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ARTICLE

Investigation of Desilylation in the Recognition Mechanism to Fluoride by a 1,8-naphthalimide Derivative

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A reaction-based chemosensor (AF-1) was designed, synthesized and applied as an optical approach for quantitative measurement of F^- in MeCN. In the presence of F^-, selective fluoride-assisted desilylation instantly gave colorimetric and fluorogenic signals, providing a dual optical channel for detection of F^-. ^1H NMR titration was carried out to investigate the desilylation process, revealing F^- triggered a rapid cleavage of Si-O bond in trimethylsilyl ether. AF-1 exhibited high sensitivity and selectivity to F^- over other anions. The detection limit to F^- was calculated to be 0.05 ppm.

Introduction

As a ubiquitous anion pervading in biosphere, the biological roles of fluoride (F^-) is largely unexplored.[1] In the past decades, understanding roles of F^- has been extended from an industry pollution to a therapeutic reagent for osteoporosis and dental protection.[1] F^- was also reported to involve in many bio-process in living cells, such as formation of reactive oxygen species (ROS) and ion transportation on cell membrane.[2] The dose and concentration of F^- completely determine its biofuctions, a beneficial or poisonous effect.[3] The Health and Human Services (HHS) and Environmental Protection Agency (EPA) proposed the recommended level of fluoride to be 0.7 mg/l in the drinking water.[4] Over taking fluoride may cause toxic effects including skeletal fluorosis, damage to kidney, liver and brain.[5] Therefore, developing a simple and reliable method for quantitative detection of F^- is highly desired for understanding its functions.[6]

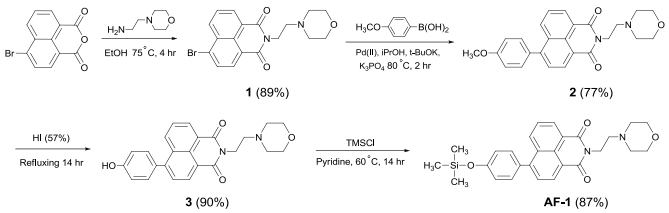
Compared to analytical approaches based on sophisticated instruments, fluorescent chemosensing provides a facile method for detection of F^- with high sensitivity and short response time.[7] Recently, reaction-based fluorescence sensors attracted great attention due to their high selectivity to F^- over other interfering anions, such as OAc^- and $H_2PO_4^-$.[8] Preparation of a silyl ether has been widely used as the protection of hydroxyl group followed by using tetrabutylammonium fluoride (TBAF) as the deprotection in organic synthesis.[9] Therefore, the irreversible desilylation and desulfonation have been used as the recognition events to discriminate F^- from other coexisting anions in reaction-based fluoride sensors, which showed high affinity to F^- in organic and aqueous media.[10]

In our research group, several reaction-based F^- sensors have been developed by using trimethylsilyl ether as the recognition unit to quantitative detection of F^- based on photophysical mechanisms, such as photoinduced electron transfer (PET) and excimer-monomer switch.[11] Compared to other silyl ethers used for F^- sensors, trimethylsilyl ether showed a short response time and had sensors more soluble in the hydrophilic media. Based on the latest results collected from our group, we report a new approach for detection of fluoride (AF-1), in which 1,8-naphthalimide and trimethylsilyl ether were used as the fluorophore and recognition unit respectively. In the presence of F^-, a instant desilylation was observed for AF-1. The cleavage of Si-O bond during the desilylation process resulted in significant change of absorption and emission spectra used as a dual optical signal for quantitative measurement of fluoride. Compared to other silyl ether based fluoride sensors, AF-1 exhibited an instantaneous color change from colorless to red as well as fluorescence quenching with addition of F^-, which provided a facile and rapid approach for detection of F^-.

Results and discussion

AF-1 was prepared via a four-step synthesis (Scheme 1). Commercially available 4-bromo-1,8-naphthalic anhydride was refluxed with 4-(2-aminoethyl)morpholine in EtOH for 4 hr to yield **1**, which reacted with 4-methoxyphenylboronic acid through Suzuki Coupling to afford **2**. Compound **3** was obtained by refluxing **2** in HI (57%) aqueous solution for 14 hr. Trimethylsilyl chloride was heated with **3** in pyridine at 60 °C for 14 hr to yield AF-1.[12] The intermediates and AF-1 were characterized by using ^1H-NMR, ^{13}C NMR and HRMS. The

detailed synthesis procedures and structure characterization are available in the Experimental section and in the ESI.†



Scheme 1: The synthetic route to prepare AF-1.

The spectroscopic properties of AF-1 were investigated in MeCN at 25 °C. As shown in Fig. 1, the major absorption peaks of AF-1 were observed at 240 nm and 362 nm that corresponded to π-π* transition. Due to major absorption in the ultra-violet region, AF-1 solution showed colorless. An intense peak centred at 486 nm was detected in the emission spectrum of AF-1 with excitation at 362 nm. In the presence of F^- (20 equiv), AF-1 exhibited significant change in the absorption and emission spectra. In the absorption spectrum, new peaks at 423 and 552 nm were observed as well as the shift of the peak at 362 nm to 330 nm, which directly caused red color change. In the emission spectrum, obvious fluorescence quenching was detected together with 7 nm red-shift. The absorption and emission spectra clearly indicated the structure change of AF-1 triggered by F^-.

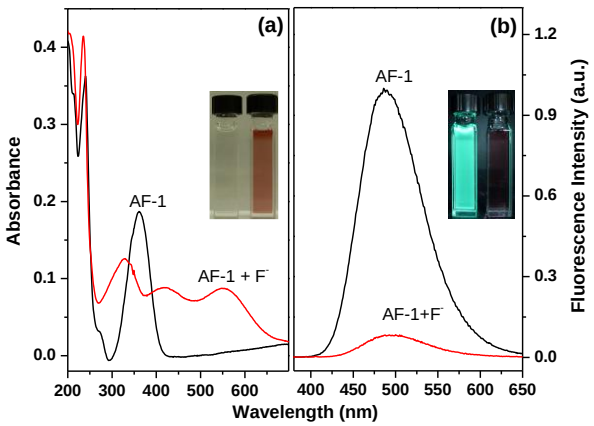


Fig. 1 Absorption spectra (a) and fluorescence emission spectra (b) of AF-1 (2.0×10^{-5} M) without/with fluoride (20 equiv) in MeCN at 25 °C (λ_{ex}=362 nm).

The fluoride triggered desilylation was designed as the major event to recognize F^- for AF-1. To verify the cleavage of Si-O bond in the AF-1 after addition of F^-, the ^1H NMR titration was carried out in $CDCl_3$. After incubating AF-1 (1.1×10^{-2} M) with F^- (0-5 equiv) for 5 min, ^1H NMR spectra were collected (Fig. 2). The protons on the phenyl ring in AF-1showed two doublet peaks at 7.05 and 7.43 ppm respectively. With addition of F^-, the peak at 7.43 ppm moved upfield, indicating a strong shielding effect. Due to the conjugated structure, the chemical shift of protons on the naphthalene moiety also showed obvious change at 8.37 and 8.67 ppm. The ^1H NMR titration strongly suggested that a structural change of AF-1 occurred in the presence of F^-. Combining to Uv-vis and fluorescence data, ^1H NMR titration demonstrated a fluoride-triggered desilylation, which yielded a phenoxide with negative charge on the phenyl ring.

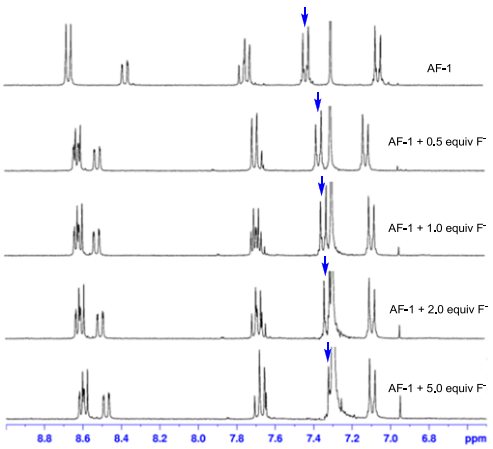


Fig. 2 ^1H NMR titration of AF-1 upon addition of 0-5 equiv F^- in $CDCl_3$.

To quantitatively investigate the fluoride-triggered desilylation, fluorescence and absorption titrations of AF-1 (2.0×10^{-5} M) were conducted upon addition of tetrabutylammonium fluoride (TBAF, 0-20 equiv) in MeCN at 25 °C (Fig 3). Although AF-1

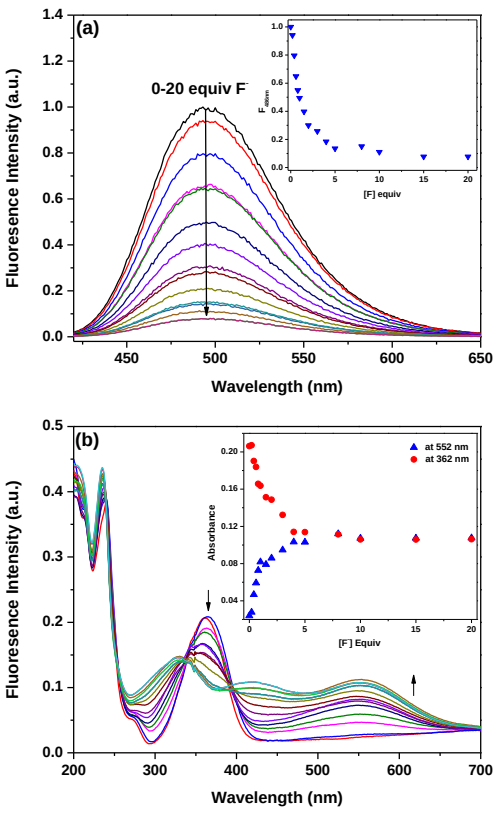


Fig. 3 The fluorescence (a) and absorption (b) change of AF-1(2.0×10^{-5}M) in the presence 0-20 equiv F^- in MeCN at 25 °C (λ_{ex}=362 nm).

displayed a strong emission at 486 nm, a rapid fluorescence quenching was observed upon addition of F^- and the maximum quenching (92%) was achieved after addition of 5 equiv F^- (Fig. 3a). Meanwhile, remarkable change also was detected in the

absorption spectra. A decline at 362 nm with a concomitant increase at 552 nm was recorded that caused significant color change from colorless to red. The maximum change was also measured after addition of 5 equiv F^-, which is consistent with the change of fluorescence spectra (Fig 3b). The spectroscopic study confirmed the fluoride-triggered desilylation in AF-1 and verified that the desilylation process could be monitored by both of absorption and fluorescence emission spectra. Moreover, these spectroscopic results demonstrated that AF-1 was highly sensitive to F^-, which resulted in complete desilylation with addition of 5 equiv. The change of fluorescence intensity (at 486 nm) and absorption (at 362 nm and 552 nm) showed a linear dependence to F^- concentration (0-2.0×10^{-5}M), which allowed AF-1 to quantitatively detect F^- in the micromolar range by using a dual spectroscopic signal (Fig. S1). The detection limit was also calculated to be 0.05 ppm that suggested the high sensitivity of AF-1 to F^-.

As a sensor designed for detection of F^-, AF-1 was investigated for selectivity by using various anions including $H_2PO_4^-$, NO_3^-, OAc^-, HSO_4^-, SCN^-, I^-, Br^-, Cl^- and F^-. Due to similar electronic structure and charge, many anions (e.g., $H_2PO_4^-$ and OAc^-) may cause significant interference during the fluoride sensing process. After mixing AF-1 (2.0×10^{-5}M) with different anions (20 equiv) in MeCN media, absorption and fluorescence spectra were collected. F^- was the only anion that caused instant color change and fluorescence quenching among nine anions. Slight color change and fluorescence quenching (up to 24% and 25 % respectively) were also observed after addition of $H_2PO_4^-$ and OAc^-, but was much less than the change caused by F^-. For the rest of other anions, no significant change was detected (Fig 4 and Fig S2). These data clearly suggested the high efficiency of fluoride-triggered desilylation, indicating AF-1 functioned as a sensitive probe with high affinity to recognize F^- over other anions.

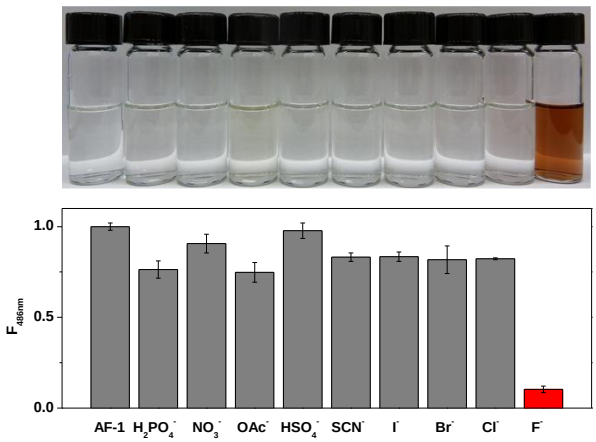


Fig. 4 AF-1 showed high affinity to F^- over other anions ($H_2PO_4^-$, NO_3^-, OAc^-, HSO_4^-, SCN^-, I^-, Br^- and Cl^-) in MeCN.

Experimental

Apparatus

Uv-vis spectra were recorded by Varian Cary® 100 UV-Vis Spectrophotometer (Agilent). Fluorescence emission spectra were collected by a FluoroMax-4 Spectrofluorometer (Horiba Jobin Yvon, USA). Both of absorption and emission spectra were measured at room temperature by using standard quartz cuvettes (10 mm path length). The slits were set at 1 nm for collection of fluorescence emission spectra. ^1H and ^{13}C NMR spectra were recorded on Bruker 300 Ultra-Shield spectrometer (^1H 300MHz, ^{13}C 75MHz) at room temperature.

Reagents

Chemicals used for synthesis and measurements were purchased from Sigma-Aldrich (MO, USA), Fisher Scientific (USA) and Acros Organics (USA) in analytical grade and used as received, unless otherwise stated. Tetrabutylammonium (TBA) salts were used as the sources for anion (F^-, Cl^-, Br^-, I^-, NO_3^-, HSO_4^-, CN^-, SCN^-, OAc^-, and $H_2PO_4^-$) measurements.

Synthesis and characterization

6-bromo-2-(2-morpholinoethyl)-1H-benzo[de]isoquinoline1,3 (2H)-dione (**1**). 4-bromo-1,8-naphthalic anhydride (1.11g, 4.0 mmol) was mixed with 2-morpholinoethanamine (1.04g, 8.0 mmol) in ethanol (40 mL) under reflux for 4 hr. After cooling reaction mixture to room temperature, a yellow solid was collected by suction filtration. The crude product was purified by column chromatography (silica gel 200-400 mesh, 60 Å) eluted by EtOAc to yield a white solid (1.38g, 89%). Melting point (m.p.): 165-167 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.62 (t, *J*= 4.56 Hz, 4H), 2.73 (t, *J*=6.63 Hz, 2H), 3.70 (t, *J*=4.62 Hz, 4H), 4.36 (t, *J*=6.99 Hz, 2H), 7.86 (t, *J*=7.98 Hz, 1H), 8.05 (d, *J*=7.86 Hz, 1H), 8.41 (d, *J*=7.89 Hz, 1H), 8.57 (d, *J*=8.52 Hz, 1H), 8.65 (d, *J*=7.26 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 37.4, 53.8, 56.2, 67.1, 122.2, 123.1, 128.1, 129.0, 130.3, 130.6, 131.1, 131.3, 132.0, 133.3, 163.8.

6-(4-methoxyphenyl)-2-(2-morpholinoethyl)1Hbenzo[de]isoqui -noline-1,3(2H)-dione (**2**). **1** (389 mg, 1.0 mmol) was mixed with 4-methoxyphenylboronic acid (198 mg, 1.3 mmol), mono(allyl(3-benzhydryl-1-(2,6-diisopropylphenyl)-1H-imida-zol-3-ium-2-yl)palladium (III)) mono-chloride (11.6 mg, 0.02 mmol), K_3PO_4 (318 mg, 1.5 mmol), and *t*-BuOK (123 mg, 1.1 mmol) in 2-propanol (3.0 ml) at 80 °C for 2 h. After cooling down to room temperature, the reaction mixture was extracted with CH_2Cl_2/acetone (15 mL) twice and gave a solid after evaporating solvent. The crude product was purified by column chromatography (silica gel 200-400 mesh, 60 Å) eluted by EtOAc:CH_2Cl_2=1:1 to yield **2** as a ligh yellow solid (320 mg, 77%). Melting point (m.p.): 187-192 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.65 (s, 4H), 2.77 (t, *J*=6.90 Hz, 2H), 3.73 (t, *J*=4.53 Hz, 4H), 3.96 (s, 3H), 4.42 (t, *J*=7.17 Hz, 2H), 7.13 (d, *J*=8.70 Hz, 2H), 7.49 (d, *J*=8.79 Hz, 2H), 7.74 (t, *J*=7.89 Hz, 2H), 8.36 (d, *J*=8.43 Hz, 1H), 8.67 (d, *J*=7.38 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 37.1, 53.7, 55.4, 56.1, 66.9, 76.6, 77.0, 77.4, 114.1, 121.2, 122.8, 126.7, 126.9, 127.7, 128.8, 130.1, 130.9, 131.0, 131.1, 132.8, 146.8, 159.9, 164.1, 164.3.

6-(4-hydroxyphenyl)-2-(2-morpholinoethyl)-1H benzo[de]iso-quinoline-1,3(2H)-dione (**3**). **2** (200 mg, 0.48 mmol) was refuxed in HI (57%, 11 mL) for 14 hr. The reaction mixture was added into cold water (20 mL) to collect a yellow solid. The crude product was purified by column chromatography (silica gel 200-400 mesh, 60 Å) eluted by EtOAc:CH_2Cl_2=5:1 to yield **3** as a yellow solid (174 mg, 90%). Melting point (m.p.): 199-202 °C. ^{1}H NMR (300 MHz, DMSO-*d*6) δ: 2.48-2.77 (m, 6H), 3.56 (m, 4H), 4.23 (m, 2H), 6.99 (d, *J*=8.55 Hz, 2H), 7.39 (d, *J*=8.52 Hz, 2H), 7.74 (d, *J*=7.65 Hz, 1H), 7.84 (t, *J*=7.92 Hz, 1H), 8.32 (d, *J*=8.55 Hz, 1H), 8.52 (t, *J*=6.48 Hz, 2H), 9.86 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 37.3, 54.0, 56.0, 66.8, 116.1, 121.0, 122.7, 127.6, 128.1, 128.6, 129.3, 129.8, 131.0, 131.3, 131.7, 133.0, 134.8, 146.9, 158.4, 163.7, 163.9.

2-(2-morpholinoethyl)-6-(4-(trimethylsilyloxy)phenyl)-1H benzo[de]iso-quinoline-1,3(2H)-dione (**AF-1**). **3** (150 mg, 0.37 mmol) chlorotriisopropylsilane (285 mg, 1.48 mmol) were dissolved in 3.0 mL pyridine at 50 °C for 14 hours. The reaction solution was added into HCl (12%, 15mL) in the ice bath to collect a yellow precipitate as the crude product by filtration. The crude product was purified by column chromatography (silica gel 200-400 mesh, 60 Å) eluted by EtOAc to yield **AF-1** as a yellow solid (153 mg, 87%). Melting point (m.p.): 162-164 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.39 (t, *J*=3.18 Hz, 9H), 2.66 (s, 4H), 2.78 (t, *J*=6.66 Hz, 2H), 3.74 (t, *J*=4.08 Hz, 4H), 4.42 (t, *J*=6.99 Hz, 2H), 7.05 (d, *J*=8.55 Hz, 2H), 7.43 (d, *J*=8.64 Hz, 2H), 7.75 (t, *J*=8.25 Hz, 2H), 8.37 (d, *J*=8.55 Hz, 1H), 8.67 (d, *J*=7.29 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 0.5, 37.3, 53.8, 56.3, 67.0, 120.3, 121.3, 122.8, 126.7, 127.9, 128.9, 130.2, 130.9, 131.2, 131.8, 132.9, 146.9, 155.8, 164.3, 164.5. TOF MS EI$^+$: M^+ *m/z* 474.1975 (calcd.), 474.1975 (found).

Conclusions

In conclusion, we reported a sensing approach (AF-1) on the basis of fluoride-triggered desilylation for quantitative measurement of F^-. High affinity and sensitivity to F^- over other eight anions were observed for AF-1. Upon addition of F^-, AF-1 showed instant color change along with fluorescence quenching, which provided a ratiometric signal for rapid detection of F^-, particularly for F^- with low concentration in the range of ppm or less.

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Notes and references

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† Electronic Supplementary Information (ESI) available: characterization data including ^{1}H NMR, ^{13}C NMR spectra, HRMS data, and absorption spectra. See DOI: 10.1039/b000000x/

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