Letters in Organic Chemistry, 2011, *8*, 648-651

Efficient Indole-Based Receptor for Cu^{2+} Ion

Huamei Geng, Na Liu, Xin Tian, Rong Li* and Jiantai Ma*

College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou, 730000, P. R. China

Received August 17, 2010: Revised July 16, 2011: Accepted September 05, 2011

Abstract: A new fluorescent sensor 1 was designed and synthesized through the condensation of indole-3-aldehyde and N-(2-hydroxyethyl)ethylenediamine. It exhibits good sensitivity and selectivity for the copper cation over other cations such as K^+, Na^+, Ca^{2+}, Cr^{2+}, Mg^{2+}, Zn^{2+}, Al^{3+} and Fe^{3+}. The fluorescence intensity of the sensor was decreased with increasing the concentration of Cu^{2+}. The analysis of the Benesi-Hildebrand equation indicated the formation 1:1 complex of 1 and Cu^{2+} with association constant $K_{ass}=3.34\times10^5$M.

Keywords: Indole-3-aldehyde, N-(2-hydroxyethyl)ethylenediamine, copper sensor.

INTRODUCTION

Cations play a fundamental and important role in a wide range of chemical, biological, medical and environmental processes. Design and development of efficient cation probes capable of sensing the targeted cations with highly selectively, have therefore attracted a great deal of attention [1]. Among all the cations, Cu^{2+} is one of the most important environmental pollutants and an essential trace element in various biological systems [2], therefore, designing an efficient sensor for Cu^{2+} is necessary. Due to high detection sensitivity and simplicity, fluorescence signaling is one of the first choices [3]. And designing fluorescence sensor for copper ion has drawn worldwide attention recently. Chen *et al.* reported a Cu^{2+} sensor based on gold nanoparticles with a detection limit of 3.6μM [4]. Huang and co-workers synthesized a colorimetric sensor for Cu^{2+} in aqueous solution based on metal ion-induced deprotonation [5]. Dr. Frigoli prepared a cascade FRET-mediated ratiometric sensor for Cu^{2+} ions based on dual fluorescent ligand-coated polymer nanoparticles [6].

Phenanthroline [7], dansyl [3a], anthracene [8] have been investigated as fluorescence molecular chemosensor for Cu^{2+}, they display good sensitivity and selectivity to Cu^{2+}. While, indole as fluorophoric group does not seem to be so widespread, though its biological ubiquity forming part of the amino acid tryptophane is of very high quantum yield [9]. Moreover, the indole ring-metal binding in biological systems has been recently identified [10], when combined with fluorescence spectroscopy, indole derivatives are potential fluorescent chemosensors [9]. In this letter, a simple fluorescence probe based on an indole derivative, chemosensor 1 was reported for the qualitative and quantitative detection of Cu^{2+} in ethanol solution. Fluorescence characterization showed that the chemosensor exhibited excellent selectivity and sensitivity to Cu^{2+}. This may be helpful for constructing new metal sensing chemical sensors.

EXPERIMENTAL

Synthesis of Sensor 1

Indole-3-carboxaldehyde (0.75 g, 5.1 mmol) dissolved in ethanol (50ml) was added dropwise to N-(2-Hydroxyethyl)ethylenedramine (1.1 g, 5.0 mmol), after the mixture was stirred for 24 h. Then over 4-fold excess of $NaBH_4$ (0.76 g, 20.1 mmol) was added and the solution was stirred for 5 h. The residue was treated with 50 ml of water and extracted with CH_2Cl_2. The organic phase was dried with anhydrous sodium sulfate and the solvent evaporated to obtain a yellow oil, which was purified by silica gel column chromatography using ethyl acetate/MeOH (v/v: 4:1). Yield: 45%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm): 9.99 (s, 1H, ArNH), 7.60 (d, 1H, J=7.8, ArCH), 6.93-7.28 (m, 4H, ArCH), 3.89 (s, 1H, OH), 3.53 (s, 2H, CH_2), 3.35(s, 2H, CH_2), 2.70 (d, 2H, J=4.2, CH_2), 2.62-2.59(m, 4H, CH_2) 2.07(s, 2H, NH); MS ESI([M+1]): 234.1, calcd for: $C_{13}H_{19}N_3O$.

All the reactions in the experimental procedure were carried out under nitrogen atmosphere at room temperature.

Stock solutions (1 mM) of the perchlorate salts of K^+, Na^+, Ca^{2+}, Cr^{2+}, Mg^{2+}, Zn^{2+}, Al^{3+}, Fe^{3+} and Cu^{2+} ions in water were prepared. Stock solutions of the sensor 1 (10 mM) were prepared in ethanol solution. Test solutions were prepared by placing 20 μL of the probe stock solution in a test tube, adding an appropriate aliquot of each stock metal salt and diluting the resulting solution to 2 mL with ethanol solution. For all measurements, fluorescence spectra were obtained by excitation at 285 nm.

RESULTS AND DISCUSSION

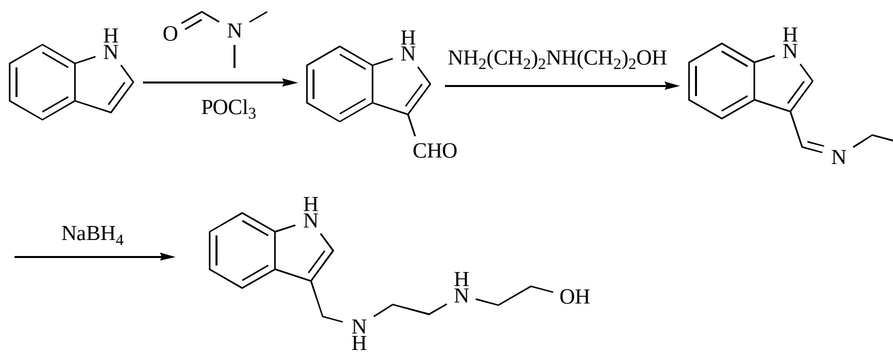
Sensor 1 (Scheme **1**) was synthesized by N-(2-hydroxyethyl)ethylenediamine and indole-3-aldehyde which was prepared by the literature method [11], followed by reduction with $NaBH_4$. The structure of compound 1 was characterized by ^{1}H NMR and MS.

Chemosensor 1 is soluble in ethanol solution. The perchlorate salts of K^+, Na^+, Ca^{2+}, Cr^{2+}, Mg^{2+}, Zn^{2+}, Al^{3+}, Fe^{3+} and Cu^{2+} ions were used to evaluate the selectivity of

---

*Address correspondence to these authors at the College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou, 730000, P. R. China; Tel: 86-931-8912577; Fax: 86-931-8912596;
E-mails: majiantai@lzu.edu.cn, liyirong@lzu.edu.cn

1875-6255/11 $58.00+.00



Sensor 1

Scheme 1. Synthesis of sensor 1.

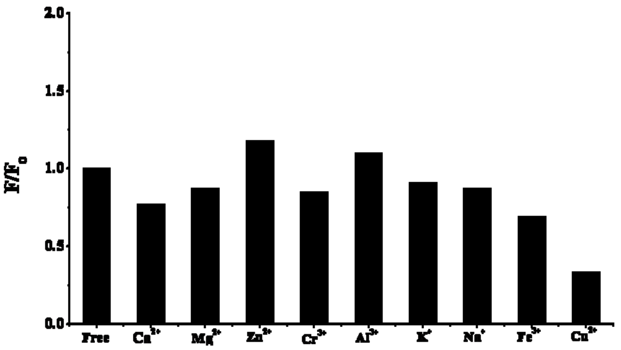


Fig. (1). Ralative fluorescence intensity of sensor 1 (10 μM) in the presence of varions ions (10 μM). λ_{ex}=285 nm. λ_{em}=349 nm.

Table 1. Ralative Fluorescence Intensity of Sensor 1 (10 μM) in the Presence of Varions Ions (10 μM). λ_{ex}=285 nm, λ_{em}=349 nm

	Free	Ca^{2+}	Mg^{2+}	Zn^{2+}	Cr^{2+}	Al^{3+}	K^+	Na^+	Fe^{3+}	Cu^{2+}
F/F$_0$	1	0.77	0.87	1.18	0.85	1.1	0.91	0.87	0.69	0.33

metal ion binding properties of 1. As shown in Fig. (**1**) and Table **1**, upon addition of 1 equiv of Zn^{2+} and Al^{3+}, the fluorescence intensity of 1 has increased. K^+, Na^+, Ca^{2+}, Cr^{2+} and Mg^{2+} had no influence on the fluorescence intensity of 1. While the fluorescence was a little quenched with Fe^{3+}, which also existed in most copper ion fluorescence probes. However, compared with other cations, Cu^{2+} has a significantly fluorescence quenching effect with sensor 1, the fluorescence intensity quenched to 33%, which indicated the selectivity and sensitivity of 1 to Cu^{2+} over other cations.

To evaluate the feasibility of a fluorescence sensor for Cu^{2+}, the sensitivity is one of the key elements. In fluorescence emission, free sensor 1 exhibits λ_{max}em at 349 nm upon excitation at 285 nm in ethanol solution (Fig. **2**). Upon addition of increasing Cu^{2+}, a remarkable 11 nm blue-shift from 349 to 338 nm of fluorescence emission and obvious decrease in fluorescence intensity ratio F/F$_0$ changed from 1 to 0.11(Fig. **3**). The detection limit for Cu^{2+} is established at 10^{-7} M under current experimental conditions. The blue-shift attributes to the intra-ligand π-π^* transitions of the indole groups [12]. The reason of fluorescence quenching of sensor 1 is probably due to the occurrence of either an electron transfer or an electronic energy transfer involving the transition metal and the excited fluorophore as observed in other Cu^{2+}-recognition sensors [13]. In Fig. (**3**) and Table **2**, the fluorescence intensity ratio F/F$_0$ shows a hyperbolic decrease with the concentration of Cu^{2+} (0-1 equiv) up to a mole ratio.

The sensor 1 associates with Cu^{2+} in 1:1 stoichiometry, this is confirmed by the Benesi-Hildebrand analysis. When assuming a 1:1 association between sensor 1 and Cu^{2+}, the Benesi-Hildebrand equation is given as follows [14]:

$$\frac{1}{F-F_0}=\frac{1}{F_\infty-F_0}\left[\frac{1}{K_{ass}[Cu^{2+}]}+1\right]$$

F$_0$ is the fluorescence intensity of 1, F_∞ is the intensity measured with excess amount of Cu^{2+}, F is the intensity measured with Cu^{2+}, K_{ass} is the association constant (M^{-1}), and $[Cu^{2+}]$ is the concentration of Cu^{2+} added (M). As shown

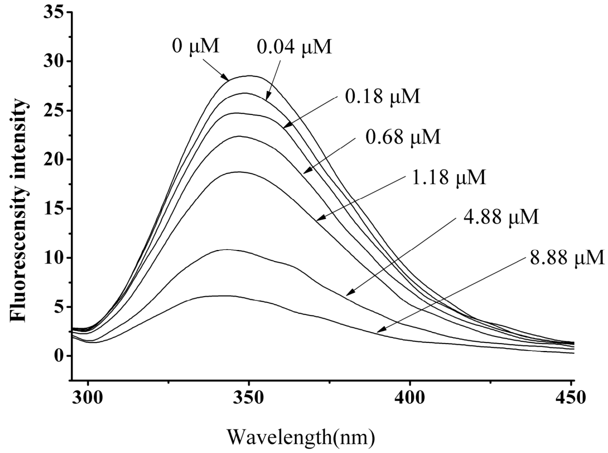


Fig. (2). Fluorescence intensity of sensor 1(10 μm) with increasing concentration of Cu^{2+} (0 μM, 0.04 μM, 0.18 μM, 0.68 μM, 1.18 μM, 4.88 μM, 8.88 μM) in ethnol solution. λ_{ex}=285 nm, λ_{em}=349 nm.

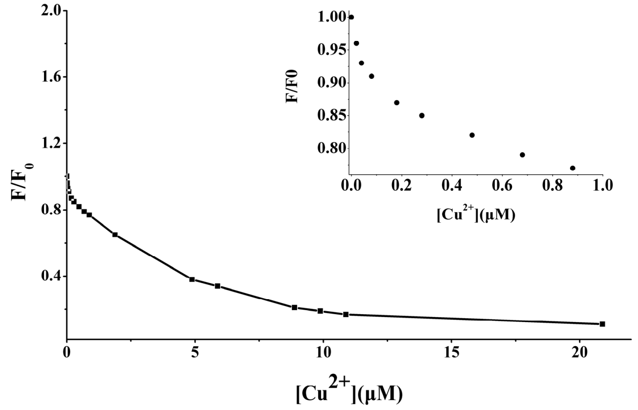


Fig. (3). Ralative fluorescence intensity of sensor 1(10 μm) at different concentration of Cu^{2+}. λ_{ex}=285 nm, λ_{em}=349 nm.

in Fig. (**4**), plot of 1/ ($F-F_0$) against 1/ [Cu^{2+}] shows a liner relationship, indicating that 1 actually associates with Cu^{2+} in 1:1 stoichiometry. The association constant K_{ass}, between 1 and one Cu^{2+}, is determined from the ratio of intercept/slope to be 3.34×10^5 M (r^2=0.998).

The association of sensor 1 and Cu^{2+} ion makes the formation of the host-guest complex through the interaction between the N atoms of sensor 1 and Cu^{2+}. As it is well known, Cu^{2+} ion is a paramagnetic ion with an empty d shell, it always desires a square planar geometry when it is coordinated [15]. So, the fluorescence intensity decreased suggesting that Cu^{2+} formed a complex with the three nitrogen atoms and one oxygen of the sensor 1 and strongly quenched the emission intensity.

Table 2. Ralative Fluorescence Intensity of Sensor 1(10 μm) at Different Concentration of Cu^{2+}. λ_{ex}=285 nm, λ_{em}=349 nm

Cu^{2+}	0	0.02	0.04	0.06	0.08	0.18	0.28	0.48	0.68
F/F_0	1	0.96	0.93	0.91	0.87	0.85	0.82	0.79	0.79
Cu^{2+}	0.88	1.88	4.88	5.88	8.88	9.88	10.88	20.88	
F/F_0	0.77	0.65	0.38	0.34	0.21	0.19	0.17	0.11	

To explore practical applicability of 1 as a Cu^{2+}-selective fluorescent chemosensor, competition experiments were also performed in the presence of Cu^{2+} at 10 μM mixed with 10 μM background metal cations such as K^+, Na^+, Ca^{2+}, Cr^{2+}, Mg^{2+}, Zn^{2+}, Fe^{3+}(Fig. **5**). The fluorescence intensity ratio F/F_0 of solution containing both background metal cations and Cu^{2+} showed no obvious variation comparing with that only containing Cu^{2+} (Table **3**). The strong formation constant of Cu^{2+} ion determines the selectivity, and thus the strong coordination of Cu^{2+} ion in the square planar environment with sensor 1 is not perturbed by the presence of the interfering metal ions. As a result, the sensor 1 shows a high selectivity to Cu^{2+} ion.

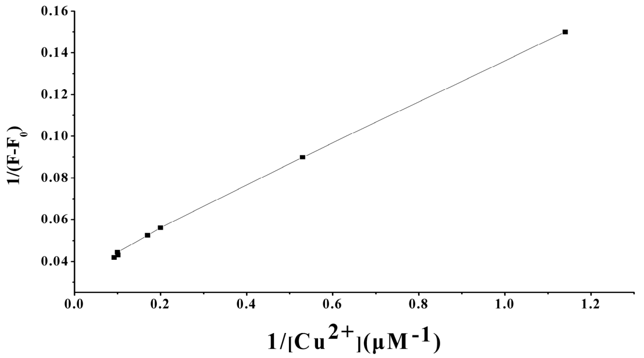


Fig. (4). Benesi-Hilderbrand plot of sensor 1 with Cu^{2+}. λ_{ex}=285 nm, λ_{em}=349 nm.

In conclusion, we developed a highly selective fluorescent sensor 1 for Cu^{2+} using the indole group as the receptors. The sensor forms a stable 1:1 complex with Cu^{2+} and has high association constant (K_{ass}). Therefore, it shows much better selectivity over some other metal ions and responds to Cu^{2+} by quenching fluorescence intensity in the 1×10^{-7} to 1×10^{-5} M range. We expect that sensor 1 will possesses practical applications in cellular Cu^{2+} imaging and other Cu^{2+} detection field.

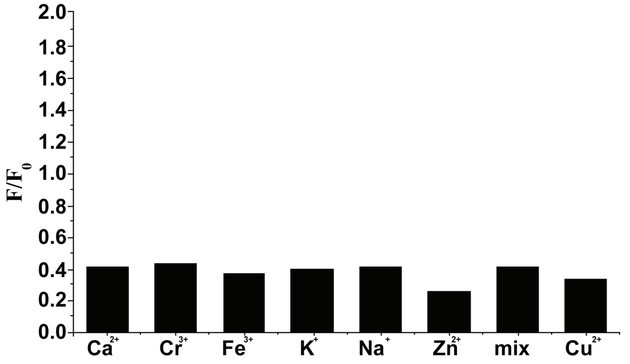


Fig. (5). Ralative fluorescence intensity of sensor 1(10 μM) containing Cu^{2+} (1 equiv) and the background ions (1 equiv). λ_{ex}=285 nm, λ_{em}=349 nm.

Table 3. Ralative Fluorescence Intensity of Sensor 1(10 μM) Containing Cu^{2+} (1 equiv) and the Background Ions (1 equiv). λ_{ex}=285 nm, λ_{em}=349 nm

	$Ca^{2+}+Cu^{2+}$	$Zn^{2+}+Cu^{2+}$	$Cr^{2+}+Cu^{2+}$	$K^{+}+Cu^{2+}$	$Na^{+}+Cu^{2+}$	$Fe^{3+}+Cu^{2+}$	Cu^{2+}+mix	Cu^{2+}
F/F_0	0.41	0.25	0.43	0.4	0.41	0.37	0.41	0.33

REFERENCES

[1] Shiraishi, Y.; Maehara, H.; Hirai, T., Indole-azadiene conjugate as a colorimetric and fluorometric probe forselective fluoride ion sensing. *Org. & Bio. Chem.,* **2009,** *7*, 2072-2076.

[2] Yang, H.; Liu, Z.-Q.; Zhou, Z.-G.; Shi, E.-X.; Li, F.-Y.; Du, Y.-K.; Yi, T.; Huang, C.-H., Highly selective ratiometric fluorescent sensor for Cu(II) with two urea groups. *Tetrahedron Lett.* **2006,** *47* (17), 2911-2914.

[3] (a) Bhalla, V.; Kumar, R.; Kumar, M.; Dhir, A., Bifunctional fluorescent thiacalix[4]arene based chemosensor for Cu^{2+} and F- ions. *Tetrahedron* **2007,** *63* (45), 11153-11159; (b) Kumar, R.; Bhalla, V.; Kumar, M., Cu^{2+} and CN--selective fluorogenic sensors based on pyrene-appended thiacalix[4]arenes. *Tetrahedron* **2008,** *64* (35), 8095-8101.

[4] Chen, W.; Tu, X.; Guo, X., Fluorescent gold nanoparticles-based fluorescence sensor for Cu^{2+} ions. *Chem Commun (Camb)* **2009,** (13), 1736-1738.

[5] Huang, J.; Xu, Y.; Qian, X., A colorimetric sensor for Cu^{2+} in aqueous solution based on metal ion-induced deprotonation: deprotonation/protonation mediated by Cu^{2+}-ligand interactions. *Dalton Trans* **2009,** (10), 1761-1766.

[6] Frigoli, M.; Ouadahi, K.; Larpent, C., A cascade FRET-mediated ratiometric sensor for Cu^{2+} ions based on dual fluorescent ligand-coated polymer nanoparticles. *Chemistry* **2009,** *15* (33), 8319-30.

[7] Wu, J.-S.; Wang, P.-F.; Zhang, X.-H.; Wu, S.-K., An efficient chloride-selective fluorescent chemosensor based on 2,9-bis(4'-hydroxyphenyl)phenanthroline Cu(II) complex. *Spectrochimica Acta Part A: Mol and Biomol. Spectroscopy* **2007,** *67* (2), 281-286.

[8] Varazo, K.; Xie, F.; Gulledge, D.; Wang, Q., Synthesis of triazolyl anthracene as a selective fluorescent chemosensor for the Cu(II) ion. *Tetrahedron Lett.* **2008,** *49* (36), 5293-5296.

[9] Ricardo Aucejo, J. A., Conxa Soriano, M. Carmen Guillem, Enrique García-España and Francisco Torres, New sensing devices part 1: indole-containing polyamines supported in nanosized boehmite particles. *J. Mat. Chem.***2005,** *15*, 2920 - 2927.

[10] Xue, Y.; Davis, A. V.; Balakrishnan, G.; Stasser, J. P.; Staehlin, B. M.; Focia, P.; Spiro, T. G.; Penner-Hahn, J. E.; O'Halloran, T. V., Cu(I) recognition *via* cation-[pi] and methionine interactions in CusF. *Nat Chem. Biol.* **2008,** *4* (2), 107-109.

[11] (a) James, P. N.; Snyder, H. R., Indole-3-carboxaldehyde. *Org.Synth* **1959,** *39*; (b) James, P. N.; Snyder, H. R., Indole-3-carboxaldehyde. *Org. Synth. Coll. Voll* **1963,** *4*.

[12] Zhou, Q.; Yang, P., Crystal structure and DNA-binding studies of a new Cu(II) complex involving benzimidazole. *Inorganica Chimica Acta*. **2006,** *359* (4), 1200-1206.

[13] (a) Zong, G.; Lu, G., A molecular half-subtractor based on a fluorescence and absorption dual-modal sensor for copper ions. *Tetrahedron Lett.* **2008,** *49* (39), 5676-5679; (b) Wu, J.-S.; Wang, P.-F.; Zhang, X.-H.; Wu, S.-K., Novel fluorescent sensor for detection of Cu(II) in aqueous solution. *Spectrochimica Acta Part A: Mol. and Biomol. Spectroscopy* **2006,** *65* (3-4), 749-752.

[14] Shiraishi, Y.; Sumiya, S.; Kohno, Y.; Hirai, T., A Rhodamine-Cyclen Conjugate as a Highly Sensitive and Selective Fluorescent Chemosensor for Hg(II). *J. Org. Chem.* **2008,** *73* (21), 8571–8574.

[15] Dong, Z.; Jin, J.; Zhao, W.; Geng, H.; Zhao, P.; Li, R.; Ma, J., Quinoline group grafted carbon nanotube fluorescent sensor for detection of Cu^{2+} ion. *App. Sur. Sci.* **2009,** *255* (23), 9526-9530.