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Quinolinotriazole-β-cyclodextrin and its adamantanecarboxylic acid complex as efficient water-soluble fluorescent Cd^{2+} sensors

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Dedicated to Professor Yoshihisa Inoue on the occasion of his 60th birthday

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ABSTRACT

A novel β-cyclodextrin derivative **1** bearing 8-hydroxyquinolino and triazole groups was synthesized in satisfactory yield by 'click chemistry'. With a good water solubility up to 0.03 mol/L, **1** exhibited an effective switch-on fluorescence response to Cd^{2+} over other common metal ions under physiological conditions. Studies on the recognition mechanism indicated that the cooperative coordination of Cd^{2+} with both the 8-hydroxyquinolino moiety excluded from the β-CD cavity and the triazole moiety was a crucial and basic factor to achieve the fluorescent sensing process. Significantly, spectrophotometric studies also demonstrated that, after inclusion complexation with 1-adamantanecarboxylic acid sodium salt (AdCA), the resultant **1**/AdCA system gave a more effective fluorescent sensing to Cd^{2+} through a cyclodextrin/substrate/Cd^{2+} triple binding mode.

1. Introduction

Detecting transition- or heavy-metal ions is of great interest to many chemists, biologists and environmentalists, mostly because these ions play important roles in living systems or have extremely toxic impact on organisms and environment.[1] Among the numerous analytical methods that are available for the detection of cations, the ones based on fluorescent sensors have been intensively studied due to their distinct advantages in terms of sensitivity, selectivity, instantaneous response, and local observation. As a result, many considerable efforts have been devoted to the development of fluorescent chemosensors and the analysis of these ions,[2] such as Cu^{2+}, Zn^{2+}, and Hg^{2+}. Since cadmium can produce a wide variety of acute and chronic effects in humans and accumulate in kidney, liver, pancreas, testes, and lung,[3] there is a great need for the design and synthesis of fluorescent sensors that can detect and monitor Cd^{2+} under physiological condition efficiently. However, most of the Cd^{2+} recognitions were carried out in non-aqueous media or water/organic mixtures,[4] and few examples of water-soluble fluorescence sensors for Cd^{2+} have been reported in the past few years. On the other hand, cyclodextrins (CDs), a class of cyclic oligosaccharides with 6–8 D-glucose units linked by α-1,4-glucose bonds, are well known to encapsulate various organic guests within their hydrophobic cavities and widely used as drug carriers and solubilizers.[5] Recently, we performed some investigations on the fluorescence sensing of Zn^{2+} and Hg^{2+} and their applications in the cell straining.[6] Herein, we wish to report a novel highly water-soluble β-CD derivative **1** modified by both 8-hydroxyquinolino and triazole moieties and its efficient fluorescence sensing towards Cd^{2+}. Significantly, owing to the strong association of β-CD cavity with adamantanyl skeleton, **1** could form the stable inclusion complex with 1-adamantanecarboxylic acid sodium salt (AdCA), which exhibited the stronger binding affinity, better sensing ability and the lower limit of detection (LOD value) to Cd^{2+} than **1**.

2. Results and discussion

2.1. Synthesis

The synthetic route of **1** was described in Scheme 1. The reaction between 8-hydroxyquinoline and propargyl bromide under a basic condition afforded 8-propargyloxyquinoline (**5**) in 70% yield. Then, **5** underwent a 'click chemistry' reaction with mono(6-deoxy-6-azido)-β-CD[7] in THF/H_2O to yield **1** in 72% yield. Benefiting from the good solubilization ability of β-CD unit, **1** showed a satisfactory solubility up to 0.03 M in water. Furthermore, in order to demonstrate the role of 8-hydroxyquinolino and triazole moieties clearly, two compounds **2** and **3** were synthesized as references (see Supplementary data).

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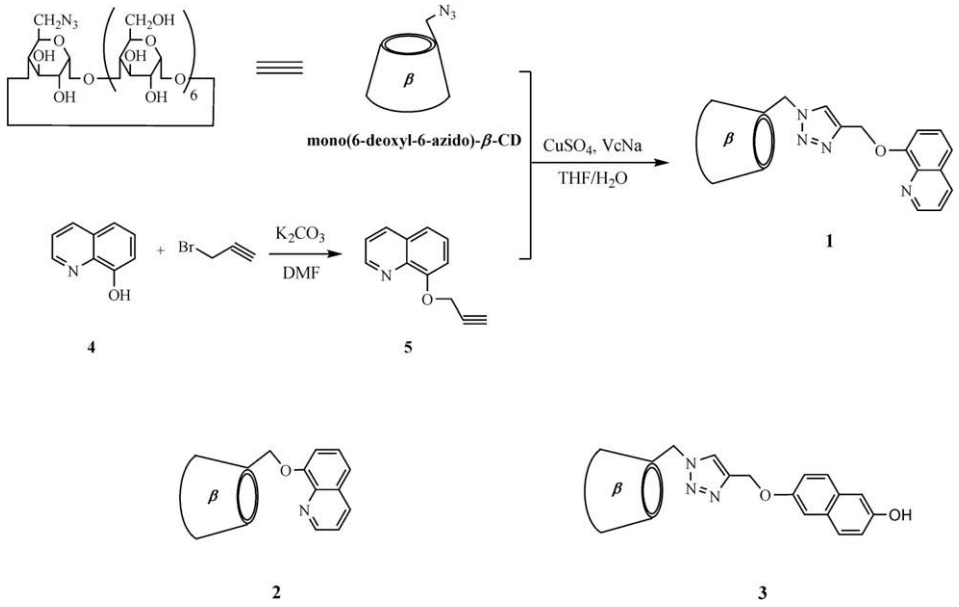


Scheme 1. Syntheses of **1**–**3**.

2.2. Determination of pK_a

Since fluorescent probes based on the electron donor/acceptor are very sensitive to the pH value in the detection of metal ions, it is necessary to consider the pH effect and determine an optimal sensing condition. The emission peak of **1** was observed at 485 nm at pH 1.13 and showed a gradual hypsochromic shift to 472 nm with decreasing the acid concentration, accompanied by the appearance of a shoulder peak around 416 nm. However, no dramatic change was observed under alkaline conditions (Fig. S1, Supplementary data). Through a plot of fluorescence intensity versus pH values (Fig. 1),[8] the pK_a value of **1** could be calculated to be 4.09 by analyzing the fluorescence changes at different pH resulted from the protonation/deprotonation of nitrogen atom of quinolino ring.[9] This result indicated that **1** would not be protonated at a neutral environment, which will be favorable to its coordination with Cd^{2+} under physiological conditions.

2.3. Fluorescence sensing of 1

The fluorescence sensing measurements of **1** towards Cd^{2+} were carried out in HEPES buffer solution (10 mM, pH 7.2). As seen in Figure 2, with the stepwise addition of Cd^{2+} to a solution of **1**, the fluorescence emission intensity of **1** at 418 nm was gradually increased. The possible mechanism for the enhanced fluorescence may be explained as follows. Before coordinated with Cd^{2+}, **1** gave the weak fluorescence because of the lone electron pairs of the N atom in the 1,2,3-triazole moiety being located close to the 8-hydroxyquinolino fluorophores, which resulted in an intramolecular photo-induced electron transfer (PET). The deexcitation of the tautomer occurred mainly via a nonradiative pathway. When **1** was coordinated with Cd^{2+}, the nonradiative channel was blocked synchronously, and thus the **1**/Cd^{2+} system exhibited the enhanced fluorescence. Moreover, the Job's plot was also performed to explore the coordination stoichiometry between **1** and Cd^{2+} in aqueous buffer solution, which showed a maximum peak

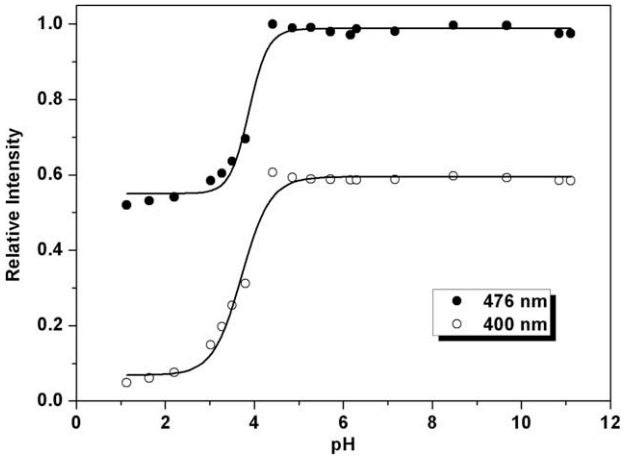


Figure 1. Plot of fluorescence intensity at 400 and 476 nm of **1** versus pH value in aqueous solution. ([**1**] = 2.0×10^{-5} M, λ_{ex} = 300 nm).

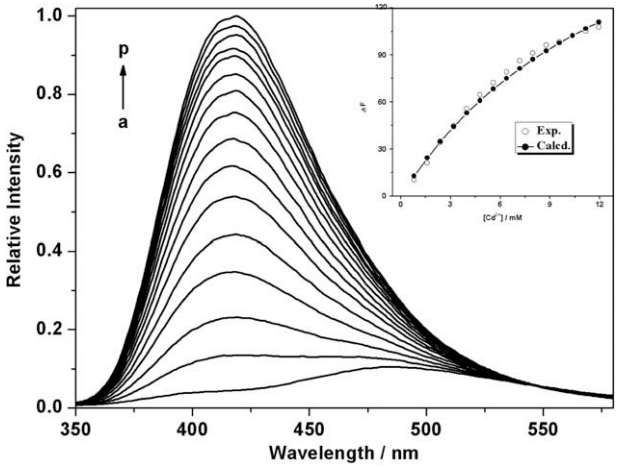


Figure 2. Fluorescence spectral changes of **1** (1.0×10^{-5} M) upon addition of $Cd(ClO_4)_2$ ($0–1.2 \times 10^{-2}$ M, from a to p) in HEPES buffer solution (10 mM, pH 7.2). Inset: The nonlinear least-squares analysis of the differential intensity (ΔF) to calculate the complex formation constant (K_s). (λ_{ex} = 303 nm, λ_{em} = 418 nm).

at a molar fraction of 0.5, corresponding to a 1:1 **1**/Cd^{2+} stoichiometry (Fig. S2, Supplementary data). After validating the 1:1 binding stoichiometry, the binding constant ($\log K_s$) between **1** and Cd^{2+} was calculated to be 2.10 ± 0.23 by analyzing the sequential changes in fluorescence intensity (ΔF) of **1** at varying concentrations of Cd^{2+} using a nonlinear least-squares curve-fitting method[10] (Fig. 1, inset). Additionally, the limit of detection (LOD value) of **1** towards Cd^{2+} was calculated to be 1.89×10^{-3} M by multiplying the standard derivation of 11 blank measurements by 3 and dividing by the slope of the linear calibration curve in lower concentration.[4c]

The fluorescence sensing selectivity of **1** for Cd^{2+} was investigated by comparing the fluorescence responses of **1** towards various metal ions. Herein, the effect of different metal ions was tested by monitoring the fluorescence intensity changes of **1** at 417 nm. As seen in Figure 3, the fluorescence of **1** showed a 1.7-fold enhancement to Cd^{2+}, while its IIB homologue Zn^{2+} only gave a 0.8-fold enhancement under the same conditions. In addition, the fluorescence of **1** showed no appreciable changes or slight quenches with the addition of various metal ions including Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Co^{2+}, Mn^{2+}, Ag^+, Hg^{2+}, Co^{2+}, Ni^{2+}, and Pb^{2+}. The selectivity of **1** to Cd^{2+} should be attributed to the semirigid structure formed by the nitrogen and oxygen atoms of quinoline and triazole ring in **1**, which well fitted the ionic radius of Cd^{2+} and limited the geometric structure of the **1**/Cd^{2+} complex.[4c,11] In addition, the effect of chelation-enhanced fluorescence (CHEF) during the chelation of **1** with Cd^{2+} by both the 8-hydroxyquinolinyl group and 1,2,3-triazole ring may also contributed to the selectivity of **1** to Cd^{2+}.[12]

2.4. Fluorescence sensing of 1/AdCA

Possessing a free β-CD cavity, **1** also had a capability of binding the guest molecules. In a preliminary report, we have shown that the association of a fluorescent quilino-β-CD with 1-adamantaneacetic acid led to an improved fluorescence sensing ability for Zn^{2+}.[13] Herein, the similar phenomenon was also observed, that is, the fluorescence sensing ability and selectivity of **1** towards Cd^{2+} significantly enhanced after its inclusion complexation with AdCA. As shown in Figure 4, the fluorescence of **1** showed an 11.6-fold enhancement to Cd^{2+}, which was seven times higher than the corresponding value without AdCA, in the presence of 200 equiv of AdCA. Moreover, although the fluorescence of **1** was strongly quenched by Fe^{3+} or Cu^{2+} under our experimental condition, the influence of Fe^{3+}or Cu^{2+} to the fluorescence sensing of **1**/AdCA system was negligible, because Fe^{3+}or Cu^{2+} would

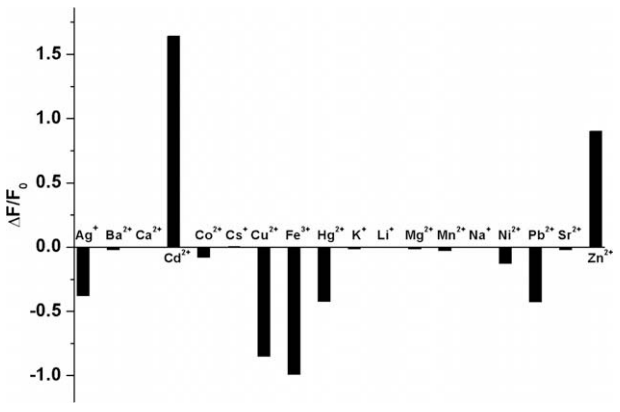


Figure 3. Fluorescence change ($\Delta F/F_0$) of **1** at 417 nm in the presence of different metal ions in HEPES buffer (10 mM, pH 7.2). ([**1**] = 2.0×10^{-5} M, [M^{n+}] = 2.0×10^{-3} M, λ_{ex} = 300 nm).

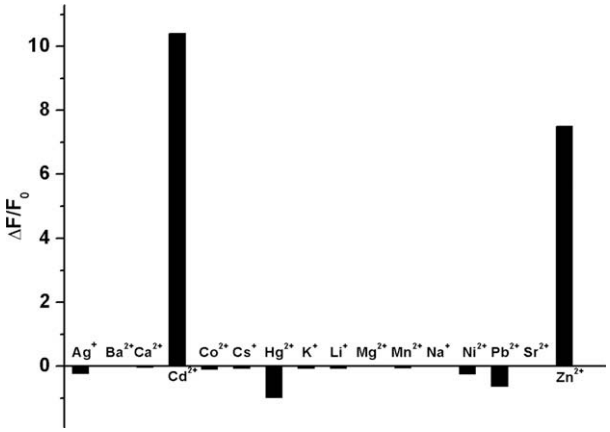


Figure 4. Fluorescence change ($\Delta F/F_0$) of **1** at 419 nm in the presence of different metal ions in HEPES buffer (10 mM, pH 7.2). ([**1**] = 2.0×10^{-5} M, [AdCA] = 4.0×10^{-3} M, [M^{n+}] = 2.0×10^{-3} M. λ_{ex} = 302 nm).

precipitate from the solution in the presence of AdCA. Simultaneously, a much lower LOD value for Cd^{2+} was also obtained as 9.07×10^{-6} M by the **1**/AdCA system.

2.5. Binding mode

To explore the possible binding modes of **1** and **1**/AdCA with Cd^{2+}, ^{1}H NMR and two-dimensional ROESY spectra were measured in D_2O. As shown in Figure 5, the ^{1}H NMR signals for the protons of both 8-hydroxyquinolino and triazole moieties of **1** showed the downfield shifts in the presence of Cd^{2+}. This phenomenon may be attributed to the electron shielding effect of Cd^{2+} on protons in its proximity. Therefore, we deduced that the quinolino and triazole moieties of **1** jointly coordinated with Cd^{2+} to form the **1**/Cd^{2+} complex as illustrated in Scheme 2, which prevented the intramolecular PET between the lone electron pairs of the N atom in the 1,2,3-triazole moiety and the 8-hydroxyquinolino moiety and thus led to the enhanced fluorescence of **1**/Cd^{2+} system. Lacking the 1,2,3-triazole (or 8-hydroxyquinolino moiety), the reference compound **2** (or **3**) showed no appreciable fluorescence changes to Cd^{2+}. This phenomenon also confirmed that the cooperative coordination of the triazole moiety and the 8-hydroxyquinolino moiety played a crucial role in the fluorescence sensing of Cd^{2+}.

Superior to **1**, the **1**/AdCA system possessed three possible binding sites for Cd^{2+}; that is the 1,2,3-triazole moiety, the 8-hydroxyquinolino moiety and the AdCA moiety. The ROESY spectrum of **1**/AdCA (Fig. S3, Supplementary data) showed the clear NOE correlations between the AdCA protons and the interior protons (H3/H5/H6) of β-CD cavity. Moreover, it could also be observed that the AdCA protons showed the stronger NOE correlations with the H5/H6 protons than with H3 protons. Because the H5/H6 protons were located near the narrow opening of β-CD cavity, while the H3 protons were located near the wide opening, these NOE correlations indicated that AdCA was included in the β-CD cavity and located near the narrow opening, like the conformation of the reported quilino-β-CD/1-adamantaneacetic acid system.[13] By analyzing the sequential changes of chemical shifts of AdCA that occurred with changes in host concentration using a nonlinear least-squares curve-fitting method, the binding constant ($\log K_s$) between **1** and AdCA can be calculated to be 5.55 ± 0.03 due to the good size fitting between β-CD cavity and adamantane derivatives (Fig. S4, Supplementary data).[14,15] Through a calculation based on the binding constant between **1** and AdCA as well as the concentrations of host and guest, more than 99% of **1** should be converted to **1**/AdCA complex under our experimental

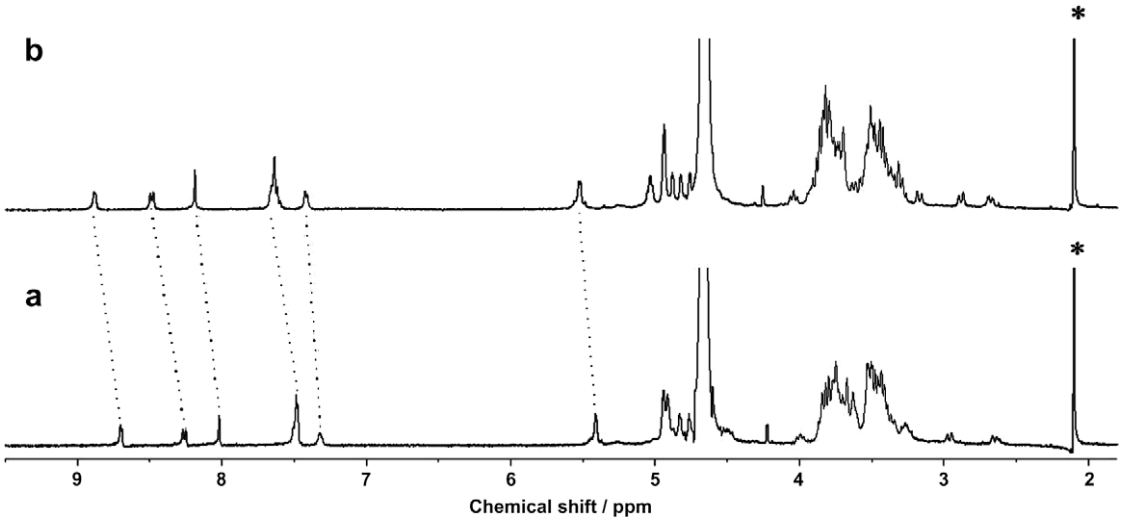
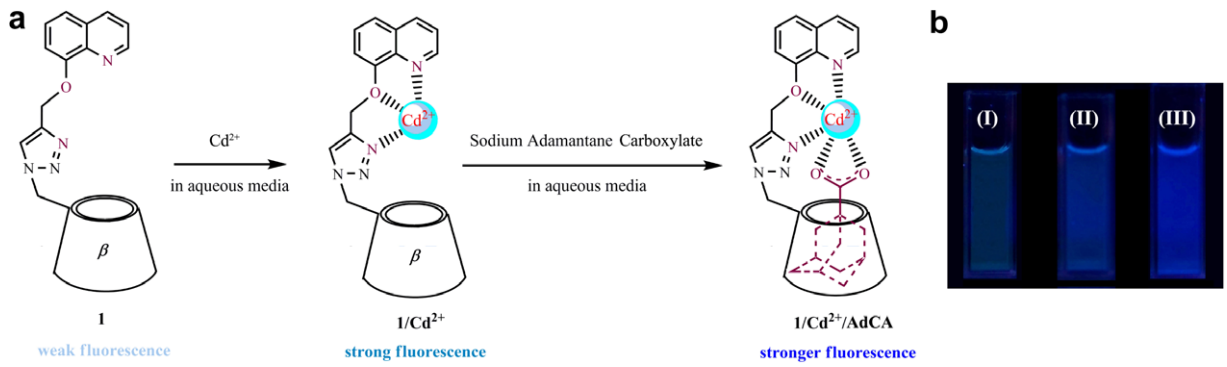


Figure 5. ^{1}H NMR spectra change of **1** (a) in the absence of and (b) in the presence of 10 equiv of Cd^{2+} in D_2O ([**1**] = 1.0×10^{-3} M, [Cd^{2+}] = 1.0×10^{-2} M). Symbol * indicates the peak of acetone as an internal standard.



Scheme 2. (a) The proposed binding mode of **1**/Cd^{2+} and **1**/AdCA/Cd^{2+} systems. (b) Visible emission observed from **1** (I), **1**/Cd^{2+} (II), and **1**/AdCA/Cd^{2+} (III) systems. ([**1**] = 2.0×10^{-5} M, [Cd^{2+}] = 2.0×10^{-3} M, and [AdCA] = 4.0×10^{-3} M, respectively).

conditions. Moreover, the carboxylate group of AdCA should be deprotonated and exist as a carboxylate anion under our experimental conditions. Therefore, we can deduce a possible binding mode of **1**/AdCA with Cd^{2+} as illustrated in Scheme 2. Besides the 1,2,3-triazole and the 8-hydroxyquinolino moiety, the anionic carboxylate group, which was expected to pointed to the coordinated Cd^{2+} attributed to the electrostatic attraction between Cd^{2+} and carboxylate anion, also actively participate in the cooperative binding of Cd^{2+}. Using the similar fluorescence titration method, the binding constant (log K_s) between **1**/AdCA and Cd^{2+} was calculated to be 3.38 ± 0.09 (Figure 6). Comparatively, **1**/AdCA also showed the fluorescence sensing ability to Zn^{2+}. That is, **1**/AdCA/Zn^{2+} system gave a peak at 422 nm under the same condition, but its intensity was weaker than that of **1**/AdCA/Cd^{2+} system, and the corresponding log K_s between **1**/AdCA and Zn^{2+} was calculated as 3.13 ± 0.02 (see the Supplementary data, Fig. S6). This result indicated that the sensing ability of **1**/AdCA towards Cd^{2+} was stronger than that towards Zn^{2+}. In order to support the triple binding mode of **1**/AdCA with Cd^{2+}, some control experiments were performed. Under the same conditions, no appreciable fluorescence responses towards Cd^{2+} could be observed by **2**/AdCA or **3**/AdCA system. These results, along with the much smaller fluorescence enhancement factor of **1** alone ($\Delta F/F_0$ = 1.7) to Cd^{2+}, unambiguously demonstrated that joint contribution of 8-hydroxyquinolino, triazole and the accommodated AdCA moiety to the more effective fluorescent sensing of **1**/AdCA system. It was noteworthy that this switch-on sensing process could be readily distinguished by not only fluo-

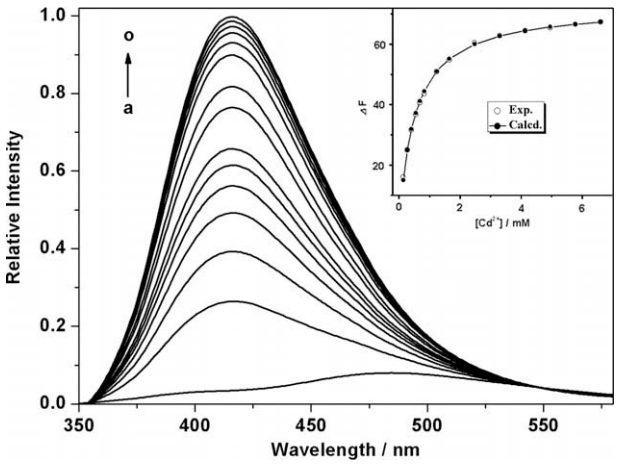


Figure 6. Fluorescence spectral changes of **1**/AdCA ([**1**] = 1.0×10^{-5} M, [AdCA] = 1.0×10^{-3} M) upon addition of Cd^{2+} (0–5.6×10^{-3} M, from a to o) in HEPES buffer solution (10 mM, pH 7.2) at 25 °C. Inset: The nonlinear least-squares analysis of the differential intensity (ΔF) to calculate the complex formation constant (K_s). (λ_{ex} = 302 nm, λ_{em} = 417 nm).

rescence spectroscopy but also naked eyes. As shown in Scheme 2 (b), **1** (2.0×10^{-5} M) alone only exhibited a weak green fluorescence, but gave a strong green–blue fluorescence in the presence of Cd^{2+} (2.0×10^{-3} M). Surprisingly, **1**/Cd^{2+} system gave a much stronger fluorescence upon the addition of AdCA (4.0×10^{-3} M) due to the formation of the cyclodextrin/substrate/metal ions complexes. In addition, the fluorescent titration of **1**/Cd^{2+} system upon addition of AdCA was also carried out to investigate the minimum value of AdCA in our case. The result showed that, within the AdCA concentration range of $0.18–4.0 \times 10^{-3}$ M, the fluorescent intensity of **1**/Cd^{2+} reached a plateau (Fig. S5).

3. Conclusion

In summary, a water-soluble fluorescent Cd^{2+} sensor **1** was synthesized by Huisgen [2+3] cycloadditions reaction and fully characterized. Studies on the binding modes between sensor **1** and Cd^{2+} indicated that the cooperative coordination of 8-hydroxyquinolino and triazole moieties led to the fluorescence sensing towards Cd^{2+}. After associating AdCA, the resultant **1**/AdCA system could be used as a more effective switch-on fluorescence sensor for Cd^{2+}, showing the stronger binding affinity, the better sensing ability as well as the lower LOD value than **1** in aqueous solutions. Considering its convenience in preparation, satisfactory water solubility and high sensing ability towards Cd^{2+}, **1** and its AdCA complex are expected to have the potential application in physiological fields or environmental monitoring and surveillance.

4. Experimental section

4.1. General

All the chemicals were used as reagent grade unless noted. β-CD was recrystallized twice from water and dried in vacuo at 90 °C for 24 h. Mono[6-*O*-(p-toluenesulfonyl)]-β-CD (**7**),[16] mono-6-deoxy-6-(8-oxymethylquinolino)-β-CD (**2**),[17] and mono-6-deoxyl-6-azido-β-CD (**8**)[7] were prepared according to the reported methods. Crude DMF was stirring in CaH_2 for three days and then distilled under reduced pressure prior to use. Elemental analyses were performed on a Perkin–Elmer-2400C instrument. NMR spectra were recorded on Bruker AV300 and Varain Mercury Plus 400 instruments. The fluorescence experiments were recorded in a conventional quartz cell (10 mm × 10 mm × 45 mm) on an Edinburgh Analytical Instruments FL900CD spectrometer or a VARIAN CARY Eclipse spectrometer at 25 °C.

4.2. Synthesis of mono-6-deoxy-6-{4-(8-oxymethylquinolino) [1,2,3]triazolyl}-β-CD (1)

A solution of **5** (330 mg, 1.80 mmol) in 15 mL of THF was added to a solution of $CuSO_4 \cdot 5H_2O$ (600 mg, 2.40 mmol) and **8** (1.39 g, 1.20 mmol) in 35 mL of water. The mixture was kept at 50 °C for 10 min, and then sodium ascorbate (1.42 g, 7.20 mmol) was added. The color of the mixture turned orange immediately and then was heated at 50 °C under an atmosphere of N_2 overnight. After cooled to room temperature, insoluble precipitates were removed by filtration, and the filtrate was evaporated in vacuo. The residue was dissolved in a small amount of water, and washed with 300 mL of acetone for at least three times. After separation by column chromatography (silica gel) using *n*-PrOH/H_2O/25% $NH_3 \cdot H_2O$ (6:3:1, v:v:v) as eluent, **1** was obtained as a pale yellow solid in 72% yield (R_f = 0.4). ^{1}H NMR (400 MHz, D_2O, ppm), δ 3.34–4.23 (m, 42 H, H of C-3, C-5, C-6, C-2, C-4 of β-CD), 4.87–4.94 (m, 7H, H of C-1 of β-CD), 5.38–5.44 (m, 2H, –C*H*$_2$–), 7.28–7.32 (m, 1H, H of quinoline), 7.39–7.61 (m, 3H, H of quinoline), 8.02 (s, 1H, H of triazole), 8.24 (d, 1H, H of quinoline), 8.70 (d, 1H, H of quinoline). Anal. Calcd for $C_{54}H_{78}N_4O_{35}$: C, 48.29; H, 5.85; N, 4.17. Found: C, 48.11; H, 5.80; N, 4.15. ESI-MS: 1343 $[M+H]^+$.

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Supplementary data

Detailed synthesis and characterization, fluorescence emission spectra of **1** as a function of pH, Job's plot of **1** and Cd^{2+}, 2D ROESY spectra of **1**/AdCA/Cd^{2+} systems, NMR titration of **1**/AdCA system, the fluorescent spectra changes of **1**/Cd^{2+} upon addition of AdCA, and the fluorescent titration and the K_s value of **1**/AdCA/Zn^{2+} system. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2010.01.024.

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