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Selective fluorescent PET sensing of fluoride (F^-) using naphthalimide–thiourea and –urea conjugates

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Abstract—The thiourea and urea functionalised 4-amino-1,8-naphthalimide sensors **1**–**3**, based on the *fluorophore–spacer–receptor* principle, were synthesised in high yield in three steps. The sensors were shown to signal selectively the detection of fluoride in the fluorescence emission spectrum in DMSO. On all occasions the emission was quenched due to enhanced photoinduced electron transfer quenching (PET) from the receptor to the excited state of the fluorophore upon recognition of F^-, particularly for the thiourea sensors **1** and **2**. In comparison, the changes in the absorption spectra were minor for all three, even after the addition of 80–100 equiv of F^-. The sensing of acetate or dihydrogenphosphate gave rise to only ~5–20% quenching.

The recognition and sensing of anions has become an important aspect of supramolecular chemistry.[1–3] This is due to the role that these ions play in physiology and in the environment. In particular, anions such as organic phosphates[4] and even fluoride (F^-), are harmful to the environment and consequently to humans. The ability to detect selectively these anions in environmental samples has become an unfortunate necessity as organophosphates are components of nerve agents and F^- is the product formed upon hydrolysis of sarin gas. Fluorescent sensors are a particularly attractive method for such monitoring due to their fast response times and high sensitivity of detection.[5] We have contributed to this field of research, by developing fluorescent[6] and colorimetric[7] sensors for anions. The use of the 4-amino-1,8-naphthalimide structure for such sensing has also been demonstrated by us,[1a,c,7] as well as by several other researchers[8] including Pfeffer et al.,[9] Tian and co-workers[10] and Fabbrizzi and co-workers.[11] Pfeffer et al. have shown that the 4-amino protons are quite acidic in such structures and that these can be used to enhance both the strength and the selectivity of the anion binding towards tetrahedral anions in organic solvents.[9] Similarly, we have demonstrated that these protons can be removed using basic anions such as F^-, which gave rise to the formation of bifluoride (HF_2^-), with concomitant colorimetric changes.[7,12] Comparable phenomena have also been observed by several other researchers.[13] Here we demonstrate that compounds **1**–**3**, developed as PET sensors, where a simple urea and thiourea receptor is tethered to the naphthalimide fluorophore via an ethylene spacer, give rise to highly selective sensing of F^-. Here, the fluorescence emission of **1** and **2** was fully quenched for F^-, while the emission of **3** was quenched by only ca. 20%. No significant emission changes were, however, observed for AcO^-, or $H_2PO_4^-$ making **1** and **2** highly selective F^- sensors. Moreover, only minor changes were observed in the absorption spectra of **1**–**3**, demonstrating that these changes were due to the interactions of the anion at the receptor site.

Sensors **1**–**3** are all based on the PET principle, where the fluorophore is separated from the anion receptor by a covalent spacer, the ethylene chain. The spacer should prevent, or reduce any ground state interactions between the two components.[5] Hence, the only communication pathway should be in the form of electron transfer. The synthesis of sensors **1**–**3**[14] was achieved from **4**,[9a] by reacting it with **5**–**7**, respectively, in dry $CHCl_3$ at room temperature for 16 h as shown in Scheme 1. This gave **1**–**3** as yellow coloured precipitates which were collected by filtration and washed with warm $CHCl_3$, giving **1**–**3** in 58%, 62% and 66% yields, respectively. The ^1H NMR (400 MHz, DMSO-d_6) of **1** is shown in Figure 1, and clearly shows the presence

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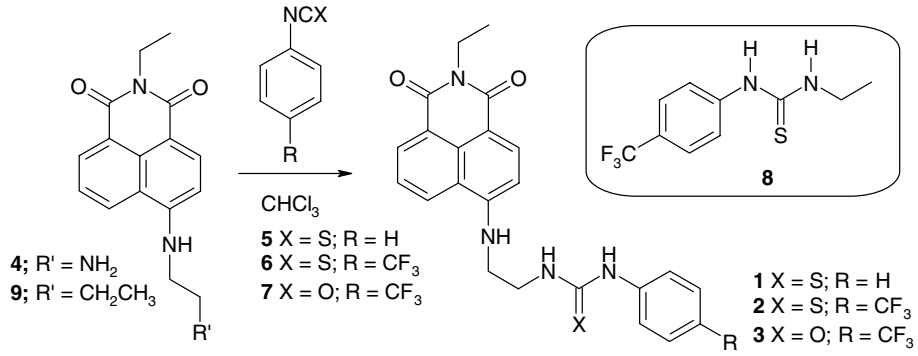

Scheme 1. Synthesis of sensors **1**–**3** from precursor **4**. Compounds **8** (inset) and **9** were both synthesised as model compounds.

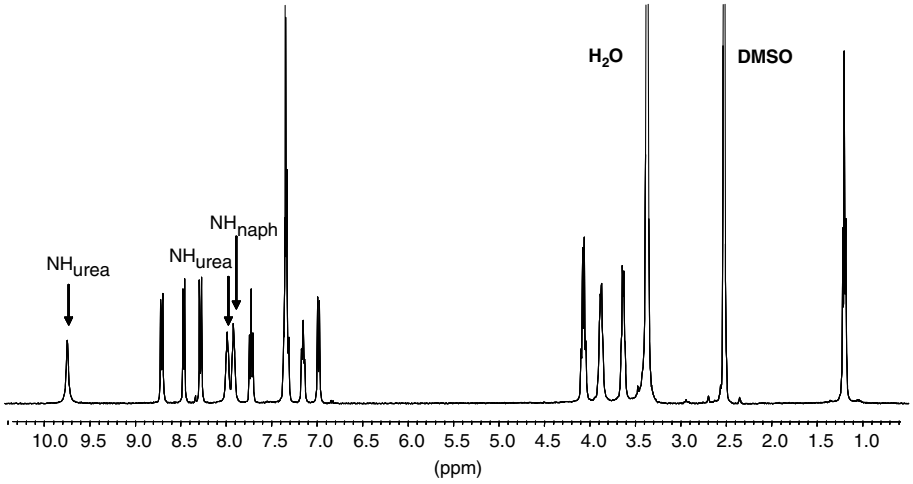

Figure 1. The ^{1}H NMR (400 MHz, DMSO-d_6) of **1**.

of the three N–H protons at δ 9.74, 7.97 and 7.87 ppm, respectively. Compounds **8** and **9** were also synthesised as reference compounds. While **9** was formed using a literature procedure,[7b] **8** was synthesised by reacting *N*-ethylamine with 4-trifluromethylphenylisothiocyanate in a single step.

The ability of **1**–**3** as well as **8** and **9** to sense anions such as AcO^-, $H_2PO_4^-$, F^-, Cl^- and Br^- was carried out in DMSO solution using the anions as their tetrabutylammonium salts (TBA^+). The absorption spectrum of the thiourea sensor **1**, in the absence of anions, exhibited a band centred at 441 nm ($\log\varepsilon = 4.18$) which was assigned to the internal charge transfer (ICT) excited state of the 4-amino-1,8-naphthalimide unit. A second band was also observed at shorter wavelength that we assigned to both the naphthalimide moiety as well as the aryl unit of the thiourea receptor. When **1** was titrated with AcO^- or $H_2PO_4^-$ only very minor changes were observed in the absorption spectra. This is to be expected as the thiourea anion receptor is separated from the fluorophore by the ethylene spacer. Similar results were seen for both **2** and **3**.

The excitation of the ICT band of **1** gave rise to a broad emission band, centred at 530 nm, shown in Figure 2, which upon titration with AcO^- was quenched by ca.

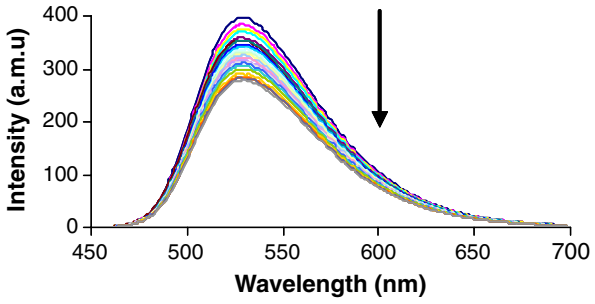

Figure 2. The changes in the emission spectra of **1** (1.18×10^{-5} M) upon titration with acetate (0→0.01 M) in DMSO.

20%. No other noticeable spectral changes, such as changes in the shape or the position of the λ_{max}, were observed within the concentration range of 0→0.01 M of AcO^-. This behaviour is typical for PET sensors[5] where the emission is quenched due to enhanced electron transfer to the excited state of the fluorophore from the anion complexed urea receptor.[6] However, these changes are rather small indicating that the reduction potential of the receptors does not change significantly enough upon binding to acetate to make the PET quenching more effective. Despite the fact that the changes observed for **1** were small, we did estimate these

to be ca. $\log K = 3.5$ by fitting the data using the non-linear regression analysis program SPECFIT. No changes were observed for either Cl^- or Br^-. Similar results were seen for **2**. While these small changes do signify the recognition of the AcO^- at the thiourea, the absence of changes in the absorption spectra suggests that there is no measurable contribution from the 4-amino moiety in the binding of acetate, as such interaction would perturb the ICT character of the naphthalimide. When these measurements were repeated using $H_2PO_4^-$, the changes were even smaller in the emission spectra, but a small blue shift was observed in the absorption spectra, which was indicative of perturbation of the ICT character of the fluorophore because of weak hydrogen bonding interaction of the tetrahedral anion with the 4-amino moiety. This observation is in agreement with the work of Pfeffer et al. who have demonstrated using ^1H NMR the selective sensing of $H_2PO_4^-$.[9a]

In contrast to these results, significant changes were seen in both the absorption and the fluorescence emission spectra of both **1** and **2** for the titration of F^-. The changes in the absorption spectra of **1** upon titrating with F^- shown in Figure 3 clearly demonstrate that the ground state is somewhat affected upon recognition of the anion, where the absorption was shifted to longer wavelength, with the formation of a clear isosbestic point at 452 nm. Furthermore, some changes were observed at shorter wavelengths. However, these changes do not support deprotonation of the 4-amino moiety, within this concentration range, as this would give rise to a shift of the ICT band towards longer wavelengths.[9–13] However, this does not rule out the possibility that such deprotonation occurs at the thiourea moiety itself.[11,15–17] Similar results were also observed for **2** and **3** in the absorption spectra upon titration with F^-. However, the changes for **2** were significantly more pronounced at short wavelength, which reflects the more electronic withdrawing nature of the receptor.

In contrast to the changes in the ground state, the fluorescence of **1** was dramatically affected upon titration of F^-. Here the emission was almost fully quenched, with no noticeable changes in λ_{max} between the addition of 0→80 equiv of the anion, as shown in Figure 4. These are significantly larger changes than those observed for

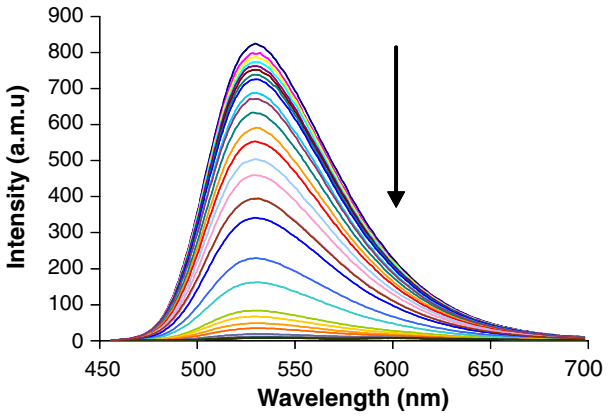

Figure 4. The changes in the fluorescence emission spectrum of **1** upon titration with F^-, showing the quenching by enhanced PET from the fluoride bound receptor.

AcO^-, and demonstrate that PET was more effective upon interaction of the thiourea receptor with F^-. As discussed above, we assign these changes to enhanced PET from the thiourea receptor to the excited state of the naphthalimide fluorophore upon anion recognition. The overall changes in the relative emission at 530 nm for the three anions discussed herein are shown in Figure 5, which clearly shows that only for F^- is the emission modulated in a dramatic way. In fact such quenching can be described as being an '*on–off*' fluorescence switching. These changes were also fully reversible, as upon addition of protic solvent the emission was restored.

In a similar way, titrations of both **2** and **3** gave rise to significant emission changes. In the case of **2**, these mirrored that observed for **1**. Hence, the emission was fully quenched, while the urea analogue **3** gave rise only to ca. 20% quenching. These results are in agreement with the fact that the thiourea is a stronger hydrogen bonding donor,[17] which would make the interaction of these with F^- stronger.[18] Hence, both **1** and **2** show extremely good selectivity for F^- over other competitive anions.[19]

To evaluate the changes at the receptor site we also made the reference compounds **8** and **9** shown in Scheme 1. In the case of **8**, the compound absorbed at

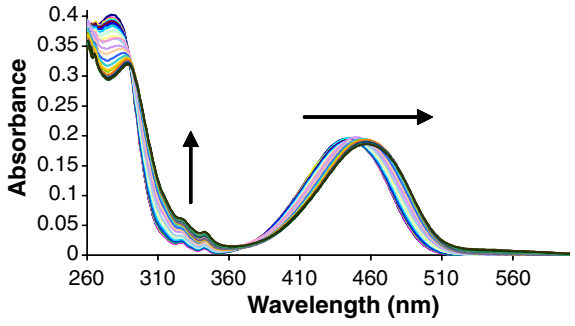

Figure 3. Changes in the absorption spectra of **1** upon addition of F^- (0→86 equiv) in DMSO. Inset: the changes at shorter wavelength, indicating the changes observed in the thiourea receptor.

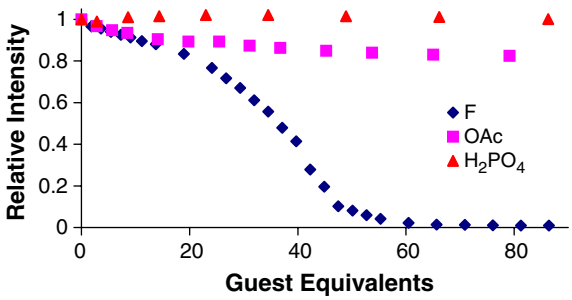

Figure 5. The changes in the emission at 530 nm upon titration with AcO^-, $H_2PO_4^-$ and F^-, respectively with **1**.

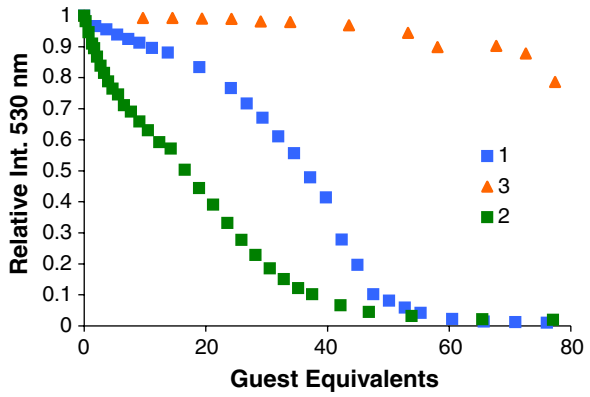

Figure 6. The changes in the emission at 530 nm upon titration of **1**–**3** with F^-.

short wavelengths, with λ_{max} at ca. 285 nm. Upon titration with F^- (0→40 equiv) this band was red shifted with the formation of a new band with λ_{max} ca. 333 nm. This represents the interaction of the urea moiety with the anion. These changes complemented the absorption changes observed at short wavelength for **2**. In comparison, compound **9** gave rise to major changes in the ICT band at long wavelength in the presence of high equivalents of F^-, but within 0→40 equiv there were no changes. No such long wavelength absorption was observed for **1**–**3**. Hence, we do not think that such deprotonation occurs in **1**. We propose that the fluoride indeed interacts at the urea receptor site, initially through hydrogen bonding. As previously mentioned, deprotonation of the receptor can possibly occur, and indeed, we observed such deprotonation in the ^1H NMR spectra of **1**, in DMSO-d_6, which gives HF_2^-.[7] Consequently, we propose that the F^- recognition occurs by the initial hydrogen bonding of the anion to the receptor, followed by deprotonation which makes the receptor highly electron rich and enhances the PET quenching of the naphthalimide excited state. The ease of this deprotonation should be reflected by the relative acidity of the N–H protons of the urea/thiourea receptor. Indeed comparing the changes in the emission at 530 nm for **1**–**3** upon interaction with F^-, Figure 6, clearly demonstrated the sensitivity of the anion sensing.

In summary, we have developed **1**–**2** as highly selective fluorescent PET sensors for F^-. For sensors **1** and **2**, the fluorescence emission was fully quenched in the presence of the anion in DMSO while being only slightly, or not at all, quenched by other competitive anions. We conclude that the sensing of F^- predominantly occurs through initial hydrogen bonding to the thiourea receptor followed by deprotonation, which makes the receptor a more efficient PET quencher.

Acknowledgements

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14. *2-Ethyl-6-[(4-lphenylthiocarbamoyl)ethylamino]-benzo[de]-iso-quinoline-1,3-dione* (**1**): Formed in 58%; mp 238–240 °C; HRMS (ES^+): (M+H) calcd for $C_{23}H_{23}N_4O_2S$, 419.1542; found, 419.1539. CHN; Calcd for $C_{23}H_{22}N_4O_2S$: C, 66.01; H, 5.30; N, 13.39. Found: C, 65.36; H, 5.31; N, 13.11; δ_H (600 MHz, DMSO-d_6), 9.74 (1H, br s, NH_{urea}) 8.69 (1H, d, $J = 8.3$ Hz, Naph-*H5*) 8.45 (1H, d, $J = 7.1$ Hz, Naph-*H7*), 8.27 (1H, d, $J = 8.7$ Hz, Naph-*H2*), 7.97 (1H, br s, NH_{urea}), 7.87 (1H, br s, NH), 7.77 (1H, t, 7.7, $J = 7.7$ Hz, Ar-H*6*), 7.37 (2H, t, $J = 7.5$ Hz, *H2*), 7.32 (2H, m, Ar-*H3*, *H5*), 7.14 (1H, m, Ar-H*4*), 6.99 (1H, d, $J = 8.7$ Hz, Naph-*H3*), 4.08 (2H, q, $J = 6.8$, NCH_2), 3.88 (2H, br s, CH_2), 3.64 (2H, br s, CH_2), 1.19 (3H, t, $J = 7.2$ Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 180.4, 163.8, 163.0, 150.9, 139.0, 134.3, 130.9, 129.6, 129.1, 128.8, 124.9, 124.6, 123.8, 122.2, 120.4, 108.3, 104.3, 103.8, 42.5, 34.5, 13.6; IR ν_{max} (cm^{-1}) 3354, 3231, 3173, 1683, 1642, 1587, 1540, 1430, 1396, 1369, 1343, 1247, 1190, 1108, 1064, 886, 769, 755, 725, 693.
2-Ethyl-6-[(4-trifluoromethylphenylthiocarbamoyl)ethylamino]-benzo[de]iso-quinoline-1,3-dione (**2**): Formed in 62%; mp 226–228 °C; HRMS (ES^+): (M+H) calcd for $C_{24}H_{22}F_3N_4O_2S$, 487.1416; found, 487.1439; CHN; Calcd for $C_{24}H_{21}F_3N_4O_2S{\cdot}0.2CHCl_3$: C, 57.09; H, 4.23; N, 11.00. Found $C_{24}H_{21}F_3N_4O_2S$: C, 56.95; H, 4.19; N, 10.98; δ_H (400 MHz, DMSO-d_6), 9.16 (1H, br s, NH_{urea}), 8.67 (1H, d, $J = 8.5$ Hz, Naph-*H5*) 8.43 (1H, d, $J = 7.0$ Hz, Naph-*H7*), 8.26 (1H, d, $J = 8.5$ Hz, Naph-*H2*), 7.89 (1H, br s, NH_{urea}), 7.69 (1H, t, $J = 8.53$, Naph-*H6*), 7.59 (4H, dd, $J = 8.5$ Hz, phenyl), 6.89 (1H, d, $J = 8.5$ Hz, Naph-*H3*), 6.62 (1H, br s, NH_{naph}), 4.04 (2H, q, $J = 7.03$, N–CH_2), 4.08 (2H, q, $J = 6.78$, NCH_2,), 3.49 (4H, m, CH_2), 1.18 (3H, t, $J = 7.03$ Hz, CH_3); δ_C (400 MHz, DMSO-d_6), 180.6 (C=S), 163.5 (C=O), 162.7 (C=O), 150.6 (CqNH), 142.9 (CqNH), 134.0, 130.6, 129.3, 128.5, 125.7, 124.3, 124.3 ($J_{C^{13}F^{19}} = 272.1$ Hz), 123.8 ($J_{C^{13}F^{19}} = 27.0$ Hz), 122.3, 121.9, 120.1, 108.0, 104.0, 42.2, 41.8, 34.2, 13.3; $\delta_{C^{13}F^{19}}$ (400 MHz, DMSO-d_6), −60; IR ν_{max} (cm^{-1}) 3383, 3259, 1672, 1639, 1614, 1586, 1527, 1396, 1371, 1343, 1328, 1319, 1244, 1156, 1110, 1065, 1053, 1015, 840, 773, 757, 681.
2-Ethyl-6-[(4-trifluoromethylphenylcarbamoyl)ethylamino]-benzo[de]iso-quinoline-1,3-dione (**3**): Formed in 66%; mp 270–272 °C; HRMS (ES^+): (M+H) calcd for $C_{24}H_{22}F_3N_4O_3$, 471.1654; found, 471.1644; CHN; Calcd for $C_{24}H_{22}F_3N_4O_3{\cdot}01\ CHCl_3$: C, 60.01; H, 4.41; N, 11.61. Found $C_{24}H_{22}F_3N_4O_3$: C, 59.78; H, 4.54; N, 11.55; δ_H (400 MHz, DMSO-d_6), 9.16 (1H, br s, NH_{urea}), 8.67 (1H, d, $J = 8.5$ Hz, Naph-*H5*) 8.43 (1H, d, $J = 7.0$ Hz, Naph-*H7*), 8.26 (1H, d, $J = 8.5$ Hz, Naph-*H2*), 7.89 (1H, br s, NH_{urea}), 7.69 (1H, t, $J = 8.5$, Naph-*H6*), 7.59 (4H, dd, $J = 8.5$ Hz, phenyl), 6.89 (1H, d, $J = 8.5$ Hz, Naph-*H3*), 6.62 (1H, br s, NH_{naph}), 4.04 (2H, q, $J = 7.0$ Hz, N–CH_2), 4.08 (2H, q, $J = 6.8$, NCH_2), 3.49 (4H, m, CH_2), 1.18 (3H, t, $J = 7.03$ Hz, CH_3); δ_C (400 MHz, DMSO-d_6) 163.9, 163.1, 155.8, 151.1, 144.5, 134.6, 131.1, 128.8, 126.4; ($J_{C^{13}F^{19}} = 3.8$ Hz), 125.1 ($J_{C^{13}F^{19}} = 270.0$ Hz), 124.8, 123.7, 122.4, 121.5 ($J_{C^{13}F^{19}} = 31.0$ Hz), 120.5, 117.8, 108.3, 104.3, 43.6, 38.3, 34.7, 13.7; IR ν_{max} (cm^{-1}) 3396, 3302, 1685, 1650, 1628, 1589, 1542, 1373, 1347, 1325, 1249, 1166, 1119, 1107, 1067, 1016, 837, 822, 774, 759.
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