Anion binding *vs.* deprotonation in colorimetric pyrrolylamidothiourea based anion sensors†

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A pyrrolylamidothiourea deprotonates in the presence of *one* equivalent of *not only* fluoride, *but also* acetate, benzoate or dihydrogen phosphate in DMSO solution with structural studies using synchrotron radiation confirming thiourea deprotonation in the solid state.

Anion recognition and sensing is currently an area of intense interest and effort within the supramolecular chemistry community.[1] One frequently used strategy to produce a colorimetric anion sensor is to functionalise an anion binding group with a chromogenic moiety capable of signaling the binding event through intramolecular charge transfer processes which leads to a change of colour visible by eye.[2] These chromophores may contain electron-withdrawing groups that enhance the acidity of the anion binding subunit. In some cases, it may not be easy to establish a clear difference between a hydrogen bond donor binding to an anion and a process in which the hydrogen bond donor is deprotonated and H$^+$ transferred to the basic anion. The nature of this process is controlled by several factors including the acidity of the receptor, the basicity of the anion and the stability of the conjugate base, all of which are solvent dependent. There are a number of examples of the deprotonation of neutral hydrogen bond donor anion receptor systems with fluoride. Many of these processes were recognised due to the colour changes that can occur upon deprotonation. For example, in 2002, we reported the deprotonation of diamidopyrroles containing electron-withdrawing groups[3] which led on to the production of a colorimetric fluoride sensor in 2003.[4] In that same year, Gunnlaugsson and co-workers reported a similar process in a naphthalimide thiourea resulting in a colour change from yellow/green to red/purple[5] whilst Costero and co-workers[6] have shown that amides are also susceptible to fluoride-triggered deprotonation. More recently, Fabbrizzi and co-workers have reported a series of detailed studies of the interaction of anions and various urea derivatives, ranging from pure hydrogen bonding to double deprotonation.[7]

Amidothiourea compounds,[8] have attracted considerable attention recently as they function as selective colorimetric and fluorescent anion sensors.[9] We synthesised a series of compounds **1–4** with expected increasing acidity (Scheme 1), in order to investigate whether the interaction of these species with anions was a binding or a deprotonation process. Whilst this work was in
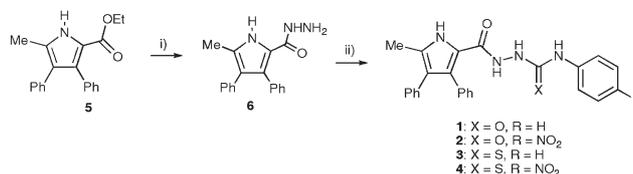
Scheme 1 Reagents and conditions: (i) NH$_2$NH$_2$·H$_2$O–EtOH–reflux (ii) RCNX (X = O or S)–CHCl$_3$.

progress, Gunnlaugsson and co-workers reported the use of a naphthalimide-amidothiourea for colorimetric sensing of anions in highly competitive aqueous media, and which was shown to deprotonate upon addition of fluoride in DMSO solution.[10]

5-Methyl-3,4-diphenyl-1*H*-pyrrole-2 carboxylic acid ethyl ester[11] was treated with an excess of hydrazine hydrate in refluxing ethanol to give the 2-carbohydrazide derivative **6** as a white crystalline solid.‡ Reaction of this compound with the corresponding isocyanate or isothiocyanate gave compounds **1–4** in good yields (see supplementary information for more details†).

The identity of receptor **2** was confirmed by single crystal X-ray crystallography (Fig. 1)§. In the solid state, the pyrrole NH group and the amidocarbonyl group adopt a *cis*-arrangement,[12] with a torsion angle of 94° between the planes defined by the pyrrole-amide and urea groups. The receptor is further arranged into hydrogen bonded sheets through urea–urea and amidopyrrole–amidopyrrole hydrogen bond interactions with N···O distances of N1···O1^i 2.857(2) Å, N3···O2^{ii} 2.811(2) and N4···O2^{ii} 3.003(2) Å
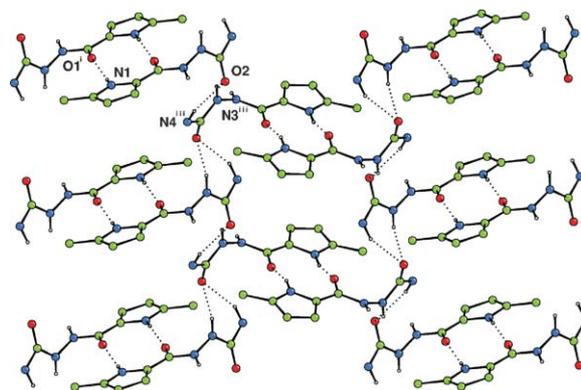
Fig. 1 Hydrogen bonded sheets formed by compound **2** in the solid state viewed looking down the *a* axis. Non-acidic hydrogen atoms, phenyl and nitrobenzene groups are omitted for clarity (i and iii in the atom labels refer to equivalent positions ($-x$, $1 - y$, $1 - z$) and ($-x$, $1/2 - y$, $1/2 + z$) respectively).

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and N–H···O bond angles of 161.3°, 135.5° and 151.0° respectively (i and ii refer to equivalent positions ($-x$, $1 - y$, $1 - z$) and ($-x$, $-1/2 + y$, $1/2 - z$) respectively).

The anion binding abilities of the new receptors were studied by means of UV-vis and ^{1}H NMR titration experiments using DMSO and DMSO-d_6 as solvent respectively. Upon addition of anions to compound **1**, no significant changes were observed in either UV-vis or ^{1}H NMR spectra, indicating that the receptor is not interacting significantly with the putative anionic guests in this competitive solvent medium. The ^{1}H NMR spectra of the more acidic 4-nitrophenyl substituted derivative **2** showed a significant broadening of all the NH signals in the ^{1}H NMR spectra upon addition of tetrabutylammonium fluoride, acetate, benzoate and dihydrogenphosphate, indicating an interaction between the receptor and the anions through hydrogen bonds.

These changes are accompanied by a gradual change of colour from an almost colourless solution to dark yellow, visible to the naked eye. UV-vis spectra reflected these changes with an increase of the absorbance in the 450 nm region and appearance of two isosbestic points at approximately 280 and 340 nm (Fig. 2). The changes in the absorbance as a function of the concentration of anion added can be fitted to a 1 : 1 binding equilibrium model,¶ giving association constants of 3010 M^{-1} (F^-), 5580 M^{-1} ($CH_3CO_2^-$), 1440 M^{-1} ($PhCO_2^-$) and 1060 M^{-1} ($H_2PO_4^-$). Smaller changes in the UV-vis spectra were observed upon addition of less basic anions (Cl^-, Br^- or HSO_4^-) that were insufficient to provide a reliable value of the association constant.

The analogous thiourea receptors **3** and **4** were evaluated, as the increased acidity of the thiourea N–H groups[13] should result either in a stronger interaction with the anions or in deprotonation of the receptor. Addition of F^-, CH_3COO^-, $PhCO_2^-$ or $H_2PO_4^-$ as tetrabutylammonium salts to solutions of compound **3** or **4** in DMSO resulted in dramatic changes in the UV-vis spectra of the receptors, with new intense absorption bands appearing at 330 and 430 nm respectively. Following the changes in the absorbance as a function of the concentration of anion resulted in a steep curve, preventing the calculation of an apparent stability constant. In the case of compound **4**, a distinctive change of colour from yellow to red is observed (see Figs. 3 and 4).

Fig. 3 DMSO solutions (2×10^{-3} M) of compounds **2** (left group) and **4** (right group). Left to right within each group: solution of receptor, and solution of receptor in the presence of one equivalent of tetrabutylammonium fluoride, acetate, benzoate and dihydrogen phosphate.
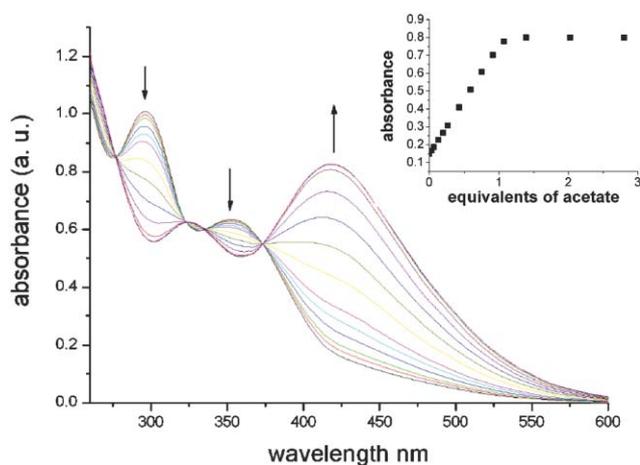
Fig. 4 UV-vis absorption spectrophotometric titration of compound **4** with tetrabutylammonium acetate in DMSO at 25 °C. Inset: variation of absorbance at 450 nm *versus* equivalents of acetate.

Proton NMR titration experiments in DMSO-d_6 shed light on the interaction of the anions and receptor **4**. Instead of a broadening of the NH signals, as was observed with compound **2**, a new set of three sharp signals at 11.3, 9.6 and 8.7 ppm, corresponding to three NH groups appeared (see ESI†) upon addition of F^-, CH_3COO^-, $PhCO_2^-$ or $H_2PO_4^-$.

Red crystals were formed upon slow evaporation of a dichloromethane–ether solution of compound **4** containing one

Fig. 2 UV-vis absorption spectrophotometric titration of compound **2** with tetrabutylammonium acetate in DMSO at 25 °C. Inset: differences in absorbance at 390 nm *versus* concentration of acetate.
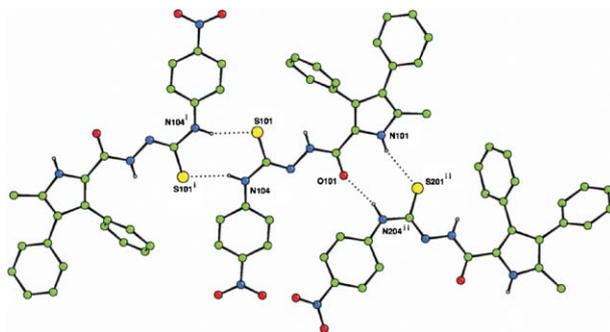
Fig. 5 Part of the hydrogen bonded chain defined by the deprotonated amidothiourea **4**–H$^+$ in the solid state. The deprotonated species adopts an essentially planar conformation (i and ii in the atom labels refer to equivalent positions ($1 - x$, $1 - y$, $-z$) and ($-x$, $1 - y$, $-z$) respectively).

equivalent of TBAF. The X-ray crystal structure showed that the crystals were the tetrabutylammonium salt of (4–H⁺)⁻ and that deprotonation of the thiourea had occurred at N103 (NH hydrogens were located in the X-ray crystal structure, see Fig. 5 and ESI).∥[14] A proton NMR of the tetrabutylammonium salt of (4–H⁺)⁻ in DMSO-d_6 gave an identical spectrum to those obtained after the addition of one equivalent of tetrabutylammonium fluoride, acetate, benzoate or dihydrogen phosphate, evidence that leads us to suggest that these four anions deprotonate compound 4 in DMSO solution. Crystallisation of compound 4 from a solution containing one equivalent of tetrabutylammonium benzoate also led to the formation of identical red crystals and also colourless needles which proved to be benzoic acid. The deprotonated species appears to be stabilized by an intramolecular hydrogen bond from the CH at the *ortho*-proton of the 4-nitrophenyl group (N103···C109 2.823 Å) with the deprotonated species now adopting an essentially planar arrangement. In the solid state the receptor forms hydrogen bonded chains through interactions of the amidopyrrole and thiourea groups (Fig. 5) with N102···S101 2.881(5) Å, N101···S201ⁱ 3.311(5) Å, N204···O101ⁱ 2.894(6) Å and N201···O201ⁱⁱ 2.826(6) Å; N102–H102···S101 11.7°, N101–H101···S201ⁱ 157.9°, N204–H204···O101ⁱ 163.3° and N201–H201···O201ⁱⁱ 159.8°.

In previous studies, two equivalents of anion (frequently fluoride) have been necessary to achieve deprotonation (the formation of HF_2^- drives the deprotonation process in these cases). However, this is not the case with compound 4, as deprotonation is complete after addition of only one equivalent of anionic guest. Receptor 3 shows similar behaviour in the ¹H NMR titration experiments, but complete deprotonation is not achieved until an excess of the anion is added (presumably due to this compound being less acidic than 4). When UV-vis titration experiments of compound 4 were performed employing a 9 : 1 mixture of DMSO–water a virtually equivalent family of spectra was obtained, indicating that the same 'neat' deprotonation process is occurring in this solvent medium. Solubility problems prevented the use of more water-rich mixtures.

Amidothiourea compounds have previously been shown to act as colorimetric anion sensors. We have shown here that in contradistinction to a number of other anion-triggered deprotonation processes[3–7] *only one equivalent of anion* (e.g. benzoate, acetate, dihydrogen phosphate or fluoride) is necessary to deprotonate receptor 4. This may be due to the non-convergent nature of the hydrogen bonding array in this system which fails to adopt a geometry suitable for the stabilization of a hydrogen-bonded complex, leading to a neat deprotonation. Care must therefore be taken when studying the interaction of this type of amidothiourea species with anionic guests as the colorimetric responses could be mistaken for a strong 1 : 1 anion binding processes.

Notes and references

‡ Crystal data for 6: $C_{18}H_{17}N_3O$, $Mr = 291.35$, $T = 120(2)$ K, monoclinic, space group $P2_1/n$, $a = 10.990(4)$, $b = 18.366(9)$, $c = 15.123(4)$ Å, $\beta = 96.53(2)°$, $V = 3033(2)$ Å³, $\rho_{calc} = 1.276$ g cm⁻³, $\mu = 0.081$ mm⁻¹, $Z = 8$, reflections collected: 27627, independent reflections: 6610 ($R_{int} = 0.1582$), final R indices [$I > 2\sigma I$]: $R1 = 0.0685$, $wR2 = 0.1249$, R indices (all data): $R1 = 0.2330$. $wR2 = 0.1765$. CCDC 292339. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b517308f

§ Data for 2 and 6 (see ESI) were collected on a BrukerNonius KappaCCD diffractometer mounted at the window of a Mo rotating anode. Data for the tetrabutylammonium salt of (4–H⁺)⁻ were collected on a Bruker SMART APEX2 CCD diffractometer at Daresbury SRS station 9.8 using a wavelength of 0.6814.[14] Crystal data for 2: $C_{25}H_{21}N_5O_4$, $Mr = 455.47$, $T = 120(2)$ K, monoclinic, space group $P2_1/c$, $a = 18.0210(4)$, $b = 8.0777(2)$, $c = 16.7769(4)$ Å, $\beta = 115.5230(10)°$, $V = 2203.86(9)$ Å³, $\rho_{calc} = 1.373$ g cm⁻³, $\mu = 0.096$ mm⁻¹, $Z = 4$, reflections collected: 20202, independent reflections: 5054 ($R_{int} = 0.0486$), final R indices [$I > 2\sigma I$]: $R1 = 0.0548$, $wR2 = 0.1218$, R indices (all data): $R1 = 0.0834$. $wR2 = 0.1352$. CCDC 292341. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b517308f

¶ Following changes at 390 nm, errors estimated to be <10%.

∥ Crystal data for the tetrabutylammonium salt of (4–H⁺)⁻: $C_{41}H_{56}N_6O_3S$, $Mr = 712.98$, $T = 120(2)$ K, monoclinic, space group $P2/c$, $a = 22.9059(19)$, $b = 8.5806(7)$, $c = 40.738(3)$ Å, $\beta = 93.308(2)°$, $V = 7993(11)$ Å³, $\rho_{calc} = 1.185$ g cm⁻³, $\mu = 0.125$ mm⁻¹, $Z = 8$, reflections collected: 43492, independent reflections: 9695 ($R_{int} = 0.0869$), final R indices [$I > 2\sigma I$]: $R1 = 0.0901$, $wR2 = 0.2368$, R indices (all data): $R1 = 0.1344$. $wR2 = 0.2735$. CCDC 292340. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b517308f

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