ChemPubSoc Europe
DOI: 10.1002/cplu.201500042
CHEMPLUSCHEM Communications

A Chalcone-Based Highly Selective and Sensitive Chromofluorogenic Probe for Trivalent Metal Cations

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A new chalcone-based probe for the chromofluorogenic sensing of trivalent (Al^{3+}, Fe^{3+}, Cr^{3+}, Ga^{3+}, In^{3+} and As^{3+}) over mono- and divalent cations and anions is reported. In the presence of trivalent metal cations, the probe was able to display a remarkable color change from yellow to colorless that was clearly visible to the naked eye. Also, the initial strong yellow emission was gradually quenched and substituted by a weakly shifted band.

Recently, increasing interest in the recognition and sensing of transition-metal cations has been boosted owing to better understanding of their biological and environmental roles in several fundamental natural and physiologic process, as well as their widespread use in industrial applications and in organic synthesis protocols.[1] Among metal cations, Al^{3+}, Fe^{3+}, Cr^{3+} Ga^{3+}, In^{3+}, and As^{3+} play crucial roles in biological processes and their detection is a timely topic. For instance, iron is the most abundant transition metal in cellular systems. More specifically, the Fe^{3+} cation is an essential element in the growth and development of living systems, as well as in many biochemical processes at the cellular level,[2] and its deficiency is associated with several diseases, such as anemia; hemochromatosis; diabetes; Parkinson's disease; and dysfunction of all principal human organs, such as the heart, pancreas, and liver.[3] On the other hand, aluminum is the third most abundant element on earth and the most abundant metallic element. Aluminum is used in several commercial applications, such as water treatment, food additives, medicines, and metallic devices. In addition, some studies indicate that abnormal levels of aluminum ions in certain human tissues and cells[4] could induce Alzheimer's[5] and Parkinson's diseases.[6] The Cr^{3+} cation is one of the most important nutrients in human and animal diets and plays a fundamental role in the metabolism of carbohydrates, proteins, lipids, and nucleic acids.[7] Deficiency of Cr^{3+} is associated with the development of diabetes and some cardiovascular diseases.[8] Similar to Al^{3+}, an overdose of Cr^{3+} cations could induce serious toxic effects;[9] moreover, their use in the metal industry has resulted in increased levels of chromium in the environment, and today it has come to be regarded as a pollutant element.[10] Gallium does not exist in the free form in nature, but is found primarily in its 3+ oxidation state. Several Ga^{3+} salts are used for the preparation of semiconductors and as radiopharmaceutical agents in several imaging procedures.[11] Indium is also only found in the earth's crust in the form of In^{3+} compounds. Similar to gallium, indium is used for electronics and in several alloys.[12] In^{3+}, similarly to Al^{3+}, can be toxic to the kidney.[13] Finally, elemental arsenic and As^{3+} compounds are toxic[14] and its poisoning is linked with a variety of neurologic, cardiovascular dermatologic and carcinogenic effects.[15] In spite of this acute toxicity, arsenic is essential as a trace element in birds and in several mammals.[16]

Consequently, trivalent cation detection is now a focus of interest and a timely topic of research. In this context, the development of optical probes that are able to selectively recognize trivalent cations are highly appealing owing to the possibility of their detection through widely available low-cost instrumentation, and also because optical probes offer the possibility of developing simple tests to sense these target species with detection by the naked eye.[17] Some selective fluoro- and chromogenic probes for the detection of Fe^{3+},[18] Al^{3+},[19] Cr^{3+},[20] Ga^{3+},[21] In^{3+},[22] and As^{3+}[23] cations have been reported. However, only a few probes that are able to recognize simultaneously two[24] or three[25] trivalent cations have been described in the literature. This lack of multiresponsive probes is, in most cases, due to severe interference from mono- and divalent metal cations.

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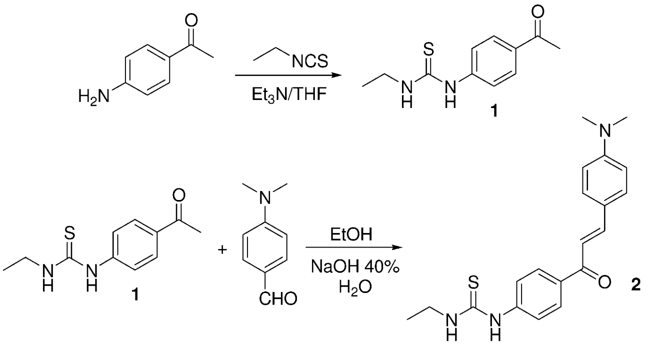
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cplu.201500042.

Taking into account the above mentioned facts and our interest in the development of new chromofluorogenic chemosensors,[17a,b,26] we report herein a simple to prepare, new probe that is able to selectively detect the trivalent cations Fe^{3+}, Al^{3+}, Cr^{3+}, Ga^{3+}, In^{3+}, and As^{3+} through remarkable changes in the UV-visible and fluorescence spectra. Moreover, low detection limits, in the nanomolar range when fluorescence was used, were determined.

Probe **2** was readily synthesized by a two-step procedure (see Scheme 1). The first step consisted of the synthesis of thiourea derivative **1** by the reaction of commercially available 4-aminoacetophenone and ethylisothiocyanate. Finally, probe **2** was obtained by an aldol condensation between compound **1** and 4-dimethylaminobenzaldehyde (see the Supporting Information for further details).



Scheme 1. Synthesis of probe **2**.

Solutions of probe **2** in acetonitrile (see Figure 1) showed an absorption band in the visible zone centered at $\lambda = 414$ nm ($\varepsilon = 2.64\times10^{4}$ M^{-1} cm^{-1}) and two less intense bands in the UV domain at $\lambda = 317$ ($\varepsilon = 1.54\times10^{4}$ M^{-1} cm^{-1}) and 257 nm ($\varepsilon = 1.50\times10^{4}$ M^{-1} cm^{-1}). As a consequence, solutions of **2** showed an intense yellow color. Furthermore, when solutions of **2** in acetonitrile were excited at $\lambda = 412$ nm, a very strong emission band at $\lambda = 538$ nm (stokes shift = 5567.23 cm^{-1}) was displayed with a remarkable quantum yield of $\Phi = 0.63 \pm 0.02$ (calculated by using fluorescein in 0.1 M NaOH as a standard).[27]

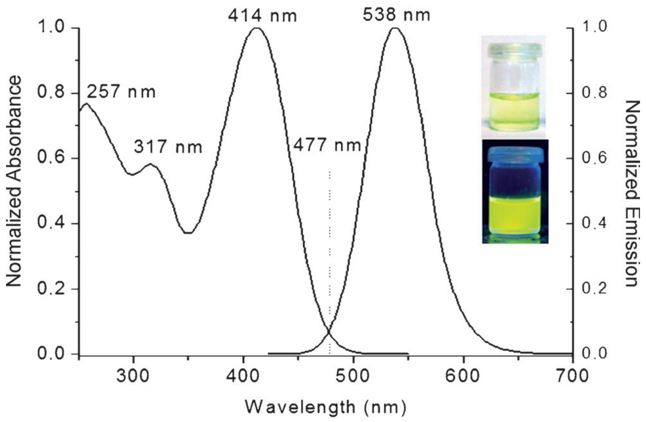


Figure 1. UV-visible and emission ($\lambda_{ex} = 412$ nm) spectra of probe **2** in acetonitrile (1.0×10^{-5} mol dm^{-3}). Inset: color and fluorescence (under UV lamp, $\lambda_{ex} = 365$ nm) of solutions of **2** in acetonitrile observed by the naked eye.

The charge-transfer character of the visible band was assessed by quantum chemical calculations at the semiempirical level by using the PM3 model (with a root-mean-square (RMS) gradient of 0.001) in HyperChem software. As seen in Figure 2, the HOMO orbital was mainly centered in the *N*,*N*-dimethylaniline donor fragment, whereas the LUMO orbital was located in the acceptor phenylthiourea moiety.

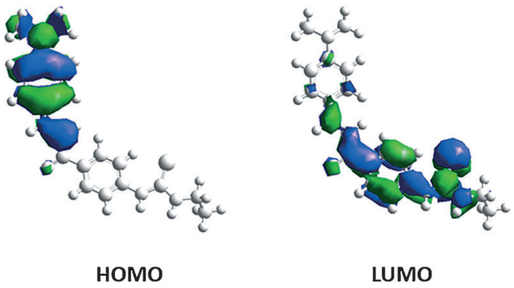


Figure 2. HOMO and LUMO orbitals for probe **2**.

Probe **2** contains, in its structure, two potential binding units, namely, the thiourea moiety (for anion coordination) and an aniline donor nitrogen atom (able to interact with cations). Therefore, the chromo and fluorogenic behavior of solutions of probe **2** in acetonitrile were tested in the presence of 10 equivalents of selected anions (F$^-$, Cl$^-$, Br$^-$, I$^-$, OH$^-$, AcO$^-$, BzO$^-$ (Bz = benzoyl), CN$^-$, OCN$^-$, $H_2PO_4^-$ HSO_4^-, and ClO_4^-) and cations (K$^+$, Li$^+$, Mg^{2+}, Co^{2+}, Fe^{3+}, Fe^{2+}, Al^{3+}, Hg^{2+}, Cr^{3+}, Pb^{2+}, Cd^{2+}, Ba^{2+}, Ni^{2+}, Zn^{2+}, Ca^{2+}, Cu^{2+}, Ga^{3+}, In^{3+}, and As^{3+}). The results obtained in the presence of cations are depicted in Figure 3. Of all cations tested, only Al^{3+}, Fe^{3+}, Cr^{3+} Ga^{3+}, In^{3+}, and As^{3+} induced remarkable and immediate color modulations. In this respect, the color of solutions of probe **2** in acetonitrile changed from yellow to colorless and the strong yellow fluorescence was quenched and substituted with a weak blue emission. Moreover, and despite the presence of a thiourea moiety in the probe, compound **2** was unable to display sensing features in the presence of the tested anions (see the Supporting Information).

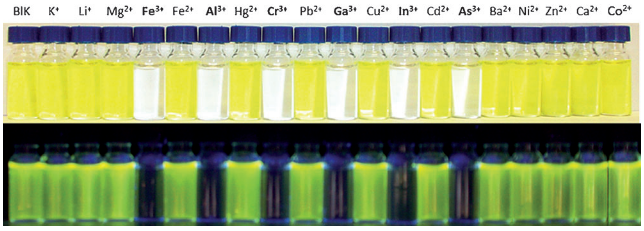


Figure 3. Photographs of color and fluorescence ($\lambda_{ex} = 365$ nm) modulation of **2** (acetonitrile, 1.0×10^{-4} mol dm^{-3}) upon the addition of 10 equivalents of selected cations.

Having assessed the highly selective response of **2** toward trivalent metal cations, we studied the sensitivity of the probe by monitoring the UV-visible and emission changes at 25 °C of solutions in acetonitrile upon the addition of increasing quantities of Fe^{3+}, Al^{3+}, Cr^{3+}, Ga^{3+}, In^{3+}, and As^{3+}. The UV-visible and emission profiles obtained in the presence of the six trivalent cations were similar and, as an example, the complete set of spectra obtained for probe **2** and the Al^{3+} cation are shown in Figure 4. As observed, the addition of increasing amounts of Al^{3+} cations induced a progressive decrease in the visible band at $\lambda=414$ nm together with the simultaneous growth of a new blueshifted absorption at $\lambda=292$ nm ($\varepsilon=1.39\times10^4\ \text{M}^{-1}\text{cm}^{-1}$) with a clear isosbestic point at $\lambda=361$ nm. The disappearance of the absorption band at $\lambda=414$ nm was responsible for the yellow-to-colorless color modulation observed (see Figure 3).

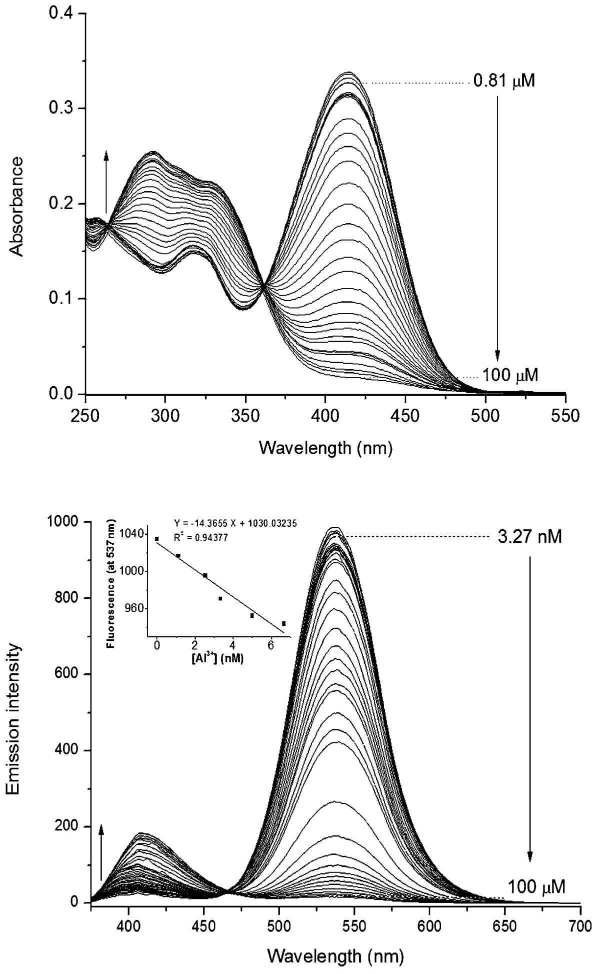


Figure 4. UV-visible (top) and emission (bottom) profile of titrations of a solution (1.0×10^{-5} mol dm^{-3}) of probe **2** in acetonitrile upon the addition of increasing quantities of Al^{3+} cations. Inset: fluorescence changes of the emission band at $\lambda=537$ nm in the nanomolar range.

On the other hand, upon excitation at the isosbestic point observed in the course of the UV-visible titration between **2** and Al^{3+} ($\lambda_{ex}=361$ nm), an intense emission at $\lambda=538$ nm was observed. The addition of increasing amounts of Al^{3+} cations induced the progressive quenching of the fluorescence at $\lambda=538$ nm together with the simultaneous growth of a new blue emission at $\lambda=406$ nm (see Figure 4). The overall result is a remarkable reduction of the quantum yield of probe **2** to 0.070 ± 0.005 in the presence of Al^{3+} cations.

From UV-visible and fluorescence titrations, the limits of detection (LOD) of probe **2** for Al^{3+}, Fe^{3+}, Cr^{3+} Ga^{3+}, In^{3+}, and As^{3+} cations were evaluated (see Table 1) by using the IUPAC regression approach (see the Supporting Information for details).[28] When changes in the absorption bands were studied, the LOD values were in the micromolar range, whereas when fluorescence was used the LOD values were in the nanomolar range (see the inset in Figure 4, bottom). The latter LOD values are remarkable when considering that the LOD values for other reported probes for trivalent metal cations are usually in the micromolar range.[18–25]

Table 1. LOD values and logarithms of binding constants for the interaction of probe **2** with trivalent cations.

Cation	Limit of detection [M^{3+}]		log *K*[a]	
	UV/Vis [μM]	Emission [nM]	UV/Vis	Emission
Al^{3+}	0.81	3.27	13.10 ± 0.043	12.35 ± 0.039
Fe^{3+}	0.43	2.87	12.79 ± 0.047	12.70 ± 0.034
Cr^{3+}	0.34	2.44	14.02 ± 0.007	15.21 ± 0.071
Ga^{3+}	0.34	2.59	13.12 ± 0.006	10.79 ± 0.042
As^{3+}	0.33	3.68	14.98 ± 0.010	10.02 ± 0.015
In^{3+}	0.34	3.88	12.67 ± 0.018	11.25 ± 0.074

[a] Log *K* values for the formation of 2:1 probe–metal complexes [Eq. (1)].

Moreover, to determine the binding stoichiometry between probe **2** and the trivalent metal cations, Job's plots were calculated.[29] As an example, Figure 5 shows the Job's plot determined for Al^{3+}, which clearly shows the formation of 2:1 probe–cation complexes. The same stoichiometries were determined for probe **2** with Fe^{3+}, Cr^{3+} Ga^{3+}, In^{3+}, and As^{3+} cations (data not shown).

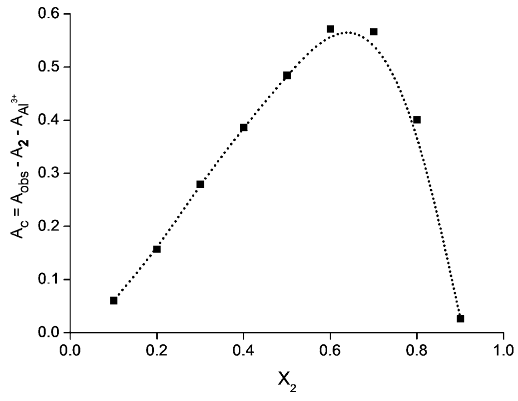


Figure 5. Job's plot for complexation between probe **2** and Al^{3+} cations, as determined by UV-visible measurements at $\lambda=414$ nm in acetonitrile with $[\mathbf{2}]+[Al^{3+}]=1\times10^{-4}$ mol dm^{-3}.

Based on the Job's plots, the corresponding stability constants for the formation of $[M(\mathbf{2})_2]^{3+}$ complexes were determined by using HypSpec software (V 1.1.18) and adjusting the data to Equation (1):

$$M^{3+} + 2L \rightleftharpoons [M(L)_2]^{3+} \quad (1)$$

The estimated values of $\log K$ obtained by UV-visible and emission titration profile data are shown in Table 1.

The remarkable hypsochromic shift observed in the visible band in the presence of the metals cations Al^{3+}, Fe^{3+}, Cr^{3+}, Ga^{3+}, In^{3+}, and As^{3+} appears to be indicative of the preferential coordination of these metals with the donor part of probe **2**, that is, the *N*,*N*-dimethylaniline moiety. Moreover, the selective response observed is most likely to be related to the small size and high charge of the trivalent cations. Both characteristics endowed Al^{3+}, Fe^{3+}, Cr^{3+} Ga^{3+}, In^{3+}, and As^{3+} with a strong polarization character that induced changes in the electronic distribution of **2**, and resulted in remarkable modulations of the UV-visible and fluorescence spectra.

To confirm the binding mode of probe **2** with trivalent cations, ^1H NMR titration studies were performed with Al^{3+}. The most representative signal of probe **2** in the aliphatic zone was a singlet centered at $\delta = 3.02$ ppm, which was ascribed to the methyl groups linked with the nitrogen atom of the aniline ring (Hj protons in Figure 6). Dealing with the aromatic zone, signals appeared as doublets at $\delta = 6.76$ and 7.63 ppm (Hh and Hd protons of the *N*,*N*-dimethylaniline 1,4-disubstituted ring) and at $\delta = 7.54$ and 8.04 ppm (He and Ha protons of the 1,4-disubstituted aromatic ring with carbonyl and thiourea moieties). Also, two doublets centered at $\delta = 7.48$ and 7.72 ppm with a coupling constant of 15.4 Hz, ascribed to the *trans*-double bond, were observed.

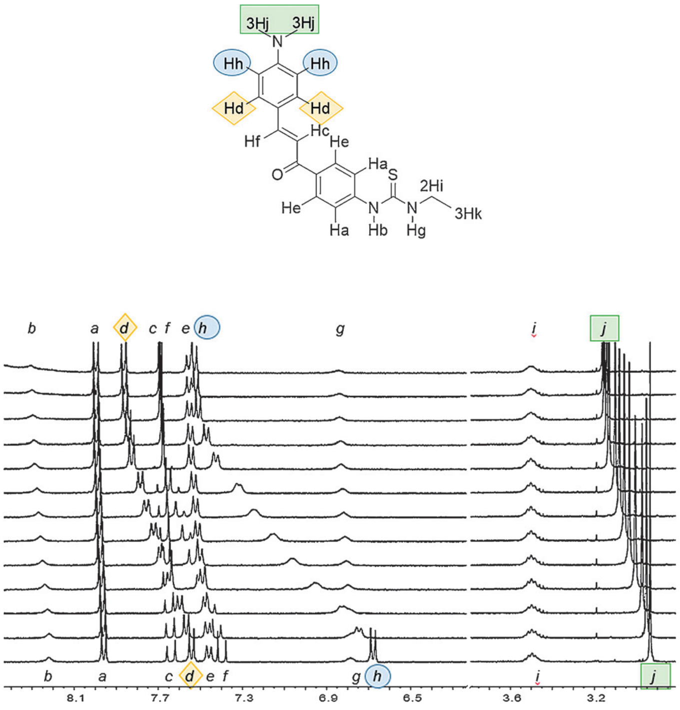


Figure 6. ^1H NMR chemical shifts of the protons of probe **2** in the presence of increasing quantities of Al^{3+} in CD_3CN.

As seen in the family of ^1H NMR spectra shown in Figure 6, the addition of increasing quantities of Al^{3+} to a solution of probe **2** in CD_3CN induced remarkable downfield shifts for protons Hh, Hd, and Hj. These protons are located in the *N*,*N*-dimethylaniline ring and indicated coordination of Al^{3+} with the nitrogen donor nitrogen atom located in this fragment. A similar coordination mode is expected for the other trivalent metal cations.

Finally, the optical response of probe **2** was also studied in a mixture of acetonitrile/water. However, it was found that the addition of more than 5% water to acetonitrile disabled the chromofluorogenic response observed upon the addition of trivalent metal cations. This could be ascribed to the fact that trivalent cations have high free solvation energies, and hence, a strong affinity for coordinating with water molecules rather than with probe **2**.

In summary, we reported herein a simple chromofluorogenic probe with a chalcone-like structure that was able to selectively detect Al^{3+}, Fe^{3+}, Cr^{3+}, Ga^{3+}, In^{3+}, and As^{3+} over mono- and divalent cations and anions. In the presence of trivalent metal cations, the probe was able to display a remarkable color change from yellow to colorless that was clearly visible to the naked eye. Also, the initial strong yellow emission was gradually quenched and substituted by a weakly shifted band. Moreover, the new probe showed remarkable LOD values in the nanomolar range when fluorescence changes were studied. The probe displayed a significant selectivity, a remarkably low limit of detection, and a simple to detect by the naked eye chromofluorogenic response; these features make it suitable for the effective, sensitive, fast, and low-cost detection of trivalent cations in organic solvents.

Acknowledgements

Financial support from the Spanish Government (Project MAT2012-38429-C04), the Generalitat Valencia (Project PROMETEOII/2014/047), and the CIBER de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN) is gratefully acknowledged. A.L.L. would like to thank the Fundación la Caixa for his doctoral fellowship. We are also grateful to the Carolina Foundation for a doctoral grant to L.E.S.-F.

Keywords: anions · chalcone-based probe · chromofluorogenic sensing · sensors · trivalent cations

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Received: January 28, 2015

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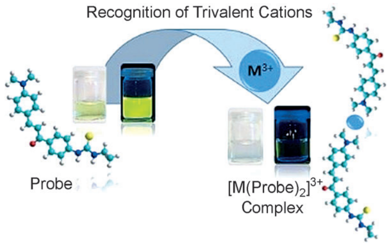
A Chalcone-Based Highly Selective and Sensitive Chromofluorogenic Probe for Trivalent Metal Cations



Recognizing trivalent cations: A new chalcone-containing probe has been devised for the chromo-fluorogenic sensing of Al^{3+}, Fe^{3+}, Cr^{3+}, Ga^{3+}, In^{3+}, and As^{3+} cations over mono- and divalent cations and several anions (see figure). The limit of detection of this probe is in the nM range.