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Rhodamine urea derivatives as fluorescent chemosensors for Hg^{2+}

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Abstract—New rhodamine derivatives bearing urea group have been synthesized for the detection of metal ions. Especially, the dimeric system **2** displayed a selective fluorescent enhancement and colorimetric change upon the addition of Hg^{2+}, in which the spirolactam (nonfluorescent) to ring opened amide (fluorescent) process was utilized. The association constant of **2** with Hg^{2+} was calculated as $3.2 \times 10^5\ M^{-1}$.

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Sensors based on the ion-induced changes in fluorescence appear to be particularly attractive due to the simplicity and high detection limit of the fluorescence.[1] Especially, a few rhodamine B derivatives have also been used as fluorescent chemosensors for metal ions, in which the spirolactam (nonfluorescent) to ring opened amide (fluorescent) process was utilized.[2–9] Czarnik et al. reported a pioneering work utilizing this unique process, in which a rhodamine B hydrazide was utilized as a fluorescent chemodosimeter for Cu^{2+}.[2] Recently, we also reported a new fluorescent sensor based on rhodamine B for Pb^{2+}.[3] The structure of chemosensor and ring-opening process was confirmed by X-ray crystallography in addition to NMR, IR, and ESI mass data. On the other hand, Tae et al. reported an intelligent and highly selective chemodosimeter system, which utilized an irreversible Hg^{2+}-promoted oxadiazole forming reaction of rhodamine derivative.[4] Shin and Tae et al. further applied this system to the biological study, recently.[5] Zheng and Xu et al. utilized a rhodamine B thiohydrazide as a fluorescent chemosensor for Hg^{2+}.[6] A bis-rhodamine-based chemosensor[7a] for Fe^{3+} and a rhodamine hydrazone derivative[7b] for Cu^{2+} have been reported by Tong et al. Kim et al. recently reported a new rhodamine derivative as a highly selective chemidosimeter for Hg^{2+}.[8]

Mercury contamination occurs through oceanic and volcanic emission,[9] gold mining,[10] solid waste incineration, etc. Due to the high toxicity of mercury, considerable attention has been devoted to the development of new fluorescent chemosensors[1,4–6,8,11] for the detection of mercury and mercuric salts with sufficient selectivity.

Herein, we synthesized two different rhodamine derivatives bearing urea groups (**1** and **2**). Among the various metal ions, chemosensor **2** displayed a highly selective colorimetric change and fluorescent change with Hg^{2+}.

The intermediate **3**[12] was efficiently synthesized from rhodamine B in a relatively good yield. Compound **3** can be a valuable intermediate as tagging material or for the introduction of various functional groups. Treatment of **3** with 4-nitrophenylisocyanate or 1,3-bis-isocyanatomethyl-benzene afforded **1**[13] or **2**[14] in 42% or 23%, respectively (Scheme 1).

The perchlorate salts of Ag^+, Ca^{2+}, Cd^{2+}, Co^{2+}, Cs^+, Cu^{2+}, Hg^{2+}, K^+, Li^+, Mg^{2+}, Mn^{2+}, Na^+, Ni^{2+}, Pb^{2+}, and Zn^{2+} ions were used to evaluate the metal ion binding properties of compounds **1** and **2** in acetonitrile. The fluorescence spectra were obtained by excitation of the rhodamine fluorophore at 554 nm. Both the excitation and emission slits were either 1.5 or 3 nm. Among these metal ions (100 equiv), compound **1** showed large

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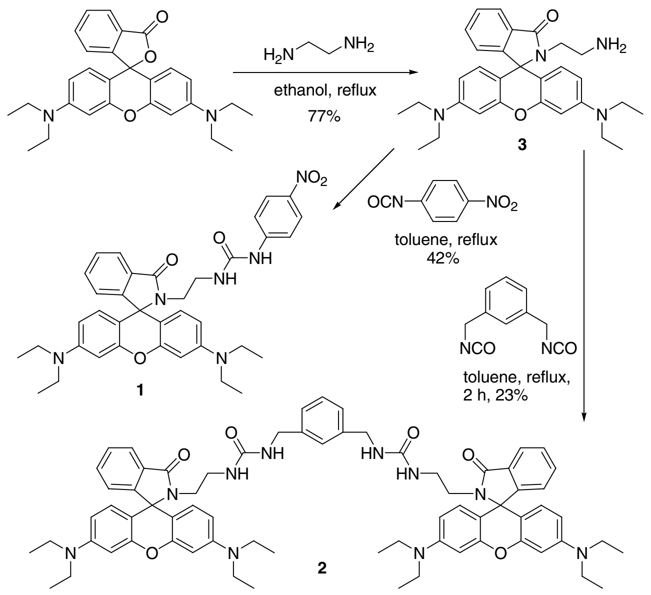

Scheme 1. Synthesis of compound **1**.

chelation enhanced fluorescence (CHEF) effects with Hg^{2+}, Pb^{2+}, and relatively smaller CHEF effects with Zn^{2+} and Cd^{2+} (Fig. 1). On the other hand, compound **2** displayed a highly selective CHEF effect with Hg^{2+} even though there was a smaller CHEF effect with Zn^{2+} (Fig. 2). An overall emission change of over 100-fold was observed for Hg^{2+}. There was also a large enhancement (~120-fold) in the UV absorption ($\lambda_{max} = 554$ nm) of compound **2** upon the addition of Hg^{2+}. The 1:1 stoichiometry was also confirmed by the Job plot using the fluorescence changes.

From the fluorescence titrations, the association constant of **1** and **2** (Fig. 3) with Hg^{2+} were observed to be 2.9×10^4 and $3.2 \times 10^5\ M^{-1}$, respectively (errors < 15%).[15]

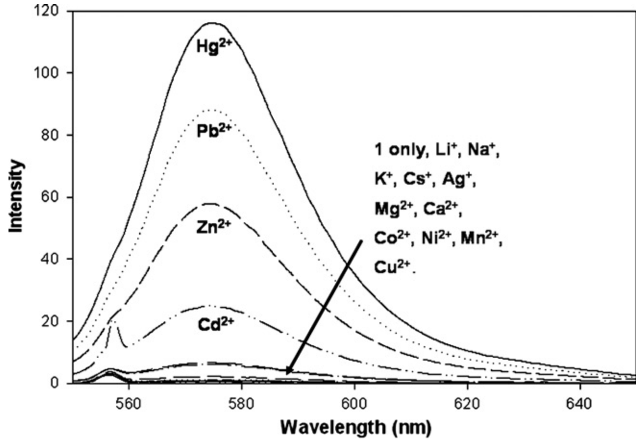

Figure 1. Fluorescent emission changes of **1** (6 μM) upon addition of various metal ions (100 equiv) in CH_3CN (excitation at 554 nm) (excitation and emission slit: 3).

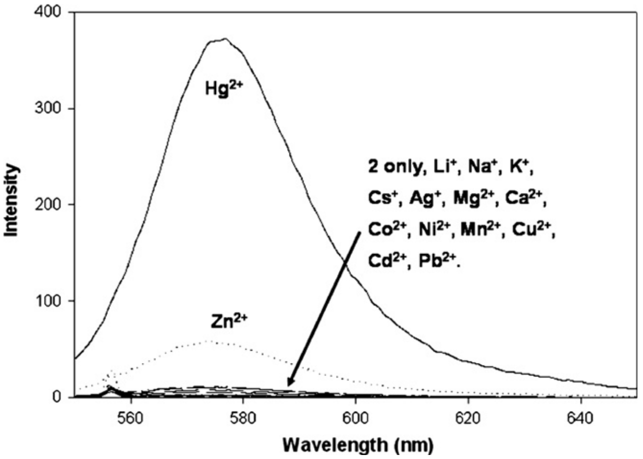

Figure 2. Fluorescent emission changes of **2** (6 μM) upon addition of various metal ions (100 equiv) in CH_3CN (excitation at 554 nm) (excitation and emission slit: 1.5).

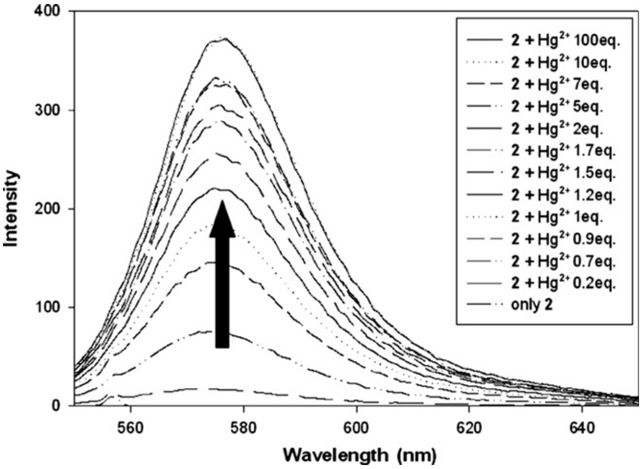

Figure 3. Fluorescent titrations of **1** (6 μM) with Hg^{2+} in CH_3CN (excitation at 554 nm) (excitation and emission slit: 1.5).

The proposed mechanism for these fluorescent changes is explained in Figure 4. Upon the addition of Hg^{2+} to a colorless solution of compound **2**, both a red color and the fluorescence characteristics of rhodamine B appear. The large fluorescence enhancement as well as the colorimetric change can be attributed to the spirolactam ring opening, which was induced by the complexation of Hg^{2+}. Two carbonyl oxygens as well as two amide oxygens can provide a nice binding pocket for Hg^{2+} as shown in Figure 4. Because both disappear upon the addition of excess 1,10-diaza-4,7,14,17-tetrathiacyclooctadecane, it is believed that this process is reversible (S-Fig. 1). Compound **2** displayed a smaller, but similar fluorescent enhancement with Hg^{2+} in acetonitrile–water (95:5) (S-Fig. 2). Also, the ring-opening process in the presence of Hg^{2+} was further confirmed by the disappearance of a spiro-carbon peak at 64.9 in ^{13}C NMR spectrum (S-Fig. 3).

In conclusion, two new rhodamine derivatives bearing urea group have been synthesized for the detection of metal ions. The dimeric system **2** displayed a highly selective fluorescent enhancement and colorimetric change upon the addition of Hg^{2+}, in which the

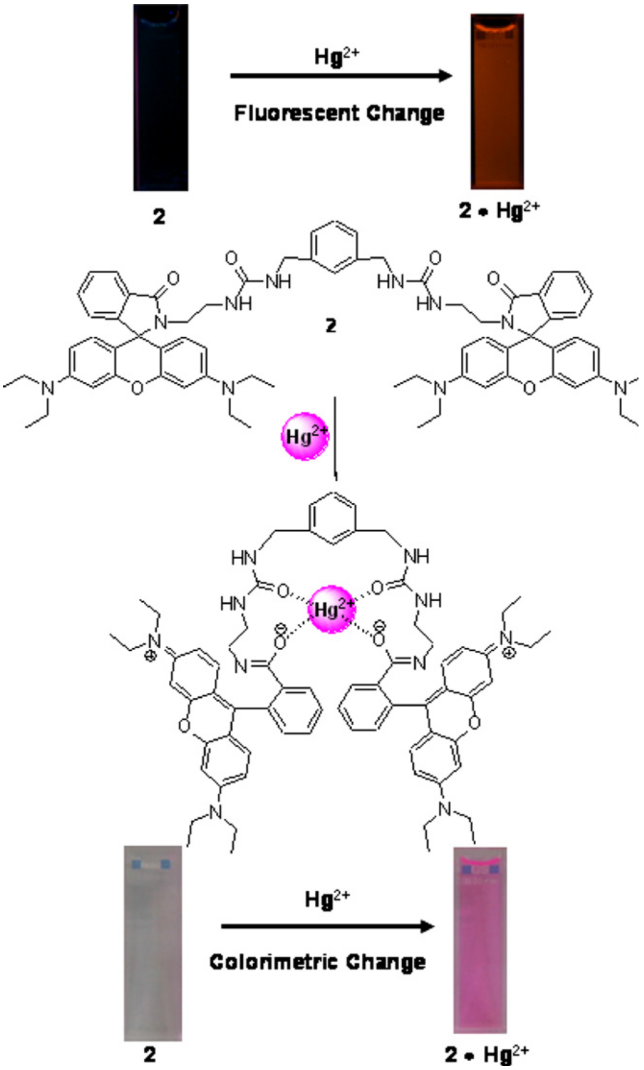

Figure 4. Fluorescent change and colorimetric change of **2** (15 μM) with Hg^{2+} (20 equiv) in $\mathrm{CH_3CN}$.

spirolactam (nonfluorescent) to ring opened amide (fluorescent) process was utilized. The association constant of **2** with Hg^{2+} was calculated as $3.2 \times 10^5\ \mathrm{M}^{-1}$. Also, an aminoethyl rhodamine **3** was synthesized in a good yield from rhodamine B, which can be a potential and practical intermediate as a tagging material for various biological purposes.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.114.

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12. *Compound* **3**. To a 250 mL flask, rhodamine B (2.40 g, 5 mmol) was dissolved in 60 mL ethanol. 0.43 mL of (6.5 mmol) ethylenediamine was then added dropwise with vigorous stirring at room temperature. After the addition, the stirred mixture was heated to reflux for 12 h. The solution became clear. Then the mixture was cooled and solvent was removed under reduced pressure. 1 M HCl (about 100 mL) was added to the residue to remove any unreacted ethylenediamine. After that, 1 M NaOH (about 140 mL) was added slowly with stirring until the pH of the solution reached 9–10. The resulting solution was extracted with dichloromethane (3 × 100 mL), washed the organic layer with 50 mL water, dried on $\mathrm{Na_2SO_4}$ and evaporated the solvents to get the crude product. Purification by silica column chromatography (MC–MeOH = 98:2, v/v) afforded 2.0 g (77%) of **3** as a foamy solid: mp 217–219 °C; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 7.91 (m, 1H), 7.44 (m, 2H), 7.10 (m, 1H), 6.45 (s, 1H), 6.41 (s, 1H), 6.37, (d, 2H, $J = 2.5$ Hz), 6.26 (dd, 2H, $J = 8.9$ Hz, 2.6 Hz), 3.34 (q, 8H, $J = 7.1$ Hz), 3.19 (t, 2H, $J = 6.7$ Hz), 2.40 (t, 2H, $J = 6.7$ Hz), 1.13 (t, 12H, $J = 7.1$ Hz); ^{13}C NMR ($\mathrm{CDCl_3}$) δ 168.6, 153.5, 153.3, 148.8, 132.4, 131.2, 128.7, 128.0, 123.8, 122.7, 108.1, 105.6, 97.7, 64.9, 44.3, 43.9, 40.8, 12.6;

HRMS (FAB) $m/z = 485.2913$ $(M+H)^+$, Calcd for $C_{30}H_{37}N_4O_2 = 485.2917$.

13. *Compound* **1**. Aminoethyl rhodamine (0.22 g, 0.45 mmol) **3** and 0.075 g (0.45 mmol) of 4-nitrophenyl isocyanate were refluxed in 5 mL of anhydrous toluene 2 h. The solvent was evaporated under reduced pressure and the crude solid was purified by column (silica gel; MC–EA = 8:2) to give 0.25 g of **1** (42%): mp 152 °C.; ^{1}H NMR ($CDCl_3$) δ 8.32 (br s, 1H), 8.07 (d, 2H, $J = 9.2$ Hz), 7.79 (d, 1H, $J = 6.8$ Hz), 7.55 (d, 2H, $J = 8.9$ Hz), 7.45 (m, 2H), 7.13 (d, 1H, $J = 6.9$ Hz), 6.44 (d, 2H, $J = 8.9$ Hz), 6.40 (d, 2H, $J = 2.6$ Hz), 6.26 (dd, 2H, $J = 8.9$ Hz, 2.5 Hz), 3.33 (m, 10H), 3.09 (m, 2H), 1.17 (t, 12H, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 170.0, 154.5, 153.8, 153.4, 149.0, 146.3, 141.6, 133.1, 130.2, 128.4, 128.3, 125.0, 124.1, 122.6, 117.3, 108.3, 104.2, 97.8, 66.1, 44.4, 40.5, 40.3, 12.6; HRMS (FAB) $m/z = 649.3137$ $(M+H)^+$, Calcd for $C_{37}H_{41}N_6O_5 = 649.3138$.
14. *Compound* **2**. Aminoethyl rhodamine (0.3 g, 0.62 mmol) **3** and 0.058 g (0.3 mmol) of *m*-xylenediisocyanate were refluxed in 5 mL of anhydrous toluene 2 h. (No solid separation was found after cooling). Solvent was evaporated under reduced pressure and the crude solid was purified by column (silica gel; EA–MeOH = 95:5) to give 0.34 g of **2** (23%): mp 168–170 °C.; ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 2H), 7.43 (m, 4H), 7.02–7.23 (m, 6H), 6.40 (d, 4H, $J = 8.8$ Hz), 6.36 (d, 4H, $J = 2.5$ Hz), 6.22 (dd, 2H, $J = 8.9$ Hz, 2.6 Hz), 5.44 (br s, 2H), 5.17 (br s, 2H), 4.32 (d, 4H, $J = 5.8$ Hz), 3.29 (m, 20H), 3.01 (m, 4H), 1.14 (t, 24H, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 169.5, 158.1, 153.8, 153.3, 148.8, 139.9, 132.6, 130.6, 128.5, 128.1, 126.0, 123.8, 122.8, 108.2, 104.9, 97.7, 65.5, 44.3, 44.2, 40.9, 40.6, 12.6; HRMS (FAB) $m/z = 1157.6345$ $(M+H)^+$, Calcd for $C_{70}H_{81}N_{10}O_6 = 1157.6341$.
15. (a) Association constants were obtained using the computer program ENZFITTER, available from Elsevier-BIOSOFT, 68 Hills Road, Cambridge CB2 1LA, United Kingdom; (b) Conners, K. A. *Binding Constants, The Measurement of Molecular Complex Stability*; Wiley: New York, 1987.