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Cu(II) complex of a flexible tripodal receptor as a highly selective fluorescent probe for iodide

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ABSTRACT

A Cu(II) complex of a tripodal receptor bearing an anthracene moiety on one pod as a fluorophore was synthesized. The anion recognition behavior of the Cu(II) complex was evaluated in CH_3CN/H_2O (95:5, v/v), resulting in an extremely high selectivity for iodide over other anions such as F^-, Cl^-, Br^-, NO_3^-, CH_3COO^-, and $H_2PO_2^-$. The Cu(II) complex acts as a selective probe for estimating iodide even in the presence of other anions without any interference.

1. Introduction

Anion recognition by artificial receptors has attracted increasing attention over the past years because anions play important roles in biological and chemical systems as well as in ecological systems.[1] Anions are recognized mainly through coordination of metal ions,[2] electrostatic interaction of ammonium and guanidinium,[3] or hydrogen bonding of amides and ureas.[4] Recently, metal-based receptors have received considerable attention in the area of the anion recognition, since they show a greater enhancement in anion-binding affinity than purely organic receptors.[5] The metal centers preorganize the binding sites structurally for optimal anion-binding and strong affinities through hydrogen bonding and metal-ion coordination.

Anion recognition through hydrogen bonding is extremely difficult in aqueous medium.[2a] Even in the presence of a small amount of water, the binding affinity of the receptors decreases drastically owing to the strong hydration of anions and the competition of water for the hydrogen bonding sites. Therefore, additional bonding interactions are required for recognizing anions in aqueous organic medium. Metal-based receptors may provide additional binding sites to the anions resulting in high affinity. These electrostatic interactions are responsible for the anion recognition in aqueous organic medium. In our continuing research on anion recognition,[6] we herein report on a new metal-based receptor that employs electrostatic interactions from a metal-ion center along with the hydrogen bonding with the receptor.

The receptor employed mixed nitrogen and sulfur donors. In nature, the Cu(II) exists in the cavities of various proteins and is coordinated through four or five sulfur and nitrogen donors.[7] These mixed sulfur and nitrogen donors afford a variety of coordination geometries in the naturally occurring proteins. Keeping these facts in mind, we designed a flexible receptor in which possible coordination modes are much more abundant than in a rigid receptor. The reasonable flexibility of the receptor will ensure that the receptor may adopt conformation for encapsulating large size anions such as iodide.

Iodide is one of the key elements that influence neurological and thyroid activities.[8] The estimation of iodide anions is performed frequently to examine thyroid disorders in clinics. Thus, there is a great demand for the development of synthetic receptors capable of selectively recognizing iodide over other anions. Although iodide is such a biologically important anion, only a few papers have reported on recognition of iodide.[6d,9]

2. Results and discussion

Tripodal receptor **2** was synthesized as shown in Scheme 1. Receptor **2** was prepared in 67% yield by condensing anthracene-9-carbaldehyde with tripodal amine **1**, which was prepared by the literature method,[10] and followed by reduction with $NaBH_4$. The structure of the product was established by using the spectroscopic methods. The ^1H NMR spectrum of receptor **2** revealed the presence of two characteristic N–H resonances at 4.39 and

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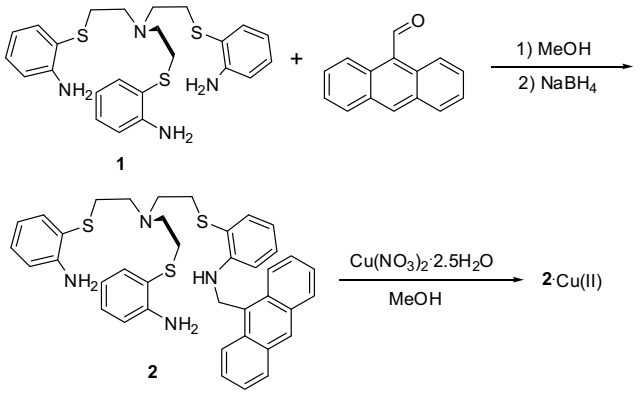

Scheme 1.

6.69 ppm, respectively, which disappeared upon adding D_2O, confirming the position of $-NH_2$ and –NH proton signals.

The photophysical behaviors of receptor **2** were investigated using 1.0 μM solutions of receptor **2** in CH_3CN/H_2O (95:5, v/v). The emission maxima at an excitation wavelength of 365 nm was observed at 412 nm, sandwiched by two other low intensity bands at 395 and 440 nm, which is a characteristic emission spectrum of anthracene moiety. Receptor **2** was designed in such a way that only a single pod of the receptor bears the fluorophore. The rationale behind the design of the receptor is based on the idea that metal binding to the receptor pods (that are devoid of fluorophore) will not bring changes in the fluorescence intensity of the receptor although the anion binding between the metal center and the NH of secondary amine will cause changes in the fluorescence intensity.

With these thoughts in mind, we prepared complex **2**·Cu(II) by reacting receptor **2** with $Cu(NO_3)_2{\cdot}2.5H_2O$ in dry MeOH at room temperature (Scheme 1). FAB mass spectrum supports the formation of mononuclear complex **2**·Cu(II), showing $m/z = 723.1711$ which corresponds to complex **2**·Cu(II) (the theoretical calculated value is $m/z = 723.1710$). Attempts to grow crystals of complex **2**·Cu(II) suitable for X-ray structure determination were not successful. The fluorescence spectrum of complex **2**·Cu(II) is similar to that of receptor **2**, indicating that the pod bearing anthracene moiety does not participate much in the coordination to Cu(II) metal center. To understand the interactions between receptor **2** and the Cu(II) metal center, the MacroModel calculations using MM2* force field were performed (Fig. 1, A).[11] The MacroModel calculations showed a binding mode of complex **2**·Cu(II), in which receptor **2** may act as a mixed nitrogen–sulfur donor ligand. In the system, receptor **2** tends to impose a trigonal bipyramidal structure. Consequently, the metal presents a vacant axial position, which is available for the coordination of an anion (Fig. 1, B). The structure of complex **2**·Cu(II) is similar to the skeleton of the Cu(II) complex with tris(2-aminoethyl)amine (Tren), which recognizes anions.[12h] Many other copper complexes have been reported for anion recognition studies, where the copper center acts as a general binding site for the anion recognition, and the selectivity of such copper complexes for a particular anion is governed by the other binding sites.[12] Thus, the copper center has no clear cut inherited binding affinity for any particular anions. The structure of complex **2**·Cu(II) also provides a hydrogen bonding array consisting of both primary and secondary amines. These structural characteristics might provide a preorganized binding site for optimal anion recognition.

We evaluated the anion-binding affinity of complex **2**·Cu(II) by following the changes in the fluorescence intensity of the complex upon addition of tetrabutylammonium salt of a particular anion.

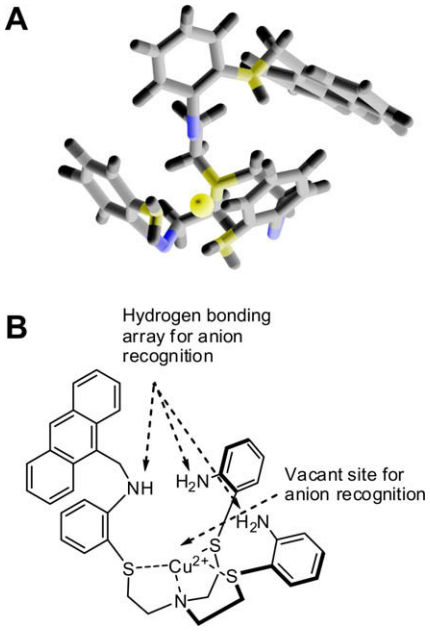

Figure 1. Energy minimized structure of complex **2**·Cu(II) calculated by MacroModel (**A**) and possible binding mode for anion recognition with complex **2**·Cu(II) (**B**).

The changes in the fluorescence intensity are shown in Figure 2, and the fluorescence ratio $(I_0 - I)/I_0$ is displayed in Figure 3. The addition of iodide caused a significant quenching in fluorescence intensity whereas much smaller quenching was observed upon addition of anions such as F^-, Cl^-, Br^-, NO_3^-, CH_3COO^-, and $H_2PO_4^-$.

The preference for iodide suggests that iodide has a complementary size to the pseudocavity formed by the receptor binding sites. Thus, it is an example of better encapsulation of iodide according to its size, not according to its basicity.[13] Iodide may also change the fluorescent intensity of the receptor because of a heavy atomic effect. However, the changes in the fluorescent intensity of the complex are not the result of heavy atomic effect of iodide because the addition of iodide did not alter the fluorescent intensity of receptor **2**. The changes in fluorescent intensity of complex **2**·Cu(II) without spectral shifts indicate that the fluorescent quenching takes place via a photo-induced electron transfer (PET) process.[1g,6g] The fluorescence behavior of complex **2**·Cu(II) was also investigated in more polar solvent systems such as

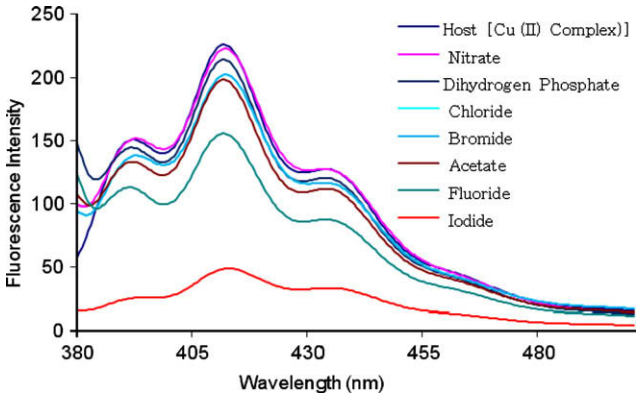

Figure 2. Changes in fluorescence intensity of complex **2**·Cu(II) (1 μM) upon addition of 5 μM of a particular tetrabutylammonium anion salt in CH_3CN/H_2O (95:5, v/v) with excitation at 365 nm.

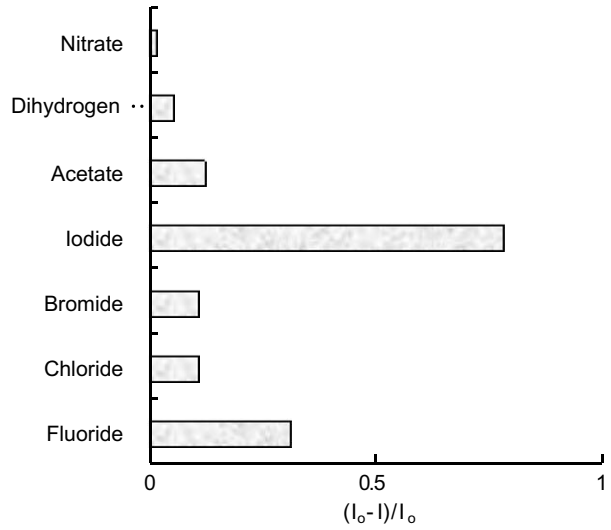

Figure 3. Fluorescence ratio ($I_0 - I/I_0$) of complex **2**·Cu(II) (1 μM) at 412 nm upon addition of 5 μM of a particular tetrabutylammonium anion salt in CH_3CN/H_2O (95:5, v/v).

CH_3CN/H_2O (90:10, v/v), resulting in inhibition in iodide binding. This is due to the fact that the an increase in the proportion of water enhances the competition of water with iodide for the hydrogen bond donor binding sites. This observation indicates that hydrogen bonding through the NH bond is responsible for iodide binding. The hydrogen bonding was further confirmed by the comparison of IR spectrum of complex **2**·Cu(II) and complex **2**·Cu(II) + I^-.

To investigate the properties of complex **2**·Cu(II) as a receptor for iodide in detail, the fluorescence titration was carried out. The fluorescence intensity of a 1 μM solution of complex **2**·Cu(II) decreased as the concentration of tetrabutylammonium iodide salt increased as shown in Figure 4.

During the course of titration, the complex exhibited a high sensitivity toward iodide, by quenching the fluorescence intensity of complex **2**·Cu(II). The association constant K_a of complex **2**·Cu(II) for iodide was calculated on the basis of the literature method,[14] and it was found to be $6.12 \times 10^5\ M^{-1}$. To determine the stoichiometric ratio of complex **2**·Cu(II) and iodide, continuous variation methods were used (Fig. 5).[15] The results illustrate that in this case, the receptor–guest complex concentration approaches a maximum when the molar fraction of complex **2**·Cu(II) is about 0.5, indicating the formation of a 1:1 complex between complex **2**·Cu(II) and iodide.

Figure 2 shows that there were no significant changes in the fluorescence intensity of complex **2**·Cu(II) upon addition of F^-, Cl^-, Br^-, NO_3^-, CH_3COO^-, and $H_2PO_4^-$, showing that complex **2**·Cu(II) is highly selective in its response to iodide as compared to the other anions. Thus, complex **2**·Cu(II) can be used as a probe for selective recognition of iodide, and it can detect iodide as low as 0.2 μM.[16] This detection limit is better than any of the iodide-selective fluorescent receptor reported in the literatures.[6d,9]

To evaluate the analytical application of complex **2**·Cu(II) as a probe for iodide, the estimation of iodide was conducted in the presence of other anions, which may interfere in the estimation (Fig. 6). In these typical experiments, the fluorescence intensities of a series of solutions were measured. These solutions contained complex **2**·Cu(II), different amounts of iodide, and other anions having a concentration five times greater than the concentration of iodide in CH_3CN/H_2O (95:5, v/v). The fluorescence intensity was almost identical to that obtained in the absence of anions.

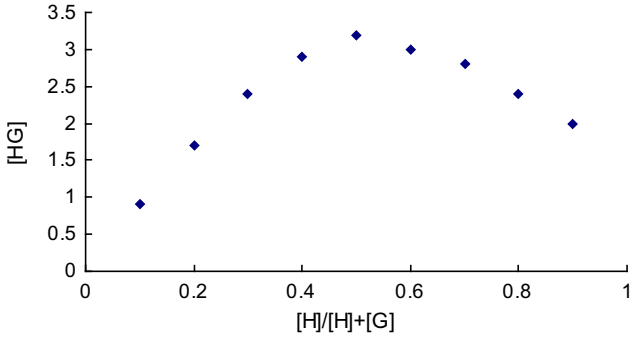

Figure 5. Job plot between complex **2**·Cu(II) and iodide. The concentration of [HG] was calculated by the equation [HG] = $\Delta I/I_0$X [H].

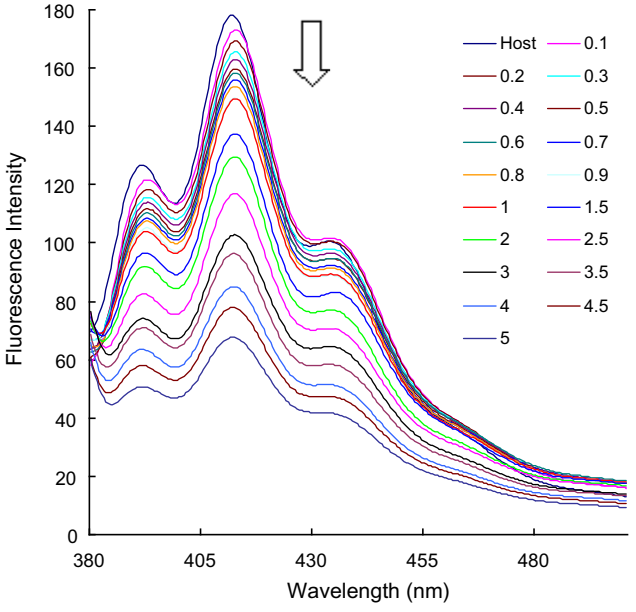

Figure 4. Fluorescence spectra changes of complex **2**·Cu(II) (1 μM) upon addition of tetrabutylammonium iodide (0–5 μM) in CH_3CN/H_2O (95:5, v/v).

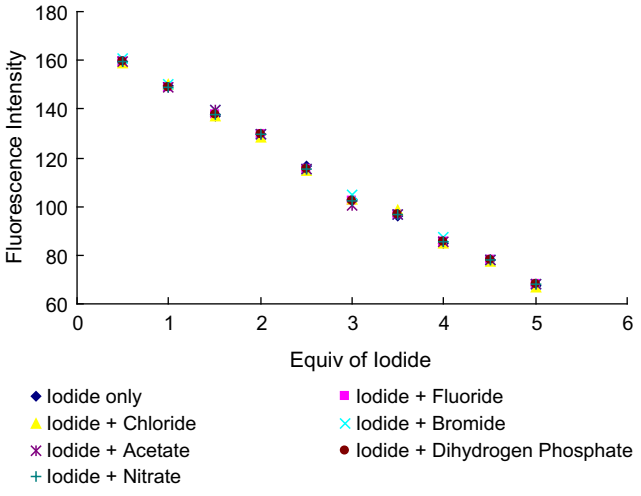

Figure 6. Estimation of iodide in the presence of other anions in CH_3CN/H_2O (95:5, v/v) at 412 nm.

3. Conclusions

We synthesized a flexible tripodal receptor comprising an anthracene moiety on one pod. The tripodal receptor forms a stable 1:1 complex with Cu(II). The complex provides a preorganized anion-binding site for optimal anion binding, resulting in high binding affinity and selectivity for iodide over a wide range of anions. The Cu(II) complex provides a selective probe for estimating iodide at the μM level in the presence of other anions in aqueous acetonitrile without any interference.

4. Experimental

4.1. Synthesis of receptor 2

To a solution of compound **1** (470 mg, 1.0 mmol) in MeOH was added anthracene-9-carbaldehyde (206 mg, 1.0 mmol) portionwise in the presence of a trace of zinc perchlorate. The reaction was monitored with TLC. Upon completion of the reaction, $NaBH_4$ (190 mg, 5.0 mmol) was added to the reaction mixture portionwise. The reaction mixture was allowed to be stirred for 3 h at room temperature. After evaporation of the solvent, the crude product was dissolved in CH_2Cl_2, washed with water, and dried over anhydrous $MgSO_4$. After evaporation, the residue was purified by column chromatography on silica gel eluting with hexane/EtOAc (8:2) to give receptor **2** (445 mg, 67%). IR ($CHCl_3$): 3465, 3355 (N–H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.32–2.41 (m, 4H, $-CH_2$), 2.64–2.71 (m, 8H, $-CH_2$), 4.39 (s, 4H, NH_2), 5.17 (s, 2H, CH_2), 6.59–6.67 (m, 5H, Ar), 6.69 (s, 1H, NH), 7.06–7.11 (m, 4H, Ar), 7.21 (d, 1H, J = 8.0 Hz, Ar), 7.31(d, 1H, J = 8.0 Hz, Ar), 7.40 (t, 2H, J = 8.0 Hz, Ar), 7.47–7.51 (m, 4H, Ar), 8.04 (t, 2H, J = 8.0 Hz, Ar), 8.24 (t, 1H, J = 8.0 Hz, Ar), 8.52 (s, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 45.9 ($-CH_2$), 47.8 ($-CH_2$), 61.1 ($-CH_2$), 65.1 ($-CH_2$), 66.6 ($-CH_2$), 94.8 (Ar), 111.0 (Ar), 120.7 (Ar), 121.2 (Ar), 121.8 (Ar), 125.4 (Ar), 125.9 (Ar), 128.1 (Ar), 129.2 (Ar), 130.0 (Ar), 130.2 (Ar), 133.4 (Ar), 136.5 (Ar), 142.4 (Ar), 147.7 (Ar), 149.3 (Ar), 149.4 (Ar), 156.6 (Ar), 161.9 (Ar); HRMS (FAB) calcd for $C_{39}H_{41}N_4S_3$ $[M+H]^+$: 661.2493, found 661.2493.

4.2. Synthesis of complex 2·Cu(II)

A solution of receptor **2** (132 mg, 0.2 mmol) and $Cu(NO_3)_2 \cdot 2.5H_2O$ (46 mg, 0.2 mmol) in dry methanol was stirred at room temperature. The color of the solution changed immediately to greenish yellow, and after 10 min the solid precipitated. The solid was filtered and washed with methanol and dried under vacuum affording complex **2**·Cu(II). (162 mg, 96%). Mp >300 °C (dec.), IR ($CHCl_3$): 3320 (N–H) cm^{-1}; HRMS (FAB) calcd for $C_{39}H_{40}CuN_4S_3$: 723.1711, found 723.1710.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.088.

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