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Sulfoxides as Response Elements for Fluorescent Chemosensors

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Supporting Information

ABSTRACT: Sulfoxides are shown to be viable reporting groups for fluorescent chemosensor development. Metal coordination of sulfoxide-appended fluorophores suppresses excited-state pyramidal inversion of the sulfoxide, leading to enhanced fluorescence emission. This new structural motif allows the construction of fluorescent chemosensors that do not require nitrogen coordination as part of the signaling process, that have a range of selectivities and affinities for oxophilic metal ions, and that can function in water.

Chemosensors that provide a fluorescence response to reversible metal ion binding have broad potential application for biological, medical and environmental analyses.[1] Numerous approaches to chemosensor development have been described, but the most common involve coordination to the lone pair of a nitrogen atom attached to a proximal fluorophore such that fluorescence emission is altered upon metal binding.[2] As effective as this approach has been, it possesses limitations such as acid sensitivity and direct dependence of the fluorescence response on nitrogen coordination chemistry. The discovery of new, non-amine signaling motifs thus broadens the scope and potential impact of chemosensor development.

We describe the first use of sulfoxides as reporting functional groups for the development of metal-responsive fluorescent chemosensors. Sulfoxides have low intrinsic affinities and selectivities for metal ion coordination,[3] explaining in part why they have not previously been studied as chemosensor response elements.[4] Despite this, we find that pyrenyl sulfoxides exhibit enhanced emission upon metal binding, that the metal binding properties of these chemosensors can be readily altered by structural variation of the sulfoxide probe (Figure 1), and that such probes can function in water.[5]

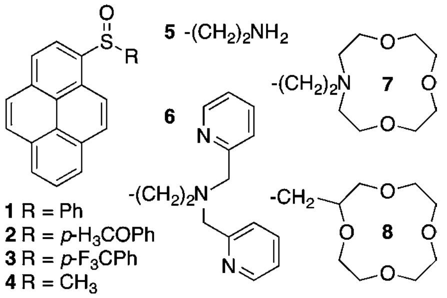

Figure 1. Sulfoxide fluorescent chemosensors **1**–**8**.

Sulfoxides **1**–**8** have optical properties very similar to those of pyrene, except that they have significantly lower quantum yields (Table 1). While **1**–**4** have limited metal ion affinity, their optical properties are instructive. Titrations of **5**–**8** with various metal ions in CH_3CN reveal their efficacy as fluorescent chemosensors (Table 2).

Table 1. Optical Properties of 1–8[a]

	$\varepsilon/10^{3b}$	ϕ^c		$\varepsilon/10^{3b}$	ϕ^c
1	35.5	0.011	**5**	31.1	0.009
2	39.7	0.006	**6**	27.6	0.004
3	35.9	0.053	**7**	28.5	0.003
4	34.7	0.012	**8**	27.5	0.015

[a] All spectra measured in CH_3CN. Emission spectra acquired at 10 μM. Longest λ absorption/excitation maxima 349–352 nm; emission maxima 377–381 nm. [b] M^{-1} cm^{-1}. [c] Absolute quantum yields.

Table 2. log(K_d) and I/I_0 for Titrations of 4–8[a,b,c]

	Li^+	Na^+	Mg^{2-}	Ca^{2+}	Zn^{2+}
4	−0.8	–	−2.6	−2.5	−1.4
	(13)[d]		(33)	(26)	(36)
5	−2.0	–	−5.7	−5.7	−5.3
	(33)		(44)	(42)	(48)
6	−5.2	−2.5	−5.7	−5.9	−5.3
	(78)	(20)	(174)	(145)	(213)
7	−5.9	−4.0	−6.6	−6.4	−5.5
	(90)	(39)	(140)	(140)	(160)
8	−2.1	−2.6	−3.6	−5.7	−1.9
	(5)	(3)	(27)	(27)	(26)

[a] Titrations in CH_3CN at 10 μM (**4**) or 0.5 μM (**5**–**8**) chemosensor. [b] K_d in M. I/I_0 in parentheses. [c] Entries marked – indicate binding too weak to allow K_d determination. [d] K_d estimated from titrations that did not reach saturation.

The low quantum yields of **1**–**8** are in keeping with the established deactivation of aryl sulfoxide excited states by pyramidal inversion of the sulfoxide.[6] It is believed that the barrier for excited state inversion is greatly reduced by intramolecular charge transfer (ICT) from the sulfoxide to the pendant aryl, which lessens electrostatic repulsions associated with the planar inversion transition state. Consistent with this, in the phenyl pyrenyl series **1**–**3** an electron donating substituent lowers the quantum yield (**1** vs **2**) and an electron

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withdrawing substituent increases the quantum yield (**1** vs **3**): the *p*-H_3CO group facilitates ICT while *p*-F_3C disfavors it.[7]

The quantum yields of these sulfoxides, especially **5**−**8**, can be enhanced by the addition of metal ions, making them viable fluorescent chemosensors. We believe the enhancement is the result of coordination to the sulfoxide oxygen, which withdraws electron density and disfavors the deactivating ICT process. The titration of **4** with $ZnCl_2$ provides representative emission spectra for this effect in the absence of other metal binding functionality (Figure 2). Although the binding is weak (log K_d ~ 0.1 M),[8] the fluorescence enhancement is significant (I/I_0 = 36).[9] The response of **4** to oxophilic metals includes Li^+, Mg^{2+}, and Ca^{2+} and occurs with similar fluorescence enhancement (Table 2). Together, these observations delineate the intrinsic binding affinities of an aryl sulfoxide in CH_3CN. The emission of **4** (10 μM) shows no change in the presence of a 10^3-fold excess of TFA and increases by only a factor of 2.6 in the presence of a ~10^4-fold excess of TFA (0.15 M), a small increase compared to metal-induced emission "turn on."

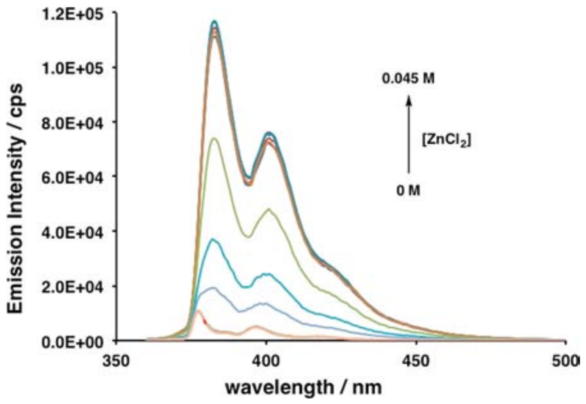

Figure 2. Titration of **4** (10 μM in CH_3CN) with $ZnCl_2$, which is representative.

Appending sulfoxide **4** with more aggressively metal-coordinating groups increases metal affinity and provides a measure of selectivity as well. The simple extension of a methyl substituent to an ethylamino group (**5**) has little influence on quantum yield in the absence of metal ion,[10] but leads to large increases in metal ion affinity (Table 2): while there is still no measurable affinity for Na^+, Li^+ affinity increases by an order of magnitude, and log K_d values for the divalent cations Mg^{2+}, Ca^{2+} and Zn^{2+} are now ≤−5.3. Elaboration to incorporate dipicolyl (**6**) or azacrown (**7**) moieties further increases affinity and leads to the emergence of a response to Na^+,[11] although the affinity for divalent cations remains stronger. The strong interaction of **7** and Mg^{2+} illustrates the limits of the current analytical system: the measured log K_d (−6.6) represents a sub-nM detection limit and the I/I_0 of 140 corresponds to a final quantum yield (ϕ_{max}) of 0.41.

Probe **8** most clearly illustrates two key aspects of this new approach to fluorescence signaling, in that it provides a strong (log K_d = −5.7, I/I_0 = 27, ϕ_{max} = 0.40), selective response to Ca^{2+} with no response to the addition of acid and no requirement that nitrogen be present in the molecule.[12,13]

The quantum yields of the sulfoxides increase in 10% CH_3CN/MOPS buffer (5 mM, pH 7.4), presumably as the result of hydrogen bonding.[14] The quantum yields of **4** and **5** rise to ~0.50 and many of the fluorescence responses seen in CH_3CN simply cannot be observed in aqueous medium. However, this effect is not uniformly overwhelming: the addition of 1.5 equiv of $ZnCl_2$ to **6** (10 μM, ϕ_0 = 0.025 in 10% CH_3CN/5 mM MOPS) still provides a 13-fold fluorescence enhancement with no reduction in apparent affinity (log K_d = −5.3).

These chemosensors are unusual and advantageous in not relying on nitrogen coordination to provide the fluorescence response: while protonation of **5**−**7** in acidic media is expected to impact metal binding, it will not produce an increase in fluorescence emission as a false positive. The oxophilic coordination properties of sulfoxides are distinct from, and less well described than, those of other functional groups routinely used in small molecule chemosensors. The ability to use sulfoxides to report metal-binding events is unprecedented, and the results described here indicate that the modification of fluorophore and metal recognition domains should provide useful and interesting probes that function in water,[15] with selectivities and affinities complementary to those of known systems.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete experimental details for compound synthesis and optical measurements; copies of ^1H NMR and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For representative reviews of fluorescent chemosensors and probes, see: (a) Formica, M.; Fusi, V.; Giorgi, L.; Micheloni, M. *Coord. Chem. Rev.* **2012**, *256*, 170−192. (b) Cho, D.-G.; Sessler, J. L. *Chem. Soc. Rev.* **2009**, *38*, 1647−1662. (c) Tsukanov, A. V; Dubanosov, A. D.; Bren, V. A.; Minkin, V. I. *Chem. Heterocycl. Compd.* **2008**, *44*, 899−923. (d) Callan, J. F.; de Silva, A. P.; Magri, D. C. *Tetrahedron* **2005**, *61*, 8551−8588. (e) Bell, T. W.; Hext, N. M. *Chem. Soc. Rev.* **2004**, *33*, 589−598. (f) Rurack, K.; Resch-Genger, U. *Chem. Soc. Rev.* **2002**, *31*, 116−127. (g) Bren, V. A. *Russ. Chem. Rev.* **2001**, *70*, 1017−1036. (h) de Silva, A. P.; Gunarathe, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 515.

(2) The majority of amine-based fluorescent chemosensors are based on modulation of photoinduced electron transfer (PET) or intramolecular charge transfer (ICT). For overviews of PET-based fluorescent chemosensors, see: (a) Bissell, R. A.; de Silva, A. P.; Gunaratne, H. Q. N.; Lynch, P. L. M.; Maguire, G. E. M.; McCoy, C. P.; Sandanayake, K. R. A. S. *Top. Curr. Chem.* **1993**, *168*, 223−264. (b) da Silva, A. P.; Uchiyama, S. *Top. Curr. Chem.* **2011**, *300*, 1−28. For an overview of ICT signaling, and other approaches, see:

(c) Demchenko, A. P. *Introduction to Fluorescence Sensing*; Springer Science: London, 2009; Chapter 6; see also ref 1.

(3) For reviews of sulfoxide metal coordination, see: (a) Calligaris, M. *Coord. Chem. Rev.* **2004**, *248*, 351−375. (b) Calligaris, M.; Carugo, O. *Coord. Chem. Rev.* **1996**, *153*, 83−154.

(4) For previous mention of the response of phenyl pyrenyl sulfoxide in CH_2Cl_2 to added metal ions, see: Malashikhin, S.; Finney, N. S. *J. Am. Chem. Soc.* **2008**, *130*, 12846−12847.

(5) See Supporting Information.

(6) For fundamental studies on the photochemistry of aryl sulfoxides, see: (a) Vos, B. W.; Jenks, W. S. *J. Am. Chem. Soc.* **2002**, *124*, 2544−2547. (b) Cubbage, J. W.; Jenks, W. S. *J. Phys. Chem. A* **2001**, *105*, 10588−10595. (c) Lee, W.; Jenks, W. S. *J. Org. Chem.* **2001**, *66*, 474−480. (d) Guo, Y.; Jenks, W. J. *J. Org. Chem.* **1997**, *62*, 857−864. (e) Cooke, R. S.; Hammond, G. S. *J. Am. Chem. Soc.* **1970**, *92*, 2739−2745. (f) Hammond, G. S.; Gotthard, H.; Coyne, L. M.; Axelrod, M.; Rayner, D. R.; Mislow, K. *J. Am. Chem. Soc.* **1965**, *87*, 4959−4960.

(7) We presume that the presence of the *p*-H_3CO group increases the driving force for excited-state ICT, while the *p*-F_3C group diminishes it. (This hypothesis is the subject of ongoing computational study.) The proposed ICT excited state bears resemblance to a sulfoxide radical cation, and we note that single-electron oxidation of enantiomerically enriched aryl sulfoxides dramatically increases rates of sulfoxide racemization: Aurisicchio, C.; Baciocchi, E.; Gerini, M. F.; Lanzalunga, O. *Org. Lett.* **2007**, *9*, 1939−1942.

(8) Binding constants were determined by nonlinear least-squares fitting of plots of emission intensity vs log[M] using the program Prism6 (Graphpad, Inc., San Diego, CA). All ligand/metal complexes were of 1:1 stoichiometry, as determined by the method of continuous variation. See: Connors, , K. A. *Binding Constants*: John Wiley & Sons: New York, **1987**,.

(9) See Supporting Information for additional representative titrations, emission spectra and binding constant determination.

(10) From evaluation of the analogous sulfones, we believe that a small degree of PET quenching from the N lone pair is also occurring in **5**−**7**. However, on the basis of quantum yields of **1**−**4**, significant fluorescent enhancement cannot occur without suppression of the sulfoxide deactivation pathway, and this "sulfoxide-gated PET" signaling cannot be a significant contributor to the observed enhancements.

(11) For a review of bis(2-pyridylmethyl)amines in molecular recognition, see: (a) Kruppa, M.; Koenig, B. *Chem. Rev.* **2006**, *106*, 3520−3560. For an overview of metal ion coordination by crown ether and cryptand species, see: (b) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S. *Chem. Rev.* **1991**, *91*, 1721−2085.

(12) Treatment of **8** (0.5 μM, 90% CH_3CN:H_2O) with up to 10^5 equiv of TFA produces no fluorescence response.

(13) While the present system is almost unique in that oxygen coordination leads to a direct perturbation of the excited state of a single chromophore, it must be mentioned that there are other oxygen coordination-based signaling motifs, such as polyether coordination that leads to changes in the degree of excimer formation between two pendant chromophores, or calixarene coordination events that lead to displacement of a chromophore and a subsequent solvatochromic shift in emission. (See refs 1 and 2.) In what may be regarded as the first designed fluorescent chemosensor, crown ethers containing an integrated naphthalene group were found to respond to metal ion binding via changes in fluorescence: Sousa, L. R.; Larson, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 307−310.

(14) Consistent with the posited H-bonding, sulfoxides are known to protonate selectively at oxygen in the presence of strong acid; see ref 3a.

(15) While our experience has been that aryl sulfoxides are consistently less emissive than the parent aryls, there are exceptions to this trend that provide a cautionary note for fluorophore variation: (a) Christensen, P. R.; Nagle, J. K.; Bhatti, A.; Wolf, M. O. *J. Am. Chem. Soc.* **2013**, *135*, 8109−8112. (b) Dane, E. L.; King, S. B.; Swager, T. B. *J. Am. Chem. Soc.* **2010**, *132*, 7758−7768.