JOC*Note*

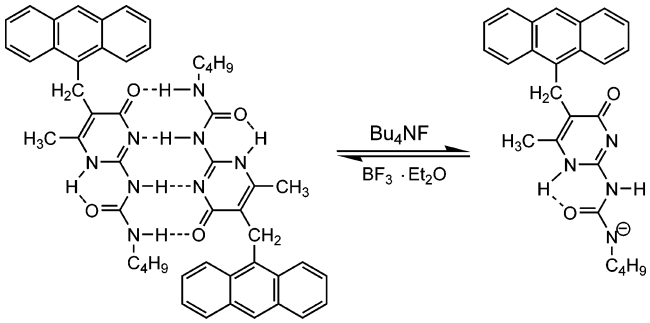
First Fluorescent Sensor for Fluoride Based on 2-Ureido-4[1*H*]-pyrimidinone Quadruple Hydrogen-Bonded AADD Supramolecular Assembly

Yao-Peng Zhao,[†,‡] Chun-Chang Zhao,[†,‡] Li-Zhu Wu,*[,‡] Li-Ping Zhang,[‡] Chen-Ho Tung,*[,‡] and Yuan-Jiang Pan[§]

Technical Institute of Physics and Chemistry, Chinese Academy of Sciences and Graduate University of Chinese Academy of Sciences, Beijing 100101, China, and the Department of Chemistry, Zhejiang University, Hangzhou 310027, China

lzwu@mail.ipc.ac.cn; chtung@mail.ipc.ac.cn

Received September 15, 2005



A simple, highly selective, neutral, fluorescent sensor for fluoride anions is reported. It is based on 2-ureido-4[1*H*]-pyrimidinone quadruple hydrogen-bonded AADD supramolecular assembly, and its assembling and disassembling processes are also able to respond to external stimuli reversibly.

Anion sensing is a current research interest from various disciplines. Among all anion sensors, those for the fluoride ion are of particular importance in revealing a number of biological processes, disease states, and environmental pollution.[1−4] Over the past decade, various elegant examples of fluoride receptors, including imidazole ion, bi-imidazolate diamides, dipyrrolequinoxaline, indolocarbazoles, pyrroles or their derivatives, and urea or thiourea receptors,[3−7] have been reported. In particular, the neutral anion receptors embracing the hydrogen-donor urea group have been extensively studied,[3−5] in which the NH-anion hydrogen bond or anion-induced deprotonation of the NH groups was observed. To gain an insight into hydrogen-bond formation and neat proton transfer existing in the anion recognition process, Fabbrizzi et al. have investigated various colorimetric anion receptors containing NH binding sites and demonstrated that the deprotonation trend is enhanced by the increase of the acidity of the hydrogen-bond donors and basicity of the anions.[4] As the smallest and the most electronegative atom, the fluoride ion shows very high affinity toward the N−H fragments of receptors containing a urea subunit and allows N−H deprotonation.

Since 1998, self-complementary, quadruple, hydrogen-bonded homodimers have received a lot of attention.[8−10] Particularly, the 2-ureido-4[1*H*]-pyrimidinone AADD (A = acceptor of the hydrogen bonding, D = donor of the hydrogen bonding) binding module developed by Meijer and Sijbesma[8a] has shown extensive applications in assembling supramolecular oligomers and polymers.[8a−d] The complementary four hydrogen bonds simplify the synthesis to just one molecule and avoid problems of the exact stoichiometry of heterodimers. At the same time, the feature of self complementary also makes it difficult to disassemble, specifically as a result of its high dimerization constants of 10^7-10^8 M^{-1} in chloroform.

In this note, we report such a novel neutral receptor **1** for fluoride on the basis of the 2-ureido-4[1*H*]-pyrimidinone

† These two authors contributed equally.

‡ Technical Institute of Physics and Chemistry, Chinese Academy of Sciences and Graduate University of Chinese Academy of Sciences.

§ Zhejiang University.

(1) Tomich, J. M.; Wallace, D.; Henderson, K.; Mitchell, K. E.; Radke, G.; Brandt, R.; Ambler, C. A.; Scott, A. J.; Grantham, J.; Sullivan, L.; Iwamoto, T. *Biophys. J.* **1998**, *74*, 256−267.

(2) (a) Lehn, J.-M. *Supramolecular Chemistry, Concepts and Perspectives*; VCH: Weinheim, Germany, 1995. (b) *Supramolecular Chemistry of Anions*; Bianchi, A., Bowman-Jameo, K., Garcia-Espana, E., Eds.; Wiley-VCH: New York, 1997.

(3) (a) Fabbrizzi, L.; Licchelli, M.; Rabaioli, G.; Taglietti, A. *Coord. Chem. Rev.* **2000**, *205*, 85−108. (b) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486−516. (c) Gale, P. A. *Coord. Chem. Rev.* **2001**, *213*, 79; **2003**, *240*, 1−226. (d) Martinez-Manez, R.; Sancenón, F. *Chem. Rev.* **2003**, *103*, 4419−4476. (e) Davis, A. P.; Wareham, R. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 2978−2996.

(4) (a) Gómez, D. E.; Fabbrizzi, L.; Licchelli, M. *J. Org. Chem.* **2005**, *70*, 5717−5720. (b) Boiocchi, M.; Del Boca, L.; Gómez, D. E.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *Chem.−Eur. J.* **2005**, *11*, 3097−3104. (c) Boiocchi, M.; Del Boca, L.; Gómez, D. E.; Fabbrizzi, L.; Licchelli, M.; Nonzani, E. *J. Am. Chem. Soc.* **2004**, *126*, 16507−16514.

(5) (a) Cho, E. J.; Ryu, B. J.; Lee, Y. J.; Nam, K. C. *Org. Lett.* **2005**, *7*, 2607−2609. (b) Xu, G. X.; Tarr, M. A. *Chem. Commun.* **2004**, 1050−1051. (c) Cho, E. J.; Moon, J. W.; Ko, S. W.; Lee, J. Y.; Kim, S. K.; Yoon, J.; Nam, K. C. *J. Am. Chem. Soc.* **2003**, *125*, 12376−12377. (d) Kim, S. K.; Yoon, J. *Chem. Commun.* **2002**, 770−771. (e) Fang, L.; Chan, W. H.; He, Y. B.; Kwong, D. W. J.; Lee, A. W. M. *J. Org. Chem.* **2005**, *70*, 7640−7646. (f) Otón, F.; Tarraga, A.; Espinosa, A.; Velasco, M. D.; Bautista, D.; Molina, P. *J. Org. Chem.* **2005**, *70*, 6603−6608.

(6) (a) Curiel, D.; Cowley, A.; Beer, P. D. *Chem. Commun.* **2005**, 236−238. (b) Peng, X. J.; Wu, Y. K.; Fan, J. L.; Tian, M. Z.; Han, K. L. *J. Org. Chem.* **2005**, *70*, 10524−10531. (c) Kang, J. M.; Kim, H. S.; Jang, D. O. *Tetrahedron Lett.* **2005**, *46*, 6079−6082. (d) Anzenbacher, P., Jr.; Palacios, M. A.; Jursiková, K.; Margnez, M. *Org. Lett.* **2005**, *7*, 5027−5030. (e) Zhang, X.; Guo, L.; Wu, F.-Y.; Jiang, Y.-B. *Org. Lett.* **2003**, *5*, 2667−2670.

(7) (a) Mizuno, T.; Wei, W.-H.; Eller, L. R.; Sessler, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 1134−1135. (b) Anzenbacher, P., Jr.; Jursíková, K.; Sessler, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 9350−9351. (c) Blake, C. B.; Andrioletti, B.; Try, A. C.; Ruiperez, C.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 10438−10439. (d) Miyaji, H.; Anzenbacher, P., Jr.; Sessler, J. L.; Bleasdale, E. R.; Gale, P. A. *Chem. Commun.* **1999**, 1723−1724. (e) Chmielewski, M. J.; Charon, M.; Jurczak, J. *Org. Lett.* **2004**, *6*, 3501−3504.

(8) (a) Sijbesma, R. P.; Meijer, E. W. *Chem. Commun.* **2003**, 5−16 and references therein. (b) Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W.; Sijbesma, R. P. *Chem. Rev.* **2001**, *101*, 4071−4098. (c) Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761−6762. (d) Corbin, P. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9710−9711.

(9) (a) Rispens, M. T.; Sánchez, L.; Knol, J.; Hummelen, J. C. *Chem. Commun.* **2001**, *2*, 161−162. (b) Sánchez, L.; Rispens, M. T.; Hummelen, J. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 838−840. (c) Söntjens, S. H. M.; van Genderen, M. H. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2000**, *122*, 7487−7488.

(10) (a) Wang, X. Z.; Li, X. Q.; Shao, X. B.; Zhao, X.; Deng, P.; Jiang, X. K.; Li, Z. T.; Chen, Y. Q. *Chem.−Eur. J.* **2003**, *9*, 2. (b) Zhao, C. C.; Tong, Q. X.; Li, Z.-T.; Wu, L.-Z.; Zhang, L.-P.; Tung, C.-H. *Tetrahedron Lett.* **2004**, *45*, 6807−6811. (c) Zhao, C. C.; Wu, L. Z.; Zhang, L.-P.; Tung, C.-H. *Chin. J. Chem.* **2004**, *22*, 1391−1394.

10.1021/jo051932u CCC: $33.50
Published on Web 01/28/2006

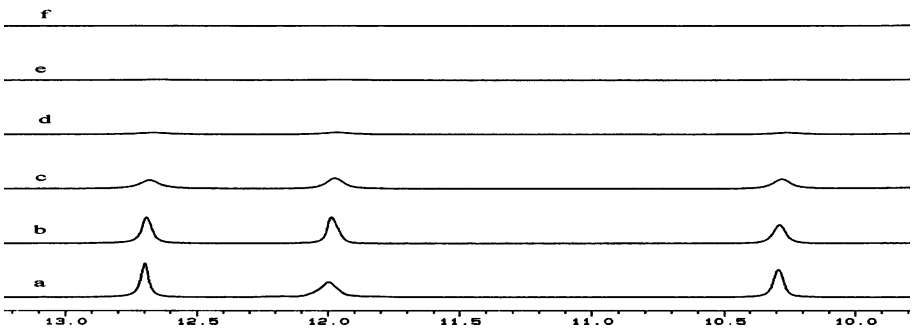


FIGURE 1. Partial ^{1}H NMR spectra of the assembly **1.1** (8.1 μmol) in the absence and presence of fluoride ions in $CDCl_3$. (a) 0; (b) 2.7 μmol; (c) 5.4 μmol; (d) 8.1 μmol; (e) 10.8 μmol; (f) 13.5 μmol.

quadruple hydrogen-bonded AADD supramolecular assembly. 9-Methlyene anthracene appended to the 2-ureido-4[1*H*]-pyrimidinone is designed to provide fluorescence spectral sensing of the recognition event. As expected, the simple anthracene chromophore can operate as an efficient fluorescence sensor for fluoride anions. From the fluorescence titration experiments, the association constant for fluoride was calculated as 13 200 M^{-1} in dichloromethane solution. Other halide ions cause almost no changes in fluorescence when interacting with the sensor molecule **1**. As a result, its selectivity for fluoride is more than 1000 times higher than that of other halide anions. More importantly, owing to the N−H deprotonation occurrence, the disassembling of the AADD receptor **1.1** is taking place. Its assembling and disassembling processes were able to respond to external stimuli reversibly.

Compounds **1**−**4** were synthesized according to the literature method[10b] and described in Supporting Information.

The ^{1}H NMR spectrum reveals that compound **1** exists as assembly **1.1** in $CDCl_3$. As shown in Figure 1a, the large downfield shift for the N−H protons provides direct evidence of the involvement of strong hydrogen bonding. Their AADD hydrogen-bonding motif was determined by NOESY spectrum (Supporting Information). No other binding modes were observed. The dilution of compound **1** solutions in $CDCl_3$ to 1×10^{-5} M did not lead to an observable dissociation, indicating the lowest estimation of the binding constant of 1×10^7 M^{-1}, which is in good agreement with the value for a similar compound.[7]

The crystal structure further confirms that compound **1** exists as an AADD assembly. Single crystals of **1** were obtained by the vapor diffusion of chloroform into the mixture of $CHCl_3$/C_2H_5OH (9:1) solution of **1**. A colorless, single-plate crystal with dimensions $0.32 \times 0.38 \times 0.42$ mm^3 in a glass capilliary was used for data collection at 293 K on a Bruker Smart 1000 X-ray diffractometer. The molecular structure and perspective drawing of compound **1** are depicted in Figure 2. The crystal belongs to the monoclinic crystal system of centrosymmetric space group *P*2(1)/*c* with unit cell parameters of $a = 22.013(6)$ Å, $b = 12.712(4)$ Å, $c = 19.506(6)$ Å; $\alpha = 90$ degrees, $\beta = 103.427(5)$ degrees, $\gamma = 90$ degrees. Important bond lengths and angles are given in Table 1. The urea functionality is in a trans−trans conformation, and an intramolecular hydrogen bond is present from the pyrimidine N−H to the urea carbonyl group [N(2)−H(2A)···O(2), N(6)−H(6A)···O(4)], which results in a preorganized AADD array of hydrogen-bonding sites. Anthryl groups are arranged side-by-side and are bridged by this AADD building block. Similar to the Meijer and Sijbesma observation,[8a] the outer N−H···O hydrogen bonds are 0.21 Å shorter than the inner N−H···N hydrogen bonds, leading to a slight deviation from linearity of the 4[1*H*]-pyrimidinone form.

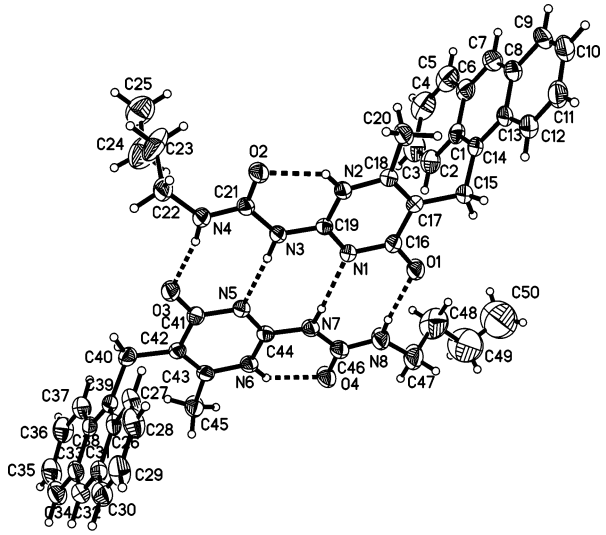


FIGURE 2. Perspective drawing of assembly **1.1** with atomic numbering.

TABLE 1. Important Bond Distances (Å) and D−H−A Angles for Assembly 1.1

D−H···A	d(D−H)	d(H···A)	d(D···A)	angle(D−H−A)
N(2)−H(2A)···O(2)	0.86	1.91	2.573(5)	133.0
N(3)−H(3A)···N(5)	0.86	2.12	2.975(6)	171.5
N(4)−H(4A)···O(3)	0.86	1.90	2.753(5)	168.8
N(6)−H(6)···O(4)	0.86	1.90	2.570(5)	133.7
N(7)−H(7A)···N(1)	0.86	2.12	2.971(6)	172.0
N(8)−H(8)···O(1)	0.86	1.90	2.734(6)	161.6

The changes in the fluorescence response of **1.1** toward fluoride ions were found to be unique. Figure 3 gives the family of fluorescence spectra taken in the course of a titration. In the absence of fluoride ions, the fluorescence spectrum showed three typical bands of anthracene at 397, 420, and 445 nm, respectively. With the addition of less than 1 equiv of fluoride into the dichloromethane solution of **1.1**, the fluorescence intensity was slightly decreased (Figure 3a). However, the introduction of a further amount of fluoride ions into the CH_2Cl_2 solution of **1.1** led to the fluorescence quenching dramatically when excited at 260 nm, while the shape and energy remained unchanged. The lifetime of the excited state for the fluorescence band at 400 nm was consistent at 6.5 ns no matter whether fluoride ions presented or not, suggesting that the fluorescence quenching is static in nature. In other words, the formed complex of **1** and the fluoride anion is actually nonemissive. On the other hand,

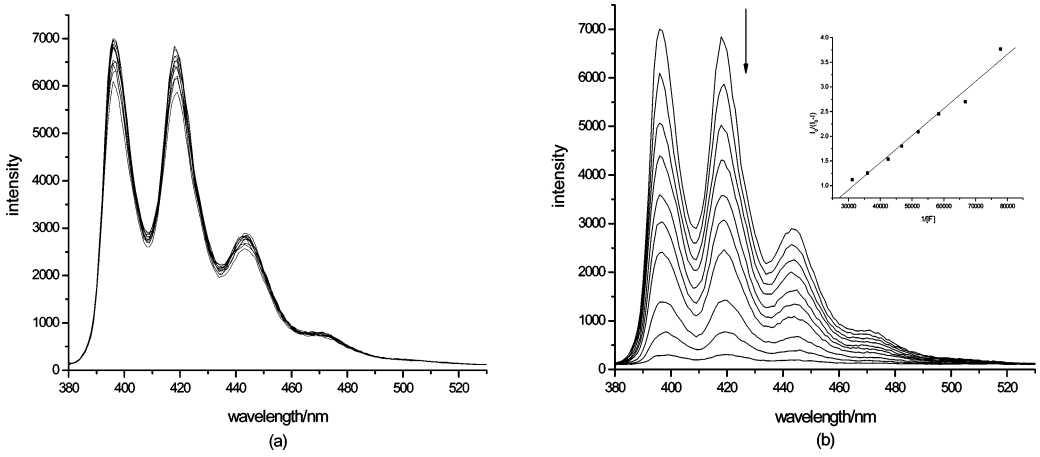


FIGURE 3. (a) Fluorescence spectra of assembly **1.1** (10.3 μM) in CH_2Cl_2 as a function of added fluoride ions. [Bu_4NF]: a, 0; b, 1.1 μM; c, 2.1 μM; d, 3.2 μM; e, 4.3 μM; f, 5.4 μM; g, 6.4 μM; h, 7.5 μM; i, 8.6 μM; j, 9.6μM; k, 10.7 μM. (b) [Bu_4NF]: a, 0; b, 10.7 μM; c, 12.8 μM; d, 15.0 μM; e, 17.1 μM; f, 19.3 μM; g, 21.4 μM; h, 23.5 μM; i, 27.8 μM; j, 32.1 μM; k, 40.7 μM. The inset gives the titration curve by the plot of the fluorescent intensity at 418 nm vs the concentration of Bu_4NF.

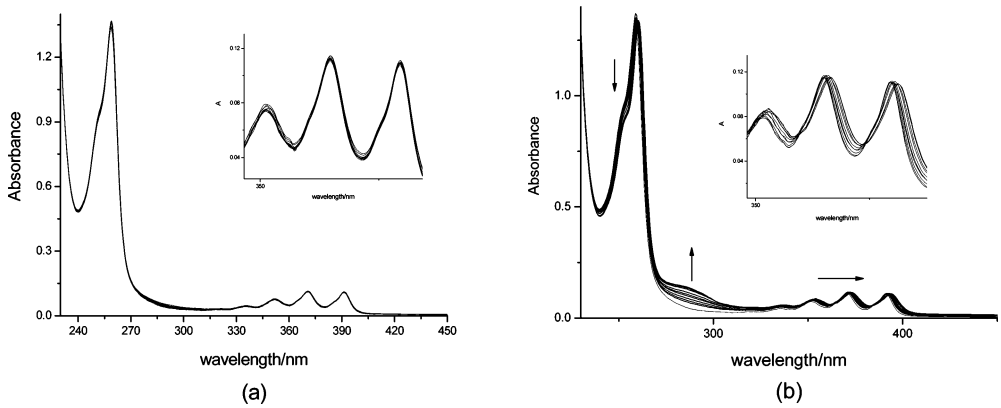


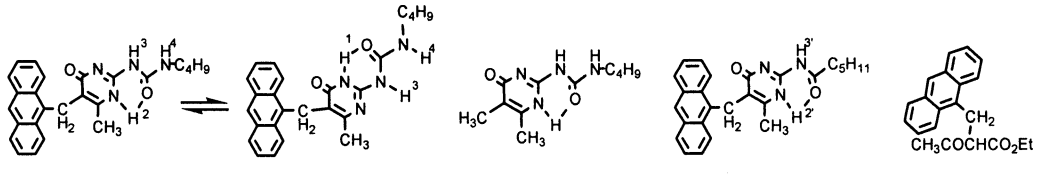
FIGURE 4. Absorption spectra of assembly **1.1** (10.3 μM) in CH_2Cl_2 as a function of added fluoride ions, available as the butylamine salt. (a) [Bu_4NF]: a, 0; b, 1.1 μM; c, 2.1 μM; d, 3.2 μM; e, 4.3 μM; f, 5.4 μM; g, 6.4 μM; h, 7.5 μM; i, 8.6 μM; j, 9.6μM; k, 10.7 μM. (b) [Bu_4NF]: a, 0; b, 10.7 μM; c, 12.8 μM; d, 15.0 μM; e, 17.1 μM; f, 19.3 μM; g, 21.4 μM; h, 23.5 μM; i, 27.8 μM; j, 32.1 μM; k, 40.7 μM.

no quenching was observed when titrated with a high concentration of Cl^-, Br^-, and I^-, respectively, ruling out a quenching by the heavy-atom effect. The inset in Figure 3(b) shows the plot of $I_0/(I_0 - I)$ versus $1/[F^-]$, where I_0 and I refer to the fluorescence intensity at 418 nm of assembly **1.1** in the absence and presence of fluoride ions. The plot yields a satisfactory straight line, confirming that the complexation of the fluoride ions and **1** is in a 1:1 ratio. The binding constant, log *K*, determined from this plot for fluoride, is 4.12 in dichloromethane. However, those for Cl^-, Br^-, and I^- are too small to be accurately determined. Obviously, the neutral receptor **1.1** shows a higher selectivity in CH_2Cl_2 for F^- than other anions, and the binding constant is comparable to the binding constants reported for fluoride detection in the literature.[5−7]

Control experiments with reference compound **4** under the same conditions showed no change in the character of the fluorescence upon the addition of fluoride ions, excluding any interactions between anthracene and fluoride ions. The successive addition of anthracene-free reference compound **2** to the mixture of **1** and F^- led to the observation of a reverse trend in which the fluorescence at 400 nm rises in intensity, indicative of the reversible nature of the anion-binding process. On the basis of the known urea−F^- deprotonation mode [4] developed by Fabbrizzi et al., the observations may be rationalized by the fact that the high charge density and the small size enable fluoride ions to deprotonate the N−H of the urea receptor of **1**, which would in turn render the nitrogen atoms of the urea group much higher in electron density, and therefore, **1.1** shows a high affinity and a more efficient fluorescence quenching for fluoride ions by the photoinduced electron-transfer mechanism.

To shed more light on the interaction of **1** with fluoride anions, detailed UV−vis spectroscopy has also been carried out on the recognition events. A dichloromethane solution of **1.1** was titrated with [Bu_4N]F. Different patterns are also observed in the titration ranges of 0−1 and 1−4 equiv of fluoride ions. Figure 4 displays the absorption spectra of assembly **1.1** (1.03×10^{-5} M) in dichloromethane as a function of added fluoride ions, available as the butylamine salt. Upon the addition of 0−1 equiv of F^- to the solution of **1.1**, the band at 280 nm was slightly developed, but almost no change was observed at higher wavelengths (Figure 4a). However, when approaching 1 equiv of F^-, the decrease in the absorption band at 240−260 nm was accompanied by a growth in the band at 270−310 nm. In addition, an ~2 nm red shift of anthracene absorption bands at 335, 350, 370, and 390 nm was observed in Figure 4b. An isobestic point was also presented at 260 nm, indicative of the presence of only two absorbing species in the solution, **1.1** and the complex **[1·F]**$^-$. The identical UV−vis spectral changes observed in the titration experiment with [Bu_4N]OH (Figure S5) as that with fluoride ions confirm that the N−H deprotonation

SCHEME 1. Structures of Monomers 1 and Compounds 2−4



1 4[1*H*]-pyrimidinone "4-keto" **1** 6[1*H*]-pyrimidinone "6-keto" **2** **3** **4**

is taking place, which is signaled by the appearance of a new absorption band at a long wavelength. From the results of the UV−vis spectra and the fluorescence titration, we can conclude that the interaction between **1.1** and fluoride involves a two-step process; at low fluoride concentration, the interaction is the authentic hydrogen bonding, and with the increase of the fluoride concentration, excess fluoride ions interact with the hydrogen-bonded complex and induce the deprotonation of **1**. Similar results were absent upon the addition of Br^- and I^-, despite very small changes at 270−310 nm, which were also reflected in the absorption spectrum upon the addition of Cl^-. Thus, the deprotonation may be due to the very high stability of the $[HF_2]^-$ complex, whose formation allows N−H deprotonation. With respect to F^-, other halide anions are unable to form a stable HX_2^- complex.[4]

The interaction between the fluoride and the assembly **1.1** was further evidenced by a ^{1}H NMR investigation. Figure 1 gives the ^{1}H NMR spectral changes of **1.1** with the addition of the fluoride ion. The signals for the N−H protons at 10.44 (H^4), 11.97 (H^3), and 12.85 (H^2) decreased dramatically in association with fluoride ions. With 1.2 equiv of fluoride ions, the N−H proton signals, including both the intermolecular hydrogen bonding of two N−H groups of urea and intramolecular hydrogen bonding from pyrimidine N−H to the urea carbonyl group, disappeared completely. However, with bromide and iodide ions, there were no chemical shift changes for the N−H peaks, even when up to 10 equiv of these anions were used. To confirm the interactions between the fluoride and the urea moiety, the chemical shift changes of the N−H protons in compound **3**, where H^4 was absent, were also assessed. DMSO-d_6 was used as an alternative solvent for a more detailed ^{1}H NMR study to exclude any effects caused by the complementary quadruple hydrogen-bonded interactions. A comparison of the chemical shift data of the compounds reported by Meijer and Sijbesma [8a] suggested that compound **1** adopted the monomeric 6[1*H*]-pyrimidinone "6-keto" form in DMSO-d_6, as shown in Scheme 1. The signals for the N−H protons at H^1 (11.75 ppm), H^3 (9.52 ppm), and H^4 (7.22 ppm) decreased dramatically in association with fluoride ions, while the chemical shift remained unchanged. With 0.3 equiv of fluoride ion, the H^4 of the urea group first disappeared, and then the N−H proton signals for H^1 vanished completely when 0.6 equiv of fluoride ion were employed. In contrast, the chemical shift changes of the N−H protons in compound **3** differed significantly when compared with those in a DMSO-d_6 solution of **1**. With the titration of fluoride ions into the DMSO-d_6 solution, the two specific N−H proton signals at 12.02 ($H^{2'}$) and 11.44 ppm ($H^{3'}$) gradually merged together to form a wide peak at 11.98 ppm. A ^{1}H NMR spectral analysis of **1** and **3** highlights key differences in the chemical shifts upon the addition of fluoride anions, which indicates that fluoride binding to compound **1** at a urea receptor indeed takes place.

It is noteworthy that the spectral changes described above are fully reversible upon the addition of $BF_3{\cdot}Et_2O$ in dichloromethane. In fact, the isobestic point listed in the absorption spectrum was maintained during the titration with $BF_3{\cdot}Et_2O$. There was no difference when the fluoride ion was added to an assembly **1.1** solution or when $BF_3{\cdot}Et_2O$ was added to a complex $\mathbf{[1{\cdot}F]^-}$ solution, suggesting that compound **1** is not decomposing and can be reversibly changed. At the same time, the fluorescence behavior of **1.1** also displays an interesting $BF_3{\cdot}Et_2O$ dependence. As mentioned above, $\mathbf{[1{\cdot}F]^-}$ is nonemissive in fluid solution. When $BF_3{\cdot}Et_2O$ is titrated into the solution of $\mathbf{[1{\cdot}F]^-}$ in CH_2Cl_2, three typical bands of anthracene grow in at 397, 420, and 445 nm, without any shift in the wavelength of the emission band. Furthermore, the process is completely reversible with the addition of fluoride quenching the fluorescence.

In summary, the assembling and disassembling processes of 2-ureido-4[1*H*]-pyrimidinone quadruple hydrogen-bonded AADD supramolecular assembly **1.1** are able to respond to fluoride ions reversibly. The simple anthracene chromophore can operate as an efficient fluorescence sensor for fluoride anions with a selectivity 1000 times higher than that of the other halide anions. This work provides a new approach for disassembling a highly stable AADD supramolecular oligomer or polymer. Further exploring of the spectroscopic properties of this attractive complementary assembly is being performed in our laboratory.

Acknowledgment. Financial support from the Ministry of Science and Technology of China (Grant Nos. 2004CB719903, 2003CB716802), the National Science Foundation of China (Nos. 20125207, 20333080, 20332040), and Chinese Academy of Sciences is gratefully acknowledged.

Supporting Information Available: Experimental section, synthesis and characterization of compounds **1**−**4**, crystal structure data (CIF), NOESY spectrum of **1.1** in $CDCl_3$, the fluorescence spectra of **1.1** in the presence of F^-, Cl^-, Br^-, and I^-, the absorption and fluorescence spectra of **1.1** in the presence of OH^-, the fluorescence spectra of the formed complex $\mathbf{[1{\cdot}F]^-}$ in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2, the whole ^{1}H NMR spectra of **1.1** in the absence and presence of fluoride ions in $CDCl_3$, ^{1}H NMR spectra of compounds **1** and **3** in the absence and presence of fluoride ions in DMSO-d_6, and ESI-MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051932U