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An azo dye-coupled tripodal chromogenic sensor for cyanide

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ABSTRACT

A tripodal receptor bearing phenol as a hydrogen bond donor site and azo dye as the signaling subunit was synthesized. The receptor had a high binding affinity for CN^- as signaled by the change in the color of a solution of sensor **4** upon addition of CN^-. Using UV–Vis spectroscopy, the system can be used to quantify 0–19 $\times$ 10^{-5} mol L^{-1} of CN^-, and the sensor was found to successfully function in the presence of other anions.

Some plants have developed protection from herbivores by the production of cyanide-bound sugars in the form of cyanogenic glycosides.[1] Small amounts of cyanide are found in certain plant seeds such as bitter almonds. While cyanide is produced in nature by certain bacteria, fungi, algae, and plants, it is a noxious waste product and pollutant due to anthropogenic usage.[2] Cyanide has been used by the mining industry to dissolve gold and silver ores during extraction in a procedure called the 'cyanide process'. In addition, cyanide is also used in electroplating and in nylon and plastics industry. Despite its widespread use, cyanide presents a health threat to animals including humans due to its high toxicity.[3] Cyanide binds with the iron of the enzyme cytochrome c oxidase, which is the fourth complex in the electron transport chain found in the mitochondrial membranes of eukaryotic cells. This binding leads to retarded transport of electrons from cytochrome c oxidase to oxygen. As a result, the potential ATP production of the cell decreases, making the energy production of the biological system inefficient for vital organs such as the central nervous system and the heart.[4]

Thus, the evaluation of cyanide content is often required for quality control of water, foodstuffs, and other materials. This need has encouraged researchers to develop methods for cyanide detection. Although a number of methods are available for cyanide analysis including voltammetry, potentiometry, electrochemical methods, and ion chromatography,[5] the major limitation of these methods is the use of time-consuming procedures that involve the use of sophisticated instrumentation.[6] On the other hand, chromogenic (optical) cyanide sensors have been actively studied due to their operational simplicity, low cost, and rapid implementation.[7]

Optical cyanide chemosensors (designed principally with covalently linked receptor and signaling subunits) generally make use of hydrogen bond donor sites from urea and thiourea binding sites.[8] However, the use of phenol hydrogen bond donor sites for anion recognition has been relatively less studied.[9] In this study, we utilized a hydrogen bond donor site from a phenolic hydroxyl group as the receptor unit that was covalently attached to an azo dye. With this design strategy, any binding to the hydroxyl group of the receptor would be indicated by a color change due to a change in the ring current of the dye. A second hydrogen bond donor site was provided by an amine moiety in such a way that an elongated anion such as CN^- could coordinate simultaneously with both of the binding sites to generate a bis-chelate ring.

The target compound was synthesized through the series of reactions detailed in Scheme 1. Compound **1**, which was recently reported by our research group,[10] underwent a condensation reaction with salicylaldehyde to yield an imine-linked compound. Compound **2** was obtained by reduction of the imine linkages with $NaBH_4$.[11] The signaling subunit (azo dye) was attached to the tripodal receptor using diazonium salt **3** under aqueous, alkaline conditions.[12] It is important to mention that our attempts to synthesize receptor **4** through the condensation reaction of compound **1** and the carboxaldehyde-bearing azo group **5** failed.

Receptor **4** produced a band at λ_{max} = 375 nm in the absorption spectrum recorded at a 1.0 $\times$ 10^{-5} mol L^{-1} concentration of the

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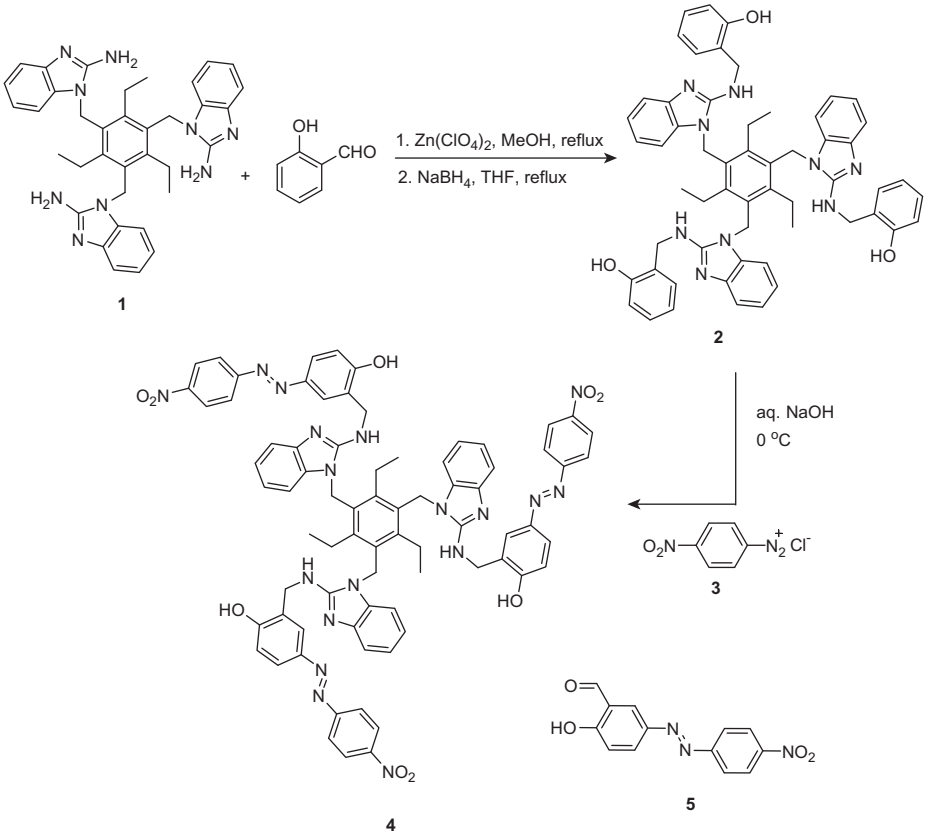

Scheme 1. Synthesis of receptor **4**.

receptor in a CH_3CN:DMSO:HEPES (93:1:6, v/v/v) solvent system. To evaluate the binding affinity of receptor **4** for various anions, solutions which contained a 1.0×10^{-5} mol L^{-1} concentration of receptor **4** together with a particular anion (5.0×10^{-5} mol L^{-1}) were prepared. The UV–Vis absorption spectrum of each solution was compared with the absorption spectrum of receptor **4** (recorded in the same solvent system). The results, shown in Figure 1A, clearly show the CN^--induced changes in the absorption spectrum of receptor **4** at two wavelengths, that is, a decrease in the absorbance at λ_{max} = 375 nm and an increase in the absorbance at λ_{max} = 520 nm, along with a clear isosbestic point at 425 nm, indicative of anion binding. This type of shift was expected for the anion binding that leads to stabilization of the excited state, thereby decreasing the energy gap between the ground and excited states. The significant shift in the absorption band was observed only with cyanide, which supports the design concept for receptor **4** in which it provides two binding sites placed in such a way that only a linear anion can take advantage of simultaneous coordination. The ratiometric change in the UV–Vis absorption spectrum of receptor **4** with various anions is depicted in Figure 1B, and the change in the color of the receptor solution upon addition of particular anions is shown in Figure 2.

To further develop the receptor for sensor applications, the change in the spectrum upon addition of the analyte must directly relate to the analyte concentration. To evaluate this point, a titration was carried out with a fixed concentration of receptor **4** (1.0×10^{-5} mol L^{-1}) and varying concentrations of tetrabutylammonium cyanide ($0–19 \times 10^{-5}$ mol L^{-1}). Changes in the spectrum on successive addition of CN^- are shown in Figure 3A. The titration results show that the stepwise binding of CN^- with receptor **4** (Fig. 3A) corresponded to the same binding pattern as was exhibited by the one-time binding of excess CN^- with **4** (Fig. 1A). Figure 3B shows the linear and ratiometric changes in the absorbance profile of receptor **4** with respect to the concentration of CN^-.

To determine the stoichiometric ratio of receptor **4** and CN^-, the method of continuous variation (Job's Plot) was used. Figure 4 shows Job's plot of the absorbance of receptor **4** versus the mole fraction of the host [H]/([H]+[G]) for a series of solutions in which the total concentration of host and guest was constant and the mole fraction of host was continuously varied.[13] The results illustrate that the receptor–guest complex concentration approaches a maximum when the mole fraction of the host is about 0.5, which indicates that the anion forms a 1:1 complex with the receptor. The association constant K_a of receptor **4** for CN^- was calculated on the basis of a Benesi–Hildebrand plot (for the 1:1 complex) and was found to be 2.3×10^3 M^{-1} (Fig. 5).[14]

^{1}H NMR spectrum of receptor **4** showed signals in the range of 6.16–6.43 responsible for aromatic protons and two broad signals at 7.91 and 8.29 for –NH and –OH protons. The binding sites of receptor **4** responsible for the coordination of CN^- anions were decided by the successive addition of the tetrabutylammonium salt of cyanide to the solution of **4** taken in CD_3CN:DMSO-d_6:D_2O (93:1:6, v/v/v) (Fig. 6). Upon complete addition of 10 equiv of CN^- to the solution, the signal at 7.91 ppm was shifted upfield by $\Delta\delta$ = 0.25 ppm and the signal at 8.29 ppm was also shifted upfield by $\Delta\delta$ = 0.05 ppm. These upfield shifts on coordination of the anion authenticate that in the pure host the magnitude of intramolecular hydrogen bonding is higher than the one that prevailed in the anion complex. However, the driving forces for the complex formation appear to be due to the formation of chelate rings. The further addition of CN^- did not cause the shift in any signals. On the other hand, upon addition of 20 equiv of CN^- the signals for –OH and –NH did not disappear while the color of the solution changed to red. This experiment confirms that CN^- is actually coordinated in the

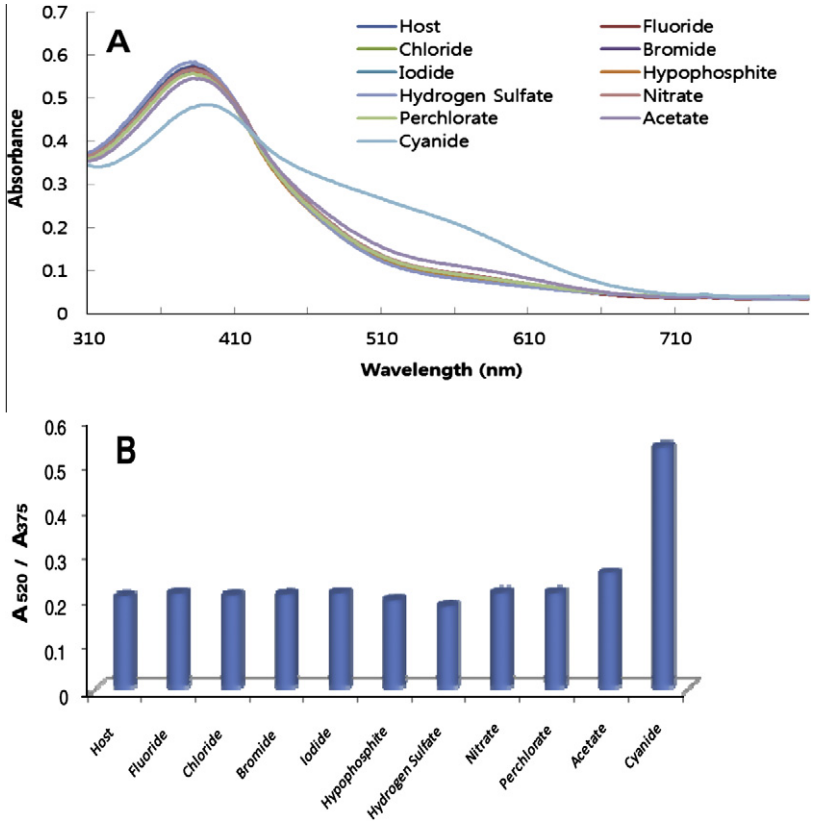

Figure 1. (A) Change in the UV–Vis absorption spectrum of receptor **4** (1.0×10^{-5} mol L^{-1}) in the presence of the tetrabutylammonium salts of different anions (5.0×10^{-5} mol L^{-1}) in CH_3CN:DMSO:HEPES (93:1:6, v/v/v, pH 7.1 ± 0.1). (B) Ratiometric absorbance (A_{520}/A_{375}) of receptor **4** upon addition of tetrabutylammonium salts of different anions in CH_3CN:DMSO:HEPES (93:1:6, v/v/v, pH 7.1 ± 0.1).

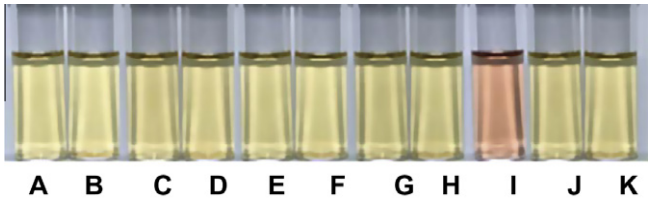

Figure 2. Change in the color of the receptor **4** solution (1.0×10^{-5} mol L^{-1} mol L^{-1}) upon addition of the tetrabutylammonium salt of a particular anion (5.0×10^{-5} mol L^{-1}) in CH_3CN:DMSO:HEPES (93:1:6, v/v/v, pH 7.1 ± 0.1). Captions correspond to a solution of (A): receptor **4** only, (B): **4** + fluoride, (C): **4** + chloride, (D): **4** + bromide, (E): **4** + iodide, (F): **4** + acetate, (G): **4** + hydrogen sulfate, (H): **4** + nitrate, (I): **4** + cyanide, (J): **4** + perchlorate, and (K): **4** + hypophosphite.

pseudocavity of the receptor and the color changed as shown in Figure 2 is not the consequence of anion-mediated deprotonation. No splitting in signals was observed during the course of titration, indicating that all the pods are in the same chemical environment that is a symmetrical complex is formed with the coordination sites offered by all the pods.

To explore the possible interference of other anions on cyanide complexation with receptor **4**, competitive binding experiments were conducted (Fig. 7). The experiments were performed by measuring the absorbance of a series of solutions containing sensor receptor **4** (1.0×10^{-5} mol L^{-1}), CN^- (2–15 equiv of the receptor concentration), and the competitive anion in the same concentration as CN^- at 375 nm. The absorbance at 375 nm was found to be almost identical to that obtained in the absence of interfering anions. These results confirmed that none of the other anions caused any interference in the analysis of CN^-.

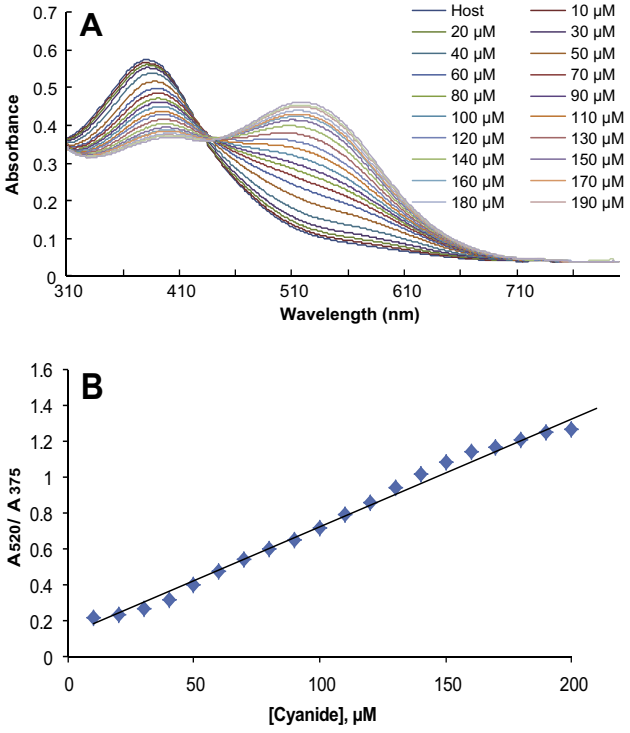

Figure 3. (A) Changes in the UV–Vis absorption spectrum of receptor **4** (1.0×10^{-5} mol L^{-1}) upon increasing concentration of tetrabutylammonium cyanide in CH_3CN:DMSO:HEPES (93:1:6, v/v/v, pH 7.1 ± 0.1). (B) Ratiometric absorbance (A_{520}/A_{375}) profile of receptor **4** with respect to CN^- concentration ($0–19 \times 10^{-5}$ mol L^{-1}).

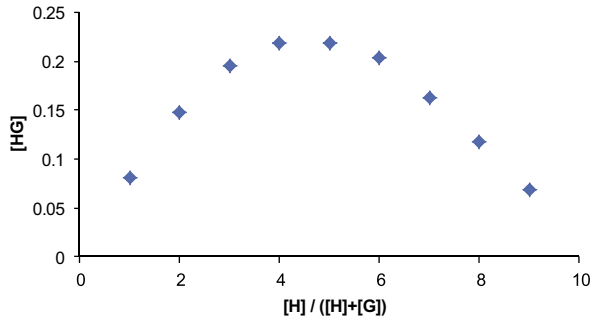

Figure 4. Job's plot to determine the stoichiometry of the complex between receptor **4** and CN^-.

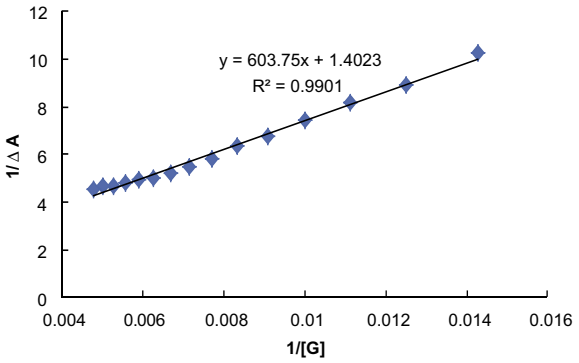

Figure 5. Benesi–Hildebrand plot to determine the stability constant of the complex between receptor **4** and CN^-.

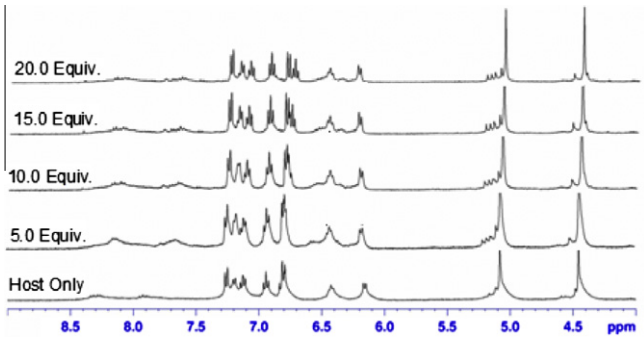

Figure 6. Family of ^1H NMR spectrum of receptor **4** upon successive addition of tetrabutylammonium cyanide in CD_3CN:DMSO-d_6:D_2O (93:1:6, v/v/v).

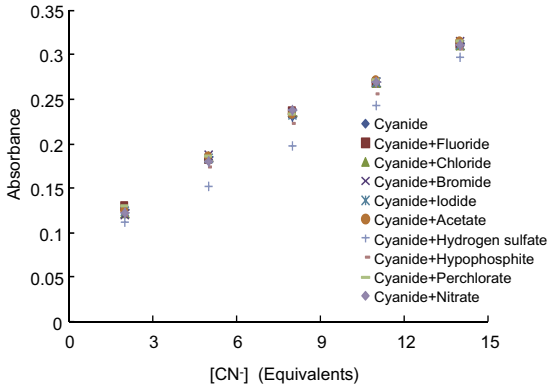

Figure 7. Analysis of CN^- in the presence of other anions in CH_3CN:DMSO:HEPES (93:1:6, v/v/v, pH 7.1 ± 0.1) (the absorbance at λ_{max} = 375 nm was used for calculations).

In conclusion, chemosensor **4** was found to provide sensitive and selective recognition of CN^- through changes in its absorption spectrum. This sensor offers the interesting opportunity of being able to monitor the CN^- concentration in a medium unaffected by other anions.

Acknowledgments

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11. *Synthesis of compound* **2**: A solution of compound **1** (125 mg, 0.21 mmol), 2-hydroxybenzaldehyde (102 mg, 0.83 mmol), and a catalytic amount of $Zn(ClO_4)_2$ in MeOH (12 mL) was stirred at 65 °C for 12 h. The reaction progress was monitored by TLC. Upon completion of the reaction, the solvent was evaporated, and the resulting solid was washed with ether to obtain the imine. The crude imine was dissolved in MeOH/THF (1:2) (12 mL) and was treated with $NaBH_4$ (80 mg, 2.1 mmol) at room temperature. The reaction mixture was heated at 65 °C for 12 h. The solvent was evaporated, water was poured into the reaction mixture, and the organic material was extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$. After filtration and evaporation, the residue was purified by column chromatography on silica gel (hexanes/EtOAc, 3:7) to give a white solid (142 mg, 74%); mp 265–267 °C, ^1H NMR (DMSO-d_6, 400 MHz) δ 0.72 (br s, 9H, $-CH_3$), 2.67 (br s, 6H, $-CH_2$, J = 6.9 Hz), 4.50 (d, 6H, $-CH_2$, J = 5.4 Hz), 5.22 (s, 6H, $-CH_2$), 6.00 (d, 3H, ArH, J = 5.4 Hz), 6.28 (br, 3H, –NH), 6.79 (d, 3H, ArH, J = 7.7 Hz), 6.85 (t, 3H, ArH, J = 7.7 Hz), 6.89 (t, 3H, ArH, J = 7.3 Hz), 7.09 (t, 3H, ArH, J = 7.3 Hz), 7.11 (d, 3H, ArH, J = 7.7 Hz), 7.25 (d, 3H, ArH, J = 7.3 Hz), 7.77 (br s, 3H, ArH), 11.58 (br s, 3H, –OH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 14.5, 23.1, 41.8, 42.1, 60.7, 109.2, 114.7, 117.1, 118.9, 119.0, 120.3, 126.6, 128.5, 130.2, 133.6, 140.8, 145.0, 154.8, 155.9. HRMS (FAB) Calcd for $C_{57}H_{58}N_9O_3$ ([M]+H$^+$): 916.4663. Found: 916.4670.
12. *Synthesis of compound* **4**: Compound **2** (100 mg, 0.11 mmol) in sodium hydroxide (1 mol L^{-1}, 2.5 mL) was added to a solution of 4-nitrophenyl diazonium salt (81 mg, 0.44 mmol) in water (2 mL) at 0 °C, and the mixture was stirred for 1 h. The precipitated solid was filtered, washed successively with cold water and ether, and then dried in vacuo to afford a dark orange solid (104 mg, 70%); mp 202–204 °C (decomposed), ^1H NMR (DMSO-d_6, 400 MHz) δ 0.74 (br, 9H, $-CH_3$), 2.69 (br, 6H, $-CH_2$), 4.51 (s, 4H, $-CH_2$), 4.65 (s, 2H, $-CH_2$), 5.22 (s, 6H, $-CH_2$), 6.02 (d, 3H, ArH, J = 7.4 Hz), 6.28 (br, 3H, -NH), 6.77 (d, 3H, ArH, J = 7.4 Hz), 6.88 (t, 3H, ArH, J = 7.4 Hz), 7.01–7.27 (m, 8H, ArH), 7.69–7.93 (m, 9H, ArH), 8.00–8.16 (m, 7H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 14.6, 23.1, 42.0, 109.0, 114.3, 116.8, 118.9, 119.0, 119.4, 120.7, 126.0, 128.6, 130.0, 133.1, 145.3, 154.1, 155.9. Anal. Calcd for $C_{75}H_{66}N_{18}O_9$: C, 66.07; H, 4.88; N, 18.49. Found: C, 66.21; H, 4.68; N, 18.37.
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