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A highly selective and synthetically facile aqueous-phase cyanide probe

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Disperse Orange 3 (4-(4-nitrophenylazo)aniline)-based chemosensor **1** has been prepared. This structurally simple receptor displays great selectivity for the cyanide anion over other common inorganic anions in aqueous environment and can detect cyanide in water sample at micromolar concentrations.

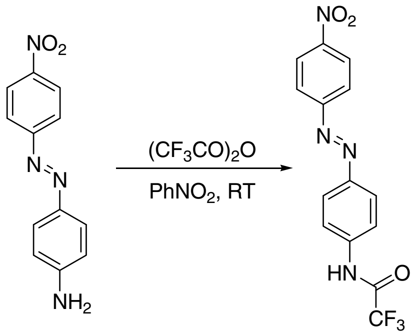
It is well known that anions play an important role in the field of biology, medicine, catalysis, and environment.[1,2] In recent years, the development of chemosensors capable of selectively recognizing and sensing anions appears to be particularly attractive. There is an increasing attention toward the development of colorimetric probes which have the advantage of showing easily observable color changes in the presence of target guests.

Recently, considerable attention has been paid to the sensing of cyanide anion for many reasons. Cyanide is one of the most toxic anions and harmful to environment or human health. For example, it is lethal to humans at concentrations of 0.5–3.5 mg per kg of body weight.[3] Recent studies have shown that the lethal cyanide concentration in the blood of fire victims is 23–26 μM.[4] The binding of cyanide to cytochrome oxidase reduces the activity of this enzyme and inhibits oxygen utilization by cells.[5] But cyanide cannot be discarded for its wide application in the production of organic chemicals and polymers, such as nitriles, nylon, and acrylic plastics.[6] In addition, it is critical to the gold-extraction process.[7]

To date, several strategies have been developed to detect cyanide anion, including the formation of cyanide complexes with transition metals,[8] boron derivatives,[9] CdSe quantum dots,[10] nucleophilic addition reactions to carbonyl group,[11] displacement approach,[12] hydrogen-bonding interaction,[13] deprotonation process,[14] and luminescence lifetime measurement.[15] Many receptors for cyanide reported so far have several limitations such as poor selectivity over fluoride or acetate, use in specific reaction conditions or utilization of expensive instruments, and complicated synthesis. In addition, many of them are reported to work only in organic media, so the search for effective sensing systems in aqueous environment is still a great challenge. With these considerations in mind, we now introduce a simple yet effective colorimetric sensor **1** (Scheme 1), which utilizes an azo dye as a chromophore and a trifluoroacetyl group as an electrophile. It is well known that cyanide anion is a strong nucleophilic reagent, and the nucleophilic attack to the carbon atom of an electron-deficient carbonyl group can achieve the so-called 'naked eye' detection of cyanide anion in aqueous environment.

Compound **1** was synthesized in a single step starting from commercially available precursor Disperse Orange 3 (4-(4-nitrophenylazo)aniline) (Scheme 1).[16] This compound and trifluoroacetic anhydride were stirred in nitrobenzene overnight. Then the mixture was filtered and the filter cake was crystallized by acetonitrile to obtain the target compound **1** in moderate yield (70%). The structure of **1** was confirmed by ^1H NMR, ^{13}C NMR, and HRMS data.

As a first step, the interaction mechanism between the compound **1** and cyanide was investigated. ^1H NMR titration experiments were carried out by addition of Bu_4CN to the acetonitrile-d_3 solution of **1** (Fig. 1). With the increasing addition of



Scheme 1. Synthetic procedure of compound **1**.

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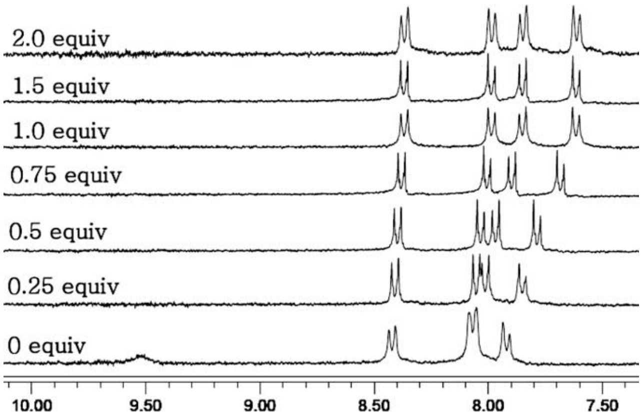
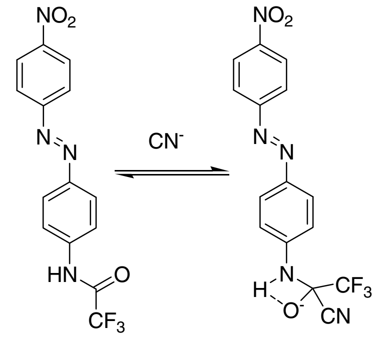


Figure 1. Plots of ^{1}H NMR spectra of **1** on addition of Bu_4CN in acetonitrile-d_3.



Scheme 2. Structure of the probe **1** and its proposed mechanism upon the addition of cyanide.

cyanide, all the aromatic protons exhibited an upfield shift to different extent, which is compatible with the proposed switching mechanism (Scheme 2).

In order to gain systematic knowledge on the effect of water on the binding affinity and selectivity for cyanide, we chose water–acetonitrile mixtures as solvents (0%, 2.5%, 5.0 %, 7.5%, and 10.0% water, respectively) and 12 anions of present interest, namely, CN^-, F^-, AcO^-, $H_2PO_4^-$, Cl^-, Br^-, I^-, HSO_4^-, NO_3^-, ClO_4^-, SCN^-, and N_3^- as their tetrabutylammonium salts were added to the solution of **1**, respectively. Figure 2 shows the color changes and the corresponding absorption spectra upon addition of different anions in CH_3CN. It can be seen that the color changed from colorless to orange/yellow in the presence of CN^-, F^-, AcO^-, $H_2PO_4^-$, and HSO_4^-. Only addition of 1 equiv of the five kinds of anions induced distinct spectra changes (Fig. 2b), while other anions such as Cl^-, Br^-, I^-, ClO_4^-, SCN^-, and N_3^- did not induce any color changes, even in large excess.

Though obvious interaction was observed on addition of CN^- in CH_3CN, the selectivity for CN^- is rather poor due to the interference of F^-, AcO^-, $H_2PO_4^-$, and HSO_4^-. When 2.5% water in water–acetonitrile mixture was chosen as solvent, only CN^-, F^-, and AcO^- showed obvious interaction with the sensor **1**. The color changed to deep yellow upon addition of CN^-, and pale yellow upon addition of F^- and AcO^-. It is not surprising considering the solvent effect. Namely, anions such as F^-, AcO^-, $H_2PO_4^-$, and HSO_4^- should interact with water through hydrogen-bonding leading to a large decrease in their nucleophilicity. While cyanide has weaker hydrogen-bonding ability and stronger nucleophilicity toward the carbonyl group[12] (see Fig. 3).

Our thought was confirmed with further water increase. 5.0% vol of water resulted in selective CN^- response (Fig. 4). Addition of other anions tested had minor influence on both the color and

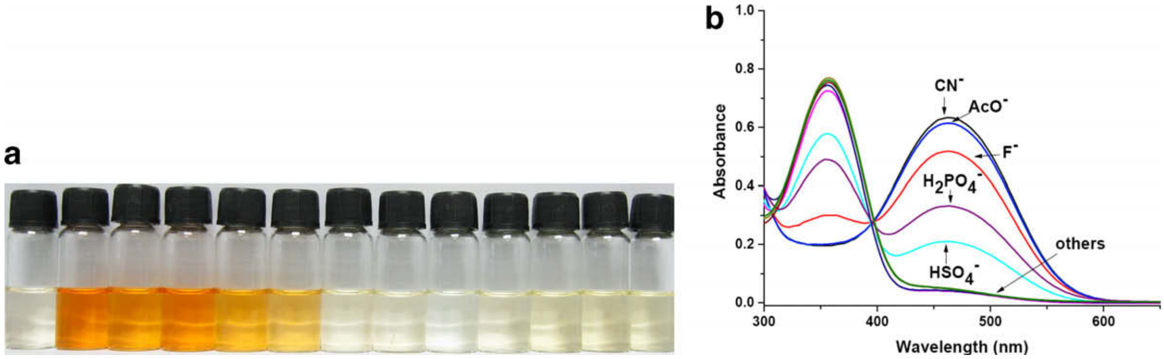


Figure 2. (a) The corresponding color changes and (b) absorption spectra when compound **1** (25 μM) was treated with various anions (vials from the left: **1** only, CN^-, F^-, AcO^-, $H_2PO_4^-$, HSO_4^-, Cl^-, Br^-, I^-, NO_3^-, ClO_4^-, SCN^-, N_3^-; CN^-, F^-, AcO^-, $H_2PO_4^-$, HSO_4^-, NO_3^-: 1 equiv; Cl^-, Br^-, I^-, ClO_4^-, SCN^-, N_3^-: 50 equiv) in CH_3CN.

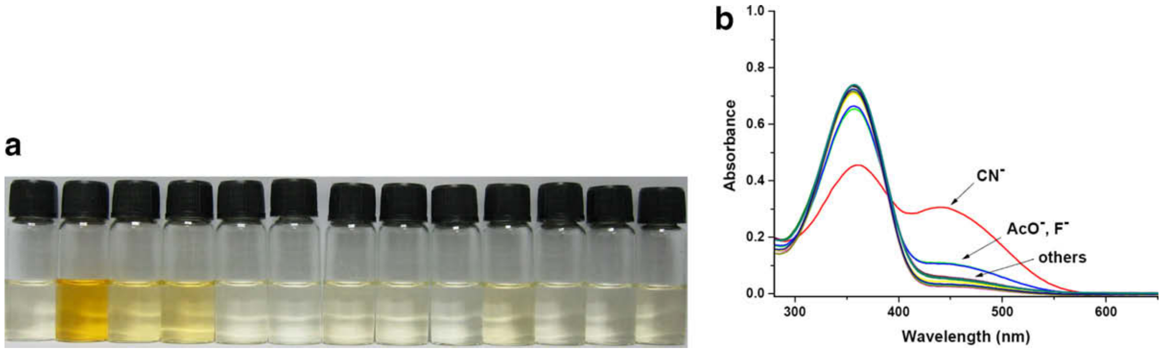


Figure 3. (a) The corresponding color changes and (b) absorption spectra when compound **1** (25 μM) was treated with various anions (vials from the left: **1** only, CN^-, F^-, AcO^-, $H_2PO_4^-$, HSO_4^-, Cl^-, Br^-, I^-, NO_3^-, ClO_4^-, SCN^-, N_3^-; CN^-, F^-, AcO^-, $H_2PO_4^-$, HSO_4^-: 1 equiv; Cl^-, Br^-, I^-, NO_3^-, ClO_4^-, SCN^-, N_3^-: 50 equiv) in $CH_3CN–H_2O$ (97.5:2.5, v:v).

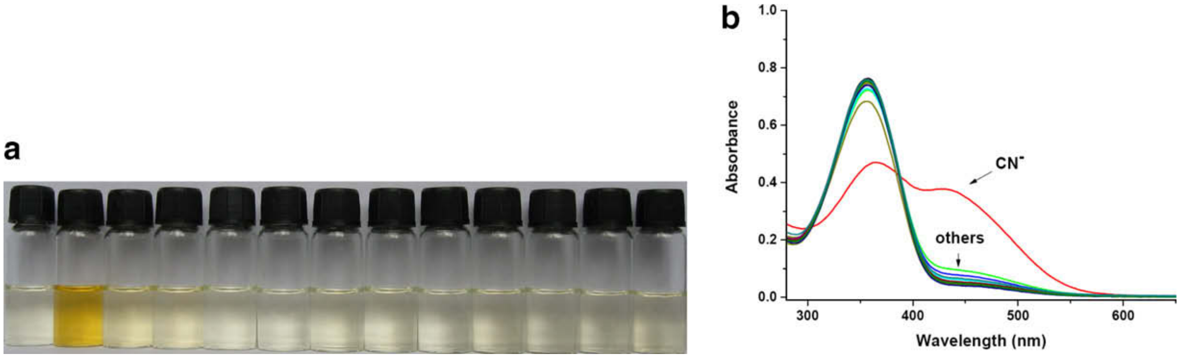


Figure 4. (a) The corresponding color changes and (b) absorption spectra when compound **1** (25 μM) was treated with various anions (vials from the left: **1** only, CN^-, F^-, AcO^-, $H_2PO_4^-$, HSO_4^-, Cl^-, Br^-, I^-, NO_3^-, ClO_4^-, SCN^-, N_3^-; CN^-, F^-, AcO^-: 2 equiv; $H_2PO_4^-$, HSO_4^-, Cl^-, Br^-, I^-, NO_3^-, ClO_4^-, SCN^-, N_3^-: 100 equiv) in $CH_3CN–H_2O$ (95:5, v:v).

the absorption spectra of the solution of **1**. 5% vol of water is enough to avoid completely the interference of F^- and AcO^-. When 7.5% vol or 10.0% vol of water was used as solvent, the selectivity of CN^- to F^- and AcO^- became higher, even when F^- and AcO^- were in large excess (Figs. S17 and S18).

To quantitatively study the binding affinity of **1** toward the anions in pure acetonitrile and in water–acetonitrile mixtures, four kinds of anions CN^-, F^-, AcO^-, and $H_2PO_4^-$ were chosen. UV–vis titration experiments were done by addition of aliquots of various anions to the solution of **1**. The association constants[17] are collected in Table 1. We can see that in pure CH_3CN, **1** interacts strongly with the four kinds of anions ($K > 10^4$). With the increase of the proportion of water, the binding constants for F^-, and AcO^-, $H_2PO_4^-$ are sharply reduced. While that for cyanide remains relatively high. The results are in agreement with the above qualitative analysis.

Both the selectivity and sensitivity are important for a sensor. As stated above, sensor **1** can recognize cyanide with high selectivity when the proportion of water is more than 5%. To determine the sensitivity of sensor **1** in practical application, the detection limit in water–acetonitrile (Fig. S19) mixtures and in corresponding pure water was calculated (Fig. 5). We can see from Figure 5 that when the proportion of water in water–acetonitrile is between 2.5% and 5.5%, the detection limit in corresponding pure water is most high, even below 5 μM. This means sensor **1** can detect cyanide in pure water sample at very low concentration, which makes sensor **1** a powerful tool for the detection of cyanide in practical application.

In summary, we have developed a Disperse Orange **3**-based chemosensor for the 'naked-eye' detection of cyanide in aqueous environment with high selectivity and sensitivity. Our method is safe, fast, simple to use and allows the detection of cyanide in pure water at a very low concentration (below 5 μM).

Table 1
Binding constants[a] of **1** with cyanide in the presence of different proportion of water in acetonitrile–water mixtures

% H_2O[b]	CN^-	F^-	AcO^-	$H_2PO_4^-$
0	—[c]	—[c]	5.6×10^5	1.5×10^4
2.5	7.7×10^4	3.6×10^3	1.6×10^3	3.3×10^2
5.0	2.1×10^4	6.4×10	3.0×10^2	4.4×10
7.5	7.1×10^3	—[d]	1.4×10^2	—[d]
10.0	2.8×10^3	—[d]	6.3×10	—[d]

[a] Errors are estimated to be <15%.
[b] % of water in acetonitrile–water mixtures (v:v).
[c] Too large to be determined.
[d] Not determined due to negligible spectra changes.

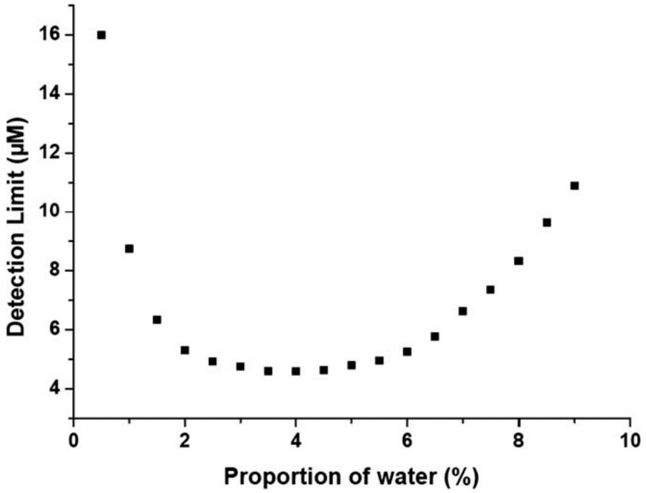


Figure 5. The corresponding detection limit of **1** in pure water for cyanide in the presence of different proportion of water in acetonitrile–water mixtures.

Acknowledgments

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Supplementary data

Experimental details, UV–vis titration spectra, colorimetric studies, and detection limit studies are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.115.

References and notes

1. *Supramolecular Chemistry of Anions*; Bianchi, A., Bowman-James, K., Garcia-España, E., Eds.; Wiley-VCH: New York, USA, 1997.
2. (a) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609; (b) Beer, P. D. *Acc. Chem. Res.* **1998**, *31*, 71; (c) Fabbrizzi, L.; Licchelli, M.; Pallavicini, P. *Acc. Chem. Res.* **1999**, *32*, 846; (d) Fabbrizzi, L.; Licchelli, M.; Rabaioli, G.; Taglietti, A. *Coord. Chem. Rev.* **2000**, *205*, 85; (e) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 487; (f) Lavigne, J. J.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **2001**, *40*, 3118; (g) Martínez-Máñez, R.; Sancenón, F. *Chem. Rev.* **2003**, *103*, 4419; (h) Kubik, S.; Reyheller, C.; Stüwe, S. *J. Inclusion Phenom. Macrocycl. Chem.* **2005**, *52*, 137; (i) Bowman-James, K. *Acc. Chem. Res.* **2005**, *38*, 671; (j) Gale, P. A. *Acc. Chem. Res.* **2006**, *39*, 465; (k) Anzenbacher, P., Jr.; Nishiyabu, R.; Palacios, M. A. *Coord. Chem. Rev.* **2006**, *250*, 2929; (l) Katayev, E. A.; Ustynyuk, Y. A.; Sessler, J. L. *Coord. Chem. Rev.* **2006**, *250*, 3004; (m) Niu, H.-T.; Yin, Z.; Su, D.; Niu, D.; Ao, Y.;

He, J.; Cheng, J.-P. *Tetrahedron* **2008**, *64*, 6300; (n) Niu, H.-T.; Yin, Z.; Su, D.; Niu, D.; He, J.; Cheng, J.-P. *Dalton Trans.* **2008**, 3694; (o) Niu, H.-T.; Su, D.; Jiang, X.; Yang, W.; Yin, Z.; He, J.; Cheng, J.-P. *Org. Biomol. Chem.* **2008**, *6*, 3038.

3. Muir, G. D. *Hazards in the Chemical Laboratory*; The Royal Chemical Society: London, 1977.
4. Ishii, A.; Seno, H.; Watanabe-Suzuki, K.; Suzuki, O.; Kumazawa, T. *Anal. Chem.* **1998**, *70*, 4873.
5. Vennesland, B.; Comm, E. E.; Knownles, C. J.; Westly, J.; Wissing, F. *Cyanide in Biology*; Academic Press: London, 1981.
6. Ullmann's Encyclopedia of Industrial Chemistry, 6th ed.; Wiley-VCH, New York, 1999.
7. Cyanide: Soc., Ind., Econ. Aspects, Proc. Symp. Annu. Meet., Miller, G. C.; Pritsos, C. A., 2001, 73.
8. (a) Kim, Y.-H.; Hong, J.-I. *Chem. Commun* **2002**, 512; (b) Liu, H.; Shao, X.-B.; Jia, M.-X.; Jiang, X.-K.; Li, Z.-T.; Chen, G.-J. *Tetrahedron* **2005**, *61*, 8095; (c) Chow, C.-F.; Lam, M. H. W.; Wong, W.-Y. *Inorg. Chem.* **2004**, *43*, 8387; (d) Zelder, F.-H. *Inorg. Chem.* **2008**, *47*, 1264; (e) Zeng, Q.; Cai, P.; Li, Z.; Qin, J.; Tang, B. Z. *Chem. Commun* **2008**, 1094.
9. (a) Badugu, R.; Lakowicz, J. R.; Geddes, C. D. *J. Am. Chem. Soc.* **2005**, *127*, 3635; (b) Ros-Lis, J. V.; Martínez-Máñez, R.; Sato, J. *Chem. Commun.* **2005**, 5260; (c) Todd, W.; Gabbaï, F. P. *J. Am. Chem. Soc.* **2007**, *129*, 3635.
10. (a) Jin, W. J.; Fernández-Argüelles, M. T.; Costa-Fernández, J. M.; Sanz-Medel, A. *Chem. Commun.* **2005**, 883; (b) Touceda-Varela, A.; Stevenson, E. I.; Galve-Gasión, J. A.; Dryden, D. T. F.; Mareque-Rivas, J. C. *Chem. Commun.* **2008**, 1998.
11. (a) Ros-Lis, J. V.; Martínez-Máñez, R.; Sato, J. *Chem. Commun.* **2002**, 2248; (b) Kim, Y. K.; Lee, Y.-H.; Lee, H.-Y.; Kim, M. K.; Cha, G. S.; Ahn, K. H. *Org. Lett.* **2003**, *5*, 4003; (c) Tomasulo, M.; Raymo, F. M. *Org. Lett.* **2005**, *7*, 4633; (d) Chung, Y. M.; Raman, B.; Kim, D.-S.; Ahn, K. H. *Chem. Commun.* **2006**, 186; (e) Yang, Y.-K.; Tae, J. *Org. Lett.* **2006**, *8*, 5721; (f) Tomasulo, M.; Sortino, S.; White, A. J. P.; Raymo, F. M. *J. Org. Chem.* **2006**, *71*, 744; (g) Chen, C.-L.; Chen, Y.-H.; Chen, C.-Y.; Sun, S.-S. *Org. Lett.* **2006**, *8*, 5053; (h) Lee, K. S.; Lee, J. T.; Hong, J.-I.; Kim, H.-J. *Chem. Lett.* **2007**, *36*, 816; (i) Sessler, J. L.; Cho, D.-G. *Org. Lett.* **2008**, *10*, 73; (j) Lee, K. S.; Kim, H.-J.; Kim, G.-H.; Shin, I.; Hong, J.-I. *Org. Lett.* **2008**, *10*, 49; (k) Ekmekci, Z.; Yilmaz, D.; Akkya, E. U. *Org. Lett.* **2008**, *10*, 461; (l) Miyaji, H.; Kim, D.-S.; Chang, B.-Y.; Park, E.; Park, S.-M.; Ahn, K. H. *Chem. Commun.* **2008**, 753; (m) Kwon, S. K.; Kou, S.; Kim, H. N.; Chen, X.; Hwang, H.; Nam, S.-W.; Kim, S. H.; Swamy, K. M. K.; Park, S.; Yoon, J. *Tetrahedron Lett.* **2008**, *49*, 4102.
12. Chung, Y.; Lee, H.; Ahn, K. H. *J. Org. Chem.* **2006**, *71*, 9470.
13. (a) Sun, S. S.; Lees, A. J. *Chem. Commun.* **2000**, 1687; (b) Miyaji, H.; Sessler, J. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 154.
14. Gimeno, N.; Li, X.; Durrant, J. R.; Vilar, R. *Chem. Eur. J.* **2008**, *14*, 3006.
15. Anzenbacher, P., Jr.; Tyson, D. S.; Jursíková, K.; Castellano, F. N. *J. Am. Chem. Soc.* **2002**, *124*, 6232.
16. Schmidtke, S. J.; Underwood, D. F.; Blank, D. A. *J. Phys. Chem. A* **2005**, *109*, 7033.
17. (a) Conners, K. A. *Binding Constants, The Measurement of Molecular Complex Stability*; Wiley-VCH: New York, 1987; (b) Bourson, J.; Pouget, J.; Valeur, B. *J. Phys. Chem.* **1993**, *97*, 4552.