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Rational design of a rapid fluorescent approach for detection of inorganic fluoride in MeCN–H_2O: a new fluorescence switch based on *N*-aryl-1,8-naphthalimide†

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A fluoride chemosensor (FCS-1) based on 1,8-naphthalimide bearing a trimethylsilyl ether has been designed and synthesized. FCS-1 displayed high selectivity and sensitivity to fluoride in inorganic forms (KF and NaF) with a short response time in MeCN–H_2O media.

In the past few years, the development of artificial approaches for anion sensing has been an enormously active research field throughout several different disciplines of chemistry.[1] In particular, the detection of hazardous anions with a high impact on the ecosystem and human health has received extremely considerable attention.[2] As an essential anion for humans, fluoride (F^-) is a common additive to drinking water and toothpaste because of its beneficial effects on human health.[3] In the biological systems, certain levels of fluoride are critical to maintaining normal physiological functions (*e.g.*, regulating cellular pH and osmosis).[4] While the optimal intake of fluoride according to the data published by the U.S. Public Health Service is 1 mg per day for humans,[5] too much will lead to poisoning effects, such as fluorosis and urolithiasis.[6] Thus, a rapid, facile and quantitative approach for the measurement of fluoride is highly needed.[7] Since fluoride is both very basic and electronegative, numerous fluorogenic sensors have been designed on the basis of molecules containing a Lewis acid boron atom or hydrogen bonds that are able to strongly interact with fluoride to trigger the fluorescence change as the detection signal.[8] The downside of this type of sensor is that other anions, like CN^-, OAc^- and $H_2PO_4^-$, may cause significant interference.[9] To improve the affinity to fluoride, desilylation-based sensors were designed by using an irreversible fluoride-triggered Si–O cleavage reaction widely used as a protection method for alcohols in organic synthesis. These reaction-based sensors have been reported for excellent selectivity and sensitivity to organic fluoride (tetrabutylammonium fluoride) over other interfering anions.[10] However, detection of inorganic fluoride has still been a challenge, particularly for samples with low fluoride concentration in water-containing media due to the high solvation that caused long reaction time.[11] Therefore, water friendly sensors with the ability to detect inorganic fluoride are quite rare and highly desirable.[12]

In the present paper, we report the design and synthesis of a robust sensor (FCS-1) based on fluoride-triggered desilylation of trimethylsilyl ether with high affinity and sensitivity to rapidly recognize fluoride over other anions in MeCN–H_2O media. 4-Methoxy-*N*-aryl-1,8-naphthalimide and trimethylsilyl (TMS) ether were employed as the fluorophore and the recognition unit for FCS-1, respectively. As a fluorescent molecule, *N*-aryl-1,8-naphthalimide has been intensively investigated and used as the fluorophore for chemosensors due to its unique photophysical properties.[13] Based on previous research work of our group, we found that the intramolecular H-bond between the phenolic and naphthalimide moieties in *N*-aryl-1,8-naphthalimide significantly affected the fluorescence properties of the whole molecule. This new result explicitly suggested that the aryl moiety may significantly affect photophysical properties of *N*-aryl-1,8-naphthalimide that could be used as an optical switch to design fluorescence sensors.[14] Inspired by this research work, we developed a new sensor (FCS-1) containing a trimethylsilyl ether on the aryl ring with a strong fluorescence emission. In the presence of fluoride, trimethylsilyl ether was hydrolyzed by cleavage of Si–O bonds that led to significant fluorescence quenching due to photoinduced electron transfer (PET) (Scheme 1).

The FCS-1 and FCS-2 were synthesized by a three-step reaction as shown in the Scheme 2. The compounds (**a**) were prepared from commercially available 4-bromo-1,8-naphthalic anhydride and *ortho*/*para*-aminophenols (*ortho* for FCS-1 and *para* for FCS-2) by a condensation reaction. Then, intermediates were refluxed with sodium methoxide in methanol to provide methoxy-substituted derivatives (**b**) that were consequently

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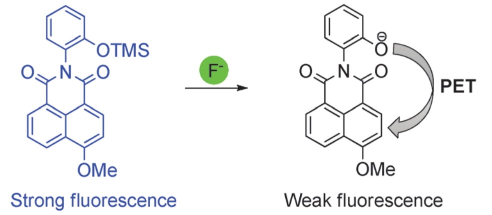
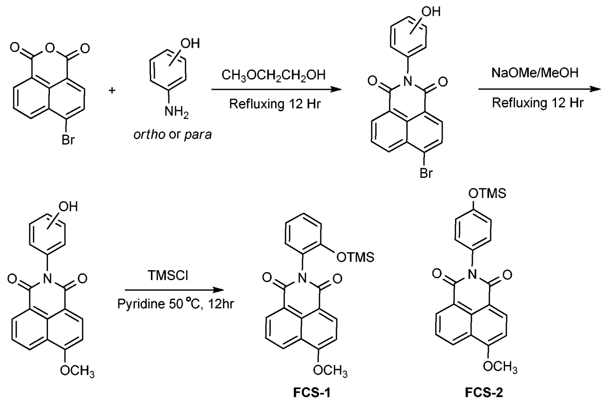


Scheme 1 Sensing process of FCS-1 for fluoride.



Scheme 2 The synthetic route of FCS-1 and FCS-2.

treated with chlorotrimethylsilane (TMSCl) in pyridine to afford FCS-1 (50.7%) or FCS-2 (40.1%). Products were characterized by ^{1}H NMR, ^{13}C NMR and HRMS.

MeOH, MeCN and MeCN–H_2O mixture (v/v = 7 : 3) were chosen to investigate the spectral properties of FCS-1 and FCS-2 (Table 1). FCS-1 exhibited the maximum absorption at 366 nm (ε = 13 600 M^{-1} cm^{-1}) and emission at 442 nm in MeCN–H_2O (v/v = 7 : 3). No significant variation was observed for absorption and emission spectra in different solvents. However, the quantum yield of FCS-1 decreased from 0.417 in MeCN to 0.213 in MeCN–H_2O and 0.152 in MeOH with increasing polarity of solvents due to the strong solvation effect. FCS-2 displayed similar absorption at 367 nm and emission at 449 nm, but low quantum yield (0.016) in MeCN–H_2O (v/v = 7 : 3).

Since FCS-1 was designed on the basis of desilylation of trimethylsilyl ether, we believed that FCS-1 would show higher sensitivity to fluoride over other anions and the fluoride-triggered Si–O bond cleavage would increase the electron density of aryl moieties that consequently induced significant fluorescence change. If rapid and quantitative deprotection of trimethylsilyl ether is achieved by fluoride, FCS-1 will provide a sensitive method for the detection of fluoride based on the change of fluorescence. The recognition properties of FCS-1 to fluoride and other anions were investigated by using fluorescence titration in the MeCN–H_2O (v/v = 7 : 3) solvent system at room temperature. As shown in Fig. 1a, FCS-1 displayed a strong fluorescence with an emission wavelength at 442 nm. Upon addition of increasing concentration of fluoride (0–10 equivalents of TBAF), a remarkable fluorescence quenching at 442 nm was observed, clearly indicating that the fluoride-triggered cleavage reaction occurred in FCS-1 and the product with a phenolate on the aryl moiety resulted in significant fluorescence quenching. The maximum quenching (20% of original fluorescence intensity) was achieved in the presence of three equivalents of TABF. This strongly supported the high efficiency of the fluoride-triggered desilylation that allowed FCS-1 to behave as a sensor with rapid response to fluoride. The detection limit was calculated to be 41.8 ppb. For comparison, fluorescence titrations were also conducted for Cl^-, Br^-, I^-, NO_3^-, HSO_4^-, CN^-, SCN^-, OAc^-, and $H_2PO_4^-$ under the same conditions, but none of them led to significant fluorescence quenching as fluoride, revealing the high affinity of FCS-1 to fluoride (Fig. 1b).

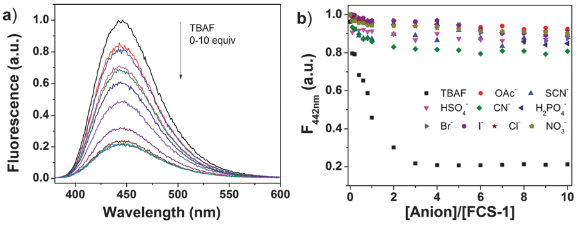


Fig. 1 (a) The fluorescence spectra change of FCS-1 (1.0 × 10^{-5} M) upon addition of 0–10 equivalents of TBAF. (b) The fluorescence intensity (at 442 nm) change of FCS-1 (1.0 × 10^{-5} M) upon addition of 0–10 equivalents of TBA salts of F^-, Cl^-, Br^-, I^-, NO_3^-, HSO_4^-, CN^-, SCN^-, OAc^-, and $H_2PO_4^-$ (the fluorescence measurements were conducted in MeCN–H_2O (v/v = 7 : 3) at 22 °C, λ_{ex} = 366 nm).

In nature, fluoride widely exists in the ionic forms that require the detecting approach possessing a high sensitivity to fluoride in inorganic form. For reaction based fluoride sensors, the responding time determined by the reaction rate is one of the most crucial factors during the sensing process. Although the desilylation based fluoride sensors significantly subsided the effects of interfering anions, long reaction time, up to several tens of minutes or even hours, has remarkably hampered their applications for samples containing inorganic fluoride with low concentration.[15] Based on these considerations, FCS-1 was designed by using trimethylsilyl ether as the recognition moiety to react with fluoride. Compared to other silyl ethers, such as *tert*-butyldimethylsilyl ether (TBDMS), *tert*-butyldiphenylsilyl ether (TBDPS), and triisopropylsilyl ether (TIPS), trimethylsilyl ether showed lower hydrophobicity and

Table 1 Photophysical properties of FCS-1 and FCS-2

	FCS-1				FCS-2			
Media	λ_{ab} (nm)	λ_{em} (nm)	ε (M^{-1} cm^{-1})	Φ (10^{-2})	λ_{ab} (nm)	λ_{em} (nm)	ε (M^{-1} cm^{-1})	Φ (10^{-2})
MeOH	366	446	13 780	15.2	367	445	14 470	1.5
MeCN	362	440	13 470	41.7	362	444	14 740	1.6
MeCN–H_2O (7 : 3)	366	442	13 600	21.3	367	449	15 090	1.6

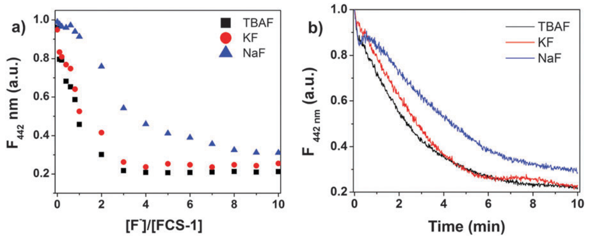


Fig. 2 The fluorescence intensity change (at 442 nm) of FCS-1 (1.0×10^{-5} M) (a) upon addition of 0–10 equivalents of TBAF, KF, and NaF (b) in the presence of 3 equivalents of TBAF, KF, and NaF within 10 min in the MeCN–H_2O (v/v = 7 : 3) media at 22 °C (λ_{ex} = 366 nm).

less steric hindrance that allowed FCS-1 to react with fluoride quickly in the water-containing media.

The fluoride titrations were conducted by using TBAF and inorganic fluoride (KF and NaF) in the MeCN–H_2O (v/v = 7 : 3) media (Fig. 2a). After incubating FCS-1 with each fluoride for 5 minutes, fluorescence quenching was observed for all three sources of fluoride. Although FCS-1 showed high sensitivity to KF and TBAF in the MeCN–H_2O media, significant fluorescence quenching was also observed with increasing concentration of NaF. The kinetics of desilylation for FCS-1 was investigated by using the three fluoride sources (Fig. 2b).[18] TABF and KF displayed a high reaction rate with FCS-1 and reached maximum fluorescence quenching within 6 minutes. NaF gave a slightly lower reaction rate, but up to 88% of FCS-1 was desilylated in 10 minutes. The overall rate constants of FCS-1 (1.0×10^{-5} M) based on pseudo-first-order reaction were calculated to be 7.8×10^{-3} s^{-1}, 7.1×10^{-3} s^{-1}, and 4.2×10^{-3} s^{-1} for TBAF, KF and NaF (3.0×10^{-5} M) respectively.

To investigate the quenching mechanism of FCS-1 triggered by fluoride, the frontier molecular orbitals of FCS-1 were calculated. Based on the recent investigation by Heagy *et al.*, the naphthalene moiety and the aryl moiety of *N*-aryl-1,8-naphthalimides could be considered as two separated systems and the aryl moiety may significantly affect the photophysical properties of the whole molecule.[16] Therefore, compared to strong fluorescence from FCS-1, the fluoride-triggered desilylation yielded a phenolate on the aryl moiety showing weak fluorescence emission. Our hypothesis is that fluorescence quenching was caused by photoinduced electron transfer (PET) from the electron-rich aryl moiety to the electron-deficient naphthalimide ring at the excited state. To verify the hypothesis, the geometric structure of FCS-1 was optimized by the B3LYP/6-31G* model and HOMO/LUMO were calculated for naphthalimide and aryl moieties by using Gaussian 09.[17] As shown in Fig. 3, FCS-1 did not show significant electron transfer at the excited state because the HOMO of naphthalene moiety (−6.13 eV) has a similar energy level to the aryl moiety (−6.11 eV). Upon addition of fluoride, the desilylation of FCS-1 yielded a phenolate, in which the HOMO of the aryl moiety increased to −5.25 eV that allowed the electron transfer to the naphthalene moiety at the excited state, resulting in significant fluorescence quenching. However, disruption of the internal charge transfer (ICT) between a methoxy group and a carbonyl group by formation of phenolate could be another reason to explain the fluoride-triggered fluorescence quenching. To distinguish these two possibilities, the UV-Vis spectra of FCS-1 were recorded upon addition of fluoride (Fig. S2, ESI†). The lack of variation in the absorption spectra of FCS-1, including the maximum absorption wavelength shift or intensity change, indicated that ICT was not considerably disrupted during the desilylation process and confirmed photoinduced electron transfer is the predominant mechanism to explain fluorescence quenching.

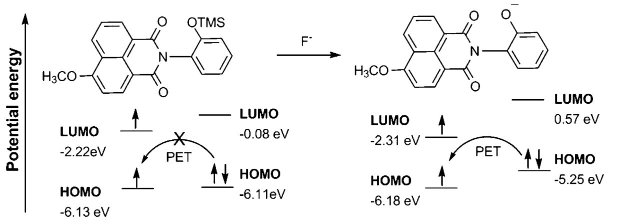


Fig. 3 Photoinduced electron transfer (PET) between naphthalene and aryl moieties led to fluorescence quenching in the presence of fluoride.

Moreover, FCS-2 with a *para*-trimethylsilyl ether on the aryl moiety was synthesized to investigate the recognition properties to fluoride as a comparison of FCS-1. FCS-2 also showed specific recognition to fluoride (TBAF) over the other nine anions as observed from FCS-1, indicating the high affinity of trimethylsilyl ether as a recognition unit for detecting fluoride (Fig. 4a). However, compared to FCS-1, FCS-2 displayed a lower quantum yield (0.016) in MeCN–H_2O (v/v = 7 : 3) and less fluorescence quenching (51% of original fluorescence intensity) triggered by fluoride, which may be caused by a weaker electron transfer effect. Because of less steric hindrance of *para*-trimethylsilyl ether, FCS-2 exhibited a high desilylation rate upon addition of fluoride in the MeCN–H_2O media, in particular for TABF and KF (Fig. 4b). The overall rate constants of FCS-2 (1.0×10^{-5} M) were calculated to be 1.9×10^{-2} s^{-1}, 1.6×10^{-2} s^{-1}, and 2.7×10^{-3} s^{-1} for TBAF, KF and NaF (3.0×10^{-5} M) respectively.

In summary, we developed a desilylation based sensor (FCS-1) by using a trimethylsilyl ether as the recognition unit for the detection of fluoride. High sensitivity and affinity to fluoride have been observed for FCS-1 over other interfering anions. Particularly, FCS-1 displayed high sensitivity to inorganic fluoride including KF and NaF in the MeCN–H_2O (v/v = 7 : 3) media with a short response time (5 min) that showed potential applications of FCS-1.

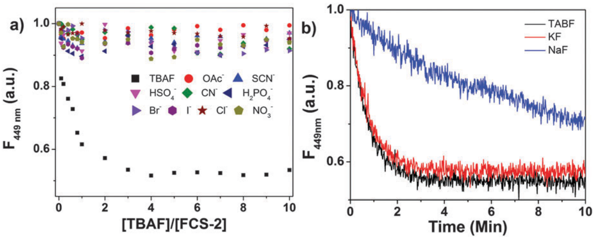


Fig. 4 The fluorescence quenching (at 449 nm) of FCS-2 (1.0×10^{-5} M) (a) in the presence of difference anions of TBA salts (0–10 equivalents), (b) upon addition of 3 equivalents of TABF, KF and NaF within 10 min in the MeCN–H_2O (v/v = 7 : 3) media at 22 °C (λ_{ex} = 367 nm).

Moreover, the phenolate formed from fluoride-triggered desilylation exhibited a strong PET effect that provided a novel sensing mechanism based on *N*-aryl-1,8-naphthalimide for designing fluorescence approaches in the future.

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18 Experimental section: (1) fluoride titration: FCS-1 (3.91 mg) was dissolved in a 10.0 mL MeCN–H_2O mixture (v/v = 7 : 3) to prepare a stock solution (1.0×10^{-3} M). The fluoride stock solutions (1.0×10^{-3} M) were prepared by dissolving TBAF·$3H_2O$ (3.15 mg) into a 10 mL MeCN–H_2O mixture (v/v = 7 : 3), KF (5.81 mg) into a 100 mL MeCN–H_2O mixture (v/v = 7 : 3), and NaF (4.20 mg) into a 100 mL MeCN–H_2O mixture (v/v = 7 : 3). FCS-1 stock solution (10 μL) was incubated with

0 to 100 μL fluoride stock solutions diluted to 1 mL for 6 min at room temperature (22 °C). Then, the samples were transferred into a fluorescence cuvette of 1.4 mL volume to record fluorescence spectra by using a FluoroMax-4 Spectrofluorometer (slit = 1 nm, λ_{ex} = 366 nm). (2) Kinetics study: FCS-1 stock solution (10 μL) was added into a 990 μL MeCN–H_2O mixture (v/v = 7 : 3) containing fluoride stock solution (30 μL). The fluorescence emission variation at 442 nm was monitored between 0 and 10 min at 22 °C by using a FluoroMax-4 Spectrofluorometer (slit = 1 nm, λ_{ex} = 366 nm).