Invited feature article

Novel PAMAM dendrimers with porphyrin core as potential photosensitizers for PDT applications

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A B S T R A C T

The photophysical properties of meso-substituted tetraphenyl porphyrins with PAMAM branches, and one peripherally-modified derivative with thiazole groups were studied in DMF solution. The singlet states of the compounds were characterized by means of absorption and fluorescence spectroscopies. The triplet state decay kinetics and the triplet–triplet absorption spectra were determined by laser flash photolysis. Triplet state spectra showed intense absorbance with a maximum at around 450 nm and other bands in the regions of 300–400 and 500–800 nm, for all compounds. The triplet quantum yields (Φ_T) and the singlet oxygen quantum yields (Φ_Δ) were estimated to be ca. 0.50 and 0.45, respectively. From the present results, it is inferred that the triplet states of these molecules allow an efficient energy transfer to molecular oxygen, which makes them potentially suitable for photodynamic therapy.

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1. Introduction

The study of quenching/sensitizing processes between dendrimers and dyes [1] has gained increasing relevance owing to multiple applications such as chemosensing [2], imaging [3], photoinduced polymerization [4], and photodynamic therapy (PDT) [5], among others [6]. By proper functionalization and sizing of the dendrimers, various processes such as host/guest binding, electron/energy transfer and energy modulation may be favored and enhanced [7–10]. This fact has led to explore the photophysical and photochemical properties of different dendrimer/probe combinations, by means of several spectroscopic techniques [11–15]. In particular, non-covalent porphyrin/dendrimer aggregates have shown to be suitable for applications in PDT, electron transfer and light harvesting processes, which are nowadays topics of particular significance [16–18].

Porphyrin-dendrimers (Pf-Ds) are interesting adduct compounds, because they merge the recognized optical properties of porphyrins with the versatility of the dendritic architecture in a unique class of macromolecules. Generally, two sub-classes of Pf-Ds can be distinguished, namely: 1) Pf-Ds with porphyrins covalently attached in the periphery, and 2) Pf-Ds from a porphyrin core [19–22]. A lot of reports deal with the synthesis methodologies and potential applications of these sensitizers [22–24]. Many Pf-Ds have been developed in order to mimic the mechanisms and performance of natural systems, in an attempt to achieve high efficiencies for solar energy conversion [25–27]. Continuous research is also underway to improve the properties of these compounds for PDT applications, such as the selective affinity for tumor cells [24,28]. In addition to specificity, it is also required that a sensitizer system for PDT be efficient, aqueous soluble and non-toxic. However, low water solubility and toxicity are characteristic of more commonly used PDT sensitizers. A strategy that has been adopted to overcome these drawbacks is the preparation of supramolecular nanocarriers based on self-assembled polymeric micelles, by electrostatic interaction of Pf-Ds with polymer chains [29].

Since PDT is driven by reactive oxygen species (ROS) generated by either energy or electron transfer from a sensitizer in an excited-state, the knowledge of the processes occurring after light absorption is essential to aim at the applicability of Pf-Ds to human diseases. Indeed, many dyes and fluorescence probes experience spectroscopic shifts when bound to or encapsulated in dendrimers. Processes such as relaxation, energy modulation and

electron transfer can be considerably favored by changes in the microenvironment polarity, confinement effects and electron-donating capability of the dendrimer. However, studies concerning the basis of the photophysical and photochemical properties of Pf-Ds are scarce. Some authors have briefly characterized the ground and singlet-excited states of either Pf-Ds or non-covalent porphyrin/dendrimer aggregates, by steady-state absorption and fluorescence spectroscopies [11,18,22,30,31]. Time-resolved measurements of anisotropy and fluorescence have also been used to study either the dynamics of the energy transfer process or the aggregate formation of sensitizers [11,19,25,32]. Nevertheless, to the best of our knowledge, there is no information in the literature about the characterization and dynamics of the triplet-excited states of Pf-Ds. This fact is surprising because this topic is relevant as singlet oxygen generation (the main ROS in PDT) is mediated by energy transfer from triplet-excited states of most sensitizers.

Recently, Hernández-Ramírez et al. synthesized a series of porphyrin-core Pf-Ds based on *meso*-substituted tetraphenyl porphyrins with PAMAM branches, and one peripherally-modified derivative with thiazole groups [33,34]. These molecules demonstrated metal-binding properties, whereby they might find applications in environment remediation. We are now interested in assessing the photosensitizing and PDT capabilities of such Pf-Ds from *in vitro* photophysical and photochemical characterizations. It is known that porphyrins are chromophores that yield triplets with high performance and this is the main reason for their efficacy as PDT sensitizers. Therefore, although a singlet-excited state study is important for a complete characterization, our focus is on triplet-excited state properties and singlet oxygen generation of these Pf-Ds.

In this work, a complete study on the photophysics of two novel porphyrin-PAMAM dendrimers of generations 1 (C5) and 2.5 (C9), and of a thiazole derivative (10A), was carried out (Scheme 1). The free-base, tetra-(*p*-methoxy)phenyl porphyrin (Pf) corresponding to dendrimer cores was also analyzed for comparison purposes. Ground and singlet-excited states were characterized by absorption and fluorescence spectroscopies, respectively. The singlet and triplet state lifetimes were obtained. The triplet-excited states of the molecules were analyzed by means of laser flash photolysis, which allows assessing the spectral and kinetic features of transient species formed after light absorption. The capability of the Pf-Ds as sensitizers in PDT was evaluated by time-resolved

phosphorescence of singlet oxygen and the corresponding quantum yields for the generation of this reactive species.

2. Materials and methods

The samples, namely free-base, tetra-(*p*-methoxy)phenyl porphyrin (Pf); porphyrin-PAMAM dendrimers of generations 1 (C5) and 2.5 (C9), and a thiazole derivative (10A) were synthesized by Hernández-Ramírez et al. according to previously reported methods, and used without further purification [33,34].

Absorption spectra were recorded on a Hewlett Packard 6453E diode array spectrophotometer. Fluorescence measurements were performed by means of a Horiba Jobin Yvon FluoroMax-4 spectrofluorometer. Fluorescence quantum yields were determined by using ZnTPP in toluene as a standard ($\Phi_f = 0.033$, [35]), and matching the sample and reference absorbances to <0.1 at 419 nm. Dimethylformamide (DMF) and toluene were acquired from Sintorgan (HPLC grade) and used as received. Fluorescence lifetime determinations were carried out using 355-nm-highly-attenuated pulses (FWHM 8 ns) from a Quantel Brilliant R Nd-YAG laser. The air equilibrated samples were excited at right angles. The fluorescence, collected by a monochromator-PM tube system, was transferred *via* a digital oscilloscope to a computer. The lifetimes were extracted from the decay curves by deconvolution using the Origin software. The estimated error of the measurements was ±0.5 ns.

Transient absorption measurements were determined by laser flash photolysis. A Spectron SL400 Nd:YAG laser generating 532 nm laser pulses (20 mJ per pulse, *ca.* 18 ns FWHM) was the excitation source. The experiments were performed with rectangular quartz cells with right angle geometry. The laser beam was defocused in order to cover all the path length (10 mm) of the analyzing beam from a 150-W-Xe lamp. The detection system comprised a PTI monochromator coupled to a Hamamatsu R666 PM tube. The signals were acquired and averaged by a digital oscilloscope (Hewlett-Packard 54504) and then transferred to a computer. All determinations were performed at 25 ± 1 °C and the solutions were de-oxygenated by bubbling with solvent-saturated high purity argon.

Photosensitization of singlet oxygen was carried out by measuring its phosphorescence decay signal by means of a time resolved detection method (TRPD). The excitation source was the aforementioned Nd:YAG laser operating at 532 nm, and the emission radiation (mainly 1270 nm) was detected at right angles with a Judson J16/8Sp amplified germanium detector, after passing through appropriate filters. The output of the detector was coupled to a digital oscilloscope. About ten shots were usually needed for averaging decay times, in order to get a good signal to noise ratio. No changes in the absorption spectra of the samples were observed after these experiments, thus indicating no significant photodegradation of the photosensitizers.

3. Results

3.1. Singlet state

In Fig. 1, the absorption and corrected fluorescence spectra of the molecules in DMF solutions are shown. Excitation spectra for each sample were also recorded and matched the corresponding absorption bands (data not shown). The main spectroscopic parameters are collected in Table 1.
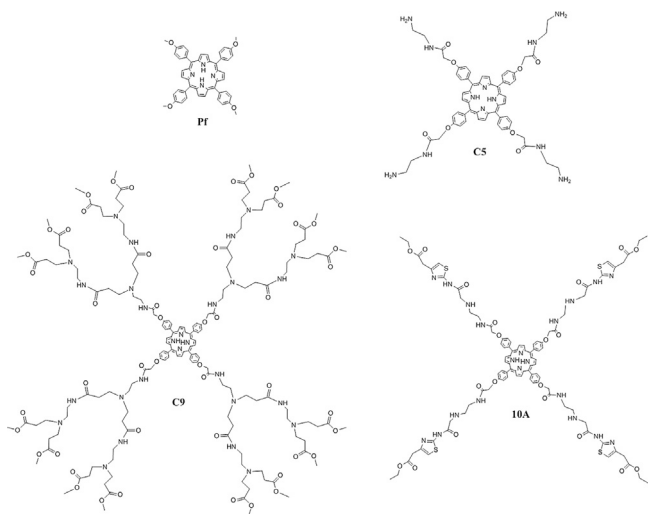
Scheme 1. Molecular structures of the analyzed compounds.
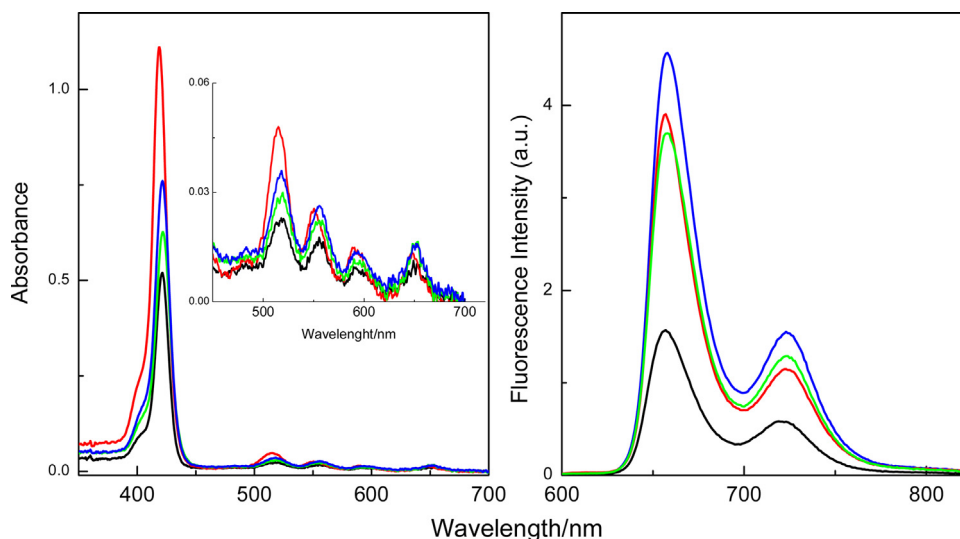
Fig. 1. Absorption and fluorescence spectra of C5 (black), C9 (red), 10A (green) and Pf (blue) in DMF solutions. Inset: Expanded Q-band regions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Spectroscopic properties of the compounds in DMF solutions.

Compound	Absorption					Fluorescence		
	λ_{max}/ nm (Soret band)	λ_{max}/ nm (Q-bands)				λ_{max}/nm	Φ_{fl}[a]	τ_{fl}/ns[a]
Pf	422	518	556	593	650	658	0.101	10.1
C5	419	518	556	592	650	657	0.036	10.1
C9	422	515	551	590	648	657	0.080	11.8
10A	422	518	556	594	650	658	0.083	12.2

[a] The estimated errors were ± 0.5 ns and $\pm 10\%$ for τ_{fl} and Φ_{fl}, respectively.

The fluorescence quantum yields (Φ_{fl}) were determined by the relative actinometry method, according to Eq. (1):

$$\phi_{fl} = \frac{(A_{ref}F_{sample}\eta^2)}{(A_{sample}F_{ref}\eta_0^2)}\phi_{ref} \qquad (1)$$

where A is the absorbance at the excitation wavelength, F is the integrated emission band area and η, η_0 are the refractive index of the solvent containing the sample and the reference, respectively. In Eq. (1), zinc tetraphenyl-porphyrin (ZnTPP) in toluene solution was used as a reference ($\Phi_{fl} = 0.033$, [35]).

As it can be seen on Table 1, the Φ_{fl} values obtained were at around 0.1 with exception of C5, whose Φ_{fl} was about half of the other samples. The singlet-state kinetics of the samples in DMF solutions were also registered, and fluorescence lifetimes (τ_{fl}) in the order of 10 ns were obtained from the corresponding monoexponential decays (Table 1). These results were in good agreement with those reported for porphyrins in organic solvents.

3.2. Triplet state

In order to assess a potential role of the porphyrin-PAMAM dendrimers in sensitizing applications, the characterization of the triplet states by laser flash photolysis experiments was carried out. Fig. 2 shows the transient spectra recorded at various times after the laser irradiation. The transient signals decayed with average times ranging in the order of a few hundred microseconds (see inset on Fig. 2). Qualitatively analog transient spectra were registered in all cases in DMF solutions, with an apparent maximum at around 450 nm (Fig. 2). This band appears partially depleted and distorted by the overlapping with the bleaching of the ground state. Fig. 2 also shows an additional band of lower intensity in the 300–400 nm region, and another even less intense at around 500–800 nm. These spectra resemble those early reported by other authors with solutions of porphyrin compounds.

The insets in Fig. 2 show the decays of the triplet states at the corresponding maximum wavelengths. The UV–vis spectra of the samples before and after transient measurements were recorded and no differences were observed between them. This was assumed as an evidence of no photo-decomposition of the samples. Further, the normalized transient spectra at the maximum wavelength (i.e. 450 nm), at short and long times after laser pulse were identical (not shown). From this result it is inferred that there is only one absorbing species present, namely the triplet state. Therefore, the fact that the decay signals do not return to zero is simply due to the timescale selected to compare the kinetic behavior.

The triplet quantum yields (Φ_T) were determined by relative actinometry to evaluate the efficiency of the intersystem crossing to the triplet state [36]. In this method, the product of Φ_T and the molar absorption coefficient (ε_T) of the triplet state at a working analysis wavelength was determined by laser flash photolysis according to Eq. (2):

$$(\varphi_T\varepsilon_T)_S = \frac{slope_S}{slope_{Ref}}(\varphi_T\varepsilon_T)_{Ref} \qquad (2)$$

where $slope_S$ and $slope_{Ref}$ refer to the initial slopes of the plots of triplet absorption versus laser energy for the samples and a reference, respectively. Actinometry was carried out with ZnTPP in
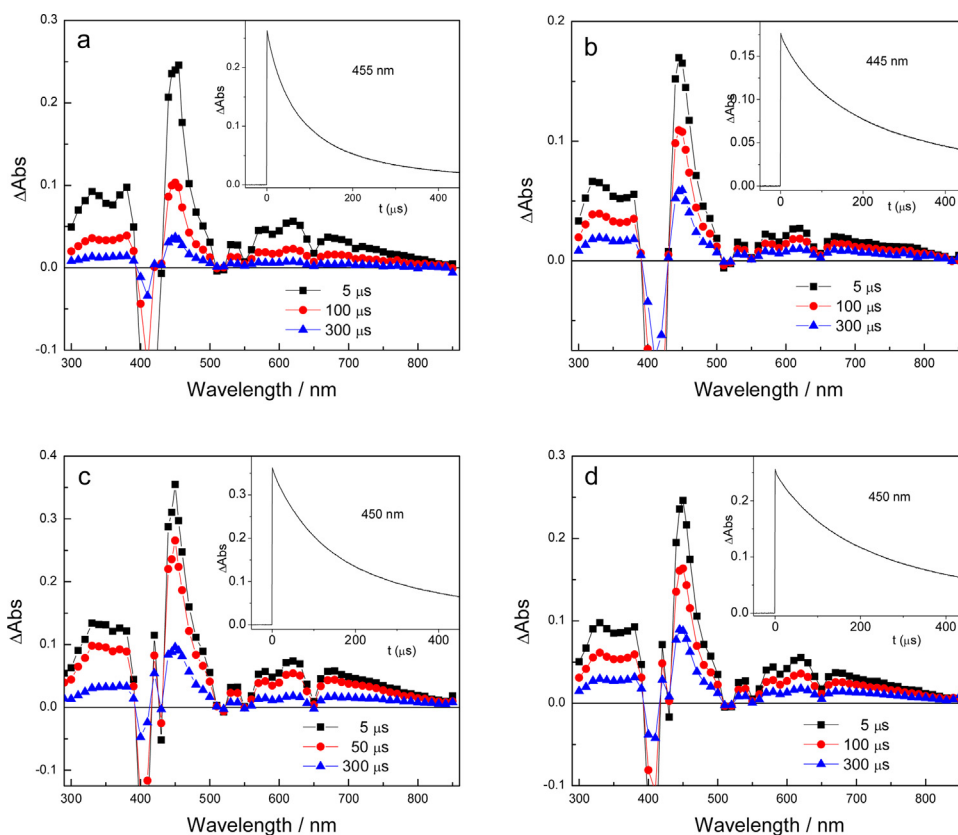
Fig. 2. Transient absorption spectra of a) Pf, b) C5, c) C9 and d) 10A in DMF solutions, at different times after laser shots. Inset: transient decays at maximum wavelengths.

toluene solution as reference, for which values of $\varepsilon_T = 7.4 \times 10^4$ $M^{-1}\,cm^{-1}$ at 470 nm and $\Phi_T = 0.83$ were used [37]. The initial absorbance change extrapolated at zero time was measured at 470 nm for the ZnTPP triplet and at the apparent λ_{max} (*ca.* 450 nm) for the samples triplet with solutions of matched absorbances at 532 nm.

In order to obtain Φ_T from Eq. (2), a value of $\varepsilon_T = 7.0 \times 10^4\,M^{-1}$ cm^{-1} at the triplet maximum wavelength was estimated for all compounds, based on early reported data for the parent compound of Pf named TPP (free-base, tetraphenyl porphyrin) [38,39]. The triplet state parameters are collected in Table 2.

3.3. Singlet oxygen generation

The obtained Φ_T data suggest that the porphyrin-PAMAM dendrimers can sensitize reactive species suitable for PDT by quenching with molecular oxygen. Therefore, singlet-oxygen ($^1O_2$) formation was evaluated by detecting the luminescence of this species at 1270 nm in DMF solutions. Singlet-oxygen generation quantum yields (Φ_Δ) were determined by comparing the phosphorescent emission of the $^1O_2$ generated from the samples

Table 2
Triplet parameters obtained for Pf, C5, C9 and 10A by laser flash photolysis in DMF solution: average decay times ($^3\tau_o$), quantum yields (Φ_T) and singlet oxygen quantum yields (Φ_Δ).

	λ_{max} (nm)	$^3\tau_o{}^a$ (μs)	$\Phi_T{}^b$	$\Phi_\Delta{}^b$
Pf	455	97	0.56	0.57
C5	445	129	0.63	0.41
C9	450	203	0.50	0.46
10A	450	320	0.45	0.41

[a] Estimated error $\pm 0.5\,\mu$s.
[b] Estimated error $\pm 10\%$.

and a reference compound with identical experimental setup and matched absorbances at irradiation wavelength (Eq. (6)).

$$\Phi_\Delta^S = \Phi_\Delta^R \frac{I_\Delta^S}{I_\Delta^R} \qquad (3)$$

where I_Δ refers to the $^1O_2$ emission intensity, and S and R stand for the samples and reference, respectively. The plots of the phosphorescence intensities (extrapolated to t = 0) as functions of laser energy were fitted to straight lines, and the I_Δ parameters were obtained from the corresponding slopes. A DMF solution of ZnTPP was used as a reference ($\Phi_\Delta = 0.74$). This Φ_Δ value was analog to that reported in benzene solution ($\Phi_\Delta = 0.73$, [40]), and was obtained by introducing a solvent correction in Eq. (3) [41]. The results are presented in Table 2.

4. Discussion

From Fig. 1, it can be seen that both absorption and emission spectra of C5, C9 and 10A are qualitatively analog to those of Pf, and they do not show any dependence on the PAMAM branches. The spectra in Fig. 1 resemble those of *meso*-substituted, free-base porphyrins, and are in good agreement with data reported for such compounds ([42–44] and references therein). In all the cases, the absorption spectra show the intense Soret band that is distinctive of porphyrins at around 420 nm, and a series of four bands of moderate intensity (Q-bands) in the 500–700 nm region. The fluorescence spectra appear split into two bands peaking at *ca.* 660 and 720 nm, which is in agreement with those reported for Pf in benzene solution [35,42]. Similar spectral features were recorded with TPP in several solvents [35,42,44] and other *meso*-substituted, free-base porphyrins in DMF solutions [43]. Quimby et al. have ascribed these bands to the transitions from the first singlet

excited-state (S1) to the one (long wavelength band), and zero (short wavelength band) vibrational levels of the ground state [35]. Identical emission spectra were obtained in this work by exciting the samples at Soret or any of the Q-bands, which denotes that excited electrons to S2 state experience fast internal conversion to S1.

As it can be seen in Table 1, Φ_{fl} and τ_{fl} data were in the order of 0.10 (except for C5) and 10.0 ns, respectively, which are reasonable values for this type of compounds. In particular, the Φ_{fl} value for Pf has been shown to be 0.12–0.13 in benzene solution [35,42]. The same values were early reported for TPP in benzene, toluene and methanol solutions in the pioneer works on the photophysics of porphyrins [35,39,42,45]. Fluorescence lifetimes of TPP in toluene and methanol solutions were reported to be 11–14 ns [39,45]. Values of $\Phi_{fl} = 0.10 \pm 0.01$ and $\tau_{fl} = 11.4 \pm 0.1$ for TPP in DMF solution were also reported [46]. Ormond et al. found Φ_{fl} values in the order of 0.1–0.2 and τ_{fl} around 7–13 ns for a series of *p*- and *m*-phenyl TPP derivatives in DMF solutions [43]. In another recent research, Ghosh et al. evaluated the photophysics of TPP and its metallo-derivative ZnTPP in several solvents [44]. The authors found Φ_{fl} and τ_{fl} values for TPP analogous to those previously reported and showed that both parameters are nearly independent of the solvent polarity. Our singlet-state results also agree with those reported by Matos et al. for a series of arylether-substituted TPP dendrimers in THF and DMF solutions [47]. They obtained photophysical properties (absorption and fluorescence spectra, Φ_{fl} and τ_{fl}) very similar to those of TPP, and concluded that dendrons exert little influence on the nonradiative and radiative deactivation processes of the porphyrin core. Therefore, it can be concluded that in general PAMAM branches do not affect the photophysics of the singlet state of the free-base porphyrin core.

The triplet–triplet absorption spectra shown in Fig. 2 are very similar to those reported in early works about the photophysics of TPP in toluene or benzene solutions [38,39], and of a series of hydroxy-TPPs in methanol solutions [39]. On the other hand, the decay triplet times showed an increase in the order Pf < C5 < C9, which correlates well with the branching grade of the molecules (Table 2). However, it is known that PAMAM dendrimers quench triplet states of dyes by electron transfer reactions [13,15]. Our present data suggest that dendritic branches stabilize the formed triplet states protecting the porphyrin core from its environment. Φ_T values around 0.5 for the three porphyrin-dendrimers were in the order of the majority of the data regarding TPP and its substituted analogous [39,45]. Table 2 also shows that Φ_T for C5 is 20–25% higher than for the other samples and this value is in agreement with the lower Φ_{fl} obtained (Table 1). Moreover, Φ_Δ values around 0.40–0.45 were in good agreement with the 0.40–0.65 values reported on this family of molecules [39,43,46,48].

5. Conclusions

As a whole, our present results of fluorescence spectra, lifetimes and fluorescence quantum yields are in excellent agreement with reported data on porphyrin compounds, and suggest that spectroscopic properties of porphyrin-PAMAM dendrimers are governed by the Pf core. Transient spectra were ascribed to the triplet-state of the compounds. The low self-quenching recorded as evidenced by the long triplet decay times is a desirable property in PDT applications. This long-lived triplet formation might be ascribed to that a low aggregation of the sensitizer is occurring, due to the steric hindrance promoted by the dendritic branches. Further, an efficient energy transfer from the triplets to molecular oxygen was measured. All these results suggest that porphyrin-based dendrimers might find applications in several sensitizing

processes such as electron and energy transfer, and PDT, whereby this issue is currently underway by our research group.

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