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Fluorescence sensing of Cu^{2+} within a pseudo 18-crown-6 cavity

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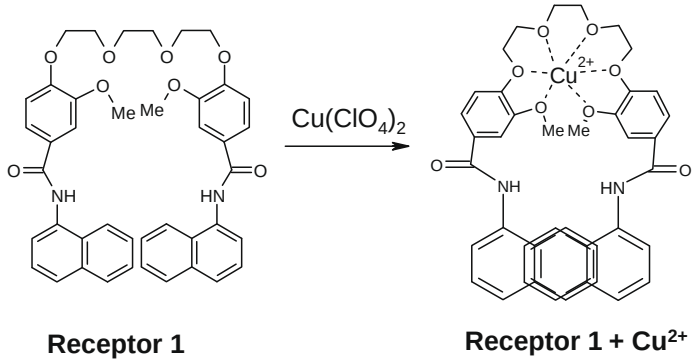
ABSTRACT

We report herein a pseudo-crown based fluorescent receptor (**1**) for the selective detection of Cu^{2+} cation. Receptor **1** can detect Cu^{2+} even in 5 μM level in acetonitrile–water (9:1 v/v). Compound **1** is very effective for the detection of Cu^{2+} amongst the series of metal ions studied (Li^+, Na^+, K^+, Ca^{2+}, Mg^{2+}, Ba^{2+}, Pb^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+} and Mn^{2+}).

Amongst the soft transition metal ions, Cu^{2+} is the third in abundance (after Fe^{2+} and Zn^{2+}). It is one of the essential heavy metal ions in human body and plays an important role in various biological systems.[1] Selective chemosensors, designed and synthesized for in vitro and in vivo purposes have now been of considerable interest and among them, sensing of Cu^{2+} ion constitutes a very active area of research.[2] Chemosensors are molecular-sized or larger devices that interact with analytes reversibly and in real time.[3] Although in recent times many signal types have been available, fluorescence proffers high sensitivity. Therefore this mode of signal transduction has been widely used for the detection of a number of transition metal ions. Among the sensors targeted towards the detection and estimation of metal ions, Cu^{2+} has got considerable attention.[4,5] Detection of specific metal ion with high specificity under physiologically relevant conditions is an important area in designing fluorescent chemosensors for applications in clinical biology. Due to its widespread use, Cu^{2+} is a pollutant in high concentration and is associated with brain diseases such as Alzheimer's, Parkinson's and Prion at a trace amount.[6] The toxicity of Cu^{2+} for human body is, however, low compared to other heavy metals but certain microorganisms are affected[7] by even submicro-molar concentration of Cu^{2+}.



Receptor 1 **Receptor 1 + Cu^{2+}**

Scheme 1. Receptor **1** and its complexation with Cu^{2+} cation.

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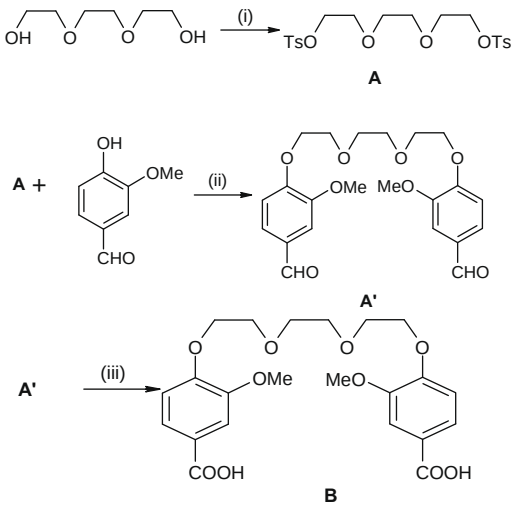
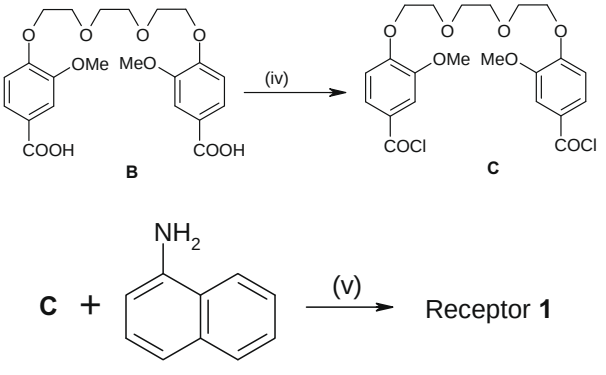


Herein we report a receptor with pseudo 18-crown-6 cavity (receptor **1**) which selectively binds Cu^{2+} even in 5 μM level concentration which can be detected by fluorescence method. Here naphthalene moiety is part of the main skeleton of the fluoroionophore and is positioned in a particular manner so that, due to the binding of metal ion they can come closer and hence aromatic stacking is possible (Scheme 1). The two naphthalene units will provide a hydrophobic environment and thus the receptor offers a high 'complex stability'. Again the benzene rings directly attached to the ether moiety can participate in cation-π interactions and thus can increase the sensitivity towards the metal ions. 18-Crown-6 has long been known for selective binding of K^+ ions. Many applications have also been known using this property.[8] But here the pseudo crown moiety (receptor **1**) shows high selectivity towards Cu^{2+} over K^+.

The synthesis of receptor **1** is described in Scheme 2. The synthesis begins with tris-ethyleneglycol which was converted to ditosylate, **A**. This, when reacted with vanillin, K_2CO_3 and dry acetone using a phase transfer catalyst (TBAB) produced the expected dialdehyde (**A′**) which on oxidation afforded the dicarboxylic acid **B.** The corresponding acid chloride **C** on coupling with 1-naphthylamine yielded the desired receptor **1** which was purified by preparative TLC using 2% MeOH in $CHCl_3$.

In preliminary fluorescence studies, the receptor **1** having naphthalene moiety as fluorophore (5 μM) in acetonitrile–water (9:1 v/v) in presence of metal ions viz. Ni^{2+}, Zn^{2+} and Pb^{2+} shows fluorescence quenching with Cu^{2+} (small quenching takes place in case of Fe^{3+}), and other metal ions do not affect so much the fluorescence of **1**. Also the presence of alkali and alkaline earth metals do not affect the fluorescence of **1** even in larger amounts. Therefore **1** shows selective fluorescence quenching with Cu^{2+} and may be used for its quantitative estimation.



Scheme 2. Reagents and conditions: (i) Et_3N, *p*-TsCl, 12 h; (ii) K_2CO_3, TBAB, dry acetone, rt, 24 h; (iii) aq $KMnO_4$, 3 h; (iv) oxalyl chloride, dry CH_2Cl_2, dry DMF (cat. amount), N_2-atmosphere, 3 h; (v) dry CH_2Cl_2, NEt_3, rt, 12 h.

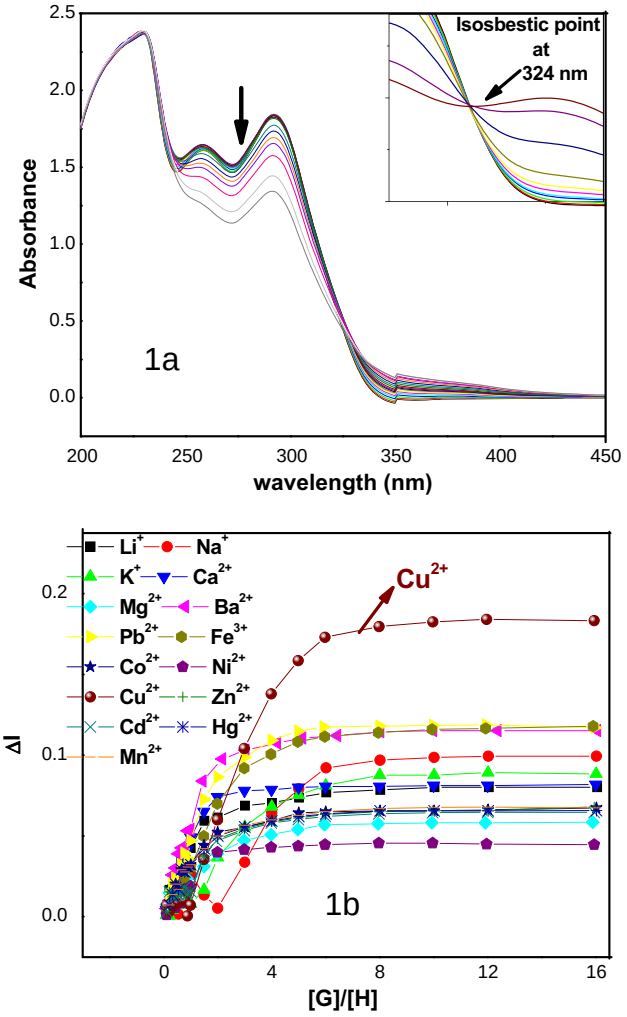


Figure 1. (1a) UV spectra of receptor **1** after addition of Cu^{2+}; (1b) UV-binding curve of receptor **1** (where change of absorbance is plotted against ratio of concentrations of host and guest).

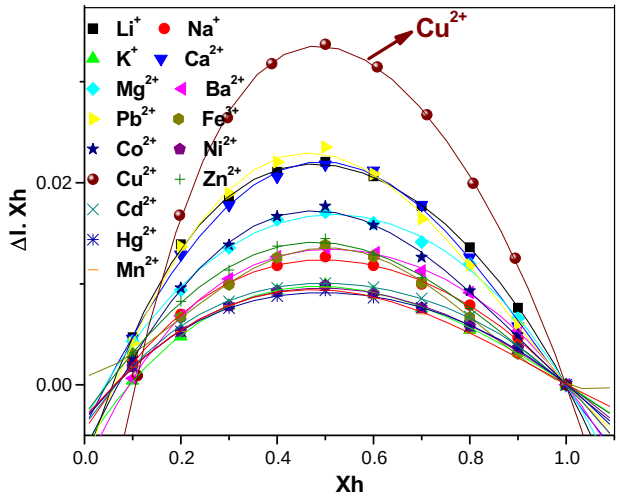


Figure 2. Job's plot of receptor **1** by UV method, where Xh stands for mol fraction of host and ΔI indicates the change of absorbance.

The cation binding properties of **1** were investigated by observing the changes in their fluorescence emission (in case of **1**) and absorption spectra in acetonitrile–water (9:1 v/v). UV–vis experiments were carried out in CH_3CN–H_2O (9:1 v/v) solvent. The titration of **1** ($c = 1.2 \times 10^{-5}$ M), which exhibits a broad strong absorption band at 294 nm due to the naphthalene moiety, was carried out with perchlorate salts of cations such as Li^+, Na^+, K^+, Ca^{2+}, Mg^{2+}, Ba^{2+}, Pb^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Mn^{2+} and Hg^{2+}. Upon addition of perchlorate salts of cations, a continuous decrease of absorbance is observed. The value of association constant (*Ka*) determined by the UV–vis method is found to be 8.96×10^5 (see Supplementary material). An isosbestic point is observed at ~324 nm, indicating the formation of a new complex between **1** and Cu^{2+} (Fig. 1a). When an isosbestic point is constructed by the superposition of the absorption spectra of two species by using the absorbance and keeping the same molar concentration for both species, the isosbestic point corresponds to a wavelength at which these spectra cross each other. The isosbestic point indicates that in spite of addition of increasing amount of guest (Cu^{2+}), for the particular concentration of the host (receptor **1**) only one complex is formed and as a result one common absorbance point is observed here. Complex formation between the host and the guest is taking place via electrostatic interactions between the receptor **1** and Cu^{2+}. The complex formation affects the electronic properties of the fluorophore resulting in a change with a subsequent new charge transfer interactions between the receptor **1** and Cu^{2+}.

The stoichiometry of the complexes was confirmed from the break in the titration curve (Fig. 1b). The break at 1:1 confirms the binding mode. Job's plot of the cations also supports the 1:1 binding mode (Fig. 2).

The fluorescence titration of fluorophore containing receptor **1** in acetonitrile with Cu^{2+} exhibited a remarkable decrease of fluorescence intensity at 348 nm (value of binding constant is 2.09×10^5) (see Supplementary material) with a simultaneous growth of new peak at 403 nm ($\Delta\lambda = 55$ nm resulting ultimately ~45% fluorescence quenching in total (Fig. 4a) that is, '*switching-off*' due to the formation of strong cation–host complexations which lock the cavity. Their corresponding fluorescence spectra are depicted in Figure 3. The fluorescence intensity is also determined in case of Fe^{3+}. But no significant change of fluorescence intensity was observed in case of other metal cations. From the instrumental read-out it can be concluded that the response of **1**

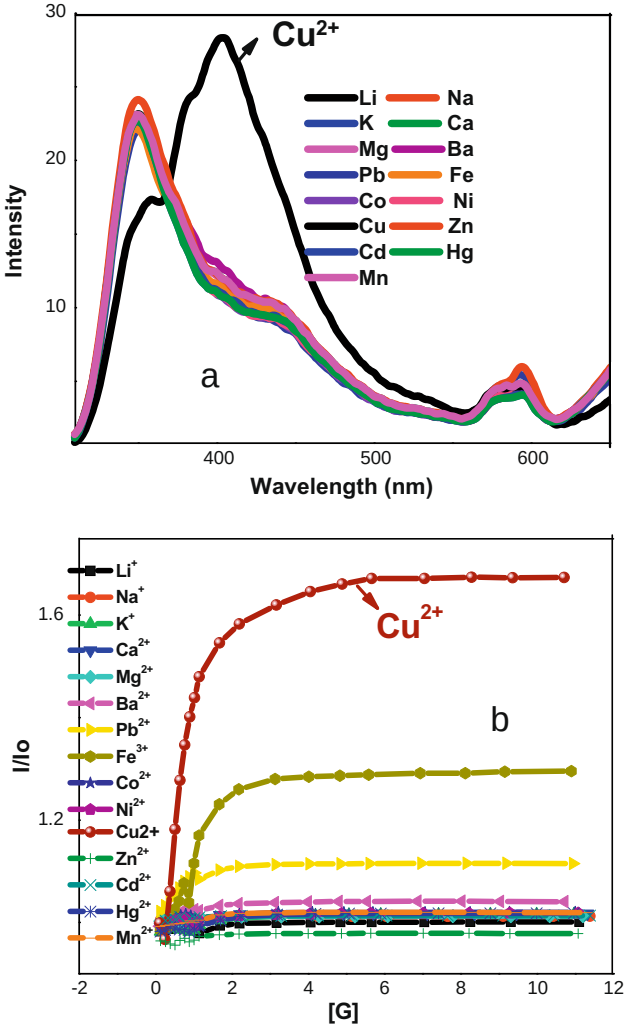


Figure 3. Fluorescence spectra of receptor **1** after addition of (a) 1 equiv of metal ions; (b) fluorescence binding constant curve of receptor **1**, where [*G*] refers to the concentration of guest solutions added and I_o stands for initial intensity and *I* stands for final intensity.

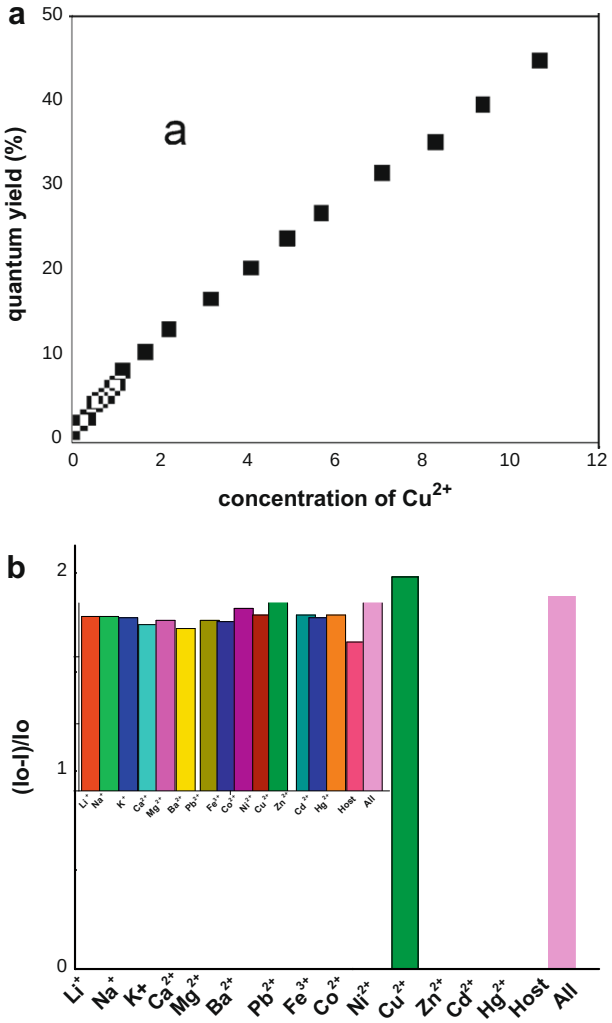


Figure 4. (a) The plot of quantum yield of receptor **1** and **1**-Cu^{2+} complex versus concentration of Cu^{2+}; (b) fluorescence response of receptor **1** towards metal ion upon addition of 5 μM solutions of individual metal ions. Inset shows the response towards Cu^{2+} ~10^{-7} M plus co-existing metal ion at ~10^{-5} M. [Here in Fig. b, the ratio of change of absorbance to the initial absorbance was plotted with the concentration of the guest molecules added.]

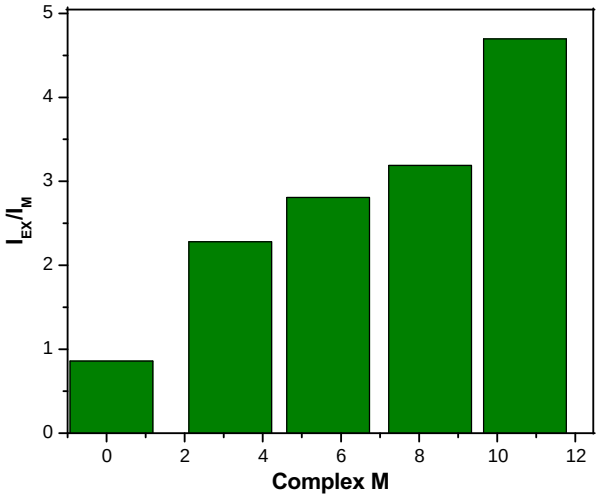


Figure 5. Plot of the ratio of excimer to monomer emission versus concentration of the complex of **1** with Cu^{2+}.

to Cu^{2+} is highest and for other cations it remains almost the same (Fig. 4b). Florescence spectrum of **1** was also recorded using acetonitrile as a solvent and we found similar results. Here we also noted the high selectivity of receptor **1** towards Cu^{2+}.

In case of Cu^{2+} an additional peak at 403 nm along with monomer emission at 348 nm was noticed due to an excimer formation (Fig. 3a). The excimer emission resulted from the intramolecular, rather than intermolecularly, as indicated by the dilution experiment at different concentrations in which the intensities of the ratio of excimer to monomer changed gradually (Fig. 5).

The MMX studies[9] of receptor **1** and its different mode of complexation with cations are very interesting with respect to the experimental findings. Receptor **1** forms a tight complex with Cu^{2+} compared to the other cations like K^+ (Fig. S2).

The interactions of host–guest complexations and their different modes of binding have been studied using MMX calculations. The stabilization energy (Table 1) is further lowered by complexation with Cu^{2+}. This calculation also fulfills the objective of stronger and better binding of host with the guest cations studied.

In summary, pseudo-crown based fluorescent receptor **1** has been designed and synthesized. The highest sensitivity and selectivity of **1** towards Cu^{2+} over other metal cations (Li^+, Na^+, K^+, Ca^{2+}, Mg^{2+}, Ba^{2+}, Pb^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+} and Hg^{2+}) as their perchlorate salts were demonstrated via its fluorescence response.

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Supplementary data

Supplementary data (^1H, ^{13}C and mass spectra of receptor **1**, general procedure for preparation, fluorescence spectra and table of binding constants) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.011.

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9. The optimization of structures was carried out using MMX (PCMODEL Serena Software 1993). Molecular modeling was performed using standard constants and the dielectric constants were maintained at 1.5.