemical Company, USA. Dimethylsulfoxide (DMSO), hematoporphyrin and other reagents of analytical grade were obtained from Beijing Chemical Plant. 4-Nitrophthalonitrile was prepared and purified according to the methods described in the literature [14]. All reaction solvents were dried over molecular sieve of 4 Å and further distilled before use.

2.2. Equipments

IR spectra were recorded on a PARAGN1000 FT-IR spectrometer using KBr pellets. The absorption and the fluorescence spectra were measured with LAMBDA20/2.0 spectrometer and Hitachi F-4500 fluorescence spectrophotometer, respectively. ^{1}H NMR spectra were obtained in D_2O on a Gemini-2000 analyzer (300 MHz, Varian Ltd.).

2.3. Synthesis of 4-(5-sulfo-1-naphthoxy)-phthalonitrile

4-Nitrophthalonitrile (3.46 g, 0.02 mol) and 5-hydroxy-1-naphthalene sulfonic acid (6.72 g, 0.03 mol) were dissolved in 50 ml of dry DMSO at room temperature. The mixture was stirred, and 5.52 g (0.04 mol) of anhydrous potassium carbonate was added over a period of 1 h under a nitrogen atmosphere. The same amount of potassium carbonate was then added after 8 h of stirring at room temperature. After about 20 h the mixture was poured into 250 ml of 1 M hydrochloric acid. After settling of the suspension within 8 h, the crude product was collected by vacuum filtration and washed with ethanol. The isolated product (yellow needles 3.85 g, 55%) was recrystallized from methanol. IR (cm^{-1}): 3440, 3100–3000 (Ar, H), 2233 (Ar–C≡N), 1598, 1570, 1493 (Ar), 1277, 1250 (Ar–O–Ar), 1200 (S–O), 785, 656 (C–S). ^{1}H NMR (D_2O): δ 8.46–7.98 (m, 3H, H–Ar(CN)$_2$), δ 7.75–7.34 (m, 6H, H–ArSO$_3$H). Elemental analysis: ($C_{18}H_{10}N_2O_4S$, FW 350). Calc: C, 61.71; H, 2.88; N, 8.00; found: C, 61.46; H, 2.84; N, 7.92.

2.4. Preparation of ZnPcLTs

4-(5-Sulfo-1-naphthoxy)phthalonitrile (1.05 g, 3 mmol), 1-pentanol (25 ml) and DBU (1.5 ml) were mixed. The mixture was stirred at 70 °C for 10 min in a nitrogen atmosphere, then 0.1 g (0.8 mmol) of anhydrous zinc

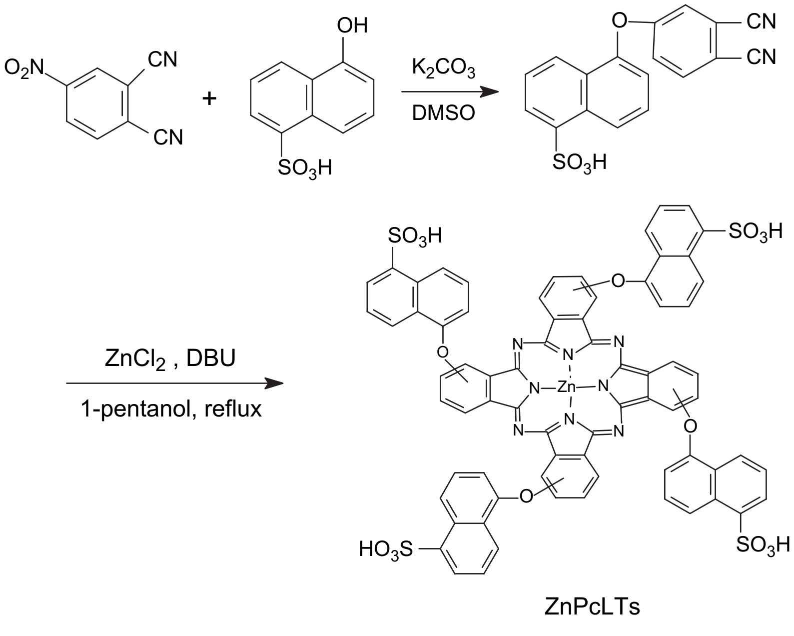

Fig. 1. The chemical structure of the phthalocyanine ZnPcLTs.