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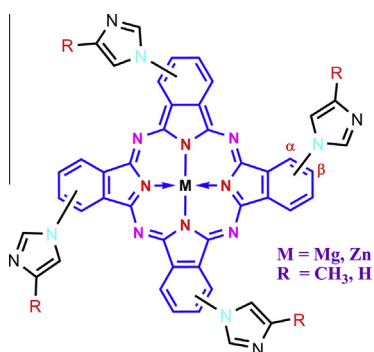
Spectroscopic insights on imidazole substituted phthalocyanine photosensitizers: Fluorescence properties, triplet state and singlet oxygen generation

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HIGHLIGHTS

- Imidazole substituted metal phthalocyanine (Im-Pc) complexes were synthesized.
- Absorption, fluorescence, triplet state and singlet oxygen formation were studied.
- All Im-Pc compounds show high quantum yield of triplet and singlet oxygen formation.
- All Im-Pc compounds still keep good fluorescence properties for PDT.

GRAPHICAL ABSTRACT



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ABSTRACT

Imidazole substituted metal phthalocyanine (Pc) complexes were synthesized. UV–vis absorption, steady state and time-resolved fluorescence, as well as laser flash photolysis were used to measure the photo-physical and photosensitizing properties. All the imidazole–phthalocyanine conjugates show high Φ_T (quantum yield of excited triplet formation), high Φ_Δ (singlet oxygen formation yield, >0.50) and good fluorescence properties (quantum yield $\Phi_f > 0.20$ and lifetime $\tau_f > 3.0$ ns). Compared to the unsubstituted Pc, both α - and β -imidazole substitutions result in the remarkable decrease in Φ_f and τ_f , but the α -substitution is stronger. The imidazole substitution, on the other hand, causes the increase of Φ_T , τ_T , and Φ_Δ values. Magnesium phthalocyanine (MgPc) is more susceptible to the substitution than zinc phthalocyanine (ZnPc). The mechanism responsible for the result is suggested based on the involvement of intramolecular photoinduced electron transfer. The high Φ_Δ and appropriate fluorescence properties make the Pcs good candidate for PDT photosensitizers.

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Introduction

Photodynamic therapy (PDT), a treatment modality for bacterial infections, acne, and malignant cancers, has been among the research focus over decades [1,2]. One challenge in PDT is obtaining the third generation photosensitizers (TGPS) [3–6]. In addition to its therapeutic applications, TGPS must meet additional requirements [7–10], including simultaneous and real-time diagnostics,

fluorescence imaging [11], vascular targeting [9], neutron capture therapy etc. [8]. The implementation of these new features of PDT requires the chemical conjugation of a photosensitizer (PS) molecule with another functional sub-unit [7–10,12–19].

For example, peptide–phthalocyanine conjugates are receptor-targeting bifunctional agents for both imaging and PDT [10]. Phthalocyanine-loaded dendrimer is a multifunctional theranostic platform for both image-guided drug delivery and photodynamic therapy [7]. Chalcone–phthalocyanine conjugates can perform the dual activity of both antivasular and PDT [9]. Phthalocyanine containing o-carborane units could do a combined boron neutron capture therapy of cancer (BNCT) and PDT [8]. In these applications and related reports, phthalocyanines have been shown to be a promising TGPS due to their desirable properties, such as strong absorption in the red visible region that allows deeper light penetration, high efficiency in singlet oxygen generation [20–26].

Other reports by other researchers and us showed that the functionalization of PSs can improve the PDT effect. Mono-PEGylated zinc(II) phthalocyanines could enhance in vitro photocytotoxicity [27]. Quinoline substituted phthalocyanines enhances cellular uptake [17]. Indole and other N containing heterocyclic substituted phthalocyanines improved the singlet oxygen formation efficiency [21,22], while the interaction of phthalocyanine with other molecules deeply affects its photosensitizing properties [28–30].

Imidazole is a highly polar compound and highly soluble in water. Imidazole ring system is present in histidine, and the related hormone histamine, as well as many other important biological building-blocks. Many drugs also contain an imidazole ring, such as antifungal drugs, nitroimidazole, and the sedative midazolam. Based on these facts, imidazole and methyl imidazole were linked to different metal phthalocyanines (Scheme 1) in this study to examine their effects on photosensitizing properties.

Experimental

Reagents and apparatus

All reagents for the synthesis were analytical grade and used as received. Dimethylformide (DMF) was dried and redistilled before use. 4-(4-Methyl-1H-imidazol-1-yl) phthalonitrile and tetra[β -4-methyl-1H-imidazol-1-yl] MgPc, MgPc(β -MeIm)₄ have been reported previously [21]. ¹H NMR spectra were recorded at room temperature on a Bruker dmx 300 MHz NMR spectrometer. MS spectra were recorded either on a Bruker APEX II or Autoflex III Mald-TOF spectrometer. IR spectra were recorded at room temperature on a Shimadzu FTIR-8900 spectrometer. UV–vis spectra

were recorded on a Shimadzu 4500 spectrophotometer using 1 cm matched quartz cuvettes.

Synthesis

The two-step procedure for the synthesis of imidazole–Pc conjugates is shown in Scheme 2, which is modified from our previous synthesis of indole substituted phthalocyanines [22].

Synthesis of 3-(4-methyl-1H-imidazol-1-yl) phthalonitrile (1)

This compound was prepared following the previous procedure [22]. White needles were obtained after recrystallization with absolute ethanol. Yield: 20%. m.p. 176–177 °C. IR(KBr), ν (cm⁻¹): 3116, 3005, 1583, 1540, 1450 (Ar–H), 2235 (C≡N), 1296 (Ar–N). ¹H NMR (CDCl₃, ppm): δ 7.97 (d, 1H), 7.93 (m, 1H), 7.83 (d, 1H), 7.73 (s, 1H), 7.08 (s, 1H), 2.31 (s, 3H). MS, m/z : 208.2 [M – 1]⁻.

Synthesis of 4-(1H-imidazol-1-yl) phthalonitrile (2)

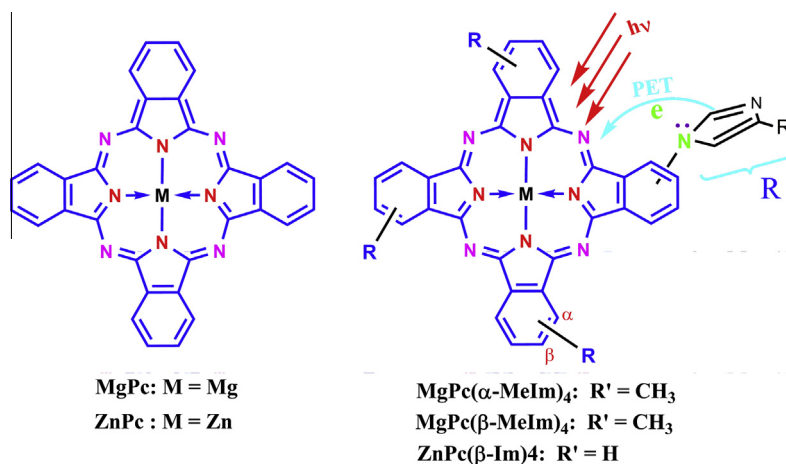
The same procedure for **1** was applied to the synthesis of **2**. After recrystallization with absolute ethanol white needles were obtained. Yield: 63%. m.p. 186–188 °C. IR(KBr), ν (cm⁻¹): 3113, 3006, 1601 1512, 1481 (Ar–H), 2233 (C≡N), 1296 (Ar–N). ¹H NMR (CDCl₃, ppm): δ 7.94 (d, 1H), 7.91 (s, 1H), 7.80 (d, 1H), 7.73 (d, 1H), 7.13(d, 1H), 7.09(s, 1H). MS, m/z : 194.1 [M – 1]⁻.

Synthesis of tetra[α -4-methyl-1H-imidazol-1-yl] MgPc (3)

Magnesium acetate (0.030 g, 0.135 mmol), 3-(4-methyl-1H-imidazol-1-yl)phthalonitrile (0.10 g, 0.467 mmol), and 7 mL dried *n*-pentanol were mixed and stirred at 135 °C for 4 h under argon atmosphere in the presence of four drops of DBU as catalyst. After cooling down, *n*-hexane was added, the green precipitate was collected by filtration and washed with *n*-pentanol and *n*-hexane. The dried crude product was dissolved in THF and purified by column chromatography (silica gel) using THF as the mobile phase. Yield: 29%. UV–vis (DMF): λ_{\max} nm 359, 687. IR [(KBr) ν_{\max} /cm⁻¹]: 3053 (Ar–H), 1608, 1519 (Ar C=C), 1490, 1332 (CH₃), 1137, 1049, 895 (N–Mg). ¹H NMR (DMSO): δ , ppm 8.50–9.13 (4H, s, broad), 8.49 (4H, s), 7.99–8.33 (4H, s, broad), 7.99 (4H, s), 7.81–7.97(4H, s, broad), 2.35 (12H, s). Anal. (C₄₈H₃₂N₁₆Mg): C, 67.26 H, 3.76 N, 26.14; found: C, 66.89 H, 4.13 N, 25.86. MALDI-TOF-MS m/z : Calculated 856.3; found 857.9 [M + 1]⁺.

Synthesis of tetra[β -1H-imidazol-1-yl] ZnPc (4)

The same procedure for **3** was applied to the synthesis of **4**. Yield: 29%. UV–vis (DMF): λ_{\max} nm 358, 678. IR [(KBr) ν_{\max} /cm⁻¹]: 3050 (Ar–H), 16,018, 1493 (Ar C=C), 1133, 1051, 893 (N–Mg). ¹H NMR



Scheme 1. Chemical structures of imidazole substituted phthalocyanines.

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