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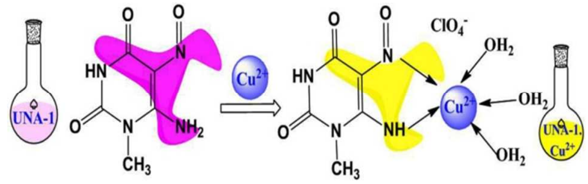

Uracil nitroso amine based colorimetric chemosensor for Cu^{2+} ions from a 100 % aqueous environment

A Uracil nitroso amine based colorimetric sensor for the detection of Cu^{2+} ions from aqueous environment and its practical applications

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Abstract

A simple uracil nitroso amine based colorimetric chemosensor (**UNA-1**) has been synthesized and screened for its cation recognition ability. Sensor **UNA-1** exhibited a high sensitivity and selectivity towards Cu^{2+} ions in aqueous medium in the presence of a wide range of other competing cations (Ag^+, Al^{3+}, Ba^{2+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cr^{3+}, Cs^+, Fe^{2+}, Fe^{3+}, Li^+, Mg^{2+}, Mn^{2+}, Na^+, Ni^{2+}, Pb^{2+}, Zn^{2+}, Hg^{2+} and Sr^{2+}). With Cu^{2+}, the sensor **UNA-1** gave a distinct color change from colorless to dark yellow by forming a complex of 1:1 stoichiometry. Furthermore, sensor **UNA-1** was successfully utilized in the preparation of test strips and supported silica for the detection of Cu^{2+} ions from aqueous environment.

Key words: Colorimetric chemosensor; Cu^{2+}; Uracil nitroso amine, aqueous environment; DFT.

Introduction

Copper, the third-most abundant transition element in the body, plays an important role in various physiological processes such as hemoglobin biosynthesis, bone development, dopamine production, nerve function regulation, gene expression, and the functional and structural enhancement of proteins.[1-6] Due to its redox-active nature, copper serves as an essential co-factor for a variety of metalloenzymes in living organisms such as cytochrome *c* oxidase, lysyl oxidase, copper-zinc superoxide dismutase and tyrosinase, which have a significant role in the enzymatic defense against oxygen toxicity.[7-9] However, at high concentration, its redox properties turn into biologically hazardous materials because of its ability to generate reactive species, which create problems in the cellular metabolism.[8,9] Apart from the biological and environmental importance, other advantages are that copper is relatively abundant, of low cost, and possess good malleability, electrical conductivity, thermal conductivity, chemical stability as well as germicidal efficiency. All of these properties make copper central to the pharmaceutical and industrial sectors for making alloys, electrical wires, machine parts, batteries, drugs and fertilizers etc.[10,11] However, with excessive loading, Cu^{2+} is highly toxic to living organisms. For example, it's over accumulation in human being leads to various diseases including neurodegenerative diseases such as Alzheimer's disease, Wilson's disease, Menkes disease, prion disease, gastrointestinal disorders, kidney damage, amyotrophic sclerosis, lipid metabolism and inflammatory disorders.[12-15]

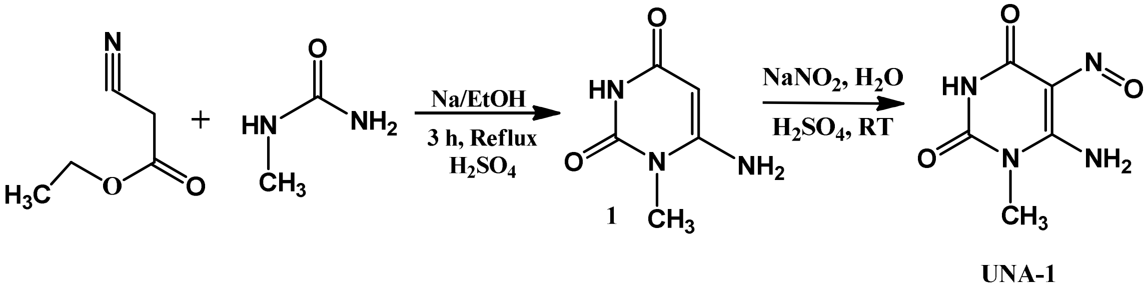
The World Health Organization (WHO) have reported that the maximum limit of copper in drinking water should be 2 ppm (30 μM).[16] Under normal conditions, the average concentration of copper in the blood should not exceed 100-150 μg/dL.[17] However, due to the widespread use of copper in household appliances, industry, agricultural and water-pipes, Cu^{2+} pollution has increased immensely throughout the world. Therefore, it is necessary to develop fast, convenient and reliable analytical methods for the qualitative and quantitative detection of copper, particularly in drinking water and in biological samples. Several analytical techniques such as atomic absorption spectrometry (AAS), inductively coupled plasma mass spectroscopy (ICP-MS), inductively coupled plasma atomic emission spectrometry (ICP-AES) and voltammetry, quantum-dot-based assay have been developed for the qualitative and quantitative detection of Cu^{2+} ions at trace levels. These technologies can detect Cu^{2+} ion selectively with high sensitivity, but tend to need highly sophisticated and expensive instrumentation, and require tedious sample preparation and highly trained operators.[18-21] By contrast, naked-eye detection methods permit detection of the target analyte at the micro/submicromolar levels without any need for expensive/sophisticated instrumentation.[22,23] Therefore, given the importance of and the hazardous roles played by copper, we were encouraged to develop a colorimetric sensor with naked-eye capability for detecting Cu^{2+} from pure aqueous media.

On surveying the literature, we have noted that most of the reported Cu^{2+} selective colorimetric sensors have a number of drawbacks, *viz* long response times, poor detection limits, tedious synthetic procedures, use of organic solvents, and interference from other transition metal ions (Table S1).[22-32] Herein, as a part of our ongoing research on chemosensors,[32-35] we have developed a simple and easy to prepare colorimetric chemosensor, namely the uracil nitroso amine derivative **UNA-1** (Scheme 1), which can be used for the highly selective and sensitive recognition of Cu^{2+} ions. This chemosensor gives a visual color change from colorless to clear dark yellow allowing for the naked-eye detection of Cu^{2+}.

Results and Discussion

Naked-eye detection of Cu^{2+}

The synthesis of the uracil nitroso amine derivative (**UNA-1)** was achieved in two steps by the reaction of ethyl-cyanoacetate and *N*-methylurea in the presence of sodium ethoxide as a catalyst under acidic medium to give pyrimidine **1**, which further undergoes nitrosation with sodium nitrite to afford **UNA-1** (Scheme 1). Then, the colorimetric sensing ability of **UNA-1** (5 x 10^{-5} M, in $CH_3OH:H_2O$, 10:90, *v/v*) was tested via the addition of 5 equivalents of various cations (1 x 10^{-2} M, in H_2O). As shown in Fig. 1, **UNA-1** exhibits a selective, sensitive and qualitative recognition of Cu^{2+} ions in day light/sunlight through a distinct visual color change from colorless to dark yellow. No noticeable color change was observed in the presence of any other cations screened herein.



Scheme 1. Synthesis of **UNA-1**

Fig. 1. Naked-eye detectable color change of ions with **UNA-1** in the presence of 5 equivalents of different cations.

The concentration dependent naked-eye study was performed (Fig. S1a) by addition of various concentrations of **UNA-1** (A =1 x 10^{-3} M, B = 1 x 10^{-4} M, C = 1 x 10^{-5} M, D = 5 x 10^{-5}, E = 1 x 10^{-6} M, F = 5 x 10^{-6} M and G = 1 x 10^{-7} M) to a fixed concentration of Cu^{2+} ions (1 x 10^{-3} M, in H_2O). The observed color change clearly suggested that the sensor was quite sensitive up to a concentration of 5 x 10^{-5} M for the detection of Cu^{2+} ions. Next, we investigated the effect of changing the concentration of Cu^{2+} ions from 1 x 10^{-3} M to 1 x 10^{-7}

M to a fixed concentration of **UNA-1** (1 x 10^{-4} M), which inferred that our sensor was able to detect Cu^{2+} up to the concentration of 1 x 10^{-5} M (Fig. S1b).

Cation sensing studies

The cation recognition behavior of sensor **UNA-1** with group I, II and III metal ions (Ba^{2+}, Ca^{2+}, Cs^{+}, Li^{+}, Mg^{2+}, Na^{+}, Al^{3+} and Sr^{2+}) and transition and heavy metal ions (Co^{2+}, Cu^{2+}, Cr^{3+}, Fe^{2+}, Cd^{2+}, Fe^{3+}, Mn^{2+}, Ni^{2+}, Pb^{2+}, Zn^{2+} and Hg^{2+}) was investigated using UV-Vis absorption spectroscopy. The absorption spectrum of sensor **UNA-1** in $CH_3OH:H_2O$ (10:90, *v/v*) solvent system exhibited two absorption bands centered at 227 nm and 315 nm due to π-π* and n-π* electronic transitions, respectively. Upon addition of 5 equivalents of different cations (50 μL, 1 x 10^{-2} M, in water) to a 5 x 10^{-5} M solution of **UNA-1** in $CH_3OH:H_2O$ (10:90, *v/v*), only the Cu^{2+} ions was able to perturb the absorption spectrum of **UNA-1** effectively. The addition of aqueous Cu^{2+} ions to the **UNA-1** solution led to the disappearance of the absorption band at 315 nm and the appearance of a new broad band between 335-500 nm due to the interaction of the paramagnetic Cu^{2+} with **UNA-1** (Fig. 2). The appearance of a new charge transfer band was responsible for the naked-eye detectable color change of **UNA-1**.

The UV-Vis absorption titration was next performed upon successive addition of 1-10 equivalents of Cu^{2+} ions to the solution of **UNA-1** to determine the binding ability and the limit of detection. With the incremental addition of Cu^{2+}, the absorbance at wavelength 315 nm decreased continuously with the appearance of the new broad peak between 335-500 nm (Fig. 3). The titration resulted in the formation of an isosbestic point at 300 nm, which suggested the formation of a complex between **UNA-1** and copper ions in solution.

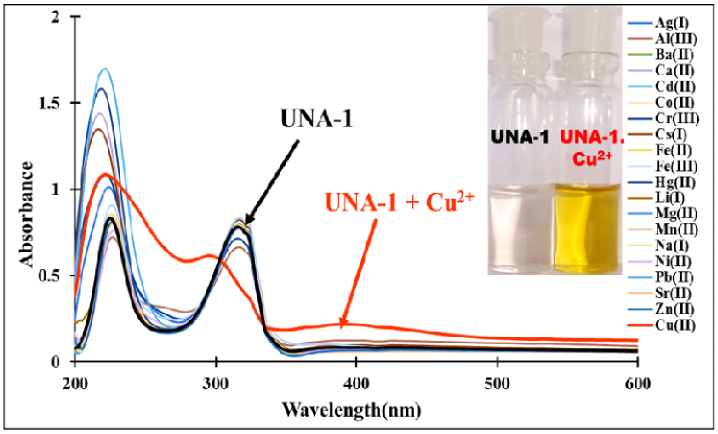


Fig. 2. Absorption spectra of **UNA-1** in the presence of 5 equivalents of different cation.

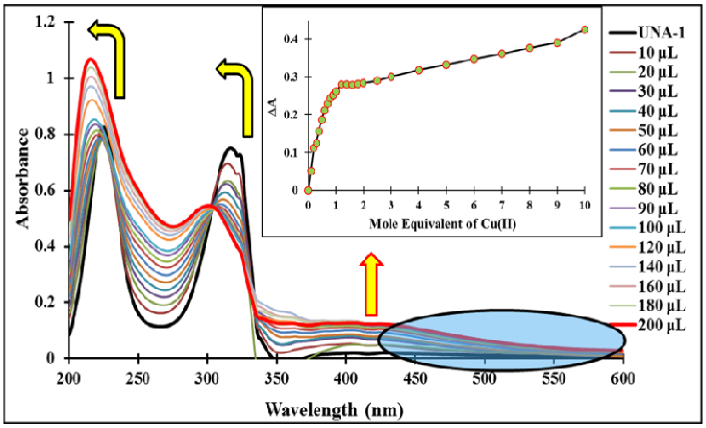


Fig. 3. Changes in absorption spectra of **UNA-1** upon incremental addition of Cu^{2+} ions (1-10 equiv.). Inset showing mole ratio plot i.e. change in absorption spectra (ΔA at λ_{max}=315 nm) as a function of concentration of Cu^{2+} ions.

The association constant (K_a) was estimated graphically by plotting $1/\Delta A$ against $1/[Cu^{2+}]$ (Fig. 4). The data was linear (fitted according to the Benesi–Hilderbrand equation) and the K_a value was obtained from the slope and intercept of the line. The Ka value for the **UNA-1** copper complex was found to be 2.8×10^4 M^{-1} (R^2=0.9933). The value suggested that the sensor **UNA-1** has high affinity towards Cu^{2+} ions. The limit of detection (LOD) and limit of quantification (LOQ) of **UNA-1** were also calculated from the absorption titration data. According to the IUPAC definition, the LOD and LOQ were calculated using the relationship LOD = (3.3 x standard deviation)/slope and LOQ = (10 x standard deviation)/slope. To calculate the relative standard deviation, the absorption measurements of ten blank samples were taken. As shown in Fig. S2, the absorbance calibration values were normalized between the minimum intensity and the maximum intensity and then a linear regression curve was fitted to these normalized data to get the slope. With this approach, the LOD and LOQ were found to be 10 µM and 33 µM, respectively.

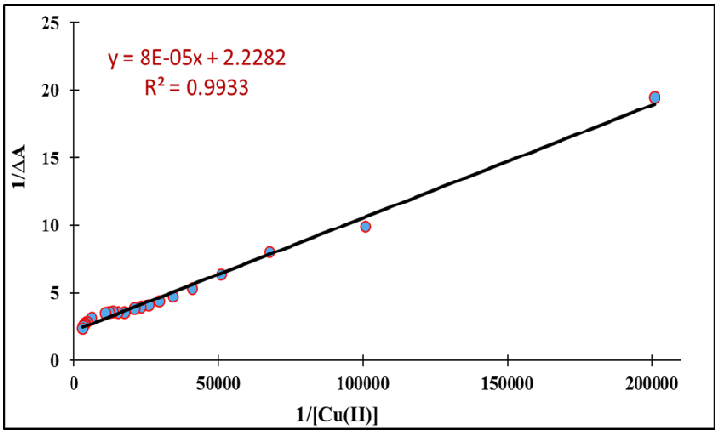


Fig. 4. Benesi–Hilderbrand plot of chemosensor **UNA-1** with Cu^{2+} ion for evaluation of association constant or binding constant (where, ΔA is at λ_{max}=315 nm).

The 1:1 binding stoichiometry for the complexation between **UNA-1** and Cu^{2+} was determined using a Job's plot experiment (Fig. 5) and a mole ratio plot (Fig. 3, inset). Furthermore, more direct evidence for the formation of this 1:1 complex was obtained from the ESI-MS spectra of **UNA-1** in the presence of 1.0 equivalent of Cu^{2+} in methanol/water (10:90, v/v) (Fig. S3). For pure **UNA-1,** a characteristic peak at m/z = 207.0405 was obtained which corresponds to the species [(**UNA-1**).$2H_2O$+H], whilst on addition of copper perchlorate, the peak at 207.0405 disappeared and a new peak appeared at m/z = 287.0051 corresponding to the species $[($**UNA-1**-H).Cu.$3H_2O]^+$ (Fig. S3). MS-MS of 287.0051 peak corresponding to the hydrated copper complex of **UNA-1** shows fragmentation giving peaks at 251.94 and 233.97 corresponding to the species [**(UNA-1)-H.Cu.H_2O**$]^+$ and [**(UNA-1)-H.Cu**$]^+$ respectively (Fig. S3).

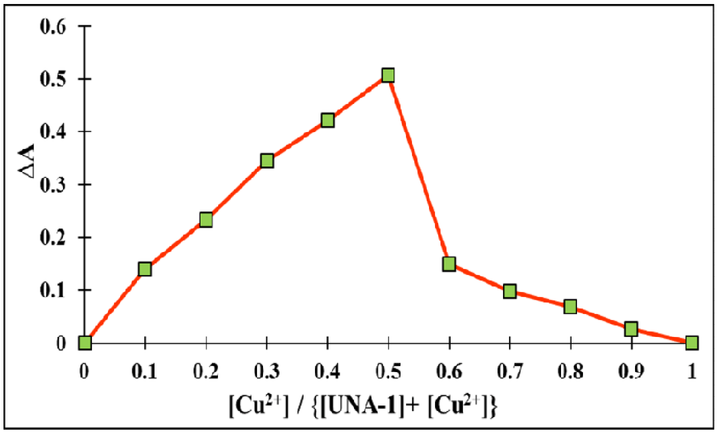


Fig. 5. Job's plot for the determination of a 1:1 stoichiometry upon complexation of **UNA-1** with Cu^{2+} ions (where, ΔA is at λ_{max}=315 nm).

The chemosensor **UNA-1** can bind to the Cu^{2+} ion via binding sites consisting of an amino and a nitroso group. All the crystal structures reported for complexes with similar ligands show the coordination through amino nitrogen and nitrogen of nitroso group.[36-41] Thus, the lone pair of electrons on the nitrogen atoms of the amino and nitroso groups of the sensor **UNA-1** are delocalized to the vacant orbital localized on the Cu^{2+} as shown in the Fig. 6. This electron donation or charge transfer gave rise to a color change from colorless to clear yellow. The charge of the copper is +2 and hence there should be two negative charges in our proposed structure for charge neutrality. Therefore, we propose the deprotonation of $-NH_2$ group and the inclusion of ClO_4^- counter ion in the complex formula. Further, for more evidence of the binding of the Cu^{2+}, we carried out ^{1}H NMR titration studies on **UNA-1** by adding Cu^{2+} solutions (Fig. S4). It was observed that the peak at δ 12.91 corresponding to the $-NH_2$ protons showed an up-field shift from 12.91 to 12.52 ppm accompanied by a broadening of the peak, while the peak at δ 9.08 corresponding to the –NH proton shows a small downfield shift from 9.08 to 9.28 ppm with broadening of the peak on addition of 1.0 equivalent of copper perchlorate. These observed shifts could be due to the complexation as proposed earlier. The possible 3D structure and the charge transfer processes occurring during the encapsulation of Cu^{2+} by **UNA-1** was investigated by density functional theory

(DFT) calculations. The optimized structure of **UNA-1** and its complex with Cu^{2+} are shown in **Fig. 7**. On complexation of **UNA-1** with Cu^{2+}, a lowering in the interaction energy by -145.16 kcal/mol was observed, which indicates the formation of a stable complex with the calculated average Cu-N bond length of 2.062 Å. Further, the analysis of the frontier molecular orbitals (FMOs) plots (**Fig. 7b-c**) of the **UNA-1.**Cu^{2+} complex indicates that the intramolecular charge transfer (ICT) occurred between the receptor **UNA-1** and Cu^{2+}. Also, the band gap between the beta HOMO and LUMO of **UNA-1.**Cu^{2+} complex was lowered than the receptor **UNA-1**, which caused the experimentally observed red-shift in the absorption band.

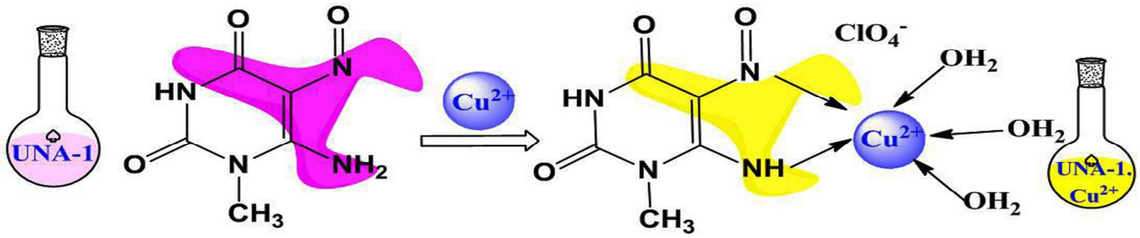


Fig. 6. Proposed mode of binding of Cu^{2+} ion with **UNA-1** as shown by the color change.

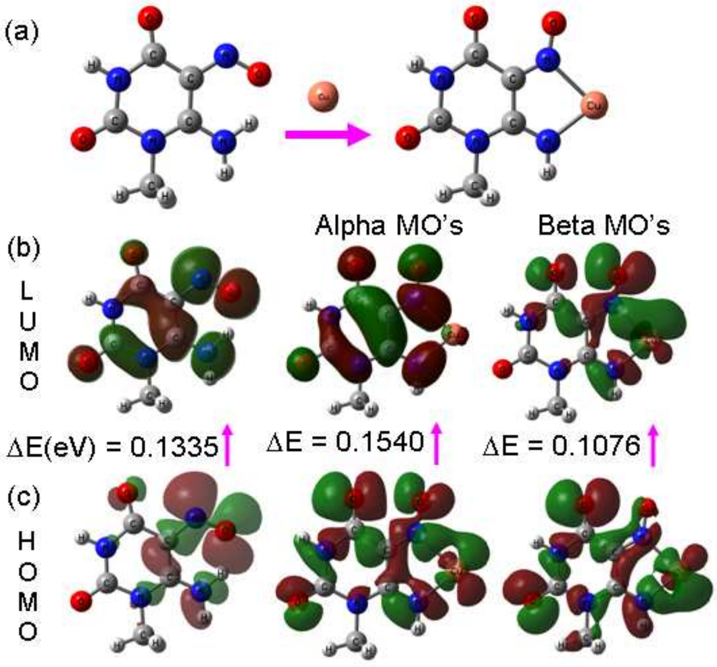


Fig. 7. DFT computed (a) optimized structure of **UNA-1** and its complex with Cu^{2+}, and the (b) LUMO and (c) HOMO diagrams of **UNA-1** and its **UNA-1**).Cu^{2+} complex.

Practical applications of UNA-1

The analytical applicability of **UNA-1** was first tested by performing competitive experiments. The absorption and color changes caused by the mixture of Cu^{2+} with the other metal ions was similar to that caused by Cu^{2+} alone (Fig. S5), which indicates that the other metal ions did not interfere with the binding of the chemosensor **UNA-1** with Cu^{2+}. Secondly, the reversibility of **UNA-1** for the detection of Cu^{2+} was examined. To perform the reversibility test, a stock solution of **UNA-1** (1 x 10^{-3} M**)** was first treated with 1 equivalent of Cu^{2+}. The color of the solution changes from colorless to yellow. To the same solution, the reverse color change from yellow to colorless was observed upon addition of 4 equivalents of aqueous EDTA solution (Fig. S6 and Supporting video). This result demonstrated the reversibility of the sensor **UNA-1**.

The sensing of Cu^{2+} by **UNA-1** worked very well on a solid support (Fig. 8 and supporting video). In this experiment, the silica gel (60–120 mesh, 10.0 g, colorless) was soaked with **UNA-1** (in methanol, 50 mL, $1x10^{-2}$ M) and then dried to afford a faint pink color silica gel due to the adsorption of the sensor on the surface. When the treated silica gel was added to a 10 mL aqueous solution of Cu^{2+} ($1x10^{-3}$ M), the faint pink color promptly turned to a dark greenish/yellow color (supporting video). The instantaneous color change of the solid silica gel in aqueous solution clearly inferred the practical application of **UNA-1** for the qualitative detection of Cu^{2+} in aqueous medium. Then, the **UNA-1** supported silica gel was treated with different concentrations of Cu^{2+} (B = 1 x 10^{-3} M, C = 1 × 10^{-4} M, D = 1 x 10^{-5} M, E = 1 x 10^{-6} M), which indicated that the silica gel can be used to detect Cu^{2+} up to 1 x 10^{-5} M by a visually detectable color change (Fig. 9). The results indicate that we can use this silica supported method not only in the determination of Cu^{2+} ions from water but also in the extraction / seperation of Cu^{2+} ions from water.

In another approach, the practical utility of **UNA-1** for the detection of Cu^{2+} was studied by developing a test paper strip. The cellulose paper (Whatman No. 42) was dipped in the methanolic solution of **UNA-1** (1x10^{-2} M) followed by drying in air to prepare the desire test strip. When this strip was dipped into an aqueous solution of Cu^{2+} (1x10^{-3} M), the colorless strip sharply turned to a yellow color (Fig. S7 and supporting video). The rapid color change of the test strip in solution clearly inferred the practical application of **UNA-1** for the qualitative detection of Cu^{2+} in aqueous medium.

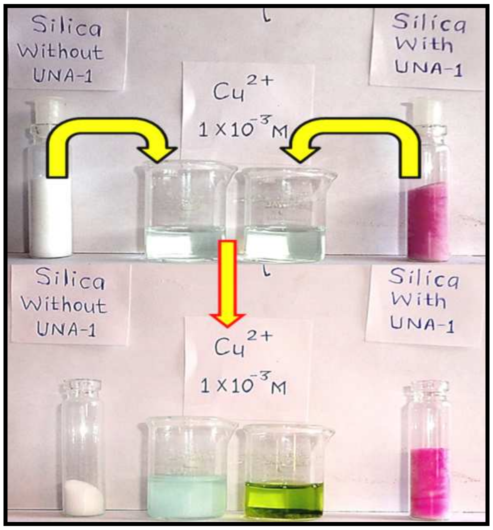


Fig. 8. Application of sensor **UNA-1** on supported silica, and color changes of silica gel with / without **UNA-1** and Cu^{2+} solution (before and after the addition).

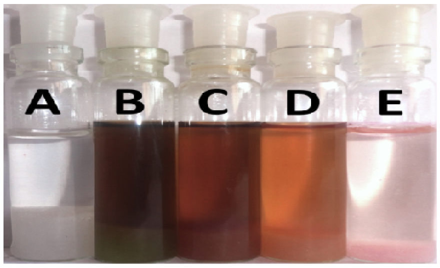


Fig. 9. UNA-1 supported silica gel was treated with different concentrations of Cu^{2+}. A=silica without **UNA-1** + 1 x 10^{-3} M Cu^{2+} as controle.

Conclusion

In summary, we have developed a simple uracil nitroso amine derivative **UNA-1** for the colorimetric detection of Cu^{2+} in aqueous media. The sensor exhibited excellent selectivity and high sensitivity towards Cu^{2+} ions. The recognition of Cu^{2+} induced a clearly distinct color change of **UNA-1** from colorless to yellow allowing for naked-eye detection. Moreover, **UNA-1** can be applied to the detection of Cu^{2+} in aqueous media by a test paper strip and silica support method. These methods offer a very simple and quick detection for Cu^{2+} in aqueous media with a detection limit down to 10 μM. The good selectivity of sensor **UNA-1** towards Cu^{2+} coupled with the use of pure water as the sole solvent in the detection process makes **UNA-1** a promising candidate for the qualitative and quantitative detection of Cu^{2+} in various chemical, environmental and biological systems.

Experimental

Chemicals and Instrumentations

Unless otherwise stated, all chemicals used for the synthesis of **UNA-1** were of AR grade and were purchased either from S.D. Fine chemicals or Sigma Aldrich. All solvents were of spectroscopic grade and were used without further treatment. The aqueous stock solutions of cations (1×10^{-2} M) such as Ag^+, Al^{3+}, Ba^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Cr^{3+}, Fe^{2+}, Fe^{3+}, Mg^{2+}, Mn^{2+}, Ni^{2+}, Pb^{2+}, and Zn^{2+} were prepared from their perchlorates salts; Ca^{2+}, Na^+, Sr^{2+} and Cs^+ were prepared from their nitrate salts; Hg^{2+} from its chloride salt and Li^+ from its bromide salt. The stock solution of **UNA-1** (1×10^{-3} M) was prepared in methanol and then diluted to 5×10^{-5} $molL^{-1}$ with methanol:water (10:90, *v/v*).

The ^1H and ^{13}C NMR spectra were recorded on a Jeol JNM-ECX 500 MHz multinuclear probe NMR spectrometer at ambient temperature in DMSO-d_6 with TMS as internal standard and chemical shifts reported in ppm. Mass spectra were recorded on a Bruker Compact HD mass spectrometer. The IR spectra were recorded on a Perkin Elmer FTIR spectrophotometer by using KBr discs and the IR bands are expressed in frequency (cm^{-1}). Absorption spectra were recorded on a Perkin Elmer U 3900 Co, USA UV/Visible double beam spectrophotometer. The purity of the compound and progress of the reaction was monitored by means of a thin layer chromatography (TLC). Pre-coated silica gel 60 F_{254}

(Merck) on alumina plate (7 x 3 cm^2) was used and visualized by using either an iodine or a short UV/Visible lamp. Melting points were recorded on the Celsius scale by open capillary method and are uncorrected.

Synthesis of UNA-1

The chemosensor **UNA-1** was synthesized by following the reported method[42] in two steps as depicted in Scheme 1. In the first step, ethyl cyanoacetate (2.1 mL, 0.019 mol) was added from a dropping funnel under vigorous stirring to a solution of sodium ethoxide prepared from 0.92 g of metallic sodium and 20 mL of ethanol. A white solid was separated from the solution. After the complete addition of ethyl cyanoacetate, the mixture was stirred for 20 min at room temperature. *N*-methylurea (1.20 g, 0.016 mol) was added and the mixture was heated for 3 h under reflux conditions on a water bath. The obtained white precipitate was filtered off, washed with ethanol, and then dissolved in 10 mL of water. The pH of the solution was adjusted to 7 by adding dilute sulphuric acid (2 N), and the mixture was stirred for 2 h to afford the pyrimidine **1** as product in 95 % yield, m.p > 300 ^{0}C.

In the second step, a solution of 1.50 g of sodium nitrite in 4.0 mL of water was added to a mixture of 2.41 g of 5-amino-2,4-dihydroxypyrimidine (**1**) and 12 mL of water. Then, 1.70 g of conc. H_2SO_4 was added dropwise under vigorous stirring. A solid precipitated, which was stirred for 6 h at room temperature, and the obtained product was filtered and washed with ethanol and water. Yield 86 %. IR spectrum, ν, cm^{-1}: 3550, 3320, 3157, 3040, 2968, 2851, 1722, 1712, 1666, 1630, 1513, 1594, 1513, 1462, 1436, 1385, 1288, 1237, 1140, 1079, 1053, 512, 491. HRMS: m/z 207.0405 corresponding to the species (UNA-1).$2H_2O$+H. ^{1}H NMR (500 MHz, DMSO d_6, δ ppm): 12.91 (s, 2H, $-NH_2$), 9.08 (s, 1H, -NH), 3.25 (s, 3H, $-CH_3$).^{13}C-NMR (125 MHz, DMSO d_6, δ ppm): 27.95 ($-CH_3$), 139.23 (-CN=O), 146.25 (C-NH_2), 149.50 (C=O), 160.40 (C=O). (Fig. S8-S11).

Computational study

The structural optimization of **UNA-1** and its host-guest complexes with Cu^{2+} was performed using the computer program Gaussian 09W[43] by applying the density functional theory (DFT) method. All the DFT calculations were performed in the gas phase with a hybrid functional B3LYP (Becke's three parameter hybrid functional using the LYP correlation functional) using the basis sets 6-31G (d,p) for C, H, N, O atoms and LANL2DZ for Cu atom.

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