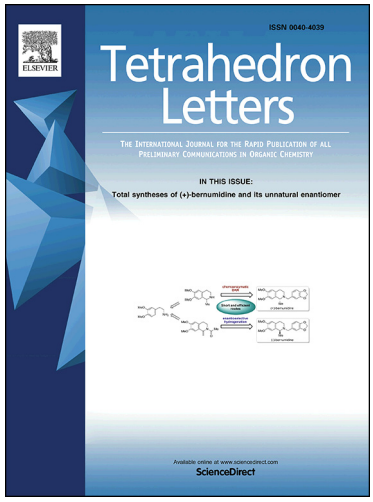

Single chemosensor for sensing multiple analytes: selective fluorogenic detection of Cu^{2+} and Br^-

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Single chemosensor for sensing multiple analytes: selective fluorogenic detection of Cu^{2+} and Br^-

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Abstract

A tripodal receptor **R1** with a combination of nitrogen and oxygen-based binding sites was designed and used for the selective determination of Cu^{2+}. The fluorescence emission profile of **R1** in the presence of Cu^{2+} showed a marked enhancement in fluorescence intensity, indicating high selectivity among other metal ions. The **R1**–Cu^{2+} complex was further explored as a sensor for anion detection. Upon addition of Br^-, switching to a fluorescence "off" state was observed. The Br^- selectivity of the complex over a wide range of concentrations was observed via titrimetric analysis through changes in the emission spectra.

Keywords: tripodal, copper, bromide, fluorescence, chemosensor, receptor

1. Introduction

The quantitative and qualitative analysis of elements in the environment is important to human health [1]. Copper is an essential element required in trace amounts for many living organisms to perform normal physiological functions [2]. It is an integral part of many enzymes that perform critical physiological activities. For example, mitochondrial electron transport and melanin production are highly regulated, with copper-based enzymes playing an active part [3]. However, while copper is beneficial within certain concentrations, it is considered toxic at higher concentrations [4]. Owing to its typical redox behavior, copper participates in reactions that ultimately produce reactive oxygen species, leading to the deterioration of cellular machineries including membranes and DNA components [5]. Furthermore, abnormal copper concentrations in plasma are frequently observed under leukemic conditions [6].

Determination of halide ions is an important research topic for sustainable development because of their many industrial applications, as well as their considerable environmental and biological impacts [7]. Bromide ions are found in diverse sources, including fresh and marine water, and many biological fluids. Exposure to bromide ions may cause various health problems including skin conditions, tissue damage, respiratory system dysfunction, and cancer induction [8].

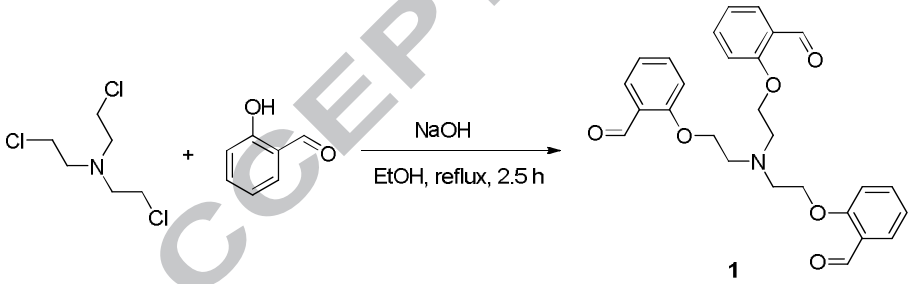
Various analytical methods have been developed for the detection of cations and anions [9]. These strategies include designing organic molecules with cation binding affinity to form a receptor–cation complex, which tends to interact with a particular anion, resulting in ion-pair recognition. Herein, upon metal binding, the electronic distribution and structural aspects of the receptors are modified, which can be observed by spectroscopic and conductometric techniques [10]. Fluorescence spectroscopic methods are frequently used because they are fast, easy, and economical [11]. The recognition of anions typically depends on hydrogen bonding, whereby there is competition between an anion and a polar solvent [12]. Ion-pair recognition provides scope for additional electrostatic interactions, improving the binding affinity for the analyte.

Several tripodal receptor systems have been reported and fabricated with three arms to which ligating groups were attached [13]. The selectivity of such tripodal receptors generally depends on the rigidity of their arms, the cavity size, and the directional orientation of binding groups [14–16]. Compared with monopodal or dipodal receptors, the typical structural features of tripodal receptors include their enhanced chelating effect, strong binding affinity, and easy tunability towards a specific metal ion [17,18]. In this study, to take advantage of these properties, a tripodal receptor was developed for the detection of Cu^{2+} and Br^{-}. Only a few receptors have been reported for the detection of Br^{-}, due to its lack of suitable binding sites, low charge density, and weak tendency to form hydrogen bonds [19–21]. Therefore, fast, reliable, and economical methods for the detection of copper and bromide ions are in high demand.

2. Results and Discussion

*2.1 Synthesis of **R1***

Compound **1** was synthesized by the reaction of tris(2-chloroethyl)amine with salicylaldehyde in the presence of NaOH under reflux [22]. **R1** was obtained by a condensation of compound **1** with *p*-toluenesulfonyl hydrazide in the presence of a catalytic amount of $Zn(ClO_4)_2 \cdot 6H_2O$ at room temperature, and was characterized by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, and ESI-MS and elemental analysis (Scheme 1).



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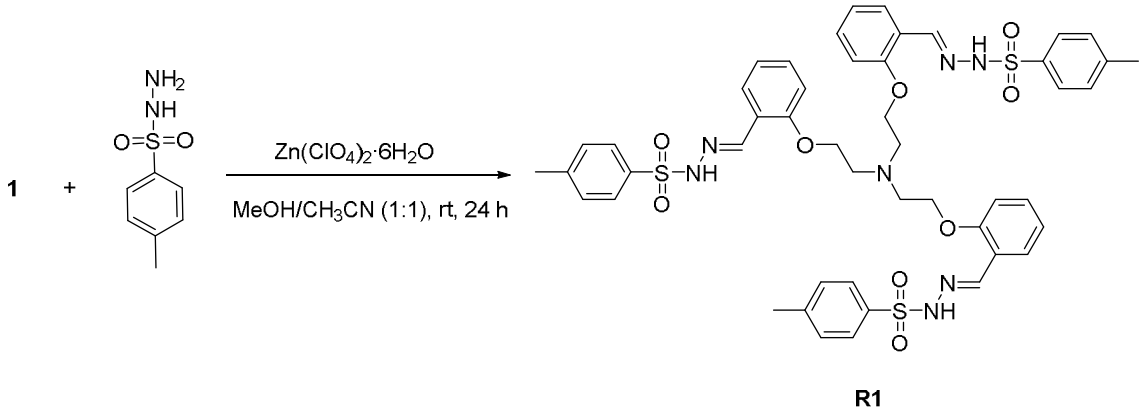


Scheme 1. Synthesis of tripodal **R1**.

2.2 Cation Binding Studies

The UV-vis spectrum of **R1** showed absorption bands at 270 and 315 nm. The fluorescence emission profile of **R1** was recorded with excitation at 270 nm, and exhibited an emission band at 415 nm. All spectroscopic studies were performed in acetonitrile. UV-vis absorption and fluorescence spectroscopic methods were used to examine the binding affinity of **R1** towards various metal ions (Na^+, K^+, Ag^+, Ba^{2+}, Ca^{2+}, Mg^{2+}, Cd^{2+}, Co^{2+}, Ni^{2+}, and Zn^{2+}) as nitrate salts. No major changes in the absorption spectra were observed in the presence of any of the metal ions, as shown in Figure S1. On the other hand, the fluorescence spectrum of **R1** showed enhanced fluorescence intensity upon the addition of Cu^{2+}. The intensity of the emission band at 415 nm decreased upon the addition of Cu^{2+}, while new emission bands at 310 and 446 nm were observed with 10-fold enhancement (Figure 1 and S2), displaying the selectivity of **R1** towards Cu^{2+}. The fluorescence enhancement of **R1** may be attributed to chelation of **R1** with Cu^{2+}, which increases the rigidity of the molecular assembly, resulting in chelation-enhanced fluorescence [23,24]. To determine the binding stoichiometry, Job's plot was drawn (Figure S3A) [25], revealing a 1:1 stoichiometry for the complex formed between **R1** and Cu^{2+}. The binding stoichiometry of was further supported by ESI-mass spectrometry analysis. A peak at m/z = 1028.14 was assigned to [**R1** + Cu^{2+}] (calcd. m/z = 1028.22) (Figure S3B). Upon the successive addition of Cu^{2+} (0–10 equiv.) to a 5 μM solution of **R1**, the emission bands at 310 and 446 nm gradually increased in intensity (Figure 2). A calibration curve for quantitative determination of Cu^{2+} with **R1** was constructed, as shown in Figure 3.

R1 exhibited a good linear correlation for concentration (0–20 µM) vs. fluorescence intensity at 310 nm, with a correlation coefficient $R^2 = 0.99$, indicating that **R1** is a suitable receptor for the quantitative estimation of Cu^{2+}. A Benesi–Hildebrand plot was used to determine the stability constant of Cu^{2+} binding, which was found to be $(1.4 \pm 0.2) \times 10^4$ M^{-1} (Figure S4) [26]. The detection limit of **R1** for Cu^{2+} was found to be 4.60 µM [27], which is significantly lower than the concentration recommended by the World Health Organization guideline (31.5 µM) for drinking water (Figure 4) [28]. This result indicates that **R1** is sensitive enough to monitor the Cu^{2+} concentration in water. Response time is also an important factor in determining analytes. The response time of **R1** towards Cu^{2+} was measured by studying the emission profile at different time intervals, indicating that 180 s was long enough to sense Cu^{2+} (Figure S5). The effect of pH on the fluorescence changes of **R1** towards Cu^{2+} was investigated at different pH values. The optimum fluorescence behavior of **R1** was observed at a range of pH 6.5-8 (Figure S6). To evaluate the possible interference of other cations with the Cu^{2+} sensing ability of **R1**, competitive binding studies were performed in the presence of potential interfering metal ions. The results are presented in Figure 5. No significant changes in fluorescence intensity at 310 nm were observed, confirming that **R1** displayed good Cu^{2+} recognition ability even in the presence of other metal ions.

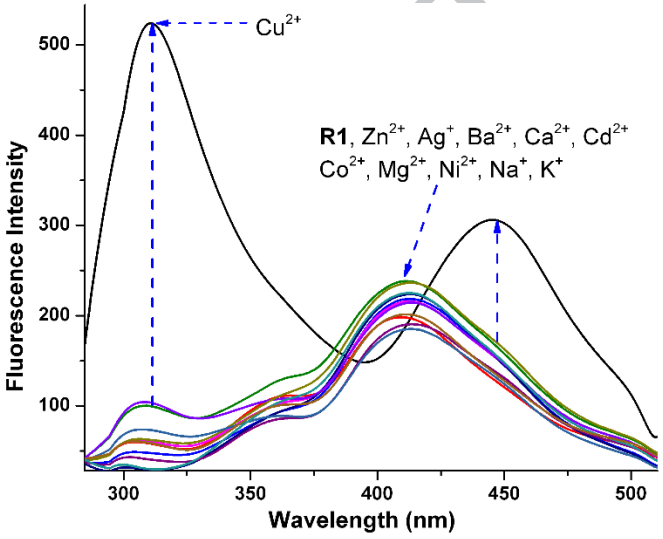


Figure 1. Fluorescence intensity of **R1** in CH_3CN (5 µM) upon addition of a metal salt (10 equiv.) excited at 270 nm.

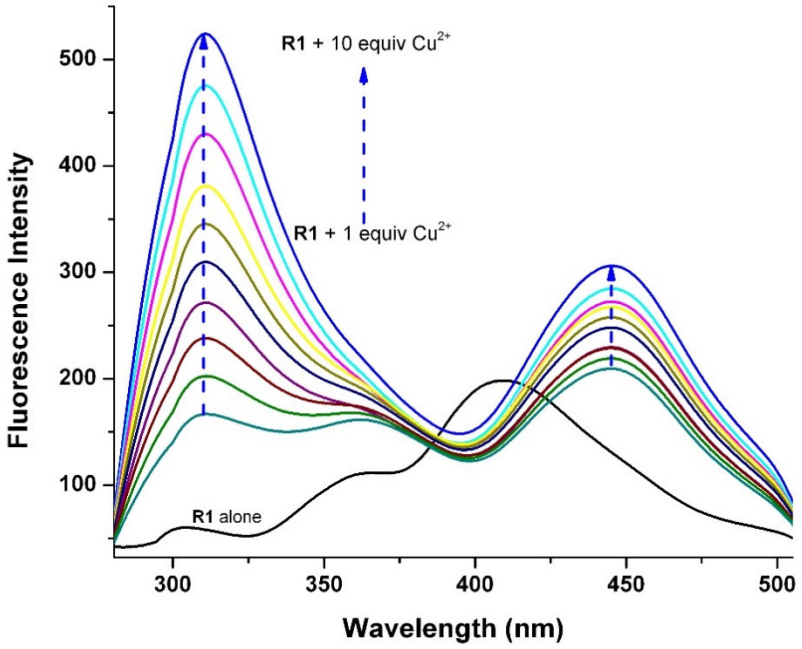


Figure 2. Changes in fluorescence intensity of **R1** (5 μM) upon successive additions of Cu^{2+} (0–10 equiv.).

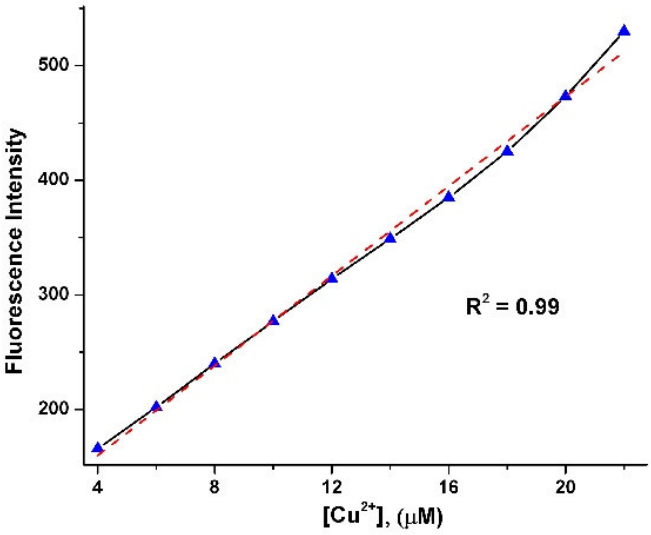


Figure 3. Plot of fluorescence intensity at 310 nm as a function of the concentration of Cu^{2+}.

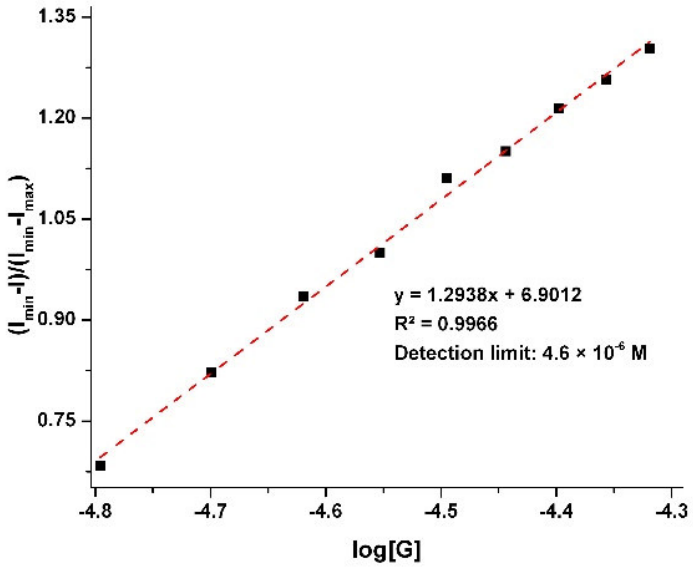


Figure 4. Calculated detection limits for the estimation of Cu^{2+} by **R1**.

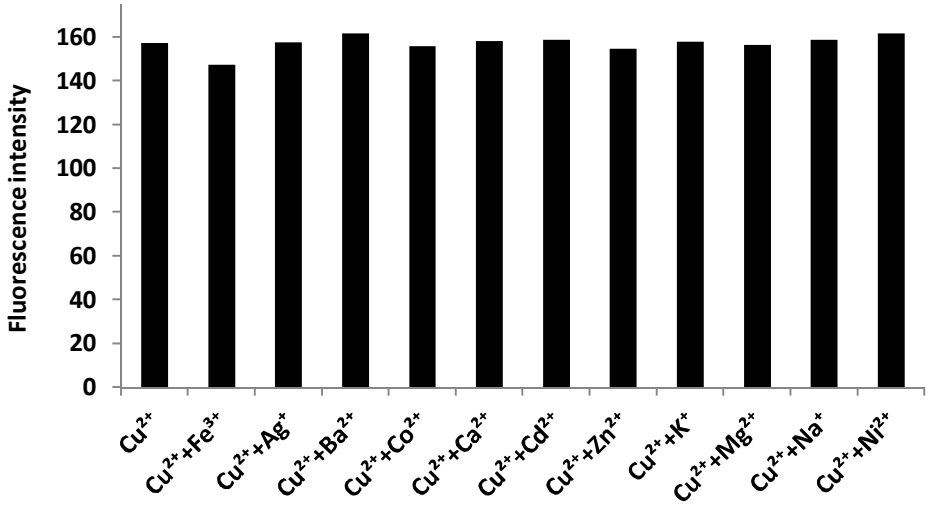


Figure 5. Fluorescence responses of **R1** (5 μM) to Cu^{2+} (3 equiv.) in the presence of equivalent amounts of other metal ions.

2.3 Anion Binding

To investigate the **R1**–Cu^{2+} complex as a secondary sensor for anion recognition, a solution of **R1**–Cu^{2+} was prepared *in situ* by the addition of 10 equiv. of Cu^{2+} to an **R1** solution (10 μM). The resulting solution was

screened with tetrabutylammonium salts of F^-, Cl^-, I^-, $H_2PO_4^-$, HSO_4^-, CN^-, NO_3^-, OAc^-, and ClO_4^- (Figure 6, S7 and S8). None of the anions examined showed spectroscopic changes in the complex. However, upon addition of Br^-, the fluorescence intensity of **R1**–Cu^{2+} was quenched drastically at 310 and 446 nm. The fluorescence intensity at 310 nm decreased to about 90% of that of **R1**–Cu^{2+}. The shape of the fluorescence spectrum at the final stage was similar to that at the beginning stage, indicating that **R1** was released from the complex by the binding of Cu^{2+} with Br^-, rather than by forming a new complex. It is noteworthy that even after adding 11 equiv. of Br^-, the fluorescence intensity of the solution could not regain the initial emission state of **R1**. This phenomenon might be attributed to the tight binding between **R1** and Cu^{2+}, resulting in incomplete displacement of Cu^{2+} from the complex. Job's plot analysis showed a 1:1 stoichiometry between **R1**–Cu^{2+} and Br^- (Figure S9). To investigate the binding properties of **R1**–Cu^{2+}, titration experiments were performed by successive additions of Br^- (0–11 equiv.) while monitoring the emission spectra (Figure 7). A linear regression in fluorescence intensity was observed in the range 0–50 μM, with a high correlation coefficient of $R^2 = 0.99$ (Figure 8). This result shows that **R1**–Cu^{2+} can be used as a probe for quantitative estimation of Br^-. The association constant of **R1**–Cu^{2+} was measured to be $(8.4 \pm 0.4) \times 10^3$ M^{-1} using the Benesi–Hildebrand equation (Figure S10). The detection limit for Br^- was calculated to be 9.33 μM (Figure 9). Competition experiments were performed in the presence of other anions to evaluate their interference in estimating Br^- with **R1**–Cu^{2+} (Figure 10). When **R1**–Cu^{2+} was treated with 10 equiv. of Br^- in the presence of equivalent amounts of other anions, no significant interference was observed.

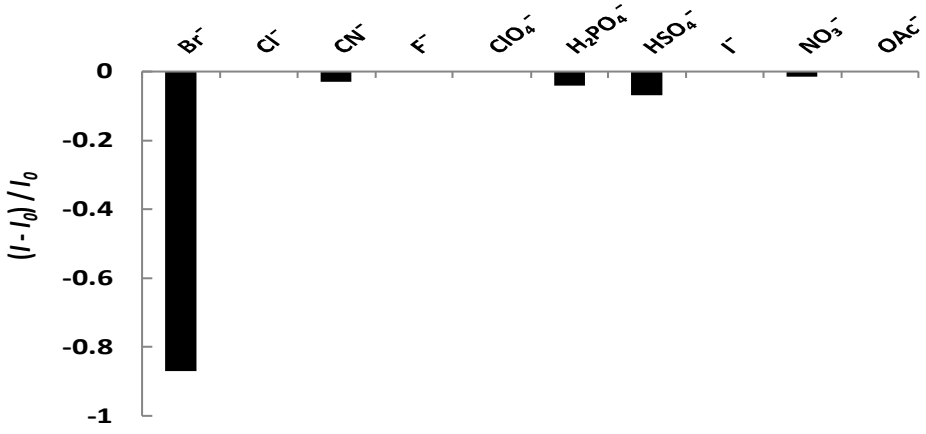


Figure 6. Anion selectivity profiles of **R1**–Cu^{2+} (5 μM) in the presence of various anions (10 equiv.) in CH_3CN at 310 nm, excited at 270 nm.

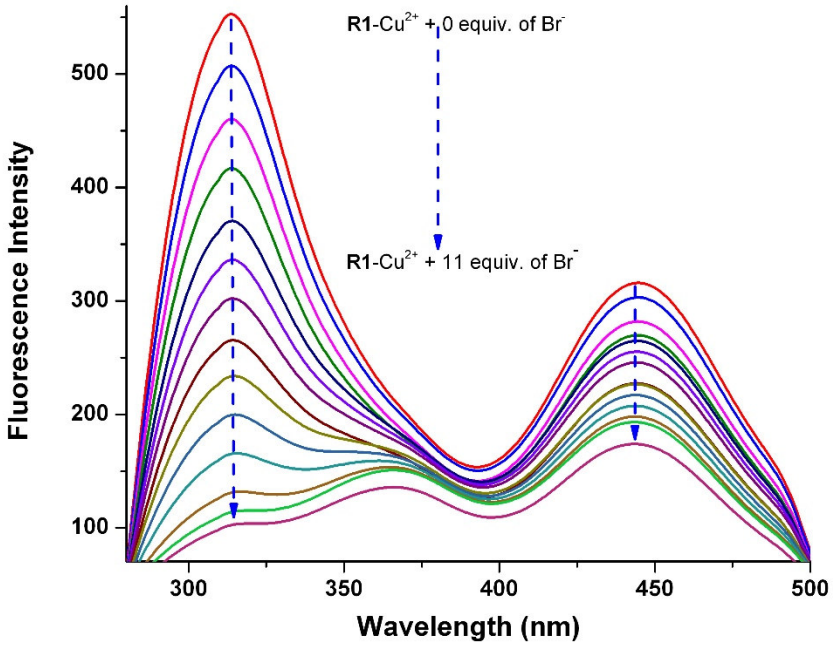


Figure 7. Changes in fluorescence intensity of **R1**–Cu^{2+} (5 μM) upon addition of Br^- (0–11 equiv.).

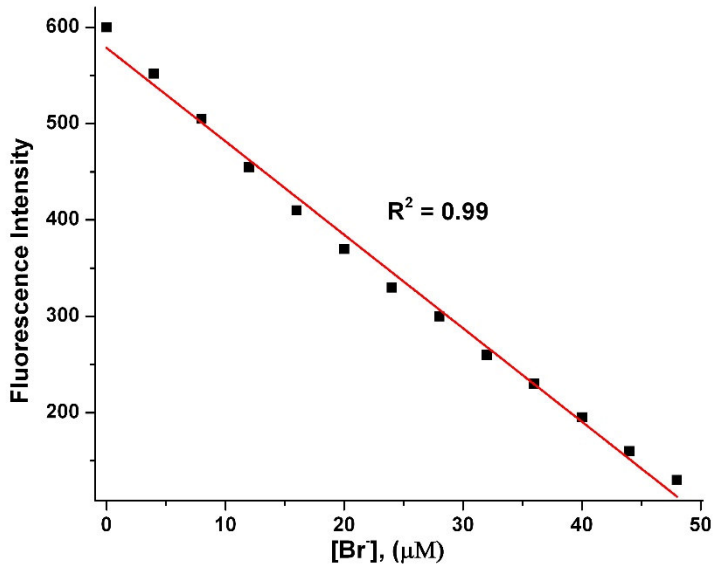


Figure 8. Fluorescence intensity vs. Br^- concentration linear regression plot of **R1**–Cu^{2+} (5 μM) upon addition of Br^- at 310 nm.

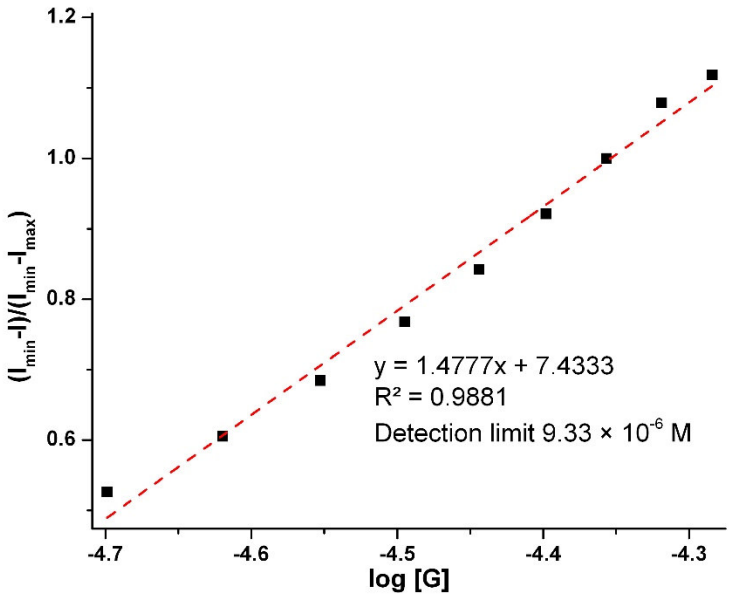


Figure 9. Detection limit calculation of **R1**–Cu^{2+} towards Br^-.

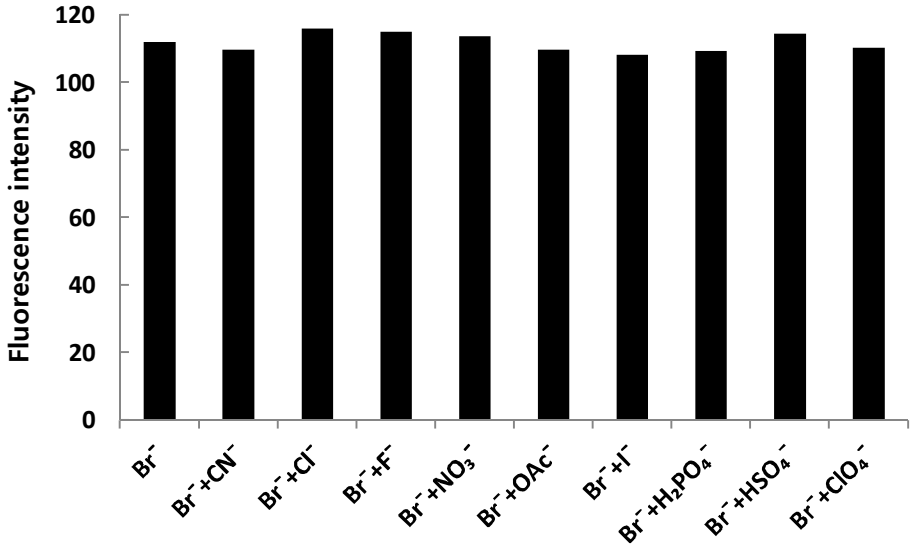


Figure 10. Interference of anions in the recognition of Br^- by **R1**–Cu^{2+}.

2.4 Sensing mechanism

To understand the binding mode of **R1** with Cu^{2+}, theoretical calculations were performed using DMoL 3 package. The generalized gradient approximations (GGA) and double numeric plus polarization (DNP) was used [29]. The HOMO-LUMO energy gaps in **R1** and **R1**–Cu^{2+} were calculated to be 1.172 eV and 0.441 eV, respectively, showing that the binding of **R1** with Cu^{2+} leads to decrease the HOMO-LUMO energy gap of the complex as shown in Figure 11. These results rationalize the changes in fluorescence intensity of **R1** upon Cu^{2+} addition. The optimized structural features of **R1**–Cu^{2+} show that Cu^{2+} ion binds to **R1** at oxygen atoms of the sulfonyl groups. In addition, upon the addition of Br^-, the shape of the fluorescence emission profile of **R1**–Cu^{2+} was unchanged while the intensity of fluorescence decreased. These results indicate that the copper ion in **R1**–Cu^{2+} is released from the complex upon the addition of Br^- rather than forming a new complex. A plausible binding mode of **R1** with Cu^{2+} and Br^- is presented in Scheme 2.

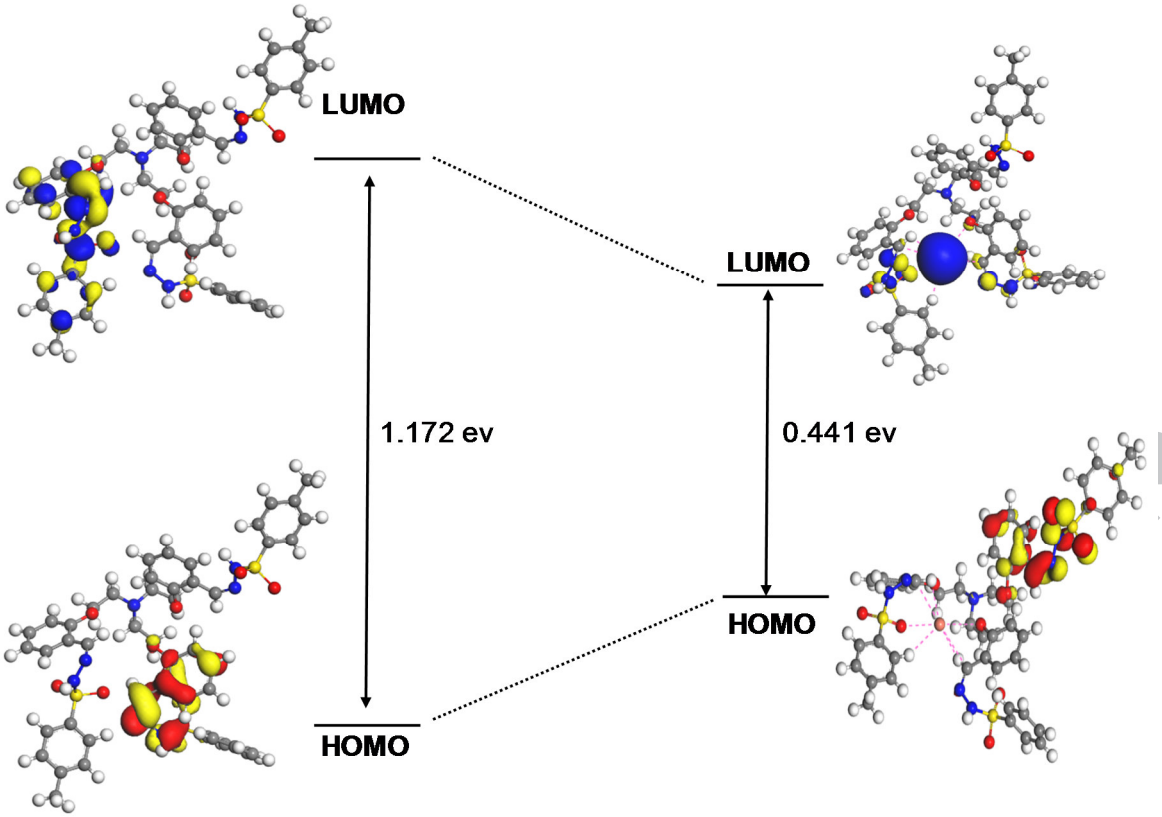
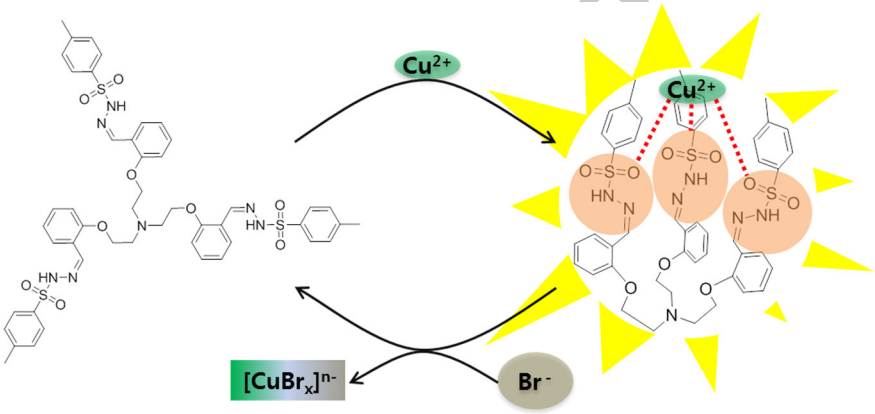


Figure 11. Energy correlation of HOMO-LUMO gaps between **R1** and **R1**–Cu^{2+} complex.



Scheme 2. Proposed mechanism of Br^- detection by the **R1**–Cu^{2+} complex.

3. Conclusions

We have synthesized a tripodal receptor **R1**, incorporating both nitrogen- and oxygen-containing binding sites, and investigated its cation binding properties towards sensor development. Herein, **R1** showed high selectivity

for Cu^{2+}, with the emergence of new peaks as well as marked enhancement of fluorescence intensity upon binding. The receptor was also found to recognize Cu^{2+} with a detection limit of 4.60 μM without interference from other metal ions. The resulting **R1**–Cu^{2+} complex was further studied for its anion recognition ability. **R1**–Cu^{2+} was found to be highly selective for Br^-, showing a concentration-dependent behavior with no interference from other anions. This sensing system may have applications in estimating biologically important Cu^{2+}, as well as Br^-.

Supplementary data

Experimental details and NMR spectra associated with this article can be found, in the online version, at https://doi.org/.

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Highlights

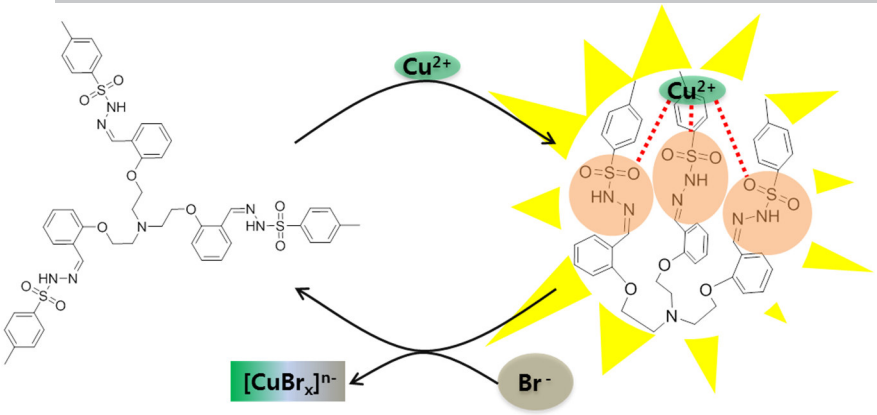
- A tripodal receptor **R1** was used to explore the selective determination of Cu^{2+}.
- **R1** in the presence of Cu^{2+} showed a fluorescence turn-on.
- **R1**–Cu^{2+} complex showed the selectivity for Br^- with a fluorescence turn-off.

[30]

Graphical Abstract

Single chemosensor for sensing multiple analytes: selective fluorogenic detection of Cu^{2+} and Br^-

Yoon Gun Ko, Mayank, Narinder Singh* and Doo Ok Jang*



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