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Attaching naphthalene derivatives onto BODIPY for generating excited triplet state and singlet oxygen: Tuning PET-based photosensitizer by electron donors

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ABSTRACT

meso-Naphthalene substituted BODIPY compounds were prepared in a facile one pot reaction. The naphthalene functionalization of BODIPY leads up to a 5-fold increase in the formation efficiency of excited triplet state and singlet oxygen in polar solvents. Steady state and time resolved fluorescence, laser flash photolysis, and quantum chemistry methods were used to reveal the mechanism. All measured data and quantum chemical results suggest that these systems can be viewed as electron donor-acceptor (D-A) pair (BODIPY acts as the acceptor), photoinduced charge transfer (PCT) or photoinduced electron transfer (PET) occurs upon photo excitation (D-A + $h\nu$ → $D^{\delta+}$-$A^{\delta-}$, $0 < \delta \leq 1$), and the charge recombination induced the formation of triplet state ($D^{\delta+}$-$A^{\delta-}$ → D-A (T_1). These novel PCT- or PET-based photosensitizers (PSs) show different features from traditional PSs, such as the strong tunability by facile structural modification and good selectivity upon medium polarity. The new character for this type of PSs can lead to important applications in organic oxygenation reactions and photodynamic therapy of tumors.

1. Introduction

Photosensitized generation of singlet oxygen has been a fast growing field due to its important applications in cancer treatment [1–4], photosensitized oxidations [5], biomolecular degradation [6,7], antibacterial and antiviral treatments [8], environmental protection and photodecomposition of pollutants [9]. Singlet oxygen generation and its oxidizing effect is also one of the key interests of the pharmaceutical industry in relation to action and photostability of drugs [10]. Photosensitisers (PS) generate singlet oxygen through energy transfer from its excited triplet state to molecular oxygen [11,12]: $T_1 + O_2 \rightarrow S_0 + {}^1O_2$. For compounds that are not efficient in forming T_1 state, external or internal heavy atom effect by I, or Br atom substitution or transition heavy metal ion ligation are often used to efficiently enhance ISC [11,12].

BODIPYs are well known highly fluorescent materials and applied in different areas [13–16]. They are recently proposed to act as PSs for PDT, although the unsubstituted BODIPY is lack of good ability to produce T_1 state due to their high fluorescence efficiency. BDP (Scheme 1), for example, shows the fluorescence quantum yield near unity (0.97 ± 0.03) and a long fluorescence lifetime of 6.89 ns in methanol [17], which leaves it little space to form T_1 state. Iodine or bromine substitution is often used to make BODIPY generate T_1 and singlet oxygen efficiently and act as good photosensitizer in photodynamic therapy [8,18–22]. However, the halogen and heavy metal atoms are highly undesirable in medicine.

Linking another BODIPY unit or an aryl group to one BODIPY can make them generate T_1 state and singlet oxygen efficiently, as shown in our previous reports [22–24]. Although the attachment of anthracene and aminophenyl to BODIPY work very well for the T_1 generation, the linkage of naphthalene did not enhance the formation of singlet oxygen [22]. We show hereby that modifying naphthalene unit as a good electron donor or acceptor (Scheme 1), the obtained naphthalene-BODIPY conjugate can also efficiently generate T_1 and singlet oxygen. Moreover, the capability is sensitive to external conditions that make them good activable PSs.

2. Experimental Section

2.1. Reagents and Apparatus

All reagents for synthesis were analytical grade and used as received. All solvents for spectrum studies were dried and redistilled

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before use. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker AVANCE III HD 600 MHz NMR spectrometer. MS spectra were recorded on a Thermal Fisher LCQ Fleet™ mass spectrometer. IR spectra were recorded at room temperature on a Shimadzu FTIR-8900 spectrometer. UV–visible spectra were recorded on an Agilent 8454 spectrophotometer using 1 cm matched quartz cuvettes.

2.2. Common Procedure for the Synthesis of Naphthalene Substituted BODIPY

50 mL anhydrous dichloromethane (CH_2Cl_2) containing a selected aldehyde (2.0 mmol) and 2,4-dimethyl-pyrrole (4.0 mmol) was stirred under argon protection. After 15 min, one drop of trifluoroacetic acid (CF_3COOH) was added, and the solution was stirred for 12 h at room temperature. Then 2.0 mmol of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) was added and the solution was stirred for 30 min. The excess of boron trifluoride diethyl etherate ($BF_3O(Et)_2$, 4 mL) and triethylamine ($N(Et)_3$, 4 mL) was added and stirring was continued for 30 min. The intense fluorescence of reaction mixture was observed on that stage. The formation of intermediates and BODIPY products on every stage was monitored by UV–vis absorption spectra. After that the reaction mixture was washed with water (100 mL × 3), the organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by silica gel chromatography (eluent CH_2Cl_2/hexane = 2:1 v/v) to afford pure samples.

2.3. 4,4-Difluoro-8-naphthyl-1,3,5,7-tetramethyl-4-boron-3a,4a-diaza-s-indacene (NP-TMBDP) Synthesis

NP-TMBDP was synthesized according to the general synthesis procedure using 1-naphthaldehyde as a precursor. The product is dark red crystals (yield: 16%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.99 (d, J = 8.3 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.61–7.58 (m, 1H), 7.54 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 6.6 Hz, 1H), 5.97 (s, 2H), 2.62 (s, 6H), 1.08 (s, 6H) ppm. ^{13}C NMR (151 MHz, Chloroform-*d*) δ 155.60, 143.03, 140.15, 133.53, 132.43, 131.95, 131.67, 129.27, 128.20, 127.27, 126.64, 125.96, 125.81, 124.92, 121.19, 14.70, 13.91 ppm. HRMS (APCI): m/z $C_{23}H_{21}BF_2N_2$, calcd. 355.1782 $[M\text{-}F]^+$, found 355.1771 $[M\text{-}F]^+$. calcd. 375.1844 $[M + H]^+$, found 375.18429 $[M + H]^+$.

2.4. 4,4-Difluoro-8-meoxynaphthyl-1,3,5,7-tetramethyl-4-boron-3a,4a-diaza-s-indacene (MeONP-TMBDP) Synthesis

MeONP-TMNDP was synthesized according to the general synthesis procedure using 1-(4-meoxy)naphthaldehyde as a precursor. The product is dark red crystals (yield: 21%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.01 (d, J = 9.1 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.40 (dt, J = 12.8, 7.3 Hz, 3H), 5.95 (s, 2H), 3.91 (s, 3H), 2.61 (s, 6H), 1.15 (s, 6H) ppm. ^{13}C NMR (151 MHz, Chloroform-*d*) δ 155.05, 153.37, 142.41, 137.47, 132.73, 131.89, 131.08, 127.78, 127.73, 124.27, 123.80, 120.87, 117.07, 112.98, 56.42, 14.72, 13.48 ppm. HRMS (APCI): $C_{24}H_{23}BF_2N_2O$, calcd. 385.1887 $[M\text{-}F]^+$, found 385.1874 $[M\text{-}F]^+$. calcd. 405.1950 $[M + H]^+$, found 405.1930 $[M + H]^+$.

2.5. 4,4-Difluoro-8-carboxynaphthyl-1,3,5,7-tetramethyl-4-boron-3a,4a-diaza-s-indacene (NPc-TMBDP) Synthesis

1,8-naphthalic dicarbonyl dichloride (0.252 g, 1 mmol) was dissolved in dried DCM (30 mL), in which argon was bubbled to remove oxygen. 2,4-dimethyl pyrrole (0.21 mL, 2 mmol) was added and the solution became red immediately, it was then stirred in the dark at 20 °C for 10 h. After that triethyl amine (2 mL, 14.24 mmol), boron trifluoride diethyl etherate (2 mL, 15.57 mmol) were added under ice bath. At room temperature, the resulted solution was stirred for 2 h. The solution was then added to deionized water (100 mL) and stirred for 2 h. The organic layer was separated and washed by water three times (3 × 150 mL), then dried by Na_2SO_4 and filtered. The filtrate was evaporated to give the solid, which was then purified by column chromatography (eluent CH_2Cl_2: *n*-hexane = 3: 1). Yield: 20 mg, 5%. mp 209–212 °C; IR (KBr)/cm^{-1}: 736, 981, 1082, 1157, 1199, 1469, 1508, 1547 (ν BODIPY环); 1307, 2856, 2926 (ν CH_3); UV/vis (DCM) λ_{max}/nm: 514; HRMS(APCI): m/z calcd for $C_{24}H_{21}BFN_2O_2$ $[M\text{-}F]^+$ 399.1680, found 399.1677. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.98 (dd, J = 11.5, 8.3 Hz, 2H), 7.72 (s, 2H), 7.61–7.56 (m, 2H), 7.49–7.46 (m, 1H), 7.40 (d, J = 7.0 Hz, 1H), 5.88 (s, 1H), 2.44 (s, 6H), 1.02 (s, 6H) ppm.

2.6. NPc-BDP Synthesis

1,8-Naphthalene dicarboxylic anhydride (0.32 g, 0.96 mmol) was dissolved in $SOCl_2$ (10 mL) and refluxed for 5 h, residual $SOCl_2$ was removed by vacuum distillation. Anhydrous dichloromethane (20 mL) was added and N_2 was bubbled for 30 min. Pyrrole (0.19 mL, 2.6 mmol) was then put in, and the reaction was carried out in the dark for 3 h at 20 °C. Triethyl amine (2 mL) was put in under ice bath and constant stirring. After the disappearance of the white smog, BF_3-etherate (0.23 g) was added and the reaction proceeded under refluxing for 2 h, which gave orange brown solution. Saturated NaCl aqueous solution (20 mL) was put in, organic phase was extracted by dichloromethane (3 × 50 mL), washed by water (3 × 50 mL), dried by anhydrous $MgSO_4$ and rotavapored. The crude product was purified by column chromatography (200–300 mesh silica, CH_2Cl_2/petroleum ether = 3:1 v/v) afforded red solid. Yield: 28 mg, 8%. m.p. 192–193 °C. IR(KBr)/cm^{-1}: 1681(C═O), 1549, 1389 (naphthalene ring), 1265(B-F), 1119, 1078, 1032, (B-F); UV/vis (DCM) λ_{max}/nm: 297, 371, 507; ^{1}H NMR (600 MHz, Methanol d_4) δ 8.12 (d, J = 8.1 Hz, 1H), 8.07 (d, J = 8.3 Hz, 1H), 7.80 (s, 2H), 7.74 (d, J = 7.1 Hz, 1H), 7.68 (d, J = 7.1 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 6.61 (d, J = 4.2 Hz, 2H), 6.39 (d, J = 4.1 Hz, 2H) ppm. ESI-MS (m/z) cal.: 361.0960 $(M\text{-}H)^-$, found: 361.0959 $(M\text{-}H)^-$.

2.7. 4,4-Difluoro-1,3,5,7-tetramethyl-4-boron-3a,4a-diaza-s-indacene (TMBDP) Synthesis

TMBDP was synthesized by modifying a literature procedure [25]. 250 mL 1,2-dichloroethane was deaerated by bubbling N_2. 2,4-dimethyl pyrrole (1 mL, 11.37 mmol), triethylorthoformate (0.95 mL, 5.69 mmol) and $POCl_3$ (0.58 mL, 6.25 mmol) were added to the deaerated solvent. Reaction was allowed to stir for 2 h at room temperature. Then 11.5 mL NEt_3 and 11.5 mL BF_3-etherate were added. After 1 h the reaction was washed with water (3 × 250 mL), the organic layer separated, dried on anhydrous $NaSO_4$ and evaporated in vacuo. Column chromatography with $CHCl_3$ as the eluent yielded the pure product as reddish solid (400 mg, 28%). ^{1}H NMR (600 MHz, Chloroform *d*) δ 7.07 (s, 1H), 6.07 (s, 2H), 2.55 (s, 6H), 2.27 (s, 6H) ppm. ^{13}C NMR (151 MHz, Chloroform *d*) δ 156.69, 133.35, 120.06, 118.99, 14.67, 11.29 ppm.

2.8. Photophysical Measurements

The details on the measurement of steady state and time resolved fluorescence, as well as laser flash photolysis have been given in our previous reports [24,26].

2.9. Computational Simulation

The calculations were carried out using density functional theory (DFT) method as implemented in the Gaussian 09 package. The B3LYP exchange-correlation functional was chosen together with a 6-31G(d) basis set for structural optimization. The solvent effect was modeled using the Polarizable Continuum Model (CPCM) method. In all the