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Highly Sensitive Fluorescence "Turn-On" Indicator for Fluoride Anion with Remarkable Selectivity in Organic and Aqueous Media

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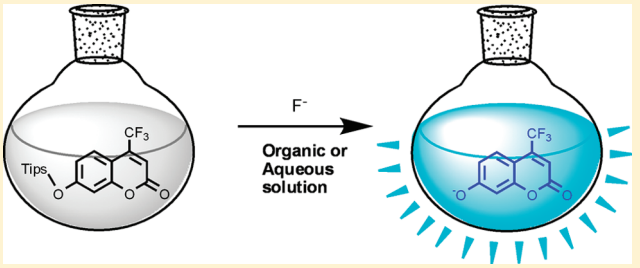
Supporting Information

ABSTRACT: A simple, convenient, and inexpensive method has been developed to quantitatively determine fluoride anion concentration in acetonitrile as well as in water. The method exhibited a high selectivity and a great sensitivity toward fluoride anions through "turn-on" chromogenic and fluorogenic dual modes. The fluoride driven silyl deprotection and the subsequent spectral changes of hydroxyl coumarin were the operating foundations for the observed selectivity and sensitivity. ^{1}H NMR spectral titration with F^- revealed that complete deprotection of a triisopropylsilyl (TIPS) group needed exactly 1 equiv of TBAF. UV−vis and fluorescence titration studies exhibited the appearance of a new intense absorption band centered at 434 nm and green emission peak at 500 nm, accompanied by bright yellow color development to the naked eye. An easy-to-prepare test paper, obtained by dipping the paper into the solution of TIPS-protected coumarin derivative, was able to detect F^- in aqueous media. The method has also shown highly promising results in detecting all kinds of fluoride salts, regardless of being organic or inorganic, and thus could be potentially useful in real applications.



INTRODUCTION

Design and development of artificial molecular systems for sensing anions in biologically relevant conditions is a challenging task in supramolecular chemistry.[1] In particular, sensing fluoride anion has attracted increasing interest in the molecular recognition community because of its pivotal importance in many areas of biological and chemical sciences.[2] In recent years high levels of fluoride in drinking water have caused numerous human diseases, creating a crucial need for artificial sensors to detect fluoride anions in an aqueous environment.[3] A large number of receptor/sensor molecules can be utilized for fluoride ion sensing, especially where recognition in organic media is concerned.[4] However, for more complex aqueous media only a few of those systems meet the requirements in terms of selectivity and affinity and are readily adaptable to practical applications.[5,6] This is mainly because of complications such as solubility, polarity, H-bonding, and ionic strength that arise in aqueous conditions, resulting in large detection limits for fluoride. Although a considerable number of fluoride sensors that work in aqueous media have been reported recently, the problems associated with some of them include (i) the need for complex syntheses, (ii) the necessity for relatively longer time (several minutes to even hours) for quantitative detection, and (iii) most of the systems being based on either colorimetric detection for which millimolar concentration of analyte is typically required, or fluorescence "turn-off", for which the sensitivity is known to be invariably low. Considering all of the relevant issues, new systems for fluoride anion detection should be simple, inexpensive, and highly selective and, achieve accurate determination with a low detection limit. In addition, for any real application an ideal sensor should be able to discriminate other coexisting anions, especially the relatively basic anions such as phosphate and acetate. A well-established strategy for sensing fluoride anions, based on the chemical affinity between silicon and fluoride, has recently undergone a quiet revolution.[6−9] Though these reaction-based sensors are irreversible in nature, they can be easily accessible for practical applications if the systems utilize fluorescence changes associated with a chemodosimeter. This intriguing approach was first reported by Kim and Swager in organic solvents, in which fluorescent response was greatly amplified using organic semiconducting polymers.[7b] Subsequently, several research groups reported different chemodosimeters that can detect fluoride anions either in water/organic solvent mixture or in only water.[5,6] However, this strenuous approach was further wielded by Hong and co-workers using simple chemodosimeter to detect fluoride ions in aqueous conditions.[6b] In this approach, the more impressive part was the ability of their sensor to detect fluoride anions inside the cells that eventually resulted in producing fluorescent images of the cells.[6c] More recently, Yang and coworkers reported another prominent and rapid aqueous fluoride ion sensor based on *N*-(3-(benzo[*d*]thiazol-2-yl)-4-(hydroxyphenyl)-benzamide (3-BTHPB, synthesized in multisteps) with outstanding sensing level of drinking water standard.[6a] However,

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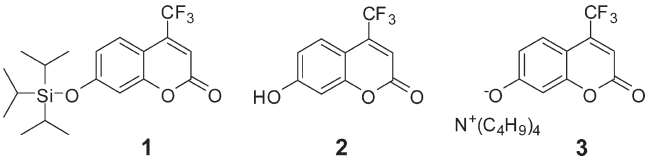
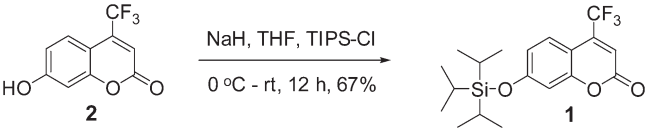


Figure 1. Molecular structures of target compound **1** and reference compounds **2** and **3**.

Scheme 1. Synthesis of Target Compound 1



due to the poor water solubility of 3-BTHPB, their sensor system had to be assembled by injecting 3-BTHPB solution in THF into a micellar solution of CTAB (cetyltrimethylammonium bromide) in water. While significant developments have been made in fluoride anion sensing, we present herein a simple and highly sensitive dual indicator system that can detect fluoride anion in both aqueous and organic media by utilizing chromogenic and fluorogenic "turn-on" signals. Additionally, in this article we are providing the basic understanding of the factors that govern both the selectivity and sensitivity in detecting fluoride anions in organic and aqueous conditions. Our present system exhibits high selectivity and sensitivity ranging from 10^{-9} M in organic media (CH_3CN) to 10^{-6} M in water.

RESULTS AND DISCUSSION

As shown in Figure 1, we designed the indicator **1**, based on the fact that the hydroxyl-protected form **1** is nonfluorescent whereas the anionic form such as **3** is highly fluorescent. We conceived that if the hydroxyl functionality in **2** was protected using a well-utilized silyl group such as triisopropylsilyl (TIPS), the resultant molecule **1** would become nonfluorescent. If a fast and quantitative deprotection of the TIPS group using fluoride anion can be achieved, the molecular system could be used in fluoride sensing via a fluorescence "turn-on" mechanism and should provide a sensitive way to detect fluoride in solution. To that end, we synthesized the TIPS-protected coumarin compound **1** (TIPS-coumarin) by slight modification of reported procedure[10] as outlined in Scheme 1. One-step reaction of commercially available 7-hydroxy-4-trifluoromethyl coumarin **2** with TIPS-Cl provided compound **1** in a reasonable yield (67%). Tetrabutylammonium (TBA) salt **3** of coumarin **2** was also synthesized as an authentic sample for comparison (Scheme 2).

The sensing performance of compound **1** toward fluoride anion was studied in three solvent systems, CH_3CN (neat), CH_3CN/H_2O (with 2.5−30% v/v water), and pure water, and monitored using UV−vis, fluorescence, and ^1H NMR spectroscopic techniques.

The UV−vis spectrum of **1** exhibited a moderately strong absorption band at 330 nm in acetonitrile (Figure 2a). Addition of increasing concentrations of fluoride (F^-) anion (as its TBA salt) resulted in dramatic color development from colorless to yellow, which is associated with gradual decrease in the absorption band at 330 nm and simultaneous growth of a new strong absorption band centered at 434 nm (Figure 2b). The appearance of the yellow color and the large red shift (104 nm) in the absorption spectrum suggested the formation of chromenolate **3** on cleavage of the TIPS group by added fluoride anion. The cleavage reaction established two clear isosbestic points at 363 and 281 nm, and the fact that the spectrum obtained from this cleavage reaction was completely superimposable with that of independently prepared **3** strongly supports quantitative cleavage of the TIPS group (Figure S7 in Supporting Information).

The most remarkable changes were seen in the fluorescence titration studies. As shown in Figure 3, the appearance of strong fluorescence emission at 500 nm from nonfluorescent **1** upon titration with F^- (as TBAF) clearly indicated that F^- triggered the removal of the TIPS moiety from compound **1**, producing the highly fluorescent chromenolate anion **3**. The fluorescence intensity increased linearly with added fluoride concentration (Figure 3 (inset)). Addition of only 1 equiv of fluoride anion saturated the system, and no more change was seen with further addition of fluoride anion, suggesting 1:1 stoichiometric reaction of **1** with fluoride anion; the corresponding Job plot provided additional support to the stoichiometric ratio (Figure S8). Complete overlay of the spectra shown in Figure 3 with that of authentic compound **3** further support the quantitative deprotection reaction (Figure S9). The estimated detection limit for fluoride anion was found to be ∼50 nM (Figure S11), which is extremely sensitive as compared to the ones observed for the other reported chemodosimeters.[9] Addition of various anions such as Cl^-, Br^-, I^-, CN^-, AcO^-, NO_3^-, $PhCO_2^-$, SCN^-, $H_2PO_4^-$, and HSO_4^- had no effect on either absorbance or fluorescence, indicating the highly selective nature of receptor **1** for fluoride anion (Figures S12 and S13).

The fluoride sensing process was also clearly seen not only by color change but also by bright fluorescence under UV lamp. Comparative fluorescence changes upon addition of various anions to compound **1** are shown in Figure 4. When the deprotection reaction of **1** was carried out in the mixture of anions containing Cl^-, Br^-, NO_3^-, and AcO^-, no fluorescence appeared, but a strong fluorescence emission appeared only when fluoride anion was added to this mixture (Figure S14). These observations suggest that compound **1** is highly selective toward F^- even in the presence of the complex mixture of anions.

The 1:1 stoichiometric deprotection reaction of compound **1** with fluoride anion was further verified by ^1H NMR titration in CD_3CN. As shown in Figure 5, a new set of signals appeared upon addition of 0.5 equiv of TBAF, and with addition of 1 equiv of TBAF all of the signals associated with compound **1** completely vanished. Upon addition of 0.5 equiv of TBAF, four new sets of signals started appearing approximately of the same intensity with the integrated proportion of the original signals. This shows that the half of the TIPS moiety of **1** have been deprotected by the added F^-. After addition of 1 equiv of TBAF, almost all of the original signals have been completely vanished and the final spectrum ended up with four signals that were upfield shifted as the result of complete deprotection of TIPS group. Further addition of F^- did not produce any significant changes in the spectrum. Here, the upfield shifts are due to the increase in electron density into the π-conjugated framework through bond propagation due to silyl removal. Also, no spectral changes were observed upon addition of other anions (Cl^-, Br^-, I^-, and NO_3^-) (Figure S15). Fortuitously, all these observations were in good agreement with the absorption and fluorescence results noted above.

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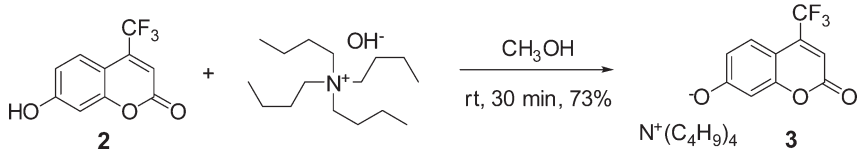
Scheme 2. Synthesis of Tetrabutylammonium (TBA) Chromenolate 3



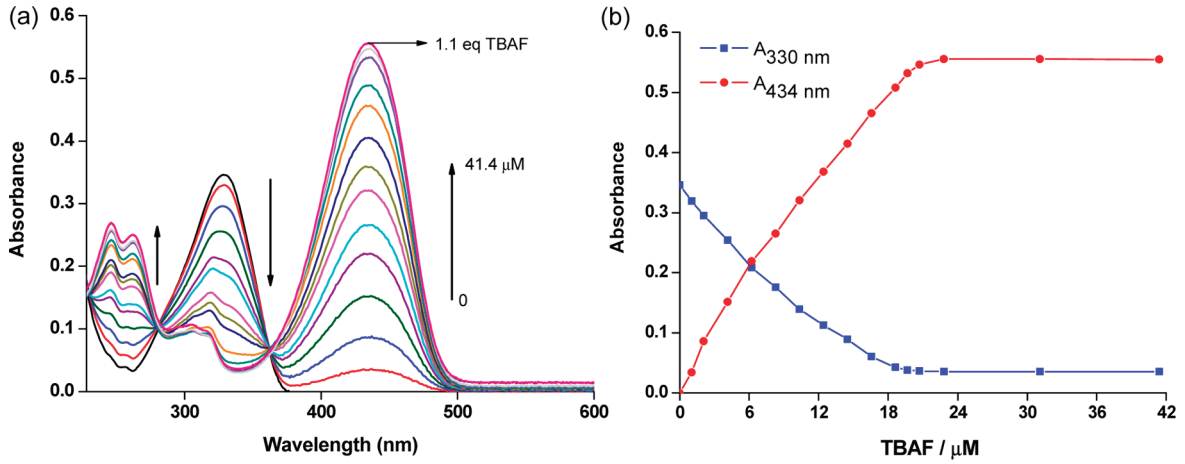


Figure 2. (a) UV−vis absorption spectral changes of **1** (20.7 μM) upon titration with TBAF (0 to 2 equiv) in acetonitrile. (b) Plot of absorption changes at 330 and 434 nm versus TBAF concentration. Absorption measurements were performed immediately after adding TBAF to the solution of compound **1**.

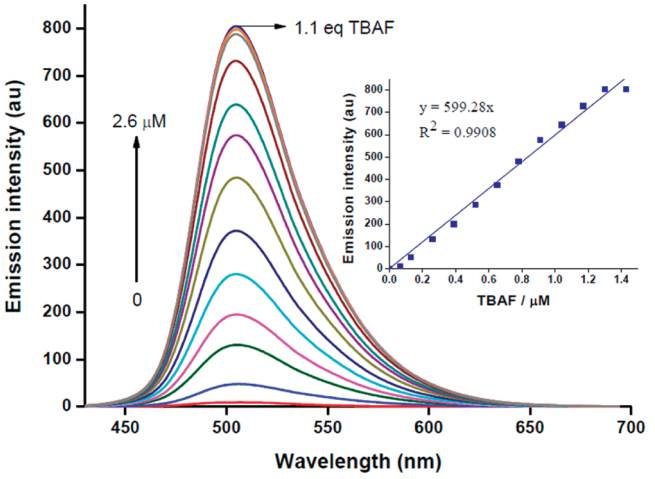


Figure 3. Fluorescence spectral changes of **1** (1.3 μM) upon addition of increasing concentrations of F^- (as its TBA salt, 0.05 to 2.0 equiv) in acetonitrile at λ_{ex} = 410 nm. Inset: Plot of emission intensity (λ_{em} = 500 nm) versus TBAF concentration. Fluorescence measurements were performed immediately after adding TBAF to **1**.

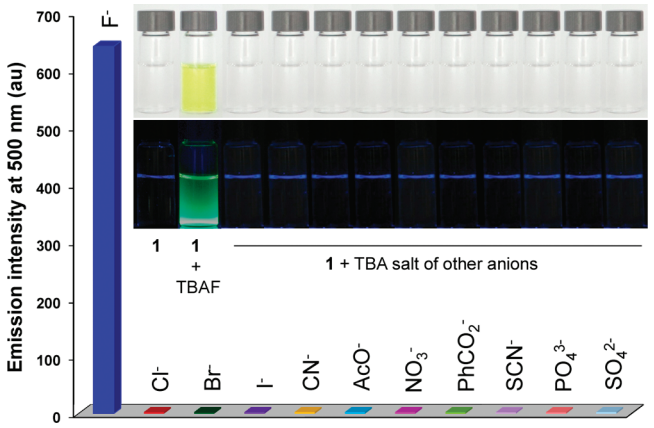


Figure 4. Relative fluorescence changes of **1** (1.3 μM) after treatment with 1.1 equiv of TBA salt of various anions in acetonitrile at λ_{ex} = 410 nm. The insets show the photographs of solutions under (top) ambient light and (bottom) a hand-held UV lamp (365 nm).

Having established selective detection of fluoride anion by compound **1** in the organic solvent, we attempted to apply this reaction-based sensing system to aqueous media. We anticipated that a high concentration of fluoride anion might be required to overcome the high hydration energy (ΔH° = −504 kJ/mol) of fluoride anion in water. Initially we carried out a series of time-dependence studies of the deprotection reaction in acetonitrile/water mixtures with gradual increase of water content from 2.5% to 30% (v/v). Time-dependent absorption (Figure S16) and emission intensity changes (Figure 6) were followed after adding 1.1 equiv of TBAF. The results demonstrate that the deprotection reaction is extremely fast in pure acetonitrile, and essentially, the reaction seems to be completed within the time (in few seconds, ≤10 s) that is needed for mixing of the fluoride solution before taking either the absorbance or fluorescence measurements. This instantaneous fast response will be definitely profitable for quick fluoride analysis in organic solvent. However, as anticipated, the increase of water content significantly delayed the cleavage reaction, which was clearly seen in the first order rate constants that are obtained with increasing water content (Table 1). In this case, an initial lag phase was observed upon addition of

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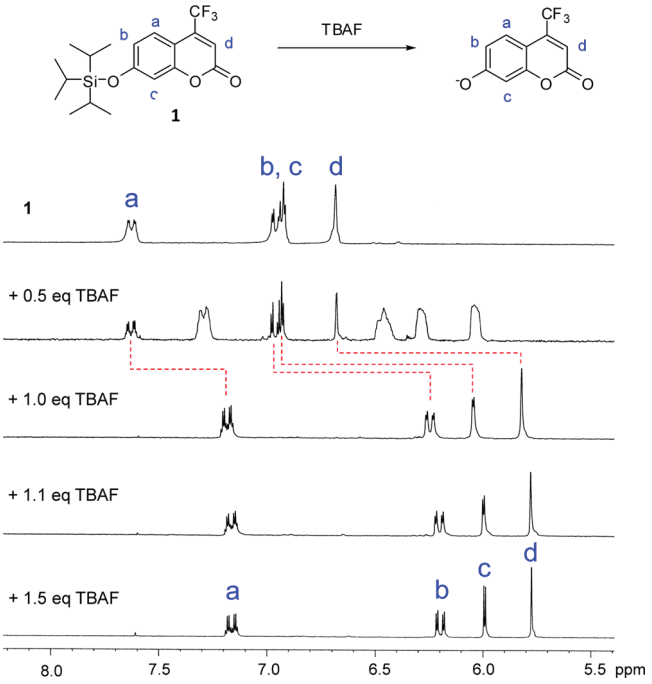


Figure 5. Partial ^{1}H NMR spectra for the titration of **1** (5.18 mM) with F^- (as its TBA salt) in CD_3CN.

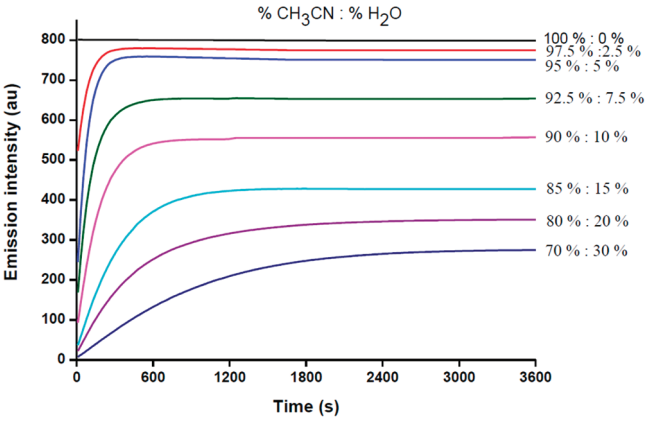


Figure 6. Time course of deprotection reaction for **1** (1.3 μM) with 1.1 equiv of TBAF by following emission change at 500 nm using different ratios of acetonitrile and water mixture at λ_{ex} = 410 nm.

water, and this observation could correspond to the emerging rapid equilibrium between protonated and unprotonated species of the generated **2** (Scheme 3). This scenario is well explained in the following section.

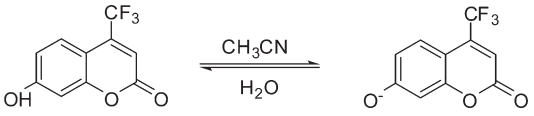
It is important to take into account that the addition of F^- not only induces the silyl deprotection of **1** but also affects the pH value of the resultant solution. In the present study, in order to nullify the effect of pH change upon addition of fluoride anion, we investigated the changes in absorbance and emission spectra of hydroxy coumarin **2** in aqueous solution by varying the pH from 3.0 to 10.0. While the absorption spectrum of **2** exhibited an intense band at λ_{max} = 335 nm in acidic conditions (at pH ≤ 7) corresponding to the protonated molecule **2**, in basic solutions (pH > 8) the band appeared at 410 nm dominates, attributing to the formation of anionic form of **2** (Figure 7a). Then we have measured the variation in fluorescence intensity of **2** at 500 nm

Table 1. First-Order Rate Constant (k) Values of Compound 1 with F^- in CH_3CN/H_2O Mixture at 25 °C[a]

CH_3CN/H_2O composition	k, s^{-1}
100:0	0.668
97.5:2.5	0.626
95:5	0.550
92.5:7.5	0.513
90:10	0.453
85:15	0.361
80:20	0.310
70:30	0.202

[a] The values were calculated from time-dependent fluorescence changes of **1** (Figure 6).

Scheme 3. Equilibrium between Protonated and Unprotonated Species of 2 in CH_3CN/H_2O Mixture



upon exciting at both 335 and 410 nm in the pH range of 3−10 (Figure 7b). Excitation at either 335 or 410 nm yields the same emission spectrum (λ_{max} = 500 nm) over the pH range of 3−10 regardless of which ground state species (protonated or anion) absorbs the excitation energy. However, the results clearly indicate that the fluorescence of **2** at λ_{ex} = 335 nm is relatively pH insensitive, whereas excitation at λ_{ex} = 410 nm exhibits drastic increase in fluorescence when the solution turns basic. Additional support for the above findings came from the excitation spectra of **2** measured in different pHs of aqueous solution (Figure S17). These pH responses of **2** at two different wavelengths are not surprising since similar results have already been reported for other coumarin derivatives.[11] Thus to avoid the complications of pH changes, which is expected to occur during silyl deprotection of **1** with excess F^- in aqueous solution, upcoming fluorescence measurements in aqueous conditions were carried out by excitation at 335 nm.

To execute the fluoride detection experiments in aqueous media, we have introduced a small amount of acetonitrile solution of **1** (~10 μL, 0.26 mM) into water (2.0 mL) due to its poor water solubility. However, it is important to note here that the percentage of acetonitrile in the resultant aqueous media was only 0.5% (also see Experimental Section for complete details). Then the fluorescence spectra were recorded with varying amounts of TBAF (0.13−3.82 mM) to test the sensing ability of **1** in aqueous media. Though much larger concentrations (in mM range) of fluoride were utilized here, Figure 8 clearly displays a gradual increase in the intensity of emission band at 500 nm. However, when time-dependent deprotection studies were carried out in the presence of the minimum amount of fluoride anion (250−550 μM), we observed a significant increase in the fluorescence intensity over a period of 10 min (Figure 9). Also a noticeable color change was seen within this period of time, which is easily visible under a hand-held UV lamp with the naked eye (Figure 9). At this point, it is important to check whether the deprotected coumarin existed in its protonated form **2** after the fluoride addition, since the fluorescence titrations at Figure 8 were carried

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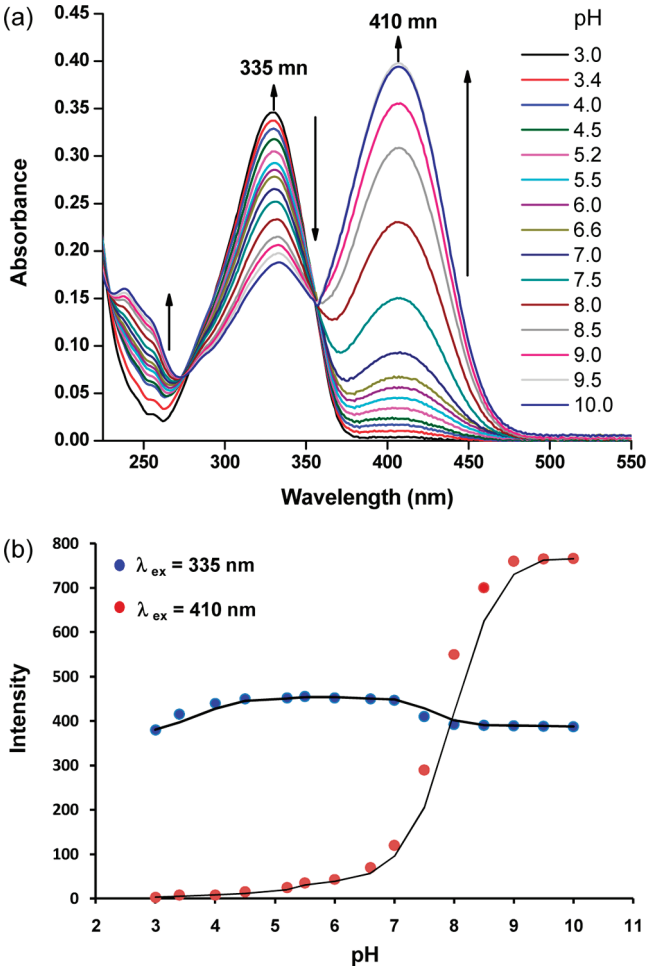

Figure 7. (a) Absorbance and (b) fluorescence intensity (λ_{em} = 500 nm) changes of **2** corresponding to various pHs of aqueous solution. Concentrations used were 20.7 μM for absorption and 1.3 μM for fluorescence.

by exciting at 355 nm, which corresponds to protonated form **2**. For this purpose, we have recorded the excitation spectra of **1** upon addition of TBA, which clearly showed the existence of protonated form **2**, by the appearance and increase in intensity of peak at 335 nm (Figure S18).

We also calculated rate constants for the above-described time-dependent measurements by plotting intensity versus time (Figure S20). The plot clearly demonstrates that the reaction follows first-order kinetics, and the rate constants for the first three concentrations of F^- (0.55, 0.50, and 0.47 mM) were found to be 1.48×10^{-3}, 1.46×10^{-3}, and 1.45×10^{-3} s^{-1}, respectively, which are almost the same irrespective of fluoride concentrations. It is worth noting that the rate of reaction should remain the same at all F^- concentrations irrespective of the pH changes that arise due to excess of F^- (pH of an aqueous solution containing 1 g L^{-1} F^- has been reported to be only 8.0[9a]), if the effect of pH changes is nullified upon exciting at 335 nm. Thus the same rate constants observed for all three F^- concentrations clearly supports the above assumption. Furthermore, these rate constant values imply that the rate of silyl deprotection of **1** with F^- in pure aqueous solution is ~450 slower than in acetonitrile solution.

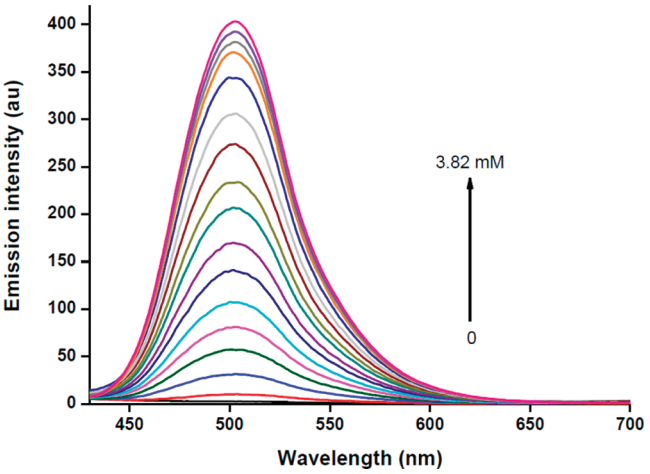

Figure 8. Fluorescence spectral changes of **1** (1.3 μM) upon addition of increasing concentrations of tetrabutylammonium fluoride (0.13 to 3.82 mM) at λ_{ex} = 335 nm in water. Fluorescence measurements were performed immediately after adding TBAF to **1**.

Since buffer solutions would nullify the slight PH changes, we have verified the same titration experiment in HEPES buffer at pH 7.4. Almost similar fluorescence changes were observed as previously seen in Figure 8, thus clearly supporting the exclusion of pH effects (Figure S21) on fluorescence responses by exciting at 335 nm. In addition, we also analyzed the change in absorption spectra during fluoride titration (Figure S23). In contrast to the drastic changes observed for 410 nm peak at pH 7.0−8.0 in Figure 7a, in this case much less significant changes were seen for both peaks at 335 and 410 nm, suggesting that the fluoride addition does not severely affect the pH of the solution. Therefore, the results obtained from these two above experiments as well as pH measurement of the resulting solution provide support for the previous report[9a] that the pH of the solution did not change by more than 0.5 during fluoride titrations.

The current system can detect up to ~0.3 ppm fluoride level in water, similar to the one reported by Yang and co-workers,[6a] thus satisfying the EPA requirement (1−4 ppm). The absorption changes of compound **1** upon addition of a small amount of fluoride anion are too small to be directly seen with the naked eye but can be efficiently detected by fluorescence spectroscopy. As shown in Figure 10, the fluorescence enhancement factor upon addition of 0−4 ppm fluoride anion is sufficiently large, and in the present system, TIPS-coumarin **1** can be successfully used as a simple tool for an easy detection of various levels of F^- ion concentrations in water.

To facilitate the use of our system for *in situ* on-site fluoride detection, we prepared test paper by immersing a filter paper in the solution of **1** in acetonitrile and then drying it by exposure to air. For the detection of fluoride ions in water, the test paper of **1** was immersed in aqueous fluoride solution and then exposed to air to remove water and to avoid further fluorescence color changes. As shown in Figure S24, the color of the test paper changed from totally colorless to bright yellow, and even the bright fluorescence can be seen very easily under UV lamp. The above changes were observed immediately (less than 1 s), which could make the present molecule a remarkably excellent indicator for very easy detection and sensing of fluoride ions in aqueous media.

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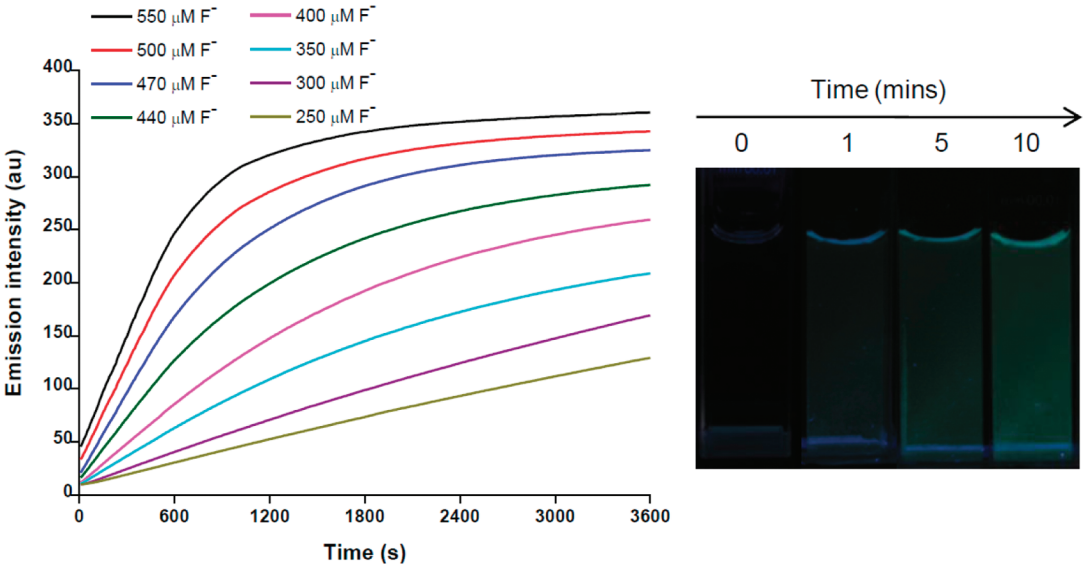

Figure 9. Time course of deprotection reaction for **1** (1.3 μM) using different concentrations of TBAF (250−550 μM) in water by following emission change at 500 nm. The photographs of the resulting solution on addition of 550 μM TBAF to the solution of **1** (1.3 μM) in water with respect to time are also shown here.

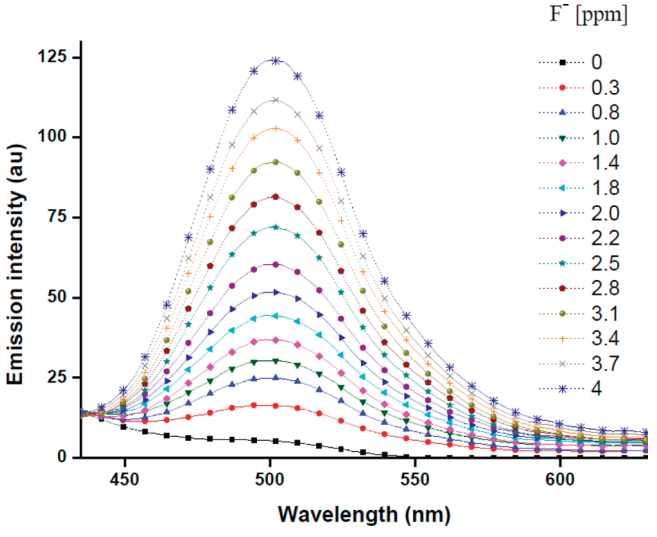

Figure 10. Fluorescence spectral changes of **1** (1.3 μM) upon addition of various amounts of fluoride anion (as its tetrabutylammonium salt) in water at λ_{ex} = 335 nm. Note that for this experiment an emission slit width of 15 nm was used for more sensitive detection (an emission slit width of 5 nm was used for data shown in Figure 8).

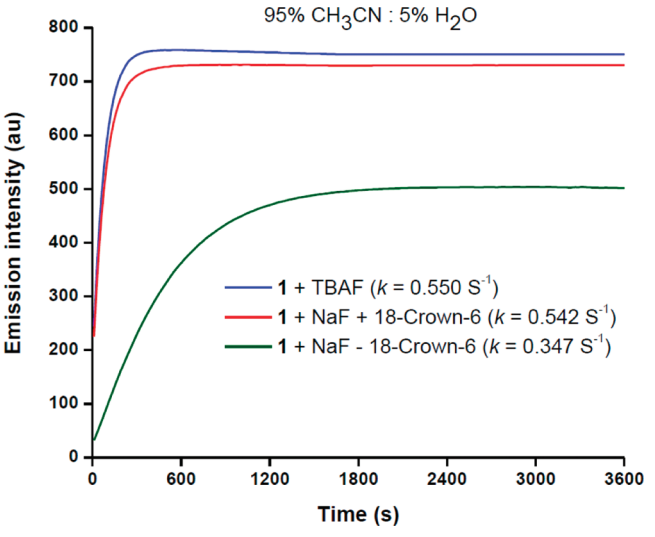

Figure 11. Comparison of time course of deprotection reaction of **1** (1.3 μM) with 1.1 equiv of TBAF (blue) and 1.1 equiv of NaF with and without 18-crown-6 (red and green, respectively) by following emission changes at 500 nm in 95:5 acetonitrile/water mixtures at λ_{ex} = 335 nm. Their corresponding rate constants are also shown for comparison.

We also investigated the fluorescence response of **1** with common inorganic fluorides including LiF, NaF, KF, and CsF in aqueous solution. This study is very important because most of the common fluorides are inorganic in nature. Our studies revealed that the rate of the deprotection with inorganic fluorides is slower than that observed with organic TBAF (Figure S25 and Table S1). CsF showed fast deprotection among the inorganic salts, which is consistent with CsF having low solvation energy and weaker ion-pairing interaction in water. To find a practical way to eliminate the interference of counter cations for accurate sensing of fluoride anion, the strong cation chelating agent 18-crown-6 was introduced. As anticipated, the cation interference caused by solvation and ion-pairing was almost completely diminished (Figure S26). Moreover, to demonstrate a potential application of the present system, **1** was treated with 1.1 equiv of NaF containing or not containing 18-crown-6 in 95:5 acetonitrile/water mixtures (Figure 11). The time-dependent fluorescence profile of **1** + NaF with no chelating agent displayed a considerably lower rate (k = 0.347 s^{-1}) compared with **1** + TBAF (k = 0.55 s^{-1}). To our delight, the one with chelating agent displayed a comparatively similar profile and nearly the same rate (k = 0.54 s^{-1}) as TBAF. The results thus verify that the added chelating agent scavenged the interfering sodium cation and made the fluoride available similar to that in TBAF. The

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Table 2.

	TIPS-coumarin **1** (mL)		TBAF (μL)	
CH_3CN/H_2O composition	amount of CH_3CN added	amount of H_2O added	amount of CH_3CN added	amount of H_2O added
97.5:2.5	2.24	0.063	87.5	2.5
95:5	2.18	0.125	85	5
92.5:7.5	2.11	0.188	82.5	7.5
90:10	2.08	0.25	80	10
85:15	1.93	0.375	75	15
80:20	1.8	0.5	70	20
70:30	1.55	0.75	60	30

Table 3.

	TIPS-coumarin **1** (mL)		TBAF (μL)	
CH_3CN/H_2O composition	amount of CH_3CN added	amount of H_2O added	amount of CH_3CN added	amount of H_2O added
97.5:2.5	1.94	0.05	87.5	2.5
95:5	1.89	0.1	85	5
92.5:7.5	1.84	0.15	82.5	7.5
90:10	1.79	0.2	80	10
85:15	1.69	0.3	75	15
80:20	1.59	0.4	70	20
70:30	1.39	0.6	60	30

fluorescence results shown in Figure 11 clearly recommend that the present coumarin based chemodosimeter could be capable of detecting fluoride ions quantitatively irrespective of its source.

CONCLUSION

In conclusion, we have developed a simple, highly selective, and sensitive system to detect fluoride anions in organic and aqueous media, utilizing the specific affinity of fluoride anion to silicon. The system provides chromogenic and fluorogenic dual signals by displaying (i) a bright yellow color and (ii) a strong green fluorescence from an initially colorless and nonfluorescent solution, upon exposure to fluoride. The response time was only few seconds in acetonitrile, and we were able to easily follow by either absorption or emission changes. The sensitivity was sufficient enough to detect fluoride anion with a reasonable response time of ~10 min in aqueous solution. Furthermore, we also showed that the system can detect inorganic fluorides as quickly as organic ones by simply introducing chelating agents such as crown ethers. The easily prepared indicator system synthesized here could be an ideal chemodosimeter for detecting and determining fluoride anion in both organic and aqueous solutions and could lead to development of a convenient and reliable detection method for fluoride anion in practical and commercial applications. Potential practical applications of the method are under intensive investigation in our laborataories.

EXPERIMENTAL SECTION

General Methods and Materials. ^{1}H NMR spectra were recorded on a 300 MHz NMR spectrometer using TMS as the internal standard. Chemical shifts are reported in parts per million (ppm). When peak multiplicities are given, the following abbreviations are used: s, singlet; br s, broad singlet; d, doublet; t, triplet; m, multiplet. ^{13}C NMR spectra were proton decoupled and recorded on a 100 MHz NMR spectrometer using TMS as the internal standard. pH was measured on a pH meter standardized against Fisher certified standard buffer solutions. All other chemicals and solvents were purchased from commercial sources and were used as such, unless otherwise mentioned. Column chromatography was performed over silica gel. All titrations (UV−vis, fluorescence and ITC) were performed using HPLC grade CH_3CN purchased from Aldrich.

Synthesis and Spectral Characterization of 4-(Trifluoromethyl)-7-(triisopropylsilyloxy)-2*H*-chromen-2-one (TIPS-Coumarin) (1). A solution of 7-hydroxy-4-trifluoromethyl coumarin **2** (200 mg, 0.87 mmol) in anhydrous THF was added dropwise to an ice-cold solution of sodium hydride (25 mg, 1.04 mmol) in anhydrous THF. After addition was complete, stirring was continued at ice temperature for 5 more minutes. Then the solution was warmed to room temperature and TIPS-Cl (22.3 μL, 1.04 mmol) was added. The reaction mixture was stirred for 12 h at room temperature. TLC analysis showed the complete disappearance of hydroxy coumarin. The solvent was evaporated, and the crude product was diluted up in $CHCl_3$, washed with H_2O and brine, dried (anhyd Na_2SO_4), and concentrated (in vacuo). The crude product was purified by silica gel column chromatography (hexane/ethyl acetate, 95:5) to yield TIPS-coumarin **1** (220 mg, 67%) as colorless viscous liquid. After being stored in a refrigerator for 1 day, the pure product **1** solidified as a white viscous solid. ^{1}H NMR (300 MHz, CD_3CN) δ 7.53 (dd, J_1 = 1.9 Hz, J_2 = 8.7 Hz,1H), 6.87−6.81 (m, 2H), 6.57 (s, 1H), 1.26−1.19 (m, 3H), 1.02 (d, J = 7.3 Hz, 18H); ^{13}C NMR (100 MHz, CD_3CN) δ 159.9, 158.5, 155.6, 139.9 (q, $^1J_{C-F}$ = 128.8 Hz), 125.7, 125.5, 122.8, 120.1, 112.8 (q, $^2J_{C-F}$ = 23.6 Hz), 111.6, 109.3, 107.4, 107.0, 16.8, 16.7, 16.6, 16.5, 12.2, 12.0, 11.9, 11.1. EI+/MS *m*/*z* calculated for $C_{19}H_{25}F_3O_3Si$ 386, found 386 (M^+, 94). HRMS (FAB+): calcd for $C_{19}H_{25}F_3O_3Si$ 386.1525, found 386.1529.

Synthesis and Spectral Characterization of Tetrabutylammonium 2-oxo-4-(Trifluoromethyl)-2*H*-chromen-7-olate (3). Commercially available 7-hydroxy-4-(trifluoromethyl)coumarin **2** (0.1 g, 0.43 mmol) in MeOH (10 mL) was added into a solution of tetrabutylammonium hydroxide (0.17 g, 0.65 mmol) in MeOH (10 mL) at room temperature. After addition was complete, stirring was continued at room temperature for 30 min. The solvent was then removed *in vacuo*, and the residue triturated with Et_2O afforded the tetrabutylammonium salt of coumarin **3** as a yellow powder that was dried under high vacuum and gave satisfactory spectroscopic data. Yield: 0.15 g (73%); ^{1}H NMR (300 MHz, CD_3CN) δ 7.23 (dd, J_1 = 2.2 Hz, J_2 = 9.1 Hz, 1H), 6.33 (dd, J_1 = 2.0 Hz, J_2 = 9.1 Hz, 1H), 6.14 (d, J = 2.0 Hz, 1H), 5.90 (s, 1H), 3.10−3.04 (m, 8H), 1.62−1.54 (m, 8H), 1.38−1.31 (m, 8H), 0.96 (t, J = 7.3 Hz, 12H); ^{13}C NMR (100 MHz, CD_3CN) δ 178.7, 161.7, 159.5, 140.9 (q, $^1J_{C-F}$ = 120.8 Hz), 127.1, 124.7, 124.4, 121.6, 120.7, 118.9, 104.0, 97.3, 96.5 (q, $^2J_{C-F}$ = 21.6 Hz), 58.2 (t, $^1J_{C-N}$ = 10.8 Hz), 23.4, 23.2, 19.2, 12.7. 12.5. This compound was further characterized by X-ray diffraction analysis. Anal. Calcd for $C_{26}H_{40}F_3NO_3.0.6H_2O$: C, 64.73; H, 8.61; N, 2.90%. Found: C, 64.90; H, 8.48; N, 2.73%.

General Details for UV−vis and Fluorescence Measurements. *Preparation of Stock Solution of **1** for Absorption and Emission Measurements.* The stock solution was prepared by dissolving 1 mg of compound **1** with HPLC grade acetonitrile in a 10 mL standard measuring flask (SMF) (2.6×10^{-4} M) at room temperature. UV−vis and fluorescence measurements were carried out by taking appropriate amount of **1** from this stock solution.

*Absorption Measurements to Monitor Silyl-Deprotection of **1** with Tetrabutylammonium Fluoride (TBAF). Preparation of Stock Solution of TBAF.* The stock solution was prepared by dissolving 8.2 mg of TBAF with HPLC grade acetonitrile in 1 mL of SMF at room temperature. Depending upon the solvent mixture (either pure acetonitrile or

acetonitrile/water mixture), 10 μL of this solution was made into 100 μL (2.60 mM), and the resulting solution was used for titrations.

Absorption Measurements in Acetonitrile. Absorption spectral changes were monitored by measuring the decrease of absorbance at 330 nm and increase of absorbance at 434 nm. For this purpose, 200 μL of the stock solution was taken in a quartz cuvette and diluted to 2.5 mL with acetonitrile. So the final concentration of **1** in this solution was 20.7 μM. The absorbance at 334 nm observed for this solution was noted as first. When 1 μL of above prepared tetrabutylammonium fluoride (2.60 mM) was added, the absorbance at 334 nm slowly started decreasing and a new absorption band at 434 nm started appearing. The concentration of TBAF in the solution now would be 1.04 μM. After each addition of tetrabutylammonium fluoride (2, 3, 4 μL, etc.), the absorbance decrease at 330 nm and the absorbance increase at 434 nm were noted until no further changes observed (up to 40 μL, ~2 equiv). Absorption measurements showed that the maximum absorption at 434 nm was reached with 1.1 equiv of TBAF added, but further additions (up to 2 equiv) were continued to verify that no more increase in absorbance were observed. However, further addition slightly lowered the absorbance due to dilution.

*Measurement of Time-Dependent Absorption Changes of **1** with TBAF in Acetonitrile/Water Mixture.* To follow the time course of the deprotection reaction for **1** (20.7 μM) with 1.1 equiv of TBAF by following absorption change at 330 nm using different ratios of acetonitrile and water mixture, the following variations of solvent mixture were prepared (see also Table 2).

(i) Amount of TIPS-coumarin **1** taken from stock solution = 200 μL. This was diluted to 2.5 mL (depending on solvent composition), so that the final concentration was 20.7 μM.

(ii) Amount of TBAF taken from stock solution = 10 μL. This was diluted to 100 μL (depending on solvent composition), so that the final concentration was 2.60 mM. From this 22 μL was added, so that the concentration of TBAF was 22.7 μM (1.1 equiv).

*Fluorescence Measurements To Monitor Silyl-Deprotection of **1** with Tetrabutylammonium Fluoride (TBAF). Preparation of Stock Solution of TBAF.* The stock solution was prepared by dissolving 0.83 mg of TBAF with HPLC grade acetonitrile in 1 mL of SMF at room temperature. Depending upon the solvent mixture (either pure acetonitrile or acetonitrile/water mixture), 10 μL of this solution was made into 100 μL (0.26 mM), and the resulting solution was used for titrations.

Fluorescence Measurements in Acetonitrile. Fluorescence spectral changes were monitored by measuring the intensity of emission band emerged at 500 nm after each addition of TBAF. For this purpose, 10 μL of the stock solution was taken in a quartz cuvette and diluted to 2.0 mL with acetonitrile, so the final concentration of **1** in this solution was 1.3 μM. The emission spectrum was first recorded by exciting at 410 nm, and the emission intensity at 500 nm was noted first. The emission of **1** was found to be negligible ~2 at 500 nm. The When 1 μL of TBAF (0.26 mM) was added, a new emission band at 500 nm started appearing. After each addition of tetrabutylammonium fluoride (2, 3, 4 μL, etc.), the emission intensity at 500 nm were noted until no further changes observed (up to 40 μL, ~2 equiv). Fluorescence measurements showed that the maximum emission at 500 nm was reached with 1.1 equiv of TBAF added, but further additions (up to 2 equiv) were continued to verify that no more increase in emissions were observed. However, further addition slightly lowered the absorbance due to dilution.

*Measurement of Time-Dependent Fluorescence Changes of **1** with TBAF in Acetonitrile/Water Mixture.* To follow the time course of the deprotection reaction for **1** (1.3 μM) with 1.1 equiv of TBAF by following emission intensity at 500 nm using different ratios of acetonitrile and water mixture, the following variations of solvent mixture were prepared (see also Table 3).

(i) Amount of TIPS-coumarin **1** taken from stock solution =10 μL. This was diluted to 2.0 mL (depending on solvent composition), so that the final concentration was 1.3 μM.

(ii) Amount of TBAF taken from stock solution =10 μL. This was diluted to 100 μL (depending on solvent composition), so that the final concentration was 0.26 mM. From this 11 μL was added, so that the concentration of TBAF was 1.4 μM (1.1 equiv).

Fluorescence Measurements in Water. It is important to mention here that distilled water was used in all experiments.

Preparation of Stock Solution of TBAF. Since much larger concentrations of fluoride would be required to overcome inactivation by strong hydrogen bond donor H_2O, a relatively higher concentrated stock solution of TBAF was prepared for this purpose. The stock solution was prepared by dissolving 8 mg of TBAF with water in 100 μL SMF (0.25 M) at room temperature and the resulting solution was directly used for the titration purpose.

Since compound **1** was not completely soluble in pure water, measurement of fluorescence spectral changes was unsuccessful in pure water. For this purpose, 10 μL of the stock solution of **1** was taken in a quartz cuvette and diluted to 2.0 mL with pure water. So the final concentration of **1** in this solution would be 1.3 μM and the composition of solvent mixture was 99.5% H_2O and only 0.5% CH_3CN. The emission spectrum was first recorded by exciting at 335 nm and the emission intensity at 500 nm was noted first. The emission of **1** was found to be negligible ~2 at 500 nm. The titration was carried in the same as mentioned above. After each addition of tetrabutylammonium fluoride in water, the emission intensity at 500 nm were noted until no further changes observed

*Measurement of Time-Dependent Fluorescence Changes of **1** with TBAF in Water.* The time course of the deprotection reaction for **1** (1.3 μM) with various concentrations of TBAF was followed in the same way by measuring the emission intensity at 500 nm in water.

Parameters Used for Fluorescence Measurements. In Acetonitrile. Excitation wavelength = 410 nm; emission wavelength = 500 nm; excitation slit (nm) = 15; emission slit (nm) = 5. Only for the spectra shown in Figure S11, the emission slit was increased to 15 nm.

In Water. Excitation wavelength = 335 nm; emission wavelength = 500 nm; excitation slit (nm) = 15; emission slit (nm) = 5. Only for the spectra shown in Figure 10, the emission slit was increased to 15 nm.

■ ASSOCIATED CONTENT

Supporting Information. Spectroscopic data, single crystal X-ray structure, and CIF file for compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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