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Influence of bromine substitution pattern on the singlet oxygen generation efficiency of two-photon absorbing chromophores

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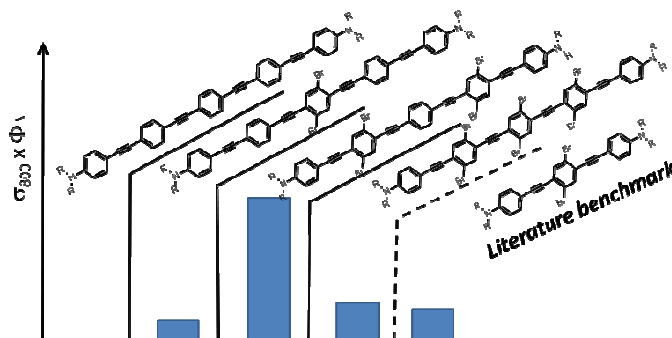
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ABSTRACT



A new molecular engineering strategy based on a rational variation of the bromine substitution pattern on two-photon absorbing photosensitizers for singlet oxygen generation is introduced. This approach allowed us to obtain a chromophore with a five fold enhanced “figure-of-merit” ($\sigma_{\text{TPA}} \cdot \Phi_{\Delta}$) at 800nm, compared to a literature benchmark. We propose a rational explanation on the relation that exists between the positioning of the Inter-system crossing (ISC) center on the charge-transfer chromophore and its ability to generate singlet oxygen.

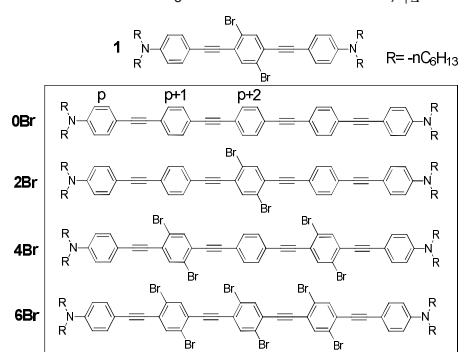
Photodynamic therapy (PDT) is a therapeutic protocol which is currently limited to the treatment of several surface diseases, like skin or mucosal cancers.¹ It requires a photosensitizer,^{1e,2} *ie* a molecule possessing an accessible triplet excited state able to generate singlet oxygen ($^1\text{O}_2$) by an energy transfer to ground state oxygen, ultimately leading to cell death.³ Two-photon sensitized PDT is an emerging approach, which allows a deeper penetration of light into tissues (since irradiation operates in the biological transparency window, 700-1100 nm) and a better control on the irradiation volume than

its one-photon counterpart.⁴ Thus, it is possible to envision more in-depth treatment of tumors, while minimizing detrimental side-effects on the neighboring healthy tissues. Ideal two-photon absorbing (TPA) chromophores for PDT must possess two essential spectroscopic characteristics, (i) a large two-photon absorption cross section (σ_{TPA}) at the excitation wavelength and (ii) a high quantum yield of singlet oxygen generation (Φ_{Δ}), which is relevant to the efficiency of singlet-to-triplet intersystem crossing (ISC) of the chromophore in its excited state.⁵

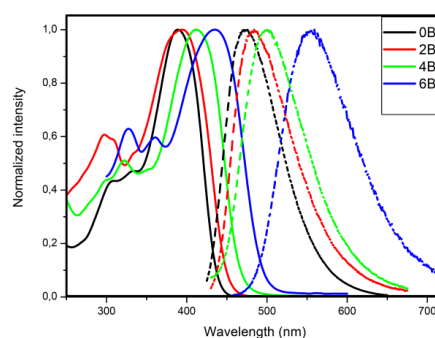
Table 1. Relevant spectroscopic data for the study.

	0Br	2Br	4Br	6Br	$I^{[d]}$
λ_{\max} (ϵ)	389 (79×10^3)	395 ($46,6 \times 10^3$)	410 ($49,9 \times 10^3$)	435 ($53,8 \times 10^3$)	421 ($91,5 \times 10^3$)
λ_{fluo} (τ_f)	476 (1.83)	490 (1.68)	500 (0.96)	560 (1.27)	458 (0.26.)
$\phi_f^{[a]}$	0.80	0.70	0.30	0.53	0.25
$\lambda_{\text{phos}}^{[b]}$	-	530, 569	594, 637	600, 674	586
$\phi_{\Delta}^{[c]}$	-	0.10	0.50	0.35	0.53
$\lambda_{\text{TPA max}}(\sigma_{\text{TPA}})$	750 (460)	760 (450)	830 (380)	880 (260)	550 (730)
$\sigma_{\text{TPA800}} \times \phi_{\Delta}$	0	30	175	40	37

λ in nm, ϵ in $\text{L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$, τ_{fluo} in ns and σ_{TPA} in Goepert-Mayer. λ_{exc} were 390 nm, 395 nm, 410 nm and 435 nm for the series [a] Coumarine 153 in MeOH was used as standard, $\phi_{\text{ref}} = 0.45$ [b] Emission in glassy solution at 77 K (MeOH/EtOH, 1/4, V/V) with a time delay of 65 μs . [c] Naphthalenone in CHCl_3 was used as standard, $\phi_{\Delta} = 1$ [d] from [ref 4m].

**Figure 1.** Compounds of the study and benchmark compound **1** [ref. 4i, 4m]. p+n (n=1,2) refers to the phenyl ring position relative to the terminal aniline

These two parameters can be used to define a “figure of merit” at 800 nm,⁶ ($\sigma_{\text{TPA800}} \times \phi_{\Delta}$), for the photosensitizer.^{4d} Two-photon absorbing chromophores have been the subject of various studies during the last two decades, and the associated rules of molecular engineering and structure-property relationship are now well established.^{2d,7} In particular, it has been established that chromophore that features electronic transition of the Internal Charge-Transfer (ICT) type are optimal candidates for TPA, especially those with quadrupolar symmetry.⁷ Comparatively, in spite of the fact that many studies have been focused on improving ISC efficiency and ultimately one-photon PDT activity in chromophores with localized excited states (porphyrin⁸ and rhodamine⁹ derivatives, mostly) only few authors have systematically studied the relationship that exists between structural parameters and $^1\text{O}_2$ generation efficiency in the context of ICT chromophores. In most cases, $^1\text{O}_2$ generation is achieved through substitution of the chromophore with a group responsible of the ISC. This approach, which we have also recently explored,¹⁰ has been successful in designing efficient chromophores for two-photon PDT;^{4g-ⁱ} yet, the relations between ISC efficiency (that is, the mechanism by which the delocalized ICT excited singlet state evolves into a localized triplet state) and the position and/or number of ISC promoters(?) remain poorly

**Figure 2.** Absorption (full) and emission (dash) spectra in CHCl_3 at 298 K.

understood in the context of ICT chromophores. With the aim to more particularly address that point, we initiated a systematic study based on an original engineering approach: it markedly differs from previously published works on the topic, since the chemical nature of the ISC group (two bromine substituents in 2,5-positions on a phenyl moiety) is maintained in all molecules, and the variations we operate concern exclusively its number and positioning along the ICT axis (“p+1” and/or “p+2” position, Figure 1). This allows to vary exclusively the ISC kinetic constant (k_{ISC}) while keeping all other kinetic constants almost unaffected (*vide infra*). In this preliminary study, we show that this systematic approach can be used to tune the $^1\text{O}_2$ quantum yield generation along with other spectroscopic features of interest, to a rather unexpected extent.

Following the aforementioned strategy, and using previously reported compound **1**^{4i,4m} (Figure 1) as a benchmark and model, a series of four quadrupolar chromophores was designed and synthesized. For convenience, those chromophores will be referred to as **0Br**, **2Br**, **4Br** and **6Br** in the following. The series was obtained through a convergent “building-blocks” synthesis, based on successive Sonogashira-Hagihara palladium cross-coupling catalyzed reactions from the electron donating group to the molecular core. For

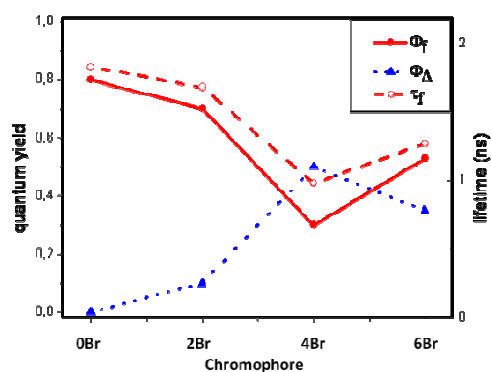


Figure 3. Evolution of the photophysical parameters (Φ_F , Φ_Δ , τ_F) among the chromophore's series (298K, CHCl_3).

experimental details and characterizations, see Supporting Information.

Absorption and emission spectra were obtained using diluted CH_2Cl_2 solutions of the compounds at 298 K (Figure 2 and Table 1). In all cases, a broad low-energy absorption band is observed, centered at 389, 395, 410 and 435 nm, for **0Br**, **2Br**, **4Br** and **6Br**, respectively. As expected, this band can be unambiguously ascribed to a ICT transition, regarding its characteristic shape, large Stokes shift and positive solvatochromism (Figure S4). The bathochromic shift along the series is in agreement with the electro-deficiency induced by the increased number of dibromophenyl moieties along the conjugated skeleton. All compounds are luminescent under irradiation in their ICT band, with a broad, solvatochromic ICT emission band centered at 476, 490, 500 and 560 nm, for **0Br**, **2Br**, **4Br** and **6Br** in chloroform, respectively. The decay times (Table 1, Figure 4) are in the ns range, which indicates a fluorescence emission process.

Attempts to observe triplet excited state emission of the compounds at room temperature have to date remained unsuccessful. However, at low temperature in glassy solution, structured phosphorescence emissions were observed, except for **0Br** in which ISC does not occur significantly (Table 1, Figure S5).

$^1\text{O}_2$ generation quantum yield (Φ_Δ) quantifies the chromophore efficiency as a potential PDT sensitizer. It was determined from the characteristic $\Delta^1\text{O}_2 \rightarrow \Sigma^3\text{O}_2$ phosphorescence at 1270 nm. All brominated compounds (**2Br**, **4Br** and **6Br**) generate singlet-oxygen, with quantum yields of 0.10, 0.50 and 0.35, respectively (Table 1, Figure S6). Interestingly, fluorescence quantum yields and lifetimes evolve opposite (and almost mirror) to the $^1\text{O}_2$ generation quantum yield (Figure 3). This tendency is in excellent agreement with the fact that, $^1\text{O}_2$ quantum yield can be directly connected to ISC efficiency, since all kinetic constants other than k_{ISC} are shown to be unchanged as a result of the structural similarity of all chromophores within the series (see SI for full demonstration). **4Br** exhibits a $^1\text{O}_2$ quantum yield ($\Phi_\Delta = 0.50$) that is five times higher than its dibrominated analogue **2Br** ($\Phi_\Delta = 0.10$) with a concomitant drop in both fluorescence quantum yields and lifetime values (Figure 3, Table 1). This trend could potentially be ascribed either

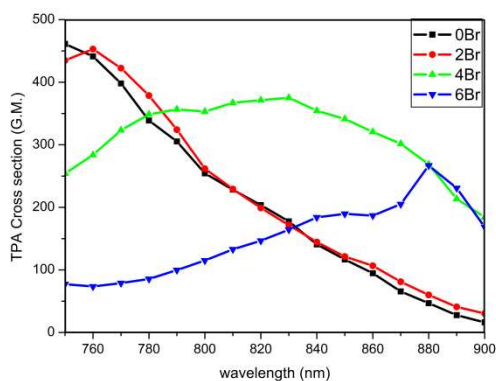


Figure 4. Two-photon absorption spectra in CH_2Cl_2 at 298 K.

to a synergistic enhancement of the ISC efficiency related to the increased number of bromine on the chromophore, or to a positional effect, with lateral (“p+1”) substitution providing higher ISC efficiency than the central (“p+2”) one in this particular series. Examination of the results obtained with **6Br** clearly rules out the first hypothesis: indeed, in spite of the increased number of heavy atom substituents, **6Br** displays a loss of $^1\text{O}_2$ generation efficiency ($\Phi_\Delta = 0.35$) and a concomitant increase of the fluorescent quantum yield and lifetime compared to **4Br**, which altogether can be ascribed to a lower ISC efficiency. Taken together, these results seem to indicate that, rather than the number of $^1\text{O}_2$ generating moieties, their detailed position on the carbon backbone is the determining parameter that drives ISC efficiency: an ideal positioning of the heavy atoms seems to be on the peripheral phenyls next to the aniline ring (“p+1” position, as in **4Br**), whereas bromine substitution on the “p+2” (**2Br**) ring provides in comparison a much lower efficiency. Interestingly, and quite unexpectedly, the presence of bromine atoms in both “p+1” and “p+2” positions has a detrimental effect on the ISC, as seen when comparing **4Br** and **6Br** (Figure 3). As a consequence, **4Br** is the best photosensitizer of the series, whereas **6Br** displays a value that is intermediate with respect to the former and that of **2Br**.

Finally, TPA cross sections were determined by two-photon induced fluorescence measurements (SI). In the biological transparency window (750 – 900 nm), all compounds show significant TPA cross sections,¹¹ with values ranging from 250 GM (**6Br**) to 460 GM (**0Br**) (Figure 4, Table 1). As for their linear absorption spectra, a significant bathochromic shift is observed throughout the series. **0Br** and **2Br** give the best results in absolute values, but their absorption maxima are slightly below the optimal transparency window. **6Br** shows a maximal TPA in the NIR but with a moderate cross section value (< 200 GM), whereas **4Br** shows a broad TPA peak, with a cross section being larger than 300 GM from 770 to 860 nm. This shows that, beside having a strong influence on $^1\text{O}_2$ generation, bromine substitution pattern can be used to tune TPA properties ($\lambda_{\text{max}}^{\text{TPA}}$) of the chromophore. Taken together, this leads **4Br** to display the best figure of merit ($\sigma_{800}^{\text{TPA}} \times \Phi_\Delta$, Table 1) among all compounds in the series (including benchmark **1**), and makes it a relevant structure for future PDT applications, provided that some

modifications are introduced to render it biocompatible, as previously illustrated with related chromophore 1.^{4m,12}

In summary, this study allowed us, owing to an original molecular engineering approach, to progress significantly in our understanding of some of the relation that exist between the position and number of a given ISC promoter (2,5-dibromophenyl) on ICT chromophores, and their ¹O₂ generation efficiency. In particular, we suggest that there exist “match” (“p+1”) and “mismatch” (“p+2”) positions for dibromophenyl moieties (Figure 1). This is of particular significance in the context of molecular engineering for two-photon PDT applications, since the position of the heavy atom has only scarcely been discussed in previous published works relying on a similar “heavy atom” strategy for ¹O₂ sensitization in ICT chromophores,¹³ and never investigated in such details for this class of chromophores. Besides, we have also shown that varying the bromine substitution pattern could be used to tune the two-photon absorption properties of the molecule, as a result of the electron withdrawing effect of the bromine atoms. Altogether, the results of this study suggest that, for works dealing with ISC improvement in ICT chromophores, caution should be taken not only with the choice of the ISC generating moiety, but also with its number and -most importantly- positioning along the chromophore ICT transition axis. Theoretical and experimental investigations are underway to gain deeper understanding on the structure-to-property relationships in this class of brominated two-photon photosensitizers, and in particular to correlate the observed trend to the orbital parameters of the ICT transition.

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Supporting Information Available synthesis, analytical characterization, discussion on the excited state kinetics, ¹H and ¹³C NMR spectra, HPLC traces, solvatochromism study, 77K time-gated luminescence, fluorescence and ¹O₂ phosphorescence plots.

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