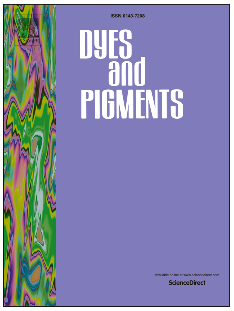

Colorimetric and fluorometric pH sensor based on bis(methoxycarbonyl)ethenyl functionalized BODIPY

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PII: S0143-7208(15)00143-6

DOI: 10.1016/j.dyepig.2015.04.021

Reference: DYPI 4743

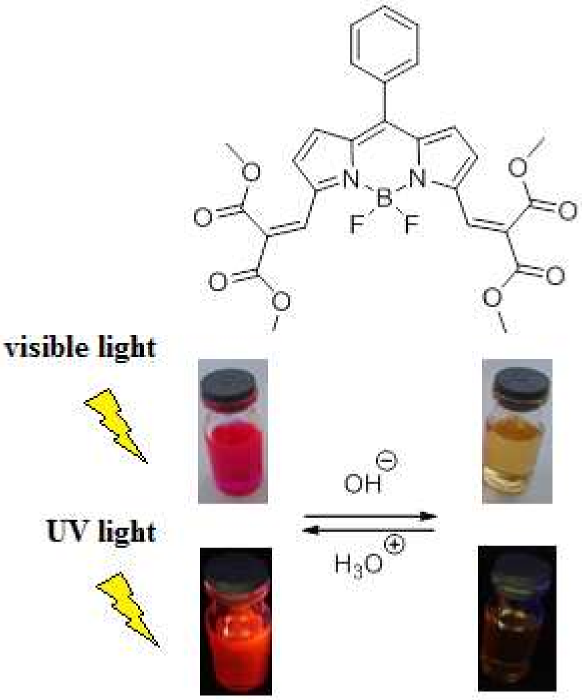
To appear in: *Dyes and Pigments*

Received Date: 9 February 2015

Revised Date: 13 April 2015

Accepted Date: 16 April 2015

Please cite this article as: Teknikel E, Unaleroglu C, Colorimetric and fluorometric pH sensor based on bis(methoxycarbonyl)ethenyl functionalized BODIPY, *Dyes and Pigments* (2015), doi: 10.1016/j.dyepig.2015.04.021.


visible light
UV light
$OH^{\ominus}$
$H_3O^{\oplus}$
N
B
N
F
F
O

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

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Abstract

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(ε)=5.0, ϕ_f= 0.77 in ethanol) and basification causes dramatic changes on these optical properties. The sensor reversibly responses to pH changes between 7.0-10.0 in ethanol/water and can easily be synthesized from 1,9-diformyldipyrromethane with a one pot procedure.

Keywords: pH sensor, colorimetric sensor, fluorometric sensor, BODIPY

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 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 (ϕ_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 x 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 ^{o}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 ^{o}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 hours. 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 ^{o}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(ε)=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 (Figure 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.

Table 1: Optical properties of **1** in different solvents.

Solvent	λ_{abs} (max) (nm)	ε x10 ^{4} ($M^{-1}cm^{-1}$)	λ_{em} (max) (nm)	Stokes shift (nm)	ϕ_f
Toluene	598	9.80	611	13	0.45
Chloroform	598	10.45	609	11	0.54
Ethanol	592	9.80	603	11	0.77
Hexane	593	11.11	603	10	0.70
Acetonitrile	590	9.28	603	13	0.76

3.3 pH Dependent Studies

When the ethanolic solution of **1** was basified, the shiny pink color of solution turned into pale yellow and its fluorescence under UV light disappeared (Insets in Fig. 3 and 4). These observations encouraged us to investigate the absorbance and emission spectra of **1** at different pH values.

Increasing pH was seen to alter absorbance spectrum dramatically (Fig. 3). Beginning from pH ca. 7.0, intensities of absorbance bands at 592 nm and 304 nm decreased and almost disappeared at pH ca. 10.5, while the intensity of the band at 356 nm increased. These changes in three bands created two isobestic points one being at 408 nm, and the other one at 322 nm. No shift in the band maxima was observed upon pH changes. Acidification of the medium recovered the initial absorbance spectrum.

When we searched the effect of pH on the fluorescence spectrum of **1**, we observed decrease in fluorescence intensity by increasing basicity (Fig. 4). Quenching started at pH ca. 7.0 and almost completed at pH ca. 10.0 with no shift at band maximum. Basification-reacidification operations resulted in recovery of fluorescence.

In order to explore the reason behind the pH dependent optical changes of **1,** we focused our attention to possible aggregation of **1** in basic medium. In the literature, there are various examples of dramatic optical changes for BODIPYs based on H- and J- type aggregations of the dye molecules [39-48]. H-type aggregates are characterized by blue-shifted, non-emissive absorbance bands compared to their monomers [49,50]. Non-emissive absorbance bands of compound **1** at 300 and 350 nm could be attributed to this type aggregation. We run a series of experiments to test this presumption. Firstly, we collected ^1H NMR spectra of **1** at concentrations from 0.3 mM to 30 mM in d-chloroform (Fig. S4). All proton signal shifts were observed to be totally concentration independent indicating the absence of self-assemblies of **1** even in concentrated solutions, whereas any aggregation should cause strong proton chemical shifts [48].

For further examination of aggregation, we collected absorbance spectra of **1** in ethanol at different concentrations (Fig. S5). We observed linear increase for all absorbance bands at with increasing concentrations. This observation confirmed that the bands at ca. 300, ca. 350 nm are not related to aggregation. However, interesting results were obtained from concentration dependent absorbance spectra of **1** in water/ethanol mixture at fixed pH of 8.70 (Fig. S6). There is a nonlinear change between the increase ratios of absorbance intensities with increasing concentration. As the concentration increased, the absorbance coefficient of the band at ca. 590 decreased (from $\varepsilon = 72000$ at 7.5×10^{-6} M to $\varepsilon = 34000$ at 5.0×10^{-7} M) while those of other bands remained nearly the same. As a consequence, no isobestic point was observed for these spectra providing further prove for the absence of aggregation.

As we found no hint of aggregation behind the pH dependent optical alteration of **1,** we searched the possible reactions of hydroxyl with the molecule causing optical changes. Firstly, we get ^1H-NMR spectrum of **1** in CD_3OD before and after addition of base (Fig. S7) to figure out if there is any conjugate addition to double bonds or hydrolysis of ester groups. Proton signals in CD_3OD is not as clear as it is in $CDCl_3$ (Fig. S1) because of low solubility of the molecule in methanol. Also, addition of basic solution of D_2O into methanolic solution of **1** caused an environmental change around the molecule. Still, these spectra were informative enough to get evidence about possible reactions. Existence of vinylic protons at 8.10 ppm in basic medium eliminated the possible conjugate addition of hydroxyl to double bonds. Additionally, presence of methoxy protons at 3.66 and 3.68 ppm in basic medium indicated that there was no sudden conversion of esters to carboxylates.

Various reported studies in the literature have shown that the BODIPY core itself is stable towards bases at room temperature [51-53]. Still, the nucleophilic attack of hydroxyl ion to boron atom and consecutive ring opening or displacement with fluorine might be thought to be other possible reactions causing observed optical changes. To confirm the existence of fluorine atoms on the BODIPY core after basification, we got ^{19}F-NMR spectrum of **1** in neutral and basic medium. In neutral CD_3OD, fluorine signals appeared at -140.2 ppm as quartet $J(^{11}B-^{19}F)$ = 32 Hz assigning chemically equivalent fluorines on boron atom (Fig. S8a). In basic medium two sets of peaks appeared at -136.1 ppm and -137.1 as doublet of quartet $J(^{11}B-^{19}F)$ = 32 Hz and $J(^{19}F-^{19}F)$ = 103 Hz (Fig. S8b). Similar ^{19}F-NMR spectra were reported for BODIPYs having chemically inequivalent fluorines on boron atom [54-56]. The observed ^{19}F-NMR spectrum for our molecule pointed out that chemical environment of fluorine atoms differed in basic medium while original BODIPY skeleton has been preserved.

The reason behind the optical behavior of **1** in basic medium seems to be different from those other sensors. No reason could be attributed to explain this unusual response of **1** to base when all experimental results were collectively evaluated and the mechanism behind this optical behavior of the molecule remains unclear. Nevertheless, we introduced **1** as a new BODIPY based alkaline pH sensor, to our knowledge, the first that does not bear a phenolic group.

4. Conclusion

We synthesized a novel BODIPY based near-IR fluorometric and colorimetric pH sensor **1** bearing bis(methoxycarbonyl)ethenyl groups. Both the absorbance coefficient and fluorescence quantum yield are very high in organic solvents. The sensor showed reversible response to pH between 7.0-10.0 in aqueous solution with both color and fluorescence changes. The sensor can easily be prepared from commercially available chemicals in good yields.

Acknowledgement

The author would like to acknowledge Assoc. Prof.Dr. Lokman Uzun for using spectrofluorometer.

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Scheme & Figure Captions

Scheme 1. Structure of BODIPYs bearing ester groups.

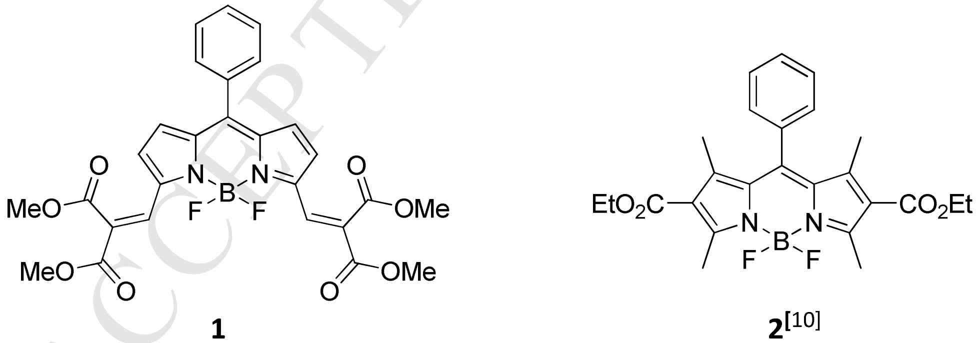
Scheme 2. Synthesis of the sensor **1**. Reagents and conditions: (a) 0.18 M HCl, rt, 60 min, 62%; (b) *i*) DMF/$POCl_3$, reflux, 2 h, *ii*) H_2O, K_2CO_3, rt, 30 min, 74%; (c) *i*) Dimethyl malonate, piperidine, toluen, reflux, 4.5 h, *ii*) DDQ, rt, 30 min, *iii*) TEA, after 3 min $BF_3.(OEt)_2$, rt, 30 min, 44%.

Fig. 1. Absorption spectra of **1** (6.0×10^{-6} M) in different solvents.

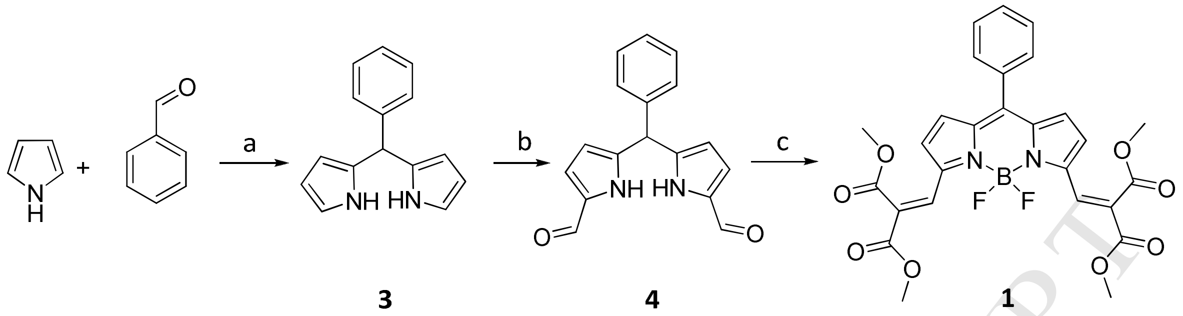
Fig. 2. Fluorescence spectra of **1** (6.0×10^{-7} M) in different solvents (λ_{exc}= 570 nm).

Fig. 3. Absorption spectra of **1** in H_2O/C_2H_5OH (1/1, v/v) borax buffer solution (6.0×10^{-6} M) as a function of pH. Inset pictures show the colors of **1** under visible light a) in neutral and b) in basic medium.

Fig. 4. Fluorescence spectra of **1** in H_2O/C_2H_5OH (1/1, v/v) borax buffer solution (6.0×10^{-7} M) as a function of pH (λ_{exc}= 570 nm). Inset pictures show the color of **1** under UV light (366 nm) a) in neutral and b) in basic medium.



Scheme 1. Structure of BODIPYs bearing ester groups.



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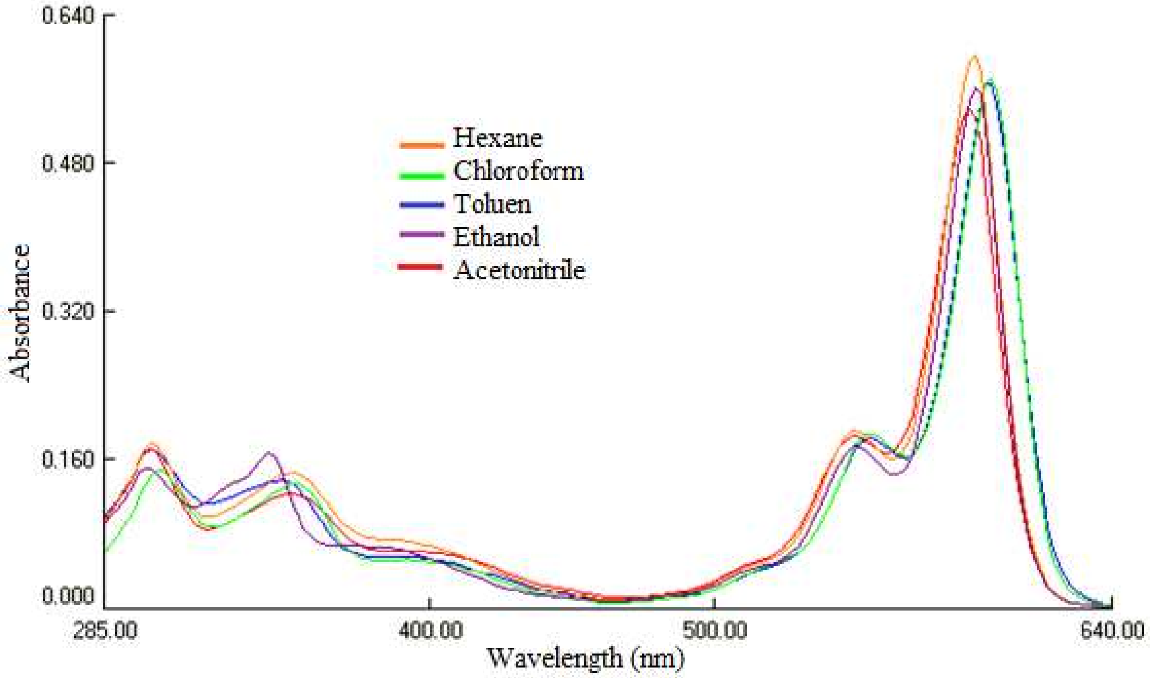

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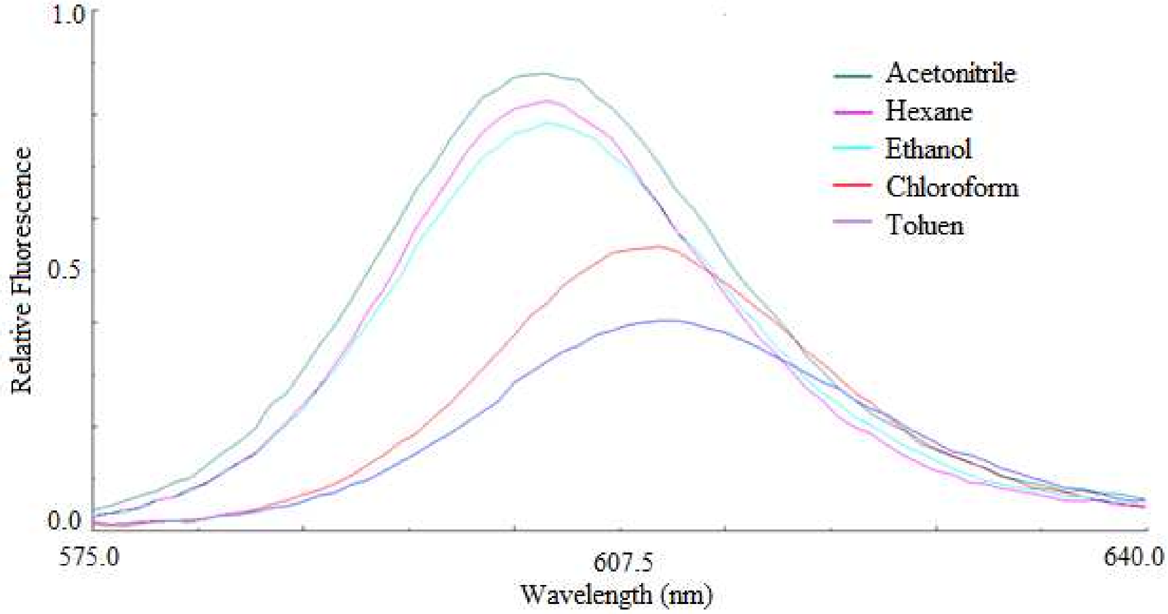
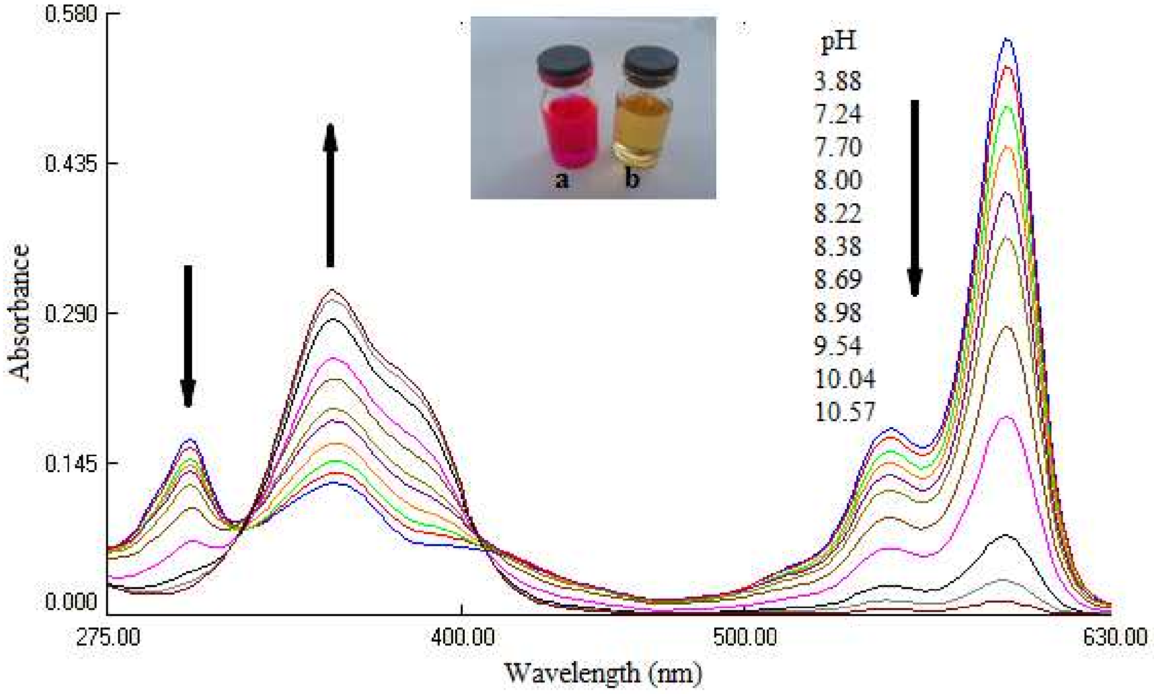


Fig. 2. Fluorescence spectra of **1** (6.0×10^{-7} M) in different solvents (λ_{exc}= 570 nm).



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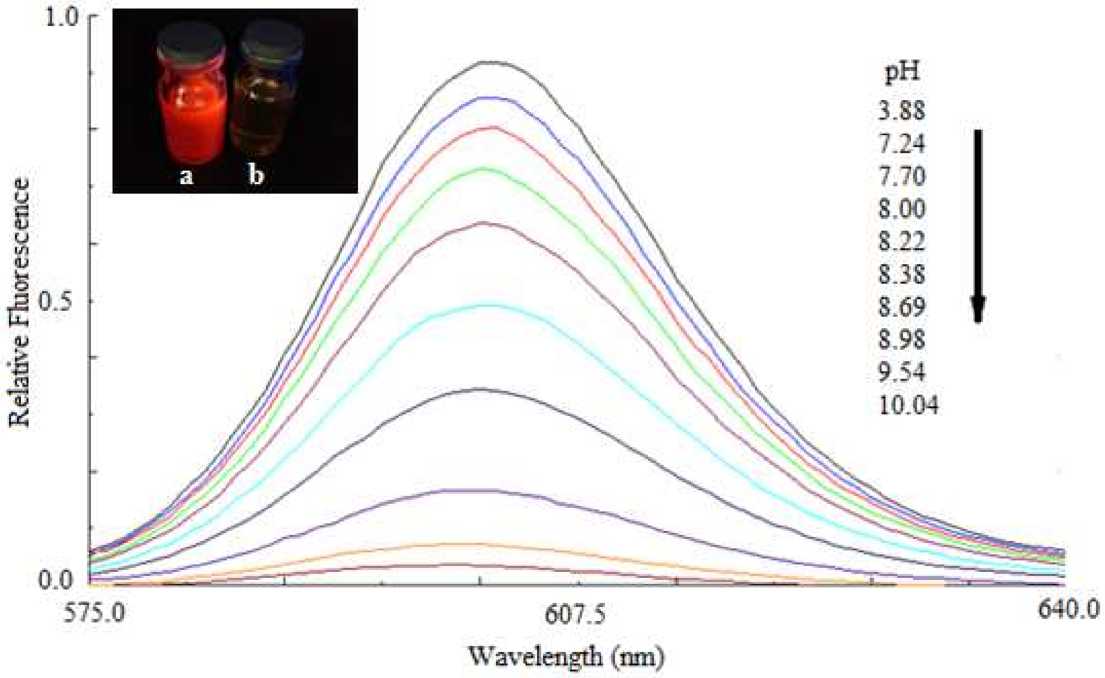

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Supplementary Information

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

Efdal Teknikel, Canan Unaleroglu*

Hacettepe University, Chemistry Department, Beytepe 06800, Ankara, Turkey

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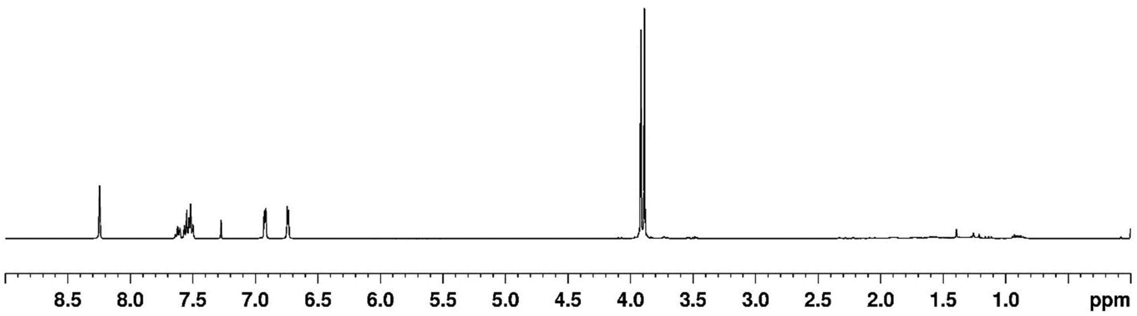

Figure S1. ^{1}H-NMR spectrum of **1** in $CDCl_3$

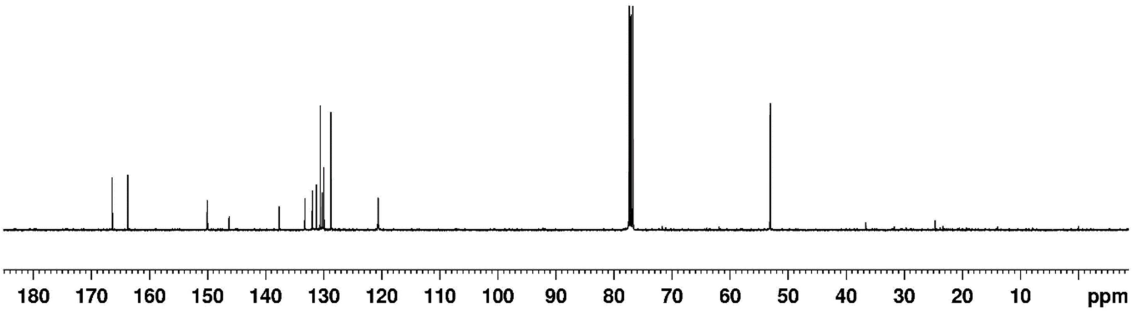

Figure S2. ^{13}C-NMR spectrum of **1** in $CDCl_3$

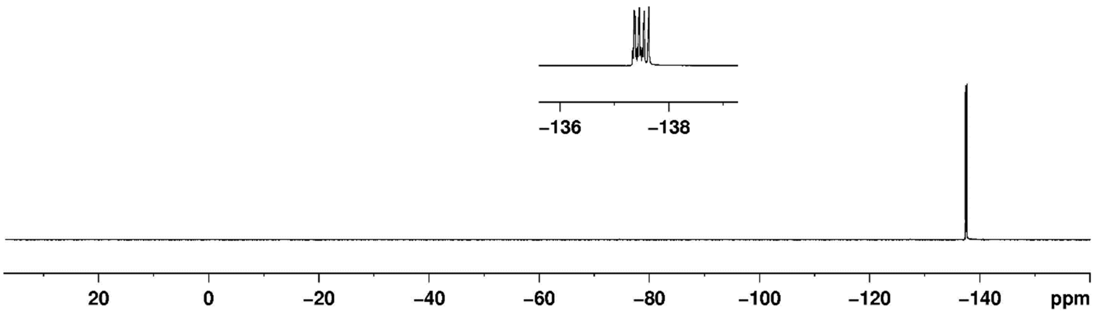

Figure S3. ^{19}F-NMR spectrum of **1** in $CDCl_3$

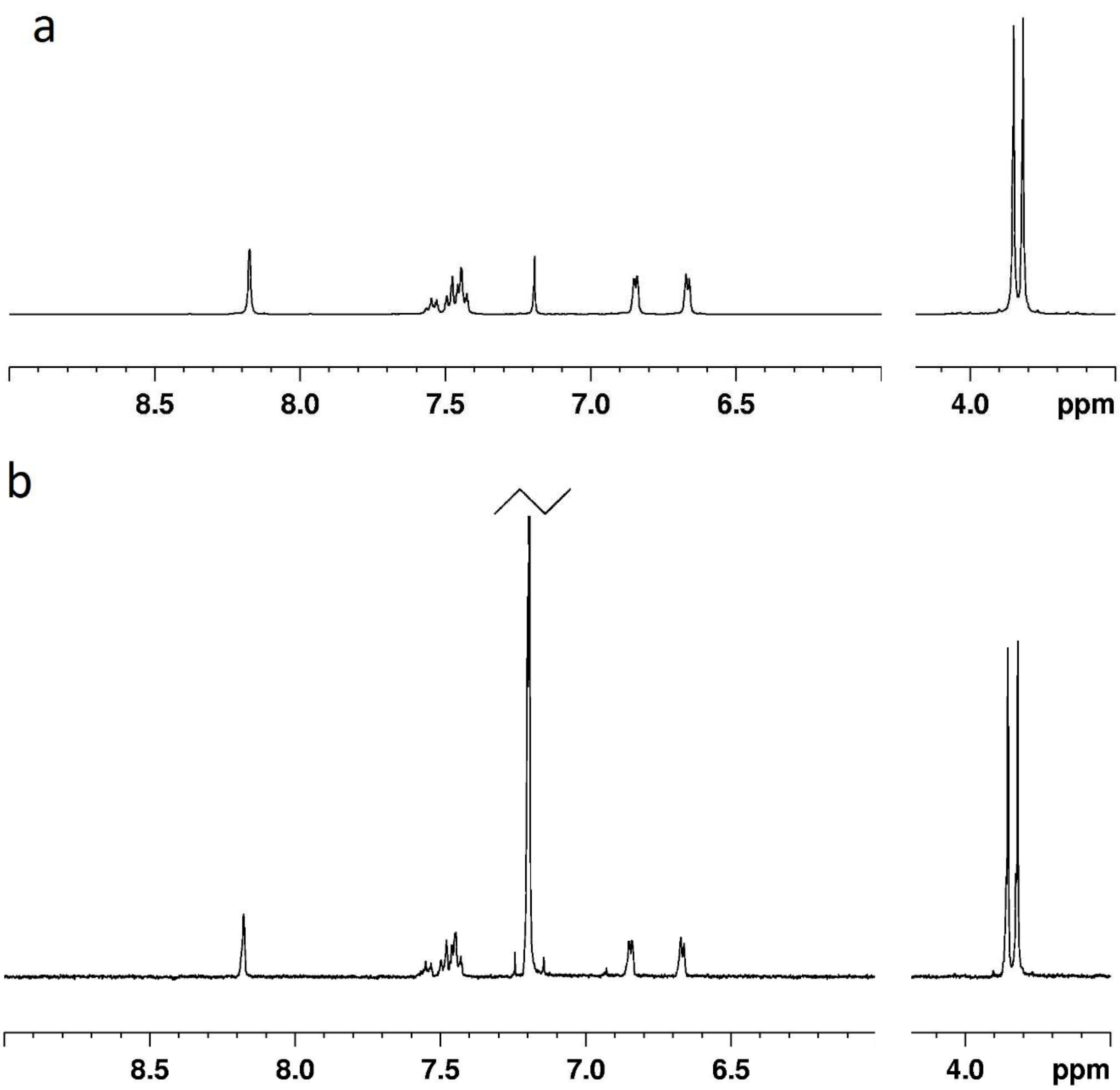

Figure S4. ^{1}H NMR spectra of **1** in d-chloroform at a) 30 mM b) 0.3 mM.

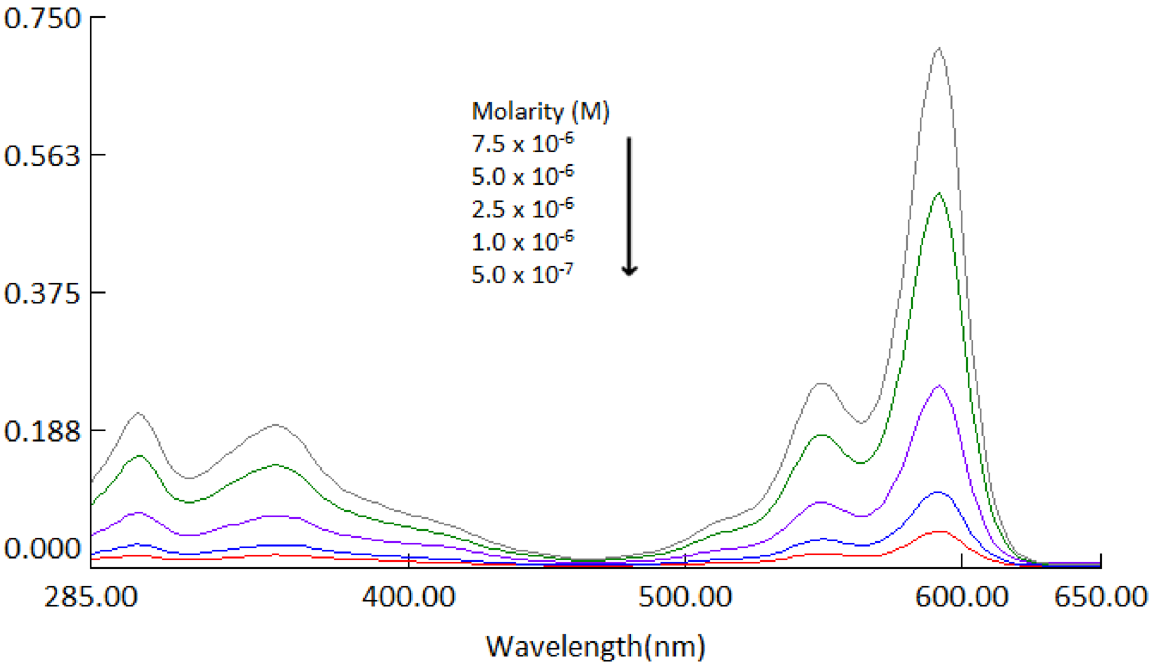

Figure S5. Absorbance spectra of **1** in ethanol at different concentrations.

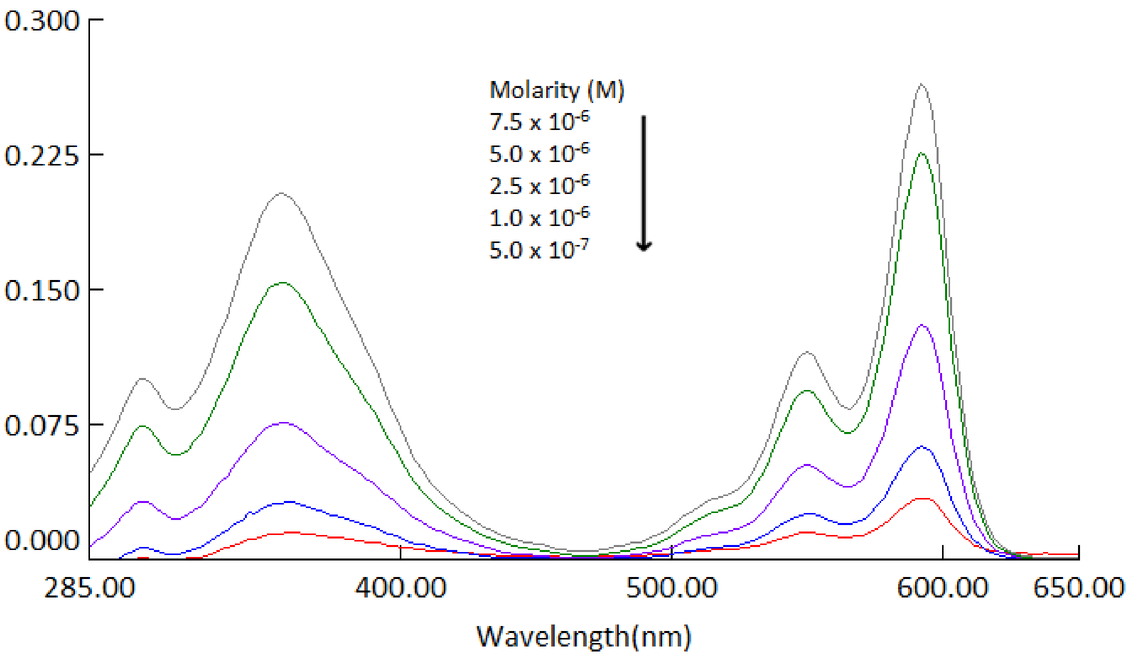

Figure S6. Absorbance spectra of **1** in water/ethanol (1/1 v/v) mixture at fixed pH of 8.70.

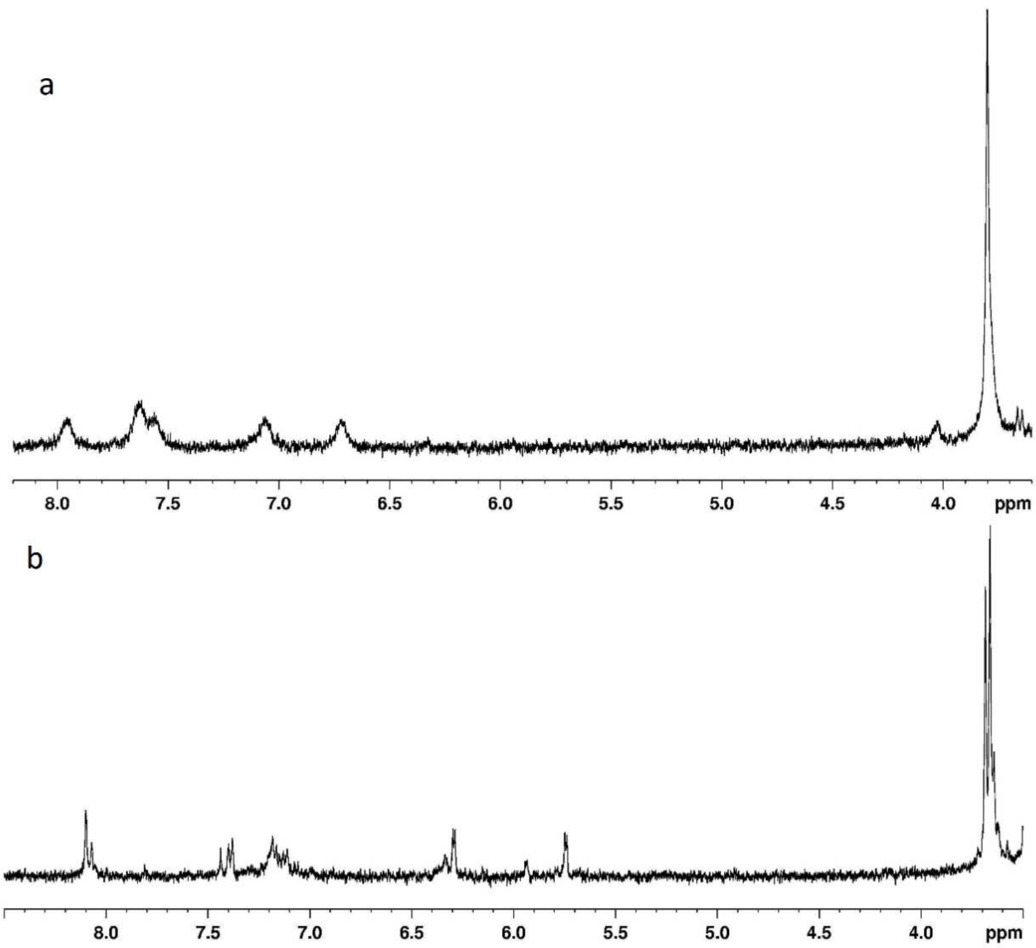

Figure S7. Comparison of ^{1}H-NMR spectra of **1** a) in neutral b) in asidic media in CD_3OD.

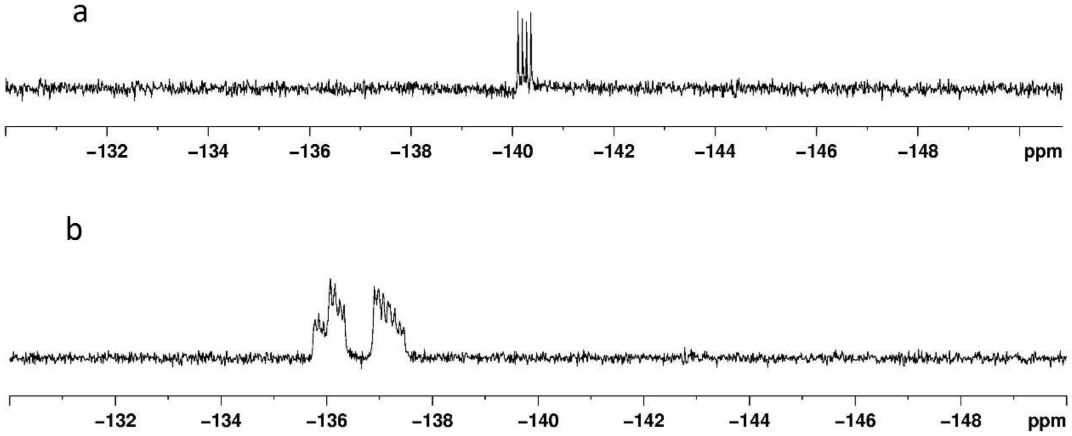

Figure S8. Comparison of ^{19}F-NMR spectra of **1** a) in neutral b) in basic media in CD_3OD.

- Bis(methoxycarbonyl)ethenyl functionalized BODIPY
- Optic pH sensor
- Alkaline sensitive sensor