

Difluorobora-*s*-diazaindacene dyes as highly selective dosimetric reagents for fluoride anions

Ali Coskun and Engin U. Akkaya*

Department of Chemistry, Middle East Technical University, 06531 Ankara, Turkey

Received 26 January 2004; revised 5 April 2004; accepted 16 April 2004

Abstract—Difluorobora-*s*-diazaindacene derivatives are shown to report fluoride ions selectively in acetone solutions; both absorption and emission characteristics are drastically altered, and as a result, this hitherto unknown reaction transforms the BODIPY® class of dyes into highly selective chromogenic and dual channel fluorogenic reagents for fluoride.
© 2004 Elsevier Ltd. All rights reserved.

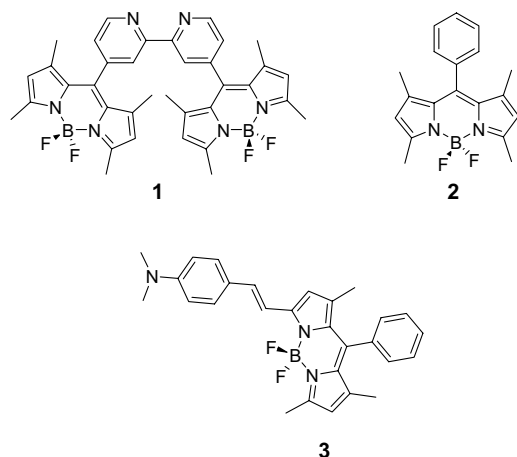
There has been an upsurge of interest in anion recognition and sensing in recent years.¹ Considering the great structural variety and lower surface charge density of anionic species, designing a selective fluorescent chemosensor is a considerable challenge. A wide variety of recognition elements (hydrogen bonding, electrostatic interactions, metal or Lewis acid coordination) and structural motifs (e.g., calixpyrrole, amide, urea and thiourea) have been utilized in synthetic anion receptors. However, coupling of recognition with sensing elements (signal transduction) is required for a chemosensor.² Fluorescence is the preferred type of signal as it offers an essentially zero background alternative to other optical sensors based on absorbance changes. A chemosensor would be even more valuable, if the anion binding would generate another species fluorescing with a different colour on binding, instead of a simple change in intensity at a given wavelength. This is sometimes referred to as dual-channel or wavelength-ratiometric sensing, and is considered to be the instrumental analogue of colour vision.³ A selective fluorescent chemosensor for fluoride is particularly relevant as fluoride sensing is important in areas as diverse as the analysis of drinking water,⁴ detection of chemical warfare agents⁵ and for a better understanding of disease states like fluorosis⁶ and Alzheimer's.⁷ A number of optical⁸ and fluorescent⁹ chemosensors for anions have been reported. The higher charge to size ratio of fluoride is in many cases responsible for the larger signals obtained

for fluoride. Exclusive selectivity is rare, ratiometric sensing is rarer still. While sensing action requires reversibility and fast response times, in some cases this cannot be achieved. Such chromogenic or fluorogenic probes or reagents are still useful and in recent literature, there are examples of both types.¹⁰ One particularly interesting strategy for selective fluoride sensing is exploiting the reactivity of sp² boron centres. Earlier examples of this class of fluoride sensors were first reported by Shinkai and co-workers.¹¹ There are more recent reports of boron-based anion sensors where a hybridization change at the boron centres from sp² to sp³, disrupts the p- π conjugation and generates a signal.¹² In a more elaborate design,¹³ a trianthrylboron moiety is coupled to a porphyrin unit, thus establishing an energy transfer pathway, which is modulated by fluoride binding.

As a part of our ongoing studies on the emission responses of various difluorobora-*s*-diazaindacene derivatives¹⁴ as chemical equivalents of logic gates,¹⁵ we discovered that fluoride binding to the zinc(II) complex¹⁶ of compound **1** had an unexpected emission response, which was not shared by other anions; the emission intensity at the normal emission peak for the dye decreased. Further investigation showed that the parent compound **1** and a simpler boradiazaindacene derivative **2**, in the presence of millimolar fluoride results in absorption and emission spectra distinctly different from that of a typical boradiazaindacene, following an equilibration period. In order to investigate the possibility of extending the fluoride signaling action into the red end of the visible spectrum, we studied the

* Corresponding author. Tel.: +90-312-210-5126; fax: +90-312-210-1280; e-mail: akkaya@metu.edu.tr

fluoride response of a recently reported¹⁷ extended-conjugation boradiazaindacene derivative **3**.



The absorption spectrum of **3** is not sensitive to solvent polarity, but emission shifts to longer wavelengths solvatochromically. Broadening of the emission peak together with decreasing quantum yield is consistent with the charge transfer (CT) character of the emissive state. In acetone, the absorption maximum is at 599 nm ($\epsilon = 81,000 \text{ M}^{-1} \text{ cm}^{-1}$), and the emission maximum is at 686 nm. The quantum yield in acetone is 0.15. The remarkable change in the colour and the emission response of compound **3** in the presence of various anions is shown in Figure 1. Among the anions studied, only the fluoride ion resulted in any change. The blue colour of the solution faded to yield a very faint yellow solution. The time course of the reaction was also studied (Fig. 2). The solution of the dye **3** in acetone in the presence of 2.5 mM tetrabutylammonium fluoride showed a decrease of the major peak at 599 nm with isosbestic points at 447 and 428 nm and the growth of a small peak at 440 nm. The emission spectrum (Fig. 3) showed even more spectacular changes: titration with increasing concentrations of fluoride, following a 30 min

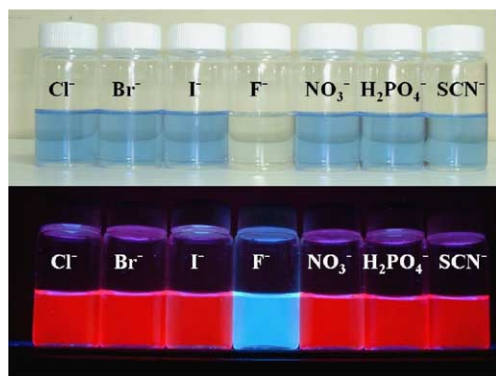


Figure 1. The colour change (under ambient light) and the fluorescence emission response of compound **3** (5 μM) on addition of 2.5 mM anions in the form of tetrabutylammonium salts in acetone. In the lower picture, acetone solutions were irradiated at 360 nm using a hand-held UV lamp.

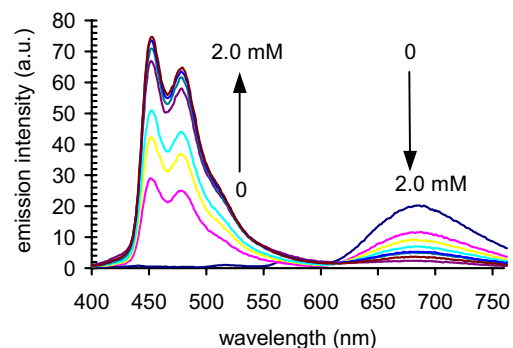


Figure 2. The time course of the reaction of difluoroboradiazaindacene **3** (8.3 μM) with TBAF (2.5 mM) in acetone. The absorbance data were collected for 80 min at 3 min intervals.

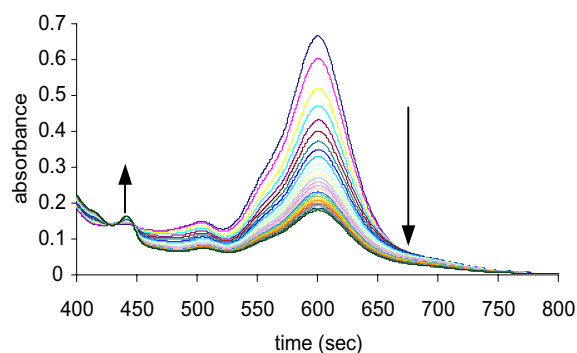


Figure 3. TBAF titration of 1.0 μM **3** in acetone. The emission spectra were obtained by excitation at 390 nm. Slit widths were 5 nm. Fluoride concentrations were 0, 0.25, 0.50, 0.75, 1.0, 1.25, 1.50 and 2.0 mM. Emission data were collected after 30 min of equilibration at 25 °C.

equilibration period, resulted in the disappearance of the emission peak at 686 nm, with a concomitant growth of two new peaks at 452 and 482 nm. Again, the effect was only observed in the case of fluoride and there was no change in the emission spectrum when high concentrations of Cl^- , Br^- , I^- , SO_4^{2-} , NO_3^- , H_2PO_4^- and SCN^- were added, even with longer equilibration times. To test whether the effect was due to, or initiated by, a simple acid base interaction, we added Et_3N to the acetone solution; no change either in the absorption or emission spectrum was observed.

Unlike other anion sensors based on boron reactivity, in compound **3**, boron is already sp^3 hybridized and one possibility seems to be a nucleophilic displacement, breaking a B–N bond and forming a B–F bond. The stronger affinity of fluorine towards boron is apparent when single bond enthalpies are compared (B–F 757 kJ/mol vs B–N 389 kJ/mol).¹⁸ Other alternatives can be proposed; fluoride is a strong base in organic solvents, thus slightly acidic methyl protons at position 7 of the boradiazaindacene system can be abstracted initiating a degradation reaction. Mechanistic details of the process certainly requires further study. In any case, this reaction is only observed in the presence of fluoride, yielding a very selective fluorescent dual-channel reagent with a 235 nm shift in the maxima of the emission peak; prac-

tically from one end of the visible spectrum to the other end. As a bonus, naked eye detection of fluoride is also possible (Fig. 1). The reaction with fluoride is stopped by the addition of an excess of the fluoride scavenger $\text{BF}_3\text{-Et}_2\text{O}$, but is not reversed in acetone.

This hitherto unrecognized fluoride-mediated reaction was observed in compounds **1–3**, but it is not expected to be limited to these particular derivatives. Considering the multitude of boradiazaindacene derivatives synthetically accessible or commercially available (BODIPY® dyes),¹⁹ we believe highly selective fluorescent reagents for a variety of niche applications are likely to appear in due course.

Acknowledgements

This work was supported in part by a Grant from DPT (BAP-01-03-DPT2003K120920-07) and the Turkish Academy of Sciences (TUBA). A.C. thanks the Scientific and Technical Research Council of Turkey (TUBITAK) for a scholarship.

References and notes

- Recent reviews: (a) Snowden, T. S.; Anslyn, E. V. *Curr. Opin. Chem. Biol.* **1999**, *3*, 740–746; (b) Sessler, J. L.; Davis, J. M. *Acc. Chem. Res.* **2001**, *34*, 989–997; (c) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486–516; (d) Best, M. D.; Tobey, S. L.; Anslyn, E. V. *Coord. Chem. Rev.* **2003**, *240*, 3–15; (e) Sessler, J. L.; Camiolo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17–55; (f) Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 191–221.
- (a) Czarnik, A. W. *Chem. Biol.* **1995**, *2*, 423–428; (b) *Chemosensors of Ion and Molecule Recognition*; Desvergne, J. P.; Czarnik, A. W., Eds.; NATO ASI Series, Ser. C492, 1997.
- Tsien, R. Y.; Poenie, M. *Trends Biochem. Sci.* **1996**, *11*, 450–455.
- Frant, M. S.; Ross, J. *Science* **1966**, *154*, 1533–1535.
- Sohn, H.; Letant, S.; Sailor, M. J.; Trogler, W. C. *J. Am. Chem. Soc.* **2000**, *122*, 5399–5400.
- Jentsch, T. *Curr. Opin. Neurobiol.* **1996**, *6*, 303–308.
- Varner, J. A.; Jensen, K. F.; Horvath, W.; Isaacson, R. L. *Brain Res.* **1998**, *784*, 284–298.
- Recent examples: (a) Miyaji, H.; Sato, W.; Sessler, J. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 1777–1780; (b) Lee, D. H.; Lee, K. H.; Hong, J.-I. *Org. Lett.* **2001**, *3*, 5–8; (c) Ward, C. J.; Patel, P.; James, T. D. *Chem. Lett.* **2001**, *5*, 406–407; (d) Mizono, T.; Wei, W.-H.; Eller, L. R.; Sessler, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 1134–1135; (e) Jimenez, D.; Martinez-Manez, R.; Sancenon, F.; Soto, J. *Tetrahedron Lett.* **2002**, *43*, 2823–2825.
- Recent examples: (a) Cooper, C. R.; Spencer, N.; James, T. D. *Chem. Commun.* **1998**, 1365–1366; (b) Anzenbacher, P.; Jursikova, K.; Sessler, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 9350–9351; (c) Gunnlaugsson, T.; Davis, A. P.; Glynn, M. *Chem. Commun.* **2001**, 2556–2557; (d) Liao, J.-H.; Chen, C.-T.; Fang, J.-M. *Org. Lett.* **2002**, *4*, 561–564; (e) Mizukami, S.; Nagano, T.; Urano, Y.; Odani, A.; Kikuchi, K. *J. Am. Chem. Soc.* **2002**, *124*, 3920–3925; (f) Gunnlaugsson, T.; Davis, A. P.; O'Brien, J. E.; Glynn, M. *Org. Lett.* **2002**, *4*, 2449–2452; (g) Aldakov, D.; Anzenbacher, P. *Chem. Commun.* **2003**, 1394–1395; (h) de Silva, A. P.; McClean, G. D.; Pagliari, S. *Chem. Commun.* **2003**, 2010–2011.
- (a) Chae, M. Y.; Czarnik, A. W. *J. Am. Chem. Soc.* **1992**, *114*, 9704–9705; (b) Lewis, P. T.; Davis, C. J.; Cabell, L. A.; He, M.; Read, M. W.; McCarroll, M. E.; Strongin, R. M. *Org. Lett.* **2000**, *2*, 589–592; (c) Ros-Lis, J. V.; Manez-Martinez, R.; Soto, J. *Chem. Commun.* **2002**, 2248–2249.
- (a) Dusemund, C.; Sandanayake, K. R. A. S.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1995**, 333–334; (b) Yamamoto, H.; Ori, A.; Ueda, K.; Dusemund, C.; Shinkai, S. *Chem. Commun.* **1996**, 407–408.
- (a) Yamaguchi, S.; Akiyama, S.; Tamao, K. *J. Am. Chem. Soc.* **2001**, *123*, 11372–11375; (b) Yamaguchi, S.; Shirasaka, T.; Akiyama, S.; Tamao, K. *J. Am. Chem. Soc.* **2002**, *124*, 8816–8817.
- Kubo, Y.; Yamamoto, M.; Ikeda, M.; Takeuchi, M.; Shinkai, S.; Yamaguchi, S.; Tamao, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2036–2040.
- Turfan, B.; Akkaya, E. U. *Org. Lett.* **2002**, *4*, 2857–2859.
- (a) de Silva, A. P.; Fox, D. B.; Moody, T. S.; Weir, S. M. *Pure Appl. Chem.* **2001**, *73*, 503–511; (b) de Silva, A. P.; McClean, G. D.; McClenaghan, N. D.; Moody, T. S.; Weir, S. M. *Nachr. Chem.* **2001**, *49*, 602–660; (c) Brown, G. J.; de Silva, A. P.; Pagliari, S. *Chem. Commun.* **2002**, 2461–2463.
- Coskun, A.; Baytekin, B. T.; Akkaya, E. U. *Tetrahedron Lett.* **2003**, *45*, 5649–5651.
- Rurack, K.; Kollmannsberger, M.; Daub, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 385–387.
- Kerr, J. A. CRC Handbook of Chemistry and Physics 1999–2000: A Ready-Reference Book of Chemical and Physical Data. In *CRC Handbook of Chemistry and Physics*; Lide, D. R., Ed.; 81st ed.; CRC: Boca Raton, Florida, USA, 2000.
- Handbook of Fluorescent Probes and Research Products*, 9th ed.; Haugland, R. P., Ed.; Eugene, Oregon, Molecular Probes, Inc. 2003. BODIPY® is a registered trademark of Molecular Probes, Inc.