Pyridyl thioureas as switchable anion receptors†

Suad Rashdan, Mark E. Light and Jeremy D. Kilburn*

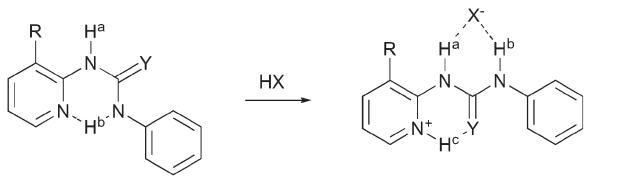
Received (in Austin, TX, USA) 15th August 2006, Accepted 5th September 2006
First published as an Advance Article on the web 26th September 2006
DOI: 10.1039/b611138f

The binding selectivity of simple pyridyl thioureas in acetonitrile can be completely switched by protonation; hence the neutral thiourea binds acetate, but not chloride or bromide, whereas the protonated thiourea binds strongly to chloride or bromide, but is deprotonated by acetate.

Synthetic receptors have been developed for a vast range of substrates, from anions to cations, from small organic molecules to large biomolecules. However, receptors whose binding properties can be switched 'on' and 'off', or whose binding selectivities can be reversed, are relatively rare,[1–3] although they have potential in molecular devices and for controlled transport properties. In particular, protonation as a trigger to regulate binding properties is frequently observed in nature, but again is rare in synthetic receptor systems.[1b,d] We have been investigating structurally very simple pyridylthioureas as anion receptors and have found that the binding selectivity for acetate, over bromide or chloride, can be completely reversed by simple protonation.

2-Pyridyl-phenylthiourea is known to adopt a confirmation (**1**) with an intramolecular hydrogen bond between the thiourea N–H^b and the pyridyl nitrogen, which is confirmed both by its the X-ray crystal structure[4] and ^{1}H NMR spectrum.[5] The latter reveals a chemical shift of 8.97 ppm (relative to TMS in CD_3CN) for the unbonded N–H and 13.82 ppm for the other (Scheme 1).

We have found that treatment of the thiourea with one equivalent of a protic acid leads to protonation of the pyridine and an alternative conformation **3**, with an intramolecular hydrogen bond between the thiourea sulfur and the protonated pyridyl N^+H (Fig. 1)[6], and hydrogen bonds from the counterion of the acid to



1 R = H, Y = S
^{1}H NMR (CD_3CN): δ H^a = 8.97; δ H^b = 13.82 ppm
2a R = CH_3, Y = S
2b R = CH_3, Y = O

3a R = H, Y = S, X^- = Br^-;
3b R = H, Y = S, X^- = Cl^-;
3c R = H, Y = S, X^- = $CF_3CO_2^-$
3d R = H, Y = S, X^- = BF_4^-
^{1}H NMR (CD_3CN): δ H^a = 9.24; δ H^b = 9.83; δ H^c = 16.50 ppm
4a R = CH_3, Y = S, X^- = BF_4^-
4b R = CH_3, Y = O, X^- = BF_4^-

Scheme 1

School of Chemistry, University of Southampton, Southampton, UK SO17 1BJ. E-mail: jdk1@soton.ac.uk; Fax: +44 (0)23 8059 6805
† Electronic supplementary information (ESI) available: All NMR titration data, and crystal structure data for **3a** and **3b**. See DOI: 10.1039/b611138f

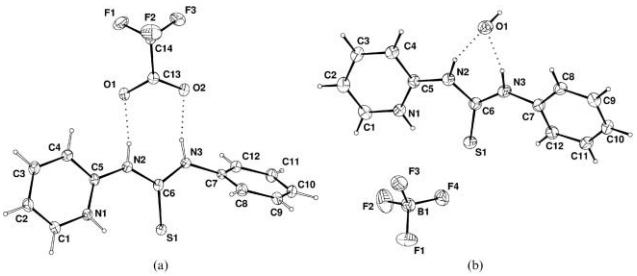


Fig. 1 (a) Thermal ellipsoid plot for **3c**. (b) Thermal ellipsoid plot for **3d**. Thermal ellipsoids are drawn at the 50% probability level.

the two, now *syn*-orientated, N–Hs of the thiourea. Crystal structures of the salts **3a–3c**, formed with HBr, HCl and CF_3CO_2H, respectively, all reveal the same conformation, and in the case of the trifluoroacetic acid salt **3c**, the crystal structure‡ (Fig. 1a) shows the expected bidentate pair of hydrogen bond interactions from the thiourea N–Hs to the carboxylate oxygen atoms. In the crystal structure of the tetrafluoroborate salt **3d** (Fig. 1b),‡ the tetrafluoroborate anion does not form strong interactions with the thiourea N–Hs, but rather is adjacent to the pyridinium N–H proton, and a water molecule sits in the thiourea hydrogen bonding pocket.

The ^{1}H NMR spectra of these salts are also very similar and, for example, in the case of the HBF_4 salt **3d**, there are two signals for the thiourea protons at 9.24 and 9.83 ppm, and a third signal for the pyridinium N–H^c at 16.50 ppm. It is therefore apparent that the neutral 2-pyridyl-phenylthiourea **1** is not in a conformation suitable for the strong anion binding normally associated with thioureas, but that protonation leads to a conformational switch and potentially strong anion binding. To investigate this possibility, we have prepared the 2-pyridyl thioureas **1** and **2a**, and their corresponding tetrafluoroborate salts **3d** and **4a**, and have investigated their solution binding properties with a range of anions.[7]

The ^{1}H NMR spectrum of 2-pyridyl-phenylthiourea **1** in CD_3CN showed no change to any of the signals upon addition of tetrabutylammonium bromide or chloride, confirming that these anions are not bound by the neutral receptor. However, addition of tetrabutylammonium acetate to the neutral thiourea led to a downfield shift of the signal for the thiourea N–H^a, accompanied by rapid broadening of the signal, meaning that it could not be effectively monitored throughout the titration. However, there was also a large downfield shift in the signal of the pyridyl proton C–H^3 ($\Delta\delta > 0.8$ ppm), whereas the other thiourea N–H^b signal was essentially unaffected. The data indicates that the acetate is bound in the bidentate motif **5** (Fig. 2). The titration data from the C–H^3 protons could be

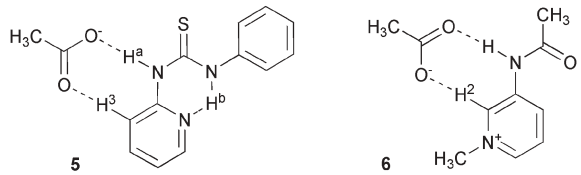


Fig. 2 Binding of carboxylates by a pyridyl thiourea and an alkyl pyridinium salt.

Table 1 Binding constants (K_a) for thiourea receptors with tetrabutylammonium salts in CD_3CN[9]

	K_a/M^{-1}		
	Guest (as tetrabutylammonium salt)		
Receptor	Br^-	Cl^-	AcO^-
1	0	0	110
2a	0	0	0
3d	$1:1 > 10^4$ ($1:2 \sim 100$)	$1:1 > 10^4$ ($1:2 \sim 100$)	Deprotonates
4a	$1:1 > 10^4$ ($1:2 \sim 100$)	$1:1 > 10^4$ ($1:2 \sim 100$)	Deprotonates

reliably fitted[8,9] to a 1 : 1 binding isotherm, giving an association constant $K_a = 1.1 \times 10^2\ M^{-1}$ (Table 1).

Although this mode of binding was not anticipated, the binding of carboxylates through C–H hydrogen bonds to alkylated pyridinium salts has been previously observed (*e.g.*, **6**).[10] Presumably the formation of the intramolecular hydrogen bond in **5** enhances the hydrogen bonding ability of C–H^3, much like alkylation of the pyridine enhances the hydrogen bonding ability of C–H^2 in **6**.

Addition of tetrabutylammonium bromide or chloride to the tetrafluoroborate salt **3d** ($X^- = BF_4^-$) led to significant downfield shifts of the signals for the thiourea N–Hs ($\Delta\delta > 3$ ppm) (Fig. 3). Signals for several of the pyridyl protons also moved during the titration, and, in particular, the signal for C–H^6 shifted upfield until one equivalent of the halide guest had been added, at which point the signal moved back downfield. The signal for the

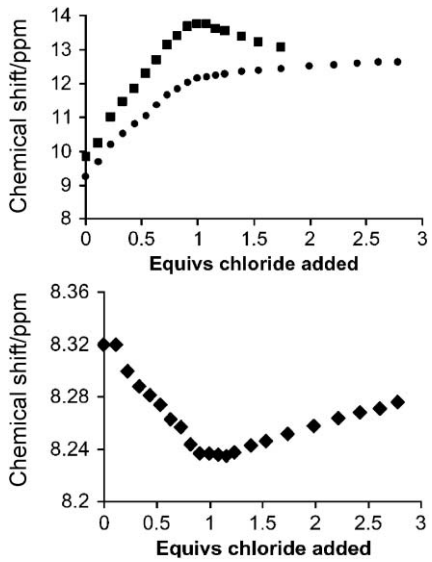
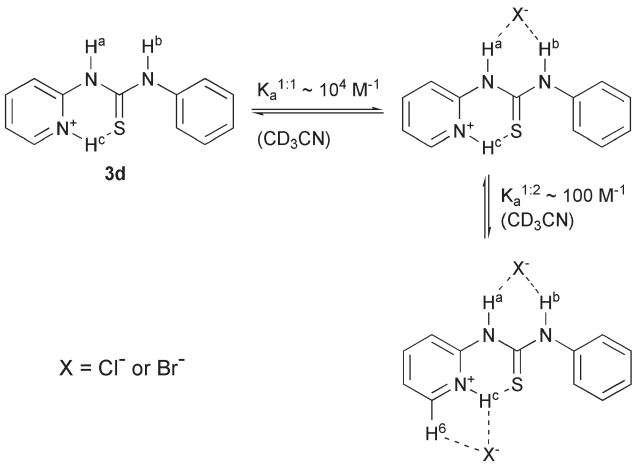


Fig. 3 Titration curves for the addition of tetrabutylammonium chloride to tetrafluoroborate salt **3d**: N–H^a (●); N–H^b (■); C–H^6 (◆).



Scheme 2

pyridinium N–H proton rapidly broadened upon addition of any guest molecule.

The titration data indicate that strong 1 : 1 association of chloride and bromide, using the thiourea N–Hs, dominates the binding, but that a second halide anion can be bound (1 : 2 association) presumably using the pyridinium proton and the adjacent pyridyl C–H^6 (Scheme 2). This mode of binding is also indicated in the crystal structure[9] of the bromide salt **3a**, with a $NH^c\cdots Br$ distance of 3.037 Å and a C–H^6…Br distance of 2.962 Å.

The titration data from all three signals (thiourea N–Hs and C–H^6) can be fitted[8] to give $K_a^{1:1} > 10^4\ M^{-1}$ and $K_a^{1:2} \sim 10^2\ M^{-1}$.§ Attempts to determine the binding selectivity for chloride *vs.* bromide were unsuccessful as addition of bromide to the chloride salt **3b** or *vice versa* led to the formation of a mixture of complexes, and the titration data could not be analysed to give individual binding constants.

Addition of tetrabutylammonium acetate to **3d**, on the other hand, led simply to deprotonation, giving back the neutral thiourea.[11] Addition of a second equivalent of acetate did not lead to any significant change to the spectrum of the now neutral thiourea, presumably due to the competing interaction of the acetate with acetic acid, formed in the initial deprotonation of **3d**.[12] Addition of further acetate does then lead to downfield shifts of the N–Hs of the now neutral thiourea, indicating that it binds to the third equivalent by the same motif (**5**) as before.

Thus, overall, the neutral thiourea can bind carboxylate anions but not halide anions, while the protonated thiourea shows opposite selectivity.

Neutral thiourea **2a** adopts a similar conformation to **1** (as evidenced by both the crystal structure and ^1H NMR), and consequently does not bind to bromide or chloride. However, the incorporation of a methyl group at C-3 of the pyridine also prevents binding of the acetate *via* hydrogen bonding to the pyridyl C–H^3 proton. Hence, by the simple replacement of the pyridyl C–H^3 with a methyl group, binding by the neutral species can be switched off altogether.

The tetrafluoroborate salt **4a** has similar binding properties to **3d**, with strong binding of bromide and chloride, however, it is deprotonated by acetate. Titration experiments with fluoride and phosphonate were also investigated. With fluoride, there was no binding to the neutral thioureas **1** and **2a** (*cf.* bromide and

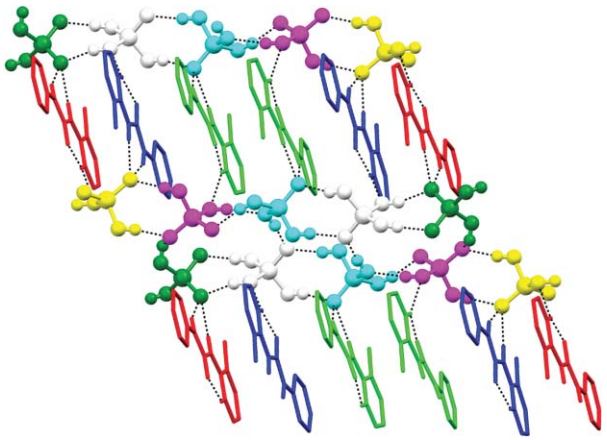


Fig. 4 Crystal structure of 3(**2b**H$^+$)·3($H_2PO_4^-$)·2(H_3PO_4): Part of a hydrogen-bonded sheet lying in the 011 plane. The differing colours represent the crystallographically independent molecules.

chloride), and the corresponding salts **3d** and **4a** were simply deprotonated. Similar results were observed with dihydrogenphosphate (*i.e.*, **3d** and **4a** were deprotonated), although addition of dihydrogenphosphate to the tetrafluoroborate salt **4b** led to a solid precipitate, which could be recrystallised to reveal its crystal structure (Fig. 4).‡ Its structure contains columns of dihydrogenphosphate anions and phosphoric acid molecules ($H_2PO_4^-$: H_3PO_4 = 3 : 2), an intricate network of hydrogen bonds within the columns, and further hydrogen bonds on the periphery to stacks of planar, protonated pyridyl ureas, reflecting the various hydrogen bonding interactions observed in the solution binding studies described above.

In conclusion, we have found that pyridyl thioureas show a variety of unexpected binding properties with carboxylate and halide anions, 'switchable' binding selectivities and intriguing solid-state structures. Given the structural simplicity of this binding motif, it should prove straightforward to incorporate it into more complex molecular architectures, which should lead to even more sophisticated receptor systems.

We thank the University of Bahrain for a studentship (S. R.).

Notes and references

‡ All crystal data were collected on a Bruker Nonius KappaCCD diffractometer with Mo-Kα radiation (0.71073 Å) using ϕ and ω scans to fill the asymmetric unit; the crystals were cooled to 120(2) K. Lp and absorption corrections were applied using SADABS or SORTAV. Structures were solved by direct methods using SHELXS-97 and refined on F^2 using SHELXL-97. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were included in calculated positions and refined using a riding model.

Crystal data for 3c: $C_{14}H_{12}N_3O_2F_3S$, M = 343.33, colourless rod, 0.2 × 0.03 × 0.02 mm, orthorhombic, space group $P2_12_12_1$, a = 5.2405(1), b = 16.2008(4), c = 17.6222(5) Å, V = 1496.13(6) Å^3, Z = 4, D_c = 1.524 g cm^{-3}, F_{000} = 704, $2\theta_{max}$ = 54.96°, 14531 reflections collected, 3408 unique (R_{int} = 0.0479). Final GoF = 1.073, $R1$ = 0.0377, w$R2$ = 0.0936, R indices based on 3408 reflections with $I > 2\sigma(I)$, 212 parameters, 0 restraints, T_{min} = 0.9395, T_{max} = 0.9948, μ = 0.262 mm^{-1}. Residual electron density = 0.175 e/Å^3. CCDC 605518.

Crystal data for 3d: $C_{12}H_{14}N_3SOBF_4$, M = 335.15, colourless block, 0.15 × 0.06 × 0.02 mm, monoclinic, space group $P2_1/c$, a = 9.2690(6), b = 22.1000(15), c = 7.1372(3) Å, β = 97.363(4)°, V = 1449.96(15) Å^3, Z = 4, D_c = 1.535 g cm^{-3}, F_{000} = 688, $2\theta_{max}$ = 54.96°, 18054 reflections collected, 3311 unique (R_{int} = 0.0764). Final GoF = 0.992, $R1$ = 0.0537, w$R2$ = 0.1167, R indices based on 3311 reflections with $I > 2\sigma(I)$, 207 parameters, 0 restraints, T_{min} = 0.9505, T_{max} = 0.9946, μ = 0.271 mm^{-1}. Residual electron density = 0.350 e/Å^3. CCDC 603103.

Crystal data for 3(2bH$^+$)·3($H_2PO_4^-$)·2(H_3PO_4): $C_{39}H_{54}N_9O_{23}P_5$, M = 1171.76, colourless needle, 0.4 × 0.04 × 0.03 mm, triclinic, space group $P\bar{1}$, a = 13.313(5), b = 13.411(5), c = 14.405(5) Å, α = 80.288(5), β = 76.135(5), γ = 84.352(5)°, V = 2456.6(16) Å^3, Z = 2, D_c = 1.584 g cm^{-3}, F_{000} = 1220, $2\theta_{max}$ = 54.96°, 31557 reflections collected, 10375 unique (R_{int} = 0.2536). Final GoF = 0.914, $R1$ = 0.0860, w$R2$ = 0.1338, R indices based on 10375 reflections with $I > 2\sigma(I)$, 700 parameters, 7 restraints, T_{min} = 0.8958, T_{max} = 0.9916, μ = 0.281 mm^{-1}. Residual electron density = 0.590 e/Å^3. CCDC 603100. The data quality for this structure did not allow the hydrogen positions on the phosphate groups to be unequivocally located. The reported model was arrived-at through consideration of peaks in the difference map, P–O bond distances, hydrogen bond geometry, spatial restrictions and the necessity for charge balance. In the case of the P5 molecule, these considerations did not all concur and a compromise was used. This results in a somewhat non-intuitive model, where one H terminates a short P–O distance, leaving another longer one un-protonated. This is believed to be a result of an average view of what is likely to be a disordered arrangement in the crystal. For crystallographic data in CIF or other electronic format, see DOI: 10.1039/b611138f

§ For comparison, titration of tetrabutylammonium chloride with diphenyl thiourea in CD_3CN gave $K_a^{1:1} \sim 400$ M^{-1}, and with the tetrafluoroborate salt of pyridine in CD_3CN gave $K_a^{1:1} \sim 800$ M^{-1}, demonstrating the synergistic effect of a thiourea hydrogen bonded to a pyridinium, as in **3d**.

1 Selected examples of switchable host–guest systems: (*a*) R. Rojanathanes, T. Tuntulani, W. Bhanthumnavin and M. Sukwattanasinitt, *Org. Lett.*, 2005, **7**, 3401; (*b*) V. V. Samoshin, V. A. Chertkov, D. E. Gremyachinskiy, E. K. Dobretsova, A. K. Shestakova and L. P. Vatlina, *Tetrahedron Lett.*, 2004, **45**, 7823; (*c*) G. Tumcharern, T. Tuntulani, S. J. Coles, M. B. Hursthouse and J. D. Kilburn, *Org. Lett.*, 2003, **5**, 4971; (*d*) M. H. Al-Sayah and N. R. Branda, *Org. Lett.*, 2002, **4**, 881; (*e*) R. Shukla, T. Kida and B. D. Smith, *Org. Lett.*, 2000, **2**, 3099.

2 For a review of electrochemically- and photochemically-switchable host–guest interactions at surfaces, see: G. Cooke, *Angew. Chem.*, 2003, **115**, 5008, (*Angew. Chem., Int. Ed.*, 2003, **42**, 4860); A. N. Shipway and I. Willner, *Acc. Chem. Res.*, 2001, **34**, 421.

3 For a review of allosteric effects in host–guest systems, see: (*a*) L. Kovbasyuk and R. Kramer, *Chem. Rev.*, 2004, **104**, 3161; (*b*) M. Takeuchi, M. Ikeda, A. Sugusaki and S. Shinkai, *Acc. Chem. Res.*, 2001, **34**, 865.

4 D. X. West, A. K. Hermetet, L. J. Ackerman, J. Valdés-Martínez and S. Hernández-Ortega, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1999, **55**, 811.

5 L. V. Sudha and D. N. Sathyanaratana, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1647.

6 Protonation of a pyridine moiety has been used to switch the conformation of pyridine-derived oligoamides: (*a*) C. Dolain, V. Maurizot and I. Huc, *Angew. Chem.*, 2003, **115**, 2844, (*Angew. Chem., Int. Ed.*, 2003, **42**, 2738); (*b*) E. Kolomiets, V. Berl, I. Odriozola, A.-M. Stadler, N. Kyritsakas and J.-M. Lehn, *Chem. Commun.*, 2003, 2868.

7 Binding studies of **1** with phosphoric acid diester have been described: K. Kumamoto, Y. Misawa, S. Tokita, Y. Kubo and H. Kotsuki, *Tetrahedron Lett.*, 2002, **43**, 1035.

8 The binding constants were calculated by fitting the data using NMRTit HG software: A. P. Bisson, C. A. Hunter, J. C. Morales and K. Young, *Chem.–Eur. J.*, 1998, **4**, 845.

9 See the ESI† for NMR titration data and the crystal structures of **3a** and **3b**.

10 (*a*) K.-S. Jeong and Y. L. Cho, *Tetrahedron Lett.*, 1997, **38**, 3279. For participation of aromatic C–Hs in hydrogen bonding see: (*b*) S. In, S. J. Choo, K. H. Lee and J. Kang, *Org. Lett.*, 2005, **7**, 3993 and references therein; (*c*) C. R. Bondy, P. A. Gale and S. J. Loeb, *J. Am. Chem. Soc.*, 2004, **126**, 5030 and references therein.

11 Deprotonation-of (rather than association-with) receptors by anionic guests is a commonly observed phenomenon. See, for example: (*a*) L. S. Evans, P. A. Gale, M. E. Light and R. Quesada, *Chem. Commun.*, 2006, 965 and references therein. See also ref. 12.

12 Competitive binding of acetate anion by acetic acid in the presence of a receptor system has been observed previously: M. Boiocchi, L. Del Boca, D. Esteban-Gómez, L. Fabbrizzi, M. Licchelli and E. Monzani, *Chem.–Eur. J.*, 2005, **11**, 3097.

