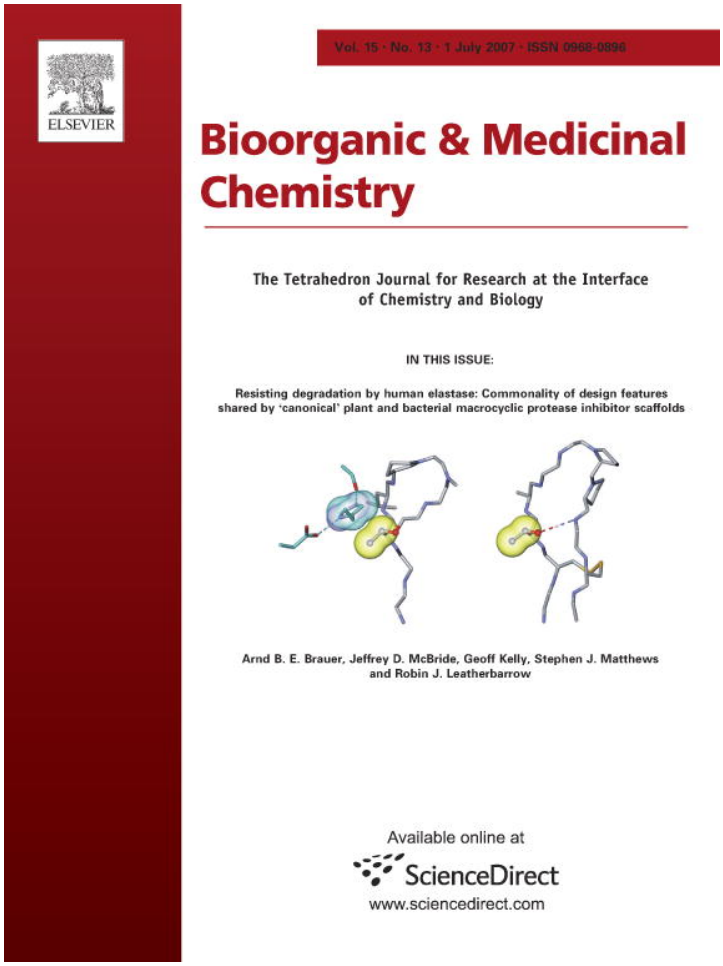

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Effective switch-on fluorescence sensing of zinc(II) ion by 8-aminoquinolino-β-cyclodextrin/adamantaneacetic acid system in water

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Abstract—A water-soluble 8-aminoquinolino-β-cyclodextrin/1-adamantaneacetic acid (**1**/ADA) system is prepared in situ and exhibits a unique switch-on fluorescence response to Zn^{2+} over other common metal ions. Spectrophotometric studies demonstrate that this system can strongly coordinate Zn^{2+} through a cyclodextrin/substrate/metal triple recognition mode, and the resulting **1**/ADA/Zn^{2+} ternary complex emits the blue-green fluorescence ($\lambda = 490$ nm) that can be easily distinguished by eyes in aqueous solution. Significantly, the switch-on fluorescence response of **1**/ADA to Zn^{2+} is barely affected by various metal ions except Cu^{2+}. As a result, this system can behave as an efficient supramolecular fluorescence sensor for Zn^{2+} in water.

1. Introduction

Zinc is the second abundant transition metal in human body only inferior to iron and plays important roles in various biological processes such as gene transcription, metalloenzyme regulation, neural signal transmission, etc.[1] Generally, the concentration of Zn^{2+} in human body is different in various physiological environments, and many other cations usually coexist with Zn^{2+} in these environments. For example, the concentration of intracellular Zn^{2+} in serum is ca. 12 μM,[2] and that value in the gray matter and brain tissue becomes ca. 0.1–0.5 mM.[3,4] Therefore, a sensitive and harmless technology to detect Zn^{2+} in living cells, especially in the presence of possible competing cations, becomes very important. Because Zn^{2+} does not give any spectroscopic or magnetic signals due to its $3d^{10}4s^0$ electronic configuration, the detection of Zn^{2+} in biological systems cannot be measured by the common analytic techniques such as UV–vis spectroscopy, Mössbauer spectroscopy, nuclear magnetic resonance (NMR) and electron paramagnetic resonance (EPR) spectroscopy. Therefore, the fluorescence spectroscopy is regarded as a good choice for the real-time and real-space detection of Zn^{2+} in living cells without damaging them.[5] In the past two decades, a number of efforts have contributed to the design and synthesis of functional chemosensors and biosensors for Zn^{2+}.[1c,6] However, the current problems for most of these Zn^{2+} sensors are their low water solubility or inconvenience in preparation, the successful examples of water-soluble Zn^{2+} sensors are still limited.[7] Especially, the comprehensive studies of the influence of competing cations on the sensing ability of water-soluble Zn^{2+} sensors are rare. On the other hand, cyclodextrins (CDs), a class of cyclic oligosaccharides mainly with six to eight D-glucose units linked by α-1,4-glucose bonds, are well known to encapsulate various organic guests within their hydrophobic cavities.[8] This fascinating property enables them to be successfully utilized as drug carriers and solubilizers.[9,10] Tabushi et al. and Lincoln et al., respectively, reported that polyamino-modified β-CDs could form the stable complexes with Zn^{2+} in the presence of guest molecules.[11] Recently, we prepared a *N*-(8-quinolyl)-*p*-aminobenzenesulfonamide-modified β-CD (HQAS-β-CD) as a water-soluble Zn^{2+} sensor, which showed the good fluorescence responses to the Zn^{2+}-contained yeast cells.[12] Herein, we wish to report a supramolecular system formed by 8-aminoquinolino-β-CD (**1**) and 1-adamantaneacetic acid (ADA). This system provides a unique fluorescence response to Zn^{2+} over possible competing cations. That is, this system can strongly coordinate Zn^{2+}, and the resulting

Keywords: Zinc; Fluorescence sensing; Cyclodextrin; 8-Aminoquinoline.
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1/ADA/Zn^{2+} ternary complex emits the blue-green fluorescence (λ = 490 nm) that can be easily distinguished by eyes in aqueous solution. As a result, the **1**/ADA system can behave as an efficient supramolecular fluorescence sensor for Zn^{2+} in water.

2. Results and discussion

Compound **1** was synthesized in a satisfactory yield by the reaction of 8-chloroacetylaminoquinoline and mono-6-amino-6-deoxy-β-CD (Scheme 1), and its inclusion complexation behaviors with ADA were investigated by fluorescence titration experiments, ROESY, and molecular modeling study. Figure 1 illustrates the fluorescence titration curves of **1** with ADA. As seen in Figure 1, the emission intensity of **1** gradually increases with the addition of varying amounts of ADA, accompanied by the appreciable bathochromic shift of the absorption peak.

After validating the 1:1 binding stoichiometry, the binding constant between **1** and ADA can be calculated to be $2.1 \times 10^4\ M^{-1}$ by analyzing the sequential changes of fluorescence intensity (ΔF) of **1** that occur with changes in guest concentration using a nonlinear least-squares curve-fitting method.[13] This result is consistent with the reported one that β-CD cavity can strongly bind adamantane derivatives due to the good size fitting between host and guest.[14] Moreover, the binding mode of **1** with ADA was investigated by the ROESY spectrum and molecular modeling study. As can be seen from Figure 2, the ROESY spectrum of an equimolar mixture of **1** with ADA shows the clear NOE correlations (peaks A) between the ADA protons and the interior protons (H3/H5/H6) of β-CD cavity. Moreover, it can also be observed that the ADA protons show stronger NOE correlations with H5/H6 protons than with H3 protons. Because the H5/H6 protons are located near the narrow opening of β-CD cavity, while the H3 protons are located near the wide opening, these NOE correlations indicate that ADA is included in the β-CD cavity and located near the narrow opening, as shown in Scheme 2A. This inclusion mode is further supported by a molecular modeling study. The results (see Supporting Information) show that the ADA is located in the interior of β-CD cavity with the carboxylate group located near the 8-acetamidoquinoline substituent of **1**. According to the reported pK_a value (pK_a = 8.5) of the mono-6-amino-6-deoxy-β-CD,[15] the –NH– group of **1** that is directly linked to the β-CD rim is partly protonated, but the carboxylate group of ADA is deprotonated

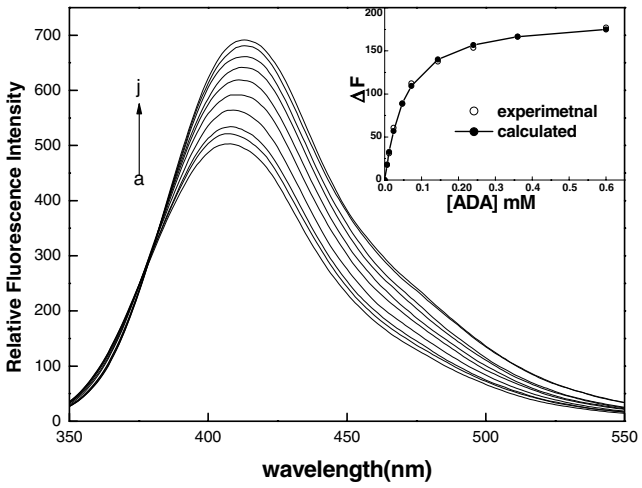
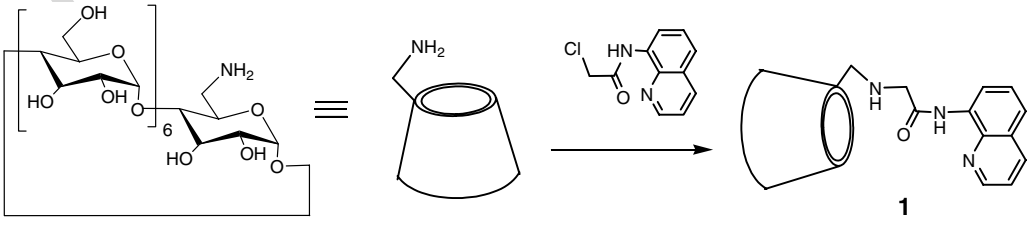


Figure 1. Fluorescence spectral changes of **1** (1.2×10^{-5} M) upon the addition of ADA (0, 0.6×10^{-5}, 1.2×10^{-5}, 2.4×10^{-5}, 4.8×10^{-5}, 7.2×10^{-5}, 14.4×10^{-5}, 24×10^{-5}, 36×10^{-5}, 60×10^{-5} M from a to j) in Tris–HCl buffer solution (pH 7.20) at 298.15 K and the curve-fitting analysis. E_x = 317 nm.

and exists as a carboxylate anion under our experimental conditions. Therefore, the electrostatic interactions between the positively charged side arm of **1** and the anionic carboxylate tail of ADA may further strengthen the inclusion complexation to some extent.

After validating the formation of stable complex between **1** and ADA, we start to investigate its fluorescence sensing ability for Zn^{2+}. The concentration of Zn^{2+} used here is 2.0×10^{-5} M, which is similar to the concentration of intracellular Zn^{2+} in serum.[2] As can be seen in Figure 3, a dilute solution of **1** (2.0×10^{-5} M) shows a moderate fluorescence emission at 412 nm, which barely changes with the addition of Zn^{2+}. In the presence of 50 equiv of ADA,[16] the fluorescence intensity of **1** shows an obvious enhancement, accompanied by the appreciable red shift of the emission peak (4 nm), due to the formation of **1**/ADA complex. Significantly, **1**/ADA system presents a new strong emission at 490 nm with the addition of Zn^{2+}, accompanied by a decrease of the emission intensity at 416 nm, indicating the switch-on fluorescence sensing ability of **1**/ADA for Zn^{2+}. It is noteworthy that this switch-on sensing process can be readily distinguished by eye. As can be seen in Figure 3B, the **1**/ADA system only exhibits the weak blue-purple fluorescence without Zn^{2+}, but gives the strong blue-green fluorescence with the addition of Zn^{2+} (2.0×10^{-5} M). In a control experiment, the 8-chloroacetylaminoquinoline/ADA (molar ratio



Scheme 1.

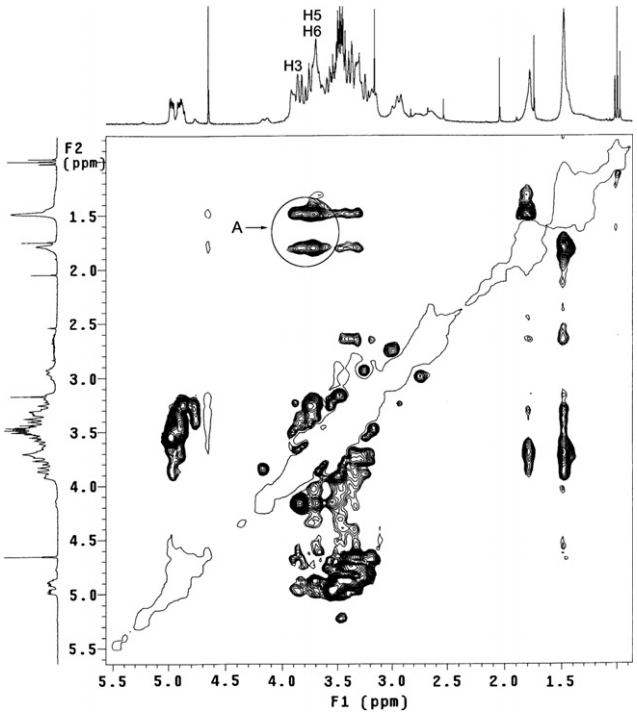
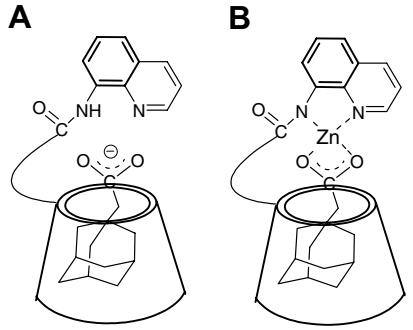


Figure 2. Partial ROESY spectrum of an equimolar mixture of **1** with ADA in a pH 7.2 buffer. ([**1**] = [ADA] = 1.0×10^{-3} M. Under this concentration, ca. 82% of **1** and ADA are converted to **1**/ADA complex through a calculation based on the binding constant between **1** and ADA.)



Scheme 2.

1:50) shows no appreciable fluorescence changes with the addition of Zn^{2+} under the same conditions. This result indicates that β-CD cavity may play an important role in the fluorescence sensing.

A quantitative study on the sensing ability of **1**/ADA system for Zn^{2+} was performed by fluorescence titration. As can be seen in Figure 4, with the stepwise addition of Zn^{2+} to a solution of **1**/ADA, the fluorescence emission at 490 nm gradually increases, but that at 416 nm gradually decreases, accompanied by the appearance of an isosbestic point at 424 nm. Control experiments reveal that the changes of the ion strength resulted from the addition of zinc salt are not the main factor leading to the significant fluorescence changes of **1**/ADA. So we can deduce that the enhanced fluorescence should be dependent on the coordination of **1**/ADA with Zn^{2+}. To explore the possible coordination mode of **1**/ADA with Zn^{2+}, some further experiments were performed. When using other adamantane derivatives, such as 1-bromoadamantane, 1-adamantanol, 1-adamantaneethanol, and 1-adamantaneamine, instead of ADA, the obtained **1**/adamantane derivative system shows no appreciable fluorescence sensing abilities for Zn^{2+} under the same conditions, which indicate that the carboxylate group of ADA may actively participate in the coordination with Zn^{2+}. On the basis of these results, along with the 1:1 coordination stoichiometry between Zn^{2+} and **1**/ADA system determined by the molar ratio method (see Supporting Information), we deduce a possible coordination mode of **1**/ADA with Zn^{2+} as shown in Scheme 2B, and the apparent binding constant of **1**/ADA with Zn^{2+} can be calculated to be 4.64×10^4 M^{-1} by analyzing the sequential changes in fluorescence intensity of **1**/ADA that occurred with changes in Zn^{2+} concentration using a nonlinear least-squares curve-fitting method.[13] It should be noted that there may exist two coordination reactions in solution, that is, the coordinations of Zn^{2+} with **1**/ADA complex and the superfluous ADA. Because the coordination of carboxylate group with Zn^{2+} is reported to be much weaker ($\log K < 2$)[17] than that of **1**/ADA, we deduce that the competing effect of the superfluous ADA on the Zn^{2+} coordination should be negligible.

Some comparative experiments were also performed to support the proposed binding mode in Scheme 2B. Generally, CD cavities always bind guest molecules strongly in water due to hydrophobic interactions but weakly in organic phase. Therefore, we examine the fluorescence spectrum of **1**/ADA with Zn^{2+} in DMF, because DMF can sufficiently exclude the ADA from the β-CD cavity. The result shows that the fluorescence of **1**/ADA system exhibits no appreciable changes with the addition of Zn^{2+}. Moreover, we also use some organic acids, such as deoxycholate, cholate, cyclohexanecarboxylic acid, 2-norbornane acetic acid, and acetic acid, instead of ADA to investigate the Zn^{2+}-sensing abilities of the resulting **1**/organic acid systems. The results show that only the systems formed by **1** with deoxycholate or cholate, either of which can strongly bind β-CD cavity,[18] give the similar fluorescence response for Zn^{2+} to that of **1**/ADA under the same conditions. These observations are in good agreement with the proposed CD/substrate/Zn^{2+} binding mode. According to this binding mode, the strong binding of β-CD cavity with adamantane skeleton allows the close location of the carboxylic group of ADA to the 8-aminoquinolino group, which is appended to the β-CD rim of **1**. This approach of 8-aminoquinolino group of **1** and the carboxylic group of ADA in space consequently leads to the cooperative coordination of **1**/ADA with Zn^{2+}.

This CD/substrate/Zn^{2+} binding mode can subsequently rationalize the fluorescence sensing behavior of **1**/ADA for Zn^{2+}. Before coordination, two nitrogen atoms of the amido quinolino group of **1** can form an intramolecular hydrogen bond,[1c,19] which results in the photo-induced electron transfer and the nonradiative

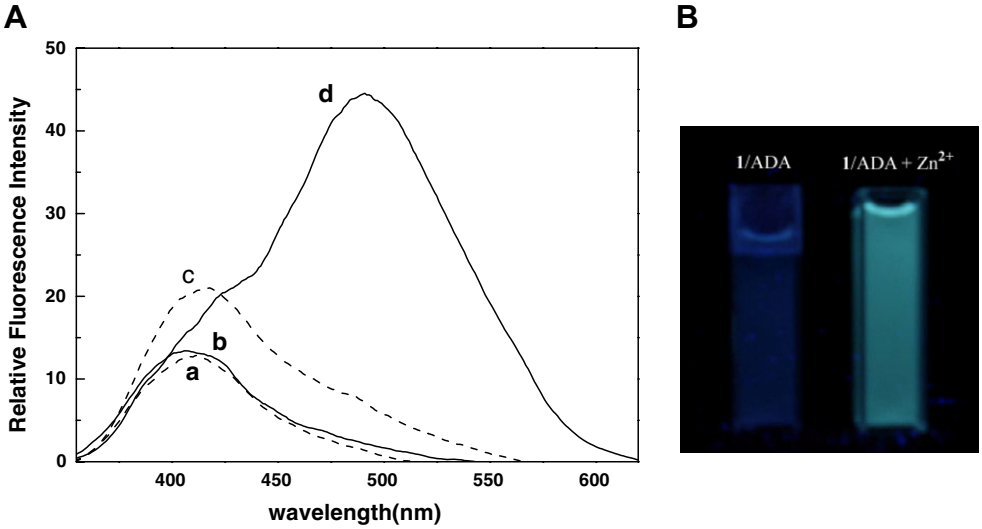


Figure 3. (A) Fluorescence spectra of (a) **1** (2.0×10^{-5} M), (b) **1** + Zn^{2+} ([**1**] = [Zn^{2+}] = 2.0×10^{-5} M), (c) **1**/ADA ([**1**] = 2.0×10^{-5} M, [ADA] = 1.0×10^{-3} M), and (d) **1**/ADA + Zn^{2+}([**1**] = [Zn^{2+}] = 2.0×10^{-5} M, [ADA] = 1.0×10^{-3} M) in Tris–HCl buffer solution (pH 7.20). (E_x = 340 nm). (B) Visible emission observed from **1**/ADA ([**1**] = 2.0×10^{-5} M, [ADA] = 1.0×10^{-3} M) in the absence (left) and presence (right) of Zn^{2+} (2.0×10^{-5} M). Counter anion = [Cl^-].

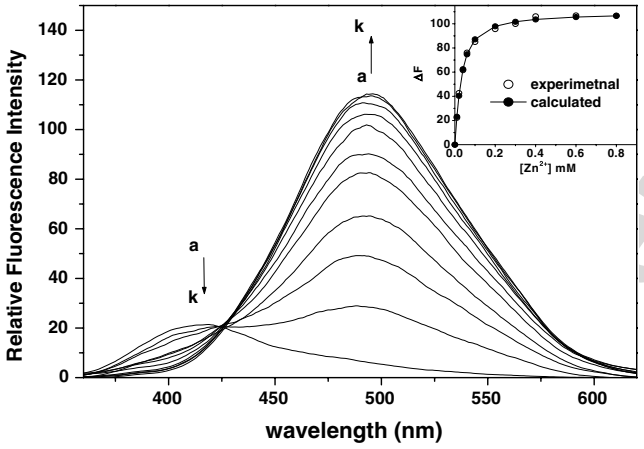


Figure 4. Fluorescence spectral changes of **1**/ADA ([**1**] = 2.0×10^{-5} M, [ADA] = 1.0×10^{-3} M) upon the addition of Zn^{2+} ([Zn^{2+}] = 0, 1.0×10^{-5}, 2.0×10^{-5}, 4.0×10^{-5}, 6.0×10^{-5}, 10×10^{-5}, 20×10^{-5}, 30×10^{-5}, 40×10^{-5}, 60×10^{-5}, 80×10^{-5} M from a to k) in Tris–HCl buffer solution (pH 7.20) at 298.15 K and the curve-fitting analysis. (E_x = 340 nm) counter anion = [Cl^-].

transition processes. These processes consequently lead to the weak fluorescence of **1**. Some reports have demonstrated that quinolyl amide proton can disassociate upon coordination with transition metal ions.[20] Moreover, the FT-IR studies also show that the absorption band corresponding to the amide group of **1** (1664 cm^{-1}) shifts to lower frequencies (1654 cm^{-1}) upon the coordination of **1**/ADA with Zn^{2+}. This phenomenon indicates the partial loss of double-bond character of the carbonyl group due to the resonance exchange between the O=C–N^- form and $^-$O–C=N form of the deprotonated amide group.[21] Therefore, we deduce that, when **1**/ADA is coordinated with Zn^{2+}, the amido group of **1** is deprotonated, and thus the electron transfer process is forbidden. Moreover, the 8-aminoquinolino fluorophore is efficiently protected from deactivating water attack through steric shielding by the β-CD cavity. Therefore, the **1**/ADA/Zn^{2+} system exhibits the enhanced fluorescence. In addition, the Zn^{2+}-sensing ability of **1**/ADA at different pH values was also investigated (see Supporting Information). The results show that **1**/ADA exhibits the poor sensing ability for Zn^{2+} at a pH value below 5.8, which may be due to the protonation of the amido group of **1** in the acidic environment leading to a weak coordination ability of Zn^{2+} with **1**/ADA, but exhibited satisfactory Zn^{2+}-sensing abilities ($I/I_0 > 5$) at a pH range of 7.2–10.6.

After validating the good Zn^{2+}-sensing ability of **1**/ADA, the sensing selectivity of **1**/ADA for Zn^{2+} was also investigated through a comparative study on the fluorescence responses of **1**/ADA to different metal ions. Herein, the effect of other metal ions is tested by monitoring the emission intensities of **1**/ADA-metal systems at 490 nm. As can be seen in Figure 5, the fluorescence of **1**/ADA system shows significant switch-on response to Zn^{2+} among the metal ions investigated, while its IIB homologues, Cd^{2+} and Hg^{2+}, only exhibit slight switch-on fluorescence responses under the same conditions. On the other hand, the fluorescence of **1**/ADA system shows no appreciable changes or slightly quenches with the addition of K^+, Na^+, Ca^{2+}, Mg^{2+}, Mn^{2+}, Pb^{2+}, Co^{2+}, Fe^{2+}, Ni^{2+}, and Fe^{3+} (the possible competing cations when Zn^{2+} sensors are used in physiological studies), but obviously quenches by Cu^{2+} due to the nonradiative energy transition in the processes of the electron or energy transfer between the unfilled d-orbit of Cu^{2+} and the fluorophore.[6c,22] It is noteworthy that the fluorescence enhancement factor (I/I_0 = 6.8) to Zn^{2+} and the water solubility limit (in the millimolar range) of **1**/ADA system are both higher than the corresponding values of HQAS-β-CD (I/I_0 = 5.7, water solubility limit 0.6 mM[12]). These

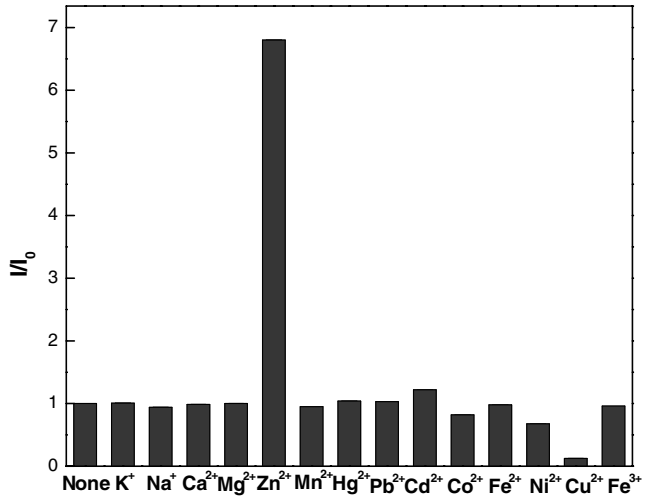


Figure 5. Fluorescence responses of **1**/ADA system to different metal ions in Tris–HCl buffer solution (pH 7.20). E_x = 340 nm, E_m = 490 nm, [**1**] = 2.0×10^{-5} M, [ADA] = 1.0×10^{-3} M, $[K^+] = [Na^+] = [Ca^{2+}] = [Mg^{2+}] = 2.0 \times 10^{-3}$, $[Zn^{2+}] = [Mn^{2+}] = [Hg^{2+}] = [Pb^{2+}] = [Cd^{2+}] = [Co^{2+}] = [Fe^{2+}] = [Ni^{2+}] = [Cu^{2+}] = [Fe^{3+}] = 2.0 \times 10^{-5}$ M. Counter anion = $[Cl^-]$.

results unambiguously demonstrate the applicability of **1**/ADA system as efficient Zn^{2+} sensor in water.

It is also interesting to compare the fluorescence sensing ability of **1**/ADA to the Zn^{2+}-contained cation mixtures, because a very important characteristic feature of a sensor is its response to the species to be measured over that to other species also present in the environment. As can be seen in Figure 6, the **1**/ADA system also shows the high fluorescence enhancement factors ($I/I_0 > 4.5$), most of which are similar to that for Zn^{2+} alone ($I/I_0 = 6.8$), for the buffer solutions containing Zn^{2+} and various

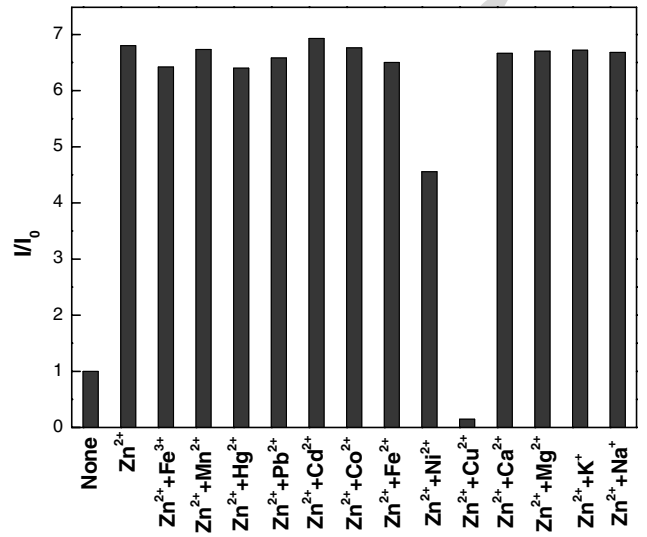


Figure 6. Fluorescence responses of **1**/ADA system to different cation mixtures in Tris–HCl buffer solution (pH 7.20). E_x = 340 nm, E_m = 490 nm, [**1**] = 2.0×10^{-5} M, [ADA] = 1.0×10^{-3} M, $[K^+] = [Na^+] = [Ca^{2+}] = [Mg^{2+}] = 2.0 \times 10^{-3}$,$[Zn^{2+}] = [Mn^{2+}] = [Hg^{2+}] = [Pb^{2+}] = [Cd^{2+}] = [Co^{2+}] = [Fe^{2+}] = [Ni^{2+}] = [Cu^{2+}] = [Fe^{3+}] = 2.0 \times 10^{-5}$ M. Counter anion = $[Cl^-]$.

alkali metal ions (Na^+ and K^+), alkali earth metal ions (Ca^{2+} and Mg^{2+}), or transition metal ions (Mn^{2+}, Hg^{2+}, Pb^{2+}, Cd^{2+}, Co^{2+}, Fe^{2+}, Ni^{2+}, Fe^{3+}). On the other hand, although Cu^{2+} is unfavorable to the Zn^{2+}-sensing of **1**/ADA system, its interference in the fluorescence response may be masked with a copper binding protein such as bovine serum albumin.[7c]

In conclusion, we successfully prepare an 8-aminoquinolino-β-CD/ADA system in situ as a switch-on fluorescence sensor for Zn^{2+}. This sensor system presents the obvious fluorescence emission, which can be readily monitored by both eyes and fluorescence spectroscopy, in the presence of Zn^{2+}. As compared with a majority of reported Zn^{2+} sensors, this sensor system has an inherent advantage for its satisfactory water solubility, convenience in preparation and separation, and high sensing specificity for Zn^{2+} over other competing cations, which will be important and helpful in its potential application to meet the selectivity requirements of a Zn^{2+} assay in physiological fields.

3. Experimental

3.1. General

All chemicals were commercially available unless noted otherwise. Reagent grade β-CD was recrystallized twice from water and dried in vacuum at 80 °C for 24 h prior to use. *N*,*N*-Dimethylformamide (DMF) was dried over calcium hydride for 2 days and then distilled under reduced pressure prior to use. 8-Chloroacetylaminoquinoline[23] and mono-6-amino-6-deoxy-β-CD[24] were prepared according to the reported procedures. Elemental analyses were performed on a Perkin-Elmer-2400C instrument. NMR spectra were recorded on a Varian Mercury VX300 instrument. Fluorescence spectra were measured in a conventional rectangular quartz cell ($10 \times 10 \times 45$ mm) at 25 °C on a JASCO FP-750 spectrometer equipped with a constant-temperature water bath, with the excitation and emission slits' width of 5 nm.

3.2. Synthesis of 1

8-Chloroacetylaminoquinoline (0.75 mmol) was added to a solution of mono-6-amino-6-deoxy-β-CD (0.5 mmol) in dry DMF (40 mL) containing triethylamine (2 mL) with stirring under N_2. The mixture was stirred at room temperature for 24 h and then was allowed to warm and reacted at 80 °C for 2 days. Then, the reaction mixture was poured into acetone to give a white precipitate. The crude solid product was collected by filtration and then recrystallized from ethanol/water (v:v = 1:1) to give **1** as a light yellow solid (300 mg, yield 51%). ESI-MS *m/z* 1318.46 (M^++H); ^{1}H NMR (D_2O, TMS, ppm): δ 2.37–4.21 (m, 44H); 4.86–5.08(m, 7H); 7.45–7.67 (m, 3H), 8.16 (d, 1H, J = 8.1 Hz), 8.46 (d, 1H, J = 7.2 Hz), 8.94 (d, 1H, J = 3.6 Hz). Anal. Calcd for $C_{53}H_{79}O_{35}N_3 \cdot 5H_2O$: C, 45.18; H, 6.40; N, 3.04. Found: C, 45.20; H, 6.37; N, 2.98.

Acknowledgment

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Supplementary data

Molecular modeling result, molar ratio plot of **1**/ADA + Zn^{2+} system, fluorescence responses of**1**/ADA to Zn^{2+} at various pH values. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2007.04.016.

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