RSC Advances

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Journal:	*RSC Advances*
Manuscript ID	RA-ART-10-2015-021038.R1
Article Type:	Paper
Date Submitted by the Author:	05-Nov-2015
Complete List of Authors:	Liu, Zengchen; Zhoukou Normal University, Yang, Weijie; Zhoukou Normal University Li, Yanxia; Zhoukou Normal University Tian, Fengshou; Zhoukou Normal University Zhu, Wenping; Zhoukou Normal University
Subject area & keyword:	Sensors < Analytical

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Journal Name

ARTICLE

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Highly water-soluble and sensitive fluorescent sensor derived from relatively lower toxicity β-cyclodextrin was synthesized. The fluorescent sensor exhibited spherical morphology under SEM observation. By the fluorescence behaviors toward several metal ions, it showed highly selectivity and sensitivity for Zn^{2+} over other commonly coexistent metal ions in pure water environment (pH = 7.2). Meanwhile, the large binding constant (2.55×10^{13} M^{-1}) between Zn^{2+} and fluorescent sensor was calculated in pure water media. The fluorescent microscope images of onion epidermal cells proved the water-soluble sensor showed high ability of cell permeability. Additionally, the Chelating Induced Fluorescence Enhancement (CIFE) and Photoinduced Electron Transfer (PET) sensing mechanism was concluded according to the fluorescence behavior. The fluorescent sensor in pure water media effectively enhanced the application value of the fluorescent sensor for tracking and detecting of Zn^{2+}.

Introduction

The study of highly selective and sensitive sensors toward metal ions are of great importance for analyzing the chemical and physiological functions in the wide range of biological and environmental system.[1-8] Because some relevant metal elements like copper, zinc, mercury and manganese *et al* play an important role in living organism and environment, which is closely related to some health and environmental pollution. Zinc is a biologically essential element in living organism and it is also very important in environment. Zinc ion serves as key structural components of a large of proteins (Zn^{2+} buffer proteins, Zn^{2+} transporters and Zn^{2+} sensor proteins) and also performs catalytic roles in some enzymes, which is relevant to many cellular processes.[9,10] And long-term insufficient intake of Zn^{2+} will cause stunted growth of children.[11] In addition, in the physiological processes such as brain, prostate and intestine locations, abnormal level of zinc ions even may cause some potential diseases like Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS) and parkinson's disease.[12-15] Moreover, the excess of zinc is regarded as a pollutant in environment, which can enter the life through the biosphere for inducing the death of plants and soil pollution even human disease.[16,17] But it remains an active topic of research because of the insufficient understanding of zinc ions. Thus, it is a considerable need for designing highly selective fluorescent sensors, which can detect zinc ion in biological and environmental system.

In living organism and environment, zinc ion mainly exists in water system at a physiological pH value condition. So it is also a challenging task for designing the sensor for Zn^{2+} in pure water system. Because some organic solvent like methanol, acetonitrile and DMF *et al* may have a negative effect on the biological system. To date, many selective fluorescent sensors for Zn^{2+} have been achieved. However, to the best of our knowledge, very few fluorescent sensors in pure water media have been designed and reported.[18-20]

At present, most of the fluorescent sensors for Zn^{2+} derived from organic molecules showed poor solubility in water. The poor water-solubility limited the application of sensors for detecting zinc ion in biological and environmental system. Consequently, considerable efforts have been devoted to developing water-soluble fluorescent sensors for Zn^{2+}.[21,22]

When aiming at the rational development of water-soluble fluorescent sensors for targeting zinc ion, the choice of binding motif is a critical factor, because in the complicated environment containing, many metal ions such as Cu^{2+}, Hg^{2+} and Cd^{2+} et al can interfere with zinc binding.[23-25] In addition, cyclodextrin is an water-soluble compound, which showed low toxicity and wide application prospects. And cyclodextrin has been widely in medicine, chemical engineering, supramolecular chemistry and materials, et al.[26-28] Thus, it is very significative to design relevant fluorescent sensors containing cyclodextrin derivates. The fluorescent sensor from cyclodextrin derivates has been studied for sensing of ions.[29] In continuation of our research topic based on water-soluble

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Electronic Supplementary Information (ESI) available: [NMR spectrum, IR spectrum and the detecting level]. See DOI: 10.1039/x0xx00000x

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fluorescent sensors in biological organism and environment.[30,31] In the present investigation, novel water-soluble β-cyclodextrin derivate schiff-base architecture is developed to increase the selectivity and sensitivity for detecting Zn^{2+}. According to the spectra analysis, the fluorescent sensor exhibits highly selectivity toward Zn^{2+} over other metal ions in pure water media (pH = 7.2).

Experimental sections

Materials

All the chemicals containing solvents were of reagent grade and were used without further purification.

Synthesis of Tetraethylenepentamine β-cyclodextrin derivate (TEPA-β-CD)

The synthesis routine was shown in Scheme 1 and the abbreviation of compounds was listed in Scheme S1.

An DMF solution (15 mL) of p-toluenesulfonyl-β-cyclodextrin (1 mmol, 0.1289 g) was added to another DMF (10 mL) containing tetraethylenepentamine (1 mmol, 0.0194 g), Then the solution was reflux for 24 h at room temperature. The mixture was filtered and dried under vacuum. Recrystallization from H_2O/Ethanol (V:V=1:4) gave tetraethylenepentamine β-cyclodextrin derivate (TEPA-β-CD), which was dried under vacuum and. The surface morphology of TEPA-β-CD is irregular block solid by SEM analysis (Fig. 1 a, a-1, a-2). Yield, 55%. m.p: 248.8–253.1 °C. ^{1}H-NMR (Fig. S1) (H_2O–d_2 400 MHz): δ 2.40–2.69 (2H, m, –C^9–H), δ 3.29–3.38 (1H, m, –C^2–H), δ 3.44–3.56 (1H, m, –C^4–H), δ 3.72–3.76 (2H, m, –C^3–H, –C^5–H), δ 3.80–3.87 (2H, m, –C^6–H), δ 4.96 (1H, m, –C^1–H). δ 7.23 (1H, m, –C^{10}–H). δ 7.52 (1H, m, –$C^{8'}$–H). δ 8.08 (1H, m, –C^8–H).

Synthesis of Tetraethylenepentamine-β-cyclodextrin-4-diethylamine salicylaldehyde (L) sensor (TEPA-β-CD-L)

An H_2O solution (20 mL) of Tetraethylenepentamine-β-cyclodextrin (1 mmol, 0.1306 g) was added to another ethanol (3 mL) containing 4-diethylamine salicylaldehyde (L) (1 mmol, 0.0193g), Then the solution was stirred for 12 h at room temperature. The mixture was filtered and dried under vacuum. Recrystallization from H_2O/Ethanol (V:V=1:3) gave tetraethylenepentamine β-cyclodextrin-4-diethylamine salicylaldehyde (TEPA-β-CD-L). By SEM analysis (Fig. 1 b, b-1, b-2), the compound showed different surface morphology compared with TEPA-β-CD-L, which could assemble homogeneous spherical solid. Yield, 35%. m.p: 278–280 °C. ^{1}H-NMR (Fig. S2) (DMSO–d_6 400 MHz): δ 1.32 (3H, m, –C^{16}–H), δ 2.40–2.69 (2H, m, –C^9–H), δ 3.08 (1H, m, –C^{15}–H), δ 3.29–3.38 (1H, m, –C^2–H), δ 3.44–3.56 (1H, m, –C^4–H), δ 3.72–3.76 (2H, m, –C^3–H, –C5–H), δ 3.80–3.87 (2H, m, –C^6–H), δ 4.96 (1H, m, –C^1–H). δ 5.70–5.79 (1H, m, –C^{11}–H), δ 6.02 (1H, s, –C^{14}–H), δ 6.90–6.95 (1H, m, –C^{12}–H), δ 7.23 (1H, m, –N^{10}H-),δ 7.92–8.03 (1H, m, –C^{13}–H), δ 9.76 (1H, s, –O^{17}H). ^{13}C-NMR (H_2O–d_2 400 MHz): 3.2, 12.5, 16.4, 46.2, 60.4, 73.8, 74.9, 82.4, 104.3, 116.5, 124.8, 135.8, 146.7, 155.1 (Fig. S3). FT–IR (cm^{-1}): 1503, –CH=N–.

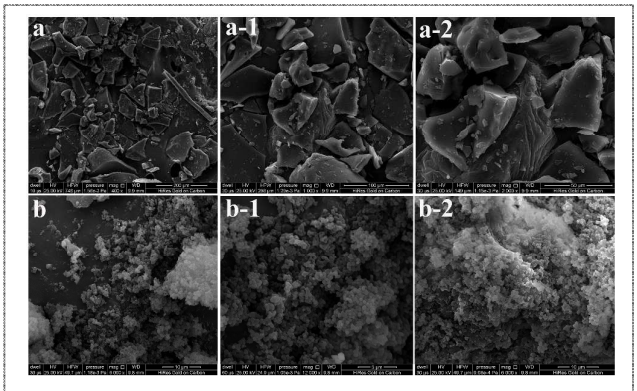
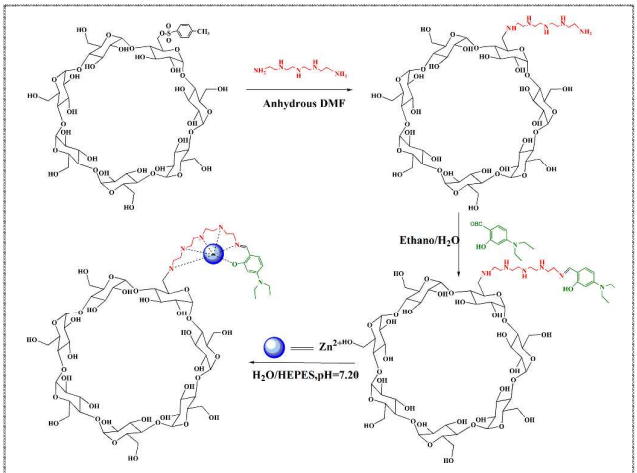


Fig. 1 a. The SEM graphs of TEPA-β-CD (block solid), b. TEPA-β-CD-L (spherical solid).



Scheme. 1 The synthesis route of TEPA-β-CD and TEPA-β-CD-L, The predicted coordination cites of TEPA-β-CD-L with

All spectroscopic measurements were performed in pure water solution (pH = 7.2). The pH was controlled by HEPES buffer solution.

Stock solutions (1.0×10^{-3} M) of metal ions (metal chloride) were prepared in two-distilled water. The stock solution of 0.3×10^{-3} M TEPA-β-CD-L was prepared in pure distilled-water, The pH was controlled by HEPES buffer solution (pH=7.2). In titration experiments, each time 2 mL water solution containing 50 μL solution of TEPA-β-CD-L (0.3×10^{-3} M) was filled in a quartz optical cell of 1cm optical path length. Then 10 μL amount of Zn^{2+} stock solution was added to the compound solution with micro-pippet. Spectral data was recorded at 2 min after the addition. In selectivity experiment, the test samples were prepared by placing appropriate amounts of metal ion stock solution into 2 mL aqueous solution of TEPA-β-CD-L (50 μL). For fluorescence measurements, excitation wavelength is at 330 nm.

The binding constant between TEPA-β-CD-L and Zn^{2+} was calculated by the linear Benesi-Hildebrand expression [32, 33].

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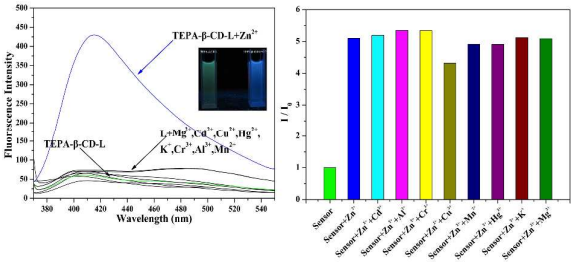

Fig. 2. a. The fluorescence selectivity spectrum TEPA-β-CD-L with various metal ions, **b.** fluorescence competition experiment of Zn^{2+} with other metal ions.

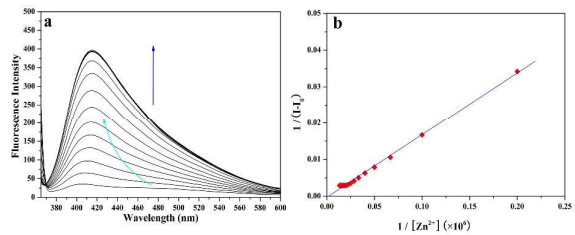

Fig. 3 a. Fluorescence titration spectra of TEPA-β-CD-L (7.5 × 10^{-6} M) upon addition of Al^{3+} in pure water solution (pH = 7.2). Excitation at 330 nm. **b.** Fitting of fluorescence titration curve of TEPA-β-CD-L in HEPES solution (pH = 7.2), R = 0.99832, SD = 5.04715E-4, The binding constant k = 2.55E13 M^{-1}.

Where I is the change of fluorescence intensity in the presence of Zn^{2+} at 410 nm, Ks is the stability constant, and [L] and [M]

$$\frac{1}{I-I_0}=\frac{1}{[L]}+\frac{1}{K_S}\cdot\frac{1}{[L][M]}$$

are the concentration of TEPA-β-CD-L and Zn^{2+}, respectively. I_0 is the fluorescence intensity of L in the absence of Zn^{2+}. On the basis of the plot of $1/(I-I_0)$ versus $1/[Zn^{2+}]$, the stability constant can be obtained.

Physical measurement

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian VR400-MHz spectrometer with TMS as an internal standard. The melting points of the compound were determined on a Beijing XT4-100X microscopic melting point apparatus. The UV-Vis spectra were recorded on a Perkin-Elmer Lambda-35 UV-Vis spectrophotometer. Fluorescence spectra were obtained on a Cary Eclipse spectrophotometer at room temperature. The Scanning Electron Microscopy was tested on FEI Quanta 200. The fluorescence image of onion epidermal cells was tested using BX61 fluorescence microscope.

Results and discussion

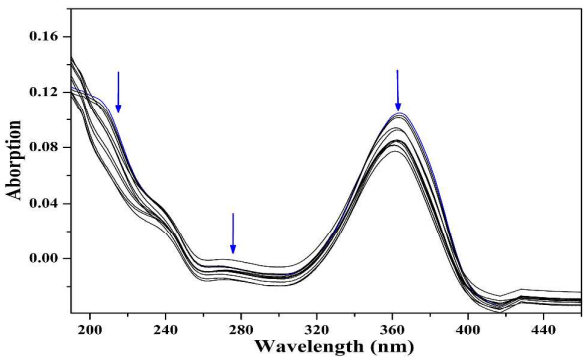

Fig. 4 The Uv-vis absorption spectra of TEPA-β-CD-L (7.5 × 10^{-6} M) in pure water media in the presence of different amounts of Zn^{2+} (0–2 equiv).

Fluorescence selectivity and competition experiments

To study the fluorescence selectivity of TEPA-β-CD-L toward various metal ion, the fluorescence selectivity experiments (Al^{3+},Zn^{2+},Cu^{2+},Cd^{2+},Hg^{2+},Mg^{2+},K^{+},Mn^{2+},Cr^{3+}) were conducted in pure water buffer solution at pH = 7.2. As Shown in Fig. 2 a, in the absence of various metal ions, the water-soluble compound TEPA-β-CD-L exhibited relatively weak green fluorescence in pure water media (pH = 7.2). However, upon addition of various metal ions, only Zn^{2+} lead to approximately obvious fluorescence enhancement in pure aqueous media, and the fluorescence changed from green to light blue along with the emissive wavelength shift. Except for weak fluorescence increase for Al^{3+} and Cd^{2+}, other metal ions could not arouse obvious fluorescence changes of TEPA-β-CD-L. It proved that the coordination between Zn^{2+} and TEPA-β-CD-L aroused the large enhancement of fluorescence and shift of wavelength in pure aqueous media. The fluorescence behaviors preliminarily indicated TEPA-β-CD-L could act as an fluorescence probe for Zn^{2+} under pure water environment and physiological pH. This absolute water-soluble condition was the characteristic advantage of the TEPA-β-CD-L sensor. Moreover, to illustrate the high selectivity of TEPA-β-CD-L toward Zn^{2+} in pure water media, the fluorescence images were also made (Fig. 2 a inset). The sensor TEPA-β-CD-L exhibited green fluorescence under UV light. Upon addition of 2 equivalent metal ion, only the solution of TEPA-β-CD-L with Zn^{2+} showed remarkable light blue fluorescence, which indicated TEPA-β-CD-L could act as a highly selective fluorescent sensor for Zn^{2+} in pure water media.

The high selectivity of TEPA-β-CD-L toward Zn^{2+} was also investigated by the fluorescence competitive experiments with other cations. 2 equivalent Zn^{2+} was added to the aqueous solution of TEPA-β-CD-L (7.5 × 10^{-6} M), then equivalent amount of other metal ions (Al^{3+},Cu^{2+},Cd^{2+},Hg^{2+},Mg^{2+},K^{+},Mn^{2+},Cr^{3+}) were also added into the solution. The change of fluorescence intensities was recorded. The histogram of fluorescence changes were listed in Fig. 2 b, As shown in histogram, only the

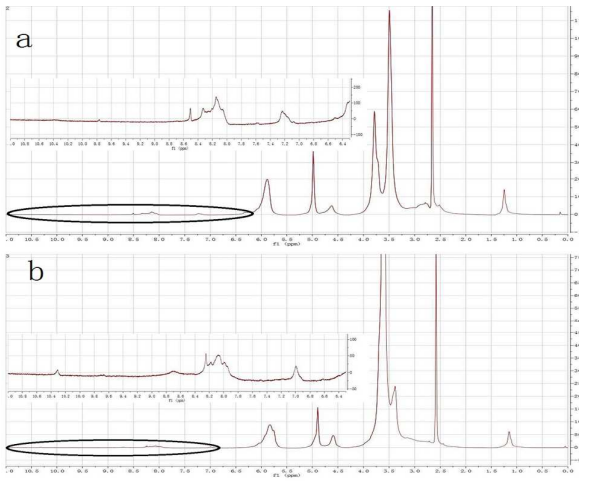

Fig. 5 a. The NMR spectrum of TEPA-β-CD-L in DMSO-d_6 media in the absence of Zn^{2+}, **b.** The NMR spectrum of TEPA-β-CD-L in DMSO-d_6 media in the presence of Zn^{2+}.

addition of Cu^{2+} lead to a little fluorescence intensity decrease, with addition of other metal ions, no significant variation from the fluorescence emission of TEPA-β-CD-L-Zn^{2+} was observed by comparison with the fluorescence property of TEPA-β-CD-L-Zn^{2+}. All the fluorescence spectra indicated the high selectivity of TEPA-β-CD-L toward Zn^{2+} over other co-existent metal ions in pure aqueous media.

In addition, the reversibility between TEPA-β-CD-L with Zn^{2+} in pure water solution was also checked (Fig. S5). The compound EDTA was conducted as an coupling reagent owing to the intense binding ability with Zn^{2+}, EDTA was added to the water solution, the fluorescence intensity was recorded. Then Zn^{2+} was added to the solution, the fluorescence was obtained, Three minutes later, EDTA was added to the system. The change of fluorescence was observed. As shown in Fig. S5, the fluorescence intensity of TEPA-β-CD-L-Zn^{2+} exhibited no significant variation, which demonstrated that the coordination between TEPA-β-CD-L and Zn^{2+} was irreversible.

Fluorescence titration and Uv-vis spectrum investigation

Fluorescence titration experiment (Fig. 3 a) of TEPA-β-CD-L with Zn^{2+} was performed in aqueous media (pH = 7.2) at room temperature. Upon addition of Zn^{2+}, the fluorescence signal at 410 nm significantly enhanced. It was explicit that the binding between TEPA-β-CD-L and Zn^{2+} induced fluorescence change of sensor, which was responsible for the fluorescence intensity increasing. It was also obvious that the fluorescence enhancement process of sensor accompanied the fluorescence emission wavelength shift from 460 nm to 410 nm. As shown in Fig. 3. b, the association constant between TEPA-β-CD-L and Zn^{2+} was estimated to be 2.55×10^{13} M^{-1} in pure water media (pH = 7.2) by fitting the data to the Benesi-Hildebrand expression with a good linear relationship.

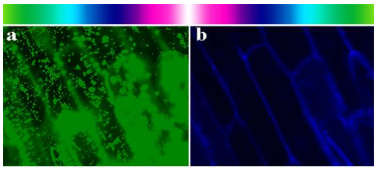

Fig. 6 The fluorescence microscope images of onion epidermal cells with TEPA-β-CD-L (a) and TEPA-β-CD-L (b) treated with Zn^{2+} under pure water environment

The Uv-vis absorption titration curve of TEPA-β-CD-L with Zn^{2+} in pure water media (pH = 7.2) was examined to illustrate the optical activities of TEPA-β-CD-L and TEPA-β-CD-L-Zn^{2+} and it was shown in Fig. 4. It exhibited characteristic absorption of molecule L at the range 200-400 nm without Zn^{2+}. With addition of Zn^{2+} in pure water environment, the intensity of absorption peaks at 360 nm decreased significantly, clearly indicating the coordination interaction between TEPA-β-CD-L and Zn^{2+}.

Investigation of ^{1}HNMR titration spectrum, IR spectra, fluorescence sensing mechanism and detection limit

NMR titration spectroscopy has widely used for studying the sensing process between sensor and target molecules. The coordination cites of sensor TEPA-β-CD-L and Zn^{2+} could be determined preliminarily. Fig. 5 showed the ^{1}HNMR spectroscopy of TEPA-β-CD-L in the absence and presence of Zn^{2+}. As shown in Fig. 5 a and b, the coordination of sensor TEPA-β-CD-L with Zn^{2+} could induce the changes and reorganization of certain H-chemical shifts from sensor TEPA-β-CD-L. The active hydrogen from –OH disappeared owing to coordination of sensor with Zn^{2+}. And the chemical shift from -NH- showed obvious changes from 7.23 to 6.99, which was affected by Zn^{2+}. By the information from H-chemical shifts, we could primarily confirm that one coordinative cites of TEPA-β-CD-L for Zn^{2+} was from nitrogen atom of -CH=N-, -OH and –NH- *et al*. And the coordination cites were also ensured by IR titration spectrum (Fig. S4). The –CH=N- peak at 1495 cm^{-1} showed a 7 cm^{-1} red shift to 1502 cm^{-1}, which was induced by the coordination between TEPA-β-CD-L and Zn^{2+}. Moreover, in accordance with reported coordination modes, the fluorescent senor was most likely to chelate Zn^{2+} via its hydroxyl O, imino N and N atoms from TEPA-β-CD. The predicted coordination mode was showed in Scheme 1. In addition, the supposed fluorescence mechanism was concluded. Before sensor TEPA-β-CD-L coordinated with Zn^{2+}, TEPA-β-CD-L exhibited green fluorescence. While TEPA-β-CD-L interacted with Zn^{2+}, intense blue fluorescence appeared, which is ascribed to the Chelating Induced Fluorescence Enhancement (CIFE) process. The CIFE process induced the stronger planarity of TEPA-L through the coordination of Zn^{2+}, which was positive for fluorescence emergence. Simultaneously, the CIFE process between Zn^{2+} and TEPA-β-CD-L lead to occurrence of Photoinduced Electron Transfer (PET). And the collaborative mechanisms of CIFE and PET was also illuminated by fluorescence titration spectrum, in which the emissive peak from TEPA-β-CD generated a obvious

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blue shift along with the enhancement of fluorescence intensity upon addition of Zn^{2+} in pure water system.

Further, to evaluate the sensitivity of sensor for Zn^{2+} in aqueous media, the detection limit of TEPA-β-CD-L in recognizing Zn^{2+} was also tested using fluorescence spectra. The fluorescence titration experiment of TEPA-β-CD-L with Zn^{2+} demonstrated the detection of Zn^{2+} in absolute water media was at the magnitude level of 1.0×10^{-7} M (Fig. S6).

Cell fluorescence microscopy

The fluorescence microscope images of onion epidermal cells with TEPA-β-CD-L (Fig. 6 a) and TEPA-β-CD-L-Zn^{2+} (Fig. 6 b) in pure water environment were tested to demonstrate its application in tracking Zn^{2+} in biological system. The onion epidermal cells were from fresh onion inner surface. And the onion epidermal was treated in pure water solution containing TEPA-β-CD-L for 10 min, then the soaked onion epidermal was observed under fluorescent microscope. Then Zn^{2+} solution was added to the onion epidermal cells handled with TEPA-β-CD-L water solution, the fluorescence signal was recorded again. As shown in Fig.6 a, the onion epidermal cells soaked in water solution of TEPA-β-CD-L showed intense green fluorescence, and the nuclei of cells was also labelled clearly. Strong blue fluorescence (Fig.6 b) was observed when the cells were treated with Zn^{2+} solution. The results suggested the water-soluble TEPA-β-CD-L sensor could permeate the cytoderm and plasma membrane of onion epidermal cells and give specific blue fluorescence signal in the presence of Zn^{2+}, which demonstrated that the water-soluble TEPA-β-CD-L could be acted as an effective fluorescence sensor for Zn^{2+} in biological system and environment.

Conclusions

In summary, we have fabricated a highly water-soluble fluorescent sensor for Zn^{2+} derived from β-Cyclodextrin, whih showed homogeneous sphericity. The energy transferred from green to blue in virtue of the binding of sensor with Zn^{2+}, which exhibited Chelating Induced Fluorescence Enhancement (CIFE) and Photoinduced Electron Transfer (PET) process. Moreover, The sensor showed high selectivity as well as good sensitivity. And live cell fluorescent imaging was also investigated by onion epidermal cells, which exhibited high penetration depth. Besides, The coordination sites between sensor and Zn^{2+} were concluded preliminarily by NMR and IR titration spectra. Such the investigation endowed the potential application in biological and environment fields for tracking and detecting of Zn^{2+}.

Acknowledgements

This work is supported by the Research Start Funds Sponsored Program of Zhoukou Normal University (zksybscx201201), Scientific research innovation fund of Zhoukou Normal University (zknuA201502), Young and middle-aged backbone teachers plan of Zhoukou Normal University. Science and Technology Research Projects of the Education Department Henan Province (14B150037), Author thank the Key Laboratory of Plant Genetics and Molecular Breeding of Zhoukou Normal University for the Cell fluorescence microscopy.

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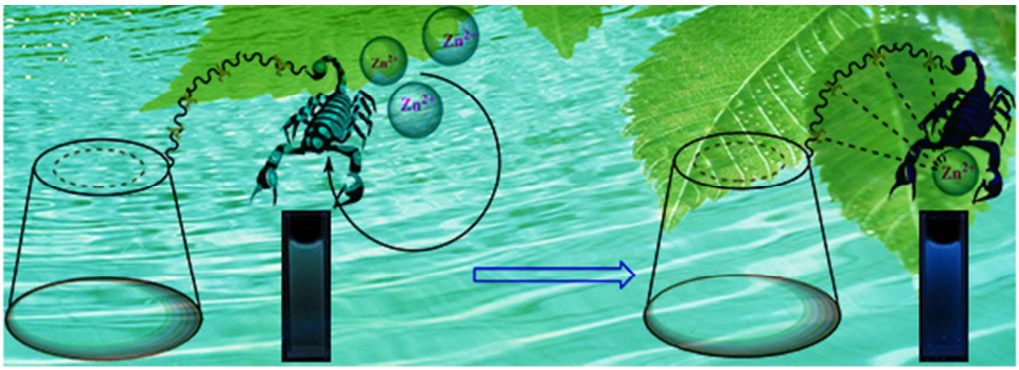

Highly selective and sensitive fluorescent sensor for Zn^{2+} derived from β-cyclodextrin derivate in pure water system was fabricated. Through fluorescence micrograph experiment, it showed excellent image effect on onion epidermal cells.