Tetrahedron Letters 54 (2013) 5971–5973

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An anthracene-based Cd^{2+} fluorescent chemosensor with a 4,7-bis(2-hydroxyethyl)-9-hydroxy-1,4,7-triazanonyl group as a highly selective chelator to Cd^{2+} over Zn^{2+}

Koji Tsukamoto *, Shogo Iwasaki, Mari Isaji, Hatsuo Maeda

School of Pharmacy, Hyogo University of Health Sciences, 1-3-6 Minatojima, Chuo-ku, Kobe 650-8530, Japan

ARTICLE INFO

Article history:
Received 28 June 2013
Revised 9 August 2013
Accepted 16 August 2013
Available online 28 August 2013

Keywords:
Fluorescence
Chemosensor
Cadmium
Zinc
Anthracene

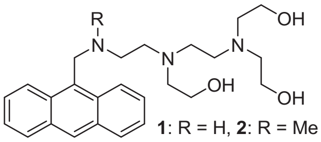
ABSTRACT

We have developed a Cd^{2+} fluorescent chemosensor with high selectivity as well as sensitivity by tethering a 4,7-bis(2-hydroxyethyl)-9-hydroxy-1,4,7-triazanonyl chelator to anthracene. This sensor features the ability to discriminate Cd^{2+} from Zn^{2+} to a high degree ($K_{dZn}/K_{dCd} = 560$) in a pH 7.2 buffer.

Although cadmium (Cd) has been recognized as a highly toxic heavy metal,[1] human and environmental health is still threatened by Cd discharged through production activity such as industry and agriculture.[2] Therefore, much effort has been made on designing high sensitive and selective fluorescent sensors for Cd^{2+} based on coordination chemistry, leading to recent development of the sensors.[3] However, in aqueous solutions, most of them can provide response toward Zn^{2+} as well. This is because both Cd^{2+} and Zn^{2+} have similar chemical and physical properties, making it difficult to distinguish between them.[3,4] One of the highest Cd^{2+}-selective sensors reported so far is the BODIPY derivative with a tetraamide group as a chelator for Cd^{2+}.[3e] With this sensor, marked reduction in response toward Zn^{2+} is realized. And yet the association constants K_{11} and K_{21} for the 1:1 and 2:1 complexes with Cd^{2+} are as low as 1.3×10^5 and 7.2×10^3 M^{-1}, respectively. Thus it could be accepted that the higher affinity to Cd^{2+} a chemosensor has, the less selectivity to Cd^{2+} over Zn^{2+} the sensor exhibits. Meanwhile, it has been described that design to make a difference between binding modes against Cd^{2+} and Zn^{2+} allowed chemosenors to provide fluorescent responses at different emission wavelengths toward these metal ions.[5] They are superior to sensors working at a single emission wavelength, due to their utility as dual sensors for Cd^{2+} and Zn^{2+}. However, in the presence of Zn^{2+}, Cd^{2+} is likely to compete with Zn^{2+} in chelation with those dual sensors. This is because the differences in dissociation constants for Cd^{2+} (K_{dCd}) and Zn^{2+} (K_{dZn}) are not sufficiently large in many cases. With these facts for a background, it is still a challenge to develop a fluorescent sensor for Cd^{2+} with a high selectivity over Zn^{2+} as well as sensitivity.

Herein, we report a novel anthracene-based Cd^{2+} sensor **1** (Scheme 1), which allows highly selective detection of Cd^{2+} even in the presence of Zn^{2+} in a pH 7.2 buffer. The sensor features a 1,4,7-triazanonyl group, which functions as a Cd^{2+}-selective chelator with three hydroxy groups as ligands, and confers high water-solubility on **1**. In addition, we describe that *N*-methylated **1**, that is, **2** exhibited very low responsiveness toward Cd^{2+}, which was informative to elucidate the origin of the performance of **1** as a Cd^{2+} sensor.

Sensor **1** was prepared by reductive amination of anthracene-9-carbaldehyde with 6-(2-aminoethyl)-3-(2-hydroxyethyl)-3,6-diazaoctan-1,8-diol in 75% yield (see Supplementary data). It should be mentioned here that **1** is water-soluble, and can be handled as aqueous working solutions without any organic solvents. Com-



Scheme 1. Chemical structures of **1** and **2**.

---

* Corresponding author. Tel.: +81 78 304 3175; fax: +81 78 304 2875.
E-mail address: kotukamoto@huhs.ac.jp (K. Tsukamoto).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.08.055

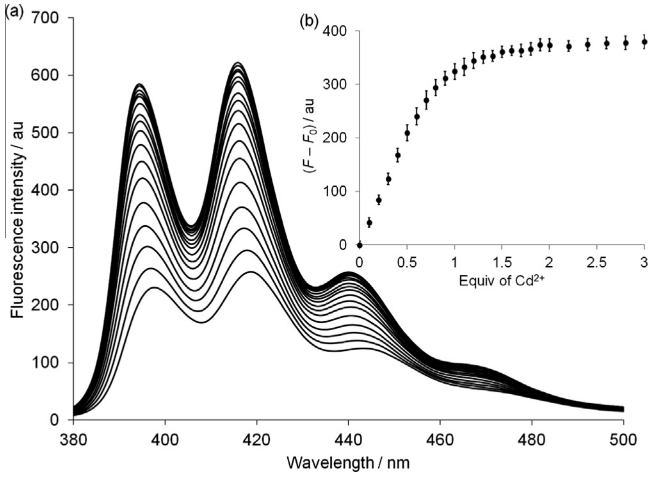


Figure 1. (a) Fluorescence spectra of **1** (5 μM) upon the addition of Cd^{2+}. (b) A plot of the difference between the fluorescence intensities ($F - F_0$) at $\lambda_{em} = 416$ nm obtained before and after the addition of Cd^{2+} into a solution of **1** (5 μM) as a function of equiv of Cd^{2+}. $CdCl_2$ was used as a Cd^{2+} reagent. All measurements were taken in a pH 7.2 HEPES buffer (50 mM, ionic strength (I) = 0.1 M (KNO_3)) and $\lambda_{ex} = 370$ nm. Error bars represent standard deviations ($n = 4$).

pound **1** exhibited a suppressed fluorescent spectrum in a pH 7.2 HEPES buffer (50 mM, $I = 0.1$ M (KNO_3)), and its quantum yield (ϕ) was estimated to be as low as 0.24 at $\lambda_{ex} = 370$ nm (Fig. 1).[6] This would be ascribed to photo-induced electron transfer (PET) from the N atom adjacent to the anthracene moiety of **1** (Scheme 2).[7] Upon the addition of Cd^{2+}, the fluorescent response from **1** was enhanced, and a linear relationship was observed between the responses and the concentration of Cd^{2+} up to 0.5 equiv (2.5 μM) (Fig. 1b). By further addition of Cd^{2+}, the fluorescence intensity increased nonlinearly, and reached a plateau. When 1.0 or 2.0 equiv of Cd^{2+} was added, the quantum yield of **1** was recovered to 0.43 or 0.47, respectively (Table S1). A Job's plot of an increase in the fluorescence intensity due to the reaction of **1** with Cd^{2+} showed a maximum at a mole fraction ([**1**]/([**1**] + [Cd^{2+}])) of 0.5, which clearly indicated the formation of a 1:1 complex (Fig. S2). The apparent dissociation constant of **1** for Cd^{2+} (K_{dCd}) was estimated to be 1.0×10^{-7} M, which is so small as to realize highly sensitive detection for Cd^{2+} (Fig. S3).[8]

In contrast with the case of Cd^{2+}, 1 equiv of Zn^{2+} was added to a solution of **1**, bringing about negligible increment in the fluorescence intensity (Fig. 2 and Fig. S5). The apparent dissociation constant of **1** for Zn^{2+} (K_{dZn}) was estimated by fluorometry to be 5.6×10^{-5} M (Fig. S3). This value was 560 times larger than the K_{dCd}, demonstrating that **1** can distinguish Cd^{2+} from Zn^{2+} with high selectivity. The effects by other metal ions (5 mM of Ca^{2+} and Mg^{2+}, and 5 μM of Cr^{3+}, Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Ag^{+}, Pb^{2+}, Cu^{2+} and Hg^{2+}) were also examined. The fluorescence response induced by the reaction of **1** with Cd^{2+} was not disturbed by the examined metal ions, except for Cu^{2+} and Hg^{2+} (Fig. 2 and Fig. S5). The presence of Cu^{2+} or Hg^{2+} quenched the fluorescence response of **1** toward Cd^{2+}. Since practical samples might include Cu^{2+}, the effect by Cu^{2+} must be solved.

Next, the effect of pH on the fluorescence intensity of **1** itself was examined (Fig. S7). The intensity was decreased from pH 6.0 to 9.2, probably due to an increase in the PET quenching effect through the deprotonation of the N atom adjacent to the anthracene in **1**. Although the background signal was significantly low in these basic conditions, the fluorescent response for the reaction of **1** not only with Cd^{2+} but also with Zn^{2+} increased greatly (Fig. S7), that is, the selectivity of **1** for Cd^{2+} over Zn^{2+} became poorer with an increase in basicity. Under acidic conditions less than pH 6, the background response became high, that would be attributed to protonation of the N atom in **1**, to prevent the PET effect in **1** from working. With these results in hands, it was concluded that a buffer around pH 7.2 is a solvent of choice for high selective detection of Cd^{2+} over Zn^{2+} using **1**.

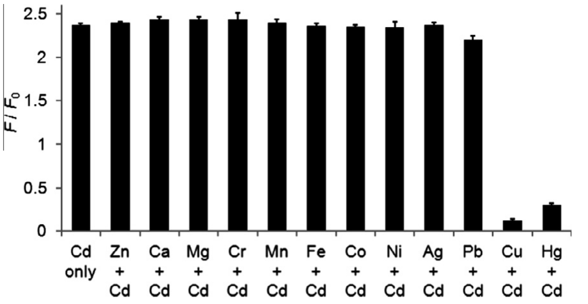


Figure 2. Effects of metal ions (5 mM of Ca^{2+} and Mg^{2+}, and 5 μM of Zn^{2+}, Cr^{3+}, Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Ag^{+}, Pb^{2+}, Cu^{2+} and Hg^{2+}) on the fluorescence intensity ratio (F/F_0) from the addition of **1** equiv of Cd^{2+} into **1** (5 μM). F_0: fluorescence intensity of **1** (5 μM) without any metal ions. As metal reagents, $CdCl_2$, $Zn(NO_3)_2$, $CaCl_2$, $MgCl_2$, $CrCl_3$, $MnCl_2$, $FeCl_3$, $CoCl_2$, $NiCl_2$, $AgNO_3$, $Pb(NO_3)_2$, $CuCl_2$, and $HgCl_2$ were used. All measurements were taken in a pH 7.2 HEPES buffer (50 mM, $I = 0.1$ M (KNO_3)), $\lambda_{ex} = 370$ nm, and $\lambda_{em} = 416$ nm. Error bars represent standard deviations ($n = 4$).

To investigate the detailed mechanism of the reaction of **1** with Cd^{2+}, *N*-methylated derivative **2** was prepared and subjected to fluorometry in the absence or presence of Cd^{2+} (Figs. S8 and S9). To our surprise, addition of 1 equiv of Cd^{2+} to a solution of **2** in any pH conditions gave rise to little or no enhancement in the fluorescence intensity. The apparent K_{dCd} of **2** at pH 7.2 was estimated to be 2.1×10^{-4} M, which was larger by three orders of magnitude than that of **1** (Fig. S3). On ^1H NMR spectra in D_2O, all signals for **1** or **2** were shifted downfield in the same manner by the addition of Cd^{2+} (Fig. 3). The downfield shift in all the region would be caused by the shielding effect of Cd^{2+} chelated with the 1,4,7-triazanonyl group in **1** or **2**.[9] Moreover, 8-(anthracen-9-yl)-1,4,7-triazaoctane **8**, lacking three 2-hydroxyethyl groups on **1**, showed a lower fluo-

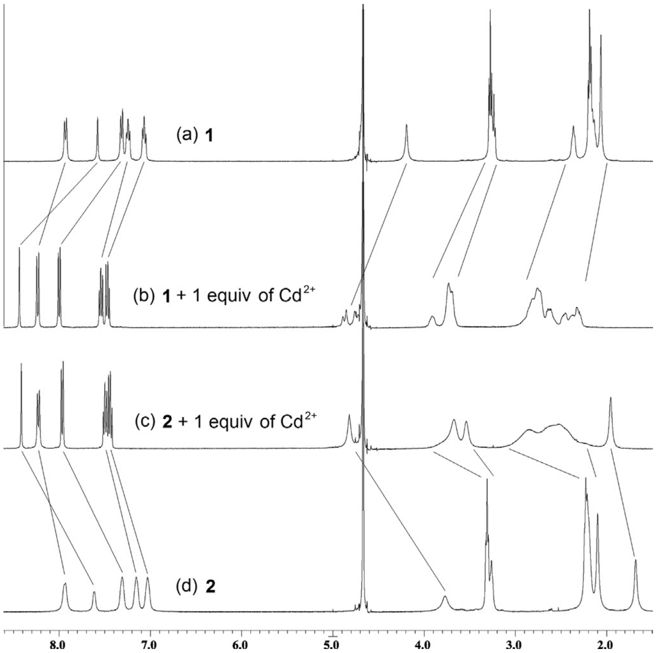
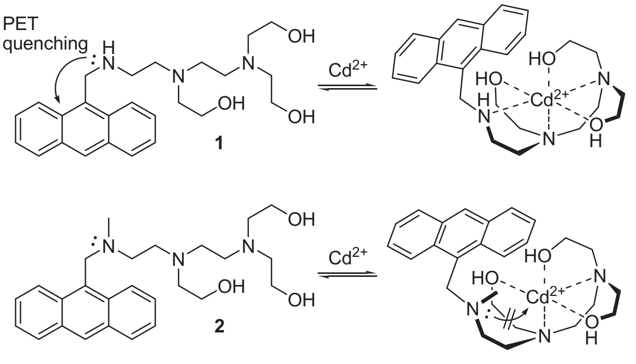


Figure 3. ^1H NMR spectra (400 MHz) of **1** and **2** (10 mM) in the absence or presence of 1 equiv of Cd^{2+} measured in D_2O: (a) **1**; (b) **1** with $CdCl_2$ (10 mM); (c) **2** with $CdCl_2$ (10 mM); (d) **2**.



Scheme 2. Proposed mechanism for coordination of **1** and **2** to Cd^{2+}.

rometric response to Cd^{2+} than **1**, which confirmed the necessity of the three 2-hydroxyethyl groups for high reactivity of **1** to Cd^{2+} (Fig. S10). Based on these results, **1** would bind Cd^{2+} tightly to cancel the PET quenching, whereas **2** might also coordinate Cd^{2+}, and yet some steric hindrance around the N atom adjacent to the anthracene could prevent the N atom from contacting the chelated Cd^{2+} (Scheme 2).

In conclusion, we have demonstrated that **1** functions as a fluorescent sensor for Cd^{2+} with high selectivity as well as high sensitivity in a pH 7.2 buffer. Especially, **1** can distinguish Cd^{2+} from Zn^{2+} to a remarkably high degree ($K_{dZn}/K_{dCd} = 560$). The difference between **1** and **2** in fluorescent responses toward Cd^{2+} suggests the important factor of the steric hindrance around the N atom adjacent to the anthracene. This finding is believed to provide useful structural information for designing more practical Cd^{2+} sensors. We are currently working on decreasing the blank signal in the absence of Cd^{2+}, and on increasing the selectivity for Cd^{2+} over Cu^{2+} and Hg^{2+} as well as Zn^{2+}.

Acknowledgments

This work was supported by the Grant-in-Aid for Academic Research from the Iijima Memorial Foundation for the Promotion of Food Science and Technology, and the Grant for Young Scientist from Hyogo University of Health Sciences.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.055.

References and notes

1. (a) Waisberg, M.; Joseph, P.; Hale, B.; Beyersmann, D. *Toxicology* **2003**, *192*, 95; (b) Bridges, C. C.; Zalups, R. K. *Toxicol. Appl. Pharmacol.* **2005**, *204*, 274; (c) Pari, L.; Murugavel, P.; Sitasawad, S. L.; Kumar, K. S. *Life Sci.* **2007**, *80*, 650.
2. Grant, C. A. *Pedologist* **2011**, 143.
3. (a) Gunnlaugsson, T.; Lee, T. C.; Parkesh, R. *Org. Lett.* **2003**, *5*, 4065; (b) Peng, X.; Du, J.; Fan, J.; Wang, J.; Wu, Y.; Zhao, J.; Sun, S.; Xu, T. *J. Am. Chem. Soc.* **2007**, *129*, 1500; (c) Liu, W.; Xu, L.; Sheng, R.; Wang, P.; Li, H.; Wu, S. *Org. Lett.* **2007**, *9*, 3829; (d) Taki, M.; Desaki, M.; Ojida, A.; Iyoshi, S.; Harayama, T.; Hamachi, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 12564; (e) Cheng, T.; Xu, Y.; Zhang, S.; Zhu, W.; Qian, X.; Duan, L. *J. Am. Chem. Soc.* **2008**, *130*, 16160; (f) Liu, Z.; Zhang, C.; He, W.; Yang, Z.; Gao, X.; Guo, Z. *Chem. Commun.* **2010**, 6138; (g) Sahana, A.; Banerjee, A.; Lohar, S.; Guha, S.; Das, S.; Mukhopadhyay, S. K.; Das, D. *Analyst* **2012**, *137*, 3910; (h) Li, Y.; Chong, H.; Meng, X.; Wang, S.; Zhu, M.; Guo, Q. *Dalton Trans.* **2012**, *41*, 6189.
4. Even excellent fluorescent sensors for Zn^{2+} can also respond to Cd^{2+}; for examples of Zn^{2+} sensors, see: (a) Maruyama, S.; Kikuchi, K.; Hirano, T.; Urano, Y.; Nagano, T. *J. Am. Chem. Soc.* **2002**, *124*, 10650; (b) Taki, M.; Wolford, J. L.; O'Halloran, T. V. *J. Am. Chem. Soc.* **2004**, *126*, 712; (c) Aoki, S.; Kagata, D.; Shiro, M.; Takeda, K.; Kimura, E. *J. Am. Chem. Soc.* **2004**, *126*, 1337; (d) Henary, M. M.; Wu, Y.; Fahrni, C. J. *Chem. Eur. J.* **2004**, *10*, 3015; (e) Komatsu, K.; Kikuchi, K.; Kojima, H.; Urano, Y.; Nagano, T. *J. Am. Chem. Soc.* **2005**, *127*, 10197; (f) Nolan, E. M.; Ryu, J. W.; Jaworski, J.; Feazell, R. P.; Sheng, M.; Lippard, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 15517; (g) Hanaoka, K.; Muramatsu, Y.; Urano, Y.; Terai, T.; Nagano, T. *Chem. Eur. J.* **2010**, *16*, 568.
5. (a) Xue, L.; Liu, C.; Jiang, H. *Org. Lett.* **2009**, *11*, 1655; (b) Xu, Z.; Baek, K.-H.; Kim, H. N.; Cui, J.; Qian, X.; Spring, D. R.; Shin, I.; Yoon, J. *J. Am. Chem. Soc.* **2010**, *132*, 601; (c) Jia, J.; Xu, Q.-C.; Li, R.; Tang, X.; He, Y.-F.; Zhang, M.-Y.; Zhang, Y.; Xing, G.-W. *Org. Biomol. Chem.* **2012**, *10*, 6279; (d) Wang, J.; Lin, W.; Li, W. *Chem. Eur. J.* **2012**, *18*, 13629; (e) Cai, Y.; Meng, X.; Wang, S.; Zhu, M.; Pan, Z.; Guo, Q. *Tetrahedron Lett.* **2013**, *54*, 1125.
6. Absorption spectra and calculation of relative quantum yields (ϕ) of **1** in the absence or presence of Cd^{2+} are summarized in Figure S1 and Table S1.
7. de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515.
8. Using $CdBr_2$, $CdSO_4$, $Cd(OAc)_2$, $Cd(ClO_4)_2$ or $Cd(NO_3)_2$ instead of $CdCl_2$ as a Cd^{2+} reagent, the fluorescent response of **1** toward Cd^{2+} was not changed, which was indicative that the counterion of Cd^{2+} would have no influence on the Cd^{2+} sensing of **1** (Fig. S4).
9. Although the anthracene moiety might form the cation-π interaction to Cd^{2+}, it would be anticipated that the cation-π interaction of Cd^{2+} is not likely to be formed in aqueous solution. Li, Z. H.; Liu, J.; Qiao, M.; Fan, K.-N. *Mol. Phys.* **2009**, *107*, 1271.