



## Original article

## Synthesis dibromo substituted BOPHY dye for the singlet oxygen generation

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## ABSTRACT

A dibromo substituted BOPHY derivative (**2**) was prepared and found to exhibit photo-sensitization capability. Rapid oxidation of 80% DPBF at the first 6 min was observed suggesting that **2** is a superior photo-sensitizer than methylene blue. The HOMO–LUMO band gap for the lowest energy absorption bands of the BOPHY **1** is smaller than that of PS **2**, which is in good agreement with the red shift in the absorption observed between **1** and **2**.

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## 1. Introduction

Singlet oxygen ( $^1\text{O}_2$ ) is of great importance to various applications of cycloaddition reactions, photodynamic therapy (PDT) and so forth [1–3]. Especially, PDT is a noninvasive technique for the treatment of a variety of tumors by the combined use of visible or near-infrared light with a photosensitizing drug [4–7]. The tumor is selectively irradiated with low-energy light of wavelength [8–11], resulting in excitation of the photosensitizer (PS). Since the singlet oxygen is the key cytotoxic agent in the PDT therapeutic process, the singlet oxygen generation from a photosensitizer is regulated by the efficiency of a spin-forbidden electronic transition from a singlet to a triplet state upon irradiation [12]. Comparing to several types of directly linked BODIPY dimers without the use of heavy atoms as a PS [13,14], the heavy atom effect was still advocated and has been a popular and applicable chemical approach to improve intersystem crossing (ISC) to generate the singlet oxygen in several molecules by attaching heavy atoms [15–17].

Due to the excellent photochemical properties of boron dipyrromethenes (BODIPY), such as high fluorescence quantum yields, high absorption coefficients and so on, such derivatives

have been widely investigated (Fig. 1) [18–31]. Recently, BODIPY based photosensitizers were reported by promoting  $S_1 \rightarrow T_1$  transition with attached heavy atoms [32].

Very recently, another type of unique pyrrole-BF<sub>2</sub>-based fluorophore bis(difluoroboron)1,2-bis((1*H*-pyrrol-2-yl)methylene)-hydrazine (BOPHY) was independently reported by Ziegler and Hao *et al.* (Fig. 1) [33,34]. The new fluorescent BOPHY dye can be smoothly obtained by the reaction of pyrrole-2-carboxaldehyde with hydrazine, and followed by complexation with Et<sub>3</sub>N·BF<sub>3</sub>·Et<sub>2</sub>O. The symmetric structure is composed of four rings at the same plane, including two BF<sub>2</sub> units in six-membered chelate rings in the center and two pyrrole units on the periphery (Fig. 1) [33,34]. The fluorescence quantum yield for the unmodified BOPHY is near 100% [33,34]. Since the new BOPHY dye has a rigid structure, excellent optical properties promote us to use the BOPHY scaffold as a template for further functionalizations. Our recent research interest lies in the novel BODIPY/aza-BODIPY family of fluorescent dyes and their application [35–43]. Very recently, our group reported the study on a (*p*-dimethylamino)-styryl-containing BOPHY as a turn-on fluorescent probe for pH [44], and Ziessel *et al.* subsequently also reported the BOPHY dye with the intramolecular cascade energy transfer [45]. However, no other modifications on BOPHY dyes were reported. Herein, we report our studies on the modifications on BOPHY dyes by attaching heavy atoms as a photosensitizer for singlet oxygen generation.

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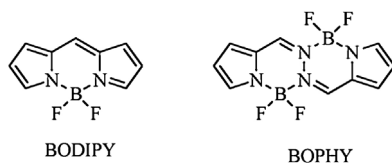


Fig. 1. The core structure of BODIPY and BOPHY.

Singlet oxygen generation was studied with 1,3-diphenylisobenzofuran (DPBF), a well-known singlet oxygen scavenger, whose maximum absorption at 416 nm diminishes upon reacting with singlet oxygen [46]. However, the reported BOPHY dyes are not suitable as a photosensitizer, due to the overlap of the absorption between BOPHY and DPBF or the no site to attach heavy atoms in the BOPHY structure [33,34]. To avoid the defect, a tetraphenyl-containing BOPHY dye as a PS was herein designed and found to be highly effective to generate the singlet oxygen.

## 2. Experimental

$^1\text{H}$  NMR spectra were recorded on a Bruker AVANCE III 500 MHz spectrometer.  $^1\text{H}$  NMR chemical shifts ( $\delta$ ) are given in ppm downfield from  $\text{Me}_4\text{Si}$ , determined by chloroform ( $\delta$  7.26).  $^{13}\text{C}$  NMR spectra were recorded on a Bruker AVANCE III 125 MHz spectrometer.  $^{13}\text{C}$  NMR chemical shifts ( $\delta$ ) are reported in ppm with the internal  $\text{CDCl}_3$  at  $\delta$  77.0 as standard. Toluene solvents were distilled over  $\text{CaH}_2$ . Merck silica gel 60 was used for the column chromatography.

Fluorescence spectra were recorded on a FluoroSENS spectrophotometer. UV/vis spectra were recorded on UV-2550 spectrophotometer at room temperature. The refractive index of the medium was measured by 2 W Abbe's refractometer at 20 °C. The fluorescence quantum yield ( $\Phi_f$ ) of the BOPHY system was calculated using the following relationship (Eq. (1) [47]):

$$\Phi_f = \Phi_{\text{ref}} F_{\text{sampl}} A_{\text{ref}} n_{\text{sampl}}^2 / F_{\text{ref}} A_{\text{sampl}} n_{\text{ref}}^2 \quad (1)$$

Here  $F$  denotes the integral of the corrected fluorescence spectrum,  $A$  is the absorbance at the excitation wavelength. Rhodamine 6G in methanol was used as the standard ( $\Phi_f = 0.95$  [48], in air equilibrated water and deaerated solutions) for BOPHY 1.

The MO calculations were performed at the DFT level, and the frontier molecular orbitals of BOPHY 1 and 2 at the MP2/6-31G\* level with Gaussian 03.

### 2.1. Synthesis of BOPHY 1

3,5-Diphenyl-1H-pyrrole-2-carbaldehyde (45 mg, 0.18 mmol) and hydrazine hydrate (5.0 mg, 0.09 mmol) were dissolved in 20 mL of ethanol. Three drops of acetic acid were added, the solution became yellow. After few seconds, a yellow precipitate formed and the reaction mixture was left to stir at room temperature for an hour. The yellow precipitate was collected by filtration and rinsed with cold ethanol ( $2 \times 10$  mL) and dried

under vacuum to afford a yellow solid. Then,  $\text{Et}_3\text{N}$  (0.5 mL) was added to a solution of this yellow solid in  $\text{CH}_2\text{Cl}_2$  (10.0 mL).  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (1.0 mL) was then added dropwise. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with crushed ice, extracted with  $\text{CH}_2\text{Cl}_2$ , and purified by chromatography on silica gel followed by recrystallization from  $\text{CH}_2\text{Cl}_2/n$ -hexane to afford BOPHY 1 (25.1 mg, 47%) as red solids. Mp: 287.0–288.0 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.21 (s, 2H), 7.84 (d, 4H,  $^3J = 7.5$  Hz), 7.42–7.51 (m, 16H), 6.82 (s, 2H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  152.2, 145.2, 138.3, 132.2, 131.4, 129.8, 129.2, 129.0, 128.9, 128.8, 128.4, 123.4, 117.1. HRMS-MALDI ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{34}\text{H}_{24}\text{B}_2\text{F}_4\text{N}_4\text{Na}$ : 609.2021; found 609.2069.

### 2.2. Synthesis of BOPHY 2

BOPHY 1 (21.5 mg, 0.036 mmol) was treated with bromine (7.6 mg, 0.095 mmol) in dry  $\text{CCl}_4$  (15 mL) at 30 °C under nitrogen for 12 h. The reaction was quenched with water, extracted with  $\text{CH}_2\text{Cl}_2$ , and purified by chromatography on silica gel followed by recrystallization from  $\text{CH}_2\text{Cl}_2/n$ -hexane to afford dye 2 (17.2 mg, 64%) as yellowish red solids. Mp: 291.0–292.0 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.98 (s, 2H), 7.69 (s, 3H), 7.47–7.55 (m, 17H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  149.6, 142.9, 139.1, 130.1, 129.9, 129.5, 129.4, 129.1, 128.9, 128.1, 126.7, 123.0, 106.3. HRMS-MALDI ( $m/z$ ):  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{34}\text{H}_{22}\text{B}_2\text{Br}_2\text{F}_4\text{N}_4\text{Na}$ : 767.0211; found 767.0356.

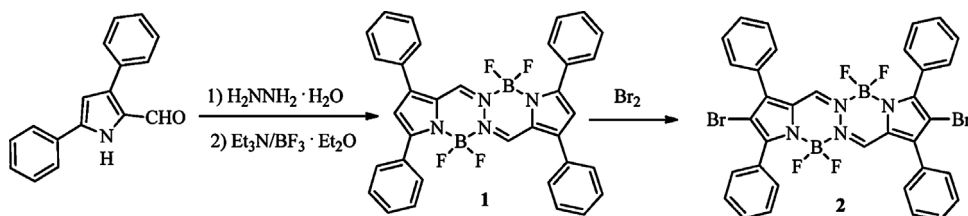
### 2.3. Detection of singlet oxygen by DPBF oxidation

Singlet oxygen generation experiment was set up, using a 150 W xenon lamp at 0.5 mW/cm<sup>2</sup>. A toluene solution of photosensitizer ( $5 \times 10^{-6}$  mol/L) and 1,3-diphenylisobenzofuran ( $6 \times 10^{-5}$  mol/L) was exposed to the monochromatic light by the optical filter at the peak absorption wavelength (500 nm) for 1–2 min at 25 °C. The absorbance was measured several times after each irradiation. Reaction of 1,3-diphenylisobenzofuran with singlet oxygen was monitored by the reduction in intensity of the absorption band at 416 nm over 32 min.

## 3. Results and discussion

Synthesis of the BOPHYs were outlined in Scheme 1. Utilizing 3,5-diphenyl-1H-pyrrole-2-carbaldehyde as the starting material, a centrosymmetric tetraphenyl-containing BOPHY 1 was smoothly obtained in a 47% yield based on the reported literatures [33,34]. The PS 2 was prepared in a 64% yield by bromination of BOPHY 1 with  $\text{Br}_2$ .

The BOPHY 1 absorbs maximally at 508 nm and emits at 524 nm in  $\text{CHCl}_3$  (Fig. 2), with the high extinction coefficients ( $\epsilon = 60,000 \text{ L mol}^{-1} \text{ cm}^{-1}$ ), the narrow full width at half maximum (Fwhm = 78 nm) and the high fluorescence quantum yield ( $\Phi_f = 0.96$ ), which optical properties are comparable to those of the reported BOPHY dyes [33,34,44,45]. Due to remarkable absorption difference between BOPHY 2 (506 nm) and DPBF



Scheme 1. Synthesis of the tetraphenyl-containing BOPHY 1 and the PS 2.

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