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# Selectively Fluorescent Sensing Behavior of Phenylaza-15-crown-5-triazolyl Coumarin for $Hg^{2+}$ and $Fe^{3+}$ in Alcohol and Aqueous Media Respectively

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A π-conjugated phenylaza-15-crown-5-triazol-substituted coumarin fluoroionophore **1** was synthesized by copper(I)-catalyzed Huisgen alkyne-azide 1,3-dipolar cycloaddition (CuAAC "click" reaction). **1** can display selective fluorescence enhancement toward $Fe^{3+}$ over $Hg^{2+}$, $Cr^{3+}$ and the other metal ions in aqueous solution. In sharp contrast, the fluorescence behavior between $Fe^{3+}$ and $Hg^{2+}$ is completely reversed in EtOH. That is, $Hg^{2+}$ gives the largest fluorescence enhancement over $Cr^{3+}$, $Fe^{3+}$ and the other metal ions.

**Keywords** coumarin, sensors, crown compounds, metal ions, fluorescence

## Introduction

A variety of selective and sensitive fluorescent probes for metal ions have been developed in recent years.[1] Among them, the small-molecule fluorescent sensor that consists of an ionophore-chromophore system has always been attracting the continuous interests because of its fast response, reversibility and potential utility in either environmental or biological contexts. Mercury ion is highly dangerous and toxic for both the environment and human health. And the mercury ion often caused fluorescence quenching upon complexation because of its heavy atom effect. Although a number of small-molecule sensors toward $Hg^{2+}$ have been reported,[2] there is still a strong demand for developing the $Hg^{2+}$ selective fluorescent sensors with "turn-on" fluorescence because of their ease in detection and low interference background. On the other hand, as a key role in many biochemical processes, iron ion is indispensable for most organisms.[3] It is an important healthcare challenge to detect and analyze the bioactive iron. However, the selective fluorescent sensors for $Fe^{3+}$ are still very rare,[4] and the signaling of iron ions is often based on fluorescence quenching because of the paramagnetic nature. For the convenience in real application, it appears to be attractive to design a multifunctional fluorescent sensor simply by modulating the selectivity toward various metal ions with the change of the testing media. Recently, several chemodosimeters that can sense different ions in different testing media have been reported.[5] However, it was very rare to use the small-molecule sensor to realize the solvent-controlled sensing behavior toward different ions.[6]

1,4-Disubstitued-1,2,3-triazole, obtained from the copper(I)-catalyzed Huisgen alkyne-azide 1,3-dipolar cycloaddition (CuAAC "click" reaction), has been used in various metal ion sensors,[7] because 1) it is easy to be prepared, 2) it can be used as a π-linker to adjust the twist angle between different units in the molecule, and 3) it can offer a potential coordination site for metal ions. As a fluorophore, coumarin has been chosen for various sensors not only because it is easy to be synthesized and derivatized, but also because it shows strong fluorescence with large Stokes shift.[8] When the coumarin fluorophore was conjugated with *N*-phenylaza-15-crown-5 ether through the 1,4-disubstitued-1,2,3-triazole linker, the fluorescence of coumarin was quenched because the photoinduced electron transfer (PET) occurs upon excitation of the free sensor, where the planar anilinotriazole unit serves as a PET donor and the coumarin serves as a PET acceptor.[9] Through binding the ions in the aza-15-crown-5 and suppressing the PET, it is expected that such a molecule can exhibit a selective "turn-on" fluorescent response toward the target ion.

## Experimental

### General methods and materials

All chemicals were commercially available unless noted otherwise. Compounds **3**,[10] **4**[11] and **5**[12] were prepared according to the literature procedure. NMR data were recorded on Bruker AV400 spectrometer and

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chemical shifts were recorded in parts per million. UV/Vis spectra were recorded in a quartz cell (light path 10 mm) on a Shimadzu UV-3600 spectrophotometer equipped with a PTC-348WI temperature controller to keep the temperature at 25 ℃. Steady-state fluorescence spectra were recorded in a conventional quartz cell (light path 10 mm) on a Varian Cary Eclipse equipped with a Varian Cary single-cell peltier accessory to control temperature. Mass spectra were recorded using Agilent 6520 Q-TOF LC/MS (ESI).

### Preparation of sensors solutions

A stock sensor solution was prepared in DMSO at 10 mmol•$L^{-1}$ concentration. An aliquot of this stock solution was then added to water or other solvents, to make a final sensor concentration of 10 μmol•$L^{-1}$. Mercury-containing solutions were prepared by adding $Hg^{2+}$ (0.01 mol•$L^{-1}$ $Hg(ClO_4)_2$ solutions prepared in water) to the final sensor solution.

### General synthetic procedure exemplified by the synthesis of 1

To a solution of **3** (80 mg, 0.25 mmol) and **4** (50.8 mg, 0.25 mmol) in THF/$H_2O$ ($V$∶$V$=1∶1, 10 mL) was added sodium ascorbate (9.9 mg, 0.05 mmol) and copper(II) sulfate pentahydrate (3.12 mg, 0.0125 mmol). The reaction mixture was stirred for 24 h at room temperature under $N_2$ atmosphere. Then the solvent was removed *in vacuo*, and water (20 mL) was added to the residue. The precipitate was filtered off, washed with water (50 mL). The crude product was recrystallized from $CH_2Cl_2$ to afford **1** as a brown solid (84.9 mg, 65%). m.p. 153－155 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.74 (s, 1H), 8.62 (s, 1H), 7.72－7.78 (m, 3H), 6.92 (d, $J$=8.7 Hz, 1H), 6.88 (s, 1H), 6.73 (d, $J$=8.4 Hz, 2H), 3.65－3.67 (m, 4H), 3.52－3.56 (m, 16H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 162.4, 156.4, 154.6, 147.3, 147.1, 136.4, 130.9, 126.6, 120.0, 119.4, 117.1, 114.3, 111.4, 110.4, 102.2, 70.3, 69.5, 69.0, 67.8, 51.9. HRMS $[M+Na]^+$ calcd for $C_{27}H_{30}N_4NaO_7^+$ 545.2007, found 545.1999.

**Compound 2** Brown solid, 69% yield; m.p. 212－214 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$: 8.78 (s, 1H), 8.63 (s, 1H), 7.80－7.73 (m, 3H), 6.92 (d, $J$=8.7 Hz, 1H), 6.88 (s, 1H), 6.81 (d, $J$=8.5 Hz, 2H), 2.95 (s, 6H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$: 162.4, 156.3, 154.6, 150.2, 147.1, 136.4, 130.9, 126.3, 120.1, 119.3, 117.7, 114.3, 112.3, 110.4, 102.2. HRMS $[M+H]^+$ calcd for $C_{19}H_{17}N_4O_3^+$ 349.1295, found 349.1298.

## Results and Discussion

The sensor molecule **1** was prepared by the Cu-AAC "click" reaction of *N*-propargylaza-15-crown-5 ether with 3-azido-7-hydroxycoumarin in a mixed solution of THF and water in 65% yield (Scheme 1).[11] The compounds were fully characterized by $^1$H and $^{13}$C NMR, and HRMS.

The selectivity of **1** toward 20 different perchlorate salts of metal ions ($Ag^+$, $Ba^{2+}$, $Ca^{2+}$, $Cd^{2+}$, $Co^{2+}$, $Cs^+$, $Cu^{2+}$, $Fe^{2+}$, $K^+$, $Cr^{3+}$, $Hg^{2+}$, $Fe^{3+}$, $Li^+$, $Mg^{2+}$, $Mn^{2+}$, $Na^+$, $Ni^{2+}$, $Pb^{2+}$, $Sr^{2+}$, and $Zn^{2+}$) in water was examined by fluorescence spectroscopy (Figures 1 and 2). Among all the ions, **1** gave clear responses toward only $Fe^{3+}$, $Cr^{3+}$ and $Hg^{2+}$, with the strongest fluorescence inten-

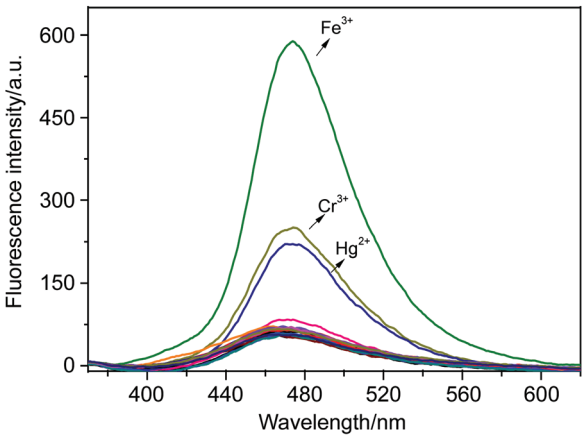



**Figure 1** Fluorescence spectra of **1** (10 μmol•$L^{-1}$) in the absence and presence of different metal ions (120 μmol•$L^{-1}$) in $H_2O$, $\lambda_{ex}$=330 nm.

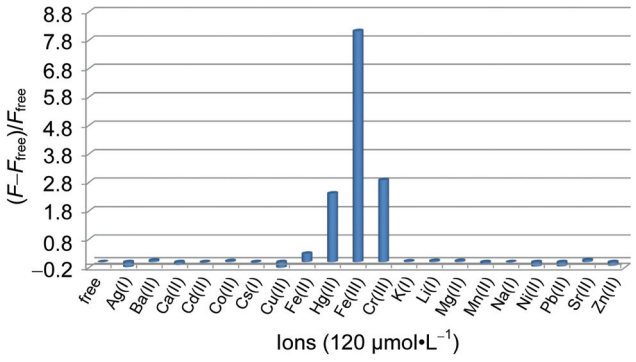
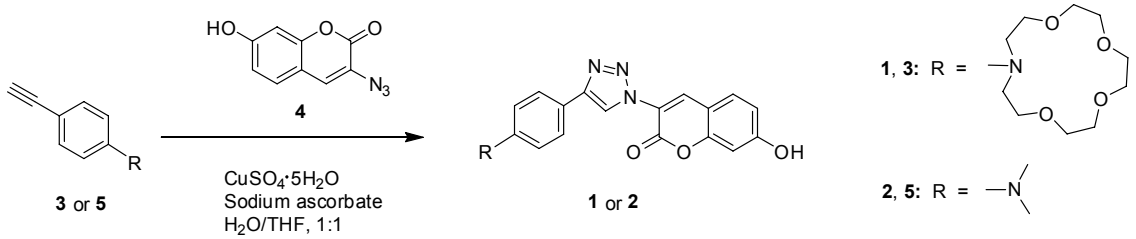



**Figure 2** The fluorescence intensity change profile of **1** (10 μmol•$L^{-1}$) in the absence and presence of different metal ions (120 μmol•$L^{-1}$) in $H_2O$, $\lambda_{ex}$=330 nm.

**Scheme 1** Synthetic routes for **1** and **2**



sity enhancement toward $Fe^{3+}$. Upon addition of 12 equiv. of metal ions, the fluorescence enhancement factor value (FEF)[13] of $Fe^{3+}$ was 9.1, which was larger than $Hg^{2+}$ (3.4) and $Cr^{3+}$ (3.9). The limit of detection (LOD value) of **1** towards $Fe^{3+}$ was calculated to be $3.6\times10^{-6}$ mol•$L^{-1}$ (Figure S15, Supporting Information). However, because the absorption of **1** is overlapped with the absorption of $Fe^{3+}$, the quantitative investigation of the binding process can not be realizable.[4a]

When we examined the metal ions selectivity in organic solvent such as MeOH and MeCN, **1** exhibited a different selectivity toward the ions. We used the ratio of fluorescence intensities $(F–F_{free})/F_{free}$ to compare the selectivity in different cases. It can be found that in MeOH, upon addition of different amounts of ions, fluorescence ratio of $Hg^{2+}$ was always higher than that of $Fe^{3+}$ (Figure 3A). After addition of more than 10 equiv. $Fe^{3+}$, the fluorescence ratio decreased which may be attributed to the effect from the absorption of $Fe^{3+}$. In $H_2O$, the fluorescence ratio of $Fe^{3+}$ was always higher than that of $Hg^{2+}$ (Figure 3B). In a mixed solvent (MeOH/$H_2O$=1∶9), upon addition of 10 equiv. ions, the fluorescence ratio of $Fe^{3+}$ was higher than that of $Hg^{2+}$. Further addition of ions caused the decreasing fluorescence ratio of $Fe^{3+}$ which was exceeded by that of $Hg^{2+}$ (Figure 3C). In $CH_3CN$, we found that **1** showed a similar fluorescence response toward the two ions. The fluorescence ratio reached the highest value in 10 equiv. which indicated a large binding affinity between **1** and the ions (Figure 3D).

We further investigated the sensing behavior of **1** in EtOH which was similar with MeOH. Although the fluorescence ratios of ions were lower than that in MeOH, the selectivity of **1** toward $Hg^{2+}$ was higher in EtOH (Figures 4 and 5). Upon addition of 12 equiv. of ions, the FEF for $Hg^{2+}$ can reach 130.1, higher than that for $Fe^{3+}$ (41.9) and $Cr^{3+}$ (48.0). The Job's plot shows that $Hg^{2+}$ and **1** formed the complex in 1∶1 stoichiometry (Figure 6). Through adding varying amounts (0—70 equiv.) of $Hg^{2+}$ to the solution of **1** and monitoring the fluorescence intensity change at $\lambda_{em}$=424 nm, the stability constant ($K_S$) was calculated to be $9.6\times10^3$ L•$mol^{-1}$ by the nonlinear least-squares analysis of the differential intensity (Figure 7). The LOD value of **1** towards $Hg^{2+}$ was calculated to be $1.0\times10^{-6}$ mol•$L^{-1}$ (Figure S16, Supporting Information).

The $^1H$ NMR experiments were performed to gain structural information on the complex (Figure 8). After addition of 1.0 equiv. of $Hg^{2+}$ into the solution of **1** (5 mmol•$L^{-1}$), protons $H_g$, $H_f$ and $H_e$ were all shifted downfield, which should be attributed to the deshielding effect arising from the decrease of the electron density of anilinotriazole unit upon the binding of metal ion. The observation on the shifts of the protons of crown ether also indicated the binding of ion with the aza-15-crown-5. On the other hand, the protons on the coumarin fluorophore were hardly shifted, which confirmed that this moiety did not participate in the complexation.

Through examining the metal ions selectivity of control compound **2** in EtOH, we noticed that **2** can give a similar fluorescence response toward the $Fe^{3+}$, $Hg^{2+}$ and $Cr^{3+}$ (Figure 5). The ratio of fluorescence intensities for $Hg^{2+}$ was lower than that for $Fe^{3+}$ and $Cr^{3+}$. However, in the case of **1**, the ratios of fluorescence intensities for $Fe^{3+}$ and $Cr^{3+}$ were both decreased while that for $Hg^{2+}$ was remarkably enhanced. This observation further confirmed the important role of the aza-15-crown-5 for the selectivity.

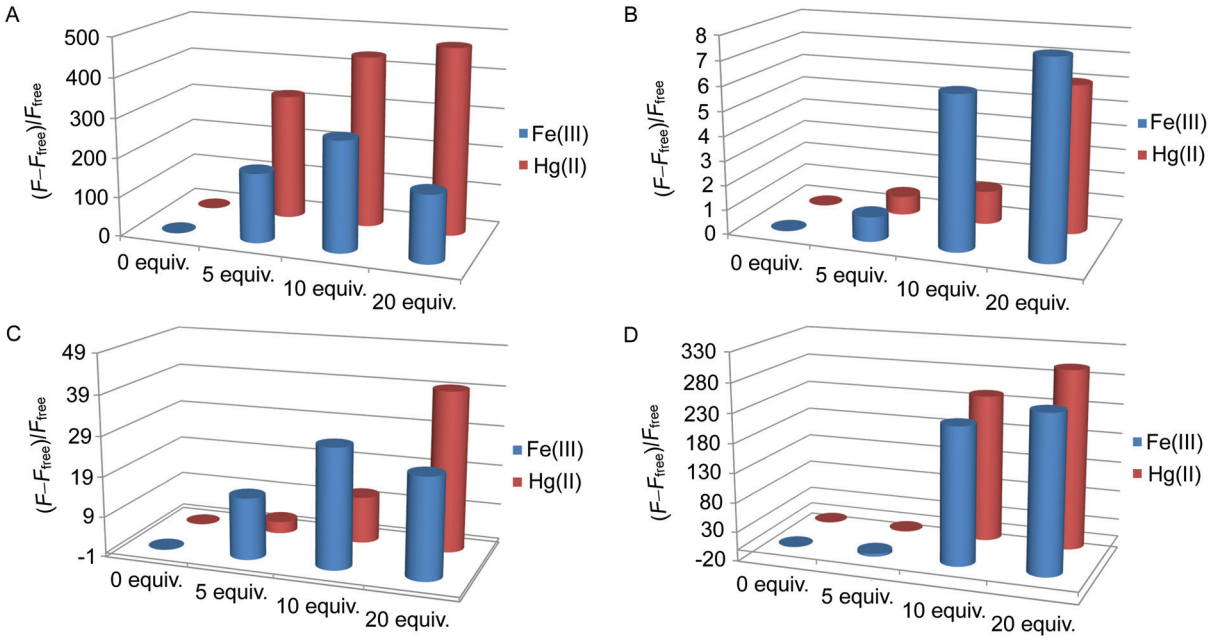



**Figure 3** The fluorescence intensity change profile of **1** (10 μmol•$L^{-1}$, back) and **2** (10 μmol•$L^{-1}$, front) in the absence and presence of $Fe^{3+}$ (blue) and $Hg^{2+}$ (red) (120 μmol•$L^{-1}$) in (A) MeOH, $\lambda_{ex}$=347 nm, $\lambda_{em}$=425 nm; (B) $H_2O$, $\lambda_{ex}$=330 nm, $\lambda_{em}$=475 nm; (C) MeOH/$H_2O$=1∶9, $\lambda_{ex}$=347 nm, $\lambda_{em}$=475 nm; (D) $CH_3CN$, $\lambda_{ex}$=338 nm, $\lambda_{em}$=423 nm.

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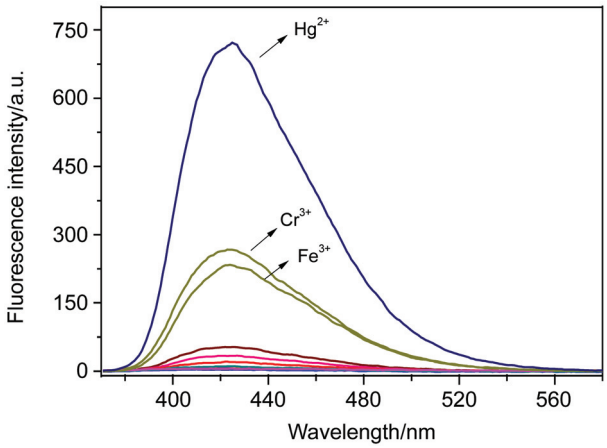


**Figure 4** Fluorescence spectra of **1** (10 μmol•L$^{-1}$) in the absence and presence of different metal ions (120 μmol•L$^{-1}$) in EtOH, $\lambda_{ex}$=347 nm.

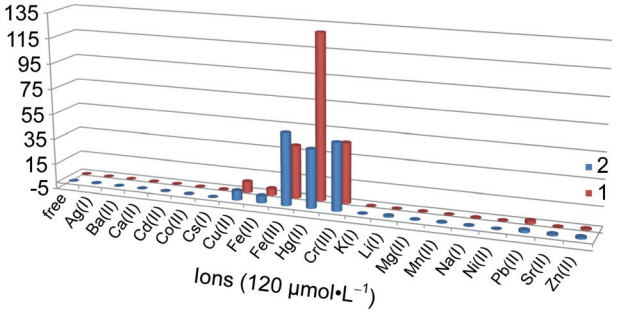


**Figure 5** The fluorescence intensity change profile of **1** (10 μmol•L$^{-1}$, back) and **2** (10 μmol•L$^{-1}$, front) in the absence and presence of different metal ions (120 μmol•L$^{-1}$) in EtOH, $\lambda_{ex}$=347 nm, $\lambda_{em}$=424 nm.

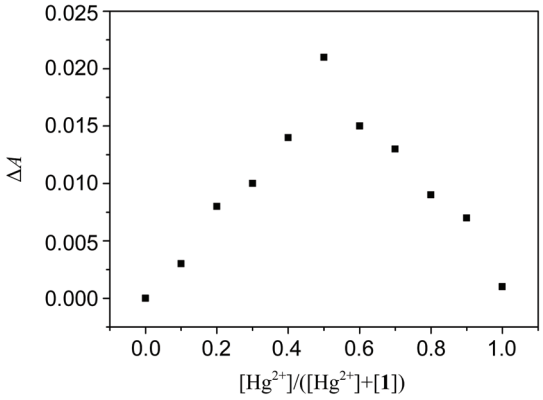


**Figure 6** Job's plot of **1** and $Hg^{2+}$ (the total concentration of **1** and $Hg^{2+}$ is 10 μmol•L$^{-1}$ in EtOH).

Through performing the UV/vis experiment in MeCN (Figure 9), we can find a long-wavelength charge transfer (CT) transition at $\lambda_{max}$=332 nm which was a typical coumarin CT absorption, and a second short-wavelength CT transition at $\lambda_{max}$=294 nm which belonged to the CT from the anilino moiety to the conjugated electron poor triazole group. Addition of $Hg^{2+}$ leads to a minor shift of $\lambda_{max}$ from 332 to 344 nm for the long-wavelength CT transition, and a complete disappearance of the short-wavelength CT absorption, which should be attributed to the removal of the aniline electron pair by binding to $Hg^{2+}$.

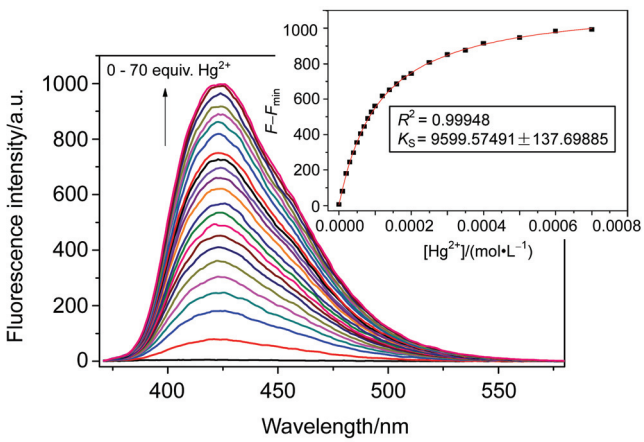


**Figure 7** Fluorescence spectral changes of **1** (10 μmol•L$^{-1}$) upon addition of $Hg(ClO_4)_2$ (0—70 equiv.) in EtOH. Inset: The nonlinear least-squares analysis of the differential intensity ($F$–$F_{min}$) to calculate the stability constant ($K_S$), $\lambda_{ex}$=347 nm.

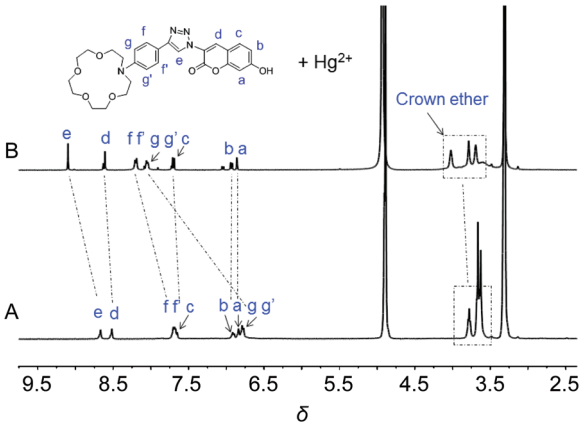


**Figure 8** Partial $^1$H NMR spectra (400 MHz, $CD_3OD$, 298 K) of (A) **1**, (B) **1**+1.0 equiv. $Hg(ClO_4)_2$.

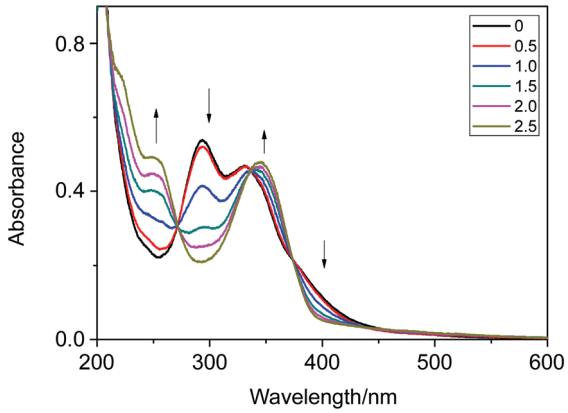


**Figure 9** Absorption spectra of **1** (20 μmol•L$^{-1}$) upon addition of $Hg(ClO_4)_2$ (0—2.5 equiv.) in $CH_3CN$.

Through the molecular energy minimization of **1** (Figure S14, Supporting Information), we can find a twist angle of ~30° between the coumarin and triazole

  

groups, and the anilino group is nearly coplanar with the triazole ring. In the structure, the twisting could result in a virtual spacer. Thus the 1,4-disubstitued-1,2,3-triazole ring results in an optimal preorientation of the two subunits, which can be used to realize a PET process.[14] In the unbound state, a fast excited-state PET process occurs from the planar anilinotriazole unit as an electron donor to the coumarin as an electron acceptor. As a result, the fluorescence of **1** is drastically quenched. Binding of $Hg^{2+}$ by the aza-15-crown-5 reduces the electron-donating potential of the anilinotriazole and "turns-on" the fluorescence by the suppression of the PET.

The $Hg^{2+}$ selectivity should partially come from the unique structure of the π-conjugated anilinotriazol-substituted coumarin fluoroionophore, and partially come from the aza-15-crown-5 receptor. Rather than the crown ether containing sulfur element, which was more popular in the reported $Hg^{2+}$ sensors, the aza-15-crown-5 was rarely used as the receptor in $Hg^{2+}$ sensor. The $Hg^{2+}$ selectivity was strongly affected by the solvents, which should be a synergistic effect from the change of solvent polarity and the binding abilities affected by the different solvation/hydration enthalpy of ions. It should be noticed that the Stokes shift increases (from 84 to 145 nm) when the solvent changed from EtOH to $H_2O$, which indicates that the emission is due to an allowed charge transfer transition.[15] Such a solvent-dependent emission behavior may also affect the fluorescent response toward the metal ions.

## Conclusions

In conclusion, we have designed and synthesized a "turn-on" fluorescent sensor which can give selectively response toward $Fe^{3+}$ or $Hg^{2+}$ in different solvents. Because $Hg^{2+}$ is toxic for human health but $Fe^{3+}$ exists in the human body, the detection toward these two kinds of ions should follow different criterions. For example, the development of $Fe^{3+}$ sensor should consider the binding preferences of the biochemically important transition metal ions such as $Zn^{2+}$ or $Cu^{2+}$ that can interfere with iron binding and transport at the cellular level.[16] From this point of view, the result presented here offers an effective strategy for designing a "turn-on" fluorescent sensor with high selectivity for $Fe^{3+}$ in water. Moreover, it can also work well in alcohol as a $Hg^{2+}$ sensor, when considering $Fe^{3+}$ is not a common interference ion. Such a unique finding in the fluoroionophore **1** may offer a promising design concept for the novel metal ion sensors with high sensing specificity and multiple functions.

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