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A new fluorescent chemosensor for iron(III) based on the β-aminobisulfonate receptor

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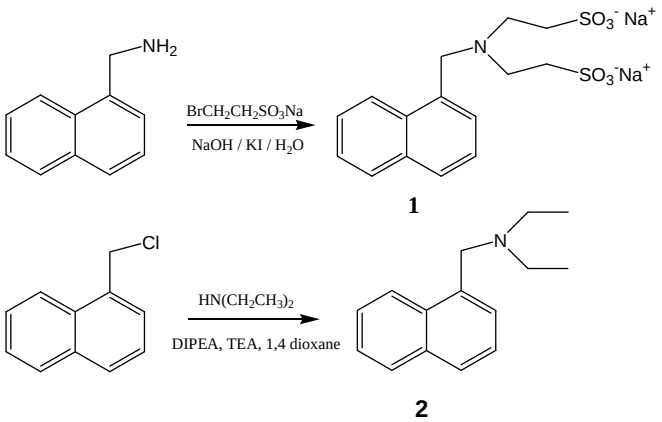
ABSTRACT

A simple fluorescent sensor **1** has been developed for the determination of Fe(III) in 100% aqueous solution at pH 7.0. The sensor comprises a novel aminobisulfonate receptor joined to a naphthalene fluorophore via a methylene spacer in the fluorophore-spacer-receptor format of photoinduced electron transfer (PET) based sensors. The fluorescence emission of the sensor was quenched upon addition of Fe(III) ions, most likely due to electron/energy transfer between Fe(III) and the excited naphthalene. The sensor displayed good selectivity for Fe(III) over other physiologically relevant metal ions and can estimate Fe(III) concentration between 16 and 63 μM. Stern Volmer analysis showed the binding stoichiometry to be 1:1 (host–guest) with a binding constant, calculated using the Benesi–Hilderbrand equation, of $(7.6 \pm 0.6) \times 10^4\ M^{-1}$.

Iron is the most abundant intracellular metal ion and plays a crucial role in a variety of vital cell functions, ranging from oxygen metabolism and electron transfer processes to DNA and RNA syntheses.[1] A surplus of iron, however, induces oxidative damage, rendering the intracellular scavenging of iron a major therapeutic target.[2] Iron chelation therapy was initially designed to alleviate the toxic effects of excess iron evident in iron-overload diseases.[3] Many iron chelators and siderophores (both biotic and artificial) have sulfonate groups present in their structure to aid water solubility, but the role of these groups (sulfonate) for iron binding is rarely investigated.[4] In addition, receptors such as iminodiacetate[5] and β-aminobisphosphonate[6] have been used as the ionophore component of luminescent sensing assemblies and were found to be selective ion binders of Zn(II) and Cu(II), respectively. Therefore, incorporating an aminobisulfonate unit as the receptor component of a luminescent sensor seems a logical progression. Not only should this serve as a site for ion binding, but it should also guarantee the ability of the sensor to operate in 100% aqueous solution.

We have designed sensor **1** according to the fluorophore-spacer-receptor format associated with photoinduced electron transfer (PET) based sensors.[7] This design principle, popularized by de Silva et al., is attractive due to its modular nature. The naphthalene fluorophore was attached via a methylene spacer to the β-aminobisulfonate receptor. In this study, we examine the selectivity of **1** for Fe(III) against a range of other physiologically relevant metal ions and determine the sensitivity range in which it operates (see Scheme 1).

Compound **1** was synthesized in one step by the reaction of 1-aminomethylnaphthalene with sodium 2-bromoethylsulfonate in basic aqueous solution. After refluxing for 18 h the product was isolated following evaporation of the aqueous solution, dissolution of the crude product in hot ethanol, and filtration. The resulting solution was allowed to cool and crystals of **1** were obtained in 56% yield.[8] We also designed compound **2** as a control compound for **1**, in which the ethylsulfonate groups were replaced with simple ethyl chains. Compound **2** was formed by refluxing 1-chloromethylnaphthalene and diethylamine in basic 1,4-dioxane for 18 h. After aqueous work-up, the product was obtained as a brown oil in 84% yield.[9]



Scheme 1.

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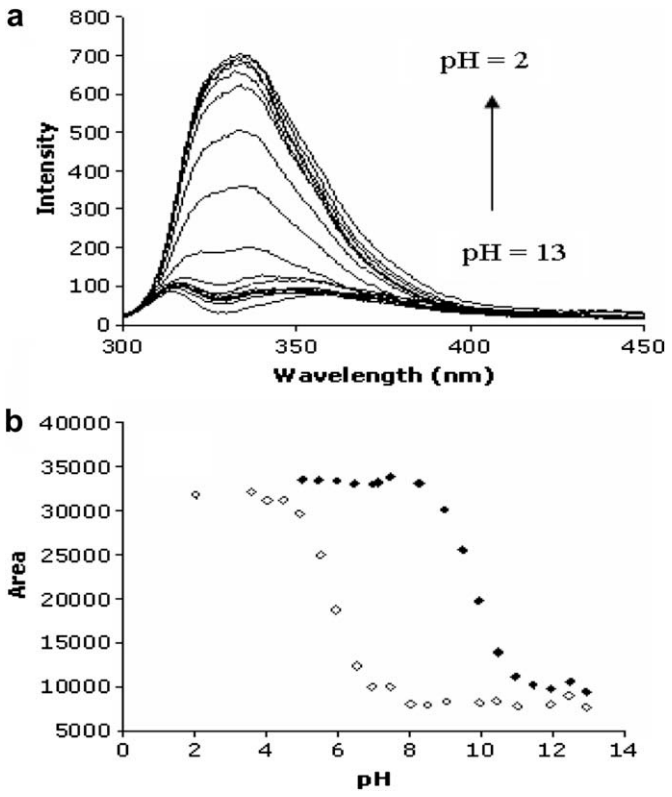

Figure 1. (a) Fluorescence spectra of **1** upon increasing pH, (b) plot of spectral area against pH for **1** (◇) and **2** (♦). [**1**] and [**2**] = 20 μM. λ_{ex} = 280 nm. Solvent = MeOH–H_2O (8:2).

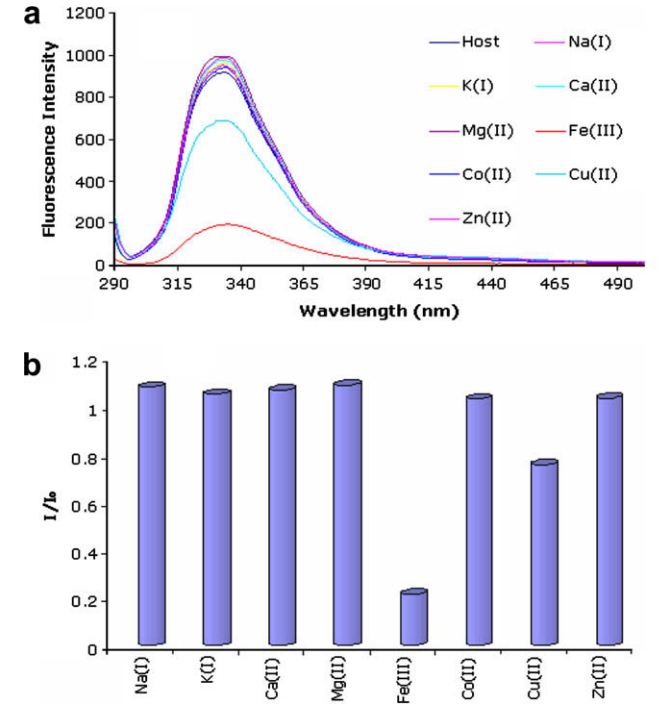

Figure 2. (a) Fluorescence spectra of **1** in the presence of various metal ions and (b) a bar chart of relative intensity against ion for the ions tested in part (a). [**1**] = 2 × 10^{-5} M, [metal ion] = 4 × 10^{-5} M. λ_{ex} = 280 nm, λ_{em} = 335 nm. HEPES buffer (10 mM, pH 7.0 ± 0.1).

The photophysical properties of **1** and **2** were investigated in aqueous solution. Both displayed an absorption at λ_{max} = 280 nm typical of the naphthalene chromophore. When excited at 280 nm, both compounds also displayed typical naphthalenic emission with λ_{max} = 335 nm.[10] There was no evidence of any longer wavelength bands associated with intramolecular exciplex formation between naphthalene and the tertiary amine unit, as has been observed in other similarly constructed systems.[11] However, the emission properties of both **1** and **2** were found to be strongly dependent on solution pH. Figure 1a shows the fluorescent spectra of **1** recorded at different pHs and illustrates that the emission is switched 'On' with decreasing pH. The reason for this is as follows: at high pH, fluorescence emission is low due to PET from the tertiary amine of the aminobisulfonate receptor to the excited naphthalene which quenches fluorescence. At lower pH, the amine nitrogen is protonated, its oxidation potential raised, and the PET process cancelled, which switches fluorescence 'On'. However, the pH range at which the On–Off transition occurs is markedly different for **1** and **2**. From a plot of spectral area against pH, it is clear that both compounds give rise to a sigmoidal profile, with the On–Off transition occurring over approximately 2 log units. This suggests a 1:1 binding stoichiometry between sensor and protons for both **1** and **2** as expected.[12] However, the transition occurs at a much lower pH for **1** than for **2**. This is most likely due to the strong inductive effect the sulfonate groups have on the amine lone pair in **1**, making them less available for binding with a proton and decreasing their pK_a value. Using a plot of $-\log(F_{MAX} - F)/(F - F_{MIN})$ against pH (where F_{MAX} is the maximum fluorescence intensity, F_{MIN} the minimum fluorescence intensity and, F the measured fluorescence intensity), the pK_as for **1** and **2** were calculated to be 5.98 and 9.91, respectively.[13]

The selectivity of **1** was then investigated against a range of physiologically relevant ions, in HEPES-buffered (10 mM) aqueous solution at pH 7.0 ± 0.1. Specifically, Na(I), K(I), Mg(II), Ca(II), Fe(III), Co(II), Cu(II), and Zn(II) were added as their chloride salts to a 20 μM solution of **1**. Figure 2 shows that the addition of Na(I), K(I), Mg(II), Ca(II), Co(II), and Zn(II) resulted in only small

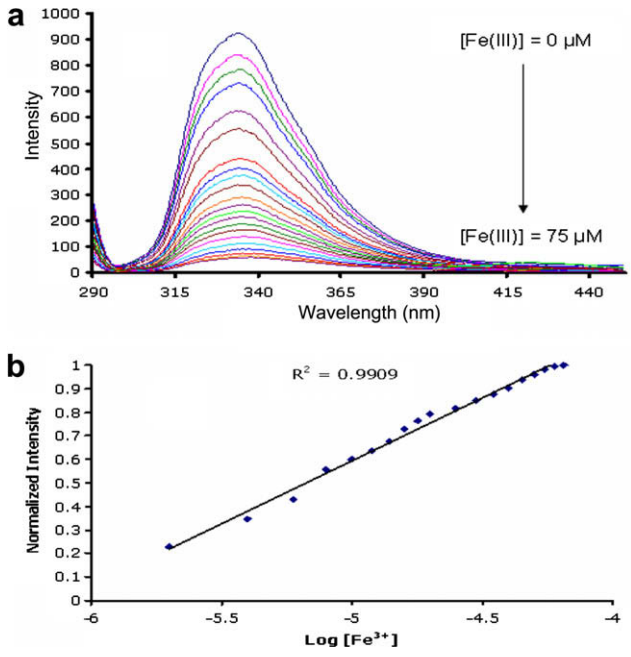

Figure 3. (a) Fluorescence spectra of **1** upon increasing Fe(III) concentration and (b) plot of normalized intensity ($I_{min} - I/I_{min} - I_{max}$) of **1** against concentration for Fe(III). [**1**] = 2 × 10^{-5} M, λ_{ex} = 280 nm. HEPES buffer (pH 7.0 ± 0.1).

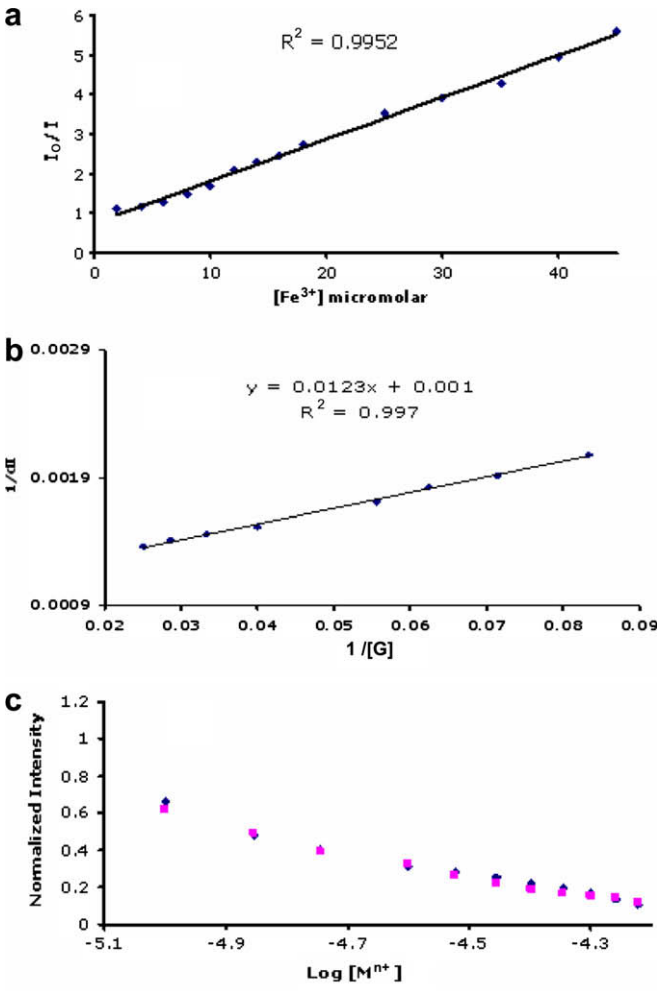

Figure 4. (a) Stern–Volmer plot for **1** in the presence of Fe(III) indicating 1:1 (host–guest) stoichiometry. (b) Benesi–Hilderbrand plot to determine the binding constant between **1** and Fe(III) and (c) plot of normalized fluorescence intensity ($I/I_{min} - I_{max}$) of **1** against metal ion concentration (6.0–60.0 μM) for Fe(III) (♦), and for Fe(III) in the presence of equimolar Cu(II) (■). [**1**] = 2×10^{-5} M, λ_{ex} = 280 nm, λ_{em} = 335, HEPES buffer (pH 7.0 ± 0.1).

changes in the fluorescence profile of **1**, suggesting that they bind only very weakly to this receptor. In contrast, Fe(III) addition resulted in a substantial quenching (~80%) of the original fluorescence intensity with Cu(II) also leading to a quench but of a much smaller magnitude (~20%). The quenching effects caused by Fe(III) and Cu(II) can be explained as it is known that paramagnetic transition metal ions can participate in electron/energy transfer processes with organic fluorophores opening a non-radiative deactivation channel.[7a,d] So, although Fe(III), and to a lesser extent Cu(II), binds to the aminobisulfonate receptor, this binding event is registered as a quench in fluorescence. Although the fluorescence intensity of **1** is low at pH 7.0, its quantum yield (ϕ) of 0.07 at this pH is sufficiently high to make it a potential On–Off fluorescent sensor for Fe(III) in 100% aqueous solution.[14]

To determine the sensitivity range of **1** toward Fe(III), a titration was performed, in which a 20 μM solution of **1** was titrated with Fe(III) in HEPES-buffered (10 mM) solution. Figure 3 shows that upon the continuous addition of Fe(III), the intensity at λ_{max} 335 nm is gradually quenched with no evidence of a shift in wavelength. This is consistent with PET designed sensors where the non-integration of the fluorophore and receptor in the excited state results in no shift in the emission wavelength upon binding the target analyte. When a plot of relative intensity of **1** against Fe(III) concentration was made (Fig. 3b), good linearity was observed in the range 1.6×10^{-5} M to 6.3×10^{-5} M.

The fluorescence quenching interaction between **1** and Fe(III) was further evaluated using the Stern–Volmer equation: $I_o/I = 1 + K_{SV}[Q]$, where I_o is the fluorescence intensity of receptor **1**, I is the fluorescence intensity in the presence of quencher (Q) and K_{SV} is the Stern–Volmer constant, derived for the 1:1 (host/guest) complex.[15] The Stern–Volmer plot, shown in Figure 4a, illustrates an excellent fit in the concentration range between 2.0 and 45.0 μM of Fe(III) indicating that the most abundant complex formed within this range has 1:1 (host/guest) stoichiometry. The binding constant, for **1** and Fe(III), calculated using the Benesi–Hilderbrand equation was found to be $(7.6 \pm 0.6) \times 10^4$ M^{-1} (Fig. 4b).[16]

As illustrated in Figure 2, the only ion of those tested that could interfere with the determination of Fe(III) using **1** was Cu(II). This interference was not unexpected due to the position copper holds in the Irving Williams series, meaning that it is a strong binder to ligands irrespective of their nature or number.[17] To prove that **1** is capable of operating in a competitive environment, we performed a titration in which Cu(II) and Fe(III) were present in equimolar concentration. Figure 4c shows the results of this and the plot illustrates a good fit between the Fe(III) only samples and those containing both Fe(III) and Cu(II). This means the binding affinity of **1** toward Fe(III) is much greater than that between **1** and Cu(II).

In summary, we have developed a novel sensor for the determination of Fe(III) ions in 100% aqueous solution. Indeed, the aminobisulfonate receptor employed not only guarantees aqueous solubility of the probe but is also an efficient receptor for Fe(III). Good linearity was observed for the probe in the concentration range 16–63 μM. Importantly, **1** was capable of measuring Fe(III) concentrations in the presence of equimolar Cu(II). To the best of our knowledge, this is the first reported example of a fluorescent sensor incorporating the aminobisulfonate receptor.

Acknowledgments

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References and notes

1. (a) Lynch, S. R. *Nutr. Rev.* **1997**, *55*, 102–110; (b) Al-Karadaghi, S.; Hansson, M.; Nikonov, S.; Jönsson, B.; Hederstedt, L. *Structure* **1997**, *11*, 1501–1510.
2. (a) Abergel, R. J.; Raymond, K. N. *J. Biol. Inorg. Chem.* **2008**, *13*, 229–240; (b) Mitchell, M. S.; Walker, D. L.; Whelan, J.; Bosnich, B. *Inorg. Chem.* **1987**, *26*, 396–400.
3. Franchini, M.; Veneri, D. *Hemat. J.* **2004**, *5*, 287–292.
4. (a) Binbuga, N.; Hasty, J. K.; Gwaltney, S. R.; Henry, W. P.; Schultz, T. P. *Inorg. Chim. Acta* **2007**, *360*, 2339–2344; (b) Dixon, D. W.; Gill, A. F.; Giribabu, L.; Vzorov, A. N.; Alam, A. B.; Compans, R. W. J. *Inorg. Biochem.* **2005**, *99*, 813–821; (c) MacKay, A. A.; Pignatello, J. J. *Helv. Chim. Acta* **2001**, *84*, 2589–2600; (d) Thomas, F.; Beguin, C.; Pierre, J.-L.; Serratrice, G. *Inorg. Chim. Acta* **1999**, *291*, 148–157; (e) Hoshi, S.; Tomizuka, T.; Enjo, C.; Haga, Y.; Uto, M.; Akatsuka, K. *Anal. Sci.* **1995**, *11*, 729–732; (f) Kappel, M. J.; Raymond, K. N. *Inorg. Chem.* **1982**, *21*, 3437–3442.
5. Gunnlaugsson, T.; Lee, T. C.; Parkesh, R. *Org. Biomol. Chem.* **2003**, *1*, 3265–3267.
6. Kamila, S.; Callan, J. F.; Mulrooney, R. C.; Middleton, M. *Tetrahedron. Lett.* **2007**, *48*, 7756–7760.
7. (a) Fabbrizzi, L.; Poggi, A. *Chem. Soc. Rev.* **1995**, *24*, 197–202; (b) de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515–1566; (c) Martinez-Manez, R.; Sancenon, F. *Chem. Rev.* **2003**, *103*, 4419–4476; (d) Callan, J. F.; de Silva, A. P.; Magri, D. C. *Tetrahedron* **2005**, *61*, 8551–8588.
8. *Characterisation data for* **1**: δ_H (400 MHz, D_2O) 3.20 (4H, m, NCH_2–CH_2), 3.55 (4H, m, NCH_2–CH_2–), 4.70 (2H, s, Ar-CH_2–), 7.46 (1H, t, J = 7.6 Hz, Ar-*H*), 7.52–7.64 (3H, m, Ar-*H*), 7.88–7.98 (3H, m, Ar-H) δ_C (100 MHz, D_2O) 44.7, 49.8, 56.9, 122.3, 124.4, 125.7, 126.8, 127.9, 129.2, 131.2, 131.3, 131.4, 133.6; *m*/*z* (ESMS) 372 (100%) $[M-H]^+$, 237 (10%) HRMS calcd for $C_{15}H_{18}NO_6S_2$ 372.0577; found 372.0579.

9. *Characterisation data for* **2**: δ_H (400 MHz, $CDCl_3$) 0.99 (6H, t, J = 6.2 Hz, 2 × $-CH_3$), 2.49 (4H, m, 2 × $-NCH_2-$), 3.90 (2H, s, Ar-CH_2-), 7.31 (4H, m, Ar-H), 7.50 (1H, d, J = 7.5 Hz, Ar-H), 7.66 (1H, d, J = 7.5 Hz, Ar-H). 7.72 (1H, d, J = 7.5 Hz, Ar-H); δ_C (100 MHz, $CDCl_3$) 11.8, 47.0, 56.3, 124.8, 125.6, 125.9, 127.4, 127.6, 127.8, 128.6, 132.7, 134.0, 135.9; m/z (ESMS) 214 (100%) $[M+H]^+$, 141 (25%); HRMS calcd for $C_{15}H_{20}N$ 214.1596; found 214.1591.
10. Turro, N. J. *Modern Moleuclar Photochemistry*; University Science Books: Sausalito, CA, 1991.
11. Galindo, F.; Becerril, M.; Burgette, I.; Luis, S. V.; Viagra, L. *Tetrahedron Lett.* **2004**, *45*, 1659–1662.
12. Gunnlaugsson, T.; Davis, A. P.; Hussey, G. M.; Tierney, J.; Glynn, M. *Org. Biomol. Chem.* **2004**, *2*, 1856–1863.
13. (a) de Silva, A. P.; Gunaratne, H. Q. N. *J. Chem. Soc., Chem. Commun.* **1990**, 186–188; (b) de Silva, A. P.; Gunaratne, H. Q. N.; Lynch, P. L. M. *J. Chem. Soc., Perkin Trans. 2* **1995**, 685–690.
14. Quantum yield calculated with reference to tryptophan.
15. Mei, X.; Wolf, C. *J. Am. Chem. Soc.* **2004**, *126*, 14736–14737.
16. Benesi, H. A.; Hilderbrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703–2704.
17. Rurack, K. *Spectrochim. Acta A* **2001**, *57*, 2161.