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# A new acridine derivative as a fluorescent chemosensor for zinc ions in an 100% aqueous solution: a comparison of binding property with anthracene derivative

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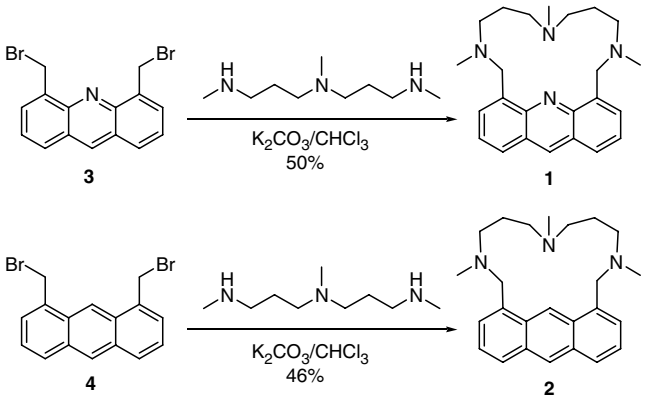
**Abstract**—A new acridine derivative was synthesized as a fluorescent chemosensor for $Zn^{2+}$ in an 100% aqueous solution. Compound **1** displayed a selective CHEF (chelation enhanced fluorescence) effect with $Zn^{2+}$, on the other hand, a similar anthracene derivative **2** did not display any significant change with the metal ions examined.


Sensors based on ion-induced changes in fluorescence appear to be particularly attractive due to the simplicity and high detection limit of fluorescence.[1] Acridine derivatives have been actively utilized as DNA intercalators,[2] and also as drugs for anticancer[3] or leishmaniases.[4] On the contrary, there has been a paucity of papers in which acridine derivatives have been used as fluorescent chemosensors. Mainly chiral acridino-18-crown-6 derivatives have been reported by a few groups.[5] As far as we are aware of, any acridine derivative bearing ligand on the 4,5-position via methylene linkage has not been studied as fluorescent chemosensors for metal ions. Herein, we report a new acridine derivative which shows a large CHEF (chelation enhanced fluorescence) effect with $Zn^{2+}$ in an 100% aqueous solution. A similar anthracene derivative **2** was synthesized and the binding affinities toward metal ions were compared productively. Compound **1** was further utilized as an INH logic gate using $H^+$ and $OH^-$ as two inputs.

4,5-Bis-bromomethylacridine **3** was prepared following a published procedure.[6] The treatment of 4,5-bis-bromomethylacridine **3** with *N*,*N*′-dimethyl-*N*-(3-methylaminopropyl)propane-1,3-diamine in anhydrous chloroform in the presence of $K_2CO_3$ and subsequent purification on basic alumina column using $CH_2Cl_2$–MeOH (99:1, v/v) as an eluent gave compound **1**[7] in a 50% yield. Adopting the similar procedure to 1,8-bis(bromomethyl)anthracene,[8] compound **2**[9] was obtained in a 46% yield (see Scheme 1).

The perchlorate salts of $Ca^{2+}$, $Cd^{2+}$, $Co^{2+}$, $Cs^+$, $Cu^{2+}$, $Hg^{2+}$, $K^+$, $Li^+$, $Mg^{2+}$, $Mn^{2+}$, $Na^+$, $Ni^{2+}$, $Rb^+$, and $Zn^{2+}$ ions were used to evaluate the metal ion binding properties of compounds **1** and **2**. Figures 1 and 2 explain the fluorescent emission changes of **1** (3 μM) and **2** (3 μM), respectively upon the addition of various metal ions at pH 7.4. For the acridine derivative **1**, a




**Scheme 1.** Syntheses of compounds **1** and **2**.

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selective CHEF effect was observed upon the addition of $Zn^{2+}$, although a relatively small CHEF effect was observed with $Cd^{2+}$. On the other hand, there was not a significant change when various metal ions were added to compound **2**. The hydrogen at the 9-position of anthracene in compound **2** may sterically prohibit the binding with metal ions. There are two possible reasons for the different binding affinities of **1** and **2**; the steric problem induced by 9-H of anthracene and the additional nitrogen on the acridine moiety. Figure 3 demonstrates the fluorescent change of **1** upon the addition of $Zn^{2+}$ and the possible binding mode. The nitrogen on the acridine moiety can participate in the binding with $Zn^{2+}$, which can induce the fluorescent increase. The CHEF effect with $Zn^{2+}$ can be also explained by the blocking of the PET (photo-induced electron transfer) process from the benzylic nitrogens.

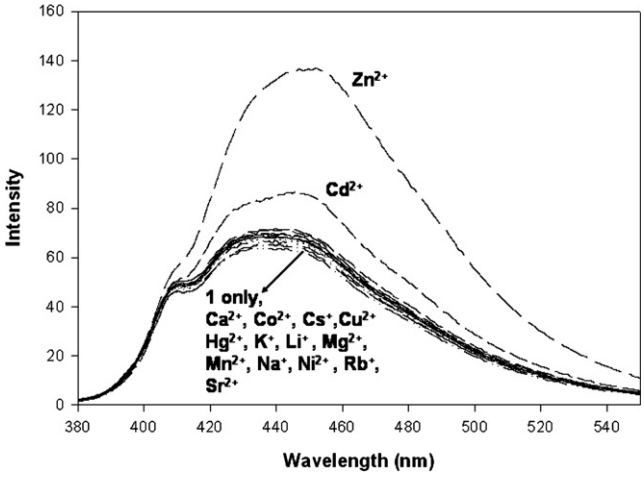



**Figure 1.** Fluorescent emission changes of **1** (3 μM) upon the addition of various metal ions (100 equiv) at pH 7.4 (0.02 HEPES) (excitation at 356 nm) (excitation and emission slit: 5 nm).

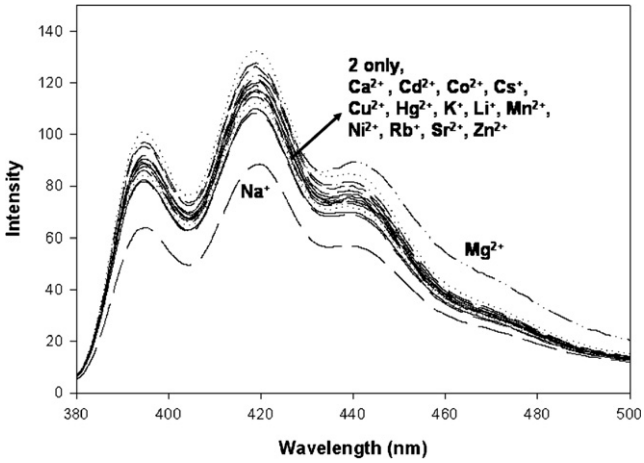



**Figure 2.** Fluorescent emission changes of **2** (3 μM) upon the addition of various metal ions (100 equiv) at pH 7.4 (0.02 M HEPES) (excitation at 368 nm) (excitation and emission slit: 5 nm).

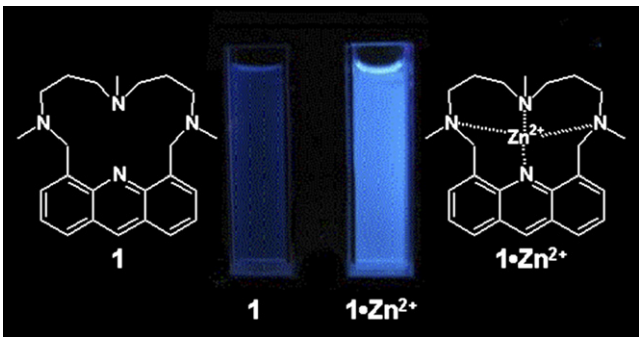



**Figure 3.** Fluorescent changes of compound **1** (10 μM) with $Zn^{2+}$ (200 equiv) in 0.02 M HEPES (pH 7.4).

$Zn^{2+}$ ion is an essential component of many enzymes, and plays important roles in maintaining the key structural features of gene transcription proteins.[10] Also, the role of $Zn^{2+}$ in neurobiology has received significant attention.[11] In this regard, considerable efforts have been devoted to the development of fluorescent chemosensors for $Zn^{2+}$ ion.[12] Our acridine derivative **1** can be

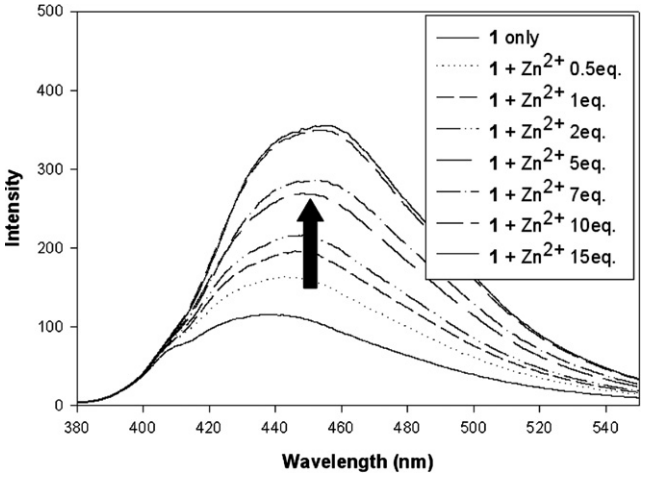



**Figure 4.** Fluorescent titrations of compound **1** (5 μM) with $Zn^{2+}$ at pH 9 (0.05 M CHES) (excitation at 356 nm) (excitation and emission slit: 5 nm).

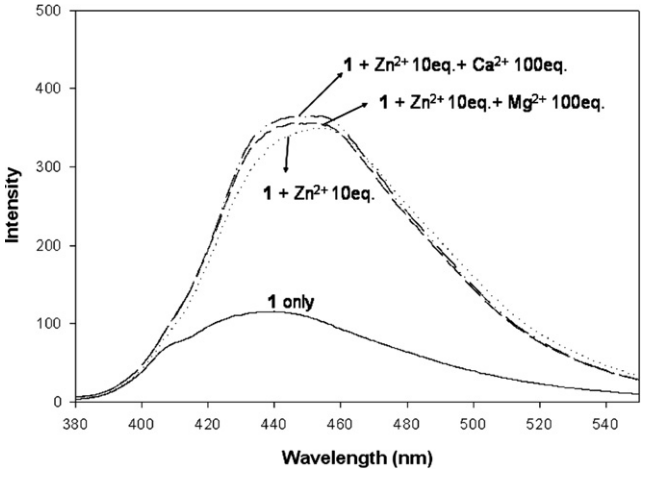
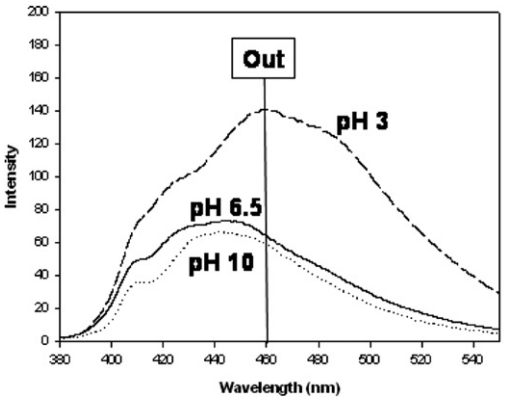



**Figure 5.** Fluorescent changes of compound **1** (5 μM) with $Zn^{2+}$ (10 equiv) in the absence or presence of $Ca^{2+}$ (100 equiv) and Mg (100 equiv) at pH 9 (0.05 M CHES) (excitation at 356 nm) (excitation and emission slit: 5 nm).




| $In_1$ ($OH^-$) | $In_2$ ($H^+$) | Out (460nm) |
|---|---|---|
| 0 | 0 | 0 (low, 64.2) |
| 1 | 0 | 0 (low, 59.0) |
| 0 | 1 | 1 (high, 141.1) |
| 1 | 1 | 0 (low, 65.9) |

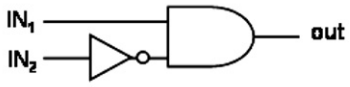



**Figure 6.** Fluorescence spectra of compound **1** (3 μM) in 0.01 M NaCl, truth table and INH logic scheme (excitation at 356 nm, excitation and emission slit: 5 nm) (pH was adjusted by the addition of 0.01 M NaOH and HCl).

also considered as a potential fluorescent chemosensor for $Zn^{2+}$ since it displays a selective CHEF effect with $Zn^{2+}$ in a 100% aqueous solution.

Fluorescence titration experiment was first tried out at pH 7.4; however, precipitation of $Zn^{2+}$ occurred at high concentrations (>1000 equiv). The fluorescent titration was repeated at pH 9 (0.05 M CHES) as shown in Figure 4 and the association constant was calculated as 90,600 $M^{-1}$ (error <15%).[13] There was a red shift (440–456 nm) upon the addition of $Zn^{2+}$ and the overall emission change was over 3.5-fold. Obviously, the association constant at pH 9 should be much larger than that at pH 7.4, which can be attributed to the partial protonation of the ligand nitrogens at pH 7.4. The emission intensities of **1** (5 μM) with 10 μM $Zn^{2+}$ in the presence of 100 μM of $Ca^{2+}$ and $Mg^{2+}$ ions were as same as that using 10 μM $Zn^{2+}$ alone (±5%) (Fig. 5). The relative quantum yields were determined using 9,10-diphenylanthracene in degassed hexane ($\Phi = 0.96$). The relative quantum yield of **1** at pH 9 (0.05 M HEPES) was calculated as 0.0417 and that in the presence of $Zn^{2+}$ (10 equiv) was 0.117.

Recently, a remarkable progress has been achieved in the development of molecular logic gate based on the fluorescent sensor.[14] Among the various logic gates, an Inhibit (INH) logic gate can be interpreted as a particular integration of an AND and a NOT logic gate, where the output signal is inhibited by one of the active inputs. As explained in Figure 6, our system can be applied to an INH logic function using $H^+$ and $OH^-$ as two inputs. Obviously, in our case, two-input INH can be constructed using $OH^-$ input 1 and either $H^+$ or $Zn^{2+}$ as input 2 and fluorescence as an output. Also, an AND gate can be easily applied by using $H^+$ and $Zn^{2+}$ as two different inputs and fluorescence as an output.

In conclusion, a new acridine derivative was synthesized as a fluorescent chemosensor for $Zn^{2+}$ in an 100% aqueous solution. Compound **1** displayed a selective CHEF (chelation enhanced fluorescence) effect with $Zn^{2+}$, on the other hand, a similar anthracene derivative **2** did not display any significant change with the metal ions examined.

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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.2006.09.029.

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7. Compound **1**. Procedure A. A clear solution of 4,5-bis-bromomethylacridine (0.2 g, 0.55 mmol) in chloroform (15 mL) was added to a mixture of *N*,*N*′-dimethyl-*N*-(3-methylaminopropyl)propane-1,3-diamine (0.1 g, 0.55 mmol), anhydrous $K_2CO_3$ (0.3 g, 2.20 mmol) and chloroform (10 mL). The reaction mixture was stirred at room temperature under nitrogen atmosphere until the disappearance of the reactants (~48 h, TLC). Solids were filtered and the solvents were evaporated under vacuum. The gummy solid obtained was purified on a basic alumina column using $CH_2Cl_2$–MeOH (99:1, v/v) as an eluent. The evaporation of the solvents and subsequent vacuum drying yielded 0.1 g (50%) a light yellowish gummy solid. $^1$H NMR ($CDCl_3$, 250 MHz) $\delta$ 8.64 (s, 1H), 7.82 (d, 2H, $J = 8.5$ Hz), 7.67 (d, 2H, $J = 5.8$ Hz), 7.41 (dd, 2H, $J = 8.4$, 6.9 Hz), 4.38 (s, 4H), 2.79 (t, 4H, $J = 7.2$ Hz) 2.30 (m, 10H), 2.16 (s, 3H), 1.79 (q, 4H, $J = 6.6$ Hz); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) $\delta$ 147.4, 137.1, 136.2, 130.6, 127.4, 126.6, 125.1, 57.7, 56.4, 55.2, 44.2, 42.0, 25.4; HRMS (FAB) $m/z = 377.2704$ $[M+H]^+$, calcd for $C_{24}H_{33}N_4 = 377.2705$.
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9. Compound **2**. Application of procedure A gave 95 mg of **2** (46% yield). $^1$H NMR ($CDCl_3$, 250 MHz) $\delta$ 9.29 (s, 1H), 8.39 (s, 1H), 7.89 (dd, 2H, $J = 7.6$, 2.1 Hz), 7.33 (m, 4H), 4.01 (s, 4H), 2.68 (t, 4H, $J = 6.9$ Hz), 2.41 (t, 4H, $J = 6.9$ Hz), 2.25 (s, 3H), 2.19 (s, 6H), 1.83 (q, 4H, $J = 6.8$ Hz); $^{13}$C NMR ($CDCl_3$, 62.5 MHz) $\delta$ 135.1, 132.0, 130.1, 128.7, 127.9, 127.4, 124.5, 120.9, 61.9, 56.4, 55.5, 44.9, 41.9, 26.1; HRMS (FAB) $m/z = 376.2745$ $[M+H]^+$, calcd for $C_{25}H_{34}N_3 = 376.2753$.
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