Discovery of a highly selective turn-on fluorescent probe for Ag^+†

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An ideal fluorescent probe should show the strongest affinity with the relevant target (binding-selectivity) by means of a selective fluorescence change (signal-selectivity). **[15]aneNO$_2$S$_2$** (1,4-dioxa-7,13-dithia-10-azacyclopentadecane) based probes usually show high binding selectivity for Ag^+ but signal selectivity for Hg^{2+}, because Ag^+ can quench or silence the fluorescence. To amplify the Ag^+ binding to the greatest extent, a carbonyl group was positioned between 1,8-naphthalimide and **[15]aneNO$_2$S$_2$** which played a key role of displaying selective fluorescence enhancements with Ag^+ through increasing the oxidation potential of the fluorophore, blocking Ag^+ from sterically interacting with the naphthalimide fluorophore, and by acting as a sacrificial donor. Probe **2** can detect Ag^+ with a selective fluorescence enhancement (~14 fold) and high affinity ($K_a = 1.64 \times 10^5$ M^{-1}).

Introduction

Fluorescent probes are powerful tools to monitor *in vitro* and/or *in vivo* heavy and transition metal (HTM) ions because of the simplicity and high sensitivity of fluorescence. For example, Ag^+ sensing has received considerable attention because of its bio-accumulation and toxicity.[1] The fluorescence enhancement (off–on signal) induced by complexation with HTM ions is more desirable than fluorescence quenching (on–off signal) in terms of increased sensitivity and selectivity. However, the development of off–on fluorescent probes for heavy and transition metal (HTM) ions remains a significant challenge, because many of these ions are typical fluorescence quenchers.[2,3] Recently, we presented three general strategies to prevent fluorescence quenching and preserve the ability for fluorescence enhancement to take place upon binding of HTM ions.[4] These strategies include: (1) prevent the close proximity of the HTM ions to the fluorophore; (2) increase the oxidation potential of the fluorophore; and (3) introduce sacrificial donors that participate in single electron transfer with the HTM ions instead of the fluorophore. In our scaffold that implemented these strategies, a carbonyl group was selected to connect a fluorophore and a receptor. To verify our methodology, various metal ion ligands were introduced as the receptor. We firstly intergrated di-2-picolyamine (DPA) as a versatile receptor into the naphthalimide fluorophore to show turn-on fluorescence with most of HTM ions.[4] A latest example was using a piperazine ring to link two *N*-butyl-4-acetamido-1,8-naphthalimides to make a ratiometric fluorescent probe for Cu^{2+}.[5] The successful applications of these three strategies encouraged us to extend our research by means of finding a more specific HTM ion receptor.

Macrocycles containing nitrogen and/or sulfur donor atoms exhibit high affinities towards HTM ions. Particularly, mixed *N*,*O*,*S*-donor crown ethers have been used as selective extractants for soft metal ions.[6] In recent years, the macrocyclic ligand **[15]aneNO$_2$S$_2$** (1,4-dioxa-7,13-dithia-10-azacyclopentadecane) (Fig. 1) has been widely used to construct chemosensors for thiophilic metal ions,[7] most of which were reported as Hg^{2+} probes with selective turn-on[8] or mostly turn-off[9] fluorescence signals. Only a few examples were reported to sense Ag^+ with a slight fluorescence enhancement.[8a,9d,f,10] Unfortunately, most of these papers reporting Hg^{2+} probes did not explain the fluorescence properties[8c,d,9a,c,e] or competition experiments[8a,9b,f] with Ag^+. In fact, **[15]aneNO$_2$S$_2$** has a higher affinity with Ag^+ than with Hg^{2+} in aqueous solutions. Therefore, it is reasonable to predict that most of **[15]aneNO$_2$S$_2$**-based probes would have a higher affinity with Ag^+ than with Hg^{2+}, and at the same time, Ag^+ would have quenched or silenced the fluorescence. Similar results were reported in a recent paper by Zhu *et al.* A probe with **[15]aneNS$_4$** as the receptor displayed the higher affinity with Ag^+ which quenched the fluorescence slightly compared with Hg^{2+} which increased the fluorescence.[11] An ideal fluorescent probe must meet two basic requirements: firstly, the receptor must have the strongest affinity with the relevant target (binding-selectivity). Secondly, on the basis of good binding-selectivity, the

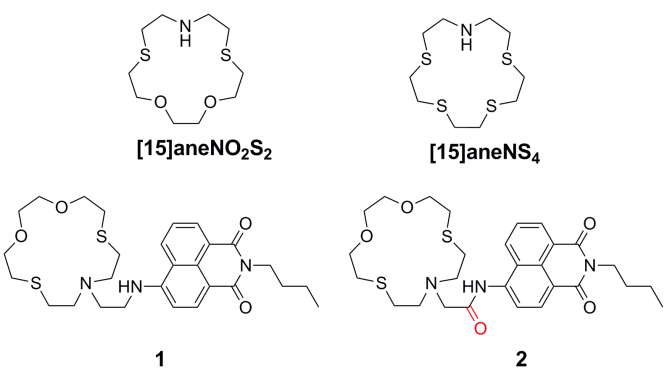

Fig. 1 Structures of the fluorescent probes studied.

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fluorescence signal should avoid environmental interferences (signal-selectivity).[12] Generally, **[15]aneNO$_2$S$_2$**-based chemosensors show high binding selectivity for Ag^+ but signal selectivity for Hg^{2+}. In order to amplify the binding event of Ag^+ by **[15]aneNO$_2$S$_2$** into a selective turn-on fluorescence signal, the three strategies described above were applied through the introduction of **[15]aneNO$_2$S$_2$** into our scaffold to make compound **2**. Compound **1** was synthesized as a reference.

Experimental

General methods

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Flash chromatography was carried out on silica gel 60 (230–400 mesh ASTM, Merck). Thin layer chromatography (TLC) was carried out using Merck 60 F_{254} plates with a thickness of 0.25 mm. Preparative TLC was performed using Merck 60 F_{254} plates with the thickness of 1 mm. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker 250 MHz or Varian 500 MHz. Chemical shifts were given in ppm and coupling constants (J) in Hz. Fluorescence emission spectra were obtained using RF-5301/PC Spectrofluorophotometer (Shimadzu).

Isothermal titration calorimetry experiments

Isothermal titration calorimetry experiments were performed on a VP-ITC microcalorimeter (Microcal Inc., Northampton, MA). All solutions were prepared into 50% MeCN aqueous solutions. For a typical ITC run, the instrument chamber (1.4 mL) contained a solution of the host ([**[15]aneNO$_2$S$_2$**] = 0.6 mM, [**1**] = 0.4 mM, [**2**] = 0.4 mM) while a 3.0 mM solution of Hg^{2+} or Ag^+ (guest) was taken up in a 300 μL injection syringe. The syringe was assembled into the chamber for equilibration while stirring at 502 rpm. The chamber temperature was set up to 25 °C. The injections were programmed at 10 μL each, added over 20 s and spaced 200 s apart. "Number of sites" (N), binding constant (K in M^{-1}) association enthalpy (ΔH in cal mol^{-1}), and association entropy (ΔS in cal mol^{-1} K^{-1}) were obtained by fitting the titration data using the "One Set of Sites model" algorithm provided in the MicroCal Origin Software package (version 7.0).

Synthesis of 1

N-*n*-Butyl-4-(2-bromoethylamino)-1,8-naphthalimide (**3**)[13] (100 mg, 0.27 mmol), **[15]aneNO$_2$S$_2$** (**4**)[14] (68 mg, 0.27 mmol), *N*,*N*-diisopropylethylamine (DIPEA) (0.5 mL) and potassium iodide (30 mg) were added to acetonitrile (20 mL). The mixture was then heated at reflux for 10 hours under nitrogen and monitored by TLC. After the reaction was completed, the solvent was removed under reduced pressure. The crude product was then purified by alumina column chromatography (CH_2Cl_2 : MeOH = 100 : 1) to give (**1**) as a yellow semi-solid in 79% yield (116 mg). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, J = 7.2 Hz, 3H), 1.38–1.47 (m, J = 7.2 Hz, 2H), 1.66–1.73 (m, J = 7.2 Hz, 2H), 2.72 (t, J = 5.4 Hz, 4H), 2.85–2.89 (m, 8H), 3.64 (s, 4H), 3.75 (t, J = 5.4 Hz, 4H), 4.15 (t, J = 7.2 Hz, 2H), 6.53 (s, 1H, NH), 6.62 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 8.38–8.45 (m, 2H), 8.55 (d, J = 7.6 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 13.55, 20.10, 30.00, 31.35, 39.59, 52.41, 53.44, 70.43, 72.74, 104.16, 120.32, 122.60, 124.10, 126.95, 129.53, 130.37, 130.68, 134.15, 149.41, 163.89, 164.48. HRMS (ESI) calcd for $C_{28}H_{40}N_3O_4S_2$ [MH^+] 546.2460, found 546.2460.

Synthesis of 2

4-(2-Chloroacetyl)amino-*N*-*n*-butyl-1,8-naphthalimide (**5**)[13] (100 mg, 0.29 mmol), **[15]aneNO$_2$S$_2$** (**4**) (87 mg, 0.35 mmol), *N*,*N*-diisopropylethylamine (DIPEA) (0.5 mL) and potassium iodide (30 mg) were added to acetonitrile (50 mL). After stirred and refluxed for 10 h under nitrogen atmosphere, the mixture was cooled to room temperature and the mixture was removed under reduced pressure to obtain a yellow semi-solid, which was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 100 : 1) to afford **2**. Yield: 122 mg (75%). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, J = 7.2 Hz, 3H), 1.39–1.48 (m, J = 7.2 Hz, 2H), 1.67–1.74 (m, J = 7.2 Hz, 2H), 2.74 (t, J = 5.2 Hz, 4H), 2.95–3.0 (m, 8H), 3.68 (s, 4H), 3.77 (t, J = 5.2 Hz, 4H), 4.16 (t, J = 7.2 Hz, 2H), 7.75 (t, J = 7.8 Hz, 1H), 8.57–8.68 (m, 4H), 10.54 (s, 1H, NH). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 13.82, 20.36, 30.18, 31.03, 32.18, 40.16, 55.07, 60.18, 70.79, 72.99, 117.29, 118.14, 123.15, 123.22, 126.25, 127.46, 128.95, 131.07, 132.59, 138.80, 163.68, 164.26, 169.91. HRMS (ESI) calcd for $C_{28}H_{38}N_3O_5S_2$ [MH^+] 560.2253, found 560.2255.

Results and discussion

Binding selectivity

We firstly obtained the binding constants of **[15]aneNO$_2$S$_2$** and compounds **1** and **2** with Hg^{2+} and Ag^+, respectively, in 50% CH_3CN aqueous solutions by means of isothermal titration calorimetry (ITC) experiments at 25 °C (Fig. 2–7), and summarized in Table 1. Compounds **1** and **2** can dissolve well in 50% CH_3CN aqueous solutions and display proper fluorescence changes with Hg^{2+} and Ag^+. The **[15]aneNO$_2$S$_2$**/Ag^+ complex is

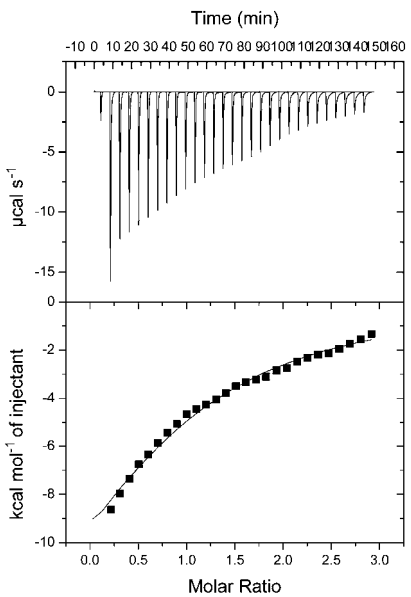

Fig. 2 ITC titration curves of **[15]aneNO$_2$S$_2$** with Hg^{2+} in 50% acetonitrile aqueous solution.

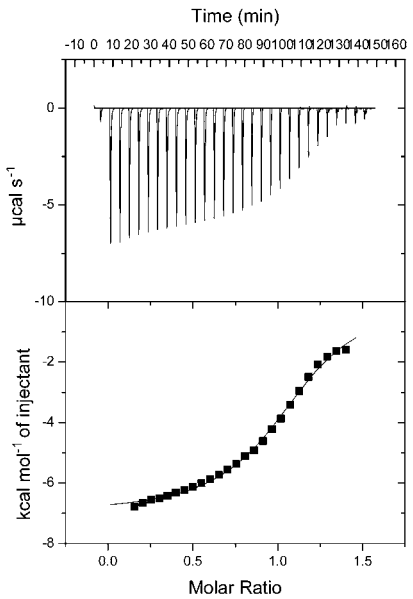

Fig. 3 ITC titration curves of **[15]aneNO$_2$S$_2$** with Ag^+ in 50% acetonitrile aqueous solution.

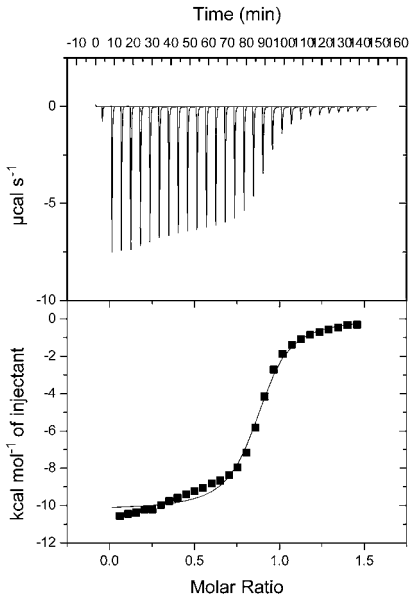

Fig. 5 ITC titration curves of **1** with Ag^+ in 50% acetonitrile aqueous solution.

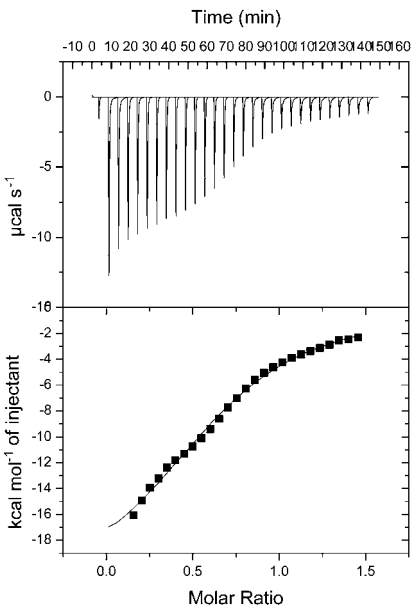

Fig. 4 ITC titration curves of **1** with Hg^{2+} in 50% acetonitrile aqueous solution.

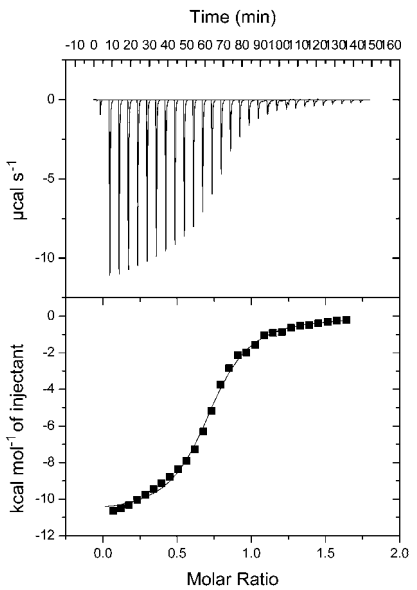

Fig. 6 ITC titration curves of **2** with Hg^{2+} in 50% acetonitrile aqueous solution.

more stable than the **[15]aneNO$_2$S$_2$**/Hg^{2+} complex by 1.53 kcal mol^{-1}. In consistent with this result, compounds **1** and **2** all show higher binding ability with Ag^+ than with Hg^{2+}. The **1**/Ag^+ complex is much more stable than **1**/Hg^{2+} complex by 1.8 kcal mol^{-1}. The **2**/Ag^+ complex is more stable than the **2**/Hg^{2+} complex by 0.33 kcal mol^{-1}. Thus we can say compounds **1** and **2** have a higher binding selectivity with Ag^+ than with Hg^{2+}.

Fluorescence selectivity

We then checked the fluorescence responses of **1** and **2** with various metal ions. It was found that most of HTM ions quenched fluorescence of **1** in acetonitrile (Fig. 8). In aqueous solution (CH_3CN : HEPES = 50 : 50, HEPES 0.5 M, pH = 7.4), only Hg^{2+}, Ag^+, Zn^{2+}, and Cd^{2+} increased the fluorescence of **1** at 532 nm slightly. As shown in Fig. 9, compound **1** displayed selective turn-on fluorescence for Hg^{2+}. Thus, judged by fluorescence enhancement, compound **1** is not an ideal fluorescent probe, in that it cannot amplify the binding events of **1** with various metal ions completely and veritably into a turn-on fluorescence signal.

The fluorescence spectrum of **2** in acetonitrile contains an emission band with a maximum at 452 nm. The presence of the amide group in **2** decreases the electron donating ability of the conjugated NH nitrogen and therefore results in a *ca.* 80 nm blue

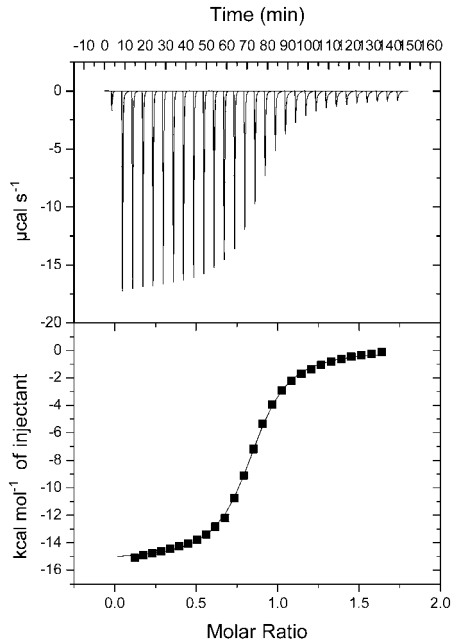

Fig. 7 ITC titration curves of **2** with Ag^+ in 50% acetonitrile aqueous solution.

Table 1 Binding constants determined by isothermal titration calorimetry (ITC) for Hg^{2+} and Ag^+ complexes of **[15]aneNO$_2$S$_2$**, **1** and **2**[a]

	[15]aneNO$_2$S$_2$		**1**		**2**	
Complex	Hg^{2+}	Ag^+	Hg^{2+}	Ag^+	Hg^{2+}	Ag^+
$K_a/\times10^4$ M^{-1}	0.29	3.82	1.63	34	9.12	16.4
ΔG/kcal mol^{-1}	−4.72	−6.25	−5.75	−7.55	−6.77	−7.10
ΔH/kcal mol^{-1}	−19.6	−6.99	−22.2	−10.22	−10.82	−15.27
ΔS/cal mol^{-1} K^{-1}	−49.9	−2.47	−55.2	−8.97	−13.6	−27.4

[a] One set of sites binding model.

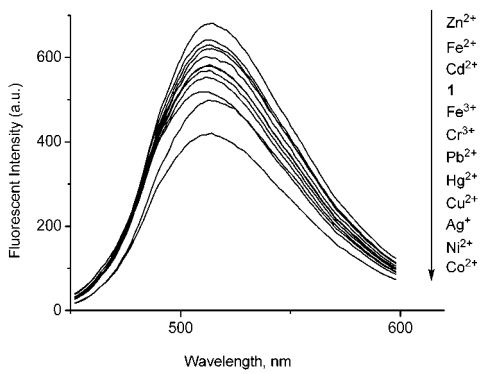

Fig. 8 Fluorescence spectra of **1** in the presence of different HTM ions in CH_3CN. Excitation at 456 nm. [**1**] = 10 μM and [HTM] = 30 μM.

shift in emission compared to that of **1** (532 nm).[4] Addition of HTM ions to acetonitrile solutions of **2** causes an increase in fluorescence intensity due to PET, the extent to which depends on the nature of the ion, and a shift in the emission maximum from 452 to *ca.* 430 nm due to internal charge transfer (ICT) (Fig. 10 and Table 2). The binding of HTM ions to the carbonyl

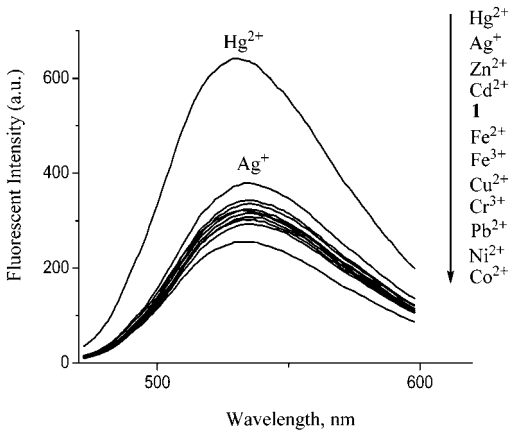

Fig. 9 Fluorescence spectra of **1** in the presence of different HTM ions in CH_3CN : HEPES = 50 : 50, HEPES 0.5 M, pH = 7.4. Excitation at 456 nm. [**1**] = 10 μM and [HTM] = 30 μM.

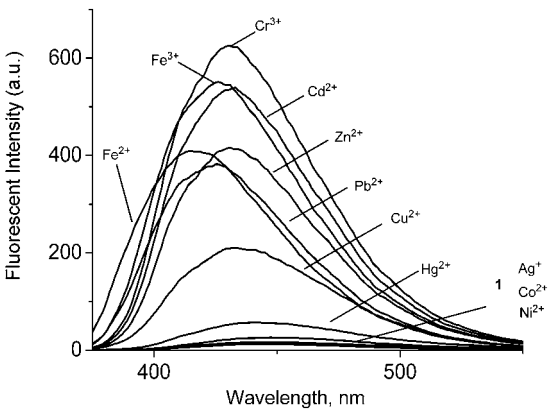

Fig. 10 Fluorescence spectra of **2** in the presence of different HTM ions in CH_3CN. Excitation at 350 nm. [**1**] = 10 μM and [HTM] = 30 μM.

oxygen causes a further decrease in electron donating ability and a blue shift of the emission maximum. Thus we can see the introduction of the carbonyl group in **2** protects fluorescence from quenching by HTM ions. Moreover, the blue-shift in emission can provide a ratiometric fluorescence assay for HTM ions.

Table 2 Maximum of fluorescence enhancement (FE) and emission wavelength changes of **2** in the presence of HTM ions in acetonitrile[a]

	λ_{em}/nm	FE[b]		λ_{em}/nm	FE
None	452	2	Cu^{2+}	433	13
Cr^{3+}	430	39	Zn^{2+}	409	26
Fe^{2+}	431	26	Ag^+	446	1.4
Fe^{3+}	433	34	Cd^{2+}	426	34
Co^{2+}	443	1.6	Hg^{2+}	441	4
Ni^{2+}	445	1.1	Pb^{2+}	426	24

[a] Experimental conditions: [**2**] = 10 μM, [M^{n+}] = 30 μM, λ_{ex} = 350 nm at 25 °C. [b] Relative quantum yield (Φ_F) in comparison to **2** in the absence of HTM ions. Calculated by comparison of corrected spectrum with that of *N*-butyl-4-butylamino-1,8-naphthalimide (Φ_F = 0.81 in absolute ethanol), taking the area under the total emission. The Φ_F of **2** is 0.0071.

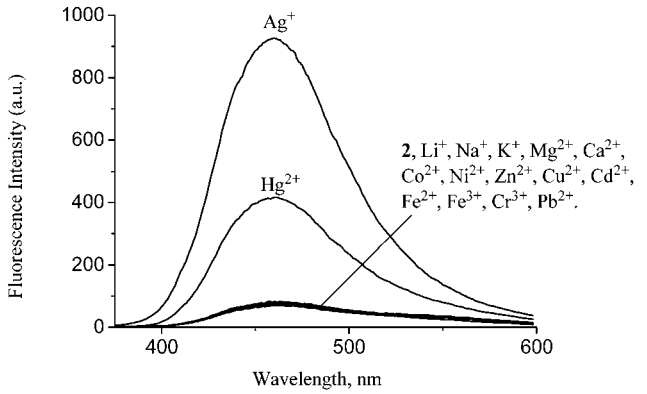

Fig. 11 Fluorescence spectra of **2** in the presence of different HTM ions in CH_3CN : HEPES = 50 : 50, HEPES 0.5 M, pH = 7.4. Excitation at 350 nm. [**2**] = 10 μM and [HTM] = 30 μM.

Significantly, the fluorescence responses of **2** to metal ions in aqueous solutions (CH_3CN : HEPES = 50 : 50) were detected (Fig. 11). As shown in Fig. 11, the addition of Ag^+ induced a selective increase by ~14 fold in emission. The addition of Hg^{2+} led to a lower increase in emission by ~6 fold. The addition of other metal ions, such as Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Fe^{2+}, Fe^{3+}, Cr^{3+}, and Pb^{2+}, produced a negligible change in the fluorescence spectra of **2**. Importantly, the ITC experiments confirmed that **2** had a higher affinity with Ag^+ than with Hg^{2+} (Table 1). Fluorescence titration experiments (Fig. 12) showed that the association constant (K_a) of **2** with Ag^+ is $1.24 \times 10^5\ M^{-1}$ (error <10%), which is consistent with the ITC data.[15] These results suggest that **2** is a highly signal-selective probe for Ag^+ with turn-on fluorescence in aqueous solutions. Furthermore, Ag^+ could be detected at least down to 1.0×10^{-8} M.

To further check the Ag^+-selective turn-on fluorescence of **2** over other metal ions, competition experiments were conducted in the presence of 3 equiv. of Li^+, Na^+, K^+, Mg^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Fe^{2+}, Fe^{3+}, Cr^{3+}, Hg^{2+} or Pb^{2+}, with the subsequent addition of 3 equiv. of Ag^+. As shown in Fig. 13, the emission profile of the **2**/Ag^+ complex is unperturbed in the presence of these metal ions, indicating the strongest affinity and selectivity for Ag^+. Therefore, **2** is also a highly binding-selective probe for Ag^+ in aqueous solutions.

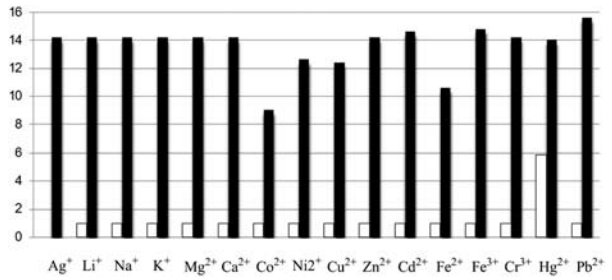

Fig. 13 Fluorescence responses of 10 μM **2** to various metal ions in aqueous solution (CH_3CN : 0.5 M HEPES (pH 7.4) = 50 : 50). Excitation at 350 nm. Bars represent the final fluorescence intensity at 452 nm (I_f). White bars represent the addition of 3 equiv. of metal ions to a 10 μM solution of **2**. Black bars represent the subsequent addition of 3 equiv. of Ag^+ to the solution.

Effect of pH on the fluorescence response of 2 with Ag^+

The influence of pH on the sensing property of **2** with Ag^+ was finally investigated by means of the fluorescence measurements for a solution of 1 equiv. of **2** and 3 equiv. of Ag^+ (Fig. 14). The fluorescence of **2** at 460 nm increase by ~14 fold complexed with Ag^+ and remained unaffected between pH 10 and 6.1, but slightly increased from pH 6.1 to 4.6 due to the protonation of the

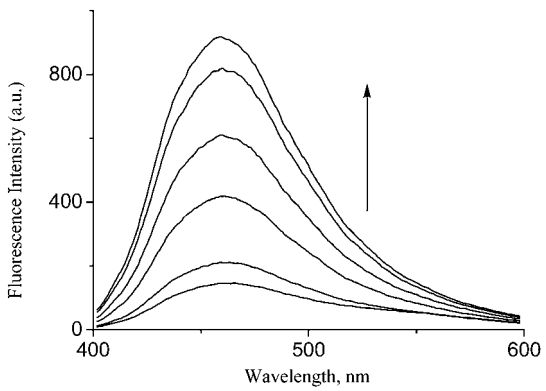

Fig. 12 Fluorescence spectra of 10 μM **2** in the presence of different concentrations of Ag^+ in aqueous solutions (CH_3CN : HEPES = 50 : 50; HEPES, 0.5 M, pH 7.4). Excitation at 350 nm.

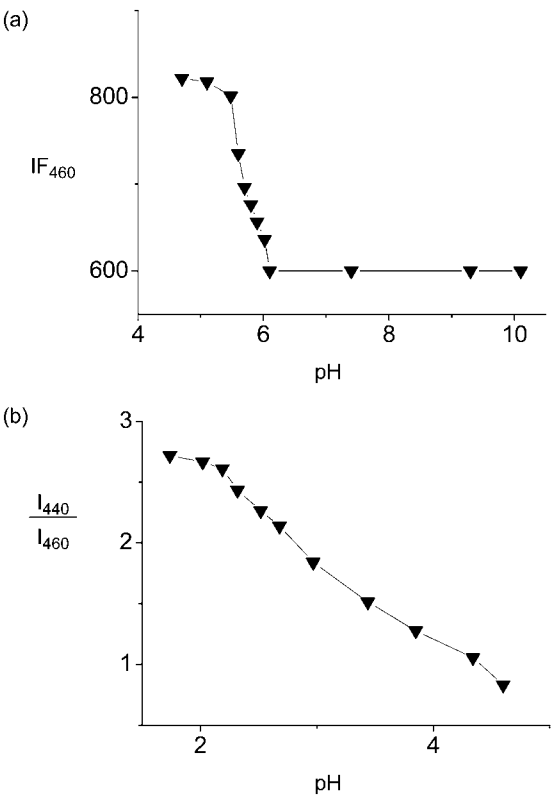

Fig. 14 Influence of pH on the fluorescence of 10 μM **2** in the presence of 30 μM Ag^+ in aqueous solutions (CH_3CN : HEPES = 50 : 50): (a) pH 4.6–10 and (b) pH 4.6–1.8.

tertiary amine which displaced Ag^+; with increasing acidity from pH 4.6 to 1.8, a significant decrease in the 460 nm emission and a blue-shifted emission band centered at 440 nm were observed. This phenomenon may be attributed to the protonation of the amide oxygen, which leads to a decrease in electron donating ability and a blue shift in emission.

Conclusions

In conclusion, probe **2** was designed based on strategies to avoid fluorescence quenching with metal ions, and was shown to detect Ag^+ with a selective fluorescence enhancement in aqueous solutions. ITC experiments revealed that **[15]aneNO$_2$S$_2$** is a highly selective receptor for Ag^+. However, the fluorescence response of **1** with the addition of Ag^+ does not reflect the strong binding event due to Ag^+'s silent character to fluorescence. It is a general phenomenon for HTM ion fluorescent probes that the binding strength of metal ions is not expressed comparably by fluorescence changes due to various personalities of HTM ions to fluorescence. In this case, our three strategies successfully guaranteed that the Ag^+ binding by **2** was amplified to the greatest extent. In future work, these strategies will be applied by changing the fluorophore and/or more specific receptors.

Acknowledgements

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