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Mono-PEGylated Zinc(II) Phthalocyanines: Preparation, Nanoparticle Formation, and In Vitro Photodynamic Activity

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Photodynamic therapy (PDT) has emerged as a promising treatment modality for some localized and superficial cancers.[1] It is based on systemic or topical administration of a tumor-localizing photosensitizer which is activated with light of appropriate wavelength. The resulting photodynamic reactions lead to production of various reactive oxygen species, including singlet oxygen, that induce cell death by necrosis and/or apoptosis.

As a versatile class of functional dyes, phthalocyanines have received considerable attention as a new generation of photosensitizers owing to their desirable properties, such as strong absorption in the red visible region that allows deeper light penetration, high efficiency in singlet oxygen generation, and ease of chemical modification that facilitates modulation of their photophysical and biological properties.[2] However, phthalocyanines have a large hydrophobic π skeleton, which reduces the solubility of these compounds in aqueous media and promotes their aggregation in biological environments. This aggregation not only complicates their administration and biodistribution in vivo but also drastically reduces their photodynamic activities. To circumvent these problems, water-soluble moieties can be introduced at the peripheral or axial positions.[3] Alternatively, nanocarriers such as liposomes, proteins, gold nanoparticles, polymeric micelles, and silica nanoparticles can also be employed.[4] The latter approach is of particular interest because the carriers can be engineered to control the release of the drugs, enhance their biocompatibility and stability, and prolong their circulation time, thereby enhancing their tumor-localization property by the enhanced permeability and retention (EPR) effect.[5] Ligands which have high affinity to tumor-associated molecular markers can also be incorporated on the surface to further enhance the targeting property of the drugs. As part of our continuing effort in the development of efficient and selective phthalocyanine-based photosensitizers,[6] we report herein a novel series of zinc(II) phthalocyanines which are monosubstituted with a polyethylene glycol (PEG) chain with different length, including their preparation, encapsulation in micelles and silica-based nanoparticles, and in vitro photodynamic activity. The compound with the shortest PEG chain (with an average molecular weight of ca. 550 $g\,mol^{-1}$), after being encapsulated into silica-based nanoparticles, exhibits high stability and in vitro photocytotoxicity and is therefore a highly promising photosensitizing system for PDT application.

These PEGylated phthalocyanines (compounds **1**–**3**) were prepared by substitution reactions of polyethylene glycol monomethyl ether monotosylate with an average molecular weight of ca. 550, 2000, or 5000 $g\,mol^{-1}$ with 2-hydroxyphthalocyaninatozinc(II) (**4**)[7] in the presence of K_2CO_3 in *N*,*N*-dimethylformamide (DMF; Scheme 1). Unlike many other substituted phthalocyanines prepared by cyclic tetramerization,[8] these compounds are isomerically pure. The hydrophilic PEG chain and the hydrophobic macrocyclic core also make the compounds amphiphilic in nature, which generally can enhance the cellular uptake and intracellular localization.[9] The products were purified by repeated silica gel column chromatography. Compound **3** was further purified by recrystallization from a mixture of CH_2Cl_2 and hexane.

The UV/Vis and fluorescence spectra of these PEGylated phthalocyanines were recorded in DMF, and the data are compiled in Table 1. As expected, their absorption and emission positions are virtually the same. The intense fluorescence emission at 677 nm suggests that these compounds are not significantly aggregated in DMF. By using 1,3-diphenylisobenzofuran as a singlet oxygen scavenger,[10] the singlet oxygen quantum yields of these compounds were also determined. As shown in Table 1, the values are comparable with that of the unsubstituted zinc(II) phthalocyanine (ZnPc).

All these PEGylated phthalocyanines could form self-assembled micelles in water. To prepare these colloidal systems, solutions of these compounds in DMF were diluted with water (5% v/v) in the absence or presence of Cremophor EL (0.5 wt.%), which is a common formulating agent for hydrophobic drugs, with ultrasonic treatment. A limpid and colored aqueous solution was obtained for all the cases. The systems prepared from compounds **1**–**3** in the absence (i.e., essentially neat water) or presence of Cremophor EL are labeled as **w1**, **w2**, **w3**, **c1**, **c2**, and **c3**, respectively. All of them were stable except **w1**, in which aggregates formed and precipitated after overnight storage. The high stability

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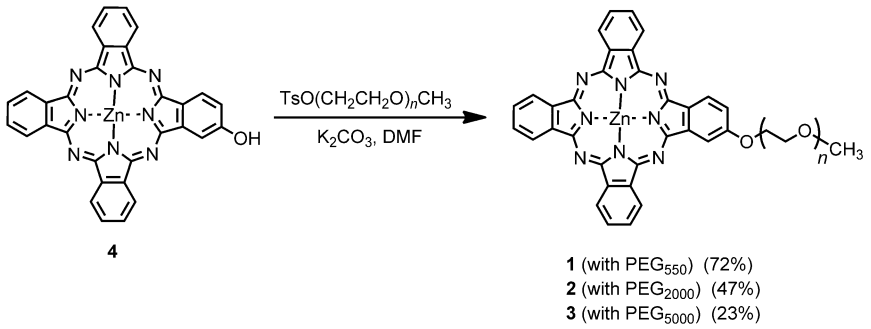

Scheme 1. Preparation of mono-PEGylated zinc(II) phthalocyanines **1**–**3**.

Table 1. Electronic absorption and photophysical properties of **1**–**3** in DMF.

Compd	λ_{max} [nm] (log ε)	λ_{em} [nm][a]	Φ_F[b]	Φ_Δ[c]
1	346 (4.70), 606 (4.46), 672 (5.23)	677	0.31	0.56
2	346 (4.59), 606 (4.36), 672 (5.14)	677	0.35	0.55
3	347 (4.32), 606 (4.11), 672 (4.86)	677	0.39	0.53

[a] Excited at 610 nm. [b] Using ZnPc as the reference (fluorescence quantum yield (Φ_F) = 0.30 in 1-chloronaphthalene).[11] [c] Using ZnPc as the reference (singlet oxygen quantum yield (Φ_Δ) = 0.56 in DMF).[10]

of the other systems may be attributed to the long PEG chain, which facilitates the formation of micelles, and the effect of Cremophor EL. As an alternative formulation method, compound **1** was encapsulated into organically modified silica-based nanoparticles using the method reported by Prasad and co-workers, which was based on controlled hydrolysis of triethoxyvinylsilane in micellar media.[12] The nanoparticles (labeled as **n1**), obtained after dialysis and filtration (0.22 μm cut-off), were found to be highly monodispersed in size and stable in aqueous media.

The size of these nanoparticles was measured by dynamic laser light scattering. In the absence of Cremophor EL, compounds **1**–**3** showed very broad distributions in size with average hydrodynamic radii (R_h) of 76 (**w1**), 15 (**w2**), and 27 nm (**w3**). Upon addition of Cremophor EL, the size distribution became narrower for all the three compounds, and the size was also significantly smaller (R_h = 12 (**c1**), 7 (**c2**), and 9 nm (**c3**)). The results clearly showed that these PEGylated phthalocyanines formed self-assembled micelles. Interestingly, the silica nanoparticles with encapsulated **1** (**n1**) had an even narrower distribution. This can be seen clearly from Figure 1 A, which compares the size distribution of **w1**, **c1**, and **n1**. The hydrodynamic radius of these nanoparticles (25 nm) was in good agreement with the value estimated by transmission electron microscopy (TEM, Figure 1 B). The TEM image also showed that the nanoparticles are spherical and uniform. It is worth noting that nanoparticles with a size of 10–100 nm generally have the advantages of high cellular uptake and enhanced EPR effect and are therefore desirable for cancer therapy.[13]

Figure 2 A shows the UV/Vis spectra of compounds **1**–**3** formulated in different ways in water. In the absence of Cremophor EL, all these compounds were highly aggregated, as shown by the very broad and blue-shifted Q band at approximately 620 nm. In the presence of Cremophor EL, the Q band arising from the monomeric species (674 nm) could be observed for all the compounds, thus indicating that their aggregation was significantly reduced with the aid of this surfactant. As inferred from the shape of the spectrum, the aggregation

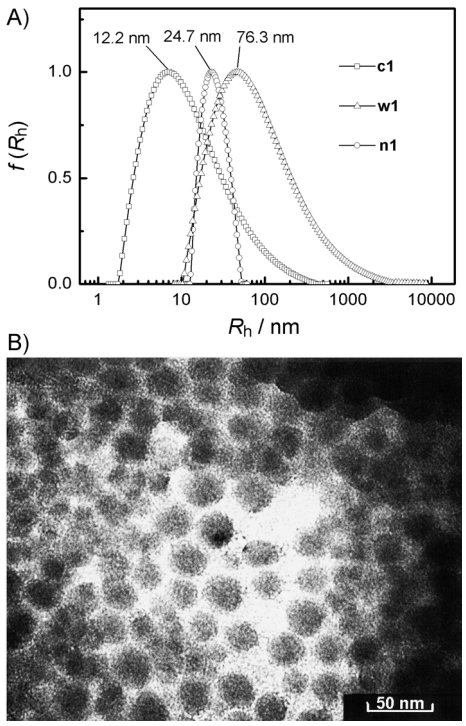

Figure 1. A) Hydrodynamic radius distribution of **1** in various formulations. B) TEM image of **n1**.

tendency of **1** in silica nanoparticles seems to lie between that in water and in Cremophor EL emulsion. The results were in accord with the fluorescence data. As shown in Figure 2 B, the fluorescence intensity generally follows the trend **c** > **n** > **w**, and the longer the PEG chain, the stronger the fluorescence. This finding suggests that a longer PEG chain can reduce the stacking of the phthalocyanine in a more effective manner.

The singlet oxygen generation efficiency of these systems in water was also evaluated by using the imidazole/4-nitrosodimethylaniline (RNO) assay.[14] In this method, the singlet oxygen produced is captured by imidazole to form a trans-annular peroxide, which is capable of bleaching RNO, and the process can be monitored spectroscopically at 440 nm (the absorption of RNO). Figure 3 A shows the results for **n1** as a typical example, in which it can be seen that

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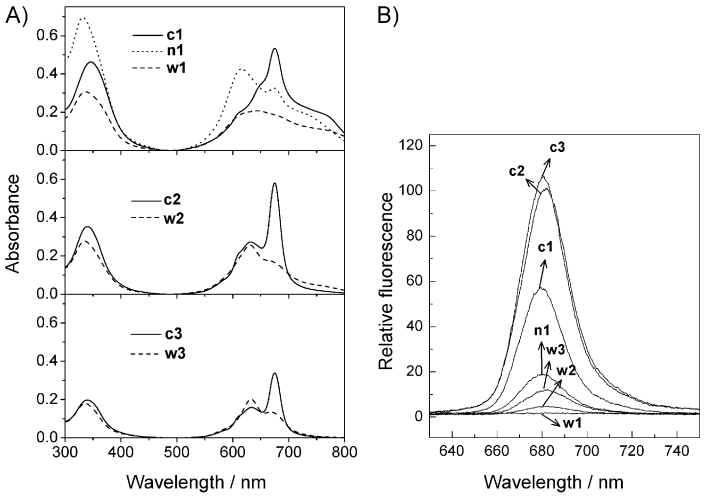

Figure 2. A) UV/Vis and B) fluorescence ($\lambda_{ex}=610$ nm) spectra of **1**–**3** in various formulations in water. The concentration of phthalocyanine was fixed at 10 μM in all cases.

the concentration of RNO decreases along with the irradiation time. Figure 3B compares the rate of degradation of RNO induced by these systems. It can be seen that **w1** cannot generate singlet oxygen due to its high aggregation tendency. The analogues **w2** and **w3** are better singlet oxygen generators, but the efficiency is still lower than that of **n1**. Cremophor EL can greatly enhance the efficiency of these compounds, as shown by the data for **c1**, **c2**, and **c3**. These observations, which can be attributed to the different aggregation tendencies of these systems, are generally in good agreement with the results from the absorption and fluorescence spectroscopic studies.

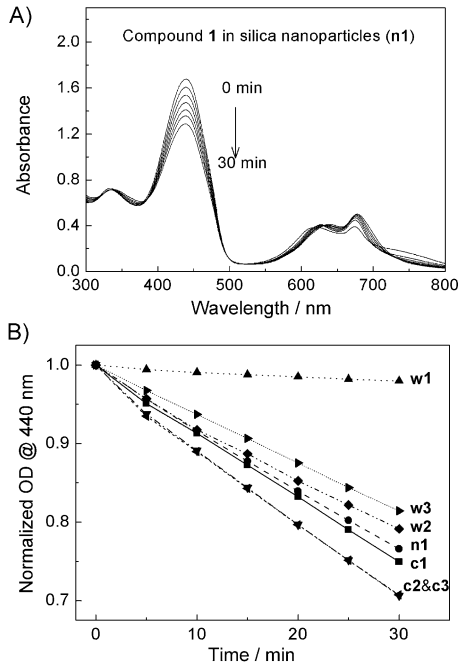

Figure 3. A) Change in UV/Vis spectrum of a mixture of **n1** ([**1**]=10 μM), RNO (50 mM), and imidazole (10 mM) in water after irradiation for 5, 10, 15, 20, 25, and 30 min. B) Plots of the absorbance at 440 nm as a function of irradiation time.

The photodynamic activity of these systems toward HepG2 human hepatocarcinoma cells was also studied. Figure 4A shows the dose-dependent survival curve for **n1**. It can be seen that the nanoparticles are not significantly toxic in the absence of light. However, upon illumination with red light ($\lambda>610$ nm, 40 mW cm^{-2}, 48 J cm^{-2}), they exhibit high cytotoxicity with an IC_{50} value of approximately 0.2 μM (of **1**). Figure 4B compares the cytotoxic effects of **1**–**3** (at 2 μM) being formulated in different ways. It is clear that compound **1**, which has the shortest PEG chain, exhibits the highest photocytotoxicity, particularly when it is formulated with Cremophor EL (**c1**) or encapsulated in silica nanoparticles (**n1**). For these two systems, more than 97% of the cells were killed under these conditions. The photocytotoxicity generally decreases as the length of the PEG chain increases.

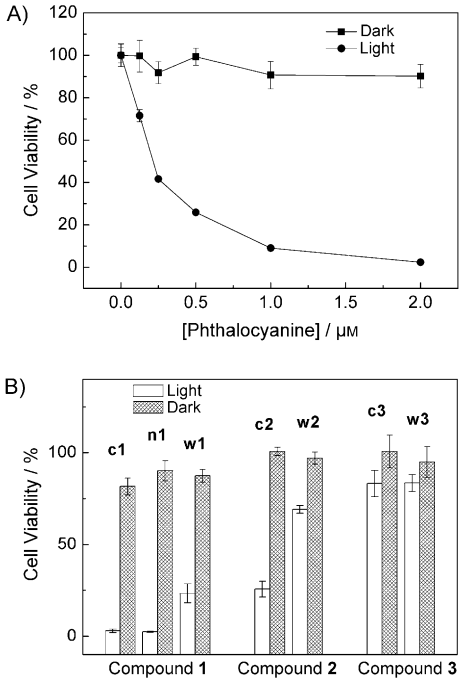

Figure 4. A) Effects of **n1** on HepG2 cells in the absence (-■-) and presence (-●-) of light ($\lambda>610$ nm, 40 mW cm^{-2}, 48 J cm^{-2}). Data are expressed as mean value ± standard error of the mean value of three independent experiments, each performed in quadruplicate. B) Comparison of the cytotoxic effects of **1**–**3** in different formulations toward HepG2 cells. The concentration of phthalocyanine was fixed at 2 μM in all cases.

To account for the different photocytotoxicities of these systems, their cellular uptake was examined by confocal fluorescence microscopy. After incubation for 2 h, compound **1** in all the three formulations (**c1**, **w1**, and **n1**) showed strong intracellular fluorescence (see Figure S1 in the Supporting Information). This observation suggested that it was taken up effectively into the cells. The fluores-

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cence was particularly strong for the silica nanoparticles **n1**, indicating that they have the highest cellular uptake. By contrast, the intracellular fluorescence was slightly weaker for compound **2** (**c2** and **w2**), while the fluorescence could just be observed for compound **3** (**c3** and **w3**). The results suggested that a longer PEG chain may hinder the uptake of the phthalocyanine, probably as a result of the larger size. The deduced trend of the cellular uptake (**1** > **2** > **3**) was in good agreement with the order of photocytotoxicity of these compounds (Figure 4B).

In summary, we have prepared and characterized three PEGylated zinc(II) phthalocyanines, which can self-assemble in water to form micelles both in the absence and presence of Cremophor EL. The analogue with the shortest PEG chain (compound **1**) has also been encapsulated in silica nanoparticles. The latter (**n1**) is a highly promising photosensitizing system due to its high stability in aqueous media, appropriate and uniform size, high singlet oxygen generation efficiency, and high cellular uptake, resulting in enhanced in vitro photocytotoxicity. Further investigation is underway to extend this formulation method to other photosensitizers and perform surface modification to enhance their tumor-targeting properties.

Experimental Section

The experimental details regarding the purification of solvents, instrumentation, photophysical measurements, laser light scattering, and in vitro studies were described previously.[15] Polyethylene glycol monomethyl ether monotosylate with an average molecular weight of ca. 550[16] and 2000 g mol^{-1}[17] were prepared as described.

$TsO(CH_2CH_2O)_nCH_3$ with an average molecular weight of ca. 5000 g mol^{-1}.

Tosyl chloride (0.37 g, 1.94 mmol) was added to a mixture of polyethylene glycol monomethyl ether with an average molecular weight of ca. 5000 g mol^{-1} (6.27 g, 1.25 mmol) and triethylamine (0.4 mL) in CH_2Cl_2 (30 mL) at ambient temperature. The mixture was kept stirring overnight at this temperature, then it was extracted with CH_2Cl_2 (100 mL) and water (20 mL). The organic phase was separated and washed with water (3×20 mL). The combined organic portions were dried with anhydrous $MgSO_4$ and volatile components were removed by evaporation. The residue was then stirred with diethyl ether (40 mL) for ca. 2 h to induce precipitation. The product was collected by filtration, washed with ether, and then dried in vacuo to give a white solid (4.76 g, 74%). ^{1}H NMR ($CDCl_3$): δ = 7.80 (d, J = 8.4 Hz, 2H, ArH), 7.36 (d, J = 8.4 Hz, 2H, ArH), 3.4–4.2 (m, ca. 500H, CH_2 and CH_3), 2.45 ppm (s, 3H, CH_3).

*Phthalocyanine **1***

A mixture of phthalocyanine **4** (56 mg, 0.09 mmol), $TsO(CH_2CH_2O)_nCH_3$ with an average molecular weight of ca. 550 g mol^{-1} (105 mg, 0.15 mmol), and K_2CO_3 (45 mg, 0.33 mmol) in DMF (2 mL) was heated with stirring at 70 °C for 3 h, then at 100 °C for a further 21 h. After the first 12 h, another portion of K_2CO_3 (45 mg, 0.33 mmol) was added. After the DMF was evaporated in vacuo, the residue was purified by column chromatography using tetrahydrofuran (THF)/hexane (1:1, v/v) and then DMF/ethyl acetate (1:9, v/v) as the eluents. The second colored band was collected to afford a dark green product, which was further purified by repeated column chromatography (76 mg, 72%). ^{1}H NMR ([D_6]DMSO): δ = 8.94–9.13 (m, 6H, Pc-H_α), 8.68 (d, J = 8.1 Hz, 1H, Pc-H_α), 8.24 (s, 1H, Pc-H_α), 8.01–8.16 (m, 6H, Pc-H_β), 7.47 (d, J = 8.1 Hz, 1H, Pc-H_β), 4.57 (br s, 2H, CH_2), 4.09 (br s, 2H, CH_2), 3.81–3.84 (m, 2H, CH_2), 3.70–3.74 (m, 2H, CH_2), 3.62–3.65 (m, 2H, CH_2), 3.2–3.6 ppm (m, ca. 40H, CH_2 and CH_3). ESI-MS: two overlapping envelopes of clusters which are separated by 44 mass units (due to the repeating unit of PEG) assigned to the protonated and sodiated species. For the isotopic clusters for n = 12, the peaks appeared at m/z 1135 $[M+H]^+$ and 1157 $[M+Na]^+$.

*Phthalocyanine **2***

A mixture of phthalocyanine **4** (61 mg, 0.10 mmol), $TsO(CH_2CH_2O)_nCH_3$ with an average molecular weight of ca. 2000 g mol^{-1} (360 mg, 0.17 mmol), and K_2CO_3 (60 mg, 0.43 mmol) in DMF (2 mL) was heated with stirring at 70 °C for 45 h, then at 100 °C for a further 27 h. After the first 24 h, another portion of K_2CO_3 (75 mg, 0.54 mmol) was added. After the DMF was evaporated in vacuo, the residue was purified by column chromatography using THF/hexane (1:1, v/v) and then DMF/ethyl acetate (1:4, v/v) as the eluents. The second colored band was collected to afford a dark green product, which was further purified by repeated column chromatography (124 mg, 47%). ^{1}H NMR ([D_6]DMSO): δ = 9.14–9.25 (m, 6H, Pc-H_α), 8.92 (d, J = 8.1 Hz, 1H, Pc-H_α), 8.50 (s, 1H, Pc-H_α), 8.10–8.21 (m, 6H, Pc-H_β), 7.61 (d, J = 8.1 Hz, 1H, Pc-H_β), 4.64 (br s, 2H, CH_2), 4.08 (br s, 2H, CH_2), 3.80–3.82 (m, 2H, CH_2), 3.2–3.7 ppm (m, ca. 200H, CH_2 and CH_3). ESI-MS: two overlapping envelopes of clusters assigned to the protonated and sodiated species. For the isotopic clusters for n = 45, the peaks appeared at m/z 2589 $[M+H]^+$ and 2611 $[M+Na]^+$.

*Phthalocyanine **3***

A mixture of phthalocyanine **4** (59 mg, 0.10 mmol), $TsO(CH_2CH_2O)_nCH_3$ with an average molecular weight of ca. 5000 g mol^{-1} (779 mg, 0.15 mmol), and K_2CO_3 (69 mg, 0.50 mmol) in DMF (4 mL) was heated with stirring at 100 °C for 24 h. After the first 6 h, another portion of K_2CO_3 (86 mg, 0.62 mmol) was added. After the DMF was evaporated in vacuo, the residue was purified by column chromatography using THF/hexane (1:1, v/v) and then DMF/ethyl acetate (1:4, v/v) as the eluents. The second colored band was collected to afford a dark green product, which was further purified by repeated column chromatography followed by recrystallization twice from CH_2Cl_2 and hexane (129 mg, 23%). ^{1}H NMR ($CDCl_3$): δ = 9.03–9.20 (m, 6H, Pc-H_α), 8.84 (d, J = 8.1 Hz, 1H, Pc-H_α), 8.38 (s, 1H, Pc-H_α), 7.93–8.04 (m, 6H, Pc-H_β), 7.44 (d, J = 8.1 Hz, 1H, Pc-H_β), 3.1–4.6 ppm (m, ca. 500H, CH_2 and CH_3). MALDI-MS: two overlapping envelopes of clusters assigned to the protonated and sodiated species, peaking at m/z 5075 $[M+Na]^+$ (for n = 101).

*Preparation of 1-encapsulated silica nanoparticles (**n1**)*

1-Butanol (400 μL) was added to a solution of dioctyl sodium sulfosuccinate (AOT) (0.22 g) in deionized water (10 mL) with vigorous magnetic stirring. A solution of **1** in DMF (7.5 mM, 100 μL) was then added with stirring, then triethoxyvinylsilane (100 μL) was added until the mixture became clear (after about 1 h). After that, 3-aminopropyltriethoxysilane (5 μL) was added and the mixture was stirred for approximately 20 h in the dark. The surfactant AOT and co-surfactant 1-butanol were then removed by dialyzing the solution against deionized water in a 12–14 kDa cut-off cellulose membrane for 50 h. The dialyzed solution was then filtered through a 0.22 μm cut-off membrane filter. The concentration of the phthalocyanine in the silica nanoparticles was determined by a spectrophotometric method. A 200 μL sample was dissolved in 5 mL of DMF, and the concentration was calculated by the Lambert–Beer law using the absorbance at 672 nm.

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