

Design and Synthetic Scheme of Water Dispersible Graphene Oxide-Coumarin Complex for Ultra-Sensitive Fluorescence Based Detection of Copper (Cu²⁺) Ion in Aqueous Environment

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Abstract

Copper oxides and its salts are now widely used as pesticides to control fungal and bacterial diseases of field crops. Copper toxicity is often a major contributor of human health problems caused through accumulation of excess copper ions in various organs via drinking water, fruits and vegetables. So, detection and estimation of cupric ions in biological organs, drinking water, fruits and vegetables are extremely important. Recently, a fluorescence based sensor using coumarin dye (high quantum yield) has been proposed to detect micro-molar Cu⁺⁺ ion in biological organs. But major problem with coumarin dye is that it is insoluble in water and undergoes dye-dye aggregation in organic solvents. We proposed here a synthetic scheme of preparation of graphene oxide conjugated coumarin dye derivative which would be water dispersible and expected to be an ideal candidate for Cu²⁺ ion estimation in biological organs and drinking water.

Keywords

Copper Ion Estimation, Fluorescence Sensor, Graphene-Oxide, Coumarin

1. Introduction

Copper salts are extensively used as pesticides (*i.e.* fungicide/bactericides) to control fungal and bacterial diseases of field crops [1]. Global annual production of metallic copper and copper compounds reached 13.6 mil-

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lion metric tons in 1979 [2] and it is projected that Cu production will continue to increase in the future. Cu is naturally found in uncontaminated water sediment at a background concentration level ranging from 0.8 to 50 $\mu\text{g}\cdot\text{g}^{-1}$ (on a sediment dry weight basis) [3] whereas Cu level in uncontaminated soil is estimated to be $\sim 30 \mu\text{g}\cdot\text{g}^{-1}$ [4]. Aggressive use of Cu pesticides in agricultural industry is responsible for the accumulation of Cu in soil. There is an increasing concern that soil bound Cu might leach out from the agricultural fields and contaminate nearby water bodies such as rivers and lakes, adversely affecting the lives of aquatic vertebrates such as fish and invertebrates organisms. It is evident that continuous release of Cu to the environment through human activity will only increase the Cu level in drinking water and it could potentially exceed the EPA-set drinking water Cu limit (currently the limit is 1.3 ppm).

Copper is an essential trace element present in animal and plant tissue. However, overdose of Cu^{++} ion is toxic and harmful to human and plant species. The average concentration of copper in human blood is estimated to be in the range 15.7 - 23.6 μM . Cu bioaccumulation and its imbalance however can cause serious health problem. A number of organ damages including stomach, kidney, liver, and brain have been related to Cu imbalance. It is reported that brain metabolism process is regulated by Cu [5] [6]. A number of neurodegenerative diseases including Alzheimer are linked to disturbance in Cu mediated metabolism processes [5] [6]. Other diseases such as Aceruloplasminemia [7], Wilson's and Menki's syndrome has been also related to Cu imbalance.

There is certainly a strong need to develop sensitive probe for the detection of trace level of Cu in biological and environmental samples. Some of important applications of the proposed probe in the environment would include monitoring of i) residual Cu pesticides in the plant surface (leaves and stems and fruits), ii) agricultural soil samples and iii) Cu level in contaminated water.

1.1. Current Cu Ions Detection Techniques

Atomic Absorption Spectroscopy (AAS), Inductively Coupled Plasma (ICP-Absorption/Emission) Spectroscopy and electrochemical sensing techniques are currently used for measuring Cu^{2+} concentration in solution in the nanomolar to micromole range [8]-[11]. These techniques are expensive to run and extremely tedious. Sample preparation process is complex and time-consuming. Moreover, it is challenging to reliably detect ultra-low concentration of Cu ions in the picomolar to sub-nanomolar range using these techniques in presence of other interfering ions and dissolved molecules. Fluorescence based sensing probes have the potential to address some of the above challenges. Because of high sensitivity of fluorescence technique, it should be possible to detect ultra-low concentration of Cu ions in solution. To minimize interference, it is possible to design Cu ion selective fluorescence probes. It is also possible to increase signal-to-noise ratio by designing activatable sensing probes. Since this is an optical based technique, fabrication of a field-deployable sensor device could be possible.

Several studies have reported detection of Cu^{2+} in micro molar concentration in biological systems using fluorescent dyes [12]-[25] and fluorescent proteins [26] [27]. Weida Wang *et al.* used a fluorescent dye (2,4,6-trihydroxyphenylsquaraine) [20] as sensing probe to detect Cu ions. Despite a very complex synthesis strategy, cellular cytotoxicity was the primary limitation. In another study, 1,2,4-triazole was used as Cu ion sensing probe [28], however low stability of the probe was an issue. A similar probe based on Rhodamine dye tagged quinaldinet was developed by Zhang *et al.* [29]. This probe was able to detect Cu ions within about 10 - 15 minutes; however a large amount of the dye ($\sim 5:1$ dye to Cu ratio) was required for reliable measurements. Fluorescent proteins, red-emitting HcRed and green-emitting GFP, mutated to have Cu binding sites were shown to effectively recognize Cu ions in biological fluids [26] [27]. Upon binding to 100 μM Cu ions, almost 100% fluorescence quenching was observed. The drawback of this sensing strategy is associated with the stability of the proteins. HcRed was shown to perform better at low temperature [27]. Recently, a coumarin dye based fluorescence probe has been reported [30] that exhibits high selectivity towards Cu^{2+} ions. Fluorescence quenching is observed when Cu^{2+} ions bind to green-emitting (450 nm emission) coumarin dye derivative. The sensitivity of the detection was directly proportional to dye concentration. The probe works well in the pH range between 4 and 10 which is desired pH range for biological applications. When excess dye was used to boost the signal-to-noise ratio, self-quenching of the coumarin dye was observed due to the formation of J-aggregation [30].

In this paper, we would propose to design synthetic scheme of coumarin conjugated Graphene Oxide (GO) nanomaterial. This design will take advantage of the high selectivity of the coumarin derivative towards Cu^{2+} ions as reported in the literature [30] and minimize the self-quenching problem. This is a feasible strategy as the coumarin dye will be covalently attached to GO surface and this attachment will hinder the formation of J-aggregation of coumarin dye molecules. The use of GO to prevent such J-aggregation has been reported in the

literature [31] [32].

1.2. Graphene—A 2D Robust Substrate Having Enormously Large Surface Area

During the recent time Graphene, GO and nanomaterial research has gained a tremendous momentum because of their potential applications in material science [33] [34]. Graphene has a two-dimensional (one atom thick) crystals of SP^2 bonded carbon atoms densely packed in a honey comb crystalline lattice. The C-C bond length of graphene is 0.142 nm and Graphene sheets are stuck to form graphite with inter planner spacing of 0.335 nm. It possesses some unique properties such as high surface area (2620 m^2/g), high electronic conductivity (electron mobility 20,000 cm/second under unit potential gradient) low resistivity (specific resistance) 10^{-6} Oh-cm) high mechanical and chemical stability [35].

Calculation based on *ab initio* shows that Graphene is thermodynamically unstable if it contains less than 6000 atoms (by Shenderovaab *et al.*) [36]. Graphene is a hydrophobic material and it has no binding sites available for ions. Graphene is chemically converted to GO (via oxidation)/GO derivatives for increasing its hydrophilicity by introducing suitable functional groups. GO can be dispersed in aqueous solution and they carry hydroxyls, acids and epoxy groups on the surface [37]. Functional groups on the GO surface can be further modified to attach suitable ligands [37]. In general, GO is considered as a biocompatible material. However, there are reports showing cytotoxic effect of GO to human fibroblast cells above 50 $\mu g/mL$ concentration [38].

2. Experimental Scheme

2.1. Synthetic Strategy

The basic idea is to attach GO, a high surface area substrate material to the Cu ion selective fluorescent dye (such as coumarin, scheme shown in **Figure 1**). For such attachment, Cu ion selective coumarin dye derivative (as reported in the literature [30]; **Figure 2**) will be further modified to obtain a terminal primary amine group.

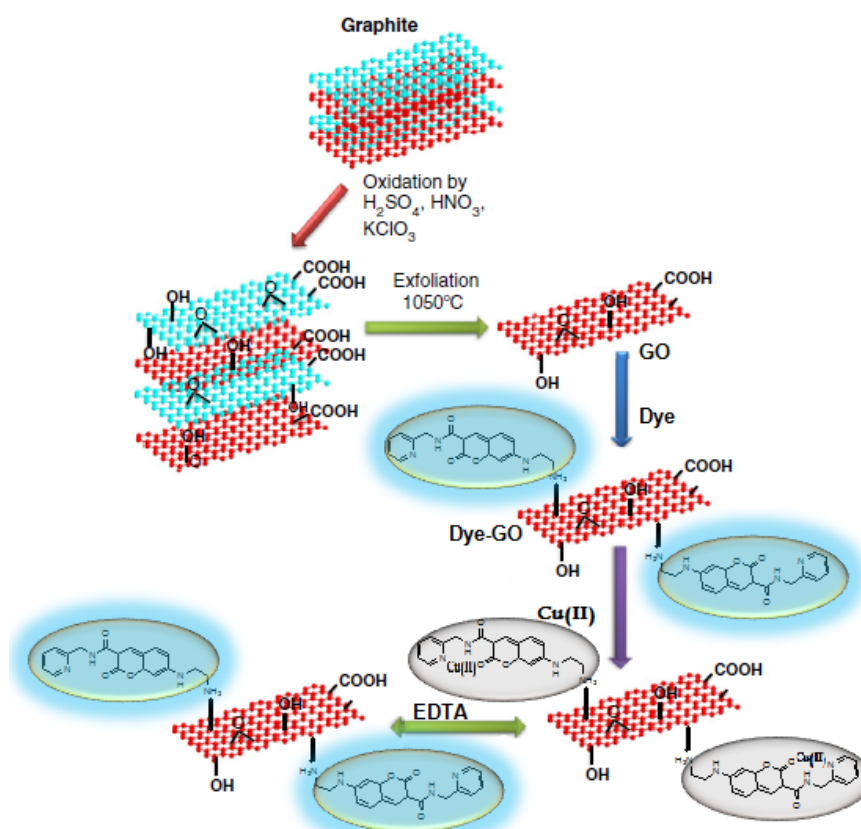


Figure 1. Pictorial representation of the scheme.

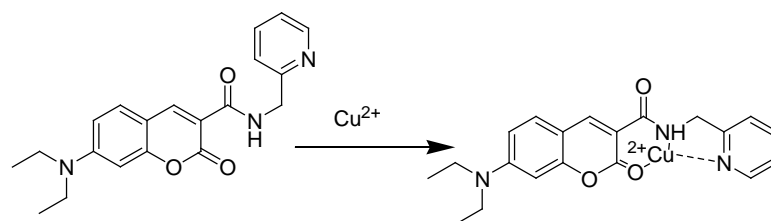


Figure 2. Schematic representation of the Cu^{2+} ion selective coumarin dye showing the active Cu^{2+} ion binding site.

The amine functionalized coumarin dye will be covalently attached to GO surface through epoxy ring opening reaction, forming the GOCD. Since the coumarin dye molecules are covalently attached to the GO substrate, it is anticipated that dye-dye interaction (J-aggregation) will be minimized. This is important for boosting the sensitivity for the Cu^{2+} ion detection in the nanomolar range. Moreover, the proposed GOCD is a new hybrid material. It would be interesting to explore the photophysical properties of the GOCD.

2.2. Schematic Representation of Overall Synthetic Strategy

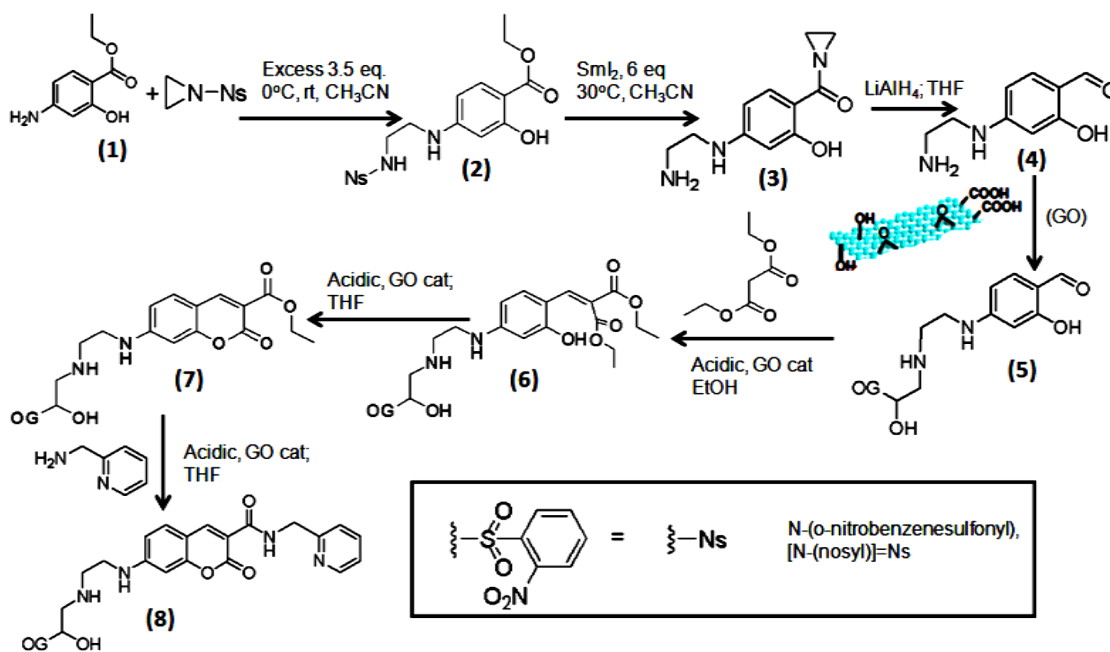


Figure 3. The proposed synthesis scheme of GOCD (compound #8).

2.3. Synthesis of Graphene-Oxide Coumarin Conjugate (GOCD)

The proposed GOCD will involve a multi-step synthesis process.

Step 1 is the preparation of the GO from graphite flakes following Hummar [39] method. This method uses chemical and sonication techniques to exfoliate GO from purified natural graphite. The resulting exfoliated GO form colloidal suspension of individual GO sheet in water. Then following the procedure of Wang *et al.* [40], pH assisted selective sedimentation will be done to separate GO of different size range.

Step 2 is the synthesis of primary amine functionalized Cu^{2+} ion selective coumarin dye (compound #4, see **Figure 3**). An amine containing precursor, methyl 4-amino-2-hydroxybenzoate (compound #1, Sigma-Aldrich; catalogue #PH001949) will be reacted with the protected aziridine to make compound #2. This addition reaction involves nucleophilic ring opening of aziridine by the NH_2 group of the compound #1 under mild acidic reaction condition to control reaction rate. Compound #3 (a cyclic ester) will be then prepared by treating the compound #2 with acetonitrile in presence of SmI_2 catalyst. Using LiAlH_4 , selective reduction reaction will be

carried out to convert the compound #3 to the corresponding aldehyde (compound #4). Similar synthetic route has been reported in the literature where Diethylamino-2-hydroxy-benzaldehyde was used as the precursor starting material [30] instead of compound #1 and therefore this proposed synthesis step is feasible.

Step 3 is the GO conjugation with the compound #4 (Figure 3), forming compound #5. The GO which is produced via Hammer method is intrinsically acidic and it has surface epoxy groups. It is expected that the compound #4 will readily react with the epoxy containing GO when combined together. The terminal amine group of the compound #4 will take part in the epoxy ring opening reaction. Similar epoxy ring opening reactions involving primary amine containing molecules and the GO have been reported in the literature [37] [41] [42].

Step 4 is a simple acid catalyzed Michael type addition reaction between the dimethyl malonate and the compound #5, forming the compound #6. Then the compound #6 will be converted to the compound #7 in acidic condition where GO is expected to serve as a catalyst. This proposed synthesis step is based on a recent research reported by the Bielawski group [43]. Their findings confirmed that GO served as a catalyst in auto tandem oxidation-aldol condensation reaction [43]. Similar catalytic/carbocatalyst [44] activity is expected in the proposed condensation and hydride elimination step.

Step 5 is the final step where the compound #7 will be converted to the compound #8 (the proposed GOCD). In this step, 2-aminomethyl pyridine addition and condensation reaction catalyzed by GO will be carried out in acidic reaction condition.

3. Conclusion

Synthetic steps proposed for synthesis of GOCD are conventional and uses of GO as catalyst are also well reported. Fluorescence of coumarin in GO-coumarin derivative (GOCD) will quench upon binding with Cu ions similar to its quenching of coumarin derivative as studied previously. Presence of GO in GOCD will not affect the strong fluorescence emission of coumarin derivative as GO is reported to exhibit a weak fluorescence property and it is covalently bonded to CD. GOCD should exhibit two distinct absorption bands characteristic to GO (200 - 450 nm absorption) and the coumarin dye (430 nm). Based on the literature reports, it is evident that the absorption band position of GO largely depends a number of factors including particle size, pH and the degree of oxidation [45] [46]. GO usually emits in the range 400 - 700 nm [46]-[48]. Depending on the pH, GO particle size [45] and extent of GO oxidation, emission of GO could vary anywhere between the 370 - 650 nm [45] [46]. Since GO is water soluble, GOCD will also be water dispersible and minimize dye-dye aggregation. Thus, GOCD will be an ideal fluorescence sensor for estimation of nanomolar concentration of cupric ion in aqueous solutions and biological organs.

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