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A naked-eye detection of fluoride with urea/thiourea receptors which have both a benzophenone group and a nitrophenyl group as a signalling group

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Two new colorimetric anion sensors have been synthesised where both a benzophenone group and a nitrophenyl group were used as signalling units and urea/thiourea moieties as binding sites. The receptors, effectively and selectively, recognised fluoride and carboxylate anions from other anions such as chloride, bromide, iodide, perchlorate, hydrogen sulphate and nitrate in DMSO.

Keywords: anion receptor; urea/thiourea; colorimetric receptor; anion recognition

Introduction

Ureas and thioureas participate in bifurcated H-bond interactions and have been used as binding fragments in the design of neutral receptors for anions (*1*). Especially, urea or thiourea derivatives connected with a series of chromogenic and fluorogenic substituents are proved to be very efficient for the anion sensors (*2–19*). The interaction with an anion typically stabilises the excited state of chromophore and induces red shift of the charge transfer absorption band, thus providing an efficient way for qualitative and quantitative evaluation of anion activity in solution (*20*, *21*). They can be often easily synthesised from commercially available reagents even by a single-step procedure (*22–24*). We have also reported on novel colorimetric receptors containing a nitrophenyl group as chromogenic signalling subunit and urea/thiourea as binding sites, which were selective for fluoride or acetate ion (*25*, *26*). The anion recognition via hydrogen-bonding interactions could be easily monitored by anion-complexation-induced changes in UV–vis absorption spectra and with the naked eye.

As a part of our efforts to develop more efficient anion receptors, we planned to design new urea/thiourea receptors with both a benzophenone group and a nitrophenyl group as a chromogenic signalling subunit. We report herein on novel urea/thiourea receptors **1** and **2**. These receptors were found to be an efficient detector for F^- by the change in UV–vis and ^{1}H NMR and the naked-eye observation.

Experimental

Synthesis and characterisation

*Compounds **1** and **2***

To a methylene chloride (60 ml) solution of 4-nitrophenyl isocyanate (0.85 g, 5 mmol) or 4-nitrophenyl isothiocyanate (0.93 g, 5 mmol), 3,4-diaminobenzophenone (1.09 g, 5 mmol) in methylene chloride (40 ml) was added slowly while being stirred vigorously. Orange solid (**1**) and light yellow solid (**2**) were precipitated, respectively, after stirring for 1 day at room temperature, filtered and dried (yield 97% for **1** and 55% for **2**; Scheme 1). For **1**, Anal. Calcd for $C_{20}H_{16}N_4O_4$ (886.84): C, 63.82; H, 4.28; N, 14.89; O, 17.00. Found: C, 63.75; H, 4.22; N, 15.01%. ^{1}H NMR (DMSO-d_6) δ 9.52 (s, 1H), 8.18 (d, 2H), 8.03 (s, 1H), 7.60 (m, 9H), 6.81 (d, 1H), 5.96 (s, 2H). IR (KBr): 3452 (N—H), 3336 (N—H), 3224 (N—H), 1706 (C═O), 1617 (C═O), 1331 (NO_2) cm^{-1}. For **2**, ^{1}H NMR (DMSO-d_6) δ 10.38 (s, 1H), 9.45 (s, 1H), 8.21 (d, 2H), 7.92 (d, 2H), 7.64 (d, 2H), 7.53 (m, 5H), 6.82 (d, 1H), 6.12 (s, 2H). IR (KBr): 3457 (N—H), 3357 (N—H), 3218 (N—H), 1623 (C═O), 1337 (NO_2), 1113 (C═S) cm^{-1}.

*Crystal data for **2***

$C_{20}H_{16}N_4O_4S$, MW = 408.43, T = 293 K, λ = 0.71073 Å, triclinic, a = 8.6646(15) Å, b = 12.366(2) Å, c = 19.082(3) Å, α = 89.530(4)°, β = 85.461(4)°, γ = 78.375(4)°, V = 1996.3(6) Å^3, Z = 4, D_{calcd} = 1.359 mg/m^3, μ(Mo Kα) = 0.196 mm^{-1}, F(000) = 848, crystal size, 0.15 × 0.15 × 0.08 mm. No. of reflections

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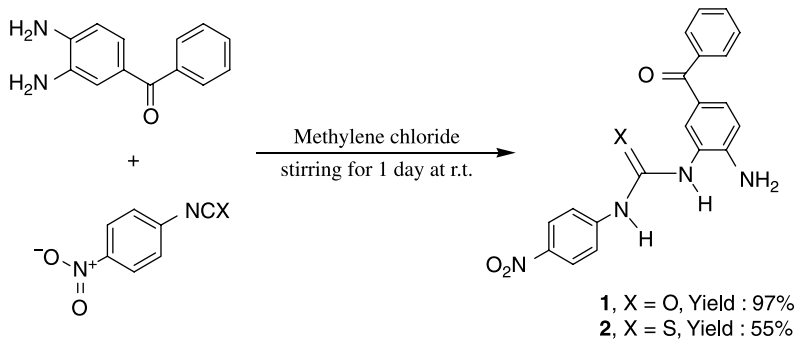

Scheme 1. The synthetic procedure for the anion receptors **1** and **2**.

measured: total, 11,309; unique, 7694 ($R_{int} = 0.0569$). Refinement method: full-matrix least squares on F^2, goodness-of-fit indicator 0.804, final R_1 [$I > 2.00\sigma(I)$] = 0.0567. The X-ray structure of **2** is shown in Figure 1. The crystallographic data, and the selected bond lengths and angles are given in Tables S1 and S2, respectively (see Supplementary Data). CCDC-738483 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk.

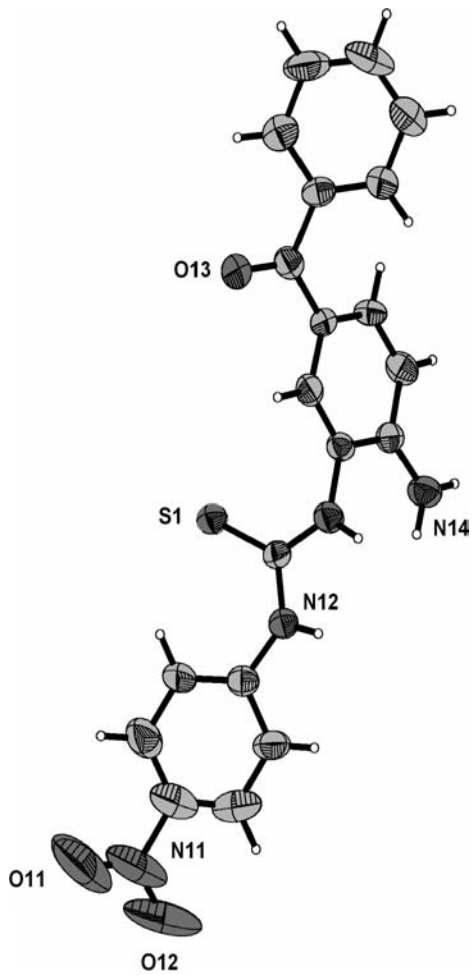

Figure 1. Crystal structure of **2**.

Results and discussion

Receptors **1** and **2** display strong absorption bands at 345 and 360 nm in DMSO, respectively. The selective recognition of urea compound **1** and thiourea compound **2** with F^- over other halides such as Cl^- and Br^- in DMSO is evident in UV–vis and ^1H NMR titration experiments. Figure 2 shows the family of spectra obtained over the course of the titration of solution **1** with tetrabutylammonium fluoride in DMSO. When 70 equivalents of fluoride are added to the 20 μM solution of **1**, λ_{max} of **1** shifts from 345 to 356 nm and the spectra show a clear isosbestic point at 370 nm. This result suggests that a typical hydrogen-bonding complex forms between the receptor and the anion because the basicity of the anion is insufficient to induce deprotonation of the receptor at this fluoride concentration. However, when an excess of fluoride ions is added, a new intense absorption band develops at 481 nm, which is attributed to the deprotonated receptor (*27*). In addition, the spectra show a new approximate isosbestic point at 420 nm (Figure 2(a)). The approximate isosbestic point indicates that deprotonation is incomplete and the hydrogen-bonded complex and the deprotonated compound **1** exist as a mixture. Therefore, fluoride ion initially forms the hydrogen-bonded complex, but with high excess of added anions, the deprotonation occurs with the formation of the hydrogen-bonded anion dimer F_2H^- (Figure 3) (*28*).

The deprotonation of receptor **1** can be seen clearly when the solution of receptor **1** is titrated with tetrabutylammonium hydroxide (Figure 2(b)). As more hydroxide ions are added, absorption band at 481 nm is developed again as in the case of fluoride. However, no isosbestic point is observed.

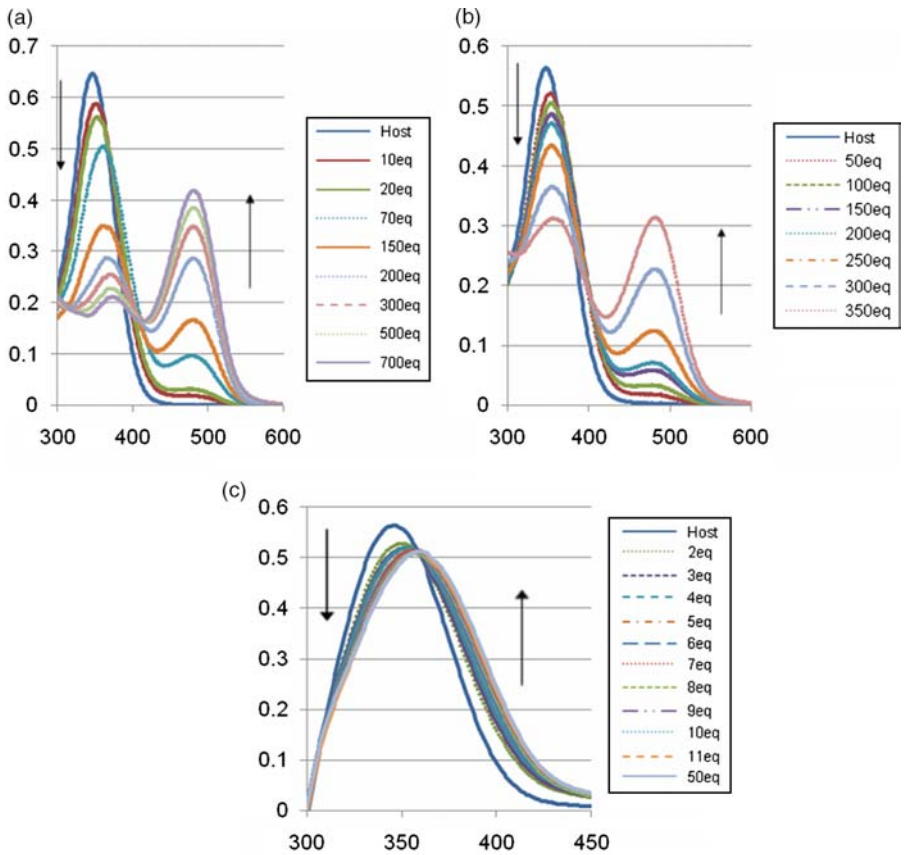

Figure 2. Family of spectra recorded over the course of titration of 20 μM DMSO solution of receptor **1** with a standard solution of (a) tetrabutylammonium fluoride, (b) hydroxide and (c) acetate.

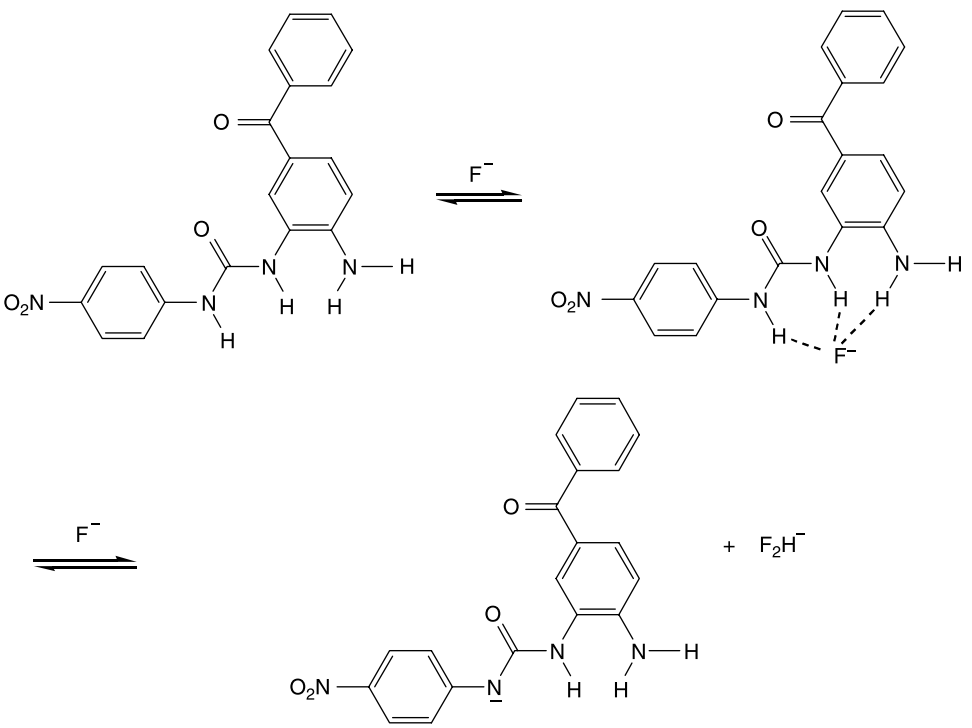

Figure 3. The interaction of receptor **1** and fluoride.

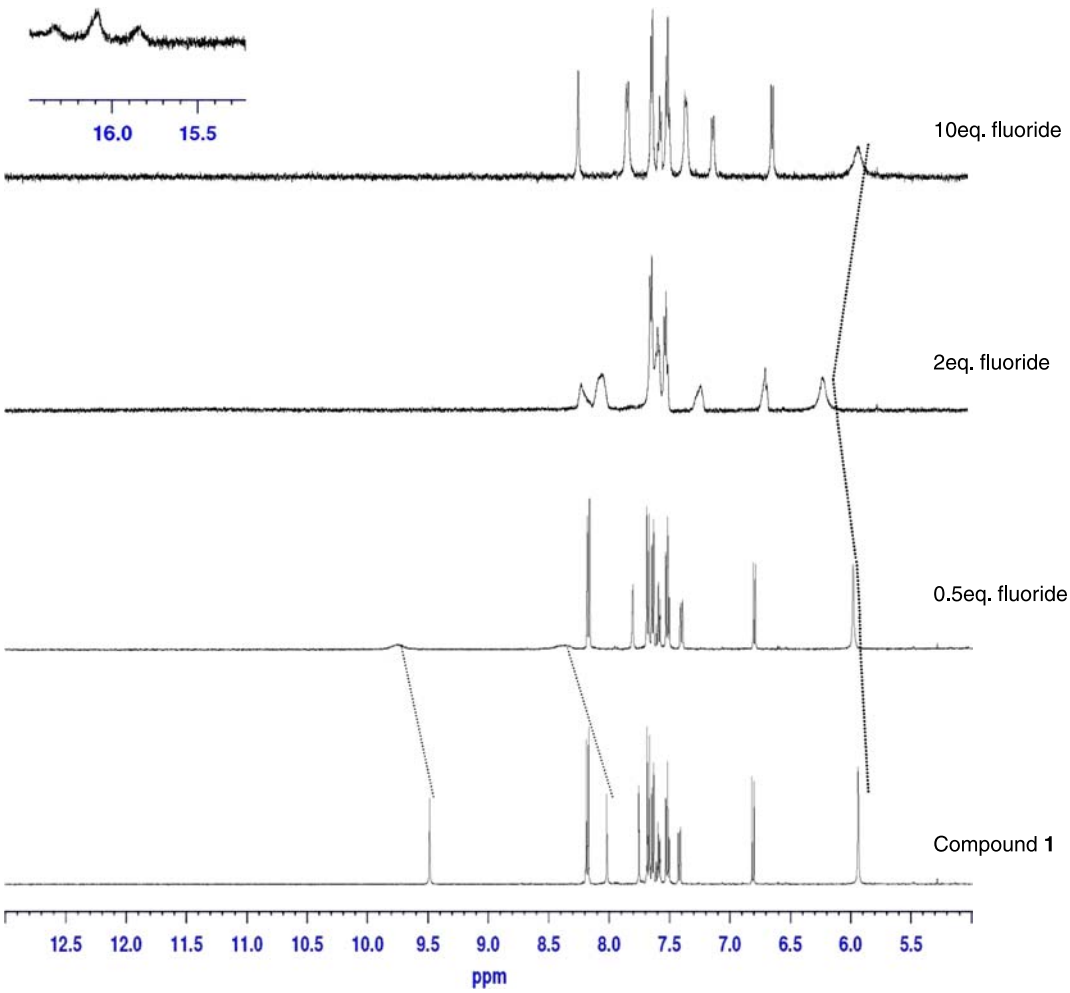

Figure 4. ^{1}H NMR spectra of 1 mM of **1** with increased amounts of tetrabutylammonium fluoride in DMSO-d_6. The shift of urea and NH_2 peaks are designated by dotted lines. F_2H^- peaks are shown in the inset.

This phenomenon can be confirmed by a ^{1}H NMR titration (Figure 4). When 0.5 equivalent of tetrabutylammonium fluoride is added to the 1 mM solution of **1** in DMSO-d_6, two urea N—H signals (9.48 and 8.01 ppm) and the adjacent NH_2 signal (5.94 ppm) in the benzophenone moiety shifted downfield (9.75, 8.40 and 6.20 ppm, respectively) with broadening of signals. This suggests that the typical hydrogen-bonding complex forms between the receptor and the anion and that not only urea but also the adjacent NH_2 group participates in hydrogen bonding with fluoride ion. When 2 equivalents of tetrabutylammonium fluoride are added, the urea N—H signals disappear. However, the adjacent NH_2 peak shifts downfield more. In addition, most of the C—H peaks became broad. Broadening of the C—H peaks suggests that the hydrogen-bonded complex and the deprotonated compound exist as a mixture. When 10 equivalents of fluoride are added to the solution, we can observe the following phenomena. First, a clear and sharp spectrum of deprotonated receptor **1** appeared. Returning to sharp NMR signals suggests that only deprotonated compound **1** exists in the solution with sufficient fluoride ions. Second, the NH_2 signal from benzophenone moiety shifts upfield (5.92 ppm). This indicates that the hydrogen bonding between receptor **1** and the fluoride ion does not exist anymore as deprotonation of receptor **1** occurs with fluoride ion. Third, around 16.1 ppm, we could observe the triplet of F_2H^- (inset in Figure 4). All of these evidences are in good agreement with our proposed mechanism.

With other anions such as acetate and benzoate, receptor **1** also shows a typical spectrum pattern for the formation of hydrogen-bonded complex (Figure 2(c)). Assuming a 1:1 stoichiometry, a Benesi–Hildebrand plot

Table 1. The association constants or equilibrium constants of receptors **1** and **2** with various anions in DMSO.

Anion	**1**	**2**
F^-	1.3×10^4	3.3×10^4
$CH_3CO_2^-$	1.2×10^4	2.5×10^4
$C_6H_5CO_2^-$	5.0×10^3	1.3×10^4

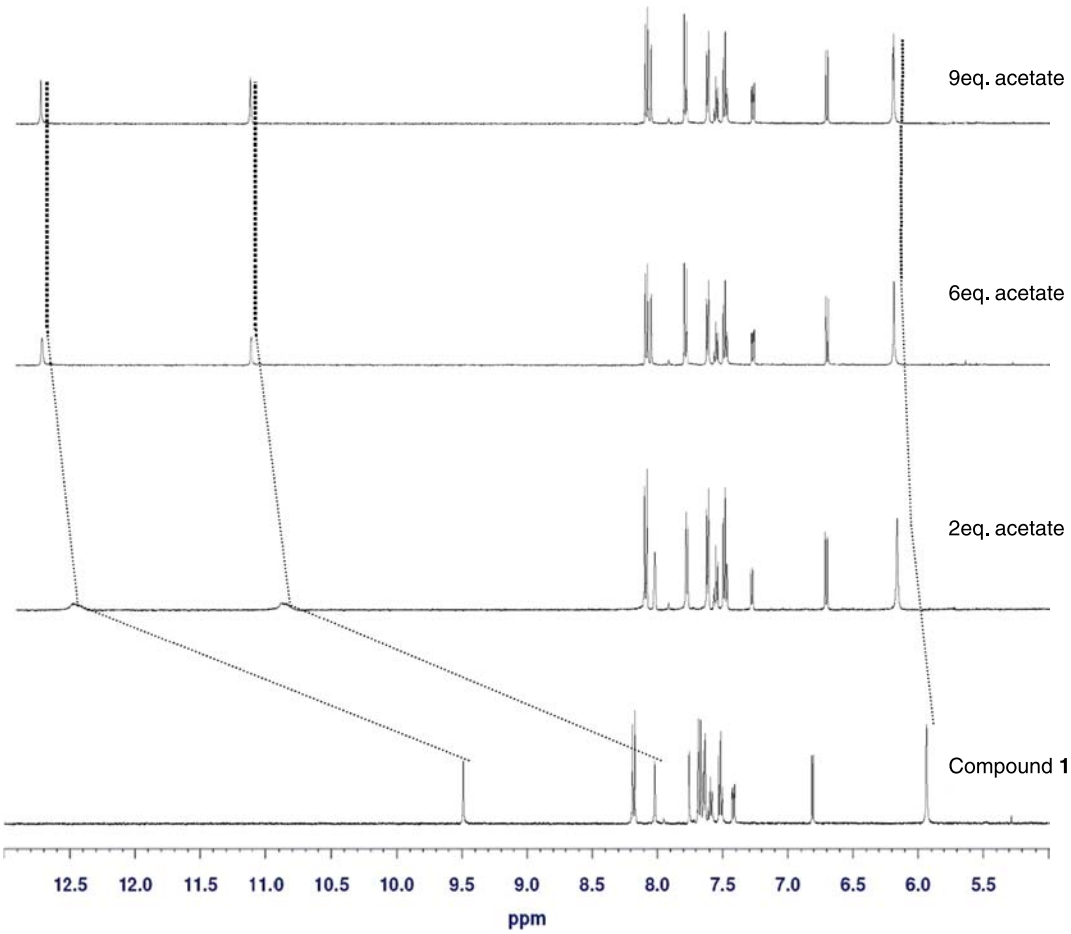

Figure 5. ^{1}H NMR spectra of 1 mM of **1** with increased amounts of tetrabutylammonium acetate in DMSO-d_6. The shift of urea and NH_2 peaks are designated by dotted lines.

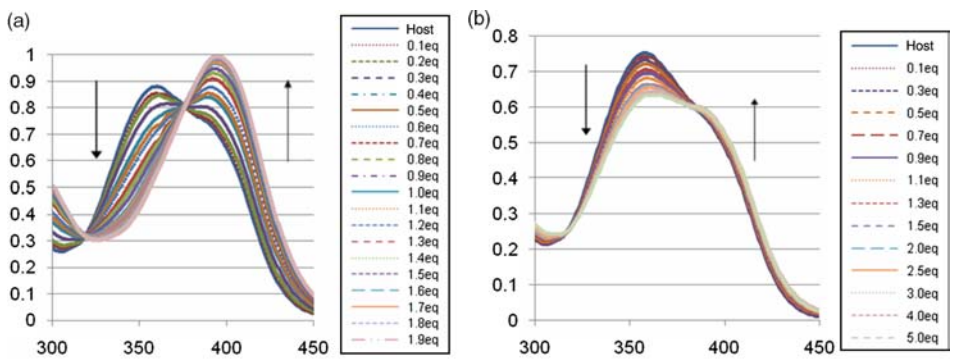

Figure 6. Family of spectra recorded over the course of titration of 50 μM DMSO solution of receptor **2** with a standard solution of (a) tetrabutylammonium fluoride and (b) benzoate.

(*29*) by use of change in the 346 nm absorption intensity gives association constants. From the experiments, receptor **1** shows association constants 1.3×10^4 and 1.2×10^4 for fluoride and acetate, respectively. The order of association constants was $F^- > CH_3CO_2^- > C_6H_5CO_2^-$. The results are summarised in Table 1.

^{1}H NMR titration with acetate also shows evidence of a discrete hydrogen-bonded complex (Figure 5). Two urea peaks move to downfield (from 9.48 and 8.02 ppm to 12.81 and 11.19 ppm) along with adjacent NH_2 peaks (from 5.93 to 6.20 ppm) as tetrabutylammonium acetate is added. During titration, urea signals undergo broadening. However, after 6 equivalents of acetate were added, all peaks including N—H urea peaks became sharp. This phenomenon is also an indication of the formation of discrete hydrogen-bonded complex. Other anions such as chloride, bromide, iodide, perchlorate, hydrogen sulphate, nitrate did not bind to receptor **1** in DMSO at all.

The more acidic thiourea fragment ($pK_a = 21.1$ in DMSO) typically interacts more strongly with anions than urea ($pK_a = 26.9$ in DMSO) (*30*). Therefore, the addition of fluoride to more acidic thiourea derivative **2** induces immediate deprotonation in DMSO. Spectroscopic titration of receptor **2** by tetrabutylammonium fluoride in DMSO shows the appearance of the new band at 360 nm characteristic of the deprotonation of the receptor (Figure 6(a)). Also, the presence of the sharp isosbestic point at 376 nm indicates that only two species are present at equilibrium over the course of the titration experiment. The equilibrium constant for the deprotonation (rather than binding constant) is calculated as 3.3×10^4 for fluoride. Acetate shows a similar behaviour and its equilibrium constant for the deprotonation is calculated as 2.5×10^4. However, benzoate shows a spectrum pattern only for the hydrogen-bonded complex (Figure 6(b)). Benzoate is not basic enough to deprotonate the thiourea moiety of receptor **2** in DMSO. The binding constant is calculated as 1.3×10^4.

The solution colour of receptors **1** and **2** changes upon addition of fluoride anion in DMSO. It can be seen that that the colour changes from colourless to yellow/orange with naked eye depending on the concentration of the solution. For example, with 20 μm solution of receptor **1** or **2**, the colour of solution changes to light yellow with 200 equivalents of fluoride ion. However, with 100 μm solution of receptor **1** or **2**, the colour of solution changes to orange with 20 equivalents of fluoride ion (see Supplementary Data).

In summary, we have developed new chromogenic anion receptors **1** and **2** with both a benzophenone group and a nitrophenyl group as a signalling group. They form the hydrogen-bonded complex when the concentration of anion is not basic enough to deprotonate receptor **1**. However, when the concentration of the anion is basic enough, it deprotonates the receptor. Therefore, they operate based on a hydrogen bonding and an acid–base equilibrium. In addition, receptors **1** and **2** have proved to be an efficient naked-eye detector for the fluoride ion.

Supplementary Data

Supplementary Data (X-ray crystallography, crystal data and structure refinement for **2**, bond lengths (Å) and angles (°) for **2**, and crystal structure of **2** containing two asymmetric molecules) associated with this article can be found in the online version.

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