Enhanced Anion Binding of *N*-(Anilino)thioureas. Contribution of the *N*-Anilino −NH Proton Acidity

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We report here that *N*-anilino-*N*′-phenythioureas in general function as a new family of thiourea-based efficient anion receptors superior to classical *N*-alkyl(aryl)thioureas, when the *N*-anilino −NH proton is acidic enough; that is, the *N*-phenyl substituent is not less electron-withdrawing than *m*-Cl. Changes due to anion binding in the absorption spectra of these *N*-anilinothioureas are much more substantial than those of *N*-alkyl(aryl)thioureas, and anion binding constants in MeCN, at 10^6-10^7 mol^{-1} L order of magnitude for AcO^- for example, are much higher despite a similar acidity of the thioureido −NH protons. Crystal structure and ^1H NMR data show that the *N*-aniline chromophore is electronically decoupled from the thiourea anion binding site by the N−N bond, and an intramolecular hydrogen bond exists in MeCN but not in DMSO between the *N*-anilino −NH nitrogen atom and the other thioureido −NH proton. Conformation changes in the *N*-anilinothioureas upon anion binding were assumed to occur and lead to a much higher increment in the electron-donating ability in the *N*-aniline chromophore that the charge transfer (CT) is enhanced or switched on, compared to not switching on a CT in the case of *N*-phenylthioureas. The anion binding constant shows a stronger dependence on the *N*-phenyl substituent than on the *N*′-phenyl substituent, opposite to that observed with *N*-benzamidothioureas, and the CT band position of the anion binding complex depends much more on the *N*-phenyl substituent than that of the anion binding complexes of *N*-benzamidothioureas. The implications of these findings for new anion-receptors design and thiourea-based organocatalysts development are discussed.

1. Introduction

Recent exciting progress in thiourea-based organocatalysis has promoted research efforts on thioureas with improved hydrogen-bonding capacity,[1] in addition to the continuing interest in the thiourea-based anion receptors and crystal engineering.[2] An extended structural diversity would therefore be needed in order to devise better organocatalysts and anion receptors. Although increasing acidity of the thioureido −NH protons in the classical *N,N*′-dialkyl(aryl)thioureas has been a straightforward means for enhancing hydrogen bonding, we alternatively showed that the hydrogen-bonding ability of the thiourea-based receptors can be substantially improved despite a not higher acidity of their thioureido −NHs.[3] In these *N*-benzamidothioureas (**1**, Chart 1), we found that anion binding induced a conformation change in the N−N single bond which is twisted in the absence of the anion, thereby accommodating a hydrogen-bonding network that involved amido $-NH^1\cdots S{=}C$ and thioureido $-NH^2\cdots O{=}C$ bonding in addition to the concerned double hydrogen bonding of two thioureido −NH protons with the anion.[3e] This was also supported by the fact that a rhodamine-based spirolactam derivative[4] of **1** bearing no amido −NH proton showed no response in its absorption and fluorescence toward anion.[3a] Compared to the O atom, S is a weaker hydrogen-bonding acceptor, which means that the acidity of the *N*-amido $-NH^1$ proton may contribute more to this hydrogen-bonding network. In acetonitrile (MeCN), we observed no influence on the anion binding ability of **1** of the substituent X at *N*-benzamido moiety,[3g] the role of the *N*-amido $-NH^1$ acidity can not be ascertained. In a recent investigation of anion binding in aqueous solutions of *N*-(isonicotinamido)thioureas bearing a more acidic amido $-NH^1$, we found that an acidic amido $-NH^1$ was indeed required to ensure an efficient anion binding in aqueous solutions.[3a] This might be a further indication of the importance of the amido $-NH^1$ acidity in determining the anion-binding ability of the *N*-amidothioureas, because under this condition, the amide C═O becomes a weaker hydrogen-bonding acceptor. It was therefore envisaged that moving the amido C═O group in **1** as an electron-withdrawing substituent on to another position of the *N*-phenyl ring would create *N*-anilinothioureas[5] with the *N*-anilino $-NH^1$ proton remaining acidic. This opens a new way of extending structural diversity of the thiourea-based anion receptors and organocatalysts. We thus started to have *N*-(*p*-nitroanilino)-*N*′-(substituted-phenyl)thioureas (**2**, Chart 1) bearing a *p*-nitroaniline charge transfer (CT) chromophore. This would allow an acidic $-NH^1$ proton and an easy monitoring of the anion binding by its strong CT absorption. We then extended to *N*-anilinothioureas (**3**, Chart 1) bearing a variety of substituent X in order to identify which acidity of the $-NH^1$ proton is required to ensure an efficient anion binding of this kind of thiourea-based receptors. We did find that **2** and part of **3** that bears a substituent X electron-withdrawing enough showed dramatically enhanced anion binding toward model anions compared to the classical *N*-alkyl(aryl)thioureas and not weaker binding than **1**. A recent report by Gunnlaugsson et al.[6] indicated that structurally relevant *N*-(naphthylamino)thioureas bearing an electron-withdrawing naphthalimide chromophore showed an efficient anion binding.

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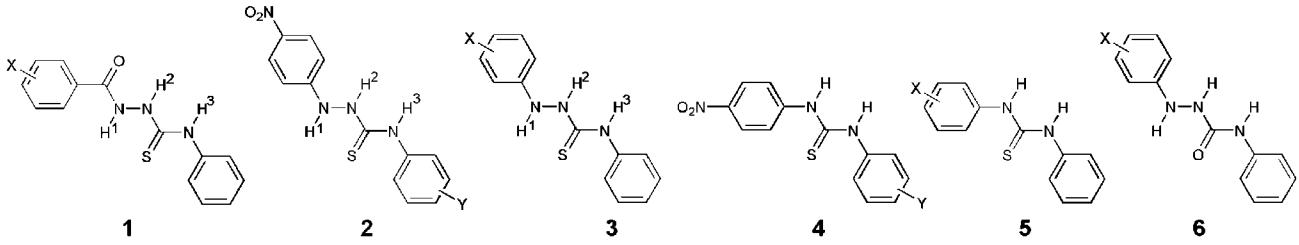
CHART 1: Molecular Structure of (Thio)urea-Based Receptors



1 **2** **3** **4** **5** **6**

2: Y = *p*-OMe (**2a**), *p*-Me (**2b**), H (**2c**), *p*-Cl (**2d**), *p*-NO_2 (**2e**)
3: X = *p*-OMe (**3a**), *p*-Me (**3b**), H (**3c**), *p*-Cl (**3d**), *m*-Cl (**3e**), *p*-CF_3 (**3f**), *p*-CO_2H (**3g**), *p*-CO_2Me (**3h**), *p*-CN (**3i**), *p*-NO_2 (**3j**)
4: Y = *p*-Me (**4a**), H (**4b**), *p*-Cl (**4c**), *p*-NO_2 (**4d**)
5: X = *p*-CN (**5a**), *p*-CO_2Me (**5b**)
6: X = *p*-NO_2 (**6a**), *p*-CO_2Me (**6b**)

N-Aminothioureas may thus be considered in general thiourea-based receptors and organocatalysts given an acidic *N*-amino −NH proton.

2. Experimental Section

Absorption spectra were recorded on a Varian Cary 300 UV−vis or a Thermo absorption spectrophotometer by using a 1 cm quartz cell. ^{1}H NMR and ^{13}C NMR data were acquired on a Varian Unity$^+$ 500 MHz or a Bruker 400 MHz spectrometer by using DMSO-d_6 as a solvent and TMS as an internal standard. ESI-MS data were collected on a Bruker Esquire 3000plus LC-MS/MS spectrometer. HRMS data were collected on a Micromass LCT MS spectrometer. Diffraction data of **2c** and **3i** crystals were collected on a Bruker SMART CCD diffractometer with graphite-monochromated Mo Kα radiation (γ = 0.71073 Å), and detailed structural data were deposited in the Cambridge Crystallographic Data Centre under reference numbers CCDC 672446 and 672447, respectively. Solvents used for spectral investigations were purified by distillation until no fluorescent impurity could be detected. Tetrabutylammonium salts of the tested anions were prepared by neutralization of the corresponding acids with tetrabutylammonium hydroxide.

Compounds **2**−**6** (Chart 1) were easily obtained in one step by following a standard method[7] by reaction of anilines or phenylhydrazines with phenyliso(thio)cyanates in ethanol. All the prepared compounds were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. Assignment in the ^{1}H NMR spectra of aromatic −CH protons of **2** and **3** was established by following a 2D-COSY spectrum of **3h** in DMSO-d_6, whereas that of −NH protons was established by following the substituent effect of their chemical shifts.

Single crystals of **2c** and **3i** were grown in MeCN−DMF (20:1, v/v). Their structures were solved by direct methods and refined anisotropically by full-matrix least-squares based on F^2 by using the SHELXTL crystallographic software package.[8] Non-hydrogen atoms in the structure were refined with anisotropic displacement parameters; hydrogen atoms attached to carbon were calculated and included as riding atoms. Crystal parameters of **2c** are FW288.33 ($C_{13}H_{12}N_4O_2S$); triclinic, *P*-1; a = 6.0591(9) Å, b = 8.06032(13) Å, c = 13.586 (2)Å, V = 677.66(18) Å^3; α = 87.514(3)°, β = 77.538(3)°, γ = 78.499(3)°; R_1 = 0.0873 (wR_2 = 0.2128) with all 2357 data points, of which 2251 data points are such that $I > 2\sigma(I)$. Those for **3i** are FW268.34 ($C_{14}H_{12}N_4S$); triclinic, *P*-1; a = 6.067(3) Å, b = 8.359(4), c = 13.400(6) Å, V = 648.6(5) Å^3; α = 85.965(9)°, β = 78.505(8)°, γ = 77.044(8); R_1 = 0.0538 (wR_2 = 0.1495) with all 3272 data points, of which 2408 data points are such that $I > 2\sigma(I)$.

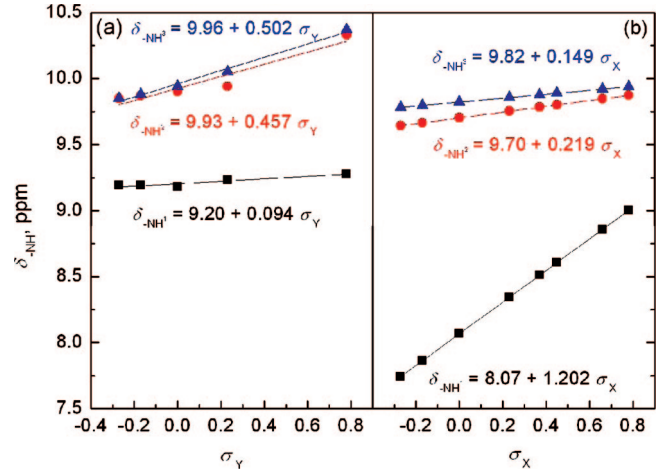


Figure 1. Plots of chemical shifts in DMSO-d_6 of −NH protons of (a) **2** and (b) **3** versus Hammett's constants of substituent Y and X.

3. Results and Discussion

3.1. Acidity of *p*-Nitroanilino −NH^1 in 2. Figure 1a plots the chemical shifts in DMSO-d_6 of −NH protons in **2a**−**e** versus Hammett's constant of substituent Y at the *N*′-phenyl ring. The NMR chemical shifts of the *p*-nitroanilino −NH^1 protons in **2a**−**e** of ca. 9.2 ppm are lower than those of the benzamido −NH^1 protons in **1** (10.5 ppm, X = H).[3g] This may not necessarily mean a lower acidity of the −NH^1 proton in **2**. Actually, a pKa of 20.9 in DMSO was reported for *p*-nitroaniline, compared to 23.3 for benzamide.[9] Therefore, it was expected that from the −NH^1 proton acidity point of view, **2a**−**e** might show an efficient anion binding similarly to **1**.[3e,g]

3.2. Anion Binding of 2. Absorption spectrum of **2c** in MeCN shows indeed a substantial response toward anions such as AcO^-, Figure 2a. In the absence of the anion, the CT absorption of **2c** from the *p*-nitroaniline chromophore peaks at 340 nm and decreases in absorbance upon anion addition along with the appearance of a new and red-shifted band at 505 nm of increasing absorbance. The solution of **2c** turns from colorless to red meanwhile. The spectral variations of **2c** in the presence of AcO^-, characterized by the appearance of distinctive isosbestic points, suggest the formation of a well-defined binding complex of **2c** with AcO^-. Job plot indicates a 1:1 stoichiometry in the binding complex. Similar observations were made in **2c** with $H_2PO_4^-$ and F^-, whereas with other anions such as HSO_4^-, ClO_4^-, NO_3^-, Cl^-, and Br^-, there was practically no response, Figure 3. Nonlinear fitting[10] of the absorbance of **2c** at 505 nm as a function of anion concentration affords binding constants of **2c** with anions, Table 1. With other members in **2** (Chart 1),

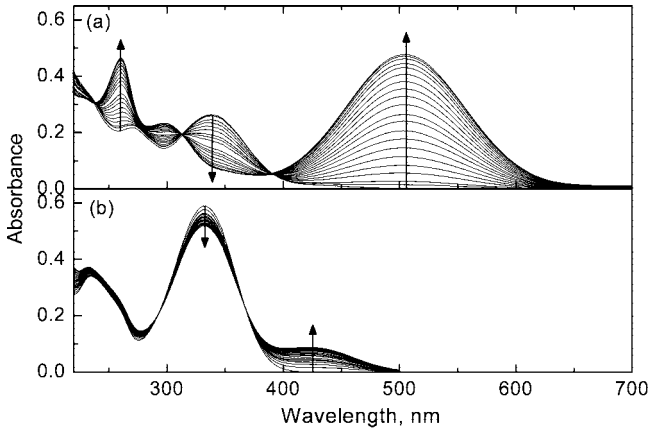


Figure 2. Absorption spectra of (a) *N*-(*p*-nitroanilino)-*N*′-phenylthiourea (**2c**) and (b) *N*-(*p*-nitrophenyl)-*N*′-phenylthiourea (**4b**) in MeCN in the presence of AcO^- over (a) $0-2.0 \times 10^{-5}$ mol L^{-1} and (b) $0-7.5 \times 10^{-5}$ mol L^{-1}, respectively. [**2c**] = [**4b**] = 2.0×10^{-5} mol L^{-1}.

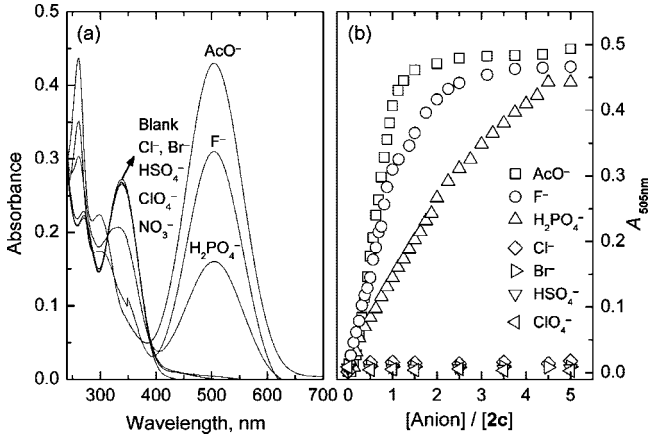


Figure 3. (a) Absorption spectra of **2c** in MeCN in the presence of various anions. The concentrations of AcO^-, F^-, and $H_2PO_4^-$ are 2.0×10^{-5} mol L^{-1}, respectively, and those of HSO_4^-, ClO_4^-, NO_3^-, Cl^-, and Br^- are 2.0×10^{-4} mol L^{-1}, respectively. (b) Absorbance of **2c** at 505 nm as a function of anion concentration. [**2c**] = 2.0×10^{-5} mol L^{-1}.

similar spectral variations were found in the presence of anions, and main spectral and binding data are summarized in Table 1.

The binding constants of **2a**−**e** given in Table 1 in the range of 10^5-10^7 mol^{-1} L are comparable to or higher than those of **1** for the same anion,[3e,g] again confirming the capability of an efficient anion binding of **2a**−**e** despite the removing of the carbonyl group next to $-NH^1$ in **1**. It is also found in Table 1 that the CT absorption of **2** only slightly shifts to the blue when substituent Y varies from electron-donating to electron-withdrawing with $h\nu_{CT}$ (eV) = $3.66 + 0.053\sigma_Y$ ($R = 0.8714$). In contrast, the red-shifted new band of **2** upon AcO^- binding, for instance, shows an enhanced blue shift with $h\nu_{CT}$ (eV) = $2.45 + 0.111\sigma_Y$ (**2a**−**d**, $R = 0.9908$), suggesting that this new band is also of CT nature and the AcO^-/*N*-aminothiourea binding block is now the electron donor. It appears that the electron-donating ability is enhanced upon anion binding but also enhanced to a higher extent with increasing electron-donating ability of the substituent Y. This actually points to an enhanced substituent effect on the electron-donating ability of the *N*-aminothiourea-based electron donor.

Previously, we confirmed that the N−N single bond in *N*-benzamidothioureas is highly twisted[3] as in neutral hydrazines.[12] It is therefore natural to examine the conformation of N−N single bond in **2a**−**e**. From the substituent dependence of the chemical shifts of −NH and aromatic −CH protons in **2a**−**e** (Figure 1a), it is found that after the N−N single bond, the substituent effect is substantially reduced. A similar consequence is also noted in **3a**−**i**, in which substituent X is located in the *N*-phenyl ring (Figure 1b). The chemical shifts of the aromatic protons in **2** and **3** show similar profiles with respect to substituent variation; the −CH protons at the aromatic ring not bearing the substituent remain more or less unchanged, whereas those of the −CH protons at the substituent-borne ring undergo sensitive changes (Figure 4). It is hence concluded that similar to that in *N*- benzamidothioureas, the N−N single bond in *N*-anilinothioureas (**2** and **3**) is twisted too, which is also nicely supported by the crystal structure of **2c** and **3i** which clearly points out a twisted conformation of the N−N bond (Figure 5). This means that the *p*-nitroaniline CT chromophore in **2** or the substituted-aniline chromophore in **3** is electronically decoupled from the thiourea moiety, the anion binding site. In principle, no or minor change in the CT absorption would have been expected for **2** upon anion binding. The fact that substantial variations are observed in the absorption spectra of **2** in the presence of anions (Figures 2a and 3) implies a change in the N−N bond conformation that allows the anion-binding message to be delivered to the CT chromophore. The aforementioned enhanced substituent effect on the CT-band position of the anion−**2** binding complex is likely related to this conformation change upon anion binding

Comparison of the absorption spectral variation upon anion binding to **2** and **4** provides further insight into the consequence of this N−N bond conformation change. Note that in **4**, the *p*-nitroaniline CT chromophore is actually a part of the thiourea anion binding site or that the CT chromophore and the anion binding site are coupled, which allows for a straightforward expectation that a more dramatic change would be observed in the absorption spectra of **4** than in that of **2** upon anion binding. However, experiments showed the opposite. Figure 2 indicates that, despite similar spectral shape of **2c** and **4b** in MeCN, the presence of a much smaller amount of AcO^- induces much more substantial changes in both the absorbance and the red-shift in the absorption spectrum of **2c** than in those of **4b**, with new absorption bands appearing at 505 and 425 nm that are red-shifted by 9610 and 6500 cm^{-1}, respectively. It is also significant to note from Table 1 that not only the anion-binding-induced red-shifts in the absorption spectra of *N*-(*p*-nitroanilino)thioureas (**2**) are much more substantial but the anion binding constants of **2** are higher than those of the corresponding *N*-(*p*-nitrophenyl)thioureas (**4**) bearing the same CT chromophore. An enhanced anion binding of **2** is thereby concluded, which likely originates from the conformation change in the N−N single bond upon anion binding. Refering to the conformation of anion−**1** complex,[3e] the anion/*N*-aminothiourea binding block in anion−**2** binding complexes is assumed to be planar in order to accommodate a hydrogen-bonding network involving both the known anion-thiourea hydrogen bonds[2] and the $-NH^1\cdots S{=}C$ hydrogen bond, the later necessitating the acidity of the $-NH^1$ proton to be high enough. Detailed investigations on the hydrogen-bonding nature of the anion binding will be discussed later.

3.3. Anion Binding of 3. The *N*-anilino $-NH^1$ protons in **2** are indeed acidic enough to possibly support this $-NH^1\cdots S{=}C$ hydrogen bond in the anion−**2** binding complex, and we do see efficient anion binding of **2**. It was then natural to test how acidic this *N*-anilino $-NH^1$ proton should be in order to enable an efficient anion binding. We therefore examined the anion-binding capacity of **3a**−**j** with various acidities of the *N*-anilino

TABLE 1: Spectral data of 2, 4 and their anion binding complexes and anion binding constants in MeCN

Y	*p*-OMe	*p*-Me	H	*p*-Cl	*p*-NO_2
			2		
λ_{CT}, nm	339	340	340	336	335
ε,10^4 mol^{-1} L cm^{-1}	1.30	1.72	1.39	1.51	2.58
			2 + AcO^-		
λ_{CT}, nm	512	508	505	500	498
ε, 10^4 mol^{-1} L cm^{-1}	2.52	2.80	3.31	3.73	2.57
$\Delta h\nu_{CT}$,[a] cm^{-1}	9967	9726	9610	9762	9770
K_b, 10^6 mol^{-1} L	1.70 ± 0.34	1.33 ± 0.44	2.00 ± 0.47	5.81 ± 1.82	17.6 ± 19.2[c]
			2 + F^-		
λ_{CT}, nm	506	508	505	503	502
ε, 10^4 mol^{-1} L cm^{-1}	0.87	2.21	1.40	2.00	2.53
K_b, 10^5 mol^{-1} L	1.54 ± 0.22	4.83 ± 0.30	1.64 ± 0.19	1.92 ± 0.56	12.2 ± 1.7
$\Delta h\nu_{CT}$[a], cm^{-1}	9736	9727	9784	9881	9930
			2 + $H_2PO_4^-$		
λ_{CT}, nm	505	506	505	505	502
ε, 10^3 mol^{-1} L cm^{-1}	2.38	5.75	7.21	1.95	6.09
K_b, 10^4 mol^{-1} L	0.51 ± 0.15	0.85 ± 0.12	1.06 ± 0.09	8.46 ± 0.98	0.71 ± 0.24
$\Delta h\nu_{CT}$[a], cm^{-1}	9697	9649	9784	9960	9930
			4		
λ_{CT}, nm		334	333	332	342
ε, 10^4 mol^{-1} L cm^{-1}		2.06	3.16	1.75	3.52
			4 + AcO^-		
λ_{CT}, nm		368	425	368	389
ε, 10^4 mol^{-1} L cm^{-1}		1.07	0.55	0.94	1.86
K_b, 10^6 mol^{-1} L		0.058 ± 0.003	0.25 ± 0.06	2.3 ± 0.43	6.0 ± 1.9
$\Delta h\nu_{CT}$[a], cm^{-1}		2766[b]	650[b]	2947[b]	3533[b]

[a] $\Delta h\nu_{CT}$ is the difference of the CT absorption energies of the anion-receptor binding complex and receptor itself. [b] With a dipyrrolylquinoxaline anion receptor containing a *p*-nitroaniline CT chromophore, fluoride-binding induced red-shift in the CT absorption was 4040 cm^{-1},[11a] and with another CT chromogenic receptor, fluoride-binding induced CT absorption red-shift was 2698 cm^{-1}.[11b] These red-shifts, those with **4** reported here and elsewhere,[11c,d] and with those classical *N*-phenylthioureas (within 1000 cm^{-1} [3g,7a]) are smaller than the red-shifts for **2**. [c] The binding constant is too high to allow for an accurate fitting.

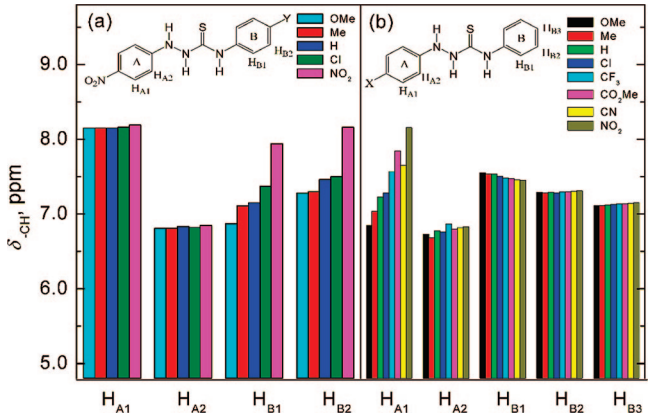


Figure 4. Chemical shifts of aromatic −CH protons in (a) **2** and (b) **3** as a function of para-substituent.

$-NH^1$ due to the X substituent (Chart 1). The latter is reflected in the chemical shift of the $-NH^1$ proton given in Figure 1b. The absorption spectra of **3a**−**i** are similar in shape, whereas **3j** shows the red-shifted CT absorption from the *p*-nitroaniline chromophore (Figure 6). Monitoring their spectral response toward anions in MeCN indicates that only after **3e** does it start to undergo substantial changes in the absorption spectrum with the appearance of a red-shifted new band (Figure 7a), a profile similar to that of **2** (Figure 2a). Compounds **3a**−**d** bearing less electron-withdrawing or electron-donating substituent X show practically no change or a minor change in their absorption spectra with a shoulder at longer wavelengths (Figure 8). This means that for a substantial spectral variation, presumably due to an efficient anion binding, to occur in the absorption spectra of **3**, its *N*-anilino $-NH^1$ indeed needs to be acidic enough. Similar anion selectivity was found with **3e**−**j** in their absorption spectral response, see for example that of **3i** in Figure 9. Because the N−N single bond in **3** was previously shown to be twisted (Figures 1b, 4b and 5), a conformation change in the N−N bond is similarly assumed with **3e**−**j** upon anion binding. Table 2 summarizes spectral data of **3** and **3**−anion complexes and anion binding constants of **3**. It is found in Table 2 that, whereas the absorption-band positions of **3a**−**j** are not very much subject to the substituent-X variation, the red-shifted new absorption band of **3e**−**j** upon anion binding does show a substantial dependence on X, being shifted to the red with increasing electron-withdrawing ability of X. A linear correlation could be established between the absorption energy of the new band and the Hammett constant of substituent X with $h\nu_{CT}$ (eV) = $4.85 - 2.72\sigma_X$ ($R = -0.8357$). This means that the new band is of CT nature too, with X being in the electron acceptor. As no CT absorption is observed in **3a**−**i** in the absence of anion (Figure 6), anion binding to **3e**−**i** is concluded to switch on a CT in the anion-binding complex. The observation that no such a red-shifted band was observed with **3a**−**d** in the presence of anion could hence be likely due to the weak electron-withdrawing ability of X which could not allow the CT to occur in the anion-binding complex. Note that with classic *N*-phenylthiourea counterparts, no CT can be switched on by anion binding irrespective of the substituent X, except *p*-NO_2, which means that the electron-donating ability is enhanced to a much higher extent upon anion binding to *N*-anilinothioureas than to *N*-phenylthioureas.

Again, the anion binding constants of **3e**−**j** are comparable to or higher than those of **1**,[3e,g] as in the case of **2**. The classic

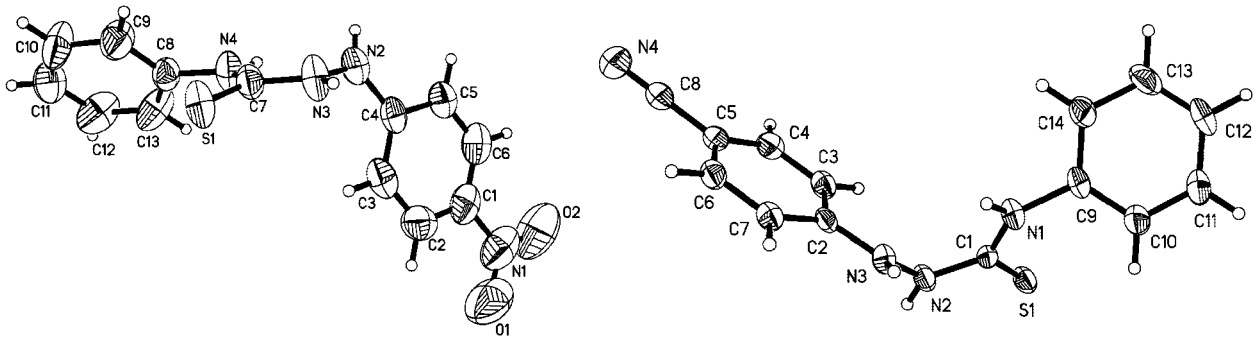


Figure 5. ORTEP diagram of the crystal structure of **2c** (left) and **3i** (right). The dihedral angle ∠H−N2−N3−H in **2c** is 111.4°, and that of ∠H−N2−N3−H in **3i** is 115.8°.

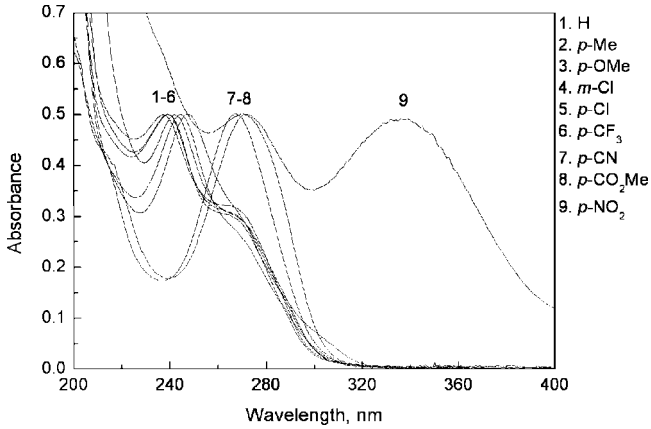


Figure 6. Normalized absorption spectra of **3** in MeCN. Substituent X is indicated in the figure. Concentration of **3** was at 10^{-5} mol L^{-1} orders of magnitude.

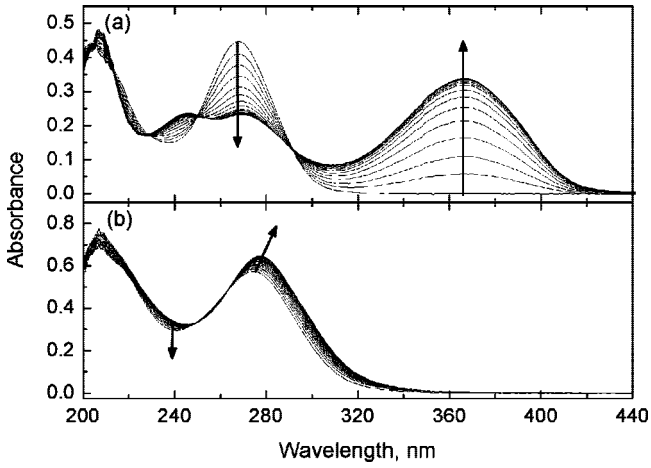


Figure 7. Absorption spectra of (a) *N*-(*p*-cyanoanilino)-*N*′-phenylthiourea (**3i**) and (b) *N*-(*p*-cyanophenyl)-*N*′-phenylthiourea (**5a**) in MeCN in the presence of AcO^- over (a) $0-2.5 \times 10^{-5}$ mol L^{-1} and (b) $0-2.0 \times 10^{-4}$ mol L^{-1}, respectively. The binding constants of **3i** with AcO^- ($4.46 \pm 0.67 \times 10^5$ mol^{-1} L) and $H_2PO_4^-$ ($1.98 \pm 0.10 \times 10^4$ mol^{-1} L) are much higher than those of **5a** ($1.11 \pm 0.06 \times 10^4$ and $1.68 \pm 0.23 \times 10^3$ mol^{-1} L). With **3h**, the corresponding binding constants are $5.69 \pm 0.50 \times 10^5$ mol^{-1} L (AcO^-) and $2.78 \pm 0.17 \times 10^4$ mol^{-1} L ($H_2PO_4^-$), respectively. The binding constants of **5b** with AcO^- and $H_2PO_4^-$ of $7.20 \pm 0.50 \times 10^4$ and $2.22 \pm 0.39 \times 10^4$ mol^{-1} L, respectively, are lower than those of **3h**. [**3i**] = [**5a**] = 1.0×10^{-5} mol L^{-1}.

counterpart of **3i**, *N*-(*p*-cyanophenyl)thiourea (**5a**), despite a direct connection of the chromophore with the anion binding site, shows fewer changes in its absorption spectrum in response to anions such as AcO^- (Figure 7), compared to those of **3i**,

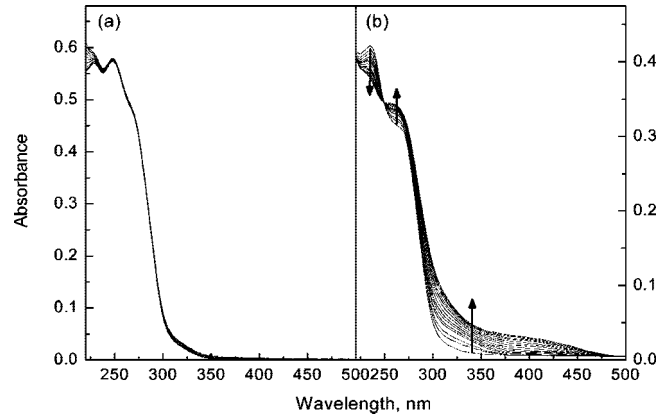


Figure 8. Absorption of (a) **3a** and (b) **3c** in MeCN in the presence of increasing concentration of AcO^-. [**3a**] = [**3c**] = 1.0×10^{-5} mol L^{-1}.

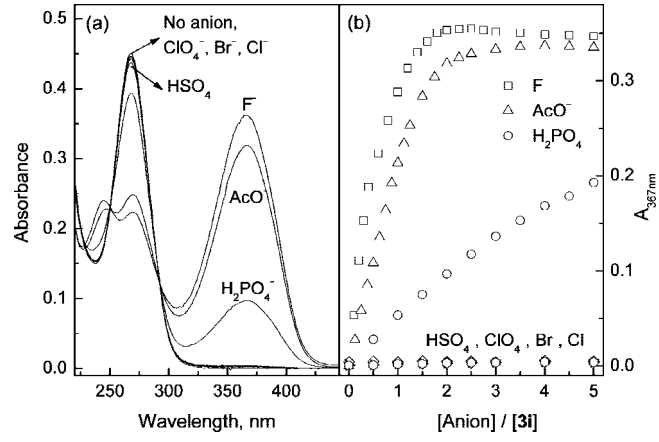


Figure 9. (a) Absorption spectra of **3i** in MeCN in the presence of various individual anions and (b) plot of absorbance of **3i** at 367 nm as a function of anion concentration. [**3i**] = 1.0×10^{-5} mol L^{-1}.

confirming the contribution of the N−N conformation change in anion-binding ability and spectral change in **3e**−**j**. We propose that this results from the CT in the anion/**3e**−**j** binding complexes that afford a positive feedback to the anion binding, as also seen in the case of **1**.[3e] It is in this regard significant to notice that the linear slope against the Hammett constant of X of the CT absorption energy of **3**−AcO^- binding complex (−2.72 eV) is much higher than that of the **1**−AcO^- binding complex (−0.345 eV).[3g] The slope value of 2.72 eV is also much higher than the theoretically expected maximum slope for a complete CT of 0.5 eV.[13] This implies that the substituent X effect on the electron-accepting ability is amplified so that the the electron acceptor in **3**−AcO^- binding complex is strength-

TABLE 2: Absorption Spectral Parameters of 3 and 3−Anion Complexes and Anion Binding Constants of 3 in MeCN

	3		**3**−anion complex				
					K_b, mol^{-1} L		
X	λ_{max}, nm	ε, 10^4 mol^{-1} L cm^{-1}	λ_{max}, nm[a]	ε, 10^4 mol^{-1} L cm^{-1}	F^-	AcO^-	$H_2PO_4^-$
p-OMe	248	2.9	ni [b]		na[c]	na[c]	>na[c]
	269	2.4					
p-Me	239	2.4	ni [b]		$(1.7 \pm 0.3) \times 10^5$	$(3.2 \pm 0.3) \times 10^4$	na[c]
	265	1.5					
H	237	2.5	ni [b]		$(3.0 \pm 0.9) \times 10^5$	$(3.3 \pm 0.5) \times 10^4$	na[c]
	265	1.6					
p-Cl	245	2.9	ni [b]		$(1.1 \pm 0.2) \times 10^5$	$(2.9 \pm 0.1) \times 10^4$	na[c]
	267	1.6					
m-Cl	242	2.1	322	0.75	$(9.6 \pm 3.2) \times 10^5$	$(2.8 \pm 0.8) \times 10^5$	$(1.6 \pm 0.4) \times 10^4$
	267	1.3					
p-CF_3	248	3.0	340	1.7	$(9.9 \pm 1.2) \times 10^5$	$(2.8 \pm 0.8) \times 10^5$	$(7.4 \pm 0.8) \times 10^4$
	268	1.9					
p-CN	268	4.5	367	3.3	$(2.4 \pm 0.6) \times 10^6$	$(2.1 \pm 0.2) \times 10^6$	$(2.5 \pm 0.1) \times 10^4$
p-CO_2H	272	3.2	375	1.3	$(3.8 \pm 2.5) \times 10^6$	$(5.7 \pm 0.5) \times 10^5$	$(2.8 \pm 0.2) \times 10^4$
p-CO_2Me	273	3.3	376	2.4	$(1.9 \pm 0.7) \times 10^6$	$(5.9 \pm 1.3) \times 10^5$	$(1.6 \pm 0.2) \times 10^4$
p-NO_2	270	2.5	505	3.7	$(3.3 \pm 0.7) \times 10^6$	$(5.8 \pm 0.6) \times 10^6$	$(1.1 \pm 0.8) \times 10^4$
340	2.5						

[a] Red-shifted new band position of **3**−AcO^- complex. [b] The new band is too weak or just a shoulder to allow for an accurate position identification (ni, not identified. [c] Not available due to minor spectral variations (na, not available).

ened to a much higher extent. This differs from the effect of substituent Y in **2** that exerts a much lower influence on the CT absorption energy with a slope of +0.111 eV. Similar profiles were also found in the anion binding constants. Correlation of the AcO^- binding constants of **2** and **3** with Hammett's constant affords $\ln K_b(\mathbf{2}) = 14.75 + 2.54\sigma_Y$ ($R = 0.9730$, $n = 5$) and $\ln K_b(\mathbf{3}) = 10.01 + 7.05\sigma_X$ ($R = 0.9966$, $n = 6$), which means that the effect of substituent Y on anion binding to **2** is close to that of the classic *N*-phenyl-*N*′-(substituted-phenyl)thioureas (slope of 2.52)[3e] without an amplification, whereas the effect of X on the anion binding to **3** is amplified. In the case of **1**, the anion binding constant is almost independent of Y at the electron-accepting *N*-benzamido phenyl ring,[3g] whereas the effect of X at the *N*′-phenyl ring is amplified.[3e] The substituent (X/Y) effect on the anion binding constants of *N*-anilino-*N*′-phenylthioureas (**2** and **3**) is hence shown to differ quite much from that in the *N*-benzamidothioureas **1**.

3.4. Intramolecular Hydrogen Bonding in and Intermolecular Hydrogen Bonding with Anions of 2 and 3. The crystal structure shown in Figure 5 indicates that the thioureido $-NH^3$ proton points toward the *N*-anilino $-NH^1$ nitrogen atom, with a $-NH^3\cdots NH^1$ distance of 2.679 and 2.663Å for **2c** and **3i**, respectively. This suggests a possible $-NH^3\cdots NH^1$ intramolecular hydrogen bonding (IHB). Although NMR data acquired in DMSO-d_6 do not point to this IHB, those in CD_3CN support it. Figure 10a shows that, as in DMSO-d_6, the chemical shifts in CD_3CN of the three $-NH$ protons in **3** correlate linearly with the Hammett constant of X. It is worth noting the negative slope with $-NH^3$ proton, indicating that this proton is indeed involved in an IHB.[3c,14] Solvent dependence in CD_3CN/DMSO-d_6 demonstrates that the chemical shift of the $-NH^3$ proton is sluggishly subject to incremental volume fraction of hydrogen-bonding DMSO-d_6, whereas those of $-NH^1$ and $-NH^2$ protons are highly sensitive to this variation (Figure 10b). This is in line of the involvement of $-NH^3$ proton in an IHB. This IHB, as in the case of *N*-acylthioureas,[3c,e] would prevent hydrogen bonding of thiourea with anions because (*Z*,*Z*)-conformation of the two $-NH$ protons is required in its hydrogen bonding in MeCN to an anion such as AcO^-.[2l,3c,6] A conformation change involving thioamido bond (C(S)−NH^2) rotation shall also occur

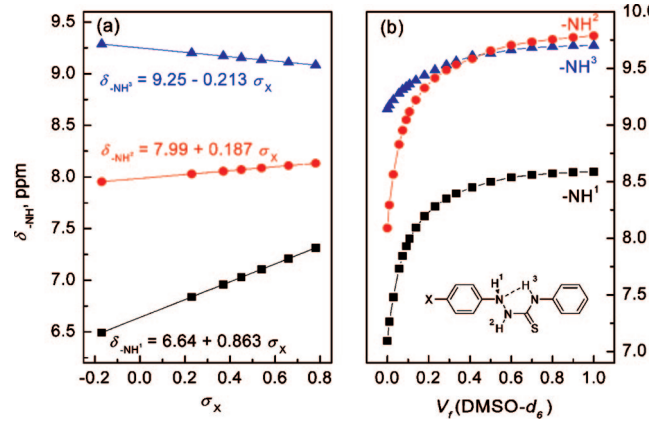


Figure 10. Plots of chemical shifts of −NH protons of (a) **3** in CD_3CN versus Hammett's constant of substituent X and (b) **3h** in CD_3CN/DMSO-d_6 versus volume fraction of DMSO-d_6. With **2a**−**e** in CD_3CN, the corresponding linear correlations of the chemical shifts of −NH protons against Hammett's constant of substituent Y are $\delta_{-NH^1} = 7.40 + 0.0257\sigma_Y$, $\delta_{-NH^2} = 8.16 + 0.288\sigma_Y$, and $\delta_{-NH^3} = 9.06 + 0.434\sigma_Y$. Although an IHB could not be similarly concluded in **2a**−**e** in CD_3CN, likely because of the lower electron density at the *N*-anilino −NH nitrogen atom, twisted conformation in CD_3CN of the N−N single bond in **2**, and **3** as well, can be inferred from the obviously different slopes of the substituent dependence of the chemical shifts of $-NH^1$ and $-NH^2$ protons. The substantially lower linear slope of $-NH^3$ in **2a**−**e** (0.434) compared to that of $-NH^1$ in **3** (0.863), however, suggests an IHB in **2a**−**e** too.

to enable an efficient anion binding. The substantially differed slopes of substituent dependence of the chemical shifts in CD_3CN of the $-NH^1$ and $-NH^2$ protons in **2** and **3** point to a twisted conformation of the N−N single bond in **2** and **3** in CD_3CN too (Figure 10).

A variety of evidence were found to support the hydrogen bonding of the thiourea moiety of **2** and **3** with anions, which is known for neutral thioureas.[2] It is noted in Tables 1 and 2 that the binding constants of **2** and **3** with AcO^- are higher than those with $H_2PO_4^-$, following the order of anion basicity. This is characteristic of the hydrogen-bonding interaction of neutral thioureas.[15] We also found that the binding constants of the corresponding urea derivatives, for example, **6a**

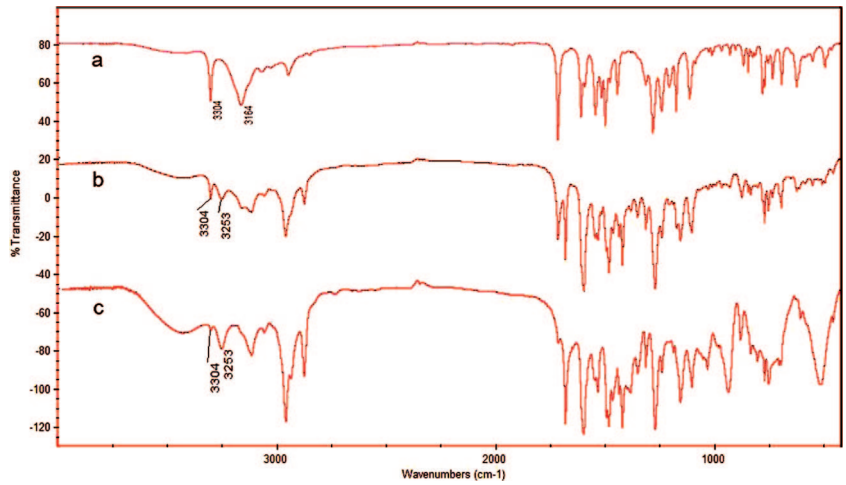


Figure 11. IR spectra of **3h** in the presence of 0 (a), 1 (b), and 2 (c) equivalents of AcO^- in KBr pellet.

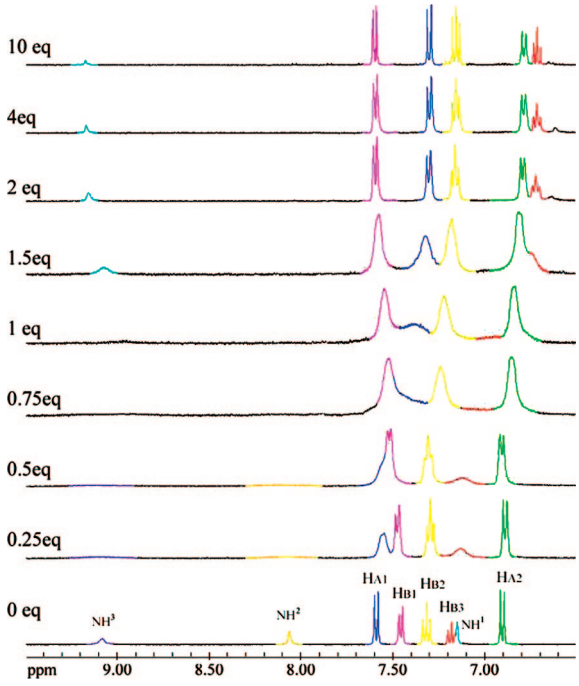


Figure 12. Portion of ^{1}H NMR spectra of **3i** in CD_3CN in the presence of increasing equivalent of F^-. [**3i**] = 20 mmol L^{-1}. For numbering of −NH and aromatic −CH protons, see Figures 1 and 4.

(Chart 1), with AcO^- and $H_2PO_4^-$ of 1.32×10^4 and 3.80×10^3 $mol^{-1}L$, respectively, were lower than those of its thiourea counterpart **2c** (Table 1); a similar comparison was made with **6b** versus **3h**, which suggests the thiourea anion binding site.[16] This is further supported by the observation that *p*-nitroaniline and (*p*-nitrophenyl)hydrazine, model molecules of **2c** bearing no thiourea residue, show in MeCN practically no response in their absorption spectra toward the tested anions.

IR data probes the interaction of anion with −NH groups. Figure 11 shows that with increasing AcO^- equivalent, the sharp −NH stretching band of **3h** at 3304 cm^{-1} is weakened with the development of a 3253 cm^{-1} centered broad band, indicative of the hydrogen bonding of −NH in **3h** with AcO^-.[17] Direct evidence for hydrogen-bonding interaction was obtained from ^{1}H NMR titrations. Figure 12 shows the traces of NMR titrations by F^- of **3i** in CD_3CN. Downfield shifts are identified in the −NH signals. Aromatic −CH signals undergo shifts of differing directions, those at the *N*′-phenyl ring next to the thiourea binding site to downfield and those a bit farther from the thiourea moiety or at the *N*-phenyl ring to the upfield, a profile indicative of the hydrogen-bonding interaction.[6,18] Similar variation profiles were found with AcO^- and $H_2PO_4^-$ too (data not shown). A hydrogen-bonding interaction with anions is hence concluded to occur.[6] The 1:1 hydrogen-bonding adduct was actually identified in the ESI-MS spectrum of **3i** (MW = 268) and AcO^- in MeCN that shows an m/Z = 330.2 peak corresponding to $(M + AcO^- + 2H^+)$.

Deprotonation of highly acidic thioureido −NH in the presence of alkaline anions has been previously reported.[2c,d,19] With **2** and **3e**−**j**, we show that hydrogen-bonding interaction occurs with anions, and the substantial spectral change of **2** and **3e**−**j** characterized by the appearance of a red-shifted new absorption band upon anion binding results from the CT absorption, as in the case with *N*-naphthylaminothioureas with a bit more acidic *N*-naphthylamino −NH proton.[6] The acidity of the −NH protons in **2** and **3**, judged on their NMR chemical shifts, is not higher than that in **1**,[3e,g] *N*-benzamido-*N*′-benzoylthioureas[3c] and *N*,*N*′-bis(benzamido)thioureas,[3b] for which hydrogen-bonding interaction with anions was suggested. Indeed, no indication of HF_2^- species (a triplet at 16.1 ppm with a *J* of 121 Hz)[20] was found in the ^{1}H NMR of **2c** in DMSO-d_6 in the presence of excess amount of F^-, ruling out deprotonation of **2c** by the highly basic F^-. Direct evidence disfavoring deprotonation is the comparison of the absorption spectral variations of **3g** and **3h** bearing substituent X = *p*-CO_2H and *p*-CO_2Me of similar electron-withdrawing ability.[21] The acidity of the *p*-CO_2H group in **3g** is higher than that of its thioureido −NH protons. No or less spectral variation would be expected in **3g** than in **3h** if deprotonation is operative upon anion addition. Figure 13 indicates, however, that the spectral variations of **3g** and **3h** are more or less the same in the presence of up to 1.5 equivalents of AcO^- in MeCN. With more AcO^-, deprotonation of the *p*-CO_2H group in **3g** occurs, which leads to a blue-shift of the CT absorption because of the less electron-withdrawing ability of *p*-CO_2^- compared to *p*-CO_2H (Figure 13a, inset).[21]

It is hence made clear that upon anion hydrogen bonding in MeCN to the thiourea moiety in **2a**−**e** and **3e**−**j**, the $NH^3\cdots NH^1$ IHB shall break to reach a (*Z*,*Z*)-conformation of the two thioureido −NH protons and the twisted N−N bond in these *N*-anilinothioureas becomes planar, thus enabling the observed electronic communication of the anion binding message to the chromophore, which is nicely reflected by the influence of substituent Y on the CT absorption of **2**−anion

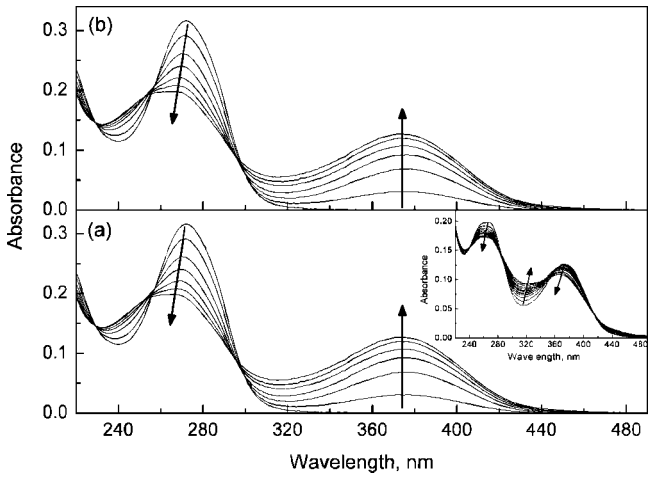


Figure 13. Absorption spectra of **3g** (a) and **3h** (b) in MeCN in the presence of up to 1.5 equivalent of AcO^-. Inset in panel a shows the spectra of **3g** with AcO^- of 1.5−7.5 equivalents. [**3g**] = [**3h**] = 1.0×10^{-5} mol L^{-1}.

binding complex (Table 1). Inspection of the absorption spectra of **2c** (Figures 2 and 3) and **3i** (Figures 7 and 9) in MeCN shows that in the presence of anions such as AcO^- and F^- that strongly bind to **2c** and **3i**, the absorption spectra below 300 nm become more structured, an indication of anion-binding induced rigidity enhancement in the chromophore moiety. In the planar anion/*N*-aminothiourea binding block, the $-NH^1\cdots S{=}C$ hydrogen bond could be well accommodated, together with the anion-thiourea hydrogen bonds, because of the high enough acidity of the *N*-anilino $-NH^1$ proton and the elevated electron density at the S atom due to anion binding. Comparison of the AcO^- binding constants of **3** versus its urea-counterpart **6** and of 1,3-diphenylthiourea versus 1,3-diphenylurea has brought about evidence for the contribution of this $-NH^1\cdots S{=}C$ hydrogen bond. In this regard, we found that, whereas the AcO^- binding constant of 1,3-diphenylthiourea (**5**, X = H) in MeCN is higher by 14% than that of 1,3-diphenylurea, AcO^- binding constants of **3** are 10−100 times those of **6** (X = H, *m*-Cl, *p*-CN, *p*-CO_2Me, and *p*-NO_2).

4. Conclusions

We showed that *N*-anilinothioureas in general are highly efficient anion receptors when the *N*-anilino $-NH$ proton is acidic enough, that is, when the *N*-anilino substituent is not less electron-withdrawing than *m*-Cl. The anion-receptor binding was probed to be hydrogen-bonding in nature. The anion binding constants in MeCN at 10^6-10^7 mol^{-1} L for AcO^-, for example, are much higher than those of the corresponding *N*-alkyl(aryl)thioureas and comparable to or higher than those of *N*-benzamidothioureas. Crystal structure and ^1H NMR data indicated that the *N*-aniline chromophore in *N*-anilinothioureas was electronically decoupled from the thiourea binding site by the twisted N−N single bond and an IHB existed in MeCN, but not in DMSO, involving *N*-anilino $-NH^1$ nitrogen atom and thioureido $-NH$ proton opposite to the *N*-anilino $-NH^1$ group. Conformation changes in the *N*-anilinothioureas, that is, breaking this IHB and planarization of the N−N bond upon anion binding, were assumed to occur. They led to a much more substantial increment in the donating ability of the electron donor in the *N*-aniline chromophore, and the CT is unprecedentedly enhanced when the *N*-anilino substituent is *p*-NO_2 or switched on when it is less electron-withdrawing than *p*-NO_2 but not less than *m*-Cl. Much more dramatic changes in the absorption spectra were found with these *N*-anilinothioureas when binding to anions than those in the corresponding *N*-alkyl(aryl)thioureas. The anion binding constant of the *N*-anilinothiourea in MeCN depends on the substituent at *N*-phenyl more than on that at the *N*′-phenyl ring, opposite to what is found with *N*-benzamidothioureas, whereas the CT absorption band of the anion binding complex is shifted to the red in a much faster step upon *N*-phenyl substituent varying from electron-donating to electron-accepting. The electron donor composed of the aminothiourea and anion is assumed to be planar to accommodate well a hydrogen-bonding network involving thiourea/anion and *N*-anilino $-NH$ proton/thiourea S atom hydrogen bonds. This can be one reason that a high enough acidity of the *N*-anilino $-NH$ proton is required to ensure its hydrogen bonding to the S atom. It is in this regard expected that *N*-amino(thio)ureas at large could be efficient anion receptors if the *N*-amino $-NH$ is made acidic enough. The nice results of Gunnlaugsson et al.[6] on efficient anion binding of *N*-(naphthylamino)thioureas bearing another acidic *N*-aromatic $-NH$ represent immediately examples of this generality. Because the existing IHB in *N*-anilinothioureas in less competitive, polar solvents such as MeCN and the twisted N−N bond undergoes changes upon hydrogen bonding to a guest molecule, *N*-anilinothioureas could be tested as organocatalysts in particular in asymmetric synthesis because the chiral sense in the organocatalyst might be transferred via this IHB and the N−N bond. The observation that the *N*-phenyl substituent effect is much stronger suggests that a chiral sense incorporated in the *N*-phenyl moiety would be transferred to an amplified extent, for example, those of 1,1′-binaphthyl-2,2′-diamine derivatives[22] could be tested. *N*-Anilinothioureas are therefore shown as a new set of thiourea-based efficient neutral anion receptors and, possibly, useful organocatalysts.

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