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Acridine-based *Switching on* Fluorescence Sensor for Cd^{2+} Functioning in Absolute Aqueous Media

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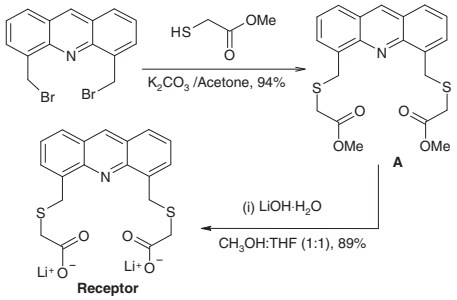
A new acridine fluoroionophore derivative bearing lithium salt of thioglycolate, is designed and synthesized. Its fluorescence sensing behavior toward metal ions has been investigated in absolutely aqueous media (HEPES buffer solution, pH 7.4). It displayed a selective CHEF (chelation-enhanced fluorescence) effect toward Cd^{2+} in presence of other heavy and transiton-metal ions. Highly sensitive *switching on* response of the fluorophore toward Cd^{2+}, facilitates it suitable for sensing of Cd^{2+} in aqueous media.

The development of artificial synthetic fluorescence chemosensors with high selectivity and sensitivity for the target ions has been receiving considerable attention in recent years due to their application in a broad area of medicine, environment, and biology.[1] Nowadays, fluorescence detection has become a promising strategy used for the detection of heavy and transition-metal ions because of its operational simplicity, low cost, real time monitoring, and also high selectivity.[2] Cadmium, the highly toxic metal is widely used in many fields, such as industry, agriculture, military affairs, etc. and it is even found in phosphate fertilizers.[3] These sources lead to cadmium exposure to the living organism through various means, such as through the ingestion of contaminated food or water and inhalation of cigarette smoke. As cadmium can be accumulated in the human body for >10 years,[4] it causes a number of lesions in many organs and tissues such as the kidney, liver, gastrointestinal tract, brain, and bone.[5] In addition, chronic exposure to Cd^{2+} has been implicated as a cause of cancers of the lung, prostate, pancreas, and kidney.[6] Consequently there is a great need for methods for detecting and monitoring cadmium levels in biological and environmental samples. The choice of the fluoroionophore in this aspect is of major importance because it governs the recognition event into an optical signal owing to the change of its photophysical characteristics due to the perturbation by the bound cation. However, there are only few reports on Cd^{2+} selective fluorescent chemosensors[7,8] and most of them easily undergo fluorescence quenching and even fewer examples are available in literature where a significant fluorescence enhancement is observed upon metal ion binding in complete aqueous media.[8] In this aspect, chelation-enhanced fluorescence (CHEF) principle provides an ideal strategy for the construction of luminescent chemical devices, that combines the ability to recognize and respond to an external input mostly with mediation of photoinduced electron transfer (PET).

In continuation of our research work in the development of *switching on* fluorescence sensors[9] for biologically important substrates, herein, we describe the design, synthesis, and photophysical properties of a new thioglycolate salt of acridine-based fluorescent receptor. Experimental studies revealed that the fluorophore exhibits remarkable affinity for Cd^{2+} in fully aqueous media which is associated with a large CHEF effect.



Scheme 1. Synthesis of the receptor.[15]

Receptor is synthesized following the three steps starting from acridine and is shown in Scheme 1. Intermediate 4,5-*bis*(bromomethyl)acridine is prepared according to the literature procedure.[10]

Treatment of 4,5-*bis*(bromomethyl)acridine with methyl thioglycolate in dry acetone in presence of K_2CO_3 and a catalytic amount of tetrabutylammonium bromide (TBAB) affords compound **A**. Then hydrolysis of compound **A** with $LiOH \cdot H_2O$ in CH_3OH/THF (1:1, v/v) followed by subsequent evaporation of the solvent finally gives the receptor. The flexible receptor is composed of acridine nitrogen, soft donor sulfurs, and carboxylate oxygens as ion recognition unit. The use of lithium salt of carboxylates imparts the water solubility of the receptor in combination they take part in binding with the selected metal ion and flexibility factor seems to increase the extent of chelation during complexation with Cd^{2+}.

The fluorogenic response of the receptor (1 μM) has been tested by employing the perchlorate salts of various metal ions at pH 7.4 in aqueous HEPES buffer solution. In absence of the metal ions fluorophore exhibits very weakly an emission band positioned around 440 nm upon excitation at 356 nm and the fluorescence quantum yield (ϕ) is only 0.005. A significant enhancement of emission intensity along with a moderate shifting ($\Delta I = 23$ nm) of emission band is observed at 463 nm (Figure 1) during gradual addition of Cd^{2+} (20 μM). Almost 15-fold enhancement of fluorescence intensity ($\phi = 0.05$) is observed up to the addition of seven equivalents of Cd^{2+} then further addition of Cd^{2+} (up to 10 equiv) produces insignificant changes in emission spectra. The association constant for the Cd^{2+} complexation process is found to be $1.05 \times 10^4\,M^{-1}$ (error ± 10%).[11] A similar enhancement (four fold) of intensity is observed upon gradual addition of Hg^{2+} (0–1 equiv) and then further addition of Hg^{2+} (up to 10 equiv) causes the quenching of emission intensity.

Hence, the receptor exhibits greater affinity and large CHEF effect toward Cd^{2+} compared to Hg^{2+} even though positioned in

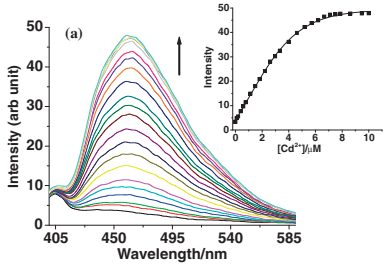


Figure 1. Fluorescence titration spectra of the receptor ($c = 1.0 \times 10^{-6}$ M) in presence of Cd^{2+} ($c = 2.0 \times 10^{-5}$ M) at pH 7.4 in HEPES buffer. Inset: Fluorescence intensity of the receptor as at 463 nm as a function of $[Cd^{2+}]$.

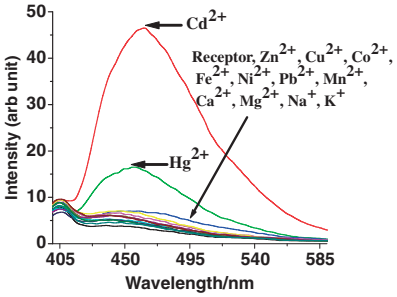


Figure 2. Emission spectra of the receptor ($c = 1.0 \times 10^{-6}$ M) in presence of 10 equiv of each of the guest cations.

the same group. The thiophilic nature and the similar chemical properties of Cd^{2+} are responsible for the interference of Hg^{2+} upon binding with fluorophore. Different ionic radii (102 pm for Hg^{2+} and 95 pm for Cd^{2+}) also may account for the selectivity of the receptor toward Cd^{2+} over Hg^{2+}. Interestingly, neither appreciable change in emission spectra nor large CHEF effect is observed even with excess addition of other tested metal ions e.g., Na^+, K^+, Ca^{2+}, Mg^{2+}, Ni^{2+}, Zn^{2+}, Cu^{2+}, Pb^{2+}, Co^{2+}, Mn^{2+}, and Fe^{2+}. Figure 2 displays the relative change of emission spectra of the receptor in presence of other competing metal ions. In addition, to confirm the Cd^{2+} selectivity of the receptor competition experiment has also been performed by adding interfering metal ions (10 equiv).

The selectivity profile diagram (Figure 3) depicts that Cd^{2+}-induced fluorescence enhancement remains unaltered by the commonly employed coexistent metal ions and this result indicates that receptor has the potential for quantitative detection of Cd^{2+} concentration with a high selectivity (except Cu^{2+}). Since paramagnetic Cu^{2+} is a notorious fluorescence quencher a decrease in intensity seems to happen either by energy- or electron-transfer process.

Cd^{2+}-Induced large CHEF effect of the acridine fluorophore[8e,12] is associated with coordination of acridine nitrogen along with the participation of two thioglycolate ($-SCH_2COO^-$) groups in the present case that possibly form a semirigid cavity which is well arranged for the target metal ion (Scheme 2). Hence fluorescence enhancement at 463 nm in presence of Cd^{2+} reflects a change in the geometry of the flexible conformation of the unbound form possibly to a conformationally more rigidified form during complexation, thus making the nonradiative decay for free fluorophore unit in the excited state less probable.[13]

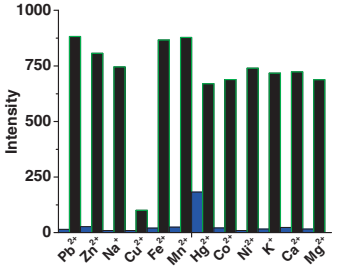
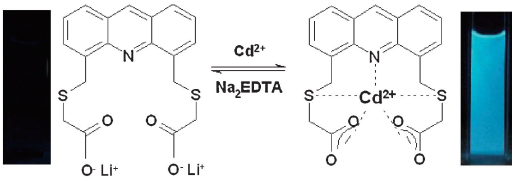


Figure 3. Metal ion selectivity profile of the receptor ($c = 1.0 \times 10^{-5}$ M): (blue bars) change of emission intensity of receptor + 10 equiv of M^{n+}; (black bars) change of emission intensity of receptor + 10 equiv of M^{n+}, followed by 3 equiv of Cd^{2+} at 463 nm.



Scheme 2. Probable mode of binding of the receptor with Cd^{2+}.

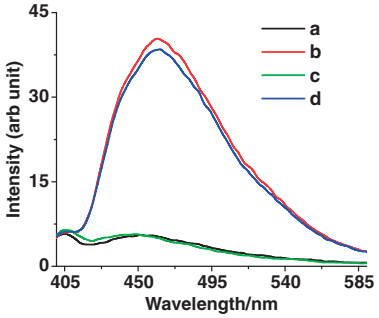


Figure 4. Fluorescence spectra of receptor (1 μM) itself (a), upon the addition of Cd^{2+} (b), followed by addition of Na_2EDTA to (receptor + Cd^{2+}) mixture (c), and finally again addition of Cd^{2+} to a solution of (receptor + Cd^{2+} + Na_2EDTA) mixture (d).

Noteworthy, the *switch on* sensing process could readily be detected not only by fluorescence spectroscopy but also by naked eye experiment. In absence of Cd^{2+}, receptor (10 μM) is almost nonfluorescent, but Cd^{2+} (100 μM) tunes its fluorescence and results in the appearance of strong blue fluorescence under UV light that facilitates its quick naked eye detection (Scheme 2).

The reversibility of the metal complexation of the process as proposed in Scheme 2 is confirmed by adding aqueous solution of excess Na_2EDTA (10 equiv) in situ to solution of receptor/Cd^{2+}. Eventually, the fluorescence is lost immediately which indicates that Na_2EDTA possibly strips away Cd^{2+} from the binding zone. However, addition of Cd^{2+} back to back again recovers the fluorescence (Figure 4).

Now to check whether the perchlorate anion has any influence on the spectral properties of the fluorophore, titration experiment is also performed by taking other counter anions

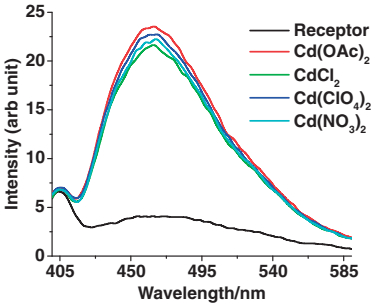


Figure 5. Fluorescence titration spectra of the receptor (1 μM) in presence of addition of other counter anions of Cd^{2+} (5 equiv in each case) in HEPES buffer.

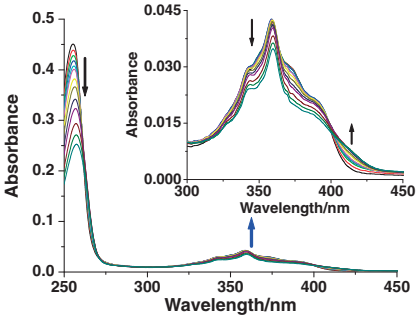


Figure 6. Absorption titration spectra of the receptor (10 μM) in presence of Cd^{2+} ion (0–10 equiv) in HEPES buffer. Inset, change of absorption intensity in between the range 300–450 nm.

(e.g., Cl^-, NO_3^-, and CH_3COO^-) of Cd^{2+} (Figure 5). Almost similar enhancement of emission intensity is observed in all cases indicating that fluorescence is unperturbed by these counter anions.

UV–vis absorption spectrum of the receptor (Figure 6) is characterized by two bands centered at 254 and 356 nm, which possibly attributes to π–π^* transitions of acridine ring.[14] Upon addition of Cd^{2+} ion, a decrease in absorption intensity at 254 and 356 nm is observed, while a new band around 420–430 nm is appeared with generation of an isosbestic point at 397 nm. The intensity of the new band is found to increase with increasing concentration of Cd^{2+}. The observed changes clearly indicate the formation of a new complex in equilibrium due to host–guest interaction in the ground state and participation of acridine nitrogen in the complexation.

In summary, a new sensor based on thioglycolate salt of acridine derivative has been synthesized and characterized, which displays selective and large CHEF effect with Cd^{2+} in presence of other competing metal ions examined. Significantly, it functions completely in aqueous media at neutral pH range and exhibits large *turn on* fluorescence enhancement in presence of Cd^{2+}.

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References and Notes

1 a) E. V. Anslyn, *J. Org. Chem.* **2007**, *72*, 687. b) A. P. de Silva, T. Gunnlaugsson, C. P. McCoy, *J. Chem. Educ.* **1997**, *74*, 53. c) B. Bodenant, T. Weil, M. Businelli-Pourcel, F. Fages, B. Barbe, I. Pianet, M. Laguerre, *J. Org. Chem.* **1999**, *64*, 7034.

2 a) A. P. de Silva, H. Q. N. Gunaratne, T. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher, T. E. Rice, *Chem. Rev.* **1997**, *97*, 1515. b) L. Fabbrizzi, M. Licchelli, P. Pallavicini, D. Sacchi, A. Taglietti, *Analyst* **1996**, *121*, 1763. c) X. Qian, Y. Xiao, Y. Xu, X. Guo, J. Qian, W. Zhu, *Chem. Commun.* **2010**, *46*, 6418. d) J. F. Zhang, Y. Zhou, J. Yoon, J. S. Kim, *Chem. Soc. Rev.* **2011**, *40*, 3416. e) S.-K. Ko, X. Chen, J. Yoon, I. Shin, *Chem. Soc. Rev.* **2011**, *40*, 2120. f) A. P. de Silva, T. S. Moody, G. D. Wright, *Analyst* **2009**, *134*, 2385. g) Z. Xu, J. Yoon, D. R. Spring, *Chem. Soc. Rev.* **2010**, *39*, 1996.

3 a) R. L. Chaney, J. A. Ryan, Y.-M. Li, S. L. Brown, in *Cadmium in Soils and Plants*, ed. by M. J. McLaughlin, B. R. Singh, Kluwer, Boston, **1999**, pp. 219–256. b) A. M. S. Mendes, G. P. Duda, C. W. A. do Nascimento, M. O. Silva, *Sci. Agric. (Piracicada, Braz.)* **2006**, *63*, 328.

4 T. Jin, J. Lu, M. Nordberg, *NeuroToxicology* **1998**, *19*, 529.

5 L. Friberg, C. G. Elinder, T. Kjellström, *Cadmium*, World Health Organization, Geneva, **1992**.

6 a) J. A. McElroy, M. M. Shafer, A. Trentham-Dietz, J. M. Hampton, P. A. Newcomb, *J. Natl. Cancer Inst.* **2006**, *98*, 869. b) V. Verougstraete, D. Lison, P. Hotz, *J. Toxicol. Environ. Health, Part B* **2003**, *6*, 227. c) A. Åkesson, B. Julin, A. Wolk, *Cancer Res.* **2008**, *68*, 6435.

7 a) X.-L. Tang, X.-H. Peng, W. Dou, J. Mao, J.-R. Zheng, W.-W. Qin, W.-S. Liu, J. Chang, X.-J. Yao, *Org. Lett.* **2008**, *10*, 3653. b) Y. Zhou, Y. Xiao, X. Qian, *Tetrahedron Lett.* **2008**, *49*, 3380. c) H. Li, Y. Zhang, X. Wang, *Sens. Actuators, B* **2007**, *127*, 593. d) C. Lu, Z. Xu, J. Cui, R. Zhang, X. Qian, *J. Org. Chem.* **2007**, *72*, 3554. e) S. Y. Park, J. H. Yoon, C. S. Hong, R. Souane, J. S. Kim, S. E. Matthews, J. Vicens, *J. Org. Chem.* **2008**, *73*, 8212. f) X. Peng, J. Du, J. Fan, J. Wang, Y. Wu, J. Zhao, S. Sun, T. Xu, *J. Am. Chem. Soc.* **2007**, *129*, 1500. g) M. Taki, M. Desaki, A. Ojida, S. Iyoshi, T. Hirayama, I. Hamachi, Y. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 12564. h) M. Mameli, M. C. Aragoni, M. Arca, C. Caltagirone, F. Demartin, G. Farruggia, G. De Filippo, F. A. Devillanova, A. Garau, F. Isaia, V. Lippolis, S. Murgia, L. Prodi, A. Pintus, N. Zaccheroni, *Chem.—Eur. J.* **2010**, *16*, 919. i) H.-Y. Luo, J.-H. Jiang, X.-B. Zhang, C.-Y. Li, G.-L. Shen, R.-Q. Yu, *Talanta* **2007**, *72*, 575. j) Z. Xu, K.-H. Baek, H. N. Kim, J. Cui, X. Qian, D. R. Spring, I. Shin, J. Yoon, *J. Am. Chem. Soc.* **2010**, *132*, 601. k) S. Goswami, N. K. Das, K. Aich, D. Sen, *J. Lumin.* **2011**, *131*, 2185. l) A. K. Mahapatra, J. Roy, P. Sahoo, *Tetrahedron Lett.* **2011**, *52*, 2965.

8 a) L. Xue, C. Liu, H. Jiang, *Org. Lett.* **2009**, *11*, 1655. b) M. Choi, M. Kim, K. D. Lee, K.-N. Han, I.-A. Yoon, H.-J. Chung, J. Yoon, *Org. Lett.* **2001**, *3*, 3455. c) T. Cheng, Y. Xu, S. Zhang, W. Zhu, X. Qian, L. Duan, *J. Am. Chem. Soc.* **2008**, *130*, 16160. d) Y. Yang, T. Cheng, W. Zhu, Y. Xu, X. Qian, *Org. Lett.* **2011**, *13*, 264. e) Y. Wang, X. Hu, L. Wang, Z. Shang, J. Chao, W. Jin, *Sens. Actuators, B* **2011**, *156*, 126. f) Z. Liu, C. Zhang, W. He, Z. Yang, X. Gao, Z. Guo, *Chem. Commun.* **2010**, *46*, 6138. g) T. Gunnlaugsson, T. C. Lee, R. Parkesh, *Org. Lett.* **2003**, *5*, 4065.

9 a) S. Goswami, D. Sen, N. K. Das, H.-K. Fun, C. K. Quah, *Chem. Commun.* **2011**, *47*, 9101. b) S. Goswami, D. Sen, N. K. Das, *Tetrahedron Lett.* **2010**, *51*, 6707. c) S. Goswami, D. Sen, N. K. Das, G. Hazra, *Tetrahedron Lett.* **2010**, *51*, 5563. d) S. Goswami, D. Sen, N. K. Das, *Org. Lett.* **2010**, *12*, 856.

10 J. Chiron, J.-P. Galy, *Synlett* **2003**, 2349.

11 a) H. A. Benesi, J. H. Hildebrand, *J. Am. Chem. Soc.* **1949**, *71*, 2703. b) D. C. Carter, J. X. Ho, *Adv. Protein Chem.* **1994**, *45*, 153.

12 a) M. S. Park, K. M. K. Swamy, Y. J. Lee, H. N. Lee, Y. J. Jang, Y. H. Moon, J. Yoon, *Tetrahedron Lett.* **2006**, *47*, 8129. b) H. N. Lee, H. N. Kim, K. M. K. Swamy, M. S. Park, J. Kim, H. Lee, K.-H. Lee, S. Park, J. Yoon, *Tetrahedron Lett.* **2008**, *49*, 1261.

13 a) R. Badugu, J. R. Lakowicz, C. D. Geddes, *J. Am. Chem. Soc.* **2005**, *127*, 3635. b) S. A. McFarland, N. S. Finney, *J. Am. Chem. Soc.* **2002**, *124*, 1178. c) L. Zhang, R. J. Clark, L. Zhu, *Chem.—Eur. J.* **2008**, *14*, 2894.

14 I. Negrón-Encarnación, R. Arce, M. Jiménez, *J. Phys. Chem. A* **2005**, *109*, 787.

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