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Colorimetric and fluorometric pH sensor based on bis(methoxycarbonyl)ethenyl functionalized BODIPY

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We report a difluoroboradiaza-*s*-indacene (BODIPY) dye substituted with bis(methoxycarbonyl)ethenyl at 3 and 5 positions as a near-IR colorimetric and fluorometric “on-off” pH sensor. The sensor absorbs and emits light at ca. 600 nm with high absorbance and fluorescence intensities ($\log(\varepsilon) = 5.0$, $\varphi_f = 0.77$ in ethanol) and basification causes dramatic changes on these optical properties. The sensor reversibly responses to pH changes between 7.0 and 10.0 in ethanol/water and can easily be synthesized from 1,9-diformyldipyrromethane with a one pot procedure.

1. Introduction

Fluorescent pH sensors have attracted great attention due to their advantageous properties such as high sensitivity, high selectivity and short response time [1,2]. Many fluorescent pH sensors based on a variety of molecular platforms like difluoroboradiaza-*s*-indacene (BODIPY) [2–13], seminapthorhodafluor [14–16], fluorescein [17,18], 1,8-naphthalimide [19,20] and some other fluorescent molecules [21–24] have been developed. Amongst these dyes, BODIPY based molecules have been studied intensively due to their convenient spectral properties such as high absorption and fluorescence intensities, high photostability and amenability to optical alterations with small changes on the molecule or its medium [2,13,25,26]. Most of these sensors emit below 600 nm and utilize the optical changes upon protonation/deprotonation of a nitrogen atom of N,N-dialkylaminophenyl [3–6,27,28], pyridyl [28], alkylamine [7], imidazolyl [8,29], imine [9] or phenolic groups [10,11,30] on BODIPY. One exception to these pH sensing functional groups was reported by Ravikanth et al. [31]. In this report, aldehyde groups on 3 and 5 positions of BODIPY were shown to give optical response to hydronium ion.

BODIPY-based pH sensors exploit either photoinduced electron transfer (PET) [3,7,8], or resonance energy transfer (RET) [32] mechanisms for pH-dependent fluorescence modulation. Such modulation includes fluorescence quenching [7,8], fluorescence enhancement [3,27] and shift of the emission wavelength [28]. In very recent studies, various BODIPY dyes were reported showing a pH dependent alteration in absorbance along with fluorescence [9,27–29,31,33,34].

Herein, we report a bis(methoxycarbonyl)ethenyl BODIPY molecule **1** (Scheme 1), giving color and fluorescent based responses to basicity. Before, Daub et al. had reported beta-ester substituted BODIPY (**2**) being unresponsive to pH changes (Scheme 1) [11].

2. Experimental

2.1. Reagents and instrumentation

Commercially available reagents and solvents were purchased from Sigma-Aldrich and Acros Organics and were used without further purification. Reactions were monitored by thin layer chromatography using silica gel plates (60, F_{254}, Merck) and crude products were purified with flash column chromatography by using silica gel (60-200 Mesh, J.T. Baker). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{19}F NMR (376 MHz) spectra were recorded using

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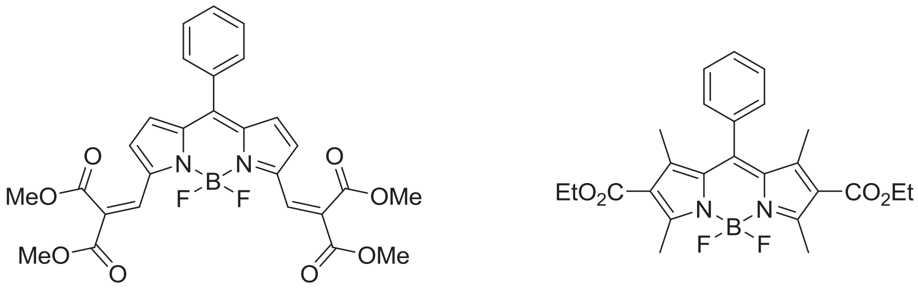

1

2[10]

Scheme 1. Structure of BODIPYs bearing ester groups.

tetramethylsilane as an internal standard with Bruker 400 FT-NMR spectrometer. UV/visible absorption measurements were performed on PG instruments T80 UV/visible spectrometer. Fluorescence spectra were recorded on Shimadzu RF-5301 PC spectrofluorometer (excitation and emission slit widths were 5 nm). Melting points were measured using Gallenkamp capillary melting point apparatus. HR-MS data were performed on Agilent (1200/6210) TOF LC/MS spectrometer. pH measurements were recorded using Ecomet pH/mV/TEMP Meter P 25.

Fluorescence quantum yield of **1** was calculated by comparative method using Cresyl Violet ($\varphi_f = 0.51$ in ethanol [35]) as fluorescence standard.

pH studies were run in deionized water/ethanol (1/1, v/v) borax buffer. Borax buffer was prepared by dissolving borax (0.477 g) in 7.2 mM NaOH (aq) (50.0 mL) and then adding ethanol (50 mL) onto this solution. pHs of the solutions were adjusted to a definite value with 0.1–10.0 M solutions of HCl and NaOH. Dye solutions were prepared by dilution of **1** (6×10^{-4} M) in THF.

2.2. Synthesis

2.2.1. Synthesis of 5-phenyldipyrromethane (3)

Compound **3** was synthesized by using a previously reported procedure [36]. Pale brown solid, yield 62%, mp 99–100 °C. Spectroscopic data were identical to those reported in the literature [37].

2.2.2. Synthesis of 1,9-diformyl-5-phenyldipyrromethane (4)

Compound **4** was synthesized from **3** by using a previously reported procedure [31]. Orange solid, yield 64%, mp 162–164 °C. R_f: 0.28 (EtOAc-hexane, 1:2). IR (ATR) (ν max/cm^{-1}): 3240, 1640, 1557, 1488, 1446, 1419, 1386, 1321, 1282, 1219, 1174, 1117, 1034, 851, 800, 744, 702. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (s, 1H, *meso*-H), 6.05 (bs, 2H), 6.85 (bs, 2H), 7.26-7.37 (m, 5H, Ar–H), 9.20 (s, 2H, -CHO), 10.47 (bs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.3, 111.5, 121.9, 127.5, 128.3, 128.8, 132.5, 138.9, 141.3, 178.7.

2.2.3. Synthesis of 3,5-Di(dimethyl-2-methenemalonate)-8-phenyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (1)

1,9-Diformyl-5-phenyldipyrromethane (**4**) (0.54 mmol, 150 mg), dimethyl malonate (2.17 mmol, 250 μL) and piperidine (0.11 mmol, 11.0 μL) were refluxed in toluene (15 mL) using a Dean-Stark apparatus. Piperidine was added throughout the reaction (11.0 μL per hour). Reaction was monitored with TLC and completed after 4.5 h. The reaction mixture was cooled down to room temperature and DDQ (0.33 mmol, 75 mg) was added and stirred for 30 min, then triethylamine (2.11 mmol, 294 μL) and $BF_3.(OEt)_2$ (2.11 mmol, 260 μL) were added respectively. The mixture was further stirred for 30 min and then the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc-hexane, 1:6) to afford **1** as an iridescent brown-green solid (131 mg), yield 44%, mp 194–196 °C. R_f: 0.49 (EtOAc-hexane, 1:1). IR (ATR) (ν max/cm^{-1}): 2963, 1740, 1711, 1581, 1534, 1475, 1443, 1369, 1298, 1267, 1214, 1183, 1127, 1082, 1062, 1022, 983, 930, 892, 843, 800, 762, 728, 689. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (s, 6H, OCH_3), 3.89 (s, 6H, OCH_3), 6.74 (d, $J = 4.5$ Hz, 2H), 6.92 (d, $J = 4.5$ Hz, 2H), 7.52–7.64 (m, 5H, Ar–H), 8.24 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.1, 120.6, 128.7, 129.9, 130.2, 130.5, 131.2, 131.9, 133.2, 137.6, 146.2, 150.0, 163.7, 166.4. ^{19}F (376 MHz, $CDCl_3$) δ −137.3–137.6 (q, $J_{B\text{-}F} = 33$ Hz). HRMS (ESI) *m/z* for $C_{27}H_{23}BF_2N_2O_8$ calcd $(M\text{-}F)^+$ 533.1531, found 533.1511.

3. Results and discussion

3.1. Synthesis

The synthesis of bis(methoxycarbonyl)ethenyl substituted BODIPY **1** is outlined in Scheme 2. Firstly, 5-phenyl-dipyrromethane **3** was synthesized in aqueous medium, using the procedure described by Dehaen et al. [36]. Vilsmeier-Haack reaction of **3** regioselectively gave the 1,9-diformylated dipyrromethane **4**. **4** was heated with dimethyl malonate in the presence of catalytic amount of piperidine in toluene and the Knoevenagel adduct was converted to BODIPY *in situ*, first by oxidizing with DDQ and then treating respectively with triethylamine and $BF_3.(OEt)_2$ at room temperature. The synthesized compounds were purified by flash column chromatography, and their structures were confirmed by using ^{1}H NMR, ^{13}C NMR, ^{19}F NMR (Fig. S1, S2 and S3) and HRMS techniques.

3.2. Photophysical characteristics

Solutions of compound **1** were highly colored and gave a bright orange color under UV light. As shown in Fig. 1, the absorption characteristics of compound **1** in common organic solvents were mainly solvent independent. The most intense band at ca. 590 nm ($\log(\varepsilon) = 5.0$ in ethanol) corresponds to low energy $S_0 \rightarrow S_1$ transition of BODIPY core. Compared to its unsubstituted analogue [38], the conjugations caused a 90 nm red-shift of this characteristic BODIPY peak. Higher energy transitions of the molecule appeared as two weaker bands at ca. 300 nm and ca. 350 nm.

Fluorescence spectra of **1** were collected in different solvents (Fig. 2). Changes in the fluorescence profile of the molecule in different solvents were more evident than the changes in absorbance spectra. In ethanol, acetonitrile and hexane, compound **1** emitted light at 603 nm with similar intensities. In chloroform and toluene, the emission bands shifted to 609 nm with lower intensities. In ethanol, **1** has a quantum yield of 0.77 which makes the dye highly fluorescent. The optical properties of **1** in different solvents were summarized in Table 1.