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Highly selective fluorescent probe for sequential recognition of copper(II) and iodide ions

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ABSTRACT

A new highly selective fluorescent probe based on 2-(2′-aminolphenyl)-4-hydroxymethylthiazole (**1**) was developed for the detection of copper and iodide ions in ethanol. Probe **1** selectively detected Cu^{2+} through a "*switch off*" response, showing a good association constant ($K_a = 1.43 \times 10^5\ M^{-1}$) and binding with Cu^{2+} ions in a 1:1 stoichiometry. An *in situ* generated **1-Cu^{2+}** (1:1) ensemble detected I^- ions sequentially through a "*switch on*" response. The "*switch off*" response occurred with selective complexation of Cu^{2+} ions due to intramolecular charge transfer (ICT). An ensemble of **1** and copper(II) showed higher selectivity towards iodide than towards any other anions due to the reduction of Cu^{2+} to Cu^+ by I^- and subsequent complexation with **1**.

1. Introduction

Fluorescent chemosensors are viable means for the nondestructive, facile monitoring of target ions with high sensitivity, specificity, simplicity, low cost, and rapid tracking of analytes in biological, toxicological, and environmental samples.[1,2] Transition metals are of great concern, in spite of the fact that trace amounts of most transition metals play crucial roles in living organisms, because they have an extremely remarkable eco- and toxicological impact on both the environment and human beings due to bioaccumulation.[3–6] In particular, Cu^{2+} is the third most abundant essential trace element in the human body, and plays a pivotal role in a variety of fundamental physiological processes such as cellular respiration, bone formation, and connective tissue development. Copper ions also play critical roles as signal messengers and cofactors for a variety of metalloenzymes, including superoxide dismutase, cytochrome C oxidase, and tyrosinase.[7,8] However, high concentrations of free copper ions in living cells catalyzes the transformation of oxygen molecules into reactive oxygen species that can cause oxidative damage to proteins, nucleic acids, and lipids.[9] Thus, excessive amounts of copper ions can cause aberrant oxidative and nitrosative stress events, which may lead to diseases such as cancer,[10] cardiovascular disorders,[11] and neurodegenerative diseases, such as Menkes, Wilson's disease, and Alzheimer's disease.[12] Higher levels of Cu^{2+} are detected in tumors, and are thought to play a role in the promotion of angiogenesis (new blood vessel growth). Furthermore, copper can also be a significant environmental pollutant because of its widespread use in industrial and agricultural practices. Hence, the U.S. Environmental Protection Agency has established the upper limit for copper in drinking water as 1.3 ppm, and the allowable concentration of copper in bloods is limited to 100–150 μg dL^{-1} (15.7–23.6 μM). Therefore, the effective and quantitative detection of Cu^{2+} is of great significance in biology, chemistry, environmental science, and medicine.[13–15] Current methods for copper screening, including atomic absorption spectrometry (AAS), inductively coupled plasma mass spectrometry (ICP-MS), and inductively coupled plasma atomic emission spectrometry or mass spectrometry (ICP-AES, ICP-MS), total reflection X-Ray fluorimetry (TXRF), and anodic stripping voltammetry (ASV) often require expensive and sophisticated instrumentation or complex sample preparation procedures.[16–18] Many traditional methods for the detection of copper using small molecular chemosensors are based on Schiff bases,[19–21] although sensors based

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on hydrazone,[22] oxadiazole,[23] carbazole,[24] and acetamide[25] moieties have also been reported.

Among biologically important anions, iodide is of particular interest, because it is an essential micronutrient and plays fundamental physiological roles during all stages of human development.[23] Iodide also plays an essential role in thyroid gland function.[26] Specifically, excessive iodine intake and deficiency can lead to thyroid diseases; for example, low iodine intake results in hypothyroidism, cretinism, congenital anomalies, endemic goiter, neurological disorders, and mental retardation.[27–32] Iodine was also recently found to display anti-inflammatory and anti-oxidative activities.[33] However, excessive uptake of iodine leads to adverse effects, such as degenerative, necrotic, and neoplastic lesions in the thyroid gland, stomach, and salivary glands.[34] Various methods have been used for the determination of iodide, including gas chromatography with mass spectrometry detection, neutron activation analysis (NAA), electrostatic ion chromatography, inductively coupled plasma-mass spectrometry (ICP-MS), capillary electrophoresis, indirect atomic absorption spectrometry, and iodide-selective electrodes (ISEs).[35–41] Among these methods, ICP-MS is the most commonly used. However, ICP-MS requires sophisticated instrumentation, as well as laborious detection procedures. On the contrary, fluorescence-based detection is highly sensitive, versatile, and is amenable to high-throughput screenings. Some small-molecule fluorescence "*turn-off*" iodide probes include bis-imidazolium and benzimidazole derivatives,[42] as well as thiophene- and carbazole-containing polymers.[43] However, the major drawback of these probes is that they only exhibit quenched fluorescence signals upon binding with iodide, due to the heavy atom effect of iodide.[44]

Moreover, the development of viable probes for iodide is challenging due to its large anionic radius, low charge density, and low hydrogen-bonding ability.[45] Cationic transition metal complexes attract anions depending on the degree of ion-pair interactions. Some metal complexes, which exhibit a "*turn on*" response upon detection of iodide, reported to date include Hg^{2+},[46] Co^{2+},[47] Cd^{2+},[48] Ag^{+},[49] and Cu^{2+}.[50] In this paper, we report a highly selective copper sensor, which upon complexation with copper, produces a highly selective "*turn on*" iodide sensor.

Previously, we reported the cation (Zn^{2+},[51–56] Cu^{2+},[57] Al^{3+},[58,59] Ga^{3+},[60,61]) and anion (F^{-},[62] OAc^{-},[63] CN^{-},[64]) sensing properties of several thiazole-based chemosensors. Specifically, we showed that by changing the moiety at the 4-position of the thiazole ring, the cation selectivity could be controlled. In most cases, we dealt with 2-hydroxyphenyl type ESIPT (Excited State Intramolecular Proton Transfer) except in two examples,[51,63] which were chemically modified 2-tosylamidophenyl derivatives, and evaluated cations binding ability. However, there are no reports which describe free NH_2 groups and heteroazoles as part of a cation sensor. This is probably due to the low acidity of the N-H protons, which produce weak intramolecular hydrogen bonds and as a consequence little or no ESIPT.[65] In this study, we used an aminophenyl thiazole moiety with a hydroxymethyl group attached at the 4 position of the thiazole ring (**1**) to enhance the selectivity and binding ability towards copper, and then used the **1**-Cu^{2+} ensemble for the selective detection of iodide. Ethyl 2-(2′-aminoyphenyl)thiazolyl-4-carboxylate (**2**) was also prepared to compare the effects of the hydroxylmethyl group to those of the ester group in Cu^{2+} sensitivity and selectivity (Fig. 1).

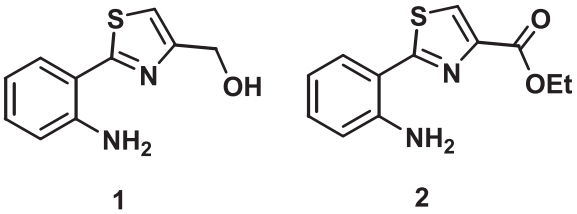

Fig. 1. Structures of probes **1** and **2**.

2. Experimental section

2.1. Materials and methods

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400, and AM-500 spectrometer using Me_4Si as the internal standard. High-resolution fast atom bombardment (HR-FAB) mass spectra were recorded on a Jeol JMS 700 High resolution mass spectrometer at the KBSI Daegu center. UV–vis absorption spectra were obtained on a Shimadzu UV-1650PC spectrophotometer, and fluorescence spectra were measured using a Shimadzu RF-5301 fluorescence spectrometer equipped with a xenon discharge lamp in 1 cm quartz cells. All of the measurements were performed at 25 °C. The fitting of the fluorescence titration data was performed using gnuplot 4.6 software. Analytical grade ethanol was purchased from Merck (Germany). All other materials were purchased from Aldrich Chemical Co. and used as received. The solutions of metal ions were prepared from their perchlorate salts (which were of analytical grade); the anions were prepared from their tetrabutylammonium (TBA) salts and the resulting solutions were subsequently diluted to prepare the working solutions. Ethyl 2-(2′-nitrophenyl)thiazole-4-carboxylate was prepared according to the procedure in the literature.[51] The quantum yield (Φ) was calculated using the literature procedure.[57]

2.1.1. Synthesis of ethyl 2-(2′-nitrophenyl)thiazolyl-4-carboxylate (**3**)

A solution of 2-nitrothiobenzamide (200 mg, 1.10 mmol) and ethyl bromopyruvate (257 mg, 1.32 mmol) in ethanol (30 mL) was heated under reflux for 2 h. The solvent was removed with an evaporator, and the residue was washed with water and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, EtOAc:hexane = 1:4) to give compound **3** (254 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.2 Hz, 3H, CH_3), 4.42 (q, J = 7.1 Hz, 2H, CH_2), 7.61–7.73 (m, 3H, $H_{a,b,c}$), 7.98 (d, J = 7.8 Hz, 1H, H_d), 8.31 (s, 1H, H_e); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.3, 61.7, 124.7, 127.8, 129.1, 131.0, 132.2, 132.7, 147.9, 148.6, 161.1, 163.0.

2.1.2. Synthesis of ethyl 2-(2′-aminohenyl)thiazolyl-4-carboxylate (**2**)

A mixture of **3** (200 mg, 0.72 mmol) and 5% Pd/C in ethanol (20 mL) was hydrogenated under H_2 gas for 10 h. After removal of the solvent, CH_2Cl_2 was added and the mixture was filtered through a Celite pad to remove the catalyst. The filtrate was concentrated and the residue was crystalized in CH_2Cl_2-hexane to give amino compound **2** (159 mg, 89%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.33 (t, J = 7.1 Hz, 3H, CH_3), 4.33 (q, J = 7.1 Hz, 2H, CH_2), 6.62 (ddd, J = 7.2, 6.9, 1.0 Hz, 1H, H_c), 6.83 (dd, J = 8.3, 1.0 Hz, 1H, H_a), 7.11 (s, 1H, NH), 7.18 (ddd, J = 7.1, 7.0, 1.4 Hz, 1H, H_b), 7.59 (dd, J = 7.9, 1.4 Hz, 1H, H_d), 8.47 (1H, H_e); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.2, 60.9, 113.1, 115.7, 116.5, 126.7, 128.9, 131.4, 145.7, 146.7, 160.5, 169.3; HR-FAB mass: calcd. for $C_{12}H_{13}N_2O_2S$ $(M+H)^{+}$: 249.0698, Found: m/z 249.0699.

2.1.3. Synthesis of 2-(2′-aminophenyl)-4-hydroxymethylthiazole (**1**)

A solution of **2** (100 mg, 0.4 0 mmol) and $LiAlH_4$ (17 mg, 0.41 mmol) in dry THF (20 mL) was stirred for 1 h. The solvent was removed by an evaporator, and the residue was washed with water