Development of *N*-Benzamidothioureas as a New Generation of Thiourea-Based Receptors for Anion Recognition and Sensing

Li Nie,[†,‡] Zhao Li,[†] Jie Han,[†] Xuan Zhang,[†] Rui Yang,[†,§] Wen-Xia Liu,[†] Fang-Ying Wu,[†,⊥] Jian-Wei Xie,[#] Yu-Fen Zhao,[†] and Yun-Bao Jiang*,[†]

Department of Chemistry, the MOE Key Laboratory of Analytical Sciences, and the Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen 361005, China, Department of Chemistry, Wanxi College, Lu'an 237012, China, Department of Chemistry, Southwest Normal University, Chongqing 400715, China, Department of Chemistry, Nanchang University, Nanchang 330047, China, and Institute of Pharmacology and Toxicology, Beijing 100850, China

ybjiang@xmu.edu.cn

Received June 1, 2004

A series of neutral *N*-(substituted-benzamido)-*N'*-phenylthioureas (substituent = *p*-OC$_2$H$_5$, *p*-CH$_3$, *m*-CH$_3$, H, *p*-Cl, *p*-Br, *m*-Cl, and *p*-NO$_2$) were designed as anion receptors, in which the thiourea binding site was attached to the benzamido moiety via an N—N bond. The absorption spectra of these *N*-benzamidothioureas in acetonitrile peaked at ca. 270 nm were found to show unprecedented red shifts by 7 373 to 14 325 cm^{-1} in the presence of anions such as AcO$^-$, F$^-$, and H$_2$PO$_4^-$. Under the same conditions, the classic neutral thiourea receptors, *N*-(substituted-phenyl)-*N'*-phenylthioureas, showed absorption spectral shifts in most cases of less than 800 cm^{-1} with one exception of 6501 cm^{-1}. Control experiments, effects of protic solvent, and ^{1}H NMR titration confirmed the formation of hydrogen-bonding complexes between the new *N*-benzamidothiourea receptors and anions. The binding constants with AcO$^-$, for example, are at 10^5–10^7 mol^{-1} L order of magnitude, which are 13 to 590 times those of the corresponding classic *N*-phenylthioureas in the same solvent. It was found that, whereas the absorption of the *N*-benzamidothiourea receptors showed essentially no dependence on the substituent, the substantially red-shifted new absorption band of the *N*-benzamidothiourea—anion binding complex was sensitively subject to the substituent. A linear relationship was found between the absorption energies of the *N*-benzamidothiourea—acetate binding complexes and the Hammett constants of the substituents with a negative slope of −0.34 eV. This led to the assignment that the substantially red-shifted absorption band was the ground-state intramolecular charge-transfer absorption with the substituent locating in the electron acceptor moiety. It was concluded that anion binding to the thiourea moiety of the *N*-benzamidothiourea receptors switched on their ground-state charge transfer. An anion-binding induced structural change was suggested to occur around the N—N bond in *N*-benzamidothioureas, which resulted in a substantially increased electron donating ability of the electron donor in the receptor molecules. As a consequence, the ground-state charge transfer takes place in the *N*-benzamidothiourea—anion binding complexes, leading to unprecedented red shifts in the absorption spectra and substantially enhanced anion binding affinities than those of the corresponding *N*-phenylthiourea receptors. *N*-Benzamido-*N'*-phenylthioureas represent a new generation of neutral thiourea-based anion receptors that show substantially improved anion binding performance important for anion sensing and recognition.

Anion recognition and sensing has recently grown into a subject of great interest in supramolecular and organic chemistry.[1] As the anion—receptor interactions, mainly of hydrogen bonding and/or electrostatic nature, are different from the metal—ligand coordination for the cation—receptor interactions,[2] the design of anion receptors differs substantially from that of cation receptors. In constructing anion receptors thiourea has been extensively employed as the anion-binding site in a hydrogen-

bonding receptor (Scheme 1).[1] It is in general attempted to modify its *N,N'*-substituents to enhance the acidity of the thioureido —NH protons for promoting the hydrogen
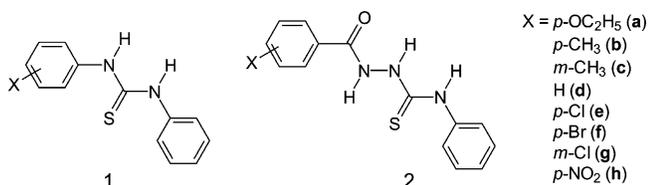
* To whom correspondence should be addressed.
† Xiamen University.
‡ Wanxi College.
§ Southwest Normal University.
⊥ Nanchang University.
Institute of Pharmacology and Toxicology.

(1) (a) Matínez-Máñez, R.; Sancenón, F. *Chem. Rev.* **2003**, *103*, 4419. (b) Suksai, C.; Tuntulani, T. *Chem. Soc. Rev.* **2003**, *32*, 192. (c) For comprehensive recent reviews, see: *Coord. Chem. Rev.* **2003**, *240*, issues 1 and 2. (d) Wiskur, S. L.; Ait-Haddou, H.; Lavigne, J. J.; Anslyn, E. V. *Acc. Chem. Res.* **2001**, *34*, 963. (e) Sessler, J. L.; Davis, J. M. *Acc. Chem. Res.* **2001**, *34*, 989. (f) Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486. (g) Gale, P. A. *Coord. Chem. Rev.* **2001**, *213*, 79. (h) Snowden, T. S.; Anslyn, E. V. *Curr. Opin. Chem. Biol.* **1999**, *3*, 740. (i) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609.
(2) (a) de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515. (b) Desvergue, J. P.; Czarnik, A. W., Ed. *Chemosensors for Ion and Molecular Recognition*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1997.

SCHEME 1.   Hydrogen Bonding of
N,N-Alkyl(aryl)thiourea with Acetate Anion

R, R' : alkyl, aryl
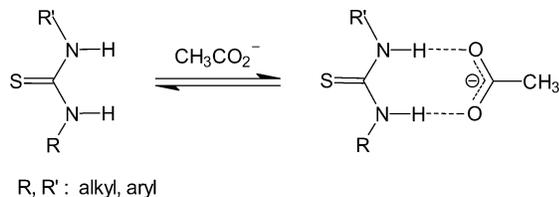
CHART 1.   Structure of
N-(Substituted-phenyl)-*N*-phenylthioureas (1) and
N-(Substituted-benzamido)-*N*-phenylthioureas (2)

$X = p\text{-}OC_2H_5$ (a)
$p\text{-}CH_3$ (b)
$m\text{-}CH_3$ (c)
H (d)
$p\text{-}Cl$ (e)
$p\text{-}Br$ (f)
$m\text{-}Cl$ (g)
$p\text{-}NO_2$ (h)

bonding.[1,3] *N*-Alkyl and/or *N*-aryl substitutions have hitherto been the major options, see for example, *N*-(substituted-phenyl)-*N*-phenylthioureas (**1**) in Chart 1.

On the basis of the observations that the charge transfer (CT) absorption of *N*-(*p*-nitrophenyl)thioureas was shifted to the red upon binding to acetate anion[3a–c] and the photoinduced electron transfer (PET) in thiourea-based fluorescent receptors was enhanced when anions were bound to the thiourea moiety locating in the electron donor,[3h] it was concluded that anion binding to the thiourea moiety increased its electron-donating ability. Considering the dipolar character of the amide bond,[4] we decided to attach the thiourea moiety to benzamide to construct *N*-benzamidothioureas as a new generation of thiourea-based anion receptors. In these new receptors one thioureido nitrogen atom is linked to the rest of the molecules via an N atom, instead of a C atom in the classic *N*-alkyl or *N*-aryl thiourea-based receptors such as **1** (Chart 1). It was expected that upon anion binding to the thiourea moiety in these *N*-benzamidothiourea receptors the electron density at the thioureido nitrogen atom would increase. This, assisted by the substitution preferably of an electron-withdrawing substituent at the benzamido phenyl ring, would enhance the dipolar

character of the amide bond to such an extent that the charge transfer occurs in the binding complex. As a consequence, the acidity of the thioureido −NH protons would be enhanced, which in turn reinforces the anion binding. Herein reported are *N*-benzamidothiourea-based anion receptors (**2a**−**h**, Chart 1) with substituents ranging from highly electron withdrawing to moderately electron donating. It will be shown that, in **2a**−**h**, the hydrazino N−N single bond stops the electronic communication between the thiourea binding site and the benzamido chromophores and the acidity of the thioureido −NH protons is actually lower than that in **1**. Yet, they show unprecedented red shifts in their absorption spectra in acetonitrile of as much as 14 325 cm^{-1} upon anion binding and substantially enhanced anion binding affinities, compared to those of the corresponding *N*-phenylthiourea counterparts (**1**, Chart 1).

Results and Discussion

It appears straightforward to directly attach the thiourea moiety to benzoyl to form *N*-benzoylthioureas, as that would be expected to deliver more efficiently the anion-binding message to the benzoyl chromophore. The intramolecular six-membered-ring hydrogen bond existing in the *N*-benzoylthiourea involving carbonyl oxygen and the other thioureido −NH proton,[7] however, might prevent its double hydrogen bonding with oxoanions. Indeed, we found that the absorption spectrum of *N*-benzoyl-*N*-phenylthiourea in acetonitrile showed practically no change upon introducing AcO$^-$ and H$_2$PO$_4$$^-$. To maintain the dipolar amide bond and the thiourea anion-binding site, a series of *N*-(substituted-benzamido)-*N*-phenylthioureas (**2a**−**h**, Chart 1) were therefore designed. These *N*-benzamidothioureas might work as anion receptors as suggested by our preliminary results with a derivative of them (X = *p*-N(CH$_3$)$_2$).[8a] The thiourea moiety in **2a**−**h** is indeed available for anion binding, as is shown by the anion-induced dramatic changes in the absorption spectra of **2a**−**h** in acetonitrile that originally peaked at ca. 235 nm and 270 nm, respectively. An isosbestic point at ca. 240 nm and a new and substantially red-shifted band at 330−435 nm appeared in the presence of AcO$^-$; see Figure 1a for the absorption spectral titration traces of **2d**. It was found in Figure 1a that as little as 10^{-6} mol L^{-1} of AcO$^-$ could already lead to appreciable change in the absorption spectrum of **2d**. With the corresponding *N,N*-diphenylthiourea (**1d**) in which the anion-binding thiourea moiety is directly linked to the phenyl chromophore, however, only a slight change in its absorption spectrum was observed (Figure 2). This shows a higher response sensitivity of **2d** toward this anion. With F$^-$ and H$_2$PO$_4$$^-$, similar observations were made (Figure 1b). Detailed data for the other members of the *N*-benzamidothiourea receptors can be found in Table 1. It deserves to be pointed out that in

(3) (a) Nishizawa, S.; Kato, R.; Hayashita, T.; Teramae, N. *Anal. Sci.* **1998**, *14*, 595. (b) Hayashita, T.; Onodera, T.; Kato, R.; Nishizawa, S.; Teramae, N. *Chem. Commun.* **2000**, 755. (c) Kato, R.; Nishizawa, S.; Hayashita, T.; Teramae, N. *Tetrahedron Lett.* **2001**, *42*, 5053. (d) Nishizawa, S.; Buhlmann, P.; Iwao, M.; Umezawa, Y. *Tetrahedron Lett.* **1995**, *36*, 6483. (e) Xiao, K. P.; Buhlmann, P.; Umezawa, Y. *Anal. Chem.* **1999**, *71*, 1183. (f) Blanco, J. L. J.; Benito, J. M.; Mellet, C. O.; Fernández, J. M. G. *Org. Lett.* **1999**, *1*, 1217. (g) Tozawa, T.; Misawa, Y.; Tokita, S.; Kubo, Y. *Tetrahedron Lett.* **2000**, *41*, 5219. (h) Gunnlaugsson, T.; Davis, A. P.; Glynn, M. *Chem. Commun.* **2001**, 2556. (i) Sasaki, S.; Citterio, D.; Ozawa, S.; Suzuki, K. *J. Chem. Soc., Perkin Tran. 2* **2001**, 2309. (j) Lee, D. H.; Lee, H. Y.; Lee, K. H.; Hong, J. I. *Chem. Commun.* **2001**, 1188. (k) Hennrich, G.; Sonnenschein, H.; Resch-Genger, U. *Tetrahedron Lett.* **2001**, *42*, 2805. (*l*) Mei, M. H.; Wu, S. K. *Acta Chim. Sin.* **2001**, *59*, 1112. (m) Jiménez, D.; Matínez-Máñez, R.; Sancenón, F.; Soto, J. *Tetrahedron Lett.* **2002**, *43*, 2823. (n) Lee, D. H.; Lee, H. Y.; Hong, J.-I. *Tetrahedron Lett.* **2002**, *43*, 7273. (o) Kondo, S.; Nagamine, M.; Yano, Y. *Tetrahedron Lett.* **2003**, *44*, 8801. (p) Gunnlaugsson, T.; Kruger, P. E.; Lee, T. C.; Parkesh, R.; Pfeffer, F. M.; Hussey, G. M. *Tetrahedron Lett.* **2003**, *44*, 6575. (q) Sansone, F.; Chierici, E.; Casnati, A.; Ungaro, R. *Org. Biomol. Chem.* **2003**, *1*, 1802.
(4) (a) Galoppini, E.; Fox, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 2299. (b) Zhang, X.; Sun, X.-Y.; Wang, C.-J.; Jiang, Y.-B. *J. Phys. Chem. A* **2002**, *106*, 5577. (c) Zhang, X.; Wang, C.-J.; Liu, L.-H.; Jiang, Y.-B. *J. Phys. Chem. B* **2002**, *106*, 12432.

(5) Otterbacher, T.; Whitmore, F. C. *J. Am. Chem. Soc.* **1929**, *51*, 1909.
(6) Karakus, S.; Rollas, S. *IL Farmaco.* **2002**, *57*, 577.
(7) Otazo-Sánchez, E.; Pérez-Martín, L.; Estévez-Hernández, O.; Rojas-Lima, S.; Alonso-Chamarro, J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2211.
(8) (a) Wu, F.-Y.; Li, Z.; Wen, Z.-C.; Zhou, N.; Zhao Y.-F.; Jiang, Y.-B. *Org. Lett.* **2002**, *4*, 3203. (b) Linton, B. R.; Goodman, M. S.; Fan, E.; van Arman, S. A.; Hamilton, A. D. *J. Org. Chem.* **2001**, *66*, 7313.
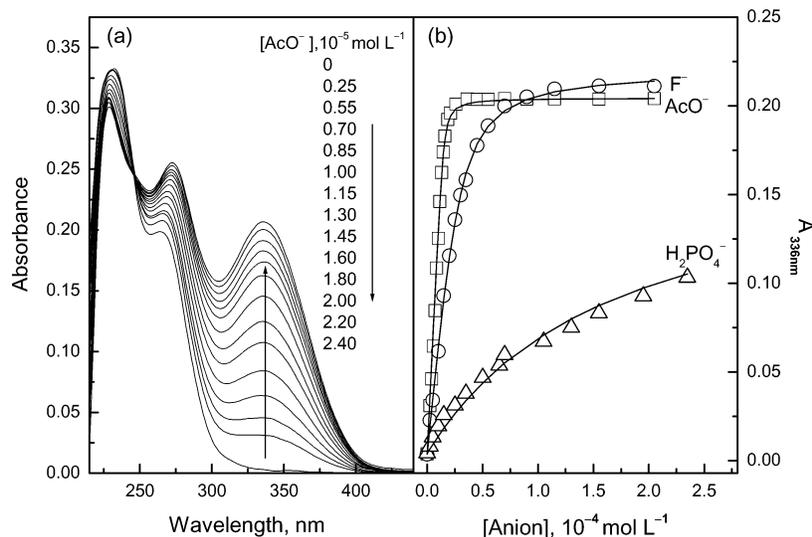
FIGURE 1. (a) Absorption spectra of **2d** in acetonitrile in the presence of acetate anion and (b) plots of the absorbance of the new band at 336 nm against anion concentration. Points in part b are experimental data and the lines through them are fitted curves. [**2d**] $= 1.0 \times 10^{-5}$ mol L^{-1}. Anions existed in their n-Bu$_4$N$^+$ salts.
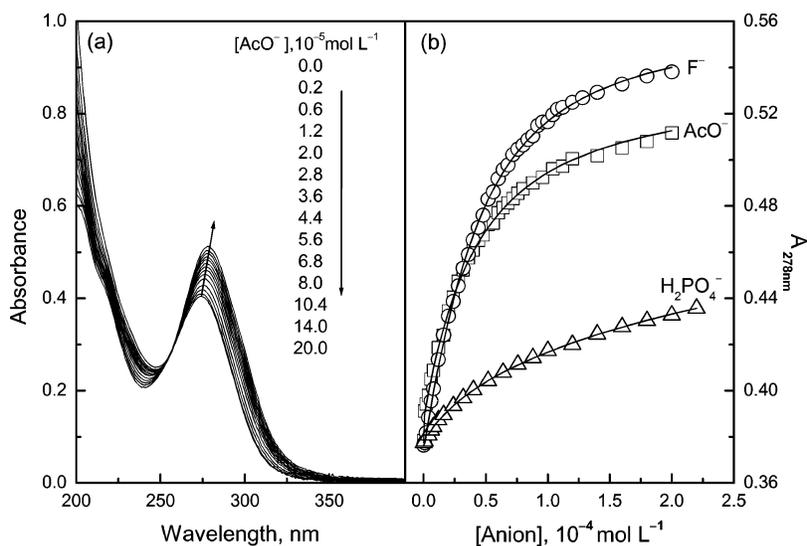
FIGURE 2. (a) Variation trace of the absorption spectrum of **1d** in acetonitrile with increasing amount of AcO$^-$ and (b) plots of the absorbance at 276 nm versus anion concentration. Points in part b are experimental data and the lines through them are fitted curves. [**1d**] $= 1.9 \times 10^{-5}$ mol L^{-1}. Anions existed in their n-Bu$_4$N$^+$ salts.

the present work only several anions such as AcO$^-$, F$^-$, and H$_2$PO$_4^-$ were tested. This was because these anions of typical planar, spherical, and tetrahedral shapes, respectively, could well be taken as model anions to demonstrate the signal mechanism. Meanwhile, these anions have also been extensively investigated on their binding with the classic N,N-diarylthiourea receptors, thereby making comparison of the N-benzamidothiourea receptors with these N,N-diarylthiourea receptors possible.

The appearance of an isosbestic point during the spectral titrations suggests the formation of well-defined binding complexes between **2a**−**h** and the tested anions that should be responsible for the new and red-shifted absorption band. Job plots confirmed the 1:1 binding stoichiometry. Similar spectral changes, however, were not found in control experiments with thiourea-free

analogues of **2d**, benzamide and benzoylhydrazine. This suggests that the spectral changes observed with **2a**−**h** are due to anion binding to the thiourea moiety. A urea counterpart of **2d**, N-benzamido-N-phenylurea, was found to bind AcO$^-$ and H$_2$PO$_4^-$ to a much less extent than that of **2d** as seen in the absorption spectral variations. This observation confirmed that the thiourea moiety in **2d** was the anion binding site, since it has been shown that thiourea has a higher anion binding affinity than the corresponding urea.[8] Evidence for the hydrogen-bonding nature of the thiourea−anion interaction was further obtained from the ^{1}H NMR titration of **2d** by AcO$^-$ in DMSO-d_6. It was noted in Figure 3 that a new and downfield signal at 10.82 ppm grew at the expense of the original signals of the −NH protons appearing at 10.54, 9.82, and 9.72 ppm, respectively. Introduction of protic solvents such as methanol into the acetonitrile solution

TABLE 1. Absorption Spectral Parameters of Receptors 1 and 2 and Receptor−Anion Binding Complexes, and Receptor−Anion Binding Constants in Acetonitrile[a]

		2						1			
				K_a, 10^6 mol^{-1} L							K_a, 10^4 mol^{-1} L
X	λ_R^{max}, nm[b]	$\lambda_{(R^+A^-)}^{max}$,[c] nm	$\Delta h\nu$,[d] cm^{-1}	AcO$^-$	F$^-$	H$_2$PO$_4^-$	λ_R^{max},[b] nm	$\lambda_{(R^+AcO^-)}^{max}$, nm[c]	$\Delta h\nu$,[d] cm^{-1}	AcO$^-$
p-OC$_2$H$_5$	260	330	8159	1.71	0.188	0.0123				
p-CH$_3$	268	334	7373	1.84	0.157	0.0169	274	278	525	1.27
m-CH$_3$	268	335	7463	12.1[e]	11.5[e]	32.4[e]	274	278	525	2.05
H	266	336	7823	0.297	0.0694	0.0053	274	278	525	1.58
p-Cl	268	346	8412	5.58	0.510	0.0399	277	283	765	4.90
p-Br	268	346	8412	1.47	0.158	0.509	279	284	631	11.32
m-Cl	268	348	8578	4.05	0.0562	0.0900				
p-NO$_2$	268	435	14325	2.48	0.685	0.138	333	425	6501	13.50

[a] Anions existed in their n-Bu$_4$N$^+$ salts. [b] Absorption maximum of the receptor. [c] Absorption maximum of the receptor−anion binding complex. [d] Anion binding induced red shift in the absorption maximum. [e] With high-fitting uncertainties because of the extremely large binding constants.
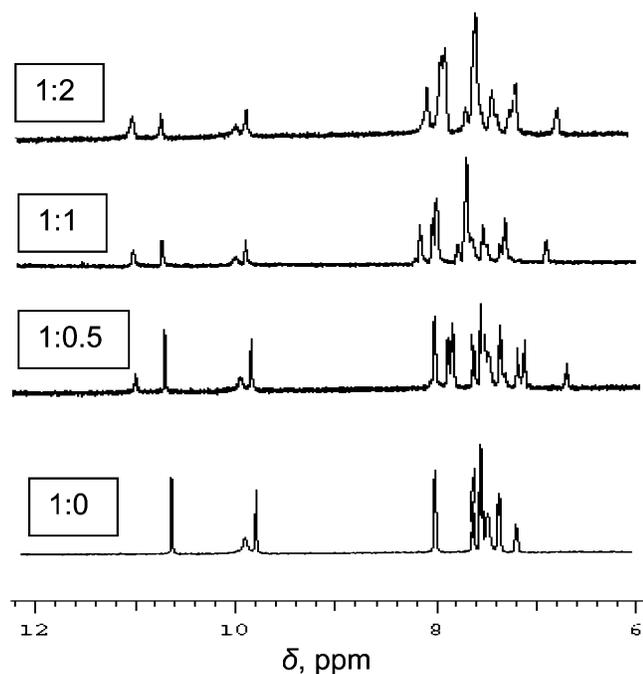
FIGURE 3. Portions of the ^{1}H NMR spectra of **2d** in DMSO-d_6 in the presence of increasing equivalents of AcO$^-$. [**2d**] = 5.0×10^{-3} mol L^{-1}.

of **2d** plus AcO$^-$ led to a gradual recovery of the absorption spectrum of **2d** itself, again supporting the hydrogen-bonding nature of the anion−receptor interaction.

The binding constants of **2a**−**h** with anions in acetonitrile were obtained by nonlinear fitting[9] of the absorbance of the new absorption band against anion concentration (Figure 1b) and were reported in Table 1. It is seen in Table 1 that the binding constants of **2a**−**h** with AcO$^-$, for instance, are over the range of 2.97×10^5 to 1.21×10^7 mol^{-1} L and in most cases are at 10^6 mol^{-1} L orders of magnitude, almost irrespective of the substituent at the benzamido moiety. It is significant to note that they are 13−590 times those of the corresponding N-(substituted-phenyl)-N-phenylthioureas (**1**, Chart 1) that range from 1.27×10^4 to 1.35×10^5 mol^{-1} L (Table 1)

(9) Valeur, B.; Pouget, J.; Bourson, J.; Kaschke, M.; Ersting, N. P. *J. Phys. Chem.* **1992**, *96*, 6545.

and in most cases are at 10^4 mol^{-1} L orders of magnitude. With the latter the highest binding constant of 1.35×10^5 mol^{-1} L was observed with N-(p-nitrophenyl)-N-phenylthiourea (**1h**), which has a strong electron-withdrawing substituent p-NO$_2$ at the N-phenyl ring and therefore has thioureido −NH protons of much higher acidity.[10] It hence follows that the new N-benzamido-thiourea receptors reported here show substantially enhanced anion binding affinity and therefore higher sensitivity for anion sensing than the corresponding N-arylthiourea receptors, despite the lower acidity of their thioureido −NH protons. The latter character would have, in the normal sense, led to lower anion binding affinities of the N-benzamidothiourea receptors because of the hydrogen-bonding nature of the anion−receptor interaction.[1a,c,2] The new receptors also showed good binding selectivity among anions such as AcO$^-$, H$_2$PO$_4^-$, and F$^-$ that in most cases followed the order K_a(AcO$^-$) > K_a(F$^-$) > K_a(H$_2$PO$_4^-$) (see Figure 1b and Table 1). With **2e**, for example, the binding constant for AcO$^-$ is 11 and 140 times that for F$^-$ and H$_2$PO$_4^-$, respectively. Exceptions occurred with receptors **2c** and **2g** bearing meta-substituent m-CH$_3$ and m-Cl, respectively. In the case of receptor **2c** a possible reason could be its extremely high binding constants toward anions at 10^7 mol^{-1} L orders of magnitude. In this case it was already hard to fit precisely the binding constants by using the employed nonlinear fitting procedures. However, it is still not possible to figure out the exact reason for these exceptions with only two sets of data.

Another important feature noted in Figures 1a and 2a and Table 1 was the unprecedented red shifts in the absorption spectra of **2a**−**h** in the presence of anions, from ca. 270 nm to 330−435 nm by 7 373 to 14 325 cm^{-1}. Note that with most of the N-(substituted-phenyl)-N-phenylthioureas (**1b**−**f**, Chart 1), with which the ground-state charge transfer (CT) did not occur in the absence of anion, anion-binding-induced red shifts were within 5 nm around 275 nm by no more than 800 cm^{-1}. In case of N-(p-nitrophenyl)-N-phenylthiourea (**1h**) with which the ground-state CT occurs the red shift in the CT absorption upon AcO$^-$ binding was 6500 cm^{-1} (Figure 2 and Table 1). It should be pointed out that the spectral variations

(10) Chemical shifts of the thioureido −NH protons of N-(p-nitrophenyl)-N-phenylthiourea (**1h**) in DMSO-d_6 were 10.01 and 9.95 ppm, respectively, which were located at much lower field than those of **2a**−**h** given in the Supporting Information.

observed with **2a**−**h** in the presence of anions also obviously differ from that of a derivative of them bearing a highly electron-donating substituent (X = *p*-N(CH₃)₂).[8a] With the latter its absorption spectrum in acetonitrile was single-banded with a maximum wavelength of 312 nm, which was shifted to 328 nm by only 1563 cm⁻¹ upon binding to AcO⁻, suggesting that **2a**−**h** did not behave the same as this derivative.

The highly improved anion binding characters of the new *N*-benzamidothiourea receptors suggested that they might be considered a new generation of the thiourea-based anion receptors. Inspection of the absorption spectral data helped in understanding the novel anion binding properties of these new receptors. It was found that, whereas the absorption maxima of **2a**−**h** in most cases (**2b**−**h**) remained at essentially the same position of ca. 270 nm, the substantially red-shifted new absorption band of the receptor−anion binding complex was sensitively subject to the substituent at the benzamido phenyl ring. The absorption of the receptor−anion binding complex was found to appear at longer wavelength when the substitutent is more electron withdrawing (Table 1). A linear correlation was found between the absorption energy of the binding complex and the Hammett constant of the substituent (σ_X) with a negative slope of −0.337 eV (**2a**−**g**: $h\nu^{max} = 3.67 - 0.337\sigma_X$, $\gamma = -0.9800$). This pointed to the CT character of the new absorption band,[4b,c,11] which means that anion binding to the thiourea moiety in the *N*-benzamidothiourea receptors **2** indeed switches on the ground-state charge transfer. The negative slope indicates that the substituent in receptors **2** exists in the electron acceptor, i.e. the benzoyl moiety. It was therefore made clear that anion binding to receptors **2a**−**h** dramatically enhanced the dipolar character of their amide bonds so that the ground-state CT was switched on. As a consequence, red shifts in their absorption spectra upon anion binding by as much as 14 325 cm⁻¹ and substantially enhanced anion binding affinities were observed. These should be at-tributed to the increase in the electron-donating ability of the electron donor upon anion binding, the *N*-amino-thiourea−anion binding unit, compared to that of the *N*-aminothiourea moiety. Obviously this increase is substantially larger than that observed with *N*-(*p*-nitro-phenyl)-*N*′-phenylthiourea (**1h**) in which anion binding takes place at the same thiourea moiety. The substantial increase in the electron-donating ability of the *N*-amino-thiourea moiety upon anion binding was also reflected by the fact that even with receptor **2a** bearing a moder-ately electron-donating substituent (X = *p*-OC₂H₅, Chart 1) at the benzamido phenyl ring of the electron acceptor the ground-state charge transfer still took place upon anion binding. Also, it might be reasonable to put forward that the anion affinities of the *N*-benzamidothiourea receptors were enhanced so much due to the anion-binding-induced ground-state charge transfer that other factors such as substituent at the benzoyl moiety became less important, explaining thereby the observation that the binding constants were practically independent of the substituent (Table 1).
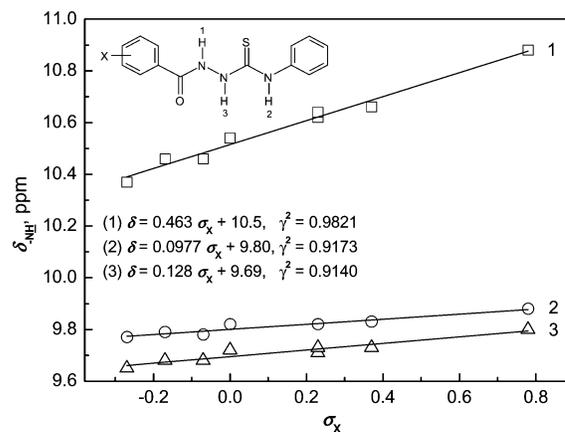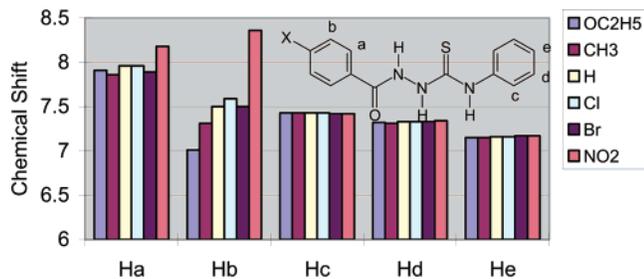

FIGURE 4. Chemical shifts of the −NH protons in **2a**−**h** versus Hammett substituent constant.

It is known that, due to the repulsion of nonpaired electrons at the neighboring nitrogen atoms, the N−N bond in neutral hydrazines is highly twisted[12a] and therefore acts as a conjugation stopper.[12b] In our previous report on a derivative of **2a**−**h** with X = *p*-N(CH₃)₂,[8a] we proposed the existence of two five-membered intramo-lecular ring hydrogen bonds between its amido −NH proton and the S atom of the thiourea moiety and between its thioureido −NH proton and the amido carbonyl O atom, respectively. The nature of the N−N single bond, twisted or not, in that derivative was not discussed.[8a] It should be pointed out that with **2a**−**h** reported here such hydrogen bonds could not be excluded, since the chemical shifts of the −NH protons in **2a**−**h** were similar to those of the X = *p*-N(CH₃)₂ derivative.[8a] With an extended series of derivatives in hand, however, we found that the ¹H NMR data of **2a**−**h** did suggest that the electronic communication of the substituent effect in **2a**−**h** to their thiourea moiety was stopped by the N−N bond. The chemical shifts of the −NH protons in **2a**−**h** were found to vary linearly with the Hammett constant of the substituent with slopes of 0.46 for the benzamido −NH protons whereas only of 0.10 and 0.13 for the thioureido −NH protons, respectively (Figure 4). It was obvious that, whereas the NMR signal of the benzamido −NH proton was, as expected, sensitive to the substitu-ent, those of the thioureido −NH protons showed much weaker dependence on the substituent. Note that the chemical shifts of the −NH protons in the X = *p*-N(CH₃)₂ derivative of **2a**−**h** (10.14, 9.71, and 9.57 ppm, respec-tively)[8a] followed these linear correlations too, which means that the N−N bond conformation in this molecule is similar to that in **2a**−**h**. With the NMR signals of the aromatic protons (Figure 5), it was noted that, while those of the aromatic protons (Ha and Hb) at the benzoyl phenyl ring bearing substituent were sensitive to the substituent, those of the other phenyl ring protons (Hc, Hd, and He) showed essentially no response to the presence of the substituent. It was therefore made clear that the thiourea moiety, the anion binding site, in these *N*-benzamidothiourea receptors was electronically de-coupled from the benzoyl moiety, the signal reporter. This should have led to a consequence that anion binding to

(11) (a) Kosower, E. M. *Acc. Chem. Res.* **1982**, *15*, 259. (b) Reichardt, C. *Solvents and Solvent Effects in Organic Solvents*, 2nd ed.; VCH: Weinheim, Germany, 1990; p 343. (c) Huang, W.; Zhang, X.; Ma, L.-H.; Wang, C.-J.; Jiang, Y.-B. *Chem. Phys. Lett.* **2002**, *352*, 401.

(12) (a) Nelsen S. F.; Pladziewicz, J. R. *Acc. Chem. Res.* **2002**, *35*, 247. (b) Lewis, M.; Glaser, R. *J. Org. Chem.* **2002**, *67*, 1441.

FIGURE 5. Chemical shifts of the aromatic protons as a function of the para substituent (X).

the thiourea moiety of these *N*-benzamidothiourea receptors would result in no or minor change in the absorption of the benzamide chromophore. Actually it was found that anion binding to **2a**−**h** switched on the ground-state charge transfer, suggesting that a structural change around the N−N bond took place that established the electronic communication through the N−N bond and hence allowed for the occurrence of the ground-state charge transfer.[13] The electron donor therefore actually varied from the benzamido −NH group before anion binding to −NH plus the thiourea−anion binding unit after anion binding. This accounts for the enlarged increment in the electron-donor strength compared to that observed with *N*-(*p*-nitrophenyl)-*N'*-phenylthiourea (**1h**) whose electron donor varied from thiourea to the thiourea−anion binding unit.

Conclusions

N-Alkyl and *N*-aryl thioureas have long been employed as binding moiety in anion receptors since the early stage of anion recognition and sensing research. *N*-Aminothioureas, however, receive much less attention.[8a] Reported in this article are a family of simple *N*-aminothiourea based anion receptors, *N*-(substituted-benzamido)-*N'*-phenylthioureas with substituents ranging from electron withdrawing to moderately electron donating. These receptors showed unprecedented red shifts in their absorption spectra by as much as 14 325 cm^{-1} upon anion binding and substantially enhanced anion affinities. This is significant since (i) the thioureido −N*H* acidity in these *N*-benzamidothiourea receptors is not higher than that in the corresponding *N*-phenylthiourea counterparts, which should have led to lower binding affinities of the new receptors because of the hydrogen-bonding nature of the receptor−anion interaction, and (ii) the thiourea anion-binding site in these *N*-benzamidothiourea receptors is electronically decoupled from the chromophore by the N−N single bond that would have been expected to produce no or minor response of the receptors toward anion binding to their thiourea moiety. A structural change around the N−N bond upon anion binding was suggested, which led to an unprecedented increase in the electron-donating ability of the *N*-amidothiourea moiety. As a consequence, the ground-state charge transfer occurs that accounts for the unprecedented red shifts in the absorption spectra and the substantially enhanced anion binding affinities. The *N*-benzamidothiourea structural framework could therefore be useful in constructing

novel anion sensors capable of naked-eye detection of current interest[1] that require not only large absorbance change but also large color change as well during binding to anion, and probably will also be of use in designing electrochemical sensors of improved performance.

Although the designing principle reported here was shown in an organic solvent, work is underway to extend this principle to anion receptors operative in aqueous solutions of practical use. Our preliminary understanding on the anion binding mechanism has actually helped to find possible structural modification to reach new *N*-benzamidothiourea receptors that show anion binding capacity at least in water-containing organic solvents. For example, we found that *N*-(*p*-ethoxybenzamido)-*N'*-(*p*-nitrophenyl)thiourea in acetonitrile containing 10% water by volume showed a sensitive and selective binding to AcO$^-$ with a binding constant of 1.74×10^5 mol^{-1} L that is even higher than that of *N*-phenyl-*N'*-(*p*-nitrophenyl)-thiourea (**1h**) for binding AcO$^-$ in pure acetonitrile (Table 1). Investigations are continuing to figure out the methods of structural modifications to achieve better *N*-benzamidothiourea-based receptors for aqueous solution use and to design related receptors with electrochemical signaling capacity.

Experimental Section

Chemicals used for synthesis were market available of AR grade. Solvents such as acetonitrile and methanol used for spectral investigations were further purified by distillation and checked to have no impurity. Tetrabutylammonium salts of anions were prepared from neutralization reactions of tetrabutylammonium hydroxide and the corresponding acids and were purified by recrystallization from ethyl acetate. *N*-(Substituted-phenyl)-*N'*-pheylthioureas (**1**) were either market available or known molecules prepared in one step according to a reported method[5] by reaction of substituted anilines with phenylisothiocyanate in ethanol.

General Procedures for Preparing *N*-(Substituted-benzamido)-*N'*-phenylthioureas (2). 2 was synthesized in three steps[6] starting from substituted-benzoic acid. Ethyl benzoate was first prepared by esterification of substituted-benzoic acid in refluxing ethanol in the presence of concentrated H$_2$SO$_4$. This benzoate was then reacted with aqueous hydrazine (50%) in ethanol under refluxing for 3 h to afford substituted-benzoylhydrazine, which was finally reacted in ethanol at room temperature with phenyl isothiocyanate until TLC showed the completion of the reaction. The as-obtained products were purified by repeated recrystallizations from ethanol. Compounds **2a**−**h** were fully characterized and the detailed spectral data were supplied in the Supporting Information.

Supporting Information Available: General description for acquiring spectra and detailed spectral data for characterization of compounds **2a**−**h** (¹H and ¹³C NMR, HRMS, and elemental analysis data). This material is available free of charge via the Internet at http://pubs.acs.org.

(13) Rurack, K.; Resch-Genger, U. *Chem. Soc. Rev.* **2002**, *31*, 116.

JO049088F