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A novel fluoride sensor based on fluorescence enhancement

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A novel halide sensor, which yields greater fluorescence upon binding to fluoride, has been synthesized and characterized.

Anion sensing has been of interest to chemists for many years, and the detection of simple anions in biological systems is highly desirable.[1] Recently, considerable efforts have been devoted to fluorescence anion sensing due to its simplicity and low detection limit.[2] Typically the sensors offer sites suitable for anion binding through amine/guanidinium groups or amide groups and function through fluorescence quenching mechanisms, such as PET (photo-induced electron transfer).[3] Different halides are distinguished by either different magnitudes of binding constants and/or different unit response.[4] For example, chloride is biologically prevalent and important. Fluorescence chloride sensors, such as SPQ (6-methoxy-*N*-3′-sulfopropylquinolinium) and lucigenin, were developed decades ago and new sensors are continuously reported.[5] However, since the underlying mechanism is fluorescence quenching, these systems are susceptible to static and collisional quenching by non-analyte species which are prevalent and unavoidable in biological systems.[6] Consequently, the accuracy of previously developed fluorescent probes for anions is poor.[7]

Here we first report a novel sensor for fluoride which yields increased fluorescence upon binding to fluoride. Other halide ions cause slight decreases in fluorescence when interacting with the sensor molecule. Synthesis details, fluorescence-based binding data, results of computer modeling with Spartan PC, and a possible mechanism are offered. Further study on this novel sensor could lead to the synthesis of other sensors that respond selectively to chloride with increased fluorescence. Such a sensor would offer a new choice for chloride detection with good selectivity and minimized interferences from quenching. Meanwhile, fluoride ion itself is an important analyte in medical applications such as dental care and the treatment of osteoporosis.[8]

Sensor **1** [1,8-bis(phenylureido)naphthalene] and analog **2** [2,3-bis(phenylureido)naphthalene] (Fig. 1) were readily synthesized from diaminonaphthalene and phenyl isocyanate.†

Because of the low solubility of both compounds in $CDCl_3$ or acetone-d_6, NMR data were obtained in DMSO-d_6, and each peak was assigned based on the COSY spectrum. Figure 2 shows the NMR spectrum of sensor **1** and illustrates spectral shifts with addition of fluoride and chloride. Upon the addition of two equiv. chloride, the NH protons shifted downfield, but showed no significant decrease in signal. In contrast, upon the addition of fluoride, the NH proton signals decreased significantly. With 0.50 equiv. fluoride, the NH proton signal almost completely disappeared due to broadening. These changes indicate that fluoride binding to sensor **1** is occurring and that the kinetics of fluoride exchange are on the NMR timescale.

Fluorescence experiments were carried out in the polar organic solvent mixture of DMSO–acetonitrile (4 : 6 v/v). Figure 3 shows changes in fluorescence emission spectra with addition of halides.

The fluorescence intensity of **1** increased with increasing fluoride concentration. In contrast, the other halide ions caused small decreases in the fluorescence of **1**. The binding constant for fluoride (1 : 1) with **1** was determined to be 73,650 M^{-1}. The binding constants for chloride, bromide and iodide were found to be 690, 345 and 76 M^{-1}, respectively.

To study the underlying reasons for the changes in fluorescence, we synthesized the analog molecule **2**. Fluorescence experiments with **2** indicated quenching effects with all four halides, including

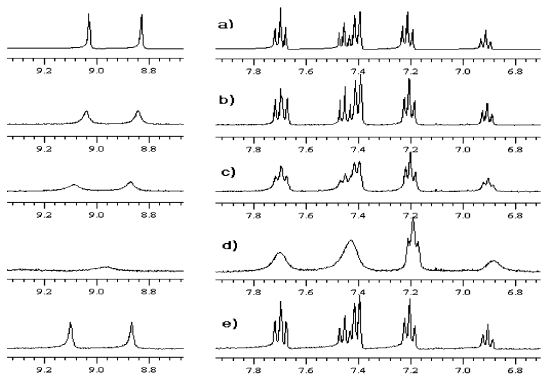

Fig. 2 ^{1}H NMR (400 MHz) spectra of sensor **1** (1 mM) in DMSO-d_6. a) Sensor **1** only; b) **1** + 0.10 equiv. tetraethylammonium fluoride; c) **1** + 0.25 equiv. tetraethylammonium fluoride; d) **1** + 0.50 equiv. tetraethylammonium fluoride; e) **1** + 2.0 equiv. tetraethylammonium chloride.

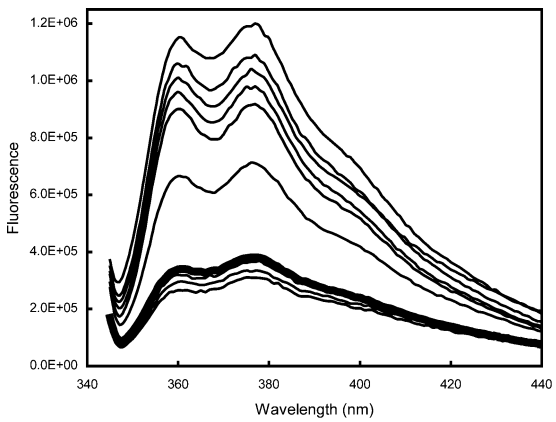

Fig. 3 Fluorescent emission spectra of sensor **1** upon addition of halides. Solvent was DMSO–acetonitrile (4 : 6 v/v). The thick line is for sensor **1** only (5 μM). The lines above are with addition of fluoride (2, 5, 10, 15, 20, and 30 equiv. from bottom to top), and the lines below in order from top to bottom are with 5 equiv. chloride, bromide and iodide, respectively.

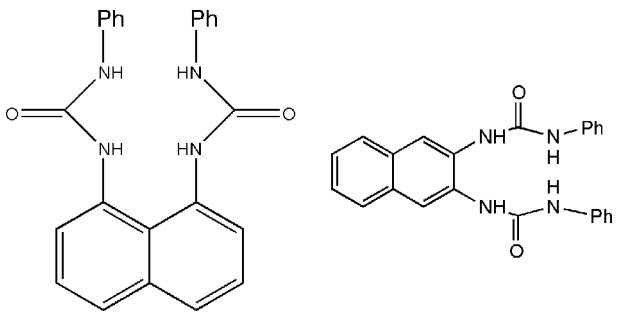

Fig. 1 Structure of sensor **1** (left) and analog **2**.

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fluoride. Since sensor **1** and molecule **2** have the same functional groups but different locations of the two urea groups, the different response to halides must result from the different relative positions of the urea groups. We performed computer modeling with energy minimization using Spartan PC. Figure 4 shows the different results for sensor **1** with fluoride and iodide (chloride and bromide gave results similar to iodide). Upon binding to fluoride, the molecule becomes more planar, which likely contributes to the increased fluorescence. The chloride, bromide, and iodide complexes do not exhibit the same degree of planarity. Furthermore, these larger ions have much weaker binding and are good fluorescence quenchers, which may offset any increase in fluorescence due to geometry changes.

The modeling results show that the fluoride ion fits well in the space between the two urea groups in **1**, although it is slightly out of the naphthalene plane. The fluoride interacts strongly with NH, as indicated by the NMR data. The space between the urea groups cannot accommodate the larger chloride, bromide and iodide species, making them less likely to interact with the NH groups. The in-plane binding of fluoride could contribute to fluorescence enhancement through formation of a near planar structure. A number of fluorophores exhibit rapid intramolecular quenching through redistribution of internal energy into various twisted conformations.[9] Sensor **1** likely undergoes such quenching through rotation around the C–N bond between the naphthalene ring and the urea linkage. Tight binding of fluoride through hydrogen bonding likely increases the activation barrier between twisted conformations, thereby increasing the stability of the photoexcited state. Such stabilization of the excited state upon binding of fluoride would result in increased fluorescence. In contrast, the larger chloride, bromide, and iodide species have very week binding to sensor **1**, and are therefore incapable of significantly stabilizing the excited state.

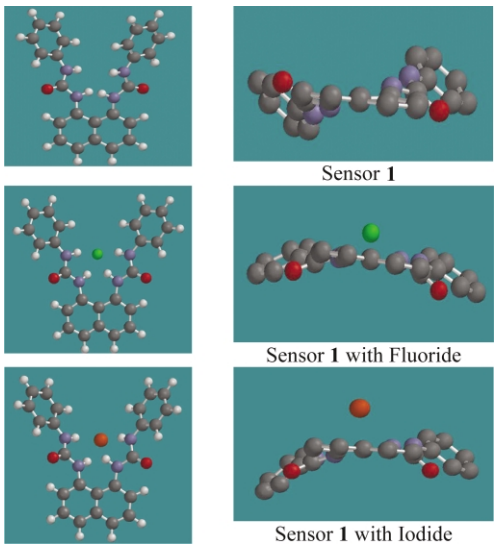

Fig. 4 Computer modeling (Spartan PC) with energy minimization. Top, sensor **1**; Middle, sensor **1** with fluoride; Bottom, sensor **1** with iodide (for clarity, hydrogens are omitted in images on right).

Previously reported halide sensors function by fluorescence quenching mechanisms. The newly reported sensor provides a novel method for ion sensing which may alleviate current problems with quenching based sensors. Furthermore, the selectivity of the sensor for fluoride makes it useful in systems with other anions present.

Notes and references

† Synthesis of 1,8-bis(phenylureido)naphthalene (sensor **1**). 0.10 g (0.63 mmol) 1,8-diaminonaphthalene was dissolved in 10 mL dry dichloromethane and 0.15 g (1.26 mmol) phenyl isocyanate was added. A white precipitate formed. The precipitate was filtered and washed with 5 mL dichloromethane and 5 mL acetone to yield analytically pure molecule **1** in 82% yield (0.20 g), mp 298 °C. ^{1}H NMR (DMSO-d_6): δ 9.02 (s, 2H), 8.82 (s, 2H), 7.71 (d, 2H, J = 8.0), 7.69 (d, 2H, J = 8.0), 7.44 (t, 2H, J = 8.0), 7.41 (d, 4H, J = 8.0), 7.22 (t, 4H, J = 8.0). ^{13}C NMR (DMSO-d_6): δ 153.29, 139.90, 135.60, 133.90, 128.55, 125.35, 124.98, 122.26, 121.61, 118.28. Calculated elemental composition: 72.71% C, 5.08% H, 14.13% N; measured elemental composition: 72.42% C, 5.04% H, 14.12% N. Analog **2** was synthesized in a similar manner: 50 mg (0.32 mmol) 2,3-diaminonaphthalene in 10 mL dry dichloromethane was mixed with 75 mg (0.63 mmol) phenyl isocyanate and stirred at room temperature overnight. The product was washed with 5 mL dichloromethane and 5 mL acetone. Yield was 70% (80 mg), mp 276 °C. ^{1}H NMR (DMSO-d_6): δ 9.15 (s, 2H), 8.26 (s, 2H), 8.16 (s, 2H), 7.79 (dd, 4H, J = 3.0), 7.51 (d, 4H, J = 8.0), 7.39 (dd, 4H, J = 3.0), 7.30 (t, 4H, J = 8.0), 6.98 (t, 2H, J = 8.0). ^{13}C NMR (DMSO-d_6): δ 153.77, 140.17, 130.88, 130.67, 129.37, 127.37, 125.55, 122.45, 120.61, 118.63. Calculated elemental composition: 72.71% C, 5.08% H, 14.13% N; measured elemental composition: 71.93% C, 5.04% H, 13.87% N.

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