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OFF-ON BODIPY-based chemosensors for selective detection of Al^{3+} and Cr^{3+} *versus* Fe^{3+} in aqueous media

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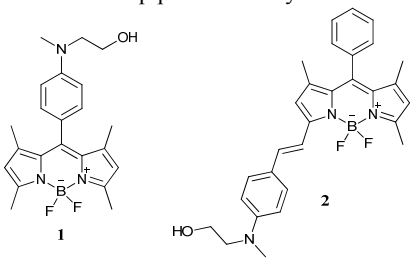
Two new OFF-ON BODIPY-based chemosensors highly sensitive for trivalent cations in aqueous solutions are described. Compound 2 exhibits a selective sensing of Al^{3+} and Cr^{3+} *versus* Fe^{3+} through two different channels (UV-vis and fluorescence).

The design of new probes for transition and p-block metal cations is an important subject within the field of supramolecular chemistry because of their impact in the environment and in human health. In this area, although a number of chemosensors for divalent transition metal cations have been described, there are a relatively small number of probes able to selectively respond to triple-charged metal cations[1] and even less in aqueous environments.[2] However, trivalent cations have important properties and play significant roles in different fields. For instance chromium is an essential element in human nutrition and has a huge impact on the metabolism of carbohydrates, fats, proteins and nucleic acids and has been reported to disturb glucose levels and lipid metabolism.[3] On the other hand Fe^{3+} also plays a key role in many biochemical processes at the cellular level and it is indispensable for most organisms, and both its deficiency and overload can induce various disorders.[4,5] Finally, it is well-known that Al^{3+} plays important roles in cells and environmental food chains and for instance was found to kill fishes in acidified water and cause damages to the central nerve system of human beings,[6] Therefore, the design of new probes for the simple and easy detection of these metal cations in a number of different situation is of much interest.

Based in these concepts, and bearing in mind our interest in the design of chemosensors, we report herein two new probes (**1** and **2**, see Scheme 1) based in dipyrromethene boron difluoride (BODIPY) scaffold, for a simple optical detection of trivalent cations. BODIPY dyes are a class of well-known fluorophores with widespread applications as fluorescent probes due to their valuable characteristics, such as high molar absorption coefficients and high quantum yields leading to intense absorption and fluorescence bands.[7] In this context, although a large number of BODIPY dyes have been designed and prepared for detecting metal cations[8], very few examples display sensing features in aqueous solutions.[9]

Probe **1** was synthesized through a bicondensation of *N*-methyl-*N*-(2-hydroxyethyl)-4-aminobenzaldehyde and 2,4-dimethylpyrrole in the presence of trifluoroacetic acid (TFA) as catalyst,[10] followed by oxidation with *p*–chloranil. The boron difluoride bridge was introduced by treatment with boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$) in the presence of triethylamine (TEA). For the synthesis of probe **2**, the BODIPY derivative **I** was prepared from 2,4-dimethylpyrrole and benzaldehyde (see Supporting Information) following the same procedure as above.[10] Condensation of **I** and *N*-methyl-N-(2-hydroxyethyl)-4-aminobenzaldehyde in benzene in presence of acetic acid and piperidine[10c,11] yielded **2**.



Scheme 1. Chemical structure of the BODIPY derivatives **1** and **2**.

Probe **1** shows in water:CH_3CN (80:20 v/v) an intense absorption band at 490 nm (ε=77600 cm^{-1} M^{-1}) yet it is scarcely fluorescent (Φ=0.002 using aqueous fluorescein as reference).[12] This low emission is tentatively attributed to a photo-electron transfer (PET) from the lone pair of the amino group to the photo-excited BODIPY group.[13] Figure 1 shows the fluorescence spectrum (λ_{exc}=480 nm) of **1** alone and in the presence of 1 equiv of different metal cations. Addition of Fe^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Li^{+}, Hg^{2+} and Ru^{3+} did not modify the emission of **1**, whereas trivalent cations Al^{3+}, Fe^{3+} and Cr^{3+} led to a very remarkable enhancement of the fluorescence emission (Φ_{Al} = 0.29; Φ_{Fe} = 0.17; Φ_{Cr} = 0.24) at 515 nm.

Moreover, no colour modulations in the presence of metal cations were found for **1**. This was an expected result bearing in mind the presence of methyl groups in the pyrrole units that most likely impose a twist position of the phenyl ring that interrupts the conjugation between the *N*-methyl-*N*-(2-hydroxyethyl) coordination site and the signaling unit.[14]

In contrast, the signaling unit and binding site in probe **2** are electronically connected and therefore changes both in colour and emission were found (*vide infra*). In water:CH_3CN (40:60 v/v), **2**

exhibited a strong absorbance with a maximum at 603 nm (ε=38400 $M^{-1}cm^{-1}$). This band is bathochromically shifted by ca. 100 nm when compared with the parent BODIPY fluorophore due to the styryl extension at the α-position. Moreover probe **2** was poorly fluorescent (λ_{exc} = 530 nm, Φ =0.007) most likely due to an efficient ICT quenching of the excited state of the BODIPY-chromophore from the electron-donating amino moiety.

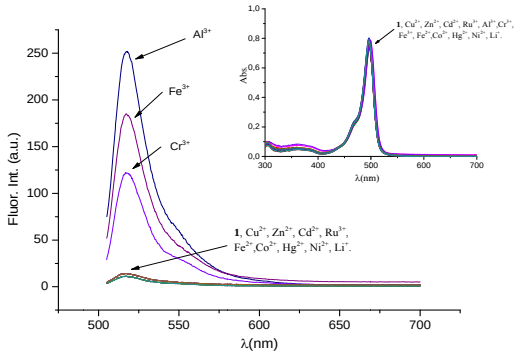


Figure 1. Fluorescence emission spectra of **1** (10^{-5} M) upon addition of 1 eq of Fe^{3+}, Fe^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Li^{+}, Hg^{2+}, Ru^{3+}, Cr^{3+} and Al^{3+} in water:CH_3CN (80:20 v/v) (λ_{ex}=480 nm). Inset: UV-Vis spectra of **1** (10^{-5} M) upon addition of 1 eq of the different cations in water:CH_3CN (80:20 v/v).

Addition of Fe^{2+}, Zn^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Li^{+}, Cu^{2+}, Hg^{2+}, Ru^{3+}, or Fe^{3+} to solutions of **2** in water:CH_3CN (40:60 v/v) did not induce any change neither in the UV-Vis nor in the fluorescence spectra. By contrast, in the presence of the trivalent cations Cr^{3+} and Al^{3+} the colour of the solutions changed dramatically from blue to pink due to the appearance of a new band at 560 nm (see Figure 2). Probe **2** also shows some colour change in the presence of Fe^{3+} but only when CH_3CN alone or mixtures with a maximum of 8% water were used. Interestingly probe **2** also displays a remarkable strong fluorescence emission at 563 nm in water:CH_3CN (40:60 v/v) upon addition of the metal cations Cr^{3+} and Al^{3+} (Φ_{Al} = 0.33; Φ_{Cr} = 0.30).

Furthermore in competitive experiments it was found that probes **1** and **2** respond to the presence of Al^{3+}, Cr^{3+} and Fe^{3+} (for **1**) and to Al^{3+} and Cr^{3+} (for **2**) in the presence of Hg^{2+}, Li^{+}, Na^{+}, K^{+}, Ag^{+}, Ca^{2+}, Mg^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Fe^{2+}, Co^{2+} and Cu^{2+} cations. In addition, limits of detection (LOD) were determined from the equation LOD=*K* x Sb_1/S, where K=3, Sb_1 is the standard deviation of the blank solution and S is the slope of the calibration curve.[15] The obtained results were 0.14, 019 and 0.10 μM for Al^{3+}, Cr^{3+} and Fe^{3+} respectively with ligand **1** and 0.08 and 0.18 μM for Al^{3+} and Cr^{3+} with ligand **2** using in both cases emission measurements. Moreover LOD of 0.18 and 0.52 μM were calculated for Al^{3+} and Cr^{3+} using **2** from UV-vis titrations.

Titration experiments of **1** and Fe^{3+}, Cr^{3+} and Al^{3+} in water:CH_3CN (80:20 v/v) (by fluorescence spectroscopy) and of **2** with Cr^{3+} and Al^{3+} in water:CH_3CN (40:60 v/v) (by either UV-Vis or fluorescence) were carried out in order to determine the complexation constants by using the software Specfit program.[16] As an example Figure 3 shows the fluorescence titration of **1** with Al^{3+}.

Table 1. Complexation constants for probes **1** and **2** with trivalent cations for the formation of 1:1 ligand-to-metal complexes.

	Ligand **1**[a]		Ligand **2**[b]
Cation	log K[c]	log K[d]	log K[c]
Al^{3+}	5.9 ± 0.2	5.9 ± 0.7	5.2 ± 0.3
Cr^{3+}	6.5 ± 0.3	5.3 ± 0.6	5.6 ± 0.3
Fe^{3+}	4.8 ± 0.2	-	-

[a] Determined in water:CH_3CN (80:20 v/v)
[b] Determined in water:CH_3CN (40:60 v/v)
[c] Determined by UV-vis titrations
[d] Determined by fluorescence titrations

A stepwise addition of Al^{3+} led to an enhancement of the band at 515 nm, which is saturated upon the addition of 1 equiv. of Al^{3+}, strongly, suggesting the formation of 1:1 ligand-to-metal complexes. This was also demonstrated via the corresponding Job´s Plot and MS. The same stoichiometry was observed for Cr^{3+} and Fe^{3+} with **1**.

Moreover, similar fluorescence titration studies with **2** also indicated the formation of 1:1 ligand-to-metal complexes with the trivalent metal cations Cr^{3+} and Al^{3+}. Moreover UV-vis spectroscopy titrations with **2** also resulted in similar results (see Table 1).

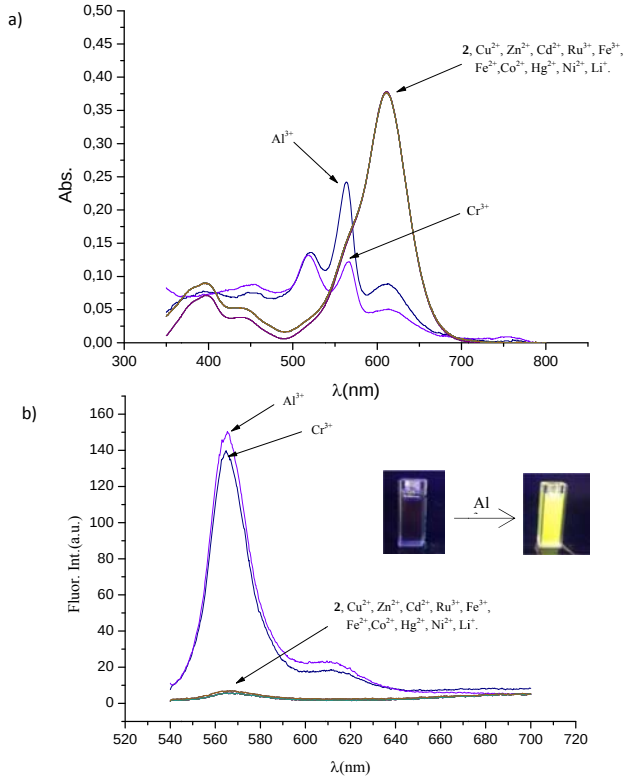


Figure 2. UV-Vis spectra (a) and fluorescence emission spectra (λ_{ex}=530 nm) (b) of **2** (10^{-5} M) upon addition of 1 eq of Fe^{3+}, Fe^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, Li^{+}, Hg^{2+},Cr^{3+} and Al^{3+} in water:CH_3CN (40:60 v/v).

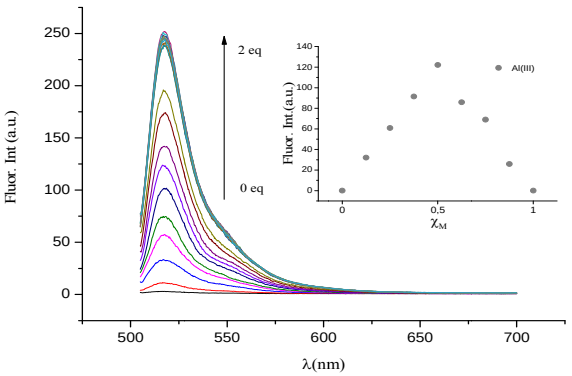


Figure 3. Fluorescence response ($\lambda_{exc.}$=480 nm) for **1** (10^{-5} M) to increasing amounts of Al^{3+} in water:CH_3CN (80:20 v/v) The inset shows the corresponding Job plot.

All these results are consistent with a sensing mechanism in which the metal cations form complexes with **1** and **2** via coordination with the *N*-methyl-*N*-(2-hydroxyethyl) moiety. The interaction of the cation with the lone pair on the nitrogen atom in **1** results in an inhibition of the PET process giving rise to the observed

enhancement of the fluorescence emission. On the other hand, the binding of the cation with the lone pair on the nitrogen atom in **2** results in a reduction of the electron-donating ability of the nitrogen atom of *N*-methyl-*N*-(2-hydroxyethyl)-)styryl group which is in conjugation to the BODIPY core, thus suppressing the ICT process causing the blue shift of the absorption spectrum band and an enhancement of the fluorescence.

To confirm the propose sensing mechanism, ^{1}H NMR experiments were carried out. Thus, ^{1}H NMR spectra of ligand **1** free and the presence of different amounts of Al^{3+} were recorded in CD_3CN (Figure 4). The most important modifications of the signals of **1** after complexation were observed in the phenyl moiety (7.10 and 6.84 ppm) which underwent a significant downfield shift upon the addition of Al^{3+} (0.52 and 0.90 ppm respectively). The change is especially important in the *ortho*-protons to the amino group. On the other hand the methylene group that in the free ligand appears at 3.44 ppm show a downfield shift of 0.20 ppm and the signal corresponding to the hydroxymethylene protons, at 3.58 ppm, displayed a different behavior with an upper field shift of 0.18 ppm. Finally, there were no changes in the protons of the pyrrole units (at 6.15 ppm). These data strongly suggest the direct involvement of the amino group in the Al^{3+} coordination.

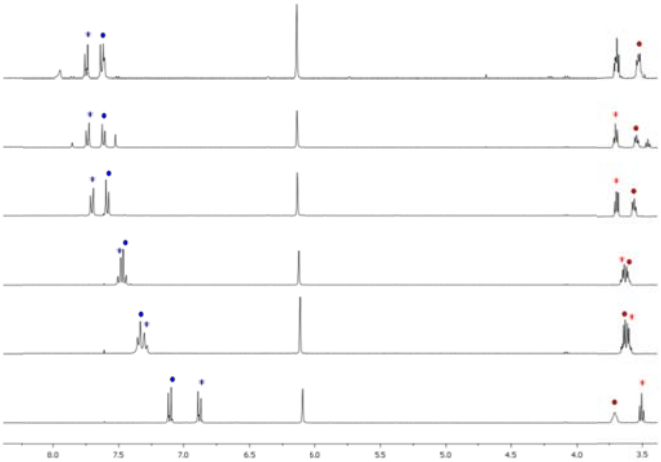


Figure 4. ^{1}H-NMR spectra of **1** and **1**+increasing amounts of Al^{3+} in CD_3CN.

A similar behavior was observed with ligand **2** (see ESI) upon addition of Al^{3+}. Remarkable changes were observed in the *N*-methyl-*N*-(2-hydroxyethyl)styryl group, especially in the ortho-protons to the amino group. On the other hand, changes in the protons of the pyrrole units and phenyl moiety in the 8 position of the BODIPY were negligible.

Conclusions

In summary, we have successfully synthesized and characterized two BODIPY-based probes which show a "turn-on" response with trivalent cations of interest whereas the probe remained silent in the presence of competitive cations (Hg^{2+}, Li^{+}, Na^{+}, K^{+}, Ag^{+}, Ca^{2+}, Mg^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Fe^{2+}, Co^{2+}, Ru^{3+}, Fe^{2+}, and Cu^{2+}). This sensing behavior is highly selective and it is observed in mixed aqueous solutions. Compound **1** can be only used in fluorescence studies whereas compound **2** gives sensing response through two different channels, UV-vis and fluorescence. The observed colour change or enhanced fluorescence emission can be attributed to the binding of M^{3+} to the 2-aminoethanol moiety which reduces the electron-donating ability of the nitrogen atom conjugated to the BODIPY core. Finally, selective sensing of Al^{3+} and Cr^{3+} *versus* Fe^{3+} was observed with ligand **2**.

Acknowledgements

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details and spectroscopic data; NMR, fluorescence and Uv titrations of **1** and **2** with Al^{3+},Cr^{3+} and Fe^{3+}.See DOI: 10.1039/c000000x/

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