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Au nanorods modulated NIR fluorescence and singlet oxygen generation of water soluble dendritic zinc phthalocyanine

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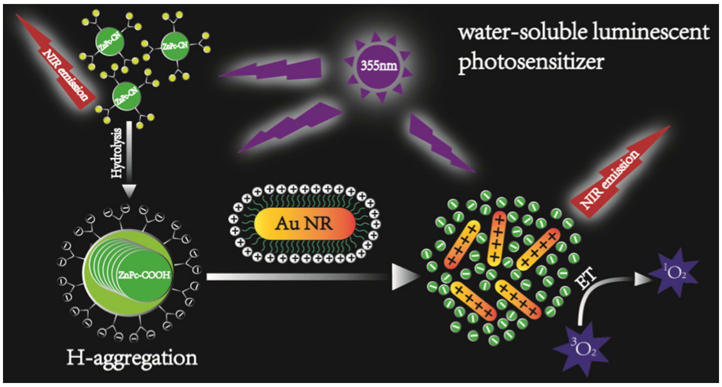
GRAPHICAL ABSTRACT



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ABSTRACT

A novel cyano-terminated zinc phthalocyanine (ZnPc-CN) exhibiting visible near infrared (vis-NIR) emitting around 690 nm in *N,N*-dimethylformamide (DMF) solvent has been synthesized. Furthermore, the peripheral cyano groups of newly synthesized zinc phthalocyanine were hydrolyzed in strong basic solution, leading to water soluble carboxylated zinc phthalocyanine (ZnPc-COOH) with completely quenched fluorescence in aqueous solution. Interestingly, we found that the NIR fluorescence of aqueous ZnPc-COOH was dramatically recovered in the presence of gold nanorods (Au NR), which was due to the alternation of ZnPc-COOH molecules self-assembling via electrostatic interaction between cetyltrimethylammonium bromide (CTAB) on the surface of Au NR and peripheral carboxyl of ZnPc-COOH. In addition, ZnPc-COOH/Au NR conjugates demonstrated an improved singlet oxygen generation, which could be served as potential bioimaging probe and photosensitizer for photodynamic therapy.

1. Introduction

Phthalocyanines (Pcs) have found versatile applications in different scenarios, such as dyes, non-linear optical devices, artificial light harvesting antenna, chemical sensors, photosensitizer for photodynamic therapy (PDT) and organic solar cells, photochemical catalysts, etc [1–6]. The wide range of phthalocyanines applications is mainly derived from their planar 18 π-electron conjugated structure and good molecular tailoring strategies [7,8]. For instance, a variety of phthalocyanine derivatives can be synthesized by introducing different metal ions into central cavity [9], coordinating with various axial ligands [10] as well as attaching diverse peripheral substituents [11]. Owing to the highly

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conjugated molecular structures, phthalocyanines exhibit large molar absorption coefficient in the far red (FR)/near infrared (NIR) wavelength, which is the ideal "biological window" for various biomedical applications [12]. Moreover, their biochemical related photophysical (e.g. fluorescence) or photochemical (i.e. oxygen sensitization) properties can be readily modulated by fine controlling the deactivation process of molecular excited state [13,14]. Nevertheless, the conventional phthalocyanines have inherent tendency to form stacked aggregates especially in aqueous solution, which is caused by their hydrophobic aromatic structures and strong intermolecular π-π interaction among their extended π-system, thus their bioimaging and biotherapy applications were notoriously hampered [15]. Nowadays, several strategies have been developed to reduce aggregation of phthalocyanine in aqueous solution, such as introducing various hydrophilic substituents or axial ligands into phthalocyanines backbone [10,14]. For instance, several water soluble phthalocyanines were synthesized by attaching anionic substituents like carboxyl or sulfonate [16]. Especially, various bioactive substances can be easily noncovalently or covalently linked with carboxylated phthalocyanine (Pc-COOH) to construct various water soluble photoactive bioconjugates [17]. In addition, the phthalonitrile moiety, one of the typical phthalocyanine precursors, can be easily hydrolyzed into phthalic acid based compounds in strong basic solution, which provides a facile route to obtain water soluble Pc-COOH [18,19]. However, the photophysical and photochemical properties of obtained Pc-COOH in aqueous solution were inevitably inhibited, mainly due to the presence of microscopic H-type aggregation [20,21]. Therefore, the self-assembling of water soluble Pc-COOH still needs to be carefully controlled to maintain their optical properties.

Gold nanorods (Au NR) have witnessed increasing research interests due to their powerful manipulation of light-matter interaction on the basis of localized surface plasmon resonance (LSPR). Moreover, anisotropic Au NR typically exhibits two distinct LSPR bands, corresponding to the collective oscillation of free electrons along transversal and longitudinal direction [22–24]. On the contrary of constant location of transversal LSPR band, the aspect ratio dependent longitudinal LSPR wavelength of Au NR can be easily tuned in the visible red and NIR spectrum [25]. Meanwhile, Au NR exhibits local dielectric environment dependent LSPR response, strong light scattering as well as highly efficient photo-thermal transitions [26], which indicates that Au NR is an ideally multifunctional photonic nanostructure for biological sensing, imaging and therapy applications [27]. Furthermore, the near field enhancement effects of Au NR can be explored to modulate the dynamic relaxation process of excited dye molecules located in the vicinity of Au NR, thus contributing to various plasmon enhanced spectroscopy such as surface enhanced Raman spectroscopy (SERS), plasmon enhanced fluorescence (PEF), and the improved singlet oxygen quantum yield of photosensitizer [28–31]. On the other hand, the majority of as-synthesized Au NRs were stabilized with a cationic surfactant cetyltrimethylammonium bromide (CTAB) layer, which was reported as a powerful surface agent to modulate the microscopic aggregation of aromatic dyes in aqueous solution [29,32,33].

In this work, zinc phthalocyanine containing cyano groups (ZnPc-CN) and the sterically demanding phenolphthalein moiety with vis-NIR emitting feature in DMF solvent was firstly synthesized, followed by hydroxylation of peripheral cyano groups, leading to a water soluble carboxylated zinc phthalocyanine (ZnPc-COOH). However, we found that the fluorescence of as-synthesized ZnPc-COOH was virtually quenched in aqueous solution due to the formation of microscopic aggregates. Therefore, the positively charged Au NR stabilized with cationic surfactant of CTAB was employed as nanoscale template and near field nano-antenna to modulate the self-assembling as well as excited state deactivation process of ZnPc-COOH in aqueous solution. Consequently, the water-soluble ZnPc-COOH/Au NR nanoconjugates with strong NIR fluorescence around 690 nm as well as improved singlet oxygen quantum yield were obtained, which will pave the way for their future application as multimodal theranostic agent in nanomedicine.

2. Experimental section

2.1. Materials

4,4′-bis(3,4-dicyanophenoxy)phenolphthalein was synthesized according to our previous work [34], zinc chloride ($ZnCl_2$), ammonium molybdate, methanol, *N,N*-dimethylformamide (DMF), tetrahydrofuran (THF), petroleum ether (C60-C90), silica gel, sodium hydroxide ($NaBH_4$), ascorbic acid, silver nitrate ($AgNO_3$), chloroauric acid ($HAuCl_4$) and 1,3-diphenylisobenzofuran (DPBF) were received from Sinopharm chemical reagent. Cetyltrimethylammonium bromide (CTAB), polyvinyl alcohol (PVA), polyethylene glycol 400 (PEG400), cysteine (Cys), sodium dodecylsulphate (SDS), sodium alginate (NaAlg), polyvinylpyrrolidone (PVP) and dodecyl trimethyl ammonium chloride (DTAC) were received from Shanghai Aladdin biological technology Co. Ltd. Deionized water was used in the experiment. All the compounds were used as received without further purification.

2.2. Synthesis of NIR emitting ZnPc-CN

A mixture of 4,4′-bis(3,4-dicyanophenoxy)phenolphthalein (2.28 g, 4 mmol), zinc chloride (0.136 g, 1 mmol) and ammonium molybdate (10 mg) was refluxed in 10 mL *N,N*-dimethylformamide (DMF) under vigorous stirring for 3 h. Then, the mixture was cooled down to room temperature and precipitated in ddH_2O, followed by thorough washing with boiling methanol for several times and dried in a vacuum oven. Next, column chromatography was employed for further purification using a mixture of tetrahydrofuran and petroleum ether (volume ratio of 3:1) as an eluent. Finally, the purified green powder was obtained via rotary evaporating and vacuum drying. The chemical structure of ZnPc-CN was characterized with ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H (400 MHz, DMSO) 8.11 (1 H, d, *J* 8.7), 8.02–7.84 (4 H, m), 7.72 (1 H, t, *J* 7.5), 7.45 (5 H, dd, *J* 13.0, 5.5), 7.24 (3 H, d, *J* 8.6), 3.34 (7 H, s), 2.50 (7 H, s), FTIR (KBr, cm^{-1}): 2370(—CN), 1765(—C=O), 1586(C=N of Pc ring), 1395(C=C of Pc ring), 1234(—O—) (see Figs. S1 and S3 in the supplementary materials) and element analysis (Anal. calcd for $C_{144}H_{72}N_{16}O_{16}Zn$ (ZnPc-CN): C, 73.688; H, 3.110; N, 9.552. found: C, 73.679; H, 3.111; N, 9.508).

2.3. Synthesis of water-soluble ZnPc-COOH

The previously synthesized ZnPc-CN (100 mg) was dispersed in 30 mL NaOH (1 mol/L) aqueous solution and heated at 100 °C in a three-necked flask with continuous stirring. After refluxing for 24 h, the sample solution was centrifuged at 15,000 rpm for 30 min to remove residual ZnPc-CN. Next, the pH of resulted supernatant solution was adjusted to around 7 via dropwise addition of 1 mL HCl solution (1 mol/L). Finally, the carboxylated zinc phthalocyanine was obtained by using ethanol as precipitation agent, followed by room temperature incubation for 12 h, filtration and drying in vacuum oven overnight. The chemical structure of purified compound was characterized with ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H (400 MHz, DMSO) 7.95 (1 H, t, *J* 13.3), 7.90–7.57 (2 H, m), 7.41 (2 H, d, *J* 8.6), 7.17 (4 H, t, *J* 13.0), 3.34 (4 H, s), 2.50 (3 H, s), FTIR (KBr, cm^{-1}): 1765(—C=O), 1586(C=N of Pc ring), 1395(C=C of Pc ring), 1234(—O—) (see Figs. S2 and S3 in the