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REGULAR ARTICLE

A quantum mechanical study of the stability and structural properties of substituted acylthiourea compounds

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Abstract The conformational, structural and electronic properties of eight acylthiourea derivatives with the general form N-acyl-N', N'-alkylthiourea have been investigated computationally at the MP2 level of theory and the 6-311G(d) basis set. Transition states between the four stable conformations were identified and characterized. There is a good correlation between the electron density at the bond critical point of each of the three C–N bonds present in the molecules, the calculated bond length, and the rotational barrier around these bonds. The calculations suggest the C(S)-N′ bond to have considerable double bond character which, according to analysis in terms of the Natural Bond Orbitals paradigm, can be attributed to a more favorable delocalization of the N′ lone pair into the antibonding π*(C=S) orbital than the lone pair on the other nitrogen. The influence of the various substituents on the structural and energetic features of the acylthiourea backbone is also investigated.

Keywords Conformations · Acylthiourea · NBO · NRF · AIM

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1 Introduction

The first synthesis of an acylthiourea, $CH_3(CO)NH(CS)NH_2$, was reported 125 years ago by Neucki [1], who also reported the first platinum complex derived from this ligand. The coordination chemistry of N-acyl-N'-alkyl- and N-acyl-N', N'-alkylthiourea compounds with various transition metals has been explored to some extent in the past three decades. Of possible industrial interest is the use of N-acyl-N'-alkylthioureas for the liquid–liquid extraction and separation of transition metal ions such as Cu(II), Hg(II), Au(III) and Pd(II) [2], and platinum group metals from hydrochloric solutions [3]. An extensive review is given by Koch [3].

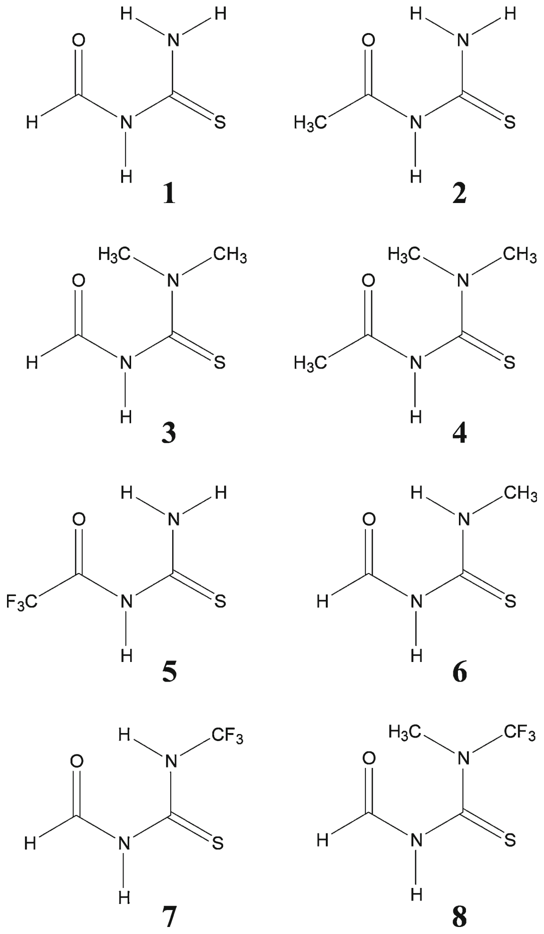
Since the publication of this review, a number of papers have appeared in the literature that cover various aspects of the chemistry of acylthiourea and it derivatives. Without the pretension of being complete, several are mentioned below.

Sacht et al. [4] synthesized and characterized Pt(II) complexes of acylthiourea for their potential use as chemotherapeutic agents. Reinel and co-workers [5] synthesized Zn- and Cd complexes with this compound, whereas Koch et al. [6] used Pt(II), Pd(II) and Rh(II). A number of papers have concentrated on the synthesis of derivatives of acylthiourea [7–10]. The biological or medicinal use of these complexes has also attracted attention [8,11–16]. The chemical isomerization of N-acylthiourea in Cu(II) complexes was studied by Hernandez et al. [17] and the use of these ligands as ionophores in solvent extraction was investigated by Koch and co-workers [18]. Novel multifunctional polymers of acylthiourea were synthesized by Mao et al. [19] whereas Koch et al. [20] investigated the use of 1D coordination polymers as chemical sensors.

A common structural feature found in acylthiourea compounds is that the C(S)-N′ bond invariably appears to have a partial double bond character, as is evident from NMR spectroscopy and from X-ray diffraction studies [3]. The adjacent N–C(S) bond on the other hand, is always found to be much longer than the former. These features have recently been reconfirmed in a detailed study of several acylthiourea compounds involving quantum mechanical calculations, X-ray diffraction, and IR spectroscopy [21–24]. In the present article, we describe part of, and report a computational extension to this work. As far as we could establish, only one paper employing ab initio methods has been devoted to a computational study of derivatives of thiourea [25], were a conformational analysis was done on a number of substituted benzoylthioureas. Hence, the aim of the current study was to investigate, by means of high level quantum mechanical calculation, the effect of various substituents on the conformational and structural properties of the acylthiourea skeleton. The compounds studied are summarized in Scheme 1.

2 Computational details

Ab initio calculations were performed on our local computer cluster with the Gaussian 98 and the Gaussian 03 [26,27] computer programs at the MP2 level of theory and the 6-311G(d) basis set. The latter was chosen because it combines flexibility with computational efficiency. All geometry optimizations were followed by an evaluation of the normal modes to establish the nature of the stationary point on the potential energy surface (PES). Transition states between any two stable conformations were identified and characterized by visual inspection of the normal mode corresponding to the imaginary frequency with an updated version of the program VIBRAM [28]. Any uncertainty about a correct assignment of the transition state was removed by either distorting the calculated geometry in both directions along the normal vector and performing, for each distortion, an energy minimization to establish whether the structure would converge to the expected energy minimum, or by a proper IRC calculation. Calculations of the electron density and characterization of critical points within the framework of the theory of Atoms in Molecules (AIM) [29,30] was performed with a computer program developed by JD. Natural Bond Orbital (NBO) [31–33] and Natural Resonance Theory (NRT) [34–36] analysis were performed with the NBO 5.0 computer program [37] installed for Gaussian 98. All analysis involving NBO 5.0 was performed with the SCF density, and geometry optimizations with deleted Fock matrix elements were done at the HF/SCF level because of the inability of NBO 5.0 to handle MP2 together with this option. The same basis set was used, however.



Scheme 1 The eight compounds considered in this study

3 Results and discussion

3.1 Conformational analysis

Four stable conformations are identified for acylthiourea and its derivatives. These are interconnected by rotations around the acyl-N bond, and by rotations around the adjacent N–C bond. A torsional change around the C–N′ bond also introduces conformational freedom, but the resulting forms can be tied to the four conformations mentioned above. To describe these four conformations we use a similar, though slightly different notation as employed by Plutin et al. [38], and denote them as *S*, *M*, *Z* and *U*, as shown in Fig. 1, and where the letter reflects the position of the C=O and C=S bonds relative to the vertically drawn N–H bond.

Although the conformations shown in Fig. 1 are drawn with a planar acylthiourea backbone, most compounds studied were found to deviate from planarity to various degrees. However, it is possible (and it proved to be useful) to characterize all structures as being one of the four forms defined above. The four stable conformations are related as shown in Fig. 2 where, for the time being, it is assumed that the N′ atom is symmetrically substituted.

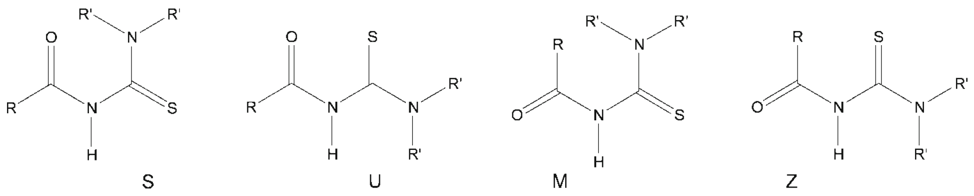


Fig. 1 The four stable conformations of acylthiourea

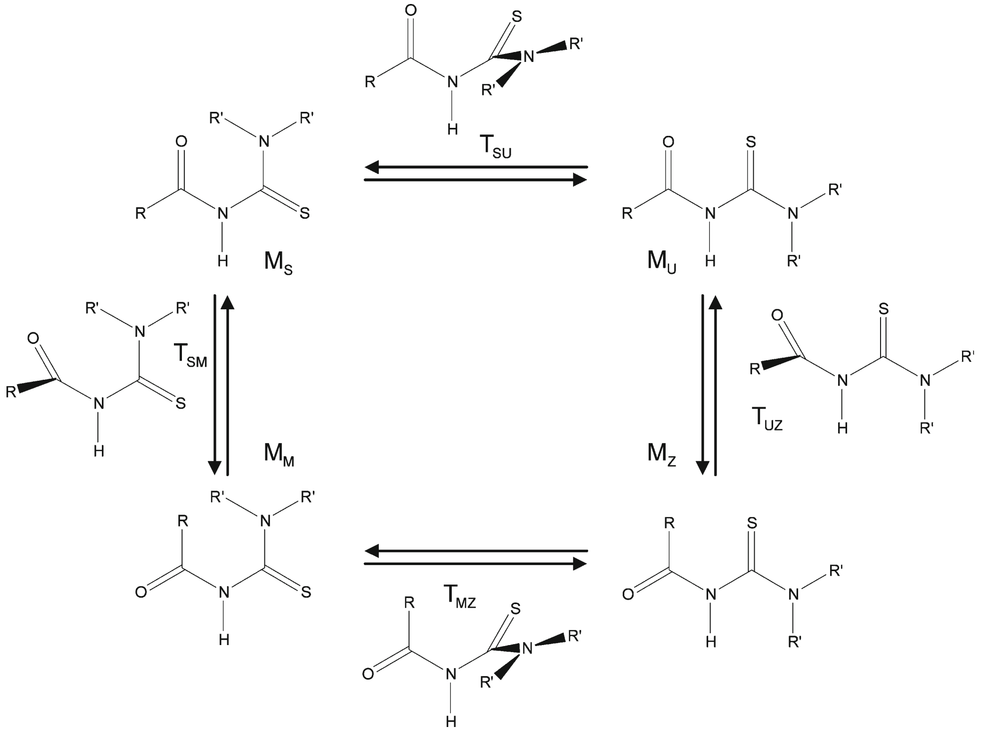


Fig. 2 Conformational pathway of symmetrically N'-substituted thioureas

In order to differentiate between the various stable conformations and the transition states that connect them, we introduce the following notation. Minima (stable conformations) on the potential energy surface are denoted as M_I, where the subscript I refers to one of the four conformations S, M, Z or U defined above. Thus M_S and M_Z refer to points on the PES that correspond to the stable S and Z conformations, respectively. Transitions states are first-order saddle points on the PES, and connect two stable conformations. They are characterized by one imaginary frequency in the vibrational spectrum. The transition states are represented as T_{IJ}, where *IJ* now represents the two energy minima, M_I and M_J, involved in the conformational change. Thus T_{SM} refers to the transition state between conformations S and M. When discussing energies, we will differentiate between T_{SM} and T_{MS}. Although both still refer to the same transition state, the distinction in notation emphasizes that a different energy is required for the transition $M_S \rightarrow M_M$ compared to $M_M \rightarrow M_S$. As is evident from Fig. 2, four unique transition states connect the four stable conformations, involving rotations around the acyl-N or the N–C bond. The C–N′ bond has a slightly higher double bond character than the other two C–N bonds and although rotation around this bond does not introduce additional stable conformations if the N′ atom is symmetrically substituted, the relatively higher rotational barrier may result in e.g., different chemical shifts in the identical R' groups. The N' atom is partially sp^2 hybridized, the amount thereof depending on the nature of the R' groups. For $R' = \mathrm{H}$, a perfectly planar local geometry is observed but even for $R' = \mathrm{CH_3}$, a noticeable pyramidalization occurs. However, a rotation around the C–N′ bond will disrupt any delocalization with the rest of the molecule, and result in an even larger deviation from planarity towards a pyramidal local geometry. The result is that, despite the fact that both substituents R' of the amine group are identical, two different rotational barriers are possible for a rotation around the C–N′ bond, shown in the lower part of Fig. 3.

We refer to these transitions as the "*inner*" and "*outer*" rotation of the amine group depending on whether, at the transition state, the substituents R' are faced towards, or away from the rest of the molecule. An alternative point of view would be to see the two paths as the result of a rotation of the amine group to the "right" or to the "left". However, our calculations show that the actual movement of the atoms is more

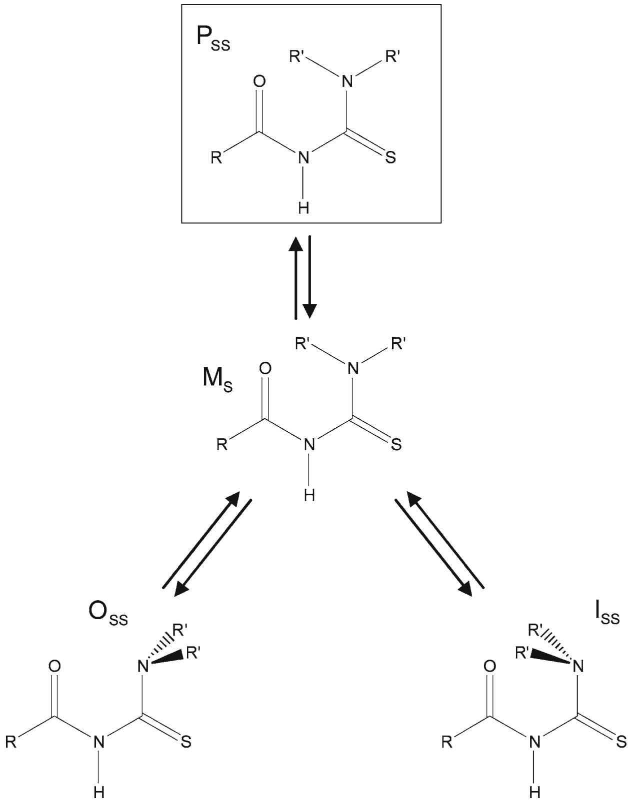


Fig. 3 Additional transition states between the conformations of symmetrically N'-substituted thioureas

a combination of a partial rotation followed by a pyramidal inversion, rather than a pure rotation. For the purpose of this study, the actual process of conversion is not so important and in any case, there is no ambiguity about the geometries of the transition states themselves are these are clearly defined as first-order saddle points on the PES. The *inner* and *outer* transition states are denoted as I_{II} and O_{II}, respectively, where as before, the subscript is one of the four stable conformations. Thus O_{SS} refers to the *outer* transition state resulting from a rotation of the NR_2' group of the molecule in its S conformation. The notation also emphasizes the fact that the conformation remains an S form, despite the rotation of the amine group.

But yet another transition is possible between the conformations. As mentioned earlier, the molecular backbone of the four conformations S, M, Z or U will, in general, deviate from the planar geometry that is suggested by the drawings. However, it turns out that for most compounds studied, an additional and energetically favorable conversion exists between each of the four stable conformations and its mirror image in the plane of the molecule. This transition requires a concerted movement of most, if not all the atoms in the molecule. In many of the cases studied, the transition state is characterized by a very flat, almost planar molecular backbone. We refer to this transition as P_{II} where, once again, the double subscript emphasizes the fact that in terms of the definitions above, the conformation of the molecule does not change during this transition. Obviously, the mirror image has the same energy as the parent conformation.

The conformational map becomes considerably more complex if the N' atom is asymmetrically substituted as demonstrated in Fig. 4.

Basically, this asymmetry doubles the number of stable conformations and hence also the number of transitions states connecting them. It is still possible to describe the conformations in terms of the description introduced above, and we differentiate between the two sets by the superscript A or B, where the actual choice depends on the nature of the groups R' and R''. For **6**, we choose $R' = \mathrm{H}$ and $R'' = \mathrm{CH_3}$, for **7** this is $R' = \mathrm{H}$ and $R'' = \mathrm{CF_3}$, and for **8**, $R' = \mathrm{CH_3}$ and $R'' = \mathrm{CF_3}$. Thus M_I^A is one of the conformations defined earlier and T_{IJ}^A represents a transition state between M_I^A and M_J^A. The energy minimum M_I^A has an equivalent M_I^B that differs mainly by the orientation of the $N'R'R''$ amine group. We write "mainly" because the R' and R'' groups differ, and thus the details of the geometry in terms of numerical values of bond lengths, angles, etc. of each conformation in the A set will differ from its equivalent in the B set. The two sets A and B are connected by a similar *outer* and *inner* rotation of the amine group as discussed above and shown in Fig. 5.

We do extend our notation for these transitions to highlight the fact that the set changes, e.g. O_{SS}^{AB} is the *outer* transition state for a rotation of the asymmetrically substituted $N'R'R''$ group between the M_S^A and M_S^B conformations. In a similar fashion as for the transition states mentioned earlier, O_{SS}^{AB} and O_{SS}^{BA} refer to the same transition state, but emphasize the direction of the transitional change involved. The conformations in each set can also have a transition state P_{II}.

3.2 Energetics

The acylthioureas studied are shown in Scheme 1. Energies of minima on the PES are tabulated in Table 1 and are given relative to the most stable conformation for each compound. Energy values of the transition states are relative to the energy value of the starting conformation in the transition involved. Thus the value for T_{SU} is relative to M_S, the value for T_{US} is relative to M_U. Despite many efforts and considerable fine tuning of the Gaussian minimizer settings, no M_U^A conformation could be located for compound **8** on the MP2/6-311G(d) energy surface. However, we had little trouble finding it with either Hartree–Fock or DFT/B3LYP using the same basis set, nor when using the smaller 6-31G(d) with MP2. Hence, we are confident that this conformation does not exist as a minimum on the MP2/6-311G(d) PES. Therefore, we report MP2/6-31G(d) values for this conformation and some of the transition states for compound **8**. In addition, we were also

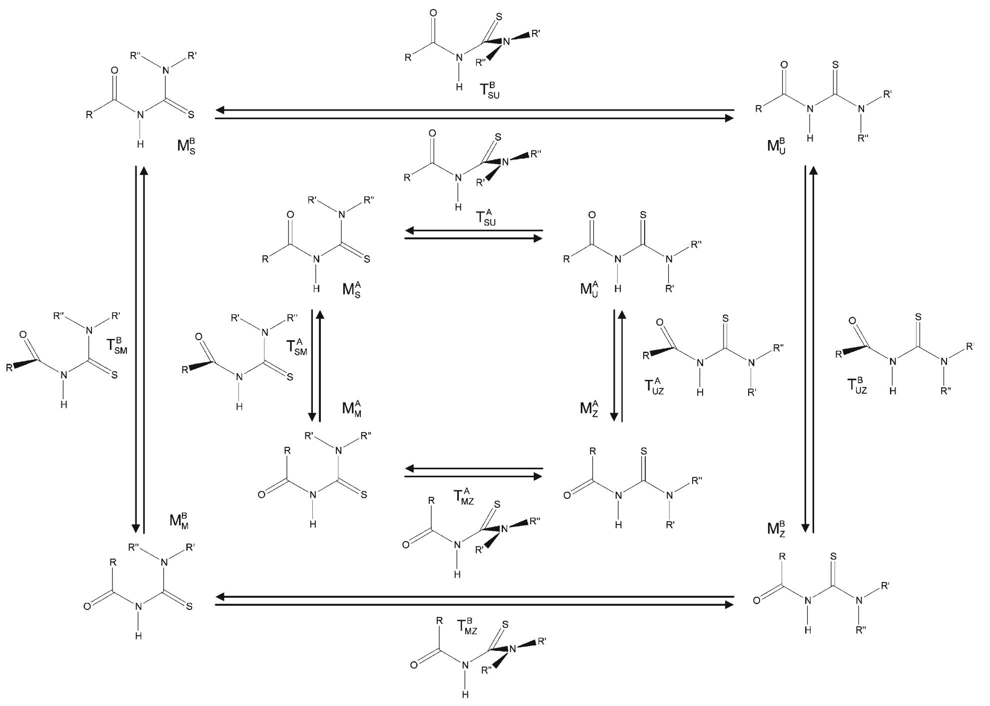


Fig. 4 Stable conformations and interconnecting transition states of asymmetrically N'-substituted thioureas

unable to locate transition states I_{MM} for **4, 7**and **8**, and P_{MM} for **4**. The latter suffers from severe steric interactions while the former three always inverted their geometry around the N' atom in the many attempts that were undertaken to locate them. No P_{SS} transition state is listed for compounds **1** and **2**, and for the A-set of **6** and **7** because the molecular backbone of the corresponding stable M_S form is already planar.

Free energies (298 K) for all the conformations and transition states that are listed in Table 1 are available in the supplementary material of this article. A *correct* calculation of these values is a bit complex, especially if low (rotational) normal modes are present [39–46]. In this work, as is most commonly done, the harmonic approximation is used to calculate the vibrational spectrum and because a transition state has an imaginary frequency, the vibrational contribution to the thermodynamic functions is calculated with one degree of freedom less than for the stable conformations. For high barriers of internal rotation, this discrepancy in the number of degrees of freedom has a negligible effect on the results but if the barrier is low, a proper treatment requires the use of a potential function that is consistent with a hindered rotation. In addition, the Gaussian program—like any other molecular modeling computer program—seeks stationary points on the PES, and not on the corresponding free energy surface. Hence, ad hoc free energies are an approximation at best. As a result, some transition states are calculated to have a free energy that is lower than the stable conformations on either side of the transition. Obviously, this is not very realistic, and hence we stick to MP2 energies in the following discussion. This restriction does not affect any conclusions resulting from this work, however.

In the overwhelming majority of derivates studied, the S conformation was found to be the most stable one. A search in the Cambridge Structural Database [47] reveals that this conformation is also predominantly present in the crystalline state, as shown in the top part of Fig. 6. During the search for suitable fragments, all structures with a connection between the amine part and the acyl part of the molecule were removed in order to prevent the appearance of conformations enforced by cyclic geometry constraints. It can also be seen from Fig. 6 that except for the S conformation, the U conformation is also present, whereas a substantial amount of structures are non-planar, adopting mainly a distorted S conformation. The M and Z conformations are not observed (although a number of cyclic acylthiourea derivatives do adopt the M conformation). From the bottom part of Fig. 6, it can be concluded that the amine part of the acylthiourea derivates is predominantly planar, as can be expected from the increased double bond character of the C–N′ bond.

In the parent all-hydrogen formylthiourea **1**, the S form is calculated to be perfectly planar, with a very short non-bonded distance (<2.0 Å) between the oxygen atom and one hydrogen atom of the primary amine group. This suggests the existence of a stabilizing hydrogen-bond interaction between the two atoms, and this notion is supported by the existence of a bond critical point (BCP) between

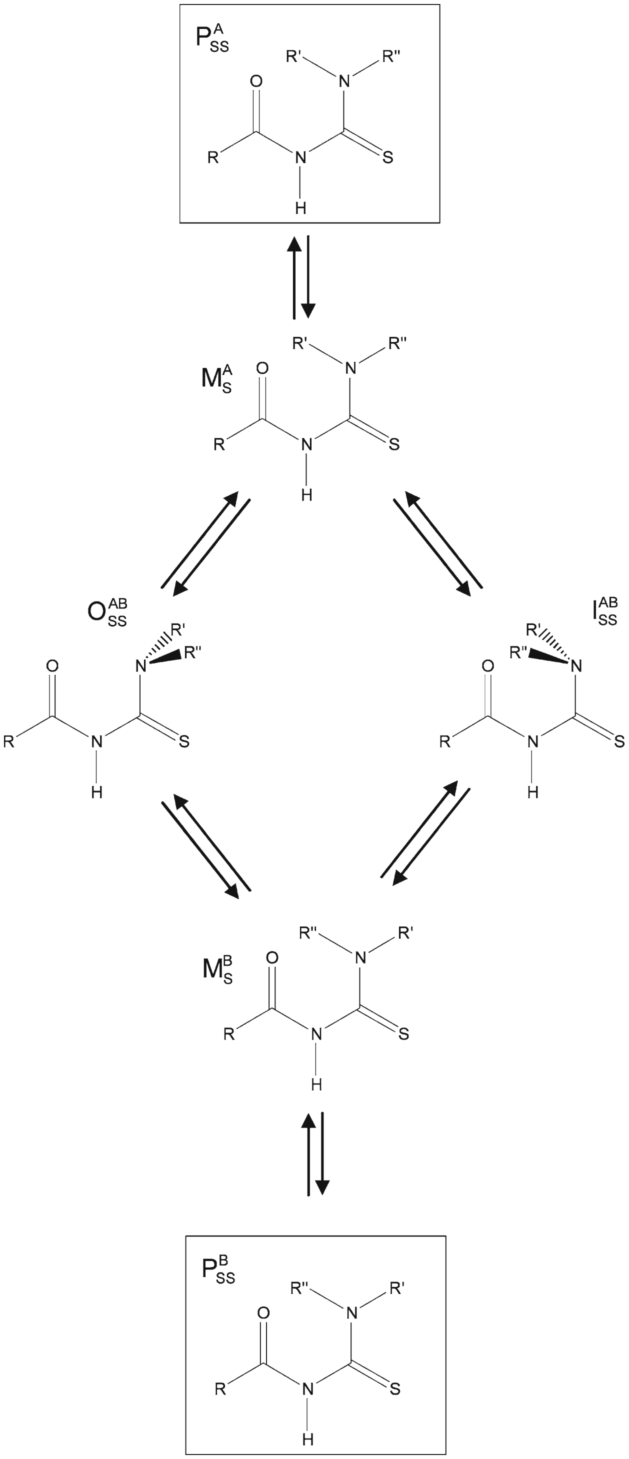


Fig. 5 Additional transition states for asymmetrically N'-substituted thioureas

the two atoms. The latter is a 1D minimum in the electron density function $\rho(\mathbf{r})$, and is an indication of the existence of a bond between the two atoms [29,30]. The values of the electron density at the BCP, $\rho_b(\mathbf{r})$, and its Laplacian (second derivatives), $\nabla^2\rho_b(\mathbf{r})$, indicate this to be a *non-sharing* interaction [29,30]. The latter includes hydrogen bonds, van der Waals bonds and ionic bonds, in contrast to valence bonds which are *sharing* interactions. The *Z* and *M* conformations are about 5.5 kcal/mol higher in energy. This value is about the same if free energies are compared. Both conformations deviate from planarity. The *U* conformation is destabilized even more as the result of a repulsive interaction between the oxygen and sulfur atoms, as is evident by the interatomic distance which is ~0.1 Å less than the sum of the van der Waals radii, and the presence of a BCP in the electron density between the two atoms. This pattern of interactions is repeated in *N*-acetylthiourea **2,** resulting in the same distribution of stable conformations, although the energy differences are higher. The same observation can be made for trifluoroacetylthiourea **5**, except that the larger fluorine atoms result in additional steric interactions, raising the energy differences even further, especially for the *M* conformation where there is a severe repulsion between the sulfur atom and one fluorine atom.

At first the relatively lower energy differences between the conformations in *N*-formyl-*N'*, *N'*-dimethylthiourea **3** appear a bit surprising, but these are not caused by the fact that the higher energy conformations are stabilized by favorable interactions, but by the replacement of the energetically advantageous hydrogen bond that exists for **1** by a repulsive oxygen–methyl interaction. This results in a considerable distortion of the molecule from planarity, and an increase in the energy of the *S* conformation. The observation is equally valid for the *N*-acetyl-*N'*, *N'*-dimethylthiourea **4**.

This pattern of stabilization/destabilization of the *S* conformation is also clearly evident in the asymmetrical *N*-formyl-*N'*, *N'*-disubstituted thioureas **6–8** where a large energy difference is calculated between the M_S^A and M_S^B conformations. In these thioureas, it is worthwhile to point to the large effect of the introduction of a CF_3 group on the N' atom which changes the energy balance between the various conformations, specifically the M_Z^B conformation which is stabilized by a short (< 2.1 Å) NH···F interaction.

The rotational barriers that separate the various conformations are much larger than one would expect for a rotation around a single C–N bond, indicating the presence of a partial double bond character. It is tempting to correlate the height of the barriers to bond order, the latter being represented either by the calculated bond length, or by the electron density at the bond critical point. To a certain extend this can be done, but from the large differences between the values for the *outer* and *inner* rotations of the amine group, it is clear that bond order alone cannot be the determining factor. A few observations are due, however. If only steric effects would play a role, and if $R' = R''$, then one would expect that for the *U*, *Z* and *S* conformations, the rotational barrier around the C–N' is relatively insensitive to the nature of *R* on the acyl group, because it is facing away

Table 1 Relative energies (kcal/mol) of the stable conformations and all the transition states connecting them

Compounds	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**	
Set						*A*	*B*	*A*	*B*	*A*	*B*
M_S	0.0	0.0	0.0	0.0	0.0	0.0	7.8	0.0	8.2	3.1	2.5
M_Z	5.6	8.3	1.8	4.4	12.4	6.8	7.4	6.5	2.7	3.6	0.0
M_U	12.1	12.7	8.6	9.2	10.5	13.2	14.9	11.9	7.8	9.3[a]	5.0
M_M	5.4	8.4	1.4	3.1	9.6	6.2	8.8	6.2	4.6	2.5	0.4
T_{SU}	14.2	14.6	8.8	9.2	11.9	13.6	8.7	13.8	4.2	8.6[a]	5.3
T_{US}	2.1	1.8	0.2	0.0	1.4	0.4	1.5	1.9	4.6	3.2[a]	2.9
T_{UZ}	7.9	5.8	7.7	6.1	9.7	8.3	7.3	8.1	8.4	9.2[a]	9.9
T_{ZU}	14.4	10.3	14.4	10.8	7.7	14.8	14.8	13.5	13.5	14.3[a]	14.9
T_{ZM}	6.9	4.4	4.4	1.9	0.8	4.5	7.2	6.0	9.1	7.7	7.2
T_{MZ}	7.1	4.2	4.9	3.2	3.6	5.0	5.8	6.4	7.2	8.8	4.7
T_{MS}	13.2	8.2	12.9	9.5	9.7	13.3	12.9	12.7	16.6	13.0	15.7
T_{SM}	18.6	16.7	14.2	12.6	19.3	19.5	13.9	18.9	12.9	12.4	13.6
I_{SS}	21.6	21.7	18.9	19.3	21.3	24.0	16.2	15.7	7.5	9.0	9.6
O_{SS}	23.2	23.5	16.0	16.2	22.0	25.2	17.4	16.8	8.5	5.4	5.9
I_{UU}	16.0	15.9	12.9	12.8	16.2	17.1	15.4	6.5	10.6	–	–
O_{UU}	7.6	7.4	5.3	5.0	8.4	9.1	7.4	3.4	7.5	–	–
I_{ZZ}	16.8	16.5	14.1	13.6	19.0	17.8	17.2	7.5	11.3	3.6	7.2
O_{ZZ}	9.5	9.1	7.4	6.8	11.5	10.9	10.3	4.6	8.4	0.0	3.6
I_{MM}	16.8	18.3	17.1	–	17.7	18.7	16.1	–	–	–	–
O_{MM}	9.4	10.4	7.3	9.3	12.2	11.0	8.4	4.6	6.2	0.4	2.5
P_{UU}	1.7	1.9	1.9	2.3	1.6	1.5	0.6	1.8	1.8	–	2.6
P_{MM}	1.8	1.7	8.5	–	1.9	1.9	5.1	2.0	5.7	12.2	9.7
P_{SS}	–	–	10.2	11.5	0.6	–	6.1	–	6.0	11.8	13.1
P_{ZZ}	0.5	0.9	0.3	1.3	3.8	0.2	0.0	0.6	4.1	2.5	1.4

For the transition states T_{IJ}, the energy for the transition $M_I \rightarrow M_J$ is relative to the conformation M_I. For compounds **6**, **7** and **8**, the values for I_{II} and O_{II} under the heading "*A*" mean I_{II}^{AB} and O_{II}^{AB}, thus the transition $M_I^A \rightarrow M_I^B$ with an energy relative to M_I^A, whereas under the heading "*B*" this means I_{II}^{BA} and O_{II}^{BA}, i.e. the energy for the transition in the opposite direction relative to M_I^B

[a] Obtained with the smaller 6–31G(d) basis set for all species involved

from the terminal amine group. Looking at the energy values of the I_{SS} to O_{ZZ} entries in Table 1, it is indeed seen that these are very similar for compounds **1** and **2**, and also for **3** and **4.** Some differences are noted for **5** where $R = CF_3$ but there does not seem to be a recognizable trend. Also the T_{SU} transition state should be fairly insensitive to the nature of R. Looking at the energy values in Table 1 for the same compounds, the entries for **1** and **2**, and also for **3** and **4** confirm this statement. Again the value for **5** differs. The lower value correlates with a slightly lower electron density, $\rho_b(\mathbf{r})$, at the BCP of the N–C bond, and a longer bond length compared to the compounds **1**–**4**. A noticeable influence of the electron withdrawing groups is also visible in the T_{UZ} values. This transition involves a rotation of the acyl group around the acyl-N bond and should—in the absence of electronic effects—be largely independent of the nature of R' and R''. This is indeed found to be the case although the barrier is about 1.5 kcal/mol higher if one of these groups is CF_3. The electron density $\rho_b(\mathbf{r})$ does not support the notion that this is as a result of electronic effects, however.

The calculated rotational barriers compare well with the scarce experimental values that are available. Using ^{15}N NMR spectroscopy, Filleux–Blanchard and Durand [48,49] conclude that the rotational barrier of the amine group around the C–N′ bond in *N*-acetylthiourea **2** should be in excess of 19.7 kcal/mol. The value calculated for the I_{SS} transition is $\Delta E^{\#} = 21.7$ kcal/mol ($\Delta G^{\#} = 21.1$ kcal)/mol. For *N*-acetyl-*N′*, *N′*-dimethylthiourea **4**, a barrier of 16.1 kcal/mol ($T = 310$ K) is reported [48,49] for a rotation around the same bond. The calculated value of the O_{SS} transition is 16.2 kcal/mol ($\Delta G^{\#} = 15.3$ kcal/mol). Sandström [50] obtains $\Delta G^{\#} = 16.1$ kcal/mol at $T = 309.7$ K for the same transition.

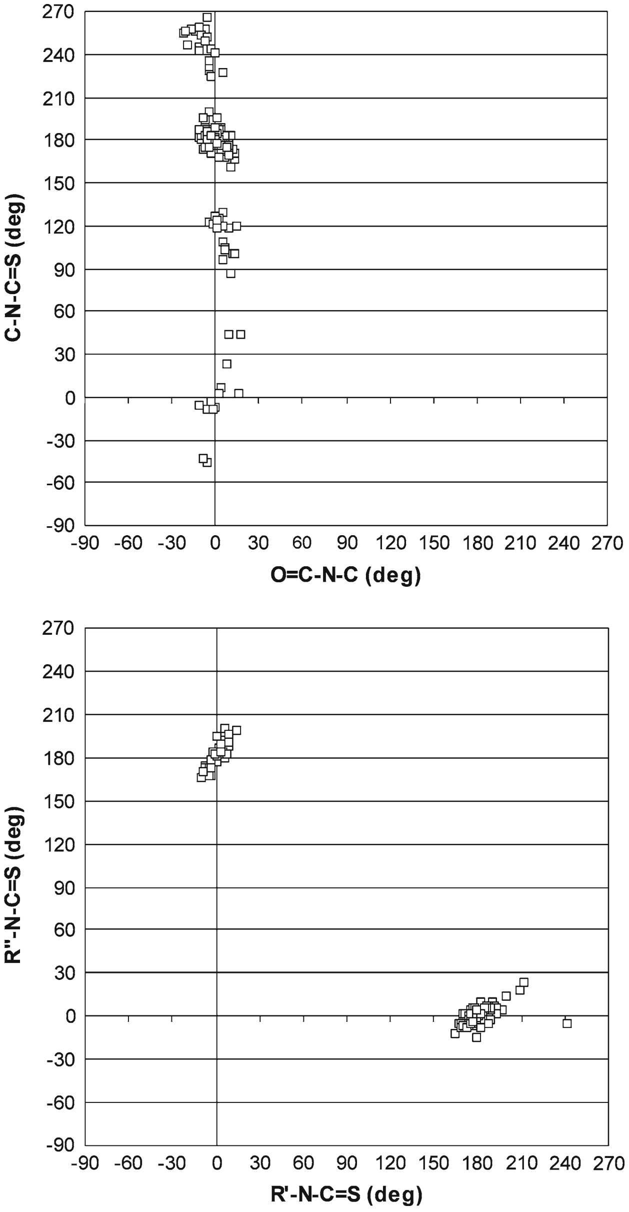


Fig. 6 Distribution of the observed conformations of acylthiourea compounds in the crystalline state. *Top* for an ideal *S* conformation, the torsion angles O=C–N–C and C–N–N=S should be 0 and 180°, respectively. Corresponding values are (0, 0) for *U*, (180, 180) for *M*, and (180, 0) for the *Z* conformation. *Bottom* perfect planarity of the amine part of the molecule is obtained if the torsion angles R'–N–C=S and R''–N–C=S are either 0° or 180°

The relationship between bond length and the electron density at the BCP, $\rho_b(\mathbf{r})$, for the three N–C bonds in all four of the stable conformations of the acylthioureas studied is graphed in Fig. 7. It has been shown [29,30,51] that $\rho_b(\mathbf{r})$ is related to the bond order and thus to the bond strength. It has been known for ages that there is a more or less linear relationship between bond order and bond length [52–55]. Although Fig. 7 shows results for three different bonds, all three are (Lewis) single bonds between the same elements, C and N. Hence, it is safe to conclude that for the three C–N bonds in acylthiourea, there is a good linear relationship between both $\rho_b(\mathbf{r})$ and bond length. Such a linear relationship can be rationalized by combining the Pauling formula [52–55] which relates the variation in bond length to the bond order, $\Delta r_i = -c \ln n_i$, with Bader's relation [29,30] between the bond order and the electron density at the bond critical point, $n_i = \exp[a\,\rho_b(\mathbf{r}) - b]$, resulting in a linear equation of the general form $\Delta r_i = A + B\,\rho_b(\mathbf{r})$, where A and B are constants. From calculations on a series of hydrocarbons, Alkorta et al. [56] have suggested that, at least for the C–H bond, a logarithmic relation is more appropriate. Applied to the data in Fig. 7, a linear fit gives the best results, although the difference with a logarithmic curve is very small ($r^2 = 89.5\%$ compared to 89.1%).

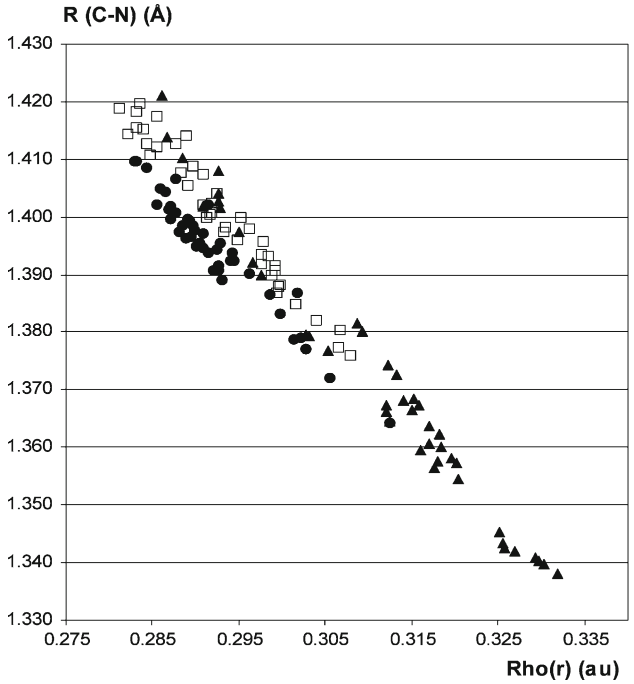


Fig. 7 The length of the C–N bonds (Å) in the acylthioureas as a function of the electron density at the BCP, $\rho_b(\mathbf{r})$ (a.u.). The acyl-N bond is represented by circles, N–C by open squares, and C–N′ by triangles

Moreover, the following additional observations can be made. First, it is noted that the scatter of the points on the graph is larger at lower values of $\rho_b(\mathbf{r})$ and longer bonds. This is not unexpected because at lower bond orders the bonds will more easily stretch as a result of steric effects. Second, it is seen that the values for the C–N′ bond are spread over the whole distance spectrum from 1.33 up to 1.42 Å, whereas the acyl-N and N–C bonds only cover roughly half this region, i.e. upwards from 1.37 Å. Hence, one has to conclude that the C–N′ bond is the most sensitive to the nature of the substituents. When looking in detail at the numerical values of electron density at the BCPs and the bond lengths, the effect of the substituents can be summarized as below.

Replacement of a formyl group by an acetyl group lengthens the acyl-N bond by ~ 0.01 Å and decreases $\rho_b(\mathbf{r})$. The effect on the other C–N bonds is substantially less, the N–C bond increasing slightly in double bond character, the effect on C–N′ being negligible. Substitution of $R = \mathrm{H}$ by $R = \mathrm{CF_3}$ has the opposite effect, i.e. the bond shortens and increases in bond order. However, this group also has a noticeable effect on the other C–N bonds with N–C lengthening and decreasing in electron density, and even a small, but systematic bond shortening effect on C–N′. Taking all conformations and all relevant compounds into account, the only effect of a methyl group on the amine part of the molecule is a small increase in $\rho_b(\mathbf{r})$ of the C–N′ bond with a corresponding bond shortening. Again, the effect of the CF_3 group is more pronounced. With $R'' = \mathrm{CF_3}$, the C–N′ bond increases in length up to 0.04 Å, and the N–C bond shortens with a corresponding increase in $\rho_b(\mathbf{r})$. Also in this case the effect is noticeable at the other side of the thiourea, and the acyl-N bond lengthens.

The C=O bond is not much affected by the nature of the substituents. If $R'' = \mathrm{CF_3}$, then C=S shortens by 0.01–0.02 Å, the actual value being dependent on the conformation of the molecule. The N–H bond is not noticeably affected at all.

The above effects should be visible directly in a structure determination and indirectly in e.g. the vibrational spectrum, but only the infrared spectrum of *N*-acetylthiourea **2** has been fully assigned [57,58], so no comparison between different molecules is possible. Using an approximative scale factor of 0.943 [59], the wave numbers of some fundamental modes are calculated as (exp. value in parentheses) 822 (820, C=S str) 1,688 (1,680, C=O str), 599 (610, C=O bend), 1,587 (1,590, NH_2 bend) cm^{-1}. N–H stretching modes are not well reproduced, giving 3,377 (3,300) cm^{-1} for the N–H group, and 3,450 (3,280) and 3,547 (3,400) cm^{-1} for the symmetrical and asymmetrical NH_2 stretching modes, respectively.

N-acetylthiourea **2** is also the only of the eight compounds studied for which a crystal structure is available [60]. In view of the discussion above, the length of the three C–N bonds in the molecule are the most interesting. These are found to be 1.376(1), 1.389(5) and 1.314(4) Å for the acyl-N, N-C(S) and C(S)-N′ bonds, respectively. The corresponding calculated values are 1.387, 1.402 and 1.340 Å, confirming the expected trend in the length of these bonds.

3.3 NBO analysis

The delocalization of the electron density in acylthiourea was also investigated within the context of the NBO paradigm [31–33]. With this method, localized orbitals are defined and optimized to accommodate as much electron density as possible, and delocalization is described in terms of donor–acceptor interactions of electron pairs into anti-bonding orbitals. The NBO analysis was applied to the *S* conformation of formylthiourea only. A list of key orbitals together with their energies and occupancies resulting from this analysis is given in Table 2. Noteworthy, is the relatively low energy of the π^*(C=S) orbital, and also the fact that the lone pair on the N' atom has a slightly higher energy than the one on the acyl part of the molecule. Two criteria are important for the characterization of suitable donor–acceptor interactions as being representative for delocalization: the interaction must result in a sizeable stabilization energy, and the acceptor orbital must have a significant electron population. Three such interactions stand out for formylthiourea. The largest stabilization energy (127 kcal/mol) is found for a donation of the N' lone pair into the C=S anti-bonding orbital, i.e. $n(N') \rightarrow \pi^*$(C=S), which corresponds to resonance structure **1a** in Scheme 2.

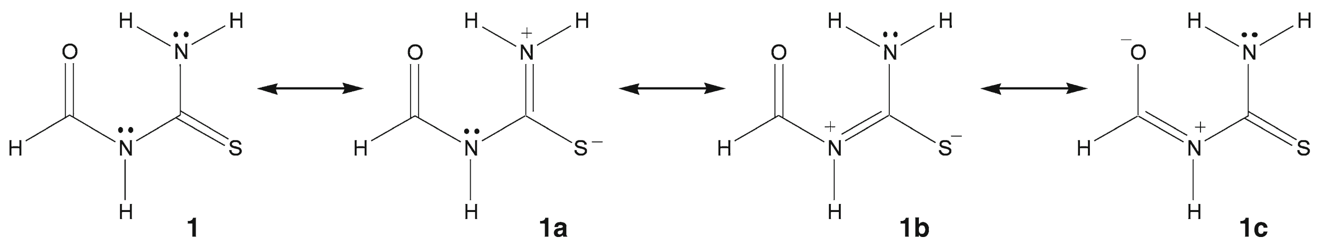
This resonance structure suggests a partial double bond character for the C–N′ bond. A look at Table 2 confirms that the π^*(C=S) orbital indeed has a relatively high electron occupancy. Two additional donor–acceptor interactions are important, one being the donation of the N lone pair into the same π^*(C=S) orbital, the other the donation of this lone pair into π^*(C=O), i.e. n(N)→ π^*(C=S) and n(N)→ π^*(C=O), with stabilization energies of 70 and 76 kcal/mol, respectively. The corresponding resonance structures in Scheme 2 are **1b** and **1c**. Because the N lone pair is involved in two interactions, one would expect the double bond character of the bonds involved resulting from the delocalization to be less pronounced, exactly as is calculated with the HF/SCF and MP2 methods. It is also noted that the delocalization into the π^*(C=S) orbital is slightly less favorable than delocalization into π^*(C=O). This correlates with the observation that the acyl-N bond is calculated to be shorter, and thus higher in bond order, than the N–C bond. This is also confirmed by the corresponding values of $\rho_b(\mathbf{r})$, but the actual difference is higher than suggested by the differences in stabilization energy.

Data for the *S* conformation of a selected number of additional structures are also compiled in Table 2. The structures included have in common that they all have a planar (or near-planar in the case of **5**) molecular backbone. Although this does not mean that steric interactions are excluded completely, they are at least minimized and make a comparison more useful. In addition, the NBO energies for the π orbitals of a structure with a non-planar molecular backbone will be totally out of line with the rest. As expected, the CF_3 group has the largest effect (compounds **5** and **7**). It lowers the energy of all σ and π bonds, of the corresponding anti-bonding orbitals, and of the non-bonding lone pair orbitals. Replacing $R = \mathrm{H}$ with $R = \mathrm{CH_3}$ as in **2** slightly increases

Table 2 Selected Natural Bond Orbitals, and important donor–acceptor interactions for the *S* conformation of selected acylthioureas

Orbital	**1**		**2**		**5**		**6**		**7**	
	E	Occ	E	Occ	E	Occ	E	Occ	E	Occ
σ(C=O)	−1.396	1.996	−1.398	1.995	−1.429	1.995	−1.388	1.996	−1.410	1.996
σ(C=S)	−0.960	1.982	−0.949	1.982	−0.978	1.982	−0.953	1.983	−1.000	1.984
π(C=O)	−0.560	1.996	−0.551	1.990	−0.588	1.992	−0.556	1.996	−0.575	1.996
n(N)	−0.422	1.723	−0.415	1.729	−0.439	1.706	−0.418	1.724	−0.438	1.721
π(C=S)	−0.395	1.989	−0.388	1.990	−0.409	1.987	−0.391	1.988	−0.421	1.987
n(N′)	−0.395	1.724	−0.388	1.724	−0.407	1.721	−0.373	1.681	−0.434	1.753
$\pi*$(C=S)	0.049	0.375	0.054	0.381	0.038	0.364	0.050	0.391	0.043	0.304
$\pi*$(C=O)	0.156	0.161	0.173	0.178	0.128	0.200	0.157	0.170	0.143	0.160
$\sigma*$(C=S)	0.525	0.009	0.527	0.009	0.516	0.009	0.524	0.011	0.517	0.009
$\sigma*$(C=O)	0.866	0.005	0.865	0.011	0.837	0.009	0.864	0.004	0.849	0.004
Interaction					$\Delta E^{(2)}$					
$n(\mathrm{N}') \rightarrow \pi^*(\mathrm{C{=}S})$	127.1		128.4		127.4		141.6		97.5	
$n(\mathrm{N}) \rightarrow \pi^*(\mathrm{C{=}S})$	69.8		71.9		64.0		66.2		68.9	
$n(\mathrm{N}) \rightarrow \pi^*(\mathrm{C{=}O})$	75.7		73.5		88.3		79.4		74.7	

Orbital energies, E, and stabilizing second order perturbation energies, $\Delta E^{(2)}$, are in eV, orbital occupancies in e



Scheme 2 Resonance structures used in the NRT analysis

the electron population in the C=S and C=O anti–bonding $\pi*$ orbitals, suggesting increased double bond character of the N–C bond. This is confirmed by the numerical values of $\rho_b(\mathbf{r})$, but the effect is small, as mentioned earlier. The $n(\mathrm{N}) \rightarrow \pi^*(\mathrm{C{=}S})$ interaction is noticeably stabilized with $R'' = \mathrm{CH_3}$ in **6**, and destabilized with $R'' = \mathrm{CF_3}$ in **7**. This is in line with the earlier observations from the AIM analysis. Note also that the $\mathrm{CF_3}$ group on the amine in **7** has an effect on the energies of all the orbitals of the C=O group and thus extends its influence over the whole molecule, as mentioned earlier when discussing the electron density.

The NBO 5.0 program contains a very elegant option that allows an additional proof that certain donor–acceptor interactions are responsible for a specific delocalization of the electron density in the molecule. This is achieved by the ability to delete individual interactions from the localized Fock matrix, followed by a re-optimization of the molecular geometry.

Table 3 shows the results obtained when deleting various donor–acceptor interactions in the *S* conformation of formylthiourea. In the first column of this table, selected bond lengths are given as obtained after a normal energy minimization with the 6-311G(d) basis set. These values differ somewhat from the MP2 values because, as mentioned earlier in the computational section, the NBO 5.0 program cannot handle a MP2 wave function in combination with this option, and hence these are HF/SCF values. The column labeled "*no star*" contains the bond lengths obtained after geometry optimization when all donor–acceptor interactions are deleted from the Fock matrix. The resulting geometry thus represents the idealized, 100% localized Lewis structure of the molecule. Note the lengthening of all the bonds, but specifically the C–N′ bond which now becomes the longest of the C–N bonds! The acyl-N bond is calculated as the shortest and hence with equal delocalization over this bond and the neighboring N–C bond, the latter will be longer, as found in the MP2 calculations. The next column contains the geometry obtained when removing the donation of the lone pair on N' into the π^*(C=S) anti-bonding orbital. To some extend this influences all the bonds compared to the calculation with no interactions being deleted, but results in a dramatic lengthening of the C–N′ bond and also a shortening of C=S, as

Table 3 Selected bond lengths (Å) of *N*-formylthiourea after geometry optimization with all ("*no star*"), or the indicated donor–acceptor interactions removed from the Fock matrix

Bond	HF/SCF	No Star	$n(N') \rightarrow \pi^*(C{=}S)$	$n(N) \rightarrow \pi^*(C{=}S)$	$n(N) \rightarrow \pi^*(C{=}O)^a$
C=O	1.185	1.280	1.175	1.197	1.162
Acyl–N	1.370	1.497	1.393	1.341	1.507
N–C	1.382	1.524	1.346	1.493	1.341
C–N′	1.319	1.536	1.482	1.303	1.331
C=S	1.671	1.703	1.621	1.644	1.692

[a] The $n(N) \rightarrow \sigma^*(C{=}O)$ interaction is also deleted because during energy minimization, the NBO 5.0 program continuously swapped the position of these two in its list of interactions, making the minimization unstable. However, this is a very weak interaction and the effect of its removal is negligible

expected from the corresponding resonance structure **1a**. In a similar fashion, deletion of $n(N) \rightarrow \pi^*(C{=}S)$ removes double bond character from N–C and shortens C=S, as anticipated. Interestingly, this deletion also shortens the other two C–N bonds, even beyond the HF/SCF values! Also, when the $n(N) \rightarrow \pi^*(C{=}O)$ is removed, the optimized geometry changes in the expected direction.

Finally, we performed a NRT analysis [34–36]. This provides a quantitative picture of the molecular electron density in terms of Lewis resonance structures. The principle behind NRT is simple: the method tries to represent the total HF/SCF electron density in terms of the electron density of a number of resonance structures by optimizing the weight of their contributions to the total. A multi reference analysis [34–36] was performed on the *S* conformation of formylthiourea. This indicates that the two major contributors to the electron density are the Lewis structure **1** with 43%, followed by the resonance structure **1a** with 30%. The structures **1b** and **1c** contribute each about 5%. This constitutes 83% of the total electron density, the remaining part being taken up by a large number of additional resonance structures. To put this figure into perspective: a similar analysis of thiourea itself results in a 53% weight of the ideal Lewis structure, plus two 20% contributions of the major resonance structures, accounting for 93% of the electron density.

4 Conclusion

A number of methyl- and trifluoromethyl substituted derivatives of acylthiourea were investigated at the MP2 level of theory. Four stable conformations have been found, and a relatively large number of rotational transition states were identified. The three C–N bonds in the molecule, formally being single bonds in terms of a Lewis point of view, do show a systematic trend in calculated properties. Invariably, the C(S)-N′ bond is found to be the shortest in length and for all the conformations of all the compounds studied. A strong correlation is noticed between the electron density at the bond critical point, $\rho_b(\mathbf{r})$, and the length of the C–N bond, indicative of electronic, rather than steric effects. The latter are more noticeable in the values of the rotational barriers separating the various conformations.

Analysis of the electron density in terms of Natural Bond Orbitals [31–33] and donor–acceptor interactions indicate that the lone pair orbital on the *N′* atom is slightly less stable then its counterpart on *N*, resulting in a more favorable delocalization into the antibonding $\pi^*(C{=}S)$ orbital. Natural Resonance Theory [34–36] suggests the dominance of two resonance structures, indicated **1** and **1a** in Scheme 2, conform with the notion of a partially double bond character in the C(S)-N′ bond.

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