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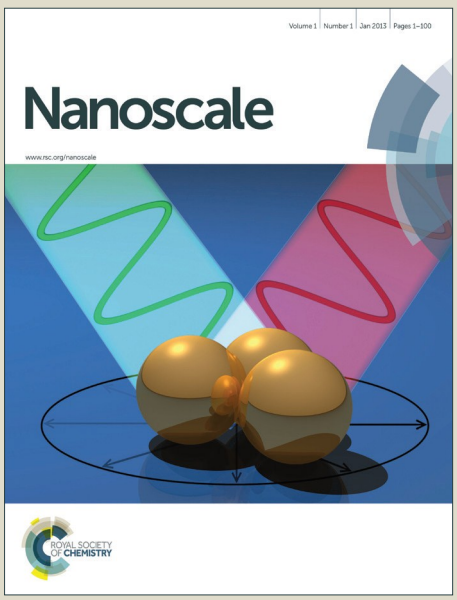

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PAPER

Highly selective and sensitive nanoprobes for cyanide based on gold nanoclusters with red fluorescence emission

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We report a novel and environmentally friendly fluorescent probe for detecting cyanide ion (CN^-) using L-amino acid oxidase (LAAOx)-protected Au nanoclusters (LAAOx@AuNCs) with red emission. The fluorescence-based sensing behaviour of LAAOx@AuNCs towards anions was investigated in buffered aqueous media. Among the anions studied, CN^- was found to effectively quench the fluorescence emission of AuNCs based on CN^- induced Au core decomposition. An excellent sensitivity and selectivity toward the detection of CN^- in aqueous solution was observed. The CN^- detection limit was determined to be approximately 180 nM, which is 15 times lower than the maximum level (2700 nM) of CN^- in drinking water permitted by the World Health Organization (WHO). Linear relationship between the fluorescence intensity and CN^- concentration were observed in two ranges of CN^- concentration, including 3.2×10^{-6} to 3.4×10^{-5} mol/L and 3.81×10^{-5} to 1.04×10^{-4} mol/L. The high sensitivity and selectivity to CN^- among 17 types of anions make the AuNCs as a good candidate for fluorescent nanoprobes of CN^-.

Introduction

The critical roles of anions in areas such as biological and chemical processes, as well as in environmental pollution[1], have been well recognized, and thus major efforts have been devoted to developing simple and efficient methods for their detection[2-4]. Among the various anions, cyanide (CN^-) is extremely toxic to living organisms because it halts the cellular respiration by strongly binding Fe^{3+} of heme cofactors in cytochrome C oxidase to rapidly deactivate its oxygen transport function[5] and it is lethal to humans when the CN^- concentration attains 0.5-3.5 mg/kg of body weight, which can directly lead to the death of human beings in several minutes[6]. Despite its high toxicity, cyanide is still widely used in several industrial activities, particularly in electroplating, metallurgy and organic polymer production, which raises the risk of its contamination to environments. Consequently, accidental cyanide release can result in serious contamination of the groundwater and even drinking water. For these reasons, it is highly desirable and imperative to develop simple, rapid, highly selective and sensitive probes that can provide determination of cyanide levels.

Toward achieving this goal, fluorescent methods based on organic molecules have been developed for cyanide sensing[7-10]. Such molecular fluorescent chemosensors could eliminate most costs associated with instruments, such as electrometric[11], chromatographic[12] and voltammetric techniques[13], which makes on-site and real-time detection of cyanide in natural samples possible. Nevertheless, molecular fluorescent methods suffer from some disadvantages, such as the involvement of complicated organic synthesis, water-insolubility, poor photostability, an unsatisfactory detection limit and easy interference from other anions.

Due to the wide range of applications, especially involving human contact, there is a growing tendency to develop eco-friendly processes for the synthesis of fluorescent nanomaterials without using toxic chemicals[14,15]. Biomolecule-mediated syntheses of metal nanoclusters (NCs) have attracted considerable attention because of the ease of synthesis, bright photoluminescence, low toxicity, good chemical stability, and high biocompatibility[16-18]. Proteins usually contain active sites for metal ion accumulation and reduction where metal NCs can be formed and stabilized. Depending on the protein and reaction conditions, metal NCs can be formed with decent fluorescence intensity. Compared with AgNCs or CuNCs, protein-stabilized AuNCs are more common, and a pioneering approach was proposed by Xie et al. in 2009[19]. They first developed a simple, "green" method to synthesize highly fluorescent (quantum yield ~6%) AuNCs using bovine serum albumin (BSA) as a template. Up to now, BSA-AuNCs have been widely used for metal ion and anion sensing[20-23], small biomolecule probing[24-26], pH probing[27] and fluorescence cell and organism imaging[28,29], and so on. Inspired by this report, researchers tried to explore other proteins such as trypsin[30], lysozyme[31], papain[32], insulin[33] and pepsin[34] for preparing AuNCs. Red fluorescence emitting AuNCs at wavelengths in the physiologically relevant "biological transparency window" are of particular interest owing to the large penetration depth of near infrared (near-IR) light in most biological media[35]. However, achieving near-IR emission fluorophores with biocompatibility and photostability has proven to be very difficult.

In this work, we have prepared L-amino acid oxidase (LAAOx)-protected Au nanoclusters (LAAOx@AuNCs) by a simple and green synthetic route. These AuNCs have high solubility in water and red fluorescence emission. We rationalize that gold is a chemically inert metal and few anions can react with it except CN^-, which allows a high selectivity towards CN^- sensing. The complexation of CN^- to AuNCs would result in the fluorescence quenching of the AuNCs, thus, providing a mechanism for CN^- sensing. Our results indeed demonstrate that one can employ the AuNCs to detect CN^- by fluorescence quenching.

Experimental

Chemicals and Instruments

Tetrachloroauric(III) acid ($HAuCl_4 \cdot 3H_2O$, >99.9%, Aldrich), L-amino acid oxidase, (LAAOx, >99.9%, Sigma), Sodium hydroxide (NaOH, >96%, Beijing). Deionized water (resistivity 18.2 MΩ cm^{-1}) was produced with a Milli-Q-RO_4 pure water system (Millipore, Bedford, MA). All the other chemicals were of analytical-reagent grade and used as received without further purification. Stock solution (0.01 mol/L) of all the anions (F^-, Cl^-, Br^-, I^-, CO_3^{2-}, NO_3^-, NO_2^-, ClO_3^-, SO_4^{2-}, $C_2O_4^{2-}$, CH_3COO^-, SCN^-, PO_4^{3-}, $S_2O_3^{2-}$, HSO_4^-, SO_3^{2-} and CN^-) were prepared by directly dissolving appropriate amounts of sodium salts in deionized water.

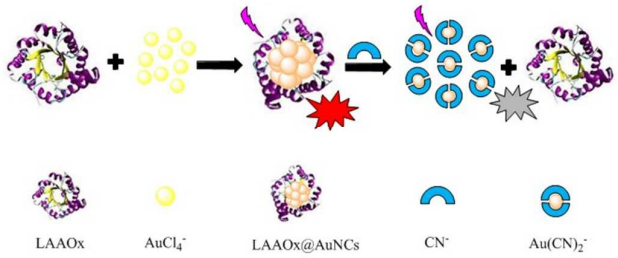
The optical absorption spectra were measured on a UV-265 spectrophotomter (Shimadzu, Japan). The fluorescence was measured with a F-4500 Fluorescence spectrometer (Hitachi, Tokyo Japan). Excitation and emission bandwidths were both set at 10 nm. Transmission electron microscopy (TEM) images were obtained on a JEM-2100 (JEOL Ltd., Tokyo, Japan) at an accelerating voltage of 200 kV. Fluorescence lifetime experiments were performed with an FLS-920 Edinburgh Fluorescence Spectrophotometer (Edinburgh Co. Ltd., England). X-ray photoelectron spectroscopy (XPS) data were obtained from an AXIS ULTRA DLD electron spectrometer (Shimadzu Japan). All experiments were carried out at room temperature.

Synthesis of LAAOx@AuNCs and characterization

LAAOx capped gold clusters were synthesized according to a BSA-AuCNs reported method[19]. Briefly, 2mL of 5mM $HAuCl_4$ aqueous solution (37◦C) was added to 2mL of 20 mg/mL LAAOx solution (37◦C) under vigorous stirring. Two minutes later, 0.2mL of 1.0M NaOH solution was introduced and the mixture was incubated at 37◦C for 12 h. The colour of the solution changed from light yellow to light brown, and then to deep brown. The obtained solution was purified by centrifugation (4000r/min, 10min) and dialysis (24h, MW:1000D). Finally, the purified LAAOx@AuNCs was obtained and then stored at 4◦C prior to use. A stock solution of AuNCs was diluted 10 times in deionized water.

Selectivity and Sensitivity Measurements

The LAAOx@AuNCs solution was diluted 10 times for the fluorescence titration. Then different concentrations of CN^- were added to 2.5mL of the diluted AuNCs solution respectively. After mixing, the fluorescent intensity of the solution was measured, respectively. The other anions (i.e. F^-, Cl^-, Br^-, I^-, CO_3^{2-}, NO_3^-, NO_2^-, ClO_3^-, SO_4^{2-}, $C_2O_4^{2-}$, CH_3COO^-, SCN^-, PO_4^{3-}, $S_2O_3^{2-}$, HSO_4^- and SO_3^{2-}) at the same concentration (3.0 μM) were added instead of CN^- to evaluate the selectivity of the method. After mixing AuNCs with anions in three minutes, the fluorescence intensity of AuNCs did not change, so we measured the fluorescence spectra of LAAOx@AuNCs after anion titrated into the solution in three minutes.



Scheme 1 Illustration of the synthesis and application of LAAOx@AuNCs.

Results and discussion

Characterization of LAAOx@AuNCs

The fluorescent L-amino acid oxidase (LAAOx)-capped Au-nanoclusters (LAAOx@AuNCs) in aqueous solutions were prepared via an "one-pot" approach (Scheme 1), and subjected to characterization by TEM, UV-vis absorption spectroscopy, fluorescence spectroscopy and IR (Fig. 1).

The TEM image (Fig. 1A) indicates that the AuNCs were spherical, well dispersed and uniform with an average size of 1.35 ± 0.10 nm (Fig. 1B). The aqueous solution of the AuNCs was deep brown in colour and exhibited bright red fluorescence under 365nm UV light irradiation. In contrast, neither pure LAAOx nor $HAuCl_4$ exhibits photoluminescence under the same conditions, demonstrating that the observed fluorescence originates from the gold core of the LAAOx@AuNCs. Fig. 1C shows the UV-vis absorption (profile a) and fluorescence spectra (profile b) of the synthesized AuNCs. It can be further concluded that the size of the AuNCs is less than 2 nm because the spectrum shows no surface plasmon resonance in UV-vis absorption[36,37]. The spatial confinement of free electrons in AuNCs results in discrete and size-tunable electronic transitions, thus offering molecular-like properties such as fluorescence. The maximum fluorescence emission

wavelength of the AuNCs is 630 nm upon excitation at 510 nm. The quantum yield (QY) of the fluorescent AuNCs is determined to be 1.03% by using rhodamine 6G (in ethanol solution) as a reference. Photographs of the solutions mentioned before under room light and 365nm UV light are provided in Fig. 1C (see the inset). The infrared (IR) spectra of the pure LAAOx (black profile) and the LAAOx@AuNCs (red profile) were also measured and the results are shown in Fig. 1D. The spectra are similar to each other, indicating that the LAAOx are combined with the surface of the AuNCs. Nevertheless, the band appeared at ~1650 cm^{-1}, relative to the other bands in the amide I region, indicates a higher content of α-helix structures of protein[38]. The appearance of a band at 1655 cm^{-1} in the AuNCs indicates an increase of unordered structures[39]. The bands at 1540 cm^{-1} for the native LAAOx evolves into a band centered at ~1535 cm^{-1} in the bioconjugates, implying that the functional groups of LAAOx may have interactions with the AuNCs. In addition, a weak band of -SH[40] appeared at 2560 cm^{-1} in the IR spectrum of LAAOx, but this band is absent in the IR spectrum of AuNCs, indicating that thiol groups were involved in the Au-SR binding for the generation of the AuNCs. Taken together, the above results show that LAAOx@AuNCs was successfully synthesized by a simple and environmentally friendly method.

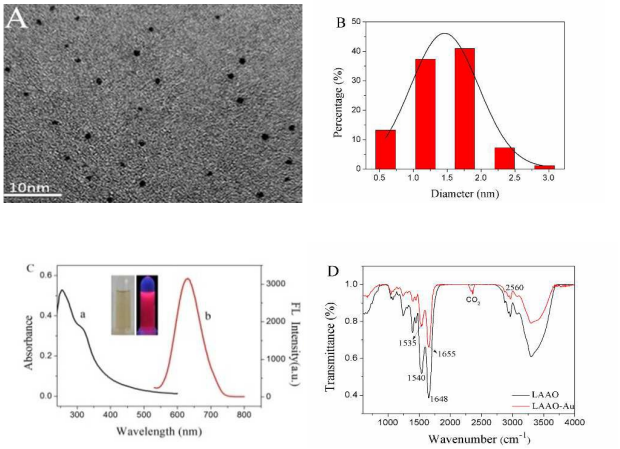


Fig. 1 (A) TEM images of the LAAOx@AuNCs; (B) Particle size distribution of the LAAOx@AuNCs; (C) UV-vis absorption (black line), fluorescence emission (red line) spectra of the LAAOx@AuNCs. Inset: the photographs of the LAAOx@AuNCs under visible light (left) and 365 nm UV light irradiation (right); (D) The infrared (IR) spectra of the pure LAAOx (black) and the LAAOx@AuNCs (red).

Fluorescence sensing of CN^- by LAAOx@AuNCs

The fluorescence sensing experiments of LAAOx@AuNCs towards CN^- were carried out at pH 11.0 in PBS buffer. On addition of CN^- to a solution of the AuNCs, a significant quenching in the emission intensity at 630 nm (excitation at 510nm) was observed (Fig. 3A(b)). Cyanide is commonly used in the metallurgical industry to leach Au from low-grade minerals by converting the Au atoms into a water-soluble cyanide-Au complex. This process is termed as gold cyanidation. The fluorescence quenching in the presence of CN^- can be attributed to the complexation between the CN^- ions and Au core of the AuNCs. Previous studies have proved that the metallic gold was finally oxidized to form the stable $Au(CN)_2^-$ complex with cyanide through strong covalent bonding in the presence of oxygen (air), which is described as the Elsner reaction[41]:

$$4Au + 8CN^- + 2H_2O + O_2 = 4Au(CN)_2^- + 4OH^-$$

By monitoring the intensities of the characteristic red emission band at 630nm, there was no sensitized luminescence and the change can be almost neglected compared with the strong emission of nanoclusters. In comparison with CN^-, other anions have much weaker etching capability to gold atoms. So, the etching chemistry can be applied to develop highly selective optical probes for CN^- based on CN^- induced gold core decomposition, which can lead to an efficient fluorescent quenching of the AuNCs.

The absorption spectra of AuNCs in the presence of varying CN^- concentrations were investigated. As shown in Fig. 2A, the main absorption band at ~280 nm decreases in the presence of 50μM CN^- without a discernable shift in wavelength. The changes of absorption spectra suggest that the quenching type of quencher CN^- may be the ground state. In order to further confirm the result, the interaction between CN^- and AuNCs has also been studied by the time-resolved fluorescence spectroscopy (Fig. 2B). The fluorescence decay spectrum of the AuCNs can be fitted with a two-exponential function, revealing two components of lifetime: a fast component τ_1= 3.20ns (38.34%) and a relative slow component τ_2= 23.70ns (61.66%), respectively. Fig. 2B showed that the fluorescence lifetime of the AuNCs did not have any obvious change with increasing concentration of CN^- ions. This observation provides further evidence that the fluorescence quenching belong to static quenching, which indicates that the interaction took place between the quencher and the ground state of the fluorescence materiel.

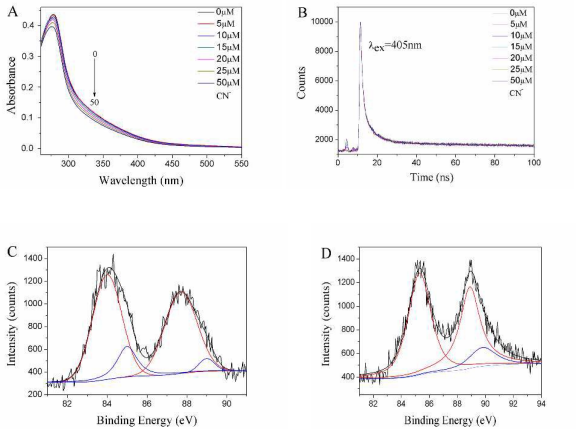


Fig. 2 (A) Absorption spectra of LAAOx@AuNCs in the presence of varying concentrations of CN^- (1-7: 0, 5, 10, 15, 20, 25, 50μM); (B) Fluorescence lifetime of LAAO@AuNCs in the presence of varying concentrations of CN^- (1-7: 0, 5, 10, 15, 20, 25, 50μM); (C) and (D): The XPS measurement of LAAO@AuNCs before and after the addition of CN^-.

The valence and composition of the AuNCs was determined by X-ray photoelectron spectroscopy (XPS). The binding energy of Au $4f_{7/2}$ and Au $4f_{5/2}$ for LAAOx@AuNCs was 84.1 eV and 87.7 eV, respectively (Fig. 2c). The Au $4f_{7/2}$ XPS spectrum of LAAOx@AuNCs can be further deconvoluted into two distinct components (red and blue curves) centered at binding energies of 84.0 and 85.0 eV, which confirms the presence of both Au (0) and Au (I), respectively[19]. The integrated area of these two bands illustrates that the majority of the gold within the nanoclusters is Au(0) in the core complemented with a minor amount of Au (I) at the core surface, which might stabilize the AuNCs. The XPS measurement of LAAO@AuNCs added CN^- as shown in Fig. 2d. Compared with Fig. 2c, it can be obviously showed that the binding energy of 85.0 eV disappeared, which could be explained that the CN^- combined with the Au (I) on the surface of Au core. The phenomenon further evidenced CN^- induced gold core of AuCNs decomposition.

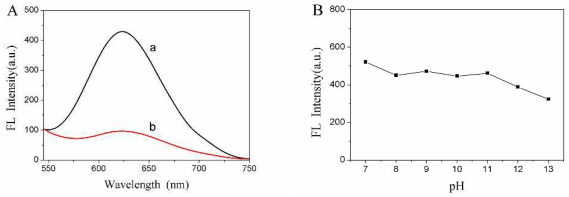
Optimization of factors influencing CN^- detection

The pH value is often a very crucial factor for the sensing systems. To explore the effect of pH on the fluorescence of AuNCs, the cluster solution was subjected to 0.01M phosphate buffer solution (combination of monosodium phosphate and disodium phosphate in water, PBS for short), then adjusted to specific pH values by adding 0.1M H_3PO_4 or NaOH. The results (Fig. 3B) showed that the fluorescence intensity of AuNCs could be maintained above 90% in the pH range of 7.0-13.0. The wide pH working range of AuNCs is advantageous in sensing experiments.

$$CN^- + H_2O \rightarrow HCN + OH^- \quad (pK_a = 9.36)$$

$$\delta_{HCN} = \frac{[H^+]}{[H^+] + Ka} \qquad \delta_{CN^-} = \frac{Ka}{[H^+] + Ka}$$

Free cyanide is a weak acid, and thus may exist in two forms in an aqueous solution, including hydrocyanic acid (HCN) and cyanide ions (CN^-). When $pH > pK_a+1$, e.g. pH>10.36, the CN^- form is predominant, and when $pH < pK_a-1$, e.g. pH<8.36, the HCN form becomes predominant due to the pK_a is 9.36. So we chose pH 11.0 as a typical value in our sensing tests.



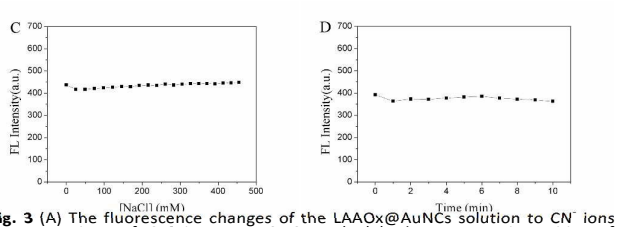


Fig. 3 (A) The fluorescence changes of the LAAOx@AuNCs solution to CN^- ions (concentrations of CN^- ions was 0.104mM); (B) Fluorescence intensities of LAAOx@AuNCs as a function of pH; (C) The fluorescence intensity of LAAOx@AuNCs in the presence of varying concentrations of aqueous NaCl solution; (D) The response time for the fluorescence quenching of the LAAOx@AuNCs in the presence of CN^-.

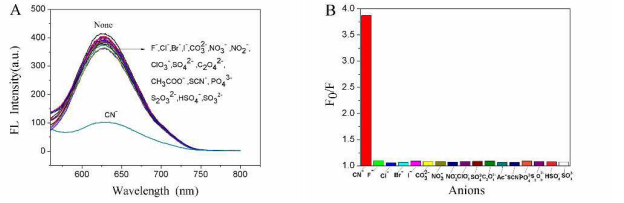
The effect of ionic strength on the response of AuNCs was also investigated by subjecting the clusters to 0-0.45M NaCl (as shown in Fig. 3C). It is obvious that the response did not change appreciably (less than -0.071% upon an increase in NaCl concentration). Thus, the ionic strength did not affect the fluorescence of AuNCs under these experimental conditions.

The response time of a probe is another important feature. In this study, the response time was defined as the time taken to obtain a 95% steady-state signal when the probe was exposed to a known concentration of CN^- standard solution. It is obvious that the response time was less than 1 min (Fig. 3D). So, we measure the fluorescence spectra of AuNCs after anion titrated into the solution in three minutes. It was reasonably acceptable for probes.

Repeatability is another crucial factor for any analytical technique, especially for a probe. The signal changes of the probe were investigated when it was alternately exposed to a phosphate solution and 5.0×10^{-5}M CN^- solution for six times. The probe exhibited a fairly desirable analytical feature of repeatability (n=6, relative standard deviation = 4.32%).

Selectivity for CN^- detection

The fluorescence sensing selectivity of LAAOx@AuNCs for anion was examined. Under the same condition as used above for CN^-, we tested the fluorescence responses of AuNCs towards other anions such as F^-, Cl^-, Br^-, I^-, CO_3^{2-}, NO_3^-, NO_2^-, ClO_3^-, SO_4^{2-}, $C_2O_4^{2-}$, CH_3COO^-, SCN^-, PO_4^{3-}, $S_2O_3^{2-}$, HSO_4^- and SO_3^{2-}. These anions were added to aqueous solutions of the AuNCs such that the final concentration was 3.0μM and the emission of the LAAOx@AuNCs was measured three minutes later after the addition of anions. Only CN^- could induce a drastic decrease in the fluorescence intensity (Fig. 4A and 4B), while other competitive anions led to no fluorescence changes at all.



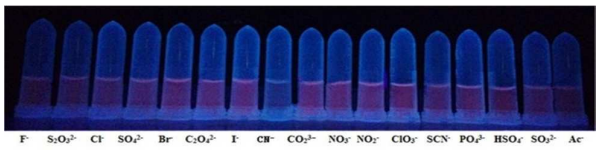


Fig. 4 (A) and (B): Effect of different anions on the fluorescence of LAAO@AuNCs in PBS buffer solutions (pH 7.0); (C) The colour of the LAAOx@AuNCs solution to different anions under UV light irradiation(365nm).

Photographs of the aqueous solutions of the AuNCs under irradiation by UV light at 365nm after the addition of various anions are also given (Fig. 4C). It was noted that a bright red fluorescence disappeared and a blue fluorescence appeared under UV light when the interaction of AuNCs with CN^-. The very weak blue fluorescence, as mentioned above, is characteristic of the aromatic side groups in the amino acid residues of the LAAOx. The specific reactivity towards CN^- can be used as a tool to detect its presence.

Detection of CN^- based on LAAOx@AuNCs

Under the conditions optimized above, we carried out the fluorescence sensing experiment of the AuNCs toward CN^-. On addition of varying amounts of CN^- to a solution of AuNCs, a significant quenching in the emission intensity at 630 nm was observed (Fig. 5A). There were two good linear relationship (R^2 = 0.997 and R^2= 0.996, respectively) between the fluorescence intensity and CN^- concentration, i.e. the ranges of 3.2×10^{-6} to 3.4×10^{-5} mol/L and 3.81×10^{-5} to 1.04×10^{-4} mol/L (Fig. 5B). The detection limit, calculated following the signal-to-noise ratio of 3:1 (the IUPAC criteria), was ~180nM, which is 15 times lower than the maximum level (2700nM) of CN^- in drinking water set up by the World Health Organization (WHO). The AuNCs were sensitive enough to monitor CN^- comparable to other reported CN^- chemosensors[9, 42-48] (Table 1).

Based on the above results, a standard addition method was applied to determine the concentrations of cyanide in the river water and tap water samples. The six water samples were determined and results are shown in Table 2. The recoveries of 96.3-103.2% of the known amount CN^- in the water samples were obtained, which further confirms that the novel sensing platform has great potential for determination of cyanide in environmental samples.

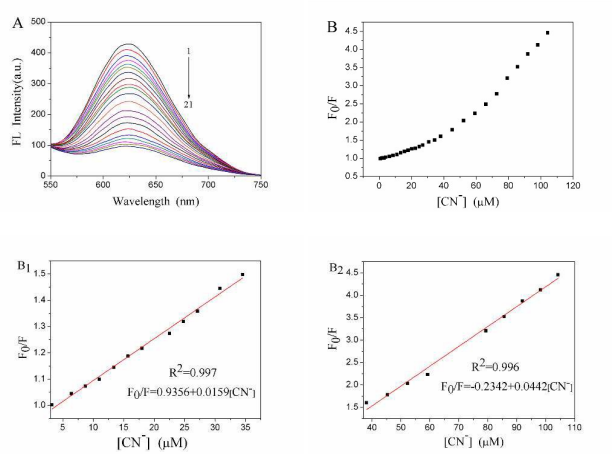


Fig. 5 (A) Fluorescence response of LAAOx@AuNCs upon addition of different concentrations of CN^- (1-21: 0, 3.2, 6.4, 11.0, 15.7, 20.3, 22.5, 27.0, 30.8, 34.4, 38.1, 45.3, 52.3, 59.2, 66.0, 72.7, 79.3, 85.7, 92.0, 98.2, 104.3μM); (B) The relative fluorescence intensity (F_0/F, where F_0 and F are the fluorescence intensity of LAAOx@AuNCs in the absence and presence of CN^- at 630 nm, respectively.) versus the concentrations of added CN^-. There were two linear relationship (B_1 and B_2) between the fluorescence intensity and CN^- concentration.

Table 2 Determination of CN^- in water samples using the proposed probe.

Sample	Added (μM)	Found (μM)	Recovery(%)	RSD* (%)
River water 1	5.00	4.92	98.4	2.2
River water 2	10.00	10.32	103.2	2.9
River water 3	20.00	19.26	96.3	3.5
Tap water 1	5.00	5.15	101.3	2.4
Tap water 2	10.00	9.65	96.5	3.1
Tap water 3	20.00	19.96	99.8	1.7

*relative standard deviation for 5 measurements

Table 1 Comparison of the linear range and detection limit for CN^- using different fluorescent probes.

Reagents	Analytical range (M)	Detection limit (nM)	Solvent	References
Phosphorescent Molecular Gold(I) Cluster in a Macroporous Polymer Film	___	2000	Solid state	[42]
Au@Ag core/shell nanoparticles as colorimetric probes	___	400	Water	[43]
Dual-functional Au-Fe3O4 dumbbell nanoparticles	4.0×10^{-7}~1.2×10^{-4}	400	Water	[44]
Colorimetric and fluorescent chemodosimeter	1.0×10^{-5}~4.5×10^{-5}	—	Tris-HCl-ethanol (8:2)	[45]
Gold-nanoparticle-based fluorescent probes	0~1.0×10^{-5}	1000	Water	[46]
Lysozyme-stabilized AuNCs as a novel fluorescence probe	5.0×10^{-6}~1.2×10^{-4}	190	Water	[47]
Colorimetric sensing of cyanide based on formation of dipyrrin adducts	___	3600	CH2Cl2	[48]
Organic turn-on fluorescence probe	5.0×10^{-7}~8.0×10^{-6}	45	DMSO	[9]
L-amino acid oxidase-protected AuNCs	3.2×10^{-6}~3.4×10^{-5} and 3.81×10^{-5}~1.04×10^{-4}	180	Water	Our method

Conclusions

In summary, a simple detection method based on fluorescent LAAOx@AuNCs probes has been developed, which allows rapid detection of CN^-. The Au NCs possess several advantages, such as sensing in pure aqueous media, no requirements of complex organic synthesis and complicated instruments, possessing a better detection limit (~180nM), displaying high selectivity over other anions. These features make the AuNCs a promising candidate as a chemosensor for CN^-. We believe that this method may act as a platform for the rapid detection of CN^- in aqueous biological and environmental samples with high selectivity and sensitivity.

Acknowledgements

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Notes and references

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