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Selective recognition of fluoride ions through fluorimetric and colorimetric response of a first mesitylene based dipodal sensor employing thiosemicarbazones

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ABSTRACT

A new dipodal chromo-fluorogenic anion sensor (2Z,2'Z)-2,2'-(((((2,4,6-trimethyl-1,3-phenylene))bis-(methyl-ene))bis-(oxy))bis(2,1-phenylene))bis(methanylylidene))bis(N-methylhydrazinecarbothio-amide) has been synthesized and characterized for the detection of F⁻ ion in DMSO. The sensor has proven to be highly selective and sensitive to F⁻ ion, moreover it can act as naked eye chromogenic sensor. The mechanism involved in the detection of fluoride ion is the deprotonation of the –NH groups, which was confirmed by using TBAOH. The pre-organization of the dipodal receptor provides chelating H-bonds with the spherical F⁻ ion. These strong H-bonding interactions result in fast deprotonation of the sensor, producing an optical response. Employing only a weak fluorescence capability of the imine groups,**1** $behaves as a fluorogenic sensor by exhibiting fluorescence enhancement at <math>\lambda_{ex}$ 438 nm upon addition of F⁻ ions.

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The design and synthesis of anion sensing receptors have drawn considerable attention because anions play an important role in biological, medical, environmental, and chemical sciences.¹ For example, Chloride ion measurements can aid in monitoring of blood brain disorders and cystic fibrosis.² The monitoring of nitrate levels is used to trace pollution from agriculture, for checking fish farms, and for surveying nutrient levels in natural water bodies. Fluoride ion is used in dental care and treatment of osteoporosis and due to its release during hydrolysis of nerve gas Sarin.³ However, its excessive use may cause fluorosis.⁴ Among various chemosensors, those which can detect the presence of anions through both chromogenic and fluorogenic response are exceptionally interesting as their sensing process is marked by simple, naked eve detection and also at very low concentration. Most of the neutral anion sensors employ polarized N-H fragments for anion recognition and are based upon ureas, thioureas, amides, amidoureas, pyrroles, and amines.⁵ The recognition phenomenon in these examples involves either H-bonding (incipient proton transfer) or complete deprotonation of N–H protons (frozen proton transfer).⁶

Previously, our group has reported sensors, based on aromatic platform which had imine and hydroxyl groups⁷ or urea/thiourea⁸ as end groups in the receptors. As an extension of our work, we have now employed thiosemicarbazide moiety as end groups on

supramolecular platform, in order to get an insight into the combined effect of imine and thiourea groups and study the sensing properties of the sensor. There are a few reports of sensors containing thiosemicarbazide moieties with⁹ or without¹⁰ appended fluorophore. Here, we present to the best of our knowledge, the first example of mesitylene based F^- ion sensor which is a dipodal probe containing thiosemicarbazones, without any additional fluorophore. Both, binding and signaling for the sensing are done by the thiosemicarbazone moiety itself. The dipodal probe contains two thiosemicarbazones lying in close proximity to each other and thus represents a simple, pre-organized, highly selective and sensitive colorimetric and fluorogenic sensor based on a supramolecular platform.

The synthesis of sensor **1** involves a three-step reaction according to Scheme 1.¹¹ Compound **2** was prepared by previously reported method.¹² Dipodal aldehyde (**3**) was prepared by the reaction of 2-hydroxybenzaldehyde with dibromide **2** in the presence of K₂CO₃ in dry acetonitrile. Then, a simple Schiff's base condensation reaction of compound **3** and 4-methyl-3-thiosemicarbazide in acetonitrile gave the desired product **1**. The products were characterized by various spectroscopic techniques (Fig. S1–S7). A pair of strong stretching bands at 3274 cm⁻¹ and 3106 cm⁻¹ shows the presence of -N-H groups. The IR band at 1527 cm⁻¹ confirms the presence of C=N group. In ¹H NMR, the signals at δ 8.4 and 11.4 correspond to NH(f) and NH(e) groups, respectively while the signal at δ 8.3 indicates the formation of imine (CH=N) group. In ¹³C NMR spectrum, signals for CH=N,





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Scheme 1. Synthesis of (2Z,2'Z)-2,2'-(((((2,4,6-trimethyl-1,3-phenylene)bis(methylene))bis(oxy))bis(2,1-phenylene))bis-(methanylylidene))bis(*N*-methylhydrazine carbothioamide).



Figure 1. Changes in the UV-vis spectrum of (1) in DMSO $(2\times10^{-5}\,M)$ on the addition of various TBAX ions $(2\times10^{-4}\,M)$ in DMSO.

C–O, and C=S appear at δ 138.5, 157.3, and 177.5, respectively. The signals corresponding to quaternary carbons are absent in DEPT 135 spectrum. The formation of sensor **1** was also confirmed by the peak in mass spectrum at 563.22 for [M+H]⁺. The CHN data are also in accordance with the molecular formula.

The anion recognition ability of sensor **1** was determined by the UV–vis and fluorescence studies upon addition of various tetrabutylammonium anions (TBAX, where X = F⁻, Cl⁻, Br⁻, I⁻, NO₃⁻, CN⁻, AcO⁻, HSO₄⁻, ClO₄⁻ and H₂PO₄⁻) in DMSO (2 × 10⁻⁴ M). The reaction mechanism proposed was confirmed by NMR spectroscopy.

The sensor **1** (2 × 10⁻⁵ M) exhibits a strong absorption band at λ_{max} 337 nm (ϵ_{max} 65,600 M⁻¹ cm⁻¹), which has been designated as an intraligand charge transfer (ICT) band involving imine (CH=N) groups. As 10 equiv of tetrabutylammonium fluoride was added to the solution of sensor **1**, the absorption band at 337 nm disappears and a new band appears at λ_{max} 402 nm (ϵ_{max} 50,200 M⁻¹ cm⁻¹) with a bathochromic shift of 65 nm (Fig. 1).

This red shift in absorption band for TBAF was accompanied by a color change from colorless to yellowish green (Fig. 2). No such spectral or visual change was observed for any other tetrabutyl ammonium anions (TBAX) under study (Fig. S8–S9).

The ratiometric response of the sensor **1** with increase in equivalents of TBAF is shown in Figure 3. The stoichiometry of the reaction of sensor **1** and TBAF is 1:1 according to Job's plot¹³ studies (Fig. S10). The equilibrium constant, *K* of the sensor **1** for the fluoride ion has been calculated as $2.66 \times 10^3 \text{ M}^{-1}$ from the Benesi–Hildebrand plot¹⁴ (Fig. S11). The stability of the complex was confirmed by the decrease in free energy of $-19.54 \text{ kJ mol}^{-1}$, calculated from the equation $\Delta G = -2.303 \text{ RT} \log K$.

Fluorescence studies of sensor **1** were also performed with the solutions of the same concentration that is, sensor **1** $(2 \times 10^{-5} \text{ M})$ and TBAX $(2 \times 10^{-4} \text{ M})$. Sensor **1** contains no additional fluorophore, hence upon excitation at λ_{ex} 267 nm, it shows a very weak broad fluorescence emission band in the range of 350–500 nm. This band has low intensity because of efficient photoinduced electron transfer (PET) quenching,¹⁵ which comes into play due to availability of the lone pair of adjacent NH group.

Upon addition of TBAF, the fluorescence spectrum exhibits an emission band at λ_{max} 438 nm with shoulder at 375 nm and at 480 nm (λ_{ex} 267 nm) but no such spectral change is observed with other TBAX ions (Fig. 4, Fig. S12). Upon complexation of the F⁻ ion, the PET phenomenon may be reduced when –NH groups are involved in H-bonding with the TBAF anions resulting in the enhancement of the signal in fluorescence spectrum (Fig. 5a). The detection limit¹⁶ for F⁻ ion was estimated to be 2 × 10⁻⁵ mol/L at $I/I_0 = 3$ (Fig. 5b).

The sensing selectivity of sensor **1** toward F^- ions was evaluated in the presence of 10 equiv of other tetrabutyl ammonium anions including Cl⁻, Br⁻, I⁻, NO₃⁻, CN⁻, AcO⁻, HSO₄⁻, ClO₄⁻ and H₂PO₄⁻. The excellent selectivity of sensor **1** for fluoride over other anions is evident from the pronounced differences in absorbance (Fig. S9), in color changes (Fig. 2), and in fluorescence (Fig. S13). The selectivity for F⁻ over other anions, especially CN⁻ and CH₃COO⁻, is important because many reported fluoride sensors suffer from the deleterious interference of these anions.

In order to investigate the binding sites of sensor **1** for the F^- ions, NMR titrations were carried out in DMSO- d_6 , with increasing amounts of TBAF as shown in Figure 6. NMR spectra of sensor **1**



Figure 2. Visual color changes in (1) in DMSO (2 \times 10⁻⁵ M) with various TBAX ions (2 \times 10⁻⁴ M).



Figure 3. (a) Changes in UV-vis spectra of sensor (1) $(2 \times 10^{-5} \text{ M})$ upon gradual addition of TBAF; (b) F⁻ titration profile at 337 nm and 402 nm.



Figure 4. Fluorescence ratio $[I/I_o]$ of sensor (1) $(2 \times 10^{-5} \text{ M})$ at λ_{max} 438 nm upon addition of various anions $(2 \times 10^{-4} \text{ M})$ with excitation at 267 nm in DMSO. I_o and I are the intensities in the absence and presence of anions, respectively.

show that the signals for the -NH(e) groups, which were observed at 11.4 ppm disappear completely much before the complete addition of 1 equiv of TBAF, indicating that the deprotonation is too fast to register the effect of H-bonding on the -NH signals in ¹H NMR. But the signals for the -NH(f) protons first get so much broadened that they almost disappear and then are restored again. This deprotonation also causes significant upfield shifts (Table S1) in the NMR signals of aromatic protons (Fig. S14).

In the present case, the H-bonding pocket defined by four -NH protons of dipodal probe 1 which has the potential to bind anions in a chelate mode through four H-bond donation sites, tends to bring the fluoride ion to their vicinity (Scheme 2). Fluoride ion though is a weaker base ($pK_a = 15$ in DMSO), but here it behaves as a very strong base second to OH^- (pK_a = 32 in DMSO) only¹⁷, due to extreme stability of [HF₂]⁻. It is known to induce deprotonation of even less acidic moieties like urea protons.¹⁸ Pre-organization of the four -NH groups to provide a cavity and chelation of F⁻ ions, coupled with the inherent basicity of F⁻ ions in DMSO probably, help in making the deprotonation so fast that the prior H-bonding step is not registered in the ¹H NMR. The existence of [FHF]⁻ however, is unequivocally proved by the presence of a tell-tale,¹⁹ well formed triplet at δ 16.15 ppm in the ¹H NMR of sensor **1** in the presence of 1.0 equiv and above of F^- ion (Fig. 6). The signal due to -NH(f) which seems to disappear, in fact first gets broadened due to chelating H-bonding and then appears again once the deprotonation of the -NH(e) protons occurs. The significant upfield shifts in the aromatic protons and not the methyl group (attached to -NH group) further ratify that it is the -NH group adjacent to the imine which is deprotonated and not the other one. The deprotonation of the sensor 1 was also confirmed



Figure 5. (a) Changes in fluorescence spectra of sensor (1) $(2 \times 10^{-5} \text{ M})$ upon gradual addition of TBAF $(2 \times 10^{-4} \text{ M})$; (b) increase in fluorescence intensity of sensor 1 at 438 nm upon F⁻ ion for the calculation of detection limit.



Figure 6. Full ¹H NMR of (1) in DMSO-*d*₆ (5 mM) showing changes on gradual addition of TBAF.



Scheme 2. Proposed reaction mechanism for formation of sensor 1.

by the Bronsted acid–base reaction between sensor and tetrabutyl ammonium hydroxide,^{20,7b,8} which produces similar absorption and fluorescence spectrum of sensor **1** as found with TBAF (Fig. S15). The negative charge brought about by the anion induced deprotonation increases the dipole moment and stabilizes the excited state causing a red shift of $\Delta \lambda = 65$ nm which results in color change of the solution. The bright yellowish green color obtained on addition of TBAF to sensor **1** is reverted back on addition of traces of water to it. This reversibility of sensor **1** is also observed in its UV–vis spectra. So this sensor cannot be used in aqueous medium for anion sensing.

In conclusion, a new mesitylene based dipodal sensor containing thiosemicarbazone moiety has been synthesized, showing a combined effect of imine and thiourea groups on the sensing properties of the receptor. Sensor **1** is a highly sensitive and selective sensor for F^- ions even in the presence of the other anions under study. The recognition phenomenon involved here is frozen proton transfer, which is confirmed by UV-vis and NMR spectroscopies.

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Supplementary data

Supplementary data associated (general experimental section, characterization of sensor **1** and compound **3** by spectroscopic techniques, absorption and fluorescence spectra, Job's plot, Benesi-Hildebrand plot and NMR studies) with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013. 03.003.

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- Synthesis of sensor 1: To a solution of 199 mg (0.513 mmol) of 2,2'-(((2,4,6-trimethyl-1,3-phenylene)bis(methylene))bis(oxy))dibenzaldehyde (compound 2) in acetonitrile was added 107 mg (1.019 mmol) of 3-methylthiosemicarbazide and the mixture was refluxed for 5 h. The mixture was then cooled to room temperature and filtered, and the solid was washed with cold methanol. The solid was dried and recrystallized in chloroform. Washing the solid with cold methanol gave a pale yellow solid product 1

(161 mg) in 56% yield. IR (KBr, cm⁻¹) 3274, 3106, 2898, 1527, 1224, 1074, 746; ¹H NMR (300 MHz, DMSO- d_6 , δ): 2.35 (s, 6H, –CH₃), 2.38 (s, 3H, –CH₃), 2.97 (d, 6H, –CH₃, *J* = 4.2), 5.15 (s, 4H, –CH₂), 6.99 (s, 1H, –Ar,), 7.02 (d, 2H, –Ar, *J* = 7.5), 7.34 (d, 2H, –Ar, *J* = 8.1), 7.42 (t, 2H, –Ar, *J* = 6.9), 8.09 (dd, 2H, *J* = 7.8), 8.30 (s, 2H, –CH=N), 8.40 (q, 2H, –NH, *J* = 9.0), 11.42 (s, 2H, –NH); ¹³C NMR (75 MHz, DMSO- d_6 , δ): 15.1 (–CH₃), 19.3 (–CH₃), 30.7 (–N–CH₃), 65.3 (–CH₂), 113.1 (–Ar), 120.7 (–Ar), 122.7 (–Ar), 126.1 (–Ar), 129.9 (–Ar), 130.8 (–Ar), 131.1 (–Ar), 137.3 (–CH=N), 138.4 (–Ar), 138.5 (–Ar), 157.4 (–C–O), 177.6 (–C=S); elemental Anal. Calcd for C₂₉H₃₄N₆O₂S₂: C 61.89; H, 6.09; N, 14.93; S, 11.40. Found: C, 61.05; H, 5.98; N, 14.34; S, 11.07; HRMS (ESI): Calcd for C₂₉H₃₄N₆O₂S₂: H m/e 563.2263; Found, 563.2240.

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