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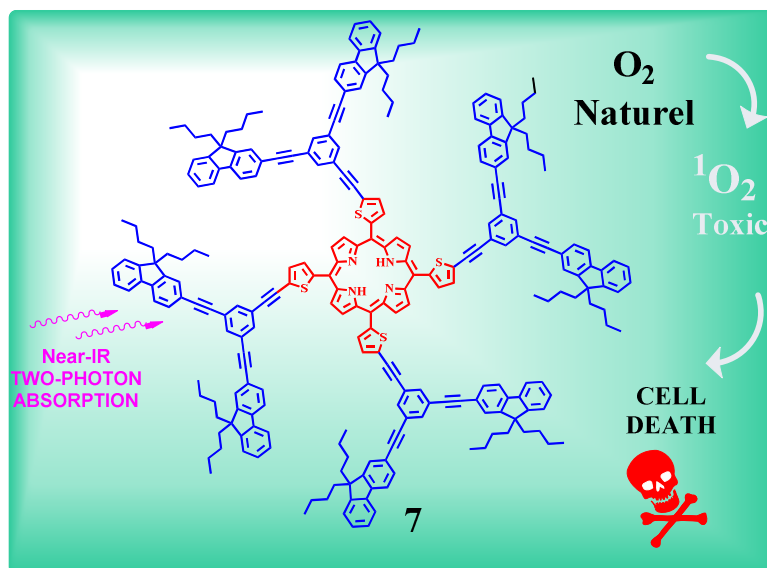
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New Conjugated *meso*-tetrathienylporphyrin-cored Derivatives as Two-photon Photosensitizers for Singlet Oxygen Generation

Xu Zhang, Seifallah Abid, Limiao Shi, Zhipeng Sun, Olivier Mongin, Mireille Blanchard-Desce, Frédéric Paul, Christine O. Paul-Roth,*



A new family of conjugated *meso*-tetrathienylporphyrin-based dendrimers with fluorenyl arms has been synthesized. Their detailed luminescence properties and selected photophysical properties are discussed in the frame of two-photon-induced theranostics.

New Conjugated *meso*-Tetra(thien-2-yl)porphyrin-Cored Derivatives as Two-photon Photosensitizers for Singlet Oxygen Generation

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ABSTRACT: A series of conjugated *meso*-porphyrin dendrimers containing conjugated fluorenyl dendrons, incorporating overall either four (**3**) or eight (**4**) fluorenyl units have been synthesized and characterized. These new molecular architectures are based on a central *meso*-tetra(thien-2-yl)porphyrin core (**TThP**). Their linear optical properties, absorption and photoluminescence, as well as selected nonlinear optical properties, were investigated and compared to those of the unsubstituted *meso*-(thien-2-yl)porphyrin core (**5**) and also to those of previously reported analogues featuring 1,4-phenylene groups (**1** and **2**) in place of 2,5-thienylene moieties. The positive role of these thienylene linkers over phenylene linkers on the two-photon absorption (2PA) cross-sections is clearly evidenced.

Keywords

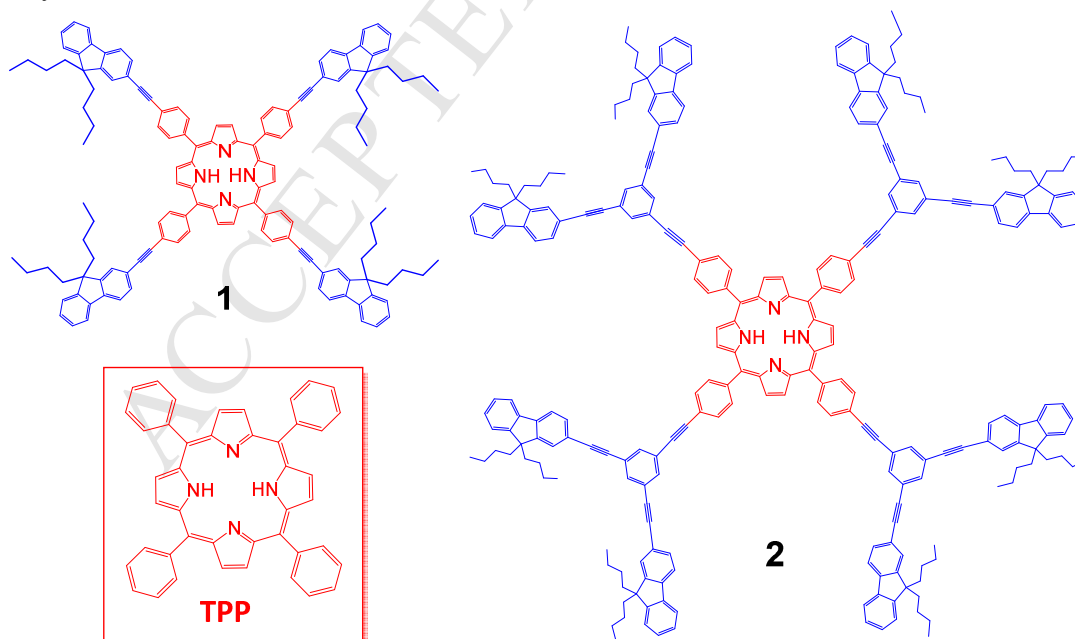
Tetrathienyl Porphyrin • Fluorenyl • Two-Photon Absorption • Luminescence • Oxygen Sensitization

INTRODUCTION

Organic molecular materials exhibiting third-order nonlinear optical (3rd NLO) properties are used nowadays in a wide range of key societal applications, such as all-optical communication,

ultra-dense optical data storage or microfabrication.^[1] This situation has fostered the extensive development of fundamental studies aimed at understanding and improving the third-order NLO responses of various classes of molecules. Classic 3rd NLO processes used for these applications rest mostly on two types of phenomena: (i) nonlinear refractive effects^[2] and (ii) nonlinear absorptive effects, namely two-photon absorption (2PA), reverse saturable absorption (RSA) and saturable absorption (SA). The first of these nonlinear absorptive effects (2PA) deserves some particular attention because it has also fostered tremendous activity in various bio-related fields since the beginning of this century.

For instance, depending on the properties of the excited state populated by biphotonic absorption, specific chromophores have now been developed for important societal tasks such as two-photon fluorescence imaging^[1b,3] or two-photon photodynamic therapy (PDT).^[4] Indeed, it is now well established that *via* 2PA, these effects can be triggered by laser light with much better spatial definition, much deeper penetration in living tissues, and in a much more innocuous way than *via* traditional one-photon (1PA) excitation using conventional light sources.^[1a,b] However there is a growing need to improve further the existing systems or to develop new systems. In this respect, the extensive literature available on third-order properties can be quite usefully used, as we shall show hereafter.^[5]

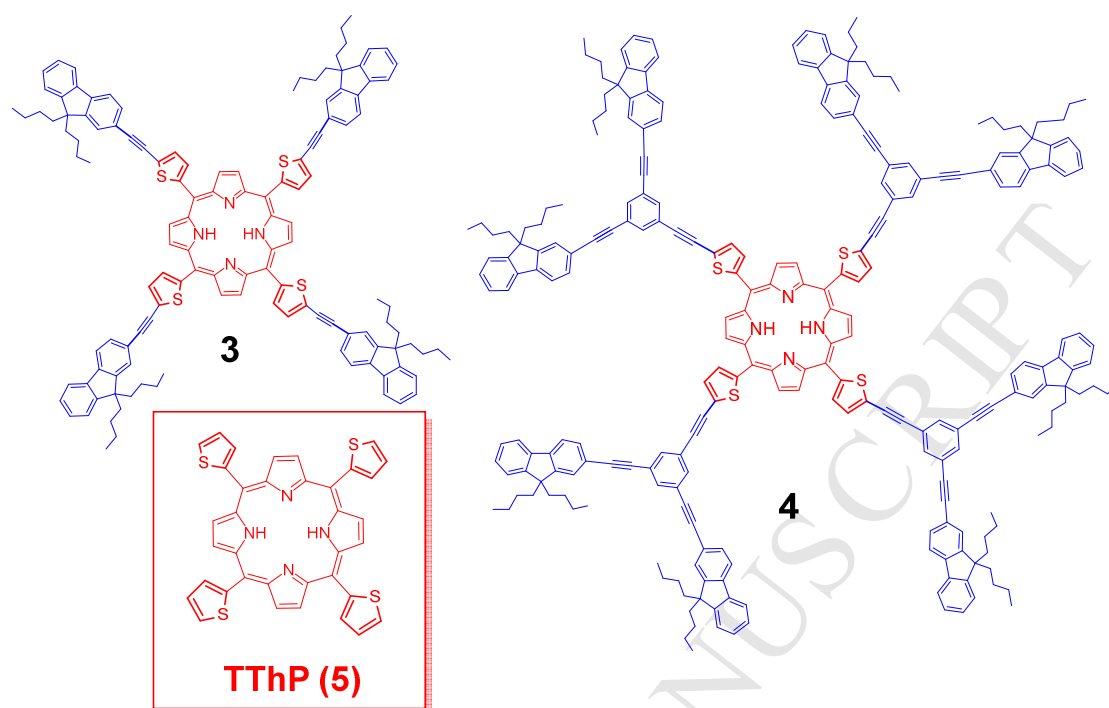


Scheme 1. *Meso*-tetraphenylporphyrin-based fluorescent oxygen photosensitizers **1** and **2** and reference **TPP**.

In the continuation of former studies aimed at identifying molecules for theranostics (*i.e.* allowing imaging and curing at the same time),^[6] we have recently reported a series of *meso*-tetraphenylporphyrin-based dendrimers such as **1** or **2** (Scheme 1).^[7] These fluorescent dendrimers were able to efficiently photogenerate singlet oxygen and also turned out to be fair two-photon absorbers, presenting thereby the attractive possibility to develop 2PA-based photosensitizers for theranostics. In order to learn a little more about the potential of this class of molecules, we have now decided to attempt the identification of analogues with improved 2PA capabilities.

As obvious from various examples,^[5,8] replacement of a 1,4-phenylene group by a 2,5-thienylene group (Scheme 2) within a given conjugated π -manifold while preserving its overall symmetry (A- π -A or D- π -D for quadrupoles) results usually in a significant improvement of the 2PA cross-section (σ_2). Based on such considerations, replacement of the *meso*-1,4-phenylene groups by *meso*-2,5-thienylene group in **1** and **2** should improve their 2PA cross-sections. We therefore targeted the dendrimers **3** and **4** (Scheme 2), which are the tetrathienyl analogues of **1** and **2** (Scheme 1), respectively, as well as *meso*-tetra(thien-2-yl)porphyrin **TThP** (**5**) which will be used as a reference compound for these studies. The latter compound has been known since 1968^[9] and was so far mainly prepared using the Alder-Longo method^[10] and also by the Lindsey method,^[11] the latter approach giving apparently better yields.^[12] [Note: We have previously also isolated a porphyrin analogous to **TThP** *via* the Lindsey method, but featuring only two *meso*-thienyl groups in *trans* positions and two *meso*-phenyl groups. Unfortunately, the nonlinear optical properties of this molecule were not studied at that time.^[13]]

In contrast to **TThP**, dendrimers **3** and **4** are new molecules. However, molecules closely related to **3** and **4** have also been isolated using the method of Lindsey,^[14] suggesting that our targets might also be synthetically accessed *via* this alternative (and often more productive) approach.



Scheme 2. Targeted *meso*-tetra(thien-2-yl)porphyrins (**3** and **4**) and reference *meso*-tetra(thien-2-yl)porphyrin **TThP** (**5**).

We thus report in the following the (i) synthesis and full characterization of *meso*-(2-((9,9-dibutylfluorenyl)ethynyl)-thienyl)porphyrin (**3**) and *meso*-(2-((3,5-bis((9,9-dibutylfluorenyl)ethynyl)phenyl)ethynyl)-thienyl)porphyrin (**4**) based on a Lindsey protocol^[15] for synthesizing the porphyrin core, followed by (ii) the study of their linear and nonlinear photophysical properties of interest in relation to theranostics. Finally, (iii) these properties will be compared to those of **1**, and **2** and the interest of the structural modification for photosensitizing oxygen will be discussed.

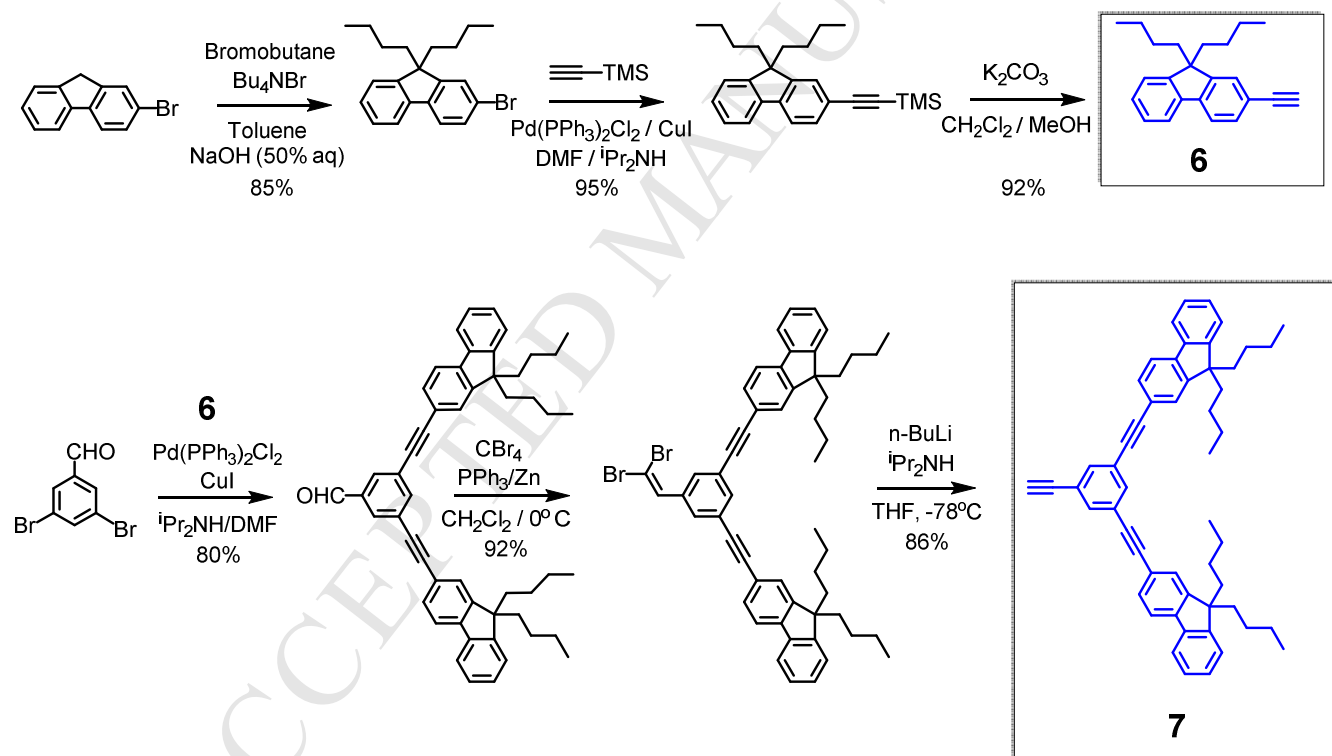
RESULTS

Synthesis of the Dendrimers

To prepare this new family of porphyrin-based dendrimers, the Lindsey method,^[15] Sonogashira couplings^[16] and Corey-Fuchs reactions^[17] were successively used to access the targeted molecules: **3**, **4** and reference **TThP**. In more detail, the strategy adopted basically involves

three steps; (i) the synthesis of dendrons **6** and **7** (Scheme 3), (ii) the isolation of the tetra-iodo porphyrin precursor **8** and, finally, (iii) the formation of the desired porphyrin-based dendrimers **3** and **4** in a final step. As previously accomplished,^[7, 18] *n*-butyl chains were firstly fixed in the 9 position of the fluorenyl unit(s) in order to improve the solubility of the final molecules.

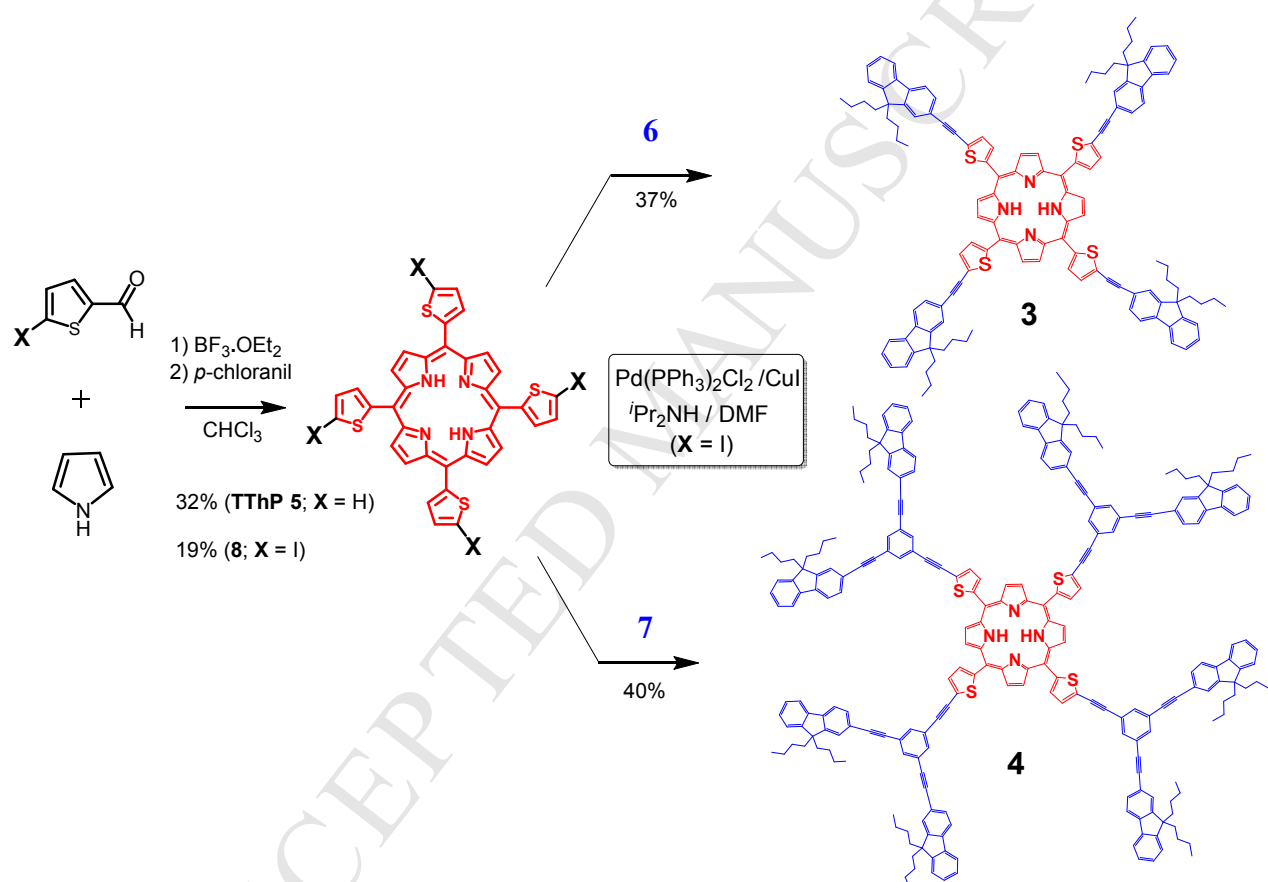
The desired dendrons were obtained *via* iterative Sonogashira couplings and Corey-Fuchs reactions, based on related chemistry previously developed in our group (Scheme 3).^[7,18-19] The isolation of dendron **6** from 2-bromofluorene in a total yield of 74% was rather straightforward. Dendron **7** was next obtained in *ca.* 63% total yield after a two-step Corey-Fuchs procedure from the corresponding aldehyde precursor,^[19] itself obtained from one equivalent of 3,5-dibromobenzaldehyde and two equivalents of dendron **6**.



Scheme 3. Synthesis of conjugated dendrons **6** and **7**.

The reference compound **TThP** (**5**) has been previously isolated following various conditions.^[12] Lindsey's conditions^[15] were eventually retained to attempt performing its synthesis (Scheme 4) and that from the other required precursor: *meso*-tetra(5-iodo-thien-2-yl)porphyrin (**8**). The

former compound **5** was thus synthesized from 2-thienylcarboxaldehyde and pyrrole in the presence of a Lewis acid ($\text{BF}_3 \cdot \text{OEt}_2$), followed by addition of *p*-chloranil as an oxidizer in 32% yield, while its iodo analogue **8** was similarly isolated in 19% yield from (5-iodo-thien-2-yl)carboxaldehyde. Subsequently, from this precursor (**8**) and the dendrons **6** and **7**, the targeted porphyrin systems **3** and **4** were obtained in good yields by Sonogashira coupling reactions^[16] (37% and 40%, resp.).



Scheme 4. Syntheses of the reference *meso*-tetra(thien-2-yl)porphyrin (**5**), of intermediate *meso*-tetra(5-iodothien-2-yl)porphyrin **8** and the corresponding targeted dendrimers **3** and **4**.

¹H NMR Characterization

The new porphyrin-based dendrimers **3** and **4** were characterized by ESI-HRMS, by elemental analysis and by ¹H and ¹³C NMR in CDCl_3 (400 and 500 MHz, resp.). In both cases the ¹H NMR spectrum was very diagnostic (see Figure 1, for compound **3**), revealing four groups of peaks: (i)

eight β -pyrrolic protons at low fields around 9.2 ppm; (ii) aromatic protons belonging to 2,5-thienylene bridges, to phenyl linkers and to fluorenyl endgroups (7.3-8.0 ppm); (iii) aliphatic protons belonging to the methyl and methylene parts of the various *n*-butyl chains (0.5-2.1 ppm), and (iv) two NH protons at high fields around -2.6 ppm.

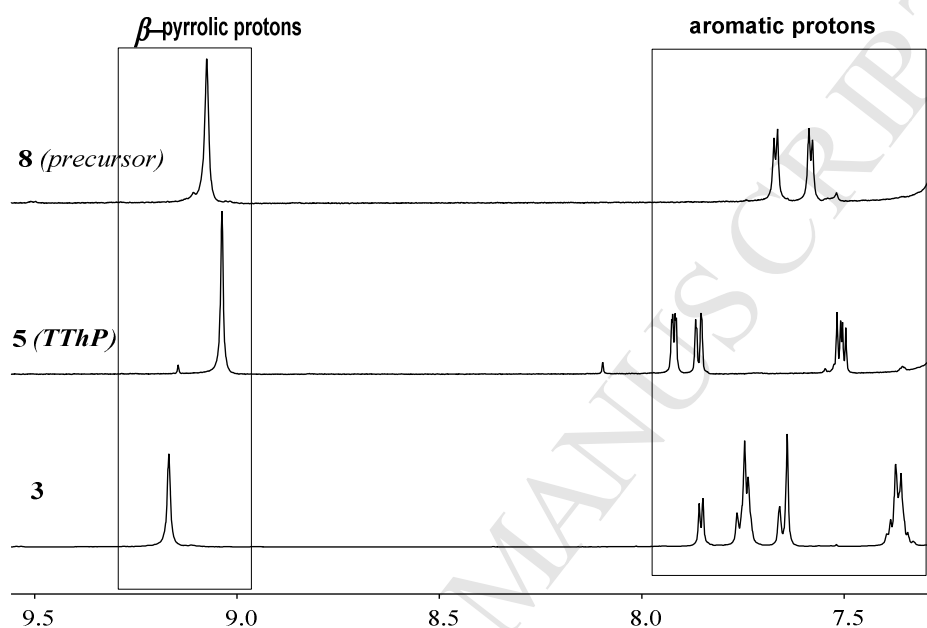


Figure 1. Comparative partial ^1H NMR spectra of the known **TThP** **5** and **8**, and of the new dendrimer **3** in the aromatic region.

Photophysical Properties

UV/Vis absorption and emission spectra were next recorded for the new tetra(thien-2-yl)porphyrin dendrimers **3** and **4** in dichloromethane solutions (Table 1). Then, for comparison, the bare **TThP** as corresponding reference, and molecules with similar structures: the tetraphenylporphyrin analogues **1** and **2**,^[7] were chosen (Scheme 1). This comparison will permit the analysis of the influence of various aromatic groups at *meso*-positions on the optical properties of these derivatives.

Absorption spectra

The dendrimers **3** and **4** present two distinct components in their UV-visible absorption spectra shown in Figure 2 : (i) an intense Soret-band around 435 nm and four Q-bands in the 500-700 nm spectral region, these are typical of free base porphyrin absorptions; (ii) a dendron-based absorption between 250-380 nm, absent for the reference compound **5** possessing no dendrons. In line with the presence of a more extended π -manifold on these porphyrins, the Soret bands for **3** and **4** are slightly red shifted when compared to that of **5** (Figure 2), while this band for **4** is slightly blue-shifted relative to **3** (427 nm vs. 425 nm); probably because the corresponding dendron (**7**) possessing two fluorenyl units in positions 3 and 5 of the phenyl linker is less conjugated with the central porphyrin than dendron **6** with only one fluorenyl group directly appended to the position 5 of the peripheral thienyl linkers. In the Q band region, **5** shows four well defined absorption bands, at energies such that $Q_y(1,0) > Q_y(0,0) > Q_x(1,0) > Q_x(0,0)$. For dendrimer **3**, $Q_y(1,0)$, $Q_y(0,0)$ and $Q_x(0,0)$ are clearly separated, whilst $Q_y(0,0)$ overlaps with $Q_x(1,0)$ and appears as a small shoulder. In contrast for dendrimer **4**, the three $Q_y(1,0)$, $Q_y(0,0)$ and $Q_x(1,0)$ bands seriously overlap, while, as before, $Q_x(0,0)$ appears in a clearly distinct spectral range around 660 nm. Regarding the dendron-based absorptions in the UV region, in line with expectations based on the number of fluorenyl groups incorporating overall four (**3**) or eight (**4**) fluorenyl units, that for **4** is largely stronger than twice that for **3**, and thereby becomes also more intense than the Soret band.

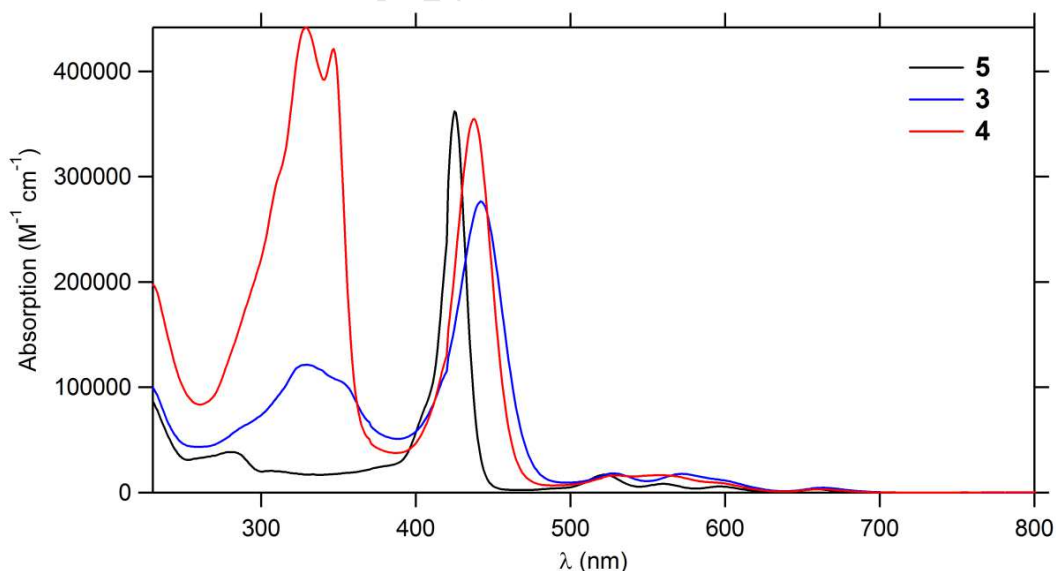


Figure 2. UV-visible absorption spectra of bare **TThP** (**5**), and of the **TThP**-cored dendrimers **3** and **4** in CH_2Cl_2 .

Emission spectra

Upon excitation in their Soret band (425 nm), the compounds **3**, **4** and **5** emit in the red spectral range, between 650 and 820 nm (Fig. 3). Their normalized emission spectra were measured in dichloromethane (HPLC grade). As shown in Figure 3, after excitation, the reference compound **5** presents the two typical Q-emission bands: Q(0,0) and Q(0,1). In contrast, the dendrimer **3** and **4**, present essentially only one broader emission band red-shifted relative to the Q(0,0) band of **5**. The shape of this band for **4**, reveals however two strongly overlapped Q-bands possibly not resolved for **3**. The spectral position of this band among **3** and **4** mirrors that of lowest energy Q bands, thus, that of **3** is also slightly red shifted compared to that of **4**.

The fluorescence quantum yields found for **3**, **4** and **5** (4%, 2.5% and 5%, respectively, see Table 1), albeit very similar, reveal a slight decrease when proceeding from reference **5** to compounds featuring higher generation dendrons at their periphery.

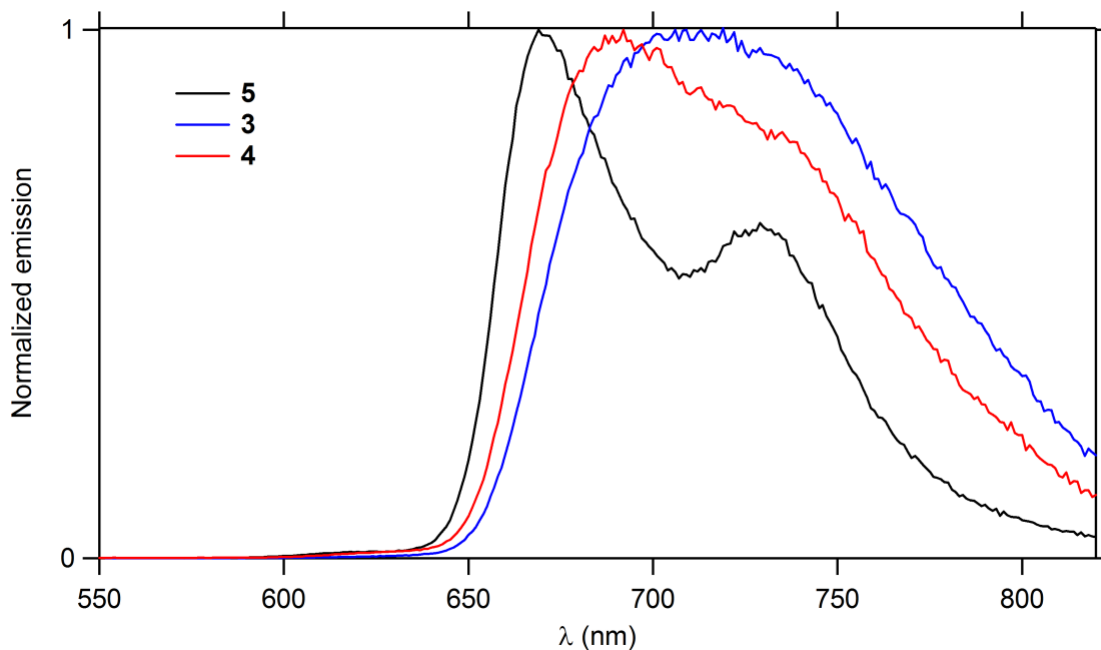


Figure 3. Emission spectra of **3**, **4** and **5** excited in their Soret band in CH₂Cl₂ solution.

Energy transfer from fluorene units to the porphyrin core

The existence of an energy transfer (ET) between the peripheral dendrons and the central tetra(thien-2-yl)porphyrin core was also probed. Thus, dendrimers **3** and **4** were excited at the wavelength corresponding to the dendron absorption (around 320 nm) and the resulting emission spectra were measured for each compound (Fig. 4). The dendrimer **3** displays exclusively red emission, which reveals a very efficient ET from the peripheral dendrons to the porphyrin core. Dendrimer **4** also shows a strong red emission, but a broad and weak residual band around 375 nm is also observed. This suggests that the ET from the peripheral dendrons to the porphyrin core in **4** is less efficient than in **3**, in line with previous findings for related dendrimers.^[18] This suggests that higher generation dendrons are less effective in transferring their energy to the porphyrin, in spite of their larger linear absorption.

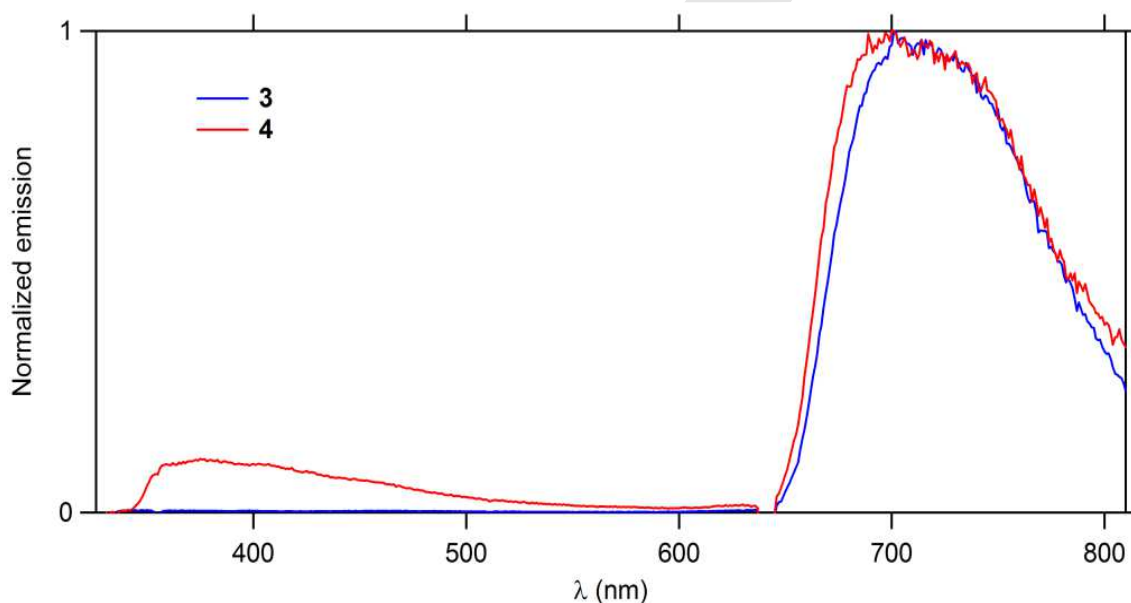


Figure 4. Emission spectra of **3** and **4** upon Excitation at Dendron Absorption ($\lambda_{\text{Ex}} = 320$ nm) in CH_2Cl_2 .

Two-photon absorption

Taking advantage of the fluorescence of these thienyl-cored dendrimers, their two-photon absorption (2PA) cross-sections were determined by two-photon excited fluorescence (TPEF) in dichloromethane, using the experimental protocol described by Xu and Webb.^[20] A fully

quadratic dependence of the fluorescence intensity on the excitation power was observed for each sample at all the wavelengths of the spectra, indicating that the cross-sections determined are only due to 2PA. Compared to the σ_2 of **5** (13 GM at 790 nm), a strong increase in the 2PA cross-sections is observed for both **3** and **4** (see Figure 5 and Table 1). Then, the “generation one; G1” dendrimer **4** exhibits a smaller 2PA than “generation zero; G0” dendrimer **3**. Thus, it appears from this data that the combination of the *meso*-tetra(thien-2-yl)porphyrin core with simple fluorenyl alkynyl groups, like in dendron **6**, is much more efficient for promoting 2PA than that with more extended dendrons such as **7**. This is likely attributable to the lower conjugation between the peripheral fluorenyl groups and the central porphyrin core operative through the 1,3,5-trisubstituted benzene connectors in the latter case, recalling observations previously made with the **TPP**-based analogues **1** and **2**.^[7]

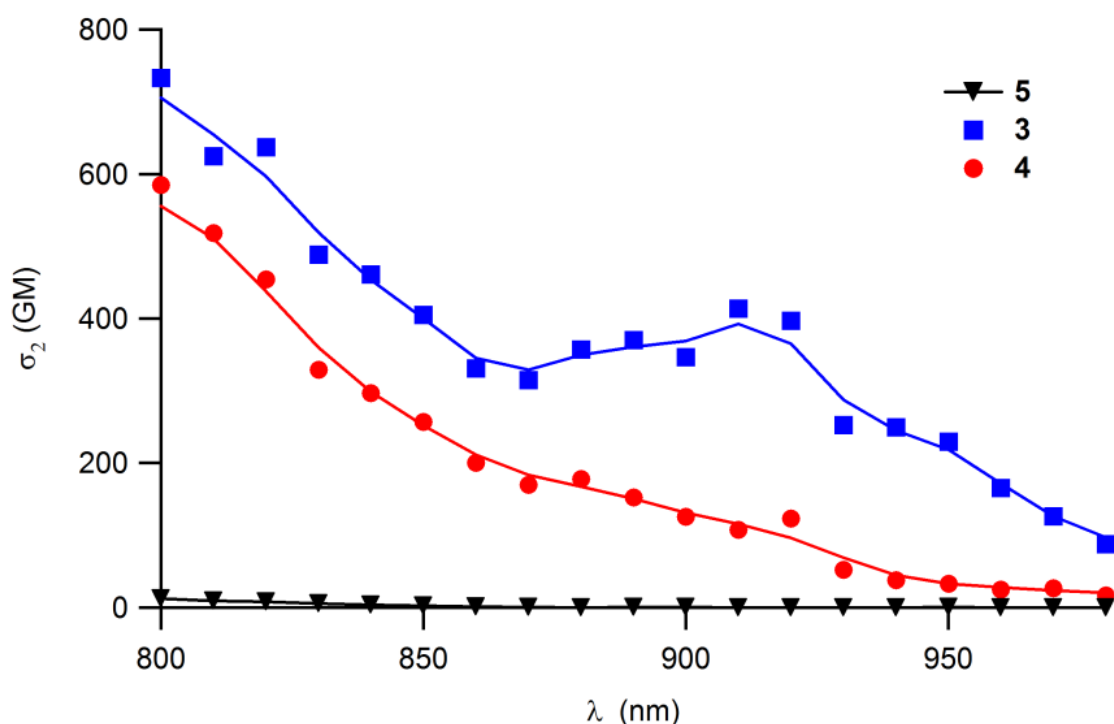


Figure 5. Two-photon absorption spectra for the reference compound **5** and for the new dendrimers **3** and **4** in CH₂Cl₂.

Oxygen sensitization

In the continuation of the comparative study between the new TThP-based dendrimers and the previously studied TPP-based dendrimers, we also wondered about the oxygen-sensitizing capabilities of **3** and **4**. So, the quantum yields of singlet oxygen generation were next determined for these **TThP**-based dendrimers (Table 1) and relevant figures of merit for 2PA-imaging and sensitization were determined (Table 2).

Table 1. Photophysical properties in CH₂Cl₂ of the new *meso*-tetra(thien-2-yl)porphyrin dendrimers **3** and **4**: comparison with the reference compound **5** and with their tetraphenylporphyrin analogues **1** and **2**.

Cpnd	λ_{abs} (dendron) (nm)	λ_{abs} (Soret) (nm)	ϵ_{max} (Soret) (M ⁻¹ cm ⁻¹)	λ_{em} (nm)	Φ_{F} ^a	Φ_{Δ} ^b	σ_2 ^c (GM)
5	-	425	362 000	670, 729	0.05 ^e	0.78 ^f	13
3	330	442	276 400	710	0.04	0.73	730
1 ^d	324	427	-	657, 724	0.20	0.70	380
4	329	438	354 000	690	0.025	0.50	580
2 ^d	330	425	-	655, 721	0.19	0.65	190

^a Fluorescence quantum yield determined relative to **TPP** in toluene ($\Phi_{\text{F}} = 0.11$).

^b Singlet oxygen formation quantum yield determined relative to tetraphenylporphyrin in dichloromethane ($\Phi_{\Delta}[\text{TPP}] = 0.60$).

^c Intrinsic 2PA cross-sections at 800 nm measured by TPEF in the femtosecond regime; a fully quadratic dependence of the fluorescence intensity on the excitation power was observed for each sample at all the wavelengths of the spectra.

^d from ref. [7b]

^e Quantum yield values (Φ_{F}) between 0.0046 and 0.012^[10b,21] have been previously reported for that compound in toluene, and of 0.01^[12] in CHCl₃.

^f Quantum yield values (Φ_{Δ}) of 0.46 have been previously reported for that compound in toluene and of 0.50 for **TPP** in CHCl₃.^[12]

Table 2. Two-photon brightness and two-photon singlet oxygen production of thienyl-cored porphyrin dendrimers **3**, **4**, and comparison with their phenyl-cored porphyrin analogues **1** and **2**.

Compound	$\sigma_2 \cdot \Phi_F$ (GM) ^a	$\sigma_2 \cdot \Phi_\Delta$ (GM) ^b
3	29	533
1 ^c	76	266
4	17	290
2 ^c	36	123

^a Two-photon brightness.

^b Figure of merit of the two-photon excited singlet oxygen production.

^c From Ref [7b].

DISCUSSION

We have synthesized and characterized a new series of thienyl-cored porphyrin dendrimers **3** and **4**. When the linear optical properties of these new derivatives are compared to those of their phenyl analogues **1** and **2**,^[7] the Soret band of the tetra(thien-2-yl) porphyrins are red shifted compared to that of their **TPP**-cored analogues, a feature initially attributed to the inductive effect of the thienyl groups,^[21] but now recognized as being indicative of a better π -conjugation of the peripheral dendrons with the central porphyrin core.^[14,21-22] The next obvious statement is a five-to-six fold decrease in their fluorescence quantum yields, which can be related to the presence of sulfur atoms at their periphery, the latter possibly favoring a non-radiative decay process *via* spin-orbit coupling.^[12,21] As expected, lifetime measurements (Supporting Information) indicate a much faster non radiative decay rate for the thienyl-cored porphyrins compared to their phenyl analogues, in line with a possible heavy atom effect. However, based on this data, the slight decrease in fluorescence quantum yield stated along the thienyl series (following the order: **5** > **4** > **3**) is more attributable to a decrease of the intrinsic fluorescence rate and not to an increase in the rate of the non-radiative process (intersystem crossing and internal conversion). Thus, due to their much lower fluorescence quantum yields, **3** and **4** exhibit

also a significantly lower two-photon brightness ($\sigma_2 \cdot \Phi_F$) than their **TPP** analogues **1** and **2** (Table 2).

Considering the significant 2PA cross-sections previously determined for phenylporphyrins **1** and **2** (Scheme 1),^[7] we have also turned our attention to the 2PA properties of the thienyl analogues **3** and **4** and determined their σ_2 values. Comparison with the former two-photon absorbers (**1** and **2**) reveals a clear improvement of the 2PA properties of the new thienyl derivatives **3** and **4**, respectively. Replacement of the 1,4-phenylene spacer at the periphery of the porphyrin core by a 2,5-thienylene one allows the significant improvement of the 2PA cross-sections (σ_2) of the resulting chromophores. Thus, a twofold enhancement when progressing from **1** to **3** and threefold enhancement when progressing from **2** to **4**, is stated (Table 1). In line with the well-known fact that the 2,5-thienylene spacer allows a better conjugation than the 1,4-phenylene one,^[21,22] this study suggests that improving the conjugation between the porphyrin core and its *meso* substituents is the key factor for improving their 2PA capabilities. Compared to previous approaches that we used to ameliorate the 2PA cross-sections of porphyrin, such as for instance appending electron-rich metal alkynyl substituents in the *para* position at the *meso*-phenyl groups,^[23] the present approach gives more modest improvements in σ_2 but allows the maintenance of a sufficient fluorescence for measuring the 2PA cross-section by TPEF.

The importance of thienyl groups for favoring third-order NLO response over phenyl ones is often attributed to the strong polarizability of the sulfur atom.^[24-26] In this respect, carbon disulfide or other sulfur-rich compounds are often used as standards in 3rd order NLO.^[25, 27] While the increased polarizability of sulfur certainly contributes to enhance the nonlinear refractive properties of a given molecule, we think that its contribution to nonlinear absorption processes such as 2PA is possibly less important here. Rather, and in line with what precedes, we believe that it is the increased conjugation through the 2,5-thienylene linker in **3** and **4** (relative to that previously operative through the 1,4-phenylene in **1** and **2**) that presently constitutes the determining factor. First, compared to *meso*-tetraphenylporphyrin (**TPP**), a reduced steric hindrance was established for the smaller **5**, because the thien-2-yl substituent lacks one *ortho*-

phenyl proton minimizing thereby the steric interaction with the β -pyrrolic protons.^[22, 28] As a consequence, thiophene rings can adopt more coplanar conformations than benzene rings and are more strongly conjugated with the porphyrin core in solution for **5** than for *meso*-tetraphenylporphyrin (**TPP**), inducing the observed bathochromic shift in the absorption spectra of the *meso*-tetra(thien-2-yl)porphyrins relative to their tetraphenyl analogues (Figure 2).^[29] Even if in the solid state, comparable dihedral angles ($\approx 60^\circ$)^[30] between the peripheral rings and the central porphyrin core, have often been observed,^[31] more possibilities to reach conjugated conformations in solution are offered by the 2,5-thiophene groups.^[22,28] Then, besides this purely conformational effect, the lower aromaticity of the thiophene ring relative to that of benzene certainly also contributes to enforce cross-conjugation between its 2 and 5 positions compared to the 1,4-phenylene spacer, as revealed by studies on conducting polyaromatic polymers.^[32]

Finally, in the continuation of our comparative study with **1** and **2**, we also wondered about the oxygen-sensitizing capabilities of new dendrimers **3** and **4**. When compared to those of their **TPP**-cored analogues (Table 2), the **TThP** derivatives **3** and **5** exhibit comparably higher values than those previously determined for **1** and for *meso*-tetraphenylporphyrin (**TPP**; $\Phi_\Delta = 0.60$),^[7] (An opposite trend had been previously reported for these two compounds in toluene; see footnote f in Table 1), the highest quantum yield of singlet oxygen generation remaining to the bare porphyrin **5**. In contrast, **TThP**-cored dendrimer **4** seems slightly less effective for photosensitizing oxygen than the corresponding phenyl one (**2**). At least for the two former compounds, this result can also be related to a faster intersystem crossing favored by the heavy sulfur atoms which enhances population of the first triplet states and therefore stimulate oxygen sensitization. However, the comparably lower efficiency in oxygen sensitization found for the dendrimer **4** relative to **2** suggests that other factors (than just this heavy atom effect) come also in play in the sensitization process. Nevertheless, even for **4**, the quantum yield of singlet oxygen formation (Φ_Δ) remains close to that of **2** (Table 1). As a result, thanks to their maintained singlet oxygen generation quantum yields and quite improved σ_2 values, **3** and **4** exhibit figures of merit for two-photon singlet oxygen production ($\sigma_2 \cdot \Phi_\Delta$) at least twice as large as those of their analogues **1** and **2** (Table 2). Thus, while certainly less attractive than **1** and **2** for 2PA-based

theranostic developments,^[33] due to their diminished fluorescence, *meso*-tetra(thien-2-yl)porphyrins remain nevertheless very interesting chromophores for developing new photosensitizers for two-photon excited photodynamic therapy (2PA-PDT) in the future after suitable functionalization to bio-compatibilize these molecules.

Conclusions

We have synthesized and characterized two new *meso*-tetra(thien-2-yl)porphyrin-based dendrimers **3** and **4**, and the known parent *meso*-tetra(thien-2-yl)porphyrin (**5**) as a reference. These new compounds were obtained via a convergent approach from the corresponding aldehyde-terminated dendrons, **6** and **7** respectively, and pyrrole under Lindsey conditions, the dendritic precursors being themselves synthesized through iterative Sonogashira and Corey-Fuchs procedures. We show that these chromophores feature conjugated arms terminated by 2-fluorenyl groups which act as light harvesting antenna, absorbing light in the UV region before transferring it to the porphyrin core which partially re-emits it by fluorescence, as red light. For this process, we show that they exhibit rather low fluorescence quantum yields (5-3%), similar to the reference compound **5**, but smaller than the corresponding TPP-cored dendrimers (**1** and **2**) and that the energy transfer (ET) process from peripheral dendrons to central porphyrin core is quite efficient, particularly for the smaller (but fully conjugated) dendrimer **3**.

The two-photon absorption (2PA) cross-sections (σ_2) of **3** and **4** were also measured by TPEF, revealing that their σ_2 values were strongly enhanced compared to that of **5**, but also compared to those of their **TPP** analogues **1** and **2**, suggesting that conjugation between the peripheral fluorenyl units and the central porphyrin core is determining for improving the 2PA performances. Finally, we have shown that both **3** and **4** can still photo-sensitize oxygen with a better or comparable efficiency than **1** and **2** when excited in their Soret band, giving rise to far better figures of merit than their **TPP** analogues for two-photon excited photodynamic therapy (2PA-PDT). Given the rather facile access to this new class of dendrimeric porphyrins and considering the relatively large versatility of the synthesis, this work opens very attractive perspectives for designing new photosensitizers for 2PA-based PDT.

EXPERIMENTAL SECTION

General

Unless otherwise stated, all solvents used in reactions were distilled using common purification protocols,^[34] except DMF and ⁱPr₂NH which were dried on molecular sieves (3 Å). Compounds were purified by chromatography on silica gel using different mixtures of eluents as specified. ¹H and ¹³C NMR spectra were recorded on BRUKER Ascend 400 and 500 at 298 K. The chemical shifts are referenced to internal tetramethylsilane. High-resolution mass spectra were recorded on different spectrometers: a Bruker MicrOTOF-Q II, a Thermo Fisher Scientific Q-Exactive in ESI positive mode and a Bruker Ultraflex III MALDI Spectrometer at CRMPO (Centre Regional de Mesures Physiques de l'Ouest) in Rennes. Reagents were purchased from commercial suppliers and used as received.

Synthesis of Porphyrin Dendrimers

The dendrons **6** and **7** were synthesized as described earlier by our group,^[7,18-19] and the intermediate 5-iodo-*tetrathienyl*porphyrin (**8**) as reported.^[30]

Meso-(2-((9, 9-dibutyl-fluoren-2-yl)ethynyl)-thienyl)porphyrin (3): In a Schlenk tube, 5-iodo-*tetrathienyl*porphyrin (**5**) (117 mg, 0.1 mmol, 1 equiv.), the dendron **6** (139 mg, 0.5 mmol, 5 equiv.), Pd(PPh₃)₂Cl₂ (1.9 mg, 0.45 mmol, 0.6% equiv.) and CuI (1 mg, 0.5 mmol, 0.3% equiv.) were stirred in a mixture of DMF (4 mL) and ⁱPr₂NH (4 mL) under argon, following the previously described protocole.^[36b] The system was degassed by freeze-pump-thaw twice and heated for 48 h at 95 °C. After evaporation of volatiles, the residue was purified by silica chromatography (heptane /CH₂Cl₂ = 5:1), and recrystallized from THF providing the title compound as a dark violet powder (72 mg, 37% yield). ¹H NMR (400 MHz, CDCl₃, ppm): δ = 9.17 (s, 8H, H_{β-Pyr}), 7.85 (d, 4H, *J* = 3.6 Hz, H_{Th}), 7.76-7.74 (m, 12H, H_{Flu}), 7.65 (m, 8H, H_{Th} + H_{Flu}), 7.40-7.33 (m, 12H, H_{Flu}), 2.09-1.98 (m, 16H, H_{Bu}), 1.17-1.08 (m, 16H, H_{Bu}), 0.72 (t, 24H, *J* = 7.2 Hz, H_{Bu}), 0.68-0.54 (m, 16H, H_{Bu}), -2.58 ppm (s, 2H, NH); ¹³C NMR (100 MHz, CDCl₃, ppm): δ = 151.1, 150.9, 144.0, 141.9, 140.4, 134.1, 131.1, 130.6, 127.6, 126.9, 126.5, 126.0,

122.9, 121.0, 120.1, 119.8, 111.9, 110.0, 95.7, 82.5, 55.2, 40.2, 31.3, 29.7, 26.0, 23.1, 13.8 ppm. UV-vis [CH_2Cl_2 , nm]: $\lambda_{\text{max}} = 442, 529, 570, 595, 662$. HRMS-ESI for $\text{C}_{128}\text{H}_{118}\text{N}_4\text{S}_4$: $m/z = 1839.8266$ [$\text{M}+\text{H}$] $^+$ (calcd: 1839.8312); $m/z = 920.4184$ [$\text{M}+2\text{H}$] $^{2+}$ (calcd: 920.4192). Anal. Calcd (%) for $\text{C}_{128}\text{H}_{118}\text{N}_4\text{S}_4 \cdot 2\text{THF}$: C 82.30; H 6.81; N 2.82 Found: C 82.46; H 7.00; N 2.34.

Meso-(2-((3,5-bis((9,9-dibutyl-fluoren-2-yl)ethynyl)phenyl)ethynyl)thienyl)porphyrin (4): In a Schlenk tube, of 5-iodo-tetrathienylporphyrin (**5**) (36 mg, 0.03 mmol, 1 equiv.), dendron **7** (100 mg, 0.1 mmol, 4.5 equiv.), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (1 mg, 0.1 mmol, 0.6% equiv.) and CuI (0.1 mg, 0.1 mmol, 0.3% equiv.) were added in a mixture of DMF (3 mL) and $^i\text{Pr}_2\text{NH}$ (3 mL) under argon (see above). The system was degassed by freeze-pump-thaw twice and heated for 48 h at 95 °C. After evaporation of volatiles, the dark residue was purified by silica chromatography (heptane/THF = 8:1), providing the title compound as a dark violet powder (41 mg, 40% yield). ^1H NMR (400 MHz, CDCl_3 , ppm): $\delta = 9.18$ (s, 8H, $\text{H}_{\beta\text{-Pyr}}$), 7.87 (d, 4H, $J = 3.2$ Hz, H_{Th}), 7.82 (m, 8H, $\text{H}_{\text{Flu}} + \text{H}_{\text{Ph}}$), 7.76 (d, 4H, $J = 3.2$ Hz, H_{Th}), 7.71 (d, 20H, $J = 7.2$ Hz, $\text{H}_{\text{Flu}} + \text{H}_{\text{Ph}}$), 7.56-7.53 (m, 14H, H_{Flu}), 7.35-7.34 (m, 26H, H_{Flu}), 2.00 (m, 32H, H_{Bu}), 1.14-1.06 (m, 32H, H_{Bu}), 0.69 (t, 48H, $J = 7.2$ Hz, H_{Bu}), 0.65-0.54 (m, 32H, H_{Bu}), -2.59 (s, 2H, NH); ^{13}C NMR (100 MHz, CDCl_3 , ppm): $\delta = 151.1, 150.9, 144.6, 141.9, 140.4, 134.2, 133.7, 131.8, 130.7, 127.7, 126.9, 126.2, 125.8, 124.5, 123.7, 123.0, 120.9, 120.1, 119.7, 111.8, 93.1, 92.0, 87.9, 83.3, 55.1, 40.2, 31.4, 29.8, 26.0, 23.1, 13.9$ ppm. UV-vis [CH_2Cl_2 , nm]: $\lambda_{\text{max}}(\epsilon_{\text{max}} \text{ in } 10^3 \text{ M}^{-1}\text{cm}^{-1}) = 438, 530, 560, 594, 660$, MS (Maldi-TOF) for $\text{C}_{252}\text{H}_{230}\text{N}_4\text{S}_4$: $m/z = 3439.658$ [$\text{M}+\text{H}$] $^+$ (calcd: 3439.69979). Anal. Calcd (%) for $\text{C}_{252}\text{H}_{230}\text{N}_4\text{S}_4$: C 87.91; H 6.73; N 1.63. Found: C 87.70; H 6.89; N 1.21.

Spectroscopic Measurements

~~All photophysical measurements 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. Steady state fluorescence measurements were performed on dilute~~

~~solutions (ca. 10^{-6} M, optical density < 0.1) contained in standard 1 cm quartz cuvettes using an Edinburgh Instrument (FLS920) spectrometer in photon counting mode. Fully corrected emission spectra were obtained, for each compound, after excitation at the wavelength of the absorption maximum, with $A_{\lambda_{\text{exc}}} < 0.1$ to minimize internal absorption. Fluorescence quantum yields were measured according to literature procedures.^[35]~~

~~Two-Photon Absorption Experiments~~

~~To span the 790–980 nm range, a Nd:YLF pumped Ti:sapphire oscillator (Chameleon Ultra, Coherent) was used generating 140 fs pulses at a 80 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/mm². The fluorescence from the sample is collected in epifluorescence mode, through the microscope objective, and reflected by a dichroic mirror (Chroma Technology Corporation, USA; ‘red’ filter set: 780dxerr). 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; ‘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&W Tek, 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 (TPEF) cross sections ($\sigma_2 \Phi_f$) and the fluorescence emission quantum yield (Φ_f). TPEF 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^[20] and the appropriate solvent-related~~

refractive index corrections.^[36] ~~The quadratic dependence of the fluorescence intensity on the excitation power was checked for each sample and all wavelengths.~~

~~Measurement of Singlet Oxygen Quantum Yields (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 ($\Phi_{\Delta}[\text{TPP}] = 0.60$) and were estimated from $^1\text{O}_2$ luminescence at 1272 nm.~~

■ ASSOCIATED CONTENT

Supporting Informations. ^1H NMR and ^{13}C NMR of all new compounds. Two-photon absorption spectra of **3**, **4** and **5** and comparison with their one-photon absorption spectra.

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- *Two new meso-tetra(thien-2-yl)porphyrins **3** and **4** have been obtained and characterized.
- *The two-photon absorption (2PA) cross-sections (σ_2) of **3** and **4** were measured by TPEF, revealing strongly enhanced σ_2
- *Replacement of the 1,4-phenylene spacer at the periphery of the porphyrin core by a 2,5-thienylene one allows improvement of the 2PA cross-sections
- *Porphyrins **3** and **4** are efficient Two-photon Photosensitizers for Singlet Oxygen Generation