A selective chromogenic molecular sensor for acetate anions in a mixed acetonitrile–water medium†

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Quinonehydrazone compound **2**, as a new chromogenic anion sensor, can selectively detect AcO^- over F^- and other anions in mixed acetonitrile–water media. The deprotonation of the N–H proton of the sensor is responsible for the drastic color change. An acidic C–H group in the receptor, probably acting as an accessorial binding site, is essential to the selectivity and affinity for sensing the acetate anions.

Introduction

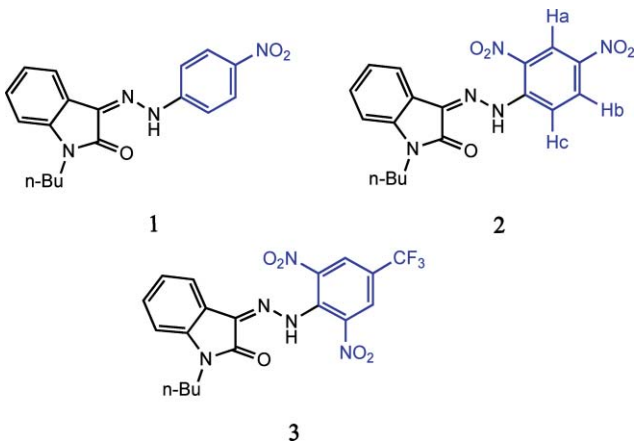
It is well known that anions play an important role in a wide range of chemical and biological processes, therefore the search for chemosensors for recognizing and sensing anions has attracted growing attention. Most chemosensors developed so far are chromogenic and/or fluorescent sensors, which efficiently change their photophysical properties (λ_{max} shift of the UV–vis spectrum, change in the quantum yield or emission wavelength *etc.*) in the presence of anions.[1] Color changes, which can be detected by the naked eye, are widely used to signal events since they are low cost and do not require any spectroscopic instrumentation. The nature of the interaction between anions and charge-neutral organic receptors is primarily based on hydrogen-bonding. In this sense, the receptors must provide one or more hydrogen-bonding donor groups, X–H, where X is typically a nitrogen or oxygen atom. The recognition studies are preferably carried out in aprotic media (*e.g.*, DMSO, acetonitrile, $CHCl_3$ *etc.*), to avoid competition of the solvent (*e.g.*, water or alcohols) as a hydrogen-bonding donor.[1b]

Carboxylate anions are important constituents of biological and synthetic organic molecules such as amino acids and proteins.[2] A number of chromogenic and/or fluorescent sensors for AcO^- have been reported in recent years.[3] Unfortunately, these AcO^- chemosensors usually also display responses to other basic anions such as $H_2PO_4^-$ and F^-, especially the latter. For many charge-neutral chromogenic and/or fluorescent anion sensors reported so far, it has been confirmed that not hydrogen-bonding but deprotonation of the receptor was the cause of the response. This issue has been explicitly discussed, for instance firstly by Gale and co-workers,[4] then Gunnlaugsson and co-workers[1a,5] and Fabbrizzi's groups[1b,6] *etc.*, in a variety of systems. Due to the strong ability of F^- to deprotonate the receptor in aprotic solvents, it is generally difficult to achieve selectivity for AcO^- over F^- using charge-neutral chromogenic sensors, yet much effort has been spent in searching for this.[7,8] On the other hand, charge-neutral organic chromogenic anion sensors applicable in highly competitive solvents such as alcohols or water are rare. Recently, Gunnlaugsson and co-workers reported a chromogenic sensor for AcO^- in a 1 : 1 EtOH–H_2O aqueous solution.[8] Duan and co-workers have reported a chromo- and fluorogenic hybrid chemosensor for F^-, this chemosensor contains a quinonehydrazone group and allows the detection of F^- in water with the naked eye.[9] Herein, we report a new chromogenic anion sensor **2** containing a quinonehydrazone group that can be used in a mixed acetonitrile–water medium and shows selectivity for AcO^- over other anions such as F^- and $H_2PO_4^-$, which have similar basicity to AcO^-.

Results and discussion

Synthesis of receptors

The compounds **1** and **2** were prepared by the reaction of *N*-butylisatin with the corresponding hydrazine in acetic acid, while compound **3** was obtained from the reaction of *N*-butylisatin with hydrazine hydrate followed by reaction with 2-chloro-1,3-dinitro-5-(trifluoromethyl)benzene. The *N*-butylisatin was prepared by a method similar to that described in the literature.[10]



UV–vis studies in acetonitrile

The interaction of the receptors **1**, **2** and **3** with anions was firstly investigated in acetonitrile by UV–vis spectroscopy. Receptor **2**

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† Electronic supplementary information (ESI) available: Titrations of **1**, **2** and **3** with various anions in various solutions; MS and ^1H NMR spectra of **1**, **2** and **3**; ^{13}C NMR spectra of **1** and **3**; and the IR spectrum of **2**. See DOI: 10.1039/b805291c

(2.5×10^{-5} M) shows an intense absorption band centered at 378 nm and a less strong, broad, shoulder peak at about 410 nm. Upon addition of anions such as F^-, Cl^-, Br^-, I^-, HSO_4^-, ClO_4^-, AcO^- and $H_2PO_4^-$ (all as their tetrabutylammonium salts), only F^-, AcO^- and $H_2PO_4^-$ remarkably changed the absorption spectrum of **2**, whereas the other anions tested induced negligible responses (Fig. 1a). During the titration of F^- with a solution of receptor **2**, the intensity of the absorptions at 378 nm and 410 nm decreased and a new absorption band centered at 552 nm appeared (Fig. 1b), which was responsible for simultaneously changing the solution of **2** from yellow to purple. The strong absorption band at 552 nm can be assigned to the deprotonated form ($[L]^-$) of the "azophenol tautomer" in the presence of the interrelated anion (*i.e.*, F^-, AcO^- or $H_2PO_4^-$) with delocalisation of the negative charge from the nitrogen atom to the oxygen atom.[11] This was confirmed by the Brønsted acid–base reaction of **2** with a strong base $[Me_4N]OH$ (see ESI, Fig. S1).† Typically, the deprotonation of the receptor induced by anions can be described by the following two equilibria developed by Fabbrizzi's group:[6]

$$LH + X^- \rightleftharpoons [LH \cdots X]^- \quad (1)$$

$$[LH \cdots X]^- + X^- \rightleftharpoons L^- + [HX_2]^- \quad (2)$$

Probably due to the strong acidity of the N–H proton in the receptor **2**, a genuine H-bond complex, $[LH \cdots X]^-$, has not been observed during the UV–vis titration, and basic anions deprotonated the receptor directly. So the process can be described by the proton-dissociation equilibrium:

$$LH + X^- \rightleftharpoons L^- + HX \quad (3)$$

The equilibrium constant (or proton-dissociation constant) K for F^- was calculated to be $3.73 \times 10^4 \pm 969$ M^{-1} through nonlinear least squares fitting according to a 1 : 1 stoichiometry. AcO^- and $H_2PO_4^-$ can induce similar absorption spectrum and color changes, and the equilibrium constant is $1.88 \times 10^4 \pm 485$ M^{-1} for AcO^- and $2.40 \times 10^3 \pm 56$ M^{-1} for $H_2PO_4^-$, respectively (see ESI, Fig. S2).† The affinity of receptor **2** toward anions in acetonitrile solution is: $F^- > AcO^- > H_2PO_4^- \gg Cl^-$, Br^-, I^-, HSO_4^- and ClO_4^-, owing to the basicity of the anions.[12] Similar results were also obtained upon addition of the representative anions to a solution of receptor **1** or **3** (see ESI, Fig. S3).†

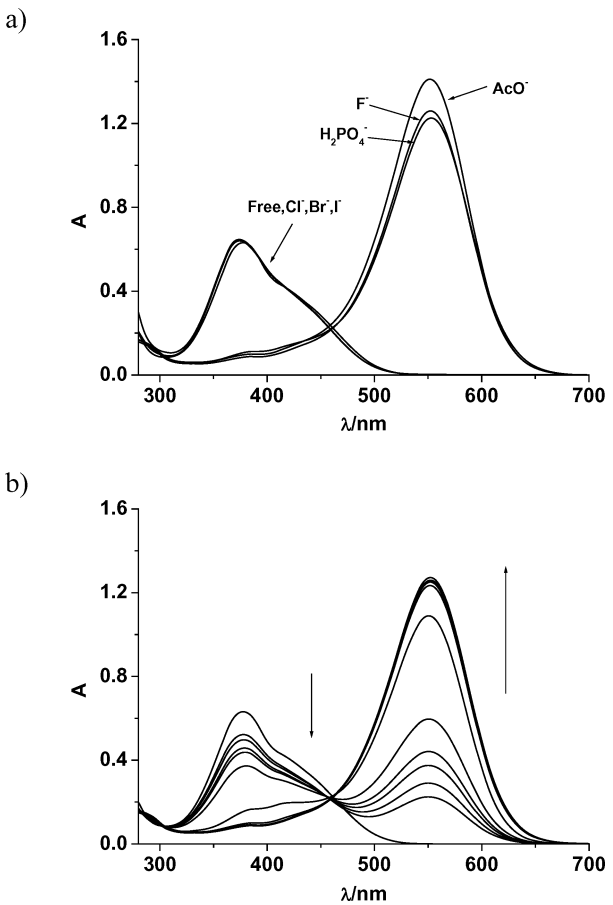

Fig. 1 Changes in the UV–vis absorption spectrum of **2** (2.5×10^{-5} M) in acetonitrile solution: (a) upon addition of 100 equiv. of various anions; (b) upon addition of F^- from 0 to 100 equiv.

UV–vis studies in acetonitrile–water

When we checked the reversibility of these responses, an exceptional result occurred in the interaction of receptor **2** with AcO^-. The absorption spectrum and color changes were not fully reversed upon addition of a small amount of a competitive hydrogen-bonding solvent such as water. To explore this further, a UV–vis spectral titration in 90 : 10 (v/v) acetonitrile–water was carried out. Under these conditions, free receptor **2** (6.25×10^{-6}M) showed an intense absorption band centered at 377 nm with a shoulder at about 410 nm. Upon the addition of anions, **2** showed high selectivity for AcO^- over other anions including F^- and $H_2PO_4^-$ (Fig. 2). The absorption band at 377 nm decreased in intensity and a new strong band at 551 nm appeared, and the color of the solution changed from yellow to purple immediately. The presence of other anions such as F^- and $H_2PO_4^-$ did not interfere in the changes to the absorption bands induced by AcO^- (see ESI, Fig. S4).† The equilibrium constant for AcO^- was calculated to be $8.62 \times 10^3 \pm 97$ M^{-1} according to a 1 : 1 stoichiometry. The results imply that receptor **2** can selectively sense AcO^- in a competitive mixed acetonitrile–water medium. The response to AcO^- can be fully reversed upon addition of a large amount of water (up to 30 vol%, the quantity of water depending upon the concentrations of receptor and anion added) to the purple acetonitrile–water solution containing receptor **2** and AcO^-, as the color of the solution turned back to yellow. However, under the same conditions, neither receptor **1** nor receptor **3** has any response to these representative anions, which means that they cannot serve as anion sensors in such media.

Possible binding mode and ^{1}H NMR studies

It seemed that the selectivity of receptor **2** for AcO^- could be ascribed to the basicity of the anions in aqueous solution (the pK_b values of AcO^-, F^- and $H_2PO_4^-$ in water are 9.24, 10.83 and 11.88, respectively[13]). Nevertheless, why can receptor **2** sense AcO^- in a competitive mixed acetonitrile–water medium but **1** and **3** cannot? Theoretically, the acidity of the N–H group of receptor **3** is stronger than that of receptor **2**. So the selectivity may not be dependent simply upon the basicity of the anions and the acidity of the N–H group. The possibility of the participation

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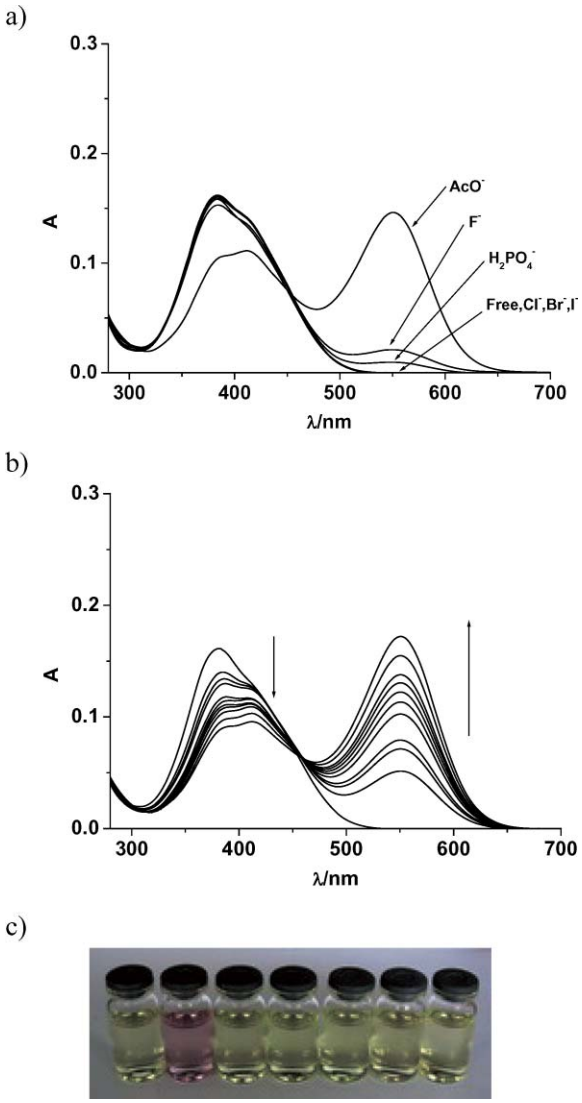

Fig. 2 (a) Changes in the UV–vis absorption spectrum of **2** (6.25×10^{-6} M) in an acetonitrile–water (90 : 10, v/v) solution upon addition of 200 equiv. of anions. (b) UV–vis titration of receptor **2** (6.25×10^{-6} M) in an acetonitrile–water (90 : 10, v/v) solution upon addition of AcO^- (0–520 equiv.). (c) Color changes of **2** (6.25×10^{-6} M) in an acetonitrile–water (90 : 10, v/v) solution induced by addition of 200 equiv. of anions (from left to right: $H_2PO_4^-$, AcO^-, I^-, Br^-, Cl^-, F^-, and anion free).

of the C–H_c group of receptor **2** in the interaction with anions cannot be ruled out. This interaction can perhaps help to stabilize the deprotonation. Whereas receptor **3**, lacking such extra binding from C–H_c, interacts with anions through the N–H group only, and such an interaction may easily be destroyed by water. In the case of receptor **1** only one electron-withdrawing group, $-NO_2$, exists and the acidity of the corresponding C–H proton is probably not strong enough to bind the anions tightly and ensure the efficient deprotonation of the receptor in a competitive mixed acetonitrile–water medium.

To further prove the interaction of receptor **2** with AcO^-, a ^{1}H NMR titration was conducted. Unfortunately, because of the limited solubility of receptor **2** in acetonitrile-d_3 solution, experiments were carried out in $CDCl_3$ solution. A $CDCl_3$ solution of **2** (2.5×10^{-2} M) was titrated with AcO^-, and the shifts of the aromatic C–H protons of the 2,4-dinitrophenyl motif, H_a, H_b and H_c, were monitored (Fig. 3a). Upon gradual addition of AcO^-, the signal of the acidic N–H proton at 12.10 ppm disappeared, and the electron density in the 2,4-dinitrophenyl motif increased with the through-bond propagation and caused a shielding effect, leading to progressive upfield shifts of the H_a and H_b signals. On the other hand, a large downfield shift of H_c from 7.93 ppm (J = 7.2 Hz) to 8.58 ppm ($\Delta\delta$ = 0.65 ppm) was observed. The result suggests that H_c was probably involved in the interaction of the anion with the receptor, and the polarization of the C–H_c bond induced by a through-space effect would cause a deshielding effect. Though the large downfield shift of H_c observed is not enough evidence to account for the C–H interaction, considering the significant selectivity of receptor **2** toward AcO^-, we tentatively ascribed the selectivity to the existence of the C–H group. There is increasing evidence that C–H groups within the charge-neutral receptors can also interact with the anion.[14] Recently, Hay and Bryantsev[15] reported that the aryl C–H group could be a strong hydrogen-bonding donor when electron-withdrawing substituents are present, exhibiting hydrogen-bonding strengths comparable to those obtained with O–H and N–H groups. Furthermore, to mimic the mixed acetonitrile–water environment, a ^{1}H NMR

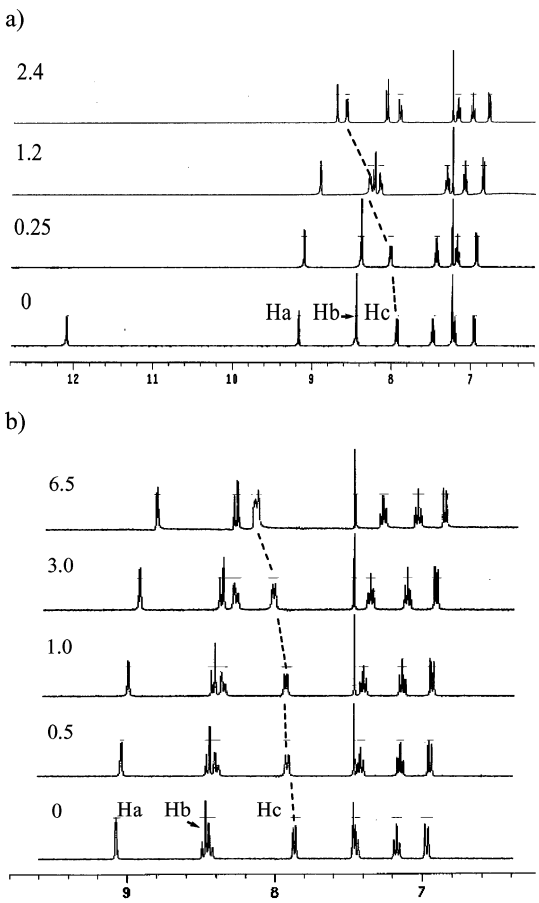

Fig. 3 (a) Titration of receptor **2** (2.5×10^{-2} M) in $CDCl_3$ solution with AcO^- (0, 0.25, 1.2, 2.4 equiv.). The dashed lines track the shift of the H_c signal. (b) Titration of receptor **2** (2.0×10^{-2} M) in a $CDCl_3$–EtOD (1 : 1, v/v) solution with AcO^- (0, 0.5, 1.0, 3.0, 6.5 equiv.). The dashed lines track the shift of the H_c signal.

spectroscopy titration of **2** with AcO^- was carried out in a 1 : 1 (v/v) $CDCl_3$–EtOD solution, as shown in Fig. 3b. The signal of the N–H proton disappeared in such a protic solvent system. Upon addition of $AcO^-$the spectra changes were similar to those found in the $CDCl_3$ solution, with the smaller shifts due to the hydrogen-bonding effect of the EtOH solvent, which weakens the interaction of **2** with the anion.

UV–vis studies in $CHCl_3$–EtOH

Corresponding UV–vis spectral titrations in a 1 : 1 (v/v) $CHCl_3$–EtOH solution were performed, as shown in Fig. 4. In this solution system, receptor **2** showed high selectivity for AcO^-, similar to that observed in the 90 : 10 (v/v) acetonitrile–water solution. Only AcO^- induced remarkable absorption and color changes, with a decrease of the absorption band at 374 nm and the appearance of a new strong absorption band at 556 nm. The equilibrium constant was calculated to be $8.76 \times 10^2 \pm 5\ M^{-1}$. F^-, Cl^-, and $H_2PO_4^-$ can induce slight changes in the absorption spectrum but no obvious color changes can be observed. Other anions such as Br^-, I^-, HSO_4^-, ClO_4^- display almost no response. However, under the same conditions, receptors **1** and **3** remained silent to the anions.

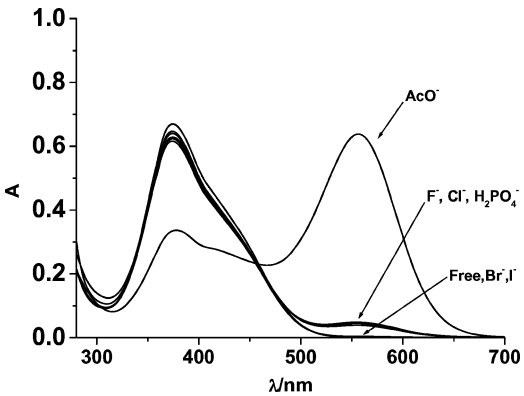

Fig. 4 Changes in the UV–vis absorption spectrum of receptor **2** (2.5×10^{-5} M) in a $CHCl_3$–EtOH (1 : 1, v/v) solution upon the addition of 100 equiv. of anions.

Conclusions

In conclusion, we have developed a new chromogenic anion molecular sensor, which can selectively detect AcO^- over F^- and other anions in a competitive mixed acetonitrile–water medium.[16] An acidic C–H group in the receptor, probably acting as an accessorial binding site, was essential to the selectivity and affinity for sensing the acetate anions.

Experimental

Synthesis of *N*-butylisatin

Sodium (0.46 g, 0.02 mol) was dissolved in 30 mL anhydrous ethanol and stirred for 30 minutes. Isatin (2.94 g, 0.02 mol) was added, the mixture was stirred for 2 h at room temperature, then the solvent was removed under reduced pressure. A large excess of 1-iodobutane (25 mL) was added and the mixture was heated to reflux for 16 h, then the excess 1-iodobutane was removed under reduced pressure. The residue was dissolved in $CHCl_3$ and washed well with water. The organic layer was dried with anhydrous Na_2SO_4 and evaporation of the solvent afforded *N*-butylisatin as a deep-red oil. Recrystallization in acetone–water afforded *N*-butylisatin as red needles. TLC indicated that it was a single compound, which was used directly in next step.

Synthesis of receptor 1

N-Butylisatin (0.406 g, 2 mmol) and 4-nitrophenylhydrazine (0.306 g, 2 mmol) were dissolved in acetic acid and heated to reflux for 2 h. After cooling to room temperature, the mixture was poured into ice–water and the precipitate was collected and dried. Recrystallization from ethanol afforded **1** as a yellow solid. Yield 86%.

MS (ESI): m/z 339.4 ($M + H^+$)

^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 12.929 (s, 1H, N–H), 8.169–8.146 (d, 2H), 7.607–7.589 (d, 1H), 7.316–7.279 (t, 3H), 7.112–7.073 (t, 1H), 6.874–6.855 (d, 1H), 3.753–3.716 (t, 2H), 1.760–1.638 (m, 2H), 1.429–1.336 (m, 2H), 0.967–0.931 (t, 3H).

^{13}C NMR (400 MHz, $CDCl_3$), δ (ppm): 161.957, 147.754, 142.297, 141.432, 130.911, 129.625, 125.761, 122.836, 120.281, 119.860, 113.356, 109.054, 39.335, 29.684, 20.142, 13.632.

Synthesis of receptor 2

N-Butylisatin (0.406 g, 2 mmol) and 2,4-dinitrophenylhydrazine (0.4 g, 2 mmol) were dissolved in acetic acid and heated to reflux for 2 h. After cooling to room temperature, the mixture was poured into ice–water and the precipitate was collected and dried. Further purification by silica column chromatography (CH_2Cl_2–petroleum ether (b.p. 60–90 °C), 3 : 1, v/v) afforded **2** as an orange-red solid. Yield 78%.

MS (ESI): m/z 382.5 ($M - H^+$)

^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 12.105 (s, 1H, N–H), 9.174–9.177 (d, 1H), 8.448–8.452 (d, 2H), 7.926–7.945 (d, 1H), 7.463–7.501 (t, 1H), 7.190–7.228 (t, 1H), 6.949–6.969 (d, 1H), 3.772–3.808 (t, 2H), 1.646–1.720 (m, 2H), 1.378–1.434 (m, 2H), 0.937–0.974 (t, 3H).

IR (KBr): 3441, 3329, 3087, 2957, 2931, 2861, 1733, 1589, 1499, 1335, 1184, 1093, 1026, 830, 738 cm^{-1}.

Synthesis of receptor 3

N-Butylisatin (0.406 g, 2 mmol) and hydrazine hydrate (1 mL, large excess) were dissolved in ethanol and heated to reflux for 12 h. After cooling to room temperature, the mixture was poured into ice–water and the precipitate was collected, washed well with water and dried. The precipitate was dissolved in ethanol, 2-chloro-1,3-dinitro-5-(trifluoromethyl)benzene (0.5 g, 1.8 mmol) was added and the mixture was heated to reflux for 12 h. After cooling to room temperature, the solvent was removed and purification by silica column chromatography (CH_2Cl_2–petroleum ether (b.p. 60–90 °C), 3 : 1, v/v) afforded **3** as a red solid. Yield 30%.

MS (ESI): m/z 450.5 ($M - H^+$)

^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 14.463 (s, 1H, N–H), 8.336 (s, 2H), 7.506–7.487 (d,1H), 7.391–7.352 (t, 1H), 7.123–7.084 (t, 1H), 6.891–6.872 (d, 1H), 3.789–3.752 (t, 2H), 1.731–1.673 (m, 2H), 1.431–1.374 (m, 2H), 0.973–0.936 (t, 3H).

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^{13}C NMR (400 MHz, DMSO-d_6), δ (ppm): 160.255, 142.956, 138.239, 136.105, 135.115, 134.389, 133.032, 131.997, 127.262, 123.177, 120.320, 118.715, 114.174, 111.174, 110.339, 29.121, 19.555, 13.569.

Acknowledgements

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16 We have to point out that the selectivity of receptor **2** for AcO^- over F^- could only be achieved in dilute solution (ranging from $\sim 10^{-6}$ M to $\sim 10^{-4}$ M); under higher concentrations (ranging from $\sim 10^{-3}$ M to $\sim 10^{-2}$ M, suitable for ^{1}H NMR spectroscopy study), F^- and $H_2PO_4^-$ can produce similar responses and thus interfere with the selectivity.