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BINOL-Based Fluorescent Sensor for Recognition of Cu(II) and Sulfide Anion in Water

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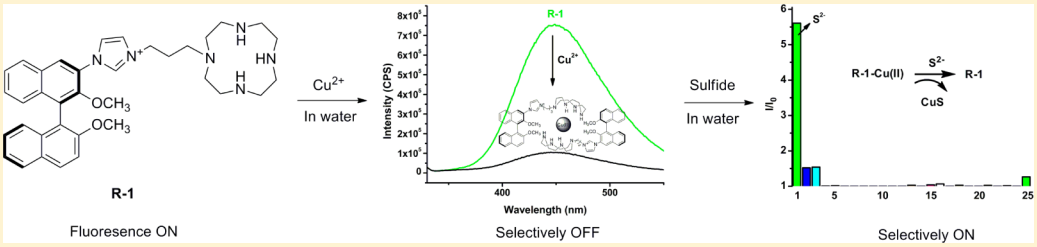
Supporting Information

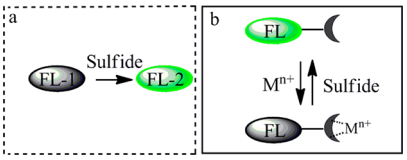


ABSTRACT: A multifunctional fluorescent sensor based on a cyclen-appended BINOL derivative (**R-1**) was synthesized and characterized. It can display on−off-type fluorescence change with high selectivity toward Cu(II) among 19 metal ions in 100% aqueous solution. Furthermore, the in situ generated **R-1−Cu(II)** ensemble could recover the quenched fluorescence upon the addition of sulfide anion resulting in a off−on-type sensing with a detection limit of micromolar range in the same medium. No interference was observed from other biothiols and anions, including GSH, L-Cys, DTT, and sulfates, making it a highly sensitive and selective sulfide probe.

Sulfide anion as a toxic traditional pollutant is widespread in the environment where it is generated from industrial processes and biological metablism.[1] Continuous exposure to sulfide anion can cause gradual and cumulative damage, such as loss of consciousness, irritation of mucous membranes, and suffocation.[2] Once protonated, it becomes more toxic and caustic. However, recent studies have demonstrated that protonated sulfide is involved in various physiological processes, and relatively high concentrations have been measured in bovine, rat, and human brains.[3] For example, H_2S has been recognized as the third gaseous transmitter (the other two are NO and CO)[4] and shown to exert protective effects in relaxation of vascular smooth muscles,[5] reduction blood pressure,[6] mediation of neurotransmission,[7] inhibition of insulin signaling,[8] and regulation of inflammation.[9] In addition, H_2S levels are altered in diseases such as Alzheimer's disease,[10] Down's syndrome,[11] diabetes,[12] and liver cirrhosis.[13] Thus, developing a method for sulfide anion detection is very important for treatments and helpful toward understanding mechanism of action and regulation.

Compared with the traditionally developed detection techniques for sulfide anion, such as titration,[14] inductively coupled plasma-atomic emission spectroscopy (ICP-AES),[15] electrochemical methods,[16] and ion chromatography,[17] fluorescent sensing has received great attention because of its simple operation and high selectivity and sensitivity. Since 2009, several fluorescent probes for sulfide anions have been reported.[6,18] Among these probes, there are two main pathways for sulfide sensing (Scheme 1). One is based on irreversible sulfide-specific chemical reactions, which are regarded as "reactive" probes; the other is based on displacement of metal ions, which are regarded as "competitive" probes. Currently, reactive probes have emerged as an important area. However, most of the organic reactions were time-consuming with poor selectivity and required relatively strict conditions, which limited the probes application. Encouraged by biologically compatible conditions, reversible sensors for sulfide ions exploiting CuS affinity attracted our specific attention. Sulfide ions can react with copper ions to form a low-solubility product CuS ($K_{sp} = 6.3 \times 10^{-36}$),[19] which is fast and stable. In addition, it may be potentially useful for sulfide ions detection at physiological pH. To date, this strategy has two substantial challenges. One is to achieve sufficient selectivity over other biothiols; the other challenge is to realize sulfide detection in 100% aqueous media without interference

Scheme 1. Illustration of Approaches for Sensing Sulfide[a]



[a](a) Sulfide-specific reactions method. FL-1 = quenched fluorescent sensors, FL-2 = recovered fluorescent products. (b) Displacement of metal ions method. FL = fluorescent molecular, M^{n+} = Metal ions.

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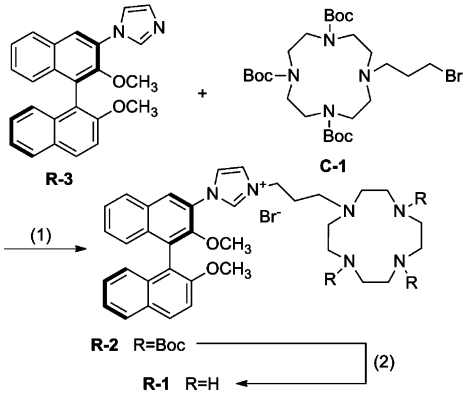
because aqueous media weaken the interaction of sensor with sulfide owing to the strong hydration.[20] Although a fluorescent probe has been developed by Nagano's group,[18b] multifunctional probes are quite rare and still highly desirable.

1,4,7,10-Tetraazacyclododecane (cyclen) has been successfully applied in biology, recognition, and imaging applications.[21] On the other hand, optically active 1,1′-bi-2-naphthol (BINOL) and its derivatives have attracted particular attention in the fluorescence-based molecular recognition.[22] In connection with our continuing research of fluorescent sensor for biologically and environmentally important ions, herein, we present a strategy for designing a water-soluble BINOL-based chemical sensor by incorporating the cyclen unit. The design principles of compound **R-1** are based on the following verities and hypothesis: (1) The imidazolium-functionalized BINOL fluorophore displays an obvious Stokes shift of approximately 100 nm (**R-1** is 160 nm). (2) The cyclen moiety may not only lead to an improvement of the solubility of **R-1** in water but also facilitate enhanced binding affinity for metal ions. Consequently, it was found that sensor **R-1** displays "ON−OFF−ON" mode fluorescence change with alternately added Cu^{2+} and S^{2-} along with reversible formation−separation of the complex in water media.

The target compound **R-1** was conveniently obtained from BINOL derivative ***R*-3**[23] and 1-[1-[4,7,10-tris(*tert*-butyloxycarbonyl)]-1,4,7,10-tetraazacyclododecane]-3-bromopropane **C-1**[24] in two steps (Scheme 2). All of the new compounds were well characterized by ^{1}H NMR, ESI-MS, HRMS, and ^{13}C NMR (see the Supporting Information).

Scheme 2. Synthesis of Compound R-1[a]



[a]Conditions: (1) CH_3CN, 80 °C, 72 h; (2) MeOH/HCl, rt, 12 h.

Target compound **R-1** is water soluble, which makes it useful for practical applications. The fluorescence spectra were obtained by excitation of the fluorophore at 291 nm in 10 mM HEPES-buffered 100% water solution at pH = 7.4, and a strong emission peak was observed at 449 nm. First, to obtain insight into the sensing properties of **R-1**, the emission was examined with various metal species. As shown in Figures 1 and S4 (Supporting Information), the addition of 5 equiv of K^+, Na^+, Li^+, Mg^{2+}, Ca^{2+}, Cr^{3+},Co^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Pb^{2+}, Mn^{2+}, Ba^{2+}, Fe^{2+}, Fe^{3+}, Ag^+, Al^{3+}, and Ni^{2+} had no obvious effect on the fluorescence emission. When 1 equiv of Cu^{2+} was added to the solution of **R-1**, dramatic fluorescent quenching (quenching efficiency $(I_0 - I)/I_0 \times 100 = 86\%$) was observed, suggesting that compound **R-1** shows a specific response to Cu^{2+} ions due to the chelation-enhanced fluorescence quenching (CHEQ)

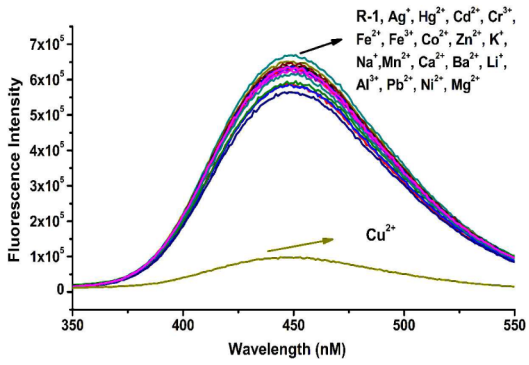


Figure 1. Fluorescence responses of **R-1** (10 μM, λ_{ex} = 291 nm) and upon the addition of ions (5 equiv for K^+, Na^+, Li^+, Mg^{2+}, Ca^{2+}, Cr^{3+},Co^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Pb^{2+}, Mn^{2+}, Ba^{2+}, Fe^{2+}, Fe^{3+}, Ag^+, Al^{3+}, and Ni^{2+}; 1 equiv for Cu^{2+}) in HEPES-buffered (pH 7.4, 10 mM) water.

effect.[25] In addition, there was almost no significant change in the UV−vis spectra of **R-1** (228, 280, 293, and 331 nm) upon addition of various amounts of Cu^{2+} ions (Figure S1, Supporting Information). Therefore, the interaction between host and guest was only evaluated by fluorescent spectra in the following experiments.

To further evaluate the Cu^{2+}-responsive nature of **R-1**, fluorescence titration with Cu^{2+} ions in varying concentrations was conducted. As shown in Figure 2, the addition of increasing

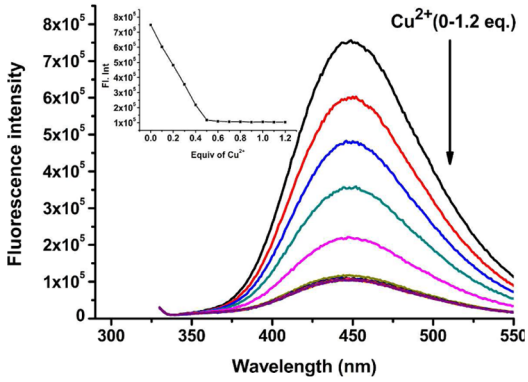


Figure 2. Fluorescence titration of **R-1** with Cu^{2+} in HEPES-buffered (pH 7.4, 10 mM) water. Inset shows the fluorescence change at 449 nm as a function of Cu^{2+} ions. [**R-1**] = 10 μM.

concentrations of Cu^{2+} ions led to a gradual diminished intensity, and the fluorescence of **R-1** was essentially quenched by 0.5 equiv of Cu^{2+} ions. The data were recorded 1 min after Cu^{2+} was added. Since the fluorescent emission of BINOL derivatives might be affected by a dilution effect, a fluorescent titration of pure water into the solution of **R-1** under the same conditions was also conducted. It had almost no effect on the fluorescent intensity, indicating that water would not affect the detection ability of **R-1** toward Cu^{2+} (Figure S2, Supporting Information). The detection limit[26] of the **R-1** for the determination of Cu^{2+} was estimated to be 4×10^{-6} M (Figure S8, Supporting Information) in water media. In good agreement with this finding, the Job plot (Figure S3, Supporting Information) and ESI-MS (Figure S15, Supporting Information) also shows the formation of a 2:1 bonding mode between **R-1** and Cu^{2+} ions (Scheme 3). Moreover, the binding constant (K) derived from the fluorescence titration data was

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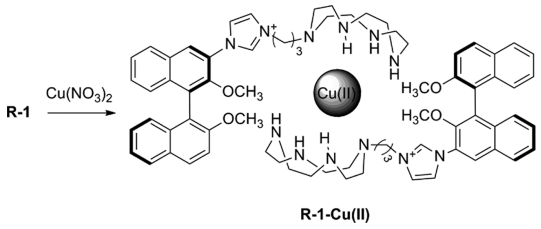
Scheme 3. In Situ Formation of Cu(II)-Containing Complex of R-1



found to be 3×10^2 (R^2 = 0.997, Figure S7, Supporting Information) using Benesi–Hildebrand plot.[27] The fluorescence responses of the **R-1** toward Cu^{2+} were pH-dependent, and the maximal signal was observed in the pH range of 6–11 (Figure S5 and S6, Supporting Information). This indicates that **R-1** can be employed to sense Cu^{2+} in a wide pH range. With such a high selectivity and sensitivity, **R-1** could serve as a fluorescent ON–OFF sensor for Cu(II).

Previously, according to the displacement strategy of Cu^{2+}-chelating ligands, S^{2-} can coordinate with Cu^{2+} to form the very stable species CuS resulting in the release of free ligand. Thus, this prompted us to hypothesize that **R-1–Cu(II)** ensemble is a potential OFF–ON fluorescent sensor for sulfide anions. On the basis of this idea, quantitative analysis of the in situ generated **R-1–Cu(II)** ensemble toward sulfide anions was investigated by fluorescent titration. As shown in Figure 3,

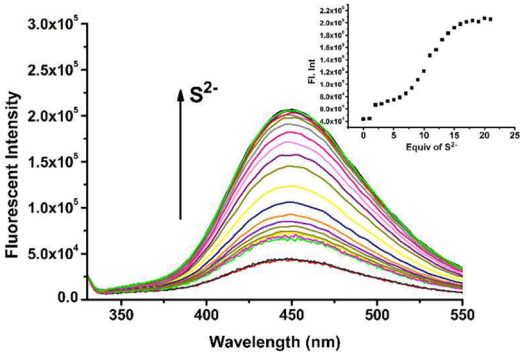


Figure 3. Fluorescence titration of the **R-1–Cu(II)** complex with sulfide ion in HEPES-buffered (pH 7.4, 10 mM) water. [**R-1–Cu(II)**] ensemble = 2 μM. Inset: fluoresence intensity as a function of S^{2-} concentration.

addition of sulfide anions increased the fluoresence of the **R-1–Cu(II)** system steadily. The titration curve revealed a somewhat sigmoidal pattern in the early part of the titration, which may be due to the multiple equilibria between **R-1**, Cu^{2+}, and added sulfide ions. Furthermore, the sensor did not show any obvious fluorescence enhancement in response to pure water under the same conditions (Figure S9, Supporting Information). From the sulfide concentration-dependent fluorescence changes, the detection limit[26] of the **R-1–Cu(II)** system for the determination of sulfide was estimated to be 1.6×10^{-5} M (Figure S10, Supporting Information).

Currently, development of sulfide-selective fluorescence probes with sufficient selectivity over other biothiols i.e., reduced glutathione (GSH, present at levels of about 10 mM), L-cysteine (L-Cys, about 100 μM), 2-mercaptoethanol (TGA), dithiothreitol (DTT), and inorganic sulfur (Na_2SO_3, $Na_2S_2O_3$ and NaSCN) is still challenging.[18a,b] Thus, to validate the selectivity in practice, the response of the **R-1–Cu(II)** ensemble toward a range of physiologically and environmentally important anions was evaluated. As shown in Figure 4,

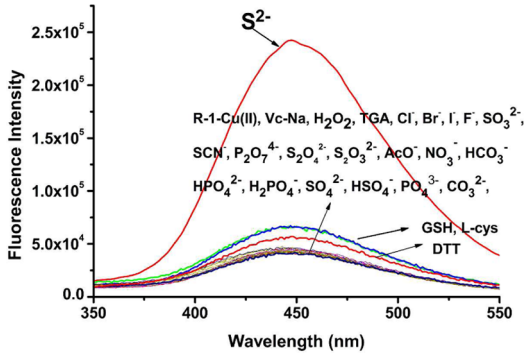


Figure 4. Fluorescence changes of **R-1–Cu(II)** (2 μM) system in the presence of various anions and biothiols (40 μM for S^{2-}; 1 mM for Cl^-, CO_3^{2-}, HCO_3^-, HSO_4^-, PO_4^{3-}, NO_3^-, $H_2PO_4^-$, I^-, Br^-, HPO_4^{2-}, $S_2O_4^{2-}$, AcO^-, SO_3^{2-}, SCN^-, F^-, SO_4^{2-}, $P_2O_7^{4-}$, $S_2O_3^{2-}$, H_2O_2; 100 μM for L-Cys, DTT, Vc-Na; 10 mM for GSH, TGA) in HEPES-buffered (pH 7.4, 10 mM) water.

R-1–Cu(II) showed high selectivity over competitive biothiols (i.e., L-Cys, TGA and DTT, even 10 mM GSH). Commom anions, such as F^-, Cl^-, Br^-, I^-, CN^-, $H_2PO_4^-$, $P_2O_7^{4-}$, NO_3^-, CO_3^{2-}, AcO^-, and HCO_3^-, reducing and oxidizing conditions, and other forms of inorganic sulfur compounds did not generate the fluorescence increment. Moreover, many probes for cyanide[28] and oxalate[29] based on the Cu(II) complexes have been reported. Upon addition of these anions (CN^- or $C_2O_4^{2-}$), the same results were not obtained (Figure S11, Supporting Information). Thus, the **R-1–Cu(II)** ensemble showed high selectivity for sulfide anion compared with previously reported fluorescent probes.

In addition, whether the **R-1–Cu(II)** complex could still retain the sensing response to sulfide anions under the potential interfering anions or molecules is very important for a fluorescent sensor. Nagano and co-workers have reported that in the presence of 10 mM GSH, sulfide selective signaling was not affected by addition of a very high concentration of sulfide.[18b] Thus, competition experiments of the **R-1–Cu(II)** were studied. As shown in Figure 5, the ensemble (2 μM) was treated with sulfide anions (20 equiv) in the presence of various test anions (50 equiv). All of the relevant anions tested have virtually no influence on the fluorescence detection of sulfide anions even in the presence of 10 mM GSH. Thus, the system to be useful for selectively sensing sulfide even involving these relevant anions. Further, The fluorescence responses toward sulfide anions can be employed in a wide pH range (Figure S12, Supporting Information) especially under physiological conditions.

The sensing mechanism was also confirmed by ESI-MS and NMR analysis. When addition of Cu^{2+} ions to **R-1** in D_2O, the ^1H NMR spectrum was very broad due to the paramagnetic nature of the complexed Cu^{2+} ions (Figure S13b, Supporting Information). However, treatment of the **R-1–Cu(II)** system with sulfide ions afforded a well-resolved spectrum that was almost identical with the ^1H NMR spectrum of **R-1** itself (Figure S13 a, Supporting Information). In the ESI-MS spectrum, after treatment of **R-1** with Cu^{2+} ions, a peak at m/z 655.4 corresponds to [2**R-1** − $2Br^-$ + Cu^{2+} + NO_3^- −

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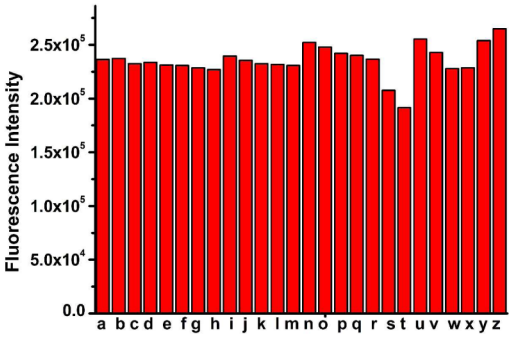

Figure 5. Fluorescence intensity changes of the **R-1**−**Cu(II)** (2 μM) to sulfide anions (40 μM) in the presence of various test anions or biothiols (100 μM) in HEPES-buffered water (pH 7.4, 10 mM). Key: (a) S^{2-}; (b) S^{2-} + Cl^-; (c) S^{2-} + CO_3^{2-}; (d) S^{2-} + HCO_3^-; (e) S^{2-} + HSO_4^-; (f) S^{2-} + PO_4^{3-}; (g) S^{2-} + NO_3^-; (h) S^{2-} + $H_2PO_4^-$; (i) S^{2-} + I^-; (j) S^{2-} + Br^-; (k) S^{2-} + HPO_4^{2-}; (l) S^{2-} + $S_2O_4^{2-}$; (m) S^{2-} + AcO^-; (n) S^{2-} + SO_3^{2-}; (o) S^{2-} + SCN^-; (p) S^{2-} + F^-; (q) S^{2-} + SO_4^{2-}; (r) S^{2-} + $P_2O_7^{4-}$; (s) S^{2-} + DTT; (t) S^{2-} + Vc-Na; (u) S^{2-} + $S_2O_3^{2-}$; (v) S^{2-} +L-Cys; (w) S^{2-} + H_2O_2; (x) S^{2-} + TGA; (y) S^{2-} + GSH; (z) S^{2-} + 10 mM GSH.

$H^+]^{2+}$ (Figure S15, Supporting Information). Further addition of sulfide anions led to the disappearance of the peak at m/z 655.4 and the formation of a new peak at 768.1, corresponding to [**R-1** + H^+ + CuS]$^+$ (Figure S16, Supporting Information). Thus, the studies of NMR, mass spectrometry, absorption spectrometry, and fluorescence spectrometry indicated that the sensor likely functioned by the displacement mechanism (Scheme 1, **path b**).

In summary, we have constructed a water-soluble BINOL fluorescent sensor **R-1** for sequential recognition of two anions (Cu^{2+} and S^{2-}) based on the displacement approach. The sensor **R-1** displayed high selectivity and sensitivity for copper ions in 100% aqueous solution, which served as an ON−OFF type sensor. Consequently, the product of the **R-1**−**Cu(II)** ensemble was an excellent indicator for sulfide ions over other common ions and other forms of biothiols in the same media without interference, constituting an ON−OFF−ON-type fluorescence recognition system. Therefore, the sensor has potential applications in physiological and environmental systems for sulfide anion detection.

EXPERIMENTAL SECTION

Materials and Methods. Mass spectrometer (ESI-MS) and high-resolution mass spectrometer (HRMS) data were recorded on a LCQDECA and a Bio TOF mass spectrometer, respectively. The ^{1}H NMR and ^{13}C NMR spectra were measured on a 400 MHz spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). Absorption spectra were recorded at 298 K between 220 and 400 nm. Fluorescence spectra were recorded in the front face mode at 298 K. All chemicals and reagents were obtained commercially and used without further purification.

Benesi−Hildebrand Method. The association constant K of the complex was then calculated with a linear relationship by the Benesi−Hildebrand method[27] (eq 1).

$$\frac{1}{F - F_{min}} = \frac{1}{K(F_{max} - F_{min})[Cu^{2+}]^{0.5}} + \frac{1}{F_{max} - F_{min}} \quad (1)$$

Here, F_{min} is the fluorescence intensity measured with an excess of Cu^{2+}, F is the intensity measured with Cu^{2+}, F_{max} is the intensity of free **R-1**, and K is the binding constant. The value of K was obtained from a plot of $1/(F_{max} - F)$ against $1/[Cu^{2+}]^{0.5}$ where K is equal to the intercept/slope.

Detection Limit. The detection limit was calculated from a plot of the fluorescence changes as a function of log[sulfide] following the procedure of literature.[26] A linear regression curve was fitted to the intermediate values of the sigmoidal plot. The point at which this line crossed the ordinate axis was taken as the detection limit.

Synthesis of R-2. A solution of ***R*-3** (380.1 mg, 1.0 mmol) and **C-1** (1.18 g, 2.0 mmol) in anhydrous acetonitrile (60 mL) was heated at 80 °C for 72 h. After being cooled to room temperature, the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2/CH_3OH (20:1, v/v) to afford **R-2** (500.8 mg, 52%) as a pale yellow solid: mp 131−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.43 (s, 1H), 8.05 (d, 2H, J = 8.0 Hz), 7.89 (d, 2H, J = 8.0 Hz), 7.79 (t, 2H, J = 1.2 Hz), 7.47 (t, 2H, J = 1.2 Hz), 7.36−7.26 (m, 2H), 7.16 (d, 1H, J = 1.6 Hz), 7.09 (d, 1H, J = 8.0 Hz), 4.71 (m, 2H), 3.50−3.10 (br, 17H), 2.80−2.67 (m, 5H), 2.21 (m, 2H), 1.43−1.39 (m, 27H), 1.23−1.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 147.9, 130.8, 128.9, 128.2, 127.3, 126.6, 125.5, 125.4, 124.0, 123.9, 123.6, 122.1,116.9, 113.2, 65.8, 61.2, 56.4, 48.8, 46.0, 28.7, 28.5, 15.2, 8.6; HRMS (ESI) m/z calcd for $C_{51}H_{69}N_6O_8$ [M − Br]$^+$ 893.5171, found 893.5178.

Synthesis of R-1. Saturated HCl−methanol solution was added to **R-2** (500.8 mg, 0.5 mmol) and monitored by TLC. After being stirred for 6 h, the solvent was removed under vocuum to afford a pale yellow solid. Then the solid was dissolved in deionized water (5 mL) and the pH was adjusted to alkalinity by saturated aqueous $NaHCO_3$. The crude product was extracted with hot $CHCl_3$ (3 × 100 mL), and the organic layer was dried with anhydrous Na_2SO_4. The residue was purified by flash column chromatography on aluminum oxide eluting with CH_2Cl_2/CH_3OH (10:1, v/v) to afford **R-1** (250.4 mg, 73%) as a yellow solid: mp 156−157 °C; ^{1}H NMR (400 MHz, D_2O) δ 8.27−8.14 (m, 2H), 7.93 (d, 2H, J = 8.0 Hz), 7.80−7.63 (m, 3H), 7.44 (d, 1H, J = 1.2 Hz), 7.31(m, 1H), 7.05−6.51 (br, 5H), 4.21 (m, 2H), 3.58−3.22 (m, 3H), 2.97−2.49 (br, 19H), 2.00 (m, 2H), 1.15−0.92 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 154.5, 148.0, 133.3, 132.9, 129.8, 128.5, 127.4, 126.8, 123.4, 116.2, 113.5, 60.8, 57.3, 56.1, 50.2, 49.5, 48.2, 45.1, 43.3, 26.3, 16.7; HRMS (ESI) m/z calcd for $C_{36}H_{45}N_6O_2$ [M − Br]$^+$ 593.3599, found 593.3606.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and fluorescence spectra of the sensor; copies of ^{1}H and ^{13}C NMR and HRMS spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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