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A highly selective and sensitive turn-on catalytic chemodosimeter for Cu^{2+} in aqueous solution

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ABSTRACT

We report herein the first diaminocyclopent-2-enone-based catalytic chemodosimeter (**3**) for naked-eye and turn-on fluorescent detections of Cu^{2+} in pure aqueous solution. Compound **3** easily made available from furan-2-carbaldehyde and 2-aminobenzoic acid was found to show a highly selective and sensitive response toward Cu^{2+} by way of Cu^{2+}-coordination promoted formation of Stenhouse salt and subsequent decomposition to highly fluorescent 2-aminobenzoate.

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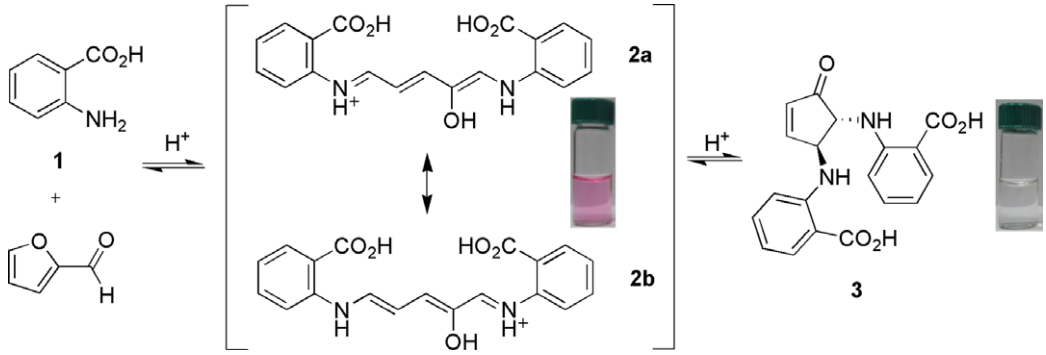
Cu^{2+} as the third abundant heavy metal ion in human body has recently attracted much attention due to its obvious biological importance and increasing environmental concerns.[1] Detection of Cu^{2+} with high selectivity and sensitivity represents hence a challenging subject. Fluorescence signaling is advantageous in many respects such as high sensitivity and easy operation. Cu^{2+} as a paramagnetic species, however, shows an inherent fluorescence quenching nature. As a consequence, most of the reported fluorescent chemosensors for Cu^{2+} operate under fluorescence quenching mode.[2,3] Fluorescence signaling showing an enhancement is for sensitivity reason prior to those exhibiting quenching,[4] especially in aqueous solutions in which fluorescence could be weak because of efficient quenching of highly polar water molecules. Fluorescent chemosensors for detection of Cu^{2+} in aqueous solutions with a fluorescence enhancement output have indeed been a subject of many recent investigations;[5] however, those successful in pure aqueous solutions remain rare.[6] We report herein a highly selective yet simple chemosensor for Cu^{2+} with an enhanced fluorescence output in pure aqueous solution.

2-Aminobenzoic acid (**1**, Scheme 1) has been widely employed as a highly fluorescent label.[7] Indeed, **1** has a high fluorescence quantum yield[7b,8] of 0.56 in aqueous HEPES buffer solution (pH 7.4, 10 mM). Obviously, there is only 2-fold fluorescence enhancement remaining for **1** upon metal binding, if any. It is known that substitution of the amino group to form a secondary amine would lead to the loss of fluorescence.[7b,9] This provides a new entry for controlling its fluorescence of **1**. Reaction of **1** with aldehyde seems suitable in this regard and would yield a good fluorescent sensing



Scheme 1. Chemical structure of **1**–**3**.

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system if the product could undergo transformations into **1** in the presence of an analyte.[10,11] **3** reported herein was therefore obtained,[11] which indeed has a low fluorescence quantum yield of 0.012 in aqueous 10 mM HEPES buffer solution of pH 7.4. Inspired by the regioselective Cu^{2+}-catalyzed amination of only 2-bromobenzoic acid rather than its 3- and 4-isomers, due probably to a similar Cu^{2+}-aminoacid coordination motif in the transition state,[6e,12] we expected that **3** might show a high selectivity toward Cu^{2+} by a fluorescence enhancement response with moiety **1** being both the binding site and fluorophore.

A criterion for designing a chemodosimeter was considered that it should be not only weakly fluorescent but also conditionally stable (Fig. S1, Supplementary data). After screening a variety of aldehydes, **3** was made available from a convenient one-pot condensation of furan-2-carbaldehyde with **1** in ethanol (yield 85%).[11,13] Absorption spectrum of **3** in 10 mM aqueous HEPES buffer solution of pH 7.4 showed three bands at 210, 252, and 330 nm, respectively (Fig. 1a). In the presence of Cu^{2+}, the band at 330 nm was attenuated, while absorbance at shorter wavelength was increased with an isosbestic point observed at 320 nm. It is worthy to note that a new band appeared at 512 nm that increases at low Cu^{2+} concentration, whereas it undergoes a decrease at higher Cu^{2+} concentration (Fig. 1a and inset). Other transition metal ions such as Hg^{2+}, Pb^{2+}, Zn^{2+}, Cd^{2+}, Ni^{2+}, Ag^{+}, Co^{2+}, and Fe^{3+}, and some alkali and alkaline earth metal ions were also tested (Fig. S2), but showed no significant influence on the absorption spectrum of **3**. Selective interaction of **3** with Cu^{2+} was therefore made obvious. The new band at 512 nm in the presence of Cu^{2+} affording a purple color makes it feasible for naked-eye detection of Cu^{2+} (Fig. 2).

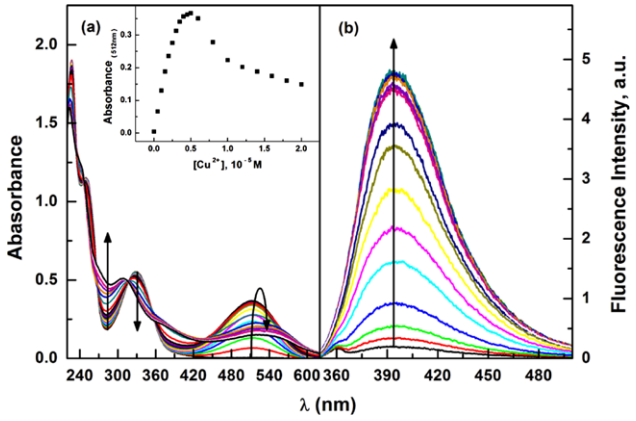

Figure 1. Absorption (a) and fluorescence (b) spectra of **3** in the presence of Cu^{2+} over 0–2.0×10^{-5} M in aqueous 10 mM HEPES buffer solution of pH 7.4. Excitation wavelength was 320 nm, an isosbestic point observed in the absorption titrations. [**3**] = 1.0×10^{-4} M (a) and 1.0×10^{-6} M (b).

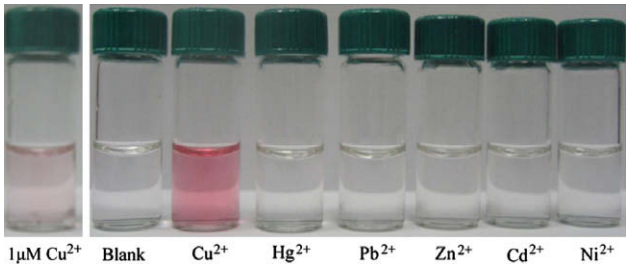

Figure 2. Naked-eye detection of metal ions (1.0×10^{-5} M) in aqueous 10 mM HEPES buffer solution of pH 7.4. [**3**] = 1.0×10^{-4} M. Note that 1 μM Cu^{2+} is easily detected by naked eyes.

Fluorescence of **3** in the presence of metal ions in aqueous HEPES buffer solution was monitored after assay condition optimizations (Figs. S1 and S3). An enhanced emission was observed at 394 nm with increasing Cu^{2+} concentration (Fig. 1b), whereas the tested other transition and alkali and alkaline earth metal ions produced no significant variations. This indicates a high selectivity in its fluorescence enhancement response of **3** toward Cu^{2+} against other metal ions (Fig. 3). The excellent selectivity was further demonstrated in that the fluorescence enhancement by Cu^{2+} was not affected by the co-existence of other metal ions (Fig. 3 inset).

Optimization established that fluorescence enhancement of **3** showed a good linearity ($r = 0.998$) over Cu^{2+} concentration of 0.5–2.25 μM in aqueous buffer solution (Fig. S4). The detection limit of Cu^{2+} calculated on the basis of $3\sigma/k$[14] is 15 nM or 1 ppb, pointing to the high detection sensitivity. Counter anion of Cu^{2+} was found to exert no obvious influence on the fluorescence response, with anions being ClO_4^-, Cl^-, AcO^-, SO_4^{2-}, and NO_3^- (Fig. S5).

On the basis of the reversibility shown in the synthetic mechanism (Scheme 1),[11] and the known selective strong binding of aminoacid with Cu^{2+},[6e,12] carbonyl oxygen in cyclopent-2-enone should also take part in Cu^{2+} binding,[11a] in addition to chelating to the aminoacid moiety so that Cu^{2+} acted as a Lewis acid to cooperatively promote decomposition of **3** to **1**. Indeed, color changes were observed for **3** in the presence of Cu^{2+} as that observed in the case of H^+ with the formation of purple Stenhouse salts **2** (Scheme 1).[11a] It should be pointed out that the purple color decreases with standing time or further increase in Cu^{2+} concentration (Fig. 1a and inset). Decomposition of Stenhouse salts **2** to colorless **1** was therefore suggested and the formation of **1** was confirmed by TLC pattern, NMR, and ESI-MS data of the isolated product. It has been proved that a catalytic chemodosimeter shows a higher affinity toward an analyte than its decomposed product so that the analyte could further re-interact with the chemodosimeter, affording a turnover number higher than 1.[6h] Although binding constant of Cu^{2+} to **1** was determined as 1.3×10^4 M^{-1}, that of Cu^{2+} to **3** is unavailable, it is not straightforward to judge if **3** is a catalytic or stoichiometric chemodosimeter.[6h] We therefore determined the reaction order of Cu^{2+} to be 1.6 (Fig. S6). It was hence expected that, if **1** and **3** have the same binding constant toward Cu^{2+}, the actual concentration of Cu^{2+} that interacts with **3** will be reduced by a half in the presence of 1 equiv of **1** in a **3**-Cu^{2+} (1:1) solution, assuming a 1:1 stoichiometry both of **1** and **3**

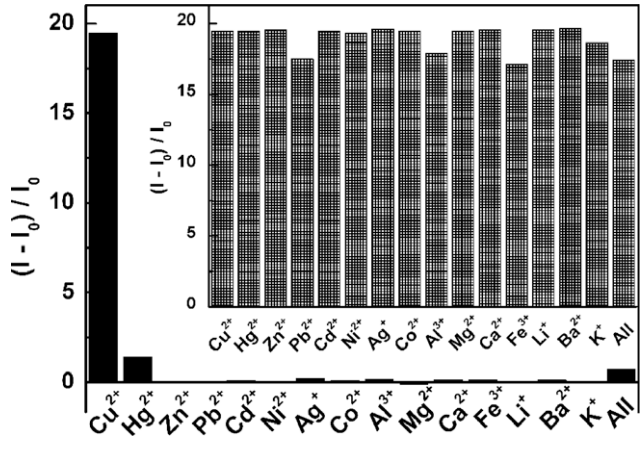

Figure 3. Fluorescent response of **3** toward metal ion at 2.5×10^{-5} M in 10 mM aqueous HEPES buffer solution of pH 7.4. Inset shows the response toward Cu^{2+} of 5×10^{-6} M plus co-existing metal ion at 2.5×10^{-5} M. 'All' means all the tested interference metal ions are present but at a concentration of 5×10^{-6} M each. [**3**] = 1.0×10^{-6} M.

toward Cu^{2+}. As a consequence, the fluorescent response rate would decrease by a factor of ca. 0.33 when Cu^{2+} concentration decreased from 1.0×10^{-6} M to 0.5×10^{-6} M (cf. Fig. S6). In competition experiments, however, it was found that the fluorescent response rate of **3** toward 1 equiv of Cu^{2+} was not affected by 2 equiv of **1** (Fig. S7). These observations indicated that **3** bound more strongly toward Cu^{2+} than **1**, likely due to more binding sites in **3**. This means that indeed Cu^{2+} could re-interact with **3** after decomposition of a previous molecule of **3**, hence less than stoichiometric amount of Cu^{2+} being able to decompose **3** into **1**. Although it is still unable to get the real stoichiometry of **3** toward Cu^{2+}, 20 turnovers of hydrolysis were observed assuming a 1:1 stoichiometry of **3**-Cu^{2+} complex (Fig. S8). Compound **3** was therefore concluded a catalytic chemodosimeter, capable of accumulating and amplifying the signal in response to Cu^{2+}.[6h] We noted that the fluorescence of **1** was not quenched by Cu^{2+} under the tested Cu^{2+} concentration (Fig. S9), which explained the observed fluorescence enhancement of **3** even at high Cu^{2+} concentration.

In summary, **3** was developed as a highly selective and sensitive catalytic chemodosimeter for naked-eye and turn-on fluorescent detections of Cu^{2+} in pure aqueous solution with a detection limit of 1 ppb. Fluorescence of aqueous solution of **3** was found substantially enhanced by Cu^{2+}, which was shown to result from a metal-coordination promoted decomposition of **3** into highly fluorescent **1**. Compound **3** therefore represents a new kind of 'turn-on' fluorescent chemodosimeter for Cu^{2+}.[6a] Other structural motifs on amine substitution are in general possible to allow for extended applications of the reported strategy in constructing chemodosimeters for supramolecular analytical chemistry.[15]

Acknowledgments

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Supplementary data

Supplementary data (synthesis of **3**, absorption spectra of **3** in the presence of metal ions, and optimal conditions for fluorescence assays) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.050.

References and notes

1. (a) Linder, M. C.; Hazegh-Azam, M. *Am. J. Clin. Nutr.* **1996**, *63*, 797S–811S; (b) Uauy, R.; Olivares, M.; Gonzalez, M. *Am. J. Clin. Nutr.* **1998**, *67*, 952S–959S.
2. (a) Fabrizzi, L.; Licchelli, M.; Pallavicini, P.; Perotti, A.; Sacchi, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1975–1977; (b) Torrado, A.; Walkup, G. K.; Imperiali, B. *J. Am. Chem. Soc.* **1998**, *120*, 609–610; (c) Li, Y.; Yang, C. M. *Chem. Commun.* **2003**, 2884–2885; (d) Brasola, E.; Mancin, F.; Rampazzo, E.; Tecilla, P.; Tonellato, U. *Chem. Commun.* **2003**, 3026–3027; (e) Zheng, Y.; Cao, X.; Orbulescu, J.; Konka, V.; Andreopoulos, F. M.; Pham, S. M.; Leblanc, R. M. *Anal. Chem.* **2003**, *75*, 1706–1712.
3. (a) Varnes, A. W.; Dodson, R. B.; Wehry, E. L. *J. Am. Chem. Soc.* **1972**, *94*, 946–950; (b) Prodi, L.; Bolletta, F.; Montaldi, M.; Zaccheroni, N. *Eur. J. Inorg. Chem.* **1999**, 455–460; (c) Mokhir, A.; Kiel, A.; Herten, D. P.; Kraemer, R. *Inorg. Chem.* **2005**, *44*, 5661–5666; (d) Guo, Z. Q.; Zhu, W. H.; Shen, L. J.; Tian, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5549–5553; (e) Huang, X. M.; Guo, Z. Q.; Zhu, W. H.; Xie, Y. S.; Tian, H., *Chem. Commun.*, **2008**. doi: 10.1039/B809983A.
4. (a) Ramachandram, B.; Saroja, G.; Sankaran, N. B.; Samanta, A. *J. Phys. Chem. B* **2000**, *104*, 11824–11832; (b) Rurack, K.; Kollmannsberger, M.; Resch-Genger, U.; Daub, J. *J. Am. Chem. Soc.* **2000**, *122*, 968–969; (c) Zhang, H.; Han, L.-F.; Zachariasse, K. A.; Jiang, Y.-B. *Org. Lett.* **2005**, *7*, 4217–4220; (d) Martinez, R.; Zapata, F.; Caballero, A.; Espinosa, A.; Tairraga, A.; Molina, P. *Org. Lett.* **2006**, *8*, 3235–3238.
5. (a) Kaur, S.; Kumar, S. *Chem. Commun.* **2002**, 2840–2841; (b) Wu, Q.; Anslyn, E. V. *J. Am. Chem. Soc.* **2004**, *126*, 14682–14683; (c) Xu, Z.-C.; Xiao, Y.; Qian, X.-H.; Cui, J.-N.; Cui, D.-W. *Org. Lett.* **2005**, *7*, 889–892; (d) Xu, Z.-C.; Qian, X.-H.; Cui, J.-N. *Org. Lett.* **2005**, *7*, 3029–3032; (e) Wen, Z.-C.; Yang, R.; He, H.; Jiang, Y.-B. *Chem. Commun.* **2006**, 106–108; (f) Martínez, R.; Zapata, F.; Caballero, A.; Espinosa, A.; Tárraga, A.; Molina, P. *Org. Lett.* **2006**, *8*, 3235–3238; (g) Kim, H. J.; Hong, J.; Hong, A.; Ham, S.; Lee, J. H.; Kim, J. S. *Org. Lett.* **2008**, *10*, 1963–1966; (h) Martínez, R.; Espinosa, Al.; Tárraga, A.; Molina, P. *Tetrahedron* **2008**, *64*, 2184–2191.
6. (a) Dujols, V.; Ford, F.; Czarnik, A. W. *J. Am. Chem. Soc.* **1997**, *119*, 7386–7387; (b) Royzen, M.; Dai, Z.; Canary, J. W. *J. Am. Chem. Soc.* **2005**, *127*, 1612–1613; (c) Kierat, R. M.; Krämer, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4824–4827; (d) Singhal, N. K.; Ramanujam, B.; Mariappanadar, V.; Rao, C. P. *Org. Lett.* **2006**, *8*, 3525–3528; (e) Kovács, J.; Rödler, T.; Mokhir, A. *Angew. Chem., Int. Ed* **2006**, *45*, 7815–7817; (f) Kamila, S.; Callan, J. F.; Mulrooney, R. C.; Middleton, M. *Tetrahedron Lett.* **2007**, *48*, 7756–7760; (g) Liu, J.; Lu, Y. *J. Am. Chem. Soc.* **2007**, *129*, 9838–9839; (h) Kovács, J.; Mokhir, A. *Inorg. Chem.* **2008**, *47*, 1880–1882.
7. (a) Florio, G. M.; Longarte, A.; Zwier, T. S. *J. Phys. Chem. A* **2003**, *107*, 4032–4040; (b) Anumula, K. R. *Anal. Biochem.* **2006**, *350*, 1–23.
8. (a) Harris, R. K.; Jackson, P. *J. Phys. Chem. Solids* **1987**, *48*, 813–818; (b) Lu, T. H.; Chattopadhyay, P.; Liao, F. L.; Lo, J. M. *Anal. Sci.* **2001**, *17*, 905–906.
9. Ito, A. S.; Turchiello, R. F.; Hirata, I. Y.; Cezari, M. H. S.; Meldal, M.; Juliano, L. *Biospectroscopy* **1998**, *4*, 395–402.
10. (a) Martell, A. E.; Herbst, R. M. *J. Org. Chem.* **1941**, *6*, 878–882; (b) Drisko, R. W.; McKennis, H. *J. Am. Chem. Soc.* **1951**, *74*, 2626–2628; (c) Cui, Y.; Ni, Y. *Synth. Commun.* **2001**, *31*, 257–261.
11. For a general review on the chemistry of Stenhouse salts including reversibility in their formation, see: (a) Lewis, K. G.; Mulquiney, C. E. *Tetrahedron* **1977**, *33*, 463–475; (b) Hofmann, T. *J. Agric. Food Chem.* **1998**, *46*, 932–940; (c) Li, S.-W.; Batey, R. A. *Chem. Commun.* **2007**, 3759–3761.
12. (a) Mei, X.; August, A. T.; Wolf, C. *J. Org. Chem.* **2006**, *71*, 142–149; (b) Wolf, C.; Liu, S.; Mei, X.; August, A. T.; Casimir, M. D. *J. Org. Chem.* **2006**, *71*, 3270–3273.
13. Compound **3** was synthesized by stirring furan-2-carbaldehyde (0.173 mL, 0.18 mmol) and **1** (0.5 g, 0.36 mmol) in 15 mL ethanol at room temperature for 24 h. After filtration and washing with diethyl ether, **3** was obtained as a yellow solid (0.63 g, yield 85%). ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 4.51–4.54 (ddd, J = 3.5, 3.7 and 3.5 Hz, 1H), 4.94–4.96 (m, 1H), 6.49 (dd, J = 1.7 and J = 4.4 Hz, 1H), 6.56–6.63 (m, 2H), 6.73 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 7.17–7.21 (m, 1H), 7.26–7.31 (m, 1H), 7.74 (dd, J = 1.8 and J = 4.3 Hz, 1H), 7.78–7.84 (m, 2H), 8.31–8.34 (m, 2H), 12.76 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm): 59.46, 65.26, 111.32, 111.41, 112.55, 112.82, 115.79, 115.96, 132.12, 132.28, 132.84, 134.63, 134.96, 150.08, 150.66, 161.21, 170.30, 170.42, 203.47. HRMS, calcd. for $(M+H)^+$ m/z 353.1132, found 353.1137.
14. Detection limit is defined by $3\sigma/k$. Here σ and k refer to standard deviation of the blank solutions and the slope of linear regression curve observed in Fig. S4, respectively, see: (a) Ono, A.; Togashi, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 4300–4302; (b) Liu, J.; Lu, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 7587–7590.
15. Anslyn, E. V. *J. Org. Chem.* **2007**, *72*, 687–699.