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Conformationally Constrained (Coumarin−Triazolyl−Bipyridyl) Click Fluoroionophore as a Selective Al^{3+} Sensor

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A conformationally constrained (coumarin−pyrrolidinyl−triazolyl−bipyridyl) fluoroionophore conjugate was synthesized through click chemistry. The fluoroionophore serves as a selective chemosensor for Al^{3+} based on internal charge transfer. The coumarin−bipyridyl chemosensor exhibited a high association constant with submicromolar detection for the aluminum ion.

Aluminum is the third most abundant metal in the earth's crust, accounting for approximately 8% of its mass. The leaching of aluminum from soil by acid rain increases the free Al^{3+} in the environment and surface water, which is deadly to growing plants.[1] Aluminum is found in its ionic form Al^{3+} in most animal and plant tissues and in natural waters. The general population is exposed to aluminum from its widespread use in water treatment, as a food additive, aluminum-based pharmaceuticals, occupational dusts, and aluminum containers and cooking utensils. Tolerable weekly aluminum dietary intake in the human body is estimated to be 7 mg/kg body weight.[2] The superfluous ingestion of aluminum influences the absorption of calcium in the bowel, causing softening of the bone, atrophy, and even aberrance, and also affects the absorption of iron in blood, causing anemia. The toxicity of aluminum causes damage of the central nervous system, is suspected to be involved in neurodegenerative diseases such as Alzheimer's and Parkinson's, and is responsible for intoxication in hemodialysis patients.[3] Therefore, detection of Al^{3+} is crucial in controlling its concentration levels in the biosphere and its direct impact on human health. In recent years, fluorescent chemosensors have attracted significant interest because of their potential application in medicinal and environmental research.

In this Communication, we report the synthesis and fluorometric properties of conformationally constrained coumarin−bipyridyl (CB) click ligand **1** for selective detection of Al^{3+} based on an internal charge-transfer (ICT) mechanism. To the best of our knowledge, only a few fluorescent sensors have been reported for detection of Al^{3+} with moderate success.[4] We recently reported the ionophore−fluorophore conjugate based design for detection of Al^{3+} using the bipyridyl−dansyl conjugate.[5] On the basis of the same design principles, we have developed a new conformationally constrained CB conjugate with a pyrrolidinyl−triazolyl backbone. Coumarin and its derivatives have been heavily used because of their tunable photophysical properties and significant fluorescent behavior in the visible region.[6] The coumarin moiety in the CB ligand can display a dual behavior, i.e., reporting as well as binding to a metal ion. Bidentate heteroaromatic 2,2′-bipyridine affords a high binding affinity toward metal ions because of the chelation effect. Synthesis of the CB **1** conjugate was achieved through azide−alkyne click transformation as one of the key intermediate reactions. The

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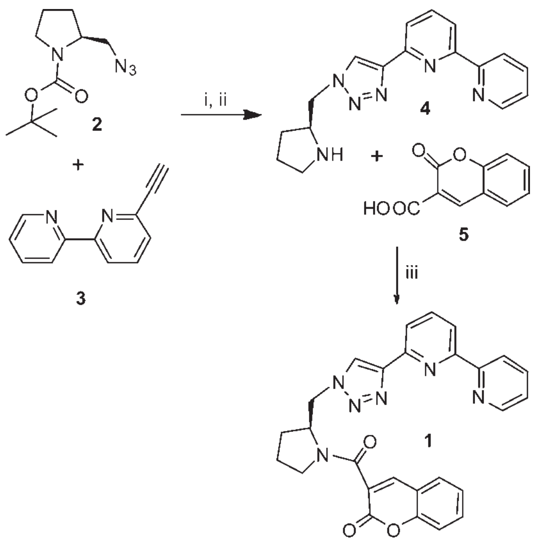
Scheme 1. [a]



[a] (i) CuI, DIPEA, toluene−tBuOH (4:1; 96%); (ii) TFA−CH_2Cl_2 (1:1; 98%); (iii) EDC·HCl, HOBt, DIPEA, DMF (98%).

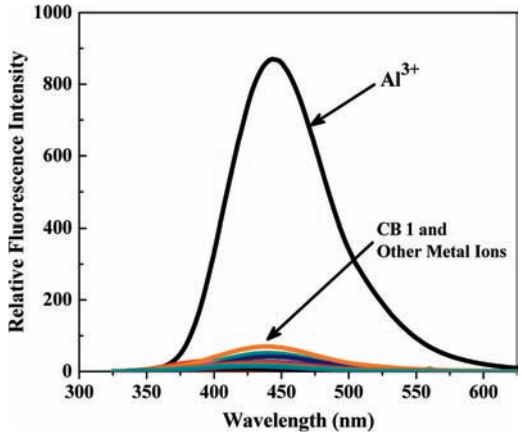


Figure 1. Fluorescence spectra of CB **1** (25.0 μM) and upon the addition of salts (50.0 equiv) of Li^+, Na^+, K^+, Ag^+, Mg^{2+}, Co^{2+}, Ba^{2+}, Sr^{2+}, Hg^{2+}, Pb^{2+}, Cd^{2+}, Zn^{2+}, Cu^{2+}, Mn^{2+}, In^{3+}, and Al^{3+} in CH_3CN.

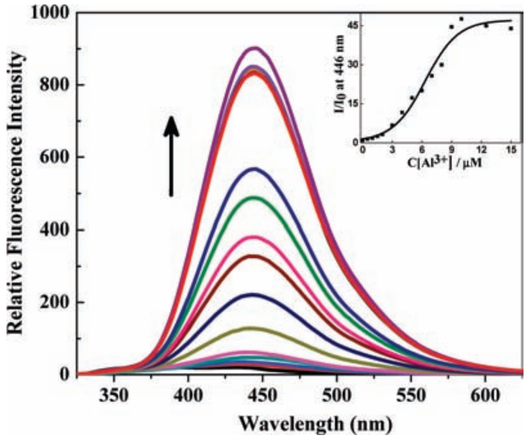


Figure 2. Fluorescence spectra of CB **1** (25 μM) in CH_3CN upon the addition of $Al(ClO_4)_3$ (0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12.5, 15, and 25 μM) with an excitation of 320 nm. Inset: Fluorescence intensity at 443 nm as a function of [Al^{3+}].

1,2,3-triazole frameworks formed by the click reaction have been widely investigated for its coordination properties.[7−10] CB **1** was obtained through a straightforward synthetic route, as shown in Scheme 1. The Boc-protected pyrrolidinyl−azide **2** and bipyridyl−alkyne **3** were subjected to Cu^I-catalyzed 1,3-cycloaddition to obtain Boc−pyrrolidinyl−triazolyl−bipyridine **4**.[5,11] Free amine generated from the Boc deprotection of triazole **4** was coupled to coumarin−3-carboxylic acid (**5**) to obtain CB **1** in excellent yield. The photophysical properties of CB **1** were investigated by monitoring the absorption and fluorescence behavior upon the addition of several metal ions such as Li^+, Na^+, K^+, Ba^{2+}, Sr^{2+}, Mg^{2+}, Mn^{2+}, Co^{2+}, Zn^{2+}, Cu^{2+}, Ag^+, Cd^{2+}, Hg^{2+}, Pb^{2+}, In^{3+}, and Al^{3+} in acetonitrile. The observed changes in the fluorescence emission are shown in Figure 1. CB **1** exhibits an absorption band centered around 301 nm, which remains unchanged upon the addition of Li^+, Na^+, K^+, Ag^+, Ba^{2+}, and Sr^{2+} (Figure S1 in the Supporting Information). Upon the addition of Mg^{2+}, Mn^{2+}, Co^{2+}, Zn^{2+}, Cu^{2+}, Hg^{2+}, Pb^{2+}, Cd^{2+}, In^{3+}, and Al^{3+}, slight red shifts in the absorption maxima to different extents were observed. In the case of Al^{3+}, the absorption maximum was red-shifted to 324 nm. A clear isosbestic point was observed at 312 nm when spectra were recorded with varying concentrations of Al^{3+} (Figure S2 in the Supporting Information). At 320 nm excitation, CB **1** alone did not show any significant fluorescence. The addition of Li^+, Na^+, K^+, Ag^+, Ba^{2+}. and Sr^{2+} has no effect on the fluorescence emission, whereas Mg^{2+}, Mn^{2+}, Co^{2+}, Zn^{2+}, Cu^{2+}, Hg^{2+}, Pb^{2+}, Cd^{2+}, and In^{3+} responded with very little enhancement in the fluorescent intensity. In contrast, the addition of Al^{3+} resulted in a large enhancement of the emission intensity positioned around 443 nm, as shown in Figure 2.

A Job plot obtained from emission data showed 1:1 stoichiometric complexation between CB **1** and Al^{3+} (Figure S3 in the Supporting Information). The response parameter α, which is defined as the ratio of the free ligand concentration to the initial concentration of the ligand, is plotted as a function of the Al^{3+} concentration (Figure 3). This plot can serve as the calibration curve for detection of Al^{3+}. The association constant (log K_a) of CB **1** for Al^{3+} was calculated to be 5.08 from Li's equations. Furthermore, Al^{3+} can be detected at least down to 1.0×10^{-7} M when CB **1** was employed at 25 μM concentration (Figure S4 in the Supporting Information).

Selectivity of CB **1** as the fluorescence chemosensor for Al^{3+} was studied in the presence of various competing metal ions. For this purpose, CB **1** was treated with 1 equiv of Al^{3+} in the presence of 20 equiv of other metal ions. Data in Figure 4 show that there is no interference for detection of Al^{3+} in the presence of Li^+, Na^+, K^+, Ba^{2+}, Sr^{2+}, Mg^{2+}, Mn^{2+}, Ag^+, Cd^{2+}, and Hg^{2+}. In the case of In^{3+} and Cu^{2+}, quenching of the fluorescence signal was observed. The response of CB **1** for Al^{3+} detection in the presence of Co^{2+}, Pb^{2+}, and Zn^{2+} is relatively low but clearly detectable. Thus, CB **1** can be used as a selective fluorescent sensor for Al^{3+} detection in the presence of most competing metal ions.

NMR spectroscopy was used to ascertain the binding mode of the ligand and Al^{3+}. ^1H NMR spectra of CB **1** were recorded in CD_3CN upon the addition of various concentrations of Al^{3+}. Significant spectral changes were observed

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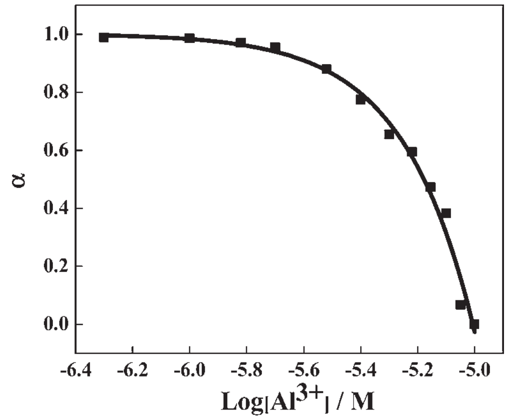

Figure 3. Response parameter values (α) as a function of the logarithm of the Al^{3+} concentration. α is defined as the ratio between the free ligand concentration and the initial concentration of the ligand.

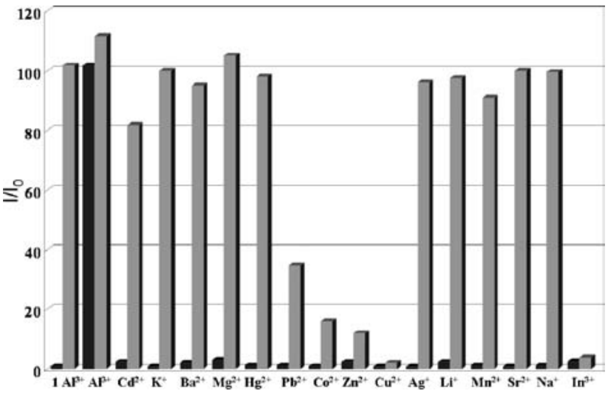

Figure 4. Relative fluorescence of CB **1** and its complexation with Al^{3+} in the presence of various metal ions. Dark-gray bar: CB **1** (25.0 μM) with 20 equiv of metal ion stated. Light-gray bar: 25.0 μM of CB **1** and 20 equiv of Al^{3+} with 20 equiv of metal ions stated (for an Al^{3+} effect, 40 equiv of Al^{3+}) ($E_\lambda = 443$ nm). The response of the CB **1** is included as controls. Dark bar: no metal ion added. Light bar: 25.0 μM of CB **1** with 20 equiv of Al^{3+}.

upon the addition of Al^{3+}, as shown in Figure 5. The main peaks considered for assignment of the binding mode of CB **1**−Al^{3+} are the β-proton (H_a) of the coumarin moiety, the triazole ring (H_b), and the ortho proton of the bipyridyl ring (H_c). Coumarin β-proton (H_a) undergoes an overall large downfield shift of 0.51 ppm upon the addition of 1.0 equiv of Al^{3+} salt. This is a clear indication of the direct involvement of the coumarin moiety in coordinating with Al^{3+}. Similarly, peaks corresponding to the triazole ring (H_b) and the ortho proton of the bipyridyl ring (H_c) were downfield-shifted by 0.16 and 0.47 ppm, respectively. There were no appreciable changes with any of the proton signals upon the addition of > 1.0 equiv of Al^{3+} to CB **1**, suggesting a 1:1 binding stoichiometry for CB **1**−Al^{3+}.

The 1:1 binding stoichiometry determined from ^{1}H NMR and emission spectral studies was further confirmed by elemental analysis data, which match with the 1:1 complex of CB **1**·$Al(ClO_4)_3$ and two coordinating water molecules.[12] These data were also supported by mass data of the CB **1**−Al^{3+} complex. MALDI/TOF-MS shows formation of the CB **1**·Al^{3+}·$2H_2O$ complex [MW = 541.14; calcd for $C_{27}H_{26}AlN_6O_5$, 541.18].[12] In IR spectra, the stretching frequency of the amide carbonyl of the coumarin moiety was significantly decreased by ~26 cm^{-1} upon Al^{3+} binding and suggests coordination to the amide carbonyl oxygen atom.[12] Thus, Al^{3+} binding to CB **1** through three nitrogen atoms (two from the bipyridyl ring and one from the triazole ring) and the amide carbonyl oxygen atom (Figure 5). The hexacoordination of Al^{3+} can be satisfied by water molecules or counterions (Figure S5 in the Supporting Information). From the above spectroscopic studies, it can be concluded that metal binding to the amide carbonyl oxygen atom leads to a red shift in the absorption band of CB **1** by ICT.[13] The proposed ICT mechanism was supported by the red shift of the emission peak (E_{max}) of the solution of CB **1** (1 equiv) and Al^{3+} (50 equiv) with increasing solvent polarity (Figure S6 in the Supporting Information). Enhancement of the fluorescence intensity of CB **1** is presumably due to metal binding to the bipyridyl−triazolyl moiety followed by photoinduced electron-transfer suppression.

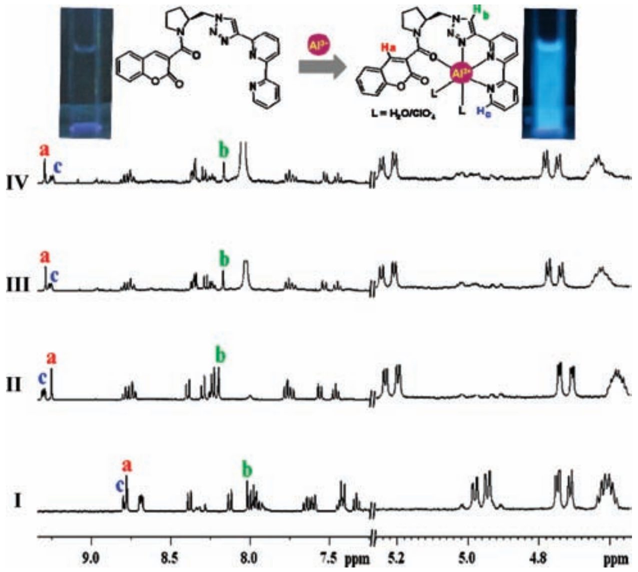

Figure 5. Binding mode of CB **1**·Al^{3+} and ^{1}H NMR spectra of CB **1** with $Al(ClO_4)_3$ in CD_3CN: (I) CB **1**; (II) CB **1** with 0.5 equiv of Al^{3+}; (III) CB **1** with 1.0 equiv of Al^{3+}; (IV) CB **1** with 1.5 equiv of Al^{3+}.

In conclusion, we have developed a conformationally constrained CB chemosensor utilizing click chemistry protocols. The triazole ring together with the bipyridyl moiety serves as an ionophore by providing one of the cation coordinating sites. The coumarin moiety plays a dual role as a reporting unit as well as a cation binding site. CB **1** shows enhanced fluorescence with high sensitivity in the presence of Al^{3+}, allowing its detection in the presence of most competing metal ions. Work is in progress in our laboratory to further improve the selectivity of the ligand and its application as a sensor for the aluminum ion.

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Supporting Information Available: Experimental details, UV−vis, fluorescence, mass, IR, and NMR spectra, and the Job plot. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See the experimental section in the Supporting Information.

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