

Tuning Photosensitized Singlet Oxygen Generation Efficiency of Novel Aza-BODIPY Dyes

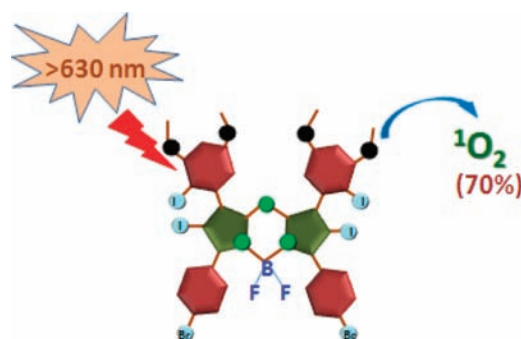
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ABSTRACT



Novel aza-BODIPY derivatives substituted with heavy atoms such as bromine and iodine were synthesized, and their triplet and singlet oxygen generation efficiencies have been investigated. These derivatives showed absorption in the NIR region with high molar extinction coefficients. The dye substituted with four iodine atoms showed yields of $\Phi_T = 0.78$ and $\Phi(^1O_2) = 0.70$, which are the highest values so far obtained for the aza-BODIPY derivatives.

Photosensitized generation of singlet oxygen $O_2(a^1\Delta_g)$ is a well studied phenomenon, which has found numerous applications from synthetic organic chemistry to wastewater treatment to photodynamic cell death.¹ Triplet sensitization of molecular oxygen $O_2(X^3\Sigma_g^-)$ is the most commonly employed method for generating singlet oxygen.² The energy transfer to molecular oxygen, yielding the singlet oxygen, occurs most efficiently from the triplet state of the sensitizer. The probability of the intersystem crossing, $S_1 \rightarrow T_1$, in the sensitizer can be enhanced through spin-orbit perturbations by incorporating heavy atoms.³ A number of organic ligands

have inherent intersystem crossing efficiency and thereby good singlet oxygen generation efficiency viz. phthalocyanines, chlorins, bacteriochlorins, and related systems.⁴ Recently, Wu et al.^{4b} have reported di(perylenebisimide)s with exceptional intersystem crossing efficiency. In contrast, the design of sensitizers such as squaraine⁵ and BODIPY⁶ dyes with high triplet quantum yields has been quite challenging for their potential applications.

The 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacenes, abbreviated as BODIPYs, hold great promise as ideal sensitizers owing to their favorable properties such as high stability, absorption, and emission in the NIR region; high extinction coefficients and fluorescence quantum yields; and negligible

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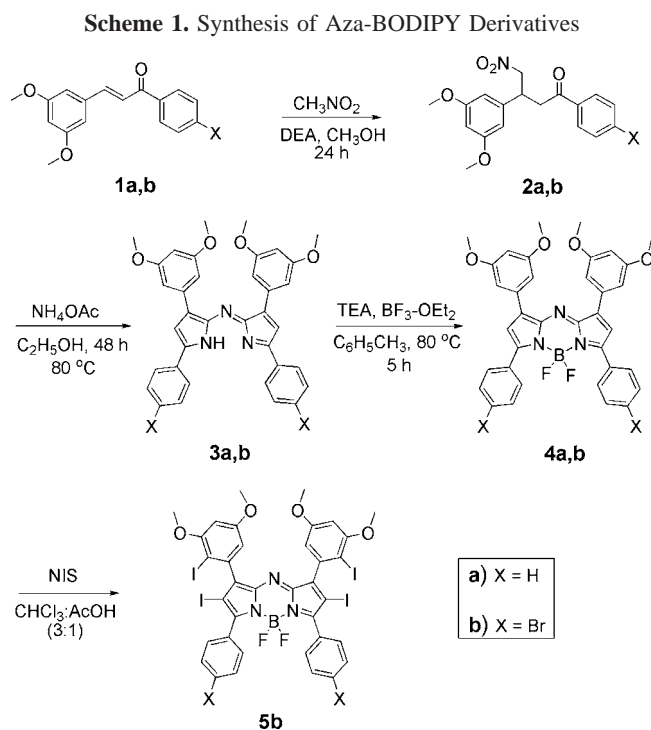
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photobleaching.⁷ Because of these reasons, in recent years there has been increased interest in the derivatization of the BODIPY dyes for various applications.^{8–10} Recent works by various research groups have demonstrated that aza-BODIPY dyes can generate singlet oxygen and thus act as efficient photodynamic therapeutic agents.¹¹ However, the triplet quantum yields and the singlet oxygen generation efficiency of those dyes were found to be relatively low. Herein, we report the synthesis and photophysical characterization of novel boron complexes of aza-dipyrromethenes (aza-BODIPYs) substituted with heavier halogen atoms such as bromine and iodine. By heavy atom substitution, we have been able to obtain a triplet quantum yield of 0.78 and singlet oxygen generation efficiencies as high as 70%. As far as we know these values are the highest reported so far for aza-BODIPY derivatives.

Scheme 1 summarizes the synthetic strategy adopted for the synthesis of various aza-BODIPY derivatives **4a–b** and **5b**. The compounds **4a–b** were synthesized in a facile three-step route starting from the chalcones **1a–b**. Addition of nitromethane to the chalcone in the presence of diethylamine gave the addition products **2a–b** in ca. 75–80% yields. Subsequently, the condensation products **3a–b** were generated by refluxing **2a–b** with ammonium acetate in ethanol for 48 h. The product precipitated during the course of the reaction was filtered and recrystallized to yield **3a–b** (40–50%) with a violet metallic luster. The azadipyrromethenes **3a–b** were subsequently converted to the



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targeted aza-BODIPY derivatives **4a–b** by modifying the reported procedure.^{6d} This was achieved by refluxing **3a–b** with boron trifluoride diethyl etherate and triethyl amine in toluene for 5 h to give **4a–b** in quantitative yields (75–80%) after purification through column chromatography.

With the goal of improving the intersystem crossing efficiency and hence the singlet oxygen generation by the aza-BODIPY derivatives, we introduced heavy atoms such as iodine in the pyrrole ring. This was achieved by reacting **4b** with 4.5 equiv of *N*-iodosuccinimide in a 3:1 mixture of chloroform/acetic acid at 25 °C for 10 h. The reaction mixture after evaporation of the solvent was subjected to column chromatography to yield the iodo substituted aza-BODIPY derivative **5b** in 65% yield. All these derivatives were characterized by various spectral and analytical techniques (Figures S1–S5, Supporting Information).

Aza-dipyrromethenes **3a–b** are characterized by their intense absorption in the near-infrared region of the visible spectrum. The free ligands **3a–b** showed a distinct absorption band in the 610–620 nm region with molar extinction coefficients in the range $(3–7) \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$ (Figure S6, Supporting Information). The incorporation of Lewis acid BF_2^+ to the ligand caused a bathochromic shift in the absorption spectra of the aza-BODIPY derivatives **4a–b** by 50–60 nm (Figure 1A). The absorption spectrum of the compound **5b** with iodo-substitution at the peripheral phenyl rings as well as at the core showed a maximum at 666 nm.

Figure 1B shows the fluorescence spectra of **4b** and **5b** in DMSO. The azadipyrromethene **3b** has an emission maximum at 655 nm (Figure S7, Supporting Information), while the aza-BODIPYs **4a–b** and **5b** exhibited emission in the 690–710 nm region with Stoke shifts in the range 30–40

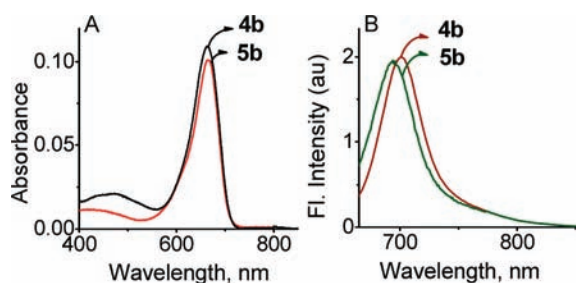


Figure 1. (A) Absorption and (B) emission spectra of the aza-BODIPY derivatives. Excitation wavelength, 630 nm.

Table 1. Photophysical Properties of Various Derivatives^{a,b}

compound	λ_{ab} , nm	ϵ , $10^4 \text{ M}^{-1} \text{ cm}^{-1}$	λ_{em} , nm
3a	619	7.05	<i>c</i>
3b	617	3.57	655
4a	681	5.97	772
4b	664	3.84	701
5b	666	6.99	694

^a Average of more than two experiments. ^b DMSO. ^c Negligible fluorescence.

nm (Table 1). Due to the presence of heavy atoms like bromine and iodine, these derivatives have fluorescence quantum yields less than 0.1. All the aza-BODIPY derivatives have high extinction coefficients in the NIR region and good solubility in common organic solvents such as CHCl_3 , CH_3CN , THF, DMSO, and DMF.

Since the photodynamic activity of the photosensitizers is expected to involve the generation of cytotoxic agents such as singlet oxygen, it is important to study the excited state properties of the synthesized compounds. To characterize the transient intermediates such as triplet excited states in these systems, we have carried out nanosecond laser flash photolysis studies of the aza-BODIPY derivatives in THF solution. Figure 2 shows the transient absorption spectra of **5b**. Excitation of **5b** by 355 nm laser pulses (10 ns, 50 mJ/pulse) led to the formation of transient absorption having peaks at 320 and 510 nm with a bleach in the region corresponding to the ground state absorption. The transient absorption at 510 nm, which is formed within the laser pulse, decays by a first-order process and leads to the recovery of the ground state absorption (inset of Figure 2), indicating negligible formation of any permanent products. This transient absorption is readily quenched by dissolved oxygen, suggesting that the absorption may be due to the triplet excited state formation.^{5a,12a} Similar transients were obtained for **4a** and **4b** at 450 and 430 nm, respectively.

The triplet quantum yields of these aza-BODIPY derivatives were determined using triplet–triplet energy transfer to β -carotene using a tris(bipyridyl)ruthenium(II) complex as the reference.^{5a,12} The nonhalogenated dye **4a** has a low triplet quantum yield of 0.01 with a lifetime of 28 μs , and the bromo derivative **4b** showed a higher triplet yield which

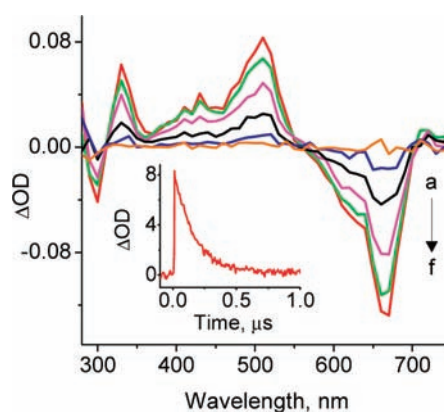


Figure 2. Transient absorption spectra of **5b** following 355 nm laser pulse excitation; time-resolved absorption spectra recorded at (a) 0.1, (b) 0.4, (c) 1, (d) 2, (e) 4, and (f) 10 μs . Inset shows the decay of the transient at 510 nm.

was found to be 0.07 with a lifetime of 44 μs . Notably, when the pyrrole ring as well as the peripheral phenyl ring was substituted with iodine atoms, as in **5b**, we could observe significant enhancement in the triplet quantum yield to 0.78 ± 0.02 with a lifetime of 1.6 μs . We have monitored the transient absorption of **5b** at 320 nm to estimate the efficiency of the energy transfer from BODIPY to β -carotene, and this is the highest triplet quantum yield reported so far in the case of the aza-BODIPY derivatives.

Singlet oxygen is considered to be the main cytotoxic agent in photodynamic therapy, and hence we have examined the efficiency of the photosensitized singlet oxygen generation. Quantum yields for singlet oxygen generation were determined by monitoring the dye-sensitized photooxidation of 1,3-diphenylisobenzofuran (DPBF).¹³ For this, a solution of the aza-BODIPY derivative and DPBF was irradiated using 630 nm long pass over a time period of 6–600 s and the decrease in the absorption band ($\leq 10\%$) of DPBF was monitored. Yields for the generation of singlet oxygen was calculated using the standard, methylene blue (MB), by plotting the ΔOD of DPBF against the irradiation time (Figure 3B).

The azadipyromethenes **3a–b** have negligible singlet oxygen generation efficiency. Upon complexation with BF_2 , we could observe a singlet oxygen generation quantum yield of 0.009 for the nonhalogenated aza-BODIPY, **4a** (Figure S8, Supporting Information). By the incorporation of two bromine atoms, we could observe an increase in the quantum

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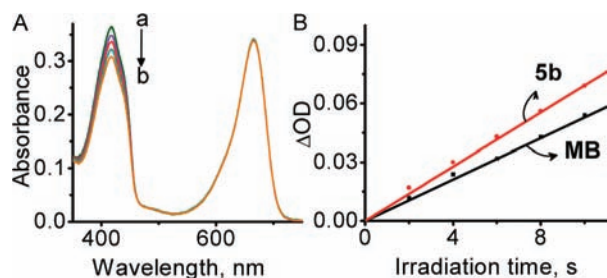


Figure 3. (A) Absorption spectra of DPBF upon irradiation in the presence of **5b** for 8 s: (a) 0 s to (b) 8 s (recorded at 2 s interval). (B) Plot of change in absorbance of DPBF at 418 nm vs irradiation time ($\lambda_{\text{irr}} = 630 \text{ nm}$) in the presence of **5b** against methylene blue (**MB**) as the standard in DMSO.

yield to 0.012 for the dye **4b** (Figure S9, Supporting Information). Interestingly, we observed a significant decrease ($\leq 10\%$) in the absorption bands of DPBF (Figure 3A) in the presence of iodinated derivative **5b** within 6 s, while the standard **MB** ($\Phi(^1\text{O}_2) = 0.52$) showed the corresponding changes in 10 s (Figure S10, Supporting Information). As evident from Figure 3B, both of the plots followed linearity. The presence of four iodine atoms significantly enhanced the singlet oxygen generation quantum yield, $\Phi(^1\text{O}_2)$, of **5b** and was calculated to be 0.70 ± 0.03 . In contrast to the aza-BODIPY derivatives reported earlier,⁶ **5b** showed the highest singlet oxygen generation efficiency of 70%.

The resistance of these dyes to photobleaching was investigated by irradiating an oxygen saturated solution of **5b** for 2 h. We observed negligible changes in its absorption spectrum (Figure S11, Supporting Information) confirming the stability of the dye toward photobleaching. Figure 4 shows the relative singlet oxygen generation quantum yields of the various azadiaryromethene and aza-BODIPY derivatives. As can be seen, the derivative **5b** shows the maximum singlet oxygen generation quantum yields among the aza-BODIPY derivatives synthesized.

In conclusion, we have developed a few novel NIR absorbing aza-BODIPY dyes through a high yielding synthetic route and investigated their excited state photophysical

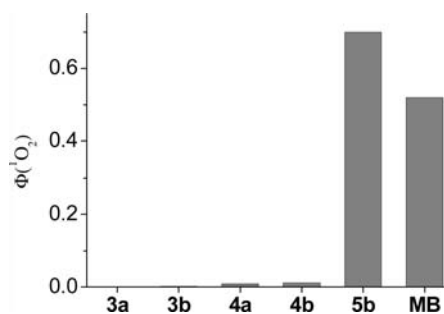


Figure 4. Relative bar diagram showing the singlet oxygen generation quantum yields of aza-BODIPY derivatives and **MB**.

properties. All these derivatives showed a strong NIR absorption in the 620–680 nm region with good molar extinction coefficients ($(3\text{--}7) \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$). The substitution of heavy atoms at the core as well as the peripheral positions resulted in a significant enhancement in the excited state properties of these derivatives. The triplet state characteristics and singlet oxygen generation studies suggest that the derivative **5b** can act as a potential candidate for PDT applications as well as in waste treatment plants. The triplet quantum yield of 78% and singlet oxygen generation efficiency of 70% exhibited by **5b** are the highest triplet and singlet oxygen generation quantum yields reported for the aza-BODIPY derivatives. Further studies are in progress to understand the cellular localization of various aza-BODIPY dyes and their potential PDT applications.

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Supporting Information Available: Experimental details and Figures S1–12 showing ^1H NMR and spectroscopic data of the dyes. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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