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Spectrochimica Acta Part A 70 (2008) 337–342
SPECTROCHIMICA ACTA PART A
www.elsevier.com/locate/saa

Synthesis of dipicolylamino substituted quinazoline as chemosensor for cobalt(II) recognition based on excited-state intramolecular proton transfer

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Received 29 October 2006; received in revised form 30 August 2007; accepted 18 September 2007

Abstract

A new fluorescent chemosensor for sensing Co(II) using di(2-picolyl)amino (DPA) as a recognition group and quinazoline as a reporting group has been synthesized and characterized. The quinazoline derivative contains an intramolecular hydrogen bond, which would undergo excited-state intramolecular proton transfer (ESIPT) at illumination. The fluorescence quenching is attributed to cation-induced inhibition of ESIPT, which constitutes the basis for the determination of Co(II) with the prepared chemosensor. The fluorophore forms 1:1 cobalt(II) complex with the logarithm of apparent dissociation constant $\log K_a = 6.8$. The analytical performance characteristics of the proposed Co(II)-sensitive sensor were investigated. The chemosensor exhibits a linear response toward Co(II) in the concentration range 3.2×10^{-8} to 1.4×10^{-6} M, with a working pH range from 7.0 to 9.5 and high selectivity.

Keywords: Fluorophore; Quinazoline derivative; DPA; ESIPT; Cobalt ion

1. Introduction

Pollution caused by heavy metals is a major environmental problem in the world. Mining and industrial operations discharge large quantities of effluents into water bodies. Thus, rivers, lakes and estuaries are polluted with heavy metals to different degrees. Cobalt is one of such type of metals. It occurs in the environment at concentrations ranging from 0.5 to 12 $\mu g\,L^{-1}$ in seawater and up to 100 $\mu g\,L^{-1}$ in wastewater [1,2]. On the other hand, cobalt is an essential trace element in plants and animals. It is widely distributed in the human body, with high concentration in liver, bones and kidneys. It is a component of vitamin B_{12}. Cobalt deficiency in animals may lead to retarded growth, loss of appetite and anaemia, and rapid recovery from these symptoms occurs upon feeding them with a cobalt-supplementary diet. The maximum dietary tolerable level of cobalt for common livestock species is 10 ppm [3]. Thus, searching for simple, sensitive and selective analytical techniques that do not use expensive or complicated test equipment for a cobalt assay attracted considerable interest to current analytical research.

The recent years have seen a growing interest in the development of spectrophotometry for cobalt determination [4–7]. However, most of the chromogenic reagents are either not selective, or the products are hydrophobic and require extraction, separation or even a computational step for the determination. Although fluorescence signaling offers the advantage of high sensitivity over absorption or reflectance signaling, only few sensors based on fluorescence are reported for cobalt determination [8–11]. Most of the fluorophores respond toward cobalt only in the presence of oxidizing agents such as hydrogen peroxide and in a basic medium [8,9]. Moreover, some of the fluorophores possess poor selectivity [11] and a relatively high background [8–10]. Searching for new fluorophores which would response toward Co(II) with sufficient high selectivity is still an active field as well as a challenge for the analytical chemistry research.

The majority of fluorescent sensors are functioned as cation-responsive optical switches that translate the binding event into

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doi:10.1016/j.saa.2007.09.012

an increase or decrease of the emission intensity [12]. They are commonly composed of two structural subunits: a fluorophore (for signal transduction) and an ionophore (for selective recognition of metal ion). The two subunits are connected through a linking bridge. Along this line we designed and synthesized a new fluorescent sensor for Co(II). The new sensor contains two subunits: di(2-picolyl)amino (DPA) moiety for selective recognition of Co(II) and quinazoline moiety for fluorescence signal transduction. The quinazoline derivative containing an intramolecular hydrogen bond would undergo excited-state intramolecular proton transfer (ESIPT) at illumination. When the three nitrogen-donor atoms of DPA chelate with the cation, the chelation process would inhibit the ESIPT process. Thus, the fluorescence is quenched. Di(2-picolyl)amine (DPA) functioning as recognition group for zinc has been extensively researched [13–16]. But its function as recognition group for cobalt has not been reported so far. In this paper, we reported that DPA could also recognize cobalt for the first time. Based on cation-induced inhibition of ESIPT, a new fluorescent chemosensor for cobalt determination was designed and characterized. The sensor exhibits linear response over the concentration range from 3.21×10^{-8} M to 1.41×10^{-6} M Co(II) with a working pH range from pH 7.0 to 9.5, and high selectivity.

2. Experimental

2.1. Reagents

Tin dichloride ($SnCl_2$), *p*-toluenesulfonic acid (TsOH) and cobalt acetate ($Co(OAc)_2$) were supplied by Shanghai Chemical Reagents (Shanghai) and used as received. Anthranilamide (Acros), 2-chloromethylpyridine hydrochloride (Lancaster), 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (Lancaster), and 2-nitrobenzaldehyde (Aldrich) were used as received. Twice-distilled water was used throughout all experiments.

2.2. Apparatus

All fluorescence measurements were carried out on an F4500 luminescence spectrometer (HITACHI) with excitation slit set at 5.0 nm and emission at 10.0 nm. The UV–vis absorbance measurements were made on MultiSpec 1501 (SHIMADZU). The pH measurements were carried out on a Mettler-Toledo Delta 320 pH meter.

2.3. Synthesis of fluorophore

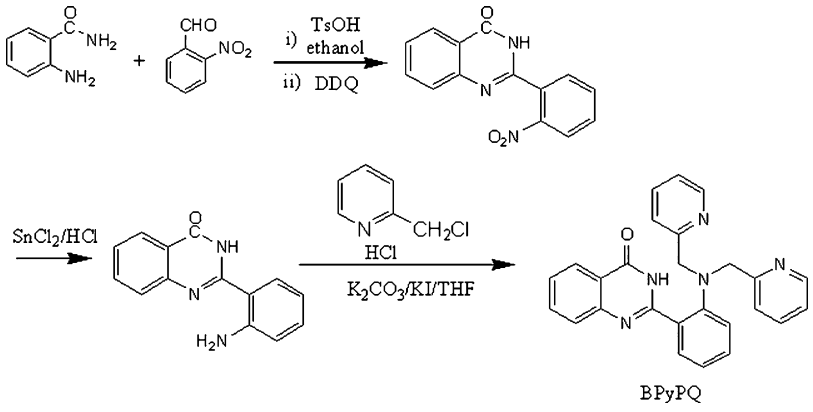
The fluorophore was synthesized in three steps (see Scheme 1).

2.3.1. 2-(2′-Nitrophenyl)-4(3H)-quinazolinone [17]

Anthranilamide (544.3 mg, 4 mmol) and 2-nitrobenzaldehyde (604.4 mg, 4 mmol) were dissolved in anhydrous ethanol and stirred at room temperature for 1 h and then *p*-toluenesulfonic acid (10.7 mg, 0.05 mmol) was added. The reaction mixture was refluxed for another 3 h. The resulting solution was cooled to 0 °C and 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (911.4 mg, 4 mmol) was added in 3 portions during 30 min. The mixture was stirred at 0 °C for 2 h. A white crystalloid was precipitated in ethanol. The solid was washed with ethanol and recrystallized from ethanol to give colorless solid (545 mg, yield: 51%). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm), 11.24 (br s, 1 H), 8.25 (d, 1 H, $J = 7.6$ Hz), 8.21 (d, 1 H, $J = 8$ Hz), 7.84–7.74 (m, 5 H), 7.55 (t, 1 H, $J = 7.6$, 7.2 Hz); EI-MS: *m*/*z* 267 ([M]$^+$, 100), 221 (13), 135 (29), 119 (48), 76 (16).

2.3.2. 2-(2′-Aminophenyl)-4(3H)-quinazolinone

2-(2′-Nitrophenyl)-4(3H)-quinazolinone (23.9 mg, 0.09 mmol) and tin dichloride (3 g, 19.4 mmol) were suspended in the mixed solution of 30 mL ethanol and 30 mL concentrated hydrochloric acid and then stirred vigorously at 60 °C for 5 h. The pH of the resulting solution was adjusted to 7–8 with concentrated ammonia. The solid was extracted with CH_2Cl_2 (3×100 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated to give a colorless solid (18.9 mg, yield: 89%). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm), 9.52 (br s, 1 H), 8.30 (d, 1 H, $J = 8$ Hz), 7.78–7.71 (m, 2 H), 7.53–7.46 (m, 2 H), 7.30–7.27 (m, 1 H), 6.83–6.8 (m, 2 H), 6.25 (br s, 2 H); EI-MS: *m*/*z* 237 ([M]$^+$, 83), 119 (100), 77 (8).



Scheme 1. Scheme for synthetic route.

2.3.3. 2-(2′-(Bispyridin-2″-ylmethylaminophenyl)-4(3H)-quinazolinone (BPyPQ)

2-(2′-Aminophenyl)-4(3H)-quinazolinone (24.1 mg, 0.1 mmol), 2-chloromethylpyridine hydrochloride (50.2 mg, 0.3 mmol), anhydrous K_2CO_3 (140.2 mg, 1.5 mmol) and KI (49.8 mg, 0.3 mmol) were dissolved in the mixed solution of 10 mL THF and 5 mL water and then stirred at room temperature for 7 days. The solution was evaporated to give red solid. The solid was dissolved in 50 mL water and extracted with CH_2Cl_2 (3×100 mL) and the organic layer was washed with water (3×100 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified on silica gel (CH_2Cl_2/CH_3OH 50:1) to give a colorless solid (8.1 mg, yield: 19%). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm), 8.62 (d, 2 H, J = 4.8 Hz), 8.38 (d, 1 H, 1.2 Hz), 7.99 (dd, 1 H, J = 7.2, 1.2 Hz), 7.82–7.74 (m, 2 H), 7.56–7.47 (m, 4 H), 7.20–7.09 (m, 7 H), 4.49 (s, 4 H), ACPI-MS Positive, m/z 420.1 ($[MH+]^+$).

2.4. Preparation of solutions

A 1×10^{-6} M stock solution of BPyPQ was prepared by dissolving BPyPQ in absolute ethanol.

A stock standard solution of Co(II) (0.01 M) was prepared by dissolving 1.2455 mg $Co(OAc)_2 \cdot 4H_2O$ in water and adjusting the volume to 500 mL in a volumetric flask. The other standard solution of Co(II) was obtained by serial dilution of 0.01 M $Co(OAc)_2$ solution.

The wide pH range buffered solution was obtained by adjustment of 0.05 M Tris–HCl solution with a HCl or NaOH solution.

The complex solution of Co(II)/BPyPQ was prepared by adding 5.0 mL of the stock solution of BPyPQ and 5.0 mL of the stock solution of Co(II) in a 10 mL volumetric flask. In the solution thus obtained, the concentrations were 0.5×10^{-6} M BPyPQ and 1×10^{-3} to 1×10^{-8} M of Co(II). The solution was protected from light and kept at 4 °C for further use. Blank solution of BPyPQ was prepared under the same conditions without Co(II).

2.5. Measurement procedure

The fluorescence intensity was measured with the maximal excitation wavelength of 309.0 nm and at the maximal emission wavelength of 471.0 nm. Before each measurement, the solution was allowed to stand for 5 min to allow complete formation of metal–ligand complex.

2.6. UV–vis spectra

For the purpose of studying the response mechanism, an ethanol solution of BPyPQ (2.0×10^{-4} M) and equivalent molar aqueous $Co(OAc)_2$ solution (pH 8.42) were mixed at room temperature. Then its UV–vis spectrum was recorded and compared with that of an ethanol solution of BPyPQ (2.0×10^{-4} M) mixed with blank buffer solution (pH 8.42).

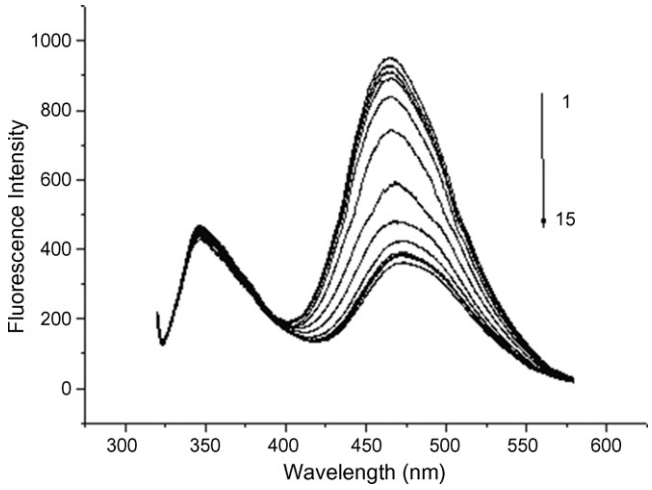


Fig. 1. Fluorescence emission of BPyPQ equilibrium with different concentration of Co(II): (1) 0 M; (2) 3.2×10^{-8} M; (3) 6.4×10^{-8} M; (4) 1.0×10^{-7} M; (5) 1.6×10^{-7} M; (6) 3.2×10^{-7} M; (7) 6.4×10^{-7} M; (8) 1.0×10^{-6} M; (9) 1.1×10^{-6} M; (10) 1.2×10^{-6} M; (11) 1.3×10^{-6} M; (12) 1.4×10^{-6} M; (13) 1.7×10^{-6} M; (14) 2.0×10^{-6} M; (15) 3.2×10^{-6} M.

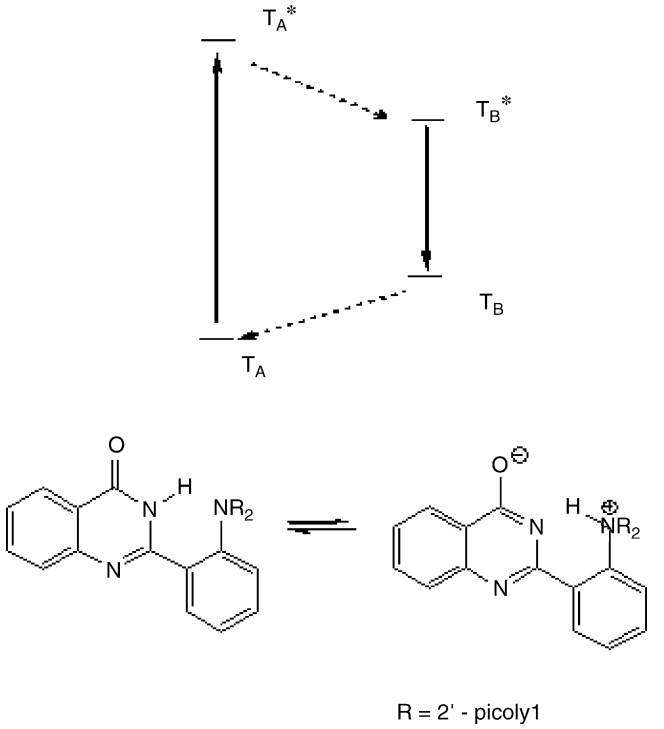
3. Results and discussion

3.1. Spectral properties

The fluorescence spectra changes of BPyPQ when excited at 309.0 nm under various Co(II) concentrations are shown in Fig. 1, which are recorded at λ_{ex} = 309.0 nm, λ_{em} = 320–580 nm. This compound exhibits fluorescence emission at 467.0 nm. As can be seen from Fig. 1, the fluorescence intensities decrease with increasing concentration of Co(II), which constitutes the basis for the determination of Co(II) with the proposed sensor.

3.2. Response mechanism

Quinazoline derivatives (T_A) containing an intramolecular hydrogen bond are good fluorophores [13,18]. They possess a highly Stokes shifted emission. Given appropriate energy, the molecules of derivatives are excited from the ground state (T_A) to the excited-state (T_A^*). The molecules in the excited-state (T_A^*) are instantaneously converted into the proton-transfer tautomer (T_B^*) through exited-stated intramolecular proton transfer (ESIPT). The proton-transfer tautomer (T_B^*) emits the fluorescence and turns to the ground-stated tautomer (T_B). Commonly, the ground-stated tautomer (T_B) is unstable and converted into the stable form (T_A). Simplified diagram illustrating the excited-state intramolecular proton transfer process is shown in Scheme 2. Thus, quinazoline derivatives possess a highly Stokes shifted emission. In this paper the BPyPQ exhibits fluorescence emission maximum at 467.0 nm when excited by the radiation of 309.0 nm. Cobalt is a paramagnetic metal cation. The DPA moiety binds cobalt tightly with three nitrogen-donor atoms. So the tertiary amine would not accept proton anymore as its lone-pair electrons participated coordination with cobalt. In this way cobalt inhibits the excited-state intramolecular proton transferring process, which results in the fluorescence quenching.



Scheme 2. Simplified diagram illustrating the excited-state intramolecular proton transfer.

For the purpose of studying the response mechanism, the absorption spectra of BPyPQ with and without equivalent Co(II) were recorded (Fig. 2). Upon addition of Co(II), the spectrum is almost not changed. Evidently, the fluorophore chelats Co(II) with three nitrogen of the DPA moiety. The nitrogen of quinazoline does not participate in coordination to Co(II) as the spectrum of BPyPQ mixed with Co(II) does not show a new redshifted absorption band [19]. A slight shift (293 → 295 nm) might be attributed to the Co(II)-coordination of the lone-pair electrons of the nitrogen of tertiary amine.

In order to determine the stoichimetry of the coordination complex, the method of continuous variations (Job's method) was used (Fig. 3). As expected, the result obtained from the Job plot unambiguously indicates the formation of a 1:1 complex between BPyPQ and Co(II) [20,21].

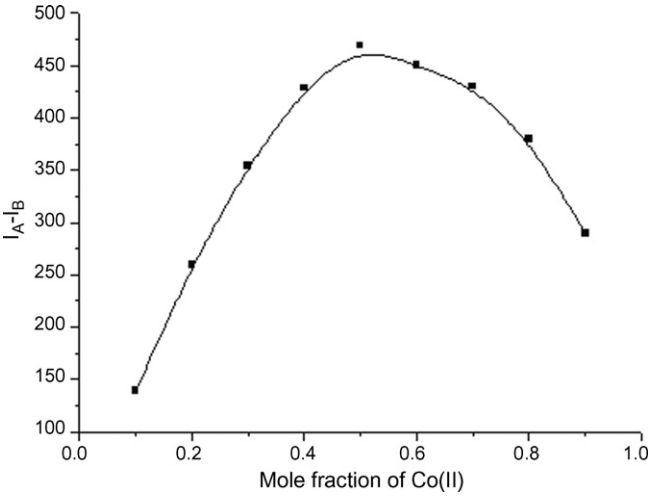


Fig. 3. Job plot for BPyPQ and Co(II): [BPyPQ] + [Co(II)] = 2.0×10^{-6} M.

Taking into account that the concentration of BPyPQ is unchanged in the complex formation, the complexation equilibrium of BPyPQ (A) with Co(II) (B) with an apparent association constant K_a can be expressed by the modified Stern–Volmer equation [22,23].

$$\log\left(\frac{\Delta F}{F}\right) = \log K_a + (n-1)\log[A] + m\log[B] \quad (1)$$

Here ΔF is the change of fluorescence intensity; F denote the fluorescence intensity of BPyPQ in presence of Co(II); m and n are the complexing ratio of the coordination complex. The response curve is shown in Fig. 4. In the Co(II) concentration range of 3.2×10^{-8} to 1.4×10^{-6} M, a linear relationship between log($\Delta F/F$) and log[Co(II)] was obtained, with a correlation coefficient of 0.9979 ($n = 8$) according to an equation: log($\Delta F/F$) = 6.811 + 1.131 log[Co(II)]. The logarithm of apparent association constant (log K_a) of the

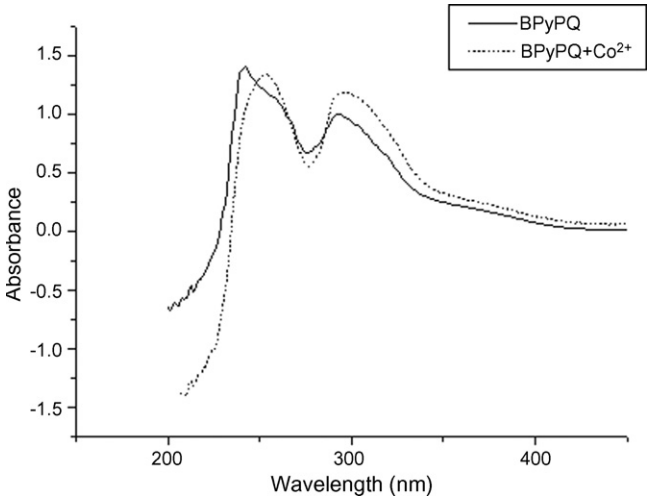


Fig. 2. Changes in the UV–vis spectra of BPyPQ (2.0×10^{-4} M) upon the addition of equivalent molar Co(II).

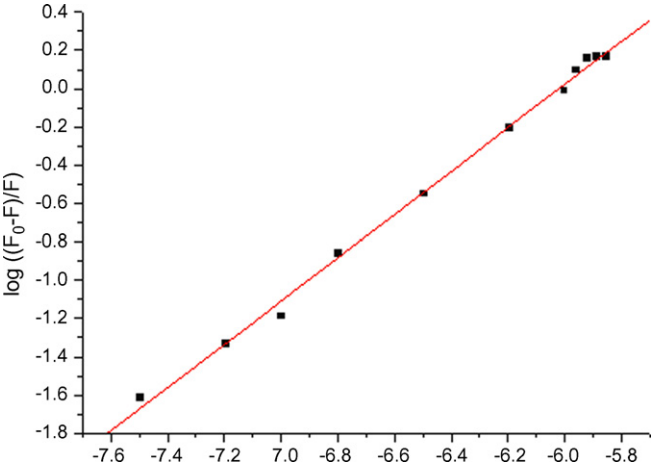


Fig. 4. The plot of log(($F_0 - F$)/F) as a function of the log[Co(II)]. (F and F_0 denote the fluorescence intensities of BPyPQ with and without Co(II), respectively).

Table 1
Interference of different species to the fluorescence determination of Co(II) with the proposed fluorophore

Interferant	Concentration (mol l^{-1})[a]	Fluorescence ($\Delta F = F_0 - F$)[b]	Relative error% ($\Delta F/F_0$) × 100
Li^+	1.0×10^{-2}	8.9	1.9
Na^+	1.0×10^{-2}	5.5	1.2
K^+	1.0×10^{-2}	12.5	2.7
Mg^{2+}	1.0×10^{-2}	3.3	0.7
Ca^{2+}	1.0×10^{-2}	15.6	3.4
Al^{3+}	2.0×10^{-2}	5.5	1.2
Ag^+	1.0×10^{-3}	Precipitated	
Pb^{2+}	5.0×10^{-4}	12.3	2.6
Mn^{2+}	5.0×10^{-4}	12.1	2.6
Ni^{2+}	1.0×10^{-4}	15.4	3.3
Hg^{2+}	1.0×10^{-4}	5.5	1.2
Cu^{2+}	1.0×10^{-4}	15.6	3.4
Fe^{3+}	1.0×10^{-4}	6.9	1.5
Fe^{2+}	1.0×10^{-4}	7.5	1.6
Zn^{2+}	1.0×10^{-5}	16.5	3.6

[a] The concentration of Co(II) is fixed at 1.0×10^{-6}M (pH 8.42).
[b] F and F_0 are the fluorescence intensities of BPyPQ contacting with 1.0×10^{-6} M Co(II) solution with and without adding the interferant ($F_0 = 460.5$).

1:1 complex formation was calculated to be 6.8 by this equation.

3.3. Effect of pH

The effects of pH on the fluorescence intensity of BPyPQ in the absence and in the presence of Co(II) were carried out by adjusting in Tris–HCl buffer with hydrochloric acid and sodium hydroxide and fixing the Co(II) concentration at 1 μM. The results are shown in Fig. 5. One may observe that the fluorescence intensity of BPyPQ increases with the pH increasing at pH 2–9.5, the intensity increases greatly at pH 7–9.5, and at pH > 9.5 the intensity decreases. It is suggested that the pH values affect the ESIPT process. According to the research of Romary [20] and Gruenwedel [21], we know that pK_a of the tertiary amine is 7.3. At pH < 7.3 the tertiary amine is protoned, which will not accept the transferring proton at this range of pH. So the fluorescence intensity is limited. At pH > 9.5 the proton might transfer to the hydroxy ion enriched solution, thus the proton-transfer tautomer (T_B^*) is not formed. So the fluorescence intensity declines. At the same time it is also observed that the fluorescence quenching effect is strongest within the range of pH 7–9.5. At this range of pH cobalt is prone to chelate the DPA moiety, thus fluorescence quenching effect is strongest. Therefore, a pH 8.48 Tris–HCl buffer (25 mL 0.2 M Tris + 12.5 mL 0.1 M HCl 6 + 2.5 mL H_2O) was used in subsequent experiments.

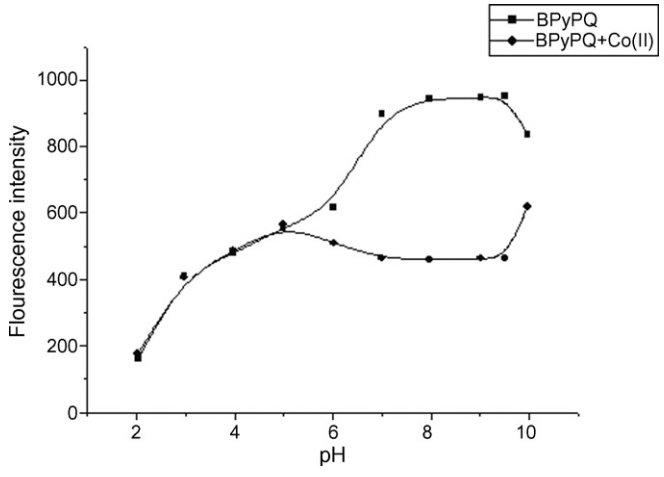


Fig. 5. Changes of fluorescence intensity of BPyPQ (1 μM) upon the addition of 1 μM Co(II) as pH varied.

3.4. Selectivity

A study of the effect of interfering ions was made by adding different amounts of other ions including Li(I), Na(I), K(I), Mg(II), Ca(II), Al(III), Pb(II), Mn(II), Ni(II), Ag(I), Hg(II), Cu(II), Fe(III), Zn(II) to solutions containing 1 μM Co(II).

For this purpose samples containing a fixed concentration of Co(II) (1 μmol L^{-1}) and different concentrations of other metal ions were analyzed by the method. A species was considered as an interferent if it causes a variation more than 5% in analytical signal when compared to the analytical signal obtained in the absence of the interfering species. Ions such as Li(I), Na(I), K(I), Mg(II), Ca(II), Al(III) show no interference on the determination of Co(II) (Table 1). Most of transition metal ions such as Pb(II), Mn(II), Ni(II), Ag(I), Hg(II), Cu(II), Fe(III), Fe(II), Zn(II) show a little interference on the determination of Co(II) in a 100-fold excess. The main interfering species in the determination of Co(II) was Zn(II). The interference is negligible in 10-fold excess.

4. Conclusion

In this paper a new fluorophore (BPyPQ) has been synthesized and characterized. We have developed a fluorescent method for Co(II) by using it. The fluorescence quenching is attributed to cation-induced inhibition of ESIPT. In the absence of Co(II) at pH 7–9.5, the fluorophore undergoes ESIPT to yield a highly Stokes shifted emission from the proton-transfer tautomer. Coordination of Co(II) inhibits the ESIPT process and

quenches the emission from the proton-transfer tautomer. Compared with some other fluorescence methods for determination of Co(II), this method has advantages such as large Stokes shift, high selectivity and not requiring separation. BPyPQ has good solubility in polar solvent such as ethanol. Accordingly, the proposed method may be used for a simple and sensitive determination of Co(II) in pharmaceutical preparations such as drinks containing of vitamin B_{12}.

Acknowledgments

Financial support from the National Natural Science Foundation of China (Grants 20435003 and 20505008) is gratefully acknowledged.

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