Ratiometric sensing of fluoride ions using Raman spectroscopy

Electronic Supplementary Information

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Materials and Methods

Raman spectroscopy

Raman spectra were acquired on a Renishaw InVia Raman microscope equipped a 785 nm diode laser providing a maximum power of 300 mW using a 1200 l/mm grating.

Neat samples: A small amount of sample compounds 1 or 2 was transferred onto a CaF$_2$ window and Raman spectra were acquired using $\lambda_{ex}$ = 785 nm and a 20× NA 0.4 NPlanEPI objective (~95 mW, Leica) for 10 s.

Reaction monitoring: The reaction mixture was prepared in a quartz cuvette (500 μL) and Raman spectra were acquired using a 5× NA 0.12 NPlanEPI objective (Leica) or a 20× NA 0.4 NPlanEPI objective (Leica). Spectra were acquired continuously using either a 0.5 s or 1 s acquisition time.

Paper test strips: Whatman™ Qualitative Filter Paper: Grade 1 Circles were cut into 1 cm × 1 cm squares and treated with sensor 1 (100 mM in THF; 10 μL). The strips were air-dried (~5 min at r.t.) and subsequently treated with TBAF (0 – 5 mM in THF up to 300 μL). The test strips were air-dried (~5 min at r.t.) and analysed as per Figure legend.

Handheld detection: Raman spectra were acquired using a handheld CBEx spectrometer with 785 nm laser excitation wavelength, from Snowy Range Instruments (now Metrohm). Measurements were acquired using a 10 s integration time. A point and shoot adaptor with a single element lens (N.A. 0.5) was fitted for detection of the filter paper samples which gave an average laser power of ~55 mW at the focus. Individual spectra were acquired from randomly selected points on the test paper sample.

UV-visible spectrometry

UV-visible spectra were acquired using a Cary 60 (Agilent Technologies) UV-Vis spectrometer. The reaction mixture was prepared in a plastic cuvette (1.5 mL) and sequential UV-Vis spectra across the range 200 – 800 nm were acquired.

Data processing

Raman spectra of reaction mixtures. All spectra were processed in WiRE 4.4™ software enabling cosmic ray removal and baseline subtraction. Peak normalisation (1450 cm$^{-1}$) was performed in OriginPro2018 software and the peak areas determined using the Integrate tool (Sensor 1 2140–2185 cm$^{-1}$; desilylated product 2 2085 –2130 cm$^{-1}$ and nitrile peak 2205 –2255 cm$^{-1}$).

Raman maps on paper test strips: All Raman maps were processed in WiRE 4.4™ software enabling cosmic ray removal, noise filtering and baseline subtraction. A custom MATLAB® script was then used to perform ratiometric analysis on the Raman spectral map (20 μm × 20 μm; 400 spectra). False-colour images for the test paper strips were created based on the peak intensity ratio: 2105 cm$^{-1}$/2160 cm$^{-1}$ and 2231 cm$^{-1}$/2237 cm$^{-1}$. The images were scaled between 0–0.2 (alkyne) or 0–1.0 (nitrile) and are presented in the Parula LUT available in MATLAB®.

Chemical Synthesis

General Procedures

All reagents were obtained from commercial sources, including Sigma-Aldrich, Alfa Aesar and Fluorochem and used without purification unless otherwise stated. The abbreviations Et$_2$O and NEt$_3$ refer to diethyl ether and triethylamine, respectively. The term “in vacuo” refers to evaporation under reduced pressure using a rotary evaporator connected to a diaphragm pump, followed by the removal of trace volatiles using a high vacuum (oil) pump. The term “purged” refers to atmospheric exchange via 3 evacuation/refill cycles using a Schenck line fitted to a cylinder of inert gas and a high vacuum (oil) pump. Flash chromatography was carried out using Fischer Scientific chromatography grade silica 60 Å particle size 35–70 micron. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Machery-Nagel pre-coated TLC sheets, coated in 0.20 mm silica gel 60 with UV$^{254}$ fluorescent indicator. Sheets were visualized under UV light (at 254 nm) or stained using p-anisaldehyde. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance
500 spectrometer, operating at 500 MHz (1H) and 125 MHz (13C). Chemical shifts were reported in parts per million (ppm) in the scale relative to CDCl₃, 7.26 ppm for 1H NMR and 77.16 for 13C NMR. Multiplicities are abbreviated as: s, singlet; d, doublet. Coupling constants are measured in Hertz (Hz). Melting points were obtained on a Stuart SMP11 device. Infrared spectra were recorded in the range 4000–600 cm⁻¹ on a Shimadzu IRAffinity-1 equipped with an ATR accessory.

Synthesis of Sensor 1, 4-((trimethylsilyl)ethynyl)benzonitrile

![Structure of Sensor 1](image)

A flame dried 20 mL reaction vial was charged with 4-bromobenzonitrile (273 mg, 1.50 mmol, 1.0 eq), bis(triphenylphosphine)palladium (II) dichloride (10.5 mg, 0.015 mmol, 1 mol%) and copper (I) iodide (3.0 mg, 0.015 mmol, 1 mol%), then sealed purged with nitrogen. NEt₃ (degassed by 3 freeze-pump-thaw cycles, 6 mL) was added to the reaction vial via syringe, followed by (trimethylsilyl)acetylene (230 μL, 1.65 mmol, 1.1 eq) and the reaction was heated to 80 °C with stirring for 4 h. After cooling to ambient temperature, the reaction mixture was diluted with Et₂O (20 mL), filtered through a pad of celite® and evaporated in vacuo. Purified by silica flash chromatography (3% Et₂O/petroleum ether 40–60) to yield the title compound 1 as a white solid (285 mg, 1.43 mmol, 95%).

M.P: 100–102 °C [Lit:¹ 102–103 °C]; FTIR (ATR, cm⁻¹): 3063.0, 2955.0, 2897.1, 2233.6, 2156.4, 1602.9, 1498.7, 1408.0, 2146.0, 1176.6; ¹H NMR (500 MHz, CDCl₃): δ 7.59 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 8.6 Hz, 2H), 0.26 (s, 9H); 13C NMR (126 MHz, CDCl₃): δ 132.6, 132.1, 128.2, 118.6, 111.9, 103.1, 99.7, -0.13.
$^1$H NMR Spectrum of Sensor 1 (500 MHz, CDCl$_3$)

$^{13}$C NMR Spectrum of Sensor 1 (126 MHz, CDCl$_3$)
Previously reported fluorescent fluoride sensors. The sensors are grouped by function: a metal chelation sensor, boronic acid fluoride sensors, fluoride sensors based on Si-O bond cleavage and fluoride sensors based on Si-C bond cleavage.

**Metal-chelation sensor**

![Metal-chelation sensor](image)

MW: 476.43 g/mol  
*Chem. Commun.* 2011, 47, 4391

**Boronic acid sensors**

![Boronic acid sensors](image)

MW: 249.08 g/mol  

MW: 317.17 g/mol  

**Fluorescent sensors based on Si-O bond cleavage**

![Fluorescent sensors based on Si-O bond cleavage](image)

MW: 472.61 g/mol  
*Chem. Commun.* 2009, 4735

MW: 496.52 g/mol  
*Org. Lett.* 2010, 12, 1400

MW: 813.94 g/mol  

MW: 520.79 g/mol  
*Chem. Commun.* 2011, 47, 7098

MW: 386.49 g/mol  
*J. Org. Chem.* 2011, 76, 3820

**Fluorescent sensors based on Si-C bond cleavage**

![Fluorescent sensors based on Si-C bond cleavage](image)

MW: 446.45 g/mol  
*Tetrahedron* 2010, 66, 1728

MW: 979.46 g/mol  
*Chem. Commun.* 2011, 47, 5503

MW: 683.05 g/mol  

MW: 587.07 g/mol  
*Org. Biomol. Chem.* 2011, 9, 4558

MW: 675.04 g/mol  
*Org. Lett.* 2013, 15, 3518

Figure S1: Previously reported fluorescent fluoride sensors. The sensors are grouped by function: a metal chelation sensor, boronic acid fluoride sensors, fluoride sensors based on Si-O bond cleavage and fluoride sensors based on Si-C bond cleavage.
**Figure S2** Analysis of sensor 1 and desilylated product 2 in solid form. Raman spectra were acquired from solid samples of sensor 1 (top, blue trace) and desilylated alkyne 2 (bottom, red trace) using $\lambda_{ex} = 785$ nm for 10 s with a 20× objective lens (~95 mW). Peak assignments are in cm$^{-1}$.

**Figure S3** Analysis of the desilylation of sensor 1 using different fluoride sources. Sensor 1 (5 mM) was treated with NaCl, NaF or CsF at a concentration of 50 mM (10 equiv.) in THF:Water (1:1 v/v). Raman spectra were acquired after 30 min at 20 °C using 785 nm for 10 s with a 20× objective lens (~180 mW). **A** Average Raman spectra acquired from 6 replicates normalised to the THF peak at 1450 cm$^{-1}$. **B** Ratio analysis of the 2109 / 2162 cm$^{-1}$ peaks from the 6 replicates in **A**. Error bars: ±S.D.
Figure S4 Control reactions for the desilylation reaction of sensor 1. A A mixture of sensor 1 (5 mM in THF:water 1:1 v/v) was analysed using Raman spectroscopy at t = 0 min and t = 30 min. The acquisitions show no peak at 2109 cm\(^{-1}\) (i.e. no desilylated product 2 was observed). Raman spectra were acquired using 785 nm excitation and a 20× objective lens (~180 mW) for 10 s. B Analysis of sensor 1 with different counter anions. Sensor 1 (5 mM in THF) was treated with either THF (Blank) or TBAX (X= F, Cl, Br; 50 mM prepared from a 100 mM stock in water). Raman spectra were acquired after 30 min at 20 °C using 785 nm for 10 s using a 20× objective lens (~180 mW). Data represents the mean peak area ratio at 2109/2162 cm\(^{-1}\) from three replicates with error bars ± S.D. C and D Analysis of sensor 1 with different counter anions. Sensor 1 (5 mM in THF) was treated with NaX (X= fluoride, acetate, ascorbate, hydrogen carbonate, citrate, nitrate and phosphate; 50 mM prepared from a 100 mM stock in water). Raman spectra were acquired after 30 min at 20 °C using 785 nm for 10 s using a 20× objective lens (~180 mW). Data represents the mean peak area ratio at 2109/2162 cm\(^{-1}\) from three replicates with error bars ± S.D. E As per C and D, but using NaI and at high pH using NaX (X = carbonate and hydroxide) showing decomposition of the sensor occurs.
**Figure S5** Solution phase analysis of sensor 1. **A** Calibration curve of sensor 1 in THF. Solutions of sensor 1 were analysed by Raman spectroscopy using $\lambda_{ex} = 785$ nm using a 5× lens (~180 mW) for 30 s (3 accumulations). A linear fitting is applied. **B** Analysis of the reaction of sensor 1 with 1 equiv. TBAF at (i) Sensor 1 (250 μM) + TBAF (250 μM) and (ii) Sensor 1 (500 μM) + TBAF (500 μM). In the samples labelled ‘Blank’, TBAF was replaced with an equal volume of THF. Raman spectra were acquired as per A. Data represent the mean peak area ($A_p$) ratio at 2109/2162 cm$^{-1}$ from three repeats with error bars ± S.D. **C** Analysis of sensor 1 in THF:PBS (1:1 v/v). A 5 mM solution of sensor 1 was treated with (i) THF:PBS (1:1 v/v) (blank) or (ii) TBAF (50 mM in THF:PBS (1:1 v/v)). Raman spectra were acquired after 15 min at RT using $\lambda_{ex} = 785$ nm using a 5× lens (~180 mW) for 10 s. Spectra representative of 3 repeats.

**Figure S6** Analysis of the desilylation of sensor 1 using UV-Vis spectrometry. **A** Sensor 1 (50 μM) was mixed with TBAF (50 μM) in THF and sequentially analysed by UV-Vis spectrometry for 10 min. **B** A plot of absorbance at 275 nm as a function of time for the reaction in A. This reaction shows a decrease in absorbance at ~280 nm which is in good agreement with a similar TMS-protected alkyne – see Supplementary Information File Ref. [2].
Figure S7 Analysing the effect of water upon the desilylation reaction of sensor 1. A Reaction profiles for the desilylation reaction of 1 (50 mM) with TBAF (75 mM) in (i) THF, (ii) THF:water (90:10 v/v) and (iii) THF-water (80:20 v/v). The peak areas ($A_p$) at 2162 cm$^{-1}$ (C≡C-TMS, 1), 2109 cm$^{-1}$ (desilylated alkyne, 2) and 2230 cm$^{-1}$ (C≡N) are plotted as a function of time. B Control reaction of sensor 1 (50 mM) in the absence of TBAF in THF solution. C Reaction profiles for the decrease in the 2162 cm$^{-1}$ signal (sensor 1) when the %water is varied in the reaction mixture. $A_p$ = peak area at 2162 cm$^{-1}$. Raman spectra were acquired using 785 nm
for 0.5 s using a 5× objective lens (~180 mW) and normalised to the intensity of the THF solvent peak at 1450 cm⁻¹ (CH₂ def). The reaction monitoring started ~5 s after the addition of TBAF. 

D Reaction profiles for the desilylation reaction of 1 (5 mM) with TBAF (7.5 mM) in (i) THF, (ii) THF:water (90:10 v/v), (iii) THF:water (80:20 v/v), (iv) THF:water (75:25 v/v) and (v) is a control reaction where [TBAF] = 0 mM. The peak areas (A₀) at 2162 cm⁻¹ (C≡C-TMS, 1) and 2109 cm⁻¹ (desilylated alkyne, 2) are plotted as a function of time. Raman spectra were acquired using 785 nm for 1 s using a 5× objective lens (~180 mW) and normalised to the intensity of the THF solvent peak at 1450 cm⁻¹ (CH₂ def).

Figure S8 Paper-based detection of fluoride using Raman sensor 1 using the ratio of the nitrile band. A These maps accompany those acquired in Figure 4. Filter paper was pre-treated with sensor 1 (100 mM in THF, 10 µL) before air-drying and subsequent treatment with TBAF in THF at the indicated concentrations. Raman maps were acquired across 20 µm × 20 µm (1 µm pixel size; 400 spectra) using 785 nm laser excitation with a 20× objective lens (~180 mW) for 0.5 s. The maps represent the ratio of the nitrile band at 2231 cm⁻¹/2237 cm⁻¹ (for desilylated product/sensor 1). B Expanded view of the Raman spectra presented in Figure 4B, indicating signal at 2109 cm⁻¹ when 125 µM TBAF is added.
Figure S9 Repeat analysis of the paper-based detection of fluoride using Raman sensor 1. Filter paper was pre-treated with sensor 1 (100 mM in THF, 10 µL) before air-drying and subsequent treatment with TBAF in THF at the indicated concentrations. Raman maps were acquired across 20 µm × 20 µm (1 µm pixel size; 400 spectra) using 785 nm laser excitation with a 20× objective lens (~180 mW) for 0.5s. The maps represent the following ratios: A 2105 cm⁻¹/2160 cm⁻¹; B 2231 cm⁻¹/2237 cm⁻¹ (for desilylated product/sensor 1) and C the average Raman spectra from the maps presented in A and B.

Figure S10 Paper-based detection of fluoride using a Raman microscope and a handheld spectrometer. Filter paper was pre-treated with sensor 1 (100 mM in THF, 10 µL) before air-drying and subsequent treatment with TBAF in THF (either 125 µM or 0 µM). Point spectra were acquired using either (A) – (B) a Raman microscope (785 nm laser excitation with a 20× objective lens (~180 mW) for 10s) or (C) a handheld spectrometer (785 nm laser excitation for 10s (~55 mW). Three repeat spectra from the same paper test strip are provided in each case.

References