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Fluorescent sensor for selective detection of Al³⁺ based on quinoline–coumarin conjugate



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HIGHLIGHTS

GRAPHICAL ABSTRACT

- We have designed a new chemosensor for aluminum ions.
 2-Methyl quinoline-4-carboxylic
- bydrazide was rarely synthesized.
 L shows a large fluorescence
- enhancement with turn-on over 200fold in ethanol.
- It has lower detection limit.



A R T I C L E I N F O

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ABSTRACT

A fluorescence probe, 8-formyl-7-hydroxyl-4-methyl coumarin – (2'-methylquinoline-4-formyl) hydrazone (L) has been synthesized. The chemosensor is found preferential binding to Al^{3+} in presence of other competitive ions with associated changes in its optical and fluorescence spectra behavior. Upon addition of Al^{3+} to a solution of L, it shows 200-fold enhancement of fluorescence intensity which might be attributed to form a 2:1 stoichiometry of the binding mode of L—Al(III) and the chelation enhanced fluorescence (CHEF) process at 479 nm in ethanol. The lowest detection limit for Al^{3+} is determined as 8.2×10^{-7} M.

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Introduction

As is known, the Al³⁺ ion existing in natural waters and most plants can enter the human body through water and foods [1]. WHO has listed aluminum ion as a source of food pollution and limited its drinking water concentration to 7.41 mM [2–4]. Accumulation of an excessive amount of the metal causes illnesses like Alzheimer's disease, Guamanian amyotrophic lateral sclerosis and Parkinsonism dementia. Therefore, it is crucial to develop some analytical methods for detecting and controlling the concentration levels of aluminum in the environment. In recent years, several methods are available for detection of Al³⁺. In comparison to some conventional methods, fluorescent chemosensor have attracted considerable attention due to its easily detectable signals upon recognition metal ions with high sensitivity and selectivity [5–9].

On the other hand, because of the low coordination ability of Al^{3+} , the development of Al^{3+} sensors has been found to be comparatively more difficult than other metals. In general, as Al^{3+} is a hard-acid, it has been found that Al^{3+} prefers a coordination sphere containing N and O as hard-base donor sites. Schiff bases (imines) are known to be good ligands for metal ions [10–14]. The

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Scheme 1. Reagents and conditions: (a) (i) acetone, aq KOH, reflux, 15 h; (ii) conc HCl; (b) conc H₂SO₄, EtOH, reflux, 18 h; (c) EtOH, N₂H₄·H₂O, 20 h; (d) EtOH, reflux, 10–12 h; (e) conc H₂SO₄, CH₃COCH₂COOC₂H₅, -5 °C; (f) HMT.



Fig. 1. Changes in the absorption spectra of L (10 $\mu M)$ in ethanol at room temperature as a function of added Al^{3*} (0, 5, 10, 15, 20, 25, 30, 35, 40, 45 equiv.).

structures of Schiff bases contain nitrogen–oxygen-rich coordination environments which provide a hard-base environment for the hard-acid Al³⁺ [15]. More importantly, Schiff base derivatives equipped with a fluorescence moiety are attractive tools for the detection of metal cations. Keeping this in mind, we have designed a Schiff-base ligand, which was synthesized by condensing 2-methyl quinoline-4-carboxylic hydrazide with 8-formyl-7hydroxyl-4-methyl coumarin. Thus far, to the best of our knowledge, there are no reports on the properties of the Schiff base.

Herein, we report a novel coumarin-based "turn-on" fluorescent probe for the determination of Al^{3+} in ethanol, which is attributed to a chelation-enhanced fluorescence (CHEF) process. It forms a 2:1 complex and the binding constants K_a is 3.3×10^6 . The free chemosensor **L** shows weak fluorescence emission. Upon binding of Al^{3+} ions, a significant fluorescence enhancement over 200-fold is achieved in ethanol.



Fig. 2. Fluorescence spectra of **L** (10 μ M) upon the addition of metal salts (1.0 equiv.) of Na⁺, K⁺, Mg²⁺, Ca²⁺, Pb²⁺, Cr³⁺, Mn²⁺, Fe²⁺, Ni²⁺, Co²⁺, Fe³⁺, Ru³⁺, Cu²⁺, Ba²⁺, Cd²⁺, Hg²⁺, Zn²⁺and Al³⁺ in ethanol (λ_{ex} = 392 nm, slit widths: 5 nm/5 nm).

Experimental

General

All chemicals were obtained from commercial suppliers and used without further purification. ¹H NMR spectra were measured on the Bruker 400 MHz instruments using TMS as an internal standard. ESI-MS were determined on a Bruker esquire 6000 spectrometer. UV–vis absorption spectra were determined on a Shimadzu UV-240 spectrophotometer. Fluorescence spectra were recorded on a Hitachi RF-4500 spectrophotometer equipped with quartz cuvettes of 1 cm path length.

Synthesis

Ethyl 2-methyl quinoline-4-carboxylate was synthesized according to the method reported [16]. The Schiff base was synthesized according to the route as shown in Scheme 1.

Synthesis of 2-methyl quinoline-4-carboxylic hydrazide

Hydrazine hydrate (80%, 4 mL) was added dropwise to an ethanol solution (40 mL) of ethyl 2-methyl quinoline-4-carboxylate (5 mmol, 1.015 g). The mixture was refluxed under stirring for 12 h. Then the solvent was concentrated under reduced pressure and stand overnight in refrigerator. A white needle crystal was observed. The final product was filtered, dried and recrystallized from ethanol. Yield: 55%; m.p.: 178–179 °C. ¹H NMR (Fig. S1): (400 MHz; CDCl₃): δ = 2.71 (s, 3H_e), 4.25 (s, 2H_h), 7.29 (s, 1H_f), 7.54 (m, 1H_b), 7.59 (s, 1H_g), 7.73 (m, 1H_c), 8.05 (d, *J* = 8.4 Hz, 1H_d).

Synthesis of 8-formyl-7-hydroxyl-4-methyl coumarin [17–19]

Sulfuric acid (98%, 2 mL) was added into the solution of m-dihydroxybenzene (0.1 mol, 11.0 g) in tetrahydrofuran (40 mL), and then acetoacetic ester (13.0 g) was added dropwise. The reaction mixture was refluxed for 3 h and monitored by TLC until m-dihydroxybenzene was completely consumed. After cooling, the solution was poured into ice water (100 mL), yellow precipitate was collected by filtration and washed with cold water. Recrystallization from ethanol. 7-Hydroxy-4-methyl-coumarin was obtained (11.3 g, Yield: 64%, m.p.: 185–186 °C). Then 7-hydroxy-4-methylcoumarin (0.03 mol, 5.3 g) and hexamine (0.07 mol, 9.8 g) in glacial acetic acid (50 mL) were refluxed for 6 h, and then 20% HCl (75 mL) was added and the solution was heated for 1 h. After cooling, the reaction mixture was extracted with ether, and the combined organic layers were evaporated under reduced pressure. The residue was poured into ice water and pale vellow solid was obtained. The product was filtered, dried and recrystallized from ethanol



Scheme 2. Proposed mechanism for detection of Al³⁺ by L.



Fig. 3. Fluorescence spectra of L (10 μ M) in ethanol upon the addition of Al(NO₃)₃ (0, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 13.0, 14.0, 15.0 μ M) with an excitation of 392 nm. Inset: fluorescence intensity at 479 nm versus the number of equivalents of Al³⁺ added.



Fig. 4. Job's plot for determining the stoichiometry of **L** and Al³⁺ in ethanol (X_L = [L]/ ([Al³⁺] + [L]), the total concentration of **L** and Al³⁺ was 10 μ M).

(0.612 g, Yield 10%). m.p.: 180–181 °C. ¹H NMR (Fig. S2): (400 MHz; acetone-d₆) δ = 2.47 (d, *J* = 2 Hz, 3H₆), 6.24 (m, 1H₅), 6.92 (d, *J* = 9 Hz, 1H₂), 7.97 (d, *J* = 9 Hz, 1H₁), 10.54 (s, 1H).

Synthesis of **L**

An ethanol solution (20 mL) of 2-methyl quinoline-4-carboxylic hydrazide (1 mmol, 0.203 g) was added to another ethanol (20 mL) containing 8-formyl-7-hydroxyl-4-methyl coumarin (1 mmol, 0.234 g), then the solution was refluxing for 12 h under stirring and some white precipitant appeared. Excess solvent was removed under reduced pressure. After cooling to room temperature, the mixture was filtered and dried. Recrystallization from DMF. Yield: 63%; m.p.: 283–284 °C. ¹H NMR (Fig. S3): (400 MHz; DMSO-d₆): δ = 12.67 (s, 1H₇), 12.61. (s, 1H₁₃), 8.99 (s, 1H₈), 8.18 (d, *J* = 8.1 Hz, 1H₁), 7.99 (d, *J* = 8.3 Hz, 1H₄), 7.76 (m, 1H₃), 7.72 (d, *J* = 9 Hz, 1H₁₁), 7.69 (s, 1H₆), 7.59 (d, *J* = 8.1 Hz, 1H₂), 6.97 (d, *J* = 9 Hz, 1H₁₂), 6.22 (d, *J* = 2 Hz, 1H₉), 2.72 (s, 3H₅), 2.38 (d, *J* = 2 Hz, 1H₁₀). EI-MS (Fig. S4): *m/z* 388.1.1 [M+H]⁺, 410.09 [M+Na]⁺, IR (KBr, cm⁻¹) (Fig. S5): 3438, 3237, 1679, 1586, 863.6.

Results and discussion

General information

Stock solutions of various cations (1 mM) were prepared using nitrate salts. A stock solution of L (1 mM) was prepared. The solution of L was then diluted to 10 μ M in ethanol. In titration experiments, each time a 2 mL solution of L (10 μ M) was filled in a quartz optical cell of 1 cm optical path length, and the ions stock solution were added into the quartz optical cell gradually by using a pipette.



Fig. 5. The ESI-MS spectra of L and Al³⁺.



Fig. 6. Fluorescence intensity of **L** and its complexation with Al³⁺ in the presence of various metal ions. Black bar: L(10.0 μ M); **L** with 1.0 equiv. of Na⁺, Pb²⁺, Ca²⁺, K⁺, Ba²⁺, Hg²⁺, Zn²⁺, Mg²⁺, Mn²⁺, Cd²⁺, Cc²⁺, Cr³⁺, Ni²⁺, Fe³⁺, Fu³⁺ and Cu²⁺, stated. Red bar: 10.0 μ M of **L** with 1.0 equiv. of Al³⁺; 10.0 μ M of **L** and 1.0 equiv. of Al³⁺ with 1.0 equiv. of metal ions stated ($\lambda_{ex} = 392$ nm). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Spectral data were recorded at 3 min after addition of the ions. In selectivity experiments, the test samples were prepared by placing appropriate amounts of ions stock into 2 mL solution of **L** (10 μ M). For fluorescence measurements, both the excitation and emission slit widths were 5 nm.

The binding constant value is determined from the emission intensity data following the modified Benesi–Hildebrand equations [20] (A):

$$\frac{1}{F - F_{\min}} = \frac{1}{K(F_{\max} - F_{\min})[AI^{3+}]} + \frac{1}{F_{\max} - F_{\min}}$$

where F_{\min} , F, and F_{\max} are the emission intensities of the organic moiety considered in the absence of aluminum ion, at an

intermediate aluminum concentration, and at a concentration of complete interaction, respectively, and where K_a is the binding constant concentration.

The detection limit was calculated based on the fluorescence titration. To determine the S/N ratio, the emission intensity of the complex (**L**–Al³⁺) without any anion was measured by 1.5 equiv. and the standard deviation of blank measurements was determined. The detection limit is then calculated with the following equation: detection limit $3\sigma/m$, where σ is the standard deviation of blank measurements, and m is the slope between intensity versus sample concentration.

UV-vis analysis

The binding ability of **L** and Al^{3+} was initially evaluated by UV-visible spectral analysis in ethanol. As shown in Fig. 1, the spectrum of **L** only shows one absorption band centered at 305 nm, Upon addition of Al^{3+} (0–45 equiv.) to a solution (2 ml) of **L** (10 μ M), the absorption band at 303 nm gradually decreases while two new absorption bands appear at 330 nm and at 392 nm with increasing Intensity. Moreover, a clear isosbestic point at 322 nm is observed. This might be attributed to chemical interaction of **L** with Al^{3+} .

Fluorescence study

The effect of Al³⁺ on the fluorescence properties of L (10 mM) in ethanol was investigated. As shown in Fig. 2, the free receptor L almost not show fluorescence emission at 479 nm when it is excited at 392 nm in ethanol. Upon the addition of 1.0 equiv. of Al³⁺, the fluorescence intensity of L shows a large fluorescence enhancement (200-fold) at 479 nm. In contrast, addition of other relevant metal ions including Na⁺, K⁺, Mg²⁺, Ca²⁺, Pb²⁺, Cr³⁺, Mn²⁺, Fe²⁺, Ni²⁺, Co²⁺, Fe³⁺, Ru³⁺, Cu²⁺, Ba²⁺, Cd²⁺, Hg²⁺ and Zn²⁺ cause almost no fluorescence increase. The increased emission intensity of L in the presence of Al³⁺ is attributed to the chelation of the oxygen atom of -C=O, the nitrogen atom of the -C=N group and the oxygen of Ar–O with Al³⁺, which results in the efficient inhibition for the **PET** process of the -C=N group [21–23] (Scheme 2). To further investigate the probe properties of receptor L, we also carried



Fig. 7. ¹H NMR spectra of L with $Al(NO_3)_3$ ·9H₂O in DMSO-d₆: (a) L; (b) L with 0.5 equiv. of Al^{3+} ; (c) L with 1 equiv. of Al^{3+} .

out fluorescence titration and competition experiment in ethanol. From the fluorescence titration profiles (Fig. 3), the binding constant of L for Al³⁺ has been estimated using the Benesi-Hildebrand equation (A). The stability constant is determined as 3.3×10^6 (Fig. S4), this is within the range $10^3 - 10^9$ of those reported for Al³⁺-binding sensors [24–27]. The Job's plot analysis has indicated that it was possible a 2:1 stoichiometry of the binding mode of L and Al³⁺ (Fig. 4). In addition, the formation of 2:1 complex between **L** and Al³⁺ is further confirmed by the appearance of a peak at m/z799.15, assignable to $[L+Al^{3+}-2H^{+}]^{+}$ in the ESI/MS (Fig. 5), The detection limit of **L** for Al^{3+} is found to be 8.2×10^{-7} M, which is sufficiently low to enable the detection of micromolar concentrations of Al³⁺ in many chemical and biological systems [28,29]. From the competition experiments, the receptor L was treated with 1.0 equiv of Al³⁺ in the presence of other metal ions. As shown in Fig. 6, in the case of Cu(II), Fe(III), Ru(III), Fe(II), although the fluorescence intensity is low but detectable. L-Al(III) complex mixing with the other metal ions show no significant variation. It means that the receptor L can be used as a selective fluorescent sensor for Al³⁺ in the presence of most competing metal ions.

¹H NMR titration

To better understand the binding behavior of receptor **L** with Al^{3+} , ¹H NMR titration, Al^{3+} (as its nitrate salt) was added to the DMSO-d₆ solution of **L** (Figs. S5 and S6). The spectral differences are depicted in Fig. 7. In the presence of Al^{3+} (1.0 equiv.), the imine proton peak (H₈) at 8.995 ppm and the signal of -NH (H₇) at 12.672 was shifted downfield towards 9.103 ppm and 12.942 ppm, respectively. Moreover, addition of Al^{3+} to **L** causes the loss of the -OH proton (H₁₃, $\delta = 12.606$ ppm) with subsequent binding to electron deficient Al^{3+} which results in the disappearance of the -OH peak and withdraw electron density from the aromatic ring resulting the ortho proton (H₁₂, $\delta = 6.999$ ppm) to the -OH group moving towards the downfield region ($\delta = 6.962$ ppm). The results suggested that **L** may chelate Al^{3+} through interactions with carboxylate oxygen, imine nitrogen and oxygen of phenolic hydroxyl group.

Conclusions

We have successfully developed a novel off-on fluorescence sensor for Al^{3+} based on 8-formyl-7-hydroxyl-4-methyl coumarin with 2-methyl quinoline-4-carboxylic hydrazide. It exhibited high selectivity for Al^{3+} over other metal ions with 200-fold fluorescence enhancement. More importantly, because of its lower detection limit, the chemosensor may find potential applications for detect micromolar concentrations of Al^{3+} in both biological systems and the environment.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.saa.2014.05.033.

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