CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.200900519

Anion Binding of *N*-(*o*-Methoxybenzamido)thioureas: Contribution of the Intramolecular Hydrogen Bond in the *N*-Benzamide Moiety

Qian-Qian Jiang, Burenkhangai Darhkijav, Hao Liu, Fang Wang, Zhao Li, and Yun-Bao Jiang*[a]

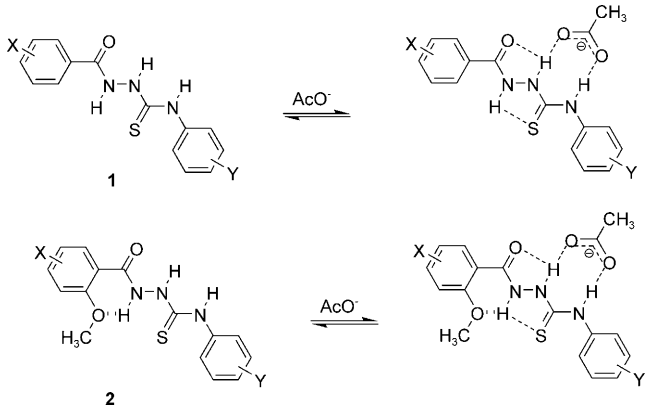
Dedicated to the 150th anniversary of Japan–UK diplomatic relations

Abstract: *N*-(*o*-Methoxybenzamido)-thioureas (**2X/2Y**) are found to show an enhanced anion binding affinity with binding constants over $10^7\ mol^{-1}L$ orders of magnitude for AcO^- and a redshifted absorption of the anion binding complexes in acetonitrile (MeCN) relative to those of *N*-benzamidothioureas (**1**) that bear no *o*-OMe in the *N*-benzamide moiety, despite the electron-donating character of *o*-OMe. Absorption of the anion–**2X/2Y** complex was shown to be of the same charge-transfer nature as that of the anion–**1** complex, but its dependence on substituent X is interestingly influenced by the *o*-MeO···HNC=O six-membered-ring intramolecular hydrogen bond identified in **2X/2Y**. Such an intramolecular hydrogen bond is suggested to be responsible for the enhanced anion binding affinity. In the presence of this intramolecular hydrogen bond, the anion binding constant of **2X** was found to be independent of substituent X at the *N*-phenyl ring, as in the case of **1**, whereas that of **2Y** showed an amplified dependence on substituent Y at the *N*′-phenyl ring, but to a lower extent than that of **1**. A similar ring intramolecular hydrogen bond was purported to exist in **2Za**, **2Zd**, and **2Ze**, which bear NHMe, F, and Cl as the *ortho* substituent in the *N*-benzamide moiety. In terms of the current roles of thiourea in not only anion recognition and sensing but also organocatalysis and crystal engineering, the present finding would be of significance for a wider structural diversity of smart thiourea derivatives with predesigned functions.

Keywords: amidothioureas · anions · arylamides · charge transfer · hydrogen bonds

Introduction

In searching for new thiourea-based receptors for anions, we found that *N*-benzamidothioureas (**1**, Scheme 1) that bear a *para* or *meta* substituent X in the *N*-benzamide moiety showed higher anion binding affinity than that of the corresponding classic *N*-phenylthiourea counterparts, despite the lower acidity of the thioureido –NH protons in **1**.[1] This was assumed to result from a charge transfer (CT) in **1** upon binding to the anion, which provides positive feedback to reinforce the anion binding. The original twisted N–N single bond in **1** was concluded to become planar upon anion bind-

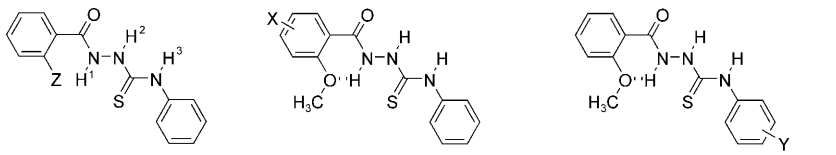


Scheme 1. Hydrogen-bonding interaction of *N*-benzamidothioureas with the AcO^- anion and hydrogen-bonding networks in the anion binding complexes. Substituent X or Y is at the *para* or *meta* position.

[a] Q.-Q. Jiang, B. Darhkijav, H. Liu, F. Wang, Prof. Dr. Z. Li, Prof. Dr. Y.-B. Jiang
Department of Chemistry
College of Chemistry and Chemical Engineering
and the MOE Key Laboratory of Analytical Sciences
Xiamen University, Xiamen 361005 (China)
Fax: (+86) 592-218-5662
E-mail: ybjiang@xmu.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.200900519. It includes absorption spectra of **2Xa–g** and **2Ya–d** in MeCN and ^1H and ^{13}C NMR spectra of **2Xa–g**, **2Ya–d**, and **2Za–f**.

ing and a hydrogen-bonding network was suggested to form in the anion binding complex that involves both C=O···HNC=S and O=CNH···S=C, in addition to the double hydrogen bonds of thiourea with the anion (Scheme 1). Recent efforts in arylamide-based foldamers have demonstrated an interesting contribution of the *ortho* substituent such as *o*-OMe and *o*-F in rigidifying the arylamide moiety by forming a six-membered-ring intramolecular hydrogen bond like *o*-MeO···HNC=O- or *o*-F···HNC=O.[2] It was therefore expected that with *N*-benzamidothioureas that bore an *ortho* substituent capable of forming an intramolecular hydrogen bond (**2**, Scheme 1) such intramolecular hydrogen bonds would facilitate the final hydrogen-bonding network in their anion binding complexes (Scheme 1). This would accordingly lead to an enhanced anion binding relative to that of **1**. Previously, intramolecular hydrogen bonding has been employed to preorganize the conformation of anion receptors for better performance.[3] We therefore decided to examine *N*-benzamide *ortho*-substituted counterparts of **1** (**2Z**, Scheme 2, and **2Zc** with Z = H is included for comparison). The investigation was started with the *o*-OMe derivative (**2Zb**), in which an intramolecular hydrogen bond was expected following the behavior of *o*-methoxybenzamide.[2] Indeed, we found that the anion binding constant of **2Zb** in MeCN was substantially enhanced compared with that of **2Zc** without such intramolecular hydrogen bonding in the *N*-benzamide moiety. A similar enhancement in anion binding was observed with **2Za**, **2Zd**, **2Ze**, and **2Zf**. In the cases of *ortho*-substituent NHMe (**2Za**), OMe (**2Zb**), F (**2Zd**), and Cl (**2Ze**), the absorption of AcO^-–**2Z** binding complex in MeCN was found to shift to the blue with decreasing electron-donating or increasing electron-withdrawing ability of the *ortho* substituent, which is opposite to that observed with **1** that bears a *para*/*meta* substituent X (Y = H, Scheme 1).[1b,d,i] We concluded that the intramolecular hydrogen bond in the *N*-benzamide moiety promoted anion binding in **2Zb** and in **2Za**, **2Zd**, and **2Ze** as well. Extended investigations into series **2X** and **2Y** were carried out to further demonstrate the contribution of such intramolecular hydrogen bonds on anion binding. The results reported here provide expanded diversity of thiourea-based functional species for not only anion receptors[4] but organocatalysts,[5] among others.



Scheme 2. Structure of *N*-(*ortho*-substituted)benzamidothioureas **2Z**, **2X**, and **2Y**. The −NH proton numbering is given in **2Z**.

Abstract in Chinese:

研究了邻甲氧基苯甲酰胺中 MeO…HNC=O 六元环状分子内氢键对 *N*-(邻甲氧基苯甲酰胺基)硫脲之阴离子结合特性的影响。X-射线晶体结构和 NMR 实验表明 *N*-(邻甲氧基苯甲酰胺基)硫脲 (**2X**/**2Y**) 分子中存在该分子内氢键，后者使邻甲氧基苯甲酰胺基的平面性提高、N-N 单键扭曲程度显著下降。MeCN 中 **2X**/**2Y** 的 AcO^- 结合常数 ($>10^7$ mol^{-1} L) 和阴离子结合物吸收波长分别远高于和略长于相应的不含邻甲氧基的 *N*-苯甲酰胺基硫脲衍生物的；取代基效应实验表明，**2X**/**2Y** 之阴离子结合物的吸收系分子内电荷转移吸收，但因之分子内氢键而显示出有趣的取代基 X 相关性。**2X** 的阴离子结合常数与 X 几乎无关，与不含邻甲氧基的 *N*-苯甲酰胺基硫脲衍生物的类似；**2Y** 的阴离子结合常数则体现出增强的取代基 Y 依赖性，但较 *N*-乙酰胺基-*N'*-取代苯基硫脲的弱。本文的结果进一步支持了 *N*-酰胺基硫脲之阴离子结合物中氢键网络的推论，为发展新型 *N*-酰胺基硫脲类功能分子提供了更为广泛的结构多样性。

Results and Discussion

Although in the cases of *o*-OMe- and *o*-F-substituted benzamides an intramolecular hydrogen bond has been identified,[2,6] we found evidence for such intramolecular hydrogen bonds in the corresponding *N*-benzamidothioureas from X-ray crystal structural analysis and 2D NMR spectroscopic data. We succeeded in growing crystals of **2Zb**[7] and **2Xb**,[8] which allowed for the identification of the intramolecular hydrogen bond between *o*-OMe and HNC=O. Figure 1 shows the crystal structure of **2Zb** grown in CH_2Cl_2, which clearly indicates the six-membered-ring intramolecular hydrogen bond. In the 2D NMR spectra of **2Zb** in $CDCl_3$, the coupling between *o*-OC*H*$_3$ and *N*-benzamido −N*H* protons was identified (Figure 2), thus supporting this ring intramolecular hydrogen bonding. From the crystal structure (Figure 1), it is noted that the *o*-methoxybenzamide moiety in **2Zb** is now planar with an expected higher rigidity. The N−N single bond in **2Zb** is found to be

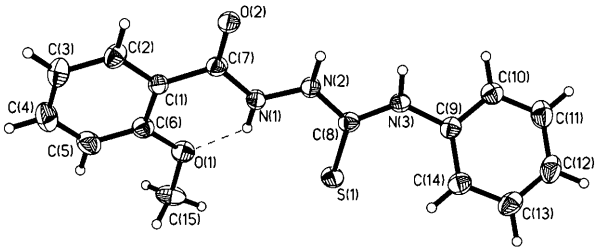


Figure 1. Crystal structure of **2Zb** grown in CH_2Cl_2. The dashed line indicates the six-membered-ring intramolecular hydrogen bond between $MeO^1\cdots H^1NC=O$ with an O···H distance of 1.90 Å.

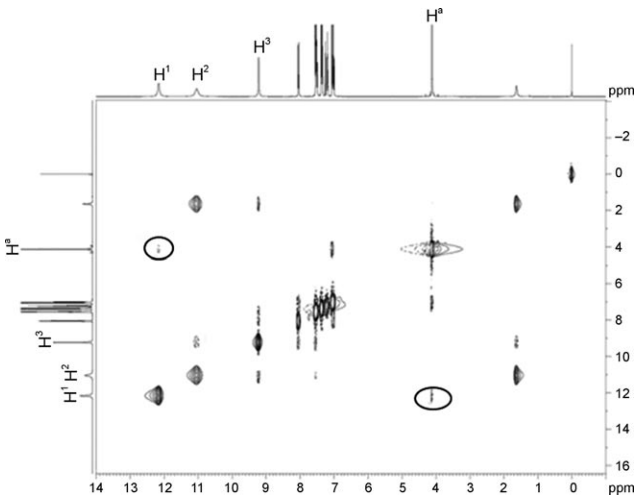


Figure 2. NOESY spectrum of **2Zb** in $CDCl_3$. Circles highlight coupling between H^1 and H^a. H^1, H^2, and H^3 are −NH protons; for their numbering, see Scheme 2. H^a is an *o*-OCH_3 proton.

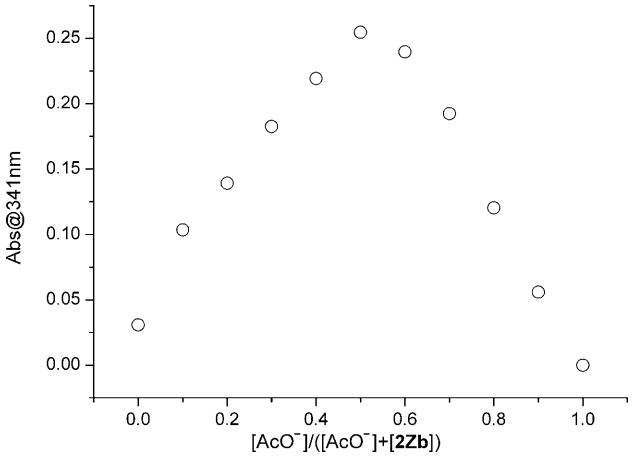


Figure 4. Job plot for the binding of AcO^- to **2Zb** in MeCN by monitoring the difference of absorbance of the mixture of AcO^- and **2Zb** and that of **2Zb** at 341 nm. The total concentration of AcO^- and **2Zb** was 5.0×10^{-5} mol L^{-1}.

less twisted than that in **1**, as the H-N^1-N^2-H dihedral angle (<20°) is much smaller than that in **1** (around 70°).[1b,d] Proton NMR spectra of **2X** and **2Y** showing substituent dependence of −NH agrees well with this observation and will be described later (in Figures 8 and 9). This means that the influence of the intramolecular hydrogen bonding has extended to the *N*-benzoylhydrazine moiety.

Anion binding of **2Zb** was monitored in MeCN by absorption spectral titrations. Traces presented in Figure 3 indicate that upon addition of AcO^- anions, the original absorption band of **2Zb** that peaked at 269 nm is redshifted to 278 nm and enhanced, and two new bands appear at 235 and 341 nm, respectively. An isosbestic point is identified at 245 nm, which is indicative of a well-defined interaction between **2Zb** and AcO^-. A Job plot confirmed that the binding stoichiometry was 1:1 (Figure 4). With F^- and $H_2PO_4^-$, similar variations in the absorption spectrum of **2Zb** were found (Figure 3b), whereas other anions such as Cl^-, Br^-, NO_3^-, HSO_4^-, and ClO_4^- led to no appreciable change in the absorption spectrum. By employing a reported nonlinear fitting procedure,[9] we determined the AcO^- binding constant of **2Zb** in MeCN to be over 10^7 $mol^{-1}L$; that is much higher than that of **1** (X=Y=H) at 10^5 $mol^{-1}L$ orders of magnitude.[1i] It is thus made clear that the intramolecular hydrogen bond in the *N*-benzamide moiety can further enhance the anion binding ability. Another important feature is that the new absorption band of the AcO^-–**2Zb** complex in MeCN that peaked at 341 nm is redshifted from that of AcO^-–**1** (X=Y=H) at 337 nm, despite the electron-donating character of the *o*-OMe substituent in **2Zb**. Previously it was shown that the absorption of the AcO^-–**1** (Y=H) complex in MeCN is of a charge-transfer (CT) nature[1i] in that it shifts to the blue when X is an electron-donating *para*/*meta* substituent. If the absorption of AcO^-–**2Zb** can be proven to be of a CT nature, the intramolecular hydrogen bond in the *N*-benzamide moiety of **2Zb** appears not only to exert steric influence but an electronic effect as well, as it makes the *N*-benzamide moiety more electron-withdrawing despite the electron-donating nature of the *o*-OMe substituent.

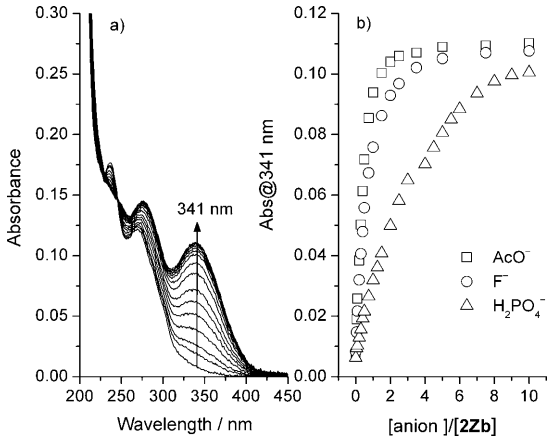


Figure 3. a) Absorption spectra of **2Zb** in MeCN in the presence of AcO^-, and b) plots of absorbance at 341 nm of **2Zb** versus anion concentration. [**2Zb**] = 1.0×10^{-5} mol L^{-1}.

We next examined the AcO^- binding properties of other members in the **2Z** series. Figure 5 shows the absorption spectral traces of **2Z** upon addition of the AcO^- anion in MeCN. The new absorption band was found to shift in general to the blue from **2Za** to **2Zf**. It has recently been shown that the effect of the *ortho* substituent consists mainly of the inductive and resonance polar effect; the pK_a value of the *o*-substituted benzoic acid thereby reflects the polar effect of the *ortho* substituent.[10] It therefore follows that the absorption of AcO^-–**2Z** binding complex shifts to the blue with the decreasing electron-donating or increasing electron-withdrawing ability of the *ortho* substituent. This is opposite to that previously observed with the absorption of AcO^-–**1** (Y=H),[1i] in the latter case it shifts to the red when X becomes less electron donating or more electron withdrawing. Taking the pK_a value of the corresponding

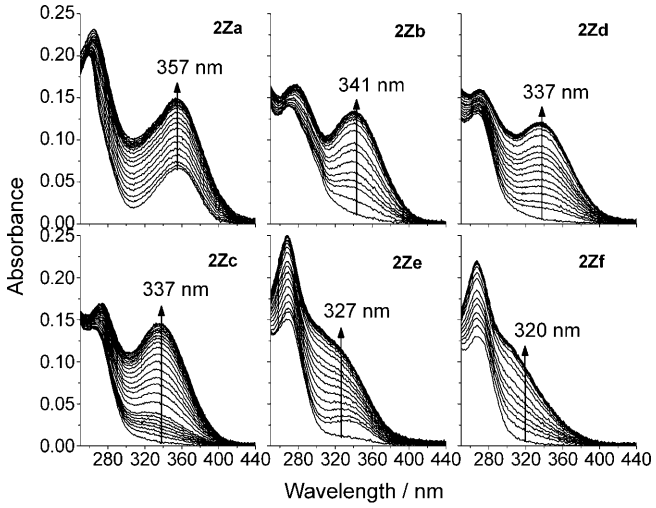


Figure 5. Absorption spectra of **2Za**–**2Zf** (1.0×10^{-5} mol L^{-1}) in MeCN in the presence of AcO$^-$ of increasing concentration.

ortho-substituted benzoic acid of **2Z** as a measure of the *ortho*-substituent constant, we found that the absorption energy of the AcO$^-$–**2Z** complex held a good linear relationship with the pK_a value (Figure 6) except for the cases without an *ortho* substituent (**2Zc**) or with a bulky *o*-Br (**2Zf**), since in these two cases no intramolecular hydrogen bond is expected. The observed linear correlation in Figure 6 might suggest that an intramolecular hydrogen bond also exists between the *o*-Cl and *N*-benzamido –NH proton in **2Ze**.[12] AcO$^-$ binding constants of **2Za**, **2Zd**, **2Ze**, and **2Zf** were all found to be over 10^7 mol^{-1} L; these are much higher than that of **2Zc**. The intramolecular hydrogen bond therefore appears to promote anion binding at least in the cases of **2Za**, **2Zb**, **2Zd**, and **2Ze**. It should be pointed out that the intramolecular hydrogen bond in **2Za** might be in the form of *o*-MeNH···O=CNH;[13] further experiments are however needed to clarify the bonding mode. In the case of **2Zf**, the bulky *o*-Br decreases the planarity of the *N*-benzamide moiety so that the arylamide becomes a somewhat aliphatic amide. As a consequence, the anion binding constant is higher and the absorption of the anion–**2Zf** complex is blueshifted (Figure 6), as expected from a comparison of *N*-acetamidothioureas with *N*-benzamidothioureas.[1a]

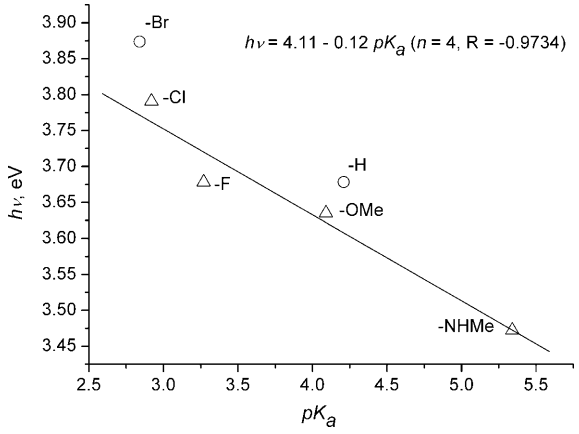


Figure 6. Absorption energy of AcO$^-$–**2Z** in MeCN versus pK_a of the corresponding *ortho*-substituted benzoic acid. Note the linear correlation between pK_a of *para*-/*meta*-substituted benzoic acid and the Hammett substituent constant σ of p$K_a=-1.03\sigma+4.21$ can be obtained by using data given in ref. [11]. Assuming this holds for the *ortho*-substituted benzoic acid, a linear relationship for the absorption energy of AcO$^-$–**2Z** of $h\nu=3.61+0.12\sigma$ was derived, which is indeed opposite in σ dependence to what was reported for that of AcO$^-$–**1** ($h\nu=3.67-0.34\sigma$).[1i]

To better understand the contribution of the intramolecular hydrogen bond in **2Z**, the nature of the absorption of the AcO$^-$–**2Z** complex was addressed. The anion binding character of **2X** (Scheme 2), which differs from **1** (Y=H) by an *o*-OMe in the *N*-benzamide moiety, was therefore examined. The crystal structure of **2Xb**[8] also shows the six-membered-ring intramolecular hydrogen bond with an *o*-MeO···HNC(O) distance of 1.86 Å. This implies that the 5-OMe substituent in the *N*-benzamide moiety of **2Xb** does not destroy this intramolecular hydrogen bond. The H-N-N-H dihedral angle is approximately 14°, which suggests that the *N*-benzoylhydrazine moiety is almost planar. The absorption spectral traces of **2X** in the presence of AcO$^-$ in MeCN are similar to those shown in Figures 3 and 5; they are characterized by the appearance of a new and redshifted absorption band (see the Supporting Information). The energy of this new band was found to be linearly related to the substituent constant of X in **2X** by $h\nu=3.60-0.28\sigma_X$ (Figure 7), with the absorption shifting to the red with increasing electron-withdrawing or decreasing electron-donating ability of X. This informs the CT character of the new absorption, as in the case of **1** (Y=H).[1i] It therefore appears that the intramolecular hydrogen bond in the *N*-benzamide moiety reverses the electronic character of the electron-donating *o*-substituent, which behaves like an electron-withdrawing substituent. Both the intercept and slope in the case of **2X** (Figure 7) are lower in value than the corresponding correlation found with **1** (Y=H) of $h\nu=3.67-0.34\sigma_X$.[1i] It thus follows that the intramolecular hydrogen bond in the *N*-benzamide moiety generally lowers the

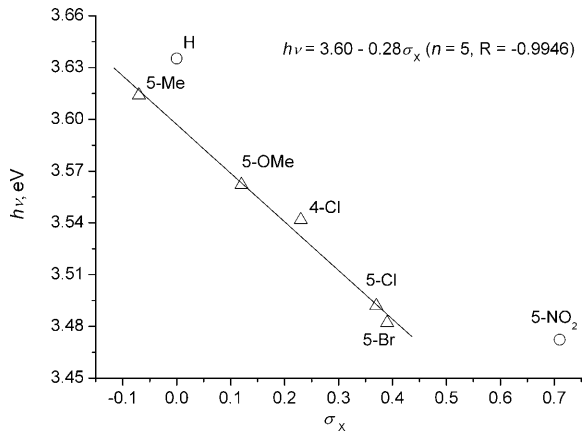


Figure 7. Absorption energy of the AcO$^-$–**2X** complex in MeCN versus the Hammett constant of substituent X in **2X**. Note a correlation of $h\nu=3.67-0.34\sigma_X$ has previously been reported for the absorption of AcO$^-$–**1** (Y=H).[1i]

absorption energy of the AcO^-–**2X** binding complex and slightly weakens the influence of the *para*/*meta* substituent X on this absorption. AcO^- binding constants of **2X** in MeCN were found to be over $10^7\ mol^{-1}\,L$ orders of magnitude, which is much higher than that of **1** (Y = H). They were, however, almost independent of the substituent X, similar to that observed with **1** (Y = H).[1i]

In the case of **2Y** (Scheme 2), the absorption of AcO^- binding complexes in MeCN at approximately 340 nm was not found to be very dependent on substituent Y (see the Supporting Information). The AcO^- binding constants in pure MeCN were found to be over $10^7\ mol^{-1}\,L$, thus not allowing for an analysis of their dependence on Y. In MeCN containing 2% H_2O by volume, the binding constants decreased to $10^5\ mol^{-1}\,L$ orders of magnitude, which thereby enables a credible correlation. The obtained correlation of $\ln K(AcO^-) = 12.84 + 2.68\sigma_Y$ ($n = 4$, $R = 0.8875$) suggests that an amplification of the effect of substituent Y on the binding constant of **2Y** exists, as in the case of **1**.[1a,g] This amplification in **2Y**, however, is to a lesser extent than that of *N*-acetamido-*N*′-(substituted-phenyl)thioureas, the corresponding slopes of which are 7.64, 5.44, and 4.31 in MeCN containing 0, 1, and 3% H_2O by volume, respectively.[1a] The presence of the amplification of substituent Y on anion binding of **2Y** is understandable, since anion-binding-induced CT is also indicated by the appearance of redshifted absorption. Crystal structures of **2Zb**[7] and **2Xb**[8] show that the N–N bond in **2** is less twisted than that in **1**, which means that the conformational changes in **2** upon its binding to an anion, if any, are smaller. This explains the observed lower amplification of the effect of substituent Y on anion binding of **2Y**. NMR spectroscopic signals of the –NH protons in **2X** and **2Y** versus the Hammett constants of substituent X or Y (Figures 8 and 9) do suggest a twisted N–N single bond. The discontinuity in the slopes of the *N*-benzamido $-NH^1$ and of the thioureido $-NH^2$ and $-NH^3$ protons indicates that the substituent electronic effect is to some extent blocked by the N–N bond.

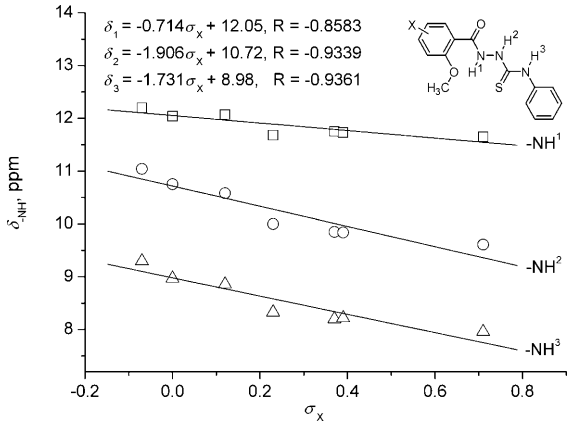


Figure 8. Chemical shifts of –NH protons of **2X** in $CDCl_3$ versus the Hammett constant of substituent X.

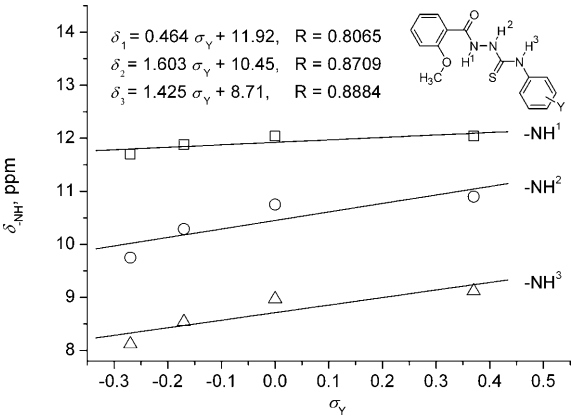


Figure 9. Chemical shifts of –NH protons of **2Y** in $CDCl_3$ versus the Hammett constant of substituent Y.

Conclusion

A six-membered-ring intramolecular hydrogen bond was indicated by X-ray crystal structural analysis and NMR spectroscopy to exist in *N*-(*o*-methoxybenzamido)thioureas (**2X** and **2Y**), which makes the *N*-benzamide moiety rigid and planar. Actually, such intramolecular hydrogen bonding even makes the N–N single bond much less twisted in **2X** and **2Y** relative to that in **1**, which bears no *o*-OMe substituent in the *N*-benzamide moiety. Although anion binding constants of **1** (Y = H) were previously shown to be independent of substituent X, the electron-donating *o*-OMe substituent was found to increase the anion binding affinity of **2Zb** with this intramolecular hydrogen bond relative to that of **2Zc**, which lacks such a bond. This clearly demonstrates the promotion of the intramolecular hydrogen bond in anion binding.

The absorption of the anion–**2X** complex was found to be of a CT nature, the wavelength being in general longer than that of anion–**1** (Y = H) and its dependence on substituent X being weaker. It appears that the intramolecular hydrogen bond buffers the substituent effect by increasing the conjugation in the *N*-benzamide moiety, presumably owing to its enhanced planarity and rigidity. Despite this intramolecular hydrogen bond in the *N*-benzamide moiety, the anion binding constant of **2X** was found to be independent of substituent X, similar to that with **1** (Y = H), whereas the effect of substituent Y on the anion binding constant of **2Y** is amplified to a lesser extent than that in the case of having no such bond. Less conformational change in the N–N bond of **2X**(**2Y**) upon anion binding was assumed to be responsible for the latter observation.

The present finding that the intramolecular hydrogen bond in the *N*-benzamide moiety promotes anion binding of *N*-(*o*-methoxybenzamido)thioureas provides further support for the formation of a hydrogen-bonding network in the anion/*N*-amidothiourea binding complex. This allows a wider structural diversity of functional thiourea derivatives to be created. For example, the fact that substituent X in

2X does not affect the anion affinity of **2X** suggests that *N*-(aliphatic amido)thioureas that bear an intramolecular hydrogen bond in the *N*-amide moiety may function similarly to that of **2X**. This would be of significance for developing new thiourea-based organocatalysts.[1a,14] Our finding also suggests that a six-membered *o*-Cl···HNC=O ring intramolecular hydrogen bond may exist in *o*-chlorobenzamide, a subject that is still controversial.[12]

Experimental Section

General Methods

Chemicals for syntheses were commercially available and used as received. Solvents for spectral investigations were further purified by distillation to ensure no fluorescence impurities at the chosen excitation wavelength. The anions employed for binding titrations in organic solvents were their commercially available nBu$_4$N$^+$ salts.

Absorption spectral titrations for anion binding were recorded using a Thermo Evolution 300 spectrophotometer with a 1 cm cell by adding an aliquot of anion solution to a bulk receptor solution of given volume and concentration. ^{1}H and ^{13}C NMR spectra in $CDCl_3$, [D$_6$]DMSO, and CD_3CN were acquired using a Bruker AV400 NMR spectrometer with TMS as an internal standard. HRMS spectra were obtained using a Micromass LCT spectrometer with methanol as the solvent. IR spectra were taken from the KBr pellet samples using a Nicolet IR200 instrument. Single-crystal X-ray diffraction data were collected using a Bruker Smart APEX 2000 CCD diffractometer.

Compounds **2Z**, **2X**, and **2Y** were synthesized from the reaction of phenylisothiocyanate with the corresponding benzoylhydrazine that was obtained from benzoate ester and hydrazine. All the prepared compounds were fully characterized by ^{1}H and ^{13}C NMR spectroscopy and HRMS. Copies of the ^{1}H and ^{13}C NMR spectra can be found in the Supporting Information.

CCDC-696246 (**2Zb**)[7] and -696247 (**2Xb**)[8] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

*Synthesis and Characterization of **2Z***

Compound **2Z** was synthesized in three steps starting from *ortho*-substituted benzoic acid. Methyl benzoate was first prepared by esterification of the substituted benzoic acid in methanol heated at reflux in the presence of concentrated H_2SO_4. This benzoate then reacted with aqueous hydrazine (80%) in ethanol heated at reflux for 8 h. The formed precipitates were filtered, washed with iced ethanol (3×5.0 mL) and iced water (3×10.0 mL), then dried, thereby leading to 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 recrystallization from ethanol. Compound **2Za**: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=10.30 (s, 1H), 9.78(s, 1H), 9.58 (s, 1H), 7.74 (s, 1H), 7.44 (s, 2H), 7.33 (q, J=7.6 Hz, 3H), 7.15 (t, J=7.2 Hz, 1H), 6.67 (t, J=7.2 Hz, 1H), 6.57 (t, J=7.2 Hz, 1H), 2.8 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=181.2, 168.7, 150.5, 139.2, 133.2, 129.2, 127.9, 125.9, 124.9, 113.7, 112.1, 110.6, 29.3 ppm; HRMS (ESI): m/z calcd for $C_{15}H_{17}N_4OS^+$: 301.1123; found: 301.1129. Compound **2Zb**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=12.04 (s, 1H), 10.75 (s, 1H), 8.97 (s, 1H), 8.07 (d, J=7.6 Hz, 1H), 7.51 (m, 3H), 7.38 (t, J=8.0 Hz, 2H), 7.22 (t, J=7.2 Hz, 1H), 7.04 (t, J=8.6 Hz, 2H), 4.12 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=180.6, 165.2, 157.2, 139.1, 133.1, 130.8, 128.2, 124.9, 124.8, 122.5, 120.6, 112.1, 56.1 ppm; HRMS (ESI): m/z calcd for $C_{15}H_{16}N_3O_2S^+$: 302.0963; found: 302.0966. Compound **2Zc**:[11] ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=10.54 (s, 1H), 9.82 (s, 1H), 9.72 (s, 1H), 7.96 (d, J=7.50 Hz, 2H), 7.58 (t, J=7.32 Hz, 1H), 7.50 (t, J=7.32 Hz, 2H), 7.43(s, 2H), 7.33 (t, J=7.54 Hz, 2H), 7.16 ppm (t, J=7.32 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=181.1, 166.0, 139.3, 132.5, 131.9, 128.2, 127.9, 126.1, 125.1 ppm; HRMS (ESI): m/z calcd for $C_{14}H_{14}N_3OS^+$: 272.0858; found: 272.0854. Compound **2Zd**: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=10.34 (s, 1H), 9.83 (s, 1H), 9.73 (s, 1H), 7.85 (s, 1H), 7.60 (q, J=6.0 Hz, 1H), 7.45 (s, 2H), 7.33 (q, J=7.2 Hz, 3H), 7.17 (t, J=7.0 Hz, 1H), 7.15 ppm (t, J=7.5 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=181.1, 163.3, 160.9, 158.4, 139.1, 133.3, 130.7, 128.1, 125.8, 125.0, 124.3, 121.7, 116.3, 116.1 ppm; HRMS (ESI): m/z calcd for $C_{14}H_{13}FN_3OS^+$: 290.0763; found: 290.0760. Compound **2Ze**: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=10.46 (s, 1H), 9.84 (s, 1H), 9.67 (s, 1H), 7.80 (d, J=6.8 Hz, 1H), 7.55–7.43 (m, 5H), 7.36 (t, J=7.6 Hz, 2H), 7.17 ppm (t, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=181.8, 165.6, 139.0, 133.9, 131.6, 130.7, 129.9, 129.8, 128.2, 126.9, 126.5, 124.9 ppm; HRMS (ESI): m/z calcd for $C_{14}H_{13}ClN_3OS^+$: 306.0468; found: 306.0474. Compound **2Zf**: ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ=10.47 (s, 1H), 9.85 (s, 1H), 9.59 (s, 1H), 7.77 (d, J=7.2 Hz, 1H), 7.70 (d, J=6.8 Hz, 1H), 7.49 (t, J=6.8 Hz, 3H), 7.44 (d, J=6.0 Hz, 1H), 7.36 (t, J=7.6 Hz, 2H), 7.18 ppm (t, J=7.4 Hz, 1H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=181.4, 166.4, 139.0, 135.9, 133.0, 131.7, 129.9, 128.2, 127.4, 125.9, 124.9, 119.6 ppm; HRMS (ESI): m/z calcd for $C_{14}H_{13}BrN_3OS^+$: 349.9963; found: 349.9969.

*Synthesis and Characterization of **2X***

Potassium carbonate (2.07 g, 15 mmol) was added to a solution of substituted 2-hydroxybenzoic acid (5 mmol) in acetone (10.0 mL). CH_3I (1.3 mL, 20 mmol) was added dropwise to the stirred mixture at room temperature. The mixture was heated at reflux in the dark for 12 h. All precipitates were filtered off and the filtrates were evaporated under reduced pressure to get methyl-substituted 2-methoxybenzoate. The ester was dissolved in ethanol (5 mL), and excess aqueous hydrazine (80%) was added. The mixture was heated to 80 °C for 8 h. After removing the solvent, the residue was washed with iced ethanol and then dried, thus producing substituted 2-methoxybenzoylhydrazine. It was then reacted with phenyl isothiocyanate in ethanol (10.0 mL) for 12 h at room temperature. After removing the solvent, the residue was purified by recrystallization from MeCN to lead to **2X**. Compound **2Xa**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=12.22 (s, 1H), 11.04 (s, 1H), 9.30 (s, 1H), 7.80 (s, 1H), 7.55 (d, J=7.2 Hz, 2H), 7.38 (t, J=7.4 Hz, 2H), 7.29 (d, J=8.4 Hz, 1H), 7.22 (t, J=7.0 Hz, 1H), 6.94 (d, J=8.4 Hz, 1H), 4.09 (s, 3H), 2.16 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=180.4, 165.2, 155.4, 139.1, 133.5, 130.8, 129.5, 128.2, 124.8, 122.6, 120.7, 112.1, 56.2, 19.8 ppm; HRMS (ESI): m/z calcd for $C_{16}H_{18}N_3O_2S^+$: 316.1120, found: 316.1122. Compound **2Xb**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=12.07 (s, 1H), 10.58 (s, 1H), 8.86 (s, 1H), 7.56 (s, 1H), 7.48 (d, J=8.0 Hz, 2H), 7.38 (t, J=7.6 Hz, 2H), 7.23 (d, J=7.2 Hz, 1H), 7.05 (d, J=8.8 Hz, 1H), 6.98 (d, J=9.2 Hz, 1H), 4.07 (s, 3H), 3.57 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=180.6, 164.8, 153.0, 151.3, 139.0, 128.2, 125.2, 124.7, 122.5, 118.4, 115.1, 113.6, 56.5, 55.5 ppm; HRMS (ESI): m/z calcd for $C_{16}H_{18}N_3O_3S^+$: 332.1069; found: 332.1075. Compound **2Xc**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=12.04 (s, 1H), 10.75 (s, 1H), 8.97 (s, 1H), 8.07 (d, J=7.6 Hz, 1H), 7.51 (m, 3H), 7.38 (t, J=8.0 Hz, 2H), 7.22 (t, J=7.2 Hz, 1H), 7.04 (t, J=8.6 Hz, 2H), 4.12 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=180.6, 165.2, 157.2, 139.1, 133.1, 130.8, 128.2, 124.9, 124.8, 122.5, 120.6, 112.1, 56.1 ppm; HRMS (ESI): m/z calcd for $C_{15}H_{16}N_3O_2S^+$: 302.0963; found: 302.0966. Compound **2Xd**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=11.68 (s, 1H), 10.00 (s, 1H), 8.33 (s, 1H), 8.02 (d, J=8.0 Hz, 1H), 7.42–7.43 (m, 4H), 7.29 (m, 1H), 7.07 (d, 1H), 7.04 (m, 1H), 4.11 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=180.4, 164.4, 157.9, 139.0, 137.3, 132.2, 128.1, 125.4, 124.8, 122.7, 120.6, 112.6, 56.6 ppm; HRMS (ESI): m/z calcd for $C_{15}H_{15}ClN_3O_2S^+$: 336.0574; found: 336.0579. Compound **2Xe**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=11.75 (s, 1H), 9.85 (s, 1H), 8.20 (s, 1H), 8.08 (d, 1H), 7.43–7.47 (m, 5H), 7.31 (d, J=6.8 Hz, 1H), 6.98 (d, J=8.8 Hz, 1H), 4.10 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=180.5, 164.0, 156.0, 139.1, 132.3, 129.9, 128.2, 125.8, 125.0, 124.4, 122.9, 114.2, 56.5 ppm; HRMS (ESI): m/z calcd for $C_{15}H_{15}ClN_3O_2S^+$: 336.0574; found: 336.0564. Compound **2Xf**: ^{1}H NMR (400 MHz, $CDCl_3$): δ=11.73 (s, 1H), 9.84 (s, 1H), 8.22 (s, 2H), 7.60 (d, J=8.4 Hz, 1H), 7.44–7.47 (m, 4H), 7.31 (d, J=6.4 Hz, 1H), 6.93 (d, J=7.6 Hz, 1H), 4.10 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ=180.3, 163.9, 156.4, 139.0, 138.9, 135.2, 132.7, 128.1, 125.7, 124.9, 123.2,

114.6, 111.9, 56.4 ppm; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}BrN_3O_2S^+$: 380.0068; found: 380.0076. Compound **2Xg**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.65$ (s, 1H), 9.61 (s, 1H), 9.03 (s, 1H), 8.40 (d, $J = 8.8$ Hz, 1H), 7.96 (s, 1H), 7.48 (t, $J = 7.4$ Hz, 2H), 7.33–7.39 (m, 3H), 7.15 (d, $J = 9.2$ Hz, 1H), 4.24 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 180.6$, 162.0, 140.4, 139.0, 128.2, 128.1, 126.3, 125.9, 125.0, 123.4, 122.2, 113.1, 57.2 ppm; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}N_4O_4S^+$: 347.0814; found: 347.0823.

Synthesis and Characterization of ***2Y***

o-Methoxybenzoic acid (5 mmol) was dissolved in methanol (15 mL). The resulting solution was heated at reflux in the presence of concentrated H_2SO_4 for 6 h. The solvent was removed under reduced pressure and water was added to the residue. The solution pH was adjusted to 8.0 using sodium bicarbonate, thus leading to methyl *o*-methoxybenzoate. It was reacted with excess aqueous hydrazine (80%) in ethanol while heating at reflux for 8 h. A precipitate was formed, which after filtration was washed with iced water and dried to produce *o*-methoxybenzoylhydrazine. Phenyl isothiocyanate was added to a solution of *o*-methoxybenzoylhydrazine in ethanol and the solution was stirred at room temperature for 12 h. Compound **2Y** was prepared after removing the solvent and purified by recrystallization from MeCN. Compound **2Ya**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.70$ (s, 1H), 9.75 (s, 1H), 8.12 (s, 1H), 8.08 (d, $J = 8.0$ Hz, 1H), 7.51 (t, $J = 7.8$ Hz, 1H), 7.32 (d, $J = 8.8$ Hz, 2H), 7.05 (q, $J = 8.0$ Hz, 2H), 6.94 (t, $J = 8.8$ Hz, 2H), 4.10 (s, 3H), 3.82 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 180.2$, 164.9, 157.1, 156.6, 133.0, 131.8, 130.7, 126.8, 125.8, 120.5, 113.3, 112.0, 56.0, 55.1 ppm; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{18}N_3O_3S^+$: 332.1069; found: 332.1075. Compound **2Yb**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.88$ (s, 1H), 10.29 (s, 1H), 8.54 (s, 1H), 8.07 (d, $J = 8.0$ Hz, 1H), 7.51 (t, $J = 8.0$ Hz, 1H), 7.33 (d, $J = 8.4$ Hz, 2H), 7.20 (d, $J = 8.4$ Hz, 2H), 7.05 (t, $J = 8.2$ Hz, 2H), 4.11 (s, 3H), 2.35 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 180.5$, 165.4, 157.7, 136.9, 134.5, 133.6, 131.1, 129.2, 125.7, 123.3, 120.8, 112.6, 56.0, 21.0 ppm; HRMS (ESI): *m*/*z* calcd for $C_{16}H_{18}N_3O_2S^+$: 316.1120; found: 316.1125. Compound **2Yc**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.04$ (s, 1H), 10.75 (s, 1H), 8.97 (s, 1H), 8.07 (d, $J = 7.6$ Hz, 1H), 7.51 (m, 3H), 7.38 (t, $J = 8.0$ Hz, 2H), 7.22 (t, $J = 7.2$ Hz, 1H), 7.04 (t, $J = 8.6$ Hz, 2H), 4.12 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 180.6$, 165.2, 157.2, 139.1, 133.1, 130.8, 128.2, 124.9, 124.8, 122.5, 120.6, 112.1, 56.1 ppm; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{16}N_3O_2S^+$: 302.0963; found: 302.0966. Compound **2Yd**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.04$ (s, 1H), 10.90 (s, 1H), 9.12 (s, 1H), 8.03 (d, $J = 6.0$ Hz, 1H), 7.54 (t, $J = 7.8$ Hz, 1H), 7.48 (d, $J = 8.$ 8 Hz, 2H), 7.32 (d, $J = 8.8$ Hz, 2H), 7.06 (t, $J = 6.8$ Hz, 2H), 4.13 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): $\delta = 180.5$, 165.0, 157.2, 138.6, 133.7, 131.4, 128.8, 127.9, 126.8, 124.7, 120.6, 112.6, 56.6 ppm; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{15}ClN_3O_2S^+$: 336.0574; found: 336.0576.

Acknowledgements

We thank the organizers of the symposium "Catalysis and Sensing for our Environment" (CASE) that brings scientists of catalysis and chemical sensing together and promotes our ongoing projects on thiourea-based functional molecules. The National Science Foundation of China is thanked for financial support (grants 20675069 and 20835005 to Y.B.J. and J0630429 to H.L.). B.D., on leave from the Mongolian Academy of Sciences, thanks the Chinese Scholar Council for partial support.

[1] a) W.-X. Liu, R. Yang, A.-F. Li, Z. Li, Y.-F. Gao, X.-X. Luo, Y.-B. Ruan, Y.-B. Jiang, *Org. Biomol. Chem.* **2009**, *7*, 4021–4028; b) Z. Li, F.-Y. Wu, L. Guo, A.-F. Li, Y.-B. Jiang, *J. Phys. Chem. B* **2008**, *112*, 7071–7079; c) R. Yang, W.-X. Liu, H. Shen, H.-H. Huang, Y.-B. Jiang, *J. Phys. Chem. B* **2008**, *112*, 5105–5110; d) Z. Li, Z. Liu, Q.-X. Liao, Z.-B. Wei, L.-S. Long, Y.-B. Jiang, *C. R. Chim.* **2008**, *11*, 67–72; e) W. X. Liu, Y.-B. Jiang, *J. Org. Chem.* **2008**, *73*, 1124–1127; f) W. X. Liu, Y. B. Jiang, *Org. Biomol. Chem.* **2007**, *5*, 1771–1775; g) F.-Y. Wu, Z. Li, L. Guo, X. Wang, M.-H. Lin, Y.-F. Zhao, Y. B. Jiang, *Org. Biomol. Chem.* **2006**, *4*, 624–630; h) J. Han, Z. Li, W. X. Liu, R. Yang, Y. B. Jiang, *Acta Chim. Sin. (Engl. Ed.)* **2006**, *64*, 1716–1722; i) L. Nie, Z. Li, J. Han, X. Zhang, R. Yang, W. X. Liu, F. Y. Wu, J. W. Xie, Y. F. Zhao, Y. B. Jiang, *J. Org. Chem.* **2004**, *69*, 6449–6454; j) F. Y. Wu, Z. Li, Z. C. Wen, N. Zhou, Y. F. Zhao, Y. B. Jiang, *Org. Lett.* **2002**, *4*, 3203–3205.

[2] For recent reviews, see: a) I. Saraogi, A. D. Hamilton, *Chem. Soc. Rev.* **2009**, *38*, 1726–1743; b) B. Gong, *Acc. Chem. Res.* **2008**, *41*, 1376–1386; c) Z.-T. Li, J.-L. Hou, C. Li, *Acc. Chem. Res.* **2008**, *41*, 1343–1353.

[3] a) J. T. Davis, P. A. Gale, O. A. Okunola, P. Prados, J. C. Iglesias-Sánchez, T. Torroba, R. Quesada, *Nat. Chem.* **2009**, *1*, 138–144; b) P. A. Gale, J. Garric, M. E. Light, B. A. McNally, B. D. Smith, *Chem. Commun.* **2007**, 1736–1738; c) P. V. Santacroce, J. T. Davis, M. E. Light, P. A. Gale, J. C. Iglesias-Sánchez, P. Prados, R. Quesada, *J. Am. Chem. Soc.* **2007**, *129*, 1886–1887.

[4] For recent reviews on thiourea-based anion receptors, see: a) C. Caltagirone, P. A. Gale, *Chem. Soc. Rev.* **2009**, *38*, 520–563; b) P. A. Gale, S. E. Garcia-Garrido, J. Garric, *Chem. Soc. Rev.* **2008**, *37*, 151–190; c) T. Gunnlaugsson, M. Glynn, G. M. Tocci, P. E. Kruger, F. M. Pfeffer, *Coord. Chem. Rev.* **2006**, *250*, 3094–3117; d) V. Amendola, D. Esteban-Gómez, L. Fabbrizzi, M. Licchelli, *Acc. Chem. Res.* **2006**, *39*, 343–353; e) P. A. Gale, *Acc. Chem. Res.* **2006**, *39*, 465–475.

[5] For recent reviews on thiourea-based organocatalysts, see: a) Z. G. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187–1198; b) J. Alemán, A. Milelli, S. Cabrera, E. Reyes, K. A. Jorgensen, *Chem. Eur. J.* **2008**, *14*, 10958–10966; c) Y. Sohtome, N. Takemura, K. Takada, R. Takagi, T. Iguchi, K. Nagasawa, *Chem. Asian J.* **2007**, *2*, 1150–1160; d) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743.

[6] Q. Gan, C. Y. Bao, B. Kauffmann, A. Grelard, J. F. Xiang, S. H. Liu, I. Huc, H. Jiang, *Angew. Chem.* **2008**, *120*, 1739–1742; *Angew. Chem. Int. Ed.* **2008**, *47*, 1715–1718.

[7] Crystal structure data for **2Zb**: $C_{12}H_{12}N_{2.4}O_{1.6}S_{0.8}$; $a = 10.439(3)$, $b = 11.681(3)$, $c = 12.527(3)$ Å; $\alpha = 96.413(5)$, $\beta = 108.390(5)$, $\gamma = 95.946(5)°$; $V = 1424.8(6)$ Å^3; $Z = 5$; final $R1 = 0.0603$, $wR2 = 0.1567$ ($I > 2\sigma(I)$).

[8] Crystal structure data for **2Xb**: $C_{21.33}H_{22.67}N_4O_4S_{1.33}$; $a = 6.0739(2)$, $b = 10.6574(4)$, $c = 24.3162(7)$ Å; $\alpha = 90$, $\beta = 95.899(3)$, $\gamma = 90°$; $V = 1565.70(9)$ Å^3; $Z = 3$; final $R_1 = 0.0438$, $wR2 = 0.1032$ ($I > 2\sigma(I)$).

[9] K. A. Connors, *Binding Constants: The Measurement of Molecular Complex Stability*, Wiley, New York, **1987**.

[10] a) S. Böhm, P. Fiedler, O. Exner, *New J. Chem.* **2004**, *28*, 67–74; b) P. Fiedler, S. Böhm, J. Kulhánek, O. Exner, *Org. Biomol. Chem.* **2006**, *4*, 2003–2011.

[11] G. W. Gokel, *Dean's Handbook of Organic Chemistry*, 2nd ed., McGraw-Hill, New York, **2004**.

[12] a) J. F. Galan, J. Brown, J. L. Wildin, Z. W. Liu, D. H. Liu, G. Moyna, V. Pophristic, *J. Phys. Chem. B* **2009**, *113*, 12809–12815; b) Y.-Y. Zhu, H.-P. Yi, C. Li, X.-K. Jiang, Z.-T. Li, *Cryst. Growth Des.* **2008**, *8*, 1294–1300.

[13] V. Bertolasi, N. Hunter, K. Vaughan, *J. Chem. Crystallogr.* **2009**, *39*, 372–376.

[14] For the most recent examples of thiourea-based organocatalysts, see: a) S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358–15374; b) S. J. Zuend, M. P. Coughlin, M. P. Lalonde, E. N. Jacobsen, *Nature* **2009**, *461*, 968–971; c) X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y.-X. Lu, *Angew. Chem.* **2009**, *121*, 7740–7743; *Angew. Chem. Int. Ed.* **2009**, *48*, 7604–7607; d) T. Bui, S. Syed, C. F. Barbas, III, *J. Am. Chem. Soc.* **2009**, *131*, 8758–8759; e) X. Han, J. Luo, C. Liu, Y. X. Lu, *Chem. Commun.* **2009**, 2044–2046; f) O. Reis, S. Eymur, B. Reis, A. S. Demir, *Chem. Commun.* **2009**, 1088–1090.

Received: October 2, 2009
Published online: February 1, 2010

