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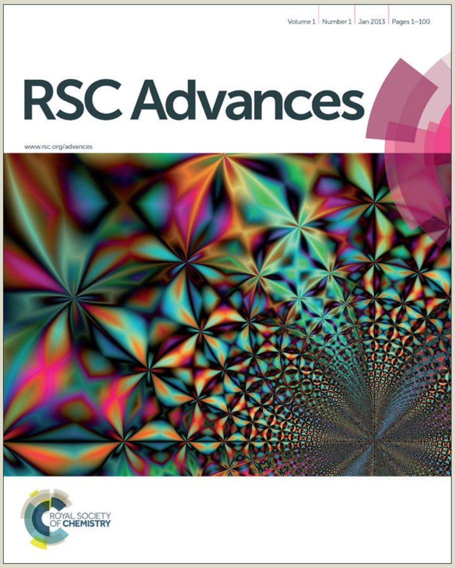

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ARTICLE

# One-pot Development of Water Soluble Copper Nanoclusters with Red Emission and Aggregation Induced Fluorescence Enhancement

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One-pot synthesis of water-soluble Cu NCs using DHLA protection ligands by different reducing reagents including $NaBH_4$, $N_2H_4$ and THPC were developed. Furthermore, it was found the as prepared Cu NCs using THPC as a reducing reagent describe fluorescence enhancement in the presence of $Zn^{2+}$ and $Al^{3+}$. It is proposed that the binding of $Zn^{2+}$ and $Al^{3+}$ to OH on the copper core of Cu NCs promotes the formation of CuNC-OH-Zn-OH-Cu NCs and CuNC-OH-Al-OH-Cu NCs aggregates respectively, which enables aggregation induced fluorescence enhancement. Additionally, it was found the fluorescence enhancement were partly reversible by the introduction of alkaline buffer solution and $Zn^{2+}$.

## Introduction

Recently, the synthesis and application of water soluble noble metal nanoclusters have drawn wide attentions in the area of green sensing and bio-imaging due to their low toxicity and excellent fluorescence behaviors such as photo stability and large stoke shift. [1-3] Though the fabrication protocols for water soluble Gold (Au NCs) and silver nanoclusters (Ag NCs) have been widely reported, less significant research activity has been contributed to the design of water soluble copper nanoclusters (Cu NCs). [4-6] However, Cu NCs may provide more cost effective sources for applications in various areas. Meanwhile, most reported water soluble Cu NCs describe blue or green emission at short wavelength. [4, 7-13] In the area of sensing or bio-applications, red emission is more expected due to the low energy, which will hardly harm living organisms. Besides, humans' eyes are sensitive to red color. Some papers reported the strategies for fabrication of Cu NCs with red emission, but the as prepared nanoclusters are not water soluble. [14, 15] Until now, only several papers reported the synthesis of water soluble Cu NCs with red emission, most of which have been using protein, peptide or the combination of polymer as templates. [16-20] For instance, Lin developed BSA protein protected Cu NCs with red emission. [18] The as prepared Cu NCs can be well applied in cell imaging and pH sensing. Li employed Transferrin protein for synthesis of Cu NCs and applied them for cancer cell imaging. Besides protein, GSH peptide (glutathione) has been used as a template for preparation of water soluble Cu NCs. [19, 20] The obtained nanoclusters could be further applied for cell study. These products for Cu NCs are well applied, but the sizes are relatively big when big molecules are used. On the other hand, fewer works contribute to the fabrication of water soluble Cu NCs with red emission using small molecules, which will possess the properties such as smaller size, easier separation and low cost. For small molecules, dihydrolipoic acid (DHLA) has been found as effective ligands for one-pot fabrication of water soluble Au NCs and Ag NCs with red emission, but it has only been employed for the preparation of Cu NCs with green and orange emission in the absence of additional ligand. [21, 22] In this work, we for the first time develop several strategies for one-pot synthesis of water soluble Cu NCs stabilized by DHLA with red emission based on the introduction of various kinds of reducing reagents. Furthermore, fluorescence enhancement was described in the presence of amphoteric metal ions such as $Zn^{2+}$ and $Al^{3+}$. The enhancement was found to be partly reversible by the introduction of metal ions such as $Zn^{2+}$ and alkaline buffer solution, which will be promising for future applications.

## Experimental

### Reagents and Instruments

(±)-α-Lipoic acid (>99%), Copper Sulfate ($CuSO_4$, >99%), Sodium hydroxide (NaOH,>99%), Sodium borohydride ($NaBH_4$, >98%) were purchased from Sigma Aldrich. Other metal salts are all of analytical grades. All the reagents for preparation of Cu NCs

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x were used as received without further purification. Deionized water (> 18 MΩ) was used through the experiment. Fluorescence spectra were recorded on a FS-2 spectrophotometer (SCINCO). Transmission electron microscope (TEM) and Energy Dispersive Spectrometer (EDS) images were obtained on a Hitachi transmission electron microscope using a JEM-1400 microscope (JEOL, Tokyo, Japan) operated at 120 kV. UV-Vis absorption spectra were performed on a UV-1600 spectrometer (Shanghai). XPS spectra were obtained on Escalab 250 X-ray photoelectron spectroscope.

### Synthesis of Cu NCs-1 using $NaBH_4$

In a typical procedure, 18.0 mg of (±)-α-Lipoic acid was dispersed in 8.0 mL of water. To the mixture, 200 µL of 1 M NaOH solution was added to decompose (±)-α-lipoic acid to DHLA. Then, 100 µL of 0.1 M $CuSO_4$ solution was combined. 3 minutes later, 100 µL of 100 mM $NaBH_4$ (100 mM) was added. The color changed to yellow within several minutes. After that, 1 mL of 100 mM $NaBH_4$ solution was combined. The mixture was allowed to stir for several minutes. Next, 500 µL of 100 mM $CuSO_4$ was combined. The mixtures were placed overnight. The final solution was stored at 4 °C.

### Synthesis of Cu NCs-2 using $N_2H_4$

In a typical procedure, 18.0 mg of (±)-α-lipoic acid was dispersed in 8.0 mL of water. 200 µL of 1 M NaOH was added to decompose (±)-α-lipoic acid to DHLA. Then, aqueous solution of $CuSO_4$ (100 µL, 100 mM) was added to DHLA solution with vigorous stirring at room temperature. 1 min later, 100 µL of $N_2H_4$ (80%) was introduced. The fluorescence can be observed after several minutes. After that, the mixture was allowed to stir for 1 hour. The final solution was stored at 4 °C.

### Synthesis of Cu NCs-3 using THPC

In a typical procedure, 18.0 mg of (±)-α-Lipoic acid was dispersed in 8.0 mL of water. 200 µL of 1 M NaOH was added to decompose (±)-α-lipoic acid to DHLA. Then, aqueous solution of $CuSO_4$ (100 µL, 100 mM) was added to the DHLA solution with vigorous stirring at room temperature. After that, 20 µL of THPC was introduced. The mixture was placed overnight. The final solution was stored at 4 °C.

### Synthesis of Cu NCs-4 using THPC in the presence of NaCl

In a typical procedure, 18.0 mg of (±)-α-lipoic acid was dispersed in 8.0 mL of water. 200 µL of 1 M NaOH was added to decompose (±)-α-lipoic acid to DHLA. Then, aqueous solution of $CuSO_4$ (100 µL, 100 mM) was added to DHLA solution with vigorous stirring at room temperature. After that, 1.0 M of NaCl was combined to facilitate the capping of DHLA. 1 min later, 20 µL of THPC was introduced. After that, the mixture was placed overnight. For the fluorescence comparison, the as prepared colloid was directly used without the separation of NaCl or other residual ions. The final solution would be stored at 4 °C.

For material characterizations including TEM, XPS and future applications in some media such as bio-culture, the as obtained DHLA-Cu NCs colloid would be dialyzed against deionized water using a 3 kDa cut-off dialysis bag for 24 h to remove the unreacted small molecules and free ions.

### Fluorescence enhancement experiments

To investigate the fluorescence behaviours of Cu NCs in the presence various metal ions, the following cations including $Co^{2+}$, $Mg^{2+}$, $NH_4^+$, $Mn^{2+}$, $Pb^{2+}$, $Cu^{2+}$, $Fe^{3+}$, $Ca^{2+}$, $Hg^{2+}$, $Al^{3+}$, $Ag^+$ and $Zn^{2+}$ were introduced. 2 mL of various metal ion solutions (400 µM) were mixed with 100 µL of Cu NCs solution to investigate the enhancement. Besides, $Zn^{2+}$ solutions at different concentrations including 0, 25, 50, 150, 250, 350, 400 and 500 µM were also studied. The fluorescence spectra of the mixtures were recorded.

## Results and discussion

### Characterization of Cu NCs

Initially, (±)-α-lipoic acid was decomposed by NaOH to DHLA ligand. The complex for DHLA-$Au^{3+}$ or DHLA-$Ag^+$ are completely dissolved in water. However, after the addition of $Cu^{2+}$, the precipitates had been observed due to the formation of DHLA-$Cu^{2+}$, $Cu(OH)_2$, and other complex such as DHLA-$Cu(OH)_x$. After that, when the reducing reagents including $NaBH_4$, $N_2H_4$ or THPC were introduced, the as formed products of Cu NCs will be soluble in water since the precipitates are soon be reduced to $Cu^0$ based on the colour change and the dissolve of the aggregates. The characterizations for the fluorescence spectra of Cu NCs are described in Fig. S1 - Fig. S5. It can be concluded from Fig. S1 to Fig. S4 that the introduction of all the reducing reagents resulted in the formation of fluorescent Cu NCs with red emission. The emission wavelength ranged from 605 nm to 680 nm (Fig. S5). However, after the investigation of the stability (see Fig. S6), it is found that the as formed Cu NCs-1 lost the fluorescence within 12 hours. This indicated Cu NCs-1 was too unstable to be employed for further applications. It is well acknowledged that water soluble $Cu^0$ tend to be oxidized in the presence of air. [23] The strong reducing reagent, $NaBH_4$ will decompose in water so fast that the residual $NaBH_4$ can't stop $Cu^0$ from further oxidation. Therefore, the as formed Cu NCs-1 will not be stable after the decomposition of $NaBH_4$. In the presence of additional $Cu^{2+}$, the forward reaction of the following equation can be inhibited due to the common ion effect.

$$Cu^{0} \xrightleftharpoons{air} Cu^{2+}$$

Thus, unlike other methods, 500 µL of $CuSO_4$ (100 mM) was used during the synthesis process. In the presence of additional $Cu^{2+}$, fluorescent Cu NCs-1 can be obtained. In previous paper, the phenylethanethiol protected Cu NCs can only be stable for 2 hours by using $NaBH_4$ as a reducing reagent. [24] The stability is similar to our Cu NCs. This reveals the as formed Cu NCs-1 will not be suitable for further applications, which is similar to the paper. Meanwhile, the introduction of $N_2H_4$ resulted in the formation of other unstable nanoclusters (Cu NCs-2) next to Cu NCs-1. Compared to $NaBH_4$, $N_2H_4$ was a weaker reducing reagent, which wouldn't decompose so fast. Thus, it has been used for synthesis of relative more stable Cu NCs by using BSA protein as a template. [18] Notwithstanding, the residual $N_2H_4$ are not enough to protect Cu NCs-2 from fast decomposition based on Fig. S6. This reveals that $Cu^0$ can't be protected just by the residual reducing reagent.

On the other hand, THPC was a weak reducing reagent, which enabled the slow formation of Cu NCs. THPC can not only act as a reducing reagent, but also it will play a role as the complexing and protection reagent that describes steric effect. [25] It can be seen from Fig. S6 that Cu NCs-3 are more stable than Cu NCs-2 and Cu NCs-1. Therefore, using THPC as a reducing reagent was further investigated. It is reported that NaCl aging will maximize the loading of thiolated single strand DNA on gold nanoparticles.[26] Since DHLA is also a thiolated ligand, it can be concluded that NaCl aging will also facilitate the modification. As well as this, it was reported the fluorescence of thiolated ligand (11-mercaptoundecanoic acid) protected gold nanodots was enhanced about 13 times in the presence of NaCl. [27] Enlightened by these phenomena, NaCl was introduced in the formation process of Cu NCs so that to facilitate the loading of DHLA on copper core. Then, it was found that Cu NCs-4 exhibited higher maxim emission intensity (see Fig. S7). The detail of NaCl effect is beyond the scope of this study, which will be discussed in the future. At the same time, we found that there was no big difference for the stability of the fluorescence for Cu NCs-3 and Cu NCs-4. In addition, the maxim fluorescence emission intensity was compared for all the obtained Cu NCs, see Fig. S7. It can be observed that Cu NCs-4 describes advantages over other nanoclusters. Based on the comparison of the fluorescence properties, Cu NCs-4 was selected for further investigation. Furthermore, the stability of Cu NCs-4 was investigated under 4 ℃ in the refrigerator, see Fig. S8. It can be seen that the fluorescence intensity decreased more slowly compared to that at room temperature. Thus, for further protection of Cu NCs-4 from oxidation, lower temperature should be applied.

The properties of the as-prepared Cu NCs-4 were characterized and described in Fig. 1. Based on the UV-Vis spectrum (Fig. 1a), no peak can be observed for normal size copper nanoparticles (around 520 - 560 nm). This is not surprising that ultra-small nanoclusters can't support surface plasmon resonance (SPR), which are similar to previous reported Cu NCs. [5] The fluorescence spectra of Cu NCs-4 had the maxim excitation and emission peaks at 362 nm and 627 nm with a quantum yield of 2.8% using Acridine Yellow as a reference (Fig. 1b). To test whether the observed fluorescence was caused by the reaction between DHLA and the reducing reagent, the emission spectra were recorded for DHLA of the same condition that has been used to synthesize Cu NCs-4, but no fluorescence was observed. This indicated the formation of fluorescent Cu NCs. Size information of Cu NCs-4 was studied by TEM. As shown in Fig. 1c and Fig. 1d, the TEM image and the size distribution diagram indicated that the average diameter of the Cu NCs was ca. 1.6 nm. Additionally, XPS characterization was carried out to determine the oxidation state of copper in Cu NCs-4. As shown in Fig. 1e, two peaks located at 931.9 eV and 951.7 eV are observed, which can be assigned to the binding energies of the 2p3/2 and 2p1/2 electrons of Cu(0), respectively. The absence of Cu2p3/2 satellite peak around 942.0 eV reveals that no Cu(II) electrons are present. Notwithstanding, the binding energy of Cu(0) is just 0.1 eV away from that of Cu(I) according to the papers. [5, 12] Therefore the valence state of copper for the obtained Cu NCs-4 most likely lies between 0 and 1, which is similar to previous reported Cu NCs. [20, 28] Moreover, it can be seen from Fig 1f that the presence of C, S and O belongs to the protecting ligand, DHLA. In summary, the optical behaviour, TEM and XPS study all confirm the formation of DHLA protected Cu NCs.

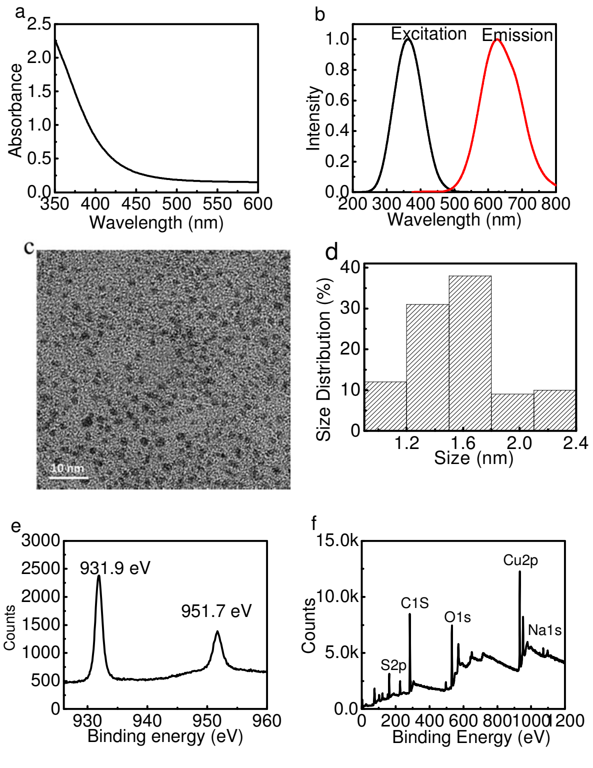

Fig. 1 UV-Vis absorption (a), fluorescence excitation, emission spectra (b), TEM (c), the corresponding size distribution (d) and XPS characterization for Cu2p (e), as well as XPS survey (f) of the as prepared Cu NCs-4.

The fluorescence behaviour of the as obtained products is demonstrated in Fig. S9. It can be observed from Fig. S9b that the maxim fluorescence intensity is obtained with 20 µL of THPC. For further increasing the amounts of THPC, the fluorescence intensity will decrease. If too much of THPC was used, the colour of the reactants would never change. Meanwhile, no fluorescence can be detected, which means no Cu NCs are formed. Thus, THPC only acts as a complexing reagent at high concentrations.

To test the effect of cations on the influence for the fluorescence of Cu NCs-4, the fluorescence emission spectra in the presence of various cations are investigated and described in Fig. 2. Among these cations, the fluorescence for Cu NCs-4 solution describe insignificant change in the presence of $Co^{2+}$, $Mg^{2+}$, $NH^{4+}$, $Mn^{2+}$, $Pb^{2+}$, $Ni^{2+}$, $Ca^{2+}$, $Ba^{2+}$. The fluorescence of Cu NCs-4 will be quenched in the presence of heavy metal ions such as $Cu^{2+}$, $Ag^{+}$, $Hg^{2+}$, $Fe^{3+}$ at the studied conditions. However, amphoteric metal ions such as $Zn^{2+}$ and $Al^{3+}$ demonstrated enhancement for the fluorescence of Cu NCs-4. Especially, the fluorescence response in the prescience of $Zn^{2+}$ is 2 times higher than that of Cu NCs-4 in the absence of $Zn^{2+}$. Both $Al^{3+}$ and $Zn^{2+}$ can combine with OH groups as well as attaching on the surface of Cu NCs to promote the formation of aggregates. This is similar to the phenomena that $Zn^{2+}$ can bind with Au NCs through the interaction with OH. [29] Then, the fluorescence enhancement was caused by the aggregation of Cu NCs-OH-Zn-OH-Cu NCs and Cu NCs-OH-Al-OH-Cu NCs respectively. It is worth noted that the fluorescence enhancement induced by $Zn^{2+}$ was more significant compared to $Al^{3+}$.The solubility product constant for $Al(OH)_3$ is much smaller than that for $Zn(OH)_2$. Thus, besides the fluorescent aggregates, the addition of $Al^{3+}$ will result in considerable chance for formation of $Al(OH)_3$ that cover on the surface of Cu NCs, which will inhibit the fluorescence measurement. On the other hand, relative less amounts of $Zn(OH)_2$ was formed on the surface at our studied condition. Then, relatively large exposure area was left for the fluorescent aggregates (Cu NCs-OH-Zn-OH-Cu NCs). The larger exposed surface area will lead to a greater enhancement of fluorescence for $Zn^{2+}$ at our studied concentrations.

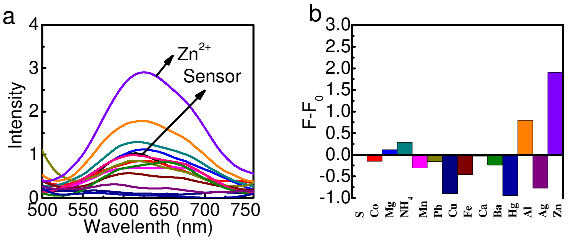

Fig.2 Fluorescence emission spectra (a) and intensity enhancement (b) of Cu NCs-4 in the presence of different cations (400 µM).

To directly view Cu NCs-4 in the presence of $Zn^{2+}$ and $Al^{3+}$, the TEM analysis was performed, and the results are displayed in Fig. 3. The aggregates are observed at lower magnifications (Fig. 3a and Fig. 3c). However, it can be seen from Fig. 3b and Fig. 3d that ultra-small particles can still be observed at higher magnifications. This indicates the aggregates may be assembled by ultra-small clusters and thus the fluorescence can be monitored. As well as this, compared to the $Al^{3+}$ aggregation product (Fig. 3d), it can be observed the $Zn^{2+}$ aggregation product are more dispersed at higher magnifications (Fig. 3b). Large aggregates are present in $Al^{3+}$ aggregation product. This reveals that some $Al(OH)_3$ may coexist as well as the assembled aggregates for nanoclusters. This is in agreement with the fluorescence measurement that the enhancement is higher for Cu NCs in the presence of $Zn^{2+}$.

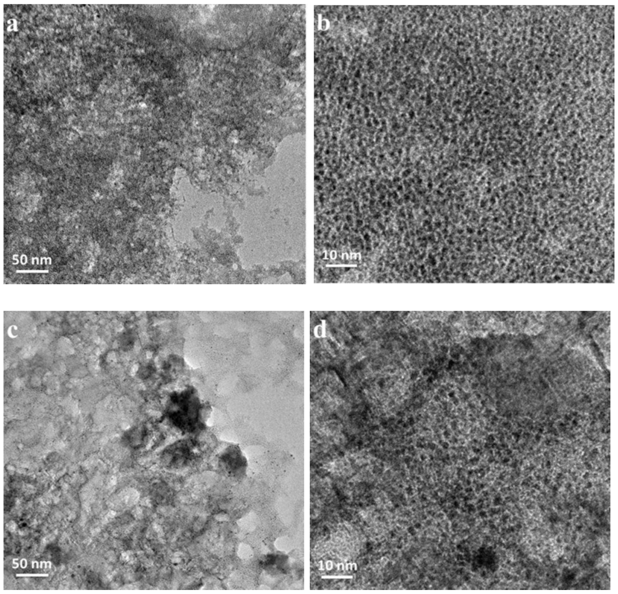

Fig.3 TEM images for Cu NCs-4 in the presence of $Zn^{2+}$ (a, lower magnification, b, higher magnification) and $Al^{3+}$ (c, lower magnification, d, higher magnification).

XPS analysis for the aggregates of Cu NCs-4 after the interaction with $Zn^{2+}$ and $Al^{3+}$ are described in Fig. S10 and Fig. S11 respectively. Cu2p described a spectrum with much weaker intensity for Fig. S10a, indicating that the surface of Cu NCs was partly covered by some hydroxides. Then, relatively small ratio of Copper could be detected by XPS. Meanwhile, the XPS study for $Al^{3+}$ binding products demonstrate even weaker peaks for Cu2p (Fig. S11a), which means relative small surface area of Cu NCs was exposed compared to $Zn^{2+}$ binding product. Furthermore, the EDS studies for the relative dispersed part of the products are described in Fig. S12. According to the EDS mapping (Fig. S12a) studies, less amounts of Al are also detected for the binding products of nanoclusters. On the other hand, Zn plays a more important role for the Zn binding nanoclusters based on the EDS study. Thus, it can be revealed that considerable ratio of Al exist in the form of $Al(OH)_3$ rather than binding with Cu NCs. This is also in agreement with the lower enhancement factor for the fluorescence of Cu NCs-4 in the presence of $Al^{3+}$.

The enhancement of the fluorescence intensity for Cu NCs-4 in the presence of $Zn^{2+}$ and $Al^{3+}$ at different pH values are investigated, see Fig. S13 and Fig. S14 respectively. It can be seen from Fig. 13 b that the fluorescence intensity of Cu NCs-4 in the presence of $Zn^{2+}$ increased more significantly than Cu NCs-4 in the absence of $Zn^{2+}$ from pH 4 to PH 7. Thus the enhancement keeps increasing until pH 7. However, when pH is higher than 8, the fluorescence intensity for Cu NCs-4 in the presence of $Zn^{2+}$ decreased due to the dissolution of the dissolution of the aggregates. Meanwhile, when pH is as high as 10, the easier oxidation of Cu NCs caused the decrease of the fluorescence of Cu NCs-4 in the absence of $Zn^{2+}$. In the presence of $Zn^{2+}$, the formation of $Zn(OH)_2$ may possibly block photo measurement of the fluorescence. Thus, more significantly decrease for the fluorescence intensity has been observed. On the other hand, for Cu NCs-4 in the presence of $Al^{3+}$ (see Fig. S14), it can be seen that the decrease for the fluorescence is even more significantly compared to Cu NCs-4 in the presence of $Zn^{2+}$ at pH 10 due to the easier formation of $Al(OH)_3$ than $Zn(OH)_2$.

Finally, a series of concentrations of $Zn^{2+}$ were introduced for investigation of the fluorescence enhancement of Cu NCs-4. Fig. 4 displays the fluorescence response of Cu NCs-4 and the fluorescence intensity change as a function of $Zn^{2+}$ concentration. It can be seen from Fig. 4a that the fluorescence intensity was rapidly enhanced with the increase of the concentration for $Zn^{2+}$ with a linear relationship in the range from 50 - 400 μM. The linear equation is fitted as Y = 0.216X + 0.0048, with correlation coefficient of 0.995, where Y indicates the fluorescence intensity enhancement ($F-F_0$) at 623 nm, X is the concentration of $Zn^{2+}$. After 400 μM of $Zn^{2+}$ was combined, the aggregates can be separated by centrifugation at 400 rpm. After that, the collected products can be re-dispersed in pH 8.0 phosphate buffer solutions. Then, the intensity change ($F-F_0$) is recorded, where F and $F_0$ are the fluorescence intensity of the new mixture and original Cu NCs-4 solution respectively. It can be seen from Fig. 4b that the fluorescence (1') is not enhanced after the aggregates are re-dispersed in buffer solution. On the other hand, the fluorescence will be enhanced again (1) after further addition of $Zn^{2+}$. However, the enhancement was not as high as the initial enhancement. This is possibly because the partly formation of $Zn(OH)_2$ that can't be dissolved in buffer solution. It can be concluded that the fluorescence is only enhanced when the aggregates are present. This further confirmed the aggregation induced fluorescence enhancement assumption.

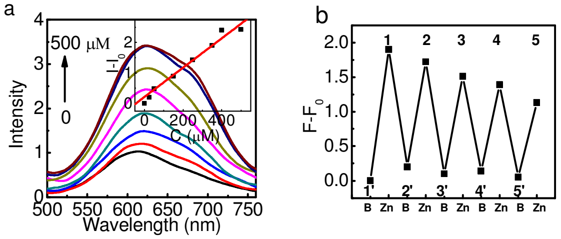

Fig. 4 (A) Fluorescence emission spectra of Cu NCs-4 solution in the presence of different concentrations of $Zn^{2+}$ (a). Inset: the fluorescence emission intensity change as a function of $Zn^{2+}$. (b) Reversibility of the fluorescence emission intensity change through consecutive disperse of the aggregates in phosphate buffer solution and addition of $Zn^{2+}$ (B indicated 10 mM of phosphate buffer solution, pH = 8.0).

Based on the fluorescence behaviour and characterization of the product, the mechanism for the enhancement of fluorescence by $Zn^{2+}$ is described in Fig. 5. Initially, OH groups are stably bound to the copper core on the surface of Cu NCs. After the addition of $Zn^{2+}$, Cu NCs will bind together through Zn-OH interactions, leading to the aggregation of the clusters. As well as this, the aggregation can be re-dispersed in alkaline buffer solution since $Zn^{2+}$ is amphoteric metal ion. Furthermore, both Al can also bind with -OH. Thus, the mechanisms for their fluorescence enhancement behaviours are quite similar.

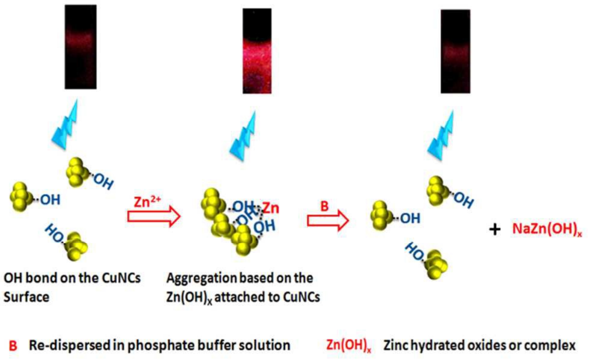

Fig. 5 Scheme for the mechanism of the aggregation induced fluorescence enhancement for Cu NCs in the presence of $Zn^{2+}$.

## Conclusions

Water soluble Cu NCs with red emission has been successfully synthesized by one-pot methods using DHLA as the protection ligand based on the introduction of various types of reducing reagents. Aggregation induced fluorescence enhancement is described for Cu NCs in the presence of $Zn^{2+}$ and $Al^{3+}$. The fluorescence enhancement is partly reversible by simply re-dispersing the aggregates in buffer solution and the addition of additional $Zn^{2+}$. We believe that our study can serve as a simple method for fabrication of Cu NCs and the applications for fluorescence enhancement.

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# One-pot Development of Water Soluble Copper Nanoclusters with Red Emission and Aggregation Induced Fluorescence Enhancement

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The binding of $Zn^{2+}$ and $Al^{3+}$ to OH on the copper core of Cu NCs promotes the formation of Cu NC-OH-Zn-OH-Cu NCs and Cu NC-OH-Al-OH-Cu NCs aggregates, which enables aggregation induced fluorescence enhancement.