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Hydrogen-Bonding Thiourea Organocatalysts: The Privileged 3,5-Bis(trifluoromethyl)phenyl Group

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We present evidence that the privileged use of the 3,5-bis(trifluoromethyl)phenyl group in thiourea organocatalysis is due to the involvement of the *ortho*-CH bond in the binding event with Lewis-basic sites. We utilized a combination of low-temperature IR spectroscopy, 2D NMR spectroscopy, nano-MS (ESI) investigations, as well as density functional theory computations [M06/6-31+G(*d*,*p*), including solvent corrections as well as natural bond orbital and atoms-in-molecules analyses] to support our conclusions that bear implications for catalyst design.

Introduction

Urea and thiourea derivatives are popular hydrogen-bonding catalysts that have been utilized successfully in a large variety of organocatalytic transformations.[1] Many catalysts display the 3,5-bis(trifluoromethyl)phenyl group[2] that was first introduced as a key structural motif in thiourea catalysis in 2002.[3] Remarkably, this moiety is also present in some of the most active proline and phosphoric acid derived catalysts (Figure 1).[4] It appears that the 3,5-bis(trifluoromethyl)phenyl moiety generally has beneficial effects on organocatalysts. This may inter alia involve an increase in catalyst polarity, polarizability, acidity,[5] and π–π interactions[2k,6] through the highly polarized aryl groups. Here we describe that the involvement of the highly polar *ortho*-CH bond is also quite important for catalyst–substrate interactions in the case of thiourea catalysis.[2k,7] Evidence for the non-negligible role of CH–heteroatom interactions comes from early IR and NMR spectroscopic studies.[8] Such interactions increase with increasing carbon *s*-content in the hybridization and in the presence of electron-withdrawing groups.[8,9] Hydrogen-bonding interactions of polar aromatic CH bonds with Lewis basic sites have been well studied but,[9,10] to the best of our knowledge, not in the context of hydrogen-bonding organocatalysis.

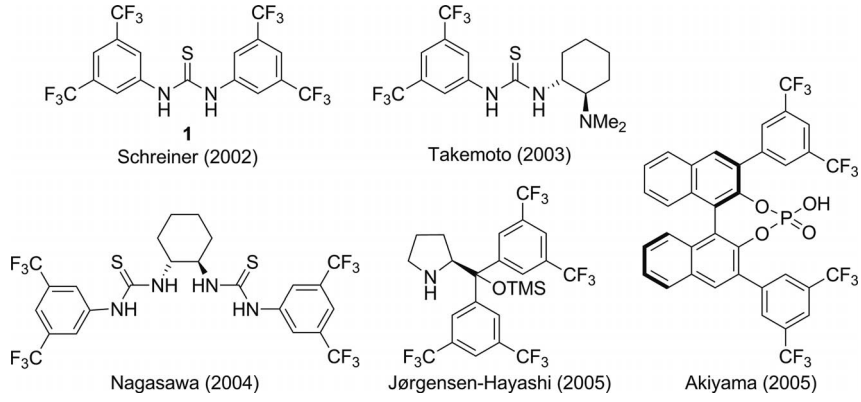

Figure 1. Selection of catalysts bearing a 3,5-bis(trifluoromethyl)phenyl group.

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Results and Discussion

We utilized low-temperature NMR and IR techniques as well as modern density functional theory (DFT) computations[11] to corroborate our findings. While there are numerous complexes of anions and neutrals with (thio)urea derivatives, we are unaware of reports on the involvement of C–H bonding in the binding event.[1g,12] A pertinent example in the context of thiourea binding to neutrals comes from the work of Waymouth and Hedrick, who examined effects of supramolecular recognition for living polymerization of lactide by utilizing catalysts bearing the 3,5-bis(trifluoromethyl)phenyl motif.[7d,13] To elucidate the structural changes upon binding between catalyst and substrate, we examined the interactions of thiourea derivatives **1**–**4** with neutrals **5**–**9** (Figure 2).

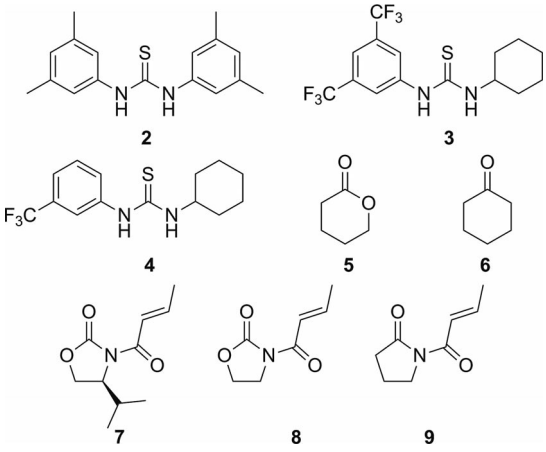

Figure 2. Investigated thiourea derivatives and substrates **5**–**9**.

Individual Components

In the absence of a Lewis basic donor, structure **2**, which has not been employed as a catalyst, displays two conformers with *E*,*Z*- (**2**_*E*,*Z*) and *Z*,*Z*-orientations (**2**_*Z*,*Z*) of the N–H bonds (Figure 3), with the **2**_*E*,*Z* form being slightly more stable as derived from computations and its crystal structure. However, our NMR spectroscopic studies imply that in [D$_8$]toluene at room temperature, conformer **2**_*Z*,*Z* is preferred, whereas **2**_*Z*,*E* predominates at temperatures below 200 K; that is, the rotation around the C–N bonds is facile (cf. Supporting Information, Figure S29).

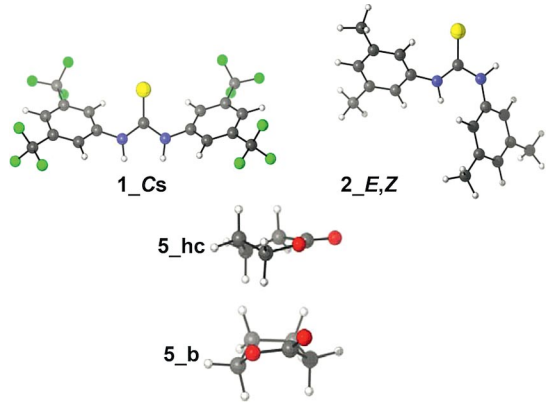

Figure 3. The lowest-lying conformers of **1**, **2**, and **5** computed at M06/6-31+G(*d*,*p*) at 0 K. Compounds **1**_Cs and **2**_*E*,*Z* are also present in the crystal structure.

Catalyst **1** prefers a *Z*,*Z*-orientation of the N–H protons (Figure 3) in solution, in the crystal, and computationally. At temperatures below 190 K in [D$_8$]THF, **1** transforms into the *Z*,*E*-conformation, as evident from the separated signals of the N–H protons (Figure 4). A ^{1}H–^{15}N HSQC spectrum

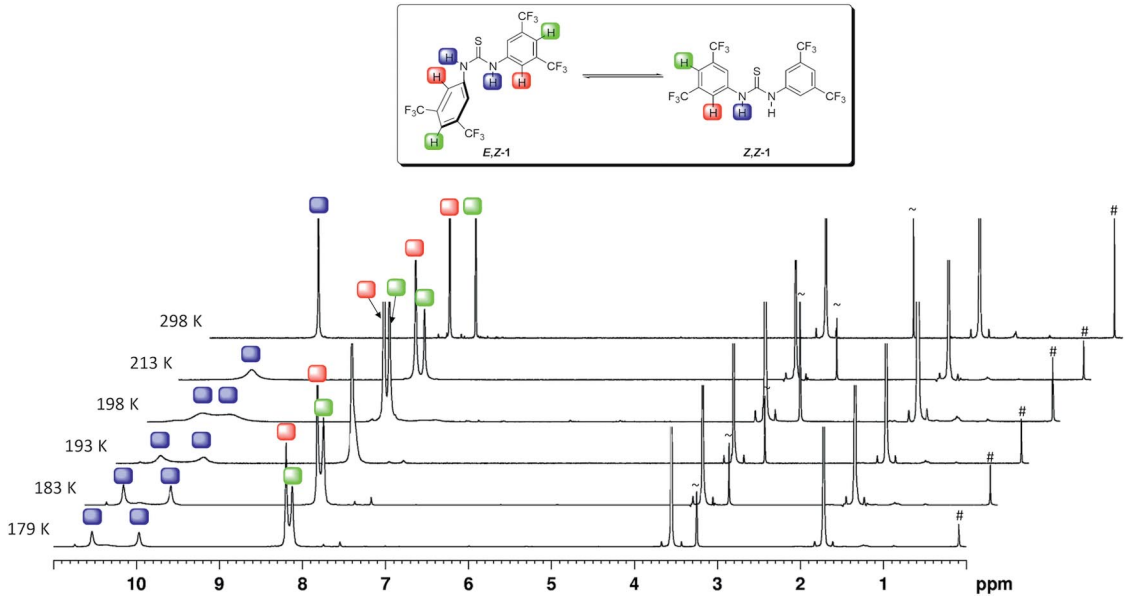

Figure 4. Stacked ^{1}H NMR (600 MHz) spectra of **1** (0.01 mmol, 13.3 mM) in [D$_8$]THF.

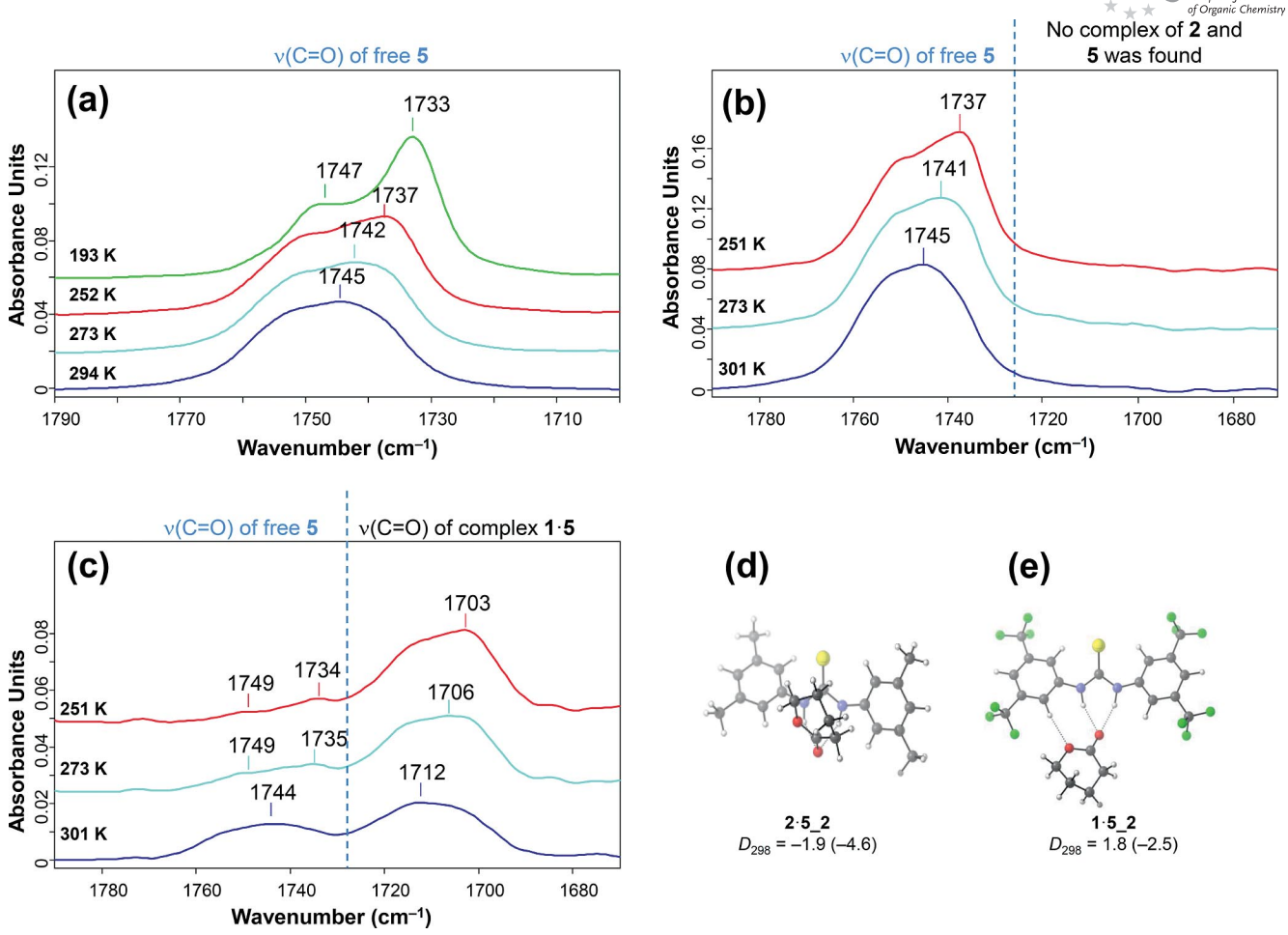

Figure 5. (a)–(c) Selected ranges of the IR spectra in [D_8]toluene; temperatures are given above each IR spectrum. (a) **5** (10 mM); (b) **2** (10 mM) and **5** (10 mM); (c) **1** (10 mM) and **5** (10 mM). (d) Lowest-lying complex of **2·5**. (e) Lowest-lying complex of **1·5**. Both complexes were computed at the M06/6-31+G(*d*,*p*) level of theory. Dissociation energies (D_{298}) given in kcal mol^{-1}. Values in parentheses were computed with the PCM model for toluene employing UAHF radii.

at 183 K clearly identifies two species with different N–H proton shifts (cf. Supporting Information, Figure S8). Again, C–N bond rotation is facile.

The half-chair (i.e., **5**_hc) conformer of uncomplexed lactone **5** is preferred computationally by 1.1 kcal mol^{-1} over the boat conformer (**5**_b, Figure 3). IR measurements in [D_8]toluene at room temperature show a broad C=O band wh a shoulder (Figure 5a, at 1745 cm^{-1}) implying a mixture of **5**_hc and **5**_b. At low temperatures, the concentration of **5**_hc increases, as evidenced from the growing band at 1733 cm^{-1}.

Complexation Studies

Turning to mixtures of the thiourea derivatives and the Lewis basic substrates we find that the ^{1}H NMR and ^{13}C NMR spectra of **2** in [D_8]toluene at room temperature in the absence and presence of **5** are rather similar (Figure 6a,b; ^{13}C NMR spectra are depicted in Figure 7) indicating that a complex does not form under these conditions. This is also supported by the absence of NOE cross peaks (Figure 8a) and the virtually unchanged (relative to free **5**) variable-temperature IR spectra (Figure 5b). M06/6-31+G(*d*,*p*) computations in the gas phase and in solution at room temperature give negative dissociation energies so that complex formation of **2·5** seems rather unlikely. On the contrary, the corresponding NMR spectra for **1** show large changes in the chemical shifts ($\Delta\delta \approx 1.8$ ppm) for the NH protons (Figure 6c,d) but also for the *ortho*-protons ($\Delta\delta \approx 0.7$ ppm). The same applies to the ^{13}C NMR absorptions (Figure 7) of the carbonyl ($\Delta\delta \approx 3.2$ ppm) and methylene carbon atoms next to the ring oxygen ($\Delta\delta \approx 1.4$ ppm).[7d] The NOESY (Figure 8b), ^{19}F–^{1}H HOESY (Figure 9), and IR spectra equally indicate **1·5** complex formation. The observed ^{19}F coupling with the hydrogen atoms of the methylene group next to the ring oxygen clearly indicate a very close spatial relationship between the *ortho*-C–H and the ring oxygen. The IR spectra of a 1:1 mixture of **1** and **5** in [D_8]toluene reveal a band at 1744 cm^{-1} originating from free **5** and a redshifted band at 1712 cm^{-1}, indicating a hydrogen-bonded complex of **1·5** (Figure 5c). These findings are also supported by MS (ESI) measurements (cf. Supporting Information) where the mass of [**1·5**+H]$^+$ = 601.08 was identified. M06/6-31G+(*d*,*p*) computations (Figure 5e) in

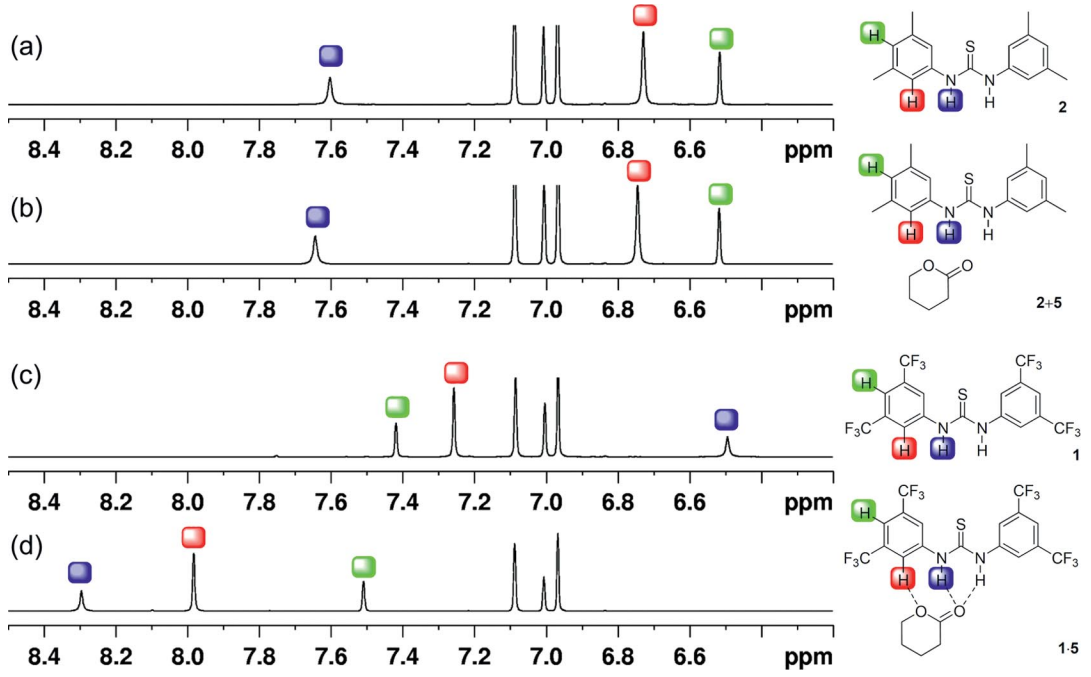

Figure 6. Sections of the ^{1}H NMR spectra in [D$_8$]toluene at 298 K. (a) Free **2** (13.3 mM); (b) complex **2·5** (**2**, 13.3 mM; **5**, 13.3 mM); (c) free **1** (13.3 mM); (d) complex **1·5** (**1**, 13.3 mM; **5**, 13.3 mM).

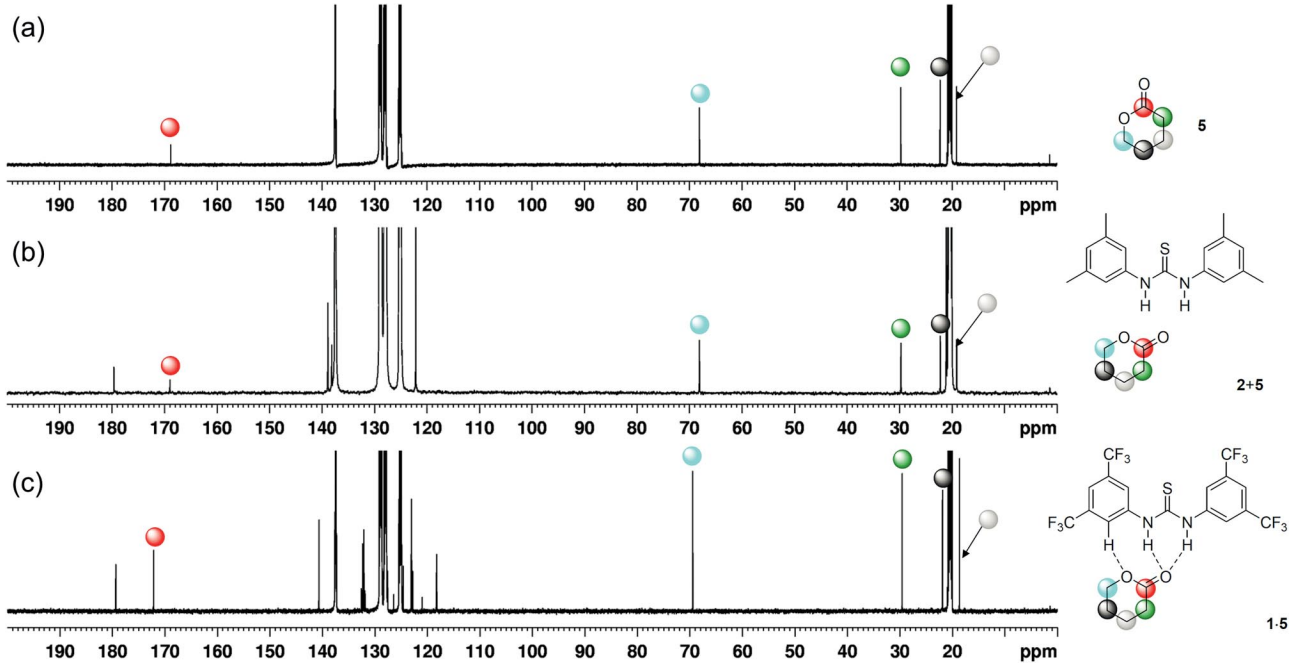

Figure 7. Sections of the ^{13}C NMR spectra in [D$_8$]toluene at 298 K. (a) Free **5** (13.3 mM); (b) complex **2·5** (**2**, 13.3 mM; **5**, 13.3 mM); (c) complex **1·5** (**1**, 13.3 mM; **5**, 13.3 mM).

the gas phase give D_{298} = 1.8 kcal mol^{-1} (in solution D_{298} = –2.5 kcal mol^{-1}) so that complex formation of **1·5** is preferred at room temperature, with **1** binding through double hydrogen bonding to the C=O group and the *ortho*-proton binding to the ring oxygen.

Natural bond order (NBO) analysis confirmed the N–H···O=C as well as the C–H···O$_{ring}$ interactions in **1·5**, with the C–H···O$_{ring}$ oxygen lone pair interaction with the C–H σ* orbital being energetically ≈2.5-fold weaker than the N–H···O=C interaction. This is confirmed through a quantum theory of atoms in molecules (QTAIM)[14] study by utilizing AIMAll:[15] an analysis of the electron density reveals bond critical points (BCPs) for the interactions noted above. In particular, we found a BCP for a hydrogen bond between the ring oxygen and the *ortho*-proton of $\rho \approx 1.20 \times 10^{-2}$ au, which is in the range of weak hydrogen bonds; there is also

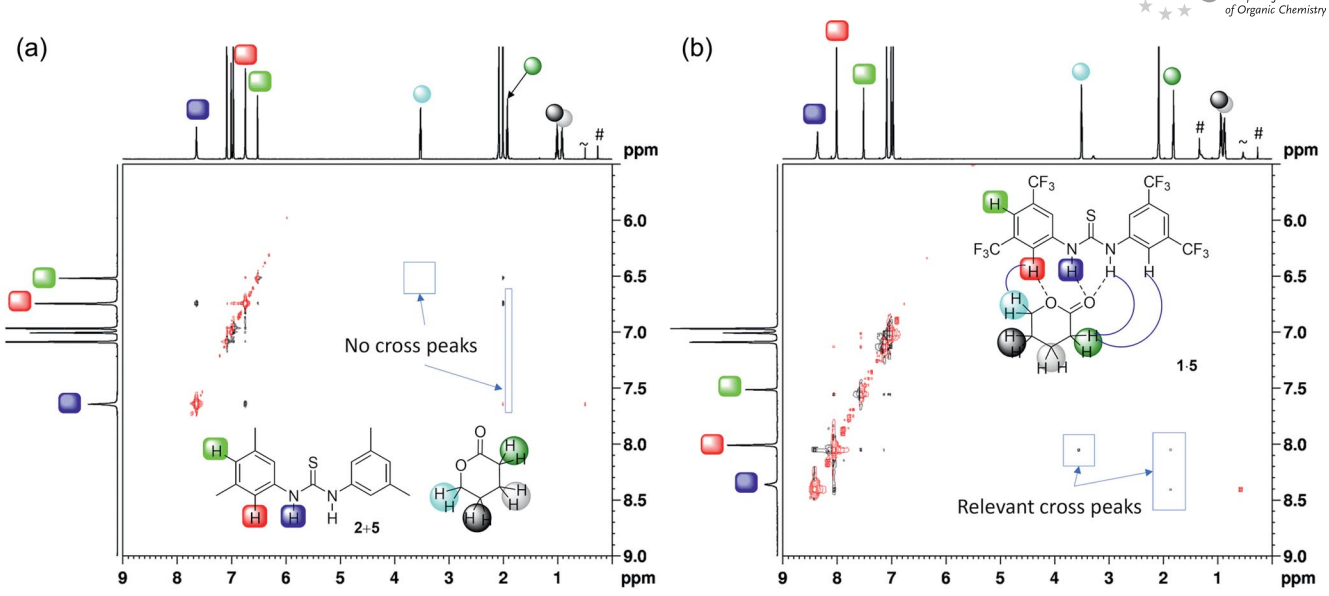

Figure 8. Sections of the NOESY spectra of 1:1 mixtures of thiourea derivatives and **5** in [D_8]toluene at 298 K. (a) **2** (13.3 mM) and **5** (13.3 mM); (b) **1** (13.3 mM) and **5** (13.3 mM). Expected and observed NOE signals are highlighted with a blue frame.

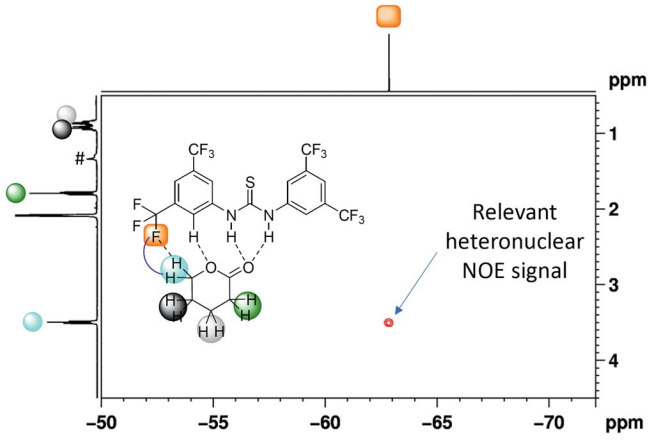

Figure 9. Section of the ^{19}F–^{1}H HOESY spectrum of a 1:1 mixture of **1** and **5** in [D_8]toluene at 298 K showing the cross peak between the fluorine of the CF_3 group and the methylene group protons adjacent to the ring oxygen; **1** (13.3 mM) and **5** (13.3 mM).

a BCP between the fluorine and the methylene proton adjacent to the ring oxygen.[14]

Thiourea derivatives **3** and **4** also bind to **5**, but the IR spectra (at the same concentrations, cf. Supporting Information) show that the amounts of complexes **3·5** and **4·5** are much lower than for **1·5**. NMR cross-peaks were only observed for **3·5**, and it can equilibrate between two low-energetically lying complexes (cf. Supporting Information). NBO analysis revealed both C–H···O_{ring} interactions through the *ortho*- or cyclohexyl methylene protons with the ring oxygen owing to an interaction of the ring oxygen's lone pair with the C–H σ* orbital (cf. Supporting Information, Figure S52 and Figure 10), similar to that found for **1·5** but weaker.[16] The hydrogen bonding in **3·5** is also evident from the downfield shifts of the NH- and *ortho*-protons. These downfield shifts correlate well with the thiourea NH acidities,[5b] and as catalytic acidity also qualitatively correlates with these pK_a values, the chemical shift differences (Δδ) may be suggestive of the potential activity of a particular catalyst. This correlation is evident from the presence of acidifying CF_3 groups, for which the pK_a values and Δδ differences follow the order **1** > **3** > **4** > **2**.[5b]

Next we investigated the complexation of **1** with **6**–**9**. Although **6** bears no ring oxygen as an additional hydrogen-bonding contact point, we identified an NH···O=C hydrogen-bonded complex through NOESY as well as IR measurements and DFT computations (Figure 10 and the Supporting Information). Both NH- and the *ortho*-protons of **1** bind to the carbonyl oxygen of **6**, because we find cross-peaks between the α-protons of **6** with the NH proton as well as with the *ortho*-proton. Computing the NBOs we found no C–H···O interaction, but this should be a consequence of long distance between the *ortho*-proton and the C=O group and according to that no correlation between the oxygen and C–H σ* orbital was visible; there is no C–H···O BCP.[17] Carbonyl derivatives bearing two C=O groups and a ring oxygen (i.e., **7** and **8**) lead to complexes as identified by IR and MS (ESI) techniques (Figure 10). The ring C=O IR redshift implies a hydrogen-bonded complex with the oxazolidinone ring. The NH and the *ortho*-protons of **1** bind to the ring C=O group of **7** and **8**, respectively. Computations reveal interactions of the *ortho*-protons with the ring oxygen for **1·7** and **1·8**. Without the ring oxygen structure **9** binds to **1** through the crotonyl C=O group (Figure 10). Complex **1·9** was found by NMR and IR spectroscopy and MS (ESI) measurements as well as DFT computations.

In the last years, many catalysts bearing the 3,5-bis(trifluoromethyl)phenyl moiety were reported and used in various hydrogen-bond-assisted organocatalytic reactions.[18] Many provide high enantioselectivities and high yields. Nevertheless, reactions for some systems fail due to a lack of substrate-specific interactions with the catalyst and show

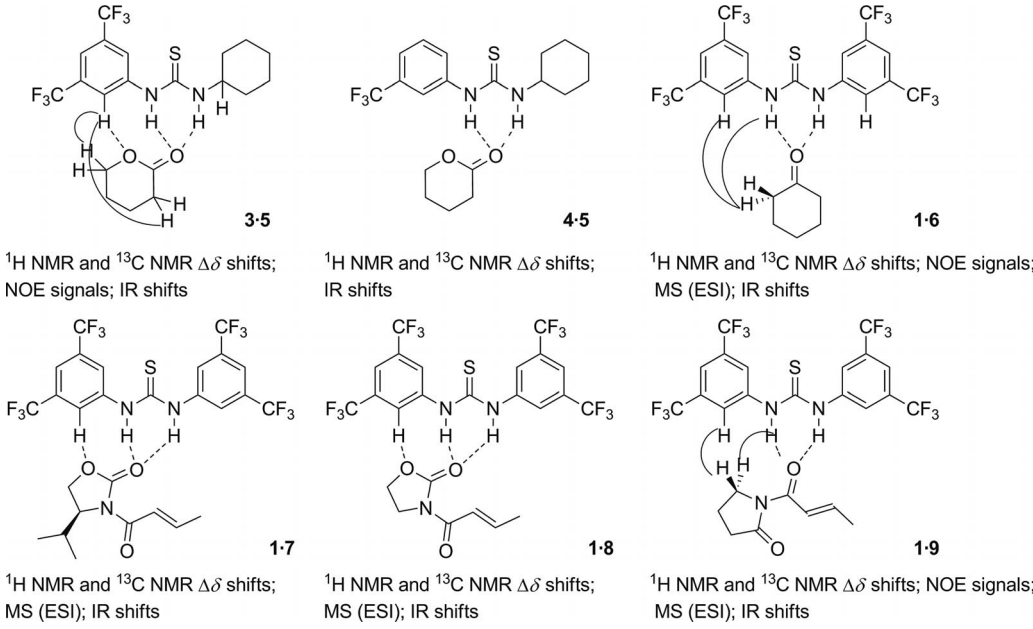

Figure 10. Complexes as identified by the indicated methods through NMR and IR spectroscopy and/or MS (ESI). Possible hydrogen bonds (dashed lines) where drawn for each complex demonstrated by relevant shortened distances between thiourea and carbonyl derivative by comparing NMR and computational results.

better results with alternatively functionalized catalysts.[5a,7b,19] For example, a phase-transfer catalyst bearing 3,4,5-trifluorophenyl substituents leads to higher enantioselectivities than a phase-transfer catalyst with pentafluorophenyl substituents[20] possibly due to the lack of polarized *ortho*-protons.[21]

Conclusions

As implied in many organocatalytic reactions utilizing **1** and its many derivatives, we find that it readily forms hydrogen-bonded complexes with Lewis basic substrates. The binding interactions do not only arise from interactions of the highly polar NH protons but also from the *ortho*-protons with Lewis bases. This is evident from NMR and IR spectroscopy, mass spectrometry (ESI), and DFT investigations and bears important implications for catalyst design.

Experimental Section

General Methods: All chemicals were purchased from Aldrich, Acros Organics, Alfa Aesar, Merck, and Lancaster in the highest purity available and were used without further purification unless otherwise noted. Liquid δ-valerolactone was freshly distilled and stored in a Schlenk tube under an argon atmosphere in the freezer. The thiourea and *N*-crotonyl derivatives were synthesized as noted below[22] or by literature-known procedures.[13c,23] Thiourea and solid *N*-crotonyloxazolidinone derivatives were stored under reduced pressure over P_2O_5. All solvents used for filtrations were distilled once. Drying was performed by following established literature procedures: THF and toluene were freshly distilled from Na/benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2 and stored over (4 Å) molecular sieves (MS) and under an argon atmosphere. All deuterated chemicals {[D_8]THF, [D_8]toluene (99.8%, purchased from Deutero GmbH or euroisotop GmbH)} were stored over (4 Å) MS. TLC was carried out on precoated Macherey–Nagel plastic sheets Polygram SiO_2 N/UV254 (40–80 mm) by using UV light for visualization. ^{1}H NMR and ^{13}C NMR were recorded with Bruker spectrometer Avance II (AV 400) [D_6]DMSO [$\delta(^1H)$ = 2.50 ppm], [D_6]DMSO [$\delta(^{13}C)$ = 39.5 ppm]. IR spectra were measured with Bruker IFS25 and IFS48 spectrophotometers. HRMS were recorded with a Sectorfield-MS: Finnigan MAT 95. CHN analyses were obtained with a Carlo Erba 1106 (balance: Mettler Toledo UMX-2) analyzer.

***N*,*N*′-Bis[3,5-(trifluoromethyl)phenyl]thiourea (1):** To a mixture of 1,1′-thiocarbonyldiimidazole[24] (1.50 g, 8.43 mmol) in CH_2Cl_2 (dried, 8 mL) was added carefully 3,5-bistrifluoromethylaniline (2.74 mL, 17.70 mmol, 2.1 equiv.) under an argon atmosphere. The resulting solution was stirred for 24 h at room temperature. The solvent was evaporated and diethyl ether (70 mL) was added to the yellowish oil. The organic phase was extracted with HCl (1 M, 3× 20 mL), aqueous $NaHCO_3$ (saturated, 3× 20 mL), and brine (3× 20 mL). The organic phase was dried with Na_2SO_4. After removing the drying agent and the solvent, the light yellow solid was recrystallized from $CHCl_3$. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from $CHCl_3$ again. The white solid was dried under vacuum in a desiccator over P_2O_5. A white solid (2.29 g, 61.3%) was afforded. Physical data were consistent with those reported in the literature.[25]

***N*,*N*′-Bis(3,5-dimethylphenyl)thiourea (2):** To a mixture of 1,1′-thiocarbonyldiimidazol[24] (1.50 g, 8.43 mmol) in CH_2Cl_2 (dried, 8 mL) was added carefully 3,5-dimethylaniline (2.21 mL, 2.14 g, 17.7 mmol, 2.1 equiv.) under an argon atmosphere. The resulting solution was stirred for 24 h at room temperature. The solvent was evaporated and ethyl acetate (150 mL) was added to the brown oil; the solution was poured into a 250-mL separatory funnel. The organic phase was extracted with HCl (aqueous, 1 M, 3× 40 mL), aqueous $NaHCO_3$ (saturated, 3× 40 mL), and brine (3× 40 mL). The organic phase was dried with Na_2SO_4. After removing the dry-

ing agent and the solvent, the light yellow solid was heated at reflux in diethyl ether (70 mL in a 250-mL flask) for 0.5 h. The solid was pumped off and washed with small portions of cooled diethyl ether to give a white solid (1.38 g, 57.6%). ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 9.56 (s, 2 H, N-*H*), 7.04 (s, 4 H, C-H_{ortho}), 6.76 (s, 2 H, C-H_{para}), 2.24 (s, 12 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]-DMSO): δ = 179.35 (*C*q), 139.16 (*C*q), 137.39 (*C*q), 126.00 (*C*-H), 121.50 (*C*-H), 20.93 ppm. IR (KBr disc): $\tilde{\nu}$ = 3360.0, 3195.5, 3017.5, 2972.2, 2913.7, 1610.2, 1537.7, 1516.6, 1470.0, 1432.3, 1342.3, 1313.3, 1270.9, 1227.6, 1166.3, 1037.0, 862.2, 847.0, 715.3, 652.3, 482.7 cm^{-1}. HRMS: calcd. for $C_{14}H_{17}F_3N_2S_1$ [M]$^+$ 284.1347; found 284.1348.

***N*-Cyclohexyl-*N*′-[3-(trifluoromethyl)phenyl]thiourea (4):** To a 10-mL flask with a gas inlet charged with dried CH_2Cl_2 (5 mL) was added cyclohexylamine (0.3 mL, 0.27 mg, 2.7 mmol) and 3-(trifluoromethyl)phenylisothiocyanate (0.41 mL, 0.55 mg, 2.7 mmol), and the mixture was stirred at room temperature under an argon atmosphere for 12 h. Afterwards the solvent was evaporated and the precipitate was washed with hexane/CH_2Cl_2 (4:1). The solvent was then removed. The white solid of **4**[26] (0.5 g, 1.64 mmol, 60%) was dried under vacuum over P_2O_5. M.p. 140–141 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.59 (s, 1 H, N-*H*), 8.05 (s, 1 H, C-H_{ortho}), 7.91 (s, 1 H, N-*H*), 7.66 (d, *J* = 7.88 Hz, 1 H, C-H_{para}), 7.51 (t, *J* = 8.9, 8.9 Hz, 1 H, C-H_{meta}), 7.39 (d, *J* = 7.55 Hz, 1 H, C-H_{ortho}), 4.10 (s, 1 H, C-*H*), 1.91 (m, 2 H, CH_2), 1.69 (m, 2 H, CH_2), 1.51 (m, 1 H, CH_2), 1.28 (m, 1 H, CH_2) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 179.18 (*C*q), 140.64 (*C*q), 129.45 (*C*-H), 128.87 (q, *J* = 30.70 Hz), 125.78 (*C*-H), 124.01 (q, *J* = 271.19 Hz), 119.67 (*C*-H), 118.27 (*C*-H), 52.07 (*C*-H), 31.70 (*C*H$_2$), 25.09 (*C*H$_2$), 24.42 (*C*H$_2$) ppm. IR (KBr disc): $\tilde{\nu}$ = 3230.8, 3076.2, 2932.7, 2852.9, 1602.4, 1543.3, 1484.8, 1459.3, 1327.4, 1273.3, 1212.0, 1163.8, 1117.3, 1093.0, 1072.8, 984.4, 887.0, 795.5, 715.6, 700.0, 654.8, 588.3 cm^{-1}. HRMS: calcd. for $C_{14}H_{17}F_3N_2S_1$ [M]$^+$ 302.1065; found 302.1088. Elemental analysis: calcd. C 55.61, H 5.67, N 9.26; found C 55.36, H 5.65, N 9.29.

NMR Spectroscopic Data Collection and Processing: The NMR spectra (^{1}H, ^{13}C, ^{1}H–^{15}N HSQC, NOESY, and ROESY) were recorded with a 600 MHz spectrometer equipped with a 5-mm broadband z-gradient probe (maximum gradient strength 53.5 G cm^{-1}). The phase-sensitive ^{1}H NOESY spectra were recorded by using a mixing time of 1 s; the ROESY had a spin-lock pulse of 70 ms. The ^{1}H–^{15}N HSQC spectra were acquired with pulsed field gradients. The delay was adjusted to a coupling constant of $^1J(^1H,^{15}N)$ = 60.8 MHz. ^{1}H: 600.13 MHz. ^{13}C: 150.90 MHz; when necessary using as the internal standard: TMS $d(^1H)$ = 0, $d(^{13}C)$ = 0, [D$_8$]-toluene [$\delta(^1H)$ = 2.09, 6.98, 7.00, 7.09 ppm], [D$_8$]toluene [$\delta(^{13}C)$ = 18.3, 25.2, 78.7 ppm], [D$_8$]THF [$\delta(^1H)$ = 1.73, 3.58 ppm], [D$_8$]THF [$\delta(^{13}C)$ = 25.37, 67.57 ppm]. ^{19}F–^{1}H HOESY measurements were performed with a 400 MHz Bruker Avance II spectrometer equipped with a 5-mm BBFO probe with *z*-gradient. For the ^{19}F–^{1}H HOESY experiments the hoesyph pulse sequence was used and 1 K data points were acquired in the directly detected dimension. All experiments were run under fluorine detection. A mixing time of 800 ms was used for the non-degassed samples and 64 scans were taken for each of the 256 T_1 increments. The delay between increments was set to 3 s. The ^{19}F signals are recorded relative to the resonance of a sample of $CFCl_3$.

IR Spectroscopic Studies: We used a Bruker IFS 25 IR or a Bruker IFS 55 FTIR spectrometer and a low-temperature cell with CaF_2 windows. Solutions of the various pure compounds and compound mixtures in [D$_8$]toluene were loaded into a low-temperature CaF_2 cell (*d* = 0.1 mm). The cell was cooled from room temperature to –95 °C with liquid nitrogen because at this temperature the solvent ([D$_8$]toluene) froze. Absorbance spectra were recorded at 2 cm^{-1} resolution (40 scans) with pure solvent at the respective temperature as reference.

Computational Studies: All computations were performed with the Gaussian09 suite of programs.[27] Geometry optimizations and frequency computations were performed using the M06 density functional in conjunction with 6-31+G(*d*,*p*) basis set. The M06 functional is recommended for computations of organometallic species and for studies of noncovalent interactions, thermochemistry, and kinetics.[11] Additional geometry optimizations and frequency computations for the determination of solvent effects were also performed by using the M06/6-31+G(*d*,*p*) method with a self-consistent reaction-field (SCRF) model.[28] SCRF methods treat the solute at the quantum mechanical level, while the solvent is represented as a dielectric continuum. Specifically, we chose the polarizable continuum model (PCM) developed by Tomasi and co-workers to describe the bulk solvent.[28,29] PCM computations were modified by using the UAHF model, a United Atom Topological Model applied on radii optimized for the HF/6-31G(*d*) level of theory.[29,30] We found shifts of the stretching vibrations of the cyclohexyl methine CH bonds of about ≈100–400 cm^{-1}; at this time the reasons for these unphysical shifts are unclear, but we note that they only occur when using the UAHF model in solvent computations. ΔH_0 values are corrected for zero-point vibrational energies (ZPVEs). All computed minima displayed only real vibrational frequencies (no imaginary frequencies). The quantum theory of atoms in molecules (QTAIM)[14] analysis was performed using AIMAll.[15] Computational results were depicted with CYLview.[31]

MS (ESI) Studies: The formation of thiourea–guest complexes was also investigated by mass spectrometry using a linear ion trap/Fourier transform orbital trapping mass spectrometer (LTQ Orbitrap Discovery, Thermo Scientific GmbH, Bremen, Germany) equipped with a nanoelectrospray ion source (Nanospray Ion Source, Thermo Scientific GmbH, Bremen, Germany).[32] Sample solutions were prepared by dissolving the host (thiourea derivative *c* = 20 mM) and guest (carbonyl derivative *c* = 20 mM) in toluene (dried). Analysis was performed in positive ion mode. Complex formation was confirmed by determination of the accurate mass of the protonated complex and of its constituents (protonated) after intentional destruction of the complex via collision induced dissociation (CID).

X-ray Crystallographic Analysis: CCDC-868394 (for **2**), -868395 (for **4**), and -206506 (for **1**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The crystal structure of **1** was previously published by Kotke and Schreiner.[25]

Supporting Information (see footnote on the first page of this article): Experimental details, remarks on NMR spectroscopic data collection and processing, matrix isolation studies, computational studies, as well as all NMR, IR, matrix-isolation IR, and mass spectra.

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[16] The NBOs analysis of **3·5_5** (cf. Supporting Information, Figures S52 and 53) reveals an interaction of the *ortho*-proton with the ring oxygen through charge transfer from the oxygen's lone pair to the C–H σ* orbital, but the interaction of the C=O σ orbital with the N–H σ* orbital is ca. sevenfold higher. The interaction energies of **3·5_5** and **3·5_7** are very similar. There are BCPs in both complexes, **3·5_5** ($\rho \approx 1.41 \times 10^{-2}$ au) and **3·5_7** ($\rho \approx 1.48 \times 10^{-3}$ au) for the C–H···O hydrogen bond.

[17] Computing complex **1·6_4** (cf. Supporting Information, Figures S76 and S77), which would be preferred at 0 K, we found a charge-transfer interaction from the oxygen's lone pair to the C–H σ* orbital. QTAIM computations also revealed a BCP ($\rho \approx 1.12 \times 10^{-2}$ au) in **1·6_4** through an interaction of the *ortho*-proton with the carbonyl oxygen, but this interaction is not visible in **1·6_2**.

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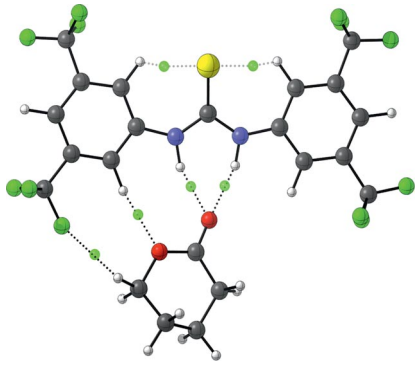
Organocatalysis

The present work reveals that thiourea derivatives bearing a 3,5-bis(trifluoromethyl)-phenyl group interact with Lewis basic sites of carbonyl derivatives through NH and highly polarized *ortho*-CH interactions in hydrogen-bonded complexes. Evidence is provided through a combination of DFT, variable-temperature IR and NMR spectroscopy, as well as MS (ESI) studies.



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Hydrogen-Bonding Thiourea Organocatalysts: The Privileged 3,5-Bis(trifluoromethyl)phenyl Group

Keywords: Density functional theory computations / IR spectroscopy / NMR spectroscopy / Organocatalysis / Thiourea derivatives

