

A Rhodamine-Based *Dual* Chemosensor for Cu(II) and Fe(III)

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Abstract An “off-on” rhodamine-based fluorescence probe for the selective signaling of Cu(II) and Fe(III) has been designed and synthesized. The optical properties of this compound have been investigated in acetonitrile-water (1:1) binary solution. Very interestingly, this compound showed sensitivity and selectivity towards Cu(II) during absorption process and towards Fe(III) during emission process. So this is a nice example of an excellent *dual* chemosensor for two biologically/physiologically very important transition metal ions using only the two very different techniques (absorption and emission); both cases displayed only intensity enhancement.

Keywords Dual chemosensor · Rhodamine 6G · Fluorescence enhancement · Cations · Quantum chemical calculation

Introduction

Everyday in our life, a significant amount of heavy metal ions (such as Pb^{2+} , Cd^{2+} , Hg^{2+} etc.) are discharged into the environment as a result of human activities. The release of

these pollutant ions leads to chemically complex environment whose characterization needs to be determined qualitatively as well as quantitatively [1–7]. In fact, the presence of these ions, even in trace amount, may be critical for human life, because most of them are toxic or poisonous elements. Along with these heavy metal ions, biologically and environmentally—important ion species, especially transition-metal ions (e.g. Cu^{2+} , Fe^{3+} , Cr^{3+} etc.), have attracted wide-spread interests of chemists, biologists, clinical biochemists and environmentalists over the years. The design of artificial chemosensors for qualitative as well as quantitative characterization of different metal ions has received immense attention. Because of their advantages of simple instrumentation and high sensitivity, many efficient colorimetric/fluorescent sensors for transition-metal ions have been developed during the last two decades or so [1–14]. Generally, a typical synthesized probe 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 sensor molecules display completely different absorption/fluorescence signals compared to free sensors in solution after binding with metal ions which enables the quantitative determination of metal ions [15–20].

On the other hand, among the transition-metal ions of interest, divalent copper (Cu^{2+}) is particularly attractive, because it is not only an environmental pollutant at high concentrations [21–24], but also an essential trace element for many biological process and systems [25, 26]. Therefore, many excellent works of Cu^{2+} sensing by colorimetric/fluorescent probes have been reported and investigated [27–32]. Among the transition metal ions, Fe^{3+} is also of much importance, as it plays an indispensable role in the growth and development of living systems. For example, numerous enzymes use iron as a catalyst for oxygen metabolism,

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electron transfer as well DNA and RNA synthesis [33]; both its lack and excess in the body can cause serious diseases [34]. Therefore, design of fluorescent chemosensors for detecting Fe^{3+} is also of great importance. However, the reported fluorescent chemosensors for Fe^{3+} in aqueous medium are still rare and most of them are signaled by fluorescence quenching due to the paramagnetic nature of Fe (III) [35, 36]. Thus, there is an urgent need to develop selective fluorescent chemosensors for Cu^{2+} and Fe^{3+} with fluorescence enhancement, which is more sensitive than that with fluorescence quenching because of high signal-to-noise ratio [37]. Works related to this area are of great challenge and increasing interest.

Among the different dyes/fluorophores, rhodamines are classic ones whose photo-physiochemical properties have already been well studied over the years. Because of their much availability, low cost, long-wavelength absorption/emission, high molar absorption coefficient and quantum yield, these dyes/fluorophores are usually utilized as reporting groups in routine optical analysis. These rhodamine-based ionophores not only exhibit the advantages of rhodamine dyes, but are also more advantageous as they exist in two different forms— one as closed ring (which is *non-fluorescent*) and the other in the form of open ring (which is *fluorescent*). The metal ion sensing behavior of these rhodamine-based optical sensors is very interesting. Typically, in the absence of metal ions, the sensor molecules prefer their *spirolactam* ring-closed state [38], which shows little absorption or fluorescence in visible range (400–700 nm). However, upon the addition of specific metal ions, the chelating or reaction of metal ions with sensor molecules will simultaneously open the

spirolactam ring and convert the sensor into their ring-opened state, which is highly absorbent and fluorescent above 500 nm. Although a number of studies are going on in recent years nevertheless, there is still only a little study focused on the detailed mechanistic study in aqueous solution using rhodamine derivatives [39].

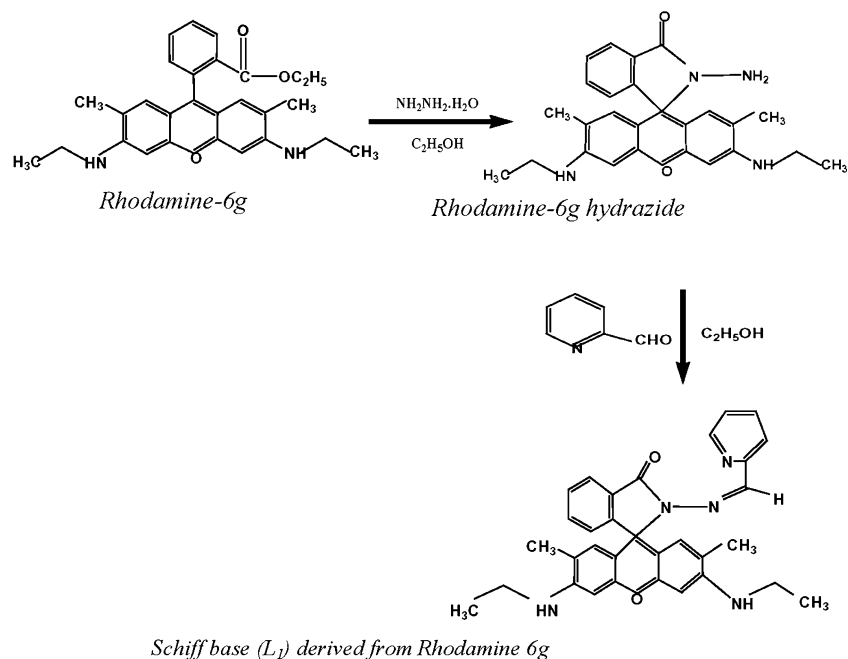
The goal of this article is to report a rhodamine-based derivative (L_1) which displayed *dual* chemosensor characteristic for Fe^{3+} and Cu^{2+} cations. The most interesting point to be noted is that, using absorption spectroscopy Cu^{2+} ion can be detected very selectively and the same chemosensor shows selectivity with very high sensitivity for Fe^{3+} while measuring emission spectra of the compound. To the best of our knowledge, there are a very few example of rhodamine-based fluorescent probe which acts as sensor for two different metal ions using absorption and emission spectra [40]. The newly synthesized rhodamine-6G derivative (L_1) was prepared in high yield as shown in scheme 1. This kind of *dual* sensor is more advantageous over the normal sensor, as here, using the same sensor two different metal ions can be detected using two different modes of measurements which makes the current sensor more versatile and widens its range of applicability.

Methods

Theoretical

The calculations for the two forms of ligand were performed at HF level of theory using Gaussian 03 package [41]. The 3–21 g basis set were employed for C,N,O and H

Scheme 1 Synthetic route of probe L_1



atoms. All geometry optimization were performed without any symmetry constraint. Minima and saddle points were identified through frequency calculations performed at the same level of theory.

Experimental

General Methods

Solvents and reagents were purchased from Aldrich and used as received. The solvents for spectroscopic studies were of HPLC grade and used as received. All the metal ions used are mainly of nitrates, chlorides or sulphates. ^1H NMR spectrum of the ligand, L_1 was recorded on Bruker DPX-300. Mass spectrum was recorded under ESI mode on a Micromass Q-TOF microTM instrument. The Fourier transform infrared spectrum of the ligand was recorded on a Thermo Nicolet iS10 spectrophotometer using KBr pellet in the range of 4,000–400 cm^{-1} (see supporting information). UV–vis spectra were measured on a Simadzu UV-1800 spectrophotometer and fluorescence spectra were recorded using a Hitachi F-2500 spectrofluorimeter. The solution was allowed to stand for 5 min at room temperature ($\sim 25^\circ\text{C}$) before an absorption/fluorescence measurement was made. The intensity of the fluorescence was measured at 552 nm ($\lambda_{\text{ex}}=500$ nm) in a 1 cm quartz cell with a slit width of 5 nm for both excitation and emission.

Synthesis

In this work, Rhodamine 6G Hydrazide was synthesized by a similar route as Yang's. To a 100 mL flask, rhodamine 6G (1.20 g, 2.5 mmol) was dissolved in 30 mL ethanol. 12.5 mL (excess) hydrazine hydrate (24%) was then added dropwise with vigorous stirring at room temperature. After the addition, the stirred mixture was heated to reflux in an air bath for 3–4 h. The solution changed from dark pink to light orange. Then the mixture was cooled and solvent was removed under reduced pressure. 1 M HCl (50 mL) was added to the solid in the flask to generate a clear red solution. After that, 1 M NaOH (70 mL) was added slowly with stirring until the pH of the solution reached 9–10. The resulting precipitate was filtered and washed 3 times with 15 mL water. After drying under an IR light, the reaction afforded 0.84 g Rhodamine 6 G Hydrazide (79%) as pink solid.

Rhodamine hydrazide (0.43 g, 1 mmol) was dissolved in 20 mL absolute ethanol. An excess of aldehyde (pyridine-2-aldehyde) (4 mmol) was added and then the mixture was refluxed in an air bath for 8 h. After that, the solution was cooled (concentrated to 10 mL) and allowed to stand at room temperature overnight. The precipitate which appeared next day was filtered and washed 3 times with

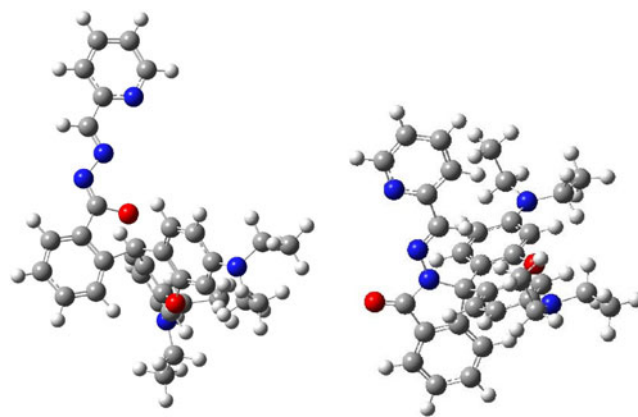


Fig. 1 Optimized structure of *Open-ring* and *closed-ring* form of compound L_1

10 mL of cold ethanol. After drying under reduced pressure, the reaction afforded 0.42 g of L_1 as light yellow solid. The resulting solid was further purified by column chromatography. ^1H NMR (300 MHz, CDCl_3): δ 8.442–8.428(d,1H), 8.228(s,1H), 8.044–7.984(t,2H), 7.598–7.549(t,1H), 7.496–7.424(t,2H), 7.119–7.039(t,1H), 6.411(s,2H), 6.355(s,2H), 3.582–3.489(s,2H), 3.195–3.174(d,5H), 1.910–1.850(s,6H), 1.315–1.208(t,6H) ppm. ESI-MS mass spectra

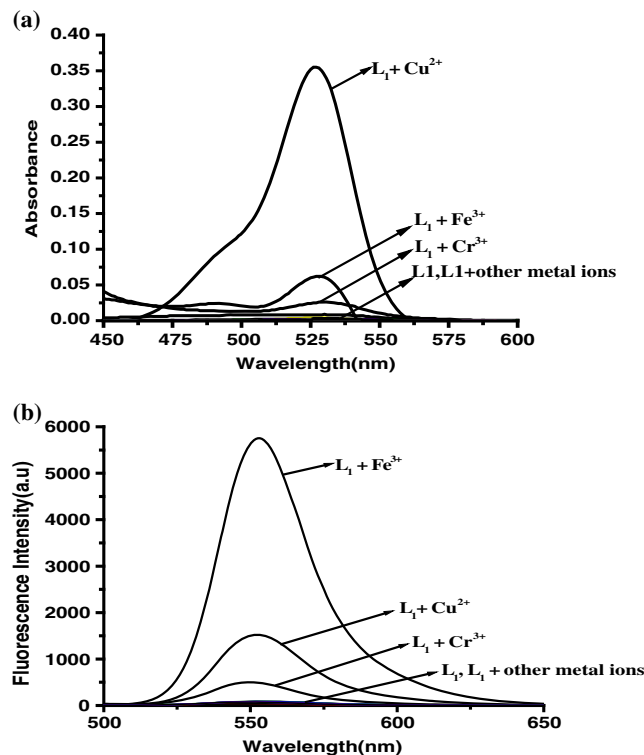


Fig. 2 Changes in the (a) absorption spectra and (b) fluorescence spectra of L_1 (1.0×10^{-5} M) in the presence of various other metal ions (Co^{2+} , Fe^{2+} , Ni^{2+} , Cu^{2+} , Hg^{2+} , Mn^{2+} , Pb^{2+} , Zn^{2+} , Cd^{2+} , Cr^{3+} , Fe^{3+} , Mg^{2+} , Ca^{2+} , Ba^{2+} , Li^{2+} , Na^+ , K^+ , Ag^+) of concentration 1.0×10^{-3} M in Tris–HCl (10 mM, pH=7.0) buffer containing 50% (v/v) water/ CH_3CN

of L_1 exhibited peak at ($m/z=518.52$) and ($m/z=540.50$) which corresponds to $[L_1 + H]^+$ and $[L_1 + Na]^+$ respectively.

Result and Discussion

Theoretical

The optimized geometry of the newly synthesized ligand (L_1) is shown in Fig. 1. Both the open-ring and closed-ring structures are shown in the figure.

Experimental

Here, we report a rhodamine-based spirolactam derivative (L_1) as a chemosensor for Cu^{2+} and Fe^{3+} . The compound (L_1) shows neither absorption nor fluorescence at wavelength region from 400 nm to 650 nm (Fig. 2). But interestingly, on addition of some specific metal ions to L_1 caused color changes, which could also be detected by the naked eye. Interestingly, binding of only Fe^{3+} to L_1 caused significant fluorescence enhancement in Tris HCl (10 mM, pH=7.04) buffer containing 50% (v/v) water/ CH_3CN

mixture and at the same time binding of Cu^{2+} to L_1 produced significant enhancement in absorption spectra at the same condition and in the later, color change could also be visualized by bare eyes. The compound (L_1) remained colorless in aqueous Tris–HCl/ CH_3CN (1:1 v/v) solution at pH 7.04 and is non-fluorescent or weakly fluorescent, indicating that the spirolactam form of L_1 exists predominantly under this pH condition. A new strong fluorescence emission band centered at 552 nm was observed on addition of Fe^{3+} with a quantum yield of 30% with respect to Rhodamine 6G, and a simultaneous color change was also found (from colorless to pink). Upon the addition of Cu^{2+} a new absorption band appeared at 527 which was attributed to the Cu^{2+} –induced ring-opening of the spirolactam moiety [17, 42] along with a very small influence of Fe^{3+} ion. On the other hand, after the addition of the respective metal ions including Li^+ , Na^+ , K^+ , Mg^{2+} , Ca^{2+} , Ba^{2+} , Pb^{2+} , Mn^{2+} , Co^{2+} , Fe^{2+} , Ni^{2+} , Ag^+ , Zn^{2+} , Cd^{2+} and Hg^{2+} , neither the fluorescence intensity at 552 nm nor the absorption intensity at 527 nm was enhanced, which clearly indicated that compound L_1 acts as *dual* sensor for Cu^{2+} and Fe^{3+} ions. In absorption study it is showing selectivity towards Cu^{2+} ion while in fluorescence study it is showing selectivity towards Fe^{3+} ion. It is assumed that

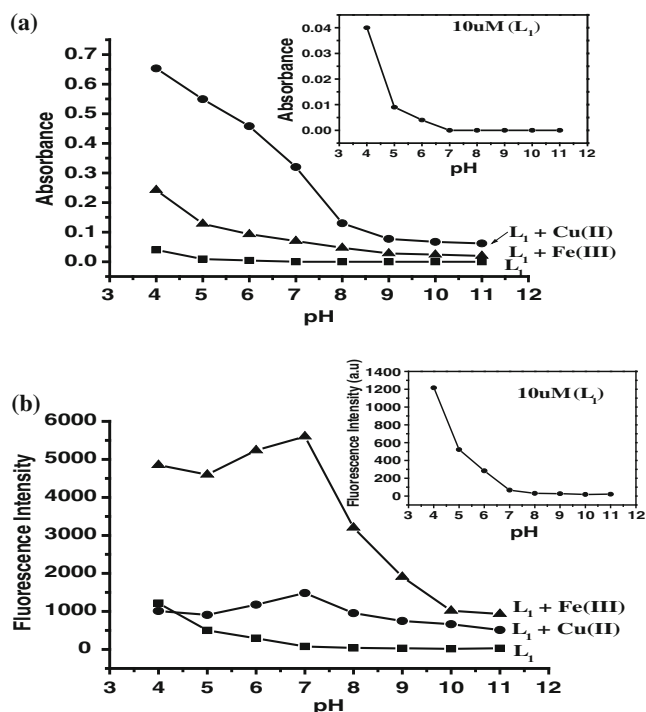


Fig. 3 **a** Absorbance of L_1 (1.0×10^{-5} M) at different pH in the absence (at λ_{max} 530 nm) and presence (at λ_{max} 527 nm) of 100 μ M Cu(II) and Fe(III). **b** Fluorescence Intensity of L_1 (1.0×10^{-5} M) at different pH in the absence (at 558 nm) and presence of 100 μ M Cu (II) (at 547 nm) and Fe(III) (at 552 nm) in Tris–HCl (10 mM, pH=7.0) buffer containing 50% (v/v) water/ CH_3CN . Inset: change of absorption and emission of bare L_1 with pH

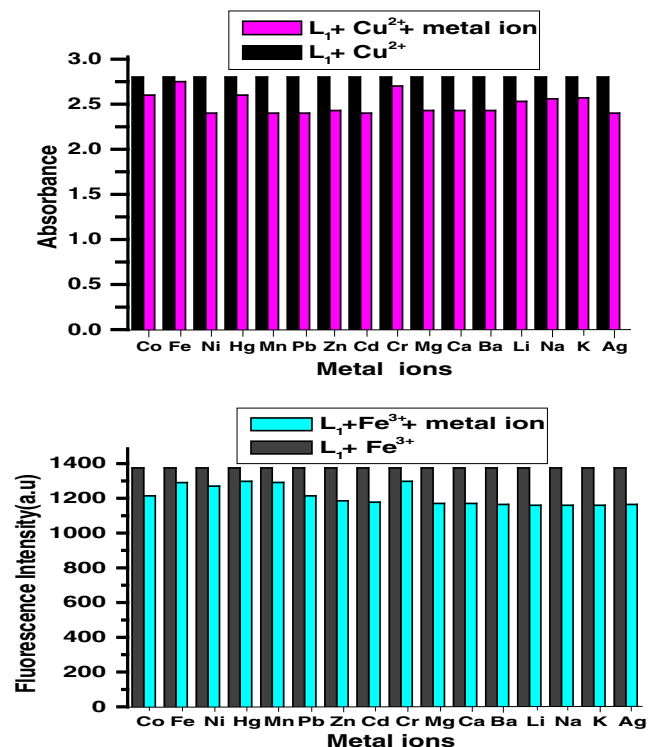


Fig. 4 Change in the absorption and fluorescence spectra of L_1 (5.0×10^{-5} M) in the presence of Cu^{2+} and Fe^{3+} (1.0×10^{-3}) respectively, with various other metal ions (Co^{2+} , Fe^{2+} , Ni^{2+} , Hg^{2+} , Mn^{2+} , Pb^{2+} , Zn^{2+} , Cd^{2+} , Cr^{3+} , Mg^{2+} , Ca^{2+} , Ba^{2+} , Li^{2+} , Na^+ , K^+ , Ag^+) (1.0×10^{-3}) in Tris–HCl (10 mM, pH=7.0) buffer containing 50% (v/v) water/ CH_3CN

the spirolactam form was opened upon the addition of Fe(III) and Cu(II) to L_1 respectively and this compound (L_1) makes a highly delocalized π -conjugated stable complex with the two above mentioned metal ions through their active donor sites (e.g. N and O atoms) of the receptor part, though other ions failed which basically indicates that the coordinate moiety of L_1 matches perfectly with the above mentioned two metal ions instead of the other ions. It is to be noted that we have done the same experiments with DMF-water binary solution and got the same result as with acetonitrile-water mixture.

As shown in Fig. 3a and b, with the increase in solution acidity, the absorbance (at 530 nm) and fluorescence (excited at 500 nm) of L_1 in 50% aqueous Tris-buffered acetonitrile gradually enhanced along with a clear color changes from colorless to pink which implies that the spirolactam ring of L_1 was opened up due to protonation. Within the pH values of 7.0 to 11.0, the fluorescence and the solution color could hardly be observed, which suggests that the rhodamine moiety of L_1 adopted a spirocyclic form and this tautomer was insensitive to such

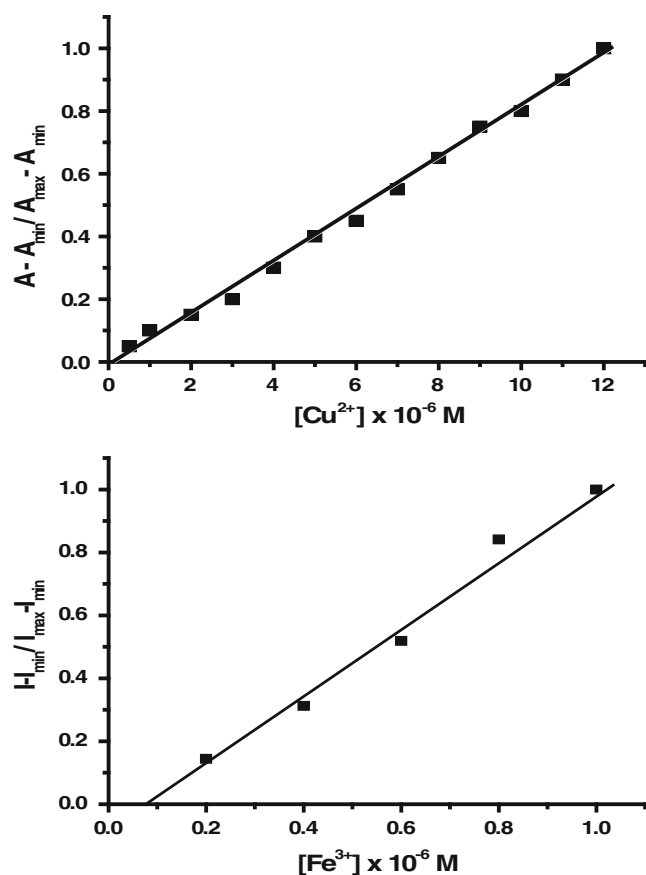


Fig. 5 Absorption and emission intensity of L_1 (10 μM) as a function of externally added Cu(II) and Fe(III) respectively in Tris-HCl : CH_3CN buffer (0.01 M, pH=7.05) (1:1, v/v). The Detection Limits are 2.5×10^{-7} and 9.0×10^{-8} respectively

pH span. Considering that higher pH range could lead to hydrolysis for transition metal ions, the proper pH span for L_1 to sense metal ions in aqueous solution was selected to be around 7.0 which is a physiological pH value too. Below the pH of 7, the probe (L_1) exists predominantly in an open ring form, it is most likely that this tautomer forms stable complexes with Cu(II) and Fe(III) which is visualized from a higher absorption and emission intensity respectively. Above pH 8, the probe exists predominantly in the closed ring form and the extent of formation of stable complexes with Cu(II) or Fe(III) is very small. This is manifested in the similar nature of absorption and emission of L_1 in the presence and absence of metal ions where both absorption and emission are of very low intensity.

Competitive recognition of Cu(II) and Fe(III) in the presence of various other metal ions, even in higher concentration, was also studied and shown in Fig. 4. It is observed that Cu(II) and Fe(III) could be detected in presence of the other metal ions like Na^+ , K^+ , Ba^{2+} , Mg^{2+} , Ca^{2+} , Co^{2+} , Ni^{2+} , Fe^{2+} , Cd^{2+} , Zn^{2+} , Hg^{2+} , Ag^+ and Pb^{2+} . From the bar diagram, it is found that the intensity during absorption or emission does not change any significant amount in presence of other metal ions. So it is clear that

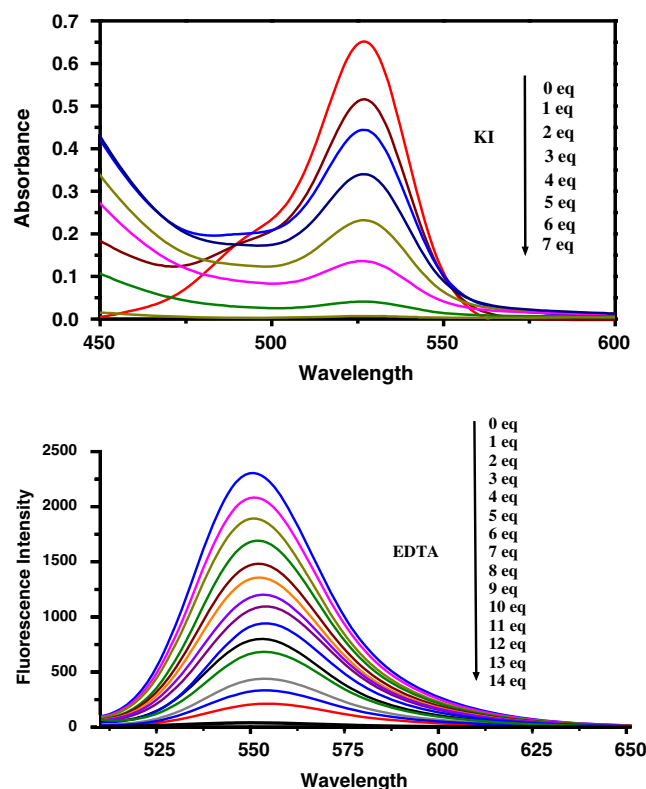
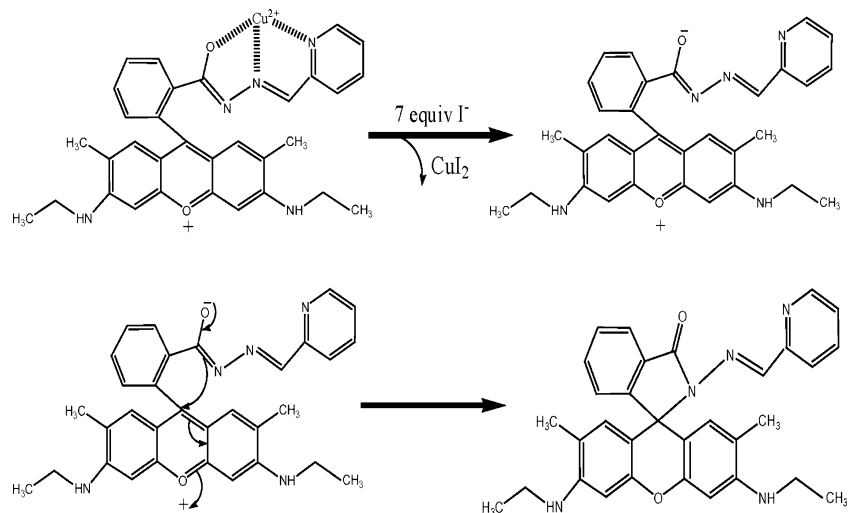


Fig. 6 Absorption and fluorescence spectra showing the reversible binding nature of L_1 with Cu(II) (using KI) and Fe(III) (using EDTA) respectively

Scheme 2 Proposed mechanism of reversible binding nature of L_1 with $Cu(II)$



other ions' interference is negligibly small during the detection of $Cu(II)$ and $Fe(III)$. The figure indicates excellent selectivity for $Cu(II)$ and $Fe(III)$ in presence of those abundant environmentally and physiologically important metal cations in aqueous system during absorption and emission measurements respectively.

The detection limit for $Cu(II)$ and $Fe(III)$, using this chemosensor (L_1), was also evaluated. The detection limit was determined from the absorption and fluorescence titration data. According to the result of the titration experiment, the intensity data were normalized between the minimum intensity and the maximum intensity and a linear regression curve was then fitted to these normalized intensity data, and the point at which this line crossed the x-axis or ordinate axis was considered as the detection limit (shown in Fig. 5). We could detect $[Cu^{2+}]$ and $[Fe^{3+}]$ as low as 2.5×10^{-7} M and 9×10^{-8} M respectively which were sufficiently low for the detection of those metal ions found in many chemical and biological systems.

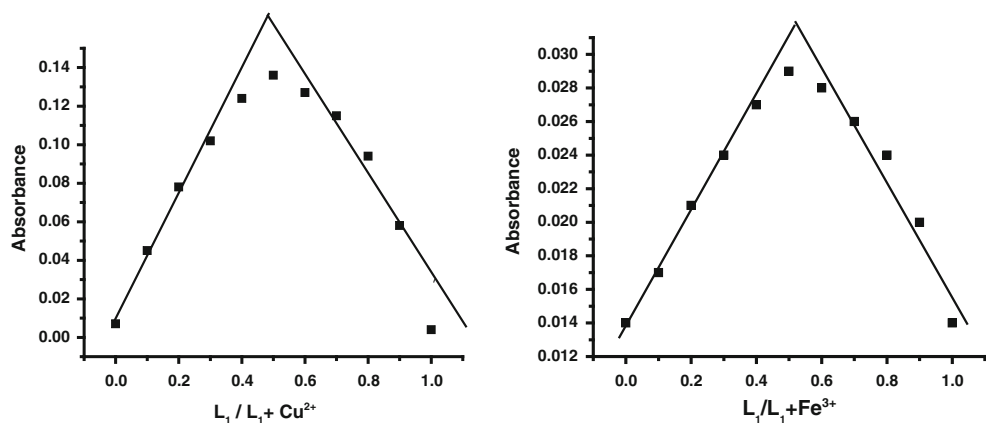
Further, it was of great interest to investigate the reversible binding nature of the sensor (shown in Fig. 6). As I^- is known to have a strong binding affinity for Cu^{2+} , upon gradual

addition of aqueous-acetonitrile (1:1) solution of KI (upto 7 equivalent) to a solution mixture of L_1 ($20 \mu M$) and $Cu(II)$ ($10 \mu M$), color changed slowly from pink to colorless. This observation is assumed to be due to decomplexation of $Cu(II)$ by I^- followed by a spirolactam ring closure reaction shown in scheme 2. Thus, L_1 can be classified as a reversible chemosensor for Cu^{2+} . In a similar way, the reversible binding nature of the sensor with $Fe(III)$ using the strong chelating ligand $EDTA$ has been shown in the same figure where the emission intensity is decreased due to decomplexation of $Fe(III)$ upon gradual addition of $EDTA$. Meanwhile, the job's plots (shown in Fig. 7) indicated 1:1 stoichiometry for the binding mode of L_1 with $Cu(II)$ and $Fe(III)$ and the binding constant was found to be $1.9 \times 10^4 \text{ mol}^{-1}$ and $1.5 \times 10^5 \text{ mol}^{-1}$ from absorption and emission data respectively.

Conclusions

We have designed and synthesized a rhodamine 6G-based chemosensor. Its optical properties have also been studied. Very interestingly, this compound displayed a *dual* sensor

Fig. 7 Job's plot of $L_1-Cu(II)$ and $L_1-Fe(III)$ complexes in Tris-HCl (10 mM, pH=7.04) buffer containing 50% (v/v) water/ CH_3CN solution give rise to a 1:1 stoichiometry for both the complex



characteristics and showed sensitivity and selectivity towards Cu(II) in absorption spectrophotometry and towards Fe(III) during emission process.

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