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Amphiphilic *meso*(sulfonate ester fluoroaryl)porphyrins: refining the substituents of porphyrin derivatives for phototherapy and diagnostics

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ABSTRACT

A set of amphiphilic fluorinated porphyrins appended with sulfonate ester groups were synthesized and fully characterized. The reaction proceeds efficiently, with high yields, with an improved methodology. Their potential use as imaging and phototherapeutic agents was assessed measuring relevant photophysical properties. It is shown that these porphyrins have good photostability, long triplet lifetimes (between 47 μs and 102 μs), high singlet oxygen quantum yields ($0.74 \leq FD \leq 1.00$), low fluorescence quantum yields (<0.04) and sharp 19F NMR peaks. The data on the new *meso*(sulfonate ester fluoroaryl) porphyrins illustrate the potential of perfluorinated sulfonate esters to improve physical properties relevant for cancer imaging and photodynamic therapy.

1. Introduction

Porphyrins are useful in many medical and industrial applications, such as phototherapy, photodiagnosis, photocatalysis, solar energy conversion, and optoelectronics.[1–3] The properties of the triplet state of these molecules are particularly important because it acts as the immediate precursor of reactive oxygen species (ROS). Another key factor in the above mentioned application is strong absorption of light in the visible region of the spectrum.[3,4]

Photodynamic therapy (PDT) is a selective cancer phototherapy under active investigation by researchers both in fundamental science and in the clinic.[5] Cancer PDT involves administration of a photosensitizer, which preferentially localizes in the tumors, followed by irradiation with visible or near-infrared light. The photosensitizer absorbs light and in the presence of molecular oxygen transfers energy to oxygen producing ROS, especially singlet oxygen, which are responsible for selective tumor destruction, tumor-associated vascular damage, and activation of anti-tumor immune responses.[6,7]

Molecules that could combine properties adequate for both therapy and diagnostics, when associated with clinically relevant tools, are particularly appealing.[1] Porphyrin-based photosensitizers were found to accumulate readily in tumors and have been extensively studied in this area because of their high vascular permeability, as well as of their affinity for proliferating endothelium, and the lack of lymphatic drainage in tumors.[8] There is also evidence that the amphiphilic character of the photosensitizer is an important factor.[9,10] Several approaches have been proposed in order to modify the lipophilicity of the photosensitizer.[11] Besides the chemical and photophysical properties of such designed sensitizers, it is interesting to see if they can be imaged in neoplastic tissue. Fluorinated derivatives are particularly attractive in this respect, as the ^{19}F nucleus is an interesting probe for nuclear magnetic resonance (NMR) imaging. Examples of ^{19}F NMR imaging of photosensitizer or other drugs in vivo have already been reported and were recently reviewed.[12] Fluorine atoms have been introduced into biologically active compounds to modulate their physicochemical and pharmacokinetic properties and improve their potency with respect to biomedical aplications.[13,14] Moreover, fluorescent sensitizers may also be used as diagnostic agents in photodetection of cancer.[1] These properties suggest that the development of fluorinated compounds for use as PDT sensitizers and

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^{19}F magnetic resonance imaging probes can be relevant contribution to this field.

We recently reported the synthesis of *meso*-halogenated sulfonated or sulfonamide porphyrins[15–17] and their dihydro[18] and tetrahydro[19–21] analogues. We have shown that they have a low toxicity in the dark, high phototoxicity and a tendency to accumulate in a range of cancer cells. The most promising candidates for new PDT-agents are the sulfonamide substituted bacteriochlorins, which produce high yields of singlet oxygen, superoxide ions and hydroxyl radicals,[22–24] extending the average tumor growth delay by 44 days, with respect to a control group in DBA mice bearing S91 melanoma tumors.[25] We have also shown that the fluorinated porphyrins belonging to this series of compounds have relatively long singlet lifetimes and sizeable fluorescence quantum yields.

In this paper we offer additional strategies to incorporate fluorine atoms in related porphyrins. We describe a simple and efficient synthetic method to tune the amphiphilicity of sulfonate ester porphyrins by selecting the type and number of fluorine atoms as well as the length of the alkyl sulfonate ester chains. We also describe the photophysical properties of the new sulfonate ester fluorinated porphyrins as well as their ^{19}F NMR spectra in order to evaluate their potential as PDT sensitizers and/or ^{19}F NMR probes.

2. Results and discussion

2.1. Synthesis

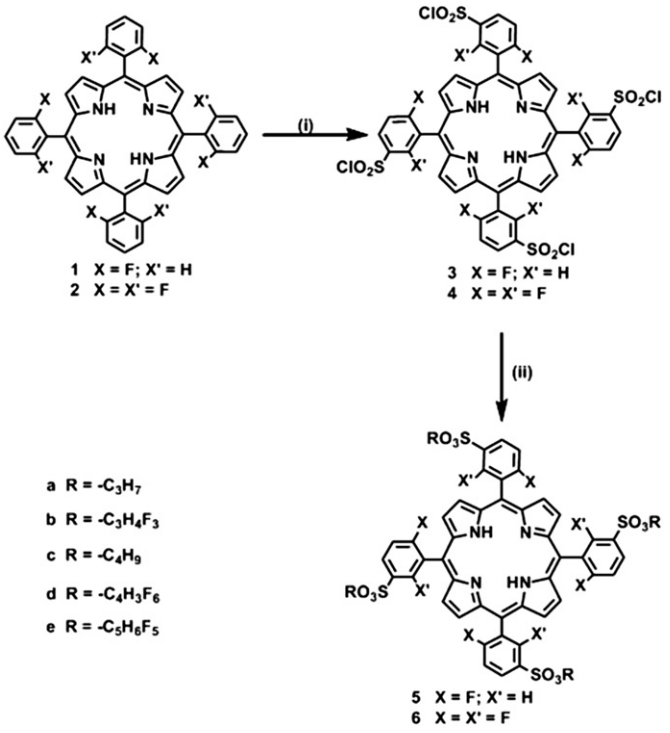
The 5,10,15,20-tetrakis(2-fluorophenyl)porphyrin **1** and 5,10,15,20-tetrakis(2,6-difluorophenyl)porphyrin **2** were prepared by one-pot condensation of pyrrole with the corresponding fluorinated benzaldehyde using acetic acid/nitrobenzene as solvent and oxidant, accordingly to our previously described methodology.[16,26,27] Using this synthetic approach, crystals with high purity from fluorinated porphyrins **1** and **2** were obtained by direct crystallization from the reaction medium, with 20% and 10%, respectively, in good agreement with literature.[16,26,27] In order to synthesize the desired fluorinated amphiphilic porphyrins, containing sulfonate ester appendices, the derivatization of **1** and **2** into the corresponding chlorosulfonated porphyrins was achieved by mixing the porphyrins with an excess of chlorosulfonic acid.

So, in a typical reaction, **1** was mixed with chlorosulfonic acid at room temperature and the reaction was maintained at 60 °C, for 1.5 h. After cooling to room temperature, dichloromethane was added and the acid was removed via continuous extraction with water. After evaporation of the solvent the 5,10,15,20-tetrakis(2-fluoro-5-chlorosulfophenyl)porphyrin **3** was obtained with 97% yield. The 5,10,15,20-tetrakis(2,6-difluoro-3-chlorosulfophenyl) porphyrin **4** was obtained in 91% yield in a similar procedure, by reaction of porphyrin **2**, chlorosulfonic acid at 100 °C for 2 h.

The chlorosulfonic acid group is susceptible to react with alcohols, in basic conditions.[28,29] In a typical experiment, the chlorosulfonyl porphyrin derivative was dissolved in dry THF and slowly added to a solution of the desired alcohol (40 equiv) in the presence of a concentrated aqueous solution of NaOH (8 equiv) in a small amount of THF. The reaction was kept at room temperature for 1 h until full consumption of the starting material was observed.

The corresponding sulfonate esters (**5a**–**e**; **6a**–**e**, see Scheme 1) were obtained, after work-up, in good yields (78–96%), independently of the alcohol used (see Table 1). This synthetic strategy allowed us not only to prepare a family of amphiphilic porphyrins, containing several sulfonate ester appendices, but also the inclusion of one or more fluorine atoms in the porphyrin structure.

As expected, all ^{19}F NMR aromatic signals appeared as multiplets ($\delta \approx 90.7$–99.8) not only due to the coupling with adjacent protons, but also due to the presence of a mixture of atropisomers



Scheme 1. Reagents and conditions: (i) **1**, HSO_3Cl, 60 °C, 1.5 h, 97%; **2**, HSO_3Cl, 100 °C, 2 h, 91%; (ii) alcohol, NaOH (aq), THF, rt, 2 h, yields greater than 75%.

Table 1
Yields of *meso*(sulfonate ester fluoroaryl)porphyrins (**5a**–**e**; **6a**–**e**)

Alcohol	$FP(SO_2Cl)_4$ **5** Derivatives	Yield%	$F_2P(SO_2Cl)_4$ **6** Derivatives	Yield%
HOC_3H_7	**a**-FPC_3H_7	94	**a**-$F_2PC_3H_7$	78
$HOC_3H_4F_3$	**b**-$FPC_3H_4F_3$	96	**b**-$F_2PC_3H_4F_3$	85
HOC_4H_9	**c**-FPC_4H_9	89	**c**-$F_2PC_4H_9$	82
$HOC_4H_3F_6$	**d**-$FPC_4H_3F_6$	84	**d**-$F_2PC_4H_3F_6$	81
$OHC_5H_6F_5$	**e**-$FPC_5H_6F_5$	95	**e**-$F_2PC_5H_6F_5$	82

in all the compounds. However, it should be emphasized that the compounds **5b** and **6b** possess an extra narrow intense peak at $\delta \approx 63.8$ and **5d** and **6d** at $\delta \approx 73.0$, due to the presence of a CF_3 fragment in the porphyrin sulfonate ester appendices, which allows them to be potential probes for ^{19}F MRI. These fluorinated amphiphilic compounds may find use as ^{19}F MRI probes for cancer detection because the fluorine atom has 100% NMR active isotope with intrinsic high sensitivity in biological systems,[12] and it is well established that porphyrins preferentially accumulate in tumors.[8]

2.2. Spectroscopic characterization of sulfonate ester substituted fluorinated porphyrins

The ground state absorption spectrum of the representative porphyrin **6d**-$F_2PC_4H_3F_6$, recorded at room temperature in ethanol is presented in Fig. 1. The spectrum shows the characteristic bands from free base porphyrins with the D_2h symmetry, described by a four orbitals model.[30] The intense Soret band is observed around 410 nm and four bands between 500 and 650 nm are assigned to the (0,0) and (1,0) vibronic progressions of the Q_x and Q_y bands, Table 2. The longest-wavelength absorption bands at 641–649 nm are crucial for PDT process, because only red light has sufficient tissue penetration ability. Using measured absorbance for various

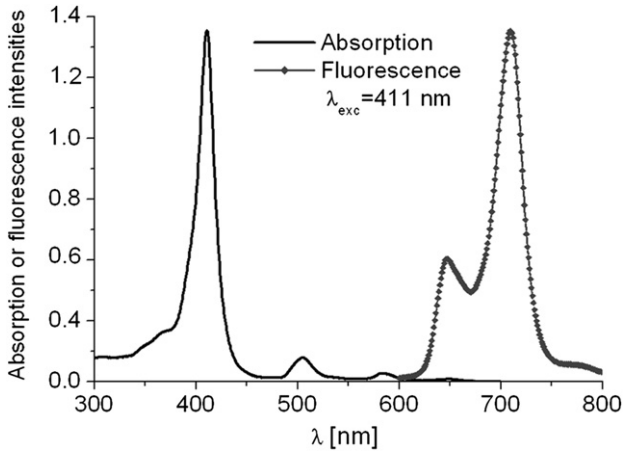


Fig. 1. Electronic absorption and fluorescence spectra of $F_2PC_4H_3F_6$ (**6d**) in ethanol, at room temperature. The fluorescence was obtained with excitation at 411 nm.

Table 2
Absorption and fluorescence properties of fluorinated porphyrins in ethanol

	Absorption					Fluorescence	
	λ (nm), ε (mM^{-1} cm^{-1})					λ (nm)	Φ_F[a]
	B	Q_y (0–1)	Q_y (0–0)	Q_x (0–1)	Q_x (0–0)	(0–0) (1–0)	
6b-$F_2PC_3H_4F_3$	410	505	535	583	648.5	656;	0.039
	208	13.7	3.27	4.53	1.6	709	
5d-$FPC_4H_3F_6$	412.5	508	538.5	584.5	641.5	648;	0.032
	1000	18.2	3.79	5.97	1.02	712	
5a-FPC_3H_7	412	508	539	585	641.5	646;	0.031
	248	12.2	2.89	3.98	0.84	712	
6d-$F_2PC_4H_3F_6$	410	505	536	583	649	647;	0.030
	286	19.4	3.96	6.73	2.18	709	
ClPOH[b]	413	513	549	581	633	638;	0.008
	160	7	1.2	2.5	0.5	698	

[a] The error associated with Φ_F is 0.001.
[b] From Ref. 20 determined in PBS, room temperature.

concentrations of this series of porphyrins, the molar absorption coefficients were determined from Beer's law. Their absorption band maxima and corresponding molar absorption coefficients are presented in Table 2. Aggregation does not seem to occur in the mM concentration range, because as the concentrations were increased, the longest wavelength absorption band was not displaced to longer wavelengths, and its bandwidth at half height did not increase. Among the studied porphyrins, **6d**-$F_2PC_4H_3F_6$ has the most promising spectroscopic properties. The Q_x band of this porphyrin derivative is four times more intense than that of published sulfonated and chlorinated porphyrin (ClPOH)[15] and is further displaced to the red (633→649 nm). Considering that ClPOH was shown to be efficient photosensitizer in vitro against different cancer cells,[15] we expect that the sulfonate ester substituents studied in this work may increase the phototoxicity of the sensitizers.

The fluorescence spectrum of **6d**-$F_2PC_4H_3F_6$ shown in Fig. 1 is representative of the fluorescence of these porphyrins. The fluorescence excitation spectra of all the compounds correspond well with their absorption spectra and confirm the purity and non-aggregation of the samples. Earlier studies with other halogenated porphyrins established that the presence of bulky *ortho*-chloro groups reduce the tendency of porphyrins to aggregation.[14] The fluorescence quantum yields of these porphyrins were also determined according to published procedures[22] and calculated relatively to that of TPP (Φ_F=0.11). All fluorescence data are given in Table 2.

2.3. Photophysical properties of sulfonate ester substituted fluorinated porphyrins

The kinetics of the transient absorption changes (ΔA) of the porphyrins in solution was determined by laser flash photolysis. The spectra were constructed from fitting data from the sets of the decay curves, collected with 10 nm intervals. The transient decay times in the presence of oxygen are independent from the monitoring wavelength and are typical of triplet states quantitatively transferring energy to molecular oxygen. Triplet lifetimes are presented in Table 3. In argon-saturated ethanol solution, the decays remain monoexponential (inset in Fig. 2) and lifetimes increase up to 100 μs. Transient absorption spectrum of **5d**-$FPC_4H_3F_6$ in ethanol is shown in Fig. 2. The strong negative absorbance change is due to the bleaching of the ground-state absorption and the clearly defined pseudoisosbestic points reflect the fact that all molecules return to this ground state, which also means that photodegradation is negligible. The rate constant of energy transfer from the triplet state of the photosensitizer to molecular oxygen (k_q) can be calculated from the triplet lifetimes in the absence (nitrogen saturated solution), τ_T^0, and in the presence of oxygen (air saturated solution), τ_T, using the relationship:

Table 3
Triplet state lifetimes in the presence and absence of oxygen determined in ethanol, with respective oxygen quenching rate constants at room temperature and singlet oxygen quantum yields for selected porphyrins

Porphyrin	τ_T^0 [μs]	$\tau_{T,air}$ [ns]	k_q ($\times10^9$)[M^{-1} s^{-1}]	Φ_Δ
6b-$F_2PC_3H_4F_3$	92±41	385±141	1.23±0.45	0.74±0.03
5d-$FPC_4H_3F_6$	102±36	361±130	1.31±0.47	0.81±0.02
5a-FPC_3H_7	47±6	337±21	1.40±0.09	0.74±0.02
6d-$F_2PC_4H_3F_6$	80±34	343±15	1.38±0.06	1.00±0.04

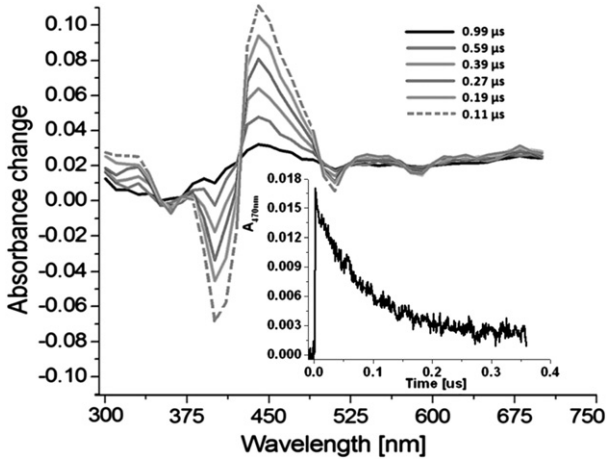


Fig. 2. Time-resolved transient absorption spectra of **5d**-$FPC_4H_3F_6$ in ethanol, measured by laser flash photolysis, 20 °C, λ_{exc}=355 nm. Inset: decay curve of the triplet state signal of the $FPC_4H_3F_6$ (**5d**) in the absence of oxygen.

$$k_q = \left(1/\tau_T - 1/\tau_T^0\right)/[O_2]$$

and the oxygen concentration in ethanol, $[O_2]=2.1\times10^{-3}$ M.[31] In fact, $\tau_T^0 >> \tau_T$ and the actual value of τ_T^0 is irrelevant to calculate the value of k_q reported in Table 3.

Spin statistics require that k_q should be 1/9 of the diffusion rate constant, k_{diff}. The value of k_{diff} was estimated from the fluorescence intensity of 5,10,15,20-tetrakis(4-sulfophenyl)porphyrin (PSO_3H) in the absence and in the presence of oxygen, its lifetime in the absence of oxygen and the oxygen concentration in ethanol.

Porphyrins triplets are quenched with a rate constants k_q value in the range $1.2–1.4\times10^9\ M^{-1}\ s^{-1}$, which is similar to $k_q=1.4\times10^9\ M^{-1}\ s^{-1}$ determined for TPP.[22] Taking into account that $k_{diff}=5.4\times10^9\ M^{-1}\ s^{-1}$ in ethanol at 20 °C, our data are in good agreement with literature values for similar systems.[32] The values of k_q reported in Table 3 indeed approach be 1/9 k_{diff}, as in related compounds.[15,20]

The internal heavy-atom effect assists halogenated porphyrins, to generate triplet states with nearly unit quantum yields.[25] The low fluorescence quantum yields obtained for all the fluorinated porphyrins reported in this work suggests that intersystems crossing to the triplet state are also a major singlet deactivation pathway for these molecules. The triplet state of the photosensitizer is the precursor of reactive oxygen species, namely singlet oxygen. Following the excitation of the porphyrins at 355 nm, we detected a species emitting at 1270 nm with a lifetime of 13–18 μs. These values are in good agreement with lifetime of singlet oxygen phosphorescence in the ethanol, which is 15 μs,[32] confirming the origin of the emission measured. Also, the shape of emission spectra taken between 1250 and 1300 nm (Fig. 3) corresponds to that of singlet oxygen. Singlet oxygen quantum yields (Φ_Δ) were obtained by comparing the intensity of singlet oxygen emission at 1270 nm in an air-equilibrated sample containing a given sensitizer against the intensity obtained from an optically matched sample containing a reference sensitizer. We used phenalenone as a reference and used its literature value for the singlet oxygen quantum yield in ethanol, 0.95.[33] Table 3 presents the singlet oxygen quantum yields (Φ_Δ) measured in ethanol according to the procedure recently recommended by us, that makes use of the linear dependence between singlet oxygen emission intensity and the energy of the exciting laser pulse at low laser energies.[22] The reason why the lines presented in Fig. 3 are not crossing through zero is probably related with scatter light heating the powermeter, which is not coming from the laser bean. Any scattered or ambient light can change the 0 of the powermeter. The error associated with Φ_Δ is 4% or less.

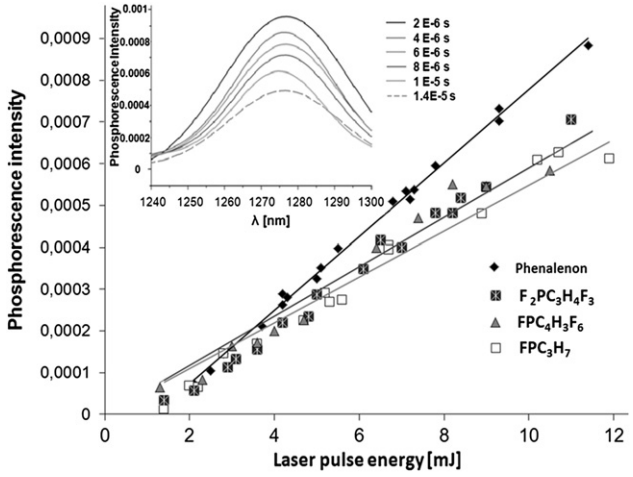


Fig. 3. 1270 nm emission intensity as a function of the laser energy. Inset: singlet molecular oxygen emission intensity as a function of wavelength for **5a**-FPC_3H_7.

It is especially interesting that the porphyrin with the highest number of fluorine atoms, **6d**-$F_2PC_4H_3F_6$, is capable of generating singlet molecular oxygen with unit quantum yield. In fact, increasing the number of fluorine atoms increases Φ_Δ but does not change k_q appreciably. This suggests that the increase in Φ_Δ is probably related with an increase in triplet quantum yield and, therefore, to a heavy-atom effect. The introduction of fluorine atoms in sulfonate ester substituents of tetraphenylporphyrin derivatives improves photophysical and photochemical properties relevant for PDT, with respect to the properties of other halogenated porphyrins that already showed relevant efficacy.[15,22] Photosensitizers with such substituents are worth further investigations for PDT and NMR imaging.

3. Conclusions

Amphiphilic *meso*(sulfonate ester fluoroaryl)porphyrins can be readily synthesized from economical starting materials. Their absorption bands at ~649 nm show values of ε of porphyrins with perfluorinated sulfonate esters representing a four fold improvement over those of photodynamically active sulfonated porphyrins.[15] Moreover, the additional fluorine atoms contribute to increase singlet oxygen quantum yields via the internal heavy-atom effect in the intersystem crossing from the singlet to the triplet state of the photosensitizers. The ^{19}F nucleus is also potentially useful as a probe for in vivo imaging with NMR spectroscopy, particularly in compounds **5b** and **6b** that possess a CF_3 group in the sulfonate ester appendices. Among the compounds studied in this work, **6d**-$F_2PC_4H_3F_6$ has the most relevant photophysical properties and the highest singlet oxygen quantum yield for PDT, which suggests that perfluorinated sulfonate esters may help improve the PDT efficacy of tetraphenylporphyrin derivatives.

4. Experimental

4.1. Instrumentation

^1H- and ^{19}F NMR spectra were obtained using a Bruker Avance III 400 MHz spectrometer and 376.5 MHz, respectively. The chemical shifts are given in parts per million (ppm) relative to tetramethylsilane at δ 0.00 ppm for proton spectra and relative to trifluoroacetic acid at δ 0.00 ppm for ^{19}F spectra. Mass spectra ESI-FIA-TOF were acquired using a Micromass Q-TOF2 spectrometer containing a Z-spray source, an electrospray probe and an injection syringe. Flash column chromatography was performed with silica gel grade 60, 70–230 mesh. Purity of the compounds was established by HPLC and is greater than 95% in all cases. The HPLC analysis were obtained in a Agilent 1100 series, equipped with a UV–visible and DAD detector Agilent 1100 series, using a Agilent Technologies Zorbax ODS, 5 μm, 4.6×250 mm and gradient acetonitrile/water as eluent, depending on the compound.

4.2. Spectroscopic and photophysical measurements

Absorption and fluorescence spectra were measured by standard techniques using Shimadzu UV-2100 and SPEX Fluoromax 3.22 spectrophotometers, respectively. The reference employed for fluorescence quantum yield measurements was TPP (Φ_F=0.11). Time-resolved singlet oxygen phosphorescence measurements were made with a modification of an Applied Photophysics LKS.60 flash photolysis spectrometer, and using the third harmonic of a Nd:YAG laser (Spectra-Physics Quanta Ray GCR 130, 5–6 ns FWHM) for excitation and HP Infinium (500 MHz, 1 GSa/s) or Tektronix DPO 7254 (2.5 GHz, 40 GSa/s) oscilloscopes. Singlet oxygen emission was detected using a Hamamatsu R5509-42 photomultiplier, cooled to 193 K in a liquid nitrogen chamber (Products for Research, model PC176TSCE005). Interposition of a Melles Griot cold mirror (03MCS005), that reflects more than 99% of the incident light in the 400–700 nm range, and of a Scotch RG665 filter, eliminated from the infrared signal all harmonic contributions of the sensitizer emission in the 400–900 nm range. A 600 line diffraction grating was mounted in place of a standard one to improve spectral resolution and sensitivity in the NIR. This

equipment allows for spectral identification of the singlet oxygen phosphorescence and measurement of singlet oxygen lifetime in the nanosecond and microsecond ranges. Fitting to the experimental data the decays of the singlet molecular oxygen emissions (I_{Δ}^{0}) measured in ethanol for the reference (phenalenone, Φ_{Δ}=0.95±0.02) and for porphyrins, at a given laser intensity, we obtain a relation between emission intensities that is identical to the relation between the singlet molecular oxygen quantum yields. The actual singlet oxygen quantum yields were obtained from the linear dependence between I_{Δ}^{0} and the energy of the laser pulse E_{hv}, for the range of laser energies where a good linear relationship was found. Good linearity was observed up to 12 mJ/pulse with fluorinated porphyrins.

4.3. General porphyrin synthesis

The synthesis of porphyrins **1** and **2** was carried out using the nitrobenzene method[16,26,27] prepared by the condensation of the desired fluorinated arylaldehyde (43 mmol) with pyrrole (3 mL, 43 mmol) in a mixture of acetic acid (140 mL, 2.45 mol) and nitrobenzene (70 mL, 0.68 mol) at 120 °C. The solution was cooled to room temperature and 50 mL of methanol was added to promote precipitation. The crystals of the porphyrins were filtered off, washed with methanol and dried. By this method, crystals of porphyrins were obtained without further purification procedures. Porphyrins **1** and **2** were obtained with yields of 20% and 10%, respectively. Their identity was confirmed by NMR, FAB and microanalysis, with good agreement with literature data.[16,26,27]

4.4. General procedure for porphyrin chlorosulfonation

Chlorosulfonation of the fluorinated porphyrins was carried out according to a method previously developed.[19] The required porphyrin (200 mg) and chlorosulfonic acid (10 mL, 150 mmol) were stirred at 60 °C for **1** and 100 °C for **2** during 1.5 h and 1 h, respectively. After this period, dichloromethane (200 mL) was added to the solution. A continuous water extraction was carried out, with stirring, until neutralization. The dichloromethane solution was then washed with sodium hydrogen carbonate and dried over anhydrous Na_2SO_4. The purification by column chromatography in silica gel using dichloromethane as eluent, and subsequent solvent evaporation yielded the desired chlorosulfonated porphyrins as purple crystals, in agreement with the literature.[19]

4.5. General procedure for the synthesis of sulfonate ester fluorinated porphyrins

In an ice bath cooled flask, (ca. 5 °C) the corresponding alcohol was placed (40 equiv) and a concentrated solution of NaOH (8 equiv), dissolved in a minimum amount of dry THF, was added with stirring, for half hour. Then, the chlorosulfonated porphyrin (0.1 mmol), dissolved in dry THF (4 mL) was added to the flask. The mixture was allowed to stir at room temperature and TLC controlled. After the reaction finished (ca. 1 h), CH_2Cl_2 (50 mL) was added and the solution was washed with distilled water (3×100 mL) and then dried over anhydrous Na_2SO_4. The solvent was concentrated by rotary evaporation then purified by column chromatography in silica gel using dichloromethane/ethyl acetate as eluent, and subsequent solvent evaporation yielded the respective sulfonate ester fluorinated porphyrins.

4.5.1. 5,10,15,20-Tetrakis[2-fluoro-5-(3-propyloxy)-sulfonylphenyl] porphyrin ***5a****-FPC$_3$H$_7$.* Yield=94%; mp >250 °C; δ_H, ppm (400 MHz, $CDCl_3$) 8.81 (s, 8H, β-*H*), 8.76–8.70 (m, 4H, Ph–*H*), 8.45–8.41 (m, 4H, Ph–*H*), 7.74 (t, 4H, *J*=8 Hz, Ph–*H*), 4.29 (td, 8H, *J*=4, 8 Hz, –O–C*H*$_2$–), 1.88–1.79 (m, 8H, –C*H*$_2$), 1.02 (t, 12H, *J*=8 Hz, –C*H*$_3$), –2.84 (s, 2H, –N*H*); δ_F, ppm (376.5 MHz, $CDCl_3$), –100.09 to –100.20 (m, 4F); HRMS (ESI-FIA-TOF) $[M+H]^+$ found: 1175.2281, calculated for $[C_{56}H_{51}F_4N_4O_{12}S_4]$ 1175.2244.

4.5.2. 5,10,15,20-Tetrakis[2-fluoro-5-(3-trifluoropropyloxy)-sulfonylphenyl] porphyrin ***5b****-FPC$_3$H$_4$F$_3$.* Yield=96%; mp >250 °C; δ_H, ppm (400 MHz, $CDCl_3$) 8.80 (s, 8H, β-*H*), 8.76–8.72 (m, 4H, Ph–*H*), 8.44 (t, 4H, *J*=4 Hz, Ph–*H*), 7.79–7.75 (m, 4H, Ph–*H*), 4.53–4.50 (m, 8H, –O–C*H*$_2$–), 2.69–2.63 (m, 8H, –C*H*$_2$CF$_3$), –2.85 (s, 2H, –N*H*); δ_F, ppm (376.5 MHz, $CDCl_3$) –63.73 (s, 12F, –C*F*$_3$), –98.94 to –99.05 (m, 4F, Ph–*F*); HRMS (ESI-FIA-TOF) $[M+H]^+$ 1391.1186, calculated for $[C_{56}H_{39}F_{16}N_4O_{12}S_4]$ 1391.1114.

4.5.3. 5,10,15,20-Tetrakis[2-fluoro-5(-3-butyloxy)-sulfonylphenyl] porphyrin ***5c****-FPC$_4$H$_9$.* Yield=89%; mp >250 °C; δ_H, ppm (400 MHz, $CDCl_3$) 8.80 (s, 8H, β-*H*); 8.74–8.70 (m, 4H, Ph–*H*), 8.44–8.41 (m, 4H, Ph–*H*), 7.74 (t, 4H, *J*=8 Hz, Ph–*H*), 3.76–3.73 (m, 8H, –O–C*H*$_2$–), 1.80–1.76 (m, 8H, –C*H*$_2$–), 1.49–1.43 (m, 8H, –C*H*$_2$–), 0.96–0.92 (m, 12H, –C*H*$_3$), –2.84 (s, 2H, –N*H*); δ_F, ppm (376.5 MHz, $CDCl_3$) –99.88 to –100.21 (m, 4F) HRMS (ESI-FIA-TOF) $[M]^+$ 1230.2750, calculated for $[C_{60}H_{58}F_4N_4O_{12}S_4]$ 1230.2870.

4.5.4. 5,10,15,20-Tetrakis[2-fluoro-5-(2,2,3,4,4,4-hexafluorobutyloxy)-sulfonylphenyl] porphyrin ***5d****-FPC$_4$H$_3$F$_6$.* Yield=84%; mp >250 °C; δ_H, ppm (400 MHz, $CDCl_3$), 8.78–8.74 (m, 12H, *β-H*+Ph–*H*), 8.47–8.45 (m, 4H, Ph–*H*), 7.80 (t, 4H, *J*=8 Hz, Ph–*H*), 5.10–4.96 (m, 4H, C*H*–F), 4.70–4.55 (m, 8H, O–C*H*$_2$), –2.85 (s, 2H, N*H*); δ_F, ppm (376.5 MHz, $CDCl_3$) –73.89 to –73.99 (m, 12F, C*F*$_3$), –97.77 to –97.87 (m, 4F, Ph-*F*), –113.02 to –119.64 (m, 8F, C*F*$_2$), –211.10 to –211.20 (m, 4F, C*F*–H); HRMS (ESI-FIA-TOF) $[M+H]^+$ 1663.0679, calculated for $[C_{60}H_{35}F_{28}N_4O_{12}S_4]$ 1663.0609.

4.5.5. 5,10,15,20-Tetrakis[2-fluoro-5-(4,4,5,5,5-pentafluoropentyloxy)-sulfonylphenyl] porphyrin ***5e****-FPC$_5$H$_6$F$_5$.* Yield=95%; mp >250 °C; δ_H, ppm (400 MHz, $CDCl_3$) 8.79 (s, 8H, β-*H*), 8.75–8.69 (m, 4H, Ph–*H*), 8.46–8.42 (m, 4H, Ph–*H*), 7.77 (t, 4H, *J*=16 Hz, Ph–*H*), 4.39 (t, 8H, *J*=8 Hz, –O–C*H*$_2$–), 2.30–2.20 (m, 8H, –C*H*$_2$–CF$_2$), 2.16–2.11 (m, 8H, –C*H*$_2$–), –2.84 (s, 2H, N*H*); δ_F, ppm (376.5 MHz, $CDCl_3$) –84.31 (s, 12F, C*F*$_3$), –99.27 to –99.47 (m, 4F, Ph-*F*), –116.99 (s, 8F, C*F*$_2$); HRMS (ESI-FIA-TOF) $[M+H]^+$ 1647.1533, calculated for $[C_{64}H_{47}F_{24}N_4O_{12}S_4]$ 1647.1612.

4.5.6. 5,10,15,20-Tetrakis[2,6-difluoro-3-(3-propyloxy)-sulfonylphenyl] porphyrin ***6a****-F$_2$PC$_3$H$_7$.* Yield=78%; mp >250 °C; δ_H, ppm (400 MHz, $CDCl_3$) 8.85 (s, 8H, *β-H*), 8.52–8.46 (dd, 4H, *J*=8z, 16 Hz, Ph–*H*), 4.38–4.34 (m, 8H, –O–C*H*$_2$–), 1.85–1.76 (m, 8H, –C*H*$_2$), 0.97 (t, *J*=8 Hz, 12H, –C*H*$_3$), –2.83 (s, 2H, N*H*); δ_F, ppm (376.5 MHz, $CDCl_3$) –94.87 to –95.68 (m, 4F), –96.88 to –99.80 (m, 4F); HRMS (ESI-FIA-TOF) $[M+H]^+$ 1247.1957, calculated for $[C_{56}H_{47}F_8N_4O_{12}S_4]$ 1247.1940.

4.5.7. 5,10,15,20-Tetrakis[2,6-difluoro-3(-3-trifluoropropyloxy)-sulfonylphenyl] porphyrin ***6b****-F$_2$PC$_3$H$_4$F$_3$.* Yield=85%; mp >250 °C; δ_H, ppm (400 MHz, $CDCl_3$) 8.84 (s, 8H, β-*H*), 8.49 (t, 4H, *J*=8 Hz, Ph–*H*), 7.61 (t, 4H, *J*=8 Hz, Ph–*H*), 4.60–4.57 (m, 8H, O–C*H*$_2$–), 2.67–2.57 (m, 8H, –C*H*$_2$CF$_3$), –2,84 (s, 2H, –N*H*–); δ_F, ppm (376.5 MHz, $CDCl_3$) –63.85 to –63.96 (m, 12F, C*F*$_3$), –93.69 to –94.22 (m, 8F, Ph–*F*), –98.78 to –98.94 (m, 4F, Ph–*F*); HRMS (ESI-FIA-TOF) $[M+H]^+$ found: 1463.0828, calculated for $[C_{56}H_{35}F_20\ N_4O_{12}S_4]$ 1463.0737.

4.5.8. 5,10,15,20-Tetrakis[2,6-difluoro-3(-3-butyloxy)-sulfonylphenyl] porphyrin ***6c****-F$_2$PC$_4$H$_9$.* Yield=82%; mp >250 °C; δ_H, ppm (400 MHz, $CDCl_3$) 8.89 (s, 8H, β-*H*); 8.59–8.54 (m, 4H, Ph–*H*), 7.67–7.64 (m, 4H, Ph–*H*), 3.77–3.74 (m, 8H, –O–C*H*$_2$–), 2.18–2.16 (m, 8H, –C*H*$_2$–), 1.87–1.84 (m, 8H, –C*H*$_2$–), 1.27–1.25 (m, 12H, –C*H*$_3$), –2,82 (s, 2H, –N*H*); δ_F, ppm (376.5 MHz, $CDCl_3$) –90.74 to –91.14

(m, 4F), −97.15 to −97.48 (m, 4F); HRMS (ESI-FIA-TOF) $[M+H]^+$ found: 1303.2483, calculated for $[C_{60}H_{55}F_8N_4O_{12}S_4]$ 1303.2493.

4.5.9. 5,10,15,20-Tetrakis[2,6-difluoro-3-(2,2,3,4,4,4-hexafluorobutyloxy)-sulfonylphenyl] porphyrin ***6d****-$F_2PC_5H_3F_6$.* Yield=81%; mp >250 °C; δ_H, ppm (400 MHz, $CDCl_3$) 8.81 (s, 8H, *β-H*), 8.52–8.49 (m, 4H, Ph–*H*), 7.67–7.50 (m, 4H, Ph–*H*), 5.01–4.87 (m, 4H, C*H*–F), 4.72–4.63 (m, 8H, CH_2), −2.80 (s, 2H, N*H*); δ_F, ppm (376. 5 MHz, $CDCl_3$) −72.91 to −74.13 (m, 12F, CF_3), −92.47 to −93.43 (m, 4F, Ph–*F*), −98.73 to −99.88 (m, 4F, Ph-*F*), −113.19 to −120.32 (m, 8F, CF_2), −211.19 (s, 4F, C*F*–H); HRMS (ESI-FIA-TOF) $[M]^+$ found: 1734.9030, calculated for $[C_{60}H_{30}F_{32}N_4O_{12}S_4]$ 1734.0232.

4.5.10. 5,10,15,20-Tetrakis[2,6-difluoro-3-(4,4,5,5,5-pentafluoropentyloxy)-sulfonylphenyl] porphyrin ***6e****-$F_2PC_5H_6F_5$.* Yield=82%; mp >250 °C; δ_H, ppm (400 MHz, $CDCl_3$) 8.79 (t, 8H, *J*=12 Hz, β-*H*), 8.50–8.43 (m, 4H, Ph–*H*), 7.57–754 (m, 4H, Ph–*H*), 4.39 (s, 4H, O–CH_2–), 2.14–1.93 (m, 16H, –CH_2–CF_2+–CH_2–), −2.90 (s, 2H, N*H*); δ_F, ppm (376,5 MHz, $CDCl_3$) −84.33 to −84.46 (m, 12F, –CF_3), −91.08 to −91.30 (m, 4F, Ph–*F*), −98.99 to −99.39 (m, 4F, Ph-*F*), −117.00 to −117.19 (m, 8F, CF_2); HRMS (ESI-FIA-TOF) $[M]^+$ found: 1718.2811, calculated for $[C_{64}H_{42}F_{28}N_4O_{12}S_4]$ 1718.1235.

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