Fluorenyl porphyrins for combined two-photon excited fluorescence and photosensitization

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Abstract

The two-photon absorption (2PA), the luminescence and the photosensitization properties of porphyrin-cored fluorenyl dendrimers and *meso*-substituted fluorenylporphyrin monomer, dimer and trimer are described. In comparison with model tetraphenylporphyrin, these compounds combine enhanced (non-resonant) 2PA cross-sections in the near infrared and enhanced fluorescence quantum yields, together with maintained singlet oxygen generation quantum yields. "Semi-disconnection" between fluorenyl groups and porphyrins (i.e. direct *meso* substitution) proved to be more efficient than non-conjugated systems (based on efficient FRET between fluorenyl antennae and porphyrins). These results are of interest for combined two-photon imaging and photodynamic therapy.

Introduction

Multiphotonics has gained increasing popularity in the life sciences over the last decade, in relation with the many advantages molecular multiphoton absorption[1-4] provides for biological or biomedical applications, such as multiphoton excited fluorescence imaging,[5-7] and photodynamic therapy (PDT),[8-14]. The advantages of two-photon absorption (2PA)

include the ability for highly selective excitation in biological media, intrinsic three-dimensional resolution as well as increased penetration depth in tissues. Chromophores exhibiting very high 2PA cross-sections in the biological spectral window (700-1100 nm) are thus required, and depending on the targeted application, additional requirements have also to be fulfilled, such as high fluorescence quantum yields for bioimaging and high singlet oxygen quantum yields for PDT, both of which are to be retained in real biological conditions. Two-photon absorbers combining brightness and photosensitization properties are highly desirable for theranostic applications, allowing in vivo monitoring and subsequent localized irradiation.

Most of the photosensitizers currently used clinically or in clinical trials are porphyrin derivatives, which exhibit high singlet oxygen quantum yields, significant red fluorescence, but low 2PA cross-sections (10 GM at 800 nm for Photofrin[15] and 12 GM at 790 nm for model tetraphenylporphyrin, TPP[16]).

Very high 2PA cross-sections have been obtained with porphyrinoids,[17] expanded porphyrins,[18,19] conjugated porphyrin dimers, trimers and oligomers,[20-24] planarized fused or bridged porphyrins[25-27] and supramolecular assemblies.[20,22,28] Such a dramatic enhancement, in relation with the extension of the π-conjugated system, leads to systems very well suited for applications of 2PA such as optical limiting, but it also leads to strong modifications of the other photophysical properties, which limit their interest for theranostic applications. In particular, a definite decrease (or even suppression) of the fluorescence is often observed, as well as residual one-photon absorption (1PA) overlapping with the 2PA band located in the NIR region, and therefore in the loss of some of the advantages resulting from selective 2PA, especially the 3D resolution which is of main importance for highly localized therapy.

To increase the 2PA cross-sections without any residual 1PA, while retaining the other photophysical properties of native porphyrins, dendritic antenna systems based on resonant energy transfer (FRET) between donor peripheral two-photon absorbers and a central porphyrin acceptor have been designed.[29-32] More recently, we have developed an alternative strategy based on "semi-disconnected" multiporphyrin assemblies with hindered conjugation between a central 2PA unit and peripheral porphyrins.[33]

On the other hand, we have previously reported[34] that tetrafluorenylporphyrin (**TFP**) exhibits a remarkably high fluorescence quantum yield (24%, instead of 11% for TPP), demonstrating the good capacity of fluorenyl units to enhance fluorescence. We have also reported an increase of the brightness with related porphyrin-cored fluorenyl dendrimers[35,36] and fluorenyl-armed linear porphyrin dimers[37] and trimers.[38] Apart from the fluorene

substituents, the other common feature of these systems is the weak conjugation between porphyrins and their *meso* substituents, ensured by deviation from planarity.[39,40]

Even if fluorene itself is not a strong two-photon absorber, it is often used as a monomer[41,42] or a building block in efficient organic[14,43,44] and organometallic[45,46] 2PA systems. Might therefore an increase of the 2PA also be expected for fluorenyl porphyrins, and what about their singlet oxygen quantum yields? The goal of the present communication is to address these two questions.

Design

Five porphyrin derivatives will be studied (Figure 1), with an increasing number of peripheral fluorenyl substituents, from 4 for **TFP** to 16 for dendrimer **16F**. These covalent assemblies can be classified in two series: (i) porphyrin-cored dendrimer antennae based on FRET, where fluorenyl groups are not conjugated to the central TPP (**8F** and **16F**); (ii) porphyrin monomer (**TFP**), dimer (**D**) and trimer (**T**) with hindered conjugation between peripheral fluorenyl *meso*-substituents and porphyrins, as well as between porphyrins and their diphenylacetylene bridges. This will allow for a comparison between systems based on FRET and systems based on hindered conjugation (*i. e.* "semi-disconnected" systems).

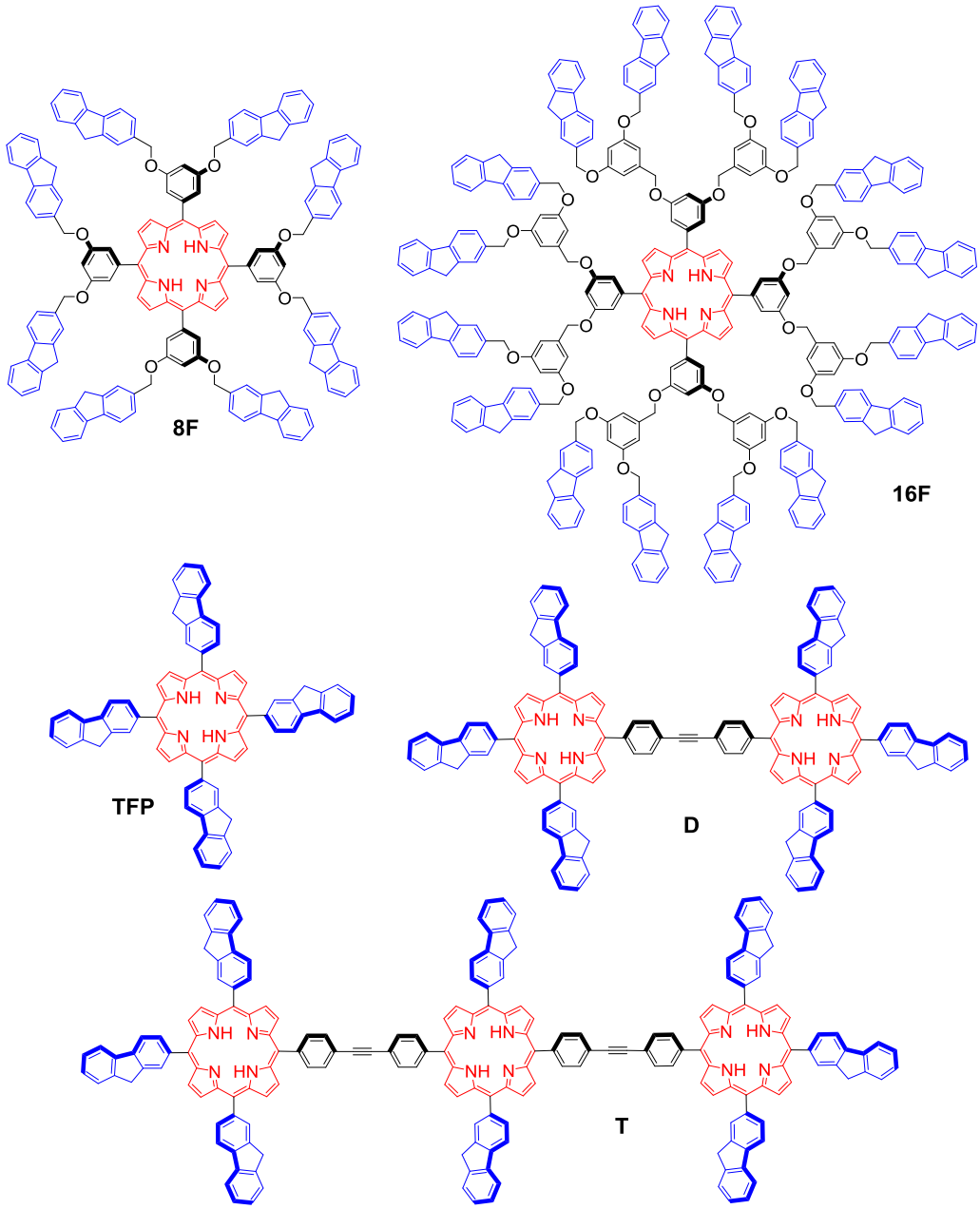


Figure 1. Chemical structures of fluorenyl porphyrins.

Synthesis

Porphyrin-cored fluorenyl dendrimers **8F** and **16F** were prepared by reaction of 5,10,15,20-tetrakis(3,5-dihydroxyphenyl)porphyrin with 2-(bromomethyl)-9*H*-fluorene and, 1-bromomethyl-3,5-bis(9*H*-fluoren-2-ylmethoxy)benzene, respectively.[35,36]

5,10,15,20-Tetra-9*H*-fluoren-2-ylporphyrin (**TFP**) was obtained from the condensation of pyrrole with 2-fluorenecarboxaldehyde.[47] Fluorenyl-armed porphyrin dimer **D** and trimer **T**

were obtained from Sonogashira coupling between iodo and ethynyl porphyrin monomers.[37,38]

Photophysical properties

The photophysical characteristics (including one-photon absorption, luminescence, singlet oxygen generation, and two-photon absorption) of the fluorenyl porphyrin derivatives are gathered in Table 1.

One-photon absorption

Absorption spectra of fluorenyl porphyrin monomers and oligomers in the visible closely resemble to those of TPP, the characteristic Soret band and Q bands being almost unaffected, except a red shift of the Soret band (Figure 2a and Table 1). This red shift is of 6 nm for dendrimers **8F** and **16F** and of 9-10 nm for the three later compounds **TFP**, **D** and **T**. The lower excited states are thus preserved and localized on the porphyrin macrocycles. This is in agreement with the absence of conjugation between porphyrin and fluorenes in the case of dendrimers **8F** and **16F**, and with the weak conjugation between the subchromophores (porphyrins and their *meso* substituents, i. e. fluorenes and diphenylacetylene bridges) in the case of **TFP**, **D** and **T**. As no significant bathochromic shift of the Q bands is observed, a full transparency in the NIR is preserved.

However, the presence of the fluorenyl groups gives rise to a new absorption band in the UV region at ~270 nm, whose intensity increases with the total number of fluorenes of the molecule. Smaller bands and shoulders are also observed between 300 and 400 nm, in particular for **TFP**, **D** and **T**. This reveals the emergence of higher excited states that modify the excitation behavior of these systems as compared to TPP.

Emission

Upon excitation at the UV band corresponding to the absorption of fluorenes, the donor UV emission (around 300-330 nm) is almost completely quenched for all the compounds (Figure 2b), even in the case of dendrimers **8F** and **16F**, where fluorenes are not conjugated with the acceptor porphyrin, and whose distances between donor and acceptor are the largest. It results almost exclusively in the red emission bands characteristic of the porphyrin. The energy transfer is therefore very efficient for all the compounds. In the case of **TFP**, where almost no

residual donor emission is observed, the phenomenon can be understood as internal conversion between excited states rather than FRET.[34]

Upon excitation at the Soret band (Figure 2c), fluorenyl porphyrins exhibit emission spectra similar to that of TPP. For dendrimers **8F** and **16F**, a very small red-shift of the emission bands (2 nm) is observed in comparison with TPP, as well as an increase of the intensity of the second sub-band at 718 nm. For **TFP**, **D** and **T**, a ~10 nm red-shift of the emission bands is clearly visible, as well as a decrease of the intensity of the second sub-band.

As the lower excited state is localized on the porphyrin units, the emission behavior if these systems is quite similar to that of TPP. However, the presence of the fluorenyl groups has a slight effect on the lower excited state, and this effect is more marked for compounds with fluorenyl groups at the *meso* position (**TFP**, **D** and **T**), than for dendrimers **8F** and **16F**, whose fluorenyl groups are not conjugated with the porphyrin.

Excitation spectra obtained through observation of the porphyrin fluorescence at 660 nm (Figure 2d) closely resemble the corresponding absorption spectra, both in the UV-vis region (corresponding to the excitation bands of the fluorenes) and in the visible region (corresponding the excitation bands of the porphyrins), confirming the efficiency of the energy transfer.

Fluorescence quantum yields

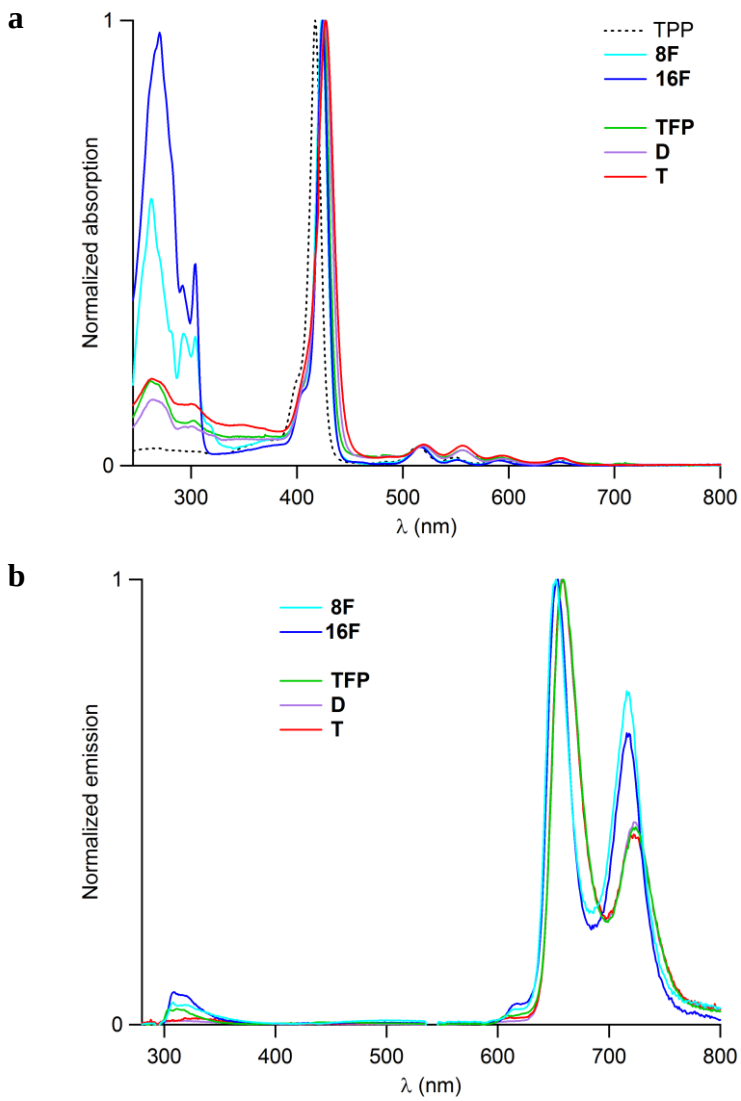
The fluorescence quantum yields of dendrimers **8F** and **16F** (respectively 13% and 14%) are slightly higher than that of TPP, whereas **TFP**, **D** and **T** exhibit higher values, up to 24% for **TFP**. The fluorescence quantum yield increases significantly with the ratio of the number of fluorenes directly substituting the *meso* positions to the number of porphyrins (**8F** ~ **16F** ~ **T** < **D** < **TFP**). In the case of **TFP**, this could be interpreted in terms of larger influence of *meso*-fluorenyl groups over phenyl ones in increasing the fluorescence radiative rate constant of the porphyrin.[34]

This improvement of the fluorescence properties in comparison with model TPP is of interest in the perspective of theranostic applications, even in the case of the dendrimers, as it should be noticed that for these antennae the brightness is dramatically increased upon excitation in the fluorene absorption band in the UV.

Singlet oxygen quantum yields

A very important issue is that the enhancement of the fluorescence quantum yield of fluorenyl porphyrins is not obtained at the expense of their singlet oxygen quantum yield.

Dendrimers **8F** and **16F** exhibit singlet oxygen quantum yields quite similar to that of TPP (or even slightly higher). **TFP**, which exhibits the highest fluorescence quantum yield (24%), maintains the same singlet quantum yield than TPP (60%). This confirms that the increase of the fluorescence quantum yield is mostly due to an increase of the radiative rate constant, along with some decrease of the internal conversion rate constant, but the intersystem crossing rate constant (whose singlet oxygen quantum yield depends) is at least maintained. A similar trend is also observed for dimer **D**, but a decrease of the singlet oxygen quantum yield is observed for trimer **T**, whose photophysical behavior is probably complicated by the presence of the bridges and by interactions between porphyrins.



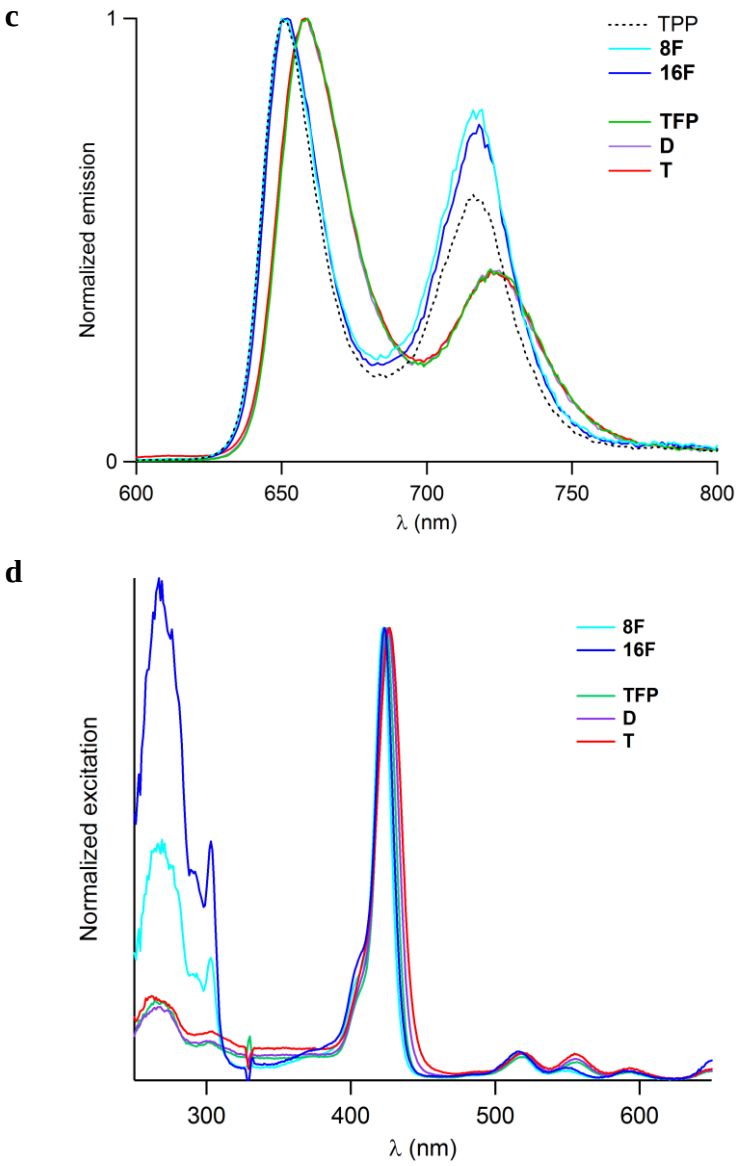


Figure 2. Absorption spectra of fluorenyl porphyrins (**a**), emission spectra upon excitation at the fluorene band (**b**), emission spectra upon excitation at the Soret band (**c**) and excitation spectra through emission at 660 nm (**d**).

Table 1. Photophysical data in dichloromethane of fluorenyl porphyrin derivatives and model TPP

Compd	fluorenes / porphyrin	*meso*-fluorenes / porphyrin	λ_{abs}^{max} (nm) UV band	λ_{abs}^{max} (nm) Soret	λ_{em} (nm)	Φ_F [a]	Φ_Δ [b]	λ_{2PA}^{max} (nm)	σ_2^{max} (GM)[c]	σ_2/porph (GM)	σ_2/fluorene (GM)
8F	8	0	263	423	652, 718	0.13	0.64	790	45	45	6
16F	16	0	270	423	652, 718	0.14	0.63	790	75	75	5
TFP	4	4	272	426	660, 725	0.24	0.60	790	90	90	23
D	3	3	268	426	658, 724	0.17	0.59	810	170	85	28
T	2.67	2.67	263	427	658, 724	0.13	0.48	810	270	90	34
TPP	0	0	-	417	650, 716	0.11	0.60	790	12[d]	12	-

[a] Fluorescence quantum yield determined relative to TPP in toluene, upon excitation at the Soret band. [b] Singlet oxygen formation quantum yield determined relative to tetraphenylporphyrin in dichloromethane (Φ_Δ[TPP] = 0.60). [c] Intrinsic 2PA cross-sections measured by TPEF in the femtosecond regime; a fully quadratic dependence of the fluorescence intensity on the excitation power is observed and 2PA responses are fully non-resonant. [d] Data from lit.[16]

Two-photon absorption

As the fluorenyl porphyrins exhibit good fluorescence properties, their 2PA cross-sections in the NIR range could be determined by investigating their two-photon excited fluorescence (2PEF). Measurements were performed in 10^{-4} M solutions, using a mode-locked titanium:sapphire laser delivering 150 fs pulses, following the experimental protocol described by Xu and Webb.[48]

A fully quadratic dependence of the fluorescence intensity on the excitation power was observed for each sample at all wavelengths of the spectra shown in Figures 3 and 4, indicating that the obtained cross-sections are only due to 2PA. The very high "apparent" 2PA cross-sections obtained at lower wavelengths were not taken into account and are not reported here, as concomitant deviation from quadraticity was observed, indicating the beginning of hot-band absorption[49] and/or 1PA resonance.

An increase of the 2PA cross-sections compared to that of TPP (12 GM at 790 nm) was observed for all the fluorenyl porphyrins (Table 1).

Dendrimers **8F** and **16F** exhibit 2PA cross-sections of 45 and 75 GM at 790 nm, respectively. They reveal significant enhancement factors (4-fold and 6-fold, respectively) with respect to TPP (Figure 3).

TFP, despite its much smaller molecular weight in comparison with dendrimers, exhibits a larger 7-fold enhancement, with a 2PA cross-section of 90 GM at 790 nm (Figure 4). Dimer **D** and trimer **T** exhibit the highest cross-sections (170 and 270 GM, respectively), and their

cross-sections per porphyrin are comparable to that of **TFP**, with an enhancement factor of ~7 with respect to TPP.

Another useful way to compare the different systems is to normalize the 2PA cross-sections by the number of fluorenes (Table 1). Dendrimers **8F** and **16F** exhibit a value of 5-6 GM/fluorene, whereas **TFP**, **D** and **T** exhibit a value of 20-30 GM/fluorene.

These results show that, in both series, fluorenyl groups have beneficial effect on the 2PA response. However, when they are not conjugated with the porphyrins, as for dendrimers **8F** and **16F**, a larger number of fluorenes are necessary to attain cross-sections comparable to those obtained when these fluorenyl groups are situated at the *meso* positions, as for **TFP**, **D** and **T**. Since dimer **D** and trimer **T** have a lower *meso*-fluorenes / porphyrin ratio than **TFP**, a lower enhancement factor would be expected, which is not the case, and therefore means that the diphenylacetylene bridges between the porphyrins also play a beneficial role for the 2PA response.

Non-conjugated and "semi-disconnected" fluorenyl groups are both involved in higher excited states that are responsible for enhanced 2PA, acting as 2PA antennae, and allow fast return (in agreement with efficient FRET in the case of dendrimers, or with Kasha's rule in the case of "semi-disconnected" systems) to a lower porphyrin-centered excited state, similar to that of model TPP, and responsible for fluorescence emission and singlet oxygen production.

Even if the through space energy transfer between fluorene donors and porphyrin acceptors is highly efficient in non-conjugated dendrimers **8F** and **16F**, the enhancement of 2PA response is lower than that observed for the "semi-disconnected" systems (**TFP**, **D**, **T**). In non-conjugated dendrimers, fluorene units behave as weak 2PA antennae, and the 2PA increase is due to large number of these units, with a 2PA cross-section of about 5-6 GM per fluorene (as these fluorene units are lacking electroactive groups). The larger enhancement of the 2PA response in "semi-disconnected" systems seems to indicate that the different moieties (meso-fluorenyl groups, diphenylacetylene bridges, and porphyrins) do not behave as fully independent chromophoric units but slightly interact in the higher excited states. This suggests that the porphyrin groups are indeed contributing to the 2PA response by acting as electro-active groups (probably in relation with field rather than resonance effects) for fluorenes (and for the diphenylacetylene bridge) in the higher excited states, thus improving the 2PA efficiency of these moieties (which leads to cross-sections of more than 20 GM per fluorene).

Both approaches allow for keeping the photosensitization properties of TPP while enhancing its 2PA and its fluorescence properties, but the "semi-disconnection" strategy appears to be

more appealing for the targeted application. The figures of merit of the two-photon-excited fluorescence (i.e. the two-photon brightness $\sigma_2\Phi_F$) and of the two-photon excited singlet oxygen production (i. e. the product $\sigma_2\Phi_\Delta$) are simultaneously enhanced with respect to TPP for all the fluorenyl porphyrins, but these enhancements are larger for "semi-disconnected" compounds (16-fold and 7-fold respectively, in the case of **TFP**).

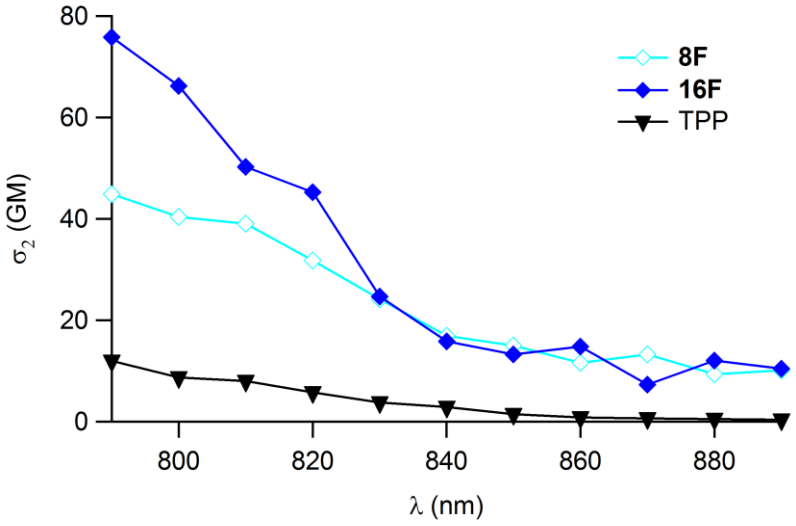


Figure 3. 2PA spectra of TPP and porphyrin-cored fluorenyl dendrimers **8F** and **16F**.

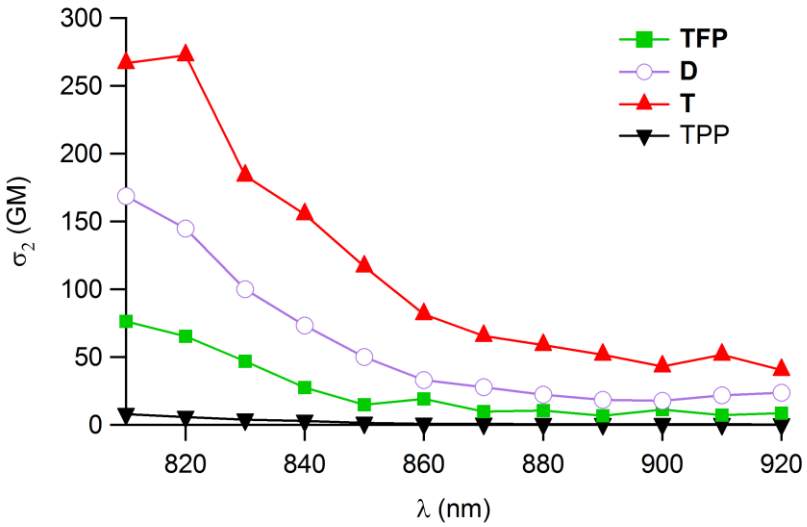


Figure 4. 2PA spectra of TPP, **TFP** and fluorenyl porphyrin oligomers **D** and **T**.

Conclusion

Fluorenyl dendrimers, tetrafluorenylporphyrin (**TFP**), and fluorenylporphyrin oligomers exhibit enhanced (non-resonant) 2PA cross sections in the NIR, as well as enhanced fluorescence quantum yields together with retained photosensitization properties. "Semi-disconnection" between fluorenyl groups and porphyrins (i.e. direct *meso* substitution) proved to be more efficient than non-conjugated systems (based on efficient FRET between fluorenyl antennae and porphyrins). Further enhancement of both 2PA and fluorescence of porphyrin oligomers might be achieved by optimizing the design of the bridges, for example by replacing diphenylacetylenes with difluorenylacetylenes.

These results are of interest, as they allow to fully benefit from the advantages of selective 2PA for theranostic applications combining two-photon fluorescence imaging and photodynamic therapy, provided that hydrophilicity and biocompatibility of the systems are improved, which may be achieved for example by introducing oligoethyleneglycol chains on the fluorenes.

Experimental section

Spectroscopic Measurements: All photophysical properties have been performed with freshly-prepared air-equilibrated solutions at room temperature (298 K). UV/Vis absorption spectra were recorded on a Jasco V-570 spectrophotometer. Fluorescence measurements were performed using an Edinburgh Instruments (FLS920) spectrometer in photon-counting mode. Fully corrected emission spectra were obtained, for each compound, under excitation at the wavelength of the absorption maximum, with $A_{\lambda ex} < 0.1$ to minimize internal absorption.

Measurements of singlet oxygen quantum yield (Φ_Δ): Measurements were performed on a Fluorolog-3 (Horiba Jobin Yvon), using a 450 W Xenon lamp. The emission at 1272 nm was detected using a liquid nitrogen-cooled Ge-detector model (EO-817L, North Coast Scientific Co). Singlet oxygen quantum yields Φ_Δ were determined in dichloromethane solutions, using tetraphenylporphyrin (TPP) in dichloromethane as reference solution (Φ_Δ [TPP] = 0.60) and were estimated from $^1O_2$ luminescence at 1272 nm.

Two-Photon Absorption Experiments: To span the 790-920 nm range, a Nd:YLF-pumped Ti:sapphire oscillator was used generating 150 fs pulses at a 76 MHz rate The excitation power is controlled using neutral density filters of varying optical density mounted in a computer-controlled filter wheel. After five-fold expansion through two achromatic doublets, the laser beam is focused by a microscope objective (10x, NA 0.25, Olympus, Japan) into a standard 1 cm absorption cuvette containing the sample. The applied average laser power arriving at the sample is typically between 0.5 and 40 mW, leading to a time-averaged light flux in the focal volume on the order of 0.1–10 mW/mm^2. The fluorescence from the sample is collected in epifluorescence mode, through the microscope objective, and reflected by a dichroic mirror (Chroma Technology Corporation, USA; ‘‘blue’’ filter set: 675dcxru; ‘‘red’’ filter set: 780dxcrr). This makes it possible to avoid the inner filter effects related to the high dye concentrations used (10^{-4} M) by focusing the laser near the cuvette window. Residual excitation light is removed using a barrier filter (Chroma Technology; ‘‘blue’’: e650–2p, ‘‘red’’: e750sp–2p). The fluorescence is coupled into a 600 µm multimode fiber by an achromatic doublet. The fiber is connected to a compact CCD-based spectrometer (BTC112-E, B&WTek, USA), which measures the two-photon excited emission spectrum. The

emission spectra are corrected for the wavelength-dependence of the detection efficiency using correction factors established through the measurement of reference compounds having known fluorescence emission spectra. Briefly, the set-up allows for the recording of corrected fluorescence emission spectra under multiphoton excitation at variable excitation power and wavelength. 2PA cross sections (σ_2) were determined from the two-photon excited fluorescence (2PEF) cross sections ($\sigma_2\Phi_F$) and the fluorescence emission quantum yield (Φ_F). 2PEF cross sections of 10^{-4} M dichloromethane solutions were measured relative to fluorescein in 0.01 M aqueous NaOH using the well-established method described by Xu and Webb,[48] and the appropriate solvent-related refractive index corrections.[50] The quadratic dependence of the fluorescence intensity on the excitation power was checked for each sample and all wavelengths.

Acknowledgments

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