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Dipyrrole Carboxamide Derived Selective Ratiometric Probes for Cyanide Ion

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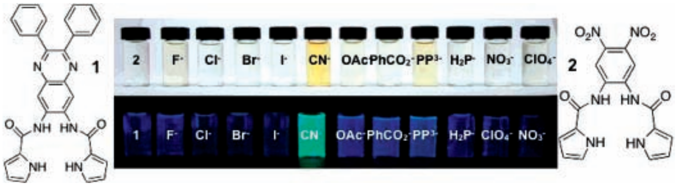
ABSTRACT



Two anion probes 1 and 2 featuring the dipyrrole carboxamide moiety for anion recognition have been prepared. These structurally simple anion probes display great selectivity for the cyanide anion over other common inorganic anions in semiaqueous environment via the formation of cyanohydrin derivatives.

The recognition and sensing of anions have received considerable attention for their important roles in biological, industrial, and environmental processes.[1] In particular, cyanide is a detrimental anion causing poisoning in biology and the environment.[2] Despite its toxic nature, its application in various areas as raw materials for synthetic fibers, resins, herbicides, and the gold-extraction process is inevitable,[3] which releases cyanide into the environment as a toxic contaminant. Thus, there exists a need for an efficient sensing system for cyanide to monitor cyanide concentration from contaminant sources. While a number of synthetic receptors for anions have been designed, relatively few have been developed for the selective sensing of cyanide.[4]

A colorimetric and ratiometric fluorescent chemosensor is of particular interest due to its simplicity.[1,5] In particular, ratiometric sensing provides a way of avoiding any misinterpretation of analyte-induced fluorescence quenching or enhancement due to photobleaching, sensor concentration, and medium effects.[6] Although the design of colorimetric and fluorescent anion chemosensors has recently attracted

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(1) (a) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486−516. (b) Amendola, V.; Esteban-Gómez, D.; Fabbrizzi, L.; Licchelli, M. *Acc. Chem. Res.* **2006**, *39*, 343−353.

(2) (a) Kulig, K. W. *Cyanide Toxicity*; U.S. Department of Health and Human Services: Atlanta, GA, 1991. (b) Baskin, S. I.; Brewer, T. G. In *Medical Aspects of Chemical and Biological Warfare*; Sidell, F. R., Takafuji, E. T., Franz, D. R., Eds.; TMM Publications: Washington, DC, 1997; pp 271−286. (c) Baird, C.; Cann, M. *Environmental Chemistry*; Freeman: New York, 2005.

(3) Miller, G. C.; Pritsos, C. A. *Cyanide*: *Soc., Ind. Econ. Aspects, Proc. Symp. Annu. Meet. TMS* 2001, 73−81.

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(5) (a) Martinez-Manez, R.; Sancenon, F. *Chem. Rev.* **2003**, *103*, 4419−4476 and references therein. (b) Brooks, S. J.; Gale, P. A.; Light, M. E. *Chem. Commun.* **2005**, 4696−4698. (c) Brooks, S. J.; Edwards, P. R.; Gale, P. A.; Light, M. E. *New J. Chem.* **2006**, *30*, 65−70. (d) Wu, C.-Y.; Chen, M.-S.; Lin, C.-A.; Lin, S.-C.; Sun, S.-S. *Chem. Eur. J.* **2006**, *12*, 2263−2269.

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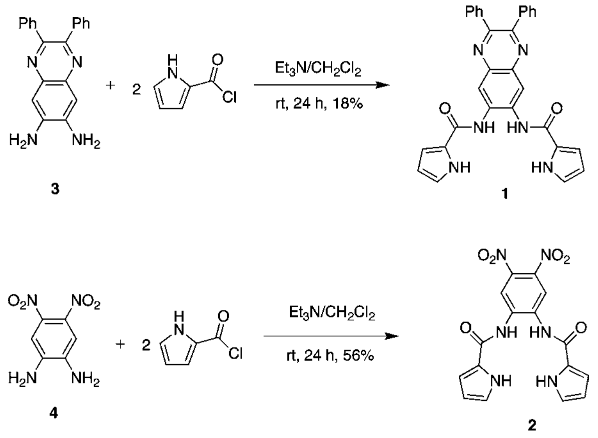
attention, there are only a few examples of ratiometric fluorescent chemosensors for anions.[7]

Amide and pyrrole groups represent the two most common anion recognition moieties, which usually form N−H···A⁻ hydrogen bonds with selective anions.[1,5] In our search for selective and sensitive sensors of biologically important anions, we recently developed a structurally simple chemical sensing system integrating both pyrrole and amide functionality, which are expected to act as hydrogen bond donors collectively.[8] Herein we report the design and synthesis of these anion probes and their unique interaction mode with cyanide.

The structures and synthesis of **1** and **2** are shown in Scheme 1. They are synthesized by condensation of 1-pyrrole-2-carbonyl chloride with corresponding aryldiamine in the presence of triethylamine to afford **1** and **2** in low to moderate yields. Compound **1** shows absorption at 290 and 379 nm and an emission at 427 nm ($\Phi_f = 0.26$) with a lifetime of 0.89 ns. Compound **2** shows an absorption band at 282 nm and a shoulder at 355 nm but showed no detectable fluorescence in solution possibly due to the oxidative electron transfer from excited **2** to the LUMO of the nitro groups upon photoexcitation.

Scheme 1. Synthesis of Chemosensors **1** and **2**



The ability of **1** and **2** to complex with anions was explored with UV−vis absorption and fluorescence spectrometry. Among the 12 anions tested in solution (CH_3CN:H_2O, 90:10, v/v), namely, CN^-, F^-, Cl^-, Br^-, I^-, NO_3^-, OAc^-, $PhCO_2^-$, $HP_2O_7^{3-}$, $H_2PO_4^-$, HSO_4^-, and ClO_4^-, both **1** and **2** responded to only CN^- resulting in a color change from colorless to yellow and the fluorescence change for **1** from blue to green. Figure 1 illustrates the absorption and emission spectral changes for **1** on addition of CN^-. The absorption bands at 291 and 378 nm decreased while three new bands at 299, 372, and 428 nm appeared. The three isosbestic points at 293, 360, and 391 nm indicated a clean conversion throughout the titration process. Concomitantly, the fluorescence maximum of **1** at 425 nm showed a bathochromic shift to 554 nm ($\Delta E_{em} = 5479$ cm^{-1}) with an isoemissive point at 476 nm. The resultant Job plot indicated a 1:2 receptor−cyanide binding stoichiometry.[9] The binding constant calculated from a 1:2 stoichiometry with global multivariate factor analysis,[10] based on absorption spectral changes, yields log $K = 5.91 \pm 0.07$ M^{-2}.

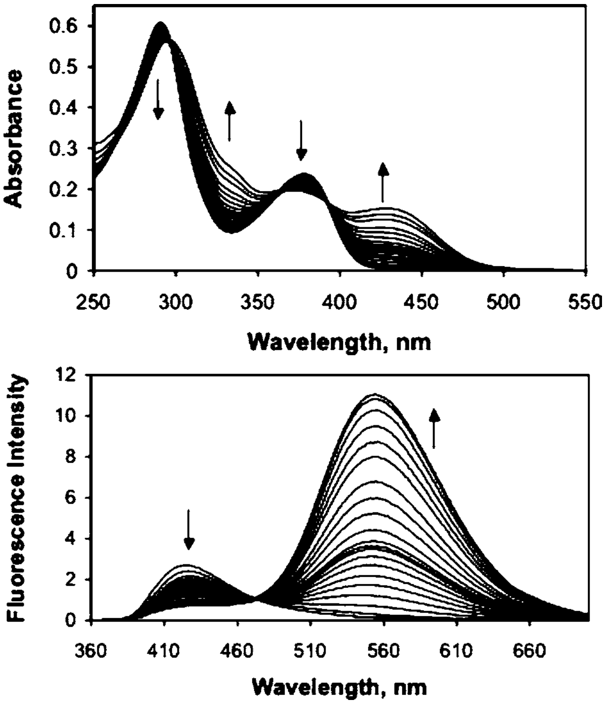


Figure 1. Changes observed in the absorption (top) and fluorescence (bottom) spectra of **1** (10 μM) upon addition of CN^- (0−5.17 × 10^{-4} M) in CH_3CN/H_2O (9:1, v/v) solution. Excitation is at 363 nm.

The absorption spectral changes of **2** on addition of cyanide in CH_3CN/H_2O (9/1, v/v) solution are illustrated in Figure 2. A new absorption band appeared at 465 nm. The resultant Job plot also indicated a 1:2 binding stoichiometry for **2**. The calculated binding constant gives log $K = 9.20 \pm 0.05$ M^{-2}. The colorimetric response of **2** to cyanide persists up to 50% water content.[11] The selectivity of CN^- over other anions, in particular fluoride, is important because most of the chemosensors reported for cyanide sensing suffer

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[7] (a) Peng, X.; Wu, Y.; Fan, J.; Tian, M.; Han, K. *J. Org. Chem.* **2005**, *70*, 10524−10531. (b) Liu, B.; Tian, H. *J. Mater. Chem.* **2005**, *15*, 2681−2686. (c) Wen, Z. C.; Jiang, Y. B. *Tetrahedron* **2004**, *60*, 11109−11115. (d) Kubo, Y.; Yamamoto, M.; Ikeda, M.; Takeuchi, M.; Shinkai, S.; Yamaguchi, S.; Tamao, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2036−2040. (e) Yann, B.; Martin, J. C.; David, P.; Rachel, S. *Chem. Commun.* **2002**, 1930−1931. (f) Nishizawa, S.; Kato, Y.; Teramae, N. *J. Am. Chem. Soc.* **1999**, *121*, 9463−9464.

[8] Cheng and coworkers reported a dipyrrole-2-carboxamide-phenylene compound that exhibited weak binding affinity to fluoride in DMSO solution. Yin, Z.; Li, Z.; Yu, A.; He, J.; Cheng, J.-P. *Tetrahedron Lett.* **2004**, *45*, 6803−6806.

[9] Connors, K. A. *Binding Constants*; John Wiley and Sons: New York, 1987.

[10] (a) *SPECFIT*, version 3.0; Spectra Software Associates. (b) Gampp, H.; Maeder, M.; Meyer, C. J.; Zuberbühler, A. D. *Talanta* **1985**, *32*, 95−101. (c) Gampp, H.; Maeder, M.; Meyer, C. J.; Zuberbühler, A. D. *Talanta* **1986**, *33*, 943−951.

[11] Compound **2** started to precipitate when water content was over 50%.

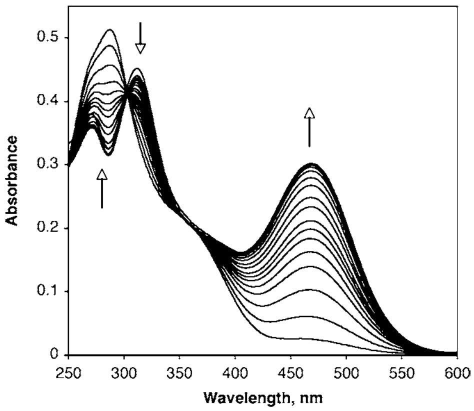


Figure 2. Absorption spectra changes of **2** (20 μM) upon addition of CN^- ($0-1.67 \times 10^{-3}$ M) in CH_3CN/H_2O (9/1, v/v) solution.

the deleterious interference of other anions.[12] The superior selectivity of **2** for cyanide in H_2O/CH_3CN (1/1, v/v) solution is evident from the absorbance response of the anions, as illustrated in Figure 3.[13] Such a selectivity in the semiaqueous environment is promising for aqueous samples.

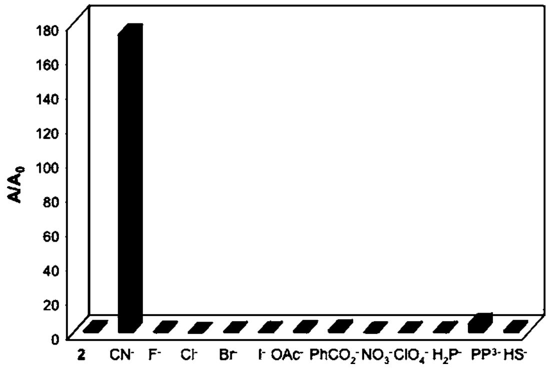


Figure 3. Absorbance response at 454 nm (A/A_0) of **2** (18 μM) in the presence of 10 equiv of selected anions in CH_3CN/H_2O (1/1, v/v) solution.

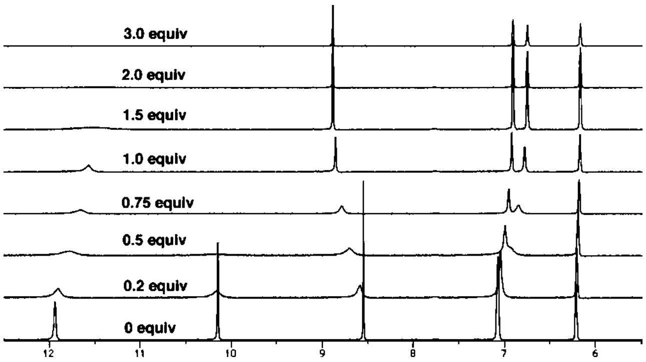
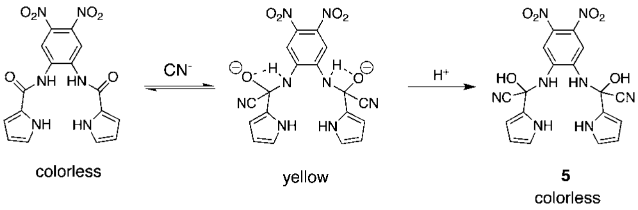


Figure 4. Plots of ^{1}H NMR spectra of **2** on addition of CN^- in DMSO-d_6.

Further insights into the nature of chemosensor−cyanide interactions were investigated by ^{1}H NMR titration experiments. Figure 4 shows the ^{1}H NMR spectra of **2** upon addition of tetrabutylammonium cyanide in DMSO-d_6 solution. To account for the ^{1}H NMR spectral changes on addition of cyanide, we propose the formation of a cyanide adduct (cyanohydrin).[4a,14] Scheme 2 outlines the possible mechanism for the formation of cyanohydrin derivative. The potential hydrogen-bonding pocket, defined by the two amide protons and two pyrrole protons, tends to bring the cyanide to the vicinity of amide carbonyl groups, and this along with the strong electron-withdrawing nature of NO_2 groups renders the amide groups highly electron deficient and susceptible to the nucleophilic addition of cyanide to carbonyl groups. The addition of cyanide resulted in a slow disappearance of amide proton signal while the pyrrole protons shifted upfield. The phenyl protons also exhibited a downfield shift due to the electrostatic through-space effect.[15] The spectral shift is virtually stopped after addition of 2 equiv of cyanide. The solution became colorless again on addition of excess acid. The formation of cyanide adduct was further confirmed by mass spectrometry and the ^{13}C NMR spectrum (see the Supporting Information). The electrospray ionization mass spectrum of the precipitated orange solid showed a molecular mass of 948.60, which corresponds to the formula of $[\mathbf{5}+2Bu_4N^+ + CN^-]^+$ (calculated m/z 948.68, see the Supporting Information).[16]

Scheme 2. Proposed Cyanohydrin Formation from Reaction of Receptor **2** and Cyanide



On the other hand, addition of cyanide anion into DMSO-d_6 solution of **1** resulted in slightly different ^{1}H NMR spectral changes compared to **2** (see Figure 5) although the final

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[12] (a) Badugu, R.; Lakowicz, J. R.; Geddes, C. D. *J. Am. Chem. Soc.* **2005**, *127*, 3635−3641. (b) Sun, S.-S.; Lees, A. J.; Zavalij, P. Y. *Inorg. Chem.* **2003**, *42*, 3445−3453. (c) Anzenbacher, P., Jr.; Tyson, D. S.; Jursiková, K.; Castellano, F. N. *J. Am. Chem. Soc.* **2002**, *124*, 6232−6233. (d) Miyaji, H.; Sessler, J. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 154−157.

[13] Compound **1** also displays high selectivity of cyanide over other common inorganic anions. See the Supporting Information for the fluorescence response of **1** in the presence of 10 equiv of selected anions.

[14] Kim, Y. K.; Lee, Y.-H.; Lee, H-Y.; Kim, M. K.; Cha, G. S.; Ahn, K. H. *Org. Lett.* **2003**, *5*, 4003−4006.

[15] Boiocchi, M.; Del Boca, L.; Esteban-Gómez, D.; Fabbrizzi, L.; Lucchelli, M.; Monzani, E. *Chem. Eur. J.* **2005**, *11*, 3097−3104.

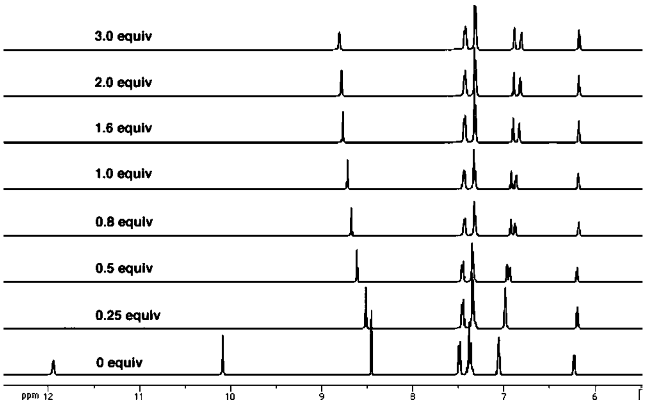

Figure 5. Plots of ^{1}H NMR spectra of **1** on addition of CN^- in DMSO-d_6.

product is also confirmed by mass spectrometry to be the cyanide adduct (see Figure S2 in the Supporting Information).[17] The most significant differences come from the gradual disappearance of the pyrrole NH proton signal and downfield shift of the β proton signal of pyrrole on addition of cyanide anion. This observation confirms the interaction of pyrrole moieties with the cyanide anion in the receptor−cyanide complex. The amide protons in **1** are expected to be less acidic compared to those in **2**. Thus, the proton exchange is expected to involve not only the amide protons but also possibly the pyrrole NH protons as well.

In summary, we have successfully developed a highly selective receptor for the sensing of cyanide in a semiaqueous environment. A unique colorimetric and ratiometric fluorescent response to cyanide is realized through the new mode of receptor−cyanide interaction by formation of the cyanohydrin derivative via a highly electron-deficient amide moiety in a semiaqueous environment. Although these two anion probes are not soluble in water, the facile synthesis and modification of the structural framework of these pyrrole carboxamide compounds reveal the potential development of a family of ratiometric chemosensors for detecting cyanide in aqueous solution.

Acknowledgment. We are grateful to the National Science Council of Taiwan (Grant Nos. 93-2113-M-001-029 and 94-2113-M-001-014) and Academia Sinica for support of this research.

Supporting Information Available: Synthesis, characterization data, experimental procedures, and mass spectra of cyanide adducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The formation of cyanide adduct is also indirectly supported by anion competition experiments. The yellow color of cyanide-chemosensor **2** complex persists in the presence of a 50 equiv excess of other anions except for $HP_2O_7^{3-}$, $H_2PO_4^-$, and HSO_4^-. The ability to protonate the cyanide adduct by these three anions and turn the solution back to colorless is consistent with the final process depicted in Scheme 2.

(17) The attempt to acquire ^{13}C NMR spectrum of the cyanide adduct was unsuccessful due to the very low solubility of **1**.