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Resum en la llengua del projecte (màxim 300 paraules)

En el present treball s'investiguen, per primer cop, les propietats de absorció bifotòniques del fotosensibilitzador 2,7,12,17-tetrafenilporficè (TPPo) i del seu complex de pal·ladi (II) (PdTPPo). Ambos compostos han rebut molta atenció com a possibles fotosensibilitzadors per a Teràpia Fotodinàmica (TFD). S'utilitza la detecció de la fosforescència de l'oxigen singlet, centrada a 1270 nm i produïda per l'absorció de dos fotons, per quantificar la magnitud de la secció d'absorció bifotònica, "delta", dels porficèns estudiats. Els experiments se han dut a terme en el marge espectral 750-850 nm i a l'infraroig proper a 1100nm. Aquestes longituds d'ona corresponen a les zones d'absorció bifotònica en les bandes de Soret i Q. Les propietats bifotòniques obtingudes es comparen i contrasten amb les dades conegudes de la tetrafenilporfirina (TPP), isòmer estructural del tetrafenilporficè però amb més gran simetria, i es troba que en la banda de Soret (que coincideix amb la regió de la pell més transparent) els valors de delta per el TPPo i PdTPPo son aproximadament 2000 GM en el màxim, pràcticament cent vegades més grans que per la TPP. A més a més, aquestos valors son dos ordres de magnitud més grans que els obtinguts a l'irradiar a 1100 nm (bandes Q). Aquestes observacions es poden explicar mitjançant la amplificació per ressonància deguda a la presència de transicions monofotòniques ressonants en la regió de les bandes Q. Els elevats valors de "delta" obtinguts per els tetrafenilporficèns estudiats junt a les principals característiques que aquestos presenten (elevat rendiment de formació d'oxigen singlet, estabilitat química i fotoquímica, absència de citotoxicitat,...) qualifiquen al TPPo y PdTPPo com a possibles fotosensibilitzadors per a Teràpia Fotodinàmica Bifotònica.

Resum en anglès(màxim 300 paraules)

In the present work we investigate, for the first time, the two-photon absorption (TPA) properties of the photosensitizer 2,7,12,17-tetraphenylporphycene (TPPo) and its palladium (II) (PdTPPo) complex, which have received much attention as possible photosensitizers for photodynamic therapy (PDT). Detection of phosphorescence from singlet molecular oxygen, 1O_2 , centered at 1270 nm and produced upon non-resonant TPA, is used to quantify the magnitude of the TPA cross section, " δ ", for the studied porphycenes. Experiments were performed in the spectral range 750-850 nm as well as in the near-IR at 1100 nm, corresponding to TPA in the sensitizer Soret and Q region, respectively. Obtained two-photon properties are compared and contrasted with known data from the structural isomer tetraphenylporphyrin (TPP), and in the Soret region it is found that the " δ " values for both TPPo and PdTPPo are around 2000 GM, almost one hundred times higher than those reported for TPP. Also, values in the Soret region, which is also part of the tissue transparency window, are around two orders of magnitude greater than in the Q region. These observations are explained in terms of resonance enhancement due to near-resonant one-photon transitions in the Q region. Together with good singlet oxygen quantum yields, chemical and photochemical stability and low cytotoxicity, the large " δ " values in the tissue transparency window reported herein promote TPPo and PdTPPo as photosensitizers ideally suited for applications in PDT following TPA.

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Index

Introduction.	2
Experimental Section	3
Materials	4
Results and discussion.	5
Two-photon absorption spectra	6
Resonant enhancement in the TPA Soret region	9
Conclusions	11
References	11

Two-Photon Absorption Properties of Tetraphenylporphycenes.

Introduction

Porphycene, a synthetic isomer of porphyrin, was first synthesized by Vogel *et. al.* in 1986.¹ Due to their interesting photophysical properties and biological activity to inactivate tumoral cells, porphycenes have previously been proposed as novel tumor markers and promising photosensitizers for photodynamic therapy (PDT).²⁻⁶ In 1995 Nonell *et. al.* synthesized the first aryl-substituted porphycene, 2,7,12,17-tetraphenylporphycene (TPPo), Chart 1, and several metallic complexes, have since been prepared, including its palladium (II) complex (PdTPPo).^{7,8} Linear photophysical and photosensitizing parameters for TPPo and PdTPPo have been quantified and compared with known values of the structural isomer, tetraphenylporphyrin (TPP).¹² Especially noteworthy is the fact that porphycenes generally generate singlet molecular oxygen, $O_2(a^1\Delta_g)$, in moderate to high yields. This is great importance for application in PDT where $O_2(a^1\Delta_g)$ is known to play an important and active role in cell death.⁹ In fact, studies of cell photoinactivation have demonstrated the usefulness of TPPo and PdTPPo as PDT photosensitizers.^{7,10,11}

Related to their photophysical properties, one-photon absorption in the Q region is significantly enhanced and shifted towards longer wavelengths for porphycenes in comparison with porphyrins (*vide infra*), due to the lower symmetry presented in porphycenes. However, directs one-photon absorption in the tissue transparency window from ~ 700-1100 nm is not feasible. For this reason we opted to study TPPo and PdTPPo, dissolved in toluene, in the spectral region 750-850 nm by detecting $O_2(a^1\Delta_g)$ near-IR phosphorescence, centered at ~ 1270 nm, following non-resonant two-photon absorption (TPA) of the sensitizer. Whereas two-photon processes have been studied extensively, both experimentally and theoretically, for a large number of porphyrins and related derivatives, to our knowledge this is the first time such as study has been conducted for porphycenes. In several reports we have established the viability and advantages offered using $O_2(a^1\Delta_g)$ detection to characterize TPA.¹³⁻¹⁵ Despite most previous work concerning porphyrins has been based on detection excited state fluorescence, efficient $O_2(a^1\Delta_g)$ generation following TPA has been demonstrated for modified porphyrins and linked porphyrin dimers.^{13,16-18} In addition to increased depth-

penetration, TPA has the further advantage of offering superior spatial resolution owing to the inherent non-linear nature. However, most common photosensitizers used in PDT only exhibit low to moderate TPA transition probabilities, *e.g.* $\delta = 7.4$ GM at 850 nm for Photofrin[®],¹⁹ and development of sensitizers with large δ values will allow administration of smaller drug doses and/or less intensity of the irradiation source.

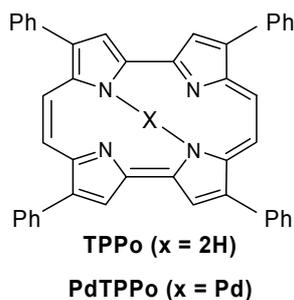


Chart 1 Structure of tetraphenylporphycenes TPPo (M = 2H) and PdTPPo (M = Pd(II)).

Experimental Section

All experiments were performed using a femtosecond (fs) excitation source and optical detection apparatus which has been presented in details elsewhere.¹⁵ Briefly, the output of a Ti:sapphire laser (Spectra Physics, Tsunami 3941) is regeneratively amplified (Spectra Physics, Spitfire), resulting in tunable fs pulses from ~ 765 -850 nm. In addition, an optical parametric amplifier (Spectra Physics, OPA-800CF) can, when pumped by the output of the Spitfire, deliver tunable fs pulses from 300-3000 nm. The spectral output characteristics were measured using a fiberoptic spectrometer (Avantes). The laser power was controlled by adjusting a Glan-Taylor polarizer, and for experiments performed at 1100 nm a long-pass filter (Schott, 830 nm) was inserted to eliminate higher harmonics from the OPA and residuals from the Spitfire pump beam. For all experiments the pulse repetition rate was 1 kHz. The sample was contained in a 1 cm path length quartz cuvette mounted in a light-tight housing with a small entrance hole for the laser beam. $O_2(a^1\Delta_g)$ phosphorescence from the sample was collected and focused onto the active area of a photomultiplier tube, PMT (Hamamatsu model R5509-42). Because the spectral response of the PMT covers the range $\sim 400 - 1500$ nm, $O_2(a^1\Delta_g)$ phosphorescence could be readily monitored using an interference filter centered at 1270 nm (Barr Associates, 50 nm fwhm). The output of the PMT was

amplified (Stanford Research Systems model 445 preamplifier) and sent to a photon counter (Stanford Research Systems model 400), operated using a program written in LabView (National Instruments, Inc.).

To obtain TPA spectra of the sensitizers studied, $O_2(a^1\Delta_g)$ phosphorescence was detected in experiments performed relative to a standard, 2,5-dicyano-1,4-bis(2-(4-diphenyl-aminophenyl)-vinyl)-benzene, CNPhVB, for which the TPA spectrum and absolute values of δ have previously been determined.¹⁵ This relative procedure eliminates issues related to emission collecting efficiency and the need to characterize the temporal and spatial properties of the laser beam. Data was obtained in steps of 10 nm which is roughly the spectral width of the fs laser pulses, and δ values at a given wavelength, λ , were calculated according to eq. 1. Here the subscript r refers to the reference compound (CNPhVB), with S , P , C and Φ_Δ being the observed two-photon signal, irradiation power at the sample, sensitizer concentration and singlet oxygen quantum yield, respectively.

$$\delta(\lambda) = \frac{S_r P_r^2 \Phi_{\Delta,r}}{S_r C P^2 \Phi_\Delta} \delta_r(\lambda) \quad (1)$$

Typical peak intensities were 1-10 GW/cm² (pulse duration ~ 120 fs and laser beam waist ~ 500 μ m). One-photon absorption spectra in the UV-VIS region were recorded using a Hewlett-Packard model 8453 diode array spectrometer, while the near-IR spectrum of toluene was recorded on a Shimadzu UV-3600 spectrophotometer. Concentrations used in two-photon experiments (~ 2x10⁻⁴ M) were calculated from known extinction coefficients (Table 1). It was confirmed that laser irradiation caused no photodegradation of the sensitizers.

Materials

TPPo and PdTPPo were synthesized and purified as described previously,^{7,20} while TPP was purchased from Porphyrin Systems. Spectroscopic grade toluene was purchased from Aldrich and used as received. Experiments performed the absence of oxygen were prepared by gently bubbling the solution in a quartz cuvette with dry nitrogen for approximately 15 minutes.

Results and Discussion

TPPo, PdTPPo and TPP share several basic electronic structure properties as they all are tetrapyrrolic molecules, and much of the two-photon behavior can be qualitatively understood from the one-photon absorption spectra, Figure 1, and selected photophysical parameters presented in Table 1. Briefly, all sensitizers show strong absorption in what we will refer to as the Soret region from ~ 350 - 430 nm. For the porphycenes, however, this band is less intense, broadened and blue-shifted in comparison with TPP. Also, for both porphycenes, transitions in the Q region between ~ 500 - 700 nm are significantly enhanced.

Table 1. Selected photophysical parameters for TPPo, PdTPPo and TPP in toluene.^a

	$\log \epsilon_{\text{Soret}}^b$ (λ_{max})	$\log \epsilon_Q^b$ ($\lambda_{\text{max}, 0-0}$)	Φ_{ic}	Φ_{r}	Φ_{Δ}	δ / GM^c	(λ)
TPPo	5.05 (378 nm)	4.70 (659 nm)	0.52 ± 0.07	0.33 ± 0.04	0.23 ± 0.02	2280 ± 350 17 ± 3^d	(770 nm) (1100 nm)
PdTPPo	4.92 (395 nm)	4.92 (632 nm)	0.22 ± 0.06	0.78 ± 0.06	0.78 ± 0.04	1750 ± 265 22 ± 3^d	(770 nm) (1100 nm)
TPP	5.62 (419 nm)	3.60 (648 nm)	0.05 ± 0.10	0.82 ± 0.10	0.66 ± 0.08^e	24^f 7^g	(760 nm) (1100 nm)

a) One-photon parameters for TPPo and PdTPPo taken from Rubio et al.⁹ Singlet oxygen quantum yields, Φ_{Δ} , were independently verified in the present study. b) ϵ values in $\text{M}^{-1} \text{cm}^{-1}$. c) $1 \text{ GM} = 10^{-50} \text{ cm}^4 \text{ s photon}^{-1} \text{ molecule}^{-1}$. d) These numbers are based on a standard value of 7 GM for TPP at 1100 nm reported by Kruk et al.. e) From Wilkinson et al.²² f) Value published by Kruk et al.²¹ Error limits for their number were not reported. g) Value reported by Kruk et al.,²¹ and used as a standard for the TPPo and PdTPPo experiments at 1100 nm.

These observations have been explained in terms of less symmetry exhibited in the porphycene macrocycle due to significant vibronic coupling.¹² This is supported by measured quantum yields of internal conversion, Φ_{ic} , which are far greater for TPPo and PdTPPo than for TPP ($\Phi_{\text{ic}} = 0.52$, 0.22 and 0.05 respectively) and is a general sign of non-rigid molecular geometry.¹² As seen by the relative magnitude of the Φ_{ic} values, this effect is most pronounced for TPPo due to the binding of the central metal in the Pd complex. The large singlet oxygen quantum yield for the latter is attributed to

enhancement of the intersystem crossing yield to the sensitizer triplet state through the heavy-atom effect introduced with Pd(II).

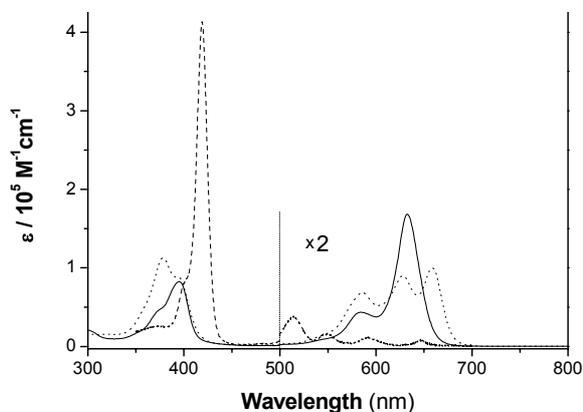


Figure 1 Absorption spectra of TPPo (···), PdTPPo (—) and TPP (---) in toluene. All compounds exhibit a Soret region around 350-430 nm and a Q region from 500-700 nm. Note the factor of 2 in the Q region.

A. Two-photon absorption spectra. For all wavelengths studied, it was ensured that the observed signal scaled quadratically with the incident laser intensity, as required for a two-photon process. This was evidenced by double logarithmic plots of the observed $O_2(a^1\Delta_g)$ emission intensity as a function of incident laser power, Figure 2. When using irradiation wavelengths ≤ 740 nm, however, the observed signal deviated from this quadratic intensity dependence, and approached linear dependence instead. This

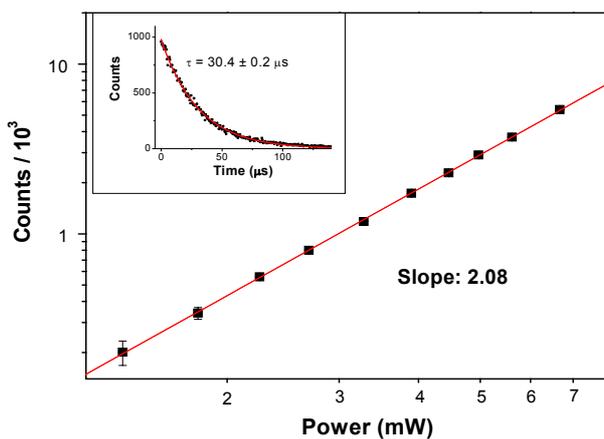


Figure 2 Double logarithmic plot of observed photon counts as a function of incident laser power. A linear fit yielded a slope of 2 as expected for TPA. Inset: time-resolved decay of the observed signal. A single exponential decay was fitted to the data, resulting in a lifetime of $\tau = 30.4 \pm 0.2 \mu\text{s}$.

indicates that for these wavelengths (keeping in mind we are using a spectrally broad fs laser pulse) one-photon absorption from the sensitizer Q region starts to dominate. This

was conformed by further analysis of Figure 1, where the absorption for TPPo and PdTPPo only vanishes completely at ~ 740 nm. This phenomenon of one-photon absorption masking the TPA signal also know to occur for a number of porphyrins, including TPP when exciting below 760 nm.^{17,18} It was ascertained that the time-resolved single exponential decay of the signal yielded a lifetime of $\tau \approx 30$ μ s (inset of Figure 2), which is in perfect agreement with the established lifetime for singlet oxygen in toluene.²² Moreover, purging the samples with dry nitrogen caused the signal to disappear, whereas the signal was re-gained subsequent to re-equilibration with air. These factors unequivocally prove that the observed signal does indeed derive from $O_2(a^1\Delta_g)$ phosphorescence produced upon TPA of the sensitizer. Finally, it was verified that neat toluene did not give a contributing signal.

The recorded TPA spectra, as calculated using eq. 1, for TPPo and PdTPPo in the Soret region between 750-850 nm are shown in Figure 3, together with the corresponding one-photon spectra. The peak values of δ are summarized in Table 1. Both sensitizers show similar overall TPA behavior, with a distinguished peak at 770 nm, but with somewhat higher values for TPPo than for PdTPPo; $\delta(770\text{nm}) = 2280$ and 1750 GM, respectively. These values are almost two orders of magnitude larger than those reported for TPP in the same spectral region, Figure 4, for which the maximum δ value is ~ 60 GM at 760 nm.²¹ Note, however, that the spectral region investigated for TPP shows no TPA peak and that the reported experiment relied on sensitizer fluorescence rather than singlet oxygen emission. Focusing first on data for TPPo it is clear from Figure 3, that the TPA spectral profile matches the corresponding one-photon absorption profile, with the TPA spectrum peaking at twice the wavelength for maximum one-photon absorption in the Soret region. This is in stark contrast to the isomer TPP, where a clear blue-shift is observed in the TPA spectrum, Figure 4.

In the latter case this shift is explained in terms of parity selection rules applied to a centrosymmetric molecular geometry; Soret and Q transitions allowed as one-photon electric dipole processes (both states being of u parity while the ground state is of g parity) are formally forbidden as two-photon processes.²¹ For TPPo, the similarity between one- and two-photon spectra shown in Figure 3, indicates that this argumentation cannot be applied to this sensitizer. The very absence of a significant spectral shift in the TPA spectrum is strong evidence that the actual geometry does not

strictly include a center of inversion. Also, for TPP and its metalloderivatives, it is established that the phenyl groups are non-coplanar with the main porphyrin macrocycle through a dihedral angle of about 60° , and that this will lead to minimum energy

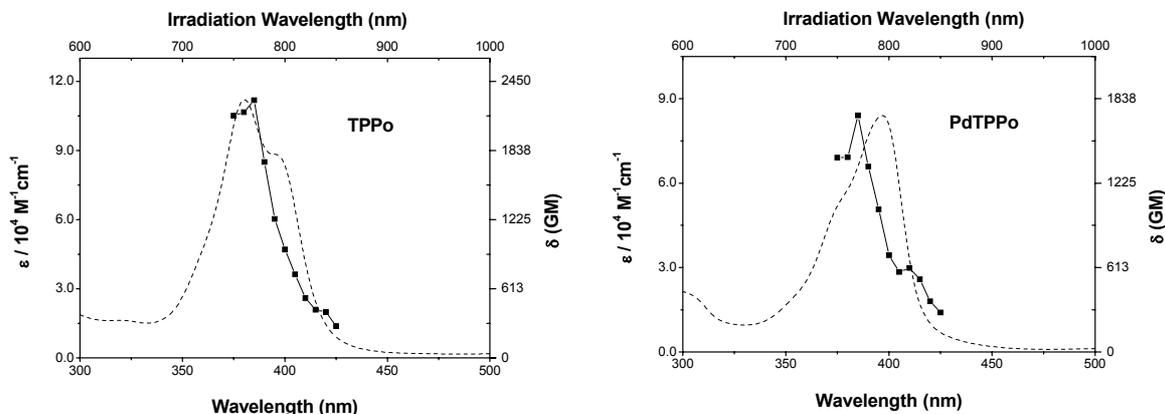


Figure 3 Recorded TPA spectrum (■, top and right axes) and one-photon spectrum (---, bottom and left axes) of TPPo and PdTPPo. The scale for the δ values was established using known values for the reference compound CNPhVB in toluene. The error on each data point (not shown for clarity) is estimated to be 10 %.

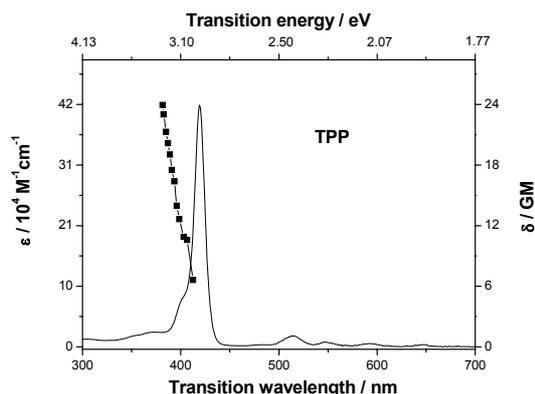


Figure 4 Recorded absolute TPA spectrum (■, top and right axes) and one-photon spectrum (—, bottom and left axes) of TPP.²¹

conformers both with and without a center of inversion.²¹ Turning our attention to the data for PdTPPo, there appear to be only a very slight blue-shift in the TPA spectrum, and that this shift is much less pronounced than for TPP. Again we assign this to reduction of the overall electronic symmetry, while noting the reduction for PdTPPo appears to have fewer ramifications than for TPPo, where no spectral shift was observed in the TPA spectrum. These observations are in line with the information gained from one-photon studies (*vide supra*), where reduction of symmetry was inferred from efficient internal conversion and vibronic coupling and was most pronounced in TPPo.¹²

To further study TPPo and PdTPPo as two-photon $O_2(a^1\Delta_g)$ sensitizers, TPA into the Q region was performed by tuning the excitation wavelength to 1100 nm. Although the

one-photon spectra indicate that excitation at 1100 nm is not expected to yield maximum δ values in the Q region, exciting at longer wavelengths was not practical, as a recorded near-IR spectrum of neat toluene revealed a strong absorption above 1120 nm, which we assign to the 2nd vibrational overtone.²³ To determine δ values for the porphycenes experiments were performed relative to TPP, for which the TPA spectrum in the Q region 1100-1400 nm has been determined by Kruk *et.al.* Using sensitizer fluorescence these authors found maximum δ values of 7 GM in this range.²¹ Obtained values for TPPo and PdTPPo were 17 and 22 GM, respectively. Again it should be emphasized that these values are not expected maximum values for TPA in the Q region, but nonetheless we get a clear indication that the values in the Soret region are greater than those in the Q region. This is also established for TPP, where the maximum δ value in Soret region is approximately 4 times larger than the maximum value in the Q region, and can be qualitatively explained through resonance enhancement effects (*vide infra*).

B. Resonance enhancement in the TPA Soret region. In describing the qualitative features of the observed TPA spectra, we will in the following refer to Figure 5 as a condensed three-level scheme including the pertinent electronic eigenstates and transition frequencies (with no reference to formal state parity). Here 0, S and Q represent the ground state, Soret and Q region, respectively. This quantum mechanical model is derived from second order time-dependent perturbation theory, and has previously been successfully applied to describe both porphyrin monomers and dimers.^{16,18}

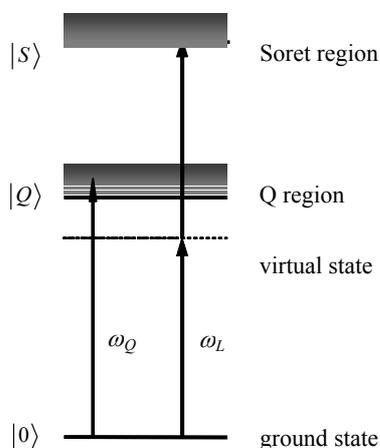


Figure 5 Generalized three-level energy diagram describing resonance enhanced two-photon excitation in porphyrins and porphycenes.

Simultaneous absorption of two photons occurs via absorption into a virtual state (dotted line in Figure 5) which is completely specified as a linear combination of all real eigenstates. The high δ values for TPPo and PdTPPo in the Soret region relative to that obtained in the Q region, is similar to observations made from TPP and other tetrapyrrolic compounds, where this phenomenon has for been explained in terms of resonance enhancement.¹⁸ This approach can equally be adopted for the porphycenes which exhibit the same basic electronic structure (*vide supra*).

In the present case, both photons used in the TPA process are derived from the same linearly polarized laser beam, and the TPA cross section upon ground state excitation into a final state n , $\delta_{n\leftarrow 0}$, can be expressed as eq. 2.^{24,25} Here μ_{ab} is the transition dipole moment between states a and b , ω_L is the laser frequency, $g_n(2\omega_L)$ is the lineshape function associated with the final state and Γ_{0i} is the homogeneous linewidth of the i th state. Note that the summation runs over all real states of the molecule.

$$\delta_{n\leftarrow 0} \propto \sum_i \frac{|\mu_{0i}|^2 |\mu_{in}|^2}{(\omega_i - \omega_L)^2 + \Gamma_{0i}^2} g_n(2\omega_L) \quad (2)$$

Referring to Figure 5 and eq. 2 it is readily found that the δ value for TPA into the Soret region will be dominated by a term of the form $\mu_{0Q}^2/[(\omega_Q - \omega_L)^2 + \Gamma_{0Q}^2]$. This is a consequence of the detuning $\Delta = \omega_Q - \omega_L$ being small due to the near-resonant one-photon allowed Q transition (although exact resonance is never achieved as $\omega_Q > \omega_L$ is always fulfilled). A similar situation will not arise for TPA into the Q-region since the one-photon allowed Soret transition is far from resonance, *i.e.* $\omega_S \gg \omega_L$. Thus it is expected, for both porphyrins and porphycenes, that the TPA cross sections are greatest in the Soret region, in agreement with the experimental data. Related argumentation can also explain why the cross section values in the Soret region are far greater for the studied porphycenes than for TPP. The red shifted Q-transitions in the porphycenes relative to TPP causes the detuning to be smallest for the porphycenes, and in addition the transition moments for one-photon absorption in the Q-region, expressed as μ_{0Q} , is far greater for the porphycenes than for TPP, as evidenced from the linear absorption spectra (Figure 1). These two effects combined result in δ values in the Soret region that are much larger for TPPo and PdTPPo than for TPP. Again, this prediction is verified

experimentally by an increase of almost two orders of magnitude in the maximum δ value in the Soret region for both studied porphycenes relative to TPP.

Conclusions

In the present study we have shown that $O_2(a^1\Delta_g)$ can be successfully and efficiently generated and detected following TPA for the photosensitizers TPPo and PdTPPo. The large δ values, reported here for the first time, combined with good singlet oxygen quantum yields and biological activity, clearly demonstrate that these sensitizers are highly promising as two-photon absorbing PDT agents. Several reports have shown the efficiency of the TPA process in porphyrins can be even further enhanced by substituting electron donating/accepting moieties onto the basic tetrapyrrolic framework, and also by generating fused porphyrin dimers.^{16,18,26} The δ values presented here are for the simplest aryl-porphycenes, and although the values are very encouraging, it seems very likely that still higher values can be obtained by optimizing the overall electronic structural motif. The new synthetic methodology developed for 2,7,12,17-tetraaryl-substituted porphycenes²⁷ opens a general route to appropriately functionalize porphycenes, thus imparting water solubility, which also presents a significant advance in terms of flexibility and application of porphycenes as sensitizers for PDT.

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