

# A Rhodamine-Cyclen Conjugate as Chromogenic and Fluorescent Chemosensor for Copper Ion in Aqueous Media

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**Abstract** A novel compound **1** containing rhodamine B and macrocyclic groups has been synthesized. It was found to exhibit a reversible colorimetric response, high selectivity and sensitivity for Cu(II) ion over other commonly coexistent metal ions. The colorimetric and fluorescent response to Cu(II) can be conveniently detected even by the naked eye, which provided a facile method for visual detection of Cu(II). Approximate 71 and 53-fold enhancement in the absorbance at about 557 nm and fluorescence intensity at about 580 nm were estimated when Cu(II) ion was added to the aqueous media of compound **1**. The detection limit was calculated to be 2  $\mu\text{M}$ .

**Keywords** Fluorescent sensor · Rhodamine · Cu(II) · Macrocyclic · Chemosensors

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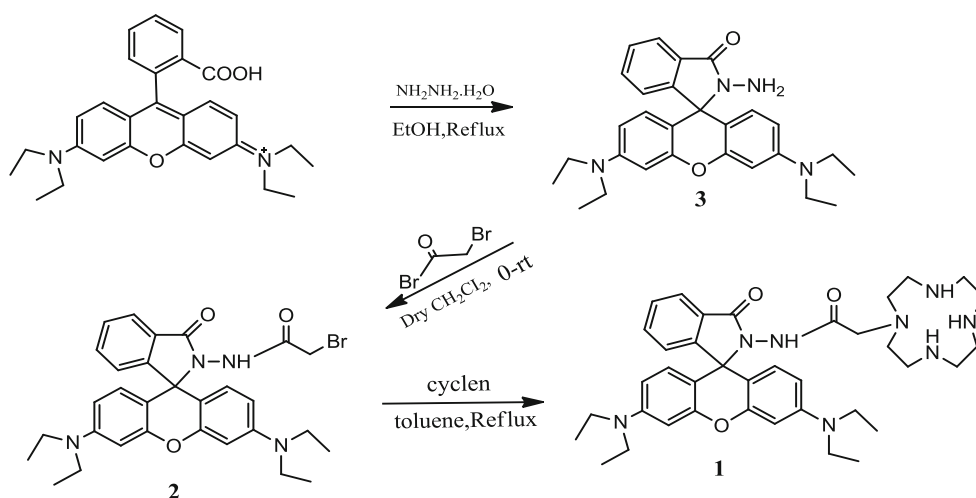
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## Introduction

Selective detection of transition metal ions has been of great interest because of their importance in biological and environmental processes [1–6]. Among transition metal ions, Cu(II) is the third most adequate and plays important roles in biological process. However, during the overloading conditions, copper exhibits toxicity and in that it causes neurodegenerative diseases [7, 8]. Thus, the quantitative detection of Cu(II) is of great importance for elucidating its complex physiological and pathological roles. Current methods for copper screening, including atomic absorption spectrometry (AAS) [9], inductively coupled plasma mass spectrometry (ICP-MS) [10], and inductively coupled plasma atomic emission spectrometry (ICP-AES) [11], often require expensive and sophisticated instrumentation or complex sample-preparation steps. Sensors based on the Cu(II)-induced changes in fluorescence would be more desirable, because it is less labor-intensive and highly sensitive. Generally, a typical sensor of this type is constructed by covalent linkage of three parts, namely, a receptor unit, a spacer and a signaling unit, though there are some examples of spacer-free probes also. These sensors molecules display completely different absorption/fluorescence signals compared to free sensors in solution after binding with metal ions which enables the quantitative determination of Cu(II) ions [12–15].

Rhodamine derivatives are nonfluorescent and colorless when existing in spirocyclic forms, whereas their ring-opening structures would give rise to strong fluorescence emission and pink color [16–22]. Owing to its high selectivity and direct visual perception, particularly

**Scheme 1** The synthesis route of **1**

with the nature of molecular switches, photochemical sensors that are useful for the detection of physiologically relevant metal ions have attracted a great deal of attention. Several fluorescent sensors based on rhodamine have been synthesized and show good selective recognition for  $\text{Cu}(\text{II})$  [23–30]. However, in most cases fluorescence changes can only be observed in non-aqueous solvent [31–33], there is still an intense demand for new efficient  $\text{Cu}^{2+}$  optical chemosensors, especially those that can work in aqueous solution with high selectivity and sensitivity. Herein we reported a new rhodamine derivative **1** containing a hydrazide rhodamine B moiety and a cyclen (1,4,7,10-tetraazacyclododecane), the hydrazide rhodamine B acted as a  $\text{Cu}(\text{II})$  selective reversible fluorescent sensor in aqueous media. Cyclen (1,4,7,10-tetraazacyclododecane) is one of the most extensively studied ligands and can coordinate strongly with many transition metal cations [22]. Derivative **1** showed reversible, highly selective and

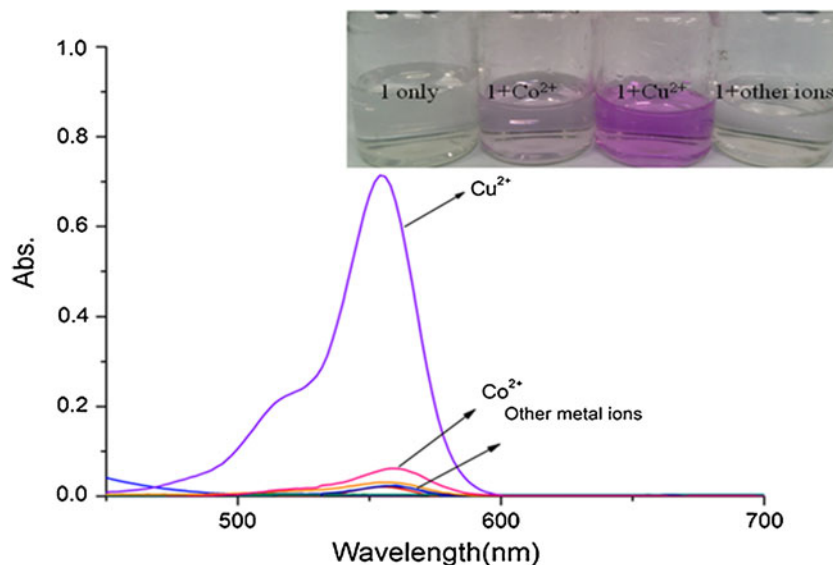
sensitive recognition toward  $\text{Cu}^{2+}$  over other examined metal ions in aqueous media.

### Experimental Section

The fluorescence spectra were recorded in  $1 \times 1$  cm quartz cells on a HITACHI F-4500 fluorescence spectrophotometer. Absorption spectra were measured on a Lambda 35 UV/VIS spectrometer, Perkin Elmer precisely. ESI mass spectra were carried out on an HPLC Q-ToF HR-MS spectrometer (Waters Micromass) by using methanol as mobile phase.  $^1\text{H}$  NMR spectra were measured on a Bruker DMX-400 spectrometer at 400 MHz in  $\text{CDCl}_3$ . All the experiments were carried out at room temperature.

All the reagents were purchased from commercial suppliers (Aldrich and Alfa Aesar Chemical Co. Ltd.). All chemicals used in this work were of analytical grade and

**Fig. 1** UV–vis spectrum of **1** (10  $\mu\text{M}$ ) in  $\text{CH}_3\text{OH}-\text{H}_2\text{O}$  (1:1, v/v) with different metal ions (300  $\mu\text{M}$ ). Insert: the photo of sensor **1** with different metal ions



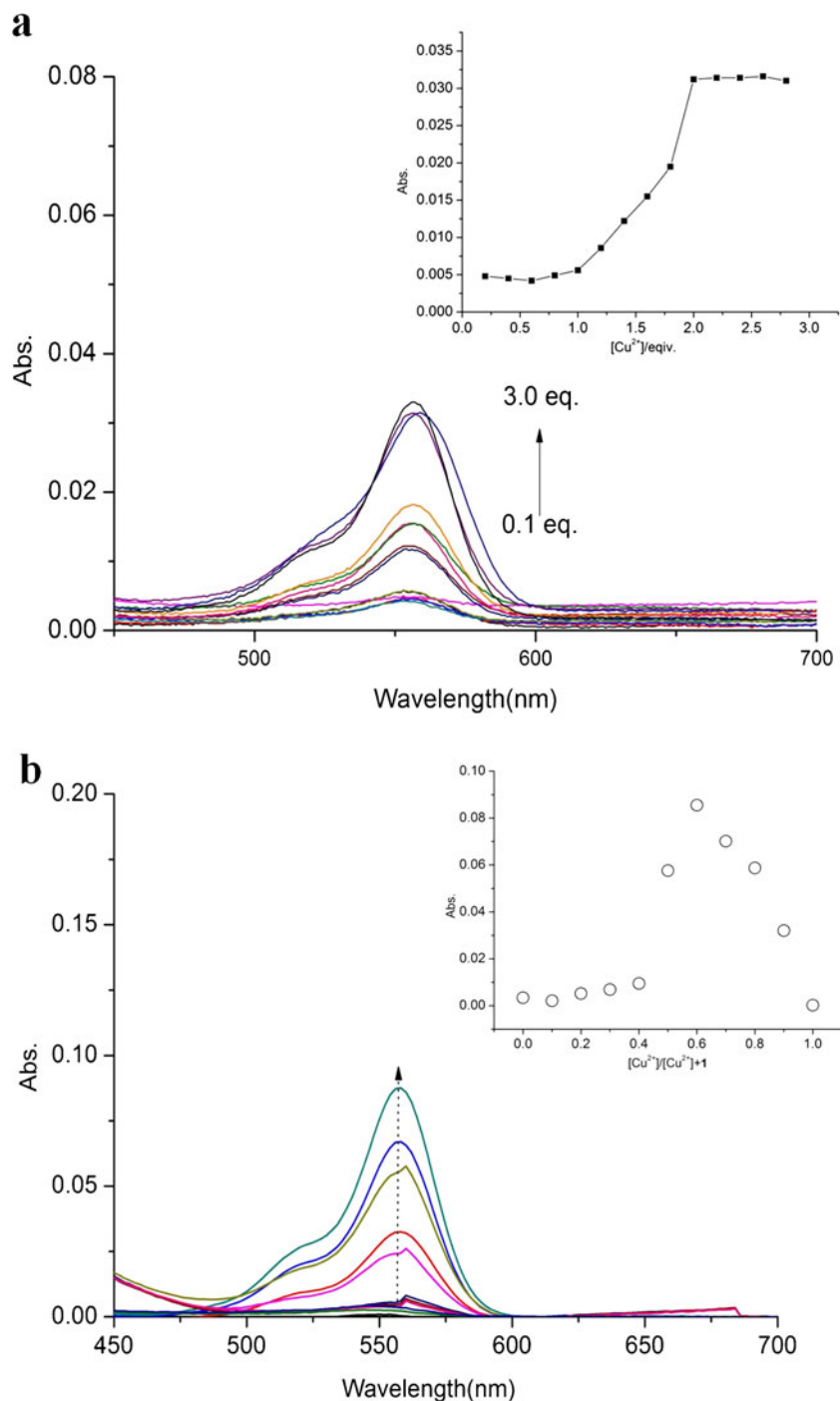
used without further purification. Double distilled water was used all through the experiment.

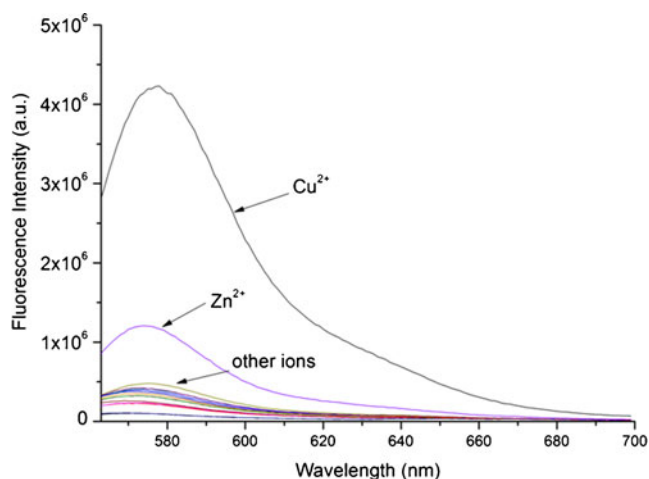
Chloride salts of metal ions ( $K^+$ ,  $Na^+$ ,  $Ca^{2+}$ ,  $Mg^{2+}$ ,  $Ba^{2+}$ ,  $Zn^{2+}$ ,  $Fe^{2+}$ ,  $Fe^{3+}$ ,  $Mn^{2+}$ ,  $Pb^{2+}$ ,  $Cu^{2+}$ ,  $Co^{2+}$ ,  $Ni^{2+}$ ,  $Cd^{2+}$ ,  $Cr^{3+}$ ,  $Hg^{2+}$ ) and the nitrate salt of  $Ag^+$  ions were used to evaluate the metal ion binding properties by synthesized compound. The stock solution of **1** ( $1.0 \times 10^{-3}$  mol/L) was prepared by dissolving the accurately weighed compound in methanol.

Rhodamine B lactam **3** was synthesized from rhodamine B and hydrazine according to reported method [34, 35].

**Synthesis of Compound 2** To a stirred solution of bromoacetyl bromide (912 mg, 2 mmol) and  $K_2CO_3$  (414 mg, 3 mmol) in anhydrous  $CH_2Cl_2$  (30 mL), a solution of compound **3** (912 mg, 2 mmol) in 15 ml  $CH_2Cl_2$  was added dropwise. The reaction mixture was stirred at room temperature for 6 h and then treated with 2 %  $NaHCO_3$  (30 mL  $\times$  3). The solution

**Fig. 2 a** Changes in absorption spectra of **1** ( $1 \mu M$ ) in  $CH_3OH-H_2O$  (1:1, v/v) solutions with various amounts of  $Cu^{2+}$  ions (0–3 equiv.). *Inset*: the titration profile evaluated from the absorption at 557 nm. **b** Different UV–vis spectra of derivative **1** upon addition of  $Cu^{2+}$ . The *inset picture* shows the Job's plot at about the absorbance 557 nm ( $[1]+[Cu^{2+}]=50 \mu M$ )



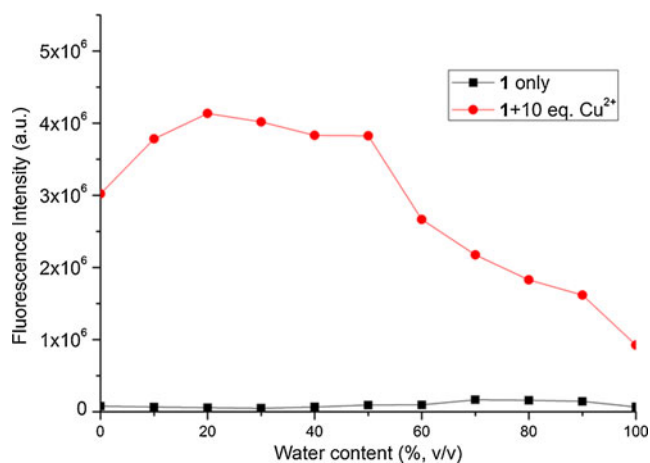
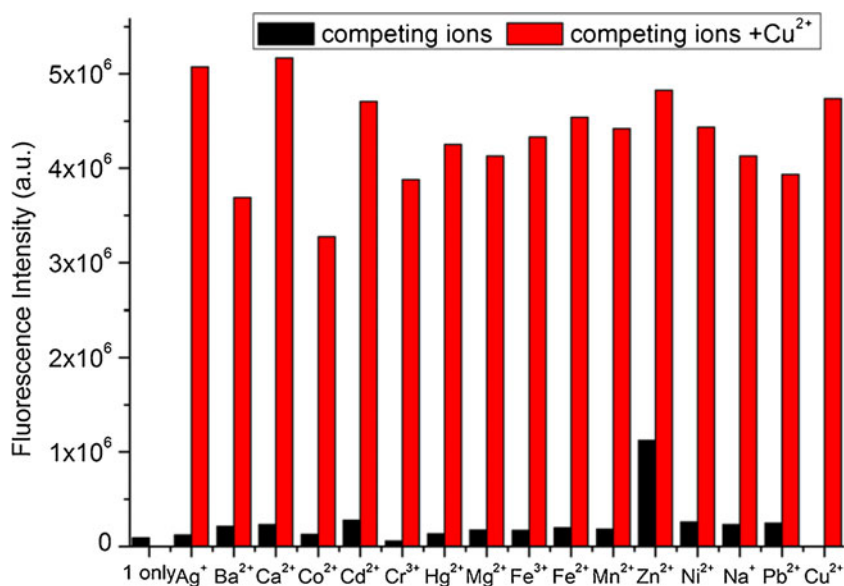


**Fig. 3** Fluorescence spectra of **1** (10  $\mu\text{M}$ ) in the absence and presence of 100  $\mu\text{M}$  different metal ions. Excitation was performed at 552 nm

was extracted with  $\text{CH}_2\text{Cl}_2$ , and the combined extracts were washed with brine and dried over  $\text{MgSO}_4$ , and then the solvents were removed. The crude product obtained was a pink powder that can be used for next step without further purification (890 mg, 77.3 % yield).

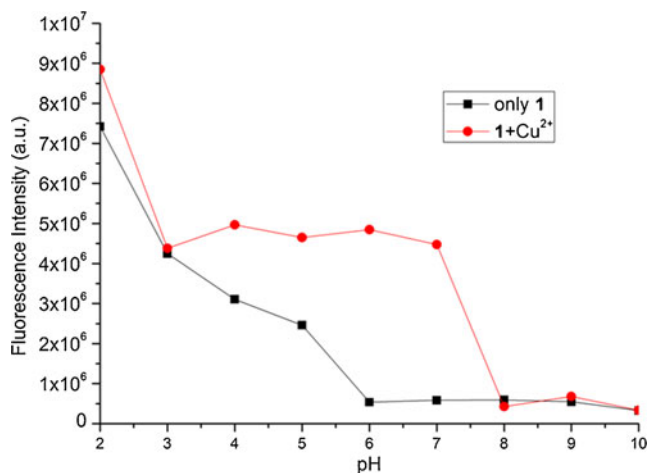
**Synthesis of Compound 1** Compound **2** (300 mg, 0.52 mmol) and cyclen (636 mg, 3.7 mmol) were refluxed in toluene (40 mL) for 48 h under dry  $\text{N}_2$ . The resulting solution was concentrated by evaporation and dissolved in ethanol (5 mL). Concentrated HCl was added to the solution, and the precipitated HCl salt of the unreacted cyclen was removed by filtration. The residue was concentrated by evaporation, dissolved in

**Fig. 4** Fluorescence intensity (at 580 nm) of **1** (10  $\mu\text{M}$ ) upon the addition of 10  $\mu\text{M}$   $\text{Cu}^{2+}$  in the presence of 10  $\mu\text{M}$  background metal ions in  $\text{CH}_3\text{OH}$ – $\text{H}_2\text{O}$  (1:1, v/v). Excitation was performed at 552 nm



**Fig. 5** Effect of the water content on the fluorescence intensity (at 580 nm) of **1** (10  $\mu\text{M}$ ) in the absence and presence of  $\text{Cu}^{2+}$  (100  $\mu\text{M}$ )

water (10 mL), and washed with  $\text{CHCl}_3$ . An aqueous NaOH solution (5 M, 15 mL) was added to the solution and extracted with  $\text{CH}_2\text{Cl}_2$  (10 mL  $\times$  5). The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated by evaporation. The residue was dried in vacuo at 353 K for 8 h, affording **1** as a yellow powder (220 mg, 64 %). ESI-MS: calcd. 668.4, found  $m/z$  669.5 [ $\text{M} + \text{H}$ ] $^+$ , 691.4 [ $\text{M} + \text{Na}$ ] $^+$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ (ppm)=1.14 (12H, t,  $\text{NCH}_2\text{CH}_3$ ,  $J=7.1$  Hz), 2.58 (16H, m, cyclen-H), 3.06 (2H,  $\text{COCH}_2$ ), 3.33 (8H, q,  $\text{NCH}_2\text{CH}_3$ ,  $J=7.1$  Hz), 6.28 (4H, m, Ar-H), 6.61 (2H, d, Ar-H,  $J=5.2$  Hz), 7.15 (1H, d, Ar-H,  $J=6.4$  Hz), 7.49 (2H, m, Ar-H), 7.91 (1H, d, Ar-H,  $J=6.8$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ (ppm) =12.6, 46.5, 54.6, 57.8, 66.1, 97.2, 105.4, 107.6, 123.2,



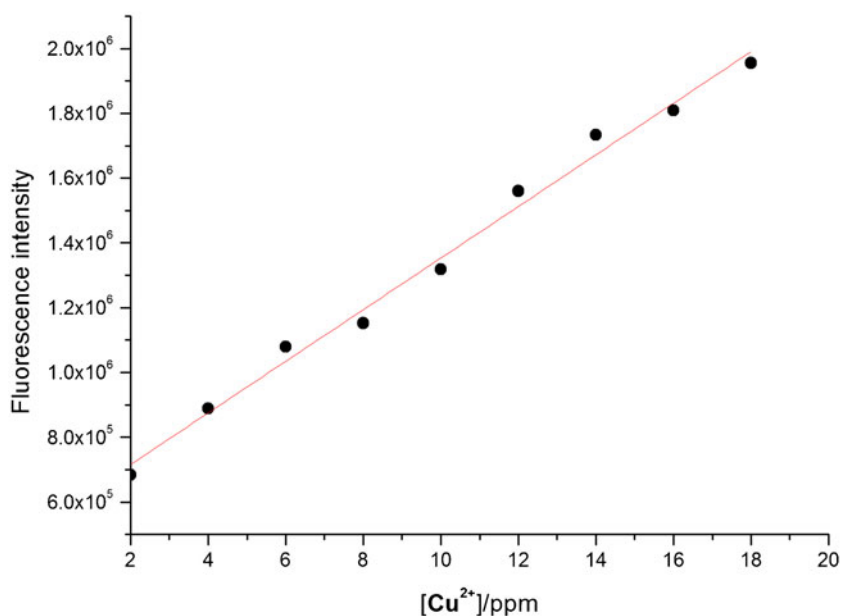
**Fig. 6** Fluorescence intensity (580 nm) of free probe **1** (10  $\mu\text{M}$ ) and in the presence of 10 equiv.  $\text{Cu}^{2+}$  in  $\text{CH}_3\text{OH}/\text{Tris-HCl}$  buffer (1:1, v/v) solutions with different pH conditions

124.2, 128.4, 129.9, 132.9, 148.8, 150.8, 154.2, 164.7, 170.6. HR-MS for  $\text{C}_{38}\text{H}_{53}\text{N}_8\text{O}_3^+$   $[\text{M} + \text{H}^+]$  calcd. 669.4235, found  $m/z$  669.4238.

## Results and Discussion

As shown in Scheme 1, compound **1** was prepared in good yield in three steps. Rhodamine B lactam **3** was synthesized from rhodamine B and hydrazine. Compound **2** was synthesized by reacting **3** with bromoacetyl bromide in the presence of  $\text{K}_2\text{CO}_3$ . Target compound **1** can be obtained by conjugating **2** with cyclen in toluene. Compound **1** was colorless and found to be very stable in methanol for more than one week,

**Fig. 7** The fluorescence intensity (580 nm) of compound **1** (1  $\mu\text{M}$ ) as a function of the  $\text{Cu}(\text{II})$  concentration (2–18  $\mu\text{M}$ ). Excitation was at 552 nm



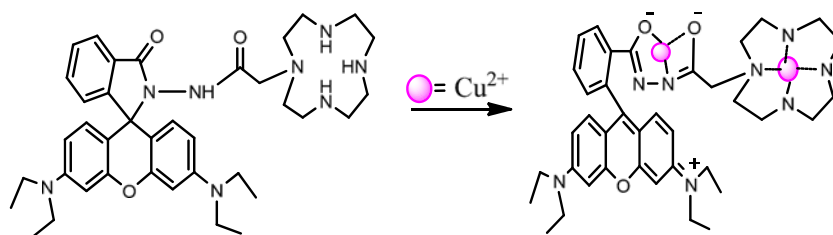
and this indicated that the presence of ring-closed spirolactone predominantly.

As shown in the Fig. 1, compound **1** (10  $\mu\text{M}$ ) exhibited only very weak bands over 500 nm and appeared colorless in the absence of metal ions indicating that only the ring-closed form is present. However, after addition of 30 equiv  $\text{Cu}^{2+}$  into solution immediately resulted in a significant enhancement of absorbance at about 557 nm (71-fold enhancement) simultaneously the color change into clear pink (Fig. 1, inset). Under the identical condition, no obvious response could be observed upon the addition of other ions including  $\text{Zn}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Hg}^{2+}$ ,  $\text{Ba}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Fe}^{2+}$ ,  $\text{K}^+$ ,  $\text{Ag}^+$ ,  $\text{Cr}^{3+}$  and  $\text{Na}^+$ . Only a little increase of absorbance at 557 nm was also detected after addition of  $\text{Co}^{2+}$  owing to its low binding affinity to **1**. The results demonstrated that compound **1** was characteristic of high selectivity toward  $\text{Cu}^{2+}$  over other competitive metal ions.

To further investigate the binding mode of derivative **1** and  $\text{Cu}(\text{II})$ , experiments of absorption spectra titration was carried out. As illustrated in Fig. 2(a), upon the addition of  $\text{Cu}(\text{II})$  ions, the absorbance of absorption band peaked at 557 nm increased steadily at first, and then reached its maximum when the amount of added  $\text{Cu}(\text{II})$  was above 2.0 equiv. The absorbance was constant. The data revealed the binding of compound **1** with  $\text{Cu}(\text{II})$  was most probably a 1:2 stoichiometry. The data of Job's method using a total concentration of 50  $\mu\text{M}$  of **1** and  $\text{Cu}(\text{II})$ , when the molecular fraction of  $\text{Cu}(\text{II})$  was close to 60 %, exhibited a maximum absorbance at 557 nm. This also suggested the 1:2 stoichiometry of **1**– $\text{Cu}(\text{II})$  complex (Fig. 2b).

The important feature of a chemodosimeter is its high selectivity towards the target compound over the other

**Scheme 2** Proposed possible binding mode of compound **1** with  $\text{Cu}^{2+}$



competitive cations. The spectral response of compound **1** (10  $\mu\text{M}$ ) to various metal ions and its selectivity for  $\text{Cu}(\text{II})$  in methanol–water solution are illustrated in Fig. 3. Excitation and emission were performed at 552/580 nm. Results revealed that probe **1** did not respond to alkaline or alkaline-earth metal ions, such as  $\text{Na}(\text{I})$ ,  $\text{K}(\text{I})$ ,  $\text{Mg}(\text{II})$ ,  $\text{Ca}(\text{II})$  and  $\text{Ba}(\text{II})$ . It either did not respond to or weakly responded to transition-metal or heavy-metal ions, such as  $\text{Cu}(\text{II})$ ,  $\text{Fe}(\text{III})$ ,  $\text{Co}(\text{II})$ ,  $\text{Mn}(\text{II})$ ,  $\text{Ni}(\text{II})$ ,  $\text{Pd}(\text{II})$ ,  $\text{Cd}(\text{II})$ ,  $\text{Ag}(\text{I})$  and  $\text{Hg}(\text{II})$ . Only a mild increase of fluorescence at 580 nm was detected after addition of  $\text{Zn}(\text{II})$  (100  $\mu\text{M}$ , causing 12-fold FE) owing to its low binding affinity to **1**. The fluorescence enhancement change over other metal ions indicated that compound **1** has an outstanding selectivity for  $\text{Cu}(\text{II})$  (53-fold enhancement). Moreover, the competitive experiments also confirmed that the background metal ions showed very low interference with the detection of  $\text{Cu}^{2+}$  in  $\text{CH}_3\text{OH}-\text{H}_2\text{O}$  (1:1, v/v) (Fig. 4). Also, it was investigated that the fluorescence response of **1** toward  $\text{Cu}^{2+}$  in the presence of various coexistent anions such as  $\text{Cl}^-$ ,  $\text{NO}_3^-$ ,  $\text{SO}_4^-$ ,  $\text{Ac}^-$  and  $\text{ClO}_4^-$ . It is gratifying to note that all the tested anions have no interference with the detection of  $\text{Cu}^{2+}$  in  $\text{CH}_3\text{OH}-\text{H}_2\text{O}$  (1:1, v/v) (Fig. S5).

The effect of water content on the fluorescent measurement of  $\text{Cu}^{2+}$  was investigated and the result was shown in Fig. 5. As shown in Fig. 5, it can be observed that the fluorescence signal reached its maximum value at about 0–50 % of water. Considering to the practical application, we selected 50 % aqueous methanol media for the fluorimetric method.

In order to investigate the influence of the different acid concentration on the spectra of probe **1** and find a suitable pH span in which probe **1** can selectively detect  $\text{Cu}^{2+}$  efficiently, an acid titration experiment was performed. As shown in Fig. 6, the fluorescence titration curve of free sensor in  $\text{CH}_3\text{OH}/\text{Tris}-\text{HCl}$  buffer did not show obvious characteristic color of rhodamine between pH 6.0 and 10.0, suggesting that spirocyclic tautomer of sensor **1** was insensitive to the pH changes in this range. However, the addition of  $\text{Cu}^{2+}$  led to the fluorescence enhancement over a comparatively wide pH range (6.0–7.0), which is attributed to opening of the rhodamine ring. Consequently, sensor **1** may be used to detect  $\text{Cu}^{2+}$  in approximate physiological conditions.

Generally, one of the most important and useful applications for a fluorescent sensor is the detection of metal ions. Under optimal conditions, the linear regime for the fluorescence

intensity response was between 1 and 20  $\mu\text{M}$ , and the detection limit for  $\text{Cu}(\text{II})$  was as low as 2.0  $\mu\text{M}$  ( $R^2=0.989$ ) from probe **1** blank solutions, establishing that **1** was capable of distinguishing safe and toxic levels of  $\text{Cu}^{2+}$  in drinking water according to China SA standard [36] (Fig. 7).

As all known, the reversibility was an important property for an excellent probe. Thus, the EDTA-adding experiments were conducted to examine the reversibility of the probe **1**. The absorbance decreased when EDTA was added into the solution containing **1** and  $\text{Cu}(\text{II})$  (Fig. S6). Besides, the color also changed from pink to colorless. When  $\text{Cu}(\text{II})$  was added to the system again, the signals were quickly reproduced and the colorless solution turned to pink. These indicated that probe **1** can reversibly coordinate with  $\text{Cu}(\text{II})$ .

It is well-known that cyclen coordinates with one metal cation [37, 38]; however, according to the above Job's plot and absorption spectra titration experimental results, the spirocycle opening of **1** required two  $\text{Cu}^{2+}$ . This meant that coordination of one  $\text{Cu}^{2+}$  didn't lead to spirocycle opening, and coordination of the second  $\text{Cu}^{2+}$  did. Herein, according to our knowledge [22, 39], we broach a conceivable mechanism of  $\text{Cu}^{2+}$  complex with **1** (Scheme 2). From the molecular structure and the spectral results of **1**, it is concluded that the addition of the  $\text{Cu}^{2+}$  induced the N atom of spirocyclic lactam to attack the C atom of carbonyl, and thus a ring opening of the spirocyclic lactam of rhodamine took place.

## Conclusion

In summary, we describe a new rhodamine-based probe **1**, which exhibited prominent absorption and fluorescence enhancements upon  $\text{Cu}(\text{II})$  addition with particular selectivity and excellent sensitivity, and is suitable for “naked-eye” detection. The molecular design might greatly contribute to the development of more efficient and useful probes based on rhodamine platform. The spectral response of **1** toward  $\text{Cu}(\text{II})$  was demonstrated to be reversible. It may therefore be applicable as rhodamine-based OFF-ON type fluorescent chemosensor for  $\text{Cu}(\text{II})$ .

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