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The effect of central metal on the photodynamic properties of silylated tetraphenylporphyrin derivative



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ABSTRACT

We have introduced central metal to 5,10,15,20-tetrakis(3'-trimethylsilyl-5'-carboxyphenyl)porphyrin tetrasodium (**1**), which shows high photodynamic activity. As central metals, Zn and Pd have been studied, and Zn and Pd improved the quantum yield of intersystem crossing by the heavy atom effect. Pd improved the quantum yield of singlet oxygen sensitization, but Zn decreased the quantum yield. The difference in the quantum yield has been discussed. Cytotoxicity has been evaluated by using a HeLa cell line, and cytotoxicity of metal complexes of **1** were sufficiently low. Pd also improved concentration of photosensitizers in cells, and thus Pd enhanced photodynamic activity. The difference of the photodynamic activity induced by the complexation could be explained by the quantity of singlet oxygen produced in cells, which was evaluated by using the quantum yield of singlet oxygen sensitization, a concentration of photosensitizers in cells, and absorption spectrum of photosensitizers.

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1. Introduction

Photodynamic therapy (PDT) is a promising treatment for cancer [1,2]. After intravenous injection of photosensitizer solution in a patient, photosensitizers are preferentially taken up/or retained by tumors. By the light irradiation to the tumors, photosensitizers are excited and reactive oxygen species such as singlet oxygen are sensitized. Reactive oxygen species induce cell death only in tumors.

Porphyrinoids are the most fundamental photosensitizers, and various kinds of modification have been studied to improve their photodynamic properties. Modifications of the porphyrin ring have been studied to improve absorption efficiencies. Chlorin or bacteriochlorin derivatives can be obtained from TPP derivatives by reduction of part of the porphyrin ring, and derivatives show high light absorption efficiencies [3–6]. Extension of the π -system is also effective in improving light absorption efficiency [7,8]. Introduction of functional units to the phenyl moiety of TPP has also been widely studied. Sugar units have been introduced to

improve preferential uptake of photosensitizers to cancer cells [3,9,10,11,12]. Folic acids have also been introduced to improve preferential uptake of photosensitizers to cancer cells [13]. We have introduced silyl groups to TPP derivatives, and found that silylation improves the quantum yield of singlet oxygen sensitization, cellular uptake efficiency, and accumulation efficiency to the tumor [14–16]. Complexations of porphyrinoids with metal are also effective in improving photosensitizers. The axial ligands can be introduced to some metal complexes of porphyrinoids. As the axial ligands, bulky substituents were introduced to suppress the aggregation of porphyrinoids [17,18]. Hydrophilic and/or hydrophobic substituents have also been introduced to adjust water solubility [19,20] and to introduce certain functions [21]. Singlet oxygen is produced by the energy transfer from the photosensitizer in the lowest triplet (T_1) state to oxygen. The quantum yield of intersystem crossing was reported to be improved by the central metal due to the heavy atom effect and thus the quantum yield of singlet oxygen sensitization may be improved by complexation with heavy metal. For example, insertion of Pd or Zn was reported to improve the quantum yield of singlet oxygen sensitization [4,22]. Insertion of Zn to porphyrins have also been reported to improve cellular uptake efficiency [23].

These modifications are very effective, and thus integration of these modifications is very important for developing efficient photosensitizers. In this study, we have introduced central metal to

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the silylporphyrin derivative (**1**) that we developed [16]. As central metals, we selected Zn and Pd, because of their high potential [4,22,23]. We have synthesized Zn (**2**) and Pd (**3**) complexes of **1**, and have clarified the effect of central metal on the photodynamic properties.

2. Results and discussion

2.1. Photochemical studies

To discuss photosensitization processes of singlet oxygen, photophysical processes have been studied. Fig. 1 shows UV–vis absorption spectra of **1**, **2**, and **3** (Chart 1) in EtOH at room temperature. As discussed later, photosensitizers are considered to be distributed not only to aqueous media but also to the hydrophobic media. Therefore we selected ethanol as a solvent to discuss the photochemical processes in the cancer cells. These absorption spectral properties are similar to those of the corresponding metal complexes of tetraphenylporphyrin (ZnTPP [24] and PdTPP [25]). These results support the finding that the metal complexes were successfully synthesized. Fluorescence spectra of **1** and **2** in EtOH are also shown in Fig. 1. For **1**, fluorescence peaks were observed at 648 and 715 nm as previously reported [16]. Fluorescence peaks were observed at 604 and 659 nm for **2**. These peak wavelengths are similar to that of ZnTPP [24]. The excitation spectrum of **2** (not shown) was essentially the same as its absorption spectrum. A very weak fluorescence peak was observed around 610 nm for **3** (not shown). This peak wavelength of **3** is similar to that of PdTPP [26]. In the case of **1**, the fluorescence rate constant was estimated to be $6.4 \times 10^6 \text{ s}^{-1}$ by using the previously reported Φ_f (0.068) and τ_f (10.6 ns) in air-saturated EtOH [16]. For **2**, the fluorescence quantum yield Φ_f and lifetime τ_f were determined in air-saturated EtOH to be 0.019 and 1.9 ns, respectively. From these values, the fluorescence rate constant was estimated to be $1.0 \times 10^7 \text{ s}^{-1}$, which is similar to that of **1**. In the case of **3**, Φ_f was less than 0.001, and τ_f was too short to be determined. Φ_f of PdTPP was reported to be ~ 0.0004 [26], and thus fluorescence properties of **3** is considered to be similar to those of PdTPP. Decreases of Φ_f may indicate that intersystem crossing to the lowest triplet (T_1) state is enhanced by the insertion of the central metal.

Next we studied the quantum yield of intersystem crossing Φ_T by using the photoacoustic (PA) measurements to discuss the heavy atom effect of central metal on the photophysical processes. To determine Φ_T by the PA measurements, the lifetime τ_T of the T_1 state has to be long enough. In the general photosensitizers, τ_T is enough long, but τ_T is considered to be shortened by the heavy

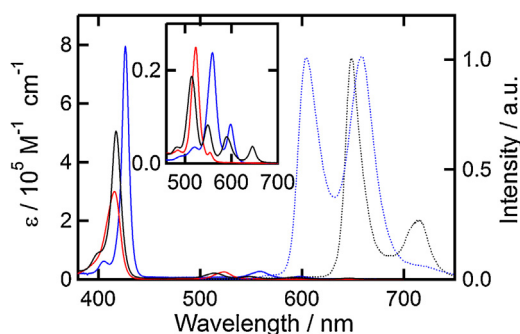


Fig. 1. Absorption (full line) and fluorescence spectra (dotted line) of **1** (black), **2** (blue), and **3** (red) in ethanol. The inset is a magnified figure of Q-bands of absorption spectra at room temperature.

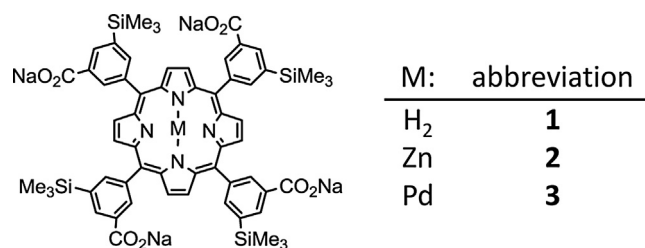


Chart 1. Molecular structures of photosensitizers.

atom effect in the case of photosensitizers in this study. Thus we checked the τ_T of photosensitizers by the transient absorption technique before the PA measurements. Fig. 2 shows transient absorption spectra of **1** (a), **2** (b), and **3** (c) in Ar-saturated EtOH. The intense negative and positive bands were observed at around 420 nm and in the region of 430–500 nm, respectively, for **1**. Weak negative and positive bands were also observed in the region of 500–800 nm. This spectral shape is very similar to that of TPP, indicating that the positive band can be assigned to the T–T absorption and the negative band can be assigned to the bleaching of the ground state. Fig. S1a shows the decay time profile of transient absorption at 440 nm observed for **1** in Ar-saturated EtOH. This could be analyzed by a single exponential function with the lifetime of the T_1 state in Ar-saturated EtOH τ_T^{Ar} of 40 μs (Table 1). The transient absorption spectra of **2** and **3** are similar to those of **1**. These spectral shapes are also very similar to that of the corresponding metal complexes of TPP. Thus the positive and negative bands can be assigned to the T–T absorption and the bleaching of the ground state, respectively, as in the case of **1**. Fig. S1b and c show the decay time profiles of transient absorption at 440 nm observed for **2** and **3**, respectively. These could be analyzed by a single exponential function with τ_T^{Ar} of 27 μs and 9.0 μs for **2** and **3**, respectively (Table 1). These lifetimes are long enough for the PA measurements.

The PA signal of photosensitizers is measured in Ar-saturated EtOH (inset of Fig. 3). The difference between the first maximum and minimum in the PA signal was taken as the signal amplitude H . The fraction of the absorbed energy released as thermal energy within the response time of the detector α is given by the following

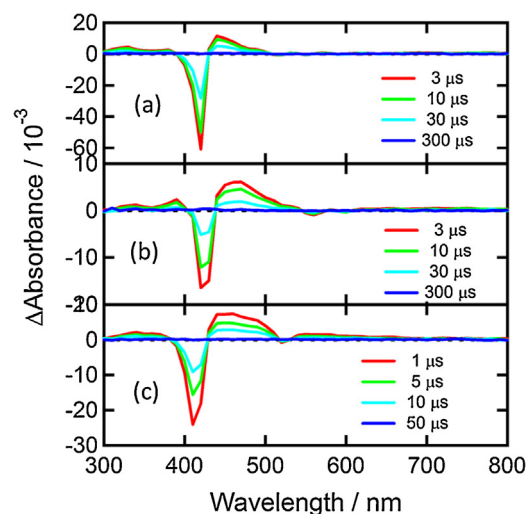


Fig. 2. Transient absorption of **1** (a), **2** (b), and **3** (c) in Ar-saturated ethanol at room temperature.

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