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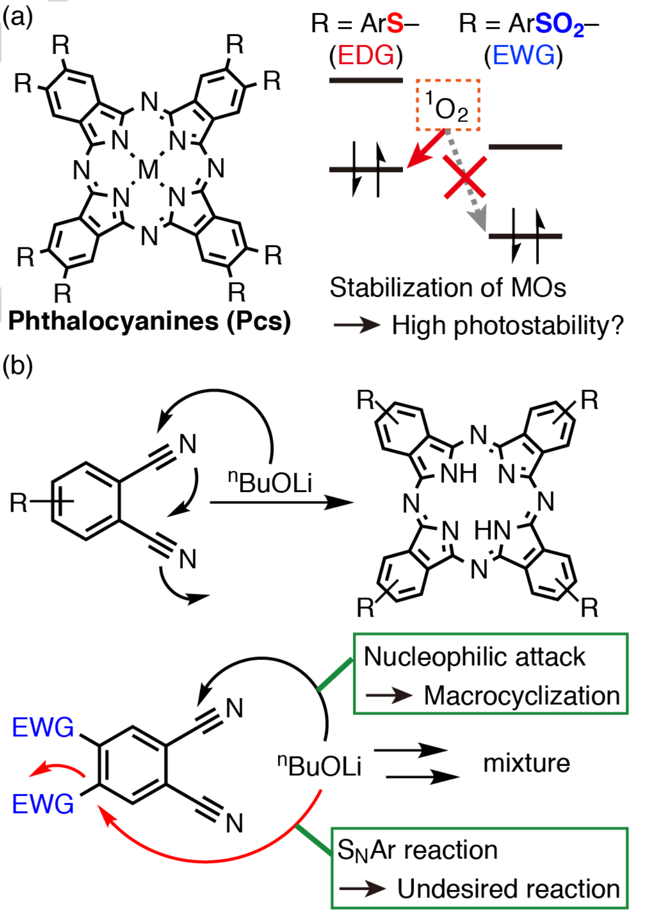
Extremely Photostable Electron-Deficient Phthalocyanines That Generate High Levels of Singlet Oxygen

Taniyuki Furuyama,* Yusuke Miyaji, Kazuya Maeda, Hajime Maeda, and Masahito Segi

Abstract: A robust lead-mediated synthetic procedure for the generation of phthalocyanines substituted with electron-withdrawing groups has been developed. The free-base phthalocyanine and various metal complexes were prepared without discernible degradation of the peripheral electron-withdrawing substituents. Upon irradiation with red light, some of the thus obtained metal complexes generated high levels of singlet oxygen. Especially a palladium complex exhibited attractive photostability upon exposure to singlet oxygen as a bleaching agent. The photostability of such complexes that may manifest concomitantly to the generation of high levels of singlet oxygen was attributed to the presence of the electron-withdrawing groups, which results in energetically low-lying highest occupied molecular orbitals.

Since the first accidental synthesis of phthalocyanines (Pcs) by Braun and Tcherniac,[1] Pcs have been used as powerful artificial dyes and pigments. Conventional Pcs exhibit an intense absorption band in the red to near-IR (650–700 nm) region, the so-called Q band. On account of their unique optical properties, Pcs have found various applications in the field of biological chemistry and materials science, such as organic photovoltaics (OPV), photosynthesis, optical imaging, and photodynamic therapy (PDT).[2] PDT, for example, involves the administration of a tumor-localizing photosensitizing agent, followed by activation using light of a specific wavelength.[3] Photosensitizing agents can generate singlet oxygen ($O_2(^1\Delta_g)$), which leads to cell death upon excitation, and the wavelength of irradiation is crucial for any application. For instance, conventional photosensitizers generally absorb light in the visible region, which limits tissue penetration. On the other hand, specific red to near-IR light (650-900 nm; the so-called near-IR window) exhibits relatively low toxicity toward human tissue and offers high levels of penetration, i.e., Pcs absorbing red to near-IR light are promising prospectives for PDT photosensitizers.[4] However, Pcs can also react with singlet oxygen. For example, the [4+2]-cycloaddition between the pyrrole moiety in the Pc macrocycle and singlet oxygen upon exposure to irradiation has been reported.[5] Hence, Pcs with the ability to generate high levels of singlet oxygen usually exhibit a concomitantly low photostability. This behavior should most likely be rationalized in terms of an interaction between the HOMO of the Pc and the LUMO of singlet oxygen, which means that Pc derivatives with low-lying HOMOs may exhibit increased photostability.

In the present study, we designed Pcs substituted with electron-withdrawing groups (EWGs), which generate high levels of singlet oxygen and exhibit high photostability. The combination of peripheral substituents and central element of the Pc can lead to a broad variety of functions. Recently, we have described main-group-element-substituted/mediated phthalocyanines, which show unique optical/electrochemical/aromatic properties.[6] Moreover, EWG-substituted Pcs are expected to exhibit stabilized HOMOs, which could decrease the orbital interaction with singlet oxygen (Scheme 1a). Heavy metals can enhance the efficiency of the generation of singlet oxygen via a spin-orbit coupling mechanism, and various metals can be introduced into the central core of free-base (metal-free) Pcs.[2a] Therefore, EWG-substituted free-base Pcs and their metal complexes may potentially represent a new type of photostable singlet oxygen sensitizers upon exposure to red to near-IR light. The so-called lithium method, which uses nucleophilic lithium alkoxides, is a representative procedure to synthesize free-base Pcs.[2] However, in EWG-substituted phthalonitriles, EWGs at the *ipso*-position react with the nucleophiles (S_NAr reaction),[7] which results in the formation of a mixture of free-base Pcs with various peripheral substituents (Scheme 1b).



Scheme 1. (a) The effects of the introduction of peripheral electron-withdrawing groups into phthalocyanines (Pcs) on the energy level of their MOs. (b) Reaction mechanism for the lithium method.

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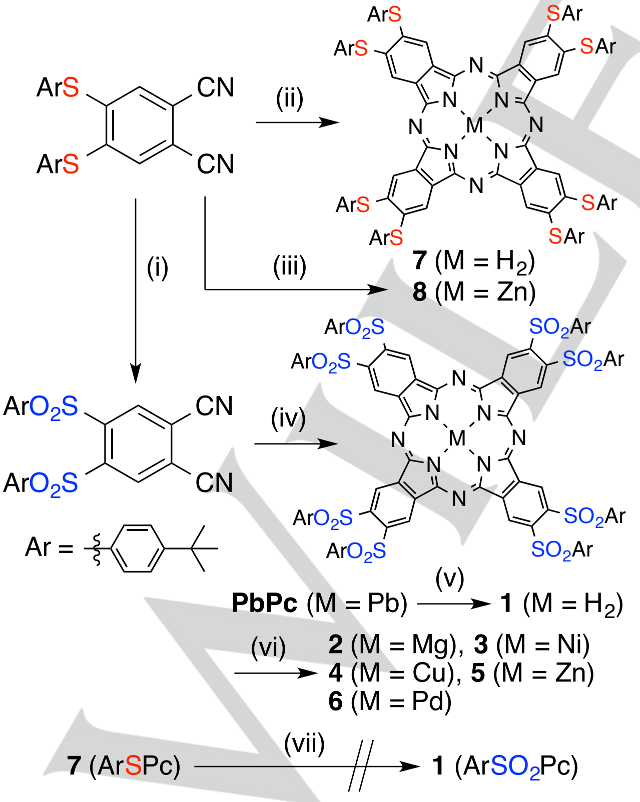
To overcome this problem, we have used lead ions as a template for the Pc synthesis. The template synthesis of Pc lead complexes proceeds in the absence of any nucleophiles.[8] As the lead ions are relatively large their position deviates from the Pc plane in the crystal.[9] The deviation indicates that the lead ion could potentially be removed to deliver the corresponding free-base Pcs.[8,10] We also motivated that some kinds of EWG-substituted Pc metal complexes have been synthesized by template method.[11] Based on this concept, the aryl sulfone ($ArSO_2$) group was chosen as a model EWG (Scheme 1a and Scheme 2). The thioaryl (ArS) group is, in contrast, a representative electron-donating group (EDG). As described above (Scheme 1b), the conventional lithium method is not able to generate EWG-substituted Pcs, and merely complex mixtures containing various alkoxy-substituted Pcs were obtained after the phthalonitrile was treated with lithium alkoxide. Although the Q band appeared clearly in the absorption spectrum of the thus obtained Pc (**1 (Li)**) (Figure S2), the mass spectrum indicates that **1 (Li)** contains a mixture of randomly substituted butoxy-substituted Pcs (Figure S3). Previously, $ArSO_2$-substituted Pcs have been generated by oxidation of ArS-substituted Pcs.[12] However, this synthetic route suffers from low reproducibility, given that the Pc macrocycle usually decomposes under typical oxidation conditions. This is also reflected in the position of the Q band, which shifts after a short (5 min) treatment of **7** with *m*CPBA (Figure S4). However, the ESI-MS spectrum of the reaction mixture indicated that the reaction was not completed (Figure S5). When the reaction was continued, the Pc macrocycle decomposed, and the targeted **1** was not obtained.



Scheme 2. Synthesis of EWG-substituted phthalocyanines. Reaction conditions: (i) *m*CPBA (10 eq), CH_2Cl_2, rt, 2 days, 92%; (ii) ^{n}BuOLi, ^{n}BuOH, reflux, 2 h, 26%; (iii) $Zn(OAc)_2{\cdot}2\ H_2O$ (0.45 eq), DBU, pentanol, reflux, 6 h, 27%; (iv) PbO (0.9 eq), 270 °C, 2 h, 46%; (v) CF_3COOH, CH_2Cl_2, rt, 15 min, 80%; (vi) metal salt (5 eq), DMSO, rt to 160 °C, 3–6.5 h, up to 68%; (vii) *m*CPBA (35 eq), CH_2Cl_2, rt, 5 min, complex mixture was obtained (*cf.* Supporting Information).

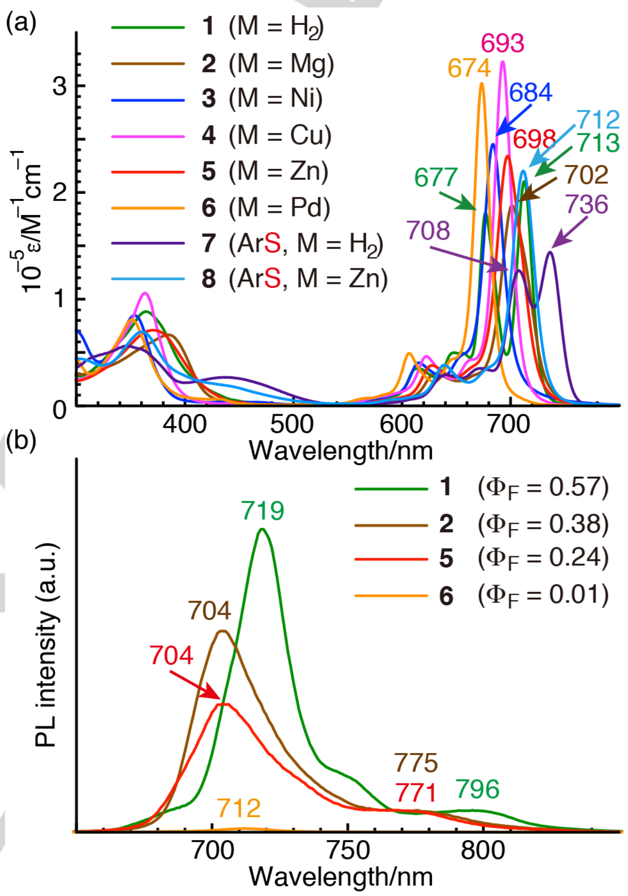


Figure 1. (a) UV-vis-NIR absorption (**1–8**) and (b) emission spectra (**1–6**, λ_{ex} = 620 nm) of in CH_2Cl_2. Under these conditions, emission peaks for **3** and **4** were not observed.

Heating sulfone-substituted phthalonitrile and lead(II) oxide in the solid state afforded the Pb complex **PbPc**, which decomposed gradually into free-base complex **1** upon treatment with trifluoroacetic acid, whereby a purification of **PbPc** was not required. ^1H NMR and HR-MALDI-FT-ICR-MS spectra confirmed that all peripheral substituents of **1** remained intact under these conditions (Figure S6). The solid-state condition is required to obtain **PbPc**, and the conditions in high-boiling solvents, such as quinoline and 1-chloronaphthalene were failed. The sharp peaks in the ^1H NMR spectra indicated that the Pcs in this study did not aggregated even in the NMR concentration (~1 mM in $CDCl_3$). With this EWG-substituted free-base Pc in hand, we examined metalation reactions. The synthesis of Pc magnesium complexes typically requires either free-base Pc[13] or nucleophilic magnesium alkoxides as a template,[14] while magnesium complex **2** was obtained from the metalation of **1** without any nucleophiles. Nickel, copper, zinc, and palladium complexes (**3-6**) were also obtained from free-base **1** with high chemoselectivity for the metallation. **1–6** showed good solubility in common organic solvents. The solid-state structure of an eightfold EWG-substituted Pc macrocycle was unambiguously determined by X-ray diffraction analysis of single crystals obtained from the diffusion of cyclohexane into a pyridine solution of **5** (Figure S7). The structure of the core macrocycle of **5** exhibits typical Pc features.[15]

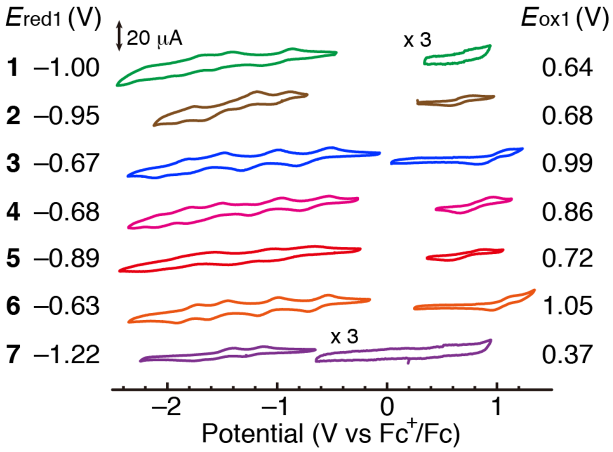


Figure 2. Cyclic voltammograms for **1–7**; [analyte] = 0.5 mM; solvent: *o*-DCB; supporting electrolyte: 0.1 M [^{n}Bu$_4$N][ClO$_4$]. All potentials referenced to the ferrocene/ferrocenium couple.

The absorption and fluorescence spectra of **1–8** are shown in Figure 1. The absorption spectra in dichloromethane are typical of nonaggregated Pcs, which strictly follow the Beer-Lambert law (Figure S8). All EWG-substituted Pcs show intense absorption bands (Q bands) in the far-red to near-IR region, and the results of magnetic circular dichroism (MCD) spectra support the presence of symmetrical chromophores (Figure S9). As the substituent effect at the β position is lower than that at the α position, similar Q band positions were obtained for **1** ($ArSO_2$; EWG) and **7** (ArS; EDG). Remarkably, free-base **1** as well as the metal complexes **2** and **5** show intense emission in the near-IR region with high fluorescence quantum yields (Φ_F). Typical Pc zinc complexes have low Φ_Fs values.[16] On the other hand, Electron-deficient pyrazinoporphyrazines also show high Φ_Fs values,[17] which could mean that EWGs may potentially enhance the fluorescence process and thus render these dyes potential near-IR fluorescence probes.

Figure 2 displays the cyclic voltammograms of **1–7** in *o*-dichlorobenzene (DCB) and contains a summary of the first redox potentials (E_{ox1} and E_{red1}). It is well established that the position of the Q band correlates well with the gap between the first redox potentials ($E_{ox1} - E_{red1}$). The similar gaps (1.54~1.68 V) of **1–7** support similar positions of their Q bands. The observed values were also comparable to previously reported voltammograms of other Pcs.[15] On the other hand, the redox potentials of EWG-substituted **1–6** shifted anodically, and multiple reduction waves were observed. The high E_{red1} values are comparable with those of fullerene derivatives such as PCBM (E_{red1} = ca. −1.0 V vs Fc$^+$/Fc),[18] indicating that EWG-substituted Pcs may potentially be applicable to soluble Pc-based non-fullerene n-type semiconductors. In order to better understand the electronic structures, MO calculations of models Pcs **1'** ($ArSO_2$) and **7'** (ArS) were carried out, where the substituents at the sulfur atoms were replaced with methyl groups for simplicity. Partial MO diagrams, theoretical calculation spectra, and components of the transition energies are summarized in Figure S10 and Table S3. The HOMO, LUMO, and LUMO+1 are derived from the typical MOs of Pcs with 18π-electron aromaticity. The low-lying MOs of **1'** are consistent with the anodic shift of the redox potentials of **1**, and the stabilized HOMO should endow such EWG-substituted Pcs with increased stability toward oxidative reactions.

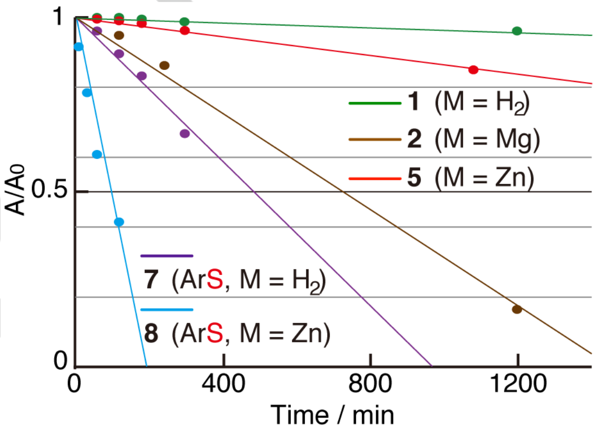


Figure 3. Time-dependent optical density of **1**, **2**, and **5**, **7**, and **8** at the absorption maximum wavelength upon irradiation. The original optical density before irradiation was normalized at the absorption maximum. Solutions of compounds in air-saturated CH_2Cl_2 (ca. 5.0 x 10^{-6} M) were irradiated using a halogen lamp (3,000 lx). The absorption intensities of **3**, **4**, and **6** remained unchanged after irradiation for 1,200 min.

To gauge the photostability of the Pcs, changes in the optical density at the Q band peak were measured under irradiation with light (Figure 3 and Figure S11). Upon the introduction of EWG groups, increased photostability was observed. Pc zinc complexes exhibit low photostability due to the generation of singlet oxygen. The decrease in intensity of **5** was less than that for the thioaryl-substituted free-base Pc **7**. The nickel, copper, and palladium complexes showed no photobleaching after irradiation for 20 hours. The copper complex is a robust organic dye, even though it could not generate singlet oxygen upon irradiation with light. The efficiency to generate singlet oxygen (Φ_Δ) of the EWG-substituted Pcs was quantified by a steady-state method using 1,3-diphenylisobenzofuran (DPBF) as the chemical quencher (Figure 4). Unfortunately, this was not possible for thioaryl-substituted **7** and **8**, as their optical density decreased during the irradiation due to their low photostability (Figure S12). The ability to generate singlet oxygen depends on the central element of the Pc complex. Nickel and copper complexes showed low photosensitization, while the zinc and palladium complexes showed the generation of high levels of singlet oxygen ($\Phi_{\Delta} \approx$ 100%), comparing the reported zinc complex.[4d] The high singlet oxygen generation abilities also supported that such Pcs did not aggregate, since the aggregation reduced the singlet oxygen quantum yield due to enhanced radiationless excited-state dissipation.[19] Especially, palladium complex **6** is extremely photostable, supporting the hypothesis that low-lying HOMOs prevent the reaction with singlet oxygen, which is generated by **6** itself. The high production of singlet oxygen of **6** by irradiation with red light was also demonstrated in a photooxygenation reaction. For that purpose, a mixture of 9,10-diphenylanthracene and **6** was exposed to red light under an atmosphere of O_2, which afforded the corresponding endoperoxide in high yield (*cf.* Supporting Information), indicating that **6** can serve as a red-light-responsive photooxidizing sensitizer.

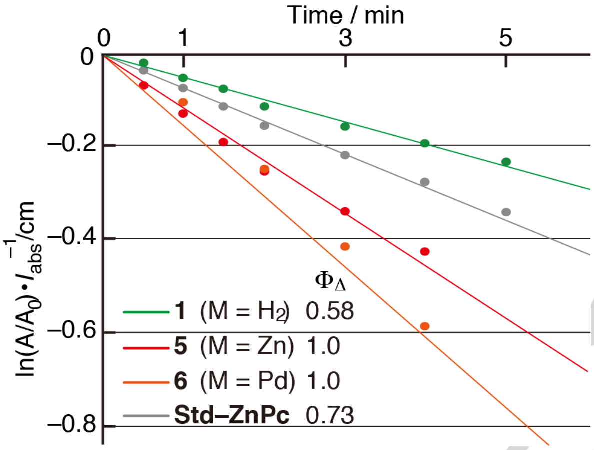


Figure 4. Comparison of the rate of decay of 1,3-diphenylisobenzofuran (DPBF) sensitized by Pcs in $CHCl_3$ (ca. 5.0 x 10^{-6} M) as shown by the decrease in the absorbance at 415 nm. The absorption coefficient was normalized by the rates of the light absorption at 680 nm. **Std–ZnPc** is a ββ-octa-(*p-tert*-butylphenoxy) phthalocyanine zinc complex[4d] (for details, see the Supporting Information).

In summary, we have developed a reliable and robust synthesis of EWG-substituted Pcs using lead ions. Free-base Pcs were obtained with high chemoselectivity, and various metal complexes were prepared subsequently. All Pcs absorb red to near-IR light, i.e., these EWG-substituted Pc macrocycles may serve as a platform for red-to-near-IR materials. These Pcs show various unique physical properties such as intense near-IR fluorescence, high reduction potentials, and the generation of high levels of singlet oxygen upon irradiation with red light. The low-lying MOs prevent the decomposition of these Pcs upon exposure to the singlet oxygen that they generate. Especially palladium complex **6** combines an attractive ability to generate high levels of singlet oxygen with high photostability. The Pcs obtained in this work demonstrate that the designed synthetic method and structure overcome the critical limitation of applications to red-to-near-IR materials.

Acknowledgements

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Keywords: phthalocyanine • electron-withdrawing group • lead • singlet oxygen • photostability

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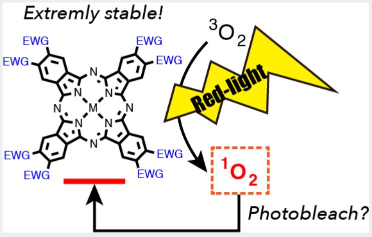

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