Synthesis of a sugar-aza-crown ether-based cavitand as a selective fluorescent chemosensor for Cu^{2+} ion

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ABSTRACT

A chemosensor based upon the sugar-aza-crown ether **7** with one anthracenetriazolymethyl moiety was prepared and its fluoroionophoric properties toward transition metal ions were investigated. Chemosensor **7** exhibits highly selective recognition toward Cu^{2+} ion among a series of tested metal ions in MeOH solution. The association constant for **7**·Cu^{2+} in MeOH solution was calculated to be $2.5 \times 10^4\,M^{-1}$.

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A cavitand is a container-shaped molecule and its cavity allows it to engage in host-guest chemistry with guest molecules of a complementary shape and size.[1–3] Examples include cyclodextrins, calixarenes, and cucurbiturils. Many of these compounds have been developed as fluorophores for the selective detection of transition or heavy metal ions.[4] Among these metal ions, the copper ion is a significant environmental pollutant and also plays a critical role in various biological processes,[5–7] for most of the reported Cu^{2+} fluorescent sensors show a turn-off (fluorescence quenching) response due to their paramagnetic nature.[8,9] However, until the present, only a few turn-on (fluorescence enhancement)-type Cu^{2+} fluorescent sensors have been found in the literature.[10–12]

In addition, new sugar-based molecular receptors such as sugar-aza-crown (SAC)[13,14] ethers also have been synthesized to form a new fluorescent molecular sensor for Cu^{2+}.[15] Therefore, modified SACs with appropriate appended chromophores would be good candidates for cation probes. Herein, we report SAC-based cavitand **7** as a fluorescent sensor for metal ions, which has the furanoid-based SAC moiety as the binding site and an anthracene moiety as the signaling unit. The designed chemosensor exhibits a turn-on-type response and a highly selective fluorescence behavior for Cu^{2+} ion in methanol solution.

Fluorescent sensor **7** was prepared as outlined in Scheme 1. The SAC ether **4** was easily obtained from C-ribosyl azido aldehyde **1** following the reported protocol.[14] Treatment of the SAC ether **4** with propargyl bromide using K$_2$CO$_3$ as a base in CH$_3$CN/KI/nBu$_4$NI

solvent under reflux conditions afforded the SAC ether alkyne **5**. Treatment of SAC ether alkyne **5** with 9-(azidomethyl)anthracene using (EtO)$_3$P·CuI as the catalyst in refluxing toluene afforded the fluorescent sensor **7** (35%).[16]

We examined the effect of different solvents (CH$_2$Cl$_2$, MeOH, CH$_3$CN) on the fluorescence spectrum of **7** (1.44×10^{-4} M). The fluorescence intensity showed a dependence on the polarity of the solvent, with more polar solvents having a greater influence (see Fig. S5 in Supplementary data). Upon excitation at 374 nm, the emission spectrum of all tested solvents was characterized by three peaks with maxima at approximately 402, 421, and 448 nm. Since the nature of the solvent did not alter the emission maxima, and because the intensity of emission was strongest in MeOH, we performed all subsequent investigations using this solvent.

We next undertook an investigation of metal complexation properties of **7** (1.42×10^{-5} M) in MeOH solution. We examined the chemosensing behavior of the SAC-based cavitand **7** by fluorescence measurements in the presence of various metal ions by comparing the fluorescence intensities of the solutions before and after addition of 10 equiv of the following 10 metal ions as their perchlorate salts: Li$^+$, Na$^+$, K$^+$, Ca^{2+}, Mg^{2+}, Hg^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}. In the presence of Cu^{2+} ion, the fluorescence spectrum of **7** was enhanced while the other metal ions had only modest effects (Fig. 1). The enhancement efficiency ($I - I_0/I_0 \times 100\%$) observed at 422 nm was ~395% greater than the control in the absence of Cu^{2+} ion (Fig. 2). The fluorescence enhancement can be attributed to the photoinduced electron transfer (PET) that occurs upon complexation of the nitrogen atoms by metal ion. These results suggest that Cu^{2+} ion can be recognized by either the triazole group or the two nitrogen atoms of the linker of **7**.
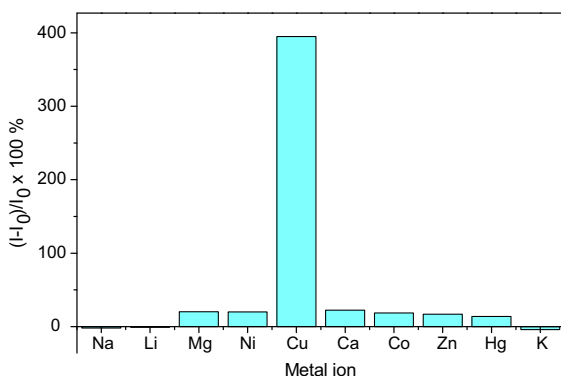
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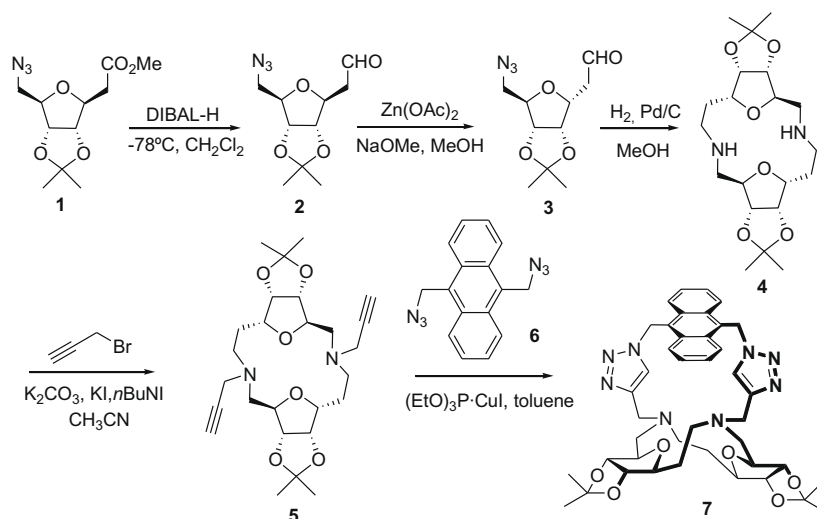
Scheme 1. Synthesis of fluorescent sensor **7**.
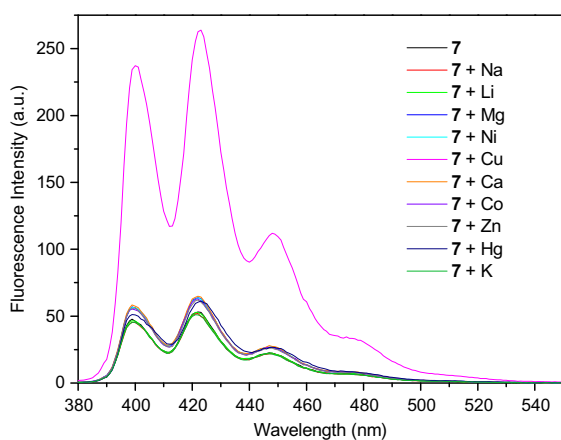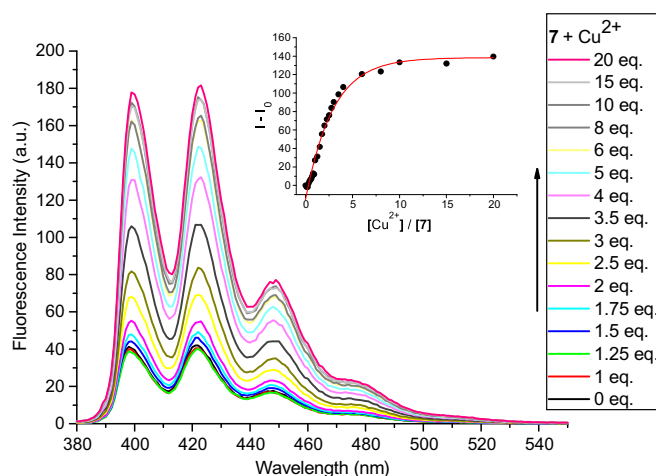

Figure 1. Fluorescence spectra of **7** (1.42×10^{-5} M) upon addition of ClO_4^- salts of Li^+, Na^+, K^+, Ca^{2+}, Mg^{2+}, Hg^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, and Cu^{2+} (10 equiv) in MeOH. λ_{ex} = 374 nm.

Figure 3. Fluorescence spectra of **7** (1.42×10^{-5} M) in MeOH upon addition of increasing concentrations $Cu(ClO_4)_2$. λ_{ex} = 374 nm.

titration profiles, the association constant for 7^*Cu^{2+} in MeOH solution was calculated to be 2.5×10^4 M^{-1} by a Stern–Volmer plot. In the Job plot (Fig. 4), a maximum fluorescence change was observed when the molar fraction of the ionophore **7** versus Cu^{2+} was 0.5, which indicated that only a 1:1 complex was formed. By using the above-mentioned fluorescence titration results, the detection limit of **7** for the analysis of Cu^{2+} ion was determined as 1.39×10^{-6} M. The selectivity toward the Cu^{2+} ion was further ascertained by the competition experiments. As shown in Figure 5, except for Hg^{2+} ion, the fluorescence intensity of **7** (4.2×10^{-6} M) in the presence of 10 equiv of the Cu^{2+} ion was almost unaffected by the addition of 10 equiv of competing metal ions (Li^+, Na^+, K^+, Ca^{2+}, Mg^{2+}, Co^{2+}, Ni^{2+}, Hg^{2+}, and Zn^{2+}). On addition of an equal amount of Hg^{2+} ion into a solution of 7^*Cu^{2+} complex, the fluorescence intensity was shown to be quenched by the Hg^{2+} ion, thus implying that **7** contains two different recognition sites. The underlying mechanism for both ions will be further studied.

A recent report indicated that the 1,2,3-triazole ring could play a role as an anion-binding motif.[17] Therefore, in addition to the cation binding properties, we also have investigated the sensing properties of **7** for anions (F^-, Cl^-, Br^-, I^-) using tetrabutylammonium as a counteraction. The fluorescence intensities of the spectra of **7** did not show any changes upon addition of the above-mentioned

Figure 2. Fluorescence intensity changes ($((I - I_0)/I_0 \times 100\%)$) of fluoroionophores **7** (1.42×10^{-5} M) with various metal ions in MeOH. λ_{ex} = 374 nm.

To further investigate the chemosensor properties of **7**, we performed fluorescence titration of **7** (1.42×10^{-5} M) with Cu^{2+} ion in MeOH solution. When the concentration of Cu^{2+} ion is increased from 1.42×10^{-6} M to 2.84×10^{-4} M, the fluorescence intensity of **7** is also increased, as shown in Figure 3. From the fluorescence
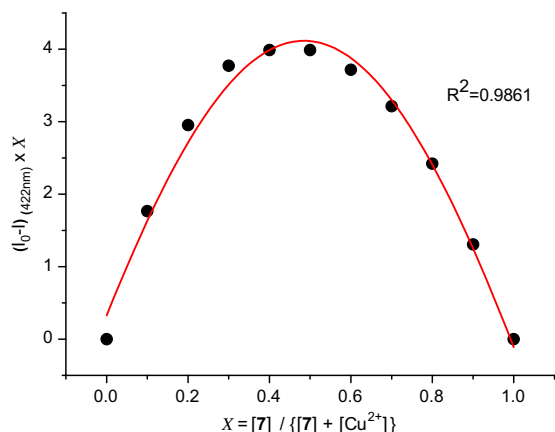
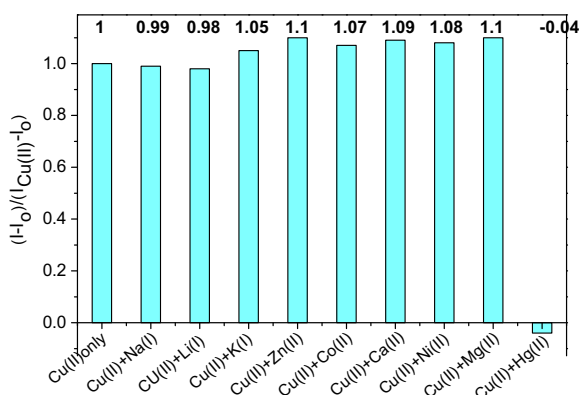**Figure 4.** Job plot of a 1:1 complex of **7** (1.42×10^{-5} M) with $Cu(ClO_4)_2$.

Figure 5. Competitive experiments in the **7** + Cu^{2+} system with interfering metal ions. [**7**] = 4.2×10^{-6} M, [Cu^{2+}] = 4.2×10^{-5} M, and [M^{n+}] = 4.2×10^{-5} M in MeOH. λ_{ex} = 374 nm.

anions, probably because the conformation of the triazole cavitand **7** was not suitable for recognition of these halide ions.

In conclusion, a new fluorescent chemosensor **7** was designed and synthesized by coupling a SAC ether and anthracenetriazolymethyl moieties. Chemosensor **7** shows high selectivity for Cu^{2+} ion over other metal ions. On addition of Cu^{2+} ion into a MeOH solution of **7**, the fluorescence intensity was enhanced because of the PET process operating between the amino group of the SAC ether and the anthracene fluorophore.

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16. *Compound* **7**: A solution of dialkyne **5** (0.492 g, 1.04 mmol), diazide **6** (0.475 g, 1.65 mmol), and the copper catalyst [$Ph_3P\cdot CuI$] (0.039 g, 0.087 mmol) in toluene (20 mL) was stirred at 85 °C for 15 min by microwave irradiation (300 W) (Milestone Start S). After evaporation of the solvent, the resulting solid mixture was washed with EtOAc. Then the solvent was removed and the residue was purified by chromatography (EtOAc/MeOH 15:1) to give **7** (0.25 g, 35%) as a yellow solid. Mp 198 °C; R_f = 0.23 (EtOAc/MeOH 8:1); ^{1}H NMR (300 MHz, CDCl$_3$) δ: 4.63 (t, *J* = 4.8 Hz, 2H), 4.47 (dd, *J* = 1.8, 6.3 Hz, 2H), 4.14–4.06 (m, 4H), 3.40 (q, *J* = 17.7 Hz, 5H), 2.86–2.83 (m, 2H), 2.72–2.47 (m, 7H), 2.13 (s, 2H), 1.82–1.68 (m, 6H), 1.46 (s, 6H), 1.30 (s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 113.0, 83.8, 82.1, 81.0, 78.6, 77.3, 72.8, 56.3, 49.7, 42.6, 27.3, 26.3, 25.0; HRMS (FAB): Calcd for $C_{42}H_{51}N_8O_6$ (M+H), *m/z* 763.3932, found *m/z* 763.3941.
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