

Crystallographic, ^1H NMR and CD studies of sterically strained thiourea anion receptors possessing two stereogenic centres†

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The synthesis and structural characterisation of three chiral bis-naphthalene thiourea receptors (**1–3**) derived from (*R*)-(+)-1-(1-naphthyl)ethylamine and (*S*)-(–)-1-(1-naphthyl)ethylamine are reported along with spectroscopic studies to screen their potential as anion receptors/sensors. Their solid state structures were analysed by X-ray crystallography and their ability to bind anions such as acetate and phosphate in DMSO solution investigated by ^1H NMR, absorption, fluorescence and circular dichroism spectroscopy.

Introduction

The development of receptors and sensors for the recognition and monitoring of anion concentrations is of great current interest in supramolecular chemistry.^{1,2} In biological systems anion recognition is driven by hydrogen bonding interactions³ found *e.g.* for amides.⁴ Therefore, molecules that possess charge neutral anion receptors which mimic those found in biological centres are of particular interest.² Many examples of such systems are those based on *N,N'*-di-substituted ureas and thioureas, indoles, *etc.* due to their ability to hydrogen bond to anions.⁵ Indeed, these potent hydrogen bond donor–acceptor motifs have also been extensively employed as synthons in supramolecular chemistry and crystal engineering as the N–H groups readily accept electron density from their corresponding S- and O-atoms from adjacent molecules.^{6,7}

We have developed several examples of urea, thiourea and amidourea-based anion receptors.^{1,8–14} These systems usually possess aryl substituents such as nitrobenzene that can give rise to a colorimetric response or act as fluorophores, which show changes in their excited state properties, such as emission wavelengths (λ_{max}), quantum yields and lifetimes upon anion binding.

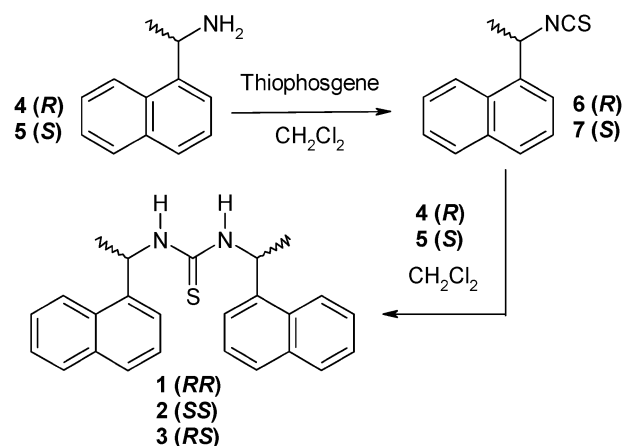
Here we present three new thiourea receptors, **1–3**, which were formed in a single step by reacting chiral amines with chiral isothiocyanates. While chiral ureas and thioureas have been extensively explored in organocatalysis,¹⁵ they have not been much explored for anion sensing.¹⁶ In our previous work, we have shown that to achieve effective enantioselective sensing of chiral anions, the receptors need to possess a minimum of two stereogenic centres.¹⁷ This has also been demonstrated by other researchers, such as Kilburn *et al.*,¹⁸ Tucker *et al.*¹⁹ and James *et al.*²⁰

The focus of our current investigation, the results of which are presented herein, was to explore the use of sterically hindered thioureas with the aim of tuning the sensitivity of the anion recognition. The three resultant stereoisomers formed in this work (*RR* **1**, *SS* **2** and *SR* **3**) can be described as being *sterically constrained*, or *hindered*, as the two naphthalene units adopt a “wing-like” conformation around the thiourea moiety, which gives rise to the formation of a potential ‘binding pocket’ for the anions. This was established conclusively by X-ray crystallography. We also evaluated the anion binding properties of **1–3** in solution using various spectroscopic techniques against simple achiral anions, and we demonstrate that the steric hindrance of these structures has significant affect on the sensitivity and the selectivity of the anion binding and recognition.

Results and discussion

Synthesis and characterisation of **1–3**

The synthesis of **1–3** was achieved as set out in Scheme 1 from commercially available chiral naphthalene-based amines,



Scheme 1 Synthesis of compounds **1–3**.

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(*R*)-(+)-1-(1-naphthyl)ethylamine, **4**, and (*S*)-(–)-1-(1-naphthyl)ethylamine, **5**. These molecules were first converted to their corresponding isothiocyanates, **6** and **7**, respectively, using thiophosgene, and isolated as pure solids.²¹ The *RR* isomer **1** and the corresponding enantiomer **2** were then formed by reacting **4** with **6** or **5** with **7** in CH₂Cl₂ under argon at room temperature for 18 h, whereas the diastereoisomer **3** was synthesised from **4** by reacting it with **7**, under the same experimental conditions.

The desired products were obtained as off-white crystalline solids in reasonable yields of 41–62%. Each product was also characterised by ¹H NMR spectroscopy (400 MHz, DMSO-*d*₆), which exhibited the expected C₂ symmetry as shown for **1** in Fig. 1 (See ESI† for **1–3**). A characteristic pattern for the chemical shifts of the naphthalene protons can be observed in this spectrum at δ 8.18, 7.96 and 7.85, and a multiplet, centred at δ 7.54, while the thiourea N–H protons resonate at δ 7.76. The chiral α-proton appeared as a broad singlet at δ 6.21, while methyl protons appeared as a doublet at δ 1.53. Compound **2** displayed an identical spectrum. The ¹H NMR spectrum for the *meso* compound **3** showed slight differences from those of **1** and **2**, especially for the thiourea protons which now resonate at δ 7.69.

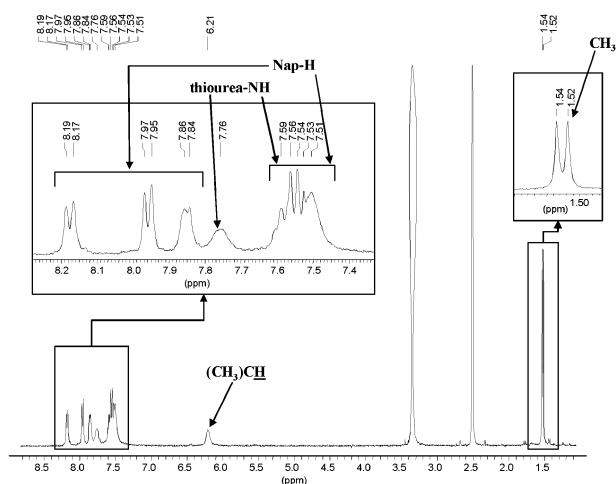


Fig. 1 The ¹H NMR (400 MHz) of **1** when recorded in DMSO-*d*₆. Inset—the expanded areas for the aromatic and the chiral moiety.

X-Ray crystal structure analysis of **1–3**

Single crystals of compounds **1–3** suitable for X-ray diffraction studies were successfully grown from DMSO solutions. The resulting crystal structures of **1**, **2** and **3**, are shown in Fig. 2 and details are given in Table 1. The crystal structures for **1** and **2** are mirror images of each other, while the diastereoisomer **3** has a plane of symmetry passing through the centre of the molecule and perpendicular to the plane of the thiourea moiety. The thiourea moieties in **1–3** adopt the *trans–trans* rotamer (relative to the HNCs angle) in the solid state. Receptors **1–3** each crystallise with one molecule of DMSO per receptor that hydrogen bonds through the oxygen atom to each thiourea N–H group (See ESI† for **1**). This interaction assists in stabilising the thiourea moiety into the *trans–trans* conformation.

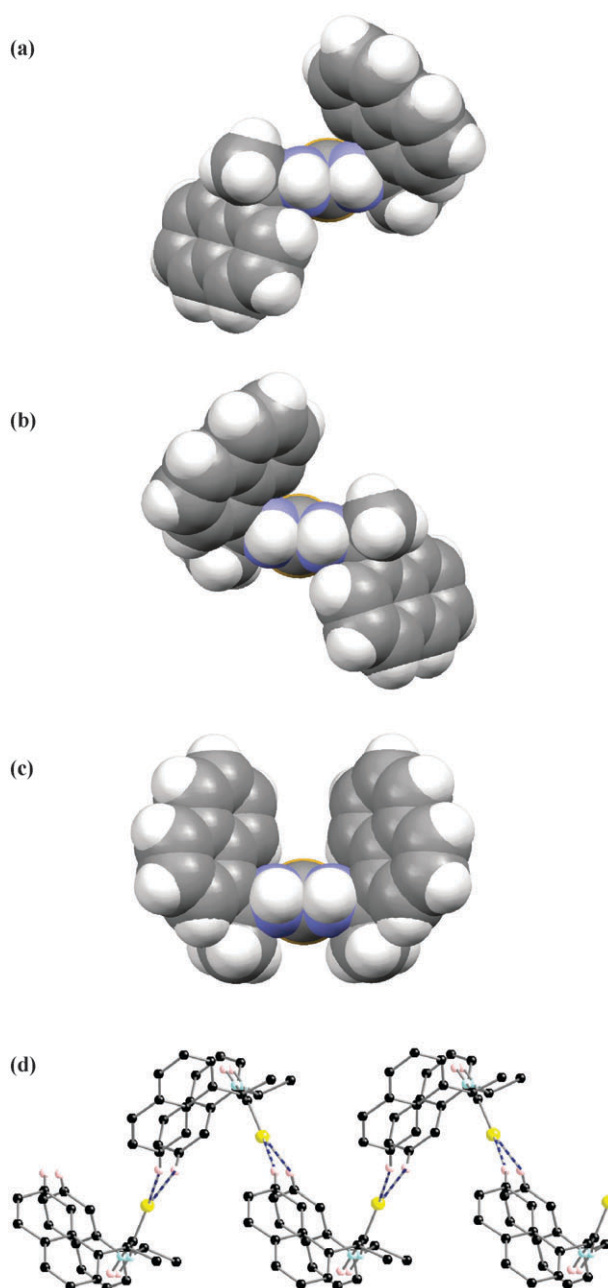


Fig. 2 Molecular structures of **1** (a), **2** (b) and **3** (c) shown in space-filling mode to emphasise the steric profile around the thiourea N–H moieties. (d) Hydrogen bond chain formed through C–H...S contacts in **3**. DMSO molecule of crystallisation omitted from each for sake of clarity.

Further inspection of the structure of **1–3** reveals there are no intermolecular interactions of interest within the structures of **1** and **2** (See ESI† for packing diagrams) although **3** shows an interesting interaction between the sulfur atom of the thiourea moiety and two naphthyl C(7)–H atoms from adjacent molecules (Fig. 2d). This hydrogen bond interaction (C–H...S: ∠ 155.4°; H...S, 2.86 Å) gives rise to an undulating S-shaped 1D chain which propagates along the crystallographic *c*-axis. This interaction probably arises as a consequence of the steric bulk of the ‘naphthyl-wings’ that

Table 1 Crystallographic data for 1–3

Compound	1	2	3
Chemical formula	C ₂₇ H ₃₀ N ₂ OS ₂	C ₂₇ H ₃₀ N ₂ OS ₂	C ₅₄ H ₄₈ N ₄ OS ₄
Formula weight	462.65	462.65	913.20
Crystal system	Monoclinic	Monoclinic	Orthorhombic
Space group	C ₂	C ₂	Cmc2(1)
μ (MoK α)/mm	0.237	0.239	0.233
$a/\text{\AA}$	17.080(2)	17.0684(15)	22.838(3)
$b/\text{\AA}$	8.1010(9)	8.0774(7)	10.8673(14)
$c/\text{\AA}$	18.903(2)	18.8459(17)	10.1015(14)
$\alpha/^\circ$	90.00	90.00	90.00
$\beta/^\circ$	109.013(2)	109.117(2)	90.00
$\gamma/^\circ$	90.00	90.00	90.00
$V/\text{\AA}^3$	2472.8(5)	2455.0(4)	2507.1(6)
Z	4	4	2
$D_c/\text{g cm}^{-3}$	1.243	1.252	1.210
T/K	150(2)	150(2)	150(2)
$2\theta_{\text{max}}$	25.00	25.00	25.00
Min/max trans. factor	0.855529	0.810283	0.805022
R_{int}	0.0382	0.0281	0.0198
R_1, wR_2 [$I > 2\sigma(I)$] ^a	0.0482, 0.0989	0.0397, 0.0922	0.0302, 0.0815
R_1, wR_2 (all data)	0.0606, 0.1082	0.0463, 0.0992	0.0304, 0.0817
Reflections: collected	12 771	12 331	12 722
Unique	4190	4269	4230
Observed	3555	2337	2240

$$^a R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|, wR_2 = [\sum w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2]^{1/2}.$$

surround the thiourea binding pocket. Indeed, Custelcean and co-workers⁶ have shown through a combination of computer modelling, crystallography and a survey of the Cambridge structural database (CSD) that the bulky nature of the substituents in *N,N'*-di-substituted thioureas can determine which of the *trans-trans* or *cis-trans* rotamers is observed in the solid state (the *cis-cis* rotamer is energetically unfavoured and is rarely observed in the solid state). The *cis-trans* rotamer is calculated to be marginally more stable than the *trans-trans* (and observed slightly more frequently in the CSD), whereas the balance is tipped toward the *trans-trans* rotamer in the solid state when the thiourea moiety is flanked by very bulky substituents. The slightly higher energetic cost associated with this rotamer is offset through the formation of extended hydrogen bonded linear chains in the solid state. Calculations show that putative *cis-trans* rotamers shield one of the N–H groups and sterically prohibit the formation of hydrogen bonding in the solid state thus favouring the *trans-trans* rotamer. Interestingly, we have tipped the balance too far in the current examples by introducing *too* great a steric bulk into the thiourea scaffold thus preventing the formation of the archetypal hydrogen bonded linear chains. Indeed, molecular models show that self-association of 1–3 to form linear hydrogen bonded chains would be very difficult on steric grounds. However, the apparently more stable *cis-trans* rotamer is not observed in 1–3 because the DMSO molecule accepts two hydrogen bonds from the *trans-trans* rotamer and probably offsets the energetic cost in forming it.⁶

Titration of 1–3 with anions as followed by ¹H NMR spectroscopy

The anion binding capabilities of compounds 1–3 were studied in wet (~2% H₂O) DMSO-*d*₆ by tracking changes in their ¹H NMR spectra at 25 °C, against a series of anions including

AcO[−], H₂PO₄[−] and F[−], Cl[−] and Br[−] (as their TBA salts). The chemical shifts of the thiourea N–H protons of 1–3, did not broaden significantly upon interaction with AcO[−] and H₂PO₄[−] and hence, it was possible to monitor changes in these resonances upon recognition of these anions, which indicates that the interaction of these anions with the receptor is through hydrogen bonding. However, the changes were only minor for Cl[−] and Br[−] and the binding affinity of these anions could not therefore be determined.

In the case of F[−], the thiourea resonances were shifted in a similar manner to that observed for AcO[−]. The binding generally resulted in a significant downfield shift in the thiourea N–H resonances, as is evident in Fig. 3 and 4, for the titration of 1 with AcO[−] and F[−], respectively. In the presence of AcO[−] the largest changes were observed for the N–H protons, which are almost shifted by *ca.* 2.5 ppm upon hydrogen bonding to the anions. However, minor shifts were also seen for the aryl protons, the most pronounced for those protons adjacent to the ‘binding pocket’ (see in Fig. 3). In the case of F[−], there was also the formation of a new resonance at *ca.* 16 ppm, which

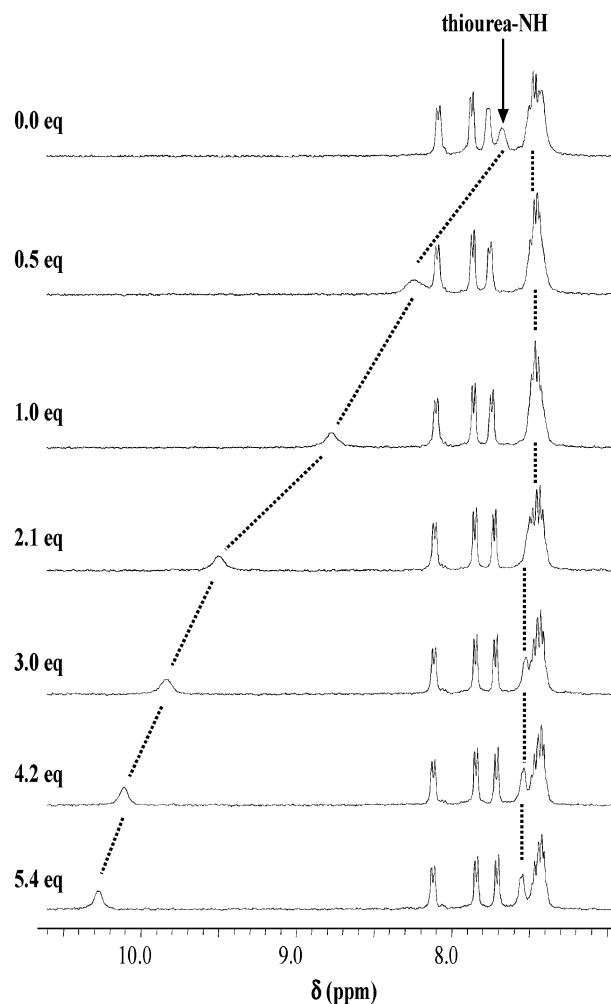


Fig. 3 The changes in the ¹H NMR spectra (400 MHz, DMSO-*d*₆) of 1 upon titration with acetate. The changes are most dramatic for the urea N–Hs, which are shifted by over >2 ppm. Minor changes are also seen for the aromatic protons adjacent to the binding site (shown above as shifting multiplet as a function of added anions).

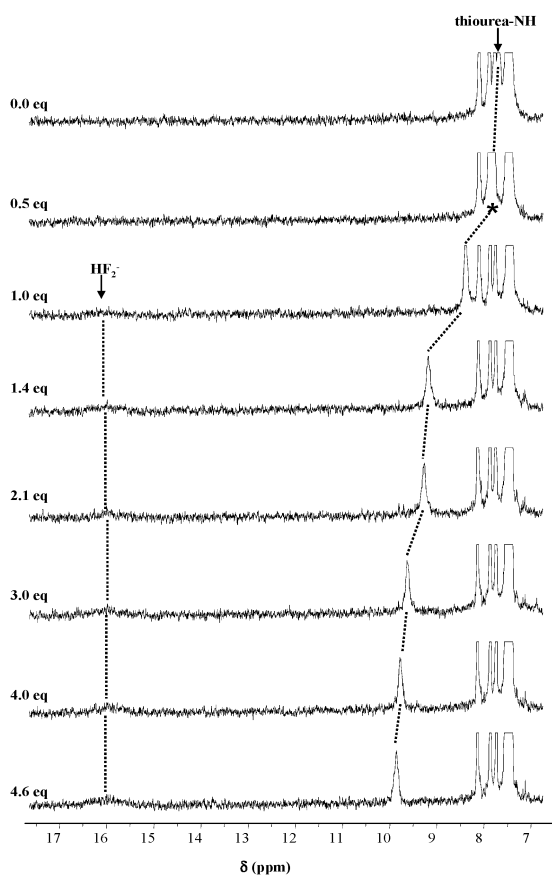


Fig. 4 The changes in the NMR spectra of **1** upon titration with fluoride. While one of the thiourea protons is shifted upon interaction with the anion, the formation of a broad signal at *ca.* 16 ppm is an indication of a deprotonation event within the structure.

increased in proportion during the course of the titration. These data are consistent with F^- interacting with the receptor *via* hydrogen bonding initially, then with increasing concentration of F^- it is able to deprotonate the thiourea protons, forming HF_2^- , which gives rise to the triplet at 16 ppm.¹² Hence, the recognition of F^- is most likely occurring through a dual mechanism of hydrogen bonding followed by deprotonation.

The changes observed for the thiourea protons in the above 1H NMR titrations were in slow exchanges on the NMR time scale and were plotted as the cumulative changes ($\Delta\delta$) against the equivalents of anion added. The binding interaction caused large shifts in these resonances reaching saturation within the addition of five equivalents of these anions (See ESI† for **1–3** for AcO^- , $H_2PO_4^-$ and F^-), which is usually an indication of rather weak binding, which might be expected given the steric strain of the thiourea binding pocket in **1–3**. From these plots it is clear that the largest shifts (up to 3 ppm) were observed for titrations involving AcO^- and F^- , while for $H_2PO_4^-$ the largest changes were up to 1 ppm. Interestingly, the changes in these resonances were not homogenous for the enantiomers **1** and **2** as larger changes were seen for the recognition of AcO^- , than F^- for **1**, while the reverse was observed for **2**.

The stability constants ($\log K$ values) for the anion binding of **1–3** were calculated by fitting the changes observed in the

Table 2 Stability constants ($\log K$) obtained from fitting the changes in the 1H NMR of **1–3** using a nonlinear regression program. The fit of these data is shown in ESI.^a Estimated error of *ca.* 10%

Receptor	AcO^-	$H_2PO_4^-$	F^- ^b
1	2.13	2.39	—
2	2.13	2.28	—
3	2.86	1.83	—

^a All measured in DMSO. ^b Unable to determine $\log K$ or $\log \beta$ accurately due to deprotonation.

1H NMR to 1 : 1 binding stoichiometry using the WinEQN MR programme (See ESI† for these fits), Table 2.²² It was not possible to obtain $\log K$ values for F^- binding due to the competing deprotonation process as mentioned above. Upon binding AcO^- or $H_2PO_4^-$ the two enantiomers **1** and **2** gave similar $\log K$ values, of 2.13 and *ca.* 2.30, respectively, which demonstrate rather poor selectivity or discrimination between these ions by these receptors. In contrast, the *meso* compound **3** gave $\log K$ values of 2.86 and 1.83 for AcO^- and $H_2PO_4^-$, respectively, which indicates a significant selectivity of **3** for AcO^- over $H_2PO_4^-$. To help rationalise this significant discrimination by **3**, which contrasts with the lack of any selectivity in **1** and **2**, we need to recall the structural data that show that the *meso* compound generates a binding pocket in the solid state, which is also the most likely geometry in solution. Indeed, it can then be envisaged that the smaller ‘Y-shaped’ planar AcO^- ion may be able to approach the sterically encumbered thiourea binding site with more ease than the larger tetrahedral $H_2PO_4^-$, whereas in the case of **1** and **2** the binding site is more accessible and permits both AcO^- and $H_2PO_4^-$ comparable access and hence binds them with similar binding constants. These examples clearly show how the sensitivity of the anion recognition can be modulated by a simple receptor design using chirality.

We also attempted to grow crystals from solutions of **1–3** and several anions. However, on all occasions, we were unable to obtain crystals that were of high enough quality for X-ray crystal structure analysis.

Titration of **1–3** with anions as followed by ground state, fluorescence and CD spectroscopy

The ground and the excited state spectra of **1–3** were measured in both DMSO and CH_3CN at 25 °C. The absorption spectra for these compounds exhibit the characteristic naphthalene fine structure, consisting of a central main band at 284 nm, with two shoulders at 274 and 296 nm and a much smaller shoulder at 314 nm. The fluorescence emissions of all three compounds when excited at 288 nm were also similar to each other, demonstrating the characteristic fine structure of naphthalene with a maximum intensity at *ca.* 338 nm.

The changes in the fluorescence and absorption spectra of **3** in MeCN upon the addition of $H_2PO_4^-$ are shown in Fig. 5 and little change was observed in either the absorption or the emission spectra. This is somewhat surprising as we have demonstrated in our previous work that generally the ground and the excited states are dramatically affected upon binding to anions.^{1,8} It is likely that this is due to the steric strain that the thiourea moiety induces in these structures and was

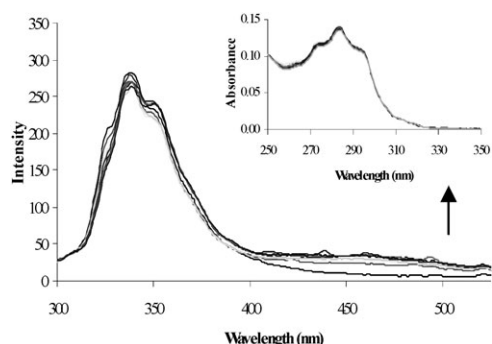


Fig. 5 The fluorescence emission spectrum of **3** in MeCN on addition of H_2PO_4^- upon excited at 284 nm. *Inset*: Changes in the absorbance spectrum of **3** (1×10^{-5} M) in MeCN upon the addition of H_2PO_4^- ($0 \text{ M} \rightarrow 1 \times 10^{-2} \text{ M}$).

obvious from the crystallographic analysis of these three receptors. However, slight changes do occur at longer wavelength with λ_{max} ca. 460 nm, which we attribute to the induced π - π interactions caused by the anion binding in **3**, which results in the formation of a weak excimer emission for the naphthalene chromophores.²³ However, as stated above, then in comparison to many photoinduced electron transfer (PET) sensors developed on the above design, these results demonstrate that neither the ground nor the excited state is significantly affected upon interaction with H_2PO_4^- .

Since compounds **1** and **2** are chiral, anion recognition was also investigated using circular dichroism spectroscopy to monitor any changes in their chiroptical properties. While such studies are commonly used to analyse the binding of metal complexes with anions²⁴ and biomolecules, such as DNA,²⁵ then the use of CD to probe the changes in organic anion receptors has, to the best of our knowledge, not been extensively used before.²⁶ The CD spectra of **1** and **2**, when recorded in DMSO (See ESI†) demonstrated that the two enantiomers have structured CD spectra where **1** gave rise to positive signals and **2** gave rise to negative signals, with main transitions at 268 and 291 nm. Upon addition of series of anions significant changes were observed in the CD spectra of both compounds. As shown in Fig. 6 for the changes in **2** for AcO^- , the main changes occurred in the band centred at 270 nm, where the negative absorption band showed an increase in the molar ellipticity from $-7.5 \rightarrow -2.5$. In a similar manner the changes observed for **1** were largely identical to that observed for **2**, except that these changes

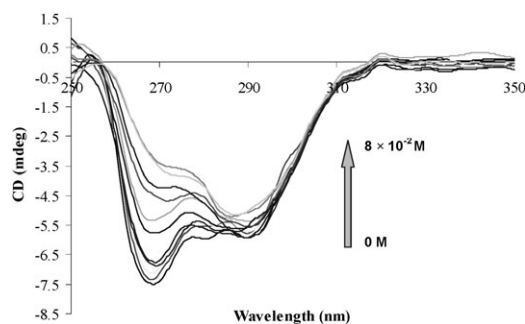


Fig. 6 The changes observed in the CD spectrum of **2** in DMSO upon titration with AcO^- : $0 \rightarrow 8 \times 10^{-2} \text{ M}$ (selective spectra used).

were observed with opposite signs to that of **2**. In comparison to that observed in the ground state (Fig. 5 inset) these changes clearly show that the chiroptical properties of these sensors are affected by the anion binding at the thiourea moiety. The CD changes were further analysed by subtracting the CD spectra of each sensor from that observed upon anion addition. This gave indication of the 'net' changes experienced by **1** and **2** upon titration with AcO^- (see ESI† for **2** with AcO^-), and clearly demonstrated that CD spectroscopy is a powerful tool to employ in anion recognition and sensing.

Similarly, the titration of **1** and **2** using F^- and H_2PO_4^- resulted in significant changes in the CD spectra of these receptors. In contrast to these significant CD changes, no such changes were observed upon the addition of Cl^- , which demonstrated that the above changes are caused due to the binding of the anions at the thiourea binding site, with concomitant changes in the chiroptical properties of receptors **1** and **2**. As expected, the *meso* compound **3** did not show any induced changes in the spectra upon anion titration.

Conclusions

The synthesis, crystallographic and various spectroscopic analyses of three thiourea based receptors have been undertaken. These sensors, **1–3**, were formed in a single step from their corresponding chiral amines and isothiocyanides. All of the compounds gave rise to significant changes in the ^1H NMR spectra, where the thiourea protons were shifted by almost 2 ppm units when titrated with a series of anions. The analysis of these changes suggest that compound **1** and **2** bound H_2PO_4^- with only slight preference over AcO^- . However, in the case of **3**, the selectivity for AcO^- is clear over H_2PO_4^- . Using F^- also gave rise to significant changes in the NMR spectrum, however, these were assigned to the combination of both hydrogen bonding and deprotonation of the thiourea binding sites by the anion. The three compounds are based on symmetrical thiourea-spacer-naphthalene structures, which can also be viewed as PET sensors. As expected, the anion recognition did not give rise to changes in the ground state of these molecules. However, and somewhat unexpectedly, the fluorescence emission spectra of these sensors did not change either in comparison to that observed for most classical PET anion sensors that often give rise to complete quenching in their emission spectra, with the exception that H_2PO_4^- , which upon binding to **3** gave rise to small changes at longer wavelength. In contrast to these results both **1** and **2** gave rise to significant changes in their corresponding CD spectra, which demonstrated that anions such as AcO^- , H_2PO_4^- and F^- were able to give significant changes in the chiroptical properties of sensors **1** and **2**. In contrast to these results, the titration of **1** and **2** with Cl^- did not give rise to any such changes. We are currently in the process of developing other chiral anion receptors with the view of using CD and circular polarised spectroscopy (CPL)²⁷ to probe the chiroptical properties of such sensors upon binding to anions.

Experimental

Starting materials were obtained from Sigma Aldrich and Fluka. Solvents used were HPLC grade unless otherwise

stated. ^1H NMR spectra were recorded at 400 MHz using a Bruker Spectrospin DPX-400, with chemical shifts expressed in parts per million (ppm or δ) downfield from the standard. ^{13}C NMR spectra were recorded at 100 MHz using a Bruker Spectrospin DPX-400 instrument. Infrared spectra were recorded on a Mattson Genesis II FTIR spectrophotometer equipped with a Gateway 2000 4DX2-66 workstation. Mass spectroscopy was carried out using HPLC grade solvents. Electrospray mass spectra were recorded on a Micromass LCT spectrometer. The system was controlled by MassLynx 3.5 on a Compaq Deskpro workstation. UV-Vis spectroscopic analysis was carried out on a Varian Cary 100 UV-Vis spectrophotometer. Luminescence measurements were carried out on Varian Carey Eclipse spectrophotometer. CD measurements were carried out on a Jasco J-810-150S spectropolarimeter. All CD spectra are represented as mdeg vs. wavelength (nm). The baseline of the solvent was taken and removed from all spectra shown.

Crystallographic measurements

Single crystal data and experimental details for **1–3** are summarised in Table 1. Single crystal analyses were performed at 396 K with a Bruker SMART APEX CCD diffractometer using graphite mono-chromated Mo- $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). A full sphere of data was obtained for each using the omega scan method. Data were collected, processed and corrected for Lorentz and polarization effects using SMART^{27a} and SAINT-NT^{27b} software. Absorption corrections were applied using SADABS.^{27c} The structures were solved using direct methods and refined using the SHELXTL^{27d} program package. For **1–3**, all non-hydrogen atoms were refined anisotropically. Aromatic hydrogen atoms were assigned to calculated positions with isotropic thermal parameters fixed at 1.2 times that of the attached carbon atom. Hydrogen atoms involved in hydrogen bond interactions were located where possible from difference maps and refined with O–H distances restrained to 0.84 \AA , and isotropic thermal parameters fixed at 1.5 times that of the respective oxygen atom.

Synthesis of isothiocyanates²¹

Triphosgene (2 equiv.) was carefully added to a solution of the amine to form the corresponding isothiocyanate. The reaction mixture was left stirring for 18 h under argon at room temperature, after which any excess phosgene or thiophosgene was quenched with water. The mixture was extracted with CH_2Cl_2 and the organic layer extracted with water ($1 \times 20 \text{ mL}$) and brine ($3 \times 10 \text{ mL}$). The solution was then dried over MgSO_4 and removed under reduced pressure to give the desired product.

(R)-1-(1-Naphthyl)ethylisothiocyanate (6). Compound **6** was synthesised in accordance with the above procedure using (R)-(+)-1-(1-naphthyl)ethylamine **4** (1.00 g, 5.84 mmol) and thiophosgene (0.67 mL, 8.76 mmol) in dry DCM (150 mL). Since the product has a low boiling point, the solvent of the filtrate obtained was allowed to evaporate naturally in the fume hood. The desired product was obtained as a brown gel-like solid (0.51 g, 40.7%). δ_{H} (400 MHz, $(\text{CD}_3)_2\text{SO}$) 7.95

(2H, m, Nap-H5, Nap-H8), 7.87 (1H, d, $J = 8.0 \text{ Hz}$, Nap-H4), 7.67 (1H, d, $J = 7.0 \text{ Hz}$, Nap-H2), 7.57 (2H, m, Nap-H3, Nap-H6, Nap-H7), 5.72 (1H, q, $J = 6.7 \text{ Hz}$, CH_3CH), 1.87 (3H, d, $J = 7.0 \text{ Hz}$, CH_3); δ_{C} (100 MHz, $(\text{CD}_3)_2\text{SO}$) 135.0, 133.4, 129.1, 128.8, 128.6, 126.4, 125.6, 125.1, 122.6, 121.8, 53.7, 23.6.

(S)-1-(1-Naphthyl)ethylisothiocyanate (7)

Compound **7** was synthesised in accordance with the above procedure using (S)-(–)-1-(1-naphthyl)ethylamine **5** (1.00 g, 5.84 mmol) and thiophosgene (0.67 mL, 8.76 mmol) in dry DCM (150 mL). Since the product has a low boiling point, the solvent of the filtrate obtained was allowed to evaporate naturally in the fume hood. The desired product was obtained as a brown gel-like solid (0.76 g, 60.8%). δ_{H} (400 MHz, $(\text{CD}_3)_2\text{SO}$) 7.95 (2H, t, $J = 8.3 \text{ Hz}$, Nap-H5, Nap-H8), 7.87 (1H, d, $J = 8.0 \text{ Hz}$, Nap-H4), 7.67 (1H, d, $J = 7.0 \text{ Hz}$, Nap-H2), 7.57 (2H, m, Nap-H3, Nap-H6, Nap-H7), 5.73 (1H, q, $J = 6.7 \text{ Hz}$, CH_3CH), 1.87 (3H, d, $J = 6.5 \text{ Hz}$, CH_3); δ_{C} (100 MHz, $(\text{CD}_3)_2\text{SO}$) 135.0, 133.4, 129.1, 128.8, 128.5, 126.3, 125.5, 125.0, 122.6, 121.8, 53.6, 23.6.

Synthesis of bis-phenylthiureas

The amine (1.3 equiv.) was carefully added to a solution of isothiocyanate (1 equiv.) in dry spectroscopic grade CHCl_3 (unless otherwise stated). The reaction mixture was left stirring under argon for 18 h at room temperature. The reaction mixture was washed with 0.1 M HCl ($1 \times 20 \text{ mL}$) and water ($2 \times 20 \text{ mL}$). The organic layer was then dried over MgSO_4 and filtered. The filtrate was reduced to give the solid product which was then dried under high vacuum.

1,3-Bis-[(R)-1-(naphthalen-1-yl)ethyl]thiourea (1). Compound **1**, was synthesised according to the above procedure, using (R)-(+)-1-(1-naphthyl)ethylamine **4** (0.19 mL, 1.19 mmol) and **6** (0.25 g, 1.19 mmol) in dry DCM (50 mL). The desired product was obtained as an off-white crystalline solid (0.23 g, 51.0%). Mp 84–86 $^{\circ}\text{C}$; calculated for $\text{C}_{25}\text{H}_{24}\text{N}_2\text{S} \cdot 0.5\text{H}_2\text{O}$: C, 76.30; H, 6.40; N, 7.12%; found: C, 76.87; H, 6.24; N, 6.90%; HRMS (MeOH, ES^+): calculated for $\text{C}_{25}\text{H}_{25}\text{N}_2\text{S}$: 385.1738 ($\text{M} + \text{H}$) $^+$; found: 385.1721; δ_{H} (400 MHz, $(\text{CD}_3)_2\text{SO}$) 8.18 (2H, d, $J = 8.0 \text{ Hz}$, Nap-H8), 7.96 (2H, d, $J = 8.0 \text{ Hz}$, Nap-H5), 7.85 (2H, d, $J = 5.5 \text{ Hz}$, Nap-H4), 7.79 (2H, br s, thiourea-NH), 7.54 (8H, m, Nap-H2, Nap-H3, Nap-H6, Nap-H7), 6.22 (2H, br s, CH_3CH), 1.53 (6H, d, $J = 6.5 \text{ Hz}$, CH_3); δ_{C} (100 MHz, $(\text{CD}_3)_2\text{SO}$) 140.0, 133.4, 130.6, 128.7, 127.5, 126.3, 125.7, 125.5, 123.4, 122.5, 48.8, 21.2; MS (MeOH, ES^+) m/z 385 ($\text{M} + \text{H}$) $^+$, 407 ($\text{M} + \text{Na}$) $^+$; IR (KBr) ν_{max} (cm^{-1}) 3223, 2973, 1527, 1447, 1328, 1237, 1171, 1113, 1076, 1023, 861, 799, 774, 727.

1,3-Bis-[(S)-1-(naphthalen-1-yl)ethyl]thiourea (2). Compound **2** was synthesised according to the above procedure, using (S)-(–)-1-(1-naphthyl)ethylamine **5** (0.58 mL, 3.56 mmol) and **7** (0.76 g, 3.56 mmol) in dry DCM (50 mL). The desired product was obtained as an off-white crystalline solid (0.56 g, 41.1%). Mp 84–86 $^{\circ}\text{C}$; calculated for $\text{C}_{25}\text{H}_{24}\text{N}_2\text{S} \cdot 1/2\text{H}_2\text{O}$: C, 76.30; H, 6.40; N, 7.12%; found: C, 76.79; H, 6.22; N, 6.86%; HRMS (MeOH, ES^+): calculated for $\text{C}_{25}\text{H}_{25}\text{N}_2\text{S}$: 385.1738

(M + H)⁺; found: 385.1755; δ_{H} (400 MHz, (CD₃)₂SO) 8.14 (2H, d, *J* = 8.0 Hz, Nap-H8), 7.95 (2H, d, *J* = 8.0 Hz, Nap-H5), 7.85 (2H, d, *J* = 5.5 Hz, Nap-H4), 7.78 (2H, br s, thiourea-NH), 7.54 (8H, m, Nap-H2, Nap-H3, Nap-H6, Nap-H7), 6.21 (2H, br s, CH₃CH), 1.53 (6H, d, *J* = 6.5 Hz, CH₃); δ_{C} (100 MHz, (CD₃)₂SO) 180.9, 139.7, 133.4, 130.6, 128.7, 127.5, 126.3, 125.7, 125.5, 123.4, 122.5, 48.8, 21.2; MS (MeOH, ES⁺) *m/z* 385 (M + H)⁺, 407 (M + Na)⁺; IR (KBr) ν_{max} (cm⁻¹) 3236, 3046, 2972, 1597, 1526, 1447, 1330, 1236, 1171, 1114, 1076, 1023, 861, 799, 774, 728.

1-[(R)-1-(Naphthalen-1-yl)ethyl]-3-[(S)-1-(naphthalen-1-yl)ethyl]-thiourea (3). Compound **3** was synthesised according to above procedure, using (R)-(+)-1-(1-naphthyl)ethylamine **4** (0.19 mL, 1.19 mmol) and **7** (0.25 g, 1.19 mmol) in dry DCM (50 mL). The desired product was obtained as an off-white crystalline solid (0.28 g, 61.7%). Mp 153–155 °C; calculated for C₂₅H₂₄N₂S·1/2H₂O: C, 76.30; H, 6.40; N, 7.12%; found: C, 76.60; H, 6.21; N, 6.92%; HRMS (MeOH, ES⁺): calculated for C₂₅H₂₄N₂S·Na: 407.1558 (M + Na)⁺; found: 407.1559; δ_{H} (400 MHz, (CD₃)₂SO) 8.14 (2H, d, *J* = 8.0 Hz, Nap-H8), 7.94 (2H, d, *J* = 9.0 Hz, Nap-H5), 7.85 (2H, d, *J* = 9.0 Hz, Nap-H4), 7.69 (2H, d, *J* = 7.5 Hz, thiourea-NH), 7.52 (8H, m, Nap-H2, Nap-H3, Nap-H6, Nap-H7), 6.18 (2H, t, *J* = 7.0 Hz, CH₃CH), 1.58 (6H, d, *J* = 6.5 Hz, CH₃); δ_{C} (100 MHz, (CD₃)₂SO) 180.8, 139.3, 133.4, 130.8, 128.6, 127.7, 126.3, 125.7, 125.4, 123.6, 122.5, 48.73, 20.6; MS (MeOH, ES⁺) *m/z* 407 (M + Na)⁺; IR (KBr) ν_{max} (cm⁻¹) 3194, 3046, 2974, 1599, 1541, 1447, 1328, 1254, 1171, 1109, 1074, 1031, 1000, 864, 797, 773, 725, 708.

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