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Selective and Sensitive Fluoride Detection through Alkyne Cruciform Desilylation

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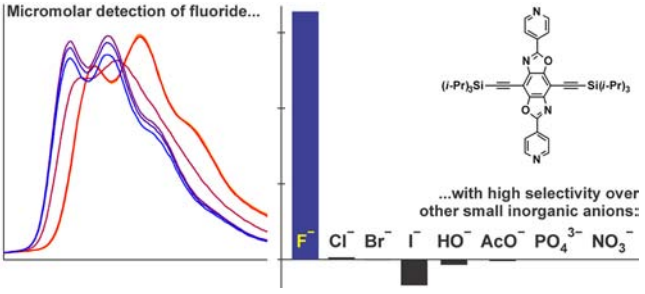
ABSTRACT



Desilylation of silylethynyl-substituted benzobisoxazole cruciforms can be achieved using stoichiometric amounts of fluoride, leading to a significant change in their UV−vis absorption and fluorescence. This response is observable at micromolar concentrations of fluoride, and, in the case of a triisopropylsilyl-substituted cruciform fluorophore, extraordinarily selective for fluoride over other small inorganic anions, including hydroxide, acetate, and phosphate.

During the past decade, cross-conjugated cruciform fluorophores[1] have been explored as versatile sensors for Brønsted and Lewis acids,[1a,2] metals,[3] anions,[4] amines,[4a,5] phenols,[2b] and other analytes. A great majority of these sensing protocols are reversible in nature, based on either coordinative or dynamically covalent interactions. While reversibility generally presents a desirable feature in sensor design, low association constants between the cruciforms and their analytes can limit the sensitivity of analyte detection. Conversely, operation of an irreversible and high-yielding covalent reaction on a cruciform sensor constitutes a pathway for highly sensitive detection, as an analyte needs to be added only in close-to-stoichiometric amounts relative to the highly dilute fluorescent sensor. In this contribution, we illustrate this principle through the first use of benzobisoxazole cruciforms[1b,2b,d,4b,6] as *irreversible, specific, and sensitive sensors* for fluoride.

Fluorine and silicon form a very strong bond (135 kcal mol^{-1}),[7] and thus fluoride-induced desilylation reactions proceed rapidly and irreversibly.[8] Sensing of fluoride ions through the cleavage of O−Si bonds (and the exploration of reactivity of the resultant O−H groups) was achieved by

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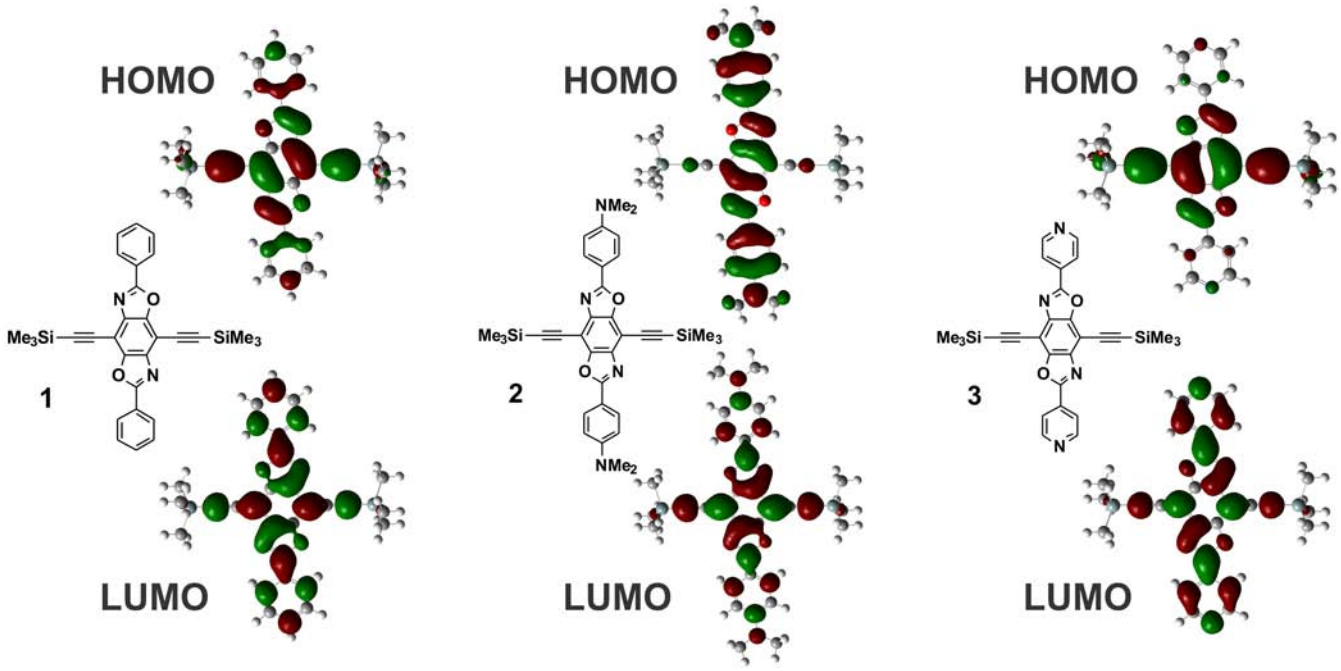
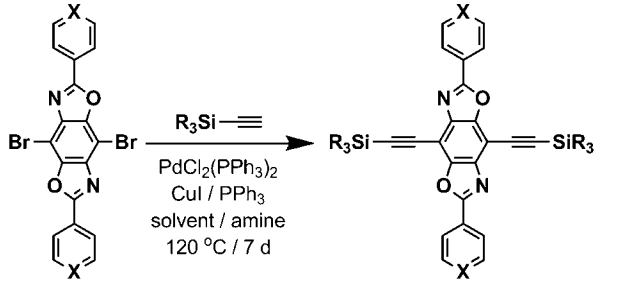


Figure 1. Frontier molecular orbitals (FMOs) of silylated cruciforms **1**–**3**. Spatial separation of FMOs is most pronounced in compound **3**.

Kim and Swager,[9] and subsequently used by other groups, including in the context of physiologically relevant[10] sensing of fluoride in aqueous solutions. We speculated that fluoride could also be sensed by cleaving the C–Si bond in silylated alkynes, and that the resultant change in the electronics of the triple bond would be readily transmitted through the conjugated circuit.

In order to assess the potential of silylated benzobisoxazole cruciforms as fluoride sensors, we first computationally evaluated the frontier molecular orbitals (FMOs) of trimethylsilyl (TMS)-substituted compounds **1**–**3** (Figure 1) using the Gaussian 09W[11] software package at the B3LYP/3-21G level of theory. Graphical representations of highest occupied (HOMOs) and lowest unoccupied molecular orbitals (LUMOs) of **1**–**3** are shown in Figure 1. In phenyl-substituted cruciform **1**, FMOs are largely overlapping, suggesting that desilylation should have a similar effect on both orbitals and thus lead to just a small change in the

Scheme 1. Synthesis of Fluorophores **1**–**3** and **7**



4 X = CH
5 X = C–NMe$_2$
6 X = N

1 X = CH R = Me 42%
2 X = C–NMe$_2$ R = Me 61%
3 X = N R = Me 44%
7 X = N R = *i*-Pr 54%

(8) The strong Si–F bond was also utilized in fluoride detection via the formation of hypervalent silicon complexes. See: (a) Lenormand, H.; Goddard, J. P.; Fensterbank, L. *Org. Lett.* **2013**, *15*, 748–751. (b) Kim, Y.; Kim, M.; Gabbaï, F. P. *Org. Lett.* **2010**, *12*, 600–602. (c) Yamaguchi, S.; Akiyama, S.; Tamao, K. *J. Am. Chem. Soc.* **2000**, *122*, 6793–6794. (d) Tamao, K.; Hayashi, T.; Ito, Y. *J. Organomet. Chem.* **1996**, *506*, 85–91. (e) Jung, M. E.; Xia, H. *Tetrahedron Lett.* **1988**, *29*, 297–300.

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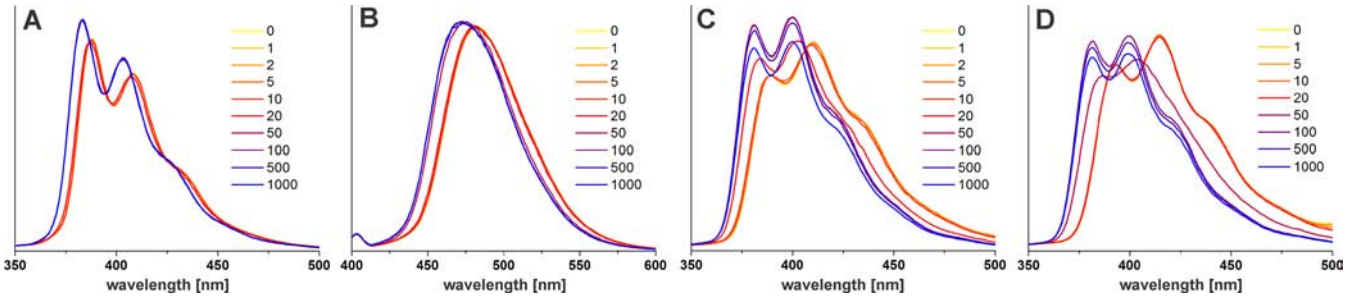

Figure 2. Normalized fluorescence intensity plots for the titrations of 10^{-7} M THF solutions of **1** (A), **2** (B), **3** (C), and **7** (D) with a 10^{-4}–10^{-2} M solution of TBA^+F^-. Excitation wavelengths were 303 nm for **1**, 360 nm for **2**, and 306 nm for **3** and **7**.

HOMO–LUMO gap. Similar situation is observed in cruciform **2** as well; in its case, the two FMOs were mostly positioned along the vertical benzobisoxazole axis but were still largely overlapping. However, in the pyridyl-based compound **3**, spatial separation of FMOs is noticeable: HOMO is positioned along the electron-richer horizontal axis, while the LUMO chiefly resides along the pyridine-bearing vertical axis. This orbital distribution suggested that the desilylation of **3** should impact HOMO and LUMO unevenly and thus constitute the basis of an optical response of cruciform **3** to fluoride addition.

Encouraged by this computational insight, we synthesized TMS-substituted cruciforms **1**–**3**, as well as compound **7**, the triisopropylsilyl (TIPS)-substituted analogue of **3** (Scheme 1). All four silylated cruciforms were expected to desilylate under the influence of fluoride, but cruciform **7** was the only one that was expected to be desilylated *exclusively* with fluoride; compounds **1**–**3** could also be deprotected by hydroxide or other basic species.[12] Starting with brominated benzobisoxazoles **4**–**6** (Scheme 1),[2d] Sonogashira coupling with TMS-acetylene produced corresponding silylated compounds **1**–**3** in moderate yields. Triisopropylsilyl-substituted cruciform **7** was prepared in 54% yield by reacting **6** with TIPS-acetylene. Compounds **1**–**3** and **7** are yellow to dark orange powders, with strong fluorescence in solution.

Optical response of silylated benzobisoxazoles to anions was evaluated by UV–vis absorption and fluorescence spectroscopy. Dilute solutions (10^{-5} M for absorption and 10^{-7} M for fluorescence measurements) of **1**–**3** and **7** in THF were titrated with concentrated solutions (10^{-2} to 10^{-4} M) of tetrabutylammonium fluoride, chloride, bromide, iodide, hydroxide, acetate, phosphate, and nitrate. In Figure 2, fluorescence titration spectra for addition of fluoride are shown. The absorption titration spectra for fluoride and all (absorption and fluorescence) spectra for the titration of **1**–**3** and **7** with other anions are given in the Supporting Information.

Following the addition of fluoride, the fluorescence emission maxima of all four fluorophores underwent a blue shift. This behavior is consistent with the broadening of the HOMO–LUMO gap, which in turn is explained by the dominant stabilization of the HOMO upon desilylation.[13] The emission of compound **1** shifted by approximately −5 nm upon exposure to ~100 equiv of fluoride, and those changes are very similar to those observed upon the addition of hydroxide anion (see Supporting Information). Small changes in absorption and fluorescence can be rationalized through the relatively similar spatial distribution of FMOs of **1**, while the nonspecific response comes from the easy cleavage of the TMS group, which can be deprotected using either hydroxide or fluoride anions. Similarly, compound **2** showed noticeable but relatively small shifts in absorption and fluorescence spectra, and these shifts were induced by fluoride and hydroxide alike.

Cruciforms **3** and **7** exhibited the most diagnostic shifts in absorption (see Supporting Information) and especially fluorescence upon addition of fluoride, with emission maxima shifting by −15 nm in the case of **7**. After the addition of an excess of fluoride (> 50 equiv), the fluorescence profiles of **3** and **7** appeared largely identical, which is logical, as both compounds desilylate to the same terminal diyne.[14]

The crucial difference between **3** and **7** resided in the lability of their silyl groups. Thus, the trimethylsilyl group of **3** can be cleaved with fluoride, but also with hydroxide, acetate, and phosphate, as evidenced by their similar fluorescence titration profiles shown in the Supporting Information.[15] On the other hand, the more stable TIPS protecting group is cleaved only with fluoride (on the time scale of our experiments), and thus only fluoride induces the noteworthy shifts in the fluorescence spectrum shown

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(14) The time required to develop full emission response to F^- is dependent on the concentration of F^-, but even for low concentrations of this analyte (50 μM), the desilylation reaction of cruciform **7** appears > 90% complete in < 1 min. See Supporting Information for plots of emission spectra of a mixture of cruciform **7** and F^- as a function of time.

(15) Desilylation of **3** still proceeds most readily with fluoride, as evidenced by the number of anion equivalents needed to induce significant shifts in fluorescence: 20–50 equiv with F^-, and approximately 10–20 times more with HO^-, AcO^-, and PO_4^{3-}. See Supporting Information for details.

in Figure 2D. In order to quantify the selectivity of fluoride detection with **7**, we plotted the relative changes in the intensity of its fluorescence emission at 381 nm, following the addition of 100 equiv of different anions (Figure 3). Fluoride addition enhances the emission of **7** at 381 nm by more than 1.5 times; in contrast, chloride, bromide, hydroxide, acetate, nitrate, and phosphate all changed the emission of **7** by less than 4%. Iodide anion somewhat quenched the fluorescence of **7** (−17.1%), but without significant shifts in the position of emission maxima. This behavior did not interfere with fluoride detection, as it required ~1000 equiv of iodide to decrease fluorescence intensity by approximately 70%.[16]

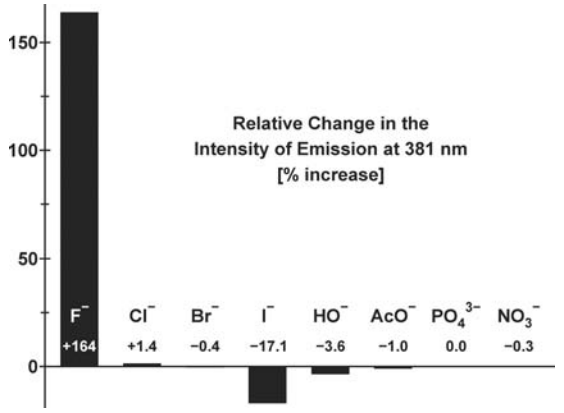

Figure 3. Relative changes in the intensity of emission of **7** at 381 nm upon addition of 100 equiv of corresponding analytes. Excitation wavelength was 306 nm, and the percentage values were calculated as $\%_{increase} = (I_{100} - I_0)/I_0$, where I_{100} and I_0 are intensities of fluorescence with 100 and 0 equiv of analyte, respectively.

The fluorescence emission changes that accompany the addition of fluoride and other anions are visible by naked eye for sensors **3** and **7** (Figure 4). The switch of the emission color from cyan to purple is clearly observable for fluoride and hydroxide in the case of **3**, and only for fluoride when cruciform **7** is used.

In conclusion, this study has shown that silylated benzobisoxazole cruciforms can serve as selective and sensitive fluorescent detectors for the fluoride anion. Their emission changes in response to fluoride addition; these changes are spectroscopically observable at fluoride concentrations as low as 50 μM and are highly specific for this anion. They operate through the desilylation of silylated alkynes, and are thus rare among other desilylation-based fluoride sensors, which are primarily exploring the cleavage of the Si−O bond.

(16) Similar behavior was observed for all examined cruciform fluorophores upon exposure to iodide and can be rationalized through heavy atom-induced collisional quenching.

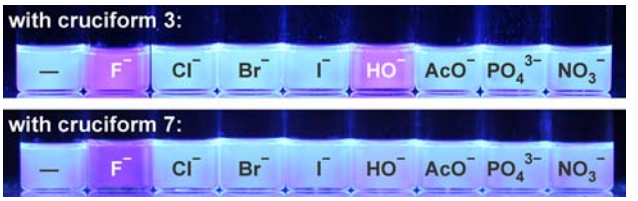

Figure 4. Changes in emission colors of dilute solutions of cruciforms **3** (top) and **7** (bottom) upon addition of 10 equiv of the corresponding anions. Excitation wavelength was 365 nm.

More generally, we believe that this work demonstrates the versatility of the "cruciform approach" to sensing. As benzobisoxazole and other conjugated cruciforms can be very easily induced to spatially isolate their FMOs, creation of a viable sensor is highly predictable. Synthetic attention can instead be focused on the relatively small modifications that can change sensor specificity and selectivity dramatically, allowing expedient adaptation of a cruciform sensor to a wide variety of analytes. This strategy is perhaps best illustrated in the current work, where silylated alkyne cruciforms, which are in fact common synthetic precursors to more complex alkynes, can be used as selective sensors of their own desilylation. Our current work is focusing on expanding the domain of chemical sensing through cruciforms.

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Supporting Information Available. Synthetic procedures, full spectroscopic characterization, anion titration, and computational data for **1**−**3** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.