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A new fluorescent fluoride chemosensor based on conformational restriction of a biaryl fluorophore

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Abstract—A new fluorescent anion sensor **1**, based on a biaryl–thiourea system, exhibits a fluorescence emission enhancement via conformational restriction upon a hydrogen bond-mediated complexation of fluoride anions.

Recently, considerable attention has been focused on the design of receptors that have the ability to selectively bind and sense anions through electrochemical and optical responses.[1] The construction of fluorescent sensors, which have specificity for target anions, is particularly attractive. A typical fluorescent sensor for anions is generally built through a modular approach, by either covalently or noncovalently attaching an appropriate photoactive fluorophore to the receptor with an affinity for the desired substrate.[1b,2,3] Following the receptor–anion interaction, an appropriate signaling process must take place. This process distinctly modifies the emission of the fluorophore, thus signaling the occurrence of the recognition event.[1b] The fluorescent mechanisms used in the signaling process for anion sensing are generally photoinduced electron transfer (PET),[4] excited-state proton transfer,[5] excimer/exciplex formation,[6] metal-to-ligand charge transfer,[1c] and modulation of the efficiency of interchromophore energy transfer.[1,7] Several groups have investigated an alternative mechanism for fluorescent chemosensor action, in which a substrate binding leads to conformational restriction of a fluorophore. This in turn produces fluorescence enhancement.[8,9]

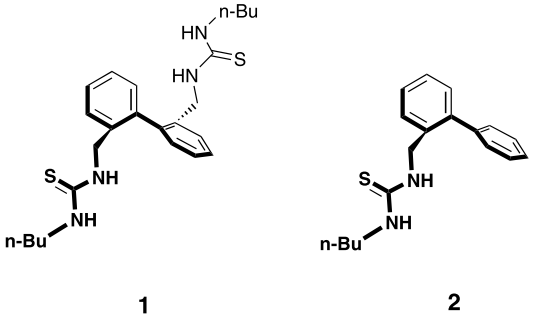
In particular, the number of fluorescent sensors for fluoride anions[3a,4c,10] is still quite small in spite of its importance in clinical treatment for osteoporosis and detection of fluoride toxicity resulting from over-accumulation of fluorides in the bone.[11]

In this paper, we present a selective fluorescent anion sensor **1**, based on a biaryl–thiourea system, which shows a fluorescence emission enhancement by conformational restriction upon a hydrogen bond-mediated complexation of F^-.

The synthesis of **1** began from a known precursor, 2,2′-bis(aminomethyl)biphenyl,[12a] which was reacted in THF with 2 equiv. of *n*-butylisothiocyanate to provide **1** in 60% yield.[12b] The control **2** was similarly prepared following the same methodology as was applied in the synthesis of **1**.[13]

Sensor **1** contains four thiourea NH groups designed for a geometrical fit for anions[12c] and a biphenyl moiety as a fluorescence-monitoring unit (Fig. 1).

The effect of anions (as tetrabutylammonium salts) on the fluorescence spectrum of **1** was investigated in $CHCl_3$, and the results are shown in Fig. 2. In the absence of anions, the emission spectrum of **1** is charac-



1 **2**

Figure 1. Fluorescent anion sensors **1** and **2**.

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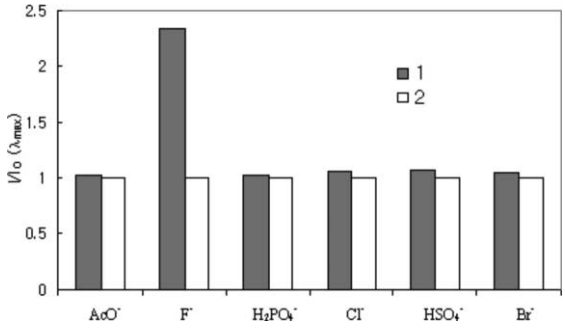


Figure 2. Fluorescence emission response profiles of **1** and **2** at emission maxima (356 nm). Excitation wavelength: 276 nm (20°C).

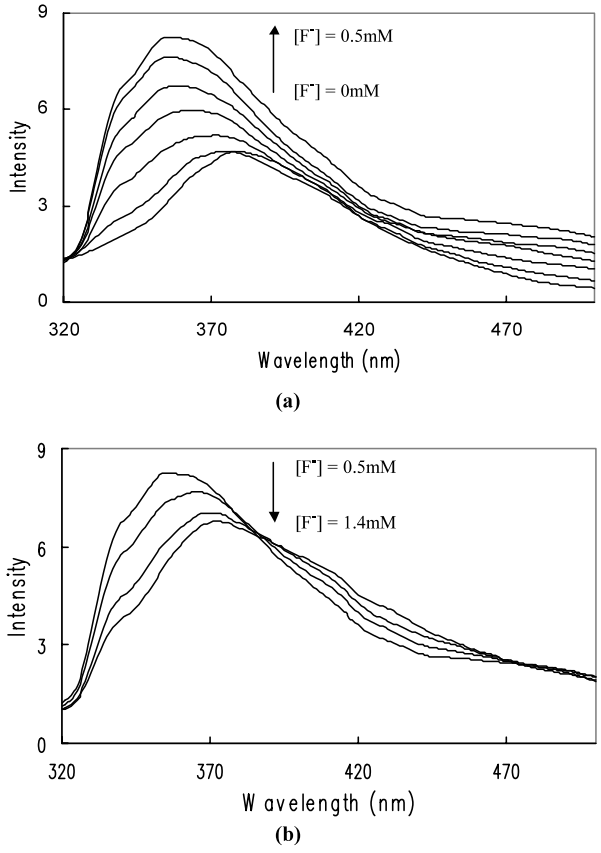


Figure 3. Fluorescence titration spectra of **1** with n-$Bu_4N^+F^-$ in $CHCl_3$ at 20°C. [**1**]=0.2 mM. Excitation wavelength: 276 nm.

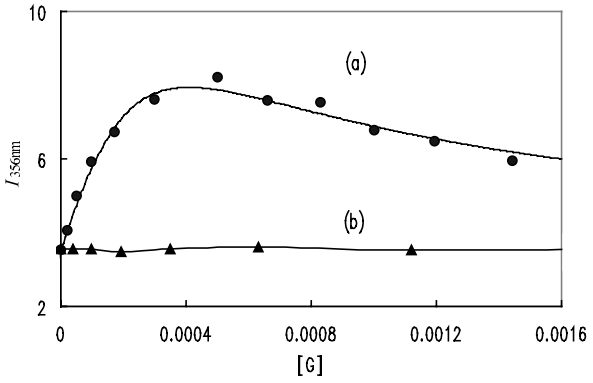
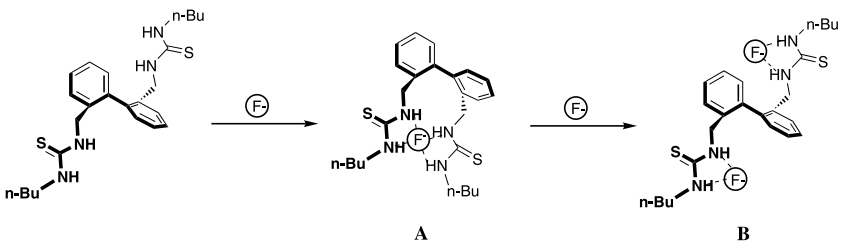


Figure 4. Dependence of fluorescence intensity of **1** at 356 nm on the concentration of (a) F^- and (b) $H_2PO_4^-$ in $CHCl_3$ at 20°C. [**1**]=0.1 mM.

terized by the presence of emission maxima at 379 nm. As shown in Fig. 2, the presence of F^- resulted in a fluorescence enhancement at 356 nm. However, **1** did not exhibit any obvious spectral change at 356 nm upon the addition of $H_2PO_4^-$, $CH_3CO_2^-$, HSO_4^-, Cl^- or Br^-.[14] These results suggested that **1** has a higher selectivity for F^- compared to the other anions.

The dependence of fluorescence spectra of **1** in $CHCl_3$ on the F^- concentration is shown in Fig. 3a.

Increasing the F^- concentration up to 2.5 equiv. relative to the concentration of **1** resulted in 2.4-fold fluorescence enhancement accompanied by a hypsochromic shift (~23 nm). The reverse change was observed upon further addition of F^-. As shown in Fig. 3b, the introduction of additional F^- shows a decrease in the fluorescence intensity along with a bathochromic shift (~16 nm). The dependence of the intensity at 356 nm on the concentration of F^- strongly suggests that two kinds of complexes are formed, both a 1:1 and 1:2 host–guest complex as shown in Scheme 1. As complex **A** is formed, **1** shows fluorescence enhancement via conformational restriction. Then, as complex **B** is formed, a decrease in the fluorescence intensity takes place by the loss of conformational restriction induced by complex **A**. The data in Fig. 4 are well fitted with an equation assuming that the fluorescence change at 356 nm is only induced by the formation of a 1:1 complex between **1** and F^-, and the association constants of the 1:1 and 1:2 complexes are calculated to be 1.08×10^4 M^{-1} (K_{11}) and 2.28×10^7 M^{-2} ($\beta_{12}=K_{11}K_{12}$), respectively.[6b,15]



Scheme 1. Proposed mechanism for the complexation of **1** with fluoride ions.

It is noteworthy that compound **2** with one thiourea group shows no fluorescence enhancement at 356 nm upon the addition of F^-. These results indicate that the introduction of bis-thiourea induces the conformational restriction upon fluoride binding, which leads to the fluorescence enhancement. However, as shown in Fig. 5, a broad emission enhancement around 470 nm was detected. This signal may originate from the biphenyl excimer formation.[4,16,17] The origin of the broad emission enhancement around 470 nm in Fig. 3, which develops upon F^- binding, also comes from this process.

The fluorescence titration of **1** with $H_2PO_4^-$, $CH_3CO_2^-$, HSO_4^-, Cl^- and Br^- only shows broad emission enhancement around 470 nm. This result indicates that even though these anions interact with thiourea groups, they do not necessarily form complexes with **1** like complex **A**. Thus, fluorescence enhancement at 356 nm via conformation restriction was not detected.

Only small changes in the UV spectrum occur during the titration with F^-, indicating that the increase in emission results primarily from an increase in the effective quantum yield.[8b]

The selectivity for F^- can be understood on the basis of the guest basicity and the complex structure. The F^- anion appears to have the proper size for the binding pocket between the two thiourea groups. It also exhibits a stronger basicity than other anions, and should exhibit a more effective hydrogen bonding interaction with the two thiourea groups comprising the binding site. An energy-minimized structure for the complex with F^- shows proper hydrogen bonds between the four thiourea NHs and a fluoride anion as expected.[18] Although **1** is flexible enough to enable hydrogen bonds to be formed with any anions, hydrogen bonds between **1** and other anions as shown in complex A (Scheme 1) are not favored due to the improper hydrogen bond angle and bond distance of NH···A (A: hydrogen bond acceptor of anions).[18]

In summary, we have developed a new fluorescent anion sensor **1** with biphenyl and bis-thiourea moieties.

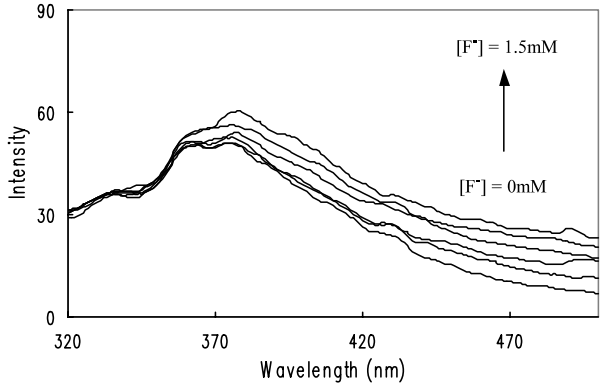


Figure 5. Fluorescence titration of **2** with n-$Bu_4N^+F^-$ in $CHCl_3$ at 20°C. [**2**] = 0.2 mM. Excitation wavelength: 276 nm.

Sensor **1** shows fluorescence emission enhancement by conformational restriction upon hydrogen bond-mediated complexation of fluoride ions.

Acknowledgements

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References

1. (a) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486; (b) Fabbrizzi, L.; Licchelli, M.; Labaioli, G. *Coord. Chem. Rev.* **2000**, *205*, 85; (c) Beer, P. D.; Cadman, J. *Coord. Chem. Rev.* **2000**, *205*, 135; (d) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609; (e) *Comprehensive Supra-molecular Chemistry*; Lehn, J.-M. Chair ed.; Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vögtle, F., Eds.; Pergamon: Oxford, 1996; Vol. 1; (f) *Chemosensors of Ion and Molecular Recognition*; Desvergne, J.-P.; Czarnik, A. W., Eds.; Kluwer: Dordrecht, 1997; Vol. 492.
2. (a) Niikura, K.; Anslyn, E. V. *J. Am. Chem. Soc.* **1998**, *120*, 8533; (b) Metzger, A.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **1998**, *37*, 649; (c) Gale, P. A.; Twyman, L. J.; Handlin, C. I.; Sessler, J. L. *Chem. Commun.* **1999**, 1851.
3. (a) Anzenbacher, P., Jr.; Jursíková, K.; Sessler, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 9350; (b) Mizukami, S.; Nagano, T.; Urano, Y.; Odani, A.; Kikuchi, K. *J. Am. Chem. Soc.* **2002**, *124*, 3920–3925.
4. (a) Valence, D. H.; Czarnik, A. W. *J. Am. Chem. Soc.* **1994**, *116*, 9397; (b) Gunnlaugsson, T.; Davis, A. P.; Glynn, M. *Chem. Commun.* **2001**, 2556; (c) Kim, S. K.; Yoon, J. *Chem. Commun.* **2001**, 770; (d) Nishizawa, S.; Teramae, N. *J. Chem. Soc., Perkin Trans. 2* **2002**, 866; (e) Nishizawa, S.; Teramae, N. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2325.
5. Choi, K.; Hamilton, A. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 3912.
6. (a) Nishizawa, S.; Kaneda, H.; Uchida, T.; Teramae, N. *J. Chem. Soc., Perkin Trans. 2* **1998**, *11*, 2325; (b) Nishizawa, S.; Kaneda, H.; Kato, Y.; Teramae, N. *J. Am. Chem. Soc.* **1998**, *121*, 9463.
7. De Santis, G.; Fabrizzi, L.; Licchelli, M.; Poggi, A.; Taglietti, A. *Angew. Chem., Int. Ed.* **1996**, *35*, 202.
8. (a) Mcfarland, S. A.; Finney, N. S. *J. Am. Chem. Soc.* **2002**, *124*, 1178; (b) Mcfarland, S. A.; Finney, N. S. *J. Am. Chem. Soc.* **2001**, *123*, 1260; (c) Mello, J. V.; Finney, N. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1536.
9. (a) Watanabe, S.; Onogawa, O.; Komatsu, Y.; Yoshida, K. *J. Am. Chem. Soc.* **1998**, *120*, 229; (b) Sandanayake, K.; Nakashima, K.; Shinkai, S. *Chem. Commun.* **1994**, 1621; (c) Ta-keuchi, M.; Mizuno, T.; Shinmori, H.; Shinkai, S. *Tetrahedron* **1996**, *52*, 1195; (d) Takeuchi, M.; Yoda, S.; Imada, T.; Shinkai, S. *Tetrahedron* **1997**, *53*, 8335.
10. (a) Yamaguchi, S.; Akiyama, S.; Tamao, K. *J. Am. Chem. Soc.* **2001**, *123*, 11372; (b) Jimenez, D.; Soto, J. *Tetrahedron Lett.* **2002**, *43*, 2823.

11. Dreisbuch, R. H. *Handbook of Poisoning*; Lange Medical Publishers: Los Altos, CA, 1980.
12. (a) Hiatt, R. R.; Shaio, M.-J.; Georges, F. *J. Org. Chem. Soc.* **1979**, *44*, 3265; (b) Taub, B.; Hino, J. B. *J. Org. Chem. Soc.* **1961**, *26*, 5238; (c) Nishizawa, S.; Bühlmann, P.; Umezawa, Y. *Tetrahedron Lett.* **1995**, *36*, 6483.
13. Synthesis of **1**: To a solution of 2,2′-bis(aminomethyl)-biphenyl (100 mg, 0.47 mmol) in 15 mL of CH_2Cl_2 were added TEA (0.19 mL, 1.3 mmol) and butyl isothio-cyanate (0.12 mL, 1.00 mmol). After stirring the reaction mixture for 1 h, it was diluted with CH_2Cl_2 and washed with water. The organic extracts were dried over Na_2SO_4, concentrated and then chromatographed to give the desired product (125 mg, 60%). Spectral data for **1**: ^{1}H NMR (300 MHz, acetone-d_6, ppm) δ 0.88–0.93 (t, 6H, CH_2CH_3), 1.29–1.39 (m, 4H, $CH_2CH_2CH_3$), 1.48–1.58 (m, 4H, CH_2-CH_2CH_2), 3.43–3.49 (dd, 4H, $NHCH_2CH_2$), 4.53–4.54 (d, 4H, $ArCH_2NH$), 6.93 (br, 2H, $CSNHCH_2$), 7.14 (br, 2H, $ArCH_2NHCS$), 7.14–1.17 (dd, 2H, Ar*H*s), 7.14–7.17 (dd, 2H, Ar*H*s), 7.29–1.40 (m, 4H, Ar*H*s), 7.50–7.52 (dd, 2H, Ar*H*s); ^{13}C NMR (300 MHz, acetone-d_6, ppm) δ 13.57, 20.16, 31.53, 44.22, 126.30, 127.20, 128.00, 128.36, 129.87, 137.15, 139.82, 183.41; HRMS (FAB) m/z = 443.2306 (M+H)$^+$, calcd for $C_{24}H_{34}N_4S_2$ = 442.2225.
14. (a) In the case of I^-, fluorescence was quenched because of heavy atom effect. Fluorescence emission change of up to 12-fold was observed in the presence of 12 equiv. I^-; (b) The experiments in CH_3CN turn out to be similar to those in $CHCl_3$. Increasing the F^- concentration up to 12 equiv. relative to the concentration of **1** resulted in 1.5-fold fluorescence enhancement around 320 nm. However, addition of $H_2PO_4^-$ resulted in broad emission enhancement around 450 nm.
15. (a) Kavallieratos, K.; Bertao, C. M.; Crabtree, R. H. *J. Org. Chem.* **1999**, *64*, 1675; (b) Conners, K. A. *Binding Constants*; John Wiley and Sons: New York, 1987.
16. Generally, excimer shows a long-wavelength emission and the λ_{max} of the emission is independent of the solvent polarity. Sensor **1**, complexed with n-$Bu_4N^+F^-$, shows a same fluorescence maximum of the long-wavelength emission around 470 nm in CH_2Cl_2, $CHCl_3$, THF, MeCN. We thank a referee for advice.
17. Lakowicz, J. R. *Principles of Fluorescence Spectroscopy*; Plenum Press: New York, 1996; Vol. 1, p. 701.
18. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.