



Can BODIPY Dimers Act as Photosensitizers in Photodynamic Therapy? A Theoretical Prediction

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The photophysical properties of some monomeric and dimeric BODIPY systems were investigated at the density functional theory level and herein reported. In particular, the absorption spectra were fully characterized, low energy singlet and triplet excited states were discussed also focusing on the energy difference gaps between them and computing the spin-orbit couplings values for the possible intersystem crossing channels. The heavy atom effect of iodine substituents on the photophysical properties of a monomer and on a dimer under investigation was also estimated. Results obtained on the considered compounds allow us to predict which is the most promising candidate to be suggested as a photosensitizer in photodynamic therapy.

Keywords: TDDFT, PDT, BODIPY, heavy atom effect, spin-orbit coupling

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INTRODUCTION

In the last decade the BF₂-chelated dipyrromethenes, known as BODIPYs, have been proposed for many applications in materials science and biotechnology because of their excellent stability, arising from the strongly electron-withdrawing BF₂ group, intense absorption band in the near-infrared region, sharp emissions and quantum fluorescence yields [1–3]. Through appropriate modifications which permit a strong reduction in the fluorescence quantum yields while enhancing singlet-to-triplet intersystem crossing, BODIPY and their aza-derivatives have emerged as excellent photosensitizers in photodynamic therapy (PDT) [4–7]. PDT is a very old medical practice, especially employed in dermatology, but it is only recently being developed as a minimally invasive therapy in the treatment of different kinds of tumors [8–12]. Moreover, its clinical efficiency is currently under exploration for other diseases such as infections, cardiovascular and wounds healing [13–15]. The main cytotoxic agent in PDT is the excited singlet molecular oxygen ¹Δ_g generated *in situ* through the so-called photodynamic process. In the medical practice, after the administration and selective accumulation of the photosensitizer (PS) in the target tissue, the region is locally irradiated with an appropriate light source able to promote the excitation of the PS from the ground (S₀) to an excited singlet electronic state S_n. In systems with low fluorescence quantum yield, the energy of the S₁ can be transferred to an excited triplet state, T₁, through a non-radiative S₁ → T₁ intersystem crossing (ISC) process. If the energy of that state is greater than that required to excite the oxygen, instead of decaying in the ground state S₀, the T₁ can transfer its energy to trigger the O₂ ³Σ_g → ¹Δ_g conversion (the so-called type II reaction). Consequently, the ability of a photosensitizer to generate singlet oxygen is strictly related to the generation of a high energy lying excited triplet T₁ able to excite the molecular oxygen (0.98 eV) and to the occurrence of an efficient singlet-triplet ISC process. To satisfy these criteria, BODIPY dyes proposed for PDT can

be modified following two ways: (i) including a heavy atom (I, Br, or a nontoxic metal) in their structures; (ii) performing a covalent dimerization. The first strategy exploits the heavy atoms to enhance the efficiency of the intersystem crossing whose constant depends on the amplitude of the spin-orbit couplings between the singlet and triplet states (the so-called heavy atom effect).

As for the second class of strategy, the mechanism through which the dimers should work is not clear from the few investigations hitherto appeared in the literature [16–19]. Very recently, BODIPY monomers and dimers with and without heavy atom in their structures were synthesized and their photophysical properties were accurately measured [16]. Using the experimental evidences given in that article as a starting point, we have undertaken a careful theoretical study of the structural and electronic characteristics of these systems (see **Scheme 1**) by using the density functional theory (DFT) and its time-dependent formulation (TDDFT). In particular, we determined the geometries of ground and excited states, the absorption features, the singlet-triplet energy gaps, and the spin orbit coupling matrix elements.

COMPUTATIONAL DETAILS

The investigation was performed by using the Density Functional Theory level (DFT) and its time-dependent density functional linear response formulation (TDDFT) as implemented in Gaussian09 code [20]. Geometry optimization (without imposing constraints) and harmonic vibrational frequencies were done by using the B3LYP [21, 22] exchange-correlation functional in conjunction with the 6-31G* basis set for all the atoms excepts Iodine, for which the SSD pseudopotential [23]

was employed. The lowest 20 vertical excitation energies were calculated by TDDFT on the previously optimized geometries by adding a diffuse function to the basis set. Solvent effects were evaluated by using the non-equilibrium implementation [24] of the polarizable continuum model [25]. The dichloromethane ($\epsilon = 8.93$) in which the experimental UV-Vis spectra were measured [16], was considered as solvent.

Spin-orbit matrix elements were computed with DALTON code [26] by using B3LYP functional and cc-pVDZ basis set for all the atoms except iodine, for which the coupled pseudopotential was considered. The atomic-mean field approximation [27] was used for the systems without iodine atoms while, for those in which this heavy atom is present, the Spin-Orbit Coupling Operators for Effective Core Potentials with an effective nuclear charge [28] was employed.

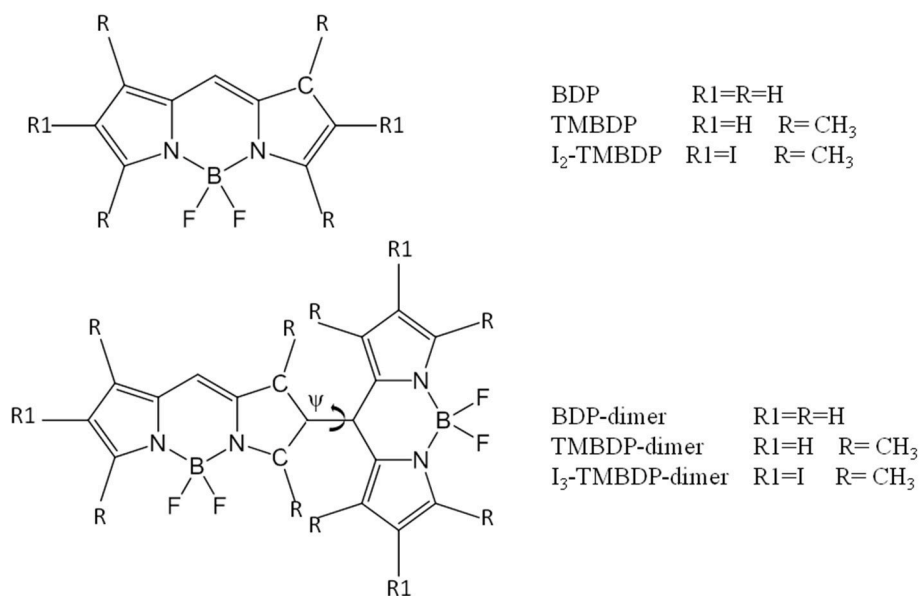
The spin-orbit couplings (SOCs) were evaluated according to the following formula:

$$SOC = \sqrt{\sum_i \left| \langle \psi_{S_1} | \hat{H}_{SO} | \psi_{T_1} \rangle \right|^2} ; \quad i = x, y, z$$

where \hat{H}_{SO} is the spin-orbit Hamiltonian.

RESULTS AND DISCUSSION

The main geometrical parameters resulting from the optimization process of examined systems, are shown in **Table 1**, while the coordinates of the obtained minima are listed in the Supplementary Information section (**Tables S1–S6**). For TMBDP-dimer, a comparison is possible with the X-ray structure recently reported [19]. The agreement with the experimental



SCHEME 1 | Chemical structures of the studied systems.

counterparts for bond lengths and valence angles, which do not vary significantly among the studied compounds, is very satisfactory. The more interesting parameter is the torsional angle Ψ that determines the position of the two linked BODIPY moieties. Values of 36.8, 86.9, and 75.3° for BDP-dimer, TMBDP-dimer and I₂-TMBDP-dimer were obtained, respectively. This trend accounts for the high steric hindrance of the four methyl groups that force the two BODIPY sub-units to be almost orthogonal to each other in both TMBDP and I₂-TMBDP dimers. This means that in these two molecules the electron delocalization is practically precluded as also confirmed by the shape of computed HOMO and LUMO orbitals, which shows a lack of mixing between the two orthogonal π moieties. Similar results were previously obtained, at CASSCF level of theory, for the TMBDP-dimer [19].

The computed TDDFT excitation energies for singlet and triplet states are collected in **Table 2** together with the available experimental and previous theoretical results. As a general trend, we note that the TDDFT method underestimates the wavelengths of the singlet excited states by about 80 nm. This behavior was previously observed in other previous studies on BODIPY-like systems [29–32]. In a recent work, Le Guennic et al. have discussed the possible sources of this error and proposed a correction based on coupled cluster computations [33]. The agreement seems to be satisfactory for the T₁ energies. In fact, the available experimental transition energy value determined for I₃-TMBDP-dimer [16] is close to that obtained at TDDFT level (1.59 vs. 1.50 eV). On the other hand, the S₁ and T₁ excitation values, computed at CASSCF level, for TMBDP-dimer, are significantly overestimated with respect to the experimental ones (see **Table 2**). From that table, one can readily see that in proceeding from the monomeric to the dimeric systems, the absorption wavelength is red-shifted. Also, the iodinated compounds suffer a small red shift in comparison with the analogs without iodine substituents. The S₁ oscillator strength in the monomeric systems assumes high values, while in the dimeric structures, it seems to be almost silent. The electronic structure of S₁ was previously studied at both DFT [16] and CASCF [19] levels. In the former study, a photo induced electron transfer is suggested on the basis of the HOMO and LUMO orbital composition of the S₀ optimized ground state, while in the latter study, S₁ wave function is proposed to derive by a double substitution and natural orbital occupation numbers show four odd electrons in four similar orbitals. Our computed S₁ frontier orbital picture is very similar to that reported by Zhang [16] for the ground state. Of course, we

cannot exclude that the higher level Interaction Configuration computations might better characterize the electronic structure of these systems. The lowest lying T₁ excitations are due to HOMO → LUMO transitions in the monomeric systems (BDP, TMBDP and I₂-TMBDP) while, in the dimers, also other Gouterman molecular orbital play an important role (see **Table 2**).

TABLE 2 | Vertical excitation energies, ΔE (eV), λ_{\max} (nm), oscillator strengths f and main transitions for studied compounds computed in dichloromethane by using B3LYP/6-31+G*.

Cmpd	State	ΔE	λ	f	Transitions	λ_{exp}
BDP	S ₁	2.97	417	0.537	H → L, 94%	
	T ₁	1.60	773		H → L, 100%	
BDP-dimer	S ₁	2.39	520	0.035	H → L, 92%	
	S ₂	2.65	467	0.743	H → L, 86%	
	T ₁	1.63	763		H → L, 28% H → L+1, 23%	
TMBDP	S ₁	2.84	436	0.643	H → L, 98%	507 ^a
	T ₁	1.48	836		H → L, 100%	
TMBDP-dimer	S ₁	2.38	520	0.002	H → L, 99%	
	S ₂	2.53	491	0.006	H → L+1, 97%	
	S ₃	2.82	440	0.813	H → L, 94%	511 ^a /354 ^b
I ₂ -TMBDP	T ₁	1.51	822		H → L+1, 99%	689 ^b
	S ₁	2.67	464	0.636	H → L, 98%	540 ^a
	T ₁	1.53	813		H → L, 97%	
I ₃ -TMBDP-dimer	S ₁	2.39	518	0.045	H → L, 77%	
	S ₂	2.40	516	0.168	H → L+1, 22% H → L, 70%	
	S ₃	2.64	469	0.537	H → L+1, 28% H → L, 72%	
	S ₄	2.73	454	0.668	H → L+1, 67% H → L, 25%	538 ^a
	T ₁	1.50	828		H → L, 53% H → L+1, 43%	782 ^a

Experimental value is taken from Zhang [16]^a, Cakmak et al. [19]^b.

TABLE 3 | Spin-orbit matrix elements (cm⁻¹) and singlet-triplet energy gaps (eV) calculated at the B3LYP/6-31G(d) level of theory.

Cmpd	$\langle \Psi_{S_1} \hat{H}_{SO} \Psi_{T_1} \rangle$	$\Delta E_{S_1-T_1}$	Φ_{Δ}
BDP	0.00	1.37	
TMBDP	0.02	1.36	0.076
I ₂ -TMBDP	9.44	1.14	0.960
BDP-dimer	1.08	0.76	
TMBDP-dimer	0.45	0.87	0.450
I ₃ -TMBDP-dimer	8.67	0.89	0.840

Singlet Oxygen quantum yields (Φ_{Δ}) are taken from Zhang [16].

TABLE 1 | Selected bond lengths [Å] and angles [deg] calculated at the B3LYP/6-31G* level for the dimers studied.

Cmpd	B-F	B-N	F-B-F	F-B-N	Ψ
BDP-dimer	1.388	1.565	111.1	110.0	42.7
TMBDP-dimer	1.401	1.551	109.6	110.1	86.9
I ₃ -TMBDP-dimer	1.394	1.563	110.2	109.9	75.3
Exp ^a (TMBDP-dimer)	1.422 ^a	1.560 ^a	111.3 ^a	109.9 ^a	

^aFrom Cakmak et al. [19].

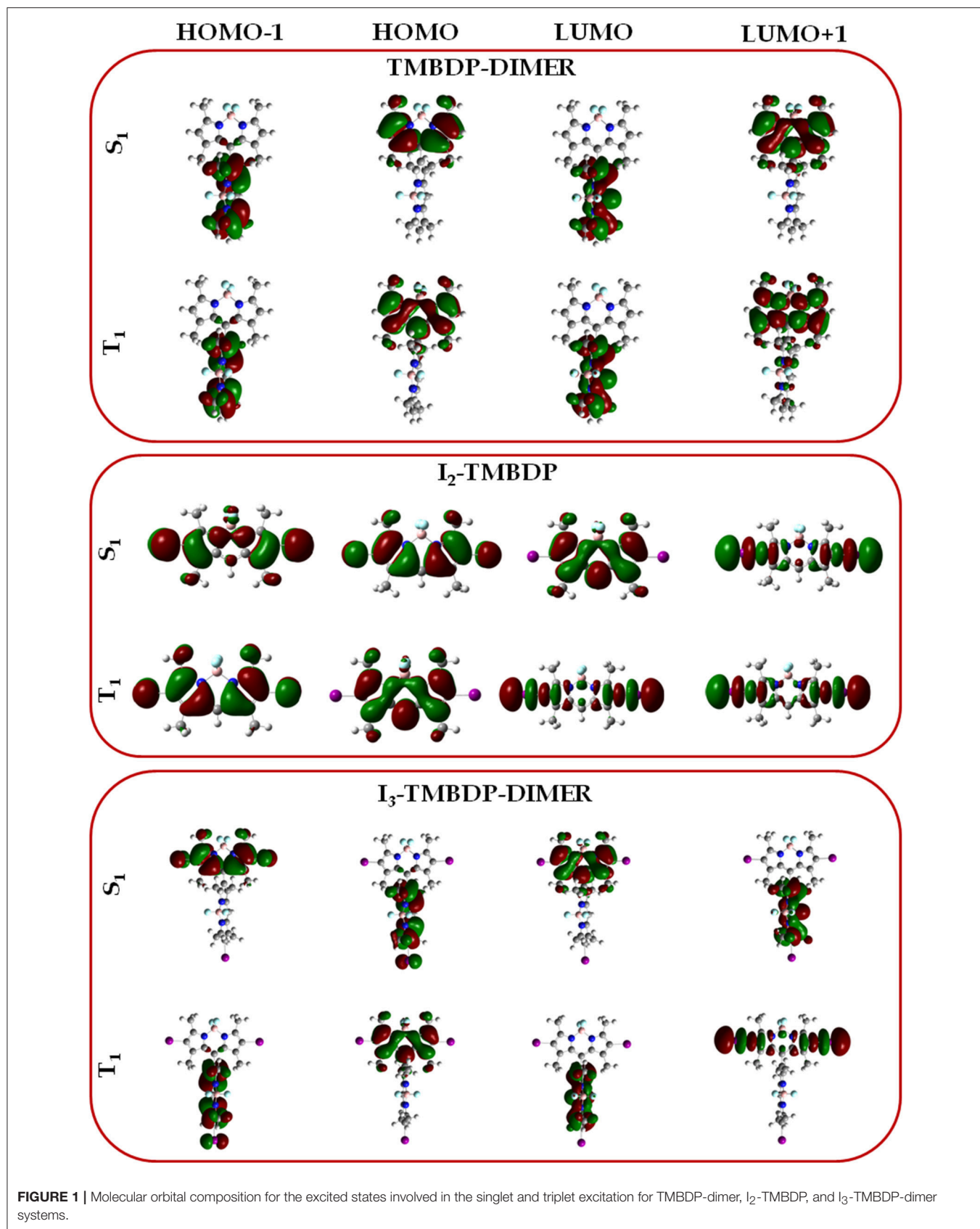


FIGURE 1 | Molecular orbital composition for the excited states involved in the singlet and triplet excitation for TMBDP-dimer, I₂-TMBDP, and I₃-TMBDP-dimer systems.

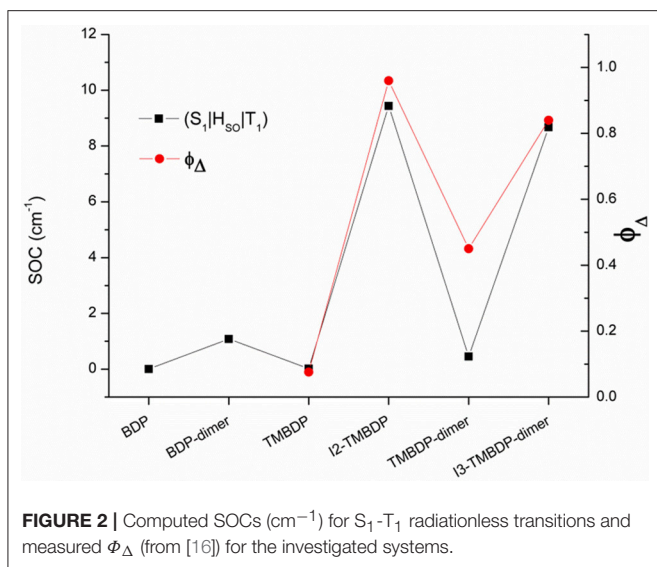


FIGURE 2 | Computed SOC (cm^{-1}) for S_1 - T_1 radiationless transitions and measured Φ_{Δ} (from [16]) for the investigated systems.

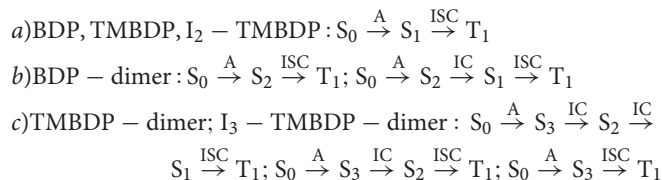
As previously mentioned, an efficient PDT photosensitizer must possess a $\Delta E_{S_0-T_1}$ energy gap higher than 0.98 eV to excite the molecular oxygen from its ground to the highly cytotoxic $^1\Delta_g$ excited singlet state. All the studied molecules have energy gaps sensibly higher than 0.98 eV and hence are in principle good candidates as PDT drugs (see **Table 2**).

The computed spin-orbit coupling constants for the transitions involving the S_1 and the T_1 , together with the corresponding singlet-triplet energy gaps and the available singlet oxygen quantum yields (Φ_{Δ}) are reported in **Table 3**. For BDP and its tetramethylate analog (TMBDP), the $\langle\langle\Psi_{S_1}|\hat{H}_{so}|\Psi_{T_1}\rangle\rangle$ spin orbit coupling matrix element has a negligible magnitude. In the corresponding dimeric form the coupling increases, attaining a magnitude of about 1 cm^{-1} . In the iodine containing systems, the SOC values become 9.44 and 8.67 cm^{-1} for I_2 -TMBDP and I_3 -TMBDP-dimer, respectively. The small variation of the SOC values in proceeding from the monomeric (BDP, TMBDP) to their respective dimeric forms (BDP-dimer, TMBDP-dimer), is attributable to the slight variation of the molecular orbitals involved in the transitions (see **Figure 1**). As in other systems previously studied [34–41], the presence of the heavy atom substantially increases the spin-orbit coupling matrix elements. This is due to the so-called heavy atom effect. Looking at the **Figure 1**, one can note that in the case of the compound I_2 -TMBDP, the HOMO \rightarrow LUMO transition has a π - π nature, while the one involved in T_1 has a π -n nature since the LUMO orbital is essentially composed by the iodine lone pairs. This is in agreement with the El Sayed rules [42] for which spin-orbit couplings increase if there is a change in the composition of the molecular orbitals involved in a given transition. For I_3 -TMBDP-dimer the situation is different since the excited state T_1 is due to two transitions: HOMO \rightarrow LUMO (53%) and HOMO \rightarrow LUMO+1 (43%) (see **Table 2**). In the former circumstance, HOMO and LUMO orbitals are localized each on the BODIPY fragments and the resulting transition, thus, has a π - π character (See **Figure 2**). Nevertheless, LUMO + 1 is mainly localized on the lone pairs of iodine atoms. Consequently, the

second transition is π -n in nature and, according to the El Sayed rules, contributes to increasing the value of the relative SOC.

In order to verify whether our SOC values agree with the available experimental data, we have plotted (**Figure 2**) the computed SOC values and the available experimental singlet oxygen quantum yields [16]. Inspection of the Figure shows that the correlation between the two set of data is quite good and the behaviors are very similar. In fact, as the values of the spin-orbit coupling constant increase, there is an increase in the production of singlet oxygen. The only significant deviation was found for the TMBDP-dimer, for which the calculated SOC values don't follow the same trend of the experimental singlet oxygen quantum yields. Anyway, it is worth of note that, according to the Fermi Golden Rule [43], the intersystem crossing kinetics is directly related to the spin-orbit matrix elements but it also depends on the Franck-Condon weighted density of states (FCWD), not considered in our investigation. For the TMBDP-dimer, thus, we can speculate that the missed FCWD could play a role in the determination of the ISC kinetic constant.

According to the Kasha rule [44], the transition $S_i \rightarrow S_1$ (with $i > 1$) should be a very fast process, and triplet state population should start from the lowest singlet excited state (S_1). For those systems for which different paths are possible, we can suggest the most feasible ISC pathways for the population of the lowest triplet states on the basis of the obtained SOC values. In all the examined cases, the favored process implies the fast decay via IC in the low-lying excited singlet state with subsequent ISC to the T_1 triplet states, as follows:



The fastest process occurs in iodinated systems for which high SOC values were computed for the S_1 - T_1 channel, which should ensure an efficient S_1 - T_1 intersystem crossing.

CONCLUSIONS

In this DFT-based investigation, the main photophysical properties required to propose BODIPY dimers as possible photosensitizers in photodynamic therapy were explored. On the basis of our study, the following conclusions can be outlined:

- All the examined systems show absorption wavelengths that fall in the lower part of the so-called therapeutic window (500–600 nm).
- The spin-orbit coupling constants for BDP and TMBDP dimeric compounds were found to be slightly higher than those computed for their corresponding monomers. Their magnitudes are close to that of FOSCAN[®], which is already used in PDT medical protocols -The systems with the largest SOC values are those containing iodine heavy atoms. Because these structures possess a more efficient singlet-triplet intersystem crossing, they are also expected to more efficiently

produce the singlet O₂ (¹Δ_g) species, which is the main cytotoxic agent in PDT based on type II reactions.

We hope that our investigation can stimulate further experimental studies on these promising systems.

AUTHOR CONTRIBUTIONS

MA, BD, NR, ES, MT equally contributed to the present version of the paper. MA, BD, NR, ES, MT analyzed the results, edited and reviewed equally the manuscript and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphy.2018.00143/full#supplementary-material>

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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