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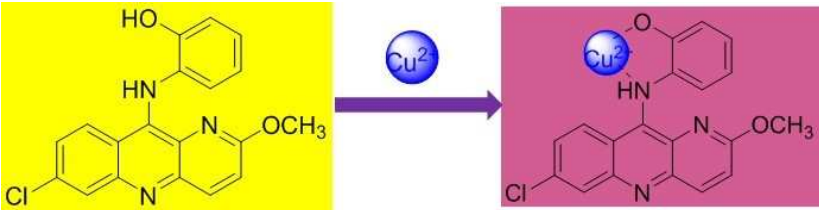
The first acridine derivative used as a colorimetric sensor for Cu^{2+} detection was reported with a color change from yellow to pink observed by naked-eyes.



Highly sensitive and selective "naked eye" sensing of Cu(II) by a novel acridine-based sensor both in aqueous solution and on the test kit

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Abstract

A highly selective and sensitive acridine-based colorimetric sensor 2-((7-chloro-2-methoxybenzo[b][1,5]naphthyridin-10-yl)amino)phenol (**NAP**) was developed for detection of Cu^{2+} ions both in aqueous solution and on test papers. Sensor **NAP** responses to Cu^{2+} ions by changing its color from yellow to pink, which could be easily observed by the naked eyes. Furthermore, the mechanism of the binding model of **NAP**-Cu^{2+} complex was investigated by ^{1}H-NMR, HRMS analysis, and DFT calculations.

Keywords: Cu^{2+} ion; acridine; Colormetric sensor; sensitive; selective; paper test.

1. Introduction

Copper (II) ion (Cu^{2+}), the third essential trace element found in the human body, plays a crucial role in many physiological processes, such as hemoglobin biosynthesis, dopamine production, nerve function regulation, gene expression, bone development, and the functional as well as structural enhancement of proteins [1-4]. However, excessive amounts of copper in cells was discovered in many neurodegenerative diseases including Menkes, Wilson's, Parkinson's, Alzheimer's, and prion diseases [5-7], and the kidney and liver damage [8-9]. Recent studies also indicate that it can regulate tumor cell growth [10-11]. Many methods have been developed for copper detection, including atomic absorption spectrometry (AAS), inductively coupled plasma mass spectrometry (ICP-MS), inductively coupled plasma atomic emission spectrometry (ICP-AES), total reflection X-Ray fluorimetry (TXRF), and anodic stripping voltammetry (ASV), which often require expensive and sophisticated instrument or complex sample preparation procedures [12-18]. Alternatively, color changing based chemical probes that can be observed by the naked eyes are widely explored in recent years owing to its convenient and efficient dection. Such as Thiadiazole [19-20], rhodamines [21-23] and quinolones [24-30] derivatives are widely used for the detection of metal ions in aqueous solution and living system.

Colormetric sensors are widely applied for the environmental inspection due to its highly selectivity, rapid and convenient dection. Our group has been focusing on developing new acridine and quinolone derivatives [31-34] to study their application in pharmaceutical chemistry and metal ions detection fields. In order to develop Cu^{2+} sensors whose performance could be detected by the naked eyes, based on our previous studies [35-36], herein we designed and synthesized a 2-((7-chloro-2-methoxybenzo[b][1,5]naphthyridin-10-yl)amino) pheno (**NAP**) sensor. We believe that the hydroxyl and nitrogen of **NAP** can bind with Cu^{2+} to form a extend conjugation plane, which might cause a great change in color. The sensitivity and selectivity of **NAP** for Cu^{2+} detection were systematically investigated. The results showed that only Cu^{2+} could induce significant changes of the absorption spectra of **NAP** accompanied with a color change from yellow to pink. The binding model of **NAP**-Cu^{2+} complex was investigated by ^{1}H-NMR, HRMS analysis, and DFT calculations. We proposed that **NAP** could recognize Cu^{2+} by forming a large conjugation plane with Cu^{2+}, resulting in a red shift of electronic transition and correspondingly color-transform of **NAP**. Meaningfully, a simple colorimetric paper-made test kit based on **NAP** was developed for detection of Cu^{2+}. Together, a convenience, low cost, effective and easily-prepared Cu^{2+} colorimetric acridine sensor was prepared, which is the first report of an acridine derivative as a colorimetric sensor for Cu^{2+}.

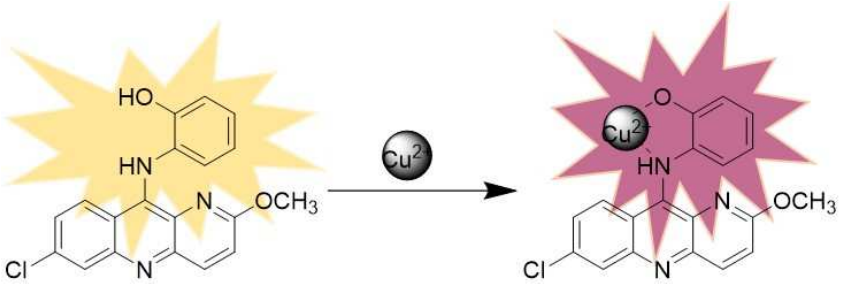


Fig. 1. Colorimetric sensor **NAP** and **NAP**-Cu^{2+} diagram.

2. Experimental section

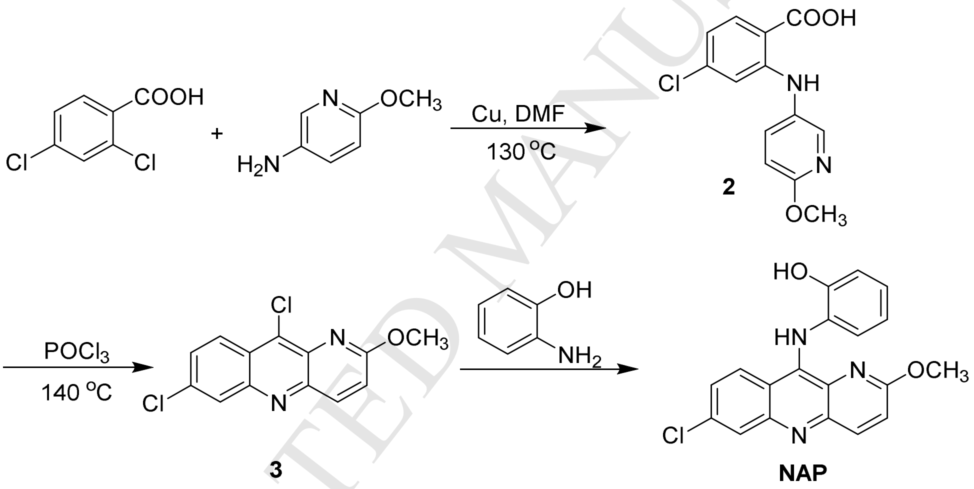
2.1 Methods and measurements

Chemicals and reagents 2, 4-dichlorobenzoic acid (98%, Energy), 5-amino-2-methoxypyridine (98%, Energy), $POCl_3$ (99.5%, Energy), 2-aminophenol (99%, Energy) were obtained commercially and used without further purification. Solutions of the metal ions were prepared from $MgCl_2 \cdot 6H_2O$, $MnCl_2 \cdot 4H_2O$ (Fuchen Chemical), $NiCl_2 \cdot 6H_2O$, $CoCl_2 \cdot 6H_2O$ (Sigma alorich), KCl, NaCl (Sangan Biotech), $PbCl_2$, $CrCl_3 \cdot 6H_2O$, $ZnCl_2 \cdot 6H_2O$, $CaCl_2 \cdot 4H_2O$, $CuCl_2 \cdot 3H_2O$, $BaCl_2$, $AlCl_3 \cdot 9H_2O$, $FeCl_3 \cdot 9H_2O$ and $SnCl_2$ (Aladin). Sodium salts (NO_2^-, HPO_4^{2-}, $S_2O_5^{2-}$, ClO^{2-}, Cl^-, OH^-, I^-, SO_4^{2-}, $H_2PO_4^-$, S^{2-}) to prepare anions solutions (0.001 M) were purchased from Energy. All the organic solvents were purchased from Adamas. All solutions were prepared using ultrapurified water (18.4 MΩ cm) deionized by a Milli-QSP reagent water system (Millipore). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Ultrashield TM 400 PLUS spectrometer. UV-Vis spectroscopy measurements were acquired on a SCINCOS-4100 UV/Vis spectrophotometer. Mass spectrum (MS) was obtained with a Waters Q-TOF premier Mass Spectrometer. Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Microplate Reader was gained from TECAN Infinite M1000PRO.

3. Results and discussion

3.1 Molecular structure of **NAP**

NAP was synthesized *via* a simple procedure that had been reported by our previous work [36] as shown in **Scheme 1**. The character identification data, ^{1}H/^{13}C-NMR and HRMS of **NAP** were shown in Figure **S1-S3**.



Scheme 1. The synthetic route for **NAP**

3.2 **NAP** color transformation towards Cu^{2+}

To tentatively evaluate the potential of using **NAP** as a colorimetric sensor for copper (II), we test its UV-Vis absorption spectrum. As shown in **Fig.2**, upon addition of 5.0 equiv of Cu^{2+} to the pure **NAP** (20 μM) dissolved in CH_3CN/H_2O (1:9, *V*/*V*), a newly-presented red shift of the absorption spectrum of **NAP**-Cu^{2+} solution was observed compared with the pure **NAP**. Consequently, the color of the **NAP** solution

(20 μM) was changed from light yellow to pink after the addition of Cu^{2+} (100 μM) （**Fig. 2**）. The obvious color change upon addition of Cu^{2+} makes **NAP** a potential colorimetric sensor for Cu^{2+} inspected by the naked-eyes.

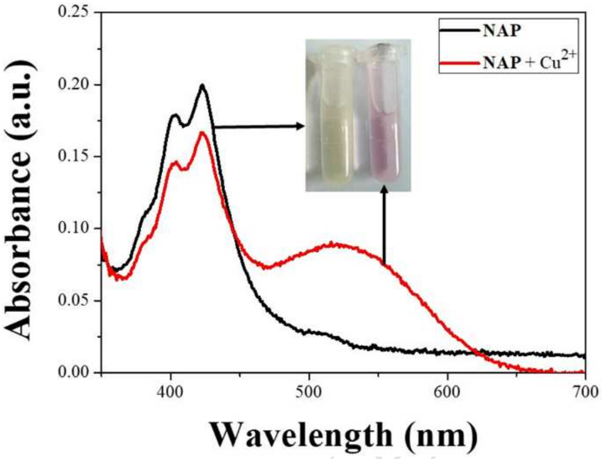


Fig. 2. UV-Vis absorption spectrum of pure **NAP** (20 μM) in CH_3CN/H_2O (*V*/*V*, 1: 9) and upon addition of 5.0 equiv of Cu^{2+}. Inset: pure **NAP** solution (left) and **NAP** + 5.0 equiv of Cu^{2+} (right)

3.3 Sensing performance of **NAP** towards Cu^{2+}

3.3.1 Selectivity and interference from other metal ions

To examine the selectivity of **NAP** to Cu^{2+}, the UV-vis absorption spectra of **NAP** in the presence of different transition metal ions were tested. As shown in **Fig. 3**, after the addition of different mental ions including Al^{3+}, Na^{+}, Fe^{3+}, K^{+}, Zn^{2+}, Sn^{2+}, Pb^{2+}, Ba^{2+}, Co^{2+}, Ni^{2+}, Ca^{2+}, Cr^{3+}, Mg^{2+}, Mn^{2+}, and Fe^{2+} to the **NAP** solution dissolved in CH_3CN-H_2O (*V*/*V*, 1: 9), no significant spectra change was observed in the absorption band of **NAP**. While for the Cu^{2+}, a new absorption band was observed around the

500 nm to 600 nm. At the same time, the color of the **NAP** solution mixed with Cu^{2+} gave rise to a yellow to pink color change.

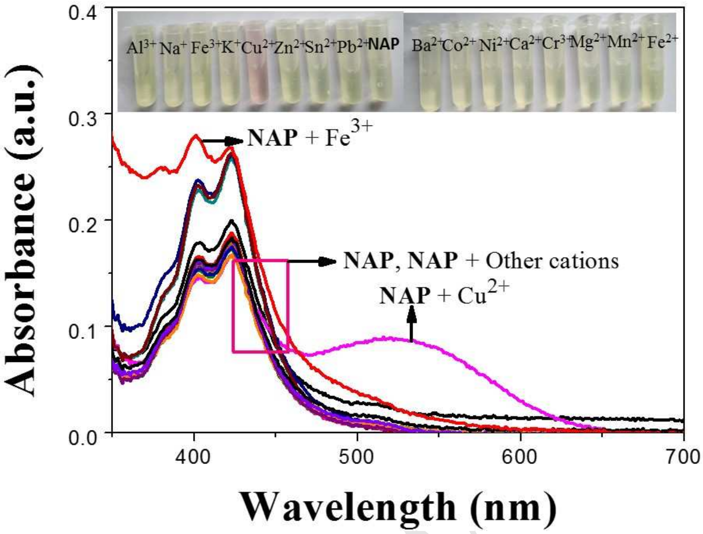


Fig. 3. UV-vis spectra responses of **NAP** (20 μM) with different metal ions: Al^{3+}, Na^{+}, Fe^{3+}, K^{+}, Cu^{2+}, Zn^{2+}, Sn^{2+}, Pb^{2+}, Ba^{2+}, Co^{2+}, Ni^{2+}, Ca^{2+}, Cr^{3+}, Mg^{2+}, Mn^{2+}, Fe^{2+}. (5 equiv., 100 μM respectively) in CH_3CN/H_2O (*V*/*V*, 1: 9). Inset: photograph of **NAP** upon addition of different metal ions.

To examine the sensitivity of **NAP** towards Cu^{2+}, a titration experiment of **NAP** (20 μM) with Cu^{2+} (0-10 μM) in the solvent CH_3CN/H_2O (*V*/*V*, 1: 9) was carried out. As shown in **Fig. 4a**, the UV-vis spectra were recorded after addition with different concentrations of Cu^{2+} from 2 μM to 20 μM. Increased absorption intensity at 540-600 nm was observed upon the addition of enhanced concentration of Cu^{2+}. As shown in **Fig. 4b**, a good linear relationship ($R^2 = 0.9655$) between the absorption intensity and Cu^{2+} concentration (0-10 μM) demonstrated that Cu^{2+} concentration can be quantitatively derived with a limitation detection of 1.6 × 10^{-7} M on the basic of 3σ/k [37-38] by the **NAP** sensor, which is below the stipulated limitation of copper concentration in drinking water (31.5 μM) with the World Health Organization (WHO) guideline [39-41], indicating its potential use in the environmental protection aspect. These results suggest that compound **NAP** has a high selectivity to Cu^{2+}, and could be exploited as a colorimetric sensor for Cu^{2+}.

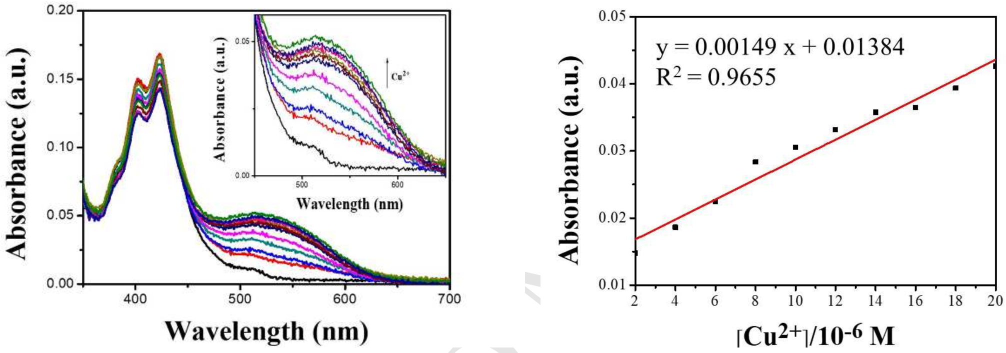


Fig. 4. (a) UV-vis spectra of **NAP** in the presence of different concentrations of Cu^{2+} in CH_3CN/H_2O (*V*/*V*, 1: 9). (b) Calibration curve obtained for UV-vis spectra intensity (at 553 nm) of **NAP** versus the concentration changes of Cu^{2+} ions (0 - 10 μM) in CH_3CN/H_2O (*V*/*V*, 1: 9)

To estimate the specificity of **NAP**, competitive experiments were carried out (**Fig. 5a**). From the instrumental read-outs, the spectral responses of **NAP** to different cations can be classified into two types. For type 1 cations such as K^+, Na^+, Zn^{2+}, Cd^{2+}, Pb^{2+}, Co^{2+}, Ni^{2+}, Ca^{2+}, and Mg^{2+}, Mn^{2+}, Ba^{2+},Sn^{2+}, the spectral changes of the solutions of **NAP** were negligible before and after these cations added. Trivalent ions

(Fe^{3+}, Cr^{3+}, Al^{3+}) are the type 2 cations that induced the slightly absorbance of **NAP**-Cu^{2+} solution, which is possible to distinguish between trivalent cations and monovalent/bivalent cations [42].

To evaluate the effect of anions on the detection efficiency of **NAP**, we investigated the binding behavior of the metal-based sensor (**NAP**-Cu^{2+} complex) towards various anions including NO_2^-, HPO_4^{2-}, ClO_2^-, Cl^-, I^-, SO_4^{2-} and S^{2-} (**Fig. 5b**). The results show that these anions except S^{2-} have modest interference in the detection of Cu^{2+}, and block the color and absorption-change of the **NAP**-Cu^{2+} system, except for S^{2-} which can coordinate with copper ions to form a more stable species copper sulfide precipitation, ensuing on release of the free **NAP (Fig. S6)**, In addition, addition of EDTA to the NAP-Cu^{2+} complex solution, the absorbance intensity of this solution was recovered (**Fig.S7**). This was attributed to the higher chelating ability of EDTA for Cu^{2+} ($\lg K_{Cu\text{–}EDTA} = 18.8$). Cu^{2+} was removed from the surface of NAP-Cu^{2+} with the addition of EDTA to the system resulting in the restoration of absorption, which is consistent with the previously reported studies [43].

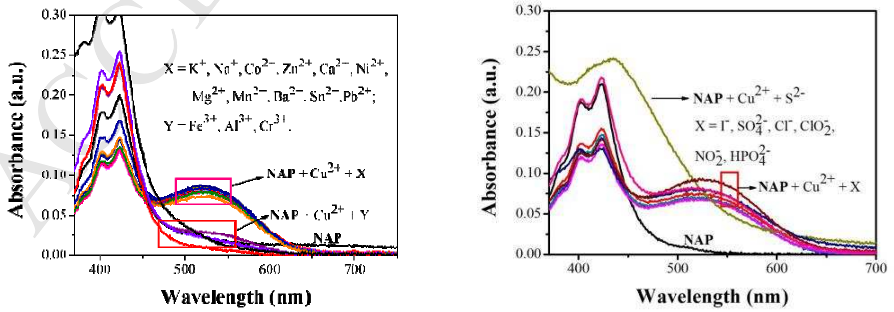


Fig. 5. UV-Vis absorption spectrum of **NAP** (20 μM) and Cu^{2+} (100 μM) upon the addition of various (a) cations (100 μM) and (b) anions (100 μM) in CH_3CN/H_2O (*V*/*V*, 1: 9).

3.3.2 Effect of pH

To explore the appropriate pH condition for successful operation of the sensor, the absorption of **NAP** was tested in buffer solution with different pH values. As shown in **Fig. 6**, **NAP** absorption performed well from pH 5 to 8. For the buffer with pH greater than 8, the absorption of the **NAP** solution decreased, likely due to the precipitation of $Cu(OH)_2$ in the alkaline conditions [44-45], which can weaken the absorption intensity of **NAP**-Cu^{2+} complex at 540-600 nm. For the buffer with pH below 5, **NAP** was failed to response to the Cu^{2+}, which might be caused by the protonation of the nitrogen atom in the acridine. Compared the absorption spectra of **NAP** alone and the mixture of **NAP** and Cu^{2+}, pH 6-7, with a maximum absorption difference, is the appropriate condition for **NAP** to identify Cu^{2+}.Thus, pH 6-7 was chosen as an optimum experimental condition for the following experiments of potential applications.

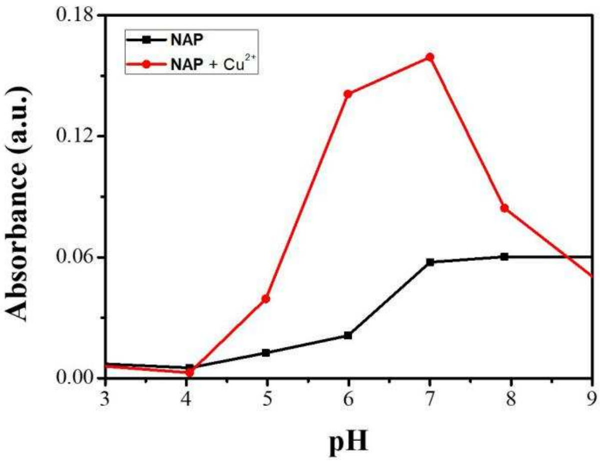


Fig 6. UV-Vis absorption spectrum of **NAP** (20 μM) at various pH values in the absence or presence of 5 equiv. Cu^{2+} in Tris-HCl buffer solution.

3.3.3 Possible sensing mechanism of **NAP** with Cu^{2+}

To determine the binding stoichiometry of **NAP** and Cu^{2+}, Job's method for UV-Vis absorption was carried out (**Fig. 7**). The maximum absorption band was reached at a molar fraction of 0.5, indicating a 1:1 ratio for **NAP**-Cu^{2+} complex, which could be further confirmed by ESI mass spectra. As shown in **Fig. 8**, the cluster peaks at 352.0852 and 412.9986 corresponded to [**NAP** + H]$^+$ (calcd = 352.0847) and [**NAP** + Cu^{2+} - H^+]$^+$ (calcd = 412.9976), respectively were observed. This results further suggested that the formation of a 1:1 **NAP**/Cu^{2+} complex. The proposed **NAP**-Cu^{2+} binding modes were discussed and shown in **Fig. S5**.

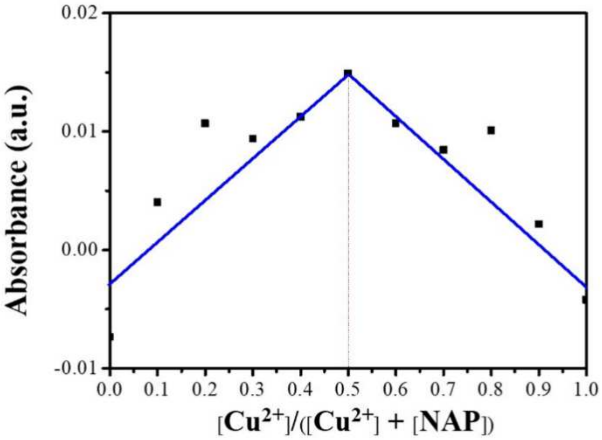


Fig. 7. Job's plot obtained for **NAP** and Cu^{2+} ion in CH_3CN/H_2O (*V*/*V*, 1: 9). The total concentration of **NAP** and Cu^{2+} was fixed at 20 μM. The UV-vis absorption was measured at 553 nm.

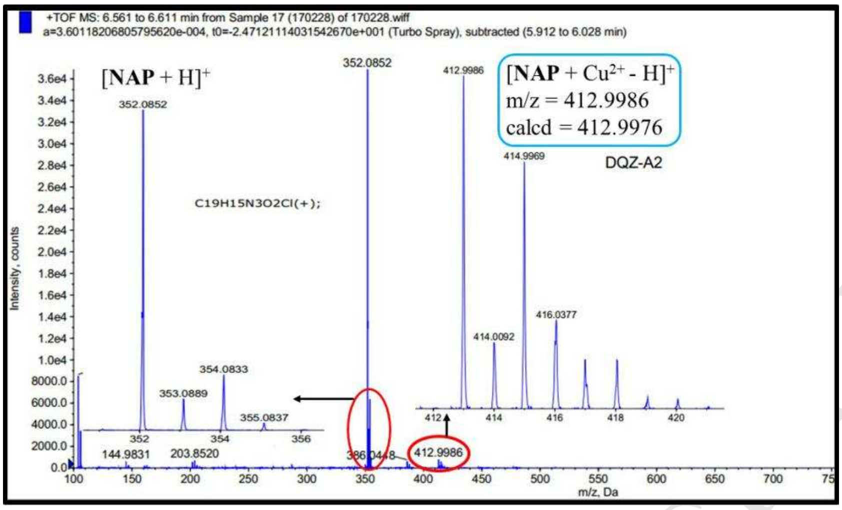


Fig. 8. ESI mass spectra of **NAP** in the presence of $CuCl_2$ (2 equiv.), indicating the formation of a 1:1 **NAP**/Cu^{2+} complex.

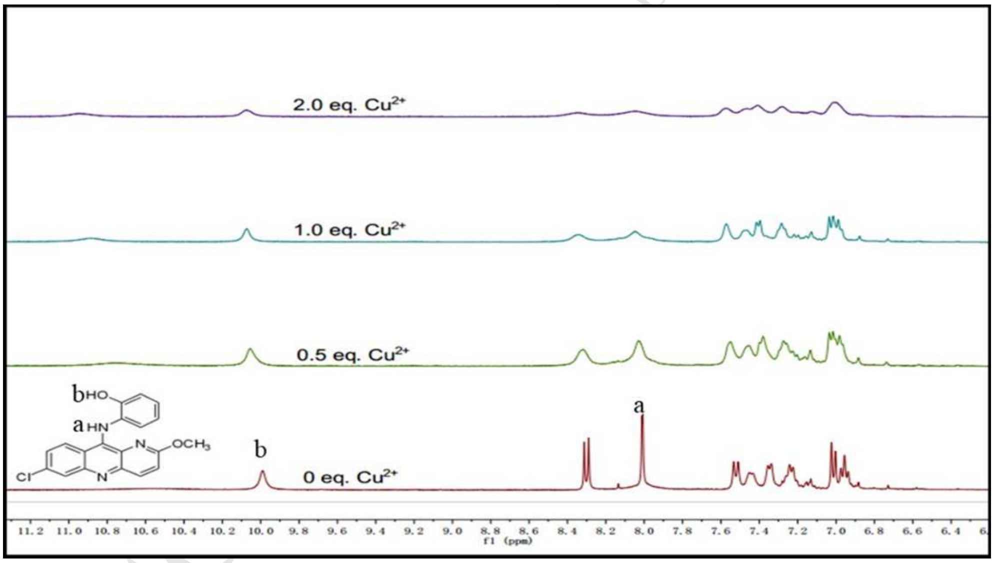


Fig. 9. ^{1}H NMR titration analysis of (1) **NAP**, (2) **NAP** + 0.5 equiv. Cu^{2+}, (3) **NAP** + 1.0 equiv. Cu^{2+}, and (4) **NAP** + 2.0 equiv. Cu^{2+} in DMSO-d_6.

Further insights into the nature of **NAP**-Cu^{2+} interactions were provided by ^{1}H NMR experiments in DMSO-d_6 solvent (**Fig. 9**). The cation-induced chemical shift changes were measured with the variation of the mole ratio (Cu^{2+}/**NAP**, 0-2 equiv.).

Cu^{2+} is a paramagnetic cation and can affect the proton signals, which leads to the tardily disappeared split of the peaks. With the addition of Cu^{2+}, all the chemical shift of the aromatic hydrogens (ArH) have few shift. Obviously, the H signals of the phenolic hydroxyl (–OH–) and secondary amine (–NH–) became broader and weaker, which indicate that the phenolic hydroxyl and nitrogen of the secondary amide might have participate in the binding with Cu^{2+}, which were in accordance with previous reports [46-47].

DFT calculation on **NAP** suggests that the highest occupied molecular orbital (HOMO) of **NAP** is mainly distributed on the phenyl group while the lowest unoccupied molecular orbital (LUMO) localizes on the phenol chain of an empty d orbital of **NAP**, as shown in **Fig. 10**. The band gap between HOMO (-5.65 eV) and LUMO (-2.15 eV) of **NAP** was calculated as 3.50 eV. On the other hand, the band gap between HOMO (-4.93 eV) and LUMO (-2.50 eV) of the **NAP**-Cu^{2+} complex had increased to 2.43 eV. From this calculation, we noticed that the color changes by Cu^{2+} could be rationalized in terms of the occupancy of the frontier orbitals, the conversion of **NAP** to **NAP**-Cu^{2+} decreases the energy gap, leading to a large-scale spectrum red shift, guaranteeing the requirement for colorimetric detection from yellow to pink, which is similar to that reported by Fang and Kim [48-49].

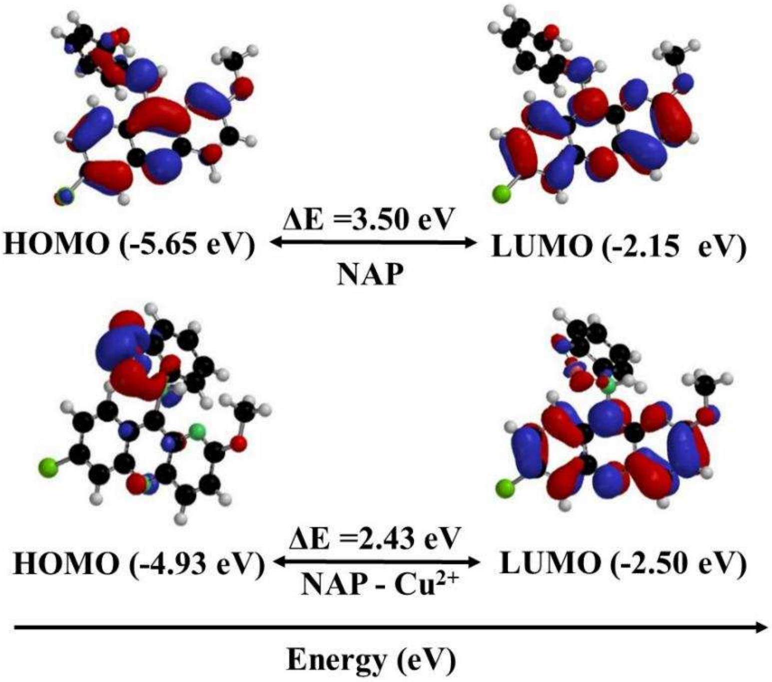


Fig. 10. Frontier molecular orbital profiles of **NAP**-Cu^{2+} based on DFT (B3LYP/6-31G*) calculations.

4. Potential applicability of NAP

To explore the potential applications of sensor **NAP**, test strips were prepared by immersing filter papers into a MeOH solution of **NAP** (20 μM) and then drying in air. The test strips containing **NAP** were utilized to sense different cations by being immersed into different cation solutions for 10 s. After several drops of ethanol (to dissolve **NAP**) were added, the obvious color change was only observed by the immersion of Cu^{2+} solution. Also, these test strips were tested for sensing different concentrations of Cu^{2+}, colorimetric changes can be observed and distinguished by naked-eyes. The pink color of the test strips intensified from increased concentration of Cu^{2+} at 0, 1.0 μM, 5.0 μM to 10 μM demonstrate that the test strips can responsive and indicate different concentrations of Cu^{2+} even at a low concentration of 1.0 μM. Different concentration of Cu^{2+} in tap water could also be detected by the **NAP** sensor (Figure **S4**).

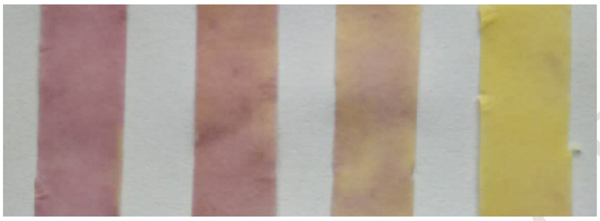


Fig. 11. Photographs of the test kits with **NAP** for detecting Cu^{2+} ion in aqueous solution with different concentrations. Left to right: 10 μM, 5.0 μM, 1.0 μM, 0 M.

5. Conclusions

In summary, an acridine-based colorimetric sensor **NAP** was designed and synthesized, which is the first report of an acridine derivative used as a colorimetric sensor for Cu^{2+} with high selectivity and sensitivity in CH_3CN/H_2O (*V*/*V*, 1: 9) solution. Mechanism study show that Cu^{2+} binds with **NAP** at 1:1 mole ratio to form a more stable and regular structure. Furthermore, **NAP** responds to paper strip tests for Cu^{2+} detection by a color change from yellow to pink. This type of highly selective naked-eye colorimetric sensor would be useful for development of new sensors for sensing ions in aqueous media.

Acknowledgement

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JCYJ20160301153959476, JCYJ20160301153753269, JCYJ20160324163734374).

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