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Amphoteric phosphorous(*V*)-phthalocyanines as proton-driven switchable fluorescers toward deep-tissue bio-imaging

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ABSTRACT

Spectral (optical absorption and emission) properties of three amphoteric phosphorous(*V*)-phthalocyanine derivatives, [P(Pc)(O)OH], where Pc = tetra(*tert*-butyl)phthalocyaninate (tbpc), tetrakis(2′,6′-dimethylphenoxy) phthalocyaninate (tppc), and octakis(4′-*tert*-butylphenoxy)phthalocyaninate (obppc), have been investigated in ethanolic solutions. Spectral changes upon protonation/deprotonation (the reaction sites have been determined to be their axial ligands by magnetic circular dichroism study) are drastic and rapid. All the initial ([P(Pc)(O)OH]), protonated ($[P(Pc)(OH)_2]^+$), and deprotonated ($[P(Pc)(O)_2]^-$) species are possessed with sufficient brightness (defined as the product of their molar extinction coefficient, ε (in $M^{-1}\,cm^{-1}$), and fluorescence quantum yield, Φ_F) in bio-imaging window (650–900 nm). For example, spectral characteristics of the tbpc derivatives have been determined as follows: $\varepsilon = 1.65 \times 10^5$ (absorption maximum 676 nm) and $\Phi_F = 0.80$ (emission maximum 686 nm) for [P(tbpc)(O)(OH)] while $\varepsilon = 1.45 \times 10^5$ (697 nm) and $\Phi_F = 0.27$ (714 nm) for $[P(tbpc)(OH)_2]^+$, and $\varepsilon = 2.25 \times 10^5$ (662 nm) and $\Phi_F = 0.90$ (667 nm) for $[P(tbpc)(O)_2]^-$. Emission of tppc and obppc derivatives behave in essentially the same manner irrespective of nature of the peripheral substituents and hence Φ_F values are greater with increasing emission peak wavenumbers in line with the "energy gap law". These characteristics make these compounds promising candidates as chemical probes for deep-tissue bio-imaging.

1. Introduction

Small fluorescent molecules play a crucial role in chemical biology as biomolecular labels, enzyme substrates, environmental indicators, cellular stains, and so on [1]. In particular, much attention has been focused in recent years on molecular imaging using fluorescence, which is a powerful tool to directly or indirectly monitor/record the spatio-temporal distribution of biochemical processes for medical (diagnostic or therapeutic) application [2]. One of the most exciting topics in this area should include photodynamic diagnosis of cancer, where luminescent materials in tumors visually inform positions of cancer cells. An earlier pioneering work has employed green light emission (a fluorescein derivative as the fluorophore) in detecting cancer cells within a mouse because naked human eyes have the greatest sensitivity to light around this wavelength and hence green luminescence is suitable for small animals or surface imaging [3]. However, this is not the case for the important emerging area of whole animal and deep tissue imaging, which has made long-wavelength and NIR imaging of special significance.

Fluorophores excitable with light of below 650 nm gives rise to excessive photoemission because the bulk of naturally occurring endogenous fluorophores, which include melanin, proteins, hemoglobin and related molecules, are also excited in the same range [4]. The optimal excitation wavelength of a fluorophore is in the deep red or near-infrared range (650–900 nm) because of the combined virtues of good tissue penetration and low autofluorescence [5,6]. The lower wavelength excitation light is less likely to penetrate sufficiently into tissue to generate emissions from the desired fluorophore: hence even though the emission light wavelength is theoretically satisfactory for imaging, the excitation light may not be sufficient to attain deeper tissue penetration. Therefore, ideally both excitation and emission wavelengths should be in the 650–900 nm range, where absorbance and autofluorescence are minimal (so-called as an "imaging window"), so that light penetration through tissue is maximal [7].

Majority of organic fluorophores with excitation/emission in the window region are categorized into one of the following four types [8]: cyanines, phthalocyanines/porphyrins/pyrroles [9], squaraines, or

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BODIPYs (boron-dipyrromethene derivatives) [10]. As mentioned above, they are required to have sufficiently high brightness (which is defined as the product of molar extinction coefficient, ε, and fluorescence quantum yield, Φ_F; that is, $\varepsilon \times \Phi_F$) in deep-red or near-infrared region because rays in this spectral range have much better tissue penetration than green ones and also suffer from lower autofluorescence from the tissue, such as blood or muscles. In this meaning, phthalocyanines are quite promising because of their remarkable brightness in this window. In addition, porphyrins and phthalocyanines would not be used for imaging purposes alone because they are potent sensitizers of reactive oxygen species (such as singlet oxygen) that are cytotoxic to cells. A successful example of a commercial phthalocyanine fluorescer is IRDye 700DX [11], which has absorption maximum at 689 nm, $\varepsilon = 1.7 \times 10^5\ M^{-1}\ cm^{-1}$, fluorescence maximum at 700 nm, $\Phi_F = 0.14$, and excellent photostability [1]. However, this compound may be not suitable for chemical probe because its fluorophore does not change according to external chemical stimuli.

The authors have investigated phthalocyanine derivatives of group-15 elements including phosphorous [12], arsenic [13], and antimony [14–16]. Among them, the phosphorous derivatives are considered the most likely candidates for this purpose. This is because they have low toxicity and much higher fluorescence efficiency due to the absence of heavy atoms. Surprisingly, little attention has been paid to optical emission of phosphorous derivatives although their efficiencies can amount to 80%. In addition, some phosphorous derivatives have been found to change their spectral characteristics upon reaction with both acids and bases unlike their arsenic or antimony analogs [13–16], hence they can be excellent chemical probes. Therefore, this work may be an important bridgehead to establish novel small molecule fluorescers for deep-tissue imaging and as molecular switch as well. In this work, emission properties of phosphorous(*V*) phthalocyanines (Fig. 1) and their rapid response to external stimuli are reported.

2. Experimental

2.1. Materials

2.1.1. Starting materials and the other chemicals

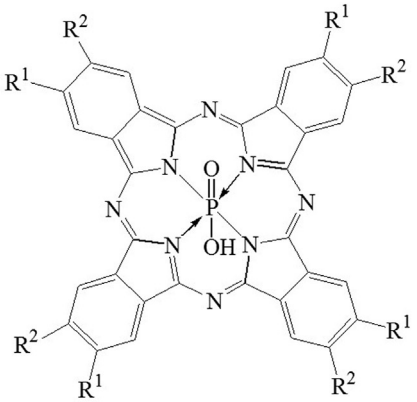
Octa(4′-*tert*-butylphenoxy)phthalocyanine, H_2obppc, was prepared from 4,5-bis-(4′-*tert*-butylphenoxy)-1,2-dicyanobenzene according to literature procedure [17]. All the other chemicals were of reagent grade and used without further purification.

2.1.2. Known phosphorous-phthalocyanines

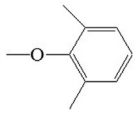
Tetra-*tert*-butyl substituted derivative, [P(tbpc)(O)(OH)]·$3H_2O$ [18] and tetra-2′,6′-dimethylphenoxy substituted derivative, [P(tppc)(O)(OH)]·$3H_2O$ [12] were prepared according to the literature procedure.

2.1.3. Synthesis of Octa(4′-tert-butylphenoxy)phthalpcyaninatophophorous (V) derivative, [P(obppc)(O)OH]·$3H_2O$

A dehydrated pyridine solution (30 ml) containing 300 mg of H_2obppc (0.18 mmol) was added to a 3 ml of dehydrated pyridine containing approximately 3.8 g of $POBr_3$ (13 mmol) in a round flask (100 ml) and the mixture was allowed to react at 80–85 °C with vigorous stirring. The blue solution containing H_2obppc alone turned dark green upon the addition of $POBr_3$ and then gradually changed to a dark brown solution within 75 min. After cooling down to room temperature, the solution was poured into water (350 ml: the reaction mixture immediately turned blue) and the resulting suspension was filtered to collect the blue solids. The solid was washed with water (2 ml) ten times until the washing turned colorless. The solids were dried in vacuum at 80 °C overnight. This was dissolved into CH_2Cl_2 (64 ml) and filtered to remove insoluble solids and the solvent was evaporated out. The residue was again dissolved into EtOH (10 ml) and then precipitated by the addition of water (40 ml). The blue solids was collected by centrifugation, washed with water (50 ml), and then dried under



tbpc; $R^1 = H$, $R^2 = {}^t$Bu — Tetra(*tert*-butyl)phthalocyanine

tppc; $R^1 = H$, $R^2 =$  — Tetra(2',6'-dimethylphenoxy)phthalocyanine

obppc; $R^1 = R^2 =$  — Octa(4-*tert*-butylphenoxy)phthalocyanine

Fig. 1. The phosphorous(V)-phthalocyanines investigated in this work. The tetra-substituted derivatives are considered to be a mixture of four regioisomers based on the positions of the peripheral substituents.

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