Sensors and Actuators B 144 (2010) 337–341

Contents lists available at ScienceDirect

Sensors and Actuators B: Chemical

journal homepage: www.elsevier.com/locate/snb

Short communication

The quinoline derivative of ratiometric and sensitive fluorescent zinc probe based on deprotonation

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ARTICLE INFO

Article history:
Received 21 July 2009
Received in revised form 2 September 2009
Accepted 14 September 2009
Available online 19 September 2009

Keywords:
Fluorescent probe
Ratiometric detection
Zinc ion
Quinoline derivatives
High sensitivity

ABSTRACT

A new quinoline derivative probe (QZn1) with DPA as recognition group was designed and prepared for selective detection of Zn^{2+} in aqueous solution. The recognizing affinity is based on the selective deprotonation and coordination. The resulting fluorescence λem via ICT is at 499 nm, while the original fluorescence is at 407 nm. The fluorescence ratio (F_{499}/F_{407}) shows high selectivity and sensitivity (nanomolar level) to Zn^{2+} in aqueous solutions. QZn1 has ideal chemical and spectroscopic properties that satisfy the criteria for further biological and environmental applications.

1. Introduction

Zinc ion (Zn^{2+}) is involved in many biochemical processes and plays a vital role in organism [1]. Although the majority of biological zinc ions are tightly sequestered by proteins, the presence of "free zinc pools" in certain cells may still be possible. Thus concerns over biological function of zinc ion have provided motivation to explore efficient methods for monitoring Zn^{2+} form biological samples. Despite having many good even commercial fluorescent probes facilitate the study of this silent metal ions in biological systems, chemists continue endeavoring to design new ones and to improve their sensitivity, selectivity, and reliability in order to satisfy various needs due to the wide existence of Zn^{2+} in organisms. Up to now, most available probes detect Zn^{2+} via measuring the metal-induced changes in fluorescence intensity based on photo-induced electron transfer (PET). It is well-known that many factors may influence the emission intensity, such as the illumination intensity, optical path length and the concentration of probes, which are prone to be disturbed in quantitative detection. Ratiometric fluorescent probes can eliminate the effects of these factors to realize the quantitative detection more effectively by measuring the ratio of fluorescence intensities at two different wavelengths. Therefore, the design of ratiometric fluorescent probes is of great current interest [2].

Quinolines and their derivatives have been used traditionally as fluorogenic agents for the chemical assay of Zn^{2+} [3]. It is regarded as a milestone in the development of fluorescent probes for biological Zn^{2+} that 6-methoxy-8-*p*-toluenesulfonamido-quinoline (TSQ) is first applied for imaging Zn^{2+} in vitro in 1987 [4]. Recently, for the development of ratiometric detection, Guo and co-workers have reported a ratio Zn^{2+} fluorescent probe (AQZ, Scheme 1) with carboxamidoquinoline based on a deprotonation process and ICT (intramolecular charge transfer) mechanism in micromolar level with the association constant $6.7 \times 10^6\ M^{-1}$ [5].

One major challenge faced by Zn^{2+} imaging in a physiological context is very low abundance (below nanomolar) in the resting states of most cell types [6]. It is well-known that DPA (bis(2-pyridylmethyl)amine) is a specific neutral chelator for Zn^{2+}. Lippard [7] and Nagano [8] described many probes based on DPA which could realize Zn^{2+} at low concentrations of nanomolar generally in the presence of high concentrations of Ca^{2+}. After the coordination of DPA with oxygen at the 8th position and the carboxylic group, the apparent dissociation constant of sensor **1** (Scheme 1) reported by Jiang and co-workers was extracted to be 0.45 ± 0.02 fM by a nonlinear curve fit [9]. The findings indicate that sensor **1** is likely to image free zinc ions in low range in biological systems by an increase of the emission intensity.

Hereby, we designed and synthesized probe QZn1 (Scheme 1), combining with the properties of quinoline derivatives in permeability and non-toxicity to cell with the high affinity for Zn^{2+} of DPA. It has been revealed that the deprotonation process of carboxamidoquinoline and ICT mechanism can provide

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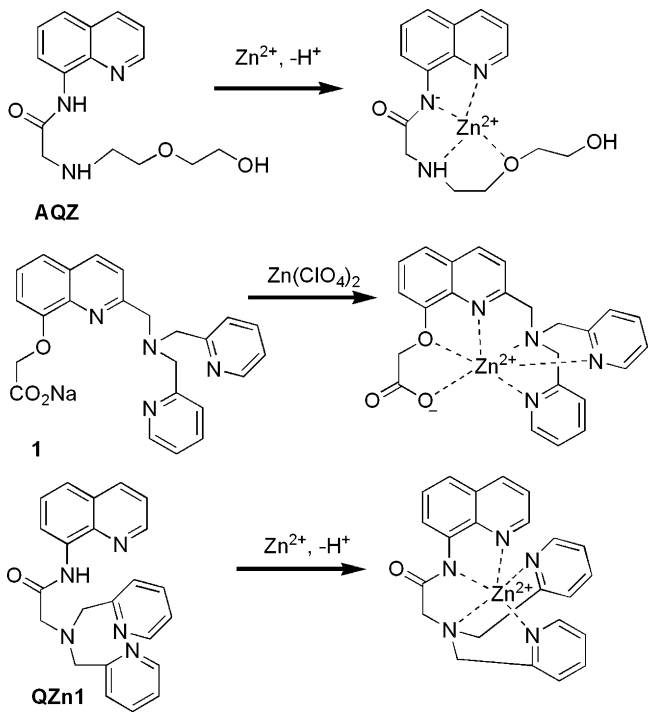
doi:10.1016/j.snb.2009.09.022



Scheme 1. The mechanism of QZn1 for Zn^{2+}.

ratiometric detection. The intramolecular electron-transfer process is not forbidden until binding metal ions [10], resulting in the increase of fluorescence emission. Qian, Cui and co-workers have exploited the deprotonation mechanism for the design of ratiometric Zn^{2+} fluorescent probe (naphthalimide derivative), which presented large red-shift in emission [11].

2. Experimental

2.1. Materials and apparatus

All the solvents were of analytic grade. The solutions of metal ions were prepared from $Pb(NO_3)_2$, $Co(NO_3)_2{\cdot}6H_2O$, $Zn(NO_3)_2{\cdot}6H_2O$, $Ca(NO_3)_2$, $NaNO_3$, $Cu(NO_3){\cdot}3H_2O$, $Ni(NO_3)_2{\cdot}6H_2O$, KNO_3, $Cd(NO_3)_2{\cdot}2H_2O$, $AgNO_3$, $Hg(NO_3)_2{\cdot}0.5H_2O$, $Cr(NO_3)_3{\cdot}6H_2O$, $Mg(NO_3)_2{\cdot}6H_2O$ and $Fe(NO_3)_3{\cdot}6H_2O$ and were dissolved in distilled water. All the samples are detected after confecting for 10 min. ^1H NMR spectra were recorded on a VARIAN INOVA-400 spectrometer. Mass spectrometric data were obtained on a HP1100LC/MSD mass spectrometry and a LC/Q-Tof MS spectrometry. Fluorescence measurements were performed on a LS 55 Luminescence spectrometer of PerkinElmer. Absorption spectra were measured on Lambda 35 UV/vis spectrophotometer of PerkinElmer. All the pH measurements were made with a Model PHS-3C meter.

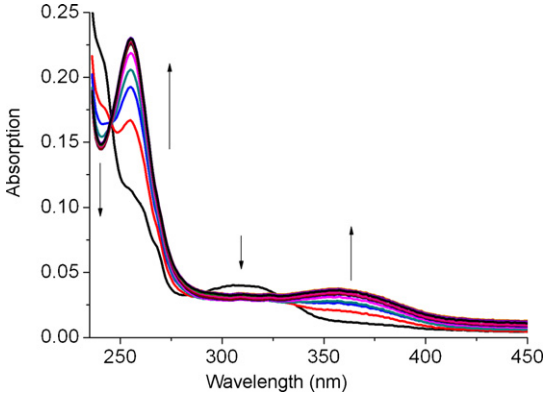


Fig. 1. Absorption spectra of QZn1 (1.5 μM) in the presence of increasing concentrations of Zn^{2+} (0–1 equiv.) in aqueous solution (ethanol/water = 1/1, v/v).

2.2. Synthesis of intermediates and probes

2.2.1. Synthesis of compound **2**

Compound **2** was facilely synthesized in high yield from 8-aminoquinoline by the procedure as published in the literature [5].

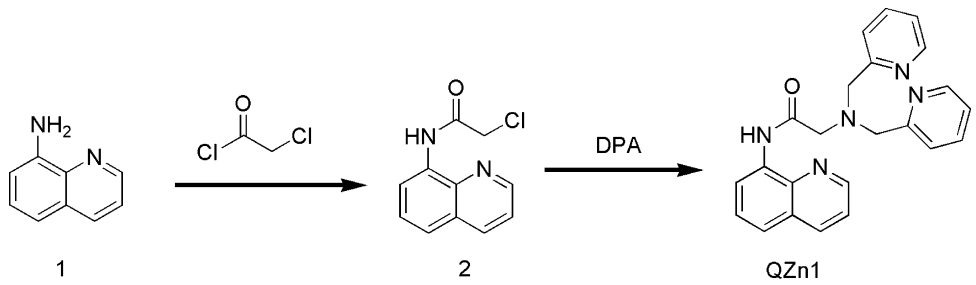
2.2.2. Synthesis of QZn1

2-Chloro-*N*-(quinol-8-yl)acetamide (0.10 g, 0.45 mmol), bis(2-pyridylmethyl)amine (0.20 g, 1.0 mmol), *N*,*N*-diisopropylethylamine (0.10 g, 1.0 mmol) and potassium iodide (10 mg) were added to acetonitrile (30 ml), after being stirred and refluxed for 1 h under nitrogen atmosphere, the mixture was cooled to room temperature and the mixture was removed under reduced pressure to obtain a yellow oil, which was purified by silica gel column chromatography using chloroform/methanol (50:1, v/v) as eluent to afford QZn1 (0.12 g). Yield: 70.5%. ^1H NMR (400 MHz, $CDCl_3$), δ: 3.54 (s, 2H), 4.02 (s, 4H), 7.15 (t, 3H), 7.52 (m, 2H), 7.65 (m, 4H), 7.98 (d, J = 8 Hz, 2H), 8.20 (m, 1H), 8.52 (d, J = 4 Hz, 2H), 8.77 (m, 1H), 8.95 (m, 1H). ^{13}C NMR, δ (100 MHz, $CDCl_3$, Me_4Si): 59.31, 61.09, 116.59, 121.69, 122.39, 123.36, 127.46, 128.11, 134.38, 136.63, 138.86, 148.06, 149.13, 158.23, 169.58. TOF MS: $[M+H]^+$ Calcd. for $C_{23}H_{22}N_5O^+$, 384.1814; found 384.1824.

3. Results and discussion

QZn1 was synthesized in a satisfactory yield by conjugating DPA and 2-chloro-*N*-(quinol-8-yl)acetamide, which was prepared from 8-aminoquinoline and 2-chloroacetyl chloride (Scheme 2).

As shown in Fig. 1, UV–vis spectra of QZn1 exhibited a maximal absorption at 235 nm and a broad band around 311 nm in ethanol/water (1/1, v/v) solution. Upon addition of Zn^{2+} (0–1 equiv.), the absorbance at 240 nm decreased obviously, whereas a new absorption peak appeared at 262 nm with an isosbestic point at 250 nm; meanwhile, the absorbance at 311 nm



Scheme 2. The synthesis of QZn1.