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A Highly Sensitive C_3-Symmetric Schiff-Base Fluorescent Probe for Cd^{2+}

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Supporting Information

ABSTRACT: A new C_3-symmetric Schiff-base fluorescent probe (**L**) based on 8-hydroxy-2-methylquinoline has been developed. As expected, the probe **L** can display high fluorescent selectivity for Cd^{2+} over Zn^{2+} and most other common ions in neutral ethanol aqueous medium. Moreover, the mechanism of the **L**−Cd^{2+} complex has been confirmed by X-ray crystallography and density functional theory calculation results. More importantly, **L** could be used to image Cd^{2+} within living cells.

Heavy-metal contamination has become a serious threat to the environment and human health.[1] As is known, cadmium is one of the important resources and has been widely used in many fields such as electroplating, metallurgy, war industry, and agriculture.[2] However, chronic exposure to Cd^{2+} sources can cause serious injury to the human kidney, lung, bone, and nervous system and even certain cancers.[3] Accordingly, it is highly desirable to develop reliable methods for detecting and monitoring cadmium levels in environmental samples, living cells, or tissue samples. Recently, fluorescent probes based on the ion-induced changes are often used to detect metal ions owing to their simplicity, high sensitivity, and real-time detection.[4] Up to now, only a few fluorescent probes for Cd^{2+} are applicable in living cells.[6] To develop Cd^{2+}-selective probes, the discrimination of Cd^{2+} from Zn^{2+} is often challenging because they show similar coordination properties.[5f,6]

It is necessary to choose an efficient fluorophore and consider the geometry of coordination sites for a certain cation.[6a] To the best of our knowledge, C_3-symmetric ligands can be regarded as triangular building blocks and offer avenues for the construction of organometallic frameworks with a variety of structures according to the geometric requirements of the metal ions.[7] Recently, we have successfully developed a novel C_3-symmetric fluorescent probe for Zn^{2+} in living cells based on 2-pyridinecarboxaldehyde.[8] These experimental results encouraged us to improve its sensing properties by replacing 2-pyridinecarboxaldehyde with other metal-chelating groups. According to the reported crystal structures of cadmium and zinc,[9] they are usually six-coordinate, but cadmium can also be seven- or eight-coordinate.[6c,d,10] This suggests that a new ligand with more multiple coordination sites in the equatorial plane direction can be designed that may chelate and coordinate with Cd^{2+} more effectively to distinguish Cd^{2+} from Zn^{2+}.

As is well-known, 8-hydroxyquinoline derivatives with multiple coordination sites have usually been used to construct fluorescent probes for transition metals because of their good photostability and strong ability to chelate metal ions.[11] Furthermore, 8-hydroxyquinoline derivatives could enhance the affinity of a ligand for Cd^{2+} according to the reported literature.[5e,6a] To take advantage of triaminoguanidinium chloride containing lone electron pairs on nitrogen, we herein report another new C_3-symmetric Schiff-base fluorescent probe (**L**) based on 8-hydroxy-2-ethylquinoline that might effectively chelate Cd^{2+} according to its ionic radius and limit the geometric structure of the complex.

The probe **L** was prepared by modified procedures[12,13] (see the Supporting Information, SI). The UV−vis absorption spectrum of **L** displayed three obvious absorption peaks at 255, 300, and 348 nm ($\varepsilon = 5.9 \times 10^3\ M^{-1}\ cm^{-1}$) (Figure 1). Upon the addition of Cd^{2+} (0−5 equiv), they decreased gradually, and a large absorption band from 450 to 505 nm emerged simultaneously with one distinct isosbestic point at 410 nm. Moreover, a significant color change from light yellow to light red could be observed easily by naked eyes. These changes were likely due to the coordination of **L** with Cd^{2+}.[14]

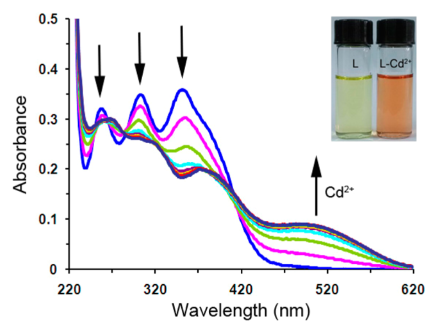

Figure 1. Absorption spectra of **L** (60 μM) upon titration of Cd^{2+} (0−5 equiv) in $EtOH/H_2O$ [1:1 (v/v)]. Inset: photographs of the solution of **L** before and after the addition of Cd^{2+} (10 equiv) under visible light.

Figure 2 showed that **L** displayed relatively weak emission at 540 nm because of the excited-state intramolecular proton transfer (ESIPT) process of 8-hydroxyquinoline from oxygen to

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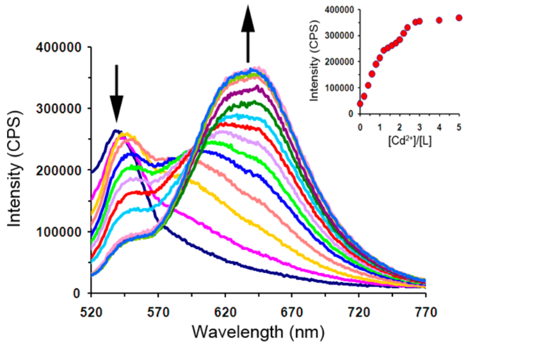

Figure 2. Fluorescence spectra of **L** (60 μM) upon titration of Cd^{2+} (0−5 equiv) in EtOH/H_2O [1:1 (v/v); λ_{ex} = 465 nm]. Inset: emission changes with changes in the ratios of the Cd^{2+} and **L** concentrations.

nitrogen[15] and C═N isomerization. Furthermore, such high concentrations of probes have also been reported in other literature.[16] Upon binding Cd^{2+}, the emission peak gradually shifted from 540 to 645 nm with remarkable fluorescence enhancement (Φ = 0.013) because the ESIPT process and C═N isomerization were inhibited. Besides, the excitation wavelengths of the yellow and orange lines in Figure 2 also corresponded to 465 nm (Figure S5 in the SI) and were in the range of a large absorption band. Moreover, the emission intensities at 645 nm stopped increasing when the molar ratio of **L**/Cd^{2+} reached 1:3 (Figure 2, inset), which indicated the 1:3 binding model. Job's plot[17] (Figure S6 in the SI) also proved the 1:3 stoichiometry. According to a reported method,[5b,c,18] the association constants of **L** with Cd^{2+} were obtained as $K_{Cd1} = 1.4 \times 10^4$, $K_{Cd2} = 1.0 \times 10^4$, and $K_{Cd3} = 9.5 \times 10^3$ (Figure S7 in the SI), respectively. The corresponding detection limit of Cd^{2+} was found to be 5.57×10^{-6} M (Figure S8 in the SI).[19]

Selectivity is one of the most important features for an excellent fluorescent probe.[20] Moreover, the selectivity of **L** for Cd^{2+} was affected by different solvents and water content, which limited its practical application. The fluorescence behavior of **L** was examined upon the addition of various cations in the optimized solvent-EtOH/H_2O [1:1 (v/v)] (Figures S9−S12 in the SI). As shown in Figure S13 in the SI, the addition of NH_4^+, Na^+, K^+, Ca^{2+} Mg^{2+}, Ba^{2+}, Al^{3+}, Cr^{3+}, and Mn^{2+} had little effect on the emission of **L**. However, only Zn^{2+} induced a red shift and very slight fluorescence enhancement. Fe^{2+}, Cu^{2+}, Co^{2+}, Ni^{2+}, and Pb^{2+} resulted in the partial quenching of **L** but without a distinct red shift. A similar phenomenon was previously reported.[5g,21] As expected, only Cd^{2+} caused an obvious red shift from 540 to 645 nm and a significant increase in the ratio. Furthermore, the excitation wavelengths of **L**, **L**−Cd^{2+}, Fe^{2+}, Cu^{2+}, and Pb^{2+} were also 465 nm (Figures S5, S14, and S15 in the SI). Although the excitation spectra of **L** and its other complexes (Fe^{2+}, Cu^{2+}, and Pb^{2+}) did not match with their absorption spectra, fluorescence emission from the object is a function of the angle and wavelength of the incident light and chemical and physical composition of the object.[22] Competition experiments (Figure 3) showed that most cations had no obvious effect on the fluorescence emission of **L**−Cd^{2+} except Cr^{3+}, Pb^{2+}, and Cu^{2+}, but their influence in vivo can be neglected because of their low concentration.[23] Besides, some anions displayed no obvious effect on the fluorescence of the **L**-Cd^{2+} complex except I^- (Figure S16 in the SI). However, the interference was of little importance at the low concentrations in nature.[24] All of the results indicated that probe **L** was suitable for detecting Cd^{2+} without interference of most common ions in neutral aqueous

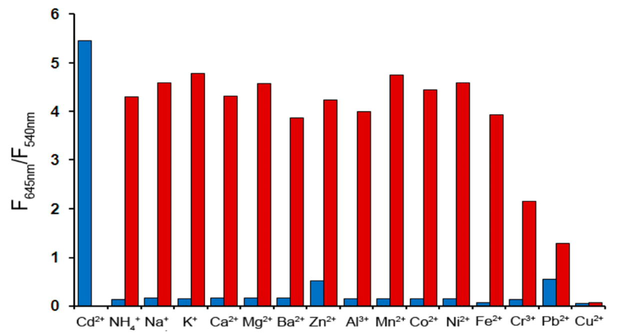

Figure 3. Metal-ion selectivity profiles of **L** (60 μM). Blue bars represent the fluorescence intensity ratio responses ($F_{645\ nm}/F_{540\ nm}$) of **L** in the presence of 10 equiv of various metal ions. Red bars represent the fluorescence intensity ratio responses of **L** in the presence of the indicated metal ions, followed by 10 equiv of Cd^{2+}.

media, especially Zn^{2+}. In addition, the sensitivity of **L** for Cd^{2+} was not reversible (Figure S17 in the SI), which limited its recycle use in biological and environmental samples.

^{1}H NMR titration (Figure S18 in the SI) showed the signals for the active protons shifted in certain degrees, the peak shapes broadened, and some new signals appeared, which indicated coordination of **L** with Cd^{2+}.[5a,25] Moreover, the 1:3 complex was also proved by ^{1}H NMR titration and ESI-MS of **L**−Cd^{2+} (Figure S18 and S19 in the SI). Besides, the coordination mode of **L**−Zn^{2+} was different from that of **L**−Cd^{2+} (Figure S20 in the SI). The X-ray crystal structure of **L**−Cd^{2+} also confirmed that L and Cd^{2+} formed a rigid trinuclear structure with 1:3 stoichiometry (Figure 4). Selected bond lengths and angles are given in Table

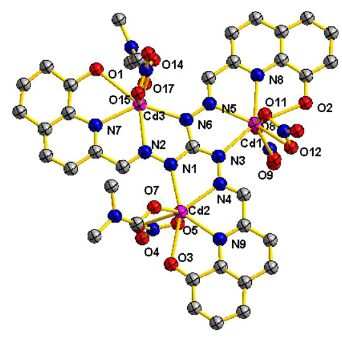

Figure 4. Thermal ellipsoid plot of $Cd_3(\mathbf{L})(NO_3)_4(DMF)_2$. All hydrogen atoms were deleted for clarity.

S2 in the SI. It crystallized in the triclinic system, with space group $P\overline{1}$ from the mixed solvents of CH_3OH and DMF. Cd1 was eight-coordinate and surrounded by O2 and N8 from quinoline, N3 and N5 from triaminoguanidinium moiety, and four O atoms (O8, O9, O11, and O12) from two NO_3^-. Cd2 was seven-coordinate and surrounded by O3 and N9 from quinoline, N1 and N4 from triaminoguanidinium, O4 and O5 from one nitrate, and O7 from DMF. The coordination environment of Cd3 was the same as that of Cd2. The density functional theory results (see the SI for calculation details) showed that π electrons on the highest occupied molecular orbital (HOMO) of **L** mainly focused on the triaminoguanidinium units, whereas those on the lowest unoccupied molecular orbital (LUMO) mainly focused on 8-hydroxyquinoline. Upon Cd^{2+} binding with **L**, the energy levels of both HOMO and LUMO were lower than those of **L**. The decreasing energy in the LUMO level was more significant than that of the HOMO, indicating that the LUMO was more stabilized. Moreover, the calculated dihedral angles of **L**−Cd^{2+} were in good agreement with the experimental crystal structure (Table S4 in the SI). The fluorescence of **L** decayed in a double-exponential manner with time constants of 179.49 and 281.01 ps (Figure S24 and Table S5 in the SI), indicating that the fluorescence spectra consisted of two contributions from free **L**. The fluorescence decay curve of **L**-Cd^{2+} at 549 nm was similar to that of **L** (Figure S25 and Table S5 in the SI), whereas a new fluorescence decay process at 645 nm was formed and the fluorescence lifetime increased to 478.55 ps (Figure S26 and Table S5 in the SI). The probe **L** and **L**-Cd^{2+} were low cytotoxic to cells and suitable for bioimaging (see the Supporting Information, SI).

In conclusion, we have developed an efficient C_3-symmetric Schiff-base fluorescent probe based on 8-hydroxy-2-methylquinoline. As expected, the probe could effectively discriminate Cd^{2+} from Zn^{2+} and showed high selectivity for Cd^{2+} with a large red emission shift over other cations in neutral ethanol aqueous media, which was confirmed by both experimental results and theoretical calculation results. Moreover, it was low cytotoxic and cell-permeable to detect Cd^{2+} sensitively in vivo.

■ ASSOCIATED CONTENT

Supporting Information

X-ray crystallographic data (CCDC 979270) in CIF format, synthetic procedures and characterization of **L**−Cd^{2+}, and other experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Zhuang, P.; McBride, M.; Xia, H.; Li, N.; Li, Z. *Sci. Total Environ.* **2009**, *407*, 1551−1561.

(2) Chaney, R. L.; Ryan, J. A.; Li, Y. M.; Brown, S. L. In *Cadmium in soils and plants*; McLaughlin, M. J., Singh, B. R., Eds.; Kluwer: Boston, 1999; pp 219−256.

(3) (a) Zalups, R. K.; Ahmad, S. *Toxicol. Appl. Pharmacol.* **2003**, *186*, 163−188. (b) Pandey, R.; Gupta, R. K.; Shahid, M.; Maiti, B.; Misra, A.; Pandey, D. S. *Inorg. Chem.* **2012**, *51*, 298−311.

(4) (a) Valeur, B.; Leray, I. *Coord. Chem. Rev.* **2000**, *205*, 3−40. (b) Fernández-Lodeiro, J.; Núñez, C.; Castro, C. S. D.; Bértolo, E.; Melo, J. S. S. D.; Capelo, J. L.; Lodeiro, C. *Inorg. Chem.* **2013**, *52*, 121−129.

(5) (a) Liu, W. M.; Xu, L. W.; Sheng, R. L.; Wang, P. F.; Li, H. P.; Wu, S. K. *Org. Lett.* **2007**, *9*, 3829−3832. (b) Peng, X. J.; Du, J. J.; Fan, J. L.; Wang, J. Y.; Wu, Y. K.; Zhao, J. Z.; Sun, S. G.; Xu, T. *J. Am. Chem. Soc.* **2007**, *129*, 1500−1501. (c) Cheng, T. Y.; Xu, Y. F.; Zhang, S. Y.; Zhu, W. P.; Qian, X. H.; Duan, L. P. *J. Am. Chem. Soc.* **2008**, *130*, 16160−16161. (d) Taki, M.; Desaki, M.; Ojida, A.; Lyoshi, S.; Hirayama, T.; Hamachi, i.; Yamamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 12564−12565. (e) Maneli, M.; Aragoni, M. C.; Arca, M.; Caltagirone, C.; Demartin, F.; Farruggia, G.; Filipo, G. D.; Devillanova, F. A.; Garau, A.; Isaia, F.; Lippolis, V.; Murgia, S.; Prodi, L.; Pintus, A.; Zaccheroni, N. *Chem.—Eur. J.* **2010**, *16*, 919−930. (f) Liu, Z. P.; Zhang, C. L.; He, W. J.; Yang, Z. H.; Gao, X.; Guo, Z. J. *Chem. Commun.* **2010**, *46*, 6138−6140. (g) Tian, H.; Li, B.; Wang, H. P.; Li, Y. R.; Wang, J. W.; Zhao, S. N.; Zhu, J. L.; Wang, Q.; Liu, W. S.; Yao, X. J.; Tang, Y. *J. Mater. Chem.* **2011**, *21*, 10298−10303. (h) Yang, Y. Y.; Cheng, T. Y.; Zhu, W. P.; Xu, Y. F.; Qian, X. H. *Org. Lett.* **2011**, *13*, 264−267. (i) Xue, L.; Li, G. P.; Liu, Q.; Wang, H. H.; Liu, C.; Ding, X. L.; He, S. G.; Jiang, H. *Inorg. Chem.* **2011**, *50*, 3680−3690. (j) Tian, H.; Li, B.; Zhu, J. L.; Wang, H. P.; Li, Y. R.; Xu, J.; Wang, J. W.; Wang, W.; Sun, Z. H.; Liu, W. S.; Huang, X. G.; Yan, X. H.; Wang, Q.; Yao, X. J.; Tang, Y. *Dalton Trans.* **2012**, *41*, 2060−2065. (k) Yang, L. L.; Liu, X. M.; Liu, K.; Zhao, F. Y.; Ruan, W. J.; Li, Y.; Chang, Z.; Bu, X. H. *Talanta* **2014**, *128*, 278−283.

(6) (a) Tang, X. L.; Peng, X. H.; Dou, W.; Mao, J.; Zheng, J. R.; Qin, W. W.; Liu, W. S.; Chang, J.; Yao, X. J. *Org. Lett.* **2008**, *10*, 3653−3656. (b) Zhao, Q.; Li, R. F.; Xing, S. K.; Liu, X. M.; Hu, T. L.; Bu, X. H. *Inorg. Chem.* **2011**, *50*, 10041−10046. (c) Zhou, X. Y.; Li, P. X.; Shi, Z. H.; Tang, X. L.; Chen, C. Y.; Liu, W. S. *Inorg. Chem.* **2012**, *51*, 9226−9231. (d) Tsukamoto, K.; Iwasaki, S.; Isaji, M.; Maeda, H. *Tetrahedron Lett.* **2013**, *54*, 479−482.

(7) (a) Hu, X. L.; Rodriguez, I. C.; Meyer, K. *J. Am. Chem. Soc.* **2004**, *126*, 13464−13473. (b) Hu, X. Y.; Wang, J.; Zhu, X.; Dong, D. P.; Zhang, X. L.; Wu, S. O.; Duan, C. Y. *Chem. Commun.* **2011**, *47*, 11507−11509.

(8) Zhou, Y.; Li, Z. X.; Zang, S. Q.; Zhu, Y. Y.; Zhang, H. Y.; Hou, H. W.; Mak, T. C. W. *Org. Lett.* **2012**, *14*, 1214−1217.

(9) Croitor, L.; Coropceanu, E. B.; Siminel, A. V.; Kravtsov, V. C.; Fonari, M. S. *Cryst. Growth Des.* **2011**, *11*, 3536−3544.

(10) Liu, C. S.; Shi, X. S.; Li, J. R.; Wang, J. J.; Bu, X. H. *Cryst. Growth Des.* **2006**, *6*, 656−663.

(11) Prodi, L.; Bargossi, C.; Montali, M.; Zaccheroni, N.; Su, N.; Bradshaw, J. S.; Izatt, R. M.; Savage, P. B. *J. Am. Chem. Soc.* **2000**, *122*, 6769−6770.

(12) Weiss, S.; Krommer, H. *Chem. Abstr.* **1986**, *104*, 206730.

(13) Hu, P.; Wang, F. S.; Jin, G. X. *Organometallics* **2011**, *30*, 1008−1012.

(14) (a) Misra, A.; Shahid, M.; Dwivedi, P. *Talanta* **2009**, *80*, 532−538. (b) Zhou, X. Y.; Yu, B. R.; Guo, Y. L.; Tang, X. L.; Zhang, H. H.; Liu, W. S. *Inorg. Chem.* **2010**, *49*, 4002−4007.

(15) Nahhas, A. E.; Pascher, T.; Leone, L.; Panzella, L.; Napolitano, A.; Sundström, V. *J. Phys. Chem. Lett.* **2014**, *5*, 2094−2100.

(16) Zhou, X. Y.; Yu, B. R.; Guo, Y. L.; Tang, X. L.; Zhang, H. H.; Liu, W. S. *Inorg. Chem.* **2010**, *49*, 4002−4007.

(17) Razi, S. S.; Ali, R.; Srivastava, P.; Misra, A. *Tetrahedron Lett.* **2014**, *55*, 1052−1056.

(18) (a) Valeur, B. *Molecular Fluorescence: Principles and Applications*; Wiley-VCH: Weinheim, Germany, 2002. (b) Li, Y. P.; Yang, H. R.; Zhao, Q.; Song, W. C.; Han, J.; Bu, X. H. *Inorg. Chem.* **2012**, *51*, 9642−9648.

(19) Maity, D.; Govindaraju, T. *Inorg. Chem.* **2010**, *49*, 7229−7231.

(20) Mi, Y. S.; Cao, Z.; Chen, Y. T.; Long, S.; Xie, Q. F.; Liang, D. M.; Zhu, W. P.; Xiang, J. N. *Sens. Actuators, B* **2014**, *192*, 164−172.

(21) Xue, L.; Liu, Q.; Jiang, H. *Org. Lett.* **2009**, *11*, 3454−3457.

(22) Momin, Md. A.; Kondo, N.; Kuramoto, M.; Ogawa, Y.; Yamamoto, K.; Shiigi, T. *EAEF* **2012**, *5*, 126−132.

(23) (a) Komatsu, K.; Urano, Y.; Kojima, H.; Nagano, T. *J. Am. Chem. Soc.* **2007**, *129*, 13447−13454. (b) Chen, X. Y.; Shi, J.; Li, Y. M.; Wang, F. L.; Wu, X.; Guo, Q. X.; Liu, L. *Org. Lett.* **2009**, *11*, 4426−4429.

(24) Riis-Johannessen, T.; Schenk, K.; Severin, K. *Inorg. Chem.* **2010**, *49*, 9546−9553.

(25) (a) Abraham, M. L.; Schulze, A. C.; Korthaus, A.; Oppel, I. M. *Dalton Trans.* **2013**, *42*, 16066−16072. (b) Tahara, K.; Abraham, M. L.; Igawa, K.; Katayama, K.; Oppel, I. M.; Tobe, Y. *Chem. Commun.* **2014**, *50*, 7683−7685.

(26) Srivastava, P.; Razi, S. S.; Ali, R.; Gupta, R. C.; Yadav, S. S.; Narayan, G.; Misra, A. *Anal. Chem.* **2014**, *86*, 8693−8699.