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Enhancement of Two-Photon Absorption Cross-Section and Singlet-Oxygen Generation in Porphyrins upon β-Functionalization with Donor–Acceptor Substituents

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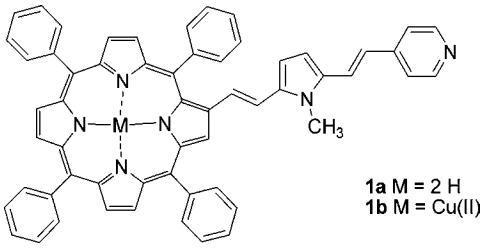
ABSTRACT



The microwave-enhanced synthesis, comparative singlet oxygen sensitization efficiency, and nonlinear optical characterization of a new β-functionalized porphyrin and its copper complex are described. We show that the introduction of a donor–acceptor push–pull conjugated fragment in the β position strongly perturbs the porphyrin electronic structure leading to a remarkable one- and two-photon NIR absorption enhancement.

In the last two decades, porphyrins have gained a considerable interest as high-performing active components in a number of rapidly growing research fields such as electrooptics,[1] photovoltaics,[2] field-effect transistors,[3] two-photon absorption,[4] phosphorescent oxygen sensors,[5] and linear[6] and two-photon absorption (TPA) induced[7] photodynamic therapy (PDT).

PDT is a noninvasive therapeutic technique for the treatment of a number of tumoral afflictions[6] and other benign diseases.[8] The central feature of PDT is the use of a specifically designed drug, the photosensitizer, showing high efficiency in the light-promoted sensitization of singlet oxygen, an extremely reactive species, readily leading to cell death.[9] Among the various classes of proposed PDT drugs,

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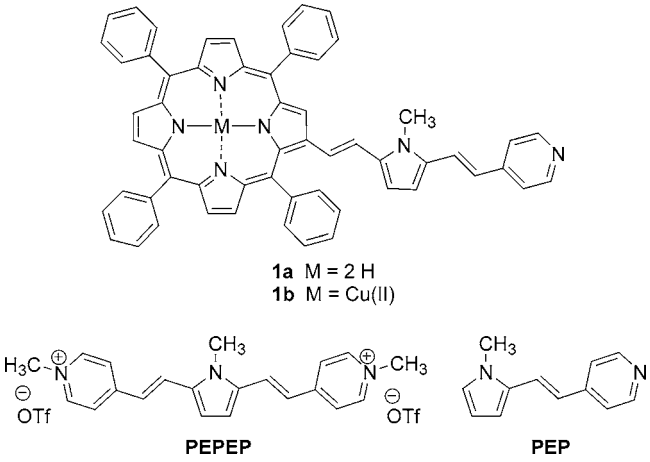
porphyrin derivatives remain so far the only one approved by the FDA for human treatment. Despite their strong ability to sensitize singlet oxygen and their low dark toxicity, porphyrin-based PDT drugs present at least one important drawback. The vast majority of PDT clinical applications require irradiation at wavelengths belonging to the so-called body therapeutic window (650−900 nm), a region where porphyrin extinction coefficient is very low. In addition, their strong absorption at 400−430 nm, combined with a rather slow clearing from the body following the therapeutic treatment, is responsible for a severe patient sensitization to environmental light. The synthesis of new sensitizers with enhanced NIR absorption represents a major task in modern PDT.[10]

Porphyrin's electronic structure can be modulated to various extents through functionalization of the macrocycle peripheral-*meso* or β positions,[11] as well as by variation of the central metal ion. In this work, we followed a β-functionalization protocol, originally proposed by Officer and coworkers[12] and already applied to the synthesis of a number of porphyrin derivatives of increasing complexity.[13] Within this approach it has been shown that the presence of an electron-poor or electron-rich styryl derivative in a number of β-functionalized porphyrins is responsible for only a *modest* perturbation on the linear absorption spectrum and electrochemistry.[13d] It has also been shown that the presence of a strong accepting group perturbs the electronic structures of porphyrin nickel complexes.[14] No information, however, was provided concerning the effect on singlet oxygen sensitization or TPA in metal-free porphyrins.

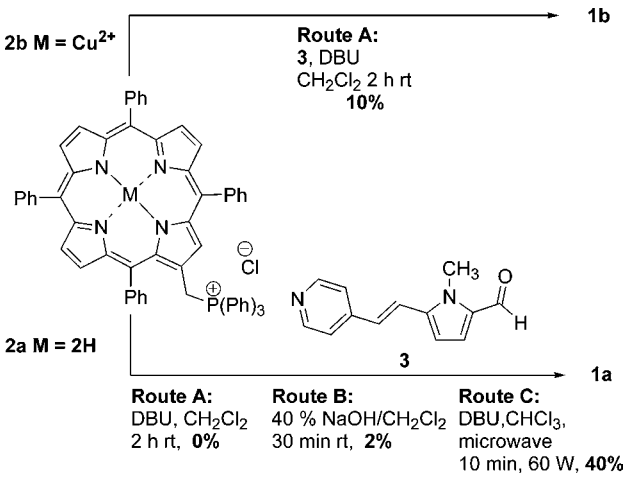
In view of the known favorable TPA performances of highly conjugated structures incorporating donor and acceptor groups,[15] we coupled the **TPP** core with the electron-donating pyrrole and the electron-deficient pyridine aiming also at mimicking the molecular structure of the very efficient and noncytotoxic TPA dye **PEPEP** (Scheme 1).[16]

Scheme 1



The triphenyl[(porphyrin-2-yl)methyl]phosphonium chlorides **2a** and its copper complex **2b** were prepared according to the literature procedure.[12] The Wittig condensation of the metal complex **2b** with the aldehyde **3**[17] under the condition previously reported for the condensation of a number of aromatic aldehydes[12,13c] (Scheme 2, route A) gave the

Scheme 2



expected compound **1b** in good yield. However, the free ligand **2a** did not yield the expected product **1a** but a mixture of the starting materials triphenylphosphinoxide and β-methyl-**TPP**.

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Porphyrin **1a** was first prepared, although in a very modest 2% yield, using a mixture of 40% aqueous sodium hydroxide and dichloromethane under stirring at room temperature (Scheme 2, route B). Recently, microwave-assisted synthesis has been applied successfully in many fields of synthetic organic chemistry.[18] We thus irradiated in a focused microwave oven a chloroform solution of **2a** and **3** in the presence of excess DBU at a constant power of 60 W for 10 min to give the porphyrin **1a** in an impressively enhanced 40% yield (Scheme 2, route C). Even more interestingly, we observed complete *trans* stereoselectivity, an unprecedented result for the DBU promoted condensation of **2a** with aromatic aldehydes.[13]

The first insight into the electronic structures of **1a** and **1b** is given by their UV−vis absorption spectra (Figure 1).

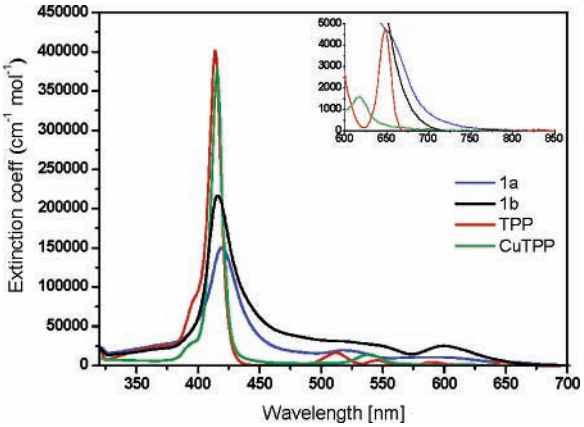

Figure 1. Linear absorption of molecules **1a**,**b**, TPP, and CuTPP in acetone solutions. The inset shows an expansion of the NIR region.

The characteristic spectral features of the porphyrin core are strongly perturbed. The usually sharp and intense B band in fact shows a remarkable broadening that cannot be explained only on the basis of a superimposition with the spectrum of the side fragment **PEP**.[19] The spectrum of **1a** also shows a long absorption tail spreading all over the Q-band region which was observed neither for **TPP** nor for **PEP** by themselves. The same effect is also apparent in the copper complex **1b**. Such a broad low energy absorption band could be a favorable feature for NIR singlet oxygen sensitization and, along with the B band broadening, evidence for the push−pull chromophore/porphyrin electron coupling.

We carried out a qualitative singlet oxygen sensitization enhancement comparative study by monitoring the reaction of 1,3-diphenylisobenzofuran (**DPBF**) with photosensitizer-promoted singlet oxygen.[20] Upon cycloaddition with singlet oxygen, **DPBF** is known to form an intermediate endoperoxide the final product of which no longer absorbs at 415 nm. We thus exposed a solution of **DPBF** (50 μM) and porphyrins (5 μM) in CH_2Cl_2 to a filtered light source of wavelength $\lambda > 550$ nm over a period of 10 min.[21] The use of filtered light enabled us to prevent **DPBF** from self-bleaching and to selectively study only the porphyrin Q-band absorption enhancement effect.

Figure 2 plots the logarithm of the decrease of the **DPBF** absorption at 415 nm as a function of the irradiation time for **1a** and **1b,** compared to that of unsubstituted **TPP**. We also investigated, as a control experiment, the properties of **Cu-TPP**, the singlet oxygen generation quantum yield of which is known to be significantly smaller than that of the free ligand.[22] As a general trend, we correctly observed a significantly faster **DPBF** decomposition for the free ligands **1a** and **TPP**. Compound **1a** is slightly more efficient than **TPP**, meaning that the absorption enhancement in the exposure range is effectively translated into an enhanced singlet oxygen generation. This result is evidence of the delocalized nature of **1a** low energy transitions.

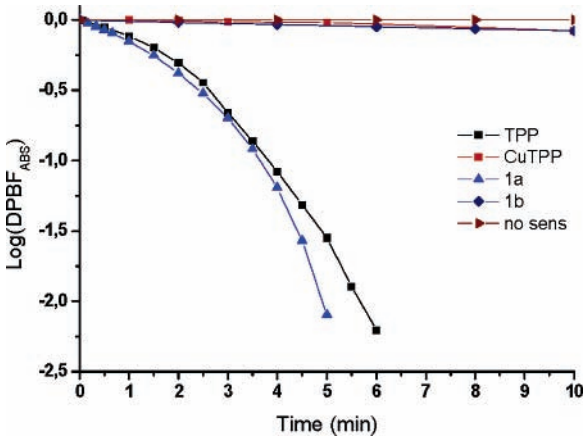

Figure 2. Comparative singlet oxygen generation of **TPP**, **CuTPP**, and new derivatives **1a**,**b**. The DPBF solution was also irradiated in the absence of sensitizers (no sens).

The TPA cross-sections of the new derivatives **1a**,**b** and of **TPP**, **CuTPP**, and **PEP** have been measured by open-aperture Z-scan experiments performed with a femtosecond (fs) laser source (pulse duration 130−150 fs) at 810 nm, where no linear absorption was observed for each compound. The use of ultrashort fs laser pulses ensures that the excited state absorption contributes negligibly to the observed TPA signal.

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Figure 3 shows the Z-scan plots for **1a**, **TPP**, and **PEP** in chloroform solution, recorded under the same experimental conditions. The plot of **1a** and **TPP** shows a well-defined dip typical of nonlinear absorption, whereas that of **PEP** is almost a flat line with a dip barely distinguishable from the noise. Table 1 summarizes the TPA data, in terms of the TPA cross-section σ_{TPA}. The value of **AF-250**,[23] often considered as a benchmark for TPA activity at 800 nm, is included for comparison.

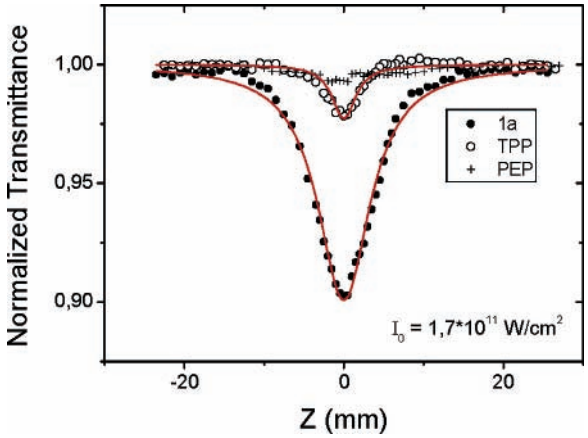

Figure 3. Z-scan plots of **1a** (full circles, 4.1×10^{-3} M), **TPP** (open circles, 1.0×10^{-2} M), and **PEP** (crosses, 9.9×10^{-2} M) in chloroform at 810 nm.

Table 1. σ_{TPA} Values[a] for Compounds **1a**,**b**, **TPP**, **CuTPP**, and **PEP**

compd	σ_{TPA} (GM)
1a	56 ± 8
1b	187 ± 62
TPP	16 ± 4
CuTPP	101 ± 32
PEP	<5
AF-250[23]	30

[a] Measurements were performed in $CHCl_3$ at 810 nm.

Although a single wavelength measurement does not necessarily allow for the formulation of general trends, it is nonetheless evident that the significant TPA enhancement on going from **TPP** to **1a** cannot be simply explained on the basis of a sum of the **TPP** and **PEP** contributions. A preresonant enhancement promoted by the Q-band is also unlikely, since the Q-band spectral position and integrated area are almost identical for **TPP** and **1a** (Figure 1, inset). One must therefore conclude that the presence of the conjugated substituent in the β position effectively leads to an extension and enhancement of the conjugation to the whole molecule.

Finally, it should be noted that the measured σ_{TPA} values of **1a** and its copper complex **1b**, although single wavelength derived, are highly ranked among those ever reported for simple chromophore−porphyrin dyads.[11g]

In conclusion, we have demonstrated that the introduction of a push−pull conjugated fragment in the β position of the **TPP** skeleton leads to an efficient electronic coupling between the two units, as assessed both by UV−vis/NIR absorption and singlet oxygen sensitization. Moreover, the perturbed electronic structure arrangement is responsible for the significant enhancement in TPA performances. The new porphyrin derivatives **1a** and **1b** represent good model compounds for the design of efficient one- and two-photon-promoted sensitizers in PDT.

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Supporting Information Available: Experimental procedures and characterization data for **1a** and **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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