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Selective and colorimetric fluoride anion chemosensor based on s-tetrazines[†]

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s-Tetrazine and their derivatives are found to be a class of selective and colorimetric chemosensors for fluoride anions. The supramolecular interaction (anion– π and charge/electron transfer) between fluoride ion and π -electron deficient tetrazines receptor could facilitate the F⁻–tetrazines electron transfer (ET) event that generates tetrazine⁻ radical anion. Accordingly, the color of its solution changed from red to green. Furthermore, the recognition of F⁻ in DMSO is tolerant to water (DMSO–H₂O = 9 : 1, v/v) and shows excellent selectivity towards other anions, especially H₂PO₄⁻ and OAc⁻.

Introduction

The construction of selective chemosensors for cations has grown very well,¹ while the design of new types of anion receptors are receiving increasing attention.² Fluoride anion plays an important diverse role from being a useful additive in the human diet and also in industrial processes.^{3a-d} It is also a dangerous pollutant.^{3e} Therefore, the sensing and recognition of fluoride anion has grown into an area of great interest in supramolecular and biological chemistry in recent years.⁴ Fluoride displays a high hydration energy compared to other anions, which makes it less easily distinguishable from water even in aqueous mixtures (organic solvent-water mixtures).⁵ Most of the fluoride anion receptors commit the binding to H-bonding interactions.⁶ However, this interaction is nonchromogenic which means it cannot display a colorimetric response.⁷ Deprotonation is an effective way to accomplish naked-eye recognition. But it can not differentiate F⁻ from other strongly basic anions, such as AcO⁻ and H₂PO₄^{-.4*a*} Recently, Saha and co-workers reported an example of a F⁻ colorimetric sensor involving π -electron deficient colorless NDI receptors.8

s-Tetrazines show some rare and useful characteristics that make them usable for several types of applications in various domains.⁹ But their applications in supramolecular chemistry are still rare. Because of their electron-deficient character, the *s*-tetrazines can accept one electron to give a stable anion radical.¹⁰ Recently, some computational results showed that the *s*-tetrazines can be used as binding units for the molecular recognition of anions.¹¹ Especially, the complexation with fluoride through the



Fig. 1 Schematic illustration of the sensing mechanism of *s*-tetrazines towards fluoride anion.

anion– π interaction would be more favorable.¹¹ For this reason, we envisioned to develop a fluoride sensor based on *s*-tetrazines.

In addition, *s*-tetrazines generally have a deep color ranging from purple to orange to red because of a weak $n-\pi^*$ transition located in the visible region.^{9*a*} This is an advantage in accomplishing the visible naked-eye detection.

Herein we report a visible fluoride anion sensor based on *s*-tetrazines and amide. The amide can locate the fluoride anion nearby the *s*-tetrazines through hydrogen-bond interaction. The anion– π interaction between the fluoride anion and the *s*-tetrazines can induce the electron transfer from fluoride anion to the *s*-tetrazines and generate an anion radical of *s*-tetrazine (Fig. 1). A visible color change from red to green was observed. Moreover, this sensor has excellent selectivity towards fluoride anion even in an aqueous environment.

Results and discussion

Synthesis

Compound **3** was obtained in three steps (Scheme 1) in 45% overall yield. The ring closure occurs with 52% yield in high dilution conditions in the presence of Et₃N. Disubstitution with the sulfur could be easily accomplished under mild conditions.¹² However, the presence of sulfur makes the tetrazines non-fluorescent.^{9a}

Energy minimized structures of 3.F⁻ complex

DFT modeling $(B3LYP/6-31G^*)$ of the complexes formed between **3** and the halides was shown in Fig. 2. The interaction

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Fig. 2 Model (B3LYP/6-31G*) of the structures for halide complexation with 3.



Fig. 3 Changes in the UV-vis spectra of 3 (2 \times 10⁻⁴ M in DMSO) upon titration with *n*-Bu₄NF from 1 to 10 equiv.

of the tetrazine and anions greatly depended on the volume of the anions. As shown in Fig. 2, there was strong hydrogen-bond interaction between the F^- and the amide N–H. The fluoride anion could lie in the cavity which was formed from amide N–H and the tetrazine. F^- located just above the tetrazine. The size of Cl^- , Br^- and I^- are too big to be inside the cavity and interact with the tetrazine. According to the modeling of $3 \cdot F^-$ complex, the interaction of the F^- and tetrazine is expected.

UV-vis spectral titration and mechanism study

Fig. 3 showed the absorption spectral changes of **3** with the increase of the F⁻ concentration in DMSO at room temperature. The UV-vis spectrum of **3** showed two peaks at 427 nm and 525 nm. The band centered at 427 nm can be attributed to a π - π * transition while the one at 525 nm corresponds to an n- π * transition.^{9a,12} Upon addition of F⁻, compound **3** showed an



Fig. 4 ESR spectra of 3 and 3 in the presence of 5 equiv. F⁻ in DMSO (2.0 \times 10⁻⁴ M).



Fig. 5 ¹H NMR titration of **3** with F^- (DMSO-d₆, 298 K).

instantaneous color change from red to green. The intensity of the absorption maximum of 3 at 525 nm decreased following the formation of a new band centered at 572 nm. The band at 427 nm increased obviously accompanied with a 20 nm blue shift. All these changes could be attributed to the formation of tetrazine radical anion.^{10a,13} Another strong evidence for the formation of the radicals 3^{-} comes from the diagnostic EPR signal which is unique to the tetrazine radical anion formed in the presence of fluoride (Fig. 4). The spin is virtually localized at the four nitrogen centers and the four tetrazine ¹⁴N nuclei display a typical widely spaced nonet with ca. 5.0 G hyperfine splitting.^{10e,14} During the titration, amide proton c down-field shifted to 9.27 ppm, proton a was split into two peaks at 8.75 ppm and 8.48 ppm, proton b showed a similar trend, the proton signal of 3 gradually disappeared after more than 1 equiv. of fluoride was added (Fig. 5), indirectly indicating the formation of the 3^{--} radical anion.⁸ All the results support our hypothesis that tetrazines-F⁻ interactions facilitate the F⁻-tetrazines ET event that generates the $3^{\cdot-}$ radical anion.

Selectivity study

An important feature of a new chemosensor is its high selectivity. To investigate the selectivity of 3 toward F^- , other



Fig. 6 (a) Absorbance spectra change of **3** $(2 \times 10^{-4} \text{ M in DMSO})$ upon addition of different anions (10 equiv.). (b) Absorbance spectra change of **3** $(2 \times 10^{-4} \text{ M in DMSO})$ upon addition of the mixed anions (mix = Cl⁻, Br⁻, I⁻, N₃⁻, PF₆⁻, AcO⁻ and H₂PO₄⁻); each one is 10 equiv. of anions and subsequent addition of 30 equiv. of F⁻ in DMSO. (c) Color change of **3** in the presence of different anions. From left to right: blank, F⁻, Cl⁻, Br⁻, I⁻, N₃⁻, PF₆⁻, AcO⁻ and H₂PO₄⁻.

competitive anions such as Cl⁻, Br⁻, I⁻, N₃⁻, PF₆⁻, AcO⁻ and H₂PO₄⁻ were chosen. As shown in Fig. 6a, under identical conditions, no significant changes were observed in the UV-vis spectra of **3** upon addition of the anions above, respectively. Therefore, compound **3** showed good selectivity for fluoride in DMSO, and the detection limit was obtained from three times the standard deviation of the blank signal (3s) as 6.7 μ M. Even in the presence of 10 equiv. mixed anions, titration with F⁻ also caused significant changes in the UV-vis spectra (Fig. 6b). In addition, the naked-eye detection of F⁻ is also accomplished. Fig. 6c showed the color change of **3** in the presence of different anions. When F⁻ was introduced, the color changed from red to green. Other anions did not induce any significant color change of **3**. The unique F⁻ induced radical anion generation process renders the sensor excellent selectivity. The F⁻ has a 2p orbital



Fig. 7 Changes in the UV-vis spectra of 3 $(2 \times 10^{-4} \text{ M in DMSO})$ upon addition of F⁻ and subsequent excess of NOBF₄.

and a smaller ionic radius (1.33 Å) compared to other anions.¹⁵ This allows F⁻ to be captured into the cavity easily and get close to the tetrazine π -surface and engage in efficient anion– π and charge transfer (CT) interactions through better orbital interactions with tetrazine.¹⁶ These interactions facilitate an electron transfer from F⁻ to the tetrazine π -system and generate the green tetrazine⁻⁻ radical anion. Other anions, because of the larger size and orbital mismatch, can not induce the tetrazine π -system to generate radical anions.

Reversibility study

The $3-F^-$ interaction is reversible by NOBF₄ oxidation of the 3^{--} radical anion to regenerate 3. As shown in Fig. 7, the original UV-vis spectra reappeared, showing the maximum absorption band at 525 nm and 427 nm. And the color of the solution changed from green to red. The result indicated that the $3-F^-$ interaction is noncovalent interaction, which also supports our hypothesis that tetrazines- F^- interactions induce the tetrazine π -system to generate a radical anion.

Detection in aqueous media

As we know, fluoride is strongly solvated in water. Its hydration free energy is about 100-110 kcal mol^{-1.17} All these factors make the detection of fluoride in aqueous media much more difficult. Indeed, there are very few receptors which can achieve anion binding in water developed so far. With respect to the proposed mechanism we presumed that it could also be possible to determine the fluoride content in aqueous solutions. Therefore, we examined the detection of F⁻ in the media containing water. Fig. 8 showed that the sensing system tolerated up to 10% water in the solvent. With the addition of F⁻, two isoabsorptive points at 453 nm and 556 nm were observed. UV-vis spectra change is similar to that with DMSO.

Conclusion

The tetrazine derivative was first exploited for sensing F^- ions. We have synthesized a macrocyclic anion receptor with a tetrazine unit. The cavity is just suitable for F^- . The supramolecular tetrazine– F^- (anion– π and CT) interactions promote an electron transfer process from the F^- ion to electron-deficient tetrazine





Fig. 8 Changes in the UV-vis spectra of **3** $(2 \times 10^{-4} \text{ M})$ upon titration by *n*-Bu₄NF from 5 to 20 equiv. in a DMSO–water solution (9 : 1, v/v).

and generates the tetrazine⁻⁻ radical anion accompanied with the color changes from red to green. A class of selective and colorimetric chemosensors for fluoride anion was developed based on this compound. This sensor showed excellent selectivity and can be used in aqueous mixtures. The applications of tetrazines as supramolecular and functional organic materials were developed.

Experimental

Synthesis of 2

A solution of 5-nitroisophthaloyl dichloride **1** (2.5 g, 10 mmol) and Et₃N (2.5 g, 25 mmol) in CH₂Cl₂ (50 mL) was cooled to 0 °C. 2.9 g 2-Aminoethanethiol hydrochloride (25 mmol) in 20 mL CH₂Cl₂ was added dropwise and the solution was stirred at room temperature (R.T.) for 5 h. The solution was concentrated under reduced pressure. The residue was washed with H₂O (50 mL × 3) and dried in vacuum to yield compound **2** (3.0 g, yield = 90%). ¹H NMR (600 MHz, DMSO-d₆) δ 9.14 (s, 2H), 8.81 (s, 2H), 8.77 (s, 1H), 3.48 (dd, *J* = 13.0, 6.5 Hz, 4H), 2.70 (dd, *J* = 14.6, 7.6 Hz, 4H); ¹³C NMR (150 MHz, DMSO-d₆) δ 164.2, 148.3, 136.5, 132.8, 124.7, 43.5, 23.6; MS (EI): *m/z* Calcd for C₁₂H₁₅N₃O₄S₂ (M) 329.05; Found 329 (M); elemental analysis calcd (%) for C₁₂H₁₅N₃O₄S₂: C 43.76, H 4.59, N 12.76; found: C 43.70, H 4.66, N 12.85.

Synthesis of 3

In a 500 mL three-necked round bottom flask, 300 mL of acetonitrile was added. 330 mg (1 mmol) of **2** and 250 mg (2.5 mmol) of triethylamine dissolved in 30 mL acetonitrile and 300 mg (2 mmol) of dichloro-*s*-tetrazine dissolved in 30 mL of acetonitrile were added dropwise at the same speed through two separate addition funnels. After completion of the addition, the solution was evaporated and the residue was purified by column chromatography (CH₂Cl₂–CH₃OH = 50 : 1 as eluent) to yield **3** as a red solid (215 mg, yield = 52%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.43 (s, 2H), 8.33 (s, 2H), 7.69 (s, 1H), 3.85 (s, 4H), 3.73 (s, 4H); ¹³C NMR (150 MHz, DMSO-d₆) δ 173.2, 165.1, 148.5, 136.6, 131.5, 124.9, 41.8, 29.7; MS (EI): *m/z* Calcd for C₁₄H₁₃N₇O₄S₂ (M) 407.05; Found 407 (M); elemental analysis calcd (%) for $C_{14}H_{13}N_7O_4S_2$: C 41.27, H 3.22, N 24.06; found: C 41.19, H 3.28, N 24.01.

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