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A dual channel sulphur-containing macrocycle functionalised BODIPY probe for the detection of Hg(II) in mixed aqueous solution

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We report herein the synthesis and chromo-fluorogenic behaviour of a new probe **1** containing a boron-dipirromethene (BODIPY) unit electronically connected with a dithia-dioxa-aza macrocycle. Acetonitrile and water-acetonitrile 95:5 v/v solutions of the probe showed an ICT band in the visible zone and are nearly non-emissive. When acetonitrile was used as solvent, addition of Hg(II) and trivalent metal cations induced an hypsochromic shift of the absorption band and moderate emission enhancements. A highly selective response was obtained when using competitive media such as water-acetonitrile 95:5 v/v. In this case only Hg(II) induced a hypsochromic shift of the absorption band and a marked emission enhancement.

Introduction

In the past decades, the detection and quantification of transition metal cations has experienced a great interest in different areas, such as environmental chemistry and clinical toxicology, because of its polluting nature.[1,2] Among them, mercury is one of the most toxic metal ions, even at very low concentrations. Accumulation of mercury over time in humans leads cognitive and motion disorders and Minamata disease.[3-13] Taking into account the above mentioned facts, detection of mercury contamination in drinking water, food, air and soil is a matter of concern.

Among strategies employed to detect and quantify metal cations in general and mercury in particular, the development of optical probes based on supramolecular and coordination concepts has been widely studied and in fact, there are a number of publications dealing with the synthesis and characterization of optical probes for Hg(II). Moreover, very recently, two review papers has been published by Lippard[14] and Chen.[15]

Most of the described probes are formed by two subunits, namely, a binding site and a signalling reporter, connected through a covalent bond. The binding site is responsible for the interaction with the metal cation and is usually designed bearing in mind coordination chemistry principles in order to achieve a high degree of complementarity between both components. In these probes, interaction between the binding site and Hg(II) is transformed in an easy-to-observe output by the signalling subunit. In the case of optical sensors the signal is based in variations in the emission (fluorescence) or absorption properties of the probe. However, although preferred, systems able to combine both properties (i.e fluorescence and colour change) are less common, in particular if they are accompanied of a "switch on" of the emission.

Regarding fluorescent signalling subunits, boron-dipirromethene moiety (BODIPY) has received great attention in recent years because of their advantageous features, such as photochemical stability, sharp absorption with high intensity in visible to NIR region and high fluorescence quantum yields.[16,17] Furthermore, the BODIPY core can be chemically modified in order to fine tune the optical properties or add new functionalities, such as receptor groups selective to analytes in the case of sensors.[18]

In most published probes the BODIPY core is chemically modified at the meso position. In general, benzene rings added into this position appear twisted with respect to the difluoro boron dipyrromethene core, and therefore are not part of the conjugated system. Interaction of these probes with selected anaytes induce changes in the fluorescence through a reductive or oxidative PET mechanisms that can be turned on or off depending of the functional groups.[16] Other probes are constructed by the functionalization at the 3 and 5 positions of the BODIPY core. In this case, the attached groups are conjugated with the BODIPY core and the recognition event

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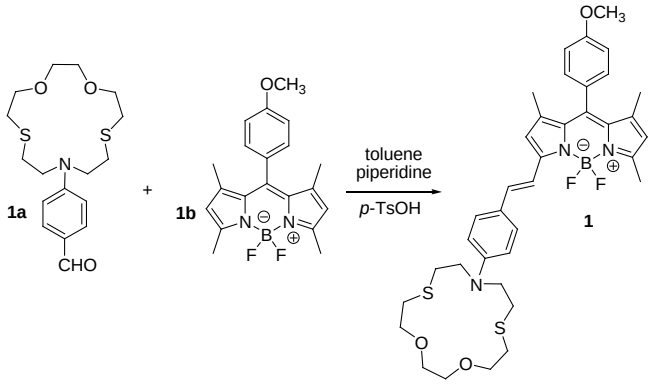
induces variations not only in the absorbance but also in the emission. Besides, in the case of functionalization with benzene rings directly linked to a nitrogen atom, an ICT process is active that red shifted the absorption band of the BODIPY core and also quenches the fluorescence. Blocking the nitrogen electron pair (by coordination or protonation), usually results in a recovering of the spectroscopic properties of the original BODIPY framework turning on its emission.[19]

Among binding sites, sulphur containing macrocycles are particularly well suited for the recognition of Hg(II) in a selective way due to the preferential and strong nature of the S-Hg interaction.[14] In particular, *N*-fenil-1-aza-4,13-dithia-7,10-dioxaciclopentadecane has been reported to display high binding affinity toward Hg(II) over other transition metal cations even in water or mixed aqueous environments. Besides, Hg(II) coordination with the macrocycle modulates the electron donor character of the nitrogen atom fact that was reflected in the ICT character of the UV-vis bands.[20,21]

Taking into account the above mentioned facts we report herein the synthesis and chromo-fluorogenic behaviour toward transition metal cations of a new, easy to prepare, BODIPY probe (**1**) which contained a *N*-fenil-1-aza-4,13-dithia-7,10-dioxaciclopentadecane macrocycle attached through the 3 position to the BODIPY fluorophore. Probe **1** showed an unselective behaviour in acetonitrile, and Hg(II) and other trivalent cations induced changes in the UV-visible and emission spectra. However, a Hg(II) selective response was observed on changing to a more competitive solvent such as water-acetonitrile 95:5 v/v.

Results and discussion

Synthesis and characterization of probe 1. Probe **1** consists of a BODIPY core functionalized with a macrocycle (containing sulphur, nitrogen and oxygen atoms) at the position 3 of the fluorophore core (see Scheme 1). Probe **1** was prepared by the piperidine-induced condensation between aldehyde **1a** and BODIPY derivative **1b** (see Scheme 1 and experimental section for details). The synthesis of **1a** and **1b** was published elsewhere.[19,22]



Scheme 1. Synthesis of probe **1**.

Probe **1** contains in its structure a methoxy groups linked to a benzene ring in the meso position that was included with the aim to increase its solubility in aqueous environments. Besides, it also contains a *N*-fenil-1-aza-4,13-dithia-7,10-dioxaciclopentadecane macrocycle as cation binding site. The ^{1}H NMR of probe **1** confirmed the proposed structure.

Spectroscopic studies in acetonitrile. In a first step, we studied the chromo-fluorogenic behaviour of **1** in an organic solvent of medium polarity such as acetonitrile. As could be seen in Figure 1, the UV-visible spectra of probe **1** in CH_3CN is characterised by the presence of an absorption band centred at ca. 600 nm. This absorption band is attributed to the 0-0 vibrational band of a S_0-S_1 transition, from the donor nitrogen atom to the acceptor BODIPY core, with a strong charge-transfer nature.[16] Also a shoulder at ca. 550 nm was observed and assigned to the 0-1 vibrational band of the same transition.[19] The ICT nature of the visible bands suggested that interactions of metal cations with the nitrogen atom of the macrocycle could modulate the HOMO and LUMO levels of the probe which could be reflected in marked colour changes.

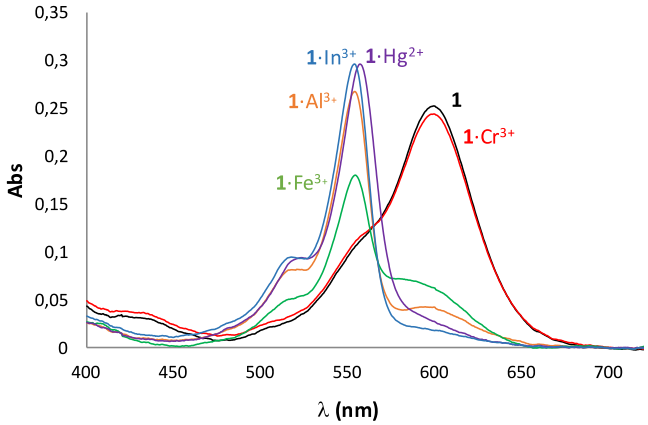


Figure 1. UV-visible spectra of probe **1** in acetonitrile (1.0 x 10^{-5} M) alone and in the presence of 1 eq. of Hg(II) and trivalent metal cations.

Bearing in mind the above mentioned facts, in a second step, changes in the colour of probe **1** upon addition of 1 eq. of selected metal cations was studied. Addition of alkaline (Li(I), Na(I), K(I)) or alkaline-earth (Ca(II) Ba(II), Mg(II)) cations to CH_3CN solutions of **1** induced negligible changes in the UV-visible spectrum of the probe. On the other hand, among certain transition metal cations tested (Hg(II), Al(III), In(III), Cr(III), Fe(III), Co(II), Zn(II), Ni(II), Pb(II), Ag(I)) only Hg(II) and the trivalent cations In(III), Al(III) and Fe(III) were able to induce hypsochromic shifts (ca. 45 nm) of the visible band (see Figure 1) together with marked colour modulation from blue to magenta. The observed changes in the visible band of **1** are attributed to cation coordination with the donor nitrogen atom of the macrocycle that inactivates the ICT contribution. The spectra obtained after metal cation coordination is similar to that of the BODIPY core with a narrower band width.[16]

However, it was apparent from these studies that the shifts of the absorption band of **1** observed for Hg(II) and the trivalent cations were slightly different. As can be seen in Figure 1, Hg(II) induced a slightly lower shift (42 nm) when compared with the obtained in the presence of Al(III), Fe(III) or In(III) (45 nm). This subtle difference could be ascribed to a stronger coordination of

Hg(II) with the macrocycle when compared with the strength of the Al(III), Fe(III) or In(III) interaction.

Although the response of **1** in the presence of Hg(II) was expected, since the probe contains a macrocycle that selectively coordinates with this thiophillic cation, **1** also responded to trivalent cations in a medium solvating solvent such as acetonitrile. However, we can observe (see again Figure 1) that the intensity of the new absorption band, formed upon coordination, varies in the order In(III) > Al(III) >> Fe(III). The observed order is most likely consequence of the Lewis acidity of the cation and of its affinity towards coordination with the amine in the macrocycle, this last factor additionally modulated by the interaction with the sulphur and oxygen atoms in the crown ether.

In spite of the fact that **1** was designed to coordinate with cationic species, the UV-visible response of acetonitrile solutions of the probe in the presence of 1 eq. of selected anions (F^-, Cl^-, Br^-, I^-, CN^-, HS^-, HCO_3^-, NO_3^-, AcO^-, BzO^-) was also tested. As expected none of the anions tested induced changes in the UV-visible spectrum of probe **1**.

On the other hand, probe **1** was slightly emissive. Upon excitation of acetonitrile solutions of probe **1** (1.0×10^{-5} M) at 540 nm, a very weak emission band at ca. 560 nm was observed (see Figure 2). The shape and intensity of this band is a direct consequence of the strength of the internal conversion processes and non radiative transitions induced by the polar nature of the solvent and the large change in dipole moment between the ground and the excited state derived from the partial CT between the strongly coupled BODIPY core and the aniline group in the macrocycle.[19]

Moreover, emission changes in the presence of selected metal cations (the same used in the UV-visible experiments) were studied. Again, only Hg(II), Fe(III), In(III) and Al(III) induced marked emission enhancements (see Figure 2) whereas Cr(III) was able to induce a small emission enhancement.

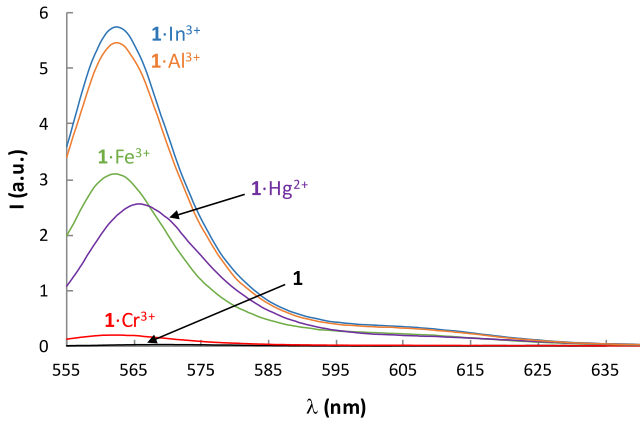


Figure 2. Emission spectra of probe **1** in acetonitrile (excitation at 540 nm) alone (1.0×10^{-5} M) and in the presence of 1 eq. of Hg(II), In(III), Al(III), Fe(III) and Cr(III).

The intense emission band, which appeared at ca. 560 nm, was due to a partial inhibition of the ICT band upon cation coordination with the macrocycle. In the case of trivalent metal cations, the new emission band appeared at 562 nm whereas for Hg(II) the fluorescence was red-shifted to 566 nm (the same effect was observed in the UV-visible measurements, see Figure 1). Besides, Stokes shifts moved from 1069 to 285 and 257 cm^{-1} for free probe, Hg(II) and trivalent cations complex respectively in agreement with the lower differences in the dipolar moment between the ground and excited states upon complexation with **1**. Regarding intensity, although probe **1** presented a very weak fluorescence, upon complexation with In(III) the emission suffered a 700-fold enhancement. For the trivalent cations, comparing Figures 1 and 2, it was clear that emission intensity is proportional to the absorbance measured at 550 nm. This fact could suggest that trivalent metal cations and probe **1** interacted in a similar fashion (although the intensity of the complexation strength varies among them). Again Hg(II) presented a different behaviour, when compared with the response obtained with trivalent cations. As could be observed in Figure 1 the intensity of the absorption band of the complex formed between probe **1** and Hg(II) is almost the same that in the case of In(III), but the intensity of emission reaches only a 44% (see Figure 2).

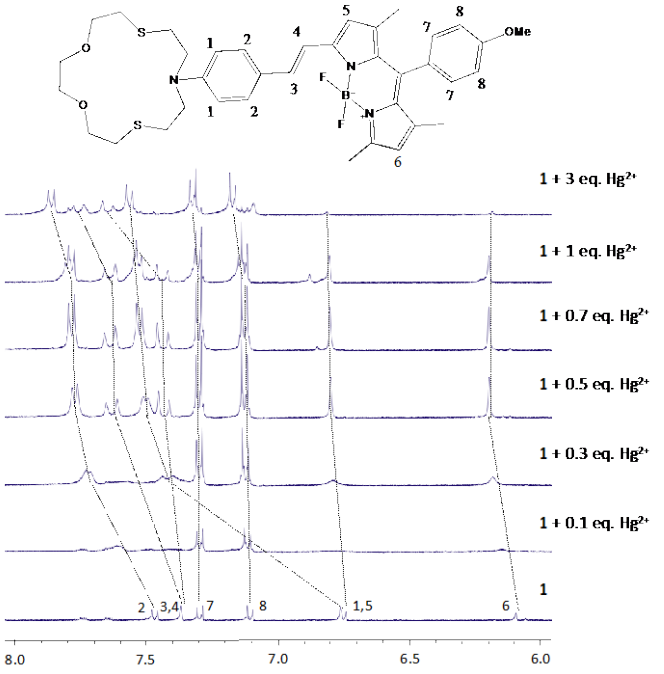


Figure 3. ^{1}H NMR titration of probe **1** in deuterated acetonitrile in the presence of increasing quantities of Hg(II) cation.

In order to assess the site of interaction of metal cations with probe **1**, ^{1}H NMR studies with Hg(II) in deuterated acetonitrile were carried out (see Figure 3). The ^{1}H NMR spectrum of **1** showed the expected signals of the aniline and methoxy phenyl moieties, the double bond and the BODIPY core protons in the aromatic region (one of them overlapped with the aniline doublet at 6.75 ppm). Probe **1** showed an strong coordination with Hg(II) cation reflected in the remarkable downfield shifts (0.7 ppm upon addition of 0.5 Hg(II) eq.) suffered by the *ortho* aromatic protons of the 1,4-disubstituted aniline ring. Also, other hydrogens of the aniline ring and the double bond (all of them close to the macrocycle) showed moderate shifts. On the contrary, protons of the 1,4-disubstituted ring at the meso position (containing the methoxy subunit) centred

at 7.1 and 7.3 ppm suffered negligible shifts. This fact could be explained bearing in mind the twisted conformation of this 1,4-disubstituted benzene ring respecting the BODIPY core. As a consequence of this conformation this benzene ring did not participate in the conjugated system of **1** and the coordination with Hg(II) was reflected in insignificant changes. Moreover, addition of 1 eq of Hg(II) cation induced moderate downfield shifts of the methylene protons adjacent to sulfur atoms from 2.78 and 2.92 ppm to 3.00 and 3.18 ppm together with a marked broadening (see Supporting Information).[23] All these facts suggested that Hg(II) coordinated with the macrocyclic subunit present in probe **1**. Besides, the peaks of the conjugated system broaden or even disappeared upon addition of 0.1-0.3 eq. of Hg(II) indicating a fluxional **1**-Hg(II) system and reinforced the assumption that coordination occurred through the macrocyclic binding site.

Spectroscopic studies in the presence of water. Taking into account the response obtained with **1** in acetonitrile and in order to assess its possible application for detection of transition metal cations in environmental applications the response of the probe in aqueous media was tested. The presence of important amounts of water is expected to modulate the selectivity of the probe toward certain cations[21,24] due to the high solvation energy of these species.

Probe **1** was not fully water soluble and, for this reason, water (pH 7.0)-acetonitrile 95:5 v/v mixtures were used to assess the sensing behaviour toward metal cations. The UV-visible spectrum of **1** in water (pH 7.0)-acetonitrile 95:5 changed markedly when compared to that observed in acetonitrile. The single relatively narrow band at 600 nm in acetonitrile was replaced by a broad absorption with two relative maxima centred at 583 and 613 nm (see Figure 4). These changes in the shape of the bands may tentatively be ascribed to the formation of aggregates that induced red shifts in the absorption.[25]

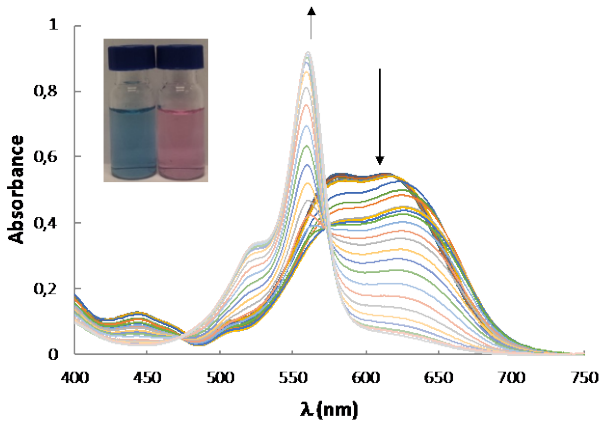


Figure 4. UV-visible titration spectra of water-acetonitrile 95:5 v/v solutions of probe **1** (5.0 x 10^{-5} M) upon addition of increasing quantities of Hg^{2+} cation (0-25 eq.). Inset: Colour changes observed in the absence (left) and in the presence (right) of 10 equivalents of Hg(II) cation to water-acetonitrile 95:5 v/v solutions of probe **1** (5.0 x 10^{-5} M).

Changes in the UV-visible spectrum of **1** in water (pH 7.0)-acetonitrile 95:5 v/v in the presence of 10 eq. of selected metal cations (i.e. Na(I), K(I), Li(I), Mg(II), Ca(II), Ba(II), Hg(II), Al(III), In(III), Cr(III), Fe(III), Co(II), Zn(II), Ni(II), Pb(II), Ag(I)) and anions (i.e F^-, Cl^-, Br^-, I^-, CN^-, HS^-, HCO_3^-, NO_3^-, AcO^-, BzO^-) was studied. The observed response was remarkable selective and only Hg(II) induced remarkable changes. As could be seen in Figure 4, addition of increasing amounts of Hg(II) induced a decrease of the broad absorptions at 613 and 583 nm together with the appearance of a narrow band centred at 560 nm (similar to that obtained in acetonitrile for the free probe in the presence of Hg(II)). Besides, the colour of the solution changed from blue to pink (see inset in Figure 4). As expected, water improves selectivity through the competition of the highly coordinating water solvating sphere with the macrocyclic binding site in probe **1**.

A closer look to the set of spectra shown in Figure 4 indicates a complex coordination pattern between **1** and Hg(II) cation (reflected in the absence of isosbestic points). Low amounts of Hg(II) induced a moderate decrease of the bands at 583 and 613 nm, while at high cation concentration, these bands continue to decrease and the narrow absorption band, centred at 561 nm, typical of BODIPY cores, was observed. This behaviour is ascribed to cation coordination with the donor nitrogen atom of the macrocycle that inactivates the ICT contribution active in **1**.

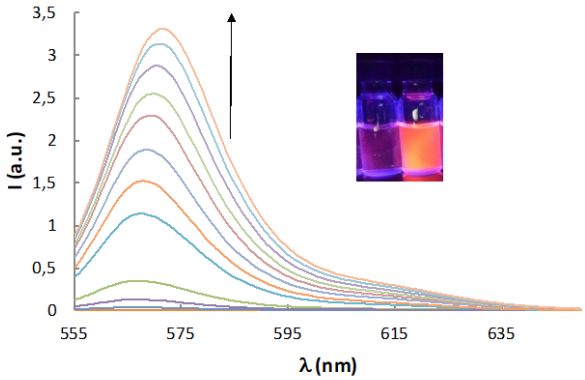


Figure 5. Set of emission spectra of probe **1** (5.0 x 10^{-5} M) titration in water (pH 7.0)-acetonitrile 95:5 v/v solutions upon addition of increasing quantities of Hg(II) cation (0-16 eq.). Inset: Fluorescence changes observed in the absence (left) and in the presence (right) of 10 equivalents of Hg(II).

On the other hand, water (pH 7.0)-acetonitrile 95:5 v/v solutions of probe **1** where practically non-emissive upon excitation at 550 nm. Moreover, it was observed that the response obtained upon addition of target cations and anions was also selective in this solvent mixture since only Hg(II) induced a remarkable emission enhancement at 570 nm (see Figure 5). As could be seen, addition of increasing amounts of Hg(II) cation to probe **1** induced a progressive enhancement in emission intensity (300-fold enhancement after addition of 20 eq. of Hg(II)). Furthermore, from the fluorescence titration profile a limit of detection of 99 ppm of Hg(II) was determined.

Finally, and taking into account the fact that BODIPY derivative **1** appears to aggregate in aqueous environments, the stability of water-acetonitrile 95:5 v/v solutions of the probe was tested. At this respect, we carried out Hg(II) detection measurements with a freshly prepared solution of probe **1** in water-acetonitrile 95:5 v/v and then, after 72 h, we used the same solution and observed an identical chromo-fluorogenic sensing behaviour. Solutions of probe

1 are quite stable for at least 1 week. After this period of time, a precipitate of the probe begins to appear and the solution loses part of its detection characteristics.

Conclusions

In summary, we presented herein the synthesis and chromo-fluorogenic behaviour toward metal cations and anions of a new BODIPY derivative. Probe **1** contains a BODIPY core and an aza-dithia-dioxa macrocycle as binding unit. **1** showed a charge-transfer transition in the visible zone that was blue shifted in acetonitrile in the presence of Hg(II), In(III), Al(III) and Fe(III). The same cations induced marked emission enhancements (ca. 700-fold enhancement for In(III)) upon coordination with probe **1**. Moreover, the selectivity of **1** was dramatically improved on changing solvent to a more competitive media such as water (pH 7.0)-acetonitrile 95:5 v/v. In this medium, only Hg(II) induced an hypsochromic shift (together with a marked colour change) of the visible band of **1** and an a marked emission enhancement. The simplicity of the presented probe indicated that this or similar compounds could be of interest for the detection of Hg(II) cation in environmental or biological applications.

Experimental section

Materials and methods. Piperidine, *p*-toluenesulfonic acid, $MgSO_4$, dry toluene and all the perchlorates (Na(I), K(I), Li(I), Mg(II), Ca(II), Ba(II), Hg(II), Al(III), In(III), Cr(III), Fe(III), Co(II), Zn(II), Ni(II), Pb(II), Ag(I)) were purchased from Aldrich and Acros. Acetonitrile was purchased from Scharlab. All commercially available reagents and solvents were used as received. The precursors BODIPY **1b**[19] and crown ether **1a**[22] were synthesized using the experimental procedures reported before.

Reaction progress was monitored by thin layer chromatography, 0.25 mm thick pre-coated silica plates (Merck Fertigplatten Kieselgel 60 F254), and spots were visualised under UV light. Purification was achieved by silica gel column chromatography (Merck Kieselgel, 230-400 mesh). NMR spectra were obtained on a Brucker Avance II 400 at an operating frequency of 400 MHz for ^{1}H and 100.6 MHz for ^{13}C, using the solvent peak as internal reference. The solvents are indicated in parenthesis before the chemical shifts values (δ relative to TMS). Peak assignments were made by comparison of chemical shifts, peak multiplicities and *J* values, and were supported by spin decoupling-double resonance and bidimensional heteronuclear HMBC (heteronuclear multiple bond coherence) and HMQC (heteronuclear multiple quantum coherence) techniques. NMR spectroscopy titration was performed in a 400 MHz magnet (Bruker Ascend 400) equipped with an ATM 5 nm probe (BBO 400 MHz 5mm Z-Grad). Melting points were determined on a Gallenkamp apparatus and are uncorrected. Infrared spectra were recorded on a BOMEM MB 104 spectrophotometer. LR-Mass spectra were recorded on a TripleTOF™ 5600 LC/MS/MS System, (AB SCIEX), a triple quadrupole time-of-flight mass spectrum, the MS was using method with infusion experiment. Data was evaluated using the PeakView™eter. High resolution mass spectrometry (HRMS) data were obtained with a TRIPLETOF T5600 (AB SCIEX, USA) spectrometer.

The absorption spectra were recorded with a JASCO V-650 Spectrophotometer. Fluorescence spectra were measured in a JASCO FP-8500 Spectrophotometer (λ_{exc} = 550 nm). The analysis was performed by adding aliquots of Hg(II) perchlorate hydrate to 5.0 x 10^{-5} M water (pH 7.0)-acetonitrile 95:5 v/v solutions of probe **1**. The UV–vis and fluorescence titrations were measured at room temperature (25 °C).

Synthesis of compound 1: The previously prepared BODIPY **1b** (50 mg, 0.14 mmol) was reacted with the formylated crown ether **1a** (50 mg, 0.14 mmol) in dry toluene (10 mL) in a round bottomed flask fitted with a Dean-Stark and a condenser, in the presence of piperidine (0.12 mL, 1.21 mmol) and a trace amount of *p*-toluenesulfonic acid. The reaction mixture was heated at reflux under nitrogen inert atmosphere for 2 h. After cooling, the mixture was transferred to a separation funnel and washed with water (10 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated. The crude residue was subjected to a preliminary dry flash chromatography followed by column chromatography on silica, both using ethyl acetate/petroleum ether (1:2) as eluent. The product was obtained as a blue greenish solid (45 mg, 30 %). Mp = 211–213 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 3H, CH_3-1), 1.48 (s, 3H, CH_3-7), 2.59 (s, 3H, CH_3-3), 2.78 (t, *J* = 5.2 Hz, 4H, S-CH_2-CH_2-O), 2.92 (t, *J* = 7.6 Hz, 4H, N-CH_2-CH_2-O), 3.66 (s, 4H, O-$(CH_2)_2$-O), 3.69 (t, *J* = 7.6 Hz, 4H, N-CH_2-CH_2-O), 3.82 (t, *J* = 5.2 Hz, 4H, S-CH_2-CH_2-O), 3.88 (s, 3H, OCH_3), 5.97 (s, 1H, H-2), 6.59 (s, 1H, H-6), 6.63 (d, *J* = 8.8 Hz, 2H, H-3'' and H-5''), 7.01 (dd, *J* = 8.8 Hz, 2H, H-3' and H-5'), 7.17–7.21 (m, 3H, Hβ, H-2'and H-6'), 7.47–7.51 (m, 3H, Hα, H-2''and H-6'') ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.4 (CH_3-1), 14.6 (CH_3-3), 14.9 (CH_3-7), 29.6 (N-CH_2-CH_2-O), 31.3 (S-CH_2-CH_2-O), 51.9 (N-CH_2-CH_2-O), 55.3 (OCH_3), 70.7 (O-$(CH_2)_2$O), 74.3 (S-CH_2-CH_2-O), 111.8 (C-3'' and C-5''), 114.4 (C-3' and C-5'), 114.6 (Cα), 117.5 (C-6), 120.4 (C-2), 124.8 (C-1''), 127.4 (C-1'), 129.5 (C-2' and C-6'), 129.6 (C-2'' and C-6''), 131.6 (C-8a), 133.4 (C-7a), 137.2 (Cβ), 139.0 (C-8), 140.9 (C-1), 142.8 (C-7), 147.7 (C-4''), 152.9 (C-3), 154.5 (C-5), 160.0 (C-4') ppm. IR (liquid film): *υ* 2922, 2856, 1737, 1591, 1539, 1520, 1501, 1467, 1413, 1353, 1295, 1247, 1200, 1177, 1119, 1076, 1030, 985, 813 cm^{-1}. HRMS-EI m/z: calcd for $C_{37}H_{44}BF_2N_3O_3S_2$ + H^+: 692.2963; measured: 692.2958. Elemental anaylsis calcd for $C_{37}H_{44}BF_2N_3O_3S_2$ 64.25% C, 6.41% H, 6.07% N, 9.27% S; measured 64.17% C, 6.44% H, 6.03% N, 9.31% S.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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