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Water-soluble gadolinium porphyrin as a multifunctional theranostic agent: Phosphorescence-based oxygen sensing and photosensitivity

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ABSTRACT

Photodynamic therapy (PDT) is the most advanced treatment method for cancer. Challenges including quantification of the photosensitizer (PS) and oxygen necessitate the development of multifunctional PS that can function as oxygen indicators and magnetic resonance imaging (MRI) contrast agents (CA). A water-soluble gadolinium-containing porphyrin, gadolinium-containing sinoporphyrin sodium (Gd-DVDMS), was developed as a multifunctional theranostic agent: a PS for PDT, an MRI CA, and a phosphorescence-based oxygen indicator. The MRI enhancing effect of the PS can be used to measure its concentration. The luminescence and photosensitivity of Gd-DVDMS were studied and compared to those of Gd-hematoporphyrin monomethyl ether (Gd-HMME). The molar absorption coefficient of Gd-DVDMS was greater than that of Gd-HMME because it has two porphyrin rings. The emission of Gd-DVDMS at 712 nm was confirmed to be phosphorescence with a lifetime of 49 μs and quantum yield of 0.015. The phosphorescence was effectively quenched by oxygen: the phosphorescence intensity in air-saturated methanol was 33% of that in deoxygenated methanol. The phosphorescence quenching highlights the potential utility of Gd-DVDMS in the quantification of oxygen in PDT. The singlet oxygen quantum yield of Gd-DVDMS was 0.46, which was slightly higher than that of Gd-HMME. Overall, Gd-DVDMS is a promising multifunctional PS with many advantages over existing PS. In particular, DVDMS with double porphyrin rings can coordinate to two different metal ions in order to design agents with more functions.

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1. Introduction

Photodynamic therapy (PDT) is the most advanced treatment method for many kinds of cancers [1–4]. PDT is based on the activation of photosensitizers (PS) with an appropriate light source, which leads to the formation of highly cytotoxic reactive oxygen species [5,6]. PDT is one of the most selective treatments for oncological maladies owing to its excellent targeting capabilities and limited side effects. However, clinical applications of PDT are restricted by the limited penetration of the most commonly used light at 630 nm, which is only about 5 mm [7]. Recently, interstitial PDT was proposed for the treatment of large and deep lesions [8,9]. Such treatment approaches require images to provide morphological and physiological information about diseased tissues. Thus, magnetic resonance imaging (MRI) and fluorescence tomography imaging [10] have been developed for the diagnosis of solid tumors. Another challenge in interstitial PDT is the estimation of its efficacy. The three elements of PDT, namely light, the photosensitizer, and oxygen, can have an effect on its efficacy. For example, the distribution of oxygen in treated tissues can greatly influence PDT [11]. Specifically, the effects on PDT are minor when tissue oxygen levels are low, even when the concentration of tissue PS and dosimetry of light are sufficient. Accurate oxygen-level measurements are

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required in PDT. Therefore, theranostic agents that can simultaneously function as photosensitizers, magnetic resonance imaging (MRI) contrast agents (CA), and oxygen indicators are desired for interstitial PDT.

Towards that end, metalloporphyrins are great multifunctional theranostic agents due to their diverse properties. Specifically, they can be used as MRI CA [12], near-infrared probes [13], oxygen sensors [14], and PS in PDT [15]. The physiochemical nature of metalloporphyrins differs depending on the central metal ion. For diagnosis and PDT, the selection of the appropriate porphyrin and metal ion combinations is critically important. Gadolinium porphyrins and associated complexes, including Gd-DTPA [16], have long been used as MRI CA due to the high paramagnetism of Gd(III). Additionally, gadolinium porphyrins have relatively high triplet state quantum yields, which affects phosphorescence and photosensitivity. During the past decade, gadolinium porphyrins have been studied as phosphorescence-based oxygen sensors and photosensitizers. The room temperature phosphorescence (RTP) of gadolinium porphyrins was first reported by Wong in 2011 [17]. In 2013, the RTP emission of gadolinium tetraphenylporphyrin was utilized for optical oxygen sensing [18]. In 2015, Tsvirko reported the RTP of a series of gadolinium porphyrins [19]. In 2016, Ke developed gadolinium extended porphyrins (porpholactones) as efficient and robust singlet oxygen photosensitizers [20]. Recently, Gd-hematoporphyrin monomethyl ether (Gd-HMME) was found to display relatively strong RTP, and exhibited potential as both an oxygen indicator and photosensitizer in PDT [21–23].

For biomedical applications, the water-solubility and cell permeability of metalloporphyrins, which are strongly dependent on the free base porphyrins, must be considered. Very recently, a novel porphyrin, sinoporphyrin sodium (DVDMS), the dominant active compound isolated from the most commonly used photosensitizer, Photofrin®, was found to exhibit significantly higher photo-activities in preclinical studies than Photofrin® [24]. DVDMS exhibited higher brightness and singlet oxygen generation as compared to other known PS, including hematoporphyrin, protoporphyrin IX (PpIX), and Photofrin® [25]. In addition, DVDMS exhibited greater water-solubility, chemical stability, and targeting abilities towards tumor cells or diseased tissues due to its amenable chemical structure [26,27]. Owing to the advantages of DVDMS, we developed a new, water-soluble Gd-containing porphyrin, Gd-DVDMS; the luminescence and photosensitivity are described herein in order to develop a potential multifunctional theranostic agent.

Gd-DVDMS was characterized using UV–visible absorption. The absorption coefficient of Gd-DVDMS was determined via spectroscopic analysis. The luminescence of Gd-DVDMS was measured and the luminescence quantum yield was determined using a relative method [22] with Gd-HMME as the reference. The influence of oxygen on the luminescence of Gd-DVDMS was also determined. The luminescence spectra of Gd-DVDMS in the presence of different concentrations of oxygen were measured. The singlet oxygen quantum yield (Φ_Δ) of Gd-DVDMS was established via a comparative method [21] using Gd-HMME as the reference.

2. Experimental section

2.1. Materials

Anhydrous gadolinium chloride ($GdCl_3$) and 1,3-diphenylisobenzofuran (DPBF) were purchased from J&K Scientific Ltd. Sinoporphyrin sodium (DVDMS) was kindly provided by Professor Qicheng Fang from the Chinese Academy of Medical Sciences. Hematoporphyrin monomethyl ether (HMME) was obtained from Shanghai Xianhui Pharmaceutical Co., Ltd. Methanol was purchased from Tianjin Fuyu Fine Chemical Co., Ltd. Highly pure nitrogen (99.99%) was obtained from Harbin Liming Co., Ltd. All reagents, solvents etc. were used as received without further purification.

2.2. Preparation of samples

Gd-DVDMS was synthesized using the method described by Srivastava [28]. Briefly, a mixture of imidazole (6 g), DVDMS (12 mg), and excess anhydrous $GdCl_3$ (53 mg) was added to a 250 mL three-necked bottle under a flow of argon for 30 min. Then, the mixture was heated to and kept at 200 °C and stirred magnetically for 2 h under a flow of argon. After cooling to room temperature, the mixture was dissolved in methanol to yield 10 mL of a 1 mM Gd-DVDMS solution. The purity of Gd-DVDMS was determined to be greater than 99% by analyzing the composition of the resulting solution.

2.3. Measurements

The mass spectra were recorded on a liquid chromatography/mass spectra (LC/MS) analyzing system (Thermo Finnigan Surveyor LCQ DECA XP plus, USA). UV–visible absorption spectra were obtained using a miniature fiber optic spectrometer (Ocean Optics QE65000) equipped with a deuterium lamp. The molar extinction coefficient was determined via absorption spectroscopic analysis. The extinction coefficient, $\varepsilon(\lambda)$, of Gd-DVDMS was determined using the Beer-Lambert law, $-\lg(I(\lambda)/I_0(\lambda)) = \varepsilon(\lambda)\cdot C\cdot L$, where $I(\lambda)$ is the transmission spectrum of Gd-DVDMS, $I_0(\lambda)$ is the transmission spectrum of the blank (methanol), C is the concentration of Gd-DVDMS, L is the optical path length, and the product of $\varepsilon(\lambda)\cdot C\cdot L$ is the absorbance. Absorption spectra of Gd-DVDMS were recorded at various concentrations to determine the correlation between the absorbance at a specific wavelength and concentration; the extinction coefficient at a specific wavelength is identical to the slope.

A diode laser centered at 405 nm was used to excite Gd-DVDMS. Photoluminescence spectra were recorded using a miniature fiber optic spectrometer (Ocean Optics USB2000). All spectra were calibrated using a mercury lamp. To determine the luminescence quantum yield of Gd-DVDMS in an air-saturated solution, Gd-HMME was used as the reference, and was excited with a 532 nm solid-state laser (CLO Laser DPGL-500L). To determine the photoluminescence lifetime of Gd-DVDMS in methanol, the decay profile was measured. The measurement process is provided on Page 2 in the SI.

To determine the singlet oxygen quantum yield of Gd-DVDMS in an air-saturated solution, a relative spectrophotometric method [29] based on Eq. (1) was used:

$$\frac{\Phi_\Delta A}{k} = \frac{\Phi_\Delta^r A^r}{k^r} \tag{1}$$

Here the superscript "r" stands for the reference reagent, k is the degradation rate of the singlet oxygen trapping reagent, and A is the absorption of excitation light by photosensitizers [30], which is dependent on the concentration of the photosensitizer, extinction coefficient, and intensity of the incident light. The following equation describes this relationship:

$$A = \int I_{532}(\lambda) \times \left(1 - e^{-\varepsilon(\lambda)CL}\right) d\lambda \tag{2}$$

$I_{532}(\lambda)$ is the normalized emission spectrum of the 532 nm laser, $\varepsilon(\lambda)$ is the absorption coefficient of each substance, C represents the concentration, and L is the light path length. To measure Φ_Δ of Gd-

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