N-(Acetamido)thiourea based simple neutral hydrogen-bonding receptors for anions†

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N-(Acetamido)-*N*′-phenylthioureas (**4–6**) were found to be efficient anion receptors with higher anion affinity than their *N*-benzamido-*N*′-phenylthiourea counterparts (**1** and **2**). The *N*′-phenylthiourea moiety in **4–6** was shown to be the chromophore with an absorption maximum at *ca.* 270 nm. It was found that, in the presence of anions, the absorption at *ca.* 270 nm of **4–6** (except **5f**) in acetonitrile (MeCN) was blue shifted and enhanced while a red-shifted shoulder appeared at *ca.* 295 nm, together with an isosbestic point at *ca.* 240 nm. The 1:1 anion binding constants of **4–6**, for example at 10^6–10^7 M^{-1} order of magnitude for AcO^- in MeCN, were found to be higher than those of **1** and **2**, although the acidity of the thioureido -NH protons in **4–6** is lower than that in **1** and **2**. ^{1}H NMR data indicates that the N–N single bond in **4–6** is twisted but less than that in **1** and **2**. A conformation change at the N–N single bond of **4–6** was suggested to occur upon anion binding which leads to a planar hydrogen-bonding network in the anion binding complex in which a charge transfer takes place with the *N*-acyl moiety being the electron acceptor. Variations in the CD signals of a proline derivative **6** bearing a chiral center in the *N*-amido moiety provide direct evidence for this conformation change upon its binding with anions in MeCN. The amplified effect of substituent X at the *N*′-phenyl ring of **5** on the anion binding constant supports the conclusion of anion-binding switched charge transfer in the anion binding complex. ^{1}H NMR and absorption titrations for **5** indicated that the anion–receptor interaction was of a hydrogen-bonding nature until the *N*′-phenyl substituent X is as electron-withdrawing as *m*-CF_3 (**5e**). With X being the more electron-withdrawing *p*-NO_2 (**5f**), deprotonation of the thioureido -NH occurs in the presence of anion. Results reported here confirm that *N*-amidothioureas derived from both *N*-aliphatic and *N*-aromatic amides can in general be a family of efficient hydrogen-bonding receptors, with the aliphatic *N*-amido derivatives being more efficient. This provides a wider structural diversity for designing thiourea-based functional molecules such as anion receptors and organocatalysts. Preliminary experiments confirm that **6** could catalyse efficiently the reduction of nitrostyrene in CH_2Cl_2 and MeCN.

Introduction

Thiourea has been a well-known neutral binding site employed in the design of anion receptors.[1] Recently it has received increasing attention in organocatalysis.[2] In order to enhance its interaction with anions, structural modifications have been attempted to increase the acidity of the thioureido -NH protons and/or to include other interactions such as additional hydrogen-bonding and electrostatic interactions. In terms of increasing thioureido -NH acidity, *N*-alkyl and/or *N*-aryl substitution is a major means hitherto employed.[1] This may suffer from deprotonation of the highly acidic thioureido NH protons in the presence of basic anions. Incorporating more binding sites in the receptor molecule has been shown to be successful.[3,4] This may need sophisticated structural design and appreciable synthetic effort. We have been interested in exploring an alternative possibility of developing simple thiourea-based anion receptors of enhanced binding ability but not by increasing the acidity of the thioureido -NH protons.[5]

We have discovered *N*-benzamidothioureas (**1** and **2**, Scheme 1) whose thioureido -NH protons are not more acidic than those in the corresponding traditional *N*-phenylthioureas, yet show higher anion-binding constants in MeCN by two orders of magnitude.[5] We suggested that the twisted N–N single bond in *N*-benzamidothioureas underwent a conformation change upon anion binding that switched on a charge transfer (CT) in the anion binding complex, resulting in an amplified substituent (X) effect on the anion binding of **1**.[5d] A hydrogen-bonding network involving an *N*-amido -NH proton was proposed in the anion binding complex.[5d] This was nicely supported by the fact that the absorption and fluorescence spectra of a model

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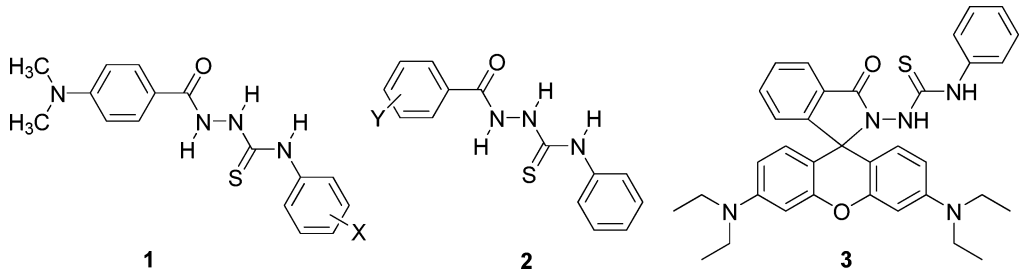
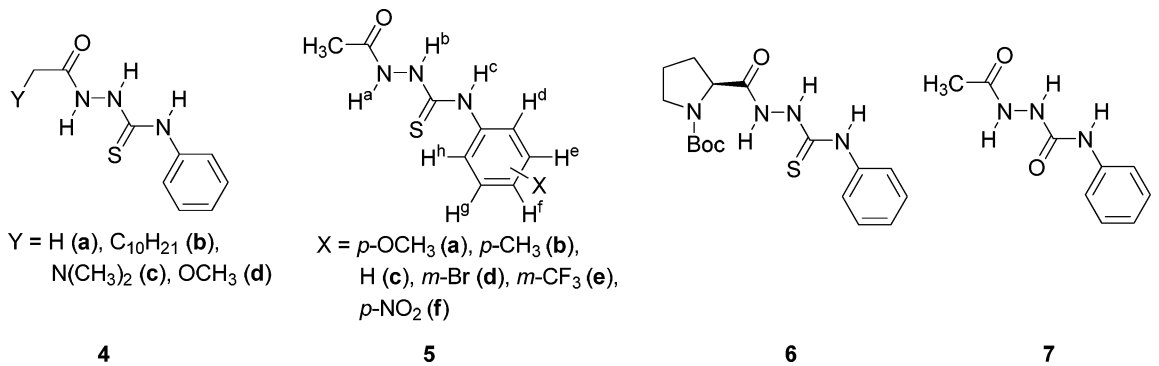
† Electronic supplementary information (ESI) available: Absorption spectra of **4** and **5** and their AcO^- binding complexes in MeCN (Fig. S1); absorption spectra of **7** in MeCN in the presence of F^- (Fig. S2); scans of ^{1}H NMR and ^{13}C NMR spectra of the new compounds. See DOI: 10.1039/b910255h



Scheme 1 Structure of *N*-benzamidothioureas.



Scheme 2 Structure of *N*-acetamido(thio)urea-based anion receptors. Proton labeling is given for **5**.

compound **3** (Scheme 1),[5a,6] bearing no amido -NH proton, showed practically no response toward anions such as AcO^- and F^- in MeCN. It was also noted that the anion binding constant of **2** did not show much dependence on the substituent Y in the *N*-benzamido moiety.[5f] This implies that the aliphatic *N*-amido counterparts of *N*-benzamidothioureas might show similar anion binding capacity. This, if proved, will certainly provide more structural diversity for the thiourea-based anion receptors and organocatalysts as well. We therefore prepared a series of *N*-acetamido-*N′*-phenylthioureas (**4** and **5** in which **4a** = **5c**, Scheme 2). It was found that **4** and **5** showed stronger hydrogen-bonding ability towards anions than **1** and **2**, despite a lower acidity of the thioureido -NH protons in **4** and **5**. *N*-Amidothioureas with both aromatic and aliphatic *N*-amide moiety are therefore shown to be hydrogen-bonding receptors with strong affinity towards hydrogen-bonding acceptors.

Results and discussion

The substituent effect on the ^{1}H NMR signals of -NH and α-methylene/methyl protons in **4** and **5** was investigated in DMSO-d_6. It was found that, with **4a–d**, the chemical shifts of the α-methylene CH_2 protons varied linearly with the electronegativity (X)[7] of the central atom in substituent Y, with a slope of 1.69. NMR signals of three -NH protons, however, were found insensitive to Y. This means that a change in Y in **4a–d** has practically no influence on the acidity of the amido and thioureido -NH protons. Fig. 1 shows that, with **5a–f**, the NMR signals of the thioureido -NHs respond linearly with the Hammett constant of substituent X[8] by slopes of 0.505 and 0.397, whereas with those of amido -NH and α-methyl -CH_3 protons the slopes are only 0.123 and 0.040, respectively. The discontinuity in these slopes

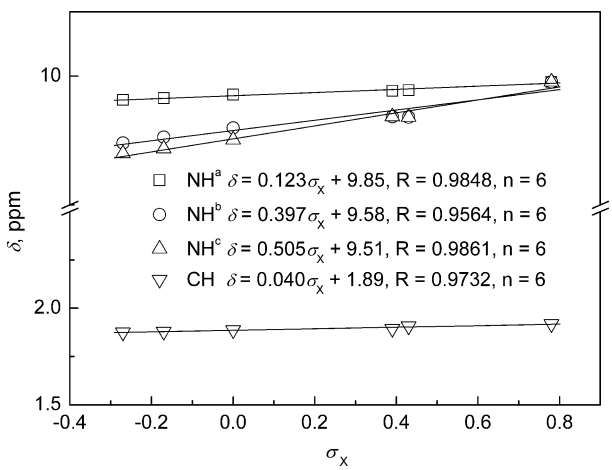


Fig. 1 Chemical shifts of -NH and α-CH_3 protons in DMSO-d_6 against the Hammett constant of substituent X in **5**. Concentration of **5** is *ca.* 10 mmol L^{-1}. The chemical shifts were found independent of the concentration, for example of **5b** over 7 to 51 mmol L^{-1}. The linear relationships found for **1** were $\delta_{-NH(a)} = 0.125\sigma_x + 10.14$ (n = 6, R = 0.9876), $\delta_{-NH(b)} = 0.467\sigma_x + 9.69$ (n = 6, R = 0.9754), $\delta_{-NH(c)} = 0.523\sigma_x + 9.58$ (n = 6, R = 0.9850).[5d]

indicates that the N–N single bond in **5** disrupts the electronic communication between the *N*-amido and thiourea moieties, as was concluded with **1** and **2** for a twisted N–N single bond.[5] On the basis of the NMR data, we found that the acidity of the -NH protons in **4** and **5** is lower than that in **1**[5d] and **2**.[5f] We also noted that, while the slopes for thioureido -NHs were lower for **1**, the slope of the *N*-acetamido -NH proton in **5** was comparable to that of **1** (Fig. 1). This probably suggests a less twisted N–N single bond in **4** and **5** than in **1** and **2**.

Table 1 Absorption spectral parameters of **4a–d** and **5a–e** and their AcO^- binding complexes, and anion binding constants in MeCN[a]

	λ_R^{max}, nm[b]	$\lambda_{R^+A^-}^{max}$, nm[c]	$\Delta h\nu$, cm^{-1}[d]	K_a, mol^{-1} L		
				AcO^-	F^-	$H_2PO_4^-$
4a	267	262	715	$(1.13 \pm 0.07) \times 10^6$	$(1.76 \pm 0.34) \times 10^6$	$(3.23 \pm 0.29) \times 10^4$
4b	267	263	570	$(2.47 \pm 0.00) \times 10^6$	$(6.48 \pm 0.62) \times 10^5$	$(1.03 \pm 0.03) \times 10^5$
4c	266	265	142	$(1.21 \pm 0.32) \times 10^7$	$(8.62 \pm 0.68) \times 10^6$	$(2.89 \pm 0.11) \times 10^4$
4d	267	265	283	$(4.42 \pm 0.50) \times 10^6$	$(8.46 \pm 0.92) \times 10^5$	$(3.41 \pm 0.25) \times 10^4$
5a	264	262	289	$(1.07 \pm 0.07) \times 10^6$	$(6.30 \pm 0.92) \times 10^6$	$(1.74 \pm 0.21) \times 10^4$
5b	266	263	429	$(1.88 \pm 0.13) \times 10^6$	[e]	$(3.50 \pm 0.38) \times 10^4$
5d	271	265	835	[e]	[e]	$(4.43 \pm 0.75) \times 10^4$
5e	272	265	971	[a]	[a]	$(1.39 \pm 0.20) \times 10^6$

[a] Data for **5c** are not given since **5c** = **4a**. [b] Absorption maximum of the receptor. [c] Absorption maximum of the receptor–AcO^- complex. [d] Anion binding induced blue shift in the absorption maximum. [e] The value is over 2×10^7 mol^{-1} L which is too high to be accurately fitted.

Compounds **4a–d** in MeCN show absorption maxima at *ca.* 270 nm that hardly changes with substituent Y. The absorption maximum of **5a–e** shows a red shift from 264 nm (**5a**) through 267 nm (**5c**) to 272 nm (**5e**), with increasing electron-withdrawing ability of the substituent X (Table 1). These observations indicate that the absorption of **4** and **5** originates from their *N′*-phenylthiourea moiety. Fig. 2a shows the absorption spectra of **4a** in MeCN in the presence of AcO^-. It is observed that, with increasing AcO^- concentration, the absorption maximum of **4a** is blue shifted from 267 nm to 262 nm and a shoulder appears over 280 to 340 nm, together with an isosbestic point at 238 nm. This means that a clear **4a**–AcO^- binding interaction occurs in the solution. Addition of competitive hydrogen-bonding solvents such as water or methanol to the **4a**–AcO^- solution in MeCN led to a reversal change in the absorption spectrum back towards that of free **4a**, an observation indicative of the hydrogen-bonding nature of the AcO^-–**4a** interaction in MeCN. Similar variation profiles were observed in the presence of F^- and $H_2PO_4^-$. HSO_4^- has a weaker impact whereas other anions such as Cl^-, Br^-, I^-, NO_3^-, and ClO_4^- exert practically no influence (Fig. 2b). Other members in series **4** and **5a–e** indicated similar spectral responses toward the tested anions in MeCN (Fig. S1 in the ESI†). Upon addition of AcO^-, the blue shift of the absorption maximum of **5**–AcO^- from that of free **5** increases from 289 cm^{-1} for **5a** to 971 cm^{-1} for **5e** (Table 1). Meanwhile, the shoulder of the **5**–AcO^- complex at *ca.* 295 nm shows a tendency to red-shift with increasing electron-withdrawing ability of the substituent X (Fig. S1†). Note that the corresponding new bands in the absorption spectra of the anion binding complexes of **2** in MeCN were at 335 nm,[5f] which are energetically much lower than those (*ca.* 295 nm) of the anion binding complexes of **4** and **5**. Referring to the CT nature of the 335 nm absorption of the anion binding complexes of **2** with an *N*-benzoyl moiety being the electron acceptor,[5f] and the less electron-accepting capacity of the aliphatic *N*-acyl moiety in **4** and **5** than that of the aromatic *N*-benzoyl in **2**, the fact that the shoulder in the absorption spectra of anion binding complexes of **4** and **5** appears at shorter wavelengths probes their CT character. The anion binding ability of the urea counterpart of **4a** (**5c**), *N*-acetamido-*N′*-phenylurea (**7**, Scheme 2), was found to be weaker than that of **4a**. For example (Fig. S2†), absorption spectral titration in MeCN gives a binding constant of F^- with **7** of $(1.27 \pm 0.44) \times 10^5$ mol^{-1} L, which is lower by one order of magnitude than that of **4a** (Table 1). This again supports the hydrogen-bonding nature of the anion interaction with the (thio)urea binding site.[5g]

Absorption spectrum of **5f** bearing a highly electron-withdrawing substituent *p*-NO_2 at the *N′*-phenyl ring, however, differs quite a lot from those of the other members of **5** (Fig. 3). Upon addition of anions (F^-, AcO^-, $H_2PO_4^-$), a new band at

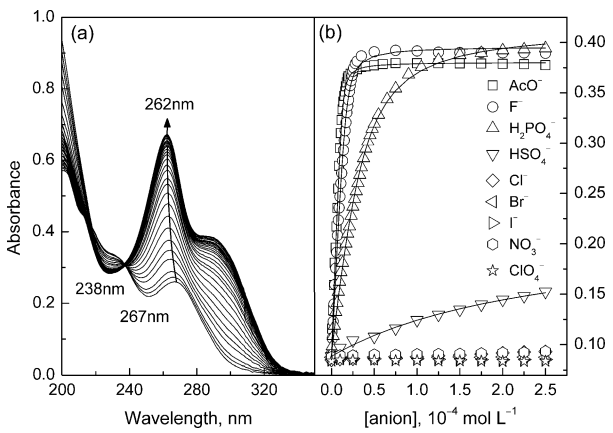


Fig. 2 (a) Absorption spectra of **4a** in MeCN in the presence of increasing concentrations of AcO^- and (b) plots of absorbance of **4a** at 290 nm *versus* anion concentration. Lines through data points in (b) are nonlinear fitted curves, for fitting details see text. [**4a**] = 1.74×10^{-5} mol L^{-1}.

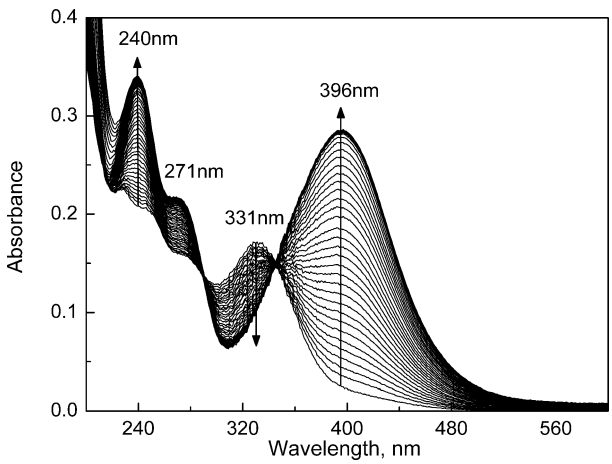


Fig. 3 Absorption spectra of **5f** in MeCN in the presence of increasing concentrations of AcO^- over 0 to 2.5×10^{-4} mol L^{-1}. [**5f**] = 1.57×10^{-5} mol L^{-1}.

396 nm is developed at the expense of the 331 nm band, accounting for the observed solution colour change from colourless to yellow. Meanwhile, the absorbance at 240 nm increases together with the appearance of two isosbestic points at 290 nm and 345 nm, respectively. We will show later that this is because of the deprotonation of thioureido -NH proton of **5f** in the presence of anions.

To probe if a conformation change occurs at the N–N bond upon anion binding,[5d] we synthesized a chiral *N*-amidothiourea (**6**, Scheme 2) bearing an *L*-proline moiety, an important component in current organocatalysts.[9] With increasing anion concentration, the absorption spectrum of **6** in MeCN varies in a manner similar to that of **4** (Fig. 4a) and its binding constants with anions AcO^-, F^-, and $H_2PO_4^-$ are at 10^5–10^6 mol^{-1} L orders of magnitude. In the CD spectrum of **6** (Fig. 4b), two positive Cotton effects centered at 216 nm and 277 nm, respectively, and a negative Cotton effect at 236 nm were observed. The CD signals at 216 nm and 236 nm are due to the proline amide group,[10] while that at 277 nm is due to the *N′*-phenylthiourea with two thioureido -NHs in *trans*-conformation.[11] Upon AcO^- addition, the CD signals of the proline amide moiety decreased and finally disappeared, while that at 277 nm due to the thiourea moiety was reversed in sign and blue-shifted to 264 nm, a wavelength that is the same as that observed in the absorption spectrum of the **6**–AcO^- binding complex (Fig. 4a). A *cis*-conformation of the two thioureido -NHs of **6** was therefore probed in its anion binding complex[11,12] and a conformation change in the proline amide moiety was indicated, which was previously assigned to occur around the N–N single bond that leads to a planar hydrogen-bonding network.[5a,d] It is important to point out that a new CD signal is developed at 264 nm, the absorption maximum of the anion binding complex (Fig. 4). This means that the anion binding complex of **6** remains chiral, which might be of relevance to the design of *N*-amidothiourea based organocatalysts since the chirality of the anion binding complex originates from the chiral center in the proline moiety.

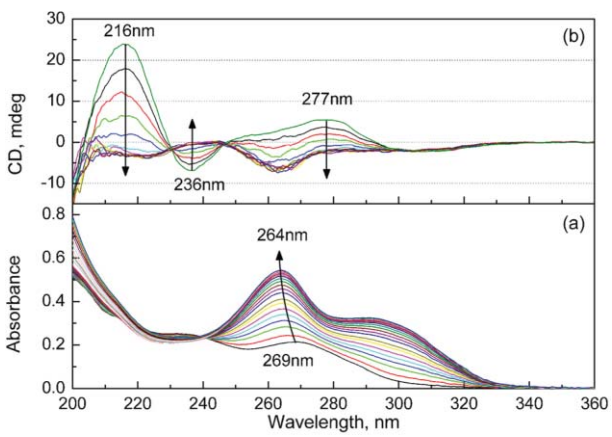


Fig. 4 Absorption (a) and CD (b) spectra of **6** in MeCN in the presence of increasing concentrations of AcO^- over 0 to 2.5×10^{-4} mol L^{-1}. [**6**] = 1.92×10^{-5} (a) and 1.46×10^{-4} (b) mol L^{-1}.

The interaction of *N*-acetamido-*N′*-phenylthioureas with anions was further investigated by ^1H NMR titrations in CD_3CN. Fig. 5 shows as an example the NMR traces of **4a** titrated by F^- in the ranges of the -NH and aromatic protons. It is observed that the signals of the -NH protons are broadened and shifted

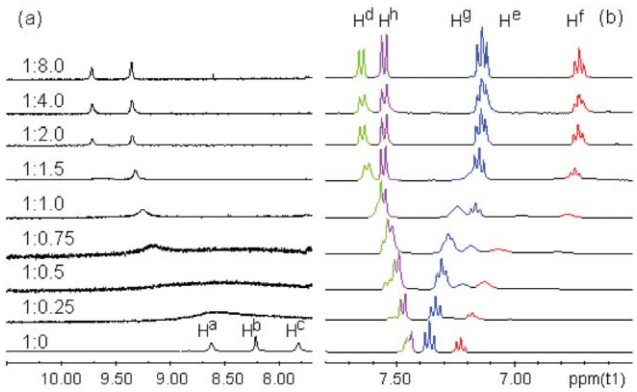


Fig. 5 Traces of the ^1H NMR titration of **4a** by F^- in CD_3CN at portions of (a) -NH and (b) aromatic CH protons of the *N′*-phenyl ring. [**4a**] is 1.5×10^{-2} mol L^{-1} and concentration ratios of **4a** to F^- are indicated in the figure.

downfield from 8.62 ppm, 8.22 ppm and 7.83 ppm to 9.72 ppm and 9.36 ppm. This reflects a hydrogen-bonding interaction of **4a** with F^-. The aromatic protons H^d and H^h that are close to the anion binding site show pronounced downfield shifts in their NMR signals, whereas protons H^g, H^e and H^f that are a bit far away from the binding site, undergo significant upfield shifts in their NMR signals. This shifting pattern has previously been assigned by Fabbrizzi *et al.*[13] to the hydrogen-bonding interaction of anions with the receptor. Similar shifting profiles were observed with **5e** titrated by F^- (Fig. 6) and AcO^- (spectra not shown). With **5f** bearing a highly electron-withdrawing substituent *p*-NO_2 at the *N′*-phenyl ring, the NMR titration profile differs a lot (Fig. 7). Upon titration by F^- and AcO^-, part of the signals of the -NH protons shifted downfield while the others shifted slightly upfield and finally disappeared. Meanwhile, the signals of all the aromatic protons now underwent upfield shifts. This is indicative of the

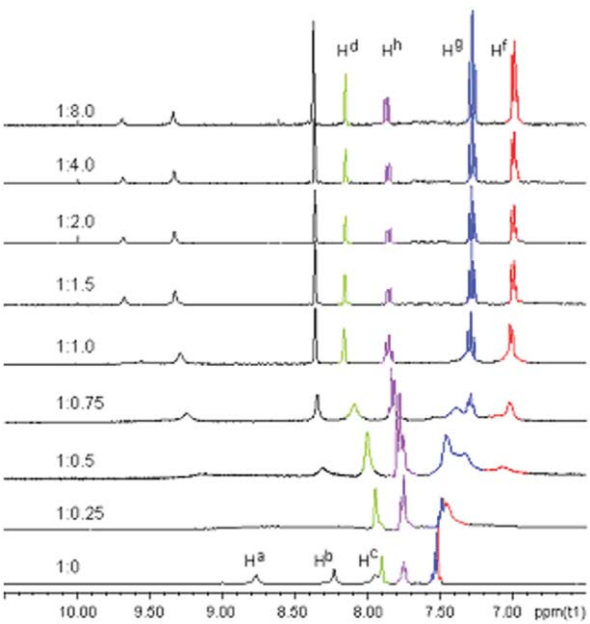


Fig. 6 Partial NMR spectra of **5e** in CD_3CN in the presence of increasing equivalents of F^-. [**5e**] = 1.3×10^{-2} mol L^{-1} and equivalents of F^- are indicated in the figure.

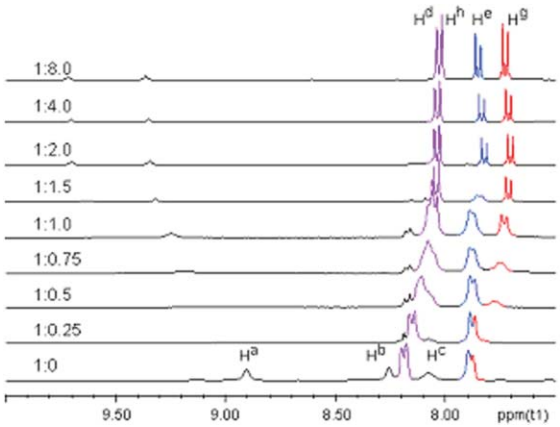


Fig. 7 NMR titration traces of **5f** in CD_3CN by F^-. [**5f**] = 1.6×10^{-2} mol L^{-1} and F^- equivalents are shown in the figure.

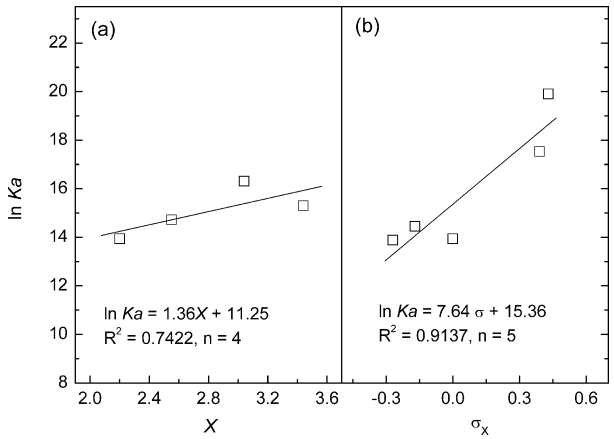


Fig. 9 Semilogarithm plots of the AcO^- binding constants of **4** and **5** in MeCN against electronegativity of the central atom in Y in **4a–d** (a) and Hammett constant of substituent X in **5a–e** (b).

deprotonation of the thioureido -NHs in **5f**. This is likely due to the highly electron-withdrawing substituent *p*-NO_2 at the *N*′-phenyl ring which substantially increases the acidity of the thioureido -NHs in **5f**. This conclusion agrees well with that of Gale *el al.*[14] on the deprotonation of highly acidic -NH protons. It was therefore concluded that with **4a–d** and **5a–e**, in particular with **5e** bearing a substantially electron-withdrawing substituent X = *m*-CF_3, it is hydrogen-bonding, and not deprotonation, that occurs with anions. The discussion below on anion binding will therefore be limited to **4a–d** and **5a–e**.

Job plots show that in MeCN **4** and **5** form anion binding complexes in 1:1 stoichiometry (Fig. 8). Anion binding constants of **4** and **5** in MeCN were obtained from absorption spectral titration data by nonlinear fitting[15] and are presented in Table 1. The binding constants of F^- and AcO^- are higher than those of $H_2PO_4^-$. In particular, anion binding constants of **4** and **5** are higher than those of their *N*-benzamido- counterparts **1** and **2**, despite a lower acidity of the NH protons in **4** and **5**. It is seen in Fig. 9 that the logarithm of the AcO^- binding constants of **4** correlates with the electronegativity of the central atom in Y by a slope of 1.36 and those of **5** correlates with the Hammett constant of substituent X by a slope of 7.64. It is hence made clear that, with *N*-(acetamido)-*N*′-phenylthioureas, it is also more effective to enhance their anion binding by varying the substituent on the *N*′-phenyl ring. The aforementioned linear slope of 7.64 for **5** was found to be lower than the corresponding slope of **1** (10.57).[5d] This is probably because of the more planar conformation of the *N*-amidothiourea moiety (less twisting of the N–N bond) in **4** and **5** that requires less conformational change upon anion binding in order to reach the final planar hydrogen-bonding network. A lower positive feedback of the substituent effect on the anion binding would hence be expected.[5d] The extended investigation reported here therefore confirms that *N*-amidothioureas with both aromatic and aliphatic *N*-amide structures are efficient anion receptors under a hydrogen-bonding motif and provide a wider diversity for *N*-amidothioua-based organocatalysts. Indeed, our preliminary experiments confirmed that **6** can catalyse the reduction of nitrostyrene by Hantzsch ester in CH_2Cl_2 and MeCN,[16] with isolated yields of 80% and 60%, respectively, which are comparable to the yield of 88% in CH_2Cl_2 and higher than the yield of 39% in MeCN obtained by using the traditional diphenylthiourea organocatalyst *N*,*N*′-bis(3,5-ditrifluoromethylphenyl)thiourea that bears highly acidic thioureido -NHs.[16]

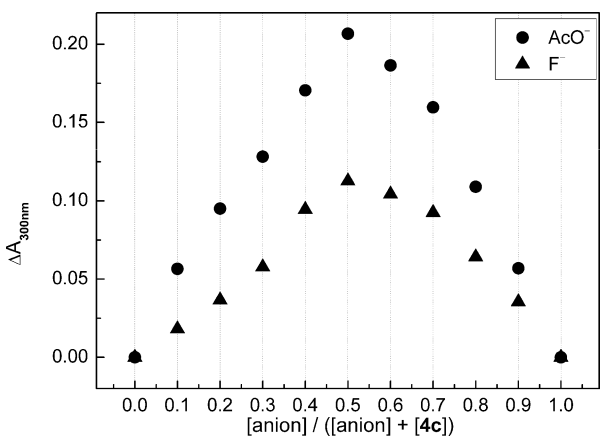


Fig. 8 Job plots for binding of AcO^- and F^- to **4c** in MeCN by monitoring the difference of absorbance at 300 nm of anion–**4c** mixture from that of **4c**. Total concentration of AcO^- and **4c** is 4.74×10^{-5} mol L^{-1} and that of F^- and **4c** is 2.58×10^{-5} mol L^{-1}.

The herein reported *N*-acetamido-*N*′-phenylthioureas are structurally extremely simple yet show a surprisingly high sensing efficiency for anions in MeCN containing water up to 10% by volume (Table 2 and Fig. 10). In H_2O–MeCN solutions the anion binding constants were found to be lower than those in pure MeCN, yet the binding is still strong enough, in particular in the case of **5e** which has a binding constant for AcO^- of 10^5 mol^{-1} L order of magnitude in 10% H_2O–MeCN. Note that the AcO^- binding constant of *N*,*N*′-diphenylthiourea decreases dramatically from 3.27×10^4 mol^{-1} L in pure MeCN to 9.12×10^1 mol^{-1} L in 1% H_2O–MeCN. The *N*-acetamido-*N*′-phenylthioureas reported here also showed a higher tolerance against the highly competitive water molecules than the corresponding *N*-benzamidothiourea counterparts.[5d,f] This observation may ease their applications in, for example, organocatalysis because dehydration of solvents will not have to be carried out.

Table 2 AcO^- binding constants in mol^{-1} L of **4a–d** and **5a–e** and $\lambda_R^{max}/\lambda_{R^+A^-}^{max}$ in nm in H_2O–MeCN[a]

$[H_2O]$, v/v	0	1%	3%	5%	8%	10%
4a	$(1.13 \pm 0.07) \times 10^6$ 267/262	$(1.09 \pm 0.14) \times 10^5$ 266/262	$(6.87 \pm 0.79) \times 10^4$ 266/263	$(2.50 \pm 1.21) \times 10^4$ 265/262	[b]	[b]
4b	$(2.47 \pm 0.00) \times 10^6$ 267/263	$(1.16 \pm 0.11) \times 10^5$ 266/262	$(7.24 \pm 0.39) \times 10^4$ 266/262	[b]	[b]	[b]
4c	$(1.21 \pm 0.32) \times 10^7$ 266/265	$(5.68 \pm 0.19) \times 10^5$ 265/264	$(1.91 \pm 0.16) \times 10^5$ 266/263	$(5.46 \pm 1.21) \times 10^5$ 265/263	[b]	[b]
4d	$(4.42 \pm 0.50) \times 10^6$ 267/265	$(5.88 \pm 0.83) \times 10^5$ 267/264	$(1.80 \pm 0.05) \times 10^5$ 266/263	$(1.37 \pm 0.04) \times 10^5$ 266/263	$(3.53 \pm 0.76) \times 10^5$ 266/262	[b]
5a	$(1.07 \pm 0.07) \times 10^6$ 264/262	$(8.64 \pm 0.85) \times 10^4$ 264/263	$(3.43 \pm 2.35) \times 10^3$ 265/263	[b]	[b]	[b]
5b	$(1.88 \pm 0.13) \times 10^6$ 266/263	$(1.53 \pm 0.15) \times 10^5$ 265/263	$(3.05 \pm 5.9) \times 10^3$ 264/263	[b]	[b]	[b]
5d	–[c] 271/265	$(5.46 \pm 0.87) \times 10^6$ 271/265	$(9.41 \pm 0.50) \times 10^5$ 272/265	$(1.06 \pm 0.05) \times 10^5$ 270/265	$(1.06 \pm 0.20) \times 10^5$ 268/266	[b]
5e	–[c] 272/265	$(1.73 \pm 0.18) \times 10^6$ 271/265	$(3.33 \pm 0.21) \times 10^5$ 268/263	$(5.24 \pm 0.43) \times 10^5$ 267/262	$(4.44 \pm 0.60) \times 10^5$ 268/262	$(3.60 \pm 0.58) \times 10^5$ 268/262

[a] Data for **5c** are not shown since **5c** = **4a**. [b] Spectral change was too minor to allow for an accurate evaluation. [c] The binding constant is too high to be fitted accurately.

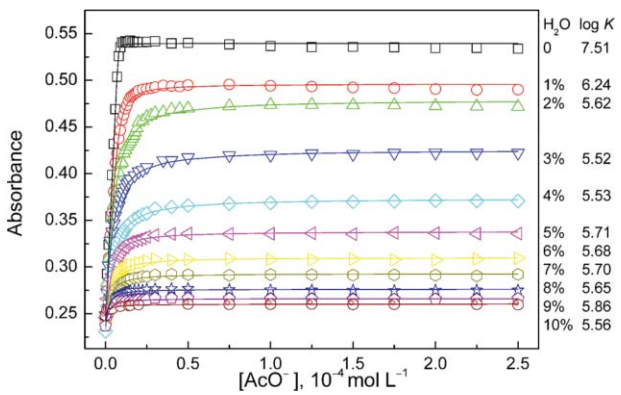


Fig. 10 Plots of absorbance at 262 nm of **5e** *versus* AcO^- concentration in H_2O–MeCN (v/v). [**5e**] = 2.5×10^{-5} mol L^{-1}. Lines through the data points are fitted curves for 1:1 complex following a reported procedure.[15] log*K* is the logarithm of anion binding constant.

Experimental

General procedures and materials

UV–vis spectra were recorded on a Varian CARY-300 spectrophotometer using a 1 cm quartz cell. ^{1}H NMR (400 MHz or 500 MHz) and ^{13}C NMR (100 MHz or 125 MHz) spectra were obtained on a Bruker AV400 or Varian Unity 500$^+$ NMR spectrometer in DMSO-d_6 or CD_3CN using TMS as an internal standard or the residual solvent peak as a standard. IR spectra were recorded on Nicolet AVATAR FT-IR360 infrared spectrophotometer using KBr pellet sample. HRMS were obtained with Micromass-LCT high resolution mass spectrometer by injection of methanol solution of the sample. CD spectra were acquired on Jasco J-810 spectropolarimeter using a 0.5 cm quartz cell. Absorption spectral titrations for anion binding were carried out by adding an aliquot of anion solution into bulk receptor solution at a given concentration. Organocatalysis by **6** of the reduction of nitrostyrene by Hantzsch ester was performed following the same procedures described in reference 16 in which *N*,*N*′-bis(3,5-ditrifluoromethylphenyl)thiourea was the catalyst.

Solvents used for the syntheses of receptors were commercially available and of AR grade. Solvents for spectral investigations were purified by re-distillations until no fluorescent impurity could be detected. Tetrabutylammonium salts of anions were prepared by neutralization of the corresponding acids by $(n\text{-}Bu)_4N^+ OH^-$. All reagents for syntheses were used as received from Aldrich or Fluka.

Synthesis and characterizations

(4b). A mixture of dodecanoic acid (0.3 g, 1.50 mmol) and $SOCl_2$ (5.0 mL) was refluxed for 6 hours and excess $SOCl_2$ were evaporated under reduced pressure to afford dodecanoyl chloride. Dodecanoyl chloride in CH_2Cl_2 (3.0 mL) was added to a solution of triethylamine (0.28 mL, 2.00 mmol) and *N*-amino-*N*′-phenylthiourea (0.25 g, 1.50 mmol) in CH_2Cl_2 (5.0 mL). The solution was stirred at room temperature for 3 hours and the solvent was removed. The product was purified by recrystallization from absolute ethanol to afford **4b** as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6, TMS), δ (ppm): 9.79 (s, 1H, NH), 9.52 (s, 1H, NH), 9.49 (s, 1H, NH), 7.43 (d, J = 6.5 Hz, 2H, Ar-H), 7.33 (t, J = 7.5 Hz, 2H, Ar-H), 7.16(t, J = 7.0 Hz, 1H, Ar-H), 2.16 (t, J = 7.5 Hz, 2H, $COCH_2$), 1.53 (m, 2H, CH_2), 1.20–1.30 (m, 16H, C_8H_{16}), 0.86 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6), δ (ppm): 181.0, 172.0, 139.1, 128.0, 125.6, 124.8, 33.3, 31.2, 29.0, 28.9, 28.7, 28.6, 24.5, 22.0, 13.8. IR (KBr, cm^{-1}): 3389, 3276, 3136, 3029, 2919, 2850, 2360, 1697, 1684, 1535, 1508, 1171, 696. HRMS exact mass calcd for $[C_{19}H_{31}N_3OS + H]^+$ 350.2266, found 350.2261.

(4c). Triethylamine (0.30 mL, 2.10 mmol) and phenyl isothiocyanate (0.13 mL, 1.05 mmol) were added to a solution of *N*,*N*-dimethylglycine hydrazide dihydrochloride (0.20 g, 1.05 mmol) in ethanol (10.0 mL). The mixture was stirred at room temperature for 3 hours and concentrated to remove the solvent. The product was purified by recrystallization from absolute ethanol to afford **4c** as a white crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6, TMS), δ (ppm): 9.80 (s, 1H, NH), 9.50 (s, 2H, NH), 7.45 (d, J = 6.0 Hz, 2H, Ar-H), 7.32 (t, J = 7.5 Hz, 2H, Ar-H), 7.16 (t, J = 6.5 Hz, 1H, Ar-H), 3.05 (s, 2H, $COCH_2$), 2.27 (s, 6H, $N(CH_3)_2$).

^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm): 180.3, 169.1, 139.3, 128.1, 125.6, 124.8, 61.1, 45.4. IR (KBr, cm^{-1}): 3303, 3272, 3023, 3009, 2680, 2614, 2552, 1604, 1587, 1528, 1395, 1273, 1140, 1069, 955, 716, 692. HRMS exact mass calcd for $[C_{11}H_{16}N_4OS + H]^+$ 253.1123, found 253.1134.

(4d). Methyl 2-chloroacetate (0.18 mL, 1.67 mmol) was added to a solution of sodium methanolate (1.67 mmol) in methanol (5.0 mL). The mixture was stirred at room temperature for 3 hours and then excess hydrazine monohydrate (80%, 0.31 mL, 5.01 mmol) was added, and the mixture was further heated at 80 °C under stirring for 8 hours. After removing the solvent, it was washed with iced ethanol and dried, 2-methoxyacetohydrazide was produced. 2-methoxyacetohydrazide was reacted with phenyl isothiocyanate (0.20 mL, 1.67 mmol) in ethanol (10.0 mL) for 3 hours at room temperature, which after removing solvent led to product that after purification by recrystallization from absolute ethanol produced **4d** as a white crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6, TMS), δ (ppm): 9.92 (s, 1H, NH), 9.54 (s, 2H, NH), 7.42 (d, $J = 5.5$ Hz, 2H, Ar-H), 7.33 (t, $J = 8.0$ Hz, 2H, Ar-H), 7.16 (t, $J = 7.0$ Hz, 1H, Ar-H), 3.95 (s, 2H, $COCH_2$), 3.34 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm): 180.9, 168.8, 139.0, 128.0, 125.7, 125.0, 70.6, 58.7. IR (KBr, cm^{-1}): 3320, 3268, 3223, 3153, 3125, 2939, 1671, 1626, 1567, 1497, 1367, 1327, 1115, 999, 730. HRMS exact mass calcd for $[C_{10}H_{13}N_3O_2S + H]^+$ 240.0807, found 240.0811.

(5a–f). Substituted phenylisothiocyanate (2.0 mmol) was added to a solution of hydrazine monohydrate (80%, 0.38 mL, 6.0 mmol) in ethanol (10.0 mL), which was stirred at room temperature for 2 hours. The formed precipitate was filtered, washed with iced ethanol (3 × 5.0 mL) and iced water (3 × 10.0 mL), respectively, and dried, leading to *N*-amino-*N*′-(substituted-phenyl)thiourea as white solid. *N*-Amino-*N*′-(substituted-phenyl)thiourea (1.5 mmol) was added to a solution of acetic anhydride (1.5 mmol) in acetic acid (3.0 mL) followed by stirring at room temperature for 1 hour. The precipitate was isolated and the solid product was recrystallized from absolute ethanol, giving **5a–f**. **5a**: ^{1}H NMR (400 MHz, DMSO-d_6, TMS), δ (ppm): 9.82 (s, 1H, NH), 9.48 (s, 1H, NH), 9.40 (s, 1H, NH), 7.25 (d, $J = 8.4$ Hz, 2H, Ar-H), 6.89 (d, $J = 8.8$ Hz, 2H, Ar-H), 3.74 (s, 3H, OCH_3), 1.88 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm): 181.3, 169.1, 156.7, 132.0, 127.4, 113.2, 55.2, 21.0. IR (KBr, cm^{-1}): 3362, 3253, 3191, 2996, 1686, 1649, 1531, 1509, 1246, 1217. HRMS exact mass calcd for $[C_{10}H_{13}N_3O_2S + H]^+$ 240.0807, found 240.0811. **5b**: ^{1}H NMR (400 MHz, DMSO-d_6, TMS), δ (ppm): 9.83 (s, 1H, NH), 9.53 (s, 1H, NH), 9.44 (s, 1H, NH), 7.28 (d, $J = 7.6$ Hz, 2H, Ar-H), 7.13 (d, $J = 8.0$ Hz, 2H, Ar-H), 2.28 (s, 3H, CH_3), 1.88 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm): 181.0, 169.1, 136.6, 134.2, 128.5, 125.7, 21.0, 20.5. IR (KBr, cm^{-1}): 3254, 3096, 3061, 2927, 2761, 2727, 1697, 1686, 1579, 1517, 1496, 1407, 1327, 1244. HRMS exact mass calcd for $[C_{10}H_{13}N_3OS + H]^+$ 224.0858, found 224.0868. **5c**: ^{1}H NMR (400 MHz, DMSO-d_6, TMS), δ (ppm): 9.86 (s, 1H, NH), 9.60 (s, 1H, NH), 9.50 (s, 1H, NH), 7.42 (d, $J = 7.6$ Hz, 2H, Ar-H), 7.33 (t, $J = 7.2$ Hz, 2H, Ar-H), 7.16 (t, $J = 7.2$ Hz, 1H, Ar-H), 1.89 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm): 181.0, 169.2, 139.2, 128.0, 125.8, 125.1, 21.0. IR (KBr, cm^{-1}): 3261, 3140, 3029, 2871, 1694, 1686, 1590, 1531, 1516, 1498, 1451, 1366, 1248, 1217. HRMS exact mass calcd for $[C_9H_{11}N_3OS + H]^+$ 210.0701, found 210.0703. **5d**: ^{1}H NMR (400 MHz, DMSO-d_6, TMS), δ (ppm): 9.89 (s, 1H, NH), 9.68 (s, 2H, NH), 7.72 (s, 1H, Ar-H), 7.49 (d, $J = 7.6$ Hz, 1H, Ar-H), 7.35 (d, $J = 8.0$ Hz, 1H, Ar-H), 7.29 (t, $J = 8.0$ Hz, 1H, Ar-H), 1.89 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, DMSO-d_6,), δ (ppm): 180.8, 169.3, 140.8, 129.9, 128.0, 127.6, 124.6, 120.4, 21.0. IR (KBr, cm^{-1}): 3266, 3241, 3124, 3023, 2871, 1696, 1685, 1589, 1575, 1533, 1516, 1470, 1243, 1221, 1121, 670. HRMS exact mass calcd for $[C_9H_{10}BrN_3OS + H]^+$ 287.9806, found 287.9819. **5e**: ^{1}H NMR (400 MHz, DMSO-d_6, TMS), δ (ppm): 9.92 (s, 1H, NH), 9.76 (s, 2H, NH), 7.82 (d, $J = 7.6$ Hz, 2H, Ar-H), 7.57 (t, $J = 8.0$ Hz, 1H, Ar-H), 7.50 (d, $J = 7.6$ Hz, 1H, Ar-H), 1.91 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm): 180.9, 169.3, 140.0, 132.6, 130.7, 129.1, 125.4, 121.8, 121.4, 21.0. IR (KBr, cm^{-1}): 3273, 3218, 3142, 3031, 2992, 1704, 1692, 1683, 1538, 1516, 1456, 1333, 1309, 1244, 1166, 1121, 1137. HRMS exact mass calcd for $[C_{10}H_{10}F_3N_3OS + H]^+$ 278.0575, found 278.0582. **5f**: ^{1}H NMR (400 MHz, DMSO-d_6, TMS), δ (ppm): 9.96 (s, 3H, NH), 8.21 (d, $J = 8.8$ Hz, 2H, Ar-H), 8.00 (d, $J = 8.8$ Hz, 2H, Ar-H), 1.92 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, DMSO-d_6, 23 °C), δ (ppm): 180.5, 169.4, 145.6, 143.3, 124.7, 123.6, 21.0. IR (KBr, cm^{-1}): 3293, 3241, 3187, 3163, 3136, 3015, 1679, 1636, 1591, 1508, 1494, 1338, 1303, 1234, 1114, 1002, 848, 750. HRMS exact mass calcd for $[C_9H_{10}N_4O_3S + H]^+$ 255.0552, found 255.0556.

(6). Triethylamine (0.48 mL, 3.4 mmol) was added to a solution of *L*-proline (0.3 g, 2.6 mmol) in methanol (10.0 mL) and the mixture was stirred at room temperature, to which a diethyl ether (5.0 mL) solution of di-*tert*-butyldicarbonate (0.57 g, 2.6 mmol) was added dropwise, followed by stirring at room temperature for 18 hours. A viscous liquid was obtained after removing the solvent under reduced pressure. Adjusting the solution's pH to 4 by 0.1 mol L^{-1} HCl led to *N*-Boc-*L*-proline. *N*-Boc-*L*-proline and triethylamine (0.36 mL, 2.6 mmol) were dissolved in THF (30 mL), to which ethyl chloroformate (0.30 mL, 2.6 mmol) was added dropwise at 0 °C within 15 min. After stirring for 30 min, *N*-amino-*N*′-phenylthiourea (0.43 g, 2.6 mmol) was added in 15 min. The resulting solution was stirred at 0 °C for 1 hour, at room temperature for 16 hours, and then refluxed for 3 hours. After cooled to room temperature, the solution was washed with ethyl acetate and all solids were filtered off. The residue was purified by chromatography on a silica gel column eluted with petroleum ether and ethyl acetate (1:2, v/v) to give **6**. ^{1}H NMR (400 MHz, DMSO-d_6, TMS), δ (ppm): 10.49 (s, 1H, NH), 9.78 (s, 1H, NH), 9.13 (s, 1H, NH), 7.59 (d, $J = 7.0$ Hz, 2H, Ar-H), 7.31 (t, $J = 7.5$ Hz, 2H, Ar-H), 7.14 (t, $J = 7.0$ Hz, 1H, Ar-H), 4.08 (s, 1H, CH), 3.37 (m, 2H, CH_2), 2.14 (m, 2H, CH_2), 1.93 (m, 2H, CH_2), 1.83 (m, 2H, CH_2), 1.35 (s, 2H), 1.30 (s, 7H). ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm): 180.2, 171.5, 154.4, 138.8, 128.4, 128.0, 124.3, 79.7, 58.5, 46.8, 29.4, 28.0, 24.2. HRMS exact mass calcd for $[C_{17}H_{24}N_4O_3S + Na]^+$ 387.1467, found 387.1460.

(7). Phenylisocyanate (0.22 mL, 2.0 mmol) was added to a solution of excessive hydrazine monohydrate (80%, 0.38 mL, 6.0 mmol) in ethanol (10.0 mL) and stirred at room temperature for 2 hours. A precipitate was formed, which after filtration, was washed with iced ethanol (3 × 5.0 mL) and iced water (3 × 10.0 mL), and dried to produce *N*-amino-*N*′-phenylurea as a white solid. *N*-amino-*N*′-phenylurea (0.23 g, 1.5 mmol) was added to a solution of acetic anhydride (1.5 mmol) in acetic acid (3.0 mL) and stirred at room temperature for 1 hour. The formed precipitate was

recrystallized from absolute ethanol, affording **7** as a white crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6, TMS), δ (ppm): 9.63 (s, 1H, NH), 8.69 (s, 1H, NH), 7.96 (s, 1H, NH), 7.44 (d, $J = 7.6$ Hz, 2H, Ar-H), 7.25 (d, $J = 7.2$ Hz, 2H, Ar-H), 6.95 (s, 1H, Ar-H), 1.86 (s, 3H, $COCH_3$). ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm): 169.2, 155.4, 139.6, 128.6, 121.8, 118.4, 20.6. IR (KBr, cm^{-1}): 3433, 3332, 3288, 3264.43, 3202, 3144, 3101, 3035, 1697, 1670, 1623, 1610, 1561, 1500, 1443, 1315, 1237, 749, 688. HRMS exact mass calcd for $[C_9H_{11}N_3O_2 + H]^+$ 194.0930, found 194.0937.

Conclusions

A systematic investigation on the anion binding behavior of *N*-(substituted-acetamido)-*N′*-(substituted-phenyl)thioureas has clearly shown that they are efficient anion receptors *via* hydrogen-bonding interactions with *N′*-phenyl substituents X as electron-withdrawing as *m*-CF_3. Together with the previously reported high anion affinity of the *N*-(substituted-benzamido)thiourea counterparts,[5] it has now been made clear that *N*-amidothioureas can in general be a family of hydrogen-bonding receptors. The *N*-acetamidothioureas reported here showed a slightly lower acidity of their thioureido -NH protons than those in the *N*-benzamidothioureas, yet demonstrated a higher anion binding constant up to 10^7 mol^{-1} L for AcO^- in MeCN. The N–N single bond in *N*-acetamidothioureas was identified to be twisted but less than that in *N*-benzamidothioureas. The substantially red-shifted absorption of the anion binding complexes of *N*-acetamidothioureas suggested the occurrence of charge transfer in the complexes with the *N*-acyl moiety being the electron acceptor. A conformation change was shown to occur around the N–N bond upon anion binding that switches on the charge transfer. This charge transfer in turn reinforces anion binding, thereby leading to an enhanced promotion of the substituent X at the *N′*-phenyl ring on the anion binding constant. The present report provides further clues for designing functional *N*-amidothioureas with much more choice in structural variations. Together with reports recently released from the laboratory of Gunnlaugsson[3a,g,17] on the anion binding of *N*-acetamidoureas, we may now make a conclusion that *N*-amido(thio)ureas are important hydrogen-bonding receptors with application potentials beyond the classic anion sensing and recognition, towards other fields such as organocatalysis.[2] Preliminary experiments confirmed that our *N*-acetamidothioureas could indeed be efficient hydrogen-bonding based organocatalysts.

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